

# 2025 Activity Report

RESEARCH CENTRE: Inria Centre at Université Grenoble Alpes  
IN PARTNERSHIP WITH: Université de Grenoble Alpes

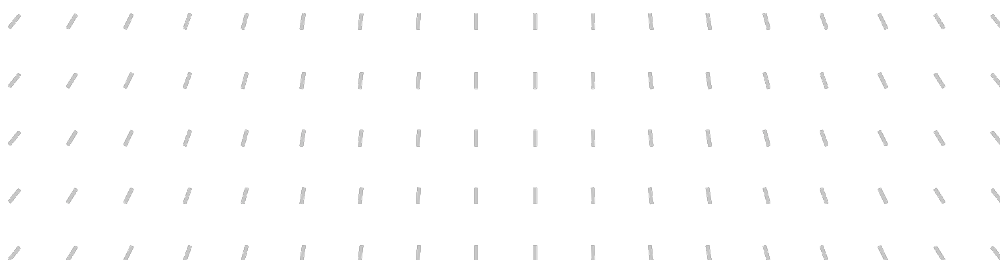
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Project-Team

## MICROCOSME

Analysis, engineering, and control of microorganisms

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## **Project-Team MICROCOSME**

*Creation of the Project-Team: 2021 October 01*

Each year, Inria research teams publish an Activity Report presenting their work and results over the reporting period. These reports follow a common structure, with some optional sections depending on the specific team. They typically begin by outlining the overall objectives and research programme, including the main research themes, goals, and methodological approaches. They also describe the application domains targeted by the team, highlighting the scientific or societal contexts in which their work is situated. The reports then present the highlights of the year, covering major scientific achievements, software developments, or teaching contributions. When relevant, they include sections on software, platforms, and open data, detailing the tools developed and how they are shared. A substantial part is dedicated to new results, where scientific contributions are described in detail, often with subsections specifying participants and associated keywords. Finally, the Activity Report addresses funding, contracts, partnerships, and collaborations at various levels, from industrial agreements to international cooperations. It also covers dissemination and teaching activities, such as participation in scientific events, outreach, and supervision. The document concludes with a presentation of scientific production, including major publications and those produced during the year.

## Keywords

### Computer sciences and digital sciences

- A3.4. – Machine learning and statistics
- A6.1.1. – Continuous Modeling (PDE, ODE)
- A6.1.2. – Stochastic Modeling
- A6.2.1. – Numerical analysis of PDE and ODE
- A6.2.4. – Statistical methods
- A6.3.1. – Inverse problems
- A6.3.2. – Data assimilation
- A6.3.3. – Data processing
- A6.4.1. – Deterministic control
- A6.4.6. – Optimal control
- A9.2.5. – Bayesian methods

### Other research topics and application domains

- B1. – Life sciences
- B1.1.2. – Molecular and cellular biology
- B1.1.4. – Genetics and genomics
- B1.1.7. – Bioinformatics
- B1.1.8. – Mathematical biology
- B1.1.10. – Systems and synthetic biology
- B2.2.4. – Infectious diseases, Virology
- B4.3.1. – Biofuels

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# 1 Team members, visitors, external collaborators

## Research Scientists

- Delphine Ropers [Team leader, INRIA, Senior Researcher, HDR]
- Eugenio Cinquemani [INRIA, Senior Researcher, HDR]
- Aline Marguet [INRIA, Researcher]
- Hidde de Jong [INRIA, Senior Researcher, HDR]

## Faculty Member

- Johannes Geiselman [UGA, Emeritus]

## Post-Doctoral Fellows

- Arnaud Belcour [INRIA, from Sep 2025, Starting Research Position]
- Arnaud Belcour [INRIA, Post-Doctoral Fellow, until Aug 2025]
- Claudia Fonte Sanchez [UGA, Post-Doctoral Fellow, until Aug 2025]

## PhD Students

- Yao Agbedoga [INRIA, from Oct 2025]
- Rand Asswad [UGA, from Sep 2025]
- Rand Asswad [INRIA, until Aug 2025]
- Eugene Ferragu [INRIA]

## Technical Staff

- Michael Baumgärtner [INRIA, Engineer, from Oct 2025]
- Judith Mokuinema Wawina [UGA, Engineer, from Feb 2025]

## Interns and Apprentices

- Nabigha Mogharbel [UGA, Intern, from Jul 2025 until Jul 2025]
- Nabigha Mogharbel [UGA, Intern, from Apr 2025 until May 2025]
- Amelio Schiavone [INRIA, Intern, from Feb 2025 until Jun 2025]
- Bony-Victor Tan [INRIA, Intern, from May 2025 until Jul 2025]

## Administrative Assistant

- Diane Courtiol [INRIA]

## Visiting Scientists

- Amélie Caddeo [iMEAN, from Jun 2025, CIFRE PhD student]
- Tomas Gedeon [Montana State University, from Apr 2025 until May 2025, Professor]

## External Collaborators

- Thibault Clavier [Unemployed]
- Muriel Coccagn-Bousquet [INRAe, Toulouse Biotechnology Institute, HDR]
- Natale Scaramozzino [CNRS, LIPhy]

## 2 Overall objectives

MICROCOSME combines computational and experimental approaches for the analysis, engineering, and control of the growth of microorganisms. Understanding and controlling the dynamics of bacterial growth is vitally important in health, medicine, biotechnology, and food industries, for instance to halt the growth of pathogens or stimulate the growth of probiotics or industrial microorganisms.

We develop multiscale models of growth, where the macroscopic observable, growth of a microbial population or community, depends on various metabolic pathways and regulatory mechanisms operating at microscopic scales within the cells. We use our (deterministic or stochastic) models to interpret experimental data or to infer the underlying growth processes from the data. This requires developing a platform for the automation of experiments, as well as methods and software for model estimation and data analysis. The analysis of microbial growth calls for new methodologies at the interface of microbiology, control theory, applied mathematics, computer science, biophysics, and molecular biology, which also leads to contributions in all of these fields. Our workhorse for the realization of this research program is the bacterium *Escherichia coli* pictured in Figure 1. Part of the microbiota of the human gut, *E. coli* is the model organism *par excellence* in microbiology and a popular platform for bio-based chemical production. We intend to extend approaches developed in-house for this specific microbe to other microorganisms including pathogens.

MICROCOSME has been created on October 1st, 2021. A recomposition and follow-up of the former IBIS project-team, MICROCOSME joins researchers from Inria and the Laboratoire Interdisciplinaire de Physique (CNRS UMR 5588) at Université Grenoble Alpes.

## 3 Research program

The research program of MICROCOSME is articulated around four research axes combining theory and experiments, which are illustrated in Figure 2 and detailed below.

### 3.1 Genome-scale analysis of microbial physiology

The molecular foundations of bacterial growth remain little understood today, because they involve large biochemical networks with physical and regulatory interactions across different levels of cellular organization. We investigate at the genome scale how the dynamics of gene expression and metabolism leads to microbial growth, using a combination of mathematical models and high-throughput data. The challenge is to integrate, in models of thousands of equations, multiple and heterogeneous datasets on the metabolic, transcriptomic, and proteomic level. We typically use constraint-based models to investigate the relations between microbial growth and metabolism, while the effect of growth on mRNA stability is analysed by means of non-linear mixed-effect models.

### 3.2 Natural and engineered resource allocation strategies in microorganisms

Microorganisms have evolved strategies to allocate their resources to different cellular functions and thus adjust their growth rate to fluctuating environments. We study these natural resource allocation strategies, by viewing cells as self-replicators that can be described using coarse-grained models and analysed by means of optimal and feedback control theory. The models take the form of systems of 5-10 nonlinear ordinary differential equations, with parameters estimated from published data or data obtained from dedicated experiments. Experimental work in the lab allows to validate model predictions on the single-cell

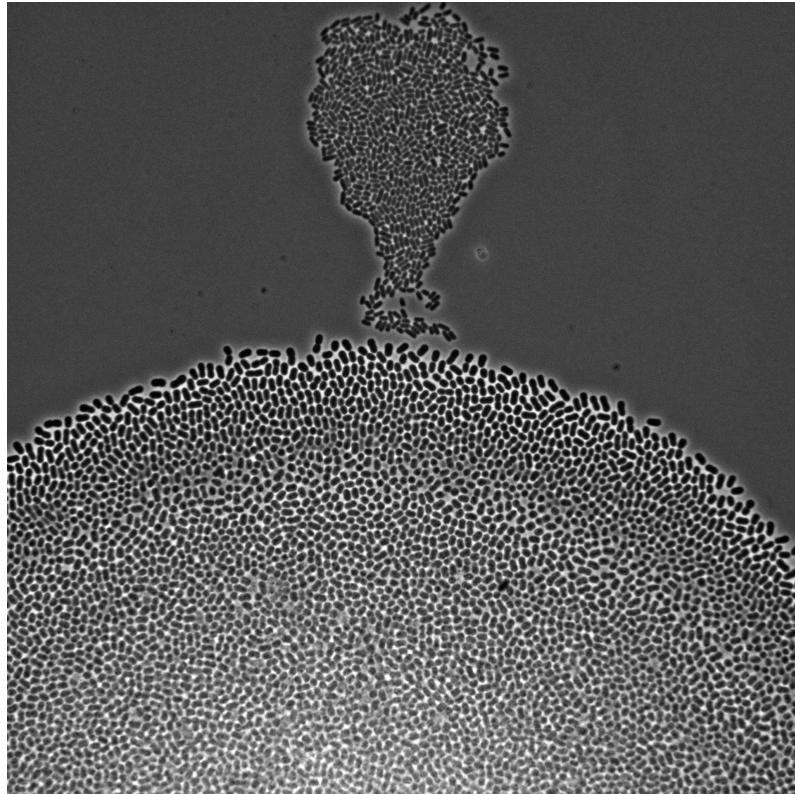


Figure 1: **Microscopy image of *Escherichia coli* bacteria growing on a solid nutrient medium.** Some bacteria have grown in the form of a hot air balloon (top) which, by colonizing the surface, will soon fuse with a second, bigger colony (bottom). The bacteria are rod shaped, 2  $\mu\text{m}$  long, and divide every 20 minutes in the conditions in which the picture was taken. Credit: Antrea Pavlou, December 2020.

and population level and to engineer new strategies for the reallocation of cell resources from growth to bioproduction.

### 3.3 Variability and robustness of microbial adaptation

The development of experimental techniques and the use of video-microscopy have led to a growing number of high-quality data showing the heterogeneity among cells in a population. We combine these single-cell data with models describing the stochastic dynamics of individual cells, such as birth-death processes, branching processes, and mixed-effect models. The models allow to investigate the origins of heterogeneity and its role in the adaptation of microorganisms to environmental changes, and to leverage population heterogeneity for biotechnological applications. In practice, this requires the extension of modelling approaches by taking into account the specificities of heterogeneity, as well as the development of appropriate methods and software for the inference of models and of biological quantities from quantitative time-course profiles of the microbial response to environmental changes.

### 3.4 Analysis and control of microbial communities

Heterogeneity also arises within communities consisting of different microbial species. Understanding microbial interactions is a challenging task that goes well beyond the characterization of single species, and offers great opportunities for applications, such as the control of the community for bioproduction. Indeed, suitably constructed microbial consortia carry the potential to outperform single species in the accomplishment of processes of societal interest, such as biofuel synthesis. On the theoretical side, we develop (deterministic or stochastic) models of microbial dynamics similar to those in the three other research axes, which can be used to investigate new control approaches for microbial communities. On the experimental side, the application of control strategies for biotechnological applications requires the engineering of microbial strains and the automation of experiments. To that aim we have been developing a platform for feedback control experiments allowing the real-time monitoring, data processing, evaluation, and application of control laws.

## 4 Application domains

The research agenda of MICROCOSME is interdisciplinary in nature, driven by fundamental questions in biology, which we address by a combination of mathematical, computational, and experimental tools. This enables us to develop and share with partners a know-how useful to address challenging problems in health, bioeconomy, biotechnology, and environmental microbiology.

### 4.1 Biotechnology and bioeconomy

Bioproduction imposes a strong metabolic burden on microorganisms, detrimental to their growth and the production yield. Our studies of natural resource allocation strategies lead us to explore and engineer various reallocation strategies to improve bioproduction through growth control. For instance, in the past, we have successfully implemented a growth switch in *E. coli* bacteria, aiming at shuttling resources, away from protein synthesis (key for bacterial growth) to the high-yield production of a metabolite of interest (glycerol) [7, 35]. We also develop and test control strategies for synthetic microbial communities, composed of populations of different *E. coli* strains or in consortia with other species. In the wake of our studies on the relation between growth and metabolism, we develop bioeconomy strategies for the transformation of vegetal waste into value-added product.

### 4.2 Health

Numerous *Mycobacteria* species pose serious threats to human and animal health. *Mycobacteria tuberculosis* strains are also known to withstand several of the antibiotics used to treat the infection. We have started to extend our microbial physiology analyses by means of constraint-based models to understand the molecular control of mycobacterial growth and characterize the relations between metabolism, pathogenicity, and

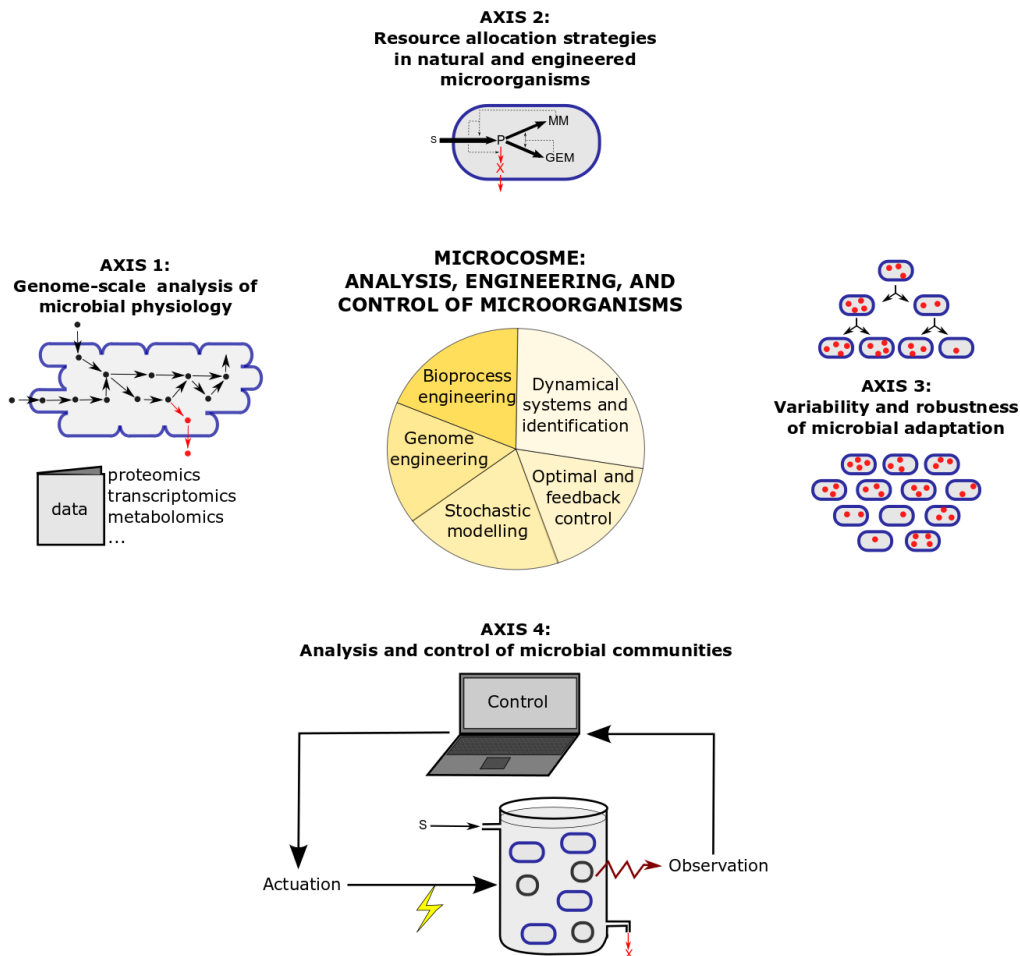


Figure 2: **Research axes and methods in the MICROCOSME project-team.** The first axis is dedicated to a genome-scale understanding of microbial physiology through model-based analysis of high-throughput data. This allows us to comprehend how cells adjust growth processes to environmental perturbations. This coordination reflects strategies evolved by microorganisms to allocate their resources to different cellular functions and (optimally) grow in their environment. The study of these natural strategies and their re-engineering is the focus of Research axis 2 which views cells as self-replicators that can be described using coarse-grained models and analysed by means of optimal and feedback control theory. In Research axis 3, we adopt a different angle by analysing the variability and robustness of microbial growth. In particular, we shift from deterministic to stochastic models, using data on the level of single cells in a population rather than averaged over all cells in the population. In Research axis 4, a different type of variability is considered, namely heterogeneity within communities consisting of different microbial species and how the community can be controlled for biotechnological applications. Research carried out in the four research axes relies on the methodological resources shown in the pie chart at the centre of the figure.

growth phenotype of mycobacterial species. This may lead, in the long term, to the development of new treatments for curing tuberculosis and other mycobacterial infections.

### 4.3 Environmental microbiology

Microbial subsurface ecology is poorly characterised. Current knowledge suggests that the subsurface is rich in microbial biodiversity, whose metabolic activity influences global biogeochemical cycles (e.g. carbon and nitrogen cycles). The metabolic potential of subsurface microbes can be inferred from high-throughput sequencing data, but this remains a difficult bioinformatics problem. We have started to extend our analyses of metabolism to the prediction of biogeochemical cycles from metabarcoding data. The approaches developed should help us to assess the microbial risk of underground hydrogen storage as part of our collaboration with BRGM and our partners in the European HyLife project.

## 5 Social and environmental responsibility

Several of our research activities have a direct societal impact. Our work on *Mycobacteria* addresses important questions of public health, while the project on the degradation and valorisation of vegetal waste meets European efforts in Circular Bioeconomy to replace fossil feedstock with renewable resources. Our Clean Energy Transition Partnership project HyLife allows us to address the issue of microbial risks associated with underground gas storage, as part of Europe's efforts to develop innovative energy system solutions towards net-zero by 2050.

## 6 Highlights of the year

Our paper, 'Predicting coarse-grained representations of biogeochemical cycles from metabarcoding data', was accepted for presentation at the main bioinformatics conference, ISMB/ECCB 2025, and was published in the *Bioinformatics* journal [16]. This work is central to Arnaud Belcour's postdoctoral research and was carried out as part of the HyLife European project, which focuses on the microbial risks associated with hydrogen underground storage.

Thibault Clavier, former PhD student in MICROCOSME, received an iPhD award from Bpifrance for a start-up project as a follow-up of his PhD project [30]. He also received support from SATT Linksium for the technology transfer project Switch2Prod (2026-2027). The project, involving several MICROCOSME members, aims at improving the bioproduction performance of microorganisms through dynamic control of their growth.

## 7 Latest software developments, platforms, open data

### 7.1 Latest software developments

#### 7.1.1 ODIN+

**Name:** Platform for advanced monitoring, control and optimisation of bioprocesses

**Keywords:** Systems Biology, Biotechnology, Automatic control, Monitoring

**Functional Description:** This application proposes a framework for on-line supervision of bioreactors. It gathers the data sampled from different on-line and off-line sensors. ODIN+ is a distributed platform, enabling remote monitoring as well as remote data acquisition. More originally, it enables researchers and industrials to easily develop and deploy advanced control algorithms, optimisation strategies, together with estimates of state variables or process state. It also contains a process simulator which can be harnessed for experimentation and training purposes. It is modular in order to adapt to any plant and to run most of the algorithms, and it can handle the high level of uncertainties that characterises the biological processes. The architecture is based on Erlang, and communication between modules through a MQTT Broker with Python for running the algorithms. ODIN+ is developed in collaboration with the INRIA MICROCOSME research team.

**News of the Year:** Several core system enhancements were implemented to improve robustness and usability. A new diagnostic module was introduced to proactively identify faults in both hardware components and inter-module communications. The calibration suite was expanded to include actuator calibration, increasing its versatility. Furthermore, the Python-based priority management system was refined for more efficient resource allocation, and the graphical user interface (GUI) underwent a significant overhaul to improve user experience. These developments were completed as part of the Hooding AMDT project.

**Contact:** Olivier Bernard

**Partner:** INRAE

### 7.1.2 GNA

**Name:** Genetic Network Analyzer

**Keywords:** Model Checking, Bioinformatics, Gene regulatory networks, Qualitative simulation

**Scientific Description:** Genetic Network Analyzer (GNA) is the implementation of methods for the qualitative modeling and simulation of gene regulatory networks developed in the IBIS (now MICROCOSME) project-team.

**Functional Description:** The input of GNA consists of a model of the regulatory network in the form of a system of piecewise-linear differential equations (PLDEs), supplemented by inequality constraints on the parameters and initial conditions. From this information, GNA generates a state transition graph summarizing the qualitative dynamics of the system. In order to analyze large graphs, GNA allows the user to specify properties of the qualitative dynamics of a network in temporal logic, using high-level query templates, and to verify these properties on the state transition graph by means of standard model-checking tools, either locally installed or accessible through a remote web server.

**Release Contributions:** (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.

**URL:** <https://team.inria.fr/microcosme/genetic-network-analyzer-gna/>

**Publications:** [hal-01417975](#), [hal-03094873](#), [hal-00762122](#)

**Contact:** Hidde De Jong

**Participants:** Hidde De Jong, Delphine Ropers

**Partner:** UGA

### 7.1.3 WellInverter

**Name:** WellInverter

**Keywords:** Bioinformatics, Statistics, Data visualization, Data modeling

**Scientific Description:** WellInverter is a web application that implements linear inversion methods for the reconstruction of gene expression profiles from fluorescent or luminescent reporter gene data. WellInverter makes the methods available to a broad audience of biologists and bioinformaticians. In particular, we have put in place a parallel computing architecture with a load balancer to distribute the analysis queries over several back-end servers, redesigned the graphical user interface, and developed a plug-in system for defining high-level routines for parsing data files produced by microplate readers from different manufacturers.

**Functional Description:** As input, WellInverter reads the primary data file produced by a 96-well microplate reader, containing time-series measurements of the absorbance (optical density) as well as the fluorescence and luminescence intensities in each well (if available). Various modules exist to analyze the data, in particular for detecting outliers, subtracting background, estimating growth rates, promoter activities and protein concentrations, visualizing expression profiles, synchronizing replicate profiles, etc. The computational core of the web application consists of the Python library WellFARE.

**URL:** <https://team.inria.fr/ibis/wellinverter/>

**Publications:** [hal-01217800](#), [hal-02195461](#)

**Contact:** Hidde De Jong

**Participants:** Delphine Ropers, Hidde De Jong, Johannes Geiselmann

**Partner:** UGA

#### 7.1.4 WellFARE

**Name:** WellFARE

**Keywords:** Bioinformatics, Statistics, Data visualization, Data modeling

**Scientific Description:** WellFARE is a Python library implementing linear inversion methods for the reconstruction of gene expression profiles from fluorescent or luminescent reporter gene data. WellFARE form the computational core of the WellInverter web application.

**Functional Description:** As input, WellFARE reads the primary data file produced by a 96-well microplate reader, containing time-series measurements of the absorbance (optical density) as well as the fluorescence and luminescence intensities in each well (if available). Various functions exist to analyze the data, in particular for detecting outliers, subtracting background, estimating growth rates, promoter activities and protein concentrations, visualizing expression profiles, synchronizing replicate profiles, etc. WellFARE is the computational core of the web application WellInverter.

**URL:** <https://github.com/ibis-inria/wellfare>

**Publication:** [hal-01217800](#)

**Contact:** Hidde De Jong

**Participants:** Delphine Ropers, Johannes Geiselmann, Hidde De Jong

**Partner:** UGA

#### 7.1.5 tabigecy

**Keywords:** Taxonomies, Metabolism

**Functional Description:** Analysis of microbial communities in their environment is crucial to understanding their environmental impact (e.g. on hydrogen or CO<sub>2</sub> storage or the carbon cycle). Thanks to high-throughput sequencing, it is now possible to characterise microbial communities taxonomically. However, linking this taxonomic information to metabolic functions related to biogeochemical cycles (such as the carbon cycle) remains a challenging task. This has motivated the development of tabigecy, a Nextflow workflow that predicts metabolic functions linked to biogeochemical cycles using taxonomic affiliations. This workflow combines the tool EsMeCaTa to predict protein sequences from taxonomic affiliations with bigecyhmm to predict functions of biogeochemical cycles using protein sequences. tabigecy then produces multiple visualisations to facilitate the interpretation of the results. This makes it possible to identify the impact of the microbial community studied on carbon, nitrogen, and sulfur cycles.

**Release Contributions:** Add the possibility to give multiple esmecata precomputed databases as input. Add a tutorial explaining the main outputs of the workflow.

**URL:** <https://github.com/ArnaudBelcour/tabigecy>

**Publication:** [hal-04938367](https://hal.archives-ouvertes.fr/hal-04938367)

**Contact:** Delphine Ropers

### 7.1.6 bigecyhmm

**Keywords:** Proteins, Metabolism

**Functional Description:** The Python package bigecyhmm is part of the tabigecy workflow. It aims at predicting metabolic functions linked to biogeochemical cycles using protein sequences as input. Hidden-Markov models associated with metabolic functions are used to search the input proteins. This makes it possible to identify the impact of the microbial community studied on carbon, nitrogen, and sulfur.

**Release Contributions:** Add new metabolic functions such as ones associated with phosphorus cycles. Add the possibility for user to give custom databases associated with specific biogeochemical cycles. Refactoring of several parts of the software to make it more flexible. Fix several bugs and typos.

**News of the Year:** Update to add more flexibility, more metabolic functions. Fix several typos and bugs.

**URL:** <https://github.com/ArnaudBelcour/bigecyhmm>

**Publication:** [hal-04938367](https://hal.archives-ouvertes.fr/hal-04938367)

**Contact:** Delphine Ropers

## 7.2 New platforms

**Participants:** Soraya Arias, Eugenio Cinquemani, Johannes Geiselman.

### 7.2.1 Automated mini-bioreactor platform for (dynamical) monitoring and control of microbial cultures

Advanced dynamical experiments with microbial cultures require regular, complex measurement operations over several days or weeks. Manual execution by human operators is error-prone and exposed to weak reproducibility, besides being a poor utilisation of human resources. Reactive control experiments, in addition, necessitate online calculation of control actions in response to all acquired measurements. MICROCOSME is actively developing an automated platform for automated monitoring and reactive control experiments on microbial cultures. The platform consists of a system of mini-bioreactors connected to nutrient sources and measurement devices via a pump-based fluidic network, and it also supports optogenetic control. Computer-operated by software ODIN+ (Section 7.1) as well as via platform-specific software developments, it enables automated monitoring and online data processing, as already achieved in week-long experiments over several bioreactors [37], and it will be exploited for feedback control experiments as part of the ongoing (Section 10) and future research projects of the group.

## 7.3 Open data

### Estimation of ribosome synthesis rate profiles from single-cell microfluidics data

**Contributors:** Hidde de Jong, Eugenio Cinquemani, Antrea Pavlou

**Description:** Estimation code, microfluidics dataset, and plotting script accompanying the *Nat. Commun.* paper of this year.

**Dataset PID (DOI,...):** DOI 10.24433/CO.6310888.v1

**Project link:** <https://codeocean.com/capsule/3939970/tree/v1>

**Publications:** [17]

**Contact:** Hidde de Jong

**Release contributions:** Hidde de Jong, Eugenio Cinquemani, Antrea Pavlou

### **Predicting coarse-grained representations of biogeochemical cycles from metabarcoding data**

**Contributors:** Arnaud Belcour, Loris Mégy, Hidde de Jong, Delphine Ropers

**Description:** Datasets and scripts accompanying the *Bioinformatics* paper of this year

**Dataset PID (DOI,...):** DOI 10.5281/zenodo.14762346

**Project link:** <https://zenodo.org/records/15211869>

**Publications:** [16]

**Contact:** Arnaud Belcour, Delphine Ropers

**Release contributions:** Arnaud Belcour, Loris Mégy, Hidde de Jong, Delphine Ropers

### **EsMeCaTa precomputed database**

**Contributors:** Arnaud Belcour, Loris Mégy, Hidde de Jong, Delphine Ropers

**Description:** EsMeCaTa [24] is a software application to infer consensus proteomes and metabolic functions from taxonomic affiliations. EsMeCaTa uses ETE3 and the NCBI Taxonomy database to parse the taxonomic affiliations and query the UniProt Proteomes database to find associated proteomes. These proteomes are clustered using MMseqs2 to create consensus proteomes, which are then annotated with eggNOG-mapper. EsMeCaTa can be time-consuming to run and requires a large number of resources to perform its various steps. A precomputed database has been created to facilitate its use.

**Dataset PID (DOI,...):** DOI 10.5281/zenodo.13354072

**Project link:** <https://zenodo.org/records/13354073>

**Publications:** [16]

**Contact:** Arnaud Belcour, Delphine Ropers

**Release contributions:** Arnaud Belcour, Loris Mégy, Hidde de Jong, Delphine Ropers

## A complementary EsMeCaTa precomputed database for phyla with fewer sequenced genomes

**Contributors:** Arnaud Belcour, Hidde de Jong, Delphine Ropers

**Description:** EsMeCaTa [24] is a software application to infer consensus proteomes and metabolic functions from taxonomic affiliations. This secondary precomputed EsMeCaTa database complements the main precomputed version by including phyla with fewer available genome sequences, which were previously excluded under EsMeCaTa's default parameters. To incorporate these underrepresented phyla, this database was generated using lower threshold values for EsMeCaTa proteomes.

**Dataset PID (DOI,...):** DOI 10.5281/zenodo.17224194

**Project link:** <https://zenodo.org/records/17224194>

**Publications:** [26]

**Contact:** Arnaud Belcour, Delphine Ropers

**Release contributions:** Arnaud Belcour, Hidde de Jong, Delphine Ropers

## 8 New results

### 8.1 Quantifying bacterial resource allocation on the single-cell level

**Participants:** E. Cinquemani, H. de Jong, J. Geiselmann, A. Marguet, A. Schiavone.

Microbial growth involves the conversion of nutrients from the environment into biomass. The main component of biomass are proteins, which also play a major role in the synthesis of new biomass by functioning as enzymes in metabolism and by constituting the molecular machinery responsible for the synthesis of proteins and other macromolecules. Microbial growth therefore requires the coordinated investment of cellular resources in different categories of proteins. Ribosomes are probably the most important protein category for two reasons. First, they are responsible for the synthesis of all proteins in the cell. Second, they are themselves very costly to make: ribosomes constitute up to 40-50% of the total protein mass in *Escherichia coli*.

Very few studies have addressed the quantification of ribosomal resource allocation on the single-cell level. How do the resources allocated to the synthesis of ribosomal proteins, both during balanced and unbalanced growth, vary over the individual cells of an isogenic population? In order to answer this question, in the framework of the PhD thesis of Antrea Pavlou [34] and the ANR project Maximic (2017-2023), we constructed chromosomal reporter systems for monitoring ribosome expression in the model organism *Escherichia coli*. We measured the ribosome concentration in individual cells growing on a rich or a poor carbon source, as well as changes in ribosome concentration during upshifts and downshifts between these carbon sources, over extended periods of time (>80 generations). Moreover, we developed a method for the statistical inference of time-varying ribosome synthesis rates from the single-cell, time-course data thus acquired.

We found that, during balanced growth in a given medium, the bacteria display a wide variety of ribosome concentrations that are only weakly correlated with the single-cell growth rate. This would not be expected if bacteria had optimized costly ribosome expression to precisely match the protein synthesis rate required for a certain growth rate. During the upshift from a poor to a rich carbon source, we observed that cells with a higher pre-shift ribosome concentration more rapidly adapt their ribosome synthesis rate, but also the ribosome synthesis activity and the growth rate, to the new environment. We remark that these observations are consistent with the existence of a variable ribosome reserve which the bacterial cells may exploit to speed up adaptation to sudden changes in the environment.

In this study published in *Nature Communications* [17], we thus quantified, using a combination of reporter genes and statistical inference algorithms, dynamic investment in ribosomes on the single-cell level. The results reveal a surprising variability in the allocation of resources to ribosomes, the most costly

molecular machine in bacterial cells, during both balanced and unbalanced growth. This raises fundamental questions on the role of the variability of ribosome concentrations in shaping the growth of a bacterial population and its adaptation to changing environments. Given the importance of growth and adaptation in biomedical and biotechnological applications, we expect our findings to have practical implications as well. The paper was selected as an Editor's Highlight in *Nature Communications*, in the category **Microbiology and infectious diseases**. In follow-up work, in the context of the internship of Amelio Schiavone, we have started to explore resource allocation models of the growth of individual cells to account for the experimental findings.

## 8.2 Biotechnological applications of bacterial growth control

**Participants:** H. de Jong, J. Geiselmann, T. Clavier, D. Ropers.

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. In recent years we obtained a foundational result for growth control in bacteria [7], in that we engineered an *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, putting the yield very close to the theoretical maximum.

In the framework of the PhD thesis of Thibault Clavier, defended in March 2024 [30], we managed to improve the genetic stability of the growth switch, by means of a redundant control mechanism of RNA polymerase expression. This reduces the occurrence of any spontaneously arising mutations disabling the growth switch to less than one in  $10^9$  cells [31]. A patent describing this improvement of the approach has been filed and is under review. The transfer of the approach is further explored in collaboration with SATT Linksum, in the framework of the maturation project Switch2Prod that will start in January 2026 (Section 9.2). Thibault Clavier is the leader of this project, aiming at the scale-up of the approach and its application to a broader range of molecules of biotechnological interest.

## 8.3 Synthetic microbial communities for bioproduction processes: modelling, analysis and real-time monitoring

**Participants:** S. Arias, R. Asswad, E. Cinquemani, T. Clavier, H. de Jong, J. Geiselmann, J. Mokuinema Wawina.

Modelling, analysis and control of microbial community dynamics is a fast-developing subject with great potential implications in the understanding of natural processes and the enhancement of biotechnological processes. With a series of collaborative projects, including project CtrlAB that ended in September 2025 (Section 10), we picked up the challenge to design and investigate the dynamics of synthetically engineered microbial communities, toward the development and *in vivo* testing of optimal control strategies.

We have addressed the design of a bacterial community of two *E. coli* strains, mimicking mutualistic relationships found in nature, and with the potential to outperform a producer strain working in isolation in the production of a heterologous protein. We previously developed an ODE model of the consortium, and analysed the model to characterize the conditions supporting coexistence and the tradeoffs involved in the

production process [11]. The engineering of the consortium and its experimental characterization revealed a more complex picture than expected [37]. The experimental scrutiny of new modelling hypotheses and the achievement of stable coexistence with the studied consortium are being addressed with an effort that involves several team members and that constitutes the subject of a paper in preparation.

In the context of project CtrlAB, modelling, analysis and control problems for an algal-bacterial consortium are addressed with the PhD thesis of Rand Asswad. The consortium consists of bacteria synthesizing vitamins that algae need for their growth, and an optogenetic control driving bacterial resource reallocation from their own growth to vitamin synthesis. Lipid content of algae is of interest for a wide range of bioproduction applications, thus the objective of maximizing algal biosynthesis. In a continuous-flow bioreactor setup, optogenetic and dilution rate control gives rise to nontrivial tradeoffs. Taking further previously published results, in [19], we extended the optimization study from a pure productivity objective to a broader set of criteria. We notably formulated and studied a Pareto-optimality problem directly related with a class of scalar economic-type objectives balancing productivity with process cost. Results have been presented at the 64th IEEE Conference on Decision and Control (CDC 2025) [19]. In parallel, we extended previous results concerning the optimization of process productivity. We notably showed that pseudo-periodic control profiles naturally emerge as optimal strategies from the concerted action of optogenetic and dilution rate control inputs, while periodicity is lost if only one control input is available. This and other results (precise quantification of the overyielding, limiting behaviours etc.) are the subject of a journal paper submitted for review.

## 8.4 Modelling and inference of cellular metabolism

**Participants:** Y. Agbedoga, M. Baumgärtner, A. Belcour, I. Cancino-Aguirre, M. Coccain-Bousquet, H. de Jong, N. Mogharbel, D. Ropers, B.-V. Tan.

Microorganisms are regularly exposed to environmental perturbations. In order to thrive in new environments, they must adapt their microbial metabolism. In order to study the mechanisms of metabolic adaptation, we use genome-scale reconstructions of cellular metabolism, such as in [13]. These networks are reconstructed using genomic annotations, in which genes encoding enzymes are linked to metabolic reactions. Such reconstructions are often available in public databases for well-studied microorganisms, but this is not the case for poorly studied species. As part of the recently defended PhD thesis of Ignacia Cancino Aguirre [22], co-advised by Delphine Ropers and Hidde de Jong, we develop such reconstructions from genome sequences for the *Mycobacterium* genus. This allows us to analyse how differences in carbon metabolism account for the variability in growth rates of mycobacterial species, which include both dangerous pathogens and non-pathogenic bacteria. The results of this study are currently being validated experimentally by our partner, L. Sorio de Carvalho (The Herbert Wertheim UF Scripps Institute for Biomedical Innovation & Technology, Florida, USA), and prepared for publication.

Inferring metabolic function from sequenced genomes is a difficult problem, but even more so when dealing with microbial communities in natural environments. In collaboration with BRGM, the French geological survey, NORCE (Norway) and Isodetect GmbH (Germany) in the framework of the European project HyLife (Section 10), Arnaud Belcour, Hidde de Jong, and Delphine Ropers have begun to address this issue. They developed a bioinformatics pipeline, Tabigecy (7.1.5), to use metabarcoding data in order to predict metabolic functions that make up biogeochemical cycles. A paper describing the approach has been presented at the main bioinformatics conference, ISMB/ECCB 2025, and published in the *Bioinformatics* journal [16] (Section 6). Tabigecy uses the tool EsMeCaTa to infer consensus proteomes and metabolic functions from taxonomic affiliations. EsMeCaTa is described in a paper that is currently under submission [24]. This software can be time-consuming to run, which prompted us to develop a precomputed database of EsMeCaTa (Section 7.3) using the Gricad infrastructure supported by the Grenoble research community, in collaboration with Loris Mégy (Gricad, Inria, CNRS, Université Grenoble Alpes, Grenoble INP).

A. Belcour and M. Baumgärtner are currently extending the pipeline Tabigecy in order to apply it to subsurface microbial communities. The aim is to characterise their metabolic activity and any potential detrimental effects on gas storage in underground reservoirs. The first results obtained from samples taken from 19 European underground reservoirs are described in a paper recently submitted for publication [26]. This study shows that geochemical conditions and anthropogenic disturbances play a key role in the structure

and functional potential of deep subsurface microbial communities. As outlined in the proceedings of the Global Energy Transition Conference & Exhibition (EAGE GET 2026, [20]), some of these communities can consume hydrogen in a laboratory setting. Further experimental and modelling work is underway to characterise the microbial interactions. Another work by A. Belcour and collaborators studied the interactions between microbial groups in the context of the holobiont formed by the brown alga *Ascophyllum nodosum* and its microbiota [18].

These studies all predict the potential of microbes to carry out certain metabolic functions. However, the actual realisation of these functions relies on the gene expression program. Our previous research has demonstrated the significance of regulating mRNA stability in adapting metabolism to environmental changes [12, 13, 33, 36]. As part of Y. Agbedoga's PhD thesis supervised by D. Ropers and M. Coccagn-Bousquet and the ANR project RECOM (see Section 10), and building on previous modelling work [4], mathematical and statistical modelling approaches are being developed to infer the regulatory mechanisms underlying the genome-wide control of mRNA stability, based on both high- and low-throughput biological data. A paper describing these results is in preparation.

## 8.5 Inference of parameters on lineage trees

**Participants:** E. Cinquemani, C. Fonte Sanchez, A. Marguet, E. Reginato, A. Schiavone.

Recent technological developments have made it possible to obtain single-cell measurements of gene expression and, in some cases, the associated lineage information. However, most of the existing methods for the identification of mathematical models of gene expression do not account for the fact that cells undergo divisions and are related to one another through parental relationships. Most methods developed for single-cell data make the simplifying assumptions that cells in a population are independent, thus ignoring cell lineages. The development of statistical tools taking into account the correlations between individual cells is needed to enable the investigation of inheritance of traits and of emerging dynamics in bacterial populations.

With the PhD thesis of E. Reginato, defended in November 2025, we have advanced on the analysis and inference of tree-structured single-cell gene expression models with mother-daughter inheritance that we had started in a previous publication [10]. We addressed inference from single-cell gene expression data in the case where lineage information is not available. We notably explored how well inheritance parameters can be inferred depending on absence or presence of dynamics in the mean and variance data. In relation with certain literature datasets from videomicroscopy, we developed statistically exact maximum-likelihood estimation methods leveraging correlation of empirical means along generations, and approximate methods also exploiting variance data. Methods, simulation-based performance analysis as well as demonstration of application to the reference dataset are presented as a first chapter of the thesis manuscript [23].

While the above modelling approach to mother-daughter inheritance is of statistical nature, it can be related with mechanisms into play at cell division. For this, within the same thesis, we looked at the regulation of the repartition of multicopy resistance plasmids at cell division and its impact on population growth in selective media. We have developed and compared several individual-based models, and obtained a first understanding of the role of plasmid repartition statistics and stochastic cell division in the emerging population dynamics. Simulation results, as well as semi-quantitative comparison with literature datasets from plasmid-mediated yeast growth in selective media, are discussed as another chapter of [23].

Related to the above studies, with the now-ended postdoc of Claudia Fonte Sanchez (funded in 2025 on project IMOCEP, PEPR MathVives; Section 10), we looked at individual-based models of population growth and gene expression under different promoter regulatory mechanisms, and the inference of the regulatory function from population-snapshot data. Our results on the nonparametric statistical estimation of these regulatory functions from stationary distributions constitute the material of a paper in preparation for journal submission.

## 8.6 Mathematical analysis of structured branching populations

**Participants:** E. Ferragu, C. Fonte-Sanchez, A. Marguet.

The investigation of cellular populations at the single-cell level has already led to the discovery of important phenomena, such as the occurrence of different phenotypes in an isogenic population. Nowadays, several experimental techniques, such as microscopy combined with the use of microfluidic devices, enable one to take investigation further by providing time-profiles of the dynamics of individual cells over entire lineage trees. The development of models that take into account the genealogy is an important step in the study of inheritance in bacterial population. In particular, their mathematical analysis is essential for the efficient analysis of single cell data.

Structured branching processes allow for the study of populations, where the lifecycle of each cell is governed by a given characteristic or trait, such as the internal concentration of proteins. The dependence on this characteristic of cellular mechanisms, like division or ageing, has been explored by Aline Marguet via the mathematical analysis of these processes. Spinal processes and many-to-one formulas have proved very useful for the study of complex structured branching processes, as they allow to reduce the problem to the study of a simpler lineage process. In the context of the now ended AnaComBa project, for the study of microbial communities, such tools appear to be needed for structured branching processes with interactions and were developed by Charles Medous during his PhD, defended in 2024 [32]. Charles Medous established a spinal construction and a Girsanov-type result for branching processes describing structured, interacting populations in continuous time, where the dynamics of each individual can be influenced by the entire population. In collaboration with Charline Smadi (INRAE Grenoble) and Sylvain Billiard (Université de Lille), Charles Medous also extended the spinal construction to diffusive population to study the role of environmental noise in growing colonies. They have proved that the repartition of the population depends crucially on the comparison between the individual and the environmental noise. The results of this study are currently under revision for *Stochastic Processes and their Applications* [25].

Interacting systems of particles are also used for the modelisation of populations of neurons. In collaboration with Marc Hoffmann (Université Paris-Dauphine), Claudia Fonte Sanchez proved theoretical properties of such systems, by controlling the fluctuations of the empirical measure of the system around the solution of the corresponding Vlasov-Fokker-Planck equation. They also studied the nonparametric statistical estimation of the classical solution of Vlasov-Fokker-Planck equation from the observation of the empirical measure and proved an oracle inequality using the Goldenshluger-Lepski methodology. Finally, they derived moment estimators for the FitzHugh-Nagumo model for populations of neurons [28].

The study of the asymptotic behavior of general semigroups is important for several aspects of branching processes, especially to prove the efficiency of statistical procedures. In this context, Claudia Fonte Sanchez, in collaboration with Pierre Gabriel (Université de Tours) et Stéphane Mischler (Université Paris-Dauphine) revisited the Krein-Rutman theory for semigroups of positive operators and provided some very general, efficient and practical results with constructive estimates on the existence of a solution to the first eigentriple problem, the geometry of the principal eigenvalue problem, and the asymptotic stability of the first eigenvector with possible constructive rate of convergence [27]. This work has been accepted for publication in *Memoirs of the European Mathematical Society*.

## 9 Bilateral contracts and grants with industry

### 9.1 Bilateral contracts with industry

Amélie Caddeo is a CIFRE PhD student at the Toulouse-based bioinformatics company **iMEAN** and the Institute of Research in Horticulture and Seeds at INRAE in Angers. The MICROCOSME team is currently hosting her for the final year of her doctoral research, which focuses on the mathematical modelling of the seed microbiome.

### 9.2 Maturation project: Switch2Prod

**Participants:** Th. Clavier, H. de Jong, J. Geiselmann.

Thibault Clavier, former PhD student in MICROCOSME, has received support from SATT Linksium for the technology transfer project **Switch2Prod** (2026-2027). The project, coordinated by Hidde de Jong and led by Thibault Clavier, aims at improving the bioproduction performance of microorganisms through dynamic control of their growth. It relies on the development of a genetic switch regulating resource allocation to maximise either biomass or the synthesis of molecules of interest (see Section 8.2 for more details).

## 10 Partnerships and cooperations

### 10.1 International initiatives

#### 10.1.1 Informal international partners

**Participants:** H. de Jong, D. Ropers.

H. de Jong and D. Ropers collaborate with T. Gedeon (Montana State University), former invited researcher in our former team IBIS and visiting scientist in MICROCOSME from 23/04/2025 to 15/05/2025, on research allocation strategies in microorganisms. The collaboration has already resulted in a paper published in *eLife* in 2023 [29] and another paper is in preparation.

H. de Jong and D. Ropers also collaborate with L. Sorio de Carvalho (The Herbert Wertheim UF Scripps Institute for Biomedical Innovation & Technology, Florida, USA), partner in our former associate-team GERM (2022-2024), on the metabolic control of mycobacterial growth (section 8.4).

### 10.2 European initiatives

#### 10.2.1 Horizon Europe

Project name	HyLife: Optimal control of microbial cells by natural and synthetic strategies
Coordinator	N. Dopffel (NORCE, Norway)
MICROCOSME participants	A. Belcour, M. Baumgärtner, H. de Jong, D. Ropers
Type	Clean Energy Transition Co-funded Partnership (CETP; 2023-2026)
Web page	<a href="#">Link to project description.</a>

### 10.3 National initiatives

Project name	Ctrl-AB : Optimization and control of the productivity of an algal-bacterial consortium
Coordinators	J.-L. Gouzé and E. Cinquemani
MICROCOSME participants	R. Asswad, S. Arias, E. Cinquemani, Th. Clavier, H. de Jong, J. Geiselmann, A. Marguet
Type	ANR project (2020-2025)
Web page	<a href="#">Link to project description</a>
Project name	ARBOREAL: Branching resource allocation processes for the analysis and inference of phenotypic growth variability
Coordinator	A. Marguet
MICROCOSME participants	E. Cinquemani, J. Geiselmann, H. de Jong, A. Marguet
Type	ANR (2024-2029)
Web page	<a href="#">Link to project description</a>
Project name	RECOM: Competition of RNAs for RNase E, a mechanism regulating their degradation and the energy and carbon metabolism in the cell
Coordinator	M. Cocaign-Bousquet
MICROCOSME participants	Y. Agbedoga, E. Cinquemani, M. Cocaign-Bousquet, D. Ropers
Type	ANR (2023-2027)
Web page	<a href="#">Link to project description</a>

Project name	IMOCEP: Innovations for modeling of growth : from a cellular level to pediatric development.
Coordinators MICROCOSME participants Type	A. Leclercq Samson, J. Stirnemann E. Cinquemani, C. Fonte Sanchez, A. Marguet, J. Judith Mokuinema Wawine ANR, PEPR Mathématiques en interaction pour le vivant, l'environnement et la société (MathVives; 2024-2029)
Web page	<a href="#">Link to project description</a>
Project name	MuSiHC: Multi-size Hybrid Cell Models
Coordinator MICROCOSME participants Type	A. Tonda (INRAE, Palaiseau) E. Cinquemani, H. de Jong, D. Ropers, N. Scaramozzino ANR, PEPR Biomasses, biotechnologies et technologies durables pour la chimie et les carburants (B-BEST; 2025-2029)
Web page	<a href="#">Link to project description</a>

## 10.4 Regional initiatives

The following project has just been accepted and will start in 2026:

Project name	BIGRE - Computational Biology in Grenoble
Coordinator MICROCOSME participants Type	M. Richard, N. Varoquaux, D. Ropers, C. Galiez D. Ropers Equipe-Action du LABEX Persyval (2026 – 2029)

## 11 Dissemination

### 11.1 Promoting scientific activities

#### 11.1.1 Scientific events: organisation

##### Member of organizing committees

MICROCOSME members	Conference, workshop, school	Date
A. Belcour	Conférence nationale de bioinformatique JOBIM	Jul 2027
H. de Jong	<a href="#">Summer school on Economic Principles in Cell Physiology</a> , Vienna (Austria)	Jul 2025
H. de Jong	Séminaire Plugin of Centre Inria de l'Université Grenoble Alpes	2024-
H. de Jong	Econophysics: interdisciplinary approach to economic and microbial modelling, Banff International Research Station, Alberta, (Canada)	Apr 2027
H. de Jong	Conférence nationale de bioinformatique JOBIM	Jul 2027
A. Marguet	Conférence nationale de bioinformatique JOBIM	Jul 2027
D. Ropers	<a href="#">5th Advanced Lecture Course on Computational Systems Biology</a> , Aussois	Oct 2025
D. Ropers	Conférence nationale de bioinformatique JOBIM	Jul 2027

#### 11.1.2 Scientific events: selection

##### Member of conference program committees

MICROCOSME members	Conference, workshop, school	Date
Eugenio Cinquemani	European Control Conference (ECC2025)	Associate editor
Eugenio Cinquemani	Computational Methods in Systems Biology (CMSB2025)	PC member
H. de Jong	<a href="#">5th Advanced Lecture Course on Computational Systems Biology</a> , Aussois	Oct 2025

### 11.1.3 Journal

#### Member of editorial boards

MICROCOSME member	Journal
H. de Jong	Journal of Mathematical Biology

### 11.1.4 Invited talks and other presentations

#### Arnaud Belcour

Title	Event and location	Date
Predicting coarse-grained representations of biogeochemical cycles from metabarcoding data	BiGRE Days, Grenoble	Feb. 2025
Predicting coarse-grained representations of biogeochemical cycles from metabarcoding data	ISMB/ECCB 2025, Liverpool (United Kingdom)	Jul. 2025

#### Rand Asswad

Title	Event and location	Date
Optimisation de la biosynthèse des microalgues via une symbiose algale-bactérienne contrôlée	SAGIP 2025, Mulhouse, France	May 2025
Single- and multi-objective performance optimization of an algal-bacterial synthetic process	CDC 2025, Rio de Janeiro, Brazil	Dec 2025
Title	Event and location	Date
Characterization and control of microbial consortia on an automated mini-bioreactor platform, St Martin d'Hères	May 2025	
Single-cell data reveal heterogeneity of resource allocation across a bacterial population	Biocontrol Seminar, online	Sept 2025

#### Hidde de Jong

Title	Event and location	Date
Dynamical models integrating metabolism and gene expression	5th Advanced Lecture Course on Computational Systems Biology (CompSysBio), Aussois	Oct 2025
Optimal cell behavior in time	Summer school "Economic Principles in Cell Biology", Vienna (Austria)	Jul 2025
Reengineering the bacterial gene expression machinery for improving bioproduction	Engineering biology session, UNITE! Research School, Autrans	Nov 2025

#### Johannes Geiselmann

Title	Event and location	Date
Resource allocation in individual cells of <i>E. coli</i> during growth transitions	50th Economic Principles in Cellular Physiology (EPCP) Forum, on-line	Oct 2025

#### Delphine Ropers

Title	Event and location	Date
Doing a PhD, good practice and pitfalls to avoid	Matinée des doctorants, Centre Inria de l'Université Grenoble Alpes	Dec 2025

### 11.1.5 Scientific expertise

MICROCOSME member	Organism	Role
Johannes Geiselmann	UMR5240 CNRS-UCBL-INSA-BayerCropScience	Member scientific council
Aline Marguet	GDR Branchement	Member of Scientific committee
Delphine Ropers	National Science Centre, Poland	Member of Expert Panel LS2
Delphine Ropers	Microbiology and Food Chain Department, INRAE	Member scientific council

### 11.1.6 Research administration

Eugenio Cinquemani	Inria - Univ. Grenoble Alpes	Member Comité des Emplois Scientifiques (CES)
Eugenio Cinquemani	Inria - Univ. Grenoble Alpes	Member Comité des Utilisateurs des Moyens Informatiques (CUMI)
Eugenio Cinquemani	Inria - Univ. Grenoble Alpes	Member Comité Développement Technologique (CDT)
Hidde de Jong	Inria - Univ Grenoble Alpes	Member of Direction du centre
Hidde de Jong	Univ Grenoble Alpes	Member of Vice-Présidence Recherche et Innovation élargie
Hidde de Jong	Inria - Univ Grenoble Alpes	President Comité des Equipes Projets (CEP)
Hidde de Jong	Inria - Univ Grenoble Alpes	Member Comité des Emplois Scientifiques (CES)
Hidde de Jong	Inria - Univ Grenoble Alpes	Member Comité Développement Technologique (CDT)
Hidde de Jong	Inria - Univ Grenoble Alpes	Member Comité des Etudes Doctorales (CED)
Hidde de Jong	Inria - Univ Grenoble Alpes	President scientific council (COS)
Hidde de Jong	Inria	Member Commission d'évaluation (CE)
Hidde de Jong	Inria	Member Comité scientifique interne (COSI)
Hidde de Jong	Univ Grenoble Alpes	Member of Collège des Ecoles Doctorales
Hidde de Jong	Univ Grenoble Alpes	Member advisory board of LabEX PERSYVAL 3
Hidde de Jong	Univ Grenoble Alpes	Member of comité des directeurs du pôle MSTIC
Hidde de Jong	Univ Grenoble Alpes	Membre Comité de pilotage Graduate School@UGA
Aline Marguet	Inria - Univ. Grenoble Alpes	Member Comité des études doctorales
Delphine Ropers	Inria - Univ Grenoble Alpes	Member scientific council (COS)
Delphine Ropers	Inria - Univ Grenoble Alpes	Mentoring follow-up committee
Delphine Ropers	Inria - Univ Grenoble Alpes	Référente chercheurs

### 11.1.7 Recruitment committees

MICROCOSME member	Organism	Recruitment
Hidde de Jong	Inria	DR2 (jury d'admissibilité)
Hidde de Jong	Inria	DR2 (jury d'admission)
Hidde de Jong	Inria - Univ Grenoble Alpes	ISFP (jury d'admission)
Aline Marguet	INRAE	CRCN
Delphine Ropers	Inria - Univ Côte d'Azur	CRCN/IFSP (présidence jury d'admissibilité)
Delphine Ropers	Inria - Univ Côte d'Azur	IFSP (jury d'admission)
Delphine Ropers	Inria - Univ Grenoble Alpes	Head of Inria SED Department

## 11.2 Teaching - Supervision - Juries - Educational and pedagogical outreach

### 11.2.1 Supervision

- PhD in progress: **Yao Agbedoga**, Computational analysis of mRNA degradation. Supervisors: Delphine Ropers and Muriel Cocaïgn-Bousquet

- PhD in progress: **Rand Asswad**, Development of control strategies for synthetic microbial consortia. Supervisors: Eugenio Cinquemani and Jean-Luc Gouzé (Inria - Univ Côte d'Azur)
- PhD in progress: **Haroune Bakour**, Development of aroma synthesis control laws for the real-time control of oenological fermentation bioprocesses. Supervisors: Céline Casenave (INRAE Montpellier), Agustín Yabo (INRAE Montpellier), Eugenio Cinquemani
- PhD completed: **Ignacia Cancino Aguirre**, Computational analysis of metabolic strategies in pathogenic bacteria. Supervisors: Delphine Ropers and Hidde de Jong
- PhD in progress: **Eugene Ferragu**, Stochastic models of host-pathogen dynamics, Supervisors: Aline Marguet and Charline Smadi (INRAE Grenoble)
- PhD completed: **Emrys Reginato**, Heterogeneity of microbial populations from stochasticity across cell divisions: individual-based modelling and inference on case studies. Supervisors: Eugenio Cinquemani and Aline Marguet

### 11.2.2 Juries

#### PhD thesis committees

MICROCOSME member	Role	PhD student	University	Date
Hidde de Jong	Supervisor	Ignacia Cancino Aguirre	Univ Grenoble Alpes	Jun 2025
Hidde de Jong	Chair	Johannes Keisers	Univ Montpellier	Nov 2025
Delphine Ropers	Supervisor	Ignacia Cancino Aguirre	Univ Grenoble Alpes	Jun 2025
Delphine Ropers	Reviewer	Arthur Lequertier	Univ Paris Saclay	Dec 2025

#### Habilitation (HDR) committees

MICROCOSME member	Role	HDR candidate	University	Date
Delphine Ropers	Reviewer	Olivier Borkowski	Univ Paris-Saclay	Oct 2025
Delphine Ropers	Member	Elie Le Quéméner	Univ Montpellier	Dec 2025

#### PhD advisory committees

MICROCOSME member	PhD student	University
Aline Marguet	Mateo Deangeli Bravo	Univ Paris Saclay
Eugenio Cinquemani	Chloé Weckel	Universités de Tours et d'Orléans
Delphine Ropers	Paul Ahavi	Univ Paris Saclay
Delphine Ropers	Mathilde Burck	Univ Paul Sabatier, Toulouse
Delphine Ropers	Marvin Ramos	Univ Paul Sabatier, Toulouse
Delphine Ropers	Sofia Pacheco-García	Univ Lyon
Delphine Ropers	Mathilde Sola	Univ Paris Saclay
Delphine Ropers	Sthyve Tatho	Univ Bordeaux

### 11.2.3 Educational and pedagogical outreach

Delphine Ropers received the title of Full Professor ("Professeur attaché") at Univ Grenoble Alpes for 3 years (2023 - 2026) in recognition of her teaching activity.

Delphine Ropers organizes a module on the mathematical modelling of biological systems at Grenoble INP - Phelma, UGA and a module on the modelling of cell systems at the Faculty of Pharmacy (Univ Grenoble Alpes). Hidde de Jong organizes a module on the modelling of genetic and metabolic networks at INSA de Lyon.

Rand Asswad is a temporary teaching researcher assistant (ATER) at Univ. Grenoble Alpes and has a full teaching service.

The following people have also contributed to courses last year:

#### **Yao Agbedoga**

- Course and practicals: Numerical skills, L2, Univ Grenoble Alpes (27 h)

#### **Eugenio Cinquemani**

- Course: Modelling and identification of metabolic networks, M1, Phelma, INP Grenoble (4 h)
- Practical: Biostatistics, M2, Univ Grenoble Alpes (24 h)

#### **Hidde de Jong**

- Course and practicals: Modeling and simulation of gene regulatory networks, M2, BIM, INSA de Lyon (32 h)

#### **Eugene Ferragu**

- Practical: Bilinear algebra, L2, Licence Mathématiques, Univ Grenoble Alpes (15 h)
- Practical: Introduction to analysis, L1, Licence Physique, Univ Grenoble Alpes (40 h)
- Practical: Cell systems biology, M1, Master ingénierie de la santé, Univ Grenoble Alpes (9 h)

#### **Delphine Ropers**

- Course and practicals: Modelling in systems biology, M1, Phelma, INP Grenoble (16 h)
- Course and practicals: Cell systems biology, M1, Master ingénierie de la santé, Univ Grenoble Alpes (24 h)
- Course: Modelling and simulation of genetic regulatory networks, M2, INSA de Toulouse (4 h)
- Course and master defense committee: Metabolic modelling with omics data, M2, IA4 Health International master course, Univ Grenoble Alpes (11 h)

## **12 Scientific production**

### **12.1 Major publications**

- [1] V. Baldazzi, D. Ropers, J.-L. Gouzé, T. Gedeon and H. de Jong. ‘Resource allocation accounts for the large variability of rate-yield phenotypes across bacterial strains’. In: *eLife* 12 (31st May 2023), pp. 1–29. DOI: [10.7554/eLife.79815](https://doi.org/10.7554/eLife.79815). URL: <https://hal.inrae.fr/hal-04145943>.
- [2] E. Cinquemani. ‘Stochastic reaction networks with input processes: Analysis and application to gene expression inference’. In: *Automatica* 101 (2019), pp. 150–156. DOI: [10.1016/j.automatica.2018.11.047](https://doi.org/10.1016/j.automatica.2018.11.047). URL: <https://hal.inria.fr/hal-01925923>.
- [3] E. Cinquemani, V. Laroute, M. Bousquet, H. De Jong and D. Ropers. ‘Estimation of time-varying growth, uptake and excretion rates from dynamic metabolomics data’. In: *Bioinformatics* 33.14 (2017), pp. i301–i310. DOI: [10.1093/bioinformatics/btx250](https://doi.org/10.1093/bioinformatics/btx250). URL: <https://hal.archives-ouvertes.fr/hal-01607919>.
- [4] T. Etienne, M. Cocaign-Bousquet and D. Ropers. ‘Competitive effects in bacterial mRNA decay’. In: *Journal of Theoretical Biology* 504 (Nov. 2020). DOI: [10.1016/j.jtbi.2020.110333](https://doi.org/10.1016/j.jtbi.2020.110333). URL: <https://hal.inria.fr/hal-02967513> (cit. on p. 18).

- [5] N. Giordano, F. Mairet, J.-L. Gouzé, J. Geiselmann and H. De Jong. ‘Dynamical allocation of cellular resources as an optimal control problem: Novel insights into microbial growth strategies’. In: *PLoS Computational Biology* 12.3 (9th Mar. 2016), e1004802. DOI: [10.1371/journal.pcbi.1004802](https://doi.org/10.1371/journal.pcbi.1004802). URL: <https://hal.inria.fr/hal-01332394>.
- [6] M. Hoffmann and A. Marguet. ‘Statistical estimation in a randomly structured branching population’. In: *Stochastic Processes and their Applications* 129.12 (2019), pp. 5236–5277. DOI: [10.1016/j.spa.2019.02.015](https://doi.org/10.1016/j.spa.2019.02.015). URL: <https://hal.archives-ouvertes.fr/hal-01662203>.
- [7] J. Izard, C. Gomez-Balderas, D. Ropers, S. Lacour, X. Song, Y. Yang, A. B. Lindner, J. Geiselmann and H. De Jong. ‘A synthetic growth switch based on controlled expression of RNA polymerase’. In: *Molecular Systems Biology* 11.11 (23rd Nov. 2015), p. 840. URL: <https://hal.inria.fr/hal-01247993> (cit. on pp. 8, 16).
- [8] A. Llamosi, A. Gonzalez, C. Versari, E. Cinquemani, G. Ferrari-Trecate, P. Hersen and G. Batt. ‘What population reveals about individual cell identity: Single-cell parameter estimation of models of gene expression in yeast’. In: *PLoS Computational Biology* 12.2 (9th Feb. 2016), e1004706. DOI: [10.1371/journal.pcbi.1004706](https://doi.org/10.1371/journal.pcbi.1004706). URL: <https://hal.inria.fr/hal-01248298>.
- [9] F. Mairet, J.-L. Gouzé and H. De Jong. ‘Optimal proteome allocation and the temperature dependence of microbial growth laws’. In: *npj Systems Biology and Applications* 7.14 (2021). DOI: [10.1038/s41540-021-00172-y](https://doi.org/10.1038/s41540-021-00172-y). URL: <https://hal.inria.fr/hal-03094908>.
- [10] A. Marguet, M. Lavielle and E. Cinquemani. ‘Inheritance and variability of kinetic gene expression parameters in microbial cells: modeling and inference from lineage tree data’. In: *Bioinformatics* 35.14 (2019), pp. i586–i595. DOI: [10.1093/bioinformatics/btz378](https://doi.org/10.1093/bioinformatics/btz378). URL: <https://hal.archives-ouvertes.fr/hal-02317115> (cit. on p. 18).
- [11] M. Mauri, J.-L. Gouzé, H. De Jong and E. Cinquemani. ‘Enhanced production of heterologous proteins by a synthetic microbial community: Conditions and trade-offs’. In: *PLoS Computational Biology* 16.4 (2020), e1007795. DOI: [10.1371/journal.pcbi.1007795](https://doi.org/10.1371/journal.pcbi.1007795). URL: <https://hal.sorbonne-universite.fr/hal-02640446> (cit. on p. 17).
- [12] M. Morin, D. Ropers, E. Cinquemani, J.-C. Portais, B. Enjalbert and M. Coccagn-Bousquet. ‘The Csr System Regulates Escherichia coli Fitness by Controlling Glycogen Accumulation and Energy Levels’. In: *mBio* 8.5 (31st Oct. 2017), pp. 1–14. DOI: [10.1128/mBio.01628-17](https://doi.org/10.1128/mBio.01628-17). URL: <https://hal.inria.fr/hal-01672038> (cit. on p. 18).
- [13] M. Morin, D. Ropers, F. Letisse, S. Laguerre, J.-C. Portais, M. Coccagn-Bousquet and B. Enjalbert. ‘The post-transcriptional regulatory system CSR controls the balance of metabolic pools in upper glycolysis of Escherichia coli’. In: *Molecular Microbiology* 100.4 (May 2016), pp. 686–700. DOI: [10.1111/mmi.13343](https://doi.org/10.1111/mmi.13343). URL: <https://hal.archives-ouvertes.fr/hal-02147255> (cit. on pp. 17, 18).
- [14] A. Pavlou, E. Cinquemani, C. Pinel, N. Giordano, M. Van Melle-Gateau, I. Mihalcescu, J. Geiselmann and H. de Jong. ‘Single-cell data reveal heterogeneity of investment in ribosomes across a bacterial population’. In: *Nature Communications* 16.1 (2nd Jan. 2025), p. 285. DOI: [10.1038/s41467-024-55394-5](https://doi.org/10.1038/s41467-024-55394-5). URL: <https://inria.hal.science/hal-04880507>.
- [15] S. Pinhal, D. Ropers, J. Geiselmann and H. De Jong. ‘Acetate metabolism and the inhibition of bacterial growth by acetate’. In: *Journal of Bacteriology* 201.13 (1st July 2019), pp. 147–166. DOI: [10.1128/JB.00147-19](https://doi.org/10.1128/JB.00147-19). URL: <https://hal.inria.fr/hal-02195459>.

## 12.2 Publications of the year

### International journals

- [16] A. Belcour, L. Megy, S. Stephant, C. Michel, S. Rad, P. Bombach, N. Dopffel, H. de Jong and D. Ropers. ‘Predicting coarse-grained representations of biogeochemical cycles from metabarcoding data’. In: *Bioinformatics* 41.Supplement\_1 (15th July 2025), pp. i49–i57. DOI: [10.1093/bioinformatics/btaf230](https://doi.org/10.1093/bioinformatics/btaf230). URL: <https://inria.hal.science/hal-04938367> (cit. on pp. 10, 14, 17).

- [17] A. Pavlou, E. Cinquemani, C. Pinel, N. Giordano, M. Van Melle-Gateau, I. Mihalcescu, J. Geiselman and H. de Jong. ‘Single-cell data reveal heterogeneity of investment in ribosomes across a bacterial population’. In: *Nature Communications* 16.1 (2nd Jan. 2025), p. 285. DOI: [10.1038/s41467-024-55394-5](https://doi.org/10.1038/s41467-024-55394-5). URL: <https://inria.hal.science/hal-04880507> (cit. on pp. 14, 15).
- [18] C. Rousseau, G. Tanguy, E. Legeay, S. Blanquart, A. Belcour, S. Rousvoal, P. Potin, C. Leblanc and S. Dittami. ‘A duo of fungi and complex and dynamic bacterial community networks contribute to shape the *Ascophyllum nodosum* holobiont’. In: *Environmental Microbiome* (11th Dec. 2025), pp. 1–53. DOI: [10.1186/s40793-025-00825-z](https://doi.org/10.1186/s40793-025-00825-z). URL: <https://inria.hal.science/hal-05413201> (cit. on p. 18).

#### International peer-reviewed conferences

- [19] R. Asswad, J.-L. Gouzé and E. Cinquemani. ‘Single and Multi-Objective Performance Optimization of an Algal-Bacterial Synthetic Process’. In: CDC 2025 - 64th IEEE Conference on Decision and Control. Rio de Janeiro, Brazil: IEEE, 2025, pp. 1–7. DOI: [10.1109/CDC57313.2025.11312718](https://doi.org/10.1109/CDC57313.2025.11312718). URL: <https://inria.hal.science/hal-05229706> (cit. on p. 17).
- [20] K. Černá, J. Říha, K. Fadrhonc, P. Bombach, S. Rad, S. Stephant, C. Michel, L. Fablet, D. Ropers, A. Belcour, J. Tremosa, K. Kyaw, N. Paltrinieri, B. A. An-Stepec and N. Dopffel. ‘Assessment of Potential Microbial Hydrogen Consumption in European Hydrogen Underground Storage Sites’. In: GET 2025 - Sixth EAGE Global Energy Transition Conference & Exhibition. Vol. 2025. 1. Rotterdam, Netherlands: European Association of Geoscientists & Engineers, Oct. 2025, pp. 1–5. DOI: [10.3997/2214-4609.202521032](https://doi.org/10.3997/2214-4609.202521032). URL: <https://inria.hal.science/hal-05448781> (cit. on p. 18).

#### Scientific books

- [21] A. G. Yabo, A. de Martino, A. Weisse, A. Kremling, A. Goelzer, B. Mauroy, C. Goupil, C. Karamaoun, D. de Groot, D. Giannari, D. Lacoste, D. Tourigny, D. Széliová, D. A. Oyarzun, E. Noor, E. Pascual Garcia, E. Herbert, F. Scott, F. Noël, G. Micali, H. Delattre, H. Sauro, H. De jong, H. J. Hindley, H. Dourado, J. Grilli, M. Rivas-Astroza, M. Cosentino Lagomarsino, M. Köbi, M. Corigliano, M. Wortel, O. Golan, O. Rivoire, O. S. Soyer, P. Grigaitis, R. West, S. Waldherr, W. Liebermeister and M. Mahout. *Economic Principles in Cell Biology*. The Economic Cell Collective, 1st July 2025, pp. 1–285. DOI: [10.5281/zenodo.8156386](https://doi.org/10.5281/zenodo.8156386). URL: <https://hal.inrae.fr/hal-04172118>.

#### Doctoral dissertations and habilitation theses

- [22] I. Cancino Aguirre. ‘Computational analysis of metabolic strategies in mycobacteria’. Université Grenoble Alpes [2020-....], 13th June 2025. URL: <https://theses.hal.science/tel-05264727> (cit. on p. 17).
- [23] E. Reginato. ‘Heterogeneity of microbial populations from stochasticity across cell divisions: individual-based modelling and inference on case studies’. Université Grenoble Alpes, 24th Nov. 2025. URL: <https://inria.hal.science/tel-05469974> (cit. on p. 18).

#### Reports & preprints

- [24] A. Belcour, P. Hamon-Giraud, A. Mataigne, B. Ruiz, Y. L. Cunff, J. Got, L. Awhangbo, M. Lebreton, C. Frioux, S. Dittami, P. Dabert, A. Siegel and S. Blanquart. *Estimating consensus proteomes and metabolic functions from taxonomic affiliations*. 2025. DOI: [10.1101/2022.03.16.484574](https://doi.org/10.1101/2022.03.16.484574). URL: <https://hal.science/hal-03697249> (cit. on pp. 14, 15, 17).
- [25] S. Billiard, C. Medous and C. Smadi. *Spinal study of a population model for colonial species with interactions and environmental noise*. 2025. URL: <https://hal.science/hal-04921079> (cit. on p. 19).

- [26] L. Fablet, A. Belcour, S. Stephant, C. Michel, D. Ropers, K. Cerna, P. Bombach, J. Riha, J. Tremosa, B. A. An-Stepec, K. Fadrhonc, N. Dopffel and S. Rad. *Microbial-geochemical interactions in underground reservoirs: Implications for hydrogen storage*. 14th Nov. 2025. DOI: [10.21203/rs.3.rs-7920847/v1](https://doi.org/10.21203/rs.3.rs-7920847/v1). URL: <https://inria.hal.science/hal-05468099> (cit. on pp. 15, 17).
- [27] C. Fonte Sánchez, P. Gabriel and S. Mischler. *On the Krein-Rutman theorem and beyond*. 2025. URL: <https://hal.science/hal-04093201> (cit. on p. 19).
- [28] C. F. Sanchez and M. Hoffmann. *Statistical estimation of a mean-field fitzhugh-nagumo model*. 8th Jan. 2025. DOI: [10.48550/arXiv.2501.04257](https://doi.org/10.48550/arXiv.2501.04257). URL: <https://inria.hal.science/hal-05469279> (cit. on p. 19).

### 12.3 Cited publications

- [29] V. Baldazzi, D. Ropers, J.-L. Gouzé, T. Gedeon and H. de Jong. ‘Resource allocation accounts for the large variability of rate-yield phenotypes across bacterial strains’. In: *eLife* 12 (May 2023), pp. 1–29. DOI: [10.7554/eLife.79815](https://doi.org/10.7554/eLife.79815). URL: <https://hal.inrae.fr/hal-04145943> (cit. on p. 20).
- [30] T. Clavier. ‘Contrôle génétique de la croissance et des conditions de culture pour maximiser la production biotechnologique chez E. coli’. Theses. Université Grenoble Alpes, Mar. 2024. URL: <https://hal.science/tel-04904078> (cit. on pp. 10, 16).
- [31] T. Clavier, C. Pinel, H. de Jong and J. Geiselmann. ‘Improving the genetic stability of bacterial growth control for long-term bioproduction’. In: *Biotechnology and Bioengineering* 121.9 (June 2024), pp. 2808–2819. DOI: [10.1002/bit.28756](https://doi.org/10.1002/bit.28756). URL: <https://inria.hal.science/hal-04880509> (cit. on p. 16).
- [32] C. Medous. ‘Spinal constructions for continuous type-space branching processes with interactions’. In: *Electronic Journal of Probability* 29 (Jan. 2024), pp. 1–46. DOI: [10.1214/24-EJP1227](https://doi.org/10.1214/24-EJP1227). URL: <https://hal.science/hal-04179190> (cit. on p. 19).
- [33] M. Morin, B. Enjalbert, D. Ropers, L. Girbal and M. Cocaign-Bousquet. ‘Genomewide Stabilization of mRNA during a “Feast-to-Famine” Growth Transition in Escherichia coli’. In: *MSphere* 5.3 (June 2020). DOI: [10.1128/mSphere.00276-20](https://doi.org/10.1128/mSphere.00276-20). URL: <https://hal.inrae.fr/hal-02967494> (cit. on p. 18).
- [34] A. Pavlou. ‘Quantification of bacterial resource allocation in changing environments on the single-cell level’. Theses. Université Grenoble Alpes [2020-....], July 2022. URL: <https://theses.hal.science/tel-03827395> (cit. on p. 15).
- [35] D. Ropers, Y. Couté, L. Faure, S. Ferré, D. Labourdette, A. Shabani, L. Trouilh, P. Vasseur, G. Corre, M. Ferro, M.-A. Teste, J. Geiselmann and H. de Jong. ‘Multiomics Study of Bacterial Growth Arrest in a Synthetic Biology Application’. In: *ACS Synthetic Biology* 10.11 (Nov. 2021), pp. 2910–2926. DOI: [10.1021/acssynbio.1c00115](https://doi.org/10.1021/acssynbio.1c00115). URL: <https://hal.inria.fr/hal-03516727> (cit. on p. 8).
- [36] C. Roux, T. Etienne, E. Hajnsdorf, D. Ropers, A. J. Carpousis, M. Cocaign-Bousquet and L. Girbal. ‘The essential role of mRNA degradation in understanding and engineering E. coli metabolism’. In: *Biotechnology Advances* (2022), pp. 1–13. DOI: [10.1016/j.biotechadv.2021.107805](https://doi.org/10.1016/j.biotechadv.2021.107805). URL: <https://hal.science/hal-03325744> (cit. on p. 18).
- [37] M. F. Sangster. ‘Development, characterization and control of E. coli communities on an automated experimental platform’. Theses. Université Grenoble Alpes, May 2023. URL: <https://inria.hal.science/tel-04276365> (cit. on pp. 13, 17).