RESEARCH CENTRE

Sophia Antipolis - Méditerranée

IN PARTNERSHIP WITH:

CNRS, INRAE, Sorbonne Université (UPMC)

2020
ACTIVITY REPORT

Project-Team
BIOCORE

Biological control of artificial ecosystems

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life Sciences

Contents

Project-Team BIOCORE

Creation of the Project-Team: 2011 January 01

Keywords

Computer sciences and digital sciences

- A1.5.1. – Systems of systems
- A6. – Modeling, simulation and control
- A6.1.1. – Continuous Modeling (PDE, ODE)
- A6.1.3. – Discrete Modeling (multi-agent, people centered)
- A6.1.4. – Multiscale modeling
- A6.2.1. – Numerical analysis of PDE and ODE
- A6.2.6. – Optimization
- A6.4. – Automatic control
- A6.4.1. – Deterministic control
- A6.4.3. – Observability and Controlability
- A6.4.4. – Stability and Stabilization
- A6.4.6. – Optimal control
- A8.1. – Discrete mathematics, combinatorics
- A8.7. – Graph theory
- A8.11. – Game Theory

Other research topics and application domains

- B1.1.7. – Bioinformatics
- B1.1.8. – Mathematical biology
- B1.1.10. – Systems and synthetic biology
- B2.4.1. – Pharmaco kinetics and dynamics
- B3.1. – Sustainable development
- B3.1.1. – Resource management
- B3.4. – Risks
- B3.4.1. – Natural risks
- B3.4.2. – Industrial risks and waste
- B3.4.3. – Pollution
- B3.5. – Agronomy
- B3.6. – Ecology
- B3.6.1. – Biodiversity
- B4.3. – Renewable energy production
- B4.3.1. – Biofuels

1 Team members, visitors, external collaborators

Research Scientists

- Jean-Luc Gouzé [Team leader, Inria, Senior Researcher, HDR]
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- Pierre Bernhard [Inria, Emeritus]
- Madalena Chaves [Inria, Senior Researcher, HDR]
- Walid Djema [Inria, Starting Research Position]
- Frédéric Grognard [Inria, Researcher]
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- Lucie Chambon [Inria, until Feb 2020]
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- Christopher Castaldello [Université de Padoue - Italie, until Mar 2020]
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External Collaborators

- Vincent Calcagno [INRAE, HDR]
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- Frédéric Hamelin [Institut Agro, HDR]
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2 Overall objectives

2.1 Introduction

BIOCORE is a joint research team between Inria (Centre of Sophia-Antipolis Méditerranée), INRAE (ISA - Institut Sophia Agrobiotech and LBE - Laboratory of Environmental Biotechnology in Narbonne) and Sorbonne Université-CNRS (Oceanographic Laboratory of Villefranche-sur-mer - LOV, UMR 7093/ Sorbonne Université, Villefranche sur Mer, Team: Processes in Pelagic Ecosystems - PEPS).

Sustainable growth of living organisms is one of the major challenges of our time. In order to tackle it, the development of new technologies is necessary, and many of these new technologies will need to use modeling and computer tools. BIOCORE contributes to this theme, in the general field of design and control of artificial ecosystems (or biosystems). Its general goal is to design devices, systems and processes containing living cells or individuals and performing some tasks to decrease pollution, use of chemicals, or to produce bioenergy in a sustainable way. We build biological/ecological models in close collaborations with biologists and bioprocess engineers, and validate them with experimental platforms. Our activities are structured in three levels: mathematical and computational methods, a methodological approach to biology, and applications.

Research themes:

Mathematical and computational methods:

- Tools for modeling in biology: model design, validation, parameter identification.
- Mathematical properties of models in biology: mathematical studies of models and of their global behavior.

- Software sensors for biological systems: using the model and on-line measurements to estimate the variables that are not measured directly.
- Control, regulation, and optimization for biological systems; design of laws to maintain a variable at a given level, or to optimize the productivity of the system.

A methodological approach to biology: system study at different scales

- At the intra-individual level: theoretical and experimental study of simple metabolic-genetic networks, coarse grained models of the internal state.
- At the level of interactions between individuals in the population: individual behavior, resource allocation.
- At the scale of interaction between populations: interaction between prey and predator populations in a trophic network or competition between species in a chemostat.
- At the scale of interaction between ecosystems: coupling of two artificial ecosystems as a unique bioprocess or interactions between an artificial ecosystem and the surrounding natural ecosystem.

Fields of application:

- Bioenergy, in particular the production of lipids (which can be used as biofuel), methane and hydrogen by microorganisms (with LOV and LBE).
- CO2 fixation by micro-algae, with the aim of capturing industrial CO2 fluxes (with LOV). This theme can also include artificial ecosystems developed to improve the prediction of carbon fluxes between the ocean and the atmosphere.
- Design and optimization of ecologically friendly protection methods for plants and micro-plants artificial production systems (with ISA and LOV). This theme focuses in particular on biological control programs to control pathogens and pest invasions in crops and bioreactors.
- Biological waste treatment with microorganisms in bioreactors to reduce pollution emission levels (in collaboration with LBE).

Software development:

- Software tools for biological modeling and supervision of biological processes.

National, international and industrial relations

- National collaborations: IFREMER (Nantes), INRA (MISTEA Montpellier, BIOGER Grignon, IAM Nancy, Agrocampus Ouest, MaIAGE Jouy-en-en-Josas, BioEpAR Nantes), CIRAD Montpellier, Institut Méditerranéen d'Océanologie, LOCEAN (Paris), GIPSA Grenoble, IBIS, ANGE, MCTAO, and VALSE Inria teams.
- Participation in French groups :

  ModStatSAP (Modélisation et Statistique en Santé des Animaux et des Plantes), GDR Invasions Biologiques.
- Participation to national programmes: ANR projects Phycover, ICycle and Maximic, Plan Cancer Imodrez, UMT Fiorimed, and Labex SIGNALIFE.
- International collaborations: Université Catholique de Louvain (Belgium), Université de Mons (Belgium), MacMaster University (Canada), University Ben Gurion (Israel), Imperial College (United-Kingdom), Massey University (New Zealand), Universidad Tecnica Federico Santa Maria and Universidad de Chile (Chile), University of Edinburgh (UK), Universities of Douala, Yaoundé I and Dschang (Cameroon).

3 Research program

3.1 Mathematical and computational methods

BIOCORE's action is centered on the mathematical modeling of biological systems, more particularly of artificial ecosystems, that have been built or strongly shaped by man. Indeed, the complexity of such systems where life plays a central role often makes them impossible to understand, control, or optimize without such a formalization. Our theoretical framework of choice for that purpose is Control Theory, whose central concept is "the system", described by state variables, with inputs (action on the system), and outputs (the available measurements on the system). In modeling the ecosystems that we consider, mainly through ordinary differential equations, the state variables are often population, substrate and/or food densities, whose evolution is influenced by the voluntary or involuntary actions of man (inputs and disturbances). The outputs will be some product that one can collect from this ecosystem (harvest, capture, production of a biochemical product, etc), or some measurements (number of individuals, concentrations, etc). Developing a model in biology is however not straightforward: the absence of rigorous laws as in physics, the presence of numerous populations and inputs in the ecosystems, most of them being irrelevant to the problem at hand, the uncertainties and noise in experiments or even in the biological interactions require the development of dedicated techniques to identify and validate the structure of models from data obtained by or with experimentalists.

Building a model is rarely an objective in itself. Once we have checked that it satisfies some biological constraints (eg. densities stay positive) and fitted its parameters to data (requiring tailor-made methods), we perform a mathematical analysis to check that its behavior is consistent with observations. Again, specific methods for this analysis need to be developed that take advantage of the structure of the model (eg. the interactions are monotone) and that take into account the strong uncertainty that is linked to life, so that qualitative, rather than quantitative, analysis is often the way to go.

In order to act on the system, which often is the purpose of our modeling approach, we then make use of two strong points of Control Theory: 1) the development of observers, that estimate the full internal state of the system from the measurements that we have, and 2) the design of a control law, that imposes to the system the behavior that we want to achieve, such as the regulation at a set point or optimization of its functioning. However, due to the peculiar structure and large uncertainties of our models, we need to develop specific methods. Since actual sensors can be quite costly or simply do not exist, a large part of the internal state often needs to be re-constructed from the measurements and one of the methods we developed consists in integrating the large uncertainties by assuming that some parameters or inputs belong to given intervals. We then developed robust observers that asymptotically estimate intervals for the state variables [86]. Using the directly measured variables and those that have been obtained through such, or other, observers, we then develop control methods that take advantage of the system structure (linked to competition or predation relationships between species in bioreactors or in the trophic networks created or modified by biological control).

3.2 A methodological approach to biology: from genes to ecosystems

One of the objectives of BIOCORE is to develop a methodology that leads to the integration of the different biological levels in our modeling approach: from the biochemical reactions to ecosystems. The regulatory pathways at the cellular level are at the basis of the behavior of the individual organism but, conversely, the external stresses perceived by the individual or population will also influence the intracellular pathways. In a modern "systems biology" view, the dynamics of the whole biosystem/ecosystem emerge from the interconnections among its components, cellular pathways/individual organisms/population. The different scales of size and time that exist at each level will also play an important role in the behavior of the biosystem/ecosystem. We intend to develop methods to understand the mechanisms at play at each level, from cellular pathways to individual organisms and populations; we assess and model the interconnections and influence between two scale levels (eg., metabolic and genetic; individual organism and population); we explore the possible regulatory and control pathways between two levels; we aim at reducing the size of these large models, in order to isolate subsystems of the main players involved in specific dynamical behaviors.

We develop a theoretical approach of biology by simultaneously considering different levels of description and by linking them, either bottom up (scale transfer) or top down (model reduction). These approaches are used on modeling and analysis of the dynamics of populations of organisms; modeling and analysis of small artificial biological systems using methods of systems biology; control and design of artificial and synthetic biological systems, especially through the coupling of systems.

The goal of this multi-level approach is to be able to design or control the cell or individuals in order to optimize some production or behavior at higher level: for example, control the growth of microalgae via their genetic or metabolic networks, in order to optimize the production of lipids for bioenergy at the photobioreactor level.

4 Application domains

4.1 Bioenergy

Finding sources of renewable energy is a key challenge for our society. We contribute to this topic through two main domains for which a strong and acknowledged expertise has been acquired over the years. First, we consider anaerobic digesters, the field of expertise of the members of the team at the Laboratory of Enviromental Biotechnology (LBE), for the production of methane and/or biohydrogen from organic wastes. The main difficulty is to make these processes more reliable and exploit more efficiently the produced biogas by regulating both its quality and quantity despite high variability in the influent wastes. One of the specific applications that needs to be tackled is the production of biogas in a plant when the incoming organic waste results from the mixing of a finite number of substrates. The development of control laws that optimize the input mix of the substrates as a function of the actual state of the system is a key challenge for the viability of this industry.

The second topic consists in growing microalgae, the field of expertise of the members of the team at the Oceanographic Laboratory of Villefranche-sur-Mer (LOV), to produce biofuel. These microorganisms can synthesize lipids with a much higher productivity than terrestrial oleaginous species. The difficulty is to better understand the involved processes, which are mainly transient, to stimulate and optimize them on the basis of modeling and control strategies. Predicting and optimizing the productivity reached by these promising systems in conditions where light received by each cell is strongly related to hydrodynamics, is a crucial challenge.

Finally, for the energy balance of the process, it is important to couple microalgae and anaerobic digestion to optimize the solar energy that can be recovered from microalgae, as was explored within the ANR Symbiose project (2009-2012) [3].

4.2 CO_2 fixation and fluxes

Phytoplanktonic species, which assimilate CO_2 during photosynthesis, have received a lot of attention in the last years. Microalgal based processes have been developed in order to mitigate industrial CO_2. As for biofuel productions, many problems arise when dealing with microalgae which are more complex than bacteria or yeasts. Several models have been developed within our team to predict the CO_2 uptake in conditions of variable light and nitrogen availability. The first modeling challenge in that context consists in taking temperature effects and light gradient into account.

The second challenge consists in exploiting the microalgal bioreactors which have been developed in the framework of the quantification of carbon fluxes between ocean and atmospheres. The SEMPO platform (simulator of variable environment computer controlled), developed within the LOV team, has been designed to reproduce natural conditions that can take place in the sea and to accurately measure the cells behavior. This platform, for which our team has developed models and control methods over the years, is an original and unique tool to develop relevant models which stay valid in dynamic conditions. It is worth noting that a better knowledge of the photosynthetic mechanisms and improved photosynthesis models will benefit both thematics: CO_2 mitigation and carbon fluxes predictions in the sea.

4.3 Biological control for plants and micro-plants production systems

This research concentrates on the protection of cultures of photosynthetic organisms against their pests or their competitors. The cultures we study are crop and micro-algae productions. In both cases, the devices are more or less open to the outside, depending on the application (greenhouse/field, photobioreactor/raceway), so that they may give access to harmful pathogens and invading species. We opt for protecting the culture through the use of biocontrol in a broad sense.

In crop production, biocontrol is indeed a very promising alternative to reduce pesticide use: it helps protecting the environment, as well as the health of consumers and producers; it limits the development of resistance (in comparison to chemicals). The use of biocontrol agents, which are, generically, natural enemies (predators, parasitoids or pathogens) of crop pests [90], is however not widespread yet because it often lacks efficiency in real-life crop production systems (while its efficiency in the laboratory is much higher) and can fail to be economically competitive. Resistant crops are also used instead of pesticides to control pests and pathogens, but the latter eventually more or less rapidly overcome the resistance, so these crops need to be replaced by new resistant crops. As resistant genes are a potentially limited resource, a challenge is to ensure the durability of crop resistance. Our objective is to propose models that would help to explain which factors are locks that prevent the smooth transition from the laboratory to the agricultural crop, as well as develop new methods for the optimal deployment of the pests natural enemies and of crop resistance.

Microalgae production is faced with exactly the same problems since predators of the produced microalgae (e.g. zooplankton) or simply other species of microalgae can invade the photobioreactors and outcompete or eradicate the one that we wish to produce. Methods need therefore to be proposed for fighting the invading species; this could be done by introducing predators of the pest and so keeping it under control, or by controlling the conditions of culture in order to reduce the possibility of invasion; the design of such methods could greatly take advantage of our knowledge developed in crop protection since the problems and models are related.

4.4 Biological depollution

These works will be carried out with the LBE, mainly on anaerobic treatment plants. This process, despite its strong advantages (methane production and reduced sludge production) can have several locally stable equilibria. In this sense, proposing reliable strategies to stabilize and optimize this process is a key issue. Because of the recent (re)development of anaerobic digestion, it is crucial to propose validated supervision algorithms for this technology. A problem of growing importance is to take benefit of various waste sources in order to adapt the substrate quality to the bacterial biomass activity and finally optimize the process. This generates new research topics for designing strategies to manage the fluxes of the various substrate sources meeting at the same time the depollution norms and providing a biogas of constant quality. In the past years, we have developed models of increasing complexity. However there is a key step that must be considered in the future: how to integrate the knowledge of the metabolisms in such models which represent the evolution of several hundreds bacterial species? How to improve the models integrating this two dimensional levels of complexity? With this perspective, we wish to better represent the competition between the bacterial species, and drive this competition in order to maintain, in the process, the species with the highest depollution capability. This approach, initiated in [94] must be extended from a theoretical point of view and validated experimentally.

5 Social and environmental responsibility

Since its creation, team BIOCORE has been actively engaged in contributing to sustainable growth of living organisms and the production of bioenergy in a sustainable way. Through our expertise in the development of new technologies, mathematical models, and computer tools, BIOCORE contributes to the general field of design and control of artificial ecosystems (or biosystems). The general goal of BIOCORE (see 2.1) is to design devices, systems and processes containing living cells or individuals and performing some tasks to decrease pollution, use of chemicals, or to produce bioenergy in a sustainable way. We build biological/ecological models in close collaborations with biologists and bioprocess engineers, and validate them with experimental platforms. Our main applications are:

- Bioenergy, in particular the production of lipids (which can be used as biofuel), methane andhydrogen by microorganisms (with LOV and LBE).

- CO2 fixation by micro-algae, with the aim of capturing industrial CO2 fluxes (with LOV).
- Design and optimization of ecologically friendly protection methods for plants and micro-plants artificial production systems (with ISA and LOV).
- Biological waste treatment with microorganisms in bioreactors to reduce pollution emission levels(in collaboration with LBE).

Some members of our team (O. Bernard, M. Chaves, and W. Djema) are also participants in the local committee for sustainable development (CLDD), which was (re-)activated in 2019 at Inria Sophia Antipolis. This committee is active in various ways, and organizes events to introduce, inform, and familiarize the community to sustainable development questions and actions.

6 Highlights of the year

- Crop variety mixture is a promising method for agroecological plant disease control. We propose a first model that takes cross-protection between varieties into account in such mixtures: plants able to resist infection by specific pathogen genotypes become more resistant to other pathogen genotypes. We then showed that this so-called priming phenomenon allowed for the existence of a priming-related optimal plant mixture that reduces the infection the most [19]
- Algae-bacteria processes for treating wastewater are becoming popular. We designed and calibrated a model, that was validated with more than one year of data [16]. The model analysis revealed that despite pH regulation, a strong limitation for inorganic carbon was found to hinder the process efficiency and to generate conditions that are favorable for N2O emission. A control strategy regulating alkalinity turns out to be necessary to enhance the performance and avoid dammageable emissions [15].
- In the work [34], we investigate a prototypical synthetic consortium of bacteria. A first E. coli strain, producing a heterologous protein, is sided by a second E. coli strain engineered to scavenge toxic byproducts, thus favoring the growth of the producer at the expense of diverting part of the resources to the growth of the cleaner. We develop a coarse-grained mathematical model that quantitatively accounts for literature data from different key growth phenotypes. Based on this, assuming growth in chemostat, we first investigate the conditions enabling stable coexistence of both strains and the effect of the metabolic load due to heterologous protein production. In these conditions, we establish when and to what extent the consortium outperforms the producer alone in terms of productivity.

6.1 Awards

- Lucie Chambon was awarded the "Prix de Thèse" (PhD thesis prize) by the doctoral school EDSTIC, for her work "Control strategies for genetic feedback loops."

7 New software and platforms

7.1 New software

7.1.1 In@lgae

Name: Numerical simulator of microalgae based processes

Keywords: Simulation, Microalgae system, Productivity

Functional Description: In@lgae simulates the productivity of a microalgae production system, taking into account both the process type and its location and time of the year. The process is mainly defined by its thermal dynamics and by its associated hydrodynamics. For a given microalgal strain, a set of biological parameters describe the response to nitrogen limitation, temperature and light. As a result, the biomass production, CO$_2$ and nitrogen fluxes, lipid and sugar accumulation are predicted.

Release Contributions: The In@lgae platform has been optimised to make it faster. Some of the key models have been rewritten in C++ to allow a faster computation. Models have been improved to include, in the growth rate computation, the composition of the light spectrum. The graphical user interface has been enhanced and several sets of parameters describing different microalgal species have been stored.

Authors: Étienne Delclaux, Francis Mairet, Olivier Bernard

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Participants: Étienne Delclaux, Francis Mairet, Olivier Bernard, Quentin Béchet

7.1.2 Odin

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

Keywords: Bioinformatics, Biotechnology, Monitoring, Automatic control

Scientific Description: ODIN is a distributed application, whose graphical interfaces can be launched remotely through the Internet. The application, developed in Erlang, is architected around an MQTT broker. It is robust and tolerant to hardware failures in order to avoid that a wrong manipulation can have harmful consequences on the biotechnological process.

Thus, the implementation of a new algorithm is done by a plugin written in Python language. Modifying one of these algorithms does not require recompiling the code.

Translated with www.DeepL.com/Translator (free version)

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 Ibis research team.

URL: `https://team.inria.fr/biocore/software/odin/`

Authors: Nicolas Niclausse, Olivier Bernard, Eugenio Cinquemani, Tamas Muszbek, Thibaud Kloczko, Nicolas Chleq, Ghada Bahloul, Tristan Cabel, Francois Caddet, Jean-Luc Szpyrka, Pierre Fernique, Erwan Demairy, Amine Lahouel, Come Le Breton, Jonathan Levy, Julia Elizabeth Luna, Riham Nehmeh, Marc Vesin, Carlos Zubiaga Pena

Contacts: Olivier Bernard, Eugenio Cinquemani, Nicolas Niclausse, Thibaud Kloczko

Participants: Olivier Bernard, Nicolas Niclausse, Eugenio Cinquemani, Tamas Muszbek, Thibaud Kloczko, Nicolas Chleq, Jean-Luc Szpyrka, Pierre Fernique, Julia Elizabeth Luna, Come Le Breton, Jonathan Levy, Amine Lahouel, Tristan Cabel, Francois Caddet, Erwan Demairy, Riham Nehmeh, Marc Vesin, Carlos Zubiaga Pena

8 New results

New results: Mathematical methods and methodological approach to biology

8.1 Mathematical analysis of biogical models

8.1.1 Mathematical study of ecological models

Participants Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Clotilde Djuikem, Yves Fotso Fotso, Israël Tankam Chedjou.

Semi-discrete models. Semi-discrete models have shown their relevance in the modeling of biological phenomena whose nature presents abrupt changes over the course of their evolution [91]. We used such models and analyzed their properties in several practical situations, some of them requiring such a modeling to describe external perturbations of natural systems such as harvest, and others to take seasonality into account. We developed these models in the context of augmentative introduction of species [1], seasonality in the dynamics of coffee leaf rust [80] and of banana and plantain burrowing nematodes [39], as well as for the protection of plant resistance against root-knot nematodes [37].

Models in plant epidemiology. We developed and analysed dynamical models describing plant-parasite interactions, in order to better understand, predict and control the evolution of damages in crops. We considered several pathosystems, further described in Section 8.6, describing and controlling the impact on plants of fungi [79], [40], nematodes [39, 37], and pests [84, 83].

8.1.2 Estimation and control

Participants Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Yves Fotso Fotso, Samuel Nilusmas, Israël Tankam Chedjou.

Optimal control and optimisation. We developed several approaches to control the evolution of crop pests. To reduce crop losses due to plant-parasitic nematodes, we optimised (i) rotation strategies between resistant and susceptible cultivars of horticultural crops [37], or (ii) fallow periods between plantain cropping seasons [39]. These optimisation problems were solved on a finite time horizon. They benefited from the resources and support of NEF computation cluster.

We also solved optimal control problem to limit the damages due to coffee berry borers [84, 83] and Coffee Leaf Rust [80] using the BOCOP software (`https://www.bocop.org/`).

8.2 Metabolic and genomic models

Participants Jean-Luc Gouzé, Olivier Bernard, Valentina Baldazzi, Lucie Chambon, Carlos Martinez von Dossow, Agustin Yabo, Alex dos Reis de Souza, Walid Djema, Sofya Maslovskaya, Hidde de Jong *(IBIS)*, Eugenio Cinquemani *(IBIS)*, Jean-Baptiste Caillau *(MCTAO)*.

8.2.1 Cell metabolism

Genetic variability in fruit sugar metabolism Predicting genotype-to-phenotype relationships is a big challenge for plant biology and breeding. Based on the model by Desnoues et al. [73], a reduction pipeline combining several reduction strategies has been developed to reduce both model size and nonlinearity and allow for further application to virtual breeding (collaboration with B. Quilot-Turion and Mohamed Memmah (INRAE Avignon) as part of the PhD thesis of Hussein Kanso). [29]. In parallel, an inter-species comparison of fruit sugar metabolism has been conducted on ten contrasted species, including both starch-free and starch-rich species. Results showed distinct coordination among cellular processes in herbaceous and perennial plants, highligting different strategies for sugar accumulation [13].

8.2.2 Resource allocation

Modeling cell growth and resource allocation. The allocation of cellular resources can strongly influence not only the rate of cell growth but also the resulting cell size [69]. To better investigate the connection between proteome allocation and cell volume, the original model by Giordano et al. [85] has been connected to a biophysical model of cell growth, explicitly describing cell volume increase as a function of cell's internal pressure and wall mechanical properties [87]. In collaboration with I. Cheddadi (University of Grenoble) we are currently investigating the link between allocation to wall biosynthetic proteins and the resulting cell wall mechanics.

With F. Mairet (Ifremer Nantes) and H. de Jong (IBIS Grenoble), we also studied the influence of temperature on microbial growth laws [30].

Modeling energy constraints in microbial growth. In the framework of the Maximic project (collab. H. de Jong, IBIS team, and T. Gedeon, Montana State University) and as a follow up of our previous work [85], we developed a coarse-grained model of coupled energy and mass fluxes in microorganisms, based on minimal assumptions, and calibrate the model with data for *E. coli.* As reported in experimental data, the model predicts the occurrence of a growth rate-yield trade-off, as a generic property of the dependence of growth rate and growth yield on the distribution of resources over the production of ribosomes, enzymes in central metabolism and nutrient uptake, and enzymes in energy metabolism. An article is currently under preparation on this topic.

Optimal allocation of resources in a bacterium. We study by techniques of optimal control the optimal allocation between metabolism and gene expression during growth of bacteria, in collaboration with Inria IBIS and MCTAO project-teams. We developed different versions of the problem, and considered a new problem where the aim is to optimize the production of a product in a bioreactor [26, 49], (ANR project Maximic, PhD thesis of A. Yabo). The precise mathematical analysis of the optimal behavior (turnpike property) is under investigation [48].

8.2.3 Bacterial communities

A synthetic community of bacteria. In the framework of IPL Cosy (E. Cinquemani), we study the coexistence of two strains of bacteria E. Coli in a bioreactor. The strains have been modified synthetically to achieve some goals. The aim is to obtain a better productivity in the consortium than in a single strain, by control methods [34]. We studied mathematical models of overflow metabolism (fermentative growth) in such bacteria [33, 46].

In collaboration with team VALSE (Lille), we also studied several problems of estimation and robust stabilization related to IPL Cosy, for two bacterial species in a bioreactor [21, 44, 22].

8.2.4 Synchronization and control using hybrid models

Participants	Nicolas Augier, Madalena Chaves, Jean-Luc Gouzé, Lucie Chambon, Agustín Yabo.

Hybrid control of genetic networks. We designed control strategies based on the measurement and control of a unique gene within positive or negative loops of genetic networks, in order to stabilize the system around its unstable fixed point. The quantized nature of genetic measurements and the new synthetic control approaches available in biology encourage the use of piecewise constant control laws. A specific partitioning of the state space and the study of successive repulsive regions allow to show global convergence and global stability for the resulting system. Several other control strategies are studied [18, 41]. This is part of the PhD thesis of L. Chambon, and a collaboration with I. Belgacem and R. Edwards, University of Victoria.

Qualitative control for synchronization of piecewise linear systems We investigated the emergent dynamics in a network of N coupled cells, each expressing a similar bistable switch [56]. The bistable switch is modeled as a piecewise affine system and the cells are diffusively coupled. We show that both the coupling topology and the strength of the diffusion parameter may introduce new steady state patterns in the network. We study the synchronization properties of the coupled network and, using a control set of only three possible values (u_{min}, u_{max}, or 1), propose different control strategies which stabilize the system into a chosen synchronization pattern, both in the weak and strong coupling regimes.

Time-optimal control of piecewise affine bistable systems In [57] we give a geometric characterization of the time-optimal trajectories for a piecewise affine bistable switch, based on an adaptation of the Hybrid Pontryagin's Maximum Principle. Such hybrid models play a major role in systems biology, as they can expressively account for the behaviors of simple gene-regulatory networks.

8.2.5 State estimation with interval observers

Participants Olivier Bernard, Frédéric Mazenc *(DISCO)*.

Dynamical systems involving Metzler matrices are convenient for designing interval observers. The necessary and sufficient condition ensuring that a real matrix of dimension 3 is similar to a Metzler matrix was exhibited. When this condition is satisfied, an interval observer for a family of continuous-time systems can be derived. We illustrated the interval observer design for the love dynamics in the case of limit cycles.

8.2.6 Modeling, analysis, and control for synthetic biology

Participants Madalena Chaves, Eleni Firippi, Jean-Luc Gouzé, Hidde de Jong *(IBIS)*.

Coupling and synchronization of piecewise linear systems We considered a piecewise affine model of a synthetic two-gene oscillator and proved existence and stability of a periodic solution for all parameters in a given region [25]. Motivated by the synchronization of circadian clocks in a cluster of cells, we next studied a network of N identical oscillators under diffusive coupling. Our results show that both all-to-all and one-to-all coupling topologies may introduce new stable steady states, in addition to the expected periodic orbit. Both topologies admit an upper bound on the coupling parameter that prevents the generation of new steady states. However, this upper bound is independent of the number of oscillators in the network and less conservative for the one-to-all-topology. This is part of the PhD thesis of Eleni Firippi.

Period-control in a coupled system of two genetic oscillators In synthetic biology circuits it is important to improve system design and study robustness and control properties. Following our recent work [82], we consider a theoretic coupling scheme for the bidirectional interaction of two classic synthetic oscillators. Using different pairs of classic oscillators (an improved Smolen oscillator, coupled with either a cell cycle model or a repressilator), we compare the effect of the same coupling scheme on the period response of the coupled system, in terms of the properties of each individual oscillator. In our methodology we use computational tools and bifurcation analysis, to propose tuning of the coupling parameters and period control of the coupled circuit. This work is part of the PhD thesis of Eleni Firippi.

Review of qualitative analysis and control methods for synthetic circuits Qualitative modeling approaches are promising for the analysis and design of synthetic circuits, as they can make predictions of circuit behavior in the absence of precise, quantitative information. Moreover, they provide direct insight into the relation between the feedback structure and the dynamical properties of a network. In the book chapter [53], in collaboration with Hidde de Jong from the IBIS team, we reviewed the approaches of Boolean networks and piecewise-linear differential equations, and illustrate their application by means of three well-known synthetic circuits. We describe various methods for the analyis of state transition graphs, the discrete representations of the network dynamics that are generated in both modeling frameworks. We also briefly present the problem of controlling synthetic circuits, an emerging topic that could profit from the capacity of qualitative modeling approaches to rapidly scan a space of design alternatives.

8.3 Biochemical and signaling models

Participants Madalena Chaves, Sofia Almeida, Marielle Péré, Luis Gomes Pereira, Jérémie Roux, Jeremy Gonin.

8.3.1 Analysis and coupling of mammalian oscillators

Modeling, analysis and coupling of the mammalian cell cycle and clock A transcriptional model of the mammalian circadian clock was developed in [12] and its parameters calibrated against experimental data from F. Delaunay's lab. A cell cycle model was also previously developed by us [68]. The interactions between the two oscillators are investigated under uni- or bi-directional coupling schemes [11]. Numerical simulations replicate the oscillators' period-lock response and recover observed clock to cell cycle period ratios such as 1:1, 3:2 and 5:4 (as observed in experiments, F. Delaunay's lab). Moreover, for an uni-directional coupling scheme, we also investigate methods of slowing down the cell cycle by the use of clock modulating inputs, some of which correspond to existing drugs [24]. This work is in collaboration with F. Delaunay (ANR ICycle) and was part of the PhD thesis of Sofia Almeida.

Analysis of asynchronous Boolean attractors: mammalian clock dynamics and robustness In asynchronous Boolean models, periodic solutions are represented by terminal strongly connected graphs (attractors), which are typically composed of hundreds of states and transitions. It is usually a challenging task to interpret the transitions inside an attractor in terms of the sequence of events in a biological cycle. Using a recent methodology to generate summary graphs [74] and a technique to find the attractors of coupled Boolean models [10], we studied a Boolean model of the mammalian circadian clock [42], for which the summary graph recovers the main phases of the cycle, in the expected order. It also suggests improvements in the design of the logical rules of the model and highlights groups of transitions that are essential for the attractor's robustness.

8.3.2 Modeling the apoptotic signaling pathway

A detailed model of the death receptor layer In a collaboration with J. Roux and within project Imodrez, the goal is to study the origins of cell-to-cell variability in response to anticancer drugs and provide a link between complex cell signatures and cell response phenotype. In a first approach, we constructed a detailed model to represent the death receptor-ligand binding and subsequent signaling cascade, with our previous PhD student Luis Gomes Pereira [45]. This model was used to study the effect of intrinsic and extrinsic noise sources, and suggested the need to expand a set of reactions on the model, to account for the observed cell heterogeneity.

Core models of receptor reactions to evaluate basic pathway designs and heterogeneous response in apoptosis In a continued collaboration with J. Roux, we investigated the core reactions leading to caspase-8 activation, based on mass-action kinetics models, to evaluate the basic mechanisms giving rise to the observed heterogeneous response. To do this, we developed a group of core models with a minimal number of components and fitted them to single-cell trajectories of time-resolved caspase-8 activation measured in clonal cells after treatment with TRAIL [47]. Several comparison and best fit measures were used to assess the relevance of each model and evaluate how well it captures the extent of biological heterogeneity observed *in vitro*. From this study, three points have a major role in establishing heterogeneity: a positive feedback loop on caspase-8, the impacts of initial condition variations and the relevance of the caspase-8 degradation. This is part of the work of the PhD student Marielle Péré.

Profiling the Non-genetic Origins of Cancer Drug Resistance We present fate-seq, a method coupling three single-cell technologies to associate the transcriptomic state of a cell to its predicted fate, based on cell response dynamics [35]. The transcriptomic profiles showed an unexpected set of target genes that once perturbed, could all improve the cell sensitivity to the drug class tested. The study is relevant to cancer drug research, as cell-to-cell variability becomes a pertinent information during cancer clinical assessment. The PhD student L. Gomes-Pereira participated in this work from the Lab of J. Roux.

New results: Fields of application

8.4 Bioenergy

8.4.1 Modelling microalgae production

Participants	Olivier Bernard, Antoine Sciandra, Walid Djema, Francesca Casagli, David Demory, Bruno Assis Pessi, Liudi Lu, Jean-Philippe Steyer, Laetitia Giraldi *(MCTAO)*.

Experimental developments

Running experiments in controlled dynamical environments. The experimental platform made of continuous photobioreactors driven by a set of automaton controlled by the ODIN software is a powerful and unique tool which gave rise to a quantity of very original experiments. Such platform improved knowledge of several biological processes such as lipid accumulation or cell cycle under light fluctuation, etc [51].

This experimental platform was used to control the long term stress applied to a population of microalgae using optimal control strategies[20, 43]. This Darwinian selection procedure generated several new strains more resistant to oxidative stresses after several months in the so called selectiostats [27].

On top of this, we carried out outdoor pilot experiments with solar light. We tested the impact of various temperatures, resulting from different shadowing configurations on microalgal growth rate.

Experimental work was also carried out in collaboration with the Inalve startup with microalgal biofilm to determine the impact of light and dark sequences on cell growth and photoacclimation. The architecture of the biofilms was also observed for different species with confocal microscopic techniques.

A review on the conditions for the production of lipids, their quality and their insustrial use was finally written in two book chapters [51, 54].

These works have been carried out in collaboration with A. Talec and E. Pruvost (CNRS/Sorbonne Université -Oceanographic Laboratory of Villefranche-sur-Mer LOV).

Metabolism of carbon storage and lipid production. A metabolic model has been set up and validated for the microalgae *Chlorella vulgaris*, on the basis of the DRUM framework , in order to simulate autotophic, heterotropic and mixotrophic growth, and to determine how to reduce substrate inhibition. The model was extended to other substrates such as glucose or glycerol. A simplified model was developed by I. Lopez to represent the dynamics of polar lipids, especially when faced to higher oxygen concentration. In particular, this model represents the microalgae growth under different conditions of temperature, light and oxygen.

Modeling the coupling between photosynthesis and hydrodynamics. We consider a coupled physical-biological model describing growth of microalgae in a raceway pond cultivation process, accounting for hydrodynamics. Our approach combines a biological model (based on the Han model) and shallow water dynamics equations that model the fluid into the raceway pond. We developped an optimization procedure dealing with the topography to maximize the biomass production over one lap or multiple laps with a paddle wheel. The results show that a flat topography is optimal in a periodic regime [58, 59]. In other frameworks, non-trivial topographies can be obtained. We then studied the influence of mixing, assuming that a mixing device can redistribute the algae so that they can have access to light [61].

A strategy to optimally mix the algae was derived. It was finally combined with the design of a non flat topography [60].

Modeling photosynthetic biofilms. Several models have been developed to represent the growth of microalgae within a biofilm. A first structured physiological model, extending the one proposed in [98] uses mixture theory to represent the microalgae growth, based on the consideration of intracellular reserves triggering the processes of growth, respiration and excretion. We consider separately the intracellular storage carbon (lipids and carbohydrates) and the functional part of microalgae . Another approach accounts for the dynamics of the light harvesting systems when cells are submitted to rapid successions of light and dark phases. A simpler model was developed and used to identify the optimal working mode of a process based on photosynthetic biofilm growing on a conveyor belt. The model was used to identify the worldwide potential of microalgal biofilms under different climates.

Modeling microalgae production processes. A model representing the dynamics of microalgae when growing in suboptimal conditions of light, nitrogen and phosphorus was developed. It consists in an extension of the Droop model accounting for the two quota of nitrogen and phosphorus. The model also represents the pigment acclimation to various light intensities. We have studied in [31] the response of a Droop model forced by periodic light or temperature signals. We transformed the model into a planar periodic system generating a monotone dynamical system. Combined with results on periodic Kolmogorov equations, the global dynamics of the system can be described.

Modeling thermal adaptation in microalgae. Experiments have been carried out in collaboration with A.-C. Baudoux (Biological Station of Roscoff) in order to study growth of various species of the microalgae genus *Micromonas* at different temperatures. After calibration of our models, we have shown that the pattern of temperature response is strongly related to the site where cells were isolated. We derived a relationship to extrapolate the growth response from isolation location. With this approach, we proved that the oceanwide diversity of *Micromonas* species is very similar to the oceanwide diversity of the phytoplankton [72]. We have used Adaptive Dynamics theory to understand how temperature drives evolution in microalgae. We could then predict the evolution of this biodiversity in a warming ocean and show that phytoplankton must be able to adapt within 1000 generation to avoid a drastic reduction in biodiversity [72].

Modeling viral infection in microalgae. In collaboration with A.-C. Baudoux (Biological Station of Roscoff) a model was developed to account for the infection of a *Micromonas* population, with population of susceptible, infected and also free viruses. The model turned out to accurately reproduce the infection experiments at various temperatures, and the reduction of virus production above a certain temperature [63]. The model was then extrapolated to the whole ocean to better understand how the warming will impact the mortality due to viruses.

8.4.2 Control and Optimization of microalgae production

Optimization of the bioenergy production systems A model predictive control algorithm was run based on simple microalgae models coupled with physical models where culture depth influences thermal inertia. Optimal operation in continuous mode for outdoor cultivation was determined when allowing variable culture depth. Assuming known weather forecasts considerably improved the control efficiency.

Interactions between species. We have proposed an optimal control strategy to select in minimal time the microalgal strain with the lowest pigment content [76]. The control takes benefit from photoinhibition to compute light stresses penalizing the strains with a higher pigment content and finally selecting microalgae with lower chlorophyll content. Another optimal control problem was considered for selecting a strain of interest within two species competing for the same substrate, when dynamics is represented by a Droop model [77, 75, 78]. In both cases, the optimal control derived from the Pontryagin maximum principle also exhibit a turnpike behaviour. This is a collaboration with team MCTAO.

Strategies to improve the temperature response have also been studied. We modelled the adaptive dynamics for a population submitted to a variable temperature [71]. This was used at the LOV to design experiments with periodic temperature stresses aiming at enhancing polyunsaturated long chain fatty acids content of *Tisochrysis lutea* [70].

8.4.3 Modelling mitochondrial inheritance patterns

Most eukaryotes inherit their mitochondria from only one of their parents. When there are different sexes, it is almost always the maternal mitochondria that are transmitted. Indeed, maternal uniparental inheritance has been reported for the brown alga Ectocarpus but we show in this study [95] that different strains of Ectocarpus can exhibit different patterns of inheritance: Ectocarpus siliculosus strains showed maternal uniparental inheritance, as expected, but crosses using different Ectocarpus species (7 strains) exhibited either paternal uniparental inheritance or an unusual pattern of transmission where progeny inherited either maternal or paternal mitochondria, but not both. A possible correlation between the pattern of mitochondrial inheritance and male gamete parthenogenesis was investigated. Moreover, in contrast to observations in the green lineage, we did not detect any change in the pattern of mitochondrial inheritance in mutant strains affected in life cycle progression. Finally, an analysis of field-isolated strains provided evidence of mitochondrial genome recombination in both Ectocarpus species.

8.5 Biological depollution

8.5.1 Control and optimization of bioprocesses for depollution

Participants Olivier Bernard, Carlos Martinez von Dossow, Jean-Luc Gouzé, Francesca Casagli.

We consider artificial ecosystems including microalgae, cyanobacteria and bacteria in interaction. The objective is to more efficiently remove inorganic nitrogen and phosphorus from wastewater, while producing a microalgal biomass which can be used for biofuel or bioplastic production. Models have been developed including predators grazing the microalgae.

Algae-bacteria processes for treating wastewater are becoming popular. We designed and calibrated a model, that was validated with more than one year of data [16]. The model analysis revealed that despite pH regulation, a strong limitation for inorganic carbon was found to hinder the process efficiency and to generate conditions that are favorable for N2O emission. A control strategy regulating alkalinity turns out to be necessary to enhance the performance and avoid dammageable emissions [15].

8.5.2 Coupling microalgae to anaerobic digestion

Participants Olivier Bernard, Antoine Sciandra, Jean-Philippe Steyer, Frédéric Grognard, Carlos Martinez von Dossow, Francesca Casagli.

The coupling between a microalgal pond and an anaerobic digester is a promising alternative for sustainable energy production and wastewater treatment by transforming carbon dioxide into methane using light energy. The ANR Phycover project is aiming at evaluating the potential of this process [99].

We have proposed several models to account for the biodiversity in the microalgal pond and for the interaction between the various species. These models were validated with data from the Saur company. More specifically, we have included in the miroalgae model the impact of the strong turbidity, and derived a theory to better understand the photolimitation dynamics especially when accounting for the photoinhibition in the illuminated periphery of the reactor [93]. Control strategies playing with the dilution rate, shadowing or modifying depth were then proposed [92].

8.5.3 Life Cycle Assessment

Participants Olivier Bernard, Jean-Philippe Steyer, Marjorie Alejandra Morales Arancibia.

Environmental impact assessment. To follow up the pioneering life cycle assessment (LCA) work of [89], we identified the obstacles and limitations which should receive specific research efforts to make microalgae production environmentally sustainable [96].

We have studied the environmental impact of protein production from microalgae in an algal biofilm process and compared it to other sources (fisheries, soy,...). This study confirms the interest of microalgae for reducing the environmental impact [36].

This work is the result of a collaboration with Arnaud Helias of INRA-LBE (Laboratory of Environmental Biotechnology, Narbonne).

8.6 Design of ecologically friendly plant production systems

8.6.1 Controlling plant arthropod pests

Participants Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Yves Fotso Fotso.

Optimization of introduction processes.

The question of how many and how frequently natural enemies should be introduced into crops to most efficiently fight a pest species is an important issue of integrated pest management. The topic of optimization of natural enemies introductions has been investigated for several years [90], and extends more generally to pulse perturbations in population dynamics. This year, our expertise allowed us to contribute to a review chapter on augmentative biological control [52], and we are currently writing a paper describing promising experimental results [81] on the combined use of food and artificial habitats supplementations to enhance augmentative biological control with predatory mites. This work has been performed in collaboration with Louise van Oudenhove (ISA).

Since this year, our research in this context expands to the modelling and optimization of introduction strategies in the context of the Sterile Insect Technique (SIT), thanks to the participation of the team in the project 'CeraTIS Corse', the first SIT pilot project in France focused on the control of an agricultural pest (the mediterranean fruit fly *Ceratitis capitata*).

Spatial population dynamics of biological control agents.

We have been involved for several years in a mixed modelling-experimental approach to explore the spatio-temporal dynamics of populations, with special interest to micro-wasp parasitoids [97, 88]. In particular, we investigated, using computer simulation models and laboratory microcosms, how expanding populations can switch from 'pulled' to 'pushed' spatio-temporal dynamics when environmental connectivity decreases [62]. Connected research has been performed on the influence of Allee effects and density dependence in dispersal on range shifts and the spatial pinning of populations, and on how Allee effects can increase population extinction risks [67]. These works have been performed in collaboration with Elodie Vercken (ISA).

Concurrently, we are exploring the correlation between biological control agents movement caracteristics at different scales, from laboratory experimental caracterization to field dispersal. This research is performed on various species of parasitoids belonging to the genus Trichogramma, and is the main topic of Melina Cointe PhD thesis that started in autumn 2020 (director Vincent Calcagno, ISA).

Modelling and control of coffee berry borers.

We developed a model describing the coffee berry borer dynamics based on the insect life-cycle and the berry availability during a single cropping season. A control was introduced, based on a biopesticide (entomopathogenic fungus such as *Beauveria bassiana*) that is sprayed and persist on the berries. An optimal control problem was solved (see Section 8.1.2). The aim was to maximise the yield at the end of the cropping season, while minimising the borer population for the next cropping season and the control costs. Depending on the initial pest infestation, the optimal solution structure varied [83, 84]. A PDE model taking the age of the berries and the preference of coffee berry borers for more mature berries was also developed. This research pertains to Yves Fotso Fotso's PhD thesis, who visited BIOCORE during 5 months in 2020 through the EPITAG associate team.

8.6.2 Controlling plant pathogens

Participants Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Clotilde Djuikem.

Sustainable management of plant resistance.

We studied other plant protection methods dedicated to fight plant pathogens. One such method is the introduction of plant cultivars that are resistant to one pathogen. This often leads to the appearance of virulent pathogen strains that are capable of infecting the resistant plants.

We developed a spatio-temporal epidemiological model of the phoma stem canker of oilseed rape, to test and assess the durability of deployment strategies of various cultivars. We made this model more generic to represent several fungal diseases on annual field crops in a multi-pathogen context. Based on this model, we are developing a user-friendly, upgradeable and efficient simulation tool designed for researchers as well as non academic partners from technical institutes and agriculture cooperatives, thanks to the SiDRes AMDT. The first code sprint took place in October 2020 and produced a first validated tool, which is a solid base for future developements.

Coffee leaf rust (CLR) is a disease caused by a basidiomycete fungus, *Hemileia vastatrix*, that has a major impact on coffee production around the world. We produced a spatio-temporal model that describes CLR propagation in a coffee plantation during the rainy and dry seasons, and investigate numerically the impact of biocontrol [79]. A multi-season hybrid model was also produced where the dry season was reduced to a discrete event; an optimal multi-season biological control for the pathogen control was then computed using the BOCOP software [80].

Taking advantage of plant diversity and immunity to minimize disease prevalence.

An epidemiological model of gene-for-gene interaction has been designed, considering increased defense to pathogen infections following previous exposure to a pathogen or an elicitor, namely priming. Priming provides a sort of immunity to virulent pathogens for resistant plants having undergone an infection attempt by an avirulent pathogen. This model showed that an optimal host mixture exists that ensures the lowest plant disease prevalence, so as to optimize the crop yield. It is especially efficient for pathogens with a low or intermediate basic reproduction rate and host plants with a high degree of priming [19]. We are currently extending this work to take mixtures of different resistant strains and the possible presence of supervirulent pathogens. This was done in collaboration with Frédéric Hamelin (Agrocampus Ouest) in the framework of Pauline Clin's thesis that started in January 2020.

8.6.3 Plant-nematode interactions

Participants Valentina Baldazzi, Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Israël Tankam Chedjou, Samuel Nilusmas.

Plant-parasitic nematodes are small little-mobile worms that feed and reproduce on plant roots, generating considerable losses in numerous crops all over the world. Most eco-friendly plant protection strategies are based on the use of resistant crops, but agricultural practices also contribute to nematode control.

Based on an interaction model between plantain roots and *Radopholus similis*, we built an impulsive model to compare two control strategies: pesticides, which are widely used, and the choice of the duration between cropping seasons (fallow deployment aimed at reducing the nematode population, followed by the plantation of a nursery-bought pest-free suckers, or vitroplant). Conditions on the pesticide load or the constant fallow duration are then derived to ensure the stability of the pest free equilibrium through the computation the effective reproduction number of pests [39]. We then solved an optimisation problem (see Section 8.1.2) aimed at determining the variable fallow periods that maximise the farmer's cumulated yield, which is affected by the nematode population, while minimising the costs of nematode control and of the vitroplants purchase, on a fixed time horizon that lasts several cropping seasons [38]. These results were extended to a situation where vitroplants are not planted every year, which reduces the costs, but also reduce the control efficiency [66] This research pertains to Israël Tankam Chedjou's PhD thesis, in the framework of the EPITAG associate team.

We also studied resistance-based root-knot nematode control. As virulent nematodes exhibit a reduced fitness on susceptible crops, alternating resistant and susceptible plants could help increase the efficiency and durability of such control methods. Optimal crop rotations (see Section 8.1.2) were characterised by low ratios of resistant plants and were robust to parameter uncertainty. Rotations provided significant gains over resistant-only strategies, especially for intermediate fitness costs and severe epidemic contexts. Switching from the current general deployment of resistant crops to custom rotation strategies could not only maintain or increase crop yield, but also preserve the few and valuable R-genes available. This research pertains to Samuel Nilusmas' PhD thesis, which he successfully defended in December 2020 and has been published this year [37]. This work forms the theoretical foundations of a user-friendly interactive simulation tool aimed at non academic partners (agricultural profession and technical institutes) which has been produced within the Interlude project, and is available and can be accessed online : here.

Based on our previous work, an ecophysiological model of plant-nematode interaction has been extended to account for nematode population dynamics. In addition, the impact of root system architecture (RSA), via its effect on plant hydraulic conductivity and nematode infection probability, are currently under study.

8.6.4 Optimality/games in population dynamics

Participants Frédéric Grognard, Ludovic Mailleret, Pierre Bernhard.

Optimal resource allocation.

Mycelium growth and sporulation are considered for phytopathogenic fungi. For biotrophic fungi, a flow of resource is uptaken by the fungus without killing its host; in that case, life history traits (latency-sporulation strategy) have been computed based on a simple model considering a single spore initiating the mycelium, several spores in competition and applying optimal resource allocation, and several spores in competition through a dynamic game through the analytico-numerical solution of the Hamilton-Jacobi-Bellman-Isaacs equation [40]. This work is done with Fabien Halkett of INRA Nancy.

Optimal foraging and residence times variations.

In this work, we built on our re-analysis of the Marginal Value Theorem (MVT) [4] to study the effect on the optimal foraging strategy of habitat conversion, whereby patches are converted from one existing type to another, hence changing the frequency of each type in the environment. We studied how realized fitness and the average rate of movement should respond to changes in the frequency distribution of patch-types, and how they should covary. We found that the initial pattern of patch-exploitation in a habitat can help predict the qualitative responses of fitness and movement rate following habitat conversion. We concluded that taking into account behavioral responses may help better understand the ecological consequences of habitat conversion [14].

9 Bilateral contracts and grants with industry

9.1 Bilateral contracts with industry

Inalve: with the Inalve start-up we develop a breakthrough process that we patented, in which microalgae grow within a moving biofilm. The objective of the collaboration is to optimize the process by enhancing productivity, while reducing environmental footprint.

9.2 Bilateral grants with industry

Exactcure: in the collaboration with the start-up Exactcure (Nice), the goal of the project is to study pharmacokinetic models.

Inalve: Inalve is funding half of the PhD thesis of Diego Penaranda-Sandoval on the life cycle analysis of processes with low technological maturity. The other half is coming from a PACA region grant.

10 Partnerships and Cooperations

10.1 International Initiatives

10.1.1 Inria International Labs

EPITAG

Title: Epidemiological Modelling and Control for Tropical Agriculture

Duration: 2020 - 2022

Coordinator: Suzanne Touzeau

Partners:

- Department of Mathematics and Computer Science, University of Douala (Cameroon)
- Department of Mathematics, University of Yaoundé I (Cameroon)
- Department of Mathematics and Computer Science, University of Douala (Cameroon)

Inria contact: Suzanne Touzeau

Summary: EPITAG gathers French and Cameroonian researchers, with a background in dynamical systems and control and with an interest in crop diseases. Crop pests and pathogens are responsible for considerable yield losses and represent a threat to food security. Their control is hence a major issue, especially in Cameroon, where agriculture is an important sector in terms of revenues and employment. To help design efficient strategies for integrated pest management, mathematical models are particularly relevant. Our main objective is to study the epidemiology and management of tropical crop diseases, with a focus on Cameroon and Sub-Saharan Africa. Our approach consists in developing and analysing dynamical models describing plant-parasite interactions, in order to better understand, predict and control the evolution of damages in crops. To ensure the relevance of our models, field experts and stakeholders need to be closely associated. We will focus on pest and pathogens that affect major staple food and cash crops, such as cocoa plant mirids, plantain and banana plant-parasitic nematodes, coffee berry borers, coffee leaf rust, maize stalk borers, cabbage diamondback moths, papaya mealybugs, etc. To tackle these issues, we jointly supervise master and PhD students. See also: `https://team.inria.fr/epitag/`

10.2 International research visitors

10.2.1 Visits of international scientists

- Yves Fotso Fotso, University of Dschang, Cameroon, February-July 2020. 6-month stay in the context of the EPITAG associate team, with the support of the AUF Collège doctoral régional de l'Afrique Centrale et des Grands Lacs "Mathématiques, Informatique, Biosciences et Géosciences de l'Environnement".

10.2.2 Visits to international teams

Research stays abroad

- Clotilde Djuikem, University of Douala, Cameroon, November 2020. 1-month stay in the context of the EPITAG associate team.

10.3 National initiatives

10.3.1 National programmes

- **ANR-PhotoBioFilm Explorer:** The first objective of the PhotoBioFilm project (2021-2024) is to explore the activity of the molecules produced within a microalgam biofilm, and explaining its resistance to contamination. The second objective is to identify, characterize and produce novel biocompounds with benefits for human or animal health. The target is antibiotics, but other activities will be tested, especially antiviral activities. Biocore will be in charge of the biofilm modelling and the optimization of the production of the molecules of interests.

- **ANR CtrlAB:** The objectives of the Ctrl-AB project (2021-2024) are (i) to develop new control methods for the optimization of the productivity of a microbial community, and (ii) to demonstrate the effectiveness of these methods on a synthetic algal-bacterial consortium. Interestingly, co-culturing of E. coli with Chlorella leads to higher biomass and lipid productivity. Improved growth of Chlorella occurs despite competition of E. coli for the same substrates. On top of its ability to produce molecules like vitamins, which are necessary for algal growth, the bacteria also produce carbon dioxide (CO2), which is the substrate of the photosynthesis of the algae. The algae can produce oxygen (O2) fuelling bacterial growth, thus giving rise to a mutualistic pattern of interactions giving rise to several challenge for modelling anc controlling this artificial ecosystem.

- **ANR-ICycle:** This project (2016-2021) aims at understanding the communication pathways between the cell division cycle and the circadian clock, using mathematical modeling and control theory to construct and implement two coupled synthetic biological oscillators. Project coordinated by M. Chaves.

- **ANR - Maximic:** The goal of the project (2017-2021) is to design and implement control strategies in a bacterium for producing at maximal rate a high value product. It is coordinated by H. de Jong (IBIS Grenoble), and involves members of Biocore and McTao.

- **Plan Cancer - Imodrez:** The objective of this project (2018-2021) is to understand cancer drug response heterogeneity using tumor single-cell dynamics and developing mathematical models and computational approaches. A project coordinated by J. Roux (IRCAN) and funded by Inserm - Plan Cancer.

- **SIGNALIFE:** Biocore is part of this Labex (scientific cluster of excellence, 2^{nd} period 2020-2024) whose objective is to build a network for innovation on Signal Transduction Pathways in life Sciences, and is hosted by the University Côte d'Azur.

- **UMT FIORIMED:** FioriMed is a Mixed Technology Unit created in January 2015 to strengthen the production and dissemination of innovation to the benefit of ornamental horticulture. Horticultural greenhouses are seen as a "laboratory" for the actual implementation of agroecology concepts with the possibility of generic outcomes being transfered to other production systems. The main partners of UMT FioriMed are ASTREDHOR (National Institute of Horticulture) and the ISA Joint Research Unit of INRA-CNRS-Univ. Nice.

- **EcoPhyto - CeraTIS Corse:** “Territorial management of the Mediterranean fruit fly in Corsica by the Sterile Insect Technique” (2020-2022). This project is based on a pilot field experiment of sterile male releases and it integrates population dynamics and socio-economic approaches.

- **EcoPhyto - INTERLUDE:** “Territorial innovations to reduce phytoparmaceutical products for the sustainable production of vegetable crops” (2020-2022). BIOCORE members participate in a case study that focuses on the agroecological management of soil pests and pathogens in Provence.

- **ORACLE:** ORACLE is a PGMO project (Gaspard Monge Program for Optimization) (2019-2020) using optimal control to solve problems of Optimal Resource Allocation in micro--organisms under changing environment. It is coordinated by T. Bayen (University of Avignon).

10.3.2 Inria funding

- **Inria Project Lab, Cosy:** (2017-2021) This proposal aims at exploiting the potential of state-of-art biological modeling, control techniques, synthetic biology and experimental equipment to achieve a paradigm shift in control of microbial communities. We will investigate, design, build and apply an automated computer-driven feedback system for control of synthetic microbial communities, not just accounting for but rather leveraging population heterogeneity in the optimal accomplishment of a population-level task. The development of methodologies of general applicability will be driven by and applied to two different applications closely connected with real-world problems in the biomedical and biotechnological industry. The consortium is composed of the four Inria project-teams IBIS, BIOCORE, COMMANDS, VALSE, INBIO, as well as the external partners BIOP (Université Grenoble Alpes, including members of IBIS), MaIAge (INRA), and YoukLAB (TU Delft).

- **AMDT, SiDRes:** (2020-) The Action mutualisée de Développement Technologique “Simulateur pour le Déploiement de Résistances” aims at developing a user-friendly, upgradeable and efficient simulation tool to assess the durability of resistant cultivar deployment strategies. It focuses on the evolution of the interactions between fungal pathogens and annual field crop cultivars in an agricultural landscape. It involves the BIOCORE project-team and engineers from the SED, as well as INRAE colleagues.

10.3.3 INRAE funding

- **ArchiNem:** INRAE AgroEcoSystems is funding the project ArchiNem "Multi-scale modelling of plant nematode interactions: root architecture, plant physiology, nematode population dynamics and control" in which Biocore is a partner with INRAE Sophia Antipolis.

- **MitesInn:** INRAE SPE is funding the project MitesInn "Mites innovated: enhancing predatory mite based biological control with micro-habitats and alternative food" (2020-2021) in which Biocore is a partner with INRAE Sophia Antipolis.

- **IMMUnE:** INRAE SPE is funding the project IMMUnE "Immunité et Modélisation Mathématique pour Unifier l’Epidémiologie" (2019-2021), headed by F. Hamelin (Agrocampus Ouest), in which BIOCORE is a partner.

10.3.4 Networks

- **Seminar:** BIOCORE organizes a seminar “Modeling and control of ecosystems” at the station zoologique of Villefranche-sur-Mer, at INRAE-ISA or at Inria (quite irregular this year, and on-line).

10.4 Regional initiatives

- **SYNCHRO**: A partnership between M. Chaves and Michèle Teboul and Franck Delaunay from Institut de Biologie de Valrose (iBV, UCA). A project in the Masters Environnés program from Académie 4-"Complexité et diversité du Vivant" of Idex UCA Jedi, Université Côte d’Azur. The project includes funding for two internships and some equipement.

11 Dissemination

11.1 Promoting scientific activities

11.1.1 Scientific events: organisation

General chair, scientific chair

- O. Bernard organized the Workshop "Convergent aquatic photosynthesis modelling for our planet" at the foundation "les Treilles" (14^{th} to 19^{th} of September 2020)

Member of the organizing committees

- M. Chaves is in the organizing committee of the following conferences: Modelling Heterogeneous Populations with applications in Biology to be held in Grenoble, France `https://project.inria.fr/mhpb/`, and DynamicDays 2021 to be held in Nice, France (August 2021).
- O. Bernard was area chair (Biosystems and Bioprocesses) for the IFAC World Conference (Berlin, Germany, 12nd-17th July 2020), and the head of the academic scientific committee of the AlgaEurope conferences (the last one took place virtually in December 1^{st} to 3^{rd} 2020).

11.1.2 Scientific events: selection

Reviewer All BIOCORE members have been reviewers for the major 2020 conferences in our field: CDC, ECC, IFAC Congress, MTNS,...

11.1.3 Journal

Member of the editorial boards

- M. Chaves is an Associated Editor of SIAM Journal on Applied Dynamical Systems (SIADS), since January 2015. She is also an Associated Editor of the Conference Editorial Board (CEB) of the IEEE Control Systems Society, since August 2020.
- S. Touzeau is an Academic Editor of PLOS ONE, since August 2018.

Reviewer - reviewing activities All BIOCORE members have been reviewers for the major journals in our fields: Automatica, IEEE Transactions on Automatic Control, Journal of Mathematical Biology, Mathematical Biosciences, Algal Research, New Phytologist,...

11.1.4 Invited talks

- M. Chaves gave a Keynote Lecture entitled “A feedback loop in apoptosis: its role in generating heterogeneity in cell response to cancer drugs” at the 4^{th} SIGNALIFE Meeting (February, Nice, France)

11.1.5 Scientific expertise

- M. Chaves is a member of the Education Board of the Master “Quantitative and Computational Sciences for Biomedical data”, Université Côte d’Azur. She is also a member of the scientific committee of Labex Signalife (since 2020).
- J.-L. Gouzé is in the scientific committee of Académie 4 of UCA-Jedi. He is a member of the board of the SFBT (French Speaking Society for Theoretical Biology).
- O. Bernard is a member of the scientific committee of the Inalve company, represents Inria at the ANCRE (Alliance Nationale de Coordination de la Recherche pour l’Energie),represents Inria at the Scientific and Pedagogic committee of the UCA- EUR LIFE and is a member of the ADT (Technological Development Actions) commission at Inria.

11.1.6 Research administration

- O. Bernard, M. Chaves, and W. Djema are members of the CLDD of Inria SAM (local committee for sustainable development).
- M. Chaves (since 2020), L. Mailleret (since 2020) and F. Grognard (since 2015) are members of the INRAE Commission Scientifique Spécialisée (CSS) for Mathématique, Informatique, Sciences et Technologies du numérique, Intelligence artificielle et Robotique (MISTI), in charge of the research scientists evaluation at INRAE.

- J.-L. Gouzé is in the Inria committee supervising the doctoral theses, and a member of the scientific committee of Labex SIGNALIFE of Université Côte d'Azur, and of COREBIO PACA.
- F. Grognard is a member of the steering committee of Academy 3, Space, Environment, Risk and Resilience of UCA-JEDI. He is co-head of the development of the MSc Risk of UCA-JEDI and is a member of the Scientific Committee of the Agroecosystems department of INRAE.
- L. Mailleret is the head of the M2P2 team (Models and Methods for Plant Protection) of ISA. He's in the Unit and scientific council of Institut Sophia Agrobiotech.
- L. Mailleret is an elected member (since 2020) of the Scientific and Pedagogic Council (CoSP) of the EUR LIFE (Graduate school in Life and Health Sciences) of Université Côte d'Azur.
- S. Touzeau is a member of the steering committee of the INRAE metaprogramme SuMCrop "Sustainable Management of Crop Health", a follow-up of the SMaCH metaprogramme (since 2016).

11.2 Teaching - Supervision - Juries

11.2.1 Teaching

- Licence: F. Grognard (45.5h ETD) and L. Mailleret (26h ETD), "Equations différentielles ordinaires et systèmes dynamiques", L3, 1st year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Côte d'Azur, France.
- Master: O. Bernard (4.5h ETD), "Bioenergy from microalgae", M2, Master International Energy Management : alternatives pour l'énergie du futur, Ecole Nationale Supérieure des Mines de Paris, France.
- Master: O. Bernard (18h ETD), "Modeling biotechnological processes", M2, Ecole CentraleSupelec, Saclay, France.
- Master: O. Bernard (18h ETD), "Automatic Control applied to biotechnological processes", M2, Ecole CentraleSupelec, Saclay, France.
- Master : J.-L. Gouzé (20.25h ETD), M. Chaves (13.5h ETD), "Modeling biological networks by ordinary differential equations", M1, 2nd year Engineering in Génie biologique, Polytech Nice Sophia, Université Côte d'Azur, France.
- Master: F. Grognard (21h ETD) and L. Mailleret (21h ETD), "Bio-Mathématiques", M1, 2nd year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Côte d'Azur, France.
- Master: F. Grognard (45h ETD), "Elements of mathematical modelling", M1, MSc in Environmental Hazards and Risks Management, Université Côte d'Azur, France.
- Professional formation: L. Mailleret (8h) "modélisation en dynamique des populations", internal formation INRAE.

11.2.2 Supervision

- PhD: L. Chambon. "Control strategies for genetic feedback loops" , defended, Université Côte d'Azur. Supervisor J.-L. Gouzé.
- PhD: S. Nilusmas. "Gestion durable des nématodes à galles en cultures maraîchères : modélisation et optimisation du déploiement des résistances et des pratiques agronomiques", Université Côte d'Azur, defended. Supervisors: S. Touzeau, C. Caporalino (ISA), V. Calcagno (ISA) and L. Mailleret.
- PhD: E. Firippi. "Mathematical analysis, control design and coupling for models of biological oscillators", defended, Université Côte d'Azur. Supervisor: M. Chaves.

- PhD in progress: I. Tankam Chedjou. “Modeling, analysis and control of plantain plant-parasitic nematodes”, University of Yaoundé I, Cameroon, since December 2015. Supervisors: J.-J. Tewa (Univ. Yaoundé I), F. Grognard, L. Mailleret, S. Touzeau.
- PhD in progress: Y. Fotso Fotso. “Modeling, analysis and control of coffee berry borers”, University of Dschang, Cameroon, since January 2017. Supervisors: B. Tsanou (Univ. Dschang), S. Bowong (Univ. Douala), F. Grognard, S. Touzeau.
- PhD in progress: M. Gachelin. “Selection pressure to improve lipid productivity of microalgae”, since March 2017, UPMC. Supervisors: O. Bernard and A. Sciandra.
- PhD in progress: F. Aubrée “Modélisation de l’adaptation des populations aux fortes pressions anthropiques”, Université Côte d’Azur, since 2017. V. Calcagno, T. Guillemaud, L. Mailleret.
- PhD in progress: A. Yabo. “Control and optimal control of bacterial growth”, since October 2018, Université Côte d’Azur. Supervisors J.-L. Gouzé and J.-B. Caillau (team McTao).
- PhD in progress: A. Dos Reis de Souza. “Estimation and Control Methods for Microbial Communities”, since October 2018, Université de Lille. Supervisors: J.-L. Gouzé and D. Efimov (team Valse, Inria Lille).
- PhD in progress: B. Assis Pessi. “Modelling and Control of outdoor microalgal processes”, since November 2019, Université Côte d’Azur. Supervisors: O. Bernard and L. Giraldi (team McTao).
- PhD in progress: C. Djuikem. “Modelling and control of perennial plant phytopathogens”, Université Côte d’Azur, since October 2019. Supervisors: F. Grognard, S. Touzeau, S. Bowong (Univ. Douala).
- PhD in progress: M. Péré. “’Modeling cancer drug response heterogeneity using experimental tumor single-cell dynamics and transcriptomics’, since October 2019, Université Côte d’Azur. Supervisors: M. Chaves and J. Roux (IRCAN, Nice).
- PhD in progress: P. Clin, "Immunity and Mathematical Modelling to ”Unify” Epidemiology", since January 2020, Université de Rennes 1. Supervisors: F. Hamelin, L. Mailleret, D. Andrivon.
- PhD in progress: M. Cointe. “Mieux prédire la propagation spatiale de groupes de trichogrammes pour améliorer le biocontrôle : de l’écologie du mouvement à la dispersion dans les cultures”, Université Côte d’Azur, since 2020. V. Calcagno, L. Mailleret.

11.2.3 Master thesis and internships

- L3: Jessica Gourdon, "Lockdown optimization for Covid-19 control", Polytech Nice Sophia, Université Côte d’Azur, MAM3, supervisors: F. Grognard and L. Mailleret
- M2: J. Nardini, “Supplémentation et lutte biologique : Booster le biocontrôle des acariens prédateurs”. Aix-Marseille Université. Supervisors : Louise van Oudenhove (ISA) L. Mailleret.
- M1: F. Ghesthem, “Caractérisation et modélisation de stratégies de gestion durable des populations de nématodes à galles Meloidogyne incognita”. Institut Agro. Supervisors : V. Calcagno (ISA) L. Mailleret, S. Touzeau.
- M2: L. Plaza Alvarez, “Microalgae growth limited by light, nitrogen, and phosphorus”. Universidad Técnica Federico Santa María, Valparaiso. Supervisors: C. Martinez von Dossow and O. Bernard.
- Other: A. Yabo supervised the short internship (projet) of 4 students from EPU MAM4, concerning optimal control of a biological model of growth.
- Other: O. Bernard supervised a project involving 4 students from CentraleSupelec (first year of engineering school), 4 months, to design a system for microalgae growing under biofilm forms.
- Other: L. Giraldi, F. Grognard and L. Mailleret supervised a project involving 3 students from Polytech Nice Sophia, Université Côte d’Azur, MAM4 to design and fit an epidemiological model on Covid-19 data.

11.2.4 Juries

- O. Bernard was referee for the jury of the PhD thesis of Angela La, “Process development for symbiotic culture of *Saccharomyces cerevisiae* and *Chlorella vulgaris* for in situ CO_2 mitigation”. University Paris-Saclay (May, 22nd 2019).
- M. Chaves was in the PhD jurys of: Daniel Figueiredo (as examiner; February, Univ. Aveiro, Portugal), Ousmane Diop (as president of the jury; December, Univ. Paris-Saclay), Eleni Firippi (as advisor; December, Université Côte d’Azur), Yacine El Alaoui-Faris (as president of the jury; December, Université Côte d’Azur).
- M. Chaves was in the Master jury of Mariana Mota as main examiner (January 2021, Instituto Superior Técnico, Portugal)
- M. Chaves is in the PhD committees of Agustin Yabo (STIC, Université Côte d’Azur) and Sandra Kovachka (BoostUrCareer program, Université Côte d’Azur)
- J.-L. Gouzé was reviewer of the HDR of Radhouene Fekih Salem, July, University of Tunis El Manar, Tunisia, and a member of the jury for the PhD thesis of José Plaza, January, ULB Belgique, of Aïda Feddaoui-Papin, May, University of Toulon, of Nelson de Figueiredo Barroso, December, University of Lille, of Lucie Chambon, September, Université Côte d’Azur.
- L. Mailleret was in the PhD Jury of Samuel Nilusmas (as advisor). Université Côte d’Azur, Décembre 2020.
- J.-L. Gouzé is in the PhD committees of P. Jacquet (Univ. Grenoble) and A. Pavlou (Univ. Grenoble).
- F. Grognard and S. Touzeau are in the thesis committee of Pauline Clin (Universoité de Rennes 1) on "Immunity and Mathematical Modelling to ”Unify” Epidemiology".
- F. Grognard is in the thesis committee of Méline Saubin (Université de Lorraine) on "Effets de la démographie sur la structure de populations dans le cadre d’une maladie émergente".
- S. Touzeau was a member of selection boards for the recruitment of junior research scientists at INRAE in applied mathematics, computer science, economics and social sciences (7 positions).

11.2.5 Internal or external Inria responsibilities

- Eleni Firippi was part of the organizing committee of the "PhD Seminars," dedicated to meetings and presentations among the doctoral students at Inria Sophia Antipolis. She helped organize MOMI2020 "Le Monde des Mathematiques Industrielles," a workshop bringing together young researchers in mathematics and industrial applications.

12 Scientific production

12.1 Major publications

[1] N. Bajeux, F. Grognard and L. Mailleret. ‘Augmentative biocontrol when natural enemies are subject to Allee effects’. In: *Journal of Mathematical Biology* 74.7 (2017), pp. 1561–1587. DOI: 10.1007/s00285-016-1063-8. URL: https://hal.archives-ouvertes.fr/hal-01402250.

[2] C. Baroukh, R. Muñoz-Tamayo, J.-P. Steyer and O. Bernard. ‘DRUM: A New Framework for Metabolic Modeling under Non-Balanced Growth. Application to the Carbon Metabolism of Unicellular Microalgae’. In: *PLoS ONE* 9.8 (Aug. 2014). e104499. DOI: 10.1371/journal.pone.0104499. URL: https://hal.inria.fr/hal-01097327.

[3] O. Bernard. ‘Hurdles and challenges for modelling and control of microalgae for CO2 mitigation and biofuel production’. In: *Journal of Process Control* 21.10 (2011), pp. 1378–1389. DOI: 10.1016/j.jprocont.2011.07.012. URL: http://hal.inria.fr/hal-00848385.

[4] V. Calcagno, F. Grognard, F. M. Hamelin, E. Wajnberg and L. Mailleret. 'The functional response predicts the effect of resource distribution on the optimal movement rate of consumers'. In: *Ecology Letters* 17.12 (Dec. 2014), pp. 1570–1579. DOI: 10.1111/ele.12379. URL: https://hal.inria.fr/hal-01084299.

[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 (Mar. 2016). e1004802. DOI: 10.1371/journal.pcbi.1004802. URL: https://hal.inria.fr/hal-01332394.

[6] N. Go, C. Bidot, C. Belloc and S. Touzeau. 'Integrative Model of the Immune Response to a Pulmonary Macrophage Infection: What Determines the Infection Duration?' In: *PLoS ONE* 9.9 (Sept. 2014). e107818. DOI: 10.1371/journal.pone.0107818. URL: https://hal.inria.fr/hal-01099937.

[7] F. Mairet, O. Bernard, P. Masci, T. Lacour and A. Sciandra. 'Modelling neutral lipid production by the microalga \textitIsochrysis affinis galbana under nitrogen limitation'. In: *Biores. Technol.* 102 (2011), pp. 142–149. URL: http://dx.doi.org/10.1016/j.biortech.2010.06.138.

[8] M. Moisan, O. Bernard and J.-L. Gouzé. 'Near optimal interval observers bundle for uncertain bioreactors'. In: *Automatica* 45.1 (Jan. 2009), pp. 291–295. DOI: 10.1016/j.automatica.2008.07.006. URL: https://hal.archives-ouvertes.fr/hal-01109396.

[9] C. Poignard, M. Chaves and J.-L. Gouzé. 'Periodic Oscillations for Non Monotonic Smooth Negative Feedback Circuits'. In: *SIAM Journal on Applied Dynamical Systems* 15.1 (2016), pp. 257–286. DOI: 10.1137/15M1033368. URL: https://hal.archives-ouvertes.fr/hal-01242157.

[10] L. Tournier and M. Chaves. 'Interconnection of asynchronous Boolean networks, asymptotic and transient dynamics'. In: *Automatica* 49.4 (2013), pp. 884–893. DOI: 10.1016/j.automatica.2013.01.015,. URL: http://hal.inria.fr/hal-00848450.

12.2 Publications of the year

International journals

[11] S. Almeida, M. Chaves and F. Delaunay. 'Control of synchronization ratios in clock/cell cycle coupling by growth factors and glucocorticoids'. In: *Royal Society Open Science* 7.2 (2020), p. 192054. DOI: 10.1098/rsos.192054. URL: https://hal.sorbonne-universite.fr/hal-02505080.

[12] S. Almeida, M. Chaves and F. Delaunay. 'Transcription-based circadian mechanism controls the duration of molecular clock states in response to signaling inputs'. In: *Journal of Theoretical Biology* 484 (Jan. 2020), p. 110015. DOI: 10.1016/j.jtbi.2019.110015. URL: https://hal.archives-ouvertes.fr/hal-02299359.

[13] C. B. Cakpo, G. Vercambre, V. Baldazzi, L. Roch, Z. Dai, P. Valsesia, M.-M. Memah, S. Colombie, A. Moing, Y. Gibon and M. Génard. 'Model-assisted comparison of sugar accumulation patterns in ten fleshy fruits highlights differences between herbaceous and woody species'. In: *Annals of Botany* 126.3 (2020), pp. 455–470. DOI: 10.1093/aob/mcaa082. URL: https://hal.inrae.fr/hal-02749663.

[14] V. Calcagno, F. M. Hamelin, L. Mailleret and F. Grognard. 'How optimal foragers should respond to habitat changes: on the consequences of habitat conversion'. In: *Theoretical Ecology* 13.2 (June 2020), pp. 165–175. DOI: 10.1007/s12080-019-00437-7. URL: https://hal.inria.fr/hal-02392973.

[15] F. Casagli, S. Rossi, J.-P. Steyer, O. Bernard and E. Ficara. 'Balancing microalgae and nitrifiers for wastewater treatment: can inorganic carbon limitation cause an environmental threat?' In: *Environmental Science and Technology* (17th Feb. 2021). URL: https://hal.inria.fr/hal-03148290.

[16] F. Casagli, G. Zuccaro, O. Bernard, J.-P. Steyer and E. Ficara. 'ALBA: A comprehensive growth model to optimize algae-bacteria wastewater treatment in raceway ponds'. In: *Water Research* 190 (Feb. 2021), p. 116734. DOI: 10.1016/j.watres.2020.116734. URL: https://hal.archives-ouvertes.fr/hal-03130712.

[17] F. Casagli, G. Zuccaro, O. Bernard, J.-P. Steyer and E. Ficara. 'ALBA: a comprehensive growth model to optimize algae-bacteria wastewater treatment in raceway ponds'. In: *Water Research* 190 (Feb. 2021), p. 116734. DOI: 10.1016/j.watres.2020.116734. URL: https://hal.inria.fr/hal-03142211.

[18] L. Chambon, I. Belgacem and J.-L. Gouzé. 'Qualitative control of undesired oscillations in a genetic negative feedback loop with uncertain measurements'. In: *Automatica* 112 (Feb. 2020), p. 108642. DOI: 10.1016/j.automatica.2019.108642. URL: https://hal.inria.fr/hal-02418421.

[19] P. Clin, F. Grognard, L. Mailleret, F. Val, D. Andrivon and F. M. Hamelin. 'Taking advantage of pathogen diversity and immune priming to minimize disease prevalence in host mixtures: a model'. In: *Phytopathology* (9th Dec. 2020). DOI: 10.1094/PHYTO-09-20-0429-R. URL: https://hal.archives-ouvertes.fr/hal-03124229.

[20] W. Djema, O. Bernard and L. Giraldi. 'Separating Two Species of Microalgae in Photobioreactors in Minimal Time'. In: *Journal of Process Control* 87 (Mar. 2020), pp. 120–129. DOI: 10.1016/j.jprocont.2020.01.003. URL: https://hal.inria.fr/hal-03148717.

[21] A. Dos Reis De Souza, D. Efimov, A. Polyakov and J.-L. Gouzé. 'Robust Stabilization of Competing Species in the Chemostat'. In: *Journal of Process Control* 87 (2020), pp. 138–146. DOI: 10.1016/j.jprocont.2020.01.010. URL: https://hal.inria.fr/hal-02462162.

[22] A. Dos Reis De Souza, J.-L. Gouzé, D. Efimov and A. Polyakov. 'Robust Adaptive Estimation in the Competitive Chemostat'. In: *Computers & Chemical Engineering* 142 (Nov. 2020), p. 107030. DOI: 10.1016/j.compchemeng.2020.107030. URL: https://hal.inria.fr/hal-02909395.

[23] P. Ezanno, M. Andraud, G. Beaunée, T. Hoch, S. Krebs, A. Rault, S. Touzeau, E. Vergu and S. Widgren. 'How mechanistic modelling supports decision making for the control of enzootic infectious diseases'. In: *Epidemics* 32 (Sept. 2020), p. 100398. DOI: 10.1016/j.epidem.2020.100398. URL: https://hal.inrae.fr/hal-02895529.

[24] S. J. Figueiredo Almeida, M. Chaves and F. Delaunay. 'Cell cycle period control through modulation of clock inputs'. In: *Journal of Bioinformatics and Computational Biology* 18.03 (June 2020), p. 2040006. DOI: 10.1142/S0219720020400065. URL: https://hal.inria.fr/hal-03105546.

[25] E. Firippi and M. Chaves. 'Topology-induced dynamics in a network of synthetic oscillators with piecewise affine approximation'. In: *Chaos: An Interdisciplinary Journal of Nonlinear Science* 30.11 (Nov. 2020), p. 113128. DOI: 10.1063/5.0020670. URL: https://hal.inria.fr/hal-03105513.

[26] A. Gabriel Yabo, J.-B. Caillau and J.-L. Gouzé. 'Optimal bacterial resource allocation: metabolite production in continuous bioreactors'. In: *Mathematical Biosciences and Engineering* 17.6 (2020), pp. 7074–7100. DOI: 10.3934/mbe.2020364. URL: https://hal.inria.fr/hal-02974185.

[27] M. Gachelin, M. Boutoute, G. Carrier, A. Talec, E. Pruvost, F. Guihéneuf, O. Bernard and A. Sciandra. 'Enhancing PUFA-rich polar lipids in Tisochrysis lutea using adaptive laboratory evolution (ALE) with oscillating thermal stress'. In: *Applied Microbiology and Biotechnology* (17th Nov. 2020). DOI: 10.1007/s00253-020-11000-4. URL: https://hal.archives-ouvertes.fr/hal-03022411.

[28] F. Jean, S. Maslovskaya and I. Zelenko. 'On Weyl's type theorems and genericity of projective rigidity in sub-Riemannian Geometry'. In: *Geometriae Dedicata* (2020). URL: https://hal-ensta-paris.archives-ouvertes.fr//hal-02453709.

[29] H. Kanso, B. Quilot-Turion, M.-M. Memah, O. Bernard, J.-L. Gouzé and V. Baldazzi. 'Reducing a model of sugar metabolism in peach to catch different patterns among genotypes'. In: *Mathematical Biosciences* 321 (Mar. 2020), p. 108321. DOI: 10.1016/j.mbs.2020.108321. URL: https://hal.inrae.fr/hal-02922359.

[30] 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* (2021). URL: https://hal.inria.fr/hal-03094908.

[31] C. Martinez, F. Mairet and O. Bernard. 'Dynamics of the periodically forced light-limited Droop model'. In: *Journal of Differential Equations* (1st Apr. 2020). DOI: 10.1016/j.jde.2020.03.020. URL: https://hal.archives-ouvertes.fr/hal-02422838.

[32] C. Martinez, F. Mairet, L. Meier, D. Jeison and A. Avila. 'Modeling and analysis of an Absorption Column Connected to a Microalgae Culture'. In: *SIAM Journal on Applied Mathematics* (2020). URL: https://hal.archives-ouvertes.fr/hal-02432325.

[33] C. Martínez and J.-L. Gouzé. 'Global dynamics of the chemostat with overflow metabolism'. In: *Journal of Mathematical Biology* 82.3 (3rd Feb. 2021). DOI: 10.1007/s00285-021-01566-6. URL: https://hal.inria.fr/hal-03130387.

[34] 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. URL: https://hal.sorbonne-universite.fr/hal-02640446.

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