RESEARCH CENTRE

Sophia Antipolis - Méditerranée

IN PARTNERSHIP WITH:

CNRS, Sorbonne Université (UPMC), INRAE

2021

ACTIVITY REPORT

Project-Team

BIOCORE

Biological control of artificial ecosystems

IN COLLABORATION WITH: Laboratoire d'océanographie de Villefranche (LOV)

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life Sciences

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Project-Team BIOCORE

Creation of the Project-Team: 2011 January 01

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Computer sciences and digital sciences

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1 Team members, visitors, external collaborators

Research Scientists

- Jean-Luc Gouzé [Team leader, Inria, Senior Researcher, HDR]
- Valentina Baldazzi [Institut national de recherche pour l'agriculture, l'alimentation et l'environnement, Researcher, HDR]
- Olivier Bernard [Inria, Senior Researcher, Team Vice-Leader, HDR]
- Pierre Bernhard [Inria, Senior Researcher, Emeritus]
- Madalena Chaves [Inria, Senior Researcher, HDR]
- Walid Djema [Inria, ISFP, from Oct. 2021]
- Frédéric Grognard [Inria, Researcher]
- Ludovic Mailleret [Institut national de recherche pour l'agriculture, l'alimentation et l'environnement, Senior Researcher, HDR]
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Post-Doctoral Fellows

- Juan Carlos Arceo Luzanilla [Inria, from May 2021]
- Nicolas Augier [Inria, until Jun 2021]
- Francesca Casagli [Inria, from Apr 2021]

PhD Students

- Bruno Assis Pessi [Univ Côte d'Azur]
- Odile Burckard [Inria, from Oct 2021]
- Clotilde Djuikem [Inria]
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- Yan Gao [Centrale-Supélec, until Aug 2021]
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- Liudi Lu [Univ Paris-Sud, until Jul 2021]
- Diego Penaranda Sandoval [Inria]
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Technical Staff

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Interns and Apprentices

- Odile Burckard [Inria, from Mar 2021 until Aug 2021]
- Jan Luka Fatras [Institut national de recherche pour l'agriculture, l'alimentation et l'environnement, from Jun 2021 until Jul 2021]
- Joel Ignacio Fierro Ulloa [Inria, from Jun 2021 until Aug 2021]
- Azouaou Ouyoucef [Inria, from Jun 2021 until Aug 2021]
- Nan Pan [Inria, from Jun 2021 until Sep 2021]
- Sacha Psalmon [Inria, from Jun 2021 until Sep 2021]
- Filipe Serra Coutinho [Inria, from Jun 2021 until Aug 2021]

Administrative Assistants

- Florence Beautier [Inria, from Jun 2021 until Dec 2021]
- Marie-Line Meirinho [Inria, until Jun 2021]

Visiting Scientist

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External Collaborators

- Hubert Bonnefond [Start-up Inalve, Nice]
- Frédéric Hamelin [Agrocampus Ouest, Rennes]
- Francis Mairet [Ifremer, HDR]
- Jérémie Roux [CNRS, Nice]
- Jacques Alexandre Sepulchre [Univ de Nice - Sophia Antipolis, HDR]

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, BIOSS (Modélisation symbolique des systèmes biologiques)
- Participation to national programmes: ANR projects PhotoBioFilmExplorer, Ctrl-AB, 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 (e.g., 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 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.

Some Biocore members did presentations and participated in events on sustainable development (see Section 11.3)

6 Highlights of the year

- Cell-to-cell variability in response to anticancer drugs is one of the major factors impairing drug efficacy. We developed an approach combining a mathematical model of apoptosis with single-cell response data that enables the identification of fate-determining reactions that drive the population response heterogeneity, providing regulatory targets to curb the cell dynamics of drug resistance. This work was published in the journal *Scientific Reports* [16].
- Marine viruses interact with microbial hosts in dynamic environments shaped by variation in abiotic factors, including temperature. Our model shows the negative consequences of high temperatures on infection and suggests a temperature-dependent threshold between viral production and degradation. Modeling long-term dynamics in environments with different average temperatures revealed the potential for long-term host-virus coexistence, epidemic free or habitat loss states. Temperature-dependent changes in the infectivity of virus particles may lead to shifts in virus-host habitats in the future warmer oceans, analogous to projected changes in the habitats of macro-, microorganisms and pathogens [18].
- Major steps have been achieved in the development of control methods for pests and pathogens of tropical crops, in the framework of the EPITAG associate team: optimized fallow deployment for the control of the nematode *Radopholus Similis*, a plantain root pest [35, 36], optimal control for the release of entompathogenic fungi to control the Coffee Berry Borer [24], and deployment of *Lecanicilium Lecanii* to limit the spread of Coffee Leaf Rust [20].

6.1 Awards

- Marielle Péré obtained a Royal Society of Edinburgh Saltire Early Career Fellowship (RSE Saltire) to visit Diego Oyarzún and his team at the University of Edinburgh, for six months. She will be developing machine learning algorithms for cell-fate prediction.
- Israël Tankam Chedjou was the 2021 recipient of the Ovide Arino Outreach Award (OAOA), a joint ESMTB and SFBT prize (the European and French societies for mathematical and theoretical biology). Israël was enrolled in the EPITAG associate team and completed his PhD thesis on the modelling, analysis and control of plantain or banana plant-parasitic nematodes, supervised by F. Grognard, L. Mailleret, and S Touzeau from Biocore and J.-J. Tewa from Univ. Yaoundé I, Cameroon.

7 New software and platforms

Let us describe new/updated software.

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, CO2 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.

Contact: Olivier Bernard

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.

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/

Contact: Olivier Bernard

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 [44] and of banana and plantain burrowing nematodes [36].

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 [20, 48] nematodes [36], and pests [24].

8.1.2 Estimation and control

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

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 fallow periods between plantain cropping seasons [35, 36]. 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 [24] and Coffee Leaf Rust [44] using the BOCOP software, which is developed by Inria team COMMANDS.

8.2 Metabolic and genomic models

Participants: Jean-Luc Gouzé, Olivier Bernard, Valentina Baldazzi, 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

Gene expression and metabolism are tightly intertwined. The study of the genetic control of metabolism was a central topic of V. Baldazzi's HdR thesis [53], as a key element of organism adaptation to environmental changes and phenotypic diversity.

Genetic diversity in sugar metabolism has been studied in peach fruit, taking advantage of the simplified model developed by Kanso et al. [88]. Thanks to the reduced parameter space and its lower complexity, the model has been calibrated over a population of 106 peach genotypes, using different calibration strategies. Results have been used to identify QTLs, providing information on the genetic control of sugar metabolism-in peach fruit. Two articles are currently under preparation on this topic.

8.2.2 Resource allocation

Modeling cell growth and resource allocation.

With F. Mairet (Ifremer Nantes) and H. de Jong (IBIS Grenoble), we studied the influence of temperature on microbial growth laws, with optimization tools. At extreme temperatures, resources are diverted away from growth to chaperone-mediated stress responses. [29].

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 [84], 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*. We used the model to explore the variability of rate-yield phenotypes obtained by change in proteome allocation strategy. We found that the predicted rates and yields in different growth conditions correspond very well with the variability of rate-yield phenotypes observed across different *E. coli* WT and mutant strains. Moreover, 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 [70, 37, 45, 56], (ANR project Maximic, PhD thesis of A. Yabo). The precise mathematical analysis of the optimal behavior (turnpike property) is precisely described [62].

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 [95]. We studied mathematical models of overflow metabolism (fermentative growth) in such bacteria [30]. We applied the results to the mathematical study of the behaviour of the consortium of two strains, and obtained optimisation results for the optimal production or yield [66].

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, 54]. It was the subject of Alex Reis PhD thesis.

8.2.4 Synchronization and control using hybrid models

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

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 [73]. 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. This work has been accepted at the journal IEEE Transactions on Automatic Control. In another example, we study the diffusive coupling of a network of identical bistable switch piecewise-affine systems and propose a control strategy which synchronizes every bistable switch sub-system of the network towards the same steady state [39].

Weak synchronization and convergence in coupled genetic regulatory networks We consider a general model of genetic networks and examine two forms of interconnection, either homogeneous or heterogeneous coupling, corresponding to coupling functions that are either equal or different from those governing the individual dynamics. In the case of individual subsystems having unique but different steady states, we prove that the homogeneous coupled system has a unique globally asymptotically stable steady state. Moreover, in the case of large coupling strength, we show that under suitable assumptions the network achieves weak synchronization in the sense that the individual steady states become arbitrarily close [58]. In the heterogeneous case, we prove a similar weak synchronization result in the case of large coupling strength. We apply the results to the synchronization of damped oscillators and to the control of multistable systems. This work is under revision at the International J. Robust and nonlinear Control.

Time-optimal control of piecewise affine bistable systems

In [59] 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 [31].

8.2.6 Modeling, analysis, and control for synthetic biology

Participants: Madalena Chaves, Hidde de Jong *(IBIS)*.

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 [52], 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, Odile Burkard, Marielle Péré, Jérémie Roux, Jeremy Gonin, Filipe Coutinho.

8.3.1 Analysis and coupling of circadian oscillators

Cycle dynamics and synchronization in a coupled network mammalian circadian clocks The intercellular interactions between peripheral circadian clocks, located in tissues and organs other than the suprachiasmatic nuclei of the hypothalamus, are still very poorly understood. To investigate this question, we performed a theoretical and computational study of the coupling between two or more clocks, using a reduced model of the mammalian circadian clock previously developed in [72]. Based on a piecewise linearization of the dynamics of the mutual CLOCK:BMAL1 / PER:CRY inactivation term, we proposed a segmentation of the circadian cycle into six stages, to help analyse different types of synchronization between two clocks, including single stage duration, total period, and maximal amplitudes. Our model reproduces some recent experimental results on the effects of different regimes of fasting/feeding alternance in liver circadian clocks of mice. This work is in collaboration with F. Delaunay (ANR ICycle, UCA Synchro), it was part of the internship of Odile Burckard and is now being further developed in the context of her PhD thesis.

8.3.2 Modeling the apoptotic signaling pathway

Analysis of the regulatory dynamics leading to drug response heterogeneity in single-cells 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. Using our death receptor apoptosis model [85], we developed an approach utilizing single-cell response data to identify regulatory reactions driving population heterogeneity in drug response. Selected reactions sets were augmented to incorporate a positive feedback mechanism that leads to the separation of the opposing response phenotypes. This positive feedback from caspase-8 is able to encapsulate high levels of heterogeneity by introducing a response delay and amplifying the initial differences arising from natural protein expression variability [16].

TRAIL-induced apoptosis signaling models and cell fate predictors To analyze the considerable amount of data from fate-seq[96], a new workflow that analyses single-cell signaling, and use them for an early prediction of cell fate in new experiments, we proposed an ODE model of the molecular pathways involved in cell death triggered by TRAIL calibrated on single-cell time-trajectories of a FRET reporter measuring apoptosis signaling dynamics in clonal HeLa cells. We then developed a method to classify the dynamical features by coupling model analysis and solutions with statistic tools and principal process analysis. With this method we identified specific time-intervals for several events leading to cell decision and a first commitment stage just after TRAIL binding associated to an additional regulation feedback for the sensitive cells. Finally, based on these results, we constructed three predictors for cell fate and the sensitive cell death time, validate their accuracy on several data sets and discuss their advantages and drawbacks. This work is part of the PhD thesis of Marielle Péré, which she presented at the CMSB 2021 conference [49]. It work in collaboration with J. Roux and his lab.

Data analysis through clustering and dimension reduction algorithms The data generated by fate-seq[96] associates the transcriptomic state of a cell to its predicted fate, based on cell response dynamics. To further analyse these data, we applied different algorithms for data clustering and dimension reduction, such as UMAP (Uniform Manifold Approximation and Projection) or Destiny (diffusion maps for large-scale single-cell data in the R language). The main goal was to identify clusters and special patterns in the data that indicate a separation between different cell phenotypes and relate the phenotypes to the transcriptomic state of the cell. This work was mainly performed by Jeremy Gonin, under the supervision of J. Roux and his lab.

New results: Fields of application

8.4 Bioenergy

8.4.1 Modeling microalgae production

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

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 [25].

This experimental platform was used to control the long term stress applied to a population of microalgae using optimal control strategies[80, 78]. This Darwinian selection procedure generated several new strains more resistant to oxidative stresses after several months in the so called selectiostats [25].

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. The benefit of a greenhouse was also assessed with various species associated with different thermal niches [34]

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 [23].

A review on the conditions for the production of lipids following a nutrient stress for 95 species of microalgae was finally written [32].

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 [28].

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 [41]. 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 [43, 61]. A strategy to optimally mix the algae was derived. It was finally combined with the design of a non flat topography [41].

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 [101] 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.

We studied the Han model for different alternation of high and low light intensities, with various durations. We showed that there are specific light levels than can enhance the biofilm growth. The experimental validation of this model, together with the extrapolation of productivities at larger scale is the topic of the PhD thesis of Yan GAO at CentraleSupelec (directed by F. Lopes and O. Bernard).

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 [93] 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. We studied a broad range of species and their response to temperature. It turns out that the optimal temperature, the minimal and the optimal temperature for growth ate strongly correlated. Relationship between these cardinal temperatures and key parameters from the environment (sea surface temperature, solar flux, ...).

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 [77]. 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 [77].

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 [18]. 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 [81]. 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 [82, 79, 83]. In both cases, the optimal control derived from the Pontryagin maximum principle also exhibits a turnpike behavior [19]. 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 [75]. 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* [25].

8.4.3 Modeling 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 [97] 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 [15]. 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 N_2O emission. A control strategy regulating alkalinity turns out to be necessary to enhance the performance and avoid dammageable emissions [14].

A work was started to simplify these models and enhance their calibration by considering artificial neural networks, which are integrated in a way that the full model respects some key constrains (positivity, boundness, ...) [51].

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.

We have proposed several models to account for the biodiversity in the microalgal pond and for the interaction between the various species. 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 [99].

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 [98].

This work is the result of a collaboration with Arnaud Helias of INRAE-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, Clotilde Djuikem.

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, we published a paper in the leading journal on biological control, describing promising experimental results on the combined use of food and artificial habitats supplementations to enhance augmentative biological control with predatory mites [22]. This work has been performed in collaboration with Louise van Oudenhove (ISA). We also contributed to a study on the links between the existence of positive density-dependence (Allee effects) in the intrinsic dynamics of a population, impaired demographic performance and chances of extinction in parasitoid wasps used in biological control [69]. This study was performed with Elodie Vercken (ISA) and reviewed through the Peer Community In (`https://peercommunityin.org`) recommandation process.

Since last year, our research in this context expands to the modeling and optimization of introduction strategies in the context of the Sterile Insect Technique (SIT). This research is part of the Ecophyto project 'CeraTIS Corse', the first SIT pilot project in France focused on the control of the mediterranean fruit fly *Ceratitis capitata*, and of the upcoming ANR project Suzukiis:me, on the control of the fruit fly *Drosophila suzukii*.

Spatial population dynamics of biological control agents.

We have been involved for several years in a mixed modeling-experimental approach to explore the spatio-temporal dynamics of populations, with special interest to micro-wasp parasitoids [100, 87]. 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 [76]. We also studied the influence of landscape connectivity on the evolution of density dependence in dispersal, experimentally evidencing that evolution during range expansions may lead pushed expansions to become pulled [63]. Connected research has been performed on the influence of Allee effects and density dependence in dispersal on range expansion, extending the concept of range pinning in Ecology and pointing out its interaction with demographic stochasticity [33]. These works have been performed in collaboration with Elodie Vercken (ISA) and partly with Vincent Calcagno (ISA), and principally published through the Peer Community In (`https://peercommunityin.org`) recommandation process.

Concurrently, we are exploring the correlation between biological control agents movement characteristics at different scales, from laboratory experimental characterization 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). In this context, interesting results have been published on the photo- an geo-tactic preferences of egg-parasitoids in the genus *Trichogramma* [13]. This research has been performed in collaboration with Vincent Calcagno (ISA).

Furthermore, we contributed to a study on the modeling and control of vectors of non-presistently transmitted plant diseases [38]. Special attention was given to the transient vs. resident properties of the disease vectors, with reference to the amplitude of their movement from plants to plants. The study of current agronomic (fertilization) or control (pesticide application) practices showed different and sometimes counter-intuitive influences of the practices on disease spread. This work was performed in collaboration with Daniele Bevacqua (UR PSH, INRAE Avignon) and Nik Cunniffe (Dep. of Plant Sciences, Cambridge), as a part of Marta Zaffaroni's PhD thesis.

Modeling 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 [24]. A PDE model taking the age of the berries and the preference of coffee berry borers for more mature berries was also developed [65] as well as an impulsive multi-seasonal model. This research pertains to Yves Fotso Fotso's PhD thesis through the EPITAG associate team.

8.6.2 Controlling plant pathogens

Participants: Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Clotilde Djuikem, Pierre Bernhard.

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 built a generic spatio-temporal epidemiological model representing 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 second code sprint took place in February 2021. It pointed out technical problems that had not been identified during the first code sprint and that should be tackled to produce the next code release. A new sprint was scheduled in autumn 2021 but had to be postponed.

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 [17]. This initial result has been extended to consider mixtures of different resistant strains and the possible presence of supervirulent pathogens; we have shown that, at equilibrium, pathogens that are present all have the same virulence complexity (number of resistant-breaking alleles) [47]. This was done in collaboration with Frédéric Hamelin (Agrocampus Ouest) in the framework of Pauline Clin's thesis that started in January 2020.

Other methods for the control of plant pathogens

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 [20]. 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 [44]. We are currently studying a multi-seasonal impulsive version of this model, with multiple biocontrol agent releases per year, as well as a stage-structured version.

A model was developed for the deployment of clean seeds as a way of eradicating crop diseases in developing countries. Static optimization was performed to maximize the long-term static payoff, as well as dynamic optimal control. Subsidies-threshold to ensure eradication were then obtained, as well the result that partial clean seed deployment is not efficient [26]. This work is done in collaboration with Frédéric Hamelin (Agrocampus Ouest).

8.6.3 Plant-nematode interactions

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

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 consider fallow deployments aimed at reducing the nematode population, followed by the plantation of a nursery-bought pest-free suckers. We 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 [35]. These results were extended to a situation where vitroplants are not planted every year, which reduces the costs, but also reduces the control efficiency [36] This research pertains to Israël Tankam Chedjou's PhD thesis [55], in the framework of the EPITAG associate team.

Based on our previous work, an ecophysiological model of plant growth has been coupled to a model of nematode population dynamics. Briefly, the plant is divided into shoots, source of carbon for the plant, and roots, source of water, that exchange and employ resources for growth. Nematodes are explicitly considered as feeding on plant resources, so that any change in the plant physiological status or plant composition will in turn affect pest growth and multiplication, and vice versa. The model is currently used to explore the dynamical behaviour of the system and to gain insight into the relative role of plant phenotypic traits (including physiology and architectural features), pest development and environmental factors in the progression of the infection.

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 assessing and reducing the 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 personalized pharmacokinetic models. A contract for cession of IP was signed with Exactcure, which hired our PhD Lucie Chambon.
- **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 Associate Teams in the framework of an Inria International Lab or in the framework of an Inria International Program

Blue Edge

Title: Artificial Intelligence and optimization for cleaner biotechnological processes

Duration: 2021 ->

Coordinator: David Jeison (david.jeison@pucv.cl)

Partners:

- Pontifical Catholic University of Valparaíso

Inria contact: Olivier Bernard

Summary: Recycling organic wastes and at the same time removing pollution, producing fertilizers and energy has become a central issue for reaching sustainable development. Fundamentally, the question is how to recycle nitrogen, carbon and phosphorus within an integrated process involving microorganisms and reduced flux of pollutants towards the natural environment. The associated artificial ecosystem are complex, non linear and their dynamics is unaccurately represented by models. Their control and optimization are therefore very challenging. Understanding and controlling such complex systems are the objective of the Blue Edge associate team. We will benefit from the developments in Artificial Intelligence, combining existing models with databases from monitoring campaigns to propose alternative models.

EPITAG

Title: Epidemiological Modelling and Control for Tropical Agriculture

Duration: 2020 ->

Coordinator: Samuel Bowong (sbowong@gmail.com)

Partners:

- Université de Douala

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. EPITAG members aim at studying the epidemiology and management of tropical crop diseases. They develop and analyse dynamical models describing plant-parasite interactions, in order to better understand, predict and control the evolution of pests and pathogens that affect major staple food and cash crops (e.g. plantain and banana plant-parasitic nematodes, coffee berry borers, coffee leaf rust, etc). To tackle these issues, they jointly supervise master and PhD students.

10.2 International research visitors

10.2.1 Visits to international teams

Research stays abroad Marielle Péré is visiting the laboratory of Diego Oyarzún at the University of Edinburgh, for six months, from 01/10/2021. She is developing machine learning algorithms for cell-fate prediction. See also Section 6.1.

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 microalgae 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. Project coordinated by O. Bernard.

- **ANR Ctrl-AB:** 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 and controlling this artificial ecosystem. Project coordinated by JL Gouzé.

- **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.

- **Ecophyto - SuzuKIISS:ME** "Gérer Drosophila SuzuKII grâce aux Insectes Super Stériles : Maturation et Efficacité" (2022-2025). This project covers the ground from the development of the operational capacity and release strategies to deploy Sterile Insect Techniques (SIT), to the socio-economic impact of SIT on the control of the fruit fly *Drosophila Suzukii.*

- **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" (2020-2021) 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 with Michèle Teboul and Franck Delaunay from Institut de Biologie de Valrose (UCA). A project at the Masters Environnés program at Université Côte d’Azur which includes funding for two internships and some equipement.

11 Dissemination

11.1 Promoting scientific activities

11.1.1 Scientific events: organisation

Member of the organizing committees

- M. Chaves was in the organizing committee of Dynamic Days Europe 2021, taking place at Université Côte d'Azur and online, on August 23-27.
- M. Chaves organized the Mini-Workshop: "Single-cell technologies, heterogeneity, and dynamics of cellular responses", sponsored by the Labex Signalife, on June 25 (online event).
- O. Bernard was the head of the academic scientific committee of the AlgaEurope conferences (the last one took place virtually in December 7st to 10st 2021).

11.1.2 Scientific events: selection

Reviewer

- All BIOCORE members have been reviewers for the major 2021 conferences in our field: CDC, ECC, IFAC Congress, FOSBE.

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 an Associated Editor of the Conference Editorial Board (CEB) of the IEEE Control Systems Society, since August 2020. She is also an Associated Editor for the new IEEE Open Access Journal on Control Systems.
- JL Gouzé is an Associated Editor of the journal Frontiers in Applied Mathematics and Statistics (Mathematical Biology).
- 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 field: Automatica, IEEE Transactions on Automatic Control, Journal of Mathematical Biology, Mathematical Biosciences, Algal Research, New Phytologist,...

11.1.4 Invited talks

- M. Chaves was an invited speaker at the Symposium "Spatio-temporal encoding and decoding in cell signaling"at the Multi-Organization Thematic Institute Cell Biology, Development & Evolution (ITMO - BCDE), on March 18th (online). She was also an invited speaker at the UCancer Symposium "Multidisciplinary approaches in Cancer Research", on 25-26 October 2021 at Sophia Antipolis. She talked on a feedback loop mechanism to explain heterogeneity in cell response to cancer drugs.
- O. Bernard was invited to give a conference at the MASS Seminar of the University of Nottingham on "Modelling and control microalgae for bioenergy production" the 2nd of June 2021. He was also invited at the LJLL seminary, Sorbonne University "Modelling and control microalgae for strain performance improvement" the 7th of June 2021.

11.1.5 Scientific expertise

- M. Chaves is a member of the Education Board of the Master "Bioinformatique et Biologie Computationnelle", Université Côte d'Azur. She is also a member of the scientific committee of Labex Signalife (since 2020).
- 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 of the Federal Recherche Institut (IFR) Marine Resources (MARRES).

- 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).
- S. Touzeau participated in selection panels for INRAE junior research scientists and Inria secondment positions.

11.1.6 Research administration

- M. Chaves, F. Grognard, and L. Mailleret are members of the INRAE Commission Scientifique Spécialisée (CSS) for Mathématique, Informatique, Sciences et Technologies du numérique, Intelligence artificielle et Robotique (MISTI).
- 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.
- J.-L. Gouzé is in the Inria committee supervising the doctoral theses, and a member of the steering committee of Labex SIGNALIFE of Université Côte d'Azur, and of COREBIO PACA.
- 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).
- O. Bernard is a member of the ADT (Technological Development Actions) commission at Inria and of the local commission for sustainable development.
- V. Baldazzi ans S. Touzeau are elected members of the Institut Sophia Agrobiotech council.

11.2 Teaching - Supervision - Juries

11.2.1 Teaching

- Licence: F. Grognard (41.5h ETD) and L. Mailleret (30h ETD), "Equations différentielles ordinaires et systèmes dynamiques", L3, 1st year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Côte d'Azur, France.
- Licence: W. Djema (20h ETD); "Mathématiques pour Biologistes: Analyse et Modélisation", L1 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: O. Bernard (6h ETD), "Cultivation and use of Microalgae", Master Mares, Université Côte d'Azur, France.
- Master : W. Djema (20h ETD); "Traitement du Signal", M1 IM, Université Côte d'Azur, 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 (30h ETD) and W. Djema (15h ETD), "Elements of mathematical modelling", M1, MSc in Environmental Hazards and Risks Management, Université Côte d’Azur, France.

11.2.2 Supervision

- PhD: I. Tankam Chedjou. “Modelling, analysis and control of plantain plant-parasitic nematodes”, University of Yaoundé I, Cameroon, defended April 9. Supervisors: J.-J. Tewa (Univ. Yaoundé I), F. Grognard, L. Mailleret, S. Touzeau.
- PhD: A. Dos Reis de Souza. “Control and Estimation Methods for Microbial Communities ”, defended September 24, Université de Lille. Supervisors: J.-L. Gouzé and D. Efimov (team Valse, Inria Lille).
- PhD: F. Aubrée. “Modélisation de l’adaptation des populations aux fortes pressions anthropiques”, defended November 8, Université Côte d’Azur. Supervisors: V. Calcagno, T. Guillemaud, L. Mailleret.
- PhD: A. Yabo. “Optimal resource allocation in bacterial growth: theoretical study and applications to metabolite production”, defended December 9, Université Côte d’Azur. Supervisors J.-L. Gouzé and J.-B. Caillau (team McTao).
- 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: I. Fierro Ulloa. “Development and analysis of a digital twin for monitoring, control and optimization applications in microalgae: the Microalgae Model”, since March 2017, UCA. Supervisors: O. Bernard. Since 2021.
- PhD in progress: A. Gharib. “Robust control of microalgae processes accounting for future meteorology ”, since March 2017, UCA. Supervisors: O. Bernard and W. Djema. Since 2021.
- PhD in progress: B. Assis Pessi. “Modelling and Control of outdoor microalgal processes”, since November 2019, Université Côte d’Azur. Since 2019. 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, Univ. 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. Supervisors V. Calcagno, L. Mailleret.
- PhD in progress: O. Burckard. "Coupling, synchronization, and control of cellular oscillators through mathematical modeling and analysis", Université Côte d’Azur, since 2021. Supervisor: M. Chaves.
- PhD in progress: L. Lu. "Lagrangian approaches for the modelling and optimisation of hydrodynamic-photosynthesis coupling ", Sorbonne University, since 2019. Supervisor: J. Salomon and O. Bernard.
- PhD in progress: Y. Gao. "Effect of dynamical light pattern on biofilm development and structure", Saclay University, since 2018. Supervisor: F. Lopes and O. Bernard.

11.2.3 Master thesis and internships

- L3: F. Serra Coutinho, “Biological oscillators and their interaction with the cellular machinery”, University College London, supervised by M. Chaves.
- L3: J.-L. Fatras, "Optimisation de la distribution des jachères pour les plantations de bananes", Sorbonne Université, supervised by F. Grognard and S. Touzeau.
- M1: M. Courtois, "Modélisation de la dynamique des populations de *Ceratitis capitata* pour la mise en place de la technique de l’insecte stérile - Projet CeraTIS", Université de Tours, supervised by F. Grognard, L. Mailleret, S. Touzeau and L. van Oudenhove.
- M1: K. Rastello, "Mathematical model of *Ceratitis capitata* population dynamics in Corsica in a context of control with the Sterile Insect Technique", Université de Rennes 1, supervised by F. Grognard, L. Mailleret, S. Touzeau and L. van Oudenhove.
- M1: C. Soto, "Prise en compte de l’immunité chez les plantes dans le cadre du déploiement de plantes résistantes dans les agrosystèmes saisonniers", Université Côte d’Azur, supervised by F. Grognard and L. Mailleret.
- M1: A. Ouyoucef, "Contrôle d’un photobioréacteur en utilisant un automate programmable et ODIN+", Sorbonne Université, Automatique, Robotique et Systèmes Avancés, supervised by W. Djema and E. Pruvost (CNRS, Villefranche-sur-Mer).
- M1: S. Psalmon , B. Schall, “Modélisation et analyse numérique de l’allocation dynamique des ressources chez une bactérie”. Polytech Nice MAM4, supervised by A. Yabo, J.-B. Caillau, J.-L. Gouzé.
- M2: C. Bourgade, "Modeling the plant – *Meloidogyne* spp. system including the coupled physiology interactions", Université Rennes 1, supervised by V. Baldazzi ans S. Touzeau.
- M2: O. Burckard, ”Coupling and synchronization of circadian oscillators in peripheral organs: mathematical modeling and analysis”, INSA Rouen Normandie, supervised by M. Chaves.
- M2: Yob Ihadjadene "Modélisation de la croissance de Dunaliella salina cultivée en bassins de production" Sorbonne Université, supervised by A. Sciandra and O. Bernard.
- Other: C. Soto, "Coûts de fitness dfférenciés dans le cadre du déploiement de plantes résistantes dans les agrosystèmes saisonniers", Projet de Fin d’Étude - Polytech-Nice, supervised by F. Grognard and L. Mailleret.

11.2.4 Juries

- M. Chaves acted as President of the PhD jury of Agustin Yabo (December 2021).
- L. Mailleret acted as President of the PhD jury of Flora Aubree (November 2021).
- J.-L. Gouzé was a member of the jury for the PhD thesis of A. Yabo (UCA) and A. dos Reis de Souza (Univ. Lille).
- S. Touzeau was a member of the jury for the PhD thesis of Israel Tankam-Chedjou (Université de Yaoundé 1)
- M. Chaves is in the PhD committees of A. Yabo and Sandra Kovachka (Univ. Côte d’Azur).
- O. Bernard was referee of the PhD of Hicham OUAZAITE, March the 9th (Univ. Montpellier).
- O. Bernard was referee of the HDR of C. Aceves, Sept the 9th (Univ. Toulouse).
- J.-L. Gouzé is in the PhD committee of P. Jacquet (Univ. Grenoble) and A. Pavlou (Univ. Grenoble).
- F. Grognard and S. Touzeau are in the PhD committee of Pauline Clin (Université de Rennes 1).

- F. Grognard is in the PhD committee of Méline Saubin (Université de Lorraine).
- L. Mailleret is in the PhD committee of Clotilde Djuikem (Université Côte d'Azur).
- O. Bernard is in the PhD committee of S. Li (Université Parsi Saclay).

11.3 Popularization

11.3.1 Articles and contents

- P. Bernhard wrote a book chapter on the contributions of Augustin Cournot (1801-1877) to economic thinking [74].
- W. Djema elaborated a draft-agreement with the Metropole Nice Côte d'Azur, to produce a scientifc popularized report on "renewable energies and sustainable mobility" for the Smart City department of Nice-Metropole (in progress, 2022).

11.3.2 Interventions

- O. Bernard did an online "CLDD" talk entitled "Vaut-il mieux consommer le Cheddar produit en Angleterre ou celui qui vient par bateau de Nouvelle-Zélande ? " the 18th of May, 2021.
- P. Bernhard was invited to present several wide-audience talks on control theory and game theory, throughout the department: Gilette (September), Venanson (October), Estienne d'Orves Nice highschool (December), or Villeneuve-Loubet (December).
- C. Djuikem did a "Café'in" talk within Inria Sophia Antipolis entitled "Biocontrôle de la rouille orangée du caféier".
- W. Djema participated or was invited at several seminars, notably he attended a workshop on "smart and sustainable mobility", organized by "Le 5ème Elément" (organizer of the annual events "Sustainable Mobility" and "CleanTech Week" in France), that was held during the French Grand Prix (F1) at Le Castellet (06/2021).

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] N. Augier, U. Boscain and M. Sigalotti. 'Effective adiabatic control of a decoupled Hamiltonian obtained by rotating wave approximation'. In: *Automatica* 136 (2022). URL: https://hal.inria.fr/hal-02562363.

[12] P. Bernhard and M. Deschamps. 'Dynamic equilibrium with randomly arriving players'. In: *Dynamic Games and Applications* 11.2 (2021), pp. 242–269. DOI: 10.1007/s13235-020-00354-z. URL: https://hal.inria.fr/hal-03266042.

[13] V. Burte, G. Perez, F. Ayed, G. Groussier, L. Mailleret, L. van Oudenhove and V. Calcagno. 'Up and to the light: intra- and interspecific variability of photo- and geo-tactic oviposition preferences in genus Trichogramma'. In: *Peer Community Journal* 2 (2022), e3. DOI: 10.24072/pcjournal.78. URL: https://hal.inrae.fr/hal-03528651.

[14] 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* 55.6 (16th Mar. 2021), pp. 3940–3955. DOI: 10.1021/acs.est.0c05264. URL: https://hal.inrae.fr/hal-03219531.

[15] 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.

[16] M. Chaves, L. Gomes-Pereira and J. Roux. 'Two-level modeling approach to identify the regulatory dynamics capturing drug response heterogeneity in single-cells'. In: *Scientific Reports* 11.1 (Dec. 2021). DOI: 10.1038/s41598-021-99943-0. URL: https://hal.inria.fr/hal-03439255.

[17] 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* 111.7 (July 2021), pp. 1219–1227. DOI: 10.1094/PHYTO-09-20-0429-R. URL: https://hal.archives-ouvertes.fr/hal-03124229.

[18] D. Demory, J. Weitz, A.-C. Baudoux, S. Touzeau, N. Simon, S. Rabouille, A. Sciandra and O. Bernard. 'A thermal trade-off between viral production and degradation drives phytoplankton-virus population dynamics'. In: *Ecology Letters* 24.6 (2021), pp. 1133–1144. DOI: 10.1111/ele.13722. URL: https://hal.archives-ouvertes.fr/hal-03066279.

[19] W. Djema, L. Giraldi, S. Maslovskaya and O. Bernard. 'Turnpike features in optimal selection of species represented by quota models'. In: *Automatica* (2021). URL: https://hal.archives-ouvertes.fr/hal-03217983.

[20] C. Djuikem, F. Grognard, R. Tagne Wafo, S. Touzeau and S. Bowong. 'Modelling coffee leaf rust dynamics to control its spread'. In: *Mathematical Modelling of Natural Phenomena* 16 (2021), p. 26. DOI: 10.1051/mmnp/2021018. URL: https://hal.inria.fr/hal-03188365.

[21] A. Dos Reis De Souza, D. Efimov, A. Polyakov, J.-L. Gouzé and E. Cinquemani. 'State observation in microbial consortia: A case study on a synthetic producer-cleaner consortium'. In: *International Journal of Robust and Nonlinear Control* (13th Dec. 2021), pp. 1–12. DOI: 10.1002/rnc.5945. URL: https://hal.inria.fr/hal-03495889.

[22] L. Etienne, C. Bresch, L. van Oudenhove and L. Mailleret. 'Food and habitat supplementation promotes predatory mites and enhances pest control'. In: *Biological Control* 159 (Aug. 2021), p. 104604. DOI: 10.1016/j.biocontrol.2021.104604. URL: https://hal.inrae.fr/hal-03210867.

[23] A. Fanesi, M. Lavayssière, C. Breton, O. Bernard, R. Briandet and F. Lopes. 'Shear stress affects the architecture and cohesion of Chlorella vulgaris biofilms'. In: *Scientific Reports* 11.1 (2021). DOI: 10.1038/s41598-021-83523-3. URL: https://hal.archives-ouvertes.fr/hal-03193722.

[24] Y. Fotso Fotso, S. Touzeau, B. Tsanou, S. Bowong and F. Grognard. 'Modelling and optimal strategy to control coffee berry borer'. In: *Mathematical Methods in the Applied Sciences* 44.18 (2021), pp. 14569–14592. DOI: 10.1002/mma.7726. URL: https://hal.inria.fr/hal-03334090.

[25] 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* (2021). DOI: 10.1007/s00253-020-11000-4. URL: https://hal.archives-ouvertes.fr/hal-03022411.

[26] F. Hamelin, B. Bowen, P. Bernhard and V. A. Bokil. 'Optimal Control of Plant Disease Epidemics with Clean Seed Usage'. In: *Bulletin of Mathematical Biology* 83.5 (May 2021), p. 46. DOI: 10.1007/s11538-021-00872-w. URL: https://hal-agrocampus-ouest.archives-ouvertes.fr/hal-03200491.

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