RESEARCH CENTRE

**Inria Centre at Université Côte d'Azur**

**IN PARTNERSHIP WITH:**

**CNRS, INRAE, Sorbonne Université**

2023

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*


## Keywords

### Computer sciences and digital sciences

A1.5.1. – Systems of systems

A6. – Modeling, simulation and control

A6.1.1. – Continuous Modeling (PDE, ODE)

A6.1.3. – Discrete Modeling (multi-agent, people centered)

A6.1.4. – Multiscale modeling

A6.1.5. – Multiphysics modeling

A6.2.1. – Numerical analysis of PDE and ODE

A6.2.6. – Optimization

A6.4. – Automatic control

A6.4.1. – Deterministic control

A6.4.3. – Observability and Controlability

A6.4.4. – Stability and Stabilization

A6.4.6. – Optimal control

A8.1. – Discrete mathematics, combinatorics

A8.2. – Optimization

A8.7. – Graph theory

A8.11. – Game Theory

A9.2. – Machine learning

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B1.1.8. – Mathematical biology

B1.1.10. – Systems and synthetic biology

B2.4.1. – Pharmaco kinetics and dynamics

B3.1. – Sustainable development

B3.1.1. – Resource management

B3.4. – Risks

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B3.4.3. – Pollution

B3.5. – Agronomy

B3.6. – Ecology

B3.6.1. – Biodiversity

B4.3. – Renewable energy production

B4.3.1. – Biofuels

# 1 Team members, visitors, external collaborators

## Research Scientists

- Olivier Bernard [Team leader, INRIA, Senior Researcher, HDR]
- Valentina Baldazzi [INRAE, Senior Researcher, until Jun 2023, HDR]
- Pierre Bernhard [INRIA, Emeritus, until Jun 2023, HDR]
- Francesca Casagli [INRIA, Researcher]
- Madalena Chaves [INRIA, Senior Researcher, until Jun 2023, HDR]
- Walid Djema [INRIA, ISFP]
- Jean-Luc Gouzé [INRIA, Senior Researcher, until Jun 2023, HDR]
- Frédéric Grognard [INRIA, Researcher, until Jun 2023, HDR]
- Ludovic Mailleret [INRAE, Researcher, until Jun 2023, HDR]
- Jérémie Roux [CNRS, until Jun 2023]
- Antoine Sciandra [CNRS, Senior Researcher, HDR]
- Suzanne Touzeau [INRAE, Researcher, until Jun 2023]

## Faculty Members

- Bastien Polizzi [UNIV FRANCHE-COMTE, Associate Professor Delegation, until Feb 2023]
- Jacques Sepulchre [UNS, until Jun 2023, HDR]

## Post-Doctoral Fellows

- Juan Carlos Arceo Luzanilla [INRIA, Post-Doctoral Fellow, until Mar 2023]
- Giada Fiandaca [INRIA, Post-Doctoral Fellow, from Nov 2023]
- Charlotte Gaviard [Inria]
- Emna Krichen [INRIA, Post-Doctoral Fellow]

## PhD Students

- Bruno Assis Pessi [INRIA, until Feb 2023]
- Benjamin Bobel [INRIA, from Apr 2023 until Jun 2023]
- Odile Burckard [INRIA, until Jun 2023]
- Marine Courtois [INRAE, until Jun 2023]
- Clotilde Djuikem [UNIV COTE D'AZUR, until Jun 2023]
- Joel Ignacio Fierro Ulloa [INRIA]
- Yan Gao [CENTRALESUPELEC, until Mar 2023]
- Ali Gharib [INRIA]
- Diego Penaranda Sandoval [INRIA]
- Joseph Junior Penlap Tamagoua [INRIA, until Jun 2023]
- Marielle Pere [INRIA, until Apr 2023]
- Romain Ranini [INRIA]

## Technical Staff

- Hubert Bonnefond [INRIA, Engineer, from Sep 2023]
- Yan Gao [INRIA, Engineer, from Apr 2023 until Jul 2023]
- Marielle Pere [Inria Startup Studio, Engineer, from Jul 2023 until Jul 2023]
- Eric Pruvost [Sorbonne Université, Engineer]
- Amélie Talec [CNRS, Engineer]

## Interns and Apprentices

- Alice Guillet [INRIA, Intern, from Feb 2023 until Aug 2023]
- Javier Innerarity Imizcoz [INRIA, Intern, from Apr 2023 until Sep 2023]
- Annalisa Reali [INRIA, Intern, from Oct 2023]
- Oscar Rousseau [INRIA, Intern, from Aug 2023 until Sep 2023]
- Morgan Scalabrino [INRIA, Intern, from Jun 2023 until Aug 2023]
- Eliane Younes [INRIA, Intern, from Mar 2023 until Aug 2023]

## Administrative Assistant

- Maeva Jeannot [INRIA]

## Visiting Scientists

- Jineth Arango Oviedo [PUC - VALPARAISO, until Apr 2023]
- Jérôme Coville [INRAE, until Feb 2023]
- Elisabeth Gualda Alonso [UNIV ALMERIA, from Sep 2023]
- Aurelien Kambeu Youmbi [UNIV DSCHANG CAMEROU, from Feb 2023 until Apr 2023]
- Frank Kemayou Mangwa [UNIV DOUALA, from Feb 2023 until Apr 2023]
- David Morgado Pereira [CENTRALESUPELEC, from Nov 2023]
- Rebecca Nordio [University of Almeria, from Mar 2023 until May 2023]
- Gustavo Ribeiro da Silva [São Paulo State University/Universidade Estadual Paulista UNESP, from Apr 2023 until May 2023]
- Tehreem Syed [TU Dresden, School of Engineering, until Mar 2023]

## External Collaborators

- Samuel Bowong Tsakou [UNIV DOUALA]
- Francis Mairet [IFREMER, HDR]

## 2 Overall objectives

BIOCORE is a joint research team between Inria (Inria centre at Université Côte d'Azur), 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).
- $CO_2$ fixation by micro-algae, with the aim of capturing industrial $CO_2$ 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), INRAE (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, MICROCOSME, 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, InSync and Maximic, Plan Cancer Imodrez, UMT Fiorimed, and Labex SIGNALIFE.
- International collaborations: Université de Mons (Belgium), Politecnico de Milano (It), Imperial College (United Kingdom), Norwegian University of Science and Technology (Norway), Pontificia Universidad Católica de Valparaíso 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 (*e.g.*, 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 [78]. 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 (*e.g.*, 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 Environmental 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) [4].

## 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 benefits 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 [81], 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 to 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 are 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 capability to consume the organic pollutant. This approach, initiated in [83] 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 Section 2) 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 and hydrogen by microorganisms (with LOV and LBE).
- $CO_2$ fixation by micro-algae, with the aim of capturing industrial $CO_2$ 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 for Inria Centre at Université Côte d'Azur. 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

- The Biocore Team arrived at the end of its life time, and gave rise to the new Macbes team (July 2023) and in 2024 the Greenowl Team should be created.
- Combining algae and bacteria in High Rate Algal/Bacterial Ponds can lead to more efficicent, yet more complex wastewater remediation and resource recovery. In [5] a modelling and optimization study is carried out to assess advantage of a solid/liquid separation system. We identified the conditions maximising the algal productivity and those optimizing the efficiency of nitrogen recycling. We propose to control alkalinity and water depth to boost the algal productivity without meeting dangerous conditions favorable to $N_2O$ emission.
- Different strains of a microorganism growing in the same environment display a wide variety of growth rates and growth yields. We developed a coarse-grained model to test the hypothesis that different resource allocation strategies, corresponding to different compositions of the proteome, can account for the observed rate-yield variability [2]. Validated by a compiled database of hundreds of published rate-yield phenotypes of *Escherichia coli* strains, the model highlights the complex nature of the relationship between metabolites, growth rate, and yield. An interesting prediction of our model is that high growth rates are not necessarily accompanied by low growth yields: high-rate,

high-yield growth of *E. coli* can be achieved by a higher saturation of enzymes and ribosomes, and thus by a more efficient utilization of proteomic resources.

### 6.1 Awards

- F. Casagli was selected to give a Ted-X talk in Cannes, the $24^{th}$ of November
- Charlotte Gaviard got the i-PhD Concours d'Innovation grand prize in the category Pharmacy and Biotechnologies for her project DareWin Evolution, proposing new approaches based on guided dynamical Darwinian selection to improve microorganisms performances.
- Marielle Péré obtained an i-PhD Concours d'Innovation grand prize for her project CellEmax, issued from her thesis work, whose goal is to propose rational identification of new targets for anti-cancer combined treatments.

## 7 New software, platforms, open data

### 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 interface 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. In a more original way, 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, François Caddet, Erwan Demairy, Riham Nehmeh, Marc Vesin, Carlos Zubiaga Pena

# 8 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, Marine Courtois.

*Semi-discrete models* have shown their relevance in modeling biological phenomena whose nature presents abrupt changes over time [82]. In plant epidemiology, they can represent seasonality or external perturbations of natural systems, such as harvest. We developed and analyzed such models in the context of biological control applied to coffee leaf rust [14] or coffee berry borers [56], and of the sterile insect technique [46]. Semi-discrete models were central in Frédéric Grognard's HDR defense [50] and Clotilde Djuikem's PhD thesis [48].

In this framework, we studied how recurrent migration events ("pulsed migration") between different spatial locations influence the evolution of populations through a population genetics approach [6]. We evidenced that migration pulsedness affects allele fixation rates in interaction with their selective value, generally reducing the level of local adaptation as compared to continuous migration. This research was part of Flora Aubree's PhD thesis (defended in 2022), and has been performed in collaboration with Vincent Calcagno (ISA).

### 8.1.2 Estimation and control

**Participants:** Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Yves Fotso Fotso, Clotilde Djuikem.

*Optimal control and optimisation.* We developed several approaches to control the evolution of crop pests. We solved optimal control problems to limit the damages due to coffee berry borers [16] and Coffee Leaf Rust [77] using the BOCOP software, which is developed by Inria team COMMANDS.

## 8.2 Network interactions for cell function and growth

**Participants:** Odile Burckard, Madalena Chaves, Giada Fiandaca, Marielle Péré, Jérémie Roux, Jean-Luc Gouzé, Valentina Baldazzi.

### 8.2.1 Cellular response and cell-to-cell variability

To analyze the considerable amount of data from fate-seq [85], we proposed an ODE model of the molecular pathways involved in cell death triggered by Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) calibrated on single-cell time-trajectories of a fluorescent time-trajectories (FRET) reporter measuring apoptosis signaling dynamics in clonal HeLa cells [88]. With this model, we constructed a timeline for the different steps in the regulation of apoptosis and located an initial cell fate decision just after TRAIL binding [90]. Furthermore, we identified three specific parameter combinations that can distinguish between drug resistant or sensitive phenotypes. The next step was to combine the ODE model's mechanistic features with predictive values for cell decision with machine-learning classification models, to determine the drug response of each cell before it commits to an irreversible decision. Our mechanistic-informed approach, combining an ODE system with machine learning classifiers, outperformed classic machine learning approaches and enabled the accurate cell response prediction of otherwise unpredictable cells [89]. This part of the work was in collaboration with Diego Oyarzún (University of Edinburgh). This methodology is part of Marielle Péré PhD thesis [51], who won a STIC Doctoral School prize.

In addition, based on her thesis work, Marielle developed her project CellEmax, whose goal is to propose rational identification of new targets for anti-cancer combined treatments, for which she obtained an i-PhD Concours d'Innovation grand prize.

### 8.2.2 Intercellular communication in peripheral 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 [1]. 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 analyze 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 [71]. This method helps to further characterize the synchronization steps between two clocks of distinct (but close) periods. This work was presented by Odile Burckard at the 48th Congress of the Société Francophone de Chronobiologie [32]. In addition, through the analytical study of the above piecewise linear model of the clock, we proposed an Algorithm to generate biologically-consistent circadian oscillators. Our study provides a characterization of the cycle dynamics in terms of four fundamental threshold parameters and one scaling parameter, shows robustness of the circadian system and its period, and identifies critical points for correct cycle progression [60, 53]. This work is in collaboration with F. Delaunay (ANR InSync), and is part of Odile Burckard PhD thesis.

### 8.2.3 Cell economy and control of cell growth

Microbial growth consists of the conversion of nutrients from the environment into biomass and small energy cofactors (ATP, NADH, NADPH, ...) driving biomass synthesis forward. Two macroscopic criteria for characterizing microbial growth are growth rate and growth yield. The former refers to the rate of conversion of substrate into biomass, and the latter to the efficiency of the process, that is, the fraction of substrate taken up by the cells that is converted into biomass.

In the framework of the ANR Maximic project (collab. H. de Jong, MICROCOSME team, and T. Gedeon, Montana State University), we developed a coarse-grained model of coupled energy and mass fluxes in microorganisms, based on minimal assumptions, and used it to explore the variability of rate-yield phenotypes obtained by change in proteome allocation strategy [8]. The model predictions were verified by means of a database of hundreds of published rate-yield and uptake-secretion phenotypes of *Escherichia coli* strains grown in standard laboratory conditions. We found a very good quantitative agreement between the range of predicted and observed growth rates, growth yields, and glucose uptake and acetate secretion rates. These results support the hypothesis that resource allocation is a major explanatory factor of the observed variability of growth rates and growth yields across different bacterial strains. An interesting prediction of our model, supported by the experimental data, is that high growth rates are not necessarily accompanied by low growth yields. The resource allocation strategies enabling high-rate, high-yield growth of *E. coli* lead to a higher saturation of enzymes and ribosomes, and thus to a more efficient utilization of proteomic resources.

The model is currently used to investigate the set of adaptation strategies that microbial cells can use to increase their growth rate or their growth yield in a given environment. Preliminary results suggest that multiple allocation choices are possible, depending on the initial allocation state of the cell and its biomass composition.

## 8.3 Dynamics and control for synthetic biology

**Participants:** Benjamin Böbel, Madalena Chaves, Javier Innerarity Imizcoz, Jean-Luc Gouzé.

### 8.3.1 Dynamics in networks of cellular oscillators

**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 since individual steady states become arbitrarily close [7]. We apply the results to the synchronization of damped oscillators and to the control of multistable systems.

**Synchronization of circadian clock models.** To study coupling and synchronization of two clock oscillator models, we have used Lyapunov function techniques to bound the difference between the two oscillators in terms of the difference between their oscillating periods. We have also analyzed the form of the periodic solutions as a function of some of the parameters, in particular one of the major degradation rates. This is part of Benjamin Böbel PhD thesis.

# Fields of application

## 8.4 Bioenergy

### 8.4.1 Modelling microalgae production

**Participants:** Olivier Bernard, Antoine Sciandra, Walid Djema, Francesca Casagli, Bruno Assis Pessi, Ignacio Fierro, Ali Gharib, Yan Gao, Emna Krichen, Jean-Philippe Steyer, Amélie Talec, Eric Pruvost.

**Experimental developments in controlled dynamical environments.** The experimental Phytopulse 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 pigment dynamics under light fluctuation, nitrogen or temperature stress... In particular, various experiments were carried out for determining the ability of biofilms to grow with different sources of nitrogen. This experimental platform was used to control the long term stress applied to a population of microalgae using optimal control strategies[37]. This Darwinian selection procedure generated several new strains with higher lipids or pigments of interests after several months in the so called selectiostats [31]. These experimental works were carried out in the frameworks of the ISS incubated Darewin project, and in the pre-maturation Pycoplus project funded by CNRS.

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 [57]. The architecture of the biofilms was also observed for different species with confocal microscopic techniques [17, 21].

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 [3] , in order to simulate autotrophic, heterotrophic and mixotrophic growth, and to determine how to reduce substrate inhibition. The model was extended to other substrates such as glucose or glycerol. After a calibration phase, the model was successfully challenged with data from 122 experiments collected from scientific literature in autotrophic, heterotrophic and mixotrophic conditions [24].

As part of B.A. Pessi PhD thesis, this metabolic modeling framework is extended to describe a co-culture of bacteria and microalgae. First, by modeling a thiamine auxotroph *E. coli* to maximize the production of lactate [52]. Then, we extend the previous developed metabolic model to describe a co-culture of *Chlorella* with the bacteria *E. coli* overproducing the vitamin biotin. We represent the influence of biotin concentration in the accumulation of lipids. The model results show that a biotin overproducer *E. coli* could support the needs of vitamin by *Chlorella* and favor lipid accumulation.

**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. We then studied the influence of mixing, assuming that a mixing device can redistribute the algae so that they can have access to light [70]. A strategy to optimally mix the algae was derived. It was finally combined with a non flat topography [69].

**Modeling photosynthetic biofilms.** Several models have been developed to represent the growth of microalgae within a biofilm. A first structured physiological model [92] 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. The model corroborated observations realized at the LGPM (CentraleSupelec) [57, 21]. Another approach accounts for the dynamics of the light harvesting systems when cells are submitted to rapid successions of light and dark phases [57]. A simpler model was developed [18] and used to identify the optimal working mode of a process based on photosynthetic biofilm growing on a conveyor belt [49]. The model was used to identify the worldwide potential of microalgal biofilms under different climates [63]. This study was extended considering the impact if the culture has to be heated in winter.

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 [15]. The experimental validation of this model, together with the extrapolation of productivities at larger scale was the topic of the PhD thesis of Yan GAO at CentraleSupelec [57] (directed by F. Lopes and O. Bernard).

**Modeling thermal adaptation in microalgae.** We studied a broad range of species and their response to temperature. Algorithms were developped to automatically calibrate the parameters of the CTMI and the Hinshelwood models[79]. It turns out that the optimal temperature, the minimal and the maximal temperature for growth are strongly correlated. Relationships between these cardinal temperatures and key parameters from the environment (sea surface temperature, solar flux, ...) were explored. It turns out that some of the relationships stay valid also for a broad range of microorganisms such as yeast, bacteria.

**Modeling $N_2O$ production in algae-bacteria systems.** F. Casagli has set up dedicated experiments guided by modelling, in partnership with F. Béline (OPAALE team, INRAE Rennes), for measuring $N_2O$

production and emissions in algae-bacteria systems for wastewater remediation. The experimental results were used for validating experimentally the model predictions [73]. The specific experimental set-up was financed by the Fondation L'Oréal - UNESCO with the prize For Women in Science and the "Prime C3" within the RIPEC.

#### 8.4.2 Control and Optimization of microalgae production

**Participants:** Olivier Bernard, Francesca Casagli, Ignacio Fierro, Ali Gharib, Yan Gao.

**Optimization of the microalgae production through light pattern**

Dynamic light regimes strongly impact microalgal photosynthesis efficiency. Finding the optimal way to supply light is then a tricky problem, especially when the growth rate is inhibited by overexposition to light and, at the same time, there is a lack of light in the deepest part of the culture. We used the Han model to study the theoretical microalgal growth rate by applying periodically two different light intensities [15]. For a large light period, we demonstrate that the average photosynthetic rate can be enhanced.

Microalgal growth is affected by the dynamics of photon harvesting processes, such as photoinhibition and photoacclimation. Taking into account these phenomena, we propose and solve an optimal control problem to maximize the production of biomass [37]. Theoretical and numerical properties of the problem were described, where Turnpike-like properties were observed using Pontryagin's maximum principle and the BOCOP software for numerical simulations.

This is the subject of the PhD thesis of Ignacio Fierro in the framework of the ITN Digitalgaesation.

**Optimization of the microalgae production through temperature control**

Temperature plays a key role in the microalgae dynamics. We developed a heat transfer model coupled with biological model to simulate the temperature evolution, depending on the meteorology, and its impact on algal productivity. We propose a general framework to simulate these multiphysics systems, keeping a balanced degree of complexity between the biological and the physical models [72]. We also considered the influence of a greenhouse on the medium temperature and subsequently on algal productivity [91] simulating different climatic conditions and the species for which the use of a greenhouse is beneficial. Based on that developed heat-transfer model, we proposed an auto-adaptive heat-transfer model[39] that can predict the temperature evolution inside different type of raceway ponds or other cultivation systems using weather measurements.

A model predictive control algorithm was elaborated 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. This is the subject of the PhD thesis of Ali Gharib in the framework of the ITN Digitalgaesation.

### 8.5 Biological depollution

**Participants:** Olivier Bernard, Jean-Luc Gouzé, Francesca Casagli, Annalisa Reali, Morgan Scalabrino.

#### 8.5.1 Control and optimization of bioprocesses for depollution

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 [87],[25]. We designed and calibrated a model, that was validated with more than one year of data [75]. 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 harmful emissions [74]. We developed a general framework for simulating biotechnological processes affected by meteorology, integrating, on top of the core biological model, a heat transfer model and a chemical sub-model for computing the speciation of all the dissociated chemical molecules [72]. The developed framework is a powerful tool for advanced control and optimization of environmental processes, which can guide the scaling-up and management of the most innovative bioprocesses. In this framework was implemented the ABACO-2 model, in order to couple the biological model with the chemical model [22]. We explored and quantified, through a modeling study, the advantage of adding a solid/liquid separation system to uncouple Hydraulic Retention Time (HRT) and Solid Retention Time (SRT), in order to maximize the algal productivity and the nitrogen recycling [5].

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 constraints (positivity, boundness, ...). A dedicated strategy was developed [34, 33] and successfully applied to experimental data from two pilot plants. This approach allows a fast calibration strategy for new processes by combining the hypothesis on mass balance and stroichiometry and the artificial neural networks. Another approach with neural ODE was also developed for representing microalgae growth in photobioreactors [43, 44].

#### 8.5.2 Coupling microalgae to anaerobic digestion

**Participants:** Olivier Bernard, Antoine Sciandra, Jean-Philippe Steyer, Francesca Casagli, Annalisa Reali.

The coupling between a microalgal-bacteria high rate 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 [87]. The challenge when dealing with anaerobic digestion effluent for feeding the algae-bacteria process is the potential low alkalinity which can induce a competition between nitrifying bacteria and algae [11]. We showed that this competition for inorganic carbon can create conditions favorable for $N_2O$ emission. We studied the metabolism of *Chlorella vulgaris* growing on fermentation products and developed a metabolic model [24] that was validated with a large number of experiments covering various working modes (autotrophic, heterotrophic, mixotrophic).

### 8.6 Life Cycle Assessment

**Participants:** Olivier Bernard, Jean-Philippe Steyer, Diego Penaranda, Francesca Casagli, Arnaud Hélias.

**Environmental impact assessment.**
We have studied the environmental impact of protein production from microalgae in an algal biofilm process, using a Life Cycle Assesment (LCA) approach and compared it to other sources (fisheries, soy,...). We have analyzed the updated version of the production system and proposed several optimization to reduce the environmental impact. This study confirms the interest of microalgae for reducing the environmental impact [64, 40] compared with other sources of proteins like fishmeal or soy. More generally, this work proposes a new approach to assess and reduce the environmental footprint of processes which use non mature technologies [64] (PhD thesis of D. Penaranda in collaboration with M. Morales from the Norwegian University of Science and Technology).

A study was carried out to assess the environmental benefit of using microalgae-bacteria to process wastewater, and in particular digestates from anaerobic digestion [87]. Various scenarios were simulated using the ALBA model [11] assuming an industrial plant located in Rennes (Britany, France) dealing with an actual climatology and for various conditions of Hydraulic and Solid retention times, alkalinity addition and biomass valorization for generating energy. In total 72 different scenarios were explored, for which LCA was carried out. The results were compared to scenarios where the digestates are classically treated in a wastewater treatment plant. It results that the microalgae approach makes sense from an environmental point of view [63, 23].

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

## 8.7 Modeling and control of cancer cell population dynamics.

**Participants:** Walid Djema, Frédéric Grognard, Jérémie Roux, Marielle Péré, Pauline Mazel.

Our research continues in the field of modeling and analysis of cancer cell populations, focusing on enhancing our comprehension of the emergence, development, and treatment improvement of cancer. We have concentrated on examining the resistance that arises with specific types of therapies. A novel model, calibrated on clinical data, has been developed to demonstrate how sequential different treatments can achieve better therapeutic outcomes. Additionally, we have explored the development of sub-optimal cancer treatment techniques [36], using network representations combined with artificial intelligence (AI) tools, particularly pathfinding algorithms. This approach aims to determine the most effective treatment infusion strategies. This advanced application of AI methods intends to refine and improve treatment protocols, thereby increasing treatment efficacy. Another line of research involves the application of optimal control to Lotka-Volterra models of competition between cancerous and healthy cells. The aim is to control cancer progression while reducing the harmful effects of chemotherapy. This strategy aims to strike a balance between eliminating cancer cells while preserving healthy tissues, providing a more refined method to manage the impact of cancer treatments. This is the subject of the PhD thesis of Pauline Mazel.

## 8.8 Optimal bacterial resource allocation for metabolite production.

**Participants:** Jean-Luc Gouzé, Walid Djema, Javier Innerarity Imizcoz.

We investigate the optimization of resource allocation in micro-organisms, specifically aiming to maximize their volumetric growth rate. This study is based on a simplified model of *E. coli* metabolism, structured around a system of two Ordinary Differential Equations with an integrated control variable. The mathematical analysis employs the Infinite Horizon Maximum Principle, an adaptation of Pontryagin's Maximum Principle. This approach is further augmented by numerical resolution and simulation of the resulting trajectories. The initial phase of our research aligns with previous studies by considering a stable environment, an assumption that simplifies the problem's complexity. However, recognizing that micro-organisms often evolve in fluctuating environments, the second phase extends this analysis to settings with periodic substrate variations. Here, we aim to determine an optimal periodic substrate that enhances growth beyond constant conditions. The third phase of our research continues the exploration of an optimal periodic environment. This aspect is particularly relevant in artificially controlled settings aimed at increasing biomass yield. As in the preceding sections, rigorous theoretical analysis is conducted, followed by numerical resolution to pinpoint the most effective environment and resource allocation strategy. This is the subject of the PhD thesis of Javier Innerarity Imizcoz.

## 8.9 Optimizing waste-to-energy systems for profitable energy production.

**Participants:** Walid Djema, Jean-Luc Gouzé.

We address the critical challenge of identifying reliable energy sources as the global energy sector transitions from fossil fuels to renewables. Our focus is on waste-to-energy (WTE) systems, which stand out as a promising alternative to solar and wind power due to their operational independence from weather conditions for instance. This aspect underscores the necessity of investing in waste-to-energy initiatives to create sustainable and economically viable activities. To this end, we have developed a comprehensive bio-economic model that takes into account the investment in a specific waste-to-energy technology, with the goal of optimizing the energy production process and establishing a sustainable business model. We use direct and indirect optimization techniques to validate and demonstrate the effectiveness of the provided optimal strategies [35].

## 8.10 Design of ecologically friendly plant production systems

**Participants:** Valentina Baldazzi, Frédéric Grognard, Suzanne Touzeau, Ludovic Mailleret, Clotilde Djuikem, Aurelien Kambeu Youmbi, Frank Kemayou Mangwa, Joseph Junior Penlap Tamagoua.

### 8.10.1 Ecophysiological modelling of plant-microbiota interactions

Root-knot nematodes (RKN) are microscopic root parasites that cause considerable yield losses in numerous crops worldwide. We are particularly interested in understanding the mechanisms that underlie plant tolerance, that is the ability of certains plants to sustain RKN infestation with limited damages. To address this, we built an ecophysiological model of plant growth, including both the vegetative and the reproductive phases, coupled with a model of nematode population dynamics. Briefly, the plant is divided into shoots, which provide carbon, and roots, which provide water for plant growth. During the reproductive phase, fruit onset marks the addition of a new carbon sink for the plant. 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 apparition of fruits, in particular, can substantially modify the ressource allocation pattern of the plant, with important consequences on plant susceptibility to pest attack. The model was calibrated for two plant species using experimental data collected in the framework of INRAE ArchiNem project (2020-2021). A dedicated calibration pipeline was developed in order to combine heterogeneous data at different time-scales. At term, the model will be used to explore the dynamical behaviour of the system and to gain insight into the relative role of plant development and phenotypic traits (including physiological and architectural features), pest development and environmental factors in the progression of the infection.

This work is part of the PhD thesis of Joseph Penlap Tamagoua (Inria-INRAE funding 2022-2025) and was presented at several international conferences [65, 47]. Two publications are currently in preparation, focusing respectively on the experimental results and on model development and calibration.

### 8.10.2 Epidemiological modelling of plant-enemy interactions

**Epidemiological models in tropical agriculture** We developed and analyzed dynamical systems describing plant-parasite interactions, in order to better understand, predict and control the evolution of damages in crops, with applications in tropical agriculture, in the framework of the EPITAG associate team with Cameroon. We considered several pathosystems.

- Coffee berry borers are insects that mostly develop and feed inside coffee berries, and hence cause major crop damages worlwide. 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. This PDE model includes a berry age structure to account for CBB preference for mature berries [16, 56]. This research pertains to Yves Fotso Fotso's PhD thesis [68].

- Coffee leaf rust (CLR) is a leaf disease caused by a fungus, *Hemileia vastatrix*, that has a major impact on coffee production around the world. We studied a multi-seasonal model of CLR development in a coffee plantation, with continuous dynamics during the rainy season and a discrete event to represent the simpler dynamics during the dry season [14, 42]. We also performed a bifurcation analysis of a more complex model taking the development stage of the leaves into account (paper under revision). This work is part of Clotilde Djuikem's PhD thesis that was defended in 2023 [48].

- Cabbage is a very important food crop for small farmers in Cameroon. We developed a self-financing model of the crop, which includes the interaction between cabbage and the diamondback moth, one of its major pest. The main point of this model is the inclusion of the financial balance of the farm, used for buying young plants and biopesticide spraying. We did a bifurcation analysis of this bioeconomic model and identified situations with forward or backward bifurcations [45]. This work is part of Aurelien Kambeu Youmbi's ongoing PhD thesis.
- Bananas, including plantains, are major staple foods in many tropical countries, including Cameroon. These plants are affected by burrowing nematodes (*Radopholus similis*) that create root lesions and induce great damages. We developed a model of the plant-pest interactions with the original feature that infestation intensity may vary within the root. We did a bifurcation analysis of this model and developed an optimal control against the pest. This work is part of Frank Kemayou Mangwa's ongoing PhD thesis.

**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 [86, 80]. With such an approach, we explored how positive density-dependence in growth or dispersal interact with spatial heterogeneity to impact population spread [20]. In this context, we showed that the expansion rate is not only determined by the current environmental conditions at the edge of the population, but is also strongly influenced by the conditions encountered at previous times and locations by the moving front of the population. This research has been performed in collaboration with Elodie Vercken (ISA).

Concurrently, we are exploring the correlation between biological control agents movement characteristics at different scales, from laboratory experimental characterization to semi-field dispersal on parasitoids belonging to the genus Trichogramma. A specific mid-scale laboratory device to study insect dispersal over several meters has been designed [13] and used to understand how insect movements shape group dispersal in such parasitoïds [10]. This research was part of the PhD theses of Victor Burte (defended 2018) and Melina Cointe (defended 2023, [76]) and was performed in collaboration with Vincent Calcagno (ISA).

## 8.11 Design and control of managed ecosystems

**Participants:** Jean-Luc Gouzé, Frédéric Grognard, Suzanne Touzeau, Ludovic Mailleret, Olivier Bernard, Juan Carlos Arceo, Francesca Casagli, Bruno Assis Pessi.

### 8.11.1 Design and control of synthetic microbial ecosystems

In the framework of ANR project Ctrl-AB, we considered a synthetic algal-bacterial consortium. The co-culture of *E. coli* with *Chlorella* could lead to higher biomass and lipid productivity. We developed a model, studied its dynamical behaviour and built observers to optimize some output [30]. Moreover, we studied the effects of control on the system (PhD thesis of Rand Aswad, Grenoble, in collaboration with E. Cinquemani (Microcosme )).

In the framework of IPL Cosy (led by E. Cinquemani), we studied the coexistence of two strains of bacteria *E. Coli* in a bioreactor. The strains had been modified synthetically. The aim was to obtain a better productivity in the consortium than in a single strain, by control methods [84]. We obtained optimization results for the optimal production or yield [19].

### 8.11.2 Design of biological control strategies

**Sterile insect technique** The sterile insect technique (SIT) consists in releasing irradiated sterile individuals, usually males, that can mate but produce no offspring. SIT is used to reduce pest populations in an agricultural context. However, a small fraction of irradiated insects may escape sterilization and remain fertile. We showed that when residual fertility is below a threshold value, wild populations can be driven to extinction by flooding the landscape with sterile males. Nevertheless, even if the residual fertility exceeds the aforementioned threshold value, substantial decreases in outbreak levels can be achieved [62, 41, 61]. In the framework of Taha Belkayate's internship, we extended these results to take remating into account. This work pertains to Marine Courtois's ongoing PhD thesis.

**Predator releases for coffee leaf rust** Biological control was added to the multi-seasonal impulsive model describing coffee leaf rust spread in a plantation (section 8.10.2), using predators through one or more discrete introduction events over the year. Analytical and semi-numerical studies were performed to identify how much and how frequently predators needed to be introduced. We showed that the best strategy to efficiently control the disease depends on the predator mortality: low mortality parasites must be released only once a year, while high mortality parasites should be released more frequently to ensure their persistence in the plantation [14]. This work pertains to Clotilde Djuikem's PhD thesis that was defended in 2023 [48].

**Optimal control for coffee berry borers** Controling coffee berry borers is particularly challenging, as the insects spend most of their life cycle inside berries. Pest control was introduced in the model describing the interactions between borers and coffee berries (section 8.10.2), based on the combination of a biopesticide (entomopathogenic fungus such as *Beauveria bassiana*), that is sprayed and persist on the berries, and traps. Using optimal control theory, we showed a synergy between the two controls for profit optimization [16]. We also investigated how to optimize biopesticide spraying considering it as an impulsive control [56]. This research pertains to Yves Fotso Fotso's PhD thesis [68].

### 8.11.3 Sustainable management of plant resistance

We studied other plant protection methods dedicated to fight plant pathogens. Among these methods, there 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) disease spread on annual field crops in a multi-pathogen context. This work benefits from data collected in INRAE projects COCODIV and DYNAMO on wheat diseases. It will pe pursued in the ENDURANCE and PAPEETE projects (section 10.4.1).

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. We developed an epidemiological model to explore how mixing two distinct resistant varieties can reduce disease prevalence. We considered a pathogen population composed of three genotypes infecting either one or both varieties. We found that host mixtures should not contain an equal proportion of resistant plants, but a biased ratio to minimize disease prevalence, and that it should contain a lower proportion of the costliest resistance for the pathogen to break [12]. This was done in collaboration with Frédéric Hamelin (Institut Agro) in the framework of Pauline Clin's thesis.

We also participated in an opinion paper advocating that the theoretical framework of population genetics could bridge the gap existing between evolution/epidemiology approaches and molecular approaches to the durability of resistance problem [26]. This paper is the basis of the ENDURANCE ANR project (section 10.4.1).

# 9 Bilateral contracts and grants with industry

**Participants:** Olivier Bernard, , Diego Penaranda, , Madalena Chaves, , Jean-Luc Gouzé.
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### 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. We have regular contacts with Exactcure, which hired our PhD student 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**

**Participants:** Olivier Bernard, Francesca Casagli, Jineth Oviedo , Ignacio Fierro, Romain Ranini.

**Title:** Artificial Intelligence and optimization for cleaner biotechnological processes

**Duration:** 2021 ->

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

**Partners:**

- Pontifical Catholic University of Valparaíso Valparaíso (Chili)

**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. We will more specifically target innovative wastewater treatment processes involving microalgae, and recirculating aquaculture systems. Developing optimal control strategies for these two dynamical processes is the subject of intense researches at the international scale. The teams involved in Blue Edge have experimental pilot systems (PUCV, Cetaqua), developed models for the considered processes (BIOCORE, PUCV), the skills to design advanced algorithms for data driven supervision (Inria CL) and control (BIOCORE) that can further be implemented thanks to the ODIN+ software (BIOCORE).

**EPITAG**

**Participants:** Suzanne Touzeau, Frédéric Grognard, Clotilde Djuikem , Joseph Penlap.

**Title:** Epidemiological Modelling and Control for Tropical Agriculture

**Duration:** 2022-2024

**Coordinator:** Samuel Bowong (sbowong@gmail.com)

**Partners:**

- Université de Douala (Cameroun)

**Inria contact:** Suzanne Touzeau

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

## 10.2 International research visitors

### 10.2.1 Visits of international scientists

- Jineth Arango Oviedo (PUC - VALPARAISO), spent one year (until Apr 2023) in the framework of the Blue Edge Associate Team.
- Elisabeth Gualda Alonso UNIV ALMERIA from Univ. Almeria spent two months (Sep 2023-Dec 2023).
- In the framework of the EPITAG Associate Team, we had the long term visit of Aurelien Kambeu Youmbi (UNIV DSCHANG CAMEROON), from Feb 2023 until Apr 2023 and Frank Kemayou Mangwa (UNIV DOUALA), from Feb 2023 until Apr 2023.
- In the framework of the ITN DigitAlgaesation, we had the visit of David Morgado Pereira (CENTRALESUPELEC, Nov-Dec 2023), Rebecca Nordio (University of Almeria, from Mar 2023 until May 2023), Tehreem Syed (TU Dresden, School of Engineering, until Mar 2023).
- Gustavo Ribeiro da Silva São Paulo State University/Universidade Estadual Paulista UNESP, from Apr 2023 until May 2023.

## 10.3 European initiatives

### 10.3.1 H2020 projects

**DigitAlgaesation** DigitAlgaesation project on cordis.europa.eu

**Title:** A knowledge-based training network for digitalisation of photosynthetic bioprocesses

**Duration:** From March 1, 2021 to February 28, 2025

**Partners:**

- INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET AUTOMATIQUE (INRIA), France

- IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE, United Kingdom
- MINT ENGINEERING GMBH, Germany
- UNIVERSITA DEGLI STUDI DI PADOVA (UNIPD), Italy
- SIEMENS PROCESS SYSTEMS ENGINEERINGLIMITED (SPSE Ltd), United Kingdom
- PROVIRON HOLDING NV (PROVIRON), Belgium
- TMCI PADOVAN SPA, Italy
- DANMARKS TEKNISKE UNIVERSITET (TECHNICAL UNIVERSITY OF DENMARK DTU), Denmark
- UNIVERSIDAD DE ALMERIA (UNIVERSIDAD DE ALMERIA), Spain
- WAGENINGEN UNIVERSITY (WU), Netherlands
- CENTRALESUPELEC, France
- TECHNISCHE UNIVERSITAET DRESDEN (TUD), Germany
- GOTTFRIED WILHELM LEIBNIZ UNIVERSITAET HANNOVER (LUH), Germany

**Inria contact:** Olivier Bernard

**Coordinator:** Fabrizio Bezzo (Univ. Padova)

**Summary:** Microalgae and other photosynthetic microorganisms represent a highly promising source for food, feed, chemicals, and fuels. Europe has been leading world research and industrial deployment of microalgae based technologies. However, despite the enormous potential and the impressive R&D effort, industrial use of microalgae is still at its first developmental stage. A major step forward can derive by the development and implementation of digital technologies, capable of automatizing and optimizing culture conditions at industrial scale. Europe has a tradition of leading researches in the field of automatic control for biotechnological processes. As envisaged by DigitAlgaesation, the widespread definition and adoption of effective tools for better design and operation urgently requires skilled multidisciplinary scientists and engineers, who can develop and implement the next generation of sustainable production process with enhanced productivity, reduced environmental impact and costs, despite climate fluctuations that may strongly affect microalgae productivity. All this demands a European commitment to concerted, inter- and transdisciplinary research and innovation.

DigitAlgaesation will train 15 early-stage researchers (ESRs) in all aspects of microalgae technological innovation to pave the way towards a knowledge-based breakthrough in monitoring methods and instrumentation, biological modeling and simulation, and automatic control. By training in scientific, technical and soft skills, they will become highly sought-after scientists and engineers for the rapidly emerging microalgae-based industry and broader bioprocessing industries of Europe.

## 10.4 National initiatives

### 10.4.1 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 modeling 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 ($CO_2$), which is the substrate of the photosynthesis of the algae. The algae can produce oxygen ($O_2$) fueling bacterial growth, thus giving rise to a mutualistic pattern of interactions giving rise to several challenges for modeling and controlling this artificial ecosystem. Project coordinated by J.-L. Gouzé.

- **ANR Maximic:** The goal of the project (2017-2022) 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.
- **ANR InSync:** This project (2022-2027) aims to decipher intercellular synchronization mechanisms responsible for robust rhythms in peripheral clocks. Focusing on hepatocytes, and using both 2D cultures and 3D spheroids, we will study cell communication patterns and cell clock synchronization. Project coordinated by M. Chaves, in collaboration with F. Delaunay (Institut Biologie de Valrose, UniCA) and L.Tournier (MaIAGE, INRAE Jouy-en-Josas).
- **ANR Barrier:** This proof of concept project (2023-20274) with multidisciplinary expertise is willing to demonstrate, from the laboratory to a pilot process, that selected bacteria can protect microalgae when growing in contaminated wastewaters, providing higher algal resilience, productivity and bioremediation efficiency in wastewater treatments. It is coordinated by O. Pringault (IRD, Mediterranean Institute of Oceanography).
- **ANR 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*.
- **Plan Cancer, Imodrez:** The objective of this project (2018-2022) 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).
- **ITMO Cancer Aviesan, Cellema:** The objective of this project (2022-2025) is to determine the molecular factors that regulate tumor cell response dynamics to immune cell cytotoxicity and contribute to the development of diagnosis tools for the rational design of cancer combination therapies. We will use single-cell response data to develop mathematical models and combine them with machine learning algorithms to enhance prediction of same-cell responses. Project coordinated by M. Chaves, in collaboration with J. Roux (IPMC, CNRS) and D. Oyarzun (Univ. Edinburgh).
- **ADEME- Biomsa:** “Development of an environmental environmental biorefinery Methane Struvite-Algae” (2021-2023)coordinated by F. Beline, INRAE. The objective of this project is to assess, through a combination of experimental and modeling approach the performance of microalgae for wastewater treatment.
- **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 INRAE-CNRS-UniCA.
- **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.
- **PEPR Agroécologie et Numérique - MISTIC** “Microbiomes de plantes cultivées et TIC” (2023-2028). Our objective within this flagship project of the PEPR is to model and analyze plant microbial communities and their functioning, as well as to design minimal microbial communities guaranteeing maintained functions.

#### 10.4.2 Inria funding

- **Inria Startup Studio, DareWin:** (2022-2023). The DareWin project is consolidating the bases of a startup which will develop Darwinian selection approaches in highly controlled bioreactors to naturally select and improve microalgal strains of industrial interest.

#### 10.4.3 INRAE funding

- **COCODIV:** “Crop disease co-occurrence in cereal systems: determinants, role and management of cultivated and wild diversity from plot scale to landscape level integration”, INRAE SuMCrop Metaprogramme (2022–2023), in which Biocore is a partner with INRAE Sophia Antipolis.
- **DYNAMO:** “Drivers of the epidemic dynamics of wheat rusts at the landscape scale of the Zone Atelier Plaine & Val de Sèvre”, INRAE SPE Division (2022-2024), in which Biocore is a partner with INRAE Sophia Antipolis.

# 11 Dissemination

## 11.1 Promoting scientific activities

### 11.1.1 Scientific events: organisation

**General chair, scientific chair**

- O. Bernard organized the ALGORESEAU workshop: "Microalgae and numerical twins", organized online by Pole Mer in December, the 6th of December.
- Francesca Casagli was elected co-chair in the new Task Group of IWA (International Water Association) on algae and phototrophic microbes modelling.
- Walid Djema co-organized, with Jean Clairambault (Inria Paris) and Catherine Bonnet (Inria Saclay), a tutorial session on the modeling and analysis of cancer as part of the European Control Conference 2023 in Romania.

**Member of the organizing committees**

- F. Casagli and O. Bernard were in the organizing committee of the Workshop on modelling phototrophic systems, in Quebec city, September the 24th. " how can we improve mathematical models to promote and optimize phototrophic systems for water remediation and resource recovery?"
- We organise a monthly scientific seminar together with the MACBES project-team in which external guests and collaborators are regularly invited. We also organise a yearly four day-retreat where we share our work of the year; this year, it took place mid-october in Porquerolles.
- Marielle Péré was one of the organizers of the Inria PhD Student Seminars, taking place every two weeks.
- Suzanne Touzeau was a member of the scientific and organizing committees of the MPDEE 2023 conference, CIRM Marseille, France, 24-28 April 2023.

#### 11.1.2 Scientific events: selection

**Chair of conference program committees**

- O. Bernard was the head of the academic scientific committee of the AlgaEurope conference which took place in December 1st to 4th 2023 in Prague.

**Reviewer**

- All BIOCORE members have been reviewers for the major 2023 conferences in our field: Conference on Decision and Control, European Control Conference, International Federation of Automatic Control.

#### 11.1.3 Journal

**Member of the editorial boards**

- Madalena 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.
- Jean-Luc Gouzé is an Associated Editor of the journal Frontiers in Applied Mathematics and Statistics (Mathematical Biology).
- Suzanne 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 their field: Automatica, IEEE Transactions on Automatic Control, Journal of Mathematical Biology, Mathematical Biosciences, New Phytologist...

#### 11.1.4 Invited talks

- Madalena Chaves gave talks at the Canceropole PACA Webinar (30 May 2023) and at the Journées Nationales de l'Informatique Mathématique, Paris (April 2023).
- Ludovic Mailleret gave a talk at the conference "Le MOnde des Mathématiques Industrielles", MOMI2023, Sophia Antipolis, April 2023.
- F. Casagli was invited to give a talk within the INRAE workshop "Sensors and numerical twins" on "Hybrid modelling of algae-bacteria systems" the 4th-5th Decembre in Lyon.
- O. Bernard was invited to give a talk at University of Quebec at Rimouski "Modelling an algae-bacteria artificial ecosystem for recovering nitrogen and phosphorus from wastewater " the 28th of September 2023.
- O. Bernard was invited to give a talk at the 3rd Inria-DFKI European Summer School on AI (IDESSAI 2023) " Hybrid modelling of artificial microbial ecosystems for bioenergy production and waste water treatment " the 5th of September 2023.

#### 11.1.5 Scientific expertise

- Walid Djema is appointed as the Inria representative on the Scientific Council of the "Académie d'Excellence 4: Complexité et Diversité du Vivant" de l'IDEX JEDI, UniCA.
- O. Bernard is in the Scientific Advisory Board of the "Ferment du futur" Grand challenge of France 2030.

- O. Bernard is a member of the scientific committe of IRD (Institute of Research for the Development) in the CSS5 section (models and data). He participated to the recruitement juries for researchers and research directors at IRD.
- O. Bernard is in the Scientific and Pedagogic committee of the UniCA- EUR LIFE and in the steering committee of Federal Recherche Institut (IFR) Marine Ressources (MARRES).
- O. Bernard is a member of the scientific committee of the Inalve company.
- Suzanne Touzeau participated in selection panels for INRAE junior research scientists.
- Madalena Chaves, Frédéric Grognard, and Ludovic Mailleret are members of the INRAE Commission Scientifique Spécialisée (CSS) for Mathématique, Informatique, Sciences et Technologies du numérique, Intelligence artificielle et Robotique (MISTI).
- Walid Djema was invited as guest participant in the CT-Control programming sprint organized by J.-B. Caillau and O. Cots. This event focused on collaborative efforts in the field of numerical optimization, specifically centered around the development of analysis tools for two distinct optimal control problems. Our team contributed to include projects from A. Gharib's research on Microalgae cultures and O. Dekkaki's work on waste management. Our involvement entailed the utilization of both direct and indirect optimization techniques tailored to address optimal control challenges within the life sciences domain.

#### 11.1.6 Research administration

- Walid Djema was elected to the Center Committee (*Comité de Centre*) of Inria Sophia Antipolis.
- Olivier Bernard and Walid Djema are members of the local sustainable development committee (*Commission Locale de Développement Durable (CLDD)*) at Inria Sophia Antipolis.
- Madalena Chaves is member of the local Inria committee for doctoral studies (CSD) and head of the committee NICE for welcoming external researchers (post-docs, "delegations"). She is also a representative of Inria at the Canceropole PCA. She is the coordinator of the UE Biologie Systémique 1 of the new Master option on Bioinformatics and Computational Biology of the EUR Sciences du Vivant et de la Santé. Madalena Chaves is a member of the scientific committee of Labex Signalife (since 2020).
- Frédéric 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 MSc Risk of UCA-JEDI and is a member of the Scientific Committee of the Agroecosysems department of INRAE.
- Ludovic Mailleret is the head of the M2P2 team (Models and Methods for Plant Protection) of ISA. He is in the Unit and scientific council of Institut Sophia Agrobiotech, and in the council of the INRAE PACA centre.
- Ludovic 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.
- Suzanne Touzeau is a member of the steering committee of the INRAE Metaprogramme SuMCrop"Sustainable Management of Crop Health" (since 2016).
- Valentina Baldazzi and Suzanne Touzeau are elected members of the Institut Sophia Agrobiotech council.
- Jean-Luc Gouzé is in the Inria committee supervising the doctoral theses (until June), a member of the steering committee of Labex SIGNALIFE of Université Côte d'Azur, and of the scientific committee of Académie 4 (Life Sciences) of UniCA. He is a member of the board of the SFBT (French Speaking Society for Theoretical Biology).
- O. Bernard is a member of the ADT (Technological Development Actions) commission at Inria and of the local commission for sustainable development.

## 11.2 Teaching - Supervision - Juries

### 11.2.1 Teaching

- 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.
- Master: O. Bernard (24h ETD) and W. Djema (24h ETD), “Enseignement d’Intégration EI – ST5 Méthanisation”, CentraleSupélec, Paris-Saclay, France.
- Licence: W. Djema (40h ETD); “Mathématiques pour Biologistes: Analyse et Modélisation", L1 Université Côte d’Azur UniCA, France.
- Licence: W. Djema (32h ETD); “Math0: Enjeux", L1 Université Côte d’Azur UniCA, France.
- Licence: W. Djema (20h ETD); “Statistiques pour les Biologistes", L1 Université Côte d’Azur UniCA, 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.
- Licence: O. Bernard (35h ETD), “Use and optimization of photobioreactors”, Université de Pau et des pays de l’Adour, France.
- BUT: Odile Burckard (12h ETD) "Fondamentaux de la programmation" 1st year, IUT de Nice Côte d’Azur (Département Réseaux et Télécommunications).
- Licence: Clotilde Djuikem (40h ETD) "Analyse et modélisation", PO1, Sciences de la vie, Université Côte d’Azur, France
- Licence: Clotilde Djuikem (16h ETD) "Fondements 2", PO1 Sciences, ingénierie, technologie, environnement, Université Côte d’Azur, France
- Licence : Clotilde Djuikem (24h ETD) "Intro. à la modélisation mathématique et numérique", L3, 1st year Engineering in "Genie de l’eau", Polytech Nice Sophia, Université Côte d’Azur, France
- Licence: Clotilde Djuikem (28h ETD)"Statistiques et R", L3, 1st year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Côte d’Azur, France
- Licence: Pauline Mazel (16h TD) and Joseph Junior Penlap Tamagoua (32h TD), “Fondements mathématiques 1 - partie algèbre linéaire”, L1, Portail Sciences et Technologies, Université Côte d’Azur, France
- Licence: Frédéric Grognard (42h ETD) and Ludovic Mailleret (24h 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: Joseph Junior Penlap Tamagoua (28h TD), "Approximation de fonctions, intégrales et EDO", L3 Mathématiques, Université Côte d’Azur, France
- Master : Jean-Luc Gouzé (20h ETD), Madalena Chaves (13.5h ETD), “Modeling biological networks by ordinary differential equations”, M1, $4^{th}$ year Engineering in Génie biologique, Polytech Nice Sophia, Université Côte d’Azur, France.

- Master: Frédéric Grognard (21h ETD) and Ludovic Mailleret (21h ETD), “Bio-Mathématiques”, M1, 2nd year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Côte d’Azur, France.
- Research School: Suzanne Touzeau gave a lecture at the CIMPA school “Mathematical and statistical modeling of complex systems", N’Djamena, Chad, 2–13 January 2023.
- Licence: C. Djuikem – ATER contract (24h ETD), "Processus Stochastiques", L3, 1st year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Côte d’Azur, France.
- Licence: C. Djuikem – ATER contract (60h ETD), "Statistiques", L1 Sciences de la vie, Université Côte d’Azur, France.

#### 11.2.2 Supervision

- HDR: Frédéric Grognard. "Modelling and control of managed ecosystems, from bioreactors to agroecosystems", Université Côte d’Azur, defended February 20th.
- PhD defended the 9th of February 2023: B. Assis Pessi. “Optimization of microalgae efficiency using reduced metabolic models”, Université Côte d’Azur. 2019-2023. Supervisors: O. Bernard and L. Giraldi (team Calisto).
- PhD defended in 2023 : Yan GAO. "Optimisation of microalgae biofilms as a future source of biomolecules", Université de Saclay, 2018-2023. Supervisors: F. Lopes and O. Bernard.
- PhD in progress: R. Ranini. "Deep leanring approaches for enhancing models in oceanography", UniCA, since 2022. Supervisors: L. Guidi and O. Bernard.
- PhD in progress: R. Asswad. “Développement de stratégies de contrôle pour les consortiums microbiens synthétiques”, since October 2022, Université Grenoble-Alpes Supervisors J.-L. Gouzé and E. Cinquemani (Microcosme, Inria Grenoble).
- PhD in progress: Pauline Mazel. “Modeling and control of cancer cell population dynamics", since oct. 2023. Supervisors: F. Grognard (director, Macbes) and W. Djema (co-director, Biocore).
- PhD in progress: Javier Innerarity Imizcoz. “Optimal bacterial resource allocation for metabolite production", since nov. 2023. Supervisors: Jean-Luc Gouzé (director, Macbes), Francis Mairet (co-director, Ifremer Nantes) and W. Djema (co-supervisor, Biocore).
- PhD: Marielle Péré. “Modeling cancer drug response dynamics in single-cells to predict the emergence of drug-tolerant cells", Université Côte d’Azur, defended March 27th. Supervisors: Madalena Chaves and Jérémie Roux.
- PhD: Clotilde Djuikem. “Modelling and control of perennial plant phytopathogens”, Université Côte d’Azur, defended January 5th. Supervisors: Frédéric Grognard, Suzanne Touzeau and Samuel Bowong (Univ. Douala, Cameroon).
- PhD: Melina 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, defended Octobre 13th. Supervisors Vincent Calcagno, Ludovic Mailleret.
- PhD in progress: Aurelien Kambeu Youmbi. "Self-Financing Model for Cabbage Crops with Pest Management", University of Dschang,Cameroon, since 2020. Supervisors: Berge Tsanou, Suzanne Touzeau and Frédéric Grognard.
- PhD in progress: Odile Burckard. "Coupling, synchronization, and control of cellular oscillators through mathematical modeling and analysis", Université Côte d’Azur, since 2021. Supervisor: Madalena Chaves.

- PhD in progress: Marine Courtois. "Modélisation de la technique de l'insecte stérile dans un contexte agricole : comment intégrer les réalités biologiques et techniques pour optimiser son déploiement ?", Université Côte d'Azur, since 2022. Supervisors Ludovic Mailleret, Suzanne Touzeau and Louise Van Oudenhove De Saint Gery.
- 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 September 2021, UniCA. Supervisor: O. Bernard.
- PhD in progress: A. Gharib. "Robust control of microalgae processes accounting for future meteorology", since September 2021. (UniCA, ITN Digitalgaesation). Supervisors: O. Bernard (director) and W. Djema (co-director).
- PhD in progress: D. Penaranda Sandoval. "Environmental impact assesment of technologically immature processes", Université Côte d'Azur. Since 2020. Supervisor: O. Bernard.
- PhD in progress: Joseph Junior Penlap Tamagoua. "Ecophysiological modeling of plant-nematode interactions: Understanding the origins and consequences of differential plant susceptibility", Université Côte d'Azur, since 2022. Supervisors: Valentina Baldazzi, Frédéric Grognard and Suzanne Touzeau.
- PhD in progress: Frank Kemayou Mangwa. "Mathematical modeling and analysis of the impact of Radopholus similis on the banana-plantain production", University of Douala, Cameroon, since 2022. Supervisors: Samuel Bowong, Suzanne Touzeau and Frédéric Grognard.
- PhD in progress: Benjamin Böbel. "Mathematical models for robustness and control of intercellular coupling and synchronization between peripheral circadian clocks", Université Côte d'Azur, since April 2023. Supervisors: Madalena Chaves and Jean-Luc Gouzé.

#### 11.2.3 Master theses and internships

- L1: M. Scalabrino 'Modelling of Algae growth with Neural Network A Computer-Model Machine-Learning Approach." UniCA, F. Casagli and O. Bernard.
- L2: Jules Baldous. "Inflation écologique, interactions proies-prédateurs et modélisation des augmentoriums." Supervisor Ludovic Mailleret.
- M2: Taha Belkhayate. "Modélisation de la technique de l'insecte stérile avec sexage imparfait", Université de Pau et des Pays de l'Adour. Supervisors: Marine Courtois, Louise Van Oudenhove De Saint Gery and Ludovic Mailleret.
- M2: Javier Innerarity Imizcoz (Sorbonne Univ.). "Optimal bacterial resource allocation", UniCA/Inria. Supervisors: Jean-Luc Gouzé (Macbes) and W. Djema (Biocore).
- M2: Eliane Younes (Montpellier Univ.). "Analysis of a healthy-cancer cell competition model", UniCA/Inria. Supervisor: W. Djema (Biocore).
- M2: Annalisa Reali (School of Civil and Environmental Engineering, Politecnico di Milano, Italy). "Modelling of algae-bacteria systems for processing marine wastewaters". Supervisor: F. Casagli and O. Bernard.
- M1: Dylan Cormet. "Développement d'un package Julia pour l'épidémiologie saisonnière des maladies des plantes", Polytech Nice. Supervisors: Ludovic Mailleret and Frédéric Grognard

#### 11.2.4 Juries

- O. Bernard was referee of the PhD of J. Sebile-Meilleroux, December 21th (Univ. Nantes).
- O. Bernard was referee of the PhD of J. Farinacci, University of Strasbourg (June, the 14th, 2023),

- O. Bernard was referee of the PhD of A. Saccardo, University of Padova (It) (2023).
- Jean-Luc Gouzé was a member of the jury for the PhD thesis of Clotilde Djuikem (UniCA), for the HDR of Frédéric Grognard (UniCA), and was a rapporteur for the HDR of D. Bichara (Univ. Bordeaux).
- Jean-Luc Gouzé was in the PhD committee of P. Jacquet (Univ. Grenoble) and A. Pavlou (Univ. Grenoble).
- Madalena Chaves was a rapporteur for the PhD thesis of Ana Bulovic (Institut für Biologie, Humboldt-Universität zu Berlin, April 17th 2023). She was a member of the jury for the PhD thesis of Maaike Sansgter (Université Grenoble Alpes, May 11th 2023).
  Madalena Chaves is in the Comité de Suivi Doctoral of: Romain Michelucci (UniCA), Adel Anabi (UniCA), Joseph Penlap (UniCA), and Clémence Métayer (Institut Curie).

## 11.3 Popularization

### 11.3.1 Education

- Madalena Chaves was selected to be part of a group of 101 Portuguese Women in Science, highlighted to showcase several branches of science and research, and motivate young generations to follow a scientific education. Photos of each scientist with a short phrase are on exhibition at the Pavilhão do Conhecimento - Ciência Viva museum in Lisbon and in a booklet.

### 11.3.2 Interventions

- Charlotte Gaviard was interviewed for the Tribune Côte d'Azur to present the DareWin Evolution project for which she received the i-PhD price.
- Walid Djema gave a presentation in PHD SEMINARS at INRIA (23/01/2023).
- Francesca Casagli was invited for a talk at TEDX Cannes 2023 to highlight her research work. (24/11/2023).
- O. Bernard gave all-public presentations in MANDELIEU and Venanson.

# 12 Scientific production

## 12.1 Major publications

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

[2] V. Baldazzi, D. Ropers, J.-L. Gouzé, T. Gedeon and H. de Jong. 'Resource allocation accounts for the large variability of rate-yield phenotypes across bacterial strains'. In: *eLife* 12 (31st May 2023), pp. 1–29. DOI: 10.7554/eLife.79815. URL: https://hal.inrae.fr/hal-04145943.

[3] 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.

[4] 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.

[5] F. Casagli, F. Béline, E. Ficara and O. Bernard. 'Optimizing resource recovery from wastewater with algae-bacteria membrane reactors'. In: *Chemical Engineering Journal* 451 (Jan. 2023), p. 138488. DOI: 10.1016/j.cej.2022.138488. URL: https://inria.hal.science/hal-03932262.

## 12.2 Publications of the year

### International journals

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