RESEARCH CENTRE

Inria Center at Université Côte d'Azur

IN PARTNERSHIP WITH:

CNRS, INRAE, Sorbonne Université

2022

ACTIVITY REPORT

Project-Team

BIOCORE

Biological control of artificial ecosystems

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

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life Sciences

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Project-Team BIOCORE

Creation of the Project-Team: 2011 January 01

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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 Catholique de Louvain (Belgium), Université de Mons (Belgium), MacMaster University (Canada), University Ben Gurion (Israel), Imperial College (United Kingdom), Massey University (New Zealand), Universidad Tecnica Federico Santa Maria and Universidad de Chile (Chile), University of Edinburgh (UK), Universities of Douala, Yaoundé I and Dschang (Cameroon).

3 Research program

3.1 Mathematical and computational methods

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

Building a model is rarely an objective in itself. Once we have checked that it satisfies some biological constraints (*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 [81]. 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) [3].

4.2 CO_2 fixation and fluxes

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

The second challenge consists in exploiting the microalgal bioreactors which have been developed in the framework of the quantification of carbon fluxes between ocean and atmospheres. The SEMPO platform (simulator of variable environment computer controlled), developed within the LOV team, has been designed to reproduce natural conditions that can take place in the sea and to accurately measure the cells behavior. This platform, for which our team has developed models and control methods over the years, is an original and unique tool to develop relevant models which stay valid in dynamic conditions. It is worth noting that a better knowledge of the photosynthetic mechanisms and improved photosynthesis models 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 [85], 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 [89] 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 at Inria Sophia Antipolis. This committee is active in various ways, and organizes events to introduce, inform, and familiarize the community to sustainable development questions and actions.

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

6 Highlights of the year

6.1 Highlights

- To study the synchronization of circadian clocks in peripheral organs such as the liver, we proposed a segmentation of the circadian cycle into six stages, to help analyse the coupling between two clocks, including single stage duration, total period, and maximal amplitudes [20]. Our model reproduces some recent experimental results on the effects of different regimes of time-restricted feeding in liver circadian clocks of mice.

- Exploiting the combination of algae and bacteria in High Rate Algal/Bacterial Ponds is an emerging approach for wastewater remediation and resource recovery. We have explored in [23], through an extensive simulation approach, the 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 favourable to N_2O emission.

- Cultivar mixtures are effective methods for plant disease control that could be boosted by priming-induced cross protection. Through a plant epidemic model, we investigated the effects *n* single-resistance cultivars mixtures on a disease caused by polymorphic pathogen populations [27]. We demonstrated that priming lowers the number of plant genotypes needed to reduce disease prevalence. Given the limited availability of resistance genes in cultivars, this mechanism should be assessed when designing host mixtures.

6.2 Awards

- Francesca Casagli won a L'Oréal-UNESCO 2022 Young Talent Award "For Women in Science" for her research contributing to the preservation of water resources. She also got an "Innovation Price" from Université Côte d'Azur.

- Marielle Péré was awarded poster prizes at the following two conferences: Labex Signalife meeting [63] and the Sophia Artificial Intelligence Summit [64], for her work "Integrating Machine Learning methods in single-cell experimental workflow increases throughput and accuracy for target identification in immuno-oncology."

- Agustin Yabo obtained the second prize of the Doctoral School EDSTIC UCA, for his PhD thesis “Optimal resource allocation in bacterial growth: theoretical study and applications to metabolite production”, defended December 9, 2021, at Inria-Université Côte d'Azur. (Supervisors J.-L. Gouzé and J.-B. Caillau (team MCTAO)).

7 New software and platforms

7.1 New software

7.1.1 In@lgae

Name: Numerical simulator of microalgae based processes

Keywords: Simulation, Microalgae system, Productivity

Functional Description: In@lgae simulates the productivity of a microalgae production system, taking into account both the process type and its location and time of the year. The process is mainly defined by its thermal dynamics and by its associated hydrodynamics. For a given microalgal strain, a set of biological parameters describe the response to nitrogen limitation, temperature and light. As a result, the biomass production, CO2 and nitrogen fluxes, lipid and sugar accumulation are predicted.

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

Contact: Olivier Bernard

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

7.1.2 Odin

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

Keywords: Bioinformatics, Biotechnology, Monitoring, Automatic control

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

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

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

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

Contact: Olivier Bernard

Participants: Olivier Bernard, Nicolas Niclausse, Eugenio Cinquemani, Tamas Muszbek, Thibaud Kloczko, Nicolas Chleq, Jean-Luc Szpyrka, Pierre Fernique, Julia Elizabeth Luna, Come Le Breton, Jonathan Levy, Amine Lahouel, Tristan Cabel, 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. Semi-discrete models have shown their relevance in the modeling of biological phenomena whose nature presents abrupt changes over the course of their evolution [86]. We used such models and analyzed their properties in several practical situations, some of them requiring such a modeling to describe external perturbations of natural systems such as harvest, and others to take seasonality into account. We developed these models in the context of augmentative introduction of species for biological control [1] or the Sterile Insect Technique [62], seasonality in the dynamics of coffee leaf rust [79, 78], of banana and plantain burrowing nematodes [97], and of coffee berry borers [50, 55]

Models in plant epidemiology. We developed and analysed dynamical models describing plant-parasite interactions, in order to better understand, predict and control the evolution of damages in crops. We considered several pathosystems, further described in Section 8.7, describing and controlling the impact on plants of fungi [76, 77] nematodes [97], and pests [33, 50].

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 [45] and Coffee Leaf Rust [79] using the BOCOP software, which is developed by Inria team COMMANDS.

8.2 Metabolic and genomic models

Participants: Jean-Luc Gouzé, Olivier Bernard, Valentina Baldazzi, Juan-Carlos Arceo, Carlos Martinez von Dossow, Agustin Yabo, Walid Djema, Hidde de Jong *(MICROCOSME)*, Eugenio Cinquemani *(MICROCOSME)*, Jean-Baptiste Caillau *(MCTAO)*.

8.2.1 Cell metabolism

Genetic variability in fruit sugar metabolism. Genetic diversity in sugar metabolism has been studied in peach fruit, taking advantage of the simplified model developed by Kanso et al. [83]. Thanks to the reduced parameter space and its lower complexity, the model has been calibrated over a population of 106 peach genotypes, using different calibration strategies. Results have been used to identify QTLs, providing information on the genetic control of sugar metabolism in peach fruit. Two articles are currently under preparation on this topic.

8.2.2 Resource allocation.

Modeling energy constraints in microbial growth. In the framework of the Maximic project (collab. H. de Jong, MICROCOSME team, and T. Gedeon, Montana State University) and as a follow up of our previous work [80], we developed a coarse-grained model of coupled energy and mass fluxes in microorganisms, based on minimal assumptions, and calibration of the model with data for *E. coli* [56]. We used the model to explore the variability of rate-yield phenotypes obtained by change in proteome allocation strategy. We found that the predicted rates and yields in different growth conditions correspond very well with the variability of rate-yield phenotypes observed across different *E. coli* wild type and mutant strains. Moreover, as reported in experimental data, the model predicts the occurrence of a growth rate-yield trade-off, as a generic property of the dependence of growth rate and growth yield on the distribution of resources over the production of ribosomes, enzymes in central metabolism and nutrient uptake, and enzymes in energy metabolism.

Optimal allocation of resources in bacteria. We studied by techniques of optimal control the optimal allocation between metabolism and gene expression during growth of bacteria, in collaboration with Inria MICROCOSME and MCTAO project-teams. We developed different versions of the problem, and considered problems where the aim is to optimize the production of a product in a batch or fedbatch bioreactor [47, 43, 59, 60], (ANR project Maximic, PhD thesis of Agustin Yabo).

Turnpike phenomena in biological optimal control problems: We addressed the problem of maximization of metabolite production in bacterial cells, formulated as an optimal control problem (in collaboration with McTAO). We proved the existence of a turnpike feature that characterizes the optimal solutions ([22]) and we extended the earlier theoretical results on turnpike properties derived in the context of the selection of microbial species ([75],[74]).

8.2.3 Bacterial communities

A synthetic community of bacteria. In the framework of ANR project Ctrl-AB, we consider a synthetic algal-bacterial consortium. The co-culture of *E. coli* with *Chlorella* could lead to higher biomass and lipid productivity. We develop a model, then study its dynamical behavior and eventually it is used to optimize some productivity criteria [44].

In the framework of IPL Cosy (E. Cinquemani), we study the coexistence of two strains of bacteria *E. Coli* in a bioreactor. The strains have been modified synthetically. The aim is to obtain a better productivity in the consortium than in a single strain, by control methods [90]. We obtain optimisation results for the optimal production or yield [58].

In collaboration with L. Sacchelli (MCTAO), we studied during the internship of T. Rolin a problem of observability and estimation in a batch bioreactor.

8.2.4 Synchronization and control using hybrid models

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

Qualitative control for synchronization of piecewise linear systems. We investigated the emergent dynamics in a network of N coupled cells, each expressing a similar bistable switch [12]. The bistable switch is modeled as a piecewise affine system and the cells are diffusively coupled. We show that both the coupling topology and the strength of the diffusion parameter may introduce new steady state patterns in the network. We study the synchronization properties of the coupled network and, using a control set of only three possible values (u_{min}, u_{max}, or 1), we propose different control strategies which stabilize the system into a chosen synchronization pattern, both in the weak and strong coupling regimes.

Weak synchronization and convergence in coupled genetic regulatory networks. We consider a general model of genetic networks and examine two forms of interconnection, either homogeneous or heterogeneous coupling, corresponding to coupling functions that are either equal or different from those governing the individual dynamics. In the case of individual subsystems having unique but different steady states, we prove that the homogeneous coupled system has a unique globally asymptotically stable steady state. Moreover, in the case of large coupling strength, we show that under suitable assumptions the network achieves weak synchronization in the sense that the individual steady states become arbitrarily close [13]. In the heterogeneous case, we prove a similar weak synchronization result in the case of large coupling strength. We apply the results to the synchronization of damped oscillators and to the control of multistable systems.

Time-optimal control of piecewise affine bistable systems. In [14] we give a geometric characterization of the time-optimal trajectories for a piecewise affine bistable switch, based on an adaptation of the

Hybrid Pontryagin's Maximum Principle. Such hybrid models play a major role in systems biology, as they can expressively account for the behaviors of simple gene-regulatory networks

8.3 Biochemical and signaling models

Participants: Madalena Chaves, Odile Burkard, Marielle Péré, Jérémie Roux.

8.3.1 Analysis and coupling of circadian oscillators.

Cycle dynamics and synchronization in a coupled network mammalian circadian clocks. The intercellular interactions between peripheral circadian clocks, located in tissues and organs other than the suprachiasmatic nuclei of the hypothalamus, are still very poorly understood. To investigate this question, we performed a theoretical and computational study of the coupling between two or more clocks, using a reduced model of the mammalian circadian clock previously developed in [66]. Based on a piecewise linearization of the dynamics of the mutual CLOCK:BMAL1 / PER:CRY inactivation term, we proposed a segmentation of the circadian cycle into six stages, to help analyse different types of synchronization between two clocks, including single stage duration, total period, and maximal amplitudes. Our model reproduces some recent experimental results on the effects of different regimes of fasting/feeding alternance in liver circadian clocks of mice [20]. This method helps to further characterize the synchronization steps between two clocks of distinct (but close) periods [61]. This work is in collaboration with F. Delaunay (ANR InSync), and is part of Odile Burckard PhD thesis.

8.3.2 Modeling the apoptotic signaling pathway

TRAIL-induced apoptosis signaling models and kinetic determinants of cell fate decision. To analyze the considerable amount of data from fate-seq [19], [91], a new workflow that analyses single-cell signaling, and uses them for an early prediction of cell fate in new experiments, we proposed an ODE model of the molecular pathways involved in cell death triggered by TRAIL calibrated on single-cell time-trajectories of a FRET reporter measuring apoptosis signaling dynamics in clonal HeLa cells [95]. 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 [46]. Furthermore, we identified three specific parameter combinations that can distinguish between drug resistant or sensitive phenotypes [65]. These parameters could be used to control or predict cell drug-response in the future. This work is part of the PhD thesis of Marielle Péré, in collaboration with J. Roux and his lab.

Integrating Machine Learning methods in single-cell experimental workflow. To more efficiently analyse single-cell data in response to anti-cancer drugs, we developed a pipeline called Fate-seq to profile drug-tolerant persisters, based on predictions of their drug response. To automatize and increase the prediction throughput, we combined a mathematical framework, composed of machine-learning classification models augmented by an ODE model. The first step is to calibrate an ODE model of the extrinsic apoptosis on time trajectories of hundreds of treated clonal HeLa cells, which leads to mechanistic features with predictive values for cell decision. The second step is to combine these 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 our ODE system with machine learning classifiers, outperformed classic machine learning approaches and enabled the accurate cell response prediction of otherwise unpredictable cells [52]. This work is part of the PhD thesis of Marielle Péré, in collaboration with Diego Oyarzun (University of Edinburgh). M. Péré presented this work as at several meetings [51] and as a poster both at the Signalife meeting [63] (November 2022) and the Sophia IA Summit [64] (November 2022). She was awarded a poster prize at both conferences.

Fields of application

8.4 Bioenergy

8.4.1 Modeling microalgae production

Participants: Olivier Bernard, Antoine Sciandra, Walid Djema, Francesca Casagli, Bruno Assis Pessi, Ignacio Fierro, Ali Gharib, Liudi Lu, Jean-Philippe Steyer, Laetitia Giraldi *(CALISTO)*.

Experimental developments

Running experiments 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. This platform improved knowledge of several biological processes such as lipid accumulation or pigment dynamics under light fluctuation, nitrogen or temperature stress... [15, 34].

This experimental platform was used to control the long term stress applied to a population of microalgae using optimal control strategies [28]. This Darwinian selection procedure generated several new strains more transparent after several months in the so called selectiostats [34] leading to an enhanced productivity at high density.

Experimental work was also carried out in collaboration with the Inalve startup with microalgal biofilm to determine the impact of light and dark sequences on cell growth and photoacclimation. The architecture of the biofilms was also observed for different species with confocal microscopic techniques [40, 30].

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

Metabolism of carbon storage and lipid production. A metabolic model has been set up and validated for the microalgae *Chlorella vulgaris*, on the basis of the DRUM framework , in order to simulate autotophic, heterotropic and mixotrophic growth, and to determine how to reduce substrate inhibition. The model was extended to other substrates such as glucose or glycerol. After a calibration phase, the model was successfully challenged with data from 122 experiments collected from scientific literature in autotrophic, heterotrophic and mixotrophic conditions [38].

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. Then, we extend the previous developed metabolic model to describe a co-culture of *Chlorella* with 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.

The mechanisms to regulate the photosynthesis in conditions of nitrogen limitation were represented in a metabolic model, using the DRUM framework [15]. Different mechanisms were hypothesized. On the basis of this model, an alternative interpretation of the Droop model was proposed, which can be understood as an accumulation of carbon during nitrogen stress, rather than the common belief of a nitrogen pool driving growth.

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 developed 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 [17]. A strategy to optimally mix the algae was derived. It was finally combined with the a non flat topography [67].

Modeling photosynthetic biofilms. Several models have been developed to represent the growth of microalgae within a biofilm. A first structured physiological model [40] 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 realised at the LGPM (CentraleSupelec) [30]. Another approach accounts for the dynamics of the light harvesting systems when cells are submitted to rapid successions of light and dark phases. A simpler model was developed and used to identify the optimal working mode of a process based on photosynthetic biofilm growing on a conveyor belt. The model was used to identify the worldwide potential of microalgal biofilms under different climates. This study was extended considering the impact if the culture has to be heat 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 [31]. The experimental validation of this model, together with the extrapolation of productivities at larger scale is the topic of the PhD thesis of Yan GAO at CentraleSupelec (directed by F. Lopes and O. Bernard).

Modeling microalgae production processes. A model representing the dynamics of microalgae when growing in suboptimal conditions of light, nitrogen and phosphorus was developed. It consists in an extension of the Droop model accounting for the two quota of nitrogen and phosphorus. The model also represents the pigment acclimation to various light intensities. We have studied in [87] the response of a Droop model forced by periodic light or temperature signals. We transformed the model into a planar periodic system generating a monotone dynamical system. Combined with results on periodic Kolmogorov equations, the global dynamics of the system can be described.

Modeling thermal adaptation in microalgae. We studied a broad range of species and their response to temperature. It turns out that the optimal temperature, the minimal and the optimal temperature for growth are strongly correlated. A relationship between these cardinal temperatures and key parameters from the environment (sea surface temperature, solar flux, ...) was identified.

Experiments have been carried out in collaboration with A.-C. Baudoux (Biological Station of Roscoff) in order to study growth of various species of the microalgae genus *Micromonas* at different temperatures. After calibration of our models, we have shown that the pattern of temperature response is strongly related to the site where cells were isolated. We derived a relationship to extrapolate the growth response from isolation location. With this approach, we proved that the oceanwide diversity of *Micromonas* species is very similar to the oceanwide diversity of the phytoplankton [71]. We have used Adaptive Dynamics theory to understand how temperature drives evolution in microalgae. We could then predict the evolution of this biodiversity in a warming ocean and show that phytoplankton must be able to adapt within 1000 generations to avoid a drastic reduction in biodiversity [71].

Modeling viral infection in microalgae. In collaboration with A.-C. Baudoux (Biological Station of Roscoff) a model was developed to account for the infection of a *Micromonas* population, with population of susceptible, infected and also free viruses. The model turned out to accurately reproduce the infection experiments at various temperatures, and the reduction of virus production above a certain temperature [72]. The model was then extrapolated to the whole ocean to better understand how the warming will impact the mortality due to viruses.

8.4.2 Control and Optimization of microalgae production

Optimization of the microalgae production through optical depth. 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 [31]. For a large light period, we demonstrate that the average photosynthetic rate can be improved.

Productivity optimization turns out to be highly dependent on how light is distributed along the reactor, and is therefore related to the extinction rate and the background turbidity. In [16], we propose a theoretical analysis of this problem, by introducing the concept of optical depth productivity for systems where background turbidity must be accounted for. A global optimum maximizing productivity is proposed, extending the concept of the compensation condition, consisting in compensating the algal growth rate at the bottom of the reactor by the respiration. This condition can drive the optimization of the surface biomass productivity depending on the minimum reachable depth. We develop a nonlinear controller and prove the global asymptotic stability of the biomass concentration towards the desired optimal value. 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 proposed a heat transfer model coupled with biological model to simulate the temperature evolution, depending on the meteorology, and its impact on the 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 [26]. This coupled model was validated on long term series in various reactor configurations [25, 24]. We also considered the influence of a greenhouse on the medium temperature and subsequently on algal productivity [39] simulating different climatic conditions and the species for which the use of a greenhouse is beneficial.

A model predictive control algorithm was run based on simple microalgae models coupled with physical models where culture depth influences thermal inertia. Optimal operation in continuous mode for outdoor cultivation was determined when allowing variable culture depth. Assuming known weather forecasts considerably improved the control efficiency. This is the subject of the PhD thesis of Ali Gharib in the framework of the ITN Digitalgaesation.

Interactions between species. We have proposed an optimal control strategy to select in minimal time the microalgal strain with the lowest pigment content [73]. The control takes benefit from photoinhibition to compute light stresses penalizing the strains with a higher pigment content and finally selecting microalgae with lower chlorophyll content. Another optimal control problem was considered for selecting a strain of interest within two species competing for the same substrate, when dynamics is represented by a Droop model. In both cases, the optimal control derived from the Pontryagin maximum principle also exhibits a turnpike behavior [75]. This is a collaboration with team MCTAO. Strategies to improve algae productivity were derived. Strategies to optimally separate algae species were derived: design of an optimization procedure to select the most productive algae strains ([28]).

We assessed the effect of predation by zooplancton and studied the role of the dilution rate in the control of zooplankton populations and in the optimization of biomass productivity. We showed that in the long-term operation the optimal constant dilution rate must ensure the eradication of the zooplankton population. In the case of time-varying dilution rate, we numerically solve an optimal control problem over a finite interval of time. We find that the optimal solution approaches the solution for the static problem most of the time, except when zooplankton actively avoid the pond outflow [35],[88].

8.4.3 Modeling mitochondrial inheritance patterns

Most eukaryotes inherit their mitochondria from only one of their parents. When there are different sexes, it is almost always the maternal mitochondria that are transmitted. Indeed, maternal uniparental inheritance has been reported for the brown alga Ectocarpus but we show in this study [92] that different strains of Ectocarpus can exhibit different patterns of inheritance: Ectocarpus siliculosus strains showed maternal uniparental inheritance, as expected, but crosses using different Ectocarpus species (7 strains) exhibited either paternal uniparental inheritance or an unusual pattern of transmission where progeny inherited either maternal or paternal mitochondria, but not both. A possible correlation between the pattern of mitochondrial inheritance and male gamete parthenogenesis was investigated. Moreover, in contrast to observations in the green lineage, we did not detect any change in the pattern of mitochondrial inheritance in mutant strains affected in life cycle progression. Finally, an analysis of field-isolated strains provided evidence of mitochondrial genome recombination in both Ectocarpus species.

8.5 Biological depollution

8.5.1 Control and optimization of bioprocesses for depollution

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

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

Algae-bacteria processes for treating wastewater are becoming a very attractive technology [36]. We designed and calibrated a model, that was validated with more than one year of data [69]. The model analysis revealed that despite pH regulation, a strong limitation for inorganic carbon was found to hinder the process efficiency and to generate conditions that are favorable for N_2O emission. A control strategy regulating alkalinity turns out to be necessary to enhance the performance and avoid dammageable emissions [68]. 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. [26].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. 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 [23]. The temperature response for two different process configurations was also explored and compared [25], [24].

A work was started to simplify these models and enhance their calibration by considering artificial neural networks, which are integrated in a way that the full model respects some key constrains (positivity, boundness, ...) [96].

8.5.2 Coupling microalgae to anaerobic digestion

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

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 [36]. 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 nitriying bacteria and algae [23]. 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 [38] 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, Marjorie Alejandra Morales Arancibia.

Environmental impact assessment. To follow up the pioneering life cycle assessment (LCA) work of [84], we identified the obstacles and limitations which should receive specific research efforts to make microalgae production environmentally sustainable.

We have studied the environmental impact of protein production from microalgae in an algal biofilm process and compared it to other sources (fisheries, soy,...). We have analysed the updated version of the production system and propose several optimisation to reduce the environmental impact. This study confirms the interest of microalgae for reducing the environmental impact [37] 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 are not mature technologically (PhD thesis of D. Penaranda).

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

8.7 Design of ecologically friendly plant production systems

8.7.1 Controlling plant arthropod pests

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

The question of how many and how frequently natural enemies should be introduced into crops to most efficiently fight a pest species is an important issue of integrated pest management. The topic of optimization of natural enemies introductions has been investigated for several years [85], and extends more generally to pulse perturbations in population dynamics. Importantly, we published a book chapter reviewing augmentative biological control methods [53]. Our research in this context has expanded to the modeling and optimization of introduction strategies in the context of the Sterile Insect Technique (SIT). In the framework of the Ecophyto project 'CeraTIS Corse' we have developed a model for the dynamics of the mediterranean fruit fly *Ceratitis capitata*, with continuous introductions of sterile males. We have shown that residual fertility among the 'sterile' males could destabilize the pest-free, and gave a condition to be satisfied to ensure that the pest-free equilibrium is the only equilibrium, and that it is stable. However practical efficacy of SIT can be ensured even beyond that threshold [62]. Initial developments for ANR project Suzukiis:me were obtained in the internship of Crésus Kounoudji, with the development of a first model of the dynamics of the fruit fly *Drosophila suzukii* with impulsive introductions.

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 [93, 82]. In particular, we studied the influence of Allee effects and density dependence in dispersal on range expansion, extending the concept of range pinning in Ecology and pointing out its interaction with demographic stochasticity [94]. These works have been performed in collaboration with Elodie Vercken (ISA) and partly with Vincent Calcagno (ISA), and principally published through the Peer Community In (PCI) recommandation process.

Concurrently, we are exploring the correlation between biological control agents movement characteristics at different scales, from laboratory experimental characterization to field dispersal. This research is performed on various species of parasitoids belonging to the genus Trichogramma, and is the main topic of Melina Cointe PhD thesis that started in autumn 2020 (director Vincent Calcagno, ISA). In this context, interesting results have been published on the photo- an geo-tactic preferences of egg-parasitoids in the genus *Trichogramma* [21]. This research has been performed in collaboration with Vincent Calcagno (ISA).

Modeling and control of coffee berry borers. We developed a model describing the coffee berry borer dynamics based on the insect life-cycle and the berry availability during a single cropping season. A control was introduced, based on a biopesticide (entomopathogenic fungus such as *Beauveria bassiana*) that is sprayed and persist on the berries. An optimal control problem was solved previously [55] (see Section 8.1.2). A PDE model taking the age of the berries and the preference of coffee berry borers for more mature berries was developed, and we derives an explicit formula of the basic reproduction number, R0, using the next generation approach and the biological interpretation of this threshold in a specific case [33]. Optimal control was also used on that model for the deployment of biological control agents. A semi-discrete multi-seasonal model was also developed, integrating the difference between the dynamics during the rainy and dry seasons, as well as harvesting and plantation cleansing as discrete events; a condition was obtained for the stability of the pest-free periodic solution, requiring sufficient cleansing to ensure that not too many borers survive from one season to the next [50]. This research pertains to Yves Fotso Fotso's PhD thesis through the EPITAG associate team [55].

8.7.2 Controlling plant pathogens

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

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

We built a generic spatio-temporal epidemiological model representing fungal diseases on annual field crops in a multi-pathogen context. This work benefits from data collected in INRAE projects COCODIV and DYNAMO. We plan to include the modeling developments in the SiDRes tool.

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. After an initial result considering mixtures between susceptible and resistant hosts, mixtures of different resistant strains and the possible presence of supervirulent pathogens were studied; we have shown that, at equilibrium, pathogens that are present all have the same virulence complexity (number of resistant-breaking alleles) [70], [48]. This was done in collaboration with Frédéric Hamelin (Agrocampus Ouest) in the framework of Pauline Clin's thesis that she defended in December 2022.

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. This paper is the basis of an ANR project proposition that is under review [42].

Other methods for the control of plant pathogens Coffee leaf rust (CLR) is a disease caused by a basidiomycete fungus, *Hemileia vastatrix*, that has a major impact on coffee production around the world. We produced a stage structured model of the disease development representing young and mature leaves, with different health status (susceptible, latent, infectious, dry), berries and spores. We deduced from its analysis that very different forms of bifurcation could occur, with the possibility of having endemic equilibrium despite a reproduction number R0 smaller than one and even destruction of the plantation for large R0 [49]. We also studied a multi-seasonal impulsive version of a simplified form of this model, with multiple biocontrol agent releases per year.

8.7.3 Plant-nematode interactions

Participants: Valentina Baldazzi, Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Joseph Penlap.

Based on our previous work, an ecophysiological model of plant growth, including both the vegetative and the reproductive phases, has been developed and coupled to a model of nematode population dynamics. Briefly, the plant is divided into shoots, source of carbon for the plant, and roots, source of water, that exchange and employ resources for growth. During the reproductive phase, fruit set 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 allocation pattern of the plant among its compartments, with important consequences on plant susceptibility to pest attack. The model will be used to explore the dynamical behavior 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. The model is currently under calibration for two plant species, using experimental data collected in the framework of a previous project (INRAE ArchiNem project, 2020-2021). This work is part of the PhD thesis of Joseph Penlap Tamagoua (Inria-INRAE funding 2022-2025). A publication is currently in preparation focusing on the experimental results.

9 Bilateral contracts and grants with industry

9.1 Bilateral contracts with industry

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

9.2 Bilateral grants with industry

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

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

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 analysing dynamical models describing plant-parasite interactions, in order to better understand, predict and control the evolution of damages in crops. To ensure the relevance of our models, field experts and stakeholders need to be closely associated. We will focus on pest and pathogens that affect major staple food and cash crops, such as cocoa plant mirids, plantain and banana plant-parasitic nematodes, coffee berry borers, coffee leaf rust, maize stalk borers, cabbage diamondback moths, papaya mealybugs, etc. To tackle these issues, we jointly supervise master and PhD students.

10.2 International research visitors

10.2.1 Visits of international scientists

Other international visits to the team

- Henrik Geltner, PhD student at Wageningen University visited us for a total duration of 2 months in the framework of the ITN DigitAlgaesation to work on pH modeling.
- Tehreem Syed visited us for a total duration of 2 months in the framework of the ITN DigitAlgaesation to work on machine learning for representing photobioreactors.
- Jineth Arango visited us for 5 months in the framework of the Associated Team Blue Edge to work on the modeling of membranes in algae-bacteria processes.

10.2.2 Visits to international teams

Research stays abroad

- M. Péré spent three months at the University of Edinburgh (UK) in the group of D. Oyarzun, in the context of a Royal Society Edinburgh Saltire Fellowship (October 2021-March 2022). She worked and gained expertise on machine learning algorithms for analysis of biological data.
- M. Chaves spent two weeks at Instituto Superior Técnico (Lisbon, Portugal) to work with Rui Dilão on internal models of cell growth (July 2022).

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 (Imperial), 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 (DTU), Denmark
- UNIVERSIDAD DE ALMERIA (UNIVERSIDAD DE ALMERIA), Spain
- WAGENINGEN UNIVERSITY (WU), Netherlands
- CENTRALESUPELEC (CentraleSupélec), France
- TECHNISCHE UNIVERSITAET DRESDEN (TUD), Germany
- GOTTFRIED WILHELM LEIBNIZ UNIVERSITAET HANNOVER (LUH), Germany

Inria contact: Olivier Bernard (vice coordinator)

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 optimising 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, UCA) and L.Tournier (MaIAGE, INRAE Jouy-en-Josas).
- **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).
- **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-UCA.
- **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.

10.4.2 Inria funding

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

- **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

- S. Touzeau, together with Nahla Abdellatif (ENSI-University of Manouba, Tunisia), organised the CIMPA School "Vert Numérique : biologie mathématique et écologie théorique" in Tunisia (24/9-03/10/2022).
- O. Bernard organized the summer-school: "Modelling and control of photobioreactors", organized from the ITN digitalgaesation, on September 2022 16th to 23rd.

Member of the organizing committees

- Walid Djema and Jean-Baptiste Caillau (McTAO) co-organized two sessions on "Optimal control applied to life sciences" at the PGMO 2022 - EDF Lab ParisSaclay, Palaiseau – November 2022.
- Marielle Péré was one of the organizers of "Le monde des mathématiques industrielles" (MOMI2022), a workshop on applied mathematics in industry, dedicated to PhD students (May 2022, Sophia Antipolis).

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 13th to 15th 2022 in Roma.

Member of the conference program committees

- M. Chaves was in the program committee of the 25th Symposium on Mathematical Theory of Networks and Systems (MTNS 2022).
- O. Bernard was in the scientific committee of the 13th IWA Specialist conference on Wastewater Ponds and Algal Technologies (Brisbane, Australia, July 3rd to 7th).

Organization of the scientific BIOCORE Seminar

- Walid Djema organizes a monthly scientific seminar in which external guests and collaborators are regularly invited (see the Table below).

Full program of the BIOCORE Seminar		
11/2021	**Francis Mairet** Ifremer Nantes -Laboratoire Physiologie et Biotechnologie des Algues.	**Microalgae photoacclimation as an optimal control problem of resource allocation**
03/2022	**Jérémy Rouot** Laboratoire de Mathématiques de Bretagne Atlantique. Université de Brest.	**Accessibilité et géodésiques anormales en contrôle optimal : une approche géométrique sur deux études de cas.**
04/2022	**Samuel Buchet** Laboratoire des Sciences du Numérique de Nantes LS2N-Ecole Centrale de Nantes.	**Qualitative modeling with Logic Programs applied to single-cell data analysis**
05/2022	**Tewfik Sari** ITAP, INRAE, Institut Agro, University of Montpellier.	**Best operating conditions for biogas production and biomass production in the chemostat**
06/2022	**Marielle Péré** BIOCORE Inria, UCA.	**Machine learning models for the early prediction of cell drug response in fluorescent single-cell essays**
09/2022	**Vincent Calcagno** Institut Sophia Agrobiotech, UCA, INRAE, CNRS, Sophia Antipolis.	**When complex movement yields simple dispersal: dissecting spatial propagation and parasitism in groups of parasitic wasps**
10/2022	**BIOCORE TEAM**	**Annual Seminar – Iles de Porquerolles**
11/2022	**Bastien POLIZZI** Laboratoire de Mathématiques de Besançon Université de Franche-Comté	**(Epi)mutation rates and the evolution of composite trait architectures**
12/2022	**Madalena Chaves** BIOCORE Inria, UCA.	**Some remarks on modeling cellular growth rate, celldivision, and their links with other internal processes**
01/2023	**Julien Arino** Department of Mathematics, University of Manitoba, Winnipeg, MB, Canada.	**Case introductions in the context of SARS-CoV-2 infections**

Reviewer

- All BIOCORE members have been reviewers for the major 2022 conferences in our field: CDC, ECC, IFAC Congress, FOSBE.

11.1.3 Journal

Member of the editorial boards

- M. Chaves is an Associated Editor of SIAM Journal on Applied Dynamical Systems (SIADS), since January 2015. She is an Associated Editor of the Conference Editorial Board (CEB) of the IEEE Control Systems Society, since August 2020. She is also an Associated Editor for the new IEEE Open Access Journal on Control Systems. In 2022 she was Guest Editor of a Special issue of Mathematical of Control, Signals, and Systems, on the occasion of Eduardo Sontag 70th birthday.
- J.-L. Gouzé is an Associated Editor of the journal Frontiers in Applied Mathematics and Statistics (Mathematical Biology).
- S. Touzeau is an Academic Editor of PLOS ONE, since August 2018.

Reviewer - reviewing activities

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

11.1.4 Invited talks

- W. Djema was an invited speaker at the 15th Viennese Conference on Optimal Control and Dynamic Games (July 12–15, 2022).
- W. Djema was invited to give a talk at LMBA Seminar (LMBA: Laboratoire de Mathématiques de Bretagne Atlantique) on 'Optimal Control of Microalgae'.

- M. Chaves was invited to give a talk at the Workshop on Hybrid Models and Methods in Systems Medicine (July, Institut Curie, Paris). She also gave an invited talk at the online GT BIOSS (Biologie des Systèmes) monthly seminars.
- F. Casagli was invited to give a talk within the IWA webinar " Modelling and Integrated Assessment Specialist Group (MIA)" the 21st of December, on the challenges for modelling algae-bacteria systems.
- O. Bernard was invited to give a conference at Sapienza, University in Roma, Department of Chemistry "Algae-bacteria systems for nitrogen recovery: promises and challenges through a modelling approach" the 16th of December 2022.

11.1.5 Scientific expertise

- M. Chaves is a member of the scientific committee of Labex Signalife (since 2020).
- M. Chaves participated in the selection committee for a post of Maître de Conférences at Polytech, Laboratoire I3S (Univ. Côte d'Azur).
- O. Bernard is a member of the scientific committee of the Inalve company.
- O. Bernard represents Inria at the ANCRE (Alliance Nationale de Coordination de la Recherche pour l'Energie).
- O. Bernard represents is a member of the scientific committee of IRD (Institute of Research for the Development) in the CSS5 section (models and data). He participated to the recruitment juries for researchers and research directors at IRD.
- O. Bernard is in the Scientific and Pedagogic committee of the UCA- EUR LIFE and in the steering committee of Federal Recherche Institut (IFR) Marine Ressources (MARRES).
- S. Touzeau participated in selection panels for INRAE junior research scientists.
- J.-L. Gouzé is in the scientific committee of Académie 4 of UCA-Jedi. He is a member of the board of the SFBT (French Speaking Society for Theoretical Biology).

11.1.6 Research administration

- M. Chaves, F. Grognard, and L. Mailleret are members of the INRAE Commission Scientifique Spécialisée (CSS) for Mathématique, Informatique, Sciences et Technologies du numérique, Intelligence artificielle et Robotique (MISTI).
- M. Chaves is a member of the local Inria committee for doctoral studies (CSD) and the committee NICE for welcoming external researchers (post-docs, "delegations"). She is also a representative of Inria at the Canceropole PACA. 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.
- O. Bernard is a member of the ADT (Technological Development Actions) commission at Inria and of the local commission for sustainable development.
- M. Péré was one of the organizers of the Inria PhD Student Seminars, taking place every two weeks.
- F. Grognard is a member of the steering committee of Academy 3, Space, Environment, Risk and Resilience of UCA-JEDI. He is co-head of the development of the MSc Risk of UCA-JEDI and is a member of the Scientific Committee of the Agroecosystems department of INRAE.
- L. Mailleret is the head of the M2P2 team (Models and Methods for Plant Protection) of ISA. He's in the Unit and scientific council of Institut Sophia Agrobiotech.

- L. Mailleret is an elected member (since 2020) of the Scientific and Pedagogic Council (CoSP) of the EUR LIFE (Graduate school in Life and Health Sciences) of Université Côte d'Azur.
- S. Touzeau is a member of the steering committee of the INRAE Metaprogramme SuMCrop "Sustainable Management of Crop Health", a follow-up of the SMaCH metaprogramme (since 2016).
- V. Baldazzi ans S. Touzeau are elected members of the Institut Sophia Agrobiotech council.
- J.-L. Gouzé is in the Inria committee supervising the doctoral theses, 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 UCA.

11.2 Teaching - Supervision - Juries

11.2.1 Teaching

- Licence: F. Grognard (42h ETD) and L. 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: W. Djema (20h ETD); "Mathématiques pour Biologistes: Analyse et Modélisation", L1 Université Côte d'Azur, France.
- Master: O. Bernard (4.5h ETD), "Bioenergy from microalgae", M2, Master International Energy Management : alternatives pour l'énergie du futur, Ecole Nationale Supérieure des Mines de Paris, France.
- Master: O. Bernard (18h ETD), "Modeling biotechnological processes", M2, Ecole CentraleSupelec, Saclay, France.
- Master: O. Bernard (18h ETD), "Automatic Control applied to biotechnological processes", M2, Ecole CentraleSupelec, Saclay, France.
- Master: O. Bernard (6h ETD), "Cultivation and use of Microalgae", Master Mares, Université Côte d'Azur, France.
- Licence: O. Bernard (35h ETD), "Use and optimization of photobioreactors", Université de Pau et des pays de l'Adour, France.
- Master: O. Bernard (27h ETD) and W. Djema (27h ETD), "Enseignement d'Intégration EI – ST5 Méthanisation", Ecole CentraleSupélec, Paris-Saclay, France.
- Licence: O. Bernard ($3\times$ 3h ETD); "Introduction to Life Cycle Assesment", L3 Université Côte d'Azur, France.
- Master : W. Djema (20h ETD); "Traitement du Signal", M1 IM, Université Côte d'Azur, France.
- Master: W. Djema (17h ETD) and M. Chaves (10h ETD); "Modélisation des réseaux biologiques", M1 Sciences du Vivant, Université Côte d'Azur, France.
- Master : J.-L. Gouzé (20h ETD), M. Chaves (13.5h ETD), "Modeling biological networks by ordinary differential equations", M1, 2nd year Engineering in Génie biologique, Polytech Nice Sophia, Université Côte d'Azur, France.
- Master: F. Grognard (21h ETD) and L. Mailleret (21h ETD), "Bio-Mathématiques", M1, 2nd year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Côte d'Azur, France.
- Master: F. Grognard (30h ETD) and W. Djema (15h ETD), "Elements of mathematical modelling", M1, MSc in Environmental Hazards and Risks Management, Université Côte d'Azur, France.

- Licence: C. Djuikem (18h ETD), "Introduction à la modélisation mathématique et numérique", L3, 1st year in Water Engineering, Polytech Nice Sophia, Université Côte d'Azur, France.
- Licence: W. Djema (16h ETD); "Math0: Enjeux", L1 Université Côte d'Azur, France.
- Licence: C. Djuikem (40h ETD), "Analyse et modélisation", L1 Sciences de la vie, Université Côte d'Azur, France.
- 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.
- Research School: J.-L. Gouzé gave extended conferences and S. Touzeau taught a course at the CIMPA School "Vert numérique", Tunisia.
- W. Djema gave lectures on 'Observers' and 'Dynamic Optimization' during the 'Summer School on Automatic Bioprocess Control' at Inria Sophia Antipolis, organized by O. Bernard on behalf of the ITN Digitalgaesation Project.

11.2.2 Supervision

- PhD: Y. Fotso Fotso. "Modeling, analysis and control of coffee berry borer", University of Dschang, Cameroon, defended January 17. Supervisors: B. Tsanou (Univ. Dschang), S. Bowong (Univ. Douala), F. Grognard, S. Touzeau.
- PhD: P. Clin, "Understanding biodiversity to sustainably prevent plant diseases", defended December 16th, Université de Rennes 1. Supervisors: F. Hamelin, L. Mailleret, D. Andrivon.
- PhD in progress: M. Péré. "'Modeling cancer drug response heterogeneity using experimental tumor single-cell dynamics and transcriptomics', since October 2019, Univ. Côte d'Azur. Supervisors: M. Chaves and J. Roux (IRCAN, Nice).
- PhD in progress: C. Djuikem. "Modelling and control of perennial plant phytopathogens", Université Côte d'Azur, since October 2019 (defense January 5th 2023). Supervisors: F. Grognard, S. Touzeau, S. Bowong (Univ. Douala).
- PhD in progress: O. Burckard. "Coupling, synchronization, and control of cellular oscillators through mathematical modeling and analysis", Université Côte d'Azur, since 2021. Supervisor: M. Chaves.
- PhD in progress: M. Cointe. "Mieux prédire la propagation spatiale de groupes de trichogrammes pour améliorer le biocontrôle : de l'écologie du mouvement à la dispersion dans les cultures", Université Côte d'Azur, since 2020. Supervisors V. Calcagno, L. Mailleret.
- PhD in progress: M. 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 L. Mailleret, S. Touzeau, L. van Oudenhove.
- 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, UCA. Supervisor: O. Bernard.
- PhD in progress: A. Gharib. "Robust control of microalgae processes accounting for future meteorology", since September 2021. (UCA, ITN Digitalgaesation). Supervisors: O. Bernard (director) and W. Djema (co-director).
- PhD in progress: B. Assis Pessi. "Modelling and Control of outdoor microalgal processes", since November 2019, Université Côte d'Azur. Since 2019. Supervisors: O. Bernard and L. Giraldi (team McTao).

- PhD in progress: D. Penaranda Sandoval. “Environmental impact assesment of technologically immature processes”, Université Côte d’Azur. Since 2020. Supervisors: O. Bernard
- PhD in progress: Yan GAO. "Response of photosynthetic biofilms to fluctuating light", Université de Saclay, since 2018. Supervisor: F. Lopes and O. Bernard.
- PhD in progress: R. Ranini. "Deep leanring approaches for enhancing models in oceanography", UCA, since 2022. Supervisor: 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).

11.2.3 Master theses and internships

- M2: K. Burger ‘Growing Algae without Water? A Computer-Model Machine-Learning Approach ‘” UCA, F. Casagli and O. Bernard.
- M1: Crésus Kounoudji. "Modéliser la dynamique des populations de Drosophila suzukii afin d’optimiser le déploiement de la Technique de l’Insecte Stérile", Aix Marseille Université, Supervisors: L. van Oudenhove, L. Mailleret, S. Touzeau, F. Grognard.
- M1: Emma Ceci. "Development and calibration of an integrated model of the plant-nematode system. Effect of phenotypic variations on plant growth.", INSA Lyon. Supervisor: V. Baldazzi and S. Touzeau.
- M1: T. Rolin, “Observability and observers for mathematical models of bacterial growth”. Polytech Nice MAM4, supervised by L. Sacchelli (MCTAO) and J.-L. Gouzé.

11.2.4 Juries

- M. Chaves was a reviewer for the PhD thesis of Samuel Buchet (École Central de Nantes) and a reviewer for the HDR of Céline Casenave (Université de Montpellier).
- S. Touzeau was in the jury and F. Grognard invited in the jury of Y. Fotso Fotso (Université de Dschang, Cameroon).
- L. Mailleret was in the jury and F. Grognard invited in the jury of P. Clin (Université de Rennes 1).
- O. Bernard was referee of the PhD of Dirk de Kobe, October 17th (Univ. Leuven).
- O. Bernard was referee of the PhD of F. Baudeau , December 15th (Univ. Toulouse).
- J.-L. Gouzé was a member of the jury for the PhD thesis of C. Djuikem (UCA), for the HDR of A. Goelzer (Univ. Paris Saclay), and was a rapporteur for the PhD thesis of Manel Dali Youcef (Univ. Montpellier).
- M. Chaves is in the PhD committee (CSI) of Sandra Kovachka and Romain Michelucci (Université Côte d’Azur), and also Pauline Delpierre (Université de Lille).
- F. Grognard and S. Touzeau are in the PhD committee of Pauline Clin (Université de Rennes 1).
- F. Grognard is in the PhD committee of Méline Saubin (Université de Lorraine) and of Christos Bountzoukis (Université Côte d’Azur)
- L. Mailleret is in the PhD committee of Clotilde Djuikem (Université Côte d’Azur).
- J.-L. Gouzé is in the PhD committee of P. Jacquet (Univ. Grenoble), A. Pavlou (Univ. Grenoble) and Odile Burckard (UCA).

11.3 Popularization

11.3.1 Articles and contents

- Diego Penaranda published a popularisation paper published in Actu-Environment magazine. "Quantifying our impact on the environment: life cycle analysis"
- Francesca Casagli was interviewed from Nice Matin magazine for the award she received from the L'Oréal-UNESCO program For Women in Science. "Avec sa science, elle lutte contre les eaux polluées".
- Francesca Casagli was interviewed from 20 minutes magazine for the award she received from the L'Oréal-UNESCO program For Women in Science. "Alpes-Maritimes : Des microalgues pour décontaminer les eaux usées, les travaux d'une chercheuse récompensés".
- Francesca Casagli was interviewed from Nice Matin magazine for the Excellence Awards winners evening. Nice Matin published an 8-page supplement on the eve of the event dedicated to research at the University of Côte d'Azur . "Purifier les eaux polluées grâce à des microalgues".
- Walid Djema participated to the supervision of Baptiste Pellegrinetti (Stagiaire Amodiation Scientifique) during his Master internship @TerraNumerica and Inria. A poster on 'Microalgae Selection' has been prepared and presented during the official opening of the new Terra Numerica building in Sophia Antipolis.

11.3.2 Interventions

- W. Djema, member of the CLDD (Commission Locale de DD à Inria), organized a conference entitled "La mobilité active et durable : quand la psychologie et la géographie se combinent pour mieux la comprendre et la promouvoir" (June 7th, 2022) at Inria Sophia Antipolis. The conference was animated by Claudia Teran-Escobar (Institut des Géosciences de l'Environnement à Grenoble), with the help of Martine Olivi (FACTAS).
- P. Bernhard gave all-public presentations at the Nice médiathèque Raoul Mille, lycée Carnot (Cannes, 2 conferences), La Trinité, Menton, La Tour sur Tinée (2 conferences, with one at small Roussillon village), Beaulieu, Contes, Bonson, and Sospel.
- O. Bernard gave all-public presentations in Biot, Contes, Colomars and Venanson.
- M. Chaves gave an all-public presentation on research in mathematics at the occasion of the ceremony of prize distribution for the regional Mathematics Olympiads, at Inria (June 2022).
- In the context of the program "1 scientist – 1 class: Chiche!", C. Djuikem presented her work and interacted with students at the Thierry Maulnier high school in Nice (January 2022) and the Jules Ferry high school in Cannes (March 2022).
- C. Djuikem participated in the MathC2+ program (June 2022), which welcomes high school students with a scientific profile, who discover more about mathematics and Inria research.

12 Scientific production

12.1 Major publications

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

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

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

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

[5] N. Giordano, F. Mairet, J.-L. Gouzé, J. Geiselmann and H. De Jong. 'Dynamical allocation of cellular resources as an optimal control problem: Novel insights into microbial growth strategies'. In: *PLoS Computational Biology* 12.3 (Mar. 2016). e1004802. DOI: 10.1371/journal.pcbi.1004802. URL: https://hal.inria.fr/hal-01332394.

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

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