Activity Report 2018

Project-Team BIOCORE

Biological control of artificial ecosystems

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Project-Team BIOCORE

Creation of the Project-Team: 2011 January 01

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2. Overall Objectives

2.1. Introduction

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

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

Research themes:

Mathematical and computational methods:

- Tools for modeling in biology: model design, validation, parameter identification.
- Mathematical properties of models in biology: mathematical studies of models and of their global behavior.
- Software sensors for biological systems: using the model and on-line measurements to estimate the variables that are not measured directly.
- Control, regulation, and optimization for biological systems; design of laws to maintain a variable at a given level, or to optimize the productivity of the system.

A methodological approach to biology: system study at different scales

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

Fields of application:

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

Software for biological modeling and supervision of biological processes.

National, international and industrial relations

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

- Participation in French groups: ModStatSAP (Modélisation et Statistique en Santé des Animaux et des Plantes), GDR Invasions Biologiques.

- Participation to national programmes: ANR projects Phycover, FunFit, ICycle, and Maximic, Plan Cancer Imodrez, UMT Fiorimed, and Labex SIGNALIFE.

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

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

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

3.2. A methodological approach to biology: from genes to ecosystems

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

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

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

4. Application Domains

4.1. Bioenergy

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

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

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

4.2. CO$_2$ fixation and fluxes

Phytoplanktonic species, which assimilate CO$_2$ during photosynthesis, have received a lot of attention in the last years. Microalgal based processes have been developed in order to mitigate industrial CO$_2$. As for biofuel productions, many problems arise when dealing with microalgae which are more complex than bacteria or yeasts. Several models have been developed within our team to predict the CO$_2$ uptake in conditions of variable light and nitrogen availability. The first modeling challenge in that context consists in taking temperature effects and light gradient into account.

The second challenge consists in exploiting the microalgal bioreactors which have been developed in the framework of the quantification of carbon fluxes between ocean and atmospheres. The SEMPO platform (simulator of variable environment computer controlled), developed within the LOV team, has been designed to reproduce natural conditions that can take place in the sea and to accurately measure the cells behavior. This platform, for which our team has developed models and control methods over the years, is an original and unique tool to develop relevant models which stay valid in dynamic conditions. It is worth noting that a better knowledge of the photosynthetic mechanisms and improved photosynthesis models will benefit both thematics: CO$_2$ mitigation and carbon fluxes predictions in the sea.

4.3. Biological control for plants and micro-plants production systems

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

In crop production, biocontrol is indeed a very promising alternative to reduce pesticide use: it helps protecting the environment, as well as the health of consumers and producers; it limits the development of resistance (in comparison to chemicals). The use of biocontrol agents, which are, generically, natural enemies (predators, parasitoids or pathogens) of crop pests [84], is however not widespread yet because it often lacks efficiency in real-life crop production systems (while its efficiency in the laboratory is much higher) and can fail to be economically competitive. Resistant crops are also used instead of pesticides to control pests and pathogens, but the latter eventually more or less rapidly overcome the resistance, so these crops need to be replaced by new resistant crops. As resistant genes are a potentially limited resource, a challenge is to ensure the durability of crop resistance. Our objective is to propose models that would help to explain which factors are locks that prevent the smooth transition from the laboratory to the agricultural crop, as well as develop new methods for the optimal deployment of the pests natural enemies and of crop resistance.

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

4.4. Biological depollution

These works will be carried out with the LBE , mainly on anaerobic treatment plants. This process, despite its strong advantages (methane production and reduced sludge production) can have several locally stable equilibria. In this sense, proposing reliable strategies to stabilize and optimise this process is a key issue. Because of the recent (re)development of anaerobic digestion, it is crucial to propose validated supervision

algorithms for this technology. A problem of growing importance is to take benefit of various waste sources in order to adapt the substrate quality to the bacterial biomass activity and finally optimize the process. This generates new research topics for designing strategies to manage the fluxes of the various substrate sources meeting at the same time the depollution norms and providing a biogas of constant quality. In the past years, we have developed models of increasing complexity. However there is a key step that must be considered in the future: how to integrate the knowledge of the metabolisms in such models which represent the evolution of several hundreds bacterial species? How to improve the models integrating this two dimensional levels of complexity? With this perspective, we wish to better represent the competition between the bacterial species, and drive this competition in order to maintain, in the process, the species with the highest depollution capability. This approach, initiated in [88] must be extended from a theoretical point of view and validated experimentally.

5. Highlights of the Year

5.1. Highlights of the Year

- A graph theoretical tool for analysis of the coupling between two Boolean networks. This tool generalizes the asymptotic graph (previously developed in [96] and [78]), by adding a quantitative dimension through the computation of relative probabilities. This tool is used for coupling two biological networks and predicting the possible attractors or asymptotic behaviors of the full system. The outcome of the probabilistic asymptotic graph is the set of attractors the full system, each attractor with an associated probability. This work was published in the journal Frontiers in Physiology [22].

- A study that predicts the evolution of phytoplankton biodiversity with global warming. After calibration of our models with experimental data on growth of various species of the microalgae Micromonas, we have shown that the pattern of temperature response is strongly related to the site where cells were isolated. With this approach, we proved that the oceanwide diversity of Micromonas species is very similar to the oceanwide diversity of the phytoplankton. Using 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. This work was published in the ISME journal [23].

6. New Software and Platforms

6.1. In@lgae

Numerical simulator of microalgae based processes
KEYWORDS: Simulation - Microalgae system - Productivity
FUNCTIONAL DESCRIPTION: In@lgae simulates the productivity of a microalgae production system, taking into account both the process type and its location and time of the year. The process is mainly defined by its thermal dynamics and by its associated hydrodynamics. For a given microalgal strain, a set of biological parameters describe the response to nitrogen limitation, temperature and light. As a result, the biomass production, CO_2 and nitrogen fluxes, lipid and sugar accumulation are predicted.

RELEASE FUNCTIONAL DESCRIPTION: 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.

- Participants: Étienne Delclaux, Francis Mairet, Olivier Bernard and Quentin Béchet
- Contact: Olivier Bernard

6.2. Odin

Platform for advanced monitoring, control and optimisation of bioprocesses

KEYWORDS: Bioinformatics - Biotechnology - Monitoring - Automatic control

SCIENTIFIC DESCRIPTION: This C++ application enables researchers and industrials to easily develop and deploy advanced control algorithms through the use of a Scilab interpreter. It also contains a Scilab-based process simulator which can be harnessed for experimentation and training purposes. ODIN is primarily developed in the C++ programming language and uses CORBA to define component interfaces and provide component isolation. ODIN is a distributed platform, enabling remote monitoring of the controlled processes as well as remote data acquisition.It is very 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 through explicit management of confidence indexes.

FUNCTIONAL DESCRIPTION: ODIN is a software framework for bioprocess control and supervision. ODIN is a distributed platform, where algorithms are described with a common structure easy to implement. Finally, ODIN can perform remote data acquisition and process these data to compute the signals to be applied to the actuators, together with estimates of state variables or process state. ODIN can handle the high level of uncertainties that characterises the biological processes through explicit management of confidence indexes.

- Participants: Fabien Dilet, Florian Guenn, Francesco Novellis, Mathieu Lacage, Melaine Gautier, Olivier Bernard, Olivier Calabro, Romain Primet and Serigne Sow
- Contact: Olivier Bernard
- URL: https://team.inria.fr/biocore/software/odin/

7. New Results

7.1. Mathematical methods and methodological approach to biology

7.1.1. *Mathematical analysis of biogical models*

7.1.1.1. Model reduction and sensitivity analysis
Participants: Suzanne Touzeau, Jean-Luc Gouzé, Valentina Baldazzi.

Analysis and reduction of biochemical models. Dynamic models representing complex biological systems with numerous interactions can reach high dimensions and include complex nonlinearities. A model reduction method based on process weighing and pruning was developed and implemented on various models. A global sensitivity analysis was performed to check the method robustness against parameter uncertainty and variability ([16]). This work was part of Stefano Casagranda's PhD thesis (2017), and is also a collaboration with Bayer (Sophia Antipolis).

7.1.1.2. Estimation and control
Participants: Suzanne Touzeau, Jean-Luc Gouzé.

Parameter identification in compartmental systems. In collaboration with F. Dayan (Startup Exactcure), we work on practical problems of identifiability of parameters in linear pharmacokinetic models. This was the subject of the internship of Jean-Baptiste Excoffier.

Parameter identification in complex systems. In complex biological systems, especially when data are scarce, identifying the model parameters is a challenge and raises identifiability issues. To fit a within-host immunological model to a large data set of individual viremia profiles, we developed an ABC-like method, less computationally expensive than standard Bayesian fitting procedures. Rather than reproducing individual profiles, we ientified several parameter sets compatible with the data and reflecting the variability among individuals [59], [26]. This work was part of Natacha Go's post-doctorate, supported by the ANR MIHMES project, in collaboration with the Roslin Institute, Edinburgh, UK. It benefited from the resources and support of NEF computation cluster.

7.1.1.3. Mathematical study of ecological models
Participants: Frédéric Grognard, Ludovic Mailleret, Pierre Bernhard, Nicolas Bajeux, Suzanne Touzeau, Israël Tankam Chedjou, Samuel Nilusmas.

Semi-discrete models have shown their relevance in the modeling of biological phenomena whose nature presents abrupt changes over the course of their evolution [85]. We used such models and analyzed their properties in several practical situations that are developed in Section 7.2.3, some of them requiring such a modeling to describe external perturbations of natural systems, and others to take seasonality into account [11]. External perturbations of interacting populations occur when some individuals are introduced or removed from a natural system, which occurs frequently in pest control applications, either through the direct removal of pests, through the introduction of artificial habitats for the predators or through the introduction of biological control agents in deterministic or stochastic fashion [72].

Seasonality is an important property of most agricultural systems in temperate environments since the year is divided into a cropping season and a 'winter' season; it gives the reference time for crop rotation between resistant and sensitive strains in a mutli-seasonal optimization of root-knot nematodes control [56]. However, it can also arise in tropical environments where, in the absence of weather-related season, time is divided into cropping and fallow seasons, and where the duration of the latter can for example be used as a control method against phytopathogenic nematodes of the plantain plant [46], [58].

7.1.1.4. Analysis of periodic behavior with hybrid models
Participants: Jean-Luc Gouzé, Madalena Chaves.

Periodic orbits in non monotonic negative feedback circuits. In [91], we studied the occurrence of periodic solutions in an n-dimensional class of negative feedback systems defined by smooth vector fields with a window of not necessarily monotonic activity. We have now [36] further established uniqueness and stability of the periodic solution under some conditions on the parameters.

Analysis tools for interconnection of Boolean networks. Following the work in [96] and [78], we have generalized the method for computation of the asymptotic graph. In [22], a quantitative dimension is added to the asymptotic graph, through the computation of relative probabilities for each final attractor. In [19], we have extended this methodology for the case of Boolean networks with synchronous updates, in a collaboration with D. Figueiredo and M.A. Martins from the University of Aveiro, Portugal (project PHC Pessoa).

7.1.1.5. Dynamics of complex feedback architectures
Participants: Jean-Luc Gouzé, Madalena Chaves.

To analyze the closed-loop dynamics of metabolic pathways under gene regulation, we propose a method to construct a state transition graph for a given regulatory architecture consisting of a pathway of arbitrary length, with any number of genetic regulators, and under any combination of positive and negative feedback loops [20]. Using this formalism, we analyze a "metabolator"-like mechanism (a pathway with two metabolites and three enzymes) and prove the existence of two co-existing oscillatory behaviors: damped oscillations towards a fixed point or sustained oscillations along a periodic orbit [21].

7.1.2. Metabolic and genomic models
Participants: Jean-Luc Gouzé, Olivier Bernard, Valentina Baldazzi, Claudia Lopez Zazueta, Lucie Chambon, Agustin Yabo.

Transcription and translation models in bacteria. We study detailed models of transcription and translation for genes in a bacterium, in particular the model of gene expression of RNA polymerase [12]. This is part of the PhD thesis of Stefano Casagranda (2017), and done in collaboration with Inria IBIS project-team, in particular with D. Ropers.

Analysis and reduction of a model of sugar metabolism in peach fruit. Predicting genotype-to-phenotype relationships is a big challenge for plant biology and breeding. A model of sugar metabolism in peach fruit has been recently developed and applied to 10 peach varieties [25]. A reduction pipeline combining serveral strategies is currently developed to reduce both model size and nonlinearity and allow for further application to virtual breeding (collaboration with B. Quilot-Turion and Mohamed Memmah (INRA Avignon) as part of the PhD thesis of Hussein Kanso).

Analysis of an integrated cell division-endoreduplication and expansion model. The development of a new organ depends on cell-cyle progression and cell expansion, but the interaction and coordination between these processes, under different environments, is still unclear [29]. An integrated model of fruit development has been developed and used to test different interaction schemes, by comparing simulation results to observed cell ditribution data in tomato fruit [65], [47].

7.1.2.1. Estimation and control

Optimal allocation of resources in a bacterium. We study by techniques of optimal control the optimal allocation between metabolism and gene expression during growth of bacteria, in collaboration with Inria IBIS project-team. We showed that a good suboptimal control solution could be implemented in the cell by ppGpp (a small molecule involved in the regulation of ribosomes) [80]. We developed different versions of the problem [40], and consider a new problem where the aim is to optimize the production of a product [39],(ANR projects Reset and Maximic, new PhD thesis of A. Yabo, collaboration with McTao Team). We also study variations of the model, including energy (ATP and ADP).

Control of a model of synthesis of a virulence factor. In collaboration with J.-A. Sepulchre (INLN Nice), we model the production of a virulence factor by a bacterium in a continuous stirred tank reactor. The production of this enzyme is genetically regulated, and degrades a polymeric external substrate into monomers. A nonlinear control is built [94], [38].

Hybrid control of genetic networks. We design control strategies based on the measurement and control of a unique gene within positive or negative loops of genetic networks, in order to stabilize the system around its unstable fixed point. The quantized nature of genetic measurements and the new synthetic control approaches available in biology encourage the use of piecewise constant control laws. A specific partitioning of the state space and the study of successive repulsive regions allow to show global convergence and global stability for the resulting system [48] . This is part of the thesis of L. Chambon.

7.1.2.2. Slow-Fast analysis of metabolic models

Metabolic modeling generally assumes balanced growth, *i.e.* that there is no accumulation of intermediate compound, and that the metabolism is rapidly at quasi steady state. We go beyond this hypothesis by considering that some metabolic reactions are slow, while other are fast. Then we analyse the differential system using Tikhonov's Theorem. We compare the results obtained using the Drum approach [2], and show that Drum is a reasonable approximation, provided that growth rate stays low. This is part of the PhD thesis of Claudia Lopez Zazueta [31], [30], [54], [55].

7.1.2.3. Large scale metabolic modeling

Metabolic modeling generally assumes balanced growth, *i.e.* that there is no accumulation of intermediate compound, and that the metabolism is rapidly at quasi steady state. We have proposed a new approach called DRUM where this hypothesis is relaxed by splitting the metabolic network into subnetworks and assuming that some compounds can accumulate between the subnetworks [2], [73]. This approach was successfully applied to several cases where the variations in light or nutrient resources induce a strong accumulation in the microalgal cells which could not be represented by the state of the art approaches [74]. More recently we have expended this approach to identify the genomic regulations explaining the change in metabolism especially when considering nitrogen starvation under a light/dark regime.

7.1.3. Biochemical and signaling models

7.1.3.1. Analysis and coupling of biological oscillators
Participants: Sofia Almeida, Madalena Chaves, Eleni Firippi.

Modeling, analysis and coupling of the mammalian cell cycle and clock. Each biological oscillator was modeled by a system of non-linear ordinary differential equations and its parameters calibrated against experimental data (both from the literature and from F. Delaunay's lab). The interactions between the two oscillators are investigated under uni- or bi-directional coupling schemes. Numerical simulations replicate the oscillators' period-lock response and recover observed clock to cell cycle period ratios such as 1:1, 3:2 and 5:4 (as observed in experiments, F. Delaunay's lab) mycitePhD:almeida. This work is in collaboration with F. Delaunay (ANR ICycle) and part of the PhD thesis of Sofia Almeida.

Improving the design of a synthetic oscillator. We analyse a two-variable model (the "Smolen" oscillator) using both numerical simulations and theoretical analysis through a piecewise affine approximation. Our objective is to investigate the existence of oscillatory behaviour and, in particular, to characterize and increase the region of parameters which admits sustained oscillations. This work is part of the PhD thesis of Eleni Firippi (ANR ICycle).

7.1.3.2. Modeling the apoptotic signaling pathway
Participants: Madalena Chaves, Luis Gomes Pereira, Jérémie Roux.

The goal is to study the origins of cell-to-cell variability in response to anticancer drugs and provide a link between complex cell signatures and cell response phenotype. To do this, we have been analysing models of the apoptosis pathway to compare the effects of different sources of variability at the transcriptional, translational and receptor levels [57] (collaboration with J. Roux, for the PhD thesis of Luis Pereira; project Imodrez).

7.2. Fields of application

7.2.1. Bioenergy
Participants: Olivier Bernard, Antoine Sciandra, Walid Djema, Ignacio Lopez Munoz, Ouassim Bara, Jean-Philippe Steyer.

7.2.1.1. Modeling microalgae production

Experimental developments

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

This experimental platform was used to control the long term stress applied to a population of microalgae. This Darwinian selection procedure generated two new strains after more than 6 months in the so called selectiostats.

Other experiments were carried out to reproduce the light signal percept by a cell in a raceway pond [24], derived from Lagrangian hydrodynamical computations. The experiments show that pigments content of the microalgae is highly related to the experimented hydrodynamic regime.

On top of this, we carried out outdoor pilot experiments with solar light. We tested the impact of various temperatures, resulting from different shadowing configurations on microalgal growth rate. This is the topic of Bruno Assis Pessi's master thesis. The impact of process configuration on CO_2 transfer rate has also been tested and quantified [17].

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 *Isochrysis luthea*, 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 for other substrates such as glucose or glycerol. A simplified model was developed by I. Lopez to represent the dynamics of polar lipids, especially when faced to higher oxygen concentration.

Modeling the coupling between hydrodynamics and biology. In collaboration with the Inria ANGE team, a model coupling the hydrodynamics of the raceway (based on an original multilayer discretisation of Navier-Stokes equations) with microalgae growth was developed [75]. This model is supported by the work of ANGE aiming at improving the discretization scheme of the Navier-Stokes equations and eventually to more accurately represent the hydrodynamics of the raceway and reconstruct Lagrangian trajectories. The accurate reconstruction of the trajectories is verified by a statistical analysis of the probability densities. As a consequence, more relevant experimental protocols have been proposed to more realistically design simplified light signal for experiments [24].

Modeling photosynthetic biofilms. Several models have been developed to represent the growth of microalgae within a biofilm. A first structured physiological model 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 [92]. 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 [41].

Modeling microalgae production processes. The integration of different models developed within BIOCORE [76] was performed to represent the dynamics of microalgae growth and lipid production in raceway systems. The model was validated at industrial scale with cultivation of the microalgae *Dunaliella salina* [15].

This model was then used to predict productivity in raceway systems, depending on climatic conditions. A Model Predictive Control strategy was developed to on-line adapt influent flow rate and water depth to temperature and light.

We have shown in [87] that a control strategy based on shadowing with solar panel can significantly improve productivity, especially during the early growth stage of the culture.

Modeling thermal adaptation in microalgae. We have studied and compared several models of microalgae growth to different temperatures [82]. 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. We have used Adaptive Dynamics theory to understand how temperature drives evolution in microalgae. We could then predict the evolution of this biodiversity in a warming ocean and show that phytoplankton must be able to adapt within 1000 generation to avoid a drastic reduction in biodiversity [23].

Modeling viral infection in microalgae. Experiments have been carried out in collaboration with A.-C. Baudoux (Biological Station of Roscoff) in order to study the impact of viral infections on the development of populations of *Micromonas* at different temperatures. This work revealed a qualitative change in viral infection when temperature increases. 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 [79].

7.2.1.2. Control and Optimization of microalgae production

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

Interactions between species. We have proposed an optimal control strategy to select the microalgal strain with the lowest pigment content. The control takes benefit from photoinhibition to compute light stresses penalizing the strains with a higher pigment content and finally select microalgae with lower chlorophyll content. This

characteristic is of particular interest for maximizing biomass production in dense cultures. The strategy has been carried out at the LOV and eventually the productivity of *Tisochrysis lutea* was improved by 75%.

Finaly, optimal strategies when selecting the strain of interest within two species competing for the same substrate has been proposed, when dynamics is represented by a Droop model [42].

7.2.2. Biological depollution

7.2.2.1. Control and optimization of bioprocesses for depollution
Participants: Olivier Bernard, Carlos Martinez Von Dossow, Jean-Luc Gouzé.

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. Experiments with nitrogen fixing cyanobacteria were carried out, and simple models of the ecosystem where developed to assess the potential of such organisms to support the nitrogen need of microalgae [18].

7.2.2.2. Coupling microalgae to anaerobic digestion
Participants: Olivier Bernard, Antoine Sciandra, Jean-Philippe Steyer, Frédéric Grognard, Carlos Martinez Von Dossow.

The coupling between a microalgal pond and an anaerobic digester is a promising alternative for sustainable energy production and wastewater treatment by transforming carbon dioxide into methane using light energy. The ANR Phycover project is aiming at evaluating the potential of this process [95].

We have proposed several models to account for the biodiversity in the microalgal pond and for the interaction between the various species. These models were validated with data from the Saur company. More specifically, we have included in the miroalgae model the impact of the strong turbidity, and derived a theory to better understand the photolimitation dynamics especially when accounting for the photo-inhibition in the illuminated periphery of the reactor [33]. Optimal control strategies playing with the dilution rate, shadowing or modifying depth were then studied [32].

7.2.2.3. Life Cycle Assessment
Participants: Olivier Bernard, Jean-Philippe Steyer, Marjorie Alejandra Morales Arancibia.

Environmental impact assessment. In the sequel of the pioneering life cycle assessment (LCA) work of [83], we continued to identify the obstacles and limitations which should receive specific research efforts to make microalgae production environmentally sustainable [62].

In the Purple Sun ANR-project, we studied a new paradigm to improve the energy balance by combining biofuel production with photovoltaic electricity. The LCA of a greenhouse with, at the same time, photovoltaic panels and low emissivity glasses is studied. Depending on the period of the year, changing the species can both improve productivity and reduce environmental footprint.

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

7.2.3. Design of ecologically friendly plant production systems

7.2.3.1. Controlling plant arthropod pests
Participants: Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Nicolas Bajeux, Yves Fotso Fotso.

Optimization of introduction processes. The question of how many and how frequently natural enemies should be introduced into crops to most efficiently fight a pest species is an important issue of integrated pest management. The topic of optimization of natural enemies introductions has been investigated for several years [84], [90] [71], and was one of the key features of L. Mailleret's HDR thesis [11]. A central theoretical result concerns the unveiling of the crucial influence of within-predator density dependent processes. To evaluate this theoretical prediction in a more realistic, stochastic and spatially explicit setting, a stochastic individual based model has been built on the multi-agent programmable modeling environment Netlogo. Extensive simulatory experiments were performed to assess the effects of density dependent processes as well as spatial structure and stochasticity on augmentative biological control performance and variability [67], [68].

In a more general setting, we studied the impact on the introduction success of a population of the interplay of Allee effects, stochasticity in introduction sizes, and occurrence of catastrophes that temporarily wipe out the population. The mean first passage time (MFPT) for a population to reach a viable size was used as a measure of establishment success for the introduction processes [72].

Characteristics of space and the behavior and population dynamics of parasitoids. We studied the influence of the spatial structure and characteristics of the environment on the establishment and spread of biological control agents through computer simulations and laboratory experiments on parasitoids of the genus Trichogramma. This was the topic of Thibaut Morel Journel [89] and is the topic of Marjorie Haond's PhD thesis (ISA, 2015-). The two last articles associated with Thibaut Morel Journel's Thesis appeared this year. In the first one [34], we investigated the effect of habitat fragmentation on the establishment and early spread of an introduced population. We showed that by increasing the risks of dispersal from the introduction site to unfavourable habitat early during the invasion, fragmentation decreased establishment success. However, by decreasing the distance between favourable habitat patches, it also improved the subsequent spread of introduced species over larger areas. In the second paper [35], we explored the influence of different characteristics of the structural connectivity of an invaded habitat on the invading population. We demonstrated how spread was hindered by habitat clusters and accelerated by the presence of hubs. These results highlight the importance of considering the structure of the invaded area to predict the outcome of invasions. In a different study stemming from Marjorie Haond Thesis, we showed how habitat richness [27] as represented by its local carrying capacity can positively influence the spreading speed of an expanding population. This work is being performed in collaboration with Elodie Vercken (ISA) and Lionel Roques (BioSP, Avignon).

In a metapopulation context, we studied the invasion success into an environment where part of the patches are sources (favourable environments) and the others are sinks; a criterion has been obtained predicting invasion success when the number of sources is larger than some threshold [70].

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. An optimal control problem was formulated by implementing chemical control (insecticides) and/or biological control (entomopathogenic fungi such as *Beauveria bassiana*, microbial parasitoids, traps). The aim was to maximise the yield at the end of the cropping season, while minimising the borer population for the next cropping season and the control costs. The existence of an optimal solution was shown and the problem was solved numerically [49], [44]. This ODE model was extended to integrate the berry maturation age. The well-posedness of the resulting PDE model was shown and an asymptotic analysis was conducted. This research pertains to Yves Fotso Fotso's PhD thesis, who visited BIOCORE during 5 months in 2018 through the EPITAG associate team.

7.2.3.2. Controlling plant pathogens
Participants: Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Pauline Clin.

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

Experiments were conducted in INRA Avignon for Potato Virus Y on pepper plants to evaluate the effect of four traits influencing evolutionary forces leading to resistance breakdown: virus effective population sizes, either at plant inoculation or during infection, virus accumulation and differential selection during infection. A generalized linear model showed a strong impact of the second and third one while a positive interection between differential selection and virus accumulation was identified [37]. Also, a stochastic model was developed to help determine the efficiency of pyramiding qualitative resistance and quantitative resistance narrowing population bottlenecks exerted on viruses, the latter aiming at slowing down virus adaptation to the qualitative resistance. It showed the efficiency of pyramiding when the fitness cost of RB virus variants in susceptible plants is intermediate [93]. These studies provide a framework to select plants with appropriate virus-evolution-related traits to avoid or delay resistance breakdown. This was done in collaboration with Frédéric Fabre (INRA Bordeaux) and Benoît Moury (INRA Avignon).

We pursued the calibration of the (spatio-)temporal epidemiological model of the phoma stem canker of oilseed rape, using field data on resistance deployment and virulence of phoma populations. Ongoing work includes the development of a simulation tool designed for researchers as well as non academic partners from technical institutes and agriculture cooperatives, who interact through the MoGeR project. It benefits from the resources and support of NEF computation cluster.

Taking advantage of plant diversity and immunity to minimize disease prevalence. An epidemiological model of gene-for-gene interaction considering a mechanism related to the specific defense response of plants, the systemic acquired resistance (SAR) was developed. SAR provides a sort of immunity to virulent pathogens for resistant plants having undergone an infection attempt by an avirulent pathogen. This model showed that there exists an optimal host mixture that ensures the lowest plant disease prevalence, so as to optimize the crop yield. It is especially efficient for pathogens with a low or intermediate basic reproduction rate and hosts with a high SAR efficiency [51], [52]. This was the topic of Pauline Clin's master thesis and was done in collaboration with Frédéric Hamelin (Agrocampus Ouest).

7.2.3.3. *Plant-nematode interactions.*
Participants: Valentina Baldazzi, Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Israël Tankam Chedjou, Samuel Nilusmas.

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

We developed a first physiological model of plant–nematode interactions, explicitly describing resource (water and carbon) allocation between roots and shoots. Indeed, nematodes draw on root carbon pool and reduce plant water uptake from the soil. The consequences on plant growth were analyzed as a function of plant physiological characteristics. In parallel, an experiment was conducted on pepper and tomato plants to monitor plant growth with or without nematodes. Data will be used to calibrate the model. This work was the topic of Thomas Brenière [77] and was done in collaboration with Caroline Djian-Caporalino (ISA, INRA Sophia Antipolis).

We studied the stability of the hybrid interaction model between nematodes and plantain roots [46]. An optimisation problem was formulated to determine the duration between cropping seasons (fallow period) that maximises the farmer's cumulated yield, which is affected by the nematode population, while minimising the costs of nematode control and nursery-bought pest-free suckers, on a fixed time horizon that lasts several cropping seasons. We first considered that the farmer buys and plants pest-free suckers at the beginning of each cropping season. This allows for a fallow period which reduces the nematode population in the soil, as these pests need roots to feed on and reproduce. Two cases were considered: a fixed or a variable fallow period. In the first case, the existence of an optimal solution was proven and its location was computed for small infestations. In the second case, the existence of an optimal strategy was proven and was numerically computed [58]. This research pertains to Israël Tankam Chedjou's PhD thesis, who visited BIOCORE during 5 months in 2018 through the EPITAG associate team.

We studied the resistance-based nematode control. As virulent nematodes exhibit a reduced fitness on susceptible crops, combining both resistant and susceptible plants can help increase the efficacy and sustainability of such control methods. In the *Solanaceae* family, there are two major resistance genes: the first one induces an early reaction when the nematode enters in the root system and the second one induces a late reaction when the nematode creates its feeding site. We used a semi-discrete model describing the plant-nematode interactions within and between cropping season to implement the action of both resistance genes. We computed and compared the optimal deployment strategies of both resistant crops [56]. This research pertains to Samuel Nilusmas' PhD thesis (2016–).

7.2.3.4. *Optimality/games in population dynamics*
Participants: Frédéric Grognard, Ludovic Mailleret, Pierre Bernhard.

Optimal resource allocation. Mycelium growth and sporulation are considered for phytopathogenic fungi. For biotrophic fungi, a flow of resource is uptaken by the fungus without killing its host; in that case, life history traits (latency-sporulation strategy) have been computed based on a simple model considering a single spore initiating the mycelium, several spores in competition and applying optimal resource allocation, and several spores in competition through a dynamic game through the analytico-numerical solution of the Hamilton-Jacobi-Bellman-Isaacs equation [97]. The solution of this dynamic game has been shown to be the equilibrium of two-trait adaptive dynamics [50]. This work, in the framework of the ANR Funfit project, is done with Fabien Halkett of INRA Nancy.

Optimal foraging and residence times variations. In this work, we built on our re-analysis of the Marginal Value Theorem (MVT) [4] to study the effect on the optimal foraging strategy of habitat conversion, whereby patches are converted from one existing type to another, hence changing the frequency of each type in the environment. We studied how realized fitness and the average rate of movement should respond to changes in the frequency distribution of patch-types, and how they should covary. We found that the initial pattern of patch-exploitation in a habitat can help predict the qualitative responses of fitness and movement rate following habitat conversion. We conclude that taking into account behavioral responses may help better understand the ecological consequences of habitat conversion. This work was published through the novel preprint reviewing system of Peer Community In Ecology [66].

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

BioEnTech: the collaboration with the BioEnTech start-up is aiming at developing new functionalities for ODIN in order to improve the advanced monitoring and control of industrial anaerobic digesters.

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

8.2. Bilateral Grants with Industry

Exactcure: in the collaboration with the start-up Exactcure (Nice), the goal of the project is to study pharmacokinetic models. Exactcure funded the M2 internship of J.B. Excoffier.

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. *National programmes*

- **ANR-Phycover:** The overall objective of the PHYCOVER project (2014-2018) is to identify a modular wastewater treatment process for the production of biogas. The method combines three modules. First, a high-rate algal pond is dedicated to the treatment of municipal wastewater. Then, an anaerobic digester capable of co-digesting biomass products (and others organic matter resources) to significantly reduce biological and chemical contaminants while producing a sustainable energy as biogas is analysed. A final module transforms the residual carbon, nitrogen and phosphorus into high-value microalgae dedicated to aquaculture and green chemistry.

- **ITE-OPALE:** The goal of the Institut de la Transition Énergétique - OPALE project (2016-2019) is to increase the lipid content of microalgae by specific selection pressure. The project relies on the strain already selected during the Facteur 4 project, whose productivity was 4 times higher than the wild type. We expect to still increase strain performances up to 10 times the productivity of the wild type.

- **ANR-FunFit:** The objective of this project (2013-2018) is to develop a trait-based approach linking individual fitness of fungal plant pathogens to ecological strategies. The idea is to derive eco-epidemiological strategies from fitness optimization in colonized environments and during colonization, as well as understanding the coexistence of sibling species. This project is co-coordinated by F. Grognard.

- **ANR-TripTic:** The objective of this project (2014-2018) is to document the biological diversity in the genus of the minute wasps *Trichogramma*, and to study the behavioral and populational traits relevant to their use in biological control programs.

- **ANR-ICycle:** This project (2016-2020) aims at understanding the communication pathways between the cell division cycle and the circadian clock, using mathematical modeling and control theory to construct and implement two coupled synthetic biological oscillators. Project coordinated by M. Chaves.

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

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

- **SIGNALIFE:** Biocore is part of this Labex (scientific cluster of excellence) whose objective is to build a network for innovation on Signal Transduction Pathways in life Sciences, and is hosted by the University of Nice Sophia Antipolis.

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

- **ADEME Phytorecolt:** The goal of this project (2017-2019) is to develop an automated and optimized procedure for microalgae harvesting. A project coordinated by H. Bonnefond.

9.1.2. Inria funding

- **Inria Project Lab, Algae** *in silico***:** (2014-2018) The Algae in silico Inria Project Lab, funded by Inria and coordinated by O. Bernard, focuses on the expertise and knowledge of biologists, applied mathematicians and computer scientists to propose an innovative numerical model of microalgal culturing devices. The latest developments in metabolic modeling, hydrodynamic modeling and process control are joined to propose a new generation of advanced simulators in a realistic outdoor environment. The project gathers 5 Inria project teams and 3 external teams.

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

9.1.3. INRA funding

- **MoGeR:** "From knowledge to modeling: towards a user-friendly simulation tool to test crop resistance management scenarios in the Phoma-oilseed rape case study", INRA Metaprogramme SMaCH, 2017–2019. This is a follow-up of the K-Masstec project, which focused on sustainable strategies for the deployment of genetic resistance in the field, based on molecular knowledge on avirulence genes.

- **ABCD:** INRA SPE is funding the project ABCD "Augmentative Biological Control; optimizing natural ennemies Deployment" (2017-2019) in which Biocore is a partner with INRA Sophia Antipolis.

9.1.4. Networks

- **GDR Invasions Biologiques:** The objectives of this GDR are to encourage multidisciplinary research approaches on invasion biology. It has five different thematic axes: 1) invasion biology scenarios, 2) biological invasions and ecosystem functioning, 3) environmental impact of invasive species, 4) modeling biological invasions, 5) socio-economics of invasion biology. L. Mailleret is a member of the scientific comittee of the GDR .

- **ModStatSAP:** The objective of this INRA network is to federate researchers in applied mathematics and statistics and to promote mathematical and statistical modeling studies in crop and animal health. S. Touzeau is a member of the scientific committee.

- **Seminar:** BIOCORE organizes a regular seminar "Modeling and control of ecosystems" at the station zoologique of Villefranche-sur-Mer, at INRA-ISA or at Inria.

9.2. European Initiatives

9.2.1. Collaborations in European Programs, Except FP7 & H2020

Program: **PHC-Pessoa** Partenariat Hubert Curien with Portugal, managed by Campus France

Project acronym: **LTSB**

Project title: Logic Tools for Systems Biology

Duration: 01/2018 - 12/2018

Coordinator: M. Chaves

Other partners: M.A. Martins, University of Aveiro

Abstract: This project aims at developing Boolean, piecewise linear and other hybrid tools for analysis of biological networks.

9.2.2. Collaborations with Major European Organizations

Imperial college, Department of Chemical engineering (UK),

Modeling and optimization of microalgal based processes.

University of Padova, Italy.

Modeling and control of microalgal production at industrial scale.

9.3. International Initiatives

9.3.1. Inria International Labs

Associate Team involved in the International Lab: **Inria Chile**

9.3.1.1. GREENCORE

Title: Modeling and control for energy producing bioprocesses

International Partners (Institution - Laboratory - Researcher):

PUCV (Chile) - Escuela de Ingenieria Bioquimica (EIB) - David Jeison

UTFSM (Chile) - Departamento de Matematica - Pedro Gajardo

Univ. Chile (Chile) - Centro de modelacion matematica - Hector Ramirez

Inria coordinator: O. Bernard

Start year: 2014

See also: https://team.inria.fr/eagreencore/

The worldwide increasing energy needs together with the ongoing demand for CO2 neutral fuels represent a renewed strong driving force for the production of energy derived from biological resources. In this scenario, the culture of oleaginous microalgae for biofuel and the anaerobic digestion to turn wastes into methane may offer an appealing solution. The main objective of our proposal is to join our expertise and tools, regarding these bioprocesses, in order to implement models and control strategies aiming to manage and finally optimize these key bioprocesses of industrial importance. By joining our expertise and experimental set-up, we want to demonstrate that closed loop control laws can significantly increase the productivity, ensure the bioprocess stability and decrease the environmental footprint of these systems. This project gathers experts in control theory and optimization (BIOCORE, UTFSM) together with experts in bioprocesses (PUCV and CMM) and software development.

Associate Team involved in the International Lab: **LIRIMA**, International Laboratory for Research in Computer Science and Applied Mathematics

9.3.1.2. EPITAG

Title: Epidemiological Modeling and Control for Tropical Agriculture

International Partner (Institution - Laboratory - Researcher):

Université de Douala (Cameroon) - Department of Mathematics and Computer Science - Samuel Bowong

Inria coordinator: S. Touzeau

Start year: 2017

See also: https://team.inria.fr/epitag/

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. 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, "end users" are closely associated. We focus on various pathosystems, such as cocoa plant mirids, coffee berry borers, coffee leaf rust and plantain plant-parasitic nematodes.

9.3.2. Inria International Partners

- NTNU (Norwegian University of Science and Technology), Trondheim, Norway. The project involves turning wastes into bioenergy with anaerobic digestion.
- University Ben Gurion : Microalgal Biotechnology Lab (Israel), Member of the ESSEM COST Action ES1408 European network for algal-bioproducts (EUALGAE). Modeling of photosynthesis.

- University of Manitoba: Department of Mathematics (Canada). Julien Arino hosted Nicolas Bajeux for 5 months. Invasion in metapopulations.

9.4. International Research Visitors

9.4.1. Visits of International Scientists

Luca Scardovi, University of Toronto, Canada, from Feb 2018 until June 2018. Long-term visit, to establish a new collaboration on the coupling and synchronization of biological oscillators.

Daniel Figueiredo, University of Aveiro, Portugal, 17-25 Oct 2018. Visit in the context of PHC-Pessoa project to work on the development of logical tools for systems biology.

Israël Tankam Chedjou, University of Yaoundé 1, Cameroon, April-August 2018. 5-month stay in the context of the EPITAG associate team.

Yves Fotso Fotso, University of Dschang, Cameroon, April-September 2018. 5-month stay in the context of the EPITAG associate team.

Clotilde Djuikem, University of Douala, Cameroon, May-July 2018. 3-month stay in the context of the EPITAG associate team.

9.4.2. Visits to International Teams

9.4.2.1. Sabbatical programme

O. Bernard is currently spending a one year sabbatical at NTNU (Norwegian University of Science and Technology), Trondheim, Norway. He works on a project to turn wastes into bioenergy with anaerobic digestion. Many challenges must be solved, from the theoretical stage up to the implementation.

9.5. Other Visits

Hussein Kanso, PhD student at INRA Avignon, a 2-week visit in the context of the work on modeling of sugar metabolism in peach fruit (collaboration with V. Baldazzi).

9.6. Project-team seminar

BIOCORE organized a 3-day seminar in September in Bauduen (Var). On this occasion, every member of the project-team presented his/her recent results and brainstorming sessions were organized.

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events Organisation

10.1.1.1. General Chair, Scientific Chair

O. Bernard is the Co-Chair of the next Dycops-CAB conference (CAB 2019 Florianópolis, Brazil, 23-26 April).

M. Chaves is organizing co-chair for the International Symposium on Molecular Logic and Computational Synthetic Biology (Santiago Chile, 17-18 December, 2018).

10.1.1.2. Member of the Organizing Committees

M. Chaves is part of the organizing committee for the Summer School on "Modélisation formelle des réseaux de régulation biologique" (Porquerolles, France, June 2019).

10.1.2. Scientific Events Selection

10.1.2.1. Member of the Conference Program Committees

O. Bernard is in the technical committee of the Computer Applied to Biotechnology (CAB) conferences, of the conference Foundations of Systems Biology in Engineering (FOSBE) and of the Algae Europe conference.

M. Chaves is a member of the program committee of Journées ouvertes de biologie informatique et mathématiques (JOBIM 2018, Marseille, France, 3-6 June; JOBIM 2019, Nantes). She is in the program committee of Foundations of Systems Biology in Engineering (FOSBE 2019).

J.-L. Gouzé is a member of the program committee for the International Conference on Positive Systems (POSTA 2018, Hangzhou, China, 25-27 August).

10.1.2.2. Reviewer

All BIOCORE members have been reviewers for the major 2018 conferences in our field: CDC, ECC, IFAC World Congress,...

10.1.3. Journal

10.1.3.1. Member of the Editorial Boards

M. Chaves is an Associated Editor of SIAM Journal on Applied Dynamical Systems (SIADS), since January 2015

S. Touzeau is an Academic Editor of PLOS ONE since August 2018

10.1.3.2. 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, New Phytologist,...

10.1.4. Invited Talks

O. Bernard was invited to give a conference on microalgae at Ecole Centrale de Paris ("Biotechnological challenge") "Use of microorganisms for biofuel production" (January, 16th, 2018).

O. Bernard was invited to give a conference at the PROMES Laboratory for solar ernergy (Odeillo) "Purple Sun-sharing photons between semi transparent PV panels and microalgae production" (July, 13rd, 2018).

M. Chaves and J. Roux gave a paired presentation on modeling heterogeneity in cell-death drug response at the group UCancer (a UCA structuring project) (December 2018).

M. Chaves gave a Colloquium at the Department of Mathematics at Universidade de Aveiro, Portugal (June 2018).

10.1.5. Other Selected Talks

M. Chaves gave a presentation on ANR project ICycle at the workshop ComplexDays, organized by Université Côte d'Azur (January 2018).

J.-L. Gouzé gave a talk at the SFBT meeting (St Flour, June 2018).

L. Chambon participated at the Workshop MOMI 2018 on the 26th and 27th of February, organised by Inria in Sophia-Antipolis about Mathematics in industry, where she presented a poster of her research. On the 18th and 19th of June, she presented a poster at the "Modelife Days" of the UCA Jedi Idex Core program "Modeling, physics and mathematics of living systems" in Nice.

10.1.6. Scientific Expertise

O. Bernard is a member of the scientific committee of the companies Inalve and BioEnTech.

J.-L. Gouzé was in several evaluation committees or juries: FWO, NWO, FNRS...

S. Touzeau evaluated a project for the "Centre d'excellence africain en Mathématiques, Informatique et Technologies de l'Information et de la Communication" (CEA-MITIC), Senegal.

10.1.7. Research Administration

O. Bernard represents Inria at the ANCRE (Alliance Nationale de Coordination de la Recherche pour l'Energie).

O. Bernard is a member of the ADT (Technological Development Actions) commission at Inria.

M. Chaves is a member of the COST-GTRI (working group on International Relations at Inria's council for scientific and technological orientation). The group is charged with evaluating Inria's Associated Teams.

M. Chaves is a member of the CLHSCT of Inria Sophia Antipolis (local committee for the safety of working conditions).

M. Chaves is in the Pedagogical Committee of the Master "Quantitative and Computational Sciences for Biomedical data", Université Côte d'Azur.

J.-L. Gouzé is in the Inria committee supervising the doctoral theses, and a member of the scientific committee of Labex SIGNALIFE of the University of Nice-Sophia-Antipolis, and of COREBIO PACA. He 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).

F. Grognard is a member of the NICE committee, which allocates post-doctoral grants and fundings for visiting scientists at Inria Sophia Antipolis. He is a member of the scientific committee of the doctoral school "Sciences de la Vie" at the University of Nice-Sophia Antipolis.

Since 2015, F. Grognard is a member of the MBIA CSS (Specialised Scientific Commission), in charge of the research scientists evaluation at INRA. He is a member of the steering committee of Academy 3, Space, Environment, Risk & Resilience of UCA-JEDI. He is co-responsible of the development of the MSc Risk of UCA-JEDI.

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.

S. Touzeau is a member of the steering committee of the metaprogramme SMaCH *Sustainable Management of Crop Health*, INRA (since 2016).

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Licence: F. Grognard (45.5h ETD) and L. Mailleret (26h ETD), "Equations différentielles ordinaires et systèmes dynamiques", L3, 1st year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Nice Sophia Antipolis, 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: F. Grognard (21h ETD) and L. Mailleret (21h ETD), "Bio-Mathématiques", M1, 2nd year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Nice Sophia Antipolis, France.

Master : J.-L. Gouzé (18h ETD), M. Chaves (12h ETD) "Modeling biological networks by ordinary differential equations", M1, 2nd year Engineering in Génie biologique, Polytech Nice Sophia, Université Nice Sophia Antipolis, France.

Master: S. Touzeau (27h ETD), "Analyse de données", M1, 2nd year Engineering in Génie biologique, Polytech Nice Sophia, Université Nice Sophia Antipolis, France.

10.2.2. Supervision

HdR : L. Mailleret. Modélisation et contrôle en dynamiques de populations. Applications en protection des plantes, 16 February 2018, Université Côte d'Azur.

PhD : S. Almeida. "Synchronization of biological oscillators: modeling, analysis and coupling of the mammalian cell cycle and circadian clock", 17 December 2018, Université Côte d'Azur. Supervisors: M. Chaves and F. Delaunay (Univ. Nice, iBV).

PhD : M. Caïa, "Characterization and modeling of a mixotrophic algae - bacteria ecosystem for waste recovery", 13 December 2018, Université Montpellier. Supervisors: J.-P. Steyer and O. Bernard.

PhD : C. Lopez-Zazueta. "Réduction dynamique de réseaux métaboliques par la théorie des perturbations singulières : application aux microalgues", 14 December 2018, Université Côte d'Azur. Supervisors O. Bernard and J.-L. Gouzé.

PhD : V. Burte. "Étude des stratégies de mouvement chez les parasitoïdes du genre Trichogramma : apports des techniques d'analyse d'images automatiques", 14 December 2018, Université Côte d'Azur. Supervisors V. Calcagno et L. Mailleret.

PhD in progress : M. Haond. "Causes et conséquences des fronts de colonisation poussés", since October 2015, Univ. Nice Sophia Antipolis. Supervisors: E. Vercken (UMR ISA), L. Mailleret and L. Roques (UR BioSP).

PhD in progress : L. Chambon. "Control of models of genetic regulatory networks", since October 2016, Université Côte d'Azur. Supervisor J.-L. Gouzé.

PhD in progress : L. Pereira. "Experimental and computational approaches to understanding the molecular origins of drug response heterogeneity, underlying resistance to cancer therapies", since October 2016, Université Côte d'Azur. Supervisors: M. Chaves and J. Roux (IRCAN, Nice).

PhD in progress: M. Gachelin, "Selection pressure to improve lipid productivity of microalgae", since March 2017, Sorbonne Université. Supervisors: O. Bernard and A. Sciandra.

PhD in progress : E. Firippi. "Mathematical analysis, control design and coupling for models of biological oscillators", since October 2017, Université Côte d'Azur. Supervisor: M. Chaves.

PhD in progress: A. Yabo, "Control and optimal control of bacterial growth", since October 2018, Université Côte d'Azur. Supervisors J.-L. Gouzé and J.-B. Caillau (McTao).

PhD in progress: A. Dos Reis de Souza, "Estimation and Control Methods for Microbial Communities", since October 2018, Université de Lille. Supervisors: J.-L. Gouzé and D. Efimov (Valse, Inria Lille).

PhD in progress: S. Nilusmas, "Gestion durable des nématodes à galles en cultures maraîchères : modélisation et optimisation du déploiement des résistances et des pratiques agronomiques", Université Côte d'Azur, since December 2016. Supervisors: S. Touzeau, C. Caporalino (ISA), V. Calcagno (ISA) and L. Mailleret.

PhD in progress: I. Tankam Chedjou, "Modeling, analysis and control of plantain plant-parasitic nematodes", University of Yaoundé 1, since December 2015. Supervisors: J.-J. Tewa, F. Grognard, L. Mailleret, S. Touzeau.

PhD in progress: Y. Fotso Fotso, "Modeling, analysis and control of coffee berry borers", University of Dschang, since January 2017. Supervisors: S. Bowong, B. Tsanou, F. Grognard, L. Mailleret, S. Touzeau.

10.2.3. Master thesis and internships

PFE: Adrien Boudin, "Controle optimal des ressources dans une cellule", EPU MAM, supervisors J.-L. Gouzé et JB. Caillau (McTao).

Engineer: Bruno Assis Pessi, "Modeling microalgal growth under a greenhouse", Ecole CentraleSupelec, supervisor O. Bernard.

M2: Jenna Balaguer, "Effect of background turbidity on microalgae growth", Sorbonne Université, supervisor O. Bernard.

M2: Jean-Baptiste Excoffier, "Modélisation in silico de médicaments, et personnalisation des traitements", Université Côte d'Azur, supervisors J.-L. Gouzé and F. Dayan (Exactcure).

M2: Pauline Clin, "Résistance systémique acquise, mélanges variétaux et épidémiologie évolutive des interactions plantes-pathogènes", Université de Rennes 1, supervisors F. Grognard and F. Hamelin (Agrocampus Ouest).

M1: David Davtian, "Modélisation multi-agent pour l'étude et l'optimisation des introductions biologiques", Université Côte d'Azur, supervisors L. Mailleret and F. Grognard.

M1: Thomas Brenière, "Physiologie de la plante attaqué par les nématodes: Modélisation et expérimentation", INSA Lyon, supervisors V. Baldazzi and C. Djian-Caporalino (ISA, INRA Sophia Antipolis).

Other: O. Bernard supervised a project involving 4 students from CentraleSupelec (first year of engineering school), 4 months, to design a system for detecting contamination in microalgae cultures.

10.2.4. Juries

V. Baldazzi and L.Mailleret participated in the thesis comitee of Marta Zaffaroni (INRA Avignon) in October 2018.

O. Bernard was reviewer for the PhD thesis of G. Jeanne "Optimization of bioprocess design: towards an intergated approach synthetic biology and process control". University Paris-Saclay (27 Sept. 2018).

M. Chaves was member of the jury for the PhD thesis of Sofia Almeida, December 2018.

J.-L. Gouzé and O. Bernard were in the jury of the PhD of Claudia Lopez Zazueta "Réduction dynamique de réseaux métaboliques par la théorie des perturbations singulières : application aux microalgues." Université Côte d'Azur, December 14, 2018.

J.-L. Gouzé was reviewer of the PhD of Hongjun Ji "Systèmes dynamiques coopératifs appliqués en biologie", Sorbonne Université, October 11, 2018.

S. Touzeau was the external examiner of Rebecca Bekker's MSc thesis in Applied Mathematics "Mathematical models of the epidemiological dynamics of soil-borne pathogens", University of Pretoria, South Africa, 2018.

S. Touzeau was a member of the selection committee MC 25–26 "Analyse des EDP pour la dynamique des populations", University of Bordeaux, France, 2018.

10.3. Popularization

10.3.1. Articles and contents

- A popularization paper has been published on the study of peach sugar metabolism [64].
- L. Mailleret was a co-author of the press kit "Les conquêtes de l'INRA pour le biocontrôle" [86].
- The activities related to microalgae have generated many articles in national newspapers (Le Monde, Nice Matin, ,...), and broadcasts on national TV (France 3). See, for instance, https://www.nicematin.com/vie-locale/ces-azureens-inventent-223249.

10.3.2. Interventions

- O. Bernard together with R. Lemée gave a general public conference on the topic "Les microalgues en Méditerranée: quels avenirs environnementaux, énergétiques, sanitaires et industriels?" (MAMAC, Nice, 6 Apr 2018).
- L. Chambon and O. Bara participated in the open doors days of Inria Sophia-Antipolis on the 7th of October. L. Chambon presented a popularization poster about Biocore scientific methodologies to general public.

- L. Chambon represented Biocore, Inria in the national event "Fête de la Science" in Mouans-Sartoux and Juan-les-Pins (13th and 20th of October). She presented scientific popularization games and experiments to children and general public.
- L. Mailleret presented three Posters on biological control with predatory mites during the visit of the national press (AFP, France Inter, Le Parisien,...) at Institut Sophia Agrobiotech on the 30th of May 2018.

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Major publications by the team in recent years

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Doctoral Dissertations and Habilitation Theses

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