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et l'environnement**

Sorbonne Université (UPMC)

Activity Report 2019

Project-Team BIOCORE

Biological control of artificial ecosystems

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
**Modeling and Control for Life Sci-
ences**

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Project-Team BIOCORE

Creation of the Project-Team: 2011 January 01

Keywords:

Computer Science and Digital Science:

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

Other Research Topics and Application Domains:

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

1. Team, Visitors, External Collaborators

Research Scientists

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Valentina Baldazzi [INRA, Researcher]

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Pierre Bernhard [Inria, Senior Researcher, Emeritus]
Madalena Chaves [Inria, Senior Researcher, HDR]
Walid Djema [Inria, Starting Research Position, from Nov 2019]
Frédéric Grognard [Inria, Researcher]
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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 Grignon, IAM Nancy, Agrocampus Ouest, MaIAGE Jouy-en-en-Josas, BioEpar Nantes), CIRAD Montpellier, Institut Méditerranéen d'Océanologie, LOCEAN (Paris), GIPSA Grenoble, IBIS, ANGE, MCTAO, and VALSE Inria teams.
- Participation in French groups: ModStatSAP (Modélisation et Statistique en Santé des Animaux et des Plantes), GDR Invasions Biologiques.
- Participation to national programmes: ANR projects Phycover, ICycle, and Maximic, Plan Cancer Imodrez, UMT Fiorimed, and Labex SIGNALIFE.
- International collaborations: Université Catholique de Louvain (Belgium), Université de Mons (Belgium), MacMaster University (Canada), University Ben Gurion (Israel), Imperial College (United-Kingdom), Massey University (New Zealand), Universidad Tecnica Federico Santa Maria and Universidad de Chile (Chile), University of Edinburgh (UK), Universities of Douala, Yaoundé I and Dschang (Cameroon).

3. Research Program

3.1. Mathematical and computational methods

BIOCORE's action is centered on the mathematical modeling of biological systems, more particularly of artificial ecosystems, that have been built or strongly shaped by 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 [83]. Using the directly measured variables and those that have been obtained through such, or other, observers, we then

develop control methods that take advantage of the system structure (linked to competition or predation relationships between species in bioreactors or in the trophic networks created or modified by biological control).

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

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

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

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

4. Application Domains

4.1. Bioenergy

Finding sources of renewable energy is a key challenge for our society. We contribute to this topic through two main domains for which a strong and acknowledged expertise has been acquired over the years. First, we consider anaerobic digesters, the field of expertise of the members of the team at the Laboratory of 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. CO₂ fixation and fluxes

Phytoplanktonic species, which assimilate CO₂ during photosynthesis, have received a lot of attention in the last years. Microalgal based processes have been developed in order to mitigate industrial CO₂. 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 CO₂ 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 thematic: CO₂ 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 [89], is however not widespread yet because it often lacks efficiency in real-life crop production systems (while its efficiency in the laboratory is much higher) and can fail to be economically competitive. Resistant crops are also used instead of pesticides to control pests and pathogens, but the latter eventually more or less rapidly overcome the resistance, so these crops need to be replaced by new resistant crops. As resistant genes are a potentially limited resource, a challenge is to ensure the durability of crop resistance. Our objective is to propose models that would help to explain which factors are locks that prevent the smooth transition from the laboratory to the agricultural crop, as well as develop new methods for the optimal deployment of the pests natural enemies and of crop resistance.

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

4.4. Biological depollution

These works will be carried out with the LBE, mainly on anaerobic treatment plants. This process, despite its strong advantages (methane production and reduced sludge production) can have several locally stable equilibria. In this sense, proposing reliable strategies to stabilize and 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 [92] must be extended from a theoretical point of view and validated experimentally.

5. Highlights of the Year

5.1. Highlights of the Year

5.1.1. Highlights

- The patented approach to produce microalgae under a biofilm form was further optimized with gradient based approaches [71] and strategies to still enhance productivities were identified and tested experimentally [26].
- The introduction of resistant plants for the protection against pathogens often leads to the appearance of virulent pathogenic strains that are capable of infecting these resistant plants. We developed a model for the pyramiding of these qualitative resistances with genetically controlled infection bottlenecks, and showed the efficiency of this technique when the fitness cost of Resistance Breaking pathogen variants in susceptible plants is intermediate [36].
- In the context of ANR project ICycle, following the PhD thesis of Sofia Almeida and in collaboration with F. Delaunay's lab (Institut Biologie Valrose, CNRS), a calibrated and validated model of the mammalian circadian clock was published in [13]. The interactions between the circadian clock and the cell cycle were then investigated [44]. The coupled models replicate the oscillators' period-lock response and recover clock to cell cycle period ratios such as 1:1 or 3:2, as observed in F. Delaunay's lab.

5.1.2. Awards

- Lucie Chambon and J.-L. Gouzé won a Best Paper award at the DYCOPS conference in Brazil (April 2019), on original control strategies for the genetic toggle switch.

BEST PAPER AWARD:

[46]

L. CHAMBON, J.-L. GOUZÉ. *A new qualitative control strategy for the genetic Toggle Switch*, in "DYCOPS 2019 - 12th IFAC Symposium on Dynamics and Control of Process Systems, including Biosystems", Florianopolis, Brazil, B. CHACHUAT, O. BERNARD, J. E. NORMEY-RICO (editors), IFAC-PapersOnLine, Ifac, 2019, vol. 52, n^o 1, pp. 532-537 [DOI : 10.1016/J.IFACOL.2019.06.117], <https://hal.inria.fr/hal-02319873>

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, CO₂ 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 biological models

7.1.1.1. Mathematical study of ecological models

Participants: Frédéric Grogard, Ludovic Mailleret, Suzanne Touzeau, Clotilde Djuikem, Israël Tankam Chedjou.

Semi-discrete models. Semi-discrete models have shown their relevance in the modeling of biological phenomena whose nature presents abrupt changes over the course of their evolution [41]. 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 such models in the context of the analysis of the effect of stochasticity and Allee effects on the introduction of populations [14], seasonality in the dynamics of coffee leaf rust [59] and of banana and plantain burrowing nematodes [67], as well as for the protection of plant resistance against root-knot nematodes [66].

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 7.2.3, describing and controlling the impact on plants of fungi [59], [39], viruses [36], nematodes [67], [66], and pests [60].

7.1.1.2. Estimation and control

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

Parameter identification in complex systems. In complex biological systems, identifying model parameters is a challenge that raises identifiability issues. To fit a within-host immunological model to a large data set of individual viremia profiles, we developed an Approximate Bayesian Computation (ABC)-like method that yielded several parameter sets compatible with the data and reflecting the variability among individuals [25]. This work benefited from the resources and support of NEF computation cluster.

Optimal control and optimisation. We developed several approaches to control the evolution of crop pests. To reduce crop losses due to plant-parasitic nematodes, we optimised (i) rotation strategies between resistant and susceptible cultivars of horticultural crops [76], or (ii) fallow periods between plantain cropping seasons [67]. These optimisation problems were solved on a finite time horizon. They benefited from the resources and support of NEF computation cluster.

We also solved an optimal control problem to limit the damages due to coffee berry borers [60]. It consisted in designing the most cost-efficient application of a biopesticide over time. Using Pontryagin’s maximum principle, we determined the existence and structure of the solution. The problem was solved numerically using BOCOP (<https://www.bocop.org/>).

7.1.1.3. Analysis of multistability and periodic behavior with hybrid models

Participants: Madalena Chaves, Eleni Firippi.

Probabilistic dynamics tool for hybrid models In a collaboration with D. Figueiredo and M.A. Martins from the University of Aveiro, Portugal (project PHC Pessoa), a tool was developed for simulating weighted reactive models [55]. These are essentially discrete models with dynamics described by state transition graphs: each transition has a given weight and the graph has the capacity to alter its accessibility relations.

M. Chaves and M.A. Martins jointly edited a book with selected papers from the Symposium on Molecular Logic and Computational Synthetic Biology [70], gathering work on different formalisms and applications of hybrid models.

Coupling and synchronization of piecewise linear systems This work studies the coupling of N identical positive feedback loops described by piecewise linear differential equations. Under diffusive coupling, and for different conditions on the coupling parameters, the N systems may synchronize or, alternatively, generate a set of new steady states that form a specific pattern [49]. An unexpected result is the existence of a special relationship between the number of components N and the maximal concentration-to-activity threshold ratio ($V_1/(\gamma_1\theta_1)$). This relationship implies that, for very specific parameter sets, the N compartments cannot be guaranteed to synchronize.

7.1.1.4. Dynamics of complex feedback architectures

Participants: Madalena Chaves, Jean-Luc Gouzé.

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 [19]. 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 [20].

7.1.2. Metabolic and genomic models

Participants: Jean-Luc Gouzé, Olivier Bernard, Valentina Baldazzi, Lucie Chambon, Carlos Martinez Von Dossow, Agustin Yabo, Alex Dos Reis de Souza, Walid Djema, Sofya Maslovskaya.

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 [80]. A reduction pipeline combining several reduction strategies has been developed to reduce both model size and nonlinearity and allow for further application to virtual breeding (collaboration with B. Quilot-Turion and Mohamed Memmah (INRA Avignon) as part of the PhD thesis of Hussein Kanso) [64]. A paper is currently under revision for Mathematical Biosciences.

Analysis of an integrated cell division-endoreduplication and expansion model. The development of a new organ depends on cell-cycle progression and cell expansion, but the interaction and coordination between these processes is still unclear [27]. An integrated model of fruit development has been developed and used to test different interaction schemes, by comparing simulation results to the observed cell size distribution in tomato fruit [15].

Modeling cell growth and resource allocation. In the framework of the Maximic project (collaboration with IBIS team) and as a follow up of our previous work [82], we investigated the impact of energy metabolism on cell's strategy for resource allocation. Preliminary results show that the inclusion of energy costs leads to the emergence of a trade-off between growth rate and yield, as experimentally observed in many bacterial cells .

The allocation of cellular resources can strongly influence not only the rate of cell growth but also the resulting cell size [78]. To better investigate the connection between proteome allocation and cell volume, the original model by Giordano et al. [82] has been connected to a biophysical model of cell growth, explicitly describing cell volume increase as a function of cell's internal pressure and mechanical properties. The resulting model will be used to investigate the mechanisms (control of osmotic pressure or wall mechanics) behind cell size control under different environmental constraints [84].

Optimal allocation of resources in a bacterium. We study by techniques of optimal control the optimal allocation between metabolism and gene expression during growth of bacteria, in collaboration with Inria IBIS and MCTAO project-teams. We developed different versions of the problem, and consider a new problem where the aim is to optimize the production of a product [68], [40], [50], (ANR project Maximic, PhD thesis of A. Yabo). We also study variations of the model, for example in the chemostat [57]. The precise mathematical analysis of the optimal behavior (turnpike property) is under investigation.

A synthetic community of bacteria. In the framework of IPL Cosy, we study the coexistence of two strains of bacteria *E. Coli* in a bioreactor. The strains have been modified synthetically to achieve some goals. The aim is to obtain a better productivity in the consortium than in a single strain, by control technics. The description of models is in revision for Plos Comp. Biol.

In collaboration with team VALSE (Lille), we also studied several problems of estimation and robust stabilization related to IPL Cosy, for two bacterial species in a bioreactor [53], [54].

Control of a model of synthesis of a virulence factor. In collaboration with J.-A. Sepulchre (UCA), we modeled 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 [37]. We also studied the problem of periodic inputs for maximization of some yield [97].

Hybrid control of genetic networks. We designed control strategies based on the measurement and control of a unique gene within positive or negative loops of genetic networks, in order to stabilize the system around its unstable fixed point. The quantized nature of genetic measurements and the new synthetic control approaches available in biology encourage the use of piecewise constant control laws. A specific partitioning of the state space and the study of successive repulsive regions allow to show global convergence and global stability for the resulting system [18]. Several other control strategies are studied [47], [48], [46]. This is part of the PhD thesis of L. Chambon.

7.1.3. Biochemical and signaling models

Participants: Madalena Chaves, Eleni Firippi, Sofia Almeida, Marielle Péré, Luis Gomes Pereira, Jérémie Roux.

7.1.3.1. Analysis and coupling of biological oscillators

Modeling, analysis and coupling of the mammalian cell cycle and clock A transcriptional model of the mammalian circadian clock was developed in [13] and its parameters calibrated against experimental data from F. Delaunay's lab. A cell cycle model was also previously developed by us [77]. The interactions between the two oscillators are investigated under uni- or bi-directional coupling schemes [44]. 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). This work is in collaboration with F. Delaunay (ANR ICycle) and part of the PhD thesis of Sofia Almeida.

Period-control in a coupled system of two genetic oscillators In the context of ANR project ICycle, we consider two reduced models that mimic the dynamics of the cell cycle and clock oscillators and study the effect of each oscillator on the coupled system, from a synthetic biology perspective [56]. The first observation is that oscillator A is more likely to be the controller of the coupled system period when the dynamics of oscillator B becomes stable due to the coupling strength. Another interesting observation is that the coupled system exhibits oscillatory dynamics over an increased region of the parameter space. This work is part of the PhD thesis of Eleni Firippi (ANR ICycle).

7.1.3.2. Modeling the apoptotic signaling pathway

A detailed model of the death receptor layer In a collaboration with J. Roux and within project Imodrez, the goal is to study the origins of cell-to-cell variability in response to anticancer drugs and provide a link between complex cell signatures and cell response phenotype. In a first approach, we constructed a detailed model to represent the death receptor-ligand binding and subsequent signaling cascade [11]. This model was used to study the effect of intrinsic and extrinsic noise sources, and suggested the need to expand a set of reactions on the model, to account for the observed cell heterogeneity (this was part of the PhD thesis of Luis Pereira).

A basic model to explore the effect of a positive feedback loop Analysis of the detailed apoptosis receptor model uncovered a set of reactions for which the introduction of a positive feedback loop from caspase 8 was able to significantly increase the range of variability in the model in response to extrinsic noise. To better understand this mechanism and the role of positive loop in cell response variability, we are constructing a reduced model representing only the basic components: death ligand and receptor, caspase 8 and two intermediate complexes. This is part of the work of the PhD student Marielle Péré.

7.2. Fields of application

7.2.1. Bioenergy

7.2.1.1. Modelling microalgae production

Participants: Olivier Bernard, Antoine Sciandra, Walid Djema, Ignacio Lopez, David Demory, Ouassim Bara, Jean-Philippe Steyer.

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 [69].

This experimental platform was used to control the long term stress applied to a population of microalgae [72]. This Darwinian selection procedure generated several new strains more resistant to oxidative stresses after several months in the so called selectiostats [58].

Experiments were run to understand the interactions in a simplified ecosystem between microalgae and cyanobacteria. The initial idea was to use a nitrogen fixing cyanobacteria providing nitrogen to the microalgae. It turns out that negative interactions appear in this ecosystem, first because of the mutual shadowing of these organisms, and second because of the production of allelopathic substances inhibiting the competitive organisms [79].

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

Experimental work was also carried out in collaboration with the Inalve startup with microalgal biofilm to determine the impact of light and dark sequences on cell growth and photoacclimation [26], [63]. The architecture of the biofilms was also observed for different species with confocal microscopic techniques [23].

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 lutea*, on the basis of the DRUM framework, in order to simulate autotrophic, heterotrophic 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. In particular, this model represents the microalgae growth under different conditions of temperature, light and oxygen.

Modeling photosynthetic biofilms. Several models have been developed to represent the growth of microalgae within a biofilm. A first structured physiological model, extending the one proposed in [95] uses mixture theory to represent the microalgae growth, based on the consideration of intracellular reserves triggering the processes of growth, respiration and excretion. We consider separately the intracellular storage carbon (lipids and carbohydrates) and the functional part of microalgae. Another approach accounts for the dynamics of the light harvesting systems when cells are submitted to rapid successions of light and dark phases [28], [71]. 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 [45]. The model was used to identify the worldwide potential of microalgal biofilms under different climates [26].

Modeling microalgae production processes.

A synthesis has been written on the different aspects for developing models of microalgae in the field of wastewater treatment [38]. The paper is completed by a position paper proposing guidelines for the development of models in biotechnology [31]. 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 [65]. This was the topic of the internship of Luis Plaza Alvarez. The model also represents the pigment acclimation to various light intensities. We have studied in [75] the response of a Droop model forced by periodic light or temperature signals. We transformed the model into a planar periodic system generating a monotone dynamical system. Combined with results on periodic Kolmogorov equations, the global dynamics of the system can be described.

Modeling thermal adaptation in microalgae.

Experiments have been carried out in collaboration with A.-C. Baudoux (Biological Station of Roscoff) in order to study growth of various species of the microalgae genus *Micromonas* at different temperatures. After calibration of our models, we have shown that the pattern of temperature response is strongly related to the site where cells were isolated. We derived a relationship to extrapolate the growth response from isolation location. With this approach, we proved that the oceanwide diversity of *Micromonas* species is very similar to the oceanwide diversity of the phytoplankton [22]. 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 [22].

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 [22]. The model was then extrapolated to the whole ocean to better understand how the warming will impact the mortality due to viruses.

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 [21].

Control of microalgal biofilms.

Determining the optimal operating conditions for a rotating algal biofilm process [63] is a difficult question. A 1D model was developed, and the gradient associated to the productivity at the process scale was computed. Then the conditions maximizing productivity were derived, playing on the conveyor belt velocity and geometry [71].

Interactions between species. We have proposed an optimal control strategy to select in minimal time the microalgal strain with the lowest pigment content [51]. 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 [52], [73], [74]. In both cases, the optimal control derived from the Pontryagin maximum principle also exhibit a turnpike behaviour. This is a collaboration with team MCTAO.

Strategies to improve the temperature response have also been studied. We modelled the adaptive dynamics for a population submitted to a variable temperature [58]. This was used at the LOV to design experiments with periodic temperature stresses aiming at enhancing polyunsaturated long chain fatty acids content of *Tisochrysis lutea* [72].

7.2.1.3. Modelling mitochondrial inheritance patterns

Most eukaryotes inherit their mitochondria from only one of their parents. When there are different sexes, it is almost always the maternal mitochondria that are transmitted. Indeed, maternal uniparental inheritance has been reported for the brown alga *Ectocarpus* but we show in this study [33] 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.

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 were developed to assess the potential of such organisms to support the nitrogen need of microalgae [79].

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 [96].

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 microalgae 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 [91]. Control strategies playing with the dilution rate, shadowing or modifying depth were then proposed [90].

Finally, a study of the possible sensors which would enhance the monitoring of these process was proposed [30], [29]

7.2.2.3. Life Cycle Assessment

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

Environmental impact assessment. To follow up the pioneering life cycle assessment (LCA) work of [87], we identified the obstacles and limitations which should receive specific research efforts to make microalgae production environmentally sustainable [93].

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 was carried out. Depending on the period of the year, changing the species can both improve productivity and reduce environmental footprint [34].

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

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

7.2.3. Design of ecologically friendly plant production systems

7.2.3.1. Controlling plant arthropod pests

Participants: Frédéric Grogard, Ludovic Mailleret, Suzanne Touzeau, Yves Fotso Fotso.

Optimization of introduction processes. The question of how many and how frequently natural enemies should be introduced into crops to most efficiently fight a pest species is an important issue of integrated pest management. The topic of optimization of natural enemies introductions has been investigated for several years [89], and extends more generally to pulse perturbations in population dynamics.

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 in Python MESA, on the basis of a previous work in 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 [88]. The modelling platform is interactive and can be accessed online at <http://popintro.sophia.inra.fr/>.

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 [14].

Characteristics of space and the behavior and population dynamics of biological control agents. 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 Journal [94] and Marjorie Haond's PhD theses [85]. The last article associated with Thibaut Morel Journal's Thesis appeared this year [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 [86] as represented by its local carrying capacity can positively influence the spreading speed of an expanding population. This work has been published as a preprint recommended by *Peer Community in Ecology* and is on the verge to be submitted to a regular scientific journal. This work has been performed in collaboration with Elodie Vercken (ISA) and Lionel Roques (BioSP, Avignon).

In a different context, we studied how predatory mite population development can be enhanced by the provision of artificial habitats. One paper focused on the influence of different artificial materials on the oviposition and survival of predatory mites appeared this year [16]. This topic was also at the core of the Master 2 internship of Lucas Etienne [81] during which he studied the combined influences of artificial habitats and additional food on the development of a predatory mite and on the control of a phytophagous mite. An article reporting on this study is currently under preparation.

Modelling and control of coffee berry borers. We developed a model describing the coffee berry borer dynamics based on the insect life-cycle and the berry availability during a single cropping season. A control was introduced, based on a biopesticide (entomopathogenic fungus such as *Beauveria bassiana*) that is sprayed and persist on the berries. An optimal control problem was solved (see Section 7.1.1.2). The aim was to maximise the yield at the end of the cropping season, while minimising the borer population for the next cropping season and the control costs. Depending on the initial pest infestation, the optimal solution structure varied [60], [62]. This research pertains to Yves Fotso Fotso's PhD thesis, who visited BIOCORE during 5 months in 2019 through the EPITAG associate team.

7.2.3.2. Controlling plant pathogens

Participants: Frédéric Grogard, Ludovic Mailleret, Suzanne Touzeau, Clotilde Djuikem.

Sustainable management of plant resistance. We studied other plant protection methods dedicated to fight plant pathogens. One such method is the introduction of plant 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.

We have developed a (spatio-)temporal epidemiological model of the phoma stem canker of oilseed rape, to test and assess the durability of deployment strategies of various cultivars. Based on this model, we aim at developing a user-friendly, upgradeable and efficient simulation tool designed for researchers as well as non academic partners from technical institutes and agriculture cooperatives. We hence applied and obtained the SiDRes AMDT, which will start in 2020.

A stochastic model was developed to help determine the efficiency of pyramiding qualitative resistance and quantitative resistance narrowing population bottlenecks exerted on plant 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 [36]. This study 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).

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 [61]. This was done in collaboration with Pauline Clin and Frédéric Hamelin (Agrocampus Ouest).

7.2.3.3. *Plant-nematode interactions*

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

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

Based on an interaction model between plantain roots and *Radopholus similis*, we solved an optimisation problem (see Section 7.1.1.2). It aimed at determining 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. Fallow periods reduce the nematode population in the soil, as these pests need roots to feed on and reproduce. For a relatively long time horizon, deploying one season less than the maximum possible number of cropping seasons resulted in a better multi-seasonal profit. The optimal solution consisted in applying long fallows at the beginning, to drastically reduce the nematode population. The profit was lower for more regular fallows, but the final soil infestation was also lower [67]. This research pertains to Israël Tankam Chedjou's PhD thesis, who visited BIOCORE during 5 months in 2019 through the EPITAG associate team.

We also studied resistance-based root-knot nematode control. As virulent nematodes exhibit a reduced fitness on susceptible crops, alternating resistant and susceptible plants could help increase the efficiency and durability of such control methods. Optimal crop rotations (see Section 7.1.1.2) were characterised by low ratios of resistant plants and were robust to parameter uncertainty. Rotations provided significant gains over resistant-only strategies, especially for intermediate fitness costs and severe epidemic contexts. Switching from the current general deployment of resistant crops to custom rotation strategies could not only maintain or increase crop yield, but also preserve the few and valuable R-genes available. This research pertains to Samuel Nilusmas' PhD thesis. This work has been published as a pre-print [76] and is currently under review. It has also been presented at several national and international conferences this year [66], [42].

7.2.3.4. *Optimality/games in population dynamics*

Participants: Frédéric Grogard, 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 [39]. This work is done with Fabien Halkett of INRA Nancy.

Optimal foraging and residence times variations. In this work, we built on our re-analysis of the Marginal Value Theorem (MVT) [4] to study the effect on the optimal foraging strategy of habitat conversion, whereby patches are converted from one existing type to another, hence changing the frequency of each type in the environment. We studied how realized fitness and the average rate of movement should respond to changes in the frequency distribution of patch-types, and how they should covary. We found that the initial pattern of patch-exploitation in a habitat can help predict the qualitative responses of fitness and movement rate following habitat conversion. We conclude that taking into account behavioral responses may help better understand the ecological consequences of habitat conversion [17].

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 and Biocore agreed for a transfer of intellectual property concerning the work of former intern L. Dragoni.

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. This project was unexpectedly arrested by the funding agency on April 2019.
- **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.
- **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 for producing at maximal rate a high value product. It is coordinated by H. de Jong (IBIS Grenoble), and involves members of Biocore and McTao.
- **Plan Cancer - Imodrez:** The objective of this project (2018-2021) is to understand cancer drug response heterogeneity using tumor single-cell dynamics and developing mathematical models and computational approaches. A project coordinated by J. Roux (IRCAN) and funded by Inserm - Plan Cancer.
- **SIGNALIFE:** Biocore is part of this Labex (scientific cluster of excellence) 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 transferred to other production systems. The main partners of UMT FioriMed are ASTREDHOR (National Institute of Horticulture) and the ISA Joint Research Unit of INRA-CNRS-Univ. Nice.
- **EcoPhyto - CeraTIS Corse:** "Territorial management of the Mediterranean fruit fly in Corsica by the Sterile Insect Technique" (2020-2022). This project is based on a pilot field experiment of sterile male releases and it integrates population dynamics and socio-economic approaches.
- **EcoPhyto - INTERLUDE:** "Territorial innovations to reduce phytopharmaceutical 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.

9.1.2. Inria funding

- **Inria Project Lab, Algae *in silico*:** (2014-2019) 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, VALSE, 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 enemies Deployment" (2017-2019) in which Biocore is a partner with INRA Sophia Antipolis.
- **IMMUnE:** INRA SPE is funding the project IMMUnE "Immunité et Modélisation Mathématique pour Unifier l'Epidémiologie" (2019-2021), headed by F. Hamelin (Agrocampus Ouest), in which BIOCORE is a partner.

9.1.4. Networks

- **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: 01/2019 - 12/2019

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),

Modelling and optimization of microalgal based processes.

University of Padova, Italy.

Modelling and control of microalgal production at industrial scale.

9.3. International Initiatives

9.3.1. Inria International Labs

Inria Chile

Associate Team involved in the International Lab:

9.3.1.1. GRENCORE

Title: Modelling 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/eagrencore/>

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.

International Laboratory for Research in Computer Science and Applied Mathematics

Associate Team involved in the International Lab:

9.3.1.2. EPITAG

Title: Epidemiological Modelling and Control for Tropical Agriculture

International Partner (Institution - Laboratory - Researcher):

Université de Douala (Cameroon) - Département de Mathématique et Informatique -
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 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.

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. O. Bernard spent a one year sabbatical at NTNU in the Enersene group working on renewable energy.

9.3.3. Participation in Other International Programs

- Univ. Ben Gurion : Microalgal Biotechnology Lab (Israel), Member of the ESSEM COST Action ES1408 European network for algal-bioproductions (EUALGAE). Modelling of photosynthesis.

9.4. International Research Visitors

9.4.1. Visits of International Scientists

Daniel Figueiredo, University of Aveiro, Portugal, 02-06 Sep. 2019. 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, Feb.-Jun. 2019. Visit in the context of the EPITAG associate team.

Yves Fotso Fotso, University of Dschang, Cameroon, Mar.-Jul. 2019. Visit in the context of the EPITAG associate team.

Clotilde Djuikem, University of Douala, Cameroon, Mar.-Jul. 2019. Visit in the context of the EPITAG associate team.

9.4.2. Visits to International Teams

9.4.2.1. Sabbatical programme

O. Bernard spent a one year sabbatical at NTNU (Norwegian University of Science and Technology), Trondheim, Norway. He worked on a project to turn wastes into bioenergy with anaerobic digestion.

9.5. Project-team seminar

BIOCORE organized a 3-day seminar in September at Peyresq (Alpes-de-Haute-Provence). 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 was the Co-Chair of the Dycops-CAB conference (CAB 2019 Florianópolis, Brazil, 23rd-26th April).

O. Bernard was the head of the academic scientific committee for the AlgaeEurope conference (Paris, France, 3rd-5th December).

10.1.1.2. Special sessions

M. Chaves together with Laetitia Giraldi (from team McTao, Inria) organized an invited session at the Conf. Decision and Control (Nice, France).

J.-L. Gouzé organized an invited session about control and biology at the FGS Conference (Nice, France).

10.1.1.3. Member of the Organizing Committees

O. Bernard was in the organizing committee of the workshop "Growing microalgae for aquaculture in a Nordic climate : opportunities and challenges" (Trondheim, Norway, 28th-29th May).

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.

O. Bernard is area chair (Biosystems and Bioprocesses) for the IFAC World Conference (Berlin, Germany, 12nd-17th July).

M. Chaves was on the PC of the following conferences: JOBIM (Nantes, France), FOSBE (Valencia, Spain), and CSBio (Nice, France).

J.-L. Gouzé is a member of the program committee for the International Conference on Positive Systems, and CSBio (Nice, France).

10.1.2.2. Reviewer

All BIOCORE members have been reviewers for the major 2019 conferences in our field: CDC, ECC, IFAC Congress, FOSBE,...

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, Algal Research, 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 workshop MADEV19, (“Mathématiques Appliquées à des questions de DEVELOPPEMENT”) (Dakar, November, 25th-27th).

O. Bernard was invited at the workshop “Control engineering concepts in systems- and synthetic biology” (Stavanger, Norway 20th-21st May).

P. Bernhard gave invited presentations at the “Rencontre interdisciplinaire: Théorie des jeux: concept mathématique et applications en économie”, University of Nice (November 2019).

M. Chaves gave a seminar on dynamics and feedback architectures in gene-metabolic pathways at the center for Modeling, Simulation and Interactions (MSI), Université Côte d’Azur (June 2019).

M. Chaves was invited to give a presentation at the Minisymposium on Modeling signal transduction/gene regulatory networks organized by T. Gedeon at the 9th International Congress on Industrial and Applied Mathematics (Valencia, Spain, July 2019).

M. Chaves was invited to give a presentation at the Symposium on Modeling approaches for cancer therapy, at Université de Lille (PHLAM) (September 2019).

Jean-Luc Gouzé was invited to give presentations at Autrans (IBIS seminar), Ifremer Nantes, Inria Paris (Kaist seminar with South-Korea).

S. Touzeau was invited to present works of the EPITAG associate team at the AgriNumA’2019 Symposium on “Digital agriculture in Africa”, Dakar, Senegal (April 30th, 2019) [43].

10.1.5. Scientific Expertise

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

M. Chaves was a member of the Selection Committee for a Maitre de Conference position at the Univ. Rennes.

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

10.1.6. 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 and W. Djema are members of the CLDD of Inria Sophia Antipolis (local committee for sustainable development).

M. Chaves is a member of the Education Board 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. Grogard is a member of the NICE committee, which allocates post-doctoral grants and fundings for visiting scientists at Inria Sophia Antipolis.

Since 2015, F. Grogard 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 INRA metaprogramme on "Plant Health", a follow-up of the SMaCH metaprogramme (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 CentraleSupélec, Saclay, France.

Master: O. Bernard (18h ETD), "Automatic Control applied to biotechnological processes", M2, Ecole CentraleSupélec, Saclay, 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: 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: F. Grognard (45h ETD), "Elements of mathematical modelling", M1, MSc in Environmental Hazards and Risks Management, Université Côte d'Azur, 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

PhD: M. Haond. "Impact de la capacité de charge de l'environnement sur les dynamiques d'expansions de métapopulations. Théories et applications à un système expérimental hôte-parasitoïde", 2015-2019, Université Côte d'Azur. Supervisors: E. Vercken (UMR ISA), L. Mailleret and L. Roques (UR BioSP). Defended on 03/26/2019.

PhD: C. Martinez von Dossow. "Modélisation, analyse et contrôle de la croissance microalgale en cultures à haute densité", 13 May 2019, Sorbonne Université. Supervisors: O. Bernard, F. Mairet and A. Sciandra.

PhD: L. Gomes Pereira "Modeling cell response heterogeneity to pro-apoptotic ligands", 26 November 2019, Univ. Côte d'Azur. Supervisors: M. Chaves and J. Roux (IRCAN, Nice).

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

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

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: Y. Fotso Fotso. “Modeling, analysis and control of coffee berry borers”, University of Dschang, Cameroon, since January 2017. Supervisors: B. Tsanou (Univ. Dschang), S. Bowong (Univ. Douala), F. Grogard, S. Touzeau.

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

PhD in progress: E. Firippi. “Mathematical analysis, control design and coupling for models of biological oscillators”, since October 2017, Univ. Côte d’Azur. Supervisors: 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. Caillaud (team McTao).

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

PhD in progress: B. Assis Pessi. “Modelling and Control of outdoor microalgal processes”, since November 2019, Université Côte d’Azur. Supervisors: O. Bernard and L. Giraldi (team McTao).

PhD in progress: C. Djuikem. “Modelling and control of perennial plant phytopathogens”, Université Côte d’Azur, since October 2019. Supervisors: F. Grogard, S. Touzeau, S. Bowong (Univ. Douala).

PhD in progress: M. Péré. “Modeling cancer drug response heterogeneity using experimental tumor single-cell dynamics and transcriptomics”, since October 2019, Univ. Côte d’Azur. Supervisors: M. Chaves and J. Roux (IRCAN, Nice).

10.2.3. Master thesis and internships

PFE: L. Guitou, EPU MAM, supervisors J.-L. Gouzé et V. Baldazzi.

M1: L. Guitou, EPU MAM, supervisors J.-L. Gouzé et V. Baldazzi.

M1: V. Tapissier, EPU MAM, supervisors J.-L. Gouzé et J. A. Sepulchre (UCA).

M2: L. Etienne. “Combinaison de microhabitats artificiels et de ressources alimentaires pour des acariens agents de lutte biologique”, Université de Montpellier & Montpellier SupAgro, supervisors: C. Bresch (ISA), L. van Oudenhove (ISA) and L. Mailleret.

M2: B. Louis. “Modélisation individu-centrée pour optimiser l’introduction de populations et Applications en biologie de la conservation et lutte biologique”. Université Côte d’Azur, supervisor: L. Mailleret.

M2: L. Plaza Alvarez, “Microalgae growth limited by light, nitrogen, and phosphorus”. Universidad Técnica Federico Santa María, Valparaiso. Supervisors: C. Martinez von Dossow and O. Bernard.

Other: O. Bernard supervised a project involving 4 students from CentraleSupélec (first year of engineering school), 4 months, to design a system for microalgae growing under biofilm forms.

10.2.4. Juries

O. Bernard was referee for the jury of the PhD thesis of Angela La, “Process development for symbiotic culture of *Saccharomyces cerevisiae* and *Chlorella vulgaris* for in situ CO₂ mitigation”. University Paris-Saclay (May, 22nd 2019).

M. Chaves was in the HDR jury of Eugenio Cinquemani as reviewer (November, Univ. Grenoble Alpes).

M. Chaves was in the PhD juries of: Mohamed Ladjimi (as reviewer; September, Univ. Lille), Hugues Mandon (as examiner; November, Univ. Paris-Saclay), Luis Pereira (as advisor; November, Univ. Côte d’Azur).

J.-L. Gouzé was reviewer of the PhD thesis of Fatima-Zahra Tani, November, University of Montpellier.

10.3. Popularization

10.3.1. Articles and contents

- A popularization article has been published in the book "Chimie verte et IAA - Vers une bioéconomie durable" [69].

10.3.2. Interventions

- O. Bernard gave two general public conferences on the topic "Will we drive cars powered by microalgae in 2030" (Saint Etienne de Tinée, 21st September and MAMAC, Nice, November, 13th).
- P. Bernhard did several interventions for a general audience in the Alpes-Maritimes (at Biot, Saint-Vallier and Sospel).
- L. Chambon participated in MASTIC activities in the school Emile Roux (5 June 2019).
- Several members of Biocore hosted schoolchildren to show them the team's research topics.

10.3.3. Internal action

- M. Chaves gave a presentation at the local PhD Seminars organized by the students, on modeling the interactions between mammalian cell cycle and circadian clock.

11. Bibliography

Major publications by the team in recent years

- [1] N. BAJEUX, F. GROGNARD, L. MAILLERET. *Augmentative biocontrol when natural enemies are subject to Allee effects*, in "Journal of Mathematical Biology", 2017, vol. 74, n^o 7, pp. 1561 - 1587 [DOI : 10.1007/s00285-016-1063-8], <https://hal.archives-ouvertes.fr/hal-01402250>
- [2] C. BAROUKH, R. MUÑOZ-TAMAYO, J.-P. STEYER, O. BERNARD. *DRUM: A New Framework for Metabolic Modeling under Non-Balanced Growth. Application to the Carbon Metabolism of Unicellular Microalgae*, in "PLoS ONE", August 2014, vol. 9, n^o 8, e104499 [DOI : 10.1371/JOURNAL.PONE.0104499], <https://hal.inria.fr/hal-01097327>
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- [7] F. MAIRET, O. BERNARD, P. MASCI, T. LACOUR, A. SCIANDRA. *Modelling neutral lipid production by the microalga *Isochrysis affinis galbana* under nitrogen limitation*, in "Biores. Technol.", 2011, vol. 102, pp. 142-149, <http://dx.doi.org/10.1016/j.biortech.2010.06.138>
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- [9] C. POIGNARD, M. CHAVES, J.-L. GOUZÉ. *Periodic Oscillations for Non Monotonic Smooth Negative Feedback Circuits*, in "SIAM Journal on Applied Dynamical Systems", 2016, vol. 15, n^o 1, pp. 257–286 [DOI : 10.1137/15M1033368], <https://hal.archives-ouvertes.fr/hal-01242157>
- [10] L. TOURNIER, M. CHAVES. *Interconnection of asynchronous Boolean networks, asymptotic and transient dynamics*, in "Automatica", 2013, vol. 49, n^o 4, pp. 884-893 [DOI : 10.1016/J.AUTOMATICA.2013.01.015,], <http://hal.inria.fr/hal-00848450>

Publications of the year

Doctoral Dissertations and Habilitation Theses

- [11] L. G. PEREIRA. *Modeling cell response heterogeneity to pro-apoptotic ligands*, Université Côte d'Azur, November 2019
- [12] C. M. VON DOSSOW. *Modélisation, analyse et contrôle de la croissance microalgale en cultures à haute densité*, Sorbonne Université, May 2019

Articles in International Peer-Reviewed Journals

- [13] S. ALMEIDA, M. CHAVES, F. DELAUNAY. *Transcription-based circadian mechanism controls the duration of molecular clock states in response to signaling inputs*, in "Journal of Theoretical Biology", January 2020, vol. 484, 110015 p. [DOI : 10.1016/J.JTBI.2019.110015], <https://hal.archives-ouvertes.fr/hal-02299359>
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