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Activity Report 2015

Project-Team BIOCORE

Biological control of artificial ecosystems

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Modeling and Control for Life Sciences

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Project-Team BIOCORE

Creation of the Project-Team: 2011 January 01

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1. Members

Research Scientists

Jean-Luc Gouzé [Team leader, Inria, Senior Researcher, HdR]
Olivier Bernard [Inria, Senior Researcher, HdR]
Pierre Bernhard [Inria, Emeritus Senior Researcher, HdR]
Madalena Chaves [Inria, Researcher, HdR]
Frédéric Grognard [Inria, Researcher]
Ludovic Mailleret [INRA, Researcher]
Francis Mairet [Inria, Starting Research position]
Antoine Sciandra [CNRS, Senior Researcher, part time, HdR]
Jean-Philippe Steyer [INRA, Senior Researcher, part time, HdR]
Suzanne Touzeau [INRA, Researcher]

Engineers

Quentin Béchet [Inria]
Melaine Gautier [Inria, from July 2015 until Sep 2015]
Martin Laviale [Inria, from Aug 2015]
Francesco Novellis [Inria]

Eric Pruvost [LOV, Univ. Paris VI]
Christophe Vasseur [Inria, from Jan 2015 until Oct 2015]

PhD Students

Sofia Almeida [Univ. Nice - Labex Signalife grant]
Nicolas Bajeux [Univ. Nice grant]
Ismail Belgacem [Inria - ANR RESET project grant, until Mar 2015]
Hubert Bonnefond [ADEME-PACA region grant]
Margaux Caia [INRA grant, from Oct 2015]
Stefano Casagranda [Inria - ANR RESET project/PACA region grant]
Charlotte Combe [Univ. Paris VI grant]
David Demory [Univ. Paris VI grant]
Ghjuvan Grimaud [Inria grant]
Elsa Rousseau [Inria - ANR Funfit grant]

Post-Doctoral Fellows

Caroline Baroukh [INRA]
Pierre-Olivier Lamare [Inria, from Nov 2015]
Camille Poignard [Inria]

Visiting Scientists

Andrei Akhmetzhanov [Univ. Montpellier II, until Feb 2015]
Riccardo de Luca [Inria, Univ. di Padova (Italy) PhD student, from May 2015 until Oct 2015]
Daniel Oliveira Figueiredo [Univ. of Aveiro (Portugal), Apr 2015]

Administrative Assistant

Stéphanie Sorres [Inria, AI, part time]

Others

Eric Benoît [External collaborator, Univ. la Rochelle, HdR]
Jérémie Roux [External collaborator, CNRS]
Nicolas Arsapin [Inria, Univ. de Toulon student intern, from Feb 2015 until Jul 2015]
Victor Bernal Arzola [Inria, Univ. Nice student intern, from Jun 2015 until Sep 2015]
Mélanie Bonneault [Inria, INSA Lyon student intern, from May 2015 until Jul 2015]
Margaux Caïa [INRA, ENSAT student intern, from Mar 2015 until Sep 2015]
Alice Chartier [Inria, Univ. François Rabelais Tours student intern, from Feb 2015 until Jul 2015]
Camila Espinoza Carvajal [Inria, PUCV Valparaiso student intern, from Mar 2015 until Jul 2015]
Ignacio Lopez Munoz [Inria, University of Chile student intern, from Aug 2015]
Philippe Moussion [Inria, ENSAT student intern, from Apr 2015 until Sep 2015]

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 UPMC-CNRS (Oceanographic Laboratory of Villefranche-sur-mer - LOV, UMR 7093/ Université P.M. Curie, 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

- Collaboration with IFREMER (Nantes), INRA (MISTEA Montpellier, BIOGER Grignon. IAM Nancy, Agrocampus Ouest, MaIAGE Jouy-en-en-Josas, BioEpAR Nantes), CIRAD Montpellier, Centre d'Océanologie de Marseille, LOCEAN (Paris), GIPSA Grenoble, IBIS, BANG, ANGE and MODEMIC Inria teams.
- Participation in the French groups ModStatSAP (Modélisation et Statistique en Santé des Animaux et des Plantes), GDR Invasions Biologiques and PROBBE (Processus biologiques et bioinspirés pour l'énergie).

- Université Catholique de Louvain (Belgium), Université de Mons (Belgium), University of Stuttgart (Germany), Rutgers University (USA), 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).
- Participation to national programmes: ANR *Blanc* projects Gemco and FunFit, ANR *BioME* projects Facteur 4 and Purple Sun, ANR projects Funfit and Phycover, *Projet d'Investissement d'Avenir* RESET, UMT Fiorimed, and Labex SIGNALIFE.

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 [86]. Using the directly measured variables and those that have been obtained through such, or other, observers, we then develop control methods that take advantage of the system structure (linked to competition or predation relationships between species in bioreactors or in the trophic networks created or modified by biological control).

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

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

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

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

4. Application Domains

4.1. Bioenergy

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

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

Finally, for the energy balance of the process, it is important to couple microalgae and anaerobic digestion to optimize the solar energy that can be recovered from microalgae, as was explored within the ANR Symbiose project (2009-2012) [2].

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 (compared to chemicals)... The use of biocontrol agents, which are, generically, natural enemies (predators, parasitoids or pathogens) of crop pests [6], 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 [103] must be extended from a theoretical point of view and validated experimentally.

4.5. Experimental Platforms

To test and validate our approach, we use experimental platforms developed by our partner teams; these are highly instrumented for accurately monitoring the state of biological species:

- At LOV: A photobioreactor (SEMPO) for experimental simulation of the Lagrangian dynamical environment of marine microalgae with computer controlled automata for high frequency measurement and on-line control. This photobioreactor is managed by Amélie Talec and Eric Pruvost.
- At LOV: the Full Spectrum platform is dedicated to experimental pilots for microalgae production. This 60 m2 greenhouse contains four instrumented raceways. The light received by the cultivation devices can be modified with spectral filters. The objective of the platform is to grow algae in outdoor conditions, with the natural fluctuations of light and temperature. Finally this pilot allows to test management strategies in conditions closer to industrial production.
- At LBE: Several pilot anaerobic digesters that are highly instrumented and computerized and the algotron, that is the coupling of a digester and a photobioreactor for microalgae production. Eric Latrille is our main contact for this platform at LBE.
- AT ISA: Experimental greenhouses of various sizes (from laboratory to semi-industrial size) and small scale devices for insect behavior testing. A device for microalgae growth in greenhouses has also been set up at ISA. Christine Poncet is our main contact regarding experimental setups at ISA.

Moreover, we may use the data given by several experimental devices at EPI IBIS/ Hans Geiselmann Laboratory (University J. Fourier, Grenoble) for microbial genomics.

4.6. Software development

4.6.1. ODIN

We are developing ODIN, a software platform for the supervision of bioreactors. ODIN [76] supports the smart management of bioreactors (data acquisition, fault diagnosis, automatic control algorithm,...). This C++ application (working under Windows and Linux) is structured in order to rapidly develop and deploy advanced control algorithms through the use of a Scilab interpreter. It also contains a Scilab-based process simulator (developed jointly with Inria Chile) which can be harnessed for experimentation and training purposes. ODIN is made of different modules which can be distributed along different platforms, and which interact through CORBA.

It has been implemented and validated with four different applications in four different laboratories. A licence with the start-up BioEnTech was signed for remote monitoring of anaerobic digesters.

4.6.2. In@lgae

The simulation platform In@lgae is jointly developed with the Inria Ange team. Its objective is to simulate the productivity of a microalgae production system, taking into account both the process type and its location and time of the year. A first module (Freshkiss) developed by Ange computes the hydrodynamics, and reconstructs the Lagrangian trajectories perceived by the cells. Coupled with the Han model, it results in the computation of an overall photosynthesis yield. A second module is coupled with a GIS (geographic information system) to take into account the meteorology of the considered area (any location on earth). The evolution of the temperature in the culture medium together with the solar flux is then computed. Finally, the productivity in terms of biomass, lipids, pigments together with CO_2, nutrients, water consumption, ... are assessed. The productivity map which is produced can then be coupled with a resource map describing the availability in CO_2 nutrients and land.

5. Highlights of the Year

5.1. Highlights of the Year

- Metabolic mathematical models are required to fully understand and optimize the microalgae lipid metabolism and finally maximize biofuel production. However, unlike heterotrophic microorganisms that use the same substrate as sources of energy and carbon, photoautotrophic microorganisms require light for energy and CO2 as carbon source. Furthermore, they are submitted to permanent fluctuating light environments due to outdoor cultivation or mixing inducing a flashing effect. Modelling these nonstandard organisms is therefore a major challenge for which classical tools are often inadequate. This year, the work consisted in assessing and comparing the potential of several approaches for modelling microalgae. As a conclusion, the DRUM approach developed within Biocore seems highly promising since it requires a lowest number of parameters while it can predict internal accumulation during transients [14].
- We study the occurrence of periodic solutions in an n-dimensional class of negative feedback systems defined by smooth vector fields. By circumscribing the smooth system by two piecewise linear ones, we show that there exists an invariant toroidal region which contains a periodic orbit of the original smooth system [37]. The strong point of this work is is that it makes a link between hybrid piecewise linear systems (where computations are easier) and smooth classical systems.
- We developed a plant epidemic model to address the epidemiological and evolutionary management of plant virus epidemics in agricultural landscapes using resistant cultivars. Based on the principles of cultivar mixtures and cultivar rotations, we explored different resistance deployment strategies and their impact on disease prevalence and pathogen evolution. Overall, combining cultivar mixtures and rotations provided most efficient and durable pathogen control [25].

6. New Software and Platforms

6.1. In@lgae

KEYWORDS: Simulation - Microalgae system - Productivity
SCIENTIFIC DESCRIPTION The in@lgae simulation plateform is dedicated to the simulation of microalgae growth at different locations and for different periods of the year. The platform runs different submodels to account for the actual climate and compute biomass productivity together with the consumption of water, nitrogen, phosphorus, ... The platform runs models which describe mechanisms from fast time scale (dynamics of photosystems) down to slow time scales (growth photoacclimation). The models also include a description of the temperature evolution in the culturing systems. The simulation can also be coupled with a model of hydrodynamics as represented by the Freshkiss software developed by the Ange EPI.

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 nitrognen fluxes, lipid and sugar accumulation are predicted.

- Participants: Étienne Delclaux, Francis Mairet, Quentin Béchet and Olivier Bernard
- Contact: Olivier Bernard
- URL: https://gforge.inria.fr/projects/inalgae

6.2. Odin

KEYWORDS: Bioinformatics - Biotechnology

SCIENTIFIC DESCRIPTION

This C++ application is dedicated to deploy advanced control algorithms on real bioprocesses through the use of a Scilab interpreter. In Biocore we develop advanced algorithms for supervision and control, and ODIN is the media to apply them. 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 also contains a Scilab-based process simulator which can be harnessed for experimentation and training purposes. It is very modular in order to adapt to any plant and to run most of the algorithms.

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: Melaine Gautier, Olivier Bernard and Francesco Novellis
- 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 semi-discrete models

Participants: Jean-Luc Gouzé, Frédéric Grognard, Ludovic Mailleret, Pierre Bernhard, Elsa Rousseau, Nicolas Bajeux.

Semi-discrete models have shown their relevance in the modeling of biological phenomena whose nature presents abrupt changes over the course of their evolution [96]. 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. 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, or through the introduction of biological control agents [71],[27]. 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, where the crop is absent, as in our analysis of the sustainable management of crop resistance to pathogens [25] or in the dynamics of plant pathogens [50].

7.1.1.2. Model reduction and sensitivity analysis

Participants: Suzanne Touzeau, Jean-Luc Gouzé, Stefano Casagranda, Victor Bernal Arzola.

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 (ERK signaling pathway, circadian rythms in Drosophila) [41]. A global sensitivity analysis was performed to check the method robustness against parameter uncertainty and variability. This work is part of Stefano Casagranda's ongoing PhD thesis and is also a collaboration with Bayer (Sophia-Antipolis).

Parameter identification in compartmental systems. In collaboration with F. Dayan (R&D Manager, Dassault Systèmes), we worked on practical problems of identifiability of parameters in linear pharmacokinetic models. This was the subject of the internship of V. A. Bernal [58].

7.1.2. Metabolic and genomic models

Participants: Jean-Luc Gouzé, Madalena Chaves, Ismail Belgacem, Olivier Bernard, Stefano Casagranda, Francis Mairet, Sofia Almeida.

7.1.2.1. Continuous models analysis

Piecewise quadratic systems for studying growth rate in bacteria. These new systems (first introduced in [82]) use an expression for growth rate that may depend on any number of variables and have several quadratic modes. Relative to the "classical" piecewise affine systems, this new formulation allows the existence of sliding motion as well as oscillatory behaviour for solutions at the thresholds where the vector fields are opposing [21].

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. We also study other models of the global cellular machinery. This is part of the PhD theses of Ismael Belgacem [11] and Stefano Casagranda, and done in collaboration with Inria IBIS project-team, in particular with D. Ropers.

Design of a bistable switch to control cellular uptake. In a joint work with Diego Oyarzún (Imperial College), we analyse the construction of a synthetic bistable system using an unbranched metabolic chain with a global enzyme regulator, as an application of [109]. Bistability can be achieved by choosing an appropriate pattern of regulation. Robustness conditions are given in terms of the promoter dynamic ranges to guarantee a bistable uptake flux [35].

A reduced model for the mammalian cell cycle. We focused on identifying and analyzing the main mechanisms behind the cell cycle and proposed a mathematical model to describe them. This reduced model successfully reproduces oscillatory behaviors including the progress towards a mitosis phase, and then mitosis itself, characterized by an increase in cyclin B. The model was the topic of a poster at the Signalife Workshop [68]. This is a collaboration with F. Delaunay (Ibv Nice) in the framework of Labex Signalife.

7.1.2.2. Hybrid models analysis

Attractor computation using interconnected Boolean networks. During the visit of Daniel Figueiredo, we have worked on an extension of the method proposed in [83]. The idea is to not only use the attractors but also an appropriate set of strongly connected components in the computation of the asymptotic graph [115]. Numerical simulations show a great improvement in the problem of discarding spurious attractors.

Periodic orbits in non monotonic negative feedback circuits. We study 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. By circumscribing the smooth system by two piecewise linear ones, we show there exists an invariant toroidal region which contains a periodic orbit of the original smooth system [37].

7.1.2.3. 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 [85], in collaboration with Inria IBIS project-team.

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 [48].

7.2. Fields of applications

7.2.1. Bioenergy

7.2.1.1. Modelling microalgae production

Participants: Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Ghjuvan Grimaud, Quentin Béchet, David Demory, Hubert Bonnefond, Jean-Philippe Steyer, Francis Mairet.

Experimental developments

Experiments have been carried out to study the effects of nitrogen limitation on the lipid production in microalgae [23] and support model development. These experiments have been carried out in the Lagrangian simulator, under constant or periodic light and temperature, varying the total amount of light dose in the day. The response in terms of storage carbon (triglycerides and carbohydrates) has been measured and correlated to the environment fluctuations.

Other experiments were carried out to reproduce the light signal percept by a cell in a raceway pond [84], derived from hydrodynamical studies [92]. An electronic platform was developed to reproduce this high frequency light signal. The experiments show that the microalgae adapt their pigments to the average light that they have received [23]. Experiments with coloured light demonstrated that the growth rate results from the absorbed light, whatever its wavelength.

A new methodology to measure cell viability has been set up. This approach is very promising to distinguish between net and gross growth rate [20]. It was used in the models to assess the impact of temperature on growth and mortality. The mortality turns out to increase exponentially with temperature. The effect of a short term temperature stress was also tested to understand the consequences of a temperature peak in a cultivation system. Finally, it was shown that microalgae can bear with temperature peaks above $T_{\max}$ if they do not last too long [57].

On top of this, we set up a new experimental platform to carry out pilot experiments with solar light. The platform includes four raceways and the equipment to inoculate and harvest the microalgae [60]. We tested the impact of coloured film mimicking possible photovoltaic material. The collected data were used to calibrate models integrating the light spectrum [64].

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

In collaboration with the IFREMER-PBA team (Nantes) we contributed to a study on the efficiency of dyes (BODIPY and Nile red) to quantify lipid content in microalgae [38].

Metabolism of carbon storage and lipid production

A macroscopic model for lipid production by oleaginous microalgae [7] has been previously proposed. This model describes the accumulation of neutral lipids (which can be turned into biofuel), carbohydrates and structural carbon. A review of the microalgal metabolism reconstruction [15] together with the associated metabolic models has been carried out [14]. A metabolic model has been set up and validated for the microalgae *Isochrysis luthea*. It predicts carbohydrate and lipid accumulation, under conditions of light/dark cycles and/or nitrogen deprivation [72], [1]. A model was developed to represent heterotrophic growth on a mixture of acetate and butyrate [39]. A metabolic model was set up, on the basis of the DRUM framework [1], in order to simulate autotophic, heterotropic and mixotrophic growth, and to determine how to reduce substrate inhibition.

Modelling the coupling between hydrodynamics and biology

In collaboration with the Inria ANGE team, a model coupling the hydrodynamics of the raceway (based on multilayer Saint Venant system) with microalgae growth was developed [79]. This model is supported by the work of ANGE aiming at improving the multi-layer Saint-Venant approach to more finely represent the hydrodynamics of the raceway [54].

Modelling the photosynthesis response to fast fluctuating light

The impact of hydrodynamics on the light perceived by a single cell was studied thanks to fluid dynamics simulations of a raceway pond [90]. The light signals that a cell experiences at the Lagrangian scale, depending on the fluid velocity, were then estimated. A Droop-Han model was used to assess the impact of light fluctuation on photosynthesis. A new model accounting for photoacclimation was also proposed [34]. Single cell trajectories were simulated, and the effect on photosynthesis efficiency was assessed using models of photosynthesis [91]. These results were compared to experimental measurements where the high frequency light was reproduced [84].

Modeling microalgae production processes

The integration of different models developed within BIOCORE [54], [19], [7] was performed to represent the dynamics of microalgae growth and lipid production in raceway systems, on the basis of the dynamical model developed to describe microalgal growth under light and nitrogen limitations. The strength of this model is that it takes into account the strong interactions between the biological phenomena (effects of light and nitrogen on growth, photoacclimation ...), temperature effect [78], [111] and the radiative transfer in the culture (light attenuation due to the microalgae).
Using these approaches, we have developed a model which predicts lipid production in raceway systems under varying light, nutrients and temperature [107]. This model is used to predict lipid production in the perspective of large scale biofuel production [54]. It was also used to assess the microalgal production potential in France, when taking into account the actual meteorology on a 2.5 degree grid, for 2012, the use of lands, slope, proximity of nutrients and CO_2 [93].
In the framework of the ANR project Purple Sun, we developed a thermic model of a raceway pond within a greenhouse in order to estimate the culture temperature. We also included in the microalgae model the effect of light wavelength. This model has been calibrated on experimental data from LOV and has been used to support lighting strategy in order to optimize microalgal productivity (a patent on this process has been submitted).

Nitrogen fixation by diazotrophs

The fixation of nitrogen by *Croccosphera watsonii* was represented with a macro metabolic model [87] quantifying te main fluxes of carbon and nitrogen in the cell. The model was calibrated and validated with the data of three experiments carried out with different duration of the light period and daily dose. Extension of the model were studied to include the effect of temperature [61].

This work is done in collaboration with Sophie Rabouille (CNRS-Oceanographic Laboratory of Villefranche-sur-Mer LOV).

Modelling thermal adaptation in microalgae

An extended statistical analysis was carried out on a database representing the temperature response of more than 200 microalgal species. First the model proposed by [78] turned out to properly reproduce the temperature response. A model was then extracted to predict the observed link between the cardinal temperatures. This lead to the reduction of the parameter number down to 2, with still a good prediction capability.

We have used Adaptive Dynamics theory to understand how temperature drives evolution in microalgae. For a constant temperature, we have shown that the optimal temperature trait tends to equal the environment temperature. We then studied the case where temperature is periodically fluctuating [88]. We now use this method at the scale of the global ocean, validating our approach with experimental data sets from 194 species [42], [49].

7.2.1.2. Control and Optimization of microalgae production

On-line monitoring

Interval observers give an interval estimation of the state variables, provided that intervals for the unknown quantities (initial conditions, parameters, inputs) are known [86]. Several developments were carried out in this direction to improve the design and performances of interval observers, and accounting for a specific structure (*i.e.* triangular) or property (*i.e.* Input to State Stable), [104]. Interval observers were designed for the estimation of the microalgae growth and lipid production within a production process [101][54] and validated experimentally [100][29].

Optimization of the bioenergy production systems

Based on simple microalgae models, analytical optimization strategies were proposed. We assessed strategies for optimal operation in continuous mode using the detailed model for raceways [106], [107]. We first solved numerically an optimal control problem in which the input flow rate of the raceway is calculated such that the productivity in microalgae biomass is maximized on a finite time horizon. Then, we re-analysed the optimization problem and derived a simplified strategy to reach biomass productivities very near to the maximal productivities obtained with the optimal control. These approaches were extended to outdoor cultivation, considering a possible variable culture depth. The optimal strategy for both depth and dilution rate was proposed in order to better manage the process inertia and finally avoid over warming periods. This work was done during the doctoral stay of Riccardo de Luca (Univ. Padova).

We also propose a nonlinear adaptive controller for light-limited microalgae culture, which regulates the light absorption factor (defined by the ratio between the incident light and the light at the bottom of the reactor). We show by numerical simulation that this adaptive controller can be used to obtain near optimal productivity under day-night cycles [31].

Interactions between species

Large scale culture of microalgae for bioenergy involves a large biodiversity. Control of such systems requires to consider the interactions between the different species. Such systems involve bacteria and microalgae, and the competition between these organisms can have several equilibrium points, which can be studied with Monod, Contois and Droop type models [28].

In the framework of the ANR Facteur 4 project, we propose to drive this competition exploring different strategies in order to select species of interest.

We had formerly proposed an adaptive controller which regulates the light at the bottom of the reactor [102]. When applied for a culture with n species, the control law allows the selection of the strain with the maximum growth rate for a given range of light intensity. This is of particular interest for optimizing biomass production as species adapted to high light levels (with low photoinhibition) can be selected. We have also proposed a strategy based on light stresses in order to penalize the strains with a high pigment content and finally select microalgae with a low Chlorophyll content [12]. This characteristic is of particular interest for maximizing biomass production in dense culture. The strategy has been carried out at the LOV and eventually the productivity of *Tisochrysis lutea* was improved by 75% [62]. A patent on this strategy is under submission. Strategies to improve the temperature response have also been proposed. First we modelled the adaptive dynamics for a population submitted to a variable temperature [88]. This was used at the LOV to design experiments with periodic temperature stresses during 200 days aiming at enlarging the thermal niche of *Tisochrysis lutea*. It resulted in an increase by 2 degrees of the thermal niche [12].
Finally, in a more theoretical framework, we studied how to select as fast as possible a given species in a chemostat with two species at the initial instant. Using the Pontryagin maximum principle, we have shown that the optimal strategy is to maintain the substrate concentration to the value maximizing the difference between the growth rates of two species [73]. We now try to extend this result for n species with mutations.

7.2.2. Biological depollution

7.2.2.1. Control and optimization of bioprocesses for depollution

Participants: Olivier Bernard, Francis Mairet, Jean-Luc Gouzé.

We have considered the problem of global stabilization of an unstable bioreactor model (e.g. for anaerobic digestion), when the measurements are discrete and in finite number ("quantized"). These measurements define regions in the state space, wherein a constant dilution rate is applied We show that this quantized control may lead to global stabilization: trajectories have to follow some transitions between the regions, until the final region where they converge toward the reference equilibrium [30].

Although bioprocesses involve an important biodiversity, the design of bioprocess control laws are generally based on single-species models. In [98], we have proposed to define and study the multispecies robustness of bioprocess control laws: given a control law designed for one species, what happens when two or more species are present? We have illustrated our approach with a control law which regulates substrate concentration using measurement of growth activity. Depending on the properties of the additional species, the control law can lead to the correct objective, but also to an undesired monospecies equilibrium point, coexistence, or even a failure point. Finally, we have shown that, for this case, the robustness can be improved by a saturation of the control.

Moreno [105] have proposed an optimal strategy for fed-batch bioreactor with substrate inhibition. Thanks to the Pontryagin maximum principle and the Hamilton-Jacobi equation, we have shown that the same strategy is still optimal when mortality is included in the model [75]. We have also studied the problem when the singular arc is non-necessary admissible everywhere (i.e. the singular control can take values outside the admissible control set). We have pointed out the existence of a frame point on the singular arc above which any singular trajectory is not globally optimal. Moreover, we have provided an explicit way for computing numerically the switching curves and the frame point [17].

7.2.2.2. Coupling microalgae to anaerobic digestion

Participants: Olivier Bernard, Antoine Sciandra, Jean-Philippe Steyer, Frédéric Grognard, Francis Mairet.

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 [113], [112].

In a first stage, we developed models for anaerobic digestion of microalgae. Two approaches were used: first, a dynamic model has been developed trying to keep a low level of complexity so that it can be mathematically tractable for optimisation [97] . On the other hand, we have tested the ability of ADM1 [114] (a reference model which considers 19 biochemical reactions) to represent the same dataset. This model, after modification of the hydrolysis step [99] has then been used to evaluate process performances (methane yield, productivity...) and stability though numerical simulations.

We have proposed and analysed a three dimensional model which represent the coupling of a culture of microalgae limited by light and an anaerobic digester. We first prove the existence and attraction of periodic solutions. Applying Pontryagin's Maximum Principle, we have characterized optimal controls, including the computation of singular controls, in order to maximize methane production. Finally, we have determined numerically optimal trajectories by direct and indirect methods [74].

Finally, we have studied the coupling between three ecosystems: an anaerobic digester, a wastewater treatment pond (with microalgae and nitrifiers) and a microalgal pond. Different possible coupling configurations were tested in simulation. A numerical optimization was carried out to identify, depending on the choice of the objective function (energy production, pollution removal) the optimal arrangement between the three processes. The optimal volume for each process was then determined. This work has been carried out in the framework of the Phycover ANR project and was the subject of the internship of Ignacio Lopez (Universidad de Chile).

7.2.2.3. Life Cycle Assessment

Participants: Olivier Bernard, Jean-Philippe Steyer.

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

In the sequel of the pioneering life cycle assessment (LCA) work of [94], we continued to identify the obstacles and limitations which should receive specific research efforts to make microalgae production environmentally sustainable.

The improvements due to technological breakthrough (leading to higher productivities) have been compared to the source of electricity. It turns out that the overall environmental balance can much more easily be improved when renewable electricity is produced on the plant [36]. As a consequence, a new paradigm to transform solar energy (in the large) into transportation biofuel is proposed, including a simultaneous energy production stage. This motivated the design of the purple sun ANR-project where electricity is produced by semi transparent photovoltaic panels [77] under which microalgae are growing.

Finally, some work are aiming at normalising LCA for microalgae and proposing guidelines to make the LCA more easily comparable [22].

These works have been carried out in collaboration with E. Latrille and B. Sialve (INRA-LBE).

7.2.3. Design of ecologically friendly plant production systems

7.2.3.1. Controlling plant pests

Participants: Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Nicolas Bajeux.

Optimization of biological control agent introductions

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 [6] [108], unveiling the crucial influence of within-predator density dependent processes. Since parasitoids may be more prone to exhibit positive density dependent dynamics rather than negative ones, which are prevalent among predatory biocontrol agents, the current modeling effort consists in studying the impact of positive predator-predator interactions on the optimal introduction strategies (PhD of Nicolas Bajeux, [70], [71]).

The influence of the spatial structure of the environment on biological control efficacy has also been investigated; first results indicate that spatial structure tends to influence it in quite a same way as intra-specific competition does [27].

Connected research on the influence of space on the establishment of biological control agents is also being pursued both through computer simulations and laboratory experiments on parasitoids of the genus *Trichogramma*. This is the topic of the PhD thesis of Thibaut Morel Journel (UMR ISA) [13]; in particular, we showed how landscape connectivity or spatial heterogeneity shape establishment dynamics in spatially structured environments [33], [51], [40]. This research linked to invasion biology also led some of us to contribute with opinion or review contributions to a special issue on biological invasions, in connexion with the GdR Invabio [26], [32].

7.2.3.2. Controlling plant pathogens

Participants: Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Elsa Rousseau, Mélanie Bonneault.

Sustainable management of plant resistance

Because plants can get sick, 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. It is therefore necessary to find ways to protect the durability of such resistances, which are a natural exhaustible resource. We looked at landscape scale spatial deployment strategies of resistant crops able to maximize crop yield [25], allowing for the modification of the spatial arrangement of resistant crops over cropping seasons, showing dramatic increases in crop yield in particular epidemic situations [25].

Experiments were also conducted in INRA Avignon, followed by high-throughput sequencing (HTS) to identify the dynamics of virus strains competing within host plants. Different plant genotypes were chosen for their contrasted effects on genetic drift and selection they induce on virus populations. Those two evolutionary forces can play a substantial role on the durability of plant resistance. Therefore we fitted a mechanistic-statistical model to these HTS data in order to disentangle the relative role of genetic drift and selection during within-host virus evolution [53], [69], [43], [44]. A stochastic model was also produced to simulate the effect of drift on the virus epidemiological dynamics and on the durability of qualitative resistances [59]. This is the topic of Elsa Rousseau's PhD thesis, and is done in collaboration with Frédéric Fabre (INRA Bordeaux) and Benoît Moury (INRA Avignon).

We also developed an epidemiological model describing the dynamics of root-knot nematodes in a protected vegetable cropping system, to design optimal management strategies of crop resistance [110]. The model was fitted to experimental and field data. Preliminary results show that alternating susceptible and resistant crops not only increased the resistance durability, but reduced the disease intensity over time [63].

Finally we developed an epidemiological model including non-conventional gene-for-gene interactions in crops, based on the phoma stem canker of oilseed rape, to assess the durability of crop resistance in the field and design efficient deployment strategies [65]. This ongoing work is part of the K-Masstec project, which also incorporates experimental and field studies in collaboration with BIOGER (INRA Grignon).

Eco-evolutionary dynamics of plant pathogens in seasonal environments

Understanding better pathogen evolution also requires to understand how closely related plant parasites may coexist. Such coexistence is widespread and is hardly explained through resource specialization. We showed that, in agricultural systems in temperate environments, the seasonal character of agrosystems is an important force promoting evolutionary diversification of plant pathogens [89]. The plant parasites reproduction mode may also strongly interact with seasonality. In this context, we investigated the special case of oak powdery mildew, an oak disease which is actually caused by a complex of two different species, combining original plant epidemic data with the semi-discrete seasonal plant epidemic model we introduced a few years ago [50] [95]

This work has been done in collaboration with Frédéric Hamelin (Agrocampus Ouest) during Anne Bisson's internship, Marie Laure Desprez Loustau and Frederic Fabre (INRA Bordeaux).

7.2.3.2.1. Optimality/games in population dynamics

Participants: Frédéric Grognard, Ludovic Mailleret, Pierre Bernhard.

Optimal foraging and residence times variations

A continued collaboration with Vincent Calcagno (UMR ISA) has yielded paper where we reanalyzed the so-called Marginal Value Theorem (MVT), first published in 1976 [80], [81]. Ongoing work aims at pointing how this latter theorem has been misused in some biological literature.

We also investigated the problem in foraging theory of evaluating the expected harvest of an animal when conspecifics may arrive on the same patch of resource in a stochastic fashion, specificaly according to a Poisson process or a Bernoulli process. A joint article with Frédéric Hamelin (Agrocampus Ouest) has been submitted for publication.

With Marc Deschamps, similar questions were studied in theoretical economy in the context of a Cournot competition on a single market. Again, an article has been submitted for publication.

The handicap paradox

We have investigated the question of "how could evolution have reached a state characterized by the handicap paradox?" with the tools of adaptive dynamics. We have reached the conclusion that, if one accepts adaptive dynamics as a model of evolution, and our model of sexual selection, the handicap paradox equilibrium is indeed the limit state of evolution [18].

This work was conducted with Frédéric Hamelin (Agrocampus Ouest).

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

BioEnTech: the contract 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.

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. National programmes

- **ANR-Purple Sun:** The objective of this project (ANR-13-BIME-004) is to study and optimize a new concept consisting in coupling the production of microalgae with photovoltaic panels. The main idea is to derive the excess of light energy to PV electricity production, in order to reduce the phenomena of photoinhibition and overwarming both reducing microalgal productivity.
- **ANR-Facteur 4:** The objective of this project to produce non OGM strain of microalgae with enhanced performance. BIOCORE is involved in the directed selection of microalgae with interesting properties from an industrial point of view. The theory of competition is used to give a competitive advantage to some species. This competitive advantage can be provided by an online closed loop controller.
- **ANR-Phycover:** The overall objective of the PHYCOVER project 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.
- **ANR-FunFit:** The objective of this project (2013-2017) 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-GESTER:** “Management of crop resistances to diseases in agricultural landscapes as a response to new constraints on pesticide use”, ANR Agrobiosphère, 2011–2016. This project aims at producing allocation scenarios of resistant varieties at the scale of cultivated landscapes, that will allow to limit disease development while ensuring sustainable efficiency of genetic resistances. BIOCORE participates in this project via MaIAGE, INRA Jouy-en-Josas.
- **ANR-MIHMES:** “Multi-scale modelling, from animal Intra-Host to Metapopulation, of mechanisms of pathogen spread to Evaluate control Strategies”, ANR – Investissement d’avenir, action Bioinformatique (ANR-10-BINF-07) & Fond Européen de Développement Régional des Pays-de-la-Loire (FEDER), 2012–2017. This project aims at producing scientific knowledge and methods for the management of endemic infectious animal diseases and veterinary public health risks. BIOCORE participates in this project via MaIAGE, INRA Jouy-en-Josas.
- **RESET:** The objective of this project is to control the growth of *E. coli* cells in a precise way, by arresting and restarting the gene expression machinery of the bacteria in an efficient manner directed at improving product yield and productivity. RESET is an “Investissements d’Avenir” project in Bioinformatics (managed by ANR) and it is coordinated by H. de Jong (Ibis, Inria)
- **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 Université Nice Sophia Antipolis.

- **OPTIBIO:** This project is devoted to the analysis of optimal control problems related to bioprocesses. The project is funded by Programme Gaspard Monge pour L'Optimisation et la Recherche Opérationnelle and coordinated by T. Bayen (U. Montpellier 2).
- **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.

9.1.2. Inria funding

- **Inria Project Lab-Algae** *in silico***:** The Algae in silico Inria Project Lab, funded by Inria and coordinated by O. Bernard, focuses on the expertise and knowledge of biologists, applied mathematician and computer scientists to propose an innovative numerical model of microalgal culturing devices. The latest developments in metabolic modelling, hydrodynamic modelling 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.

9.1.3. INRA funding

- **Take Control:** This project, "Deployment strategies of plant quantitative resistance to take control of plant pathogen evolution," is funded by the PRESUME call of the SMAcH INRA metaprogram (Sustainable Management of Crop Health). BIOCORE is a partner together with INRA PACA (Sophia Antipolis and Avignon) and INRA Toulouse (2013-2016). This project provides the major part of the funding for the experiments held for Elsa Rousseau's thesis.
- **K-Masstec:** "Knowledge-driven design of management strategies for stem canker specific resistance genes", INRA Metaprogramme SMaCH, PRESUME action, 2013–2016. The project aims at developing efficient strategies for the deployment of genetic resistance in the field, based on knowledge issued from the understanding of the molecular interaction between distinct avirulence genes, and mainly the discovery of non-conventional gene-for-gene interactions.

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 modelling 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. FP7 & H2020 Projects

SysBioDRez: Marie Curie International Incoming Fellowship FP7 (EC-PEOPLE) is a multidisciplinary CNRS-Inria project for the collaboration of Jeremie Roux (researcher) with both Paul Hofman (scientist in charge) and Jean-Luc Gouzé (partner lab), with the objective of linking in vitro quantitative dynamics to primary tumor samples profiling in order to determine the resistance probability of a specific combination of anti-cancer drugs in lung cancer, using computational methods (see [66]).

9.2.2. Collaborations with Major European Organizations

Imperial college, Department of Chemical engineering (UK),

Modelling and optimization of microalgal based processes.

Imperial College, Centre for Synthetic Biology and Innovation, Dept. of Bioengineering (UK):

Study of metabolic/genetic models

University of Stuttgart, Institute for Systems Theory and Automatic Control (D):

Identification of gene networks

9.3. International Initiatives

9.3.1. Inria International Labs

Inria Chile

Associate Team involved in the International Lab:

9.3.1.1. GREENCORE

Title: Modelling and control for energy producing bioprocesses

International Partners (Institution - Laboratory - Researcher):

- CIRIC (Chile) - Mélaine Gautier
- PUCV (Chile) - Escuela de Ingenieria Bioquimica (EIB) - Gonzalo Ruiz Filippi
- UTFSM (Chile) - Departamento de Matematica - Eduardo Cerpa
- UFRO (Chile) - Chemical Engineering Department - David Jeison

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 expertises 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 UFRO) and software development (CIRIC).

9.3.1.2. Other IIL projects

BIOCORE is involved in the Bionature project from Inria Chile – CIRIC (the Communication and Information Research and Innovation Center), in collaboration with four Chilean universities (Universidad de Chile, Universidad Tecnica Federico Santa Maria, Pontificia Universidad Catolica de Valparaiso, and Universidad de la Frontera). The Bionature project is devoted to natural resources management and the modeling and control of bioprocesses.

9.3.2. Inria International Partners

9.3.2.1. Informal International Partners

GRIMCAPE, Université de Douala, Cameroon. Epidemiology.

National Institute of Technology Meghalaya, India. Modelling of augmentative biological control.

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

Universidad de la Frontera (CL), Modelling of CO_2 transfer in a microalgal absorption column.

9.4. International Research Visitors

9.4.1. Visits of International Scientists

- Samuel Bowong (Université de Douala, Cameroon), 1 week;
- Daniel Figueriedo (University of Aveiro, Portugal), 3 weeks;
- Benoît Chachuat (Imperial College, Department of chemical engineering, UK), 1 week
- Claude Aflalo (Ben Gurion University of the Neguev, Israel), 1 week;
- Andrei Akhmetzhanov (Université Montpellier II), 2 weeks.

9.5. Project-team seminar

BIOCORE organized a 4-day seminar in November in Peyresq. On this occasion, every member of the project-team presented his/her recent results and brainstorming sessions were organised. Claude Lobry (Univ. Nice and Modemic) was invited as a guest speaker.

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific events selection

10.1.1.1. Members of the conference program committee

J.-L. Gouzé is a member of the program committee for the conference BIOMATH, held in Sofia (Bulgaria). He is in the editorial committee of the proceedings of the conference in honor of E. Benoît (La Rochelle 2013), and in the scientific committees of several summer schools.

O. Bernard is in the technical committee of the Computer Applied to Biotechnology (CAB) conferences, and of the FOSBE conference (Foundations of Systems Biology in Engineering). He is in the scientific committee of the French conference "Stic et Environnement".

10.1.1.2. Reviewers

All BIOCORE members have been reviewers for the major 2015 conferences in our field: CDC, ECC, MED,...

10.1.2. Journal

10.1.2.1. Members of the editorial board

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

10.1.2.2. Reviewers

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

10.1.3. Invited talks

O. Bernard gave a lecture on control and observation of anaerobic digestion in the framework of the 14th World Congress on Anaerobic Digestion (Vina del Mar, December, 13th).

O. Bernard was invited to give a conference on microalgae at Ecole Centrale de Paris (“Biotechnological challenge”) ‘Use of microorganisms for biofuel production” (January, 22nd, 2015).

O. Bernard was invited to give a conference for the 50th anniversary of the Society for Energy from Ardeche (June, 1st, 2015).

O. Bernard gave a presentation at the EABA conference "Combining photovoltaic panels and microalgae: How to deflect the excess of solar energy to ensure optimal conditions of light and temperature for growth" (Lisbon, December, 2nd)

10.1.4. Scientific expertise

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

J.-L. Gouzé was in several evaluation committees: Stic Amsud, INSEP...

10.1.5. Research administration

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 a member of the board of the SFBT (French Speaking Society for Theoretical Biology).

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 as well as some project proposals (EuroMed 3+3), and ERCIM post-docs. M. Chaves is a member of the CLHSCT (local committee for the safety of working conditions).

O. Bernard represents Inria at the ANCRE (Alliance Nationale de Coordination de la Recherche pour l'Energie), in the biomass committee. He is a member of the ADT (Technological Development Actions) at Inria.

S. Touzeau is an elected member of the scientific committee of the MIA departement at INRA (2011–2015). She is a member and a board member of the MBIA CSS (Specialised Scientific Commission), in charge of the research scientist evaluation at INRA (2011–2015). S. Touzeau was a member of a jury for the recruitment of junior research scientists at INRA in "Applied mathematics and computer science" (2 positions) and of a jury for the recruitment of a lecturer at Agroparistech in "mathematics applied to the analysis of deterministic models".

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. F. Grognard is a member of the MBIA CSS since 2015.

L. Mailleret is the head of the M2P2 team (Models and Methods for Plant Protection) of ISA.

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Bachelor: F. Grognard (45.5h ETD) and L. Mailleret (26h ETD), "Equations différentielles ordinaires et systèmes dynamiques", L3, 1st year Engineering in Modelling and Applied Mathematics, Polytech'Nice, Université of Nice Sophia Antipolis, France.

Bachelor: N. Bajeux (64h ETD), "Initiation to Scilab", L3, 1st year Engineering in Modelling and Applied Mathematics, Polytech'Nice, Université of Nice Sophia Antipolis, France.

Master: F. Grognard (21h ETD) and L. Mailleret (21h ETD), "Bio-Mathématiques", M1, 2nd year Engineering in Modelling and Applied Mathematics (eq. M1), Polytech'Nice, Université of Nice Sophia Antipolis, France.

Master: L. Mailleret (18h ETD) "Modélisation pour la biologie des populations et l'écologie". Université d'Oran.

Master: J.-L. Gouzé (9h ETD), M. Chaves (9h ETD), "Discrete and continuous approaches to model gene regulatory networks", Master of Science in Computational Biology (M2), University of Nice - Sophia Antipolis.

Master: J.-L. Gouzé (18h ETD), M. Chaves (12h ETD) "Modelling biological networks by ordinary differential equations", 4th year students, Génie Biologie, Polytech'Nice, University of Nice - Sophia Antipolis.

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), “Modelling biotechnological processes”, M2, Ecole Centrale de Paris, France.

Master: S. Touzeau (26.25h ETD), “Analyse de données”, M1, 2nd engineering year in Génie Biologie, Polytech’Nice – Université Nice Sophia Antipolis, France.

O. Bernard together with F. Mairet and Q. Béchet supervised two projects for engineering school students. The first project involved 6 students of Ecole Nationale Supérieure des Mines de Paris (last year of engineering school, 1 week ("Combining photovoltaic panels and microalgae") and the second project involved three groups of 4 students from the Ecole Centrale de Paris (first year of engineering school), 4 months, to design a process with microalgae growing on a biofilm.

10.2.2. Supervision

PhD : I. Belgacem, "Modelling, analysis and control of biological networks", Univ. Nice, defended March 20, 2015. Supervisor: J.-L. Gouzé. [11]

PhD : H. Bonnefond, "Continuous improvement of microalgae for bioenergy production by selection pressure ", UPMC, defended December 9, 2015. Supervisors: A. Sciandra and O. Bernard. [12]

PhD : T. Morel Journel, “Stratégies d’introduction d’organismes dans un environnement spatialement structuré", Univ. Nice, defended December 9, 2015. Supervisors: E. Vercken (UMR ISA) and L. Mailleret. [13]

PhD in progress : G. Grimaud, "Controlled competition for the selection of microalgal species of interest ", since September 2012, Univ. Nice. Supervisors: O. Bernard, F. Mairet and S. Rabouille.

PhD in progress : C. Combe, "Effect of light spectrum and quality on microalgal growth ", since September 2012, UPMC. Supervisors: A. Sciandra, S. Rabouille and O. Bernard.

PhD in progress : D. Demory, "Impact of virus dynamics on microalgae mortality ", since September 2013, UPMC. Supervisors: A. Sciandra and O. Bernard.

PhD in progress : E. Rousseau, ”Plant viruses adaptation to quantitative resistance: from the study of their impact on within-host viral evolutionary dynamics to their durable management in agro-ecosystems”, since November 2012, Univ. Nice. Supervisors: F. Grognard, L. Mailleret, B. Moury, and F. Fabre (INRA Avignon).

PhD in progress : N. Bajeux, "Influence d’une densité dépendance dans les modèles impulsionnels de dynamiques des populations", since October 2013, Univ. Nice. Supervisors: F. Grognard and L. Mailleret.

PhD in progress : S. Casagranda. “Analysis and control of cell growth models”, since November 2013, Univ. Nice. Supervisors: J.-L. Gouzé and D. Ropers (Inria IBIS).

PhD in progress : S. Almeida. "Theoretical design of synthetic biological oscillators and their coupling", since October 2014, Univ. Nice. Supervisors: M. Chaves and F. Delaunay (Univ. Nice, iBV).

PhD in progress : M. Caïa, "Characterization and modelling of a mixotrophic algae - bacteria ecosystem for waste recovery", since September 2015, University Montpellier. Supervisors: J.-P. Steyer and O. Bernard.

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

10.2.3. Juries

L. Mailleret was in the PhD jury of T. Morel Journel "Stratégies d’introduction d’organismes dans un environnement spatialement structuré", Univ. Nice, defended December 9, 2015.

O. Bernard was reviewer for the PhD of G. Van Vooren "Influence of environmental conditions on microalgae lipids profile for biodiesel production", University of Nantes, January 23, 2015.

O. Bernard was in the PhD jury of H. Bonnefond "Continuous improvement of microalgae for bioenergy production by selection pressure ", UPMC, December 9, 2015.

M. Chaves was in the PhD jury of P. Trairatphisan "Studying signal transduction networks with a probabilistic Boolean network approach", University of Luxemburg, July 16, 2015.

M. Chaves was reviewer for the PhD of Christian Breindl "Identification, analysis and control of discrete and continuous models of gene regulation networks", University of Stuttgart, Germany, December 7, 2015.

M. Chaves was in the PhD jury of Vincent Picard "Réseaux de réactions : de l'analyse probabiliste à la réfutation", Université de Rennes, December 16, 2015.

J.-L. Gouzé was reviewer for the HDR of J.J. Tewa "Modélisation et Analyse Mathématique des Systèmes Complexes : Applications en Epidémiologie, Immunologie et Ecologie", Université du Havre, November 10, 2015.

J.-L. Gouzé was in the PhD jury of P.J. Meyer "Invariance and symbolic control of cooperative systems for temperature regulation in intelligent buildings", Université Grenoble Alpes, September 24, 2015.

J.-L. Gouzé was in the PhD jury of I. Belgacem, "Modelling, analysis and control of biological networks", Univ. Nice, March 20, 2015.

F. Mairet was reviewer for the PhD of Diego De Pereda "Methods for the treatment of uncertainty in dynamical systems: Application to diabetes", Universitat Politecnica de Valencia, July 23, 2015.

F. Mairet was in the PhD jury of Micaela Benavides "Parameter identication and robust state estimation of microalgae cultures", Université de Mons, Feb. 24, 2015.

O. Bernard is in the thesis committees of N. Giordano (University of Grenoble), Valeria Villanova (University of Grenoble) and Julie Laniau (Univ. of Rennes).

S. Touzeau is in the thesis committees of David Demory (UPMC, 2013–2016) and Eric Breton (Université de Nantes, 2013–2016).

10.3. Popularization

The activities related to microalgae have generated many articles in national newspapers (Le Monde, Nice Matin, La Principauté, ...), and broadcasts on national TV (France 3, France 2, Arte). Several articles were written by the team members to explain the hurdles and potential of microalgae [77].

Biocore received an award from the Alpes-Maritimes department for its activities in sustainable development. Moreover, Biocore took part to the COP21 Inria stand, where the challenges for the use of mathematics dedicated to microalgae where presented. Biocore was involved in the "Spring of Researchers" and in the "Fête de la Science", the latter through Stefano Casagranda in the framework of his regional grant.

We have also made a short movie to explain the advantages of our supervision software ODIN and to present the pilot photovoltaic greenhouses which will be developed within the ANR Purple Sun project.

S. Touzeau, L. Mailleret, and F. Grognard gave talks on the importance of modelling during the Modelling day of UMT Fiorimed.

F. Mairet gave a talk during the Mediterranean Days (Feb 20, 2015; http://leat.unice.fr/MEDDAYS2015), to present Biocore's activities to various students from Greece, Italy, Spain, Algeria, Morocco...

P. Bernhard has given conferences in highschool Guillaume Appolinaire, in Nice, on February 5 ("Des insectes et des mathématiques", optimal foraging theory) and March 17 ("Un paradoxe en trafic automobile", Wardrop equilibrium and Evolutionary Stable Strategies in evolutionary biology), and in highschool Marcel Pagnol, in Marseille, on April 3rd ("Game theory", for a class of Social and Economic Sciences).

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Major publications by the team in recent years

[1] 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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Publications of the year

Doctoral Dissertations and Habilitation Theses

[11] I. BELGACEM. *Modelling, analysis and control of biological networks*, Université Nice Sophia-Antipolis, March 2015, https://hal.inria.fr/tel-01243874

[12] H. BONNEFOND. *Continuous improvement of microalgae for bioenergy production by selection pressure*, Université Pierre et Marie Curie, December 2015

[13] T. MOREL JOURNEL. *Introduction strategies for organisms in spatially structures envrionments*, Université Nice Sophia Antipolis, December 2015, https://hal.inria.fr/tel-01241402

Articles in International Peer-Reviewed Journals

[14] C. BAROUKH, R. MUÑOZ-TAMAYO, O. BERNARD, J.-P. STEYER. *Mathematical modeling of unicellular microalgae and cyanobacteria metabolism for biofuel production*, in "Current Opinion in Biotechnology", 2015, vol. 33, pp. 198-205 [*DOI :* 10.1016/J.COPBIO.2015.03.002], https://hal.archives-ouvertes.fr/hal-01163456

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