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Activity Report 2016

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

Keywords:

Computer Science and Digital Science:

1.5.1. - Systems of systems
6.1.1. - Continuous Modeling (PDE, ODE)
6.1.3. - Discrete Modeling (multi-agent, people centered)
6.1.4. - Multiscale modeling
6.2.1. - Numerical analysis of PDE and ODE
6.2.6. - Optimization
7.2. - Discrete mathematics, combinatorics

Other Research Topics and Application Domains:

1.1.9. - Bioinformatics
1.1.10. - Mathematical biology
1.1.11. - Systems biology
1.1.12. - Synthetic biology
1.2. - Ecology
2.4.1. - Pharmaco kinetics and dynamics
3.1. - Sustainable development
3.1.1. - Resource management
3.4.1. - Natural risks
3.4.2. - Industrial risks and waste
3.4.3. - Pollution
4.3.1. - Biofuels

1. Members

Research Scientists

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Engineers

Martin Laviale [Inria, until Aug 2016]
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David Demory [Inria, ANR PHYCOVER project grant]
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Elsa Rousseau [Inria, granted by ANR FUNFIT project]

Post-Doctoral Fellows

Ivan Egorov [Inria, granted by ANR FUNFIT and RESET projects, from Jul 2016]
Natacha Go [INRA, from May 2016]
Pierre-Olivier Lamare [Inria]
Marjorie Alejandra Morales Arancibia [Inria, from Sep 2016]
Camille Poignard [Inria, until May 2016]

Visiting Scientist

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Others

Jérémie Roux [External collaborator, CNRS]
Anaïs Bacquet [Univ. Nice student intern, from Feb 2016 until Jul 2016]
Jérome Grenier [Ecole Centrale de Paris student intern, from Apr 2016 until Oct 2016]
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Ambre Vaisseix [Université de Nantes student intern, from Apr 2016 until Aug 2016]

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 [73]. 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 [85] 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.

5. Highlights of the Year

5.1. Highlights of the Year

- 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, which depends on the pest-natural enemies interaction. Since some natural enemies may exhibit positive predator density dependence in the predation interaction, we studied its impact on the optimal biological control introduction strategies [15].
- Optimal allocation of resources in a bacterium. We studied by techniques of optimal control the optimal allocation between metabolism and gene expression during growth of bacteria, in collaboration with Inria IBIS project-team. We showed that a good suboptimal control solution could be implemented in the cell by ppGpp (a small molecule involved in the regulation of ribosomes) [23].

6. New Software and Platforms

6.1. In@lgae

Numerical simulator of microalgae based processes
KEYWORDS: Simulation - Microalgae system - Productivity
FUNCTIONAL DESCRIPTION

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

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

6.2. Odin

Platform for advanced monitoring, control and optimisation of bioprocesses
KEYWORDS: Bioinformatics - Biotechnology
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: Melaine Gautier, Florian Guenn, Fabien Dilet, Olivier Calabro, Romain Primet, Serigne Sow, Olivier Bernard, Mathieu Lacage 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: Frédéric Grognard, Ludovic Mailleret, Pierre Bernhard, Elsa Rousseau, Nicolas Bajeux, Bapan Ghosh.

Semi-discrete models have shown their relevance in the modeling of biological phenomena whose nature presents abrupt changes over the course of their evolution [81]. 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 in deterministic [15] or stochastic [43], [33] fashion. 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 the dynamics of plant pathogens [24].

7.1.1.2. Model reduction and sensitivity analysis

Participants: Suzanne Touzeau, Jean-Luc Gouzé, Stefano Casagranda, Valentina Baldazzi.

Analysis and reduction of biochemical models. Dynamic models representing complex biological systems with numerous interactions can reach high dimensions and include complex nonlinearities. A model reduction method based on process weighing and pruning was developed and implemented on various models [67]. A global sensitivity analysis was performed to check the method robustness against parameter uncertainty and variability. A more general method robust to initial conditions has been elaborated [31]. This work is part of Stefano Casagranda's ongoing PhD thesis and is also a collaboration with Bayer (Sophia-Antipolis).

7.1.1.3. Estimation and control

Participants: Suzanne Touzeau, Natacha Go, Jean-Luc Gouzé.

Parameter identification in complex systems. In complex biological systems, especially when data are scarce, identifying the model parameters is a challenge and raises identifiability issues. So we developed a specific procedure based on sensitivity analysis, to select the parameters to be estimated, to define their ranges and to set the values of the remaining parameters [72]. We used this method to fit a within-host immunological model to a large data set of individual viremia profiles. Our aim was not to reproduce individual profiles, but to identify parameter sets compatible with the data. So we based our fitting criterion on viral indicators rather than the whole viremia dynamics and we defined realistic data-based ranges for these indicators. We used a genetic algorithm for the minimisation. This ongoing work is part of Natacha Go's post-doctorate, supported by the MIHMES project, in collaboration with the Roslin Institute, Edinburgh, UK. It benefits from the resources and support of NEF computation cluster.

Parameter identification in compartmental systems. In collaboration with F. Dayan (R&D Manager, Dassault Systèmes), we work on practical problems of identifiability of parameters in linear pharmacokinetic models.

7.1.2. Metabolic and genomic models

Participants: Jean-Luc Gouzé, Madalena Chaves, Olivier Bernard, Valentina Baldazzi, Stefano Casagranda, Francis Mairet, Sofia Almeida, Claudia Lopez Zazueta, Lucie Chambon, Ivan Egorov.

7.1.2.1. Hybrid models analysis

Attractor computation using interconnected Boolean networks Following the work in [94] and [68], we have generalized the method for computation of the asymptotic graph. In addition, we have extended this methodology for the case of Boolean networks with synchronous updates (collaboration with D. Figueiredo and M.A. Martins from the University of Aveiro, Portugal).

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 [29]. This orbit is unique under some conditions on the parameters.

Piecewise linear representation of genetic regulatory networks The main goal was to develop a methodology for constructing piecewise linear and discrete models from a continuous model: given an initial partition of the state space, or grid, a piecewise constant vector field and diagram of transitions were computed based on the original ODE in the grid (M2 thesis of C. Kozia).

7.1.2.2. Continuous models analysis

A reduced model for the mammalian cell cycle This work focuses on identifying and analysing the main mechanisms underlying the cell cycle. A reduced two-dimensional model was proposed and calibrated against experimental data on cyclin B. As a validation, the model faithfully predicts the period of the cell cycle in response to an external growth factor input (experimental data on the periods is from F. Delaunay's lab). This work in collaboration with F. Delaunay (and part of the PhD thesis of Sofia Almeida) has been submitted to a journal.

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

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 thesis of Stefano Casagranda, and done in collaboration with Inria IBIS project-team, in particular with D. Ropers.

Reduction of metabolic networks. We develop a dynamical reduction reduction for metabolic networks through Elementary Flux Modes and Quasi Steady State Approximation. The aim is, in the spirit of [1], to obtain a system of lower dimensions, with some accumulative variables. This is part of the PhD thesis of Claudia Lopez Zazueta.

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, in collaboration with Inria IBIS project-team. We showed that a good suboptimal control solution could be implemented in the cell by ppGpp (a small molecule involved in the regulation of ribosomes) [23]. We developed different versions of the problem, and consider a new problem where the aim is to optimize the production of a product (ANR project Reset).

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 [74].

7.1.2.4. Slow-Fast analysis of metabolic models

Metabolic modelling generally assumes balanced growth, *i.e.* that there is no accumulation of intermediate compound, and that the metabolism is rapidly at quasi steady state. We go beyond this hypothesis by considering that some metabolic reactions are slow, while other are fast. Then we analyse the differential system using Tikhonov's Theorem. We compare the results obtained using the Drum approach [16], and show that Drum is a reasonable approximation, provided that growth rate stays low.

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, Anaïs Bacquet, 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 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 [11]. 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 [71], derived from hydrodynamical studies [79]. 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 [70]. 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 [66]. It was used in the models to assess the impact of temperature on growth and mortality [20], [30].

On top of this, we carried out pilot experiments with solar light. We tested the impact of coloured film mimicking possible photovoltaic material. The collected data were used to calibrate models integrating the light spectrum in Ambre Veisseix's master thesis.

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).

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 [57], [56][16]. A metabolic model has been set up and validated for the microalgae *Isochrysis luthea*. A model was developed to represent heterotrophic growth on a mixture of acetate and butyrate [95]. 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. The model was extended for other substrates such as glucose or glycerol in Anais Bacquet's master thesis.

Modelling the coupling between hydrodynamics and biology

The evolution of the biomass of microalgae in a raceway may be analyzed through an advection-diffusion-reaction Partial Differential Equations (PDE). First, the advection part corresponds to the transportation of the biomass through the raceway. Second, the diffusion coefficient allows to consider a Brownian motion for each particular trajectory of the particle. Finally, the reaction term corresponds to the biological dynamics. The optimization of the raceway was carried out by a vertical discretization of the raceway and an adjoint-based approach. In a similar way, the shape optimization was considered with the steady solutions of the Saint-Venant equations.

In collaboration with the Inria ANGE team, a model coupling the hydrodynamics of the raceway (based on a new multilayer discretisation of Navier-Stokes equations) with microalgae growth was developed [63]. This model is supported by the work of ANGE aiming at improving the discretization scheme to more finely represent the hydrodynamics of the raceway and more accurately reconstruct Lagrangian trajectories.

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 [78]. 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 [28]. Single cell trajectories were simulated, and the effect on photosynthesis efficiency was assessed using models of photosynthesis. These results were compared to experimental measurements where the high frequency light was reproduced.

Modelling photosynthetic biofilms

Several models have been developed to represent the growth of microalgae within a biofilm. A first structured physiological model uses mixture theory to represent the microalgae growth, based on the consideration of intracellular reserves triggering the processes of growth, respiration and excretion. We consider separately the intracellular storage carbon (lipids and carbohydrates) and the functional part of microalgae. A simpler model was developed and used to identify the optimal working mode of a process based on photosynthetic biofilm growing on a conveyer belt, in Jérome Grenier's internship.

Modeling microalgae production processes

The integration of different models developed within BIOCORE [61], [65], [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.

Using these approaches, we have developed a model which predicts lipid production in raceway systems under varying light, nutrients and temperature [36]. This model is used to predict lipid production in the perspective of large scale biofuel production [61].

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).

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 [12]. First the model proposed by [62] turned out to properly reproduce the temperature response. A model was then extracted to predict the observed link between the cardinal temperatures.

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 [12]. We now use this method at the scale of the global ocean, validating our approach with experimental data sets from 194 species [75], [76].

Modelling viral infection in microalgae

Experiments have been carried out in collaboration with A.-C. Baudoux (Biological Station of Roscoff) in order to study the impact of viral infections on the development of populations of *Micromonas* at different temperatures. This work revealed a qualitative change in viral infection when temperature increases. A model was developed to account for the infection of a *Micromonas* population, with population of susceptible, infected and also free viruses. The model turned out to accurately reproduce the infection experiments at various temperatures, and the reduction of virus production above a certain temperature.

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 [73], [86]. Interval observers were designed for the estimation of the microalgae growth and lipid production within a production process [61] and validated experimentally [83].

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 [88]. We first solved numerically an optimal control problem on a finite time horizon. Then, we re-analysed the optimization problem and derived a simplified sub-optimal strategy. These approaches were extended to outdoor cultivation, considering a possible variable culture depth. Assuming known weather forecasts considerably improved the control efficiency [21].

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).

Interactions between species

We had formerly proposed an adaptive controller which regulates the light at the bottom of the reactor [84]. 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 [64][39]. 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%. A patent on this strategy has been submitted.

Strategies to improve the temperature response have also been proposed. First we modelled the adaptive dynamics for a population submitted to a variable temperature [12]. 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 [64].

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 [58]. 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 [82].

Although bioprocesses involve an important biodiversity, the design of bioprocess control laws are generally based on single-species models. In [26], 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.

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 [93], [92].

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 [59].

7.2.2.3. Life Cycle Assessment

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

In the sequel of the pioneering life cycle assessment (LCA) work of [80], 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 [90]. 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 [60] under which microalgae are growing. The LCA of such innovative processes where microalgae are grown under greenhouses has been carried out.

Finally, some work are aiming at normalising LCA for microalgae and proposing guidelines to make the LCA more easily comparable [69].

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

7.2.3. Design of ecologically friendly plant production systems

7.2.3.1. Controlling plant 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] [89], unveiling the crucial influence of within-predator density dependent processes. Since some natural enemies may be more prone to exhibit positive density dependent dynamics rather than negative ones, we studied the impact of positive predator-predator interactions on the optimal biological control introduction strategies (PhD of Nicolas Bajeux, [15]). Current research aims to understand the influence of different forms of stochasticity in the introduction process or the population dynamics on the efficacy of the introduction program [43], [33]. This last part of N. Bajeux's PhD si performed in collaboration with Vincent Calcagno (ISA).

Characteristics of space and the behavior and population dynamics of parasitoids

We tested the influence of the spatial heterogeneity of resource (hosts) distribution on the movements and fitness of individual parasitoids on a laboratory and a wild strain of the same species of *Trichogramma.* We showed that the level of resource aggregation has not the same influence on the different strains of the parasitoid, pointing out a behavioral adaptation of the laboratory strain [44]. This work is part of Victor Burte PhD Thesis (ISA, 2015-) and is done in close collaboration with V. Calcagno (ISA).

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 *Trichogramma* [50]. This was the topic of the PhD thesis of Thibaut Morel Journel (ISA, defended in December 2015) [87] and is the present topic of Marjorie Haond (ISA, 2015-). In particular, we showed both theoretically and experimentally how landscape connectivity [27] or habitat richness [45], [37], [46] shape the spatio-temporal dynamics of populations in spatially structured environments. This work is being performed in collaboration with Elodie Vercken (ISA) and Lionel Roques (BioSP, Avignon).

7.2.3.2. Controlling plant pathogens

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

Sustainable management of plant resistance

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

Experiments were 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 [41], [42]. A stochastic model was also produced to simulate the effect of drift on the virus epidemiological dynamics and on the durability of qualitative resistances [32], [40]. This was the topic of Elsa Rousseau's PhD thesis [14], and was 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. 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 [47]. This research is the main topic of Samuel Nilusmas PhD thesis (ISA, 2016-).

We extended the epidemiological model describing the phoma stem canker of oilseed rape, which aims at assessing the durability of crop resistance in the field and design efficient deployment strategies. We introduced a spatial structure based on real landscapes, as well as plant rotation strategies based on surveys conducted among farmers and cooperatives. We also performed a sensitivity analysis, to guide the model calibration. This ongoing work is part of (i) the K-Masstec project, which also incorporates experimental and field studies in collaboration with BIOGER (INRA Grignon); (ii) the GESTER project, with close collaborations with various INRA partners. It benefits from the resources and support of NEF computation cluster.

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 [77]. 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 [24]. This work has been done in collaboration with Frédéric Hamelin (Agrocampus Ouest), 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, Ivan Egorov.

Optimal resource allocation

Mycelium growth and sporulation is considered for phytopathogenic fungi. For biotrophic fungi, a flow of resource is uptaken by the fungus without killing its host; in that case, the life history traits (latence-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. This work, in the framework of the ANR Funfit project, is done with Fabien Halkett of INRA Nancy.

Optimal foraging and residence times variations

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 [18].

With Marc Deschamps, similar questions were studied in theoretical economy in the context of a Cournot competition on a single market [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.

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.
- **ITE-OPALE:** The goal of the Institut de la Transition Énergétique - OPALE project is to increase the lipid content of microalgae by specific selection pressure. The project relies on the strain already selected during the facteur 4 project, whose productivity was 4 times higher than the wild type. We expect to still increase strain performances up to 10 times the productivity of the wild type.
- **ANR-FunFit:** The objective of this project (2013-2017) 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. This project supports Natacha Go’s postdoctoral position.
- **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.
- **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 University of Nice Sophia Antipolis.
- **UMT FIORIMED:** FioriMed is a Mixed Technology Unit created in January 2015 to strengthen the production and dissemination of innovation to the benefit of ornamental horticulture. Horticultural

greenhouses are seen as a "laboratory" for the actual implementation of agroecology concepts with the possibility of generic outcomes being transfered to other production systems. The main partners of UMT FioriMed are ASTREDHOR (National Institute of Horticulture) and the ISA Joint Research Unit of INRA-CNRS-Univ. Nice.

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 [91]).

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 Aveiro, Portugal

Interconnected boolean networks

Roslin Institute, Edinburgh, UK

Epidemiology

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. 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 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 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

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.

GRIMCAPE, Université de Douala, Cameroon. Epidemiology.

9.4. International Research Visitors

9.4.1. Visits of International Scientists

- Claude Aflalo (Ben Gurion University of the Neguev, Israel), 1 week;
- Eduardo Sontag (Rutgers University);
- Laurent Tournier (Inra Jouy-en-Josas), 1 week;
- Bapan Ghosh (National Institute of Technology Meghalaya, India), 1 month.

9.5. Project-team seminar

BIOCORE organized a 4-day seminar in September in La Colle-sur-Loup. On this occasion, every member of the project-team presented his/her recent results and brainstorming sessions were organized. Jacques-Alexandre Sepulchre (INLN, Univ. Nice) was invited as a guest speaker.

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events Organisation

J.-L. Gouzé organized with P. Brest, H. Barelli and F. Besse the Signalife Maths-Bio workshop held at the Inria Sophia Antipolis center, on November 25.

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), and POSTA (Rome, Italy). He is in the scientific committees of several summer schools.

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

Valentina Baldazzi co-organised the HortiModel2016 international symposium on *Models for plant growth, environment control and farming management in protected cultivation*, Avignon, 16–22 September 2016.

10.1.1.2. Reviewers

All BIOCORE members have been reviewers for the major 2016 conferences in our field: CDC, IFAC NOLCOS,...

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

J.-L. Gouzé was invited to give the plenary introductory lecture at POSTA, the 5th International Symposium on Positive Systems, Università Campus Bio-Medico di Roma , Italy.

M. Chaves gave a talk at the workshop on "Asynchronous dynamics of logical models: assessing biologically relevant properties", at CIRM, Marseille (November 2016).

O. Bernard was invited to give a conference on microalgae at Ecole Centrale de Paris ("Biotechnological challenge") 'Use of microorganisms for biofuel production" (December, 8th, 2016).

O. Bernard was invited to give a talk at the ALgoReso workshop related to the development of innovative photobioreactors (May, 12th, 2016).

O. Bernard was invited for a presentation at the Metabolism in Systems Biology (Lille, 24th of November, 2016) workshop organized by the BIOSS working group.

O. Bernard was invited for a talk at the Days of the SFR Condorcet (Namur, 5-6 july, 2016).

10.1.4. Scientific expertise

J.-L. Gouzé was in several evaluation committees or juries: Stic Amsud, Région Région Aquitaine- Limousin - Poitou Charentes, Université de Grenoble, Centrale-Supelec.

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

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 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).

M. Chaves and J.-L. Gouzé were part of the committee for the selection of the 2016 Signalife PhD students.

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 department at INRA (2011–2016). She is a member of the steering committee of the metaprogramme SMaCH *Sustainable Management of Crop Health*, INRA (since 2016).

F. Grognard is a member of the NICE committee, which allocates post-doctoral grants and fundings for visiting scientists at Inria Sophia Antipolis. He is a member of the scientific committee of the doctoral school "Sciences de la Vie" at the University of Nice-Sophia Antipolis. Since 2015, F. Grognard is a member of the MBIA CSS (Specialised Scientific Commission), in charge of the research scientists evaluation at INRA. He is member of the steering committee of Academy 3, Space, Environment, Risk & Resilience of UCA-JEDI.

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 (192h ETD) is ATER at IUT Nice Côte d'Azur of Université of Nice Sophia Antipolis, France.

Master: F. Grognard (33h ETD) and L. Mailleret (33h ETD), "Bio-Mathématiques", M1, 2nd year Engineering in Modelling and Applied Mathematics (eq. M1), Polytech'Nice, Université of Nice Sophia Antipolis, France.

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 (30.75h ETD), "Analyse de données", M1, 2nd engineering year in Génie Biologie, Polytech'Nice – Université Nice Sophia Antipolis, France.

Doctorat: M. Chaves gave courses at the Research School on "Modelling Complex Biological Systems in the Context of Genomics, advances in Systems and Synthetic Biology" (1.5h, Évry, March 2016) and the Summer School on "Modélisation formelle de réseaux de régulation biologique" (3h, Porquerolles, June 2016).

Doctorat: S. Touzeau (8h), "Mathematical modelling in animal and plant epidemiology", CIMPA-Cameroun-CETIC research school *Mathematical and Computer Models in Epidemiology, Ecology and Agronomy*,Yaoundé, Cameroon, September 2016.

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

HDR: F. Mairet, "Control theory applied to microorganism growth: from physiological insights to bioprocess management", December 7th, 2016.

PhD : C. Combe, "Quantitative and qualitative effects of light on the Growth of microalgae in dense cultures ", May, 9th, 2016, UPMC. Supervisors: A. Sciandra, S. Rabouille and O. Bernard.

PhD : E. Rousseau, "Impact of genetic drift and selection on the durability of plant resistance to viruses" ", May 27th, 2016, Univ. Nice Sophia Antipolis. Supervisors: F. Grognard, L. Mailleret, B. Moury, and F. Fabre (INRA Avignon).

PhD : G. Grimaud, "Modeling of the effect of temperature on phytoplankton: from acclimation to adaptation", June, 14th, 2016 Univ. Nice Sophia Antipolis. Supervisors: O. Bernard, F. Mairet and S. Rabouille.

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

PhD in progress : S. Casagranda. “Analysis and control of cell growth models”, since November 2013, Univ. Nice Sophia Antipolis. 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 Sophia Antipolis. 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 Sophia Antipolis. Supervisors: E. Vercken (UMR ISA), L. Mailleret and L. Roques (UR BioSP).

PhD in progress : C. Martinez von Dossow . "Modélisation et optimisation de consortia microalgues-bactéries", since February 2016, UPMC. Supervisors: O. Bernard, F. Mairet and A. Sciandra.

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

PhD in progress : L. Chambon. “Control of models of genetic regulatory networks”. since October 2016, Univ. Nice Sophia Antipolis. Supervisor J.-L. Gouzé.

PhD in progress : C. Lopez-Zazueta. “Use of Perturbation Theory to optimize metabolic production of biofuels by microalgae.”, since January 2016, Univ. Nice Sophia Antipolis, supervisors O. Bernard and 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”, since December 2016, Univ. Nice Sophia Antipolis. Supervisors: S. Touzeau, C. Caporalino (ISA), V. Calcagno (ISA), P. Castagnone (ISA) and L. Mailleret.

Master theses and engineering internships supervision

M1: Ambre Vaisseix, "Effet de la température pour des cultures de microalgues sous serre", Université de Nantes

M1: Anais Bacquet, "Modélisation métabolique de Chlorella sorokiniana, en condition mixotrophe pour identifier des stratégies optimales de consommation de déchets organiques", Univ. Nice Sophia Antipolis.

Engineer: Jérome Grenier, "Développement et modélisation d’un système innovant de production de microalguessous forme de biofilm", Ecole Centrale de Paris

M2: Christina Kozia, "Dynamical representation and analysis of models of genetic regulatory networks", Univ. Nice Sophia Antipolis.

Engineer: Arthur Péré, "Évaluation in silico de la durabilité de résistances variétales avec interaction entre gènes par une approche de modélisation", INSA Lyon.

M2: Samuel Nilusmas, "Évolution de la virulence chez un nématode phytoparasite : déploiement optimal et robuste de plantes résistantes", Université Claude Bernard Lyon 1.

10.2.3. Juries

M. Chaves was reviewer for the PhD defense of Simona Catozzi "Retroactivity in signal transduction: a comparative study of forward and backward responses in signaling cascades", University of Nice Sophia Antipolis, December 15, 2016.

J.-L. Gouzé was reviewer for the PhD of Hafiz Ahmed “Modeling and synchronization of biological rhythms: from cells to oyster behavior”, University of Lille 1, September 22, 2016.

J.-L. Gouzé was reviewer for the PhD of Clément Aldebert, “Uncertainty in predictive ecology: consequence of choices in model construction ”, Univ Aix-Marseille, November 29, 2016.

J.-L. Gouzé was in the jury of the HDR of Francis Mairet, “ Control theory applied to microorganism growth: from physiological insights to bioprocess management ”, University of Nice Sophia Antipolis, December 7, 2016.

J.-L. Gouzé was in the jury of the PhD of Dominique Lamonica, “Capturer les interactions écologiques en microcosme sous pression chimique à travers le prisme de la modélisation”, Université Claude Bernard Lyon 1,April 8, 2016.

J.-L. Gouzé was in the jury of the PhD of Elsa Rousseau “Effect of genetic drift and selection on plant resistance durability to viruses”, University of Nice Sophia Antipolis, May 27, 2016. F. Grognard and L. Mailleret were invited members of this jury

O. Bernard was reviewer for the HDR of S. Tebbani "Contribution à l’étude des systèmes non linéaires incertains : application à la commande de systèmes biotechnologiques ", University of Paris-Sud, November 7th, 2016.

O. Bernard was reviewer for the PhD thesis of C. E. Robles Rodriguez " Modeling and optimization of bio-lipid production by oleaginous yeasts ", University of Toulouse, October 19th, 2016.

O. Bernard was in the PhD jury of J. Rumin "Non-GMO improvement of microalgae performances", University of Nantes, March, 16th, 2016.

O. Bernard was in the PhD jury of G. Grimaud, "Modeling of the effect of temperature on phytoplankton: from acclimation to adaptation", Univ. Nice, June 14th, 2016.

O. Bernard was in the PhD jury of C. Combe, "Quantitative and qualitative effects of light on the Growth of microalgae in dense cultures ", UPM, May 9th, 2016.

S. Touzeau is in the thesis committees of David Demory (UPMC, 2013–2016).

10.3. Popularization

The activities related to microalgae have generated many articles in national newspapers (Le Monde, Nice Matin, journal du CNRS,...) where ...), and broadcasts on national radio (Europe 1) and TV (France 2, France 3). Several articles were written by the team members explaining the hurdles and potential of microalgae.

M. Chaves was part of the jury for the PhD student contest "Ma thèse en 180 sec" (regional stage, April 2016, Nice).

Biocore, especially Stefano Casagranda and Lucie Chambon, was involved in the "Spring of Researchers" and in the "Fête de la Science".

P. Bernhard has given conferences in Lycée René Gosciny, in Drap on January 12th (Le nombre d’or: mythes et curiosités), in Lycée Alexandre Dumas, in Cavaillon on February 29th ("Game Theory") and in Lycée Costebelle, in Hyères on March 15th (Le nombre d’or: mythes et curiosités).

11. Bibliography

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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[3] V. CALCAGNO, F. GROGNARD, F. M. HAMELIN, E. WAJNBERG, L. MAILLERET. *The functional response predicts the effect of resource distribution on the optimal movement rate of consumers*, in "Ecology Letters", December 2014, vol. 17, n^o 12, pp. 1570-1579 [*DOI :* 10.1111/ELE.12379], https://hal.inria.fr/hal-01084299

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Publications of the year

Doctoral Dissertations and Habilitation Theses

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[12] G. M. GRIMAUD. *Modelling the temperature effect on phytoplankton : from acclimation to adaptation*, Université Nice Sophia Antipolis, June 2016, https://tel.archives-ouvertes.fr/tel-01383294

[13] F. MAIRET. *Control theory applied to microorganism growth: from physiological insights to bioprocess management*, Université de Nice Sophia Antipolis, December 2016, Habilitation à Diriger des Recherches, Ph. D. Thesis

[14] E. ROUSSEAU. *Impact of genetic drift and selection on the durability of plant resistance to viruses*, Université de Nice Sophia Antipolis, May 2016

Articles in International Peer-Reviewed Journals

[15] N. BAJEUX, F. GROGNARD, L. MAILLERET. *Augmentative biocontrol when natural enemies are subject to Allee effects*, in "Journal of Mathematical Biology", 2016 [*DOI :* 10.1007/S00285-016-1063-8], https://hal.archives-ouvertes.fr/hal-01402250

[16] C. BAROUKH, R. MUÑOZ-TAMAYO, O. A. BERNARD, J.-P. STEYER. *Reply to the Comment on "Mathematical modeling of unicellular microalgae and cyanobacteria metabolism for biofuel production" by Baroukh et al. [Curr. Opin. Biotechnol. 2015, 33:198–205]*, in "Current Opinion in Biotechnology", March 2016, vol. 38, pp. 200 - 202 [*DOI :* 10.1016/J.COPBIO.2016.02.018], https://hal.inria.fr/hal-01410975

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Invited Conferences

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International Conferences with Proceedings

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