# Activity Report 2014

# Project-Team BIOCORE

# Biological control of artificial ecosystems

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**Keywords:** Models, Bioenergy, Control Theory, Computational Biology, Population Dynamics, Environment

*Creation of the Project-Team:* 2011 January 01.

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# 2. Overall Objectives

## 2.1. Introduction

BIOCORE is a joint research team between Inria (Centre of Sophia-Antipolis Méditerranée), INRA (ISA - Institut Sophia Agrobiotech and LBE - Laboratory of Environmental Biotechnology in Narbonne) and UPMC-CNRS (Oceanographic Laboratory of Villefranche-sur-mer - LOV, UMR 7093/ Université P.M. Curie, Villefranche sur Mer, Team: Plankton Dynamics, Physical and Chemical Processes).

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

**Research themes:**

*Mathematical and computational methods:*

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

*A methodological approach to biology: system study at different scales*

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

*Fields of application:*

- Bioenergy, in particular the production of lipids (which can be used as biofuel), methane and hydrogen by microorganisms (with LOV and LBE).
- $CO_2$ fixation by micro-algae, with the aim of capturing industrial $CO_2$ fluxes (with LOV). This theme can also include artificial ecosystems developed to improve the prediction of carbon fluxes between the ocean and the atmosphere.
- Design and optimization of ecologically friendly protection methods for plants and micro-plants artificial production systems (with ISA and LOV). This theme focuses in particular on biological control programs to prevent 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 (MIA Montpellier, GMPA Grignon. IAM Nancy, Agrocampus Ouest, MIA 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 M3D (Mathématiques et décision pour le développement durable), 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).

- Participation to national programmes: ANR *Blanc* project Gemco and FunFit, ANR *BioME* projects Facteur 4 and Purple Sun, FUI Salinalgue, *Projet d'Investissement d'Avenir* RESET, 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 [91]. 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) [81].

## 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 work concentrates on the protection of cultures of photosynthetic organisms against their pests or their competitors. The forms of cultures that 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 invading species which can be harmful to the cultures; we opt for protecting the culture through the use of biocontrol agents which are, generically, natural enemies of these noxious populations [6].

In crop production, biological control is indeed a very promising alternative to pesticide usage; the use of predators, parasitoids or pathogens of crop pests in order to fight them has many advantages with respect to environmental protection, health of the consumers and the producers, the limited development of resistance (compared to chemicals),... It 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. 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.

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 [105] 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 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. 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 [80] 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. New Software and Platforms

## 5.1. Supervision software

### 5.1.1. *ODIN*

**Participants:** Olivier Bernard, Francesco Novellis.

The latest developments of the bioreactor supervision platform ODIN were dedicated to software restructuration (together with Mélaine Gauthier, from Inria Chile) in order to get more fluidity and more flexibility between modules and in order to support an on line simulator. The connection with a local data base has simplified the management of previous data acquisition and it also allows to "replay" data which were previously recorded. The coupling with the software developed by INRA (Silex) was refactored into a software named MEMO.

ODIN has been tested on four different processes especially (with Eric Latrille) to supervise the 66m2 high rate pond at the LBE, INRA Narbonne. It has also been used at Lesaffre facilities by the BioEnTech company. New algorithms have been successfully tested to control a high-rate anaerobic digestion process.

### 5.1.2. *In@lgae*

**Participants:** Etienne Delclaux, Francis Mairet, Quentin Béchet, Olivier Bernard.

The In@lgae platform has been optimised to make it faster. Some of the key models have been rewritten in C++ to allow a faster computation. Models have been improved to include, in the growth rate computation, the composition of the light spectrum. The graphical user interface has been enhanced and several sets of parameters describing different microalgal species have been stored. Post treatments with Matlab have been implemented to account for slope of the land, its nature, and the distance to CO2 and nutrient sources. The platform supported a study for the French Agency for the development and master of energy (ADEME) managed by ENEA consulting. We could simulate the potential of micro -and macro-algal cultivation in France in 2030, after using the NEF cluster with 300 CPUs (it took 10 days of computation).

# 6. New Results

## 6.1. Highlights of the Year

- We reanalyzed the so-called Marginal Value Theorem (MVT), first published in 1976, in a paper published in Ecology Letters [23]. This theorem, also used in human behavior and economics, establishes how individuals should behave to optimize resource exploitation. Despite the thousands of papers written on the subject, we obtained the first mathematical characterization of how habitat characteristics affect the optimal foraging strategy. Mathematical foundations for this work were given in [24].
- The analysis of metabolic networks is generally made under the assumption (so called "balanced growth") that there is no internal accumulation of metabolites. However, this hypothesis is clearly wrong for microalgae, which store lipids and carbohydrates during the day and consume it during the night. A new formalism, called DRUM (Dynamic Reduction of Unbalanced Metabolism) was developed [16], assuming that the balanced growth is valid only in subnetworks, but that there can be accumulation between these modules (which often represent spatial distribution in the cell). This approach was successfully used to represent the dynamics of carbon accumulation in the microalgae *Tisochrysis lutea* under light/dark cycles, or in response to a nitrogen starvation. It also well described the diauxic heterotrophic growth of *Chlorella pyrernoidosa* [11].

## 6.2. Mathematical methods and methodological approach to biology

### 6.2.1. *Mathematical analysis of biological models*

#### 6.2.1.1. *Mathematical study of semi-discrete models*

**Participants:** Jean-Luc Gouzé, 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 [99]. We used such models and analyzed their properties in several practical situations that are developed in Section 6.3.2, 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 [62], or through the introduction of biological control agents [45], [60], [54]. 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 eco-evolutionary dynamics of plant pathogens [25], [59]

*6.2.1.2. Model reduction and sensitivity analysis*
**Participant:** Suzanne Touzeau.

Dynamic models representing complex biological systems with numerous interactions can reach high dimensions and include complex nonlinearities. Especially if data are scarce, identifying the model parameters is then a challenge. So we designed an ad-hoc method based on global sensitivity analysis to simplify the model and determine the most influential parameters. It was applied to a within-host immunological model [30], [61]. This application was part of Natacha Go's PhD thesis, supervised by S. Touzeau and C. Belloc (BioepAR, INRA & Oniris Nantes) [90].

## 6.2.2. *Metabolic and genomic models*
**Participants:** Jean-Luc Gouzé, Madalena Chaves, Alfonso Carta, Ismail Belgacem, Olivier Bernard, Caroline Baroukh, Jean-Philippe Steyer, Diego de Pereda Sebastian, Francis Mairet.

*6.2.2.1. Continuous models analysis*

*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. With techniques of monotone systems, and time scale hypotheses, we can show the stability of the fast part of these systems, and reduce them to much smaller models [49], [48], [47]. We also study other models of the global cellular machinery. This is part of the PhD theses of Ismael Belgacem and Alfonso Carta [12], and done in collaboration with Inria IBIS project-team.

*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.

*Analysis and reduction of biochemical models* In collaboration with D. Ropers (Inria IBIS project team), we address the problem of reduction of large biochemical networks, to decompose the dynamic behavior of the whole system into simpler models. This is the subject of the thesis of S. Casagranda.

*Design of a bistable switch to control cellular uptake* In joint work with Diego Oyarzún (Imperial College), we explore the idea of constructing a synthetic bistable system using an unbranched metabolic chain with a global enzyme regulator. Bistability can be achieved by choosing an appropriate pattern of regulation and deriving conditions on the promoter dynamic ranges to guarantee a bistable uptake flux. This work started during the visit of Diego to Biocore in October 2014.

*Analysis of signaling pathways leading to apoptosis* In joint work with Jérémie Roux (Marie Curie Fellow, IRCAN Nice), a cascade of signaling modules leading to apoptosis (or programmed cell death) was implemented and studied through simulations. The goal of this work is to determine whether, and at which stage in the pathway, the system may exhibit bistability. This was the work of Xiao Han's internship.

*6.2.2.2. Hybrid models analysis*

*Piecewise quadratic systems for studying growth rate in bacteria* The class of piecewise affine systems was extended to deal with dynamics dependent on dilution due to cell growth rate, leading to switched-piecewise quadratic systems [85]. These new systems use an expression for growth rate that may depend on any number of variables and have several quadratic modes. The behavior of piecewise quadratic systems introduces new features, notably regarding solutions at the thresholds when the vector fields are opposing: not only sliding mode solutions but also oscillatory behavior may happen. Part of this work is in the PhD thesis of Alfonso Carta [12].

*Attractor computation using interconnected Boolean networks* The method developed in [10] has been extended towards a better characterization of the attractors of the interconnected system in terms of invariant sets [26]. The method was used to test growth rate models in E. Coli using Boolean networks.

*Analysis of circadian rhythms in cyanobacteria* The model describing the system responsible for the circadian rhythm of cyanobacteria previously proposed in [86] has been improved in [50]. Here, we have tested the robustness of the circadian rhythm with respect to the perturbations inherent to the noisy environment of the cell, including cell growth and division. The interconnection between two models was studied: circadian rhythm and a stochastic model for cell division.

*Structure estimation for Boolean models of gene regulation networks* The problem of estimating Boolean models of gene networks from few and noisy measurements is addressed in [84], joint work with C. Breindl and F. Allgöwer from the University of Stuttgart. The class of unate or canalizing Boolean functions has been further considered and represented by multi-affine polynomials, leading to a reformulation of the estimation problem as a mixed integer linear program.

*Structural principles for the existence of limit cycles in two-dimensional piecewise affine models* Using concavity and continuity properties of Poincaré maps, we have derived some structural principles which link the topology of the transition graph to the existence, number and stability of limit cycles in a class of two-dimensional piecewise affine biological models of genetic networks [14].

*6.2.2.3. 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 [52], in collaboration with Inria IBIS project-team.

*Estimation of biological models* In a joint work with Diego de Pereda (visiting PhD student), we studied observers and interval observers for models of glucose concentration in diabetes.

# 6.3. Fields of application

## 6.3.1. Bioenergy

*6.3.1.1. Modelling of microalgae production*
**Participants:** Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Philipp Hartmann, 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 [28] 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 observed.

Other experiments were carried out to reproduce the light signal perceived by a cell in a raceway pond [89], derived from hydrodynamical studies [55]. 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 [28].

The effect in the cell cycle of both the light periodic signal, the temperature and a nitrogen limitation were studied. The strong interactions between the different phases of the cell cycle through checkpoints was highlighted [106]. Temperature turned out to play a key role in modulating metabolic fluxes and synchronization.

The effect of cement flue gas on microalgae growth has been tested. It was demonstrated that this $CO_2$ source can be used to feed microalgal industrial cultures [114].

Finally a new methodology to measure cell viability has been set up. This approach is very promising to distinguish between net and gross growth rate [22].

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

In collaboration with the IFREMER-PBA team (Nantes) we contributed to a study of the possible associations between microalgae and bacteria to enhance overall productivity [98].

*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 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 [78], [88], [16].

*Modeling 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 [83]. This model is supported by the work of ANGE aiming at reproducing the hydrodynamics of the raceway, with a specific attention to the effect of the paddle wheel on the fluid [55].

*Modeling the photosynthesis response to fast fluctuating light*

The impact of the hydrodynamics on the light perceived by a single cell was studied thanks to fluid dynamics simulations of a raceway pond [34]. 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 [96]. Single cell trajectories were simulated by this software, and the effect on photosynthesis efficiency was assessed using models of photosynthesis [95]. These results were compared to experimental measurements where the high frequency light was reproduced [89].

We also developed a model to reproduce the fluorescence of microalgae during a PAM protocol [51]

*Modeling microalgae production processes*

The integration of different models developed in the group [81], [101], [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 in a photobioreactor 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 [82], [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 [109]. This model is used to predict lipid production in the perspective of large scale biofuel production. It was also used to assess the potential of France for microalgae, when taking into account the actual 2012 meteorology at the scale of France the use of lands, slope, proximity of nutrients and $CO_2$ [73].

In the framework of the ANR project Purple Sun, we develop an innovative system for microalgae production: a raceway pond under a greenhouse with semi-transparent photovoltaic panels. To this end, we include in the microalgae model the effect of light wavelength, and we develop a thermic model of the system in order to estimate the culture temperature.

Finally, we provide guidelines for the design of experiments with high informative content that allows an accurate estimation of the parameters concerning the effect of temperature and light on microalgae growth. The optimal experiment design problem was solved as an optimal control problem. E-optimal experiments were obtained by using two discretization approaches namely sequential and simultaneous. Simulation results showed the relevance of determining optimal experimental inputs for achieving an accurate parameter estimation [39].

*Nitrogen fixation by nitrogenotrophs*

The fixation of nitrogen by *Croccosphera watsonii* was represented with a macro metabolic model [92]. The main fluxes of carbon and nitrogen are represented in the cell. The accumulation of starch during the day to fuel the nitrogenase working in the absence of oxygen during the night was the key process to explain the nitrogen fixation. The strong influence of the cell cycle was also included in the model. Finally, the model was calibrated and validated with the data of 3 experiments carried out with different duration of the light period and daily dose. The model succeeded to efficiently reproduce the experimental data.

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

*Modeling thermal adaptation in microalgae*

We have used the 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 study the case where the temperature is periodically fluctuating [53]. We now use this method at the scale of the global ocean, validating our approach with experimental data sets from 194 species.

*Including phytoplankton photoadaptation into biogeochemical models*

The complexity of the marine ecosystem models and the representation of biological processes, such as photoadaptation, is very challenging to tackle so that their representation remains an open question. We compared several marine ecosystem models with increasing complexity in the phytoplankton physiology representation in order to assess the consequences of the complexity of photoadaptation models in biogeochemical model predictions. Three models of increasing complexity were considered, and the models were calibrated to reproduce ocean data acquired at the Bermuda Atlantic Time-series Study (BATS) from in situ JGOFS (Joint Global Ocean Flux Study) data. It turns out that the more complex models are trickier to calibrate and that intermediate complexity models, with an adapted calibration procedure, have a better prediction capability [77], [15].

This work is done in collaboration with Sakina Ayata (UPMC-Oceanographic Laboratory of Villefranche-sur-Mer).

6.3.1.2. *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 [91]. 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), [38]. Interval observers were designed for the estimation of the microalgae growth and lipid production within a production process [37] and validated experimentally [36].

*Optimization of the bioenergy production systems*

Based on simple microalgae models, analytical optimization strategies were proposed. We first focused on the optimal operating conditions for the biomass productivity under day/night cycles using Pontryagin's maximum principle (assuming a periodic working mode) [32].

On the other hand, we assessed strategies for optimal operation in continuous mode using the detailed model for raceways [108], [109]. Two strategies were developed. The first one consists in solving 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. In the second strategy, we translated the optimization problem into a regulation problem. We proposed a simple operational criterion that when integrated in a strategy of closed-loop control allows to attain biomass productivities very near to the maximal productivities obtained with the optimal control. We demonstrated that the practical advantages for real implementation makes our proposed controller a suitable control strategy for optimizing microalgae production in raceways.

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 [103].

*Interactions between species*

Large scale culture of microalgae for bioenergy involves a large biodiversity (different mutants, invasion, growth-promoting bacteria [98]...). 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 [33].

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 have proposed an adaptive controller which regulates the light at the bottom of the reactor [104]. 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.

Strategies to improve the temperature response have been proposed. First we modeled the adaptive dynamics for a population submitted to a variable temperature [53]. This was then used to design experiments aiming at enlarging the thermal niche of a species. Experiments with periodic temperature stresses are currently carried out at the LOV.

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 [17]. We now try to extend this result for $n$ species with mutations.

## 6.3.2. Design of ecologically friendly plant production systems

### 6.3.2.1. Controlling plant pests
**Participants:** Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Nicolas Bajeux, Bapan Ghosh.

*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 natural enemies introductions optimization has been investigated for several years [6] [110], 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, [45]). 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 [60]. An extension of that modeling framework was also studied, that considered state dependent impulsive feedback for the stabilization of a positive equilibrium [54].

Connected research on the influence of space on the establishment capacities 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); in particular, we show how landscape connectivity or spatial heterogeneity shape establishment dynamics in spatially structured environments [63], [64], [65].

*Plant compensation, pest control and plant-pest dynamics*

Introducing a plant compartment into our models, we first focused on plant-insect interactions and showed how the level and timing of the pest invasion and pests control interventions could have important effects on the plant's growth pattern and its final biomass. We then modeled plant compensation, which is the process by which some plants respond positively to recover from the effects of pest injury. We have shown that depending on plants and pests characteristics, as well as the level of pest attack, plant overcompensation may or may not happen [35]. Experiments have then been held at UMR ISA on tomato plants facing tutta absoluta invasion; tendencies to compensation have been evidenced, but need to be confirmed through larger scale experiments.

This work is part of the PhD thesis of Audrey Lebon (Cirad), supervised in collaboration with Yves Dumont (Cirad), which has been defended in December 2014.

### 6.3.2.2. Controlling plant pathogens

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

*Sustainable management of plant resistance*

Because in addition to being eaten, plants can also get sick, we studied other forms of biological control 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. Experiments were conducted in INRA Avignon, followed by high-throughput sequencing (HTS) to identify the dynamics of several virus strains in competition 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 [68], [67]. This is the topic of Elsa Rousseau's PhD thesis, and is done in collaboration with Frédéric Fabre and Benoit Moury (INRA Avignon).

We also represented the pathogen spread in agricultural landscapes [40]. At this scale, we looked at how the landscape structure facilitates or impedes the disease spread among host patches. We showed that, when deploying a host with complete resistance to the pathogen along with a susceptible host, mixed landscapes were always more efficient to hamper the disease spread. However, when using a quantitatively resistant host, aggregating the hosts in different regions could result in a better control of the pathogen spread [41]. This work is part of Julien Papaïx's PhD thesis (MIA, INRA Jouy-en-Josas & 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. Indeed, 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 [94]. Plant parasites reproduction mode may also strongly interact with seasonality. In this context, we investigated the influence of cyclical parthenogenesis, i.e. the alternation of sexual and asexual reproduction phases, on the eco-evolutionary dynamics of plant parasites [25].

This work was part of the PhD thesis of Magda Castel (Agrocampus Ouest) and has been done in collaboration with Frédéric Hamelin (Agrocampus Ouest), Didier Andrivon (INRA Rennes) and Virginie Ravigné (CIRAD Montpellier).

### 6.3.3. Biological depollution

#### 6.3.3.1. 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 [71].

Although bioprocesses involve an important biodiversity, the design of bioprocess control laws are generally based on single-species models. In [56], 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. We now start to develop control laws more robust to the presence of additional species.

Moreno [107] has 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 [79]. We have also studied the problem when the singular arc is non-necessarily 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 [46], [19].

#### 6.3.3.2. Coupling microalgae to anaerobic digestion
**Participants:** Olivier Bernard, Antoine Sciandra, Jean-Philippe Steyer, Frédéric Grognard, Philipp Hartmann, 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 optimization [100] . On the other hand, we have tested the ability of ADM1 [115] (a reference model which considers 19 biochemical reactions) to represent the same dataset. This model, after modification of the hydrolysis step [102] has then been used to evaluate process performances (methane yield, productivity...) and stability though numerical simulations.

Finally, we have proposed and analysed a three dimensional model which represents 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 determine numerically optimal trajectories by direct and indirect methods [18].

*6.3.3.3. Life Cycle Assessment*
**Participants:** Olivier Bernard, Jean-Philippe Steyer.

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

In the sequel of the pioneering life cycle assessment (LCA) work of [97], 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 [27]. 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 [74] under which microalgae are growing.

These studies have allowed to identify the obstacles and limitations which should receive specific research efforts to make this process environmentally sustainable [93].

Finally, some works are aiming at normalizing LCA for microalgae and proposing guidelines to make the LCA more easily comparable [87].

These works have been carried out in collaboration with E. Latrille and B. Sialve (INRA - Laboratory of Environmental Biotechnology, Narbonne).

### 6.3.4. *Models of ecosystems*

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

*Optimal foraging and residence times variations*

In a pair of papers [23], [24], we reanalyzed the so-called Marginal Value Theorem (MVT), first published in 1976. This theorem, also used in human behavior and economics, establishes how individuals should behave to optimize resource exploitation. This result has been has been routinely applied in ecology to understand the foraging strategy of animals such as insect parasitoids used for biological control purposes. We obtained the first mathematical characterization of how habitat characteristics (e.g. patch quality, or the distance between resource patches) affect the optimal foraging strategy. This allowed to confirm or refine MVT predictions, and to provide new predictions in the more realistic case of heterogeneous habitats. Some counterintuitive predictions emerged: making resource patches richer can actually make individuals move more rapidly, contradicting generally admitted earlier predictions.

This work was conducted with Vincent Calcagno (UMR ISA) and Frédéric Hamelin (Agrocampus Ouest).

*The handicap paradox*

We have continued our investigation of the handicap paradox of sexual selection with the tools of signaling theory. Zahavi's handicap principle, and our game theoretic analysis, explain why an equilibrium displays the "handicap" feature [21]. However, the explanation seems somewhat contrived, so the next question is "how could evolution have reached such a state ?" We have investigated that question with the tools of adaptive dynamics, and reached the conclusion that, if one accepts adaptive dynamics as a model of evolution, and our model of sexual selection, the equilibrium described in our previous article is indeed the limit state of evolution [20].

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

# 7. Bilateral Contracts and Grants with Industry

## 7.1. Bilateral Contracts with Industry

**La Compagnie du Vent:** the objective of the contract is to predict the impact of large scale raceway design on microalgal productivity using our Inalgae software platform.

**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

**Enea Consulting:** the contract is dealing with the estimation of the potential overall microalgae production in France, using the light-temperature models that we have developed.

# 8. Partnerships and Cooperations

## 8.1. National initiatives

### 8.1.1. National programmes

- **ANR-GeMCo:** The objective of this project is to do model reduction, experimental validation, and control for the gene expression machinery in E. coli. The project is funded by ANR (2010-BLAN-0201-01) coordinated by M. Chaves, and ran through April 2014.

- **ANR-Facteur 4:** The objective of this project (2012-2015) is to propose non OGM strains 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-Purple Sun:** The objective of this project (ANR-13-BIME-004: 2013-2017) is to propose, 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 both the phenomena of photoinhibition and process overwarming.

- **ANR-Phycover:** The overall objective of the project (2014-2018) is to draw the scientific, technical and industrial contexts for an evolution of wastewater treatment plants, combining three modules: a high-rate algal pond dedicated to the treatment of municipal wastewater, an anaerobic digester, and a module aiming at enhancing the digestate valorization.

- **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, 2011–2015. 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 MIA, 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)

- **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), 2012–2016. 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 MIA, INRA Jouy-en-Josas.

- **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.
- **Peps BMI 2013** -J-A Sepulchre (INLN CNRS UNS) - Projet "Pectolyse". Study of a virulence factor of a bacterium.
- **FUI-Salinalgue:** The objective of this project is to take benefit of endemic microalgae species in areas of high salinity (previously used to produce salt) to produce both biofuel (either lipid based or methane) and co-products. BIOCORE is in charge of lab scale experiments and of the modeling of the process.
- **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).

## 8.1.2. *INRA funding*

- **Dynamique spatiale:** INRA-SPE is funding the project "Intégration des approches comportementales et démographiques de la dynamique spatiale des populations d'insectes" in which Biocore is a partner with INRA Sophia Antipolis and Agrocampus Ouest (2012-2014).
- **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. 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.
- **Coexistence:**. INRA-SPE is funding the project "Coexistence d'espèces cryptiques par différenciation temporelle de niches écologiques : de la théorie à l'application via l'exemple des oïdiums du chêne et de la vigne", which aims at understanding the co-existence of closely related plant pathogens in temperate environments. It is closely related to the FunFit ANR project.
- **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 demonstrating that the knowledge issued from the understanding of the molecular interaction between distinct avirulence genes, and mainly the discovery of non-conventional gene-for-gene interactions, can be used to develop efficient strategies for the deployment of genetic resistance in the field.
- **PRRSeval:** "An integrated approach to PRRS (Porcine Reproductive and Respiratory Syndrome)", INRA Metaprogramme GISA, 2013–2015. PRRSeval has three main objectives: to develop a live-attenuated, miRNA-controlled vaccine effective to protect from emerging PRRSV strains; to identify and prioritize relevant parameters for dynamic epidemiology of herds based on in vivo profiling of PRRSV and vaccine response; and to consolidate and empower the existing French networks and collaborations with external partners and stakeholders. BIOCORE participates in this project via MIA, INRA Jouy-en-Josas.

## 8.1.3. *Networks*

- **M3D:** "Mathématiques et décision pour le développement durable", supported by the RNSC (Réseau National des Systèmes Complexes) and INRA, MIA department. BIOCORE participates in the M3D network. L. Mailleret and S. Touzeau are among the network's co-leaders.
- **GDR PROBBE:** The objective of this GDR is the development of new biotechnological processes based on microorganisms producing metabolites which can be used as fuel for transportation (lipids, sugars, methane, hydrogen, ...). BIOCORE is taking part mainly in the modeling and control aspects of the processes involving anaerobic bacteria or microalgae.
- **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

- **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.

## 8.2. European Initiatives

### 8.2.1. FP7 & H2020 Projects

#### 8.2.1.1. PURE

Title: Pesticide Use-and-Risk reduction in European farming systems with Integrated Pest Management

Type: COOPERATION (ICT)

Instrument: Collaborative Project (CP)

Duration: 2011 - 2014

Coordinator: Françoise Lescourret (INRA Avignon, FR)

Other partners: **Research:** Institut National de la Recherche Agronomique - INRA (FR) Rothamsted Research - RReS (UK) Aarhus University - AU (DK) Julius Kühn Institut - JKI (DE) Stichting DLO - DLO (NL) Wageningen University - WU (NL) Consiglio Nazionale delle Ricerche - CNR (IT) Agricultural Institute of Slovenia - KIS (SLO) James Hutton Institute - JHI (UK) Fondazione Edmund Mach - FEM (IT) Instituto Valenciano de Investigacio- nes Agrarias - IVIA (ES) Institute of Plant Protection - IOR (PL) University of Debrecen - Centre of Agricultural Sciences - UDCAS (HU) Joint Research Centre - Institute for Prospective Technological Studies - JRC-IPTS (EU **Extension:** Knowledge Centre for Agriculture - VFL (DK) Association de Coordination Technique Agricole - ACTA (FR) **Industry:** Bayer Crop Science (DE) BIOTOP (FR) Natural Plant Protection (FR) Burkard Manufacturing Co Ltd (UK) Blgg Bv (NL) **Management:** INRA Transfert (FR)

See also: http://www.pure-ipm.eu/project

Abstract: The overall objective of PURE is to provide practical integrated pest management (IPM) solutions to reduce dependence on pesticides in selected major farming systems in Europe, thereby contributing to a reduction of the risks to human health and the environment and facilitating the implementation of the pesticides package legislation while ensuring continued food production of sufficient quality.

PURE will provide IPM solutions and a practical toolbox for their implementation in key European farming systems (annual arable and vegetable, perennial, and protected crops) in which reduction of pesticide use and better control of pests will have major effects. In that project, L. Mailleret develops modeling approaches dedicated to the optimization of plant protection methods relying on biological control and integrated pest management.

### 8.2.2. Collaborations with Major European Organizations

Imperial college, Department of Chemical engineering (UK):

Modeling 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

## 8.3. International Initiatives

### 8.3.1. Inria International Labs

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.

### 8.3.2. Inria Associate Teams

*8.3.2.1. GREENCORE*

Title: Modelling and control for energy producing bioprocesses

International Partner (Institution - Laboratory - Researcher):

Communication and information Research and Innovation Center (CHILI)

Duration: 01/2014 - 12/2016

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).

### 8.3.3. Inria International Partners

*8.3.3.1. Inria informal international partners*

Universidad Técnica Federico Santa María, Departamento de Matemática, Valparaíso, Chile
Universidad de Chile, Departamento de Matemáticas, Ñuñoa Santiago, Chile
Ben-Gurion University of the Negev, Microalgal Biotechnology Laboratory, Beer Sheva, Israel
Center for Environmental Technology and Engineering, Massey University , Palmerston North, New Zealand.

## 8.4. International Research Visitors

### 8.4.1. Visits of International Scientists

- Benoit Chachuat (Imperial College, Department of chemical engineering, UK), 1 week;
- Claude Aflalo (Ben Gurion University of the Neguev, Israel), 1 week;
- Diego Oyarzún (Imperial College London), 1 week;
- Andrei Akhmetzhanov (Université de Montpellier II, F), 1 week.

## 8.5. Project-team seminar

BIOCORE organized a 3-day seminar in November in Saint-Etienne de Tinée. On this occasion, every member of the project-team presented his/her recent results and brainstorming sessions were organised. Alain Rapaport of the Inria MODEMIC team was invited as a guest speaker.

An additionnal 2-day seminar was dedicated to modeling and control of microalgae.

# 9. Dissemination

## 9.1. Promoting Scientific Activities

### 9.1.1. Scientific events selection

*9.1.1.1. member 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. Benoit (La Rochelle 2013). O. Bernard is in the technical committee of the Computer Applied to Biotechnology (CAB) conferences. He is in the scientific committee of the French conference "Stic et Environnement".

All BIOCORE members have been reviewers for the major 2014 conferences in our field: CDC, MTNS, IFAC World Congress,...

### 9.1.2. *Journal*

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,...

### 9.1.3. *Other animations*

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 the coordinator of ANR project GEMCO. Since September 2011, she is a member of the COST-GTRI (the Working Group on International Relations in 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 was in the Inria (Sophia) committee for the selection of new CR2 researchers (May 12-13) and in the Labex Signalife committee for the selection of new PhD students (June 16-17).

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

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.

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). She is a member of the scientific committee of the INRA-ModStatSAP network "Modélisation et Statistique en Santé des Animaux et des Plantes". S. Touzeau was a member of 3 juries for the recruitment of junior research scientists at INRA in April–June: "Epidemiology and plant architecture" (1 position), "Epidemiology and modeling" (2 positions) and "Mathematics for the life sciences and environment" (3 positions). She participated in the panel of experts for the evaluation of the LIRIMA in September 2014.

## 9.2. Teaching - Supervision - Juries

### 9.2.1. *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.

Master: O. Bernard (4.5 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: 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: J.-L. Gouzé (9h ETD), M. Chaves (4.5h ETD), "Discrete and continuous approaches to model gene regulatory networks", M2, Master of Science in Computational Biology, University of Nice - Sophia Antipolis, France.

Master: J.-L. Gouzé (18h ETD), M. Chaves (12h ETD) "Modelling biological networks by ordinary differential equations", M1, 4th year students, Génie Biologie, Ecole Polytechnique University of Nice - Sophia Antipolis, France.

Master : S. Touzeau (17.25h ETD), "Analyse de données", M1, 2nd engineering year in Génie Biologie, Polytech'Nice – Université Nice Sophia Antipolis, France.

PhD program: J.-L. Gouzé and M. Chaves (3h ETD), seminar course on "Introduction to mathematical modeling of biological networks", to the students of the Labex Signalife PhD program, University of 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 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.

### 9.2.2. *Supervision*

PhD : P. Hartmann, " Effect of hydrodynamics on light utilization in large scale cultures of microalgae ", UNS, defended May 14, 2014. Supervisors: O. Bernard and A. Sciandra. [13]

PhD : A. Carta, "Modelling, analysis and control for systems biology: application to bacterial growth models", UNS, defended May 22, 2014. Supervisors: J.-L. Gouzé and M. Chaves.[12]

PhD : C. Baroukh, "Metabolic modeling under non-balanced growth. Application to microalgae for biofuels production", U. Montpellier 2, defended October 10, 2014. Supervisors: J.-P. Steyer and O. Bernard.[11]

PhD : Natacha Go, "Modelling the immune response to the Porcine Respiratory and Reproductive Syndrome virus", AgroParisTech, defended December 8, 2014. Supervisors: S. Touzeau & C. Belloc (BioepAR, INRA & Oniris Nantes) [90]

PhD : A. Lebon, "La compensation dans les interactions plantes insectes : modélisation, simulation et expérimentation", University of Montpellier 2, defended December 10, 2014. Supervisors : Y. Dumont (CIRAD), F. Grognard and L. Mailleret.

PhD in progress : G. Grimaud, "Controlled competition for the selection of microalgal species of interest ", since September 2011, UNS. Supervisor: O. Bernard and S. Rabouille.

PhD in progress : I. Belgacem "Controle de systèmes de régulation génétique", since November 2011, UNS. Supervisor: J.-L. Gouzé.

PhD in progress : H. Bonnefond, "Experimental development of selection oriented photobioreactors", since september 2012, UNS. Supervisor: A. Sciandra and O. Bernard

PhD in progress : T. Morel Journel, "Où, quand, combien? Stratégies d'introduction d'organismes dans un environnement spatialement structuré", since October 2012, UNS. Supervisors: T. Guillemaud, E. Vercken and L. Mailleret.

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, UNS. Supervisors: F. Grognard, L. Mailleret, B. Moury, and F. Fabre (INRA Avignon).

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

PhD in progress : N. Bajeux, "Influence d'une densite dépendance dans les modèles impulsionnels de dynamiques des populations", since October 2013, UNS. Supervisor: F. Grognard.

PhD in progress : S. Casagranda. "Analysis and control of cell growth models", since November 2013, UNS. 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, UNS. Supervisors: M. Chaves and F. Delaunay (UNS, iBV).

### 9.2.3. *Juries*

O. Bernard was referee for the PhD of Cyril Marcilhac "Studies of the culture conditions of a complex ecosystem microalgae / bacteria: application to the development of an a process to extract and recover nutrients from the digestate", University of Rennes 1, Dec. 18, 2014.

O. Bernard was in the PhD jury of G. Bougaran "Co-limitation by nitrogen and phosphorus : study of the mechanisms in the microalgae *Tisochrysis lutea*", Nantes University, Oct. 22, 2014.

O. Bernard was in the PhD jury of T. Dinh. "Interval observers and positive observers", Paris-Sud University (Nov. 24, 2014).

O. Bernard was in the PhD jury of P. Hartmann, " Effect of hydrodynamics on light utilization in large scale cultures of microalgae ", UNS, May 14, 2014.

O. Bernard was in the PhD jury of C. Baroukh, "Metabolic modeling under non-balanced growth. Application to microalgae for biofuels production", U. Montpellier 2, October 10, 2014.

S. Touzeau was in the PhD thesis jury of Natacha Go,"Modelling the immune response to the Porcine Respiratory and Reproductive Syndrome virus", AgroParisTech, December 8, 2014.

M. Chaves and J.-L. Gouzé were in the PhD thesis jury of Alfonso Carta, "Modelling, analysis and control for systems biology: application to bacterial growth models," University of Nice Sophia Antipolis, May 22, 2014.

J.L. Gouzé was referee for the PhD thesis of J.S. Nelva Pasqual. " Exploration des réseaux d'interactions en écologie : de la structure vers la dynamique. Signification des analyses des matrices de communauté en écologie des estuaires". Université Bordeaux 1.

F. Grognard and L. Mailleret were in the PhD jury of A. Lebon, "La compensation dans les interactions plantes insectes : modélisation, simulation et expérimentation", University of Montpellier 2, December 10, 2014.

O. Bernard is in the thesis committee of S. Bellini (University of Montpellier), G. Bougaran (University of Nantes), Valeria Villanova (University of Grenoble) and Sofiane Mazeghrane (University of Montpellier).

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

F. Mairet is in the thesis committee of Alessandro Solimeno (Universidad Politecnica de Catalunya).

## 9.3. Popularization

The activities related to microalgae have generated many articles in national newspapers (Le Monde.fr, Libération, Le Point.fr, ...), and broadcasts on national TV. Several articles were written by the team members to explain the hurdles and potential of microalgae [74]. A book [93] was also written with C. Gudin (formerly at CEA Cadarache) on the potential of microalgae. We also developed a Java applet for the simulation of microalgae growth and biological pest control. The aim of the applet is for the general public to understand the goals and difficulties of controlling such systems.

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 developped within the ANR Purple Sun project.

## 9.4. Conferences, invited conferences

Conferences cited in the bibliography are not repeated here.

O. Bernard was invited to give a conference on microalgae at Ecole Centrale de Paris ("Défi biotechnologie") 'Use of microorganisms for biofuel production" (November 27).

O. Bernard was invited to give a conference at University of Padova "Towards predicting microalgal productivity at large scale from lab experiments", June 26, and at University of Valparaiso "A new framework for metabolic modelling under non-balanced growth. Application to carbon metabolism of unicellular microalgae", March 26.

O. Bernard and F. Mairet gave a lecture (3h) on Modelling microalgal based processes at the 3rd French-Chilean Workshop on Bioprocess Modelling (March, Valparaiso, Chile)

F. Mairet gave a joint talk with Magali Ribot entitled Modeling of micro-algae biofilms at the 1st Symposium Physics of living matter: experiments and theoretical models (Nice, Dec. 18).

M. Chaves was invited to give a semi-plenary talk on "Predictive analysis for biological regulatory systems combining discrete and continuous formalisms," at the Symposium on Mathematical Theory of Networks and Systems (MTNS'14) (July 7-11)

M. Chaves and J.-L. Gouzé organized an invited session on "Discrete and Continuous Formalisms in Systems Biology," at MTNS'14 (July 7-11)

M. Chaves was invited to give presentations at the following meetings: 1st Lyon Control Day (Feb 27-28) and AANS (IEEE International Meeting on Analysis and Applications of Nonsmooth Systems) (Como, Italy, Sep. 10-12),

M. Chaves was invited to give seminars at the department of Mathematics at Imperial College (Mar 25) and at University of Aveiro (Dec 4).

P. Bernhard was invited to give epistemology talks at a small international workshop [42], and later in the seminar of the CIRED (Centre International de Recherches sur l'Environnement et le Développement, CNRS, Ecole des Ponts et Chaussées ParisTech, and Agro ParisTech).

# 10. 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° 8, e104499 [*DOI :* 10.1371/JOURNAL.PONE.0104499], https://hal.inria.fr/hal-01097327

[2] O. BERNARD. *Hurdles and challenges for modelling and control of microalgae for CO2 mitigation and biofuel production*, in "Journal of Process Control", 2011, vol. 21, n[o] 10, pp. 1378–1389 [*DOI :* 10.1016/J.JPROCONT.2011.07.012], http://hal.inria.fr/hal-00848385

[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] A. CARTA. *Modelling, analysis and control for systems biology : application to bacterial growth models*, Universite de Nice Sophia-Antipolis (UNS), May 2014, https://hal.inria.fr/tel-01094091

[13] P. HARTMANN. *Effect of hydrodynamics on light utilization in large scale cultures of microalgae*, Univeristé Nice Sophia Antipolis, May 2014, https://hal.inria.fr/tel-01108529

### Articles in International Peer-Reviewed Journals

[14] W. ABOU-JAOUDÉ, M. CHAVES, J.-L. GOUZÉ. *Links between topology of the transition graph and limit cycles in a two-dimensional piecewise affine biological model*, in "Journal of Mathematical Biology", December 2014, vol. 69, n° 6-7, pp. 1461-1495 [*DOI : 10.1007/S00285-013-0735-X*], https://hal.archives-ouvertes.fr/hal-00919872

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### Invited Conferences

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[43] M. CHAVES. *Hybrid mathematical formalism for analysis of biological regulatory networks*, in "IEEE International Meeting on Analysis and Applications of Nonsmooth Systems", COMO, Italy, September 2014, https://hal.inria.fr/hal-01096270

[44] M. CHAVES. *Predictive analysis for biological regulatory systems – combining discrete and continuous formalisms*, in "Symposium on Mathematical Theory of Networks and Systems (MTNS'14)", Groningen, Netherlands, July 2014, Semi-Plenary talk, https://hal.inria.fr/hal-01096263

### International Conferences with Proceedings

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