IN PARTNERSHIP WITH:
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Activity Report 2013

Project-Team BIOCORE

Biological control of artificial ecosystems

IN COLLABORATION WITH: Institut Sophia Agrobiotech

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Modeling and Control for Life Sciences

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Project-Team BIOCORE

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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 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 prevent pest invasions in crops and bioreactors.
- Biological waste treatment with microorganisms in bioreactors to reduce pollution emissions (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), CIRAD Montpellier, Centre d'Océanologie de Marseille, LOCEAN (Paris), GIPSA Grenoble, IBIS, BANG, ANGE and MODEMIC Inria teams.
- Participation in the French groups CoReV (Modèles et théories pour le Contrôle de Ressources Vivantes, Models and Control of Living Resources), M3D (Mathématiques et décision pour le développement durable) 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).
- The participants of national programmes we take part in: ANR *Blanc* project Gemco and FunFit, ANR *BioME* projects Facteur 4 and Purple Sun, FUI Salinalgue, and *Projet d'Investissement d'Avenir* RESET.

2.2. Highlights of the Year

- Based on simple microalgae models, optimal operating conditions were theroretically identified for the biomass productivity under day/night cycles using Pontryagin's maximum principle [25]. This results paves the way for the theoretical and numerical development of (near)-optimal control laws for lipid production based on more complex models.
- The dynamical behaviour of biological networks can often be qualitatively described by piecewise affine systems. We developped a probabilistic approach for describing the trajectories and predicting periodic orbits in such models. In the state transition graph, a *transition probability* between two nodes can be defined in terms of model parameters [22]. This approach could be used for design or control of genetic networks.

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 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, be it 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 [7]. 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 [9].

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 [103] must be extended from a theoretical point of view and validated experimentally.

4.5. Experimental Platforms

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

- At LOV: A photobioreactor (SEMPO) for experimental simulation of the Lagrangian dynamical environment of marine microalgae with computer controlled automata for high frequency measurement and on-line control. This photobioreactor is managed by Amélie Talec and Eric Pruvost.
- At 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 and Alexandre Bout are our main contacts 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. Software and Platforms

5.1. Supervision software

We are developing a software for the supervision of bioreactors: this platform, named ODIN, has been built for the smart management of bioreactors (data acquisition, fault diagnosis, automatic control algorithm,...). This software was developed in C++ and uses a Scilab engine to run the advanced algorithms developed within BIOCORE. It has been implemented and validated with four different applications.

6. New Results

6.1. Mathematical methods and methodological approach to biology

6.1.1. Mathematical analysis of biological models

6.1.1.1. Mathematical study of semi-discrete models

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

Semi-discrete models have shown their relevance in the modeling of biological phenomena whose nature presents abrupt changes over the course of their evolution [99]. We used such models and analysed their properties in several practical situations that are developed in Section 6.2.2, most of them requiring such a modeling in order to take seasonality into account. Such is the case when the year is divided into a cropping season and a 'winter' season, where the crop is absent, as in our analysis of the sustainable management of crop resistance to pathogens [53] or in the co-existence analysis of epidemiological strains [21]. Seasonality also plays a big role in the semi-discrete modeling required for the analysis of consumers' adaptive behavior in seasonal consumer-resource dynamics, where only dormant offspring survive the 'winter' [61].

6.1.1.2. Model design, identification and validation

Participants: Olivier Bernard, Francis Mairet.

One of the main families of biological systems that we have studied involves mass transfer between compartments, whether these compartments are microorganisms or chemical species in a bioreactor, or species populations in an ecosystem. We have developed methods to estimate the models of such systems [79]. These systems can be represented by models having the general structure popularized by [78], [84], and based on an underlying reaction network:

$$\frac{d\xi}{dt} = K\, r(\xi, \psi) + D(\xi_{in} - \xi) - Q(\xi)$$

We address two problems: the determination of the pseudo-stoichiometric matrix K and the modelling of the reaction rates $r(\xi, \psi)$.

In order to identify K, a two-step procedure has been proposed. The first step is the identification of the minimum number of reactions to be taken into account to explain a set of data. If additional information on the process structure is available, we showed how to apply the second step: the estimation of the pseudo-stoichiometric coefficients.

This approach has been applied to various bioproduction processes, among which activated sludge processes [77], anaerobic digestion [92], [106] and anaerobic digestion of microalgae [100]. Recently it was also used to reduce the ADM1 model in the case of winery effluent wastewater [24].

6.1.2. Metabolic and genomic models

Participants: Jean-Luc Gouzé, Madalena Chaves, Alfonso Carta, Ismail Belgacem, Olivier Bernard, Caroline Baroukh, Rafael Muñoz-Tamayo, Jean-Philippe Steyer.

Global stability for metabolic models and full Michaelis-Menten equations

With techniques of monotone and compartmental systems, we studied full (i.e. not reduced by any time-scale argument) Michelis-Menten reactions or chains of reactions: we prove global stability when the equilibrium exists, and show that it may not exist. This fact has important consequences for reduction of metabolic systems in a coupled genetic-metabolic system [17].

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 [13].

Probabilistic approach for predicting periodic orbits in piecewise affine models

In the state transition graph, a *transition probability* between two nodes can be defined in terms of the parameters of the piecewise affine models. For a cyclic transition graph, this approach can be used to predict the most likely periodic orbit for a given a set of parameters [22].

Growth rate models in bacteria: piecewise affine systems with a dilution term

We have extended the class of piecewise affine systems to deal with dynamics dependent on dilution due to cell growth rate. Considering that growth rate is determined by two limiting factors (RNA polymerase and ribosomes), in [42] we propose and analyze a switched system with two piecewise quadratic modes. This is part of the PhD thesis of Alfonso Carta, and done in collaboration with IBIS project-team.

Transcription and translation models in bacteria

We study detailed models of transcription and translation for genes in a bacterium. 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 [40], [39]. We also study other models of the global cellular machinery. This is part of the PhD theses of Ismael Belgacem, Alfonso Carta, and done in collaboration with IBIS project-team. Moreover, in collaboration with IBIS, we studied and experimentally validated the time scale reduction of the classical two-step model for gene expression [51]

Analysis of circadian rhythms in cyanobacteria

A hierarchy of models (from Boolean to continuous) was used in [23] to successively characterize the wiring structure, qualitative dynamical properties, and then perform parameter estimation on a model describing the system responsible for the circadian rhythm of cyanobacteria.

Interconnections of Boolean modules: asymptotic and transient behaviour

The asymptotic dynamics of high-dimensional networks (e.g., genetic) can be obtained from the interconnection of two input/output Boolean subnetworks, and the analysis of their attractors. This computational cost reducing method is described in [34]. Some extensions include the characterization of the attractors of the interconnected system in terms of invariant sets.

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 [41], joint work with C. Breindl and F. Allgöwer from the University of Stuttgart. The class of unate or canalizing Boolean functions is considered and represented by multi-affine polynomials, leading to a reformulation of the estimation problem as a mixed integer linear program.

Analysis of dynamical systems by combining discrete and continuous formalisms

The work reviewed in the HDR of M. Chaves [11] highlights methods of analysis that use and combine techniques from discrete and piecewise affine modeling formalisms, such as construction of the transition graph and its association with the parameters of the system. Some basic methods for generating a discrete transition graph from a given continuous system are described in the internship project of F. Todoran [75].

State estimation for gene networks

We address state estimation for gene regulatory networks with intrinsic and extrinsic noise at the level of single cells. We take the Chemical Master Equation (CME) with random parameters as a reference modeling approach, and investigate the use of stochastic differential model approximations for the construction of practical real-time filters (based on non-linear Kalman filtering) [43]. This is a collaboration with Ibis team.

Modelling the metabolic network in non balanced growth conditions

On the basis of the knowledge of the metabolic network, we propose a new methodology to go beyond the “balanced growth paradigm”(assuming that there is no storage within the cell). We have therefore a tool to represent the possible storage of some key biochemical compounds. This approach was applied to describe the effect of both a light cycle and a nitrogen starvation on the lipid accumulation [37]. The first stage of the approach consists in splitting the metabolic network into sub-networks, which are assumed to satisfy balanced growth condition. The left metabolites interconnecting the sub-networks are allowed to behave dynamically. Then, thanks to Elementary Flux Mode analysis, each sub-network is reduced to macroscopic reactions, for which simple kinetics are assumed. This approach was applied to the accumulation of lipids and carbohydrates of the microalgae *Tisochrysis lutea* under day/night cycles. The resulting model described accurately experimental data obtained in day/night conditions; it efficiently predicts the accumulation and consumption of lipids and carbohydrates.

6.2. Fields of application

6.2.1. Bioenergy

6.2.1.1. Modelling of microalgae production

Participants: Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Philipp Hartmann, Rafael Muñoz-Tamayo, Ghjuvan Grimaud, David Demory, Frédéric Chazalon, 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 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 percept by a cell in a raceway pond [74], that is a large-scale raceway-track shaped open-air photobioreactor with circulating medium. An electronic platform was developed to reproduce the flashing light which, from the hydrodynamical studies, is likely to happen in a raceway at the cell scale. The experiments show that the microalgae adapt their pigments to the average light that they have received.

The effect in the cell cycle of both the light periodic signal and a nitrogen limitation were studied. The strong interactions of the interactions between the different phases of the cell cycle through checkpoints was highlighted [104].

Finally, we have tested the effect of cement flue gas on microalgae growth and demonstrated that this CO_2 source can be used to feed microalgal industrial cultures [33].

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

In collaboration with the IFREMER-PBA team (Nantes) we contributed to a study (within the Symbiose project) of the possible associations between microalgae and bacteria to enhance overall productivity [27].

Metabolism of carbon storage and lipid production

A macroscopic model for lipid production by oleaginous microalgae [10] has been previously proposed. This model describes the accumulation of neutral lipids (which can be turned into biofuel), carbohydrates and structural carbon. We now start to progressively dig deeper in the metabolism, with the objective to better predict carbohydrate and lipid accumulation[37], [64].

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 [86]. 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.

Modeling the photosynthesis response to fast fluctuating light

The impact of the hydrodynamics on the light percept by a single cell was studied thanks to fluid dynamics simulations of a raceway pond [26]. 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 [46]. Single cell trajectories were simulated by this tool, and the effect on photosynthesis efficiency was assessed using models of photosynthesis [94]. These results were compared to experimental measurements where the high frequency light was reproduced [74].

Modeling a microalgae production process

The integration of different models developed in the group [81], [101], [10] 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 [85],[31] 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 [30]. This model is used to predict lipid production in the perspective of large scale biofuel production.
Finally, we provide guidelines for the design of experiments with high informative content that allows an accurate parameter estimation of this model, 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 [50].

Nitrogen fixation by nitrogenotrophs

The fixation of nitrogen by *Croccosphera watsonii* was represented with a macro metabolic model [44]. 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 succeded to efficiently reproduce the experimental data.

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

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 [15].

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

6.2.1.2. 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 [7]. Several developments were carried out in this direction to improve the design and performances of interval observers. The approach has been applied to estimation of the microalgae growth and lipid production within a production process [28].

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 Pontryiagin's maximum principle (assuming a periodic working mode) [25].

On the other hand, we assessed strategies for optimal operation in continuous mode using the detailed model for raceways [49], [30]. Two strategies were developed. The first one resides 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 aimed at translating 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 [47].

Interactions between species

Large scale culture of microalgae for bioenergy involves a huge biodiversity (different mutants, invasion, growth-promoting bacteria [96]...). Control of such system requires to consider the interactions between the different species.

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 [48]. 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.
Other strategies (e.g. periodic temperature stress) are now under investigation through simulations (in order to design selection experiments that will be performed at LOV) and model analysis.
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 [66].

6.2.2. Design of ecologically friendly plant production systems

6.2.2.1. Controlling plant pests

Participants: Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Mickaël Teixeira-Alves, 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 natural enemies introductions optimization has been investigated for several years [9] [105], unveiling the crucial influence of within-predator density dependent processes. Because contrarily to predatory biocontrol agents, parasitoids may be more prone to exhibit positive density dependent dynamics rather than negative ones, the current modeling effort concentrates on studying the impact of positive predator-predator interactions on the optimal introduction strategies [72]. Connected experimental research is also being pursued in the laboratory on *trichogramma spp.* which tends to show positive density dependence because of demographic stochasticity [35], and the PhD thesis of Thibaut Morel Journel (UMR ISA) has just started on this topic. Non-impulsive positive feedback control of predator-prey systems in that framework was also addressed in [45].

Food source diversity and classical biological control efficiency using generalist natural enemies

Because generalist biocontrol agents can feed on different food sources like, e.g. a given pest and pollen, they are capable of surviving pest absence within crops and, when supplied with different food types, generalist biocontrol agents are expected to thrive. However, feeding on different food sources means that a given individual cannot feed on each food source at the same moment, which thus potentially reduces the overall predation pressure imposed by the natural enemy population. We exhibited conditions under which the predator distraction effects can dominate the demographic response of the predator populations, potentially disrupting pest control [12]. Such results were at the center of Mickaël Teixeira Alves's PhD thesis.

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 modelled 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 [97].

This work is part of the PhD thesis of Audrey Lebon (Cirad), and done in collaboration with Yves Dumont (Cirad).

6.2.2.2. 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 develop ways of introducing such resistance into crop production without jeopardizing its future efficiency. Considering plant viruses, we computed the proportion of resistant plants that should be cropped together with the non-resistant ones in a seasonal model, in order to optimize the resistance for production or patrimonial objectives [53]. The study of factors influencing resistance breakdown from the within-plant to the landscape level is the topic of Elsa Rousseau's PhD thesis, with emphasis both on experimental and modelling approaches. Experiments have been held in Avignon to determine the respective impacts of selection and genetic drift on resistance breakdown.

This work is done in collaboration with Frédéric Fabre and Benoit Moury (INRA Avignon).

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 can induce complex plant-pathogens dynamics [98] and is an important force promoting evolutionary diversification of plant pathogens [93]. 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 [59], [60], [21].

This work is part of the PhD thesis of Magda Castel (Agrocampus Ouest) and is done in collaboration with Frédéric Hamelin (Agrocampus Ouest).

6.2.3. Biological depollution

6.2.3.1. 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 Symbiose project is aiming at evaluating the potential of this process [108], [107].

In a first stage, we developed models for anaerobic digestion of microalgae. Two approaches were used: first, a dynamic model has been developed trying to keep a low level of complexity so that it can be mathematically tractable for optimisation [100] . Considering three main reactions, this model fits adequately the experimental data of an anaerobic digester fed with *Chlorella vulgaris* (data from INRA LBE). On the other hand, we have tested the ability of ADM1 [109] (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.

6.2.3.2. Life Cycle Assessment

Participants: Olivier Bernard, Jean-Philippe Steyer.

This work is the result of a collaboration with Laurent Lardon and Arnaud Helias of INRA-LBE through the co-supervision of Pierre Collet's PhD thesis [88].

An analysis of the potential environmental impacts of biodiesel production from microalgae has been carried out using the life cycle assessment (LCA) methodology [95]. This study has allowed to identify the obstacles and limitations which should receive specific research efforts to make this process environmentally sustainable. This study has been updated and the effects of technological improvements (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 electricty is produced on the plant [91], [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.

These studies have allowed to identify the obstacles and limitations which should receive specific research efforts to make this process environmentally sustainable [65].

A LCA has been carried out to assess the environmental impact of methane production by coupling microalgae and anaerobic digestion. The study highlights the limitation derived by the low biodegradability of the considered microalgae [89] which induces a large digester design and thus more energy to mix and heat it.

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

6.2.4. Models of ecosystems

6.2.4.1. Optimality/games in population dynamics

Participants: Frédéric Grognard, Ludovic Mailleret, Pierre Bernhard.

Adaptive behavior in seasonal consumer-resource dynamics

In this work we studied the evolution of a consumer-resource (or predator-prey) system with seasonal character of the dynamics. We specified two main parts of the process. First, we considered the system during one season with a fixed length: the prey lay eggs continuously and the predators lay eggs or hunt the prey (choose their behavior) according to the solution of an optimal control problem [76]. We then showed that, in most situations, mutants can take advantage of their low frequency and fare better than the residents. Over the course of a large number of seasons, the mutants replace the residents, only to find themselves applying the original resident behavior [61].

Optimal foraging and residence times variations

Charnov's marginal value theorem (MVT) [87] is a central tenet of ecological theory. In fragmented environments, the MVT connects the quality and distribution of patches to the optimal time an individual should spend on any patch, and thus the rate of movement in the habitat. Unfortunately, it does not offer explicit predictions regarding how changing habitat quality would affect residence times. In this work, we answer that question in a very general setting, for habitats with homogeneous or heterogeneous patches and with general fitness functions. We then particularize it to the resource consumption framework and indicate how the residence times variations relate to the curvatures of the functional responses,[20].

This last work is done in collaboration with Vincent Calcagno and Eric Wajnberg (INRA Sophia Antipolis)

The handicap paradox

We have investigated the “handicap paradox” of sexual selection, and more specifically revisited Grafen’s mathematical models of Zahavi’s “handicap principle”. The paradox is that in many species, male secondary sexual characters that clearly attract the females are so developed as to be a handicap to the male’s viability, and therefore should be counter-selected by evolution. Zahavi’s explanation, made mathematical by Grafen, is that if this secondary sexual character is a signal to the female of the male’s quality that she cannot observe otherwise, if this signal were costless, it could be cheated, a low quality male being induced to mimic the signal of a high quality one. We have cast this problem into a signaling game, using the bayesian equilibrium of game theory. This easily shows that indeed, under mild conditions, at equilibrium the signal should be “costly”. We have developed several models inspired by Grafen, and to a lesser extent Getty, with explicit solutions, and explained why an undesirable feature appeared in Grafen’s model (as well as in one of ours) and proposed a model free of this artifact [19].

6.3. Software design

6.3.1. Odin

Participants: Olivier Bernard, Mélaine Gautier.

Over the years, BIOCORE has been developing a software framework for bioprocess control and supervision called ODIN [80]. This C++ application (working under Windows and Linux) enables researchers and industrials to easily develop and deploy advanced control algorithms through the use of a Scilab interpreter [82], [83]. 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. Recently, a software development effort has been directed to the graphical user interface, a synoptic view component, new drivers for the experimental hardware and integration of the PlantML data exchange format. ODIN has been tested on four different processes and has been set up with Eric Latrille to supervise the 66m2 high rate pond at the LBE, INRA Narbonne.

6.3.2. In@lgae

Participants: Etienne Delclaux, Francis Mairet, Olivier Bernard.

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 percept 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.

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 developped.

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) and coordinated by M. Chaves.
- **ANR-Facteur 4:** The objective of this project to propose 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-Purple Sun:** The objective of this project (ANR-13-BIME-004) 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-FunFit:** The objective of this project 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.
- **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 Nice Sophia Antipolis.
- **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)
- **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 modelling of the process.

8.1.2. Inria funding

- **ColAge:** The goal of this joint Inria-INSERM consortium is to study bacterial growth and aging by using mathematical modelling and computational predictions to design and implement a *de novo* biological system. This Large-Scale Initiative Action is partly funded by Inria and supervised by H. Berry (Beagle, Inria).

8.1.3. INRA funding

- **Propagules:** INRA-SPE is funding the project “Effet de différentes composantes de la pression de propagules sur le succès d’établissement d’un auxiliaire de lutte biologique" in which BIOCORE is a partner with INRA Sophia Antipolis (2011-2013).

- **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 will provide the major part of the funding for the experiments held for Elsa Rousseau’s thesis.

8.1.4. Networks

- **RTP-M3D:** BIOCORE is a participant in the RTP-M3D workgroup (Mathématiques et décision pour le développement durable) that is supported by the “Environment and sustainable growth” department of CNRS. L. Mailleret is one of the co-leaders of M3D.
- **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 modelling and control aspects of the processes involving anaerobic bacteria or microalgae.
- **COREV:** BIOCORE is an active participant in the research group COREV (Modèles et théories pour le contrôle de ressources vivantes et la gestion de systèmes écologiques).
- **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 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)

Modelling and optimization of microalgal based processes.

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

Study of metabolic/genetic models

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

Identification of gene networks

8.3. International Initiatives

8.3.1. Inria International Partners

8.3.1.1. 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.

8.3.2. Participation In International Programs

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.

8.4. International Research Visitors

8.4.1. Visits of International Scientists

We only list the visitors that stayed more than 2 days in our project-team or presented a seminar

- Claude Aflalo (Ben Gurion University of the Neguev, Israel), 1 week;
- Andrei Akhmetzhanov (Université de Montpellier II, F), 1 week;
- Gonzalo Ruiz (Catholic University of Valparaiso, Chile), 2 days;
- David Jeison (University of La Frontera, Chile), 2 days;
- Benoit Guieysse (Massey University, New Zealand), 1 day;
- Quentin Béchet(Massey University, New Zealand). 6 days;
- Yves Dumont (CIRAD, F), 1 week;
- Andreas Kremling (TU Munchen, Germany), 1 day;
- Leon Glass (McGill University, Canada), 3 days;

8.5. Project-team seminar

BIOCORE organized a 3-day seminar in October in Tourrettes-sur-Loup. On this occasion, every member of the project-team presented his/her recent results and brainstorming sessions were organised.

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

9. Dissemination

9.1. Scientific Animation

J.-L. Gouzé is a member of the scientific committee for the conference BIOMATH ; also for the conference for E. Benoit (La Rochelle 2013). He 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.

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". He is a member of the scientific comity of the competitivity pole “Trimatec”. O. Bernard 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 (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 committees of the doctoral school "Sciences de la Vie" at the University of Nice-Sophia Antipolis.

P. Bernhard is a member of the scientific committees of the doctoral school “Sciences fondamentales et appliquées” at the University of Nice-Sophia Antipolis.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

O. Bernard (9h ETD), “Mathematical models in Biology”. Master on biological oceanography in Villefranche-sur-Mer (M2), Universit Pierre et Marie Curie, France.

O. Bernard (4.5 ETD), “Bioenergy from microalgae”, Master International Energy Management : alternatives pour l'énergie du futur, Ecole Nationale Supérieure des Mines de Paris, France.

O. Bernard (18h ETD), “Modelling biotechnological processes”, Ecole Centrale de Paris, France.

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

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

J.-L. Gouzé (9h ETD), M. Chaves (4.5h ETD), “Discrete and continuous approaches to model gene regulatory networks”, Master of Science in Computational Biology (M2), University of Nice - Sophia Antipolis. M. Chaves and J.-L. Gouzé have participated in a book chapter entitled “Modeling and analysis of gene regulatory networks” on the topics taught in this course [62].

J.-L. Gouzé (18h ETD), M. Chaves (9h ETD), A. Carta (6h ETD), “Modelling biological networks by ordinary differential equations”, 4th year students, Génie Biologie, Ecole Polytechnique University of Nice - Sophia Antipolis

O. Bernard supervised two projects for engineer school students. The first project involved 6 students of Ecole Nationale Supérieure des Mines de Paris (last year of engineering school, 1 week ("Using thermal flux to agitate microalgae cultures") and the second project involved 4 students from the Ecole Centrale de Paris (first year of engineering school), 4 months, to design biofilm for microalgae.

9.2.2. Supervision

PhD : M. Teixeira-Alves, “Modélisation de réseaux écologiques dans un cadre de protection des cultures: applications à la lutte biologique”, UNS, defended January 25, 2013. Supervisors: F. Grognard and L. Mailleret.

PhD : M. Castel “Modélisation des trajectoires évolutives des pathogènes de plantes dans les écosystèmes agricoles", University of Rennes, defended November 12, 2013. Supervisors : F. Hamelin and D. Andrivon (Agrocampus Ouest) and L. Mailleret.

PhD in progress : P. Hartmann, "Developement of a model for microalgal photoadaptation", since september 2010, UNS. Supervisor: O. Bernard.

PhD in progress : A. Carta, “Analysis and Control of models of biological regulatory systems. Application to growth control in *E. coli*”, since december 2010, UNS. Supervisors: J.-L. Gouzé and M. Chaves.

PhD in progress : C. Baroukh, “Modeling the coupling of microalgae with anaerobic digestion”, since September 2011, University of Montpellier 2. Supervisors: J.-P. Steyer and O. Bernard.

PhD in progress : A. Lebon, “Modélisation couplée plantes-ravageurs-ennemis naturels dans un contexte de lutte biologique", since October 2011, University of Montpellier 2. Supervisors : Y. Dumont (CIRAD), F. Grognard and L. Mailleret.

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, UPMC. Supervisors: A. Sciandra and O. Bernard

PhD in progress : C. Combe, "Response of microalgae to fluctuating light", since september 2012, UPMC. Supervisors: A. Sciandra and S. Rabouille.

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

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: O. Bernard.

PhD in progress : S. Casagranda. “Analysis and control of cell growth models”, since November 2013, UNS. Supervisor: J.-L. Gouzé.

9.2.3. Juries

O. Bernard was referee for the HDR of J. Morchain, Nov. 19, Title: "Bioreactor modelling by coupling fluid mechanics and population balance” Toulouse University

O. Bernard was in the PhD jury of A. Besson, Dec. 9. Title: "Multi scale study of the harvesting of Dunaliella salina”

O. Bernard was in the PhD jury of B. Sialve, Jul 15. Title: “Coupling microalgal cultivation with anaerobic digestion”, INSA Lyon

O. Bernard was in the PhD jury of A.-C. Boulanger, Sep.13. Title: "Modelling, simulation and data assimilation for a hydrodynamics-biology coupling problem", University Pierre et Marie Curie.

M. Chaves was in the PhD thesis jury of Luca Grieco, May 3. Title: “Integrative modelling and analysis of MAPK network deregulations in human cancers,” University of Marseille and TAGC (INSERM U928).

J.L. Gouzé was referee for the PhD thesis of Radhouane Fekih-Salem, Sept. 30. Title: “Modèles Mathématiques pour la Compétition et la Coexistence des Espèces Microbiennes dans un Chemostat”, UM2 Montpellier

J.L. Gouzé was in the PhD thesis jury of Olivier Borkowski, Feb. 19. Title: “ Growth-rate-dependent protein production in bacteria”. Univ. Paris Descartes.

J.L. Gouzé was referee for the PhD thesis of Mohamed Amin Ben Sassi, Apr. 15. Title: "Analyse et contrôle des systèmes dynamiques polynomiaux". UJF Grenoble.

J.L. Gouzé, F. Grognard and L. Mailleret were in the PhD thesis jury of Mickael Teixeira Alves, Jan. 25. Title: "Des interactions indirectes entre les proies : modélisation et influence du comportement du prédateur commun". UNS.

J.L. Gouzé was in the HDR jury of Madalena Chaves, Oct. 24. Title: "Predictive analysis of dynamical systems: combining discrete and continuous formalisms", UNS.

L. Mailleret was in the PhD thesis jury of Magda Castel, Nov. 12. Title: "Écologie et évolution théoriques des parasites de plantes annuelles", Université de Rennes.

J.-L. Gouzé is in the thesis committee of C. Baroukh (University of Montpellier).

M. Chaves is in the thesis committee of F. Fourré (University of Luxembourg).

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).

9.3. Popularization and media

The activities related to microalgae have generated many articles in national newspapers (Le Monde.fr, Libration, Le Point.fr, ...), and broadcasts on national TV. Several articles were written by the team members to explain the hurdles and potential of microalgae [36], [70]. A book [65] 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.

P. Bernhard has given conferences in high schools in the framework of the program “Sciences et culture au lycée”.

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 8, 2013).

O. Bernard and J.-L. Gouzé gave two keynote lectures at the CAB2013 conference, Mumbai, India.

F. Grognard was invited to give a talk entitled "Commande des systèmes proies-prédateurs: rétroactions et impulsions" at the workshop "Des dynamiques singulièrement perturbées aux dynamiques de populations" in honour of Eric Benoît (La Rochelle, December 16-18, 2013)

P. Bernhard gave a talk on the handicap paradox at the International Workshop on Biodiversity and Environment at the Mathematical Research Center of Montreal.

E. Rousseau gave a talk on " Sustainable plant resistance management in agricultural landscapes" at the Réunions de Virologie Vegetale (RVV) at Aussois, France (January 13-17, 2013). She presented a poster on the "Impact of quantitative plant resistance on within-host viral demo-genetic dynamics" at the "Workshop Bridging theoretical and experimental evolution" in La Fouly, Switzerland (June 12-15, 2013) and at the "5èmes Journées de Rencontre des Doctorants du Département SPE" in Montpellier, France (June 26-28, 2013).

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