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Activity Report 2012

Project-Team BIOCORE

Biological control of artificial ecosystems

IN COLLABORATION WITH: Institut Sophia Agrobiotech

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Observation, Modeling, and Control for Life Sciences

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Project-Team BIOCORE

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

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

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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, ANR *Bioénergie* project Symbiose, ANR *BioME* project Facteur 4, FUI Salinalgue, *Projets d'Investissement d'Avenir* RESET and Green Stars.

2.2. Highlights of the Year

- A model was developed in order to determine how to mix resistant and sensitive plants to vector-borne plant pathogens in order to best protect the crop. The model includes a process that would allow for the resistance breakdown through adaptation of the virus population and the wintering of the virus in the environment. The best mixing rate was then proposed in order to either maximize the production over a 15 year period or prevent the resistance breakdown [16]. This work is done with Frédéric Fabre and Benoît Moury of INRA Avignon.
- Green Stars, Institute of Excellence for Decarbonated Energy, was created this year, supported by a *Projet d'Investissement d'Avenir* funding. Recent Biocore developments in microalgae modeling strongly support the Green Stars Institute: including the temperature effect [14], [28], representing fast time scales of photosynthesis [37], coupling with hydrodynamics [13], representing N_2 fixation [89], modeling metabolism of microalgae [67], modeling anaerobic digestion of microalgae [20], developing observers [21] [101] and optimal strategies to produce biomass [90], [109].

BEST PAPER AWARD :

[36] **A simple model to control growth rate of synthetic E. coli during the exponential phase: model analysis and parameter estimation in 10th Conference on Computational Methods in Systems Biology**.
A. CARTA, M. CHAVES, J.-L. GOUZÉ.

3. Scientific Foundations

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 the living 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 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 the living, 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. The interplay and information transfer between the different levels and scales within a biosystem/ecosystem introduces many new dynamical aspects. 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 to optimize some production or behavior at higher level: for example, control the growth of microalgae via their genetic or metabolic networks, 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 LBE members of the team, 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 LOV members of the team, 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) [72].

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:

- A photobioreactor (SEMPO) for Lagrangian simulation of the dynamical environment of marine microalgae (LOV) with computer controlled automata for high frequency measurement and on-line control. This photobioreactor is managed by Amélie Talec.
- 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 (LBE). Eric Latrille is our main contact for this platform at LBE.
- Experimental greenhouses of various sizes (from laboratory to semi-industrial size) and small scale devices for insect behavior testing 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

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

Participants: Jean-Luc Gouzé, Olivier Bernard, Frédéric Grognard, Ludovic Mailleret, Pierre Bernhard, Francis Mairet, Rafael Muñoz-Tamayo, Elsa Rousseau.

6.1.1.1. Mathematical study of semi-discrete models

Semi-discrete models have shown their relevance in the modeling of biological phenomena whose nature presents abrupt changes over the course of their evolution [95]. We used such models and analysed their properties in several situations that are developed in 6.2.3, 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 [59] or in the co-existence analysis of epidemiological strains [19], [50]. 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 survives the 'winter' [52].

6.1.1.2. Mathematical study of models of competing species

When several species are in competition for a single substrate in a chemostat, and when the growth rates of the different species only depend on the substrate, it is known that the generic equilibrium state for a given dilution rate consists in the survival of only one of the species. In [30], we propose a model of competition of n species in a chemostat, where we add constant inputs of some species. We achieve a thorough study of all the situations that can arise when having an arbitrary number of species in the chemostat inputs; this always results in a Globally Asymptotically Stable equilibrium where all input species are present with at most one of the other species.

The competition of several microalgal species was also studied in order to determine conditions that may give a competitive advantage to a species of interest. We study the competition for two species subject to photoinhibition at high light. This leads to a closed loop control strategy based on the regulation of the light intensity at the bottom of the reactor. The winning species is the one with the highest growth rate at high light. Then we show that the proposed controller allows the selection of a species of interest among n species [102].

6.1.2. 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 [2]. These systems can be represented by models having the general structure popularized by [69], [74], 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 modeling 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 [68], anaerobic digestion [87], [114] and anaerobic digestion of microalgae [20]. Recently it was also used to reduce the ADM1 model in the case of winery effluent wastewater [88].

6.1.3. Nonlinear observers

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

Interval observers

Interval observers give an interval estimation of the state variables, provided that intervals for the unknown quantities (initial conditions, parameters, inputs) are known [7]. We have extended the interval observer design to new classes of systems. First, we designed interval observers, even when it was not possible in the original basis, by introducing a linear, time-varying change of coordinates [105]. This approach was then extended to n-dimensional linear systems, leading to the design of interval observers in high dimensions [106]. Interval observers for non linear triangular systems satisfying Input to State Stability has been proposed [22]. Extension to time-delay systems have also been proposed [23]. The efficiency of the interval observer design, even with chaotic systems has been developed and applied considering parameters uncertainties of the system and biased output [108], [105].

The combination of the observers has also been improved in the case where various types of interval observers are run in parallel in a so-called "bundle of observers" [73]. These algorithms have been improved by the estimation of the observer gain providing the best estimate [40], [21]. The approach has been applied to estimation of the microalgae growth and lipid production [101].

These works are done in collaboration with Frédéric Mazenc (DISCO, Inria) and Marcelo Moisan (EMEL S.A., Chile).

6.1.4. Metabolic and genomic models

Participants: Jean-Luc Gouzé, Madalena Chaves, Alfonso Carta, Ismail Belgacem, Xiao Dong Li, Olivier Bernard, Wassim Abou-Jaoudé, Luis Casaccia, Caroline Baroukh, Rafael Muñoz-Tamayo, Jean-Philippe Steyer.

Multistability and oscillations in genetic control of metabolism

Genetic feedback is one of the mechanisms that enables metabolic adaptations to environmental changes. The stable equilibria of these feedback circuits determine the observable metabolic phenotypes. Together with D. Oyarzun from Imperial College, we considered an unbranched metabolic network with one metabolite acting as a global regulator of enzyme expression. Under switch-like regulation and exploiting the time scale separation between metabolic and genetic dynamics, we developed geometric criteria to characterize the equilibria of a given network. These results can be used to detect mono- and bistability in terms of the gene regulation parameters for any combination of activation and repression loops. We also find that metabolic oscillations can emerge in the case of operon-controlled networks; further analysis reveals how nutrient-induced bistability and oscillations can emerge as a consequence of the transcriptional feedback [27].

Global stability for metabolic models and unreduced Michaelis-Menten equations

We are interested in the uniqueness and stability of the equilibrium of reversible metabolic models. For biologists, it seems clear that realistic metabolic systems have a single stable equilibrium. However, it is known that some types of metabolic models can have no or multiple equilibria. We have made some contribution to this problem, in the case of a totally reversible enzymatic system. We prove that the equilibrium is globally asymptotically stable if it exists; we give conditions for existence and behavior in a more general genetic-metabolic loop [26]. Moreover, with the same techniques, 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 [34], [45], [70].

Interconnections of Boolean modules: asymptotic and transient behavior

A biological network can be schematically described as an input/output Boolean module: that is, both the states, the outputs, and the inputs are Boolean. The dynamics of a Boolean network can be represented by an asynchronous transition graph, whose attractors describe the system's asymptotic behavior. We have shown that the attractors of the feedback interconnection of two Boolean modules can be fully identified in terms of cross-products of the semi-attractors (states of the attractor with same output) of each module. In [82], the *asymptotic graph* was proposed, which is quite fast to compute and identifies all attractors of the interconnected system, but may also generate some spurious attractors. In [31] the *cross graph* is proposed, which exactly identifies the attractors of the interconnected system but is slower to compute. The asymptotic dynamics of high-dimensional biological networks can thus be predicted through the computation of the dynamics of two isolated smaller subnetworks. An application is, for instance, to interconnect four individual "cells" to obtain all the attractors of the segment polarity genes model in *Drosophila*.

Probabilistic approach for predicting periodic orbits in piecewise affine differential models

The state space of a piecewise affine system is partitioned into hyperrectangles which can be represented as nodes in a directed graph, so that the system's trajectories follow a path in a transition graph. Using this property we defined a *transition probability* between two nodes A and B of the graph, based on the volume of the initial conditions on the hyperrectangle A whose trajectories cross to B [15]. The parameters of the system can thus be compared to the observed or experimental transitions between two hyperrectangles. This definition is useful to identify sets of parameters for which the system yields a desired periodic orbit with a high probability, or to predict the most likely periodic orbit given a set of parameters, as illustrated by a gene regulatory system composed of two intertwined negative loops.

Structure estimation for unate Boolean models of gene regulation networks

Estimation or identification of the network of interactions among a group of genes is a recurrent problem in the biological sciences. Together with collaborators from the University of Stuttgart, we have worked on the reconstruction of the interaction structure of a gene regulation network from qualitative data in a Boolean framework. The idea is to restrict the search space to the class of unate functions. Using sign-representations, the problem of exploring this reduced search space is transformed into a convex feasibility problem. The sign-representation furthermore allows to incorporate robustness considerations and gives rise to a new measure which can be used to further reduce the uncertainties. The proposed methodology is demonstrated with a Boolean apoptosis signaling model [35].

E. coli modeling and control

In the framework of ANR project Gemco, we developed and analyzed a model of a minimal synthetic gene circuit, that describes part of the gene expression machinery in *Escherichia coli*, and enables the control of the growth rate of the cells during the exponential phase.

This model is a piecewise non-linear system with two variables (the concentrations of two gene products) and an input (an inducer). We studied the qualitative dynamics of the model and the bifurcation diagram with respect to the input. Moreover, an analytic expression of the growth rate during the exponential phase as function of the input has been derived. A relevant problem was that of parameters identifiability of this expression supposing noisy measurements of exponential growth rate. We presented such an identifiability study that we validated in silico with synthetic measurements [36].

We also studied a model of the global cellular machinery designed by D. Ropers and collaborators (IBIS team, Grenoble). This model has 11 variables and many parameters ; we explored different techniques for reduction and simplification [56], [57].

Transition graph and dynamical behavior of piecewise affine systems

We investigated the links between the topology of the transition graph and the number and stability of limit cycles in a class of two-dimensional piecewise affine biological models. To derive these structure-to-dynamics principles, we use the properties of continuity, monotonicity and concavity of Poincare maps associated with transition cycles of the transition graph [64].

Robust estimation for a hybrid model of genetic networks

State estimation problems with Boolean measurements for a classical negative loop genetic network governed by a piecewise affine (PWA) model have been studied in [39]. Observers are proposed for the cases where either full state or only partial state Boolean measurements are available. In the first case, sliding modes may occur, which leads to finite time convergence for the observer. In the second case, an algebraic computation is proposed to solve the initial condition inverse problem. The robustness of the observer for a parametric uncertain model is investigated, and we show that the error bound is proportional to the magnitude of the uncertainty.

Modeling the metabolic network in non balanced growth conditions

We have developed a new approach to represent the metabolic network of organisms for which the hypothesis of balanced growth is not satisfied [67]. This is especially true for microalgae which store carbon during the day and nitrogen during the night [44]. The proposed formalism is based on the assumption that some parts of the metabolic network satisfy the balance growth conditions, *i.e.* there is no accumulation of intermediate compounds. This hypothesis specifically applies to the main functions in the cell (respiration, photophosphorylation,...). Between two functions, some compounds can accumulate with storage/reuse kinetics. The resulting system is thus a slow-fast system.

6.2. Fields of application

6.2.1. Bioenergy

6.2.1.1. Modeling of microalgae production

Participants: Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Philipp Hartmann, Rafael Muñoz-Tamayo, Ghjuvan Grimaud, Charlotte Combe, 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 [18], [17], [48] and support model development. These experiments have been carried out in the Lagrangian simulator (SEMPO), 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 [58]. 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 [24].

This work is done in collaboration with Amélie Talec, Thomas Lacour, and Christophe Mocquet (CNRS-Océanographic Laboratory of Villefranche-sur-Mer).

Modeling the effect of temperature

The effect of temperature on microalgae has been represented by adapting the CTMI model developed for bacteria [115]. The proposed model [14], [28], was able to correctly represent the growth response to temperature for 15 different species. A procedure for model calibration and estimation of the parameter uncertainties was specially developed, allowing to gather experimental data from various sources. It was shown that different strains of the same species have a very similar response to temperature fluctuations. Moreover, for low light intensities, a simple model can represent both effects of light and temperature [14].

Modeling light distribution within a photobioreactor

The light distribution within a photobioreactor was estimated thanks to a multi photon Monte-Carlo simulation. From measurements of absorption and scattering properties, it was thus possible to extrapolate and validate the light distribution within a photobioreactor or a raceway.

Modeling lipid accumulation

We have proposed a new model for lipid production by microalgae which describes the fate of the CO_2 incorporated during photosynthesis [10]. This model describes the accumulation of neutral lipids (which can be turned into biofuel), carbohydrates and structural carbon. It has been calibrated and validated with experimental data. This model highlights and explains the phenomenon of hysteresis in lipid production which has been experimentally verified. It has been extended to account for light/dark cycles [96].

Modeling a microalgae production process

The integration of different models developed in the group [72], [96], [10],[14] 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 [72]. 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 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], [110]. This model is used to predict lipid production in the perspective of large scale biofuel production.

6.2.1.2. *Coupling growth of microalgae with hydrodynamics*

Participants: Olivier Bernard, Antoine Sciandra, Philipp Hartmann, Charlotte Combe.

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 [13]. 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 [37] [92]. 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 [93].

6.2.1.3. *Optimization of microalgae production*

Participants: Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Rafael Muñoz-Tamayo.

Numerical optimization

Using the detailed model for raceway systems, we assessed strategies for optimal operation in continuous mode [109]. 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 reach biomass productivities very near to the 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.

Analytical optimization

Optimization strategies were based on simple microalgae models : first, biomass production has been optimized in a constant light environment [104], yielding results emphasizing the importance of the optical depth of the reactor. In a second work, we focused on the optimal operating conditions for the biomass productivity under day/night cycles using Pontryiagin's maximum principle (assuming a periodic working mode) [61] [90].

6.2.2. CO_2 fixation by microalgae

Participants: Olivier Bernard, Antoine Sciandra, Ghjuvan Grimaud.

Experimental work

We have run experiments to observe the response of a population of microalgal cells to various periodic light/dark or nitrate signals. The measurements show the synchronicity of the cells for some conditions. These experiments support the hypothesis that uptake of nitrogen stops during cell division [24].

Modeling cell cycle

On this basis, we have developed a structured model representing the development of microalgal cells through three main phases of their cell cycle: G1, G2 and M. The model is made of three interdependent Droop models [107]. The model was validated through extensive comparison with experimental results in both condition of periodic light forcing and nitrogen limitation. The model turns out to accurately reproduce the experimental observations [107].

Calcification of coccolithophorids

The effect of CO_2 partial pressure increase on photosynthesis and calcification of the calcareous microalgae *Emiliania huxleyi* have been experimentally observed. It results in an increase of the coccolith size together with a decrease in the calcification rate [25].

Three models accounting for the possible coupling between photosynthesis and calcification [75] were included in an ocean model; they account for settling and predation by grazers, and a bloom of coccolithophorids was simulated [76], [77].

Nitrogen fixation by nitrogenotrophs

The fixation of nitrogen by *Croccosphera watsonii* was represented with a macro metabolic model [60] [89]. 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, remain 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 [12], [43], [42].

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

6.2.3. Design of ecologically friendly plant production systems

6.2.3.1. Controlling plant pests

Participants: Frédéric Grognard, Ludovic Mailleret, 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] [111]. It had allowed to unveil the crucial influence of within-predator density dependent processes, and especially negative density dependence. In particular, we concluded that pest control is more efficiently achieved through the frequent introduction of small populations of natural enemies as compared to larger and rarer ones. 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 [55].

Connected experimental research is also being pursued in the laboratory on *trichogramma spp.* which tends to show positive density dependence because of demographic stochasticity [32], and the PhD thesis of Thibaut Morel Journel (UMR ISA) has just started on this topic.

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 [118]. From the biological control point of view, this makes it possible to sustain natural enemies populations able to fight pests at the onset of pest attacks. Moreover, when supplied with different food types, generalists organisms are expected to thrive. Alternative prey, banker plants or more generally habitat enhancement based biological control strategies are thus becoming popular IPM (Integrated Pest Management) methods [112]. Although it has clear advantages, the simultaneous presence of various food sources also has important drawbacks: feeding on different food sources means that a given individual cannot feed on each food source at the same moment. This distraction effect thus potentially reduces the overall predation pressure imposed by the natural enemy population, and the interaction between the demographic response of the predator population and individual behavior is complex. To investigate such questions, we developed and analyzed behavioral-demographic population models taking into account the negative density dependent character of most generalist biocontrol agents. We found out that predator distraction effects can dominate the demographic response of the predator populations, potentially disrupting pest control [120]. An additional conclusion of our study, is that higher predator densities can actually bring about lesser pest suppression. Such results question current biological control practices, and show that, counter-intuitively, recording a lot of predators within fields does not ensure efficient pest control.

Plant compensation, pest control and plant-pest dynamics

Plant compensation is the process by which plants respond positively to recover from the effects of pest injury on plant growth. It is a common phenomenon, which has been repeatedly reported in various plant taxa during the last thirty years. Of special interest is the overcompensation phenomenon: consecutively to a pest attack, a plant may reach a higher biomass or have a better fitness compared to the no-pest-attack situation [65]. Although this phenomenon has mainly been documented in wild plants [65] it has also been observed on agricultural plants [121], [113]. To understand better this plant-herbivore interaction and to assess the efficacy of different pest control strategies we built a plant-pest model of plant compensatory growth. We have shown that depending on plants and pests characteristics, plant overcompensation may or may not happen. Moreover, because the model undergoes a backward bifurcation, it is shown that plant overcompensation is also dependent on the level of pest attacks and does not necessarily show up even when the plant-pest couple do have the potential to produce overcompensation [38].

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

6.2.3.2. Controlling plant pathogens

Participants: Frédéric Grognard, Ludovic Mailleret, Elsa Rousseau.

Sustainable management of plant resistance

The introduction of plant strains that are resistant to one pathogen often leads to the appearance of virulent pathogenic strains that are capable of infecting the resistant plants. The resistance strain then becomes useless. It is therefore necessary to develop ways of introducing such resistance into crop production without jeopardizing its future efficiency. We did so by choosing the proportion of resistant plants that are mixed with the non-resistant ones. We studied a vector borne pathogen in a seasonal environment, with healthy crop being planted at the beginning of each season and cropped at its end, the pathogen surviving in the environment during the 'winter'. Two strategies have been proposed, one that aims at minimizing the cumulated damage over a 15 years horizon and one that aims at preventing the virulent strain outbreak. We showed that pathogen's fitness cost associated with resistance breakdown was one of the main factors governing damage reduction at the landscape scale, although the optimal resistance deployment also strongly relied on epidemic characteristics and landscape coonnectivity [16], [51]. The capacity for a virulent virus to establish itself in such an environment, as well as the evolution of the virus characteristics have been studied [59].

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

Eco-evolutionary dynamics of plant pathogens in seasonal environments

The coexistence of closely related plant parasites is widespread. Yet, understanding the ecological determinants of evolutionary divergence in plant parasites remains an issue. Niche differentiation through resource specialization has been widely researched, but it hardly explains the coexistence of parasites exploiting the same host plant. Most agricultural systems in temperate environments are characterized by the cyclical presence and absence of the crop, due to cropping practices such as harvest and planting. The seasonal character of agrosystems can induce complex plant-pathogens dynamics [19] and is an important force promoting evolutionary diversification of plant pathogens [91]. Plant parasites reproduction mode may 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 [80]. By means of a theoretical approach, we show that an obligate sexual event prior to overseasoning promotes evolutionary divergence in terms of investment into asexual reproduction in plant parasites. Yet, polymorphism may be transient; namely, morphs mostly investing into sexual reproduction may eventually exclude morphs mostly investing into asexual reproduction. Our findings nicely echo with recent population genetics results on *Leptosphaeria maculans*, the causal agent of the blackleg disease of canola, reporting differential investments into sexual and asexual reproduction both at the global and continental scales.

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

6.2.4. Biological depollution - Anaerobic digestion

6.2.4.1. Coupling microalgae to anaerobic digestion

Participants: Olivier Bernard, Antoine Sciandra, Jean-Philippe Steyer, Frédéric Grognard, Philipp Hartmann.

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 [117], [116].

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 [97], [79], [20]. 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 [119] (a reference model which considers 19 biochemical reactions) to represent the same dataset. This model, after modification of the hydrolysis step [99], [100], [98] has then been used to evaluate process performances (methane yield, productivity...) and stability though numerical simulations.

6.2.4.2. Life Cycle Assessment of microalgae production

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 [83].

An analysis of the potential environmental impacts of biodiesel production from microalgae has been carried out using the life cycle assessment (LCA) methodology [94]. 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 [86], [85]. As a consequence, a new paradigm to transform solar energy (in the large) into transportation biofuel is proposed, including a simultaneous energy production stage.

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 [84] which induces a large digester design and thus more energy to mix and heat it.

6.2.5. Models of ecosystems

6.2.5.1. Optimality in consumer-resource 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 [66]. We then examined how (resident) predators adopting this optimal behavior would fare when faced with a small population of selfish mutants that would be identical to the resident but would have the freedom to choose a different behavior. We studied the resulting optimal control problem where the mutants maximize their own number of offspring using the knowledge of the resident's behavior, and 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 [52].

Optimal foraging and residence times variations

Charnov's marginal value theorem (MVT) [81] 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 [49], [78].

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

6.2.5.2. Growth models of zooplankton

Participants: Jean-Luc Gouzé, Jonathan Rault, Eric Benoît.

The model built to describe a zooplankton community is some variant of the McKendrick-Von Foerster Equation. The model includes cannibalism within zooplankton communities and predation on phytoplankton. Dynamic mass budget theory is used in order to describe individual behavior and allows mass conservation. Also we have added phytoplankton dynamics, and we use environmental data as an input for the model. The aim is to compare simulations with data provided by the Laboratoire d'Océanographie de Villefranche (Lars Stemmann). We have also built a discrete size-structured model. Discrete models are less numerically demanding and so can be more easily incorporated into bigger models. Moreover the study of discrete models are often easier than that of continuous ones. We focus our study on the impact of cannibalism within the zooplankton community and show that under some hypotheses, cannibalism can stabilize the equilibrium of the model [29], [11]. We also address the problem of control of such models (by harvesting or biological control); we obtain results for stabilization of the equilibrium [41], [11].

6.3. Software design

Participants: Olivier Bernard, Mélaine Gautier.

Over the years, BIOCORE has been developing a software framework for bioprocess control and supervision called ODIN [71]. 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 [46], [47]. 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.

7. Bilateral Contracts and Grants with Industry

7.1. Microalgae for biofuel production

Biocore takes part in a project for assessment of microalgal biofuel productivity whose other partners are Alpha Biotech, EADS and PSA Peugeot Citroen.

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 coordinated by M. Chaves (BIOCORE, Inria)
- **ANR-Symbiose:** The objective of this project is both to improve the energetic balance of biofuel microalgal productions and to recycle nitrogen and phosphorus. The project proposes to study the coupling between a microalgal production system and an anaerobic digester. The objectives of BIOCORE are to propose a model of the coupled system, and to compute the optimal fluxes between the various compartments in order to optimize the energy recovery. See http://anr-symbiose.org/
- **ANR-Facteur 4:** The objective of this project to propose non GMO 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.
- **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 modeling of the process.
- **Green Stars:** Green Stars was laureate of the French call for projects known as the “French Stimulus Initiative” (Investissements d’Avenir), Institute of Excellence on Carbon-Free Energies. It federates a network of collaborative platforms bringing together all the players in the development of microalgae in France. The Institute includes 45 partners, including academics, large companies and SME. BIOCORE plays a key role in the project set up.

8.1.2. Inria funding

- **ColAge:** The goal of this joint Inria-INSERM consortium is to study bacterial growth and aging by using mathematical modeling 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).
- **Nautilus:** O. Bernard is coordinating the Inria-Nautilus ARC whose objective is to understand and model the coupling between hydrodynamics and microalgae photosynthesis.

8.1.3. INRA funding

- **Eco-tuta:** INRA-SPE is funding the project “Ecologie des communautés dans les agro-écosystèmes et implications pour la lutte biologique contre une espèce invasive: le cas Tuta absoluta sur tomate" in which BIOCORE is a partner with INRA Sophia Antipolis (2010-2012).
- **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).
- **Metacarpe:** This INRA SPE-GAP-EFPA-EA project (call “Gestion durable des résistances des bio-agresseurs”) is entitled “Modélisation de l’évolution des traits d’histoire de vie en lien avec l’agressivité des champignons parasites biotrophes : application au pathosystème rouille-peuplier”. BIOCORE is taking part with CIRAD, INRA Sophia Antipolis, Nancy and Rennes (2010-2012).

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 modeling 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 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

Univ. Polytechnique Mons: Service d'Automatique (B)

Modeling of photosynthesis

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 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

- Benoit Chachuat (Imperial College, Department of Chemical Engineering, UK), 1 week;
- Andreas Nikolaou (Imperial college, Department of Chemical Engineering, UK), 2 months;
- Claude Aflalo (Ben Gurion University of the Neguev, Israel), 1 week;
- Jaime Moreno (UNAM, Automation and Environmental Bioprocesses Departments, Institute of Engineering, Mexico), 1 week;
- Andrei Akhmetzhanov (McMaster University, Department of Biology, Canada), 2 weeks;
- Gonzalo Robledo (Universidad de Chile, Facultad de Ciencias, Departamento de Matemáticas, Chile) , 2 weeks;
- Tomas Gedeon (Montana State University, Department of Mathematical Sciences, USA), 2 days.

8.4.1.1. Internships

Luis CASACCIA (from Apr 2012 until Sep 2012)

Subject: Mathematical and computational analysis of genetic regulatory networks

Institution: National University of Rosario (Argentina)

8.5. Project-team seminar

BIOCORE organized a 3-day seminar in October in Peyresq. On this occasion, every member of the project-team presented his/her recent results and brainstorming sessions were organised. Jérôme Harmand of the Inria MODEMIC team was invited to give talks on this occasion.

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

9. Dissemination

9.1. Scientific Animation

J.-L. Gouzé is a member of the scientific committees for the conferences "Stic et Environnement", BIOMATH and CIFA ; also for the conference for G. Sallet (Senegal 2012). He is in the Inria committee supervising the doctoral theses, and a member of the 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 the ANR project GEMCO. Since September 2011 she is also a member of the COST-GTRI (the Working Group on International Relations in Inria's Council for Scientific and Technological Orientation). The Group is in charge of evaluating the 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 committee 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.

P. Bernhard is a member of the scientific committees of the doctoral school “Sciences fondamentales et appliquées” at the University of Nice-Sophia Antipolis. On behalf of the Chairman of PERSAN, he is also in the scientific committee of the “Parc naturel régional des Alpes d’Azur”.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Jonathan Rault , (192h ETD over 2011-2012) “Mathematical analysis and probabilities”, initial cycle of Polytech’Nice (eq. L1-L2), Université of Nice Sophia Antipolis, France.

J.-L. Gouzé (18h ETD), P. Hartmann (8h ETD), “Modeling biological networks”, 4th year students, Génie Biologique, Polytech’Nice, University of Nice - Sophia Antipolis

O. Bernard (9h ETD), “Mathematical models in Biology”. Master on biological oceanography in Villefranche-sur-Mer (M2), Université 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), “Modeling 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.

F. Grognard (10h ETD) and L. Mailleret (10h ETD) supervised a four-student three-week project for students in 2nd year Engineering in Modeling and Applied Mathematics (eq. M1), Polytech’Nice, Université of Nice Sophia Antipolis, France.

M. Chaves (4.5h ETD), J.-L. Gouzé (9h 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 prepared (jointly with other researchers) a book chapter entitled “Modeling and analysis of gene regulatory networks” on the topics taught in this last course, to appear in a Springer volume [54].

9.2.2. Supervision

PhD : J. Rault, “Modélisation mathématique structurée en taille du zooplancton, UNSA, defended December 11, 2012. Supervisors: J.-L. Gouzé and E. Benoit.

PhD in progress : M. Teixeira-Alves, “Modélisation de réseaux écologiques dans un cadre de protection des cultures: applications à la lutte biologique”, since september 2009, UNSA. Supervisors: F. Grognard and L. Mailleret.

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

PhD in progress : M. Castel “Modélisation des trajectoires évolutives des pathogènes de plantes dans les écosystèmes agricoles", since October 2010, University of Rennes. Supervisors : F. Hamelin and D. Andrivon (Agrocampus Ouest) and L. Mailleret.

PhD in progress : A. Carta, “Analysis and Control of models of biological regulatory systems. Application to growth control in *E. coli*”, since december 2010, UNSA. 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, UNSA. 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, UNSA. 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, UNSA. 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 agroecosystems”, since November 2012, UNSA. Supervisors: F. Grognard, L. Mailleret, B. Moury, and F. Fabre (INRA Avignon).

9.2.3. Juries

J.-L. Gouzé was referee for the thesis of Josephine Kagunda “Mathematical Analysis and Dynamical Systems Modeling of Highland Malaria in Western Kenya.”, Université de Lorraine, November 23.

J.-L. Gouzé was in the jury for the thesis of Matthieu Sebbah, « Stabilité d’inégalités variationnelles et prox-régularité, équations de Kolmogorov périodiques contrôlées », University of Montpellier 2, July 2.

J.-L. Gouzé was referee for the thesis of Giovanna De Palo “Dynamics and adaptation in the olfactory and phototransduction pathways”, SISSA - International School for Advanced Studies, Trieste (Italy), Octobre 29.

J.-L. Gouzé was in the jury for the thesis of Jonathan Rault “Modélisation mathématique structurée en taille du zooplancton,” UNSA, December 11.

J.-L. Gouzé was referee for the thesis of Giovanni Iacono “Systems biology approaches to the analysis of large-scale biological networks”, SISSA- International School for Advances Studies, Trieste (Italy), October 29.

M. Chaves was in the thesis jury of Sara Berthoumieux “Méthodes pour l’identification de modèles de réseaux biochimiques,” University of Lyon 1 Claude Bernard and Inria GRA, June 13.

M. Chaves was in the thesis jury of Abibatou Mbodj, “Qualitative modeling of mesoderm differentiation in *Drosophila melanogaster*,” University of Marseille and TAGC (INSERM U928), December 17.

O. Bernard was referee for the thesis of J. Mailier, ”Contribution to mathematical modeling of bioprocesses with application to cultures of microalgae and anaerobic digestion.“, Université de Mons (Belgium), May 25.

O. Bernard was president of the jury for the thesis of P. Collet, ”Analyse de Cycle de Vie de la valorisation énergétique de la biomasse algale : prise en compte des aspects dynamiques dans l’étape d’inventaire”, University of Montpellier, April 4.

O. Bernard was referee for the thesis of Y. Eynaud, "Contribution à la gestion de la complexité des modèles en sciences de l’environnement ", University of Aix-Marseille, December 6.

P. Bernhard was in the thesis jury of Lorenzo Maggi, ”Markovian competitive and cooperative games with applications to communications”, at Eurecom Sophia Antipolis, October 9.

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), and S. Mazeghrane (University of Montpellier).

9.3. Popularization and media

The activities related to biofuel and microalgae have generated many articles and broadcasts in the media: “Où en est-on des biocarburants de 2e et 3e générations?”, Le Monde.fr, October 19; “De la flore et du phosphore”, Libération, Novembre 18; “La filière microalgues reprend des couleurs en PACA”, La Tribune, March 19; “Vive le pétrole sur nos côtes”, Le Point.fr, May 3; “Mettez des microalgues dans votre moteur”, Sciences et avenir N^{O} 784 (June).

Aurélie Schmitt, “Ecole Nationale Supérieure de l’eau, l’énergie et l’environnement” student intern, has developed a *Java* applet using the AnyLogic software 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 [63].

Mélaine Gautier did a presentation at the Centre International de Valbonne for the ”Fête de la Science“ entitled ”Petits jeux des mathématiques pour représenter la vie, la lutte biologique, la croissance des plantes”, October 13.

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

31/01/2012	Lycée Léonard de Vinci, Sophia Antipolis.
13/03/2012	Lycée technique de la montagne, Valdeblore.
12/04/2012	Lycée technique de la montagne, Valdeblore.
20/11/2012	Lycée Aristide Briand, Gap (two conferences)

and one conference to visiting Bahrain students (July 12) at Fondation Sophia Antipolis. He helped several high school pupils with their TIPE and in hosting younger highshool interns. He gave a seminar in Inria’s “C@fé-in” on Game theory (October 22).

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 the Coriolis Conference (Ecole Polytechnique), Paris (February 6), and at Ecole Centrale de Paris (“Défi biotechnologie”) “Use of microorganisms for biofuel production” (October 25).

O. Bernard was invited to make a presentation at JojoFest to celebrate Georges Bastin’s emeritus. (University of Louvain, Belgium, October 9). J.-L. Gouzé and F. Grognard also attended the JojoFest workshop

Pierre Bernhard gave a seminar in Inria Lille-Nord Europe and ENSAM Lille (October 18)

M. Chaves was invited to make a presentation on mathematical methods in bioinformatics at the 2012 ECFS conference - New Frontiers in Basic Science of Cystic Fibrosis, Special group discussion: New Approaches for Exploring the CFTR Interactome, Sainte Maxime, France (March 31).

10. Bibliography

Major publications by the team in recent years

[1] J. Arino, J.-L. Gouzé, A. Sciandra. *A discrete, size-structured model of phytoplankton growth in the chemostat. Introduction of non constant cell division.*, in "J. Math. Biol.", 2002, vol. 45, p. 313-336, http://dx.doi.org/10.1007/s002850200160.

[2] O. Bernard, G. Bastin. *On the estimation of the pseudo-stoichiometric matrix for mass balance modeling of biotechnological processes*, in "Math. Biosciences", 2005, vol. 193, p. 51-77, http://dx.doi.org/10.1016/j.mbs.2004.10.004.

[3] O. Bernard, J.-L. Gouzé. *Closed loop observers bundle for uncertain biotechnological models*, in "J. Process. Contr.", 2004, vol. 14:7, p. 765-774, http://dx.doi.org/10.1016/j.jprocont.2003.12.006.

[4] O. Bernard, Z. Hadj-Sadok, D. Dochain, A. Genovesi, J.-P. Steyer. *Dynamical model development and parameter identification for an anaerobic wastewater treatment process*, in "Biotech.Bioeng.", 2001, vol. 75, n^o 75, p. 424-438, http://dx.doi.org/10.1002/bit.10036.

[5] M. Chaves. *Input-to-state stability of rate-controlled biochemical networks*, in "SIAM Journal of Control and Optimization", 2005, vol. 44, p. 704-727, http://dx.doi.org/10.1137/S0363012903437964.

[6] B. Faugeras, O. Bernard, A. Sciandra, M. Levy. *A modelling and data assimilation approach to estimate the carbon/chlorophyl and carbon/nitrogen ratios in a coupled hydrodynamical-biological model*, in "Nonlinear Processes in Geophysics", 2004, vol. 11, p. 515-533, http://dx.doi.org/10.5194/npg-11-515-2004.

[7] J.-L. Gouzé, A. Rapaport, Z. Hadj-Sadok. *Interval observers for uncertain biological systems*, in "Ecological modelling", 2000, vol. 133, p. 45-56, http://dx.doi.org/10.1016/S0304-3800(00)00279-9.

[8] L. Mailleret, O. Bernard, J.-P. Steyer. *Nonlinear adaptive control for bioreactors with unknown kinetics*, in "Automatica", 2004, vol. 40-8, p. 1379-1385, http://dx.doi.org/10.1016/j.automatica.2004.01.030.

[9] L. Mailleret, F. Grognard. *Global stability and optimisation of a general impulsive biological control model*, in "Mathematical Biosciences", 2009, vol. 221, n^o 2, p. 91-100, http://dx.doi.org/10.1016/j.mbs.2009.07.002.

[10] F. Mairet, O. Bernard, P. Masci, T. Lacour, A. Sciandra. *Modelling neutral lipid production by the microalga Isochrysis affinis galbana under nitrogen limitation*, in "Biores. Technol.", 2011, vol. 102, p. 142-149, http://dx.doi.org/10.1016/j.biortech.2010.06.138.

Publications of the year

Doctoral Dissertations and Habilitation Theses

[11] J. Rault. *Modélisation mathématique structurée en taille du zooplancton*, UNSA, 2012.

Articles in International Peer-Reviewed Journals

[12] S.-D. AYATA, M. LÉVY, O. AUMONT, A. SCIANDRA, J. SAINTE-MARIE, A. TAGLIABUE, O. BERNARD. *Phytoplankton growth formulation in marine ecosystem models: should we take into account photo-acclimation and variable stochiometry in oligotrophic areas?*, in "Journal of Marine Systems", 2012, to appear.

[13] O. BERNARD, A.-C. BOULANGER, M.-O. BRISTEAU, J. SAINTE-MARIE. *A 2D model for hydrodynamics and biology coupling applied to algae growth simulations*, in "Mathematical Modelling and Numerical Analysis", 2012, to appear.

[14] O. BERNARD, B. RÉMOND. *Validation of a simple model accounting for light and temperature effect on microalgal growth*, in "Bioresource Technology", 2012, vol. 123, p. 520-527., http://dx.doi.org/10.1016/j.biortech.2012.07.022.

[15] M. CHAVES, E. FARCOT, J.-L. GOUZÉ. *Probabilistic approach for predicting periodic orbits in piecewise affine differential models*, in "Bull. Math. Biol.", 2012, to appear, http://dx.doi.org/10.1007/s11538-012-9773-6.

[16] F. FABRE, E. ROUSSEAU, L. MAILLERET, B. MOURY. *Durable strategies to deploy plant resistance in agricultural landscapes*, in "New Phytologist", 2012, vol. 196, p. 1064-1075, http://dx.doi.org/10.1111/j.1469-8137.2011.04019.x.

[17] T. LACOUR, A. SCIANDRA, A. TALEC, P. MAYZAUD, O. BERNARD. *Diel variations of carbohydrates and neutral lipids in N-sufficient and N-limited cyclostat cultures of Isochrysis sp.*, in "Journal of Phycology", 2012, vol. 48, p. 966-975, http://dx.doi.org/10.1111/j.1529-8817.2012.01177.x.

[18] T. LACOUR, A. SCIANDRA, A. TALEC, P. MAYZAUD, O. BERNARD. *Neutral lipids and carbohydrates productivities as a response to the nitrogen status in the Haptophyceae Isochrysis sp. (T-iso): starvation vs. limitation*, in "Journal of Phycology", 2012, vol. 48, p. 647-656, http://dx.doi.org/10.1111/j.1529-8817.2012.01154.x.

[19] L. MAILLERET, M. CASTEL, J. MONTARRY, F. HAMELIN. *From elaborate to compact seasonal plant epidemic models and back: is competitive exclusion in the details?*, in "Theoretical Ecology", 2012, vol. 5, p. 311-324, http://dx.doi.org/10.1007/s12080-011-0126-0.

[20] F. MAIRET, O. BERNARD, E. CAMERON, M. RAS, L. LARDON, J.-P. STEYER, B. CHACHUAT. *Three-reaction model for the anaerobic digestion of microalgae*, in "Biotech. Bioeng.", 2012, vol. 109, p. 415-425, http://dx.doi.org/10.1002/bit.23350.

[21] F. MAIRET, M. MOISAN, O. BERNARD. *Interval observer with near optimal adaptation dynamics. Application to the estimation of lipid quota in microalgae*, in "International Journal of Robust and Nonlinear Control", 2012, to appear., http://dx.doi.org/10.1002/rnc.2934.

[22] F. MAZENC, O. BERNARD. *ISS Interval Observers for Nonlinear Systems Transformed Into Triangular Systems*, in "International Journal of Robust and Nonlinear Control", 2012, to appear.

[23] F. MAZENC, S. NICULESCU, O. BERNARD. *Exponentially stable interval observers for linear systems with delay*, in "Siam Journal Contr. Optim.", 2012, vol. 50, n^o 1, p. 286 - 305, http://dx.doi.org/10.1137/100812124.

[24] C. MOCQUET, A. SCIANDRA, A. TALEC, O. BERNARD. *Cell cycle implication on nitrogen acquisition and synchronization in Thalassiosira weissflogii (Bacillariophyta)*, in "Journal of Phycology", 2012, to appear.

[25] M. N. MÜLLER, L. BEAUFORT, O. BERNARD, M.-L. PEDROTTI, A. TALEC, A. SCIANDRA. *Influence of CO_2 and nitrogen limitation on the coccolith volume of Emiliania huxleyi (Haptophyta)*, in "Biogeosciences", 2012, vol. 9, n^{o} 4, p. 4155–4167, http://dx.doi.org/10.5194/bgd-9-4979-2012.

[26] I. NDIAYE, J.-L. GOUZÉ. *Global stability of reversible enzymatic metabolic chains*, in "Acta Biotheoretica", 2012, to appear.

[27] D. A. OYARZÚN, M. CHAVES, M. HOFF-HOFFMEYER-ZLOTNIK. *Multistability and oscillations in genetic control of metabolism*, in "Journal of Theoretical Biology", 2012, vol. 295, p. 139-153, to appear, http://dx.doi.org/10.1016/j.jtbi.2011.11.017.

[28] M. RAS, J.-P. STEYER, O. BERNARD. *Temperature effect on microalgae : a crucial factor for outdoor production*, in "Reviews in Environmental Science and Bio/Technology", 2012, to appear.

[29] J. RAULT, E. BENOÎT, J.-L. GOUZÉ. *Stabilizing effect of cannibalism in a two stages population model*, in "Acta Biotheoretica", 2012, to appear.

[30] G. ROBLEDO, F. GROGNARD, J.-L. GOUZÉ. *Global stability for a model of competition in the chemostat with microbial inputs*, in "Nonlinear Analysis: Real World Applications", 2012, vol. 13, n^{o} 2, p. 582 - 598, http://dx.doi.org/10.1016/j.nonrwa.2011.07.049.

[31] L. TOURNIER, M. CHAVES. *Interconnection of asynchronous Boolean networks, asymptotic and transient dynamics*, in "Automatica", 2012, to appear.

[32] E. VERCKEN, F. VINCENT, L. MAILLERET, N. RIS, E. TABONE, X. FAUVERGUE. *Time-lag in extinction dynamics in experimental populations: evidence for a genetic Allee effect*, in "Journal of Animal Ecology", 2012, to appear.

Invited Conferences

[33] P. BERNHARD. *Option pricing in a tychastic market model*, in "Around Viability Boundaries", Paris, 2012.

International Conferences with Proceedings

[34] I. BELGACEM, J.-L. GOUZÉ. *Global Stability of Full Open Reversible Michaelis-Menten Reactions*, in "8th IFAC Symposium Advanced Control of Chemical Processes (ADCHEM)", Singapore, 2012, p. 591–596.

[35] C. BREINDL, M. CHAVES, J.-L. GOUZÉ, F. ALLGÖWER. *Structure estimation for unate Boolean models of gene regulation networks*, in "Proc. 16th IFAC Symposium on System Identification", Brussels, Belgium, July 2012, http://dx.doi.org/10.3182/20120711-3-BE-2027.00278.

[36] *Best Paper*
A. CARTA, M. CHAVES, J.-L. GOUZÉ. *A simple model to control growth rate of synthetic E. coli during the exponential phase: model analysis and parameter estimation*, in "10th Conference on Computational Methods in Systems Biology", London, D. GILBERT, M. HEINER (editors), Springer, 2012, p. 107-126, Lecture Notes in Computer Science 7605, http://dx.doi.org/10.1007/978-3-642-33636-2_8.

[37] P. HARTMANN, Q. BECHET, O. BERNARD. *Interaction between Time Scales in Microalgae Based Processes*, in "20th Mediterranean Conference on Control & Automation (MED)", Barcelona, Spain, IEEE, July 2012, p. 561–566, http://dx.doi.org/10.1109/MED.2012.6265697.

[38] A. LEBON, L. MAILLERET, F. GROGNARD, Y. DUMONT. *Modelling plant compensatory effects in plant-insect dynamics*, in "4th International Symposium on Plant Growth Modeling, Simulation, Visualization and Applications, (PMA 2012)", Shangai (China), 2012.

[39] X.-D. LI, M. CHAVES, J.-L. GOUZÉ. *Robust estimation for a hybrid model of genetic network*, in "20th Mediterranean Conference on Control & Automation (MED)", Barcelona, Spain, July 2012, http://dx.doi.org/10.1109/MED.2012.6265629.

[40] F. MAIRET, M. MOISAN, O. BERNARD. *Adaptative interval observer with application to the estimation of biofuel production by microalgae*, in "20th Mediterranean Conference on Control Automation (MED)", Barcelona, Spain, july 2012, p. 567 -572, http://dx.doi.org/10.1109/MED.2012.6265698.

[41] J. RAULT, J.-L. GOUZÉ. *Stabilization of an oscillating n-dimensional structured population model*, in "20th Mediterranean Conference on Control & Automation (MED)", Barcelona, Spain, IEEE, July 2012, p. 372–377, http://dx.doi.org/10.1109/MED.2012.6265666.

Conferences without Proceedings

[42] S.-D. AYATA, M. LÉVY, O. AUMONT, O. BERNARD. *Modélisation de la croissance du phytoplancton et de la production primaire dans les océans*, in "Journée de l'IMREED", 2012.

[43] S.-D. AYATA, J. LLORT, A. TAGLIABUE, M. LÉVY. *Bloom triggering in the Southern Ocean : Sensitivity to biological parameters*, in "Workshop TANGGO", 2012.

[44] C. BAROUKH. *A new modelling framework: application to microalgae growth*, in "Young Algaeneers Symposium", Wageningen, Netherlands, June 2012.

[45] I. BELGACEM. *Global stability of full open reversible Michaelis-Menten reactions*, in "32ème Séminaire de la Société Francophone de Biologie Théorique", Saint-Flour, 2012.

[46] O. BERNARD, M. GAUTIER. *ODIN: plateforme de supervision de bioreacteur*, in "Bioenergiesud", Nîmes, France, 2012.

[47] O. BERNARD, M. GAUTIER. *ODIN: supervision avancée de procédés de production de bioénergie*, in "Journée de la métrologie et de la mesure (J2M)", Le Croisic, France, 2012.

[48] H. BONNEFOND. *Growth and neutral lipid production of Dunaliella salina, in light/dark cycles and periodic temperature variations*, in "Young Algaeneers Symposium", Wageningen, Netherlands, June 2012.

[49] V. CALCAGNO, F. GROGNARD, L. MAILLERET, E. WAJNBERG. *Habitat quality and optimal foraging: the Marginal Value Theorem revisited*, in "First Joint Congress on Evolutionary Biology (Evolution 2012)", Ottawa, Canada, 2012.

[50] M. CASTEL, L. MAILLERET, V. RAVIGNÉ, F. HAMELIN. *On the evolutionary ecology of cyclically asexual plant parasites*, in "Models in Population Dynamics and Ecology (MPDE12)", Santa Maria, Brazil, 2012.

[51] F. FABRE, E. ROUSSEAU, L. MAILLERET, B. MOURY. *Sustainable plant resistance management in agricultural landscapes*, in "Plant Resistance Sustainability 2012", La Colle sur Loup, France, 2012.

Scientific Books (or Scientific Book chapters)

[52] A. R. AKHMETZHANOV, L. MAILLERET, F. GROGNARD, P. BERNHARD. *Join forces or cheat: evolutionary analysis of a consumer-resource system*, in "Advances in Dynamic Games, Annals of the International Society of Dynamic Games", P. CARDIALIAGUET, R. CRESSMAN (editors), Springer, 2013, p. 73-95, http://dx.doi.org/10.1007/978-0-8176-8355-9_4.

[53] P. BERNHARD, J. ENGWERDA, B. ROORDA, H. SCHUMACHER, V. KOLOKOLTSOV, J.-P. AUBIN, P. SAINT-PIERRE. *The Interval Market Model in Mathematical Finance: Game Theoretic Methods*, Birkhaüser, 2012, http://www.springer.com/mathematics/applications/book/978-0-8176-8387-0.

[54] G. BERNOT, J.-P. COMET, A. RICHARD, M. CHAVES, J.-L. GOUZÉ, F. DAYAN. *Modeling and analysis of gene regulatory networks*, in "Modeling in Computational Biology and Biomedicine", F. CAZALS, P. KORNPROBST (editors), Springer, 2013, p. 47-80, to appear, http://dx.doi.org/10.1007/978-3-642-31208-3_2.

Research Reports

[55] N. BAJEUX. *Lutte biologique inondative et effet Allee chez les prédateurs*, UNSA, Polytech'Nice Sophia, 2012.

[56] L. CASACCIA, W. ABOU-JAOUDÉ, J.-L. GOUZÉ. *GEMCO Deliverable D2T1: Analysis and reduction of a model of the gene expression machinery in E.coli*, ANR, 2012.

[57] L. CASACCIA. *Analysis of cell machinery models in E.coli*, Universidad Nacional de Rosario, Argentina, 2012.

[58] C. COMBE. *Etude expérimentale de la réponse adaptative de Dunaliella salina (Chlorophyta) à des signaux lumineux haute fréquence*, Centre d'Océanologie de Marseille, 2012.

[59] P. GBEHOUNOU. *Modélisation de l'évolution de maladies virales chez les plantes dans un paysage agricole*, UNSA, Polytech'Nice Sophia, 2012.

[60] G. M. GRIMAUD. *Modélisation de l'influence de la photopériode sur la dynamique du métabolisme du carbone et de l'azote chez une cyanobactérie diazotrophe, Crocosphaera watsonii WH8501*, Centre d'Océanologie de Marseille, 2012.

[61] F. GROGNARD, A. R. AKHMETZHANOV, O. BERNARD. *Periodic optimal control for biomass productivity maximization in a photobioreactor using natural light*, Inria, April 2012, n$^{\text{o}}$ RR-7929, 28, http://hal.inria.fr/hal-00687322.

[62] P. MASCI, F. GROGNARD, E. BENOÎT, O. BERNARD. *Competition between phytoplankton and bacteria: exclusion and coexistence*, Inria, August 2012, n$^{\text{o}}$ RR-8038, 47, http://hal.inria.fr/hal-00722429.

[63] A. SCHMITT. *Création d'outils de simulation pour la vulgarisation scientifique*, Ecole Nationale Supérieure de l'eau, l'énergie et l'environnement, INPG, 2012.

References in notes

[64] 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 network model*, In preparation.

[65] A. AGRAWAL. *Overcompensation of plants in response to herbivory and the by-product benefits of mutualism*, in "Trends in Plant Science", 2000, vol. 5, p. 309-313.

[66] A. R. AKHMETZHANOV, F. GROGNARD, L. MAILLERET. *Optimal life-history strategies in seasonal consumer-resource dynamics.*, in "Evolution", 2011, vol. 65, n$^{\text{o}}$ 11, p. 3113–3125, http://dx.doi.org/10.1111/j.1558-5646.2011.01381.x.

[67] C. BAROUKH, R. MUÑOZ-TAMAYO, J.-P. STEYER, O. BERNARD. *A reduction approach for metabolic modeling under non-balanced growth: Application to the green algae Chlamydomonas reinhardtii* , in "European Control Conference", Zurich, Switzerland, July 2013, submitted.

[68] O. BARROU, A. KARAMA, E. LAKHAL, O. BERNARD, M.-N. PONS, J.-P. CORRIOU. *Estimation of a Reduced Model of the BSM1 Activated Sludge Wastewater Treatment Plant*, in "International Journal of Chemical Reactor Engineering", 2008, vol. 6, A63.

[69] G. BASTIN, D. DOCHAIN. *On-line estimation and adaptative control of bioreactors*, Elsevier, 1990.

[70] I. BELGACEM, J.-L. GOUZÉ. *Global stability of enzymatic chain of full reversible Michaelis-Menten reactions*, in "Acta Biotheoretica", 2012, submitted.

[71] O. BERNARD. *TELEMAC Deliverable 3.4: Final version of the Telemac advanced control module*, 2004.

[72] 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$^{\text{o}}$ 10, p. 1378–1389, http://dx.doi.org/10.1016/j.jprocont.2011.07.012.

[73] O. BERNARD, J.-L. GOUZÉ. *Closed loop observers bundle for uncertain biotechnological models*, in "J. Process. Contr.", 2004, vol. 14:7, p. 765-774.

[74] O. BERNARD, I. QUEINNEC. *Dynamic models of biochemical processes: properties of models*, in "Bioprocess Control", D. DOCHAIN (editor), Wiley, Hoboken, 2008.

[75] O. BERNARD, A. SCIANDRA, S. MADANI. *Multimodel analysis of the response of the coccolithophore Emiliania huxleyi to an elevation of pCO_2 under nitrate limitation*, in "Ecol. Model.", 2008, vol. 211, p. 324-338.

[76] O. BERNARD, A. SCIANDRA, S. RABOUILLE. *Carbon fixation prediction during a bloom of Emiliania huxleyi is highly sensitive to the assumed regulation mechanism*, in "Biogeosciences Discussions", 2009, vol. 6, n^{o} 3, p. 5339–5372, http://www.biogeosciences-discuss.net/6/5339/2009/.

[77] O. BERNARD, A. SCIANDRA, S. RABOUILLE. *Predictions of carbon fixation during a bloom of Emiliania huxleyi as a function of the regulating inorganic carbon species*, in "Proceedings of the Mathmod 09 conference", Vienna, Austria, 2009.

[78] V. CALCAGNO, F. GROGNARD, L. MAILLERET, E. WAJNBERG. *Habitat quality and optimal foraging: the Marginal Value Theorem revisited*, in "Ecology", 2012, submitted.

[79] E. CAMERON, F. MAIRET, O. BERNARD, M. RAS, L. LARDON, J.-P. STEYER, B. CHACHUAT. *Anaerobic Digestion of Microalgae: Identification for Optimization and Control*, in "IFAC World Congress", Milano, Italy, 2011, n^{o} 1.

[80] M. CASTEL, L. MAILLERET, D. ANDRIVON, V. RAVIGNÉ, F. HAMELIN. *Hit-and-miss affair of mating prior to overseasoning and the evolutionary interplay between sexual and asexual reproduction in plant parasites*, in "The American Naturalist", 2012, submitted.

[81] E. CHARNOV. *Optimal foraging: the marginal value theorem*, in "Theoretical Population Biology", 1976, vol. 9, p. 129-136.

[82] M. CHAVES, L. TOURNIER. *Predicting the asymptotic dynamics of large biological networks by interconnections of Boolean modules*, in "50th IEEE Conference on Decision and Control and European Control Conference", Orlando, Florida, USA, December 2011.

[83] P. COLLET. *Analyse de Cycle de Vie de la valorisation énergétique de la biomasse algale : prise en compte des aspects dynamiques dans l'étape d'inventaire*, University Montpellier II, 2012.

[84] P. COLLET, A. HÉLIAS, L. LARDON, M. RAS, R.-A. GOY, J.-P. STEYER. *Life-cycle assessment of microalgae culture coupled to biogas production*, in "Bioresource Technology", 2011, vol. 102, p. 207-214, http://dx.doi.org/10.1016/j.biortech.2010.06.154.

[85] P. COLLET, J. LANGLOIS, M. CORNELUS, L. LARDON, J.-P. STEYER, O. BERNARD, A. HÉLIAS. *Environmental assessment and ecodesign perspectives*, in "Ecotech-tools conference", Montpellier, France, 2011.

[86] P. COLLET, L. LARDON, A. HÉLIAS, S. BRICOUT, I. LOMBAERT-VALOT, B. PERRIER, O. LÉPINE, J.-P. STEYER, O. BERNARD. *Can we produce biofuel from microalgae without a renewable source of electricity and heat?*, in "Algn'n'Chem conference", Montpellier, France, 2011.

[87] C. G. DIÉGUEZ, E. ROCA, O. BERNARD. *Reduction of the Anaerobic Digestion Model N° 1 for an industrial wastewater treatment plant by Principal Component Analysis*, in "Proc. of the 10th ECC conference", Budapest, Hungary, 2009.

[88] C. G. Diéguez, E. Roca, O. Bernard. *Reducing the Anaerobic Digestion Model N^O 1 for its application to an industrial wastewater treatment plant treating winery effluent wastewater*, in "Bioresource Technology", 2012, submitted.

[89] G. M. Grimaud, A. Dron, S. Rabouille, A. Sciandra, O. Bernard. *Modelling photoperiod influence on the carbon-nitrogen metabolism in a unicellular diazotrophic cyanobacterium*, in "European Control Conference", Zurich, Switzerland, July 2013, submitted.

[90] F. Grognard, A. R. Akhmetzhanov, O. Bernard. *Optimal strategies for biomass productivity maximization in a photobioreactor using natural light*, in "Automatica", 2012, submitted.

[91] F. Hamelin, M. Castel, S. Poggi, D. Andrivon, L. Mailleret. *Seasonality and the evolutionary divergence of plant parasites*, in "Ecology", 2011, vol. 92, p. 2159-2166, http://dx.doi.org/10.1890/10-2442.1.

[92] P. Hartmann, Q. Bechet, O. Bernard. *Interaction between time scales in microalgae based processes*, in "Bioprocess and Biosystems Engineering", 2012, submitted.

[93] P. Hartmann, A. Nikolaou, B. Chachuat, O. Bernard. *A Dynamic Model coupling Photoacclimation and Photoinhibition in Microalgae*, in "European Control Conference", 2013, submitted.

[94] L. Lardon, A. Hélias, B. Sialve, J.-P. Steyer, O. Bernard. *Life-Cycle Assessment of Biodiesel Production from Microalgae*, in "Environ. Sci. Technol.", 2009, vol. 43, p. 6475-6481.

[95] L. Mailleret, V. Lemesle. *A note on semi-discrete modelling in the life sciences*, in "Philosophical Transactions of the Royal Society A: Mathematical,Physical and Engineering Sciences", 2009, vol. 367, n^o 1908, p. 4779-4799 [*DOI :* 10.1098/RSTA.2009.0153], http://rsta.royalsocietypublishing.org/content/367/1908/4779.abstract.

[96] F. Mairet, O. Bernard, T. Lacour, A. Sciandra. *Modelling microalgae growth in nitrogen limited photobiorector for estimating biomass, carbohydrate and neutral lipid productivities*, in "IFAC World Congress", Milano, Italy, 2011.

[97] F. Mairet, O. Bernard, M. Ras, L. Lardon, J.-P. Steyer. *A Dynamic Model for Anaerobic Digestion of Microalgae*, in "IFAC World Congress", Milano, Italy, 2011.

[98] F. Mairet, O. Bernard, M. Ras, L. Lardon, J.-P. Steyer. *Anaerobic digestion of microalgae: evaluation of process performances using ADM1*, in "Stic & Environnement 2011", Saint-Etienne, France, 2011.

[99] F. Mairet, O. Bernard, M. Ras, L. Lardon, J.-P. Steyer. *Modeling anaerobic digestion of microalgae using ADM1.*, in "Biores. Technol.", 2011, vol. 102, n^o 13, p. 6823–6829, http://dx.doi.org/10.1016/j.biortech.2011.04.015.

[100] F. Mairet, O. Bernard, M. Ras, L. Lardon, J.-P. Steyer. *Testing the ability of ADM1 to represent the anaerobic digestion of microalgae*, in "Proceedings of the Watermatex conference", San Sebastian, Spain, 2011.

[101] F. MAIRET, M. MOISAN, O. BERNARD. *Estimation of neutral lipid and carbohydrate quotas in microalgae using adaptive interval observers*, in "Bioprocess and Biosystems Engineering", 2012, submitted.

[102] F. MAIRET, R. MUÑOZ-TAMAYO, O. BERNARD. *Driving species competition in a light-limited chemostat*, in "9th IFAC Symposium on Nonlinear Control Systems", 2013, submitted.

[103] P. MASCI, O. BERNARD, F. GROGNARD. *Continuous Selection of the Fastest Growing Species in the Chemostat*, in "Proceedings of the IFAC conference", Seoul, Korea, 2008.

[104] P. MASCI, F. GROGNARD, O. BERNARD. *Microalgal biomass surface productivity optimization based on a photobioreactor model*, in "Proceedings of the 11th CAB conference", Leuven, Belgium, 2010.

[105] F. MAZENC, O. BERNARD. *Interval observers for planar systems with complex poles*, in "IEEE Transactions on Automatic Control", 2010, vol. 55, n^{o} 2, p. 523–527.

[106] F. MAZENC, O. BERNARD. *Interval observers for linear time-invariant systems with disturbances*, in "Automatica", 2011, vol. 47, n^{o} 1, p. 140 - 147, http://dx.doi.org/10.1016/j.automatica.2010.10.019.

[107] C. MOCQUET, O. BERNARD, A. SCIANDRA. *Cell cycle modelling for microalgae grown under light/dark cycles*, in "Proceedings of the 11th CAB conference", Leuven, Belgium, 2010.

[108] M. MOISAN, O. BERNARD. *Robust interval observers for global Lipschitz uncertain chaotic systems*, in "Systems & Control Letters", 2010, vol. 59, n^{o} 11, p. 687 - 694, http://dx.doi.org/10.1016/j.sysconle.2010.08.005.

[109] R. MUÑOZ-TAMAYO, F. MAIRET, O. BERNARD. *Optimizing microalgal production in raceway systems*, in "Biotechnology Progress", 2012, submitted.

[110] R. MUÑOZ-TAMAYO, F. MAIRET, O. BERNARD. *Driving microalgal production in raceway systems to near optimal productivities*, in "European Control Conference", Zurich, Switzerland, July 2013, submitted.

[111] S. NUNDLOLL. *Dos and don'ts in augmentative biological control: insights from mathematical modelling*, Université de Nice-Sophia Antipolis, 2010.

[112] P. PAROLIN, C. BRESCH, N. DESNEUX, R. BRUN, A. BOUT, R. BOLL, C. PONCET. *Secondary plants used in biological control: a review*, in "International Journal of Pest Management", 2012, vol. 58, p. 91-100.

[113] K. POVEDA, M. GOMES JIMENEZ, A. KESSLER. *The ennemy as ally: herbivore-induced increase in crop yield*, in "Ecological Applications", 2010, vol. 20, p. 1787-1793.

[114] J. RODRIGUEZ, E. ROCA, J. LEMA, O. BERNARD. *Determination of the adequate minimum model complexity required in anaerobic bioprocesses using experimental data*, in "J. Chem. Tech. Biotech.", 2008, vol. 83, p. 1694-1702.

[115] L. ROSSO, J. LOBRY, J. FLANDROIS. *An Unexpected Correlation between Cardinal Temperatures of Microbial Growth Highlighted by a New Model*, in "Journal of Theoretical Biology", 1993, vol. 162, n^{o} 4, p. 447 - 463 [*DOI :* 10.1006/JTBI.1993.1099], http://www.sciencedirect.com/science/article/pii/S0022519383710994.

[116] B. SIALVE, N. BERNET, O. BERNARD. *Anaerobic digestion of microalgae as a necessary step to make microalgal biodiesel sustainable*, in "Biotechnol. Advances", 2009, vol. 27, p. 409-416.

[117] B. SIALVE, J.-P. STEYER, E. LATRILLE, O. BERNARD, G. BOUGARAN, R. KAAS, J.-P. CADORET. *Procédé de fixation de CO2 et de traitement des déchets organiques par couplage d'un système de digestion anaérobie et d'un système de production de microorganismes phytoplanctoniques*, 2009, n° 09/50334.

[118] S. SYMONDSON, K. SUNDERLAND, M. GREENSTONE. *Can generalist predators be effective biocontrol agents?*, in "Annual Review of Entomology", 2002, vol. 47, p. 561-594.

[119] TASK GROUP FOR MATHEMATICAL MODELLING OF ANAEROBIC DIGESTION PROCESSES, I. W. A.. *Anaerobic Digestion Model No. 1 (ADM1)*, IWA Publishing, London, 2002.

[120] M. TEIXEIRA ALVES, L. MAILLERET, F. GROGNARD. *Shared predation: positive effects of predator distraction*, in "PLoS One", 2012, submitted.

[121] V. THOMSON, S. CUNNINGHAM, S. BALL, A. NICOTRA. *Compensation for herbivory by Cucumis sativus, through increased photosynthetic capacity and efficiency*, in "Oecologia", 2003, vol. 134, p. 167-175.