Activity Report 2011

Project-Team BIOCORE

Biological control of artificial ecosystems

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

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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 modelling 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 of waste, 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 modelling in biology: model design, validation, parameter identification.
- Mathematical properties of models in biology: mathematical studies of models and of their global behaviour.
- 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 behaviour, 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 ecosystem 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, particularly 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 atmosphere.
- Design and optimisation 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 modelling and supervision of biological processes.

National, international and industrial relations

- Collaboration with IFREMER (Nantes), INRA (MIA Montpellier, LBE Narbonne, GMPA Grignon, ISA Sophia-Antipolis. IAM Nancy, Agrocampus Ouest), CIRAD Montpellier, Centre d'Océanologie de Marseille, LOCEAN (Paris), GIPSA Grenoble, IBIS, BANG 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 (Israël), Imperial College (United-Kingdom), Massey University (New Zealand), Universidad Tecnica Federico Santa Maria and Universidad de Chile (Chile).
- ANR *Blanc* project Gemco
- ANR *Bioénergie* project Symbiose and FUI Salinalgue.

2.2. Highlights

- We developed a seasonal model of interaction between a consumer population and its resource that takes the consumers' behaviour into account. We showed how the optimal behaviour of the consumer during the season is indeterminate or determinate depending on the season length, but also on the consumer density and how optimality has a stabilizing effect on the multi-season dynamics [12]; this is a step in the study of how the environment and the evolution influence the individual's behaviour.
- We have developed a novel method for analysis of high-dimensional networks, based on the interconnection of two (smaller) input/output asynchronous Boolean modules. The asymptotic behaviour (or attractors) of the interconnected system, can be obtained from the analysis of the *asymptotic graph*, which is constructed from products of the attractors of each individual Boolean module. This is a model reduction method which significantly decreases the computational cost of the analysis of large, complex biological networks [33].
- The Algotron process at the LBE, which consists in the coupling of a 56 m^2 outdoor microalgal production process together with a 1 m^3 anaerobic digester producing methane, is now supervised by the ODIN supervision software developed within BIOCORE (cf. Section 6.3). ODIN centralises the information from several online sensors and from off line databases to compute advanced control strategies maximising the process productivity.

3. Scientific Foundations

3.1. Mathematical and computational methods

BIOCORE's action is centered on the mathematical modelling 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 modelling 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 requires 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 behaviour 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 modelling 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 a control law, that imposes to the system the behaviour 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 [8]. 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 modelling approach: from the biochemical reactions to ecosystems. The regulatory pathways at the cellular level are at the basis of the behaviour 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 behaviour 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 behaviours.

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 behaviour 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 that needs to be tackled 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 modelling 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) [13].

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 modelling 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 behaviour. 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 [10].

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 or other competing species of the pest and so keeping it under control; 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 substrates 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 [78] 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 for Lagrangian simulation of the dynamical environment of marine microalgae (LOV) with computer controlled automata for high frequency measurement and on-line control.

- Several pilots of 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).

- Experimental greenhouses of various sizes (from laboratory to semi-industrial size) and small scale devices for insect behaviour 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, Andrei Akhmetzhanov.

Mathematical study of semi-discrete models

Semi-discrete models have shown their relevance in the modelling of biological phenomena whose nature presents abrupt changes over the course of their evolution [77]. We used such models and analysed their properties in several situations that are developed in 6.2.3, most of them requiring such a modelling 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 [58] or in the co-existence analysis of epidemiological strains [17], [21]. Seasonality also plays a big role in the semi-discrete modelling required for the analysis of consumers' adaptive behaviour in seasonal consumer-resource dynamics, where only dormant offspring survives the 'winter' [12], [52].

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 [28], 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.

6.1.2. *Model design, identification and validation*

Participants: Olivier Bernard, Jean-Luc Gouzé.

Model design and identification

One of the main families of biological systems that we have studied involves mass transfer between compartments, whether these compartments are microorganisms or substrates in a bioreactor, or species populations in an ecosystem. We have developed methods to estimate the models of such systems [62]. These systems can be represented by models having the general structure popularized by [61], [65], [66], and based on an underlying reaction network:

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

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

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

This approach has been applied to various bioproduction processes, most recently on activated sludge processes [60], anaerobic digestion [71], [87] and anaerobic digestion of microalgae [22].

6.1.3. *Nonlinear observers*

Participants: Jean-Luc Gouzé, Olivier Bernard.

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 [8]. 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, [80]. This approach was then extended to n-dimensional linear systems, leading to the design of interval observers in high dimensions [25]. Extension to time-delay systems have also been proposed [26]. 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" [64]. The approach has been applied to estimation of the microalgae growth and lipid production [39].

In order to demonstrate the efficiency of the interval observer design, even with chaotic systems, a special application of the interval observer has been developed for Chua's chaotic systems. The interval estimation of the state variables are performed considering parameters uncertainties of the system and biased output [83], [80].

6.1.4. *Metabolic and genomic models*

Participants: Jean-Luc Gouzé, Madalena Chaves, Alfonso Carta, Ismail Belgacem, Xiao Dong Li, Olivier Bernard, Christian Breindl, Frédéric Grognard.

Qualitative control of piecewise affine models

In the control of genetic networks, the construction of feedback control laws is subject to many specific constraints, including positivity, appropriate bounds and forms of the input. In addition, control laws should be liable to implementation in the laboratory using gene and protein components. In this context, under the hypothesis that both the observations and control functions are qualitative (or piecewise constant), and using sliding mode solutions, we analysed the controllability and stabilizability with respect to either of the steady states, for a piecewise affine model of the bistable switch with single input. It is also possible to find a qualitative control law that leads the system to a periodic orbit passing through the unstable steady state [14]. Moreover, we designed some preliminary control laws for the negative loop with two genes, which has an oscillatory behaviour [54].

Interconnections of Boolean modules: asymptotic behaviour

A biological network can be schematically described as an input/output Boolean module: that is, both the states, the outputs and inputs are Boolean. The dynamics of a Boolean network can be represented by an asynchronous transition graph, whose attractors describe the system's asymptotic behaviour. 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 attractors of each module. Based on this result, a model reduction technique is proposed in [33], to predict the asymptotic dynamics of high-dimensional biological networks through the computation of the dynamics of two isolated smaller subnetworks. Applications include a model of cell-fate decision (represented as an interconnection of two 3-input/3-output modules).

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 [70].

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 [40]. 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].

Uniqueness and global stability for metabolic models

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 type of metabolic systems 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 behaviour in a more general genetic-metabolic loop [84].

Birhythmicity in the p53-Mdm2 network

The p53-Mdm2 network is one of the key protein module involved in the control of proliferation of abnormal cells in mammals. Recently, a differential model of the p53-Mdm2 biochemical network which shows birhythmicity has been proposed to reproduce the two experimentally observed frequencies of oscillations of p53. Our study aimed at investigating the mechanisms at the origin of this birhythmic behaviour. To do so, we approximated this continuous non-linear model into a lower dimensional piecewise affine model and performed a first return map analysis. Based on this analysis, an experimental strategy has been proposed to test the existence of birhythmicity in the p53-Mdm2 network [31], [11].

E. coli modelling and control

In the framework of ANR project Gemco, with the aim of better understanding how to build a controller for *Escherichia coli* growth, three reduced models of *E. coli* gene expression machinery have been developed: the *wild-type model*, the *open-loop model* and the *closed-loop model*. Each one of these models is made up of two piece-wise non-linear differential equations.

Notably, the wild-type model describes the qualitative dynamics of the unmodified bacterium in terms of two relevant protein concentrations (RNAP and CRP) and a carbon source as input, which can be either glucose or maltose. Bacteria prefer glucose, which leads to a higher growth rate in wild type.

The open-loop model describes the qualitative dynamics of RNAP end CRP concentrations when the gene encoding for RNAP is controlled externally by an IPTG-inducible promoter. This control, biologically implemented by our collaborators in Grenoble—yielding different *E. coli* growth rates depending on IPTG concentration—shows that a controller for the bacterial growth can be built acting on the gene expression machinery level. Moreover, lumped parameters related to RNAP dynamics and IPTG regulation function have been estimated by means of *E. coli* growth curves.

Finally, the closed-loop model implements a possible feedback control-loop able to theoretically generate *inverse diauxie*, i.e. higher growth on maltose than on glucose.

Observation problems of a class of genetic regulatory networks

A state reconstruction problem with Boolean measurements is considered for a piecewise affine genetic network model. The problem has two distinct aspects with respect to classical ones: 1) the model is a hybrid system, and 2) the measurements (of genes expression) are only qualitative due to the experimental techniques. A Luenberger-like observer is proposed which can present some sliding modes and has *finite-time* convergence. A transition graph is given for the coupled observer-nominal system. To minimize the convergence time, different convergence scenarios are discussed for optimizing the choice of initial condition of the observer [35], [57]. Robustness of the observer is checked for two types of parametric perturbed systems:

1) the observer is used to identify an unknown but fixed variation on the synthesis coefficient, via an adaptive dichotomy algorithm; and 2) the observer is robust in practical sense for the model with an uncertainty on the threshold value [76].

6.2. Fields of application

6.2.1. Bioenergy

6.2.1.1. Modelling and optimization of microalgae production

Participants: Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Philipp Hartmann, Rafael Munoz Tamayo, Andrei Akhmetzhanov, Nina Moelants, Hubert Bonnefond.

Experiments have been carried out to study the effects of nitrogen limitation on the lipid production in microalgae [74] and support model development. We have proposed a new model for lipid production by microalgae which describes the fate of the CO_2 incorporated during photosynthesis [23]. 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. Experiments have also attempted to simultaneously represent the effect of an osmotic stress [55]. 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 [36].

On the other hand, a new dynamical model has been developed to describe microalgal growth in a photobiore-actor under light and nitrogen limitations [13]. 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 [34], [48] ...) and the radiative transfer in the photobioreactor (light attenuation due to the microalgae).

Using these two approaches, we have developed a model which describes lipid production in a photobioreactor under light limitation. This model is used to predict lipid production in the perspective of large scale biofuel production. Simpler models have also been developed and have been used to provide optimization strategies: first, biomass production has been optimized in a constant light environment [79], 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) [72], [73].

Another model has been developed to represent growth of microalgae colimited by nitrogen and phosphorus [69]. It has been shown, from qualitative analysis of the model that uptake of nitrogen and phosphorus are non symmetric.

6.2.1.2. Modelling the effect of light and temperature on microalgae

Participants: Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Philipp Hartmann, Rafael Munoz Tamayo, Kerstin Ebert, Nina Moelants, Hubert Bonnefond.

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.

The impact of the hydrodynamics on the light percept by a single cell was studied thanks to fluid dynamics simulations of raceway pond [48]. 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 [48].

Finally, the effect of temperature on microalgae has been represented by adapting the CTMI model developped for bacteria [88]. The proposed model [59], associated with a parameter identification procedure, was able to correctly represent the growth response to temperature for 12 different species [48].

6.2.2. CO_2 fixation by microalgae

Participants: Olivier Bernard, Antoine Sciandra, Philipp Hartmann, Nina Moelants.

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 [82]. 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 [13]. 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 [81]. The effect of cell synchronization on lipid content were experimentally studied [18] and included into microalgae growth models [36].

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

Three models accounting for the possible coupling between photosynthesis and calcification were included in an ocean model, including settling and predation by grazers, and a bloom of coccolithophorids was simulated [67], [68]. It was shown using Monte Carlo simulations that the uncertainty on the mechanisms driving calcification together with parametric uncertainties lead to uncertainties which are in the same range as the effect of an increase or the CO_2 partial pressure.

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.

The influence of an alternative prey in biological control programs

We have developed a model based on the classical Leslie-Gower predator prey model, that allows for the choice that a predator might have for its diet. In a biological control framework, this choice might be between a pest that we want to eradicate and another prey that could be fed to the predator in order to help the biological control efficiency or between the pest and an alternative prey that is present in the field and might keep the predator from acting as a natural enemy of the pest. We put the problem in a time-partitioning framework: the predator has to split its time between the two prey. We then compared two time-partitioning strategies: one where the predator always spends a fixed proportion of its time on each prey and one where the predator always chooses the prey that is instantaneously most profitable (adaptive foraging). We then studied the effect of the presence of one prey on the other (indirect effect since it is mediated by the presence of the predator). We showed that, in the Leslie-Gower framework, one of the two prey always benefits from the presence of the other and that this effect is even stronger in the adaptive foraging framework, where the presence of the other prey is never detrimental to the one considered. That way, with very little assumptions, we showed the existence of apparent predation, commensalism and apparent mutualism, while most existing theoretical results tend to evidence apparent competition [51]. Such mechanisms may explain why generalist biological control agents are, in general, not as efficient as specialists in controlling crop pests.

The influence of plant dynamics on pest eradication

Pests-biocontrol agents models have been developed in order to build biological control strategies that can achieve pest eradication through augmentative biological control [85]. In the present work, we aim at introducing a plant compartment since its dynamics clearly have an influence on that of the pests and since the final objective of biological control is to maintain a sufficient plant yield. In a first step, we focused on plant-insect interactions and showed how the level and timing of the pest invasion could influence the final plant yield. Introducing pests control interventions and studying its timing, we showed how it eventually could have important effects on the growth pattern and the final biomass. As a reference, we consider the novel invasive pest Tuta absoluta on tomato plants [56].

This work is done in collaboration with Yves Dumont (Cirad).

6.2.3.2. *Controlling plant pathogens*
Participants: Frédéric Grognard, Ludovic Mailleret.

Sustainable management of plant resistance

The introduction of plants 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. In this work, 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. In the first case, both plant strains need to be mixed, but it results in the loss of the resistance at the end of the 15 year period; in the second case, the damage is higher and the maximal proportion of resistant plant is smaller, but the resistance is preserved [58], [16].

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

Plant pathogen dynamics and cropping management practices

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. Agricultural systems are characterized by the cyclical presence and absence of the crop, due to cropping practices such as harvest and planting. We studied the influence that time-partitioning, *i.e.* the specialization of a parasite for the beginning or the end of crop presence, can have on co-existence. In modelling the epidemiology through a semi-discrete model we showed through an evolutionary invasion analysis that evolutionary divergence, and thus co-existence of different strains, of the parasite phenotype can occur [17], [44]. Also, in a similar context, we underlined why modelling seasonal plant epidemiology did not necessarily lead to competitive exclusion; indeed, generating a compact model by rigorously isolating the slow dynamics from a large detailed model of plant epidemiology, we found out the possibility of coexistence [49], [21]. Such a result contrasts with classical competitive exclusion principles found in compact models which rely on the arguable density independent nature of the pathogen infections occuring during the very beginning of the cropping seasons.

This work is done in collaboration with Frédéric Hamelin (Agrocampus Ouest).

6.2.4. Biological depollution

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 [90], [89].

In a first stage, we developed models for anaerobic digestion of microalgae. Two approaches were used: First, a dynamic model has been developed trying to keep a low level of complexity so that it can be mathematically tractable for optimisation [37], [32], [22]. 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 [91] (a reference model which considers 19 biochemical reactions) to represent the same dataset. This model, after modification of the hydrolysis step [24], [38], [41] has then been used to evaluate process performances (methane yield, productivity...) and stability though numerical simulations.

In a second stage, a model describing the coupling between anaerobic digestion process and microalgae culture (including the feeding of the algae with anaerobic digestion effluents) has been developed. The model is based on the three steps model for anaerobic digestion, and on the photoacclimation model for microalgae [13]. The model also includes the modelling of heterotrophs in the microalgae pond.

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.

An analysis of the potential environmental impacts of biodiesel production from microalgae has been carried out using the life cycle assessment (LCA) methodology [75]. 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 [47], [46]. 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 [15] 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. Adaptive behaviour in seasonal consumer-resource dynamics
Participants: Frédéric Grognard, Ludovic Mailleret, Pierre Bernhard, Andrei Akhmetzhanov.

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 preys (choose their behaviour) according to the solution of an optimal control problem [12]. Secondly, we studied the long-scale discrete dynamics over seasons. We investigated the qualitative behaviour of the dynamics with respect to the parameters of the problem and showed that, depending on the parameters of the model, extinction or co-existence of the predators and preys can be evidenced [12].

We then examined how (resident) predators adopting this behaviour 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 behaviour. We studied the resulting optimal control problem where the mutants maximize their own number of offspring using the knowledge of the resident's behaviour, 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 behaviour [52]. We have then proposed a strategy for the predator in which it would prevent the invasion by the mutant instead of maximizing its number of offspring, which corresponds to the computation of evolutionarily stable life history strategies.

We have then considered that the resource itself could adapt its behaviour over time to limit the damage caused by the consumer, and maximize its own offspring. This problem requires the solution of a non zero-sum differential game, the consumer and the resource being the two players. We showed that the patterns of the strategies of the consumers and the resources are identical to the ones that can be obtained if the opposing player adopts a constant behaviour; the timing of the switchings varies however [42].

6.2.5.2. Including phytoplankton photoadaptation into biogeochemical models
Participant: Olivier Bernard.

8. Partnerships and Cooperations

8.1. National initiatives

- **Shamash:** Shamash is a project funded by the ANR in the national program for research in bioenergy. Its objective is to produce biodiesel from microalgae. Shamash, coordinated by O. Bernard, includes 9 partners, for a total budget of 2.8 Millions Euros. The role of BIOCORE is to design a model of the process in order to better understand the dynamical mechanisms that lead to the transient storage of lipids. The second step will then consist in defining optimal conditions to maximize the oil production. See http://www- sop.inria.fr/comore/shamash/

- **Symbiose:** BIOCORE takes part in the Symbiose ANR project. 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/

- **Salinalgue:** BIOCORE is involved in the FUI Salinalgue project. The objective of this project is to take benefit of endemic microalgae species in areas of high salinity (previously used to produce salt) to produce both biofuel (either lipid based or methane) and co products. BIOCORE is in charge of lab scale experiments and of the modelling of the process.

- **GDR PROBBE:** The objective of this GDR is the development of new biotechnological processes based on microorganisms producing metabolites which can be used as fuel for transportation (lipids, sugars, methane, hydrogen, ...). BIOCORE is taking part mainly in the modelling and control aspects of the processes involving anaerobic bacteria or microalgae.

- **Nautilus:** O. Bernard is coordinating the Nautilus ARC whose objective is to understand and model the coupling between hydrodynamics and microalgae photosynthesis.

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

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

- **RBHS:** INRA-SPE is funding the project "Rôle de la biodiversité et des hétérogénéités spatio-temporelles de la distribution des ravageurs et de leurs ennemis naturels dans les phénomènes de régulations biologiques" in which BIOCORE is a partner with INRA Sophia Antipolis and INRA Avignon (2009-2011)

- **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).

- **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).

- **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).

- **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.

- **Seminar:** BIOCORE organizes a regular seminar "Modelling 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 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 integrated pest management (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 modelling approaches dedicated to the optimisation of plant protection methods relying on biological control and integrated pest management.

8.2.2. Major European Organizations with which you have followed Collaborations

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

Imperial college, Department of Chemical engineering (UK)
Modelling and optimization of microalgal based processes.

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

Study of metabolic/genetic models

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

Identification of gene networks

8.3. International Initiatives

8.3.1. INRIA International Partners

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. 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
- Claude Aflalo (Ben Gurion University of the Neguev, Israel), 1 week;
- Hugh McIntyre (Dalhousie University, Department of Oceanography, Halifax, Canada), 1 week.
- Quentin Béchet (Center for Environmental Technology and Engineering, School of Engineering and Advanced Technology, Massey University , Palmerston North, New Zealand), 1 month.
- Mihaela Sbarciog (Université de Mons, Belgium), 2 days.
- Delphine Ropers, Eugenio Cinquemani, Sara Berthoumieux, Stephane Pinhal (INRIA Rhone-Alpes) 3 days.

8.3.2.1. Internship

Ismail Belgacem (University of Tlemcen, Algeria) received an internship grant from the DRI and stayed in BIOCORE between april and august. He is now pursuing a PhD Thesis in BIOCORE.

8.4. Project-team seminar

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

9. Dissemination

9.1. Leadership with scientific community

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 "Ecole Doctorale 85 Sciences de la Vie et de la Santé" of the University of Nice-Sophia-Antipolis. He is a member of the board of the SFBT (French Speaking Society for Theoretical Biology).

O. Bernard is the leader of the ANR project Shamash. He is in the technical committee of the Computer Applied to Biotechnology (CAB) conferences. He is in the scientific committee of the French conference "Stic et Environnement". He is a member of the scientific comity of the competitivity pole "Trimatec". O. Bernard represents INRIA at the ANCRE (Alliance Nationale de Coordination de la Recherche pour l'Energie), in the biomass committee. He is member of the ADT (Technological Development Actions) at INRIA.

M. Chaves is the coordinator of 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 charged with evaluating Inria's Associated Teams as well as some project proposals (EuroMed 3+3), and ERCIM post-docs.

F. Grognard is a member of the NICE committee, which allocates post-doctoral grants and fundings for visiting scientists at INRIA Sophia Antipolis.

9.2. Scientific popularisation - media

The Shamash project and the activities related to microalgae have generated many articles and broadcasts in the media: The most important newspapers are "Le Monde" (La recherche francaise pour les carburants extraits de microalgues, 24th-25th July, 2011),"Nice matin" (Des algues au coeur de l'OIN), "20minutes" 'Des chercheurs azuréens veulent mettre des algues dans votre moteur, October, 27th 2010), etc.

P. Bernhard has taken a large part in the "culture scientifique" program of INRIA, towards the public at large and also more specifically aimed at high school pupils. In this program, he gave conferences on optimal foraging theory, evolutionary biology, game theory, Wardrop equilibrium and Braess Paradox in road trafic and behavioural ecology, at Lycée Aubanel, Avignon, (February 3, 2 conferences), Lycée Amiral de Grasse, Grasse, (March 18), Lycée Audiberti, Antibes (May, 10) Lycée Simon Veil, Valbonne-Sophia Antipolis, (May 23) Lycée Matisse, Vence, (October 11, 2 conferences) and Lycée Marcel Pagnol, Marseille, (Nov 10). He also hosted highschool pupils at INRIA (June, 30, 2 conferences), hosted students from "classes préparatoires" at INRIA to help them set up their "Travaux d'Initiative Personnelle Encadrés" (December 9), and gave a conference to highschool maths teachers in a program ran by INRIA to help them embrace new highschool programs in computer sciences (January 26).

In another science popularization program, he gave a conference at Cannes Université (March 9) on "Mathematics in every-day life".

At the request of Fondation Sophia Antipolis, he gave a conference to Bahrain students visiting Sophia Antipolis (July 19) on "The role of mathematical modelization for the decision makers: the example of the Braess paradoxe in road trafic".

As president of PERSAN (Pôle Enseignement Recherche de Sophia Antipolis et Nice) until March, 2011, he organized together with Pascale Limozin the "Printemps des Chercheurs" in Grasse, (May 21-22)

After he left the chairmanship of Persan, he was named by the new chairman to (continue to) represent PERSAN at the Scientific Board of the "(Syndicat de préfiguration du) Parc Naturel Régional des Préalpes d'Azur".

9.3. Teaching

9.3.1. *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.

> Mickael Teixeira Alves (25 ETD) "Mathématiques pour la Biologie", L1 Life Sciences, University of Nice - Sophia Antipolis, France.

> F. Grognard (45.5h ETD) and L. Mailleret (26h ETD), "Equation différentielles ordinaires et systèmes dynamiques", 1st year Engineering in Modelling 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 Modelling and Applied Mathematics (eq. M1), Polytech'Nice, Université of Nice Sophia Antipolis, France.

O. Bernard (9h ETD), J.-L. Gouzé (9h ETD), F. Grognard (4.5h ETD), P. Hartmann (7.5h 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.

M. Chaves (18h ETD), X.-D. Li (8h ETD), "Modelling biological networks by ordinary differential equations", 4th year students, Génie Biologie, Ecole Polytechnique University of Nice - Sophia Antipolis, France.

M. Chaves (9h 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, France.

O. Bernard supervised two projects for engineer school students. The first project involved 10 students of Ecole Nationale Supérieure des Mines de Paris (last year of engineering school, 1 week, "Modelling temperature evolution in microalgal growth process") and the second project involved 4 students from the Ecole Centrale de Paris (first year of engineering school, 4 months, developing a simulator to predict algal growth in a culturing device; Solutions to regulate temperature".

M. Chaves and J.-L. Gouzé have prepared (jointly with the other teachers) a book chapter entitled "Modeling and analysis of gene regulatory networks" on the topics taught in the course Computational Biology, to appear in a Springer volume [53].

9.3.2. *Theses*

PhD in progress : J. Rault, "Modélisation mathématique du plancton, structuré en taille. Conséquence sur la séquestration du carbone dans l'océan", since september 2008, UNSA. Supervisors: E. Benoît and J.-L. Gouzé.

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. Supervisor: F. Grognard and L. Mailleret.

PhD in progress : P. Hartmann, "'Développement d'un modèle de photoadaptation phytoplanctonique", 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 : Frédéric Hamelin and Didier 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, "Modelling the coupling of microalgae with anaerobic digestion", since September 2011, U.Montpellier 2. Supervisors: J.-P. Steyer and O. Bernard.

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

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

9.3.3. *Participation in PhD juries*

O. Bernard is in the thesis committee of J. Mailier (Université polytechnique de Mons), P. Collet (University of Montpellier), Sofiane Mazeghrane (University of Montpellier).

J.-L. Gouzé was referee for the thesis of Yassin Refahi (Université Montpellier 2, Informatique) "Multi-scale modelling of Arabidopsis thaliana phyllotaxis perturbation"; referee for the thesis of Ihab Haidar, (Université Montpellier 2 (Mathématiques Appliquées)), "Dynamiques microbiennes et modélisation des cycles biogéochimiques terrestres" ; he was in the jury of the thesis of Flora Cordoleani (Université Aix-Marseille (Océanographie)) "Représentation de la réponse fonctionnelle dans un modèle prédateur-proie : du chemostat à l'écosystème " ; the thesis of Gustavo Olivera-Botello (Université Claude Bernard Lyon 1, Modélisation), "Modélisation numérique des aspects immunologiques de la réaction à l'infection à HPV et de la vaccination anti-HPV par Gardasil" ; the thesis of Roukaya Keinj (Université Nancy I, Mathématiques Appliquées) "Modélisation de la croissance d'une tumeur après traitement par radiothérapie".

M. Chaves attended the meeting for the 3rd year of the thesis of F. Fourré (University of Luxembourg).

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 Cluster of Excellence "Tailor-Made Fuels from Biomass", Aachen, Germany (January, 24th, 2011). and at the IFP School " Microalgae: towards a new generation of biofuel ? ", Rueil-Malmaison, France (January, 17th, 2011). O. Bernard was invited to give a conference on the Green Stars Institute for Decarbonated Energy at the French ambassy , London, UK (December, 9th, 2011).

M. Chaves was invited to make a presentation at SontagFest to celebrate Eduardo Sontag's 60th birthday: "DIMACS Workshop on Perspectives and Future Directions in Systems and Control Theory" (Rutgers University, NJ, US, May 2011). She was also invited to make a presentation at the workshop "Formalisme logique, apports et défis pour la modélisation de réseaux de régulation biologique", (Rabat, Morocco, April 2011).

J.-L. Gouzé gave two talks at the meeting of the SFBT (Autrans May 2011)

P. Bernhard was invited to give a talk in the Epistemology seminar of Nice-Sophia Antipolis University : "Réflexions éparses sur l'Automatique, la théorie des jeux et le vivant".

10. Bibliography

Major publications by the team in recent years

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[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.

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