INRIA

Project-Team Comore

Modeling and control of renewable resources

Sophia Antipolis - Méditerranée

Theme : Observation, Modeling, and Control for Life Sciences

Activity Report

2010

Table of contents

Comore is a joint research team between INRIA (Research Unit of Sophia-Antipolis, France) and CNRS (Laboratory of Biological Oceanography and Marine Plankton Ecology, UMR 7093/ Université P.M. Curie, Villefranche sur Mer, France).

1. Team

Research Scientists

Jean-Luc Gouzé [Team leader, Senior Researcher INRIA, HdR]

Antoine Sciandra [Senior Researcher CNRS UMR 7093, Villefranche-sur-Mer, part time, HdR]

Olivier Bernard [Senior Researcher INRIA, HdR]

Frédéric Grognard [Junior Researcher INRIA]

Madalena Chaves [Junior Researcher INRIA]

Pierre Bernhard [Senior Researcher INRIA emeritus, HdR]

External Collaborators

Ludovic Mailleret [Junior Researcher, INRA]

Eric Benoît [Professor, Université de La Rochelle, HdR]

Jean-Philippe Steyer [Senior Researcher, INRA]

Technical Staff

Fabien Dilet [until November]

Olivier Calabro [from February until November]

Eric Pruvost [ACET, ANR funding, March-September]

PhD Students

Sapna Nundloll [INRIA funding, UNSA, until February]

Ibrahima Ndiaye [MESR funding, UNSA, until January]

Pierre Masci [MESR funding, UNSA, until September]

Jonathan Rault [MESR funding, UNSA]

Mickaël Teixeira-Alves [INRA-INRIA funding, UNSA]

Thomas Lacour [MESR funding, Université P.M. Curie, part time until October]

Alfonso Carta [ANR funding, UNSA, since December]

Philipp Hartmann [MESR funding, UNSA, since August]

Post-Doctoral Fellows

Diego Oyarzún [Hamilton Institute, Marie Curie Fellowship, February-July]

Xiao Dong Li [INRIA funding, from October]

Andrei Akhmetzhanov [INRIA funding]

Wassim Abou Jaoudé [INRIA funding, until November]

Francis Mairet [ANR funding, until December]

Thomas Lacour [Salinalgue funding, since November]

Nina Moelants [ANR funding, since October]

Administrative Assistant

Stéphanie Sorres [TR, part time]

Others

Aline Dannappe [UTC student intern, until February]

Cédric Adam [ENSTA ParisTech student intern, May-August]

Gaëlle Drouot [ENSTA ParisTech student intern, May-August]

Raphael Madeleine [UNSA student intern, until February]

Federica Spiriti [UNSA student intern, until February]

Mohamed Machat [Enit Tunis student intern, March-May]

Lorenzo Baldacchini [UNSA student intern, March-August]

Nacer Bouhireb [ENIT Tunis student intern, April-September]

Aurore Lebrun [EPU student intern, July-September]
Elodie Girard [INSA Lyon/CIRAD student intern, April-August]

2. Overall Objectives

2.1. Overall objectives

Comore is a joint research team between INRIA (Research Unit of Sophia-Antipolis, France) and CNRS (Laboratory of Biological Oceanography and Marine Plankton Ecology, UMR 7093/ Université P.M. Curie, Villefranche sur Mer, France, Team: Plankton Dynamics, Physical and Chemical Processes).

The endeavor of Comore is to develop and apply methods from control theory (feedback control, estimation, identification, optimal control) and from dynamical systems theory, to the mathematical modelling of living exploited resources (renewable resources) and their management. We apply and validate our results to various fields: phyto- and zooplankton growth, bioprocesses, pest control, fisheries, cell models...

Research themes:

Methodology:

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

Fields of application:

- Modelling and control of the growth of marine phytoplankton: phytoplankton is the basis of food chains in oceans (fishes, etc), and plays a key role in the carbon cycle. In Villefranche-sur-Mer, we develop a fully automated chemostat (open bioreactor where cells grow) which is managed by computers for that objective.
- Modelling, estimation and control of bioreactors: the bioreactors have a growing importance in many domains related to the human environment: food (production), pharmaceuticals (production of medicines), environment (wastewater treatment), etc.
- Dynamics and control of ecosystems: we build models for ecosystems (insects, fishes, zooplankton) and try to achieve optimal regulation.
- Modelling of metabolic and genetic networks: we study the dynamical behavior of regulation networks in cells.

Software for biological modelling.

National, international and industrial relations

- Collaboration with IFREMER (Nantes), INRA (MIA Montpellier, LBE Narbonne, GMPA Grignon, URIH Sophia-Antipolis), CIRAD Montpellier, Centre d'Océanologie de Marseille, LOCEAN (Paris), GIPSA Grenoble, IBIS and MERE INRIA teams.
- Participation in the French groups CoReV (Modèles et théories pour le Contrôle de Ressources Vivantes, Models and Control of Living Resources) and M3D (Mathématiques et décision pour le développement durable).
- Université Catholique de Louvain (Belgium), University of Marrakech (Marocco), Faculté Polytechnique de Mons (Belgium), University of Stuttgart (Germany), Rutgers University (USA), MacMaster University (Canada).
- ANR *Blanc* project Gemco
- ANR *PNRB* project Shamash and ANR *Bioénergie* project Symbiose.

2.2. Highlights

- Comore developed a theoretical analysis of the mechanisms at the origin of birhythmicity, i.e., the coexistence of two oscillatory regimes for the same external conditions, a complex dynamical behavior which is present in some chemical and physiological phenomena. This study is accepted in PLoS One, an open-access journal dedicated to a general audience in biological/medical research.

- We developed a model to predict the methane productivity of an anaerobic digester fed with microalgae. The model predicts the fate of the microalgal carbon (transformed into CO_2 and methane) and nitrogen (remineralized into ammonium). It has been validated experimentally with experiments carried out at the LBE-INRA. This model with be the basis for an optimisation strategy in the framework of the Symbiose project.

- This year has seen the defense of four PhD. theses in the Comore project-team. These theses epitomize the progresses made by the team in the different research directions it pursues: experimental [11] and theoretical [12] study of microalgae growth for biofuel production, study of metabolic and genetic regulatory networks models [13] and optimization of augmentative biological control [14].

3. Scientific Foundations

3.1. Scientific Foundations

Comore is interested in the mathematical modelling of biological systems, more particularly of ecosystems subject to a human action; the framework is thus that of renewable resources. It is now clear that it is important to understand how these complex dynamical systems work in order to regulate the exploitation of such resources by man. Our framework 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). The systems that we consider are, mainly, ecosystems, that we generally model through a set of differential equations. The variables are, for example, the size or the density of populations. The inputs can be actions exerted on the ecosystem: e.g. action of man (fishing effort, introduction of food, etc), or action of an external factor (pollution, light, etc). 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).

The Control Theory approach begins with the mathematical modelling of the system. This stage is fundamental and difficult, because one does not have rigorous laws as it is the case in physics. We develop techniques to identify and validate the structure of a model from a set of available noisy measurements: qualitative analysis of the data (extrema, relative position,...) is used to build a model which is able to reproduce the same qualitative pattern. We also work on methods that are dedicated to the identification of the mathematical functions that link the dynamics of a state variable to other variables. Finally, we verify that the model satisfies some biological constraints: for example the concentrations must remain positive or some mass balance relationship must be satisfied. A fundamental problem is the validation, or invalidation, of these models: how to accept, with a certain precision, a model by comparing it with noisy experimental data ? The traditional approach, which consists in identifying the parameters of the model by minimizing a criterion of variation between the outputs of the model and the data, is often inefficient. We are developing new methods that are more relevant experimentally.

Having built a model that synthesizes the behavior of such a complex nonlinear biological system, we can now study its properties and understand the way it works. However, specific problems are posed by the biological origin of the models: functions or parameters are uncertain, or unknown. The quantitative conclusions that we can draw are therefore limited. One then seeks to study the qualitative behavior of the system, the existence of equilibria, their stability, the existence of periodic solutions... Answers to these qualitative questions are fundamental because they tell us whether or not the system is viable (does the model predict the extinction of any species, etc). Answers can often be found, in particular when the models have a strong structure belonging to a general class of systems, for which one develops adjusted techniques: for example the well-known Lotka-Volterra models in dimension n, describing the interactions between n species.

Once the dynamics of the considered living system have been understood we consider problems of regulation: how to maintain a variable at a given level. This is important, for example, in the framework of wastewater treatment where the tolerated pollution levels are determined by governmental laws. The main problem that we have to address is the control of a complex system when the model is uncertain. We mainly work on one class of biological systems, the bioreactors, that have a growing importance in many domains related to the human environment: food (production), pharmaceuticals (production of medicine), environment (wastewater treatment, plankton study), etc. The strong structure of these systems, for which the hydraulic flow plays an important role, is used in order to derive controllers.

Finally, we develop observers that use the model and on-line measurements to asymptotically estimate the variables that are not directly measured. These so called "software sensors" help monitoring some systems and replace some expensive measurements. For the design of such observers, we are faced with uncertainties that are specific to biological modelling: the model is uncertain (parameters, functions) while the inputs can also be affected by disturbances and the outputs highly variable. Therefore, we have to deal with these uncertainties in the design of observers. We have developed robust observers that assume that some parameter or input belongs to a given interval. The observer then asymptotically estimates intervals for the state variables. Other estimators are also considered.

The methods developed by our group are validated and tested on several applications.

4. Application Domains

4.1. Application Domains

In our work, applications are not clearly separated from methodology elements: often, "applications" raise methodological questions which can give rise to fundamental research problems for biology; as mentioned in the above section, we consider and analyze such questions, also in collaboration with biologists.

Modelling of Marine Plankton growth

This part of the work takes place at the Station Zoologique of the CNRS (Villefranche-sur-Mer, France), where we have developed a fully automated, computer driven, set of chemostats (continuous bioreactors where microalgae are growing). This system is particularly well suited to the application of methods resulting from control theory. Our current work consists in designing, studying and validating models of phytoplankton growth in a variable environment (light, nutrients, etc). Phytoplankton is the basis of the oceanic food web (zooplankton, fishes, etc). The existing traditional models (Monod, Droop) are often unsatisfactory and do not reproduce observed features well. We seek to obtain models which are valid during the transitory stages, far from the usually considered steady state conditions that are rarely reached in the sea. For the zooplancton, a size-structured model is considered, governed by predation. These two models are then incorporated in hydrodynamic models or models for the whole food web in order to predict the carbon fluxes within the ocean and at the interface between ocean and atmosphere.

Wastewater Treatment Processes

In collaboration with the Laboratory of Environmental Biotechnology of INRA (Narbonne, France), we work on anaerobic treatment plants. We build dynamical models that can reproduce the behavior of the system in standard operating mode and in degraded working modes (after a failure). Since only few on-line measurements are available, we design robust observers that take the large uncertainties encountered in this field into account and predict the internal state of the process. As an example, the concentration of influent organic matter to be treated, which is an important input, is rarely measured. The software sensors are used to monitor the processes and to help detecting failures.Control laws are build for the outputs of the wastewater to satisfy regulation policies and for the reactor to behave optimally.

Bioenergy

Finding sources of renewable energy is a key challenge for our society. We contribute to this topic in two main domains. First, we are working to improve the efficiency of anaerobic digesters that produce methane and/or biohydrogen from organic carbon. The main difficulty is to make these processes more reliable and valorise more efficiently their biogas. The second topic consists in growing microalgae to produce biodiesel. 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.

Ecosystems and Fisheries

The scale of the problems changes here; data are rare and noisy. We consider some important methodological problems in collaboration with IFREMER Nantes: how to model the stock-recruitment relationship of the fish (the relationship between the number of fertile adults and eggs they produce). How does one optimize the exploitation of fisheries with respect to some criteria? How can we prevent undesirable oscillations of the fishing stock?

We also consider (with URIH, INRA Sophia-Antipolis) problems of biological control in crop protection (e.g. the introduction of ladybirds to control pests). We first consider the problem of reactive biological control: upon detection of the presence of pests in the greenhouse, we determine the quantity and timing of the release of their natural enemies to control this pest population. In another framework, we study prophylactic biological control: we determine the periodicity and quantity of natural enemies releases in order to prevent a pest outbreak in high-valued crops (such as roses).

Metabolic and genetic networks

This application has many links with our previous work: in fact, we consider large networks made of small biological nonlinear elements (metabolic network, genes network, ...) and are interested in methods enabling us to describe the dynamical behavior of the system. The classical methods of analysis are difficult to apply here, because the dimension of the networks is too large. Therefore, we search for methods that use qualitative information on the network (the linear substructure, the graph of the network, the monotonicity of interactions and/or the order of magnitude of the concentrations and the interactions) or we describe the system by only using "idealized" nonlinearities, such as step functions (the resulting piecewise linear system being more amenable to a qualitative description).

In parallel with the analysis of systems of large dimension, we are also interested in identifying fundamental mechanisms underlying the complex networks of cellular interactions. These may comprise several levels of regulation, such as metabolic, signaling or genetic regulatory systems. In particular, we are interested in finding and studying basic groups of elements and interactions (i.e. reduced models), that are responsible for a given observed dynamical behavior. For this approach, we use the tools of model reduction theory. The interconnections among various cell regulatory systems are also studied, for instance, how can metabolism be regulated and/or controlled by genetic networks. For this analysis we will use more qualitative methods, such as piecewise linear ordinary differential equations, in conjunction with techniques from control theory (interconnected systems, feedback loops, stability notions).

5. Software

5.1. 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 Comore. It has been implemented and validated with 4 different applications.

6. New Results

6.1. Methodology

6.1.1. Mathematical analysis of biological models

Participants: Jean-Luc Gouzé, Olivier Bernard, Frédéric Grognard, Madalena Chaves, Pierre Bernhard, Francis Mairet, Pierre Masci, Thomas Lacour, Andrei Akhmetzhanov.

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. The most efficient species, that is the one that requires the smallest substrate concentration in order to have a growth rate equivalent to the dilution rate, wins the competition. This observation has been validated through laboratory experiments [87]. This competitive exclusion principle was already demonstrated in the Monod and the Droop model with n species. By a qualitative study of projecting the evolution of all species densities on the substrate axis, we demonstrated that this principle still holds when species modelled by Droop, Contois and Monod models compete [92], [12].

Life history traits

In this work we study the evolution of a prey-predator system with seasonal character of the dynamics. We specify two main parts of the process. First, we consider the system during one season with a fixed length: the preys lay eggs continuously and the predators lay eggs or hunt the preys (choose their behaviour) according to the solution of an optimal control problem [65]. Secondly, we study the long-scale discrete dynamics over seasons. We investigate the qualitative behavior of the dynamics with respect to the parameters of the problem and show that, depending on the parameters of the model, extinction or co-existence of the predators and preys can be evidenced [65].

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 study the resulting optimal control problem where the mutants maximize their own number of offspring using the knowledge of the resident's behaviour, and show that, in most situations, mutants can 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 [31], [49], [66].

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. This problem requires the solution of a zero-sum differential game. In the process of this research, we have unearthed a new kind of singular arc in the computation of a non-invadable strategy (an ESS) with an infinite dimensional trait space (a control). In this singular arc, the singular control explicitly appears after a single differentiation of the switch function —the coefficient of the control in the hamiltonian [33], [53]; the resulting control leads to overexploitation of the resource so that it does not lead to a long term positive equilibrium: prevention leads to evolutionary suicide.

Populations expansion

Two directions have been pursued in the frameworks of internships. We have first considered the expansion of a population, say an invasive pest, in a patchy environment, and we have analyzed the influence of an Allee effect on the effectiveness of the expansion [58]. We have then analyzed how a mutation that occurs on the wave-front of a population in expansion can fix itself on the front even if the mutation is deleterious [60], this is the gene-surfing phenomenon.

Methods for qualitative analysis of genetic networks and model comparison

See Section 6.2.5 Metabolic and genomic models in the Fields of Application part.

Birhythmicity in the p53-Mdm2 network

See Section 6.2.5 Metabolic and genomic models in the Fields of Application part.

6.1.2. Model design, identification and validation

Participants: Olivier Bernard, Jean-Luc Gouzé, Madalena Chaves.

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 [71]. These systems can be represented by models having the general structure popularized by [69], [77], [78], 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 is presented. 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 matrix associated with the reaction network [70]. These methods lead to identifiability conditions on the pseudo-stoichiometric coefficients and provide a framework for their estimation. They have been improved in order to better filter noise using modulating functions [73]. This approach has been applied to various bioproduction processes, most recently on activated sludge processes [68], anaerobic digestion [84], [96] and anaerobic digestion of microalgae.

These approaches have been combined with neural networks, in order to better constrain the network design and to ensure that it keeps a realistic behaviour even far from the training data set [20].

Interaction between signaling and gene expression networks

See Section 6.2.5 Metabolic and genomic models in the Fields of Application part.

6.1.3. Nonlinear observers

Participants: Jean-Luc Gouzé, Olivier Bernard.

Interval observers

We designed so-called bundles of observers [74], [75] made of *a set of* interval observers. Each observer computes intervals in which the state lies, provided intervals for parameters and initial conditions (and more generally, all the uncertainties) are known. We then take the lower envelope of this set to improve the overall estimation.
The combination of the observers has also been improved in the case where various types of interval observers are run in parallel [89], and the approach has been applied to estimation of the microbial growth rate [22].

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 system. The interval estimation of the state variables are performed considering parameters uncertainties of the system and biased output [94]. These techniques have been improved by introducing a linear, time-varying change of coordinates. For some class of systems, this method allows the design of interval observers when it was not possible in the original basis [24]. This approach was then extended to n-dimensional linear systems, leading to the design of interval observers in high dimensions [42], [23].

6.1.4. Nonlinear control

Participants: Jean-Luc Gouzé, Olivier Bernard, Frédéric Grognard, Pierre Masci, Sapna Nundloll, Andrei Akhmetzhanov.

Control of competition in the chemostat

We have designed a closed loop control procedure for microorganisms in the chemostat [12] [91]. The objective is to select species with interesting characteristics in chosen environmental conditions [54]. In particular, by controlling the dilution rate and the input substrate concentration, it is possible to select a species which maximises a criterion. This selection method was adapted to a model of anaerobic digestion during its start-up phase [12] [90]. In such a model, we proposed controls which enable to select, among several hundred of species, the ones with maximum growth rate in the reactor steady state operating mode. A first experimental validation of this control strategy was done at the INRA-LBE Laboratory.

Mathematical study of impulsive biological control models

The global stability of the interconnection of a continuous prey-predator ODE model and periodic impulses has been studied. This work was motivated by the biological control of pests in a continuously grown greenhouse and was the center of Sapna Nundloll's thesis [14]. The prey-predator dynamics are continuous and are augmented by discrete components representing the periodic release of predators.

The influence of various parameters on the local and global stability conditions of the prey-free solution has been investigated. The most recent studies considered the effects of two types of intrapredatory interferences: Beddington-DeAngelis and squabbling interferences. The first one represents interference for the access to the prey and the second represents squabbling between the predators through the addition of a quadratic term to the predators mortality (which is otherwise linear). In both cases, we show that the minimal rate that ensures stability is increasing with the period of release [27]. This result has also been shown for a generalised form of the Beddington-DeAngelis interference [26].

This work has been done in collaboration with L. Mailleret (URIH, INRA Sophia-Antipolis).

Control of genetic regulatory networks

See Section 6.2.5 Metabolic and genomic models in the Fields of Application part.

6.1.5. *Evolutionary games*
Participants: Pierre Bernhard, Frédéric Grognard, Andrei Akhmetzhanov.

As an addition to our investigations in population dynamics and optimal control, we have embraced evolutionary games dynamics per se as one of our domains of investigation, adding Evolutionary Stable Strategies (ESS) and non-invadable strategies as equilibrium paradigms.

After characterizing ESS's as Wardrop equilibria (the so-called Nash property or "first ESS condition" of ESS's), we have provided a simple test for a matrix Wardrop equilibrium to actually be an ESS. In the same vein, we have also obtained a sufficient condition for the nonlinear theory. Because our main focus is on dynamic systems, we have developped this test in the infinite dimensional case [46] [97], [83].

It turns out that the theory of evolutionary games, born in the investigation of biological populations, has found many applications in other domains. This, together with our experience in mathematical economy, was the origin of more publications in networking theory, as joint investigations with our colleagues of the Maestro research project [15], [50]. Our paper [51] was in the ten most downloaded list of the network for several weeks in a row. It was expanded into the articles [29], [45].

As an outlet of earlier research in other applications of dynamical games, we obtained in a joint work with Guy Barles, of the university François Rabelais, of Tours, and Naïma El Farouq, of the university Blaise Pascal of Clermont-Ferrand, a new technical result concerning the uniqueness of viscosity solutions of some quasi-variational inequalities associated with minimax impulse control problems with zero infimal cost of the jumps, beyond the result mentioned lat year and appeared since as [18]. This was the object of two conference communications [32], [36]. This result had eluded us for years, and puts an end to the development of our theory of option hedging and pricing in an interval market model.

6.2. Fields of application

6.2.1. *Growth of marine plankton*
Participants: Olivier Bernard, Jean-Luc Gouzé, Antoine Sciandra, Thomas Lacour, Jonathan Rault.

Modelling phytoplankton cellular cycle

We have run experiments to observe the response of a population of microalgal cells to various periodic light/dark or nitrate signals. The measurements performed with the diatom *Thalassiosira weissflogii* show the synchronicity of the cells for some conditions. These experiments support the hypothesis that uptake of nitrogen stops during cell division [93]. 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. 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 [43].

Carbon fixation by coccolithophorids

A set of 18 models was developed and studied [80], [79] to describe the possible coupling between photo-synthesis and calcification for algae that are responsible for large carbon fluxes in the ocean. The qualitative study of this set showed that the standard hypotheses usually made by physiologists disagree with observed behaviours, since experiments have shown that an increase in the CO_2 partial pressure paradoxically leads to a decrease in the calcification rate.

Three of these models were included in an ocean model, including settling and predation by grazers, and a bloom of coccolithophorids was simulated [81], [82]. 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.

Experiments about the phytoplankton cellular cycle

We have run experiments to observe the response of a population of microalgal cells to various periodic light/dark or nitrate signals. The measurements performed with the diatom *Thalassiosira weissflogii* show the synchronicity of the cells for some conditions. These experiments support the hypothesis that uptake of nitrogen stops during cell division [93].

Growth models of zooplankton

The model built to describe zooplankton community is some variant of the McKendrick-Von Foerster Equation. The model includes cannibalism within zooplankton 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. Since the model incorporates lots of parameters, which are not always known in the literature, we have to use optimization techniques to find them. Further, equilibria of such models and their local stability is studied in using strongly the continuous semigroup approach. This work was the topic of a talk of J. Rault at the Third Conference on Computational and Mathematical Population Dynamics (CMPD3). We have also built a discrete size-structured model. The discrete models are less numerically demanding, are more easily incorporated into bigger models, and can more often be studied analytically.

This work has been done in collaboration with Eric Benoît (Université de La Rochelle).

6.2.2. *Modelling and optimization of lipid production*

Participants: Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Francis Mairet, Pierre Masci, Thomas Lacour, Andrei Akhmetzhanov.

In the framework of the ANR Shamash project, experiments have been carried out to study the effects of nitrogen limitation on the lipid production in a culture of microalgae (*Isochrysis affinis galbana*)[11]. We have proposed a new model for lipid production by microalgae which describes accurately the fate of the CO_2 incorporated during photosynthesis [39], [21]. 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.

On the other hand, a new dynamical model has been developed to describe microalgal growth in a photobiore-actor under light and nitrogen limitations [30], [40]. 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, photoadaptation [52] ...) 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 [41], yielding results emphasizing the importance of the optical depth of the reactor: growth and respiration must be equal at the bottom 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; biomass production is optimized over one day, with the constraint that the state of the system must be identical at the beginning and at the end of the day, so that operation can start again optimally for the next day [38], [59].

An other model has been developed to represent growth of microalgae colimited by nitrogen and phosphorus [16]. It has been shown, from qualitative analysis of the model that uptake of nitrogen and phosphorus are non symmetric in the sense that the phosphorus status intervenes in the nitrogen uptake rate. The model has been validated using experimental data for various species.

Finally, an analysis of the potential environmental impacts of biodiesel production from microalgae has been realised using the life cycle assessment (LCA) methodology [88]. This study has allowed to identify the obstacles and limitations which should receive specific research efforts to make this process environmentally sustainable.

6.2.3. *Coupling microalgae to anaerobic digestion*

Participants: Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Francis Mairet, Pierre Masci.

The coupling between a microalgal pond and an anaerobic digester is a promising alternative for sustainable energy production by transforming carbon dioxide into methane using light energy. The ANR Symbiose project is aiming at evaluating the potential of this process [99], [98][56].

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. 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 [100] (a reference model which considers 19 biochemical reactions) to represent the same dataset. This model 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 developped. The model is based on the three step model for anaerobic digestion, and on the photoacclimation model for microalgae [76]. The model also includes the modelling of heterotrophs in the microalgae pond.

6.2.4. *Models of ecosystems*

Participants: Jean-Luc Gouzé, Frédéric Grognard, Sapna Nundloll.

Biological control

With L. Mailleret (URIH, INRA Sophia-Antipolis), we have a collaboration about biological control. The studied problem consists in evaluating the effect of periodic release of predators and periodic harvest on the population of pests. We investigate the minimal predator-budget that should be invested in order to ensure pest eradication. The model proposed in [26] has been shown to be valid for a pest-natural enemy couple present in the greenhouses of INRA and the proposed strategy has been experimentally shown to be the most efficient. More details on the methodological aspects of this problem are given in Section 6.1.4, Nonlinear Control.

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 an optimal foraging framework so that the predator always chooses the prey that is instantaneously most profitable. We compared the effect that a static or a dynamic prey would have and noticed that, in an optimal foraging framework, apparent competition does not occur, so that the introduction of the alternative prey is always harmful (or neutral) for the biological control's efficiency when the predator prey dynamics are of the Leslie-Gower type. This work was the topic of a talk of M. Teixeira-Alves at the Third Conference on Computational and Mathematical Population Dynamics (CMPD3)

Fungi energy allocation

Models of energy allocation to growth and reproduction have been built and analyzed for spore-producing pathogens in the framework of the Mod-Pea project. A model showing that a bang-bang strategy is employed by necrotrophic pathogens has been developed: the fungi start by allowing the whole uptaken energy to growth of their mycellium before stopping growth and allowing everything to spore production (this result can currently be found in a chapter of A. Andanson's thesis [67] and was presented at the workshop Ecologie 2010). We have then built a model for biotrophic fungi, pathogens that keep their host alive in order to exploit it. This model shows that the pathogen should first invest the uptaken energy to growth until an optimal mycellium size is reached; at this moment energy should be split between spore production and mycellium maintenance. This result has been validated by experiments in C. Morineau's internship at INRA Nancy [95].

6.2.5. *Metabolic and genomic models*

Participants: Olivier Bernard, Jean-Luc Gouzé, Frédéric Grognard, Wassim Abou Jaoudé, Ibrahima Ndiaye, Madalena Chaves.

Dynamics of genetic regulatory networks

We are studying a class of piecewise affine dynamical systems (PWA), $\dot{x} = f(x) - g(x)x$, where x is a n-vector of protein concentrations, the vector $f(x)$ and matrix $g(x)$ are piecewise constant and represent synthesis and degradation rates respectively. Piecewise-affine systems form the basis of an important class of models used for genetic regulatory networks, where the regulatory interactions between the genes are approximated as step functions. The piecewise-affine models have the advantage that they are amenable to qualitative analysis and are well-suited to the qualitative character of the majority of experimental data from genetic regulatory networks. Current work in this project consists in continuing the work of Gouzé and Sari [86] and de Jong *et al* [101] by characterizing the equilibrium points and periodic orbits in this special class of systems. This year we have described and analyzed several systems made of feedback loops [61]. Moreover, larger and more realistic models for carbon growth of *E. coli* have been studied (thesis of I. Ndiaye [13]).

Periodic solutions of models of genetic regulatory networks

An important family of piecewise-affine systems consists of systems that have a negative loop involving all variables in their state transition graph. We have shown that this loop always corresponds to a unique, stable limit cycle [85].
Moreover, we have generalized this result to more complex interaction graphs (multiple intricate loops of any sign, multiple thresholds...). Our main result is an alternative theorem showing that, if a sequence of regions is periodically visited by trajectories, then under some hypotheses, there exists either a unique stable periodic solution, or the origin attracts all trajectories in this sequence of regions [19]. We used this property to control the appearance or disappearance of limit cycles by a qualitative control [37].

Control of genetic regulatory networks

Since recent biological techniques allow for the synthesis of more and more elaborate gene regulatory networks, it seems appropriate to develop control-theoretic methodologies for these networks. We have thus introduced new mathematical techniques for the control of piecewise-affine equations towards a prescribed behavior. Namely, we suppose that the piecewise constant terms $f(x)$ and $g(x)$ depend on an input vector u.

We elaborated on our previous work about control problems for this class of models, using also some recent results guaranteeing the existence and uniqueness of limit cycles (see above), based solely on a discrete abstraction of the system and its interaction structure. Our aim is to control the transition graph of the piecewise-affine system to obtain oscillatory behaviour, which is of primary functional importance in numerous biological networks. We show how to control the appearance or disappearance of a unique stable limit cycle by hybrid qualitative action on the degradation rates of the PWA system, both by static and dynamic feedback [37].

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 [35], 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 [55].

Transition probabilities for piecewise affine models

The dynamics of PWA models may be described through a discrete transition graph where the nodes are regular domains. We have studied a method for associating a *probability* of transition to each of the edges in the discrete transition graph, in terms of the parameters of the PWA model. If the transition probabilities between domains can be experimentally measured, this idea could be applied to estimate some of the model's parameters. In [47], the bistable switch example is analyzed, and in[34], this method is applied to a system composed of two negative feedback loops, to identify the sets of parameters that will lead to a given periodic orbit (several periodic orbits are possible, passing through different regions of state space).

Methods for qualitative analysis of genetic networks and model comparison

Different modeling formalisms have different advantages and provide distinct sources of knowledge on a given system. In [17] we compare piecewise-affine, discrete multi-valued models and Boolean models for a genetic network involved in the response of *E. coli* to carbon availability. A procedure is suggested to show that, under appropriate conditions, multi-valued discrete models can be written as strictly Boolean models. The advantage of a Boolean model for large systems is its tractability through graph theoretical and computational tools. Boolean models recover many of the properties of piecewise affine models (steady states, oscillatory orbits).

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 [44].

Global regulation of a metabolic chain

Gene expression can impact metabolic levels through changes in enzyme concentration and, conversely, metabolic species can influence gene transcription and hence modulate enzyme synthesis. To analyze these interactions, we have studied an unbranched metabolic chain (described by classical kinetic equations) with one metabolite acting as a global regulator of enzyme expression (described by PWA systems). Under the hypothesis that metabolic reactions happen in a faster time scale when compared to gene transcription or translation, we develop geometric criteria to characterize the equilibria (mono- or bi-stability) of the network [63].

Interaction between signaling and gene expression networks

8. Other Grants and Activities

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 Comore 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:** Comore 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 Comore 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.

- **Salinalgue:** Comore 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. Comore is in charge of lab scale experiments and of the modelling of the process.

- **GDR BioH2:** The objective of this GDR is the development of new biotechnological processes based on microorganisms producing hydrogen. Comore is taking part mainly in the modelling and control aspects of the H_2 production processes involving anaerobic bacteria or microalgae.

- **MetaGenoReg:** The objective of this project is to model and analyze the interaction between metabolic and genetic regulations, with the example of the carbon metabolism of E. coli. The project is funded by ANR (Systems Biology) and coordinated by D. Kahn (Helix, INRIA).

- **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 (Comore, 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 Comore is a partner with INRA Sophia Antipolis and INRA Avignon.

- **Mod-Pea:** Comore is a partner of the project "Dynamics and evolution of life history traits in plant pathogens and pests" that is funded by the Agropolis foundation. The group of partners of this project includes CIRAD Montpellier (BGPI), INRA Sophia Antipolis, INRA Nancy and Agrocampus Ouest.

- **TUMOSTAT:** This project "Modélisation de l'équilibre nutritionnel tumoral" is an INRIA Sophia Antipolis funded Color project between Comore and the Laboratoire J.-A. Dieudonné of CNRS-UNSA. The objective of this project is to model tumor growth in analogy with the chemostat: a competition between two different cell populations ("healthy" and "cancerous") feeding on the same substrate (glucose).

- **ERBARCÉ:** This Color project "Evolution des Résistances de Bio-Agresseurs au Cours de leur Expansion" brought together CIRAD Montpellier, INRA Avignon and Comore. It aimed at studying the expansion of invasive species in patchy or continuous environments, as well as the methods that can be used to counter this expansion.

- **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". Comore is taking part with CIRAD, INRA Sophia Antipolis and INRA Nancy.

- **RNSC:** Comore is taking part in the project "Dynamique de populations complexes" of the "Réseau National des Systèmes Complexes."

- **COREV:** Comore 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:** Comore 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.

- **Seminar:** Comore organizes a regular seminar "Modelling and control of ecosystems" at the station zoologique of Villefranche-sur-Mer or at INRIA.

8.2. Visits

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

- Ludovic Mailleret (INRA Sophia-Antipolis, France), external collaborator, once a week;

- Eric Benoît (Université de La Rochelle, France), external collaborator, once every two weeks;

- Benoit Chachuat (Imperial College, UK), 4 days

- Claude Aflalo (Ben Gurion University of the Neguev, Israel), 1 week;

- Hugh McIntyre (Univ. South Alabama, Dauphin Island, USA), 4 days.

- Gonzalo Robledo (Univ. du Chili, Chili), 7 days.

- Yves Dumont (CIRAD, France), 3 days;

- Suzanne Touzeau (INRA Jouy-en-Josas, France), 2 days.

8.3. Project-team seminar

Comore organized a 3-day seminar in November in Peyresq. 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", and CIFA 2010. He is a member of the board of the project-team committee at INRIA (Bureau du comité des projets) (until July), the co-head of 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".

O. Bernard represents INRIA at the ANCRE (Alliance Nationale de Coordination de la Recherche pour l'Energie), in the biomass committee.

M. Chaves is a member of CUMIR, the committee for the users of computer and internet ressources at INRIA Sophia Antipolis. 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 has generated many articles and broadcasts in the media: The most important newspapers are "Figaro" (Les microalgues : le carburant du futur, November, 30th, 2010), "20minutes" 'Des chercheurs azuréens veulent mettre des algues dans votre moteur, October, 27th 2010), "Le Figaro" (Les microalgues pour faire rouler les voitures, 7 janvier 2009), "'Les Echos'" (Bientôt des algues dans votre moteur ?, 13 janvier 2009), 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 a joint endeavour with Thierry Vieville, they set up a series of conferences at the Médiathèque d'Antibes.

As president of the PERSAN association, regrouping the higher education and research organisms of the Alpes Maritimes, P. Bernhard was in charge, with a big help from Pascale Limozin, of the organization of two events: the "Printemps des chercheurs", May 18 to 29, and the "Fête de la science", October 21–24.

P. Bernhard also gave some scientific popularization conferences : January 22 at the Médiathèque (inaugural conference of the series), March 31 in high school Audiberti (Antibes), June 1st in Centre International de Valbonne for students of the Classes Préparatoires aux Grandes Écoles, and July 27 in Sophia Antipolis for visiting students from Bahrain.

9.3. Teaching

J.-L. Gouzé, O. Bernard, F. Grognard gave two weeks of courses in November on mathematical models in biology at the Master on biological oceanography, Pierre et Marie Curie, Paris VI. J.-L. Gouzé (6h) and F. Grognard (3h+3h of clasworks) taught courses on dynamical systems and O. Bernard on identification (3h+6h classworks).

O. Bernard gave lectures at the Ecole Nationale Supérieure des Mines de Paris (3h) on bioenergy from microalgae. O. Bernard gave 12h lectures at the University of Santiago de Compostella (Spain) on advanced modelling, analysis and observation of bioprocesses.

M. Chaves (12 hours) and W. Abou-Jaoudé (8 hours, project) taught the course "Modelling biological networks by ordinary differential equations" at the Ecole Polytechnique University of Nice - Sophia Antipolis (Genie Biologie, 4th year students)

M Chaves and J.-L. Gouzé taught 6 hours each on the course "Discrete and continuous approaches to model gene regulatory networks", which is part of the new Master of Science in Computational Biology, at the University of Nice - Sophia Antipolis.

F. Grognard taught 18 hours of classes on modelling and control of biological systems to 4th year students in the MAM orientation (Applied Mathematics and Modelling - MAM4) of EPU and 13 hours of classes (+26 hours of classworks) on ordinary differential equations and dynamical systems for the MAM3 students at EPU.

P. Bernhard gave the inaugural lecture of an INRIA course for MBA students at the SKEMA business school. (October 1st "Game Theory and its Avatars : Economy, Transportation, Evolution")

J. Rault gave classes in mathematics (analysis) in the first year of the initial cycle of EPU (64h).

9.3.1. *Theses*

- Ongoing theses:
  1. J. Rault, "Modélisation mathématique du plancton, structuré en taille. Conséquence sur la séquestration du carbone dans l'océan", UNSA. Supervisors: E. Benoît and J.-L. Gouzé.

2. M. Teixeira-Alves, "Modélisation de réseaux écologiques dans un cadre de protection des cultures: applications à la lutte biologique", UNSA. Supervisor: F. Grognard.

3. P. Hartmann, "'Développement d'un modèle de photoadaptation phytoplanctonique'" UNSA. Supervisor: O. Bernard.

4. A. Carta, "Analysis and Control of models of biological regulatory systems. Application to growth control in E. coli", UNSA. Supervisors: J.-L. Gouzé and M. Chaves.

- Defended theses

    1. S. Nundloll, "Dos and don'ts in augmentative biological control: insights from mathematical modelling", UNSA, defended March 30th. Supervisor: J.-L. Gouzé (jury member); Advisors: F. Grognard and L. Mailleret (invited jury members).

    2. I. Ndiaye, "Méthodes d'analyse de modèles de régulation cellulaire", UNS, defended February 1st. Supervisor: J.-L. Gouzé (jury member); Advisor: M. Chaves (invited jury member).

    3. T. Lacour, "Influence du statut azoté et du cycle lumineux diurne sur le métabolisme lipidique d'Isochrysis sp", Université P.M. Curie, defended October 7th. Supervisors: A. Sciandra and P. Mayzaud. Jury member: O. Bernard.

    4. P. Masci, "Control and optimization of ecosystems in bioreactors for bioenergy production", UNSA, defended November 9th. Supervisors: O. Bernard and F. Grognard.

- Participation in PhD juries:

    J.-L. Gouzé was referee for the HDR of A. Iggidr, Université de Metz : "Analyse, observation et controle de certains bio-systèmes", and for the HDR of B. Laroche, "Identification et simplification de modèles dynamiques. Applications à la biologie".

    J.-L. Gouzé is in the thesis committee of Y. Refahi (Virtual Plants, Montpellier). M. Chaves is in the theses committees of S. Berthoumieux (INRIA Rhone-Alpes, Grenoble) and F. Fourré (University of Luxembourg)

    O. Bernard was in the PhD jury of Carlos Garcia Dieguez, Modelling and control of anaerobic wastewater treatment processes",March 18th, University of Santiago de Compostela

9.4. Conferences, invited conferences

Conferences with proceedings are not repeated here.

O. Bernard was invited to give a plenary talk for both conferences CAB and DYCOPS "'Hurdles and Challenges for Modelling and Control of Microalgae for CO2 Mitigation and Biofuel Production'", Leuven, July 7th.

O. Bernard was invited to give a conference on observers at the Ecole des Mines de Paris, (October 21st, 2010).

O. Bernard presented the Shamash project and its results at the AlgaSud conference in Montpellier (May 11, 2010).

O. Bernard organised a special session at the Adebiotec conference : "'Algues: filière du futur" (November 18th, 2010).

O. Bernard gave a talk at the 8th European Workshop on Biotechnology of microalgae, "'Hurdles and challenges to extrapolate microalgal TAG production from lab to field: towards reliable numerical predictions'", Nuthetal (DE) June 7th, 2010

F. Mairet gave a talk at the 8th European Workshop on Biotechnology of microalgae, "Modelling neutral lipid productivity in photobioreactors under nitrogen deprivency'", June 8th, 2010

M. Chaves was invited to make a presentation at the meeting of the "conseil scientifique" on bioinformatics of the INRA Jouy-en-Josas center (Paris, May 2010). She was also invited to give a seminar at the Institute for Systems Theory and Automatic Control, University of Stuttgart (Germany, June 2010).

J.-L. Gouzé and Jonathan Rault were invited to give talks at the annual meeting of ANR ANAR (La Rochelle, December). J.-L. Gouzé gave a talk at the meeting of the "Biointelligence" consortium (July 5, Sophia-Antipolis).

F. Grognard gave a talke at the REID Champignon meeting in Montpellier (November 26th), entitled "Quelques digressions sur l'évolution des stratégies d'histoire de vie dans les systèmes consommateurs-ressources".

Jonathan Rault, M. Teixeira-Alves and A. Akhmetzhanov gave presentations at the Third Conference on Computational and Mathematical Population Dynamics (CMPD3, Bordeaux, July 2010) on "Hopf bifurcation in some continuous size-structured model", "Optimal Foraging in Leslie-Gower Predator-Prey Models with Alternative Food" and "ESS versus cooperative behavior in a consumer-resource model", respectively.

A. Akhmetzhanov gave a talk on "ESS versus cooperative behavior in a consumer-resource model" at the Workshop on Game Theory for Finance, Social and Biological Sciences in Warwick, UK (April 2010) and a talk on "Games and Evolution" at the Summer School of the M3D Network in Roscoff (July 2010).

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.

[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.

[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.

[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° 75, p. 424-438.

[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.

[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.

[7] J.-L. Gouzé. *Positive and negative circuits in dynamical systems*, in "Journal Biol. Syst.", 1998, vol. 6, n° 1, p. 11-15.

[8] J.-L. Gouzé, A. Rapaport, Z. Hadj-Sadok. *Interval observers for uncertain biological systems*, in "Ecological modelling", 2000, vol. 133, p. 45-56.

[9] L. MAILLERET, O. BERNARD, J.-P. STEYER. *Nonlinear adaptive control for bioreactors with unknown kinetics*, in "Automatica", 2004, vol. 40-8, p. 1379-1385.

[10] L. MAILLERET, F. GROGNARD. *Global stability and optimisation of a general impulsive biological control model*, in "Mathematical Biosciences", 2009, vol. 221, n° 2, p. 91-100.

Publications of the year

Doctoral Dissertations and Habilitation Theses

[11] T. LACOUR. *Influence du statut azoté et du cycle lumineux diurne sur le métabolisme lipidique d'Isochrysis sp*, Université P.M. Curie, 2010.

[12] P. MASCI. *Control and optimization of ecosystems in bioreactors for bioenergy production*, Université de Nice-Sophia Antipolis, 2010.

[13] I. NDIAYE. *Méthodes d'analyse de modèles de régulation cellulaire*, Université de Nice-Sophia Antipolis, 2010.

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

Articles in International Peer-Reviewed Journal

[15] E. ALTMAN, P. BERNHARD, M. DEBBAH, A. SILVA. *Continuum Equilibria for Routing in Dense static Ad-hoc Networks*, in "Computer Networks", 2010, vol. 54, p. 1005–1018.

[16] G. BOUGARAN, O. BERNARD, A. SCIANDRA. *Modelling continuous cultures of microalgae colimited with nitrogen and phosphorus*, in "Journal of Theoretical Biology", 2010, vol. 265, n° 3, p. 443–454.

[17] M. CHAVES, L. TOURNIER, J.-L. GOUZÉ. *Comparing Boolean and piecewise affine differential models for genetic networks*, in "Acta Biotheoretica", 2010, vol. 58(2), p. 217-232.

[18] N. EL FAROUQ, G. BARLES, P. BERNHARD. *Deterministic minimax impulse control*, in "Applied Mathematics and Optimization", 2010, vol. 61, p. 353–378.

[19] E. FARCOT, J.-L. GOUZÉ. *Limit cycles in piecewise-affine gene network models with multiple interaction loops*, in "International Journal of Systems Science", 2010, vol. 41, n° 1, p. 119-130.

[20] A. KARAMA, O. BERNARD, J.-L. GOUZÉ. *Constrained Hybrid Neural Modelling of Biotechnological Processes*, in "International Journal of Chemical Reactor Engineering", 2010, vol. 8, A21.

[21] F. MAIRET, O. BERNARD, P. MASCI, T. LACOUR, A. SCIANDRA. *Modelling neutral lipid production by the microalga Isochrysis affinis galbana under nitrogen limitation*, in "Bioresource Technology", 2011, vol. 102, p. 142-149.

[22] F. MAIRET, M. MOISAN, O. BERNARD. *Interval observer-based estimator of specific growth rate in bioreactors*, in "Journal Européen des Systèmes Automatisés", 2010, vol. 44, n° 4-5, p. 493-507.

[23] F. MAZENC, O. BERNARD. *Interval observers for linear time-invariant systems with disturbances*, in "Automatica", 2010, to appear.

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

[25] I. NDIAYE, M. CHAVES, J.-L. GOUZÉ. *Oscillations induced by different timescales in signal modules regulated by slowly evolving protein-protein interactions*, in "IET Systems Biology", 2010, vol. 4(4), p. 263-276.

[26] S. NUNDLOLL, L. MAILLERET, F. GROGNARD. *Influence of Intrapredatory Interferences on Impulsive Biological Control Efficiency*, in "Bulletin of Mathematical Biology", 2010, vol. 72, n° 8, p. 2113-2138, http://dx.doi.org/10.1007/s11538-010-9531-6.

[27] S. NUNDLOLL, L. MAILLERET, F. GROGNARD. *Two models of interfering predators in impulsive biological control*, in "Journal of Biological Dynamics", 2010, vol. 4, n° 1, p. 102-114.

[28] M. SERHANI, J.-L. GOUZÉ, N. RAISSI. *Dynamical study and robustness for a nonlinear wastewater treatment model*, in "Nonlinear Analysis: Real World Applications", 2010, vol. 12, p. 487-500.

Articles in Non Peer-Reviewed Journal

[29] E. ALTMAN, P. BERNHARD, S. CARON, G. KESIDIS, S. WONG, J. ROJAS-MORA. *A study of non-neutral networks with usage-based prices*, in "Telecommunications and Regulated Industries eJournal", 2010, to appear.

Invited Conferences

[30] O. BERNARD. *Hurdles and challenges for modelling and control of microalgae for CO_2 mitigation and biofuel production*, in "Proceedings of the DYCOPS 2010 conference", Leuven, Belgium, 2010.

International Peer-Reviewed Conference/Proceedings

[31] A. AKHMETZHANOV, L. MAILLERET, F. GROGNARD, P. BERNHARD. *Join forces or cheat: evolutionary analysis of a consumer-resource system*, in "14th International Symposium on Dynamic Games and Applications", 2010.

[32] P. BERNHARD, N. EL FAROUQ. *A Robust Control Approach to Option Pricing: the Uniqueness Theorem*, in "EPSRC Symposium Workshop on game theory for finance, social and biological sciences", University of Warwick, GB, 2010.

[33] P. BERNHARD, F. GROGNARD, L. MAILLERET, A. AKHMETZHANOV. *ESS for life history of cooperating consumers facing cheating mutants*, in "14th International Symposium on Dynamic Games and Applications", Banff, Canada, 2010.

[34] M. CHAVES, E. FARCOT, J.-L. GOUZÉ. *Transition probabilities for piecewise affine models of genetic networks*, in "Proc. Int. Symp. Mathematical Theory of Networks and Systems (MTNS'10)", Budapest, Hungary, July 2010.

[35] M. CHAVES, J.-L. GOUZÉ. *Qualitative control of genetic networks: the bistable switch example*, in "Proc. IFAC Nonlinear Control Systems Symp. (NOLCOS'10)", Bologna, Italy, September 2010.

[36] N. EL FAROUQ, P. BERNHARD. *Option pricing with zero lower bound of impulse cost*, in "14th International Symposium on Dynamic Games and Applications", 2010.

[37] E. FARCOT, J.-L. GOUZÉ. *Qualitative control of periodic solutions in piecewise affine models of genetic networks*, in "Proc. IFAC Nonlinear Control Systems Symp. (NOLCOS'10)", Bologna, Italy, September 2010.

[38] F. GROGNARD, A. AKHMETZHANOV, P. MASCI, O. BERNARD. *Optimization of a photobioreactor biomass production using natural light*, in "Proceedings of the 49th IEEE CDC conference", Atlanta, USA, 2010.

[39] F. MAIRET, O. BERNARD, P. MASCI, T. LACOUR, A. SCIANDRA. *Modelling lipid production in microalgae*, in "Proceedings of the DYCOPS 2010 conference", Leuven, Belgium, 2010.

[40] F. MAIRET, M. TITICA, O. BERNARD, J. PRUVOST. *Coupling biological and radiative models to describe microalgal growth in a photobioreactor*, in "Proceedings of the 11th CAB conference", Leuven, Belgium, 2010.

[41] 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.

[42] F. MAZENC, O. BERNARD. *Interval observers for linear systems with additive disturbances*, in "Proceedings of the NOLCOS conference", Bologna, Italy, 2010.

[43] 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.

National Peer-Reviewed Conference/Proceedings

[44] I. NDIAYE, J.-L. GOUZÉ. *Unicité et stabilité globale de l'équilibre de modèles métaboliques réversibles*, in "Actes de la Conférence Internationale Francophone d'Automatique CIFA 2010", Nancy, France, 2010.

Scientific Books (or Scientific Book chapters)

[45] E. ALTMAN, P. BERNHARD, S. CARON, G. KESIDIS, J. ROJAS-MORA, S. WONG. *A Study of Non-neutral Networks with Usage-Based Prices*, in "Incentives, Overlays, and Economic Traffic Control", B. STILLER, T. HOSSFELD, G. D. STAMOULIS (editors), Lecture Notes in Computer Sciences, Springer, 2010, vol. 6236.

[46] P. BERNHARD. *ESS, Population games, replicator dynamics: dynamics and games if not dynamic games*, in "Advances in the Theory and Applications of Dynamic Games", M. BRETON, K. SZAJOWSKI (editors), Annals of the International Society of Dynamic Games, Birkhaüser, 2011, n° 11.

[47] J.-L. GOUZÉ, M. CHAVES. *Piecewise affine models of regulatory genetic networks: review and probabilistic interpretation*, in "Advances in the Theory of Control, Signals and Systems, with Physical Modelling", J. LÉVINE, P. MÜLLHAUPT (editors), Lecture Notes in Control and Information Sciences, Springer, 2010, vol. 407.

Research Reports

[48] W. Abou-Jaoude, M. Chaves, J.-L. Gouzé. *A theoretical exploration of birhythmicity in the p53-Mdm2 network*, INRIA, 10 2010, n⁰ RR-7406, http://hal.inria.fr/inria-00523270/en/.

[49] A. Akhmetzhanov, F. Grognard, L. Mailleret, P. Bernhard. *Join forces or cheat: evolutionary analysis of a consumer-resource system*, INRIA, Jun 2010, n⁰ RR-7312, http://hal.inria.fr/inria-00491434/en.

[50] E. Altman, P. Bernhard, G. Kesidis, J. Rojas-Mora, S. Wong. *A study of non-neutral networks*, INRIA, May 2010, http://hal.inria.fr/inria-00481702/en.

[51] E. Altman, P. Bernhard, G. Kesidis, S. Wong, J. Rojas-Mora. *A Study of Non-Neutral Networks*, Social Sciences Research Network, 2010, http://ssrn.com/abstract=1654306.

[52] L. Baldacchini. *Development of a model of photoadaption to predict CO2 flow and the accumulation of biolipides in fluctuating environment*, Université Nice Sophia-Antipolis, 2010.

[53] P. Bernhard, F. Grognard, L. Mailleret, A. Akhmetzhanov. *ESS for life-history traits of cooperating consumers facing cheating mutants*, INRIA, Jun 2010, n⁰ RR-7314, http://hal.inria.fr/inria-00491489/en.

[54] N. Bouhireb. *Mise au point d'un procédé de sélection des microalgues en vue d'optimiser des souches oléagineuses dans le cadre du projet Shamash*, Université de Caen Basse Normandie, 2010.

[55] M. Chaves, J.-L. Gouzé. *Exact control of genetic networks in a qualitative framework: the bistable switch example*, INRIA, HAL, 2010, n⁰ RR-7359, http://hal.archives-ouvertes.fr/inria-00507040/en/.

[56] A. Dannappe. *Méthanisation de biomasse algale : le projet Symbiose*, Université Technologique de Compiègne, 2010.

[57] G. Drouot, C. Adam. *Étude d'un modèle de croissance tumorale*, ENSTA, 2010.

[58] E. Girard. *Modélisation de la propagation de ravageurs dans des milieux fragmentés*, INSA Lyon, 2010.

[59] F. Grognard, A. Akhmetzhanov, P. Masci, O. Bernard. *Optimization of a photobioreactor biomass production using natural light*, INRIA, Sep 2010, n⁰ RR-7378, http://hal.archives-ouvertes.fr/hal-00516705/en/.

[60] A. Lebrun. *Modélisation de la propagation d'une mutation lors de l'expansion spatiale d'une population*, UNSA, 2010.

[61] M. Machat. *Analyse mathématique et numérique de réseaux de régulation génétique*, ENIT Tunis, 2010.

[62] R. Madeleine. *Étude d'un modèle de croissance tumorale*, EPU UNSA, 2010.

[63] D. A. Oyarzún, M. Chaves. *Global Gene Regulation in Metabolic Networks*, INRIA, HAL, 2010, n⁰ RR-7468, http://hal.archives-ouvertes.fr/inria-00541112/en/.

[64] F. SPIRITI. *Evolution of a population of cancer cells in a tissue*, UNSA, 2010.

References in notes

[65] A. AKHMETZHANOV, F. GROGNARD, L. MAILLERET. *Optimal life-history strategies in seasonal consumer-resource interactions*, in "Evolution", 2010, submitted.

[66] A. AKHMETZHANOV, L. MAILLERET, F. GROGNARD, P. BERNHARD. *Join forces or cheat: evolutionary analysis of a consumer-resource system*, in "Annals of the International Society of Dynamic Games", 2010, submitted.

[67] A. ANDANSON. *Evolution de l'agressivité des champignons phytopathogènes, couplage des approches théorique et empirique*, Nancy-Université, 2010.

[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] O. BERNARD, G. BASTIN. *Identification of reaction schemes for bioprocesses: determination of an incompletely known yield matrix*, in "Bioprocess and Biosystem Engineering", 2005, vol. 27, p. 293-302.

[71] 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.

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

[73] O. BERNARD. *Use of modulating functions for reaction network identification*, in "Proceedings of the 10th CAB conference", Cancun, Mexico, 2007.

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

[75] O. BERNARD, J.-L. GOUZÉ. *State estimation for bioprocesses*, in "Bioprocess Control", D. DOCHAIN (editor), Wiley, Hoboken, 2008.

[76] O. BERNARD, P. MASCI, A. SCIANDRA. *A photobioreactor model in nitrogen limited conditions*, in "Proceedings of the Mathmod 09 conference", Vienna, Austria, 2009.

[77] O. BERNARD, I. QUEINNEC. *Dynamic models of biochemical processes: properties of the models*, in "Automatic Control of Bioprocesses", D. DOCHAIN (editor), ISTE, 2006, chap. 2, p. 23-52.

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

[79] O. BERNARD, A. SCIANDRA. *Generic analysis of the response of calcifying microalgae to an elevation of pCO_2 : qualitative vs quantitative analysis*, in "ARIMA", 2008, vol. 9, p. 57-84.

[80] 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.

[81] 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° 3, p. 5339–5372, http://www.biogeosciences-discuss.net/6/5339/2009/.

[82] 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.

[83] P. BERNHARD. *Nonzero-sum dynamic games in the management of biological systems*, in "Third International Conference on Game Theory and Managment", Sankt Petersburg, Russia, 2009.

[84] 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.

[85] E. FARCOT, J.-L. GOUZÉ. *Periodic solutions of piecewise affine gene network models: the case of a negative feedback loop*, in "Acta Biotheoretica", 2009, vol. 57(4), p. 429-455.

[86] J.-L. GOUZÉ, T. SARI. *A class of piecewise linear differential equations arising in biological models*, in "Dynamical systems", 2002, vol. 17, p. 299–316.

[87] S. HANSEN, S. HUBBEL. *Single-nutrient microbial competition*, in "Science", 1980, vol. 207, n° 28, p. 1491-1493.

[88] 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.

[89] F. MAIRET, O. BERNARD. *Coupling framers to get enhanced interval observers. Application to growth rate estimation in a photobioreactor*, in "Proceedings of the 48th CDC conference", Shangai, China, 2009.

[90] P. MASCI, O. BERNARD, F. GROGNARD, E. LATRILLE, J.-B. SORBA, J.-P. STEYER. *Driving competition in a complex ecosystem: application to anaerobic digestion*, in "Proc. of the 10th ECC conference", Budapest, Hungary, 2009.

[91] 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.

[92] P. MASCI, F. GROGNARD, O. BERNARD, E. BENOÎT. *Theoretical study of the competition for substrate between N microorganism species*, in "Mathematical Biosciences and Engineering", 2010, submitted.

[93] C. MOCQUET. *Interférence entre les processus mitotiques et la prise d'azote chez Thalassiosira weissflogii. Implications en modélisation et sur les flux globaux*, Université Paris VI, 2009.

[94] M. MOISAN. *Synthèse d'observateurs par intervalles pour des systèmes biologiques mal connus*, Université de Nice Sophia–Antipolis, 2007.

[95] C. MORINEAU. *Dynamique d'infection paraistaire chez les plantes: confrontation des approches empiriques et par modélisation. Etude du couple Melampsora larici-populina/peuplier.*, Agroparistech/INRA Nancy, 2010.

[96] 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.

[97] A. SHAIJU, P. BERNHARD. *Evolutionarily Stable Strategies: Two Nontrivial Examples and a Theorem*, in "Advances in Dynamic Games and their Applications (also in 12th International Symposium on Dynamic Games and Applications, Sophia Antipolis, France, 2006)", P. BERNHARD, V. GAITSGORY, O. POURTAL-LIER (editors), Annals of the International Society of Dynamic Games, Birkhaüser, 2009, n⁰ 10, p. 377–398.

[98] 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.

[99] 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, n⁰ 09/50334.

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

[101] H. DE JONG, J.-L. GOUZÉ, C. HERNANDEZ, M. PAGE, T. SARI, J. GEISELMANN. *Qualitative simulation of genetic regulatory networks using piecewise-linear models*, in "Bulletin of Mathematical Biology", 2004, vol. 66, n⁰ 2, p. 301-340.