



INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

*Project-Team COMORE*

*Modelling and Control of Renewable  
Resources*

*Sophia Antipolis - Méditerranée*

THEME BIO

*Activity*  
*R* *eport*

2007



## Table of contents

<b>1. Team</b>	<b>1</b>
<b>2. Overall Objectives</b>	<b>1</b>
2.1. Overall objectives	1
2.2. Highlights of the year	2
<b>3. Scientific Foundations</b>	<b>3</b>
<b>4. Application Domains</b>	<b>4</b>
<b>5. Software</b>	<b>5</b>
<b>6. New Results</b>	<b>6</b>
6.1. Methodology	6
6.1.1. Mathematical study of models	6
6.1.2. Model design, identification and validation	7
6.1.3. Nonlinear observers	8
6.1.4. Nonlinear control	8
6.2. Fields of application	9
6.2.1. Growth of marine plankton	9
6.2.2. Bioprocesses	10
6.2.3. Models of ecosystems	10
6.2.4. Metabolic and genomic models	11
6.3. Software design	12
<b>7. Contracts and Grants with Industry</b>	<b>12</b>
<b>8. Other Grants and Activities</b>	<b>13</b>
8.1. National initiatives	13
8.2. European initiatives	13
8.3. Visits	14
<b>9. Dissemination</b>	<b>14</b>
9.1. Leadership with scientific community	14
9.2. Teaching	15
9.3. Conferences, invited conferences	16
<b>10. Bibliography</b>	<b>16</b>



# 1. Team

*COMORE is a joint research team 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).*

## **Head of project-team**

Jean-Luc Gouzé [ DR Inria, HdR ]

## **Administrative assistant**

France Limouzis [ AI, part time ]

Stéphanie Sorres [ AI, part time ]

## **Staff members (INRIA)**

Olivier Bernard [ DR Inria, HdR ]

Madalena Chaves [ CR Inria ]

Frédéric Grogard [ CR Inria ]

## **Staff members (CNRS)**

Antoine Sciandra [ DR UMR 7093, Villefranche-sur-Mer, part time, HdR ]

## **Post-Doctoral fellows**

Laurent Tournier

Etienne Farcot [ until march ]

Serena Esposito [ since july ]

## **Ph. D. students**

Marcelo Moisan [ Conicyt (Chili)-INRIA funding, UNSA ]

Jonathan Hess [ Ademe-Regional funding, UNSA ]

Christophe Mocquet [ MESR funding, Université P.M. Curie, part time ]

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

Sapna Nundloll [ INRIA funding, UNSA ]

Ibrahima Ndiaye [ MESR funding, UNSA ]

Pierre Masci [ MESR funding, UNSA, since september ]

Pedro Ascencio [ Conicyt (Chili)-INRIA funding, UNSA, february-april ]

## **Temporary engineer**

Romain Primet

Bruno Sialve [ since february ]

## **Student interns**

Pierre Masci [ EPU, april-august ]

Aurélie Gentil [ IAE Aix-en-Provence, may-october ]

Hamad Hazim [ UNSA, june-september ]

## **Visiting scientist**

Eric Benoît [ Université de La Rochelle, délégation since september ]

Andrei Akhmetzhanov [ INRIA funding, Moscow Institute of Physics and Technology, since october ]

# 2. Overall Objectives

## 2.1. Overall objectives

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: phytoplankton growth, bioprocesses, pest control, fisheries, cell models...

Comore is a common research team with the CNRS, UMR 7093, Team: Analysis and Simulation of the Functioning of Ecosystems (Station Zoologique, Villefranche sur Mer).

**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: we develop a fully automated chemostat (open bioreactor where cells grow) which is managed by computers. The phytoplankton is the basis of food chains in the oceans (fishes, etc), and plays a key role in the carbon cycle.
- 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, of fisheries: we build models for ecosystems (insects, fishes) 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 (BIA Montpellier, LBE Narbonne, GMPA Grignon, URIH Sophia-Antipolis), Centre d'Océanologie de Marseille, LODYC (Paris), LAG Grenoble, HELIX and MERE INRIA teams.
- Participation in the French group CoReV (Modèles et théories pour le Contrôle de Ressources Vivantes, Models and Control of Living Resources).
- Collaboration with Ecole Polytechnique de Montréal (Canada), Université Catholique de Louvain (Belgium), University of Marrakech (Marocco), Ecole Polytechnique de Mons (Belgium).
- European project Hygeia.
- ANR Biosys project Metagenoreg.
- ANR PNRB project Shamash

## 2.2. Highlights of the year

- The ANR Shamash project was in focus on an AFP News report (February 2007), seizing the attention of the media with its innovative ideas for biofuel production. News reports appeared in almost all national newspapers and all TV evening news, creating quite a stir on the national mediatic front. The Shamash project (<http://www-sop.inria.fr/comore/shamash/>) studies the possible production of biofuel by microalgae and its scientific head is Olivier Bernard. The contribution of Comore to this goal will consist in modelling the oil production by microalgae and then defining the optimal conditions for the maximization of oil production.

- Jonathan Hess defended his PhD thesis dedicated to modelling and control of the biogas quality produced by an anaerobic digester. One of the key results of this thesis is a control strategy for the regulation of biogas quality suitable for cogeneration. A patent application for this result is currently in progress.
- Marcelo Moisan defended his PhD thesis dedicated to robust observer design for bioprocesses. He proposed new and innovative methods to strongly improve the interval estimates of state variables. The efficiency of these new algorithms were tested and validated on applications ranging from chaotic systems to anaerobic digestion processes.

## 3. Scientific Foundations

### 3.1. Scientific Foundations

**Keywords:** *biological models, bioreactors, cell models, dynamical systems, ecosystems, environment, nonlinear control theory, optimization.*

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 conceptual framework is Control Theory: a 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. 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 for the experimentalists.

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 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

**Keywords:** *biological models, biological networks, bioreactors, cell models, ecosystems, environment, plankton growth, wastewater treatment.*

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. These 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 activated sludge wastewater treatment plants and 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.

#### *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?

We also consider (with INRA) problems of biological control in a greenhouse (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, and/or the monotonicity of 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 have developed software focusing on three objectives:

*Modelling*: software has been developed as a tool for modelling, in order to help biologists or modelers, and emphasis is made on the interaction with the user. We also build more pedagogical software, aiming at demonstrating some issue of modelling or control.

*Data acquisition*: we have developed an innovative Java software (SEMPO) aiming at the coordination of several computers acquiring experimental data on line and monitoring experimental devices. This software is applied to the automated chemostat in Villefranche-sur-Mer.

*Control:* software has been developed for smart management of bioreactors (data acquisition, fault diagnosis, control algorithm,...). This platform, named ODIN, is developed in C++ and uses a Scilab engine to run the advanced algorithms developed within COMORE.

## 6. New Results

### 6.1. Methodology

#### 6.1.1. Mathematical study of models

**Keywords:** *biological models, dynamical systems.*

**Participants:** Jean-Luc Gouzé, Olivier Bernard, Frédéric Grognard, Madalena Chaves, Jonathan Hess, Pierre Masci, Laurent Tournier.

##### *Study of structured models of cell growth*

We have developed a small structured mathematical model aiming at a macroscopic description of the whole cell population during its cycle, taking the total number or the total biomass of cells into account. This model is structured with respect to the cell position in its cycle. We show that the proposed model exhibits a limit cycle which is validated by the oscillatory behaviors observed in biological experiments. To prove the existence of a closed orbit, properties of competitive systems and the Bendixson criterion are used [22].

##### *Mathematical study of models of anaerobic plants.*

We have studied an unstable biological process used for an anaerobic wastewater treatment plant [28], [21], [11]. This ecosystem can have two locally stable equilibria and an unstable one. The risk of destabilization associated to a control policy has first been evaluated on a static basis by estimating the size of the attraction basin associated to the working point. To study the dynamical behavior of the system we split the phase plane according to the sign of the derivatives of the state vector. A methodology has been proposed to monitor in real time the trajectory of the system across these zones; we show that a sequence of transitions from one zone to another allows determination of the position of the system in the phase plane. A dynamical risk has been defined based on the sequence of transitions and the zones are classified according to their dangerousness [28]. The proposed approach does not depend on the parameter values and is thus very robust.

##### *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 species that requires the smallest substrate concentration in order to have a growth-rate equivalent to the dilution rate wins the competition; it is the survival of the most efficient species at this rate. This observation has been validated through laboratory experiments. Also, we have proposed an original proof (through transition graphs) for this exclusion principle both in the classical Monod model case with  $n$  species in competition and the Droop model with two species in competition [39].

It is to be noted that coexistence of the species can also be observed in real-world applications. This coexistence has been explained in different cases by a time-varying nutrient feed, multi-resource models, a crowding effect,... We showed that the coexistence of the different species can also be explained by an intra-specific dependency of the growth functions, which represents an intra-specific competition. We prove this result by showing that the stability analysis of the equilibrium reduces to the stability analysis of the equilibrium of a family of interconnected scalar systems. The analysis of these interconnected systems is achieved by the construction of a polytopic Lyapunov function, built as a sum of monotonic continuous functions [20]. This work was done in collaboration with F. Mazenc and A. Rapaport of the INRA-INRIA MERE project-team.

##### *Towards a qualitative analysis of Lotka-Volterra systems*

We study the dynamical behavior of  $n$ -dimensional nonlinear differential equation of Lotka-Volterra in  $n$ -dimensional rectangles [43]. More precisely, we give some necessary and sufficient conditions on the matrix of the system for the existence of rectangles (containing the unique positive equilibrium), the faces of which are *transverse* with respect to the flow (*ie* each face is crossed by the flow in a unique sense). These conditions are directly related to the type of stability of the equilibrium, and therefore to the *local* dynamics of the system around the equilibrium. Furthermore, we have been able, thanks to Lyapunov theory, to describe the *global* dynamics of the system within such transverse rectangles. Together with the analysis of the dynamics on rectangles that do not contain the positive equilibrium, these results provide a first step towards a qualitative analysis of the Lotka-Volterra nonlinear equation [37].

#### *Bistability in biological systems*

From a mathematical point of view, a system is bistable if it has two distinct, stable fixed points. In [16], the following generalization of the concept of bistability is proposed: a system is bistable if its state space contains two disconnected invariant sets. A general framework for analysis is proposed, where the interactions among variables are defined qualitatively as activation or inhibition functions, that is, differentiable, but defined within a (narrow) step-like tube. Bistability, with respect to two invariant sets, is characterized through a notion of input-to-state stability. This is work in collaboration with T. Eissing and F. Allgöwer (University of Stuttgart, Germany).

As an example of activation or inhibition functions, consider the class of functions which are differentiable and differ from the step function only on a small interval around the jump threshold. These functions can be used to study the validity of the approximation of continuous systems by strictly piecewise linear systems. In [52], we compare strictly piecewise linear models and a continuous approach, for the 2-dim negative feedback loop. Using a (flat) Lyapunov function, it is shown that the region of the state space where the dynamics of continuous and piecewise linear systems differ can be made arbitrarily small.

### **6.1.2. Model design, identification and validation**

**Keywords:** *biological modelling, bioreactors, qualitative analysis.*

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

#### *Model design and identification*

One of the main families of biological systems that we have been studying involves mass transfer between compartments, whether these compartments are bacteria or substrates in a bioreactor, or species populations in an ecosystem. We have developed methods to estimate the models of such systems [46]. These systems can be represented by models having the general structure popularized by [44], [50], 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 [45]. 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 [25]. This approach has been applied to various bioproduction processes: vanillin production [46], lipase production [25] and cheese production [29] (in collaboration with A. Hélias, INRA-GMPA, Grignon).

#### *The feasible parameter space for biochemical networks*

We address the question of determining the space of all feasible sets of parameters for a given biological model, that is, those sets which produce results compatible with the outcome of the biological system. A method is proposed in [38] for writing a full description of the feasible or “allowed” parameter set, as a hierarchy of intervals. When this method is applied to the segment polarity genes network (of the fruit fly), it is found that there are 5 disconnected regions of parameters. If perturbations in the parameters are viewed as mutations, the existence of disconnected regions in the parameter space is related to the degree of robustness of the system’s outcome with respect to parameter perturbations. This is work in collaboration with E. Sontag and A. Sengupta from Rutgers University, USA.

### 6.1.3. *Nonlinear observers*

**Keywords:** *bioreactors, hybrid observers, nonlinear observers, uncertain models.*

**Participants:** Jean-Luc Gouzé, Olivier Bernard, Marcelo Moisan.

#### *Interval observers*

We designed so-called bundle of observers [49] made of a set of interval observers. Each observer computes intervals in which the state lies, provided that the intervals inside which the parameters, the initial conditions and more generally all the uncertainties lie are known. We then take the lower envelope of this set to improve the overall estimation.

We have extended the results of hybrid interval observers [59], introducing an optimality criterion to compute an optimal gain, leading to the best interval estimates [64],[30].

Recently, we have also introduced reverse time interval observers [32]. The objective is to improve the initial state estimate by running interval estimators in reverse time. The technique has been developed considering the optimal framework of [64], achieving remarkable improvements of the convergence rate. Application of this estimation scheme to an industrial wastewater treatment plant has demonstrated its efficiency on a real problem [31]. Our latest work allows for the estimation of the inputs of the biological process [65].

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 uncertainties on the parameters of the system and biased output [12].

These interval observers have been extended to the case where only discrete time measurements are available [27], and applied to experimental data of phytoplankton growth.

### 6.1.4. *Nonlinear control*

**Keywords:** *Positive systems, adaptive regulation, bioreactors control, structural stabilization, uncertain systems.*

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

#### *Global stabilization of partially known positive systems*

We deal with the problem of global output feedback stabilization of a class of  $n$ -dimensional nonlinear positive systems possessing a one-dimensional unknown, though measured, component. We propose an output feedback control procedure, taking advantage of measurements of the uncertain part, which is able to globally stabilize the system towards an adjustable equilibrium point in the interior of the positive orthant. Though quite general, this result is based on hypotheses that might be difficult to check in practice. Then in a second step, through a theorem on a class of positive systems linking the existence of a strongly positive equilibrium to its global asymptotic stability, we propose other hypotheses for our main result. These new hypotheses are more restrictive but much simpler to check [58],[23].

We have constructed strict Lyapunov functions for general nonlinear systems satisfying Matrosov type conditions [62], [63]. We illustrate the practical interest of our design using two globally asymptotically stable biological models.

### *Control of competition in the chemostat*

We have designed a closed loop control procedure for microorganisms in the chemostat [61], [39]. The objective is to select species with interesting characteristics in chosen environmental conditions. In particular, by controlling the dilution rate and the input substrate concentration, it is possible to select a species which maximizes a criterion. In a first step controls are proposed for Monod's and Droop's models in order to achieve periodic substrate stresses, and to regulate the total biomass concentration. We show that this regulation causes the selection of the fastest growing species if the system has a periodic behavior, and derive new selection criteria. Finally, the method is simulated using Droop's model for selecting species which maximize these criteria.

We also studied the feedback control of competition in a chemostat with a single substrate and two species. In a recent paper, P. De Leenheer and H.L. Smith [53] present a control law that ensures coexistence between the two species (as a unique globally asymptotically stable equilibrium). Nevertheless their analysis requires the assumption that the mortality rates can be neglected. We generalize this approach by allowing non zero mortality death rates. Our main tools are differential inequalities and Lyapunov-like functionals. We obtain sufficient conditions (given by upper bounds on mortality rates) for the existence of a unique positive critical point which is globally asymptotically stable [56], [55].

### *Mathematical study of impulsive biological control models*

The stability of the interconnection of a continuous prey-predator model in ODE and periodic impulses has been studied. This work has been done in the context of biological control of pests in a continuously grown greenhouse. The prey-predator dynamics is continuous and it is augmented by discrete components representing the periodic release of predators and periodic harvest that take place at periods that are multiple of each other. Using Floquet Theory, a stability condition of the prey-less periodic solution of this system is found. It involves a minimal bound on the number of predators to release per unit time [66], [67], [40]. Other variants of the model are currently under study whereby different forms of intraspecific predator interference - such as squabbling, cannibalism and competition - are taken into account. This work has been done in collaboration with L. Mailleret (INRA Sophia-Antipolis).

## 6.2. Fields of application

### 6.2.1. Growth of marine plankton

**Keywords:** *biological models, bioreactors, chemostat, plankton, population dynamics.*

**Participants:** Olivier Bernard, Jean-Luc Gouzé, Antoine Sciandra, Serena Esposito, Christophe Mocquet, Thomas Lacour.

#### *Growth of phytoplankton limited by light and nitrogen*

A model which describes growth of phytoplankton while light and nitrogen are both deficient was developed and studied in [70], and compared with Geider's classical model and with Pahlow's model. It was validated with data from *Rhodomonas salina*. The previous model was coupled to hydrodynamical equations to obtain a 1-D model (with the LOBSTER model issued from the LODYC, in collaboration with Marina Levy). The 1-D model was calibrated by assimilating data from the DYFAMED experiments [6]. A Large Eddy Simulation model (LES) describing at microscale the physical processes in the water column is developed, including BioLOV model. The objective is to reproduce the dynamics of the environmental conditions at small time scale that influence phytoplankton growth. Then this model is used to generate Lagrangian trajectories which are reproduced in the computer-controlled experimental chemostats [68].

#### *Carbon fixation by coccolithophorides*

A set of 18 models was developed and studied [14] to describe the coupling between photosynthesis 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 behaviors, since experiments have shown that an increase in the CO<sub>2</sub> partial pressure paradoxically leads to a decrease in the calcification rate. An alternative where pH drives the carbon assimilation process is proposed and validated .

### *Nonlinear Control for phytoplankton's growth in the chemostat*

Phytoplanktonic populations in the chemostat can be difficult to maintain in high nutrient concentrations corresponding to high dilution rates. We propose a control law which is able to reduce this structural sensitivity and is only based on qualitative structural properties of a class of models to which the classical Droop model belongs [60]. We assume that the  $CO_2$  incorporation rate (or oxygen production rate) can be measured. The model is kept qualitative in the sense that the growth rate is not specified, and we only assume qualitative hypotheses (positivity, monotonicity)

### *Modelling and optimization of lipid production*

In the framework of the ANR project Shamash, a model has been developed to predict the lipid production in a culture of microalgae after a nitrogen starvation. The model is an extension of the Biolo model, including a description of a lipid storage compartment. A procedure to calibrate the model has been deployed in order to rapidly evaluate the main parameters for various oil producing species.

## **6.2.2. Bioprocesses**

**Keywords:** *biological depollution, bioreactors, wastewater treatment.*

**Participants:** Jean-Luc Gouzé, Olivier Bernard, Frédéric Grognard, Jonathan Hess.

### *Anaerobic digestion monitoring and control*

COMORE has developed models for the anaerobic digestion process and proposed dedicated methods to select the appropriate model [48] and calibrate them [11]. Finally, this work has mainly been focused on the design of control laws that stabilize Wastewater Treatment Plants (WWTPs), which tend to be unstable without feedback control [71].

The mechanistic model of the liquid-gas exchange coefficient  $k_{La}$  [11] has been simplified to be incorporated in a general model of anaerobic digestion. The simplified version still exhibits a linear trend between the  $k_{La}$  and the biogas flow-rate. It has been used to modify the model of [4]. This simplified model keeps a good accuracy and can be used to construct a control strategy.

The new model shows a linear relation between the dissolved  $CO_2$  and the biogas quality (in terms of  $\%CO_2$ ), which gives new prospects for the control of the biogas quality. A strategy based on the regulation of the alkalinity has been proposed, and two feedback control laws tested; a simple PI based on the measurement of the partial pressure of  $CO_2$ , and a mixed law based on a linearising control of the alkalinity plus a PI to account for potential modelling errors. Experiments have been carried out at the LBE Narbonne to validate these two controls.

Asymptotic, interval based software sensors have been developed based on the possible sets of measurements [33], [31], [11], [12].

### *Experiments for the modelling of the quality of the biogas that is produced by anaerobic digestion*

Our current work is aiming at the modelling of the quality of the biogas which is produced by the digester in order to design regulation strategies, so that this biogas keeps a constant quality and can be used as an energy source [11].

Experiments have been carried out with the LBE Narbonne, for testing the effect of the influent pH composition and pH on the quality of the biogas.

## **6.2.3. Models of ecosystems**

**Keywords:** *biological models, ecosystems, population dynamics.*

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

### *Biological control*

With L. Mailleret (INRA Sophia-Antipolis team “Integrated Research in Horticulture”), 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 that no pest outbreak is possible. Given the harvesting period, we also identify the optimal choice of predator release that yields eradication while requiring the smallest predator budget [66], [67],[40].

#### 6.2.4. Metabolic and genomic models

**Keywords:** *biological networks, cell models, qualitative analysis.*

**Participants:** Olivier Bernard, Jean-Luc Gouzé, Frédéric Grognard, Etienne Farcot, Laurent Tournier, Ibrahima Ndiaye, Madalena Chaves, Eric Benoît.

##### *Dynamics of genetic regulatory networks*

We are studying a class of piecewise-linear dynamical systems,  $\dot{x} = f(x) - g(x)x$ , 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-linear 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 use of step functions is motivated by the switch-like behavior seen experimentally in many of the interactions in gene expression and breakdown of proteins. The piecewise-linear 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. We apply a technique due to Filippov to study these systems on their surfaces of discontinuity by extending them into systems of differential inclusions. Current work in this project consists in continuing the work of Gouzé and Sari [57] and de Jong *et al* [73] by characterizing the equilibrium points and periodic orbits in this special class of systems, in addition to characterizing their stability [15]. These methods and algorithms are used by the software GNA (Genetic Network Analyzer) developed by de Jong *et al* (HELIX, INRIA Rhône-Alpes) and are applied to the study of regulatory networks underlying transcription in the bacteria *E. coli* and *Synechocystis* [13].

##### *Model reduction of genetic regulatory networks*

As the dimension of the system increases, it becomes useful to reduce it, in some sense, in order to facilitate its analysis. Based on the discrete structure of piecewise affine systems, we developed a reduction method (see [36], [42], [72]) using the strongly connected components decomposition of the interaction graph. Thanks to this decomposition, we are able to express the initial dynamical system in a hierarchical form, allowing to decompose the dynamical analysis of the whole system (neglecting some transients) by subsequently analyzing asymptotic behaviors of the different subsystems [41]. Such a method has been successfully applied to 6- and 9-dimensional piecewise affine models of the regulatory network underlying the response of bacterium *Escherichia coli* to a nutritional stress described by Ropers *et al.* [69] [24]. The study of this last system permits to show the Filippov modes, and the converging oscillating behavior near the equilibrium ([19]). We are currently attempting to refine this decomposition by seeking efficient algorithmic ways to find positively invariant regions in the phase space.

##### *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 some control theoretic methodologies for these networks. We have thus introduced some new mathematical techniques whose purpose is the control of piecewise-linear equations towards a prescribed behavior. Namely, we suppose that the piecewise constant terms  $f(x)$  and  $g(x)$  depend on an input vector  $u$ . Then, our aim is to find piecewise constant feedback laws  $u(x)$ , such that the state transition graph mentioned above has a prescribed shape. We have characterized these feedback laws in terms of a system of affine inequalities for each vertex in the transition graph. If, moreover, each input variable affects at most one variable, the solutions of these inequalities can in fact be obtained explicitly [17],[26].

##### *Periodic solutions of models of genetic regulatory networks*

One important problem of piecewise-linear models of gene networks is their comparison with discrete analogues, which are all based on the state transition graph. Notably, loops in this graph may correspond to limit cycles of the piecewise-linear system, but also equilibria situated at the intersection of several thresholds. An important family of piecewise-linear systems is composed of those systems whose interaction structure is a negative loop involving all variables. These systems do all have a loop in their state transition graph. Using theorems about monotone operators acting on positive variables, we have shown that this loop always correspond to a unique, stable limit cycle [18].

#### *The role of microRNAs in regulatory mechanisms*

Micro RNAs are small messenger RNAs which do not code for any protein, but are thought to interact at the level of gene transcription, and thus add a new regulatory mechanism to genetic networks. In a collaboration with the group of P. Barbry (Institut de Pharmacologie Moléculaire et Cellulaire), we are developing models to understand and study the mechanisms of micro RNA in genetic networks. Based on experimental results on the differentiation process of a type of blood cells [54], three models were proposed for a genetic network involving the micro RNA mir-223 and two other proteins [51]. Properties such as bistability, and predictions from each model help discriminate which mechanism best describes this regulatory system.

#### *Interaction between signaling and gene expression networks*

A simple model, consisting of one protein ( $x$ ) and one mRNA ( $y$ ), was developed and fully analyzed [34]: the protein  $x$  activates transcription of the gene and also contributes to its own synthesis. The mRNA  $y$  (or its corresponding protein) contributes to the degradation of protein  $x$ . The idea that signaling or metabolic networks achieve an operational steady state much faster than the dynamics of gene expression was used to study the model in a “fast-slow” framework. It is shown how the signaling network can be regulated, by switching between two operational modes (or steady states), in response to gene expression patterns. Conditions for the existence of an oscillatory cycle, as well as an estimate of its period, are provided.

#### *Transitions analysis of models of genetic regulatory networks*

Another question that was studied is the detection of a transition between two space regions in experimental data. An algorithm has been developed, based on change in the dynamics when an hyperplane between two regions is crossed [35]. These results have been tested and validated with experimental data.

## 6.3. Software design

**Keywords:** C++, Matlab, Scilab, monitoring platform, simulation platform, wastewater treatment.

**Participants:** Olivier Bernard, Romain Primet.

Project-team COMORE develops a software framework for bioprocess control and supervision called ODIN [47]. This C++ application enables researchers and industrials to easily develop and deploy advanced control algorithms through the use of a Scilab interpreter. It also contains a Scilab-based process simulator which can be harnessed for experimentation and training purposes. ODIN is primarily developed in the C++ programming language and uses CORBA to define component interfaces and provide component isolation. ODIN is a distributed platform, enabling remote monitoring of the controlled processes as well as remote data acquisition. In 2007, software development effort has been directed to architecture rework (focusing on robustness and maintainability), implementation of a new graphical user interface, a synoptic view component, drivers for the experimental hardware and integration of the PlantML data exchange format. PlantML is an XML format used to describe plant data which helps quickly porting ODIN to new processes and brings easier integration with other software tools using this standard. ODIN is now undergoing tests at the Laboratoire des Biotechnologies de l'Environnement in Narbonne.

## 7. Contracts and Grants with Industry

### 7.1. Microalgae for CO<sub>2</sub> trapping

A contract between COMORE, the Laboratory of Oceanography in Villefranche and Lafarge has been signed in order to assess and quantify the potential of microalgae for CO<sub>2</sub> trapping.



## 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 is coordinated by O. Bernard, it includes 8 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/>
- **BFN - LEFE :** Comore takes part in the BFN project funded by INSU (Institut National des Sciences de l'Univers) within the LEFE program. The objective is to provide new data assimilation algorithms for improving state and parameter estimation in oceanography. <http://www.mip.ups-tlse.fr/~auroux/LEFE/>.
- **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<sub>2</sub> production processes involving anaerobic bacteria or microalgae.
- **MetaGenoReg:** The objective of this project, funded by ANR (Systems Biology), 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 directed by D. Kahn (Helix, INRIA).
- **StepContr:** The aim of this project is the advanced control of wastewater treatment bioprocesses when the input is known and periodic. This project, funded by "l'Agence Universitaire de la Francophonie", is steered by A. Karama (Univ. Marrakech), and also involves M. Perrier (Ecole Polytechnique de Montréal, Canada).
- **ARC CODA:** The objective of this INRIA funded project is to optimize the starting of anaerobic treatment plants. This is a joint project with the INRIA SEQUEL project, INRA LBE and the start-up Naskeo.
- **ECOGER:** We participate in one of the themes of this project, which is funded by INRA: "Ecology and adaptation of phytophagous insects and management of their populations". Our objective in this project is the mathematical modelling and optimization of biological control.
- **Color LutIns&co:** This INRIA funded project aims at modelling the influence of intra-guild predation on biological control; it merges techniques of game theory and control theory. This a joint project with INRA Sophia-Antipolis and I3S.
- **IA2L:** INRA-SPE is also funding a project on intra-guild predation in which we are taking part: "Interactions antagonistes entre auxiliaires : conséquences pour la lutte biologique".
- **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:** Jean-Luc Gouzé, Olivier Bernard, Frédéric Grognard and Antoine Sciandra organize a regular seminar "Modelling and control of ecosystems" at the station zoologique of Villefranche-sur-Mer or at INRIA. Some of those seminars were joint events with the JOB workgroup organized by Pierre Bernhard. In parallel with that seminar, we have had working group seminars with the MERE project-team of Montpellier, in order to maintain our collaborations.

### 8.2. European initiatives

- **European project HYGEIA:** HYGEIA (Hybrid Systems for Biochemical Network Modelling and Analysis) is a NEST ADVENTURE STREP European project. The objective of HYGEIA is to exploit recent developments in the area of hybrid systems to address open problems in modelling and analysis of biochemical networks, see <http://www.hygeiaweb.gr/home.html>.
- **European Network of Excellence HYCON:** The objective of the NoE HYCON (Hybrid Control: Taming Heterogeneity and Complexity of Networked Embedded Systems) is establishing a long-lasting community of leading researchers and practitioners who develop and apply the hybrid systems approach to the design of networked embedded control systems as found, e.g., in industrial production, transportation systems, generation and distribution of energy, communication systems, genetic systems (see <http://www.ist-hycon.org/>).
- **BOOM:** The BOOM project - Biodiversity of Open Ocean Microcalcifiers - is aiming at elucidating the biodiversity of calcifying species. This encompasses the study of phylogeny from existing cultures and bulk DNA as well as culture isolation from in situ sample collection, genome size screening. Environmental and functional diversity are concerned with experimental lab physiological studies. Participants : Station Biologique de Roscoff (UPMC-CNRS), Laboratoire d'Océanographie de Villefranche/Mer (UPMC-CNRS), CEREGE, Université de Caen, Laboratoire Arago de Banyuls (UPMC-CNRS), Museum of Natural History (UK), Alfred Wegener Institute (GER), California State University (USA) <http://www.obs-vlfr.fr/~gattuso/boom.php>.

### 8.3. Visits

- Hidde de Jong (INRIA Helix, France), 1 week (cumulated visits);
- Ludovic Mailleret (INRA Antibes, France), 1 month (cumulated visits);
- Asma Karama (Université de Marrakech), 2 weeks;
- Rafik Chana (Université de Marrakech), 1 week;
- INRIA-MERE project-team (Montpellier) for a joint seminar, 2 days;
- Pierre Auger (UR GEODES, IRD, Bondy; Académie des Sciences), 2 days;
- Swanny Fouchard (Laboratoire GEPEA, UMR CNRS-6144, Univ. Nantes), 1 week;
- Claude Manté, David Nerini (UMR 6117 LMGEM CNRS, Centre d'Océanologie de Marseille), 2 days;
- Guillaume Goffaux (Fac. Polytechnique de Mons, Belgium), 2 days;
- Jaime Moreno (Universidad Nacional Autónoma de México, Mexico), 1 week;
- Jan Van Impe (KULeuven, Belgium), 3 days;
- Jean-Philippe Steyer, Eric Latrille, Eveline Volcke, Cesar Aceves (LBE, INRA Narbonne), 2 days;
- Georges Bastin (Université de Louvain, Belgium), 2 days.

## 9. Dissemination

### 9.1. Leadership with scientific community

In march, Comore organized a joint seminar with the *Laboratoire de Biotechnologie de l'Environnement* (INRA Narbonne) and the *Laboratoire d'Océanographie de Villefranche* (CNRS, Université P.M. Curie) entitled "From the marine ecosystems to the wastewater treatment ecosystems". This two-day seminar took place at Villefranche-sur-Mer and Sophia-Antipolis and was aimed at bringing together two communities that face similar challenges (data-acquisition, modelling of biological/ecological networks...).

J.-L. Gouzé is a member of scientific committees for the conferences POSTA 2009 Multidisciplinary International Symposium on Positive systems, theory and applications, Valencia, Spain), for the conference "Stic et Environnement", Lyon 2007, for the conference RIAMS 2007, Lyon, for the conference in honor of C. Lobry (St- Louis, Senegal, september).

He is a member of the board of the project-team committee at INRIA (Bureau du comité des projets), the co-head of an INRIA committee supervising the doctoral theses and is 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 was the scientific leader for the European project Telemac.

O. Bernard belongs to the COST committee, GTAI ("Groupe de travail sur les actions incitatives") and of the Color committee; he belongs to the committee « Bioenergy and biotechnology », from the PNRB (National Research Program on Bioenergy) from the ANR. He is also an expert for the CEPIA software platform of INRA.

M. Chaves is in the international program committee for FOSBE 2007 (Foundations of Systems Biology in Engineering, Stuttgart 2007). She is a member of the INRIA-INSERM working-group that seeks to promote interdisciplinary discussion and develop collaborations among experimentalists and theoreticians from both institutes.

## 9.2. Teaching

J.-L. Gouzé, O. Bernard, F. Grogard and A. Sciandra 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 taught courses on dynamical systems (6h), O. Bernard on modelling and identification (9h) and classworks (8h), and F. Grogard on control of biological systems (3h) and classworks (4h).

F. Grogard taught a class on modelling and control of biological systems at EPU (6h) to 2nd year engineering students.

J.-L. Gouzé gave lectures for the UNESCO chair "Mathematics and development", concerning "Mathematics and life sciences", during one week in January in Tunis. He taught in an INRA school for researchers in La Grande Motte (1 day, october).

O. Bernard gave lectures at the Institut National Agronomique Paris-Grignon (3h) on bioreactor modelling and optimization. O. Bernard gave 12h lectures at the University of Santiago de Compostella (Spain) on advanced, modelling, analysis and observation of bioprocesses.

### 9.2.1. Theses

- Ongoing theses:
  1. S. Nundloll, "Modélisation et optimisation de la lutte biologique", UNSA.
  2. I. Ndiaye, "Analyse mathématique et contrôle de modèles de réseaux de régulation génétique", UNSA.
  3. C. Mocquet, "Interférence entre les processus de division cellulaire et de croissance somatique chez les autotrophes. Effets résultant sur la production primaire et modélisation des phénomènes en environnement variable", Université P.M. Curie.
  4. T. Lacour, "Etude expérimentale des mécanismes de production de lipides par des microalgues", Université P.M. Curie.
  5. P. Masci, "Etude et développement d'un système de sélection d'espèces dans un environnement dynamique multivariable", UNSA.

- Defended theses:
  1. M. Moisan, "Synthèse d'observateurs par intervalles pour des systèmes biologiques mal connus", PhD Thesis, Université de Nice Sophia-Antipolis (supervisor: O. Bernard).
  2. J. Hess, "Modélisation de la qualité du biogaz produit par un fermenteur méthanogène et stratégie de régulation en vue de sa valorisation", PhD Thesis, Université de Nice Sophia-Antipolis (supervisor: O. Bernard).
- Participation in PhD juries:
 

O. Bernard was in the PhD Jury of A. Grosfils. « First principles and black box modelling of biological systems », Université libre de Bruxelles.

O. Bernard was president of the PhD Jury of C. Aceves Lara. "Modélisation, estimation et commande de procédés de digestion anaérobie en vue de l'optimisation de la production d'hydrogène". University of Montpellier II.

He was also in the PhD jury of M. Eichinger. "Dégradation bactérienne du carbone organique dissous dans la colonne d'eau. Une approche couplée expérimentation - modélisation." University of Marseille.

J.-L. Gouzé was referee for the HDR (tenure) de F. Mazenc, "Analyse de stabilité et commande de systèmes non linéaires", Univ. Montpellier.

J.-L. Gouzé was referee for the thesis of C. Lopez, "Dynamique d'un système hôte parasitoïde en environnement spatialement hétérogène et lutte biologique; Application au puceron Aphis gossypii et au parasitoïde Lysiphlebus testaceipes en serre de melon", INRA, Paris.

### 9.3. Conferences, invited conferences

Conferences with proceedings are not repeated here.

M. Chaves was a visiting member at the Kavli Institute for Theoretical Physics, University of California at Santa Barbara, USA, during July 2007. She was invited to participate in and present a seminar at the 6-week workshop "Biological Switches and Clocks" organized by R. Albert, A. Goldbeter, P. Ruoff, J. Sible, and J. Tyson. She was also invited to give a seminar at the workshop "Mathematical Models of Cell Regulatory Systems," organized by E. Pecou and A. Pumir, Université de Nice, France (October 2007).

M. Chaves and J.-L. Gouzé were invited to give seminars at the workshop "Control Systems for Systems Biology," organized by J. Van Schuppen and A. van der Schaft, University of Groningen, Netherlands (November 2007).

JL Gouzé was invited to give a talk for the workshop "Dynamics of Gene-Regulatory Networks", organized by R. Edwards et P. van den Driessche, CAIMS SCMAI 2007 Annual Conference, Banff, Canada. He gave an invited talk in the conference of the SFBT (Winnipeg, Canada).

O. Bernard was invited to give a seminar at the symposium "Données et modèles pour les systèmes complexes: application à l'environnement" in Grenoble.

O. Bernard and J.-L. Gouzé gave invited talks in the conference in the honor of C. Lobry, St Louis, Senegal.

S. Nundloll did a talk on "The effect of crop harvest on biological pest control" at the Fourth International Conference on Mathematical Biology (May 29-June 1, 2007) in Wuyishan, China.

## 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.", vol. 45, 2002, 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", vol. 193, 2005, p. 51-77.
- [3] O. BERNARD, J.-L. GOUZÉ. *Closed loop observers bundle for uncertain biotechnological models*, in "J. Process. Contr.", vol. 14:7, 2004, 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.", vol. 75, n<sup>o</sup> 75, 2001, p. 424-438.
- [5] M. CHAVES. *Input-to-state stability of rate-controlled biochemical networks*, in "SIAM Journal of Control and Optimization", vol. 44, 2005, p. 704-727.
- [6] B. FAUGERAS, O. BERNARD, A. SCIANDRA, M. LEVY. *A modelling and data assimilation approach to estimate the carbon/chlorophyll and carbon/nitrogen ratios in a coupled hydrodynamical-biological model*, in "Nonlinear Processes in Geophysics", vol. 11, 2004, p. 515-533.
- [7] J.-L. GOUZÉ. *Positive and negative circuits in dynamical systems*, in "Journal Biol. Syst.", vol. 6, n<sup>o</sup> 1, 1998, p. 11-15.
- [8] J. L. GOUZÉ, A. RAPAPORT, Z. HADJ-SADOK. *Interval observers for uncertain biological systems*, in "Ecological modelling", vol. 133, 2000, p. 45-56.
- [9] F. GROGNARD, F. MAZENC, A. RAPAPORT. *Polytopic Lyapunov functions for persistence analysis of competing species*, in "Discrete and Continuous Dynamical Systems-Series B", vol. 8, n<sup>o</sup> 1, 2007, p. 73-93.
- [10] L. MAILLERET, O. BERNARD, J.-P. STEYER. *Nonlinear adaptive control for bioreactors with unknown kinetics*, in "Automatica", vol. 40-8, 2004, p. 1379-1385.

## Year Publications

### Doctoral dissertations and Habilitation theses

- [11] J. HESS. *Modélisation de la qualité du biogaz produit par un fermenteur méthanogène et stratégie de régulation en vue de sa valorisation*, Ph. D. Thesis, Université de Nice-Sophia Antipolis, 2007.
- [12] M. MOISAN. *Synthèse d'observateurs par intervalles pour des systèmes biologiques mal connus*, Ph. D. Thesis, Université de Nice Sophia-Antipolis, 2007.

### Articles in refereed journals and book chapters

- [13] G. BATT, H. DE-JONG, J. GEISELMANN, J.-L. GOUZÉ, M. PAGE, D. ROPERS, T. SARI, D. SCHNEIDER. *Analyse qualitative de la dynamique de réseaux de régulation génique par des modèles linéaires par morceaux*, in "TSI Technique et Science Informatiques", vol. 26, 2007, p. 11-46.
- [14] 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 "Ecological Modelling", to appear, 2007.

- [15] R. CASEY, H. DE JONG, J.-L. GOUZÉ. *Stability of equilibria for hybrid models of genetic regulatory networks*, in "Taming Heterogeneity and Complexity of Embedded Control, Paris", F. LAMNABHI-LAGARRIGUE, A. LORIA, E. PANTELEY, S. LAGHROUCHE (editors), ISTE, Hermes Science, 2007.
- [16] M. CHAVES, T. EISSING, F. ALLGÖWER. *Bistable biological systems: a characterization through local compact input-to-state stability*, in "IEEE Trans. Autom. Control and Trans. Circuits Syst. I", to appear, vol. Special issue on Systems Biology, 2007.
- [17] E. FARCOT, J. GOUZÉ. *A mathematical framework for the control of piecewise affine models of gene networks*, in "Automatica", to appear, 2007.
- [18] E. FARCOT, J.-L. GOUZÉ. *Periodic solutions of piecewise affine gene network models: the case of a negative feedback loop*, in "Acta Biotheorica", to appear, 2007.
- [19] F. GROGNARD, J.-L. GOUZÉ, H. DE JONG. *Piecewise-linear models of genetic regulatory networks: theory and example*, in "Biology and control theory: current challenges", I. QUEINNEC, S. TARBOURIECH, G. GARCIA, S. NICULESCU (editors), Lecture Notes in Control and Information Sciences (LNCIS) 357, Springer-Verlag, 2007, p. 137-159.
- [20] F. GROGNARD, F. MAZENC, A. RAPAPORT. *Polytopic Lyapunov functions for persistence analysis of competing species*, in "Discrete and Continuous Dynamical Systems-Series B", vol. 8, n<sup>o</sup> 1, 2007, p. 73-93.
- [21] J. HESS, O. BERNARD. *Design and study of a risk management criterion for an unstable anaerobic wastewater treatment process*, in "Journal of Process Control", to appear, 2007.
- [22] V. LEMESLE, J.-L. GOUZÉ. *A simple unforced oscillatory growth model in the chemostat*, in "Bulletin of Mathematical Biology", to appear, 2007.
- [23] L. MAILLERET, J.-L. GOUZÉ, O. BERNARD. *Global stabilization of a class of partially known positive systems*, in "Automatica", to appear, 2007.
- [24] D. ROPERS, H. DE JONG, J.-L. GOUZÉ, M. PAGE, D. SCHNEIDER, J. GEISELMANN. *Piecewise-linear models of genetic regulatory networks: Analysis of the carbon starvation response in Escherichia coli*, in "Mathematical Modeling of Biological Systems, Volume I (Proceedings of the European Conference on Mathematical and Theoretical Biology (ECMTB) 2005)", A. DEUTSCH, L. BRUSCH, H. BYRNE, G. DE VRIES, H.-P. HERZEL (editors), Birkhäuser, Boston, 2007, p. 85-98.

### Publications in Conferences and Workshops

- [25] O. BERNARD. *Use of modulating functions for reaction network identification*, in "Proceedings of the 10th CAB conference", Cancun, Mexico, 2007.
- [26] E. FARCOT, J. GOUZÉ. *Piecewise constant feedback control of piecewise affine gene network models*, in "Hybrid Systems: Computation and Control HSCC 07", A. BEMPORAD, A. BICCHI, G. BUTTAZZO (editors), Lecture Notes in Computer Sciences (LNCS) 4416, Springer-Verlag, Pisa, Italy, 2007, p. 688-692.
- [27] G. GOFFAUX, A. VANDE WOUWER, O. BERNARD. *Discrete-time interval observers applied to continuous cultures of phytoplankton*, in "Proceedings of the 7th NOLCOS conference", Pretoria, South Africa, 2007.

- [28] J. HESS, O. BERNARD. *Advanced dynamical risk analysis for monitoring anaerobic digestion process*, in "Proceedings of the 10th CAB conference", Cancun, Mexico, 2007.
- [29] A. HÉLIAS, O. BERNARD. *Assessing the main reactions in a bioprocesses: application to cheese ripening*, in "Proceedings of the 10th CAB conference", Cancun, Mexico, 2007.
- [30] M. MOISAN, O. BERNARD, J.-L. GOUZÉ. *Near optimal interval observers bundle for uncertain bioreactors*, in "Proceedings of the 9th European Control Conference, Kos, Greece", 2007.
- [31] M. MOISAN, O. BERNARD, J.-L. GOUZÉ. *Robust estimation using direct–reverse time interval observers: Application to an industrial bioreactor*, in "Proceedings of the STIC et Environnement 2007 Conference, Lyon, France", 2007.
- [32] M. MOISAN, O. BERNARD. *A direct-reverse time interval observer. Application to biotechnological models*, in "Proceedings of the 7th IFAC Symposium on Nonlinear Control Systems, Pretoria, South Africa", 2007.
- [33] M. MOISAN, O. BERNARD. *An interval observer for non-monotone systems: Application to an industrial anaerobic digestion process*, in "Proceedings of the 10th CAB Conference", Cancún, Mexico, 2007.
- [34] I. NDIAYE, M. CHAVES, J.-L. GOUZÉ. *Un petit modèle d'interaction entre expression génétique et signalisation*, in "Réseaux d'Interactions: Analyse, Modélisation, Simulation", Lyon, France, 2007.
- [35] R. PORRECA, G. FERRARI-TRECATÉ, D. CHIEPPI, L. MAGNI, O. BERNARD. *Switch detection in genetic regulatory networks*, in "Hybrid Systems: Computation and Control HSCC 07", A. BEMPORAD, A. BICCHI, G. BUTTAZZO (editors), Lecture Notes in Computer Sciences (LNCS) 4416, Springer-Verlag, Pisa, Italy, 2007.
- [36] L. TOURNIER, J.-L. GOUZÉ. *Hierarchical analysis of piecewise affine models of gene regulatory networks*, in "Proceedings of ECCS (European Conference on Complex Systems), Dresden, Germany", 2007.
- [37] L. TOURNIER, J.-L. GOUZÉ. *Qualitative stability patterns for Lotka-Volterra systems on rectangles*, in "Proceedings of the conference HSCC (Hybrid Systems, Computation and Control)", to appear, Saint-Louis, USA, 2008.

### Internal Reports

- [38] M. CHAVES, E. SONTAG, A. SENGUPTA. *Shape, size and robustness: feasible regions in the parameter space of biochemical networks*, Technical report, n<sup>o</sup> arXiv:0710.4269v1 [q-bio.MN], 2007, <http://arxiv.org/abs/0710.4269v1>.
- [39] P. MASCI. *Sélection d'espèces de microorganismes par compétition contrôlée*, Internship report, Technical report, EPU, 2007.
- [40] S. NUNDLOLL, L. MAILLERET, F. GROGNARD. *The effects of partial crop harvest on biological pest control*, Research Report, n<sup>o</sup> 6284, INRIA, 09 2007, <https://hal.inria.fr/inria-00171093>.
- [41] L. TOURNIER, J.-L. GOUZÉ. *Deterministic hierarchical modeling of biochemical networks*, Deliverable, n<sup>o</sup> D1.3, European Project HYGEIA (Hybrid Systems for Biochemical Network Modeling and Analysis), 01 2007.

- [42] L. TOURNIER, J.-L. GOUZÉ. *Hierarchical analysis of piecewise affine models of gene regulatory networks*, Research Report, n° 6189, INRIA, 01 2007, <http://hal.inria.fr/inria-00145357>.
- [43] L. TOURNIER, J.-L. GOUZÉ. *Qualitative stability patterns for Lotka-Volterra systems on rectangles*, Research Report, n° 6346, INRIA, 11 2007, <http://hal.inria.fr/inria-00186247>.

## References in notes

- [44] G. BASTIN, D. DOCHAIN. *On-line estimation and adaptative control of bioreactors*, Elsevier, 1990.
- [45] O. BERNARD, G. BASTIN. *Identification of reaction schemes for bioprocesses: determination of an incompletely known yield matrix*, in "Bioprocess and Biosystem Engineering", vol. 27, 2005, p. 293-302.
- [46] O. BERNARD, G. BASTIN. *On the estimation of the pseudo-stoichiometric matrix for mass balance modeling of biotechnological processes*, in "Math. Biosciences", vol. 193, 2005, p. 51-77.
- [47] O. BERNARD. *TELEMAC Deliverable 3.4: Final version of the Telemac advanced control module*, 2004, <http://www.ercim.org/telemac/>.
- [48] O. BERNARD, B. CHACHUAT, A. HÉLIAS, J. RODRÍGUEZ. *Can we assess the model complexity for a bioprocess ? Theory and example of the anaerobic digestion process*, in "Wat. Sci. Tech.", vol. 53, 2005, p. 85-92.
- [49] O. BERNARD, J.-L. GOUZÉ. *Closed loop observers bundle for uncertain biotechnological models*, in "J. Process. Contr.", vol. 14:7, 2004, p. 765-774.
- [50] O. BERNARD, I. QUEINNEC. *Dynamic models of biochemical processes: properties of the models*, in "Automatic Control of Bioprocesses", D. DOCHAIN (editor), chap. 2, ISTE, 2006, p. 23-52.
- [51] M. CHAVES. *A minicircuit involving miR-223, NFI-A and C/EBP*, Preliminary Report, 2007.
- [52] M. CHAVES. *Quantifying the correspondence between continuous and piecewise linear systems in the 2D negative feedback loop*, Preliminary Report, 2007.
- [53] P. DE LEENHEER, H. SMITH. *Feedback control for chemostat models*, in "Journal of Mathematical Biology", vol. 46, 2003, p. 48-70.
- [54] F. FAZI, A. ROSA, A. FATICA, V. GELMETTI, M. DE MARCHIS, C. NERVI, I. BOZZONI. *A minicircuitry comprised of microRNA-223 and transcription factors NFI-A and C/EBP $\alpha$  regulates human granulopoiesis*, in "Cell", vol. 123, 2005, p. 819-831.
- [55] J.-L. GOUZÉ, G. ROBLEDO. *Feedback control for competition models with different removal rates*, in "Journal of Mathematical Biology", submitted.
- [56] J.-L. GOUZÉ, G. ROBLEDO. *Feedback control for competition models with different removal rates*, Technical report, n° 5555, INRIA, 2005, <http://hal.inria.fr/inria-00070451>.



- [57] J.-L. GOUZÉ, T. SARI. *A class of piecewise linear differential equations arising in biological models*, in "Dynamical systems", vol. 17, 2002, p. 299–316.
- [58] J.-L. GOUZÉ, O. BERNARD, L. MAILLERET. *Global stabilization of a class of partially known positive systems*, Research Report, n<sup>o</sup> 5952, INRIA, 2006, <https://hal.inria.fr/inria-00086788>.
- [59] J.-L. GOUZÉ, M. MOISAN, O. BERNARD. *A simple improvement of interval asymptotic observers for biotechnological processes*, in "Proceedings of the ROCOND 2006 conference", Toulouse, France, 2006.
- [60] L. MAILLERET, J.-L. GOUZÉ, O. BERNARD. *Nonlinear control for algae growth models in the chemostat*, in "Bioprocess and Biosystem Engineering", vol. 27, 2005, p. 319-328.
- [61] P. MASCI, O. BERNARD, F. GROGNARD.. *Continuous selection of the fastest growing species in the chemostat*, in "Proceedings of the IFAC World Congress", submitted, Seoul, Korea, 2008.
- [62] F. MAZENC, M. MALISOFF, O. BERNARD. *A Simplified Design for Strict Lyapunov Functions under Matrosov Conditions*, in "IEEE Transactions on Automatic Control", submitted.
- [63] F. MAZENC, M. MALISOFF, O. BERNARD. *Lyapunov functions and robustness analysis under Matrosov conditions with an application to biological systems*, in "Proceedings of the ACC conference", submitted, Seattle, USA, 2008.
- [64] M. MOISAN, O. BERNARD, J.-L. GOUZÉ. *Near optimal interval observers bundle for uncertain bioreactors*, in "Automatica", submitted.
- [65] M. MOISAN, O. BERNARD, J.-L. GOUZÉ. *A high/low gain interval observer: Application to the input estimation of a bioreactor model*, in "Proceedings of the IFAC World Congress", submitted, Seoul, Korea, 2008.
- [66] S. NUNDLLOLL, L. MAILLERET, F. GROGNARD. *The effect of partial crop harvest on biological pest control*, in "Rocky Mountain Journal of Mathematics", submitted.
- [67] S. NUNDLLOLL, L. MAILLERET, F. GROGNARD. *Global Stability in a General Impulsive Biological Control Model with Harvest*, in "Proceedings of the IFAC World Congress", submitted, Seoul, Korea, 2008.
- [68] L. PAWLOWSKI. *Modélisation de l'incorporation du carbone photosynthétique en environnement marin contrôlé par ordinateur*, Ph. D. Thesis, Université Pierre et Marie Curie, Paris VI, 2004.
- [69] D. ROPERS, H. DE JONG, M. PAGE, D. SCHNEIDER, J. GEISELMANN. *Qualitative simulation of the carbon starvation response in Escherichia Coli*, in "Biosystems", vol. 84 (2), 2006.
- [70] A. SCIANDRA, L. PAWLOWSKI, O. BERNARD. *A growth model for autotrophic phytoplankton and its validation using chemostat experiments co-limited by light and nitrogen*, in "Environmental Microbiology", submitted.
- [71] J.-P. STEYER, O. BERNARD, D. BATSTONE, I. ANGELIDAKI. *Lessons learnt from 15 years of ICA in anaerobic digestion processes*, in "Wat. Sci. Tech. ", vol. 53, 2006, p. 25-33.

- [72] L. TOURNIER, J.-L. GOUZÉ. *Hierarchical analysis of piecewise affine models of gene regulatory networks*, in "Theory in Biosciences", submitted, 2007.
- [73] 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", vol. 66, n<sup>o</sup> 2, 2004, p. 301-340.