

*Project-Team COMORE**Modelling and Control of Renewable
Resources**Sophia Antipolis*

THEME 4A

Activity
Report

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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).

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2. Overall Objectives

The endeavor of Comore is to develop and apply methods from control theory (feedback control, estimation, identification, optimal control, game theory) and from the theory of dynamical systems, to the mathematical modeling of living exploited resources (renewable resources) and their management. We apply and validate

our results to various fields: phytoplankton growth, bioprocesses, wastewater treatment processes, pest control, fisheries...

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 modeling 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 keep a variable at a given level, or to optimize the yield of the system.

Fields of application:

- Modeling and control of the growth of the marine phytoplankton: we develop a chemostat (open bioreactor where algae or cells grow on a substrate) fully automated and managed by computers. The growth of the plankton is the basis of all the production of the organic matter of the oceans (fishes, etc), and plays a key role in the carbon cycle.
- Modeling, estimation and control of bioreactors: the bioreactors have a growing importance in many domains related to the human environment: alimentary (food production), pharmaceuticals (production of medicine), environment (waste water treatment), etc.
- Dynamics and control of ecosystems, of fisheries: we build models for ecosystems (insects, fishes) and try to regulate them optimally.
- Modeling of metabolic and genetic networks.

National, international and industrial relations

- Collaboration with IFREMER (Nantes), INRA (BIA Montpellier, LBE Narbonne), Centre d'Océanologie de Marseille, LODYC (Paris).
- 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 (Belgique), University of Marrakech (Marocco), University of Twente (Netherlands).
- European project IST TELEMAT on waste-water treatment.

3. Scientific Foundations

Key words: *biological models, environment, ecosystems, nonlinear control theory, dynamical systems, bio-reactor, optimization .*

COMORE is interested in the mathematical modeling 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 the working of these complex dynamical systems in order to regulate the exploitation of these resources by man. Our conceptual framework is that of Control Theory: a system, described by state variables, with inputs (action on the system), and outputs (the measurements available on the system). In our case, the system is an ecosystem, modeled by a mathematical model (generally a differential equation). Its variables

are, for example, the number or the density of populations. The inputs can be the actions which one exerts 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).

This approach begins with the mathematical modeling of the system. This stage is fundamental and difficult, because one does not have rigorous laws as in physics. We develop techniques to identify and validate the structure of a model from a set of available noisy measurements. This approach is based on the qualitative analysis of the data (extrema, relative position,...) that we use to build a model able to reproduce the same qualitative pattern. We work also on methods 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 that of 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 of 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 more pertinent for the biologists.

From a model that synthesizes the behavior of such a complex nonlinear biological system, we can study its properties and understand the way it works. One seeks to study the qualitative behavior of the system, the existence of equilibria, their stability, the existence of periodic solutions... These qualitative questions are fundamental because they tell us whether or not the system is viable (if the model does not predict the extinction of any species, etc). Specific problems are posed by the biological origin of the models: functions or parameters are uncertain, or unknown; what can we say on the behavior of the model? Often, the models have a strong structure belonging to a general class of systems, for which one develops adapted techniques: for example the well-known models of Lotka-Volterra in dimension n , describing the interactions between n species.

Once the dynamics of the considered living system has been understood we consider problems of regulation: how to keep a variable at a given level. This is important for example in the framework of waste water treatment where the pollution levels are imposed by laws. The main problem that we have to address is to try to control a complex system when the model is uncertain. We work mainly on a class of biological systems: the bioreactors that have a growing importance in many domains related to the human environment: alimentary (food production), pharmaceuticals (production of medicine), environment (waste water 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 estimate asymptotically the variables that are not measured directly. These so called "software sensors" can help the monitoring of some systems but also replace some expensive measurements. We are faced with the problem of various uncertainties that are specific to biological modeling: the model is uncertain (parameters, functions), but also the inputs can be uncertain and the outputs highly variable. We have to deal therefore with these uncertainties in the design of the 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 considered also.

The methods that we develop are validated and tested on several applications.

4. Application Domains

Key words: *biological models, environment, ecosystems, bioreactor, wastewater treatment, plankton growth, biological networks.*

Of course, these “applications” also generate methodological problems that we consider (see the above section); they can give rise to fundamental research problems for biology that have to be considered in collaboration with biologists.

Growth of the Marine Plankton

We work in collaboration with the Station Zoologique of the CNRS (Villefranche-sur-Mer, France), which has developed a chemostat (open bioreactor where algae or cells grow on a substrate) fully automated and managed by computers; this system is well adapted to the application of the methods resulting from the theory of control. Our current work consists of studying and validating models of growth for the plankton in a variable environment (light, food, etc). The growth of plankton is the basis for all production of organic matter in the oceans (fishes, etc); however, the existing traditional models (Monod, Droop) are often unsatisfactory. We seek to obtain models valid during the transitory stages, away from the equilibrium.

Waste Water 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 digesters. We build dynamical models and we design robust observers that take into account the large uncertainties encountered in this field. As an example, the amount of waste water to treat, which is an important input, is rarely measured. The software sensors are used to monitor the processes and help to detect a failure.

Ecosystems and Fisheries

The scale of the problems changes here; data are rare and noisy. We consider (in collaboration with IFREMER Nantes) some important methodological problems: 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 consider also (with INRA) problems of biological control, e.g. the introduction of ladybirds to control pests bugs) in a greenhouse.

Metabolic and genomic networks

This application is more recent, but has many links with our previous work: in fact, we consider large networks made of small biological nonlinear elements (ecosystems, metabolic network, genes network, ...) and are interested in methods enabling us to describe the dynamical behavior of the system. The classical methods are difficult to apply, because the dimension is too high. We are searching for more qualitative methods, that use for example the linear substructure (the graph) of the network, and/or the monotony of interactions; we try to reduce the system; finally, we describe the system as made by “idealized” nonlinearities, such as step functions; the resulting piecewise linear system is more amenable to a qualitative description.

5. Software

We build some software as a tool for modeling, that could be of some help to biologists or modelers. The emphasis is on the interaction with the user. We also build more pedagogical softwares, aiming at demonstrating some point of modeling or control.

Moreover, we have developed an innovative Java software aiming at the coordination of several computers acquiring experimental data on line and monitoring experimental devices. This is applied to the automated chemostat in Villefranche-sur-Mer.

6. New Results

6.1. Methodology

6.1.1. *Mathematical study of models*

Participants: Jean-Luc Gouzé, Mustapha Serhani, Valérie Lemesle.

Key words: *dynamical systems, biological models.*

Study of structured models of cell growth

Macroscopic *unstructured* mathematical models are often employed to describe cell growth in continuous culture devices, so called chemostats. This approach is based on very strong assumptions which cannot be able to characterize the physiological state of the whole cell population. Then, another modeling approach is required in order to adequately represent this physiological state. In fact, macroscopic or microscopic *structured* models are very efficient for this purpose.

Indeed, our first interest is a macroscopic description of the whole cell population growth during its cycle, taking into account the total number or the total biomass of cells. The structuration of the model is done with respect to the cell position in its cycle. This kind of modeling allows richer mathematical behavior than classical unstructured models. Indeed, as oscillatory behaviors can be observed in biological experiences, we show that the model with numbers have a limit cycle. To prove the existence of a closed orbit, properties of competitive systems, and the Bendixson criterion are used [33].

Then, a description of the cell growth based on biological mechanisms is studied. The structuration of this model is done with respect to metabolized and un-metabolized components. Moreover, cell ageing and cell respiration are taken into account. The mathematical study of this model gives the existence of either a global asymptotic equilibrium or a non trivial periodic orbit. To prove this, properties of loop systems, Poincaré - Bendixson theorem and Dulac criterion are used [58].

Mathematical study of a wastewater model.

A classical model of wastewater treatment is studied which describes an activated sludge process in which the substrate is removed by suspended one bacterial population. Three phenomena are considered: The reaction kinetics in the aerator linked to microbial growth, the substrate degradation and the recycle of the biomass. For this model, we study the basic properties of invariance, dissipation, and persistence and we prove that under a condition on parameters, there exists a interior equilibrium point which is globally asymptotically stable. Furthermore, by using properties of cooperative dynamical systems, we prove that the model is robust in the sense that when the growth rate function is not well known, but only its upper and lower bounds, we prove that there is an invariant interior cube.

6.1.2. Model design, identification and validation

Participants: Olivier Bernard, Jean-Luc Gouzé, Lionel Pawlowski, Valérie Lemesle.

Key words: *biological modeling, bioreactor, qualitative analysis.*

Model design and identification

We have developed methods to estimate the model of a system involving mass transfers between compartments [23]. These systems can be represented by a model with the general structure popularised by [47] based on an underlying reaction network:

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

Our modeling approach focuses either on the determination of the pseudo-stoichiometric matrix K or on the modeling of the reaction rates $r(\xi, \psi)$. The identification of the minimum number of reactions to be taken into account to explain a set of data is the first step [22]. Then, if additional information on the process structure is available we showed how to estimate the pseudo-stoichiometric matrix associated with the reaction network [22], [48]. The approach has been applied to bioproduction processes (vanillin production, lipase production) and to anaerobic digestion [38]. Finally we developed methods to test and validate the proposed reaction network [38]. These methods lead to identifiability conditions on the pseudo-stoichiometric coefficients and provide a framework for their estimation. The approach has been applied to bioproduction processes and to anaerobic digestion [55].

In order to test the possible structures for reaction rates $r(\xi)$, a criterion has been developed which allows us to qualitatively test possible several structures. The criterion is based on the test of the monotony of an application.

In order to validate the qualitative behavior of a dynamical model, a method has been developed to link the signs of the jacobian matrix with the possible succession of the extrema of all the state variables and with their position toward reference values such as equilibria [52]. This method was extended to time delay equations and applied to the detection of unusual interaction in planktonic nets [21].

Finally we have developed a method for determining the experimental conditions to be performed in order to better distinguish the answer from a set of models. This methodology, based on interval computation, finally leads to a criterion updated by the new available data assessing the validity associated to each model [46], [62].

Model reduction

The goal of this work is to reduce the order of state space models describing large biological or chemical networks. The state equations are assumed to be (generally) nonlinear, time-invariant, ordinary differential equations which build a modular structure together. This structure should be preserved during reduction, which can be achieved by applying existing reduction methods to modular parts of the whole system. As a first step, we consider balancing linear and nonlinear methods. [42].

6.1.3. *Nonlinear observers*

Participants: Jean-Luc Gouzé, Olivier Bernard, Valérie Lemesle.

Key words: *nonlinear observer, uncertain model, bioreactor.*

Multi-observers

We developed Bayesian observers [26], which estimate the probability density function (pdf) of the state, provided that the pdf of the parameters, of the initial conditions and of the uncertainties is known. This is applied to anaerobic digestion to estimate the biomass or the substrate.

We designed so-called bundle of observers [24][10][39]. The idea consists of considering together a set of interval observers. Each observer provides intervals in which the state is sure to lie, provided that the intervals in which the parameters, the initial conditions and more generally all the uncertainties are known. We are able to take the lower envelope of this set to improve the overall estimation.

Hybrid observers for uncertain systems

We built bounded error observers for a common class of partially known bioreactor models in two dimensions. The main idea is to build hybrid bounded observers “between” the high gain observer, which has an adjustable convergence rate but requires a perfect knowledge of the model, and the asymptotic observer which is very robust to uncertainty but with a fixed convergence rate. We build an hybrid bounded error observer which reconstructs the two states variables in two steps : the first step gives a fast convergence rate but an error depending on the knowledge of the model; the second step gives the switch to an observer similar to the asymptotic one, converging at a fixed convergence rate towards an error as small as we want. Thus, we obtain a better convergence rate for the estimated states than the classical asymptotic observer.

Moreover, it is possible to generalize this hybrid observer to higher dimensional systems. The main hypotheses are that the error of the model is on the penultimate unmeasured variables and the last variable is a linear combination of the state variables verifying a linear differential equation[32].

6.1.4. *Nonlinear control*

Participants: Jean-Luc Gouzé, Olivier Bernard, Ludovic Mailleret.

Key words: *uncertain systems, nonlinear control, bioreactor.*

Stabilization and Adaptive Regulation for Uncertain Positive Systems

A positive system is a system of ordinary differential equations, which variables remain structurally positive (or non-negative) for all positive time. We consider the control problem for some n -dimensional “uncertain” positive systems, lying in the framework of qualitatively known systems of the form:

$$\dot{x} = f(x, u) + \psi(x)$$

x denoting the state vector, u the input(s), $f(\cdot)$ a well known function and $\psi(\cdot)$ a function on which we only know some qualitative properties (such as positivity...). It is worth noting that, due to the lack of analytical knowledge on biological phenomena, these qualitatively known systems are frequently encountered in biological modeling. Since the analytical expression of $\psi(\cdot)$ is unknown, it might be impossible to predict the dynamical behavior of these system's trajectories. Our aim in this work is, from measurements of the function $\psi(\cdot)$, to design a control law, taking advantage of the qualitative properties of the function $\psi(\cdot)$ and ensuring a specific global behavior: a single, globally asymptotically stable equilibrium. A result on a specific class of such systems has been proved [35].

Moreover, as we aim at choosing the stable equilibrium value in spite of some parameters uncertainties, we derived an adaptive control law [15]. Same results have been obtained for the broader class of systems introduced in [35].

Control of competition in the chemostat

We consider the problem of feedback control of competition between two species with one substrate in the chemostat with nonmonotone growth functions. Without control, the generic behavior is competitive exclusion. The aim is to find a feedback control of the dilution rate, depending only on the total biomass such that coexistence holds. We obtain a sufficient condition for the global asymptotic stability of a unique equilibrium point in the positive orthant for a three dimensional differential system which arises from this controlled competition model [44].

Nonlinear control

F. Gognard studied the computation of the switching times of the time-optimal control law for linear systems with bounded control. He extended a result that he obtained during his PhD Thesis, and that was only valid for systems with real poles to systems with complex poles ([31]).

F. Gognard also studied the design of orbitally stable zero-dynamics for a class of cascade nonlinear systems during his post-doctoral stay at the Laboratoire d'Automatique de Grenoble ([36], [13]).

6.1.5. Game theory

Bio-economy of fishery

Participants: Odile Pourtallier, Nadia Maizi (CMA École des Mines de Paris), Gorca Merino (CISM, Barcelona, Spain).

This work is done as participation of the project-team in an European contract (BEMMFISH). The aim of the European contract is to develop a decision tool for managing fishery in Mediterranean countries. The tool developed should include both biological and economic aspects. The objective of our participation in the contract is to analyze the impact of the decentralization of the decision, using a game theory approach. Usually the search of "optimal" behavior of the agent is done by using optimization or optimal control. Nevertheless, as in many economic activities, this approach may not be the most relevant due to the non cooperation of the agents. As a matter of fact there exists a high level of concurrence in this activity, at different levels (countries (for trans boundary stocks), harbor, fleets, and vessels), and the "optimal" behavior may be different when the decision is decentralized, *i.e.* when each agent takes its own decision.

The model developed in BEMMFISH takes lot of details into account and consequently is far too complex to be used for a game theory approach. We have based our approach on a more simple model. We started from a classical global model (Schafer model) and added an economic loop. Then we analyzed the Nash equilibrium of the agents at equilibrium of the system. We studied the impact of the level of decentralization (what happens to the behavior and consequently to the stock when the number of decision makers increases), and the impact of the introduction of economic aspects in the evaluation function of the agents.

A game theory approach for pricing in electricity spot market

Participants: Mireille Bossy (OMEGA), Nadia Maizi (CMA École des Mines de Paris), Geert Jan Olsder (Delft University, the Netherland), Odile Pourtallier, Etienne Tanre (OMEGA).

The deregulation of the market of electricity in European countries, initiated in December 1996, has caused a lot of modifications and new problems in this field. Among those is the emergence of the new spot markets

of electricity. The special features of electricity, in particular the fact that it cannot be stored, implies that the classical market analysis methods are not well adapted. The specificity of these markets are closed to the pollution right markets that start to appear as a consequence of the application of the Kyoto protocol. For these new markets, new approaches have to be explored.

We have analyzed a simple model with one market and N producers using game theory. In particular we showed that for a simple bid (quantity-price), it is not possible to find a Nash equilibrium. This has raised the necessity to introduce more complex bids, and consequently, in terms of game theory, more complex strategy set. On a theoretical ground, we have analyzed the possibility to use conjectural strategies and inverse Stackelberg equilibrium.

6.2. Fields of application

6.2.1. Growth of marine plankton

Participants: Olivier Bernard, Jean-Luc Gouzé, Ludovic Mailleret, Antoine Sciandra, Gilbert Malara, Lionel Pawlowski, Cédric Prévost.

Key words: *bioreactor, plankton, population dynamics, biological models, chemostat.*

A model which describes growth of phytoplankton while light and nitrogen are both deficient was developed and studied [60]. It was validated with data from *Rhodomonas salina*. The effect of temperature was also introduced in the model. The previous model was coupled to hydrodynamical models. A 3-D model (SYMPHONIE, in collaboration with the Centre for Oceanography of Marseille, Y. Leredde) and 1D model (with the LOBSTER model issued from the LODYC, in collaboration with Marina Levy). The 1D model was calibrated using data from the DYFAMED experiments. These models were used to generate lagrangian trajectories followed by the model, and which should be reproduced in the computer-controlled experimental chemostats [45].

A set of 18 models was developed and studied to describe the coupling between photosynthesis and calcification for algae (coccolithophorids) that are responsible for very high carbon fluxes in the ocean. The qualitative study of the model showed that the standard hypotheses usually made by physiologists disagree with observed behavior.

Nonlinear Control for phytoplankton's growth in the chemostat

The chemostat is able to maintain alive a phytoplanktonic population in most of the various environmental conditions found in the oceans. However, the device becomes really sensitive as nutrient rich environmental conditions are to be reproduced. Indeed, such conditions makes phytoplanktonic population's future life hazardous, due to the chemostat's technology itself.

We propose then a control law able to reduce this structural sensitivity and based only on qualitative structural properties of the classical Droop model, work presented in [34]. An adaptive version able to drive the system towards a specific equilibrium value, despite some parameter uncertainties, is at the moment under development.

6.2.2. Bioprocesses

Participants: Jean-Luc Gouzé, Olivier Bernard, Ludovic Mailleret, Benoit Chachuat.

Key words: *bioreactor, waste water treatment, biological depollution.*

Anaerobic digestion

Within the TELEMAT European project [51][50], COMORE provides models for the anaerobic digestion process and proposes dedicated methods to calibrate these models [37], [55][53]. These models have been analysed, and the destabilisation process was studied. From this analysis, a stability criterion was proposed.

Software sensors (asymptotic, interval based or bayesian) have been developed based on the possible sets of measurements [49]. methods to assess the consistency of the information within a sensor network have been designed and tested with the available data sets [54].

Bioprocesses control

Within the context of the TELEMAC, dedicated to anaerobic waste water treatment bioprocesses, the main problem remains the structural instability of such processes. Indeed, these efficient WWTPs are well known to have two stable ways to operate in, depending on the process conditions: one is interesting for water treatment (the bacterial population is maintained alive, purifying waste water) while the other is not (the bacterial population is removed from the reactor, wastes being no more consumed). Considering the conditions of such a process at a particular moment, it is almost impossible to predict which operating condition would be reached in the future, rendering the use of such processes hazardous.

We proposed a feedback control taking advantage of online measurements of biogas production (that is directly related to biomass activity). This controller structurally achieves the global stabilization of an equilibrium point corresponding to working conditions: it ensures that waste water is purified by the bacterial population. Results are obtained for the classical AMOCO model developed by O. Bernard et al. and validated in real life on the fully instrumented anaerobic process located at the “Laboratoire de Biotechnologie de l’Environnement” of the INRA. A theoretical version of this result has been published [14] as well as a more applied version dedicated to directed towards engineers in biotechnologies [16].

Following the same approach, we presented an adaptive version of this control for simple bioprocesses suffering from modeling uncertainties. Results are structural stabilization of the processes towards a chosen equilibrium value, despite some parameter uncertainties [15].

6.2.3. Models of ecosystems

Participants: Olivier Bernard, Jean-Luc Gouzé.

Key words: *ecosystems, biological models, population dynamics.*

Biological control

In collaboration with INRA Antibes team « Biology of Interacting Populations », we study models of biological control. Our work concerns the use of the ladybird *Harmonia axyridis Pallas (Coleoptera : Coccinellidae)* against the aphid *A. gossypii (Homoptera : Aphididae)* inside greenhouses. Our research was rather theoretical this year, consisting in trying to apply methods from optimization and dynamical programming to a simple model [43].

Models of fisheries

Marion Verdoit (IFREMER) defended her thesis, done under the codirection of D. Pelletier (IFREMER) ; the second part of this thesis is devoted to the modeling of exploited resources dynamics, with an application to Celtic Sea whiting.

We describe a spatio-temporal model of the whiting population dynamics, constructed from the results of the preceding chapters in the thesis. It is a spatialized, linear, discrete time and multisite model, whose main objective is to test and explore a variety of management measures consisting in reducing or reallocating fishing effort according to areas and/or seasons characteristic of species life cycles.

However, many processes occurring in population dynamics are nonlinear, thus we introduced a nonlinear model. It is studied more theoretically to evaluate the global asymptotic stability of a class of nonlinear population models, in discrete time and without spatial component. This model is again applied to whiting population of the Celtic Sea [9].

6.2.4. Metabolic and genomic models

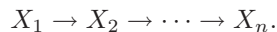
Participants: Olivier Bernard, Jean-Luc Gouzé, Frédéric Grogard, Richard Casey.

Key words: *biological networks, qualitative analysis.*

Metabolic networks

Our work has consisted in an equilibria and stability analysis of two families of metabolic networks whose models were given by a set of mass-balanced based differential equations.

The first class consists in simple metabolic pathways which are made up of a sequence of mono-molecular enzyme-catalysed reactions as where X_i ($i = 1, \dots, n$) represent the successive metabolites of the pathway:



Moreover, the last metabolite (X_n) acts as an inhibitor of the first reaction $X_1 \rightarrow X_2$. A typical situation is when such a simple pathway is located between two branch points of a complex metabolic network. The proof of global attractivity of the unique equilibrium uses the construction of converging upper and lower bounds of the trajectories ([27], [56]).

The second class of systems is made of metabolic networks whose graphic representation (with the different metabolites as nodes and the different reactions as oriented edges) is an arborescence with X_1 as root (X_1 being the only metabolite which is fed into the network). Also, the inhibition of a reaction $X_s \rightarrow X_p$ belonging to the network can only come from metabolites lying in the (sub)-arborescence having its root at X_p . This kind of inhibition is often termed “regulation” because, if an inhibiting metabolite is in large excess, it will shut-down the reaction that it inhibits (and which is at the top of its own pathway), so that the concentration of this metabolite will eventually decrease (it is “regulated” to a lower value). A notable system of this class is the aspartate amino-acid pathways ([61]). Uniqueness of the equilibrium is shown in general and its global attractivity is shown when the only present inhibitions act on the reactions having X_1 as substrate ([30], [57]). A new small-gain theorem for interconnected cooperative systems has been used for this proof ([59]).

GDyn: dynamics of genetic regulatory networks

As part of the GDyn project of Actions de Recherche Coopérative (ARC) of INRIA, 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. We apply a technique due to Filippov to study these systems on their surfaces of discontinuity by extending them into systems of differential inclusions. These 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. Current work in this project consists of continuing the work of Gouzé and Sari [12] and de Jong *et al* [11] by characterizing the equilibrium points and periodic orbits in this special class of systems, in addition to characterizing their stability. This mathematical work lays the foundation for computational methods we are developing for the qualitative analysis of genetic regulatory networks. These methods and algorithms will be integrated into the software GNA (Genetic Network Analyzer) developed by de Jong *et al* (HELIX, INRIA Rhône-Alpes) and will be applied to the study of regulatory networks underlying transcription in the bacteria *E. coli* and *Synechocystis*.

6.3. Software design

Software aiming at centralising data and managing a set of automatons associated to a bioprocess has been developed. Based on Java, it allows remote monitoring and allows us to apply a control strategy. This software is in use for the management of the chemostat at Villefranche-sur-Mer.

Software whose role is to simulate an anaerobic digestion process is currently being developed. It is aimed at teaching an operator how to manage it. The player can try a strategy, and compare with automatic controllers. This software is linked to the European project Telemac.

7. Contracts and Grants with Industry

7.1. Waste water treatment

The European project TELEMAC (Tele-monitoring and Advanced Tele-control of High-Yield Wastewater Treatment Plants) is coordinated by O. Bernard (Comore) from the scientific point of view and B. Le Dantec (Ercim) for administration (see <http://www.ercim.org/telemac>).

Partners are ERCIM, INRIA COMORE, INRA (Laboratoire des Biotechnologies de l'environnement, Narbonne), APPLITEK (captors, Belgium), Department of Applied Mathematics, Biometrics and Process Control, Gent University, Belgique), Council for the Central Laboratory of the Research Councils (CCLRC), Information Technology Department, (England), SPES (Information technologies, Italy), University of Santiago de Compostela (USC)(Spain), ENEA Waste water Treatment and Water Cycle Unit (Italy), AGRALCO (Spain), PSPc (Belgium), Tequila SAUZA S.A. (Mexico), The University of Guadalajara (UDG) (Mexico), ALLIED DOMEQ SPIRITS and WINE LTD. (DOMEQ UK), Allied Domecq Brasil Industria e Comercio Limitada (Brazil).

The TELEMAT projects is aiming at developing a general, but adaptable, remote supervision and monitoring system for water treatment. By using a network of smart sensors and web technologies, this project focuses on bringing new methodologies coming from the IST field to the water treatment units. The framework of the TELEMAT project will integrate the data collected by the sensors, detect fault or abnormal working conditions, and activate model based controllers to optimise the technology of anaerobic depollution and solve its instability.

8. Other Grants and Activities

8.1. National initiatives

- **APPLE:** A. Sciandra is the responsible for the project APPLE (Adaptation of Photosynthesis: Parametrisation from Laboratory Experiments) in the framework of PROOF (PROduction Océanique et Flux). COMORE participates in the project, funded by INSU (Institut National des Sciences de l'Univers).
- **ARC GDyn:** COMORE is a participant in the Action de Recherche Coopérative GDyn, funded by INRIA. J.-I. Gouzé coordinates the action with H. de Jong (HELIX INRIA). The aim is the analysis of piecewise linear models of gene networks (see <http://www-sop.inria.fr/comore/arcgdyn/arcgdyn-eng.html>).
- **Action ACI IMPBIO BacAttract:** COMORE is a participant in this action funded by the Ministère de la Recherche. The aim is the modelling and analysis of some well known gene networks.
- **Action ACI IMPBIO MathResoGen:** COMORE is a participant in this action funded by the Ministère de la Recherche. The aim is the analysis of metabolic networks.
- **Action Bioinformatique:** O. Bernard is responsible for the SEMPO project funded by the Action Bioinformatique (common action funded by several research institutes). The Laboratoire d'Océanographie et Biogéochimie CNRS de Marseille also participates.
- **AS Asinbio:** COMORE is a participant in the Action Spécifique "Observers for systems with unknown inputs" of the RTP50 "STIC et Environnement" funded by the CNRS.
- **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), see http://www.inapg.fr/ens_rech/bio/Ecologie/corev/corev-accueil.htm.
- **Seminar:** Jean-Luc Gouzé, Olivier Bernard et Antoine Sciandra organize a regular seminar « Modelling and control of ecosystems » at the station zoologique of Villefranche-sur-Mer or at INRIA.

8.2. European initiatives

Participation in the European project BEMMFISH: "Bio-economic modelling of Mediterranean fisheries" (O. Pourtallier). Duration 3 years.

8.3. Visits

Gorka Merino from ICM (Instituto de Ciencias del Mar, Barcelona, Spain) has been invited for one month. He worked on game theory approach of fishery management, in relation with the BEMMFISH European project.

Asma Karama (1 month) University of Marrakech- "Hybrid modelling of bioprocesses using mass balance models and neural networks"

Alain Vande Wouwer (2 days)- University of Mons, Belgium

H. de Jong (INRIA Helix, France, two weeks)

F. Mazenc (INRIA Conge, three weeks)

Georges Zaccour, from GERAD, HEC (Montreal, Canada) had a been invited for 3 days.

9. Dissemination

9.1. Leadership with scientific community

J.L. Gouzé is a member of the expert committee for Aquae INRA/Cemagref projects, for RTP50 CNRS "STIC et Environnement", of scientific committees for Alcalá 2nd international conference on mathematical ecology and POSTA 2003. He organized invited sessions for these conferences.

He is a member of the "Commission d'évaluation" of INRIA and of the Commission Scientifique Spécialisée MBIA of INRA.

O. Bernard is the scientific responsible for the European project Telemac, and is in the technical committee of the CAB conferences.

Odile Pourtallier is a member of the executive committee of ISDG (International Society in Dynamic games).

9.2. Teaching

J.L. Gouzé, O. Bernard et A. Sciandra gave two weeks of courses on mathematical models in biology at the DEA biological oceanography, Pierre et Marie Curie, Paris VI. J.L. Gouzé gave courses on dynamical systems, (15 h) and O. Bernard gave courses on modeling and classworks(20h).

J.L. Gouzé participated in a CIMPA school in Tlemcen (Algérie, May); he gave lectures on models of bioprocesses.

O. Bernard gave courses at ENS Lyon "Software sensors for biological systems", 3h, and USC (Spain) "modelling and monitoring biological systems", 9h.

Odile Pourtallier taught a class in game theory and a class in non-linear optimization to the master OSE (Optimization des Systèmes Énergétiques- Energetic system optimization) co-organized by HEDEC, l'École des Mines de Paris and the Creden, a class of optimization to the DESS IMAFA of the university of Nice Sophia Antipolis.

9.2.1. Theses

- Ongoing theses:
 - i. V. Lemesle, « Observateurs pour des systèmes dynamiques non-linéaires issus de la biologie », UNSA
 - ii. L. Mailleret, « Méthodes de l'Automatique non-linéaire pour le contrôle d'écosystèmes en bioréacteur », UNSA

- iii. L. Pawlowski, « Etude théorique et expérimentale de la croissance phytoplanctonique carencée par divers substrats », université P.M. Curie
- iv. M. Moisan « Méthodes d'identification et d'estimation pour des modèles biologiques », UNSA
- v. G. Robledo « Etude et contrôle des réseaux trophiques », UNSA
- Participation to PhD jurys: J.-L. Gouzé was the “rapporteur” for the HDR of D. Pelletier (Ifremer, Univ. Montpellier), and was in the jurys of Marion Verdoit (Paris VI) and Sophie Malherbe (Montpellier)

9.3. Conferences, invited conferences

Conferences with proceedings are not repeated here.

JL Gouzé, workshop on gene dynamics in Marseille, November 27.

O. Bernard, GreenOcean, Villefranche-sur-mer, March, 10-14, Villefranche-sur-mer, France

Bourguet N, Goutx M, Van Wambeke F, Guigue C, Sciandra A, Gattuso J-P. (2003). Effects of increased CO₂ partial pressure on the chemical composition and microbial degradation of the microalgae *Emiliana huxleyi*, EGS-AGU-EUG Joint Assembly, Nice, France, April 06-11.

Sciandra A, Harlay J, Lefèvre D, Lemée R, Rimmelin P, Denis M, Gattuso J-P. (2003a). Response of the coccolithophorid *Emiliana huxleyi* to elevated pCO₂ under nitrate limitation, EGS-AGU-EUG Joint Assembly, Nice, France, April 06-11.

Some members of COMORE participated in the annual COREV meeting (see 8.1) and gave talks.

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