Project-Team COMORE

Modelling and Control of Renewable Resources

Sophia Antipolis

THEME BIO

Activity Report

2006

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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

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

Fields of application:

- Modelling and control of the growth of the 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), 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

3. Scientific Foundations

3.1. Scientific Foundations

Keywords: *biological models*, *bioreactors*, *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 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).

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 biologists.

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... 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). They can often be answered because 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 keep 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 laws. The main problem that we have to address is the control of a complex system when the model is uncertain. We mainly work on one class of biological systems, the bioreactors, that have a growing importance in many domains related to the human environment: food (production), pharmaceuticals (production of medicine), environment (wastewater treatment, plankton study), etc. The strong structure of these systems for which the hydraulic flow plays an important role is used in order to derive controllers.

Finally we develop observers that use the model and on-line measurements to asymptotically estimate the variables that are not directly measured. These so called "software sensors" help monitoring some systems and replace some expensive measurements. For the constructions of these 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 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 also considered.

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

4. Application Domains

4.1. Application Domains

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

In our work, applications are not clearly separated from methodology elements: these "applications" raise methodological questions 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.

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 the 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.

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 the 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 genomic networks

This application 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 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). The last approach that we consider consists in using the tools of model reduction theory.

5. Software

5.1. Software

We have developed software aiming at three objectives:

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

Coordination: 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: a software has been developed for the 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, Jonathan Hess.

Study of structured models of cell growth

Unstructured macroscopic mathematical models are often employed to describe cell growth in chemostats. This modelling method is based on very strong assumptions and the resulting models are not able to characterize the physiological state of the whole cell population. Therefore, another modelling approach is required; *structured* macroscopic or microscopic models are very efficient for this purpose.

We have developed a 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 presents a limit cycle which is validated by the oscillatory behaviors that can be observed in biological experiments. To prove the existence of a closed orbit, properties of competitive systems and the Bendixson criterion are used [27].

Mathematical study of models of anaerobic plants.

A generalized Haldane model that represents the behavior of an anaerobic plant has been studied [71]. It can have three steady states, two of them being locally stable (only one of them, the "working point", is acceptable). 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 [40], [39] [71] associated to the working point. A qualitative dynamical analysis has lead to the characterization of the dynamical behavior of this system, in terms of trends of the state variables. Moreover, it has been demonstrated that, even on the basis of limited information, it is possible to identify the qualitative region of the state-space occupied by a trajectory [72].

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. Yet 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 $\mathcal{C}^0$ functions [25].

6.1.2. *Model design, identification and validation*

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

Participants: Olivier Bernard, Jean-Luc Gouzé.

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 [59]. These systems can be represented by models having the general structure popularized by [57][18], 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 [58].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 [61]. This approach has been applied to various bioproduction processes: vanillin production [59], lipase production [61], anaerobic digestion [15][47] and cheese production [74] (in collaboration with A. Hélias, INRA-GMPA, Grignon).

Modelling an experimental system often results in a number of alternative models that are all justified by the available experimental data. In order to choose the most appropriate model of this set, we have to carry out additional experiments. Therefore, we have developed, in collaboration with I. Vatcheva (German Cancer Research Center) and H. de Jong (INRIA Helix), a method for determining the experimental conditions to be performed in order to best discriminate between the set of alternative models. This methodology, based on interval computation, finally leads to a criterion which is updated by the new available data assessing the validity associated to each model [30].

6.1.3. *Nonlinear observers*

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

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

Bayesian observers

We developed Bayesian observers [21], which estimate the probability density function (*pdf*) of the state, provided that the *pdf* of the parameters, the initial conditions and the uncertainties are known. This was applied to real experiments on an anaerobic digestion plant to estimate the biomass or the substrate [21].

Interval observers

We designed so-called bundle of observers [63]. The idea consists in considering *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 [37], [36], by introducing an optimality criterion which provides the best interval estimates [82]. New results have been obtained for the case of non-monotone systems [83], and applied to an industrial anaerobic digestion plant using the measurements of the methane flow rate [84].

The observers were improved by running some of them in reverse time in order to improve the estimate of the initial condition together with some unknown parameters [43]. This approach drastically improved the observer convergence.

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 [45].

These interval observers have been extended to the case where only discrete time measurements are available [34] [68].

Moreover two book chapters dedicated to observer design for biotechnological processes have been written [17], [16].

6.1.4. *Nonlinear control*

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

Participants: Jean-Luc Gouzé, Olivier Bernard, Frédéric Grognard, Gonzalo Robledo.

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 [52], [78].

Robust control of a chemostat

The control problem for an uncertain chemostat model with a general monotone growth function has been treated in [23], where we consider one limiting substrate and one biomass species. The considered uncertainty affects the model (growth function) as well as the outputs (measurements of substrate). Despite this lack of information, an upper bound and a lower bound for these uncertainties are assumed to be known a priori.

We have been able to build a family of feedback control laws, using the dilution rate as control variable, and giving a guaranteed estimate of the unmeasured variable (biomass). These control laws asymptotically stabilize the two variables in a rectangular set, around a reference value of the substrate, so that the washout of the bioreactor is avoided.

Control of competition in the chemostat

We studied the feedback control of competition in a chemostat with a single substrate and two species (without feedback, it is known that, in most cases, one of the species eventually disappears). In a recent paper, P. De Leenheer and H.L. Smith [65] 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 (summarized as upper bounds on mortality rates) for the existence of a unique critical point which is globally asymptotically stable [69], [35].

Orbital stabilization

A method for the generation of attractive and neutrally stable limit cycles has been developed. It consists in designing an output that, when regulated through a suitable feedback, forces the existence of a limit cycle or oscillations in the zero dynamics [26].

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, Fabien Lombard.

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 [85], [88], and compared with Geider's classical model in [73] and with Pahlow's model in [56]. 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 [67]. These models were used to generate Lagrangian trajectories which should be reproduced in the computer-controlled experimental chemostats [86].

Finally, the data produced within chemostat experiments [86] in dynamical environments were used as a basis to validate a model that was implemented with the numerical tool Eco3M dedicated to biogeochemical modelling [13].

Carbon fixation by coccolithophorides

A set of 18 models was developed and studied [31], [64] 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_2 partial pressure paradoxically leads to a decrease in the calcification rate. An alternative where pH drives the carbon assimilation process is proposed and validated [64].

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 [79], [81]. 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)

Model of the growth of Oikopleura dioica

We propose a model of the growth of the appendicularian *Oikopleura dioica*, a marine planktonic filter feeder. This model is based on the metabolic balance calculated from the principal physiological functions: ingestion, assimilation, somatic and gonadic growth, respiration and production of small houses, and is validated with experimental data acquired for various conditions of food and temperature [28], [11].

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

Within the TELEMAC European project [19], COMORE has provided models for the anaerobic digestion process and proposed dedicated methods to select the appropriate model [15] and calibrate them [62]. Finally this work has mainly been focused on the design of control laws that stabilize the Wastewater Treatment Plants (WWTPs), which tend to be unstable without feedback control [29].

Asymptotic, interval based and Bayesian software sensors have been developed based on the possible sets of measurements [21], [84], [16], [44].

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 [41]. This is the topic of the ongoing Ph.D. thesis of J. Hess.

Experiments have been carried out with the LBE Narbonne, for testing the effect of the choice of the influent on the quality of the biogas (ratio CO_2/CH_4). Several COD/VFA ratios (Chemical Oxygen Demand/Volatile Fatty Acids), as well as several pH values in the input have been tested (the pH is regulated). The model presented in [5] qualitatively reproduces these observations. An improvement of this model for a more quantitative description is in construction; an important feature of this new mechanistic model is that it describes the bubbles formation (bubble nucleation and bubble rise) inside the digester [41]. It leads to a model of the liquid-gas exchange coefficient, $k_L a$.

Bioprocesses control

One of the main problems of anaerobic waste water treatment processes is their instability after too high loading. In such circumstances, the process may crash due to its complete acidification.

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 adequate operating conditions [75], [76] and is generalized in [52], [78].

An adaptive version of this control for simple bioprocesses suffering from modelling uncertainties allows for structural stabilization of the process towards a chosen equilibrium value, despite some parameter uncertainties [77]. This approach has been validated through the application of the controller on a virtual WWTP [80].

Another proposed approach assumes the online-measurement or reconstruction via software sensors of the substrate concentration in the plant (the COD), and proposes the regulation of this COD towards a safety zone via a saturated proportional controller [24]. The stability analysis of the closed-loop system shows that the safety zone is attractive and, after some finite time, invariant.

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 (in roses greenhouses). We consider that, once the presence of pest is detected, it is too late; the roses cannot be sold anymore. Therefore, the predators have to be introduced in order to prevent the appearance of the pests in the greenhouse. Early theoretical and experimental results tend to show that it is better to regularly introduce small amounts of predator (so that the predator population is kept at an average level) rather than introduce large amounts of predators less often ([42], [53]). In this last case, there is a risk that the predator population dies out (due to the lack of preys/pests) before the pests outbreak. The effect of periodic partial harvest on the biological control's efficiency also has been analyzed ([55]).

6.2.4. *Metabolic and genomic models*

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

Participants: Olivier Bernard, Jean-Luc Gouzé, Frédéric Grognard, Etienne Farcot, Laurent Tournier, Ibrahima Ndiaye.

Metabolic and genetic networks

We study the equilibria and their stability for a family of metabolic networks whose models are given by a set of mass-balance based differential equations. Those networks have a graphic representation (with the different metabolites X_i as nodes and the different reactions as oriented edges) as an arborescence with X_1 as root (X_1 being the only metabolite which is fed into the network). We also imposed that the inhibition of a reaction $X_s \to X_p$ belonging to the network can only come from metabolites lying in the (sub)-arborescence having its root at X_p. 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 a substrate [22].
We have considered the large class of metabolic models regulated by genetic networks, and several small models in this class. We apply different techniques: time scale reduction or a recent small-gain theorem for non-monotone systems that can be split into two inter-connected monotone systems ([54], [46]).

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 [70] and de Jong *et al* [89] by characterizing the equilibrium points and periodic orbits in this special class of systems, in addition to characterizing their stability. We prove several theorems that characterize the stability of these singular equilibria directly from the state transition graph, which is a qualitative representation of the dynamics of the system. We also formulate a stronger conjecture on the stability of these singular equilibrium sets [20], [32].

These methods and algorithms will be used into 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* [14].

We have considered the mathematical model of the regulatory network of the carbon starvation response in *Escherichia coli* described by Ropers et al. [87], [48]. This model has six state variables, and can be studied by the qualitative methods cited above. A finer study is also possible, restricting the behavior to a two-dimensional system after some transients. The study of this last system permits to show the Filippov modes, and the converging oscillating behavior near the equilibrium ([38]).

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. A way to perform this reduction is to consider the interaction graph underlying the system and to decompose it into strongly connected components. We then use this decomposition to express the initial dynamical system in a hierarchical form. A quasi-linear algorithm for such a decomposition has been implemented as a GNA module [49]. Current work consists in studying the dynamical behavior of the whole system, after some transient, according to the dynamical properties of the isolated subsystems, particularly when these subsystems have stable equilibria.

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 the each input variable affects at most one variable, the solutions of these inequalities can in fact be obtained explicitly [50], [66].

Transitions analysis of models of genetic regulatory networks

Another aspect of these equations is that they lead to efficient numerical simulations, based on the reduction to a discrete-time dynamical systems defined on the hyperplanes where the vector field is discontinuous. Using this technique, we have simulated a large numbers of randomly generated systems, automatically detecting whether their asymptotic behavior was steady, periodic, or chaotic. This has led us to the conclusion that systems with several thresholds per variable present significantly more oscillatory behavior than those with a unique threshold per variable [33].

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 [51].

6.3. Software design

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

Participants: Olivier Bernard, Serigne Sow, Romain Primet.

A C++ advanced monitoring platform, using a Scilab computation engine, has been developed in collaboration with INRA (Laboratoire de Biotechnologie de l'Environnement). It provides a framework for the smart management of bioreactors. This software, called ODIN [60], receives data from the process in XML format, displays the results, computes software sensors, fault diagnosis and runs control algorithms. It explicitly manages the uncertainty characterizing bioprocesses. It is highly modular to adapt to any type of plant.

Within the framework of the TELEMAC project we have developed a Matlab-based simulation platform allowing us to emulate an anaerobic wastewater treatment plant. The platform developed in collaboration with the University of Santiago de Compostella allows to define the type of available sensors and their characteristics, the used actuators, and the influent characteristics. The model can then run and produce XML files as if it was a normal process. This virtual plant can be accessed and steered as if it were a real plant. This can then be used to train experts to manage anaerobic plants through the Internet.

7. Contracts and Grants with Industry

7.1. Wastewater treatment

The European project TELEMAC (Tele-monitoring and Advanced Tele-control of High-Yield Wastewater Treatment Plants) was coordinated by O. Bernard (Comore) from the scientific point of view and B. Le Dantec (Ercim) for administration (see http://www.ercim.org/telemac). This project that ended in 2005 included 15 partners, among which 5 industrials. The TELEMAC project aimed at developing a general, modular, remote supervision and monitoring system for wastewater treatment. It lead to commercialization of a sensor and to development of the ODIN platform which is currently in the process of being improved for commercial use. It also produced more than 67 conference proceedings and 21 publications in scientific journals.

7.2. Microalgae for CO_2 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_2 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.

- **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_2 production processes involving anaerobic bacteria or microalgae.

- **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 (see http://www.inrialpes.fr/helix/people/dejong/projects/aci03/bacattract-eng.html).

- **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/genetic networks.

- **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.

- **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).

- **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, 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.

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'Oceanographie 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

- Hugh Mac Intyre (University of Alabama), 3 months at Villefranche-sur-Mer;

- Jean-Philippe CASSAR (LAGIS - Lille), 1 day;

- Guillaume Goffaux (Fac. Polytechnique de Mons, Belgium), 3 days;

- Laurence Pottier (CIRAD, Montpellier), 1 day;

- Madalena Chaves (University of Stuttgart), 2 days;

- Arnaud Muller-Feuga (IFREMER, Montpellier), 1 day;

- Hidde de Jong (INRIA Helix, France), 1 week (cumulated visits);

- Ludovic Mailleret (INRA Antibes, France), 1 month (cumulated visits);

- Ouadiaa Barrou (Université de Marrakech), 3 months;

- Asma Karama (Université de Marrakech), 3 days;

- INRIA-MERE project-team (Montpellier) for a joint seminar, 2 days.

9. Dissemination

9.1. Leadership with scientific community

J.-L. Gouzé is a member of the expert committee for Aquae INRA/Cemagref projects and of scientific committees for the conferences POSTA2006 (Second Multidisciplinary International Symposium on Positive systems, theory and applications, Grenoble 2006) and CIFA (Conférence Internationale Francophone d'Automatique, Bordeaux 2006).

He is a member of the international visiting committee for the evaluation of the MIA department of INRA, of the Commission Scientifique Spécialisée MIA of INRA, and of juries of INRA. He is the co-head of an INRIA committee supervising the doctoral theses and is in charge of the relations with the University of Nice-Sophia-Antipolis.

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.

9.2. Teaching

J.-L. Gouzé, O. Bernard, F. Grognard and A. Sciandra gave two weeks of courses in December 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. Grognard on control of biological systems (3h) and classworks (4h).

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.

J.-L. Gouzé gave lectures for a summer school école CEA-EDF-INRIA: "Nonsmooth dynamical systems. Analysis, control, simulation and applications", 29 May to 02 June, INRIA Rocquencourt. Title: "Applications of nonsmooth systems: Genetic networks" .

9.2.1. Theses

- Ongoing theses:

    1. M. Moisan, "Méthodes d'identification et d'estimation pour des modèles biologiques", UNSA

    2. J. Hess, "Modélisation de la qualité du biogaz d'un méthaniseur et stratégie de régulation et de surveillance en vue de sa valorisation", UNSA.

    3. S. Nundloll, "Modélisation et optimisation de la lutte biologique", UNSA.

    4. I. Ndiaye, "Analyse mathématique et contrôle de modèles de réseaux de régulation génétique", UNSA.

    5. 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.

- Defended theses:

    1. G. Robledo, "Quelques Résultats sur la Commande du Chemostat", PhD Thesis, Université de Nice Sophia-Antipolis (supervisor: J.-L. Gouzé).

    2. F. Lombard, "Etude et modélisation du couplage des dynamiques prédateur-proie entre un organisme du zooplancton (Oikopleura dioica) et une algue en environnement contrôlé (Chémostat)", PhD Thesis, Université Pierre et Marie Curie, Paris VI, (supervisors: G. Gorsky and A. Sciandra).

- Participation in PhD juries:
    J.-L. Gouzé was referee for the thesis of B. Juillet, "Modélisation compartimentale du métabolisme interrégional de l'azote alimentaire chez l'homme", INAPG, Paris.
    J.-L. Gouzé was referee for the thesis of X. Hulhoven "Bioprocess software sensors development facing modelling and model uncertainties", Univ. Libre de Bruxelles, Belgium.
    J.-L. Gouzé was referee for the "Habilitation" of F. Mazenc, "Analyse de stabilité et commande de systèmes non linéaires", Univ. Montpellier.

O. Bernard was in the PhD Jury of Caroline Tolla "Modélisation des populations microbiennes en environnements variables", Univ. Of Marseille.

O. Bernard was referee in the PhD Jury of Jorge Rodriguez "Modelling anaerobic mixed culture fermentations", Univ. Of Santiago de Compostella.

9.3. Conferences, invited conferences

Conferences with proceedings are not repeated here.

O. Bernard was invited to give a seminar at the Univ. Polytechnique de Mons (Belgium) and for a conference/workshop on modelling anaerobic digestion together with D. Batstone (Queensland, Australia).

JL Gouzé was invited to give a talk at the AIMS' Sixth International Conference on Dynamical Systems, Differential Equations and Applications, Université de Poitiers, France (june 25-28) and gave a talk at the conference CIMODE (Conférence Internationale sur les Mathématiques de l'Optimisation et de la Décision), Université Antilles-Guyane Guadeloupe (april 18-21).

F. Grognard was invited to give a talk at the Workshop CNRS-NSF "Biology and control theory : current challenges" (Toulouse).

E. Farcot gave a talk at the workshop "Dynamics and structure of biological networks", part of the GEO-CAL'06 event in Marseille Luminy, in january. He also gave a talk at the conference ICMSB (International Conference on Molecular Systems Biology) in august, in Munich.

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