

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

THEME BIO

The logo consists of the word "Activity" in a white serif font, with a large, stylized, light grey letter "A" to its left. Below this, the word "Report" is written in a white serif font, with a large, stylized, light grey letter "R" to its left. A horizontal white line is positioned between the "Activity" and "Report" text.

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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) 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) which is 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: food (production), pharmaceuticals (production of medicine), environment (wastewater treatment), etc.
- Dynamics and control of ecosystems, of fisheries: we build models for ecosystems (insects, fishes) and try to achieve optimal regulation.
- Modeling of metabolic and genetic networks.

Software for biological modeling.

National, international and industrial relations

- Collaboration with IFREMER (Nantes), INRA (BIA Montpellier, LBE Narbonne), 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 (Belgique), University of Marrakech (Marocco), University of Twente (Netherland).
- European project IST TELEMAT on waste-water treatment.

3. Scientific Foundations

Keywords: *biological models, bioreactor, dynamical systems, ecosystems, environment, nonlinear control theory, 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 how these complex dynamical systems work 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 available measurements on the system). In our case, the system is an ecosystem, modeled by a mathematical model (generally a set of differential equations). 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 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. This approach is based on the qualitative analysis of the data (extrema, relative position,...) that we use 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 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 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. 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 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 to try to control 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" 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. 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

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

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.

Modeling 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 adapted to the application of the methods resulting from the theory of control. Our current work consists in designing, studying and validating models of phytoplankton growth in a variable environment (light, nutrients, etc). The 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 the ocean and the 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 (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 also consider (with INRA) problems of biological control in a greenhouse (e.g. the introduction of ladybirds to control pests).

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 analysis methods are difficult to apply here, because the dimension of the networks is too large. Therefore, we are searching for more qualitative 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

Building a software is mostly seen as a tool for modeling, that could be of some help to biologists or modelers, and the emphasis is made 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*

Keywords: *biological models, dynamical systems.*

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

Study of structured models of cell growth

Macroscopic *unstructured* mathematical models are often employed to describe cell growth in chemostats. This 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 modeling approach is required: macroscopic or microscopic *structured* models are very efficient for this purpose.

Our first model aims at a macroscopic description of the whole cell population during its cycle, taking the total number or the total biomass of cells into account. The structuration of the model is done with respect to the cell position in its cycle. This kind of modeling allows for richer mathematical behaviors than classical unstructured models. Indeed, as oscillatory behaviors can be observed in biological experiences, we show that the proposed model presents a limit cycle. To prove the existence of closed orbit, properties of competitive systems, and the Bendixson criterion are used [62],[12].

Our second approach is based on a microscopic description of the cell growth, that relies on biological mechanisms. The structuration of this model is done with respect to metabolized and un-metabolized components. The mathematical study of this model results in the existence of either a globally asymptotically stable equilibrium or a locally stable non trivial periodic orbit. To prove this, properties of monotone loop systems, Poincaré - Bendixson theorem and Dulac criterion are used [23][47].

Furthermore, we have considered model reduction methods by applying singular perturbation analysis to systems that are such that their reduced model is one of the above models [12].

Mathematical study of models of anaerobic plants.

The classical model that is used to describe the anaerobic degradation of organic carbon has three equilibrium points. Two of them are locally stable. The study of this system under various conditions has allowed for the estimation of the size of the attraction basins associated to each of the equilibria. The size of these attraction basins has served for the design of a criterion that estimates (online) the destabilization risk associated to a control policy.

We have also studied the structure and stability of the equilibria of an n -step model of degradation of substrate by a cascade of bioreactions (anaerobic digestion being a two-step model). In particular, we have been interested in determining if this family of models could generate equilibria presenting any pattern of persistence or extinction of the successive biomasses [50].

6.1.2. Model design, identification and validation

Keywords: *biological modeling, bioreactor, qualitative analysis.*

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

Model design and identification

One of the main families of biological systems that we have been studying involves mass transfers between compartments, whether those compartments are bacterias and substrates in a bioreactor or species populations in an ecosystem. We have recently developed methods to estimate the models of such systems [16]. These systems can be represented by models having the general structure popularized by [56], and based on an underlying reaction network:

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

We try to give an answer to two problems: the determination of the pseudo-stoichiometric matrix K and the modeling 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 [15]. 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 [15]. Finally we developed methods to test and validate the proposed reaction network [15][16]. These methods lead to identifiability conditions on the pseudo-stoichiometric coefficients and provide a framework for their estimation. This approach has been applied to bioproduction processes (vanillin production, lipase production) and to anaerobic digestion (estimation [31] and validation [40]).

In order to test the possible structures of the reaction rates $r(\xi)$, a first criterion has been developed which allows us to qualitatively test several possible structures. The criterion is based on the test of the monotonicity of an application [11].

A second structural criterion to validate the qualitative behavior of a dynamical system still has to be extended. The method links the signs of the Jacobian matrix with the possible succession of the extrema with respect to time of all state variables along a solution of the dynamical system and with their position toward reference values such as equilibria [58][11].

Finally, we noticed that modeling 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 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 updated by the new available data assessing the validity associated to each model [69], [70].

6.1.3. Nonlinear observers

Keywords: *bioreactor, hybrid observers, nonlinear observer, uncertain model.*

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

Multi-observers

We developed Bayesian observers [36][30][37], which estimate the probability density function (*pdf*) of the state, provided that the *pdf* of the parameters, the initial conditions and the uncertainties is known. This was applied to real experiments on an anaerobic digestion plant to estimate the biomass or the substrate.

We designed so-called bundle of observers [18][34][35]. The idea consists in considering a *set of* interval observers. Each observer computes intervals in which the state is sure to lie, provided that the intervals inside which the parameters, the initial conditions and more generally all the uncertainties lie are known. We are able to take the lower envelope of this set to improve the overall estimation. The approach has been extended to a broader class of systems (e.g. including mortality) and to non-monotone (and thus non cooperative) systems.

Hybrid observers for uncertain systems

We build bounded error observers for a classical family 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 towards 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 consists in switching 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 [24].

Moreover, it is possible to generalize this hybrid observer to higher dimensional systems in a generalized chained form. The main hypotheses are that the first variable of the chain is measured, that the error of the model is on the derivative of the penultimate unmeasured variable and that the last variable is a linear combination of the other state variables verifying a linear differential equation [12].

6.1.4. Nonlinear control

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

Participants: Jean-Luc Gouzé, Olivier Bernard, Ludovic Mailleret, Frédéric Grogard, Gonzalo Robledo.

Stabilization and Adaptive Regulation for Uncertain Positive Systems

A positive system is a system of ordinary differential equations, whose variables remain structurally positive (or non-negative) for all positive times.

We consider the control problem for some n -dimensional “uncertain” positive systems, lying in the framework of qualitatively known systems of the form:

$$\begin{cases} \dot{x} &= f(x, u) + \psi(x) \\ y &= \psi(x) \end{cases}$$

with x denoting the state vector, u the input(s), $f(\cdot)$ a well known function and $\psi(\cdot)$ a function which is only qualitatively known (by features such as positivity,...), but which is measured online.

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 systems. In order to overcome this difficulty, the aim of this work has been to design a control law taking advantage of the qualitative properties and of the online measurements of $\psi(x(t))$. Through our proposed control law, the closed-loop behavior of the system presents a single, globally asymptotically stable equilibrium for some family of functions $f(\cdot)$.

Moreover, as we aim at choosing the globally asymptotically stable equilibrium value in spite of some parameters uncertainties and/or time variations, we derive an adaptive control law. Up to now, this adaptive version has only been published in a specific low dimensional case [25], but similar results have been proved for the more general case [13].

Robust control of a chemostat

The control problem for an uncertain chemostat model with a general monotone growth function has been treated ([52][20]). 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 those 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 estimation on the unmeasured variable (biomass), and asymptotically stabilizing 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

The feedback control of competition in a chemostat with a single substrate and two species is now considered (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 [60] 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.

On the other hand we have accomplished (in [42]) the study of a model of competition chemostat with more general functional responses. We generalize the result obtained by De Leenheer and Smith [60] by allowing non-monotone uptake functions.

Control of predator-prey systems

We have developed a Lyapunov-based control law for the regulation of the equilibrium of n -dimensional Lotka-Volterra systems of differential equations representing the predator-prey interaction between n species. This control law is sign-definite because we suppose that we can only decrease the growth-rate of the considered species (through harvesting or pesticides) or increase it (through a release in the considered ecosystem of some elements of some species). The Lyapunov function that we use is the classical first-integral of Lotka-Volterra systems, and the stability analysis requires the use of LaSalle's invariance principle (it is completed for $n = 2$ and $n = 4$ in [45]).

Nonlinear control

In many applications, the natural operating mode of a control system is an oscillating one, whether this oscillation is present in the open-loop dynamics, like in Lotka-Volterra predator-prey systems, or not. In [22] and [21], we were inspired by the oscillating aspect of the walking mechanism to design a controller that ensures stability of a limit cycle in the dynamics of underactuated robots, like the pendubot (through the design of orbitally stable zero-dynamics).

6.2. Fields of application

6.2.1. Growth of marine plankton

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

Participants: Olivier Bernard, Jean-Luc Gouzé, Ludovic Mailleret, Antoine Sciandra, Lionel Pawlowski, Fabien Lombard.

A model which describes growth of phytoplankton while light and nitrogen are both deficient was developed and studied in [65], and compared with Geider's classical model in [53]. 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 equations to obtain a 3-D model (SYMPHONIE, in collaboration with the Centre for Oceanography of Marseille, Y. Leredde) and 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 [19]. These models were used to generate Lagrangian trajectories which should be reproduced in the computer-controlled experimental chemostats [66].

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 this set showed that the standard hypotheses usually made by physiologists disagree with observed behaviors, since experiments have shown that an increase in the partial CO₂ pressure paradoxically leads to a decrease in the calcification rate [11].

Nonlinear Control for phytoplankton's growth in the chemostat

The chemostat is the main device that is used for macroscopic marine phytoplankton's growth experimental study. It is able to maintain a phytoplanktonic population alive in most of the various environmental conditions that can be found in the oceans. However, the device becomes really sensitive when nutrient rich environmental conditions (such as in atolls' lagoons) are to be reproduced. Indeed, such conditions make the phytoplanktonic population's future life hazardous, due to the chemostat's technology itself.

We propose a control law which is able to reduce this structural sensitivity and is only based on qualitative structural properties of the classical Droop model [26]. An adaptive version that can drive the system towards a specific equilibrium value, despite some parameters uncertainties, is under development.

6.2.2. Bioprocesses

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

Participants: Jean-Luc Gouzé, Olivier Bernard, Ludovic Mailleret, Arnaud Hélias, Frédéric Grognard, Jonathan Hess.

Anaerobic digestion

Within the TELEMAC European project [33][32][17], COMORE provides models for the anaerobic digestion process and proposes dedicated methods to calibrate these models [68], [39][40][31]; this work has mainly been done in order to design control laws that stabilize the Wastewater Treatment Plants (WWTPs), which tend to be unstable without feedback control. Our latest and future work is aimed at the modeling of the quality of the biogas which is produced by the digester in order to design regulation strategies for this quality, so that this biogas can be used as an energy source (this is the topic of the ongoing Ph.D. thesis of J. Hess).

Methods to assess the consistency of the information within the sensor network have been designed and tested with the available data sets [38][41][46][28][49].

Software sensors (asymptotic, interval based or Bayesian) have been developed based on the possible sets of measurements [30][38].

Bioprocesses control

Within the context of the TELEMAC project, 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 operating points, depending on the process conditions: one is interesting for water treatment (the bacterial population is maintained alive, purifying wastewater) while the other is

not (the bacterial population is removed from the reactor, wastes being no longer 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 wastewater is purified by the bacterial population. Results are obtained for the classical AMOCO model developed by O. Bernard et al. [3] 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 [63] as well as a more applied version dedicated towards engineers in biotechnologies [64].

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 [25]. This approach has been validated through the application of the controller on a virtual WWTP [48].

Another proposed approach supposes the online-measurement or reconstruction via software sensors of the waste concentration in the plant (the Chemical Oxygen Demand, COD), and proposes the regulation of this COD towards a safety zone via a saturated proportional controller [43]. 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: Olivier Bernard, Jean-Luc Gouzé, Mounir Jerry.

Biological control

In collaboration with INRA Antibes team “Biology of Interacting Populations”, we study models of biological control. Our work deals with the use of the ladybird *Harmonia axyridis Pallas (Coleoptera : Coccinellidae)* against the aphid *A. gossypii (Homoptera : Aphididae)* inside greenhouses. This year’s research on that subject was rather theoretical in considering non classical optimal control problems for a prey-predator system: we look for the optimal initial condition of the predators population in order to reduce the damages caused by the aphids; we consider several criteria for optimizing and several models, both of increasing complexity [54].

6.2.4. Metabolic and genomic models

Keywords: *biological networks, qualitative analysis.*

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

Metabolic networks

The problem that we handle is the equilibria and stability analysis of a family of metabolic networks whose models are given by a set of mass-balance based differential equations. This family of networks that is made of those networks whose graphic representation (with the different metabolites X_i 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). We also imposed that 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 the aspartate amino-acid pathways [67]. 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 [44]. A new small-gain theorem for interconnected cooperative systems has been used for this proof [59].

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 in continuing the work of Gouzé and Sari [61] and de Jong *et al* [29] 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 [51].

This mathematical work lays the foundation for computational methods that 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*.

We also have more accurately studied the influence of discretization (Euler type method), and the possibility of using simple controls for two very basic networks: repressor-repressor and activator-repressor. The control is a third exterior gene or the degradation rates of the proteins [55].

6.3. Software design

We have developed an innovative Java software named SEMPO aiming at the centralization of the data issued from several heterogeneous and complex automaton driven by computers. The acquired data are merged within a data base. The set of data can be displayed and serve to compute a control action which is applied through the desired automaton. This generic and modular SEMPO software is actually used to manage the automated chemostat in Villefranche-sur-Mer.

A Matlab-based software has been developed in collaboration with INRA (Laboratoire de Biotechnologie de l'Environnement) within the European project TELEMAT to provide a framework for the smart management of bioreactors. The application, called ODIN [57], receives data from the process in XML format, displays the results, computes software sensors, fault diagnosis and isolation algorithms, and applies control algorithms. It explicitly manages the uncertainty characterizing bioprocesses. It is highly modular to adapt to any type of plant. It is currently used by partners of the TELEMAT project to control anaerobic digesters, both at pilot and industrial scales.

Within the framework of the TELEMAT 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 piloted as if it were a real plant. This can then be used to train experts to manage anaerobic plants through the Internet.

We also 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.

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) 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 Compostella (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 DOMEQC SPIRITS and WINE LTD. (DOMEQC UK), Allied Domecq Brasil Industria e Comercio Limitada (Brazil).

The TELEMAC projects is aiming at developing a general, modular, remote supervision and monitoring system for wastewater 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 field. The TELEMAC system integrates the data collected by the sensors, estimates the non-measured variables, detects faults or abnormal working conditions, and activates model based controllers to guarantee the efficiency of the depollution, a constant quality of the produced biogas, as well as the perennality of the process .

8. Other Grants and Activities

8.1. National initiatives

- **APPLE:** A. Sciandra is the responsible for the APPLE project (Adaptation of Photosynthesis: Parameterization 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/arcgdn/arcgdn-eng.html>).
- **Action ACI IMPBIO BacAttract:** COMORE is a participant in this action funded by the Ministère de la Recherche. The aim is the modeling 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/genetic networks, (see <http://name.math.univ-rennes1.fr/ovidiu.radulescu/ACI.html>).
- **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 "Modeling 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 Modeling 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 modeling and analysis of biochemical networks.
- **European Network of Excellence HYCON:** The objective of the NoE HYCON (Hybrid Control: Taming Heterogeneity and Complexity of Networked Embedded Systems) is establishing a durable 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/>).
- **European project BEMMFISH:** “Bio-economic modeling of Mediterranean fisheries” (O. Pourtallier, now with Coprin research team) whose duration is 3 years. The aim of the European contract is to develop a decision tool for managing fisheries in Mediterranean countries. This tool 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.
- **PAI Tournesol:** F. Grognard is the responsible for the PAI project Tournesol (Belgique, communauté française) entitled “Modélisation dynamique et stabilité de réseaux dynamiques”. This project is a bilateral collaboration of COMORE with the CESAME laboratory (Université Catholique de Louvain, Belgium).

8.3. Visits

- H. de Jong (INRIA Helix, France, one week)
- R. Edwards (University of Victoria, Canada)
- G. Bastin (CESAME, Université Catholique de Louvain, Belgium)
- J. Van Schuppen (CWI, The Netherlands)

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”, and a member of scientific committees for various conferences.

He is a member of the “ Commission d’évaluation” of INRIA and of the Commission Scientifique Spécialisée MBIA of INRA. He was a member of the juries for INRIA candidates (researcher and senior researcher competitive examination).

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

O. Bernard has organized an INTECH-Sophia Meeting (technological workshop, gathering research and industry) on May 19 entitled “Great challenges for wastewater treatment” (with researchers from INRA, ADEME, and people of the waste treatment industry)

9.2. Teaching

J.-L. Gouzé, O. Bernard et A. Sciandra gave two weeks of courses in January on mathematical models in biology at the DEA biological oceanography, Pierre et Marie Curie, Paris VI. J.-L. Gouzé gave courses on dynamical systems, (12 h) and O. Bernard gave courses on modeling and classworks(12h). In December, J.-L.

Gouzé again gave those courses on dynamical systems (6h) in the now Master on biological oceanography, with F. Grognaud teaching a course on control of biological systems (3h).

J.-L. Gouzé participated in a school/workshop on mathematics and renewable resources at the Centro de Modelamiento Matemático of the Universidad de Chile (in Santiago, Chile, two weeks in April); he gave lectures and conferences.

O. Bernard gave courses at the Institut National Agronomique Paris-Grignon (3h).

9.2.1. Theses

- Ongoing theses:
 - i. M. Moisan, “Méthodes d’identification et d’estimation pour des modèles biologiques”, UNSA
 - ii. G. Robledo, “Etude et contrôle des réseaux trophiques”, UNSA
 - iii. 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)”, Université P.M. Curie.
 - iv. J. Hess, “Modélisation de la qualité du biogaz d’un méthaniseur et stratégie de régulation et de surveillance en vue de sa valorisation”, UNSA.
- Participation to PhD juries: J.-L. Gouzé was the “rapporteur” for the HDR (habilitation) of J. Harmand (INRA), and the PhD thesis of Ruben Sierra (UNED Madrid).
O. Bernard was in the PhD Jury of Asma Karama (Univ. Of Marrakech) and in the jury of Laurent Lardon (LBE-INRA).

9.3. Conferences, invited conferences

Conferences with proceedings are not repeated here.

J.-L. Gouzé was invited to give a talk in the session “Mathematical Biology”, organized by Gail Wolkowicz (MacMaster University, Toronto, Canada) during the French-Canadian mathematical conference (Toulouse, July).

G. Robledo gave a talk at the joint Seventh International Conference on Mathematical Population Dynamics (MPD7) and Third International Conference on Deterministic and Stochastic Modeling of Bionteraction (DESTOBIO 3) in Trento (Italy) entitled “Robust control for an uncertain chemostat”.

B. Faugeras and L. Pawlowski gave talks at the EGS-AGU-EUG Joint Assembly, Nice, France, April.

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