INRIA

Project-Team COMORE

Modelling and Control of Renewable Resources

Sophia Antipolis

THEME BIO

Activity Report

2005

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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 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 TELEMAC on waste-water treatment.

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 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 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 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: 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 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. 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 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 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" help monitoring some systems and replace some expensive measurements. For the constructions of these observers, we are faced with uncertainty specific to biological modeling: the model is uncertain (parameters, functions) while the inputs can also 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

4.1. Application Domains

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

In our work, the "applications" part is not clearly separated from the methodology part: these "applications" 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 well suited 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 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).

Metabolic and genomic networks

This application is more recent, but has many links with our previous work: in fact, we consider large networks made of small biological nonlinear elements (ecosystems, metabolic network, genes network, ...) and are interested in methods enabling us to describe the dynamical behavior of the system. The classical methods 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:

Modeling: software has been developed 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 software, aiming at demonstrating some point of modeling or control.

Coordination: 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.

Control: a software has been developed in collaboration with INRA (Laboratoire de Biotechnologie de l'Environnement) within the European project TELEMAC to provide a framework for the smart management of bioreactors (data acquisition, fault diagnosis, control algorithm,...).

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

Macroscopic *unstructured* mathematical models are often employed to describe cell growth in chemostats. This modeling 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 model is structured 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 experiments, 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 [66], [67].

Our second approach is based on a microscopic description of the cell growth, that relies on biological mechanisms. This model is structured 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 [24].

Mathematical study of models of anaerobic plants.

The classical Haldane 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 led to 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. This criterion has been extended to account for the estimated state of the process [62].

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, that is the species that requires the smallest substrate concentration to have a growth-rate equivalent to the dilution rate: 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 [33], [61]. 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.

6.1.2. *Model design, identification and validation*

Keywords: *biological modeling*, *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 those compartments are bacteria and substrates in a bioreactor or species populations in an ecosystem. We have developed methods to estimate the models of such systems [14]. These systems can be represented by models having the general structure popularized by Bastin & Dochain [39], 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 [13]. Finally we developed methods to test and validate the proposed reaction network [14]. 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 [43] and validation [53]). This approach led to the estimation of the required complexity to represent a set of data from an anaerobic plant [15], [29]

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 [28].

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 [49], [42], [50], [18], 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 [18].

Multi-observers

We designed so-called bundle of observers [46], [45], [30]. 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. The approach has been extended to a broader class of systems (e.g. including mortality) and to non-monotone (and thus non cooperative) systems [34]. The predictions of these observers were compared with other estimations provided by ellipsoidal approaches [64]. These techniques were improved by mixing various types of interval observers associated to different gains [75]. In particular, the hybrid observers developed in [25] were used to design a bundle of observers providing an optimized state interval estimate [59] (see another application of the hybrid observer in [11]). Observers running backward to improve both initial state estimate and unknown input were also proposed [74]. A method to guarantee estimates in the case of discrete measurements is currently under study.

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.

Robust control of a chemostat

The control problem for an uncertain chemostat model with a general monotone growth function has been treated in [21], [57], 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 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 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.

Preliminary results for the stabilization of the uncertain chemostat while taking a delay in the measurements into account have been submitted for publication [78] and other initial results have been obtained in collaboration with Eduardo Liz of the University of Vigo (Spain).

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 [54] 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 [22], [38], [56].

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 [32].

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.

A model which describes growth of phytoplankton while light and nitrogen are both deficient was developed and studied [76], and compared with Geider's classical model [63] and with Pahlow's model [36]. It was validated with data from *Rhodomonas salina*. 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 [20]. These models were used to generate Lagrangian trajectories which should be reproduced in the computer-controlled experimental chemostats [77].

A set of 18 models was developed and studied to describe the coupling between photosynthesis and calcification for algae (coccolithophorids) 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 partial CO_2 pressure paradoxically leads to a decrease in the calcification rate [40], [47].

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 model to which the classical Droop model belongs [26], [73]. 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 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 [68].

6.2.2. *Bioprocesses*

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

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

Anaerobic digestion

Within the TELEMAC European project [16], [48], [44], COMORE provides models for the anaerobic digestion process and proposes dedicated methods to select the appropriate model [15], [29] calibrate them [52], [53], [43]; 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 [35]. Our current work is aiming at the modeling of the quality of the biogas which is produced by the digestor in order to design regulation strategies, so that this biogas keeps a constant quality and 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 [27], [51], [55], [65], [80].

Software sensors (asymptotic, interval based or Bayesian) have been developed based on the possible sets of measurements [18], [42], [51].

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

Experiments have been carried out with the LBE at Narbonne, for testing the effect of the choice of the influent on the quality of the biogas (ratio CO_2/CH_4). Several ratios COD/VFA, as well as several pH values in the input have been tested (the pH is regulated). The experiments have shown the influence of the preacidification of the influent, as well as the importance of the pH and the alkalinity for the quantity of methane that is contained in the biogas. The model presented in [3] qualitatively reproduces these observations. An improvement of this model for a more quantitative description is in construction; an important feature of this new model is that it describes the bubbles formation inside the digester.

Bioprocesses control

One of the main problems of anaerobic waste water treatment bioprocesses is their instability after too high loading. In such circumstances, the process crashes 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 [69], [70].

An adaptive version of this control for simple bioprocesses suffering from modelling uncertainties allows structural stabilization of the process towards a chosen equilibrium value, despite some parameter uncertainties [71]. This approach has been validated through the application of the controller on a virtual WWTP [72].

Another proposed approach assumes 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 [23], [60]. 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, Frédéric Grognard.

We discussed with S. Ben Miled and A. Khebir (ENIT Tunisie) a model of the life cycle of the grouper, and its optimization with a fishing rate.

We have an ongoing collaboration with the INRA Sophia-Antipolis team "Biology of Interacting Populations", with which 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. Once an aphids invasion occurs, we study the optimal quantity and time of introduction of the ladybirds in order to minimize the damages caused by the aphids.

With L. Mailleret (INRA Sophia Antipolis team "Integrated Research in Horticulture"), we began another collaboration about biological control (in roses greenhouses this time). In this case, we consider that, once the presence of the 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 apparition 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. 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.

6.2.4. *Metabolic and genomic models*

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

Participants: Olivier Bernard, Jean-Luc Gouzé, Frédéric Grognard, Etienne Farcot.

Metabolic 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 $X_s \rightarrow X_p$ 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 substrate [19].

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. We apply a technique due to Filippov to study these systems on their surfaces of discontinuity by extending them into systems of differential inclusions. 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 [58] and de Jong *et al* [81] 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 [17], [31].

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* [12].

We have considered the mathematical model of the regulatory network of the carbon starvation response in *Escherichia coli* described by Ropers et al. [79]. 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 [37].

6.3. Software design

A Matlab-based prototype software has been developed in collaboration with INRA (Laboratoire de Biotechnologie de l'Environnement) within the European project TELEMAC to provide a framework for the smart management of bioreactors. This software, called ODIN [41], receives data from the process in XML format, displays the results, computes software sensors, fault diagnosis and runs isolation algorithms, and control algorithms. It explicitly manages the uncertainty characterizing bioprocesses. It is highly modular to adapt to any type of plant. We are currently working on an industrial robust version powered by Scilab.

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

The TELEMAC project aims 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 survival of the process.

8. Other Grants and Activities

8.1. National initiatives

- **APPLE:** A. Sciandra leads 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) .

- **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 (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, (see http://name.math.univ-rennes1.fr/ovidiu.radulescu/ACI.html).

- **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 "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, 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/).

- **European project BEMMFISH:** The project "Bio-economic modeling of Mediterranean fisheries" involves O. Pourtallier, now with the Coprin project-team, and has a duration of 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.

8.3. Visits

- A Vande Wouwer (Fac. Polytechnique de Mons, Belgium), 2 days;
- Guillaume Goffaux (Fac. Polytechnique de Mons, Belgium), 2 months;
- Mario Jolicoeur (Univ. Polytechnique de Montreal, Canada), 3 days;
- Slimen Ben Milled (ENIT, Tunisia), 1 week;
- Amira Kebir (ENIT, Tunisia), 1 month;
- Hidde de Jong (INRIA Helix, France), 1 week (cumulated visits);
- Sophie Chareyron (INRIA Bipop, France), 1 day;
- Lionel Pawlowski (Monterey Bay Aquarium Research Institute, U.S.A.), 3 days;
- Ludovic Mailleret (INRA Antibes, France), 1 week (cumulated visits);
- Damien Eveillard (Texas A&M University, U.S.A.), 1 day;
- Marcel Souren (EMBL, Germany), 2 days;
- Mariana Titica (LGP, CRTT Saint-Nazaire, France), 1 day.

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: POSTA2006 (Second Multidisciplinary International Symposium on Positive systems, theory and applications, Grenoble 2006), CIFA (Conférence Internationale Francophone d'Automatique, Bordeaux 2006), "Dynamical modelling of biological networks" C.I.R.M. (Centre International de Rencontres Mathématiques) Marseille-Luminy, May 9 -13 2005.

He is a member of the " Commission d'évaluation" of INRIA and of the Commission Scientifique Spécialisée MIA of INRA. He was a member of the juries for INRIA candidates (researcher and senior researcher competitive examination). 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.

He organized the evaluation seminar of the "Bio" research theme in Dourdan (March 31, April 1).

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

O. Bernard belongs to the COST committee, GTAI ("Groupe de travail sur les actions incitatives"); he belongs to the committee « Bioenergy and biotechnology », from the PNRB (National Research Program on Bioenergy) from the ANR.

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 and F. Grognard gave lectures at ISIA on modelling, observation and control of bioprocesses. O. Bernard gave 6h of lectures and 8h of classworks while F. Grognard gave 3h of lectures and 8h of classworks.

J.-L. Gouzé participated in a CIMPA-UNESCO school "Mathematical Tools and Methods for the Analysis and the Regulation of Fisheries" July 11-24 in Nouadhibou, Mauritania.

O. Bernard participated to a school/workshop on mathematics and renewable resources at the Universidad de Conception (in Santiago, Chile, one week in April); he gave lectures, classworks and conferences. He gave a course in the University of Santiago de Compostella.

O. Bernard gave courses at the Institut National Agronomique Paris-Grignon (3h) and in the Ecole Centrale of Lyon (3h).

9.2.1. Theses

- Ongoing theses:

  1. M. Moisan, " Méthodes d'identification et d'estimation pour des modèles biologiques ", UNSA
  2. G. Robledo, " Etude et contrôle des réseaux trophiques", UNSA
  3. 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.
  4. 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: O. Bernard was referee in the PhD Jury of Laurence Pottier (Univ. Of Nantes).

9.3. Conferences, invited conferences

Conferences with proceedings are not repeated here.

O. Bernard was invited to give a seminar at the Univ. Polytechnique Fédérale de Lausanne, and at the Catholic University of Valparaiso.

F. Grognard and G. Robledo were invited to give talks at the Workshop on Differential Equations in Mathematical Biology (Le Havre).

G. Robledo gave a talk at the European Conference on Mathematical and Theoretical Biology (Dresden) and seminars at the University of Vigo (Spain), at the University of Santiago de Compostella (Spain) and at the University of Talca (Chile).

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