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INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team Comore

Modeling and control of renewable resources

Sophia Antipolis - Méditerranée

Theme : Observation, Modeling, and Control for Life Sciences

Activity
Report

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Comore is a joint research team between 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

Comore is a joint research team between 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, Team: Plankton Dynamics, Physical and Chemical Processes).

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: phyto- and zooplankton growth, bioprocesses, pest control, fisheries, cell models...

Research themes:

Methodology:

- Mathematical properties of models in biology: mathematical studies of models and of their global behavior.
- Tools for modelling in biology: model design, validation, parameter identification.
- Software sensors for biological systems: using the model and on-line measurements, we estimate the variables that are not measured directly.
- Control and regulation for biological systems: we design laws to maintain a variable at a given level, or to optimize the yield of the system.

Fields of application:

- Modelling and control of the growth of marine phytoplankton: phytoplankton is the basis of food chains in oceans (fishes, etc), and plays a key role in the carbon cycle. In Villefranche-sur-Mer, we develop a fully automated chemostat (open bioreactor where cells grow) which is managed by computers for that objective.
- 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: we build models for ecosystems (insects, fishes, zooplankton) 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 (MIA Montpellier, LBE Narbonne, GMPA Grignon, URIH Sophia-Antipolis), CIRAD Montpellier, Centre d'Océanologie de Marseille, LOCEAN (Paris), GIPSA Grenoble, IBIS and MERE INRIA teams.
- Participation in the French groups CoReV (Modèles et théories pour le Contrôle de Ressources Vivantes, Models and Control of Living Resources) and M3D (Mathématiques et décision pour le développement durable).
- Université Catholique de Louvain (Belgium), University of Marrakech (Marocco), Faculté Polytechnique de Mons (Belgium), University of Stuttgart (Germany), Rutgers University (USA), MacMaster University (Canada).
- ANR *Biosys* project Metagenoreg and ANR *Mathematics and Interactions* project ANAR
- ANR *PNRB* project Shamash and ANR *Bioénergie* project Symbiose.

2.2. Highlights

- Comore developed a method to identify a family of operational interactions associated with a given asymptotic dynamical behaviour of a system [34]. The method analyses the asynchronous transition graph of a Boolean model of the system. This method has been used for model reduction of biological regulatory networks as well as for comparison between continuous and discrete modelling formalisms [54].
- Comore has developped a new model to predict lipid accumulation in microalgae. This model has been validated with experimental data, and was used as a basis for microalgal biofuel process optimization [90].

3. Scientific Foundations

3.1. Scientific Foundations

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 framework is Control Theory, whose central concept is “the system”, described by state variables, with inputs (action on the system), and outputs (the available measurements on the system). The systems that we consider are, mainly, ecosystems, that we generally model through a set of differential equations. The variables are, for example, the size or the density of populations. The inputs can be actions exerted on the ecosystem: e.g. action of man (fishing effort, introduction of food, etc), or action of an external factor (pollution, light, etc). The outputs will be some product that one can collect from this ecosystem (harvest, capture, production of a biochemical product, etc), or some measurements (number of individuals, concentrations, etc).

The Control Theory approach begins with the mathematical modelling of the system. This stage is fundamental and difficult, because one does not have rigorous laws as it is the case in physics. We develop techniques to identify and validate the structure of a model from a set of available noisy measurements: qualitative analysis of the data (extrema, relative position,...) is used to build a model which is able to reproduce the same qualitative pattern. We also work on methods that are dedicated to the identification of the mathematical functions that link the dynamics of a state variable to other variables. Finally, we verify that the model satisfies some biological constraints: for example the concentrations must remain positive or some mass balance relationship must be satisfied. 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 experimentally.

Having built a model that synthesizes the behavior of such a complex nonlinear biological system, we can now study its properties and understand the way it works. However, specific problems are posed by the biological origin of the models: functions or parameters are uncertain, or unknown. The quantitative conclusions that we can draw are therefore limited. One then seeks to study the qualitative behavior of the system, the existence of equilibria, their stability, the existence of periodic solutions... Answers to these qualitative questions are fundamental because they tell us whether or not the system is viable (does the model predict the extinction of any species, etc). Answers can often be found, in particular when the models have a strong structure belonging to a general class of systems, for which one develops adjusted techniques: for example the well-known Lotka-Volterra models in dimension n, describing the interactions between n species.

Once the dynamics of the considered living system have been understood we consider problems of regulation: how to maintain a variable at a given level. This is important, for example, in the framework of wastewater treatment where the tolerated pollution levels are determined by governmental laws. The main problem that we have to address is the control of a complex system when the model is uncertain. We mainly work on one class of biological systems, the bioreactors, that have a growing importance in many domains related to the human environment: food (production), pharmaceuticals (production of medicine), environment (wastewater treatment, plankton study), etc. The strong structure of these systems, for which the hydraulic flow plays an important role, is used in order to derive controllers.

Finally, we develop observers that use the model and on-line measurements to asymptotically estimate the variables that are not directly measured. These so called "software sensors" help monitoring some systems and replace some expensive measurements. For the design of such observers, we are faced with uncertainties that are specific to biological modelling: the model is uncertain (parameters, functions) while the inputs can also be affected by disturbances and the outputs highly variable. Therefore, we have to deal with these uncertainties in the design of observers. We have developed robust observers that assume that some parameter or input belongs to a given interval. The observer then asymptotically estimates intervals for the state variables. Other estimators are also considered.

The methods developed by our group are validated and tested on several applications.

4. Application Domains

4.1. Application Domains

In our work, applications are not clearly separated from methodology elements: often, “applications” raise methodological questions which can give rise to fundamental research problems for biology; as mentioned in the above section, we consider and analyze such questions, also in collaboration with biologists.

Modelling of Marine Plankton growth

This part of the work takes place at the Station Zoologique of the CNRS (Villefranche-sur-Mer, France), where we have developed a fully automated, computer driven, set of chemostats (continuous bioreactors where microalgae are growing). This system is particularly well suited to the application of methods resulting from control theory. Our current work consists in designing, studying and validating models of phytoplankton growth in a variable environment (light, nutrients, etc). Phytoplankton is the basis of the oceanic food web (zooplankton, fishes, etc). The existing traditional models (Monod, Droop) are often unsatisfactory and do not reproduce observed features well. We seek to obtain models which are valid during the transitory stages, far from the usually considered steady state conditions that are rarely reached in the sea. For the zooplancton, a size-structured model is considered, governed by predation. These two 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 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.Control laws are build for the outputs of the wastewater to satisfy regulation policies and for the reactor to behave optimally.

Bioenergy

Finding sources of renewable energy is a key challenge for our society. We contribute to this topic in two main domains. First, we are working to improve the efficiency of anaerobic digesters that produce methane and/or biohydrogen from organic carbon. The main difficulty is to make these processes more reliable and valorise more efficiently their biogas. The second topic consists in growing microalgae to produce biodiesel. These microorganisms can synthesize lipids with a much higher productivity than terrestrial oleaginous species. The difficulty is to better understand the involved processes, which are mainly transient, to stimulate and optimize them on the basis of modelling and control strategies.

Ecosystems and Fisheries

The scale of the problems changes here; data are rare and noisy. We consider some important methodological problems in collaboration with IFREMER Nantes: how to model the stock-recruitment relationship of the fish (the relationship between the number of fertile adults and eggs they produce). How does one optimize the exploitation of fisheries with respect to some criteria? How can we prevent undesirable oscillations of the fishing stock?

We also consider (with URIH, INRA Sophia-Antipolis) problems of biological control in crop protection (e.g. the introduction of ladybirds to control pests). We first consider the problem of reactive biological control: upon detection of the presence of pests in the greenhouse, we determine the quantity and timing of the release of their natural enemies to control this pest population. In another framework, we study prophylactic biological control: we determine the periodicity and quantity of natural enemies releases in order to prevent a pest outbreak in high-valued crops (such as roses).

Metabolic and genetic networks

This application has many links with our previous work: in fact, we consider large networks made of small biological nonlinear elements (metabolic network, genes network, ...) and are interested in methods enabling us to describe the dynamical behavior of the system. The classical methods of analysis are difficult to apply here, because the dimension of the networks is too large. Therefore, we search for methods that use qualitative information on the network (the linear substructure, the graph of the network, the monotonicity of interactions and/or the order of magnitude of the concentrations and the interactions) or we describe the system by only using "idealized" nonlinearities, such as step functions (the resulting piecewise linear system being more amenable to a qualitative description).

In parallel with the analysis of systems of large dimension, we are also interested in identifying fundamental mechanisms underlying the complex networks of cellular interactions. These may comprise several levels of regulation, such as metabolic, signaling or genetic regulatory systems. In particular, we are interested in finding and studying basic groups of elements and interactions (i.e. reduced models), that are responsible for a given observed dynamical behavior. For this approach, we use the tools of model reduction theory. The interconnections among various cell regulatory systems are also studied, for instance, how can metabolism be regulated and/or controlled by genetic networks. For this analysis we will use more qualitative methods, such as piecewise linear ordinary differential equations, in conjunction with techniques from control theory (interconnected systems, feedback loops, stability notions).

5. Software

5.1. Software

We have developed a software for *Data acquisition and Control*: a platform, named ODIN, has been developed for the smart management of bioreactors (data acquisition, fault diagnosis, control algorithm,...). This software was developed in C++ and uses a Scilab engine to run the advanced algorithms developed within Comore. It has been been implemented and validated with 4 different applications.

6. New Results

6.1. Methodology

6.1.1. Mathematical study of models

Participants: Jean-Luc Gouzé, Olivier Bernard, Frédéric Grognard, Madalena Chaves, Pierre Bernhard, Pierre Masci, Andrei Akhmetzhanov.

Study of structured models of cell growth

We have developed a structured model representing the development of microalgal cells through three main phases of the cell cycle: G1, G2 and M. The model is made of three interdependent Droop models. The model was validated through extensive comparison with experimental results in both condition of periodic light forcing and nitrogen limitation. The model turns out to accurately reproduce the experimental observations [96].

Mathematical study of models of anaerobic plants.

We have studied an unstable biological model of an anaerobic wastewater treatment plant [86], [87]. This ecosystem can have two locally stable equilibria and an unstable one. The risk of destabilization associated to a control policy has first been evaluated on a static basis by estimating the size of the attraction basin of the working point. A dynamical risk has been defined based on the sequence of transitions, and zones of the state-space have been classified according to their dangerousness [23]. The proposed approach relies on the model structure; it does not depend on the parameter values and is thus very robust.

Mathematical study of models of competing species

When several species are in competition for a single substrate in a chemostat, and when the growth rates of the different species only depend on the substrate, it is known that the generic equilibrium state for a given dilution rate consists in the survival of only one of the species. The species that requires the smallest substrate concentration in order to have a growth rate equivalent to the dilution rate wins the competition; the most efficient species at this rate survives. This observation has been validated through laboratory experiments [85]. This competitive exclusion principle was already demonstrated in the Monod and the Droop model with n species. By a qualitative study of the microorganisms'internal quota, we demonstrated that it still holds when species modelled by Droop and Monod models compete [94].

Moreover, it is in some cases theoretically possible to change the result of competition by changing the dilution rate. We are currently validating this theoretical result experimentally, in collaboration with the LOV (Laboratoire d'Oceanographie de Villefranche-sur-mer).

Bistability in biological systems

The following notion of bistability was proposed in [80]: a system is bistable if its state space contains two disconnected invariant sets. In [18] this notion of bistability is used to analyze a small model of a caspase cascade at the core of apoptosis, or programed cell death. Conditions on the parameters are given that characterize different biological scenarios (e.g., healthy or malfunctioning cells). This is work in collaboration with T. Eissing and F. Allgöwer from the University of Stuttgart, Germany.

Towards an algorithmic reduction of models using orders of magnitude

We consider large biological models, described by an ordinary differential equation, with different scales with respect to time and space; moreover, the parameters have different order of magnitude. We use orders of magnitudes of these variables and parameters to obtain a partition of the state space in boxes (hyper-rectangles). From the fast system in each box, we derive rules of transition, and obtain a transition graph. This graph can be used for a qualitative simulation and validation of the system [51].

Life history traits

In this work we study the evolution of a prey-predator system with seasonal character of the dynamics. We specify two main parts of the process. First, we consider the system during one season with a fixed length: the preys lay eggs continuously and the predators lay eggs or hunt the preys according to the solution of an optimal control problem [57], [63]. Secondly, we study the long-scale discrete dynamics over seasons. We investigate the qualitative behavior of the dynamics with respect to the parameters of the problem and show that, depending on the parameters of the model, extinction or co-existence of the predators and preys can be evidenced [63].

In a second work, we suppose that the evolution of the system during a season of fixed length is governed by optimal game dynamics with two players. On the one hand, the predator has the choice between foraging the food (eating preys) or reproducing for the next year (laying eggs at a rate proportional to its energy). On the other hand, the prey has a chance to hide from the predator but in this case the prey only has a mortality rate and its population can decrease faster than when foraged by the predator. The preys lay eggs at a constant rate whether they are hiding or eating. The aim of both is to maximize their population (the number of offsprings) for the next season. This non-zero sum dynamic game yields complex dynamics whose analysis gives rise to bang-bang control or bi-singular region depending on the initial condition [37].

6.1.2. Model design, identification and validation

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

Model design and identification

One of the main families of biological systems that we have studied involves mass transfer between compartments, whether these compartments are microorganisms or substrates in a bioreactor, or species populations in an ecosystem. We have developed methods to estimate the models of such systems [68]. These systems can be represented by models having the general structure popularized by [65], [76], [77], 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 [67]. 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 [70]. This approach has been applied to various bioproduction processes, most recently on activated sludge processes [64] and anaerobic digestion [43] [105].

These approaches have been combined with neural networks, in order to better constrain the network design and to ensure that it keeps a realistic behaviour even far from the training data set [24].

Identifying operational interactions in genetic networks

For Boolean networks, we introduce the notion of *operational interactions*, corresponding to those interactions that are “active” in a certain region of the state space, and hence responsible for the dynamical behaviour in that region of the space. In [34], we develop a method to identify operational interactions, in two steps. The first step consists in the decomposition of the asynchronous transition graph of the Boolean network into its strongly connected components (SCCs). The second step consists of choosing a desired region of this transition graph (for instance, a SCC), computing its reachable set and use an identification algorithm to reconstruct the interactions which are responsible for the dynamics in this set of states. This method was applied to a Boolean model of an apoptosis network [42], and two distinct subsystems were found: one is responsible for generating oscillatory behaviour in the presence of an input, while the other subsystem is responsible for generating bistability in the absence of an input. To re-introduce the notion of time into this modelling approach, transition probabilities can be associated with the asynchronous transition graph, and the most frequent dynamics can be analysed [48].

The feasible parameter space for biochemical networks

For biological models in general, the parameters can be identified up to a given set. The properties (namely, volume, geometry and topology) of the set of all biologically feasible parameters provide a measure of the robustness of the system. For example, a feasible parameter set which is composed of various disconnected components will, in general, be less robust than a simply connected set with the same volume. A method is proposed in [16] for writing a full description of the feasible parameter set, as a hierarchy of intervals. Application of this method to the segment polarity genes network (fruit fly) shows that the space of parameters is composed of five disconnected regions, which are connected by faces of lower dimension. The effect of random perturbations in the parameters is studied in [17]. This is work in collaboration with E. Sontag, A. Sengupta, and A. Dayarian from Rutgers University, USA.

6.1.3. Nonlinear observers

Participants: Jean-Luc Gouzé, Olivier Bernard.

Interval observers

We designed so-called bundles of observers [72], [73] made of *a set of* interval observers. Each observer computes intervals in which the state lies, provided intervals for parameters and initial conditions (and more generally, all the uncertainties) 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 [83], introducing an optimality criterion to compute an optimal gain, leading to the best interval estimates [97],[31].

The combination of the observers has also been improved in the case where various types of interval observers are run in parallel [44], and the approach has been applied to estimation of the microbial growth rate [50].

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 parameters uncertainties of the system and biased output [100]. These techniques have been improved by introducing a linear, time-varying change of coordinates. For some class of systems, this method allows the design of interval observers when it was not possible in the original basis [46], [29]. This approach was then extended to n-dimensional linear systems, leading to the design of interval observers in high dimensions [95].

These interval observers have been extended to the case where only discrete time measurements are available [22], [21], and applied to experimental data of phytoplankton growth.

Finally, our approach was also extended to deal dynamical systems with time delay [47].

6.1.4. Nonlinear control

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

Global stabilization of partially known positive systems

We have constructed strict Lyapunov functions for general nonlinear systems satisfying Matrosov type conditions [30]. We illustrate the practical interest of our design using two globally asymptotically stable biological models.

Control of competition in the chemostat

We had designed a closed loop control procedure for microorganisms in the chemostat [92]. The objective is to select species with interesting characteristics in chosen environmental conditions. In particular, by controlling the dilution rate and the input substrate concentration, it is possible to select a species which maximises a criterion. This selection method was adapted to a model of anaerobic digestion during its start-up phase [45]. In such a model, we proposed controls which enable to select, among several hundred of species, the ones with maximum growth rate in the reactor steady state operating mode. A first experimental validation of this control strategy was done at the INRA-LBE Laboratory.

Mathematical study of impulsive biological control models

The global stability of the interconnection of a continuous prey-predator ODE model and periodic impulses has been studied. This work was motivated by the biological control of pests in a continuously grown greenhouse. The prey-predator dynamics are continuous and are augmented by discrete components representing the periodic release of predators. Our analysis consists in establishing the existence and global stability of a pest-free periodic solution of the system driven by the repeated predator releases. The latter is achieved using Floquet Theory and is explicitly formulated as a minimal bound on the number of predators to release per unit of time (the minimal rate of predator release).

The influence of various parameters on the stability conditions has been investigated. We first considered the general predator-prey model with density-dependent functional response, and showed that the minimal rate is independent of the release period, but that this period should be as small as possible in order to be able to optimally counter unexpected pest invasions [28].

Then, the effects of two types of intrapredatory interferences have been analyzed: Beddington-DeAngelis and squabbling interferences. The first one represents interference for the access to the prey and the second represents squabbling between the predators through the addition of a quadratic term to the predators mortality (which is otherwise linear). In both cases, we show that the minimal rate that ensures stability is increasing with the period of release [32]. This result has also been shown for a generalised form of the Beddington-DeAngelis interference [103].

This work has been done in collaboration with L. Mailleret (URIH, INRA Sophia-Antipolis).

6.1.5. Evolutionary games

Participants: Pierre Bernhard, Frédéric Grognard, Andrei Akhmetzhanov.

As an addition to our investigations in population dynamics and optimal control, we have embraced evolutionary games dynamics per se as one of our domain of investigation, adding Evolutionary Stable Strategies (ESS) and non-invadable strategies as equilibrium paradigms.

After characterizing ESS's as Wardrop equilibria (the so-called Nash property or "first ESS condition" of ESS's), we have provided a simple test for a matrix Wardrop equilibrium to actually be an ESS. In the same vein, we have also obtained a sufficient condition for the nonlinear theory. Because our main focus is on dynamic systems, we have developped this test in the infinite dimensional case. [53], [36], [52]

It turns out that the theory of evolutionary games, born in the investigation of biological populations, has found many applications in other domains. This has lead to some publications in networking theory, as joint work with our colleagues of the Maestro research project [12].

As an outlet of earlier research in other applications of dynamical games, we obtained in a joint work with Guy Barles, of the university François Rabelais of Tours, and Naïma El Farouq, of the university Blaise Pascal of Clermont-Ferrand, rather technical results concerning the uniqueness of viscosity solutions of some quasi-variational inequalities associated with minimax impulse control problems [35].

6.2. Fields of application

6.2.1. Growth of marine plankton

Participants: Olivier Bernard, Jean-Luc Gouzé, Antoine Sciandra, Christophe Mocquet, Thomas Lacour, Eric Benoît, Jonathan Rault.

Experiments about the phytoplankton cellular cycle

We have run experiments to observe the response of a population of microalgal cells to various periodic light/dark or nitrate signals. The measurements performed with the diatom *Thalassiosira weissflogii* show the synchronicity of the cells for some conditions. These experiments support the hypothesis that uptake of nitrogen stops during cell division [11].

Growth models of zooplankton

The model built in [66] was adapted to zooplankton. Some parts of the model had to be modified, most notably the death by starvation and the maintenance energy. The simulations of the model were compared to the measurements done using the Zooscan in the bay of Villefranche-sur-Mer. For this comparison, statistical tools were applied on the Villefranche data and some parameters were found in the literature. The model and the Villefranche data allowed us to identify other parameters [104]. This model was then integrated in a size-structured model of detritus (faeces of zooplankton for example) describing the sedimentation, which is a central piece of the carbon pump in the ocean. We also studied discrete size-structured models and compared them with continuous models. The discrete models are less numerically demanding, are more easily incorporated into biggest models, and can more often be studied analytically.

Zooplankton growth models were validated using data acquired in laboratory with various species of appendicularians [26]. These models represent the main pathways of filtered material transformation into somatic growth and reproduction. These models led to an estimate of optimal growth conditions depending on temperature and food, combined with ecological niches for each species. Transposed to the natural environment, these models turned out to be capable of simulating the worldwide biogeography of the species, which constitutes a further validation [27].

Carbon fixation by coccolithophorids

A set of 18 models was developed and studied [79], [78] 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.

One model was then included in an ocean model where a bloom of coccolithophorids was simulated [14], [39]. It was shown that the uncertainty on the mecanisms driving calcification leads to uncertainties which are in the same range as the effect of an increase or the CO_2 partial pressure.

6.2.2. Modelling and optimization of lipid production

Participants: Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Francis Mairet, Pierre Masci, Thomas Lacour.

In the framework of the ANR project Shamash, experiments have been carried out to study the effects of nitrogen limitation on the lipid production in a culture of microalgae (*Isochrysis affinis galbana*) [89]. We have proposed a new model for lipid production by microalgae which describes accurately the complex behavior of the lipid quota [90]. This model highlights and explains the phenomenon of hysteresis in lipid production which has been experimentally verified.

On the other hand, a new dynamical model has been developped to describe microalgal growth in a photobioreactor under light and nitrogen limitations [38] [91], [75]. The strength of this model is to take into account the strong interactions between the biological phenomena (effects of light and nitrogen on growth, photoadaptation...) and the radiative transfer in the photobioreactor (light attenuation due to the microalgae).

Using these two approaches, we have developped a model which describes lipid production in a photobioreactor under light limitation. This model is used to predict lipid production in the perspective of large scale biofuel production. Simpler models have also been developed and have been used to provide optimization strategies [93]. In this work, we focus on the effects of the reactor design (depth) and the operating conditions on the lipid productivity under day/night cycles.

Finally, an analysis of the potential environmental impacts of biodiesel production from microalgae has been realised using the life cycle assessment (LCA) methodology [25]. This study has allowed to identify the obstacles and limitations which should receive specific research efforts to make this process environmentally sustainable.

6.2.3. Coupling microalgae to anaerobic digestion

Participants: Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Francis Mairet, Pierre Masci.

The ANR Symbiose project is aiming at coupling microalgae to anaerobic digestion in order to produce methane from CO_2 [62], [33]. A model describing this process has been developped coupling and adapting existing models for each subsystem (microalgae growth [38] and anaerobic digestion [4]). The mathematical analysis of this model is not straightforward due to its complexity. Nevertheless, the model's behavior has been analysed under operating conditions for which the model can be simplified [58]. This analysis has enhanced the understanding of the coupled system dynamics and guided the design of the process.

6.2.4. Bioprocesses

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

Anaerobic digestion monitoring and control

Comore has developed models for anaerobic digestion processes and proposed dedicated methods for model selection [71] and calibration [87]. This work has mainly been focused on the design of control laws that stabilize Wastewater Treatment Plants (WWTPs), which tend to be unstable without feedback control [106].

The new model linking the Henry constant $k_L a$ and the biogas flow-rate shows a linear relation between the dissolved CO_2 and the biogas quality (in terms of $\%CO_2$), which gives new prospects for the control of the biogas quality. A strategy based on the regulation of the alkalinity has been proposed, and two feedback control laws were tested; a simple PI controller based on the measurement of the partial pressure of CO_2, and a mixed law based on an advanced control of the alkalinity [88]. Experiments have been carried out at the LBE INRA Narbonne to validate these two controllers. The regulation strategies turn out to accurately keep the biogas quality constant so that it can be used as an energy source [87], [88]. This result has been patented [74].

Various asymptotic, interval based software sensors have also been developed based on the possible sets of measurements [99], [98], [87], [100],[31].

6.2.5. Models of ecosystems

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

Biological control

With L. Mailleret (URIH, INRA Sophia-Antipolis), we have a collaboration about biological control. The studied problem consists in evaluating the effect of periodic release of predators and periodic harvest on the population of pests. We investigate the minimal predator-budget that should be invested in order to ensure pest eradication. The model proposed in [103] has been shown to be valid for a pest-natural enemy couple present in the greenhouses of INRA and the proposed strategy has been experimentally shown to be the most efficient. More details on the methodological aspects of this problem are given in Section 6.1.4, Nonlinear Control.

6.2.6. Metabolic and genomic models

Participants: Olivier Bernard, Jean-Luc Gouzé, Frédéric Grognard, Wassim Abou Jaoudé, Ibrahima Ndiaye, Madalena Chaves, Eric Benoît.

Dynamics of genetic regulatory networks

We are studying a class of piecewise-linear dynamical systems, $\dot{x} = f(x) - g(x)x$, where x is a n-vector of protein concentrations, the vector $f(x)$ and matrix $g(x)$ are piecewise constant and represent synthesis and degradation rates respectively. Piecewise-linear systems form the basis of an important class of models used for genetic regulatory networks, where the regulatory interactions between the genes are approximated as step functions. The use of step functions is motivated by the switch-like behavior seen experimentally in many of the interactions in gene expression and breakdown of proteins. The piecewise-linear models have the advantage that they are amenable to qualitative analysis and are well-suited to the qualitative character of the majority of experimental data from genetic regulatory networks. Current work in this project consists in continuing the work of Gouzé and Sari [84] and de Jong *et al* [107] by characterizing the equilibrium points and periodic orbits in this special class of systems. These methods and algorithms are used by the software GNA (Genetic Network Analyzer) developed by de Jong *et al* (HELIX, INRIA Rhône-Alpes). This year we have described and analyzed several systems made of intricated loops [60]. Moreover, larger and more realistic models for carbon growth of *E. coli* have been studied (thesis of I. Ndiaye).

Periodic solutions of models of genetic regulatory networks

An important family of piecewise-linear systems consists of systems that have a negative loop involving all variables in their state transition graph. Using theorems about monotone operators acting on positive variables, we have shown that this loop always corresponds to a unique, stable limit cycle [20].
Moreover, we have generalized this result to more complex interaction graphs (multiple intricate loops of any sign, multiple thresholds...). Our main result is an alternative theorem showing that, if a sequence of regions is periodically visited by trajectories, then under some hypotheses, there exists either a unique stable periodic solution, or the origin attracts all trajectories in this sequence of regions [55], [19].

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 control-theoretic methodologies for these networks. We have thus introduced new mathematical techniques for 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.

We elaborated on our previous work about control problems for this class of models, using also some recent results guaranteeing the existence and uniqueness of limit cycles (see above), based solely on a discrete abstraction of the system and its interaction structure. Our aim is to control the transition graph of the piecewise-affine (PWA) system to obtain oscillatory behaviour, which is of primary functional importance in numerous biological networks. We show how to control the appearance or disappearance of a unique stable limit cycle by hybrid qualitative action on the degradation rates of the PWA system, both by static and dynamic feedback [82].

In the control of genetic networks, the construction of feedback control laws is subject to many specific constraints, including positivity, appropriate bounds and forms of the input. In addition, control laws should be liable to implementation in the laboratory using gene and protein components. In this context, we analysed the controllability and stabilizability with respect to each steady state, for a piecewise-affine model of the bistable switch with a single input, and using piecewise constant control laws (constant in given regions of the state space, or constant for a given time interval) [81].

Uniqueness and global stability for metabolic models

We are interested in the uniqueness and stability of the equilibrium of reversible metabolic models. For biologists, it seems clear that realistic metabolic systems have a single stable equilibrium. However, it is known that some type of metabolic systems can have no or multiple equilibria. We have made some contribution to this problem, in the case of a totally reversible enzymatic system. We prove that the equilibrium is globally asymptotically stable if it exists; we give conditions for existence [102].

Methods for qualitative analysis of genetic networks and model comparison

There are several methods to qualitatively study genetic models, which are adapted to the type and frequency of the experimental data available. These methods range over different degrees of description, from Boolean networks, to discrete multi-valued models, piecewise affine systems and continuous models. A brief overview can be found in [41]. To compare these different modelling approaches, we analyzed a genetic network involved in the response to carbon availability in *E. coli* [54]. It is shown that a discrete multi-valued model can in general be obtained from a piecewise affine model. Then, a procedure is suggested to show that, under appropriately biological conditions, multi-valued discrete models can be written as strictly Boolean models. The advantage of a Boolean model for large systems is its tractability through graph theoretical and computational tools. Boolean models recover many of the properties of piecewise-affine models (steady states, oscillatory orbits). A special type of solutions which often appear in piecewise-affine models, namely the "sliding mode" solutions, can also be recovered, if the Boolean model is more finely analysed.

Interaction between signaling and gene expression networks

A simple model, consisting of one protein (x) and one mRNA (y), was developed and fully analyzed [101]: the protein x activates transcription of the gene and also contributes to its own synthesis. The mRNA y (or its corresponding protein) contributes to the degradation of protein x. The idea that signaling or metabolic networks achieve an operational steady state much faster than the dynamics of gene expression was used to study the model in a "fast-slow" framework. It is shown how the signaling network can be regulated by switching between two operational modes (or steady states) in response to gene expression patterns. Conditions for the existence of an oscillatory cycle, as well as an estimate of its period, are provided. Using experimental data on the cell cycle of *Xenopus laevis* oocytes (both oscillatory response and bistability) some of the parameters were estimated, with the corresponding confidence intervals. This work is part of the thesis of I. Ndiaye.

6.3. Software design

Participants: Olivier Bernard, Fabien Dilet.

Over the years, Comore has been developing a software framework for bioprocess control and supervision called ODIN [69]. This C++ application enables researchers and industrials to easily develop and deploy advanced control algorithms through the use of a Scilab interpreter. It also contains a Scilab-based process simulator which can be harnessed for experimentation and training purposes. ODIN is primarily developed in the C++ programming language and uses CORBA to define component interfaces and provide component isolation. ODIN is a distributed platform, enabling remote monitoring of the controlled processes as well as remote data acquisition. Recently, software development effort has been directed to the graphical user interface, a synoptic view component, new drivers for the experimental hardware and integration of the PlantML data exchange format. PlantML is an XML format used to describe plant data wich helps quickly porting ODIN to new processes and brings easier integration with other software tools using this standard. ODIN has been tested on four different processes. ODIN is undergoing tests at the LBE-INRA in Narbonne.

7. Contracts and Grants with Industry

7.1. Microalgae for biofuel production

A contract between Comore, Alpha Biotech, EADS and PSA Peugeot Citroen has been signed for assessment of microalgal biofuel productivity.

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, coordinated by O. Bernard, includes 9 partners, for a total budget of 2.8 Millions Euros. The role of Comore is to design a model of the process in order to better understand the dynamical mechanisms that lead to the transient storage of lipids. The second step will then consist in defining optimal conditions to maximize the oil production. See http://www- sop.inria.fr/comore/shamash/
- **Symbiose:** Comore takes part in the Symbiose ANR project. The objective of this project is both to improve the energetic balance of biofuel microalgal productions and to recycle nitrogen and phosphorus. The project proposes to study the coupling between a microalgal production system and an anaerobic digester. The objectives of Comore are to propose a model of the coupled system, and to compute the optimal fluxes between the various compartments in order to optimize the energy recovery.
- **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.
- **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 (INRA).
- **ColAge:** This is a joint INRIA-INSERM consortium, and a proposal for an “Action d'Envergure”, which is partly funded by INRIA. The goal is to study bacterial growth and aging by using mathematical modelling and computational predictions to design a *de novo* biological system, and then implement this design *in vivo*. The project is directed by H. Berry (Alchemy, INRIA).

- **ARC CODA:** The objective of this project is to optimize the starting of anaerobic treatment plants. This is a joint project with the INRIA SEQUEL project, INRA LBE and the company Naskeo. Originally funded by INRIA for two years, the project is now funded by INRA.
- **IA2L:** INRA-SPE is funding a project on intra-guild predation in which we are taking part: “Interactions antagonistes entre auxiliaires : conséquences pour la lutte biologique”.
- **RBHS:** INRA-SPE is funding the project "Rôle de la biodiversité et des hétérogénéités spatio-temporelles de la distribution des ravageurs et de leurs ennemis naturels dans les phénomènes de régulations biologiques" in which Comore is a partner with INRA Sophia Antipolis and INRA Avignon.
- **Mod-Pea:** Comore is a partner of the project "Dynamics and evolution of life history traits in plant pathogens and pests" that is funded by the Agropolis foundation. The group of partners of this project includes CIRAD Montpellier (BGPI), INRA Sophia Antipolis, INRA Nancy and Agrocampus Ouest.
- **RNSC:** Comore is taking part in the project “Dynamique de populations complexes” of the “Réseaux National des Systèmes Complexes."
- **COREV:** Comore is an active participant in the research group COREV (Modèles et théories pour le contrôle de ressources vivantes et la gestion de systèmes écologiques).
- **RTP-M3D:** Comore is a participant in the RTP-M3D workgroup (Mathématiques et décision pour le développement durable) that is supported by the “Environment and sustainable growth” department of CNRS.
- **Seminar:** Comore organizes a regular seminar “Modelling and control of ecosystems” at the station zoologique of Villefranche-sur-Mer or at INRIA.

8.2. Visits

We only list the visitors that stayed more than 2 days or that presented a seminar in our project-team

- Ludovic Mailleret (INRA Sophia-Antipolis, France), 1 month (cumulated visits);
- Chris Barot (INRIA Ibis, France), 1 week ;
- Johan Mailer (Faculté Polytechnique de Mons, Belgium), 3 weeks;
- Claude Aflalo (Ben Gurion University of the Neguev, Israel), 1 week;
- Benoit Chachuat (McMaster University, Canada), 2 days;
- Hugh McIntyre (Univ. South Alabama, Dauphin Island, USA), 4 days.

8.3. Project-team seminar

Comore organized a 3-day seminar in november in Annot. On this occasion, every member of the project-team presented its recent results and brainstorming sessions were organised.

9. Dissemination

9.1. Leadership with scientific community

J.-L. Gouzé is a member of the scientific committees for the conferences POSTA 2009 (Multidisciplinary International Symposium on Positive Systems, Theory and Applications, Valencia, Spain), "Stic et Environnement", and CIFA 2010. He is a member of the board of the project-team committee at INRIA (Bureau du comité des projets), the co-head of the INRIA committee supervising the doctoral theses, and a member of the committee “Ecole Doctorale 85 Sciences de la Vie et de la Santé” of the University of Nice-Sophia-Antipolis. He is a member of the board of the SFBT (French Speaking Society for Theoretical Biology).

He was in the organizing committee of the school "Modelling complex biological systems in the context of genomics“ in La-Colle-sur-Loup, France (March 2009).

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".

O. Bernard belongs to the Color committee of INRIA Sophia-Antipolis. He represents INRIA at the ANCRE (Alliance Nationale de Coordination de la Recherche pour l'Energie), in the biomass committee.

E. Benoît is vice-head (at the University of La Rochelle) of the ANR project ANAR (Analyse Non Linéaire et Application aux Rythmes Complexes du Vivant).

M. Chaves is a member of CUMIR, the committee for the users of computer and internet ressources at INRIA Sophia Antipolis. Olivier Bernard is a member of the INRIA CDT (Technological Development Commission) for software development management.

9.2. Scientific popularisation - media

An article was written in a generalist scientific magazine to explain our contribution in microalgae modelling [61].

A movie was made on the Shamash project, and it was included in an article in the Interstices web page: http://interstices.info/jcms/c_24036/projet-shamash-production-de-biocarburants-lipidiques-par-des-microalgues

The Shamash project has generated many articles and broadcasts in the media: The most important newspapers are "Le Monde" (Des microalgues pour les biocarburants du futur, octobre 23d, 2008), "Figaro magazine" (Les algues, nouveau pétrole vert ? april 2008), "Enjeux - les Echos" (Les chercheurs carburent sur les microalgues, march 2008), "L'Usine Nouvelle" (La modélisation numérique sied aux algues, june 11, 2008), "Le Figaro" (Les microalgues pour faire rouler les voitures, 7 janvier 2009), "'Les Echos"' (Bientôt des algues dans votre moteur ?, 13 janvier 2009), etc.

9.3. Teaching

J.-L. Gouzé, O. Bernard, F. Grognard and A. Sciandra gave two weeks of courses in november on mathematical models in biology at the Master on biological oceanography, Pierre et Marie Curie, Paris VI. J.-L. Gouzé (6h) and F. Grognard (3h) taught courses on dynamical systems, O. Bernard on identification (3h) and classworks were taught by P. Masci (6h).

O. Bernard gave lectures at the Ecole Nationale Supérieure des Mines de Paris (3h) on bioenergy from microalgae. O. Bernard gave 12h lectures at the University of Santiago de Compostella (Spain) on advanced modelling, analysis and observation of bioprocesses.

M. Chaves (12 hours) and I. Ndiaye (8 hours, project) taught the course “Modelling biological networks by ordinary differential equations” at the EPU (Ecole Polytechnique Nice - Sophia Antipolis) to 4th year students in Bioengineering.

M. Chaves and J.-L. Gouzé taught 6 hours each of the course “Discrete and continuous approaches to model gene regulatory networks”, which is part of the new Master of Science in Computational Biology, at the University of Nice - Sophia Antipolis.

F. Grognard taught 9 hours of classes on modeling and control of biological systems to 4th year students in the MAM orientation (Applied Mathematics and Modelling) of EPU.

J. Rault gave classes in mathematics (analysis) in the first year of the initial cycle of EPU (64h).

9.3.1. Theses

- Ongoing theses:
  1. S. Nundloll, “Modélisation et optimisation de la lutte biologique”, UNSA.
  2. I. Ndiaye, “Analyse mathématique et contrôle de modèles de réseaux de régulation génétique”, UNSA.
  3. C. Mocquet, “Interférence entre les processus mitotiques et la prise d’azote chez *Thalassiosira weissflogii*. Implications en modélisation et sur les flux globaux” , Université P.M. Curie. Defended December 3rd, 2009.
  4. T. Lacour, “Etude expérimentale des mécanismes de production de lipides par des microalgues”, Université P.M. Curie.
  5. P. Masci, “Etude et développement d’un système de sélection d’espèces dans un environnement dynamique multivariable”, UNSA.
  6. J. Rault, “Modélisation mathématique du plancton, structuré en taille. Conséquence sur la séquestration du carbone dans l’océan”, UNSA.
  7. M. Teixeira-Alves, “Modélisation de réseaux écologiques dans un cadre de protection des culturesÂ : applications à la lutte biologique”, UNSA.
- Participation in PhD juries:
  J.-L. Gouzé was referee for the thesis of Joseph Mbang, Université de Metz : “Analyse de la stabilité des modèles intra-hôtes avec retard: application à des modèles intra-hôtes de paludisme et du VIH-1”.
  O. Bernard was in the PhD Jury of Eva Van Derlinden. " Quantifying microbial dynamics as function of temperature: towards an optimal trade-off between biological and model complexity ", University of Leuven, March, 13th.
  O. Bernard was in the PhD Jury of Nina Moelants. "Optimizing the design and the sustainable performance of onsite individual wastewater treatment systems ", University of Leuven on December, 21st.
  J.-L. Gouzé is in the thesis committee of Y. Refahi (Virtual Plants, Montpellier). M. Chaves is in the theses committees of S. Berthoumieux (INRIA Rhone-Alps, Grenoble) and F. Fourré (University of Luxembourg)

9.4. Conferences, invited conferences

Conferences with proceedings are not repeated here.

O. Bernard and A. Sciandra organized a specific session on CO_2 mitigation and energy production with microalgae at the ASLO conference. 13 papers and posters where presented.

O. Bernard gave two presentations at the ASLO conference on bioreactor modelling and on the coupling between anaerobic digestion and microalgae. J. Rault presented a poster at ASLO entitled “Zooplankton size spectra: part 2, model development”.

O. Bernard was invited to give a conference on reaction network identification (March, the 12th) by J.Van Impe, KUL, Leuven, Belgium.

O. Bernard was invited by B. Perhame in the Jacques-Louis Lions Laboratory to give a presentation on modelling the coupling between biology and physics (November, the 10th).

O. Bernard presented the Shamash project and its results at the PNRB forum in Paris (February 5, 2009).

J.-L. Gouzé was invited to give a seminar at the annual meeting of SFBT (French Speaking Society for Theoretical Biology), Solignac, France, (June 2009).

J.-L. Gouzé was invited during one week for the Program “Advances in the Theory of Control, Signals and Systems with Physical Modeling”, Centre Interfacultaire Bernoulli, hosted by EPFL, Lausanne, Suisse (June 2009) and gave a presentation.

M. Chaves was invited to make a presentation at the following control meetings: "Control Theory: On the Way to New Application Fields", at the Mathematisches Forschungsinstitut Oberwolfach, Germany (February 2009); the DIMACS workshop “Control Theory and Dynamics in Systems Biology”, at Rutgers University, USA (May 2009); and the JOBIM 2009 satellite meeting “Dynamical modelling and simulation of biological networks”, in Nantes (June 2009).

M. Chaves also did a presentation at the 2nd INRIA-NIH Biomedical Computing Workshop, in Paris-Rocquencourt (June 2009).

"Dynamic Life Cycle Assessment of Biogas Production from Microalgae" by P. Collet, A. Hélias, L. Lardon, J-P. Steyer, and O. Bernard. was presented at the Conference "Life Cycle Assessment IX" Boston, September 29th to October 2nd, 2009. This presentation gives some ideas on how to take into account the dynamic nature of biological processes in order to more accurately assess their environmental impact.

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