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Project-Team MERE

Modelling and Water Resources

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Theme : Observation, Modeling, and Control for Life Sciences

Activity Report

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2. Overall Objectives

2.1. Microbial ecology for environmental preservation

Populations of cities and modern industrial techniques, particularly in agronomy, reject considerable quantities of chemicals (carbon, nitrogen, phosphorus) which are substrates (food) of choice for microorganisms. Direct rejection in nature of these products leads to uncontrolled growth of microorganisms perturbing the growth of more evolved forms of life. "Biological cleanup" (waste-water treatment) consists simply in reproducing this natural process in a controlled process in bioreactors (the "waste-water treatment plant").

The study of biological waste-water treatment requires knowledge in a large number of domains, notably:

- physics and chemistry of the environment,
- microbiology,
- microbial ecosystems,
- process engineering,
- automatic control,
- mathematical and computer modelling,
- mathematics,

Obviously, a small team like ours is not able to master this variety of research areas. Our expertise covers *only the last three items*, and we are used to having *strong collaborations* with biologists and engineers. About one third of our publications is co-authored by such collaborators.

The transformation of pollution into biomass is performed in a *microbial ecosystem*. Thus, a good understanding of microbial ecology is essential. On the other hand, microbial ecosystems have an increasing importance in ecological theory. Microbial ecosystems present an interesting double feature:

- They are small and therefore can be “observed” and ‘manipulated” in the laboratory;
- Molecular biology methods have recently become available to measure microbial population sizes,

which makes them particularly attractive, see [60].

Our research focuses mainly on *biodiversity*: What are the mechanisms that explain the presence of a large number of species in microbial ecosystems? What are the functional consequences of biodiversity? We are working on mathematical models associated with these issues.

We strongly believe that good research is built upon a good knowledge of reality and, conversely, that good quality applications are based on the best available knowledge of current theories. That is why, along with its fundamental concerns, our team is involved in concrete activities ranging from simple *technical helps* and participation in networks within the framework of national and international programs to the establishment and running of such networks. Most notably is our network TREASURE (**Trea**tment and **Su**stainable **R**euse of **E**ffluents in semi-arid climates) that includes participants from around the Mediterranean sea on a very specific development problem: *Relevance of anaerobic digestion followed by membranes for water reuse for agriculture in semi-arid countries*.

The industry of waste-water treatment is considered today as the first industry in terms of matter to be processed. Therefore, the design, the control and, in more general terms, the optimization of treatment processes are real challenges. One of our objectives is also to better understand these processes in order to optimize their functioning in the presence of uncertainties and of unknown and unmeasured external disturbances. To do so,

- We approach the problems at two levels: the microscopic scale (the micro-organism) and the macroscopic one (the plant);
- We use macroscopic modelling and control system science tools to develop new design rules, estimation techniques and control system that we calibrate on real biological pilot plants.

Our methodology starts with the development of mathematical models of the biological reactions and transports in the reactor. At this stage, we have very strong interactions with micro-biologists. Next, we analyze the model with the available mathematical tools or/and through computer simulations. We focus mainly on the effects of the spatial distribution of the biomass. This questioning can be understood at various scales.

- At the macroscopic level, we compare the performances of various designs, from infinitely stirred reactors to purely non-mixed reactors through cascade of reactors;
- At the microscopic level, we are interested in the growth process of the biomass, limitations caused by the diffusion of the substrate, and the role of the bio-films.

We are interested in fundamental questions of microbial ecology, like biodiversity of biomass, competition and predation, since they are at the roots of the understanding of biological waste-water treatment and, at the same time, we address very practical questions like the minimization of the size of the bioreactors.

2.2. Highlights of the year

1. MERE is coordinator of the ANR SYSCOMM project DISCO (2010-2012), a three-years project of 500 keuros on biofilm modelling (see Section 7.4).
2. F. Mazenc and his collaborator M. Malisoff have published a monograph in the Springer Communications and Control Engineering Series [44]. This book is geared to advanced graduate students and researchers.

3. Scientific Foundations

3.1. Bioprocess engineering and mathematical ecology

The chemostat is a laboratory device which goes back to the second world war, with the work of Monod and Szilard. It is used to study the growth of micro-organisms. The principle is simple: a continuous flow rate through a constant volume reactor provides nutrients to a population or a community of micro-organisms. At equilibrium the growth-rate must equal the artificial mortality induced by the outflow of the reactor. A simple model, for the case where the reactor is perfectly stirred, is given by a set of two differential equations, one for the variations of the nutrient concentration, the other one for the variations of the biomass concentration. This model is based on the classical law of mass action used in the modelling of chemical kinetics: the rate of a reaction is proportional to the product of the concentrations of the two reactants. In the case of population growth, this means that the growth-rate of a population depends on the nutrient concentration. This system of two equations has been perfectly understood for more than half a century.

The chemostat model is a good first approximation of a waste-water treatment plant. From this simple model one can develop models which incorporate more realistic assumptions like:

- existence of a complicated trophic chain in the digestion process,
- consideration of non-perfect mixing inducing diffusion processes,
- consideration of mass transport in plug-flow reactors,
- parallel or cascade connections of reactors,
- re-circulation of the biomass,
- aggregation of micro-organisms in flocks,
- constitution of bio-films,

which lead to complicated systems of coupled partial differential equations of transport-diffusion type. Due to the presence of non-monotonic kinetics the theory of equations of this type is not yet perfectly understood. Determination of stable stationary solutions is often a question of current research and numerical simulations are used. Moreover, the control of industrial plants addresses new questions in the domain of robust control and observers.

Since a waste-water treatment plant is a microbial ecosystem, microbial ecology is fundamental for the understanding of our processes. Microbial ecology in “perfectly stirred bio-reactors” is certainly the field of ecology, in which the representation of species by concentrations changing over time and governed by ordinary differential equations (ODE) is the most justified; this is the point of view we adopt in this objective.

In a chemostat (or bioreactor) the classical model of growth of a species on one limiting substrate is well known, widely used and very efficient. The growth model of several species competing for the same substrate built upon the same assumptions, predicts the extinction of all species except one. This is known as the *Competitive Exclusion Principle* (CEP). This predictions has caused much debate, as it turns out that, in nature as well as in the laboratory, species coexist in a very great number. This paradox of a model that seems to be valid for one species but not for many, requires clarification. We address it in the specific case of the chemostat.

To our knowledge this question is not studied in France, at least in terms of modelling. In the United States, beyond the “historical researchers” (Waltman, Armstrong and McGehee, Hansen and Hubbell ...), we are aware of the work of Wolkowicz and her collaborators. However, we do not know any teams that have addressed this subject as systematically as we do in conjunction with biologists.

An ecosystem is a system in which various populations of different species are interacting between them and reacting to the environmental abiotic parameters. Concepts of competition, predation, symbiosis are used to describe these interactions and try to understand important questions like the biodiversity and the productivity of the ecosystem. The biodiversity is related to the number of species which is supported by the ecosystem. There are many ways of quantifying the biodiversity of a microbial ecosystems. The most intuitive measurement of diversity consists in evaluating the richness, which simply is the number of species. The productivity measures the rate at which abiotic resources are transformed into biomass. An old prediction of theoretical population models says that, in a constant environment, an ecosystem with n different kinds of resources can support at most n different species (different means that the ways two species use resources are different). This prediction is not realized in waste-water treatment plants where it was demonstrated, using tools of molecular biology (fingerprinting techniques such as SSCP, see below), that a small number of resources (maintained at a constant level) is able to maintain a huge number of species. This shows that the classical model of the perfectly stirred reactor is no longer valid if one wants to model the biodiversity in the reactor. We explore alternative models based on the consideration of growth-rates which are not solely nutrient-dependent, but are also density-dependent, which means that the growth rate may depend not only on the nutrient concentration but also on the density of the biomass. More specifically, based on physical arguments, we currently work with models where the growth rates decrease with the biomass concentration. A special case of density-dependence is so-called ratio-dependence which was much discussed recently.

Since a density-dependent model is a macroscopic model, it is important to understand how the density-dependence is a consequence of the microscopic behaviors of individuals. Since direct observation of the behavior of bacteria is difficult, mathematical modelling is of great help. The hypotheses, at the microscopic level, are expressed in terms of partial differential equations or in terms of individually based models so that macroscopic consequences are derived, either by using mathematical reasoning or computer simulations. Finally, mathematical analysis is the starting point for the design of new experiments which could validate hypotheses of the theoretical models. But conducting biological experiments requires time, energy and qualified people for rigorous validation (many protocols have to be checked for ensuring that contamination or side-effects do not degrade the results).

3.2. Markovian modelling, simulation-based inference and decision

The Mathematical modelling of systems exposed to randomness is of particular interest whenever we seek an in depth understanding of complex stochastic phenomena or if we wish to infer noise-corrupted data. The underlying system can be static or dynamic. The state variables, the parameters and the observations can be finite, continuous, hybrid (continuous/discrete), graphical, time varying, pathwise, etc.

The first step in modelling is to describe the dependency graph connecting the different variables and parameters. Note that in the Bayesian networks framework this graph can be inferred from the data. The Markovian hypothesis is made in order to limit the complexity of the model and to allow for tractable algorithms. It consists in supposing that the dependency graph is limited to local connections. It appears in dynamic contexts (Markov random processes), in static contexts (Markov random field), as well as in spatio-temporal frameworks. From a statistical point of view, Markovian models can also feature hidden variables.

The Monte Carlo (MC) methods have expanded considerably over the past two decades, and have been successful in many areas.

In MC approaches, the quantity of interest is formulated in a probabilistic way as a functional of the distribution law of a stochastic process (or simply a random variable). By sampling independent trajectories of this process, we empirically approximate the underlying targeted distribution law. The convergence of this procedure is provided by the law of large numbers and the speed of convergence by central limit theorems.

MC approaches can be used for numerical approximation of complex systems distribution laws through empirical approximations [55] [61]. They are intensively used in Bayesian inference: “Markov chain Monte Carlo” (MCMC) in the static context [63] and “sequential Monte Carlo” (SMC, also called “particle filter”) in the dynamic context [56]. In the non-Bayesian approach, Monte Carlo techniques are used to explore likelihood functions [64]. They also gave rise to general algorithmics [57]. Monte Carlo methods are also used to approximate deterministic quantity of interest, usually represented as the expected value of a functional of a process trajectory. This quantity can also be the probability that a given event has occurred. Finally, simulation-based approaches allow for approximating Markov decision problems in random and partially observed situations [54].

MC methods can lead to very poor results because trajectories are generated blindly. Classically, adequacy to the specific problem or to data is handled afterwards by weighting the different trajectories: the higher the weight, the more the trajectory matches the targeted phenomenon or data. Some of these weights could be negligible, in which case the corresponding trajectories will not contribute to the estimator, i.e. computing power has been wasted. Recent advances, like sequential Monte Carlo or population Monte Carlo, focus on mutation-selection mechanisms that automatically concentrate MC simulations, i.e. the available computing power, into regions of interest of the state space.

Markovian modelling and algorithmics are applied successfully in numerous fields, a reason for this is its strong theoretical background. The limit behaviors of Markov processes are reasonably well identified [62], allowing for precise analyses of the asymptotic behavior of the proposed models, as well as convergence properties of the simulation-based inference algorithms. The development of these sophisticated MC methods, together with the associated mathematical analysis, which we can summarize as Markovian engineering, represents one of the major breakthroughs in applied probability.

The Markovian approach presents many features that can be exploited for modeling in ecology. This approach integrates the tools from statistical physics and allows to model the dynamics of large number of individuals with interactions. This type of dynamics is frequently encountered in ecology, e.g., in individual-based models (IBM). The Markov and statistical physics approaches are also suitable for multi-scale modeling and analysis which also is one of the main features of ecological systems. They also bridge spatially explicit and individual-based models with aggregated models. This framework also includes the analysis of so-called neutral community models [59].

4. Application Domains

4.1. Process engineering tools for the understanding of complex biosystems

The study of complex biological systems, such as bioprocesses used for the treatment of waste-water or systems like soils, are complex systems involving living entities. The understanding of the interactions of these ecosystems with their environments necessitates to model them in such a way their main characteristics are captured. For these systems, many accurate models have been developed for many years and for very different levels of description. For instance, some models of soils describe very accurately the behavior of the main variables at the level of the aggregate (order of mm) as well as the behavior of different important variables at the level of a cultured field or even at the level of a large watershed. The same diversity of models exists with respect to bioprocesses: one may either study the behavior of an ecosystem at the individual level or at the level of a large waste-water treatment plant. Within the framework of this project, we try to use the tools available in the field of chemical engineering in order to design simple models of such complex systems. In particular, the notions of perfect unitary processes (Chemostats or Continuous Stirred-Tank Reactors as well as Plug-Flow Reactors) are used. More specifically, the interaction of such unit entities are studied in order to describe the spatialization of physical and biological phenomena in these systems. Particular cases of these configurations include the study of a series of chemostats or the interactions of chemostats connected by diffusion and recirculation fluxes. Following the general study of these systems, a number of practical problems such as the optimal design of biological systems or the development of specific simulation software are investigated.

4.2. Observation and control of waste-water treatment plants

Control problems frequently arise in the context of the study of biological systems such as waste-water treatment plants. In general, in order to cope with disturbances, modelling errors or parameter uncertainty, one has to take advantage of robust non-linear control design results. These results are based on central theories of modern non-linear control analysis, such as disturbance attenuation of Lyapunov functions.

Waste-water treatments plants are often unstable as soon as bacteria growths exhibit some inhibition. Typically, under a constant feed rate, the wash-out of the reactor (i.e., when biomass is no longer present) becomes an attracting but *undesirable equilibrium point*. Choosing the dilution rate as the manipulated input is usually a mean for the stabilization about a desired set point, but the most efficient control laws often require a perfect knowledge of the state variables of the system, namely the on-line measurement of all the concentrations, which are generally not accessible (for technical or economical reasons). Most often, only a few sensors are available.

A popular way to achieve stabilization of a control dynamical system under partial knowledge of the state is to first design an “observer” or “software sensor” for the reconstruction of the unobserved variables, and then to couple this estimate with a stabilizing feedback control law, if some “separation principle” is satisfied. Unfortunately, in industrial operating conditions, one cannot thoroughly trust the models that were developed and identified in well-controlled environments such as in laboratory experiments. Engineers have to deal with several uncertainties on parts of the model, as well as on the output delivered by the sensors. During the initialization stage or hitches on the process, the system can be far away from the nominal state, where few empirical data are available. Generally, probabilistic hypotheses cannot be justified regarding the nature of the uncertainty for stochastic models to be considered. On the opposite, reasonable bounds on the unknown parts of the models are available, so that uncertainties can be considered as unknown deterministic inputs.

Consequently, robust observers and control laws need to be developed to cope with the particularities of the uncertainty on the models.

4.3. Interpretation of molecular techniques in microbial ecology

Dynamical studies of bioreactors as used in waste-water treatment are hampered by the lack of measurement techniques to assess the microbial community structure. Typically only global system variables (biomass and substrate densities, gas production, etc) are measured, so that the community dynamics as such cannot be followed in any detail. Nevertheless, it is commonly believed that monitoring the microbial composition in bioreactors is crucial for their performances (in terms of efficiency and stability). Accurate, rapid and inexpensive techniques to estimate microbial community properties are therefore of crucial importance.

Molecular fingerprinting techniques seem to be good candidates to fill this gap. They are based on a small region (so-called 16S ribosomal DNA) present in all bacterial genomes. This region is relatively constant over many generations (compared to other parts of the genome), so that it can be used as a signature of a bacterial species. The fingerprinting protocol then consists in, first, extracting all the DNA of the microbial community, next, selecting and amplifying the genomic region of interest (using the PCR (polymerase chain reaction) technique), and finally, separating the PCR products belonging to different species by electrophoresis migration. Compared to other molecular techniques (such as cloning/sequencing), fingerprinting is rapid and inexpensive, and therefore well suited to follow microbial community dynamics.

A quantitative interpretation of fingerprints is however troublesome. Under the assumption that all species are perfectly separated in the migration step, the fingerprinting profile would consist of a succession of sharp rays, each one corresponding to a species, and with ray heights proportional to the abundance of the corresponding species. In this ideal scenario, the complete community structure could be read off from the profile. Unfortunately, due to biases in the different experimental steps (DNA extraction + PCR amplification + electrophoresis migration), real profiles are composed of a number of peaks, all with more or less the same width, where some species can occasionally contribute several peaks, and with peak heights only approximately proportional to the species abundance. Moreover, as soon as the community is somehow diverse, different peaks overlap each other, resulting in a complex profile.

Although one cannot hope to recuperate the complete community structure from such complex profiles, partial community information is still encoded in them. Our objective is to develop quantitative methods to extract this information from the profiles. Given a single profile, the genetic diversity of the microbial community is contained in the fingerprint. In recent years, we have developed an accurate diversity estimator; the corresponding patent has now been published [45]. Given a sequence of profiles, additional information can be obtained by comparing successive profiles. Once this information is extracted, it can be coupled to mathematical models describing the dynamics of microbial communities. We are investigating how to tackle this signal processing problem.

4.4. Experimentation in ecology

When confronted to the modeling of biological processes, a very important question arises: how to model the kinetics of biological reactions that take place in bioreactors? In order to evaluate the structure of mass-balance model kinetics (testing whether a kinetics is better described by substrate- or by density-dependent kinetics) and in the framework of the TREASURE network (cf. Section 8.1.5), new experiments have been planned in collaboration with the CBS in Sfax. Indeed, this Tunisian research center operates membranes bioreactors that are particularly adapted to make experiments in which a series of reactors is used such that no biomass circulates from one tank to another. Based on a qualitative analysis of steady states of such a process configuration (cf. [52]), we should be able to characterize the kinetics nature of an anaerobic process. The results will be used to update traditional simple models used for control design, such as the AMOCO model that is being studied and extended to describe a larger class of processes within the PhD thesis of Boumediene Benyahia.

4.5. Modelling and inference of ecological and environmental dynamics

Ecological and environmental dynamics are at the heart of some of today's leading issues (greenhouse effect, global warming, deforestation, loss of biodiversity, natural resources assessment etc.). For more than a decade, biologists and ecologists have been increasingly using computation modelling for a deeper understanding of the intricacies of these complex dynamics. This approach allows for improved assessments, accurate predictions and effective decision-making. Crucially, random effects need to be considered in this domain. Most of the dynamical problems considered here are contrasted with the classical applications of hidden Markov models, such as automated speech recognition, target tracking or DNA sequence analysis. Indeed, the measurement data are highly noise-corrupted, acquired at very low frequencies, and on short time series (e.g. one measurement per year for several decades). From the statistical point of view, the poor quality of data is an argument for using the Bayesian approach. The knowledge of ecological and environmental scientists allows for the choice of model used, as well as its structure. The Markovian framework offers a wide spectrum of possible models adapted to the Bayesian inference (see Section 3.2). Hence, in this context, we are drawn toward a model-driven approach. We adopted the Markovian formalism presented in Section 3.2. The hierarchical structure of these models allows for an efficient simulation-based inference of the a posteriori distribution law of the latent variables given the observation data. We considered dynamics of terrestrial plant populations (see Section 6.2.4). Beyond "simple" economic production issues, recent developments in this area incorporate the concerns of biodiversity conservation and sustainable management. In this context, the need for spatial-temporal models becomes essential. Again, the Markovian framework offers many possibilities. In a statistical point of view, the main difficulty is to strike a compromise between the complexity of the model and the limitations of available data.

5. Software

5.1. BACSON

Participants: Nabil Mabrouk, Bart Haegeman, Claude Lobry.

We developed an individual-based model for simulating flock-forming bacteria. It includes aggregation and breakage processes of the flocks, together with the dilution dynamics of the reactor. Local nutrient concentration heterogeneities surrounding the flocks are explicitly taken into account. Our goal is to compare the predictions of this model with more macroscopic approaches as presented in Section 6.1.7.

5.2. JPADE

Participant: Nabil Mabrouk.

JPADE is a simulator for two-dimensional biofilms grown on a planar surface. The simulator is written in Java and solves a system of three diffusion-reaction equations for the substrate, the bacteria and a product excreted by the bacteria [23].

The substrate consumption rate is modeled using a Monod equation. A fraction of the consumed substrate is supposed to be released back in the form of a product whereas the remaining part is transformed to biomass. The biomass, the substrate and the excreted product are allowed to diffuse. The diffusion factors may be constant or may depend on other variables. For instance, the simulator has been used for simulating the spatial patterns that arise for Pseudomonas Aeruginosa biofilms grown in flow chamber when the diffusion of the biomass is reduced by the accumulation of the self-excreted product.

The model parameters and the simulation results are displayed using a Graphical User Interface. JPADE is available on demand under the General Public License issued by the Free Software Foundation.

5.3. SMC DEMOS

Participant: Fabien Campillo.

SMC DEMOS (Sequential Monte Carlo demos) proposes a set of demonstration Matlab procedures for nonlinear filtering approximation via particle filtering (sequential Monte Carlo): bearing-only tracking with obstacles, tracking in digital terrain model, track-before-detect in a sequence of digital picture, mobile phone tracking based on the signal strength to nearby antenna. This software is deposited with the “Agence pour la Protection des Programmes” (APP, 7/7/2009), available at http://www-sop.inria.fr/mere/personnel/campillo/software.html.

5.4. VITELBIO

Participants: Jérôme Harmand, Alain Rapaport, Aline Libres.

In the scope of the VITELBIO project (see 7.9), we have developed a first prototype of a simulation software, in partnership with the ITK company and all the partners of the project. The software allows to draw interactively small networks of chemostats interconnected by transport and diffusion terms. Then, biological characteristics of a limited numbers of biotic/abiotic reactions in each reactor are chosen. The dynamical simulations of such networks are conducted within two main objectives:

- to help exploring the role of a spatial structure in the dynamics of substrates consumptions by micro-organisms, mimicking a network of microbial “hot-spots” as it can be observed in soil ecosystems;
- to help (micro)biologists training modelling simple ecosystem on a spatial structure they can choose themselves, and exploring on it the concepts of ecology.

This first version is downloadable on the web site of the project (http://sites.google.com/site/vitelbio/logiciel), and is expected to be substantially enriched in a near future.

6. New Results

6.1. Theoretical results

6.1.1. Control of continuous bioreactors

Participants: Jérôme Harmand, Frédéric Mazenc, Alain Rapaport.

The team maintains a regular research activity on the automatic control of continuous stirred bioreactors, with several objectives:

- the stabilization about a reference target, despite model uncertainties, disturbances and partial measurements;
- the determination of optimal strategies for reaching a target, with minimal time as a usual criterion;
- the tracking of prescribed trajectories, for instance periodic regimes allowing the coexistence of several species in competition on a single resource.

This year, the team has begun to study a new kind of optimal control problems for the preservation of water quality in natural environment. In natural sites, such as lake or water table, to be depolluted from toxic substrates, the introduction of micro-organisms in order to collect the pollution is not suited because of the eutrophisation attempting to the preservation of other living organisms (fish, plankton,...). A typical problem is the control of the input flow of a bioreactor pumping water from the site, treating it and rejecting it cleanup, after biomass filtration. Under the consideration that the dynamics of the bioreactor is much faster than the one of the average concentrations in the lake or the water table, because of the large differences of volumes, we have shown that a non-constant optimal feedback could provide significant gains in time for the depollution of the site. With the help of the Maximum Principle, we have derived optimal feedback laws, considering the concentrations diffusion between the pumping and rejecting locations [42] [50]. This work is conducted in cooperation with the CMM (Santiago de Chile) and UTFSM (Valparaiso) within the INRIA/CONICYT program.

The team has pursued its work on the problem of ensuring the persistence of several species through control. In [27], we have designed feedback controllers for chemostats with two species and one limiting substrate so that a positive equilibrium (with arbitrary prescribed species concentrations) becomes globally asymptotically stable. The design uses a new, global, explicit, strict Lyapunov function construction. By taking advantage of the Lyapunov function we have proposed, we have quantified the effects of disturbances using the input-to-state stability paradigm. The control we use requires only the measure of a linear combination of the species concentrations: this feature of our result is a crucial advantage from a practical point of view.

In the literature, all control strategies aiming at ensuring persistence of species for chemostats described by classical equations ensure only the persistence of two species. For the first time, in the paper [39], we presented a technique that ensures the stable persistence of an arbitrary number of species competing for a single limiting substrate. This technique is based on an appropriate choice for the substrate input concentration and for the dilution rate. The control laws we obtained, are given by explicit, nonlinear formulas, are time-varying, positive everywhere and of class C^1. They require the measurement of all the species concentrations. They stabilize a periodic trajectory. We gave a local version of this result in the situation where only the substrate concentration is available for feedback design. The stabilization result of [39] applies only when the growth functions satisfy some conditions. We show that when they are violated, persistence by trajectory-stabilization cannot be achieved.

6.1.2. Designs under Matrosov's conditions and robust adaptive control

Participant: Frédéric Mazenc.

In [26] the design of explicit, global, strict Lyapunov functions is performed under conditions of Matrosov-type. The advantages of [26] are (a) the results are simpler than the known constructions relying on the Matrosov's approach; (b) the Lyapunov functions are locally lower bounded by positive definite, quadratic functions for a large class of systems; (c) they only require a non-strict *positive definite* function whose derivative along the trajectories is non-positive instead of a (radially unbounded) non-strict Lyapunov function. The motivation for (c) is that for biological models, one can frequently find non-strict Lyapunov-like functions which are not proper. Another useful property of the construction of [26] is that it yields some robustness results. We used them to prove robustness for a waste-water treatment process stabilized through adaptive feedback. This illustrates the value added by strict Lyapunov functions for biological models.

One difficulty in applying the known Matrosov theorems is that one needs to know some special functions, called auxiliary functions, to build the global Lyapunov function. This was overcome in [25] for the special case of the tracking-error dynamics for adaptively controlled, nonlinear systems that are affine in the unknown parameter. The main assumption was a classical persistence-of-excitation condition.

The contribution of [26] involved (a) constructing explicit auxiliary functions for adaptive controlled error dynamics; (b) extending the resulting global Lyapunov function construction to cases where the unknown parameter also has additive, time-varying uncertainty. This made it possible to explicitly quantify the effects of the uncertainty using the celebrated input-to-state stability paradigm, provided the regressor satisfies an additional affine growth condition. The results in [26] apply under general adaptation laws that could include, for example, projection operators, least-squares estimators, and prediction-error-based estimators. The practical interest of this work is that it leads to uniform, global, asymptotic stability of the error dynamics by constructing explicit, global, strict Lyapunov functions.

In [28], we have presented two new strict Lyapunov function constructions, based on transforming non-strict Lyapunov functions into strict ones, under Lie-derivative conditions. The main novelty of the first construction is that it allows us to cope with the difficult case of *periodic time-varying* systems. It applies even when the higher-order Lie derivatives of the weak Lyapunov function vanish at some points outside the equilibrium, on some time intervals, provided a suitable persistence-of-excitation property is satisfied. The simplicity of the construction is also one of its advantages. The second result uses the Matrosov approach. We already mentioned that, in general, Matrosov's method can be difficult to apply, because one needs to find the necessary auxiliary functions. In addition, one needs to select the auxiliary functions so that the resulting strict Lyapunov function has the most desirable properties. Here we gave simple sufficient conditions leading to a systematic design of auxiliary functions. Another important feature of our work is that it applies to cases where the state space of the system is a general subset of Euclidean space, instead of the whole Euclidean space. This is desirable for biological systems, whose state spaces are often restricted by the requirement that physical quantities need to be non-negative. We have chosen to illustrate our approach using an error dynamics associated with the celebrated Lotka-Volterra system.

6.1.3. Systems with delays

Participant: Frédéric Mazenc.

We worked on three distinct problems related to the presence of delays in a model. In this section, we describe two of them, and in the next section, we will explain the last one because it is related to the design of interval observers.

A central result of the theory of the chemostat is the Competitive Exclusion Principle. It states that for a chemostat model with several species with increasing growth rates at most one competitor can survive when there is a single limiting resource. However, this result is valid only in the absence of delay in the equations while they naturally occur in biological models; in particular, chemostats models with delays in the dynamics of the species concentrations are more realistic than models without delays. In [17] it is proved that, for models of this type, the competitive exclusion principle still holds true, provided that the delays are smaller than an upper bound for which an explicit expression is given. The proof is established through the construction of Lyapunov-Krasovskii functional.

Quantized control systems are systems in which the control law is a piece-wise constant function of time taking values in a finite set. For a family of these systems, which contains nonlinear systems, we have used Lyapunov-Krasowskii functionals to design quantized continuous-time control laws in the presence of time-invariant point-wise delays in the input. Our quantized control laws are implemented via hysteresis which allows us to avoid chattering. Our analysis applies to a fairly large class of systems, namely the class of the stabilizable nonlinear systems and for any value of the quantization density. The quantized feedbacks we obtained are parametrized with respect to the quantization density. Moreover, the maximal allowable delay tolerated by the system is characterized as a function of the quantization density.

6.1.4. Interval observers

Participant: Frédéric Mazenc.

The *interval-observer* method is a recent state-estimation technique. It is used in particular in biological contexts, where taking into account the presence of uncertainties is essential. We have completed the theory of the linear interval observers in several works.

The contribution of the work [24] (see also [38]) is twofold. A first part of our work is devoted to the problem of exhibiting necessary and sufficient conditions which guarantee that, for a time-invariant linear system of dimension two, a time-invariant, linear and exponentially stable interval observer can be constructed. In the second part of the work, we have shown that when these conditions are violated, one can still construct exponentially stable, linear interval observers, but these interval observers have the remarkable feature of being *time-varying*. Thus, we managed to give a complete picture of the difficulties and of the solutions which can be given for systems of dimension two. To illustrate the power of our approach, we have applied it to a chaotic system which is known to be highly sensitive to uncertainties in the initial conditions.

In [41], we have investigated the problem of constructing interval observers for exponentially stable, linear systems with point-wise delays. First, we have proved that classical interval observers for systems without delays are *not robust* with respect to the presence of delays that appear in a specific structure location, no matter how small the delay is. Next, we have shown that, in general, for linear systems classical interval observers endowed with a point-wise delay are not satisfactory because they are exponentially unstable. Finally, we have designed interval observers of a new type. Our construction relies on framers that incorporate *distributed delay* terms. These framers are interval observers when the delay is smaller than an upper bound that we have estimated.

6.1.5. Optimal control of fed-batch reactors

Participants: Jérôme Harmand, Alain Rapaport.

In industrial biotechnology, it is not always possible to operate bioreactors in continuous mode like the chemostat. The batch mode, that consists in cycles of sequential feeding and emptying the tank, can be used instead. But each sequence has to be optimized with respect to the occupancy time. The initialization phase of continuous bioreactor of very large volume may also present an issue as far as the time necessary for filling the reactor up to reference values of the concentrations is considered.

The problem of feeding in minimal time a batch reactor with one reaction involving one substrate and one biomass has been originally solved by J. Moreno in 1999 using a technique based on Green's theorem. Recently, the team has contributed to extensions with several species and impulse controls, using techniques based on Hamilton-Jacobi-Bellman equation and Maximum Principle, instead of the one proposed by Moreno that is suited for planar dynamics only.

When the growth function is non monotonic, the optimal control synthesis may present singular arcs. The case of growth functions with only one maximum, such as the Haldane law, has been completely solved by the Moreno's approach and presents a single singular arc. But for complex non monotonic kinetics, characterized for instance by the combination of two Haldane models, the minimal time problem exhibits several candidate singular arcs, and the technique based on the Green's theorem provides only local optimal conditions. and the problem exhibits several candidate singular arcs. The analytical determination of which singular arc is optimal, and for how long, appears to be a tricky problem. We have proposed an approximation procedure, that considers a family of approximate optimal control problems with smooth controls (i.e. without singular arc), based on former idea of C. Lobry. This has led us, very recently, to a new numerical method for determining the optimal selection of singular arcs.

6.1.6. Modelling and identification of batch processes

Participants: Miled El Hajji, Jérôme Harmand, Alain Rapaport.

With INRA Dijon, we conduct experiments of batch cultures of micro-organisms collected in soil ecosystems, in a modelling perspective. Before mixing several species in experiments for the investigation of their interactions, we have first revisited and fitted on the data the usual models in microbiology. Most often, theses models are well suited for the growth phase but not longer for situations with restricted nutrient availability, as it happens in soil ecosystems.

Last year, we have proposed a model of batch reaction with an explicit compartment of inactive (or dead) cells and an additional nutrient recycling term in the substrate dynamics. The dynamical behavior of this model fits qualitatively well the experimental data collected at INRA Dijon, in the framework of El Hajji's PhD thesis. The on-line observation made on this system are the concentration S and an optical density that provides a measurement of the total biomass, and not the proportion of viable cells. A particularity of this model is to be non-identifiable and non-observable at steady state. So we cannot use the usual techniques of on-line reconstruction, that requires the global observability of the system. We have developed a decomposition technique into cascade of observers in different time scales. Each sub-system is observable on its own time scale. But one of the time scale is bounded (i.e. the time does not go toward infinite), which freezes the observer before the system approaches the steady state. Nevertheless, this technique has allowed us to derive and prove the practical convergence of the cascade of observers.

6.1.7. Theory of competition for a substrate

Participants: Claude Lobry, Frédéric Mazenc, Denis Dochain, Miled El Hajji, Alain Rapaport, Bart Haegeman, Jérôme Harmand, Tewfik Sari.

A microbial ecosystem is a complex ecosystem where multiple interactions are initiated involving, in addition to the *substrate consumption*, the *production of substrate* through the degradation by enzimes produced by bacteria, *"consumption" of bacteria by viruses*, the *chemotaxis and "quorum sensing"*[1], the *mutations* and a *variable environment in time*. For each of these specific traits we construct a "toy model" which reproduces it ; the model is analyzed mathematically from the point of view of bio-diversity. This is a "reductionist approach" that we assume but that does not prevent us from taking advantage of more "global" approaches. Below are the topics that we considered in 2009.

- *Coexistence through oscillations* We considered "substrate-dependent" models but in the case of a three trophic level system: *substrate-bacteria-bacteriophage*. We produced models which show through simulation the following picture:
  - there are three competing species: A, B, and C. If the three species are present then there is coexistence through oscillations.
  - Species B and C alone do not coexist and species B eliminates C. Thus species A appears to organize the coexistence.

  By itself the possibility of coexistence through periodic solution is not original, it goes back to the seventies ! Actually, it was the main emphasis of the seminal paper of Armstrong and Mc Gehee [53] but our rationale is different and our model has more than two competitors. This model was the subject of a public presentation within the network TREASURE in Tlemcen. Karim Yadi, a doctoral student of T. Sari in Tlemcen mathematically proved that the observed simulations are really a property of the model. This is a rather technical work - it uses the techniques of singular perturbations

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[1] Some species of microorganism produce at a constant rate a specific molecule which is spread in the environment. The concentration of the chemical is proportional to the population size ; the individuals have a receptor for the specific molecule and, thus, are informed about the size of their own species.

with two parameters - which is a part of the thesis of Yadi. The work was also presented at the school "Modeling of complex biological systems in the context of genomics", La Colle sur Loup 30/03-3/04/09 (http://epigenomique.free.fr/fr/orateurs.php) and at the workshop "System theory in Chemical and Life Science" (03-05/06/09),Centre Interfacultaire Bernoulli, EPFL (Lausanne). A paper, *Coexistence of three predators competing for a single biotic resource* by Lobry, Sari and Yadi is submitted for publication in a Book to be edited by the Bernoulli center.

- *Slowly varying environment* Imagine a microbial ecosystem subject to a "slow" variation of its environment. For example, a seasonal cycle is slowly varying compared to time constants of cellular division (of the order of the day). One might wonder about coexistence when all species are favored at a given time. We have recently shown a mathematical technique (based on earlier work by some members of the project) that can predict and understand the coexistence on the basis of knowledge of growth rates of various species. Notice also that there are some previous results when the environment varies on a periodic basis, but our technique also works when the forcing term is not periodic. The work is largely in progress. Some results are published [37] or exposed [49].
- *Coexistence during transients* In these papers we consider that in many circumstances we do not observe the asymptotic behavior but a transient. We started to investigate the conditions for "practical coexistence", that is to say during a long transient. We have some results published in 2008 and 2009 [16], [32].
- *Mutualism* Bacteria might produce chemicals that can be substrates for other species. A case of such an "obligate mutualism" is when the species 1 produces the substance B necessary for growth of species 2 that produces the substance A necessary for the growth of species 1. We have published a model of this situation [15].
- *Systems with viruses* We compare classical mathematical work [65] to recent experimental work where the technique of "fingerprints" povides insight into the changes in concentrations of various species along time. One can observe, in a constant environment, a *dynamic equilibrium* where species dominates one after another. Biologists believe that this phenomenon is explained through the relationship "bacterium-virus" in the form of "kill the winner" mechanism: each species of bacteria B_i is accompanied by a species of virus V_i , when the species B_i becomes sufficiently large and begins to dominate this favors the virus V_i who growths to the detriment of B_i. We can reproduce this phenomenon in simulation and the mathematical justification is in progress.
- The effect of a *delay* is studied in [17].
- The paper [51] is a contribution to an old open mathematical problem related to *Competitive Exclusion Principle*. It is submitted.

6.1.8. Neutral community models for microbial ecology

Participant: Bart Haegeman.

Hubbell's neutral model [59] describes the dynamics of an ecological community in terms of random birth, death and immigration events, attributing equivalent characteristics to all species. Although the absurd simplicity of these assumptions, remarkable agreement between neutral model predictions (species-abundance distributions and species-area relationships) and empirical observations has been reported for some, mostly rather diverse, ecological communities.

There is some evidence that also certain aspects of microbial communities can be well described by the neutral model. Highly diverse microbial communities have been difficult to deal with using more traditional modelling approaches from community ecology. The neutrality assumption could lead to an effective global description, without requiring quantitative species data (growth characteristics, interaction strengths, etc). We are actively participating in the development of neutral community models, with a focus on microbial systems (e.g., [19]). This is joint work with R. Etienne of Univeristy of Groningen, The Netherlands.

We are especially interested in the description of microbial microplate experiments. Microplates consists of a large number of tiny batch reactors, in each of which a microbial community grows on the substrate available. Due to the small dimensions of these systems, many (identical or different) experimental conditions can be studied in parallel. For example, the same microbial community can be grown on a large number of substrates; or the performance of microbial communities with a different past can be measured on a given substrate. Communities from different reactors can be mixed together, thus creating a spatial network of reactors. Together with D. Vanpeteghem, KULeuven, Belgium, we are developping a theoretical framework for this type of microbial systems [33]. Experiments are conducted by J. Hamelin at INRA-LBE.

The modelling framework of neutral community theory is close in spirit to statistical mechanics. Many individual contributions (organisms in ecology, particles in physical systems) yield some global, averaged system behavior (a community in ecology, a gas or a solid in physics). The model outcome on this global level is often rather insensitive to the modelling assumptions on the detailed level, justifying an oversimplified microscopic description. This mapping between global and detailed level can be formulated as a so-called entropy maximization problem, also known as the MaxEnt algorithm.

Entropy-maximization ideas could be particularly useful to infer community structure characteristics based on a limited number of global, community-averaged properties. This could lead to ecological models of drastically reduced complexity. We have studied the entropy-maximization ideas for two ecological problems:

- First, to predict abundances of the species present in an ecological community [20]. This is joint work with M. Loreau of McGill University, Montreal;
- Second, to predict the spatial distribution of an ecological community [18]. This is joint work with R. Etienne of University of Groningen, The Netherlands.

Both studies consider ecological communities in general, but might be particularly relevant for microbial communities. Indeed, due to the large number of species and individuals in such communities, model complexity reduction is both necessary (the full complexity is impossible to deal with) and effective (due to averaging effects over many components).

6.1.9. Individual-based modeling

Participants: Fabien Campillo, Marc Joannides.

Individual-based modeling (IBM) has been very active over the past fifteen years. It allows to account for the dynamics of complex ecological systems. Although there are many computer realizations of such models, there is a strong need for their mathematical representations. Such a framework is given by birth-death and branching Markov processes, it allows to analyze IBMs at different scales. Indeed, the asymptotic analysis in large population size bridges individual-based models (at microscropic scale) to aggregate models (at macroscopic scale). These last models are usually of integro-differential type. This approach allows one to propose rigorous Monte Carlo simulation algorithms.

We have extended the work of Fournier and Méléard [58] for terrestrial populations to the case of individuals with explicit zone of influence. We have proposed a complete study of the underlying Markov process, its Monte Carlo simulation and its limiting behavior in large populations size [47]. Also as part of the ANR MODECOL in collaboration with Nicolas Champagnat (EPI TOSCA, Sophia Antipolis) and Pierre Del Moral (EPI ALEA, Bordeaux), we have proposed IBMs for terrestrial population dynamics. We propose a description of the underlying Markovian dynamics and of its Monte Carlo simulation. Here the dynamics of individuals is coupled with the dynamics of resources. We also describe the large population size approximation of this process as an integro-differential/partial differential system [34], [46].

6.2. Applications

6.2.1. Modelling and control of Anaerobic Membrane BioReactors (AMBR)

Participants: Claude Lobry, Jérôme Harmand.

The advanced control of AMBR is a new problem since most plants are working under aerobic mode. However, using anaerobic systems present the advantages of allowing the valorization of the biogas produced. However, the main drawback of such processes is the membrane fouling phenomenon which is difficult to control. Models including a number of new variables, such as the Soluble Microbial Product (SMP) that are recognized to play an important role in the membrane fouling, are needed. Furthermore, the integration of models describing the biological phenomena together with the fouling of membranes must be developed. Such objectives are at the heart of the PhD thesis of Boumediene Benyahia and are realized within the framework of the TREASURE project (cf. Section 8.1.5).

6.2.2. Observers for investigating microbial ecology problems

Participants: Jérôme Harmand, Alain Rapaport.

One of the most important challenges in microbial ecology is to determine the ecological function of dominant microbial populations in their environment. In the framework of the PhD thesis of Maxime Dumont, we proposed a generic method coupling fingerprinting and mathematical tools to achieve the functional assigning of bacteria detected in microbial consortia (cf. [14]). This approach was tested on a nitrification bioprocess where two functions carried out by two different communities could be clearly distinguished. The mathematical theory of observers of dynamical systems has been used to design a dynamic estimator of the active biomass concentration of each functional community from the available measurements on nitrifying performance. Then, the combination of phylotypes obtained by fingerprinting that best approximated the estimated trajectories of each functional biomass was selected through a random optimization method. By this way, a nitration or nitration function was assigned to each phylotype detected in the ecosystem by means of functional molecular fingerprints. The results obtained by this approach were successfully compared with the information obtained from 16S rDNA identification. This original approach can be used on any biosystem involving n successive cascading bioreactions performed by n communities.

6.2.3. Modelling and control of cascade biosystems to mimick batch wine making processes

Participants: Jérôme Harmand, Alain Rapaport, José Fernandez.

Wine making processes are operated in batch mode during which the physiological state of yeasts used for converting sugar into alcohol evolves. In particular, at the initial step the biological process is mainly the growth of biomass, while at the end of the batch (when there is almost no nitrogen nor sugar anymore), the main biological process is characterized by an activity without growth. In these different process stages, the yeasts are in very different physiological states. Because the process is operating in batch mode, it is difficult for biologists to study these different microbial states. Thus, a configuration of continuous reactors in series has been proposed to mimic the behavior of a batch process as a set of steady-state points along the reactor cascade. The steady state in each chemostat corresponds to a state at a given time (characterized by the progress of the reaction) in the batch process. In order to control the steady states to be mimicked, it is necessary to model this process and to develop an appropriate time-optimal control strategy in order to leave the possibility to the user to choose the interesting yeast physiological states to be studied. This work is part of the PhD thesis of José Fernandez in the framework of the CAFE European project (see Section 7.2).

6.2.4. Modelling and simulating terrestrial plant ecological dynamics

Participants: Fabien Campillo, Audrey Dubourg.

We propose individual-based models (IBMs) for prairial plant dynamics. We propose models of dynamics of a simplified grassland ecosystem, then develop simulation techniques for these models and finally establish their mathematical properties. The ecosystem is a community of individuals (ramets) linked by connections (stems). This ecosystem relies on resources (nitrates) and can store a portion of these resources. We propose different individual-based models coupled with continuous models for the available resources and the stored resources, in this case the individual is the ramet; or the available resources only, in this case the individual is the ramet or the rhizome [46].

6.2.5. Modelling and inferring agricultural dynamics

Participants: Fabien Campillo, Angelo Raherinirina.

This work is supported by the AUF and is done in collaboration with the University of Fianarantsoa in Madagascar and with Dominique Hervé (IRD, Fianarantsoa, Madagascar).

To study the dynamics of agricultural plots on the edge of primary forest we use Markov chains models. The problem of identification of the transition matrix is ill-posed since the underlying dynamics is not at equilibrium and most states are transient, hence maximum likelihood approaches are not feasible. We adopt a Bayesian approach and work in collaboration with specialists of agricultural dynamics to limit the size of the parameter space.

6.2.6. Modelling for soil ecosystems

Participants: Ihab Haidar, Jérôme Harmand, Alain Rapaport.

In cooperation with the UMR Eco&Sols (Montpellier) and INRA Theix, we study the impact of a spatial structure in microbial activity. Several numerical models have already been developed for the geochemical transfers in soil. Most of them are based on a spatial discretization by elementary volumes, but are not well suited for biotic/abiotic interactions, because most of the time it is not possible to consider that the mobility of micro-organisms in each elementary volume is different from the one of their chemical nutrients. In the framework of Haidar's PhD thesis, we have begun to study theoretically the impact of diffusion among simple motifs of elementary volumes, considering each of these volumes as a chemostat. For the moment, the study has concerned motifs of two or three reactors at steady state.

6.2.7. Decision making tools for the management of natural resources

Participant: Alain Rapaport.

A small part of the activity of the team concerns the bio-economics of natural resources at the decision maker scale, with the help of control theoretic and optimization tools. We distinguish two kinds of natural resources:

- No or weak seasonality-dependency in the reproduction (fisheries, food crops, ...). Typically, the models are in continuous time. We have studied theoretically the benefit of the creation of protected areas, assuming that the reproduction rate is improved in absence of harvesting, in terms of viability analysis of the economics of the exploitation [22];
- Strong seasonality-dependency in the reproduction (forests, water tables, ...). The models are usually in discrete time. We have studied theoretically the benefit of an alternative use of the space allocated to the exploitation of resources with slow growth mature, in terms of discounted utility over a large time horizon [30].

7. Contracts and Grants with Industry

7.1. BioInh

Participants: Jérôme Harmand, Alain Rapaport, Ahlem Saddoud.

The project BioInh (Modelling and optimization of bio-conversion of plant materials in inhomogeneous media) proposed by the UMR IATE (Ingénierie des Agropolymères et Technologies Emergentes, Montpellier) and the team MERE is funded by the Agropolis foundation (Montpellier) for two years since 2009. The project aims at studying inhomogeneity effects in enzymatic reactors with the help of models of cascade of reactors. The presence of inhibition in the growth function may lead to instabilities and drive the system toward several possible equilibria, one of them only being interesting in terms of yield and productivity. Experiments are planned for the coming year, and the final objective is to derive control strategies for driving the system toward the best equilibrium. The project hires A. Saddoud in a postdoctoral position for two years, and R. Lortie (NRC Biotechnology Research Institute, Montréal, Québec) as a regular visitor.

7.2. CAFE

Participants: Jérôme Harmand, Alain Rapaport.

The objective of the CAFE project is to provide new paradigms for the smart control of food processes, on the basis of four typical processes in the areas of bioconversion, separation, preservation and structuring. The novelty of the project lies in the capacity of combining PAT (Process Analytical Technology) and sensing devices with models and simulation environment with the following objectives:

- to extract as much as possible information from the process/plant in the form of precise estimations of unmeasured variables defining, in particular, product quality, and of physical parameters changing as the process dynamics does or difficult to know beforehand;
- to save and encode the information in a reliable and usable way, basically via physical/deterministic models;
- to develop control methods to keep uniform quality and production, despite the variability in the raw material and/or to respond to sudden changes in the demand.

MERE is involved in the wine making optimization part of the project, part of the PhD thesis of José Fernandez.

7.3. DIMIMOS

Participants: Jérôme Harmand, Alain Rapaport.

This fundamental research project aims at better understanding of functional microbial soil ecosystems with respect to the turnover of soil organic matter (SOM). More specifically, we aim at evaluating the role of the microbial diversity in transforming SOM, in order to better manage the carbon in its biochemical global cycle within agro-ecosystems. This project must deliver new insights for managing agricultural productivity (allow better agricultural practices) while maintaining a high quality of soil over the long term.

7.4. DISCO

Participants: Bart Haegeman, Fabien Campillo, Jérôme Harmand, Claude Lobry, Alain Rapaport.

DISCO (Multi-scale modelling bioDIversity Structure COupling in biofilms) is a three-years project from the ANR programm SYSCOMM, started in November 2009.

The objectives of the project is to generate new insights in

- microbial ecology, contributing to a better understanding of the links between the spatial structures (physical and morphological characteristics) and the biodiversity of biofilms, and how these links at the same time impact and depend on macro-variables (concentrations, flow rates, ...) and studying biological properties(e.g., functional differences between fresh and mature biofilm, mechanisms such as the “barrier effect”);
- waste and waste-water treatment processes, investigating how these links impact on the biological and physical performances of the biofilm (surface colonization, substrate degradation, detachment resistance,...) and proposing improvements of decision making tools (e.g. criteria for detecting the maturity of the biofilm, strategies of improving the start-up phase of biofilm reactors).

The consortium is composed of

- the team MERE,
- the Cemagref LISC (Laboratoire d’Ingénierie pour les Systèmes Complexes, Clermont) and HBAN (Hydrosystèmes et Bioprocédés d’ANtony),
- the INRA LBE (Laboratoire de Biotechnologies de l’Environnment), Narbonne,
- the UMR LPTMC (Laboratoire de Physique Théorique de la Matière Condensée), Univ. P. et M. Curie, Paris,

and will hire two postdoctoral fellows and one engineer.

7.5. MODECOL

Participants: Fabien Campillo, Audrey Dubourg.

The ANR SYSCOMM Project MODECOL (2009-2011) involves three INRIA project-teams (MERE, MAESTRO and TOSCA) with the UMR Ecobio (Rennes, France), the University of La Rochelle and the Universities of Houston and Berkeley. The aim of the MERE project-team is to propose individual-based models for terrestrial prairial plant communities' dynamics in the context of water purifying from nitrate and pesticides .

7.6. RNSC – appel à idées

Participants: Jérôme Harmand, Alain Rapaport.

The project E-MICRAM (Emergence of properties of reconstituted microbial ecosystems) proposed jointly by BIOEMCO (Laboratoire de Biogéochimie et écologie des milieux continentaux, Paris), the UMR Eco& Sols (Montpellier) and the team MERE has been selected as a young project of the national network of complex systems for one year. The objective of the project is to conduct experiments and modelling of microbial ecosystems composed of several species in interaction, each of them being well studied alone, and to study gradually how interactions are responsible of the properties of the overall ecosystem.

7.7. STIC-AmSud

Participants: Fabien Campillo, Jérôme Harmand, Marc Joannides, Claude Lobry, Tewfik Sari.

The MERE project-team is animating a STIC AMSUD project MOMARE (Modelamiento Matematico por Manejo de Recursos Naturales) that has just been accepted. This project from 2010 to 2011 aims at developing a scientific network (Chile, Peru, Argentina, France), consisting of applied mathematicians, around several case studies of estimation and management of renewable resources. It will permit to share different approaches for modeling renewable resources dynamics and proposing algorithms for identification and control. See http://www-sop.inria.fr/mere/personnel/campillo/momare/.

7.8. TREASURE

Participants: Jérôme Harmand, Claude Lobry, Tewfik Sari.

The TREASURE network benefits from financial support from INRIA, INRA and African partners of about 20 Keuros/year for the next three years (2009-2011). In addition, a European IRSES (called COADVISE) project has been accepeted and includes 42 man months available for exchanging PhD and postdoc students within the next 48 months.

7.9. VITELBIO

Participants: Ihab Haidar, Jérôme Harmand, Alain Rapaport.

VITELBIO stands for VIrtual TELluric BIOreactors and is co-sponsored by INRIA (ARC) and INRA (AAP) for two years starting in 2009. The scientific challenge is to study and identify models of small networks of virtual interconnected bioreactors as a simplified representation of the microbial activity in soils. The focus is made on input/output representations of particular functions of the microbial communities : carbon sequestration, availability of nutrients for plant roots,... The project gathers ten teams and aims at developing a user-friendly software (see 5.4) and experiments on a network of four interconnected chemostats.

8. Other Grants and Activities

8.1. International cooperations

8.1.1. Cooperation with African countries

The MERE project-team is involved in cooperation with Africa in different but related ways.

- C. Lobry, as a former director of CIMPA, has been involved for a long time in cooperation with African mathematical teams. He visits Africa very often and delivers lectures in summer schools or universities.
- The team has also a close relationship with the LANI (Laboratoire d'Analyse Numérique et Informatique de l'Université Gaston Berger de Saint-Louis du Sénégal).

8.1.2. Cooperation with Maghreb countries

Claude Lobry and Tewfik Sari are involved in the program Aires-Sud (2009-2011). The program runs under the title "Epuration des Eaux par Procédés Membranaires: Modélisation et Commande", is managed by Brahim Cherki, University of Tlemcen, Algeria, and also associates the University of Saint Louis, Senegal.

8.1.3. Cooperation with Latin America

The MERE project-team is carrying on his cooperation with Chile in the scope of the INRIA/CONICYT projet 'ECOLOMICRO2'. The First Franco-Chilean workshop on bioprocesses modelling is scheduled in January 2010 at Valparaiso, and is organized by both the team MERE and researchers from CMM (Santiago) and UTFSM (Valparaiso). Our Chilean collaborators will be an "associated team" from 2010 onwards.

8.1.4. Cooperation with North America

F. Mazenc interacts with researchers of the Department of Mathematics of the Louisiana State University in Baton Rouge in the framework of the NSF/DMS Grants 0424011 and 0708084. In particular, in collaboration with M. Malisoff and M.S. de Queiroz, several papers have been written in the past few years. A research monograph appeared this year. This book, entitled "Construction of Strict Lyapunov Functions" and geared to advanced graduate students and researchers, is published in the Springer Communications and Control Engineering Series. F. Mazenc also paid a visit in August 2009 to Jiang Zhong Ping (Polytechnic Institute of New York) in order to prepare future collaborations with him. Their first paper has been presented in the Conference on Decision and Control.

B. Haegeman has an on-going collaboration with the Theoretical Ecology laboratory at McGill University, Montreal, led by M. Loreau. Two common papers have now been published; other work is in preparation. B. Haegeman initiated a new collaboration with the Theoretical Ecology laboratory at Georgia Institute of Technology, Atlanta, led by J. Weitz. A number of joint research projects have been defined.

8.1.5. The TREASURE network

The 3+3 Mediterranean program (Algeria, Spain, France, Italy, Morocco, Tunisia) is a collaborative INRIA research program initiative. It aims at selecting thematic research actions associating at least two North and two South Countries in order to finance mobility and research. The actual TREASURE project is coordinated by the MERE research team and a research group in mathematics and automatic control of the University of Tlemcen, Algeria. Initially, the involved partners only consisted in France, Algeria, Italy and Tunisia. During the first project year (2006), we defined the research program and extended the consortium to Spain. The diffusion of knowledge is one component of the project. Bilateral meetings have been organized together with meetings and seminars, and several workshops are regularly organized with all partners in partners countries (cf. the website http://www.treasure.fr for further information). From a scientific point of view, the TREASURE project aims at developing an innovative treatment integrated process in order to treat waters to be reused in agriculture in semi-arid climate countries. The main innovation consists in the coupling of advanced anaerobic technology and membrane bioreactors. This configuration offers many advantages.

- First, the nitrogen is not degraded and can be used to amend the soils to improve its fertility;
- Second, anaerobic digestion produces less sludge than aerobic processes, thus decreasing the running costs of the integrated process;
- Third, the use of membrane allows the water to be used for unrestricted agriculture;
- Finally, the biogas produced can eventually be valorized to produce energy.

Membranes allow the quality of the rejected water to be in accordance with the microbial normative constraints imposed for agriculture reuse. This important, ambitious program not only includes development and industrial challenges, but is also concerned with theoretical research questions related to microbial ecology (how to decrease the membrane fouling?) allowing the pluridisciplinary to express deeply within the program.

8.2. European collaborations

- The team has strong connections with the Centre for Systems Engineering and Applied Mechanics (CESAME), Université Catholique de Louvain-la-Neuve, Belgium. D. Dochain regularly visits the team.
- J. Harmand is a participant of a Large Scale Collaborative European Project, called “CAFE” or “Computer-Aided Food processes for control Engineering”, coordinated by Denis Dochain, Université Catholique de Louvain-la-Neuve, Belgium (2008-2012). This project aims at developing an integrated solution for the robust monitoring and control of food processes. INRA is an important partner through the participation of four labs and one Experimental Unit (UMR GMPA, Grignon, UMA ASB and SPO, Montpellier, LBE, Narbonne and UE Pech Rouge, Gruissan).
- F. Mazenc works with C. de Persis, researcher at the University of Twente, Enschede, the Netherlands, and at the Dipartimento di Informatica e Sistemistica, Sapienza Università di Roma, Italy.
- B. Haegeman collaborates with R. Etienne, researcher at Community and Conservation Ecology group, University of Groningen, The Netherlands.

8.3. National initiatives

- J. Harmand and A. Rapaport, with the help of J.J. Godon (INRA LBE, Narbonne) are the animators of the INRA methodology network “Populations microbiennes, modèles et systèmes dynamiques”, supported by several INRA Departments (MIA, EA, MICA).
- F. Campillo is the animator of STIC-AMSUD project MOMARE for the mathematical modeling for Natural resources management regrouping teams from Chile, Peru, Argentina and France. See the web page http://www-sop.inria.fr/mere/personnel/campillo/momare/.
- F. Mazenc organized with M. Czarnecki a *workshop* entitled “Contrôle et Optimization” in Ardaillers, Gard, May 21-24, 2009.

8.4. Visits

- Visits of national researchers : J.-R. de Dreuzy (CNRS Géosciences Rennes), J.-C. Poggiale (CNRS Océanographie, Luminy), T. Bayen (Dept. Math., Univ. Montpellier II), F. Hamelin (Agrocampus Rennes), E. Trélat (Dept. Math., Univ. Orléans).
- Visits of foreign researchers for short periods : R. Beardmore (Imperial College, London), P. Gajardo (UTFSM, Valparaiso, Chile), G. Acuna (Univ. de Santiago de Chile), R. Lortie (NRC Biotechnology Research Institute, Montréal, Québec).
- Visits of foreign researchers for long periods : D. Dochain (CESAME, Louvain-la-Neuve, Belgium, 2 months).

9. Dissemination

9.1. Leadership with scientific community

- C. Lobry was President of an AERES evaluation committee; he was President of the evaluation committee of the University of Saint-Louis, Sénégal.
- A. Rapaport is the head of the UMR INRA/SupAgro "Analyse des Systèmes et Biométrie" (ASB) since January 1, 2009.
- F. Campillo and C. Lobry are members of the Scientific Committee of the 10th African Conference on Research in Computer Science and Applied Mathematics.
- F. Campillo was expert for the GRAISyHM (Federation of Automatic Control Laboratories in North France).
- F. Mazenc is member of the COST (Scientific and Technological Orientation Council) in the team GTAI (Groupe de travail Actions Incitatives). The main mission of the GTAI: organization, selection and supervision of INRIA's incentive initiatives, such as the Cooperative Research Initiatives (ARC) of the Scientific Management and the Software Development Operations (ODL) and Standardization operations of the Department of Development and Industrial Relations.

9.2. Teaching

- The MERE project team has organized a one-week research school entitled "From Data-Driven to Model-Driven Microbial Ecology" in the month of December, in Saint-Martin-de-Londres (France). The school has brought together about 40 researchers, both micro-biologists and mathematicians, interested in modelling microbial ecosystems. The school was organized with the practical help of the INRA Montpellier "Formation Permanente", and was financially supported by INRA. See the web page http://sites.google.com/site/datamodeldriven2009/.
- A. Rapaport is responsible for an optional modulus at SupAgro Montpellier entitled "Mathématiques de la gestion des ressources naturelles renouvelables" (two weeks). F. Campillo, J. Harmand and T. Sari are participating.
- F. Campillo gave, together with M. Joannides, a course on "Continuous-time stochastic processes for ecological modeling" at Université Montpellier 1, within the Master degree "Bio-statistique" (20 hours).

9.3. Ongoing theses

- Nabil Mabrouk develops individual-based computer models for bacterial communities, taking spatial structure (like flocks and bio-film) into account. The simulator has been validated by comparison with analytical models, which under certain conditions approximate the individual-based models quite accurately. In particular, the behavior of a population-balance model for bacterial flocculation has been reproduced. Nabil will defend his thesis January 7, 2010.
- Miled El Hajji is preparing a PhD thesis since December 2007, under the supervision of A. Rapaport and L. Ranjard (INRA Dijon). Microbial communities of soil ecosystems appear to possess some similitude with waste-water ecosystems that are worth being studied more deeply, which is the main purpose of this thesis, granted by INRA. An originality of the work relies on experiments on simple ecosystems conducted at INRA Dijon.
- Ihab Haidar is funded by the French Ministry of Research (MESR grant) since November 2008, for preparing a PhD thesis under the supervision of A. Rapaport and F. Gerard (INRA Montpellier). His research subject focuses on coupling geochemical models of soil with microbial dynamical models, in partnership with UMR Eco & Sols (Montpellier).

- The PhD thesis of Diagne Mamadou Lamine is co-directed by Mary Teuw Niane (Saint-Louis, Sénégal) and T. Sari on the subject “Modélisation mathématique de la dynamique de prolifération du Typha dans le Parc National du Djoudj”.
- Boumediene Benyahia has just begun his PhD Thesis in September 2008 within the TREASURE network (cf. 8.1.5). His thesis aims at evaluating classical anaerobic process models for AMBRs. In close cooperation with Amine Charfi (cf. herebelow) and all partners of the TREASURE network, he will try to modify such models to link their variables to those used to characterize the membranes. The final objective is to be able to predict and control the clogging of membranes. The first work to be realized is the modelling of an AMBR working in the Biotechnological Center of Sfax (CBS, Sfax, Tunisia). At the same time, he will be in charge of the design and the building of an AMBR pilot plant in Tlemcen which should begin soon.
- Amine Charfi will begin his PhD soon within the TREASURE network (cf. 8.1.5). His thesis aims at characterizing the membranes used in AMBRs in order to link their characteristics to biological compartment of bioprocess models. In close cooperation with Boumediene Benyahia and all partners of the TREASURE network, he will conceive and realize experiments on membranes modules both with and without biomass in order to better understand chemical and physical properties of the membranes and its capacity to clog. The first work to be realized is, on the one side, an extensive literature survey on the membrane models, and, on the other side, on classical models of anaerobic bioreactors.
- Angelo Raherinirina has just begun his PhD (prepared in Madagascar) under the supervision of F. Campillo and R. Rakotozafy. The thesis aims at developping Markovian models for agricultural dynamics. A. Raherinirina spent three months in Montpellier.

9.4. Participation to thesis committees

- C. Lobry (referee): J.-B. Pomet, “Equivalence et linéarisation des systèmes de contrôle”, thèse d’Habilitation à Diriger des Recherches, Univesité de Nice Sophia-Antipolis, October 23, 2009.
- A. Rapaport (referee): G. Goffaux, “Exploration of robust software sensor techniques with applications in vehicle positioning and bioprocess state estimation”, thèse de doctorat, Faculté Polytechnique de Mons, December 2009.
- F. Campillo (referee): B. Landelle, “Étude statistique du problème de la Trajectographie Passive”, thèse de doctorat, Université Paris Sud Orsay, June 30, 2009.
- F. Campillo (referee): J. Cornebise, “Methodes de Monte-Carlo Sequentielles Adaptatives”, thèse de doctorat, Université Pierre et Marie Curie, Paris 6, June 25, 2009.
- F. Mazenc (referee): R. Postoyan, “Commande et construction d’observateurs pour les systèmes non linéaires incertains à données échantillonnées et en réseau”, thèse de doctorat, Université Paris XI, 2009. (advisors: F. Lamnabhi-Lagarrigue, T. Ahmed-Ali, E. Panteley).

9.5. Conferences, Invited conferences

- C. Lobry was invited at the “Centre Interfacultaire Bernoulli” de l’Ecole Polytechnique de Lausanne for a 3 weeks stay. He gave a lecture at the workshop “Moddélisation de systèmes biologiques complexes dans le contexte de la génomique”.
- A. Rapaport was invited at the Laboratoire d’Automatique of EPFL, Lausanne, Switzerland.
- A. Rapaport has presented a communication at the national conference “STIC et Environnement”, Calais.
- J. Harmand and A. Rapaport have spent two weeks in Chile (at CMM, Santiago and at UFSM, Valparaiso), and delivered two seminars.
- F. Campillo attented the ANR-MODECOL kick-off workshop (Rennes, January 16, 2009).

- F. Campillo organized the ANR-MODECOL meeting in Bordeaux and gave two talks on “MODECOL: using mathematical modeling to improve ecological services of prairial ecosystems” and “Markovian IBM for terrestrial plant dynamics” (Bordeaux, February 16-19, 2009).
- F. Campillo was invited to give a talk at the Probability seminar of the University of Pau and Pays de l’Adour on “Analysis of Markovian individul-based models” (Pau, June 9, 2009).
- F. Campillo gave a talk at the 3rd International Conference on Approximation Methods and Numerical Modeling in Environment and Natural Resources (MAMERN 2009) on “A spatially explicit Markovian individual-based model for terrestrial plant dynamics” (Pau, June 10, 2009).
- F. Campillo gave a scientific seminar at the INRIA Sophia Antipolis project committee on “The individual and the stochastic behind $\dot{x} = f(x)$ – Stochastic models for population dynamics” (December 10, 2009).
- F. Mazenc has given a talk on “Backstepping design for systems with a delay in the input” at the Polytechnic Institute of New York (August 2009).
- B. Haegeman was invited at the Theoretical Ecology laboratory of Dr. Joshua Weitz at the Georgia Institute of Technology, Atlanta for a two months stay. He gave a Mathematical Biology seminar entitled “Neutral community theory and speciation modes”.
- B. Haegeman gave an Ecology and Evolution seminar at the Université Pierre et Marie Curie, Paris 6 (May 29, 2009). The title was “Exploring ecological mechanisms with neutral community models”.

9.6. Miscellaneous

- F. Campillo, B. Haegeman, J. Harmand and A. Rapaport have participated in the INRA research school “Diversity of Ecosystems”, Alénya, March 2009.
- T. Sari animates the MERE seminar on modeling.
- In collaboration with I3M (Université Montpellier 2), F. Campillo and M. Joannides animate a working group on stochastic modeling for ecology and biology.

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