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*Project-Team MERE*

*Modélisation Et Ressources en Eau (Water  
Resource Modeling)*

*Sophia Antipolis - Méditerranée*

Theme : Observation, Modeling, and Control for Life Sciences

*Activity*  
*R* *eport*

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# 1. Team

## Research Scientists

Fabien Campillo [DR2 since October 2010 , INRIA Sophia-Antipolis, HdR]  
Bart Haegeman [CR1, INRIA Sophia-Antipolis]  
Jérôme Harmand [CR1, INRA Narbonne, HdR]  
Alain Rapaport [Team leader; DR2, INRA Montpellier, HdR]  
Tewfik Sari [Professor, on leave from Université de Mulhouse, “délégation”, HdR]

## Faculty Member

Claude Lobry [Professor emeritus, Université de Nice, HdR]

## External Collaborators

Marc Joannides [MdC, Université de Montpellier 2, part time]  
Terence Bayen [MdC, Université de Montpellier 2, part time]  
Frédéric Mirman [ITK company, part time]

## PhD Students

Boumediene Benyahia [COADVISE grant]  
Amine Charfi [COADVISE grant]  
Jose Fernandez [CONYCIT/INRIA and INRA grant]  
Ihab Haidar [MESR grant]  
Miled El Hajji [INRA grant until november 2010]  
Angelo Raheiririna [University of Fianarantsoa, Madagascar, LIRIMA grant]  
Radhouene Fekih-Salem [AVERROES grant]

## Post-Doctoral Fellows

Chloé Deygout [ANR DISCO grant]  
Ahlem Saddoud [Fondation Agropolis grant, until august 2010]  
Niloufar Abourashchi [MODECOL grant, february-June]

## Administrative Assistant

Sylvie Lelaidier [AI, part time]

## Others

Denis Dochain [Visitor, 1 month]  
Rivo Rakotozafy [Visitor, 1 month]  
Damien Juery [Student Université Montpellier 2, 3 monthes]  
Mathieu Lauze [Student, DUT Université Montpellier 2, 3 monthes]  
Gwendal Resnay [Student, 3 monthes]  
Daoud Youssef [Student Université Saint-Esprit Kaslik (Liban) , 6 monthes]

# 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 modeling,
- 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 (**T**reatment and **S**ustainable **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 modeling 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

F. Campillo was cited as a "most successful 2009 IMACS paper".

# 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 modeling 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 prediction 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 modeling. 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 such as 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 ecosystem. 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 modeling 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 modeling, simulation-based inference and decision

The mathematical modeling 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 MERE team-project mainly focuses on time-dependant systems. The state variables, the parameters and the observations can be finite, continuous, hybrid (continuous/discrete), graphical, time varying, pathwise, etc.

The first step in modeling 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 [56] [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 [57]. In the non-Bayesian approach, Monte Carlo techniques are used to explore likelihood functions [64]. They also gave rise to general algorithmics [58]. 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 [55].

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 modeling 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 natural as well as artificial biological systems, such as bioprocesses used for the treatment of wastewaters or systems like soils, are complex systems involving living entities. The understanding of these ecosystems - at all spatial and temporal levels - necessitates the study of (i) how different species of microorganisms interact, (ii) how microorganisms interact with their environment and (iii) how such a variety of interactions determines the behavior of the entire ecosystem which allows us to link ecosystem functioning with the biological system properties. Understanding complex ecosystems necessitates to model them in such a way their main characteristics are captured. For the biosystems considered within this project, 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 some variables (essentially physico-chemical species) 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 (but in this case, main variables are rather biomass or substrate densities). In any case, one may either study the behavior of an ecosystem at the individual level or at the level of a bioprocess as a whole, as for instance a large wastewater treatment plant. Within the framework of this project, we propose 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 softwares 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 wastewater treatment plants. In general, in order to cope with disturbances, modeling errors or parameter uncertainty, one has to take advantage of robust nonlinear control design techniques. These methods are based on central theories of modern nonlinear control analysis, such as disturbance attenuation or Lyapunov functions.

Wastewater treatment plants are often unstable as soon as bacteria growths exhibit some inhibition. Typically, under a constant feed rate, the washout 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 online measurement of all variable concentrations, which are generally not accessible (for technical or economical reasons). Most often, only few sensors are available.

A popular way to achieve stabilization of a control dynamical system under partial knowledge of the state consists (i) first in designing an "observer" or "software sensor" for the reconstruction of the unobserved variables, and (ii) in a second step, in coupling 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 startup of 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. The search for new configurations of processes as well as for innovative control actions (bioaugmentation for instance) is also an objective we follow.

## 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 functioning (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 (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 gene libraries, or metagenomic approaches), 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, with more or less the same width, in which some species can occasionally contribute several peaks, and with peak height only approximately proportional to 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 recover the complete community structure from such complex profiles, it is possible to recover specific aspects of the community structure. Our objective is to develop quantitative methods to extract this information from the profiles. We have shown that a specific index of genetic diversity can be extracted from a single fingerprinting profile. We have patented an accurate estimator for this diversity index. Several questions remain for the analysis of a sequence of fingerprinting profiles. We want to exploit correlations between successive profiles to extract more detailed information than separate profiles. We also try to couple the analysis of fingerprinting profiles with mathematical models describing the dynamics of microbial communities.

#### 4.4. Modeling 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 modeling 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 3.2). Hence, in this context, we are drawn toward a model-driven approach. We adopted the Markovian formalism presented in Section sec.markov. 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. VITELBIO

**Participants:** Jérôme Harmand, Alain Rapaport, Frédéric Mirman.

VITELBIO (VIRtual TELluric BIOreactors) is a simulation tool for studying networks of interconnected chemostats with the objective of mimic microbial activities in soil. The software is accessible on a server from any web navigator and has been developed with Flex for the user interface and calls Octave for the numerical integration, with the help of ITK compagny. An important effort has been made for obtaining a pleasant and easy interface appealing for microbiologists: the network can be drawn graphically on the screen and simulation results can be easily compared between (virtual) experiments, superposing trajectories curves.

Several known and new configurations have been already tested thanks to this tool (see Section 6.2.6 and 7.9).

## 6. New Results

### 6.1. Theoretical results

#### 6.1.1. *Minimal time control of continuous bioprocesses*

**Participants:** Jérôme Harmand, Alain Rapaport.

Minimal time control problems often occur in biotechnology when one has to fill tanks. Typically, the objective to be reached is to have the tank full with a prescribed value of substrate or product concentrations, the tank being filled with a high concentration of nutrient. In continuous bioprocesses, for which the volume is constant as in the chemostat models, the objective is rather to reach a desired steady state. In both case, one has to separate biomass from the purified liquid phase, that is not possible when the tank is a natural reservoir such as lakes or water tables.

We have proposed a new operation strategy that consists in treating with the help of a bioreactor aside. No bacteria is introduced in the main tank but water is pumped and treated by micro-organisms in a smaller tank, and treated water returns to the main tank after being separated from the biomass. There is no need of a separation operation for the main tank.

The minimal time control problem consists in controlling the flow rate for having the substrate concentration of the main tank below a given reference value as fast as possible.

Under the assumption that the volume of the bioreactor is much smaller compared to the volume of the main tank, we have characterized with the help of the Maximum Principle, the optimal feedback strategies for a general class of growth functions in the two following situations [13] :

- the concentration is assumed to be uniform in the main tank. We have shown that the optimal control is necessarily decreasing with time.
- the heterogeneity of the substrate concentration in the main tank is measured in two distinct points. We have shown that the two points optimal feedback is non monotonic and has to terminate with a constant flow.

#### 6.1.2. *Input/output map of interconnected chemostats*

**Participants:** Alain Rapaport, Ihab Haidar.

Patch or island models are popular in ecology, and are a convenient way to study the influence of a spatial structure of a geography on the distribution of the abundance of resources. Coupling such a structure with abiotic/biotic models and studying its input-output properties has been very rarely tackled in the literature. In biotechnology engineering, dead-zones models, that distinguish two sub-domains (a “living” and a “dead” one) are often used for approximating non perfectly mixed tanks. No more sophisticated representation, apart continuous space models (systems of partial differential equations), have been investigated.

We consider an hydric capacity and an nutrient flow that are fixed, and analyse the influence of different structures, of the same total hydric volume, on the output concentrations at steady-state. Three configurations are compared, under the assumption of a monotonic growth rate : perfectly-mixed, serial and parallel with diffusion rate. In each case, we show the uniqueness of a steady-state different to the wash-out equilibrium and its global asymptotic stability on the positive orthant. We prove the existence of a threshold on the input concentration of nutrient for which the benefits of the serial and parallel configurations over the perfectly-mixed one are reversed. In addition, we show that the dependency of the output concentrations on the diffusion rate can be non-monotonic, and give precise conditions for the diffusion effect to be advantageous [49]. The study encompasses the dead-zone models.

The possibly non-monotonic influence of the diffusion parameter on the output steady state is not intuitive, and leave further investigations open for understanding or taking benefit of this property for natural ecosystems (such as saturated soils or wetlands) as well as for bioprocesses (such as waste-water treatments). This result can be also of interest for reverse engineering when deciding which among serial or parallel configurations is better fit for the modeling of chemostat-like ecosystems, providing that one has an estimation of the hydric capacity of the system.

### 6.1.3. *Theory of competition for a substrate*

**Participants:** Claude Lobry, Tewfik Sari, Radhouene Fekih-Salem.

The paper [43] was written for an invited conference in june 2009 at the “Centre Interfacultaire Bernoulli, EPFL (Lausanne)” ; it appears now. See 2009 activity report for more details.

In the paper [29], we give a global asymptotic stability result for a mathematical model of competition between several species in a chemostat, by using a new Lyapunov function. The model includes both monotone and non-monotone response functions, distinct removal rates for the species and variable yields, depending on the concentration of substrate. We obtain, as corollaries of our result, three global stability theorems which were considered in the literature.

In the paper [30] we correct erroneous results published in the journal “Mathematical computer modeling”.

In the paper [37], we consider the mathematical model of two species microbial competition on a single food resource in a chemostat, when one takes into account species interactions between the two populations of micro-organisms and intraspecific interactions between individuals themselves, using strictly monotonic growth functions and distinct dilution rates.

### 6.1.4. *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, immigration and speciation events, attributing equivalent characteristics to all species. Although the absurd simplicity of these assumptions, remarkable agreement between neutral model predictions (e.g., the distribution of the abundance of the species present in the community) 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 modeling 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.

(1) Effect of speciation process

It has been argued that the neutral model predictions are rather insensitive to its assumptions. However, we have found that the details of the way new species appear in the community (i.e., the speciation process) do matter, and can drastically change the model predictions. In particular, we have studied the neutral community model with random fission speciation. This speciation model is quite different from the point mutation model usually considered in neutral community model, and is generally believed to be more realistic.

Using a technique from theoretical physics [15], we have obtained the stationary distribution of species abundances for the random fission model. We have compared our solution with the well-known stationary distribution of species abundances for the point mutation model on empirical data (tree communities in tropical forests) [12]. Surprisingly, we found that the point mutation model fits the data better than the random fission model, although the latter is believed to be more realistic.

(2) Spatial community structure

Several spatial extensions of the standard, spatially implicit, neutral community model have been proposed. The analysis of these spatial community models often relies on time-consuming simulations. We have proposed a neutral community model with spatial structure that can be studied analytically using (spatial and dynamical) correlation functions [31]. The model consists of a large number of small communities coupled to each other by migration flows, i.e., a meta-community model.

Our model describes microbial microplate experiments, as carried out at INRA-LBE. Microplates consists of a large number of small batch reactors, in each of which a microbial community grows on the available substrate available. Due to the small dimensions of these systems, many (identical or different) experimental conditions can be studied in parallel. This experimental system allows us to study, for example, the community dynamics as a function of the migration flows between the batch reactor, and compare experimental results with the predictions of our spatial neutral community model.

### (3) Niche-based community models

Neutral community models challenge more traditional, niche-based models in community ecology. Niche theory states that species can coexist only if they differ sufficiently in their characteristics (for example, their use of available substrates). Neutral theory assumes that all species have approximately equal characteristics. Hence, the two theories describe species coexistence in fundamentally different ways.

Nevertheless, we have proposed a mathematical model that combines essential features of niche-based and neutral community models [16]. It integrates species niches, described as Lotka-Volterra interactions, in the standard neutral community model. The model respects some kind of neutral symmetry, by assuming that all species pairs interact with equal strength. The analysis of this model indicates that the addition of species interactions has a limited effect on the neutral model predictions.

### (4) Entropy maximization

The success of the neutral model has been compared with 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 rather insensitive to the modeling 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.

We have been trying to setup applications of entropy maximization ideas to infer community structure characteristics based on a limited number of global, community-averaged properties. In particular, we have used MaxEnt to derive a series of spatial distributions for an ecological community using MaxEnt [14]. This suggests that these distributions contain limited information about ecological processes, and are mainly determined by a statistical averaging procedure. These results might be especially relevant for microbial communities, in which model complexity reduction is both necessary (the full complexity is impossible to deal with) and effective (due to averaging over many individuals).

## 6.1.5. Individual-based modeling

**Participants:** Fabien Campillo, Marc Joannides, Claude Lobry.

In terms of computational modeling of ecosystems, individual-based models (IBMs) are an interesting path to explore. We can outline two types of IBMs. On the one hand “detailed IBM” attempt to integrate in an ad-hoc way all the knowledge available about an ecosystem. On the other hand, “simplified IBM” are limited to one or several mechanisms to simplify the analysis. The former may be more realistic but are often difficult to analyze. Although the latter are too simplistic in realistic situations they lend themselves to the analysis and numerical analysis. We focus on the latter.

The IBMs offer an interdisciplinary language between biologists, biotechnologists, mathematicians, computer scientists, to develop models in the form of relatively simple rules. In the case of simplified IBMs it is possible to translate these rules in the form of a branching Markov process with values in a space of measures. Using scaling methods, the IBMs can be approximated by integro-differential equations; using model simplification methods IBMs can be reduced to stochastic or ordinary differential equations. The mathematical interpretation



of the IBMs and their analysis is relatively recent and still very few studies exist [Méléard]. The numerical analysis of these models is yet to be built. Under certain conditions, IBMs themselves can be simulated through adapted Monte Carlo procedures.

The MERE team-project develops two studies in the field of IBMs. The first is part of the ANR MODECOL on the modeling of clonal plant growth (see Section 7.5); the second, more recent, is part of the ANR DISCO on modeling of biofilms (see Section 7.4).

In both cases, we aim at developing the Monte Carlo simulation of the IBM as well as analyzing their links with integro-differential models.

Part of the thesis of Nabil Mabrouk (co-advised by G. Deffuant and C. Lobry, defended in december 2009) devoted to spatially explicit I.B.M. models of bacterial growth is published as [21].

In 2010 we have started to revisit the chemostat model in the spirit of I.B.M. models. Namely, in a paper in progress [50] we consider bacteria as a collection of cells which growth from a “size”  $l$  to a “size”  $2.l$  and then divide into two cells. On the other side concentration of the substrate is maintained, like in the classical model, as a continuous variable. We compare the predictions of this model with those of the classical continuous one. As expected, for large number of cells (more than  $10^4$ ), the predictions of the two models are the same. But, and this was not completely expected, when the number of cells decay is below  $10^4$  there is a very high stochasticity in the process and the continuous model, which still represents the average of different outcomes, has not much practical interest. We explain this phenomenon by the fact that “branching processes”, which are at the core of growth through division of cells, are, as it is well known, very irregular processes. Due to algorithmic complexity, in more realistic cases than “one species”-“one substrate”, it is not possible to simulate a bioreactor with a fully developed I.B.M. model. This is why we are looking for “stochastic approximations” of I.B.M. models (see 6.1.6).

#### 6.1.6. Stochastic modeling of the chemostat

**Participants:** Fabien Campillo, Marc Joannides, Claude Lobry, Damien Juery, Daoud Youssef.

This year we started to study stochastic models for population models like logistic growth [35] or the chemostat [45]. Starting from the well-known ordinary differential equation systems, we propose first a pure jump process model at the microscopic scale that leads to a stochastic differential equation at the intermediate scale and to an ordinary differential equation at the macroscopic level (fluid limit model). We also investigate the associated simulation algorithms. We aim at proposing alternate models that can be used in specific situations notably in extinction cases. Other population models, like the logistic models, have also been investigated according to the same approach.

## 6.2. Applications

### 6.2.1. Modeling and control of Anaerobic Membrane BioReactors (AMBR)

**Participants:** Jérôme Harmand, Boumediene Benyahia, Tewfik Sari.

In the papers [33] and [34], we consider the mathematical analysis of the so-called AM2 or AMOCO model developed by O. Bernard, Z. Hadj-Sadock, D. Dochain A. Genovesi and J.P. Steyer (2001). Depending on the model parameters, the steady states are analytically characterized and their stability is analyzed. Following this study, it is shown that the overloading tolerance, a parameter proposed by J. Hess and O. Bernard (2007) to on-line monitoring anaerobic processes, may be not adapted under certain operating conditions and even lead to bad operating decisions.

### 6.2.2. Cellobiose hydrolysis

**Participants:** Jérôme Harmand, Alain Rapaport, Tewfik Sari, Ahlem Saddoud.

In the paper [40], we study a mathematical model for an enzymatic reaction with both substrate and product inhibition in two interconnected Continuous Stirred Tank Reactors (ICSTRs) where one of them is a dead zone. A sufficient condition which guarantees the steady states multiplicity was achieved. The main purpose of this work is to estimate the kinetic and operating parameters which give, in experimental data, the steady states multiplicity and guarantees the presence of the best equilibrium that has the optimum biological performance in a non homogeneous reaction system.

### 6.2.3. *Modeling and control of cascade biosystems to mimick batch wine making processes*

**Participants:** Jérôme Harmand, Alain Rapaport, Jose Fernandez.

An experimental setup of four tanks connected in series has been designed by the research unit SPO (Montpellier) for studying four physiological stages of yeast as steady state. The manipulated variables are the flow rates  $Q_i$  of each tank with the constraint  $Q_i \geq Q_{i-1} \geq 0$ , and the objective is to reach simultaneously four set-points in the four tanks. We are studying two kinds of control strategies:

- a linearizing feedback law that drives exponentially the dynamics to the target. This is not the fastest strategy but it has good robustness properties. Nevertheless, the inputs constraint imposes to use saturation functions that provide satisfactory convergence on simulations but that is hard to prove mathematically.
- a minimal time feedback. Due to lack of local controllability imposed by the constraint on the inputs, the optimal synthesis is not smooth, with the presence of “barrier” singularities similar to the well-known Zermelo navigation problem.

Those feedback laws will be implemented and tested on real pilot plant at SPO lab in the scope of the European project CAFE.

### 6.2.4. *Modeling and simulating terrestrial plant ecological dynamics*

**Participant:** Fabien Campillo.

This study is part of the ANR Syscomm MODECOL that is done in collaboration particularly with the University of Rennes I, the University of La Rochelle and INRIA. This is the second year of the three years program. We propose a stochastic individual-based model for clonal plant dynamics in continuous time and space, focusing on the effects of the network structure of the plants on the reproductive strategy of ramets. This model is coupled with an explicit advection-diffusion dynamics for resources. We develop a partially exact simulation scheme of the model ; the capacity of the model to reproduce specific features of clonal plants, such as their efficiency to forage resources over the field, is numerically studied. Next, we propose a large population approximation of the model for phalanx-type populations, taking the form of an advection-diffusion PDE for population densities, where the influence of the local graph structure of the plant takes the form of a nonlinear dependence in the gradient of resources [46].

### 6.2.5. *Modeling and inferring agricultural dynamics*

**Participants:** Fabien Campillo, Angelo Raheiririna.

The International Laboratory LIRMA supports this work that is done in collaboration with the University of Fianarantsoa in Madagascar and with Dominique Hervé (IRD, Fianarantsoa, Madagascar). The aim is to study the dynamics of agricultural plots on the edge of primary forest. We propose a Markov chain model where the transition matrix is estimated both by maximum likelihood and Bayesian approaches. We also test if the Markov chain model is adapted to this problem.

### 6.2.6. *Modeling for microbial ecosystems in soils*

**Participants:** Ihab Haidar, Jérôme Harmand, Alain Rapaport.



The team studies simple representations of the spatial inhomogeneity for bioprocesses, in terms of networks of interconnected compartments. Each compartment is modeled as a perfectly mixed bioreactor. Simulation of such networks are performed with the software developed by the VITELBIO project. Comparisons of simple structures (cascade of bioreactors) with numerical simulators based on REV (Representative Elementary Volumes) have been performed. The objective is to understand the role of the topology of the network on the biological functions of the overall system. For the moment simple configurations with two to four nodes and one single species have been investigated.

### 6.2.7. *Optimisation in non perfectly mixed bioreactors*

**Participants:** Jérôme Harmand, Alain Rapaport.

The optimisation of series of bioreactors in terms of minimizing the total residence time have been already investigated in the literature. In such models, the space has a one dimensional representation. There is comparatively much less work on 2D or 3D space models. We consider different shapes of reactors of the same volume, and simulate with the help of multi-physics numerical software the coupling of the hydrodynamics laws in 3D or 2D (under cylindrical symmetry), solved numerically by the Navier-Stokes equations, with the system of differential equations of biotic/abiotic concentrations. We are studying the influence of the shape of the domain and possible obstacles on the output concentration at steady state.

## 7. Contracts and Grants with Industry

### 7.1. BioInh

**Participants:** Jérôme Harmand, Alain Rapaport, Ahlem Saddoud.

The project BioInh (Modeling 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 have been runned but have not been finished due the interruption of A. Saddoud postdoc for health reasons. The project has then been delayed for several months. Recently, a new applicant has been recruited and experiments should continue soon.

### 7.2. CAFE

**Participants:** Jérôme Harmand, Alain Rapaport.

The objective of the CAFE European 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:

- 1- 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;
- 2- to save and encode the information in a reliable and usable way, basically via physical/deterministic models;
- 3- 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 which constitutes the PhD thesis of Jose Fernandez.

### 7.3. DIMIMOS

**Participants:** Jérôme Harmand, Alain Rapaport.

This fundamental research project aims at better understanding of the 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, Chloé Deygout.

DISCO (Multi-scale modeling bioDIversity Structure COupling in biofilms) is a three years project funded by the ANR SYSCOMM since the end of 2009, that aims at developing and studying computational and mathematical models of biofilm dynamics, taking into account the biodiversity (distribution of bacteria species) and spatial structure.

In 2010, Chloé Deygout has been hired as a postdoctoral fellow. She is developing a double modeling approach of the formation of single species biofilms in tubular bioreactors. One approach is based on a IBM model with a large number of individuals, while the second one is a system of PDE at the macroscopic level. We aim at understanding the links between the characteristics of the random events (consumption, growth, death, movement) at individual level with the functional expressions of growth, detachment and attachment at the population level.

A new collaboration has been launched with the HBAN team at Cemagref Antony, within this project, about the modeling of cellulose degradation. Cellulose is typically available in small balls (but ten times larger than the average size of micro-organisms) that are first converted by enzymatic activity into carbon substrate that can then be assimilated by the micro-organisms. Some of the micro-organisms are attached to these balls, creating a particular aggregates structure.

### 7.5. MODECOL

**Participant:** Fabien Campillo.

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 prairie plant communities' dynamics in the context of water purifying from nitrate and pesticides. This year the INRIA team proposed a new model [45] its analysis and the development of a simulation software. The project-team was also involved in the organization of a workshop in Rennes.

### 7.6. RNSC – appel à idées

**Participants:** Jérôme Harmand, Alain Rapaport.

E-Micram is a project supported within the framework of the French RNSC (Réseau National des Systèmes Complexes). It aims at investigating whether the performance of a microbial ecosystem is related to its diversity or not. Regarding the prospective property of the project, until now, we have limited our research to a number simulations taking into account the results of the PhD thesis of Miled El Hajji.

### 7.7. VITELBIO

**Participants:** Ihab Haidar, Jérôme Harmand, Alain Rapaport, Frédéric Mirman.

The ARC VITELBIO (Virtual TELluric BIOreactors) gathers biologists, agronomist, micro-biologists, soil physicists and mathematicians about the modeling of heterogeneity in soil, and its role on microbiological functions. An important activity of the project has consisted in the development of a user friendly software for designing networks, simulating the dynamics and exploiting the results, with the help of ITK company.

A new interconnection configuration, denoted as “pocket” configuration, has been discovered to have interesting stability robustness properties for growth functions with inhibition. This configuration has yet to be understood in terms of soil faults.

## 7.8. International Initiatives

### 7.8.1. DYMECOS

**Participants:** Fabien Campillo, Jérôme Harmand, Claude Lobry, Alain Rapaport, Tewfik Sari, Terence Bayen.

DYMECOS is a associated team with Chile, mainly with CMM (Centro de Modelamiento Matematico), Univ. de Chile, Santiago, DIM (Departamento de Ingenieria Matematica), Universidad de Chile, Santiago and Departamento de Matematica, Universidad Tecnica Federico Santa Maria (UTFSM).

Two kinds of investigations have been conducted:

- minimal time control problems of fedbatch processes with several species, and optimal strategies for the bioremediation of natural water resources,
- stochastic modeling of the chemostat.

The First Franco-Chilean Workshop on Bioprocess Modeling has been co-organized with the Chilean partners in January at Valparaiso. This workshop has gathered mathematicians, process engineers and micro-biologists.

### 7.8.2. MOMARE

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

The MERE Team-Project is coordinator of the Stic-Amsud project MOMARE "Mathematical models of natural resources management" between INRIA, IMCA (Peru), DIM-CMM (Chile) and PLAMEDA (Argentina). This project has funded the travel of researchers from France to South America and from South America to France. In this context, the MERE Team-Project was visited by E. Ocana (IMCA), H. Ramirez-Cabrera (DIM-CMM), J. Fontbona (DIM-CMM). The project is structured it on two subthemes: "microbiology" (bioreactors, waste water treatment) and "harvesting" ("fishery" and "forestry", but also "mines"). This year was mainly devoted to regional meetings in South America, next week a global workshop will be organized.

### 7.8.3. 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 ending in 2012 includes 42 man months available for exchanging PhD and postdoc students within the next 48 months.

## 8. Dissemination

### 8.1. Animation of the scientific community

C. Lobry gave an interview in "La Recherche" concerning its activity for the development of computer sciences and mathematics in Africa [44]

## 8.2. Teaching

- F. Campillo, A. Rapaport and T. Sari have delivered a 20 hours doctoral module at University Montpellier II, entitled "Modeling for biology and ecology – mathematical and computational methods".
- F. Campillo, C. Lobry and A. Rapaport have given introductory lectures on mathematical modeling for 1st year students of SupAgro Montpellier.
- A. Rapaport has given two lectures on Modeling and numerical simulations at the "EcoSystèmeS" Master at University of Montpellier II.
- J. Harmand, C. Lobry, T. Sari delivered introductory lectures on mathematical modeling of bioprocesses at the Tlemcen school organized by TREASURE.

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