Activity Report 2011

Team MODEMIC

Modelling and Optimisation of the Dynamics of Ecosystems with MICro-organisms

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Team MODEMIC

Keywords: Models, Microbial Ecology, Control Theory, Population Modeling, Multiscale Models, Individual-based Models.

MODEMIC is a common INRA-INRIA team that aims at sharing skills of researchers of both Institutes for developing, analysing and simulating new models of microbial ecosystems as efficient tools to understand, explore, pilot and manage industrial and natural bioprocesses.

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2. Overall Objectives

2.1. Build, simulate and analyze new models of microbial ecosystems

We investigate different models of microbial ecosystems at different scales, that are related to various research questions for better understanding, predicting or piloting real plants.

Eight families of problems are covering our modelling activities:

1. study the mathematical properties (equilibriums, stability, limit cycles, bifurcation...) of macroscopic models that distinguish compartments of attached and free bacteria. We are looking for ecological conclusions in terms of coexistence of species.

2. study the mathematical properties of trajectories of a model that switches from a populational representation by differential equations to an individual-based model when the population falls below a given threshold. We expect from this study new insights on validity domains of macroscopic models and quantitative estimations of the variability about average trajectories.

3. build a framework for modelling the chemostat with stochastic processes at a macroscopic scale justified from hypotheses at the individual level. The classical "deterministic" chemostat is expected to be found as an average dynamics for large populations, but second order moments should provide relevant information about the variability about the deterministic approximation.

4. build and simulate IBMs (individual based models) of 1D biofilm and compare the spatial densities of biofilm and planktonic biomass with the numerical solutions of 1D PDE models.

   The output of this study is to propose and justify attachment/detachment terms in the PDE, that are crucial in the determination of the thickness of the biofilm, and that are usually chosen in an heuristic way.

5. compare detailed ecological models of a multi-species community at a fine scale with low-complexity models at a coarser scale, in the spirit of the neutral model. Within a stochastically varying environment (that is assumed to have different impacts on each species), the coarse model could describe in an effective way the interaction between species and environment as a stochastic variability. The goal is to interpret the parameters of the global model in terms of properties of the fine-scale model.

6. study chemostat-like models with multi-resources and nutrient recycling, within the objective of representing microbial activity in soil ecosystems. The goal is to understand the influence of the choice of hypotheses about the growth terms (dependency in terms of product or minimum functions of each resource) and the recycling terms (from the dead biomass or during the division process) on the qualitative behavior of the system and its performances at steady state.

7. investigate the properties of a network of interconnected chemostats and understand the role of the size of the nodes and the connectivity (with the help of the VITELBIO software, see Section 5.1).

8. couple numerical simulation of fluids dynamics in tanks with models of biotic/abiotic reactions. Then, we plan to compare the input/output behavior of these models with simple representations of networks of interconnected chemostats (see the previous point).

2.2. Validate hypotheses and identify models with experimental data

Among our current collaborations and projects (ANR DIMIMOS, ANR DISCO, ARC VITELBIO, Agropolis Foundation BioInh, RNSC E-MICRAM), we have identified five experimental devices that we consider relevant for back and forth exchanges between models and real-world observations for the coming years.

1. Molecular fingerprints. The LBE at Narbonne is a world leader for one of these techniques, the SSCP (Single Strand Conformation Polymorphism) that allows to estimate the biodiversity of a microbial ecosystem and serve as a comparison instrument over time or between ecosystems. A similar kind of signal from the proteins expressions is also obtained within the ANR DIMIMOS with UMR MSE (Dijon).

2. Continuous cultures in chemostats. The chemostat device is the typical investigating device in microbiology. Spatial structures can be mimicked and controlled using interconnected chemostats. Because of contamination risks, experimentation in chemostat requires an adequate expertise which the LBE holds. We plan to launch new such experiments with microbial populations of interest for specialists of soil ecosystems, in collaboration with UMR Eco & Sols (Montpellier) and UMR Bioemco (Grignon).

3. Taylor-Couette reactors (with LBE Narbonne). These bioreactors are specifically designed for the culture of biofilms on *coupons*, that can be removed from the system for static analyses of biodiversity (SSCP) and microscopy. Experiments are already scheduled within a task of the ANR DISCO.

4. Flow-cell bioreactors (with Cemagref Antony). It consists in small capillary tubular reactors continuously fed by a pump, under a microscope that has been designed for a continuous acquisition of images. We aim to compare biofilm models with the information provide by theses images.

5. Micro-plates cultures (with UMR MSE Dijon and LBE Narbonne). It contains a hundred of small wells in each of which a microbial community is grown in batch on the available substrate. Optical density measurements allow one to monitor simultaneously the biomass growth in the wells. These devices are convenient to study the effects of different initial composition of the community under the same environmental conditions. We believe that it is also well suited to test neutral-like community models

Each measurement technique requires its own data analysis (filters, statistical analysis, image analysis...) to provide information that are relevant for the models. On the basis of these experimental observations, qualitative and quantitative validations of the models will be performed. Observers and image correlations are one of the techniques we are using.

2.3. Propose new strategies to pilot and optimize microbial ecosystems

We study optimal design and feedback control laws within the framework of ongoing projects, and distinguish two kinds of contributions:

1. based on already known models of chemostat or fed-batch reactors, but with explicit spatial considerations, for

   – the biological treatment of natural water resources, one of the main objective of the associated team DYMECOS with Chile, in collaboration with B. Ivorra from MOMAT (Madrid) for the numerical computation of the pollutant spreading,

– the design of interconnected networks of chemostats, in the following of the former ARC VITELBIO and also in collaboration with the MOMAT for the comparison and identification with hydrodynamics models.

2. based on new models developed in the scope of projects:
   – the Euro-Mediterranean project TREASURE coordinated by the team, where membranes are at the heart of a new generation of bioreactors of smaller size and well suited for Southern countries where the temperature is not too low.
   – the ANR DISCO 2010-2013, for which one of the output is expected in terms of control of biofilm reactors.

We plan to contribute to the development of new decision making tools to design, control, observe and optimize current and future bioprocesses, for the preservation of natural (aquatic or telluric) resources, where modelling and numerical simulations are clearly expected, and for the biotechnology industry whose objectives are to improve efficiency of bioprocesses under constraints of sustainable development (energetic consumption, biogas production...)

The tools based on geometric and optimal control of nonlinear systems and possibly on viability theory should be enhanced by software developments. We also expect to contribute to the numerical determination of optimal feedback laws for a class of problems relevant for the mentioned applications.

2.4. Develop a strategy of software production

Although the software production is not the main objective of the team, we aim to assemble models within *virtual ecosystems* (with the objective that it can replace or guide real experiments) in the four coming years. Co-developments of simulation software will be required within INRIA or outside. Our working plan is in three steps:

1. In a first step, we shall develop a `Scilab` or `Matlab` toolbox within the team.
2. Simulations of IBM or PDE require significant efforts, in terms of computer implementation and numerical methods.

   The main problem in the implementation of IBM's is the size of the population, particularly for applications in microbiology where the size of populations of bacteria can be very large. In agent-based models (ABM), population sizes are smaller and each individual features sophisticated behavior, while in IBM, population sizes are usually larger but with limited individual activities. The population size impacts both the execution time and the memory size, but the main bottleneck is the execution time because of the communication between the individuals. The idea will be to propose, through an object-oriented approach, data structures that will limit this communication. From the hardware point of view, grid computing could lower execution time but only on a limited range. New techniques exploiting the architecture of graphics processing units (GPU), that are specifically adapted to IBM simulations, seems very promising. These activities will have to be developed in association with specialists for our most ambitious developments: MOMAT already cited but also possibly the EPI OASIS and researchers from the LIRMM.

3. For the design and development of user-friendly and graphical interfaces that need to be easily accessible by biologists and bioprocess engineers, we shall look for the help of service companies specialized in agronomy and biotechnology applications (such as ITK Company).

2.5. Highlights

- The Euro-Mediterranean "3+3" project TREASURE, conducted by the team, has been renewed for three years.

- Our study of interconnections of chemostats with and without diffusion has revealed configurations that can enhance the performances of degradation of microbial ecosystems. The characterization of thresholds on input nutrient concentration and the role of diffusion for such improvements over simpler or well-known configurations are new results. This approach is based on an implicit representation of spatial inhomogeneity in modelling natural soil ecosystems, and brings potential applications for the waste-water industry [19].

- This year the first models of population dynamics taking into account the demographic randomness have been proposed. The random terms in these models are not artificial superimposed on classical ordinary differential equation models but are derived from descriptions at microscopic scales with individual birth and death processes [12]. We also proposed some examples where this randomness, even at small intensity, can radically alters the qualitative behavior of the considered systems [40].

3. Scientific Foundations

3.1. Modelling and simulating microbial ecosystems

Microbial ecosystems naturally put into play phenomena at different scales, from the individual level at a microscopic scale to the population level at a macroscopic scale, with sometimes intermediate levels. The size of substrate molecules is a thousand time smaller than the size of microorganisms and usually diffuse much faster. The substrate consumption of one microorganism is negligible at the population level but the sum of the consumption of its neighbors can modify the local concentration of substrate, which itself modifies microorganism growth, acting as a *feedback loop*. For other variables that change slowly (pH, temperature...) cumulative effects create intermediate time scales, coupling individual and environment dynamics. The very large populations justify macroscopic modelling but for some ecosystems, spatial structures seen at intermediate scale need to be tackled. This is typically the case of biofilm ecosystems, for which the biofilm structure is responsible of characteristics of the overall ecosystem. Models that are purely individual-based or purely populational are rarely truly satisfactory to incorporate current knowledge on microbial ecosystems at various scales and to push ahead mathematical analysis or to derive operational rules.

3.1.1. *Macroscopic models*

The starting point is the knowledge of biologists that report a large number of mechanisms discovered or shown on laboratory experiments at a population level, such as competition for a growth-limiting substrate, predation interactions, obligate mutualism or communication between bacteria. If each *elementary* mechanism is today well understood and modelled at a macroscopic level, the consideration of several mechanisms together in a single model is still raising several questions of understanding and prediction. This is typically the case when there is more than one growth-limiting substrate in the chemostat model or when one couples species competition with a spatial structure (flocculation, niches...).

1. *Non-spatial models.*
   Ordinary differential equations (ODE) are the common way to describe the evolution of the size or concentration of species populations and their functional contribution in resource transformation (such as substrate degradation) in homogeneous or perfectly mixed compartments (or ecological niches). The well-known chemostat model used in microbiology for single strain:

$$\begin{aligned} \dot{s} &= -\tfrac{1}{y}\mu(s)b + D(s_{in} - s) \\ \dot{b} &= \mu(s)b - Db \end{aligned}$$

(where s and b stand respectively for the substrate and biomass concentrations), has to be extended to cope with the specificity of microbial ecosystems in the following directions.

– very large number (hundreds or thousands) of species. This leads to characterization of their distribution during the transients, that is a way to study the *functional redundancy* of ecosystems.

– environmental fluctuations (input flow rate, input concentration, temperature, pH...). This impacts the efficiency of a microbial ecosystem, when biological and environmental time scales are different. *Singular perturbations* is the technique we use to separate *slow* variables from *fast* ones, leading to approximations of the dynamics on *slow manifolds* to be determined and analyzed.

– interactions due to several limited resources and trophic chains. Most of the literature on the chemostat considers models with single limited resource, while some work studied purely essential or substitutable resources.

– several populations of bacteria (for each species) to describe the effects of certain spatial structures that are artificially created in bioreactors or naturally found in soils, like flocks, colonies or biofilms: the planktonic (or free) cells and the biofilm (or fixed) biomass (for telluric ecosystems, such a distinction is also relevant to represent the sticking/non sticking characteristics of soil). Considering simple models of aggregates (that are not spatialized) can provide a simplified model of the dynamics of the overall biomass.

– *active* and *dormant* bacteria. This distinction is motivated by the observations made on ecosystems of sparse resources such as arid soils.

2. *Spatial models.*
In the spirit of lattice differential equations, representations in terms of networks of (abstract) interconnected bioreactors propose an intermediate level between models of average biomass (a single ODE) and a continuous representation of space (PDE). A model of interconnected bioreactors is a way to *implicitly* take into account spatial heterogeneity, without requiring a precise knowledge of it. It is similar to the island models used in ecology but coupled with the dynamics of abiotic resources and hydrodynamics laws (transport, percolation, diffusion) governing the transfers between patches. This approach appears to be relevant for telluric ecosystems, for which pedologists report that microbial activities in soil are usually concentrated in *hot-spots* that could be seen as small bioreactors. Understanding the role of the topology of the interconnection network and how a spatial structure impacts the outputs is also relevant in biotechnology to improve the yield or stability of processes.

3.1.2. Microscopic models

In these models (birth and death processes, neutral models, individual-based models) the dynamic of the population is described in terms of discrete events: birth and death of individuals, or jumps in terms of biomass. These models can be gathered under the same framework that could be called *Markov stochastic processes with discrete events*. Most of the time they should be coupled with continuous components like the size of each individual or the dynamic of the resources (represented in terms of ODE or PDE).

The Markovian framework allows on the one hand sharp analyses and rescaling techniques; on the other hand it induces a simplification in the memory structure that is important in terms of simulation. Indeed, as the future state of the system depends from the past only through the present state, only the current state should be kept in memory for simulation.

We will consider three families of processes with discrete events, from simplest to most complex.

1. *Birth and death processes.*

These models are of first importance in small population size. They indeed allow investigation of near-to-extinction situations in a more realistic ways than the classical ODE models: they permit the computation, analytically but most of the time numerically, the distribution of extinction time and the probability of extinction. Efforts should be made to developed efficient Monte Carlo simulation procedures and approximation techniques for extinction probability and time distribution evaluation. In larger population sizes, they are advantageously approximated by diffusion models (see next section).

2. *The neutral models.*
   In *neutral* models sizes of different species evolve as birth and death processes with immigration: all individuals have the same characteristics and are not spatialized. Such hypotheses could be considered unrealistic from a purely biological perspective, but these models focus on some precise properties to be simulated and predicted (for instance the biodiversity).

   Comparing the prediction of species abundance of these models to real observations provides a way to justify or invalidate the neutral hypothesis. Extensions of the neutral model, that was originally introduced for forest ecology, have to be developed in order to better suit the framework of microbial ecology, such as the non constant size of the populations and spatialized variations.

3. *The individual based models.*
   IBM's appear to be well suited to describe colonies or biofilms: in addition to birth, death and movement events, one has to consider *aggregation* and *detachment* events. The mechanisms that lead to the emergence of spatial patterns of colonies, or the formation of biofilms, which adhere to surface via polymers generated by the bacteria under specific hydrodynamics conditions, are not well understood yet. Typically, one can consider that bacteria inside the aggregates are disadvantaged to access the nutrient.

IBM modelling is a convenient way to propose aggregation and detachment mechanisms at the individual level in terms of random events connected to the geometry of the neighborhood, and to compare generated images with microscopic observations (for instance the confocal microscopy).

One has to be aware that few methods are available to study systematically and rigorously the properties of IBM, contrary to models based on differential equations (ODE, PDE...).

3.1.3. Bridges between models

The "theory of a computational model", that combine two kinds of models (typically ODE and IBM) that are different representations of the same objects, relies on two steps: the "program making" and the "theoretical study", in the spirit of the *double modelling* approach (roughly speaking, it consists in grasping the complexity of a IBM by analyzing accurately the consequences of each hypothesis on the macroscopic behavior of the model, building an approximate model of its global dynamics). Two main tools can be considered.

1. *Change of scale.*
   For IBM models (neutral or Markovian), we consider mean field and moments approximation techniques that provide information at the macroscopic (i.e. populational) level, to be compared with macroscopic models. From a birth-and-death process describing the individual level, a renormalisation can provide a stochastic differential equation at a meso-scale. The *diffusion approximation* technique can be understood as a numerical acceleration technique where the number of births and deaths follows a normal law. These stochastic models at meso-scale can provide additional information compared to deterministic models at a macro-scale, such as parameter identifiability or finite time extinction. The price to pay is to give much more conceptual and numerical efforts, that become less relevant for very large populations.
   For PDE models on spatial domains described with regular patterns (such as models of biofilm), the homogenization technique allows to obtain simpler PDE with constant parameters.

2. *The multi-scale modelling.*

The spatial heterogeneity in microbial ecosystems require to consider simultaneously several scales:

- a *physical* scale. In batch processes, nutrient diffusion can be modelled by adapting the heat equation with Dirichlet boundary conditions. In continuous reactors, a convection-diffusion equation with Neumann boundary conditions is considered instead, the speed vector field being provided by the equations of fluid mechanics. The spatial scale used for the discretization is given by diffusion and flow parameters.

- a *biological* scale, given by the size and mobility of bacteria. Usually, this scale is larger than the physical one (at least in the liquid phase).

- an *aggregation* scale of colonies or biofilms, even larger, that provides the spatial patterns.

Theoretically, it is always possible to describe all the processes at the smaller common scale and then use particle methods for a global representation, but this leads to extremely long computation times. The challenge is to manage these overlapping scales together and guarantee the stability of the numerical schemes. This is the goal of the *multi-scale* approaches. For microbial ecosystems, it consists in

1. proposing new representations of the various scales of aggregation of bacteria in a model, taking into account the attachment-detachment processes determined by the local hydrodynamics conditions. Here, discussions with specialists of fluid mechanics are required.

2. coupling diversity models (e.g. models based on the neutral assumption) with spatial models (that reproduce the patterns observed on images of microscopy) to better understand the link biodiversity/structure.

3. introducing new *control* variables, considered as independent variables, each of them describing a proper scale. For this purpose, we investigate different techniques available to determine such variables: *mean-field* approximation, *singular perturbations*, *unification by limiting layers* or

4. *renormalising*, that aims at detecting invariants among models of different scales.

3.2. Interpreting and analyzing experimental observations

The validation of microbial models on data is rarely a straightforward task, because observations are most of the time not directly related to the variables of the models. Techniques such as abundance spectrum provided by molecular biology or confocal imagery are relatively recent in the field of microbial ecosystems. The signals provided by theses devices leave many research questions open in terms of data interpretation and experiments design. One can distinguish three kinds of key information that are needed at the basis of model assumptions:

- structure of the communities (i.e. who is present?),

- nature of interactions between species (competition, mutualism, syntrophism...),

- spatial structure of the ecosystems.

3.2.1. Assessment of community structures

Ecosystems biodiversity can be observed at different levels, depending on the kind of observations. One usually distinguish

1. *The taxonomic diversity.* Several techniques developed by molecular biologists can gather information on the genetic structure of communities:

   - *sequencing of a given gene in the community.* The RNA 16S gene is often chosen to identify bacteria or Archeae.

   - *molecular fingerprints.* Some regions in the sequence of the RNA 16S gene encode faithfully the taxa species and can be amplified by PCR techniques.

   - *the sequencing of the overall genetic material of a community* (meta-genomic)

All these techniques bring new problems of data interpretation to estimate in a robust manner the properties of communities. The signals are combinations of contributions of abundances from each taxon. For an ecosystem with a limited diversity, composed of known species, the signal allows to determine with no ambiguity the abundances. In natural ecosystems, the signal is more complex and it is hopeless to determine uniquely the taxa distribution.

2. *The functional diversity.* It is usually observed at a larger scale, measuring the performances of the overall ecosystem to convert organic matter. The taxonomic diversity does not usually provide such information (it is possible to study *functional genes* but this is much more difficult than studying the 16S one).

   A convenient way to study the functional performance of microbial community dynamics is to grow the same microbial community on different substrate compositions, and monitor its performance on these different substrates. Neutral community models provide a reference for what would happen if no functional differences are present in the community. The deviation of experimental observations from neutral model predictions can be considered as a measure of functional diversity.

Understanding the links between taxonomic and functional diversity is currently a tremendous research question in biology about genotype/phenotype links, that one can also find in the specific context of microbial ecosystems.

3.2.2. Characterization of the interactions

The role of biodiversity and its preservation in ecosystems are research questions currently largely open in ecology. The nature and number of interactions between bacterial populations are poorly known, and are most probably a key to understand biodiversity. In the classical chemostat model, inter-specific interactions are rarely considered. In theoretical ecology, interaction information is typically encoded in an *interaction matrix*, but the coupling with common abiotic resources and the stoichiometry is rarely considered in the models.

The information provided by confocal microscopy is also a way to estimate the distance of interactions between microorganisms and substrates. This knowledge is rarely documented although it is crucial for the construction of IBM.

3.2.3. Observation of spatial structures

Schematically, one can distinguish two origins of spatialization:

1. due the physics of the environment. In bioprocesses, this happens typically for large tank size (inducing *dead zones*) or sludge accumulation making the suspension closer from a porous medium than a liquid one. Numerical experimentation can be driven, coupling a solver of the equations of the fluid mechanics with microbiology equations. Then, the spatial distribution of the biomass can be observed and used to calibrate simpler models. Typically, a dead zone is modelled as a diffusive interconnection between two perfect (abstract) tanks.

   But the biotechnology industry aims at considering more sophisticated devices than simple tanks. For instance, the fluidized bed technique consists in creating a counter-current with oxygen bubbles for preventing the biomass to leave the rector. In more complex systems, such as soil ecosystems, it is difficult to obtain faithful simulations because the spatial structure is rarely known with accuracy. Nevertheless, local observations at the level of pores can be achieved, providing information for the construction of models.

2. due to the formation of aggregates (flocks, biofilms...) or biomass wall attachment. Patterns (from ten to a hundred micro-meters) can be observed with confocal microscopy.

   Spatial distribution of bacteria, shape of patterns and composition of the aggregates help express hypotheses on individual behaviors. But quantification and variability of images provided by confocal microscopy are difficult. An open question is to determine the relevant morphological indicators that characterize aggregation and the formation of biofilms.

3.3. Identifying, controlling and optimizing bioprocesses

The dynamics of the microbial models possess specificities that do not allow the application of the popular methods of the theory of automatic control, such as linear control, feedback linearization or canonical forms.

- positivity constraints. State variables, as well as control inputs, have to stay non-negative (input flow pump cannot be reversed because of contamination issues).
- non-linearity. Several models have non-controllable or non-observable linearizations when inhibition effects are present (i.e. change of monotonicity in the growth curves).
- model and measurement uncertainties. In biology, it is rarely relevant to consider model uncertainties as additive Gaussian or finite energy signals.

3.3.1. *Software sensors and identification*

Sensors in biology are often poor and do not provide the measurements of all the state variables of the models: substrate, strain and product concentrations. In addition, measurements are often spoilt by errors. For instance optical density measurements give an indirect measure of the biomass, influenced by abiotic factors that share the same medium.

Analytical techniques are well suited to ODE models of small dimension, such as:

- guaranteed set-membership observers, when the system is non observable or in presence of unknown inputs,
- (non-linear) changes of coordinates, when the system is observable but not in a canonical form for the construction of observers with exponential convergence.

Software sensors can be also derived with the help of simulation based approaches like particle filtering techniques. This method is suited to diffusion models that approximate birth and death processes. They will allow us to investigate the different sources of randomness: demography, environment, but mainly imprecision of the sensors.

Similarly, identification techniques for constant parameters are based on sensor models as well as demography and environmental randomness models. In this case, Bayesian and non-Bayesian statistical techniques can be used.

3.3.2. *Bioprocess stabilization*

In bioprocesses, the most efficient bacterial species at steady state are often inhibited by too large concentrations of substrates (this corresponds to assuming that the growth function $S \mapsto \mu(S)$ in the classical chemostat model is non-monotonic). This implies that the washout equilibrium (i.e. disappearance of the biomass) can be attractive, making the bioprocess bi-stable.

A common way to globally stabilize the dynamics toward the efficient equilibrium is to manipulate the dilution rate D. But a diminution of the input flow rate for the stabilization requires to have enough room for an upstream storage, which is an expensive solution especially for developing countries that need to be equipped with new installations.

Alternative ways are proposed to stabilize bioprocesses without restricting the input flow rate:

- either by *physical means*, in terms of recirculation and bypass loops, or membranes as a selective way to keep bacteria and their aggregates inside the tank and improve its efficiency.
- either by *biological means*. The *biological control* consists in adding a small quantity another species with particular growth characteristics, that will help the other species to win the competition in the end.

3.3.3. Optimal control of bioreactors

The filling stage of bioreactors, or "fed-batch", is often time consuming because the quantity of initial biomass is small and consequently the population growth is slow. The minimal time is a typical criterion for designing a filling strategy, but the optimal feedback synthesis is non trivial and may present singular arcs when the growth function is non-monotonic.

Recent progress have been made in the consideration of

- multi-species in sequential reactors (having more than one strain makes significantly more difficult to analyze singular arcs because of the higher dimensions of the state space, and there is little literature on the subject),

- energy consumption of flow pumps and the value of byproducts of the biological reactions such as biogas in the criterion (instead of minimal time or as penalties). Recent concerns about sustainable development encourage engineers to look for compromises between those objectives under constraints on output concentrations.

3.3.4. Plant design and optimization

We distinguish two kind of setups:

1. *The industrial setup.* A research question, largely open today, is to identify networks of interconnections of bioreactors that are the most relevant for industrial applications in terms of the following objectives:

   – reasonably simple configurations (i.e. with a limited number of tanks and connections),

   – significant improvement of the residence time at steady state over single or simpler configurations, or shapes of the reservoirs such that the total volume required for a given desired conversion factor at steady state is reduced.

2. *The bioremediation setup.* Typically, the concentration of pollutant in a natural reservoir is solution of a transport-diffusion PDE, but the optimal control of the transport term is almost not studied in the literature.

   An approach consists in finding satisfactory approximations of the solutions of transport-diffusion-reaction PDE (for which the Eulerian speed of the fluid is determined by the Navier & Stokes equation), in terms of a network of ODEs, that makes effective the application of the Pontryagin Maximum Principe.

4. Application Domains

4.1. Preservation of water resources

The biological decontamination of wastewater is our main application domain, in the continuation of the long collaboration with the INRA research laboratory LBE. We target applications from the decontamination industry, held by large groups as well as small companies specialized in specific pollutants (for instance in fish farming). We aim also to study connected application domains for

- the aquatic ecology where microorganisms play an important role in the quality of natural water resources,

- the re-use of water in arid climates for countries of North of Africa, within the euro-Mediterranean project TREASURE.

4.2. Microbial ecology of soil

This application domain is more recent for the team members. We target

- the research questions raised by agronomists, about the better understanding of the interactions and the biodiversity of microbial communities in soils, with the help of models and numerical simulations,

- the role of spatial structures on the functions or *ecological services* of microbial ecosystems, notably the soil fertility and the carbon sequestration.

4.3. Control of fermentation processes

Very closely to our studies about wastewater bioreactors and chemostat models, we target applications in fermentation processes:

- either for agro-food products. A typical application is the control of cascade fermenters in the study of wine fermentation with UMR SPO (Montpellier), within the European project CAFE.

- either for the green chemistry. A typical application is the consideration of spatialization in enzymatic models of production of agro-polymers with UMR IATE (Montpellier), within the BioInh project financed by Agropolis Foundation.

4.4. Animal digestive ecosystem

Ruminants absorb plant cells, mainly constituted by cellulose, from which the microbial population of their digestive system extracts carbon and energy to provide proteins and energetic molecules. This bio-conversion produces also important quantities of methane, a gas responsible of part of the greenhouse effect (the billion of cows on earth reject 20% of the methane linked to human activities). INRA researchers have shown that this methane production could be reduced by 30% by changing the proportion of fat acids in the their food, that also implies that the composition of their microbial ecosystem is modified.

This application domain of the microbial ecology is at an early stage. URH team (Clermont) has developed an artificial rumen that is close to a chemostat, for testing different kind of nutrition diets. Preliminaries contacts have been taken, and a modelling demand has been clearly formulated. This theme falls into the research priorities for the environment preservation.

5. Software

5.1. VITELBIO

Participants: Jérôme Harmand, Alain Rapaport.

VITELBIO (VIrtual TELluric BIOreactors) is a simulation tool for studying networks of interconnected chemostats with the objective of mimicking microbial activities in soil. The software, developed with the help of ITK Company, is accessible on a server from any web navigator and make use of Flex for the user interface and Octave for the numerical integration. An important effort has been made for obtaining a pleasant and easy interface that is 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.

This software is used by several researchers, from LBE (INRA Narbonne), UMR Eco & Sols (Montpellier), UREP (INRA Theix), Biomeco (Paris-Grignon), UMR EGC (Paris-Grignon).... and also as a teaching support. See the web page http://sites.google.com/site/vitelbio/

6. New Results

6.1. Theoretical results

6.1.1. Theory of competition for one limited resource

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

In the paper [24], 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.

In the paper [14], 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 microorganisms and intraspecific interactions between individuals themselves, using strictly monotonic growth functions and distinct dilution rates.

6.1.2. Study of input/output maps 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 analyze the influence of different structures, having 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 washout equilibrium and its global asymptotic stability in 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 [19], [33]. 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 leaves 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 wastewater treatments). This result can be also of interest for reverse engineering when deciding which among serial or parallel configurations is a better fit for the modelling of chemostat-like ecosystems, providing that one has an estimation of the hydric capacity of the system.

This work is part of the material thesis of I. Haidar [11].

6.1.3. Aggregation models in the chemostat

Participants: Claude Lobry, Alain Rapaport, Jérôme Harmand, Tewfik Sari, Radhouene Fekih-Salem.

Bacteria aggregation often occurs in bioprocesses, creating flocks or biofilms (the latter being attached to the tank walls). At a macroscopic level with large populations of aggregated and non-aggregated individuals, a simple way of modelling this phenomenon in the chemostat is to distinguish explicitly two populations: planktonic or free bacteria and attached ones. The main differences between flocks and biofilms rely in the attachment/detachment terms and the effective dilution rate (assumed to be zero or very small for biofilms). Typically, the specific growth rate of free bacteria is expected to be larger than the attached one (that have in average a restricted access to nutrient and use part of their energy to glue together).

Based on former works of the team and the main assumption that attachment and detachment dynamics are much faster than the biological one, we have shown that a significant difference between the specific dilution rates of the free and attached populations can surprisingly lead to bi-stability, even for a single species and monotonic growth rates [30], [42], [43].

A work in progress addresses the case of two species, one of them having a non-monotonic growth rate (due to substrate inhibition) and the ability to form flocks. Without flock, the Competitive Exclusion Principle extended by G. Wolkowicz and her co-authors [47] shows the possibility to have one of the two species winning the competition depending on their initial repartition. Here, the presence of flocks may lead on the contrary to a single winner.

6.1.4. *Neutral community models for microbial ecology*
Participant: Bart Haegeman.

Hubbell's neutral model [50] describes the dynamics of an ecological community in terms of random birth, death, immigration and speciation events, attributing equivalent characteristics to all species. Despite 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 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.

(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, 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) [13]. 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) Comparison with niche 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.

We have tried to narrow the gap between the two theories. We have proposed a mathematical model that combines essential features of niche-based and neutral community models [17]. It integrates species niches, described as Lotka-Volterra interactions, in the standard neutral community model. The analysis of this model indicates that the addition of species interactions has a limited effect on the species abundance distribution. We have further clarified this result using a slightly different model that also combines niche and neutral features [16]. For the latter model we have proved that the niche structure does not affect at all the species abundance distribution.

6.1.5. *Quantifying genetic diversity of bacteria*
Participant: Bart Haegeman.

With the wide availability of DNA sequencing, microbiologists are now able to rapidly sequence entire bacterial genomes. Comparison of these genomes has revealed a large genetic diversity within bacterial species. For example, one genome of the bacteria *E. coli* has about 4000 different genes, but a set of 10 genomes of *E. coli* has typically over 10000 different genes. Some of these genes are shared by all or almost all of the genomes, but many other genes are only present in one or a few of the genomes. This observation has important implications for the definition of bacterial species and for the description of the functional characteristics of bacteria.

We have been dealing with the problem of how to quantify this observed genetic diversity. Microbiologists have introduced notions like the pan genome of a bacterial species (that is, the set of genes that are present in at least one of the organisms from the species) and the core genome of a bacterial species (that is, the set of genes that are present in every organisms from the species). However, we have argued that both the pan and core genome are difficult to estimate, and should not be used for quantitative purposes [21]. Instead, we have proposed a measure of genetic diversity that has much better estimation properties. It is based on the average number of genes shared by a pair of genomes when sequencing two randomly sampled organisms from the species under consideration. We have applied our estimator on six bacterial species (about 100 sequenced genomes in total). Software for our robust estimation procedure of genetic diversity is freely available, see http://ecotheory.biology.gatech.edu/downloads/genomic-fluidity-scripts.

6.1.6. *Individual-based modelling*

Participants: Fabien Campillo, Chloé Deygout, Coralie Fritsch, Marc Joannides, Claude Lobry.

In terms of computational modelling 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, and 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 [48]. 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 MODEMIC project-team develops three studies in the field of IBMs. The first is part of the ANR MODECOL on the modelling of clonal plant growth (see Section 7.5); the second is part of the ANR DISCO on modelling of biofilms (see Section 7.4), the last one is a starting thesis.

In all cases, we aim at developing the Monte Carlo simulation of the IBM as well as analyzing their links with integro-differential models. We also seek to make connections with non-IBM models proposed in Section 6.1.8.

In October 2011, Coralie Fritsch started a thesis at the École Doctorale I2E of the University of Montpellier 2, under the supervision of Fabien Campillo, Jérôme Harmand and Marc Joannides. This thesis is supported by a grant of the MESR and a grant of INRA from the MEM Meta-program (Méta-omiques des écosystèmes microbiens). The thesis aims at developing and analyzing individual-based microbial ecosystems models that capture both the spatial, biodiversity and function of these ecosystems. The thesis received the Agreenium label in December.

6.1.7. *Hybrid modelling of biofilms in plug-flow reactors*

Participants: Fabien Campillo, Chloé Deygout, Annick Lesne, Alain Rapaport.

Within the DISCO project of the SYSCOMM program founded by the ANR, we have proposed a multi-scaled modelling that combines three scales: a microscopic one for the individual bacteria, a mesoscopic or "coarse-grained" one that homogenises at an intermediate scale the quantities relevant to the attachment/detachment process, and a macroscopic one in terms of substrate concentration (see the Section 7.4).

Such an "hybrid" approach allows for modelling and understanding in plug-flow reactors [41] the interplay between

- the formation of the biofilm at a microscopic scale, that starts from a small number of bacteria (thus a stochastic individual based description),
- the limitation of the biofilm, due the carrying capacity of the wall attachment, at a mesoscopic scale,
- the consumption of nutrient along the flow at a macroscopic level, as a solution of a coupled transport-reaction partial differential equation.

The numerical computation of such a model requires a software architecture that allows the simultaneous simulation of stochastic events at the bacteria scale and the continuous evolution (in space an time) of the substrate density.

Experiments on real tubular plug-flow reactors are currently driven at Cemagref HBAN with the perspective of comparison with numerical simulations. After spending one year at Montpellier for deriving and simulating the theoretical model, our post-doctoral fellow C. Deygout is presently participating to the real experiments at Cemagref Antony.

The multi-species case with different bacteria specialized in different environments (poor or rich in nutrient) is a work in progress.

6.1.8. *Stochastic modelling for biotechnology*

Participants: Fabien Campillo, Marc Joannides, Claude Lobry.

This year we continue to study stochastic models for the chemostat [12], [39], [27]. 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). After developing the model, we establish the Fokker-Planck partial differential equation for the diffusion model. This PDE integrates a specific washing-out term. We proposed an ad hoc numerical integration scheme for the simulation of this PDE [39].

In [40], we consider a stochastic version of the basic predator-prey differential equation model. The model, which contains a parameter ω which represents the number of individuals for one unit of prey – if x denotes the quantity of prey in the differential equation model $x = 1$ means that there are ω individuals in the discontinuous one – is derived from the classical birth and death process. It is shown by the mean of simulations and explained by a mathematical analysis based on results in singular perturbation theory (the so called theory of Canards) that qualitative properties of the model like persistence or extinction are dramatically sensitive to ω. For instance, in our example, if $\omega = 10^7$ we have extinction and if $\omega = 10^8$ we have persistence. This means that we must be very cautious when we use continuous variables in place of jump processes in dynamic population modelling even when we use stochastic differential equations in place of deterministic ones.

6.1.9. *Minimal time control of batch bioprocesses*

Participants: Denis Dochain, 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.

When a single reaction occurs, the optimal solution is already known and has been rigorously proved by. J. Moreno in 1999 [51] using the Green's theorem: it consists in a "bang-bang" strategy (fill as fast as possible or do not fill) and possibly a singular arc when the growth function presents an inhibition (i.e. a maximum growth for a precise concentration of nutrient). When impulse controls in addition to regular control are allowed, an extension of this result has been recently proposed with a different technique that do not use the Green's theorem [4]. This technique has also allowed to solve partially the problems when several species compete for the degradation of the substrate, but when all of them have a monotonic growth.

In the presence of complex non monotonic kinetics, typically characterized by the combination of two non-monotonic growth functions, aimed at emphasizing the presence of two parallel metabolic pathways to transform the limiting substrate into the biomass, the candidate singular arcs are multiple and determining which singular arc is eventually optimal is clearly a crucial issue. The local optimality conditions based on the Pontryagin Maximum Principle allow to characterize the geometric structure of the extremal trajectories, in which there may be singular arcs, but these necessary conditions are not always sufficient for determining which extremals are (globally) optimal. Then one has to compute the cost of each extremal or use global optimization methods such as dynamic programming or Hamilton-Jacobi- Bellman equation. The extremals are traditionally determined numerically by considering shooting methods, but for bang-bang control, it is well known that one may face numerical troubles because the shooting function is in general not smooth. For this problem, we have used an approximation technique first proposed and studied by C. Lobry and his students [53] and later by C. Silva and E. Trélat [52], that consist in adding an artificial control. In [22], we have proposed a new proof of convergence based on differential inclusions arguments that allows to relax the assumption of the uniqueness of the optimal solution for the convergence of the optimal paths of [52]. Then we have shown how to apply numerically this approximation procedure for analyzing the field of extremals on the whole state space. This technique appears to be quite effective for the practical determination of optimal synthesis in the planar case even in presence of multiple singular arcs.

6.1.10. *Optimal control of continuous bioprocesses*

Participants: Jérôme Harmand, Alain Rapaport, José Fernandez, Walid Bouhafs, Amel Ghouali.

In continuous bioprocesses, a usual objective is to stabilize the output of the bioreactors about a desired steady state (in wastewater industry, this value is typically chosen under the norm of authorized discharge). It happens more and more frequently that transient trajectories are expected also to maximize a product of interest.

We have begun to study the maximization of the gaseous production of methane in anaerobic processes over a given period of time on specific problems. For the moment we have proved that the optimal trajectory consists in approaching a unique singular arc as fast as possible when only one limiting substrate has to be converted, but the problem is still open when involving several substrates. These works are part of the PhD work of A. Ghouali and W. Bouhafs.

Reference points in batch processes can be mimicked by a series of continuously stirred bioreactors in series at steady state (see applications 6.2.2 and 7.2). We study the minimal time problem to drive the nutrients concentrations of a cascade of chemostats. The control variable is the dilution rates of each tank, under the constraint that each dilution rate is bounded by the one of the previous tank, that makes the system not locally controllable. For the particular case of two tanks with total mass at steady state, the planar feedback synthesis has been found but the problem is still under investigation for the general case.

6.1.11. *Minimal time bioremediation of natural resources*

Participants: Jérôme Harmand, Alain Rapaport, Antoine Rousseau.

In biological wastewater treatment (batch or continuous bioprocesses), one has always to separate biomass from the purified liquid phase at the output of the tanks, that is not possible when tanks are rather natural reservoirs 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 are introduced in the reservoir but water is pumped and treated by microorganisms in a smaller tank, and treated water returns to the reservoir after being separated from the biomass. Consequently, there is no need of a separation operation for the reservoir.

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

Last year, we have determined analytical expressions of optimal feedback strategies for a general class of growth functions under the assumptions that the volume of the bioreactor is much smaller than the reservoir one, and that the spatial repartition of the concentration of the pollutant in the reservoir can be modelled by simple spatial representations: either perfectly mixed or discrete one directional gradient [44], [15]. This year, we have studied more realistic spatial motifs:

- dead-zones: we have shown that the optimal synthesis is identical to the perfectly mixed case, even though the time to reach the target is larger [31],

- two parallel zones, allowing to control the repartition of the flow rate between the two zones. Without diffusion between the zones, the optimal solution is almost straightforward and under investigation in presence of lateral diffusion.

This work is mainly achieved in cooperation with Chilean researchers and PhD students within the associated team DYMECOS.

6.2. Applications

6.2.1. *Modelling and control of Anaerobic Digestion processes*

Participants: Amine Charfi, Radhouene Fekih-Salem, Jérôme Harmand, Boumediene Benyahia, Tewfik Sari.

We consider the AM2 or AMOCO model developed in [46] and extend both the model in itself and its analysis to the following cases:

- Depending on the AM2 model parameters, the steady states were analytically characterized and their stability were analyzed. Following this study, it was shown that the overloading tolerance, a parameter proposed in [49] to on-line monitoring anaerobic processes, may be not adapted under certain operating conditions and even lead to bad operating decisions.

- Within the framework of the PhD theses of Amine Charfi and Boumediene Benyahia, we have included the fouling dynamics of membranes into the AM2 and we have analyzed the resulting model (called the AM2b).

- We actually work towards two directions: (i) we are extending these results in including into the AM2 an additional process, *i. e.* the hydrolysis step in order to study bioprocesses treating solid waste (the resulting model being called the AM3); (ii) we try to find links between complex models such as the ADM1 model and simple models such as the AM2b or the AM3.

6.2.2. *Modelling and control of cascade biosystems to mimic batch wine making processes*

Participants: Jérôme Harmand, Alain Rapaport, José 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 is has good robustness properties. Nevertheless, the inputs constraint imposes to use saturation functions that provide satisfactory convergence in 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 "barriers" (see Section 6.1.10).

Those feedback laws will be implemented and tested on real pilot plant at SPO lab in the scope of the European project CAFE described in Section 7.2.

6.2.3. *Modelling and simulating terrestrial plant ecological dynamics*

Participants: Fabien Campillo, Ihab Haidar.

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. This year we improved the simulation code that was proposed last year and made three communications in international conferences [26] [36] [35].

6.2.4. *Modelling and inferring agricultural dynamics*

Participants: Fabien Campillo, Angelo Raherinirina.

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. In [38] 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. In an ongoing work we develop semi-Markov models for an extended data set.

6.2.5. *Modelling and simulating 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 modelled as a perfectly mixed bioreactor. Simulation of such networks is performed with the software developed by the VITELBIO project (see 5.1). 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.

In addition, we study in simulation how software implementations of transport reactions models such as MIN3P, can mimic such simple configurations. Transport reactions models are often used in the community of soil functioning modelling by simulation. Here we compare their numerical computation with the exact solutions that can be approximated with a a good accuracy using classical o.d.e. solvers. We found that one has to be careful when the trajectories are close to a non-hyperbolic equilibrium [45], [18].

6.2.6. *Numerical optimisation in non perfectly mixed tanks*

Participants: Jérôme Harmand, Alain Rapaport, Antoine Rousseau.

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 [34].

We are studying the influence of the shape of the domain and possible obstacles on the output concentration at steady state.

With A. Rousseau (EPI MOISE, INRIA Rhône-Alpes) we study with simulation of 2D Navier-Stokes equations the benefits of having several pumping points and how to control the pumps speed to minimize the treatment duration for the bioremediation of natural reservoirs presented in Section 6.1.11. We evaluate the feedback strategies that are derived to be optimal for simple models of o.d.e. in the more realistic framework of hydrodynamics simulation.

6.2.7. *Individual-based models for the bacterial degradation of the cellulose*

Participants: Fabien Campillo, Chloé Deygout, Marc Joannides.

We propose an individual-based model for the degradation of one cellulose bead (dozens of micrometers in diameter) by cellulolytic bacteria. Our aim is to determine the macroscopic degradation behavior. The initial stages of the degradation process may involve a very limited number of bacteria that cannot be properly modelled by classical models based on deterministic equations. In the present work we only consider a two-dimensional model for the degradation of a cellulose disc.

6.2.8. *Non-linear filtering for the chemostat*

Participants: Boumediene Benyahia, Fabien Campillo, Jérôme Harmand.

We propose numerical non-linear filtering approaches for the identification of non-observed components of dynamical systems in the context of the chemostat. This recently started study relies on the work of the project-team in the stochastic modelling of the chemostat. In a preliminary work we consider the bootstrap particle filter.

7. Contracts and Grants with Industry

7.1. BioInh

Participants: Jérôme Harmand, Alain Rapaport, Tewfik Sari.

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 MODEMIC 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 unstabilities and drive the system toward several possible equilibria, one of them only being interesting in terms of yield and productivity. First experiments have been run but have not been finished due the interruption of our former postdoc for health reasons.

7.2. CAFE

Participants: Jérôme Harmand, José Fernandez, 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.

MODEMIC is involved in the wine making optimization part of the project which constitutes the PhD thesis of José Fernandez (see Sections 6.1.10 and 6.2.2).

7.3. DIMIMOS

Participants: Jérôme Harmand, Alain Rapaport.

This fundamental research project aims at better understanding 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.

The results obtained within the E-MICRAM project turn out to be of direct interest for the DIMIMOS project (see Section 7.6).

7.4. DISCO

Participants: Fabien Campillo, Chloé Deygout, Bart Haegeman, Jérôme Harmand, Claude Lobry, Alain Rapaport, Tewfik Sari.

DISCO (Multi-scale modelling 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, C. Deygout has been hired as a postdoctoral fellow. She is developing a double modelling 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 (see Section 6.1.7). 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.

In 2011, C. Deygout has spent most of her time at HBAN Cemagref to contribute to experiments in tubular plug-flow reactors, the biofilm being observed with the help of confocal microscopy. At that time, the set-up has not allowed yet a fair comparison between model simulations and experimental data.

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

7.5. MODECOL

Participants: Fabien Campillo, Ihab Haidar.

The ANR SYSCOMM Project MODECOL (2009-2011) involves three INRIA project-teams (MODEMIC, 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 MODEMIC component is to propose individual-based models for terrestrial prairial plant communities' dynamics in the context of water purifying from nitrate and pesticides. This year the INRIA team proposed a new model [26], its analysis and the development of a simulation software. The project-team was also involved in the organization of a session at the 54th Symposium of the International Association for Vegetation Science (IAVS) in Lyon (20-24 June 2011). This work has been presented in three international conferences [36] [35] [26].

7.6. E-MICRAM

Participants: Florent Dayle, 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.

With researchers of UMR Eco & Sols (Montpellier) and Bioemco (Paris-Grignon), we are investigating the influence of the size of samples on the probability of obtaining a "positive" reconstituted ecosystem, on the basis of experimental data (MSc subject of F. Dayle).

7.7. VITELBIO

Participants: Fadia Gafsi, Ihab Haidar, Jérôme Harmand, Mouna Jraou, Alain Rapaport.

The former ARC VITELBIO (VIrtual TELluric BIOreactors) gathers biologists, agronomist, micro-biologists, soil physicists and mathematicians about the modelling 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 (see Section 5.1).

The software has allowed to explore the yield properties of several configurations of interconnections (serial, parallel, diffusive, dead zone and more sophisticated ones). Part of them has then being analytically studied in the PhD work of H. Haidar.

The VITELBIO project has been also financed by INRA for the purchase of four experimental chemostats settled at the LBE Narbonne. The training period of F. Gafsi and M. Jraou at the LBE and then in Montpellier have aimed to compare numerical predictions with real experiments.

8. Partnerships and Cooperations

8.1. International Initiatives

8.1.1. Associated team DYMECOS

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

DYMECOS is an associated team with Chile, mainly with CMM (Centro de Modelamiento Matemático), Univ. de Chile, Santiago, DIM (Departamento de Ingeniería Matemática), 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 modelling of the chemostat.

In 2011, the team has been visited by the Chilean researchers D. Jeson (U. Frontera), P. Gajardo (UTFSM, Valparaiso), H. Ramirez (DIM, Santiago) and G. Ruiz (PUCV, Valparaiso). Two Chilean students V. Riquelme and E. Tapia have spent some time in MODEMIC team, and two PhD students J. Fernandez and M. Sebbah have been sent to Chile.

A second Franco-Chilean Workshop on Bioprocess Modelling, co-organized with the Chilean partners, is scheduled in January at Pucón. The workshop gathers mathematicians, process engineers and micro-biologists.

Activities and results are described on the web site Eadymecos.

8.1.2. MOMARE

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

The MODEMIC Project-Team 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 MODEMIC Project-Team was visited by E. Ocana (IMCA), H. Ramirez-Cabrera (DIM-CMM), J. Fontbona (DIM-CMM). The project is structured in two subthemes: "microbiology" (bioreactors, waste water treatment) and "harvesting" ("fishery" and "forestry", but also "mines"). The project will be ended at the second French-Chilean Workshop on Bioprocess Modelling January 16-17, 2012 (Pucón, Chile).

8.1.3. 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 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 48 months.

This project was recently extended in a renewed form for a period of four years from January 2012.

8.1.4. LIRIMA Stic-Mada

Participants: Fabien Campillo, Angelo Raherinirina.

The MODEMIC Project-Team is coordinator of the LIRIMA/Stic-Mada project for the theme: modelling and management of natural resources. The thesis of Angelo Raherinirina is prepared in this context in association with the University of Fianarantsoa and IRD. In Antananarivo (Madagascar), September 19-30, we organized the first "Ecole Mathématique Africaine" together with the CIMPA. One of the themes of this school was on Markov modelling for ecological successions.

9. Dissemination

9.1. Animation of the scientific community

- A. Rapaport is presently the head of the UMR INRA-SupAgro MISTEA (Mathematics, Informatics and STatistics for Environment and Agronomy) where the team is housed. A. Rapaport is: member of the piloting board of the "modelling" axis of the LabEx Numev (Digital and Hardware Solutions, Modelling for the Environment and Life Sciences)) at Montpellier; member of the scientific board of the "Ecotechnologies" department of IRSTEA (Cemagref); member of the scientific board of the "BIOS" department of CIRAD.

- F. Campillo is member of the NICE (long term invited scientists selection); deputy elected member of the INRIA Scientific Council; member of the internal communication working group of INRIA Sophia Antipolis. F. Campillo was member of the INRA selection board for the selection of junior scientists (statistics and modelling).

- J. Harmand is the responsible for the treasure-2 network (a 3+3 Euromed project) that has been accepted for funding for the next 4 years); member of the scientific council of the Environment and agronomic INRA department; member of the advisory board of the INRA metaprogram MEM (Meta-omic and Microbial Ecosystems); member of the INRA evaluation commission STEA ("Sciences de la Terre, de l'eau et de l'atmosphère").

- F. Campillo and A. Rapaport are co-organizers of the MIA-Montpellier network that gathers about 70 researchers on applied mathematics and informatics for environmental and agronomics sciences on Montpellier [link].

- J. Harmand and A. Rapaport are responsible of the INRA network MODYM (MOdèles DYnamiques et Métabolites).

- B. Haegeman is Academic Editor for PLoS ONE.

9.2. Seminars and schools

The MODEMIC project-team animates several seminars:

- The MODEMIC seminar on mathematical modelling [link].

- I3M and MODEMIC working group on stochastic models for ecology and biology [link]; this working group is supported by the "laboratory of excellence" (LabEx) NUMEV (Digital and Hardware Solutions, Modelling for the Environment and Life Sciences).

- Within the framework of the TREASURE network, an international school has been co-organized with the INRA LBE in Narbonne From June the 6th to the 10th. About 35 Master, PhD students, junior as well as senior researchers from 6 countries have followed these courses about water treatment technology.

- MODEMIC has organized its internal annual seminar in Saint-Martin-de-Londres, France, November September 6-8, 2011.

9.3. Teaching

- F. Campillo gave a 10 hours lecture on "Markov models for successions in ecology and agronomy" at the first "Ecole Mathématique Africaine" organized by the CIMPA and the LIRIMA in Antananarivo (Madagascar), September 19-30.

- F. Campillo and M. Joannides have given a 20 hours lecture on "Stochastic modelling of ecosystems" at the Master 2 in Biostatistics in Université de Montpellier II.

- Fabien Campillo, C. Lobry and T. Sari gave a 6h lecture at the Summer School/Workshop "Modèles mathématiques de la dynamique des populations", April 18–22, Ecole Polytechnique, Tunis.

- A. Rapaport gave a 25 hours lecture on differential equations with applications in the "Practical Mathematics" module for 1st year students in MSc in Mathematics at University Montpellier II.

- F. Campillo, J. Harmand and A. Rapaport are in charge of a new 50 hours module on "Introduction to mathematical modelling" in the new MSc program "STIC - Environnement" at University Montpellier II.

- F. Campillo and A. Rapaport have delivered a 20 hours doctoral module at University Montpellier II, entitled "Modelling for biology and ecology – mathematical and computational methods".

- F. Campillo, J. Harmand, A. Rapaport and T. Sari have given introductive lectures on mathematical modelling for 1st year students of SupAgro Montpellier.

- A. Rapaport has given three lectures on Modelling and numerical simulations at the "EcoSystèmes" Master at University of Montpellier II.

- J. Harmand, C. Lobry, T. Sari delivered introductory lectures on mathematical modelling of bioprocesses at the Tlemcen school organized by TREASURE.

9.4. PhD's

Defended thesis:

- Ihab Haidar, "Dynamiques microbiennes et modélisation des cycles biogéochimiques terrestres"; grant: MESR (Univ. Montpellier II); started october 2008, defended december 2011; advisors: A. Rapaport and F. Gérard (UMR Eco & Sols).

Theses in progress:

- Mamadou Lamine Diagne, "Modélisation mathématique du Typha"; grant: AUF; thesis in co-supervision Mulhouse-Saint Louis (Senegal); started in October 2009; advisors: T. Sari and M.T Niane (Saint Louis, Senegal).
- Boumediène Benyahia, "Modélisation et contrôle de bioréacteurs à membrane"; grant: Coadvise and Treasure; thesis in co-supervision Montpellier-Tlemcen (Algeria); started in October 2008; advisors: J. Harmand and B. Cherki (Tlemcen, Algeria).
- José Fernandez, "Modelling and control of cascade reactors for the study of wine making"; grant: INRIA/CONYCIT(Chile) and INRA grant; started april 2009; advisors: A. Rapaport.
- Radhouene Fekih-Salem, "La compétition et la coexistence dans le Chemostat"; grant: Averroes; thesis in co-supervision Montpellier-Tunis; started in October 2010; advisors: A. Rapaport, T. Sari and N. Gmati (Tunis).
- José Fernandez, "Modelling and control of cascade reactors for the study of wine making"; grant: INRIA/CONYCIT(Chile) and INRA grant; started april 2009; advisors: A. Rapaport and J. Harmand.
- Amel Ghouali, "control en tamps minimal des réacteurs de digestion anaérobie"; grant: Averroes; thesis in co-supervision Montpellier-Tlemcen (Algeria); started in October 2011; advisors: J. Harmand and B. Cherki (Tlemcen, Algeria).
- Angelo Raherinirina, "Modélisation markovienne de dynamique d'usage des sols"; grant: AUF, SCAC Madagascar, LIRIMA; started March 1st 2009; advisors: F. Campillo and R. Rakotozafy (Uni. Fianarantsoa Madagascar).
- Coralie Fritsch, "Simulation et analyse de modèles individu-centrés d'écosystèmes bactériens pour des procédés biotechnologiques", école doctorale I2S; grant: INRA Metaprogram MEM and Univ. Montpellier II; started October 1st 2011; advisors: F. Campillo, M. Joannides, J. Harmand.
- Guilherme Pimentel, "Modelling and control of bioreactors with membrane"; grant: Univ. Mons (Belgium) and INRA; thesis in co-supervision Montpellier-Mons; started October 2011; advisors: A. Rapaport, J. Harmand and A. VandeWouver (Univ. Mons).
- Amine, "Modélisation du colmatage dans les réacteurs à membranes" grant: Coadvise and University of Tunis; started October 2009; advisors: J. Harmand and Nihel Benamar.

9.5. Participation to thesis committees

- A. Rapaport (member): J.D. Mathias, "De la double modélisation à la validation expérimentale par des méthodes de mesure de champs sans contact du comportement des matériaux", thèse d'Habilitation à Diriger des Recherches, Univ. B. Pascal, Clermont II.
- A. Rapaport (member): M. Mazade, "Ensembles localement prox-réguliers et inéquations variationnelles", Univ. Montpellier II.
- A. Rapaport (advisor): I. Haidar, "Dynamiques microbiennes et modélisation des cycles biogéochimiques terrestres", Univ. Montpellier II.
- F. Campillo (referee): M. Xuan-Binh Lam, "Uncertainty quantication for stochastic subspace identification method", Uni. Rennes I.
- F. Campillo (referee): Mme Nelly Jean-Baptiste, "Assimilation de données pour l'estimation de l'état hydraulique d'un aménagement hydroélectrique du Rhône équipé de la commande prédictive", Uni. Toulouse III.

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