IN PARTNERSHIP WITH:
INRA

Activity Report 2015

Project-Team MODEMIC

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

IN COLLABORATION WITH: Mathématiques, Informatique et STatistique pour l'Environnement et l'Agronomie

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Modeling and Control for Life Sciences

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Project-Team MODEMIC

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- 6.1. - Mathematical Modeling
- 6.2. - Scientific Computing, Numerical Analysis & Optimization
- 6.4. - Automatic control

Other Research Topics and Application Domains:
- 1.1. - Biology
- 1.2. - Ecology
- 3.1. - Sustainable development

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2. Overall Objectives

2.1. Introduction

In complex processes of material and energy transformations on Earth, the microbial compartment is an essential link for major biochemical cycles that sustain life on Earth and regulate the climate. There are presently growing social demands for preservation of water quality, regeneration or soil fertility or development of new ecosystem services for the environment, for which the role of micro-organisms is fundamental. Micro-organisms are also responsible of fermentation processes that can be found specifically in food production. Knowledge, control and management of microbial ecosystems appear then to be essential to satisfy the expectations of our society. Aside observations and experiments, modeling and computer simulations have to play an important role in the fields of microbiology and microbial ecology.

In this context, MODEMIC aims at cross-fertilizing Inra and Inria researchers' competences for developing, analyzing and simulating new models of microbial ecosystems as efficient tools to understand, explore, pilot and manage natural or industrial bio-processes. Being a joint team with the MIA (Applied Mathematics and Informatics) Department of Inra, an important issue for the team is to develop relevant and useful techniques for scientists and engineers in biology, micro-biology, microbial ecology and agronomy.

For this purpose, we study mathematical and/or computer models of the dynamics of populations of micro-organisms. These models can be complex or reduced ones. We carry simulations and possibly mathematical analyses. We put an emphasis on the understanding of the dynamical behaviors out of equilibrium, because most of real processes represented by these models are either not stationary, or one needs to drive them out of an equilibrium.

For concrete applications in laboratory and/or within industrial perspectives, we also study control strategies and identification techniques of these models, based on tools from Automatic Control.

Our objective is twofold: on the one hand to build, simulate and analyze models of microbial ecosystems; on the other hand to develop methods for the identification, the control and the optimization of microbial ecosystems.

2.2. Build, simulate and analyze models of microbial ecosystems

We investigate different models of microbial ecosystems at various scales, depending on the observations reported by biologists and questions of interest. The models we intend to develop and study cover the usual three scales of ecology: the individual in its community, the community in interaction with its environment and the overall ecosystem.

The main questions we address concern the roles of biotic and abiotic interactions on the coexistence or exclusion of species, the behavior of transient dynamics and the performances of bio-processes.

For this purpose, we build population models both deterministic (differential equations) and stochastic (stochastic differential equations, birth and death processes), as well as individual-based models (usually stochastic). We study their dynamical properties combining mathematical analysis (determination of equilibria and their stability, construction of Lyapunov functions, analysis of limit cycles, weak convergence between models...) and numerical simulations (Monte-Carlo techniques, Gillespie-like algorithms...). Some of our models include spatial considerations, with explicit (transport and/or diffusion terms) or implicit (compartments or "gradostat"-like equations) representations.

We aim at determining the validity and the effective limits of these models, and at developing tools for change of scales (e.g. from an individual-based model to a deterministic macroscopic model and vice-versa). We consider also multi-scale modeling, for instance in biofilm simulations for which the scale of micro-organisms and the scale of the exo-polymer matrix impact each other. The scope of our research program stops at the individual level as its smallest level. We do not intend to model the mechanisms inside micro-organisms but rather to focus on populations, and especially on the effects of large numbers of individuals sharing the same environment.

2.3. Identification, control and optimization of microbial ecosystems

Biologists have often to deal with data and use statistical tools to reveal or quantify variables correlations. We focus on situations for which models can bring complementary knowledge or lightning over these statistical treatments. In many practical cases, the state variables of the dynamical models (nutrient concentrations, composition of the biomass...) are not all accessible through direct observations. Instead, indirect effects of the internal states are observed with time by way of the system outputs. State observers or filters, that are built on the precise knowledge of a dynamical model and its outputs, allow on-line reconstruction of unknown state variables or parameters, and could in principle replace missing sensors. Moreover, knowing the system state is often necessary to solve many control problems (for instance stabilizing a system using state feedback) that we describe below. In practice, several obstacles due to model non-linearity, imperfect measurements, disturbances or simply lack of observability appear when one tries to apply the usual constructions of state estimators. We aim at proposing and studying reconstruction methods dedicated to the family of models we are considering in Objective 2.2, with the possible considerations of multi-valued systems or probabilistic estimations.

Among most of our collaborations about real life bio-processes (waste-water treatments, food fermentation...), we also often met questions related to the driving, design or supervision, that we aim at considering at both methodological and practical scopes. Our objective is to look for state or output feedback strategies for stabilizing bio-processes, or optimizing paths with respect to a given criterion such as minimum time. We focus on the derivation of global controllers based on the nature of non-linearity and input constraints (such as positivity of the manipulated variables), and investigate how these realizations can be applied under uncertainties on both model and measurements. Our final goal is to provide satisfactory solutions (optimal or sub-optimal) relevant to be implemented on real processes that possesses a limited number of sensors.

3. Research Program

3.1. Modeling and simulating microbial ecosystems

The chemostat model is quite popular in microbiology and bioprocess engineering [58], [60]. Although the wording "chemostat" refers to the experimental apparatus dedicated to continuous culture, invented in the fifties by Monod and Novick & Szilard, the chemostat model often serves as a mathematical representation of biotic/abiotic interactions in more general (industrial or natural) frameworks of microbial ecology. The team carries a significant activity about generalizations and extensions of the classical model (see Equation (1) and Section 3.1.1) which assumes that the sizes of the populations are large and that the biomass can be faithfully represented as a set of deterministic continuous variables.

However recent observations tools based notably on molecular biology (e.g. molecular fingerprints) allow to distinguish much more precisely than in the past the internal composition of biomass. In particular, it has been reported by biologists that minority species could play an important role during transients (in the initialization phase of bio-processes or when the ecosystem is recovering from disturbances), that cannot be satisfactorily explained by the above deterministic models because the size of those populations could be too small for these models to be valid.

Therefore, we are studying extension of the classical model that could integrate stochastic/continuous macroscopic aspects, or microscopic/discrete aspects (in terms of population size or even with explicit individually based representation of the bacteria), as well as hybrid representations. One important question is the links between these chemostat models (see Section 3.1.2).

3.1.1. About the chemostat model

The classical mathematical chemostat model:

$$
\begin{aligned}
\dot{s} &= -\sum_{j=1}^{n} \frac{1}{y_j} \mu_j(s)\, x_j + D\,(s_{in} - s) \\
\dot{x}_i &= \mu_i(s)\, x_i - D\, x_i \qquad (i = 1 \cdots n)
\end{aligned}
\tag{1}
$$

for n species in concentrations x_i competing for a substrate in concentration s, leads to the so-called "Competitive Exclusion Principle", that states that generically no more species than limiting resources can survive on a long term [59]. Apart some very precise laboratory experiments that have validated this principle, such an exclusion is rarely observed in practice.

Several possible improvements of the model (1) need to be investigated, related to biologists' knowledge and observations, in order to provide better interpretations and predictive tools. Various extensions have already been studied in the literature (e.g. crowding effect, inter-specific interactions, predating, spatialization, time-varying inputs...) to which the team has also contributed. This is always an active research topic in bio-mathematics and theoretical ecology, and several questions remains open or unclear, although numerical simulations guide the results to be proven.

Thanks to the proximity with biologists, the team is in position to propose new extensions relevant for experiments or processes conducted among the application partners. Among them, we can mention: intra and inter-specific interactions terms between microbial species; distinction between planktonic and attached biomass; effects of interconnected vessels; consideration of maintenance or variable yield in the growth reactions; coupling with membrane fouling mechanisms.

Our philosophy is to study how complex or not very well known mechanisms could be represented satisfactorily by simple models. It often happens that these mechanisms have different time scales (for instance the flocculation of bacteria is expected to be much faster than the biomass growth), and we typically use singular perturbations

techniques to produce reduced models.

3.1.2. Stochastic and multi-scale models

Comparatively to deterministic differential equations models, quite few stochastic models of microbial growth have been worked out in the literature. Nonetheless, numerous problems could benefit from such an approach (dynamics with small population sizes, persistence and extinction, random environments...).

For example, the need to clarify the role of minority species conducts to revisit thoroughly the chemostat model at a microscopic level, with birth and death or pure jump processes, and to investigate which kind of continuous models it raises at a macroscopic scale. For this purpose, we consider the general framework of Markov processes [57].

It also happens that minority species cohabit with other populations of much larger size, or fluctuate with time between small and large sizes. There is consequently a need to build new "hybrid" models, that have individual-based and deterministic continuous parts at the same time. The persistence (temporarily or not) of minority species on the long term is quite a new questioning spread in several applications domains at the Inra Institute.

Continuous cultures of micro-organisms often face random abiotic environments, that could be considered as random switching between favorable or unfavorable environments. This feature could lead to non-intuitive behaviors in long run, concerning persistence or extinction of populations. We consider here the framework of piece-wise deterministic Markov processes [55].

3.1.3. Computer simulation

The simulation of dynamical models of microbial ecosystems with the features described in Section 3.1.2 raises specific and original algorithmic problems:

- simultaneous presence in the same algorithms of both continuous variables (concentration of chemicals or very large populations) and discrete (when the population has a very small number of individuals),
- simultaneous presence in the same algorithms of stochastic aspects (for demographic and environmental noises) and deterministic ones (when the previous noises are negligible at macroscopic scales)
- use of individual-based models (IBM) (usually for small population sizes).

We believe that these questions must be addressed in a rigorous mathematical framework and that their solutions as efficient algorithms are a formidable scientific challenge.

3.2. Identification and control

3.2.1. Models identification and state estimation

Growth kinetics is usually one of the crucial ingredients in the modeling of microbial growth. Although the specific growth rate functions and their parameters can be identified in pure cultures (and can be estimated with accuracy in laboratory experiments), it is often an issue to extrapolate this knowledge in industrial setup or in mixed cultures. The parameters of these functions could change with their chemical and physical environment, and species interactions could inhibit or promote a strain that is expected to dominate or to be dominated in an multi-species ecosystem. Moreover, we need to estimate the state variables of the models.

We aim at developing effective tools for the on-line reconstruction of growth curves (and of their parameters) and/or state variables, along with the characteristics of microbial ecosystems:

- It is not always possible to drive a biological system for exploring a large subset of the state space, and open-loop dynamics could be unstable when far from locally stable equilibria (for instance under inhibition growth).
- The number of functional groups of species and the nature of their interactions (competition, mutualism, neutral) are not always known a priori and need to be estimated.

We look for observers or filters based methods (or alternatives), as well as estimation procedures, with the typical difficulty that for biological systems and their outputs it is rarely straightforward to write the models into a canonical observation form. However, our objective is to obtain an adjustable or guaranteed speed of convergence of the estimators.

3.2.2. Optimal design and control

For practitioners, an expected outcome of the models is to bring improvements in the design and real-time operation of the processes. This naturally leads to mathematical formulations of optimization, stabilizing control or optimal control problems. We distinguish two families of problems:

- *Process design and control within an industrial setup.* Typically one aims at obtaining small residence times for given input-output performances and (globally) stable processes. The design questions consist in studying on the models if particular interconnections and fill strategies allow to obtain significant gains. The specificity of the models and the inputs constraints can lead to systems that are not locally controllable, and thus the classical linearizing techniques do not work. This leaves open some problems for the determination of globally stabilizing feedback or optimal syntheses.
- *Design and control for resource preservation in natural environments (such as lakes, soil bio-remediation...).* Here, the spatial heterogeneity of the resource might be complex and/or not well known. We look for sparse spatial representations in order to apply finite dimensional tools of state-space systems.

In both cases, one faces model uncertainty and partial measurements that often require to couple the techniques developed in Section 3.2.1.

4. Application Domains

4.1. Wastewater treatment systems

The water resources of our planet are limited, and today the quality of drinking water is considered to be responsible of more human deaths than malnutrition. Pollution and over-exploitation of water resources affect almost all the water reservoirs on Earth. Preserving the quality of water has thus become a worldwide problem. The industry of decontamination is thus a necessity, but waste-water treatment is costly and requires large plants. It relies on the use of micro-organisms that concentrate toxic soluble substances into sludge (that can be used as a fertilizer in agriculture). Today, a water decontamination plant costs about 1000 to 5000 euros per inhabitant. 30 to 40% of its running costs are devoted to the energy necessary for pool ventilation.

The waste-water treatment industry use software to optimize the plant design (number, size, interconnections of tanks), but design and improvements of bio-processes remain costly. This is why modeling allows numerical simulations of *virtual* bio-processes that can save substantial amount of money, avoiding tests at a real scale.

There is presently a growing need to conceive treatment systems in a more global framework, including the valorization of the “outputs” such as:

- the bio-gas production,
- the reuse of treated water for agriculture or dam refill in case of drought.

This requires to re-think the use of the models or to couple them with other models with new outputs and novel criteria to be optimized.

This is our most important domain of transfer and dissemination.

4.2. Environmental microbiology

Chemostat-like models (see Section 3.1.1) are also quite popular in theoretical marine ecology or in soil bio-chemistry, because micro-organisms play again a crucial role in the bio-geo-chemical cycles on Earth. Questioning are here a bit different than the ones depicted in Section 4.1, because it is much more oriented towards comprehension and prediction than decision making (at the present time). Grasping the role of the microbial biodiversity appears to be an everlasting and common important question among scientists of various domains.

Nevertheless, mathematical models are quite similar but with some specificity (much more resources are available in marine microbiology; the spatial heterogeneity play a crucial role in underground processes).

A recent trend of considering natural microbial ecosystems on Earth to be able to delivering new 'eco-systemic services' has emerged, especially in terms of bio-remediation. Modeling and simulating tools are much relevant as in site experiments are quite costly and time-consuming.

4.3. Bioprocesses industry

Several industries use micro-organisms or yeasts to product substances of commercial interest (in pharmaceutics, green biotechnology, food making...). Novel investigation techniques in microbiology (such as multistage continuous bioreactors) brings new insights on the metabolic functioning of the various strains. This conducts to revisit old models such as Monod's one, and to look for new estimation and piloting strategies. Those questions are quite closed from the ones studied in 4.1 and 4.2, although the ecological dimension is less present (most of the culture are pure ones). The team is naturally solicited to contribute together with the specialists about problems related to modeling, simulation and control of these bio-processes.

5. Highlights of the Year

5.1. Highlights of the Year

The project Soil$\mu 3D$, which Modemic is a partner, has been selected and funded by the ANR (French National Research Agency) for the 2015-2019 period.

Alain Rapaport has been invited to give a plenary session at the next CMPDE'16 [1] (Conference in Mathematical Population Dynamics and Epidemiology), Marseille, 5–9 September 2016.

6. New Software and Platforms

6.1. Landfill Recirculation Management Simulator

FUNCTIONAL DESCRIPTION

Following the first works on modeling and control of landfills performed in the framework of the associated team DYMECOS with Chile, that have proposed an optimal feedback strategy for the leachate recirculation under the assumption of a perfectly mixed medium [40], a first mock-up software has been conceived in view of studying the effects of inhomogeneity along with identification procedures of spatial network structures on data (interconnection of bioreactors as in VITELBIO project). The development of the software is in progress.

- Participants: Andres Donoso-Bravo (PUCV, Chile), J.R. de Dreuzy (GéoSciences Rennes), Alain Rapaport, Hector Ramirez, Alejandro Rojas Palma
- Contact: Alain Rapaport
- URL: https://sites.google.com/site/eadymecos/resultats

6.2. Action Dépollution

FUNCTIONAL DESCRIPTION

[1] http://mpde16.mio.univ-amu.fr/

Action Dépollution is a serious game made for learning how to purify fast and well a water reservoir, such as lakes. In the scope of the international initiative Mathematics of Planet Earth, this game shows an application of mathematics related to environmental education and sustainable development. The player can act as a researcher, that compares different strategies and looks for the best solution.

- Participants: Alain Rapaport, Antoine Rousseau (EPI LEMON)
- Contact: Antoine Rousseau
- URL: https://depollution.inria.fr/

6.3. VITELBIO (VIrtual TELluric BIOreactors)

FUNCTIONAL DESCRIPTION

Vitelbio is a simulator of the microbial activity in soils, for which the spatialization is represented as a network of interconnected reservoirs. The software allows to draw an interconnections graph, that respects the constraint of the maximum flow, and to choose the biological characteristics of various bacterial species in competition for a single nutrient. The simulator computes the time evaluations of the different populations in each compartment, and compares the overall yielding of the ecosystem in terms of bio-conversion of the substrate. This software has been developed in the framework of the INRA/Inria project VITELBIO (VIrtual TELluric BIOreactors), with the help of the company ITK. It is today mainly used for educational purposes (in MSC and PhD lectures).

- Participants: Jérôme Harmand, Alain Rapaport
- Contact: Alain Rapaport
- URL: http://vitelbio.itkweb.fr/vitelbio/

7. New Results

7.1. Mathematical models for microbial ecology

7.1.1. Differential equations models

Participants: Jérôme Harmand, Claude Lobry, Alain Rapaport, Yessmine Daoud, Sonia Hassam, Zeyneb Khedim, Alejandro Maximiliano Rojas.

Anaerobic digestion refers to the transformation of biodegradable material by micro-organisms in absence of oxygen (it can be found in waste-water treatments or industrial fermentation, and occurs naturally in soils). It receives an increasing consideration due to recent technological advances, but also because it is a source of renewable energy (bio-gas, fuel...). The anaerobic digestion is a complex set of bio-processes, for which there is a strong expectation of tractable models. We have proposed and studied new mathematical models that takes into account the following features:

- Microbial food chains are present in anaerobic digestion where the different reaction steps can be seen as such: the waste products of the organisms at one trophic level (i.e. one reaction step) are consumed by organisms at the next trophic level (i.e. the next reaction step). In [54] we study a model of a two-tiered microbial ‘food chain’ with feedback inhibition, which was recently presented as a reduced and simplified version of the anaerobic digestion model ADM1 of the International Water Association (IWA) (cf. [61]). It is known that in the absence of maintenance (or decay) the microbial ‘food chain’ is stable. In [61], using a purely numerical approach and ADM1 consensus parameter values, it was shown that the model remains stable when decay terms are added. In [54] we prove that introducing decay in the model preserves stability whatever its parameters values are and for a wide range of kinetics.

- In the thesis by Sonia Hassam [13], we have proposed a new procedure to easily and systematically obtain a simple model useful for control purposes of any process for which an ADM1 is available. The simplified model has two major characteristics : its states keep their physical meaning and it remains nonlinear. The technique is based on the state association technique proposed in [26].
- Zeyneb Khedim (University of Tlemcen, Algeria) has began her PhD in 2014. She is working on the modeling and control of anaerobic digestors. In particular, she works on the reduction of models using the state association approach proposed by Sonia Hassam but for substrates highly loaded in nitrogen such as algae. She has published this year a survey with Sonia Hassam [36].
- Yessmine Daoud (ENIT-LAMSIN, Tunis, Tunisia) continues her work on the analysis of a model of the literature to optimize anaerobic processes [35]. She is preparing a journal paper which should be submitted during 2016.

Formerly, the team has studied chemostat models where the bacterial compartment is split into “planktonic” and “attached” bacteria (such as in flocculation or biofilms formation), under the hypothesis that attachment and detachment are fast phenomena. Under certain mixing conditions, this last condition is no longer satisfied. We have studied on the non-reduced model the competition between a species that presents growth inhibition in planktonic form with a species that does not attach. This consideration leads to multiple positive equilibria but surprisingly it can also conduct to limit cycles [53] (paper under revision for Applied Math. Model.).

Spatial heterogeneity is often observed in non perfectly mixed bioprocesses or in populations in natural environments. The representation o spatial heterogeneity in population models with patches or interconnected models, rather than p.d.e., is one of the specialties of the team, that allows us to characterize non intuitive effects of spatialization :

- The very basic Rosenzweig-MacArthur model is subject to the "atto-fox" problem [2] when considered for homogeneous populations. Is it still true in case of heterogeneous populations? The idea is: the resource population being not small at the same time in different places is it possible that, thanks to dispersal, it will not disappear? One possible idealization of heterogeneous populations is to use reaction-diffusion equations. We do not take this direction for two reasons
- (i) Due to the presence of a limit cycle in the homogeneous system mathematics of such reaction diffusion are difficult.
- (ii) Idealization through reaction-diffusion is not the best one; patch-systems (or lattice differential equations in mathematical terms) are better in many cases.

Our ultimate objective is to provide mathematical results for systems with a large number of patches but, as a first step, in the paper [27] we consider two patches. It is proved that for some migration rates, stable periodic solutions avoiding "atto-fox" exist.

- The standard model for the dynamics of a fragmented density-dependent population is built from several local logistic models coupled by migrations.

First introduced in the 1970s and used in innumerable articles, this standard model applied to a two-patch situation has never been completely analyzed. The motivation for studying this problem came out from discussions at the Bernoulli semester organized in 2014 and 2015 by the team at the EPFL (see the 2014 activity report and Section 8.3.3.1). It addresses very fundamental issues in theoretical ecology. In the paper [15] written in collaboration with R. Arditi (U. Fribourg) an T. Sari (IRSTEA Montpellier), we complete this analysis and we delineate the conditions under which fragmentation associated to dispersal is either beneficial or detrimental to total population abundance. Therefore, this is a contribution to the SLOSS question. Importantly, we also show that, depending on the underlying mechanism, there is no unique way to generalize the logistic model to a patchy situation. In many cases, the standard model is not the correct generalization. We analyze several alternative models and compare their predictions. Finally, we emphasize the shortcomings of the logistic model when written in the r-K parameterization and we explain why Verhulst’s original polynomial expression is to be preferred.

- We have carried on our former work on the role of particular interconnections patterns on the global stability of chemostat model with inhibition. While we focused formerly on the conditions for which a spatial structure ensures the global stability when the chemostat model is bi-stable in homogeneous environment, we have shown that at the opposite a spatial structure can make unstable the dynamics of the chemostat model with inhibition when it is stable in a homogeneous environment [30].
- In collaboration with Géosciences Rennes (Jean-Raynald de Dreuzy, Tristan Babey) and in the scope of the co-supervision of the PhD of Alejandro Rojas (also in the collaboration within the associated team with Chile), we have carried on the complete equivalence between several models used in Geosciences to characterize soil fractures : MINC (Multiple INteracting Continua), MRMT (Multi-Rate Mass Transfer) and SINC (Structured INteracting Continua). We have shown that the irreducibility of the network graph is not sufficient to obtain equivalence : a controllability assumption has also to be fulfilled [42]. Moreover, this kind of models has been used to fit experimental data of reconstituted soils at Inra Grignon and has shown the role of convection in the acquisition of pesticides by micro-organisms [46] (paper in preparation). This work will be continued in the framework of the new ANR project Soil$\mu 3D$ (see Section 8.2.1).

In resources/consumers models, heterogeneity can be also due to time varying inputs of resources (e.g. light in micro-algae populations). While, most of the literature studies periodic inputs, we have begun investigations of more general time varying inputs in chemostat like models, having in mind to characterize “pull-back attractors” (rather than forward attractors) [43].

7.1.2. Stochastic and hybrid discrete-continuous dynamical models

Participants: Bertrand Cloez, Claude Lobry.

7.1.3. Approximation of quasi-stationary distributions

The study of the long-time behavior of a stochastic process is one of the main questions of interest for modeling. In a standard Markov setting, this leads to the study of the convergence towards the invariant distribution. However, in many applications such as population dynamics for instance, the stochastic dynamics is killed in a finite (random) time so that the standard asymptotic regime is trivial. In this case, it can be interesting to focus on the behavior of the process conditionally to its non-extinction before a given time t Under appropriate assumptions, one can exhibit a convergence of this conditional distribution towards a law called *Quasi-Stationary Distribution*. Properties of this law is then fundamental. In [21], we study an algorithm to approximate this distribution and we provide proof of convergence as well as precise rates for convergence. This one is based on a reinforced random walk.

7.1.3.1. Lotka Volterra in fluctuating environment

In the paper [49], we consider two dimensional Lotka-Volterra systems in a fluctuating environment. Relying on recent results on stochastic persistence and piecewise deterministic Markov processes, we show that random switching between two environments that are both favorable to the same species can lead to the extinction of this species or coexistence of the two competing species. This work has been accepted in Journal of applied probabilities, provided major revisions. We submitted a new version with the new title: Lotka Volterra with randomly fluctuating environments or "how switching between beneficial environments can make survival harder".

7.2. Analysis and supervision of bioprocesses

7.2.1. Models development and identification

Participants: Yessmine Daoud, Jérôme Harmand, Nesrine Kalboussi, Guilherme Pimentel, Alain Rapaport.

Membrane bioreactors combine a filtration process (with a membrane) and a suspended growth rate bioreactor. This recent technology present many advantages compared to conventional ones, but is more sophisticated and requires refined control because of possible problems related to the risk of membrane fouling. After the PhD by Amine Charfi defensed in 2014 we continue to work on the modeling and control of membrane bioreactors.

- Within this framework, new results have been obtained and a new model including several fouling mechanisms has been proposed [22].
- In the scope of the PhD of Guilherme Pimentel (defensed in February 2015, [11]), we have proposed a simple three time scales model in view of the control of the cake formation [14], [33]. This model has been validated on real data from a pilot plant at Univ. Mons (Belgium).
- The PhD thesis by Nesrine Kalboussi (ENIT-LAMSIN, Tunis, Tunisia) has just begun. It is dedicated to the early detection and control of membrane fouling. At present time, Nesrine is working on the bibliography about modeling and control of membrane bioreactors.

In many bioprocesses models, the loss of nutrient used for the maintenance of bacteria is neglected compared to the important nutrient supply. In poor environment, such as natural one in the oceans, this is no longer verified. In our collaboration with the LOMIC lab (Banyuls-sur-Mer), we have shown that the consideration of a maintenance term in the chemostat model allows to fit the data observed in experimental chemostats, and moreover that the level of maintenance is correlated to the activities of bacteria under the presence of light [23]. This gives a possible explanation of the variable yield observed in the bacterial compartment of marine ecosystems.

7.2.2. Synthesis of control laws

Participants: Térence Bayen, Walid Bouhafs, Amel Ghouali, Jérôme Harmand, Claude Lobry, Guilherme Pimentel, Alain Rapaport, Victor Riqueleme.

We investigate two kinds of bioprocesses to be controlled, arising in industrial biotechnology (digesters, waste-water purification...) or in the bioremediation of natural environments (lakes, landfill...).

7.2.2.1. Industrial biotechnology

In the framework of the PhD of Guilherme Pimentel [11] and the pilot plant at Mons, a nonlinear predictive law based on the model exposed in 7.2.1 has been tested and validated for piloting the process[34].

Control of biological reactors are still of great interest, notably but not only with respect to anaerobic digestors that can be destabilized due to the accumulation of intermediate metabolites that can inhibate the growth of some bacteria.

- Amel Ghouali (Cotutelle Univ. Montpellier and Univ. of Tlemcen, Algeria) who has defensed her PhD in December has developed an optimal control strategy to optimize the production of biogas over a given period of time [12]. In particular, she has solved an original optimal control problem using the maximum principle of Pontryagin [25].
- Within the scope of the PhD thesis by Walid Bouhafs (ENIT-LAMSIN, Tunis, Tunisia), we have proposed a new optimal control strategy for systems in which two specific substrates are degraded by two different bacterial consortia, one being limited by the oxygen while the other is inhibited. Walid will defense his PhD in next February.

The minimal time criterion is of particular interest in biotechnology, as it leads to time-independent feedback controllers.

- The paper [19] is devoted to the study of the minimal time problem of a fed-batch reactor, under the presence of a saturation point on the singular locus (this typically occurs whenever the growth rate function is of Haldane type and when typically the maximum input flow rate is not high enough to maintain the substrate concentration constant). This brings non-intuitive issues for the optimal synthesis (existence of switching curve and point of prior saturation).

- In the work [47], we study the minimal time control to drive a chemostat model to a target point. Such a problem finds application typically in the case where the input substrate concentration changes yielding in a new steady state. Converging fast towards this new reference point is much desired in practice. One essential feature of the present work is that the system takes into account a recirculation of biomass (as it is more and more often the case in modern biotechnology). We depict an optimal synthesis and provide an optimal feedback control by using the Pontryagin Maximum Principle and geometric control theory for both Monod and Haldane kinetics.

7.2.2.2. Bioremediation of natural environments

In the scope of the associated team with Chile (see 8.3.1.1) and the co-supervision of the PhD of Victor Riquelme, we have carried on the study of optimal syntheses for the minimal time treatment of natural water reservoirs (such as lakes) [41]. We have proved that the minimal time strategy consists in a most-rapid approach to homogeneous concentrations, even though the optimal control problem is non convex. Moreover, we have shown that a large diffusion increases the treatment time when the resource is everywhere highly polluted, while it can at the opposite be beneficial when only part of the resource is polluted (paper under revision for SIAM J. Cont. & Optim.). This feature should serve the practitioners in the choice of pumps positioning in a originally clean water resource that is suddenly affected by a local pollution. Moreover, we have shown, in collaboration with A. Rousseau (EPI LEMON), how these analytic feedback laws obtained on a over-simplified representation of the spatial heterogeneity behave quite satisfactorily when simulated [17]. This year we have started to study to problem of treating two different pollutants, with a anaerobic/aerobic process in series.

Also in the scope of the associated team with Chile, we have characterized the optimal strategy to treat as fast as possible a landfill with the recirculation as a manipulated variable [40], [29], based on a model that we have proposed last year. In presence of singular arcs that are non-admissible (in the sense that the upper bound of the recirculation pump does not allow to stay on the singular arc), we have shown that a kind of *anticipation* law is necessary before operating optimally the switching. This analyses reveals several sub-domains for which the optimal policy requires different kind of measurements. Knowing in which sub-domain the initial stage of landfill could be inform then the practitioners about which concentration (leachate or solubilized or both) should be ideally measured. This primarily work has led to the co-development of a software mock-up with Chilean partner (see 6.1), in order the study the consideration of spatial heterogeneity in landfill, with the approach exposed in 7.1.1.

This year, again in the scope of the associated team with Chile and Inria Chile, we have begun a new investigation on modeling and control strategy for the regulation of a lagoon that communicates temporarily with the sea and whose water is exploited by pumping.

7.2.2.3. Theoretical development

The time crisis is an interesting criterion that measures the time spent by a system in a “bad” zone or in “danger”. Typically, when a desired species is under a given (low) threshold, one can consider that this defines a crisis domain. For controlled system, the minimal time crisis has already been proposed in the literature [56]. Nevertheless, only sufficient conditions (i.e. characterization of the solutions of the associated Hamilton-Bellman-Jacobi equation) have been given, and no necessary conditions have been yet proposed, due to the lack of continuity of the integrand cost. We have proposed a regularization of this problem by a family of optimal control problems for which the usual necessary conditions can be derived, and studied the convergence [20]. Practically, this allows to use classical software, such as Bocop, to approximate the optimal solutions. In the internship of C. Romero (U. Chile), this technique has been successfully applied on the Lotka-Volterra model with a control on the predator, and a threshold on the prey.

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. Labex Numev

Within the Labex Numev (Solutions Numériques, Matérielles et Modélisation pour L'Environnement et le Vivant [2]), the team has obtained several funding for internships and invitation of international visitors, for the coming year:

- six months of MsC internships on optimal control for bioprocesses (jointly with the LBE unit, Inra Narbonne),
- the venue of Prof. Chris Klausmeir from Michigan State Univ. about micro-algae modeling (jointly withe the UMR EcoSols, Montpellier).

8.1.2. Inter-teams seminar

J. Harmand is the coordinator of the inter-teams seminar about the modeling of bioprocesses [3], involving the labs INRA-LBE (Narbonne), UMR LISPB (Toulouse) and the two Inria project teams BIOCORE and MODEMIC.

C. Lobry has been invited to participate to the "Séminaire au vert" of BIOCORE team in November 2015.

8.2. National Initiatives

8.2.1. ANR Soil$\mu 3D$

The team is partner of the ANR project SoilMicro-3D: *Emergent properties of soil microbial functions: Upscaling from 3D modeling and spatial descriptors of pore scale heterogeneity*, conducted by the UMR EGC for 4 years (2015-19). The other partners are UMR iEES, UMI UMMISCO, SIMBIOS (Scotland), UMR Géosciences Rennes, UMR JJL and UR Inra Science du Sol Orléans). The main goal of the project are

- develop new descriptors of the pore scale 3D soil heterogeneity that explain the fluxes measured at the core scale,
- improve the performance of 3D pore scale models to simulate processes from pores to cores with a reduction of the computational time,
- develop new simple models describing the soil micro-heterogeneity and integrating these micro-features into field-scale models.

The kick-off meeting is held in Jan 2016.

8.2.2. PGMO "OPTIBIO"

OPTIBIO (New challenges in the optimal control of bioprocesses [4]) is a new project funded by the french Fundation FMJH (Fondation Mathématique Jacques Hadamard) in 2014 for three years, within the program PGMO (Gaspard Monge Program for Optimization and operations research).

The project is coordinated by T. Bayen (ACSIOM, Univ. Montpellier II) and the other partners are: MODEMIC, Univ. Limoges, EPI COMMANDS (Saclay) and EPI BIOCORE (Sophia Antipolis).

The overall objective of this project is to address the optimization of bioprocesses over an *infinite horizon*. Infinite horizon optimal control is well suited for every problem where the time horizon is uncertain and can be expected to be large: e.g. economics models related to optimal growth and sustainable development, biological models such as the optimal control of interacting species and pest control, stabilization of controlled mechanical systems...The recent expectations of sustainable development raise new optimization problems that take into account auxiliary outputs, such as bio-gas production, that were neglected in the past. It appears that mathematical problems that come from the modeling of these processes are often difficult to solve, and one objective of the proposal is to develop new mathematical methods in order to address these issues. More precisely, the objective of the project is to study the following issues:

[2] http://www.lirmm.fr/numev
[3] https://sites.google.com/site/journeesthematiquesdulbe/
[4] http://www.math.univ-montp2.fr/~bayen/articles/posterPGMO.pdf

- Optimization of bioprocess over an infinite horizon.
- Development of accurate methods in order to deal with uncertainties that affects the chemostat model (uncertainties come from unknown parameters or noise from the measurements).
- Stabilization of the chemostat model including delay in the system.

8.2.3. INRA-MIA methodological networks

The team is involved in two new networks of the MIA (Applied Mathematics and Informatics) Department of INRA:

- MEDIA [5] (Modèles d'Équations DIfférentielles et Autres systèmes dynamiques pour l'écologie),
- REM [6] (RÉduction de Modèles),

that have been launched last year.

8.3. International Initiatives

8.3.1. Inria International Labs

Inria Chile

Associate Team involved in the International Lab:

8.3.1.1. DYMECOS2

Title: Modeling of microbial ecosystems, bioprocesses control and numerical simulations

International Partner (Institution - Laboratory - Researcher):

Universidad de Chile (Chile) - Center for Mathematical Modeling (CMM) - Hector Ramirez

Start year: 2014

See also: https://sites.google.com/site/eadymecos/

The objective is to develop, from expert knowledge and experimental observations, models of microbial ecosystems that are simple enough to carry out the determination of explicit "control laws", and realistic enough to represent real bio-processes. One of the difficulties is to identify the limits of the validity of these models, in terms of spatial heterogeneity and microbial population size. We aim also to obtain outcomes of the modeling for the optimal design of waste-water treatment plants.

8.3.2. Inria International Partners

8.3.2.1. Informal International Partners

CESAME, Univ. Louvain, Belgium : D. Dochain

3BIO, Univ. Mons, Belgium : A. Vande Wouver

Univ. Neuchâtel, Switzerland : M. Benaim

Univ. Newcastle, U.K. : M. Wade

MOMAT, Univ. Madrid, Spain : B. Ivorra

Univ. Sevilla, Spain : T. Caraballo

8.3.3. Participation In other International Programs

8.3.3.1. CIB (Centre Interfacultaire Bernoulli)

Program: Bernoulli workshops

Title: The role of mathematics and computer science in ecological theory

Inria principal investigator: MODEMIC (C. Lobry),

[5] http://www.netvibes.com/reseaumiamedia
[6] https://sites.google.com/site/reseaurem2/

Partners: EPFL, Lausanne (Switzerland).

Duration: July 2014 to Feb 2015

Abstract: A former collaboration of Inria with ecologists (the COREV network presently animated by R. Arditi) initiated (at the beginning of the 90s) by J-L. Gouzé and C. Lobry within the framework of the Inria project team COMORE, pursued then by MERE and COMORE raised an important event: the half-year *Mathematics and computer sciences in theoretical ecology* which we co-organize with R. Arditi (associated with D. de Angelis and L. Ginzburg) at the Federal Polytechnical School of Lausanne (Centre Interfacultaire Bernoulli).

The program lasted from July 1 to December 31, 2014 (see the 2014 activity report), but a follow-up workshop has been organized in February 2015 on the Persistence of population models in temporally fluctuating environments. This workshop has led to the writing of a review paper [31] in common.

Web-site: http://mathcompecol.epfl.ch/

8.3.3.2. TREASURE

Program: Euromediterranean 3+3

Title: Treatment and Sustainable Reuse of Effluents in semiarid climates

Inria principal investigator: MODEMIC (J. Harmand),

Partners: Centre de Biotechnology de Sfax, Department of environmental engineering (Tunisia), Ecole Nationale des Ingénieurs de Tunis, Dept. de Mathématiques (Tunisia), Institut National de la Recherche Agronomique, Dept. EA, MICA et MIA (France), National Research Center, Water Pollution Control (Egypt), University of Patras, Process Control Laboratory (Greece), University of Tlemcen, Automatic control (Algeria), University of santiago de compostella, Environmental engineering (Spain) Université Cadi Ayyad de Marrakech, Faculté des Sciences de Semlalia, Dépt. de Mathématiques (Morocco), Centre National de Recherche sur l'Eau et l'Energie, Université Française d'Egypte (Egypt)

Duration: Jan 2012 - Dec 2015

Abstract: The TREASURE network aims at integrating knowledge on the modeling, the control and the optimization of biological systems for the treatment and reuse of waste-waters in countries submitted to semi-arid climates under both socio-economical and agronomic constraints within the actual context of global changes. A special focus of the actual project concerns the integration of technical skills together with socio-economical and agronomic studies for the integrated solutions developed within the network to be evaluated and tested in practice in the partner's countries and, as possible as it may be within the context of the actual research network, valorizing these proposed technologies with the help of industrial on site in partners from South.

Web-site: https://project.inria.fr/treasure

8.3.3.3. TASSILI

Program: Hubert Curien Program

Title: Procédés membranaires pour le traitement anaérobie des eaux usées - Modélisation, commande et optimisation

Inria principal investigator: MODEMIC (J. Harmand),

Partners: LBE-INRA (Narbonne), Univ. Tlemcen (Algeria)

Duration: 3 years since 2014

Abstract: This project aims at promoting collaborations with our historical Algerian partners of the department of automatic control of the University of Tlemcen. The objectives of the project are to develop research on the modeling and the control of anaerobic systems through the co-advisoring of Zeyneb Khedim (PhD 'co-tutelle' between UM2 and Univ. Tlemcen).

8.3.3.4. MOSTICAW

Program: STIC AmSud
Title: MOdeling the Spread and (opTImal) Control of Arboviroses by Wolbachia
Inria principal investigator: P.A. Bliman (Inria Rocquencourt and Fundção Vargas, Rio de Janeiro, Brazil)
Partners: Inria (Rocquencourt and Metz), UPMC, CIRAD, MISTEA, Fundção Vargas (Brazil), Univ. Fed. Fluminense (Brazil), Fiocruz (Brazil), Univ. Buenos Aires (Argentina), UTFSM (Chile), Univ. de Chile, Univ. de Quindio (Colombia), Univ. Aut. de Occidente (Colombia), Nat. Univ. Nac. Mayor de San Marcos (Peru), Univ. of Asuncion (Paraguay).
Duration: 2016-2017
Abstract: The present project is concerned with new method of control of dengue fever, and potentially other severe diseases transmitted by mosquitoes Aedes (chikungunya, yellow fever). The goal of the project is to elaborate and analyze related models, along with control strategies, with the aim of testing concepts and estimating feasibility. The team is mainly involved in the modeling of interactions of bacteria Wolbachia with mosquitoes, and control systems tools (observers and optimal control).

8.4. International Research Visitors

8.4.1. Visits of International Scientists

Matthieu Sebbah
- Subject: Optimal control for lagoon management
- Date: from June 2015 until Sept 2105
- Institution: Univ. Tecnico Federico Santa Maria, Valparaiso, Chile.

8.4.1.1. Internships

Maria Crespo (PhD)
- Subject: Consideration of inhomogeneity in activated sludge bioreactors for the bioremediation of water resources
- Date: Feb 2015
- Institution: Univ. Complutense, Madrid (Spain)

Pascale Cuevas (MsC)
- Subject: Numerical simulation of the heterogeneity in transport diffusion with nutrients
- Date: from Sep 2015 until Nov 2015
- Institution: Univ. Santiago (Chile)

Yessmine Daoud (PhD)
- Subject: Mathematical analysis of anaerobic digestion models
- Date: from Mar 2015 until Jul 2015
- Institution: LAMSIN, Tunis (Tunisia)

Alejandro Rojas-Palma (PhD)
- Subject: Study of some problems related to modeling and optimization of bioprocesses
- Date: from May 2015 until Oct 2015
- Institution: Univ. of Chile

Victor Riquelme (PhD)
- Subject: Optimal control for the preservation of exploited water resources
- Date: from April 2015 until Nov 2015
- Institution: Univ. of Chile

Camila Romero (MsC)
- Subject: Minimal time crisis problem for Lotka-Volterra prey-predator model.
- Date: from Jan 2015 until Mar 2015
- Institution: Univ. of Chile

8.4.2. Visits to International Teams

8.4.2.1. Research stays abroad

B. Cloez has spent one month in Switzerland at Univ. Neuchâtel and at CIB-EPFL, Lausanne.

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific events organisation

9.1.1.1. Member of the organizing committees

The team has co-organized with UMR Eco& Sols a one-week Research School on resources-consumers models, in September 2015 (see https://team.inria.fr/modemic/fr/francais-ecole-chercheur-modeles-ressources-consommateurs/). The objectives of the school were

- filling the gap between lectures on dynamical population models given in theoretical ecology and the ones given in bioprocess or biochemical engineering,
- gathering biologists from different application fields (food fermentation, farming, marine ecosystems...) and mathematicians, about models that couple biotic and abiotic compartments.

Another similar school is scheduled in 2016, and we plan to propose later a methodological network on this subject.

9.1.2. Scientific events selection

9.1.2.1. Reviewer

European Control Conference, IEEE Conference on Decision and Control, International Conference on System Theory, Control and Computing, Mediterranean Conference on Control and Automation.

9.1.3. Journal

9.1.3.1. Reviewer - Reviewing activities

Applied Mathematical Modelling, Automatica, Biotechnology & Bioengineering, Continuous and Distributed Systems, Computational and Applied Mathematics, European J. of Control, J. of Dynamical and Control Systems, J. of Process Control, J. of Membrane Science, Mathematical Biosciences and Engineering, SIAM J. on Optimization & Control.

9.1.4. Invited talks

Alain Rapaport has been invited to give a plenary session at the next CMPDE'16 (Conference in Mathematical Population Dynamics and Epidemiology), Marseille, Sep 2016.

9.1.5. Scientific expertise

Jérôme Harmand has been a member of the selection commitee for the recutement of a Junior Professor ("Maître de Conférences") at University Montpellier.

Alain Rapaport has been a member of the HCERES evaluation panel of the CHRONO-ENVIRONNEMENT research unit, Jan. 2016.

9.1.6. Research administration

J. Harmand is member of the steering committee of the Inra meta-program 'MEM' (Metagenomics of Microbial Ecosystems), and member of the INRA evaluation committee "commission scientifique spécialisée" STEA.

A. Rapaport is member of the scientific committee of BIOS dept. of CIRAD, and is member of the scientific committee of Ecotechnologies department of Irstea.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Engineering degree

B. Cloez and A. Rapaport, “Introduction à la modélisation”, 12 hours, 1st year, SupAgro Montpellier.

Master

T. Bayen and A. Rapaport, “Commande optimale: conditions nécessaires et suffisantes”, 21 hours, Master 2R ’MANU’ (Modélisation et Analyse Numérique), Univ. Montpellier.

PhD

T. Bayen and A. Rapaport have proposed a new doctoral module on control, observation and optimization tools for modelling (24 hours) that will be launched in March 2016 at the Doctoral School ’I2S’ (Information, Structures, System), Univ. Montpellier.

9.2.2. Supervision

Guilherme Pimentel

PhD: Modélisation dynamique, analyse et supervision d’un réacteur membranaire.

cotutelle Univ. Montpellier II/Univ. Mons (Belgique), defended in Feb. 2015.

Advisors: A. VandeWouver (Univ. Mons) and A. Rapaport.

Sonia Hassam

PhD: Réduction de modèles biotechnologiques : application à la digestion anaérobie.

Univ. Tlemcen, defended in Dec. 2015.

Advisors: B. Cherki (Univ. Tlemcen) and J. Harmand.

Amel Ghouali

PhD: Analyse et commande optimale d’un bioréacteur de dépollution des eaux usées

cotutelle Univ Montpellier II/Univ. Tlemcen (Algeria), defended in Dec. 2015.

Advisors: J. Harmand and T. Sari (UMR ITAP, Montpellier).

Walid Bouhafs

PhD in progress: Commande optimale des réacteurs biologiques séquentiels discontinus.

ENIT (Tunis), since 2010.

Advisors: N. Abdellatif (ENIT-LAMSIN, Tunis), F. Jean (ENSTA) and J. Harmand.

Victor Riqueleme

PhD in progress: Commande optimale pour la préservation de ressources hydriques exploitées.

cotutelle Univ. Montpellier II/Univ. Chile, since Sept. 2013.

Advisors: H. Ramirez (Univ. Chile) and A. Rapaport.

Alejandro Rojas-Palma

PhD in progress: Etude de quelques problèmes dans la modélisation et l’optimisation de bioprocédés.

cotutelle Univ. Montpellier II/Univ. Chile, since Sept. 2014.

Advisors: H. Ramirez (Univ. Chile) and A. Rapaport.

Yessmine Daoud

PhD in progress: Analyse de modèles de la digestion anaérobie : application à l’optimisation de la production du biogaz.

cotutelle ENIT (Tunis)-Univ. Montpellier II, since sep. 2014.

Advisors: N. Abdellatif (ENIT, Tunis) and J. Harmand.

Zeyneb Khedim

PhD in progress: Modélisation et contrôle de la digestion anaérobie : vers une meilleure prise en compte des phénomènes d'inhibition.

cotutelle Univ. Tlemcen - Univ. Montpellier II, since nov. 2014.

Advisors: B. Benyahia (Univ. Tlemcen) and J. Harmand.

Anne Bisson

PhD in progress: Modélisation probabiliste du fonctionnement d'écosystèmes considérés comme des assemblages de communautés.

Univ. Montpellier II, since Dec. 2014 until Sep 2015

Advisors: B. Jaillard (UMR Eco & Sols, Montpellier) and A. Rapaport.

Maha Hmissi

PhD in progress: Contribution a l'élaboration d'un modèle de simulation d'un procédé de biomethanisation- Application a la digestion des boues résiduaires et au prétraitement d'un effluent industriel

ENIT, Tunsia, since 2011

Advisors: Hedi Shayeb (ENIT) and J. Harmand

Nesrine Kalboussi

PhD in progress: Détection précoce et contrôle du colmatage dans les réacteurs à membranes

INSAT, Tunisia, since 2014

Advisors: Nihel Benamar (INSAT) et J. Harmand

The team has supervised MsC and Engineering School internships [50], [44].

9.2.3. Juries

S. Martin. "D'oxymore en oxymore : du développement durable au contrôle complexe." Habilitation à diriger des recherches, Univ. B. Pascal (Clermont-Ferrand), Jan 2015 (referee : A. Rapaport).

J. Qian. "Identification paramétrique en boucle fermée par une commande optimale basée sur l'analyse d'observabilité." Thèse de doctorat, Univ. C. Bernard (Lyon), Sep 2015 (examinator : A. Rapaport).

N. Lebaz "Modélisation de l'hydrolyse enzymatique de substrats lignocellulosiques pat bilan de population" Thèse de Doctorat, Université Toulouse, Sep 2015 (referee : A. Rapaport).

A. Hammoudi "Modélisation et analyse mathématique de la dynamique du carbone organique dans le sol" Thèse de Doctorat, Université Montpellier, Sep 2015 (examinator : A. Rapaport).

M. Diaby "Analyse globale de quelques modèles épidémiologiques: application à des modèles de la bilharziose" Thèse de Doctorat, Université Gaston Berger (Saint-Louis du Sénégal), Jan 2016 (referee : A. Rapaport).

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Major publications by the team in recent years

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Doctoral Dissertations and Habilitation Theses

[11] G. Araujo Pimentel. *Nonlinear Modeling, Identification and Control of Membrane Bioreactors*, Université Montpellier 2, February 2015, https://hal.inria.fr/tel-01130312

[12] A. Ghouali. *Analyse et contrôle optimal d'un bioréacteur de digestion anaérobie*, Université de Montpellier et Université de Tlemcen (Algérie), December 2015, https://hal.archives-ouvertes.fr/tel-01245124

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