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Activity Report 2017

Project-Team BIOCORE

Biological control of artificial ecosystems

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Modeling and Control for Life Sciences

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Project-Team BIOCORE

Creation of the Project-Team: 2011 January 01

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1. Personnel

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2. Overall Objectives

2.1. Introduction

BIOCORE is a joint research team between Inria (Centre of Sophia-Antipolis Méditerranée), INRA (ISA - Institut Sophia Agrobiotech and LBE - Laboratory of Environmental Biotechnology in Narbonne) and UPMC-CNRS (Oceanographic Laboratory of Villefranche-sur-mer - LOV, UMR 7093/ Université P.M. Curie, Villefranche sur Mer, Team: Processes in Pelagic Ecosystems - PEPS).

Sustainable growth of living organisms is one of the major challenges of our time. In order to tackle it, the development of new technologies is necessary, and many of these new technologies will need to use modeling and computer tools. BIOCORE contributes to this theme, in the general field of design and control of artificial ecosystems (or biosystems). Its general goal is to design devices, systems and processes containing living cells or individuals and performing some tasks to decrease pollution, use of chemicals, or to produce bioenergy in a sustainable way. We build biological/ecological models in close collaborations with biologists and bioprocess engineers, and validate them with experimental platforms. Our activities are structured in three levels: mathematical and computational methods, a methodological approach to biology, and applications.

Research themes:

Mathematical and computational methods:

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

A methodological approach to biology: system study at different scales

- At the intra-individual level: theoretical and experimental study of simple metabolic-genetic networks, coarse grained models of the internal state.
- At the level of interactions between individuals in the population: individual behavior, resource allocation.
- At the scale of interaction between populations: interaction between prey and predator populations in a trophic network or competition between species in a chemostat.
- At the scale of interaction between ecosystems: coupling of two artificial ecosystems as a unique bioprocess or interactions between an artificial ecosystem and the surrounding natural ecosystem.

Fields of application:

- Bioenergy, in particular the production of lipids (which can be used as biofuel), methane and hydrogen by microorganisms (with LOV and LBE).
- CO2 fixation by micro-algae, with the aim of capturing industrial CO2 fluxes (with LOV). This theme can also include artificial ecosystems developed to improve the prediction of carbon fluxes between the ocean and the atmosphere.
- Design and optimization of ecologically friendly protection methods for plants and micro-plants artificial production systems (with ISA and LOV). This theme focuses in particular on biological control programs to control pathogens and pest invasions in crops and bioreactors.
- Biological waste treatment with microorganisms in bioreactors to reduce pollution emission levels (in collaboration with LBE).

Software for biological modeling and supervision of biological processes.

National, international and industrial relations

- National collaborations: IFREMER (Nantes), INRA (MISTEA Montpellier, BIOGER Grignon. IAM Nancy, Agrocampus Ouest, MaIAGE Jouy-en-en-Josas, BioEpAR Nantes), CIRAD Montpellier, Institut Méditerranéen d'Océanologie, LOCEAN (Paris), GIPSA Grenoble, IBIS, BANG, and ANGE Inria teams.
- Participation in French groups: ModStatSAP (Modélisation et Statistique en Santé des Animaux et des Plantes), GDR Invasions Biologiques.
- Participation to national programmes: ANR projects Phycover, FunFit, ICycle, and Maximic, ANR *BioME* projects Facteur 4 and Purple Sun, *Projet d'Investissement d'Avenir* RESET, UMT Fiorimed, and Labex SIGNALIFE.
- International collaborations: Université Catholique de Louvain (Belgium), Université de Mons (Belgium), University of Stuttgart (Germany), Rutgers University (USA), MacMaster University (Canada), University Ben Gurion (Israel), Imperial College (United-Kingdom), Massey University (New Zealand), Universidad Tecnica Federico Santa Maria and Universidad de Chile (Chile), Roslin Institute / University of Edinburgh (UK).

3. Research Program

3.1. Mathematical and computational methods

BIOCORE's action is centered on the mathematical modeling of biological systems, more particularly of artificial ecosystems, that have been built or strongly shaped by human. Indeed, the complexity of such systems where life plays a central role often makes them impossible to understand, control, or optimize without such a formalization. Our theoretical framework of choice for that purpose is Control Theory, whose central concept is "the system", described by state variables, with inputs (action on the system), and outputs (the available measurements on the system). In modeling the ecosystems that we consider, mainly through ordinary differential equations, the state variables are often population, substrate and/or food densities, whose evolution is influenced by the voluntary or involuntary actions of man (inputs and disturbances). The outputs will be some product that one can collect from this ecosystem (harvest, capture, production of a biochemical product, etc), or some measurements (number of individuals, concentrations, etc). Developing a model in biology is however not straightforward: the absence of rigorous laws as in physics, the presence of numerous populations and inputs in the ecosystems, most of them being irrelevant to the problem at hand, the uncertainties and noise in experiments or even in the biological interactions require the development of dedicated techniques to identify and validate the structure of models from data obtained by or with experimentalists.

Building a model is rarely an objective in itself. Once we have checked that it satisfies some biological constraints (eg. densities stay positive) and fitted its parameters to data (requiring tailor-made methods), we perform a mathematical analysis to check that its behavior is consistent with observations. Again, specific methods for this analysis need to be developed that take advantage of the structure of the model (eg. the interactions are monotone) and that take into account the strong uncertainty that is linked to life, so that qualitative, rather than quantitative, analysis is often the way to go.

In order to act on the system, which often is the purpose of our modeling approach, we then make use of two strong points of Control Theory: 1) the development of observers, that estimate the full internal state of the system from the measurements that we have, and 2) the design of a control law, that imposes to the system the behavior that we want to achieve, such as the regulation at a set point or optimization of its functioning. However, due to the peculiar structure and large uncertainties of our models, we need to develop specific methods. Since actual sensors can be quite costly or simply do not exist, a large part of the internal state often needs to be re-constructed from the measurements and one of the methods we developed consists in integrating the large uncertainties by assuming that some parameters or inputs belong to given intervals. We then developed robust observers that asymptotically estimate intervals for the state variables [61]. Using the directly measured variables and those that have been obtained through such, or other, observers, we then develop control methods that take advantage of the system structure (linked to competition or predation relationships between species in bioreactors or in the trophic networks created or modified by biological control).

3.2. A methodological approach to biology: from genes to ecosystems

One of the objectives of BIOCORE is to develop a methodology that leads to the integration of the different biological levels in our modeling approach: from the biochemical reactions to ecosystems. The regulatory pathways at the cellular level are at the basis of the behavior of the individual organism but, conversely, the external stresses perceived by the individual or population will also influence the intracellular pathways. In a modern “systems biology” view, the dynamics of the whole biosystem/ecosystem emerge from the interconnections among its components, cellular pathways/individual organisms/population. The different scales of size and time that exist at each level will also play an important role in the behavior of the biosystem/ecosystem. We intend to develop methods to understand the mechanisms at play at each level, from cellular pathways to individual organisms and populations; we assess and model the interconnections and influence between two scale levels (eg., metabolic and genetic; individual organism and population); we explore the possible regulatory and control pathways between two levels; we aim at reducing the size of these large models, in order to isolate subsystems of the main players involved in specific dynamical behaviors.

We develop a theoretical approach of biology by simultaneously considering different levels of description and by linking them, either bottom up (scale transfer) or top down (model reduction). These approaches are used on modeling and analysis of the dynamics of populations of organisms; modeling and analysis of small artificial biological systems using methods of systems biology; control and design of artificial and synthetic biological systems, especially through the coupling of systems.

The goal of this multi-level approach is to be able to design or control the cell or individuals in order to optimize some production or behavior at higher level: for example, control the growth of microalgae via their genetic or metabolic networks, in order to optimize the production of lipids for bioenergy at the photobioreactor level.

4. Application Domains

4.1. Bioenergy

Finding sources of renewable energy is a key challenge for our society. We contribute to this topic through two main domains for which a strong and acknowledged expertise has been acquired over the years. First, we consider anaerobic digesters, the field of expertise of the members of the team at the Laboratory of Enviromental Biotechnology (LBE), for the production of methane and/or biohydrogen from organic wastes. The main difficulty is to make these processes more reliable and exploit more efficiently the produced biogas by regulating both its quality and quantity despite high variability in the influent wastes. One of the specific applications that needs to be tackled is the production of biogas in a plant when the incoming organic waste results from the mixing of a finite number of substrates. The development of control laws that optimize the input mix of the substrates as a function of the actual state of the system is a key challenge for the viability of this industry.

The second topic consists in growing microalgae, the field of expertise of the members of the team at the Oceanographic Laboratory of Villefranche-sur-Mer (LOV), to produce biofuel. These microorganisms can synthesize lipids with a much higher productivity than terrestrial oleaginous species. The difficulty is to better understand the involved processes, which are mainly transient, to stimulate and optimize them on the basis of modeling and control strategies. Predicting and optimizing the productivity reached by these promising systems in conditions where light received by each cell is strongly related to hydrodynamics, is a crucial challenge.

Finally, for the energy balance of the process, it is important to couple microalgae and anaerobic digestion to optimize the solar energy that can be recovered from microalgae, as was explored within the ANR Symbiose project (2009-2012) [3].

4.2. CO_2 fixation and fluxes

Phytoplanktonic species, which assimilate CO_2 during photosynthesis, have received a lot of attention in the last years. Microalgal based processes have been developed in order to mitigate industrial CO_2. As for biofuel productions, many problems arise when dealing with microalgae which are more complex than bacteria or yeasts. Several models have been developed within our team to predict the CO_2 uptake in conditions of variable light and nitrogen availability. The first modeling challenge in that context consists in taking temperature effects and light gradient into account.

The second challenge consists in exploiting the microalgal bioreactors which have been developed in the framework of the quantification of carbon fluxes between ocean and atmospheres. The SEMPO platform (simulator of variable environment computer controlled), developed within the LOV team, has been designed to reproduce natural conditions that can take place in the sea and to accurately measure the cells behavior. This platform, for which our team has developed models and control methods over the years, is an original and unique tool to develop relevant models which stay valid in dynamic conditions. It is worth noting that a better knowledge of the photosynthetic mechanisms and improved photosynthesis models will benefit both thematics: CO_2 mitigation and carbon fluxes predictions in the sea.

4.3. Biological control for plants and micro-plants production systems

This research concentrates on the protection of cultures of photosynthetic organisms against their pests or their competitors. The cultures we study are crop and micro-algae productions. In both cases, the devices are more or less open to the outside, depending on the application (greenhouse/field, photobioreactor/raceway), so that they may give access to harmful pathogens and invading species. We opt for protecting the culture through the use of biocontrol in a broad sense.

In crop production, biocontrol is indeed a very promising alternative to reduce pesticide use: it helps protecting the environment, as well as the health of consumers and producers; it limits the development of resistance (compared to chemicals)... The use of biocontrol agents, which are, generically, natural enemies (predators, parasitoids or pathogens) of crop pests [66], is however not widespread yet because it often lacks efficiency in real-life crop production systems (while its efficiency in the laboratory is much higher) and can fail to be economically competitive. Resistant crops are also used instead of pesticides to control pests and pathogens, but the latter eventually more or less rapidly overcome the resistance, so these crops need to be replaced by new resistant crops. As resistant genes are a potentially limited resource, a challenge is to ensure the durability of crop resistance. Our objective is to propose models that would help to explain which factors are locks that prevent the smooth transition from the laboratory to the agricultural crop, as well as develop new methods for the optimal deployment of the pests natural enemies and of crop resistance.

Microalgae production is faced with exactly the same problems since predators of the produced microalgae (e.g. zooplankton) or simply other species of microalgae can invade the photobioreactors and outcompete or eradicate the one that we wish to produce. Methods need therefore to be proposed for fighting the invading species; this could be done by introducing predators of the pest and so keeping it under control, or by controling the conditions of culture in order to reduce the possibility of invasion; the design of such methods could greatly take advantage of our knowledge developed in crop protection since the problems and models are related.

4.4. Biological depollution

These works will be carried out with the LBE , mainly on anaerobic treatment plants. This process, despite its strong advantages (methane production and reduced sludge production) can have several locally stable equilibria. In this sense, proposing reliable strategies to stabilize and optimise this process is a key issue. Because of the recent (re)development of anaerobic digestion, it is crucial to propose validated supervision algorithms for this technology. A problem of growing importance is to take benefit of various waste sources in order to adapt the substrate quality to the bacterial biomass activity and finally optimize the process. This generates new research topics for designing strategies to manage the fluxes of the various substrate sources meeting at the same time the depollution norms and providing a biogas of constant quality. In the past years, we have developed models of increasing complexity. However there is a key step that must be considered in the future: how to integrate the knowledge of the metabolisms in such models which represent the evolution of several hundreds bacterial species? How to improve the models integrating this two dimensional levels of complexity? With this perspective, we wish to better represent the competition between the bacterial species, and drive this competition in order to maintain, in the process, the species with the highest depollution capability. This approach, initiated in [71] must be extended from a theoretical point of view and validated experimentally.

5. Highlights of the Year

5.1. Highlights of the Year

- Determining ways of preventing the appearance of virulent pathogenic strains that are capable of infecting resistant plants is crucial to the durability of a resistant trait as a crop protection method. Genetic drift could be used in such a way by eliminating initially rare resistant breaking pathogens, but it is necessary to quantify this drift in the considered/developed plant strains to know if it can be of any help. In this work, we developed a method to disentangle the relative role of genetic drift and selection during within-host pathogen evolution, by the development and identification of the parameters of a Wright-Fisher model, based on time-series of the frequencies of the various pathogen variants [31].
- We have proposed a metabolic model [15] of the diauxic growth of microalgae on different substrates. The model, with 172 metabolic reactions is derived using the Drum approach [2]. This model was successfully validated for a broad variety of cases where algae grow under heterotrophic, autotrophic or mixotrophic conditions, and the transient accumulation of metabolites.

6. New Software and Platforms

6.1. In@lgae

Numerical simulator of microalgae based processes
KEYWORDS: Simulation - Microalgae system - Productivity
FUNCTIONAL DESCRIPTION: In@lgae simulates the productivity of a microalgae production system, taking into account both the process type and its location and time of the year. The process is mainly defined by its thermal dynamics and by its associated hydrodynamics. For a given microalgal strain, a set of biological parameters describe the response to nitrogen limitation, temperature and light. As a result, the biomass production, CO_2 and nitrogen fluxes, lipid and sugar accumulation are predicted.

RELEASE FUNCTIONAL DESCRIPTION: The In@lgae platform has been optimised to make it faster. Some of the key models have been rewritten in C++ to allow a faster computation. Models have been improved to include, in the growth rate computation, the composition of the light spectrum. The graphical user interface has been enhanced and several sets of parameters describing different microalgal species have been stored.

- Participants: Étienne Delclaux, Francis Mairet, Olivier Bernard and Quentin Béchet
- Contact: Olivier Bernard

6.2. Odin

Platform for advanced monitoring, control and optimisation of bioprocesses

KEYWORDS: Bioinformatics - Biotechnology - Monitoring - Automatic control
SCIENTIFIC DESCRIPTION: This C++ application enables researchers and industrials to easily develop and deploy advanced control algorithms through the use of a Scilab interpreter. It also contains a Scilab-based process simulator which can be harnessed for experimentation and training purposes. ODIN is primarily developed in the C++ programming language and uses CORBA to define component interfaces and provide component isolation. ODIN is a distributed platform, enabling remote monitoring of the controlled processes as well as remote data acquisition.It is very modular in order to adapt to any plant and to run most of the algorithms, and it can handle the high level of uncertainties that characterises the biological processes through explicit management of confidence indexes.
FUNCTIONAL DESCRIPTION: ODIN is a software framework for bioprocess control and supervision. ODIN is a distributed platform, where algorithms are described with a common structure easy to implement. Finally, ODIN can perform remote data acquisition and process these data to compute the signals to be applied to the actuators, together with estimates of state variables or process state. ODIN can handle the high level of uncertainties that characterises the biological processes through explicit management of confidence indexes.

- Participants: Fabien Dilet, Florian Guenn, Francesco Novellis, Mathieu Lacage, Melaine Gautier, Olivier Bernard, Olivier Calabro, Romain Primet and Serigne Sow
- Contact: Olivier Bernard
- URL: https://team.inria.fr/biocore/software/odin/

7. New Results

7.1. Mathematical methods and methodological approach to biology

7.1.1. Mathematical analysis of biological models

7.1.1.1. Mathematical study of semi-discrete models

Participants: Frédéric Grognard, Ludovic Mailleret, Pierre Bernhard, Nicolas Bajeux, Bapan Ghosh.

Semi-discrete models have shown their relevance in the modeling of biological phenomena whose nature presents abrupt changes over the course of their evolution [67]. We used such models and analyzed their properties in several practical situations that are developed in Section 7.2.3, some of them requiring such a modeling to describe external perturbations of natural systems, and others to take seasonality into account. External perturbations of interacting populations occur when some individuals are introduced or removed from a natural system, which occurs frequently in pest control applications, either through the direct removal of pests, through the introduction of artificial habitats for the predatores or through the introduction of biological control agents in deterministic [13] or stochastic fashion. This was the main topic of Nicolas Bajeux's PhD thesis [11].

Seasonality is an important property of most agricultural systems in temperate environments since the year is divided into a cropping season and a 'winter' season, where the crop is absent, as in the study of the durability of plant resistance to root-knot nematodes [28], [41].

7.1.1.2. Model reduction and sensitivity analysis

Participants: Suzanne Touzeau, Jean-Luc Gouzé, Stefano Casagranda, Valentina Baldazzi.

Analysis and reduction of biochemical models. Dynamic models representing complex biological systems with numerous interactions can reach high dimensions and include complex nonlinearities. A model reduction method based on process weighing and pruning was developed [57] and implemented on various models [39]. A global sensitivity analysis was performed to check the method robustness against parameter uncertainty and variability. A more general method robust to initial conditions has been elaborated. This work was part of Stefano Casagranda's PhD thesis [12] and is also a collaboration with Bayer (Sophia-Antipolis).

7.1.1.3. Estimation and control

Participants: Suzanne Touzeau, Natacha Go, Jean-Luc Gouzé.

Parameter identification in complex systems. In complex biological systems, especially when data are scarce, identifying the model parameters is a challenge and raises identifiability issues. So we developed a specific ABC-like method, less computationally expensive than standard Bayesian fitting procedures such as ABC [6]. We used this method to fit a within-host immunological model to a large data set of individual viremia profiles. Our aim was not to reproduce individual profiles, but to identify several parameter sets compatible with the data and reflecting the variability among individuals. So we based our fitting criterion on viral indicators rather than the whole viremia dynamics [44]. This work was part of Natacha Go's post-doctorate, supported by the MIHMES project, in collaboration with the Roslin Institute, Edinburgh, UK. It benefited from the resources and support of NEF computation cluster.

Parameter identification in compartmental systems. In collaboration with F. Dayan (Exactcure), we work on practical problems of identifiability of parameters in linear pharmacokinetic models. This was the subject of the internship of Laurent Dragoni.

7.1.2. Metabolic and genomic models

Participants: Jean-Luc Gouzé, Madalena Chaves, Olivier Bernard, Valentina Baldazzi, Stefano Casagranda, Francis Mairet, Ivan Egorov, Sofia Almeida, Claudia Lopez Zazueta, Lucie Chambon, Luis Gomes Pereira, Eleni Firippi, Ignacio Lopez Munoz.

7.1.2.1. Hybrid models analysis

Applying differential dynamic logic to biological networks. In [26] we have explored the framework of differential dynamic logic for the analysis of hybrid systems and, in particular, piecewise linear models of biological networks (collaboration with D. Figueiredo and M.A. Martins from the University of Aveiro, Portugal).

Attractor computation using interconnected Boolean networks. Following the work in [10] and [58], we have generalized the method for computation of the asymptotic graph. In addition, we have extended this methodology for the case of Boolean networks with synchronous updates (collaboration with D. Figueiredo and M.A. Martins from the University of Aveiro, Portugal).

Periodic orbits in non monotonic negative feedback circuits. We study the occurrence of periodic solutions in an n-dimensional class of negative feedback systems defined by smooth vector fields with a window of not necessarily monotonic activity. By circumscribing the smooth system by two piecewise linear ones, we show there exists an invariant toroidal region which contains a periodic orbit of the original smooth system [9]. We prove that this orbit is unique under some conditions on the parameters.

7.1.2.2. Continuous models analysis

Reduced models for the mammalian cell cycle and clock. In the context of project ANR ICycle, we have focused on identifying and analysing the main mechanisms underlying the cell cycle and the circadian clock in mammalian cells. A reduced two-dimensional model of the cell cycle is described [38]; the model faithfully predicts the period of the cell cycle in response to an external growth factor input (experimental data on the periods is from F. Delaunay's lab). This work is in collaboration with F. Delaunay and part of the PhD thesis of Sofia Almeida.

Interconnection of reduced models of the mammalian cell cycle and clock. Also in the context of project ANR ICycle, we have studied several possibilities for the interconnection between these two mammalian oscillators, using the reduced model already described in [38] and two different possible oscillatory circuits of low dimension. This work is part of the Master's thesis of Eleni Firippi.

Modeling the apoptotic signaling pathway. The goal is to study the origins of cell-to-cell variability in response to anticancer drugs and provide a link between complex cell signatures and cell response phenotype [45]. To do this, we have been analysing models of the apoptosis pathway to compare the effects of different sources of variability at the transcriptional, translational and receptor levels (collaboration with J. Roux, for the PhD thesis of Luis Pereira).

Transcription and translation models in bacteria. We study detailed models of transcription and translation for genes in a bacterium, in particular the model of gene expression of RNA polymerase [17]. We also study other models of the global cellular machinery, and growth models ([22]). This is part of the PhD thesis of Stefano Casagranda, and done in collaboration with Inria IBIS project-team, in particular with D. Ropers.

Analysis and reduction of a model of sugar metabolism in peach fruit. Predicting genotype-to-phenotype relationships under contrasting environments is a big challenge for plant biology and breeding. A model of sugar metabolism in peach fruit has been recently developed and applied to 10 peach varieties [25]. The aim of this ongoing work is to reduce model's size and complexity to allow for calibration on a whole progeny of 106 genotypes and for further application to virtual breeding (collaboration with B. Quilot-Turion and Mohamed Memmah (INRA Avignon) and part of the PhD thesis of Hussein Kanso).

Analysis of an integrated cell division-endoreduplication and expansion model. The development of a new organ depends on cell-cyle progression and cell expansion, but the interaction and coordination between these processes is still unclear. An integrated model of fruit development has been developed and used to investigate the regulation of cell expansion capabilities. To this aim, different control schemes are tested by means of specific model variants and simulation results compared to observed data in tomato [14].

7.1.2.3. Estimation and control

Optimal allocation of resources in a bacterium. We study by techniques of optimal control the optimal allocation between metabolism and gene expression during growth of bacteria, in collaboration with Inria IBIS project-team. We showed that a good suboptimal control solution could be implemented in the cell by ppGpp (a small molecule involved in the regulation of ribosomes) [5]. We developed different versions of the problem [43], [36], and consider a new problem where the aim is to optimize the production of a product (ANR projects Reset and Maximic).

Control of a model of synthesis of a virulence factor. In collaboration with J.-A. Sepulchre (INLN Nice), we model the production of a virulence factor by a bacterium in a continuous stirred tank reactor. The production of this enzyme is genetically regulated, and degrades a polymeric external substrate into monomers. A nonlinear control is built [32].

7.1.2.4. Large scale metabolic modeling

Metabolic modeling generally assumes balanced growth, *i.e.* that there is no accumulation of intermediate compound, and that the metabolism is rapidly at quasi steady state. We have proposed a new approach called DRUM where this hypothesis is relaxed by splitting the metabolic network into subnetworks and assuming that some compounds can accumulate between the subnetworks [2], [49]. This approach was successfully applied to several cases where the strong variations in light or nutrient resources induce a strong accumulation in the microalgal cells which could not be represented by the state of the art approaches [48]. More recently we have expended this approach to the modeling of diauxic growth for heterotrophic or mixotrophic microalgae [15].

7.1.2.5. Slow-Fast analysis of metabolic models

Metabolic modeling generally assumes balanced growth, *i.e.* that there is no accumulation of intermediate compound, and that the metabolism is rapidly at quasi steady state. We go beyond this hypothesis by considering that some metabolic reactions are slow, while other are fast. Then we analyse the differential system using Tikhonov's Theorem. We compare the results obtained using the Drum approach [2], and show that Drum is a reasonable approximation, provided that growth rate stays low. This is part of the PhD thesis of Claudia Lopez Zazueta.

7.2. Fields of application

7.2.1. Bioenergy

7.2.1.1. Modeling microalgae production

Participants: Olivier Bernard, Antoine Sciandra, Frédéric Grognard, Walid Djema, Ignacio Lopez Munoz, David Demory, Ouassim Bara, Jean-Philippe Steyer.

Experimental developments

Running experiments in controlled dynamical environments. The experimental platform made of continuous photobioreactors driven by a set of automaton controlled by the ODIN software is a powerful and unique tool which gave rise to a quantity of very original experiments. Such platform improved knowledge of several biological processes such as lipid accumulation or cell cycle under light fluctuation, etc. [55],[19].

This experimental platform was used to control the long term stress applied to a population of microalgae. This Darwinian selection procedure generated two new strains after more than 6 months in the so called selectiostats. A strain with $+92\%$ lipids was obtained, another more transparent resulting in $+92\%$ enhancement in productivity [18].

Other experiments were carried out to reproduce the light signal percept by a cell in a raceway pond [60], derived from hydrodynamical studies [64]. An electronic platform was developed to reproduce this high frequency light signal. The experiments show that the microalgae adapt their pigments to the average light that they have received [59]. Experiments with coloured light demonstrated that the growth rate results from the absorbed light, whatever its wavelength.

On top of this, we carried out outdoor pilot experiments with solar light. We tested the impact of various temperatures, resulting from different shadowing configurations on microalgal growth rate [56],[40]. This is the topic of Bruno Assis Pessi's master thesis.

These works have been carried out in collaboration with A. Talec and E. Pruvost (CNRS/UPMC - Oceanographic Laboratory of Villefranche-sur-Mer LOV).

Metabolism of carbon storage and lipid production. A metabolic model has been set up and validated for the microalgae *Isochrysis luthea*, on the basis of the DRUM framework , in order to simulate autotophic, heterotropic and mixotrophic growth, and to determine how to reduce substrate inhibition [15]. The model was extended for other substrates such as glucose or glycerol. A simplified model was developped by I. Lopez to represent the dynamics of polar lipids, especially when faced to a high oxygen concentration.

Modeling the coupling between hydrodynamics and biology. In collaboration with the Inria ANGE team, a model coupling the hydrodynamics of the raceway (based on a new multilayer discretisation of Navier-Stokes equations) with microalgae growth was developed [51]. This model is supported by the work of ANGE aiming at improving the discretization scheme to more finely represent the hydrodynamics of the raceway and more accurately reconstruct Lagrangian trajectories. The statistical analysis of both theoretical properties of probability densities for perfectly mixed systems and output of Lagrangian simulations demonstrate the accurate reconstruction of the trajectories. As a consequence, more relevant experimental protocols have been proposed to more realistically design simplified light signal for experiments.

Modeling photosynthetic biofilms. Several models have been developed to represent the growth of microalgae within a biofilm. A first structured physiological model uses mixture theory to represent the microalgae growth, based on the consideration of intracellular reserves triggering the processes of growth, respiration and excretion. We consider separately the intracellular storage carbon (lipids and carbohydrates) and the functional part of microalgae [29]. Another approach accounts for the dynamics of the light harvesting systems when cells are submitted to rapid successions of light and dark phases. A simpler model was developed and used to identify the optimal working mode of a process based on photosynthetic biofilm growing on a conveyor belt.

Modeling microalgae production processes. The integration of different models developed within BIOCORE [52] was performed to represent the dynamics of microalgae growth and lipid production in raceway systems.

Using these approaches, we have developed a model which predicts lipid production in raceway systems under varying light, nutrients and temperature [72]. A simplified version of this model, describing microalgal growth under varying light and temperature conditions predicts microalgal productivity in the perspective of large scale biofuel production [23].

In the framework of the ANR project Purple Sun, we developed a thermal model of a raceway pond within a greenhouse in order to estimate the culture temperature. We also included in the microalgae model the effect of light wavelength. This model has been calibrated on experimental data from LOV and has been used to support lighting strategy in order to optimize microalgal productivity (a patent on this process has been submitted). We have shown in [40] that a control strategy based on shadowing with solar panel can significantly improve productivity, especially during the early growth stage of the culture.

A procedure for rapid outdoor model calibration, from lab data, has been proposed and applied to the microalgae *Dunaliella salina* [56].

Modeling thermal adaptation in microalgae. We have studied several models of microalgae growth to different temperatures [27]. In particular, we have detailed the impact of higher temperatures on cell mortality [20]. Experiments have been carried out in collaboration with A.-C. Baudoux (Biological Station of Roscoff) in order to study growth of various species of the microalgae genus *Micromonas* at different temperatures. After calibration of our models, we have shown that the pattern of temperature response is strongly related to the site where cells were isolated. We derived a relationship to extrapolate the growth response from isolation location. With this approach, we proved that the oceanwide diversity of *Micromonas* species is very similar to the oceanwide diversity of the phytoplankton. We have used Adaptive Dynamics theory to understand how temperature drives evolution in microalgae. We could then predict the evolution of this biodiversity in a warming ocean and show that phytoplankton must be able to adapt within 1000 generation to avoid a drastic reduction in biodiversity.

Modeling viral infection in microalgae. Experiments have been carried out in collaboration with A.-C. Baudoux (Biological Station of Roscoff) in order to study the impact of viral infections on the development of populations of *Micromonas* at different temperatures. This work revealed a qualitative change in viral infection when temperature increases. A model was developed to account for the infection of a *Micromonas* population, with population of susceptible, infected and also free viruses. The model turned out to accurately reproduce the infection experiments at various temperatures, and the reduction of virus production above a certain temperature [24].

7.2.1.2. Control and Optimization of microalgae production

Optimization of the bioenergy production systems. A model predictive control approach was run based on simple microalgae models coupled with thermal physical models. Optimal operation in continuous mode for outdoor cultivation was determined when allowing variable culture depth. Assuming known weather forecasts considerably improved the control efficiency [23].

Interactions between species. We had formerly proposed an adaptive controller which regulates the light at the bottom of the reactor [70]. When applied for a culture with n species, the control law allows the selection of the strain with the maximum growth rate for a given range of light intensity. This is of particular interest for optimizing biomass production as species adapted to high light levels (with low photoinhibition) can be selected. We have also proposed a strategy based on light stresses in order to penalize the strains with a high pigment content and finally select microalgae with a low Chlorophyll content [69]. This characteristic is of particular interest for maximizing biomass production in dense culture. The strategy has been carried out at the LOV and eventually the productivity of *Tisochrysis lutea* was improved by 75%. A patent on this strategy has been submitted.

Strategies to improve the temperature response have also been studied. We modelled the adaptive dynamics for a population submitted to a variable temperature [62]. This was used at the LOV to design experiments with periodic temperature stresses during 200 days aiming at enlarging the thermal niche of *Tisochrysis lutea*. It resulted in an increase by 2 degrees of the thermal niche [18].

Finaly, optimal strategies when selecting the strain of interest within a set of n species competing for the same substrate has been proposed [16].

7.2.2. Biological depollution

7.2.2.1. Control and optimization of bioprocesses for depollution

Participants: Olivier Bernard, Carlos Martinez Von Dossow, Jean-Luc Gouzé.

Although bioprocesses involve an important biodiversity, the design of bioprocess control laws are generally based on single-species models. In [68], we have proposed to define and study the multispecies robustness of bioprocess control laws: given a control law designed for one species, what happens when two or more species are present? We have illustrated our approach with a control law which regulates substrate concentration using measurement of growth activity. Depending on the properties of the additional species, the control law can lead to the correct objective, but also to an undesired monospecific equilibrium point, coexistence, or even a failure point. Finally, we have shown that, for this case, the robustness can be improved by a saturation of the control.

7.2.2.2. Coupling microalgae to anaerobic digestion

Participants: Olivier Bernard, Antoine Sciandra, Jean-Philippe Steyer, Frédéric Grognard, Carlos Martinez Von Dossow.

The coupling between a microalgal pond and an anaerobic digester is a promising alternative for sustainable energy production and wastewater treatment by transforming carbon dioxide into methane using light energy. The ANR Phycover project is aiming at evaluating the potential of this process [74].

We have proposed several models to account for the biodiversity in the microalgal pond and for the interaction between the various species. These models were validated with data from the Saur company. More specifically, we have included in the miroalgae model the impact of the strong turbidity, and derived a theory to better understand the photolimitation dynamics especially when accounting for the photo-inhibition in the illuminated periphery of the reactor. Optimal control strategies playing with the dilution rate, shadowing or modifying depth were then studied [40].

7.2.2.3. Life Cycle Assessment

Participants: Olivier Bernard, Jean-Philippe Steyer, Marjorie Alejandra Morales Arancibia.

Environmental impact assessment. In the sequel of the pioneering life cycle assessment (LCA) work of [65], we continued to identify the obstacles and limitations which should receive specific research efforts to make microalgae production environmentally sustainable.
We studied a new paradigm to improve the energy balance by combining biofuel production with photovoltaic electricity. This motivated the design of the purple sun ANR-project where electricity is produced by semi transparent photovoltaic panels [50] under which photosynthetic microalgae are growing. The LCA of a greenhouse with, at the same time, photovoltaic panels and low emissivity glasses is studied. Depending on the period of the year, changing the species can both improve productivity and reduce environmental footprint.

This work is the result of a collaboration with Arnaud Helias of INRA-LBE (Laboratory of Environmental Biotechnology, Narbonne) and Pierre Collet (IFPEN).

7.2.3. Design of ecologically friendly plant production systems

7.2.3.1. Controlling plant arthropod pests

Participants: Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Nicolas Bajeux, Bapan Ghosh.

Optimization of biological control agent introductions. The question of how many and how frequently natural enemies should be introduced into crops to most efficiently fight a pest species is an important issue of integrated pest management. The topic of optimization of natural enemies introductions has been investigated for several years [66], [73], unveiling the crucial influence of within-predator density dependent processes. Since some natural enemies may be more prone to exhibit positive density dependent dynamics rather than negative ones, we studied the impact of positive predator-predator interactions on the optimal biological control introduction strategies [13]. Extension of this result have been performed to take into account stochasticity by develeoping a master equation for the combined continuous-stochastic process and a purely stocastic model. This last part of N. Bajeux's PhD thesis mycitePhD:bajeux was performed in collaboration with Vincent Calcagno (ISA).

Characteristics of space and the behavior and population dynamics of parasitoids. We studied the influence of space on the spread of biological control agents through computer simulations and laboratory experiments on *Trichogramma*. This is the topic of Marjorie Haond's PhD thesis (ISA, 2015-). In particular, we showed both theoretically and experimentally how habitat richness [63] shape the spatio-temporal dynamics of populations in spatially structured environments. This work is being performed in collaboration with Elodie Vercken (ISA) and Lionel Roques (BioSP, Avignon).

Model of coffee berry borer dynamics. We built a first model describing the coffee berry borer dynamics, in order to design efficient and sustainable control strategies, including alternative methods to pesticides (cropping practices, trapping, biological control). This single-season model is based on the insect life-cycle and includes the berry availability during a cropping season. Local and global stability results, the latter using Lyapunov functions, were obtained for both the pest-free and the endemic equilibria. Furthermore, this model was extended to integrate the berry maturation age. The well-posedness of the resulting PDE model was shown. This research pertains to Yves Fotso Fotso's PhD thesis, who visited BIOCORE during 4 months in 2017 in the framework of the EPITAG associate team.

7.2.3.2. Controlling plant pathogens

Participants: Frédéric Grognard, Ludovic Mailleret, Suzanne Touzeau, Julien Guégan, Yves Fotso-Fotso, Israel Tankam-Chedjou.

Sustainable management of plant resistance. We studied other plant protection methods dedicated to fight plant pathogens. One such method is the introduction of plant strains that are resistant to one pathogen. This often leads to the appearance of virulent pathogenic strains that are capable of infecting the resistant plants.

Experiments were conducted in INRA Avignon, followed by high-throughput sequencing (HTS) to identify the dynamics of virus strains competing within host plants. Different plant genotypes were chosen for their contrasted effects on genetic drift and selection they induce on virus populations. Those two evolutionary forces can play a substantial role on the durability of plant resistance. Therefore we fitted a mechanistic-statistical model to these HTS data in order to disentangle the relative role of genetic drift and selection during within-host virus evolution [31]. Also, the Quantitative Trait Loci (QTL) controlling viruses effective population sizes (linked to genetic drift) have been identified for two different viruses, showing the genetic origin of these parameters and the presence of general and virus specific QTLs [34]. This was done in collaboration with Frédéric Fabre (INRA Bordeaux) and Benoît Moury (INRA Avignon).

We also developed an epidemiological model describing the dynamics of root-knot nematodes in a protected vegetable cropping system, to design optimal management strategies of crop resistance. The model was fitted to experimental and field data. Preliminary results show that alternating susceptible and resistant crops not only increased the resistance durability, but reduced the disease intensity over time [28], [41]. This research pertains to Samuel Nilusmas' PhD thesis.

We developed and partly calibrated a (spatio-)temporal epidemiological model of the phoma stem canker of oilseed rape, to design sustainable resistance deployment strategies. Ongoing work includes the completion of this study and the development of a user-friendly simulation tool. It will be achieved through the MoGeR project, in collaboration with BIOGER (INRA Grignon) and partners from technical institutes and cooperatives. It benefits from the resources and support of NEF computation cluster.

Model of nematodes-plantain roots dynamics. We developed and analysed a seasonal model describing the interactions between nematodes and plantain roots, to design efficient and sustainable control strategies, including alternative methods to pesticides (cropping practices, resistant or tolerant banana cultivars, biological control). It is a doubly hybrid system, so as to take into account the plantain root growth. A slow-fast dynamics approximation was used to obtain local stability results for the pest-free equilibrium and exact solutions around this equilibrium. Conditions were derived for nematode extinction, depending in particular on the delay between cropping seasons. This research pertains to Israël Tankam Chedjou's PhD thesis, who visited BIOCORE during 4 months in 2017 in the framework of the EPITAG associate team.

Mate limitation and cyclic epidemics. We studied the effect of mate limitation in parasites which perform both sexual and asexual reproduction in the same host. Since mate limitation implies positive density dependence at low population density, we modeled the dynamics of such species with both density-dependent (sexual) and density-independent (asexual) transmission rates. A first simple SIR model incorporating these two types of transmission from the infected compartment, suggested that combining sexual and asexual spore production can generate persistently cyclic epidemics [30].

7.2.3.3. Optimality/games in population dynamics

Participants: Frédéric Grognard, Ludovic Mailleret, Pierre Bernhard, Ivan Egorov, Pierre-Olivier Lamare.

Optimal resource allocation. Mycelium growth and sporulation are considered for phytopathogenic fungi. For biotrophic fungi, a flow of resource is uptaken by the fungus without killing its host; in that case, life history traits (latency-sporulation strategy) have been computed based on a simple model considering a single spore initiating the mycelium, several spores in competition and applying optimal resource allocation [42], and several spores in competition through a dynamic game. The solution of this dynamic game has been shown to be the equilibrium of two-trait adaptive dynamics in Julien Guégan's internship. Also, the obtained sporulation strategy has been put in a PDE model to evaluate how the characteristics of the fungus evolve along a colonization gradient. This work, in the framework of the ANR Funfit project, is done with Fabien Halkett of INRA Nancy.

Dynamic games as a model of animal foraging. P. Bernhard has continued his investigations of dynamic games with randomly arriving players as a model of animal foraging and of competition in open markets. He has written the chapter "Robust Control and Dynamic Games"in the Handbook of Dynamic Games Theory [54].

7.3. Patents

Two patents were proposed for improving growth of microalgae with green light [53] and for enhancing the thermal niche after long term thermal stress in a continuous reactor [47].

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

BioEnTech: the collaboration with the BioEnTech start-up is aiming at developing new functionalities for ODIN in order to improve the advanced monitoring and control of industrial anaerobic digesters.

Inalve: with the Inalve start-up we develop a breakthrough process that we patented, in which microalgae grow within a moving biofilm. The objective of the collaboration is to optimize the process by enhancing productivity, while reducing environmental footprint.

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. National programmes

- **ANR-Purple Sun:** The objective of this project (ANR-13-BIME-004, 2013-2017) is to study and optimize a new concept consisting in coupling the production of microalgae with photovoltaic panels. The main idea is to derive the excess of light energy to PV electricity production, in order to reduce the phenomena of photoinhibition and overwarming both reducing microalgal productivity.

- **ANR-Facteur 4:** The objective of this project (2012-2017) is to produce non OGM strain of microalgae with enhanced performance. BIOCORE is involved in the directed selection of microalgae with interesting properties from an industrial point of view. The theory of competition is used to give a competitive advantage to some species. This competitive advantage can be provided by an online closed loop controller.
- **ANR-Phycover:** The overall objective of the PHYCOVER project (2014-2018) is to identify a modular wastewater treatment process for the production of biogas. The method combines three modules. First, a high-rate algal pond is dedicated to the treatment of municipal wastewater. Then, an anaerobic digester capable of co-digesting biomass products (and others organic matter resources) to significantly reduce biological and chemical contaminants while producing a sustainable energy as biogas is analysed. A final module transforms the residual carbon, nitrogen and phosphorus into high-value microalgae dedicated to aquaculture and green chemistry.
- **ITE-OPALE:** The goal of the Institut de la Transition Énergétique - OPALE project (2016-2019) is to increase the lipid content of microalgae by specific selection pressure. The project relies on the strain already selected during the Facteur 4 project, whose productivity was 4 times higher than the wild type. We expect to still increase strain performances up to 10 times the productivity of the wild type.
- **ANR-FunFit:** The objective of this project (2013-2018) is to develop a trait-based approach linking individual fitness of fungal plant pathogens to ecological strategies. The idea is to derive eco-epidemiological strategies from fitness optimization in colonized environments and during colonization, as well as understanding the coexistence of sibling species. This project is co-coordinated by F. Grognard.
- **ANR-TripTic:** The objective of this project (2014-2018) is to document the biological diversity in the genus of the minute wasps *Trichogramma*, and to study the behavioral and populational traits relevant to their use in biological control programs.
- **ANR-MIHMES:** “Multi-scale modeling, from animal Intra-Host to Metapopulation, of mechanisms of pathogen spread to Evaluate control Strategies”, ANR – Investissement d’avenir, action Bioinformatique (ANR-10-BINF-07) & Fond Européen de Développement Régional des Pays-de-la-Loire (FEDER), 2012–2017. This project aimed at producing scientific knowledge and methods for the management of endemic infectious animal diseases and veterinary public health risks. BIOCORE participated in this project via MaIAGE, INRA Jouy-en-Josas. This project supported Natacha Go’s postdoctoral position.
- **ANR-ICycle:** This project (2016-2020) aims at understanding the communication pathways between the cell division cycle and the circadian clock, using mathematical modeling and control theory to construct and implement two coupled synthetic biological oscillators. Project coordinated by M. Chaves.
- **ANR - Maximic:** The goal of the project (accepted in July 2017) is to design and implement control strategies in a bacterium from producing at maximal rate a high value product. It is coordinated by H. de Jong (IBIS Grenoble), and involves members of Biocore and McTao.
- **RESET:** The objective of this project (2012-2017) is to control the growth of *E. coli* cells in a precise way, by arresting and restarting the gene expression machinery of the bacteria in an efficient manner directed at improving product yield and productivity. RESET is an “Investissements d’Avenir” project in Bioinformatics (managed by ANR) and it is coordinated by H. de Jong (Ibis, Inria)
- **SIGNALIFE:** Biocore is part of this Labex (scientific cluster of excellence) whose objective is to build a network for innovation on Signal Transduction Pathways in life Sciences, and is hosted by the University of Nice Sophia Antipolis.
- **UMT FIORIMED:** FioriMed is a Mixed Technology Unit created in January 2015 to strengthen the production and dissemination of innovation to the benefit of ornamental horticulture. Horticultural greenhouses are seen as a "laboratory" for the actual implementation of agroecology concepts with

the possibility of generic outcomes being transfered to other production systems. The main partners of UMT FioriMed are ASTREDHOR (National Institute of Horticulture) and the ISA Joint Research Unit of INRA-CNRS-Univ. Nice.

- **AMIES-PEPS Exactcure:** The goal of the project is to study pharmacokinetic models, in collaboration with the start-up Exactcure (Nice). This funded the M2 internship of L. Dragoni.

9.1.2. Inria funding

- **Inria Project Lab, Algae** *in silico***:** (2014-2018) The Algae in silico Inria Project Lab, funded by Inria and coordinated by O. Bernard, focuses on the expertise and knowledge of biologists, applied mathematicians and computer scientists to propose an innovative numerical model of microalgal culturing devices. The latest developments in metabolic modeling, hydrodynamic modeling and process control are joined to propose a new generation of advanced simulators in a realistic outdoor environment. The project gathers 5 Inria project teams and 3 external teams.
- **Inria Project Lab, Cosy:** (2017-...) This proposal aims at exploiting the potential of state-of-art biological modeling, control techniques, synthetic biology and experimental equipment to achieve a paradigm shift in control of microbial communities. We will investigate, design, build and apply an automated computer-driven feedback system for control of synthetic microbial communities, not just accounting for but rather leveraging population heterogeneity in the optimal accomplishment of a population-level task. The development of methodologies of general applicability will be driven by and applied to two different applications closely connected with real-world problems in the biomedical and biotechnological industry. The consortium is composed of the four Inria project-teams IBIS, BIOCORE, COMMANDS, NON-A, the Inria Action Exploratoire INBIO, as well as the external partners BIOP (Université Grenoble Alpes, including members of IBIS), MaIAge (INRA), and YoukLAB (TU Delft). The project began in November.

9.1.3. INRA funding

- **MoGeR:** “From knowledge to modeling: towards a user-friendly simulation tool to test crop resistance management scenarios in the Phoma-oilseed rape case study”, INRA Metaprogramme SMaCH, 2017–2019. This is a follow-up of the K-Masstec project, which focused on sustainable strategies for the deployment of genetic resistance in the field, based on molecular knowledge on avirulence genes.
- **ABCD:** INRA SPE is funding the project ABCD "Augmentative Biological Control; optimizing natural ennemies Deployment" (2017-2019) in which Biocore is a partner with INRA Sophia Antipolis.

9.1.4. Networks

- **GDR Invasions Biologiques:** The objectives of this GDR are to encourage multidisciplinary research approaches on invasion biology. It has five different thematic axes: 1) invasion biology scenarios, 2) biological invasions and ecosystem functioning, 3) environmental impact of invasive species, 4) modeling biological invasions, 5) socio-economics of invasion biology. L. Mailleret is a member of the scientific comittee of the GDR .
- **ModStatSAP:** The objective of this INRA network is to federate researchers in applied mathematics and statistics and to promote mathematical and statistical modeling studies in crop and animal health. S. Touzeau is a member of the scientific committee.
- **Seminar:** BIOCORE organizes a regular seminar “Modeling and control of ecosystems” at the station zoologique of Villefranche-sur-Mer, at INRA-ISA or at Inria.

9.2. European Initiatives

9.2.1. Collaborations with Major European Organizations

Imperial college, Department of Chemical engineering (UK),

Modeling and optimization of microalgal based processes; with B. Chachuat.

Imperial College, Centre for Synthetic Biology and Innovation, Dept. of Bioengineering (UK):

Study of metabolic/genetic models; with D.A. Oyarzún.

University of Padova (Italy):

Modelling and control of microalgal production at industrial scale; with F. Bezzo.

University of Aveiro, Dept. of Mathematics (Portugal):

Hybrid models and boolean networks; with M.A. Martins.

9.3. International Initiatives

9.3.1. Inria International Labs

Inria Chile

Associate Team involved in the International Lab:

9.3.1.1. GREENCORE

Title: Modeling and control for energy producing bioprocesses

International Partners (Institution - Laboratory - Researcher):

- CIRIC (Chile) - Mélaine Gautier
- PUCV (Chile) - Escuela de Ingenieria Bioquimica (EIB) - David Jeison
- UTFSM (Chile) - Departamento de Matematica - Pedro Gajardo
- Univ. Chile (Chile) - Centro de modelacion matematica - Hector Ramirez

Inria coordinator: O. Bernard

Start year: 2017

See also: https://team.inria.fr/eagreencore/

The worldwide increasing energy needs together with the ongoing demand for CO2 neutral fuels represent a renewed strong driving force for the production of energy derived from biological resources. In this scenario, the culture of oleaginous microalgae for biofuel and the anaerobic digestion to turn wastes into methane may offer an appealing solution. The main objective of our proposal is to join our expertise and tools, regarding these bioprocesses, in order to implement models and control strategies aiming to manage and finally optimize these key bioprocesses of industrial importance. By joining our expertise and experimental set-up, we want to demonstrate that closed loop control laws can significantly increase the productivity, ensure the bioprocess stability and decrease the environmental footprint of these systems. This project gathers experts in control theory and optimization (BIOCORE, UTFSM) together with experts in bioprocesses (PUCV and CMM) and software development (CIRIC).

LIRIMA

Associate Team involved in the International Lab:

9.3.1.2. EPITAG

Title: Epidemiological Modeling and Control for Tropical Agriculture

International Partner (Institution - Laboratory - Researcher):

Université de Douala (Cameroon) - Mathematics Department - Samuel Bowong

Inria coordinator: S. Touzeau

Start year: 2017

See also: https://team.inria.fr/epitag/

EPITAG gathers French and Cameroonian researchers, with a background in dynamical systems and control and with an interest in crop diseases. Crop pests and pathogens are responsible for considerable yield losses. Their control is hence a major issue, especially in Cameroon, where agriculture is an important sector in terms of revenues and employment. To help design efficient strategies for integrated pest management, mathematical models are particularly relevant. Our main objective is to study the epidemiology and management of tropical crop diseases, with a focus on Cameroon and Sub-Saharan Africa. Our approach consists in developing and analysing dynamical models describing plant-parasite interactions, in order to better understand, predict and control the evolution of damages in crops. To ensure the relevance of our models, "end users" will be closely associated. We will focus on three pathosystems: cocoa plant mirids, coffee berry borers and plantain plant-parasitic nematodes.

9.3.2. Inria International Partners

9.3.2.1. Informal International Partners

Univ. Ben Gurion : Microalgal Biotechnology Lab (IL), Member of the ESSEM COST Action ES1408 European network for algal-bioproducts (EUALGAE). Modeling of photosynthesis.

9.3.3. Participation in Other International Programs

Biocore is involved in the IFCAM project, with India, PULSPOP "PULses in Spatial POPulation dynamics" (2016-2017) whose partners are Institut Sophia Agrobiotech and National Institute of Technology, Meghalya (India). This project financed the visit of Bapan Ghosh to ISA and BIOCORE, and the visit of Nicolas Bajeux to India.

9.4. International Research Visitors

9.4.1. Visits of International Scientists

- Claude Aflalo (Ben Gurion University of the Neguev, Israel), 6 months.
- Samuel Bowong (University of Douala, Cameroon), 5 days.
- Myriam Djoukwe Tapi (University of Douala, Cameroon), 1 week.
- Bapan Ghosh (National Institute of Technology Meghalaya, India), 1 month.
- Yves Fotso Fotso (University of Dschang, Cameroon), 4 months.
- Israël Tankam Chedjou (University of Yaoundé 1, Cameroon), 4 months.

9.5. Project-team seminar

BIOCORE organized a 4-day seminar in September in Porquerolles. On this occasion, every member of the project-team presented his/her recent results and brainstorming sessions were organized.

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events Organisation

10.1.1.1. General Chair, Scientific Chair

O. Bernard is the Chair of the next CAB conference (CAB 2019 in Brazil).

10.1.1.2. Member of the Organizing Committees

J.-L. Gouzé is a member of the scientific committee of several summer schools.

10.1.2. Scientific Events Selection

10.1.2.1. Member of the Conference Program Committees

O. Bernard is in the technical committee of the Computer Applied to Biotechnology (CAB) conferences, of the FOSBE conference (Foundations of Systems Biology in Engineering) and of the Algae Europe conference.

M. Chaves is a member of the program committee of JOBIM 2018 (Marseille).

J.-L. Gouzé is a member of the program committee for the conference POSTA (Italy, China).

10.1.2.2. Reviewer

All BIOCORE members have been reviewers for the major 2017 conferences in our field: CDC, ECC, IFAC World Congress,...

10.1.3. Journal

10.1.3.1. Member of the Editorial Boards

V. Baldazzi has been editor of the volume 1182 of Acta Horticulturae on the 'Proceedings of the V International Symposium on Models for Plant Growth, Environment Control and Farming Management in Protected Cultivation (Hortimodel2016)'.

M. Chaves is an Associated Editor of SIAM Journal on Applied Dynamical Systems (SIADS), since January 2015

10.1.3.2. Reviewer - Reviewing Activities

All BIOCORE members have been reviewers for the major journals in our field: Automatica, IEEE Transactions on Automatic Control, Journal of Mathematical Biology, Mathematical Biosciences, New Phytologist,...

10.1.4. Invited Talks

O. Bernard was invited to give a conference on microalgae at Ecole Centrale de Paris ("Biotechnological challenge") 'Use of microorganisms for biofuel production" (January, 16th, 2017).

O. Bernard was invited to do a presentation at the AlgaEurope conference 2017 (December, 5th - 7th, Berlin, D) "'Potential of evolution engineering for enhancing productivity of microalgae"'.

O. Bernard was invited for an oral presentation at the 1st IWA Conference on Algal Technologies for Wastewater Treatment and Resource Recovery conference 2017 (Delft, 16th - 17th, Delft, NL) "The role played by predators in a high rate algal pond for wastewater treatment".

M. Chaves was an invited speaker at the Workshop on Molecular Logic, Universidade de Aveiro, Portugal (June 2017).

S. Touzeau was invited to give a talk at the MADEV 17 "Mathématiques Appliquées à des questions de DEVeloppement" International Conference, organised by the French "Académie des Sciences" and the Moroccan "Académie Hassan II des Sciences et Techniques", Rabat, Morocco (October 2017).

10.1.5. Scientific Expertise

O. Bernard is a member of the scientific committee of the companies Inalve and BioEnTech.

J.-L. Gouzé was in several evaluation committees or juries: FWO, NWO, FNRS...

10.1.6. Research Administration

O. Bernard represents Inria at the ANCRE (Alliance Nationale de Coordination de la Recherche pour l'Energie), in the biomass committee. He is a member of the ADT (Technological Development Actions) at Inria.

M. Chaves is a member of the COST-GTRI (working group on International Relations at Inria's council for scientific and technological orientation). The group is charged with evaluating Inria's Associated Teams as well as some project proposals (EuroMed 3+3), and ERCIM post-docs. She is also member of the CLHSCT (local committee for the safety of working conditions)

J.-L. Gouzé is in the Inria committee supervising the doctoral theses, and a member of the scientific committee of Labex SIGNALIFE of the University of Nice-Sophia-Antipolis, and of COREBIO PACA. He is in the scientific committee of Académie 4 of UCA-Jedi. He is a member of the board of the SFBT (French Speaking Society for Theoretical Biology).

F. Grognard is a member of the NICE committee, which allocates post-doctoral grants and fundings for visiting scientists at Inria Sophia Antipolis. He is a member of the scientific committee of the doctoral school "Sciences de la Vie" at the University of Nice-Sophia Antipolis. Since 2015, F. Grognard is a member of the MBIA CSS (Specialised Scientific Commission), in charge of the research scientists evaluation at INRA. He is a member of the steering committee of Academy 3, Space, Environment, Risk & Resilience of UCA-JEDI.

L. Mailleret is the head of the M2P2 team (Models and Methods for Plant Protection) of ISA. He's in the scientific council of Institut Sophia Agrobiotech.

S. Touzeau is a member of the steering committee of the metaprogramme SMaCH *Sustainable Management of Crop Health*, INRA (since 2016).

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Licence: F. Grognard (45.5h ETD) and L. Mailleret (26h ETD), "Equations différentielles ordinaires et systèmes dynamiques", L3, 1st year Engineering in Modeling and Applied Mathematics, Polytech'Nice, Université of Nice Sophia Antipolis, France.

Licence: N. Bajeux (192h ETD) is ATER at IUT Nice Côte d'Azur of Université of Nice Sophia Antipolis, France. ing in Modeling and Applied Mathematics, Polytech'Nice, Université of Nice Sophia Antipolis, France.

Master: O. Bernard (4.5h ETD), "Bioenergy from microalgae", M2, Master International Energy Management : alternatives pour l'énergie du futur, Ecole Nationale Supérieure des Mines de Paris, France.

Master: O. Bernard (18h ETD), "Modelling biotechnological processes", M2, Ecole CentraleSupelec, France.

Master: J.-L. Gouzé (9h ETD), M. Chaves (9h ETD), "Discrete and continuous approaches to model gene regulatory networks", Master of Science in Computational Biology (M2), University of Nice - Sophia Antipolis.

Master: J.-L. Gouzé (18h ETD), M. Chaves (12h ETD) "Modeling biological networks by ordinary differential equations", 4th year students, Génie Biologie, Polytech'Nice, University of Nice - Sophia Antipolis.

Master: F. Grognard (21h ETD) and L. Mailleret (21h ETD), “Bio-Mathématiques”, M1, 2nd year Engineering in Modelling and Applied Mathematics (eq. M1), Polytech’Nice, Université of Nice Sophia Antipolis, France.

Master: S. Touzeau, “Analyse de données”, 36.75 ETD, M1 (2nd engineering year in Génie Biologie), Polytech’Nice – Université Nice Sophia Antipolis, France.

O. Bernard together with M. Morales supervised a project involving 6 students of Ecole Nationale Supérieure des Mines de Paris (last year of engineering school, 1 week ("Combining photovoltaic panels and microalgae"). O. Bernard supervised a project involving 6 students from the Ecole Centrale de Paris (first year of engineering school), 4 months, to design a system for detecting contamination in microalgae cultures.

10.2.2. Supervision

PhD : D. Demory, "Impact of temperature on phytoplankton-virus interactions ", January, 17th, 2017, UPMC. Supervisors: A. Sciandra, S. Rabouille and O. Bernard.

PhD : S. Casagranda. “Modeling, analysis and reduction of biological systems”,June 30, Université Côte d’Azur. Supervisors: J.-L. Gouzé and D. Ropers (Inria IBIS).

PhD : N. Bajeux. “Modélisation de stratégies d’introduction de populations, effets Allee et stochasticité”, July 7, Université Côte d’Azur. Supervisors: O. Bernard, F. Grognard, and L. Mailleret.

PhD in progress : S. Almeida. “Theoretical design of synthetic biological oscillators and their coupling”, since October 2014, Université Côte d’Azur. Supervisors: M. Chaves and F. Delaunay (Univ. Nice, iBV).

PhD in progress : M. Caïa, "Characterization and modelling of a mixotrophic algae - bacteria ecosystem for waste recovery", since September 2015, University Montpellier. Supervisors: J.-P. Steyer and O. Bernard.

PhD in progress : M. Haond. “Causes et conséquences des fronts de colonisation poussés”, since October 2015, Univ. Nice Sophia Antipolis. Supervisors: E. Vercken (UMR ISA), L. Mailleret and L. Roques (UR BioSP).

PhD in progress : C. Lopez-Zazueta. “Use of Perturbation Theory to optimize metabolic production of biofuels by microalgae.”, since January 2016, Université Côte d’Azur, supervisors O. Bernard and J.-L. Gouzé.

PhD in progress : C. Martinez von Dossow . "Modélisation et optimisation de consortia microalgues-bactéries", since February 2016, UPMC. Supervisors: O. Bernard, F. Mairet and A. Sciandra.

PhD in progress : L. Chambon. “Control of models of genetic regulatory networks”. since October 2016, Université Côte d’Azur. Supervisor J.-L. Gouzé.

PhD in progress : L. Gomes Pereira. “Experimental and computational approaches to understanding the molecular origins of drug response heterogeneity, underlying resistance to cancer therapies”, since October 2016, Université Côte d’Azur. Supervisors: M. Chaves and J. Roux (IRCAN, Nice).

PhD in progress: S. Nilusmas, “Gestion durable des nématodes à galles en cultures maraîchères : modélisation et optimisation du déploiement des résistances et des pratiques agronomiques”, Université Côte d’Azur, since December 2016. Supervisors: S. Touzeau, C. Caporalino (ISA), V. Calcagno (ISA) and L. Mailleret.

PhD in progress: M. Gachelin, “Selection pressure to improve lipid productivity of microalgae”, since March 2017, UPMC. Supervisors: O. Bernard and A. Sciandra.

PhD in progress : E. Firippi. “Mathematical analysis, control design and coupling for models of biological oscillators”, since October 2017, Université Côte d’Azur. Supervisors: M. Chaves.

PhD in progress: I. Tankam Chedjou, “Modeling, analysis and control of plantain plant-parasitic nematodes”, University of Yaoundé 1, since December 2015. Supervisors: J.-J. Tewa, F. Grognard, L. Mailleret, S. Touzeau.

PhD in progress: Y. Fotso Fotso, “Modeling, analysis and control of coffee berry borers”, University of Dschang, since January 2017. Supervisors: S. Bowong, B. Tsanou, F. Grognard, L. Mailleret, S. Touzeau.

Master theses and engineering internships supervision

Engineer: Bruno Assis Pessi, "Modélisation de la croissance de microalgues en raceways sous serre ", Ecole CentraleSupelec.

Engineer: Selma Benzekri. “Recherche de matériaux biomimétiques des acarodomatia pour la lutte biologique basée sur les phytoseïdes”, 2nd year Agroparistech, supervisors L. Mailleret, C. Bresch, P. Parolin and M. Ferrero.

Engineer: Olivier Fauré. “Augmentative Biological Control - optimizing natural enemies deployment”, 2nd year engineering Polytech’Nice, Université Côte d’Azur, supervisors L. Mailleret and F. Grognard.

Engineer: Julien Guégan. “Évolution des traits d’histoires de vie de champignons phytopathogènes”, 2nd year engineering Polytech’Nice, Université Côte d’Azur, supervisors F. Grognard and L. Mailleret.

M2: Laurent Dragoni, “Personnalisation de modèles numériques de médicaments”, Université Côte d’Azur, supervisors J.-L. Gouzé and F. Dayan (Exactcure).

M2: Eleni Firippi. “Analysis and Control of models of genetic regulatory networks”, Université Côte d’Azur, supervisor M. Chaves.

M1: Meng Zhang, "Study of the interactions between microalgae and cyanobacteria", UPMC.

IUT: Elie Varengot. “Recherche de matériaux biomimétiques des acarodomatia pour la lutte biologique basée sur les phytoseïdes”, IUT Aix Marseille Université, supervisors L. Mailleret, C. Bresch, P. Parolin and M. Ferrero.

10.2.3. Juries

O. Bernard was in the jury, while F. Grognard and L. Mailleret were invited members in the jury of the PhD of Nicolas Bajeux, "Modélisation de stratégies d’introduction de populations, effets Allee et stochasticité", Université Côte d’Azur, July 7.

O. Bernard was reviewer for the PhD thesis of L. Haustenne " Mathematical modeling of the genetic regulatory network controlling comptetence for natural transformation in Steptococcus thermophilus", Université Louvain-La-Neuve (Belgium). (24 march 2017)

O. Bernard was reviewer for the PhD thesis M. Budinich " Modélisation des réseaux métaboliques en interaction avec l’Environnement ", Nantes Université. (28 april 2017)

O. Bernard was reviewer for the PhD thesis of R. Schaap "UV radiation as a new tool to control microalgal bio-product yield and quality". Massey University (20 Oct. 2017).

O. Bernard was reviewer and J.-L. Gouzé was in the jury of the PhD thesis of N. Giordano “Microbial growth control in changing environments: theoretical and experimental study of resource allocation in *Escherichia coli*”, Grenoble University. (23 march 2017)

J.-L. Gouzé was in the jury and S. Touzeau was an invited member in the jury of the PhD of Stefano Casagranda, “Modeling, analysis and reduction of biological systems”, Université Côte d’Azur, June 30.

O. Bernard was reviewer for the HDR of S. Tebbani "Contribution à l’étude des systèmes non linéaires incertains : application à la commande de systèmes biotechnologiques ", University of Paris-Sud, November 7th, 2016.

M. Chaves was reviewer for the HDR of Elisabeth Remy “Modélisation logique pour l’analyse des réseaux de régulation biologiques”, Univ. Aix-Marseille, April 24, 2017.

10.3. Popularization

The activities related to microalgae have generated many articles in national newspapers (Le Monde, Nice Matin, ,...), and broadcasts on national TV (France 3).

O. Bernard gave a popularization conference “Will we drive with fuels brought algae in 2030?” in the framework of the “science for all” cycle of conferences organized by the city of Biot. 30th of March, 2017.

P. Bernhard has been involved in popularization of applied mathematics with two highschool conferences: Lycée Alexandre Dumas, Cavaillon and Centre International de Valbonne, Valbonne-Sophia Antipolis, on January 10 and 11 respectively.

M. Chaves gave a “180s” presentation “A mathematical tool for determining the dynamics of biological modules interconnection”, at Journées Scientifiques Inria, Sophia Antipolis (June 2017).

M. Chaves gave a presentation on circadian clocks at Café-in, for all Inria personnel, at Inria Sophia Antipolis (October 2017).

11. Bibliography

Major publications by the team in recent years

[1] N. BAJEUX, F. GROGNARD, L. MAILLERET. *Augmentative biocontrol when natural enemies are subject to Allee effects*, in "Journal of Mathematical Biology", 2017, vol. 74, n° 7, pp. 1561 - 1587 [*DOI :* 10.1007/S00285-016-1063-8], https://hal.archives-ouvertes.fr/hal-01402250

[2] C. BAROUKH, R. MUÑOZ-TAMAYO, J.-P. STEYER, O. BERNARD. *DRUM: A New Framework for Metabolic Modeling under Non-Balanced Growth. Application to the Carbon Metabolism of Unicellular Microalgae*, in "PLoS ONE", August 2014, vol. 9, n° 8, e104499 [*DOI :* 10.1371/JOURNAL.PONE.0104499], https://hal.inria.fr/hal-01097327

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[4] V. CALCAGNO, F. GROGNARD, F. M. HAMELIN, E. WAJNBERG, L. MAILLERET. *The functional response predicts the effect of resource distribution on the optimal movement rate of consumers*, in "Ecology Letters", December 2014, vol. 17, n° 12, pp. 1570-1579 [*DOI :* 10.1111/ELE.12379], https://hal.inria.fr/hal-01084299

[5] N. GIORDANO, F. MAIRET, J.-L. GOUZÉ, J. GEISELMANN, H. DE JONG. *Dynamical allocation of cellular resources as an optimal control problem: Novel insights into microbial growth strategies*, in "PLoS Computational Biology", March 2016, vol. 12, n° 3, e1004802 p. [*DOI :* 10.1371/JOURNAL.PCBI.1004802], https://hal.inria.fr/hal-01332394

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[9] C. POIGNARD, M. CHAVES, J.-L. GOUZÉ. *Periodic Oscillations for Non Monotonic Smooth Negative Feedback Circuits*, in "SIAM Journal on Applied Dynamical Systems", 2016, vol. 15, n^{o} 1, pp. 257–286 [*DOI :* 10.1137/15M1033368], https://hal.archives-ouvertes.fr/hal-01242157

[10] L. TOURNIER, M. CHAVES. *Interconnection of asynchronous Boolean networks, asymptotic and transient dynamics*, in "Automatica", 2013, vol. 49, n^{o} 4, pp. 884-893 [*DOI :* 10.1016/J.AUTOMATICA.2013.01.015,], http://hal.inria.fr/hal-00848450

Publications of the year

Doctoral Dissertations and Habilitation Theses

[11] N. BAJEUX. *Modélisation de stratégies d'introduction de populations, effets Allee et stochasticité*, Université Côte d'Azur, July 2017

[12] S. CASAGRANDA. *Modeling, analysis and reduction of biological systems*, Université Côte d'Azur, Nice Sophia Antipolis, France, June 2017, Spéciality: Control, Signal and Image Processing

Articles in International Peer-Reviewed Journals

[13] N. BAJEUX, F. GROGNARD, L. MAILLERET. *Augmentative biocontrol when natural enemies are subject to Allee effects*, in "Journal of Mathematical Biology", 2017, vol. 74, n^{o} 7, pp. 1561 - 1587 [*DOI :* 10.1007/S00285-016-1063-8], https://hal.archives-ouvertes.fr/hal-01402250

[14] V. BALDAZZI, M. GÉNARD, N. BERTIN. *Cell division, endoreduplication and expansion processes: setting the cell and organ control into an integrated model of tomato fruit development*, in "Acta Horticulturae", November 2017, n^{o} 1182, pp. 257 - 264 [*DOI :* 10.17660/ACTAHORTIC.2017.1182.31], https://hal.inria.fr/hal-01661920

[15] C. BAROUKH, V. TURON, O. BERNARD. *Dynamic metabolic modeling of heterotrophic and mixotrophic microalgal growth on fermentative wastes*, in "PLoS Computational Biology", June 2017, vol. 13, n^{o} 6 [*DOI :* 10.1371/JOURNAL.PCBI.1005590], https://hal.inria.fr/hal-01576858

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[17] I. BELGACEM, S. CASAGRANDA, E. GRAC, D. ROPERS, J.-L. GOUZÉ. *Reduction and stability analysis of a transcription-translation model of RNA polymerase*, in "Bulletin of Mathematical Biology", 2017, pp. 1-25, forthcoming [*DOI :* 10.1007/S11538-017-0372-4], https://hal.inria.fr/hal-01655367

[18] H. BONNEFOND, G. M. GRIMAUD, J. RUMIN, G. BOUGARAN, A. TALEC, M. O. GACHELIN, M. O. BOUTOUTE, E. PRUVOST, O. BERNARD, A. SCIANDRA. *Continuous selection pressure to improve temperature acclimation of Tisochrysis lutea*, in "PLoS ONE", August 2017, https://hal.inria.fr/hal-01576865

[19] H. BONNEFOND, N. MOELANTS, A. TALEC, P. MAYZAUD, O. BERNARD, A. SCIANDRA. *Coupling and uncoupling of triglyceride and beta-carotene production by Dunaliella salina under nitrogen limitation and starvation*, in "Biotechnology for Biofuels", January 2017, vol. 10, n^o 1, 25 p. [*DOI :* 10.1186/S13068-017-0713-4], https://hal.inria.fr/hal-01450081

[20] Q. BÉCHET, M. LAVIALE, N. ARSAPIN, H. BONNEFOND, O. BERNARD. *Modeling the impact of high temperatures on microalgal viability and photosynthetic activity*, in "Biotechnology for Biofuels", December 2017, vol. 10, n^o 1, 136 p. [*DOI :* 10.1186/S13068-017-0823-Z], https://hal.inria.fr/hal-01530933

[21] A. CAMUEL, B. GUIEYSSE, C. ALCÁNTARA, Q. BÉCHET. *Fast algal eco-toxicity assessment: Influence of light intensity and exposure time on Chlorella vulgaris inhibition by atrazine and DCMU*, in "Ecotoxicology and Environmental Safety", March 2017, vol. 140, pp. 141 - 147 [*DOI :* 10.1016/J.ECOENV.2017.02.013], https://hal.inria.fr/hal-01578039

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[24] D. DEMORY, L. ARSENIEFF, N. SIMON, C. SIX, F. RIGAUT-JALABERT, D. MARIE, P. GE, E. BIGEARD, S. JACQUET, A. SCIANDRA, O. BERNARD, S. RABOUILLE, A.-C. BAUDOUX. *Temperature is a key factor in Micromonas-virus interactions*, in "ISME Journal", 2017, vol. 11, pp. 601-612 [*DOI :* 10.1038/ISMEJ.2016.160], http://hal.upmc.fr/hal-01464528

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Invited Conferences

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International Conferences with Proceedings

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trol", Toulouse, France, IFAC papers online, Elsevier, July 2017, vol. 50, n^o 1, pp. 8734 - 8739 [*DOI :* 10.1016/J.IFACOL.2017.08.1725], https://hal.inria.fr/hal-01666463

[41] S. NILUSMAS, M. MERCAT, T. PERROT, S. TOUZEAU, V. CALCAGNO, C. DJIAN-CAPORALINO, P. CASTAGNONE, L. MAILLERET. *A multi-seasonal model of plant-nematode interactions and its use for durable plant resistance deployment strategies*, in "EASYs 2017 - Ecology & Agriculture Summit for Young scientists", Chizé, France, March 2017, https://hal.archives-ouvertes.fr/hal-01606132

[42] I. YEGOROV, F. GROGNARD, L. MAILLERET, F. HALKETT. *Optimal resource allocation for biotrophic plant pathogens*, in "IFAC 2017 - 20th World Congress of the International Federation of Automatic Control", Toulouse, France, July 2017, pp. 1-6, https://hal.inria.fr/hal-01572090

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Conferences without Proceedings

[44] N. GO, S. TOUZEAU, C. BELLOC, A. DOESCHL-WILSON. *Neutralising antibodies prevent PRRS viremia rebound: evidence from a data-supported model of immune response*, in "ModAH 2017 - Modelling in Animal Health conference", Nantes, France, INRA, June 2017, https://hal.inria.fr/hal-01577647

[45] L. PEREIRA, M. MEYER, P. HOFMAN, J.-L. GOUZÉ, M. CHAVES, J. ROUX. *Modeling cell death dynamics at the receptor level*, in "CompSysBio, Advanced Lecture Course on Computational Systems Biology", Aussois, France, March 2017, https://hal.inria.fr/hal-01568506

Research Reports

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