

RESEARCH CENTRE

**Inria Centre at Université Côte
d'Azur**

IN PARTNERSHIP WITH:

INRAE, CNRS, Université Côte d'Azur

2024

ACTIVITY REPORT

Project-Team

MACBES

Modelling And Control of Biological and Ecological Systems

IN COLLABORATION WITH: Institut Sophia Agrobiotech, Institut de
pharmacologie moléculaire et cellulaire

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life Sciences

Inria

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Project-Team MACBES

Creation of the Project-Team: 2023 July 01

Keywords

Computer sciences and digital sciences

- A6. – Modeling, simulation and control
- A6.1.1. – Continuous Modeling (PDE, ODE)
- A6.1.4. – Multiscale modeling
- A6.2.6. – Optimization
- A6.3.4. – Model reduction
- A6.4.1. – Deterministic control
- A6.4.4. – Stability and Stabilization
- A6.4.6. – Optimal control
- A8.7. – Graph theory
- A8.11. – Game Theory

Other research topics and application domains

- B1.1.2. – Molecular and cellular biology
- B1.1.7. – Bioinformatics
- B1.1.8. – Mathematical biology
- B1.1.10. – Systems and synthetic biology
- B2.4.1. – Pharmacokinetics and dynamics
- B3.1. – Sustainable development
- B3.5. – Agronomy
- B3.6. – Ecology

1 Team members, visitors, external collaborators

Research Scientists

- Frédéric Grogard [Team leader, INRIA, Researcher, Senior researcher from Oct. 2024., HDR]
- Valentina Baldazzi [INRAE, Researcher, HDR]
- Madalena Chaves [INRIA, Senior Researcher, HDR]
- Jean-Luc Gouzé [INRIA, Senior Researcher, HDR]
- Ludovic Mailleret [INRAE, Senior Researcher, HDR]
- Jérémie Roux [CNRS, Researcher]
- Suzanne Touzeau [INRAE, Researcher]

Post-Doctoral Fellow

- Giada Fiandaca [INRIA]

PhD Students

- Benjamin Bobel [INRIA]
- Odile Burckard [INRIA, until Nov 2024]
- Javier Innerarity Imizcoz [UNIV COTE D'AZUR]
- Aurelien Kambeu Youmbi [UNIV DSCHANG, CAMEROON]
- Frank Kemayou Mangwa [UNIV DOUALA, CAMEROON]
- Armando Kenne Meli [École Nationale Supérieure Polytechnique, CAMEROON, from Nov 2024]
- Pauline Mazel [UNIV COTE D'AZUR]
- Joseph Junior Penlap Tamagoua [INRIA]

Interns and Apprentices

- Omar Sabir [INRAE, Intern, from May 2024 until Sep 2024]

Administrative Assistant

- Maeva Jeannot [INRIA]

Visiting Scientist

- Tomas Gedeon [Univ Montana, from Sep 2024 until Sep 2024]

External Collaborators

- Pierre Bernhard [INRIA]
- Odile Burckard [Grenoble, from Dec 2024]
- Vincent Calcagno [INRAE]
- Clotilde Djuikem [UNIV MANITOBA]
- Frédéric Hamelin [INSTITUT AGRO RENNES-ANGERS]
- Louise Van Oudenhove De Saint Gery [INRAE]

2 Overall objectives

Understanding and controlling dynamics are at the core of major challenges in biology and ecology central to human and environmental health. With the increasing availability of experimental data time-series in these fields and better comprehension of the fundamental biological mechanisms, building models is required to fully grasp these dynamics. The objective of MACBES is to apply and develop methodologies of control theory and computational biology to specific applications in biology and ecology: the ecologically friendly protection and management of ecosystems, such as agroecosystems, and the characterization and deciphering of mammalian cell responses to their environment, in particular the effect of network interactions and developments in synthetic biology. MACBES has privileged access to biological data generated by the partners within the Common Project Team which allows for the development of the most relevant models related to its applications.

Control theory provides answers to questions related to identify parameters, reconstruct non-measured quantities of interest, regulate and control the system towards a desired state and optimize the yield of a given product. In computational biology, the tools of theoretical ecology and evolutionary biology provide answers on what a system will become.

The development of dynamical models representing mechanisms and interactions within our systems of interest is a first step in our approach. We develop models built in continuous ordinary differential equations, impulsive models, discrete models, or hybrid models, to better represent the variety of biological processes. In their diversity, these models are often built on representations of simplified biological processes, which yield systems that have particular structures that can be exploited: their variables are positive, some interactions can be modeled as mass transfers, they can be monotonic, . . . Such models allow for analytical and numerical developments that help explaining the dynamics and the functioning of biological processes. These models are the cornerstones on which we can apply the comprehensive toolbox of control theory.

The link of our models to data depends on the context. On the one hand, we are at a turning point where the availability of “omics” and cell level data exceeds our capacity of interpretation, while on the other hand it may still be difficult to obtain reliable and useful data time-series to understand ecosystem dynamics, though that could soon change too with the development, reliability and increasing affordability of remote sensing data through drones. Therefore, apprehending the complexity of these processes and interactions through this abundance of data or despite data scarcity, requires the construction of specific mathematical models with specific calibration approaches, that face the large uncertainties and variability that are intrinsic to biological systems. In addition, to limit the impact of uncertainties and calibration errors on our results, we also develop models and control theoretic approaches relying on qualitatively described functions, through which generic answers can be sought that are valid over a wide range of situations and parameter values.

MACBES is a common project-team between Inria, INRAE, CNRS and Université Côte d’Azur, associating researchers of Inria d’Université Côte d’Azur, Institut Sophia Agrobiotech (ISA - UMR INRAE CNRS and Université Côte d’Azur, Models and Methods for Plant Protection team), and Institut de Pharmacologie Moléculaire et Cellulaire (IPMC - UMR CNRS and Université Côte d’Azur). MACBES was created on July 1st, 2023 and is one of the two project-teams following the Biocore project-team.

3 Research program

The research program is organized around four axes involving common tools from control theory and computational biology, with models built using continuous ordinary differential equations, impulsive models, discrete models, or hybrid models. Control theory provides answers to questions related to the need to identify parameters, reconstruct non-measured quantities of interest, regulate and control the system towards a desired state and optimize the yield of a given product. In computational biology, we use the tools of theoretical ecology and evolutionary biology to provide answers on what a system will become. The four research axes of MACBES are:

3.1 Network interactions for cell function and growth

Cells have evolved highly sophisticated intracellular communication pathways to enable their development and growth, under multiple environmental stresses and stimuli (growth factors, hormones, different types of drugs, temperature or light changes, etc.). In a modular view of a biological organism, each task is executed by a specific network, or module. These modules often interact with each other, one task triggering the next in a chain of events or cyclic phenomena: cascades of signaling networks, genetic-metabolic interactions, oscillatory behavior. One of the greatest challenges at the interface between biology and mathematics is to decipher and reproduce the complex behavior arising from the interconnection of two or more modules. The ability to reproduce the complexity of cellular responses will lead to a better capacity for regulation and balancing of factors towards healthy behaviors.

3.2 Dynamics and control for synthetic biology

Synthetic biology aims at joining elements from both biology and engineering to construct cellular circuits that perform a desired function or induce a particular type of response. It is also a complementary approach to (traditional) molecular biology: newly creating and assembling synthetic cellular circuits from basic biological components (such as DNA, proteins, or metabolites) to form a “whole organism”, serves as a proof of principle towards understanding the mechanisms of biological networks. One of the main bottlenecks in synthetic biology is how to integrate the new circuit into the cell’s machinery, without upsetting the cellular resource allocation balance. To tackle this problem, understanding resource allocation in the cell and the interconnection of cellular oscillators is a crucial challenge.

3.3 Modeling agro-ecological interactions

Plants are involved in a wide range of biotic interactions. Some are beneficial to plant health, as for pollinators or symbiotic organisms, whereas others are detrimental, as in the case of pathogens or herbivores. The dynamics and outcome of these interactions depend on the ecological conditions, including the phenotypes of the interacting species, their physiology and the abiotic environment in which the interactions take place. Our aim is to develop models relevant to several biotic interactions involving plants and other organisms, from the ecophysiological scale and the intimate interaction between plants and their partners, to the ecological interactions between populations and communities inhabiting crop fields.

3.4 Design and control of managed ecosystems

In several contexts, such as bioreactors in industry or cropping systems in agriculture, it might be desirable to create an ecosystem that does not exist as is in nature. Putting together species that have mutualistic behaviors, whose synergy allows for the production of some desired output, or that protect one another, can enhance the functioning of the resulting ecosystem. Without fully designing an ecosystem from scratch, it might also be necessary to take control actions to improve the functioning of an existing ecosystem or to restore a degraded ecosystem to a previous, desirable, state. The exploitation of natural or synthetic microbial communities for the accomplishment of processes of interest is being pursued in a vast range of scenarios, from established applications in the biotechnology and pharmaceutical industries, to innovative applications in medicine and environmental sciences. Larger scale managed ecosystems can simply be natural ecosystems into which one wants to re-introduce or maintain endangered species, but they can also be exploited ecosystems such as forests, agricultural fields, fish farms. . . A special focus is put in MACBES on the development of pest/pathogen control methods in agroecosystems.

4 Application domains

As highlighted in the research program, in MACBES, we tackle real-life problems and contemporary challenges with respect to safe food, food security, human and environmental health. We develop mathematical techniques to characterize and decipher cell responses to their environment in research

axes 3.1 and 3.2, and we deal with ecologically friendly methods for the protection and management of ecosystems, in particular of agroecosystems, in research axes 3.3 and 3.4.

5 Social and environmental responsibility

5.1 Impact of research results

The application of MACBES research for the development of ecologically friendly methods for crop protection aim at sustainable agroecosystems. Central to our work is the reduction of chemical pesticide usage, whose deleterious impact on health and the environment is well-documented. The applications concerning cell dynamics may impact the development of new anti-cancer drugs and in general aim at a better understanding of mechanisms affecting human health.

6 Highlights of the year

- **Benchmark for characterizing circadian cycles.** To study and compare quantitatively the properties of different mathematical models of the circadian clock, their periodic cycles and correspondence to experimental data, we developed a method based both on theoretical and numerical analysis [10]. Our method requires only a set of three time series for three main clock proteins (CLOCK:BMAL1, PER:CRY, REV-ERB) along a cycle, for instance obtained numerically from a mathematical model. The method then assesses the agreement of the cycle with biological properties and also detects possible inconsistencies [11].
- **Bioeconomic modeling.** We developed a model of self-financing of a smallholder cabbage crop farm undergoing a diamondback moth infestation. The main point of this model is the inclusion of the financial balance of the farm, used for buying young plants and biopesticide spraying. We identified parameter values for which the diamondback moth is eradicated and others where the pest survives which greatly reduces the farm profitability [17].

7 New software, platforms, open data

7.1 New software

7.1.1 LCM&Mat

Name: Live-cell microscopy & microdissection analytics tools

Keywords: Deep learning, Live-cell microscopy, Cancer, Signal processing, GUI (Graphical User Interface)

Scientific Description: CM&Mat can be used to analyse data extracted by the phenotrack software from microscopy videos on single living cells to create an automatic experiment report and predict the response of each cancer cell observed to a death ligand before the microdissection stage from a graphical interface. To achieve this, LCM&Mat uses signal and image processing methods, mathematical modelling using ODE and neural networks.

Functional Description: LCM&Mat is divided into three parts: - `post_processing`: opens the files generated by the phenotrack software from the microscopy videos to create experiment reports for biological research engineers. - `prediction`: trains and tests a neural network to predict the response of each cancer cell to a death ligand from microscopy data. - `user_interface`: transforms python code into a graphical interface to make it easier for biologists to use.

News of the Year: this software have been developped this year.

Contact: Jérémie Roux

Participants: Neva Cherniavsky, Marielle Pere, Jérémie Roux

8 New results

8.1 Network interactions for cell function and growth

Participants: Odile Burckard, Madalena Chaves, Giada Fiandaca, Jérémie Roux, Jean-Luc Gouzé, Valentina Baldazzi, Pauline Mazel, Frédéric Grognard.

8.1.1 Cellular response and cell-to-cell variability

Cell response through the apoptotic pathway To analyze the considerable amount of data from fate-seq [45], we proposed an ODE model of the molecular pathways involved in cell death triggered by Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). This model reproduces the trajectories along time of the apoptosis signaling dynamics, in particular the amount of active caspase-8 protein. To calibrate the model, we use single-cell time-trajectories from clonal HeLa cells [46], where the concentration of active caspase-8 is monitored by a Förster resonance energy transfer (FRET) reporter.

Based on this model and using the method previously developed in [3], we successively identified several new elements that play a role in caspase-8 apoptosis signaling. First, two mathematical factors to better reproduce the signaling kinetics include the saturated form of caspase degradation (as opposed to linear degradation) and the interaction between TRAIL and its receptors, where the latter appear according to a cooperative (sigmoidal) form. Second, a new component (protein Flip) should be included in the model, by its capacity to modulate the model's signaling response. Flip has both an anti-apoptotic role by competing with pre-caspase-8 at death-inducing signaling complex (DISC) level, and also a pro-apoptotic role since the complex composed of TRAIL, its receptor, Flip and two pre-caspase-8 molecules contributes to caspase-8 activation. These results were presented by Giada Fiandaca at the European Conf. Mathematical and Theoretical Biology [34].

Optimization of cancer treatment Another line of research involves the application of optimal control to Lotka-Volterra models of competition between cancerous and healthy cells. The aim is to control cancer progression while reducing the harmful effects of chemotherapy. This strategy aims to strike a balance between eliminating cancer cells while preserving healthy tissues, providing a more refined method to manage the impact of cancer treatments [28]. Recent developments are more specific to acute myeloid leukemia and grounded on a model representing cell renewal and cell differentiation built with Thomas Stiehl (University of Aachen, Germany). This is the subject of the PhD thesis of Pauline Mazel.

8.1.2 Intercellular communication in peripheral clocks

Coupling of peripheral clocks The intercellular interactions between peripheral circadian clocks, located in tissues and organs other than the suprachiasmatic nuclei of the hypothalamus, are still very poorly understood. To investigate this question, we performed a theoretical and computational study of the coupling between two or more clocks, using a reduced model of the mammalian circadian clock previously developed in [1]. Based on a piecewise linearization of the dynamics of the mutual CLOCK:BMAL1 / PER:CRY inactivation term, we proposed a segmentation of the circadian cycle into six stages, to help analyze different types of synchronization between two clocks, including single stage duration, total period, and maximal amplitudes. Our model reproduces some recent experimental results on the effects of different regimes of fasting/feeding alternance in liver circadian clocks of mice [43]. Through the analytical study of the above piecewise linear model of the clock, we proposed an Algorithm to generate biologically-consistent circadian oscillators. Our study provides a characterization of the cycle dynamics in terms of four fundamental threshold parameters and one scaling parameter, as it recapitulates the main observations from the literature. Moreover, our analysis shows robustness of the circadian system and its period, and identifies critical points for correct cycle progression [10]. This work is a collaboration with F. Delaunay (IBV, Univ. Côte d'Azur) through the ANR InSync project, and part of Odile Burckard PhD thesis.

Characterization of circadian cycles A large variety of mathematical models have been developed to study the dynamics and quantitative properties of the circadian oscillator and better understand circadian clock mechanisms. To better analyze and compare quantitatively all these circadian cycles, we developed a method based on a previously proposed circadian cycle segmentation into stages [43]. We notably identify a sequence of eight stages that characterize the progress of the circadian cycle. To distinguish these stages in a given cycle, our method requires only a set of three time series for three main clock proteins (CLOCK:BMAL1, PER:CRY, REV-ERB), either from an experimental dataset or obtained numerically from a mathematical model. Our method permits to assess the agreement of mathematical model cycles with biological properties or to detect possible inconsistencies. The strength of our method is to provide a benchmark for characterization, comparison and improvement of new mathematical models of circadian oscillators in a wide variety of model systems [11]. This work is a collaboration with F. Delaunay (IBV, Univ. Côte d'Azur) through the ANR InSync project, and part of Odile Burckard PhD thesis.

8.1.3 Cell economy and control of cell growth

Microbial growth consists of the conversion of nutrients from the environment into biomass and small energy cofactors (ATP, NADH, NADPH, ...) driving biomass synthesis forward. Two macroscopic criteria for characterizing microbial growth are growth rate and growth yield. The former refers to the rate of conversion of a substrate into biomass, and the latter to the efficiency of the process, that is, the fraction of substrate taken up by the cells that is converted into biomass.

In the framework of a previous ANR project (collaboration with H. de Jong, MICROCOSME team, and T. Gedeon, Montana State University), we developed a coarse-grained model of coupled energy and mass fluxes in microorganisms, based on minimal assumptions, and used it to explore the variability of rate-yield phenotypes obtained by change in proteome allocation strategy [42].

The cloud of predicted rate-yield phenotypes shows a characteristic shape. First, possible combinations of rate and yield are bounded. A maximum growth rate and growth yield exist for any given environment, due to internal allocation constraints. Moreover, the upper boundary of the cloud is a Pareto frontier, connecting the maximum yield and the maximum growth rate points. It corresponds to a trade-off between growth rate and growth yield, which cannot be simultaneously increased in this region.

Preliminary tests with other published allocation models suggest that the existence of a Pareto frontier may be a general feature. A mathematical analysis of the mapping from resource allocation parameters to rate and yield, is currently under way.

8.1.4 Modeling microbial communities

Microbial communities are ubiquitous in life. Despite their importance, their description remains challenging due to the number of microbes involved and the complexity of possible interaction mechanisms. Advances in sequencing and measuring technologies have enabled the collection of multi-omics data, including metagenomics, metabolomics and metatranscriptomic data. In collaboration with the Inria team PLEIADE (Bordeaux), the PhD thesis of Sthyyve Tatho aims to develop a mathematical model of microbial community capable of integrating these time series of multi-omics data at a community scale. Such a model will help to better decipher interactions and functioning of microbial communities, knowing what each individual consumes and produces. In particular, assuming that we have at hand a list (\mathcal{M}) of time series of experimentally measured rates, including growth, production, and consumption rates of observed extracellular metabolites, we aim to infer the extracellular and intracellular rates (v) for each member of the microbial community by solving a high-dimensional inference problem, informed by the knowledge of metabolic network of each microbe and constrained by the stationarity of the metabolic system ($S \cdot v = 0$).

This approach, that we called community-scale metabolic flux analysis (cMFA), has been successfully tested on a set of benchmark communities of different structure, using synthetic data [41]. Next steps include the extension of the method to a dynamic framework and its application to available experimental data from a three-species microbial community involved in cheese fermentation.

8.2 Dynamics and control for synthetic biology

Participants: Benjamin Böbel, Madalena Chaves, Javier Innerarity Imizcoz, Jean-Luc Gouzé.

8.2.1 Dynamics in networks of cellular oscillators

Synchronization of circadian clock models To study coupling and synchronization of two clock oscillator models, we have used Lyapunov function techniques to bound the difference between the two oscillators in terms of the difference between their oscillating periods. We have also analyzed the form of the periodic solutions as a function of some of the parameters, in particular one of the major degradation rates. This is part of Benjamin Böbel PhD thesis.

Phase response curves to characterize oscillator coupling One of the features of the mammalian circadian clock (also present in the model of [1]) is a “sequestration mechanism” which consists of the mutual inhibition of two protein complexes, by their binding to each other. While bound, the activities of both complexes are repressed. We show that this sequestration repression mechanism plays a fundamental role in the dynamics of the circadian clock. By analyzing a reduced piecewise affine model derived from [1] and a simplification associated to the sequestration mechanism, we first prove the existence of a periodic trajectory and then construct the phase response curve (PRC) for this reduced system. The PRC exhibits a short time window where interactions with another signal are possible. The form of the PRC can thus be used to understand the effective interaction between several coupled oscillators and the robustness of synchronization in a coupled network of oscillators. This is part of Ben Böbel PhD thesis.

8.2.2 Optimization and optimal control in the cell

Optimal allocation of resources in bacteria Using optimal control techniques, we study the optimal allocation between metabolism and gene expression during bacteria growth, in collaboration with Inria Microcosme and MCTAO project-teams. We developed different versions of the problem, and considered problems where the aim is to optimize the production of a product in a batch or fedbatch bioreactor; the input of substrate may also be fluctuating (e.g. periodic) or controlled [18, 16, 26]. This work was part of the PhD thesis of Agustin Yabo (INRAE), and of the ongoing PhD work of Javier Innerarity Imizcoz, in collaboration with W. Djema (GreenOwl) and F. Mairet (IFREMER Nantes)).

In collaboration with W. Djema (GreenOwl) and T. Bayen (Univ. Montpellier), we also worked on species selection in competition for two substitutable substrates. We studied by control and optimal control techniques the maximization of cell growth rate.

8.3 Modeling agro-ecological interactions

Participants: Valentina Baldazzi, Frédéric Grogard, Suzanne Touzeau, Ludovic Mailleret, Clotilde Djuikem, Aurelien Kambeu Youmbi, Frank Kemayou Mangwa, Joseph Junior Penlap Tamagoua, Armando Kenne Meli, Jean-Luc Gouzé.

8.3.1 Ecophysiological modeling of plant-microbiota interactions

Plant-RKN interactions. Root-knot nematodes (RKN) are microscopic root parasites that cause considerable yield losses in numerous crops worldwide. We are particularly interested in understanding the mechanisms that underlie plant tolerance, that is the ability of certain plants to sustain RKN infestation with limited damages. To address this, we built an ecophysiological model of plant growth coupled with a model of nematode population dynamics. The model was calibrated for two plant species with contrasted RKN susceptibility, using experimental data produced at INRAE. Comparison of the estimated

parameters suggested a handful of physiological traits that might be important for plant tolerance. The model is currently being used to systematically identify other possible mechanisms for tolerance and to test their robustness under a range of infection and environmental scenarios.

In order to get a better grip on the system dynamics, a reduced version of the plant-nematode model was developed. Mathematical analysis showed that the model admits three equilibria: a trivial extinction equilibrium, a pest-free equilibrium, and a coexistence equilibrium which corresponds to a tolerant plant. We performed a stability analysis and identified a transcritical bifurcation, with a stability exchange between pest-free and coexistence equilibria, when the pest aggressiveness increases. For even larger values, a Hopf bifurcation occurs, leading to periodic oscillations.

This work is part of the PhD thesis of Joseph Junior Penlap Tamagoua and was presented at several national and international conferences [29, 35].

Plant-microbial community interactions. In natural soils, plants interact with a remarkable diversity of micro-organisms. The excretion of inorganic and organic molecules from living roots is thought to influence the structure of microbial communities, providing substrates and signals for specific classes of bacteria.

Using a classical consumer-resource model, the M1-internship of Omar Sabir investigated to which extent the release of new substrates from the plant can control the relative abundance of specific microbial species, as a function of community structure (interaction topology).

8.3.2 Epidemiological modeling of plant-enemy interactions

Semi-discrete models Semi-discrete models have shown their relevance in modeling biological phenomena whose nature presents abrupt changes over time [44]. In plant epidemiology, they can represent seasonality or external perturbations of natural systems, such as harvest. We developed and analyzed such models in the context of biological control applied to coffee leaf rust [20] or coffee berry borers [15], and of the sterile insect technique in Manon Pugno's internship. They were also exploited in Diego Petit's internship for the development of models representing yearly choices by the growers between clean seeds and farmer seeds in a seasonal environment.

Epidemiological models in tropical agriculture We developed and analyzed dynamical systems describing plant-parasite interactions, in order to better understand, predict and control the evolution of damage in crops, with applications in tropical agriculture, in the framework of the EPITAG associate team with Cameroon (section 10.1.1) [20].

- Coffee berry borers (CBB) are insects that mostly develop and feed inside coffee berries, and hence cause major crop damage worldwide. We developed a model describing the coffee berry borer dynamics based on the insect life cycle and the berry availability during a single cropping season. This PDE model includes a berry age structure to account for CBB preference for mature berries. We investigated how to optimize an impulsive control based on biopesticide (entomopathogenic fungus such as *Beauveria bassiana*) spraying [15].
- Coffee leaf rust (CLR) is a leaf disease caused by a fungus, *Hemileia vastatrix*, that has a major impact on coffee production around the world. We studied a model of CLR development in a plantation representing the development stage of the leaves, taking higher infection risk for mature leaves into account [14]. We identified a bifurcation in the case of higher sporulation on young leaves compared to mature ones.
- Cabbage is a very important food crop for small farmers in Cameroon. We developed a model of self-financing of the crop, which includes the interaction between cabbage and the diamondback moth, one of its major pest. The main point of this model is the inclusion of the financial balance of the farm, used for buying young plants and biopesticide spraying. We did a bifurcation analysis of this bioeconomic model and identified situations with forward or backward bifurcations [17]. We extended this work to model biological control deployment by considering a parasitoid presenting mutual interference [27, 25]. This work is part of Aurelien Kambeu Youmbi's ongoing PhD thesis.

- Bananas are major staple foods in many tropical countries. These plants are affected by burrowing nematodes (*Radopholus similis*) that create root lesions and induce great damages. We developed a model of plant-pest interactions with the original feature that infestation intensity may vary within the root. We did a bifurcation analysis and solved an optimal control against the pest, consisting in maximizing profit thanks to the application of biostimulants. The optimal control obtained is pseudo-periodic, suggesting the overyielding occurs [30, 40]. This work is part of Frank Kemayou Mangwa's ongoing PhD thesis.
- Cassava is another major staple food in many African countries. It is affected by African cassava mosaic disease, which is a viral disease whose vector is the white fly. We are in the process of developing an epidemiological model representing these dynamics. This work is part of Armando Kenne Meli's ongoing PhD thesis.

Impact of predation risk on optimal foraging In this work, we built on our re-analysis of the Marginal Value Theorem (MVT) to study the effect of predation risk on the optimal foraging strategy, thereby building a risk-MVT. This risk-MVT is at the intersection between Charnov's MVT and Brown's giving-up density (GUD) theory. It can incorporate most types of predation risks, from mere disturbance situations to death of the forager. It gives contrasting answers depending on the type of risk, but always tends to predict that individuals should be bolder in riskier environments [38].

8.4 Design and control of managed ecosystems

Participants: Jean-Luc Gouzé, Frédéric Grogard, Suzanne Touzeau, Ludovic Mailleret, Aurelien Kambeu Youmbi, Frank Kemayou Mangwa, Armando Kenne Meli, Joseph Junior Penlap Tamagoua.

8.4.1 Design and control of synthetic microbial ecosystems

In the framework of ANR project Ctrl-AB, we considered a synthetic algal-bacterial consortium. The co-culture of *E. coli* with *Chlorella* could lead to higher biomass and lipid productivity. We developed a model, studied its dynamical behavior and built observers and filters [21]. Moreover, we studied the effects of control on the system in the framework of optimization or optimal control [22] (PhD thesis of Rand Asswad, Grenoble, in collaboration with E. Cinquemani (Microcosme) as well as O. Bernard and W. Djema (GreenOwl)).

8.4.2 Waste valorization for biogas production

In collaboration with O. Cherkaoui (University of Rabat) and W. Djema (GreenOwl), a model for optimal waste valorization and investment strategies was developed to enhance biogas production and reduce pollution [12]. This work involved the analysis of a bioeconomic model designed to optimize both waste storage management and financial investments in the sector. The model is dynamic and incorporates two control variables, where turnpike phenomena and singular arcs prominently emerge in the control strategy. A detailed analysis was conducted under conditions of periodic waste input, complemented by a sensitivity analysis of the control problem with respect to the system's key parameters.

8.4.3 Design of biological control strategies

Sterile insect technique The sterile insect technique (SIT) consists in releasing irradiated sterile individuals, usually males, that can mate but produce no offspring. SIT is used to reduce pest populations in an agricultural context. However, a small fraction of irradiated insects may escape sterilization and remain fertile. We showed that when residual fertility is below a threshold value, wild populations can be driven to extinction by flooding the landscape with sterile males. Nevertheless, even if the residual fertility exceeds the aforementioned threshold value, substantial decreases in outbreak levels can be achieved [13, 33]. We extended these results to take remating into account through both a continuous

dynamics formalism and an agent based model, showing the importance of reproductive mechanisms in shaping the efficiency of SIT control strategies [23, 32, 31, 24]. Finally, the impact and optimization of discrete-time impulsive sterile male releases was considered in Manon Pugnet's internship. This work pertains to Marine Courtois's ongoing PhD thesis.

Optimal control for tropical agriculture Controlling tropical pests is particularly challenging, as their dynamics are often explosive in tropical environments. Optimal control is relevant to counter this spread; hence we made use of this tool against coffee berry borers and burrowing nematodes, as described in section 8.3.2.

8.4.4 Sustainable management of plant resistance

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

We built a generic spatio-temporal epidemiological model representing (fungal) disease spread on annual field crops in a multi-pathogen context. This work benefits from data collected in INRAE projects COCODIV and DYNAMO on wheat diseases. It will be pursued in the ENDURANCE and PAPEETE projects (section 10.2).

Previous work we performed on plant resistance, especially online interactive platforms we developed such as RNem, open new opportunities for collaborations on the use of service plants [37].

8.4.5 Behavioral Epidemiology and Evolution of Plant Pathogens

In this work, we aimed at better understanding the interaction between human behavior and plant epidemiology. Our work on this topic started with the consideration of clean seed systems, and their use dynamics at landscape scale in a seasonal context. We considered that growers could choose between clean seeds and farmer seeds at the beginning of each cropping season, with clean seeds devoid of disease and farmer seeds carrying some disease depending on the epidemiological status of the crop the year before. We supposed that this choice was made following imitation dynamics, the proportion of growers adopting clean seeds depending on this proportion and on the disease prevalence the year before. We uncovered bistability situations where the usage of clean seeds could not spread within the grower population from a small group of users, though it was stable at large usage proportion. Also, we found the counterintuitive situation where the usage of more resistant strains resulted in a reduced usage of clean seeds and so in a more important disease impact. This work was part of Diego Petit's internship within the BEEP project.

9 Bilateral contracts and grants with industry

Participants: Jérémie Roux, Marielle Péré, Madalena Chaves.

CellEmax: is an ongoing project of start-up creation. The start-up biotech will be a spin-off of our team and the experimental biology group led by Jérémie Roux at IPMC, to exploit our previous research results [45] and an invention disclosure (Jérémie Roux, Marielle Péré et al.). The future biotech will be an innovation-driven company, partnering with pharmaceutical labs to provide its proprietary technology on Target Discovery for combination treatment in oncology. In addition to experimental workflows, the biotech will develop software and algorithmic frameworks of cells dynamics analyses, integrating machine learning and signal processing.

10 Partnerships and cooperations

10.1 International initiatives

10.1.1 Associate Teams in the framework of an Inria International Lab or in the framework of an Inria International Program

EPITAG

Title: Epidemiological Modelling and Control for Tropical Agriculture

Duration: 2022-2024

Coordinator: Samuel Bowong (sbowong@gmail.com)

Partners:

- University of Douala (Cameroon)

Inria contact: Suzanne Touzeau

Summary: 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 and represent a threat to food security. 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 analyzing 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, field experts and stakeholders need to be closely associated. We will focus on pest and pathogens that affect major staple food and cash crops, such as cocoa plant mirids, plantain and banana plant-parasitic nematodes, coffee berry borers, coffee leaf rust, maize stalk borers, cabbage diamondback moths, papaya mealybugs, etc. To tackle these issues, we jointly supervise master and PhD students.

10.1.2 Visits of international scientists

Other international visits to the team

Tomas Gedeon

Status: Professor

Institution of origin: Montana State University

Country: United States

Dates: September 1-30, 2024

Context of the visit: Collaboration with Madalena Chaves, Jean-Luc Gouzé, and Valentina Baldazzi, for the development of new qualitative approaches to model complex biological systems.

Mobility program/type of mobility: research stay funded by Académie 1 “Réseaux, Information et Société Numérique” (Idex UniCA, DS4H)

10.1.3 Visits to international teams

Research stays abroad

Pauline Mazel

Visited institution: University of Aachen

Country: Germany

Dates: December 9-13, 2024.

Context of the visit: Collaboration with Pr. Thomas Stiehl for the development of a model and control for acute myeloid leukemia.

Mobility program/type of mobility: research stay

10.2 National initiatives

- **ANR Ctrl-AB:** The objectives of the Ctrl-AB project (2021-2025) are (i) to develop new control methods for the optimization of the productivity of a microbial community, and (ii) to demonstrate the effectiveness of these methods on a synthetic algal-bacterial consortium. This project is now coordinated by Eugenio Cinquemani, Microcosme Grenoble.
- **ANR - InSync:** “Circadian clock synchronization in hepatocytes” (2022-2027). This project aims to decipher intercellular synchronization mechanisms responsible for robust rhythms in peripheral clocks. Focusing on hepatocytes, and using both 2D cultures and 3D spheroids, we will study cell communication patterns and cell clock synchronization. Project coordinated by Madalena Chaves.
- **ANR - SuzuKIISS:ME** “Gérer *Drosophila* SuzuKII grâce aux Insectes Super Stériles : Maturation et Efficacité” (2022-2025). This project covers the ground from the development of the operational capacity and release strategies to deploy Sterile Insect Techniques (SIT), to the socio-economic impact of SIT on the control of the fruit fly *Drosophila Suzukii*.
- **ANR - BEEP:** “Behavioural Epidemiology and Evolution of Plant Pathogens” (2024-2028). This project is the first to couple behavioral dynamics and pathogen evolution in plant health, aiming at identifying where the interplay between growers’ behavior and pathogen epidemiological and evolutionary dynamics leads. This project is coordinated by Frédéric Hamelin.
- **ANR - ENDURANCE:** “ENhanced DURability AgaiNst Crop Enemies” (2024-2027). This projects aims at giving elements of answers on how to use and deploy pathogen resistances in crops in order to prevent rapid pathogen adaptation. It will study the genetic determinism(s) of resistance breakdown (the so-called virulence in the phytopathology literature), the evolution over time of the virulence allele(s) in pathogen populations and integrate this information into relevant epidemiological models.
- **EcoPhyto - PAPEETE:** “Promouvoir l’Agroécologie par la prédiction intégrative du risque sanitaire à partir de données Participatives d’Épidémiosurveillance à l’Échelle du TErritoire” (2024-2027). This project aims at using epidemiosurveillance data to reduce the intensive use of agrochemicals. It will assess health, production and economic risks to help farmers in their decision-making. By focusing on wheat diseases in an intensive agricultural zone and by involving players from the farming world, the tool developed in the project will constitute a proof of concept that can be generalized to other crops and regions.
- **EcoPhyto - CACOLAC:** “Conceptual framework for analyzing combinations of agroecological levers” (2024-2027). The models developed in this project will provide a better understanding of the impact of management measures on the local and landscape dynamics of pests and diseases. These results will complement previous scientific work by better representing the effects of levers, taking into account the landscape dimension of practices and/or the multitude of direct and indirect interactions in communities.

- **PEPR Agroécologie et Numérique - MISTIC** “Microbiomes de plantes cultivées et TIC” (2023-2028). The objective of MACBES within this flagship project of the PEPR is to model and analyze plant microbial communities and their functioning, as well as to design minimal microbial communities guaranteeing maintained functions.
- **ITMO Cancer Aviesan - Cellema**: The objective of this project (2022-2025) is to determine the molecular factors that regulate tumor cell response dynamics to immune cell cytotoxicity and contribute to the development of diagnosis tools for the rational design of cancer combination therapies. We will use single-cell response data to develop mathematical models and combine them with machine learning algorithms to enhance prediction of same-cell responses. Project coordinated by Madalena Chaves, in collaboration with Jérémie Roux and D. Oyarzun (Univ. Edinburgh).
- **SIGNALIFE**: Our team is part of this Labex (scientific cluster of excellence, 2nd period 2020-2024) whose objective is to build a network for innovation on Signal Transduction Pathways in life Sciences, and is hosted by the University Côte d’Azur. The Labex SIGNALIFE is funding the Innovation Program Young Entrepreneur Program (YEP) coordinated by Jérémie Roux, entitled “Combination Target Discovery in Oncology Drug Development: Accelerating Precision Treatment for immunotherapies, using Predictive Single-cell Pharmacodynamics” (2022-2025).
- **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 transferred 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. Côte d’Azur.
- **EcoPhyto - INTERLUDE**: “Territorial innovations to reduce phytopharmaceutical products for the sustainable production of vegetable crops” (2020-2024). MACBES members participate in a case study that focuses on the agroecological management of soil pests and pathogens in Provence.
- **IHU RespirERA** This project for a new Institut Hospitalo-Universitaire (running over 10 years, 2023-2033), is dedicated to Respiratory Health, Environment and Aging, to improve treatment and reduce incidence of pulmonary diseases linked to pollution and aging. Partners include University Côte d’Azur, the Centre Hospitalier Universitaire de Nice, and Inserm for a 20 million Euros funding. MACBES will participate on modeling signaling pathways related to tumor cell death and identification of drug targets, with the expected supervision of a PhD student and a Post-doctoral fellow. Project coordinated by Paul Hofman, Charles-Hugo Marquette and Marius Ilie.

10.2.1 Inria funding

- **Inria Startup Studio**: The CellEmax startup project is supported by the Inria Startup Studio for 12 months (2023-2024), granted to Marielle Péré (see Section 9). The Start-up Studio is helping with the entrepreneurial development of the project.

10.2.2 INRAE funding

- **DYNAMO**: “Drivers of the epidemic dynamics of wheat rusts at the landscape scale of the Zone Atelier Plaine & Val de Sèvre”, INRAE SPE Division (2022-2024), in which MACBES is a partner with INRAE Sophia Antipolis.

10.3 Regional initiatives

- **Idex-Académie 4 OSCILLA12** This is a one-year project (2024-2025) aimed at the experimental analysis and mathematical modeling of biological rhythms of 12 hours. A collaboration between F. Delaunay (IBV) and Madalena Chaves, this is an interdisciplinary internship by pairs (“stages

environnés en binômes interdisciplinaires”) project funded by Académie 4 “Complexité et Diversité du Vivant” (I dex UniCA).

- **I dex-Académie 1 Visitor grant** A grant from Académie 1 “Réseaux, Information et Société Numérique” (I dex UniCA, DS4H), to fund the one-month stay of Prof. Tomas Gedeon in our team.

11 Dissemination

11.1 Promoting scientific activities

11.1.1 Scientific events: organisation

- We organize a monthly scientific seminar together with the BIOCORE/GREENOWL project-team in which external guests and collaborators are regularly invited. We also organize a yearly four day-retreat where we share our work of the year; this year, it took place from September 30 till October 3, 2024 in Peyresq.

Member of conference program committees

- Suzanne Touzeau was a member of CARI 2024 (African Conference on Research in Computer Science and Applied Mathematics - Digital Science in Africa) program committee.
- Madalena Chaves is an Associate Editor of the Conference Editorial Board (CEB) of the IEEE Control Systems Society, since August 2020.

11.1.2 Journal

Member of the editorial boards

- Madalena Chaves is an Associate Editor of SIAM Journal on Applied Dynamical Systems (SIADS), since January 2015. She is also an Associate Editor for the new IEEE Open Access Journal on Control Systems since 2021.
- Madalena Chaves is the Guest Editor of a special issue of the Interface Focus journal on “Combinatorial models for evolving representation of dynamical behaviors in biological networks”, following a workshop on the same topic organized at the Lorentz Center (Leiden) in 2023.

Reviewer - reviewing activities

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

11.1.3 Invited talks

- Madalena Chaves was a keynote speaker at the International Conference on Computational Methods in Systems Biology (CMSB24) in Pisa, on modeling and characterization of cycle dynamics in circadian clocks.
- Madalena Chaves gave two invited seminars (both online events) at the Control and Optimization group at Louisiana State University (April 2024) and at the Center for Mathematical Medicine and Biology at the University of Nottingham (December 2024). Both seminars on the topic of coupling and synchronization dynamics in a network of biological oscillators.

11.1.4 Scientific expertise

- Suzanne Touzeau and Ludovic Mailleret participated in selection panels for INRAE research scientists.
- Madalena Chaves is a member of the scientific committee of Labex Signalife (since 2020).
- Madalena Chaves was a member of the jury for the selection of (6) PhD fellowships of the PEPR “Santé des Femmes, Santé des Couples”.
- Jean-Luc Gouzé is a member of the steering committee of Labex SIGNALIFE of Université Côte d’Azur. He is a member of the board of the SFBT (French Speaking Society for Theoretical Biology).
- Suzanne Touzeau was a member of the Ibni Prize awarding committee.
- Suzanne Touzeau is a CIMPA (Centre International de Mathématiques Pures et Appliquées) scientific officer (since 2024).

11.1.5 Research administration

- Madalena Chaves, Frédéric Grogard and Ludovic Mailleret are members of the INRAE Commission Scientifique Spécialisée (CSS) for Mathématique, Informatique, Sciences et Technologies du numérique, Intelligence artificielle et Robotique (MISTD).
- Madalena Chaves is the president of the local Inria committee NICE for welcoming external researchers (post-docs, “delegations”). She is also a member of the local Inria committee for doctoral studies (CSD) and a representative of Inria at the Canceropole PACA. She is the coordinator of the UE Biologie Systémique 1 of the new Master option on Bioinformatics and Computational Biology of the EUR Sciences du Vivant et de la Santé.
- Within UniCA, Frédéric Grogard is a member of the scientific council of the Center of Modeling, Simulation and Interactions (MSI) and of the steering committee of Academy 3, Space, Environment, Risk and Resilience of UniCA. In that framework, he co-edited the Green Book of the Academy [36]. He is co-head of the MSc Risk.
- Frédéric Grogard is a member of the Scientific Committee of the Agroecosystems department of INRAE.
- Ludovic Mailleret is the head of the M2P2 team (Models and Methods for Plant Protection) of ISA. He is in the Unit and scientific council of Institut Sophia Agrobiotech, and in the council of the INRAE PACA centre.
- Ludovic Mailleret is an elected member (since 2020) of the Scientific and Pedagogic Council (CoSP) of the EUR LIFE (Graduate school in Life and Health Sciences) of Université Côte d’Azur.
- Suzanne Touzeau is a member of the steering committee of the INRAE Metaprogramme SuM-Crop “Sustainable Management of Crop Health” (since 2016).
- Valentina Baldazzi and Suzanne Touzeau are elected members of the Institut Sophia Agrobiotech council.

11.2 Teaching - Supervision - Juries

11.2.1 Teaching

- Licence: Pauline Mazel (20h TD), “Analyse et modélisation”, L1, Portail Sciences de la Vie, Université Côte d’Azur, France
- Licence: Pauline Mazel (26h TD), “Statistiques”, L1, Portail Sciences de la Vie, Université Côte d’Azur, France

- Licence: Joseph Junior Penlap Tamagoua (28h TD), "Approximation de fonctions, intégrales et EDO", L3 Mathématiques, Université Côte d'Azur, France
- Licence: Javier Innerarity Imizcoz (30h TD), "Mathématiques I", L1, Bachelor Sciences et Ingénierie, École Centrale Méditerranée, France
- Licence: Frédéric Grogard (42h ETD) and Ludovic Mailleret (24h ETD), "Equations différentielles ordinaires et systèmes dynamiques", L3, 1st year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Côte d'Azur, France
- Master: Frédéric Grogard (14h ETD) and Ludovic Mailleret (17.5h ETD), "Bio-Mathématiques", M1, 2nd year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Côte d'Azur, France.
- Master: Frédéric Grogard (30h ETD) "Elements of mathematical modelling", M1, MSc in Environmental Hazards and Risks Management, Université Côte d'Azur, France.
- Master: Madalena Chaves (10h ETD), "Biologie Systémique", M2 Bioinformatics and Computational Biology, Université Côte d'Azur.
- Master: Jean-Luc Gouzé (20.25h ETD), Madalena Chaves (13.5h ETD), "Modeling biological networks by ordinary differential equations", M1, 2nd year Engineering in Génie biologique, Polytech Nice Sophia, Université Côte d'Azur.

11.2.2 Supervision

- PhD defended: Odile Burckard. "Mathematical analysis of cycle dynamics and synchronization of mammalian peripheral circadian clocks", Université Côte d'Azur, November 27th, 2024. Supervisor: Madalena Chaves.
- PhD in progress: Aurelien Kambeu Youmbi. "Self-Financing Model for Cabbage Crops with Pest Management", University of Dschang, Cameroon, since 2020. Supervisors: Berge Tsanou, Suzanne Touzeau and Frédéric Grogard.
- PhD in progress: Marine Courtois. "Modélisation de la technique de l'insecte stérile dans un contexte agricole : comment intégrer les réalités biologiques et techniques pour optimiser son déploiement ?", Université Côte d'Azur, since 2022. Supervisors: Ludovic Mailleret, Suzanne Touzeau and Louise Van Oudenhove De Saint Gery.
- PhD in progress: Rand Asswad. "Développement de stratégies de contrôle pour les consortiums microbiens synthétiques", since 2022, Université Grenoble-Alpes. Supervisors: Jean-Luc Gouzé and Eugenio Cinquemani (Microcosme, Inria Grenoble).
- PhD in progress: Joseph Junior Penlap Tamagoua. "Ecophysiological modeling of plant-nematode interactions: Understanding the origins and consequences of differential plant susceptibility", Université Côte d'Azur, since 2022. Supervisors: Valentina Baldazzi, Frédéric Grogard and Suzanne Touzeau.
- PhD in progress: Frank Kemayou Mangwa. "Mathematical modeling and analysis of the impact of Radopholus similis on the banana-plantain production", University of Douala, Cameroon, since 2022. Supervisors: Samuel Bowong, Suzanne Touzeau and Frédéric Grogard.
- PhD in progress: Benjamin Böbel. "Mathematical models for robustness and control of intercellular coupling and synchronization between peripheral circadian clocks", Université Côte d'Azur, since April 2023. Supervisor: Madalena Chaves and Jean-Luc Gouzé.
- PhD in progress: Pauline Mazel. "Modeling, analysis and control of cancer cell population dynamics", Université Côte d'Azur, since 2023. Supervisors: Walid Djema and Frédéric Grogard.

- PhD in progress: Javier Innerarity Imizcoz "Allocation optimale de ressources pour des modèles mathématiques de micro-organismes dans des conditions environnementales dynamiques", since October 2023, Université Côte d'Azur, Supervisors: Jean-Luc Gouzé, Walid Djema (GreenOwl) and Francis Mairet (Ifremer Nantes).
- PhD in progress: Sthyyve Tatho. "Intégration de données multi-omiques pour l'analyse de la dynamique de communautés microbiennes en santé des plantes", Université Bordeaux, since January 2024. Supervisors: Simon Labarthe and Valentina Baldazzi.
- PhD in progress: Armando Kenne Meli. "Modélisation et analyse de la dynamique de la mouche blanche, vecteur de la mosaïque africaine du manioc", University of Yaoundé I, since September 2024. Supervisors: Jean-Jules Tewa, Suzanne Touzeau, Frédéric Grogard.

11.2.3 Master theses and internships

- M1: Omar Sabir. "Microbial community responses to host-derived substrate change", Polytech Nice. 5 months. Supervisors: Valentina Baldazzi and Jean-Luc Gouzé.
- M1: Diego Petit. "Imitation dynamics for the choice of clean or farmer seeds for crop protection", Polytech Nice. 5 months. Supervisors: Ludovic Mailleret, Frédéric Grogard and Joseph Penlap.
- M2: Manon Pugnet. "Modeling the population dynamics of *Drosophila suzukii* and optimizing releases for the deployment of the Sterile Insect Technique", Université Claude Bernard Lyon I. 6 months. Supervisors: Marine Courtois, Frédéric Grogard and Ludovic Mailleret.

11.2.4 Juries

- Madalena Chaves was president of the jury for the PhD thesis of Asma Chalabi (Université Côte d'Azur, May 28th 2024). She was a member of the jury of Zakarya El-Khiyati (December 13, 2024)
- Madalena Chaves is in the Comité de Suivi Doctoral of: Romain Michelucci (UniCA), Adel Anabi (UniCA), Joseph Penlap (UniCA), Clémence Métayer (Institut Curie), and Pauline Delpierre (Université de Lille).
- Jean-Luc Gouzé was a member of the jury for the PhD thesis of H. Sun (Université de Nantes), Odile Burkhard (Unica), Othman Cherkaoui-Dekkaki (Université de Rabat, Morocco).

12 Scientific production

12.1 Major publications

- [1] S. Almeida, M. Chaves and F. Delaunay. 'Control of synchronization ratios in clock/cell cycle coupling by growth factors and glucocorticoids'. In: *Royal Society Open Science* 7.2 (2020), p. 192054. DOI: [10.1098/rsos.192054](https://doi.org/10.1098/rsos.192054). URL: <https://hal.sorbonne-universite.fr/hal-02505080> (cit. on pp. 6, 8).
- [2] V. Baldazzi, D. Ropers, J.-L. Gouzé, T. Gedeon and H. de Jong. 'Resource allocation accounts for the large variability of rate-yield phenotypes across bacterial strains'. In: *eLife* 12 (31st May 2023), pp. 1–29. DOI: [10.7554/eLife.79815](https://doi.org/10.7554/eLife.79815). URL: <https://hal.inrae.fr/hal-04145943>.
- [3] M. Chaves, L. Gomes-Pereira and J. Roux. 'Two-level modeling approach to identify the regulatory dynamics capturing drug response heterogeneity in single-cells'. In: *Scientific Reports* 11.1 (Dec. 2021). DOI: [10.1038/s41598-021-99943-0](https://doi.org/10.1038/s41598-021-99943-0). URL: <https://inria.hal.science/hal-03439255> (cit. on p. 6).
- [4] P. Clin, F. Grogard, D. Andrivon, L. Mailleret and F. M. Hamelin. 'Host mixtures for plant disease control: Benefits from pathogen selection and immune priming'. In: *Evolutionary Applications* 15.6 (23rd May 2022), pp. 967–975. DOI: [10.1111/eva.13386](https://doi.org/10.1111/eva.13386). URL: <https://inria.hal.science/hal-03676499>.

- [5] S. Nilusmas, M. Mercat, T. Perrot, C. Djian-caporalino, P. Castagnone-Sereno, S. Touzeau, V. Calcagno and L. Mailleret. ‘Multi-seasonal modelling of plant-nematode interactions reveals efficient plant resistance deployment strategies’. In: *Evolutionary Applications* 13.9 (2020), pp. 2206–2221. DOI: [10.1111/eva.12989](https://doi.org/10.1111/eva.12989). URL: <https://hal.inrae.fr/hal-02775269>.
- [6] C. Poignard, M. Chaves and J.-L. Gouzé. ‘A Stability Result for Periodic Solutions of Nonmonotonic Smooth Negative Feedback Systems’. In: *SIAM Journal on Applied Dynamical Systems* 17.2 (3rd Apr. 2018), pp. 1091–1116. DOI: [10.1137/17M1141205](https://doi.org/10.1137/17M1141205). URL: <https://inria.hal.science/hal-01872255>.
- [7] E. Rousseau, M. Bonneault, F. Fabre, B. Moury, L. Mailleret and F. Grogard. ‘Virus epidemics, plant-controlled population bottlenecks and the durability of plant resistance’. In: *Philosophical Transactions of the Royal Society B: Biological Sciences* 374.1775 (24th June 2019), p. 20180263. DOI: [10.1098/rstb.2018.0263](https://doi.org/10.1098/rstb.2018.0263). URL: <https://inria.hal.science/hal-02149025>.
- [8] I. Tankam Chedjou, S. Touzeau, L. Mailleret, J. J. Tewa and F. Grogard. ‘Modelling and control of a banana soilborne pest in a multi-seasonal framework’. In: *Mathematical Biosciences* 322 (Apr. 2020), p. 108324. DOI: [10.1016/j.mbs.2020.108324](https://doi.org/10.1016/j.mbs.2020.108324). URL: <https://hal.inrae.fr/hal-02775460>.

12.2 Publications of the year

International journals

- [9] P. Bernhard. ‘There is no known nonlinear Markov perfect equilibrium strategies for the infinite horizon linear quadratic differential game’. In: *Journal of Economic Theory* 222 (Dec. 2024), p. 4. DOI: [10.1016/j.jet.2024.105927](https://doi.org/10.1016/j.jet.2024.105927). URL: <https://inria.hal.science/hal-04912486>.
- [10] O. Burckard and M. Chaves. ‘Analytic solutions for the circadian oscillator characterize cycle dynamics and its robustness’. In: *Journal of Mathematical Biology* 90.1 (2025), p. 5. DOI: [10.1007/s00285-024-02164-y](https://doi.org/10.1007/s00285-024-02164-y). URL: <https://hal.science/hal-04391710> (cit. on pp. 5, 6).
- [11] O. Burckard, M. Teboul, F. Delaunay and M. Chaves. ‘Benchmark for quantitative characterization of circadian clock cycles’. In: *BioSystems* 247 (Jan. 2025), p. 105363. DOI: [10.1016/j.biosystems.2024.105363](https://doi.org/10.1016/j.biosystems.2024.105363). URL: <https://inria.hal.science/hal-04834066> (cit. on pp. 5, 7).
- [12] O. Cherkaoui-Dekkaki, W. Djema, N. Raissi, J.-L. Gouzé and N. El Khattabi. ‘Optimal control of waste recovery process’. In: *International Journal of Dynamics and Control* (2024). DOI: [10.1007/s40435-024-01484-7](https://doi.org/10.1007/s40435-024-01484-7). URL: <https://inria.hal.science/hal-04711930> (cit. on p. 10).
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