RESEARCH CENTRE

Inria Centre at Université Côte d'Azur

IN PARTNERSHIP WITH:

INRAE, CNRS, Université Côte d'Azur

2023

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

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Project-Team MACBES

Creation of the Project-Team: 2023 July 01

Keywords

Computer sciences and digital sciences

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B3.6. – Ecology

1 Team members, visitors, external collaborators

Research Scientists

- Frédéric Grognard [Team leader, INRIA, Researcher, HDR]
- Valentina Baldazzi [INRAE, Researcher, HDR]
- Pierre Bernhard [INRIA, Emeritus, until Aug 2023]
- Madalena Chaves [INRIA, Senior Researcher, Vice-team leader, HDR]
- Jean-Luc Gouzé [INRIA, Senior Researcher, HDR]
- Ludovic Mailleret [INRAE, Senior Researcher, HDR]
- Jérémie Roux [CNRS, Researcher, HDR]
- Suzanne Touzeau [INRAE, Researcher]

Post-Doctoral Fellows

- Clotilde Djuikem [UNIV COTE D'AZUR, until Aug 2023]
- Giada Fiandaca [INRIA, from Nov 2023]

PhD Students

- Odile Burckard [INRIA]
- Benjamin Böbel [INRIA]
- Javier Innerarity Imizcoz [UNIV COTE D'AZUR, from Nov 2023]
- Pauline Mazel [UNIV COTE D'AZUR, from Oct 2023]
- Joseph Junior Penlap Tamagoua [INRIA]

Interns and Apprentices

- Javier Innerarity Imizcoz [INRIA, Intern, from Apr 2023 until Aug 2023]

Administrative Assistant

- Maeva Jeannot [INRIA]

Visiting Scientists

- Aurelien Kambeu Youmbi [UNIV DSCHANG, CAMEROON, from Dec 2023]
- Frank Kemayou Mangwa [UNIV DOUALA, CAMEROON, from Dec 2023]

External Collaborators

- Vincent Calcagno [INRAE, from Oct 2023, HDR]
- Frédéric Hamelin [INSTITUT AGRO RENNES-ANGERS, from Oct 2023, HDR]
- Marielle Péré [Inria Start-up studio, from Jul 2023]
- Louise Van Oudenhove De Saint Gery [INRAE, from Oct 2023]

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 callibration 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 inolving common tools from control theory and computational biology, with models built in 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 fours 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 going as far as designing an ecosystem de novo, 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

- Marielle Péré was awarded the i-PhD Concours d'Innovation grand prize for her participation, based on her thesis work, in the start-up project CellEmax which goal is to propose rational identification of new targets for anticancer combination treatments.
- Different strains of a microorganism growing in the same environment display a wide variety of growth rates and growth yields. We developed a coarse-grained model to test the hypothesis that different resource allocation strategies, corresponding to different compositions of the proteome, can account for the observed rate-yield variability [2]. Validated by a compiled database of hundreds of published rate-yield phenotypes of *Escherichia coli* strains, the model highlights the complex nature of the relationship between metabolites, growth rate, and yield. An interesting prediction of our model is that high growth rates are not necessarily accompanied by low growth yields: high-rate, high-yield growth of *E. coli* can be achieved by a higher saturation of enzymes and ribosomes, and thus by a more efficient utilization of proteomic resources.
- A workhop on mathematical modelling in tropical agriculture was organised in Dschang, Cameroon, 1-4 November 2023. Its aims were twofold: bring together people involved in the EPITAG associate team to present scientific achievements and discuss planned work, so as to capitalise on the experience gained; present EPITAG and foster interest in its approaches, in particular among young researchers. The workshop was a success: there were 18 presentations and more than 30 participants from the universities of Dschang, Douala, Yaoundé, and from France (hybrid meeting), among which a majority of young scientists. Most participants were applied mathematicians, but biologists also attended the workshop.
  More details on the EPITAG website.

6.1 Awards

- Marielle Péré obtained a STIC Doctoral School prize for her thesis "Modeling cancer drug response dynamics in single-cells to predict the emergence of drug-tolerant cells".

7 New software, platforms, open data

7.1 New software

7.1.1 EASIDRUG

Name: EArly Single-cell Isolation with a Drug Response Up-Graded forecaster for live-cell microscopy assays

Keywords: Machine learning, Live-cell microscopy, FRET (Foster resonance energy transfert), Forecasting, Pharmacology, Cancer, Time-trajectories classification

Scientific Description: This software will be used by the experimental team to select cancer cells during live-cell microscopy expriments.

Functional Description: This software follows 4 steps: 1 - Download FRET trajectories of Hela clonal cancer cells treated with TRAIL from the article database: Roux, Jérémie, et al. "Fractional killing arises from cell-to-cell variability in overcoming a caspase activity threshold." Molecular systems biology 11.5 (2015): 803 and identification of the TRAIL treatment response phenotype. 2 - Extraction of more than 900 mechanical and statistical features of the FRET signal for each cell. 3 - Selection of a group of N characteristics to identify the future response (tolerant/sensitive) to TRAIL treatment for a maximum number of cells and creation of a response forecasting algorithm (SVM 1d) taking these fetaures as input. 4 - Cross-validation of the algorithm

Release Contributions: First version, to be improved and transformed into a platform

Publications: hal-03868577, hal-03868542, hal-03868569, hal-03868584, hal-03522480

Contact: Marielle Pere

Participants: Marielle Pere, Jeremie Roux, Asma Chalabi, Madalena Chaves

Partner: Institut de Pharmacologie moléculaire et cellulaire (IPMC)

8 New results

The MACBES project-team was created on July 1st, 2023. However, in order to present a sufficient body of work covering all the aspects of our activity, we decided to present works covering the whole 2023 year.

8.1 Network interactions for cell function and growth

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

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[58], we proposed an ODE model of the molecular pathways involved in cell death triggered by Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) calibrated on single-cell time-trajectories of a Förster resonance energy transfer (FRET) reporter measuring apoptosis signaling dynamics in clonal HeLa cells [60]. With this model, we constructed a timeline for the different steps in the regulation of apoptosis and located an initial cell fate decision just after TRAIL binding [62]. Furthermore, we identified three specific parameter combinations that can distinguish between drug resistant or sensitive phenotypes. The next step was to combine the ODE model's mechanistic features with predictive values for cell decision with machine-learning classification models, to determine the drug response of each cell before it commits to an irreversible decision. Our mechanistic-informed approach, combining an ODE system with machine learning classifiers, outperformed classic machine learning approaches and enabled the accurate cell response prediction of otherwise unpredictable cells [61]. This part of the work was in collaboration with Diego Oyarzún (University of Edinburgh). This methodology is part of Marielle Péré PhD thesis [37], who won a STIC Doctoral School prize.

In addition, based on her thesis work, Marielle participated to the start-up project CellEmax, which goal is to propose rational identification of new targets for anticancer combination treatments, for which she was awarded an i-PhD Concours d'Innovation grand prize.

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. This is the subject of the PhD thesis of Pauline Mazel.

8.1.2 Intercellular communication in 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 [53]. This method helps to further characterize the synchronization steps between two clocks of distinct (but close) periods. This work was presented by Odile Burckard at the 48th Congress of the Société Francophone de Chronobiologie [28]. In addition, 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 [46], [38]. This work is in collaboration with F. Delaunay (ANR InSync), and is 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 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 the ANR Maximic project (collab. 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 [11]. The model predictions were verified by means of a database of hundreds of published rate-yield and uptake-secretion phenotypes of *Escherichia coli* strains grown in standard laboratory conditions. We found a very good quantitative agreement between the range of predicted and observed growth rates, growth yields, and glucose uptake and acetate secretion rates. These results support the hypothesis that resource allocation is a major explanatory factor of the observed variability of growth rates and growth yields across different bacterial strains. One of the main outcomes of our model, supported by the experimental data, is that high growth rates are not necessarily accompanied by low growth yields. The resource allocation strategies enabling high-rate, high-yield growth of *E. coli* lead to a higher saturation of enzymes and ribosomes, and thus to a more efficient utilization of proteomic resources.

The model is currently used to investigate the set of adaptation strategies that microbial cells can use to increase their growth rate or their growth yield in a given environment. Preliminary results suggest that multiple allocation choices are possible, depending on the initial allocation state of the cell and its biomass composition.

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

Weak synchronization and convergence in coupled genetic regulatory networks. We consider a general model of genetic networks and examine two forms of interconnection, either homogeneous or heterogeneous coupling, corresponding to coupling functions that are either equal or different from those governing the individual dynamics. In the case of individual subsystems having unique but different steady states, we prove that the homogeneous coupled system has a unique globally asymptotically stable steady state. Moreover, in the case of large coupling strength, we show that under suitable assumptions the network achieves weak synchronization since the individual steady states become arbitrarily close [10]. We apply the results to the synchronization of damped oscillators and to the control of multistable systems.

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.

8.2.2 Optimization and optimal control in the cell

Optimal allocation of resources in a bacteria. We study by techniques of optimal control the optimal allocation between metabolism and gene expression during growth of bacteria, in collaboration with Inria IBIS 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 [21], (ANR project Maximic, PhD thesis of Agustin Yabo, internship then ongoing PhD of Javier Innerarity Imizcoz , in collaboration with W. Djema (Biocore) and F. Mairet (IFREMER Nantes)).

8.3 Modeling agro-ecological interactions

Participants: Valentina Baldazzi, Frédéric Grognard, Suzanne Touzeau, Ludovic Mailleret, Clotilde Djuikem, Aurelien Kambeu Youmbi, Frank Kemayou Mangwa, Joseph Junior Penlap Tamagoua.

8.3.1 Ecophysiological modeling of plant-microbiota 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 certains plants to sustain RKN infestation with limited damages. To address this, we built an ecophysiological model of plant growth, including both the vegetative and the reproductive phases, coupled with a model of nematode population dynamics. Briefly, the plant is divided into shoots, which provide carbon, and roots, which provide water for plant growth. During the reproductive phase, fruit onset marks the addition of a new carbon sink for the plant. Nematodes are explicitly considered as feeding on plant resources, so that any change in the plant physiological status or plant composition will in turn affect pest growth and multiplication, and vice versa. The apparition of fruits, in particular, can substantially modify the ressource allocation pattern of the plant, with important consequences on plant susceptibility to pest attack. The model was calibrated for two plant species using experimental data collected in the framework of INRAE ArchiNem project (2020-2021). A dedicated calibration pipeline was developed in order to combine heterogeneous data at different time-scales. Eventually, the model will be used to explore the dynamical behaviour of the system and to gain insight into the relative role of plant development and phenotypic traits (including physiological and architectural features), pest development and environmental factors in the progression of the infection.

This work is part of the PhD thesis of Joseph Penlap Tamagoua (Inria-INRAE funding 2022-2025) and was presented at several international conferences [49, 33, 34]. Two publications are currently in preparation, focusing respectively on the experimental results and on model development and calibration.

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 [56]. 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 [16] or coffee berry borers [42], and of the sterile insect technique [32]. Semi-discrete models were central in Frédéric Grognard's HDR defense [36] and Clotilde Djuikem's PhD thesis [35].

In this framework, we studied how recurrent migration events ("pulsed migration") between different spatial locations influence the evolution of populations through a population genetics approach [9]. We evidenced that migration pulsedness affects allele fixation rates in interaction with their selective value, generally reducing the level of local adaptation as compared to continuous migration. This research was part of Flora Aubree's PhD thesis (defended in 2022), and has been performed in collaboration with Vincent Calcagno (ISA).

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 damages in crops, with applications in tropical agriculture, in the framework of the EPITAG associate team with Cameroon (section 10.1.1). We considered several pathosystems.

- Coffee berry borers are insects that mostly develop and feed inside coffee berries, and hence cause major crop damages worlwide. 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 [17, 42]. This research pertains to Yves Fotso Fotso's PhD thesis [52].

- 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 multi-seasonal model of CLR development in a coffee plantation, with continuous dynamics during the rainy season and a discrete event to represent the simpler dynamics during the dry season [16, 30]. We also performed a bifurcation analysis of a more complex model taking the development stage of the leaves into account (paper under revision). This work is part of Clotilde Djuikem's PhD thesis that was defended in 2023 [35].

- Cabbage is a very important food crop for small farmers in Cameroon. We developed a model self-financing model 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 [31]. This work is part of Aurelien Kambeu Youmbi's ongoing PhD thesis.

- Bananas, including plantains, are major staple foods in many tropical countries, including Cameroon. These plants are affected by burrowing nematodes (*Radopholus similis*) that create root lesions and induce great damages. We developed a model of the plant-pest interactions with the original feature that infestation intensity may vary within the root. We did a bifurcation analysis of this model and developed an optimal control against the pest. This work is part of Frank Kemayou Mangwa's ongoing PhD thesis.

Spatial population dynamics of biological control agents We have been involved for several years in a mixed modeling-experimental approach to explore the spatio-temporal dynamics of populations, with special interest to micro-wasp parasitoids [59, 55]. With such an approach, we explored how positive density-dependence in growth or dispersal interact with spatial heterogeneity to impact population spread [19]. In this context, we showed that the expansion rate is not only determined by the current environmental conditions at the edge of the population, but is also strongly influenced by the conditions encountered at previous times and locations by the moving front of the population. This research has been performed in collaboration with Elodie Vercken (ISA).

Concurrently, we are exploring the correlation between biological control agents movement characteristics at different scales, from laboratory experimental characterization to semi-field dispersal on parasitoids belonging to the genus *Trichogramma*. A specific mid-scale laboratory device to study insect dispersal over several meters has been designed [15] and used to understand how insect movements shape group dispersal in such parasitoïds [13]. This research was part of the PhD theses of Victor Burte (defended 2018) and Melina Cointe (defended 2023, [54]) and was performed in collaboration with Vincent Calcagno (ISA).

8.4 Design and control of managed ecosystems

Participants: Jean-Luc Gouzé, Frédéric Grognard, Suzanne Touzeau, Ludovic Mailleret, Clotilde Djuikem, Aurelien Kambeu Youmbi, Frank Kemayou Mangwa, 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 behaviour and built observers to try to optimize some output [26]. Moreover, we studied the effects of control on the system (PhD thesis of Rand Aswad, Grenoble, in collaboration with E. Cinquemani (Microcosme)).

In the framework of IPL Cosy (led by E. Cinquemani), we studied the coexistence of two strains of bacteria *E. Coli* in a bioreactor. The strains had been modified synthetically. The aim was to obtain a better productivity in the consortium than in a single strain, by control methods [57]. We obtained optimization results for the optimal production or yield [18].

8.4.2 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 [48, 29, 47]. In the framework of Taha Belkayate's internship, we extended these results to take remating into account. This work pertains to Marine Courtois's ongoing PhD thesis.

Predator releases for coffee leaf rust Biological control was added to the multi-seasonal impulsive model describing coffee leaf rust spread in a plantation (section 8.3.2), using predators through one or more discrete introduction events over the year. Analytical and semi-numerical studies were performed to identify how much and how frequently predators needed to be introduced. We showed that the best strategy to efficiently control the disease depends on the predator mortality: low mortality parasites can be released only once a year, while high mortality parasites should be released more frequently to ensure their persistence in the plantation [16]. This work pertains to Clotilde Djuikem's PhD thesis that was defended in 2023 [35].

Optimal control for coffee berry borers Controling coffee berry borers is particularly challenging, as the insects spend most of their life cycle inside berries. Pest control was introduced in the model describing the interactions between borers and coffee berries (section 8.3.2), based on the combination of a biopesticide (entomopathogenic fungus such as *Beauveria bassiana*), that is sprayed and persist on the berries, and traps. Using optimal control theory, we showed a synergy between the two controls for profit optimization [17]. We also investigated how to optimize biopesticide spraying considering it as an impulsive control [42] (accepted in ARIMA). This research pertains to Yves Fotso Fotso's PhD thesis [52].

8.4.3 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 pe pursued in the ENDURANCE and PAPEETE projects (section 10.4).

An epidemiological model of gene-for-gene interaction has been designed, considering increased defense to pathogen infections following previous exposure to a pathogen or an elicitor, namely priming. Priming provides a sort of immunity to virulent pathogens for resistant plants having undergone an infection attempt by an avirulent pathogen. We developed an epidemiological model to explore how mixing two distinct resistant varieties can reduce disease prevalence. We considered a pathogen population composed of three genotypes infecting either one or both varieties. We found that host mixtures should not contain an equal proportion of resistant plants, but a biased ratio to minimize disease prevalence, and that it should contain a lower proportion of the costliest resistance for the pathogen to break [14]. This was done in collaboration with Frédéric Hamelin (Institut Agro) in the framework of Pauline Clin's thesis.

We also participated in an opinion paper advocating that the theoretical framework of population genetics could bridge the gap existing between evolution/epidemiology approaches and molecular approaches to the durability of resistance problem [20]. The ENDURANCE ANR project is built upon the findings presented in this paper (section 10.4).

9 Bilateral contracts and grants with industry

Participants: Jérémie Roux, Marielle Péré, Madalena Chaves, Jean-Luc Gouzé.

CellEmax: is an ongoing project of start-up creation. The startup 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 [58] and an invention disclosure (Jérémie Roux, Marielle Péré et al.). The future biotech will be an innovation-driven company, partnering with pharmaceuticals 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.

9.1 Bilateral Grants with Industry

Exactcure: in the collaboration with the start-up Exactcure (Nice), the goal of the project is to study personalized pharmacokinetic models. We have regular contacts with Exactcure, which hired our PhD student Lucie Chambon.

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.

10.2 International research visitors

10.2.1 Visits of international scientists

Other international visits to the team

Julien Arino

Status: professor

Institution of origin: University of Manitoba

Country: Canada

Dates: 3-6 January 2023

Context of the visit: Clotilde Djuikem's PhD defense

Mobility program/type of mobility: seminar

Samuel Bowong

Status: professor

Institution of origin: University of Douala

Country: Cameroon

Dates: 3-8 January 2023

Context of the visit: EPITAG associate team

Mobility program/type of mobility: Clotilde Djuikem's PhD defense

Aurelien Kambeu Youmbi

Status: PhD student

Institution of origin: University of Dschang

Country: Cameroon

Dates: 6 February – 1 May 2023 & 15 November 2023 – 15 April 2024

Context of the visit: EPITAG associate team

Mobility program/type of mobility: research stay

Frank Kemayou Mangwa

Status: PhD student

Institution of origin: University of Douala

Country: Cameroon

Dates: 6 February – 1 May 2023 & 15 November 2023 – 15 April 2024

Context of the visit: EPITAG associate team

Mobility program/type of mobility: research stay

10.2.2 Visits to international teams

Research stays abroad

Madalena Chaves

Visited institution: Instituto Superior Técnico (Lisbon)

Country: Portugal

Dates: 8-31 July 2023

Context of the visit: collaboration with Rui Dilão on models of cell growth

Mobility program/type of mobility: research stay

Suzanne Touzeau

Visited institution: University of Dschang

Country: Cameroon

Dates: 29 October – 6 November 2023

Context of the visit: EPITAG associate team

Mobility program/type of mobility: workshop

10.3 European initiatives

10.3.1 Horizon Europe

- **NEM-EMERGE:** "An integrated set of novel approaches to counter the emergence and proliferation of invasive and virulent soil-borne nematodes" (2023-2027). This project aims at providing sustainable, science-based solutions for both conventional and organic farming sectors based on the principles of IPM (integrated pest management), including optimized crop rotations schemes, tailored host plant resistances, and optimal use of the native antagonistic potential of soils. Moreover, monitoring and risk assessment tools will be generated to support plant health authorities in decision and policy making.

10.4 National initiatives

- **ANR Ctrl-AB:** The objectives of the Ctrl-AB project (2021-2024) 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 coordinated by Jean-Luc Gouzé.

- **ANR - Maximic:** The goal of the project (2017-2023) is to design and implement control strategies in a bacterium for producing at maximal rate a high value product. It is coordinated by H. de Jong (IBIS Grenoble), and involves members of Biocore and McTao.

- **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 behavioural dynamics and pathogen evolution in plant health, aiming at identifying where the interplay between growers’ behaviour 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.

- **EcoPhyto CeraTIS Corse:** "Territorial management of the Mediterranean fruit fly in Corsica by the Sterile Insect Technique" (2020-2023). This project is based on a pilot field experiment of sterile male releases and it integrates population dynamics and socio-economic approaches.

- **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 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. Côte d'Azur.

- **EcoPhyto - INTERLUDE:** "Territorial innovations to reduce phytoparmaceutical 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.

10.4.1 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.

10.4.2 INRAE funding

- **COCODIV:** “Crop disease co-occurrence in cereal systems: determinants, role and management of cultivated and wild diversity from plot scale to landscape level integration”, INRAE SuMCrop Metaprogramme (2022–2023), in which MACBES is a partner with INRAE Sophia Antipolis.
- **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.

11 Dissemination

11.1 Promoting scientific activities

11.1.1 Scientific events: organisation

Member of the organizing committees

- We organise a monthly scientific seminar together with the BIOCORE project-team in which external guests and collaborators are regularly invited. We also organise a yearly four day-retreat where we share our work of the year; this year, it took place 16-19 october 2023 in Porquerolles.
- Marielle Péré was one of the organizers of the Inria PhD Student Seminars, taking place every two weeks.
- Valentina Baldazzi participated in the organisation of the ICTP Advanced school on "Quantitative Principles in Microbial Physiology: from Single Cells to Cell Communities", that took place in Trieste, Italy in October 2023. link
- Suzanne Touzeau participated in the organisation of the EPITAG workshop at the University of Dschang, Cameroon, 1–4 November 2023. Cf. 6.
- Suzanne Touzeau was a member of the organizing committee of the International Congress of Plant Pathology - ICPP 2023 satellite event “How to combine remote sensing with epidemiological modelling to improve plant disease management?”, Lyon, France, 19–20 August 2023.
- Suzanne Touzeau was a member of the scientific and organizing committees of the Mathematical Population Dynamics, Ecology and Evolution - MPDEE 2023 conference, CIRM Marseille, France, 24-28 April 2023.

11.1.2 Journal

Member of the editorial boards

- Madalena Chaves is an Associated Editor of SIAM Journal on Applied Dynamical Systems (SIADS), since January 2015. She is an Associated Editor of the Conference Editorial Board (CEB) of the IEEE Control Systems Society, since August 2020. She is also an Associated Editor for the new IEEE Open Access Journal on Control Systems.
- Jean-Luc Gouzé is an Associated Editor of the journal Frontiers in Applied Mathematics and Statistics (Mathematical Biology).
- Suzanne Touzeau is an Academic Editor of PLOS ONE, since August 2018.

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

- Jean-Luc Gouzé and Madalena Chaves gave talks at the "Computing combinatorial dynamics in high dimensional biological networks", October 2023, Lorenz Center, Leiden, Netherlands.
- Madalena Chaves gave a talk at a Focus session on Network Biology at the Network Science Conference, July 2023, Vienna, Austria [23]. She also gave talks at the Canceropole PACA Webinar (30 May 2023) and at the Journées Nationales de l'Informatique Mathématique, Paris (April 2023).
- Ludovic Mailleret gave a talk at the conference "Le MOnde des Mathématiques Industrielles", MOMI2023, Sophia Antipolis, April 2023.

11.1.4 Scientific expertise

- Suzanne Touzeau participated in selection panels for INRAE junior research scientists.
- Madalena Chaves, Frédéric Grognard, and Ludovic Mailleret are members of the INRAE Commission Scientifique Spécialisée (CSS) for Mathématique, Informatique, Sciences et Technologies du numérique, Intelligence artificielle et Robotique (MISTI).

11.1.5 Research administration

- Madalena Chaves is member of the local Inria committee for doctoral studies (CSD) and head of the committee NICE for welcoming external researchers (post-docs, "delegations"). She is also a representative of Inria at the Canceropole PCA. 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. Madalena Chaves is a member of the scientific committee of Labex Signalife (since 2020).
- Frédéric Grognard is a member of the steering committee of Academy 3, Space, Environment, Risk and Resilience of UCA-JEDI. He is co-head of the MSc Risk of UCA-JEDI and is a member of the Scientific Committee of the Agroecosysems 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 SuMCrop"Sustainable Management of Crop Health" (since 2016).
- Valentina Baldazzi and Suzanne Touzeau are elected members of the Institut Sophia Agrobiotech council.
- Jean-Luc Gouzé is in the Inria committee supervising the doctoral theses (until June), a member of the steering committee of Labex SIGNALIFE of Université Côte d'Azur, and of the scientific committee of Académie 4 (Life Sciences) of UCA. He is a member of the board of the SFBT (French Speaking Society for Theoretical Biology).

11.2 Teaching - Supervision - Juries

- BUT: Odile Burckard (12h ETD) "Fondamentaux de la programmation" 1st year, IUT de Nice Côte d'Azur (Département Réseaux et Télécommunications).
- Licence: Clotilde Djuikem (40h ETD) "Analyse et modélisation", PO1, Sciences de la vie, Université Côte d'Azur, France
- Licence: Clotilde Djuikem (16h ETD) "Fondements 2", PO1 Sciences, ingénierie, technologie, environnement, Université Côte d'Azur, France
- Licence : Clotilde Djuikem (24h ETD) "Intro. à la modélisation mathématique et numérique", L3, 1st year Engineering in "Genie de l'eau", Polytech Nice Sophia, Université Côte d'Azur, France
- Licence: Clotilde Djuikem (28h ETD)"Statistiques et R", L3, 1st year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Côte d'Azur, France
- Licence: Pauline Mazel (16h TD) and Joseph Junior Penlap Tamagoua (32h TD), "Fondements mathématiques 1 - partie algèbre linéaire", L1, Portail Sciences et Technologies, Université Côte d'Azur, France
- Licence: Frédéric Grognard (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
- Licence: Joseph Junior Penlap Tamagoua (28h TD), "Approximation de fonctions, intégrales et EDO", L3 Mathématiques, Université Côte d'Azur, France
- Master : Jean-Luc Gouzé (20h 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, France.
- Master: Frédéric Grognard (21h ETD) and Ludovic Mailleret (21h ETD), "Bio-Mathématiques", M1, 2nd year Engineering in Modeling and Applied Mathematics, Polytech Nice Sophia, Université Côte d'Azur, France.
- Master: Frédéric Grognard (30h ETD) "Elements of mathematical modelling", M1, MSc in Environmental Hazards and Risks Management, Université Côte d'Azur, France.
- Research School: Suzanne Touzeau gave a lecture at the CIMPA school "Mathematical and statistical modeling of complex systems", N'Djamena, Chad, 2–13 January 2023.

11.2.1 Supervision

- HDR: Frédéric Grognard. "Modelling and control of managed ecosystems, from bioreactors to agroecosystems", Université Côte d'Azur, defended February 20th.
- PhD: Marielle Péré. "Modeling cancer drug response dynamics in single-cells to predict the emergence of drug-tolerant cells", Université Côte d'Azur, defended March 27th. Supervisors: Madalena Chaves and Jérémie Roux.
- PhD: Clotilde Djuikem. "Modelling and control of perennial plant phytopathogens", Université Côte d'Azur, defended January 5th. Supervisors: Frédéric Grognard, Suzanne Touzeau and Samuel Bowong (Univ. Douala, Cameroon).
- PhD: Melina Cointe. "Mieux prédire la propagation spatiale de groupes de trichogrammes pour améliorer le biocontrôle : de l'écologie du mouvement à la dispersion dans les cultures", Université Côte d'Azur, defended Octobre 13th. Supervisors: Vincent Calcagno, Ludovic Mailleret.
- 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 Grognard.

- PhD in progress: Odile Burckard. "Coupling, synchronization, and control of cellular oscillators through mathematical modeling and analysis", Université Côte d'Azur, since 2021. Supervisor: Madalena Chaves.
- 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 Grognard 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 Grognard.
- 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. Supervisors: 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 Grognard.
- 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 (team Biocore) and Francis Mairet (Ifremer Nantes).

11.2.2 Master theses and internships

- L2: Jules Baldous. "Inflation écologique, interactions proies-prédateurs et modélisation des augmentoriums." Supervisor: Ludovic Mailleret.
- M2: Taha Belkhayate. "Modélisation de la technique de l'insecte stérile avec sexage imparfait", Université de Pau et des Pays de l'Adour. Supervisors: Marine Courtois, Louise Van Oudenhove De Saint Gery and Ludovic Mailleret.
- M2: Javier Innerarity Imizcoz "Optimisation de la croissance microbienne sous conditions périodiques", Sorbonne Université. Supervisors: Jean-Luc Gouzé and Walid Djema (Biocore team).
- M1: Dylan Cormet. "Développement d'un package Julia pour l'épidémiologie saisonnière des maladies des plantes", Polytech Nice. Supervisors: Ludovic Mailleret and Frédéric Grognard

11.2.3 Juries

- Jean-Luc Gouzé was a member of the jury for the PhD thesis of Clotilde Djuikem (UniCA), for the HDR of Frédéric Grognard (UniCA), and was a rapporteur for the HDR of D. Bichara (Univ. Bordeaux). Jean-Luc Gouzé was in the PhD committee of P. Jacquet (Univ. Grenoble) and A. Pavlou (Univ. Grenoble).
- Madalena Chaves was a rapporteur for the PhD thesis of Ana Bulovic (Institut für Biologie, Humboldt-Universität zu Berlin, April 17th 2023) and for the PhD thesis of Gian-Karlo Aguirre-Samboní (Université Paris-Saclay, December 14th 2023). She was a member of the jury for the PhD thesis of

Maaike Sansgter (Université Grenoble Alpes, May 11th 2023). Madalena Chaves is in the Comité de Suivi Doctoral of: Romain Michelucci (UniCA), Adel Anabi (UniCA), Joseph Penlap (UniCA), and Clémence Métayer (Institut Curie).

- Suzanne Touzeau was a member of the PhD examination committee of Andrea Radici (Avignon Université, December 11th 2023).

11.3 Popularization

11.3.1 Internal or external Inria responsibilities

- Madalena Chaves is in the local committee for selection of speakers for the monthly Inria Colloquium Morgenstern.

11.3.2 Education

- Madalena Chaves was selected to be part of a group of 101 Portuguese Women in Science, highlighted to showcase several branches of science and research, and motivate young generations to follow a scientific education. Photos of each scientist with a short phrase are on exhibition at the Pavilhão do Conhecimento - Ciência Viva museum in Lisbon and in a booklet.

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. URL: https://hal.sorbonne-universite.fr/hal-02505080.

[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. 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. URL: https://inria.hal.science/hal-03439255.

[4] P. Clin, F. Grognard, 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. 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. 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. URL: https://inria.hal.science/hal-01872255.

[7] E. Rousseau, M. Bonneault, F. Fabre, B. Moury, L. Mailleret and F. Grognard. '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. URL: https://inria.hal.science/hal-02149025.

[8] I. Tankam Chedjou, S. Touzeau, L. Mailleret, J. J. Tewa and F. Grognard. '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. URL: https://hal.inrae.fr/hal-02775460.

12.2 Publications of the year

International journals

[9] F. Aubree, B. Lac, L. Mailleret and V. Calcagno. 'Migration pulsedness alters patterns of allele fixation and local adaptation in a mainland-island model'. In: *Evolution - International Journal of Organic Evolution* 77.3 (1st Mar. 2023), pp. 718–730. DOI: 10.1093/evolut/qpac067. URL: https://hal.inrae.fr/hal-04047090.

[10] N. Augier, M. Chaves and J.-L. Gouzé. 'Weak synchronization and convergence in coupled genetic regulatory networks: Applications to damped oscillators and multistable circuits'. In: *International Journal of Robust and Nonlinear Control* 33.9 (June 2023), pp. 4867–4892. DOI: 10.1002/rnc.6061. URL: https://inria.hal.science/hal-03270268.

[11] 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. URL: https://hal.inrae.fr/hal-04145943.

[12] P. Bernhard, M. Deschamps and G. Zaccour. 'Large satellite constellations and space debris: exploratory analysis of strategic management of the space commons'. In: *European Journal of Operational Research* 304.3 (1st Feb. 2023), pp. 1140–1157. DOI: 10.1016/j.ejor.2022.04.030. URL: https://inria.hal.science/hal-03909662.

[13] V. Burte, M. Cointe, G. Perez, L. Mailleret and V. Calcagno. 'When complex movement yields simple dispersal: behavioural heterogeneity, spatial spread and parasitism in groups of micro-wasps'. In: *Movement Ecology* 11.1 (Dec. 2023), p. 13. DOI: 10.1186/s40462-023-00371-8. URL: https://hal.inrae.fr/hal-04047110.

[14] P. Clin, F. Grognard, D. Andrivon, L. Mailleret and F. M. Hamelin. 'The proportion of resistant hosts in mixtures should be biased towards the resistance with the lowest breaking cost'. In: *PLoS Computational Biology* 19.5 (25th May 2023), e1011146. DOI: 10.1371/journal.pcbi.1011146. URL: https://hal.inrae.fr/hal-04143995.

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