RESEARCH CENTRE

Inria Saclay Centre

IN PARTNERSHIP WITH:

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ACTIVITY REPORT

Project-Team

MUSCA

MUltiSCAle population dynamics for physiological systems

IN COLLABORATION WITH: Physiologie de la reproduction et des comportements (PRC), Mathématiques et Informatique Appliquée du Génome à l'Environnement (MAIAGE)

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life Sciences

Inria

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Project-Team MUSCA

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Keywords

Computer sciences and digital sciences

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2 Overall objectives

MUSCA is intrinsically interdisciplinary and brings together applied mathematicians and experimental biologists. We address crucial questions arising from biological processes from a mathematical perspective. Our main research line is grounded on deterministic and stochastic population dynamics, in finite or infinite dimension. We study open methodological issues raised by the modeling, analysis and simulation of multiscale in time and/or space dynamics in the field of physiology, with a special focus on developmental and reproductive biology, and digestive ecophysiology.

3 Research program

3.1 General scientific positioning

The formalism at the heart of our research program is that of structured population dynamics, both in a deterministic and stochastic version. Such a formalism can be used to design multiscale representations (say at the meso and macro levels), possibly embedding two-way (bottom-up and top-down) interactions from one level to another. We intend to couple structured population dynamics with dynamics operating on the microscopic level -typically large biochemical networks (signaling, metabolism, gene expression)-, whose outputs can be fed into the higher level models (see section 3.4). To do so, model reduction approaches have to be designed and implemented to properly formulate the "entry points" of the micro dynamics into the meso/macro formalism (e.g. formulation of velocity terms in transport equations, choice of intensities for stochastic processes) and to enable one to traceback as much as possible the variables and parameters from one scale to another. This approach is common to EPC MUSCA's two main applications in reproductive/developmental biology on one side, and microbiota/holobiont biology on the other side, while being applied to different levels of living organisms. Schematically, the meso level corresponds to the cells of a multi-cellular organism in the former case, and to the individual actors of a microbial community for the latter case.

Our general multiscale framework will be deployed on the study of direct problems as well as inverse problems. In some situations these studies will be accompanied with a post-processing layer of experimental data, which may be necessary to make the observations compatible with the model state variables, and will be based on dedicated statistical tools. Even if our approach may use classical modeling bricks, it is worth highlighting that the design of *de novo* models, specifically suited for addressing dedicated physiological questions, is a central part of our activity. Due to their intrinsic multiscale nature (in time and/or space), infinite dimensional formulation (PDE and/or measure-valued stochastic processes) and nonlinear interactions (across scales), such models raise most of the time open questions as far as their mathematical analysis, numerical simulation, and/or parameter calibration. We intend to cope with the resulting methodological issues, possibly in collaboration with external experts when needed to tackle open questions.

3.2 Design, analysis and reduction of network-based dynamic models

We will deal with models representing dynamic networks, whether in a biochemical or ecological context. The mathematical formulation of these models involve Ordinary Differential Equations (ODE), Piecewise Deterministic Markov Processes (PDMP), or Continuous Time Markov Chains (CTMC). A prototypical example is the (mass-action) Chemical Reaction Network (CRN) [54], defined by a set of d species and a directed graph $\mathscr{R}$ on a finite set of stoichiometric vectors $\{y \in \mathbb{N}^d\}$ (the linear combination of reactant and product species). A subclass of CRN corresponds to a standard interaction network model in ecology, the generalized Lotka-Volterra (gLV) model, that lately raised a lot of interest in the analysis of complex microbial communities [77, 49]. The model describes the dynamics of interacting (microbial) species through an intrinsic d-dimensional growth rate vector μ and a directed weighted interaction graph given by its $d \times d$ matrix A. The stochastic versions of these models correspond respectively to a Continuous Time Markov Chain (CTMC) in the discrete state-space $\mathbb{N}^d$, and a birth-death jump process. This general class of models is relatively standard in biomathematics [54, 48], yet their theoretical analysis can be challenging due to the need to consider high dimensional models for realistic applications. The curse of

dimensionality (state space dimension and number of unknown parameters) makes also very challenging the development of efficient statistical inference strategies.

Most of EPC MUSCA's models based on CRNs deal with (unstructured) population dynamics (complex microbial communities, neutral models in ecology, cell dynamics in developmental processes, macromolecule assemblies), biochemical kinetics and chemical reaction networks (signaling, gene, and metabolic networks), coagulation-fragmentation models (in particular Becker-Döring model). Notwithstanding the diversity of our modeling applications, we have to face common methodological issues to study such models, ranging from the theoretical analysis of model behavior to parameter inference.

Network behavior In the case of autonomous systems (with no explicit dependency on time), the main theoretical challenge is the prediction of the long time dynamics, given the algebraic complexity associated with putative stationary states in high dimension. In physiological systems, the intracellular reaction networks are not under a static or constant input stimulation but rather subject to complex and highly dynamic signals such as (neuro-)hormones [21] or metabolites. These systems are thus non-autonomous in nature. Understanding to what extent reaction network motifs are able to encode or decode the dynamic properties of a time-dependent signal is a particularly challenging theoretical question, which has yet been scarcely addressed, either in simplified case-studies [71],[11] or in the framework of "pulse-modulated systems" [52].

Network reduction The high dimension of realistic networks calls for methods enabling to perform model reduction. Our strategy for model reduction combines several tools, that can be applied separately or sequentially to the initial model. Both in stochastic biochemical systems and population dynamics, large species abundance calls in general for the functional law of large number and central limit theorems, for which powerful results are now established in standard settings of finite dimension models [59]. However, in more and more biological applications, the very large spectrum of orders of magnitude in reaction rates (or birth and death rates) leads naturally to consider simultaneously large species abundance with timescale separation, which generally results in either algebraic-differential reduced models, or to hybrid reduced models with both deterministic and stochastic dynamics. We will apply the generic methodology provided by the singular perturbation theory of Fenichel-Tikhonov in deterministic systems, and Kurtz's averaging results in stochastic systems, which, in the context of high dimensional reaction networks or population dynamics, are still the matter of active research both in the deterministic [60, 53] and stochastic context [42, 58, 70].

Other reduction approaches of deterministic systems will consist in combining regular perturbation expansion with standard linear model order reduction (MOR) techniques. We will continue our previous work [14, 13] on the derivation of convergence and truncation error bounds for the regular perturbation series expansion (also known as Volterra series expansion) of trajectories of a wide class of weakly nonlinear systems, in the neighborhood of stable hyperbolic equilibria. The challenge will be to obtain biologically interpretable reduced models with appropriate features such as for instance positivity and stability. Finding a general approach for the reduction of strongly nonlinear systems is still an open question, yet it is sometimes possible to propose ad-hoc reduced models in specific cases, using graph-based decomposition of the model [74], combined with the reduction of weakly nonlinear subsystems.

Statistical Inference, Data-fitting Once again, a key challenge in parameter estimation is due to the high dimension of the state space and/or parameter space. We will develop several strategies to face this challenge. Efficient Maximum likelihood or pseudo-likelihood methods will be developed and put in practice [12] [8], using either existing state-of-the art deterministic derivative-based optimization [75] or global stochastic optimization [50]. In any case, we pay particular attention to model predictivity (quantification of the model ability to reproduce experimental data that were not used for the model calibration) and parameter identifiability (statistical assessment of the uncertainty on parameter values). A particularly challenging and stimulating research direction of interest concerning both model reduction and statistical inference is given by identifiability and inference-based model reduction [62]. Another strategy for parameter inference in complex, nonlinear models with fully observed state, but scarce and noisy observations, is to couple curve clustering, which allows reducing the system state dimension, with robust network structure and parameter estimation. We are currently investigating this option, by

combining curve clustering [56] based on similarity criteria adapted to the problem under consideration, and an original inference method inspired by the Generalized Smoothing (GS) method proposed in [73], which we call Modified Generalized Smoothing (MGS). MGS is performed using a penalized criterion, where the log-likelihood of the measurement error (noisy data) is penalized by a model error for which no statistical model is given. Moreover, the system state is projected onto a functional basis (we mainly use spline basis), and the inference simultaneously estimates the model parameters and the spline coefficients.

3.3 Design, analysis and simulation of stochastic and deterministic models for structured populations

The mathematical formulation of structured population models involves Partial Differential Equation (PDE) and measure-valued stochastic processes (sometimes referred as Individual-Based Models–IBM). A typical deterministic instance is the McKendrick-Von Foerster model, a paragon of (nonlinear) conservation laws. Such a formalism rules the changes in a population density structured in time and (possibly abstract) space variable(s). The transport velocity represents the time evolution of the structured variable for each "individual" in the population, and might depend on the whole population (or a part of it) in the case of nonlinear interactions (for instance by introducing nonlocal terms through moment integrals or convolutions). The source term models the demographic evolution of the population, controlled by birth or death events. One originality of our multiscale approach is that the formulation of velocities and/or source terms may arise, directly or indirectly, from an underlying finite-dimension model as presented in section 3.2. According to the nature of the structuring variable, diffusion operators may arise and lead to consider second-order parabolic PDEs. For finite population dynamics, the stochastic version of these models can be represented using the formalism of Poisson Measure-driven stochastic differential equations.

From the modeling viewpoint, the first challenge to be faced with this class of models yields in the model formulation itself. Obtaining a well-posed and mathematically tractable formulation, that yet faithfully accounts for the "behavioral law" underlying the multiscale dynamics, is not an obvious task.

On one side, stochastic models are suited for situations where relatively few individuals are involved, and they are often easier to formulate intuitively. On the other side, the theoretical analysis of deterministic models is generally more tractable, and provides one with more immediate insight into the population behavior. Hence, the ideal situation is when one can benefit from both the representation richness allowed by stochastic models and the power of analysis applicable to their deterministic counterparts. Such a situation is actually quite rare, due to the technical difficulties associated with obtaining the deterministic limit (except in some linear or weakly nonlinear cases), hence compromises have to be found. The mathematical framework exposed above is directly amenable to multiscale modeling. As such, it is central to the biomathematical bases of MUSCA and transverse to its biological pillars. We develop and/or analyze models for structured cell population dynamics involved in developmental or tissue-homeostasis processes, structured microbial populations involved in eco-physiological systems and molecule assemblies.

As in the case of finite dimension models, the study of these various models involve common methodological issues.

Model behavior The theoretical challenges associated with the analysis of structured population models are numerous, due to the lack of a unified methodological framework. The analysis of the well-posedness [19] and long-time behavior [7], and the design of appropriate numerical schemes [1, 3] often rely on more or less generic techniques [69, 64] that we need to adapt in a case-by-case, model-dependent way: general relative entropy [65, 47], measure solution framework [57, 44, 51], martingale techniques [45], finite-volume numerical schemes [61], just to name a few.

Due to their strong biological anchorage, the formulation of our models often leads to new mathematical objects, which raises open mathematical questions. Specific difficulties generally arise, for instance from the introduction of nonlocal terms at an "unusual place" (namely in the velocities rather than boundary conditions [19]), or the formulation of particularly tricky boundary conditions [9]. When needed, we call to external collaborators to try to overcome these difficulties.

Model reduction Even if the use of a structured population formalism leads to models that can be considered as compact, compared to the high-dimensional ODE systems introduced in section 3.2, it can be useful to derive reduced versions of the models, for sake of computational costs, and also and above all, for parameter calibration purposes.

To proceed to such a reduction, we intend to combine several techniques, including moment equations [68], dimensional reduction [6], timescale reduction [4], spatial homogenization [40][10], discrete to continuous reduction [9] and stochastic to deterministic limit theorems [15].

Once again, all these techniques need to be applied on a case-by-case basis, and they should be handled carefully to obtain rigorous results (appropriate choice of metric topology, *a priori* estimates).

Statistical inference, Data-fitting The calibration of structured population models is challenging, due to both the infinite-dimensional setting and the difficulty to obtain rich enough data in our application domains. Our strategy is rather empirical. We proceed to a sequence of preliminary studies before using the experimental available data. Sensitivity analyses [55, 46], and theoretical studies of the inverse problems associated with the models [5] intend to preclude unidentifiable situations and ill-posed optimization problems. The generation and use of synthetic data (possibly noised simulation outputs) allow us to test the efficiency of optimization algorithms and to delimit an initial guess for the parameters. When reduced or simplified versions of the models are available (or derived specifically for calibration purposes) [2], these steps are implemented on the increasingly complex versions of the model. In situations where PDEs are or can be interpreted as limits of stochastic processes, it is sometimes possible to estimate parameters on the stochastic process trajectories, or to switch from one formalism to the other.

3.4 Coupling biochemical networks with cell and population dynamics

A major challenge for multiscale systems biology is to rigorously couple intracellular biochemical networks with physiological models (tissue and organic functions) [72, 41, 76, 63]. Meeting this challenge requires reconciling very different mathematical formalisms and integrating heterogeneous biological knowledge in order to represent in a common framework biological processes described on very contrasting spatial and temporal scales. On a generic ground, there are numerous methodological challenges associated with this issue (such as model or graph reduction, theoretical and computational connection between different modeling formalisms, integration of heterogenous data, or exploration of the whole parameter space), which are far from being overcome at the moment.

Our strategy is not to face frontally these bottlenecks, but rather to investigate in parallel the two facets of the question, through (i) the modeling of the topology and dynamics of infra-individual networks or dynamics, accounting for individual variability and local spatialization or compartmentalization at the individual level, as encountered for instance in cell signaling; and (ii) the stochastic and/or deterministic multiscale modeling of populations, establishing rigorous link between the individual and population levels. To bridge the gap, the key point is to understand how intracellular (resp. infra-individual) networks produce outputs which can then be fed up in a multicellular (resp. microbial population) framework, in the formulation of terms entering the multiscale master equations. A typical example of such outputs in individual cell modeling is the translation of different (hormonal or metabolic) signaling cues into biological outcomes (such as proliferation, differentiation, apoptosis, or migration). In turn, the dynamics emerging on the whole cell population level feedback onto the individual cell level by tuning the signal inputs qualitatively and quantitatively.

4 Application domains

The multiscale modeling approach described in section 3 is deployed on biological questions arising from developmental and reproductive biology, as well as digestive ecophysiology.

Our main developmental and reproductive thematics are related to gametogenesis, and gonad differentiation and physiology. In females, the gametogenic process of oogenesis (production and maturation of egg cells) is intrinsically coupled with the growth and development of somatic structures called ovarian follicles. Ovarian folliculogenesis is a long-lasting developmental and reproductive process characterized

by well documented anatomical and functional stages. The proper morphogenesis sequence, as well as the transit times from one stage to another, are finely tuned by signaling cues emanating from the ovaries (especially during early folliculogenesis) and from the hypothalamo-pituitary axis (especially during late folliculogenesis). The ovarian follicles themselves are involved in either the production or regulation of these signals, so that follicle development is controlled by direct or indirect interactions within the follicle population. We have been having a longstanding interest in the multiscale modeling of follicle development, which we have tackled from a "middle-out", cell dynamics-based viewpoint [2], completed progressively with morphogenesis processes [17].

On the intracellular level, we are interested in understanding the endocrine dialogue within the hypothalamo-pituitary-gonadal (HPG) axis controling the ovarian function. In multicellular organisms, communication between cells is critical to ensure the proper coordination needed for each physiological function. Cells of glandular organs are able to secrete hormones, which are messengers conveying information through circulatory systems to specific, possibly remote target cells endowed with the proper decoders (hormone receptors). We have settled a systems biology approach combining experimental and computational studies, to study signaling networks, and especially GPCR (G Protein-Coupled Receptor) signaling networks [12]. In the HPG axis, we focus on the pituitary hormones FSH (Follicle-Stimulating Hormone) and LH (Luteinizing Hormone) – also called gonadotropins-, which support the double, gametogenic and endocrine functions of the gonads (testes and ovaries). FSH and LH signal onto gonadal cells through GPCRs, FSH-R and LH-R, anchored in the membrane of their target cells, and trigger intracellular biochemical cascades tuning the cell enzymatic activity, and ultimately controlling gene expression and mRNA translation. Any of these steps can be targeted by pharmacological agents, so that the mechanistic understanding of signaling networks is useful for new drug development.

Our main thematics in digestive ecophysiology are related to the interactions between the host and its microbiota. The gut microbiota, mainly located in the colon, is engaged in a complex dialogue with the large intestinal epithelium of its host, through which important regulatory processes for the host's health and well-being take place. Through successive projects, we have developed an integrative model of the gut microbiota at the organ scale, based on the explicit coupling of a population dynamics model of microbial populations involved in fiber degradation with a fluid dynamics model of the luminal content. This modeling framework accounts for the main drivers of the spatial structure of the microbiota, specially focusing on the dietary fiber flow, the epithelial motility, the microbial active swimming and viscosity gradients in the digestive track [16].

Beyond its scientific interest, the ambitious objective of understanding mechanistically the multiscale functioning of physiological systems could also help on the long term to take up societal challenges.

In digestive ecophysiology, microbial communities are fundamental for human and animal wellbeing and ecologic equilibrium. In the gut, robust interactions generate a barrier against pathogens and equilibrated microbiota are crucial for immune balance. Imbalances in the gut microbial populations are associated with chronic inflammation and diseases such as inflammatory bowel disease or obesity. Emergent properties of the interaction network are likely determinant drivers for health and microbiome equilibrium. To use the microbiota as a control lever, we require causal multiscale models to understand how microbial interactions translate into productive, healthy dynamics [20].

In reproductive physiology, there is currently a spectacular revival of experimental investigations (see e.g. [66, 78]), which are driven by the major societal challenges associated with maintaining the reproductive capital of individuals, and especially female individuals, whether in a clinical (early ovarian failure of idiopathic or iatrogenic origin in connection with anticancer drugs in young adults and children), breeding (recovery of reproductive longevity and dissemination of genetic progress by the female route), or ecological (conservation of germinal or somatic tissues of endangered species or strains) context. Understanding the intricate (possibly long range and long term) interactions brought to play between the main cell types involved in the gonadal function (germ cells, somatic cells in the gonads, pituitary gland and hypothalamus) also requires a multiscale modeling approach.

5 Social and environmental responsibility

5.1 Impact of research results

Given our positioning in comparative physiology, future outcomes of MUSCA's basic research can be expected in the fields of Medicine, Agronomy (breeding) and Ecophysiology, in a *One Health* logic. For instance, a deep understanding of female gametogenesis can be instrumental for the clinical management of ovarian aging, the development of sustainable breeding practices, and the monitoring of micro-pollutant effects on wild species (typically on fish populations). These issues will be especially investigated in the framework of the OVOPAUSE project and they are also implemented as part of our collaboration with INERIS (GinFiz project). In the same spirit, we intend to design methodological and sofware tools for the model-assisted validation of alternatives to hormone use in reproduction control (ovarian stimulation, contraception). This line is driven by the Contrabody project, which has stimulated associated actions such as that dedicated to the automatic assessment of the reproductive status from ovary imaging. In the same spirit, our mechanistic view of the interactions between the host and gut microbiota leads to new approaches of the antibioresistance phenomenon, which is the topic of the PARTHAGE project and has already been the matter of a translational project (COOPERATE). Finally, our systems biology and computational biology approaches dedicated to cell signaling and structural biology clearly target pharmacological design and screening, and, on the long term, have the potential to accelerate and improve drug discovery in the field of reproduction and beyond. Such approaches have proven particularly fruitful with the MabSilico start-up (a spin-off of the BIOS group), which continues to interact with BIOS and MUSCA on antibody-related projects (SELMAT and Contrabody for example).

6 Highlights of the year

- Six month scientific stay of Prof. Mauricio Sepúldeva (Universidad del Concepción) in the framework of the d'Alembert program from Université Paris-Saclay
- Half-time delegation of Prof. Magali Ribot (Université d'Orléans)
- Sabbatic stay of Romain Yvinec in Duke University (from Sept. 2023)

7 New software, platforms, open data

7.1 New software

7.1.1 pyDynPeak

Keywords: Data processing, Endocrinology

Scientific Description: Analysis of time series taking into account the inherent properties of secretion events (form and pulse half-life, regularity of changes in rhythm)

Functional Description: Detection of LH pulses (luteinizing hormone) and analysis of their rhythm. Visualisation, diagnostic and interactive correction of the detections.

URL: https://gitlab.inria.fr/musca/pydynpeak

Authors: Frédérique Clément, Hande Gozukan, Christian Poli

Contact: Frédérique Clément

8 New results

8.1 Deterministic and stochastic compartmental models

8.1.1 Nonlinear compartmental modeling to monitor ovarian follicle population dynamics on the whole lifespan

Participants: Guillaume Ballif, Frédérique Clément, Romain Yvinec.

In the framework of Guillaume Ballif's PhD, we have introduced an ODE-based compartmental model of ovarian follicle development all along lifespan [43]. The model monitors the changes in the follicle numbers in different maturation stages with aging. Ovarian follicles may either move forward to the next compartment (unidirectional migration) or degenerate and disappear (death). The migration from the first follicle compartment corresponds to the activation of quiescent follicles, which is responsible for the progressive exhaustion of the follicle reserve (ovarian aging) until cessation of reproductive activity. The model consists of a data- driven layer embedded into a more comprehensive, knowledge-driven layer encompassing the earliest events in follicle development. The data-driven layer is designed according to the most densely sampled experimental dataset available on follicle numbers in the mouse. Its salient feature is the nonlinear formulation of the activation rate, whose formulation includes a feedback term from growing follicles. The knowledge-based, coating layer accounts for cutting-edge studies on the initiation of follicle development around birth. Its salient feature is the co-existence of two follicle subpopulations of different embryonic origins. We have then setup a complete estimation strategy, including (i) the study of structural identifiability based on differential elimination, using the *Structural identifiability* Julia package, (ii) a sensitivity analysis based on the elementary effect method of Morris, (iii) the elaboration of a relevant optimization criterion combining different sources of data (the initial dataset on follicle numbers, together with data in conditions of perturbed activation, and data discriminating the subpopulations) with appropriate error models, and a model selection step. We have finally illustrated the model potential for experimental design (suggestion of targeted new data acquisition) and *in silico* experiments.

8.1.2 A stochastic model for neural progenitor dynamics in the mouse cerebral cortex

Participants: Frédérique Clément, Jules Olayé.

We have designed and analyzed a stochastic model of embryonic neurogenesis in the mouse cerebral cortex, within the framework of compound Poisson processes, with time-varying, probabilistic fate decisions, and possibly stochastic cell cycle durations [33]. The core of the model is the stochastic counterpart of our former deterministic compartmental model based on transport equations [18]. The model accounts for the dynamics of different progenitor cell types and neurons. The expectation and variance of the cell number of each type are derived analytically and illustrated through numerical simulations. The effects of stochastic transition rates between cell types, and stochastic duration of the cell division cycle have been investigated sequentially. The model does not only predict the number of neurons, but also their spatial distribution into deeper and upper cortical layers. The model outputs are consistent with experimental data providing the number of neurons and intermediate progenitors according to embryonic age in control and mutant situations.

8.1.3 Modeling compartmentalization in cell signaling networks

Participants: Frédérique Clément, Léo Darrigade, Romain Yvinec.

In the framework of the COMPARTIMENTAGE exploratory action, we have initiated a new thematics on the compartmentalization of cell signaling, with a special focus on the compartimentalization of G Protein-Coupled Receptors

During the CEMRACS 2022 summer school, Romain Yvinec, Erwan Hingant and Juan Carlo supervised a project dedicated to the modeling of compartmentalization within intracellular signaling pathways. Together with Claire Alamichel, Nathan Quiblier, and Saoussen Latrach, they have introduced a new modeling approach for the signaling systems of G protein-coupled receptors, taking into account the compartmentalization of receptors and their effectors, both at the plasma membrane and in dynamic intra-cellular vesicles called endosomes [31]. The first building block of the model is about compartment dynamics. It takes into account creation of *de novo* endosomes, i.e. endocytosis, recycling of endosomes back to the plasma membrane, degradation through transfer into lysosomes, as well as endosome fusion through coagulation dynamics. The second building block corresponds to the biochemical reactions arising in each compartment and to the transfer of molecules between the dynamical compartments. They have proven sufficient conditions to obtain exponentially the ergodicity for the size distribution of intracellular compartments. In parallel, they have designed a finite volume scheme to simulate the model and illustrated two application cases for receptor trafficking and spatially biased second effector signaling.

In the framework of Leo Darrigade's post-doc, we have then designed a piecewise deterministic Markov process of intracellular GPCR trafficking and cAMP production. The stochastic part of the model accounts for the formation, coagulation, fragmentation and recycling of intracellular vesicles carrying the receptors, while the deterministic part of the model represents the chemical reactions mediating the response to the activated receptor. Assuming that the different stochastic jump rates are constant, and that the deterministic flow associated with chemical reactions is exponentially contractive, we have proven that this process converges exponentially to a unique stationary measure. In parallel, we have developped a simplified ODE-based model of receptor signaling and trafficking to analyze experimental time series of cAMP concentration. The goal is to estimate kinetic parameters of receptor trafficking and signaling activity in different compartments. Special care has been devoted to describe rigorously the metadata (e.g. type of ligand, dose, pharmacological perturbations) related to each dataset.

8.1.4 Modeling the inactivation of chromosome-X

Participants: Frédérique Clément, Alice Fohr, Hélène Leman.

In the framework of the master internship of Alice Fohr (M2 Mathématiques pour les Sciences du Vivant, Université Paris-Saclay), we have initiated a new thematics on mathematical modeling for the understanding of X chromosome inactivation. In mammals, females are endowed with two X chromosomes, which could lead to an over-transcription of X-linked genes compared to males. Early during embryonic development, a compensation mechanism settles, which ends up by silencing either the father-inherited or the mother-inherited X chromosome, in a random manner. We have studied the qualitative behavior of an ODE-based toggle-switch model proposed in [67]. Using the theory of bifurcation analysis, we have confirmed the numerical results obtained in [67] on the stationary states, from which one can select different configurations of small-size gene networks ensuring the initiation and maintenance of a single X chromosome inactivation. We have then derived the deterministic model as the large-size limit of a continuous-time Markov process representing the unitary events associated with transcription. Finally, we have started investigating the clonal propagation of the X-chromosome inactivation status along cell lineages in the framework of branching processes.

8.2 Size-structured population dynamics

8.2.1 A size-structured model of fish oocytes population dynamics

Participants: Frédérique Clément, Louis Fostier, Romain Yvinec.

Oogenesis is the process of production and maturation of female gametes (oocytes), which ends up in fish with spawning. This process is critical to the survival of species, and particularly sensitive to environmental alterations (e.g. temperature, pollutants). In the framework of Louis Fostier's PhD, we have developed a model representing the oocyte population dynamics, from the earliest phases to egg laying, and taking into account the key stages of physiological and environmental controls. The model formulation is based both on knowledge available in two model fish species, the zebrafish and medaka, and on mathematical models that we have previously developed for mammalian oogenesis. The evolution of the oocyte population is governed by a size-structured population dynamics model, formalized in the form of a transport partial differential equation, with nonlocal nonlinearities on the velocity term and boundary conditions, capturing the effect of interactions between oocytes on the recruitment of new oocytes and on the growth rate. We have shown the well-posedness of the model in its generic formulation, and we have studied the associated stationary problem. Under certain additional hypotheses, concerning the growth rate term, we have determined the long-time behavior of the model, and in particular the local stability of the stationary solutions, by linearization methods.

8.2.2 Mathematical modeling of adipocyte size distributions: identifiability and parameter estimation from rat data

Participants: Léo Meyer, Magali Ribot, Romain Yvinec, and collaborators.

Fat cells, called adipocytes, are designed to regulate energy homeostasis by storing energy in the form of lipids. The adipocyte size distribution is assumed to play a role in the development of obesity-related diseases. The population of adipocytes is characterized by a bimodal size distribution. We have proposed a model based on a partial differential equations to describe the adipocyte size distribution [35]. The model includes a description of the lipid fluxes and cell size fluctuations. From the formulation of a stationary solution we can obtain a fast computation of bimodal distributions. We have investigated the parameter identifiability and estimated parameter values with the CMA-ES algorithm. We have first validated the procedure on synthetic data, then estimated parameter values with experimental data of thirty-two rats. We have discussed the estimated parameter values and their variability within the population, as well as the relation between estimated values and their biological significance. Finally, a sensitivity analysis has been performed to specify the influence of parameters on the cell size distribution and explain the differences between the model and measurements. The proposed framework enables the characterization of adipocyte size distribution with four parameters and can be easily adapted to measurements of cell size distribution in different health conditions.

8.2.3 A Lifschitz-Slyozov type model for adipocyte size dynamics : limit from Becker-Döring system and numerical simulation

Participants: Léo Meyer, Magali Ribot, Romain Yvinec, and collaborators.

Biological data show that the size distribution of adipocytes follows a bimodal distribution. In [39], we have introduced a Lifshitz-Slyozov type model, based on a transport partial differential equation, for the dynamics of the size distribution of adipocytes. We have proven a new convergence result from the related Becker-Döring model, a system composed of several ordinary differential equations, toward mild solutions of the Lifshitz-Slyozov model using distribution tail techniques. This result allowed us to propose a new advective-diffusive model, the second-order diffusive Lifshitz-Slyozov model, which is expected to better fit the experimental data. Numerical simulations of the solutions to the diffusive Lifshitz-Slyozov model have been performed using a well-balanced scheme and the model outputs

have been compared to solutions to the transport model. The simulations show that both bimodal and unimodal profiles can be reached asymptotically, depending on several parameters. We put in evidence that the asymptotic profile for the second-order system does not depend on initial conditions, unlike for the transport Lifshitz-Slyozov model.

8.2.4 Long-time asymptotic of the Lifshitz-Slyozov equation with nucleation

Participants: Romain Yvinec, and collaborators.

We have studied the Lifshitz-Slyozov model with inflow boundary conditions of nucleation type [23]. We have shown that, for a collection of representative rate functions, the size distributions approach degenerate states concentrated at zero size for sufficiently large times. The proof relies on monotonicity properties of some quantities associated with an entropy functional. Moreover, we have given numerical evidence on the fact that the convergence rate to the goal state is algebraic in time. Besides their mathematical interest, these results can be relevant for the interpretation of experimental data.

8.2.5 Some remarks about the well-posedness of Lifshitz-Slyozov equations with nucleation kinetics

Participants: Romain Yvinec, and collaborators.

The Lifshitz-Slyozov model is a nonlocal transport equation that can describe certain types of phase transitions in terms of the temporal evolution of a mixture of monomers and aggregates. Most applications of this model so far do not require boundary conditions. However, there is a recent interest in situations where a boundary condition might be needed-e.g. in the context of protein polymerization phenomena. Actually, the boundary condition may change dynamically in time, depending on an activation threshold for the monomer concentration. This new setting raises a number of mathematical difficulties for which the existing literature is scarce. In [32], we have constructed examples of solutions for which the boundary condition becomes activated (resp. deactivated) dynamically in time. We also discussed how to approach the well-posedness problem for such situations.

8.3 Coupling biochemical dynamics with cell population dynamics

8.3.1 Modeling the interplay between the gut microbiota and its host : application to the analysis of diet impact on symbiosis

Participants: Marie Haghebaert, Béatrice Laroche, Lorenzo Sala, and collaborators.

The health and well-being of a host are deeply influenced by the interactions with its gut microbiota. Diet, especially the amount of fiber intake, plays a pivotal role in modulating these interactions impacting microbiota composition and functionality. We have introduced a novel mathematical model [37], designed to delve into these interactions, by integrating dynamics of the colonic epithelial crypt, bacterial metabolic functions and sensitivity to inflammation as well as colon flows in a transverse colon section. Unique features of our model include accounting for metabolic shifts in epithelial cells based on butyrate and hydrogen sulfide concentrations, representing the effect of innate immune pattern recognition receptors activation in epithelial cells, capturing bacterial oxygen tolerance based on data analysis, and considering the effect of antimicrobial peptides on the microbiota. Using our model, we show a proof-of-concept that a high-protein, low-fiber diet intensifies dysbiosis and compromises symbiotic resilience. Our simulation results highlight the critical role of adequate butyrate concentrations in maintaining mature epithelial crypts. Through differential simulations focused on varying fiber and protein inputs, our study offers insights into the system's resilience following the onset of dysbiosis. The

present model, while having room for enhancement, offers essential understanding of elements such as oxygen levels, the breakdown of fiber and protein, and the basic mechanisms of innate immunity within the colon environment.

8.3.2 Deterministic limit of a PDMP model of epithelial tissue interacting with diffusing chemicals and application to the intestinal crypt

Participants: Léo Darrigade, Béatrice Laroche, Simon Labarthe.

Mathematical models of biological tissues are a promising tool for multiscale data integration, computational experiments and system biology approaches. While some data and insights are rooted at the cell level, macroscopic mechanisms emerge and are observed at the tissue scale, rendering tissue modeling an inherently multiscale process. As a consequence, tissue models can be broadly categorized as either individual-based or continuous population-based. In [34], we have introduced a generic individual-based model of epithelial tissue including the main regulation processes such as cell division, differentiation, migration and death, together with cell-cell mechanical interactions. We have also considered the coupling with diffusing molecules. The model is a measure-valued piecewise-deterministic Markov process, coupled with reaction-diffusion PDEs. The well-posedness of the model is assessed, and the large population deterministic limit is rigorously derived. Finally, numerical experiments are conducted: the model is applied to the context of epithelial tissues in the intestinal crypt and the convergence towards the deterministic model is illustrated numerically.

8.3.3 Study of the numerical method for an inverse problem of a simplified intestinal crypt

Participants: Marie Haghebaert, Béatrice Laroche, Mauricio Sepúldeva.

We have considered the study of an inverse problem for an intestinal crypt model [38]. The original model is based on the interaction of epithelial cells with microbiota-derived chemicals diffusing in the crypt from the gut lumen. The five types of cells considered in the original model were reduced in this work to three types of cells for simplifications of the inverse problem. The inverse problem consists in determining the shape of the secretory cells of the deep crypt from observations of the stem cells and progenitor cells at a fixed time. The method used is the calculation of the adjoint state associated with the second-order BGK numerical scheme, which allows calculating the critical points of the Lagrangian associated with the inverse problem, and applying a gradient method in order to minimize the cost function. The algorithm is described, and some numerical examples are given.

8.4 Computational modeling

8.4.1 Four functional profiles for fiber and mucin metabolism in the human gut microbiome

Participants: Simon Labarthe, Béatrice Laroche, and collaborators.

Deciphering the complex interactions between the gut microbiome and host requires evolved analysis methods focusing on the microbial ecosystem functions. We have integrated *a priori* knowledge on anaerobic microbiology with statistical learning to design synthetic profiles of fiber degradation from metagenomic analyses [26]. We have identified four distinct functional profiles related to diet, dysbiosis, inflammation and disease. We have used non-negative matrix factorization to mine metagenomic datasets, after selecting manually 91 KEGG orthologies and 33 glycoside hydrolases, further aggregated in 101 functional descriptors. The profiles were identified from a training set of 1153 samples and thoroughly validated on a large database of 2571 unseen samples from 5 external metagenomic cohorts. Profiles 1 and

2 are the main contributors to the fiber-degradation-related metagenome. Profile 1 takes over Profile 2 in healthy samples, and the unbalance of these profiles characterizes dysbiotic samples. Profile 3 takes over Profile 2 during Crohn's disease, inducing functional reorientations towards unusual metabolism such as fucose and H2S degradation or propionate, acetone and butanediol production. Profile 4 gathers under-represented functions, like methanogenesis. Two taxonomic makes up of the profiles were investigated, using either the covariation of 203 prevalent genomes or metagenomic species, both providing consistent results with their functional characteristics. It appeared that Profiles 1 and 2 were respectively mainly composed of bacteria from the phyla *Bacteroidetes* and *Firmicutes*, while Profile 3 is representative of *Proteobacteria* and Profile 4 of *Methanogens*.

8.4.2 Harnessing Fc/FcRn Affinity Data from Patents with Different Machine Learning Methods

Participants: Anne Poupon, and collaborators.

Monoclonal antibodies are biopharmaceuticals with a very long half-life due to the binding of their Fc portion to the neonatal receptor (FcRn), a pharmacokinetic property that can be further improved through engineering of the Fc portion, as demonstrated by the approval of several new drugs. Many Fc variants with increased binding to FcRn have been found using different methods, such as structure-guided design, random mutagenesis, or a combination of both, and are described in the literature as well as in patents. Our hypothesis is that this material could be subjected to a machine learning approach in order to generate new variants with similar properties. We therefore compiled 1323 Fc variants affecting the affinity for FcRn, which were disclosed in twenty patents. These data were used to train several algorithms, with two different models, in order to predict the affinity for FcRn of new randomly generated Fc variants [24]. To determine which algorithm was the most robust, we first assessed the correlation between measured and predicted affinity in a 10-fold cross-validation test. We then generated variants by *in silico* random mutagenesis and compared the prediction made by the different algorithms. As a final validation, we produced variants, not described in any patent, and compared the predicted affinity with the experimental binding affinities measured by surface plasmon resonance (SPR). The best mean absolute error (MAE) between predicted and experimental values was obtained with a support vector regressor (SVR) using six features and trained on 1251 examples. With this setting, the error on the log(KD) was less than 0.17. The obtained results show that such an approach could be used to find new variants with better half-life properties that are different from those already extensively used in therapeutic antibody development.

8.4.3 Maching Learning Models on Time Series Data to predict the behavior of the Bioluminescence Resonance Energy Transfer

Participants: Misbah Razzaq, Pamela Romero, Romain Yvinec.

In the framework of the international internship of Pamela Romero, we have used Machine Learning to predict BRET time series in the context of cell signaling. Bioluminescence Resonance Energy Transfer (BRET) is used in to measure dynamic events on the molecular scale, such as protein-protein interactions. We have selected Random Forest Regression models and tested different numerical experiments. The first case was based on a point-to-point prediction: for each time step in the series the next one is predicted, which requires knowing a lot of information, not available in practice. The second case introduced a feedback in the prediction: the result of the previous prediction is used as an input for the current prediction, which requires knowing only the first point of the time series, a much more realistic situation. The third case corresponds to a prediction spanning multiple time steps. The inputs of the different test cases are the BRET time series, and relative information on the cell signaling experiments, such as the nature and dose of the ligand (stimulus), the type of receptor, and possible pharmacological perturbations. In all three experiments, we obtained good results in the testing set with errors close to zero and accuracy between 80% and 98%.

8.5 Exploration of signaling networks

8.5.1 A single domain intrabody targeting the follicle-stimulating hormone receptor (FSHR) impacts FSH-induced G protein-dependent signalling

Participants: Pascale Crépieux, Frédéric Jean-Alphonse, Eric Reiter, and collaborators.

Intracellular variable fragments from heavy-chain antibody from camelids (intra-VHH) have been successfully used as chaperones to solve the 3D structure of active G protein-coupled receptors bound to their transducers. However, their effect on signaling has been poorly explored, although they may provide a better understanding on the relationships between receptor conformation and activity. We have isolated and characterized iPRC1, the first intra-VHH recognizing a member of the large glycoprotein hormone receptors family, the follicle-stimulating hormone receptor (FSHR) [27]. This intra-VHH recognizes the third intracellular loop of FSHR and decreases cAMP production in response to FSH, without altering Gαs recruitment. Hence, iPRC1 behaves as an allosteric modulator and provides a new tool to complete structure/activity studies performed so far on this receptor.

8.5.2 Towards the convergent therapeutic potential of G protein-coupled receptors in autism spectrum disorders

Participants: Pascale Crépieux, Xavier Leray, and collaborators.

Autism spectrum disorders (ASDs) are diagnosed in 1/100 children worldwide, based on two core symptoms: deficits in social interaction and communication, and stereotyped behaviors. G protein-coupled receptors (GPCRs) are the largest family of cell surface receptors that transduce extracellular signals to convergent intracellular signaling and downstream cellular responses that are commonly dysregulated in ASD. Despite hundreds of GPCRs being expressed in the brain, only 23 are genetically associated with ASD according to the Simons Foundation Autism Research Initiative (SFARI) gene database: oxytocin OTR; vasopressin V_{1A} and V_{1B} ; metabotropic glutamate $mGlu_5$ and $mGlu_7$; $GABA_{B2}$; dopamine D_1, D_2 and D_3 ; serotoninergic 5-HT_{1B} ; β 2-adrenoceptor; cholinergic M_3 ; adenosine A_{2A} and A_3 ; angiotensin AT_2 ; cannabinoid CB_1 ; chemokine CX_3 CR1; orphan GPR37 and GPR85; and olfactory OR1C1, OR2M4, OR2T10 and OR52M1. We have reviewed the therapeutic potential of these 23 GPCRs, as well as 5-$HT_{2A}$and 5-HT_7 , for ASD [22]. For each GPCR, we discuss its genetic association, genetic and pharmacological manipulation in animal models, pharmacopoeia for core symptoms of ASD and rank them based on these factors. Among these GPCRs, we highlight D_2 , 5-HT_{2A} , CB_1 , OTR and V_{1A} as the more promising targets for ASD. We discuss that the dysregulation of GPCRs and their signaling is a convergent pathological mechanism of ASD. Their therapeutic potential has only begun as multiple GPCRs could mitigate ASD.

9 Partnerships and cooperations

9.1 International initiatives

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

ANACONDA

Title: Theoretical and numerical ANAlysis of CONservation laws for multicellular DynAmics

Duration: 2021 -> 2023

Coordinator: Mauricio Sepúlveda

Partners: Universidad de Concepción, Chile

Inria contact: Romain Yvinec

Summary: ANACONDA focuses on the analysis of mathematical models dedicated to multicellular dynamics. It is based on the formalism of structured population dynamics, which is formulated as PDE (partial differential equation) conservation laws. We intend to study two main classes of structured populations PDE models, phase separation models (of Lifshitz-Slyozov type) and moving/free-boundary problems, to investigate respectively biological issues of cellular growth (mainly of adipocytes), and morphogenesis processes (tissue homeostasis of intestinal crypts, development of ovarian follicles). In both cases, thanks to the complementary expertise gathered in the consortium, we aim to perform the theoretical and numerical analysis of the models, design specific numerical schemes, and conceive appropriate strategies for inverse problems, in a synergistic way.

9.1.2 Participation in other International Programs

- ECOS SUD-CHILI 2020 : ECOS n° C20E03, "Coarsening dynamics: numerical and theoretical analysis of the Lifshitz-Slyozov equation with nucleation and applications to biology." PIs: Romain Yvinec and Mauricio Sepúlveda (Universidad de Concepción, Chile)
- i-GPCRNet, International Research Network (IRN) on GPCRs, involved musca members: Pascale Crépieux, Frédéric Jean-Alphonse, Eric Reiter, Romain Yvinec
- Bill & Melinda Gates Foundation, ContraBody (2021-2025, PI Eric Reiter, 1.8 M US$) "Non-hormonal contraception by nanobody produced from within the body". In partnership with University of Modena E Regio Emilia, Italy, MabSilico, France and InCellArt, France. Involved MUSCA members : Eric Reiter, Pascale Crépieux, Frédéric Jean-Alphonse, Romain Yvinec
- Medical Research Council, MICA (2022-2025, PI Waljit Dhillo, 642k€) "Investigating kisspeptin receptor signalling to improve the treatment of reproductive disease". Involved MUSCA member: Eric Reiter

9.2 International research visitors

9.2.1 Visits of international scientists

International visits to the team

Visitor: Mohammed Akli Ayoub

Status: Associate Professor

Institution of origin: Khalifa University

Country: United Arabian Emirates

Dates: June-August (3 months)

Context of the visit: Collaboration on the direct action of steroid hormones on gonadotropin receptors' activities

Mobility program/type of mobility: Le Studium Loire Valley Institute for Advanced Studies, Visiting researcher program. Host MUSCA member: Frédéric Jean-Alphonse

Visitor: Livio Casarini

Status: Professor

Institution of origin: University of Modena and Reggio Emilia

Country: Italy

Dates: November 2022-November 2023

Context of the visit: Collaboration on antibody fragments targeting ovarian GPCRs to control reproduction

Mobility program/type of mobility: Le Studium Loire Valley Institute for Advanced Studies, Visiting researcher program. Host MUSCA member: Eric Reiter

9.2.2 Visits to international teams

Sabbatical programme

Musca member: Romain Yvinec

Visited institution: Duke University (États-Unis)

Dates of the stay: August 14 2023-July 14 2024

Topic of the stay: Multiscale mathematical modeling in reproductive physiology

Funding: INRAE Phase/Digit-BIO/DRI + INRIA Sabbatical program

Research stays abroad Magali Ribot: one week stay in Roma in December Collaboration with Roberto Natalini and Maya Briani about numerical schemes for PDE set on a network, using some relaxation techniques

9.3 European initiatives

9.3.1 H2020 projects

- ERC Advanced grant, Homo.Symbiosus (2019-2024, PI Joël Doré, 2.5 M€) "Assessing, preserving and restoring man-microbes symbiosis". Involved MUSCA member: Béatrice Laroche.
- ERC Starting grant, Therautism (2020-2024, PI Lucie Pellissier, 1.5 M€) "New molecular targets and proof-of-concept therapies for Autism Spectrum Disorders". Involved MUSCA member: Pascale Crépieux.
- ERNEST (European Research Network on Signal transduction) COST Action 18133.

9.4 National initiatives

- ANR OVOPAUSE (2022-2026, PI Romain Yvinec, 447 K€) "Dynamics and control of female germ cell populations: understanding aging through population dynamics models". Involved MUSCA Members: Frédérique Clément, Pascale Crépieux, Louis Fostier, Frédéric Jean-Alphonse, Eric Reiter, Romain Yvinec.
- ANR MOSDER (2022-2025, PI Frédéric Jean-Alphonse, 420 K€) "Multi-dimensional Organization of Signaling Dynamics Encoded by gonadotropin Receptors". Involved MUSCA members: Pascale Crépieux, Frédéric Jean-Alphonse, Eric Reiter, Romain Yvinec.
- ANR PARTHAGE (2022-2026, PI Lulla Opatowski, 620 k€) "Prédire la transmission de la résistance au sein et entre les hôtes en combinant modélisation mathématique, génomique et épidémiologie". Involved MUSCA member: Béatrice Laroche.
- ANR YDOBONAN (2021-2025, PI Vincent Aucagne, 497 K€) "Mirror Image Nanobodies: pushing forward the potential of enantiomeric proteins for therapeutic and pharmacological applications". Involved MUSCA member: Eric Reiter.

- ANR PHEROSENSOR (2021-2026, PI Philippe Lucas, 1492K€) “Early detection of pest insects using pheromone receptor-based olfactory sensors”. Involved MUSCA member: Béatrice Laroche.
- ANR ABLISS (2019-2023, PI Anne Poupon, 441 K€) “Automating building from Literature of Signalling Systems”. Involved MUSCA members: Anne Poupon, Eric Reiter, Pascale Crépieux, Romain Yvinec.
- LabEx MAbImprove (2011-2025, PI Hervé Watier). Involved MUSCA members : Eric Reiter, Frédéric Jean-Alphonse, Pascale Crépieux, Anne Poupon, Romain Yvinec.
- INRAE metaprogram DIGIT-BIO, IMAGO project (2022-2024, PIs Frédéric Jean-Alphonse and Béatrice Laroche, 47 K€), “Imagerie et modélisation des dynamiques spatio-temporelles de la signalisation et du trafic des récepteurs couplés aux protéines G (RCPG)”. Involved MUSCA members: all permanent members.
- INRAE metaprogram DIGIT-BIO, IMMO project (2021-2023, PIs Violette Thermes and Romain Yvinec, 51.4 K€), “IMagerie et MOdélisation multi-échelles pour la compréhension de la dynamique ovarienne chez le poisson”. Involved MUSCA members: Frédérique Clément, Romain Yvinec.
- INRAE metaprogram HOLOFLUX, MOTHERS project (2023-2024, PI Florent Kempf). “Monitoring the gut microbiota, resistance against salmonella, animal performance and immune response through an adult, pathogen-free microbiota”. Involved MUSCA members: Béatrice Laroche, Lorenzo Sala.
- ANSES GinFiz project (2021-2024, PI Rémy Beaudouin), “Gonadal aromatase inhibition and other toxicity pathways leading to Fecundity Inhibition in Zebrafish: from initiating events to population impacts”. Involved MUSCA members: Frédérique Clément, Romain Yvinec.
- Action Exploratoire Inria Compartimentage (2022-2024, PI Romain Yvinec, 120 K€) : “Imagerie et Modélisation Spatio-Temporelles de la Compartimentation des Voies de Signalisation”. Involved MUSCA Members: all permanent members.

9.5 Regional initiatives

- Ambition recherche développement Centre Val de Loire SELMAT (2020-2023, PI Eric Reiter, 630 K€) “Méthodes in silico pour la sélection et la maturation d’anticorps : développement, validation et application à différentes cibles thérapeutiques”. Involved MUSCA members: Eric Reiter, Pascale Crépieux, Frédéric Jean-Alphonse, Romain Yvinec.
- Appel à projet région Centre Val de Loire, INTACT (2019-2023, PI Pascale Crépieux, 200 K€) “Pharmacologie réverse à l’aide d’anticorps intracellulaires anti-RFSH actif”. Involved MUSCA members: Pascale Crépieux, Eric Reiter, Frédéric Jean-Alphonse, Anne Poupon, Romain Yvinec. Industrial partner: McSAF, Tours.

10 Dissemination

10.1 Promoting scientific activities

10.1.1 Scientific events: organization

Member of the organizing committees

Frédérique Clément, ReproSciences 2023, May 03-05, Paris

Frédéric Jean-Alphonse, i-GPCRnet annual meeting, October 25-27, Strasbourg

Magali Ribot, Journées Maths-Bio-Santé, Université, November 27 - December 1, Marne la Vallée

Mauricio Sepúlveda, online Seminars in EDP and Applied Mathematics, Brazil ; INRIA-CHILE 2023 Scientific Days, December 4-7, Santiago, Chile

10.1.2 Scientific events: selection

Member of the conference program committees

Frédérique Clément, ReproSciences 2023, May 03-05, Paris

Magali Ribot, Member of the selection board, RTR Rouen workshop on maths for biology, June 28-30

Reviewer

Magali Ribot, Banff International Research Station 2025 Proposal Submission

10.1.3 Journal

Member of the editorial boards

Pascale Crépieux and Eric Reiter, associate editors Front. Endocrinol.

Romain Yvinec, associate editor J. Math. Biol.

Reviewer - reviewing activities

Frédérique Clément, Biol. Reprod., J. Math. Biol.

Pascale Crépieux, Sci. Rep. Front. Endocrinol.

Eric Reiter, Front. Endocrinol., Sci. Rep., Endocrinology, Proc. Natl. Acad. Sci. USA, eLife, Science, Nature Comm.

Magali Ribot, J. Comp. Phys., J. Math. Anal. Appl.

Romain Yvinec, Stoch. Models, Stoch. Process. Appl., Math. Model. Nat. Phenom., J. Math. Biol., ESAIM Proc., J. Stat. Phys.

10.1.4 Invited and contributed talks

Frédérique Clément

Introduction to the development of ovarian follicles, Kickoff ai4scmed, PEPR 22-PESN-0002, September 26, Paris

Léo Darrigade

Compartimentation cellulaire et signalisation des GPCRs at Journée Institut Denis Poisson - PRC, July 13, Orléans

Modeling of the compartmentalized GPCR signaling, 3rd International I-GPCR NET meeting, October 25-27, Strasbourg

Modeling intracellular compartmentalized GPCR signaling, poster communication, Journées Math Bio Santé, November 29- December 01, Marne La Vallée

Louis Fostier

Un modèle de dynamique de population cellulaire pour l'ovogenèse des poissons, Journées Math Bio Santé, November 29- December 01, Marne La Vallée

Fish oogenesis modeling: Oocyte population dynamics, poster communication, ReproSciences 2023, May 03-05, Paris

Nested neural SINDy approach, together with Clément Flint and Reyhaneh Hashemi, closure of the CEMRACS 2023 Hackathon, August 24, Marseille

Eric Reiter

Development of nanobodies to allosterically modulate the follicle stimulating hormone receptor, Bill & Melinda Gates Foundation, Nonhomonal Contraceptive Discovery Program Meeting, April 26, Cornell University, Ithaca, USA

Des fragments d'anticorps pour contrôler la reproduction sans injecter d'hormone, Colloque Biotechnocentre, October 19, Nouans-le-Fuzelier, France

Mauricio Sepúlveda

Inverse problem for an intestinal crypt model, CFR23 Control and Related Fields conference, March 27-29, Sevilla, Spain

Inverse problem for an intestinal crypt model, PDEMAS Days, March 27-29, Granada, Spain

Inverse problem for an intestinal crypt model, Mathematics Days of the South Zone, April 17-19, Santiago, Chile

Inverse problem for an intestinal crypt model, World Conference on Physics and Mathematics, May 22-23, Berlin, Germany

Inverse problems for some biological models, 5th workshop on Mathematics, Computer Science and Complex systems, July 14-15, Essaouira, Marroco

Seminars

Magali Ribot, PDE models on networks
Bio-Maths seminar, Institut Camille Jordan, Université Lyon 1–Claude Bernard

Léo Meyer, Modeling and analysis of adipocyte size distribution, Bio-Maths seminar, Institut Camille Jordan, Université Lyon 1–Claude Bernard; INTERFACE team's seminar, Laboratoire Jean-Alexandre Dieudonné, Université côte d'azur; Maths-Bio-Santé Seminar, Institut de Mathématiques de Toulouse, Université Toulouse III–Paul Sabatier

Mauricio Sepúlveda, Inverse Problem for an intestinal crypt model, Seminar PDE Analysis and Applications, Université de Lorraine ; LAMFA seminar, Université de Picardie Jules Verne

10.1.5 Leadership within the scientific community

Frédérique Clément

- expert of ITMO BCDE
- member of the steering committee of RT REPRO
- member of the scientific board of PIXANIM (Phénotypage par Imagerie in/eX vivo de l'ANImal à la Molécule)
- scientific member of the FC3R COR

Pascale Crépieux

- member (and board member) of CNRS section 24 , "Physiologie, physiopathologie, biologie du cancer"

Frédéric Jean-Alphonse

- coordinator of Key Question 1 (How can target activity be modulated through antibody binding?), LabEx MAbImprove
- member of the Early career scientist comittee (ECS) at the IRN iGPCRnet

Béatrice Laroche

- member of the Steering Committee of the INRAE metagrogram HOLOFLUX

Anne Poupon

- coordinator of “Central Development Instrument 1 (Interdisciplinary Innovation)”, LabEx MAbImprove

Magali Ribot

- co-head of the SMAI group SMAI-MABIOME dedicated to maths for biology and medicine
- member of SMAI scientific committee
- member of the GDR MATHSAV scientific committee

Romain Yvinec

- co-head of WP “Biomathematics, Bioinformatics and Biophysics for Reproduction”, GDR 3606 REPRO
- member of the Directory committee of the i-GPCRnet International Research Network (IRN)

10.1.6 Scientific expertise

Frédérique Clément, reviewer for the Swiss National Fundation for Science

Pascale Crépieux, reviewer for BPI-France, ANSES, Medical Research Council UK

Romain Yvinec, member of the CE 45: Interfaces: mathematics, digital sciences–biology, health, ANR AAPG 2023

Magali Ribot, member of the selection boards for the recruitment of a professor (Université de Tours), and associate professors (Université de Marseille et Université Paris Cité) ; member of the admission board for the recruitment of Chargés de Recherche, CNRS, section 41

10.1.7 Research administration

Frédérique Clément is invited member of the scientific council of Graduate School Life Sciences and Health of University Paris-Saclay, and member of Bureau du comité des équipes-projets du Centre Inria de Saclay

Béatrice Laroche is director of MaIAGE

Léo Meyer was a PhD students’ representative in the council of Doctoral School MIPTIS (Mathématiques, Informatique, Physique Théorique et Ingénierie des Systèmes)

Eric Reiter is deputy director of UMR PRC

Magali Ribot is deputy director of Institut Denis Poisson, UMR, Universités d’Orléans–Tours, and member of CIRM administrative committee

Romain Yvinec is co-head of the Bios team in UMR PRC

10.2 Teaching - Supervision - Juries

10.2.1 Teaching

Pascale Crépieux, M2 Biology of Reproduction, Université de Tours (4h)

Pascale Crépieux, M2 Infectiology, Immunity, Vaccinology and Biopharmaceuticals, Université de Tours (4h)

Pascale Crépieux, M2 Physiopathology, Université de Tours (4h)

Louis Fostier, L1 Computer Science, Université de Tours, Algebra and Analysis (54h)

Léo Meyer, L3 Mathematics, Université d'Orléans, Numerical tools (32h)

Eric Reiter, M2 Infectiology, Immunity, Vaccinology and Biopharmaceuticals, Université de Tours (4h)

Eric Reiter, M2 Physiopathology, Université de Tours (2h)

Magali Ribot, L3 Numerical analysis, Université d'Orléans (52h)

Magali Ribot, M2 Modeling for the agrégation de mathématiques, Université de Tours (38h)

Magali Ribot, M1 Scientific computing and modeling, Université d'Orléans (30h)

Magali Ribot, M2 Lessons to prepare the agrégation interne de mathématiques, Université d'Orléans (20h)

10.2.2 Supervision

PhD: Camille Gauthier, "Manipulation of the activity and physiology of LH receptor through a small fragment of antibody", defended on December 7, supervisors: Pascale Crépieux and Eric Reiter

PhD: Marie Haghebaert, "Tools and methods for modeling the dynamics of complex microbial ecosystems from temporal experimental observations: application to the dynamics of the intestinal microbiota", defended on December 20, supervisor: Béatrice Laroche

PhD: Léo Meyer, "Modeling and analysis of models for adipocyte growth", defended on September 09, supervisors: Magali Ribot and Romain Yvinec

PhD: Pauline Raynaud, "Intracellular antibodies to explore the relationships between conformations and activity of hormone receptors, and their application in reverse pharmacology", defended on December 12, supervisors: Pascale Crépieux and Gilles Bruneau

PhD: Anielka Zehnaker, "Selective modulation of FSH receptor signaling pathways in vivo, consequences on ovarian and testicular functions ", defended on December 12, supervisor: Eric Reiter

PhD in progress: Marlène Davilma, "Role of miRNAs in the control of oocyte reserve in fish", started October 2023, supervisors: Frédérique Clément and Violette Thermes

PhD in progress: Louis Fostier, "Multiscale mathematical modeling of oogenesis in fish", started November 2022, supervisors: Frédérique Clément and Romain Yvinec, associate supervisor: Violette Thermes

PhD in progress: Juliette Gourdon, "Manipulation of the intracellular traffic and endosomal signaling of gonadotropin receptors, LH/CGR and FSHR, by nanobodies: deciphering the molecular mechanisms and the consequences on reproduction", started October 2021, supervisors: Eric Reiter and Frédéric Jean-Alphonse

PhD in progress: Paguiel Hossie, "Fixation and competition within the gut microbiota", started October 2022, supervisors : Cécile Carrère and Magali Ribot

PhD in progress: Marion Meutelet, “Study of convection-reaction-diffusion PDEs with membrane transmission conditions” started October 2023, supervisors : Boris Andreainov and Magali Ribot

PhD in progress: Eleonora Pastremoli, “Towards a digital twin of the gut microbiota: a multidisciplinary approach for an in-depth understanding of composition, function and interaction with the host”, started October 2023, supervisors : Béatrice Laroche and Lorenzo Sala

PhD follow-up committee of Simone Nati Poltri (INRIA - Université de Bordeaux), member Magali Ribot

PhD follow-up committee of Tu-Ky Ly (ED ABIES), members Frédérique Clément and Romain Yvinec

Master internship: Lucille Berthet, M1 Biologie de la Reproduction, Université de Tours, supervisor: Pascale Crépieux

Master internship: Zoé Chamard, M2 Infectiology, Immunity, Vaccinology and Biopharmaceuticals, Université de Tours, supervisor: Eric Reiter

Master internship: Alice Fohr, M2 Mathématiques pour les Sciences du Vivant, Université Paris-Saclay, supervisors: Frédérique Clément and Hélène Leman

Master internship: Chloé Weckel, M2 Mathématiques, Données et apprentissage, Université Paris Cité, supervisor: Romain Yvinec

International internship: Pamela Romero Jofré, Master in Computer Science, Master of Science in Engineerig, Pontificia Universidad Católica de Chile, supervisors: M. Razzaq and Romain Yvinec

CEMRACS 2023 Hackathon, July 24-August 25, collective project on “Estimation of interactions in microbial communities via a neural network-based generalized smoothing algorithm”, supervisors: Béatrice Laroche and Lorenzo Sala

10.2.3 Juries

Béatrice Laroche

- PhD jury of Clotilde Djuikem, Université Côte d’Azur, January 5

Frédérique Clément

- PhD Jury of Manon Lesage (referee), Université de Rennes 1, January 26
- HDR Jury of Xavier Druart, Université de Tours, December 05

Magali Ribot

- PhD Jury of Sébastien Tran Tien (referee), Université Claude Bernard - Lyon 1 , July 3
- PhD Jury of Pedro Jaramillo, INRIA - Université de Bordeaux, December 8
- PhD Jury of Marie Haghebaert, INRAE - Université Paris Saclay, December 20
- HDR Jury of Annabelle Collin, INRIA - Université de Bordeaux, December 7
- HDR Jury of Vincent Perrollaz, Université de Tours, December 18

10.3 Popularization

10.3.1 Articles and contents

Explorations au coeur du système reproducteur, L’Edition de l’Université Paris-Saclay #20 Hiver 2022/2023

Des chercheurs italiens en immersion dans l’unité PRC, e-Confluence, Journal interne du Centre INRAE Val-de-Loire, n°12, Juillet 2023

Pharmacologie réverse à l’aide d’anticorps intracellulaires anti-RFSH actif, Echosciences

10.3.2 Education

Magali Ribot was a member of the national olympiades jury of mathematics for high school students in Première

11 Scientific production

11.1 Major publications

[1] B. Aymard, F. Clément, F. Coquel and M. Postel. 'A numerical method for kinetic equations with discontinuous equations : application to mathematical modeling of cell dynamics'. In: *SIAM Journal on Scientific Computing* 35.6 (2013), 27 pages. DOI: 10.1137/120904238. URL: https://hal.archives-ouvertes.fr/hal-00751454.

[2] B. Aymard, F. Clément, D. Monniaux and M. Postel. 'Cell-Kinetics Based Calibration of a Multiscale Model of Structured Cell Populations in Ovarian Follicles'. In: *SIAM Journal on Applied Mathematics* 76.4 (2016), pp. 1471–1491. DOI: 10.1137/15M1030327. URL: https://hal.archives-ouvertes.fr/hal-01186381.

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[5] F. Clément, B. Laroche and F. Robin. 'Analysis and numerical simulation of an inverse problem for a structured cell population dynamics model'. In: *Mathematical Biosciences and Engineering* 16.4 (2019). Le DOI n'est pas actif, voir http://www.aimspress.com/article/10.3934/mbe.2019150, pp. 3018–3046. DOI: 10.3934/mbe.2019150. URL: https://hal.archives-ouvertes.fr/hal-02154588.

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[9] J. Deschamps, E. Hingant and R. Yvinec. 'Quasi steady state approximation of the small clusters in Becker–Döring equations leads to boundary conditions in the Lifshitz–Slyozov limit'. In: *Communications in Mathematical Sciences* 15.5 (2017), pp. 1353–1384. DOI: 10.4310/CMS.2017.v15.n5.a7. URL: https://hal.archives-ouvertes.fr/hal-01608844.

[10] T. El Bouti, T. Goudon, S. Labarthe, B. Laroche, B. Polizzi, A. Rachah, M. Ribot and R. Tesson. 'A mixture model for the dynamic of the gut mucus layer'. In: *ESAIM: Proceedings* 55.décembre (2016). Ed. by E. Frénod, E. Maitre, A. Rousseau, S. Salmon and M. Szopos, pp. 111–130. DOI: 10.1051/proc/201655111. URL: https://hal.archives-ouvertes.fr/hal-01421708.

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International journals

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[27] P. Raynaud, V. Jugnarain, O. Vaugrente, A. Vallet, T. Boulo, C. Gauthier, A. Inoue, N. Sibille, C. Gauthier, F. Jean-Alphonse, E. Reiter, P. Crépieux and G. Bruneau. 'A single domain intrabody targeting the follicle-stimulating hormone receptor (FSHR) impacts FSH-induced G protein-dependent signalling'. In: *FEBS Letters* (7th Aug. 2023). DOI: 10.1101/2023.08.07.552286. URL: https://hal.science/hal-04269864.

[28] A. Zehnaker, A. Vallet, J. Gourdon, C. Sarti, V. Jugnarain, M. Haj Hassan, L. Mathias, C. Gauthier, P. Raynaud, T. Boulo, L. Beauclair, Y. Bigot, L. Casarini, P. Crépieux, A. Poupon, B. Piégu, F. Jean-Alphonse, G. Bruneau and É. Reiter. 'Combined Multiplexed Phage Display, High-Throughput Sequencing, and Functional Assays as a Platform for Identifying Modulatory VHHs Targeting the FSHR'. In: *International Journal of Molecular Sciences* 24.21 (Nov. 2023), p. 15961. DOI: 10.3390/ijms242115961. URL: https://hal.science/hal-04274818.

Conferences without proceedings

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Reports & preprints

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[33] F. Clément and J. Olayé. *A stochastic model for neural progenitor dynamics in the mouse cerebral cortex*. 18th Dec. 2023. URL: https://inria.hal.science/hal-04351283.

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11.3 Cited publications

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