RESEARCH CENTRE

Inria Saclay Center

IN PARTNERSHIP WITH:

CNRS, INRAE

2022

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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B1.1.10. – Systems and synthetic biology

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1 Team members, visitors, external collaborators

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- Frédéric Jean-Alphonse [CNRS, Researcher]
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- Bahar Carabetta [INRIA]

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) [49], 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 [71, 44]. 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 [49, 43], 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 [65],[11] or in the framework of "pulse-modulated systems" [47].

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 [54]. 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 [55, 48] and stochastic context [38, 53, 64].

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 [68], 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 [69] or global stochastic optimization [45]. 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 [57]. 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 [51] based on similarity criteria adapted to the problem under consideration, and an original inference method inspired by the Generalized Smoothing (GS) method proposed in [67], 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 [63, 59] that we need to adapt in a case-by-case, model-dependent way: general relative entropy [60, 42], measure solution framework [52, 39, 46], martingale techniques [40], finite-volume numerical schemes [56], 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 [62], dimensional reduction [6], timescale reduction [4], spatial homogenization [36][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 [50, 41], 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) [66, 37, 70, 58]. 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. [61, 72]), 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 fallouts of MUSCA's basic research can be expected in the fields of Medicine, Agronomy (breeding) and Ecophysiology. 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

- Funding of ANR OVOPAUSE
- Successful application of Mauricio Sepúlveda to the Jean d'Alembert senior researcher fellowship program of Université Paris-Saclay

7 New software and platforms

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

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8 New results

8.1 Stochastic modeling and stochastic processes

8.1.1 A PDMP model of the epithelial cell turn-over in the intestinal crypt including microbiota-derived regulations

Participants: Léo Darrigade, Marie Haghebaert, Claire Cherbuy, Simon Labarthe, Béatrice Laroche.

Human health and physiology is strongly influenced by interactions between human cells and intestinal microbiota in the gut [24]. In mammals, the host-microbiota crosstalk is mainly mediated by regulations at the intestinal crypt level: the epithelial cell turnover in the crypts is directly influenced by metabolites produced by the microbiota. Conversely, the colonocytes maintain hypoxia in the gut, favorable to anaerobic bacteria which dominate the gut microbiota. We have constructed an individual-based model

of epithelial cells interacting with the microbiota-derived chemicals diffusing in the crypt lumen. This model is formalized as a piecewise deterministic Markov process (PDMP). It accounts for local interactions due to cell contact (among which are mechanical interactions), for cell proliferation, differentiation and extrusion which are regulated spatially or by chemicals concentrations. It also includes chemicals diffusing and reacting with cells. A deterministic approximated model is also introduced for a large population of small cells, expressed as a system of porous media type equations. Both models are extensively studied through numerical exploration. Their biological relevance is thoroughly assessed by recovering bio-markers of an healthy crypt, such as cell population distribution along the crypt or population turn-over rates. Simulation results from the deterministic model are compared to the PMDP model and we take advantage of its lower computational cost to perform a sensitivity analysis by the Morris method. We finally use the crypt model to explore butyrate supplementation to enhance recovery after infections by enteric pathogens.

8.1.2 Stochastic modeling of neurogenesis in the cerebral cortex

Participants: Frédérique Clément, Jules Olayé.

In the framework of the master internship of Jules Olayé (M2 Mathématiques pour les sciences du vivant, Université Paris-Saclay), we have designed a stochastic formulation of our deterministic model of embryonic neurogenesis in the cerebral cortex [18]. A population dynamics model for the different progenitor cell types and neurons has been designed using the formalism of branching process. The expectation and variance of the cell numbers of each type has been derived analytically and checked/illustrated through numerical simulations. The effect of stochastic transition rates between cell types, and stochastic duration of the whole division cycle and cell cycle phases have been investigated sequentially. The model has been extended to account not only for the number of neurons, but also for their spatial repartition into lower and upper cortical layers. The complete model is in accordance with experimental data supplied in [18], providing the number of neurons and intermediate progenitors according to embryonic age in a control and mutant situation. Finally, we have started investigating how information retrieved from cell lineage tree could be exploited to infer the dynamics of the earliest progenitors.

8.2 Deterministic modeling and model reduction

We have designed deterministic models for oogenesis in mammals and fish, including the very early events of ovarian follicle formation. The mammal model is stage-structured, as available data on follicle numbers are distributed over maturation stages, while the fish model is size-structured as available data consist of size distributions.

8.2.1 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 [32]. 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 the study of theoretical identifiability, 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.

8.2.2 A size-structured model of ovarian follicle population dynamics

Participants: Frédérique Clément, Louis Fostier, Romain Yvinec.

In the framework of the master internship of Louis Fostier (M2 Calcul Scientifique et Modélisation, Université Rennes 1), we have designed a PDE-based model of advection-reaction type, describing the renewal and growth of ovarian follicles up to spawning. The generic formulation of the model accounts for the direct and indirect interactions between follicles, leading to both nonlocal and nonlinear terms. We have shown the well-posedness of the problem and started investigating stationary solutions. This work is being followed-up by a PhD thesis.

8.2.3 Mathematical modeling of adipose tissue size distributions

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. Lipid accumulation results in a population of cells that do not have a characteristic size, indeed a bimodal size distribution is observed in adipose tissues. In addition, adipocyte size distribution is assumed to play a role in the development of obesity-related diseases. We have designed a mathematical model to describe adipocyte size density based on the Lifshitz-Slyozov partial differential equation. This equation is derived from the discrete-size Becker-Döring model which describes the number of lipid vesicles inside each cell.nUsing a suitable rescaling, we have obtained the convergence of the Becker-Döring model to the Lifshitz-Slyozov equation, together with the speed of convergence.
To reproduce the adipocyte size distribution data, we have further used the second order approximation of the Becker-Döring model, which leads to a modified Lifshitz-Slyozov equation, with either constant diffusion or size-dependent diffusion. We have studied both stationary problems and considered their respective stationary distribution to fit adipocyte size distribution data. We have studied the identifiability properties of the parameters shaping the stationary distribution. The proposed framework enables the characterization of adipocyte size density with four parameters, by insuring the uniqueness of the estimated parameters. We have characterized adipocyte size distribution in healthy rats, but this method can be adapted to characterize adipocyte size distribution in other species and different health conditions.

8.3 Exploration of signaling networks

8.3.1 Transducer Cascades for Biological Literature-Based Discovery

Participants: Anne Poupon, and collaborators.

G protein-coupled receptors (GPCRs) control the response of cells to many signals, and as such, are involved in most cellular processes. As membrane receptors, they are accessible at the surface of the cell.

GPCRs are also the largest family of membrane receptors, with more than 800 representatives in mammal genomes. For this reason, they are ideal targets for drugs. Although about one third of approved drugs target GPCRs, only about 16% of GPCRs are targeted by drugs. One of the difficulties comes from the lack of knowledge on the intra-cellular events triggered by these molecules. In the last two decades, scientists have started mapping the signaling networks triggered by GPCRs. However, it soon appeared that the system is very complex, which led to the publication of more than 320,000 scientific papers. Clearly, a human cannot take into account such massive sources of information. These papers represent a mine of information about both ontological knowledge and experimental results related to GPCRs, which have to be exploited in order to build signaling networks. The ABLISS project aims at the automatic building of GPCRs networks using automated deductive reasoning, allowing to integrate all available data. Therefore, we have processed the automatic extraction of network information from the literature using Natural Language Processing (NLP) [26]. We mainly focused on the experimental results about GPCRs reported in the scientific papers, as so far there is no source gathering all these experimental results. We have designed a relational database in order to make them available to the scientific community later. After introducing the more general objectives of the ABLISS project, we have described the formalism in detail. We have then explained the NLP program using the finite state methods (Unitex graph cascades) we implemented and we have discussed the extracted facts obtained. Finally, we have presented the design of the relational database that stores the facts extracted from the selected papers.

8.3.2 Serodolin, a β-arrestin–biased ligand of 5-HT 7 receptor, attenuates pain-related behaviors

Participants: Eric Reiter, and collaborators.

Transmembrane signaling through G protein–coupled receptors (GPCRs), originally described as requiring coupling to intracellular G proteins, also uses G protein–independent pathways through β-arrestin recruitment. Biased ligands, by favoring one of the multiple bioactive conformations of GPCRs, allow selective signaling through either of these pathways. In this study [25], we have identified Serodolin as the first β-arrestin–biased agonist of the serotonin 5-HT 7 receptor. This new ligand, while acting as an inverse agonist on Gαs signaling, selectively induces ERK activation in a β-arrestin–dependent way. Importantly, we have reported that Serodolin decreases pain intensity caused by thermal, mechanical, or inflammatory stimuli. Our findings suggest that targeting the 5-HT 7 R with β-arrestin–biased ligand could be a valid alternative strategy to the use of opioids for the relief of pain.

8.4 Computational modeling

8.4.1 A New in Silico antibody similarity measure both identifies large sets of epitope binders with distinct CDRs and accurately predicts off-target reactivity

Participants: Pascale Crépieux, Anne Poupon, Eric Reiter, and collaborators.

Developing a therapeutic antibody is a long, tedious, and expensive process. Many obstacles need to be overcome, such as biophysical properties (issues of solubility, stability, weak production yields, etc.), as well as cross-reactivity and subsequent toxicity, which are major issues. No *in silico* method exists today to solve such issues. We hypothesized [27] that if we were able to properly measure the similarity between the complementarity-determining regions (CDRs) of antibodies (Ab) by considering not only their evolutionary proximity (sequence identity) but also their structural features, we would be able to identify families of Ab recognizing similar epitopes. As a consequence, Ab within the family would share the property to recognize their targets, which would allow (i) to identify off-targets and forecast the cross-reactions, and (ii) to identify new Ab specific for a given target. Testing our method on 238D2, an antagonistic anti-CXCR4 nanobody, we were able to find new nanobodies against CXCR4 and to identify influenza hemagglutinin as an off-target of 238D2.

8.4.2 TNB-738, a biparatopic antibody, boosts intracellular NAD+ by inhibiting CD38 ecto-enzyme activity

Participants: Anne Poupon, and collaborators.

Cluster of differentiation 38 (CD38) is an ecto-enzyme expressed primarily on immune cells that metabolizes nicotinamide adenine dinucleotide (NAD+) to adenosine diphosphate ribose or cyclic ADP-ribose and nicotinamide. Other substrates of CD38 include nicotinamide adenine dinucleotide phosphate and nicotinamide mononucleotide, a critical NAD+ precursor in the salvage pathway. NAD+ is an important coenzyme involved in several metabolic pathways and is a required cofactor for the function of sirtuins (SIRTs) and poly (adenosine diphosphate-ribose) polymerases. Declines in NAD+ levels are associated with metabolic and inflammatory diseases, aging, and neurodegenerative disorders. To inhibit CD38 enzyme activity and boost NAD+ levels, we have developed TNB-738, an anti-CD38 biparatopic antibody that pairs two non-competing heavy chain-only antibodies in a bispecific format [30]. By simultaneously binding two distinct epitopes on CD38, TNB-738 potently inhibited its enzymatic activity, which in turn boosted intracellular NAD+ levels and SIRT activities. Due to its silenced IgG4 Fc, TNB-738 did not deplete CD38-expressing cells, in contrast to the clinically available anti-CD38 antibodies, daratumumab, and isatuximab. TNB-738 offers numerous advantages compared to other NAD-boosting therapeutics, including small molecules, and supplements, due to its long half-life, specificity, safety profile, and activity. Overall, TNB-738 represents a novel treatment with broad therapeutic potential for metabolic and inflammatory diseases associated with NAD+ deficiencies.

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

Participants: 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 [33]. We have identified 4 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 unbalance of these profiles characterize 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*.

8.5 Bibliographic reviews

8.5.1 An overview of deep learning applications in precocious puberty and thyroid dysfunction

Participants: Frédérique Clément, Misbah Razzaq, Romain Yvinec.

In the last decade, deep learning methods have garnered a great deal of attention in endocrinology research. In this review [29], we have provided a summary of current deep learning applications in endocrine disorders caused by either precocious onset of adult hormone or abnormal amount of hormone production. To give access to the broader audience, we have started with a gentle introduction to deep learning and its most commonly used architectures, and then focused on the research trends of deep learning applications in thyroid dysfunction classification and precocious puberty diagnosis. We have highlighted the strengths and weaknesses of various approaches and discuss potential solutions to different challenges. We have also gone through the practical considerations useful for choosing (and building) the deep learning model, as well as for understanding the thought process behind different decisions made by these models. Finally, we have given concluding remarks and future directions.

8.5.2 Intracellular VHHs to monitor and modulate GPCR signaling

Participants: Gilles Bruneau, Pascale Crépieux, Camille Gauthier, Frédéric Jean-Alphonse, Vinesh Jugnarain, Pauline Raynaud, Eric Reiter.

Single-domain antibody fragments, also known as VHHs or nanobodies, have opened promising avenues in therapeutics and in exploration of intracellular processes. Because of their unique structural properties, they can reach cryptic regions in their cognate antigen. Intracellular VHHs/antibodies primarily directed against cytosolic proteins or transcription factors have been described. In contrast, few of them target membrane proteins and even less recognize G protein-coupled receptors. These receptors are major therapeutic targets, which reflects their involvement in a plethora of physiological responses. Hence, they elicit a tremendous interest in the scientific community and in the industry. Comprehension of their pharmacology has been obscured by their conformational complexity, which has precluded deciphering their structural properties until the early 2010's. To that respect, intracellular VHHs have been instrumental in stabilizing G protein-coupled receptors in active conformations in order to solve their structure, possibly bound to their primary transducers, G proteins or β-arrestins. In contrast, the modulatory properties of VHHs recognizing the intracellular regions of G protein-coupled receptors on the induced signaling network have been poorly studied. In this review [28], we have presented the advances that the intracellular VHHs have permitted in the field of GPCR signaling and trafficking. We have also discussed the methodological hurdles that linger the discovery of modulatory intracellular VHHs directed against GPCRs, as well as the opportunities they open in drug discovery.

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 ->

Coordinator: Mauricio Sepúlveda (mauricio@ing-mat.udec.cl)

Partners:

- Universidad de Concepción, Chile (Chili)

Inria contact: Romain Yvinec

Summary: This project 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 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 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: R. Yvinec and M. Sepúlveda (Universidad de Concepción, Chile).
- i-GPCRNet, International Research Network (IRN) on GPCRs, http://www.i-gpcrnet.com/
- Bill & Melinda Gates Foundation, ContraBody (2021-2023, 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 : E. Reiter, P. Crépieux, F. Jean-Alphonse, R. Yvinec.
- Medical Research Council, MICA (2022-2025, PI (Investigating kisspeptin receptor signalling to improve the treatment of reproductive disease), Involved MUSCA members : E. Reiter

9.2 International research visitors

9.2.1 Visits of international scientists

Rita Singh

Status Professor

Institution of origin: Delhi University

Country: India

Dates: May 23-August 19

Context of the visit: Interaction between the FSH receptor and Insulin receptor substrates (IRS-1 and IRS-2) in the physiopathology of the polycystic ovary syndrome

Mobility program/type of mobility: Le Studium Loire Valley Institute for Advanced Studies, Visiting researcher program

Livio Casarini

Status Professor

Institution of origin: University of Modena and Reggio Emilia

Country: Italy

Dates: November 2022-November 2023

Context of the visit: Antibody fragments targeting ovarian GPCRs to control reproduction

Mobility program/type of mobility: Le Studium Loire Valley Institute for Advanced Studies, Research Fellow program, associated with the Biopharmaceuticals ARD CVL program.

9.2.2 Visits to international teams

Guillaume Ballif

Visited institution: Concordia University

Country: Canada

Dates: November 16,2021-February 17 ; June 03-30

Context of the visit: stochastic averaging for multiple timescale models

Mobility program/type of mobility:

Romain Yvinec

Visited institution: Granada University

Country: Spain

Dates: December 19-23

Context of the visit: Analysis of Becker-Döring models

Mobility program/type of mobility: research stay

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: B. 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: P. Crépieux.
- ERNEST (European Research Network on Signal transduction) COST Action 18133.

9.4 National initiatives

- ANR OVOPAUSE (2022-2026, PI R. Yvinec, 447 K€) "Dynamics and control of female germ cell populations: understanding aging through population dynamics models". Involved MUSCA Members: F. Clément, P. Crépieux, L. Fostier, F. Jean-Alphonse, E. Reiter, R. Yvinec
- ANR MOSDER (2022-2025, PI F. Jean-Alphonse, 420 K€) "Multi-dimensional Organization of Signaling Dynamics Encoded by gonadotropin Receptors". Involved MUSCA members: P Crépieux, F. Jean-Alphonse, E. Reiter, R. 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: B. Laroche
- ANR YDOBONAN (2021-2024, PI Vincent Aucagne, 497 K€) "Mirror Image Nanobodies: pushing forward the potential of enantiomeric proteins for therapeutic and pharmacological applications". Involved MUSCA member: E. Reiter.
- ANR PHEROSENSOR (2021-2026, PI Philippe Lucas, 1492K€) "Early detection of pest insects using pheromone receptor-based olfactory sensors". Involved MUSCA member: B. Laroche.
- ANR ABLISS (2019-2023, PI A. Poupon, 441 K€) "Automating building from Literature of Signalling Systems". Involved MUSCA members: A. Poupon, E. Reiter, P. Crépieux, R. Yvinec.

- LabEx MAbImprove (2011-2025, PI Hervé Watier). Involved MUSCA members : E. Reiter, F. Jean-Alphonse, P. Crépieux, A. Poupon, R. 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: F. Clément, R. Yvinec.

- INRAE metaprogram HOLOFLUX, Egg-to-Meat project (2020-2022, PI Monique Zagorec). Involved MUSCA member: B. Laroche.

- 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: F. Clément, R. Yvinec.

- Action Exploratoire Inria Compartimentage (2022-2024, PI R. 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

- SATT Paris-Saclay POC'UP 2020 project COOPERATE, awarded to B. Laroche (together with L. Rigottier, P. Serror, V. Loux and O. Rué): "COnsortium de bactéries cOmmensales pour augmenter l'effet barrière du microbiote et limiter la Persistance et la prolifération des Entérocoques Résistants à la vancomycine après traitement AnTibiotiquE".

- Ambition recherche développement Centre Val de Loire SELMAT (2020-2023, PI E. 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: E. Reiter, P. Crépieux, F. Jean-Alphonse, R. Yvinec.

- Appel à projet région Centre Val de Loire, INTACT (2019-2023, PI P. Crépieux, 200 K€) "Pharmacologie réverse à l'aide d'anticorps intracellulaires anti-RFSH actif". Involved MUSCA members: P. Crépieux, E. Reiter, F. Jean-Alphonse, A. Poupon, R. Yvinec. Industrial partner: McSAF, Tours.

10 Dissemination

10.1 Promoting scientific activities

10.1.1 Scientific events: organisation

F. Clément, member of the organizing committee (together with Yohanns Bellaiche, Evelyn Houliston, Jean-Stéphane Joly, Sakina Mhaouty-Kodja, and Nadine Peyrieras) of the ITMO BCDE symposium"Cell, Developmental and Evolutionary biology meets Environmental Change: Lessons and Impacts", May 10 (Paris with remote transmission)

F. Clément, member of the organizing committee and scientific chair (together with Catherine Patrat, Marie-Émilie Terret and Katja Wassmann) of the ITMO BCDE symposium "From gametes to embryo: basic research and clinical applications", November 24 (Paris with remote transmission),

P. Crépieux, organizer (together with Rita Singh) of the Studium symposium "Gonadotropins in the Physiopathology: Current advances in the Mechanisms of Action", September 14-15, online

F. Jean-Alphonse IRN “Challenges & future direction in the GPCR field”, i-GPCRnet workshop, September 26-29, Leipzig

R. Yvinec, organizer of the Mini-symposium “Modeling the female reproductive system at different scales”, in European Conference on Mathematical and Theoretical Biology (ECMTB 2022), September 19-23, Heidelberg (Germany)

10.1.2 Scientific events: selection

F. Clément, member of the conference program committee and reviewer (together with Catherine Patrat, Marie-Émilie Terret and Katja Wassmann) of the ITMO BCDE symposium “From gametes to embryo: basic research and clinical applications”, November 24 (Paris with remote transmission)

10.1.3 Journal

Member of the editorial boards

F. Clément, guest editor (together with Joseph DiStefano, and Fady Hannah-Shmouni) of the Research Topic “Mechanistic, Machine Learning and Hybrid Models of the ‘Other’ Endocrine Regulatory Systems in Health and Disease” in Front. Endocrinol.

P. Crépieux and E. Reiter, associate editors Front. Endocrinol. (cellular endocrinology)

F. Jean-Alphonse and E. Reiter, guest editors (together with Francesco De Pascali, Aylin C. Hanyaloglu, and Francesco Poti) of the Research Topic “Pharmacology of endocrine related GPCR‘” in Front. Endocrinol.

A. Poupon, guest editor (together with Hervé Watier) of the special issue “Therapeutic Antibody Development: What Are We Learning along the Way?”, in Int. J. Mol. Sci.

R. Yvinec, associate editor J. Math. Biol.

Reviewer - reviewing activities

F. Clément, Biol. Reprod., J. Math. Biol.

P. Crépieux, Mol. Cell. Endocrinol., Front. Endocrinol., Reproduction

A. Poupon, mAbs, Sci. Rep.

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

10.1.4 Invited talks

E. Reiter

- “Beta-arrestins and GPCRs”, i-GPCRnet IRN, April 15th, 2022, online.
- “Nonhormonal contraception by nanobody-mediated modulation of ovarian GPCRs”, Bill & Melinda Gates Foundation, Nonhomonal Contraceptive Discovery Program Meeting, October 21, Bruxelles, Belgium.

R. Yvinec

- Stochastic Becker-Döring model: large population and large time results for phase transition phenomena. Chemical Reaction Networks Workshop, July 6–8, Torino, Italy

10.1.5 Leadership within the scientific community

F. Clément

- expert of ITMO BCDE
- member of the direction and scientific boards of GDR 3606 REPRO, and co-head of WP “Biomathematics, Bioinformatics and Biophysics for Reproduction”
- member of the scientific board of PIXANIM (Phénotypage par Imagerie in/eX vivo de l’ANImal à la Molécule)

P. Crépieux

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

F. 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

B. Laroche

- member of the Steering Committee of the INRAE metagrogram HOLOFLUX

A. Poupon

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

R. 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

F. Clément, member of the INRAE juries “Agriculture, Numérique et Société”, for the recruitment of research directors (DR2, admissibility and admission) and research scientists (CRCN, admissibility)

F. Clément, member of the selection board for the URGO foundation open call for a post-doctoral fellowship on endometriosis at Inserm

F. Clément, reviewer for ANR AAPG 2022 call (committee #56)

R. Yvinec, member of an INRAE jury for the recruitment of a research scientist in MaiAGE (Dynamic models for modeling in microbial ecology, concours CRCN sur profil n° 8)

10.1.7 Research administration

F. Clément is invited member of the scientific council of Graduate School Life Sciences and Health of University Paris-Saclay

M. Haghebaert is a PhD student member of EDMH (École Doctorale Mathématiques Hadamard) council

B. Laroche is director of MaIAGE since 01/07/2022

E. Reiter is deputy director of UMR PRC

R. Yvinec is co-head of Fédération CaSciModOT (Calcul Scientifique et Modélisation Orléans-Tours)

10.2 Teaching - Supervision - Juries

10.2.1 Teaching

G. Ballif, 1st year IUT Orsay, Université Paris-Saclay, graphs (42h), probabilities (42h)

F. Clément, Data challenge on automatic ovarian follicle detection, in the framework of the data camp of Master program Data Science Institut Polytechnique de Paris (PI Alexandre Gramfort, collaboration François Caud, Céline Guigon, Raphaël Corre)
https://ramp.studio/problems/follicles_detection

P. Crépieux, Master Biology of Reproduction (2h), Université de Tours

P. Crépieux, Master Infectiology, Immunity, Vaccinology and Biodrugs (4h), Université de Tours

P. Crépieux, Master Physiopathology (2h)

L. Meyer, L3 Mathématiques, Université d'Orléans, numerical tools (32h)

L. Meyer L2 Informatique, Université d'Orléans, probabilities (24h)

L. Meyer L1 level support in algebra and analysis (8h)

E. Reiter, Master Infectiology, Immunity, Vaccinology and Biodrugs (4h), Université de Tours

E. Reiter, Master Physiopathology (2h), Université de Tours

R. Yvinec, Master Infectiology, Immunity, Vaccinology and Biodrugs (3h), Université de Tours

10.2.2 Supervision

PhD: Guillaume Ballif "Multiscale stochastic modeling and analysis in population dynamics: Application to the ovarian follicle population", defended on September 27, supervisors : F. Clément and R. Yvinec

PhD in progress: Louis Fostier, "Multiscale mathematical modeling of oogenesis in fish", started November 2022, supervisors: F. Clément and R. Yvinec, associate supervisor: V. Thermes

PhD in progress: Camille Gauthier, "Manipulation of the activity and physiology of LH receptor through a small fragment of antibody", started October 2020, supervisors: P. Crépieux and E. Reiter

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: E. Reiter and F. Jean-Alphonse)

PhD in progress: Marie Haghebaer, "Tools and methods for modeling the dynamics of complex microbial ecosystems from temporal experimental observations: application to the dynamics of the intestinal microbiota", started November 2020, supervisor: B. Laroche

PhD in progress: Léo Meyer, "Modeling and analysis of models for adipocyte growth", started October 2020, supervisors: M. Ribot and R. Yvinec

PhD in progress: Pauline Raynaud, "Intracellular antibodies to explore the relationships between conformations and activity of hormone receptors, and their application in reverse pharmacology", started October 2019, supervisors: P. Crépieux and G. Bruneau

PhD in progress: Anielka Zehnaker, "Selective modulation of FSH receptor signaling pathways in vivo, consequences on ovarian and testicular functions ", started October 2020, supervisor: E. Reiter

PhD follow-up committee of Tu-Ky Ly (ED ABIES), members F.Clément and R. Yvinec

Master internships: Jules Olayé (M2 Mathématiques pour les Sciences du Vivant, Université Paris-Saclay, supervisor: F. Clément), Louis Fostier (M2 Calcul Scientifique et Modélisation, Université Rennes 1, supervisors: F. Clément and R. Yvinec)

10.2.3 Juries

F. Clément

- HDR Jury of Violette Thermes, Université de Rennes 1, February 28
- PhD Jury of Bachar Tarraf (referee), Université de Bordeaux, January 25

P. Crépieux

- PhD jury of Florian Pontheaux (referee), Sorbonne Université, March 23
- PhD jury of Rim Baccouch (referee), Université de Bordeaux, March 11
- PhD jury of Cui Yuanxu, Paris Cité, October 26

B. Laroche

- HDR jury of Claude Loverdo (referee), September 5, Sorbonne Université
- PhD jury of Ousmane Suwareh (referee), December 4, Institut Agro Rennes-Angers

E. Reiter

- HDR jury of Chérine Béchara, Université de Montpellier, May 23

R. Yvinec

- PhD Jury of Eléa Thibault Greugny (referee), Institut Polytechnique de Paris, October 4
- PhD Jury of Elias Ventre, Université Claude Bernard Lyon 1 September 28

10.3 Popularization

10.3.1 Articles and contents

MUSCA, des experts en modélisation multiéchelle pour la biologie https://www.inria.fr/fr/musca-experts-modelisation-biologie

F. Jean-Alphonse. Des anticorps de lama pour contrôler la reproduction. CNRS MICROSCOOP March (Number 85)

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.

[3] B. Aymard, F. Clément and M. Postel. 'Adaptive mesh refinement strategy for a nonconservative transport problem'. In: *ESAIM: Mathematical Modelling and Numerical Analysis* (Aug. 2014), pp. 1381–1412. DOI: 10.1051/m2an/2014014. URL: https://hal.archives-ouvertes.fr/hal-00865429.

[4] C. Bonnet, K. Chahour, F. Clément, M. Postel and R. Yvinec. 'Multiscale population dynamics in reproductive biology: singular perturbation reduction in deterministic and stochastic models'. In: *ESAIM: Proceedings and Surveys* 67 (2020), pp. 72–99. DOI: 10.1051/proc/202067006. URL: https://hal.inria.fr/hal-03047923.

[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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[7] F. Clément, F. Robin and R. Yvinec. 'Analysis and calibration of a linear model for structured cell populations with unidirectional motion : Application to the morphogenesis of ovarian follicles'. In: *SIAM Journal on Applied Mathematics* 79.1 (Feb. 2019), pp. 207–229. DOI: 10.1137/17M1161336. URL: https://hal.archives-ouvertes.fr/hal-01852560.

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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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