RESEARCH CENTRE

Inria Saclay Centre at Université Paris-Saclay

IN PARTNERSHIP WITH:

CNRS, INRAE

2024

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

Creation of the Project-Team: 2020 July 01

Keywords

Computer sciences and digital sciences

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1 Team members, visitors, external collaborators

Research Scientists

- Frédérique Clément [Team leader, INRIA, Senior Researcher, HDR]
- Pascale Crepieux [CNRS, Senior Researcher, HDR]
- Stefan Haar [INRIA, Senior Researcher, HDR]
- Frédéric Jean-Alphonse [CNRS, Researcher, HDR]
- Pawan Kumar [INRIA, Starting Research Position, from Oct 2024]
- Béatrice Laroche [INRAE, Senior Researcher, HDR]
- Anne Poupon [CNRS, Senior Researcher, CTO of Mabsilico half-time, HDR]
- Eric Reiter [INRAE, Senior Researcher, HDR]
- Lorenzo Sala [INRAE, Researcher]
- Romain Yvinec [INRAE, Senior Researcher, HDR]

Faculty Member

- Chloé Audebert [Sorbonne Université, Associate Professor, from Sep 2024]

Post-Doctoral Fellows

- Léo Darrigade [INRIA, Post-Doctoral Fellow]
- Rosario Medina Rodriguez [INRIA, Post-Doctoral Fellow, from Jun 2024]

PhD Students

- Marlene Davilma [INRAE]
- Alice Fohr [UNIV PARIS SACLAY, from Sep 2024]
- Louis Fostier [INRAE]
- Eleonora Pastremoli [INRAE]
- Pamela Ignacia Romero Jofre [INRAE, from Oct 2024]
- Chloé Weckel [INRIA, from Oct 2024]

Interns and Apprentices

- Julien Joachim [INRIA, Intern, from Mar 2024 until May 2024]

Administrative Assistant

- 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) [81], 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 [104, 76]. 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 [81, 75], 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 [26] 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 [98],[14] or in the framework of "pulse-modulated systems" [79].

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 [86]. 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 [87, 80] and stochastic context [70, 85, 97].

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 [18, 17] 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 [101], combined with the reduction of weakly nonlinear subsystems.

Bridging the gap between discrete and continuous networks through most permissive semantics Since their introduction in the late 1960s, *state- and time-discrete frameworks* such as Thomas Networks and Boolean Networks (BNs), which belong to the subclass of *logical models* with only two values possible in any variable, have been widely adopted for reasoning about signaling and gene networks, as they require few parameters and can easily integrate information from omics datasets and genetic screens. Two-way translations from BNs to discrete Petri nets (PNs) allow one to transfer both theoretical results and efficient algorithms from one model class to the other (see [6]) ; we therefore regard BNs and discrete PNs as one class, which we call *discrete models*. These models represent processes with a high degree of generalization and can offer coarse-grained but robust predictions. That makes them particularly suitable for large biological networks, for which ample global knowledge exists about potential interactions with little precise data on actual molecules abundances and reaction kinetics. In this way, discrete models provide one with an approach orthogonal to that enabled by continuous deterministic dynamics (via

differential equations). In fact, whereas deterministic models reflect in a very fine way the spatio-temporal dynamics in chemical reactions and biological networks, the reliability of their predictions strongly depends on the precision of the knowledge concerning existence and strength of interactions, and of precise measurements of all parameters, initial conditions and external influences; perturbations in either domain are hard to apprehend, and their impact very difficult to predict. Typically, such models are useful for conducting campaigns of large numbers of *simulations* with varying parameters, giving a panorama of some possible types of system evolution. Obviously, there remains an irreducible *coverage problem*: do the simulations we performed capture all the evolutions that the *wild* system could have undergone?

By contrast, discrete models are fundamentally *non-deterministic* in their behavior, allowing one to extract at moderate computational cost a *complete, possibilistic* overview of *any* evolution the system may take (see [15, 5, 61]). Some of these evolutions may be actually ruled out by intrinsic quantitative features; discrete models thus may predict as possible some behaviors that will *not* actually occur. It has long been believed that discrete models systematically *over-approximate* the system evolution. Our previous work on the *most permissive semantics* [7, 22] has shown that this is the case if, but also only if, the semantics of the discrete system is sufficiently enriched (by one additional, intermediate state PLUS the liberty, for every function, to read this ambiguous value as either 0 or 1). Integrating into a new execution paradigm, called Most Permissive Boolean Networks (MPBNs), one can therefore ensure that a carefully crafted discrete model predicts at least the actual possible behaviors of the system. Moreover, MPBNs significantly reduce the complexity of dynamical analysis (e.g. reachability verification can be done in linear time), enabling one to model genome-scale networks. A recent line of research in MUSCA studies the dynamics of *continuous Petri nets (CPNs)*. These models differ from their discrete counterparts in the facts that transitions may be enabled with real rather than integer enabling degrees, and may fire with any fraction of their enabling degree, leading to a continuous state space. A crucial tool is to use abstract and symbolic semantics, in which state classes lump together all continuous states that have the same *activity*, that is, the same set of transitions that are eventually firable in some sequence initiated in those states. While being of great interest in its own right, this allows one to capture the long-run behavior efficiently. The particularly helpful mathematical properties of CPN allow for very efficient verification of reachability and limit-reachability; all attractors are leaves, and vice versa. Emerging research directions are followed in MUSCA to (i) efficiently explore the dynamics of biological networks ; (ii) further study the relationships between CPN, MPBN and related models; (iii) investigate the passageways between discrete and continuous *stochastic* system models ; and develop attractor search and reprogramming algorithms.

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 [16] [11], using either existing state-of-the art deterministic derivative-based optimization [102] or global stochastic optimization [77]. 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 [89]. 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 [83] based on similarity criteria adapted to the problem under consideration, and an original inference method inspired by the Generalized Smoothing (GS) method proposed in [100], 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 [24] and long-time behavior [10], and the design of appropriate numerical schemes [1, 3] often rely on more or less generic techniques [96, 91] that we need to adapt in a case-by-case, model-dependent way: general relative entropy [92, 74], measure solution framework [84, 71, 78], martingale techniques [72], finite-volume numerical schemes [88], 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 [24]), or the formulation of particularly tricky boundary conditions [12]. 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 [95], dimensional reduction [9], timescale reduction [4], spatial homogenization [68][13], discrete to continuous reduction [12] and stochastic to deterministic limit theorems [19].

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 [82, 73], and theoretical studies of the inverse problems associated with the models [8] 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) [99, 69, 103, 90]. 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 [21].

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 [16]. 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 [20].

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 [25].

In reproductive physiology, there is currently a spectacular revival of experimental investigations (see e.g. [93, 105]), 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

- Integration of Stefan Haar
- Delegation of Chloé Audebert
- Research article “Nonlinear compartmental modeling to monitor ovarian follicle population dynamics on the whole lifespan” [29] selected as a REPRO highlight
- Best poster prize awarded to Louis Fostier at the European Conference on Mathematical and Theoretical Biology, ECMTB2024

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

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 [29]. 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 [31]. The core of the model is the stochastic counterpart of our former deterministic compartmental model based on transport equations [23]. 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 impact of the neurogenic pathway on the variance of the final number of neurons is studied in details. 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, Frédéric Jean-Alphonse, 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 [28]. 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. We have analyzed the asymptotic behavior of the model under two distinct assumptions: either the deterministic flow of chemical reactions is exponentially contractive, or it satisfies a linear conservation law. In both cases, we have demonstrated the exponential convergence of the process to a unique stationary measure. In the latter case, we have collaborated with Professor Jonathan C. Mattingly (Duke University, USA) to adapt techniques from switching ordinary differential equations to our proof. In parallel, from the derivation of moment expressions, we have developed a simplified ODE-based model focused on the GPCR-induced production of cAMP. To analyze experimenal AMPc time series, we have designed a dedicated database with a web interface storing the metadata (e.g. type of ligand, dose, pharmacological perturbations) related to each experimental dataset.

8.1.4 Modeling the inactivation of chromosome-X

Participants: Frédérique Clément, Alice Fohr, Hélène Leman.

In the framework of Alice Fohr's PhD, 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 [94]. Using the theory of bifurcation analysis, we have confirmed the numerical results obtained therein 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 spawning, 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 quasilinear size-structured population model with nonlinearities accounting for nonlocal interactions between individuals [53]. The recruitment (immigration), growth and death rates are inhomogeneous in time and/or space and depend on weighted averages of the density. We first prove the existence and uniqueness of globally bounded weak solutions using the characteristic curves and Banach fixed point Theorem, after transforming the partial differential equation into an equivalent system of integral equations. We then investigate the long-time behavior of the PDE in the case when the growth rate is separable. Applying a classical time-scaling transformation, the problem boils down to a PDE with linear growth rate and nonlinear inflow boundary condition, entering the theoretical framework of abstract semilinear Cauchy problems. We can then perform a bifurcation analysis which reveals the richness of the model behavior. Depending on the ratio of the recruitment to the growth rate, the model can exhibit multistability and stable oscillatory solutions, emanating respectively through saddle-node and Hopf bifurcations. We illustrate these theoretical results on the different phases of the oogenesis process.

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

Participants: Chloé Audebert, 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 [33]. 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 [38], 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 [30]. 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 [45], 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 A mechanistic modelling approach of the host–microbiota interactions to investigate beneficial symbiotic resilience in the human gut

Participants: Béatrice Laroche, Eleonora Pastremoli, 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 [35], 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 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.

In the framework of Eleonora Pastremoli's PhD, this model has been further enriched to incorporate a newly identified hard mucus layer, with additional specific boundary conditions and reaction terms such

as the degradation rate. The completed model intends to capture accurately the micro-scale processes within the crypt, such as cell-microbe interactions and nutrient absorption, and their impact on the macro-scale dynamics of the colon. With this comprehensive framework, we can establish a virtual laboratory to test various hypotheses about gut microbiota interactions, such as simulating different dietary regimes or studying the inflammatory response associated to microbial groups. Current efforts are focused on enhancing the computational efficiency of the model simulations by developping model order reduction techniques.

8.3.2 Multiscale modeling of single cell-based dynamics of ovarian development

Participants: Chloé Audebert, Frédérique Clément, Fabien Crauste, Pawan Kumar.

In mammals, females are endowed at birth with a limited number of germ cells (oocytes) hosted in somatic structures called ovarian follicles. The pool of primordial (not yet activated) follicles corresponds to the ovarian reserve, which will get progressively exhausted with ovarian aging. In the framework of the AI4scMED axis of PEPR Santé numérique and Pawan Kumar's postdoc, we have started to develop a multiscale model representing the selection of the future oocytes among the germ cell population, which occurs within germ cysts during ovarian development, and involves complex interactions between germ cells and somatic cells. The model is being implemented in the SiMuScale environment that enables one to couple biochemical dynamics, namely gene regulatory dynamics (GRN), with spatially-distributed cell population dynamics. The 3D individual-based model accounts for the different types of germ cells and their neighboring somatic cells within a spatially explicit framework describing the structure of a germ cyst, and embeds a minimal GRN for oocyte differentiation derived from scRNA seq-based studies of ovarian development. We are studying the effects of the cyst geometry and cell content, as well as the range of somatic cell signaling onto germ cells, on the final oocyte selection output.

8.4 Bridging discrete and continuous netwok dynamics

Participants: Stefan Haar, and collaborators.

8.4.1 Abstract and symbolic semantics for identifying attractors in continuous Petri nets

Continuous Petri nets (CPNs) form a model of (uncountably infinite) dynamical systems that has been successfully explored for modeling and theoretical purposes. To harness the size of the state space and to identify the long-run stabilities (attractors), we proceed in [47] as follows: Let the mode of a marking be the set of transitions fireable in the future. Along a firing sequence, the sequence of different modes is non increasing, and forms what we call the trajectory of the sequence. In CPNs, a marking can be reachable by a finite sequence, or lim-reachable by an infinite convergent sequence. The set of trajectories (resp. markings) obtained via lim-reachability (sometimes strictly) includes the set of trajectories (resp. markings) obtained via reachability. Here, we introduce transfinite firing sequences over countable ordinals and establish several results: (1) while trans-reachability is equivalent to lim-reachability, the set of trajectories associated with trans-reachability may be strictly larger than that associated with lim-reachability; (2) w.r.t. trajectories, transfinite sequences over ordinals smaller than $\omega 2$ are enough; and (3) checking whether a trajectory is achievable is NP-complete. We then turn to a more difficult problem: the specification, for all trans-finite firing sequences, of their achievable signatures, i.e. the sequences of markings witnessing the changes of mode along the trajectory. In view of this goal, we define a finite symbolic reachability tree (SRT) that tracks the possible signatures of the system; in the SRT, a set of markings with same mode is associated with each vertex. We establish that, for bounded CPNs, reversibility holds inside the leaves of the SRT (showing that they represent indeed attractors). Finally, from an algorithmic point of view, we show how to build an effective representation of the SRT in exponential time, even when the CPN is unbounded.

8.4.2 Attractor basins in concurrent systems

A crucial question in analyzing a concurrent system is to determine its long-run behavior, and in particular, whether there are irreversible choices in its evolution, leading into parts of the reachability space from which there is no return to other parts. Casting this problem in the unifying framework of safe Petri nets, our previous work has provided techniques for identifying attractors, i.e. terminal strongly connected components of the reachability space. What we aim at is to determine the attraction basins associated with those attractors; that is, those states from where all infinite runs are doomed to end in the given attractor, as opposed to those that are free to evolve differently. In [61], we have provided a solution for the case of safe Petri nets. Our algorithm uses net unfoldings and provides a map of all of those configurations (concurrent executions of the system) that lead onto cliff-edges, i.e. any maximal extension for those configurations lies in some basin that is considered fatal.

8.4.3 Modeling a Natech scenario with Petri net unfoldings

The multirisk can be defined as a complex system made up of different hazards (natural and/or technological), which can act in combination - with or without coincidence in time - and have an impact on potentially dependent issues and their vulnerability. Indeed, under certain conditions, different combinations of risks are likely to occur. Smaller events can also lead to cascades of events that are highly damaging to communities. To better understand and prevent this type of event, a major challenge lies in formalism knowledge and in particular to provide a representation of scenarios. The scientific challenges mainly concern the representation of interactions between the many components of this complex system and understanding the dynamics of the system. To meet these challenges, approaches based on Petri nets and their unfolding are a relevant solution. Petri nets and their unfolding can be used to represent dynamics between hazards and their effects. In this possibilistic approach, we look at the case of a NaTech event caused by a forest fire [51]. The aim is to understand the dynamics and interactions of the variables involved in a forest fire in order to prevent and possibly avoid major impacts. This feasibility study is carried out on a simplified but realistic system, using the ECCO and Ecofolder tools. Beyond the industrial aspects characteristic of NaTech events, we also consider the impacts on the forest. In terms of multi-hazard management, the Petri nets process has made it possible to identify scenarios with damaging outcomes. This makes it possible to prevent the steps leading to devastating events.

8.5 Deep-learning based inference from data and images

8.5.1 Symbolic regression : Generalizing the SINDy approach with nested neural networks

Participants: Louis Fostier, and collaborators.

Symbolic Regression (SR) is a widely studied field of research that aims to infer symbolic expressions from data. A popular approach for SR is the Sparse Identification of Nonlinear Dynamical Systems (SINDy) framework, which uses sparse regression to identify governing equations from data. During the CEMRACS 2023 summer school, Louis Fostier together with Camilla Fiorini, Clément Flint, Emmanuel Franck, Reyhaneh Hashemi, Victor Michel-Dansac and Wassim Tenachi have introduced an enhanced method, Nested SINDy, that aims to increase the expressivity of the SINDy approach thanks to a nested structure [54]. Indeed, traditional symbolic regression and system identification methods often fail with complex systems that cannot be easily described analytically. Nested SINDy builds on the SINDy framework by introducing additional layers before and after the core SINDy layer. This allows the method to identify symbolic representations for a wider range of systems, including those with compositions and products of functions. We demonstrate the ability of the Nested SINDy approach to accurately find symbolic expressions for simple systems, such as basic trigonometric functions, and sparse (false but accurate) analytical representations for more complex systems. Our results highlight Nested SINDy's potential as a tool for symbolic regression, surpassing the traditional SINDy approach in terms of expressivity. However, we also note the challenges in the optimization process for Nested SINDy and suggest future research

directions, including the designing of a more robust methodology for the optimization process. This study proves that Nested SINDy can effectively discover symbolic representations of dynamical systems from data, offering new opportunities for understanding complex systems through data-driven methods.

8.5.2 Automatic detection and classification of ovarian follicles from 2D histological images

Participants: Frédérique Clément, Rosario Medina-Rodriguez.

In the framework of Rosario Medina's postdoctoral research within the OVOPAUSE project, we have explored the use of deep learning models for the automatic detection and classification of ovarian follicles from 2D histological images of mouse ovaries. The primary objective of this task is to determine the location of each follicle within the image and classify its stage of maturity. We first prepared the dataset, which includes more than 1,500 scanned ovary sections. We performed extensive image preprocessing, including cleaning, color stain normalization, and contrast enhancement, to ensure consistency and quality across the dataset. From this dataset, the follicles in half of the images were annotated by domain expert collaborators. The analysis of the images and annotations revealed two major challenges: (i) a significant variation in follicle sizes depending on the maturity stages, and (ii) a limited number of annotated instances for each category, particularly for the smallest follicles. To address these issues, we have approached the problem of automatic detection and classification of ovarian follicles using object detection with the Detectron2 framework. As a baseline model, we have employed a Mask R-CNN with Feature Pyramid Networks (FPN) architecture pre-trained on ImageNet to achieve faster convergence. The annotated dataset was further augmented during training, using data augmentation techniques and oversampling of underrepresented classes, specifically the smallest follicles, to mitigate class imbalance and improve model performance. While the performance metrics are promising, the limited number of annotated instances for small-sized follicles requires further improvement. To address this limitation, we are settling a pseudo-labeling strategy, which involves pseudo-labeling the remaining images in the dataset using the baseline model. After validation, the newly annotated images can be added to the dataset, and the baseline model iteratively refined by retraining with the expanded dataset and corresponding annotations.

8.5.3 3D imaging-based analysis of the germline in teleost

Participants: Frédérique Clément, Marlène Davilma, and collaborators.

In teleost fish, female fecundity depends essentially on the oocyte reserve, which determines the number of eggs spawned in each reproductive cycle. Unlike mammals, which have a limited and predefined stock of oocytes at birth, this reserve can be renewed throughout a female's life. In adult teleosts, this reserve is, on the one hand, used to generate mature oocytes ready to be spawned and, on the other hand, replenished from germline stem cells present in specialized structures called germline cradles. A main issue is to understand the contribution of these germline stem cells in the renewal of the oocyte reserve in both juveniles and adults, as well as the involved regulatory mechanisms. In the framework of Marlène Davilma's PhD, co-supervised by Violette Thermes and Frédérique Clément, we have implemented a 3D whole ovary imaging strategy in Medaka to provide quantitative data and study the cell dynamics in the germinal cradle. We have refined ovary clearing protocols combined with immunolabelings (e.g., anti-vasa, anti-pH3, anti-GFP), and imaged the ovaries using light sheet microscopy. In addition, we have set up 3D image analysis pipelines that integrate pre-trained open-source neural networks suitable for precise segmentation. These deep-learning based pipelines have greatly improved our ability to manage complex 3D analysis of the germinal cradle and allow us to access quantitative data at the level of the entire ovary. We are now analyzing the number, distribution and composition of germinal cradles in wild-type females, as well as in two KO lines showing a drastic decrease in female fecundity, to uncover the miRNA-mediated regulatory mechanisms

8.6 Exploration of signaling networks

8.6.1 A single-domain intrabody targeting the follicle-stimulating hormone receptor impacts FSH-induced G protein-dependent signaling

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

Intracellular variable fragments of antibody heavy-chains 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 of 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 receptor family, the follicle-stimulating hormone receptor (FSHR) [42]. This intra-VHH recognizes the FSHR third intracellular loop 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 thus far on this receptor.

8.6.2 An intracellular VHH targeting the Luteinizing Hormone receptor modulates G protein-dependent signaling and steroidogenesis

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

Luteinizing hormone (LH) is essential for reproduction, since it controls ovulation and steroidogenesis. LH receptor (LHR) recruits various transducers, leading to the activation of a complex signaling network. We recently identified iPRC1, the first variable fragment from heavy-chain-only antibody (VHH) interacting with intracellular loop 3 (ICL3) of the follicle-stimulating hormone receptor (FSHR). Because of the high sequence similarity of the human FSHR and LHR (LHCGR), we have examined in [32] the ability of the iPRC1 intra-VHH to modulate LHCGR activity. We have demonstrated that iPRC1 binds LHCGR, to a greater extent when the receptor was stimulated by the hormone. In addition, it decreased LH-induced cAMP production, cAMP-responsive element-dependent transcription, progesterone and testosterone production. These impairments are not due to Gs nor β-arrestin recruitment to the LHCGR. Consequently, iPRC1 is the first intra-VHH to bind and modulate LHCGR biological activity, including steroidogenesis. It should help further understand signaling mechanisms elicited at this receptor and their outcomes on reproduction.

9 Partnerships and cooperations

9.1 International initiatives

9.1.1 Participation in other International Programs

- 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

Other international visits to the team

Rita Singh

Status: Professor

Institution of origin: University of Delhi

Country: India

Dates: April 30-July 07

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

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

Louis Fostier and Léo Darrigade visited Duke University, from March 11 to May 10, in the framework of Romain Yvinec's sabbatical stay.
Louis Fostier worked in collaboration with Kevin Flores (NC state University) on BINN (biologically informed neural network) methods.
Léo Darrigade worked in collaboration with Prof. John Mattingly (Duke University) to study the stationarity of a stochastic model of compartmentalized signaling.

Lorenzo Sala: one week stay in Pasadena in November at Caltech. Collaboration with Sergey Lapin, Marcela Szopos and Mohamed Zaid about multiscale modeling of ODE systems with applications in biomedicine. Funded by the American Institute of Mathematics.

9.3 National initiatives

- PEPR SAMS pillar project CULTISSIMO (2024-2030, PI Lionel Rigottier, 80 K€ over 5,68 M€) "Plateforme de culturomique partagée pour accéder à un large répertoire de micro-organismes, dont les non cultivés, afin de comprendre les fonctions clés des microbiomes sur les écosystèmes humains". Involved MUSCA members: Béatrice Laroche, Lorenzo Sala.

- PEPS AMIES SIFAREA (2024-2025, PI Chloé Audebert, 26 K€)"Digital simulator for the training of critical care anesthesiologists". Involved MUSCA members: Chloé Audebert, Lorenzo Sala.

- FC3R digital approaches OVOTOX (2024-2026, PI Frédérique Clément, 50 K€) “Coupling physiologically-based kinetic models of endocrine axes with structured cell population dynamics models: An integrative approach of reproductive toxicity”. Involved MUSCA members: Frédérique Clément, Romain Yvinec.

- 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.

- LabEx MAbImprove (2011-2025, PI Hervé Watier). Involved MUSCA members: Pascale Crépieux, Frédéric Jean-Alphonse, Anne Poupon, Eric Reiter, Romain Yvinec.

- LabEx MAbImprove ANR-10- LABX-53 (2024, PI Pascale Crépieux, 51 K€) “Perturbations physiologiques induites par un VHH intra-cellulaire qui biaise le trafic intracellulaire du récepteur de la FSH”’. Involved MUSCA members: Pascale Crépieux, Frédéric Jean-Alphonse, Anne Poupon, Eric Reiter, Romain Yvinec.

- INRAE metaprogram DIGIT-BIO, FermenTwin project (2024-2025, PI Guillaume Gautreau, 10 K€) “Using digital twins to predict the evolution of food microbiota during plant fermentation”. Involved MUSCA members: Lorenzo Sala and Béatrice Laroche.

- INRAE metaprogram Holoflux, MiMiSiPi (2024-2025, PI Florent Kempf) “Metagenomics and metatranscriptomics of the gut microbiota in the context of Salmonella super shedding induced dysbiosis in pigs”. Involved MUSCA members: Lorenzo Sala and Béatrice Laroche.

- 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 - Inria 2022 AMI Risques naturels et environnementaux, SMART project (2022-2025, PIs Stefan Haar and Corinne Curt-Patat, 139 K€), “Multirisk scenarios on a territory: A Petri net approach to represent them all”. Involved MUSCA member: Stefan Haar.

- 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.

10 Dissemination

10.1 Promoting scientific activities

10.1.1 Scientific events: organisation

Member of the organizing and selection committees

Chloé Audebert, MATIDY workshop on mathematical models of lipid transport and storage, November 5-7, Paris

Frédérique Clément, AI & imaging for Cell and developmental biology : Insights, limits and perspectives, September 26, Paris

Pascale Crépieux, ICGR-V - 5th International Conference on Gonadotropins and Receptors (chairman of Symposium 9 – How to stimulate spermatogenesis in male infertility), March 12-15, Tours

Pascale Crépieux, 24th International Conference on Reproductive Sciences and Molecular Medicine (ICRSMM, chairman of session Ovarian Mechanisms and PCOS), November 15-17, New Delhi (India)

Stefan Haar, Foundations of Software Technology and Theoretical Computer Science, December 16-18, IIT Gandhinagar, India;

Stefan Haar, International Workshop on Petri Nets and Software Engineering, June 24-25, Geneva, Switzerland

Eric Reiter, ICGR-V - 5th International Conference on Gonadotropins and Receptors (organizer, together with Livio Casarini and chairman of Symposium 6 – Antibodies to control reproduction), March 12-15, Tours

Eric Reiter, Scientific seminar “Florian Guillou, quatre décennies de recherches sur la fonction testiculaire”, October 10, Nouzilly

10.1.2 Journal

Member of the editorial boards

Stefan Haar, associate editor Discrete Event Dyn. Syst.

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

Romain Yvinec, associate editor J. Math. Biol.

Reviewer - reviewing activities

Chloé Audebert, Math. Biosci.

Pascale Crépieux, FASEB J., Mol. Cell. Endocrinol., Pharmacol. Ther.

Eric Reiter, Endocrinology, Proc. Natl. Acad. Sci. USA, eLife, Nature Comm.

Romain Yvinec, Open Biol., Stochastic Process. Appl., Nature Com., ESAIM Proc.

10.1.3 Invited and contributed talks

Chloé Audebert

Adipose tissue size distribution modeling, Rencontres normandes sur les aspects théoriques et numériques des EDP, November 8, Rouen

Frédérique Clément

Modéliser les effets reprotoxiques des perturbateurs endocriniens, Journées FC3R, November 21-22, Maisons-Alfort

Pascale Crépieux

Intra-cellular VHH targeting the FSHR and LHR, ICGR-V, March 12-15, Tours

Gonadotropin receptors and their modulation by intracellular VHH, ICRSMM, November 15-17, New Delhi (India)

La traduction à travers les âges, de l'époque Mag à nos jours, Scientific seminar "Florian Guillou, quatre décennies de recherches sur la fonction testiculaire", October 10, Nouzilly

Léo Darrigade, Modeling intracellular compartmentalized GPCRs signaling

Poster communication: Journées Math-Bio-Santé, June 24-28, Nantes ; European Conference on Mathematical and Theoretical Biology, July 22-26, Toledo

Oral communication: Mathbio seminar, March 22, Duke University (USA) ; Biology and Medicine Through Mathematics Conference, May 15-17, Richmond (USA)

Marlène Davilma, 3D imaging-based analysis of the germline in teleost

Poster communication: AI & imaging for Cell and developmental biology : Insights, limits and perspectives, September 26, Paris ; From Cell to Embryo, October 16-19, Paris

Louis Fostier, Fish oogenesis modeling: Oocyte population dynamics

Poster communication: Journées Math-Bio-Santé, June 24-28, Nantes ; European Conference on Mathematical and Theoretical Biology, July 22-26, Toledo (best poster prize award)

Oral communication: Semaine des doctorants Institut Denis Poisson, June 17-19, Courcimont ; Mathbio seminar, March 22, Duke University (USA) ; Biology and Medicine Through Mathematics Conference, May 15-17, Richmond (USA) ; Congrès des Jeunes Chercheur.e.s en Mathématiques Appliquées, October 28-30, Lyon ; Séminaire du métaprogramme DIGIT-BIO, December 12-13, Lyon

Stefan Haar

Bridging the discrete-continuous gap: Continuous Petri nets, Journées annuelles 2024 du GT Bioss, May 27, Paris

Rosario Medina-Rodriguez

Poster communication: Detection and classification of ovarian follicles in histology images, AI & imaging for Cell and developmental biology : Insights, limits and perspectives, September 26, Paris

Eric Reiter

Antibody fragments for controlling reproduction without exogenous hormone", ICGR-V - 5th International Conference on Gonadotropins and Receptors (plenary lecture), ICGR-V, March 12-15, Tours

Antibody fragments to control reproduction and treat associated dysfunctions, Institute of Reproductive and Development Biology, Imperial College London, October 31, London (UK),

Connecting academic research and industrial application, ICRSMM, November 15-17, New Delhi (India)

Antibody fragments for controlling reproduction without exogenous hormone, ICRSMM, November 15-17, New Delhi (India)

Lorenzo Sala

First steps towards a gut digital twin: mechanistic modeling of host–microbiota interactions to explore symbiotic resilience, CMSB 2024 Computational Methods in Systems Biology, September 16-18, Pisa (Italy)

Understanding gut microbiota dynamics: Enhancing generalized smoothing algorithm efficiency with data-driven neural network, Journée thématique SPE NUM sur les approches hybrides IA-systèmes dynamiques, December 3, Montpellier

Global sensitivity analysis of a hemodynamic digital twin in post-hepatectomy liver failure, SIAM Conference on Uncertainty Quantification 2024, February 27 - March 1, Trieste (Italy)

Romain Yvinec

Oral communication: Time scale separation in life-long ovarian follicles population dynamics model, Biology and Medicine Through Mathematics Conference, May 15-17, Richmond (USA)

Poster communication: Kinetic biased and compartmentalized signaling : a system biology approach, Mechanistic Understanding of G-Protein and Kinase Signaling Leading to Development of Novel Therapeutics, Gordon Research conference, June 10-14, Waterville Valley (USA)

Chloé Weckel

Spatiotemporal modeling of signaling pathways : Impact of endosomal compartmentalization and application to gonadotropin receptors, Forum des Jeunes Mathématiciennes et Mathématiciens, November 20-22, Montpellier

10.1.4 Leadership within the scientific community

Frédérique Clément

- member of the direction board 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
- member of the steering committee of OI NFC (New Frontiers in Cancer) Paris-Saclay

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) of 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

Romain Yvinec

- member of the steering committee of RT REPRO
- member of the Directory committee of iGPCRnet

10.1.5 Scientific expertise

Frédérique Clément, reviewer for the Marsden Fund (New Zealand) and the Émergence recherche call from Idex Université Paris Cité

Pascale Crépieux, reviewer for BPI-France, ESF France-China, Dutch Cancer Society (KWF)

Béatrice Laroche, member of the phase 1 selection board for the recruitment of an INRAE CRCN on job profile “ Epidémiologie, génétique et modélisation pour la santé”

Anne Poupon, member of the selection board for the recruitment of a CNRS CPJ on job profile “AI and multi-scale data derived from genomes” (CPJ2024-16 Omik-IA)

10.1.6 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, which has gone through HCERES evaluation in 2024

Eric Reiter is deputy director of UMR PRC

Romain Yvinec is co-head of the Bios team in UMR PRC, co-head of the regional federative structure CaSciModOT (Calcul Scientifique et Modélisation Orléans Tours)

10.2 Teaching - Supervision - Juries

10.2.1 Teaching

Pascale Crépieux, M2 Biology of Reproduction, Université de Tours, M2 Infectiology, Immunity, Vaccinology and Biopharmaceuticals, and M2 Physiopathology (7h), Université de Tours

Alice Fohr, L1 Biologie, Chimie, Sciences de la Terre (Mathematics, 32h), Université Paris-Saclay

Stefan Haar, M2 Bioinformatics (Analysis of dynamics in biological networks, 24h), and M1 Master Parisien de Recherche en Informatique (Introduction to research 24h), Université Paris-Saclay

Louis Fostier, L1 Computer Science (Calculations and mathematical reasoning, 34h), Université de Tours

Eric Reiter, M2 Infectiology, Immunity, Vaccinology and Biopharmaceuticals (6h), and M2 Physiopathology (2h), Université de Tours

10.2.2 Supervision

PhD: 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”, defended on June 3, supervisors: Frédéric Jean-Alphonse and 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: Alice Fohr, “Modeling of X chromosome inactivation”, started September 2024, supevisors: Frédérique Clément and Hélène Leman

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: Souhila Founas, “Development of a territorial approach for the representation of multirisk scenarios using Petri nets”, started October 2023, supervisors: Corinne Curt and Stefan Haar

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 in progress: Pamela Romero Jofré, “Computational modeling of biased signaling in G protein-coupled receptors”, started October 2024, supervisors: Misbah Razzaq and Romain Yvinec

PhD in progress: Chloé Weckel, “Spatiotemporal modeling of signaling pathways: impact of endosomal compartmentalization and application to gonadotropin receptors”, started October 2024, supervisors: Stefan Haar and Romain Yvinec, associate supervisor: Frédéric Jean-Alphonse

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

PhD follow-up committee of Virginie Loison (ED STIC) member Chloé Audebert

PhD follow-up committee of Federica Padovano (ED 386), member Chloe Audebert

Master internship: Julien Joachim, M1 MPRI (Master Parisien de Recherche en Informatique), Université Paris-Saclay, supervisor: Stefan Haar

Master internship: Yanis Jouanaud M1 Mathématiques appliquées, Université Paris-Saclay, supervisors: Béatrice Laroche and Lorenzo Sala

Master internship: Gratien-Alexandre De Souza, M1 Biologie de la reproduction, Université de Tours, supervisor: Frédéric Jean-Alphonse

Master internship: Lucille Berthet, M2 Biologie de la reproduction, Université de Tours, supervisor: Pascale Crépieux

Master internship: Ambre Dechamps, M2 Computational and Mathematical Biology, Aix-Marseille Université, supervisors: Béatrice Laroche and Lorenzo Sala

Master internship: Kélian Hezez, M2 Bioinformatique et Modélisation, Sorbonne Université, supervisors: Chloé Audebert and Lorenzo Sala

Master internship (ERASMUS): Anastasia Sist, M2 Endocrinology, UNIMORE university, supervisor: Eric Reiter

Master internship (ERASMUS): Ginevra Pelagatti, M2 Endocrinology, UNIMORE university, supervisor: Frédéric Jean-Alphonse

Licence internship: Nabil Ould-Hamou, L3 Informatique, Université de Tours, supervisors: Nicolas Azzopardi, Léo Darrigade and Olivier Gallant

Postdoc: Léo Darrigade, “PDMP-based modeling of the GPCR compartmentalized signaling”, started June 2022, supervisor: Romain Yvinec

Postdoc: Camille Gauthier, “Manipulation of the activity and physiology of LH receptor through a small fragment of antibody”, January-September, supervisor: Eric Reiter

Postdoc: Pawan Kumar, “Multiscale modeling of single cell-based dynamics of ovarian development”, started October 2024, supervisors: Chloé Audebert, Frédérique Clément and Fabien Crauste

Postdoc: Rosario Medina-Rodríguez, “Deep learning models for automatic ovarian follicle detection from 2D and 3D imaging data”, started June 2024, supervisor: Frédérique Clément

Postdoc: Pauline Raynaud, “Intracellular VHHs targeting gonadotropin receptors”, January-September, supervisor: Pascale Crépieux

10.2.3 Juries

Chloé Audebert

- PhD Jury of Valentin Pannetier, Université de Bordeaux, December 6

Frédérique Clément

- PhD Jury of Rachel Topno (referee), Université de Montpellier, December 12

Pascale Crépieux

- PhD Jury of Alessandro Rabito (referee), Université de Montpellier, June 27
- PhD Jury of Mariama Diawara (external referee), Université de Moncton (Canada), September 20
- PhD Jury of Fabian Jeanne, Université de Caen, October 12
- PhD Jury of Anaïs Djébara (referee), Université de Montpellier, December 12
- HdR Jury of Hervé Nozach, Université Paris-Saclay, October 7

Stefan Haar

- PhD Jury of Nick Würdemann, Universität Oldenburg (Germany) May 31
- PhD Jury of Danilo Dursoniah (president), Université de Lille, October 23
- PhD Jury of Hamza Chakraa (president), Université du Havre, December 5

Frédéric Jean-Alphonse

- PhD Jury of Ikrame Dadi, Université de Montpellier, November 27

Béatrice Laroche

- PhD Jury of Mathilde Massard, Université de Besançon-Franche Comté, November 26
- HDR Jury of Simon Labarthe, Université de Bordeaux, July 10

Eric Reiter

- HDR Jury of Frédéric Jean-Alphonse, Université de Tours, December 17

Romain Yvinec

- PhD Jury of Laurent Freoa (referee), Université Paris Cité, December 9
- PhD Jury of Sarah Dandou (referee), Université de Montpellier, November 19

10.3 Popularization

10.3.1 Participation in Live events

Chloé Audebert, Participation to "Fête de la science", October 2024 (presentation in a school, Paris).

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 (cit. on p. 6).

[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 (cit. on pp. 7, 8).

[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 (cit. on p. 6).

[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 (cit. on p. 6).

[5] T. Chatain, S. Haar, L. Jezequel, L. Paulevé and S. Schwoon. 'Characterization of Reachable Attractors Using Petri Net Unfoldings'. In: CMSB 2014. Vol. 8859. LNCS/LNBI. Manchester, United Kingdom: Springer International Publishing, 17th Nov. 2014, p. 14. DOI: 10.1007/978-3-319-12982-2_10. URL: https://hal.science/hal-01060450 (cit. on p. 5).

[6] T. Chatain, S. Haar, J. Kolčák, L. Paulevé and A. Thakkar. 'Concurrency in Boolean networks'. In: *Natural Computing* 19.1 (2020), pp. 91–109. DOI: 10.1007/s11047-019-09748-4. URL: https://inria.hal.science/hal-01893106 (cit. on p. 4).

[7] T. Chatain, S. Haar and L. Paulevé. 'Boolean Networks: Beyond Generalized Asynchronicity'. In: AUTOMATA 2018 - 24th IFIP WG 1.5 International Workshop on Cellular Automata and Discrete Complex Systems. Vol. 10875. Lecture Notes in Computer Science. Ghent, Belgium: Springer, 20th June 2018, pp. 29–42. DOI: 10.1007/978-3-319-92675-9_3. URL: https://hal.science/hal-01768359 (cit. on p. 5).

[8] 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 (cit. on p. 7).

[9] F. Clément and D. Monniaux. 'Multiscale modelling of ovarian follicular selection.' In: *Progress in Biophysics and Molecular Biology* 113.3 (Dec. 2013), pp. 398–408. DOI: 10.1016/j.pbiomolbio.2012.12.005. URL: https://hal.inria.fr/hal-00776209 (cit. on p. 6).

[10] 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 (cit. on p. 6).

[11] F. Clément, F. Robin and R. Yvinec. 'Stochastic nonlinear model for somatic cell population dynamics during ovarian follicle activation'. In: *Journal of Mathematical Biology* 82.3 (2021), pp. 1–52. DOI: 10.1007/s00285-021-01561-x. URL: https://hal.inria.fr/hal-02057983 (cit. on p. 5).

[12] 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 (cit. on p. 6).

[13] 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 (cit. on p. 6).

[14] P. A. Fletcher, F. Clément, A. Vidal, J. Tabak and R. Bertram. 'Interpreting frequency responses to dose-conserved pulsatile input signals in simple cell signaling motifs.' In: *PLoS ONE* 9.4 (2014), e95613. DOI: 10.1371/journal.pone.0095613. URL: https://hal.inria.fr/hal-00981377 (cit. on p. 4).

[15] S. Haar, L. Paulevé and S. Schwoon. 'Drawing the Line: Basin Boundaries in Safe Petri Nets'. In: CMSB 2020 - 18th International Conference on Computational Methods in Systems Biology. Konstanz / Online, Germany, 2020. DOI: 10.1007/978-3-030-60327-4_17. URL: https://hal.science/hal-02898841 (cit. on p. 5).

[16] D. Heitzler, G. Durand, N. Gallay, A. Rizk, S. Ahn, J. Kim, J. D. Violin, L. Dupuy, C. Gauthier, V. Piketty, P. Crépieux, A. Poupon, F. Clément, F. Fages, R. J. Lefkowitz and E. Reiter. 'Competing G protein-coupled receptor kinases balance G protein and β-arrestin signaling.' In: *Molecular Systems Biology* 8 (June 2012), pp. 1–17. DOI: 10.1038/msb.2012.22. URL: https://hal.inria.fr/hal-00776169 (cit. on pp. 5, 8).

[17] T. Hélie and B. Laroche. 'Computable convergence bounds of series expansions for infinite dimensional linear-analytic systems and application'. In: *Automatica* 50.9 (2014), pp. 2334–2340. DOI: 10.1016/j.automatica.2014.07.011. URL: https://hal.archives-ouvertes.fr/hal-01123435 (cit. on p. 4).

[18] T. Hélie and B. Laroche. 'Computation of Convergence Bounds for Volterra Series of Linear-Analytic Single-Input Systems'. In: *IEEE Transactions on Automatic Control* 56.9 (Sept. 2011), pp. 2062–2072. DOI: 10.1109/TAC.2010.2091435. URL: https://hal-supelec.archives-ouvertes.fr/hal-00655910 (cit. on p. 4).

[19] E. Hingant and R. Yvinec. 'The Becker-Doring Process: Pathwise Convergence and Phase Transition Phenomena'. In: *Journal of Statistical Physics* 177.5 (2018), pp. 506–527. DOI: 10.1007/s10955-019-02377-2. URL: https://hal.archives-ouvertes.fr/hal-01852561 (cit. on p. 6).

[20] S. Labarthe, B. Polizzi, T. Phan, T. Goudon, M. Ribot and B. Laroche. 'A mathematical model to investigate the key drivers of the biogeography of the colon microbiota.' In: *Journal of Theoretical Biology* 462.7 (2019), pp. 552–581. DOI: 10.1016/j.jtbi.2018.12.009. URL: https://hal.archives-ouvertes.fr/hal-01761191 (cit. on p. 8).

[21] D. Monniaux, P. Michel, M. Postel and F. Clément. 'Multiscale modeling of ovarian follicular development: From follicular morphogenesis to selection for ovulation'. In: *Biology of the Cell* 108.6 (June 2016), pp. 1–12. DOI: 10.1111/boc.201500087. URL: https://hal.inria.fr/hal-01294630 (cit. on p. 8).

[22] L. Paulevé, J. Kolčák, T. Chatain and S. Haar. 'Reconciling Qualitative, Abstract, and Scalable Modeling of Biological Networks'. In: *Nature Communications* 11 (2020), p. 4256. DOI: 10.1038/s41467-020-18112-5. URL: https://hal.science/hal-02518582 (cit. on p. 5).

[23] M. Postel, A. Karam, G. Pézeron, S. Schneider-Maunoury and F. Clément. 'A multiscale mathematical model of cell dynamics during neurogenesis in the mouse cerebral cortex'. In: *BMC Bioinformatics* 20.1 (Dec. 2019). DOI: 10.1186/s12859-019-3018-8. URL: https://hal.inria.fr/hal-01783141 (cit. on p. 10).

[24] P. Shang. 'Cauchy problem for multiscale conservation laws: Application to structured cell populations'. In: *Journal of Mathematical Analysis and Applications* 401.2 (2013), pp. 896–920. DOI: 10.1016/j.jmaa.2013.01.001. URL: https://hal.inria.fr/hal-00841184 (cit. on p. 6).

[25] S. Widder, R. J. Allen, T. Pfeiffer, T. P. Curtis, C. Wiuf, W. T. Sloan, O. X. Cordero, S. P. Brown, B. Momeni, W. Shou, H. Kettle, H. J. Flint, A. F. Haas, B. Laroche, J.-U. Kreft, P. B. Rainey, S. Freilich, S. Schuster, K. Milferstedt, J. R. van der Meer, T. Groszkopf, J. Huisman, A. Free, C. Picioreanu, C. Quince, I. Klapper, S. Labarthe, B. F. Smets, H. Wang, J. Hamelin, J. Harmand, J.-P. Steyer, E. Trably, I. N. Institute Fellows and O. S. Soyer. 'Challenges in microbial ecology: building predictive understanding of community function and dynamics.' In: *ISME Journal* 10 (2016). Marco Cosentino Lagomarsino (LCQB) is a member of Isaac Newton Institute Fellows consortium., pp. 1–12. DOI: 10.1038/ismej.2016.45. URL: https://hal.archives-ouvertes.fr/hal-01512087 (cit. on p. 8).

[26] R. Yvinec, P. Crépieux, E. Reiter, A. Poupon and F. Clément. 'Advances in computational modeling approaches of pituitary gonadotropin signaling'. In: *Expert Opinion on Drug Discovery* 13.9 (2018), pp. 799–813. DOI: 10.1080/17460441.2018.1501025. URL: https://hal.archives-ouvertes.fr/hal-01913612 (cit. on p. 4).

11.2 Publications of the year

International journals

[27] D. D. Acar, W. Witkowski, M. Wejda, R. Wei, T. Desmet, B. Schepens, S. de Cae, K. Sedeyn, H. Eeckhaut, D. Fijalkowska, K. Roose, S. Vanmarcke, A. Poupon, D. Jochmans, X. Zhang, R. Abdelnabi, C. S. Foo, B. Weynand, D. Reiter, N. Callewaert, H. Remaut, J. Neyts, X. Saelens, S. Gerlo and L. Vandekerckhove. 'Integrating artificial intelligence-based epitope prediction in a SARS-CoV-2 antibody discovery pipeline: caution is warranted'. In: *EBioMedicine* 100 (Feb. 2024), p. 104960. DOI: 10.1016/j.ebiom.2023.104960. URL: https://hal.science/hal-04449723.

[28] C. Alamichel, J. Calvo, E. Hingant, S. Latrach, N. Quiblier and R. Yvinec. 'Modeling compartmentalization within intracellular signaling pathway'. In: *ESAIM: Proceedings and Surveys* 77 (18th Nov. 2024), pp. 100–122. DOI: 10.1051/proc/202477100. URL: https://hal.science/hal-04098543 (cit. on p. 10).

[29] G. Ballif, F. Clément and R. Yvinec. 'Nonlinear compartmental modeling to monitor ovarian follicle population dynamics on the whole lifespan'. In: *Journal of Mathematical Biology* 89.9 (6th June 2024), p. 43. DOI: 10.1007/s00285-024-02108-6. URL: https://hal.science/hal-03739205 (cit. on pp. 9, 10).

[30] J. Calvo, E. Hingant and R. Yvinec. 'Long-time asymptotic of the Lifshitz-Slyozov equation with nucleation'. In: *Kinetic and Related Models* 17.5 (2024), pp. 755–773. DOI: 10.3934/krm.2023041. URL: https://hal.science/hal-04098262 (cit. on p. 13).

[31] F. Clément and J. Olayé. 'A stochastic model for neural progenitor dynamics in the mouse cerebral cortex'. In: *Mathematical Biosciences* 372 (June 2024), p. 109185. DOI: 10.1016/j.mbs.2024.109185. URL: https://inria.hal.science/hal-04351283 (cit. on p. 10).

[32] C. Gauthier, P. Raynaud, F. Jean-Alphonse, A. Vallet, O. Vaugrente, V. Jugnarain, T. Boulo, C. Gauthier, E. Reiter, G. Bruneau and P. Crépieux. 'An intracellular VHH targeting the Luteinizing Hormone receptor modulates G protein-dependent signaling and steroidogenesis'. In: *Molecular and Cellular Endocrinology* 589 (Aug. 2024), p. 112235. DOI: 10.1016/j.mce.2024.112235. URL: https://hal.inrae.fr/hal-04564514 (cit. on p. 17).

[33] A.-S. Giacobbi, L. Meyer, M. Ribot, R. Yvinec, H. Soula and C. Audebert. 'Mathematical modeling of adipocyte size distributions: identifiability and parameter estimation from rat data'. In: *Journal of Theoretical Biology* 581 (2024), p. 111747. DOI: 10.1016/j.jtbi.2024.111747. URL: https://hal.science/hal-04141173 (cit. on p. 12).

[34] C. Gora, A. Dudas, L. Court, A. Annamneedi, G. Lefort, T. Nakahara, N. Azzopardi, A. Acquistapace, A.-L. Laine, A.-C. Trouillet, L. Drobecq, E. Pecnard, B. Piégu, P. Crépieux, P. Chamero and L. Pellissier. 'Effect of the social environment on olfaction and social skills in wild-type and a mouse model of autism'. In: *Translational Psychiatry* 14.1 (7th Nov. 2024), p. 464. DOI: 10.1038/s41398-024-03174-6. URL: https://hal.inrae.fr/hal-04785377.

[35] M. Haghebaert, B. Laroche, L. Sala, S. Mondot and J. Doré. 'A mechanistic modelling approach of the host–microbiota interactions to investigate beneficial symbiotic resilience in the human gut'. In: *Journal of the Royal Society Interface* 21.215 (20th June 2024). DOI: 10.1098/rsif.2023.0756. URL: https://hal.inrae.fr/hal-04623171 (cit. on p. 13).

[36] M. H. Hassan, E. Reiter and M. Razzaq. 'Automatic ovarian follicle detection using object detection models'. In: *Scientific Reports* 14.1 (30th Dec. 2024), p. 31856. DOI: 10.1038/s41598-024-82904-8. URL: https://hal.inrae.fr/hal-04884151.

[37] L. Lamendour, M. Gilotin, N. Deluce-Kakwata Nkor, Z. Lakhrif, D. Meley, A. Poupon, T. Laboute, A. Di Tommaso, J.-J. Pin, D. Mulleman, G. Le Mélédo, N. Aubrey, H. Watier and F. Velge. 'Bispecific antibodies tethering innate receptors induce human tolerant-dendritic cells and regulatory T cells'. In: *Frontiers in Immunology* 15 (26th Mar. 2024), p. 1369117. DOI: 10.3389/fimmu.2024.1369117. URL: https://hal.inrae.fr/hal-04601179.

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[39] A. Musnier, C. Dumet, S. Mitra, A. Verdier, R. Keskes, A. Chassine, Y. Jullian, M. Cortes, Y. Corde, Z. Omahdi, V. Puard, T. Bourquard and A. Poupon. 'Applying artificial intelligence to accelerate and de-risk antibody discovery'. In: *Frontiers in Drug Discovery* 4 (5th Mar. 2024), p. 1339697. DOI: 10.3389/fddsv.2024.1339697. URL: https://hal.science/hal-04672537.

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