RESEARCH CENTRE

Saclay - Île-de-France

IN PARTNERSHIP WITH:

CNRS, INRAE

2020

ACTIVITY REPORT

Project-Team

MUSCA

MUltiSCAle population dynamics for physiological systems

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

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life Sciences

Contents

Project-Team MUSCA 1

1 Team members, visitors, external collaborators 2

2 Overall objectives 2

3 Research program 2
3.1 General scientific positioning . . . 2
3.2 Design, analysis and reduction of network-based dynamic models . . . 3
3.3 Design, analysis and simulation of stochastic and deterministic models for structured populations . . . 4
3.4 Coupling biochemical networks with cell and population dynamics . . . 6

4 Application domains 6

5 New software and platforms 7
5.1 New software . . . 7
5.1.1 pyDynPeak . . . 7

6 New results 7
6.1 Stochastic modeling . . . 7
6.1.1 Stochastic nonlinear model for somatic cell population dynamics during ovarian follicle activation . . . 7
6.1.2 Quasi-stationary distribution and metastability for the stochastic Becker-Döring model . . . 8
6.2 Deterministic modeling . . . 8
6.2.1 The Initial-boundary value problem for the Lifshitz-Slyozov equation with non-smooth rates at the boundary . . . 8
6.2.2 Exploring the bacterial impact on cholesterol cycle: A numerical study . . . 8
6.3 Multiscale modeling . . . 9
6.3.1 Multiscale population dynamics in reproductive biology: singular perturbation reduction in deterministic and stochastic models . . . 9
6.3.2 Averaging of a stochastic, multiple timescale model : Application to ovarian follicle populations . . . 9
6.3.3 A multi-scale epidemic model of salmonella infection with heterogeneous shedding 10
6.3.4 Modeling of the host-microbiota dialog near the large intestine epithelial wall . . . 10
6.4 Exploration of signaling networks . . . 10
6.4.1 A novel mutation in the FSH Receptor (I423T) affecting receptor activation and leading to primary ovarian failure . . . 10
6.4.2 Direct impact of gonadotropins on glucose uptake and storage in preovulatory granulosa cells: Implications in the pathogenesis of polycystic ovary syndrome . . . 11
6.4.3 Pharmacological programming of endosomal signaling activated by small molecule ligands of the follicle-stimulating hormone receptor . . . 11
6.4.4 Membrane estrogen receptor (GPER) and follicle-stimulating hormone receptor (FSHR) heteromeric complexes promote human ovarian follicle survival . . . 12
6.4.5 Allosteric interactions in the parathyroid hormone GPCR-arrestin complex formation 12
6.4.6 Gq/11-dependent regulation of endosomal cAMP generation by parathyroid hormone class B GPCR . . . 12
6.4.7 PTH hypersecretion triggered by a GABA B1 and Ca2+-sensing receptor heterocomplex in hyperparathyroidism . . . 13
6.5 Computational biology . . . 13
6.5.1 Exploring epitope and functional diversity of anti-SARS-CoV2 antibodies using AI-based methods . . . 13

6.5.2 Characterization of new monoclonal PF4-specific antibodies as useful tools for studies on typical and autoimmune heparin-induced thrombocytopenia . . . 13
6.5.3 4C3 human monoclonal antibody: A proof of concept for non-pathogenic proteinase 3 anti-neutrophil cytoplasmic antibodies in granulomatosis with polyangiitis . . . 14
6.6 Bibliographic reviews . . . 14
6.6.1 Mathematical modeling approaches of cellular endocrinology within the hypothalamo-pituitary-gonadal axis . . . 14
6.6.2 The follicle-stimulating hormone signaling network in gonadal cells . . . 14
6.6.3 Mathematical modeling of ovarian follicle development : A population dynamics viewpoint . . . 15
6.6.4 Follicle-stimulating hormone (FSH) action on spermatogenesis: A focus on physiological and therapeutic roles . . . 15
6.6.5 FSH for the treatment of male infertility . . . 15

7 Partnerships and cooperations **16**
7.1 International initiatives . . . 16
7.1.1 Participation in other international programs . . . 16
7.2 International research visitors . . . 16
7.2.1 Visits of international scientists . . . 16
7.3 European initiatives . . . 16
7.3.1 FP7 & H2020 Projects . . . 16
7.4 National initiatives . . . 17
7.5 Regional initiatives . . . 17

8 Dissemination **17**
8.1 Promoting scientific activities . . . 17
8.1.1 Scientific events: organisation . . . 17
8.1.2 Scientific events: selection . . . 18
8.1.3 Journal . . . 18
8.1.4 Invited talks . . . 18
8.1.5 Leadership within the scientific community . . . 19
8.1.6 Scientific expertise . . . 19
8.1.7 Research administration . . . 20
8.2 Teaching - Supervision - Juries . . . 20
8.2.1 Teaching . . . 20
8.2.2 Supervision . . . 20
8.2.3 Juries . . . 21

9 Scientific production **21**
9.1 Major publications . . . 21
9.2 Publications of the year . . . 23
9.3 Cited publications . . . 25

Project-Team MUSCA

Creation of the Project-Team: 2020 July 01

Keywords

Computer sciences and digital sciences

A3.4. – Machine learning and statistics

A6.1.1. – Continuous Modeling (PDE, ODE)

A6.1.2. – Stochastic Modeling

A6.1.4. – Multiscale modeling

A6.2.1. – Numerical analysis of PDE and ODE

A6.2.3. – Probabilistic methods

A6.3.1. – Inverse problems

A6.3.4. – Model reduction

Other research topics and application domains

B1.1.2. – Molecular and cellular biology

B1.1.3. – Developmental biology

B1.1.7. – Bioinformatics

B1.1.8. – Mathematical biology

B1.1.10. – Systems and synthetic biology

B2.2. – Physiology and diseases

B2.3. – Epidemiology

B3.6. – Ecology

1 Team members, visitors, external collaborators

Research Scientists

- Frédérique Clément [Team leader, Inria, Senior Researcher, from Jul 2020, HDR]
- Pascale Crépieux [CNRS, Senior Researcher, from Jul 2020, HDR]
- Frédéric Jean-Alphonse [CNRS, Researcher, from Nov 2020]
- Béatrice Laroche [INRAE, Senior Researcher, from Jul 2020, HDR]
- Anne Poupon [CNRS, Senior Researcher, from Jul 2020, HDR]
- Eric Reiter [INRAE, Senior Researcher, from Jul 2020, HDR]
- Romain Yvinec [INRAE, Researcher, from Jul 2020, HDR]

Post-Doctoral Fellow

- Frédéric Jean-Alphonse [Le Studium Orléans, from Jul 2020 until Oct 2020]

PhD Students

- Guillaume Ballif [Inria, from Jul 2020]
- Léo Darrigade [INRAE, from Jul 2020]
- Marie Haghebaert [INRAE, from Nov 2020]
- Léo Meyer [Université d'Orléans, from Oct 2020]

Administrative Assistant

- Bahar Carabetta [Inria, from Oct 2020]

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) [61], 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 [83, 56]. 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 [61, 55], 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 [18] 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 [77],[9] or in the framework of "pulse-modulated systems" [59].

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 [66]. 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 [67, 60] and stochastic context [50, 65, 76].

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 [12, 11] 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 [80], combined with the reduction of weakly nonlinear subsystems.

Statistical Inference, Data-fitting Once again, a key challenge in parameter estimation is due to the high dimension of the state space and/or parameter space. We will develop several strategies to face this challenge. Efficient Maximum likelihood or pseudo-likelihood methods will be developed and put in practice [10] [29], using either existing state-of-the art deterministic derivative-based optimization [81] or global stochastic optimization [57]. 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 [69]. 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 [63] based on similarity criteria adapted to the problem under consideration, and an original inference method inspired by the Generalized Smoothing (GS) method proposed in [79], 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 [16] and long-time behavior [6], and the design of appropriate numerical schemes [1, 3] often rely on more or less generic techniques [75, 71] that we need to adapt in a case-by-case, model-dependent way: general relative entropy [72, 54], measure solution framework [64, 51, 58], martingale techniques [52], finite-volume numerical schemes [68], 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 [16]), or the formulation of particularly tricky boundary conditions [7]. 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 [74], dimensional reduction [5], timescale reduction [19], spatial homogenization [48][8], discrete to continuous reduction [7] and stochastic to deterministic limit theorems [13].

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 [62, 53], and theoretical studies of the inverse problems associated with the models [4] 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) [78, 49, 82, 70]. 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 [15].

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 [10]. 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 [14].

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 [17].

In reproductive physiology, there is currently a spectacular revival of experimental investigations (see e.g. [73, 84]), 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 New software and platforms

5.1 New software

5.1.1 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 and analysis of their rhythm. Visualisation, diagnostic and interactive correction of the detections.

Authors: Frédérique Clément, Hande Ozaygen, Christian Poli

Contacts: Frédérique Clément, Christian Poli, Hande Ozaygen

6 New results

6.1 Stochastic modeling

6.1.1 Stochastic nonlinear model for somatic cell population dynamics during ovarian follicle activation

Participants Frédérique Clément, Romain Yvinec, in collaboration with Frédérique Robin.

In mammals, female germ cells are sheltered within somatic structures called ovarian follicles, which remain in a quiescent state until they get activated, all along reproductive life. We have investigated the sequence of somatic cell events occurring just after follicle activation, starting by the awakening of precursor somatic cells, and their transformation into proliferative cells. We have introduced a nonlinear stochastic model accounting for the joint dynamics of the two cell types, and allowing us to investigate the potential impact of a feedback from proliferative cells onto precursor cells [29]. To tackle the key issue of whether cell proliferation is concomitant or posterior to cell awakening, we have assessed both the time needed for all precursor cells to awake, and the corresponding increase in the total cell number with respect to the initial cell number. Using the probabilistic theory of first passage times, we have designed a numerical scheme based on a rigorous Finite State Projection and coupling techniques to compute the mean extinction time and the cell number at extinction time. We find that the feedback term clearly lowers the number of proliferative cells at the extinction time. We have calibrated the model parameters using an exact likelihood approach. We have carried out a comprehensive comparison between the initial model and a series of submodels, which helps to select the critical cell events taking place during activation, and suggests that awakening is prominent over proliferation.

6.1.2 Quasi-stationary distribution and metastability for the stochastic Becker-Döring model

Participants Romain Yvinec, in collaboration with Erwan Hingant.

We have studied a stochastic version of the classical Becker-Döring model, a well-known kinetic model for cluster formation that predicts the existence of a long-lived metastable state before a thermodynamically unfavorable nucleation occurs, leading to a phase transition phenomena. This continuous-time Markov chain model has received little attention, compared to its deterministic differential equations counterpart. We have shown that the stochastic formulation leads to a precise and quantitative description of stochastic nucleation events thanks to an exponentially ergodic quasi-stationary distribution for the process conditionally on nucleation has not yet occurred [47].

6.2 Deterministic modeling

Participants Romain Yvinec, in collaboration with Erwan Hingant, and Juan Calvo.

6.2.1 The Initial-boundary value problem for the Lifshitz-Slyozov equation with non-smooth rates at the boundary

We have proven existence and uniqueness of solutions to the initial-boundary value problem for the Lifshitz–Slyozov equation (a nonlinear transport equation on the half-line), focusing on the case of kinetic rates with unbounded derivative at the origin [21]. Our theory covers in particular those cases with rates behaving as power laws at the origin, for which an inflow behavior is expected and a boundary condition describing nucleation phenomena needs to be imposed. The method introduced to prove existence is based on a formulation in terms of characteristics, with a careful analysis on the behavior near the singular boundary. As a byproduct we have provided a general theory for linear continuity equations on a half-line with transport fields that degenerate at the boundary. We also address both the maximality and the uniqueness of inflow solutions to the Lifshitz–Slyozov model, exploiting monotonicity properties of the associated transport equation.

6.2.2 Exploring the bacterial impact on cholesterol cycle: A numerical study

Participants Béatrice Laroche, and collaborators.

High blood cholesterol levels are often associated with cardiovascular diseases. Therapeutic strategies, targeting different functions involved in cholesterol transport or synthesis, were developed to control cholesterolemia in human. However, the gut microbiota is also involved in cholesterol regulation by direct biotransformation of luminal cholesterol or conversion of bile salts, opening the way to the design of new strategies to manage cholesterol level. We have developed a whole-body human model of cholesterol metabolism including the gut microbiota in order to investigate the relative impact of host and microbial pathways [20]. We first used an animal model to investigate the ingested cholesterol distribution *in vivo*. Then, using *in vitro* bacterial growth experiments and metabolite measurements, we modeled the population dynamics of bacterial strains in the presence of cholesterol or bile salts, together with their bioconversion function. Next, after correct rescaling to mimic the activity of a complex microbiota, we developed a whole body model of cholesterol metabolism integrating host and microbiota mechanisms. This global model was validated with the animal experiments. Finally, the model was numerically explored to give a further insight into the different flux involved in cholesterol turnover. According to this model, bacterial pathways appear as an important driver of cholesterol regulation, reinforcing the need for development of novel 'bacteria-based' strategies for cholesterol management.

6.3 Multiscale modeling

6.3.1 Multiscale population dynamics in reproductive biology: singular perturbation reduction in deterministic and stochastic models

Participants Frédérique Clément, Romain Yvinec, and collaborators.

We have described different modeling approaches for ovarian follicle population dynamics, based on either ordinary (ODE), partial (PDE) or stochastic (SDE) differential equations, and accounting for interactions between follicles [19]. We have put a special focus on representing the population-level feedback exerted by growing ovarian follicles onto the activation of quiescent follicles. We have taken advantage of the timescale difference existing between the growth and activation processes to apply model reduction techniques in the framework of singular perturbations. We have first studied the linear versions of the models to derive theoretical results on the convergence to the limit models. In the nonlinear cases, we have provided detailed numerical evidence of convergence to the limit behavior. We have reproduced the main semi-quantitative features characterizing the ovarian follicle pool, namely a bimodal distribution of the whole population, and a slope break in the decay of the quiescent pool with aging.

6.3.2 Averaging of a stochastic, multiple timescale model : Application to ovarian follicle populations

Participants Guillaume Ballif, Frédérique Clément, Romain Yvinec.

In the framework of Guillaume Ballif's PhD thesis, we have studied a birth, death and migration process, introduced in [19], in which individuals are ovarian follicles. The model encompasses the whole folliculogenesis on a lifespan horizon. It is formulated as a Continuous-time Markov Chains (CTMC), whose states (compartments) represent different stages of follicle development. The first compartment corresponds to the pool of quiescent follicles, while all others correspond to growing follicles. Death can occur in any compartment, migration from any compartment but the last one. Follicle renewal (birth) may only feed the first compartment (depending on the zoological class, no renewal occurs in mammals). The intensities of jumps due to migration, death, or birth are expressed through nonlocal and nonlinear terms, accounting for the (direct or indirect) interactions between follicles. Taking advantage of a timescale difference between the slow dynamics in the first compartment and the faster dynamics in the other ones, together with a difference in abundance of individuals (much more numerous in the first compartment), we can study a stochastic process rescaled with a small parameter ε.

We have studied, both theoretically and numerically, the convergence of this process in the limit $\varepsilon = 0$. The strategy of the proof is based on tightness arguments in an appropriate topology, together with the uniqueness of the candidate limit model, obtained by averaging the fast process [65]. The limit model identified in [19] is a deterministic ordinary differential equation for the (slow) quiescent follicles, coupled with a quasi-stationary probability distribution for the (fast) growing follicles.

6.3.3 A multi-scale epidemic model of salmonella infection with heterogeneous shedding

Participants Béatrice Laroche, and collaborators.

Salmonella strains colonize the digestive tract of farm livestock, such as chickens or pigs, without affecting them, and potentially infect food products, representing a threat for human health ranging from food poisoning to typhoid fever. It has been shown that the ability to excrete the pathogen in the environment and contaminate other animals is variable. This heterogeneity in pathogen carriage and shedding results from interactions between the host's immune response, the pathogen and the commensal intestinal microbiota. We have proposed a novel generic multiscale modeling framework of heterogeneous pathogen transmission in an animal population [31]. At the intra-host level, the model describes the interaction between the commensal microbiota, the pathogen and the inflammatory response. Random fluctuations in the ecological dynamics of the individual microbiota and transmission at between-host scale are added to obtain a drift-diffusion PDE model of the pathogen distribution at the population level. The model has been further extended to represent transmission between several populations. The asymptotic behavior as well as the impact of control strategies including cleaning and antimicrobial administration have been investigated through numerical simulation.

6.3.4 Modeling of the host-microbiota dialog near the large intestine epithelial wall

Participants Léo Darrigade, Béatrice Laroche.

In mammals, the intestinal epithelium is very densely folded, and the smallest fold is called the intestinal crypt. It is also the simplest unit of the host-microbiota crosstalk. The size of a crypt, which is made of approximately 700 cells, and the wealth of knowledge available on its functioning are amenable to build a detailed mathematical model.

In the framework of Léo Darrigade's PhD thesis, we have constructed a first, individual-based model of epithelial cells interacting with chemicals produced by the microbiota and diffusing in the crypt lumen. This model is formulated as a piecewise determinist Markov process (PDMP). It accounts for (i) local interactions due to cell-cell contact (including mechanical interactions) (ii) cell fate events : proliferation, differentiation and extrusion, which are regulated according to the cell anatomical location or local chemical concentrations (iii) diffusion of chemicals and their interaction with cells. We have obtained a second model as the limit of the PDMP under the assumption of large population. We have rigorously proved the convergence towards a deterministic limit, that takes the form of a *self-aggregation* equation with reaction terms, structured according to space and the cellular type. A third model was derived formally, when letting the size of cells go to 0. This model is a *porous media* type equation. We have implemented the three models, and illustrated or shown their convergence numerically. We have analyzed simulations of the individual-based model with parameters drawn from the literature to show that the qualitative behavior of the crypt is well reproduced.

6.4 Exploration of signaling networks

6.4.1 A novel mutation in the FSH Receptor (I423T) affecting receptor activation and leading to primary ovarian failure

Participants Eric Reiter, and collaborators.

Follicle-stimulating hormone (FSH) plays an essential role in gonadal function. Loss-of-function mutations in the follicle-stimulating hormone receptor (FSHR) are an infrequent cause of primary ovarian failure. We have analyzed the molecular physiopathogenesis of a novel missense mutation (I423T) in the FSHR identified in a woman with primary ovarian failure, employing *in vitro* and *in silico* (Molecular dynamics simulations) approaches, and compared the features of this dysfunctional receptor with those shown by the trafficking-defective D408Y FSHR mutant [38]. Our data indicate that conformational differences during the inactive and active states account for the distinct expression levels, differential signaling, and phenotypic expression of the I423T and D408Y mutant FSHRs.

6.4.2 Direct impact of gonadotropins on glucose uptake and storage in preovulatory granulosa cells: Implications in the pathogenesis of polycystic ovary syndrome

Participants Pascale Crépieux, Eric Reiter, and collaborators.

The impact of abnormally high levels of LH on FSH-mediated metabolic responses, as observed in polycystic ovary syndrome (PCOS) patients is not clearly understood. We have examined the effect of FSH and LH (hCG) on glucose uptake and glycogen synthesis in preovulatory granulosa cells, both *in vitro* and *in vivo* [24]. In normal human or immature rat granulosa cells, hCG inhibited the FSH-stimulated glucose uptake as well as glycogen synthesis through inhibition of FSH-stimulated IRS-2 expression. Similarly, high levels of hCG inhibited the FSH-stimulated glucose uptake in HEK293N cells overexpressing both LHCGR and FSHR. The proximity of LHCGR and FSHR was increased only in cells treated with both hCG and FSH but not by each hormone alone, suggesting heterodimerization of the receptors. Our findings indicate a selective attenuation of metabolic responses to FSH by high LH level that might rely on receptor heterodimerization, resulting in depleted glycogen stores and follicular growth arrest in PCOS granulosa cells.

6.4.3 Pharmacological programming of endosomal signaling activated by small molecule ligands of the follicle-stimulating hormone receptor

Participants Eric Reiter, and collaborators.

Follicle-stimulating hormone receptor (FSHR) is a G protein-coupled receptor (GPCR) with pivotal roles in reproduction. One key mechanism dictating the signal activity of GPCRs is membrane trafficking. Upon activation, FSHR undergoes internalization to very early endosomes (VEEs) for its acute signaling and sorting to a rapid recycling pathway. Low molecular weight (LMW) allosteric FSHR ligands provide novel pharmacological tools to study FSHR. We have assessed whether these compounds exhibit differential abilities to alter receptor endosomal trafficking and signaling within the VEE [35]. Two chemically distinct LMW agonists (benzamide, termed B3 and thiazolidinone, termed T1) were employed. T1 was able to induce a greater level of cAMP than FSH and B3. Strikingly, T1 was able to induce a 3-fold increase in recycling events compared to FSH and two-fold more compared to B3. As T1-induced internalization was only marginally greater, the dramatic increase in recycling and cAMP signaling may be due to additional mechanisms. All compounds exhibited a similar requirement for receptor internalization to increase cAMP and proportion of FSHR endosomes with active Gαs. While T1-induced FSHR recycling was APPL1-dependent, its elevated cAMP signaling was only partially increased following APPL1 knockdown. In contrast, B3-induced FSHR endosomal signaling was negatively regulated by APPL1, whereas B3-induced FSHR recycling was APPL1-independent. Overall, FSHR allosteric compounds have the potential to reprogram FSHR activity via altering engagement with VEE machinery and also suggests that these two distinct functions of APPL1 can potentially be selected pharmacologically.

6.4.4 Membrane estrogen receptor (GPER) and follicle-stimulating hormone receptor (FSHR) heteromeric complexes promote human ovarian follicle survival

Participants Eric Reiter, and collaborators.

Classically, follicle-stimulating hormone receptor (FSHR)-driven cAMP-mediated signaling boosts human ovarian follicle growth and oocyte maturation. However, contradicting *in vitro* data suggest a different view on physiological significance of FSHR-mediated cAMP signaling. We have found that the G-protein-coupled estrogen receptor (GPER) heteromerizes with FSHR, reprogramming cAMP/death signals into proliferative stimuli fundamental for sustaining oocyte survival [23]. In human granulosa cells, survival signals are missing at high FSHR:GPER ratio, which negatively impacts follicle maturation and strongly correlates with preferential Gas protein/cAMP-pathway coupling and FSH responsiveness of patients undergoing controlled ovarian stimulation. In contrast, FSHR/GPER heteromers triggered anti-apoptotic/proliferative FSH signaling delivered via the G$\beta\gamma$dimer, whereas impairment of heteromer formation or GPER knockdown enhanced the FSH-dependent cell death and steroidogenesis. Therefore, our findings indicate how oocyte maturation depends on the capability of GPER to shape FSHR selective signals, indicating hormone receptor heteromers may be a marker of cell proliferation.

6.4.5 Allosteric interactions in the parathyroid hormone GPCR-arrestin complex formation

Participants Frédéric Jean-Alphonse, and collaborators.

Peptide ligands of class B G protein-coupled receptors (GPCRs) act via a two-step binding process, but the essential mechanisms that link their extracellular binding to intracellular receptor–arrestin interactions are not fully understood. Using NMR, crosslinking coupled to mass spectrometry, signaling experiments, and computational approaches on the parathyroid hormone (PTH) type 1 receptor (PTHR), we have shown that initial binding of the PTH C-terminal part constrains the conformation of the flexible PTH N-terminal signaling epitope before a second binding event occurs [26]. A “hot spot” PTH residue, His9, that inserts into the PTHR transmembrane domain at this second step allosterically engages receptor–arrestin coupling. A conformational change in PTHR intracellular loop 3 permits favorable interactions with β-arrestin’s finger loop. These results unveil structural determinants for PTHR–arrestin complex formation and reveal that the two-step binding mechanism proceeds via cooperative fluctuations between ligand and receptor, which extend to other class B GPCRs.

6.4.6 Gq/11-dependent regulation of endosomal cAMP generation by parathyroid hormone class B GPCR

Participants Frédéric Jean-Alphonse, and collaborators.

cAMP production upon activation of Gs by G protein-coupled receptors has classically been considered to be plasma membrane- delimited, but a shift in this paradigm has occurred in recent years with the identification of several receptors that continue to signal from early endosomes after internalization. The molecular mechanisms regulating this aspect of signaling remain incompletely understood. We have investigated the role of Gq/11 activation by the parathyroid hormone (PTH) type 1 receptor (PTHR) in mediating endosomal cAMP responses [37]. Inhibition of Gq/11 signaling by FR900359 markedly reduced the duration of PTH-induced cAMP production, and this effect was mimicked in cells lacking endogenous Gαq/11. We have determined that modulation of cAMP generation by Gq/11 occurs at the level of the heterotrimeric G protein via liberation of cell surface G$\beta\gamma$ subunits, which, in turn, act in a phosphoinositide-3 kinase-dependent manner to promote the assembly of PTHR– βarrestin–G$\beta\gamma$ signaling complexes that mediate endosomal cAMP responses. These results unveil insights into the spatiotemporal regulation of Gs-dependent cAMP signaling.

6.4.7 PTH hypersecretion triggered by a GABA B1 and Ca2+-sensing receptor heterocomplex in hyperparathyroidism

Participants Frédéric Jean-Alphonse, and collaborators.

Molecular mechanisms mediating tonic secretion of parathyroid hormone (PTH) in response to hypocalcemia and hyperparathyroidism (HPT) are unclear. We have demonstrated increased heterocomplex formation between the calcium-sensing receptor (CaSR) and metabotropic GABAB1 receptor (GABAB1R) in hyperplastic parathyroid glands (PTGs) of patients with primary and secondary HPT [25]. Targeted ablation of GABAB1R or glutamic acid decarboxylase 1 and 2 in PTGs produces hypocalcemia and hypoparathyroidism and prevents PTH hypersecretion in PTGs cultured from mouse models of hereditary HPT and dietary calcium-deficiency. Co-binding of CaSR/GABAB1R complex by baclofen and high extracellular calcium blocks the coupling of heterotrimeric G-proteins to homomeric CaSRs in cultured cells and promotes PTH secretion in cultured mouse PTGs. These results combined with the ability of PTG to synthesize GABA support a critical autocrine action of GABA/GABAB1R in mediating tonic PTH secretion of PTGs and ascribe aberrant activities of CaSR/GABAB1R heteromer to HPT.

6.5 Computational biology

6.5.1 Exploring epitope and functional diversity of anti-SARS-CoV2 antibodies using AI-based methods

Participants Anne Poupon, and collaborators.

Since the beginning of the COVID19 pandemics, an unprecedented research effort has been conducted to analyze the antibody responses in patients, and many trials based on passive immunotherapy — notably monoclonal antibodies — are ongoing. Twenty-one antibodies have entered clinical trials, 6 having reached phase 2/3, phase 3 or having received emergency authorization. These represent only the tip of the iceberg, since many more antibodies have been discovered and represent opportunities either for diagnosis purposes or as drug candidates. The main problem facing laboratories willing to develop such antibodies is the huge task of analyzing them and choosing the best candidate for exhaustive experimental validation. We have shown how artificial intelligence-based methods can help in analyzing large sets of antibodies in order to determine in a few hours the best candidates in few hours [46]. The MAbCluster method, which only requires knowledge of the amino acid sequences of the antibodies, allows to group the antibodies having the same epitope, considering only their amino acid sequences and their 3D structures (actual or predicted), and to infer some of their functional properties. We then use MAbTope to predict the epitopes for all antibodies for which they are not already known. This allows an exhaustive comparison of the available epitopes, but also gives a synthetic view of the possible combinations. Finally, we have shown how these results can be used to predict which antibodies might be affected by the different mutations arising in the circulating strains of the virus, such as the N501Y mutation that has started to spread in Great-Britain.

6.5.2 Characterization of new monoclonal PF4-specific antibodies as useful tools for studies on typical and autoimmune heparin-induced thrombocytopenia

Participants Anne Poupon, and collaborators.

Heparin-induced thrombocytopenia (HIT) is typically caused by platelet-activating immunoglobulin G (IgG) antibodies (Abs) against platelet factor 4 (PF4) complexed with heparin (H). Much less frequent “autoimmune” HIT is distinguished from typical HIT by platelet activation without heparin and the

presence of both anti-PF4/H and anti-PF4 IgG. We have developed three murine monoclonal anti-PF4 Abs, 1E12, 1C12, and 2E1, resembling autoimmune HIT Abs, and characterized them in comparison to monoclonal anti-PF4/H Abs (5B9 and KKO), and polyclonal Abs from patients with typical HIT (group-2) and autoimmune HIT (group-3) [36]. 1C12, 1E12, and 2E1 displayed higher affinity for PF4/H complexes than 5B9 and KKO, comparable to human group-3 Abs. Only 1C12, 1E12, 2E1, and group-3 Abs formed large complexes with native PF4, and activated platelets without heparin. The predicted binding sites on PF4 differed from those of KKO and 5B9, but were close to each other. 2E1 exhibited unique bivalent binding, involving its antigen recognition site to PF4 and charge-dependent interactions with heparin. 1C12, 1E12, and 2E1 are tools for studying the pathophysiology of autoimmune HIT.

6.5.3 4C3 human monoclonal antibody: A proof of concept for non-pathogenic proteinase 3 anti-neutrophil cytoplasmic antibodies in granulomatosis with polyangiitis

Participants Anne Poupon, and collaborators.

Granulomatosis with polyangiitis (GPA) is a severe autoimmune vasculitis associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA) mainly targeting proteinase 3 (PR3), a neutrophilic serine proteinase. PR3-ANCA binding on neutrophils induce their auto-immune activation responsible for vascular lesions. However, the correlation between PR3-ANCA level and disease activity remains inconsistent, suggesting the existence of non-pathogenic PR3-ANCA. In order to prove their existence, we have immortalized B lymphocytes from blood samples of GPA patients in remission having persistent PR3-ANCA to isolate non-activating PR3-ANCA. We have obtained for the first time a non-activating human IgG1κ anti-PR3 monoclonal antibody (mAb) named 4C3 [30], which binds close to the PR3 hydrophobic patch. 4C3 did not induce activation of neutrophils and could inhibit human polyclonal PR3-ANCA-induced activation suggesting that 4C3 is non-pathogenic. The existence of non-pathogenic PR3-ANCA, which do not activate neutrophils, could explain the persistence of high PR3-ANCA levels in some GPA patients in remission and why PR3-ANCA would not predict relapse. Finally, these results offer promising perspectives particularly regarding the understanding of PR3-ANCA pathogenicity and the development of new diagnostic and therapeutic strategies in GPA.

6.6 Bibliographic reviews

6.6.1 Mathematical modeling approaches of cellular endocrinology within the hypothalamo-pituitary-gonadal axis

Participants Frédérique Clément, Pascale Crépieux, Romain Yvinec, with Danielle Monniaux.

The reproductive neuroendocrine axis, or hypothalamo-pituitary-gonadal (HPG) axis, is a paragon of complex biological system involving numerous cell types, spread over several anatomical levels communicating through entangled endocrine feedback loops. The HPG axis exhibits remarkable dynamic behaviors on multiple time and space scales, which are an inexhaustible source of studies for mathematical and computational biology. In this review, we have described a variety of modeling approaches of the HPG axis from a cellular endocrinology viewpoint. We have in particular investigated the questions raised by some of the most striking features of the HPG axis [27]: (i) the pulsatile secretion of hypothalamic and pituitary hormones, and its counterpart, the cell signaling induced by frequency-encoded hormonal signals, and (ii) the dual, gametogenic and glandular function of the gonads, which relies on the tight control of the somatic cell populations ensuring the proper maturation and timely release of the germ cells.

6.6.2 The follicle-stimulating hormone signaling network in gonadal cells

Participants Frédérique Clément, Pascale Crépieux, Romain Yvinec, and collaborators.

Given the prominent role of FSH in reproductive biology and its pleiotropic actions, we have performed a thorough literature review on the signaling pathways induced by FSH in gonadal (Sertoli and granulosa cells) [44]. Deciphering the molecular bases of the developmental switch in FSH biological activities that is observed during Sertoli cell post-natal development and during folliculogenesis requires to gain insights into FSH-induced signaling pathways. This quest has led to the identification of a complex interconnected signaling network affected by testicular paracrine factors, implying not only protein post-translational modifications, but also regulations by microRNA and chromatin remodeling. In the ovary, emphasis is put on deciphering the complex functional relationships between the LHCGR and the FSHR, that trigger intertwined signaling networks in the same granulosa cell type. Breakthroughs in the organization and dynamic functioning of the FSH-induced signaling network are expected to identifying novel regulatory processes and therapeutic strategies for infertilities and contraception.

6.6.3 Mathematical modeling of ovarian follicle development : A population dynamics viewpoint

Participants Frédérique Clément, with Danielle Monniaux.

Amongst endocrine organs, ovaries are unique because their function is supported by an ever-changing number of histological entities, the ovarian follicles, which are themselves subject to asynchronous development from their formation up to ovulation. Follicle development combines finely controlled processes of cell dynamics with original morphogenesis steps. Understanding the dynamics of follicle populations, on the whole ovary level, and the coupled dynamics of the oocyte and somatic cells, on the follicle level, is crucial to understand ovarian physiology and ovarian aging. Mathematical modeling studies joint with proper experimental approaches can be particularly helpful for gaining insight into follicle dynamics on different scales [28].

6.6.4 Follicle-stimulating hormone (FSH) action on spermatogenesis: A focus on physiological and therapeutic roles

Participants Pascale Crépieux, Eric Reiter, and collaborators.

Human reproduction is regulated by the combined action of the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH) on the gonads. Although FSH is largely used in female reproduction, in particular in women attending assisted reproductive techniques to stimulate multi-follicular growth, its efficacy in men with idiopathic infertility is not clearly demonstrated. Indeed, whether FSH administration improves fertility in patients with hypogonadotropic hypogonadism, the therapeutic benefit in men presenting alterations in sperm production despite normal FSH serum levels is still unclear. We have evaluated the potential pharmacological benefits of FSH administration in clinical practice, in a narrative review, describing the FSH physiological role in spermatogenesis and its potential therapeutic action in men [34]. The FSH role on male fertility has been reviewed starting from the physiological control of spermatogenesis, throughout its mechanism of action in Sertoli cells, the genetic regulation of its action on spermatogenesis, until the therapeutic options available to improve sperm production. FSH administration in infertile men has potential benefits, although its action should be considered by evaluating its synergic action with testosterone, and well-controlled, powerful trials are required. Prospective studies and new compounds could be developed in the near future.

6.6.5 FSH for the treatment of male infertility

Participants Pascale Crépieux, Eric Reiter, and collaborators.

Follicle-stimulating hormone (FSH) supports spermatogenesis acting via its receptor (FSHR), which activates trophic effects in gonadal Sertoli cells. These pathways are targeted by hormonal drugs used for clinical treatment of infertile men, mainly belonging to sub-groups defined as hypogonadotropic hypogonadism or idiopathic infertility. While, in the first case, fertility may be efficiently restored by specific treatments, such as pulsatile gonadotropin releasing hormone (GnRH) or choriogonadotropin (hCG) alone or in combination with FSH, less is known about the efficacy of FSH in supporting the treatment of male idiopathic infertility. We have reviewed the role of FSH in the clinical approach to male reproduction, addressing the state-of-the-art from the little data available and discussing the pharmacological evidence [22]. New compounds, such as allosteric ligands, dually active, chimeric gonadotropins and immunoglobulins, may represent interesting avenues for future personalized, pharmacological approaches to male infertility.

7 Partnerships and cooperations

7.1 International initiatives

7.1.1 Participation in other international programs

- ECOS SUD-CHILI 2020 : ECOS n° C20E03, “Coarsening dynamics: numerical and theoretical analysis of the Lifshitz-Slyozov equation with nucleation and applications to biology.” PIs: R. Yvinec and E. Hingant (Universidad del Bío-Bío, Chile).
- Bill & Melinda Gates Foundation, ContraBody (2021-2023, PI Eric Reiter, 1.8 M US $) “Non-Hormonal Contraception by Nanobody Produced from Within the Body”. In partnership with University of Modena E Regio Emilia, Italy; MabSilico, France and InCellArt, France. Involved MUSCA members : E. Reiter, P. Crépieux, F. Jean-Alphonse, R. Yvinec.

7.2 International research visitors

7.2.1 Visits of international scientists

Manuela Simoni, Professor of Endocrinology, University of Modena and Emilia-Romagna, Italy, Research fellowship Le Studium, 1/05/2019 – 1/04/2020 (left on the 11th of March because of the COVID pandemia). Host scientist : P. Crépieux

Elia Paradiso, PhD student, University of Modena and Emilia-Romagna, Italy, 1/09/2020– 1/04/2020 (left on the 11th of March because of the COVID pandemia). Co-supervisor for this period : P. Crépieux

7.3 European initiatives

7.3.1 FP7 & H2020 Projects

- One Health EJP project MoMIR-PPC “Monitoring the gut microbiota and immune response to predict, prevent and control zoonoses in humans and livestock in order to minimize the use of antimicrobials” (2018-2021, WP co-led by B. Laroche).
- ERC Advanced grant, Homo.Symbiosus (2019-2024, PI Joël Doré, 2.5 M€) “Assessing, preserving and restoring man-microbes symbiosis”. Involved MUSCA member: B. Laroche.
- ERC Starting grant, Therautism (2020-2024, PI Lucie Pellissier, 1.5 M€) “New molecular targets and proof-of-concept therapies for Autism Spectrum Disorders” Involved MUSCA member: P. Crépieux.
- ERNEST (European Research Network on Signal transduction) COST Action 18133.

7.4 National initiatives

- ANR ABLISS (2019-2022, PI A. Poupon, 441 K€) “Automating building from Literature of Signalling Systems”. Involved MUSCA members: A. Poupon, E. Reiter, P. Crépieux, R. Yvinec.
- ANR YDOBONAN (2021-2024, PI V. Aucagne, 497 K€) “Mirror Image Nanobodies: pushing forward the potential of enantiomeric proteins for therapeutic and pharmacological applications”. Involved MUSCA member: E. Reiter.
- LabEx MAbImprove (2011-2025, PI H. Watier). Involved MUSCA members : E. Reiter, F. Jean-Alphonse, P. Crépieux, A. Poupon, R. Yvinec.
- INRAE metaprogram HOLOFLUX (2020-2022), Egg-to-Meat project. Involved MUSCA member: B. Laroche.

7.5 Regional initiatives

- SATT Paris-Saclay POC’UP 2020 project COOPERATE, awarded to B. Laroche (together with L. Rigottier, P. Serror, V. Loux and O. Rué): “COnsortium de bactéries cOmmensales pour augmenter l’effet barrière du microbiote et limiter la Persistance et la prolifération des Entérocoques Résistants à la vancomycine après traitement AnTibiotiquE”.
- Ambition recherche développement 2020, région Centre Val de Loire, GPCRAb 2 (2018-2021, PI E. Reiter, 1 M€) “Ciblage et modulation pharmacologique de GPCRs avec des fragments d’anticorps”. Involved MUSCA members: E. Reiter, P. Crépieux, A. Poupon, R. Yvinec.
- Ambition recherche développement Centre Val de Loire SELMAT (2020-2023, PI E. Reiter, 630 K€) “Méthodes in silico pour la sélection et la maturation d’anticorps : développement, validation et application à différentes cibles thérapeutiques”. Involved MUSCA members: E. Reiter, P. Crépieux, F. Jean-Alphonse, R. Yvinec.
- Appel à projet région Centre Val de Loire, LipiCAbs (2018-2021, PI M. Potier-Cartereau, 200 K€) “Développement de protéoliposomes pour l’étude de canaux ioniques et le criblage d’anticorps”. Involved MUSCA member : E. Reiter.
- Appel à projet région Centre Val de Loire, INTACT (2019-2022, PI P. Crépieux, 200 K€) “Pharmacologie réverse à l’aide d’anticorps intracellulaires anti-RFSH actif”. Involved MUSCA members: P. Crépieux, E. Reiter, F. Jean-Alphonse, A. Poupon, R. Yvinec. Industrial partner: McSAF, Tours.
- Appel à projet région Centre Val de Loire, NeuroMAbster (2018-2021, PI S. Morisset-Lopez, 200 K€) “Identification de nanobodies modulateurs du récepteur 5HT7 pour le traitement de maladies du SNC”. Involved MUSCA members: E. Reiter, A. Poupon.

8 Dissemination

8.1 Promoting scientific activities

8.1.1 Scientific events: organisation

General chair, scientific chair

E. Reiter: 9th international GDR3545 meeting on GPCRs, November 6-9, online

Member of the organizing committees

F. Clément (together with Y. Bellaiche, L. Héliot, P. Lemaire, R-M. Mège, M.-H. Verlhack, and K. Wassmann),“From cells to embryo, patterning and self-organisation”, ITMO BCDE symposium, November 16-17, online

E. Reiter, P. Crépieux, F. Jean-Alphonse and R. Yvinec, 9th international GDR3545 meeting on GPCRs, November 6-9, online

8.1.2 Scientific events: selection

Member of the conference program committees

F Clément “From cells to embryo, patterning and self-organisation”, ITMO BCDE symposium, November 16-17, online

E. Reiter, P. Crépieux, F. Jean-Alphonse and R. Yvinec, 9th international GDR3545 meeting on GPCRs, November 6-9, online

Reviewer

B. Laroche, reviewer for ECC (European Control Conference) 2020

8.1.3 Journal

Member of the editorial boards

P. Crépieux, associate editor Front. Endocrinol.

A. Poupon, editorial board member (molecular biology) Sci. Rep.

E. Reiter, guest editor (with A. Hanyaloglu) of the special issue on “G protein-coupled receptors: from molecules to medicine” in Curr. Opin. Endocrin. Metab. Res. (publication February 2021)

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

Reviewer - reviewing activities

G. Ballif, J. Math. Biol.

F. Clément, J. Roy. Soc. Interface, Front. Endocrinol. (review editor)

P. Crépieux, Curr. Opin. Endocr. Metab. Res., FASEB J., Front. Endocrinol., Front. Pharmacol., Oncotarget, Reproduction

F. Jean-Alphonse, Curr. Opin. Endocr. Metab. Res., Front. Pharmacol.

B. Laroche, ISME J., Nonlinear Dyn.

A. Poupon, Front. Bioeng. Biotechnol. (review editor)

E. Reiter, Science, Front. Endocrinol., Cell Signal.

R. Yvinec, J. Math. Biol., Eur. J. Appl. Math., J. Theor. Biol, Math. Biosci. Eng., modcov19, mathematical reviews

8.1.4 Invited talks

G. Ballif, selected poster “Stochastic multiscale modeling of ovarian follicles”, CIRM Thematic month on mathematical issues in biology: PDE and probability for biology. February 3-7, Luminy, France

F. Jean-Alphonse, “Mechanisms in GPCR cAMP endosomal signaling”, European Research Network on Signal Transduction meeting (ERNEST Cost Action 18133), October 13-14, online

B. Laroche, “A model coupling microbial physiology, spatial heterogeneity and fluid mechanics to investigate factors impacting the microbiota spatial organization in the human colon ”, Sorbonne Université workshop "Transport in the digestive tract : experiments, modeling, applications to microbiology", October 22-23 , online

B. Laroche, INRAE microbiology department webinars, “Comprendre et valoriser les communautés microbiennes”, September 24-25

A. Poupon, “Bioinformatics methods for antibody development”, Biokorea 2020, Seoul, Korea, May 13-18 (in TC)

R. Yvinec, “Kinetic biased signaling: towards a system biology definition of drugs selectivity” [40], CIRM Thematic month on mathematical issues in biology: Networks and molecular biology, March 2-6, Luminy, France

R. Yvinec, “Modeling (some aspects of) the female reproductive system” [41], CIRM Thematic month on mathematical issues in biology: Mathematics of complex systems in biology and medicine, February 24-28, Luminy, France

R. Yvinec, “Modeling GPCR-induced biased signaling Towards a system biology definition of drugs selectivity” [42], 9th GDR3545-GPCR international meeting, November 6-9, online

R. Yvinec, “Dynamical modeling of reaction networks Mathematics of system biology” [39], 8th workshop of GDR 3545: Bioinformatics and biomathematical approaches to integrate the GPCR signal, November 5, online

8.1.5 Leadership within the scientific community

F. Clément, member of the direction and scientific boards of GDR 3606 REPRO (Integrative and translational approaches of human and animal reproduction), and co-head of WP “Biomathematics, Bioinformatics and Biophysics for Reproduction”

F. Clément, expert of the BCDE (Cell Biology, Development and Evolution) ITMO (Multi-Organization Thematic Institute) of the French National Alliance for Life and Health Sciences (Aviesan)

F. Jean-Alphonse, coordinator of Key Question 1 (How can target activity be modulated through antibody binding?), LabEx MAbImprove

B. Laroche, member of the Steering Committee of the INRAE metagrogram HOLOFLUX

A. Poupon, coordinator of “Central Development Instrument 1 (Interdisciplinary Innovation)”, LabEx MAbImprove

E. Reiter, member of the direction board of GDR 3545 RCPG-PhysioMed

R. Yvinec, co-head of WP “Biomathematics, Bioinformatics and Biophysics for Reproduction”, GDR 3606 REPRO

8.1.6 Scientific expertise

F. Clément, member of the Inria Saclay–Île-de-France research center selection committee for junior scientists

F. Clément, member of an Université Côte d’Azur selection committee for an assistant professor position

P. Crépieux, reviewer for ESF (European Science Foundation)

P. Crépieux, member of an expert board on “FSH and LH deficiency management” for Merck (Darmstadt, Germany)

B. Laroche, reviewer for ANR, JCJC project (committee #31, Physics)

A. Poupon, member of an INRAE selection committee for a technician in computer science

8.1.7 Research administration

B. Laroche is deputy head of MaIAGE lab.

E. Reiter is deputy director of UMR PRC

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

8.2 Teaching - Supervision - Juries

8.2.1 Teaching

G. Ballif, linear algebra (42h, tutorials) first-year IUT d'Orsay

G. Ballif, discrete mathematics (21h, tutorials) first-year IUT d'Orsay

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

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

E. Reiter, Master Infectiology, Immunity, Vaccinology and Biodrugs (6h), Université de Tours

R. Yvinec, L3 Economy (24h), Université de Tours

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

8.2.2 Supervision

PhD: Léo Darrigade, "Modeling of the host-microbiota dialogue in the vicinity of the epithelium of the distal intestine", defended on December 16, supervisor: B. Laroche

Phd: Chayma El Khamlichi, "Serotonin 5-HT7 receptor transduction mechanisms: molecular bases and characterization of pharmacological tools", defended on December 15, supervisors: E. Reiter and S. Morisset-Lopez

PhD in progress: Guillaume Ballif "Stochastic multiscale modeling in developmental and reproductive biology", started October 2019, supervisors : F. Clément and R. Yvinec

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

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

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

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

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

8.2.3 Juries

B. Laroche, PhD jury of Stefan Vet, Université Libre de Bruxelles-Katholieke Universiteit Leuven, private defense (referee), May 29, and public defense, July 8

B. Laroche, PhD jury of Vincent Quedeville (president), Université de Toulouse, June 4

B. Laroche, PhD jury of Pablo Ugade, Université de Montpellier, November 2

B. Laroche, PhD jury of Julia Delacour (president), Sorbonne Université, December 14

B. Laroche, HDR jury of Romain Yvinec (referee), Université de Tours, Dec 2

A. Poupon, PhD jury of Grégory Deicsics (referee), Université Paris-Saclay, October 21

A. Poupon, PhD jury of Christophe Dumet (referee), Université de Tours, June 12

A. Poupon, HDR jury of Véronique Giudicielli (referee), Université de Montpellier, December 20

E. Reiter, PhD jury of Julien Mambu, Université de Tours, December 4

E. Reiter, PhD jury of Wenwen Gao (referee), Université de Paris, September 28

E. Reiter, PhD jury of Caroline Vayne, Université de Tours, June 12

R. Yvinec, PhD jury of Céline Bonnet, Université Paris Saclay, May 27

9 Scientific production

9.1 Major publications

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

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

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

[4] 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.

[5] 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.

[6] 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.

[7] 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.

[8] 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.

[9] 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.

[10] 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.

[11] 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.

[12] 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.

[13] 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.

[14] 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.

[15] 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.

[16] 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.

[17] 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.

[18] 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.

9.2 Publications of the year

International journals

[19] 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.

[20] M. Bourgin, S. Labarthe, A. Kriaa, M. Lhomme, P. Gérard, P. Lesnik, B. Laroche, E. Maguin and M. M. Rhimi. 'Exploring the Bacterial Impact on Cholesterol Cycle: A Numerical Study'. In: *Frontiers in Microbiology* 11 (2020), p. 1121. DOI: 10.3389/fmicb.2020.01121. URL: https://hal.archives-ouvertes.fr/hal-02863236.

[21] J. Calvo, E. Hingant and R. Yvinec. 'The initial-boundary value problem for the Lifshitz-Slyozov equation with non-smooth rates at the boundary'. In: *Nonlinearity* (2021). URL: https://hal.inrae.fr/hal-03109431.

[22] L. Casarini, P. Crépieux, E. Reiter, C. Lazzaretti, E. Paradiso, V. Rochira, G. Brigante, D. Santi and M. Simoni. 'FSH for the Treatment of Male Infertility'. In: *International Journal of Molecular Sciences* 21.7 (25th Mar. 2020), p. 2270. DOI: 10.3390/ijms21072270. URL: https://hal.archives-ouvertes.fr/hal-03020922.

[23] L. Casarini, C. Lazzaretti, E. Paradiso, S. Limoncella, L. Riccetti, S. Sperduti, B. Melli, S. Marcozzi, C. Anzivino, N. S. Sayers, J. Czapinski, G. Brigante, F. Potì, A. La Marca, F. De Pascali, E. Reiter, A. Falbo, J. Daolio, M. T. Villani, M. Lispi, G. Orlando, F. Klinger, F. Fanelli, A. Rivero-Müller, A. Hanyaloglu and M. Simoni. 'Membrane Estrogen Receptor (GPER) and Follicle-Stimulating Hormone Receptor (FSHR) Heteromeric Complexes Promote Human Ovarian Follicle Survival'. In: *iScience* 23.12 (Dec. 2020), p. 101812. DOI: 10.1016/j.isci.2020.101812. URL: https://hal.inrae.fr/hal-03112804.

[24] N. Chahal, A. Geethadevi, S. Kaur, R. Lakra, A. Nagendra, T. Shrivastav, F. De Pascali, E. Reiter, P. Crépieux, M. G. Devi, N. Malhotra, K. Muralidhar and R. Singh. 'Direct impact of gonadotropins on glucose uptake and storage in preovulatory granulosa cells: Implications in the pathogenesis of polycystic ovary syndrome'. In: *Metabolism* 115 (Feb. 2021), p. 154458. DOI: 10.1016/j.metabol.2020.154458. URL: https://hal.inrae.fr/hal-03112818.

[25] W. Chang, C.-L. Tu, F. Jean-Alphonse, A. Herberger, Z. Cheng, J. Hwong, H. Ho, A. Li, D. Wang, H. Liu, A. White, I. Suh, W. Shen, Q.-Y. Duh, E. Khanafshar, D. Shoback, K. Xiao and J.-P. Vilardaga. 'PTH hypersecretion triggered by a GABAB1 and Ca2+-sensing receptor heterocomplex in hyperparathyroidism'. In: *Nature Metabolism* 2.3 (Mar. 2020), pp. 243–255. DOI: 10.1038/s42255-020-0175-z. URL: https://hal.archives-ouvertes.fr/hal-03117169.

[26] L. Clark, J. Krieger, A. White, V. Bondarenko, S. Lei, F. Fang, J. Y. Lee, P. Doruker, T. Böttke, F. Jean-Alphonse, P. Tang, T. Gardella, K. Xiao, I. Sutkeviciute, I. Coin, I. Bahar and J.-P. Vilardaga. 'Allosteric interactions in the parathyroid hormone GPCR–arrestin complex formation'. In: *Nature Chemical Biology* 16.10 (Oct. 2020), pp. 1096–1104. DOI: 10.1038/s41589-020-0567-0. URL: https://hal.archives-ouvertes.fr/hal-03117168.

[27] F. Clément, P. Crépieux, R. Yvinec and D. Monniaux. 'Mathematical modeling approaches of cellular endocrinology within the hypothalamo-pituitary-gonadal axis'. In: *Molecular and Cellular Endocrinology* 518 (19th June 2020). DOI: 10.1016/j.mce.2020.110877. URL: https://hal.inria.fr/hal-03046096.

[28] F. Clément and D. Monniaux. 'Mathematical modeling of ovarian follicle development : A population dynamics viewpoint'. In: *Current Opinion in Endocrine and Metabolic Research* (2021). URL: https://hal.inria.fr/hal-03146955.

[29] F. Clément, F. Robin and R. Yvinec. 'Stochastic nonlinear model for somatic cell population dynamics during ovarian follicle activation'. In: *Journal of Mathematical Biology* 82.12 (2021). URL: https://hal.inria.fr/hal-02057983.

[30] J. Granel, R. Lemoine, E. Morello, Y. Gallais, J. Mariot, M. Drapeau, A. Musnier, A. Poupon, M. Pugnière, S. Seren, D. Nouar, V. Gouilleux-Gruart, H. Watier, B. Korkmaz and C. Hoarau. '4C3 Human Monoclonal Antibody: A Proof of Concept for Non-pathogenic Proteinase 3 Anti-neutrophil Cytoplasmic Antibodies in Granulomatosis With Polyangiitis'. In: *Frontiers in Immunology* 11 (25th Sept. 2020), pp. 1–17. DOI: 10.3389/fimmu.2020.573040. URL: https://hal-cnrs.archives-ouvertes.fr/hal-03039822.

[31] S. Labarthe, B. Laroche, T. N. T. Nguyen, B. Polizzi, F. Patout, M. Ribot and T. Stegmaier. 'A Multi-Scale Epidemic Model of Salmonella Infection With Heterogeneous Shedding'. In: *ESAIM: Proceedings and Surveys* 67 (2020), pp. 261–284. DOI: 10.1051/proc/202067015. URL: https://hal.archives-ouvertes.fr/hal-02043742.

[32] T. Laboute, J. Gandía, L. Pellissier, Y. Corde, F. Rebeillard, M. Gallo, C. Gauthier, A. Léauté, J. Diaz, A. Poupon, B. Kieffer, J. Le Merrer and J. A. Becker. 'The orphan receptor GPR88 blunts the signaling of opioid receptors and multiple striatal GPCRs'. In: *eLife* 9 (31st Jan. 2020). DOI: 10.7554/eLife.50519. URL: https://hal-cnrs.archives-ouvertes.fr/hal-03039847.

[33] S. Le Feunteun, A. Al-Razaz, M. Dekker, E. George, B. Laroche and G. Van Aken. 'Physiologically Based Modeling of Food Digestion and Intestinal Microbiota: State of the Art and Future Challenges. An INFOGEST Review'. In: *Annual Review of Food Science and Technology* 12 (21st Jan. 2021), pp. 16/1–16/19. DOI: 10.1146/annurev-food-070620-. URL: https://hal.inrae.fr/hal-03117715.

[34] D. Santi, P. Crépieux, E. Reiter, G. Spaggiari, G. Brigante, L. Casarini, V. Rochira and M. Simoni. 'Follicle-Stimulating Hormone (FSH) Action on Spermatogenesis: A Focus on Physiological and Therapeutic Roles'. In: *Journal of Clinical Medicine* 9.4 (Apr. 2020), p. 1014. DOI: 10.3390/jcm9041014. URL: https://hal.inrae.fr/hal-02930237.

[35] S. Sposini, F. De Pascali, R. Richardson, N. S. Sayers, D. Perrais, H. N. Yu, S. Palmer, S. Nataraja, E. Reiter and A. C. Hanyaloglu. 'Pharmacological Programming of Endosomal Signaling Activated by Small Molecule Ligands of the Follicle Stimulating Hormone Receptor'. In: *Frontiers in Pharmacology* 11 (30th Nov. 2020). DOI: 10.3389/fphar.2020.593492. URL: https://hal.archives-ouvertes.fr/hal-03039198.

[36] C. Vayne, T.-H. Nguyen, J. Rollin, N. Charuel, A. Poupon, C. Pouplard, N. Normann, Y. Gruel and A. Greinacher. 'Characterization of New Monoclonal PF4-Specific Antibodies as Useful Tools for Studies on Typical and Autoimmune Heparin-Induced Thrombocytopenia'. In: *Thrombosis and Haemostasis* (13th Aug. 2020). DOI: 10.1055/s-0040-1717078. URL: https://hal-cnrs.archives-ouvertes.fr/hal-03039816.

[37] A. White, F. Jean-Alphonse, F. Fang, K. Pena, S. Liu, G. König, A. Inoue, D. Aslanoglou, S. Gellman, E. Kostenis, K. Xiao and J.-P. Vilardaga. 'G q/11 -dependent regulation of endosomal cAMP generation by parathyroid hormone class B GPCR'. In: *Proceedings of the National Academy of Sciences of the United States of America* 117.13 (31st Mar. 2020), pp. 7455–7460. DOI: 10.1073/pnas.1918158117. URL: https://hal.archives-ouvertes.fr/hal-03117167.

[38] T. Zariñán, J. Mayorga, E. Jardón Valadez, R. Gutiérrez Sagal, J. L. Maravillas Montero, N. Mejía Domínguez, I. Martínez Luis, O. Yacini Torres, M. d. C. Cravioto, E. Reiter and A. Ulloa Aguirre. 'A Novel Mutation in the FSH Receptor (I423T) Affecting Receptor Activation and Leading to Primary Ovarian Failure'. In: *Journal of Clinical Endocrinology and Metabolism* (29th Oct. 2020). DOI: 10.1210/clinem/dgaa782. URL: https://hal.inrae.fr/hal-03112820.

Conferences without proceedings

[39] R. Yvinec. 'Dynamical modeling of reaction networksMathematics of system biology'. In: 2020 Workshop - 'bioinformatics and biomathematical approaches to integrate the GPCR signal. Online, France, 5th Nov. 2020, pp. 1–70. URL: https://hal.archives-ouvertes.fr/hal-03115099.

[40] R. Yvinec. 'Kinetic biased signaling: towards a system biology definition of drugs selectivity'. In: Thematic Month on Mathematical Issues in Biology - Networks and molecular biology. Luminy, France, 2nd Mar. 2020, pp. 1–75. URL: https://hal.archives-ouvertes.fr/hal-03115087.

[41] R. Yvinec. 'Modeling (some aspects of) the female reproductive system'. In: Thematic Month on Mathematical Issues in Biology - Mathematics of complex systems in biology and medicine. Luminy, France, 24th Feb. 2020, pp. 1–65. URL: https://hal.archives-ouvertes.fr/hal-03115069.

[42] R. Yvinec. 'Modeling GPCR-induced biased signalingTowards a system biology definition of drugs selectivity'. In: 9th GDR3545-GPCR international meeting. Online, France, 6th Nov. 2020, pp. 1–42. URL: https://hal.archives-ouvertes.fr/hal-03115093.

[43] R. Yvinec. 'Ovarian follicle morphogenesis'. In: CompuCell3D Multicell Virtual-Tissue Modeling Summer School. Online, United States, 3rd Aug. 2020. URL: https://hal.archives-ouvertes.fr/hal-03115079.

Scientific book chapters

[44] F. Clément, P. Crépieux, R. Yvinec, N. Gallay, L. Gagniac and F. Guillou. 'The Follicle-Stimulating Hormone Signaling Network in Gonadal Cells.' In: *Cellular Endocrinology in Health and Disease, Second Edition*. 2021. URL: https://hal.archives-ouvertes.fr/hal-03128409.

Doctoral dissertations and habilitation theses

[45] R. Yvinec. 'Some contributions to the study of population dynamics models and coagulation-fragmentation'. Université de Tours, 2nd Dec. 2020. URL: https://tel.archives-ouvertes.fr/tel-03138658.

Reports & preprints

[46] C. Dumet, Y. Jullian, A. Musnier, P. Rivière, N. Poirier, H. Watier, T. Bourquard and A. Poupon. *Exploring epitope and functional diversity of anti-SARS-CoV2 antibodies using AI-based methods*. 31st Dec. 2020. DOI: 10.1101/2020.12.23.424199. URL: https://hal-cnrs.archives-ouvertes.fr/hal-03091531.

[47] E. Hingant and R. Yvinec. *Quasi-stationary distribution and metastability for the stochastic Becker-Döring model*. 14th Jan. 2021. URL: https://hal.archives-ouvertes.fr/hal-03110670.

9.3 Cited publications

[48] G. Allaire. 'Homogenization and two-scale convergence'. In: *SIAM J. Math. Anal.* 23.6 (1992), pp. 1482–1518.

[49] V. Andasari, R. Roper, M. Swat and M. Chaplain. 'Integrating intracellular dynamics using CompuCell3D and Bionetsolver: Applications to multiscale modelling of cancer cell growth and invasion'. In: *PLoS One* 7.3 (2012).

[50] K. Ball, T. Kurtz, L. Popovic and G. Rempala. 'Asymptotic analysis of multiscale approximations to reaction networks'. In: *Ann. Appl. Probab.* 16.4 (2006), pp. 1925–1961.

[51] J. Cañizo, J. Carrillo and S. Cuadrado. 'Measure solutions for some models in population dynamics'. In: *Acta Appl. Math.* 123.1 (2013), pp. 141–156.

[52] N. Champagnat, R. Ferrière and S. Méléard. 'Individual-based probabilistic models of adaptive evolution and various scaling approximations'. In: *Progr. Probab.* 59 (2005), pp. 75–113.

[53] T. Crestaux, O. Le Maître and J.-M. Martinez. 'Polynomial chaos expansion for sensitivity analysis'. In: *Reliab. Eng. Syst. Safe* 94.7 (2009), pp. 1161–1172.

[54] T. Dębiec, P. Gwiazda, K. Lyczek and A. Świerczewska-Gwiazda. 'Relative entropy method for measure-valued solutions in natural sciences'. In: *Topol. Methods Nonlinear Anal.* 52.1 (2018), pp. 311–335.

[55] P. Érdi and J. Tóth. *Mathematical Models of Chemical Reactions: Theory and Applications of Deterministic and Stochastic Models*. Princeton University Press; 1st edition, 1989.

[56] K. Faust, F. Bauchinger, B. Laroche, S. De Buyl, L. Lahti, A. Washburne, D. Gonze and S. Widder. 'Signatures of ecological processes in microbial community time series'. In: *Microbiome* 6.1 (2018), p. 120.

[57] A. Gábor and J. Banga. 'Robust and efficient parameter estimation in dynamic models of biological systems'. In: *BMC Syst. Biol.* 9.1 (2015), p. 74.

[58] P. Gabriel. 'Measure solutions to the conservative renewal equation'. In: *arXiv:1704.00582* (2017).

[59] A. Gelig and A. Churilov. 'Frequency methods in the theory of pulse-modulated control systems'. In: *Autom. Remote Control* 67 (2006), pp. 1752–1767.

[60] A. Gorban. 'Model reduction in chemical dynamics: slow invariant manifolds, singular perturbations, thermodynamic estimates, and analysis of reaction graph'. In: *Curr. Opin. Chem. Eng.* 21 (2018), pp. 48–59.

[61] B. Ingalls. *Mathematical Modeling in Systems Biology. An Introduction*. The MIT Press; 1st edition, 2013.

[62] B. Iooss and P. Lemaître. 'A review on global sensitivity analysis methods'. In: *Uncertainty management in simulation-optimization of complex systems*. Springer, 2015, pp. 101–122.

[63] J. Jacques and C. Preda. 'Functional data clustering: a survey'. In: *Adv. Data Ana. Classif.* 8.3 (2014), pp. 231–255.

[64] G. Jamróz. 'Measure-transmission metric and stability of structured population models'. In: *Nonlinear Anal. Real World Appl.* 25 (2015), pp. 9–30.

[65] H.-W. Kang, T. Kurtz and L. Popovic. 'Central limit theorems and diffusion approximations for multiscale Markov chain models'. In: *Ann. Appl. Probab.* 24.2 (2014), pp. 721–759.

[66] T. Kurtz. 'Strong approximation theorems for density dependent Markov chains'. In: *Stochastic Process. Appl.* 6 (1978), pp. 223–240.

[67] C. Lee and H. Othmer. 'A multi-time-scale analysis of chemical reaction networks: I. Deterministic systems'. In: *J. Math. Biol.* 60.3 (2009), pp. 387–450.

[68] R. Leveque. *Finite Volume Methods for Hyperbolic Problems*. Cambridge ; New York: Cambridge University Press, Aug. 2002.

[69] T. Maiwald, H. Hass, B. Steiert, J. Vanlier, R. Engesser, A. Raue, F. Kipkeew, H. Bock, D. Kaschek, C. Kreutz and J. Timmer. 'Driving the model to its limit: Profile likelihood based model reduction'. In: *PLoS One* 11.9 (2016), pp. 1–18.

[70] C. Marr, M. Strasser, M. Schwarzfischer, T. Schroeder and F. Theis. 'Multi-scale modeling of GMP differentiation based on single-cell genealogies: Multi-scale modeling of GMP differentiation'. In: *FEBS J.* 279.18 (2012), pp. 3488–3500.

[71] S. Méleard and V. Bansaye. *Stochastic Models for Structured Populations*. Cham: Springer International Publishing, 2015.

[72] P. Michel, S. Mischler and B. Perthame. 'General relative entropy inequality: an illustration on growth models'. In: *J. Math. Pures Appl.* 84.9 (2005), pp. 1235–1260.

[73] K. Morohaku. 'A way for in vitro/ex vivo egg production in mammals'. In: *J. Reprod. Dev.* 65.4 (2019), pp. 281–287.

[74] O. Ovaskainen, D. Finkelshtein, O. Kutoviy, S. Cornell, B. Bolker and Y. Kondratiev. 'A general mathematical framework for the analysis of spatiotemporal point processes'. In: *Theor. Ecol.* 7.1 (2014), pp. 101–113.

[75] B. Perthame. *Transport equations in biology*. en. Frontiers in Mathematics. Basel: Birkhäuser Basel, 2007.

[76] L. Popovic. 'Large deviations of Markov chains with multiple time-scales'. In: *Stoch. Process. Appl.* (2018).

[77] A. Pratap, K. Garner, M. Voliotis, K. Tsaneva-Atanasova and C. McArdle. 'Mathematical modeling of gonadotropin-releasing hormone signaling'. In: *Mol. Cell. Endocrinol.* 449 (2017), pp. 42–55.

[78] S. Prokopiou, L. Barbarroux, S. Bernard, J. Mafille, Y. Leverrier, J. Arpin C.and Marvel, O. Gandrillon and F. Crauste. 'Multiscale modeling of the early CD8 T-cell immune response in lymph nodes: An integrative study'. In: *Computation* 2.4 (2014), pp. 159–181.

[79] J. Ramsay, G. Hooker, D. Campbell and J. Cao. 'Parameter estimation for differential equations: a generalized smoothing approach'. In: *J. Roy. Statist. Soc. Ser. B* 69.5 (2007), pp. 741–796.

[80] S. Rao, A. Van der Schaft, K. Van Eunen, B. Bakker and B. Jayawardhana. 'A model reduction method for biochemical reaction networks'. In: *BMC Syst. Biol.* 8.1 (2014), p. 52.

[81] A. Raue, B. Steiert, M. Schelker, C. Kreutz, T. Maiwald, H. Hass, J. Vanlier, C. Tönsing, L. Adlung, R. Engesser, W. Mader, T. Heinemann, J. Hasenauer, M. Schilling, T. Höfer, E. Klipp, F. Theis, U. Klingmüller, B. Schöberl and J. Timmer. 'Data2Dynamics: A modeling environment tailored to parameter estimation in dynamical systems'. In: *Bioinformatics* 31.21 (2015), pp. 3558–3560.

[82] J. Starruß, W. de Back, L. Brusch and A. Deutsch. 'Morpheus: A user-friendly modeling environment for multiscale and multicellular systems biology'. In: *Bioinformatics* 30.9 (2014), pp. 1331–1332.

[83] R. Stein, V. Bucci, N. Toussaint, C. Buffie, G. Rätsch, E. Pamer, C. Sander and J. Xavier. 'Ecological modeling from time-series inference: insight into dynamics and stability of intestinal microbiota'. In: *PLoS Comput. Biol.* 9.12 (2013), e1003388.

[84] S. Xiao, J. Coppeta, H. Rogers, B. Isenberg, J. Zhu, S. Olalekan, K. McKinnon, D. Dokic, A. Rashedi, D. Haisenleder, S. Malpani, C. Arnold-Murray, K. Chen, M. Jiang, L. Bai, C. Nguyen, J. Zhang, M. Laronda, T. Hope, K. Maniar, M. Pavone, M. Avram, E. Sefton, S. Getsios, J. Burdette, J. Kim, J. Borenstein and T. Woodruff. 'A microfluidic culture model of the human reproductive tract and 28-day menstrual cycle'. In: *Nat. Commun.* 8 (2017), p. 14584.