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Project-Team MUSCA

MUltiSCAle population dynamics for physiological systems

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

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life Sciences

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Project-Team MUSCA

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1 Team members, visitors, external collaborators

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2 Overall objectives

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

3 Research program

3.1 General scientific positioning

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

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

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

We will deal with models representing dynamic networks, whether in a biochemical or ecological context. The mathematical formulation of these models involve Ordinary Differential Equations (ODE), Piecewise Deterministic Markov Processes (PDMP), or Continuous Time Markov Chains (CTMC). A prototypical example is the (mass-action) Chemical Reaction Network (CRN) [58], 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 [80, 53]. 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 [58, 52], 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 [19] 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 [74],[10] or in the framework of "pulse-modulated systems" [56].

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 [63]. 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 [64, 57] and stochastic context [47, 62, 73].

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 [13, 12] 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 [77], 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 [11] [26], using either existing state-of-the art deterministic derivative-based optimization [78] or global stochastic optimization [54]. 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 [66]. 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 [60] based on similarity criteria adapted to the problem under consideration, and an original inference method inspired by the Generalized Smoothing (GS) method proposed in [76], 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 [17] and long-time behavior [7], and the design of appropriate numerical schemes [1, 3] often rely on more or less generic techniques [72, 68] that we need to adapt in a case-by-case, model-dependent way: general relative entropy [69, 51], measure solution framework [61, 48, 55], martingale techniques [49], finite-volume numerical schemes [65], 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 [17]), or the formulation of particularly tricky boundary conditions [8]. 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 [71], dimensional reduction [6], timescale reduction [4], spatial homogenization [45][9], discrete to continuous reduction [8] and stochastic to deterministic limit theorems [14].

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 [59, 50], and theoretical studies of the inverse problems associated with the models [5] intend to preclude unidentifiable situations and ill-posed optimization problems. The generation and use of synthetic data (possibly noised simulation outputs) allow us to test the efficiency of optimization algorithms and to delimit an initial guess for the parameters. When reduced or simplified versions of the models are available (or derived specifically for calibration purposes) [2], these steps are implemented on the increasingly complex versions of the model. In situations where PDEs are or can be interpreted as limits of stochastic processes, it is sometimes possible to estimate parameters on the stochastic process trajectories, or to switch from one formalism to the other.

3.4 Coupling biochemical networks with cell and population dynamics

A major challenge for multiscale systems biology is to rigorously couple intracellular biochemical networks with physiological models (tissue and organic functions) [75, 46, 79, 67]. 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 [16].

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 [11]. 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 [15].

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 [18].

In reproductive physiology, there is currently a spectacular revival of experimental investigations (see e.g. [70, 81]), 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 (luteinizing hormone) and analysis of their rhythm. Visualisation, diagnostic and interactive correction of the detections.

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

Authors: Frederique Clement, Hande Gozukan, Christian Poli

Contact: Frederique Clement

6 New results

6.1 Stochastic modeling and stochastic processes

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

Participants: Guillaume Ballif, Frédérique Clément, Romain Yvinec.

We have analyzed a birth, migration and death stochastic process modeling the dynamics of a finite population, in which individuals transit unidirectionally across successive compartments [20]. The model is formulated as a continuous-time Markov chain, whose transition matrix involves multiscale effects;

the whole (or part of the) population affects the rates of individual birth, migration and death events. Using the slow-fast property of the model, we have proved the existence and uniqueness of the limit model in the framework of stochastic singular perturbations. The derivation of the limit model is based on compactness and coupling arguments. The uniqueness is handled by applying the ergodicity theory and studying a dedicated Poisson equation. The limit model consists of an ordinary-differential equation ruling the dynamics of the first (slow) compartment, coupled with a quasi-stationary distribution in the remaining (fast) compartments, which averages the contribution of the fast component of the Markov chain on the slow one. We have illustrated numerically the convergence, and highlighted the relevance of dealing with nonlinear event rates for our application in reproductive biology. The numerical simulations involve a simple integration scheme for the deterministic part, coupled with the nested algorithm to sample the quasi-stationary distribution.

6.1.2 Modeling the populations of ovarian follicles on a whole life scale

Participants: Guillaume Ballif, Frédérique Clément, Romain Yvinec.

We have designed a data-driven compartmental model of ovarian follicle development all along lifespan, in which the number of compartments is dictated by the developmental stages considered in the available experimental datasets on follicle numbers according to age. Following the framework introduced in [20], we account for the interactions between follicle stages by means of a nonlinear activation rate. We then settle a parameter estimation strategy using complementary information from KO mice in which the activation of quiescent follicles, corresponding to the first compartment, is unregulated. This model version is particularly suited for describing the follicle population after puberty in a compact way. In a next step, we have completed the original model to investigate more deeply follicle development in the prenatal period, at a time when the population of follicles is composed of two co-existing different subpopulations. We end up with an augmented state variable space with unchanged observable variables. We have performed a theoretical identifiability analysis and estimated the new parameter sets from a multi-objective criterion, including supplemental experimental information discriminating the two subpopulations.

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

Participants: Erwan Hingant, Romain Yvinec.

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 [30]. 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.

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

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

Human health and physiology are strongly influenced by interactions between human cells and intestinal microbiota in the gut. In mammals, the host-microbiota crosstalk is mainly mediated by

regulations at the intestinal crypt level: the epithelial cell turnover in the crypts is directly influenced by metabolites produced by the microbiota. Conversely, the colonocytes maintain hypoxia in the gut, favorable to anaerobic bacteria which dominate the gut microbiota. We have constructed an individual-based model of epithelial cells interacting with the microbiota-derived chemicals diffusing in the crypt lumen [43]. This model is formalized as a piecewise deterministic Markov process (PDMP). It accounts for local interactions due to cell contact (among which are mechanical interactions), for cell proliferation, differentiation and extrusion which are regulated spatially or by chemicals concentrations. It also includes chemicals diffusing and reacting with cells. A deterministic approximated model is also introduced.

6.1.5 Discrete to continuous models of coarsening: second order approximation

Participants: Léo Meyer, Magali Ribot, Romain Yvinec.

Motivated by a model of adipocyte cell size dynamics, we study the scaling limit from a discrete size coarsening model to a continuous one, namely from the Becker-Döring model to the Lifshitz-Slyozov. Specifically, we intend to derive a second order approximation that leads to a non linear Fokker-Planck equation. Our strategy to obtain a convergence result is to use a probabilistic interpretation of both models, using a suitable nonlinear Markov process whose law is given by the coarsening dynamics.

6.2 Deterministic modeling and model reduction

6.2.1 Input/output reduced model of a damped nonlinear beam based on Volterra series and modal decomposition with convergence results

Participants: Thomas Hélie, Béatrice Laroche.

We have dealt with the model reduction and the simulation of a damped Euler-Bernoulli-von Karman pinned beam excited by a distributed force [29]. This nonlinear problem is formulated as a PDE and reformulated as a well-posed state-space system. The model order reduction and simulation have been derived by combining two approaches: a Volterra series expansion and truncation and a pseudo-modal truncation defined from the eigenbasis of the linearized problem. The interest of this approach lies in the large class of input waveshapes that can be considered and in the simplicity of the simulation structure. This structure only involves cascades of finite-dimensional decoupled linear systems and multilinear functions. Closed-form bounds depending on the model coefficients and the truncation orders are provided for the Volterra convergence domain and the approximation error. These theoretical results have been generalized to a large class of nonlinear models, and refinement of bounds have also been proposed for a large sub-class. Numerical experiments confirm that the beam model is well approximated by the very first Volterra terms inside the convergence domain.

6.2.2 Modeling the growth of Staphylococcus aureus on cooked broccoli under isothermal conditions

Participants: Béatrice Laroche, and collaborators.

We have developed predictive models describing the growth of Staphylococcus aureus on cooked broccoli florets [31]. A pool of 3.5 log CFU/g of five S. aureus strains were inoculated on 10 g broccoli portions. The samples were then stored at 10, 20, 30 and 37 degrees C, and colonies were enumerated at different time intervals. Baranyi and Roberts model was fitted to the data using a Bayesian Adaptive Markov Chain Monte Carlo for estimation of the growth parameters. S. aureus showed low growth at 10 degrees C on broccoli samples and at 20-37 degrees C interval, Baranyi and Roberts model fitted well to the experimental data

(R-2>0.97). Estimated growth parameters were correlated with the possibility of toxin production and indicate the potential presence of these biological hazards on contaminated broccoli after heat treatment. Additionally, linear regression was performed for growth rate as storage temperature function. This secondary model followed a linear tendency with R-2=0.997 and was compared with two tertiary models (ComBase Predictor and Pathogen Modeling Program) and literature data, demonstrating similar growth rate values of both. These results can be helpful for food services and managers to establish food safety standards for S. aureus growth on cooked broccoli.

6.3 Exploration of signaling networks

6.3.1 Pharmacological characterization of low molecular weight biased agonists at the follicle stimulating hormone receptor

Participants: Pascale Crépieux, Frédéric Jean-Alphonse, Anne Poupon, Eric Reiter, Romain Yvinec, and collaborators.

Follicle-stimulating hormone receptor (FSHR) plays a key role in reproduction through the activation of multiple signaling pathways. Low molecular weight (LMW) ligands composed of biased agonist properties are highly valuable tools to decipher complex signaling mechanisms as they allow selective activation of discrete signaling cascades. However, available LMW FSHR ligands have not been fully characterized yet. In this context, we have explored the pharmacological diversity of three benzamide and two thiazolidinone derivatives compared to FSH [27]. Concentration/activity curves were generated for Gαs, Gαq, Gαi, β-arrestin 2 recruitment, and cAMP production, using BRET assays in living cells. ERK phosphorylation was analyzed by Western blotting, and CRE-dependent transcription was assessed using a luciferase reporter assay. All assays were done in either wild-type, Gαs or β-arrestin 1/2 CRISPR knockout HEK293 cells. Bias factors were calculated for each pair of read-outs by using the operational model. Our results have shown that each ligand presented a discrete pharmacological efficacy compared to FSH, ranging from super-agonist for β-arrestin 2 recruitment to pure Gαs bias. Interestingly, LMW ligands generated kinetic profiles distinct from FSH (i.e., faster, slower or transient, depending on the ligand) and correlated with CRE-dependent transcription. In addition, clear system biases were observed in cells depleted of either Gαs or β-arrestin genes. Such LMW properties are useful pharmacological tools to better dissect the multiple signaling pathways activated by FSHR and assess their relative contributions at the cellular and physio-pathological levels.

6.3.2 Spatial bias in cAMP generation determines biological responses to PTH type 1 receptor activation

Participants: Frédéric Jean-Alphonse, and collaborators.

The parathyroid hormone (PTH) type 1 receptor (PTHR) is a class B G protein–coupled receptor (GPCR) that regulates mineral ion, vitamin D, and bone homeostasis. Activation of the PTHR by PTH induces both transient cell surface and sustained endosomal cAMP production. To address whether the spatial (location) or temporal (duration) dimension of PTHR-induced cAMP encodes distinct biological outcomes, we have engineered a biased PTHR ligand (PTH7d) that elicits cAMP production at the plasma membrane but not at endosomes [37]. PTH7d stabilized a unique active PTHR conformation that mediated sustained cAMP signaling at the plasma membrane due to impaired β-arrestin coupling to the receptor. Experiments in cells and mice have revealed that sustained cAMP production by cell surface PTHR failed to mimic the pharmacological effects of sustained endosomal cAMP production on the abundance of the rate-limiting hydroxylase catalyzing the formation of active vitamin D, as well as increases in circulating active vitamin D and Ca2+ and in bone formation in mice. Thus, similar amounts of cAMP generated by PTHR for similar lengths of time in different cellular locations, plasma membrane and endosomes, mediate distinct physiological responses. These results unveil subcellular signaling location as a means

to achieve specificity in PTHR-mediated biological outcomes and raise the prospect of rational drug design based upon spatiotemporal manipulation of GPCR signaling.

6.3.3 In vitro effects of the endocrine disruptor p,p' DDT on human choriogonadotropin/luteinizing hormone receptor signalling

Participants: Eric Reiter, and collaborators.

Dichlorodiphenyltrichloroethane (p,p'DDT) is an endocrine-disrupting chemical (EDC). Several studies have shown an association between p,p' DDT exposure and reprotoxic effects. We have shown that p,p' DDT is a positive allosteric modulator of human follitropin receptor (FSHR). In contrast, we have demonstrated that p,p' DDT decreases the cyclic AMP (cAMP) production induced by human choriogonadotropin (hCG). We have evaluated further the effects of p,p' DDT on Gs-, β-arrestin 2- and steroidogenesis pathways induced by hCG or luteinizing hormone (LH) [33]. We used Chinese hamster ovary cells line stably expressing hCG/LHR. The effects of 10-100 μM p,p' DDT on cAMP production and on β-arrestin 2 recruitment were measured using bioluminescence and time-resolved resonance energy transfer technology. The impact of 100 μM of p,p' DDT on steroid secretion was analysed in murine Leydig tumor cell line (mLTC-1). In cAMP assays, 100 μM p,p' DDT increased the EC50 by more than 300% and reduced the maximum response of the hCG/LHR to hCG and hLH by 30%. This inhibitory effect was also found in human granulosa cells line and in mLTC-1 cells. Likewise, 100 μM p,p' DDT decreased the hCG- and hLH-promoted β-arrestin 2 recruitment down to 14.2 and 26.6%, respectively. Moreover, 100 μM p,p' DDT decreased by 30 and 47% the progesterone secretion induced by hCG or hLH, respectively, without affecting testosterone secretion. This negative effect of p,p' DDT was independent of cytotoxicity. p,p' DDT acted as a negative allosteric modulator of the hCG/LHR signalling. This emphasizes the importance of analyzing all receptor-downstream pathways to fully understand the deleterious effects of EDC on human health.

6.4 Computational modeling

6.4.1 Accurate determination of epitope for antibodies with unknown 3D structures

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

MAbTope is a docking-based method for the determination of epitopes. It has been used to successfully determine the epitopes of antibodies with known 3D structures. However, during the antibody discovery process, this structural information is rarely available. Although we already have evidence that homology models of antibodies could be used instead of their 3D structure, the choice of the template, the methodology for homology modeling and the resulting performance still have to be clarified. We have shown that MAbTope has the same performance when working with homology models of the antibodies as compared to crystallographic structures [35]. Moreover, we have shown that even low-quality models can be used. We applied MAbTope to determine the epitope of dupilumab, an anti-interleukin 4 receptor alpha subunit therapeutic antibody of unknown 3D structure, that we validated experimentally. Finally, we have shown how the MAbTope-determined epitopes for a series of antibodies targeting the same protein can be used to predict competitions, and demonstrated the accuracy with an experimentally validated example.

6.4.2 The RanBP2/RanGAP1-SUMO complex gates beta-arrestin2 nuclear entry to regulate the Mdm2-p53 signaling axis

Participants: Anne Poupon, and collaborators.

Mdm2 antagonizes the tumour suppressor p53. Targeting the Mdm2-p53 interaction represents an attractive approach for the treatment of cancers with functional p53. Investigating mechanisms underlying Mdm2-p53 regulation is therefore important. The scaffold protein β-arrestin2 (β-arr2) regulates tumour suppressor p53 by counteracting Mdm2. β-arr2 nucleocytoplasmic shuttling displaces Mdm2 from the nucleus to the cytoplasm resulting in enhanced p53 signalling. β-arr2 is constitutively exported from the nucleus, via a nuclear export signal, but mechanisms regulating its nuclear entry are not completely elucidated. β-arr2 can be SUMOylated, but no information is available on how SUMO may regulate β-arr2 nucleocytoplasmic shuttling. We have found β-arr2 SUMOylation to be dispensable for nuclear import, and identified a non-covalent interaction between SUMO and β-arr2, via a SUMO interaction motif (SIM), that is required for β-arr2 cytonuclear trafficking [21]. This SIM promotes association of β-arr2 with the multimolecular RanBP2/RanGAP1-SUMO nucleocytoplasmic transport hub that resides on the cytoplasmic filaments of the nuclear pore complex. Depletion of RanBP2/RanGAP1- SUMO levels result in defective β-arr2 nuclear entry. Mutation of the SIM inhibits β-arr2 nuclear import, its ability to delocalize Mdm2 from the nucleus to the cytoplasm and enhanced p53 signalling in lung and breast tumour cell lines. Thus, a β-arr2-SIM nuclear entry checkpoint, coupled with active β-arr2 nuclear export, regulate its cytonuclear trafficking function to control the Mdm2-p53 signalling axis.

6.4.3 Agonist anti-ChemR23 mAb reduces tissue neutrophil accumulation and triggers chronic inflammation resolution

Participants: Anne Poupon, and collaborators.

We have discovered an antibody targeting the ChemR23 receptor and performed pre-clinical tests to assess its effects [36]. This antibody is under development for the treatment of chronic inflammation. In the context of this study, we have predicted, and then experimentally validated the epitope of the antibody.

6.5 Bibliographic reviews

6.5.1 Physiologically Based Modeling of Food Digestion and Intestinal Microbiota: State of the Art and Future Challenges. An INFOGEST Review

Participants: Béatrice Laroche, and collaborators.

We have reviewed modeling methodologies of the gastrointestinal tract during digestion that have adopted a systems-view approach and, more particularly, on physiologically based compartmental models of food digestion and host-diet-microbiota interactions [32]. This type of modeling appears very promising for integrating the complex stream of mechanisms that must be considered and retrieving a full picture of the digestion process from mouth to colon. We may expect these approaches to become more and more accurate in the future and to serve as a useful means of understanding the physicochemical processes occurring in the gastrointestinal tract, interpreting postprandial in vivo data, making relevant predictions, and designing healthier foods. This review intends to provide a scientific and historical background of this field of research, before discussing the future challenges and potential benefits of the establishment of such a model to study and predict food digestion and absorption in humans.

6.5.2 Beta-arrestins, their mechanism of action and multiple roles in the biology of G protein-coupled receptors

Participants: Eric Reiter.

The stimulation of G protein-coupled receptors (GPCRs) induces biological responses to a wide range of extracellular cues. The heterotrimeric G proteins, which are recruited to the active conformation of GPCRs, lead to the generation of various diffusible second messengers. Only two other families of proteins exhibit the remarkable characteristic of recognizing and binding to the active conformation of most GPCRs: GPCR kinases (GRKs) and β-arrestins. These two families of proteins were initially identified as key players in the desensitization of G protein activation by GPCRs. Over the years, β-arrestins have been implicated in an increasing number of interactions with non-receptor proteins, expanding the range of cellular functions in which they are involved. It is now well established that β-arrestins, by scaffolding and recruiting protein complexes in an agonist-dependent manner, directly regulate the trafficking and signaling of GPCRs. In [34], we have reviewed the remarkable advances made in recent years, which have made it possible to i) identify biased ligands capable, by stabilizing particular conformations of a growing number of GPCRs, of activating or blocking the action of β-arrestins independently of that of G proteins, some of these ligands holding great therapeutic interest; ii) to demonstrate β-arrestins' role in the compartmentalization of GPCR signaling within the cell and iii) to understand the molecular details of their interaction with GPCRs and of their activation through structural and biophysical approaches.

6.5.3 Beta-arrestins and endocrine-related GPCRs

Participants: Pascale Crépieux, Frédéric Jean-Alphonse, Anne Poupon, Eric Reiter, Romain Yvinec, and collaborators.

G protein-coupled receptors (GPCRs) allow target cells to respond to a wide array of hormones. Mounting evidences point to GPCRs being functionally coupled to multiple transduction mechanisms, some of them not involving heterotrimeric G proteins. Among these emerging mechanisms, it has been well established that β-arrestins recruited to active GPCRs control not only their desensitization and internalization, but also assemble and activate signaling modules in different intracellular compartments. Importantly, β-arrestin-dependent transduction applies to most GPCRs, including those involved in endocrine mechanisms. This concept, in conjunction with remarkable advances made over the last decade in structural biology and biophysics of GPCRs, supports the notion of ligand-selective signaling also known as pharmacological bias. We have reviewed the role of β-arrestin recruitment in the signaling and trafficking of endocrine-related GPCRs [40]. We have also focused on biased ligands capable of selectively activating intracellular pathways downstream of endocrine-related GPCRs and discuss their potential therapeutic applications.

6.5.4 Confocal and TIRF microscopy based approaches to visualize arrestin trafficking in living cells

Participants: Frédéric Jean-Alphonse, Silvia Sposini.

Arrestins are key proteins that serve as versatile scaffolds to control and mediate G protein coupled receptors (GPCR) activity. Arrestin control of GPCR functions involves their recruitment from the cytosol to plasma membrane-localized GPCRs and to endosomal compartments, where they mediate internalization, sorting and signaling of GPCRs. Several methods can be used to monitor trafficking of arrestins; however, live fluorescence imaging remains the method of choice to both assess arrestin recruitment to ligand-activated receptors and to monitor its dynamic subcellular localization. We have presented two approaches based on Total Internal Fluorescence (TIRF) microscopy and confocal microscopy to visualize arrestin trafficking in live cells in real time and to assess their co-localization with the GPCR of interest and their localization at specific subcellular locations [41].

6.5.5 Receptors | Thyroid-Stimulating Hormone/Luteinizing Hormone/Follicle-Stimulating Hormone Receptors

Participants: Pascale Crépieux, Yves Combarnous, Eric Reiter.

We have reviewed the signaling of the thyroid-stimulating hormone receptor (TSHR), luteinizing hormone receptor (LHCGR, and follicle-stimulating hormone receptor (FSHR), which are collectively referred to as the glycoprotein hormone receptors because they bind structurally similar glycoprotein hormones [39]. The glycoprotein hormones consist of the pituitary thyroid-stimulating hormone (thyrotropin, TSH), luteinizing hormone (lutropin, LH), and follicle-stimulating hormone (follitropin, FSH) as well as the chorionic gonadotropin (choriogonadotropin, CG) placental hormone. The glycoprotein hormones are each composed of two dissimilar subunits (α and β) that are noncovalently associated. Within a given species, the α-subunit is identical and the β-subunits are distinct but homologous. Due to the largely similar nature of LHβ and CGβ, the LHCGR binds either LH or CG. The binding specificity of LH/CG to the LHCGR, FSH to the FSHR, and TSH to the TSHR is fairly strict. However, in some cases, extremely high levels of hormone can cause activation of the inappropriate receptor. Because the LHCGR and FSHR are localized primarily to the gonads, these two receptors are also referred to as the gonadotropin receptors. The glycoprotein hormone receptors belong to the family A (rhodopsin-like) of G protein-coupled receptors (GPCRs). However, they share the relatively unique feature of having a large extracellular domain that mediates high affinity binding of the hormone. In spite of their different physiological roles, the glycoprotein hormone receptors share a similar structural organization and mechanism of action.

6.5.6 Reduced FSH and LH action: implications for medically assisted reproduction

Participants: Pascale Crépieux, and collaborators.

Impairment of the production or action of gonadotropins causes relative or absolute LH and FSH deficiency that compromises gametogenesis and gonadal steroid production, thereby reducing fertility. In women, LH and FSH deficiency is a spectrum of conditions with different functional or organic causes that are characterized by low or normal gonadotropin levels and low oestradiol levels. While the causes and effects of reduced LH and FSH production are well known, the notion of reduced action has received less attention by researchers. Recent evidence show that ageing and some polymorphisms negatively affect gonadotropin action. These findings have important clinical implications, in particular for medically assisted reproduction in which diminished action determined by the aforementioned factors, combined with reduced endogenous gonadotropin production caused by GnRH analogue protocols, may lead to resistance to gonadotropins and, thus, to an unexpected hypo-response to ovarian stimulation. Indeed, the importance of LH and FSH action has been highlighted by the International Committee for Monitoring Assisted Reproduction Technologies (ICMART) in their definition of hypogonadotropic hypogonadism as gonadal failure associated with reduced gametogenesis and gonadal steroid production due to reduced gonadotropin production or action. In this review [22], we provide an overview of determinants of reduced FSH and LH action that are associated with a reduced response to ovarian stimulation.

7 Partnerships and cooperations

7.1 International initiatives

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

ANACONDA

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

Duration: 2021 ->

Coordinators: Romain Yvinec and Mauricio Sepúlveda Cortés

Partners:

- Universidad del Bío-Bío, Concepción, Chile
- Inria Chile

Inria contact: Romain Yvinec

Summary: The formalism at the heart of our research program is that of structured population dynamics, which are well-suited for describing multicellular dynamics in a compact way. The standard workflow in biological modeling of such objects starts with an individual-based stochastic formalism, specially relevant to represent cellular process such as growth, aging, division and apoptosis. The complexity of both the mathematical and numerical analysis of these stochastic models calls for the use of reduced models, among which partial differential equations (PDEs) of conservation law type are a good intermediate choice, and can be obtained from stochastic models by appropriate functional law of large numbers. The expected added value of the associate team will be to perform the theoretical analysis of PDE models, to design adapted numerical schemes and, whenever relevant, innovative inverse problems strategies, and to apply them in a synergistic way to various cell biology processes. Two main directions will be investigated thanks to the complementarity of the partners: scalar conservation laws and coarsening dynamics for cellular growth processes (WP1), and moving/free-boundary problems for multicellular morphodynamics (WP2).

See also https://team.inria.fr/musca/anaconda/

7.1.2 Participation in other International Programs

- ECOS SUD-CHILI 2020 : ECOS n° C20E03, “Coarsening dynamics: numerical and theoretical analysis of the Lifshitz-Slyozov equation with nucleation and applications to biology.” PIs: R. Yvinec and M. Sepúlveda (Universidad del Bío-Bío, Chile).
- i-GPCRNet, International Research Network (IRN) on GPCRs, http://www.i-gpcrnet.com/
- Bill & Melinda Gates Foundation, ContraBody (2021-2023, PI Eric Reiter, 1.8 M US $) “Non-Hormonal Contraception by Nanobody Produced from Within the Body”. In partnership with University of Modena E Regio Emilia, Italy; MabSilico, France and InCellArt, France. Involved MUSCA members : E. Reiter, P. Crépieux, F. Jean-Alphonse, R. Yvinec.
- Medical Research Council, MICA(2022-2025, PI (Investigating kisspeptin receptor signalling to improve the treatment of reproductive disease), Involved MUSCA members : E. Reiter

7.1.3 Visits to international teams

Research stays abroad Since mid-October, Guillaume Ballif has been visiting Lea Popovic in Concordia University (Montréal, Québec), for a four month stay, in the framework of the “Programme Visibilité Scientifique Junior" of Fondation Mathématique Jacques Hadamard.

7.2 European initiatives

7.2.1 FP7 & H2020 Projects

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

7.3 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 Vincent Aucagne, 497 K€) “Mirror Image Nanobodies: pushing forward the potential of enantiomeric proteins for therapeutic and pharmacological applications”. Involved MUSCA member: E. Reiter.
- ANR PHEROSENSOR (2021-2026, PI Philippe Lucas 1492K€) “Early detection of pest insects using pheromone receptor-based olfactory sensors”. Involved MUSCA member: B. Laroche.
- LabEx MAbImprove (2011-2025, PI Hervé Watier). Involved MUSCA members : E. Reiter, F. Jean-Alphonse, P. Crépieux, A. Poupon, R. Yvinec.
- INRAE metaprogram HOLOFLUX, Egg-to-Meat project (2020-2022, PI Monique Zagorec). Involved MUSCA member: B. Laroche.
- INRAE metaprogram DIGIT-BIO; IMMO project (2021-2024, PI Violette Thermes), “IMagerie et MOdélisation multi-échelles pour la compréhension de la dynamique ovarienne chez le poisson”. Involved MUSCA members: F. Clément, R. Yvinec.
- ANSES GinFiz project (2021-2024, PI Rémy Beaudouin), “Gonadal aromatase inhibition and other toxicity pathways leading to Fecundity Inhibition in Zebrafish: from initiating events to population impacts”. Involved MUSCA members: F.Clément, R. Yvinec.

7.4 Regional initiatives

- SATT Paris-Saclay POC’UP 2020 project COOPERATE, awarded to B. Laroche (together with L. Rigottier, P. Serror, V. Loux and O. Rué): “COnsortium de bactéries cOmmensales pour augmenter l’effet barrière du microbiote et limiter la Persistance et la prolifération des Entérocoques Résistants à la vancomycine après traitement AnTibiotiquE”.
- Ambition recherche développement Centre Val de Loire SELMAT (2020-2023, PI E. Reiter, 630 K€) “Méthodes in silico pour la sélection et la maturation d’anticorps : développement, validation et application à différentes cibles thérapeutiques”. Involved MUSCA members: E. Reiter, P. Crépieux, F. Jean-Alphonse, R. Yvinec.
- Appel à projet région Centre Val de Loire, INTACT (2019-2022, 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

F. Clément (together with Geneviève Dupont and Laurent Combettes),“Spatio-temporal encoding and decoding in cell signaling”, ITMO BCDE symposium, March 18, online (chair, organizing and scientific committee)

F. Clément (together with Joelle Cohen-Tannoudji, Yves Combarnous, Florian Guillou, Sakina Mhaouty-Kodja, and François Vialard), ReproSciences 2021, April 12-14, online (chair and scientific committee)

- A. Poupon, 9th Antibody Industrial Symposium, June 22-25, online (chair)

8.1.2 Scientific events: selection

F. Clément,"Spatio-temporal encoding and decoding in cell signaling", ITMO BCDE symposium, March 18, online

8.1.3 Journal

Member of the editorial boards

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

P. Crépieux, associate editor Front. Endocrinol. (cellular endocrinology)

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

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

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

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

Reviewer - reviewing activities

F. Clément, J. Theor. Biol.

P. Crépieux, Mol. Cell. Endocrinol., Reproduction, Reprod. Sci.

F. Jean-Alphonse, Proc. Natl. Acad. Sci. USA

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

E. Reiter, J. Clin. Endocrinol. Metab., Front. Endocrinol., Sci. Rep., Mol. Cell. Endocrinol., Endocrinology, Proc. Natl. Acad. Sci. USA, eLife, Science, Nature Comm.

R. Yvinec, J. Math. Biol., J. Theor. Biol

8.1.4 Invited talks

B. Laroche. Workshop "Mathématiques et Microbiote", Besançon, November 8-9.

E. Reiter. ITMO BCDE symposium on Spatio-temporal encoding and decoding in cell signaling, March 18.

E. Reiter. Société de Biologie, June 22

E. Reiter. Aging Pituitary Gonadal Axis Spring Retreat, June 28.

E. Reiter. Society for the Study of Reproduction meeting, July 28.

E. Reiter. Bill & Melinda Gates Foundation, Nonhomonal Contraceptive Discovery Program Meeting, May 20.

R. Yvinec. Mapping group online symposium, European Research Network on Signal Transduction, COST ACTION CA 18133, December 15.

8.1.5 Leadership within the scientific community

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. 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, member of scientific board of PIXANIM (Phénotypage par Imagerie in/eX vivo de l'ANImal à la Molécule)

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

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

F. Jean-Alphonse, guest researcher at Le Studium

F. Jean-Alphonse, member of the Young investigator comittee of the International Research Network (IRN)

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

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

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

8.1.6 Scientific expertise

B. Laroche, member of the jury for the recruitment of a contractual lecturer at CentraleSupélec

B. Laroche, member of the jury for the recruitment of a junior scientist at INRAE

A. Poupon, member of the jury for the recruitment of a professor of mathematics at University of Tours

A. Poupon, member of the jury for the recruitment of a research engineer at INRAE

A. Poupon, member of the jury for the recruitment of a technician in IT at INRAE

8.1.7 Research administration

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

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

B. Laroche is 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

F. Clément has participated in the preparation of a data challenge on automatic ovarian follicle detection, in the framework of the data camp of Master program Data Science Institut Polytechnique de Paris (PI Alexandre Gramfort, collaboration François Caud, Céline Guigon, Raphaël Corre)

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

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

P. Crépieux, Master Physiopathology (2h)

M. Haghebaert, Introduction to programming, first-year Ecole Nationale des Ponts et Chaussées (30h)

L. Meyer, L1 Mathématiques, Université d'Orléans, algebra (18h)

L. Meyer L2 Informatiques, Université d'Orléans, probabilities (22h)

L. Meyer L3 Mathématiques, Université d'Orléans, numerical tools (24h)

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

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

8.2.2 Supervision

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: Juliette Gourdon "Manipulation of the intracellular traffic and endosomal signaling of gonadotropin receptors, LH/CGR and FSHR, by nanobodies: deciphering the molecular mechanisms and the consequences on reproduction", started October 2021, supervisors: E. Reiter and F. Jean-Alphonse)

PhD in progress: Marie Haghebaer, "Tools and methods for 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

- P. Crépieux, HDR Jury of Mathilde Munier (referee), Université d'Angers, October 4
- P. Crépieux, PhD Jury of Myriam Guillien (referee), Université de Montpellier, December 14
- P. Crépieux, PhD Jury of Alexey Koshkin (referee and president), Université de Lyon, December 16
- B. Laroche, HDR Jury of Annabelle Ballesta (referee), Université Paris Saclay, June 18

- B. Laroche, PhD Jury of Lou Zonca (referee), Sorbonne Université, July 16
- B. Laroche (referee), PhD Jury of Arthur Carcano, Université de Paris, December 13

8.3 Popularization

8.3.1 Articles and contents

F. Jean-Alphonse. Des anticorps de lama pour contrôler la reproduction. CNRS MICROSCOOP (publication scheduled in 2022 first term)

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.

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[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.

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