Activity Report 2017

Project-Team MYCENAE

Multiscale dYnamiCs in neuroENdocrine AxEs

RESEARCH CENTER
Paris

THEME
Modeling and Control for Life Sciences

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Project-Team MYCENAE

Creation of the Project-Team: 2014 January 01, end of the Project-Team: 2017 December 31

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Computer Science and Digital Science:

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A6.1.2. - Stochastic Modeling (SPDE, SDE)
A6.1.3. - Discrete Modeling (multi-agent, people centered)
A6.1.4. - Multiscale modeling
A6.2.1. - Numerical analysis of PDE and ODE
A6.2.3. - Probabilistic methods
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A6.3.4. - Model reduction

Other Research Topics and Application Domains:

B1.1.3. - Cellular biology
B1.1.4. - Developmental biology
B1.1.10. - Mathematical biology
B1.2.1. - Understanding and simulation of the brain and the nervous system
B2.2.2. - Nervous system and endocrinology

1. Personnel

Research Scientists

Frédérique Clément [Team leader, Inria, Senior Researcher, HDR]
Jonathan Touboul [Inria, Researcher, detached from Corps des Mines, HDR, until Apr 2017]

PhD Students

Richard Bailleul [CIRB,until Apr 2017]
Yi Cui [UPMC,until Apr 2017]
Frédérique Robin [Inria]

Intern

Matthieu Perez [Inria, from Apr 2017 until Sep 2017]

Administrative Assistant

Martine Verneuille [Inria]

External Collaborators

Jean-Pierre Françoise [Univ Pierre et Marie Curie]
Marie Postel [Univ Pierre et Marie Curie]
Alexandre Vidal [Univ d'Evry Val d'Essonne]

2. Overall Objectives

2.1. Overall Objectives

MYCENAE (Multiscale dYnamiCs in neuroENdocrine AxEs) is a project-team dedicated to mathematical neuroendocrinology and mathematical neuroscience. We are interested in the modeling, analysis and simulation of multiscale in time and/or space dynamics in the fields of neuroscience, endocrinology and physiology. Our main research topics are the followings:

- Numerical and theoretical studies of slow-fast systems with complex oscillations
- Non conservative transport equations for cell population dynamics
- Macroscopic limits of stochastic neural networks and neural fields

3. Research Program

3.1. Project team positioning

The main goal of MYCENAE is to address crucial questions arising from both Neuroendocrinology and Neuroscience from a mathematical perspective. The choice and subsequent study of appropriate mathematical formalisms to investigate these dynamics is at the core of MYCENAE's scientific foundations: slow-fast dynamical systems with multiple time scales, mean-field approaches subject to limit-size and stochastic effects, transport-like partial differential equations (PDE) and stochastic individual based models (SIBM).

The scientific positioning of MYCENAE is on the way between Mathematical Biology and Mathematics: we are involved both in the modeling of physiological processes and in the deep mathematical analysis of models, whether they be (i) models developed (or under development) within the team (ii) models developed by collaborating teams or (iii) benchmark models from the literature.

Our research program is grounded on previous results obtained in the framework of the REGATE (REgulation of the GonAdoTropE axis) Large Scale Initiative Action and the SISYPHE project team on the one hand, and the Mathematical Neuroscience Team in the Center for Interdisciplinary Research in Biology (Collège de France), on the other hand. Several of our research topics are related to the study and generalization of 2 master models: a 4D, multiscale in time, nonlinear model based on coupled FitzHugh-Nagumo dynamics that has proved to be a fruitful basis for the study of the complex oscillations in hypothalamic GnRH dynamics [27], [26], and a nD, multiscale in space, system of weakly-coupled non conservative transport equations that underlies our approach of gonadal cell dynamics [28],[8]. Most our topics in mathematical neuroscience deal with the study of complex oscillatory behaviors exhibited either by single neurons or as emergent macroscopic properties of neural networks, from both a deterministic and stochastic viewpoint.

3.2. Numerical and theoretical studies of slow-fast systems with complex oscillations

In dynamical systems with at least three state variables, the presence of different time scales favors the appearance of complex oscillatory solutions. In this context, with (at least) two slow variables MixedMode Oscillations (MMO) dynamics can arise. MMOs are small and large amplitude oscillations combined in a single time series. The last decade has witnessed a significant amount of research on this topic, including studies of folded singularities, construction of MMOs using folded singularities in combination with global dynamics, effects of additional time scales, onset of MMOs via singular Hopf bifurcations, as well as generalization to higher dimensions. In the same period, many applications to neuroscience emerged [9]. On the other hand, bursting oscillations, another prototype of complex oscillations can occur in systems with (at least) two fast variables. Bursting has been observed in many biological contexts, in particular in the dynamics of pancreatic cells, neurons, and other excitable cells. In neuronal dynamics a burst corresponds to a series

of spikes, interspersed with periods of quiescent behavior, called inter-burst intervals. We are interested in systems combining bursting, MMOs and canards. One of the interesting directions is torus canards, which are canard-like structures occurring in systems combining canard explosion with fast rotation [5]. Torus canards help understand transitions from spiking or MMO dynamics to bursting. Another study on the boundary of bursting and MMOs is the work of [36] on the so-called plateau bursting. A major challenge in this direction is to gain a complete understanding of the transition from "3 time scales" to "2 fast/ 1 slow" (bursting) and then to "1 fast/ 2 slow (MMOs)". Also, a key challenge that we intend to tackle in the next few years is that of large dynamical systems with many fast and many slow variables, which additionally are changing in time and/or in phase space. We aim to pursue this research direction both at theoretical and computational level, using numerical continuation approaches based on the location of unstable trajectories by using fixed point methods, rather than simulation, to locate trajectories.

3.3. Non conservative transport equations for cell population dynamics

Models for physiologically-structured populations can be considered to derive from the so-called McKendrick-Von Foerster equation or renewal equation that has been applied and generalized in different applications of population dynamics, including ecology, epidemiology and cell biology. Renewal equations are PDE transport equations that are written so as to combine conservation laws (e.g. on the total number of individuals) with additional terms related to death or maturation, that blur the underlying overall balance law [33]. Renewal equations can be deployed only in contexts where a deterministic and continuous formalization is suitable to describe the populations. In the case of low or very low number of individuals, the probabilistic nature of the events driving the population dynamics has to be accounted for. In that context, the formalism initially developed in the framework of ecological modeling (see e.g. [30]) is particularly interesting since it can bridge the gap between branching processes and renewal equations for structured populations.

The development of ovarian follicles is a tightly-controlled physiological and morphogenetic process, that can be investigated from a middle-out approach starting at the cell level.

To describe the terminal stages of follicular development on a cell kinetics basis and account for the selection process operated amongst follicles, we have developed a multiscale model describing the cell density in each follicle, that can be roughly considered as a system of weakly-coupled, non conservative transport equations with controlled velocities and source term. Even if, in some sense, this model belongs to the class of renewal equations for structured populations, it owns a number of specificities that render its theoretical and numerical analysis particularly challenging: 2 structuring variables (per follicle, leading as a whole to $2n$D system), control terms operating on the velocities and source term, and formulated from moments of the unknowns, discontinuities both in the velocities and density on internal boundaries of the domain representing the passage from one cell phase to another. On the theoretical ground, the well-posedness (existence and uniqueness of weak solutions with bounded initial data) has been established in [12], while associated control problems have been studied in the framework of hybrid optimal control [6]. On the numerical ground, the formalism dedicated to the simulation of these hyperbolic-like PDEs is that of finite volume method. Part of the numerical strategy consists in combining in the most efficient way low resolution numerical schemes (such as the first-order Godunov scheme), that tend to be diffusive, with high resolution schemes (such as the Lax Wendroff second-order scheme), that may engender oscillations in the vicinity of discontinuities [2], with a critical choice of the limiter functions. The 2D finite volume schemes are combined with adaptive mesh refinement through a multi-resolution method [4] and implemented in a problem-specific way on parallel architecture [1].

To describe the first stages of follicular development, which only involve a few cells, we call to a stochastic and discrete formalism. We have designed an individual-based, stochastic model [7] embedding specific laws of morphodynamics, which leads to a multiscale model where individual cells are endowed with a non-zero size and occupy space partitions of predefined sizes, which can bear a limit rate of overcrowding.

3.4. Macroscopic limits of stochastic neural networks and neural fields

The coordinated activity of the cortex is the result of the interactions between a very large number of cells. Each cell is well described by a dynamical system, that receives non constant input which is the superposition

of an external stimulus, noise and interactions with other cells. Most models describing the emergent behavior arising from the interaction of neurons in large-scale networks have relied on continuum limits ever since the seminal work of Wilson and Cowan and Amari [37], [25]. Such models tend to represent the activity of the network through a macroscopic variable, the population-averaged firing rate.

In order to rationally describe neural fields and more generally large cortical assemblies, one should yet base their approach on what is known of the microscopic neuronal dynamics. At this scale, the equation of the activity is a set of stochastic differential equations in interaction. Obtaining the equations of evolution of the effective mean-field from microscopic dynamics is a very complex problem which belongs to statistical physics. As in the case of the kinetic theory of gases, macroscopic states are defined by the limit of certain quantities as the network size tends to infinity. When such a limit theorem is proved, one can be ensured that large networks are well approximated by the obtained macroscopic system. Qualitative distinctions between the macroscopic limit and finite-sized networks (finite-size effects), occurs in such systems. We have been interested in the relevant mathematical approaches dealing with macroscopic limits of stochastic neuronal networks, that are expressed in the form of a complex integro-differential stochastic implicit equations of McKean-Vlasov type including a new mathematical object, the spatially chaotic Brownian motion [15].

The major question consists in establishing the fundamental laws of the collective behaviors cortical assemblies in a number of contexts motivated by neuroscience, such as communication delays between cells [14], [13] or spatially extended areas, which is the main topic of our current research. In that case additional difficulties arise, since the connection between different neurons, as well as delays in communications, depend on space in a correlated way, leading to the singular dependence of the solutions in space, which is not measurable.

4. Application Domains

4.1. Introduction

MYCENAE addresses rather “upstream” questions in neuroendocrinology and neuroscience. Nevertheless, MYCENAE’s expected results can contribute to more applied issues in these fields, mainly by helping understand the mechanisms underlying physiological and pathological processes and also by designing new concepts for biomedical data analysis. MYCENAE thematics are related to societal issues concerning endocrine disruptors, reproductive biotechnologies, and neurological diseases, especially in case of pathological synchronizations encountered in epilepsy and Parkinson’s disease.

4.2. Neuroendocrinology and Neuroscience

We are interested in the complex dynamical processes arising within neuroendocrine axes, with a special focus on the reproductive (hypothalamo-pituitary-gonadal) axis. This axis can be considered as the paragon of neuroendocrine axes, since it both concentrates all remarkable dynamics that can be exhibited by these axes and owns its unique specificities, as gonads are the only organs that host germ cells. Since, in neuroendocrine axes, neural systems are embedded within endocrine feedback loops and interact with peripheral organs, one also needs to get interested in the peripheral dynamics to be able to “close the loop” and account for the effect of peripheral inputs on neural dynamics. In the case of the HPG axis, these dynamics are especially complex, because they involve developmental processes that occur even in adult organisms and combine the glandular function of the gonads with their gametogenic function.

Neuroendocrinology is thus a scientific field at the interface between Neuroscience, Endocrinology and Physiology (and even of Developmental Biology in the case of the HPG axis). On a neuroscience ground, mathematical neuroendocrinology is specifically interested in endocrine neurons, which have the uncommon ability of secreting neurohormones into the blood stream. Neuroendocrine networks are characterized by the emergence of very slow rhythms (on the order of an hour), finite size effects due to their relative small number of neurons (on the order of a few thousands for the Gonadotropin-Releasing-Hormone network)

and neuroanatomical particularities, that impact the way they can synchronize and desynchronize. On a physiological ground, gonadal cell biology raises specific cell biology issues on more than one account. First, the gonads are the only organs sheltering the germ cell lines (corresponding to oogenesis in ovaries and spermatogenesis in testes). Hence, the two modes of cell division, mitosis and meiosis are encountered in these tissues. Second, there are intricate interactions between the gonadal somatic cells (granulosa cells in the ovaries, sertoli cells in the testes) and the germ cells. Third, the control of gonadal cell populations is exerted within endocrine feedback loops involving both the hypothalamus and pituitary, which results naturally in multiscale population dynamics coupled with hormonally-controlled cell kinetics.

MYCENAE's research topics in mathematical neuroscience deal with complex oscillations, synchronization and plasticity.

We study (i) the emergence of network-level behaviors from individual dynamics of excitable cells (mainly neurons, but not exclusively, as the pituitary cells belong to the family of excitable cells): complete synchronization or synchronization of specific events, effect of the recruitment rate in the synchronization process, dependence on the neuro-anatomical and functional coupling properties; (ii) the control of the different possible configurations of the network depending on external (e.g. daylength) and/or internal inputs (e.g. metabolic status), at the source of plasticity processes in cognitive (vision learning) or neuroendocrine systems (differential sensitivity to gonadal steroids and peptides across the different steps of the reproductive life); (iii) the encoding of neuro-hormonal signals as complex oscillations, on the electrical, ionic (calcium dynamics) and secretory levels; and (iv) the decoding of these signals by their target neuronal or non-neuronal cells.

More recently, we have been interested into developmental biology issues in neurosciences: neurogenesis and brain development. The anatomical and functional organization of the nervous system, and especially the brain, is highly structured and tightly regulated. The surface of the cortex, its thickness, but also the size and shape of the brain areas associated to the different sensory or motor areas are very reliable quantities across different individuals. In collaboration with different teams of biologists, we develop and investigate models of the development of the brain, at different time and spatial scale.

The biological relevance of our modeling and model-based signal analysis approaches is grounded on our network of collaborations with teams of experimentalist biologists. In particular, we have long standing collaborations with the UMR 6175 (INRA-CNRS-Université François Rabelais-Haras Nationaux) "Physiologie de la Reproduction et des Comportements" that covers most our research topics in reproductive neuroendocrinology. We have especially close links with the Bingo (Integrative Biology of the ovary) and Bios (Biology and Bioinformatics of Signaling Systems) teams, which were partners of the REGATE LSIA. We have been jointly investigating issues relative to terminal or basal follicular development [7], [8], analysis of neurosecretory patterns [16] and modeling of GPCR (G-Protein Coupled Receptors) signaling networks [10]. We also have special links with the Center for Interdisciplinary Research in Biology (CIRB, Collège de France), headed by Alain Prochiantz, that help us get a better understanding of how the brain connectivity develops and how it is functionally organized. An instance of a recent collaborative work is the study of the organization of spatial frequencies in the primary visual cortex [34].

5. Highlights of the Year

5.1. Highlights of the Year

- We have completed in [17] our series of studies [8], [12], [6], [2], [4], [3] on the mathematical and numerical analysis of our multiscale model of structured cell populations in terminally developing ovarian follicles.
- We have completed in [19] our series of studies [27], [26], [35], [29], [32] on the mathematical and numerical analysis of our model of GnRH pulse and surge generator.

6. New Software and Platforms

6.1. DynPeak

KEYWORDS: Biology - Health - Physiology
SCIENTIFIC DESCRIPTION: DynPeak is an algorithm for pulse detection and frequency analysis in hormonal time series.

- Participants: Alexandre Vidal, Claire Médigue, Frédérique Clément, George Rosca, Qinghua Zhang and Serge Steer
- Partner: INRA
- Contact: Frédérique Clément
- URL: https://team.inria.fr/mycenae/en/software/

7. New Results

7.1. Numerical and theoretical studies of slow-fast systems with complex oscillations

7.1.1. Coupled multiple timescale dynamics in populations of endocrine neurons: Pulsatile and surge patterns of GnRH secretion

Participants: Elif Köksal Ersöz, Alexandre Vidal, Frédérique Clément.

We have finalized the study of a 6D extension of our model of GnRH pulse and surge generator, which has now been published [19]. The gonadotropin releasing hormone (GnRH) is secreted by hypothalamic neurons into the pituitary portal blood in a pulsatile manner. The alternation between a frequency-modulated pulsatile regime and the ovulatory surge is the hallmark of the GnRH secretion pattern in ovarian cycles of female mammals. In this work, we aimed at modeling additional features of the GnRH secretion pattern: the possible occurrence of a two-bump surge ("camel surge") and an episode of partial desynchronization before the surge. We have proposed a six-dimensional extension of a former four-dimensional model with three timescale and introduced two mutually-coupled, slightly heterogenous GnRH subpopulations (secretors) regulated by the same slow oscillator (regulator). We have considered two types of coupling functions between the secretors, including dynamic state-dependent coupling, and we have used numerical and analytic tools to characterize the coupling parameter values leading to the generation of a two-bump surge in both coupling cases. We have revealed the impact of the slowly varying control exerted by the regulator onto the pulsatile dynamics of the secretors, which leads to dynamic bifurcations and gives rise to desynchronization. To assess the occurrence time of desynchronization during the pulsatile phase, we have introduced asymptotic tools based on quasi-static and geometric approaches, as well as analytic tools based on the H-function derived from phase equation and numerical tracking of period-doubling bifurcations. We discuss the role of coupling parameters in the two-bump surge generation and the speed of desynchronization.

7.1.2. Wild oscillations in a nonlinear neuron model with resets

Participants: Jonathan Rubin [University of Pittsburgh], Justyna Signerska-Rynkowska, Jonathan Touboul, Alexandre Vidal.

We have finalized the work undergone in a series of two studies, where we have investigated the mechanisms by which complex oscillations are generated in a class of nonlinear dynamical systems with resets modeling the voltage and adaptation of neurons. These studies have been published as a two-part article [21], [22].

The first study [21] presents a mathematical analysis showing that the system can support bursts of any period as a function of model parameters, and that are organized in a period-incrementing structure. In continuous dynamical systems with resets, such period-incrementing structures are complex to analyze. In the present context, we have used the fact that bursting patterns correspond to periodic orbits of the adaptation map that governs the sequence of values of the adaptation variable at the resets. Using a slow-fast approach, we have shown that this map converges towards a piecewise linear discontinuous map whose orbits are exactly characterized. That map shows a period-incrementing structure with instantaneous transitions. We have further shown that the period-incrementing structure persists for the full system with non-constant adaptation, yet the transitions are more complex. We have also established the presence of chaos at the transitions.

The second study [22] shows that these neuron models can generically display a form of mixed-mode oscillations (MMOs), which are trajectories featuring an alternation of small oscillations with spikes or bursts (multiple consecutive spikes). The mechanism by which these are generated relies fundamentally on the hybrid structure of the flow: invariant manifolds of the continuous dynamics govern small oscillations, while discrete resets govern the emission of spikes or bursts, contrasting with classical MMO mechanisms in ordinary differential equations involving more than three dimensions and generally relying on a timescale separation. The decomposition of mechanisms reveals the geometrical origin of MMOs, allowing a relatively simple classification of points on the reset manifold associated to specific numbers of small oscillations. We have shown that the MMO pattern can be described through the study of orbits of a discrete adaptation map, which is singular as it features discrete discontinuities with unbounded left- and right-derivatives. We have studied the orbits of the map via rotation theory for circle maps and elucidated in detail complex behaviors arising in the case where MMOs display a single small oscillation per cycle.

7.1.3. Studies of the Petrov module for a family of generalized Liénard integrable systems

Participants: Lucile Megret [UPMC], Jean-Pierre Françoise [UPMC].

In [20], we have used the Lambert function in order to study a family of integrable generalized Liénard equations X_f which display a center. We have first proven a conjugation lemma inside a continuum of nested periodic orbits. Then we have deduced an explicit operator of Gelfand-Leray associated with the Hamiltonian of equation X_f. Afterwards, we have provided a generating family for the associated Petrov module. Finally, by using the Lambert function, we have studied the monotonicity of the Abelian integral of this generating family's elements.

7.2. Non conservative transport equations for cell population dynamics

7.2.1. Dimensional reduction of a multiscale model based on long time asymptotics

Participants: Frédérique Clément, Frédéric Coquel [CMAP], Marie Postel, Kim Long Tran.

We have finalized the study on the dimensional reduction of our multiscale model of terminal follicle development, which has now been published [17]. We have considered a class of kinetic models for which a moment equation has a natural interpretation. We have shown that, depending on their velocity field, some models lead to moment equations that enable one to compute monokinetic solutions economically. We have detailed the example of a multiscale structured cell population model, consisting of a system of 2D transport equations. The reduced model, a system of 1D transport equations, is obtained from computing the moments of the 2D model with respect to one variable. The 1D solution is defined from the solution of the 2D model starting from an initial condition that is a Dirac mass in the direction removed by reduction. For arbitrary initial conditions, we have compared 1D and 2D model solutions in asymptotically large time. Finite volume numerical approximations of the 1D reduced model can be used to compute the moments of the 2D solution with proper accuracy, both in the conservative and non conservative framework. The numerical robustness is studied in the scalar case, and a full scale vector case is presented.

7.2.2. Analysis and calibration of a linear model for structured cell populations with unidirectional motion : application to the morphogenesis of ovarian follicles

Participants: Frédérique Clément, Frédérique Robin, Romain Yvinec [INRA].

We have analyzed a multi-type age dependent model for cell populations subject to unidirectional motion, in both a stochastic and deterministic framework [23]. Cells are distributed into successive layers; they may divide and move irreversibly from one layer to the next. We have adapted results on the large-time convergence of PDE systems and branching processes to our context, where the Perron-Frobenius or Krein-Rutman theorem can not be applied. We have derived explicit analytical formulas for the asymptotic cell number moments, and the stable age distribution. We have illustrated these results numerically and we have applied them to the study of the morphodynamics of ovarian follicles. We have proven the structural parameter identifiability of our model in the case of age independent division rates. Using a set of experimental biological data, we have estimated the model parameters to fit the changes in the cell numbers in each layer during the early stages of follicle development.

This work has been undergone in the framework of the PhD of Frédérique Robin. It has been the matter of a poster at ReprosSciences2017 [24] (April 10-12) and of an oral presentation (Dynamiques de populations cellulaires structurées) at the annual meeting (September 27-29) of GDR MaMovi (Mathématiques Appliquées à la MOdélisation du VIvant).

7.2.3. Mathematical modeling of progenitor cell populations in the mouse cerebral cortex

Participants: Frédérique Clément, Alice Karam [IBPS], Matthieu Perez, Marie Postel, Sylvie Schneider-Maunoury [IBPS].

We have finalized the study of our PDE-based model of structured cell populations during the development of cerebral cortex. The model accounts for three main cell types: apical progenitors (APs), intermediate progenitors (IPs), and neurons. Each cell population is structured according to the cell age distribution. Since the model describes the different phases of the cell division cycle, we could derive the numeric equivalents of many of the experimental indexes measured in experimental setups, including classical mitotic or labeling indexes targeting the cells in phase S or mitosis, and more elaborated protocols based on double labeling with fluorescent dyes. We have formulated a multi-criterion objective function which enables us to combine experimental observations of different nature and to fit the data acquired in the framework of the NeuroMathMod project (Sorbonne-Universités Émergence call with IBPS, Institut de Biologie Paris Seine). Great efforts have been put on the experimental side to provide the model with the quantitative values of cell numbers for both progenitors and neurons. With the retrieved parameters, the model can provide useful information not supplied by the data, such as the cell origin of neurons (direct neurogenesis from AP or IPgenic neurogenesis) and the proportion of IPs cells undergoing several rounds of cell cycles. In addition, we have compared the cell dynamics patterns observed in wild-type mice with respect to mutant mice used as an animal model of human ciliopathies.

In the framework of the internship of Matthieu Perez (INSA Rouen, co-supervised by Frédérique Clément and Marie Postel), we have investigated numerically the link between our deterministic, PDE-based model of progenitor and neuron cell dynamics, and possible stochastic counterparts inspired from previous work in the team [31]. The deterministic approach is averaged with respect to the deterministic one, since it does not account for the trajectories of individual cells, yet it describes in more details the progression of cells within the cell cycle since it explicitly embeds the structuring of the cell cycle into different phases. The work has consisted in comparing the main model outputs (numbers of progenitors and neurons as a function of time) obtained by numerical simulations based on characteristics, on the deterministic side, or Gillespie algorithms, on the stochastic side. A proper strategy had to be settled to deal with the main difficulties raised by this comparison, namely the time-varying rates involved in the stochastic transition rates from one cell type to another, and the matching between the average stochastic rates and the deterministic rates ruling cell kinetics, especially the cell cycle duration.

8. Partnerships and Cooperations

8.1. European Initiatives

Together with our BIOS INRA partner, we have participated in a synergistic way in the proposal EVE (*In-Silico Safety and Efficacy Assessment of Reproductive Endocrinology Treatments*) submitted to the H2020-SC1-2016-2017 call (Personalised Medicine), whose PI was Enrico Tronci (Sapienza, Roma).

8.2. National Initiatives

8.2.1. ANR

Jonathan Touboul is member of the Kibord (KInetic models in Biology Or Related Domains) project obtained in 2014.

He is also PI of the projects "Mathematical modeling of synaptic plasticity" (with Laurent Venance, CIRB) funded as an interdisciplinary structuring project of INSB (Institut des Sciences Biologiques in CNRS) and "Altering Fear Memory" (with Sidney Wiener, CIRB and Karim Benchenane, ESPCI) funded by the PSL Labex MemoLife.

8.2.2. National Networks

- GdR REPRO (F. Clément is member of the direction board)
- MIA REM network: Réduction de modèles (PI Béatrice Laroche, INRA Jouy)

8.2.3. National Collaborations

- UMR Physiologie de la Reproduction et des Comportements, INRA Centre- Val de Loire (Bios and Bingo teams)
- Université Pierre & Marie Curie (UPMC)
  - Jacques-Louis Lions Laboratory, Pierre & Marie Curie University (Jean-Pierre Françoise, Marie Postel)
  - Developmental Biology Laboratory, Institut de Biologie Paris Seine (IBPS), Pierre & Marie Curie University (Alice Karam, Sylvie Schneider Maunoury), in the framework of the NeuroMathMod, Sorbonne-Universités Émergence call
- Center for Interdisciplinary Research in Biology (CIRB), Collège de France (Alain Prochiantz, Marie Manceau, Laurent Venance)

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Organisation

9.1.1.1. Member of the Organizing Committees

- Reprosciences 2017, April 10-12, Tours, co-organized by Frédérique Clément, Yves Combarnous, Florian Guillou, Joëlle Cohen-Tannoudji and François Vialard.

9.1.2. Journal

9.1.2.1. Member of the Editorial Boards

Jonathan Touboul participates in the editorial boards of *Plos One* and *Frontiers in neuronal circuits*

9.1.2.2. Reviewer - Reviewing Activities

Journal of Ovarian research, Journal of Mathematical Biology, SIAM Journal on Applied Dynamical Systems

9.1.3. Invited Talks

Frédérique Clément gave a talk dedicated to "'Multiscale modeling in reproductive and developmental biology : A middle-out, cell dynamics-based approach" during the Journées Scientifiques Inria, June, 14-16, Sophia-Antipolis.

Our study on the analysis and calibration of a linear model for structured cell populations with unidirectional motion was the matter of an invited presentation, given by Romain Yvinec, at the annual meeting of GDR MaMovi , September 27-29, Villeurbanne (https://gdr-mamovi-2017.sciencesconf.org).

9.1.4. Scientific Expertise

Frédérique Clément belongs to the expert board of the BCDE (Cell Biology, Development and Evolution) ITMO (Multi OrganizationThematic Institute) of the French National Alliance for Life and Health Sciences Aviesan.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Frédérique Robin gave lectures in the framework of the UFR de Mathématiques de Jussieu (L2 and L3 level)

UE P2.2M003 Vector analysis (L3) 85h

UE E.2M261 Integer and integral series with parameters (L2), 20h

UE 3M100 Initiation to Python language (L3), 15h

9.2.2. Supervision

PhD in progress : Richard Bailleul. Modeling of the developmental mechanisms underlying the formation of color and appendage patterns in birds, since September 2015. Université Pierre & Marie Curie (ED515), supervisors: Benoît Perthame, Marie Manceau and Jonathan Touboul (funded by the ERC starting grant of Marie Manceau)

PhD in progress: Yi Cui. Role of Pax6 in neurodevelopment: experiments and models, since September 2014, Université Pierre & Marie Curie (ED158), supervisors: Jonathan Touboul, Alain Prochiantz and Alessandra Pierani

PhD in progress: Frédérique Robin. Multiscale modeling of the morphodynamics in ovarian follicles, since October 2016, Université Pierre & Marie Curie (ED386), supervisors: Frédérique Clément and Romain Yvinec (INRA)

Master degree: Matthieu Perez. Simulations de modèles déterministes et stochastiques de la neurogenèse corticale. INSA Rouen, supervisors: Frédérique Clément and Marie Postel

9.3. Popularization

Frédérique Robin participated in a regional committee in the framework of the "Tournoi français des jeunes mathématiciennes et mathématiciens" (TFJM).

Book chapter in the new edition of the Encyclopedia of Endocrine Diseases
D. Monniaux, V. Cadoret, F. Clément, R. Dalbies-Tran, S. Elis, S. Fabre, V. Maillard, P. Monget, and S. Uzbekova
Editors Ilpo Huhtaniemi and Luciano Martini, Section Editor Sophie Christin-Maitre
Folliculogenesis (2017) p1-26.

10. Bibliography

Major publications by the team in recent years

[1] B. AYMARD, F. CLÉMENT, F. COQUEL, M. POSTEL. *Numerical simulation of the selection process of the ovarian follicles*, in "ESAIM Proc.", 2012, vol. 28, pp. 99-117

[2] B. AYMARD, F. CLÉMENT, F. COQUEL, M. POSTEL. *A numerical method for cell dynamics; kinetic equations with discontinuous coefficients*, in "SIAM J. Sci. Comput.", 2013, vol. 35, pp. A2442-A2468

[3] B. AYMARD, F. CLÉMENT, D. MONNIAUX, M. POSTEL. *Cell-kinetics based calibration of a multiscale model of structured cell populations in ovarian follicles*, in "SIAM J. Appl. Math.", 2016, vol. 76, n^{o} 4, pp. 1471–1491

[4] B. AYMARD, F. CLÉMENT, M. POSTEL. *Adaptive mesh refinement strategy for a non conservative transport problem*, in "ESAIM Math. Model. Numer. Anal.", 2014, vol. 48, n^{o} 5, pp. 1381-1412

[5] J. BURKE, M. DESROCHES, A. BARRY, T. KAPER, M. KRAMER. *A showcase of torus canards in neuronal bursters*, in "J. Math. Neurosci.", 2012, vol. 2

[6] F. CLÉMENT, J.-M. CORON, P. SHANG. *Optimal control of cell mass and maturity in a model of follicular ovulation*, in "SIAM J. Control Optim.", 2013, vol. 51, n^{o} 2, pp. 824-847

[7] F. CLÉMENT, P. MICHEL, D. MONNIAUX, T. STIEHL. *Coupled somatic cell kinetics and germ cell growth: multiscale model-based insight on ovarian follicular development*, in "Multiscale Model. Simul.", 2013, vol. 11, n^{o} 3, pp. 719-746

[8] F. CLÉMENT, D. MONNIAUX. *Multiscale modelling of follicular selection*, in "Prog. Biophys. Mol. Biol.", 2013, vol. 113, pp. 398-408

[9] M. DESROCHES, J. GUCKENHEIMER, B. KRAUSKOPF, C. KUEHN, H. OSINGA, M. WECHSELBERGER. *Mixed-mode oscillations with multiple time scales*, in "SIAM Rev.", 2012, vol. 54, pp. 211–288

[10] D. HEITZLER, G. DURAND, A. RIZK, S. AHN, J. KIM, J. VIOLIN, L. DUPUY, C. GAUTHIER, V. PIKETTY, P. CRÉPIEUX, A. POUPON, F. CLÉMENT, F. FAGES, R. LEFKOWITZ, E. REITER. *Competing G protein-coupled receptor kinases balance G protein and β-arrestin signaling*, in "Mol. Syst. Biol.", 2012, vol. 8, n^{o} 590

[11] M. KRUPA, A. VIDAL, F. CLÉMENT. *A network model of the periodic synchronization process in the dynamics of calcium concentration in GnRH neurons*, in "J. Math. Neurosci.", 2013, vol. 3, 4 p.

[12] P. SHANG. *Cauchy problem for multiscale conservation laws: Application to structured cell populations*, in "J. Math. Anal. Appl.", 2013, vol. 401, n^{o} 2, pp. 896-920

[13] J. TOUBOUL. *Limits and dynamics of stochastic neuronal networks with random delays*, in "J. Stat. Phys.", 2012, n^{o} 149, pp. 569–597

[14] J. TOUBOUL. *Mean-Field equations for stochastic firing-rate neural fields with delays: derivation and noise-induced transitions*, in "Phys. D", 2012, vol. 241, pp. 1223–1244

[15] J. TOUBOUL. *Propagation Of Chaos In Neural Fields*, in "Ann. Appl. Probab.", 2014, vol. 24, n^{o} 3, pp. 1298–1327

[16] A. VIDAL, Q. ZHANG, C. MÉDIGUE, S. FABRE, F. CLÉMENT. *DynPeak: An algorithm for pulse detection and frequency analysis in hormonal time series*, in "PloS One", 2012, vol. 7, e39001

Publications of the year

Articles in International Peer-Reviewed Journals

[17] F. CLÉMENT, F. COQUEL, M. POSTEL, K. L. TRAN. *Dimensional Reduction of a Multiscale Model Based on Long Time Asymptotics*, in "Multiscale Modeling and Simulation: A SIAM Interdisciplinary Journal", 2017, vol. 15, n^{o} 3, pp. 1198 - 1241 [*DOI :* 10.1137/16M1062545], http://hal.upmc.fr/hal-01325275

[18] E. KÖKSAL ERSÖZ, M. DESROCHES, M. KRUPA. *Synchronization of weakly coupled canard oscillators*, in "Physica D: Nonlinear Phenomena", June 2017, vol. 349, pp. 46-61 [*DOI :* 10.1016/J.PHYSD.2017.02.016], https://hal.inria.fr/hal-01558897

[19] E. KÖKSAL ERSÖZ, A. VIDAL, F. CLÉMENT. *Coupled multiple timescale dynamics in populations of endocrine neurons: Pulsatile and surge patterns of GnRH secretion*, in "SIAM Journal on Applied Dynamical Systems", 2017, pp. 1-29, forthcoming, https://hal.inria.fr/hal-01666251

[20] L. MÉGRET. *Studies of the Petrov Module for a Family of Generalized Liénard Integrable Systems*, in "Qualitative Theory of Dynamical Systems", 2017, vol. 20, n^{o} 2, pp. 1-21 [*DOI :* 10.1007/S12346-017-0250-3], https://hal.inria.fr/hal-01571808

[21] J. RUBIN, J. SIGNERSKA-RYNKOWSKA, J. TOUBOUL, A. VIDAL. *Wild oscillations in a nonlinear neuron model with resets: (I) Bursting, spike adding and chaos*, in "Discrete and Continuous Dynamical Systems - Series B (DCDS-B)", September 2017, vol. 22, pp. 3967-4002, https://arxiv.org/abs/1611.02740 , https://hal.inria.fr/hal-01416002

[22] J. SIGNERSKA-RYNKOWSKA, J. TOUBOUL, A. VIDAL, J. RUBIN. *Wild oscillations in a nonlinear neuron model with resets: (II) Mixed-mode oscillations*, in "Discrete and Continuous Dynamical Systems - Series B", 2017, vol. 22, pp. 4003-4039, https://arxiv.org/abs/1509.08282 , https://hal.inria.fr/hal-01256368

Other Publications

[23] F. CLÉMENT, F. ROBIN, R. YVINEC. *Analysis and calibration of a linear model for structured cell populations with unidirectional motion : Application to the morphogenesis of ovarian follicles*, December 2017, working paper or preprint, https://hal.inria.fr/hal-01666373

[24] F. CLÉMENT, F. ROBIN, R. YVINEC. *Multiscale modeling of the morphogenesis of ovarian follicles: a cell-dynamics based approach*, April 2017, 75 p. , 2. Journées du GdR 3606 Repro , Poster, https://hal.archives-ouvertes.fr/hal-01606594

References in notes

[25] P. BRESSLOFF. *Spatiotemporal dynamics of continuum neural fields*, in "J. Phys. A: Math. Theor.", 2012, vol. 45, pp. 033001–

[26] F. CLÉMENT, A. VIDAL. *Foliation-based parameter tuning in a model of the GnRH pulse and surge generator*, in "SIAM J. Appl. Dyn. Syst.", 2009, vol. 8, n^{o} 4, pp. 1591–1631

[27] F. CLÉMENT, J.-P. FRANÇOISE. *Mathematical modeling of the GnRH-pulse and surge generator*, in "SIAM J. Appl. Dyn. Syst.", 2007, vol. 6, pp. 441-456

[28] N. ECHENIM, D. MONNIAUX, M. SORINE, F. CLÉMENT. *Multi-scale modeling of the follicle selection process in the ovary*, in "Math. Biosci.", 2005, vol. 198, pp. 57-79

[29] S. FERNÁNDEZ-GARCÍA, M. DESROCHES, M. KRUPA, F. CLÉMENT. *A Multiple Time Scale Coupling Of Piecewise Linear Oscillators. Application To A Neuroendocrine System*, in "Siam Journal On Applied Dynamical Systems", 2015, vol. 14, n^{o} 2, 31 p.

[30] N. FOURNIER, S. MÉLÉARD. *A microscopic probabilistic description of a locally regulated population and macroscopic approximations*, in "Ann. Appl. Probab", 2004, vol. 14, pp. 119-144

[31] B. FRERET-HODARA, Y. CUI, A. GRIVEAU, L. VIGIER, Y. ARAI, J. TOUBOUL, A. PIERANI. *Enhanced Abventricular Proliferation Compensates Cell Death in the Embryonic Cerebral Cortex*, in "Cereb. Cortex", 2016, pp. 1-18

[32] E. KÖKSAL-ERSÖZ, M. DESROCHES, M. KRUPA, F. CLÉMENT. *Canard-Mediated (De)Synchronization in Coupled Phantom Bursters*, in "SIAM J. Appl. Dyn. Syst.", 2016, vol. 15, n^{o} 1, pp. 580-608

[33] B. PERTHAME. *Transport equations in biology*, Frontiers in Mathematics, Birkhauüser, Basel, 2007

[34] J. RIBOT, A. ROMAGNONI, C. MILLERET, D. BENNEQUIN, J. TOUBOUL. *Pinwheel-dipole configuration in cat early visual cortex*, 2014, pp. 63–73

[35] A. VIDAL, F. CLÉMENT. *A dynamical model for the control of the GnRH neurosecretory system*, in "J. Neuroendocrinol.", 2010, vol. 22, pp. 1251–1266

[36] T. VO, R. BERTRAM, J. TABAK, M. WECHSELBERGER. *Mixed mode oscillations as a mechanism for pseudo-plateau bursting*, in "J. Comput. Neurosci.", 2010, vol. 28, n^{o} 3, pp. 443–458

[37] H. WILSON, J. COWAN. *Excitatory and inhibitory interactions in localized populations of model neurons*, in "Biophys. J.", 1972, vol. 12, pp. 1–24