Activity Report 2016

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

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Computer Science and Digital Science:

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6.1.3. - Discrete Modeling (multi-agent, people centered)
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Other Research Topics and Application Domains:

1.1.3. - Cellular biology
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2.2.2. - Nervous system and endocrinology

1. Members

Research Scientists

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Jonathan Touboul [Inria, Researcher, detached from Corps des Mines, HDR]

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Yi Cui [UPMC]
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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 [34], [33], and a nD, multiscale in space, system of weakly-coupled non conservative transport equations that underlies our approach of gonadal cell dynamics [35],[7]. 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 [8]. 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 [4]. 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 [37] 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.

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 [11], while associated control problems have been studied in the framework of hybrid optimal control [5]. 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 [3] and implemented in a problem-specific way on parallel architecture [1].

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 [38], [32]. 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 [14].

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 [13], [12] 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 [6], [7], analysis of neurosecretory patterns [15] and modeling of GPCR (G-Protein Coupled Receptors) signaling networks [9]. 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 [36].

5. Highlights of the Year

5.1. Highlights of the Year

- PhD defense of Lucile Megret. Explosion of limit cycles : qualitative analysis, numerical simulations and models. Université Pierre & Marie Curie – Sorbonne Universités, November 25th 2016.
- PhD defense of Elif Köksal Ersöz. A mathematical study on coupled multiple timescale systems, synchronization of populations of endocrine neurons. Université Pierre & Marie Curie – Sorbonne Universités, December 13th 2016.
- PhD defense of Tanguy Cabana. Limits of randomly connected networks and their dynamics. Université Pierre & Marie Curie – Sorbonne Universités, December 14th 2016.
- Invited plenary conference at ICAR2016 http://www.icar2016.org 18th International Congress on Animal Reproduction. Multiscale mathematical modeling of the hypothalamo-pituitary-gonadal axis. Tours (France), June 26-30th 2016.

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. A new release of the DynPeak Scilab atom toolbox has been delivered in 2016 https://atoms.scilab.org/toolboxes/Dynpeak/2.1.0

- Participants: Frédérique Clement, Serge Steer, Thierry Martinez
- Partner: INRA
- Contact: Frédérique Clement
- 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.

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. Symmetric coupling of multiple timescale systems with mixed-mode oscillations

Participants: Soledad Fernández García, Alexandre Vidal, Fabrizio de Vico Fallani [EPI Aramis], Frédérique Clément.

We have analyzed a six-dimensional slow-fast system consisting of two coupled identical oscillators. Each oscillator is a three-dimensional system consisting of a FitzHugh-Nagumo system with an additional variable representing the calcium concentration. Individually, each three-dimensional subsystem possesses an attractive Mixed-Mode oscillations limit cycle, displaying small oscillations due to the presence of a folded saddle-node type II singularity for a certain range of the parameters values. We have considered a linear coupling through the fast variable in the slow equation and study the synchronization patterns of two identical systems with identical coupling parameter. Apart from stable in-phase and stable anti-phase synchronization patterns, the system presents almost-in-phase synchronization, oscillation death of one of the oscillators and total oscillation death, intertwined with complex transitions involving period doubling cascade, period adding phenomena and chaos. We have pointed out the role of Mixed-Mode oscillations in the birth of the different patterns and the transitions from one regime to another.

Part of these results have been presented as a contributed talk to the SIAM conference on life science https://www.siam.org/meetings/ls16/: (A Study of the Synchronization Between Two Coupled Neuron Models Generating Mixed-Mode Oscillations. A. Vidal, S.Fernández García, F. Clément, F. De Vico Fallani). MS48 Applications of Multiple Time Scale Dynamics in Biological Systems.

7.1.3. 3D-Explosion of cycles and spike-adding in the Hindmarsh-Rose model

Participants: Lucile Megret, Mathieu Desroches [Sophia], Jean-Pierre Françoise, Maciej Krupa [Sophia].

We have considered slow-fast systems that feature bursting oscillations, the minimal configuration being two fast variables and one slow variable. In the Hindmarsh-Rose model, as the slow variable z evolves, the fast dynamics undergoes several bifurcations (two Hopf bifurcations, two homoclinic bifurcations, two focus-node and two saddle-node bifurcations). We have focused on the existence of a sequence of 3D-candidate limit periodic sets of a new type. Numerical simulations have shown that it generates for the full 3D-dynamics and (the small parameter) " small enough a 3D-explosion of cycles. We have discussed the relation between this 3D-explosion and the spike-adding. We have also emphasized another new phenomenon induced by the slow-crossing of a saddle-node bifurcation with solutions which after coming close to the fold point, continue to follow it along its non-hyperbolic center manifold. We have shown how this phenomenon is also involved in the spike-adding mechanism taking place in square-wave bursters such as the Hindmarsh-Rose system.
Part of these results have been presented at the "36e Séminaire de la Sociéte Francophone de Biologie théorique", St-Flour (France), June 12-15 2016.

7.1.4. Wild oscillations in a nonlinear neuron model with resets

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

In a series of two studies, 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.

The first study [30] 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 [31] 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.

7.1.5. Canard Explosions in delay differential equations

Participants: Jonathan Touboul, Maciej Krupa [Sophia].

We have analyzed in [21] canard explosions in delayed differential equations with a one-dimensional slow manifold. This study is applied to explore the dynamics of the van der Pol slow-fast system with delayed self-coupling. In the absence of delays, this system provides a canonical example of a canard explosion. We have shown that as the delay is increased a family of "classical" canard explosions ends as a Bogdanov-Takens bifurcation occurs at the folds points of the S-shaped critical manifold.

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 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 [29].

These results have been partly presented in a workshop on "Asymptotic behavior of systems of PDEs arising in physics and biology : theoretical and numerical points of view" (ABPDE II), Lille, June 15-17, 2016.

7.2.2. Analysis of the asymptotic behavior of a model for the morphogenesis in ovarian follicles

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

We have designed and analyzed a simplified version of our multiscale model for the morphogenesis of ovarian follicles [6]. We have formulated both a stochastic model, in the framework of branching processes, and a deterministic one, in the framework of nonconservative transport equations. The simplifications result in linear models, in which the oocyte growth is uncoupled from the proliferation of the surrounding follicular cells. The cell population is distributed into concentric layers around the oocyte, and structured according to the cell age. Cells are subject to the process of cell division, which resets their age and allow them to possibly move to the adjacent outer layer. Since there is no symmetry in the cell displacements (the only allowed cell motion is centrifugal), we have faced the problem of the model irreducibility. To study the asymptotic behavior, we thus had to adapt the classical results based on entropy or the computation of stochastic moments. We have proved that there is, as expected, an exponential asymptotic growth led by a Malthus parameter, which can be computed analytically in the simplest (Markovian) case, or numerically. Interestingly, the value of this global parameter merges with one of the local Malthus-like parameters defined on the layer level. In both the deterministic and stochastic cases, we could derive accurate information on the time-varying mean cell number per layer and we also got additional information on the asymptotic age distribution.

This work has been undergone in the framework of the master thesis of Frédérique Robin (M2 Mathématiques du Vivant, Université Paris-Saclay), and pursued as a PhD subject. Preliminary results have been the matter of a presentation during the "Journées INRA-Inria" held in Mallemort (France) on October 6-7th: F. Clément, F. Robin, R Yvinec. Dynamiques de populations cellulaires structurées individus-centrées : Morphogenèse des follicules ovariens.

7.2.3. Numerical study of a mathematical model for the dynamics of progenitor cell populations in the mouse cerebral cortex

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

We have studied numerically our multi-scale mathematical 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 already acquired in the framework of the NeuroMathMod project (Sorbonne-Universités Émergence call with IBPS, Institut de Biologie Paris Seine). 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.

7.3. Macroscopic limits of stochastic neural networks and neural fields

7.3.1. Limit theorems and effective dynamics

Participants: Jonathan Touboul, Philippe Robert [EPI RAP], Cristobal Quiñinao [IMT], Stéphane Mischler [CEREMADE].

We have pursued our investigations on the dynamics of large-scale neural networks modeling the brain, in two main directions:

We have studied in [26] the mean-field limit and stationary distributions of a pulse-coupled network modeling the dynamics of a large neuronal assemblies. Our model takes into account explicitly the intrinsic randomness of firing times, contrasting with the classical integrate-and-fire model. The ergodicity properties of the Markov process associated with finite networks have been investigated. We have derived the limit in distribution of the sample path of the state of a neuron of the network when its size gets large. The invariant distributions of this limiting stochastic process have been analyzed as well as their stability properties. We have shown that the system undergoes transitions as a function of the averaged connectivity parameter, and can support trivial states (where the network activity dies out, which is also the unique stationary state of finite networks in some cases) and self-sustained activity when connectivity level is sufficiently large, both being possibly stable.

We have investigated in [23] existence and uniqueness of solutions of a McKean-Vlasov evolution PDE representing the macroscopic behavior of interacting Fitzhugh-Nagumo neurons. This equation is hypoelliptic, nonlocal and has unbounded coefficients. We have proven the existence of a solution to the evolution equation and non trivial stationary solutions. Moreover, we have demonstrated the uniqueness of the stationary solution in the weakly nonlinear regime. Eventually, using a semigroup factorisation method, we have shown exponential nonlinear stability in the small connectivity regime.

7.3.2. Spectrum of random matrices

Participants: Jonathan Touboul, Gilles Wainrib [ENS], Luis Carlos Garcia Del Molino [New-York University], Khashayar Pakdaman [IJM].

We have considered in [20] the ensemble of Real Ginibre matrices with a positive fraction $\alpha > 0$ of real eigenvalues. We have demonstrated a large deviation principle for the joint eigenvalue density of such matrices and we have introduced a two phase log-gas whose stationary distribution coincides with the spectral measure of the ensemble. Using these tools we have provided an asymptotic expansion for the probability $p^n_{\alpha n}$ that an $n \times n$ Ginibre matrix has $k = \alpha n$ real eigenvalues and we have characterized the spectral measures of these matrices.

7.4. Modeling of brain development and brain functions

7.4.1. Organization of the visual cortex

Participants: Jonathan Touboul, Jérôme Ribot [CIRB], Alberto Romagnoni [ENS], Daniel Bennequin [IMG-PRG], Chantal Milleret [CIRB].

In the early visual cortex, information is processed within functional maps whose layout is thought to underlie visual perception. However, the precise organization of these functional maps as well as their interrelationships remains unresolved. We have investigated using new data acquisition and analysis as well as mathematical modeling, the inter-relationship between different visual maps in cat visual cortex.

We have shown in [25] that spatial frequency representation in cat areas 17 and 18 exhibits singularities around which the map organizes like an electric dipole potential. These singularities are precisely co-located with singularities of the orientation map: the pinwheel centers. We have first shown, using high resolution optical imaging, that a large majority (around 80%) of pinwheel centers exhibit in their neighborhood semi-global extrema in the spatial frequency map. These extrema create a sharp gradient that was confirmed with electrophysiological recordings. Based on an analogy with electromagnetism, a mathematical model of a dipolar structure has been proposed and accurately fitted to optical imaging data for two third of pinwheel centers with semi-global extrema. We have concluded that more than half of orientation pinwheel centers form spatial frequency dipoles in cat early visual cortex.

We have demonstrated mathematically in [27] that two natural principles, local exhaustivity of representation and parsimony, would constrain the orientation and spatial frequency maps to display co-located singularities around which the orientation is organized as a pinwheel and spatial frequency as a dipole. We have further focused on the theoretical implications of this structure. Using a computational model, we have shown that this architecture allows a trade-off in the local perception of orientation and spatial frequency, but this would occur for sharper selectivity than the tuning width reported in the literature. We therefore re-examined physiological data and have shown that indeed the spatial frequency selectivity substantially sharpens near maps singularities, bringing to the prediction that the system tends to optimize balanced detection between different attributes.

7.4.2. Modeling the timing of neurogenesis and control of the neuron pool : Enhanced abventricular proliferation compensates cell death in the embryonic cerebral cortex

Participants: Betty Freret-Hodara [IJM], Yi Cui, Amélie Griveau [IJM], Lisa Vigier [IJM], Yoko Arai [IJM], Jonathan Touboul, Alessandra Pierani [IJM].

Loss of neurons in the neocortex is generally thought to result in a final reduction of cerebral volume. Yet, little is known on how the developing cerebral cortex copes with death of early-born neurons. We have tackled this issue by taking advantage of a transgenic mouse model in which, from early embryonic stages to mid-corticogenesis, abundant apoptosis is induced in the postmitotic compartment. Unexpectedly, the thickness of the mutant cortical plate at E18.5 was normal, due to an overproduction of upper layer neurons at E14.5. We have developed and simulated a mathematical model to investigate theoretically the recovering capacity of the system and found that a minor increase in the probability of proliferative divisions of intermediate progenitors (IPs) is a powerful compensation lever. Combined with our experimental observations, these results illustrate the remarkable plasticity of neocortical progenitors to adapt to major embryonic insults via the modulation of abventricular divisions thereby ensuring the production of an appropriate number of neurons.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. 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.

8.1.2. National Networks

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

8.1.3. National Collaborations

- Center for Interdisciplinary Research in Biology (CIRB), Collège de France (Alain Prochiantz, Marie Manceau, Laurent Venance)
- 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
- Jacques Monod Institute (IJM)
  - Computational Biology and Biomathematics (Khashayar Pakdaman)
  - Génétique et développement du cortex cérébral (Alessandra Pierani)
- Centre de Recherche en Mathématiques de la Décision (CEREMADE), Paris Dauphine University (Stéphane Mischler)
- Unité de Neurosciences, Information & Complexité (UNIC), CNRS Gif-sur-Yvette (Alain Destexhe)

8.2. International Research Visitors

8.2.1. Visits to International Teams

Jonathan Touboul has visited Simon Levin in Princeton University (December 15-26)

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Organisation

9.1.1.1. General Chair, Scientific Chair

Colloquium on Dynamical Systems and Applications, May 19th 2016

Thematic session co-organized by Jonathan Touboul and Khashayar Pakdaman within the framework of the CIRB

9.1.2. Scientific Events Selection

9.1.2.1. Member of the Conference Program Committees

Jonathan Touboul was member of the program committee of ICMNS 2016 (International Conference on Mathematical Neuroscience, Juan-les-Pins)

9.1.3. Journal

9.1.3.1. Member of the Editorial Boards

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

9.1.3.2. Reviewer - Reviewing Activities

Annals of Applied Probability, Journal of Statistical Physics, eLife, PloS Computational Biology, SIAM Journal on Applied Dynamical Systems, SIAM Journal on Discrete Mathematics, Bulletin of Mathematical Biology

9.1.4. Invited Talks

Invited plenary conference of Frédérique Clément at ICAR2016 http://www.icar2016.org 18th International Congress on Animal Reproduction (over 900 attendees). Multiscale mathematical modeling of the hypothalamo-pituitary-gonadal axis. Tours (France) June 26-30th 2016.

9.1.5. 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.

Jonathan Touboul has been reviewer for the ANR and European Research Council in 2016.

9.2. Teaching - Supervision - Juries

9.2.1. 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)

PhD: Tanguy Cabana. Limits of randomly connected networks and their dynamics. Defended on December14th 2016, Université Pierre & Marie Curie (ED386), supervisors: Raphaël Krikorian, Jonathan Touboul

PhD: Elif Köksal Ersöz. A mathematical study on coupled multiple timescale systems, synchronization of populations of endocrine neurons. Defended on December 13th, Université Pierre & Marie Curie (ED386), supervisors: Frédérique Clément and Jean-Pierre Françoise, with the involvement of Mathieu Desroches

PhD: Lucile Megret, Explosion of limit cycles : qualitative analysis, numerical simulations and models. Defended on November 25th, Université Pierre & Marie Curie (ED386), supervisors: Jean-Pierre Françoise and Frédérique Clément, with the involvement of Mathieu Desroches

HDR: Alexandre Vidal. From qualitative analysis of complex dynamics to parameter estimation in neuronal models. Université d'Évry-Val-d'Essonne – Université Paris-Saclay, December 14th 2016

9.2.2. Juries

Jonathan Touboul participated in the PhD committee of Takafumi Arakaki (ED3C, supervisors: D. Hansel and A. Leblois), in the selection committee for the hiring of a professor at Technische Universitat Berlin, as well as in the Bernstein Award for Computational Neuroscience committee.

9.3. Popularization

Jonathan Touboul has given a presentation in the framework of the "demi-heure de science" : Mathematical exploration of the brain activity (January 7th).

Frédérique Clément has given a 3h lecture on “Multiscale modeling of folliculogenesis in mammals” in the M2 master “Predictive & integrative animal biology” (PRIAM) of Université Paris-Saclay.

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, 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

[4] 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

[5] 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

[6] 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

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

[8] 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

[9] 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

[10] 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.

[11] 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

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

[13] 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

[14] J. TOUBOUL. *Propagation Of Chaos In Neural Fields*, in "Ann. Appl. Probab.", 2014, vol. 24, n° 3, pp. 1298–1327

[15] 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

[16] 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 Journal on Applied Mathematics", 2016, vol. 76, n° 4, pp. 1471–1491 [*DOI :* 10.1137/15M1030327], https://hal.archives-ouvertes.fr/hal-01186381

[17] F. CLÉMENT. *Multiscale mathematical modeling of the hypothalamo-pituitary-gonadal axis*, in "Theriogenology", July 2016, vol. 86, n° 1, pp. 11-21 [*DOI :* 10.1016/J.THERIOGENOLOGY.2016.04.063], https://hal.inria.fr/hal-01334304

[18] S. FERNÁNDEZ-GARCÍA, M. KRUPA, F. CLÉMENT. *Mixed-Mode Oscillations in a piecewise linear system with multiple time scale coupling*, in "Physica D: Nonlinear Phenomena", July 2016, vol. 332, pp. 9–22 [*DOI :* 10.1016/J.PHYSD.2016.06.002], https://hal.inria.fr/hal-01342978

[19] 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 "Cerebral Cortex", September 2016, https://hal.archives-ouvertes.fr/hal-01412093

[20] L. C. GARCIA DEL MOLINO, K. PAKDAMAN, J. TOUBOUL, G. WAINRIB. *The real Ginibre ensemble with k=O(n) real eigenvalues*, in "Journal of Statistical Physics", 2016, vol. 163, n° 2, pp. 303-323, https://hal.archives-ouvertes.fr/hal-01412352

[21] M. KRUPA, J. TOUBOUL. *Canard explosion in delayed equations with multiple timescales*, in "Journal of Dynamics and Differential Equations", 2016, vol. 28, n° 2, pp. 471-491, https://hal.archives-ouvertes.fr/hal-01253412

[22] E. KÖKSAL ERSÖZ, M. DESROCHES, M. KRUPA, F. CLÉMENT. *Canard-Mediated (De)Synchronization in Coupled Phantom Bursters*, in "SIAM Journal on Applied Dynamical Systems", March 2016, vol. 15, n° 1, pp. 580–608 [*DOI :* 10.1137/15M101840X], https://hal.inria.fr/hal-01256389

[23] S. MISCHLER, C. QUIÑINAO, J. TOUBOUL. *On a Kinetic Fitzhugh–Nagumo Model of Neuronal Network*, in "Communications in Mathematical Physics", 2016, vol. 342, n° 3, pp. 1001–1042 [*DOI :* 10.1007/S00220-015-2556-9], https://hal.archives-ouvertes.fr/hal-01108872

[24] D. MONNIAUX, P. MICHEL, M. POSTEL, F. CLÉMENT. *Multiscale modeling of ovarian follicular development: From follicular morphogenesis to selection for ovulation*, in "Biology of the Cell", June 2016, vol. 108, n° 6, pp. 1-12 [*DOI :* 10.1111/BOC.201500087], https://hal.inria.fr/hal-01294630

[25] J. RIBOT, A. ROMAGNONI, C. MILLERET, D. BENNEQUIN, J. TOUBOUL. *Pinwheel-Dipole configuration in cat visual cortex*, in "NeuroImage", 2016, vol. 128, pp. 63-73, https://hal.archives-ouvertes.fr/hal-01412346

[26] P. ROBERT, J. TOUBOUL. *On the dynamics of random neuronal networks*, in "Journal of Statistical Physics", September 2016, vol. 165, n° 3, pp. 545-584 [*DOI :* 10.1007/s10955-016-1622-9], https://hal.inria.fr/hal-01075242

[27] A. ROMAGNONI, J. RIBOT, D. BENNEQUIN, J. TOUBOUL. *Parsimony, exhaustivity and balanced detection in neocortex*, in "PLoS Computational Biology", 2016, vol. 11, n° 11, e1004623 p. [*DOI :* 10.1371/JOURNAL.PCBI], https://hal.archives-ouvertes.fr/hal-01412347

Scientific Books (or Scientific Book chapters)

[28] F. CLÉMENT, A. VIDAL. *Modeling the Dynamics of Gonadotropin-Releasing Hormone (GnRH) Secretion in the Course of an Ovarian Cycle* , in "Computational Neuroendocrinology", D. J. MACGREGOR, G. LENG (editors), Wiley-INF neuroendocrinology series, John Wiley & Sons, April 2016, https://hal.inria.fr/hal-01294646

Other Publications

[29] F. CLÉMENT, F. COQUEL, M. POSTEL, K. L. TRAN. *Dimensional reduction of a multiscale model based on long time asymptotics*, June 2016, working paper or preprint, http://hal.upmc.fr/hal-01325275

[30] J. RUBIN, J. SIGNERSKA-RYNKOWSKA, J. TOUBOUL, A. VIDAL. *Wild oscillations in a nonlinear neuron model with resets: (I) Bursting, spike adding and chaos*, December 2016, working paper or preprint, https://hal.inria.fr/hal-01416002

[31] J. SIGNERSKA-RYNKOWSKA, J. TOUBOUL, A. VIDAL. *A geometric mechanism for mixed-mode bursting oscillations in a hybrid neuron model*, January 2016, working paper or preprint, https://hal.inria.fr/hal-01256368

References in notes

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

[33] 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° 4, pp. 1591–1631

[34] 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

[35] 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

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

[37] 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° 3, pp. 443–458

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