Activity Report 2014

Project-Team MYCENAE

Multiscale dYnamiCs in neuroENdocrine AxEs

RESEARCH CENTER
Paris - Rocquencourt

THEME
Modeling and Control for Life Sciences

Table of contents

Project-Team MYCENAE

Keywords: Multiscale Models, Dynamic Networks, Mathematical Biology, Computational Neuroscience, Integrative Physiology, Cell Biology

Creation of the Project-Team: 2014 January 01.

1. Members

Research Scientists

Frédérique Clément [Team leader, Inria, Senior Researcher, HdR]
Mathieu Desroches [Inria, Researcher]
Jonathan Touboul [Inria, detached from le corps des Mines]
Maciej Krupa [Inria, Advanced Research position]

Faculty Members

Marie Postel [Univ. Paris VI, Associate Professor, on half-time delegation, HdR]
Alexandre Vidal [Univ. Évry-Val-d'Essonne, Associate Professor, on half-time delegation until Sep 2014]

PhD Students

Benjamin Aymard [Univ. Paris VI, until Oct 2014]
Elif Köksal Ersoz [Inria]
Lucile Megret [Univ. Paris VI]
Kim Long Tran [Univ. Paris VI, from Oct 2014]

Post-Doctoral Fellows

Soledad Fernández García [Inria]
Justyna Hanna Signerska-Rynkowska [Inria, from Nov 2014]
Albert Granados Corsellas [Inria, until Sep 2014]

Visiting Scientist

Jean-Pierre Françoise [Univ. Paris VI, Professor, HdR]

Administrative Assistant

Martine Verneuille [Inria]

Other

Kim Long Tran [Master degree in Applied Mathematics]

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 [38], [37], and a nD, multiscale in space, system of weakly-coupled non conservative transport equations that underlies our approach of gonadal cell dynamics [39],[6]. 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 [7]. 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 [3]. 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 [43] 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 [10], while associated control problems have been studied in the framework of hybrid optimal control [4]. 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 [16] 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 [44], [36]. 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 [24].

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 [12], [11] 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.

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 closed 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 [5], [6], analysis of neurosecretory patterns [13] and modeling of GPCR (G-Protein Coupled Receptors) signaling networks [8]. 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 [42].

5. New Software and Platforms

5.1. Platforms

5.1.1. DynPeak

In collaboration with the SED (George Rosca) and Serge Steer (SISYPHE), we have deployed a web resource version of our algorithm for the detection of peaks in pulsatile hormone patterns, DynPeak, that is accessible at the https://dynpeak.inria.fr url.

6. New Results

6.1. Highlights of the Year

- Picture of the Conference poster of the 2014 SIAM annual meeting (July 7-11, Chicago, USA), adapted from [7]
- Invitation to organize the mini symposium "The stochastic brain" at the Stochastic Processes and Applications Conference (Jul 28-Aug1, Buenos-Aires, Argentina)
- Selection of the NeuroMathMod project in the framework of the Sorbonne Université Emergence 2014 call

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

6.2.1. A multiple time scale coupling of piecewise linear oscillators: Application to a neuroendocrine system

Participants: Frédérique Clément, Mathieu Desroches, Soledad Fernández García, Maciej Krupa.

We have analyzed a four dimensional slow-fast piecewise linear system consisting of two coupled oscillators [32]. Each oscillator is a continuous slow-fast piecewise linear system with three zones of linearity. The coupling is one-way, that is, one subsystem evolves independently and is forcing the other subsystem. We have analyzed not only the qualitative behavior, but also quantitative aspects such as the period, frequency and amplitude of the oscillations. The system is used to reproduce all the features endowed in a former smooth model and reproduce the secretion pattern of the hypothalamic neurohormone GnRH along the ovarian cycle in different species.

6.2.2. Border collision bifurcations of stroboscopic maps in periodically driven spiking models

Participants: Frédérique Clément, Albert Granados Corsellas, Maciej Krupa.

In [21], we have considered a general nonautonomous hybrid system based on the integrate-and-fire model, widely used as simplified version of neuronal models and other types of excitable systems. Our assumptions are that the system is monotonic, possesses an attracting subthreshold equilibrium point, and is forced by means of a periodic pulsatile (square wave) function. In contrast to classical methods, in our approach we use the stroboscopic map (time-T return map) instead of the so-called firing map. It becomes a discontinuous map potentially defined in an infinite number of partitions. By applying theory for piecewise-smooth systems, we avoid relying on particular computations, and we develop a novel approach that can be easily extended to systems with other topologies (expansive dynamics) and higher dimensions. More precisely, we have rigorously studied the bifurcation structure in the two-dimensional parameter space formed by the amplitude of the pulse and the ratio between T and the duration of the pulse (duty cycle). We show that it is covered by regions of existence of periodic orbits given by period adding structures. The period adding structures completely describe not only all the possible spiking asymptotic dynamics but also the behavior of the firing rate, which is a devil's staircase as a function of the parameters.

6.2.3. Interpreting frequency responses to dose-conserved pulsatile input signals in simple cell signaling motifs

Participants: Richard Bertram, Patrick Fletcher, Joël Tabak [Florida State University], Frédérique Clément, Alexandre Vidal.

Many hormones are released in pulsatile patterns. This pattern can be modified, for instance by changing pulse frequency, to encode relevant physiological information. Often other properties of the pulse pattern will also change with frequency. How do signaling pathways of cells targeted by these hormones respond to different input patterns? We have asked if a given dose of hormone can induce different outputs from the target system, depending on how this dose is distributed in time [20]. We have used simple mathematical models of feedforward signaling motifs to understand how the properties of the target system give rise to preferences in input pulse pattern. We frame these problems in terms of frequency responses to pulsatile inputs, where the amplitude or duration of the pulses is varied along with frequency to conserve input dose. We have found that nonlinearity in the steady state input-output function of the system predicts the optimal input pattern. It does so by selecting an optimal input signal amplitude. Our results predict the behavior of common signaling motifs such as receptor binding with dimerization, and protein phosphorylation. The findings have implications for experiments aimed at studying the frequency response to pulsatile inputs, as well as for understanding how pulsatile patterns drive biological responses via feedforward signaling pathways.

6.2.4. Mixed-mode oscillations due to a singular Hopf bifurcation in a forest pest model

Participants: Morten Brøns [Technical University of Denmark], Mathieu Desroches, Maciej Krupa.

We have revisited a three-dimensional model of forest pest where MMOs play an important role [17]. In this model, young trees are distinguished from old trees, and the pest feeds on old trees. The pest grows on a fast scale, the young trees on an intermediate scale, and the old trees on a slow scale. We have established that the main organizing center for the shape and oscillatory patterns of the solutions is not a folded-node singularity, which does exist in the system, but rather a singular Hopf bifurcation. A combination of a singular Hopf bifurcation and a weak return mechanism, characterized by a very small change in one of the variables, determines the features of the mixed-mode oscillations. Period-doubling and saddle-node bifurcations lead to closed families (called isolas) of periodic solutions in a bifurcation corresponding to a singular Hopf bifurcation.

6.2.5. On the Dynamics of the adenylate energy system: homeorhesis versus homeostasis

Participants: Jesús M Cortés, Ildefonso M. de La Fuente, Iker Malaina, Luis Martínez, Edelmira Valero [University of Bilbao], Serafim Rodrigues [Plymouth University], Mathieu Desroches.

We have developed and analyzed a new model of the ATP-ADP-AMP biochemical system in order to understand some of the functional elements involved in the cellular energy status [18]. In this model based on a delayed differential system, the enzymatic rate equations and all the physiological kinetic parameters have been explicitly considered and experimentally tested in vitro. Our central hypothesis is that cells are characterized by changing energy dynamics (homeorhesis). The results have shown that the adenylate energy charge (AEC) presents stable transitions between steady states and periodic oscillations and, in agreement with experimental data these oscillations range within the narrow AEC window. Furthermore, the model shows sustained oscillations in the Gibbs free energy and in the total nucleotide pool.

6.2.6. Adaptative algorithms for the simulation of slow-fast coupled oscillators in networks

Participants: Frédérique Clément, Marie Postel, Alexandre Vidal.

The numerical simulation of a slow fast system is usually performed using an explicit scheme with an adaptive time step, in order to preserve the numerical accuracy during the fast dynamic events. In the case of large sized networks of coupled slow-fast systems, one need to use the same very small time step for all components of the network, since the integration is performed simultaneously on the whole network. We have proposed a new algorithm based on a dynamic split of the network components, in the framework of symplectic integrators [40], and applied it to a model describing the intracellular calcium oscillations in a network of embryonic GnRH neurons [9]. At each time step, the systems currently in the fast dynamic parts, are identified from their distance to the fast manifold. These components are accordingly integrated using a small time step, while a larger time step is used for the remaining of the network (cf poster abstract in the CANUM 2014 conference). Although the CPU time saving is proportional to the time constant ratio between the slow and fast dynamics, it hardly compensates the drop in the convergence order as the size of the network increases.

6.3. Non conservative transport equations for cell population dynamics

6.3.1. Adaptive mesh refinement strategy for a nonconservative transport problem

Participants: Benjamin Aymard, Frédérique Clément, Marie Postel.

In the framework of transport equations it is usual to need long time simulations, and therefore large physical domains to cover a phenomenon. On the other hand it can happen that only a small time varying portion of the domain is interesting. This motivates the use of adaptivity for the spatial discretization. Biological models involving cell development are often nonconservative to account for cell division. In that case the threshold controlling the spatial adaptivity may have to be time-dependent in order to keep up with the progression of the solution. In [16], we tackle the difficulties arising when applying a Multiresolution method to a transport equation with discontinuous fluxes modeling localized mitosis. The analysis of the numerical method is performed on a simplified model and numerical scheme. An original threshold strategy is proposed and validated thanks to extensive numerical tests. It is then applied to a biological model in both cases of distributed and localized mitosis.

6.3.2. Calibration of a multiscale model for cell dynamics

Participants: Benjamin Aymard, Frédérique Clément, Marie Postel, Kim Long Tran.

In the framework of the PhD of Benjamin Aymard and the master training of Kim Long Tran, we have tackled the issue of the numerical calibration of our multiscale model of cell populations in ovarian follicles, in collaboration with Danielle Monniaux (INRA Tours). The strategy has consisted in designing quantitative specifications from the available biological knowledge, most of which fall within the field of cell population kinetics (e.g. growth fraction, mitotic index ...), and translating them into constraints on the model parameters, as well as in performing a detailed a priori analysis of the properties of the mathematical functions entering the model equations. Using visualization approaches appropriate both for following the trajectory of a given ovarian follicle with time and comparing the follicles together, we have confronted the model outputs on different levels (from the local cell density to the overall cell number) to the corresponding specifications. We have been able to reproduce instances of the selection process occurring within a cohort of terminally

growing follicles. To enable one to do systematic explorations of the model behavior in different parameter configurations associated with either physiological (e.g. species-specific ovulation number) or pathological situations (dysovulation), we have undertaken a reduction approach inspired from [41]. We have generalized these results by relaxing some simplifying assumptions to account for some important features of the original model as the distinction between different phases in the cell division cycle.

6.4. Macroscopic limits of stochastic neural networks and neural fields

6.4.1. Pulsatile localized dynamics in delayed neural-field equations in arbitrary dimension

Participants: Jonathan Touboul, Grégory Faye [EHESS].

Neural field equations are integro-differential systems describing the macroscopic activity of spatially extended pieces of cortex. In such cortical assemblies, the propagation of information and the transmission machinery induce communication delays, due to the transport of information (propagation delays) and to the synaptic machinery (constant delays). We have investigated the role of these delays on the formation of structured spatiotemporal patterns for these systems in arbitrary dimensions [19]. We have focused on localized activity, either induced by the presence of a localized stimulus (pulses) or by transitions between two levels of activity (fronts). Linear stability analysis allows to reveal the existence of Hopf bifurcation curves induced by the delays, along different modes that may be symmetric or asymmetric. We show that instabilities strongly depend on the dimension, and in particular may exhibit transversal instabilities along invariant directions. These instabilities yield pulsatile localized activity, and depending on the symmetry of the destabilized modes, either produce spatiotemporal breathing or sloshing patterns.

6.4.2. Limits and dynamics of randomly connected neuronal networks

Participants: Cristóbal Quiñinao [CIRB], Jonathan Touboul.

Networks of the brain are composed of a very large number of neurons connected through a random graph and interacting after random delays that both depend on the anatomical distance between cells. In order to comprehend the role of these random architectures on the dynamics of such networks, we have analyzed the mesoscopic and macroscopic limits of networks with random correlated connectivity weights and delays [35]. We have addressed both averaged and quenched limits, and shown propagation of chaos and convergence to a complex integral McKean-Vlasov equations with distributed delays. We have then instantiated a completely solvable model illustrating the role of such random architectures in the emerging macroscopic activity. We have particularly focused on the role of connectivity levels in the emergence of periodic solutions.

6.4.3. The propagation of chaos in neural fields

Participant: Jonathan Touboul.

We have considered the problem of the limit of bio-inspired spatially extended neuronal networks including an infinite number of neuronal types (space locations), with space-dependent propagation delays modeling neural fields [24]. The propagation of chaos property is proved in this setting under mild assumptions on the neuronal dynamics, valid for most models used in neuroscience, in a mesoscopic limit, the neural-field limit, in which we can resolve the quite fine structure of the neuron activity in space and where averaging effects occur. The mean-field equations obtained are of a new type: they take the form of well-posed infinite-dimensional delayed integro-differential equations with a nonlocal mean-field term and a singular spatio-temporal Brownian motion. We have also shown how these intricate equations can be used in practice to uncover mathematically the precise mesoscopic dynamics of the neural field in a particular model where the mean-field equations exactly reduce to deterministic nonlinear delayed integro-differential equations.

6.4.4. Spatially extended networks with singular multi-scale connectivity patterns

Participant: Jonathan Touboul.

In [24], we took care of a number of technical difficulties arising in the description of large-scale systems that are spatially extended. The organization of neurons in space (within cortical columns) and their interactions (fully connected networks) were relatively far from what is known of the anatomy of neuronal networks. In [25], we have further taken into account the fine and macroscopic structure of the cortex, which is a very large network characterized by a complex connectivity including at least two scales. On the microscopic scale, the interconnections are non-specific and very dense, while macroscopic connectivity patterns connecting different regions of the brain at larger scale are extremely sparse. This motivates to analyze the behavior of networks with multiscale coupling, in which a neuron is connected to its $v(N)$ nearest-neighbors where $v(N) = o(N)$, and in which the probability of macroscopic connection between two neurons vanishes. These are called singular multi-scale connectivity patterns. We have introduced a class of such networks and derived their continuum limit. We show convergence in law and propagation of chaos in the thermodynamic limit. The limit equation obtained is an intricate non-local McKean-Vlasov equation with delays which is universal with respect to the type of micro-circuits and macro-circuits involved.

6.4.5. Index Distribution of the Ginibre Ensemble

Participants: Romain Allez [Stastlab, Cambridge University], Gilles Wainrib [ENS], Jonathan Touboul.

Complex systems, and in particular random neural networks, are often described by randomly interacting dynamical systems with no specific symmetry. In that context, characterizing the number of relevant directions necessitates fine estimates on the Ginibre ensemble. We have computed analytically the probability distribution of the number of eigenvalues N_R with modulus greater than R (the index) of a large $N \times N$ random matrix in the real or complex Ginibre ensemble [15]. We have shown that the fraction $N_R/N = p$ has a distribution scaling as $exp(-\beta N^2 \psi_R(p))$ with $\beta = 1$ (respectively $\beta = 1/2$) for the complex (resp. real) Ginibre ensemble. For any $p \in [0, 1]$, the equilibrium spectral densities as well as the rate function $\psi_R(p)$ are explicitly derived. This function displays a third order phase transition at the critical (minimum) value $p_R^* = 1 - R^2$, associated to a phase transition of the Coulomb gas. We have deduced that, in the central regime, the fluctuations of the index N_R around its typical value $p_R^* N$ scale as $N^{1/3}$.

6.4.6. The heterogeneous gas with singular interaction: Generalized circular law and heterogeneous renormalized energy

Participants: Luis-Carlos Garcia Del Molino, Khashayar Pakdaman [Institut Jacques Monod], Jonathan Touboul.

We have introduced and analyzed d dimensional Coulomb gases with random charge distribution and general external confining potential [23]. Our long term motivation is to understand the spectrum of random matrices with non identical distributions, for instance with independent elements with distinct statistics. We have shown that these gases satisfy a large deviation principle. The analysis of the minima of the rate function (which is the leading term of the energy) reveals that at equilibrium, the particle distribution is a generalized circular law (i.e. with spherical support but non-necessarily uniform distribution). In the classical electrostatic external potential, there are infinitely many minimizers of the rate function. The most likely macroscopic configuration is a disordered distribution in which particles are uniformly distributed (for $d = 2$, the circular law), and charges are independent of the positions of the particles. General charge-dependent confining potentials unfold this degenerate situation: in contrast, the particle density is not uniform, and particles spontaneously organize according to their charge. In that picture the classical electrostatic potential appears as a transition at which order is lost. Sub-leading terms of the energy are derived: we show that these are related to an operator, generalizing the Coulomb renormalized energy, which incorporates the heterogeneous nature of the charges. This heterogeneous renormalized energy informs us about the microscopic arrangements of the particles, which are non-standard, strongly depending on the charges, and include progressive and irregular lattices.

7. Partnerships and Cooperations

7.1. Regional Initiatives

PSL☆ project NeuroMathematics (of Sensory Switch)- NeuroMath(SensoS)

7.2. National Initiatives

7.2.1. ANR

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

7.2.2. National Networks

- GdR REPRO (member of the direction board, F. Clément)
- DLeRBio network: Dynamiques Lentes-Rapides avec applications Biologiques (animation, M. Desroches)
- MIA REM network: Réduction de modèles (PI Béatrice Laroche, INRA Jouy)

7.2.3. National Collaborations

- Center for Interdisciplinary Research in Biology, Collège de France (Alain Prochiantz)
- Jacques-Louis Lions Laboratory, Pierre & Marie Curie University (Jean-Pierre Françoise, Marie Postel)
- UMR Physiologie de la Reproduction et des Comportements, INRA Tours (Bios and Bingo teams)
- Group for Neural Theory, École Normale Supérieure, Paris (Boris Gutkin)
- Centre de Recherche en Mathématiques de la Décision, Paris Dauphine University (Stéphane Mischler)
- Computational Biology and Biomathematics, Jacques Monod Institute, Paris Diderot University (Khashayar Pakdaman)
- LAGA (Laboratoire Analyse, Géométrie et Applications), Paris-Nord University (Gilles Wainrib)
- Unité de Neurosciences, Information & Complexité (UNIC), CNRS Gif-sur-Yvette (Alain Destexhe)

7.3. International Initiatives

7.3.1. Inria International Partners

7.3.1.1. Informal International Partners

- **USA**: Florida State University (Richard Bertram, Patrick Fletcher, Joël Tabak), University of Pittsburgh (Bard Ermentrout, Jonathan Rubin), Princeton University (William Bialek, Thibault Taillefumier)
- **UK**: University of Bristol (Alan R. Champneys), University of Nottingham (Daniele Avitabile), Plymouth University (Serafim Rodrigues)
- **Spain**: University of the Balearic Islands (Antonio .E. Teruel, Rafel Prohens), Polytechnic University of Catalunya (Toni Guillamon), University of Sevilla (Enrique Ponce)
- **Denmark**: Technical University of Denmark (Morten Brøns and Frank Schilder)

7.4. International Research Visitors

7.4.1. Visits of International Scientists

- William Bialek (Princeton University), May 2014
  seminar More than the sum of their parts: Collective behavior in flocks of birds and networks of neurons, Grands séminaires du Collège de France
- Bard Ermentrout (University of Pittsburgh), June 2014
  seminar Keeping the beat : Homeostatic frequency control in coupled oscillators held in EITN (European Institute for Theoretical Neuroscience)

- Jacques Cowan (University of Chicago, USA), October 2014 (two weeks)
  Mathematics of the Brain Colloquium
- Alexey Kuznetsov (Indiana University-Purdue, University Indianapolis, USA, July 2014 (one week
  seminar A highly-reduced model of the dopaminergic neuron: mechanisms of oscillations
- Martin Wechselberger (University of Sydney, Australia), November 2014 (one week)
  seminar Neuronal Excitability and Canards

7.4.2. Visits to International Teams

7.4.2.1. Research stays abroad

- M. Desroches, one-month research stay in the Department of Mathematics of the University of the Balearic Islands (UIB, Palma, Spain), funded by a scholarship from the UIB, in the framework of a collaboration with Antonio E. Teruel and Rafel Prohens (June 2014).
- J. Touboul, twice one-month research stay in Princeton University, partially funded by the NeuroInfo PEPS PTI project, in the framework of a collaboration with the group of William Balek (March 2014 and December 2014).

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Scientific events organisation

8.1.1.1. Member of the organizing committee:

- Kick-off Meeting of the GdR REPRO, April 7th, 2014
  F. Clément together with Olivier Kah (CNRS), Florian Guillou (INRA), Yves Combarnous (CNRS) and Joëlle Cohen-Tannoudji (University Paris VII).
- Second workshop "Biologie & Mathématiques sur la Montagne", October 28, 2014.
  J. Touboul together with : Gérard Berry (Collège de France), Amaury Lambert (UPMC), Alain Prochiantz (Collège de France)
- Workshop Multi-scale models, slow-fast differential equations, averaging in ecology and neuroscience, November 17-21, 2014
  M. Desroches, together with Olivier Faugeras (Inria Sophia-Antipolis Méditerrané), Claude Lobry (Nice University) and Tewfik Sari (IRSTEA), as a part of a thematic semester on mathematical ecology (July-December 2014), Bernoulli Centre of the EPFL (Lausanne, Switzerland).

8.1.2. Journal

8.1.2.1. Reviewer:

Electronic Journal of Probability, Physica D, Frontiers in Neuroscience, Journal of Statistical Physics, Mathematical Biosciences, Mathematics and Computers in Simulation, Nonlinear Dynamics, Nonlinearity, SIAM Journal on Applied Dynamical Systems, SIAM Journal on Applied Mathematics

8.1.3. Participation in committees and examination boards

8.1.3.1. F. Clément:

- member of the direction board of the GdR REPRO (Integrative and translational approaches of human and animal reproduction)
- appointed member of the scientific board of the BCDE (Cell Biology, Development and Evolution) ITMO (Multi OrganizationThematic Institute) of the French National Alliance for Life and Health Sciences http://www.aviesan.fr/en

- Inria Research Director open competitions (admission)
- Selection committee for the Assistant Professor position no 4240, 26-MC-0375 in Université Pierre & Marie Curie

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

M. Desroches

M1 course on "Mathematical and Computational Neuroscience" as part of the Master program in Bioinformatics (BIM) of the University Pierre et Marie Curie (UPMC, Paris)
This teaching has been organised over a five-week period (January-February 2014) with a total of 30 hours, including lectures, example classes and computer labs (2 hours per week each). This first half of the course was focused on an introduction to mathematical slow-fast models of spiking and bursting neurons using bifurcation theory, slow-fast dissection and numerical analysis (simulation and continuation) with the software package XPPAUT.

8.2.2. Supervision

Benjamin Aymard, Numerical study of multiscale non conservative transport equations modeling cell kinetics [14] , Université Pierre & Marie Curie, October 10th, 2014, supervisors: Marie Postel and Frédérique Clément.

Elif Köksal Ersoz, Synchronization of GnRH neurons: a multiscale mathematical study, since November 2013, Université Pierre & Marie Curie, supervisors: Frédérique Clément and Jean-Pierre Françoise, with the involvement of Mathieu Desroches.

Lucile Megret, Mathematical analysis of complex oscillations in models with multiple time scales, since October 2013, Université Pierre & Marie Curie, supervisors: Jean-Pierre Françoise and Frédérique Clément, with the involvement of Mathieu Desroches.

Kim Long Tran, Reduction and calibration of mutiscale models for structured cell populations, since October 2014, Université Pierre & Marie Curie, supervisors: Marie Postel and Frédérique Clément.

Luis Carlos García del Molino, Dynamics of randomly connected networks and spectral theory of random matrices, since September 2012, Université Denis Diderot, supervisor: Khashayar Pakdaman (Jacques Monod Institute), co-supervisor: Jonathan Touboul.

Cristóbal Quiñinao, Mean-field limits in non fully connected networks and noise-induced synchronization, since September 2012, Université Pierre & Marie Curie, supervisor: Benoît Perthame, co-supervisors: Stéphane Mischler (CEREMADE) and Jonathan Touboul.

8.2.3. Juries

J. Touboul: evaluation of the ENS Ulm PhD scholarships

8.3. Popularization

- M. Desroches is section-chief editor of the media gallery of DSWeb, a website dedicated to dynamical systems http://www.dynamicalsystems.org/pi/.
- Participation to the scientific popularization book "La Reproduction animale et humaine" [29]

9. 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] 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

[4] 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

[5] 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

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

[7] 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

[8] 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

[9] 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.

[10] 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

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

[12] 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

[13] 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

Doctoral Dissertations and Habilitation Theses

[14] B. AYMARD. *Numerical study of multiscale non conservative transport equations modeling cell kinetics*, Université Pierre et Marie Curie - Paris VI, October 2014, https://tel.archives-ouvertes.fr/tel-01087504

Articles in International Peer-Reviewed Journals

[15] R. ALLEZ, J. TOUBOUL, G. WAINRIB. *Index Distribution of the Ginibre Ensemble*, in "Journal of Physics A: Mathematical and Theoretical", 2014, vol. 47, n^{o} 4, 5 pages, 2 figures [*DOI :* 10.1088/1751-8113/47/4/042001], https://hal.inria.fr/hal-00942203

[16] B. AYMARD, F. CLÉMENT, M. POSTEL. *Adaptive mesh refinement strategy for a nonconservative transport problem*, in "ESAIM: Mathematical Modelling and Numerical Analysis", August 2014, pp. 1381 - 1412 [*DOI :* 10.1051/M2AN/2014014], https://hal.archives-ouvertes.fr/hal-00865429

[17] M. BRØNS, M. DESROCHES, M. KRUPA. *Mixed-mode oscillations due to a singular Hopf bifurcation in a forest pest model*, in "Mathematical Population Studies", 2014, pp. 1-22, https://hal.inria.fr/hal-00924098

[18] I. M. DE LA FUENTE, J. M. CORTÉS, E. VALERO, M. DESROCHES, S. RODRIGUES, I. MALAINA, L. MARTÍNEZ. *On the Dynamics of the Adenylate Energy System: Homeorhesis vs Homeostasis*, in "PLoS ONE", October 2014, vol. 9, n^{o} 10, e108676 [*DOI :* 10.1371/JOURNAL.PONE.0108676], https://hal.inria.fr/hal-01091238

[19] G. FAYE, J. TOUBOUL. *Pulsatile localized dynamics in delayed neural-field equations in arbitrary dimension*, in "SIAM Journal on Applied Mathematics", 2014, 33 p. , https://hal.inria.fr/hal-01095239

[20] P. A. FLETCHER, F. CLÉMENT, A. VIDAL, J. TABAK, R. BERTRAM. *Interpreting frequency responses to dose-conserved pulsatile input signals in simple cell signaling motifs*, in "PLoS ONE", 2014, vol. 9, n^{o} 4, e95613 [*DOI :* 10.1371/JOURNAL.PONE.0095613], https://hal.inria.fr/hal-00981377

[21] A. GRANADOS, M. KRUPA, F. CLÉMENT. *Border collision bifurcations of stroboscopic maps in periodically driven spiking models*, in "SIAM Journal on Applied Dynamical Systems", October 2014, vol. 13, n^{o} 4, 30 p. [*DOI :* 10.1137/13094637X], https://hal.inria.fr/hal-01092688

[22] D. MONNIAUX, F. CLÉMENT, R. DALBIÈS-TRAN, A. ESTIENNE, S. FABRE, C. MANSANET, P. MONGET. *The Ovarian Reserve of Primordial Follicles and the Dynamic Reserve of Antral Growing Follicles: What Is the Link?*, in "Biology of Reproduction", April 2014, vol. 90, n^{o} 4, 11 p. [*DOI :* 10.1095/BIOLREPROD.113.117077], https://hal.inria.fr/hal-00961546

[23] J. TOUBOUL, L. C. GARCIA DEL MOLINO, K. PAKDAMAN. *The heterogeneous gas with singular interaction: Generalized circular law and heterogeneous renormalized energy*, in "Journal of Physics A General Physics", 2014, 26 p. , https://hal.inria.fr/hal-01095228

[24] J. TOUBOUL. *Propagation of chaos in neural fields*, in "Annals of Applied Probability", 2014, vol. 24, n^{o} 3, pp. 1298–1327, forthcoming [*DOI :* 10.1214/13-AAP950], https://hal.archives-ouvertes.fr/hal-00942210

[25] J. TOUBOUL. *Spatially extended networks with singular multi-scale connectivity patterns*, in "Journal of Statistical Physics", 2014, 27 p. [*DOI :* 10.1007/S10955-014-1015-X], https://hal.inria.fr/hal-00942201

Invited Conferences

[26] M. DESROCHES. *Canards in 3D piecewise-linear slow-fast systems, application to neuron models*, in "The 10th AIMS Conference on Dynamical Systems, Differential Equations and Applications", Madrid, Spain, July 2014, https://hal.inria.fr/hal-01091239

[27] M. DESROCHES. *Mixed-Mode Bursting Oscillations (MMBOs): slow passage through spike-adding canard explosion*, in "Multi-Scale Models, Slow-Fast Differential Equations, Averaging in Ecology and Neuroscience", Bernoulli Centre, EPFL, Lausanne, Switzerland, November 2014, https://hal.inria.fr/hal-01091242

[28] J. TOUBOUL. *The pinwheel-dipole organization of orientation and spatial frequency maps, and their common organizing principles.* , in "5th France-Israël binational conference on neurosciences", Sde Boker, Israel, February 2014, https://hal.inria.fr/hal-01097888

Scientific Popularization

[29] D. MONNIAUX, R. DALBIÈS-TRAN, S. FABRE, N. GÉRARD, P. MONGET, F. CLÉMENT. *Le développement folliculaire ovarien et l'ovulation*, in "La reproduction animale et humaine", Editions Quae, October 2014, https://hal.inria.fr/hal-01092675

Other Publications

[30] P. CHOSSAT, M. KRUPA. *Heteroclinic cycles in Hopfield networks*, December 2014, https://hal.inria.fr/hal-01096505

[31] M. DESROCHES, J.-P. FRANÇOISE, L. MÉGRET. *Canard-induced loss of stability across a homoclinic bifurcation*, October 2014, submitted for publication, https://hal.inria.fr/hal-01093445

[32] S. FERNÁNDEZ-GARCÍA, M. DESROCHES, M. KRUPA, F. CLÉMENT. *A multiple timescale coupling of piecewise linear oscillators. Application to a neuroendocrine system*, August 2014, submitted for publication, https://hal.inria.fr/hal-01093198

[33] S. MISCHLER, C. QUIÑINAO, J. TOUBOUL. *On a kinetic FitzHugh-Nagumo model of neuronal network*, January 2015, https://hal.archives-ouvertes.fr/hal-01108872

[34] B. PERTHAME, C. QUIÑINAO, J. TOUBOUL. *Competition and boundary formation in heterogeneous media: Application to neuronal differentiation*, August 2014, https://hal.archives-ouvertes.fr/hal-01054813

[35] C. QUIÑINAO, J. TOUBOUL. *Limits and dynamics of randomly connected neuronal networks*, May 2014, https://hal.archives-ouvertes.fr/hal-01054802

References in notes

[36] P. BRESSLOFF. *Spatiotemporal dynamics of continuum neural fields*, in "J. Phys. A", 2012, vol. 45, 033001 p.

[37] 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

[38] 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

[39] 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

[40] J. LASKAR, P. ROBUTEL. *High order symplectic integrators for perturbed hamiltonian systems*, in "Celestial Mech. Dynam. Astronom.", 2001, vol. 80, pp. 9-62

[41] P. MICHEL. *Multiscale modeling of follicular ovulation as a mass and maturity dynamical system*, in "Multiscale Model. Simul.", 2011, vol. 9, n^{o} 1, pp. 282-313

[42] J. RIBOT, A. ROMAGNONI, C. MILLERET, D. BENNEQUIN, J. TOUBOUL. *Pinwheel-dipole configuration in cat early visual cortex*, 2014, http://dx.doi.org/10.1101/009308

[43] 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

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