Activity Report 2015

Project-Team MYCENAE

Multiscale dYnamiCs in neuroENdocrine AxEs

RESEARCH CENTER
Paris - Rocquencourt

THEME
Modeling and Control for Life Sciences

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Project-Team MYCENAE

Creation of the Project-Team: 2014 January 01

Keywords:

Computer Science and Digital Science:

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6.1.2. - Stochastic Modeling (SPDE, SDE)
6.1.3. - Discrete Modeling (multi-agent, people centered)
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6.2.1. - Numerical analysis of PDE and ODE
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Other Research Topics and Application Domains:

1.1.10. - Mathematical biology
1.1.3. - Cellular biology
1.1.4. - Developmental biology
1.3.1. - Understanding and simulation of the brain and the nervous system
2.2.2. - Nervous system and endocrinology

1. Members

Research Scientists

Frédérique Clément [Team leader, Inria, Senior Researcher, HdR]
Mathieu Desroches [Inria, Researcher, until Oct 2015]
Maciej Krupa [Inria, Advanced Research position, until Jul 2015]
Jonathan Touboul [Inria, detached from Corps des Mines, HdR]

Faculty Member

Marie Postel [Univ. Paris VI, Associate Professor, on half-time delegation until Sep 2015, HdR]

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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 [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],[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 [41] 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 [42], [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 [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 [40].

5. Highlights of the Year

5.1. Highlights of the Year

- HDR defense of Jonathan Touboul : Contribution to the theoretical study of large neuronal ensembles. June 5th 2015, ED3C
- Co-organization of founding events to federate the national scientific communities in Reproduction: Reprosciences 2015, and in Modeling for cell and developmental biology: 2015 ITMO BCDE workshop on Modeling in Cell and Developmental Biology

6. New Results

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

6.1.1. Canard-Mediated (De)Synchronization in Coupled Phantom Bursters

Participants: Elif Köksal Ersöz, Mathieu Desroches, Maciej Krupa, Frédérique Clément.

In [32], we study canard-mediated transitions in mutually coupled phantom bursters. We extend a multiple-timescale model which provides a sequence of dynamic events, i.e. transition from a frequency modulated relaxation cycle to a quasi-steady state and resumption of the relaxation regime through small amplitude oscillations. Folded singularities and associated canard solutions have a particular impact on the dynamics of the original system, which consists of two feedforward coupled FitzHugh-Nagumo oscillators, where the slow subsystem (regulator) controls the periodic behavior of the fast subsystem (secretor). We first investigate the variability in the dynamics depending on the canard mechanism that occurs near the folded singularities of the 4D secretor- regulator configuration. Then, we introduce a second secretor and focus on the slow-fast transitions in the presence of a linear coupling between the secretors. In particular, we explore the impact of the relationship between the canard structures and the coupling on patterns of synchronization and desynchronization of the collective dynamics of the resulting 6D system. We identify two different sources of desynchronization induced by canards, near a folded-saddle singularity and a folded-node singularity, respectively.
Part of these results have also been presented as posters at the *SIAM Conference on Applications of Dynamical Systems* (Snowbird, May 17-21, 2015) and 1st *International Conference on Mathematical Neuroscience* (Antibes Juan les Pins, June 8-10-2015).

6.1.2. Mixed-Mode Oscillations in a piecewise linear system with multiple time scale coupling

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

We analyze a four dimensional slow-fast piecewise linear system with three time scales presenting Mixed-Mode Oscillations. The system possesses an attractive limit cycle along which oscillations of three different amplitudes and frequencies can appear, namely, small oscillations, pulses (medium amplitude) and one surge (largest amplitude). In addition to proving the existence and attractiveness of the limit cycle, we focus our attention on the canard phenomena underlying the changes in the number of small oscillations and pulses. We analyze locally the existence of secondary canards leading to the addition or subtraction of one small oscillation and describe how this change is globally compensated for or not with the addition or subtraction of one pulse.

6.1.3. Noise-induced canard and mixed-mode oscillations in large stochastic networks with multiple timescales

Participants: Jonathan Touboul, Maciej Krupa, Mathieu Desroches.

We investigate in [28] the dynamics of large stochastic networks with different timescales and nonlinear mean-field interactions. After deriving the limit equations for a general class of network models, we apply our results to the celebrated Wilson-Cowan system with two populations with or without slow adaptation, paradigmatic example of nonlinear mean-field network. This system has the property that the dynamics of the mean of the solution exactly satisfies an ODE. This reduction allows to show that in the mean-field limit and in multiple populations with multiple timescales, noise induces canard explosions and Mixed-Mode Oscillations on the mean of the solution. This sheds new light on the qualitative effects of noise and sensitivity to precise noise values in large stochastic networks. We further investigate finite-sized networks and show that systematic differences with the mean-field limits arise in bistable regimes (where random switches between different attractors occur) or in mixed-mode oscillations, were the finite-size effects induce early jumps due to the sensitivity of the attractor.

6.1.4. Canard explosion in delayed equations with multiple timescales, applications to the delayed Fitzhugh-Nagumo system

Participants: Maciej Krupa, Jonathan Touboul.

In two contributions, we investigated theoretically the presence of canard explosions of delayed differential equations, and have applied these results to the FitzHugh-Nagumo neuronal model.

- In [21] we analyze 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 show 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.
- Motivated by the dynamics of neuronal responses, we analyze in [21] the dynamics of the Fitzhugh-Nagumo slow-fast system with delayed self-coupling. Beyond the regime of small delays, delays significantly enrich the dynamics, leading to mixed-mode oscillations, bursting and chaos. These behaviors emerge from a delay-induced subcritical Bogdanov-Takens instability arising at the fold points of the S-shaped critical manifold. Underlying the transition from canard-induced to delay-induced dynamics is an abrupt switch in the nature of the Hopf bifurcation.

6.1.5. Canard-induced loss of stability across a homoclinic bifurcation

Participants: Mathieu Desroches, Jean-Pierre Françoise, Lucile Megret.

In [16], we investigate the possibility of bifurcations which display a dramatic change in the phase portrait in a very small (on the order of 10^{-7} in the example presented here) change of a parameter. We provide evidence of existence of such a very rapid loss of stability on a specific example of a singular perturbation setting. This example is strongly inspired of the explosion of canard cycles first discovered and studied by E. Benoît, J.-L. Callot, F. Diener and M. Diener. After some presentation of the integrable case to be perturbed, we present the numerical evidences for this rapid loss of stability using numerical continuation. We discuss then the possibility to estimate accurately the value of the parameter for which this bifurcation occurs.

6.1.6. Analysis of Interspike-Intervals for the General Class of Integrate-and-Fire Models with Periodic Drive

Participant: Justyna Signerska-Rynkowska.

In [27], we study one-dimensional integrate-and-fire models of the general type $\dot{x} = F(t, x)$ and analyze properties of the firing map which iterations recover consecutive spike timings. We impose very week constraints for the regularity of the function $F(t, x)$ e.g. often it suffices to assume that F is continuous. If additionally F is periodic in t, using mathematical study of the displacement sequence of an orientation preserving circle homeomorphism, we provide a detailed description of the regularity properties of the sequence of interspike-intervals and behaviour of the interspike-interval distribution.

6.1.7. A geometric mechanism for mixed-mode bursting oscillations in a hybrid neuron model

Participants: Justyna Signerska-Rynkowska, Jonathan Touboul, Alexandre Vidal.

In [35], we exhibit and investigate a new type of mechanism for generating complex oscillations featuring an alternation of small oscillations with spikes (MMOs) or bursts (MMBOs) in a class of hybrid dynamical systems modeling neuronal activity. These dynamical systems, called nonlinear adaptive integrate-and-fire neurons, combine nonlinear dynamics modeling input integration in a nerve cell with discrete resets modeling the emission of an action potential and the subsequent return to reversal potential. We show that presence of complex oscillations in these models relies on a fundamentally hybrid structure of the flow: invariant manifolds of the continuous dynamics govern small oscillations, while discrete resets govern the emission of spikes or bursts. The decomposition into these two mechanisms leads us to propose a purely geometrical interpretation of these complex trajectories, and this relative simplicity allows to finely characterize the MMO patterns through the study of iterates of the adaptation map associated with the hybrid system. This map is however singular: it is discontinuous and has unbounded left- and right-derivatives. We apply and develop rotation theory of circle maps for this class of adaptation maps to precisely characterize the trajectories with respect to the parameters of the system. In contrast to more classical frameworks in which MM(B)Os were evidenced, the present geometric mechanism neither requires no more than two dimensions, does not necessitate to have separation of timescales nor complex return mechanisms.

Part of these results have also been presented as posters at the *SIAM Conference on Applications of Dynamical Systems* (Snowbird, May 17-21, 2015) and 1st *International Conference on Mathematical Neuroscience* (Antibes Juan les Pins, June 8-10-2015).

6.2. Non conservative transport equations for cell population dynamics

6.2.1. Cell-kinetics based calibration of a multiscale model: application to cell population dynamics in ovarian follicles

Participants: Benjamin Aymard [ICL], Frédérique Clément, Danielle Monniaux [INRA], Marie Postel.

In [30], we present a strategy for tuning the parameters of a multiscale model of structured cell populations in which physiological mechanisms are embedded into the cell scale. This strategy allows one to cope with the technical difficulties raised by such models, that arise from their anchorage in cell biology concepts: localized mitosis, progression within and out of the cell cycle driven by time- and possibly unknown-dependent, and nonsmooth velocity coefficients. We compute different mesoscopic and macroscopic quantities from the microscopic unknowns (cell densities) and relate them to experimental cell kinetic indexes. We study the expression of reaching times corresponding to characteristic cellular transitions in a particle-like reduction of the original model. We make use of this framework to obtain an appropriate initial guess for the parameters and then perform a sequence of optimization steps subject to quantitative specifications. We finally illustrate realistic simulations of the cell populations in cohorts of interacting ovarian follicles.

6.2.2. Dimensional reduction of a multiscale cell population model

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

We have designed a dimensional reduction of a multiscale structured cell population model, consisting of a system of 2D transport equations, into a system of twice as many 1D transport equations. The reduced model is obtained by computing the moments of the 2D model with respect to one space 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. Long time properties of the 1D model solution are obtained in connection with properties of the support of the 2D solution for general case initial conditions. Finite volume numerical approximations of the 1D reduced model can be used to compute the moments of the 2D solution with satisfying accuracy. The numerical robustness is studied in the scalar case and a full scale vector case is presented.

6.3. Macroscopic limits of stochastic neural networks and neural fields

6.3.1. Pinwheel-Dipole configuration in cat visual cortex

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

One fascinating aspect of the brain is its ability to process information in a fast and reliable manner. The functional architecture is thought to play a central role in this task, by encoding efficiently complex stimuli and facilitating higher level processing. In the early visual cortex of higher mammals, information is processed within functional maps whose layout is thought to underlie visual perception. The possible principles underlying the topology of the different maps, as well as the role of a specific functional architecture on information processing, is however poorly understood.

- In [25], we show 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 first show, 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 created a sharp gradient that was confirmed with electrophysiological recordings. Based on an analogy with electromagnetism, a mathematical model of a dipolar structure is proposed, that was accurately fitted to optical imaging data for two third of pinwheel centers with semi-global extrema.

- Mathematically, this pinwheel-dipole architecture is fascinating. We demonstrated mathematically in [26] that two natural principles, local exhaustivity of representation and parsimony, would indeed 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. Moreover, using a computational model, we showed 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 show 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.

These results shed new light on the principles at play in the emergence of functional architecture of cortical maps, as well as their potential role in processing information.

6.3.2. Absorption properties of stochastic equations with Hölder diffusion coefficients

Participants: Jonathan Touboul, Gilles Wainrib [ENS].

In [29], we address the absorption properties of a class of stochastic differential equations around singular points where both the drift and diffusion functions vanish. According to the Hölder coefficient alpha of the diffusion function around the singular point, we identify different regimes. Stability of the absorbing state, large deviations for the absorption time, existence of stationary or quasi-stationary distributions are discussed. In particular, we show that quasi-stationary distributions only exist for alpha < 3/4, and for alpha in the interval (3/4, 1), no quasi-stationary distribution is found and numerical simulations tend to show that the process conditioned on not being absorbed initiates an almost sure exponential convergence towards the absorbing state (as is demonstrated to be true for alpha = 1). Applications of these results to stochastic bifurcations are discussed.

6.3.3. On a kinetic FitzHugh-Nagumo model of neuronal network

Participants: Stéphane Mischler [CEREMADE], Cristóbal Quiñinao [CIRB], Jonathan Touboul.

We investigate in [33] the 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 proved existence of a solution to the evolution equation and non trivial stationary solutions. Moreover, we demonstrated uniqueness of the stationary solution in the weakly nonlinear regime. Eventually, using a semigroup factorisation method, we showed exponential nonlinear stability in the small connectivity regime.

6.4. Modeling of neurogenesis and brain development

6.4.1. Lhx2 regulates the timing of β-catenin-dependent cortical neurogenesis

Participants: Lea-Chia-Ling Hsu [Taipei], Sean Nama [Taipei], Yi Cui, Ching-Pu Chang [Taipei], Chia-Fang Wang [Taipei], Hung-Chih Kuo [Taipei], Jonathan Touboul, Shen-Ju Chou [Taipei].

The timing of cortical neurogenesis has a major effect on the size and organization of the mature cortex. The deletion of the LIM-homeodomain transcription factor Lhx2 in cortical progenitors by Nestin-cre leads to a dramatically smaller cortex. In [19] we report that Lhx2 regulates the cortex size by maintaining the cortical progenitor proliferation and delaying the initiation of neurogenesis. The loss of Lhx2 in cortical progenitors results in precocious radial glia differentiation and a temporal shift of cortical neurogenesis. We further investigated the underlying mechanisms at play and demonstrated that in the absence of Lhx2, the Wnt/β-catenin pathway failed to maintain progenitor proliferation. We developed and applied a mathematical model that reveals how precocious neurogenesis affected cortical surface and thickness. Thus, we concluded that Lhx2 is required for β-catenin function in maintaining cortical progenitor proliferation and controls the timing of cortical neurogenesis.

6.4.2. Competition and boundary formation in heterogeneous media: Application to neuronal differentiation

Participants: Cristóbal Quiñinao [CIRB], Benoît Perthame [LJLL], Jonathan Touboul.

We analyze in [22] an inhomogeneous system of coupled reaction-diffusion equations representing the dynamics of gene expression during differentiation of nerve cells. The outcome of this developmental phase is the formation of distinct functional areas separated by sharp and smooth boundaries. It proceeds through the competition between the expression of two genes whose expression is driven by monotonic gradients of chemicals, and the products of gene expression undergo local diffusion and drive gene expression in neighboring cells. The problem therefore falls in a more general setting of species in competition within a non-homogeneous medium. We show that in the limit of arbitrarily small diffusion, there exists a unique monotonic stationary solution, which splits the neural tissue into two winner-take-all parts at a precise boundary point: on both sides of the boundary, different neuronal types are present. In order to further characterize the location of this boundary, we use a blow-up of the system and define a traveling wave problem parametrized by the position within the monotonic gradient: the precise boundary location is given by the unique point in space at which the speed of the wave vanishes.

6.4.3. Local homeoprotein diffusion can stabilize boundaries generated by graded positional cues

Participants: Cristóbal Quiñinao [CIRB], Alain Prochiantz [CIRB], Jonathan Touboul.

Boundary formation in the developing neuroepithelium decides on the position and size of compartments in the adult nervous system. In [23], we started from the French Flag model proposed by Lewis Wolpert, in which boundaries are formed through the combination of morphogen diffusion and of thresholds in cell responses. In contemporary terms, a response is characterized by the expression of cell-autonomous transcription factors, very often of the homeoprotein family. Theoretical studies suggest that this sole mechanism results in the formation of boundaries of imprecise shapes and positions. Alan Turing, on the other hand, proposed a model whereby two morphogens that exhibit self-activation and reciprocal inhibition, and are uniformly distributed and diffuse at different rates lead to the formation of territories of unpredictable shapes and positions but with sharp boundaries (the 'leopard spots'). Here, we have combined the two models and compared the stability of boundaries when the hypothesis of local homeoprotein intercellular diffusion is, or is not, introduced in the equations. We find that the addition of homeoprotein local diffusion leads to a dramatic stabilization of the positioning of the boundary, even when other parameters are significantly modified. This novel Turing/Wolpert combined model has thus important theoretical consequences for our understanding of the role of the intercellular diffusion of homeoproteins in the developmental robustness of and the changes that take place in the course of evolution.

6.4.4. Designing a mathematical model of the dynamics of progenitor cell populations in the mouse cerebral cortex

Participants: Marie Postel, Alice Karam [UPMC], Mérina Latbi [UPMC], Guillaume Pezeron [UPMC], Kim Long Tran, Frédérique Clément, Sylvie Schneider-Maunoury [UPMC].

The mammalian cortex is a laminar structure in the dorsal telencephalon, composed of distinct cell types with different spatial and temporal origins. Cortical projection neurons display different patterns of layering and connectivity that depend on their birth date. We have designed a multi-scale mathematical model of structured cell populations, taking into account three main cell types: apical progenitors (APs), intermediate progenitors (IPs) and neurons (N). APs self-renew and produce IPs that divide to give Ns. The main originality of this spatio-temporal model is to explicitly represent the different phases of the cell cycle, G1, S, G2 and M. Biological data from the experiments and from the literature provide values for parameters of the model (e.g. duration of each cell cycle phase and division rates for each cell type). The outputs of the model are interpretable in terms of cell kinetics (e.g. mitotic index, labelling index, cell numbers). They are adjusted to experimental observations by numerical simulation.

7. Partnerships and Cooperations

7.1. National Initiatives

7.1.1. ANR

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

Mathieu Desroches is the coordinator of the SloFaDyBio (SLOw-FAst Dynamics applied to the BIOsciences) network mounted in 2014.

7.1.2. National Networks

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

7.1.3. National Collaborations

- UMR Physiologie de la Reproduction et des Comportements, INRA Tours (Bios and Bingo teams)
- Jacques-Louis Lions Laboratory, Pierre & Marie Curie University (Jean-Pierre Françoise, Marie Postel)
- Developmental Biology Laboratory, Pierre & Marie Curie University (Alice Karam, Sylvie Schneider Maunoury), in the framework of the NeuroMathMod, Sorbonne-Universités Émergence call
- Center for Interdisciplinary Research in Biology, Collège de France (Alain Prochiantz)
- 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)
- Département d'Informatique de l'ENS, équipe DATA, Paris-Nord University (Gilles Wainrib)
- Unité de Neurosciences, Information & Complexité (UNIC), CNRS Gif-sur-Yvette (Alain Destexhe)

7.2. International Initiatives

7.2.1. 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, Simon Levi)
- **Spain**: University of the Balearic Islands (Antonio .E. Teruel, Rafel Prohens), Polytechnic University of Catalunya (Toni Guillamon), University of Sevilla (Enrique Ponce)

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Scientific events organisation

8.1.1.1. Member of the organizing committees

- Reprosciences 2015, April 13-15, Rennes, co-organized by Frédérique Clément, Yves Combarnous, Florian Guillou, Joëlle Cohen-Tannoudji and Olivier Kah.
  2 oral presentations were given by the team

1. Aymard B, Clément F, Monniaux D, Postel. *Multiscale modeling of terminal folliculogenesis*.
2. Clément F, Monniaux D, Michel P, Stiehl T.*Mathematical model of the basal follicular development*

- "Modeling in Cell and Developmental Biology", ITMO BCDE annual workshop. Dec 1st, Paris, co-organized by Frédérique Clément, Kaurent Héliot, Nadine Peyrieras and Sylvie Schneider-Maunoury. 3 posters were presented by the team
  1. Fernández-García S, Desroches M, Krupa, Vidal A, de Vico Fallani F, Clément F. *Modeling ionic and secretory rhythms in adult and embryonic neural networks with multiple time scale dynamical systems.*
  2. Köksal Ersöz E, Vidal A, Clément F. Complex oscillatory rhythms in neurohormone secretion : the instance of the GnRH neurosecretory system.
  3. Postel M, Karam A, Latbi M, Pezeron G, Tran L, Clément F, Schneider-Maunoury S. *Designing a mathematical model of the dynamics of progenitor cell populations in the mouse cerebral cortex.*

  Organization of mini-symposia at the SIAM Conference on the Application of Dynamical Systems May 17-21, SnowBird
  - Mathieu Desroches co-organized (with Morten Brøns) the *Model Reduction and Epsilon-free Methods in Singular Perturbation Problems* minisymposium
  - Jonathan Touboul co-organized (with Zack Kilpatrick and Bard Ermentrout) the *Stochastic neuronal dynamics* minisymposium

  Thematic sessions organized within the framework of the CIRB
  - Troisième journée "Biologie & Mathématiques sur la Montagne", November 4th, 2015, co-organization Jonathan Touboul Amaury Lambert and Alain Prochiantz
  - Colloquium *Mathematics of the brain*, Dec. 8th 2015, co-organization Jonathan Touboul and Khashayar Pakdama

8.1.2. Journal

8.1.2.1. Member of the editorial boards

Jonathan Touboul is Associate Editor of *PloS One* and *Frontiers in Neuronal Circuits*

8.1.2.2. Reviewer - Reviewing activities

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

8.1.3. 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.

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 2015) 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

Tanguy Cabana, Limits of randomly connected networks and their dynamics, since September 2013, Université Pierre & Marie Curie (ED386), supervisors: Raphaël Krikorian, Jonathan Touboul and Gilles Wainrib

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

Elif Köksal Ersoz, Synchronization of GnRH neurons: a multiscale mathematical study, since November 2013, Université Pierre & Marie Curie (ED386), 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 (ED386), 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 (ED386), supervisors: Marie Postel and Frédérique Clément.

Luis Carlos García del Molino, Dynamics of randomly connected networks and spectral theory of random matrices, Université Denis Diderot (ED393), October 1st, supervisors: Khashayar Pakdaman and Jonathan Touboul.

Cristóbal Quiñinao, Mathematical modeling in Neuroscience: collective behavior of neuronal networks & the role of local homeoproteins diffusion in morphogenesis. Université Pierre & Marie Curie (ED386), June 2nd, 2015, supervisors: Benoît Perthame, Stéphane Mischler (CEREMADE) and Jonathan Touboul.

Mérina Latbi, Modélisation mathématique de la neurogenèse corticale, Centrale Lyon and Master M2 Maths en action (Lyon 1), co-supervisors Frédérique Clément & Marie Postel.

8.2.3. Juries

Jonathan Touboul participated in the selection committee of the Bernstein Award for Computational Neuroscience (BPCN)

Frédérique Clément participated in the admission committee of the Inria Senior Researcher (DR2) open competition

8.3. Popularization

- *The hipster effect: when anticonformists all look the same*. Popularization on the synchronization of random elements inspired from a simplification of brain dynamics. International press coverage in scientific (Science, AMS news, Science et Vie,...) and general information journals (Washington post, JDD, Le soir,...)
- *La recherche sur la reproduction animale et humaine*. Booklet edited by GdR REPRO, including an interview of Alexandre Vidal and a dedicated chapter on "Reproduction, biomathe´matiques et bioinformatique"

9. Bibliography

Major publications by the team in recent years

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[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

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