RESEARCH CENTRE

**Inria Branch at the University of Montpellier**

**IN PARTNERSHIP WITH:**

**CNRS, Université Côte d'Azur**

2024

# ACTIVITY REPORT

## Project-Team

# MATHNEURO

## Mathematics for Neuroscience

**IN COLLABORATION WITH: Laboratoire Jean-Alexandre Dieudonné (JAD)**

**DOMAIN**

**Digital Health, Biology and Earth**

**THEME**

**Computational Neuroscience and Medicine**

Inria

# Contents

# Project-Team MATHNEURO

*Creation of the Project-Team: 2019 January 01*

## Keywords

**Computer sciences and digital sciences**

A6. – Modeling, simulation and control

A6.1. – Methods in mathematical modeling

A6.1.1. – Continuous Modeling (PDE, ODE)

A6.1.2. – Stochastic Modeling

A6.1.4. – Multiscale modeling

A6.2. – Scientific computing, Numerical Analysis & Optimization

A6.2.1. – Numerical analysis of PDE and ODE

A6.2.2. – Numerical probability

A6.2.3. – Probabilistic methods

A6.3. – Computation-data interaction

A6.3.4. – Model reduction

**Other research topics and application domains**

B1. – Life sciences

B1.2. – Neuroscience and cognitive science

B1.2.1. – Understanding and simulation of the brain and the nervous system

B1.2.2. – Cognitive science

# 1 Team members, visitors, external collaborators

## Research Scientists

- Mathieu Desroches [Team leader, INRIA, Senior Researcher]
- Emre Baspinar [INRIA, Researcher]
- Fabien Campillo [INRIA, Senior Researcher]
- Anton Chizhov [INRIA, Advanced Research Position, until Jun 2024]
- Pascal Chossat [CNRS, Emeritus]

## Post-Doctoral Fellow

- Louisiane Lemaire [INRIA, Post-Doctoral Fellow, from May 2024]

## PhD Student

- Guillaume Girier [BCAM]

## Interns and Apprentices

- Camilla Nouveau [INRIA, Intern, from Sep 2024]

## Administrative Assistant

- Marie-Cecile Lafont [INRIA]

## External Collaborator

- Frederic Lavigne [UNIV COTE D'AZUR, until Oct 2024]

# 2 Overall objectives

MathNeuro specializes in multiscale computational modeling of neural dynamics, with a strong emphasis on experimental validation and finalized applications, particularly in pathological behaviors. Our work includes the modeling, analysis, and simulation of systems operating across multiple temporal and spatial scales, ranging from single-cell models to microcircuits and large-scale networks.

In neuroscience, we focus on phenomena such as synaptic plasticity and neuronal excitability, with particular attention to pathological conditions including epileptic seizures, migraines, and neurodegenerative diseases like Alzheimer's.

In terms of methodology, the team brings together specialists in dynamical systems theory, stochastic processes, and data analysis, with a strong emphasis on computational expertise.

We have made a clear commitment to collaborate closely with experimental neuroscience groups, staying as connected to the data as possible, and we aim to strengthen our expertise in this area.

The research in MathNeuro is organized around key thematics and questions coming from Neuroscience, around the prominent concepts of **neuronal (hyper)excitability**, **synaptic plasticity**, **ageing** and **cognition**. Then, we work on these questions in collaboration with experimentalists, in link with experimental data, using mathematical modeling, analysis and simulation. We analyze these questions for both healthy and pathological brain states. The recruitment of Emre Baspinar in the team, in 2023, has brought two novel research topics, on *neurogeometry* (transversal to excitability and plasticity) and on *decision-making* (as part of our research line on cognition).

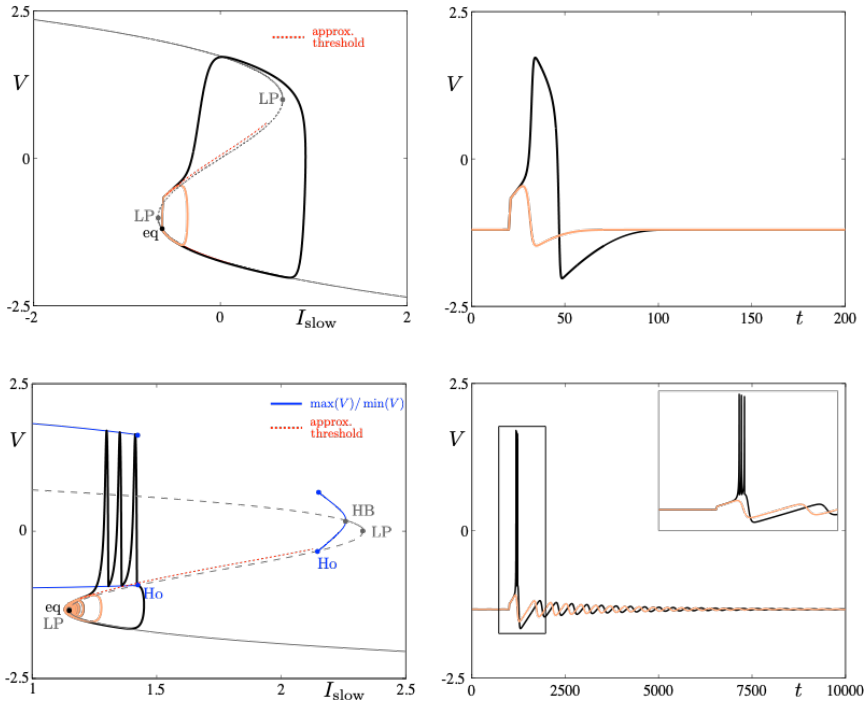


Figure 1: Excitability threshold as slow manifolds in a simple spiking model, namely the FitzHugh-Nagumo model, (top panels) and in a simple bursting model, namely the Hindmarsh-Rose model (bottom panels). This figure is unpublished.

# 3 Research program

We have chosen to structure the MathNeuro research program around two main axes: excitability and cognition. Questions related to plasticity arise within both axes, while aging and memory can be encompassed under cognition.

## 3.1 Excitability

Excitability refers to the all-or-none property of neurons [45, 49]. That is, the ability to respond nonlinearly to an input with a dramatic change of response from "none" — no response except a small perturbation that returns to equilibrium — to "all" — large response with the generation of an action potential or spike before the neuron returns to equilibrium. The return to equilibrium may also be an oscillatory motion of small amplitude; in this case, one speaks of resonator neurons as opposed to integrator neurons. The combination of a spike followed by subthreshold oscillations is then often referred to as mixed-mode oscillations (MMOs) [41]. Slow-fast ordinary differential equation (ODE) models of dimension at least three are well capable of reproducing such complex neural oscillations. Part of our research expertise is to analyze the possible transitions between different complex oscillatory patterns of this sort upon input change and, in mathematical terms, this corresponds to understanding the bifurcation structure of the model. In particular, we also study possible combinations of different scenarios of complex oscillations and their relevance to revisit unexplained experimental data, e.g. in the context of bursting oscillations [42]. In all case, the role of noise [37] is important and we take it into consideration, either as a modulator of the underlying deterministic dynamics or as a trigger of potential threshold crossings. Furthermore, the shape of such time series (i.e., with a given oscillatory pattern) can be analyzed within the mathematical framework of dynamic bifurcations; see section 3.1.4. The main example of abnormal neuronal excitability is hyperexcitability and it is important to understand the biological factors which lead to such excess of excitability and to identify (both in detailed biophysical models and reduced phenomenological ones) the mathematical structures leading to these anomalies. Hyperexcitability is one important trigger for pathological brain states related to various diseases such as

chronic migraine [57], epilepsy [59] or even Alzheimer's Disease [53].

A central axis of research within our group is to revisit models of such pathological scenarios, in relation with a combination of advanced mathematical tools and in partnership with biological labs.

In particular, we started in 2024 an Inria Exploratory Action whose PI is Fabien Campillo. It is focused on the multiscale modeling of Dravet Syndrome (DS) [44], which is a severe encephalopathy that affects children, has a strong genetic component and is characterized, amongst other adverse symptoms, by epileptic crises. Our exploratory action is called 2MDS and it aims to develop mathematical models of neuronal activity in the context of DS, focusing on a specific mutation of a Sodium ion channel present in the majority of patients affected by this disease [54]. Namely, we are developing Markov-state models of ion channels with this mutation, at various population scales, as well as macroscopic models of Hodgkin-Huxley type in order to compare the outputs of our models to experimental data from our partners. This project involves a collaboration with the Inria Project-Team Astral (Pierre Del Moral), as well as, partners in Spain: MathNeuro's external collaborator Serafim Rodrigues, who leads the research group MCEN on mathematical, computational and experimental neuroscience at the Basque Center for Applied Mathematics (BCAM, Bilbao, Spain), and Juan Manuel Encinas, an experimentalist at Achucarro Basque Center for Neuroscience, who leads a research group interested in neurogenesis with a particular focus on DS. Through the 2MDS exploratory action, we have recruited Louisiane Lemaire as a postdoc for 24 months (April 2024-March 2026). She is a specialist on biophysical modeling and she is in charge of the macroscopic model of DS that we are developing. This project caught the attention of the Spanish Dravet Foundation, which invited the team to participate in a COST action proposal aimed at bridging the gap between research on *developmental and epileptic encephalopathies* (DEE). This collaborative network will develop computational models and improve diagnostic tools to better understand and treat DEE.

Around the questions of neuronal excitability and hyperexcitability, we have a number of subprojects, which are listed below.

#### 3.1.1 Neuronal networks dynamics

The study of neuronal networks is certainly motivated by the long term goal to understand how brain is working. But, beyond the comprehension of brain or even of simpler neural systems in less evolved animals, there is also the desire to exhibit general mechanisms or principles at work in the nervous system. One possible strategy is to propose mathematical models of neural activity, at different space and time scales, depending on the type of phenomena under consideration. However, beyond the mere proposal of new models, which can rapidly result in a plethora, there is also a need to understand some fundamental keys ruling the behavior of neuronal networks, and, from this, to extract new ideas that can be tested in real experiments. Therefore, there is a need to make a thorough analysis of these models. An efficient approach, developed in our team, consists of analyzing neuronal networks as dynamical systems. This allows to address several issues. A first, natural issue is to ask about the (generic) dynamics exhibited by the system when control parameters vary. This naturally leads to analyze the bifurcations [2] occurring in the network and which phenomenological parameters control these bifurcations. Another issue concerns the interplay between the neuron dynamics and the synaptic network structure.

#### 3.1.2 Mean-field and stochastic approaches

Modeling neural activity at scales integrating the effect of thousands of neurons is of central importance for several reasons. First, most imaging techniques are not able to measure individual neuron activity (microscopic scale), but are instead measuring mesoscopic effects resulting from the activity of several hundreds to several hundreds of thousands of neurons. Second, anatomical data recorded in the cortex reveal the existence of structures, such as the cortical columns, with a diameter of about 50 $\mu m$ to 1 $mm$, containing of the order of one hundred to one hundred thousand neurons belonging to a few different species. The description of this collective dynamics requires models which are different from individual neurons models. In particular, when the number of neurons is large enough, averaging effects appear, and the collective dynamics is well described by an effective mean-field, summarizing the effect of the interactions of a neuron with the other neurons, and depending on a few effective control parameters. This vision, inherited from statistical physics requires that the space scale be large enough to include a

large number of microscopic components (here neurons) and small enough so that the region considered is homogeneous.

Our group is both using and developing mathematical methods allowing to study neural activity at multiple temporal [19] and spatial scales [4], reproducing and predicting brain states in both healthy [14] and pathological conditions [25, 26].

#### 3.1.3 Neural fields

Neural fields are a phenomenological way of describing the activity of a population of neurons by integro-differential equations. This continuous approximation turns out to be very useful to model large brain areas such as those involved in migraine and visual perception. The mathematical properties of these equations and their solutions are still imperfectly known, in particular in the presence of delays, different time scales and noise.
Our group is developing mathematical and numerical methods for analyzing these equations. These methods are based upon techniques from functional analysis, bifurcation theory, equivariant bifurcation analysis, delay equations, and stochastic partial differential equations. We have been able to characterize the solutions of these neural fields equations and their bifurcations, apply and expand the theory to account for such perceptual phenomena as edge, texture [38], and motion perception. We have developed a neural field model to study migraine-related phenomena [31]. We have also developed a theory of singular perturbations for neural fields equations [3], based in particular on center manifold and normal forms ideas [4].

#### 3.1.4 Slow-fast dynamics in neuronal models

Neuronal rhythms typically display many different timescales, therefore it is important to incorporate this slow-fast aspect in models. We are interested in this modeling paradigm where slow-fast point models, using Ordinary Differential Equations (ODEs), are investigated in terms of their bifurcation structure and the patterns of oscillatory solutions that they can produce. To gain insight into the dynamics of such systems, we use a mix of theoretical techniques — such as geometric desingularization and centre manifold reduction [51] — and numerical methods such as pseudo-arclength continuation [43]. We are interested in families of complex oscillations generated by both mathematical and biophysical models of neurons. In particular, so-called *mixed-mode oscillations (MMOs)* [16], [41, 50], which represent an alternation between subthreshold and spiking behavior, and *bursting oscillations* [42, 48], also corresponding to experimentally observed behavior [39] (see Figure 1). We are working on extending these results to spatio-temporal neural models [3].

#### 3.1.5 Neurogeometry

The primary visual cortex (V1) is the part of the brain which is responsible for first step processing of visual input [47, 61]. This processing is based on identifying local features of the objects in a visual scene and integrating these features to provide a global representation of the objects in V1. This is crucial for a complete visual perception of the objects.

Our goal is to contribute to understanding of V1 functional architecture [55, 56]. To achieve it, we develop geometric modeling of V1 by using tools from differential geometry and partial differential equations [5]. We apply our geometric models to visual perception phenomena and pathological dynamics generating visual hallucinations [35]. This will effectively embed the topic of neurogeometry within the thematics of (hyper)excitability.

### 3.2 Cognition

#### 3.2.1 Modeling associative memory

The processes by which memories are formed and stored in the brain are multiple and not yet fully understood. What is hypothesized so far is that memory formation is related to the activation of certain groups of neurons in the brain. Then, one important mechanism to store various memories is to associate certain groups of memory items with one another, which then corresponds to the joint activation of

certain neurons within different subgroup of a given population. In this framework, plasticity is key to encode the storage of chains of memory items. Yet, there is no general mathematical framework to model the mechanism(s) behind these associative memory processes. We are aiming at developing such a framework using our expertise in multi-scale modeling, by combining the concepts of heteroclinic dynamics, slow-fast dynamics and stochastic dynamics.

The general objective that we wish to pursue in this project is to investigate non-equilibrium phenomena pertinent to storage and retrieval of sequences of learned items. In previous works by team members [13, 1, 22], it was shown that with a suitable formulation, heteroclinic dynamics combined with slow-fast analysis in neural field systems can play an organizing role in such processes, making the model accessible to a thorough mathematical analysis. Multiple choice in cognitive processes require a certain flexibility in the neural network, which has recently been investigated in the submitted paper [23].

Our goal is to contribute to identify general processes under which cognitive functions can be organized in the brain.

#### 3.2.2 Decision-making

Decision-making refers to making a choice between multiple alternatives. It is important to make the choice by taking into account short- and long-term consequences of each alternative. This requires complex interactions between intricate neural mechanisms. These mechanisms are far from being fully understood.

Our goal is to contribute to a better understanding of the neural mechanisms relevant to decision-making. For this, we develop computational models based on mean-field approximations of large dimensional neuronal networks. We test our models on experimental data at behavioral level [34]. Finally, these mean-field models can be integrated to brain simulators. This is useful to study decision-making processes at the whole-brain scale.

## 4 Application domains

The first focus area involves studying various pathologies, their initiation, and propagation. Our research particularly addresses epilepsies [25] and Dravet syndrome; cortical spreading depression in connection with certain types of migraine with aura [12]; and Alzheimer's disease [6]. Additionally, our work on cognition has the potential to contribute to the study of mental disorders such as schizophrenia [60] and obsessive-compulsive disorders [58].

A second key aspect of our work is the development of an independent research focus on experimental approaches, carried out in close collaboration with Serafim Rodrigues' experimental laboratory at BCAM Bilbao. This initiative has been supported by Inria's direction, including contributions toward funding specialized equipment. In particular, MathNeuro has been allowed to purchase electrophysiology and optogenetics equipments and put them at the disposal of the Rodrigues lab in Bilbao via the signature of agreement letters.

## 5 Highlights of the year

- The most significant recent development for MathNeuro is its relocation. During the first half of 2024, MathNeuro moved to the Inria branch at the University of Montpellier. The entire team is now based in Montpellier, a change that fosters optimal collaboration and synergy among team members. The team took advantage of a period with fewer student supervision duties, to carry out this relocation.

- Our move to Montpellier was motivated by essentially three elements. First of all, the strong wish to have all team members in the same place, maximizing the synergy. Second, the will to take part to the construction of what will be in a few years time an independent Inria center. Last but not least, Montpellier has a lot of research activities in the area of experimental neuroscience but little in mathematical and computational neuroscience, which gives us a unique opportunity to place MathNeuro and Inria on the local map, with national and international resonance, strengthening

our existing network of collaborations. Since the team has entirely moved to Montpellier, we have initiated research discussions with several groups, namely: at the IES in the group of Benoît Charlot with whom we plan a collaboration, together with Serafim Rodrigues (Bilbao), on using micro-electrode arrays to control the excitability of neural populations in real time; at the LIRMM in the group of Ganesh Gowrishankar, with whom we plan a modeling study related to motor control; at the INM in the group of Karine Loullier, with whom we plan to collaborate on the modeling of corticogenesis; at the IGMM in the group of Eric J. Kremer, with whom we are discussing a possible research collaboration on Dravet Syndrome.

- In addition, MathNeuro has gained access to a critical database on ageing research, known as Baltimore Longitudinal Study on Aging (BLSA), which represents a major opportunity for the team. This access was made possible thanks to the dedicated efforts of several Jurists and CPPI from Inria, as well as, the DPO department.

  As a result, a *Data Transfer Agreement (DTA)* was signed by Inria and the National Institute on Aging (NIA), part of the National Institute of Health (NIH, USA). This will allow the MathNeuro team to access and work on the BLSA database collected by NIA (see above for details). This DTA is part of an international research project to which MathNeuro participate together with the the Basque Center for Applied Mathematics (BCAM, Bilbao, Spain), the University of Sherbrooke (Canada), and VU Amsterdam Medical Center (VUMC, Netherlands). This project focuses on ageing with the overarching aim to obtain new biomarkers for pathological ageing.

- This year marks the first time the partner experimental lab of Serafim Rodrigues in Bilbao has provided results and data that we are beginning to analyze and utilize. This endeavor has been actively supported by Inria's direction.

# 6 New software, platforms, open data

## 6.1 New Platforms

**Participants:** Emre Baspinar, Damien Depannemaecker *(Institut de Neurosciences des Systèmes, Aix-Marseille Université)*.

The Virtual Brain (TVB) is a platform which is used for brain simulations. This tutorial aims to create familiarity with TVB through simulations related to different brain states and epileptic dynamics. This tutorial is organized in PYTHON notebooks and it was prepared for a hands-on session taught during the EBRAINS Brain Simulation Workshop, in Bilbao, on 4th June 2024. It is accessible via the EBRAINS wiki page.

The objective of this hands-on session was to create a familiarity with TVB for the participant by performing simulations related to different brain states and epileptic dynamics. At the beginning, the TVB framework and its building blocks are described. Then, in Part Ia, a mean-field framework is introduced for modeling neuronal population dynamics. We use this framework to simulate brain states at population level. In Part Ib, a generalization of this framework is introduced, to be able to simulate at the scale of the entire brain via TVB. In Part II, an examplary epileptic scenario of seizure propagation is introduced using TVB. Part Ia and Part Ib can be found in the drive, and they are accessible in the lab. For Part II, we refer to the following collaboration.

# 7 New results

This section is organized according to the three main neuroscience thematics currently treated in MathNeuro, namely: **excitability**, **ageing** and **cognition** (which includes memory and decision-making).

## 7.1 Excitability

**Participants:** Emre Baspinar, Fabien Campillo, Mathieu Desroches, Serafim Rodrigues *(BCAM, Spain)*.

### 7.1.1 Neuronal networks and neural fields

We have initiated about one year ago a new collaboration with the *Institut de Neuroscience des Systèmes* in Marseille, in particular with Damien Depannemaecker and Viktor Jirsa, on multiple-timescale dynamics of neuronal networks. We have already one article accepted for publication, described next. To model the dynamics of neuron membrane excitability many models can be considered, from the most biophysically detailed to the highest level of phenomenological description. Recent works at the single neuron level have shown the importance of taking into account the evolution of slow variables such as ionic concentration. A reduction of such a model to models of the integrate-and-fire family is interesting to then go to large network models. In this paper, we introduce a way to consider the impairment of ionic regulation by adding a third, slow, variable to the adaptive Exponential integrate-and-fire model (AdEx). We then implement and simulate a network including this model. We find that this network was able to generate normal and epileptic discharges. This model should be useful for the design of network simulations of normal and pathological states. The manuscript [32] has been accepted for publication in Journal of Computational Neuroscience.

We are also pursuing our long-term project on the modeling of hyperexcitability, in particular in the context of Cortical spreading depolarization (CSD). This collaboration is historical in MathNeuro and it continues to be the subject of a strong collaboration with Massimo Mantegazza (IPMC, Inserm, Sophia Antipolis). Recently, we have extended our temporal model for the initiation of CSD (topic of the PhD thesis of Louisiane Lemaire in MathNeuro, defended in 2021) towards spatially-extended activity to account for the propagation of the phenomenon throughout the cortex. Emre Baspinar is now actively participating to the project, which constituted a part of his research program for his recruitment at Inria. The latest work, recently submitted for publication, is described below.

CSD is a wave of neural depolarization that initiates locally and then slowly spreads across the cortex. It is characterized by (i) initial neural hyperexcitability, (ii) prolonged neural silence following the hyperexcitability. CSD is implicated in several pathologies, particularly in migraine. Although there is an extensive literature on the role of excitatory neurons in CSD, much less is known about the role of inhibitory neurons. In this work, we study the role of inhibitory neurons in migraine-related CSD initiation and propogation, at both experimental and computational levels. We perform experiments in mouse brain slices and develop a novel computational model to unveil the mechanisms underlying the experimental results. In the experiments, we test the role of inhibitory neurons in CSD propagation by modulating their activity with optogenetic and pharmacological tools. In the modeling part, we simulate the activity of large excitatory and inhibitory populations of excitatory and inhibitory neurons by using a neural field model. The model is based on an excitatory-inhibitory population pair which is coupled to a potassium concentration variable. Our experimental and simulation results show that the decrease of the synaptic activity of inhibitory neurons can enhance CSD propagation, because of the reduction of the inhibitory synaptic weight, whereas their spiking activity can enhance CSD propagation because of increased extracellular potassium. The manuscript [31] has been submitted for publication to the journal PLoS Computational Biology and is under review.

We are currently exploring the role of astrocytes in the propagation of CSD, which is the topic of the internship of Camilla Nouveau in MathNeuro, which started in September 2024 and will end in February 2025.

### 7.1.2 Multiple-timescale dynamics at the level of single neurons

We have an ongoing collaboration with Piotr Kowalczyk (Wrocław University, Poland) and S. Rodrigues (BCAM, Spain) on integrate-and-fire model of single neuron activity. Over the past year, we have finalized and published a second article on the topic, following [18]. In this new work, we present a computational study of the Conductance-Based Adaptive Exponential (CAdEx) integrate-and-fire neuronal model, focusing on its multiple timescale nature, and on how it shapes its main dynamical regimes. In particular, we show that the spiking and so-called delayed bursting regimes of the model are triggered by

discontinuity-induced bifurcations that are directly related to the multiple-timescale aspect of the model, and are mediated by canard solutions. By means of a numerical bifurcation analysis of the model, using the software package COCO [40], we can precisely describe the mechanisms behind these dynamical scenarios. Spike-increment transitions are revealed. These transitions are accompanied by a fold and a period-doubling bifurcation, and are organized in parameter space along an isola of periodic solutions with resets. Finally, we also unveil the presence of a homoclinic bifurcation terminating a canard explosion which, together with the presence of resets, organizes the delayed bursting regime of the model. This work has been partially done during stays of Serafim Rodrigues in MathNeuro, and the manuscript [28] has been published in the Bulletin of Mathematical Biology.

This year, we have initiated a new collaboration with an experimental group in Bilbao, at Achucarro the Basque Center for Neuroscience, together with our close collaborator Serafim Rodrigues (BCAM). Namely, we are now working with the lab of Joaquin Piriz, a specialist of mood disorder, in particular in link with a specific brain region, the lateral Habenula (LHb). Mathieu Desroches and Fabien Campillo, together with Serafim Rodrigues, are working on a multiscale mathematical model of recordings of LHb neural data collected by Joaquin Piriz. LHb neurons have general bursting activity and there are already a number of studies modeling these. The novelty here is the presence of two different bursting patterns observed in the data from the Piriz lab. We have made a phenomenological multiple-timescale model generating these two bursting patterns based upon the behavior of two slow processes, which we suspect are related to slow potassium and calcium currents. The model reproduces the collected data, both in a deterministic and in a stochastic environment. We are also developing a burst-detection algorithm in order to be able to automatically analyze the data from our collaborator. A manuscript is in preparation and will be submitted for publication towards the end of the winter 2025.

In 2024, we have also pursued our long-term collaboration with the Applied Mathematics Department of the University of Balearic Island, especially with Antonio E. Teruel, with whom we have published 5 articles over the past 10 years, in particular [16]. This research line is focusing on piecewise-linear (PWL) models of neural activity, with the aim to construct simple models that are more amenable to analysis and simulation while retaining all salient features of smooth biophysical models. In particular, in the context of the PhD project of Jordi Penalva Vadell (successfully defended in January 2024 and co-supervised by Mathieu Desroches), we have focused on PWL models of bursting oscillations. In the work published this year, we construct a PWL version of the Morris–Lecar neuron model, denoted PWL-ML, and we thoroughly analyze its bifurcation structure with respect to three main parameters. Then, focusing on the homoclinic connection present in our PWL-ML, we study the slow passage through this connection when augmenting the original system with a slow dynamics for one of the parameters, thereby establishing a simplified framework for this slow-passage phenomenon. Our results show that our model exhibits equivalent behaviors to its smooth counterpart. In particular, we identify canard solutions that are part of spike-adding transitions. Focusing on the one-spike and on the two-spike scenarios, we prove their existence in a more straightforward manner than in the smooth context. In doing so, we present several techniques that are specific to the piecewise-linear framework and with the potential to offer new tools for proving the existence of dynamical objects in a wider context. The manuscript [29] has been published in the Journal of Nonlinear Science.

#### 7.1.3 Multiscale modeling of Dravet Syndrome

**Participants:** Fabien Campillo, Mathieu Desroches, Louisiane Lemaire, Serafim Rodrigues *(BCAM, Spain, and external collaborator of MathNeuro).*

This project started in early 2024, and is funded by the Exploratory action 2MDS. In particular, we recruited Louisiane Lemaire to work on this project. She is an expert in the modeling of hyperexcitability, in particular in the context of ion channel mutations. She had done her PhD in MathNeuro on the CSD project. She joined our team in Montpellier in April 2025.

Dravet syndrome is a developmental and epileptic encephalopathy (DEE) that typically begins in the first year of life. This complex pathology is characterized by drug-resistant seizures, various comorbidities such as cognitive delay, and a risk of early death. Most cases are due to mutations of $Na_V1.1$,

a voltage-gated sodium channel expressed in fast-spiking (FS) inhibitory neurons. The pathological mechanism in the initial stage of the disease involves impaired function of those neurons, leading to network hyperexcitability. However, the details remain unclear.

Mutations of $Na_V1.1$ may result in non-functional channels or channels with altered gating properties. We focus on the less studied case of altered gating, by investigating how it impairs neuronal activity in the case of a specific mutation (A1783V). Using recordings in cell lines, Layer *et al.* [52] showed that A1783V alters the voltage dependence of channel activation, as well as the voltage dependence and kinetics of slow inactivation. Slow inactivation is a mechanism distinct from the fast inactivation of sodium channels at each spike, developing much more slowly, during prolonged trains of depolarization. Implementing the three effects of the mutation in a conductance-based model, Layer *et al.* predict that altered activation has the largest impact on channel function, as it causes the most severe reduction in firing rate.

Using conductance-based models tailored to the dynamics of FS inhibitory neurons, we examine how the three alterations affect susceptibility to depolarization block, another firing deficit aside from frequency reduction. We look deeper into slow inactivation, exploiting the timescale difference with the rest of the system. We find that slow inactivation of mutant channels at lower voltage values than wild type channels favors depolarization block upon sustained stimulation. More precisely, shifting the steady-state voltage dependence of slow inactivation destroys the stable limit cycle of the full system corresponding to tonic spiking, and creates a stable equilibrium corresponding to depolarization block. The accelerated kinetics of slow inactivation in mutant channels hastens the transition from tonic spiking to depolarization block. These findings suggest that alterations of $Na_V1.1$ slow inactivation should not be neglected as they might play an important pathological role, adding to the conclusions of Layer et al. on the consequences of altered $Na_V1.1$ activation. We test our predictions with classical ramped electrophysiology protocols.

A manuscript is in preparation and should be submitted for publication at the end of the winter 2025.

#### 7.1.4 Neuronal excitability: Interface with electrophysiological experiments

**Participants:** Fabien Campillo, Mathieu Desroches, Serafim Rodrigues *(BCAM, Spain)*.

In 2024, several key developments occurred in the experimental laboratory project at BCAM, the so-called *NeuroMATH* lab. A dual protocol was implemented to study neuronal excitability dynamics. The “voltage-clamp” (VC) protocol with a slow ramp on the target stabilized membrane potential to reveal the excitability structure of neurons, while the “current-clamp” (CC) protocol with slow ramp on the target confirmed the separation between slow and fast components of the neuronal model. As a result, we are currently investigating the bifurcation structure of real neurons directly from experimental data, which is a great tool to validate model as well as explore the parameter space of neurons. Furthermore, we are currently using a *dynamic-clamp* protocol to adjust the neuron’s behavior, transforming an integrator neuron into a resonator neuron; we are effectively confirming experimental and theoretical predictions obtained in the PhD project of Guillaume Girier (successfully defended in September 2024) and published in 2023 [21].
These experiments were initiated during a one-month stay in Bilbao by Fabien Campillo and Mathieu Desroches in the winter 2024, and they are still running in order to obtain enough trials and material prior to writing a research article.

### 7.2 Ageing

We have continued our research activities on pathological ageing, in particular in the context of Alzheimer’s Disease (AD). We have been part for a few years of an international consortium investigating these questions with biological experiments, data-scientific approaches and some modeling. The consortium brings together medical doctors, biologists, data scientists and modelers. Within this context, our core collaboration involves Tàmas Fülöp (a geriatrician) and his team at the University of Sherbrooke (Canada) and our close collaborator Serafim Rodrigues (BCAM, Bilbao, Spain) and his team MCEN. We have already published a number of articles, both on data-scientific approaches to ageing studies [20] and also on the

so-called *infection hypothesis* of AD [6]. In 2024, we have published a book chapter (see description below) on this hypothesis, and we have also obtained access to a major database on aging, BLSA, via a data transfer agreement (DTA) signed by Inria and the National Institute on Aging (NIA, NIH, USA). We plan to study using variable data-scientific approaches in order to identify new biomarkers of pathological ageing and inform future models that we wish to build up.

Alzheimer disease (AD) is a disastrous neurodegenerative disease for which presently no consensus exists neither for the etiology nor for the efficacity of treatments. The amyloid hypothesis of the disease pathogenesis predominated during decades stating that amyloid beta (A$\beta$) formation and oligomerization is the major cause for AD. Recently, beside the amyloid plaques and neurofibrillary tangles, the neuroinflammation was added as a derivative of these misfolded proteins. However, the recent clinical failure of trials targeting the A$\beta$ raised again the hypothesis of a possible infectious origin for AD. Even if this hypothesis was first evoked already by Alois Alzheimer, it is not yet fully accepted. Many studies have supported that microorganisms, including spirochetes, herpesviruses and *Porphyromonas gingivalis* play a role in AD and beta-amyloid peptide (A$\beta$) is an antimicrobial peptide. These data gave new impetus to the infection hypothesis. In this chapter, we have discussed why the amyloid hypothesis by itself does not explain AD, how the infection hypothesis may induce AD, and what are the consequences for a healthy brain considering the numerous treatment avenues for improving the quality of life of the older subjects. This work was partially done during a stay of Serafim Rodrigues in MathNeuro, and the manuscript [30] was published as a book chapter in the book Brain and Mental Health in Ageing (Healthy Ageing and Longevity vol. **21**, Springer).

## 7.3 Cognition

**Participant:** Emre Baspinar, Fabien Campillo, Pascal Chossat, Mathieu Desroches.

### 7.3.1 Memory

We have continued along the year 2024 our research line on modeling memory processes with different strategies, both with dynamical systems and Bayesian inference.

**Associative memory**

In the context of the ANR project HEBBIAN (PI: Arnaud Rey, CNRS, Marseille), we are working on modeling associative memory using multiple-timescale dynamical systems and heteroclinic dynamics in the context of attractors networks. This research line has given a number of articles [1, 13, 22, 24], all of them mostly focused on abstract mechanism and computations. In the context of this ANR project, we are working on data collected in the lab of Arnaud Rey, and we are adapting the model and its plasticity rules to be able to reproduce the data. This project still involves Elif Köksal Ersöz, who started to work on it as a postdoc in MathNeuro in 2017-2019 and continued to contribute to it during her follow-up postdoc at Inserm in Rennes. She was recruited as IFSP in 2024 at the Inria Center of Lyon (EP Cophy currently in creation) and she will continue to collaborate with us on this research line. In particular, we invited her to participate to the ANR HEBBIAN. The annual meeting of the ANR was organized in Marseille in December 2024, to which Pascal Chossat and Mathieu Desroches participated and made informal presentations.

In 2024, the manuscript [33] by Pascal Chossat, Elif Köksal Ersöz and Frédéric Lavigne (BCL lab, UniCA) was submitted for publication and is currently under review. This work focuses on gain modulation of actions selection without synaptic relearning. Adaptation of behavior requires the brain to change goals in a changing environment. Synaptic learning has demonstrated its effectiveness in changing the probability of selecting actions based on their outcome. In the extreme case, it is vital not to repeat an action to a given goal that led to harmful punishment. The present model proposes a simple neural mechanism of gain modulation that makes possible immediate changes in the probability of selecting a goal after punishment of variable intensity. Results show how gain modulation determine the type of elementary navigation process within the state space of a network of neuronal populations of excitatory neurons regulated by inhibition. Immediately after punishment, the system can avoid the punished populations by going back or by jumping to unpunished populations. This does not require particular

credit assignment at the “choice" population but only gain modulation of neurons active at the time of punishment. Gain modulation does not require statistical relearning that may lead to further errors, but can encode memories of past experiences without modification of synaptic efficacies. Therefore, gain modulation can complement synaptic plasticity.

**Bayesian brain and the free energy principle.**

The *Principle of Free Energy* (FEP) is a mathematical and conceptual framework proposed by Karl Friston [46]. This principle posits that living organisms (their organs, brains, and the neurons therein) aim to minimize surprise or uncertainty about their environment. According to this theory, this minimization is achieved by creating internal models of their environment to predict sensory inputs. By reducing the discrepancy between predicted and actual sensory data—referred to as free energy or surprise—organisms adapt effectively, learn, and make predictions. This principle extends beyond the Bayesian brain hypothesis; it underpins theories of perception, action, and cognition while offering insights into how biological systems maintain stability and navigate complex environments through predictive processing. Although proposed nearly two decades ago, this theory has gained significant traction in recent years, spreading far beyond neuroscience and into other scientific fields. Furthermore, experimental validations have begun to confirm its premises. While this approach generates excitement, it also faces criticism for its abstract and ambitious nature.

This year, we have started to address this topic through the lens of *nonlinear filtering (NLF)* [7]. Bayesian NLF, an area of expertise for Fabien Campillo (who leads this research line in Mathneuro), is a fundamental yet underexplored component of the FEP. This novel direction within Mathneuro has benefitted from discussions in 2024 with Serafim Rodrigues, whose network of collaborators include Karl Friston. Additionally, we have initiated discussions with Daniele Avitabile, a professor at VU Amsterdam, who focuses on inverse problems and NLF in the context of neuroscience. This collaborative approach aims to provide a deeper understanding of the FEP and its applications, particularly in neuroscience.

We are preparing an opinion article on this topic, which should be submitted for publication towards the Spring 2025.

### 7.3.2 Decision-making

This is a new research line in MathNeuro, led by Emre Baspinar and for which he has brought to the team novel collaborations, in particular with Alain Destexhe (CNRS, Paris-Saclay) and Rubén Moreno-Bote (UPF, Barcelona, Spain). This year, two projects have been finalized, one submitted for publication and the other one published. They are both described below.

Decision-making refers to choosing one of the existing alternatives. A decision is often made based on a strategy which maximizes long term benefits of the chosen alternatives. Neural mechanisms underlying strategy-based decision-making are far from fully understood. In this work, we propose a strategy-based decision-making model to contribute to better understanding of relevant neural mechanisms in human and macaque. The model is based on two neural populations. Each population is composed of a pair of excitatory-inhibitory subpopulations in cortical layer 2/3. The model is biophysically plausible since it is based on long-range cortico-cortical connections between the layer 2/3 populations. These connections are excitatory. This long-range excitation is conflicted by an inhibition based on local connections within the populations. This configuration introduces a competition between the layer 2/3 populations, sufficient for making a decision to choose between two alternatives shown on the monitor. We integrate the model with a learning mechanism. This allows the model to learn the optimal decision-making strategy which maximizes the long term benefits. We test the model on two decision-making tasks applied on human and macaque. This model elaborates certain biophysical details, which were not considered by the previous models proposed for similar decision-making tasks. Finally, it can be embedded in a brain simulator such as The Virtual Brain to study large-scale brain dynamics. The manuscript [34] has been submitted for publication and is currently under review.

Learning to make adaptive decisions involves making choices, assessing their consequence(s), and leveraging this assessment to attain higher rewarding states. Despite vast literature on value-based decision-making, relatively little is known about the cognitive processes underlying decisions in highly uncertain contexts. Here we aim at understanding and formalizing the brain mechanisms underlying these processes. To this end, we first designed and performed an experimental task. Second, we formalized the neurocognitive processes underlying decision-making within this task. Both the experimental

results and the model contribute to understanding how uncertain scenarios are incorporated into the neural dynamics of decision-making. The manuscript [36] has been published in Frontiers in Behavioral Neuroscience.

# 8 Partnerships and cooperations

**Participants:** Emre Baspinar, Fabien Campillo, Mathieu Desroches.

## 8.1 International research visitors

### 8.1.1 Visits to international teams

**Research stays abroad**

**Emre Baspinar**

**Visited institution:** Basque Center for Applied Mathematics, Bilbao

**Country:** Spain

**Dates:** March 1-31, 2024

**Context of the visit:** Collaboration with Serafim Rodrigues on contact geometry in the context of slow-fast neural dynamics

**Mobility program/type of mobility:** Research stay

**Fabien Campillo**

**Visited institution:** Basque Center for Applied Mathematics, Bilbao

**Country:** Spain

**Dates:** February 13-16, March 1-15 and October 7-10, 2024

**Context of the visit:** Collaboration with Serafim Rodrigues on the Bayesian brain hypothesis, on Topological Data Analysis and on Dravet Syndrome, in the context of the M&M's Dialogue Days (see Section 9.1.2) and of the 2MDS Inria Exploratory Action (see Section 8.2.2 below), respectively.

**Mobility program/type of mobility:** Research stay

**Mathieu Desroches**

**Visited institution:** MCEN team, Basque Center for Applied Mathematics, Bilbao

**Country:** Spain

**Dates:** January 9-19, March 11-22, July 1-12 and October 7-10, 2024

**Context of the visit:** Collaboration with Serafim Rodrigues on neuronal excitability, in the context of the PhD of Guillaume Girier, on data-science methods in Neuroscience (also with MCEN postdoc Danillo Souza) and on Dravet Syndrome, in the context of the M&M's Dialogue Days (see Section 9.1.2) and of the 2MDS Inria Exploratory Action (see Section 8.2.2 below), respectively.

**Mobility program/type of mobility:** Research stay

## 8.2 National initiatives

### 8.2.1 ANR projects

**HEBBIAN**

**Title:** Apprentissage hebbien de séquences

**Duration:** From October 1, 2023 to September 30, 2027

**Inria contact:** Mathieu Desroches

**Coordinator:** Arnaud Rey (CNRS, Marseille)

**Summary:** This project is articulated around three main research questions that are central to better understand sequence learning mechanisms: Q1) What is the relationship between the spacing between two repetitions of the same sequence and the development of a memory trace of that sequence? Q2) How does sequence encoding vary with sequence size, number, and learning context? Q3) How are small, regular sequences that are embedded in larger sequences, encoded (i.e., the parts and whole problem)? Our project is also based on two main research hypotheses. We first assume that the mechanisms supporting the learning of sequential information are based on elementary associative learning mechanisms that are evolutionarily ancient and shared by humans and non-human primates (Rey et al., 2012, 2019a, 2022). Our second main hypothesis assumes that these associative learning mechanisms are mainly supported by Hebbian learning principles (Brunel & Lavigne, 2009; Köksal Ersöz et al., 2020, 2022; Tovar & Westermann, 2023).

### 8.2.2 Inria Exploratory Action

**2MDS**

**Title:** Multiscale Modeling of Dravet Syndrome

**Duration:** From May 1, 2024 to April 30, 2026

**Inria contact:** Fabien Campillo

**Coordinator:** Fabien Campillo

**Webpage** : Inria Exploratory Action 2MDS

**Summary:** The Inria Exploratory Action 2MDS is being co-directed by Fabien Campillo (EPI MathNeuro), and Pierre Del Moral (EPI Astral). Mathieu Desroches, head of MathNeuro project, and Serafim Rodrigues, head of the “Mathematical, Computational and Experimental Neuroscience” MCEN research group at BCAM (Bilbao, Spain) are also participating in this project. The aim of 2MDS is to develop a multiscale modeling framework for channelopathies, a group of diseases caused by the dysfunction of ion channels or their interacting proteins. These pathologies include the Dravet Syndrome (DS), a severe form of child epilepsy. This project will also have a substantial experimental component, conducted by our collaborator Serafim Rodrigues in his experimental laboratory (The “NeuroMath” lab, University of the Basque Country campus, Leioa.), also in collaboration with Juan Manuel Encinas of the Basque center for neuroscience, an expert in DS (Martín-Suárez et al., 2020).

# 9 Dissemination

## 9.1 Promoting scientific activities

### 9.1.1 Scientific events: organisation

**Emre Baspinar** and **Mathieu Desroches** were co-organizer of EBRAINS Brain Simulation Workshop, Bilbao, Spain, June 3-7, 2024.

### 9.1.2 Scientific events: selection

**m&m's Dialogue Days**

**Fabien Campillo** and **Mathieu Desroches** organized, together with Serafim Rodrigues *(BCAM, Bilbao, Spain)*, a series of short events with scientific talks entitled "m&m's dialogue days". The goal of these days is to strengthen the collaboration between the MATHNEURO and MCEN teams. Each event may focus on a specific theme and can also provide an opportunity to invite a prominent figure in the field of neuroscience, or a related field, to engage in in-depth discussions and collaborations between our teams over several days; see the website of this series for a details of the m&m's days organized in 2024. Invited scientists in 2024 included Alain Destexhe (CRNS, NeuroPSI, Saclay) and Juan-Manual Encinas (Achucarro Center for Neuroscience, Leioa, Spain)

**Member of the conference program committees**

**Mathieu Desroches** has been board member of the International Conference on Mathematical Neuroscience since September 2024.

**Reviewer**

**Fabien Campillo** acted as a reviewer for the conference CARI (the African Conference for the Research in Computer Science and Applied Mathematics).

### 9.1.3 Journal

**Member of the editorial boards**

**Fabien Campillo** is a member of the editorial board of Arima.

**Mathieu Desroches** is co-founder and co-Editor-in-Chief of the SIAM series on Mathematical Neuroscience.

**Reviewer - reviewing activities**

**Emre Baspinar** acted as a reviewer for Journal of Mathematical Imaging and Vision, and Discrete and Continuous Dynamical Systems - B.

**Fabien Campillo** acted as a reviewer for the Journal of Mathematical Biology, for ARIMA.

**Pascal Chossat** acted as reviewer for the Journal of Computational Neuroscience.

**Mathieu Desroches** acted as a reviewer for Chaos: An International Journal of Nonlinear Science, Physica D: Nonlinear Phenomena, PLoS Computational Biology, Scientific Reports and SIAM Journal on Applied Dynamical Systems.

### 9.1.4 Invited talks

**Emre Baspinar** and **Damien Depannemaecker**[Institut de Neurosciences des Systèmes, Aix-Marseille Université] gave a hands-on session entitled "TVB environment for whole brain models" in EBRAINS Brain Simulation Workshop, Bilbao, Spain, June 3-7, 2024.

**Emre Baspinar** gave an invited talk entitled "A biologically plausible decision-making model based on interacting cortical columns" in Workshop Challenges in Mathematical Neuroscience, Nice, February 20-23, 2024.

**Emre Baspinar** gave an invited talk entitled "A neural field model for ignition and propagation of cortical spreading depression" in European Nonlinear Oscillations Conference, Delft, Netherlands, May 23-27, 2024.

**Fabien Campillo** and **Mathieu Desroches** gave an invited seminar talk entitled "Présentation de l'équipe-projet Inria MathNeuro : *Mathematics for Neuroscience*" at the Institut des Neurosciences de Montpellier, Montpellier, November 22, 2024.

**Pascal Chossat** gave an invited talk entitled "Sequences and branching of learned states in neural networks, with an application to decision making" at the Workshop on Nonlinear Dynamics, Hamburg, Germany, July 24, 2024.

**Mathieu Desroches** gave an invited presentation entitled "Complex neuronal bursting oscillations: the role of slow variables" at the *Galvani in-person meeting*, Saint-Malo, May 16, 2024.

**Mathieu Desroches** gave an invited talk entitled "Endocannabinoids and neurodegeneration: two examples of collaboration between mathematicians and biologists" at the *Mathematics and Life ealth Forum*, Shanghai, China, November 3, 2024.

**Mathieu Desroches** gave an invited seminar talk entitled "Classification of complex oscillations in slow-fast dynamical systems with one and two slow variables" in the School of Mathematical Sciences, Shanghai Jiao Tong University, China, November 4, 2024.

**Fabien Campillo** was invited to give two talks in March 2024 at the BCAM in Bilbao, the first on "the free energy principle"' and the second on "the nonlinear filtering."

#### 9.1.5 Contributed talks

**Emre Baspinar** gave a talk entitled "A neural field model for ignition and propagation of cortical spreading depression" at the International Conference on Mathematical Neuroscience, Dublin, Ireland, June 12, 2024.

**Pascal Chossat** gave a talk entitled "Analyzing sequential activity in neural networks from the dynamical systems perspective" at the International Conference on Mathematical Neuroscience, Dublin, Ireland, June 14, 2024.

**Mathieu Desroches** gave a talk entited "Observing unstable states in experiments" at the International Conference on Mathematical Neuroscience, Dublin, Ireland, June 14, 2024.

**Louisiane Lemaire** gave a talk entitled "Integrate-and-fire neurons with potassium dynamics that capture switches in neuronal excitability class and firing regime" at the International Conference on Mathematical Neuroscience, Dublin, Ireland, June 12, 2024.

#### 9.1.6 Leadership within the scientific community

**Fabien Campillo** is a founding member of the African scholarly Society on Digital Sciences (ASDS).

**Mathieu Desroches** was member of the scientific committee of the Complex System Academy of the UCA$^{JEDI}$ IDEX until June 2024.

#### 9.1.7 Scientific expertise

**Mathieu Desroches** has been reviewing grant proposals for German Research Foun dation (DFG).

**Mathieu Desroches** has been evaluating a promotion case to Associate Professor for the Department of Mathematics, University of California Irvine (USA).

**Mathieu Desroches** has been evaluating a promotion case to Associate Professor for the Department of Mathematics and Statistics, University of Exeter (UK).

#### 9.1.8 Research administration

**Fabien Campillo** is member of the "Inria Evaluation Committee" (CE).

**Fabien Campillo** is member of the "Formation Spécialisé de Site (FSS)" of the Inria centre at UniCa.

**Mathieu Desroches** was member of the "Comité de Suivi Doctoral (CSD)" of the Inria Centre at UniCa until June 2024.

**Mathieu Desroches** was mentoring the PhD seminar of the Inria centre at UniCa until June 2024.

### 9.2 Teaching - Supervision - Juries

#### 9.2.1 Teaching

**Master: Mathieu Desroches**, Modèles Mathématiques et Computationnels en Neuroscience (Lectures, example classes and computer labs), 18 hours (February 2024), M1 (BIM), Sorbonne Université, Paris, France.

**Master: Mathieu Desroches**, Multiple Timescale Dynamics in Neuroscience, (Lectures, example classes and computer labs), 9 hours (January 2024) and 18 hours (November-December 2024), M1 (Mod4NeuCog), Université Côte d'Azur, Sophia Antipolis, France.

**Masters and Engineer schools:** With the project to write a book, **Fabien Campillo** proposes a set of applications of particle filtering, developed in the context of lectures given during many years in Masters and Engineer schools. See the associated web page and git repository.

#### 9.2.2 Supervision

**PhD Guillaume Girier:** Basque Center for Applied Mathematics (BCAM, Bilbao, Spain)was doing a PhD on "A mathematical, computational and experimental study of neuronal excitability", co-supervised by S. Rodrigues (BCAM) and Mathieu Desroches, and successfully defended at the University of the Basque Country (Leioa, Spain) on September 20, 2024.

**PhD Jordi Penalva Vadell:** University of the Balearic Islands (UIB, Palma, Spain) was doing a PhD on "Neuronal piecewise linear models reproducing bursting dynamics", co-supervised by A. E. Teruel (UIB), C. Vich (UIB) and Mathieu Desroches, and successfully defended at UIB on January 24, 2024.

**Master 2 internship: Camilla Nouveau**, University of Bologna (Italy), is doing a Master 2 internship on "Modeling of astro-neural population dynamics and its application to cortical spreading depression", supervised by Emre Baspinar, September 2024 - February 2025.

#### 9.2.3 Juries

**Emre Baspinar** was a member of Comité de Suivi Individuel (CSI) of PhD student Jawad Ali at EHESS (CAMS, Paris).

**Fabien Campillo** was a member of the jury for the recruitment of a Chairs of junior professor at Inria centre at Rennes University; he was also a member of the jury for the recruitment of directors of research (grade DR2).

**Mathieu Desroches** was a member of the Comité de Suivi Individuel (CSI) of PhD student Benjamin Böbel at the Inria Center of UniCa (EPI Macbes).

**Mathieu Desroches** was a member of the Comité de Suivi Individuel (CSI) of PhD student Hélène Todd at ENS Paris (Laboratoire de Neurosciences Cognitives Computationnelles).

**Mathieu Desroches** was a member of the Comité de Suivi Individuel (CSI) of PhD student Linda Tomy at Inserm (Laboratoire LTSI, Rennes).

# 10 Scientific production

## 10.1 Major publications


[1] C. Aguilar, P. Chossat, M. Krupa and F. Lavigne. 'Latching dynamics in neural networks with synaptic depression'. In: *PLoS ONE* 12.8 (Aug. 2017), e0183710. DOI: 10.1371/journal.pone.0183710. URL: https://hal.inria.fr/hal-01402179 (cit. on pp. 6, 11).

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[12] O. Chever, S. Zerimech, P. Scalmani, L. Lemaire, L. Pizzamiglio, A. Loucif, M. Ayrault, M. Krupa, M. Desroches, F. Duprat, I. Léna, S. Cestèle and M. Mantegazza. 'Initiation of migraine-related cortical spreading depolarization by hyperactivity of GABAergic neurons and NaV1.1 channels'. In: *The Journal of clinical investigation* 131.21 (1st Nov. 2021), e142203. DOI: 10.1172/JCI142203. URL: https://hal.science/hal-03411366 (cit. on p. 6).

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