RESEARCH CENTER

FIELD
Digital Health, Biology and Earth

Activity Report 2019

Section Partnerships and Cooperations

Edition: 2020-03-21

ABS Project-Team

6. Partnerships and Cooperations

6.1. Regional Initiatives

– Frédéric Cazals is endowed chair within the 3IA Côte d'Azur (http://3ia.univ-cotedazur.fr/), within the focus area *Computational Biology and Bio-Inspired AI.*

6.2. International Research Visitors

6.2.1. Visits of International Scientists

6.2.1.1. Internships

- Internship of Maria Guramare, Harvard University, Cambridge, Massachusetts. Supervision: Frédéric Cazals and Dorian Mazauric. *Shortest Paths under Constraints Problem with Application for Structural Alignments.*
- Internship of Guilherme Santa Cruz, Polytech Nice. Supervision: Frédéric Cazals and Dorian Mazauric. *New method for assessing protein-phenotype relevance interpolating gene expression and biological networks*.
- Internship of Gabriel Djebbar, École Polytechnique de l'Université Nice Sophia Antipolis. Filière Sciences Informatiques, deuxième année du cursus ingénieur (niveau Master 1). Supervision: Frédéric Havet and Dorian Mazauric. *Graph Coloring Games with application on Algorithmic Geometry.*
- Projet de fin d'études de Youssef Benjelloun et Quentin Sautel, École Polytechnique de l'Université Nice Sophia Antipolis. Filière Mathématiques Appliquées et Modélisation, deuxième année du cursus ingénieur (niveau Master 1). Supervision: Dorian Mazauric. *Algorithmes pour le calcul de motif commun d'un ensemble de conformations d'une protéine.*

BEAGLE Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

- CPER LECO++: Parallel HPC architectures evolve and the calculation codes are naturally bound to vary over time. Indeed, the architectures change every 2-3 years while the lifespan of a scientific code is much longer (at least 10 years). Knowing how to control the impacts of these changes in order to automatically adapt the digital simulation codes to maintain a high level of performance is a necessity to guarantee a certain sustainability of the developed code. Currently, these variations are manually managed by programmers which require a high level of expertise as well as time.

  A collaboration between the AVALON teams from LIP and BEAGLE from LIRIS on this subject involved one master trainees this year (funding from Federation Informatique de Lyon – PMSISEE project). More specifically, BEAGLE is interested in designing AEVOL a high performance parallel code for simulating the evolution of a population of bacteria. The different parts of the code have been adapted to the hardware characteristics of current architectures (multicore, vector computing, etc.) for which certain operations have several implementations (CPU or vector) or several parallel variants. Designing the assembly of the right versions and choosing the right parameters remains a difficult problem. In this issue, the AVALON team brings its expertise in the development and exploitation of component models, in parallel programming models and in the expertise of executive supports for HPC.

  A PhD thesis between Avalon and Beagle (Laurent Turpin) linked to the CPER LECO++ project (coordinator: T. Gautier, AVALON) has started with the aim of studying the robustness of computer codes on modern parallel architectures and their evolution. Thus, the targeted hardware is that being acquired through the LECO++ project (ARM machine, massively multi-GPU (10)).

  The work of this thesis aims to study the methods and approaches allowing to contribute to a solution to the problems of composition, choice of parameters and efficient execution on a parallel architecture in HPC. The problem addressed in the thesis concerns the portability of the performance of a parallel application for managing code variants and variations at runtime. The solutions that will be studied will be those at the interface between a programming model and its exploitation by executive support. In order to exploit the performance of a class of machines in a portable manner, the candidate will propose the necessary adaptations, whether to the existing component-based programming model (typically Comet) and to executive support (OpenMP type or an executive engine with task base). A major constraint of this work is the performance at execution: the evaluation will be based on an experimental methodology with AEVol as target application. The target hardware is that of an HPC computing node of tomorrow: a multi-core server coupled with a large number of hardware accelerators - GPUs - allowing to have a significant computing density (approximately from 30 to 128 TFlops double precision for 4 to 16 GPUs).

8.2. National Initiatives

8.2.1. ANR

- Evoluthon (2019-2022): Artificial Life as a benchmark for evolutionary studies, a 4-year project leaded by E Tannier with 2 partners, Beale Inria and Le Cocon, LBBE.
- Dopaciumcity (2014-2018): Dopamine modulation of calcium influx underlying synaptic plasticity, a 4-year project funded by a grant from the ANR-NSF-NIH Call for French-US Projects in Computational Neuroscience. With L. Venance, College de France, CIRB, CNRS/UMR 7241 - INSERM U1050, Paris, France and K Blackwell, Krasnow Institute of Advanced Studies, George Mason University, Fairfax, VA, USA. Supervisor: L Venance (for France) and K.L. Blackwell (for US). Participants: H Berry, I Prokin, A Foncelle

- Dallish (2016-2020): Data Assimilation and Lattice LIght SHeet imaging for endocytosis/exocytosis pathway modeling in the whole cell, Call AAPG ANR 2016. With C. Kervrann (Inria Rennes), J. Salamero (Institute Curie, Paris), B. Laroche (INRA, Jouy-en-Josas). Participants: H. Berry.
- Storiz (2018-2020): Horizontal transfers as documents from extinct or unknown species. Call ANR JCJC 2018. Leaded by Damien de Vienne (LBBE, Lyon) Participant: Eric Tannier
- LncEvoSys (2017-2019): An evolutionary systems approach to understand long non-coding RNA functionality, Call ANR JCJC 2017. Leaded by Anamaria Necsulea (LBBE, Lyon). Participant: Eric Tannier

8.2.2. Inria

- Naviscope (Inria Project Lab, 2018-2022): image-guided Navigation and VIsualization of large data sets in live cell imaging and microSCOPy. Nowadays, the detection and visualization of important localized events and process in multidimensional and multi-valued images, especially in cell and tissue imaging, is tedious and inefficient. Specialized scientists can miss key events due to complexity of the data and the lack of computer guidance. In Naviscope we develop original and cutting-edge visualization and navigation methods to assist scientists, enabling semi-automatic analysis, manipulation, and investigation of temporal series of multi-valued volumetric images, with a strong focus on live cell imaging and microscopy application domains. We build Naviscope upon the strength of scientific visualization and machine learning methods in order to provide systems capable to assist the scientist to obtain a better understanding of massive amounts of information. Such systems will be able to recognize and highlight the most informative regions of the dataset by reducing the amount of information displayed and guiding the observer attention. Head: C. Kervrann (Serpico), other EPIs: Aviz, Beagle, Hybrid, Morpheme, Mosaic, Parietal, and MaIage (INRA unit).
- Action Exploratoire "Community Garden Book": IPBES's recent report on declining biodiversity calls for generalization of agroecological, productive, biodiversity and environmental friendly methods, oriented towards participatory action research. This exploratory action is a proposal to develop tools from open science, evolution science and algorithmics for the co-construction and use of an agroecological network of interactions between groups, species, varieties found in fields and gardens.
- Action Exploratoire ExODE: In biology, the vast majority of systems can be modeled as ordinary differential equations (ODEs). Modeling more finely biological objects leads to increase the number of equations. Simulating ever larger systems also leads to increasing the number of equations. Therefore, we observe a large increase in the size of the ODE systems to be solved. A major lock is the limitation of ODE numerical resolution so ware (ODE solver) to a few thousand equations due to prohibitive calculation time. The AEx ExODE tackles this lock via 1) the introduction of new numerical methods that will take advantage of the mixed precision that mixes several floating number precisions within numerical methods, 2) the adaptation of these new methods for next generation highly hierarchical and heterogeneous computers composed of a large number of CPUs and GPUs. For the past year, a new approach to Deep Learning has been proposed to replace the Recurrent Neural Network (RNN) with ODE systems. The numerical and parallel methods of ExODE will be evaluated and adapted in this framework in order to improve the performance and accuracy of these new approaches.

8.3. International Initiatives

8.3.1. Inria International Partners

8.3.1.1. Declared Inria International Partners

- Beagle is a member of the CNRS Laboratoire International Associé "EvoAct" (Evolution in Action). Other members of EvoAct are the TIMC-IMAG (Grenoble) and the Beacon Center (Michigan State University, USA).

8.3.1.2. Informal International Partners

- Collaboration with Alexander Fleischmann at Brown University (USA) on neuro-evo-devo.
- Collaboration with Cedric Chauve, SFU, Vancouver (Canada) on phylogeny and rearrangements.
- Collaboration with Tom Williams, Bristol (UK) on phylogeny.

8.4. International Research Visitors

8.4.1. Visits of International Scientists

- We welcomed Leonardo Trujillo (Venezuela) as a visiting professor from January 2019 to July 2019. Leonardo Trujillo worked on the innovation dynamics in evolution using NK Fitness-Landscapes.
- Corrado Cali, BESE Division, KAUST University, Saudi Arabia, 1 week in november

8.4.1.1. Internships

- Barbara Genocchi (PhD candidate, Tampere University of Technology, Tampere, Finland) visited us for 16 days (Sept 9 - Sept 24).

BIGS Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

- Lorraine Université d'Excellence LUE, Impact Project GEENAGE (Functional **G**enomic, **E**pigenomic and **EN**vironment interplay to imptact the understanding, diagnosis and management of healthy and pathological **AGE**ing). Anne Gégout-Petit, Lionel Lenôtre, Emma Horton.

9.2. National Initiatives

- FHU CARTAGE (Fédération Hospitalo Universitaire Cardial and ARTerial AGEing ; leader : Pr Athanase Benetos), Jean-Marie Monnez, Benoît Lalloué, Anne Gégout-Petit.
- RHU Fight HF (Fighting Heart Failure ; leader : Pr Patrick Rossignol), located at the University Hospital of Nancy, Jean-Marie Monnez, Benoît Lalloué.
- Project "Handle your heart", team responsible for the creation of a drug prescription support software for the treatment of heart failure, head: Jean-Marie Monnez
- A. Gégout-Petit, N. Sahki, S. Mézières are involved in the learning aspect of the clinical protocol "EOLEVAL" with Assistance Publique des Hopitaux de Paris (APHP)
- "ITMO Physics, mathematics applied to Cancer" (2017-2019): "Modeling ctDNA dynamics for detecting targeted therapy", Funding organisms: ITMO Cancer, ITMO Technologies pour la santé de l'alliance nationale pour les sciences de la vie et de la santé (AVIESAN), INCa, Leader: N. Champagnat (Inria TOSCA), Participants: A. Gégout-Petit, A. Muller-Gueudin, P. Vallois.
- PEPS AMIES (2019-2020), Etude Biométrique en foetopathologie et développement de l'enfant, Collaboration between Institut Elie Cartan and the CRESS INSERM, S. Ferrigno.
- Modular, multivalent and multiplexed tools for dual molecular imaging (2017-2020), Funding organism: ANR, Leader: B Kuhnast (CEA). Participant: T. Bastogne.
- Sophie Mézières belongs to GDR 720 ISIS, Funding organism: CNRS, leader: Laure Blanc-Féraud.

9.3. International Research Visitors

9.3.1. Visits of International Scientists

Juhyun Park from Bath University spent a week in Nancy in June 2019 to work on tests for paired distributions in the framework of functional analysis with Anne Gégout-Petit.

CAPSID Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. CPER – IT2MP

Participants: Marie-Dominique Devignes [contact person], Malika Smaïl-Tabbone, David Ritchie.

Project title: *Innovations Technologiques, Modélisation et Médecine Personnalisée*; PI: Faiez Zannad, Université de Lorraine (Inserm-CHU-UL). Value: 14.4 M€ ("SMEC" platform – Simulation, Modélisation, Extraction de Connaissances – coordinated by Capsid and Orpailleur teams for Inria Nancy – Grand Est, with IECL and CHRU Nancy: 860 k€, approx); Duration: 2015–2020. Description: The IT2MP project encompasses four interdisciplinary platforms that support several scientific pôles of the university whose research involves human health. The SMEC platform supports research projects ranging from molecular modeling and dynamical simulation to biological data mining and patient cohort studies.

8.1.2. LUE-FEDER – CITRAM

Participants: Marie-Dominique Devignes [contact person], Isaure Chauvot de Beauchêne, Bernard Maigret, Philippe Noel, Dominique Mias-Lucquin, Antoine Moniot, David Ritchie.

Project title: *Conception d'Inhibiteurs du Transfert de Résistances aux agents Anti-Microbiens: bio-ingénierie assistée par des approches virtuelles et numériques, et appliquée à une relaxase d'élément conjugatif intégratif*; PI: N. Leblond, Université de Lorraine (DynAMic, UMR 1128); Other partners: Chris Chipot, CNRS (LPCT, UMR 7565); Value: 200 k€ (Capsid: 80 k€); Duration: 2017–2018. Description: This project follows on from the 2016 PEPS project "MODEL-ICE". The aim is to investigate protein-protein interactions required for initiating the transfer of an ICE (Integrated Conjugative Element) from one bacterial cell to another one, and to develop small-molecule inhibitors of these interactions.

8.1.3. IMPACT GeenAge

Participant: Marie-Dominique Devignes [contact person].

The IMPACT project GeenAge (Lorraine Université d'Excellence) is composed of four axes dedicated to research in high-throughput molecular biology. The Capsid team is involved in a transversal axis for numerical sciences. In the frame of this project, Marie-Dominique Devignes co-supervises with Amedeo Napoli a post-doc hired by the Orpailleur team. She is also responsible with Thierry Bastogne (CRAN) and Anne Gegout-Petit (IECL) for creating a Center of Competencies in Artificial Intelligence and Health.

8.2. National Initiatives

8.2.1. FEDER – SB-Server

Participants: Marie-Dominique Devignes [contact person], Bernard Maigret, Isaure Chauvot de Beauchêne, Sabeur Aridhi, David Ritchie.

Project title: *Structural bioinformatics server*; PI: David Ritchie, Capsid (Inria Nancy – Grand Est); Value: 24 k€; Duration: 2015–2020. Description: This funding provides a small high performance computing server for structural bioinformatics research at the Inria Nancy – Grand Est centre.

8.2.2. ANR

8.2.2.1. FIGHT-HF

Participants: Marie-Dominique Devignes [contact person], Malika Smaïl-Tabbone [contact person], Emmanuel Bresso, Bernard Maigret, Sabeur Aridhi, Kévin Dalleau, Claire Lacomblez, Gabin Personeni, Philippe Noel, David Ritchie.

Project title: *Combattre l'insuffisance cardiaque : Projet de Recherche Hospitalo-Universitaire FIGHT-HF*; PI: Patrick Rossignol, Université de Lorraine (FHU-Cartage); Value: 9 m€ (Capsid and Orpailleur: 450 k€, approx); Duration: 2015–2020. Description: This "Investissements d'Avenir" project aims to discover novel mechanisms for heart failure and to propose decision support for precision medicine. The project has been granted € 9M, and involves many participants from Nancy University Hospital's Federation "CARTAGE". Marie-Dominique Devignes and Malika Smaïl-Tabbone are coordinating a work-package dedicated to network-based science, decision support and drug discovery for this project.

8.2.2.2. IFB

Participants: Marie-Dominique Devignes [contact person], Sabeur Aridhi, Isaure Chauvot de Beauchêne, David Ritchie.

Project title: *Institut Français de Bioinformatique*; PI: Claudine Médigue and Jacques van Helden (CNRS UMS 3601); Value: 20 M€ (Capsid: 126 k€); Duration: 2014–2021. Description: The Capsid team is a research node of the IFB (Institut Français de Bioinformatique), the French national network of bioinformatics platforms (http://www.france-bioinformatique.fr). The principal aim is to make bioinformatics skills and resources more accessible to French biology laboratories. Marie-Dominique Devignes is coordinating with Alban Gaignard the Interoperability task in the Integrative Bioinformatics Workpackage.

8.3. European Initiatives

8.3.1. FP7 & H2020 Projects

8.3.1.1. H2020 ITN RNAct

Participants: Isaure Chauvot de Beauchêne [contact person], Marie-Dominique Devignes, Malika Smaïl-Tabbone, Hrishikesh Dhondge, Anna Kravchenko, David Ritchie.

Program: H2020 Innovative Training Network

Project acronym:RNAct

Project title: Enabling proteins with RNA recognition motifs for synthetic biology and bio-analytics

Duration: octobre 2018 - octobre 2022

Coordinator: Wim Vranken (Vrije University Bruxelles, Belgium)

Other partners: Loria, CNRS (France), Helmholtz Center Munich (Germany), Conseio Superior de Investigaciones Cientificas, Instituto de Biologia Molecular y Celular de Plantas (Spain), Ridgeview instruments AB (Sweden), Giotto Biotech Srl (Italy), Dynamic Biosensors GmbH (Germany).

Abstract: This project aims at designing new proteins with "RNA recognition motifs (RRM)" that target a specific RNA, for exploitation in synthetic biology and bio-analytics. It combines approaches from sequence-based and structure-based computational biology with experimental biophysics, molecular biology and systemic biology. Our scientific participation regards the creation and usage of a large database on RRMs for KDD, and the development of RNA-protein docking methods.

URL: http://rnact.eu

8.3.2. Informal European Partners

EBI: European Bioinformatics Institute, Maria Martin team (UK). We are working with the EBI team to validate and improve our graph-based approaches for protein function annotation.

ELIXIR: 3D-bioinfo Community. We participated in the creation of the new ELIXIR 3D-bioinfo community. ELIXIR Communities enable the participation of communities of practice in different areas of the life sciences in the activities of ELIXIR. The goal is to underpin the evolution of data, tools, interoperability, compute and training infrastructures for European life science informatics (see https://www.elixir-europe.org/use-cases). ELIXIR supports its formally recognised Communities by providing funding for workshops and short collaborative projects associated with the Community. More specifically, Isaure Chauvot de Beauchene is member of the sub-section "Tools to describe, analyze, annotate, and predict nucleic acid structures" of this community.

ELIXIR: Interoperability Platform Marie-Dominique Devignes is collaborating with the ELIXIR Interoperability Platform aa a member of the IFB (the ELIXIR French Node: ELIXIR FR). She coordinates and reviews projects in the field of FAIR data, Data Management Plans and Recommended Interoperability Resources (RIR).

8.4. International Initiatives

8.4.1. TempoGraphs

Project: Analyzing big data with temporal graphs and machine learning. Application to urban traffic analysis and protein function annotation.

Participants: Sabeur Aridhi (PI), Marie-Dominique Devignes, Malika Smaïl-Tabbone, Bishnu Sarker, Wissem Inoubli, Dave Ritchie.

Partners: LORIA/Inria NGE, Federal University of Ceará (UFC).

Value: 20 k€.

Duration: 2017–2020.

Description: This project aims to investigate and propose solutions for both urban traffic-related problems and protein annotation problems. In the case of urban traffic analysis, problems such as traffic speed prediction, travel time prediction, traffic congestion identification and nearest neighbors identification will be tackled. In the case of protein annotation problem, protein graphs and/or protein–protein interaction (PPI) networks will be modeled using dynamic time-dependent graph representations.

8.4.2. Inria Associate Teams Not Involved in an Inria International Labs

Project: FlexMol. Algorithms for Multiscale Macromolecular Flexibility:

Participants: Maria-Elisa Ruiz-Echartea, Dave Ritchie, Isaure Chauvot de Beauchêne.

Partners: Nano-D, ChaconLab team, Rocasolano Institute of Physical Chemistry (IQFR-CSIC), Madrid, Spain, as non-beneficiary associated lab.

Description: Developing representations of molecular flexibility at different scales, for the 3D modeling of multi-molecular assemblies.

8.4.3. Informal International Partners

Project: Characterization, expression and molecular modeling ofTRR1 and ALS3 proteins of Candida spp., as a strategy to obtain new drugs with action on yeasts involved in nosocomial infections. Participant: Bernard Maigret. Partner: State University of Maringá, Brasil. Publication: [14], [18].

Project: Fusarium graminearum target selection. Participant: Bernard Maigret. Partner: Embrapa Recursos Geneticos e Biotecnologia, Brasil. Publication: [13].

Project:The thermal shock HSP90 protein as a target for new drugs against paracoccidioidomicose. Participant: Bernard Maigret. Partner: Brasília University, Brasil.

Project:Protein-protein interactions for the development of new drugs. Participant: Bernard Maigret. Partner: Federal University of Goias, Brasil.

DYLISS Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

9.1.1. MoDaL (Brittany and Pays de la Loire regions)

Participant: Olivier Dameron.

The MoDaL project is a federated project funded by BioGenOuest (Région Bretagne-Pays de la Loire) project involving scientists and engineers from IRISA/inria rennes (Genouest, Empenn, Dyliss) and the Institut du Thorax lab in Nantes. The project aims to decompartmentalize the resources dedicated to biomedical imaging and genetics. MoDaL focuses on i) establishing an inventory of the actors and infrastructures available at the inter-regional level, ii) proposing technological demonstrators that address the management, analysis and reuse of multi-infrastructure data (in-vivo, in-vitro and genomic imaging).

2019-2020. Total grant (hosted in the Empenn team): 100,000€.

9.1.2. PhenoMiR (European Maritime and Fisheries Fund)

Participant: Emmanuelle Becker.

The PhenoMiR project is a collaboration between Fishes Physiology and Genomics Laboratory (LPGP - INRAE), eight other laboratories of the INRAE, and the Dyliss team. Its objective is first (i) to settle the first complete repository of microRNAs for the trout, exploring different physiological and breeding conditions, and then (ii) to study the potentiality of some micro-RNAs to act as bio-markers of trout breeding and development condition. The Dyliss team is responsible for the design and development of the analysis pipeline of the genomics data, including the search of potential bio-markers.

2019-2022. Total grant: 495,000€. Dyliss grant: 33,000€.

9.1.3. UBIQUITIN

Participant: Emmanuelle Becker.

The Ubiquitin project is a collaboration between G. Rabut's team at the Institute of Developmental Biology of Rennes and the Dyliss team. It was funded as a cross-disciplinary emerging project by the University of Rennes 1.

G. Rabut's team is developing a new method to detect weak affinity protein-protein interactions based on protein complemantation with Luciferase. However the method may generate a very noisy signal depending on the *in-vivo* concentration of the partners. In the Ubiquitin project, we developped a R workflow to separate the signal from the noise in the experiments. As an application, this allowed us to decipher the intricate interplay between E2 and E3 enzymes during ubiquitination process in Yeast. This work was done during a master 2 internship. We are now continuing the project in two directions : (i) comparing the interactions identified with previously known databases, using web semantic technologies and ontologies describing protein interaction detection methods, and (ii) using formal classification to understand the structural properties of E2 and E3 that lead to their interactions. 2019-2020. Total grant: 7,000€. Dyliss grant: 4,200€.

9.1.4. Ph.D. fundings from Université, Inria Rennes and Inserm

The team benefits from PhD. theses fundings by Univ. Rennes (L. Bourneuf, 2016-2019 – H. Talibart, 2017-2020 – N. Guillaudeux, 2018-2021), by Inria (A. Belcour, 2019-2022 – V. Kmetzsch, 2019–2022), by Inserm (M. Louarn, 2017-2020, Inria-Inserm PhD Grant program), and by our collaborators from IRSET (M. Conan, 2017-2020 – P. Vignet, 2018-2020, O. Dennler, 2019–2022).

9.2. National Initiatives

9.2.1. IDEALG (ANR/PIA-Biotechnology and Bioresource)

Participant: Méziane Aite.

The project gathers 18 partners from Station Biologique de Roscoff (coordinator), CNRS, IFREMER, UEB, UBO, UBS, ENSCR, University of Nantes, INRA, AgroCampus, and the industrial field in order to foster biotechnology applications within the seaweed field. Dyliss is co-leader of the WP related to the establishment of a virtual platform for integrating omics studies on seaweed and the integrative analysis of seaweed metabolism. Major objectives are the building of brown algae metabolic maps, metabolic flux analysis and the selection of symbiotic bacteria for brown algae. We will also contribute to the prediction of specific enzymes (sulfatases and haloacid dehalogenase) [More details]. 2012–20. Total grant: 11M€. Dyliss grant: 534k€.

9.2.2. TGFSysBio (ITMO Cancer)

Participant: Olivier Dameron.

Partners are INSERM (coordinator) (IRSET, Univ. Rennes 1) CNRS (Dyliss team) and Inria (Antique, Paris). The TGFSYSBIO project aims at developing the first model of extracellular and intracellular TGF-beta system by combining a ruled-based modelling approach (kappa) and a Petri net modelling approach (cadbiom). 2015–18, extended in 2019. Total grant: 418k€. Dyliss grant: 129k€.

9.2.3. Programs funded by Inria

9.2.3.1. IPL Neuromarkers

Participant: Emmanuelle Becker.

This project involves mainly the Inria teams Aramis (coordinator) Dyliss, Genscale and Bonsai. The project aims at identifying the main markers of neurodegenerative pathologies through the production and the integration of imaging and bioinformatics data. Dyliss is in charge of facilitating the interoperability of imaging and bioinformatics data. In 2019 V. Kmetzsch started his PhD (supervized by E. Becker from Dyliss and O. Colliot from Aramis). 2017–20.

9.2.3.2. Askomics (ADT)

Participant: Olivier Dameron.

AskOmics [url] is a visual SPARQL query interface supporting both intuitive data integration and querying while avoiding the user to face most of the technical difficulties underlying RDF and SPARQL. The underlying motivation is that even though Linked (Open) Data now provide the infrastructure for accessing large corpora of data and knowledge, life science end-users seldom use them, nor contribute back their data to the LOD cloud by lack of technical expertise. AskOmics aims at bridging the gap between end users and the LOD cloud. 2018–2020.

9.3. European Initiatives

9.3.1. Collaborations in European Programs, Except FP7 & H2020

- Program: Polish National Science Center
- Project acronym: NCN 2016/21/B/ST6/02158
- Project title: Grammatical inference methods in classification of amyloidogenic proteins
- Duration: January 2017 - January 2020
- Coordinator: Olgierd Unold, Politechnika Wroclawska
- Other partners: Politechnika Wroclawska (Polland)
- Abstract: The objective is to develop the methods for induction of context-free and probabilistic grammars to describe a language matching amyloidogenic protein sequences.

9.3.2. Collaborations with Major European Organizations

Partner: Potsdam (Germany)

Title: Modeling combinatorial and hybrid optmization problems with Answer Set Programming

9.4. International Initiatives

9.4.1. Informal International Partners

We have a cooperation with Univ. of Chile (MATHomics, A. Maass) on methods for the identification of biomarkers and software for biochip design. It aims at combining automatic reasoning on biological sequences and networks with probabilistic approaches to manage, explore and integrate large sets of heterogeneous omics data into networks of interactions allowing to produce biomarkers, with a main application to biomining bacteria. The program is co-funded by Inria and CORFO-chile from 2012 to 2016. In this context, Integrative-BioChile was an Associate Team between Dyliss and the Laboratory of Bioinformatics and Mathematics of the Genome hosted at Univ. of Chile funded from 2011 to 2016. The collaboration is now supported by Chilean programs.

9.5. International Research Visitors

9.5.1. Visits of International Scientists

- **Niger:** Oumarou Abdou-Arbi (University of Maradi)

9.5.1.1. Research Stays Abroad

- **Germany:** Maël Conan visited the Zentrum für Bioinformatik at Hamburg University with Prof. Johannes Kirchmair for 2 months. During this stay, he learned how to predict metabolism sites using the tool developped in Pr. Kirchmair unit (FAME2/FAME3) and initiated the development of a new method to predict xenobiotics metabolism.
- **Germany:** Clémence Frioux visited the lab of Oliver Ebenoh (Heidelberg) for one week.

ERABLE Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. Muse

- Title: Multi-Omics and Metabolic models iNtegration to study growth Transition in *Escherichia coli*
- Coordinators: Delphine Ropers (EPI Ibis) and Marie-France Sagot
- ERABLE participants: Marie-France Sagot and Arnaud Mary.
- Type: IXXI Project (2018-2020).
- Web page: none for now.

8.2. National Initiatives

8.2.1. ANR

8.2.1.1. Aster

- Title: Algorithms and Software for Third gEneration Rna sequencing
- Coordinator: Hélène Touzet, University of Lille and CNRS.
- ERABLE participants: Vincent Lacroix (ERABLE coordinator), Audric Cologne, Eric Cumunel, Alex di Genova, Leandro I. S. de Lima, Arnaud Mary, Marie-France Sagot, Camille Sessegolo, Blerina Sinaimeri.
- Type: ANR (2016-2020).
- Web page: http://bioinfo.cristal.univ-lille.fr/aster/.

8.2.1.2. GraphEn

- Title: Enumération dans les graphes et les hypergraphes : Algorithmes et complexité
- Coordinator: D. Kratsch
- ERABLE participant(s): A. Mary
- Type: ANR (2015-2019)
- Web page: http://graphen.isima.fr/

8.2.1.3. GrR

- Title: Graph Reconfiguration
- Coordinator: N. Bousquet
- ERABLE participant(s): A. Mary
- Type: ANR JCJC (2019-2021)
- Web page: Not available

8.2.1.4. Green

- Title: Deciphering host immune gene regulation and function to target symbiosis disturbance and endosymbiont control in insect pests
- Coordinator: A. Heddi
- ERABLE participant(s): M.-F. Sagot, C. Vieira
- Type: ANR (2018-2021)
- Web page: Not yet available

8.2.1.5. Hmicmac

- Title: Host-microbiota co-adaptations: mechanisms and consequences
- Coordinator: F. Vavre
- ERABLE participant(s): F. Vavre
- Type: ANR PRC (2017-2020)
- Web page: Not available

8.2.1.6. Networks

- Title: Networks
- Coordinator: Michel Mandjes, University of Amsterdam
- ERABLE participant(s): S. Pissis, L. Stougie
- Type: NWO Gravity Program (2014-2024)
- Web page: https://www.thenetworkcenter.nl/

8.2.1.7. Resist

- Title: Rapid Evolution of Symbiotic Interactions in response to STress: processes and mechanisms
- Coordinator: N. Kremer
- ERABLE participant(s): F. Vavre
- Type: ANR JCJC (2017-2020)
- Web page: Not available

8.2.1.8. Swing

- Title: Worldwide invasion of the Spotted WING Drosophila: Genetics, plasticity and evolutionary potential
- Coordinator: P. Gibert
- ERABLE participant(s): C. Vieira
- Type: ANR PCR (2016-2020)
- Web page: Not available

8.2.1.9. U4atac-brain

- Title: Rôle de l'épissage mineur dans le développement cérébral
- Coordinator: Patrick Edery, Centre de Recherche en Neurosciences de Lyon.
- ERABLE participants: Vincent Lacroix (ERABLE coordinator), Audric Cologne.
- Type: ANR (2018-2021).
- Web page: Not available.

8.2.2. Idex

8.2.2.1. Micro-be-have

- Title: Microbial Impact on insect behaviour: from niche and partner selection to the development of new control methods for pests and disease vectors
- Coordinator: F. Vavre
- ERABLE participant(s): F. Vavre
- Type: AO Scientific Breakthrough (2018-2021)
- Web page: Not available

8.2.3. Others

Notice that were included here national projects of our members from Italy and the Netherlands when these have no other partners than researchers from the same country.

8.2.3.1. AHeAD

- Title: efficient Algorithms for HArnessing networked Data
- Coordinator: G. Italiano
- ERABLE participant(s): R. Grossi, G. Italiano
- Type: MUIR PRIN, Italian Ministry of Education, University and Research (2019-2022)
- Web page: https://sites.google.com/view/aheadproject

8.2.3.2. CMACBioSeq

- Title: Combinatorial Methods for analysis and compression of biological sequences
- Coordinator: G. Rosone
- ERABLE participant(s): N. Pisanti
- Type: SIR, MIUR PRIN, Italian Ministry of Research National Projects (2015-2019)
- Web page: http://pages.di.unipi.it/rosone/CMACBioSeq.html

8.2.3.3. MyOwnResearch

- Title: MyOwnResearch: Homogeneous subgroup identification in fatigue management across chronic immune diseases through single subject research design
- Coordinator: A. Schönhuth
- ERABLE participant(s): A. Schönhuth
- Type: Health Holland project (2018-2021)
- Web page: Not available

8.2.3.4. Open Innovation: Digital Innovation for Driving

- Title: Open Innovation: Digital Innovation for Driving
- Coordinator: G. Italiano
- ERABLE participant(s): G. Italiano
- Type: Bridgestone (2018-2019)
- Web page: Not available

8.3. European Initiatives

8.3.1. Collaborations in European Programs, Except FP7 & H2020

8.3.1.1. Pangaia

- Title: Pan-genome Graph Algorithms and Data Integration
- Coordinator: Paola Bonizzoni, University of Milan, Italy
- ERABLE participant(s): S. Pissis, A. Schönhuth, L. Stougie
- Type: H2020 MSCA-RISE (2020-2022)
- Web page: Not available

8.3.2. Collaborations with Major European Organizations

By itself, ERABLE is built from what initially were collaborations with some major European Organisations (CWI, Sapienza University of Rome, Universities of Florence and Pisa, Free University of Amsterdam) and then became a European Inria Team.

8.4. International Initiatives

8.4.1. Inria Associate Teams Not Involved in an Inria International Lab

Compasso

- Title: COMmunity Perspective in the health sciences: Algorithms and Statistical approacheS for explOring it
- Duration: 2018, renewable from 2 to 5 years more
- Coordinator: On the Portuguese side, Susana Vinga, IST, Lisbon, Portugal; on the French side, Marie-France Sagot
- ERABLE participant(s): R. Andrade, M. Ferrarini, G. Italiano, A. Marchetti-Spaccamela, A. Mary, H. T. Pusa, M.-F. Sagot, B. Sinaimeri, L. Stougie, A. Viari, I. Ziska
- Web page: http://team.inria.fr/erable/en/projects/inria-associated-team-compasso/

8.4.2. Participation in Other International Programs

ERABLE is coordinator of a CNRS-UCBL-Inria Laboratoire International Associé (LIA) with the Laboratório Nacional de Computação Científica (LNCC), Petrópolis, Brazil. The LIA has for acronym LIRIO ("Laboratoire International de Recherche en bIOinformatique") and is coordinated by Ana Tereza Vasconcelos from the LNCC and Marie-France Sagot from BAOBAB-ERABLE. The LIA was created in January 2012 for 4 years, renewable once for 4 more years. This year (2019) is the final one. A web page for the LIA LIRIO is available at this address: http://team.inria.fr/erable/en/cnrs-lia-laboratoire-international-associe-lirio/.

Erable also participates in Network for Organismal Interactions Research (NOIR), a project funded by Conicyt in Chile within the call Internation Networking between Research Centers. The project started in 2019 and will last until the end of 2020. The coordinator on the Chilean side is Elena Vida from the Universidad Mayor, Santiago, Chile, and the Erable participants are Carol Moraga Quinteros, Mariana Ferrarini and Marie-France Sagot.

Finally, Marie-France Sagot participates in a Portuguese FCT project, Perseids for "Personalizing cancer therapy through integrated modeling and decision" (2016-2019), with Susana Vinga and a number of other Portuguese researchers. The budget of Perseids is managed exclusively by the Portuguese partner. Perseids ended in December 2019.

8.5. International Research Visitors

8.5.1. Visits of International Scientists

In 2019, ERABLE greeted the following International scientists:

- In France: Alexandra Carvalho and Susana Vinga, Assistant and Associate professors resp., Instituto Superior Técnico, Lisbon, Portugal; Helisson Faoro, researcher, Instituto Carlos Chagas, Fiocruz, Paraná, Brazil; Ariel Silber, professor, Universidade de São Paulo, Brazil; Arnaldo Zaha, professor at Universidade Federal do Rio Grande do Sul, Brazil.
- In Italy: Travis Gaggie, Associate professor, Dalhousie University; Nicola Prezza, postdoc, University of Pisa; Elena Arseneva, Assistant professor, St Petersburg State University, Blerina Sinaimeri, Junior Researcher, Inria (see below); Marie-France Sagot, Senior researcher, Inria (see below).
- In the Netherlands: Wiktor Zuba, PhD student, University of Warsaw; Lorraine Ayad, Lecturer, King's College London; Grigorios Loukides, Lecturer, King's College London; Martin Farach-Colton, Professor, Rutgers University; Grigorios Loukides, Lecturer, King's College London; Martin Dyer, Professor, University of Leeds.

8.5.1.1. Internships

In 2019, ERABLE in France greeted the following Internships:

- Phablo Moura, postdoc, University of Campinas, Brazil.
- Diego Pérez and Evelyn Sanchéz, PhD students of Elena Vidal, Universidad Mayor, Santiago, Chile.

In the Netherlands, ERABLE greeted the following Internships: Luca Denti, University Bicocca of Milano, Italy, from October 2018 to January 2019, Mick van Dijk, TU Delft, from May 2018 to January 2019, Giulia Barnardini, University Bicocca of Milano, Italy, from September 2018 to November 2019.

8.5.2. Visits to International Teams

8.5.2.1. Sabbatical programme

From July 2019 to June 2020, Blerina Sinaimeri was on Sabbatical at Luiss University to work with Giuseppe Italiano, member of Erable.

8.5.2.2. Research Stays Abroad

In 2019, Marie-France Sagot visited Luiss University for 11 days as Visiting Professor from LUISS University to work with Blerina Sinaimeri who is on Sabbatical at Luiss University from July 2019 to June 2020, and with Giuseppe Italiano, member of Erable. While there, M.-F. Sagot also worked with Alberto Marchetti-Spaccamela from Sapienza University of Rome and from Erable.

GENSCALE Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

9.1.1. Project Thermin: Differential characterization of strains of a bacterial species, Streptococcus thermophilus, with a Nanopore MinION

Participants: Jacques Nicolas, Emeline Roux, Grégoire Siekaniec, Dominique Lavenier.

Coordinator: J. Nicolas (Inria/Irisa, GenScale, Rennes)
Duration: 36 months (Oct. 2018 – Sept. 2021)
Partners: INRA (STLO, Agrocampus Rennes, E. Guédon and Y. Le Loir).

The Thermin project aims at exploring the capacities of a low cost third generation sequencing device, the Oxford Nanopore MinION, for rapid and robust pan-genome discrimination of bacterial strains and their phenotypes. It started with the recruitments of E. Roux (délégation Inria, Oct, 2018), a biochemist from Lorraine University, and G. Siekaniec (INRA -Inria collaboration, INRA grant), a new PhD student. We study pan-genomic representations of multiple genomes and the production of characteristic signatures of each genome in this context.

9.1.2. Project DNA-Store: Advanced error correction scheme for DNA-based data storage using nanopore technology

Participants: Dominique Lavenier, Emeline Roux.

Coordinator: L. Conde-Canencia (UBS, Lab-STCC, IAS)
Duration: 12 months (Feb. 2019 - Feb. 2020)
Partners: UBS (Lab-STCC, IAS, L. Conde-Canencia)

The DNA-Store project is funded by the Labex CominLabs. The goal is to explore the possibility to store information on DNA molecules. As DNA sequencing (the reading process) is performed with the Oxford Nanopore technology, powerful error correcting codes need to be developed together with dedicated genomic data processing.

9.2. National Initiatives

9.2.1. ANR

9.2.1.1. Project HydroGen: Metagenomics applied to ocean life study

Participants: Dominique Lavenier, Pierre Peterlongo, Claire Lemaitre.

Coordinator: P. Peterlongo (Inria/Irisa, GenScale, Rennes)
Duration: 42 months (Nov. 2014 – Apr. 2019)
Partners: CEA (Genoscope, Evry), INRA (AgroParisTech, Paris – MIG, Jouy-en-Jossas).

The HydroGen project aims to design new statistical and computational tools to measure and analyze biodiversity through comparative metagenomic approaches. The support application is the study of ocean biodiversity based on the analysis of seawater samples generated by the Tara Oceans expedition.

9.2.1.2. Project SpeCrep: speciation processes in butterflies

Participants: Dominique Lavenier, Fabrice Legeai, Claire Lemaitre, Pierre Peterlongo.

Coordinator: M. Elias (Museum National d'Histoire Naturelle, Institut de Systématique et d'Evolution de la Biodiversité, Paris)
Duration: 48 months (Jan. 2015 – Jul. 2019)

Partners: MNHN (Paris), INRA (Versailles-Grignon), Genscale Inria/IRISA Rennes.

The SpeCrep project aims at better understanding the speciation processes, in particular by comparing natural replicates from several butterfly species in a suture zone system. GenScale's task is to develop new efficient methods for the assembly of reference genomes and the evaluation of the genetic diversity in several butterfly populations.

9.2.1.3. Project Supergene: The consequences of supergene evolution.

Participants: Anne Guichard, Dominique Lavenier, Fabrice Legeai, Claire Lemaitre, Pierre Peterlongo.

Coordinator: M. Joron (Centre d'Ecologie Fonctionnelle et Evolutive (CEFE) UMR CNRS 5175, Montpellier)
Duration: 48 months (Nov. 2018 – Oct. 2022)
Partners: CEFE (Montpellier), MNHN (Paris), Genscale Inria/IRISA Rennes.

The Supergene project aims at better understanding the contributions of chromosomal rearrangements to adaptive evolution. Using the supergene locus controlling adaptive mimicry in a polymorphic butterfly from the Amazon basin (*H. numata*), the project will investigate the evolution of inversions involved in adaptive polymorphism and their consequences on population biology. GenScale's task is to develop new efficient methods for the detection and genotyping of inversion polymorphism with several types of re-sequencing data.

9.2.1.4. Project SeqDigger: Search engine for genomic sequencing data

Participants: Dominique Lavenier, Claire Lemaitre, Pierre Peterlongo.

Coordinator: P. Peterlongo
Duration: 48 months (jan. 2020 – Dec. 2024)
Partners: Genscale Inria/IRISA Rennes, CEA genoscpoe, MIO Marseille, Institut Pasteur Paris

https://www.cesgo.org/seqdigger/

The central objective of the SeqDigger project is to provide an ultra fast and user-friendly search engine that compares a query sequence, typically a read or a gene (or a small set of such sequences), against the exhaustive set of all available data corresponding to one or several large-scale metagenomic sequencing project(s), such as New York City metagenome, Human Microbiome Projects (HMP or MetaHIT), Tara Oceans project, Airborne Environment, etc. This would be the first ever occurrence of such a comprehensive tool, and would strongly benefit the scientific community, from environmental genomics to biomedicine.

9.2.2. PIA: Programme Investissement d'Avenir

9.2.2.1. RAPSODYN: Optimization of the rapeseed oil content under low nitrogen

Participants: Dominique Lavenier, Claire Lemaitre, Pierre Peterlongo, Gwendal Virlet.

Coordinator: N. Nesi (Inra, IGEPP, Rennes)
Duration: 99 months (2012-2020)
Partners: 5 companies, 9 academic research labs.

The objective of the Rapsodyn project is the optimization of the rapeseed oil content and yield under low nitrogen input. GenScale is involved in the bioinformatics work package to elaborate advanced tools dedicated to polymorphism detection and their application to the rapeseed plant. (http://www.rapsodyn.fr)

9.2.3. Programs from research institutions

9.2.3.1. Inria Project Lab: Neuromarkers

Participants: Dominique Lavenier, Pierre Peterlongo, Claire Lemaitre, Céline Le Beguec, Téo Lemane.

Coordinator: O. Colliot (Inria, Aramis, Paris)
Duration: 4 years (2017-2020)
Partners: Inria (Aramis, Pasteur, Dyliss, GenScale, XPOP), ICM

The Neuromarkers IPL aims to design imaging bio-markers of neuro-degenerative diseases for clinical trials and study of their genetic associations. In this project, GenScale brings its expertise in the genomics field. More precisely, given a case-control population, a first step is to identify small genetic variations (SNPs, small indels) from their genomes. Then, using these variations together with brain images (also partitioned into case-control data sets), the challenge is to select variants that present potential correlation with brain images.

9.3. European Initiatives

9.3.1. Collaborations in European Programs, Except FP7 & H2020

Program: ITN (Initiative Training Network)

Project acronym: IGNITE

Project title: Comparative Genomics of Non-Model Invertebrates

Duration: 48 months (April 2018, March 2022)

Coordinator: Gert Woerheide

Partners: Ludwig-Maximilians-Universität München (Germany), Centro Interdisciplinar de Investigação Marinha e Ambiental (Portugal), European Molecular Biology Laboratory (Germany), Université Libre de Bruxelles (Belgium), University of Bergen (Norway), National University of Ireland Galway (Ireland), University of Bristol (United Kingdom), Heidelberg Institute for Theoretical Studies (Germany), Staatliche Naturwissenschaftliche Sammlungen Bayerns (Germany), INRA Rennes (France), University College London (UK), University of Zagreb (Croatia), Era7 Bioinformatics (Spain), Pensoft Publishers (Bulgaria), Queensland Museum (Australia), Inria, GenScale (France), Institut Pasteur (France), Leibniz Supercomputing Centre of the Bayerische Akademie der Wissenschaften (Germany), Alphabiotoxine (Belgium)

Abstract: Invertebrates, i.e., animals without a backbone, represent 95 per cent of animal diversity on earth but are a surprisingly underexplored reservoir of genetic resources. The content and architecture of their genomes remain poorly characterised, but such knowledge is needed to fully appreciate their evolutionary, ecological and socio-economic importance, as well as to leverage the benefits they can provide to human well-being, for example as a source for novel drugs and biomimetic materials. IGNITE will considerably enhance our knowledge and understanding of animal genome knowledge by generating and analyzing novel data from undersampled invertebrate lineages and by developing innovative new tools for high-quality genome assembly and analysis.

9.3.2. Collaborations with Major European Organizations

Partner : PHC RILA 2019, Bulgaria

Two years France-Bulgaria bilateral Partnership Hubert Curien (PHC) RILA 2019 (project code : 43196Q). The topic of this project is "Integer Programming Approaches for Long-Reads Genome Assembly". Start year: 2019.

9.4. International Initiatives

9.4.1. HipcoGen

Title: High-Performance Combinatorial Optimization for Computational Genomics

International Partner (Institution - Laboratory - Researcher):

> Information Sciences group of Los Alamos National Laboratory (LANL), Los Alamos, NM 87544, USA. coordinator - Hristo Djidjev

Start year: 2017

See also: https://team.inria.fr/genscale/presentation/associated-team/

Genome sequencing and assembly, the determination of the DNA sequences of a genome, is a core experiment in computational biology. During the last decade, the cost of sequencing has decreased dramatically and a huge amount of new genomes have been sequenced. Nevertheless, most of recent genome projects stay unfinished and nowadays the databases contain much more incompletely assembled genomes than whole stable reference genomes. The main reason is that producing a complete genome, or an as-complete-as-possible-genome, is an extremely difficult computational task (an NP-hard problem) and, in spite of the efforts and the progress done by the bioinformatics community, no satisfactory solution is available today. New sequencing technologies (such as PacBio or Oxford Nanopore) are being developed that tend to produce longer DNA sequences and offer new opportunities, but also bring significant new challenges. The goal of this joint project, a cooperation between Los Alamos National Laboratory, US and Inria, is to develop a new methodology and tools based on novel optimization techniques and massive parallelism suited to these emerging technologies and able to tackle the complete assembly of large genomes.

9.4.2. Inria International Partners

9.4.2.1. Informal International Partners

- Free University of Brussels, Belgium: Genome assembly [P. Perterlongo, D. Lavenier]

9.5. International Research Visitors

9.5.1. Visits of International Scientists

- Visit of Hristo Djidjev from Los Alamos National Laboratory, USA, June 2019
- Visit of Alla Lapidus and Anto korobeynikov, Center for Algoritmic Biotechnology, St. Petersburg State University, Russia, October 2019

9.5.2. Visits to International Teams

9.5.2.1. Research Stays Abroad

- Visit of R. Andonov at Los Alamos National Laboratory, USA, from March 23 to April 30th, 2019.
- Visit of D. Lavenier at Los Alamos National Laboratory, USA, from May 13th to May 24th, 2019

IBIS Project-Team

7. Partnerships and Cooperations

7.1. Regional Initiatives

Project name	MuSE: MUlti-Omics and Metabolic models integration to study growth transition in Escherichia coli
Coordinator	D. Ropers
IBIS participants	D. Ropers, T. Etienne
Type	IXXI/BioSyl project (2018-2020)
Web page	http://www.biosyl.org/news/muse-2013-multi-omics-and-metabolic-models-integration-to-study-growth-transition-in-escherichia-coli

Project name	RNAfluo: Quantification d'ARN régulateurs *in vivo*
Coordinator	S. Lacour
IBIS participants	S. Lacour
Type	AGIR project Univ Grenoble Alpes (2016-2019)

7.2. National Initiatives

Project name	MEMIP – Modèles à effets mixtes de processus intracellulaires : méthodes, outils et applications
Coordinator	G. Batt
IBIS participants	E. Cinquemani, A. Marguet, D. Ropers
Type	ANR project (2016-2020)

Project name	ENZINVIVO – Détermination in vivo des paramètres enzymatiques dans une voie métabolique synthétique
Coordinator	G. Truan
IBIS participants	J. Geiselmann, H. de Jong
Type	ANR project (2016-2020)

Project name	MAXIMIC: Optimal control of microbial cells by natural and synthetic strategies
Coordinator	H. de Jong
IBIS participants	C. Boyat, E. Cinquemani, J. Geiselmann, H. de Jong, A. Pavlou, C. Pinel, D. Ropers
Type	ANR project (2017-2021)
Web page	https://project.inria.fr/maximic

Project name	RIBECO (RIBonucleotide ECOnomy): Engineering RNA life cycle to optimize economy of microbial energy
Coordinator	M. Cocaign-Bousquet
IBIS participants	E. Cinquemani, T. Etienne, D. Ropers
Type	ANR project (2018-2022)
Web page	https://project.inria.fr/ribeco/

Project name	COSY: real-time COntrol of SYnthetic microbial communities
Coordinator	E. Cinquemani
IBIS participants	E. Cinquemani, H. de Jong, J. Geiselmann, M. Mauri, T. Muszbek, C. Pinel, D. Ropers, M. Sangster
Type	Inria Project Lab (2017-2021)
Web page	https://project.inria.fr/iplcosy/

Project name	OPTICO : OPTImal COntrol software for microbial communities in a system of minibioreactors
Coordinator	E. Cinquemani
IBIS participants	E. Cinquemani, H. de Jong, J. Geiselmann, T. Muszbek
Type	Inria ADT (2019-2021)

Project name	AlgeaInSilico: Prédire et optimiser la productivité des microalgues en fonction de leur milieu de croissance
Coordinator	O. Bernard
IBIS participants	H. de Jong
Type	Inria Project Lab (2015-2019)
Web page	https://project.inria.fr/iplalgaeinsilico/

Project name	Analyse intégrative de la coordination entre stabilité des ARNm et physiologie cellulaire chez Escherichia coli
Coordinators	D. Ropers, M. Cocaign-Bousquet (Inra, LISBP)
IBIS participants	T. Etienne, D. Ropers
Type	Contrat Jeune Scientifique Inra-Inria (2016-2019)

7.3. International Research Visitors

7.3.1. Visits of International Scientists

Tomas Gedeon, professor in Mathematics at Montana State University (USA), visited the IBIS project-team during two months (May-July 2019) to work on modeling and analysis of resource allocation in microorganisms. His stay at Inria was funded by the Visiting researcher program of the research center Grenoble - Rhône-Alpes.

7.3.1.1. Internships

Emmanouil Sideris, enrolled in the MSc program in Computer Science at the University of Patras (Greece), did a Master internship with Eugenio Cinquemani.

LIFEWARE Project-Team

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. ANR Projects

- ANR-FWF CyberCircuits (2018-2022): "Cybergenetic circuits to test composability of gene networks", co-coordinated by C. Guet (IST Austria, Klosterneuburg, Austria) and J. Ruess (Inria EPI Lifeware);
- ANR-DFG SYMBIONT (2018-2021) on "Symbolic Methods for Biological Systems", coordinated by T. Sturm (CNRS, LORIA, Nancy, France) and A. Weber (Univ. Bonn, Germany) with F. Fages and F. Boulier (U. Lille), O. Radulescu (U. Montpellier), A. Schuppert (RWTH Aachen), S. Walcher (RWTH Aachen), W. Seiler (U. Kassel);
- ANR-MOST BIOPSY (2016-2020) on "Biochemical Programming System", coordinated by F. Molina (CNRS, Sys2diag, Montpellier) and J.H. Jiang (National Taiwan University), with F. Fages;
- ANR MEMIP (2016-2020) on "Mixed-Effects Models of Intracellular Processes", coordinated by G. Batt, with P. Hersen, (CNRS/Paris7), E. Cinquemani (Inria EPI IBIS) and M. Lavielle (Inria/CNRS/Polytechnique, EPI XPOP);
- ANR COGEX (2016-2019) on "Computer Aided Control of Gene Expression" coordinated by P. Hersen (MSC lab, CNRS/Paris7), with G. Batt and G. Truan (LISBP, CNRS/INSA);

9.1.2. Inria Project Lab

- IPL COSY (2017-2021) on "real-time control of synthetic microbial communities", coordinated by Eugenio Cinquemani (Ibis, Inria), with Jean-Luc Gouzé (Biocore, Inria), Grégory Batt, Frédéric Bonnans (Commands, Inria), Efimov Denis (Non-A, Inria), and Hans Geiselmann (BIOP, Université Grenoble-Alpes), Béatrice Laroche (Maiage, Inra Jouy-en-Josas).

9.2. European Initiatives

9.2.1. FP7 & H2020 Projects

- H2020 FET-OPEN COSY-BIO (2017-2020), on "Control Engineering of Biological Systems for Reliable Synthetic Biology Applications", coordinated by Diego di Bernardo (Tigem), with Filippo Menolascina (Edinburgh U), Mario di Bernardo (Naples U), Pascal Hersen (Paris7 U), Mustafa Khammash (ETHZ), Grégory Batt, Guy-Bart Stan (Imperial College), and Lucia Marucci (Bristol U).

9.3. International Research Visitors

9.3.1. Visits of International Scientists

The following researchers have been invited for short visits:

- Jean-Louis Lassez, retired IBM Yorktown, USA
- Lucia Nasti, Univ. Pisa, Italy
- Claudia Lopez Zazueta, NTNU, Norway

9.3.1.1. Internships

- Orianne Bargain (TU Dresden Germany)
- Elisabeth Degrand (KTH, Stockholm Sweden)

MORPHEME Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. Labex Signalife

The MORPHEME team is member of the SIGNALIFE Laboratory of Excellence.

Florence Besse and Xavier Descombes are members of the Scientific Committee.

8.1.2. Idex UCA Jedi

Luca Calatroni is responsible of the project "Action 2, DEP attractivité du territoire du IDEX JEDI, Académie 2 'Systemes complexes'".

Xavier Descombes is co-PI of the MOORPHEUS project funded by the Academy 4 of IDEX-JEDI ("Modélisation computationnelle de la croissance et de l'organisation spatiale dynamique des organoides/tumoroides de prostate"), in collaboration with C3M.

Biological Image Super-resolution Enhanced with Tensor (Biset) supported by Académie 1 RISE. Participants : E. Debreuve, L. Blanc-Féraud, S. Schaub.

Multiscale Tomography : imaging and modelling ancient materials, technical traditions and transfers, (ToMaT), supported by Idex UCA JEDI structuring Project, Participants: L. Blanc-Féraud, Vanna-Lisa Coli, Juliette Leblond, Didier Binder, Louise Gomart, Serge Cohen.

The PhD grant of Clara Sanchez is funded by the IDEX EUR DS4H. Participants: E. Debreuve, C. Rovère (IPMC).

8.1.3. 3AI Côte d'Azur

Laure Blanc-Féraud and Grégoire Malandain are chair holders of the 3AI Côte d'Azur, in the "Computational Biology and Bio-Inspired AI" axis.

The PhD grant of Vasiliki Stergiopoulou is funded by the 3AI Côte d'Azur.

8.2. National Initiatives

8.2.1. ANR RNAGRIMP

Participants: Florence Besse [PI], Fabienne de Graeve, Xavier Descombes, Eric Debreuve, Somia Rahmoun.

Here, we propose to study the molecular bases underlying the assembly and regulation of RNA granules, using the highly conserved IMP-containing granules as a paradigm. Specifically, we propose to perform an unbiased genome-wide RNAi screen on Drosophila cultured cells to identify mutant conditions in which the organization and/or distribution of IMP-containing granules is altered. To quantitatively and statistically analyze mutant conditions, and to define precise and coherent classes of mutants, we will combine high throughput microscopy with the development of a computational pipeline optimized for automatic analysis and classification of images. The function of positive hits isolated in the screen will then be validated in vivo in Drosophila neurons using fly genetics and imaging techniques, and characterized at the molecular and cellular levels using biochemical assays, in vitro phase transition experiments and live-imaging. Finally, the functional conservation of identified regulators will be tested in zebrafish embryos combining gene inactivation and live-imaging techniques. This integrative study will provide the first comprehensive analysis of the functional network that regulates the properties of the conserved IMP RNA granules. Our characterization of the identified regulators in vivo in neuronal cells will be of particular significance in the light of recent evidence linking the progression of several degenerative human diseases to the accumulation of non-functional RNA/protein aggregates.

This 4-years project started january, 2016 and is leaded by F. Besse (iBV, Nice). Participants are iBV, institut de biologie Paris Seine (IBPS, Paris), and Morpheme.

8.2.2. ANR HMOVE

Participants: Xavier Descombes, Eric Debreuve, Somia Rahmoun.

Among the signaling molecules involved in animal morphogenesis are the Hedgehog (Hh) family proteins which act at distance to direct cell fate decisions in invertebrate and vertebrate tissues. To study the underlying process we will develop accurate tracking algorithm to compare trajectories of different Hh pools transportation in live animals. This will allow us to analyze the contribution of the different carriers in the establishment of the Hh gradient. Moreover, we will develop new methods to modify the spatio-temporal and dynamical properties of the extra-cellular Hh gradient and separate the contribution of the apical versus basal Hh pools. We will complete this study with a genome-wide screen to identify genes and related cellular processes responsible for Hh release. The particular interest of this collaboration lies in the combination of development of tracking algorithm to analyze Hh distribution and trajectories with extremely powerful genetics, ease of in vivo manipulation and lack of genetic redundancy of Drosophila.

This 4-years project started january, 2016 and is leaded by P. Thérond (iBV, Nice). Participants are iBV and Morpheme.

8.2.3. ANR Cell Whisper

Participant: Grégoire Malandain.

Successful embryogenesis requires the differentiation of the correct cell types, in defined numbers and in appropriate positions. In most cases, decisions taken by individual cells are instructed by signals emitted by their neighbours. A surprisingly small set of signalling pathways is used for this purpose. The FGF/Ras/ERK pathway is one of these and mutations in some of its individual components cause a class of human developmental syndromes, the RASopathies. Our current knowledge of this pathway is, however, mostly static. We lack an integrated understanding of its spatio-temporal dynamics and we can imperfectly explain its highly non-linear response to a graded increase in input stimulus.

This systems biology project combines advanced quantitative live imaging, pharmacological/optogenetics perturbations and computational modelling to address 3 major unanswered questions, each corresponding to a specific aim:

- Aim 1: What is the spatio-temporal dynamic of intracellular signal transduction in response to FGF?
- Aim 2: What is the molecular basis of the switch-like response to graded extracellular signals?
- Aim 3: Can the results be integrated into a predictive computational model of the pathway?

Through this approach, in a simplified model system, we hope to gain an integrated view of the pathway's dynamics.

This 4-years project started october the 1st, 2019 and is leaded by P. Lemaire (CRBM, Montpellier). Participants are CRBM (Montpellier), LIRMM (Montpellier), MOSAIC (Inria Grenoble) and Morpheme.

8.2.4. Inria Large-scale initiative Naviscope

Participant: Grégoire Malandain.

This action gathers the expertise of seven Inria research teams (Aviz, Beagle, Hybrid, Morpheme, Parietal, Serpico and Mosaic) and other groups (MaIAGE, INRA, Jouy-en-Josas and UMR 144, Institut Curie Paris) and aimed at developing original and cutting-edge visualization and navigation methods to assist scientists, enabling semi-automatic analysis, manipulation, and investigation of temporal series of multi-valued volumetric images, with a strong focus on live cell imaging and microscopy application domains. More precisely, the three following challenges will be addressed:

- Novel machine learning methods able to detect the main regions of interest, and automatic quantification of sparse sets of molecular interactions and cell processes during navigation to save memory and computational resources.

- Novel visualization methods able to encode 3D motion/deformation vectors and dynamics features with color/texture-based and non-sub-resolved representations, abstractions, and discretization, as used to show 2D motion and deformation vectors and patterns.
- Effective machine learning-driven navigation and interaction techniques for complex functional 3D+Time data enabling the analysis of sparse sets of localized intra-cellular events and cell processes (migration, division, etc.).

8.3. International Research Visitors

8.3.1. Visits of International Scientists

Alin Achim, professor at Bristol university, is an invited professor in Morpheme since september 2019 for a ten months period (Leverhulme grant).

MOSAIC Project-Team

7. Partnerships and Cooperations

7.1. Regional Initiatives

7.1.1. ENS de Lyon projets Emergents - Phyllo (2018 - 2019)

Participants: Christophe Godin, Bruno Leggio, Teva Vernoux [External Collaborator].

The aim in this project is to develop a model of phyllotaxis that would be compatible with the recent detailed and quantitative observations made by our group of the distribution of auxin in space and time at the SAM. In particular the work will seek at using the new quantitative data to estimate the parameters of the stochastic model previously developed of organ patterning.

7.1.2. IDEX Lyon Impulsion - MecaField (2019 - 2020)

Participants: Christophe Godin, Bruno Leggio, Teva Vernoux [External Collaborator].

In a previous work, we have shown that the coupling of mechanical and hydraulical descriptions in a 2D model of multicellular tissue growth induces the emergence of remarkable phenomena at tissue level. In particular, we have shown that the growth of an organ may induce a lateral inhibition surrounding the organ that prevents other organs to grow in its vicinity. The goal of this project is to estimate the hydraulic and mechanical parameters of such a model from confocal images of a growing SAM and to compare observations with the order of magnitude of the predicted inhibitory zones and of their amplitude at cellular resolution.

7.2. National Initiatives

7.2.1. Inria ADT - Gnomon

Participants: Olivier Ali, Romain Azaïs, Guillaume Cerutti, Florian Gacon, Christophe Godin, Jonathan Legrand, Grégoire Malandain [External Collaborator], Teva Vernoux [External Collaborator].

Gnomon is a user-friendly computer platform developed by the Mosaic team for seamless simulation of form development in silico. It is intended to be a major tool for the team members to develop, integrate and share their models, algorithms and tools. Flexible components (plugins) make it possible to up-load or to create such data-structures, to program their development, to analyze, visualize them and interact with them in 3D+time.

Based on the past experience of the team with the OpenAlea platform, the goal of this ADT is to develop a more scalable software engineering solution based on the dtk kernel developed by the group of software engineers (SED) from the Sophia-Antipolis Inria Center.

Partners:

- SED Sophia Antipolis Inria Research Centre
- Morpheme Inria projec-team, Sophia Antipolis, France

7.2.2. Inria IPL - Naviscope

Participants: Guillaume Cerutti, Emmanuel Faure [External Collaborator], Christophe Godin, Jonathan Legrand, Grégoire Malandain [External Collaborator].

In this project, we plan to develop original and cutting-edge visualization and navigation methods to assist scientists, enabling semi-automatic analysis, manipulation, and investigation of temporal series of multi-valued volumetric images, with a strong focus on live cell imaging and microscopy application domains. We will build Naviscope upon the strength of scientific visualization and machine learning methods in order to provide systems capable to assist the scientist to obtain a better understanding of massive amounts of information. Such systems will be able to recognize and highlight the most informative regions of the dataset by reducing the amount of information displayed and guiding the observer attention. Finally, we will overcome the technological challenge of gathering up the software developed in each team to provide a unique original tool for users in biological imaging, and potentially in medical imaging.

7.2.3. ANR - Imago (2016 - 2019)

Participants: Guillaume Cerutti, Christophe Godin, Jonathan Legrand.

The goal of this project is to investigate the role of ovule growth constraints on germ cell fate establishment. This project is motivated by recent findings from the partners' groups suggesting that disturbances in cell divisions and expansion in early (pre-meiotic) ovules are sufficient to induce ectopic germ cells. These observations suggest novel routes to engineer apomixis in plants but remains poorly understood. Recent developments in high-resolution 3D imaging, image processing, and modeling offer a powerful combination of approaches to investigate this question. IMAGO proposes to elucidate patterning rules governing ovule growth, and their contribution to female germ cell fate acquisition. We use a combination of high-resolution static and real-time 3D imaging, quantitative image processing, cell-based growth models and functional approaches to (1) define cellular growth patterns in the ovule primordium using quantitative imaging (2) test patterning rules in silico by cell-based growth models (3) validate patterning rules in vivo using genetic, pharmacological and mechanical perturbations.

Partners:

- UMR DIADE, IRD, Montpellier, France
- Department of Plant and Microbial Biology, Zurich, Swisszerland
- RDP, ENS de Lyon, France

7.2.4. ANR DigEM (2015 - 2019)

Participants: Christophe Godin, Bruno Leggio, Patrick Lemaire [External Collaborator], Grégoire Malandain [External Collaborator].

In this project, we will use advanced ligh-sheet imaging of live embryos to quantitatively describe embryonic morphogenesis in ascidians, a class of animals that undergo very rapid genomic divergence, yet show an extraordinary stasis of embryonic morphologies, based on invariant early cell lineages shared by all studied species. The global aims of the proposal, which will bridge micro- and macroevolutionary scales of analysis, are: i) to provide a global systems-level description at cellular resolution of an animal embryonic program; ii) to use this description to characterize intra-specific and inter-specific patterns of morphogenetic variations; iii) to analyze possible molecular mechanisms explaining the unusual robustness of this program to environmental and genetic perturbations. To achieve these aims, we will combine advanced live light-sheet microscopy, computational biology, functional gene assays and evolutionary approaches.

Partners:

- UMR CRBM, CNRS Montpellier, France
- Morpheme Inria projec-team, Sophia Antipolis, France

7.2.5. ERA-CAPS Genes2shape (2018 - 2021)

Participants: Olivier Ali, Guillaume Cerutti, Christophe Godin, Bruno Leggio, Jan Traas [External Collaborator].

This project is aimed at understanding how molecular regulation integrates with mechanics to control overall plant shape, an unresolved problem with wide implications for both fundamental and applied biology. We will address this issue in the Arabidopsis flower, which, besides their obvious importance as reproductive structures, are amongst the best characterised systems in plant developmental biology. From a mechanistic point of view, it is widely accepted that regulatory molecular networks interfere with the properties of the structural cellular elements (cell wall, cytoskeleton) to induce particular growth patterns. How this occurs and how this is coordinated in space is not known. To obtain a mechanistic understanding of such a complex process, information from multiple scales, from molecular networks to physical properties and geometry have to be combined into a single picture. An integrated tool to do so is currently not available. Building on our complementary experience in interdisciplinary research on plant development, we will therefore develop a tool, called the "Computable Flower" that permits (i) integration of data on geometry, gene expression and biomechanics and (ii) the user to explore, interpret and generate hypotheses based on data supported by mechanistic modelling approaches. The tool therefore provides an integrated description in the form of a 3D dynamic template of the growing flower bud.

Partners:

- University of Cambridge (Sainsbury Lab.)
- California Institute of Technology
- MaxPlanck Institutes of Molecular Plant Physiology

7.2.6. MITI - MISGIVING (2019)

Participant: Romain Azaïs.

The diving performance of lung-breathing vertebrates, such as seabirds, can be quantified using measurement devices equipped on animals that allow us to reconstruct their activity at sea. During a classic dive, diving animals are faced with a dilemma: on the one hand, they want to optimize the time spent in contact with prey and therefore increase the time spent in diving; but, on the other hand, they are forced to return to the surface to breathe and will want to minimize this duration which remains however constrained by physiological rules. In addition, the dives are gathered in sequences because the prey are generally grouped in patches. In this project, we propose to use specific mathematical models to understand the complexity of the multi-scale decision processes that condition not only the optimal duration of the dive but also dives within a bout and therefore the total duration of the bout.

Partners:

- Centre d'Etudes Biologiques de Chizé
- Inria team CQFD in Bordeaux

7.3. European Initiatives

7.3.1. FP7 & H2020 Projects

Program: H2020

Project acronym: ROMI

Project title: RObotics for MIcrofarms

Duration: November 2017 - October 2021

Coordinator: Sony

Other partners: Iaac, (Spain), FEI (France), Inria (France), CNRS (France), UBER (Germany), Chatelain (France)

Abstract: All over Europe, young farmers are starting small market farms and direct sales businesses. These farms can be found both in rural, peri-urban and urban areas. They grow a large variety of crops (up to 100 different varieties of vegetables per year) on small surfaces (0.01 to 5 ha) using organic farming practices. These farms have proven to be highly productive, sustainable and economically viable. However, a lot of work is done manually, resulting in physically challenging work conditions. ROMI will develop an open and lightweight robotics platform for these microfarms. We will assist these farms in weed reduction and crop monitoring. This will reduce manual labour and increase the productivity through advanced planning tools. Thanks to ROMI's weeding robot, farmers will save 25 percents of their time. This land robot will also acquire detailed information on sample plants and will be coupled with a drone that acquires more global information at crop level. Together, they will produce an integrated, multi-scale picture of the crop development that will help the farmer monitor the crops to increase efficient harvesting. For this, ROMI will have to adapt and extend state-of-the-art land-based and air-borne monitoring tools to handle small fields with complex layouts and mixed crops. To achieve this, we will: (i) develop and bring to the market an affordable, multi-purpose, land-based robot, (ii) develop a weeding app for this robot that is adapted for organic microfarms, (iii) apply advanced 3D plant analysis and modelling techniques to in-field data acquisition, (iv) integrate these analysis techniques in the robot for detailed plant monitoring, (iv) integrate these techniques also in the aerial drone N-E-R-O for multi-scale crop monitoring, (v) extend the robot with novel, adaptive learning techniques to improve sensorimotor control of the plant monitoring app, and (vii) test the effectiveness of our solution in real-world field conditions.

7.3.2. Collaborations with Major European Organizations

Laboratoire International Associé (LIA): Computing Plant Morphogenesis

The focus of this LIA headed by Teva Vernoux (RDP) and Ottoline Leyser (SLCU) is on plant morphogenesis i.e. the mechanisms allowing the generation of plant shapes at different scales. Both the RDP and SLCU Laboratories are leaders of this field. The scenario for morphogenesis that has recently emerged is that chemical signals controlling cell identities lead to changes in mechanical properties of cells, triggering changes in shapes feeding back on the gene regulatory network. This in turn affects the distribution of chemical signals and mechanical forces, thus channeling morphogenesis. However, our understanding of the molecular and physical basis of morphogenesis in plants or in any other eukaryotic system is still in its infancy due to the complexity and non-linearity of processes involved in morphogenesis dynamics (or Morphodynamics). Understanding morphodynamics requires a modeling environment for the explicit representation of forms at multiple scales and for incorporating complex data from different origins and nature (chemical, mechanical, geometrical). In addition to creating a unique scientific environment, this LIA will gather the critical mass and interdisciplinary expertise required to create such a computational platform and to generate the data to produce an integrated vision of how chemical and mechanical signals interaction drive morphogenesis.

Partners: Sainsbury Lab. University of Cambridge (SLCU)

7.4. International Research Visitors

7.4.1. Visits of International Scientists

- Farah Ben Naoum, associate professor in computer science at the University of Sidi Bel Abbes, Algeria, visited the team in March 2019 for 3 weeks and worked with Romain Azais and Christophe Godin on the definition of a strategy to make efficient random walks in spaces of trees.
- Gabriela Mosca was a visiting researcher from Celia Baroux's Lab (U. Zurich, Switzerland) in the context of the ANR project IMAGO. She spent 3 weeks in the team working with Guillaume Cerutti, Jonathan Legrand, Olivier Ali and Christophe Godin to set up a protocol to reconstruct ovule development from confocal imaging.

7.4.1.1. Internships

- Salah Eddine Habibeche is a PhD student supervised by Farah Ben Naoum from the University of Sidi Bel Abbes. The PhD subject of Salah consists of developing compressing schemes for semi-ordered trees. During his visit, he will study methods of compression of trees with loss of information.
- Caro Chavez Hernandez is a PhD student from Elena Alvarez-Buylla, UNAM University, Mexico. Caro visited the MOSAIC group to work with Christophe Godin to integrate the extensive gene regulatory network she assembled of key molecular processes involved at different phases of plant development into a model of plant architecture development written in LPy.

PLEIADE Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. Malabar

This is a project funded by labex COTE (University of Bordeaux) as a collaboration with IFREMER at Arcachon, EPOC (Talence), and ETI chair of the labex. The guideline of the project is to build models in statistical ecology on a series of molecular based invetories (300 samples) from occurence matrices of OTUs in samples, with environmental variables. The samples have been collected in 2018-2019, the sequences produced by BioGeCo in 2019, and data analysis will begin in 2020.

8.1.2. High-performance computing and metabarcoding

PLEIADE is member of two projects, one funded by the Région Nouvelle Aquitaine and one funded as Inria ADT Gordon, connecting Chameleon, StartPU and NewMadeleine, where the use case of metabarcoding (questions, data sets) hase been selected to link these layers together. This will permit us to address unsupervised clustering of one million reads next year. These projects are in collaboration with the HiePACS, TADAAM, and STORM project-teams.

8.1.3. COTE – Continental to Coastal Ecosystems

The Labex cluster of excellence COTE (Continental To coastal Ecosystems: evolution, adaptability and governance) develops tools to understand and predict ecosystem responses to human-induced changes as well as methods of adaptative management and governance to ensure their sustainability. The LabEx includes nine laboratories of the University of Bordeaux and major national research institutes involved in research on terrestrial and aquatic ecosystems (INRA, CNRS, IFREMER and IRSTEA).

8.2. National Initiatives

8.2.1. Agence Française pour la Biodiversité

The AFB is a public law agency of the French Ministry of Ecology that supports public policy in the domains of knowledge, preservation, management, and restoration of biodiversity in terrestrial, aquatic, and marine environments. PLEIADE is a partner in two AFB projects developed with the former ONEMA: one funded by ONEMA, the second by labex COTE, where BioGeCo/Pleiade is responsible for data analysis, with implementaton of the tools recently developed for scaling MDS. Calculations have been made on CURTA at MCIA and PlaFRIM at Inria.

8.2.2. Inria Projet Lab in silico Algae

In 2017 PLEIADE joined the IPL “In silico Algae” coordinated by Olivier Bernard. The IPL addresses challenges in modeling and optimizing microalgae growth for industrial applications. PLEIADE worked this year on comparative genomic analysis of genes implicated in lipid production by the picoalgae *Ostreococcus tauri*, in collaboration with Florence Corellou of the CNRS UMR 5200 (Laboratoire de Biogénèse Membranaire). The goal of this work is the production of long-chain polyunsaturated fatty acids, developed as nutritional additives. Mercia Ngoma Komb’s two-month internship in PLEIADE contributed to this work.

8.3. European Initiatives

8.3.1. Collaborations in European Programs, Except FP7 & H2020

Program: COST

Project title: COST Action DNAqua.net

Abstract: PLEIADE is responsible for the WG "Data Analysis and storage" in this action. As such, we have organized with CNR Verbana (Italy) two Europeanwide workshops: one in Lyon in February 2019, and one in Limassol (Cyprus) in October 2019. As a follow up of these workshops, Pleiade and BioGeCo will be responsible for taking in charge data analysis of OTU picking in two European wide projects:

- a benchmark for different tools for OTU picking, with datasets from different European teams
- a comparison between different organisms (metabarcoding inventories) for assessing the quality of the water of Danube river, in collaboration with raparian countries

Program: EOSC

Project title: EOSC-Pillar

Abstract: This is a follow up of our former participation in EOSC-Pilot. In collaboration with HiePACS, PLEIADE is involved in task 7.4, for bringing use cases in metabarcoding as testbeds for circulation of codes between different infrastructures, including PlaFRIM.

8.4. International Initiatives

8.4.1. Vitapalm – Food and nutrition security and sustainable agriculture in Africa

PLEIADE participates in the Vitapalm program financed by LEAP-Agri [0], the joint Europe Africa Research and Innovation (R&I) initiative related to Food and Nutrition Security and Sustainable Agriculture. Vitapalm uses genomics and selection to improve the nutritional quality and the stability of palm oil produced by Africa smallholdings for local consumption. Project partners are from Cameroon, France, Germany, and Ghana.

8.4.2. Simulation of metacommunities

In collaboration with the Pasteur Institute in Cayenne and the INRA MIA Research Team in Toulouse, PLEIADE is developing a stochastic model for simulation of metacommunities, in the framework of patch occupancy models. The objective is a better understanding of zoonose propagation, namely rabies through bat hosts in connection with disturbances of pristine forests in French Guiana, which have an impact on the exposure of human populations to wildlife that act as reservoirs of zoonoses.

8.4.3. CEBA – Center for the study of biodiversity in Amazonia

The Laboratoire of excellence CEBA promotes innovation in research on tropical biodiversity. It brings together a network of internationally-recognized French research teams, contributes to university education, and encourages scientific collaboration with South American countries. PLEIADE participates in three current international projects funded by CEBA:

- *MicroBIOMES: Microbial Biodiversities*. 2017-19.
- *Neutrophyl: Inferring the drivers of Neotropical diversification*. 2017-19.
- *Phyloguianas: Biogeography and pace of diversification in the Guiana Shield*. 2015-present

PLEIADE is involved with BioGeCo as partner of Institut Pasteur de Guyane at Cayenne for developing the domain of so-called Ecoviromics for some zoonoses in French Guiana. The spine of this collaboration is co-supervizing of a PhD student at IPG in cayenne, in bioinformatics and statistical ecology to decipher the respective roles of host phylogeny and environmetal variables in the virome of different hosts (bats, rodents, birds).

[0] http://www.leap-agri.com/

SERPICO Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

9.1.1. Motion saliency analysis in videos

Participants: Léo Maczyta, Patrick Bouthemy.
Duration: 36 months (Oct 2017 – Sep 2020).

See Section 8.1.2.

Funding: DGA (National Defense Agency) and Région-Bretagne.

9.2. National Initiatives

9.2.1. France-BioImaging project

Participants: Sylvain Prigent, Patrick Bouthemy, Charles Kervrann, Jean Salamero.
Duration: 2011 – 2024.

The goal of the France-BioImaging project (http://france-bioimaging.org/) is to build a distributed coordinated French infrastructure for photonic and electronic cellular bioimaging, dedicated to innovation, training and technology transfer. High-computing capacities are needed to exhaustively analyse image flows. SERPICO is co-head of the IPDM (Image Processing and Data Management) node of the FBI network composed of 6 nodes. In this context, we address the following scientific problems: i/ exhaustive analysis of bioimaging data sets; ii/ deciphering of key steps of biological mechanisms at organ, tissular, cellular and molecular levels through the systematic use of time-lapse 3D microscopy and image processing methods; iii/ storage and indexing of extracted and associated data and metadata through an intelligent data management system. SERPICO recruited R&D engineers to disseminate image processing software, to build the Mobyle@serpico web portal and to manage the IGRIDA-SERPICO cluster (200 nodes; batch scheduler: OAR; File management: Puppet/Git/Capistrano; OS: Linux Debian 7; User connexion: public ssh key) opened for end-users and dedicated to large scale computing and data sets processing (storage: 200 TeraBytes) (see Section 6.13).

Funding: Investissement d'Avenir, ANR INBS-PIA 2011.
Coordinator: CNRS (J. Salamero, UMS 3714 CEMIBIO & CNRS-UMR 144, Institut Curie, PSL Research University).
Partners: CNRS, University of Paris-Diderot-Paris 7, Aix-Marseille University, University of Bordeaux, University of Montpellier, Institut Pasteur, Institut Curie, Inria, ENS Paris, University of Paris Descartes, UPMC, Ecole Polytechnique, INSERM.

9.2.2. ANR NucleoPLASTIC: Plasticity of the Nuclear Pore Complex

Participant: Jean Salamero.
Duration: 48 months (Oct 2015 – Sep 2019).

In this project, we have deciphered molecular/structural changes on the nuclear face of the Nuclear Pore Complex, their dynamics during cell division, and highlighted their role in the dynamics of association with the heart of the pore with consequences on maintaining the integrity of the genome. This was possible through the development of a 3D localization software GenLoc3D (https://team.inria.fr/serpico/software/genloc3d/, FIJI/ImageJ plug-in).

Funding: ANR (Agence Nationale de la Recherche).
Coordinator: C. Dargemont (INSERM, Hopital St Louis, Paris).
Partners: CNRS-UMR 144, Institut Curie, PSL Research, Paris.

9.2.3. ANR DALLISH project: Data Assimilation and Lattice LIght SHeet imaging for endocytosis/exocytosis pathway modeling in the whole cell

Participants: Antoine Salomon, Anca-Georgiana Caranfil, Sandeep Manandhar, Cesar Augusto Valades Cruz, Patrick Bouthemy, Ludovic Leconte, Jean Salamero, Charles Kervrann.
Duration: 48 months (Oct 2016 – Sep 2020).

Cutting-edge Light Lattice Sheet microscopy represents the novel generation of 3D fluorescence microscopes dedicated to single cell analysis, generating extraordinarily high resolved and sharp, but huge 3D images and videos. One single live cell experiment in one single biological condition can result into up to one terabyte of data.The goal of the project is to develop new paradigms and computational strategies for image reconstruction and 3D molecule motion estimation and tracking. Furthermore, establishing correspondences between image-based measurements and features, stochastic motion models, and underlying biological and biophysical information remains a challenging task. In a larger perspective, the quantitative description of image data corresponding to protein transport will be a prerequisite for understanding the functioning of a cell in normal and pathological situations including cancer, viral infection and neurodegenerative diseases (see Sections 7.2–7.6 and 7.8).

Funding: ANR (Agence Nationale de la Recherche) PRC (Collaborative Research Project).
Coordinator: C. Kervrann.
Partners: Inria (SERPICO, BEAGLE, FLUMINANCE teams), INRA MaIAGE Unit Jouy-en-Josas, Institut Curie (CNRS-UMR 144 & U1143 INSERM / UMR 3666) Paris.

9.2.4. Inria Project Labs (IPL / DEFI), Exploratory Research Actions and Technological Development Actions

9.2.4.1. NAVISCOPE: image-guided NAvigation and VISualization of large data sets in live cell imaging and microCOPy

Participants: Gwendal Fouché, Cesar Augusto Valades Cruz, Ludovic Leconte, Anais Badoual, Jean Salamero, Charles Kervrann.
Duration: 60 months (2018 – 2022).

In the frame of the "Naviscope" IPL project (https://project.inria.fr/naviscope/), our objective is to develop original and cutting-edge visualization and navigation methods to assist scientists, enabling semi-automatic analysis, manipulation, and investigation of temporal series of multi-valued volumetric images, with a strong focus on live cell imaging and microscopy application domains. Naviscope, built upon the strength of scientific visualization and machine learning methods, will provide systems capable to assist the scientist to obtain a better understanding of massive amounts of information. Such systems will be able to recognize and highlight the most informative regions of the dataset by reducing the amount of information displayed and guiding the observer attention. We address the three following challenges and issues:

- Novel machine learning methods able to detect the main regions of interest, and automatic quantification of sparse sets of molecular interactions and cell processes during navigation to save memory and computational resources.
- Novel visualization methods able to encode 3D motion and deformation vectors and dynamics features with color and texture-based and non-sub-resolved representations, abstractions, and discretization, as used to display 2D motion and deformation vectors and patterns.
- Effective machine learning-driven navigation and interaction techniques for complex functional 3D+Time data enabling the analysis of sparse sets of localized intra-cellular events and cell processes (migration, division, etc.) (see Section 7.9).

Meanwhile, we address the technological challenge of gathering up the software developed in each team to provide a unique original tool for users in biological imaging, and potentially in medical imaging.

Funding: Inria (IPL / DEFI).
Coordinator: C. Kervrann.
Partners: AVIZ Inria team (Saclay); BEAGLE Inria team (Lyon), HYBRID Inria team (Rennes), MORPHEME Inria team (Sophia-Antipolis); MOSAIC Inria team (Lyon), PARIETAL Inria team (Saclay), SERPICO Inria team (Rennes); MaIAGE INRA Unit (Jouy-en-Josas); CNRS-UMR 144, Institut Curie, PSL Research University (Paris).

9.3. European Initiatives

9.3.1. Collaborations in European Programs, Except FP7 & H2020

9.3.1.1. ESFRI initiative programm

SERPICO is involved in the ESFRI Euro-BioImaging (https://www.eurobioimaging.eu/) initiative, one of the four new biomedical science projects in the roadmap of the European Strategic Forum on Research Infrastructures (ESFRI). The mission of Euro-BioImaging is to provide access, service and training to state-of-the-art imaging technologies and foster the cooperation and networking at the national and European level including multidisciplinary scientists, industry, regional, national and European authorities. SERPICO is also involved in the French initiative, the so-called "France-BioImaging" (FBI) network which gathers several outstanding cellular imaging centers (microscopy, spectroscopy, probe engineering and signal processing) as described in Section 9.2.1 .

Coordinator: Turku University (J. Eriksson, Turku, Finland).
Funding: Member states of the European Union.
Partners: 15 European countries.

9.3.1.2. EIT Digital program
Participants: Sylvain Prigent, Charles Kervrann.
Duration: 12 months (Nov 2019 – Oct 2020).

SERPICO is involved in a European project which aims at developing a connected wearable device for diagnosis and treatment of photodermatoses. Using the data on skin sun sensitivity and UV exposure habits with machine learning algorithms will enable to make more precise optimal sun exposure predictions for patients. The wearable device will be useful for a larger population to increase awareness around overexposure to UV as a main cause of sun damage and worst-case skin cancer.

Funding: EIT Digital.
Inria coordinator: C. Kervrann.
Partners: UVisio and Nobleo Projects B.V., Eindhoven, The Netherlands.

9.4. International Initiatives

9.4.1. Inria International Partners

9.4.1.1. Informal International Partners

- Collaboration with Max-Planck Institute, Martinsried, Germany (with A. Martinez and W. Baumeister): Detection and segmentation of macromolecules in cryo-electron tomography (project in progress with E. Moebel and C. Kervrann) (see Sections 6.9 [30] and 6.12 [22]).
- Collaboration with University of Texas SouthWestern (UTSW) Medical Center, Dallas, United States (P. Roudot, E. Welf and G. Gaudenz): 3D optical flow for cell migration quantification (project in progress with S. Manandhar, P. Bouthemy and C. Kervrann) (see Sections 6.11 and 7.4 [21]).
- Collaborations with the MRC laboratory of Molecular Biology (with E. Derivery and J. Boulanger) and the Cambridge Advanced Imaging Centre (with L. Muresan), Cambridge, UK (project in progress with A. Salomon and C. Kervrann) (see Section 7.2).
- Collaboration with the PKU University, Institute of Molecular Medicine, Beijing (with L. Chen and Y.M. Liu): 3D reconstitution of the biogenesis of Endoplasmic Reticulum-plasma membrane contact sites (ER-PM MSCs upon Ca2+ store depletion or replenishment) (project in progress with C.A. Valades Cruz and J. Salamero).

9.5. International Research Visitors

9.5.1. Visits to International Teams

- Charles Kervrann visited the MRC laboratory of Molecular Biology and the Cambridge Advanced Imaging Centre (June, 1 week, Cambridge, UK).

ARAMIS Project-Team

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. Health Data Hub

Participant: Stanley Durrleman.

Project acronym: Precise-PD-HDH

Project title: Modélisation et prédiction de la progression de la maladie de Parkinson

Duration: 1 year (pilot project)

Coordinator: Jean-Christophe Corvol

Other partners: Inserm, réseau NS-PARK, ICM

9.1.2. ANR

9.1.2.1. ANR-NIH-NSF CANDT

Participant: Fabrizio de Vico Fallani [Correspondant].

Project acronym: CANDT

Project title: Advancing neuroscientific discovery and training by lowering the barrier of entry to network neuroscience via open science

Duration: Oct 2019 - Sep 2023

Amount: 137k€

Coordinator: Fabrizio De Vico Fallani

Other partners: Indiana Univ., US; UPenn, US

Abstract: This project will use open science methods and cloud-computing, effectively lowering the barrier of entry to network neuroscience and increase the widespread availability of well-maintained and reproducible network neuroscience tools. We will use the platform brainlife.io as a digital marketplace for network neuroscience analysis methods; network neuroscience tools and software will be packaged into self-contained, standardized, reproducible Apps, shared with and modified by a burgeoning community of users, and seamlessly integrated into existing brainlife.io processing and analysis pipelines. This approach will engage both experts in network science, scientists from other domains, and users of the proposed methods. In addition, it will ensure correct implementation, a high level of reproducibility, and maximal reusability of network neuroscience methods. As a requirement, Apps will also be accompanied by links to primary sources, in-depth tutorials, and documentation, and worked-through examples, highlighting their correct usage and offering solutions for mitigating possible pitfalls. This proposed research lowers the barrier of entry to network neuroscience, standardizes the software sharing process, and provides a cloud-based repository of expertly-maintained network neuroscientific tools and software that is made available to the broader neuroscientific community.

9.1.2.2. ANR-NIH-NSF NETBCI

Participants: Fabrizio de Vico Fallani [Correspondant], Mario Chavez, Denis Schwartz.

Project acronym: NETBCI

Project title: Modeling and predicting brain-computer interface learning from dynamic networks

Duration: Avr 2016 - Avr 2020

Amount: 322k€

Coordinator: Fabrizio De Vico Fallani

Other partners: Complex system group, UPenn, USA

Abstract: This project will bring together expertise in computational and experimental neuroscience, signal processing and network science, statistics, modeling and simulation, to establish innovative methods to model and analyze temporally dynamic brain networks, and to apply these tools to develop predictive models of brain-computer interface (BCI) skill acquisition that can be used to improve performance. Leveraging experimental data and interdisciplinary theoretical techniques, this project will characterize brain networks at multiple temporal and spatial scales, and will develop models to predict the ability to control the BCI as well as methods to engineer BCI frameworks for adapting to neural plasticity. This project will enable a comprehensive understanding of the neural mechanisms of BCI learning, and will foster the design of viable BCI frameworks that improve usability and performance.

9.1.2.3. ANR-NIH-NSF HIPLAY7

Participants: Olivier Colliot [Correspondant], Marie Chupin, Stanley Durrleman, Anne Bertrand.

Project acronym: HIPLAY7

Project title: Hippocampal layers: advanced computational anatomy using very high resolution MRI at 7 Tesla in humans

Duration: Jan 2017 - Jan 2020

Amount: 770k€

Coordinator: Olivier Colliot and Pierre-François Van de Moortele

Other partners: University of Minnesota, Neurospin

Abstract: The overall goal of this proposal is to develop a coherent mathematical framework for computational anatomy of the internal structures of the hippocampus based on cutting edge MRI acquisition techniques at 7 Tesla. These mathematical and computational approaches are expected to significantly advance the field of computational anatomy of the human brain, breaking down the millimeter barrier of conventional brain morphometry and providing a coherent analysis framework for anatomical data at ultra-high spatial resolution.

9.1.2.4. ANR PREV-DEMALS

Participants: Olivier Colliot [Correspondant], Marie Chupin, Stanley Durrleman, Anne Bertrand.

Project acronym: PREV-DEMALS

Project title: Predict to prevent frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS)

Duration: Avr 2015 - Avr 2019

Amount: 487k€

Coordinator: Isabelle Le Ber

Other partners: ICM, AP-HP, CHR de Lille, CHU Limoges, CHU Rouen, Laboratory of Biomedical Imaging

Abstract: The project focuses on C9ORF72, the most frequent genetic form of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). Since 2006, major discoveries have helped elucidate the pathological bases and linked FTLD and ALS: 1) TDP-43 aggregates in neurons and 2) C9ORF72 mutations in both disorders. Two major pathological subtypes are now defined in FTLD, FTLD-TDP and FTLD-TAU. C9ORF72 mutations (associated to FTLD-TDP) are the most frequent genetic causes of FTLD (15%), FTLD-ALS (65%) and ALS (40%). No curative treatment actually exists, but therapeutics emerged against tau aggregation. The objectives of the project are to develop appropriate cognitive, brain imaging markers and peripheral biomarkers of the early phase of FTLD, to follow disease progression and to guide future targeted therapeutic trials. To address this questions, we will conduct a multimodal study (cognition, brain structural MRI, brain metabolism - FDG-PET) in C9ORF72 families. The cohort will be followed at 3-time points (M0, M18, M36). Longitudinal analyses will aim at characterizing the trajectory of decline across time. Brain structural changes will be evaluated by 1) morphometric analysis to assess global brain atrophy, cortical thickness and study of the cortical sulci; 2) functional connectivity analysis of resting-state MR data; 3) structural connectivity analysis of diffusion-weighted MRI. Brain metabolism will be evaluated with FDG-PET. We will use the most recent RNA sequencing technology to detect gene expression and RNA splicing alterations in lymphocytes of patients and presymptomatic carriers. The discovery of new markers involved in FTLD will have practical consequences for early and accurate diagnosis of FLD and ALS disease.

9.1.2.5. ANR IVMRS

Participants: Anne Bertrand [Correspondant], Alexandra Petiet, Mathieu Santin, Francesca Branzoli, Benoit Delatour, Marc Sanson.

Project acronym: IVMRS

Project title: Implantable miniaturized probe for In-vivo Magnetic Resonance Spectroscopy: Application to Murine models of Alzheimer's disease and Gliomas.

Duration: Oct 2016 - Oct 2020

Amount: 633k€

Coordinator: Luc Hebrard

Other partners: ICube - Unistra, Strasbourg; ISA Laboratory, Lyon; NYU School of Medicine, NY, USA.

Abstract: During the development of new therapeutics against brain diseases, the pre-clinical phase, i.e. the validation of treatment delivery, safety and efficacy in animal models of the disease, represents a crucial step. Magnetic Resonance Imaging (MRI) is a method of particular interest at this stage, as it provides non-invasive surrogate endpoints that can help selecting appropriate candidates during the process of drug development. Single Voxel Magnetic Resonance Spectroscopy (SVS) provides non-invasive, in-vivo quantitative measurements of brain metabolites, which reflects functional changes at the cellular and subcellular levels, and can be repeated longitudinally. As high-field MRI has become the benchmark in preclinical research on animal models, it appears possible to investigate the cerebral metabolomics changes in animals, and to use it as a surrogate marker in preclinical therapeutic trials. However, the number of relevant metabolites is much higher than the low number of measurable metabolites with conventional in-vivo high-field SVS. Moreover, considering also the subtle changes of these metabolites at the early stage of the disease, the use of conventional high-field SVS in preclinical studies remains strongly limited. The high volume of the Voxel-of-Interest (VOI), ranging from 10 to 30mm3, which is required to have a usable signal in conventional SVS, and the inherent variability of longitudinal SVS measurement due to the variable position of the VOI in the successive experiments, remain the two major issues when looking during time for small changes in metabolic concentrations and metabolites ratios in a specific small region of the animal brain. The IvMRS project aims at filling this gap by developing the first chronic implantable MRS micro-probe, minimally invasive, exhibiting very high signal sensitivity, and sharp

spectral peaks, from sub-millimetric VOI. Such a probe will allow detecting a much higher number of metabolites than conventional in-vivo SVS. The probe will work at frequencies ranging from 300MHz to 500MHz in ultra-high field Magnetic Resonance Imaging scanners, 7T and 11.7T. It will embed a specific micro-coil antenna, a low-noise signal conditioning circuit designed in CMOS microelectronics technology, as well as an accurate on-chip positioning sensor. It will be dedicated to the study of changes in brain metabolite markers of two major diseases, Alzheimer's disease and cerebral gliomas, and to the assessment of effective therapeutic strategies.

9.1.3. Inria Project Labs

9.1.3.1. IPL Neuromarkers

Participants: Stanley Durrleman [Correspondant], Olivier Colliot [Correspondant], Fabrizio de Vico Fallani, Anne Bertrand, Stéphane Epelbaum.

Project acronym: Neuromarkers

Project title: Design of imaging biomarkers of neurodegenerative diseases for clinical trials and study of their genetic associations

Duration: 2017-2021

Coordinators: Stanley Durrleman and Olivier Colliot

Other partners: Inria GENSCALE, Inria BONSAI, Inria DYLISS, Inria XPOP, ICM, IHU/ICM iConics

Abstract: The Inria Project Lab Neuromarkers aims to develop new statistical and computational approaches to integrate multimodal imaging and omics data and to demonstrate their potential to identify early alterations and predict progression of neurodegenerative diseases. To tackle this challenge, the project brings together multidisciplinary expertise from Inria and ICM (Brain and Spine Institute) in the fields of statistical learning, brain imaging, bioinformatics, knowledge modeling, genomics and neurodegenerative diseases.

9.1.4. IHU

9.1.4.1. General program

Participants: Olivier Colliot, Stanley Durrleman, Didier Dormont, Ninon Burgos, Stéphane Epelbaum, Fabrizio de Vico Fallani.

Project acronym: IHU-A-ICM

Project title: Institute of Translational Neuroscience

Founded in 2011

General Director: Bertrand Fontaine

The IHU-A-ICM program was selected, in 2011, in a highly competitive national call for projects. A 10-year, 55M€ program, has been implemented by a recently created foundation for scientific cooperation. Based on the clinical and scientific strenghts of the ICM and the hospital Department of Nervous System Diseases, it mainly supports neuroscience research, but is also invested in improving care and teaching. ARAMIS is strongly involved in the IHU-A-ICM project, in particular in WP6 (neuroimaging and electrophysiology), WP7 (biostatistics), WP2 (Alzheimer) and WP5 (epilepsy). We have started collaborations with the new bioinformatics/biostatistics platform (IHU WP7, head: Ivan Moszer), in particular through a joint project on the integration of imaging and genomics data.

9.1.4.2. ICM-Internal Research projects

Participants: Anne Bertrand [Correspondant], Takoua Kaaouana, Benoit Delatour, Alexandra Petiet, Olivier Colliot, Arnaud Marcoux.

Project title: The Histo-MRI project: targeting MR signature of tauopathy from micro- to macroscopy

Started in 2014

Coordinator: Anne Bertrand

Identifying morphological MR signatures of brain diseases usually follows a top-down process, which starts by describing a pattern of MR signal changes in patients, hypothesizes an underlying pathological mechanism, and confirms this mechanism by correlating the observed MR signal changes with histological lesions on post-mortem examination. This top-down process, relevant for large, centimetric brain lesions, becomes inappropriate when targeting the MR signal intensity changes associated with microscopic lesions. Our project aims at developing an MR biomarker of NFT using a new bottom-up approach. We will start by identifying the MR signal changes associated with the presence of NFT at the level of the histological slice, and utilize these findings to develop a method of NFT quantification on clinical, millimetric 3D MR images. To achieve this goal, we will develop and implement a 11.7T histological coil dedicated to the scanning of histological slices, which allows both ultra-high resolution MR imaging (up to 33 microns in-plane) and perfect co-registration with histological staining, performed subsequently on the same slice. This method has the potential to provide a novel biomarker of tauopathy that could not have been identified using the usual top-down approach. It also envisions the possibility to describe and understand new MRI contrasts in other neurodegenerative diseases associated with microscopic deposition of various proteins.

9.1.4.3. ICM BBT Program - project PredictICD

Participants: Olivier Colliot [Correspondant], Jean-Christophe Corvol [Correspondant], Johann Faouzi.

Project title: Predict impulse control disorders in Parkinson's disease (PREDICT-ICD)

Started in 2018

Coordinators: Olivier Colliot and Jean-Christophe Corvol (ICM)

In Parkinson's disease (PD), the therapeutic strategy is based on the dopamine replacement therapy. Although available since the 1960s', it is only relatively recently that behavioral disorders associated with these drugs have been described. Gathered under the term of "behavioral addiction", they include impulse control disorders (ICDs), dopamine dysregulation syndrome (DDS), and punding. Interestingly, whereas addiction to L-dopa itself occurs quasi exclusively with L-dopa, ICDs appear electively under dopamine agonist (DA) therapy. The objectives of this project are: i) to elucidate the genetic basis of DA induced ICDs in PD patients from several international cohorts; ii) to develop and validate a machine learning model to predict the occurrence of ICDs from the combination of clinical and genetic data.

9.1.4.4. ICM BBT Program - project DYNAMO

Participants: Stanley Durrleman [Correspondant], Harald Hampel [Correspondant], Sabrina Fontanella, Simone Lista, Olivier Colliot, Stephanie Allassonniere, Jean-Baptiste Schiratti, Bruno Dubois, Hovagim Bakardjian, Remi Genthon, Enrica Cavedo, Katrine Rojkowa.

Project title: Dynamic models of disease progression across Alzheimer's disease stages informed by multimodal neuroimaging and biological data

Started in 2016

Coordinator: Stanley Durrleman and Harald Hampel

Other partners: Institut de la Mémoire et de la maladie d'Alzheimer

The estimation of data-driven models of disease progression for neurodegenerative diseases, including Alzheimer's disease (AD), is crucial to confirm, refine and extend the current hypothetical models. The estimation of such quantitative models from longitudinal data sets is notably difficult because of the lack of principled methodological frameworks for the analysis of spatiotemporal data.

The project builds on an innovative mathematical, statistical, and computational framework to automatically align the dynamics and the direction of individual trajectories of the evolving pathology, and then to infer a normative scenario of disease progression across different disease stages. The estimated scenario will combine spatiotemporal maps of lesion propagation, such as maps of amyloid deposition or cortical atrophy, and global measurements such as levels of CSF biomarkers. It will be possible to estimate not only a normative scenario but also the inter-individual variability in the values, dynamics and direction of both topographical and pathophysiological biomarkers changes during the course of the disease.

The application of this technology to publicly available and in-house longitudinal data sets of individuals from the asymptomatic at risk to the prodromal and dementia stages will yield new insights into the pathophysiology of AD from the preclinical to the AD dementia stages. This quantitative data-driven approach will be exploited to assess and refine the current qualitative hypothetical models of AD progression. Notably, it will complement these models with typical pathways of lesion propagation in the brain during disease progression. It will also highlight the effect of the known risk factors of AD such as apolipoprotein E genotype on the disease progression profile.

The project will open up the concrete possibility to derive a computer-aided diagnosis, staging, and prognosis tool for a better recruitment of patients in clinical studies and to assist clinicians in the diagnosis and the monitoring of both disease progression and treatment efficacy.

9.1.4.5. ICM BBT Program - project SEMAPHORE

Participants: Stanley Durrleman [Correspondant], Stéphane Lehéricy [Correspondant], Jean-Christophe Corvol, Marie Vidailhet, Raphael Couronné, Safia Said.

Project title: Personalized progression model of Parkinson's disease

Started in 2018

Coordinator: Stanley Durrleman and Stéphane Lehéricy

Other partners: Neurology and Neuro-radiology departments, Pitié-Salpêtrière Hospital, AP-HP

The aim of this project is to build a personalizable model of Parkinson's disease (PD) progression integrating the complex dynamical interplay between phenotypic, imaging, genetic and metabolic alterations. We will identify and validate markers for monitoring of progression of brain damage in early and prodromal PD and identify conversion markers in subjects at risk of PD (idiopathic rapid eye movement sleep behavior disorders iRBD, PD- related mutation carriers). We will describe the appearance, characterize clinical phenotypes of PD, and identify modifier genes of disease phenotype. To this aim, we will relie on a novel statistical learning method using Bayesian non-linear mixed-effects model allowing to combine and realign short term sequence data to estimate a long-term scenario of disease progression. This method is able to estimate individual stages of disease progression and to analyze automatically non-linear spatiotemporal patterns of data change. It estimates both a group-average scenario of PD progression as well as the inter-individual variability of this model in terms of age at onset, pace of disease progression and variability in the spatiotemporal trajectory of data changes. We will analyse the effect of genetic variants in the modulation of these non-linear progression patterns, and assess the statistical power of the individual parameters encoding for these patterns. The method will be applied to two sets of longitudinal data from the local prospective NUCLEIPARK (60 PD patients, 20 patients with iRBD, 60 controls) and ICEBERG studies (200 early idiopathic PD, 50 iRBD, 30 GBA and LRRK2 PD-related mutation carriers, 50 controls). Examinations included clinical, biological, and neurophysiological data, and multimodal 3T MRI, DATScan, and skin and salivary gland biopsies. The models of PD progression for each category of subjects will be released to the community, as well as the software for reproducibility purposes.

9.1.4.6. ICM BBT Program - project ATTACK

Participants: Fabrizio de Vico Fallani [Correspondant], Charlotte Rosso [Correspondant], Marie-Constance Corsi, Laurent Hugueville.

Project title: ATTACK Brain Network Models Of Motor Recovery After Stroke

Started in 2018

Coordinator: Fabrizio De Vico Fallani, Charlotte Rosso

Other partners: Neurology and Stroke departments, Pitié-Salpêtrière Hospital, AP-HP

Like in other connected systems, studying the structure of the interactions between different brain regions has profound implications in the comprehension of emergent complex phenomena as, for example, the capability of the human brain to functionally reorganize after cerebrovascular "attacks" or stroke. This dynamic skill, which is known in neuroscience as neural plasticity, is not only interesting from a network science perspective, but it also plays a crucial role in determining the motor/cognitive recovery of patients who survive a stroke. As a critical innovation, this project proposes to develop a systematic and rigorous approach based on neuroimaging techniques, signal processing, and network science for the modeling and analysis of temporally dynamic neural processes that characterize motor recovery after stroke. To achieve these goals, this project is organized around the following objectives: i) acquiring a comprehensive longitudinal dataset of brain and behavioral/clinical data after stroke, ii) developing new analytic tools to characterize and generate temporally dynamic brain networks, iii) building network-based models of motor recovery after stroke, accounting for individual patients. These objectives involve an intensive gathering of heterogeneous mass data, their processing, the subsequent outcome interpretation and statistical simulation, as well as the development of longitudinal models and network-based diagnostics of the patient's motor recovery progress. Results will be first characterized from pure network-theoretic and neuroscience perspectives, so as to highlight fundamental research challenges, and then validated to clarify the importance and the applicability to the clinical scenario. Our results will unveil multiscale properties of dynamic brain networks and identify predictive neuromarkers for motor recovery after stroke. This project has a two-fold impact on the society. On the one hand, it will provide new methods and robust tools to properly characterize and model temporally dynamic networks in neuroscience. On the other hand, it will provide longitudinal models of motor recovery in stroke patients that can potentially unveil the neural substrate that underpins rehabilitation, improve prognosis, and eventually lower cost of hospitalization time. From a broader perspective this interdisciplinary project proposes a transformative approach to analyze large-scale neural systems.

9.1.5. 3IA Institutes - PRAIRIE

Participants: Olivier Colliot, Stanley Durrleman, Ninon Burgos.

Project acronym: PRAIRIE

Project title: Paris Artificial Intelligence Research Institute

Founded in 2019

Director: Isabelle Ryl

Website: https://prairie-institute.fr/

PRAIRIE is one of the four selected French Institutes of AI. It was selected within a call for creation of interdisciplinary AI research institutes (or "3IAs" for "Instituts Interdisciplinaires d'Intelligence Artificielle"), as part of the national French initiative on Artificial Intelligence (AI). PRAIRIE aspires to become within five years a world leader in AI research and higher education, with an undeniable impact on economy and technology at the French, European and global levels. ARAMIS team members N. Burgos, O. Colliot and S. Durrleman hold a chair at PRAIRIE.

9.1.6. National Networks

- GdR Statistics and Medicine - http://gdr-stat-sante.math.cnrs.fr/spip/
- GdR (MaDICS) Masses de Données, Informations et Connaissances en Sciences Big Data - Data ScienceStatistics and Medicine - http://www.madics.fr/reseaux/
- F. De Vico Fallani participated to the GdR (HANDICAP) in the framework of the future strategy of Inria
- F. De Vico Fallani was founding member of the CORTICO national network for brain-computer interfaces

9.1.7. Other National Programs

9.1.7.1. Fondation Vaincre Alzheimer

Participants: Olivier Colliot, Vincent Henry, Martin Hoffman-Apitius.

Project title: Integrative multiscale knowledge model of Alzheimer's disease pathophysiology

2019-2020

Amount: 100K€

Coordinator: Olivier Colliot

Other partners: Frauhofer SCAI (Germany)

Abstract: Alzheimer's disease (AD) pathophysiology is still imperfectly understood. In particular, we currently lack an integrative view of the disease to interconnect knowledge about the molecular, cellular, clinical and systems levels that remain scattered. Computational knowledge models have the potential to provide such an integrative view. The aim of this project is to provide a multiscale knowledge model of AD pathophysiology by aggregating existing heterogeneous resources (disease maps, ontologies, databases) using Semantic Web standards. The resulting model and associated software tools will be made publicly available to the scientific community.

9.1.7.2. France Parkinson

Participants: Jean-Christophe Corvol, Olivier Colliot, Stanley Durrleman.

Project title: PRECISE-PD - From pathophysiology to precision medicine for Parkinson's disease

2019-2024

Amount: 3M€

Coordinator: Jean-Christophe Corvol

Other partners: Inserm CIC-1436, Inserm CIC-P1421, Inserm U1171, Université de Bordeaux (IMN), University of Glasgow, University of Calgary,

Abstract: Parkinson's disease (PD) is a complex neurodegenerative disease characterized by the progression of motor and non-motor symptoms resulting from the spreading of the disease into dopaminergic and non-dopaminergic areas. Clinical trials have failed to demonstrate efficacy to slow PD progression because the relationships between progression profiles and their underlying molecular mechanisms remain to be identified. The objective of PRECISE-PD is to propose a mechanismsbased progression model of PD by combining genetic and longitudinal clinical data from a large cohort of patients. We will implement a biobank to the NS-PARK/FCRIN cohort collecting motor and non-motor symptoms from >22,000 PD patients followed in the 24 expert centers in France. Genomic data will be generated by using a microarray platform developed for neurodegenerative diseases studies, and brain imaging will be obtained from a subgroup of patients. Computational and machine learning approaches will be developed to address the challenges of analyzing the high dimensionality and the mixture of data necessary to move beyond empirical stratification of patients. Replication will be performed in independent cohorts, and biological validation will combine biomarkers and preclinical research. PRECISE-PD is an unpreceded opportunity to open the path to the new era of precision and personalized medicine for PD.

9.2. European Initiatives

9.2.1. FP7 & H2020 Projects

9.2.1.1. H2020 - Project EuroPOND

Participants: Olivier Colliot, Stanley Durrleman, Manon Ansart, Igor Koval, Alexandre Bône.

Project acronym: EuroPOND

Project title: Data-driven models for Progression Of Neurological Disease

Duration: Jan 2016 - Dec 2019

Amount: 6M€

Coordinator: Daniel Alexander

Other partners: University College London (UK), EMC Rotterdam (The Netherlands), VUMC (The Netherlands), Fate Bene Fratelli (Italy), Carol Besta Institute (Italy), Université de Genève (Switzerland), Icometrix (Belgium)

Abstract: EuroPOND will develop a data-driven statistical and computational modeling framework for neurological disease progression. This will enable major advances in differential and personalized diagnosis, prognosis, monitoring, and treatment and care decisions, positioning Europe as world leaders in one of the biggest societal challenges of 21st century healthcare. The inherent complexity of neurological disease, the overlap of symptoms and pathologies, and the high comorbidity rate suggests a systems medicine approach, which matches the specific challenge of this call. We take a uniquely holistic approach that, in the spirit of systems medicine, integrates a variety of clinical and biomedical research data including risk factors, biomarkers, and interactions. Our consortium has a multidisciplinary balance of essential expertise in mathematical/statistical/computational modelling; clinical, biomedical and epidemiological expertise; and access to a diverse range of datasets for sporadic and well-phenotyped disease types.The project will devise and implement, as open-source software tools, advanced statistical and computational techniques for reconstructing long-term temporal evolution of disease markers from cross-sectional or short-term longitudinal data. We will apply the techniques to generate new and uniquely detailed pictures of a range of important diseases. This will support the development of new evidence-based treatments in Europe through deeper disease understanding, better patient stratification for clinical trials, and improved accuracy of diagnosis and prognosis. For example, Alzheimer's disease alone costs European citizens around €200B every year in care and loss of productivity. No disease modifying treatments are yet available. Clinical trials repeatedly fail because disease heterogeneity prevents bulk response. Our models enable fine stratification into phenotypes enabling more focussed analysis to identify subgroups that respond to putative treatments.

9.2.1.2. H2020 - Project VirtualBrainCloud

Participant: Stanley Durrleman.

Project acronym: TVBCloud

Project title: Personalized Recommendations for Neurodegenerative Disease

Duration: Jan 2019 - Dec 2022

Amount: 15 M€

Coordinator: Petra Ritter

Other partners: Charite Berlin, Université Aix Marseille, Fraunhofer Gesellschaft, University of Oxford, Forschungzentrum Juelich, Institut du Cerveau et de la Moëlle épinière, Inria, Fundacio institut de bioenginyeria de catalunya, Helsingin yliopisto, Universita degli studi di genova, Universidad complutense de Madrid, Codebox Computer-Dienste, Codemart, Eodyne Systems, Universität Wien, TP21, Alzheimer Europe

Abstract: The annual worldwide cost of Alzheimer's dementia was 777.81 billion Euro in 2015. This number will rise to 7.41 trillion Euro in 2050. Early diagnosis would save up to $7.9 trillion in medical and care costs by 2050 in the US alone. However, the emergent pathology is highly variable across people, necehighly variable across people, necessitating individualized diagnostics and interventions. The VirtualBrainCloud addresses this by bridging the gap between computational neuroscience and subcellular systems biology, integrating both research streams into a unifying computational model that supports personalized diagnostics and treatments in NDD. TheVirtualBrainCloud not only integrates existing software tools, it also merges the efforts of two big EU initiatives, namely The Virtual Brain large scale simulation platform of the EU Flagship Human Brain Project and IMI-EPAD initiative (European prevention of Alzheimer's dementia consortium). VirtualBrainCloud will develop and validate a decision support system that provides access to high quality multi-disciplinary data for clinical practice. The result will be a cloud-based brain simulation platform to support personalized diagnostics and treatments in NDD. The EU PRACE (Partnership for Advanced Computing in Europe) initiative, will provide the required computing infrastructure. TheVirtualBrainCloud will develop robust solutions for legal and ethical matters by interacting with EU projects such as European Open Science Cloud (EOSC), 'cloud4health', Alzheimer's Europe patient organizations and ELIXIR, an organization that manages and safeguards EU research data. Our software developers have already produced highly successful brain simulation and clinical decision support tools. The resulting software will be a cloud based computational modeling system that is tailored to the individual, and bridges multiple scales to identify key mechanisms that predict NDD progression and serves as Precision Decision Support System.

9.2.1.3. FET Flagship - Human Brain Project

Participants: Olivier Colliot, Stanley Durrleman.

Project acronym: HBP

Project title: Human Brain Project

Sub-project: SP8 - Medical Informatics Platform

Duration: 2016-

Abstract: The Human Brain Project (HBP) is a European Commission Future and Emerging Technologies Flagship. The HBP aims to put in place a cutting-edge, ICT-based scientific Research Infrastructure for brain research, cognitive neuroscience and brain-inspired computing. The Project promotes collaboration across the globe, and is committed to driving forward European industry. Our team is involved in the Subproject SP8 (Medical Informatics Platform). The Medical Informatics Platform (MIP) is an innovative data management system that gives researchers the means to access and analyse large amounts of anonymized clinical neuroscience data. Within that framework, we will develop and implement a method to construct disease progression models from longitudinal biomarkers. The method will use statistical learning techniques to infer a long-term disease progression model from multiple short term data from a series of individuals. The model will account for variability in age at disease onset, pace of disease progression and trajectories of biomarkers changes across individuals in the observed population.

9.2.1.4. ERC - LEASP

Participant: Stanley Durrleman.

Project acronym: LEASP

Project title: Learning Spatiotemporal Patterns in Longitudinal Image Data Sets of the Aging Brain

Duration: 2016-2021

Abstract: Time-series of multimodal medical images offer a unique opportunity to track anatomical and functional alterations of the brain in aging individuals. A collection of such time series for several individuals forms a longitudinal data set, each data being a rich iconic-geometric representation of the brain anatomy and function. These data are already extraordinary complex and variable across individuals. Taking the temporal component into account further adds difficulty, in that each individual follows a different trajectory of changes, and at a different pace. Furthermore, a disease is here a progressive departure from an otherwise normal scenario of aging, so that one could not think of normal and pathologic brain aging as distinct categories, as in the standard case-control paradigm.

Bio-statisticians lack a suitable methodological framework to exhibit from these data the typical trajectories and dynamics of brain alterations, and the effects of a disease on these trajectories, thus limiting the investigation of essential clinical questions. To change this situation, we propose to construct virtual dynamical models of brain aging by learning typical spatiotemporal patterns of alterations propagation from longitudinal iconic-geometric data sets.

By including concepts of the Riemannian geometry into Bayesian mixed effect models, the project will introduce general principles to average complex individual trajectories of iconic-geometric changes and align the pace at which these trajectories are followed. It will estimate a set of elementary spatiotemporal patterns, which combine to yield a personal aging scenario for each individual. Disease-specific patterns will be detected with an increasing likelihood.

This new generation of statistical and computational tools will unveil clusters of patients sharing similar lesion propagation profiles, paving the way to design more specific treatments, and care patients when treatments have the highest chance of success.

9.3. International Initiatives

9.3.1. Informal International Partners

- O. Colliot has an enduring collaboration with the Center for Magnetic Resonance Research, University of Minnesota, USA (P-F Van de Moortele, T. Henry).
- S. Durrleman and O. Colliot have a collaboration with the Center for Medical Image Computing (CMIC) at University College London (UCL), London, UK (D. Alexander, H. Zhang).
- F. De Vico Fallani has a collaboration with Penn University, US (Prof. D. Bassett) and Queen Mary University London, UK (Prof. Vito Latora).

9.4. International Research Visitors

9.4.1. Visits of International Scientists

We hosted Prof Bruno Jedynak from Portland State University (USA) in June and July 2019.

ATHENA Project-Team

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ADT

8.1.1.1. ADT BCI-Browser

Participants: Théodore Papadopoulo, Maureen Clerc.

Duration: 1 year

Most often, BCI techniques are demonstrated in simple toy applications made. The only "few" real BCI applications are specific developments and are not used much as they lack of functionality, maintenance, ... The goal of this development contract is to demonstrate a new approach to BCI, in which BCI interactions are integrated in existing applications. Ideally, the original software is not modified and not even recompiled. It is modified by providing either modified GUI libraries or providing extensions as plugins. As a proof of concept, we aim at modifying C++/Qt applications with a focus on web browsing, by redefining some of its basic interactions (mouse clicks, keyboard, ...) using some BCI components. In this manner, it might be possible to drive standard and state-of-the-art application using BCI and at a limited maintenance cost.

This contract is part of the AMDT initiative.

8.1.1.2. ADT OpenMEEG

Participants: Théodore Papadopoulo, Maureen Clerc, Kostiantyn Maksymenko, Alexandre Gramfort [PARIETAL], Joan Massich [PARIETAL].

Duration: *24 months.*

The OpenMEEG ADT aims at improving OpenMEEG along 3 main directions:

1. Offer a user interface for the creation and verification of head models most importantly for a simpler management of non-nested head models.
2. Improve the Python interface (extension and reliability). This will also be useful to develop new research axes (in connection with point 3).
3. Enrich the available operators and refactor the code to offer new possibilities in OpenMEEG and reduce the cost of maintenance.

In addition to the expected gains in code maintenance, these improvements will allow a number of new – more sophisticated – applications as well as open OpenMEEG to a larger audience with a simplified interface for classical use-cases.

This contract is part of the AMDT initiative.

8.2. European Initiatives

8.2.1. FP7 & H2020 Projects

8.2.1.1. ERC AdG CoBCoM

Program: H2020-EU.1.1. (ERC-ADG-2015 - ERC Advanced Grant)

Project acronym: CoBCoM - **ID:** 694665

Project title: *Computational Brain Connectivity Mapping*

Start date: 2016-09-01, End date: 2021-08-31

P.I. : R. Deriche

Partners: ATHENA project-team

Abstract:

One third of the burden of all the diseases in Europe is due to problems caused by diseases affecting brain. Although exceptional progress has been obtained for exploring it during the past decades, **the brain is still terra-incognita** and calls for specific research efforts to better understand its architecture and functioning.

COBCOM is our response to this great challenge of modern science with the overall goal to **develop a joint Dynamical Structural-Functional Brain Connectivity Network (**DSF-BCN**)** solidly grounded on advanced and integrated methods for diffusion Magnetic Resonance Imaging (dMRI) and Electro & Magneto-Encephalography (EEG & MEG).

To take up this grand challenge and achieve new frontiers for brain connectivity mapping, we will develop a new generation of computational models and methods for identifying and characterizing the structural and functional connectivities that will be at the heart of the DSF-BCN. Our strategy is to break with the tradition to incrementally and separately contributing to structure or function and develop **a global approach involving strong interactions between structural and functional connectivities.** To solve the limited view of the brain provided just by one imaging modality, our models will be developed under a rigorous computational framework integrating complementary non invasive imaging modalities: dMRI, EEG and MEG.

COBCOM will push far forward the state-of-the-art in these modalities, developing **innovative models and ground-breaking processing tools** to provide in-fine a joint DSF-BCN solidly grounded on a detailed mapping of the brain connectivity, both in space and time.

Capitalizing on the strengths of dMRI, MEG & EEG methodologies and building on the **bio-physical and mathematical foundations** of our new generation of computational models, COBCOM will be applied to high-impact diseases, and its **ground-breaking computational nature and added clinical value** will open new perspectives in neuroimaging.

8.3. International Initiatives

8.3.1. Inria International Partners

8.3.1.1. Declared Inria International Partners

- Sherbrooke University, CA (M. Descoteaux)
- CMRR, University of Minnesota, USA (C. Lenglet)
- Verona University, It (G. Menegaz)
- Department of CISE, the University of Florida, Gainesville, USA (B. C. Vemuri)
- Centre for Medical Image Computing (CMIC), Dept. Computer Science, UCL, UK (D. Alexander)
- SBIA, University of Pennsylvania Medical School, USA (R. Verma).
- EEMagine company on EEG/MEG hardware.

8.3.2. Participation in Other International Programs

- University Houari Boumedienne (USTHB, Algiers) (L. Boumghar) and University of Boumerdes, (D. Cherifi), Algeria.

8.4. International Research Visitors

8.4.1. Visits of International Scientists

- Pr Gloria Menegaz, Department of Computer Science, University of Verona (March 23 - Sept 20, 2019)

8.4.1.1. Internships

- Imogen Den otter-Moore - Queen's University, Kingston, Canada, From early May to late July, 2019
- Federica Cruciani - Department of Computer Science, University of Verona (March 1 - June 30, 2019)
- Enes Albay - Ph.D. student in Computer Engineering (Cont.), Istanbul Technical University, From Nov. 4, 2019 to Oct. 3, 2020.

BIOVISION Project-Team

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. ANR

9.1.1.1. Trajectory

Title: Encoding and predicting motion trajectories in early visual networks

Programme: ANR

Duration: October 2015 - September 2020

Coordinator: Invibe Team, Institut des Neurosciences de la Timone, Frédéric Chavane,

Partners:

Institut de Neurosciences de la Timone (CNRS and Aix-Marseille Université, France)

Institut de la Vision (IdV), Paris, France

Universidad Tecnico Federico Santa María (Electronics Engineering Department, Valparaíso, Chile)

Inria contact: Bruno Cessac

Global motion processing is a major computational task of biological visual systems. When an object moves across the visual field, the sequence of visited positions is strongly correlated in space and time, forming a trajectory. These correlated images generate a sequence of local activation of the feed-forward stream. Local properties such as position, direction and orientation can be extracted at each time step by a feed-forward cascade of linear filters and static non-linearities. However such local, piecewise, analysis ignores the recent history of motion and faces several difficulties, such as systematic delays, ambiguous information processing (e.g., aperture and correspondence problems) high sensitivity to noise and segmentation problems when several objects are present. Indeed, two main aspects of visual processing have been largely ignored by the dominant, classical feed-forward scheme. First, natural inputs are often ambiguous, dynamic and non-stationary as, e.g., objects moving along complex trajectories. To process them, the visual system must segment them from the scene, estimate their position and direction over time and predict their future location and velocity. Second, each of these processing steps, from the retina to the highest cortical areas, is implemented by an intricate interplay of feed-forward, feedback and horizontal interactions. Thus, at each stage, a moving object will not only be processed locally, but also generate a lateral propagation of information. Despite decades of motion processing research, it is still unclear how the early visual system processes motion trajectories. We, among others, have proposed that anisotropic diffusion of motion information in retinotopic maps can contribute resolving many of these difficulties. Under this perspective, motion integration, anticipation and prediction would be jointly achieved through the interactions between feed-forward, lateral and feedback propagations within a common spatial reference frame, the retinotopic maps. Addressing this question is particularly challenging, as it requires to probe these sequences of events at multi-scale (from individual cells to large networks) and multiple stages (retina, primary visual cortex (V1)). “TRAJECTORY” proposes such an integrated approach. Using state-of-the-art micro- and mesoscopic recording techniques combined with modeling approaches, we aim at dissecting, for the first time, the population responses at two key stages of visual motion encoding: the retina and V1. Preliminary experiments and previous computational studies demonstrate the feasibility of our work. We plan three coordinated physiology and modeling work-packages aimed to explore two crucial early visual stages in order to answer the following questions: How is a translating bar

represented and encoded within a hierarchy of visual networks and for which condition does it elicit anticipatory responses? How is visual processing shaped by the recent history of motion along a more or less predictable trajectory? How much processing happens in V1 as opposed to simply reflecting transformations occurring already in the retina? The project is timely because partners master new tools such as multi-electrode arrays and voltage-sensitive dye imaging for investigating the dynamics of neuronal populations covering a large segment of the motion trajectory, both in retina and V1. Second, it is strategic: motion trajectories are a fundamental aspect of visual processing that is also a technological obstacle in computer vision and neuroprostheses design. Third, this project is unique by proposing to jointly investigate retinal and V1 levels within a single experimental and theoretical framework. Lastly, it is mature being grounded on (i) preliminary data paving the way of the three different aims and (ii) a history of strong interactions between the different groups that have decided to join their efforts.

9.2. European Initiatives

9.2.1. Collaborations in European Programs, Except FP7 & H2020

- Program: Leverhulme Trust
- Project acronym:
- Project title: A novel approach to functional classification of retinal ganglion cells
- Duration: 2017-2020
- Coordinator: Evelyne Sernagor, Institute of Neuroscience (ION), Newcastle, UK
- Inria contact: Bruno Cessac
- Other partners:

  Melissa Bateson Institute of Neuroscience (ION), Newcastle, UK

  Matthias Hennig Institute for Adaptive and Neural Computation (ANC, School of Informatics University of Edinburgh, UK)

  Gerrit HilgenInstitute of Neuroscience (ION), Newcastle, UK
- Abstract: Vision begins with photoreceptors converting light from different parts of the visual scene into electrical signals, compressing our visual world into a parsimonious code of impulses at the retinal output level, the retinal ganglion cells (RGCs). This information is sent to the brain via only $\approx$1m RGCs (45,000 in mouse). Amazingly, the brain can recreate images from interpreting these "barcodes" or trains of impulses. This ability is partly due to the astonishing functional diversity of RGCs, each interpreting a different feature of the visual scene. It is all these parallel streams of information that impart the complexity of visual scenes to our brain visual areas. At present, at least 30 RGC subtypes have been identified. Classification is typically based on common anatomical features, or on basic functions (e.g. whether cells respond to the onset or offset of the light, or whether they are sensitive to motion direction) and it has recently progressed to include molecular markers. Recent studies have successfully characterised common physiological properties between RGCs sharing gene expression, suggesting that their molecular signature may indeed be a good indicator of function. However, according to mouse genetics repositories (e.g., the Allen Brain Project) many genes are expressed in subpopulations of RGCs for which we have no phenotype yet. Genes that are expressed in most RGCs probably do not reflect specific functional populations, but some other genes are expressed only in sparse RGC groups. Each gene-specific class exhibits a distinct spatial mosaic pattern across the retina, suggesting that the cells belong to a common group. Many classes, even sparse, exhibit asymmetric distributions across the retina, e.g., with larger numbers on the ventral or dorsal side, suggesting specific roles in ecological vision, e.g., specialised in detecting moving objects in the sky (ventral) or on the ground (dorsal).

  We propose to develop a multidisciplinary approach to functionally phenotype new RGC subclasses sharing gene expression. Rather than inferring knowledge about the entire population from studying

individual cells, we will take a global approach based on large-scale, high-density pan-retinal recordings, pharmacogenetics (allowing us to selectively silence defined cell populations at will) and high-resolution imaging combined with computational approaches and behaviour. This novel approach necessitates collaboration between retinal neurophysiologists, animal behaviour specialists (Newcastle) and modellers (Inria) who specialise in visual processing and have sophisticated mathematical tools and software to handle and interpret the encoding of visual information at the pan-retinal level.

9.3. International Initiatives

9.3.1. Inria International Labs

Inria Chile

Associate Team involved in the International Lab:

9.3.1.1. MAGMA

Title: Modelling And understandinG Motion Anticipation in the retina

International Partner (Institution - Laboratory - Researcher):

Universidad Técnica Federico Santa Marı´a, Valparaiso (Chile) - Department of Electric Engineering - Maria-José Escobar

Start year: 2019

See also: https://team.inria.fr/biovision/associated-team-magma/.

Motion processing represents a fundamental visual computation ruling many visuomotor features such as motion anticipation which compensates the transmission delays between retina and cortex, and is fundamental for survival. We want to strengthen an existing collaborative network between the Universidad de Valparaiso in Chile and the Biovision team, gathering together skills related with physiological recording in the retina, data analysis numerical platforms and theoretical tools to implement functional and biophysical models aiming at understanding the mechanisms underlying anticipatory response and the predictive coding observed in the mammalian retina, with a special emphasis on the role of lateral connectivity (amacrine cells and gap junctions).

9.4. International Research Visitors

9.4.1. Visits of International Scientists

Helene Schreyer (University of Göttingen, Germany)

Dr Cyril Eleftheriou (IIT, Genova)

R. Cofré (Universidad Valparaíso, Chile).

9.4.1.1. Internships

- **September-November 2019 (M1).** Ignacio Ampuero, Université de Valparaiso.
- **March-August 2019 (M1).** Min-Toan Nguyen, Cycle Ingénieur Polytechnicien 3A. (co-direction with A. Muzy (I3S) et P. Reynaud-Bourret (LJAD)).
- **March-May 2019 (M1)** Safia Mensor, Master Mod4NeuCog (co-direction with A. Guyon (IPMC)) [35].
- **March-May 2019 (M1) et September 2019 - February 2020 (M2)** Simone Ebert, Master Mod4NeuCog (Co-direction with O. Marre Institut de la Vision (IdV), Paris, France et R. Veltz (Mathneuro)).
- **March-August 2019 (M2)** Téva Andreoletti, ENSEA Cergy.

CAMIN Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

- Occitanie Region finances half of the PhD thesis salary of Lucie William.
- Occitanie Region gave a grant to CAMIN for the PhD thesis of XinYue Lu (PILE-CIFRE) - 10.000 euros.

8.2. National Initiatives

- Inria ADT STIMBIO

  Participants : Christine Azevedo, Daniel Simon, Ronan Le Guillou, Benoît Sijobert.

  A 1-year engineer (R. LeGuillou) was funded by Inria ADT on the development of an architecture dedicated to FES-cycling platform.
- I-SITE MUSE COMPANIES AND CAMPUS grant - SPINSTIM project

  Collaboration with academic local partners (CHU, IES) and NEURINNOV company on the spinal stimulation for bladder and bowel functions restoration. This is linked to an ongoing collaboration with Oslo University (Norway).
- LABEX NUMEV - MEDITAPARK project Collaboration with Montpellier Hospital (Neurology service) and the Montpellier Mindfulness Center to analyze the impact of meditation on upper limb tremor.
- EDF Foundation - CYCLOSEF project

  Collaboration with La Châtaigneraie Hospital on FES-assisted cycling. Financial support for a study on FES-cycling training method and performance otimization on individuals with complete spinal cord injury.
- I-SITE MUSE - EXPLORE

  Support for the visit of Henrique Resende (UFMG, Brazil) and Emersion Fachin (UNB, Brazil) as guest researchers from December to February 2019. Completed with a LIRMM laboratory financial aid.
- I-SITE MUSE - EXPLORE

  Support for the visit of François Bonnetblanc at the Karolinska institute Hospital, Neurosurgery and Neurology Department
- ANR Grasp-It (2019-2023) - Leader LORIA, Nancy.

8.3. European Initiatives

8.3.1. Collaborations with Major European Organizations

CAMIN team is leader of a EIT Health project "AGILIS" on Grasping rehabilitation in individuals with quadriplegia (http://www.lirmm.fr/camin/agilis-project/).

8.4. International Initiatives

8.4.1. Inria Associate Teams Not Involved in an Inria International Labs

8.4.1.1. CACAO

Title: Lower limb electrical stimulation for function restoration

International Partner (Institution - Laboratory - Researcher):

UNB (Brazil) Physiology Faculty - FACHIN-MARTINS Emerson

Start year: 2019

See also: https://team.inria.fr/cacao/

The CACAO team has developed an expertise in the application of electrical stimulation for assisting seat-to-seat transfers and pedaling for people with paraplegia. The team shared a unique experience in 2016 by participating in the first Cybathlon techno-sports games with a Brazilian driver and a French driver in the assisted bicycle race. The team wishes to continue the work by optimizing the quality of pedaling to participate in the Cybathlon 2020 and extending the technique for the rehabilitation of patients with hemiplegia in a rehabilitation context.

8.4.1.2. Informal International Partners

We have an ongoing informal collaboration with Andrew Murray (DIMLAB, Dayton University) on the design of complex mechanisms in the context of cycling (trike design) and grasping (orthosis design).

8.5. International Research Visitors

Henrique Resende (UFMG, Brazil) and Emerson Fachin (UNB, Brazil) spent 3 months in CAMIN team from December 2018 to February 2019 to work on FES-cycling project (I-SITE MUSE Explore program and LIRMM support).

8.5.1. Internships

Camilo Silva is achieving a 6-months ERASMUS internship in the team on motion recognition using Deep Learning techniques.

EMPENN Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

9.1.1. Défis scientifiques 2019 of University of Rennes 1: Compensating analytic variability for a better use of open data (2019, 6500€).

Participant: Camille Maumet.

In neuroimaging, open data are now well developed with hundred of thousands of images available for the research community. However, those data are still mainly studied in isolation, limiting the potential for new discoveries. Here we focus our efforts on developing neuroinformatics standards and algorithms that will support publication and combination of open datasets.

9.1.2. Region Bretagne: project VARANASI

Participants: Christian Barillot, Camille Maumet, Xavier Rolland.

Thanks to the development of open science practices, more and more public datasets are available to the research community. In the field of brain imaging, these data, combined, bring a critical increase in sample size, necessary to build robust models of the typical and atypical brain. However, in order to build valid inferences on these data, we need to take into account their heterogeneity. Variability can arise due to multiple factors such as: differences in imaging instruments, in acquisitions protocols and even, in post-processing pipelines. In particular, the expansion of open source machine learning workflows creates a multitude of possible outputs out of the same dataset. The variations induced by this methodological plurality can be reFerréd to as 'analytic variability' which will be the focus of the thesis funded in half by region Bretagne. The thesis of Xavier Rolland (2018-2021) will address two challenges: 1) How to combine neuroimaging data generated by different analysis pipelines? 2) How to publish neuroimages with an adequate level of metadata to enable their reuse? Methodological developments will combine machine learning techniques with methods from knowledge representation.

9.2. National Initiatives

9.2.1. Projet Fondation de France: PERINE: 99k€ (33 k€ for IRM acquisition and 22 k€ for image analysis) for 2011-2021

Participants: Élise Bannier, Isabelle Corouge, Julie Coloigner, Maia Proisy, Jean-Christophe Ferré, Christian Barillot.

The PELAGIE cohort evaluates the effect of prenatal exposure to neurotoxicants on child development. Following previous studies, the PERINE study focuses on the assessment of brain developement at 10-12 years old using MRI (ASL, Diffusion imaging, Working memory as well as motor inhibition BOLD fMRI together with neuropsychological tests). A total of 101 children were included. A PhD of Anne-Claire Binter was defended in December 2019 linking epidemiology with functional imaging during a GoNoGo task and neuropsychological scores. This work is done in collaboration with Fabienne Pele´ and Ce´cile Chevrier (IRSET).

9.2.2. Fondation de l'Avenir: EPMR-MA

Participants: Pierre-Yves Jonin, Élise Bannier, Christian Barillot, Quentin Duché.

Recognition memory refers to our ability to discriminate between previously experienced vs. unexperienced stimuli. It is impaired very early in the course of Alzheimer's Disease (AD), both regarding behavioural performance and related brain activity. When the memoranda is associated or with existing knowledge, subsequent memory increases in healthy subjects. Moreover, existing knowledge related to prior exposures may alter the brain network underlying successful memory formation. While much is known regarding the brain substrates of recognition memory in early AD, little is known about the impact of prior exposure. Yet, this factor could both enhance memory formation in patients, and highlight a pattern of memory impairments and related brain activity that might accurately discriminates between early AD, before dementia, and healthy aging. The present task-based fMRI study aims at assessing the influence of prior exposures on recognition memory and its neural underpinnings in patients with Mild Cognitive Impairment due to AD. Inclusions were performed between 2016 and 2017 and data analysis is ongoing.

9.2.3. Projet Fondation de France: Connectivity of the amygdala in depression: (PI: M.-L. Paillère Martinot, Paris Descartes University), €200k for 2018-2021

Participants: Christian Barillot, Olivier Commowick, Emmanuel Caruyer, Julie Coloigner.

The onset of depression in teenagers and young adults increases the risk to develop a drug-resistant depression in the adulthood. This project aims at evaluating the role of early changes in the microstructure and connectivity of the amygdala. Using a cohort of drug-resistant patients (N=30), non drug-resistant patients (N=30) and controls (N=30), the aim is to identify imaging biomarkers of the pathology and to compare these with emotional and cognitive phenotypes in this population, searching for early differences in the development of the amygdala connectivity.

9.2.4. CNRS-Inserm Défi Santé numérique – AAP 2019: Imagerie Multimodale de l'Amygdale limbiquE pour le pronostic de la Dépression (IMpAirED): 19k€ for 2019

Participants: Julie Coloigner, Olivier Commowick, Élise Bannier, Emmanuel Caruyer, Christian Barillot.

This grant is an extension of the Projet Fondation de France: Connectivity of the amygdala in depression.

In order to identify early features of this depression disease, the aim of this project is to develop multimodal modeling of the limb amygdala and its network from MR imaging combining activation and rest functional imaging and MR brain microstructure imaging quantitative (diffusion and relaxometry). The development of this model will allow us to define three imaging biotypes corresponding to depressed adult patients responding to antidepressant treatments, depressed resistant patients and controls. These multimodal imaging biomarkers will be used to stratifie a large longitudinal cohort of young adults into three sub-groupsgroups, in order to retrospectively identify early differences in development trajectories of amygdala.

Inclusions of the patients will begin in early 2020.

9.2.5. ANR "MAIA", generic projects program: €150k for 2016-2019 (PI: F. Rousseau, IMT Atlantique, Brest)

Participants: Maia Proisy, Pierre Maurel, Antoine Legouhy, Olivier Commowick, Isabelle Corouge, Jean-Christophe Ferré, Christian Barillot.

Each year in France, 55 000 children are born prematurely, i.e., before the 37th week of gestation. Long-term studies of the outcome of prematurely born infants have clearly documented that the majority of such infants may have significant motor, cognitive, and behavioral deficits.

However, there is a limited understanding of the nature of the cerebral abnormality underlying these adverse neurologic outcomes. In this context, the emergence of new modalities of 3D functional MRI, e.g., Arterial Spin Labeling (ASL), or optical imaging technologies, e.g., Near InfraRed Spectroscopy (NIRS), brings new perspectives for extracting cognitive information, via metabolic activity measures. Other classical techniques devoted to cerebral signal measurement, such as ElectroEncephaloGraphy (EEG), provide cognitive information at the cortical level. Each of these various non-invasive imaging technologies brings substantial and specific information for the understanding of newborn brain development.

This project is developing innovative approaches for multi-image / multi-signal analysis, in order to improve neurodevelopment understanding methods. From a fundamental point of view, mathematics and computer science have to be considered in association with imaging physics and medicine, to deal with open issues of signal and image analysis from heterogeneous data (image, signal), considered in the multiphysics contexts related to data acquisition (magnetic, optic, electric signals) and biophysics modeling of the newborn brain. A sustained synergy between all these scientific domains is then necessary.

Finally, the sine qua non condition to reach a better understanding of the coupled morphological cognitive development of premature newborns, is the development of effective software tools, and their distribution to the whole medical community. The very target of this project is the design of such software tools for medical image / signal analysis, actually operational in clinical routine, and freely available. Academic researchers and industrial partners are working in close collaboration to reach that ambitious goal.

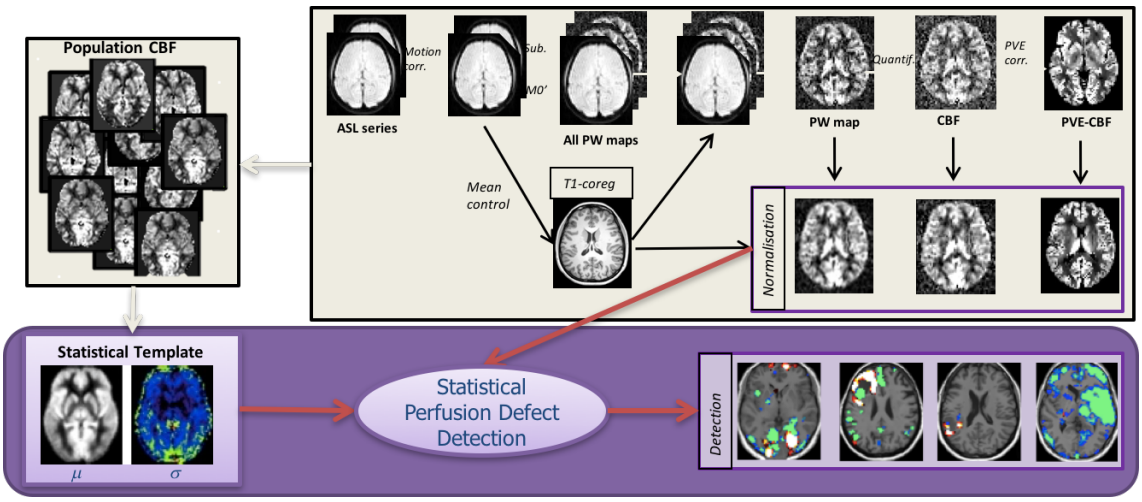

Figure 2. Processing workflow for quantification of Arterial Spin Labelling Cerebral Blood Flow with detection of abnormal perfusion

9.2.6. Fondation pour la recherche médicale (FRM) - Project Hybrid EEG/IRM Neurofeedback for rehabilitation of brain pathologies: 370k€ (2017-2021)

Participants: Élise Bannier, Isabelle Bonan, Isabelle Corouge, Jean-Christophe Ferré, Jean-Yves Gauvrit, Pierre Maurel, Mathis Fleury, Giulia Lioi, Christian Barillot.

The goal of this project is to make full use of neurofeedback (NF) paradigm in the context of brain rehabilitation. The major breakthrough will come from the coupling associating functional and metabolic information from Magnetic Resonance Imaging (fMRI) to Electro-encephalography (EEG) to "optimize" the neurofeedback protocol. We propose to combine advanced instrumental devices (Hybrid EEG and MRI platforms), with new hybrid Brain computer interface (BCI) paradigms and new computational models to provide novel therapeutic and neuro-rehabilitation paradigms in some of the major mental and neurological disorders of the developmental and the aging brain (stroke, language disorders, Mood Depressive Disorder (MDD), ...). Though the concept of using neurofeedback paradigms for brain therapy has somehow been experimented recently (mostly through case studies), performing neurofeedback through simultaneous fMRI and EEG has almost never been done before so far (two teams in the world including us within the HEMISFER CominLabs project). This project will be conducted through a very complementary set of competences over

the different involved teams: Empenn U1228, HYBRID and PANAMA Teams from Inria/Irisa Rennes and EA 4712 team from University of Rennes I.

9.2.7. PHRC EMISEP: Evaluation of early spinal cord injury and late physical disability in Relapsing Remitting Multiple Sclerosis: €200k for 2016-2019

Participants: Élise Bannier, Christian Barillot, Emmanuel Caruyer, Benoit Combès, Olivier Commowick, Gilles Edan, Jean-Christophe Ferré, Haykel Snoussi.

Multiple Sclerosis (MS) is the most frequent acquired neurological disease affecting young adults (1 over 1000 inhabitants in France) and leading to impairment. Early and well adapted treatment is essential for patients presenting aggressive forms of MS. This PHRC (Programme hospitalier de recherche clinique) project focuses on physical impairment and especially on the ability to walk. Several studies, whether epidemiologic or based on brain MRI, have shown that several factors are likely to announce aggressive development of the disease, such as age, number of focal lesions on baseline MRI, clinical activity. However, these factors only partially explain physical impairment progression, preventing their use at the individual level. Spinal cord is often affected in MS, as demonstrated in postmortem or imaging studies. Yet, early radiological depiction of spinal cord lesions is not always correlated with clinical symptoms. Preliminary data, on reduced number of patients, and only investigating the cervical spinal cord, have shown that diffuse spinal cord injury, observed via diffusion or magnetisation transfer imaging, would be correlated with physical impairment as evaluated by the (EDSS) Expanded Disability Status Scale score. Besides, the role of early spinal cord affection (first two years) in the evolution of physical impairment remains unknown.

In this project, we propose to address these different issues and perform a longitudinal study on Relapsing Remitting Multiple Sclerosis (RRMS) patients, recruited in the first year of the disease. Our goal is to show that diffuse and focal lesions detected spinal cord MRI in the first two years can be used to predict disease evolution and physical impairment at 5 years. Twelve centers are involved in the study to include 80 patients.

To date, all subjects have been included. Haykel Snoussi defended his PhD Thesis on diffusion imaging in the spinal cord starting with distortion correction.

B. Combe`s started as a post-doc in November 2016 to process the EMISEP imaging data, starting with morphological data processing (registration, segmentation) and magnetization transfer data processing.

9.2.8. MS-TRACTS (ARSEP and COREC funding): Estimating the impact of multiple sclerosis lesions in motor and proprioceptive tracts, from the brain to the thoracic spinal cord, on their functions, assessed from clinical tests and electrophysiological measurements: 45k€ (2019-2021).

Participants: Élise Bannier, Benoit Combès.

Previous studies, whether epidemiologic or based on brain MRI, have shown that several factors were likely to announce aggressive development of the disease, such as age, clinical relapses, number of focal lesions on baseline MRI. However, these factors only partially explain physical disability progression, preventing their use at the individual level. The access to advanced brain and cord MR images, the development of associated processing tools combined. We hypothesize that a fine assessment of damage on specific networks, from the brain to the thoracic cord, offers a relevant biomarker of disability progression in MS. Such damage assessments must take into account both lesion location, assessed on structural brain and cord MR images and lesion severity, assessed using quantitative MR images. We propose to test this hypothesis by combining assessments of lesion location and severity on corticospinal and proprioceptive tracts from the brain to the thoracic cord with clinical and electrophysiological measurements. This study includes two French centers (Rennes, Marseille) and includes a total of 60 patients. The expected outcome is to obtain early biomarkers of physical impairment evolution in RRMS patients, first treated with immunomodulatory treatment. The long-term goal is to provide the clinician with biomarkers able to anticipate therapeutic decisions and support the switch to alternative more aggressive treatment.

9.2.9. PIA projects

9.2.9.1. The HEMISFER Project: (€400k for 2017-2019)

Participants: Élise Bannier, Isabelle Bonan, Isabelle Corouge, Claire Cury, Jean-Christophe Ferré, Jean-Yves Gauvrit, Pierre Maurel, Christian Barillot.

The HEMISFER project ("Hybrid Eeg-MrI and Simultaneous neuro-FEedback for brain Rehabilitation") is conducted at Inria Rennes with the support of the Labex "CominLabs" [0]. The goal of HEMISFER is to make full use of the neurofeedback paradigm in the context of rehabilitation and psychiatric disorders. The major breakthrough will come from the use of a coupling model associating functional and metabolic information from Magnetic Resonance Imaging (fMRI) to Electro-encephalography (EEG) to "enhance" the neurofeedback protocol. We combine advanced instrumental devices (Hybrid EEG and MRI platforms), with new man-machine interface paradigms (Brain computer interface and serious gaming) and new computational models (source separation, sparse representations and machine learning) to provide novel therapeutic and neuro-rehabilitation paradigms in some of the major neurological and psychiatric disorders of the developmental and the aging brain (stroke, attention-deficit disorder, language disorders, treatment-resistant mood disorders, etc.). This project involves with the HYBRID and PANAMA Teams from Inria Rennes, the EA 4712 team from University of Rennes I and the ATHENA team from Inria Sophia-Antipolis. This work benefits from the research 3T MRI and MRI-compatible EEG systems provided by the NeurInfo in-vivo neuroimaging platform on which these new research protocols aree set up. A budget of 500K€ is provided by CominLabs to support this project (through experimental designs, PhDs, post-docs and expert engineers).

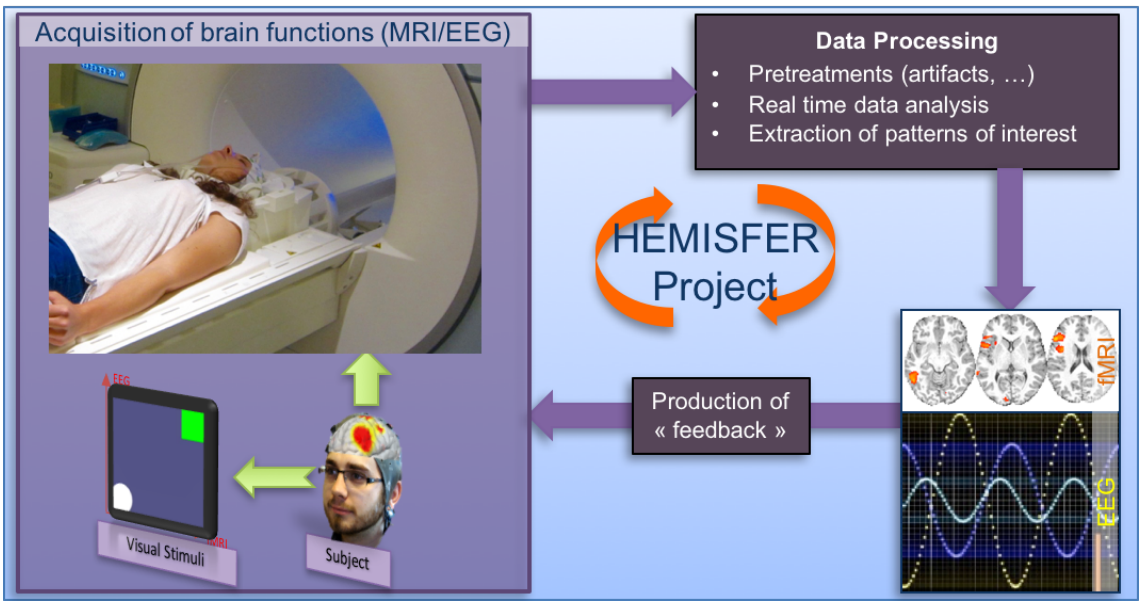

Figure 3. Principle of the Hemisfer project.

9.2.9.2. France Life Imaging (FLI): 2012-2023, €2000k (phase 1) + €1200k (phase 2)

Participants: Christian Barillot, Olivier Commowick.

[0] https://iww.inria.fr/cominlabs-newsletter/april-2013-four-projects-selected/#hemisfer

France Life Imaging (FLI) is a large-scale research infrastructure project to establish a coordinated and harmonized network of biomedical imaging in France. This project was selected by the call "Investissements d'Avenir - Infrastructure en Biologie et Santé". One node of this project is the node Information Analysis and Management (IAM), a transversal node built by a consortium of teams that contribute to the construction of a network for data storage and information processing. Instead of building yet other dedicated facilities, the IAM node use already existing data storage and information processing facilities (LaTIM Brest; CREATIS Lyon; CIC-IT Nancy; Empenn U1228 Inria Rennes; CATI CEA Saclay; ICube Strasbourg) that increase their capacities for the FLI infrastructure. Inter-connections and access to services are achieved through a dedicated software platform that is developed based on the expertise gained through successful existing developments. The IAM node has several goals. It is building a versatile facility for data management that inter-connects the data production sites and data processing for which state-of-the-art solutions, hardware and software, are available to infrastructure users. Modular solutions are preferred to accommodate the large variety of modalities acquisitions, scientific problems, data size, and to be adapted for future challenges. Second, it offers the latest development that are made available to image processing research teams. The team Empenn fulfills multiple roles in this nation-wide project. Christian Barillot is the chair of the node IAM, Olivier Commowick is participating in the working group workflow and image processing and Michael Kain is the technical manager. Apart from the team members, software solutions like MedInria and Shanoir are part of the software platform.

9.2.9.3. OFSEP: €175k for 2017-2019

Participants: Élise Bannier, Christian Barillot, Olivier Commowick, Gilles Edan, Jean-Christophe Ferré, Francesca Galassi.

The French Observatory of Multiple Sclerosis (OFSEP) is one of ten projects selected in January 2011 in response to the call for proposal in the "Investissements d'Avenir - Cohorts 2010" program launched by the French Government. It allows support from the National Agency for Research (ANR) of approximately 10 million € for 10 years. It is coordinated by the Department of Neurology at the Neurological Hospital Pierre Wertheimer in Lyon (Professor Christian Confavreux), and it is supported by the EDMUS Foundation against multiple sclerosis, the University Claude Bernard Lyon 1 and the Hospices Civils de Lyon. OFSEP is based on a network of neurologists and radiologists distributed throughout the French territory and linked to 61 centers. OFSEP national cohort includes more than 50,000 people with Multiple Sclerosis, approximately half of the patients residing in France. The generalization of longitudinal monitoring and systematic association of clinical data and neuroimaging data is one of the objectives of OFSEP in order to improve the quality, efficiency and safety of care and promote clinical, basic and translational research in MS. For the concern of data management, the Shanoir platform of Inria has been retained to manage the imaging data of the National OFSEP cohort in multiple sclerosis.

9.3. European Initiatives

9.3.1. FP7 & H2020 Projects

9.3.1.1. OpenAire-Connect

Participants: Christian Barillot, Camille Maumet, Xavier Rolland.

Project title: **OpenAire-Connect**

Partners: PI: CNR, Italy; Athena Research And Innovation Center In Information Communication & Knowledge Technologies, Greece; Uniwersytet Warszawski, Poland; JISC LBG, UK; Universitaet Bremen, Germany; Universidade Do Minho, Portugal; CNRS (Empenn, Creatis), France; Universita Di Firenze, Italy; Institut De Recherche Pour Le Developpement (IRD), France; European Organization For Nuclear Research (CERN), Switzerland; International Center For Research On The Environment And The Economy, Greece

Budget: 2M € (120k€ for CNRS)

The OpenAire-Connect H2020 project introduces and implements the concept of Open Science as a Service (OSaaS) on top of the existing OpenAIRE infrastructure, delivering out-of-the-box, on-demand deployable tools. OpenAIRE-Connect adopts an end-user driven approach (via the involvement of five prominent research communities), and enriches the portfolio of OpenAIRE infrastructure production services with a Research Community Dashboard Service and a Catch-All Notification Broker Service. The first offers publishing, interlinking, packaging functionalities to enable them to share and re-use their research artifacts (introducing methods, e.g., data, software, protocols). This effort, supported by the harvesting and mining "intelligence" of the OpenAIRE infrastructure, provides communities with the content and tools they need to effectively evaluate and reproduce science. OpenAIRE-Connect combines dissemination and training with OpenAIRE's powerful NOAD network engaging research communities and content providers in adopting such services. These combined actions bring immediate and long-term benefits to scholarly communication stakeholders by affecting the way research results are disseminated, exchanged, evaluated, and re-used. In this project Empenn is acting, through CNRS, as the French coordinator to develop the link with the Neuroimaging research community. This is performed in the context of the FLI-IAM national infrastructure.

9.3.1.2. EIT-Health

Participant: Christian Barillot.

EIT Health aims to promote entrepreneurship and develop innovations in healthy living and active ageing, providing Europe with new opportunities and resources. EIT Health will enable citizens to lead healthier and more productive lives by delivering products, services and concepts that will improve quality of life and contribute to the sustainability of healthcare across Europe. EIT Health is a strong, diverse and balanced partnership of best-in-class organisations in education, research, technology, business creation and corporate and social innovation. EIT Health intends to foster cooperation and unlock Europe's innovation and growth potential – developing and retaining the best talents, creating high-quality jobs and boosting the global competitiveness of European industry. Empenn is involved in this project through the Inserm and Inria institutions. Christian Barillot is representing Inria as one expert in the dedicated WG "Healthy Brain". Empenn is also concerned by the WG "big data".

9.4. International Initiatives

9.4.1. Inria International Labs

9.4.1.1. MMINCARAV

EPFL-Inria

Associate Team involved in the International Lab:

Title: Multimodal Microstructure-Informed Neuronal Connectivity: Acquisition, Reconstruction, Analysis and Validation

International Partner (Institution - Laboratory - Researcher):

Ecole Polytechnique Fédérale de Lausanne (Switzerland) - Laboratoire de Traitement du Signal 5 - Jean-Philippe Thiran

Start year: 2019

See also: https://team.inria.fr/empenn/research/mmincarav-inria-epfl/

Participants: Emmanuel Caruyer, Olivier Commowick, Julie Coloigner, Élise Bannier and Christian Barillot.

The objectives of this associate team will be to address new scientific challenges related to the use of multimodal magnetic resonance imaging (MRI) to derive microstructure indices and apply them to the measure of brain connectivity. We will focus on 4 aspects of this: first we will develop novel sampling techniques, with the objective to reduce acquisition time for the accurate reconstruction of microstructure indices using diffusion MRI; next we will propose joint T2 relaxometry and diffusion models for the description of microstructure, to take advantage of the complementarity of both modalities in the estimation of microstructure indices; in continuation, we will propose new statistical and network analysis methods using the microstructure-informed connectome, and evaluate its potential to reduce bias and false positives; last we will develop a realistic simulation tool combining a fine macroscopic description of fiber bundles, with a fast and realistic simulator at the mesoscopic scale developed by LTS5.

9.4.1.2. Other projects

Participants: Pierre Maurel, Christian Barillot, Claire Cury.

Gundishapur Program (Partenariat Hubert Curien franco-iranien)

This project is a collaboration between the Empenn team and the Institute of medical science and technologies (Shahid Beheshti university, Iran).

Combining EEG (Electroencephalogram) and fMRI (functional Magnetic Resonance Imaging) shows great promise in helping scientists to better understand the complex function of the brain. It can also be used in understanding the brain dysfunctions or specific behaviors. The integration of these two modalities can provide a good spatio-temporal resolution of the neuronal activities, and therefore, it can bring a good insight on the brain function. EEG is the recording of the electrical activity of the brain through scalp surface electrodes. We are already working in this area through the HEMISFER project, whose goal is to make full use of neurofeedback paradigm by using a coupling model associating functional and metabolic information from Magnetic Resonance Imaging (fMRI) and Electro-encephalography (EEG) to “enhance” the neurofeedback protocol. A former member of our team, Dr. Noorzadeh, has already worked on a part of this project, and is now in IMSAT (Iran). He is our main contact for this collaboration.

This project works on the integration methods, in order to first acquire the simultaneous data of high quality with the minimum possible artifacts, and also on biomedical applications in this regard. One of these applications is the source localization using the multi-modal data. Identifying neuronal sources in both high spatial and temporal resolution can open up a bright way to understand lots of diseases, among which epilepsy is the main one. The epileptic seizures or the inter-ictal discharges are nowadays only detected by EEG, but the origin of the activity is only inferred in terms of brain lobes. This spatial precision can be augmented and the method can be used in the precise detection of the focal points of epilepsy for the pre-surgical evaluations.

9.4.1.3. Informal International Collaborations

- Emmanuel Caruyer collaborates with Alice Bates, research fellow at Australian National University, Canberra, on "Dimensionality sampling for B-tensor encoding in diffusion MRI".
- Camille Maumet collaborates with Prof. Thomas Nichols and his group, NISOx at the Oxford Big Data Institute, with Prof. Jean-Baptiste Poline and his group at McGill University, with Prof. Satrajit Ghosh and his group at MIT, with Dr David Keator at UCI Irvine, with Dr. Karl Helmer at MGH, with Dr Tristan Glatard and his group at Concordia University and with international members of the INCF on neuroimaging data sharing.
- Julie Coloigner collaborates with Prof. Natasha Leporé and Dr. John Wood, Children’s hospital Los Angeles, University Southern California.

9.5. International Research Visitors

9.5.1. Visits of International Scientists

- David Kennedy, Professor at University of Massachusetts Medical School, US visited the team on Feb 27 and gave a talk on Repronim: a center for reproducible neuroimaging.

- Natasha Leporé, Professor at Children's hospital Los Angeles, University of Southern California, US visited the team on April 4-5. She gave a talk on "Understanding pediatric brain anatomy through MRI".
- Jan Petr, Researcher at the HZDR in Dresden visited the team in March 1st, 2019 and give a talk on "Processing ASL data with ExploreASL - technical improvement and clinical applications".

9.5.2. Visits to International Teams

9.5.2.1. Research Stays Abroad

- Corentin Vallée visited Brainnetome center, Institute of Automation, Chinese Academy of Science, Beijing from June 1, 2019 to July 31, 2019; he was awarded a grant for international mobility from the MathSTIC doctoral school.

EPIONE Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

- Marco Lorenzi is principal investigator of the project Big Data for Brain Research, funded during 2017-20 by the Départment des Alpes Maritimes.
- Marco Lorenzi is principal investigator of the project MetaImaGen, funded by Idex Jedi UCA (2018-2020, 37k€).
- Maxime Sermesant is principal investigator of the project "The Digital Heart" and the innovation action "Digital Heart Phantom" with General Electrics, funded by Idex UCA Jedi. These projects gather the local cardiac research in academia, clinics and industry.
- Hervé Delingette is the principal investigator of the LungMark project funded by Idex Jedi UCA (2018-2021).
- Hervé Delingette is the principal investigator of the CIMPLE project, funded by Idex Jedi UCA (2018-2021), the region PACA and Oticon Medical. The region PACA and Oticon Medical are co-funding the Phd of Zihao Wang.
- N. Ayache and P. Robert are principal investigators of the project MNC3 (Médecine Numérique, Cerveau, Cognition, Comportement) funded by Idex Jedi UCA (2017-2021, 450k€). M. Lorenzi (Inria) actively participates to the supervision of this project with the help of V. Manera (ICP).

8.2. National Initiatives

8.2.1. Consulting for Industry

- Marco Lorenzi is a scientific consultant for the company MyDataModels (Sophia Antipolis), and for the company Flexper (Sophia Antipolis.)
- Maxime Sermesant is a scientific consultant for the company inHEART (Bordeaux)
- Nicholas Ayache is a scientific consultant for the company Mauna Kea Technologies (Paris).

8.2.2. Institute 3IA Côte d'Azur

The 3IA Côte d'Azurhttp://univ-cotedazur.fr/institutes/3IA/home is one of the four "Interdisciplinary Institutes of Artificial Intelligence" that were created in France in 2019. Its ambition is to create an innovative ecosystem that is influential at the local, national and international levels, and a focal point of excellence for research, education and the world of AI.

Epione is heavily involved in this institute since its 5 permanents researchers (N. Ayache, H. Delingette, M. Lorenzi, M. Sermesant and X.Pennec) are chair holders in this institute, and N. Ayache is its scientific director.

8.2.3. Collaboration with national hospitals

The Epione-project team collaborates with the following 3 French IHU (University Hospital Institute): the IHU-Strasbourg (Pr J. Marescaux and L. Soler) on image-guided surgery, the IHU-Bordeaux (Pr M. Haïssaguere and Pr P. Jaïs) on cardiac imaging and modeling and the IHU-Pitié Salpétrière (Dr. O. Colliot and S. Durrleman) on neuroimaging.

We also have long term collaborations with the CHU Nice and Centre Antoine Lacassagne in Nice.

8.3. European Initiatives

8.3.1. FP7 & H2020 Projects

8.3.1.1. ERC ECSTATIC

Title: Electrostructural Tomography – Towards Multiparametric Imaging of Cardiac Electrical Disorders

Programm: H2020

Type: ERC

Duration: 2017 - 2022

Coordinator: U. Bordeaux

Inria contact: Maxime Sermesant

Cardiac electrical diseases are directly responsible for sudden cardiac death, heart failure and stroke. They result from a complex interplay between myocardial electrical activation and structural heterogeneity. Current diagnostic strategy based on separate electrocardiographic and imaging assessment is unable to grasp both these aspects. Improvements in personalized diagnostics are urgently needed as existing curative or preventive therapies (catheter ablation, multisite pacing, and implantable defibrillators) cannot be offered until patients are correctly recognized.

ECSTATIC aims at achieving a major advance in the way cardiac electrical diseases are characterized and thus diagnosed and treated, through the development of a novel non-invasive modality (Electrostructural Tomography), combining magnetic resonance imaging (MRI) and non-invasive cardiac mapping (NIM) technologies.

The approach will consist of: (1) hybridising NIM and MRI technologies to enable the joint acquisition of magnetic resonance images of the heart and torso and of a large array of body surface potentials within a single environment; (2) personalising the inverse problem of electrocardiography based on MRI characteristics within the heart and torso, to enable accurate reconstruction of cardiac electrophysiological maps from body surface potentials within the 3D cardiac tissue; and (3) developing a novel disease characterisation framework based on registered non-invasive imaging and electrophysiological data, and propose novel diagnostic and prognostic markers.

This project will dramatically impact the tailored management of cardiac electrical disorders, with applications for diagnosis, risk stratification/patient selection and guidance of pacing and catheter ablation therapies. It will bridge two medical fields (cardiac electrophysiology and imaging), thereby creating a new research area and a novel semiology with the potential to modify the existing classification of cardiac electrical diseases.

8.3.1.2. ERC G-statistics

Title: Biophysical Modeling and Analysis of Dynamic Medical Images

Programme: FP7

Type: ERC

Period: 2018-2023

Coordinator: Inria

PI: Xavier Pennec

G-Statistics aims at exploring the foundations of statistics on non-linear spaces with applications in the Life Siences. Invariance under gauge transformation groups provides the natural structure explaining the laws of physics. In life sciences, new mathematical tools are needed to estimate approximate invariance and establish general but approximate laws. Rephrasing Poincaré: a geometry cannot be more true than another, it may just be more convenient, and statisticians must find the most

convenient one for their data. At the crossing of geometry and statistics, G-Statistics aims at grounding the mathematical foundations of geometric statistics and to exemplify their impact on selected applications in the life sciences.

So far, mainly Riemannian manifolds and negatively curved metric spaces have been studied. Other geometric structures like quotient spaces, stratified spaces or affine connection spaces naturally arise in applications. G-Statistics will explore ways to unify statistical estimation theories, explaining how the statistical estimations diverges from the Euclidean case in the presence of curvature, singularities, stratification. Beyond classical manifolds, particular emphasis will be put on flags of subspaces in manifolds as they appear to be natural mathematical object to encode hierarchically embedded approximation spaces.

In order to establish geometric statistics as an effective discipline, G-Statistics will propose new mathematical structures and characterizations of their properties. It will also implement novel generic algorithms and illustrate the impact of some of their efficient specializations on selected applications in life sciences. Surveying the manifolds of anatomical shapes and forecasting their evolution from databases of medical images is a key problem in computational anatomy requiring dimension reduction in non-linear spaces and Lie groups. By inventing radically new principled estimations methods, we aim at illustrating the power of the methodology and strengthening the "unreasonable effectiveness of mathematics" for life sciences.

8.3.2. Collaborations in European Programs, Except FP7 & H2020

Program: ERA CoSysMed

Project acronym: SysAFib

Project title: Systems medicine for diagnosis and stratification of atrial fibrillation

Duration: Mai 2016 - Mai 2019

Coordinator: Simula, Norway

Inria contact: Maxime Sermesant

Other partners: Inria, Helmholtz Zentrum München, Oslo University Hospital, Maastricht University, CardioCentro Ticino/CCMC

Abstract: Atrial fibrillation (AF) sharply increases the risk of stroke and is associated with a number of other severe complications, including heart failure. The SysAFib project aims to combine advanced data analysis and computer simulations with classical clinical approaches to create a decision support tool for treating AF. Diverse data sources, such as the individual patient's medical history, clinical measurements and genetic data will be combined into a single tool for optimizing and personalizing AF therapy. SysAFib's ultimate goal is to deliver the right treatment to the right patient at the right time, stopping AF in its tracks and ending the need for repeat invasive procedures.

8.4. International Initiatives

8.4.1. Inria International Labs

Inria@SiliconValley
Associate Team involved in the International Lab:

8.4.1.1. GeomStats

Title: Geometric Statistics in Computational Anatomy: Non-linear Subspace Learning Beyond the Riemannian Structure

International Partner (Institution - Laboratory - Researcher):

Stanford (United States) - Department of Statistics - Susan Holmes

Start year: 2018

See also: http://www-sop.inria.fr/asclepios/projects/GeomStats/

The scientific goal of the associated team is to develop the field of geometric statistics with key applications in computational anatomy. Computational anatomy is an emerging discipline at the interface of geometry, statistics, image analysis and medicine that aims at analysing and modelling the biological variability of the organs shapes at the population level. An important application in neuroimaging is the spatial normalization of subjects that is necessary to compare anatomies and functions through images in populations with different clinical conditions. Following the developments of the last 3 years of the associated team GeomStat, the new research directions have been broken into three axes. The first axis aims at continuing the progresses in theoretical and applied Geometric statistics, with a first theme studying the impact of curvature on the estimation with a finite sample, and a second axis extending the current work on Barycentric Subspace Analysis (BSA), notably with algorithms. The second axis aims at developing a hierarchical atlas of the brain anatomy based on the stratification of the space of image orbits under diffeomorphisms. The third axis explores three important applications of low-dimensional subspace learning in manifolds using BSA in neuroscience: the approximation of EEG signals for brain-computer interfaces (BCI); the acceleration and robustification of Tensor Distribution Functions (TDF) estimation in diffusion images; and the efficient inference in spaces of rank-deficient symmetric matrices for imaging-genetics from multi-centric databases.

8.4.2. Inria Associate Teams Not Involved in an Inria International Labs

8.4.2.1. PERSOCARDIOLEARN

Title: Personalization of Cardiac Models using Experimental Data and Machine Learning

International Partner (Institution - Laboratory - Researcher):

University of Toronto (Canada) - Sunnybrook Research Institute - Mihaela Pop

Start year: 2017

See also: https://team.inria.fr/asclepios/research/associated-team-persocardiolearn/

Multi-scale computer modelling is a powerful tool that could be used to simulate in silico cardiac electrical activity and biomechanical function of individual heart. Imaging and 3D heart models built from images can help us understand the basis of structurally-diseased hearts at organ level and to predict in silico the changes in electro-mechanical function as a consequence of muscle remodelling in pathologic state (e.g. chronic infarction, a major cause of death). We hypothesize that MRI-based predictive models can help us identify new opportunities to intervene or to predict the outcome of ablation therapy, which currently has low clinical success. However, these predictive models need to be validated and thoroughly tested in preclinical experiments prior to their integration into the clinical stage. Hence, the next logical step for our joint Inria-SB efforts is to expand our experimental-theoretical framework and to personalize fast 3D heart models from in vivo MR-EP data. This translational step involves numerous challenging tasks from the modelling perspective since the in vivo imaging and physiological signals are rather noisy and obtained at a poor spatial resolution, potentially leading to erroneous customization of mathematical model parameters. However, this collaboration employs a rare combination of experiments and modelling specialists. Moreover, the originality of the proposed approach is to build upon machine-learning techniques rather than on data assimilation methods that are more explored in the literature but have inherent limitations (robustness to noise, local minima. . .).

8.4.3. Inria International Partners

8.4.3.1. Informal International Partners

8.4.3.1.1. University College London (UCL), London, UK

Marco Lorenzi is collaborator of the Translational Imaging Group of UCL, and with the UCL Institute od Ophtalmology. His collaboration is around the topic of spatio-temporal analysis of medical images, with special focus on brain imaging analysis and biomarker development. He is also collaborating with the "Progression Over Neurodegenerative Disorders" (POND) group (Prof. Daniel Alexander) for developing new computational models and techniques for learning characteristic patterns of disease progression using large longitudinal clinical data sets, with special focus on dementias.

8.4.3.1.2. Imaging Genetics Center (IGC), University of Southern California (USC), CA, USA

Marco Lorenzi is currently collaborator of IGC for the investigation of the complex relationship between brain atrophy and genetics in Alzheimer's disease, in particular for demonstrating the effectiveness of multivariate statistical models in providing a meaningful description of the relationship between genotype and brain phenotype.

8.4.3.1.3. St Thomas' Hospital, King's College London, United Kingdom

Maxime Sermesant is a visiting lecturer in the Division of Imaging Sciences and Biomedical Engineering, St Thomas' Hospital, King's College London lead by Pr Reza Razavi. The XMR facility within this hospital is a unique opportunity to validate and exploit the cardiovascular modelling work.

8.4.3.1.4. Other International Hospitals

Collaborations with several other European hospitals have been established through the European projects VP2HF, MD PAEDIGREE, SysAFib and with BarcelonaBeta research centre for Alzheimer.

8.5. International Research Visitors

8.5.1. Visits of International Scientists

- Dr. Gabriel Ziegler (German Center for Neurodegenerative Disorder, DE) visited the group from Oct 14th to Oct 18t.
- Guillaume Lajoinie (Physics of Fluid laboratory, University of Twente, NL) visited the team from April until October 2019.
- Wilhelm Wimmer (Center ARTORG, University of Bern, CH) visited the team from Nov. 2018 until Oct. 2019.
- Pr. Dmitri Alekseevky (The Institute for Information Transmission Problems, Moscow) visited the Geometric Statistics group from february 6 to 13 2019.

8.5.1.1. Internships

- Buntheng LY, Master student at the University Claude Bernard Lyon 1, visited the Epione team from March to September 2019 to work with Maxime Sermesant on Machine Learning methods for the prediction of Sudden Cardiac Death.
- YingYu Yang, Master student at Ecole Polytechnique, visited the Epione team from April to September 2019 to work with Maxime Sermesant on Machine Learning and Pulmonary hypertension.
- Gaetan Desrues, Master student at University of Bordeaux, visited the Epione team from March to September 2019 to work with Maxime Sermesant on hyper-reduction of cardiac models using poly-affine deformation.
- Paul Blanc Durand, Master student at University Paris-Est Créteuil, visited the Epione team from April to October 2019 to work with Hervé Delingette on Mesh-based Registration of lung CT scans between inhale and exhale phases.
- Bastien Manach-Perennou, Master student at Ecole Central Supélec, visited the Epione team from September to January 2019 to work with Xavier Pennec on Registration synchronisation.
- Julien Moreira, Master student from University Côte d'Azur, visited the Epione team from April to June 2019 to work with Marco Lorenzi on the analysis of apathy and depression in the UK Biobank. The internship is within a collaboration with Centre de la Memoire de Nice.
- Yann Fraboni visited the Epione team from December 2019 to work with Marco Lorenzi on the analysis of bias of federated learning methods in distributed application. The internship is within a collaboration with Accenture Labs of Sophia Antipolis.

MATHNEURO Project-Team

6. Partnerships and Cooperations

6.1. European Initiatives

6.1.1. FP7 & H2020 Projects

6.1.1.1. HBP

Title: The Human Brain Project

Program: FP7

Duration: October 2013 - March 2016 (first part), then : April 2016 - March 2018 (second part) and then : April 2018 - March 2020 (third part)

Coordinator: EPFL

Partners:
see the webpage of the project.

Olivier Faugeras is leading the task T4.1.3 entitled “Meanfield and population models” of the Worpackage W4.1 “Bridging Scales”.

Inria contact: Olivier Faugeras (first part) and then : Romain Veltz (second and third part)

Understanding the human brain is one of the greatest challenges facing 21st century science. If we can rise to the challenge, we can gain profound insights into what makes us human, develop new treatments for brain diseases and build revolutionary new computing technologies. Today, for the first time, modern ICT has brought these goals within sight. The goal of the Human Brain Project, part of the FET Flagship Programme, is to translate this vision into reality, using ICT as a catalyst for a global collaborative effort to understand the human brain and its diseases and ultimately to emulate its computational capabilities. The Human Brain Project will last ten years and will consist of a ramp-up phase (from month 1 to month 36) and subsequent operational phases.
This Grant Agreement covers the ramp-up phase. During this phase the strategic goals of the project will be to design, develop and deploy the first versions of six ICT platforms dedicated to Neuroinformatics, Brain Simulation, High Performance Computing, Medical Informatics, Neuromorphic Computing and Neurorobotics, and create a user community of research groups from within and outside the HBP, set up a European Institute for Theoretical Neuroscience, complete a set of pilot projects providing a first demonstration of the scientific value of the platforms and the Institute, develop the scientific and technological capabilities required by future versions of the platforms, implement a policy of Responsible Innovation, and a programme of transdisciplinary education, and develop a framework for collaboration that links the partners under strong scientific leadership and professional project management, providing a coherent European approach and ensuring effective alignment of regional, national and European research and programmes. The project work plan is organized in the form of thirteen subprojects, each dedicated to a specific area of activity.
A significant part of the budget will be used for competitive calls to complement the collective skills of the Consortium with additional expertise.

6.2. International Initiatives

6.2.1. Inria Associate Teams Not Involved in an Inria International Labs

6.2.1.1. NeuroTransSF

Title: NeuroTransmitter cycle: A Slow-Fast modeling approach

PI for Inria MathNeuro: Mathieu Desroches

International Partner (Institution - Laboratory - Researcher):

Basque Center for Applied Mathematics (BCAM) (Spain) - Mathematical, Computational and Experimental Neuroscience (MCEN) Team - Serafim Rodrigues

Start year: 2019

See also: https://team.inria.fr/neurotranssf/

This associated team project proposes to deepen the links between two young research groups, on strong Neuroscience thematics. This project aims to start from a joint work in which we could successfully model synaptic transmission delays for both excitatory and inhibitory synapses, matching experimental data, and to supplant it in two distinct directions. On the one hand, by modeling the endocytosis so as to obtain a complete mathematical formulation of the presynaptic neurotransmitter cycle, which will then be integrated within diverse neuron models (in particular interneurons) hence allowing a refined analysis of their excitability and short-term plasticity properties. On the other hand, by modeling the postsynaptic neurotransmitter cycle in link with long-term plasticity and memory. We will incorporate these new models of synapse in different types of neuronal networks and we will then study their excitability, plasticity and synchronisation properties in comparison with classical models. This project will benefit from strong experimental collaborations (UCL, Alicante) and it is coupled to the study of brain pathologies linked with synaptic dysfunctions, in particular certain early signs of Alzheimer's Disease. Our initiative also contains a training aspect with two PhD student involved as well as a series of mini-courses which we will propose to the partner institute on this research topic; we will also organise a "wrap-up" workshop in Sophia at the end of it. Finally, the project is embedded within a strategic tightening of our links with Spain with the objective of pushing towards the creation of a Southern-Europe network for Mathematical, Computational and Experimental Neuroscience, which will serve as a stepping stone in order to extend our influence beyond Europe.

6.2.2. Inria International Partners

6.2.2.1. Informal International Partners

VU Amsterdam (Netherlands), Faculty of Science, Mathematics: Daniele Avitabile

ENS Paris, Laboratoire de Neurosciences Cognitives: Boris Gutkin

University of the Balearic Islands (Spain), Dept of Applied Mathematics: Antonio Teruel

Polytechnic University of Catalunya (Spain), Dept of Applied Mathematics: Antoni Guillamon

6.3. International Research Visitors

6.3.1. Visits of International Scientists

Invitation of Nikola Popovic, University of Edinburgh (UK), April 2019

Invitation of Tomás Lázaro, Polytechnic University of Catalunya (Spain), May 2019

6.3.1.1. Internships

Ariane Delrocq (étudiante Ecole Polytechnique, Paris): April - July 2019

6.3.2. Visits to International Teams

Visit of Yuri Rodrigues and Romain Veltz to Cian O'Donnell (University of Bristol, UK) in December 2019

6.3.2.1. Research Stays Abroad

One-month research stay of Mathieu Desroches at BCAM (Bilbao, Spain) on an invited professor scholarship to work with Serafim Rodrigues, June-July 2019

MIMESIS Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

At the regional level, the MIMESIS team collaborates with

9.1.1. ICube Automatique Vision et Robotique (AVR)

We have been collaborating with the medical robotics team on percutaneous procedures, in particular robotized needle insertion (with Prof. Bernard Bayle), and needle tracking in medical images (with Elodie Breton). We are also collaborating with Jonathan Vappou on elastography.

9.1.2. ICube Informatique Géométrique et Graphique

MIMESIS joined the IGG team to collaborate in the domain of dynamic topologies, mainly through the use of the CGoGN framework. CGoGN is a C++ library for the manipulation of meshes. It implements combinatorial maps and their multiresolution extensions and has been used in various high level application like the simulation of crowds of autonomous agents and the simulation of cuts, tears and fractures in the context of surgical simulations.

9.1.3. Institute of Image-Guided Surgery (IHU)

We have several active projects and collaborations with IHU Strasbourg in order to collect and use medical images (such as MRI, CT, Fluoroscopy and Ultrasound) before, during and after minimally-invasive surgical procedures (percutaneous, endovascular and laparoscopic). Such images represent an essential support for the development of numerical simulations for intra-operative assistance through augmented and virtual reality. We also collaborate in the field of elastic registration with X-ray images and surgical training for flexible endoscopy.

9.2. National Initiatives

9.2.1. ADT (Action de Développement Technologique)

MIMESIS received a support for the development of the project **LOSAR: Liver Open Surgery with Augmented Reality** that aims at developing tools for a per-operative usage of registration algorithms developed in the team. Our goal is to be able to repeatedly test our method for one or more important publications in medical conferences. This type of publication requires to methodically repeat our solution on several patients. However, the steps are still insufficiently automated and the algorithm needs to be improved for greater reliability. These essential elements lie outside traditional research missions and require significant development and engineering effort. Indeed, an effort of automation and ergonomics will have to be made to make the use of the software sufficiently simple to be used in the operating room. Furthermore, the accuracy of the deformed model (anatomical distances modeled versus actual anatomical relationships) must also be verified and validated through experimentation. This project is done in collaboration with Paul Brousse Hospital in Paris.

9.2.2. ANR (Agence Nationale de la Recherche)

MIMESIS coordinates the ANR project entitled **SPERRY: SuPervisEd Robotic suRgerY** - application to needle insertion. Percutaneous medical procedures (using surgical needles) are among the least invasive approaches to accessing deep internal structures of organs without damaging surrounding tissues. Today, many surgical procedures rely on the use of needles allowing for complex interventions such as curie-therapies or thermo-ablations of tumors (cryoablation, radio frequencies). Unlike traditional open surgery, these approaches only affect a localized area around the needle, reducing trauma and risks of complications. These treatments also offer new solutions for tumors or for metastases for which traditional methods may be contraindicated due to the age of the patient and the extent or location of the disease. In this project, we want to develop new solutions for the control of medical robots interacting with soft tissues. This work is motivated by recent advances in the field of medical simulation achieving a sufficient level of realism to help surgeons during the operation. The maturity of these techniques now suggests the ability to use a simulation intra-operatively to control the motion of a robotic system for needle insertion. This is really a challenge, because in general, few information can be extracted in real time from images during an intervention. We believe that even minimal knowledge of the mechanical behavior of structures, associated with the use of images can make it possible and allow a robot to reach a pre-identified target during a planning stage, without human intervention.

9.2.3. Inria Collaborations

MIMESIS is closely connected to the SOFA Consortium, created by Inria in November 2015 with the objective to support the SOFA community and encourage contributions from new SOFA users. The consortium should also be a way to better answer to the needs of academic or industrial partners. MIMESIS actively participates at the development of SOFA and contributes to the evolution of the framework. Moreover, MIMESIS also participates in an initiative aiming at verification and validation of codes and algorithms of SOFA. Further, MIMESIS actively collaborates with the following Inria teams:

MAGRIT: The team at Inria Grand-Est focuses on research in computer vision and is also actively involved in computer-based solutions for the planning or the simulation of interventional radiology procedures. Currently, two PhD are co-supervised by researcher from Magrit: Jaime Garcia and Guevara Raffaella Trivisonne.

DEFROST: The team conducts research in soft robotics. We continue mutual interaction with DEFROST mainly in the context of contact modeling.

9.2.4. National Collaborations

At the national level, the MIMESIS team collaborates with:

The LML laboratory*(Laboratoire de Mécanique de Lille)*: a French research laboratory (UMR CNRS 8107) part of the Carnot institute ARTS. With more than two hundred researchers, LML focuses on the following research areas: mechanical reliability and tribology, fluid mechanics, civil engineering and soil mechanics.

Hôpital Paul-Brousse a hospital in South Paris. We collaborate with *Centre Hépato-Biliaire* via the co-supervision of the Ph.D. thesis of Nicolas Golse, MD, who is a surgeon specialized in hepatic surgery.

IRMA Research Institut on Advanced Mathematics, a research laboratory at Strasbourg university. A collaboration started in the fields of shape optimisation methods via the co-supervision of the PhD of Guillaume Mestdagh.

9.3. European Initiatives

9.3.1. FP7 & H2020 Projects

- **HiPerNav** is an Innovative Training Network (ITN) funded through a Marie Skłodowska-Curie grant. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 722068. There is 14 fully funded and 2 partially funded PhD working on the project. The project aims to improve soft tissue navigation through research and development, to improve several bottleneck areas:
  - Creating effective pre-operative model(s) and planning
  - Faster and more accurate intra-operative model updates
  - Faster and more accurate model-to-patient registration
  - More intuitive user-interaction and effective workflow
  - Usage of high performance computing (e.g. GPU)

  From these 14 PhD students, two of them are from the Mimesis team: **Jean-Nicolas Brunet** and **Sergei Nikolaev**
- **Driven** The overall aim of the DRIVEN project is to boost the scientific excellence and innovation capacity in data-driven simulation of the University of Luxembourg (UL) and partners (Inria, University of Limerick, and University of Texas at Austin). To boost their scientific excellence and technology transfer capacity in data-driven simulation, the partners will implement a research and innovation strategy focused on three sub-topics:
  - Mathematical foundations for data-driven simulations – UL with UT Austin,
  - Data-driven simulations for computer-assisted therapy – UL with Inria,
  - Data-driven simulations for functional composite materials –UL with ULIM.

9.4. International Initiatives

9.4.1. Informal International Partners

- **CAMERA group, University of Bath, UK:** Collaboration on non-rigid registration using **RGB-D** sensors
- **PRISMA Lab, University of Naples, Italy:** Collaboration on soft object robotic manipulation, along with DEFROST team at Inria Lille, and collaboration on visual perception for robotic surgery.
- **University of Twente, Netherlands:** we collaborate with Prof. Stefano Stramigioli, head of a group in Robotics and Mechatronics laboratory, on the development of a low-cost training system for flexible endoscopy.
- **Verona University, Italy:** we collaborate with the ALTAIR Robotics Lab on computer-aided ultrasound guidance using real-time registration. This resulted in 2 publications this year: [19] and [23].
- **Faculty of Informatics, Masaryk University, Czech Republic:** We collaborate on simulation of living cells in fluorescent microscopy.
- **Team Legato, University of Luxembourg:** We have an active collaboration with Prof. Stéphane Bordas on error estimation in real-time simulations of deformable objects.
- **ARTORG Center for Biomedical Engineering Research, Bern, Switzerland:** Collaboration in the projects related to deep learning.
- **CIMIT and Harvard Medical School:** we collaborate with members of the Center for Minimally Invasite Therapy and faculty from HMS on the development of a training system for Resuscitative endovascular balloon occlusion of the aorta (REBOA).

9.5. International Research Visitors

Eleonora Tagliabue, PhD student at the robotics laboratory of Verona University, visited the team from April to June 2019. During her stay we collaboration of the comparison of different physics-based approaches to model soft tissues. This led to a publication in the International Journal of Computer Assisted Radiology and Surgery. We also applied our deep physics network to the problem od registration of breast model onto ultrasound data. This was presented at the MICCAI workshop on Computational Biomechanics in September 2019.

9.5.1. Visits to International Teams

Jean-Nicolas Brunet and Sergei Nikolaev spent 2 weeks in Forchheim (Germany) to visit Siemens R&D and product development groups, as part of the H2020 HiPerNav project.

MNEMOSYNE Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

9.1.1. EcoMob

Participants: Frédéric Alexandre, Snigdha Dagar, Nicolas Rougier.

Project gathering researchers from: University of La Rochelle (Cerege lab in social sciences and L3I lab in computer science); University of Bordeaux (IRGO lab in organisation management); Town and suburbs of La Rochelle.

The goal of this project is to study and model user urban mobility behaviours in an eco-responsibility context. Interactive mobile applications are used to measure the effective evolution of behaviour. Our team is in charge of studying models of decision in such complex contexts, in interaction with teams in social sciences aiming at influencing user behaviours.

9.1.2. PsyPhINe

Participant: Nicolas Rougier.

Project gathering researchers from: MSH Lorraine (USR3261), InterPsy (EA 4432), APEMAC, EPSaM (EA4360), Archives Henri-Poincaré (UMR7117), Loria (UMR7503) & Mnemosyne.

PsyPhiNe is a pluridisciplinary and exploratory project between philosophers, psychologists, neuroscientists and computer scientists. The goal of the project is to explore cognition and behavior from different perspectives. The project aims at exploring the idea of assignments of intelligence or intentionality, assuming that our intersubjectivity and our natural tendency to anthropomorphize play a central role: we project onto others parts of our own cognition. To test these hypotheses, we ran a series of experiments with human subject confronted to a motorized lamp that can or cannot interact with them while they're doing a specific task. We've organized our third national conference in Nancy gathering speakers from philosophy, robotics, art and psychology and closed a three years cycle. The group now aims at publishing a book gathering text from all the invited speakers.

9.2. National Initiatives

9.2.1. FUI Sumatra

Participants: Frédéric Alexandre, Thalita Firmo Drumond, Xavier Hinaut, Nicolas Rougier, Thierry Viéville.

This FUI project, supported by the Aerospace Valley Innovation Pole, gathers two industrial groups (Safran Helicopter and SPIE), three research labs and four SME. Its goal is to provide contextualized information to maintenance operators by the online analysis of the operating scene. We are concerned in this project with the analysis of visual scenes, in industrial contexts, and the extraction of visual primitives, categories and pertinent features, best decribing the scenes, with biologically inspired neuronal models.

Firstly, this is an opportunity for us to revisit the principles of deep network architectures by adapting principles that we will elaborate from the context of the hierarchical architecture of the temporal visual cortex. Secondly, we intend to exploit and adapt our model of hippocampus to extract more heterogenous features. This project is an excellent opportunity to associate and combine our models and also to evaluate the robustness of our models in real-world applications.

9.2.2. ANR SOMA (PRCI)

Participants: Nicolas Rougier, Remya Sankar.

This project is a convergence point between past research approaches toward new computational paradigms: adaptive reconfigurable architecture, cellular computing, computational neuroscience, and neuromorphic hardware:

1. SOMA is an adaptive reconfigurable architecture to the extent that it will dynamically re-organize both its computation and its communication by adapting itself to the data to process.
2. SOMA is based on cellular computing since it targets a massively parallel, distributed and decentralized neuromorphic architecture.
3. SOMA is based on computational neuroscience since its self-organization capabilities are inspired from neural mechanisms.
4. SOMA is a neuromorphic hardware system since its organization emerges from the interactions between neural maps transposed into hardware from brain observation.

This project represents a significant step toward the definition of a true fine-grained distributed, adaptive and decentralized neural computation framework. Using self-organized neural populations onto a cellular machine where local routing resources are not separated from computational resources, it will ensure natural scalability and adaptability as well as a better performance/power consumption tradeoff compared to other conventional embedded solutions.

9.2.3. ANR MACAQUE40

Participant: Nicolas Rougier.

Most of the theoretical models in economics proposed so far to describe money emergence are based on three intangible assumptions: the omniscience of economic agents, an infinite time and an extremely large number of agents (not bounded). The goal of this interdisciplinary study is to investigate the condition of apparition of a monetary economy in a more ecological framework provided with the assumption that the market is made up of a finite number of agents having a bounded rationality and facing a time constraint.

In this study, we propose a generic model and environment of monetary prospecting. Our first objective is to artificially identify structural (trading organisation, agents specialisation) and cognitive conditions (learning skills, memory and strategic anticipation abilities, tradeoff exploration/exploitation) that allowed money emergence. This will provide relevant environmental constraints that we will use during our manipulations in the laboratory. The agents that will be involved in these manipulations will be of two types: non-human primates (rhesus macaques) and humans.

9.3. International Initiatives

9.3.1. Participation in Other International Programs

9.3.1.1. Project LingoRob with Germany

LingoRob - Learning Language in Developmental Robots - is a project of the Programme Hubert Curien PHC Procope with Germany (University of Hamburg). The scientific objective of the collaboration is to better understand the mechanisms underlying language acquisition and enable more natural interaction between humans and robots in different languages, while modelling how the brain processes sentences and integrates semantic information of scenes. Models developed in both labs involve artificial neural networks, and in particular Echo State Networks (ESN), also known as pertaining to the Reservoir Computing framework. These neural models allow insights on high-level processes of the human brain, and at the same time are well suited as robot control platform, because they can be trained and executed online with low computational resources. The collaborators will also combine Deep Learning networks to the reservoir models already used in order to benefit from their very good feature extraction abilities.

NEUROSYS Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

Within the *Contrat de Projet État Région (CPER) IT2MP* 2015-2020 on *Technological innovations, modeling and Personalized Medicine*, we are contributing on platform SCIARAT (*cognitive stimulation, Ambient Intelligence, Robotic assistance and Telemedicine*) observing electroencephalographic activity of humans during motor tasks. The acquisition of a new 64-channel EEG system has been approuved.

8.2. National Initiatives

8.2.1. ANR

Program: PRCE CES 33 (interaction, robotics)

Project acronym: Grasp-IT

Project title: Design and evaluation of a tangible and haptic brain-computer interface for upper limb rehabilitation after stroke

Duration: Jan 2020 - Jan 2024

Coordinator: Laurent Bougrain (Neurosys)

Other partners: 4 research teams (UL/Perseus, Inria/Camin, Inria/Hybrid) and 3 centers or hospital departments for physical medicine and rehabilitation (IRR/CMPR Lay St Christophe, CHU Rennes, CHU Toulouse) and 1 manufacturer of 3D printers (Alchimies/OpenEdge)

Abstract: This project aims to recover upper limb control improving the kinesthetic motor imagery (KMI) generation of post-stroke patients using a tangible and haptic interface within a gamified Brain-Computer Interface (BCI) training environment. (i) This innovative KMI-based BCI will integrate complementary modalities of interactions such as tangible and haptic interactions in a 3D printable flexible orthosis. We propose to design and test usability (including efficacy towards the stimulation of the motor cortex) and acceptability of this multimodal BCI. (ii) The GRASP-IT project proposes to design and integrate a gamified non-immersive virtual environment to interact with. This multimodal solution should provide a more meaningful, engaging and compelling stroke rehabilitation training program based on KMI production. (iii) In the end, the project will integrate and evaluate neurofeedbacks, within the gamified multimodal BCI in an ambitious clinical evaluation with 75 hemiplegic patients in 3 different rehabilitation centers in France.
The GRASP-IT project represents a challenge for the industrial 3D printing field. The materials of the 3D printable orthosis, allowing the integration of haptic-tangible interfaces, will come from a joint R & D work performed by the companies Alchimies and Open Edge.

8.3. International Research Visitors

8.3.1. Visits of International Scientists

- Hiroaki Wagatsuma, Ass. Prof, 11-28 Jun. 2019, Kyutech (Japan). Methodological design for integration of human EEG data with behavioral analyses into human-human/robot interactions in a real-world context.

8.3.1.1. Internships

- Asako Watanabe, Master Student, Jan-Mar 2019, Kyutech (Japan). Feature Extraction of EEG Signals Using Power Spectral Entropy.

8.3.2. Visits to International Teams

L. Bougrain, A. Aussel and S. Rimbert participated in the Kyutech-LORIA workshop organized jointly by University of Lorraine and Kyutech (4-8 March 2019).

OPIS Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

- DATAIA UltraBioLearn (2019-2022). The project aims to research machine learning approaches for medical applications, in particular by leveraging semi-supervised learning using generative, graph-based and certifiable networks, in the context of predicting patient response to cancer treatments. Responsible: H. Talbot, F. Malliaros (N. Lassau, Institut Gustave Roussy).

9.2. National Initiatives

9.2.1. ANR

- Program: ANR PRC

  Project acronym: CoMeDIC

  Project title: Convergent Metrics for DIscrete Calculus

  Duration: 2016-2021

  Coordinator: J.-O. Lachaud (Univ. Rhones Alpes Savoie Mont-Blanc), Local: H. Talbot
- Program: ANR PRCE

  Project acronym: R-Vessel-X

  Project title: Extraction et interprétation robustes des réseaux vasculaires dans les images biomédicales hépatiques

  Duration: 2018-2022

  Coordinator: A. Vacavant (Univ. Clermont Auvergne), local: H. Talbot
- Program: ANR JCJC

  Project acronym: MajIC

  Project title: Majorization-Minimization Algorithms for Image Computing

  Duration: 2017-2021

  Coordinator: E. Chouzenoux
- Program: ANR JCJC

  Project acronym: AVENUE

  Project title: A Visual memory network for scene understanding

  Duration: 2018-2022

  Coordinator: Dr. Karteek Alahari (Inria Grenoble - Rhône-Alpes). Local: F. Malliaros.

9.2.2. Others

- Program: CNRS-CEFIPRA

  Project acronym: NextGenBP

  Project title: Looking Beyond Backpropagation in Deep Learning

  Duration : 2017-2019

  Coordinator: E. Chouzenoux
- Program: PHC - Campus France

  Projet acronym: POLONIUM

Project title: When Poisson and Gauss meet in imaging
Duration: 2018-2020
Coordinator: J.C. Pesquet

9.3. European Initiatives

9.3.1. FP7 & H2020 Projects

- Program: H2020 ITN Marie Sklodowska-Curie
  Projet acronym: SUNDIAL
  Project Title: SUrvey Network for Deep Imaging Analysis and Learning
  Duration: 2017-2021
  Coordinator: Reynier Peletier (U. Groningen, NL), local: Hugues Talbot

9.4. International Initiatives

9.4.1. Inria International Partners

9.4.1.1. Informal International Partners

- Sup'Com Tunis - Prof. Amel Benazza-Benhayia. Collaboration Topic: Multispectral imaging and image compression.
- North Carolina State University - Prof. Patrick Louis Combettes. Collaboration Topic: Fixed point theory.
- Heriot-Watt University, UK - Prof. Audrey Repetti and Prof. Yves Wiaux. Collaboration Topic: Large-scale image restoration.
- University of Edinburgh, UK - Prof. Victor Elvira. Collaboration Topic: Bayesian signal processing.
- Indraprastha Information Institute Technology, Delhi, India - Prof. Angshul Majumdar. Collaboration Topic: Dictionary learning.
- Universidad Técnica Federico Santa María, Valparaíso, Chile - Prof. Luis M. Briceño-Arias. Collaboration Topic: Stochastic optimization.

9.5. International Research Visitors

9.5.1. Visits of International Scientists

- Prof. Angshul Majumdar, IIIT Delhi, India, June 2019 and December 2019
- Prof. Apostolos N. Papadopoulos, Aristotle University of Thessaloniki, June 2019 to July 2019
- Prof. Patrick L. Combettes, North Carolina State University, US, 18-22 February 2019
- W. Tang (PhD student), North Carolina State University, US, 2-29 May 2019
- S. Sharma (PhD student), IIIT Delhi, India, June 2019 to August 2019

9.5.2. Visits to International Teams

9.5.2.1. Research Stays Abroad

- M. Vakalopoulou, visiting researcher for 1 month (June-July 2019): Stony Brook University, research team of D. Samaras.
- T. Estienne, 4 months internship (May-August 2019): Center for Biomedical Image Computing and Analytics (CBICA) of University of Pennsylvania.
- E. Battistella, 4 months internship (August-December 2019): Computational Robotics, AI & Biomedicine Lab of RICE University.
- M. Sahasrabudhe, 2 months intership (November-December 2019): Boston Children's Hospital & Harvard Medical School.

PARIETAL Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

9.1.1. Inserm-Inria project

This project is funded by the joint Inserm and Inria program 'médecine numérique' and is conducted in collaborations with our clinical partners from the Lariboisière hospital, Inserm uni U942 BioCANVAS (Biomarkers in Cardio-Neuro-VAScular diseases). It supports the PhD thesis of David Sabbagh.

Participants:

- Denis Engemann [coordinator, co-advisor]
- Alexandre Gramfort [thesis director, co-advisor]
- Etienne Gayat [clinical collaborator, co-advisor]
- Fabrice Vallée [clinical collaborator]
- David Sabbagh [PhD Student]

Post-operative delirium (POD) is a potential complication of anesthesia during surgery. It is often associated with adverse outcomes and is aggravated by aging. In elderly patients, post-operative complications have been estimated to incur tens of million US dollars of costs each year in the United States by prolonging hospitalization and potentially affecting health prognosis. Recent studies suggest that POD can already be prevented by improving electrophysiological monitoring of anesthesia depth and individual dosage of anesthetic agents. Doing so probably minimizes the time patients spend in a coma-like state that manifests itself in isoelectric burst suppression, an electroencephalogram (EEG) pattern characterized by alternation between quiescence and high-amplitude bursts, and causally linked to POD. However, such an enterprise, currently, depends on the trained clinical electrophysiologist and guidance by commercially provided EEG indices of states of consciousness. One such metric is the bispectral index (BIS), which, like other related metrics, does not explicitly take into account baseline changes related to normative aging and may therefore be biased when used naively.

While electrophysiological signatures of aging (e.g. drop in Alpha and Gamma band power), states of consciousness (e.g. drop in Theta band long-range connectivity) and drug response (e.g. anteriorization of alpha band power in propofol anesthesia) have been separately investigated in the past years, their common denominators are not known. It is therefore difficult to detect individual risk, choose the optimal dosage, and automate anesthesia monitoring readily for any patient in any hospital.

The goal of this research project is to build statistical models that enable prediction of burst suppression and subsequent POD by exploiting diverse EEG-signatures of states of consciousness in the context of aging. We approach this challenge by recasting it as a problem of learning brain-age from the point of view of electrophysiology of consciousness.

9.1.2. CoSmic project

Participants: Philippe Ciuciu [Correspondant], Nicolas Chartier, Loubna El Gueddari, Zaccharie Ramzi, Chaithya Giliyar Radhkrishna.

This project is funded by CEA DRF-Impulsion.

the DRF-impulsion CEA program which has been transformed into a CEA PTC program for 2 years (2018-2020), in collaboration with Pierre Kestener, La Maison de la Simulation (CEA/CNRS).

Compressed Sensing is a recent theory in maths that allows the perfect recovery of signals or images from compressive acquisition scenarios. This approach has been popularized in MRI over the last decade as well as in astrophysics (noticeably in radio-astronomy). So far, both of these fields have developed skills in CS separately. The aim of the COSMIC project is to foster collaborations between CEA experts in MRI (Parietal team within NeuroSpin) and in astrophysics (CosmoStat lab within the Astrophysics Department). These interactions will allow us to share different expertise in order to improve image quality, either in MRI or in radio-astronomy (thanks to the interferometry principle). In this field, given the data delivered by radio-telescopes, the goal consists in extracting high temporal resolution information in order to study fast transient events.

9.1.3. Metacog

Participants: Bertrand Thirion [Correspondant], Gaël Varoquaux, Jérome Dockès.

This project is funded by Digiteo.

This is a Digicosme project (2016-2019) and a collaboration with Fabian Suchanek (Telecom Paritech).

Understanding how cognition emerges from the billions of neurons that constitute the human brain is a major open problem in science that could bridge natural science –biology– to humanities –psychology. Psychology studies performed on humans with functional Magnetic Resonance Imaging (fMRI) can be used to probe the full repertoire of high-level cognitive functions. While analyzing the resulting image data for a given experiment is a relatively well-mastered process, the challenges in comparing data across multiple datasets poses serious limitation to the field. Indeed, such comparisons require to pool together brain images acquired under different settings and assess the effect of different *experimental conditions* that correspond to psychological effects studied by neuroscientists.

Such meta-analyses are now becoming possible thanks to the development of public data resources –OpenfMRI http://openfmri.org and NeuroVault http://neurovault.org. As many others, researchers of the Parietal team understand these data sources well and contribute to them. However, in such open-ended context, the description of experiments in terms of cognitive concepts is very difficult: there is no universal definition of cognitive terms that could be employed consistently by neuroscientists. Hence meta-analytic studies loose power and specificity. On the other hand, http://brainspell.org provide a set of curated annotation, albeit on much less data, that can serve as a seed or a ground truth to define a consensual ontology of cognitive concepts. Relating these terms to brain activity poses another challenge, of statistical nature, as brain patterns form high-dimensional data in perspective with the scarcity and the noise of the data.

The purpose of this project is to learn a semantic structure in cognitive terms from their occurrence in brain activation. This structure will simplify massive multi-label statistical-learning problems that arise in brain mapping by providing compact representations of cognitive concepts while capturing the imprecision on the definition these concepts.

9.1.4. HidimStat

Participants: Bertrand Thirion [Correspondant], Jerome-Alexis Chevalier, Joseph Salmon.

This project is funded by Digiteo.

This is a Digicosme project (2017-2020) and a collaboration with Joseph Salmon (Telecom Paritech).

The HiDimStat project aims at handling uncertainty in the challenging context of high dimensional regression problem. Though sparse models have been popularized in the last twenty years in contexts where many features can explain a phenomenon, it remains a burning issue to attribute confidence to the predictive models that they produce. Such a question is hard both from the statistical modeling point of view, and from a computation perspective. Indeed, in practical settings, the amount of features at stake (possibly up to several millions in high resolution brain imaging) limit the application of current methods and require new algorithms to achieve computational efficiency. We plan to leverage recent developments in sparse convex solvers as well as more efficient reformulations of testing and confidence interval estimates to provide several communities with practical software handling uncertainty quantification. Specific validation experiments will be performed in the field of brain imaging.

9.1.5. Template estimation for arbitrary alignments: application to brain imaging.

Participants: Bertrand Thirion [Correspondant], Thomas Bazeille.

This project is funded by Digiteo.

In the recent years, the nature of scientific inference has shifted quite substantially from model-based to predictive approaches, thanks to the generalization of powerful machine learning techniques. While this has certainly improved scientific standards, this has also obscured the objects and concepts on which inference is drawn. For instance, it is now possible –based on some initial data– to predict individual brain activity topographies, yet the very notion of a standard brain template has become increasingly elusive. Given the importance of establishing models for the progress of knowledge, we revisit the problem of model inference on data with high variance. Specifically, in a context where almost arbitrary transformation can successfully warp observations to each other with high accuracy, what is the common definition of a population model underlying all these observations? What is the working definition of a template ? We plan to leverage recent developments on optimal transport and multivariate analysis to build working definition of templates; we will use them in a brain imaging context to build a novel generation of brain templates.

9.1.6. CDS2

Participants: Alexandre Gramfort [Correspondant], Gaël Varoquaux, Maria Telenczuk, Jiaping Liu.

CDS2 is an "Strategic research initiative" of the Paris Saclay University Idex https://www.datascience-paris-saclay.fr/. Although it groups together many partners of the Paris Saclay ecosystem, Parietal has been deeply involved in the project. It currently funds 2 engineers: Maria Telenczuk and Jiaping (Lucy) Liu.

9.2. National Initiatives

9.2.1. ANR

9.2.1.1. Neuroref: Mathematical Models of Anatomy / Neuroanatomy / Diffusion MRI

Participants: Demian Wassermann [Correspondant], Antonia Machlouzarides Shalit, Valentin Iovene.

While mild traumatic brain injury (mTBI) has become the focus of many neuroimaging studies, the understanding of mTBI, particularly in patients who evince no radiological evidence of injury and yet experience clinical and cognitive symptoms, has remained a complex challenge. Sophisticated imaging tools are needed to delineate the kind of subtle brain injury that is extant in these patients, as existing tools are often ill-suited for the diagnosis of mTBI. For example, conventional magnetic resonance imaging (MRI) studies have focused on seeking a spatially consistent pattern of abnormal signal using statistical analyses that compare average differences between groups, i.e., separating mTBI from healthy controls. While these methods are successful in many diseases, they are not as useful in mTBI, where brain injuries are spatially heterogeneous.

The goal of this proposal is to develop a robust framework to perform subject-specific neuroimaging analyses of Diffusion MRI (dMRI), as this modality has shown excellent sensitivity to brain injuries and can locate subtle brain abnormalities that are not detected using routine clinical neuroradiological readings. New algorithms will be developed to create Individualized Brain Abnormality (IBA) maps that will have a number of clinical and research applications. In this proposal, this technology will be used to analyze a previously acquired dataset from the INTRuST Clinical Consortium, a multi-center effort to study subjects with Post-Traumatic Stress Disorder (PTSD) and mTBI. Neuroimaging abnormality measures will be linked to clinical and neuropsychological assessments. This technique will allow us to tease apart neuroimaging differences between PTSD and mTBI and to establish baseline relationships between neuroimaging markers, and clinical and cognitive measures.

9.2.1.2. DirtyData: Data integration and cleaning for statistical analysis

Participants: Gaël Varoquaux [Correspondant], Patricio Cerda Reyes, Pierre Glaser.

Machine learning has inspired new markets and applications by extracting new insights from complex and noisy data. However, to perform such analyses, the most costly step is often to prepare the data. It entails correcting errors and inconsistencies as well as transforming the data into a single matrix-shaped table that comprises all interesting descriptors for all observations to study. Indeed, the data often results from merging multiple sources of informations with different conventions. Different data tables may come without names on the columns, with missing data, or with input errors such as typos. As a result, the data cannot be automatically shaped into a matrix for statistical analysis.

This proposal aims to drastically reduce the cost of data preparation by integrating it directly into the statistical analysis. Our key insight is that machine learning itself deals well with noise and errors. Hence, we aim to develop the methodology to do statistical analysis directly on the original dirty data. For this, the operations currently done to clean data before the analysis must be adapted to a statistical framework that captures errors and inconsistencies. Our research agenda is inspired from the data-integration state of the art in database research combined with statistical modeling and regularization from machine learning.

Data integrating and cleaning is traditionally performed in databases by finding fuzzy matches or overlaps and applying transformation rules and joins. To incorporate it in the statistical analysis, an thus propagate uncertainties, we want to revisit those logical and set operations with statistical-learning tools. A challenge is to turn the entities present in the data into representations well-suited for statistical learning that are robust to potential errors but do not wash out uncertainty.

Prior art developed in databases is mostly based on first-order logic and sets. Our project strives to capture errors in the input of the entries. Hence we formulate operations in terms of similarities. We address typing entries, deduplication -finding different forms of the same entity- building joins across dirty tables, and correcting errors and missing data.

Our goal is that these steps should be generic enough to digest directly dirty data without user-defined rules. Indeed, they never try to build a fully clean view of the data, which is something very hard, but rather include in the statistical analysis errors and ambiguities in the data.

The methods developed will be empirically evaluated on a variety of dataset, including the French public-data repository, http://www.data.gouv.fr. The consortium comprises a company specialized in data integration, Data Publica, that guides business strategies by cross-analyzing public data with market-specific data.

9.2.1.3. FastBig Project

Participants: Bertrand Thirion [Correspondant], Jerome-Alexis Chevalier, Tuan Binh Nguyen.

In many scientific applications, increasingly-large datasets are being acquired to describe more accurately biological or physical phenomena. While the dimensionality of the resulting measures has increased, the number of samples available is often limited, due to physical or financial limits. This results in impressive amounts of complex data observed in small batches of samples.

A question that arises is then : what features in the data are really informative about some outcome of interest ? This amounts to inferring the relationships between these variables and the outcome, conditionally to all other variables. Providing statistical guarantees on these associations is needed in many fields of data science, where competing models require rigorous statistical assessment. Yet reaching such guarantees is very hard.

FAST-BIG aims at developing theoretical results and practical estimation procedures that render statistical inference feasible in such hard cases. We will develop the corresponding software and assess novel inference schemes on two applications : genomics and brain imaging.

9.2.1.4. MultiFracs project

Participant: Philippe Ciuciu [Correspondant].

The scale-free concept formalizes the intuition that, in many systems, the analysis of temporal dynamics cannot be grounded on specific and characteristic time scales. The scale-free paradigm has permitted the relevant analysis of numerous applications, very different in nature, ranging from natural phenomena (hydrodynamic turbulence, geophysics, body rhythms, brain activity,...) to human activities (Internet traffic, population, finance, art,...).

Yet, most successes of scale-free analysis were obtained in contexts where data are univariate, homogeneous along time (a single stationary time series), and well-characterized by simple-shape local singularities. For such situations, scale-free dynamics translate into global or local power laws, which significantly eases practical analyses. Numerous recent real-world applications (macroscopic spontaneous brain dynamics, the central application in this project, being one paradigm example), however, naturally entail large multivariate data (many signals), whose properties vary along time (non-stationarity) and across components (non-homogeneity), with potentially complex temporal dynamics, thus intricate local singular behaviors.

These three issues call into question the intuitive and founding identification of scale-free to power laws, and thus make uneasy multivariate scale-free and multifractal analyses, precluding the use of univariate methodologies. This explains why the concept of scale-free dynamics is barely used and with limited successes in such settings and highlights the overriding need for a systematic methodological study of multivariate scale-free and multifractal dynamics. The Core Theme of MULTIFRACS consists in laying the theoretical foundations of a practical robust statistical signal processing framework for multivariate non homogeneous scale-free and multifractal analyses, suited to varied types of rich singularities, as well as in performing accurate analyses of scale-free dynamics in spontaneous and task-related macroscopic brain activity, to assess their natures, functional roles and relevance, and their relations to behavioral performance in a timing estimation task using multimodal functional imaging techniques.

This overarching objective is organized into 4 Challenges:

1. Multivariate scale-free and multifractal analysis,
2. Second generation of local singularity indices,
3. Scale-free dynamics, non-stationarity and non-homogeneity,
4. Multivariate scale-free temporal dynamics analysis in macroscopic brain activity.

9.2.1.5. DARLING: Distributed adaptation and learning over graph signals

Participant: Philippe Ciuciu [Correspondant].

The project will be starting in 2020 with a post-doc to be hired probably in 2021.

The DARLING project will aim to propose new adaptive learning methods, distributed and collaborative on large dynamic graphs in order to extract structured information of the data flows generated and/or transiting at the nodes of these graphs. In order to obtain performance guarantees, these methods will be systematically accompanied by an in-depth study of random matrix theory. This powerful tool , never exploited so far in this context although perfectly suited for inference on random graphs, will thereby provide even avenues for improvement. Finally, in addition to their evaluation on public data sets, the methods will be compared with each other using two advanced imaging techniques in which two of the partners are involved: radio astronomy with the giant SKA instrument (Obs. Côte d'Azur) and magnetoencephalographic brain imaging (Inria Parietal at NeuroSpin, CEA Saclay). These involve the processing of time series on graphs while operating at extreme observation scales.

9.2.1.6. meegBIDS.fr: Standardization, sharing and analysis of MEEG data simplified by BIDS

Participant: Alexandre Gramfort [Correspondant].

The project accepted by ANR in 2019 will be starting in 2020 with an engineer to be hired in 2020. This project is in collaboration with the MEG groups at CEA NeuroSpin and the Brain and Spine Institute (ICM) in Paris.

The neuroimaging community recently started an international effort to standardize the sharing of data recorded with magnetoencephalography (MEG) and with electroencephalography (EEG). This format, known as the Brain Imaging Data Structure (BIDS), now needs a wider adoption, notably in the French neuroimaging community, along with the development of dedicated software tools that operate seamlessly on BIDS formatted datasets. The meegBIDS.fr project has three aims: 1) accelerate the research cycles by allowing analysis software tools to work with BIDS formated data, 2) simplify data sharing with high quality standards thanks to automated validation tools, 3) train French neuroscientists to leverage existing public BIDS MEG/EEG datasets and to share their own data with little efforts.

9.3. European Initiatives

9.3.1. FP7 & H2020 Projects

9.3.1.1. VirtualBrainCloud

Title:

Programm: H2020 FET Open

Duration: 01/01/2019 - 31/12/2022

Coordinator: Petra Ritter

Inria contact: Bertrand Thirion

Summary:

The central goal of this project is the development of a cloud-based platform for biomedical research and clinical decision-making that helps to improve early patient-specific diagnosis and treatment of NDD and has substantial potential for significant positive socioeconomic impact.

The platform integrates several aims that revolve around early diagnosis, prognosis, and personalized treatment of neurodegenerative diseases (NDD) like Alzheimer's disease (AD) and Parkinson's disease (PD). It is becoming increasingly clear that meeting this objective requires a multifactorial approach that takes into account individual genetic, metabolic and environmental aspects, and that integrates them with the understanding of the biophysical processes underlying NDD.

More information can be found here https://virtualbraincloud-2020.eu/tvb-cloud-main.html.

9.3.1.2. Neurolang

Title: Accelerating Neuroscience Research by Unifying Knowledge Representation and Analysis Through a Domain Specific Language

Programm: ERC Starting researcher

Duration: 01/03/2018 - 28/02/2023

Coordinator: Demian Wassermann

Inria contact: Demian Wassermann

Summary:

Neuroscience is at an inflection point. The 150-year old cortical specialization paradigm, in which cortical brain areas have a distinct set of functions, is experiencing an unprecedented momentum with over 1000 articles being published every year. However, this paradigm is reaching its limits. Recent studies show that current approaches to atlas brain areas, like relative location, cellular population type, or connectivity, are not enough on their own to characterize a cortical area and its function unequivocally. This hinders the reproducibility and advancement of neuroscience.

Neuroscience is thus in dire need of a universal standard to specify neuroanatomy and function: a novel formal language allowing neuroscientists to simultaneously specify tissue characteristics, relative location, known function and connectional topology for the unequivocal identification of a given brain region.

The vision of NeuroLang is that a unified formal language for neuroanatomy will boost our understanding of the brain. By defining brain regions, networks, and cognitive tasks through a set of formal criteria, researchers will be able to synthesize and integrate data within and across diverse studies. NeuroLang will accelerate the development of neuroscience by providing a way to evaluate anatomical specificity, test current theories, and develop new hypotheses.

NeuroLang will lead to a new generation of computational tools for neuroscience research. In doing so, we will be shedding a novel light onto neurological research and possibly disease treatment and palliative care. Our project complements current developments in large multimodal studies across different databases. This project will bring the power of Domain Specific Languages to neuroscience research, driving the field towards a new paradigm articulating classical neuroanatomy with current statistical and machine learning-based approaches.

9.3.1.3. SLAB (698)

Title: Signal processing and Learning Applied to Brain data

Programm: ERC Starting researcher

Duration: 01/04/2017 - 31/08/2021

Coordinator: Alexandre Gramfort

Partner: LTCI , Telecom ParisTech (France)

Inria contact: Alexandre Gramfort

Summary:

Understanding how the brain works in healthy and pathological conditions is considered as one of the challenges for the 21st century. After the first electroencephalography (EEG) measurements in 1929, the 90's was the birth of modern functional brain imaging with the first functional MRI and full head magnetoencephalography (MEG) system. In the last twenty years, imaging has revolutionized clinical and cognitive neuroscience.

After pioneering works in physics and engineering, the field of neuroscience has to face two major challenges. The size of the datasets keeps growing. The answers to neuroscience questions are limited by the complexity of the signals observed: non-stationarity, high noise levels, heterogeneity of sensors, lack of accurate models. SLAB will provide the next generation of models and algorithms for mining electrophysiology signals which offer unique ways to image the brain at a millisecond time scale.

SLAB will develop dedicated machine learning and signal processing methods and favor the emergence of new challenges for these fields. SLAB focuses on five objectives: 1) source localization with M/EEG for brain imaging at high temporal resolution 2) representation learning to boost statistical power and reduce acquisition costs 3) fusion of heterogeneous sensors 4) modeling of non-stationary spectral interactions to identify functional coupling between neural ensembles 5) development of fast algorithms easy to use by non-experts.

SLAB aims to strengthen mathematical and computational foundations of brain data analysis. The methods developed will have applications across fields (computational biology, astronomy, econometrics). Yet, the primary impact of SLAB will be on neuroscience. The tools and high quality open software produced in SLAB will facilitate the analysis of electrophysiology data, offering new perspectives to understand how the brain works at a mesoscale, and for clinical applications (epilepsy, autism, tremor, sleep disorders).

9.3.1.4. HBP SGA2

Title: Interactive Computing E-Infrastructure for the Human Brain Project

Programm: FET Flagship

Duration: 01/04/2018 - 31/03/2020

Coordinator: Katrin Amunts

Partners: see https://www.humanbrainproject.eu/en/open-ethical-engaged/contributors/partners/

Inria contact: Bertrand Thirion

Summary:

The HBP Flagship was launched by the European Commission's Future and Emerging Technologies (FET) scheme in October 2013, and is scheduled to run for ten years. The Flagships, represent a new partnering model for visionary, long-term European cooperative research in the European Research Area, demonstrating the potential for common research efforts. The HBP has the following main objectives:

- Create and operate a European scientific Research Infrastructure for brain research, cognitive neuroscience, and other brain-inspired sciences

- Gather, organise and disseminate data describing the brain and its diseases
- Simulate the brain
- Build multi-scale scaffold theory and models for the brain
- Develop brain-inspired computing, data analytics and robotics
- Ensure that the HBP's work is undertaken responsibly and that it benefits society.

More information on the HBP's Flagship Objectives is available in the Framework Partnership Agreement.

The timeline of the Project is split into multiple phases, each of which will be covered by a separate funding agreement. The current phase is Specific Grant Agreement Two (SGA2), which spans the two-year period from April 2018–April 2020. The HBP is funded via several sources. Total funding is planned to be in the region of EUR 1 billion; around one half of which will be provided by the European Union, and the other by Member States and private funding sources. The European Union contributed EUR 54 million to the Project in the Ramp-Up Phase (October 2013 to March 2016), EUR 89 million for the second phase (SGA1), and EUR 88 million for the current phase (SGA2). The FET Flagships Staff Working Document provides further information on how Flagships are funded.

9.4. International Initiatives

9.4.1. Inria International Labs

Inria@SiliconValley
Associate Team involved in the International Lab:

9.4.1.1. Meta&Co

Title: Meta-Analysis of Neuro-Cognitive Associations

International Partner (Institution - Laboratory - Researcher):

Stanford (United States) - Psychology department. - Russel Poldrack

Start year: 2018

See also: http://team.inria.fr/parietal

Cognitive science and psychiatry describe mental operations: cognition, emotion, perception and their dysfunction. Cognitive neuroimaging bridge these mental concepts to their implementation in the brain, neural firing and wiring, by relying on functional brain imaging. Yet aggregating results from experiments probing brain activity into a consistent description faces the roadblock that cognitive concepts and brain pathologies are ill-defined. Separation between them is often blurry. In addition, these concepts and subdivisions may not correspond to actual brain structures or systems. To tackle this challenge, we propose to adapt data-mining techniques used to learn relationships in computational linguistics. Natural language processing uses distributional semantics to build semantic relationships and ontologies. New models are needed to learn relationships from heterogeneous signals: functional magnetic resonance images (fMRI), on the one hand, combined with related psychology and neuroimaging annotations or publications, on the other hand. Such a joint effort will rely on large publicly-available fMRI databases shared by Podrack Lab, as well as literature mining.

Inria@SiliconValley
Associate Team involved in the International Lab:

9.4.1.2. LargeSmallBrainNets

Title: Characterizing Large and Small-scale Brain Networks in Typical Populations Using Novel Computational Methods for dMRI and fMRI-based Connectivity and Microstructure

International Partner (Institution - Laboratory - Researcher):

Stanford (United States) - Stanford Cognitive and Systems Neuroscience Laboratory - Vinod Menon

Start year: 2019

See also: http://pages.saclay.inria.fr/demian.wassermann/largesmallbrainnets/

In the past two decades, brain imaging of neurotypical individuals and clinical populations has primarily focused on localization of function and structures in the brain, revealing activation in specific brain regions during performance of cognitive tasks through modalities such as functional MRI. In parallel, technologies to identify white matter structures have been developed using diffusion MRI. Lately, interest has shifted towards developing a deeper understanding of the brain's macroscopic and microscopic architectures and their influence on cognitive and affective information processing. Using for this resting state fMRI and diffusion MRI to build the functional and structural networks of the human brain.

The human brain is a complex patchwork of interconnected regions, and graph-theoretical approaches have become increasingly useful for understanding how functionally connected systems engender, and constrain, cognitive functions. The functional nodes of the human brain, i.e. cortical regions, and their structural inter-connectivity, collectively the brain's macrostructure or "connectome", are, however, poorly understood. Quantifying in vivo how these nodes' microstructure, specifically cellular composition or cytoarchitecture, influences the cognitive tasks in which these are involved is fundamental problem in understanding the connectome. Furthermore, the coupling between within and across-subject contributions to the connectome and cognitive differences hampers the identification and understanding of the link between brain structure and function, and human cognition.

Critically, there is a dearth of computational methods for reliably identifying functional nodes of the brain, their micro and macrostructure in vivo, and separating the population and subject-specific effects. Devising and validating methods for investigating the human connectome has therefore taken added significance.

The first major goal of this project is to develop and validate appropriate sophisticated computational and mathematical tools relate the brain's macrostructure with its function. Specifically, we will focus on being able to separate population and subject-specific contributions within these models using state-of-the-art human brain imaging techniques and open-source data from the Human Connectome Project (HCP) and the Adolescent Brain Cognitive Development study (ABCD). To this end, we will first develop and validate novel computational tools for (1) formulating and fitting large scale random effect models on graphs derived from functional and structural connectivity and (2) implement techniques enabling us to impose different regularization schemes based on sparsity and multicollinearity of the model parameters.

The second major goal of this project is characterizing the cytoarchitecture of the nodes, i.e. cortical regions, at the microscopic level and their relationship with the brain's hemodynamical function and cognition. For this, we will (1) identify cortical areas with specific cytoarchitecture in the human cortex and use them to develop diffusion MRI-based models, (2) validate these models with numerical simulations of the dMRI signal and animal models, and (3) establish the relationship between cytoarchitecture and hemodynamical function measured from fMRI and cognition. For this we will leverage multi-shell high-angular diffusion MRI from public databases such as HCP and ABCD.

Finally, we will use to use our newly developed computational tools to characterize normal structural and functional brain networks in neurotypical adults. Due to the complementarity of the cognitive

science and imaging techniques expertise the synergy between the two laboratories of this associate team will allow us to reveal in unprecedented detail the structural and functional connectivity of the human brain and its relation to cognition.

9.5. International Research Visitors

9.5.1. Visits of International Scientists

- Aapo Havärinen has been with parietal since April 2019 for a one-year visit, funded by the Dataia convergence institute.
- Luigi Gresele (MPI Tübingen) has been visiting the team in November-December 2019.
- Cedric Xu (UPenn) visited the team for three months in June-August 2019.
- James Cole (UCL) visited the team in December 2019.
- Yu Zhang (BIC, Montreal) visited the team during one week in September 2019
- Bemsibom Toh (HWU, Edinburgh) visited the team during two months in September-November 2019

9.5.2. Visits to International Teams

9.5.2.1. Sabbatical programme

Gael Varoquaux is spending one year in Montreal (September 2019-September 2020), hosted at MILA and Montreal Neuroimaging Institute at McGill Unviversity.

AIRSEA Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

C. Prieur is co-leader of work-package 3 of the cross-disciplinary-project Trajectories from Idex Grenoble.

8.2. National Initiatives

8.2.1. ANR

A 4-year contract : ANR COCOA (COmprehensive Coupling approach for the Ocean and the Atmosphere). PI: E. Blayo. (Jan. 2017 - Dec. 2020). Other partners: Laboratoire des Sciences du Climat et de l'Environnement (UMR8212, Gif-sur-Yvette), Laboratoire de Météorologie Dynamique (UMR8539, Paris), Laboratoire d'Océanographie Physique et Spatiale (UMR6523, Brest), Centre National de Recherche Météorologique (UMR3589, Toulouse), Cerfacs (Toulouse). This project aims at revisiting the overall representation of air-sea interactions in coupled ocean-atmosphere models, and particularly in climate models, by coherently considering physical, mathematical, numerical and algorithmic aspects.

A 4-year contract : ANR HEAT (Highly Efficient ATmospheric modelling) http://www.agence-nationale-recherche.fr/?Project=ANR-14-CE23-0010.

A 4-year contract : ANR ADOM (Asynchronous Domain decomposition methods)

A 5-year contract : ANR MELODY (Bridging geophysics and MachinE Learning for the modeling, simulation and reconstruction of Ocean DYnamic)

A 5-year contract with the French Navy (SHOM) on the improvment of the CROCO ocean model http://www.croco-ocean.org.

C. Prieur and E. Arnaud are involved as experts in project High-Tune http://www.agence-nationale-recherche.fr/Projet-ANR-16-CE01-0010 funded by ANR.

8.2.2. Inria Challenge

Sea Uncertainty Representation and Forecast (SURF),

Coord : Airsea (A. Vidard),

Partenaires Inria : Ange, Cardamom, Fluminance, Lemon, Mingus, Defi

Partenaires extérieurs: BRGM, Ifremer, SHOM

8.2.3. Other Initiatives

A. Vidard leads a group of projects gathering multiple partners in France and UK on the topic "Variational Data Assimilation for the NEMO/OPA9 Ocean Model", see 5.3 .

C. Prieur is co-advising the PhD thesis of Henri Mermoz Kouye, ine the framework of the Inria-INRA collaboration.

C. Prieur chaired GdR MASCOT NUM 2010-2017, in which are also involved M. Nodet, E. Blayo, C. Helbert, E. Arnaud, L. Viry, S. Nanty, L. Gilquin. She is still strong involved in the group (co-chair). In particular, she will co-chair next GdR annual meeting in Aussois (May 2020). http://www.gdr-mascotnum.fr/doku.php.

LEFE/GMMC CASIS, Coupled Assimilation Strategies for the Initialisation of an ocean- atmospheric boundary layer System, A. Vidard en collaboration avec Mercator océan

8.3. European Initiatives

8.3.1. FP7 & H2020 Projects

H2020 project IMMERSE (Improving Models for Marine EnviRonment SErvices) is funded from 2018-12-01 to 2022-11-30 (Inria contact: Florian Lemarié, coordinator: J. Le Sommer, CNRS). The overarching goal of the project is to ensure that the Copernicus Marine Environment Monitoring Service (CMEMS) will have continuing access to world-class marine modelling tools for its next generation systems while leveraging advances in space and information technologies, therefore allowing it to address the ever-increasing and evolving demands for marine monitoring and prediction in the 2020s and beyond. See also https://cordis.europa.eu/project/rcn/218810/factsheet/fr and https://immerse-ocean.eu/

8.3.2. Collaborations in European Programs, Except FP7 & H2020

Program: C3S

Project acronym: ERGO

Project title: Enabling an Ensemble of Data Assimilation for the Ocean

Duration: Février 2019 - juillet 2021

Coordinator: Arthur Vidard

Other partners: Cerfacs (France), Met Office (U.K.), CMRE (int, Italie)

Abstract: The scope of this contract is to improve ocean data assimilation capabilities at ECMWF, used in both initialization of seasonal forecasts and generation of coupled Earth System reanalyses. In particular it shall focus on i) improving ensemble capabilities in NEMO and NEMOVAR and the use of their information to represent background error statistics; ii) extend NEMOVAR capabilities to allow for multiple resolution in multi-incremental 3D-Var; iii) make better use of ocean surface observations. It shall also involve performing scout experiments and providing relevant diagnostics to evaluate the benefit coming from the proposed developments.

8.3.3. Collaborations with Major European Organizations

Partner: European Center for Medium Range Weather Forecast. Reading (UK)

World leading Numerical Weather Center, that include an ocean analysis section in order to provide ocean initial condition for the coupled ocean atmosphere forecast. They play a significant role in the NEMOVAR project in which we are also partner.

Partner: Met Office (U.K) National British Numerical Weather and Oceanographic service. Exceter (UK).

We do have a strong collaboration with their ocean initialization team through both our NEMO, NEMO-ASSIM and NEMOVAR activities. They also are our partner in the NEMOVAR consortium.

Partner : SAMO board

SAMO board is in charge of the organization of the SAMO (sensitivity analysis of model outputs) conferences, every three years. It is strongly supporter by the Joint Research Center of the European Commission. In 2019, Clémentine Prieur, which is part of this board, as also co-chair of a satellite event on the future of sensitivity analysis. A position paper is under construction, as a synthesis of the discussions hold in Barcelona (autumn 2019).

8.4. International Initiatives

8.4.1. Inria Associate Teams Not Involved in an Inria International Labs

8.4.1.1. UNQUESTIONABLE

Title: UNcertainty QUantification is ESenTIal for OceaNic & Atmospheric flows proBLEms.

International Partner: Massachusetts Institute of Technology (United States) - Aerospace Computational Design Laboratory - Youssef Marzouk

Start year: 2018

See also: https://team.inria.fr/unquestionable/

The ability to understand and predict the behavior of geophysical flows is of greatest importance, due to its strong societal impact. Numerical models are essential to describe the evolution of the system (ocean + atmosphere), and involve a large number of parameters, whose knowledge is sometimes really poor. The reliability of the numerical predictions thus requires a step of parameter identification. The Inria-AIRSEA team has a strong expertise in variational approaches for inverse problems. An alternative is the use of particle filters, whose main advantage is their ability to tackle non-gaussian frameworks. However, particle filters suffer from the curse of dimensionality. The main objective of the collaboration we propose between the Inria-AIRSEA team and the MIT UQ group is the understanding of potential low-dimensional structure underlying geophysical applications, then the exploitation of such structures to extend particle filter to high-dimensional applications.

8.4.2. Inria International Partners

F. Lemarié and L. Debreu collaborate with Hans Burchard and Knut Klingbeil from the Leibniz-Institut für Ostseeforschung in Warnemünde (Germany) [32], [12].

C. Prieur collaborates with Jose R. Leon (Universdad de la república de Uruguay, Montevideo).

C. Prieur collaborates with K. Bertin (CIMFAV, Valparaíso).

F.-X. Le Dimet is a Honorary Professor of the Institut of Mechanics, Ac.Sci. Vietnam.

F.-X. Le Dimet is a Honorary Professor of the Institut of Numerical Mathematics, Russian Ac.Sci.

8.5. International Research Visitors

8.5.1. Visits of International Scientists

Alistair Adcroft (Princeton Univ.) visited the team in Jan. 2019

Jose R. León was visiting the team during two weeks. He is working with Clémentine Prieur, in collaboration with Pierre Etoré and Adeline Samson (DATA department of LJK) on UQ for models described by SDE.

Nicholas Kevlahan, from McMaster University (Canada) was a visiting scientist of the AIRSEA team for 10 months in 2018-2019.

Victor Shutyaev, from the Institut of Numerical Mathematics (Moscow, Russian Ac.Sci.) was visiting the team during two weeks to collaborate with F.-X. Le Dimet [17].

ANGE Project-Team

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. ANR MFG (2016-2021)

Participant: Julien Salomon.

Project acronym: MFG

Project title: Mean Field Games

Coordinator: Sébastien Boyaval (LHSV/ENPC)

Funding: 299 160 euros.

Mean field game theory (MFG) is a new and active field of mathematics, which analyses the dynamics of a very large number of agents. Introduced about ten years ago, MFG models have been used in different fields: economics, finance, social sciences, engineering,... MFG theory is at the intersection of mean field theory, mathematical game theory, optimal control, stochastic analysis, variation calculation, partial differential equations and scientific calculation. Drawing on an internationally recognized French team on the subject, the project seeks to obtain major contributions in 4 main directions: the "medium field" aspect (i.e., how to obtain macroscopic models from microscopic models); the analysis of new MFG systems; their numerical analysis; the development of new applications. In this period of rapid expansion of MFG models, the project seeks to foster French leadership in the field and attract new researchers from related fields.

9.1.2. ANR INFAMIE (2015-2019)

Participant: Boris Haspot.

Program: ANR Défi de tous les savoirs (DS10) 2015

Project acronym: INFAMIE

Project title: INhomogeneous Flows : Asymptotic Models and Interfaces Evolution

Coordinator: Raphaël Danchin (Univ. Paris-Est)

Funding: 232 960 euros.

Our project aims at a better mathematical understanding of several models for the evolution of inhomogeneous flows. Through three main lines of research (see below), we will pursue a twofold final objective. First, we want to develop the current theory of regular solutions for several equations for the evolution of fluids, proposing a new approach and developing tools that are likely to be efficient in various areas of PDEs. Second, for a few selected concrete systems that describe flows in the earth environment or in astrophysics, we wish to use this general approach to extract as much information as possible concerning the qualitative behavior of the solutions.

9.1.3. ANR SEDIFLO (2015-2019)

Participants: Emmanuel Audusse, Martin Parisot.

Program: ANR Défi 1 “Gestion sobre des ressources et adaptation au changement climatique” (JCJC)

Project acronym: SEDIFLO

Project title: Modelling and simulation of solid transport in rivers

Coordinator: Sébastien Boyaval (LHSV/ENPC)

Based on recent theoretical and experimental results, this project is aimed at modelling transport of sediments within rivers. It will rely on innovations from the point of view of rheology as well as advanced mathematical tools (asymptotic model reduction, PDE discretisation).

9.1.4. ANR Hyflo-Eflu (2016-2019)

Participants: Jérémy Ledoux, Martin Parisot, Jacques Sainte-Marie, Julien Salomon.

ANR project call: Energies marines renouvelables

Project acronym: Hyflo-Eflu

Project title: Hydroliennes flottantes et énergie fluviale

Coordinator: Julien Salomon

The project is a collaboration between the Inria-team ANGE, specialist of free surface flow and optimisation, and the industrial developers of the turbine, HydroTube Energie. The objective of the project HyFlo-EFlu is to deliver a numerical software able to simulate the dynamic of a floating water turbine in real context. For the academic partner, the main challenge is in the simulation of the floating structure at the scale of the river, and the modelling of the vertical and horisontal axis turbine. For the industrial partner, the objective is the validation of the stability of the structure and the performance in term of energy production.

9.1.5. ANR CHARMS (2016-2020)

Participant: Cindy Guichard.

ANR project call: Transformations et inter-conversions énergétiques

Project acronym: CHARMS

Project title: Modèles de réservoirs quantitatifs pour les systèmes hydrothermaux complexes

Coordinator: Simon Lopez (BRGM)

Funding: 73k euros for LJLL (in 767k euros for the whole project)

CHARMS ANR project is focused on the mathematical methods and software tools dedicated to the simulation of the physical models issued from geothermal engineering. The final objective is the achievement of a highly parallel code, validated on realistic cases.

9.1.6. GdR EGRIN (2017–2021)

Participants: Emmanuel Audusse, Bernard Di Martino, Nicole Goutal, Cindy Guichard, Anne Mangeney, Martin Parisot, Jacques Sainte-Marie.

EGRIN stands for Gravity-driven flows and natural hazards. J. Sainte-Marie is the head of the scientific committee of this CNRS research group and A. Mangeney is a member of the committee. Other members of the team involved in the project are local correspondents. The scientific goals of this project are the modelling, analysis and simulation of complex fluids by means of reduced-complexity models in the framework of geophysical flows.

9.1.7. ANR FireCaster (2017-2020)

Participants: Frédéric Allaire, Vivien Mallet.

ANR project call: DS0104

Project acronym: FireCaster

Project title: Plateforme de prévision incendie et de réponse d'urgence

Coordinator: Jean-Baptiste Filippi (Univ. Corse)

Funding: 442k euros

The goal of the FireCaster project is to prototype a fire decision support system at the national scale to estimate upcoming fire risk (H+24 to H+48) and in case of crisis, to predict fire front position and local pollution (H+1 to H+12).

9.1.8. ANR CENSE (2017-2020)

Participants: Antoine Lesieur, Vivien Mallet.

ANR project call: DS0601

Project acronym: CENSE

Project title: Caractérisation des environnements sonores urbains : vers une approche globale associant données libres, mesures et modélisations

Coordinator: Judicaël Picaut (IFSTTAR)

Funding: 856k euros

The CENSE project aims at proposing a new methodology for the production of more realistic noise maps, based on an assimilation of simulated and measured data through a dense network of low-cost sensors.

9.1.9. ANR RAVEX (2017-2020)

Participant: Anne Mangeney.

ANR project call: DS0106

Project acronym: RAVEX

Project title: Développement d'une approche intégrée pour la réduction des Risques Associés au Volcanisme EXplosif, de la recherche sur l'aléa aux outils de gestion de crise : le cas de la Martinique

Coordinator: Olivier Roche (IRD)

Funding: 619k euros

9.1.10. ANR CINE-PARA (2015-2019)

Participant: Julien Salomon.

ANR project call: DS0708

Project acronym: CINE-PARA

Project title: Méthodes de parallélisation pour cinétiques complexes

Coordinator: Yvon Maday (LJLL)

9.1.11. PGMO Project ORACLE (2019-2021)

Participant: Julien Salomon.

PGMO Call

Project acronym: Oracle

Project title: Optimal Resource Allocation in micro-organisms under Changing Environment

Coordinator: Térence Bayen

9.2. European Initiatives

9.2.1.

Participants: Martin Parisot, Yohan Penel, Jacques Sainte-Marie.

CNRS PICS NHML (2017-2019)

Program: CNRS PICS (projet international de collaboration scientifique)

Project acronym: NHML

Project title: non-hydrostatic multilayer models

Duration: 01/17-12/19

Coordinator: Yohan Penel (Inria)

Other partners: IMUS (Sevilla, Spain)

Other Participants: Enrique Fernández-Nieto (Sevilla), Tomas Morales de Luna (Cordoba)

Funding: 12k euros

Abstract: This collaboration aims at designing a hierarchy of multilayer models with a non-hydrostatic pressure as a discretisation along the vertical axis of the Euler equations. The hierarchy relies on the degree of approximation of the variables discretised with a Discontinuous Galerkin method for the vertical direction. These innovative models will imply a theoretical study and the development of numerical tools in dimensions 1 and 2 before the modelling of other physical phenomena (viscosity effects, ...).

9.3. International Initiatives

9.3.1. Inria International Partners

Three long-term collaborations with foreign colleagues have to be mentioned:

- **Spain** - A collaboration with spanish researchers has been initiated in 2016 to derive accurate models and effecient algorithms for free surface flows including non-hydrostatic effects.
- **Germany** A collaboration with researchers from the University of Constance is in progress about domain decomposition and identifaction algorithms (G. Ciaramella, S. Volkwein). The internship (Masterarbeit) of S. Buchwald has been co-supervised by J. Salomon.
- **Hong-Kong, Switzerland** A collaboration with F. Kwok and M. Gander on time parallelization for assimilation algorithm is in progress. A first paper has been submitted in october.

9.4. International Research Visitors

- Y. Penel made two two-week stay (March, October) at the university of Sevilla (Spain) to collaborate with E. Fernández-Nieto.
- M. Parisot spent two months (October, November) at the university of Aachen (Germany) to collaborate with S. Noelle.

9.4.1. Visits of International Scientists

- G. Ciaramella (Constance University) visited J. Salomon (20.05-23.05) to work on algorithms related to design of experiments and identification.
- F. Kwok (Baptist University, Hong-Kong) visited J. Salomon (8.07-11.07) to work on algorithms related to time parallelization for identification.

CASTOR Project-Team

5. Partnerships and Cooperations

5.1. National Initiatives

5.1.1. ANR Sistem

Member of the ANR SISTEM, Oct. 2019 - Sept. 2023 coordinated by the M2P2 Institute of Aix-Marseille Univ. "SImulations with high-order schemes of tranSport and TurbulencE in tokaMak" programme Modeles numeriques 2019

- Participants: Francesca Rapetti, Blaise Faugeras, Didier Auroux, Jacques Blum, Cédric Boulbe

Contact: F. Rapetti

5.2. European Initiatives

5.2.1. FP7 & H2020 Projects

EuroFusion Consortium

CASTOR participates to the following EuroFusion consortium projects :

EUROfusion WPCD (Working Package Code Development):

- EWE-2: Enabling Workflow Exploitation Area - Enabling the exploitation of the equilibrium reconstruction and MHD stability workflow (participation)
- WDEV-2: Workflow Development Area - Free boundary equilibrium and feedback control (participation and coordination)

EuroFusion Enabling Research CfP-AWP19-ENR-01, Strengthening the non-linear MHD code JOREK for application to key questions of the fusion roadmap.

EUROfusion WPSA(Work Package JT-60SA) 2018-2010

5.3. International Initiatives

5.3.1. Informal International Partners

The team collaborates with TUC (Technical University of Crete, Prof. Argyris Delis) on the modelling of acoustic streaming phenomena. In this framework, Argyris Delis has visited the Castor team in November 2019.

COFFEE Project-Team

7. Partnerships and Cooperations

7.1. Regional Initiatives

The team is involved in the IDEX project UCA-JEDI.

7.2. National Initiatives

7.2.1. ANR

- ANR CHARMS (Quantitative Reservoir Models for Complex Hydrothermal Systems), Roland Masson and Konstantin Brenner: december 2016 - december 2020, partners BRGM (leader), LJAD-Inria, Storengy, MdS, LJLL.
- ANR JCJC PRECIS (Effect of a shock wave on a structure with contact using mesh refinement and parallelism), Laurent Monasse: april 2018 - april 2021, partners Inria (leader), Ecole des Ponts, CEA, Université Paris-Est.

7.2.2. National and European networks

- GdR MANU.

  The research group MANU has activities centered around scientific computing, design of new numerical schemes and mathematical modelling (upscaling, homogenization, sensitivity studies, inverse problems,...). Its goal is to coordinate research in this area, as well as to promote the emergence of focused groups around specific projects
- S. Junca is involved in GdR 3437 DYNOLIN “Dynamique non linéaire” and GdR MecaWave.
- LJAD-Inria and BRGM are the French partners of the Norvergian, German French project InSPiRE "International Open Source Simulation Software Partnership in Research and Education” which has just been accepted by the Research Council of Norway with the code ComPASS as one of the softwares of this project together with Dune, Dumux and OPM.

7.3. International Initiatives

7.3.1. Inria Associate Teams Not Involved in an Inria International Labs

7.3.1.1. HDTHM

Title: Mathematical and numerical methods for thermo-hydro-mechanical models in porous media with discontinuities

International Partner (Institution - Laboratory - Researcher):

Monash University (Australia) - School of Mathematics - Jérome Droniou

Start year: 2019

See also: https://math.unice.fr/~massonr/HDTHM/HDTHM.html

The objective of this project is to extend a recent successful joint work between the two project leaders into a tight collaboration between the Monash and the Coffee teams involving several permanent members and students. The present project focuses on challenging directions of research related to the numerical simulation of thermo-hydro-mechanical models in fractured porous media that take advantage of the complementarity of both teams’ expertise as well as of the recent arrival of Laurent Monasse in the Coffee team. It is an opportunity to extend our collaborations with the Coffee team industrial partners in geosciences as well as to submit in common a research project to the Australian Research Council toward the end of the project.

7.3.2. Inria International Partners

The team has many interactions abroad: UFRJ, Ut Austin, India, Geneva, ICL,...

7.3.3. Participation in Other International Programs

Coffee is member of the Interdisciplinary Union of Porous Media Research at the University of Stuttgart (NUPUS).

Principal areas of research cooperation to be pursued under this program include free flow and porous medla flow interaction, fracture and fluid flow interactlon, fluid-solid phase change interaction, and simulation methods and tools.

7.4. International Research Visitors

7.4.1. Visits of International Scientists

The team has welcomed Paulo Amorim, from UFRJ, for research on the modeling of self-organization in f population dynamics, Corrado Mascia, from La Sapienza, on the analysis of hyperbolic systems and Martin Gander, from Univ. Geneva, for research on domain decomposition methods.

FLUMINANCE Project-Team

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. Comins'lab: SEACS : Stochastic modEl-dAta-Coupled representationS for the analysis, simulation and reconstruction of upper ocean dynamics

Participant: Etienne Mémin.

duration 48 months. The SEACS project whose acronym stands for: "Stochastic modEl-dAta-Coupled representationS for the analysis, simulation and reconstruction of upper ocean dynamics" is a Joint Research Initiative between the three Britanny clusters of excellence of the "Laboratoires d'Excellence" program: Cominlabs, Lebesgue and LabexMer centered on numerical sciences, mathematics and oceanography respectively. Within this project we aim at studying the potential of large-scale oceanic dynamics modeling under uncertainty for ensemble forecasting and satellite image data assimilation.

8.1.2. ANR BECOSE : Beyond Compressive Sensing: Sparse approximation algorithms for ill-conditioned inverse problems.

Participant: Dominique Heitz.

duration 48 months. The BECOSE project aims to extend the scope of sparsity techniques much beyond the academic setting of random and well-conditioned dictionaries. In particular, one goal of the project is to step back from the popular L1-convexification of the sparse representation problem and consider more involved nonconvex formulations, both from a methodological and theoretical point of view. The algorithms will be assessed in the context of tomographic Particle Image Velocimetry (PIV), a rapidly growing imaging technique in fluid mechanics that will have strong impact in several industrial sectors including environment, automotive and aeronautical industries. The consortium gathers the Fluminance and Panama Inria research teams, the Research Center for Automatic Control of Nancy (CRAN), The Research Institute of Communication and Cybernetics of Nantes (IRCCyN), and ONERA, the French Aerospace Lab.

8.1.3. IFPEN project

Participants: Jocelyne Erhel, Bastien Hamlat.

Contract with IFPEN (Institut Français du Pétrole et Energies Nouvelles) Duration: three years from October 2016. Title: Fully implicit Formulations for the Simulation of Multiphase Flow and Reactive Transport Coordination: Jocelyne Erhel. Contract with IFPEN (Institut FranÃ§ais du Pétrole et Energies Nouvelles). Duration: three years October 2016-September 2019. Title: Fully implicit Formulations for the Simulation of Multiphase Flow and Reactive Transport. Coordination: Jocelyne Erhel. Abstract: Modeling multiphase flow in porous media coupled with fluid-rock chemical reactions is essential in order to understand the origin of sub-surface natural resources and optimize their use. This project focused on chemistry models, with kinetic reactions. We developed a mathematical tool, which can be embedded into a reactive transport code.

8.1.4. GDR MANU

Participants: Yvan Crenner, Jocelyne Erhel, Bastien Hamlat.

Title: Mathematics for Nuclear industry
Duration: From 2016 to 2019
Coordination: C. Cancès
Webpage: http://gdr-manu.math.cnrs.fr/

Abstract: The working group MANU is a follow-up to the group MOMAS. It covers many subjects related to mathematical modeling and numerical simulations for problems arising from nuclear industry and nuclear waste disposal. We participated in a workshop on reactive transport (SITRAM), Pau, December 2019.

8.1.5. LEFE MANU: MSOM

Participants: Etienne Mémin, Long Li.

Title: Multiple Scale Ocean Model
Duration: From 2018 to 2021
Coordination: Bruno Deremble (CNRS LMD/ENS Paris)
Abstract: The objective of this project is to propose a numerical framework of a multiscale ocean model and to demonstrate its utility in the understanding of the interaction between the mean current and eddies.

8.2. International Initiatives

8.2.1. Inria International Partners

8.2.1.1. Informal International Partners

Imperial College, London (UK), Collaboration with Dan Crişan and Darryl Holm on Stochastic transport for the upper ocean dynamics

Chico California State University (USA), We have pursued our collaboration with the group of Shane Mayor on the GPU implementation of wavelet based motion estimator for Lidar data. This code is developped in coproperty between Inria and Chico.

8.2.1.2. International Initiatives

MATH-GEO

Title: MATHematical methods for GEOphysical flows

International Partners (Institution - Laboratory - Researcher):

Universidad de Buenos Aires (Argentina) - CIMA - Juan Ruiz

Universidad de la Republica Uruguay (Uruguay) - IMFIA, INCO

CMM (Chile) - Center for Mathematical Modeling - Axel Osses

Universidad San Ignacio de Loyola (USIL) (Peru) - Faculty of Engineering Alejandro Paredes

Duration: 2018 - 2019

Start year: 2018 http://mathgeo.cima.fcen.uba.ar

Nonlinear processes, such as advection and turbulent mixing, play a central role in geophysical sciences. The theory of nonlinear dynamical systems provides a systematic way to study these phenomena. Its stochastic extension also forms the basis of modern data analysis techniques, predictability studies and data assimilation methods. Contributions in the field of Topology and Dynamics of Chaos include methods conceived to unveil the structure organizing flows in phase space, building the gap between data and l ow-dimensional modeling. Low-order models in climate dynamics are highly desirable, since they can provide solutions in cases where high-resolution numerical simulations cannot be implemented, as in short-term wind forecasting. At the same time, the procedure provides a tool-kit for model validation, emulation or inter-model comparison, with interesting prospects in all fields of oceanographic and atmospheric sciences, including climate detection and attribution. The strategy constitutes an unprecedented and promising perspective, offering an original approach to the subject, with mathematical concepts that are not necessarily widespread in the geophysics scientific community. This proposal gathers specialists with a know-how in the most challenging aspects of the focused research field: coherent structure detection in fluid flows for the exploration and interactive visualization of scientific data (LIMSI France), data assimilation and fluid motion analysis from image sequences (Inria Rennes), numerical models

and data assimilation (CMM-Chile) stochastic models for climate dynamics with application to El Niño Ocean models (USIL-Peru), mathematical methods for weather and climate (CIMA-UBA & IMIT / IFAECI, Argentina), geophysical flows and dynamical systems (LMD France), mixing structures and Lagrangian analysis of multisatellite data (LOCEAN France), marine and estuarine hydrodynamic and water properties numerical models (INCO & IMFIA-Uruguay), in situ measurements of oceanographic conditions (CEBC France, in program with CNES France and CONAE Argentina), global modelling technique and topological characterization of flows (CORIA with CESBIO, France).

8.3. International Research Visitors

8.3.1. Visits of International Scientists

- 1 week visit of Alejandro Paredes Universidad San Ignacio de Loyola (USIL) (Peru) to work with Etienne Mémin
- 1 week visit of André Cavaleri (Instituto Tecnologico de Aeronautica, SP, Brésil) to work with Gilles Tissot
- 3 months visit of Ruediger Brecht (May to August), PhD student at Memorial University of Newfoundland, Canada, supported by funding from Inria-Mitacs Globalink.

LEMON Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

The MeDo project (lead by N. Chahinian) in which Carole Delenne participates is funded by Occitanie Region.

8.2. National Initiatives

Antoine Rousseau is member of the ANR project ANSWER (PI Céline Casenave), 2016-2020

Gwladys Toulemonde is head of a project (2019-2021) funded by INSU via the action MANU (MAthematical and NUmerical methods) of the LEFE program. This project, called Fraise, is focused on rainfall forcing by stochastic simulation for hydrological impact studies from dry periods to extreme events. The consortium involved in this project is larger than the Cerise one (14 researchers from 8 partners : AgroParisTech, CNRS, INRA, Inria, IRD, Université de Lyon 1, Université de Montpellier and the University of Venise in Italy).

Gwladys Toulemonde is member of the ANR project Gambas (PI Frédéric Mortier, Cirad), 2019-2023. The project GAMBAS focuses on joint species distribution models. These models can provide a better understanding and more accurate predictions of species distributions based on environmental variables while taking into account the effects of all other co-occurring species (e.g. competition).

Pascal Finaud-Guyot is member of the ANR project DEUFI (PI André Paquier, IRSTEA Lyon), 2019-2022

All the team is involved in the Inria ADT named SW2D-Lemon. This development project led to 2 coding sprints (of 2 weeks each) with the development team in Sophia. Thanks to this project, SW2D is now a C++ platform, with a dedicate GUI.

8.3. International Initiatives

Gwladys Toulemonde is member of the PHC Utique project (with Tunisia) AMANDE (PI Julie Carreau, IRD), 2019-2021. The project AMANDE focuses on stochastic and semi-parametric approaches combined to teledetection for the study of the water stress.

8.3.1. Inria International Labs

Inria Chile. Associate Team involved in the International Lab: NEMOLOCO

Title: NEw MOdeLing tOols for Coastal Oceanography

International Partner (Institution - Laboratory - Researcher): Pontificia Universidad Católica de Chile (Chile) - CIGIDEN - Rodrigo Cienfuegos

Start year: 2017

See also: https://team.inria.fr/lemon/en/

The NEMOLOCO project targets the improvement of models in the coastal zone. Expected contributions concern: 1) design and implementation of domain decomposition and coupling techniques for coastal modeling; 2) high resolution ocean simulation (including nesting) thanks to the software ROMS-CROCO, applied to biological tracers tracking.

8.3.2. Inria International Partners

8.3.2.1. Informal International Partners

A research collaboration agreement was signed with LSIA, Fès University, Morocco in the framework of Yassine Bel-Ghaddar PhD thesis.

8.4. International Research Visitors

8.4.1. Visits of International Scientists

Carlo Gaetan from the University of Venise in Italy has been invited thanks to the Fraise project one week in april, 2019.

MAGIQUE-3D Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

9.1.1. Partnership with I2M in Bordeaux supported by Conseil Régional d'Aquitaine

title: COFIMUS.

Coordinator:Juliette Chabassier

Other partners: I2M CNRS Université Bordeaux I

The objective is to develop a virtual workshop for wind musical instrument makers.

This project is supported by the Conseil Régional d'Aquitaine, for a duration of 2 years and has funded the postdoctoral position of Augustin Ernoult since March 2019.

9.2. National Initiatives

9.2.1. Depth Imaging Partnership

Magique-3D maintains active collaborations with Total. In the context of Depth Imaging, Magique-3D coordinates research activities dealing with the development of high-performance numerical methods for solving wave equations in complex media. This project has involved 2 other Inria Team-Projects (Hiepacs and Nachos) which have complementary skills in mathematics, computing and in geophysics. DIP is fully funded by Total by the way of an outline agreement with Inria .

In 2014, the second phase of DIP has begun. Lionel Boillot has been hired as engineer to work on the DIP platform. Six PhD students have defended their PhD since 2014 and they are now post-doctoral researchers or engineers in Europe. DIP is currently employing 2 PhD students and one post-doctoral researcher.

9.2.2. PRE Concert

Magique 3D is hosting an Inria "exploratory research project" (PRE) about modeling and designing wind musical instruments. This project has funded the post-doctoral position of Robin Tournemenne from July 2017 until July 2019.

9.2.3. ANR Num4Sun

The ANR has launched a specific program for supporting and promoting applications to European or more generally International projects. Magique-3D has been selected in 2016 after proposing a project to be applied as a FET project on the occasion of a call that will open in 2017 April. This project will gather researchers of the MPS (https://www.mps.mpg.de/en), of the BSC (https://www.bsc.es/), of the BCAM (http://www.bcamath.org/en/), of Heriot-Watt University (https://www.hw.ac.uk/) and Inria teams.
A kick-off meeting has been held in November 2016 in Strasbourg and a second one in Paris in July 2017. Thanks to this support, we have submitted a ETPHPC proposal in September 2017 The project is funded for 18 months starting from August 2016. The funding amounts 30000€.

9.2.4. Grant from Fondation Blaise Pascal

The project Louis 14.0 has been selected by the Fondation Blaise Pascal as one of their supported projects for 2019. See more about the project at https://project.inria.fr/louis14point0/, in french.

9.3. European Initiatives

9.3.1. FP7 & H2020 Projects

9.3.1.1. Mathrocks

Title: Multiscale Inversion of Porous Rock Physics using High-Performance Simulators: Bridging the Gap between Mathematics and Geophysics

Program: H2020

Duration: April 2018 - March 2022

Coordinator: Universidad Del Pais Vasco (EHU UPV)

Partners:

Bcam - Basque Center for Applied Mathematics Asociacion (Spain)

Barcelona Supercomputing Center - Centro Nacional de Supercomputacion (Spain)

Universidad Del Pais Vasco Ehu Upv (Spain)

Universitat Politecnica de Catalunya (Spain)

REPSOL SA (Spain)

Pontificia Universidad Catolica de Valparaiso (Chile)

Curtin University of Technology (Australia)

The University of Texas System (USA)

University Nacional de Columbia (Colombia)

Pontificia Universidad Catolica de Chile (Chile)

Universidad Central de Venezuela (Venezuela)

University de Buenos Aires (Argentina)

Macquarie University (Australia)

Inria contact: Hélène BARUCQ

We will develop and exchange knowledge on applied mathematics, high-performance computing (HPC), and geophysics to better characterize the Earth´s subsurface. We aim to better understand porous rocks physics in the context of elasto-acoustic wave propagation phenomena. We will develop parallel high-continuity isogeometric analysis (IGA) simulators for geophysics. We will design and implement fast and robust parallel solvers for linear equations to model multi-physics electromagnetic and elasto-acoustic phenomena. We seek to develop a parallel joint inversion workflow for electromagnetic and seismic geophysical measurements. To verify and validate these tools and methods, we will apply the results to: characterise hydrocarbon reservoirs, determine optimal locations for geothermal energy production, analyze earthquake propagation, and jointly invert deep-azimuthal resistivity and elasto-acoustic borehole measurements. Our target computer architectures for the simulation and inversion software infrastructure consists of distributed-memory parallel machines that incorporate the latest Intel Xeon Phi processors. Thus, we will build a hybrid OpenMP and MPI software framework. We will widely disseminate our collaborative research results through publications, workshops, postgraduate courses to train new researchers, a dedicated webpage with regular updates, and visits to companies working in the area. Therefore, we will perform a significant role in technology transfer between the most advanced numerical methods and mathematics, the latest super-computer architectures, and the area of applied geophysics.

9.4. International Initiatives

9.4.1. Inria Associate Teams Not Involved in an Inria International Labs

9.4.1.1. ANTS

Title: Advanced Numerical meThods for helioSeismology

International Partner (Institution - Laboratory - Researcher):

Max Plank Institut für Sonnensystemforschung (Germany) – Department Solar and Stellar Interiors – Laurent Gizon.

Start year: 2019

See also: https://team.inria.fr/ants/

Magique-3D has started an Associate Team project, ANTS (Advanced Numerical meThods for helioSeismology), with the Max Planck Institute for Solar System Research (MPS), led by Laurent Gizon. This helps promote the collaboration between Magique3D and the Solar group at the Max Planck Institute for Solar System Research at Göttingen (MPS) for the direct and inversion of solar models from Doppler data obtained at the surface of the Sun. The scientific project benefits from the expertise of Magique-3D in seismic imaging, and the expert knowledge of the MPS group on Solar physics, in order to design accurate and efficient methodology. A joint workshop was held at Inria Bordeaux Sud-Ouest in December 2019: https://project.inria.fr/antsworkshop201912/.

9.4.2. Inria International Partners

9.4.2.1. New international partner: The Berkeley Seismological Laboratory, University of California, Berkeley.

In September 2019, together with Barbara Romanowicz at the University of California Berkeley https://seismo.berkeley.edu/, we initiated a collaboration aiming at developing and deploying novel tomographic methods for imaging localized structures in the deep Earth that are either blurred out or not visible in the current global models.This effort is supported by the France-Berkeley Fund which granted our project for a period of 2 years. Amount: 11000€, Management: Berkeley University url: https://fbf.berkeley.edu/project/development-and-application-advanced-seismic-imaging-techniques-key-target-structures-deep

9.4.2.2. Declared Inria International Partners

9.4.2.2.1. MAGIC2

Title: Advance Modeling in Geophysics

International Partner (Institution - Laboratory - Researcher):

California State University at Northridge (United States) - Department of Mathematics - Djellouli Rabia

The Associated Team MAGIC was created in January 2006 and renewed in January 2009. At the end of the program in December 2011, the two partners, MAGIQUE-3D and the California State University at Northridge (CSUN) decided to continue their collaboration and obtained the “Inria International Partner” label in 2013.

See also: https://project.inria.fr/magic/

The ultimate objective of this research collaboration is to develop efficient solution methodologies for solving inverse problems arising in various applications such as geophysical exploration, underwater acoustics, and electromagnetics. To this end, the research program will be based upon the following three pillars that are the key ingredients for successfully solving inverse obstacle problems. 1) The design of efficient methods for solving high-frequency wave problems. 2) The sensitivity analysis of the scattered field to the shape and parameters of heterogeneities/scatterers. 3) The construction of higher-order Absorbing Boundary Conditions. In the framework of Magic2, Rabia Djellouli (CSUN) visited Magique 3D in February 2018

9.5. International Research Visitors

9.5.1. Visits of International Scientists

- Vianey Villamizar (Department of Mathematics, Brigham Young University) visited the team in September 2019

- Mounir Tlemcani (Université d'Oran, Algeria) visited Magique 3D in March 2019.
- Sevan Adourian (Univesity of California, Berkeley) visited Magique 3D for a week in June 2019, this visit has been sponsored by the France-Berkeley Fund.

9.5.2. Visits to International Teams

9.5.2.1. Research Stays Abroad

- Nathan Rouxelin visited MPS at Göttingen in April 2019, during a month.
- Rose-Cloé Meyer visited prof. Steve Pride from Lawrence Berkeley National Laboratory in June 2019 during 1 month and in December 2019 during 3 weeks.
- In the framework of DIP, Pierre Jacquet visited Total Research Center at Houston, USA, in December 2019 during 1 week.
- Yder Masson, visited Barbara Romanowicz at the Berkeley Seismological Laboratory and Steve R. Pride at the Lawrence Berkeley Laboratory for two days the week following the AGU Fall Meeting Dec 9-13, 2019 , San Francisco, CA, USA)

SERENA Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

MILC (DMI RFSI, 2018–2019): "Mesure et Intégrale de Lebesgue en Coq", with LIPN (Université de Paris 13), and TOCCATA (Inria Saclay - Île-de-France). SERENA representants are François Clément and Vincent Martin (UTC).

GiS: scientific collaboration network between ten public institutions from the Paris (Ile-de-France) region, focused on natural resources and environment. The project-team SERENA is a member.

9.2. European Initiatives

9.2.1. FP7 & H2020 Projects

- ERC GATIPOR: "Guaranteed fully adaptive algorithms with tailored inexact solvers for complex porous media flows". The subject of this consolidator grant are new approaches to porous media multiphase flows: inexact Newton-multigrid solvers, local stopping criteria, adaptivity, and a posteriori error control. The goal is to guarantee the overall simulation error and to speed-up importantly the present-day simulations. SERENA representant is M. Vohralík (grant leader, 75% commitment), period 2015–2020.
- ERC EMC2: " Extreme-scale Mathematically-based Computational Chemistry". The goal of this project is to develop physical and chemical models in chemistry, condensed matter physics, molecular biology, materials science, and nanosciences, altogether with mathematically-certified and numerically-efficient algorithms, and to implement them in a scalable way on various computer architectures. There are 4 principal investigators and a little more than 10 co-investigators. SERENA representant is M. Vohralík (co-investigator, 10% commitment), period 2019–2025.

9.3. International Initiatives

9.3.1. Inria International Partners

9.3.1.1. Informal International Partners

Erik Burman, Professor, University College London, unfitted methods.

Ulrich Rüde, Professor, University of Erlangen-Nürnberg, multigrid methods.

Iain Smears, Lecturer, University College London, local-global approximations.

Benjamin Stamm, Professor, RTWH Aachen University, eigenvalue problems (first-principle molecular simulation).

Barbara Wohlmuth, professor, Technical University Munich, multigrid methods.

9.3.2. Participation in Other International Programs

9.3.2.1. Inria International Chairs

IIC GUERMOND Jean-Luc

Title: Curved H(div), H(curl) elements, and magnetohydrodynamics & Approximation of hyperbolic systems

International Partner (Institution - Laboratory - Researcher):

Texas A&M University (United States) - Department of Mathematics - Jean-Luc Guermond

Duration: 2019 - 2023

Start year: 2019

See also: https://www.math.tamu.edu/~guermond/

The program is articulated around two themes: (1) Theoretical aspects in finite elements and applications to multi-physics magneto-hydrodynamics; (2) Finite element approximation of hyperbolic systems and applications. The results from this research will have applications in problems related to porous media flows, magnetohydrodynamics, water management, and compressible and incompressible fluid flows.

9.4. International Research Visitors

9.4.1. Visits of International Scientists

Hend Ben Ameur, Professor at IPEST and member of ENIT-Lamsin, Tunis, Tunisia, November 4–15.

Gregor Gantner, Vienna University of Technology. Collaboration on IGA methods. September 23–27.

Thirupathi Gudi, Indian Institute of Science, Bangalore. Collaboration on local-global approximations. June 10–17.

Dirk Praetorius, Vienna University of Technology. Collaboration on cost-optimality of fully adaptive algorithms. March 21–23.

Ivan Yotov, Professor, University of Pittsburgh. Inria Paris invited professor, September 1–December 15, 2019. Collaboration on multilevel and space-time domain decomposition methods.

9.4.1.1. Internships

Théo Kaprélian, internship at Ecole Centrale de Lyon, from September 2019 to February 2020, supervised by Martin Vohralík.

9.4.2. Visits to International Teams

9.4.2.1. Research Stays Abroad

+ Géraldine Pichot was invited for a one week stay at Pennstate University, USA for a collaboration with Pr. Ludmil Zikatanov.
+ Géraldine Pichot was invited for a one week stay at University of Bergen, Norway for a collaboration with Pr. Florin Radu.

STEEP Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. QAMECS / MOBIL'AIR : ATMOSPHERIC POLLUTION: Characterization of novel exposure markers, of biological, health, economic and societal impacts and evaluation of public policies

Project funded by ADEME, Grenoble metropolis, IDEX Université Grenoble Alpes
Duration: 2016–2022
Project coordinator: Remy Slama (INSERM) and Sandrine Mathy (GAEL, CNRS). Inria Coordinator: Emmanuel Prados
Other partners: Air Rhône-Alpes, CNRS, Sciences Po Grenoble, Inserm, IAB, Université Grenoble-Alpes
Abstract: Urban atmospheric pollution is one of the main threats to human health that can be to some extent controlled by public action. In Europe, many cities have implemented various types of low emission zones (LEZ, focused on traffic and heating emissions), France being a notable exception. Although fine particulate matter (PM2.5) is usually assessed through its mass concentration, other metrics, such as PM chemical speciation as well as the so far little considered oxidative potential (OP) of PM, are worth considering, both in terms of associations with human health and in the context of monitoring of the efficiency of LEZ. QAMECS covers all dimensions from atmospheric emissions, impact of meteorological conditions on air pollution human behaviours related to transportation, environmental levels, health, associated economic costs and societal awareness. The project relies on environmental measurements, modelling, repeated observational (representative) population studies, an existing mother-child cohort, a controlled human experiment, health impact and related economic assessment. It is conducted by a consortium of specialists of chemistry and physics of air pollution, economics, sociology, epidemiology, geography, in relation with local authorities. It will bring results important for urban planning, public health, and more fundamental research on the measurement of PM and assessment of their biological and health impact.

8.2. National Initiatives

8.2.1. AF Filières : Analyse des Flux des Filières biomasse pour des stratégies régionales de bioéconomie

Project funded by ADEME
Duration: 2017-2019
Coordinator: Jean-Yves COURTONNE (Equipe STEEP, Inria) [Emmanuel Prados (STEEP/Inria) for Inria partner]
Other partners: Equipe STEEP, Inria, Grenoble Rhônalpénergie-Environnement (RAEE), Lyon Laboratoire d'Economie Forestière (LEF), INRA / AgroParisTech Nancy.
Keywords: Environmental assessment, Ecological accounting, Material Flow Analysis, Sustainable supply chains, Multicriteria analysis.
Abstract: Flow analyses of biomass supply chains for regional bioeconomy policies. The goals of the project are the following:

- Improve knowledge on the material flows of the forest-wood and agri-food supply chains in France at national and regional levels,
- Provide a holistic vision of the situation by associating environmental and socio-economic indicators to material flows,
- Provide a more precise assessments (quantitatively and qualitatively) in the case of the Auvergne-Rhône-Alpes region.

8.3. International Initiatives

8.3.1. Inria International Partners

8.3.1.1. Informal International Partners

University of Lausanne (UNIL), Department of Ecology and Evolution (Jérôme Gippet): development of the MoRIS model of propagation of invasive species.

8.3.2. Participation in Other International Programs

Pierre-Yves Longaretti is involved in TARA (Transition adaptation research alliance); he animated the theme *Operationalizing reflexive sustainability* at the TARA Workshop in Bogor, Indonesia, November 2019.

TONUS Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

The thesis of Pierre Gerhard devoted to numerical simulation of room acoustics is supported by the Alsace-region. It is a joint project with CEREMA (Centre d'études et d'expertise sur les risques, l'environnement, lamobilité et l'aménagement) in Strasbourg.

9.2. National Initiatives

9.2.1. National projects

PEPS "initiative Jeunes" CNRS. E. Franck with A. Crestetto (leader), M. Badsi, "Asymptotic scheme for multiscale problems in Plasma".

PEPS "initiative Jeunes" CNRS. C. Courtès with R. Côte (IRMA), P. A. Hervieux (IPCMS), R. Ignat (IMT), G. Manfredi (IPCMS), "Study of the influence of the temperature and the external magnetic field on the magnetization reversal".

9.2.2. HPC resources

Big Challenge GENCI: Simulation of electromagnetic interaction between connected objects and the human body. We solve the 3D Maxwell equations to compute the antena emission Bluetooth Low Energy (BLE) close to the body. The main goal is to scale the computation on the new supercomputer Jean Zay to treat a realistic test case.

9.3. European Initiatives

9.3.1. FP7 & H2020 Projects

Eurofusion project MAGYK, *Mathematics and Algorithms for GYrokinetic and Kinetic models* (2019-2021), led by E. Sonnendrucker.
Participants: L. Navoret

Eurofusion project *Strengthening the non-linear MHD code JOREK for application to key questions of the fusion roadmap* (2019-2021), led by M. Hoelzl.
Participants: E. Franck

BIOCORE Project-Team

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. National programmes

- **ANR-Phycover:** The overall objective of the PHYCOVER project (2014-2018) is to identify a modular wastewater treatment process for the production of biogas. The method combines three modules. First, a high-rate algal pond is dedicated to the treatment of municipal wastewater. Then, an anaerobic digester capable of co-digesting biomass products (and others organic matter resources) to significantly reduce biological and chemical contaminants while producing a sustainable energy as biogas is analysed. A final module transforms the residual carbon, nitrogen and phosphorus into high-value microalgae dedicated to aquaculture and green chemistry.
- **ITE-OPALE:** The goal of the Institut de la Transition Énergétique - OPALE project (2016-2019) is to increase the lipid content of microalgae by specific selection pressure. The project relies on the strain already selected during the Facteur 4 project, whose productivity was 4 times higher than the wild type. We expect to still increase strain performances up to 10 times the productivity of the wild type. This project was unexpectedly arrested by the funding agency on April 2019.
- **ADEME Phytorecolt:** The goal of this project (2017-2019) is to develop an automated and optimized procedure for microalgae harvesting. A project coordinated by H. Bonnefond.
- **ANR-ICycle:** This project (2016-2020) aims at understanding the communication pathways between the cell division cycle and the circadian clock, using mathematical modeling and control theory to construct and implement two coupled synthetic biological oscillators. Project coordinated by M. Chaves.
- **ANR - Maximic:** The goal of the project (2017-2021) is to design and implement control strategies in a bacterium for producing at maximal rate a high value product. It is coordinated by H. de Jong (IBIS Grenoble), and involves members of Biocore and McTao.
- **Plan Cancer - Imodrez:** The objective of this project (2018-2021) is to understand cancer drug response heterogeneity using tumor single-cell dynamics and developing mathematical models and computational approaches. A project coordinated by J. Roux (IRCAN) and funded by Inserm - Plan Cancer.
- **SIGNALIFE:** Biocore is part of this Labex (scientific cluster of excellence) whose objective is to build a network for innovation on Signal Transduction Pathways in life Sciences, and is hosted by the University of Nice Sophia Antipolis.
- **UMT FIORIMED:** FioriMed is a Mixed Technology Unit created in January 2015 to strengthen the production and dissemination of innovation to the benefit of ornamental horticulture. Horticultural greenhouses are seen as a "laboratory" for the actual implementation of agroecology concepts with the possibility of generic outcomes being transfered to other production systems. The main partners of UMT FioriMed are ASTREDHOR (National Institute of Horticulture) and the ISA Joint Research Unit of INRA-CNRS-Univ. Nice.
- **EcoPhyto - CeraTIS Corse:** “Territorial management of the Mediterranean fruit fly in Corsica by the Sterile Insect Technique” (2020-2022). This project is based on a pilot field experiment of sterile male releases and it integrates population dynamics and socio-economic approaches.
- **EcoPhyto - INTERLUDE:** “Territorial innovations to reduce phytoparmaceutical products for the sustainable production of vegetable crops” (2020-2022). BIOCORE members participate in a case study that focuses on the agroecological management of soil pests and pathogens in Provence.

9.1.2. Inria funding

- **Inria Project Lab, Algae** *in silico***:** (2014-2019) The Algae in silico Inria Project Lab, funded by Inria and coordinated by O. Bernard, focuses on the expertise and knowledge of biologists, applied mathematicians and computer scientists to propose an innovative numerical model of microalgal culturing devices. The latest developments in metabolic modeling, hydrodynamic modeling and process control are joined to propose a new generation of advanced simulators in a realistic outdoor environment. The project gathers 5 Inria project teams and 3 external teams.
- **Inria Project Lab, Cosy:** (2017-...) This proposal aims at exploiting the potential of state-of-art biological modeling, control techniques, synthetic biology and experimental equipment to achieve a paradigm shift in control of microbial communities. We will investigate, design, build and apply an automated computer-driven feedback system for control of synthetic microbial communities, not just accounting for but rather leveraging population heterogeneity in the optimal accomplishment of a population-level task. The development of methodologies of general applicability will be driven by and applied to two different applications closely connected with real-world problems in the biomedical and biotechnological industry. The consortium is composed of the four Inria project-teams IBIS, BIOCORE, COMMANDS, VALSE, INBIO, as well as the external partners BIOP (Université Grenoble Alpes, including members of IBIS), MaIAge (INRA), and YoukLAB (TU Delft).

9.1.3. INRA funding

- **MoGeR:** “From knowledge to modeling: towards a user-friendly simulation tool to test crop resistance management scenarios in the Phoma-oilseed rape case study”, INRA Metaprogramme SMaCH, 2017–2019. This is a follow-up of the K-Masstec project, which focused on sustainable strategies for the deployment of genetic resistance in the field, based on molecular knowledge on avirulence genes.
- **ABCD:** INRA SPE is funding the project ABCD "Augmentative Biological Control; optimizing natural ennemies Deployment" (2017-2019) in which Biocore is a partner with INRA Sophia Antipolis.
- **IMMUnE:** INRA SPE is funding the project IMMUnE "Immunité et Modélisation Mathématique pour Unifier l’Epidémiologie" (2019-2021), headed by F. Hamelin (Agrocampus Ouest), in which BIOCORE is a partner.

9.1.4. Networks

- **ModStatSAP:** The objective of this INRA network is to federate researchers in applied mathematics and statistics and to promote mathematical and statistical modeling studies in crop and animal health. S. Touzeau is a member of the scientific committee.
- **Seminar:** BIOCORE organizes a regular seminar “Modeling and control of ecosystems” at the station zoologique of Villefranche-sur-Mer, at INRA-ISA or at Inria.

9.2. European Initiatives

9.2.1. Collaborations in European Programs, Except FP7 & H2020

Program: **PHC-Pessoa** Partenariat Hubert Curien with Portugal, managed by Campus France

Project acronym: **LTSB**

Project title: Logic Tools for Systems Biology

Duration: 01/2019 - 12/2019

Coordinator: M. Chaves

Other partners: M.A. Martins, University of Aveiro

Abstract: This project aims at developing Boolean, piecewise linear and other hybrid tools for analysis of biological networks.

9.2.2. Collaborations with Major European Organizations

Imperial college, Department of Chemical engineering (UK),

Modelling and optimization of microalgal based processes.

University of Padova, Italy.

Modelling and control of microalgal production at industrial scale.

9.3. International Initiatives

9.3.1. Inria International Labs

Inria Chile

Associate Team involved in the International Lab:

9.3.1.1. GREENCORE

Title: Modelling and control for energy producing bioprocesses

International Partners (Institution - Laboratory - Researcher):

PUCV (Chile) - Escuela de Ingenieria Bioquimica (EIB) - David Jeison

UTFSM (Chile) - Departamento de Matematica - Pedro Gajardo

Univ. Chile (Chile) - Centro de modelacion matematica - Hector Ramirez

Inria coordinator: O. Bernard

Start year: 2014

See also: https://team.inria.fr/eagreencore/

The worldwide increasing energy needs together with the ongoing demand for CO2 neutral fuels represent a renewed strong driving force for the production of energy derived from biological resources. In this scenario, the culture of oleaginous microalgae for biofuel and the anaerobic digestion to turn wastes into methane may offer an appealing solution. The main objective of our proposal is to join our expertise and tools, regarding these bioprocesses, in order to implement models and control strategies aiming to manage and finally optimize these key bioprocesses of industrial importance. By joining our expertise and experimental set-up, we want to demonstrate that closed loop control laws can significantly increase the productivity, ensure the bioprocess stability and decrease the environmental footprint of these systems. This project gathers experts in control theory and optimization (BIOCORE, UTFSM) together with experts in bioprocesses (PUCV and CMM) and software development.

International Laboratory for Research in Computer Science and Applied Mathematics

Associate Team involved in the International Lab:

9.3.1.2. EPITAG

Title: Epidemiological Modelling and Control for Tropical Agriculture

International Partner (Institution - Laboratory - Researcher):

Université de Douala (Cameroon) - Département de Mathématique et Informatique - Samuel Bowong

Inria coordinator: S. Touzeau

Start year: 2017

See also: https://team.inria.fr/epitag/

EPITAG gathers French and Cameroonian researchers, with a background in dynamical systems and control and with an interest in crop diseases. Crop pests and pathogens are responsible for considerable yield losses and represent a threat to food security. Their control is hence a major issue, especially in Cameroon, where agriculture is an important sector in terms of revenues and employment. To help design efficient strategies for integrated pest management, mathematical models are particularly relevant. Our main objective is to study the epidemiology and management of tropical crop diseases, with a focus on Cameroon and Sub-Saharan Africa. Our approach consists in developing and analysing dynamical models describing plant-parasite interactions, in order to better understand, predict and control the evolution of damages in crops. To ensure the relevance of our models, field experts and stakeholders need to be closely associated. We will focus on pest and pathogens that affect major staple food and cash crops, such as cocoa plant mirids, plantain and banana plant-parasitic nematodes, coffee berry borers, coffee leaf rust, maize stalk borers, cabbage diamondback moths, papaya mealybugs, etc. To tackle these issues, we jointly supervise master and PhD students.

9.3.2. Inria International Partners

- NTNU (Norwegian University of Science and Technology), Trondheim, Norway. The project involves turning wastes into bioenergy with anaerobic digestion. O. Bernard spent a one year sabbatical at NTNU in the Enersene group working on renewable energy.

9.3.3. Participation in Other International Programs

- Univ. Ben Gurion : Microalgal Biotechnology Lab (Israel), Member of the ESSEM COST Action ES1408 European network for algal-bioproducts (EUALGAE). Modelling of photosynthesis.

9.4. International Research Visitors

9.4.1. Visits of International Scientists

Daniel Figueiredo, University of Aveiro, Portugal, 02-06 Sep. 2019. Visit in the context of PHC-Pessoa project to work on the development of logical tools for systems biology.

Israël Tankam Chedjou, University of Yaoundé 1, Cameroon, Feb.-Jun. 2019. Visit in the context of the EPITAG associate team.

Yves Fotso Fotso, University of Dschang, Cameroon, Mar.-Jul. 2019. Visit in the context of the EPITAG associate team.

Clotilde Djuikem, University of Douala, Cameroon, Mar.-Jul. 2019. Visit in the context of the EPITAG associate team.

9.4.2. Visits to International Teams

9.4.2.1. Sabbatical programme

O. Bernard spent a one year sabbatical at NTNU (Norwegian University of Science and Technology), Trondheim, Norway. He worked on a project to turn wastes into bioenergy with anaerobic digestion.

9.5. Project-team seminar

BIOCORE organized a 3-day seminar in September at Peyresq (Alpes-de-Haute-Provence). On this occasion, every member of the project-team presented his/her recent results and brainstorming sessions were organized.

CARMEN Project-Team

8. Partnerships and Cooperations

8.1. Regional Initiatives

The project "Cardiac Arrhythmia Localization Methods," granted by the Région Nouvelle-Aquitaine, with matching from funds held by our clinical collaboraters H. Cochet and P. Jaïs, has started. The purpose of this project is to develop a tool that can predict the exit site of an arrhythmia with moderate accuracy (1 cm) in an absolute sense, with respect to the anatomy of the heart in situ, and with a resolution of about 2 mm in a relative sense, with respect to a nearby pacing site. This tool must fulfill the following criteria:

- it uses only data that are already recorded in the cathlab by other systems: ECG data and electroanatomical mapping data;
- it must work in nearly real-time; catheter displacement advice must be available within 5 seconds after a paced beat;
- it must work automatically, requiring the operator only to indicate which ECG data correspond to the target arrhythmia; and
- it must be safe and easy to operate.

We will in the first place test a number of proposed methods using synthetic data, produced with our realistic models of cardiac electrophysiology and accurate geometric models of different patients. This in-silico testing phase will answer a number of important practical questions. Subsequently we will use offline clinical data, and within 2 years we aim to build a clinical prototype that can be tested (without interfering in the procedure) in the cathlab. In order to work real-time we will initially use very simple methods. However, the clinical prototype and the collectoin of synthetic data that we created will later serve also as a platform to test also more sophisticated inverse methods.

8.2. National Initiatives

8.2.1. ANR EXACARD

We started a collaboration with the STORM team at Inria Bordeaux Sud-Ouest to work on further scaling of the Propag code, to push the limit from about 10^4 to 10^6 parallel processors. A proposal for this project was funded this year by ANR. It allows a postdoc to be employed for 2 years.

8.2.2. ANR MITOCARD

The MITOCARD project (Electrophysiology of Cardiac Mitochondria), coordinated by S. Arbault (Université de Bordeaux, ISM), was granted by the ANR in July 2017. The objective of MITOCARD is to improve understanding of cardiac physiology by integrating the mitochondrial properties of cell signaling in the comprehensive view of cardiac energetics and rhythm pathologies. It was recently demonstrated that in the heart, in striking contrast with skeletal muscle, a parallel activation by calcium of mitochondria and myofibrils occurs during contraction, which indicates that mitochondria actively participate in Ca2+ signaling in the cardiomyocyte. We hypothesize that the mitochondrial permeability transition pore (mPTP), by rhythmically depolarizing inner mitochondrial membrane, plays a crucial role in mitochondrial Ca2+ regulation and, as a result, of cardiomyocyte Ca2+ homeostasis. Moreover, mitochondrial reactive oxygen species (ROS) may play a key role in the regulation of the mPTP by sensing mitochondrial energetics balance. Consequently, a deeper understanding of mitochondrial electrophysiology is mandatory to decipher their exact role in the heart's excitation-contraction coupling processes. However, this is currently prevented by the absence of adequate methodological tools (lack of sensitivity or selectivity, time resolution, averaged responses of numerous biological entities). The MITOCARD project will solve that issue by developing analytical tools and biophysical approaches to monitor kinetically and quantitatively the Ca2+ handling by isolated mitochondria in the cardiomyocyte.

MITOCARD is a multi-disciplinary project involving 4 partners of different scientific fields: the CARMEN team as well as

ISM, the largest chemistry laboratory of the Université de Bordeaux, where the necessary measurement methods will be developed;

Liryc, where mitochondria are studied at all levels of integration from the isolated mitochondrion to the intact heart; and

LAAS, the MiCrosystèmes d'Analyse (MICA) group at the Laboratory of Analysis and Architecture of Systems, which develops the biological microsensors for this project.

The project will

- develop chips integrating 4 different electrochemical microsensors to monitor in real-time key mitochondrial signaling parameters: Ca2+, membrane potential, quinone reduction status, O2 consumption, and ROS production;
- develop microwell arrays integrating ring nanoelectrodes to trap single mitochondria within micrometric chambers and measure locally by combined fluorescence microscopy and electrochemical techniques intra- (by fluorescence) and extra-mitochondrial (electrochemistry) metabolites; and
- develop a mathematical model of mitochondrial Ca2+ and ROS handling built on existing knowledge, new hypotheses, and the measured data.

The model may serve both to assess biological assumptions on the role of mitochondria in Ca2+ signaling and to integrate pathological data and provide clues for their global understanding.

8.2.3. GENCI

GENCI (*grand équipement national de calcul intensif*) is the agency that grants access to all national high-performance resources for scientific purposes in France. GENCI projects have to be renewed yearly. Our project renewal *Interaction between tissue structure and ion-channel function in cardiac arrhythmia*, submitted in September 2018, has been granted 8 million core-hours on the three major systems Irene, Occigen, and Turing. This compute time is primarily destined for our research into the interaction between ionic and structural heart disease in atrial fibrillation, Brugada syndrome, and early repolarisation syndrome [7] [71], and for new HPC developments [72].

8.2.4. PHRCN Multi-centric project

This project has been accepted for funding in December 2019. N Zemzemi is partner of the project and Prof. Emmanuel Cuny (PU-PH CHU de Bordeaux) is the Principal investigator. It is entitled "Deep brain stimulation for Parkinson disease: Probabilistic STN Targeting under general anaesthesia without microelectrode recordings (MER) vs current surgical procedure." It will start in 2020 and end in 2023.

8.2.5. BOUM project on ECGi

This project is coordinated by 2 PhD students (A. Karoui and O. Bouhamama) and 1 postdoc (M. Diallo), and is funded by the French applied and industrial math society (SMAI). It consists in organizing a national workshop on ECGI.

8.2.6. Inria Ciescard project

This project entitled "Combiner des Information Electriques et Structurelles pour aider les cardiologues à mieux Cibler la thérApie caRDiaque" funds an engineer for 2 years to develop some plugins in the software platform Music. The PI is N. Zemzemi.

8.2.7. Inria project OptimDBS

This project is designed to develop a software for the prediction of the optimal Deep stimulation targets based on machine learning techniques. It is funded by Inria as part of the ATT program. The PI is N. Zemzemi

8.3. Transfert

Together with Prof. Emmanuel Cuny and the help of AST (Aquitaine Science Transfert) and Inria Startup Studio, we are working on the creation of a startup company based on the software OptimDBS, and an associated the submitted patent. We follow the Founders 101 program of Inria to help us with the business, marketing, and management parts. The associated patent entitled Méthode de détermination d'une cible cérébrale stéréotaxique has been submitted to INPI by N. Zemzemi, J. Engelhardt, and E. Cuny under the number 71959FR. Our Software is currently used for the treatment of Essential Trauma in a Phase I clinical study at the CHU de Bordeaux and CHU de Lyon. A new PHRC-National multi-centric project has been accepted in December 2019 (see above, funded projects). This project is led by Emmanuel Cuny and aims at assessing the efficiency of our solution in the treatment of Parkinson Disease. The OptimDBS software will be used by 11 medical centers in France.

8.4. European Initiatives

8.4.1. Collaborations in European Programs, Except FP7 & H2020

Program:MSCA-ITN
Project title: "Personalized Therapies for Atrial Fibrillation. A Translational Approach."
Start Feb 2020 - End 2024
Coordinator: for UB/Liyrc: N. Zemzemi, PI: M. Guillem (University of Valencia, Spain)

8.4.2. Collaborations with Major European Organizations

BCAM (Basque Center for Applied Mathematics), Bilbao, Spain: L. Gerardo-Giorda.
We develop surrogate models of Radiofrequency Catheter Ablation for machine learning purposes, with the ambition to provide real-time estimations of lesion depths to clinicians (M. Leguèbe, Y. Coudière).

8.5. International Initiatives

8.5.1. Inria International Labs

International Laboratory for Research in Computer Science and Applied Mathematics
Associate Team involved in the International Lab:

8.5.1.1. EPICARD

Title: inversE Problems In CARDiac electrophysiology
International Partner (Institution - Laboratory - Researcher):

ENIT (Tunisia) - Department of Intelligence Science and Technology - Mourad Bellassoued

Start year: 2018
See also: https://team.inria.fr/carmen/epicard/
Model personalization is a very challenging question in the numerical modeling community, especially for medical applications like cardiac electrophysiology. Our main idea is to adapt the input data like model parameters and boundary conditions of the electrophysiological measurements. There are two mathematical problems raising from this challenge. The first issue is the identifiability of the parameters and the sensitivity of the identification problem to the measured data. The question is: For given measurements, could we prove that there exist a set of parameters that allows to fit these measurements? The second issue is, how can we estimate parameters, when they are identifiable,? Our idea is to provide a theoretical analysis for the identification of each of the parameters and to construct suitable numerical methods to estimate them.

8.5.1.2. Informal International Partners

Y. Coudière works with the group of Prof. Y. Bourgault from the Department of Mathematics and Statistics of the University of Ottawa (Canada). Some results on the numerical analysis of time-stepping methods from C. Douanla's PhD were carried out together, as well as some theoretical results on parameter identification in the PhD of A. Gérard.

M. Potse works with the group of Prof. U. Schotten at Maastricht University (The Netherlands) and the Center for Computational Medicine in Cardiology at the *Università della Svizzera italiana* (Lugano, Switzerland) on simulation studies of atrial fibrillation [60]. The Maastricht group was partially funded by the FP7 project EUTRAF and our simulations were supported by GENCI (section 8.2.3).

N. Zemzemi works with Cesare Corrado at King's College London on the development of new eikonal models allowing conduction velocity adaptation [55].

Mostafa Bendahmane works with Kenneth H. Karlsen at university of Oslo (Norway) on the stochastic bidomain model in electrocardiology [46].

8.6. International Research Visitors

8.6.1. Visits of International Scientists

- Yassine Abidi, Ecole Nationale d'Ingénieurs de Tunis, Jun 2019,
- Abir Amri, Tunis El Manar University, from May 2019 until Jun 2019,
- Veronica Anaya, Universidad Nacional Autonoma de Mexico, from Jun 2019 until Jul 2019
- Yves Bourgault, University of Ottawa, Jun 2019
- Elmahdi Erraji, Cadi Ayyad University, Jun 2019
- Moncef Mahjoub, Tunis El Manar University, from Oct 2019 until Nov 2019

COMMEDIA Project-Team

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. ANR

9.1.1.1. ANR Project "IFSMACS"

Participants: Muriel Boulakia, Céline Grandmont [local coordinator].

Period: 2015-2019.
The objective of this project, coordinated by Takéo Takahashi (Inria Nancy Grand-Est), is the mathematical analysis of systems involving structures immersed in a fluid. This includes the asymptotic analysis, the study of the controllability and stabilization of fluid-structure interaction systems, the understanding of the motion of self-propelled structures and the analysis and development of numerical methods to simulate fluid-structure systems.

9.1.1.2. ANR Project "ADAPT"

Participants: Maria Fuente-Ruiz, Damiano Lombardi [coordinator], Olga Mula.

Period: 2018-2022.
Adaptive Dynamical Approximations by Parallel Tensor methods. The main goal of the ANR is to investigate the numerical approximation of the solution of high-dimensional problems. In particular, the applications that motivate this study are the Uncertainty Quantification and the Kinetic theory. The main objective is to construct in an adaptive way parsimonious discretisations starting from arbitrarily chosen separated discretisations.

DRACULA Project-Team

6. Partnerships and Cooperations

6.1. Regional Initiatives

- The Région ARA project INGERENCE dedicated to “INferring GEne REgulatory NEtworks from single CEll Data to improve vaccine design", 2018-2021.
  Participants: Olivier Gandrillon, Fabien Crauste [Coordinator].

6.2. National Initiatives

6.2.1. ANR

- ANR SinCity “Single cell transcriptomics on genealogically identified differentiating cells” (https://anr.fr/Projet-ANR-17-CE12-0031), 2017-2020.
  Participant: Olivier Gandrillon [Coordinator].
- Olivier Gandrillon participates in the ANR MEMOIRE (head Jacqueline Marvel) dedicated to “MultiscalE MOdeling of CD8 T cell Immune REsponses”, 2018-2021.

6.2.2. Other projects

- Thomas Lepoutre is a member of the ERC MESOPROBIO (head Vincent Calvez) dedicated to "Mesoscopic models for propagation in biology", 2015-2020: (http://vcalvez.perso.math.cnrs.fr/mesoprobio.html).

6.3. European Initiatives

6.3.1. FP7 & H2020 Projects

- Olivier Gandrillon and Alexey Koshkin participate in the EU RTN network COSMIC (head Antpoine van Kampen) dedicated to “Combatting disorders of adaptive immunity with systems medicine”, 2018-2021, https://cosmic-h2020.eu

6.4. International Initiatives

6.4.1. Inria Associate Teams Not Involved in an Inria International Labs

6.4.1.1. MathModelingHematopoiesis

Title: Mathematical modeling of hematopoietic stem cell dynamics in normal and pathological hematopoiesis with optimal control for drug therapy

International Partner (Institution - Laboratory - Researcher):

Presidency University, Kolkata (India) - Subhas Khajanchi

Start year: 2019

The project proposes to develop and analyse new mathematical models of Hematopoietic Stem Cell population dynamics in normal and pathological hematopoiesis. Two important questions will be explored in this project: i) the biological data concerning the hematopoiesis process evolves constantly, and new understanding modifies the established mathematical models, ii) modeling constraints us to simplify the complicated biological scenarios, which moving away from the reality, but enabling us to reach a certain comprehension of the hematopoiesis process.

The project will shed new light on the different physiological mechanisms that converge toward the continuous regeneration of blood cells, for example: the behavior of hematopoietic stem cells under stress conditions, the understanding of deregulation of erythropoiesis under drug treatments (this can lead to lack of red blood cells (anemia), or a surplus of red blood cells (erythrocytoses)), the appearance of oscillations in patients with Chronic Myeloid Leukemia (CML); Or, the overproduction of blasts in patients with Acute Myeloid Leukemia (AML)). The effect of the immune system and drug therapy in the presence of CML or AML will be included in the model and optimal control method will also be used.

6.4.2. Participation in Other International Programs

6.4.2.1. Indo-French Center of Applied Mathematics

Title: Mathematical modeling of hematopoiesis process in application to chronic and acute myelogenous leukemia

International Partner (Institution - Laboratory - Researcher):

Department of Mathematics - Presidency University, Kolkata (India) - Subhas Khajanchi

Duration: 2018 - 2021

Start year: 2018

6.5. International Research Visitors

6.5.1. Visits of International Scientists

Jairo Gomes da Silva, PhD student at Institute of Biosciences, São Paulo State University (UNESP), Botucatu, Brazil, visiting the team for 6 months (from September 2019 to February 2020).

6.5.2. Visits to International Teams

Paul Lemarre is visiting University of California, Merced, USA, in 2019-2020.

M3DISIM Project-Team

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR

ANR JCJC LungManyScale, M. Genet, P. Moireau, D. Chapelle (383 k€) – The lungs' architecture and function are well characterized; however, many fundamental questions remain (e.g., there is no quantitative link between tissue- and organ-level material responses), which represent real health challenges (e.g., Idiopathic Pulmonary Fibrosis is a poorly understood disease, for which a mechanical vicious cycle has been hypothesized, but not demonstrated). The general objective of this project is twofold: (i) scientifically, to better understand pulmonary mechanics, from the alveola to the organ in health and disease; (ii) clinically, to improve diagnosis and prognosis of patients through personalized computational modeling. More precisely, This project aims at developing a many-scale model of the pulmonary biomechanics, linked by computational nonlinear homogenization. The model will integrate the experimental and clinical data produced by partners, through an estimation pipeline that will represent augmented diagnosis and prognosis tools for the clinicians.

ANR ODISSE, P. Moireau, S. Imperiale (154 k€) – Motivated by some recent developments from two different fields of research, that is, observer design for finite-dimensional systems and inverse problems analysis for some PDE systems, the ODISSE project aims at developing rigorous methodological tools for the design of estimating algorithms for infinite-dimensional systems arising from hyperbolic PDE systems.

ANR SIMR, P. Moireau, D. Chapelle (97 k€) SIMR is a multi-disciplinary project seeking a better understanding of the biophysical mechanisms involved in mitral valve (MV) regurgitation diseases, to improve decision-making in patients by helping to determine the optimal timing for surgery. This project aims at facing this major issue with the following main two objectives: (1) Evaluate the biophysical consequences of MV repair and (2) Design numerical tools, for cardiac hemodynamics, fluid-structure interaction and myocardium biomechanics to provide an in silico counterpart of the in vivo data obtained by tension measurement and imaging.

8.1.2. Other funding

IPM-MS project (for Imagerie Polarimétrique de Mueller pour la réalisation d'un système original de caractérisation des propriétés mécaniques des Matériaux Structurés), J.M. Allain (50k€ funded by the LABEX Lasips) – This project, which involves the LPICM laboratory (Ecole Polytechnique, CNRS), the LMS (Ecole Polytechnique, CNRS, Mines ParisTech) and the Centre des Matériaux (Mines ParisTech), aims at developing an optical tool to study the link between the mechanical properties of a material and its hierarchical organization. Despite the development of new methods to observe the microstructure, one of the limitations is the number of observations that can be obtained on a given sample in a realistic experimental time. To overcome this difficulty, we are planning to use the Mueller polarimetry to obtain at a fast rate (a few frames per second, compared to a few frames per half-hour) relevant information on the local anisotropy of biological (heart, skin) and composite (short fibers composite) samples.

8.2. European Initiatives

8.2.1. Collaborations with Major European Organizations

Partner 1: Division of Biomedical Engineering & Imaging Sciences (BMEIS), St Thomas' Hospital, King's College London, UK

Clinical-modeling topics mostly encompassing congenital heart diseases (BMEIS) acts as "Other participant" in the Inria Associate team ToFMOD, and R. Chabiniok additionally performs clinical MRI exams at St Thomas' hospital 0.5 days / week.

Partner 2: Department of Mathematics, Faculty of Nuclear Sciences and Physical Engineering, Czech Technical University in Prague, Czech Republic

Model-constrained image registrations, trans-valvular flow in pathological valves.

Partner 3: Institute for Clinical and Experimental Medicine in Prague

Cardiovascular MRI.

8.3. International Initiatives

8.3.1. Inria Associate Teams Not Involved in an Inria International Labs

8.3.1.1. ToFMod

Title: Cardiac Biomechanical Modeling of Chronic Right Ventricular Loading

International Partner (Institution - Laboratory - Researcher):

UT Southwestern Medical Center, Dallas,Texas (United States), Mohammad Tarique Hussain

Start year: 2018

See also: https://m3disim.saclay.inria.fr/associated-team/

This collaboration aims at addressing a crucial issue in cardiology of congenital heart diseases, namely, the optimal timing of pulmonary valve replacement (PVR) in patients with surgically repaired tetralogy of Fallot (ToF) prone to chronic pulmonary regurgitation or right ventricular outflow tract stenosis. Our strategy consists in exploiting the predictive power of biomechanical modeling to shed light in the decision process. We will start by a detailed proof-of-concept study, based on datasets that will be acquired in patients indicated for percutaneous PVR, prior to the procedure, and in the follow-up at 3- and 12-months post-PVR. These datasets will be first used to calibrate the Inria M3DISIM patient-specific heart model simulating a cardiac cycle (at each follow-up time point) to access the myocardial properties – namely, the active contractility and passive stiffness. The instantaneous tissue properties will be statistically analyzed and compared with the level of reverse remodeling – i.e. the positive outcome of PVR. Secondly, the data at each time point will be used to calibrate and further develop the models of long-term tissue remodeling created by the M3DISIM researchers. It is only by combining such invaluable longitudinal data with biomechanical modeling expertise that progress can be achieved in the above objective, indeed.

8.4. International Research Visitors

8.4.1. Invited researchers

- T. Hussain, A. Tandon (Senior researchers at UTSW Medical Center Dallas): joint work in the scope of the Inria Associate team ToFMOD
- F. Regazzoni (3rd year PhD student from MOX, Milan, Italy): From January until March 2019 and from December 2019, joint work on model learning and data assimilation coupling.

MAMBA Project-Team

8. Partnerships and Cooperations

8.1. National Initiatives

Mamba (Marie Doumic and Philippe Robert) participates to the GDR "MeDyna" (mechanisms and dynamics of assemblies of peptides and proteins), coordinated by Stéphane Bressanelli from IBPC.

8.1.1. ANR

8.1.1.1. ANR Blanc 2014-2018 "Kibord"

This project gathers several members of the MAMBA team together with the ENS Cachan and Université Paris-Dauphine on the mathematical study of PDE models with application to biology.

8.1.1.2. ANR iLITE 2016 - 2020

Jean-Charles Duclos-Vallée, Paul Brousse Hospital, Villejuif. Partners are several departments in Paul Brousse Hospital, ENS Cachan, University of Compiègne and several companies all over France, and COMMEDIA team, Inria Paris. The pursued objective is the bioengineering design of an artificial liver intended for liver replacement.

8.1.1.3. ANR InTelo 2017-2020

Telomere dynamics, headed by Teresa Teixeira (IBPC, Paris).

8.1.1.4. INCa/DGOS; PRT-K 2018-2021

Khê HOANG-XUAN, Hôpital Universitaire La Pitié Salpêtrière, Paris. Mathematical modeling at micro and macroscopic level of primary central nervous system lymphomas (PCNSL).

8.1.2. ITMO Cancer 2016 - 2020, HTE call (heterogeneity of tumours in their ecosystems)

8.1.2.1. ITMO Cancer EcoAML

Early leukaemogenesis in Acute Myelogenous Leukaemia (AML), 8 teams headed by François Delhommeau (CDR St Antoine, Paris).

8.1.2.2. ITMO Cancer MoGlImaging

Treatment-induced treatment resistance and heterogeneity in glioblastoma, 8 teams headed by Elizabeth Moyal (INSERM, Toulouse).

8.2. International Initiatives

- **STIC AmSud 20-STIC-05**
  - Title: New Methods for Biological Control of the Arboviruses
  - International Partner (Institution - Laboratory - Researcher):

    CIRAD (Montpellier), UMR MISTEA (Montpellier), Université Paris 13, Université de Bordeaux, Université de Strasbourg, Université Paris-Dauphine - PSL; Universidad de Buenos Aires and Universidad Nacional de Salta (Argentina); Universidad de Chile (Chile); Universidad del Quindio, Universidad Autónoma de Occidente and Universidad del Valle (Colombia); National University of Asuncion (Paraguay).
  - Duration: 2020 - 2021
  - Start year: 2020

  - The main focus of this project is modeling and analysis, using mathematical methods, of new strategies aimed at controling the spread of the dengue fever and other vector-borne diseases similar to Dengue and transmitted by Aedes mosquitoes, like Chikungunya and Zika virus.
  - The key topics are the following.
    * Spatial aspects of biological control techniques
    * Estimation issues for vector-borne epidemics
    * Optimal and non-optimal control approaches for biological control techniques
    * Modelling the effects of conventional control methods on the success of biological control
    * Modelling the competition effects in larval phase during biological control
    * Modelling and efficacy measures for self-propagating genetic interventions
    * Genome-scale models for Wolbachia

- **ERC Advanced grant No 740623 ADORA**

  ADORA is the acronym for *Asymptotic approach to spatial and dynamical organizations*.

  Adora ERC project aims at understanding of spatial, social and dynamical organization of large numbers of agents, presently a fundamental issue in science. ADORA focuses on problems motivated by biology because, more than anywhere else, access to precise and numerous data has opened the route to novel and complex mathematical models. The address ed problems are written in terms of **nonlinear partial differential equations**. The flux-limited Keller-Segel system, the integrate-and-fire Fokker-Planck equation, kinetic equations with internal state, nonlocal parabolic equations and constrained Hamilton-Jacobi equations are among examples of the equations under investigation.

  The role of mathematics is not only to understand the analytical structure of these new problems, but it is also to **explain the qualitative behavior of solutions and to quantify their properties**. The challenge arises here because these goals should be achieved through a hierarchy of scales. Indeed, the problems under consideration share the common feature that the large scale behavior cannot be understood precisely without access to a hierarchy of finer scales, down to the individual behavior and sometimes its molecular determinants.

  Major difficulties arise because the numerous scales present in these equations have to be discovered and singularities appear in the asymptotic process which yields deep compactness obstructions. Our vision is that **the complexity inherent to models of biology can be enlightened** by mathematical analysis and a classification of the possible asymptotic regimes.

  However an enormous effort is needed to uncover the equations intimate mathematical structures, and bring them at the level of conceptual understanding they deserve being given the applications motivating these questions which range from medical science or neuroscience to cell biology.

8.2.1. MaMoCeMa

Title: Mathematical modeling of cell motility and of autophagy

International Partner (Institution - Laboratory - Researcher):

University of Vienna (Austria) - Wolfgang Pauli Institute - Christian Schmeiser

Start year: 2018

Numerous fruitful collaborations have been developed these last years between the WPI and the Inria team MAMBA. Diane Peurichard – newly recruited permanent member of the team MAMBA- worked two years (2016-2017) with Christian Schmeiser -member of the present project- through a post-doctoral contract at the university of Vienna. In collaboration with the biologists of IST, they developed mathematical tools to understand how cells move through adhesion-based and adhesion-free motion with applications in cancer development, prevalent theme of the team MAMBA.

Collaborations WPI-MAMBA have been maintained and ensured by the sabbatical of Marie Doumic (2016-2018) -, working at the university of Vienna with Christian Schmeiser and the PhD student Julia Delacour. They have initiated a collaboration on the mathematical modeling of autophagy, which requires both C. Schmeiser's expertise in biomechanics and M. Doumic's knowledge on aggregation processes. This team will also benefit of the strong links that C. Schmeiser has developed with the two biologists teams of S. Martens (on autophagy) and M. Sixt (on cell movement).

8.2.2. Participation in Other International Programs

- **BMBF (Germany) / LiSym; 2016-2020** LiSym addresses liver diseases and regeneration, namely, steatosis, fibrosis and cirrhosis, and acute on chronic liver failure. (Dirk Drasdo)
- **BMBF (Germany) / MSDILI; 2016-2019** MS-DILI addresses multiscale modeling of drug-induced liver disease focusing on the role of APAP. Dirk Drasdo participates in this project. (Dirk Drasdo)

8.3. International Research Visitors

Visitors in Paris (LJLL) invited by J. Clairambault: Zineb Kaïd, PhD student, University Abou Bekr Belkaïd, Tlemcen, Nov. 25 - Dec. 13; Jean-François Mascari, researcher, IAC-CNR, Rome, Dec. 9-13.

Visitors in Paris (Inria) invited by D. Drasdo: Jieling Zhao, Postdoc from IfADo, Jules Dichamp, Postdoc from ifADo, Paul van Liedekerke, Research engineer from IfADo.

Visitors in Paris (LJLL) invited by D. Peurichard and M. Doumic: P. Degond (Imperial College London) Nov 20 - 22, C. Schmeiser (University of Vienna), Dec. 1 - 7, Claudia Wytrzen (University of Vienna) feb 4-8 2019, M. Tournus and M. Escobedo (February 18-22), .

Visitors in Paris (LJLL) invited by P. A. Bliman: Prof. Héctor Jairo Martínez Romero (Universidade del Valle, Cali, Colombia) for two weeks, together with Oscar Eduardo Escobar Lasso, PhD student who was present one month.

Visitors in Paris (LJLL) invited by B. Perthame: Shugo Yasuda (University of Hyogo, Kobe, Japan), Min Tang (SJTU, China), Maria Caceres (Granada, Spain), Zhenan Zhou (Peking University), Weizhu Bao (Singapore university).

MONC Project-Team

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. Plan Cancer

9.1.1.1. NUMEP

Plan Cancer NUMEP: 2016–2019. Numerics for Clinical Electroporation
Funding: 460 kE.
Partners: Institut de Pharmacologie de Toulouse, CHU J. Verdier de Bondy.
Duration: Octobre 2016—Septembre 2019.
Project leader: C. Poignard
Co-PI: M-P. Rols (IPBS), O. Séror (CHU J. Verdier)

9.1.1.2. Moglimaging

Project acronym - Moglimaging: Modeling of Glioblastoma treatment-induced resistance and heterogeneity by multi-modal imaging.
Partners - Inria Monc, IUCT, Institut Pasteur, Univ. Grenoble, INSERM, Inria Mamba.
Duration - from Nov. 2016 to May 2020.
Coordinator - E. Cohen-Jonathan Moyal, Institut Universitaire du Cancer Toulouse / Local coordinator - O. Saut.
Team participants - S. Benzekry, A. Collin, C. Poignard, O. Saut.

9.1.1.3. Systems Biology of Renal Carcinoma

Title: Plan Cancer Systems Biology of Renal Carcinoma using a Mouse RCC model
Partners : LAMC, INSERM-Univ. Bordeaux.
Duration - June 2018 to June 2021
Team participants: O. Saut, S. Benzekry (co-PI)
Funding: 116.64k€

9.1.1.4. QUANTIC

Plan Cancer QUANTIC: 2020–2022. QUANTitative modeling combined to statistical learning to understand and predict resistance to Immune-checkpoint inhibition in non-small cell lung Cancer.
Funding: 338 k€
Partners: Inria Team MONC, SMARTc (Centre de Recherche sur le Cancer de Marseille, Inserm, CNRS), Assistance Publique Hôpitaux de Marseille
Duration: Décembre 2019 — Décembre 2022
Project leader: S. Benzekry
Co-PI: D. Barbolosi (SMARTc), F. Barlési (AP-HM)

9.1.2. Transnation call: INCA/ARC

Title: Minimally and non-invasive methods for early detection and/or progression of low grade glioma
Partners: Inria Monc, Inria SISTM, INSERM, Humanitas Research Hostital, Univ. Bergen
Acronym: Glioma PRD
Team participants: A. Collin, C. Poignard, O. Saut (local PI)
Total funds: 1M150, Monc's share 275k€.

9.1.3. Competitivity Clusters

Labex TRAIL (http://trail.labex.u-bordeaux.fr): MOD Project Consolidation. 1 2-years post-doc position (100k€), led by A. Collin, 1 PhD funding (100k€) led by O. Saut.

9.2. International Initiatives

9.2.1. Inria International Labs

Inria@SiliconValley
Associate Team involved in the International Lab:

9.2.1.1. Num4SEP

Title: Numerics for Spherical Electroporation

International Partner (Institution - Laboratory - Researcher):

University of California, Santa Barbara (United States) Frederic Gibou

Start year: 2017

See also: http://num4sep.bordeaux.inria.fr/

Electroporation-based therapies (EPTs) consist in applying high voltage short pulses to cells in order to create defects in the plasma membrane. They provide interesting alternatives to standard ablative techniques, for instance for deep seated badly located tumors. However their use is still limited due to a lack of knowledge of tissue electroporation. The goal of the associate team is to focus on the multiscale numerical modeling of spheroid electroporation, in order to provide new insights in electroporation at the mesoscopic scales (spheroids provide interesting tumor-like biological models). Benefiting from the expertise of F. Gibou's team in HPC for multiphysics, and the expertise of the team MONC in tumor growth and cell electroporation modeling, the goal of the associate team Num4SEP is to obtain accurate and efficient numerical tools for the quantitative evaluation of the EPTs at the mesoscopic scale.

9.2.2. Inria Associate Teams Not Involved in an Inria International Labs

9.2.2.1. METAMATS

Title: Modeling ExperimenTAl MetAsTasiS

International Partner (Institution - Laboratory - Researcher):

Roswell Park Cancer Institute (United States) - Department of Cancer Genetics Department of Medicine Department of Pharmacology and Therapeutics (Graduate Program) - John Ebos

Start year: 2017

See also: http://metamats.bordeaux.inria.fr/

The aim of the METAMATS associate team is to bring together a cancer biology experimental laboratory led by John ML Ebos (Roswell Park Cancer Institute) and the inria MONC team composed of applied mathematicians. The Ebos laboratory is specialized in the study of anti-cancer therapeutics (in particular, novel biologically targeted therapeutics such as anti-angiogenics and immunotherapies) on the development of metastases and produces unique, hard-to-obtain data sets on this process' dynamics. The MONC team is specialized in mathematical models in oncology, with a dedicated axis about modeling support and methodological development for analysis of data from preclinical studies. In particular, the work of S. Benzekry puts emphasis on proposing, studying and validating mathematical models of metastatic development under the action of various therapeutic modalities. Indeed, metastatic expansion remains the main challenge in the treatment of cancer and integrative studies combining experiments, mathematical models and clinical data have the potential to yield predictive computational tools of help to assist both the design of clinical trials and clinical oncologists in therapeutic decisions such as the control of the toxicity/efficacy balance or the optimal combination of treatment modalities.

NUMED Project-Team

5. Partnerships and Cooperations

5.1. National Initiatives

INSERM / Plan Cancer 2019 - 2022: Evolutionary Mechanisms of Metabolic Adaptation and Scheduling of Therapy in ONcology (250 kE).

Project: This project combines mathematical models integrating heterogeneous phenotypic and genetic data with multiple in vitro models of cancer evolution. Triple Negative Breast Cancers (TNBC) are unsuited to targeted therapy and display high diversity and resistance. We will thus use 3 existing TNBC models, of common origin but subjected to different tumor initiating oncogenic insults, treated over several generations with two drugs targeting antagonist receptors involved in metabolism. By following phenotypic and genetic properties over time, we aim to uncover and quantify how distinct tumor initiation contexts shape evolutionary trajectories and the emergence of resistance. Using mathematical models and simulations, we will investigate how to optimise therapeutic regimens based on the intrinsic evolutionary properties of each model, before validating our predictions in vivo via murine xenografts. Results: The results of this project will help better characterize the influence of the initiating genetic alterations on the ensuing dynamics of development and resistance in TNBC. It will also pave the way to optimise novel therapeutic strategies aiming to leverage cell metabolism to control tumor evolution in the clinic.

5.2. International Research Visitors

5.2.1. Visits to International Teams

5.2.1.1. Research Stays Abroad

Paul Vigneaux spend one year at UCB (University British Columbia)

REO Team

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR

Irene Vignon Clementel is a member of the project iLite (09/16-10/21), RHU-santé grant, a large French hospital-medical research consortium that aims at developing innovations for liver and tissue engineering (Inria PI: Dirk Drasdo).

8.1.2. APHP-Inria collaboration

Participants: Nour Bou Saleh, Quentin Nicolas, Nicolas Golse, Irene Vignon-Clementel [local coordinator].

Collaboration with Eric Vibert (APHP - Inserm U1193) for cosupervision of surgery interns (N. Bousaleh, D. Dousse) and engineering intern (Q Nicolas) in the context of the APHP-Inria PhD of N. Golse, on liver modeling and ICG fluorescence.

8.2. European Initiatives

8.2.1. Collaborations in European Programs, Except FP7 & H2020

SimInhale COST Action MP1404, a pan-European network of experts in the field of inhaled medicine, coordinated by Prof. Stavros Kassinos, end: 2019 (http://www.siminhale-cost.eu).

8.3. International Initiatives

8.3.1. Inria International Partners

8.3.1.1. Informal International Partners

Collaboration with :

- Prof. Pal Dag Line from U. of Oslo, Oslo hospital U. with E. Vibert (APHP, Inserm) - N. Golse, I. Vignon-Clementel
- CHUM Centre Hospitalier de l'Université de Montreal (G Soulez and colleagues) - F. Joly (Inria), I. Vignon-Clementel

SISTM Project-Team

9. Partnerships and Cooperations

9.1. Regional Initiatives

The team have strong links with :

- Research teams of the research center Inserm U1219 : "Injury Epidemiology, Transport, Occupation" (IETO), "Biostatistics", "Pharmacoepidemiology and population impact of drugs", "Multimorbidity and public health in patients with HIV or Hepatitis" (MORPH3Eus), "Computer research applied to health" (ERIAS) emerging research team.
- Bordeaux CHU ("Centre Hospitalier Universitaire").
- Institut Bergonié, Univ Bordeaux through the Euclid F-CRIN Clinical Trials platform and CIC-EC (CIC1401)
- Inria Project-team MONC, M3DISIM and CQFD

The project team members are involved in:

- EUCLID/F-CRIN clinical trials platform (Laura Richert)
- The Clinical Epidemiology module of the Clinical Investigations Center (CIC1401) (Laura Richert)
- The research project “Self-management of injury risk and decision support systems based on predictive computer modelling. Development, implementation and evaluation in the MAVIE cohort study” funded by the Nouvelle-Aquitaine regional council (Marta Avalos).
- Phenotyping from Electronic Health Records pilot project in cooperation with with the ERIAS Inserm emerging team in Bordeaux and the Rheumatology service from the Bordeaux Hospital (Boris Hejblum)
- A cancer research project (GLIOMA-PRD) in collaboration with Inria MONC team and with the the Inserm Angiogenesis and Tumor micro-environment team on glioblastoma

9.2. National Initiatives

- Labex Vaccine Research Institute (VRI) There are strong collaborations with immunologists involved in the Labex Vaccine Research Institute (VRI) as Rodolphe Thiébaut and Laura Richert are leading the Data science division (previously Biostatistics/Bioinformatics) http://vaccine-research-institute.fr.
- Collaboration with Inserm PRC (pôle Recherche clinique).
- Collaboration with Inserm Reacting (REsearch and ACTion targeting emerging infectious diseases) network
- Collaboration with Inserm RECap (Recherche en Epidémiologie Clinique et en Santé Publique) network

9.2.1. Expert Appraisals

- Rodolphe Thiébaut is a member of the CNU 46.04 (Biostatistiques, informatique médicale et technologies de communication).
- Rodolphe Thiébaut is a member of the Scientific Council of Inserm.
- Mélanie Prague is an expert for ANRS (France Recherche Nord&Sud Sida-HIV Hépatites) in the CSS 3 (Recherches cliniques et physiopathologiques dans l’infection à VIH) and AC 47 (Dynamique et contrôle des épidémies VIH et hépatites).
- Laura Richert is an expert for the PHRC (Programme hospitalier de recherche Clinique).

- Marta Avalos is an expert for the ANSM (Agence nationale de sécurité du médicament et des produits de santé)

9.2.2. Various Partnership

The project team members are involved in:

- DRUGS-SAFE platform funded by ANSM (Marta Avalos). Initiated in 2015-2018. Renewed for 2019.
- F-CRIN (French clinical research infrastructure network), initiated in 2012 by ANR under "Programme des Investissements d'avenir". (Laura Richert)
- INCA (Institut National du Cancer) funded the project *Evaluation de l'efficacité d'un traitement sur l'évolution de la taille tumorale et autres critères de survie : développement de modèles conjoints.* (Principal PI Virginie Rondeau Inserm U1219, Mélanie Prague is responsible of Work package 4 "mechanistic modeling of cancer: 5800 euros").
- Contrat Initiation ANRS MoDeL-CI: Modeling the HIV epidemic in Ivory Coast (Principal PI Eric Ouattara Inserm U1219 in collaboration with University College London, Mélanie Prague is listed as a collaborator).

9.3. European Initiatives

9.3.1. FP7 & H2020 Projects

The member of SISTM Team are involved in EHVA (European HIV Vaccine Alliance):

EHVA: European HIV Vaccine Alliance: a EU platform for the discovery and evaluation of novel prophylactic and therapeutic vaccine candidates

Coordinator: Inserm/University of Lausanne. Other partners: EHVA consortium gathers 41 partners. Duration: 60 months. 01 /01 /2016 - 31 /12 /2020

With 37 million people living with HIV worldwide, and over 2 millions new infections diagnosed each year, an effective vaccine is regarded as the most potent public health strategy for addressing the pandemic. Despite the many advances in the under-standing, treatment and prevention of HIV made over the past 30 years, the development of broadly-effective HIV vaccine has remained unachievable. The EHVA international alliance, which includes academic and industrial research partners from all over Europe, as well as sub-Saharan Africa and North America, will work to discover and progress novel vaccine candidates through the clinic. EHVA fosters a multidisciplinary approach to the challenge of developing broadly effective HIV vaccines. EHVA's program primary goals are:

- To develop a Multidisciplinary Vaccine Platform (MVP) for prophylactic and therapeutic HIV vaccines
- To move at least two novel prophylactic vaccine candidates to clinical development
- To identify immune correlates associated with control of HIV replication following immunological intervention
- To establish a strong scientific basis for further development of EHVA vaccine candidates in larger clinical trials

  To this purpose, EHVA bring to the field 4 multidisciplinary research platforms representative of the latest advances in clinical trials and preclinical vaccine development. These four platforms cover all aspects of vaccine development from early-stage discovery to clinical trials.
- The Discovery Platform will work to disclose promising vaccine candidates based on the induction of T-cell and antibody responses (ie, neutralizing antibody and non-neutralizing antibody).

- The Immune-Profiling Platform will advance assays to predict the immunogenicity of potential vaccine candidates. The ability to generate a profile of a potential vaccine candidate, using models that emulate the immune system's response, will assist with benchmarking novel and existing vaccine candidates.
- The Data Management/Integration and Down-Selection Platform is developed around the WP10 led by Rodolphe Thiébaut. SISTM provides here state-of-the-art statistical tools for the analysis and interpretation of complex data and algorithms for the efficient selection of vaccines.
- The Clinical Trial Platform includes pharmaceutical industry expertise for late stage development, a network of top European clinical centers for conducting large cohort studies, as well as relationships with leading scientists based in Africa. Future testing of EHVA vaccine in Sub-Saharan Africa is a research priority because it is the area of the world with the greatest number of people infected with HIV.

IP-CURE-B: Immune profiling to guide host-directed interventions to cure HBV infections. Coordinated by Inserm (France), the project includes a total of 13 Beneficiaries: Centre Hospitalier Universitaire Vaudois (Switzerland), Karolinska Institutet (Sweden), Institut Pasteur (France), Universita degli studi di Parma (Italy), Fondazione IRCCS CA' Granda – Ospedale maggiore policlinico (Italy), Universitaetsklinikum Freiburg (Germany), Ethniko Kai Kapodistriako Panepistimio Athinon (Greece), Fundacio Hospital Universitari vall d'Hebron (Spain), Gilead Sciences Inc. (USA), Spring Bank Pharmaceuticals, Inc (USA), European Liver Patients Association (Belgium), Inserm Transfert SA (France). Duration: 60 months. $01/01/2020 - 31/12/2024$

HBV infections, are a major global public health threat with over 257 million people worldwide chronically infected and over 887,000 deaths per year. 4.7 million people live with HBV in the European Union (EU) and European Economic Area (EEA). W.H.O. estimates that HBV causes almost 40% of the cases of hepatocellular carcinoma (HCC), which is the 2nd leading cause of cancer-related mortality worldwide. HBV kills nearly 900,0000 people around the world each year. The current prophylactic vaccine has no impact on established chronic infection.

The objective of the IP-CURE-B project is to develop novel curative concepts for chronic hepatitis B (CHB). Specific aims will be to: 1) improve the rate of functional cure of CHB by boosting innate immunity with immune modulators and stimulating adaptive immune responses with a novel therapeutic vaccine; ii) characterize immune and viral biomarker signatures for patient stratification and treatment response monitoring; iii) integrate biological and clinical data to model the best combination treatment for future trials; iv) model the effectiveness of novel curative therapies with respect to disease spectrum, patient heterogeneity, and constraints of National Health Systems.

The project organization combines: i) a Proof of Concept clinical trial of a combination of 2 novel compounds stimulating innate immunity; ii) a preclinical immune therapy platform in humanized mice combining immune-modulatory strategies to stimulate innate immunity, rescue exhausted HBV-specific T cells and generate anti-HBV adaptive responses; iii) extensive virologic and immune profiling to identify correlates of cure in patients, iv) the integration of large biological and clinical data-sets, v) a cost-effectiveness modelling of new therapeutic interventions, vi) project management, vii) results exploitation and dissemination.

In the IP-CURE-B project, SISTM coordinates WP6 Data science platform for data integration and statistical modeling which will provide powerful data management and statistical tools for the analysis and interpretation of the complex heterogeneous and high-dimensional data generated in the other WPs. For data management and data sharing, SISTM will leverage on a data warehouse system, based on Lab-key Server, the primary structure already established within the EU funded H2020 EHVA project. SISTM will develop and apply statistical methods for integrating data from several assay platforms to better describe and understand the mechanisms of the experimental products and to define predictive signatures of viral control and functional cure. Indeed, the immune system forms a sophisticated network of tissues, cells and molecules that interact in order to achieve viral control.

Understanding how this complex network responds to interventions aimed at HBV functional cure requires the use and integration of data from multiple assay technologies. Two main strategies will be used: 1) statistical approaches to relate and down-select several high-dimensional data from the various assays in humanized mice and humans; 2) a modelling approach, taking into account biological knowledge and the results from the first step, to better capture and understand the non-linear relationships between the components of the immune system, viral control and their dynamics over time. Statistical and mechanistic models will be used, based on ordinary differential equation systems or other approaches. At the end of the process, if an adequate model is identified, this can be used to down-select immunomodulatory and vaccine regimens and make in silico predictions about optimized strategies or stratified treatment approaches. These approaches have been successfully applied in HIV immunotherapy trials and in vaccine trials by SISTM.

9.3.2. Collaborations in European Programs, Except FP7 & H2020

The members of SISTM are also involved in Innovative Medicine Initiative 2 (IMI2) projects which are all under the IMI Ebola+ program that was launched in response to the Ebola virus disease outbreak of 2014. SISTM is active in 3 projects which are all in collaboration with Janssen Vaccines & Preventions B.V. The overall aim of the EBOVAC program is to assess the safety, immunogenicity and efficacy of a novel 2-dose Ad26 + MVA prophylactic vaccine regimen against Ebola Virus Disease. In this context, the 3 projects develop as follows:

EBOVAC1: Development of a Prophylactic Ebola Vaccine Using an Heterologous Prime-Boost Regimen.

Coordinated by London School of Hygiene & Tropical Medicine (United Kingdom). Other beneficiaries: Janssen a Pharmaceutical Companies of Johnson & Johnson, The Chancellor, Masters and Scholars of the University of Oxford (United Kingdom), Inserm (France), University of Sierra Leone (Sierra Leone). Duration: 84 months. 01 /12 /2014 - 30 /11 /2021.

EBOVAC1 is dedicated to the Phase I and III development of prime-boost vaccine based on Ad26.ZEBOV and MVA-BN-Filo. Phase I was conducted in the US, the UK and in Africa (Sierra Leone, Uganda, Kenya and Tanzania) for a total of 231 volunteers enrolled. Phase III was conducted in Sierra Leone in several phases leading to the successful enrolment of more than 2800 volunteers including around 500 children aged 1-17 years. In EBOVAC1, SISTM is modelling the immune response to the Ad26.ZEBOV and MVA-BN-Filo, using the data obtained in the project.

EBOVAC2: Development of a Prophylactic Ebola Vaccine Using a 2-Dose Heterologous Vaccination Regimen: Phase 2.

Coordinated by Rodolphe Thiébaut with the following partners: Inserm (France), Labex VRI (France), Janssen Pharmaceutical Companies of Johnson & Johnson, London School of Hygiene & Tropical Medicine (United Kingdom), The Chancellor, Masters and Scholars of the University of Oxford (United Kingdom), Le Centre Muraz (Burkina Faso), Inserm Transfert (France). Duration: 72 months. 01 /12 /2014 - 30 /11 /2020.

EBOVAC2 main objective is to provide extensive and robust data on the safety and immunogenicity of the Ad26.ZEBOV and MVA-BN-Filo vaccine. This was designed by: 1. Carrying out translational studies to link vaccine elicited immune responses in humans to protection from Ebola in vaccinated non-human primates 2. Carrying out Phase II trials in African and European volunteers in approximately 6 countries, four in Africa and two in the EU with an overall target enrolment of approximately 1,500 subjects. Given the compressed nature of this development program, the Phase II studies were conducted in parallel with the planned Phase III study (EBOVAC1). The rationale for inclusion of European volunteers in Phase 2, in addition to the trials in Africa, is to allow for higher sensitivity in safety signal detection in populations with low incidence of febrile illnesses, to generate negative control specimens for assay development, to allow for inclusion of health care workers or military personnel that may be deployed to Ebola-endemic regions. 3. Evaluating the vaccine response in special population groups, such as children (ages 1-17 years), the elderly (ages

50-65) and individuals infected with HIV, to confirm safety and immunogenicity. The Phase II trials started as soon as preliminary safety data were available from Phase I trials. 4. Monitoring and characterizing immune response to the proposed vaccine through different set of analysis of the humoral and cellular response with different approaches (ICS, luminex, gene expression analysis, T and B cell activation assays, Virus neutralization assays...) leading to a unique set of data. In EBOVAC2, in addition to the coordination of the whole project, SISTM is involved in the statistical analysis of the results obtained by the VRI lab responsible for an important part of the exploratory work, but also in the integrative data analysis of these high dimension and complex data. A Labkey environment was established in SISTM for EBOVAC2 to facilitate the exchange and following treatment of the project data.

EBOVAC3: Bringing a prophylactic Ebola vaccine to licensure.

Coordinated by the London School of Hygiene & Tropical Medicine (United Kingdom). Other beneficiaries: Janssen a Pharmaceutical Companies of Johnson & Johnson, Inserm (France), The University of Antwerpen (Belgium), University of Sierra Leone (Sierra Leone). Duration: 60 months. 01 /06 /2018 - 30 /05 /2023.

EBOVAC3 aims at supporting an essential part of the remaining clinical and manufacturing activities required for licensure in the European Union (EU) and the United States (US) for the candidate heterologous Ad26.ZEBOV and MVA-BN-Filo prophylactic vaccine regimen against Ebola virus disease. As a follow-up project, the IMI2 funded EBOVAC3 project, has started in June 2018. In this project, the vaccine strategy is further evaluated in specific populations in Africa (infants in Guinea and Sierra Leone; and front line workers in RDC). The project includes a work package on modelling, which is led by Rodolphe Thiébaut. Three workshop have been organized in Bordeaux (October 29th-30th, 2018), Arcachon (May 2nd-3rd, 2019) and Leiden (November 20th, 2019) to discuss and collaborate with the EBOVAC3 partners on the planned modelling work.

PREVAC-UP: The Partnership for Research on Ebola VACcinations-extended follow-UP and clinical research capacity build-UP.

SISTM is also involved in PREVAC-UP, an EDCTP2 project in direct link with the research carried out on the Ebola vaccines.

Coordinated by Inserm (France). Other beneficiaries: CNFRSR (Guinea), CERFIG (Guinea), LSHTM (UK), COMAHS (Sierra-Leone), NIAID (USA), NPHIL (Liberia), USTTB (Mali), Centre pour le Développement des Vaccins (Mali), Inserm Transfert SA (France). Duration: 60 months. 01 /01 /2019 - 31 /12 /2023.

Human-to-human transmission of Ebola virus in West Africa was interrupted in 2016 but the risk of reemergence of the disease is real. Thus, efforts to develop a safe and effective vaccine against Ebola virus disease with a durable prophylactic effect in communities must continue. The PREVAC-UP project is built around the PREVAC consortium. The Partnership for Research on Ebola Vaccinations (PREVAC) is an international consortium including the French Institute of Health and Medical Research, the London School of Hygiene & Tropical Medicine, the US National Institutes of Health, health authorities and scientists from Guinea, Liberia, Mali and Sierra Leone, a non-governmental organization (Alliance for International Medical Action), and Merck, Johnson & Johnson and Bavarian Nordic companies. The PREVAC trial is a phase IIB, randomized, placebo controlled, multicentre trial evaluating the safety and immunogenicity over 12 months of three vaccine strategies in children and adults. Participants are randomized to one of five groups: (i) vaccination with Ad26.ZEBOV prime and MVA-BN-Filo boost, (ii) vaccination with rVSVδG-ZEBOV-GP prime and a boost of the same vaccine, (iii) vaccination with rVSVδG-ZEBOV-GP vaccine without boost, (iv) placebo group 1 and (v) placebo group 2. Preliminary phases started in Liberia and Guinea in March 2017; the main phase of the trial evaluating the five regimens will begin in Liberia, Guinea Sierra Leone and Mali in April 2018 with an enrolment targets of 1,400 adults and 1,400 children.

PREVAC-UP two primary objectives are to determine (i) the long-term immunogenicity and safety and (ii) durability of humoral and cellular immune responses of Ebola vaccine regimes over 60

months. We will also evaluate the effect of co-infections, such as malaria and helminths on the immune response to vaccination. An integrative statistical analysis of the immune response will be used under the coordination of SISTM to explore the mechanism of action of the vaccines and to identify early correlates of durable antibody induction. PREVAC-UP will also build on the extensive community mobilization efforts previously generated through PREVAC to provide a trans-national platform for social and health science research and training. Finally, this research proposal will expand and sustain capacity building and training of scientists in the four participant African countries. This program is expected to significantly impact Ebola prevention and control in adults and children in Africa. PREVAC-UP will also strengthen capacity for science relevant to the development and evaluation of new vaccines in sub-Saharian Africa.

In PREVAC-UP, SISTM leads the WP4 Utilisation of a system vaccinology approach using integrative statistical analyses and mechanistic modelling of the immune response to explore the interrelationship of immune response to Ebola vaccines. System vaccinology approach helps in better understanding and predicting the response to vaccines as demonstrated in the context of yellow fever, flu and many other vaccines. The idea is to integrate the massive data generated by high-throughput technologies (transcriptomics, flow cytometry, multiplex data) and population characteristics (sociodemographics and coinfections) to isolate the main markers/signatures associated to the vaccine response. Then, a mechanistic model of the response can be built and hopefully predict the individual long-term response. The PREVAC trial is a unique opportunity for setting up such an approach and apply it to the most advanced vaccine platforms against Ebola. The Inserm-SISTM team has produced several publications highlighting how within-host mechanistic models could play an important role in predicting vaccine efficacy and in improving treatment regimens, notably in HIV. The team has started to work on modelling the response to the Ad26.ZEBOV/MVA platform. In PREVAC-UP, it is expected that signatures and the mechanistic model itself will be different according to the type of vaccine as, specifically, the rVSV is a replicative vector. Two main outcomes are expected. One is a better understanding of the individual variability of the immune response and another is the prediction of the response with two specific aspects: after a new boost and on the long-term (5 years) for a new vaccinees. Identification and validation of an early correlate of later antibody responses would allow early prediction of whether an individual, or group of individuals is likely to be a poor responder and then to recommend subsequent interventions to test in this subset (such as change in vaccination strategy or additional boosts). Heterogeneity in antibody responses is expected within each group as it has been observed in former studies. In PREVAC-UP, information will be collected to inform the reason of this variability. Specific aspects will be explored such as the impact of malaria and various infectious agents on the immune response. Integrating such information in a mechanistic model of the immune response may help understanding the pathway leading to blunted response in vaccines and also to generate new hypotheses that could be biologically validated later on. Another important aspect of the modelling approach is the quantification of the impact of each potential factor helping to order the relative importance of various factors. In conclusion, this work is definitely at the confluence of the other work packages, integrating and ordering all the available information to understand and predict the effects of the promising vaccine strategy evaluated in the PREVAC trial.

9.3.3. Collaborations with Major European Organizations

University of Oxford;

London School of Hygiene and Tropical Medicine;

University Hospital Hambourg (UKE);

Heinrich Pette Institute for Experimental Virology, Hambourg;

MRC, University College London;

MRC Biostatistics Unit, University of Cambridge;

The University of Antwerpen;

University of Milan;

University of Bergen.

9.4. International Initiatives

9.4.1. Inria International Labs

Inria@EastCoast

Associate Team involved in the International Lab:

9.4.1.1. DYNAMHIC

Title: DYNAMical modeling of HIV Cures

International Partner (Institution - Laboratory - Researcher):

Harvard University (United States) - Harvard Program for Evolutionary Dynamics - Alison HILL

Start year: 2019

See also: https://team.inria.fr/dynamhic/

The aim of the DYNAMHIC Associate Team is to bring together a mathematical biology team at Harvard and the Inria team SISTM of applied statisticians at Bordeaux Sud-ouest. This collaboration will allow the analysis of unique pre-clinical non human primates data of HIV cure interventions. In particular, we will focus on immunotherapy and therapeutic vaccine, which are very promising in term of efficacy and are at the leading edge of pre-clinical research in the area. The novelty of the approach is to propose an integrative project studying complex biological processes with novel mathematical statistical models, which has the potential to yield predictive computational tools to assist in the design of both therapeutic products and clinical trials for HIV cure

Finally, the associate team is the opportunity to provide the research group with an official administrative framework. And, to continue to develop a promising research topic connected but different from those funded up to now.

Inria@SiliconValley

Associate Team involved in the International Lab:

9.4.1.2. SWAGR

Title: Statistical Workforce for Advanced Genomics using RNAseq

International Partner (Institution - Laboratory - Researcher):

RAND Corporation (United States) - Statistics group - Denis Agniel

Start year: 2018

See also: https://team.inria.fr/swagr/

The SWAGR Associate Team aims at bringing together a statistical workforce for advanced genomics using RNAseq. SWAGR combines the biostatistics experience of the SISTM team from Inria BSO with the mathematical expertise of the statistics group at the RAND Corporation in an effort to improve RNAseq data analysis methods by developing a flexible, robust, and mathematically principled framework for detecting differential gene expression. Gene expression, measured through the RNAseq technology, has the potential of revealing deep and complex biological mechanisms underlying human health. However, there is currently a critical limitation in widely adopted approaches for the analysis of such data, as edgeR, DESeq2 and limma-voom can all be shown to fail to control the type-I error, leading to an inflation of false positives in analysis results. False positives are an important issue in all of science. In particular in biomedical research when costly studies are failing to reproduce earlier results, this is a pressing issue. SWAGR propose to develop a rigorous statistical framework modeling complex transcriptomic studies using RNAseq by leveraging the synergies between the works of B. Hejblum and D. Agniel. The new method will be implemented in open-source

software as a Bioconductor R package, and a user friendly web-application will be made available to help dissemination. The new method will be applied to clinical studies to yield significant biological results, in particular in vaccine trials through existing SISTM partnerships. The developed method is anticipated to become a new standard for the analysis of RNAseq data, which are rapidly becoming common in biomedical studies, and has therefore the potential for a large impact.

9.5. International Research Visitors

9.5.1. Visits of International Scientists

9.5.1.1. Internships

- Eva Reiner (Germany), intern in the Translational Vaccinology axis (March-July 2019)
- Aaron Sonabend, PhD student from Harvard University, collaborator in the High-dimensional statistical learning axis (June-August 2019) funded by the Harvard Rose Fellowship.

9.5.2. Visits to International Teams

9.5.2.1. Research Stays Abroad

- Boris Hejblum did a research stay at the Biostatistics Unit of The Medical Research Council at the University of Cambridge (Cambridge, UK) for a cumulative period of 1.5 month in 2019. This stay was devoted to collaborative work with Paul DW Kirk on scalalble bayesian computational methods.
- Boris Hejblum did a research stay at the Rand Corporation (offices in both Santa Monica CA and Boston MA) and at the Harvard Medical School (Boston MA, USA) for a cumulative period of 2 weeks in 2019. This stay was devoted to collaborative work with Denis Agniel in the context of the SWAGR Associate Team and with Tianxi Cai on high-dimensional statistical inference.
- Mélanie Prague did a research stay abroad in Harvard.

XPOP Project-Team

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. ANR

Mixed-Effects Models of Intracellular Processes: Methods, Tools and Applications (MEMIP)

Coordinator: Gregory Batt (InBio Inria team)

Other partners: InBio and IBIS Inria teams, Laboratoire Matière et Systèmes Complexes (UMR 7057; CNRS and Paris Diderot Univ.)

9.1.2. Institut National du Cancer (INCa)

Targeting Rac-dependent actin polymerization in cutaneous melanoma - Institut National du Cancer

Coordinator: Alexis Gautreau (Ecole Polytechnique)

Other partners: Laboratoire de Biochimie (Polytechnique), Institut Curie, INSERM.

9.2. International Initiatives

9.2.1. International Initiatives

SaSMoTiDep

Title: Statistical and Stochastic modeling for time-dependent data

International Partners (Institution - Laboratory - Researcher):

Universidad de Valparaiso (Chile) - Centro de Investigación y Modelamiento de Fenómenos Aleatorios Valparaíso (CIMFAV) - Cristian Meza Becerra

Universidad Nacional de Colombia (Colombia) - Department of Statistics - Viswanathan Arunachalam

Duration: 01/01/2018 - 31/12/2019

Start year: 2018

See also: https://sasmotidep.uv.cl

In many applications, multiple measurements are made on one or several experimental units over a period of time. Such data could be called time-dependent data. From a statistical point of view, if we consider only one experimental unit, we can use a time series analysis. In the other hand, if we consider experimental designs (or observational studies) for several experimental units (or subjects) where each subject is measured at several points in time, we can use the term longitudinal data. In this project, we propose to study several statistical and stochastic models for repeated measures using parametric and non-parametric approaches. In particular, we will study the inference in complex mixed effects models, we will propose novel segmentation models for multiple series, non-parametric methods in dependent models and stochastic models. We will apply these methods to real data from several fields as biometrics, reliability, population dynamics and finance.

9.3. International Research Visitors

9.3.1. Visits of International Scientists

Ricardo Rios, Universidad Central de Venezuela, Caracas: September 2019.

Cristian Meza, Universidad de Valparaiso, Chile, September 2019.