RESEARCH CENTRE

**Paris**

**IN PARTNERSHIP WITH:**

**CNRS, INSERM, Sorbonne Université (UPMC)**

# 2021 ACTIVITY REPORT

# Project-Team ARAMIS

## Algorithms, models and methods for images and signals of the human brain

**IN COLLABORATION WITH: Institut du Cerveau et de la Moelle Epinière**

**DOMAIN**

**Digital Health, Biology and Earth**

**THEME**

**Computational Neuroscience and Medicine**

# Contents

# Project-Team ARAMIS

*Creation of the Project-Team: 2014 July 01*

## Keywords

**Computer sciences and digital sciences**

A3.4. – Machine learning and statistics

A3.4.1. – Supervised learning

A3.4.2. – Unsupervised learning

A3.4.4. – Optimization and learning

A3.4.6. – Neural networks

A3.4.8. – Deep learning

A5.3. – Image processing and analysis

A5.4. – Computer vision

A5.9. – Signal processing

A9. – Artificial intelligence

A9.2. – Machine learning

A9.3. – Signal analysis

A9.6. – Decision support

**Other research topics and application domains**

B2. – Health

B2.2.6. – Neurodegenerative diseases

B2.6. – Biological and medical imaging

B2.6.1. – Brain imaging

# 1 Team members, visitors, external collaborators

## Research Scientists

- Olivier Colliot [Team leader, CNRS, Senior Researcher, HDR]
- Ninon Burgos [CNRS, Researcher]
- Baptiste Couvy-Duchesne [Inria, from Oct 2021, Starting Faculty Position]
- Stanley Durrleman [Inria, Senior Researcher, HDR]
- Fabrizio de Vico Fallani [Inria, Researcher, HDR]

## Faculty Members

- Didier Dormont [Sorbonne Université, Professor, HDR]
- Stephane Epelbaum [Assistance publique/Hôpitaux de Paris, Hospital Staff, Until Sept. 2021, HDR]
- Daniel Racoceanu [Sorbonne Université, Professor, HDR]
- Sophie Tezenas du Montcel [Sorbonne Université, Associate Professor, From Dec 2021, HDR]

## Post-Doctoral Fellows

- Janan Arslan [Inserm, From Sept 2021]
- Marie-Constance Corsi [Inria, from Jun 2021]
- Marie-Constance Corsi [Institut du Cerveau et de la Moelle Epinière, until May 2021]
- Baptiste Couvy-Duchesne [CNRS, until Sep 2021]
- Johann Faouzi [Institut du Cerveau et de la Moelle Epinière]
- Anuradha Kar [ICM, From 01/10/2021]
- Thomas Nedelec [Institut du Cerveau et de la Moelle Epinière]

## PhD Students

- Remy Ben Messaoud [Inria]
- Simona Bottani [Inria]
- Federica Cacciamani [Institut du Cerveau et de la Moelle Epinière, until Nov 2021]
- Tiziana Cattai [Inria, until Mar 2021]
- Raphaël Couronné [Inria, until Sep 2021]
- Vito Dichio [Inria]
- Nemo Fournier [Institut du Cerveau et de la Moelle Epinière, from Sep 2021]
- Juliana Gonzalez Astudillo [Sorbonne Université]
- Ravi Hassanaly [CNRS]
- Lisa Hemforth [CNRS, from Oct 2021]
- Virgilio Kmetzsch Rosa E Silva [Inria]

- Sophie Loizillon [Sorbonne Université, from Oct 2021]
- Clement Mantoux [Inria]
- Juliette Ortholand [Inria, from Sep 2021]
- Mehdi Ounissi [Sorbonne Université (cofunding SCAI - Inria), From 01/11/2021 ]
- Pierre Emmanuel Poulet [Inria]
- Charley Presigny [Inria]
- Benoit Sauty De Chalon [Inria]
- Sophie Skriabine [Inria]
- Elina Thibeau-Sutre [Sorbonne Université]
- Tristan Venot [Inria]
- Paul Vernhet [Inria, until May 2021]

## Technical Staff

- Kevin De Matos [CNRS, Engineer, from Oct 2021]
- Arthur Desbois [Inria, Engineer]
- Cecile Di Folco [Inria, Engineer]
- Mauricio Diaz Melo [Inria, Engineer]
- Omar El Rifai [Inria, Engineer, from Mar 2021]
- Matthieu Joulot [Institut du Cerveau et de la Moelle Epinière, Engineer, from Jun 2021]
- Igor Koval [Inria, Engineer, until Jun 2021]
- Quentin Madura [Inria, Engineer, from Nov 2021]
- Etienne Maheux [Inria, Engineer]
- Juliette Ortholand [Institut du Cerveau et de la Moelle Epinière, Engineer, until Aug 2021]
- Thibault Rolland [Inria, Engineer, from Apr 2021]
- Ghislain Vaillant [CNRS, Engineer, from May 2021]
- Arnaud Valladier [Inria, Engineer, until Feb 2021]
- Mkrtich Vatinyan [Institut du Cerveau et de la Moelle Epinière, Engineer]

## Interns and Apprentices

- Sasha Collin [INSERM, from Apr 2021 until Sep 2021]
- Kevin De Matos [Sorbonne Université, from May 2021 until Sep 2021]
- Alice Longhena [Inria, from Feb 2021 until Jul 2021]
- Alexandre Martin [Univ Paris-Saclay, from Apr 2021 until Sep 2021]
- Marius Schmidt-Mengin [INSERM, from Apr 2021 until Sep 2021]

### Administrative Assistant

- Helene Milome [Inria]

# 2 Overall objectives

## 2.1 Context

**ARAMIS is an Inria project-team within the Paris Brain Institute (ICM) at the Pitié-Salpêtrière hospital (AP-HP) in Paris**. ARAMIS was created as a team of the Inria Paris Center in 2012 and became a project-team in 2014. ARAMIS has a joint affiliation to Inria, CNRS, Inserm and Sorbonne University.

The **Pitié-Salpêtrière hospital** is the largest adult hospital in Europe. It is a leading center for neurological diseases: in terms of size (around 20,000 neurological patients each year), level of clinical expertise and quality of the technical facilities. Created in 2010, the **Paris Brain Institute (ICM)** gathers all research activities in neuroscience and neurology of the Pitié-Salpêtrière hospital. The ICM is both a private foundation and a public research unit (affiliated to CNRS, Inserm and Sorbonne University). It hosts about 25 research teams as well as various high level technical facilities (neuroimaging, genotyping/sequencing, cell culture, cellular imaging, bioinformatics ...), and gathers over 700 personnel. In addition, the ICM hosts one of the six IHU (*Instituts Hospitalo-Universitaires*).

ARAMIS is thus located both within a leading neuroscience institute and within a large hospital. This unique position has several advantages: direct contact with neuroscientists and clinicians allows us to foresee the emergence of new problems and opportunities for new methodological developments, provides access to unique datasets, and eases the transfer of our results to clinical research and clinical practice.

## 2.2 General aim

The ARAMIS team is devoted to the design of **computational, mathematical and statistical approaches for the analysis of multimodal patient data**, with an emphasis on neuroimaging data. The core methodological domains of our team are: machine learning, statistical modeling of complex geometric data, connectivity and network analysis. These new approaches are applied to clinical research in neurological diseases in collaboration with other teams of the ICM, clinical departments of the Pitié-Salpêtrière hospital and external partners. **The team has a pluridisciplinary composition**, bringing together researchers in mathematics, computer science and engineering (N. Burgos, O. Colliot, B. Couvy-Duchesne, F. De Vico Fallani, S. Durrleman, D. Racoceanu) and clinicians (D. Dormont, S. Epelbaum, S. Tezenas du Montcel).

We develop various clinical applications of our research, in particular in neurodegenerative disorders (Alzheimer's disease and other dementias, Parkinson's disease), multiple sclerosis, developmental disorders, stroke and to design brain-computer interfaces for rehabilitation.

# 3 Research program

## 3.1 From geometrical data to multimodal imaging

Brain diseases are associated to alterations of brain structure that can be studied in vivo using anatomical and diffusion MRI. The anatomy of a given subject can be represented by sets of anatomical surfaces (cortical and subcortical surfaces) and curves (white matter tracks) that can be extracted from anatomical and diffusion MRI respectively. We aim to develop approaches that can characterize the variability of brain anatomy within populations of subjects. To that purpose, we propose methods to estimate population atlases that provide an average model of a population of subjects together with a statistical model of their variability. Finally, we aim to introduce representations that can integrate geometrical information (anatomical surfaces, white matter tracts) together with functional (PET, ASL, EEG/MEG) and microstructural information.

### 3.2 Models of brain networks

Functional imaging techniques (EEG, MEG and fMRI) allow characterizing the statistical interactions between the activities of different brain areas, i.e. functional connectivity. Functional integration of spatially distributed brain regions is a well-known mechanism underlying various cognitive tasks, and is disrupted in brain disorders. Our team develops a framework for the characterization of brain connectivity patterns, based on connectivity descriptors from the theory of complex networks. More specifically, we propose analytical tools to infer brain networks, chacterize their structure and integrate multiple networks (for instance from multiple frequency bands or multiple modalities). The genericity of this approach allows us to apply it to various types of data including functional and structural neuroimaging, as well as genomic data.

### 3.3 Spatiotemporal modeling from longitudinal data

Longitudinal data sets are collected to capture variable temporal phenomena, which may be due to ageing or disease progression for instance. They consist in the observation of several individuals, each of them being observed at multiple points in time. The statistical exploitation of such data sets is notably difficult since data of each individual follow a different trajectory of changes and at its own pace. This difficulty is further increased if observations take the form of structured data like images or measurements distributed at the nodes of a mesh, and if the measurements themselves are normalized data or positive definite matrices for which usual linear operations are not defined. We aim to develop a theoretical and algorithmic framework for learning typical trajectories from longitudinal data sets. This framework is built on tools from Riemannian geometry to describe trajectories of changes for any kind of data and their variability within a group both in terms of the direction of the trajectories and pace.

### 3.4 Decision support systems

We then aim to develop tools to assist clinical decisions such as diagnosis, prognosis or inclusion in therapeutic trials. To that purpose, we leverage the tools developed by the team, such as multimodal representations, network indices and spatio-temporal models which are combined with advanced classification and regression approaches. We also dedicate strong efforts to rigorous, transparent and reproducible validation of the decision support systems on large clinical datasets.

### 3.5 Clinical research studies

Finally, we aim to apply advanced computational and statistical tools to clinical research studies. These studies are often performed in collaboration with other researchers of the ICM, clinicians of the Pitié -Salpêtrière hospital or external partners. Notably, our team is very often involved ”ex-ante” in clinical research studies. As co-investigators of such studies, we contribute to the definition of objectives, study design and definition of protocols. This is instrumental to perform clinically relevant methodological development and to maximize their medical impact.

The studied clinical applications include neurodegenerative disorders (Alzheimer’s disease and other dementias, Parkinson’s disease), multiple sclerosis, developmental disorders, stroke and the design of brain-computer interfaces for rehabilitation.

## 4 Application domains

### 4.1 Introduction

We develop different applications of our new methodologies to brain pathologies, mainly neurodegenerative diseases. These applications aim at:

- better understanding the pathophysiology of brain disorders;
- designing systems to support clinical decisions such as diagnosis, prognosis and design of clinical trials;

- developing brain computer interfaces for clinical applications.

### 4.2 Understanding brain disorders

Computational and statistical approaches have the potential to help understand the pathophysiology of brain disorders. We first aim to contribute to better understand the relationships between pathological processes, anatomical and functional alterations, and symptoms. Moreover, within a single disease, there is an important variability between patients. The models that we develop have the potential to identify more homogeneous disease subtypes, that would constitute more adequate targets for new treatments. Finally, we aim to establish the chronology of the different types of alterations. We focus these activities on neurodegeneratives diseases: dementia (Alzheimer's disease, fronto-temporal dementia), Parkinson's disease, multiple sclerosis.

### 4.3 Supporting clinical decisions

We aim to design computational tools to support clinical decisions, including diagnosis, prognosis and the design of clinical trials. The differential diagnosis of neurodegenerative diseases can be difficult. Our tools have the potential to help clinicians by providing automated classification that can integrate multiple types of data (clinical/cognitive tests, imaging, biomarkers). Predicting the evolution of disease in individual patients is even more difficult. We aim to develop approaches that can predict which alterations and symptoms will occur and when. Finally, new approaches are needed to select participants in clinical trials. Indeed, it is widely recognized that, to have a chance to be successful, treatments should be administered at a very early stage.

### 4.4 Brain computer interfaces for clinical applications

A brain computer interface (BCI) is a device aiming to decode brain activity, thus creating an alternate communication channel between a person and the external environment. BCI systems can be categorized on the basis of the classification of an induced or evoked brain activity. The central tenet of a BCI is the capability to distinguish different patterns of brain activity, each being associated to a particular intention or mental task. Hence adaptation, as well as learning, is a key component of a BCI because users must learn to modulate their brainwaves to generate distinct brain patterns. Usually, a BCI is considered a technology for people to substitute some lost functions. However, a BCI could also help in clinical rehabilitation to recover motor functions. Indeed, in current neuroscience-based rehabilitation it is recognized that protocols based on mental rehearsal of movements (like motor imagery practicing) are a way to access the motor system because they can induce an activation of sensorimotor networks that were affected by lesions. Hence, a BCI based on movement imagery can objectively monitor patients' progress and their compliance with the protocol, monitoring that they are actually imagining movements. It also follows that feedback from such a BCI can provide patients with an early reinforcement in the critical phase when there is not yet an overt sign of movement recovery.

## 5 Highlights of the year

- Lydia Chougar was granted a Poste d'accueil Inria/AP-HP.
- Baptiste Couvy-Duchesne was granted a Inria Starting Faculty Position.
- Olivier Colliot is Conference Chair of the SPIE Medical Imaging: Image Processing conference for the period 2022-2025.
- Daniel Racoceanu was Keynote to the SIPAIM 2021 conference, the 17th International Symposium on Medical Information Processing and Analysis, Nov. 17-19, 2021 - the major Latin American conference in this area.
- We published the first paper on AI for medical imaging based on the data warehouse of the Greater Paris hospitals (AP-HP) ( [6].).

- We got awarded a JPND (EU Joint Programme – Neurodegenerative Disease Research) grant, to establish a consortium with Sweden and Australia in order to analyse electronic health records. Stanley Durrleman is the coordinator of the project.
- We got awarded a Big Brain Theory (BBT3) project founded by the Paris Brain Institute and co-funded by private sponsors through the ICM foundation. This project, entitled STRATIFIAD (granted for 2 years), is led by Daniel Racoceanu, being dedicated to Refining Alzheimer Disease Patients' stratification using effective, traceable and explicable artificial intelligence approaches in computational histopathology.

# 6 New software and platforms

The team coordinates and/or contributes to the development of the following software packages.

## 6.1 New software

### 6.1.1 Clinica

**Name:** Clinica

**Keywords:** Neuroimaging, Brain MRI, MRI, Clinical analysis, Image analysis, Machine learning, Deep learning

**Scientific Description:** Clinica is a software platform for multimodal brain image analysis in clinical research studies. It makes it easy to apply advanced analysis tools to large scale clinical studies. For that purpose, it integrates a comprehensive set of processing tools for the main neuroimaging modalities: currently anatomical MRI, diffusion MRI, PET. For each modality, Clinica allows to easily extract various types of features (regional measures, parametric maps, surfaces, curves, networks). Such features are then subsequently used as input of machine learning, statistical modeling, morphometry or network analysis methods. Processing pipelines are based on combinations of freely available tools developed by the community. It provides an integrated data management specification to store raw and processing data. Clinica is written in Python. It uses the Nipype system for pipelining. It combines widely-used software for neuroimaging data analysis (SPM, Freesurfer, FSL, MRtrix...), morphometry (Deformetrica), machine learning (Scikit-learn) and the BIDS standard for data organization.

**Functional Description:** Clinica is a software platform for multimodal brain image analysis in clinical research studies. It makes it easy to apply advanced analysis tools to large scale clinical studies. For that purpose, it integrates a comprehensive set of processing tools for the main neuroimaging modalities: currently anatomical MRI, diffusion MRI, PET. For each modality, Clinica allows to easily extract various types of features (regional measures, parametric maps, surfaces, curves, networks). Such features are then subsequently used as input of machine learning, statistical modeling, morphometry or network analysis methods. Clinica also provides an integrated data management specification to store raw and processing data. Overall, Clinica helps to: i) apply advanced analysis tools to clinical research studies, ii) easily share data and results, iii) make research more reproducible.

**URL:** http://www.clinica.run

**Publications:** hal-02308126, hal-02562504, hal-01518785, hal-01578479, hal-01858384, hal-01907482, hal-01654000, hal-02566361, hal-01950933

**Contact:** Olivier Colliot

**Participants:** Jeremy Guillon, Thomas Jacquemont, Pascal Lu, Arnaud Marcoux, Tristan Moreau, Alexandre Routier, Jorge Samper Gonzalez, Junhao Wen, Olivier Colliot, Stanley Durrleman, Michael Bacci, Simona Bottani, Ninon Burgos, Sabrina Fontanella, Pietro Gori, Mauricio Diaz, Elina Thibeau-Sutre, Ravi Hassanaly, Omar El Rifai, Ghislain Vaillant, Matthieu Joulot

**Partners:** Institut du Cerveau et de la Moelle épinière (ICM), CNRS, INSERM, UPMC

#### 6.1.2 ClinicaDL

**Keywords:** Deep learning, Neuroimaging, Reproducibility

**Scientific Description:** As deep learning faces a reproducibility crisis and studies on deep learning applied to neuroimaging are contaminated by methodological flaws, there is an urgent need to provide a safe environment for deep learning users to help them avoid common pitfalls that will bias and discredit their results. Several tools have been proposed to help deep learning users design their framework for neuroimaging data sets. ClinicaDL has been developed to bring answers to three common issues encountered by deep learning users who are not always familiar with neuroimaging data: (1) the format and preprocessing of neuroimaging data sets, (2) the contamination of the evaluation procedure by data leakage and (3) a lack of reproducibility. The combination of ClinicaDL and its companion project Clinica allows performing an end-to-end neuroimaging analysis, from the download of raw data sets to the interpretation of trained networks, including neuroimaging preprocessing, quality check, label definition, architecture search, and network training and evaluation.

**Functional Description:** ClinicaDL is a Python open-source software for neuroimaging data processing with deep learning. This software includes many functionalities, such as neuroimaging preprocessing, synthetic dataset generation, label definition, data split with similar demographics, architecture search, network training, performance evaluation and trained network interpretation. The three main objectives of ClinicaDL are to (1) help manipulate neuroimaging data sets, (2) prevent data leakage from biasing results and (3) reproduce deep learning experiments.

**URL:** https://clinicadl.readthedocs.io

**Publications:** hal-02562504, hal-03351976

**Contact:** Ninon Burgos

**Participants:** Elina Thibeau-Sutre, Mauricio Diaz, Ravi Hassanaly, Alexandre Routier, Olivier Colliot, Ninon Burgos

**Partners:** Institut du Cerveau et de la Moelle épinière (ICM), CNRS, INSERM, Sorbonne Université

#### 6.1.3 Deformetrica

**Keywords:** 3D modeling, C++, Automatic Learning, Mesh, Anatomy, Image analysis

**Scientific Description:** Deformetrica is a software for the statistical analysis of 2D and 3D shape data. It essentially computes deformations of the 2D or 3D ambient space, which, in turn, warp any object embedded in this space, whether this object is a curve, a surface, a structured or unstructured set of points, or any combination of them.

Deformetrica comes with two applications:

registration, which computes the best possible deformation between two sets of objects, atlas construction, which computes an average object configuration from a collection of object sets, and the deformations from this average to each sample in the collection.

Deformetrica has very little requirements about the data it can deal with. In particular, it does not require point correspondence between objects!

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- Registration, which computes the optimal deformation between two sets of objects,

- Atlas construction, which computes an average object configuration from a collection of object sets, and the deformations from this average to each sample in the collection.

Deformetrica has very little requirements about the data it can deal with. In particular, it does not require point correspondence between objects!

**URL:** http://www.deformetrica.org/

**Contact:** Stanley Durrleman

**Participants:** Alexandre Routier, Ana Fouquier, Barbara Gris, Benjamin Charlier, Cedric Doucet, Joan Alexis Glaunès, Marcel Prastawa, Michael Bacci, Pietro Gori, Stanley Durrleman

**Partners:** University of Utah, Université de Montpellier 2, Université Paris-Descartes

#### 6.1.4 leaspy

**Name:** Learning spatiotemporal patterns in python

**Keywords:** Clinical analysis, Medical applications, Personalized medicine

**Functional Description:** Leaspy, standing for LEArning Spatiotemporal Patterns in Python, has been developed to analyze longitudinal (or sequential) data that correspond to the measurements of a long-term progression. Said differently, each sequence of repeated observations derives from a portion of the global process, with a certain variability between sequence.

**Contact:** Stanley Durrleman

#### 6.1.5 Brain Networks Toolbox

**Keywords:** Neuroimaging, Medical imaging

**Functional Description:** Brain Networks Toolbox is an open-source package of documented routines implementing new graph algorithms for brain network analysis. It mainly contains Matlab code of new methods developed by the team and associated to publications (e.g., brain network thresholding, extraction of the information redundancy, node accessibility, etc). It requires, as input, adjacency matrices representing brain connectivity networks. Thus, it is independent on the specific approach used to construct brain networks and it can be used to extract network properties from any neuroimaging modality in healthy and diseased subjects.

**URL:** https://github.com/brain-network/bnt

**Contact:** Fabrizio de Vico Fallani

**Participants:** Fabrizio de Vico Fallani, Jeremy Guillon, Mario Chavez

#### 6.1.6 OpenVIBE

**Keywords:** Neurosciences, Interaction, Virtual reality, Health, Real time, Neurofeedback, Brain-Computer Interface, EEG, 3D interaction

**Functional Description:** OpenViBE is a free and open-source software platform devoted to the design, test and use of Brain-Computer Interfaces (BCI). The platform consists of a set of software modules that can be integrated easily and efficiently to design BCI applications. The key features of OpenViBE software are its modularity, its high performance, its portability, its multiple-user facilities and its connection with high-end/VR displays. The designer of the platform enables users to build complete scenarios based on existing software modules using a dedicated graphical language and a simple Graphical User Interface (GUI). This software is available on the Inria Forge under

the terms of the AGPL licence, and it was officially released in June 2009. Since then, the OpenViBE software has already been downloaded more than 60000 times, and it is used by numerous laboratories, projects, or individuals worldwide. More information, downloads, tutorials, videos, documentations are available on the OpenViBE website.

**Release Contributions:** Python2 support dropped in favour of Python3 New feature boxes: - Riemannian geometry - Multimodal Graz visualisation - Artefact detection - Features selection - Stimulation validator

Support for Ubuntu 18.04 Support for Fedora 31

Contributions: - Encephalan driver: Alexey Minin from (UrFU) - GTec Unicorn driver: Anton Andreev (Gipsa-Lab) - Box pybox-manager: Jimmy Leblanc & Yannis Bendi-Ouis (Polymont ITS)

**News of the Year:** Python2 support dropped in favour of Python3 New feature boxes: - Riemannian geometry - Multimodal Graz visualisation - Artefact detection - Features selection - Stimulation validator

Support for Ubuntu 18.04 Support for Fedora 31

**URL:** http://openvibe.inria.fr

**Contact:** Anatole Lecuyer

**Participants:** Cedric Riou, Thierry Gaugry, Anatole Lecuyer, Fabien Lotte, Jussi Tapio Lindgren, Laurent Bougrain, Maureen Clerc, Théodore Papadopoulo

**Partners:** INSERM, GIPSA-Lab

### 6.2 New platforms

**Platform Brain-computer interface**

**Participants:** Marie-Constance Corsi, Arthur Desbois, Fabrizio De Vico Fallani *(Correspondant)*.

Our team coordinates the developments of the Brain-Computer Interface (BCI) platform at the Centre EEG/MEG of the neuroimaging core facility of the ICM. Several projects, including our NETBCI NNIH/ANR and ATTACK Big-brain theory funded projects, as well as experiments by different researchers of the Institute (ANR BETAPARK Project), and the BCINET ERC Consolidator grant are currently being run. To reinforce the impact of the platform we have recently recruited an Inria ADT engineer, who has significantly contributed to the extension of the Inria software OpenVibe allowing for new functionalities based on our methodological development on brain connectivity (A. Desbois)

## 7 New results

### 7.1 Automatic quality control of brain T1-weighted magnetic resonance images for a clinical data warehouse

**Participants:** Simona Bottani, Ninon Burgos, Aurelien Maire, Didier Dormont, Olivier Colliot *(Correspondant)*.

We published the first paper on AI for medical imaging based on the data warehouse of the Greater Paris hospitals (AP-HP). We developed and validated an automatic quality control system for brain MRI data. This is an important step to allow fast data curation and thus perform very-large scale studies using this data warehouse which comprises several million of participants. More details about the paper below.

Many studies on machine learning (ML) for computer-aided diagnosis have so far been mostly restricted to high-quality research data. Clinical data warehouses, gathering routine examinations from hospitals, offer great promises for training and validation of ML models in a realistic setting. However, the use of such clinical data warehouses requires quality control (QC) tools. Visual QC by experts is time-consuming and does not scale to large datasets. In this paper, we propose a convolutional neural network (CNN) for the automatic QC of 3D T1-weighted brain MRI for a large heterogeneous clinical data warehouse. To that purpose, we used the data warehouse of the hospitals of the Greater Paris area (Assistance Publique-Hôpitaux de Paris [AP-HP]). Specifically, the objectives were: 1) to identify images which are not proper T1-weighted brain MRIs; 2) to identify acquisitions for which gadolinium was injected; 3) to rate the overall image quality. We used 5000 images for training and validation and a separate set of 500 images for testing. In order to train/validate the CNN, the data were annotated by two trained raters according to a visual QC protocol that we specifically designed for application in the setting of a data warehouse. For objectives 1 and 2, our approach achieved excellent accuracy (balanced accuracy and F1-score > 90%), similar to the human raters. For objective 3, the performance was good but substantially lower than that of human raters. Nevertheless, the automatic approach accurately identified (balanced accuracy and F1-score > 80%) low quality images, which would typically need to be excluded. Overall, our approach shall be useful for exploiting hospital data warehouses in medical image computing.

More details in [6].

## 7.2 Anomaly detection for the individual analysis of brain PET images

**Participants:** Ninon Burgos *(Correspondant)*, Jorge Cardoso, Stanley Durrleman, Sébastien Ourselin, Olivier Colliot.

In clinical practice, positron emission tomography (PET) images are mostly analysed visually, but the sensitivity and specificity of this approach greatly depends on the observer's experience. Quantitative analysis of PET images would alleviate this problem by helping define an objective limit between normal and pathological findings. We present an anomaly detection framework for the individual analysis of PET images. We created subject-specific abnormality maps that summarise the pathology's topographical distribution in the brain by comparing the subject's PET image to a model of healthy PET appearance that is specific to the subject under investigation. This model was generated from demographically and morphologically-matched PET scans from a control dataset. We generated abnormality maps for healthy controls, patients at different stages of Alzheimer's disease and with different frontotemporal dementia syndromes. We showed that no anomalies were detected for the healthy controls and that the anomalies detected from the patients with dementia coincided with the regions where abnormal uptake was expected. We also validated the proposed framework using the abnormality maps as inputs of a classifier and obtained higher classification accuracies than when using the PET images themselves as inputs. The proposed method was able to automatically locate and characterise the areas characteristic of dementia from PET images. The abnormality maps are expected to i) help clinicians in their diagnosis by highlighting, in a data-driven fashion, the pathological areas, and ii) improve the interpretability of subsequent analyses, such as computer-aided diagnosis or spatio-temporal modelling.

More details in [8].

## 7.3 Multilevel survival modeling with structured penalties for disease prediction from imaging genetics data

**Participants:** Pascal Lu, Olivier Colliot *(Correspondant)*.

We introduced a framework for disease prediction from multimodal genetic and imaging data. We propose a multilevel survival model which allows predicting the time of occurrence of a future disease

state in patients initially exhibiting mild symptoms. This new multilevel setting allows modeling the interactions between genetic and imaging variables. This is in contrast with classical additive models which treat all modalities in the same manner and can result in undesirable elimination of specific modalities when their contributions are unbalanced. Moreover, the use of a survival model allows overcoming the limitations of previous approaches based on classification which consider a fixed time frame. Furthermore, we introduce specific penalties taking into account the structure of the different types of data, such as a group lasso penalty over the genetic modality a a l2-penalty over the imaging modality. Finally, we propose a fast optimization algorithm, based on a proximal gradient method. The approach was applied to the prediction of Alzheimer's disease (AD) among patients with mild cognitive impairment(MCI) based on genetic (single nucleotide polymorphisms) and imaging (anatomical MRI measures) data from the ADNI database. The experiments demonstrate the effectiveness of the method for predicting the time of conversion to AD. It revealed how genetic variants and brain imaging alterations interact in the prediction of future disease status. The approach is generic and could potentially be useful for the prediction of other diseases.

More details in [59].

## 7.4 Clinica: an open source software platform for reproducible clinical neuroscience studies

**Participants:** Alexandre Routier, Ninon Burgos, Mauricio Diaz-Melo, Simona Bottani, Omar El-Rifai, Ravi Hassanaly, Arnaud Marcoux, Jorge Samper-Gonzalez, Elina Thibeau-Sutre, Ghislain Vaillant, Junhao Wen, Stanley Durrleman, Olivier Colliot *(Correspondant)*.

We present Clinica (www.clinica.run), an open-source software platform designed to make clinical neuroscience studies easier and more reproducible. Clinica aims for researchers to i) spend less time on data management and processing, ii) perform reproducible evaluations of their methods, and iii) easily share data and results within their institution and with external collaborators. The core of Clinica is a set of automatic pipelines for processing and analysis of multimodal neuroimaging data (currently, T1-weighted MRI, diffusion MRI and PET data), as well as tools for statistics, machine learning and deep learning. It relies on the brain imaging data structure (BIDS) for the organization of raw neuroimaging datasets and on established tools written by the community to build its pipelines. It also provides converters of public neuroimaging datasets to BIDS (currently ADNI, AIBL, OASIS and NIFD). Processed data include image-valued scalar fields (e.g. tissue probability maps), meshes, surface-based scalar fields (e.g. cortical thickness maps) or scalar outputs (e.g. regional averages). These data follow the ClinicA Processed Structure (CAPS) format which shares the same philosophy as BIDS. Consistent organization of raw and processed neuroimaging files facilitates the execution of single pipelines and of sequences of pipelines, as well as the integration of processed data into statistics or machine learning frameworks. The target audience of Clinica is neuroscientists or clinicians conducting clinical neuroscience studies involving multimodal imaging, and researchers developing advanced machine learning algorithms applied to neuroimaging data.

More details in [26].

## 7.5 Deep learning for brain disorders: from data processing to disease treatment

**Participants:** Ninon Burgos, Simona Bottani, Johann Faouzi, Elina Thibeau-Sutre, Olivier Colliot *(Correspondant)*.

We were invited to publish a review paper on "Deep learning for brain disorders" in the high impact journal *Briefings in Bioinformatics*.

In order to reach precision medicine and improve patients' quality of life, machine learning is increasingly used in medicine. Brain disorders are often complex and heterogeneous, and several modalities such as demographic, clinical, imaging, genetics and environmental data have been studied to improve

their understanding. Deep learning, a subpart of machine learning, provides complex algorithms that can learn from such various data. It has become state of the art in numerous fields, including computer vision and natural language processing, and is also growingly applied in medicine. In this article, we review the use of deep learning for brain disorders. More specifically, we identify the main applications, the concerned disorders and the types of architectures and data used. Finally, we provide guidelines to bridge the gap between research studies and clinical routine.

More details in [39].

## 7.6 Converting disease maps into heavyweight ontologies: general methodology and application to Alzheimer's disease

**Participants:** Vincent Henry, Ivan Moszer, Olivier Dameron, Marie-Claude Potier, Martin Hoffman-Apitius, Olivier Colliot *(Correspondant)*.

Omics technologies offer great promises for improving our understanding of diseases. The integration and interpretation of such data pose major challenges, calling for adequate knowledge models. Disease maps provide curated knowledge about disorders' pathophysiology at the molecular level adapted to omics measurements. However, the expressiveness of disease maps could be increased to help avoiding ambiguities and misinterpretations and to reinforce their interoperability with other knowledge resources. Ontologies are an adequate framework to overcome this limitation, through their axiomatic definitions and logical reasoning properties. We introduce the Disease Map Ontology (DMO), an ontological upper model based on systems biology terms. We then propose to apply DMO to Alzheimer's disease (AD). Specifically, we use it to drive the conversion of AlzPathway, a disease map devoted to Alzheimer's disease, into a formal ontology: AD Map Ontology (ADMO). We demonstrate that it allows one to deal with issues related to redundancy, naming, consistency, process classification and pathway relationships. Furthermore, we show that it can store and manage multi-omics data. Finally, we expand the model using elements from other resources, such as clinical features contained in the ADO (AD Ontology), resulting in an enriched model called ADMO-plus. The current versions of DMO, ADMO and ADMOplus are freely available here.

More details in [55].

## 7.7 Exploratory analysis of the genetics of impulse control disorders in Parkinson's disease using genetic risk scores

**Participants:** Johann Faouzi *(Correspondant)*, Baptiste Couvy-Duchesne, Samir Bekadar, Olivier Colliot, Jean-Christophe Corvol.

We studied the association between impulse control disorders (ICDs) in Parkinsons disease (PD) and genetic risk scores (GRS) for 40 known or putative risk factors (e.g. depression, personality traits). In absence of published genome-wide association studies (GWAS), little is known about the genetics of ICDs in PD. GRS of related phenotypes, for which large GWAS are available, may help shed light on the genetic contributors of ICDs in PD. We searched for GWAS on European ancestry populations with summary statistics publicly available for a broad range of phenotypes, including other psychiatric disorders, personality traits, and simple phenotypes. We separately tested their predictive ability in two of the largest PD cohorts with clinical and genetic available: the Parkinsons Progression Markers Initiative database (N = 368, 33% female) and the Drug Interaction With Genes in Parkinsons Disease study (N = 373, 40% female). We considered 40 known or putative risk factors for ICDs in PD for which large GWAS had been published. After Bonferroni correction for multiple comparisons, no GRS or the combination of the 40 GRS were significantly associated with ICDs from the analyses in each cohort separately and from the meta-analysis. Albeit unsuccessful, our approach will gain power in the coming years with increasing availability of genotypes in clinical cohorts of PD, but also from future increase in GWAS sample sizes

of the phenotypes we considered. Our approach may be applied to other complex disorders, for which GWAS are not available or limited.

More details in [50].

## 7.8 Association and prediction of phenotypic traits from neuroimaging data using a multi-component mixed model excluding the target vertex

**Participants:** Baptiste Couvy-Duchesne *(Correspondant)*, Naomi Wray, Peter Visscher, Jian Yang, Olivier Colliot.

Mass-univariate association analyses aim at mapping the brain regions associated with a trait/disorder. The correlation between vertices may cause a true association to spread locally (cluster of association) or distally (false positive cluster). We previously showed that controlling for all vertices in the model (using a linear mixed model: LMM), could greatly reduce the probability of false positive and improve mapping precision. Here, we investigated a new LMM called MOMENT which reduces false positive rate in methylome-wide association studies. Compared to LMM, MOMENT had enhanced power and mapping precision but failed at reducing the rates of false positives clusters.The increasing sample sizes from neuroimaging studies should allow detection of image measures are associated with phenotypic traits with smaller effect sizes, which will advance progress in the mapping of the brain regions associated with traits and diseases. The UK Biobank (UKB) is one of the best example of this new generation of samples. Multimodal Brain MRI collection is currently ongoing, with tens of thousands of individuals already imaged out of a target of 100,000. The large sample size, together with the breadth of phenotyping (incl. self-reports, in lab assessments, prescription and medical history), should allow new insights into the factors contributing to brain differences between older adults.

More details in [70].

## 7.9 Primary Progressive Aphasia Associated With GRN Mutations: New Insights Into the Non-amyloid Logopenic Variant

**Participants:** Dario Saracino *(Correspondant)*, Sophie Ferrieux, Simona Bottani, Olivier Colliot, Marc Teichmann, Raphaella Migliaccio, Isabelle Le Ber.

We aimed to determine relative frequencies and linguistic profiles of primary progressive aphasia (PPA) variants associated with progranulin (GRN) mutations, and study their neuroanatomical correlates. PPA patients carrying GRN mutations (PPA-GRN) were selected amongst a national prospective research cohort of 1,696 frontotemporal dementia (FTD) patients, including 235 patients with PPA. All PPA patients with amyloid-positive CSF biomarkers were excluded. In this cross-sectional study, speech/language and cognitive profiles were characterized with standardized evaluations, and grey matter (GM) atrophy patterns using voxel-based morphometry. Comparisons were performed with controls, and sporadic PPA patients. Among the overall population of 235 patients, 45 (19%) carried GRN mutations. We studied 32 of these and showed that logopenic PPA (lvPPA) was the most frequent linguistic variant (13, 41%), followed by non-fluent/agrammatic (nfvPPA: 9, 28%) and mixed forms (8, 25%). Semantic variant was rather rare (2, 6%). LvPPA patients, qualified as non-amyloid-lvPPA, presented canonical logopenic deficit. Seven out of 13 had a pure form, six showed subtle additional linguistic deficits not fitting criteria for mixed PPA, hence labelled as "logopenic-spectrum variant". GM atrophy primarily involved left posterior temporal gyrus, mirroring neuroanatomical changes of amyloid-positive-lvPPA. NfvPPA patients presented agrammatism (89%) rather than apraxia of speech (11%). This study shows that most frequent PPA variant associated with GRN mutations is non-amyloid lvPPA, preceding nfvPPA and mixed forms, and illustrates that language network may be affected at different levels. GRN testing is indicated for PPA patients, whether familial or sporadic. This finding is important for upcoming GRN gene-specific therapies.

## 7.10 A diffeomorphic vector field approach to analyze the thickness of the hippocampus from 7T MRI

**Participants:** Alexis Guyot, Ana Graciano-Fouquier, Emilie Gerardin, Marie Chupin, Joan Glaunès, Linda Marrakchi-Kacem, Johanne Germain, Claire Boutet, Claire Cury, Lucie Hertz-Pannier, Alexandre Vignaud, Stanley Durrleman, Thomas Henry, Pierre-Francois van de Moortele, Alain Trouvé, Olivier Colliot *(Correspondant)*.

7-Tesla MRI of the hippocampus enhances the visualization of its internal substructures. Among these substructures, the cornu Ammonis and subiculum form a contiguous folded ribbon of gray matter. We have proposed a method to analyze local thickness measurements of this ribbon. We introduced an original approach based upon the estimation of a diffeomorphic vector field that traverses the ribbon. The method was designed to handle specificities of the hippocampus and corresponding 7-Tesla acquisitions: highly convoluted surface, non closed ribbon, incompletely defined inner/outer boundaries, anisotropic acquisitions. We furthermore proposed to conduct group comparisons using a population template built from the central surfaces of individual subjects. We first assessed the robustness of our approach to anisotropy, as well as to inter-rater variability, on a post-mortem scan and on in vivo acquisitions respectively. We then conducted a group study on a dataset of in vivo MRI from temporal lobe epilepsy (TLE) patients and healthy controls. The method detected local thinning patterns in patients, predominantly ipsilaterally to the seizure focus, which is consistent with medical knowledge. This new technique allows measuring the thickness of the hippocampus from 7-Tesla MRI. It shows good robustness with respect to anisotropy and inter-rater variability and has the potential to detect local atrophy in patients. As 7-Tesla MRI is increasingly available, this new method may become a useful tool to study local alterations of the hippocampus in brain disorders. It is made freely available to the community (code: here, postmortem segmentation: here).

More details in [54].

## 7.11 Reproducible evaluation of diffusion MRI features for automatic classification of patients with Alzheimer's disease

**Participants:** Junhao Wen *(Correspondant)*, Jorge Samper-Gonzalez, Simona Bottani, Alexandre Routier, Ninon Burgos, Thomas Jacquemont, Sabrina Fontanella, Stanley Durrleman, Stéphane Epelbaum, Anne Bertrand, Olivier Colliot.

Diffusion MRI is the modality of choice to study alterations of white matter. In past years, various works have used diffusion MRI for automatic classification of AD. However, classification performance obtained with different approaches is difficult to compare and these studies are also difficult to reproduce. In the present paper, we first extend a previously proposed framework to diffusion MRI data for AD classification. Specifically, we add: conversion of diffusion MRI ADNI data into the BIDS standard and pipelines for diffusion MRI preprocessing and feature extraction. We then apply the framework to compare different components. First, FS has a positive impact on classification results: highest balanced accuracy (BA) improved from 0.76 to 0.82 for task CN vs AD. Secondly, voxel-wise features generally gives better performance than regional features. Fractional anisotropy (FA) and mean diffusivity (MD) provided comparable results for voxel-wise features. Moreover, we observe that the poor performance obtained in tasks involving MCI were potentially caused by the small data samples, rather than by the data imbalance. Furthermore, no extensive classification difference exists for different degree of smoothing and registration methods. Besides, we demonstrate that using non-nested validation of FS leads to unreliable and over-optimistic results: 0.05 up to 0.40 relative increase in BA. Lastly, with proper FR and FS, the performance of diffusion MRI features is comparable to that of T1w MRI. All the code of the framework and the experiments are publicly available: general-purpose tools have been integrated into the Clinica software package) and the paper-specific code is available here.

More details in [67].

## 7.12 Step-wise target controllability identifies dysregulated pathways of macrophage networks in multiple sclerosis

**Participants:** Bassignana Giulia, Fransson Jennifer, Henry Vincent, Colliot Olivier, Zujovic Violetta, De Vico Fallani Fabrizio *(Correspondant)*.

Identifying the nodes able to drive the state of a network is crucial to understand, and eventually control, biological systems. Despite recent advances, such identification remains difficult because of the huge number of equivalent controllable configurations, even in relatively simple networks. Based on the evidence that in many applications it is essential to test the ability of individual nodes to control a specific target subset, we develop a fast and principled method to identify controllable driver-target configurations in sparse and directed networks. We demonstrate our approach on simulated networks and experimental gene networks to characterize macrophage dysregulation in human subjects with multiple sclerosis.

More details in [37].

## 7.13 Predicting the Progression of Mild Cognitive Impairment Using Machine Learning: A Systematic, Quantitative and Critical Review

**Participants:** Manon Ansart, Stéphane Epelbaum, Ninon Burgos, Didier Dormont, Olivier Colliot, Stanley Durrleman.

We performed a systematic review of studies focusing on the automatic prediction of the progression of mild cognitive impairment to Alzheimer's disease (AD) dementia, and a quantitative analysis of the methodological choices impacting performance. This review included 172 articles, from which 234 experiments were extracted. For each of them, we reported the used data set, the feature types, the algorithm type, performance and potential methodological issues. The impact of these characteristics on the performance was evaluated using a multivariate mixed effect linear regressions. We found that using cognitive, fluorodeoxyglucose-positron emission tomography or potentially electroencephalography and magnetoencephalography variables significantly improved predictive performance compared to not including them, whereas including other modalities, in particular T1 magnetic resonance imaging, did not show a significant effect. The good performance of cognitive assessments questions the wide use of imaging for predicting the progression to AD and advocates for exploring further fine domain-specific cognitive assessments. We also identified several methodological issues, including the absence of a test set, or its use for feature selection or parameter tuning in nearly a fourth of the papers. Other issues, found in 15 percent of the studies, cast doubts on the relevance of the method to clinical practice. We also highlight that short-term predictions are likely not to be better than predicting that subjects stay stable over time. These issues highlight the importance of adhering to good practices for the use of machine learning as a decision support system for the clinical practice.

More details in [33].

## 7.14 Gaussian Graphical Model exploration and selection in high dimension low sample size setting

**Participants:** Thomas Lartigue, Simona Bottani, Olivier Colliot, Stanley Durrleman, Stéphanie Allassonnière.

Gaussian Graphical Models (GGM) are often used to describe the conditional correlations between the components of a random vector. In this article, we compare two families of GGM inference methods:

nodewise edge selection and penalised likelihood maximisation. We demonstrate on synthetic data that, when the sample size is small, the two methods produce graphs with either too few or too many edges when compared to the real one. As a result, we propose a composite procedure that explores a family of graphs with an nodewise numerical scheme and selects a candidate among them with an overall likelihood criterion. We demonstrate that, when the number of observations is small, this selection method yields graphs closer to the truth and corresponding to distributions with better KL divergence with regards to the real distribution than the other two. Finally, we show the interest of our algorithm on two concrete cases: first on brain imaging data, then on biological nephrology data. In both cases our results are more in line with current knowledge in each field.

More details in [57].

## 7.15 Enhanced Methods for Lymphocyte Detection and Segmentation on H&E-Stained Images using eXclusive Autoencoders

**Participants:** Chao-Hui Huang, Daniel Racoceanu.

We propose a generalized solution for lymphocyte detection and segmentation, based on a novel image feature extraction method, named exclusive autoencoder (XAE). XAE is compatible with conventional autoencoder (AE) and able to provide additional information about the categorization in the feature space. For the task of lymphocyte detection, XAE was able to reach the an F-score of 99.96%, outperforming the state-of-the-art methods (reporting an F-score of 90%). Further, based on the integration of XAE+FCN (fully connected network) and conventional image processing function blocks provided in CellProfiler, we propose a lymphocyte segmentation pipeline. The obtained Dice coefficient reached 88.31% while the cutting-edge approach was at 74%.

More details in [16].

## 7.16 Tau Protein Discrete Aggregates in Alzheimer's Disease: Neuritic Plaques and Tangles Detection and Segmentation using Computational Histopathology

**Participants:** Kristina Maňoušková, Valentin Abadie, Mehdi Ounissi, Gabriel Jimenez, Lev Stimmer, Benoit Delatour, Stanley Durrleman, Daniel Racoceanu *(Correspondant)*.

Tau proteins in the gray matter are widely known to be a part of Alzheimer's disease symptoms. They can aggregate in three different structures within the brain: neurites, tangles, and neuritic plaques. The morphology and spatial disposition of these three aggregates are hypothesised to be correlated to the advancement of the disease. In order to establish a behavioural disease model related to the Tau proteins aggregates, it is necessary to develop algorithms to detect and segment them automatically. We present a 4-folded pipeline aiming to perform with clinically operational results. This pipeline is composed of a non-linear colour normalisation, a CNN-based image classifier, an Unet-based image segmentation stage, and a morphological analysis of the segmented objects. The tangle detection and segmentation algorithms improve state-of-the-art performances (75.8% and 91.1% F1-score, respectively), as well as for neuritic plaques detection and segmentation (81.3% and 78.2% F1-score, respectively). These results constitute an initial baseline in an area where no prior results exist, as far as we know. Even if overall, the results need to be robustified to fully meet biologists' expectations, the pipeline is complete and based on a promising state-of-the-art architecture. Therefore, we consider this study a handy baseline of an impactful extension to support new advances in Alzheimer's disease. Moreover, building a fully operational pipeline will be crucial to create a 3D histology map for a deeper understanding of clinico-pathological associations in Alzheimer's disease and the histology-based evidence of disease stratification among different sub-types.

More details in [18]

## 7.17 Phase/Amplitude Synchronization of Brain Signals During Motor Imagery BCI Tasks

**Participants:** Tiziana Cattai, Stefania Colonnese, Dani Bassett, MarieConstance Corsi, De Vico Fallani Fabrizio *(Correspondant)*.

In the last decade, functional connectivity (FC) has been increasingly adopted based on its ability to capture statistical dependencies between multivariate brain signals. However, the role of FC in the context of brain-computer interface applications is still poorly understood. To address this gap in knowledge, we considered a group of 20 healthy subjects during an EEG-based hand motor imagery (MI) task. We studied two well-established FC estimators, i.e. spectral- and imaginary-coherence, and we investigated how they were modulated by the MI task. We characterized the resulting FC networks by extracting the strength of connectivity of each EEG sensor and we compared the discriminant power with respect to standard power spectrum features. At the group level, results showed that while spectral-coherence based network features were increasing in the sensorimotor areas, those based on imaginary-coherence were significantly decreasing. We demonstrated that this opposite, but complementary, behavior was respectively determined by the increase in amplitude and phase synchronization between the brain signals. At the individual level, we eventually assessed the potential of these network connectivity features in a simple off-line classification scenario. Taken together, our results provide fresh insights into the oscillatory mechanisms subserving brain network changes during MI and offer new perspectives to improve BCI performance.

More details in [42].

## 7.18 Improving J-Divergence of Brain Connectivity States by Graph Laplacian Denoising

**Participants:** Tiziana Cattai, MarieConstance Corsi, Dani Bassett, Fabrizio De Vico Fallani, Stefania Colonnese *(Correspondant)*.

Functional connectivity (FC) can be represented as a network, and is frequently used to better understand the neural underpinnings of complex tasks such as motor imagery (MI) detection in brain-computer interfaces (BCIs). However, errors in the estimation of connectivity can affect the detection performances. In this work, we address the problem of denoising common connectivity estimates to improve the detectability of different connectivity states. Specifically, we propose a graph signal processing based denoising algorithm that acts on the network graph Laplacian. Further, we derive a novel formulation of the Jensen divergence for the denoised Laplacian under different states. Numerical simulations on synthetic data show that denoising improves the Jensen divergence of connectivity patterns corresponding to different task conditions. Furthermore, we apply the Laplacian denoising technique to brain networks estimated from real EEG data recorded during MI-BCI experiments. A novel formulation of the J-divergence allows to quantify the distance between the FC networks in the motor imagery and resting states, as well as to understand the contribution of each Laplacian variable to the total J-divergence between two states. Experimental results on real MI-BCI EEG data demonstrate that the Laplacian denoising improves the separation of motor imagery and resting mental states, and it shortens the time interval required for connectivity estimation. We conclude that the approach shows promise for robust detection of connectivity states while being appealing for implementation in real-time BCI applications.

More details in [43].

## 7.19 BCI learning induces core-periphery reorganization in M/EEG multiplex brain networks

**Participants:** MarieConstance Corsi, Mario Chavez, Dani Bassett, Fabrizio De Vico Fallani *(Correspondant)*
.

Brain-computer interfaces (BCIs) constitute a promising tool for communication and control. However, mastering non-invasive closed-loop systems remains a learned skill that is difficult to develop for a non-negligible proportion of users. The involved learning process induces neural changes associated with a brain network reorganization that remains poorly understood. Approach: To address this inter-subject variability, we adopted a multilayer approach to integrate brain network properties from electroencephalographic (EEG) and magnetoencephalographic (MEG) data resulting from a four-session BCI training program followed by a group of healthy subjects. Our method gives access to the contribution of each layer to multilayer network that tends to be equal with time. Main results: We show that regardless the chosen modality, a progressive increase in the integration of somatosensory areas in the $\alpha$ band was paralleled by a decrease of the integration of visual processing and working memory areas in the $\beta$ band. Notably, only brain network properties in multilayer network correlated with future BCI scores in the $\alpha$ 2 band: positively in somatosensory and decision-making related areas and negatively in associative areas. Significance: Our findings cast new light on neural processes underlying BCI training. Integrating multimodal brain network properties provides new information that correlates with behavioral performance and could be considered as a potential marker of BCI learning.

Mores details in [45].

## 7.20 Learning Riemannian metric for disease progression modeling

**Participants:** Samuel Gruffaz, Pierre-Emmanuel Poulet, Etienne Maheux, Bruno Jedynak, Stanley Durrleman *(Correspondant)*.

Linear mixed-effect models provide a natural baseline for estimating disease progression using longitudinal data. They provide interpretable models at the cost of modeling assumptions on the progression profiles and their variability across subjects. A significant improvement is to embed the data in a Riemannian manifold and learn patient-specific trajectories distributed around a central geodesic. A few interpretable parameters characterize subject trajectories at the cost of a prior choice of the metric, which determines the shape of the trajectories. We extend this approach by learning the metric from the data allowing more flexibility while keeping the interpretability. Specifically, we learn the metric as the push-forward of the Euclidean metric by a diffeomorphism. This diffeomorphism is estimated iteratively as the composition of radial basis functions belonging to a reproducible kernel Hilbert space. The metric update allows us to improve the forecasting of imaging and clinical biomarkers in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Our results compare favorably to the 56 methods benchmarked in the TADPOLE challenge.

More details in [71]

## 7.21 Mixture of Conditional Gaussian Graphical Models for unlabelled heterogeneous populations in the presence of co-factors

**Participants:** Thomas Lartigue, Stanley Durrleman, Stéphanie Allassonnière.

Conditional correlation networks, within Gaussian Graphical Models (GGM), are widely used to describe the direct interactions between the components of a random vector. In the case of an unlabelled Heterogeneous population, Expectation Maximisation (EM) algorithms for Mixtures of GGM have been proposed to estimate both each sub-population's graph and the class labels. However, we argue that, with most real data, class affiliation cannot be described with a Mixture of Gaussian, which mostly groups

data points according to their geometrical proximity. In particular, there often exists external co-features whose values affect the features' average value, scattering across the feature space data points belonging to the same sub-population. Additionally, if the co-features' effect on the features is Heterogeneous, then the estimation of this effect cannot be separated from the sub-population identification. In this article, we propose a Mixture of Conditional GGM (CGGM) that subtracts the heterogeneous effects of the co-features to regroup the data points into sub-population corresponding clusters. We develop a penalised EM algorithm to estimate graph-sparse model parameters. We demonstrate on synthetic and real data how this method fulfils its goal and succeeds in identifying the sub-populations where the Mixtures of GGM are disrupted by the effect of the co-features.

More details in [58]

## 7.22 Longitudinal self-supervision to disentangle inter-patient variability from disease progression

**Participants:** Raphaël Couronné, Paul Vernhet, Stanley Durrleman.

The problem of building disease progression models with longitudinal data has long been addressed with parametric mixed-effect models. They provide interpretable models at the cost of modeling assumptions on the progression profiles and their variability across subjects. Their deep learning counterparts, on the other hand, strive on flexible data-driven modeling, and additional interpretability-or, as far as generative models are involved, disentanglement of latent variables with respect to generative factors-comes from additional constraints. In this work, we propose a deep longitudinal model designed to disentangle inter-patient variability from an estimated disease progression timeline. We do not seek for an explicit mapping between age and disease stage, but to learn the latter solely from the ordering between visits using a differentiable ranking loss. Furthermore, we encourage inter-patient variability to be encoded in a separate latent space, where for each patient a single representation is learned from its set of visits, with a constraint of invariance under permutation of the visits. The modularity of the network architecture allows us to apply our model on various data types: a synthetic image dataset with known generative factors, cognitive assessments and neuroimaging data. We show that, combined with our patient encoder, the ranking loss for visits helps to exceed models with supervision, in particular in terms of disease staging.

More details in [79]

## 7.23 Changes in the use of psychotropic drugs during the course of Alzheimer's disease: A large-scale longitudinal study of French medical records

**Participants:** Manon Ansart, Stéphane Epelbaum, Marion Houot, Thomas Nedelec, Béranger Lekens, Laurène Gantzer, Didier Dormont, Stanley Durrleman *(Correspondant)*.

Introduction: We aim to understand how patients with Alzheimer's disease (AD) are treated by identifying in a longitudinal fashion the late-life changes in patients' medical history that precede and follow AD diagnosis. Methods: We use prescription history of 34,782 patients followed between 1996 and 2019 by French general practitioners. We compare patients with an AD diagnosis, patients with mild cognitive impairment (MCI), and patients free of mental disorders. We use a generalized mixed-effects model to study the longitudinal changes in the prescription of eight drug types for a period 15 years before diagnosis and 10 years after. Results: In the decades preceding diagnosis, we find that future AD patients are treated significantly more than MCI patients with most psychotropic drugs and that most studied drugs are increasingly prescribed with age. At the time of diagnosis, all psychotropic drugs except benzodiazepines show a significant increase in prescription, while other drugs are significantly less prescribed. In the 10 years after diagnosis, nearly all categories of drugs are less and less prescribed

including antidementia drugs. Discussion: Pre-diagnosis differences between future AD patients and MCI patients may indicate that subtle cognitive changes are recognized and treated as psychiatric symptoms. The disclosure of AD diagnosis drastically changes patients' care, priority being given to the management of psychiatric symptoms. The decrease of all prescriptions in the late stages may reflect treatment discontinuation and simplification of therapeutic procedures. This study therefore provides new insights into the medical practices for management of AD. More details in [34]

### 7.24 A machine learning approach to screen for preclinical Alzheimer's disease

**Participants:** Sinead Gaubert, Marion Houot, Manon Ansart, Marie-Constance Corsi, Marie-Odile Habert, Bruno Dubois, Fabrizio de Vico Fallani, Stanley Durrleman, Stéphane Epelbaum *(Correspondant)*.

Combining multimodal biomarkers could help in the early diagnosis of Alzheimer's disease (AD). We included 304 cognitively normal individuals from the INSIGHT-preAD cohort. Amyloid and neurodegeneration were assessed on 18F-florbetapir and 18F-fluorodeoxyglucose PET, respectively. We used a nested cross-validation approach with non-invasive features (electroencephalography [EEG], APOE4 genotype, demographic, neuropsychological and MRI data) to predict: 1/ amyloid status; 2/ neurodegeneration status; 3/ decline to prodromal AD at 5-year follow-up. Importantly, EEG was most strongly predictive of neurodegeneration, even when reducing the number of channels from 224 down to 4, as 4-channel EEG best predicted neurodegeneration (negative predictive value [NPV] = 82%, positive predictive value [PPV] = 38%, 77% specificity, 45% sensitivity). The combination of demographic, neuropsychological data, APOE4 and hippocampal volumetry most strongly predicted amyloid (80% NPV, 41% PPV, 70% specificity, 58% sensitivity) and most strongly predicted decline to prodromal AD at 5 years (97% NPV, 14% PPV, 83% specificity, 50% sensitivity). Thus, machine learning can help to screen patients at high risk of preclinical AD using non-invasive and affordable biomarkers.

More details in [52]

### 7.25 Gaussian Graphical Model exploration and selection in high dimension low sample size setting

**Participants:** Thomas Lartigue, Simona Bottani, Olivier Colliot, Stanley Durrleman, Stéphanie Allassonnière.

Gaussian graphical models (GGM) are often used to describe the conditional correlations between the components of a random vector. In this article, we compare two families of GGM inference methods: the nodewise approach and the penalised likelihood maximisation. We demonstrate on synthetic data that, when the sample size is small, the two methods produce graphs with either too few or too many edges when compared to the real one. As a result, we propose a composite procedure that explores a family of graphs with a nodewise numerical scheme and selects a candidate among them with an overall likelihood criterion. We demonstrate that, when the number of observations is small, this selection method yields graphs closer to the truth and corresponding to distributions with better KL divergence with regards to the real distribution than the other two. Finally, we show the interest of our algorithm on two concrete cases: first on brain imaging data, then on biological nephrology data. In both cases our results are more in line with current knowledge in each field.

More details in [57]

### 7.26 Mixture modeling for identifying subtypes in disease course mapping

**Participants:** Pierre-Emmanuel Poulet, Stanley Durrleman.

Disease modeling techniques summarize the possible trajectories of progression from multimodal and longitudinal data. These techniques often assume that individuals form a homogeneous cluster, thus ignoring possible disease subtypes within the population. We extend a non-linear mixed-effect model used for disease course mapping with a mixture framework. We jointly estimate model parameters and subtypes with a tempered version of a stochastic approximation of the Expectation Maximisation algorithm. We show that our model recovers the ground truth parameters from synthetic data, in contrast to the naive solution consisting in post hoc clustering of individual parameters from a one-class model. Applications to Alzheimer's disease data allows the unsupervised identification of disease subtypes associated with distinct relationship between cognitive decline and progression of imaging and biological biomarkers.

More details in [73]

## 7.27 AD Course Map charts Alzheimer's disease progression

**Participants:** Igor Koval, Alexandre Bône, Maxime Louis, Thomas Lartigue, Simona Bottani, Arnaud Marcoux, Jorge Samper-Gonzalez, Ninon Burgos, Benjamin Charlier, Anne Bertrand, Stéphane Epelbaum, Olivier Colliot, Stéphanie Allassonnière, Stanley Durrleman *(Correspondant)*.

Alzheimer's disease (AD) is characterized by the progressive alterations seen in brain images which give rise to the onset of various sets of symptoms. The variability in the dynamics of changes in both brain images and cognitive impairments remains poorly understood. This paper introduces AD Course Map a spatiotemporal atlas of Alzheimer's disease progression. It summarizes the variability in the progression of a series of neuropsychological assessments, the propagation of hypometabolism and cortical thinning across brain regions and the deformation of the shape of the hippocampus. The analysis of these variations highlights strong genetic determinants for the progression, like possible compensatory mechanisms at play during disease progression. AD Course Map also predicts the progression of patient data in the future with a better accuracy than the 56 methods benchmarked in the open challenge TADPOLE. Finally, AD Course Map is used to simulate cohorts of virtual patients developing Alzheimer's disease. AD Course Map offers therefore new tools for exploring the progression of AD and personalizing patients care.

More details in [56]

## 7.28 Understanding the Variability in Graph Data Sets through Statistical Modeling on the Stiefel Manifold

**Participants:** Clément Mantoux, Baptiste Couvy-Duchesne, Federica Cacciamani, Stéphane Epelbaum, Stanley Durrleman, Stéphanie Allassonnière.

Network analysis provides a rich framework to model complex phenomena, such as human brain connectivity. It has proven efficient to understand their natural properties and design predictive models. In this paper, we study the variability within groups of networks, i.e., the structure of connection similarities and differences across a set of networks. We propose a statistical framework to model these variations based on manifold-valued latent factors. Each network adjacency matrix is decomposed as a weighted sum of matrix patterns with rank one. Each pattern is described as a random perturbation of a dictionary element. As a hierarchical statistical model, it enables the analysis of heterogeneous populations of adjacency matrices using mixtures. Our framework can also be used to infer the weight of missing edges. We estimate the parameters of the model using an Expectation-Maximization-based algorithm. Experimenting on synthetic data, we show that the algorithm is able to accurately estimate the latent structure in both low and high dimensions. We apply our model on a large data set of functional brain connectivity matrices from the UK Biobank. Our results suggest that the proposed model accurately describes the complex variability in the data set with a small number of degrees of freedom.

More details in [61]

# 8 Bilateral contracts and grants with industry

## 8.1 Bilateral grants with industry

### 8.1.1 Carthera

**Participants:** Stéphane Epelbaum *(Correspondant)*, Alexandre Carpentier, Anne Bertrand, Marie Odile Habert.

- Project title: Open label phase 1/2 study evaluating the safety and usefulness of transient opening of the blood-brain barrier using low intensity pulsed ultrasounds generated by the implantable device SONOCLOUD in patients with mild Alzheimer's disease
- Started in 2016
- Amount: 400 K€
- Coordinator: Stéphane Epelbaum
- Other partners: Sorbonne University, AP-HP
- Abstract: This project aims at opening the blood brain barrier (BBB) in 10 mild Alzheimer's disease patients in order to improve the clearance of beta-amyloid and tau deposits in their brain as suggested in mice models of the disease. This first in man study will evaluate the safety and efficacy of an implanted device, SONOCLOUD, to open the BBB 7 times in each participant. Efficacy will be evaluated on the ability of the method to decrease the amyloid load evidenced by AV45 Positron Emission Tomography (PET), increase the brain metabolism analyzed by Fluorodeoxyglucose PET and improve cognition. If successful, this study will pave the way for future trials in which drugs can be used in addition to BBB opening to maximize their effect.

### 8.1.2 Sanofi

**Participants:** Stanley Durrleman *(Correspondant)*.

- This project aims at modeling Parkinson disease progression for patients with mutations in the GBA genes, selecting potential good responders in clinical trials based on their progression profile, and evaluating new measures of drug efficacy.
- Coordinator: Stanley Durrleman
- Started in 2020

# 9 Partnerships and cooperations

## 9.1 International initiatives

**Informal International Partners**

- O. Colliot has a collaboration with the Center for Magnetic Resonance Research, University of Minnesota, USA (P-F Van de Moortele, T. Henry).
- O. Colliot and B Couvy-Duchesne have a collaboration with the University of Queensland, Australia (P. Visscher, N. Wray, M. Wright).

- 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).
- S. Durrleman has collaboration with Portland State University (B. Jedynak)
- D. Racoceanu has a collaboration with the Pontifical Catholic University of Peru (G. Jiménez). A recent publication [17] has been generated from this collaboration.
- D. Racoceanu has a collaboration with the Bioinformatics Institute, Agency for Science, Technology and Research (BII/A*STAR) Singapore (H.K. Lee) - one PhD (Ms. Oumeima Laifa) was jointly co-supervised and recently defended her PhD.
- D. Racoceanu had a collaboration with M. Ryad Zemouri (CNAM) concerning a state review about DL in biomedical applications [32].
- N. Burgos has a collaboration with the Centre for Biomedical Image Analysis, Masaryk University, Czech Republic (D. Svoboda).
- B. Couvy-Duchesne has a collaboration with Dr. Romain Colle (Kremlin Bicetre) and the ENIGMA consortium (Enhancing NeuroImaging Genetics using Meta-Analyses), to perform neuroimaging studies.
- B. Couvy-Duchesne has a collaboration with King's College London (Social, Genetic and Developmental Psychiatry (SGDP) Centre Institute of Psychiatry, Psychology and Neuroscience), for a project led by Anna Furtjes a PhD student of Dr. Stuart Ritchie.
- F. De Vico Fallani has a collaboration with the Penn University (D. Bassett) and Queen Mary Univ. (V. Latora).

## 9.2 European initiatives

### 9.2.1 FP7 & H2020 projects

**LEASP**

**Title:** Learning spatiotemporal patterns in longitudinal image data sets of the aging brain

**Duration:** September 2016 - August 2021

**Coordinator:** Inria

**Inria contact:** Stanley Durrleman

**Summary:** 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.

**VirtualBrainCloud**

**Title:** Personalized Recommendations for Neurodegenerative Disease

**Duration:** December 2018 - November 2022

**Coordinator:** CHARITE - UNIVERSITAETSMEDIZIN BERLIN

**Partners:**

- ALZHEIMER EUROPE (Luxembourg)
- CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE CNRS (France)
- CODEMART SRL (Romania)
- EODYNE SYSTEMS SL (Spain)
- FORSCHUNGSZENTRUM JULICH GMBH (Germany)
- FRAUNHOFER GESELLSCHAFT ZUR FOERDERUNG DER ANGEWANDTEN FORSCHUNG E.V. (Germany)
- FUNDACIO INSTITUT DE BIOENGINYERIA DE CATALUNYA (Spain)
- INSTITUT DU CERVEAU ET DE LA MOELLE EPINIERE (France)
- THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD (UK)
- TP21 GMBH (Germany)
- UNIVERSIDAD COMPLUTENSE DE MADRID (Spain)
- UNIVERSITA DEGLI STUDI DI GENOVA (Italy)
- UNIVERSITAT WIEN (Austria)
- UNIVERSITE D'AIX MARSEILLE (France)

**Inria contact:** Stanley Durrleman

**Summary:** 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. The VirtualBrainCloud 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.

**BCINET**

**Title:** Non-invasive decoding of brain communication patterns to ease motor restoration after stroke

**Duration:** October 2020 - September 2025

**Coordinator:** Inria

**Partners:**

- INSTITUT DU CERVEAU ET DE LA MOELLE EPINIERE (France)

**Inria contact:** Fabrizio De Vico Fallani

**Summary:** Human-computer interfaces are increasingly explored to facilitate interaction with the external world. Brain-computer interfaces (BCIs), bypassing the skeletomuscular system, are particularly promising for assisting paralyzed people in control and communication, but also for boosting neuromotor rehabilitation. Despite their potential, the societal impact of BCIs is dramatically limited by the poor usability in real-life applications. While many solutions have been proposed - from the identification of the best classification algorithm to the type of sensory feedback - the accuracy is still highly variable across subjects and BCIs cannot be used by everyone. Critically, these approaches have implicitly assumed that the user's intent could be decoded by examining the activity of single brain areas. Today, we know that this is not true as the brain functioning essentially depends on a complex network of interactions between differently specialized areas. The grand challenge of this project is to develop a novel generation of BCIs that integrate the user's brain network information for enhancing accuracy and usability. Based on this approach, we will experiment innovative BCI prototypes to restore the lost motor functions in patients suffering from stroke. This project relies on a unifying framework that analyses and models brain networks by means of analytical tools derived from graph theory and complex systems science. By recruiting diverse neuroimaging and experimental methods, within a modern computational framework, we aim to i) identify new control features for enhancing BCI accuracy, ii) study the brain dynamics of human learning for improving adaptive BCI architectures, and iii) optimize brain stimulation techniques for boosting BCI skill acquisition. This project can significantly improve BCI usability as well as determining how brain lesions compromise brain functioning and which solutions are most effective to unlock motor restoration after stroke.

**FET Flagship - Human Brain Project**

**Title:** Human Brain Project

**Duration:** 2016-2026

**Coordinator:** EPFL, Lausanne, Switzerland

**Inria contact:** Olivier Colliot, Stanley Durrleman

**Summary:** 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.

### 9.2.2 Other european programs/initiatives

**E-DADS**

**Participants:** Stanley Durrleman.

- Project acronym: E-DADS
- Project title: Early detection of Alzheimer's disease subtypes
- Duration: 2019 - 2022
- Amount: 1.7M€
- funding scheme: Joint Program in Neurodegenerative Diseases (JPND)
- Coordinator: Daniel Alexander
- Other partners: University College London (UK), Stichting VU University Medical Center (VUmc,The Netherlands), IRCCS Fatebenefratelli (Italy), Commonwealth scientific and industrial research organization (CSIRO, Australia)
- Abstract: Alzheimer's disease (AD) is a global health and economic burden with currently about 47 million affected individuals worldwide. No provably disease-modifying treatments exist. Delaying disease onset in dementia patients by five years can reduce care costs by 36 percent about 88 billions euros per year across the EU. A key confound preventing successful outcomes in most treatment trials to date has been AD's high variation in onset, mechanism, and clinical expression. E-DADS aims to untangle this heterogeneity by defining data-driven subtypes of the clinical manifestation of AD based on brain imaging, cognitive markers, and fluid biomarkers that are robustly identifiable from predictive risk factors (genetics, co-morbidities, physiological and lifestyle factors) years before disease onset. To achieve this we develop a novel multi-view learning strategies that relates end-stage disease manifestations observable in clinical cohorts to features of early-stage or at-risk individuals in preclinical cohorts and the general pre-affected population from population or aging studies. This approach is only possible now due to the availability of large population data, richly phenotyped AD cohorts and advances in machine learning. E-DADS uniquely assembles the necessary data and expertise. The ability to identify AD subtypes and predict them years before onset will significantly advance AD research and clinical management via precision medicine. First, it identifies distinct homogeneous groups, shedding new light on that nature and variability of disease mechanisms ultimately pinpointing effective drug targets. Second, it enables enrichment of future clinical trials for specific groups of patients likely to benefit from a particular intervention. Third, it highlights potential lifestyle interventions that may affect or delay disease onset at very early stages. E-DADS delivers the underpinning technology to achieve this through machine learning and big-data analytics together with a prototype software tool enabling future translation and uptake.

## 9.3 National initiatives

**Health Data Hub**

**Participants:** 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

**AVIESAN - ITMO Cancer**

**Participants:** Daniel Racoceanu.

- Project acronym: MALMO
- Project title: Mathematical Approaches to Modelling Metabolic Plasticity and Heterogeneity in Melanoma
- Duration: 3 years
- Coordinator: Ovidiu Radulescu
- Other partners: University of Montpellier (LPHI - UMR CNRS 5235, LIRMM - UMR CNRS 5506) and the Institut de Recherche en Cancérologie de Montpellier (IRCM – Inserm U1194), Paris Brain Institute (CNRS UMR 7225 – Inserm U 1127).
- Abstract: Cutaneous melanoma is a highly invasive tumor and despite recent therapeutic advances, most patients with advanced melanoma have a poor clinical outcome. At the molecular level, the most frequent mutations in melanoma affect the BRAF oncogene, a protein kinase of the MAPK pathway. Therapies targeting BRAF/MEK are effective for only 50% of the patients and almost systematically generate resistance. Some non-genetic mechanisms of drug resistance are associated with the strong heterogeneity and the plasticity and melanoma cells that still remain poorly understood. In the proposed project, we will address the importance of metabolic plasticity in melanoma cells in the context of drug resistance. In order to understand the mechanistic origin of the resistance to targeted therapies, we will build a predictive multiscale mathematical model. This model describes intracellular dynamics of the metabolic pathways and the dynamics of the melanoma cell sub- populations in interaction with their micro-environment. The model has spatial extension and takes into account cellular heterogeneity. Model initial conditions and parameters describing the microenvironment are learned from image analysis of tumour sections using deep learning as segmentation approach. In order to validate the model, we use a multiplexed imaging technique applied to the detection of metabolic markers in samples prepared from murine xenografted tumours submitted to treatment. Using the mathematical model and the in situ imaging data, we expect to prove the role of the metabolic reprogramming in generating melanoma heterogeneity and its contribution to resistance to targeted therapies. Our predictive mathematical model will also allow us to investigate in silico the relationship between micro-environment, metabolic/cellular plasticity and drug resistance, as well as the potential of combining several therapies simultaneously or with optimized scheduling.

### 9.3.1 ANR

**ANR-PRC BETPARK**

**Participants:** Fabrizio De Vico Fallani *(Correspondant)*.

- Project acronym: BETPARK
- Project title: Neurofeedback for Parkinson's disease
- Duration: Apr 2021 - Mar 2025
- Amount: 712k€

- Coordinator: Nathalie George
- Other partners: CNRS CCLE; ICM
- Abstract: Parkinson's disease (PD) is a complex neurodegenerative disease caused by death of midbrain dopaminergic neurons. This calls for better understanding the pathophysiology of PD in order to pave the way to new non-pharmacological and non-invasive treatment options for PD. We propose to use neurofeedback (NF) to test whether PD patients can learn to self-regulate their brain activity to reduce pathological neural activity and thereby motor symptoms. We will leverage NF to target regulation of pathological beta band (8-35 Hz) oscillations, and we will characterize training-induced changes in cortical network activity and their relationship with symptom severity. Our goal is to provide direct evidence of the functional role of beta rhythms in the pathophysiology of PD while assessing NF as a new non-pharmacological and non-invasive tool for ameliorating PD motor symptoms.

**ANR-PRC BRANDY**

**Participants:** Fabrizio De Vico Fallani *(Correspondant)*.

- Project acronym: BRANDY
- Project title: Brain attention network's dynamics
- Duration: Apr 2019 - Mar 2023
- Amount: 650k€
- Coordinator: Paolo Bartolomeo
- Other partners: ICM
- Abstract: Attention allows us to explore the environment and to effectively respond to external events. Attention sets priorities on the basis of our goals and of the salience of external stimuli. Human visual attention relies on distinct dorsal and ventral fronto-parietal networks, but little is known about their dynamics, because hitherto our knowledge mostly depends on fMRI, which has limited temporal resolution. BRANDY aims at building an anatomo-functional model of human visual attention. Specifically, BRANDY has three main objectives: Work Package (WP) 1 will determine the precise dynamics of normal visual attention on a fine-scale; WP2 will provide important evidence on neurotypical and impaired attention in neglect patients using a network-perspective. WP3 will build comprehensive anatomical and functional models of neurotypical and pathological human visual attention.

**ANR-NIH-NSF CANDT**

**Participants:** 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.

**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 - Jun 2021
- 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.

### 9.3.2 Inria Project Labs

**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.

### 9.3.3 IHU

**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
- Since 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.

**ICM BBT Program - project ImagingDealInMS**

**Participants:** Olivier Colliot *(Correspondant)*, Bruno Stankoff *(Correspondant)*, Arya Yazdan-Panah.

- Project title: Translating the biological mechanisms underlying neurodegeneration into multimodal imaging signatures using deep learning in Multiple Sclerosis (ImagingDealInMS)
- Started in 2021
- Coordinators: Olivier Colliot and Bruno Stankoff (ICM)
- Following the impressive advancements in the treatment of the relapsing phase of multiple sclerosis (MS), the major challenge remaining ahead is the development of treatments effective for preventing or delaying the irreversible accumulation of disability in this disease. A deep understanding of the mechanisms underlying neuro-axonal degeneration, which is the substrate of clinical progression, together with the development of reliable biomarkers, are pre-conditions for the advent and the evaluation of breakthrough therapies. The Stankoff group has pioneered an innovative imaging approach combining positron emission tomography and MRI, and succeeded in generating individual maps or key biological processes such as endogenous remyelination,

neuroinflammation, or early damage preceding lesion formation. We further showed that these mechanisms were influencing disability worsening over the disease course, and recently obtained preliminary results suggesting that a multimodal combination of advanced MRI sequences may have the potential to identify these mechanisms and reproduce the PET results. In this project we propose a totally novel imaging approach that will capture remyelination of lesions, ongoing inflammation invisible on T1 and T2 MRI sequences (subacute/chronic active lesions) and to predict short-term future disease activity (identify prelesional areas), from a single multimodal MRI acquisition in patients with MS. Using PET results as a reference, multimodal signatures of these processes will be identified, and a deep learning approach integrating the whole MRI information in the training procedure will be applied to generate masks for each of them. The accuracy of the discovered algorithms will be validated on independent datasets acquired on a PET-MR system, and their long-term clinical relevance will be tested in a clinical study evaluating patients around 10 years following their enrolment in pilot PET studies. As a result, novel tools assessing key biological processes driving neurodegeneration and disability worsening in MS will become largely available for the medical community, allowing an improved patients' stratification and prognostication, and opening the perspective of tailored care. These tools could also be use as novel endpoints in clinical trials, and may serve to capture similar processes in other neurological diseases.

**ICM BBT3 Program - project STRATIFIAD**

**Participants:** Daniel Racoceanu *(Correspondant)*, Benoit Delatour *(Correspondant)*, Stanley Durrleman, Lev Stimmer, Lars Jorgensen.

- Project title: STRATIFIAD - Refining Alzheimer Disease Patients' stratification using effective, traceable and explicable artificial intelligence approaches in computational histopathology.
- Started in 2021
- Coordinators: Daniel Racoceanu and Benoit Delatour (ICM)
- Other partners: Histology Core plateform (HYSTOMICS) and the Data Analysis Core plateform (DAC), IHU/ICM
- Alzheimer's Disease (AD), the most frequent neurodegenerative disease, is defined by the misfolding and accumulation of Aß peptides and of tau proteins in the brain. Sporadic AD is most commonly present in later life as an amnestic syndrome. However, the clinical presentation of the patients is heterogeneous and different subtypes of the disease have been described, including a rapidly progressive subtype of AD (rAD). Until now, neuropathological assessment of rAD cases was not able to identify specific neuropathological traits for this clinico-pathological entity, despite its unusual fast progression and clinical presentation leading to frequent misdiagnosis as Creutzfeldt-Jakob disease. Our hypothesis is that rAD brains, as well as other atypical variants of AD, display subtle histological changes that would be undercovered by high-throughput automated microscopic analysis. The topography and morphology of the tau and Aß aggregates, the two main brain lesions characterizing the disease are heterogeneous. Aß accumulation takes the form of focal deposits or diffuse plaques; tau lesions form the so-called neurofibrillary tangles but also present different morphologies in dendrites or axons. We propose to study the topography and morphology of these aggregates to better understand the morphological substratum of AD heterogeneity. To address this question at a large scale, one needs to develop software systems for the automatic segmentation, annotation and quantitation of brain lesions in histo-pathological whole slide images (WSI). Therefore, the goal of the STRATIFIAD project is twofold:

  1. to develop fully automated, traceable and explainable artificial intelligence (AI) approaches for the histological location and characterization of the tau and Aß aggregates in whole slide brain images, and to deploy it for routine use on the Histomics core facility of the Paris Brain Institute,

2. to use the previous analytics tool to study to which extent the topography and morphology of the different peptide aggregates present in the brain can be associated with the diversity of symptoms observed in various AD variants.

We propose to design, test and implement a modern supervised (initial stratification) and semi-supervised (advance refined stratification) deep reinforcement learning pipeline, combining methods able to generate high performances (quality and speed), high traceability / explicability and facilitate its usability in biomedical research and discovery. Our pathologists have started to acquire and to extensively annotate a unique set of histological images of postmortem brains from the rare form of rpAD and from other identified AD variants. Preliminary results of the consortium suggests that morphological features analysis is eligible for the first level of stratification. We believe that combining these features with topology and semantic-driven image exploration approaches (see MICO TecSan project's references) would be able to guide our research toward a refined stratification. Therefore, causal knowledge-based elements, together with semantic-driven WSI exploration will be likely to create a reusable pipeline, able to structure our experience plan, as to justify the numeric results. The tools within this project will contribute to open-source initiatives, and would be therefore available to the scientific community for replicable massive data analysis. STRATIFIAD will therefore contribute to advance the knowledge in AD and push forward the technological development in this area.

**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.

**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.

**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.

#### 9.3.4 3IA Institutes - PRAIRIE

**Participants:** Ninon Burgos, Olivier Colliot, Stanley Durrleman.

- Project acronym: PRAIRIE
- Project title: Paris Artificial Intelligence Research Institute
- Since 2019
- Director: Isabelle Ryl
- Website: PRAIRIE
- 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.

#### 9.3.5 National Networks

- GdR Statistics and Medicine
- GdR (MaDICS) Masses de Données, Informations et Connaissances en Sciences Big Data - Data Science, Statistics and Medicine
- 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
- GdR ISIS (Signal and Image Processing)

#### 9.3.6 Other National Programs

**Fondation Vaincre Alzheimer**

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

- Project title: Integrative multiscale knowledge model of Alzheimer's disease pathophysiology
- 2019-2021
- 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.

**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.

# 10 Dissemination

## 10.1 Promoting scientific activities

### 10.1.1 Scientific events: organisation

**General chair, scientific chair**

- Olivier Colliot is Conference Chair of the SPIE Medical Imaging: Image Processing conference for the period 2022-2025.

**Member of the organizing committees**

- N. Burgos co-organized the international workshop on Simulation and Synthesis in Medical Imaging (SASHIMI) 2021, a satellite workshop of MICCAI 2021.
- S. Durrleman and N. Burgos co-organized the AI4Health 2021 winter school with the Health Data Hub, held virtually.
- F. De Vico Fallani co-organized Network Neuroscience 2021, held virtually.
- D. Racoceanu was a member of the MICCAI 2021 Organising Committee - the 24th International Conference on Medical Image Computing and Computer Assisted Intervention.

### 10.1.2 Scientific events: selection

- O. Colliot served as Award Committee member for the international conference of the Organization for Human Brain Mapping.

**Member of the conference program committees**

- N. Burgos co-chaired the international workshop on Simulation and Synthesis in Medical Imaging (SASHIMI) 2021, a satellite workshop of MICCAI 2021.
- F. De Vico Fallani served as Program Committee member for the international conference of Complex networks. 2021
- F. De Vico Fallani served as Program Committee member for the Complenet Conference. 2021

**Reviewer**

- O. Colliot acted as a reviewer for the international conferences SPIE Medical Imaging, Annual meeting of the Organization for Human Brain Mapping (OHBM), and the IEEE International Symposium on Biomedical Imaging (IEEE ISBI).
- N. Burgos acted as a reviewer for the International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI), the international workshop on Simulation and Synthesis in Medical Imaging (SASHIMI), and the IEEE International Symposium on Biomedical Imaging (IEEE ISBI).
- F. De Vico Fallani acted as a reviewer for the NETSCI, Complenet, Complex networks, conferences.

### 10.1.3 Journal

**Member of the editorial boards**

- O. Colliot is an Associate Editor and a member of the Editorial Board of the journal Medical Image Analysis (Elsevier).
- O. Colliot is an Associate Editor of the journal Frontiers in Brain Imaging Methods.
- B. Couvy-Duchesne is an Associate Editor of the journal Frontiers Genetics (section Behavioral and Psychiatric Genetics).
- F. De Vico Fallani is an Associate Editor of the journal PLoS One.
- F. De Vico Fallani is an Associate Editor of the journal IEEE TNSRE.
- F. De Vico Fallani is an Associate Editor of the journal Brain Topography.
- S. Durrleman is an associate editor of the Journal of Imaging

**Reviewer - reviewing activities**

- O. Colliot acted as a reviewer for The Lancet Neurology, Medical Image Analysis, and Neuroradiology.
- N. Burgos acted as a reviewer for IEEE Transactions on Medical Imaging, Medical Image Analysis, Frontiers in Neuroscience, the Journal of Nuclear Medicine, Neurocomputing and the Artificial Intelligence Review.
- B. Couvy-Duchesne acted as a reviewer for Nature Neuroscience,Neuroimage, Human Brain Mapping, Frontiers in Genetics, Frontiers in Neurology, Frontiers in Psychology, Medical Image Analysis, eLife and the European Medical Journal.
- F. De Vico Fallani acted as a reviewer for Brain, PloS Biology, Network Neuroscience, J Neural Engineering, Neuroimage.

#### 10.1.4 Keynote

- D. Racoceanu was keynote to the SIPAIM 2021 conference, the 17th International Symposium on Medical Information Processing and Analysis, Nov. 17-19, 2021 - the major Latin American conference in this area.

#### 10.1.5 Invited talks

- N. Burgos gave an invited talk at the “Congrès des Jeunes Chercheuses et Chercheurs en Mathématiques Appliquées” (Palaiseau, France).
- N. Burgos gave an invited talk at the “Registering Medical Images” workshop (Paris, France).
- N. Burgos gave an invited talk at the “Mathematics and Image Analysis - MIA’21” conference (virtual).
- N. Burgos gave an invited seminar at the Labex Memolife.
- F. De Vico Fallani gave an invited talk at the International conference of Complex Systems, 2021

#### 10.1.6 Leadership within the scientific community

- Olivier Colliot is a member of the steering committee of the European infrastructure EBRAINS.
- F. De Vico Fallani is a member of the Executive Committee of the Complex Systems Society (CSS)
- D. Racoceanu is a member of the Board of Directors of the MICCAI Society (Medical Image Computing and Computer-Assisted Intervention Society)
- D. Racoceanu is a member of the Advisory Board of the European Society of Integrative Digital Pathology (ESDIP)

#### 10.1.7 Scientific expertise

- O. Colliot acts as an expert for GENCI (the national facility for high-performance computing).
- N. Burgos acted as reviewer for the ERC Advanced Grants.
- N. Burgos acted as reviewer for the National Science Centre Poland.
- N. Burgos acted as reviewer for the DIM ELICIT.
- B. Couvy-Duchesne acted as reviewer for the Medical Resarch Council UK.
- Stanley Durrleman is member of the scientific advisory board of the Health Data Hub.

### 10.1.8 Research administration

- O. Colliot is a member of the "Bureau du Comité des Projets" of the Inria Paris Center.

## 10.2 Teaching - Supervision - Juries

### 10.2.1 Teaching

- Master: Olivier Colliot coordinates the course "Deep Learning for Medical Imaging" of the Master 2 MVA (Mathematics, Vision, Learning) of ENS Paris-Saclay, University of Paris, Centrale-Supelec and teaches 15 hours (CM).
- Master: Olivier Colliot coordinates the course "Artificial Intelligence" of the Master 2 Bioentrepreneur of Paris-Descartes University and teaches 20 hours (CM).
- Master: Daniel Racoceanu coordinates the teaching module (UE) "Introduction to Artificial Intelligence" of the Master 1 : Control Sciences and Robotics (AR - Automatique, Robotique) and Electronics, Electrical Energy, Control Sciences (E3A - Électronique, Énergie Électrique, Automatique) at Sorbonne University, Faculty of Science and Engineering (110 students / 3 ECTS) and teaches 30 hours (CM/courses and TP/labs).
- Master: Daniel Racoceanu coordinates the teaching module (UE) "Computer Vision for Biomedical" of the Master 1 : Electronics, Electrical Energy, Control Sciences (E3A - Électronique, Énergie Électrique, Automatique) at Sorbonne University, Faculty of Science and Engineering (50 students / 3 ECTS) and teaches 32 hours (CM/courses and TP/labs).
- Master: Daniel Racoceanu coordinates the teaching module (UE) "Image Processing" of the Master 1 : Control Sciences and Robotics (AR - Automatique, Robotique) at Sorbonne University, Faculty of Science and Engineering (80 students / 3 ECTS) and teaches 36 hours (CM/courses and TP/labs) - courses in English.
- Master: Daniel Racoceanu coordinates the teaching module (UE) "3D Computer Graphics" of the Master 1 : Computer Sciences (Informatique) at Sorbonne University, Faculty of Science and Engineering (20 students / 3 ECTS) and teaches 24 hours (CM/courses and TP/labs) - courses in English (within the european programme EIT Health).
- Engineering school: Olivier Colliot, 5 hours (eqTD), Mines ParisTech
- Medical school: Didier Dormont is the Director of the University Diploma (DIU) “Diagnostic and Therapeutic Neuroradiology", Sorbonne University
- Medical school: Didier Dormont, Courses for Medical Students, Sorbonne University
- Medical school: Stéphane Epelbaum organizes the national teaching course on Alzheimer’s disease and related diseases.
- Medical school: Didier Dormont organizes and participates in the practical teaching of Neuroradiology for Medical Students in the Department of Diagnostic Neuroradiology of Pitié Salpêtrière University Hospital
- Medical school: Didier Dormont organizes and participates in the practical teaching of Neuroradiology for Radiology Specializing Residents in the Department of Diagnostic Neuroradiology of Pitié Salpêtrière University Hospital
- N. Burgos gave lectures on deep learning for medical imaging as part of the the DU Intelligence artificielle IA appliquée en santé (1h, March 2021, virtual) and the CENIR courses (1h, March 2021, virtual).
- Master: F. De Vico Fallani gave a lecture at UE Closed-loop Neuroscience, Central Supelec)

- Master: Daniel Racoceanu gives lectures / labs (14 hours) in "Visual Perception for Robotics" - Master 2 : Control Science and Robotics (AR - Automatique, Robotique) at Sorbonne University, Faculty of Science and Engineering.
- Master: Daniel Racoceanu gives lectures / labs (14 hours) in "Machine Learning" - Master 1 : Control Science and Robotics (AR - Automatique, Robotique) at Sorbonne University, Faculty of Science and Engineering.
- Master: Daniel Racoceanu gives lectures / labs (20 hours) in "Object-Oriented Programming" - Master 1 : Control Science and Robotics (AR - Automatique, Robotique) at Sorbonne University, Faculty of Science and Engineering.
- Licence: Daniel Racoceanu gives seminars (TD) and labs (TP) in "Programming" - Licence 1 : all Licences - option Control Sciences at Sorbonne University, Faculty of Science and Engineering (40 hours).
- Licence: Daniel Racoceanu gives courses (CM), seminars (TD) and labs (TP) in "Computer Science for Biologists" - Licence 2 : Live Sciences at Sorbonne University, Faculty of Science and Engineering (40 hours).
- Master : S. Durrleman gave 21 hours lecture for the Master MVA (Mathématiques, Vision et Apprentissage), ENS Paris-Saclay
- Master : S. Durrleman gave 4hrs lecture for the Master bio-entrepreneur of the University of Paris.
- F. De Vico Fallani was invited to give a teaching lesson at School on Complex Networks, Lake Como School Advanced Studies, Italy.
- S. Durrleman gave a lecture at the DU Intelligence artificielle et santé of the Université de Paris.
- B. Couvy-Duchesne was invited to be a tutor at the International Statistical Genetics Workshop, organised in Boulder, Colorado (remote).
- B. Couvy-Duchesne gave a lecture in the NeuroEthics session of the IMind Master.

#### 10.2.2 Supervision

- PhD in progress : Virgilio Kmetzsch, “CMultimodal analysis of neuroimaging and transcriptomic data in genetic fronto-temporal dementia”, Sorbonne University, Started in 2019, advisors: Olivier Colliot, Emmanuelle Becker and Olivier Dameron
- PhD in progress: Simona Bottani, “Machine learning for differential diagnosis of neurodegenerative diseases from multimodal data”, started in 2018, advisors: O. Colliot and N. Burgos
- PhD in progress: Ravi Hassanaly, “Deep generative models for the detection of anomalies in the brain”, started in 2020, advisors: O. Colliot and N. Burgos
- PhD in progress: Guanghui Fu, “Segmentation, classification and generative models for computer-aided diagnosis of neurological diseases from neuroimaging data”, started in 2021, advisors: O. Colliot and D. Dormont
- PhD in progress: Sophie Loizillon, “Deep learning for assisting diagnosis of neurological diseases using a very large-scale clinical data warehouse”, started in 2021, advisors: O. Colliot, N. Burgos and D. Dormont
- PhD in progress: Lisa Hemforth, “Deep learning for rating of atypical anatomical patterns on MRI data”, started in 2021, advisors: O. Colliot, B. Couvy-Duchesne and C. Cury
- PhD in progress: Arya Yazdan-Panah, “Deep learning for multimodal image analysis in multiple sclerosis”, started in 2021, advisors: O. Colliot and B. Stankoff

- PhD in progress: Mehdi Ounissi, “Explainable Artificial Intelligence”, started in 2021, advisor: D. Racoceanu
- PhD in progress: Gabriel Alexandro Jimenez Garay, “Interpretable Deep Learning in Computational Histopathology for Alzheimer Disease Patients’ Stratification Refinement”, started in 2021, advisor: D. Racoceanu
- PhD in progress: Raphael Couronne‘, “Spatiotemporal analysis of the progression of the Parkinson’s Disease informed by multimodal longitudinal data”, started in 2018, advisor: S. Durrleman
- PhD in progress: Vianney Debavelaere, Analysis of distribution of spatiotemporal trajectories in heterogeneous populations, started in 2018, advisors: S. Durrleman and S. Allassonnière
- PhD in progress: Federica Cacciamani, “Awareness for cognitive decline in the earliest stages of Alzheimer’s disease”, started in 2018, advisor: S. Epelbaum
- PhD in progress: Clément Mantoux, Statistical analysis of graphs, started in 2019, advisors: S. Durrleman and S. Allassonnière
- PhD in progress: Benoit Sauty, Multimodal models of neurodegenerative disease progression, started in 2020, advisor: S. Durrleman
- PhD in progress: Pierre-Emmanuel Poulet,Models of progression of multiple risks,started in 2020, advisor: S. Durrleman
- PhD in progress: Nemo Fournier, English title Heterogeneous Population Stratification using Longitudinal and Genetic Data,started in 2021, advisor: S. Durrleman
- PhD in progress: Juliette Ortholand, Modeling changes of dynamics with longitudinal data,started in 2021, advisor: S. Durrleman

#### 10.2.3 Juries

- O. Colliot acted as a referee for the PhD committee Vikram Venkatraghavan (Erasmus MC - University Medical Center Rotterdam, the Netherlands).
- O. Colliot participated, as thesis supervisor, to the PhD committee of Elina-Thibeau Sutre (Sorbonne University).
- N. Burgos participated, as thesis supervisor, to the PhD committee of Elina-Thibeau Sutre (Sorbonne University).
- D. Racoceanu participated as examiner to the HDR committee of M. Thomas WALTER (Sorbonne University).
- D. Racoceanu acted as referee and for and participated to the HDR committee of M. Julien HENRIET (Burgundy-Franche-Comté University).
- D. Racoceanu acted as referee for the HDR committee of Ms. Maria ZULUAGA (Côte d’Azur University).
- S. Durrleman acted as supervisor to the PhD committee of Vianney Debavelaere (Ecole Polytechnique)
- S. Durrleman acted as supervisor to the PhD committee of Raphaël Couronné (Ecole Polytechnique)
- S. Durrleman was member of the PhD Committee of Maryan Morel (Ecole Polytechnique)
- S. Durrleman acted as president to the PhD Committee of Nicolas Guigui (Université Côte d’Azur)
- S. Durrleman acted as reviewer to the PhD Committee of Clément Abi Nader (Université Nice Côte d’Azur)

## 10.3 Popularization

### 10.3.1 Education

- B. Couvy-Duchesne is a member of the COMETH (Committee of Ethics and Deontology) of the Paris Brain Institute. The COMETH advises the direction on ethical questions, and organizes training sessions about current ethical problems and research best practices.

### 10.3.2 Interventions

- N. Burgos gave a presentation for the “Rendez-vous des Jeunes Mathématiciennes et Informaticiennes”.
- N. Burgos participated to a panel discussion during the “MIT Symposium on AI & Medicine: Promises and Limits”
- S. Durrleman gave an interview for the Data Analytics Post, the Boston Consulting Group and le Guide du big data et de l’IA.

# 11 Scientific production

## 11.1 Major publications

[1] M. Ansart, S. Epelbaum, G. Bassignana, A. Bône, S. Bottani, T. Cattai, R. Couronné, J. Faouzi, I. Koval, M. Louis, E. Thibeau-Sutre, J. Wen, A. Wild, N. Burgos, D. Dormont, O. Colliot and S. Durrleman. ‘Predicting the Progression of Mild Cognitive Impairment Using Machine Learning: A Systematic, Quantitative and Critical Review’. In: *Medical Image Analysis* 67 (Jan. 2021), p. 101848. DOI: 10.1016/j.media.2020.101848. URL: https://hal.archives-ouvertes.fr/hal-02337815.

[2] M. Ansart, S. Epelbaum, G. Gagliardi, O. Colliot, D. Dormont, B. Dubois, H. Hampel and S. Durrleman. ‘Reduction of recruitment costs in preclinical AD trials. Validation of automatic pre-screening algorithm for brain amyloidosis’. In: *Statistical Methods in Medical Research* (Jan. 2019), p. 096228021882303. DOI: 10.1177/0962280218823036. URL: https://hal.archives-ouvertes.fr/hal-01964942.

[3] F. Battiston, J. Guillon, M. Chavez, V. Latora and F. De Vico Fallani. ‘Multiplex core–periphery organization of the human connectome’. In: *Journal of the Royal Society Interface* 15.146 (Sept. 2018). DOI: 10.1098/rsif.2018.0514. URL: https://hal.archives-ouvertes.fr/hal-01874871.

[4] A. Bertrand, J. Wen, D. Rinaldi, M. Houot, S. Sayah, A. Camuzat, C. Fournier, S. Fontanella, A. Routier, P. Couratier, F. Pasquier, M.-O. Habert, D. Hannequin, O. Martinaud, P. Caroppo, R. Levy, B. Dubois, A. Brice, S. Durrleman, O. Colliot, I. Le Ber and P. Study. ‘Early cognitive, structural and microstructural changes in c9orf72 presymptomatic carriers before 40 years of age’. In: *JAMA neurology* 75.2 (Feb. 2018), pp. 236–245. DOI: 10.1001/jamaneurol.2017.4266. URL: https://hal.inria.fr/hal-01654000.

[5] A. Bône, O. Colliot and S. Durrleman. ‘Learning the spatiotemporal variability in longitudinal shape data sets’. In: *International Journal of Computer Vision* (July 2020). DOI: 10.1007/s11263-020-01343-w. URL: https://hal.inria.fr/hal-02091549.

[6] S. Bottani, N. Burgos, A. Maire, A. Wild, S. Ströer, D. Dormont and O. Colliot. ‘Automatic quality control of brain T1-weighted magnetic resonance images for a clinical data warehouse’. In: *Medical Image Analysis* Volume 75 (2021). DOI: 10.1016/j.media.2021.102219. URL: https://hal.inria.fr/hal-03154792.

[7] N. Burgos, S. Bottani, J. Faouzi, E. Thibeau-Sutre and O. Colliot. ‘Deep learning for brain disorders: from data processing to disease treatment’. In: *Briefings in Bioinformatics* (Dec. 2020). DOI: 10.1093/bib/bbaa310. URL: https://hal.archives-ouvertes.fr/hal-03070554.

[8] N. Burgos, J. M. Cardoso, J. Samper-González, M.-O. Habert, S. Durrleman, S. Ourselin and O. Colliot. 'Anomaly detection for the individual analysis of brain PET images'. In: *Journal of Medical Imaging* 8.02 (5th Apr. 2021), p. 024003. DOI: 10.1117/1.JMI.8.2.024003. URL: https://hal.inria.fr/hal-03193306.

[9] N. Burgos and O. Colliot. 'Machine learning for classification and prediction of brain diseases: recent advances and upcoming challenges'. In: *Current Opinion in Neurology* 33.4 (2020), pp. 439–450. DOI: 10.1097/WCO.0000000000000838. URL: https://hal.inria.fr/hal-02902586.

[10] M.-C. Corsi, M. Chavez, D. Schwartz, N. George, L. Hugueville, A. E. Kahn, S. Dupont, D. Bassett and F. De Vico Fallani. 'Functional disconnection of associative cortical areas predicts performance during BCI training'. In: *NeuroImage* (Jan. 2020), p. 116500. DOI: 10.1016/j.neuroimage.2019.116500. URL: https://hal.inria.fr/hal-02438794.

[11] F. De Vico Fallani and D. Bassett. 'Network neuroscience for optimizing brain–computer interfaces'. In: *Physics of Life Reviews* 31 (Dec. 2019), pp. 304–309. DOI: 10.1016/j.plrev.2018.10.001. URL: https://hal.archives-ouvertes.fr/hal-02428684.

[12] F. De Vico Fallani, V. Latora and M. Chavez. 'A Topological Criterion for Filtering Information in Complex Brain Networks'. In: *PLoS Computational Biology* 13.1 (Jan. 2017), pp. 1–18. DOI: 10.1371/journal.pcbi.1005305. URL: https://hal.inria.fr/hal-01443254.

[13] B. Dubois, M. Chupin, H. Hampel, S. Lista, E. Cavedo, B. Croisile, G. Louis Tisserand, J. Touchon, A. Bonafe, P. J. Ousset, A. Ait Ameur, O. Rouaud, F. Ricolfi, A. Vighetto, F. Pasquier, C. Delmaire, M. Ceccaldi, N. Girard, C. Dufouil, S. Lehericy, I. Tonelli, F. Duveau, O. Colliot, L. Garnero, M. Sarazin and D. Dormont. 'Donepezil decreases annual rate of hippocampal atrophy in suspected prodromal Alzheimer's disease'. In: *Alzheimer's and Dementia* 11.9 (Sept. 2015), pp. 1041–1049. DOI: 10.1016/j.jalz.2014.10.003. URL: https://hal.inria.fr/hal-01249861.

[14] F. Fraggetta, V. L'Imperio, D. Ameisen, R. Carvalho, S. Leh, T.-R. Kiehl, M. Serbanescu, D. Racoceanu, V. Della Mea, A. Polonia, N. Zerbe and C. Eloy. 'Best Practice Recommendations for the Implementation of a Digital Pathology Workflow in the Anatomic Pathology Laboratory by the European Society of Digital and Integrative Pathology (ESDIP)'. In: *Diagnostics* 11.11 (22nd Nov. 2021), p. 2167. DOI: 10.3390/diagnostics11112167. URL: https://hal.sorbonne-universite.fr/hal-03456592.

[15] A. Guyot, A. B. Graciano Fouquier, E. Gerardin, M. Chupin, J. Glaunès, L. Marrakchi-Kacem, J. Germain, C. Boutet, C. Cury, L. Hertz-Pannier, A. Vignaud, S. Durrleman, T. Henry, P.-F. Van De Moortele, A. Trouvé and O. Colliot. 'A Diffeomorphic Vector Field Approach to Analyze the Thickness of the Hippocampus from 7T MRI'. In: *IEEE Transactions on Biomedical Engineering* 68.2 (Feb. 2021), pp. 393–403. DOI: 10.1109/TBME.2020.2999941. URL: https://hal.inria.fr/hal-02359660.

[16] C.-H. Huang and D. Racoceanu. 'Enhanced Methods for Lymphocyte Detection and Segmentation on H\&E Stained Images using eXclusive Autoencoders'. In: *International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC'20)*. Montreal, Canada, July 2020. URL: https://hal.archives-ouvertes.fr/hal-03140992.

[17] G. Jiménez and D. Racoceanu. 'Deep Learning for Semantic Segmentation vs. Classification in Computational Pathology: Application to Mitosis Analysis in Breast Cancer Grading'. In: *Frontiers in Bioengineering and Biotechnology* 7 (2019), p. 145. DOI: 10.3389/fbioe.2019.00145. URL: https://hal.sorbonne-universite.fr/hal-02182488.

[18] K. Maňoušková, V. Abadie, M. Ounissi, G. Jimenez, L. Stimmer, B. Delatour, S. Durrleman and D. Racoceanu. 'Tau Protein Discrete Aggregates in Alzheimer's Disease: Neuritic Plaques and Tangles Detection and Segmentation using Computational Histopathology'. In: SPIE Medical Imaging 2022. San Diego, United States, 20th Feb. 2022. URL: https://hal.archives-ouvertes.fr/hal-03522378.

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[20] A. L. Martel, P. Abolmaesumi, D. Stoyanov, D. Mateus, M. A. Zuluaga, S. K. Zhou, L. Joskowicz and D. Racoceanu, eds. *Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part II (image reconstruction; prediction and diagnosis; cross-domain methods and reconstruction; domain adaptation; machine learning applications; generative adversarial networks)*. 4th Oct. 2020. URL: https://hal.archives-ouvertes.fr/hal-03144838.

[21] A. L. Martel, P. Abolmaesumi, D. Stoyanov, D. Mateus, M. A. Zuluaga, S. K. Zhou, L. Joskowicz and D. Racoceanu, eds. *Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part III (CAI applications; image registration; instrumentation and surgical phase detection; navigation and visualization; ultrasound imaging; video image analysis)*. 4th Oct. 2020. URL: https://hal.archives-ouvertes.fr/hal-03144839.

[22] A. L. Martel, P. Abolmaesumi, D. Stoyanov, D. Mateus, M. A. Zuluaga, S. K. Zhou, L. Joskowicz and D. Racoceanu, eds. *Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part IV (segmentation; shape models and landmark detection)*. 4th Oct. 2020. URL: https://hal.archives-ouvertes.fr/hal-03144840.

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