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Activity Report 2019

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

RESEARCH CENTER
Paris

THEME
**Computational Neuroscience and
Medicine**

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Project-Team ARAMIS

Creation of the Team: 2012 October 01, updated into Project-Team: 2014 July 01

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Computer Science and Digital Science:

- A3.4. - Machine learning and statistics
- A3.4.1. - Supervised learning
- A3.4.2. - Unsupervised learning
- A3.4.4. - Optimization and learning
- A5.3. - Image processing and analysis
- A5.4.4. - 3D and spatio-temporal reconstruction
- 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
- B2.6.1. - Brain imaging

1. Team, Visitors, External Collaborators

Research Scientists

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Technical staff

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Visiting Scientist

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2. Overall Objectives

2.1. Context

ARAMIS is an Inria project-team within the Brain and Spinal cord Institute (ICM - <http://www.icm-institute.org>) at the Pitié-Salpêtrière hospital 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 **Brain and Spinal cord 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 University Pierre and Marie Curie). It hosts 25 research teams as well as various high level technical facilities (neuroimaging, genotyping/sequencing, cell culture, cellular imaging, bioinformatics ...), and gathers over 600 personnel. In addition, the ICM hosts one of the six IHU (*Instituts Hospitalo-Universitaires*), which are 10-year research programs funded for 55M euros each.

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: statistical and 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, F. De Vico Fallani, S. Durrleman) and clinicians (D. Dormont, S. Epelbaum). This general endeavor is addressed within the five following main objectives.

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, characterize 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. A large part of these clinical studies were in the field of dementia (Alzheimer's disease, fronto-temporal dementia). Recently, we expanded our scope to other neurodegenerative diseases (Parkinson's disease, multiple sclerosis).

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 neurodegenerative 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

5.1. Highlights of the Year

- F. De Vico Fallani was awarded an ERC Consolidator Grant.
- N. Burgos was awarded a Chair at the Paris Artificial Intelligence Research Institute (PRAIRIE).
- O. Colliot was awarded a Chair at the Paris Artificial Intelligence Research Institute (PRAIRIE).
- S. Durrleman was awarded a Chair at the Paris Artificial Intelligence Research Institute (PRAIRIE).
- S. Epelbaum holds a "Poste d'accueil" Inria since november 2019.

5.1.1. Awards

- N. Burgos received the Cor Baayen Young Researcher Award from ERCIM.
- V. Debavelaere was awarded a best paper award at the MICCAI conference in Shenzhen .

BEST PAPER AWARD:

[32]

V. DEBAVELAERE, A. BÔNE, S. DURRLEMAN, S. ALLASSONNIÈRE. *Clustering of longitudinal shape data sets using mixture of separate or branching trajectories*, in "Medical Image Computing and Computer Assisted Intervention – MICCAI", Shenzhen, China, Medical Image Computing and Computer Assisted Intervention – MICCAI 2019, October 2019, pp. 66-74, <https://hal.archives-ouvertes.fr/hal-02103355>

6. New Software and Platforms

6.1. 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.

- Participants: Fabrizio de Vico Fallani, Jeremy Guillon and Mario Chavez
- Contact: Fabrizio de Vico Fallani
- URL: <https://github.com/brain-network/bnt>

6.2. 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!

- Participants: Alexandre Routier, Ana Fouquier, Barbara Gris, Benjamin Charlier, Cédric Doucet, Joan Alexis Glaunès, Marcel Prastawa, Michael Bacci, Pietro Gori and Stanley Durrleman
- Partners: University of Utah - Université de Montpellier 2 - Université Paris-Descartes
- Contact: Stanley Durrleman
- URL: <http://www.deformetrica.org/>

6.3. Clinica

KEYWORDS: Neuroimaging - Brain MRI - MRI - Clinical analysis - Image analysis - Machine 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 MRI (anatomical, functional, diffusion) and PET, in the future, EEG/MEG. 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 MRI (anatomical, functional, diffusion) and PET, in the future, EEG/MEG. 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.

NEWS OF THE YEAR: - Three clinical studies made with Clinica Clinica : Bertrand et al, JAMA Neurology, 2018 , Jacquemont et al, Neurobiol Aging, 2017, Wen et al, JNNP, 2018 - Clinica presented at OHBM 2018 conference - Clinica was the support for the tutorial "Pattern Recognition for Neuroimaging" at OHBM 2018

- 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 and Elina Thibeau-Sutre
- Partners: Institut du Cerveau et de la Moelle épinière (ICM) - CNRS - INSERM - UPMC
- Contact: Olivier Colliot
- Publications: [Amyloidosis and neurodegeneration result in distinct structural connectivity patterns in mild cognitive impairment](#) - [Yet Another ADNI Machine Learning Paper? Paving The Way Towards Fully-reproducible Research on Classification of Alzheimer's Disease](#) - [Reproducible evaluation of classification methods in Alzheimer's disease: Framework and application to MRI and PET data](#) - [Neurite density is reduced in the presymptomatic phase of C9orf72 disease](#) - [Early cognitive, structural and microstructural changes in c9orf72 presymptomatic carriers before 40 years of age](#)
- URL: <http://www.clinica.run>

6.4. Platforms

6.4.1. Platform Brain-computer interface

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 NSF/NIH/ANR and ATTACK Big-brain theory funded projects, as well as experiments by different researchers of the Institute, are currently being run. To reinforce the impact of the platform we have recently recruited an engineer (J. Gonzalez-Astudillo) and a master student (Tristan Venot) for the software and technical development.

7. New Results

7.1. Predicting PET-derived Demyelination from Multimodal MRI using Sketcher-Refiner Adversarial Training for Multiple Sclerosis

Participants: Wen Wei, Emilie Poirion, Benedetta Bodini, Stanley Durrleman, Nicholas Ayache, Bruno Stankoff, Olivier Colliot [Correspondant].

Multiple sclerosis (MS) is the most common demyelinating disease. In MS, demyelination occurs in the white matter of the brain and in the spinal cord. It is thus essential to measure the tissue myelin content to understand the physiopathology of MS, track progression and assess treatment efficacy. Positron emission tomography (PET) with [11C]PIB is a reliable method to measure myelin content in vivo. However, the availability of PET in clinical centers is limited. Moreover, it is expensive to acquire and invasive due to the injection of a radioactive tracer. By contrast, MR imaging is non-invasive, less expensive and widely available, but conventional MRI sequences cannot provide a direct and reliable measure of myelin. In this work, we therefore propose, to the best of our knowledge for the first time, a method to predict the PET-derived myelin content map from multimodal MRI. To that purpose, we introduce a new approach called Sketcher-Refiner generative adversarial networks (GANs) with specifically designed adversarial loss functions. The first network (Sketcher) generates global anatomical and physiological information. The second network (Refiner) refines and generates the tissue myelin content. A visual attention saliency map is also proposed to interpret the attention of neural networks. Our approach is shown to outperform the state-of-the-art methods in terms of image quality and myelin content prediction. Particularly, our prediction results show similar results to the PET-derived gold standard at both global and voxel-wise levels indicating the potential for clinical management of patients with MS.

More details in [25].

7.2. Reproducible evaluation of methods for predicting progression to Alzheimer's disease from clinical and neuroimaging data

Participants: Jorge Samper-González, Ninon Burgos, Simona Bottani, Marie-Odile Habert, Stéphane Epelbaum, Theodoros Evgeniou, Olivier Colliot [Correspondant].

Various machine learning methods have been proposed for predicting progression of patients with mild cognitive impairment (MCI) to Alzheimer's disease (AD) using neuroimaging data. Even though the vast majority of these works use the public dataset ADNI, reproducing their results is complicated because they often do not make available elements that are essential for reproducibility, such as selected participants and input data, image preprocessing and cross-validation procedures. Comparability is also an issue. Specially, the influence of different components like preprocessing, feature extraction or classification algorithms on the performance is difficult to evaluate. Finally, these studies rarely compare their results to models built from clinical data only, a critical aspect to demonstrate the utility of neuroimaging. In our previous work, 1, 2 we presented a framework for reproducible and objective classification experiments in AD, that included automatic conversion of ADNI database into the BIDS community standard, image preprocessing pipelines and machine learning evaluation. We applied this framework to perform unimodal classifications of T1 MRI and FDG-PET images. In the present paper, we extend this work to the combination of multimodal clinical and neuroimaging data. All experiments are based on standard approaches (namely SVM and random forests). In particular, we assess the added value of neuroimaging over using only clinical data. We first demonstrate that using only demographic and clinical data (gender, education level, MMSE, CDR sum of boxes, ADASCog) results in a balanced accuracy of 75% (AUC of 0.84). This performance is higher than that of standard neuroimaging-based classifiers. We then propose a simple trick to improve the performance of neuroimaging-based classifiers: training from AD patients and controls (rather than from MCI patients) improves the performance of FDG-PET classification by 5 percent points, reaching the level of the clinical classifier. Finally, combining clinical and neuroimaging data, prediction results further improved to 80% balanced accuracy and an AUC of 0.88). These prediction accuracies, obtained in a reproducible way, provide a base to develop on top of it and, to compare against, more sophisticated methods. All the code of the framework and the experiments is publicly available at <https://github.com/aramis-lab/AD-ML>.

More details in [34].

7.3. Disrupted core-periphery structure of multimodal brain networks in Alzheimer's disease

Participants: Jeremy Guillon, Mario Chavez, Federico Battiston, Yohan Attal, Valentina Corte, Michel Thiebaut de Schotten, Bruno Dubois, Denis Schwartz, Olivier Colliot, Fabrizio de Vico Fallani [Correspondant].

In Alzheimer’s disease (AD), the progressive atrophy leads to aberrant network reconfigurations both at structural and functional levels. In such network reorganization, the core and peripheral nodes appear to be crucial for the prediction of clinical outcome because of their ability to influence large-scale functional integration. However, the role of the different types of brain connectivity in such prediction still remains unclear. Using a multiplex network approach we integrated information from DWI, fMRI, and MEG brain connectivity to extract an enriched description of the core-periphery structure in a group of AD patients and age-matched controls. Globally, the regional coreness—that is, the probability of a region to be in the multiplex core—significantly decreased in AD patients as result of a random disconnection process initiated by the neurodegeneration. Locally, the most impacted areas were in the core of the network—including temporal, parietal, and occipital areas—while we reported compensatory increments for the peripheral regions in the sensorimotor system. Furthermore, these network changes significantly predicted the cognitive and memory impairment of patients. Taken together these results indicate that a more accurate description of neurodegenerative diseases can be obtained from the multimodal integration of neuroimaging-derived network data.

More details in [20]

7.4. Network neuroscience for optimizing brain–computer interfaces

Participants: Fabrizio de Vico Fallani [Correspondant], Danielle Bassett.

Human-machine interactions are being increasingly explored to create alternative ways of communication and to improve our daily life. Based on a classification of the user’s intention from the user’s underlying neural activity, brain-computer interfaces (BCIs) allow direct interactions with the external environment while bypassing the traditional effector of the musculoskeletal system. Despite the enormous potential of BCIs, there are still a number of challenges that limit their societal impact, ranging from the correct decoding of a human’s thoughts, to the application of effective learning strategies. Despite several important engineering advances, the basic neuroscience behind these challenges remains poorly explored. Indeed, BCIs involve complex dynamic changes related to neural plasticity at a diverse range of spatiotemporal scales. One promising antidote to this complexity lies in network science, which provides a natural language in which to model the organizational principles of brain architecture and function as manifest in its interconnectivity. Here, we briefly review the main limitations currently affecting BCIs, and we offer our perspective on how they can be addressed by means of network theoretic approaches. We posit that the emerging field of network neuroscience will prove to be an effective tool to unlock human-machine interactions.

More details in [13]

7.5. Quality Assessment of Single-Channel EEG for Wearable Devices

Participants: Fanny Grosseclin, Xavier Navarro-Sune, Alessia Vozzi, Katerina Pandremmenou, Fabrizio de Vico Fallani, Yohan Attal, Mario Chavez [Correspondant].

The recent embedding of electroencephalographic (EEG) electrodes in wearable devices raises the problem of the quality of the data recorded in such uncontrolled environments. These recordings are often obtained with dry single-channel EEG devices, and may be contaminated by many sources of noise which can compromise the detection and characterization of the brain state studied. In this paper, we propose a classification-based approach to effectively quantify artefact contamination in EEG segments, and discriminate muscular artefacts. The performance of our method were assessed on different databases containing either artificially contaminated or real artefacts recorded with different type of sensors, including wet and dry EEG electrodes. Furthermore, the quality of unlabelled databases was evaluated. For all the studied databases, the proposed method is able to rapidly assess the quality of the EEG signals with an accuracy higher than 90

More details in [19]

7.6. Reduction of recruitment costs in preclinical AD trials. Validation of automatic pre-screening algorithm for brain amyloidosis

Participants: Manon Ansart [correspondant], Stéphane Epelbaum, Geoffroy Gagliardi, Olivier Colliot, Didier Dormont, Bruno Dubois, Harald Hampel, Stanley Durrleman.

We propose a method for recruiting asymptomatic Amyloid positive individuals in clinical trials, using a two-step process. We first select during a pre-screening phase a subset of individuals which are more likely to be amyloid positive based on the automatic analysis of data acquired during routine clinical practice, before doing a confirmatory PET-scan to these selected individuals only. This method leads to an increased number of recruitments and to a reduced number of PET-scans, resulting in a decrease in overall recruitment costs. We validate our method on 3 different cohorts, and consider 5 different classification algorithms for the pre-screening phase. We show that the best results are obtained using solely cognitive, genetic and socio-demographic features, as the slight increased performance when using MRI or longitudinal data is balanced by the cost increase they induce. We show that the proposed method generalizes well when tested on an independent cohort, and that the characteristics of the selected set of individuals are identical to the characteristics of a population selected in a standard way. The proposed approach shows how Machine Learning can be used effectively in practice to optimize recruitment costs in clinical trials.

More details in[7]

7.7. Learning low-dimensional representations of shape data sets with diffeomorphic autoencoders

Participants: Alexandre Bône [Correspondant], Maxime Louis, Olivier Colliot, Stanley Durrleman.

Contemporary deformation-based morphometry offers parametric classes of diffeomorphisms that can be searched to compute the optimal transformation that warps a shape into another, thus defining a similarity metric for shape objects. Extending such classes to capture the geometrical variability in always more varied statistical situations represents an active research topic. This quest for genericity however leads to computationally-intensive estimation problems. Instead, we propose in this work to learn the best-adapted class of diffeomorphisms along with its parametrization, for a shape data set of interest. Optimization is carried out with an auto-encoding variational inference approach, offering in turn a coherent model-estimator pair that we name diffeomorphic auto-encoder. The main contributions are: (i) an original network-based method to construct diffeomorphisms, (ii) a current-splating layer that allows neural network architectures to process meshes, (iii) illustrations on simulated and real data sets that show differences in the learned statistical distributions of shapes when compared to a standard approach.

More details in[30]

7.8. Learning disease progression models with longitudinal data and missing values

Participants: Raphaël Couronné [correspondant], Marie Vidailhet, Jean-Christophe Corvol, Stéphane Lehericy, Stanley Durrleman.

Statistical methods have been developed for the analysis of longitudinal data in neurodegenerative diseases. To cope with the lack of temporal markers- i.e. to account for subject-specific disease progression in regard to age- a common strategy consists in realigning the individual sequence data in time. Patient's specific trajectories can indeed be seen as spatiotemporal perturbations of the same normative disease trajectory. However, these models do not easily allow one to account for multimodal data, which more than often include missing values. Indeed, it is rare that imaging and clinical examinations for instance are performed at the same frequency in clinical protocols. Multimodal models also need to allow a different profile of progression for data with different structure and representation. We propose to use a generative mixed effect model that considers the progression trajectories as curves on a Riemannian Manifold. We use the concept of product manifold to handle multimodal data, and leverage the generative aspect of our model to handle missing values. We assess the robustness of our methods toward missing values frequency on both synthetic and real data. Finally we apply our model on a real-world dataset to model Parkinson's disease progression from data derived from clinical examination and imaging.

More details in[31]

7.9. Learning the clustering of longitudinal shape data sets into a mixture of independent or branching trajectories

Participants: Vianney Debavelaere [correspondant], Stéphanie Allasonnière, Stanley Durrleman.

Given repeated observations of several subjects over time, i.e. a longitudinal data set, this work introduces a new model to learn a classification of the shapes progression in an unsupervised setting: we automatically cluster a longitudinal data set in different classes without labels. Our method learns for each cluster an average shape trajectory (or representative curve) and its variance in space and time. Representative trajectories are built as the combination of pieces of curves. This mixture model is flexible enough to handle independent trajectories for each cluster as well as fork and merge scenarios. The estimation of such non linear mixture models in high dimension is known to be difficult because of the trapping states effect that hampers the optimisation of cluster assignments during training. We address this issue by using a tempered version of the stochastic EM algorithm. Finally, we apply our algorithm on different data sets. First, synthetic data are used to show that a tempered scheme achieves better convergence. We then apply our method to different real data sets: 1D RECIST score used to monitor tumors growth, 3D facial expressions and meshes of the hippocampus. In particular, we show how the method can be used to test different scenarios of hippocampus atrophy in ageing by using an heterogeneous population of normal ageing individuals and mild cognitive impaired subjects.

More details in[32]

7.10. Auto-encoding meshes of any topology with the current-splating and exponentiation layers

Participants: Alexandre Bône [Correspondant], Olivier Colliot, Stanley Durrleman.

Deep learning has met key applications in image computing, but still lacks processing paradigms for meshes, i.e. collections of elementary geometrical parts such as points, segments or triangles. Meshes are both a powerful representation for geometrical objects, and a challenge for network architectures because of their inherent irregular structure. This work contributes to adapt classical deep learning paradigms to this particular type of data in three ways. First, we introduce the current-splating layer which embeds meshes in a metric space, allowing the downstream network to process them without any assumption on their topology: they may be composed of varied numbers of elements or connected components, contain holes, or bear high levels of geometrical noise. Second, we adapt to meshes the exponentiation layer which, from an upstream image array, generates shapes with a diffeomorphic control over their topology. Third, we take advantage of those layers to devise a variational auto-encoding architecture, which we interpret as a generative statistical model that learns adapted low-dimensional representations for mesh data sets. An explicit norm-control layer ensures the correspondence between the latent-space Euclidean metric and the shape-space log-Euclidean one. We illustrate this method on simulated and real data sets, and show the practical relevance of the learned representation for visualization, classification and mesh synthesis.

More details in[29]

7.11. Riemannian Geometry Learning for Disease Progression Modelling

Participants: Maxime Louis, Raphael Couronne, Igor Koval, Benjamin Charlier, Stanley Durrleman.

The analysis of longitudinal trajectories is a longstanding problem in medical imaging which is often tackled in the context of Riemannian geometry: the set of observations is assumed to lie on an a priori known Riemannian manifold. When dealing with high-dimensional or complex data, it is in general not possible to design a Riemannian geometry of relevance. In this work, we perform Riemannian manifold learning in association with the statistical task of longitudinal trajectory analysis. After inference, we obtain both a submanifold of observations and a Riemannian metric so that the observed progressions are geodesics. This is achieved using a deep generative network, which maps trajectories in a low-dimensional Euclidean space to the observation space.

More details in[33]

7.12. How many patients are eligible for disease-modifying treatment in Alzheimer’s disease? A French national observational study over 5 years.

Participants: Stéphane Epelbaum [Correspondant], Claire Paquet, Jacques Hugon, Julien Dumurgier, David Wallon, Didier Hannequin, Thérèse Jonveaux, Annick Besozzi, Stéphane Pouponneau, Caroline Hommet, Frédéric Blanc, Laetitia Berly, Adrien Julian, Marc Paccalin, Florence Pasquier, Julie Bellet, Claire Boutoleau-Bretonniere, Tiphaine Charriau, Olivier Rouaud, Olivier Madec, Aurélie Mouton, Renaud David, Samir Bekadar, Roxanne Fabre, Emmanuelle Liegey, Walter Deberdt, Philippe Robert, Bruno Dubois.

We aimed to study the epidemiology of the prodromal and mild stages of Alzheimer’s disease (AD) patients who are eligible for clinical trials with disease-modifying therapies. We analyzed two large complementary databases to study the incidence and characteristics of this population on a nationwide scope in France from 2014 to 2018. The National Alzheimer Database contains data from 357 memory centres and 90 private neurologists. Data from 2014 to 2018 have been analyzed. Patients, 50–85 years old, diagnosed with AD who had an Mini-Mental State Exam (MMSE) score greater or equal to 20 were included. We excluded patients with mixed and non-AD neurocognitive disorders. Descriptive statistics of the population of interest was the primary measure. Results In the National Alzheimer Database, 550,198 patients were assessed. Among them, 72,174 (13.1%) were diagnosed with AD and had an MMSE greater or equal to 20. Using corrections for specificity of clinical diagnosis of AD, we estimated that about 50,000 (9.1%) had a prodromal or mild AD. In the combined electronic clinical records database of 11 French expert memory centres, a diagnosis of prodromal or mild AD, certified by the use of cerebrospinal fluid AD biomarkers, could be established in 195 (1.3%) out of 14 596 patients. AD was not frequently diagnosed at a prodromal or mild dementia stage in France in 2014 to 2018. Diagnosis rarely relied on a pathophysiological marker even in expert memory centres. National databases will be valuable to monitor early stage AD diagnosis efficacy in memory centres when a disease-modifying treatment becomes available. More details in [15]

7.13. EEG evidence of compensatory mechanisms in preclinical Alzheimer’s disease

Participants: Sinead Gaubert, Federico Raimondo, Marion Houot, Marie-Constance Corsi, Jacobo Diego Sitt, Bertrand Hermann, Delphine Oudiette, Geoffroy Gagliardi, Marie Odile Habert, Bruno Dubois, Fabrizio de Vico Fallani, Hovagim Bakardjian, Stéphane Epelbaum [Correspondant].

Early biomarkers are needed to identify individuals at high risk of preclinical Alzheimer's disease and to better understand the pathophysiological processes of disease progression. Preclinical Alzheimer's disease EEG changes would be non-invasive and cheap screening tools and could also help to predict future progression to clinical Alzheimer's disease. However, the impact of amyloid-beta deposition and neurodegeneration on EEG biomarkers needs to be elucidated. We included participants from the INSIGHT-preAD cohort, which is an ongoing single-centre multimodal observational study that was designed to identify risk factors and markers of progression to clinical Alzheimer's disease in 318 cognitively normal individuals aged 70-85 years with a subjective memory complaint. We divided the subjects into four groups, according to their amyloid status (based on 18F-florbetapir PET) and neurodegeneration status (evidenced by 18F-fluorodeoxyglucose PET brain metabolism in Alzheimer's disease signature regions). The first group was amyloid-positive and neurodegeneration-positive, which corresponds to stage 2 of preclinical Alzheimer's disease. The second group was amyloid-positive and neurodegeneration-negative, which corresponds to stage 1 of preclinical Alzheimer's disease. The third group was amyloid-negative and neurodegeneration-positive, which corresponds to 'suspected non-Alzheimer's pathophysiology'. The last group was the control group, defined by amyloid-negative and neurodegeneration-negative subjects. We analysed 314 baseline 256-channel high-density eyes closed 1-min resting state EEG recordings. EEG biomarkers included spectral measures, algorithmic complexity and functional connectivity assessed with a novel information-theoretic measure, weighted symbolic mutual information. The most prominent effects of neurodegeneration on EEG metrics were localized in frontocentral regions with an increase in high frequency oscillations (higher beta and gamma power) and a decrease in low frequency oscillations (lower delta power), higher spectral entropy, higher complexity and increased functional connectivity measured by weighted symbolic mutual information in theta band. Neurodegeneration was associated with a widespread increase of median spectral frequency. We found a non-linear relationship between amyloid burden and EEG metrics in neurodegeneration-positive subjects, either following a U-shape curve for delta power or an inverted U-shape curve for the other metrics, meaning that EEG patterns are modulated differently depending on the degree of amyloid burden. This finding suggests initial compensatory mechanisms that are overwhelmed for the highest amyloid load. Together, these results indicate that EEG metrics are useful biomarkers for the preclinical stage of Alzheimer's disease.

More details in [17]

7.14. Latent class analysis identifies functional decline with Amsterdam IADL in preclinical Alzheimer's disease

Participants: Sarah-Christine Villeneuve, Marion Houot, Federica Cacciamani, Merike Verrijp, Marie Odile Habert, Bruno Dubois, Sietske Sikkes, Stéphane Epelbaum [Correspondant].

Trials in Alzheimer's disease (AD) now include participants at the earliest stages to prevent further decline. However, the lack of tools sensitive to subtle functional changes in early-stage AD hinders the development of new therapies as it is difficult to prove their clinical relevance. We assessed functional changes over three years in 289 elderly memory complainers from the Investigation of Alzheimer's Predictors in subjective memory complainers cohort using the Amsterdam Instrumental-Activities-of-Daily-Living questionnaire (A-IADL-Q). No overall functional decline related to AD imaging markers was evidenced. However, five distinct classes of A-IADL-Q trajectories were identified. The largest class (212 [73.4%]) had stable A-IADL-Q scores over 3 years. A second group (23 [8.0%]) showed a persistent functional decline, higher amyloid load ($P < .0005$), and lower education ($P < .0392$). The A-IADL-Q identified a subtle functional decline in asymptomatic at-risk AD individuals. This could have important implications in the field of early intervention in AD

More details in [24]

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: UPMC, 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.

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. Health Data Hub

Participant: Stanley Durrleman.

Project acronym: Precise-PD-HDH

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

Duration: 1 year (pilot project)

Coordinator: Jean-Christophe Corvol

Other partners: Inserm, réseau NS-PARK, ICM

9.1.2. ANR

9.1.2.1. ANR-NIH-NSF CANDT

Participant: Fabrizio de Vico Fallani [Correspondant].

Project acronym: CANDT

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

Duration: Oct 2019 - Sep 2023

Amount: 137k€

Coordinator: Fabrizio De Vico Fallani

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

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

9.1.2.2. ANR-NIH-NSF NETBCI

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

Project acronym: NETBCI

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

Duration: Avr 2016 - Avr 2020

Amount: 322k€

Coordinator: Fabrizio De Vico Fallani

Other partners: Complex system group, UPenn, USA

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

9.1.2.3. ANR-NIH-NSF HIPLAY7

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

Project acronym: HIPLAY7

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

Duration: Jan 2017 - Jan 2020

Amount: 770k€

Coordinator: Olivier Colliot and Pierre-François Van de Moortele

Other partners: University of Minnesota, Neurospin

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

9.1.2.4. ANR PREV-DEMALS

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

Project acronym: PREV-DEMALS

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

Duration: Avr 2015 - Avr 2019

Amount: 487k€

Coordinator: Isabelle Le Ber

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

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

9.1.2.5. ANR IVMRS

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

Project acronym: IVMRS

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

Duration: Oct 2016 - Oct 2020

Amount: 633k€

Coordinator: Luc Hebrard

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

Abstract: During the development of new therapeutics against brain diseases, the pre-clinical phase, i.e. the validation of treatment delivery, safety and efficacy in animal models of the disease, represents a crucial step. Magnetic Resonance Imaging (MRI) is a method of particular interest at this stage, as it provides non-invasive surrogate endpoints that can help selecting appropriate candidates during the process of drug development. Single Voxel Magnetic Resonance Spectroscopy (SVS) provides non-invasive, in-vivo quantitative measurements of brain metabolites, which reflects functional changes at the cellular and subcellular levels, and can be repeated longitudinally. As high-field MRI has become the benchmark in preclinical research on animal models, it appears possible

to investigate the cerebral metabolomics changes in animals, and to use it as a surrogate marker in preclinical therapeutic trials. However, the number of relevant metabolites is much higher than the low number of measurable metabolites with conventional in-vivo high-field SVS. Moreover, considering also the subtle changes of these metabolites at the early stage of the disease, the use of conventional high-field SVS in preclinical studies remains strongly limited. The high volume of the Voxel-of-Interest (VOI), ranging from 10 to 30mm³, which is required to have a usable signal in conventional SVS, and the inherent variability of longitudinal SVS measurement due to the variable position of the VOI in the successive experiments, remain the two major issues when looking during time for small changes in metabolic concentrations and metabolites ratios in a specific small region of the animal brain. The IvMRS project aims at filling this gap by developing the first chronic implantable MRS micro-probe, minimally invasive, exhibiting very high signal sensitivity, and sharp spectral peaks, from sub-millimetric VOI. Such a probe will allow detecting a much higher number of metabolites than conventional in-vivo SVS. The probe will work at frequencies ranging from 300MHz to 500MHz in ultra-high field Magnetic Resonance Imaging scanners, 7T and 11.7T. It will embed a specific micro-coil antenna, a low-noise signal conditioning circuit designed in CMOS microelectronics technology, as well as an accurate on-chip positioning sensor. It will be dedicated to the study of changes in brain metabolite markers of two major diseases, Alzheimer's disease and cerebral gliomas, and to the assessment of effective therapeutic strategies.

9.1.3. Inria Project Labs

9.1.3.1. IPL Neuromarkers

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

Project acronym: Neuromarkers

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

Duration: 2017-2021

Coordinators: Stanley Durrleman and Olivier Colliot

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

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

9.1.4. IHU

9.1.4.1. General program

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

Project acronym: IHU-A-ICM

Project title: Institute of Translational Neuroscience

Founded in 2011

General Director: Bertrand Fontaine

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

9.1.4.2. ICM-Internal Research projects

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

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

Started in 2014

Coordinator: Anne Bertrand

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

9.1.4.3. ICM BBT Program - project PredictICD

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

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

Started in 2018

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

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

9.1.4.4. ICM BBT Program - project DYNAMO

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

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

Started in 2016

Coordinator: Stanley Durrleman and Harald Hampel

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

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

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

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

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

9.1.4.5. ICM BBT Program - project SEMAPHORE

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

Project title: Personalized progression model of Parkinson's disease

Started in 2018

Coordinator: Stanley Durrleman and Stéphane Lehéricy

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

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

9.1.4.6. ICM BBT Program - project ATTACK

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

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

Started in 2018

Coordinator: Fabrizio De Vico Fallani, Charlotte Rosso

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

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

9.1.5. 3IA Institutes - PRAIRIE

Participants: Olivier Colliot, Stanley Durrleman, Ninon Burgos.

Project acronym: PRAIRIE

Project title: Paris Artificial Intelligence Research Institute

Founded in 2019

Director: Isabelle Ryl

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

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

9.1.6. National Networks

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

9.1.7. Other National Programs

9.1.7.1. Fondation Vaincre Alzheimer

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

Project title: Integrative multiscale knowledge model of Alzheimer's disease pathophysiology
2019-2020

Amount: 100K€

Coordinator: Olivier Colliot

Other partners: Fraunhofer SCAI (Germany)

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

9.1.7.2. France Parkinson

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

Project title: PRECISE-PD - From pathophysiology to precision medicine for Parkinson's disease
2019-2024

Amount: 3M€

Coordinator: Jean-Christophe Corvol

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

Abstract: Parkinson's disease (PD) is a complex neurodegenerative disease characterized by the progression of motor and non-motor symptoms resulting from the spreading of the disease into dopaminergic and non-dopaminergic areas. Clinical trials have failed to demonstrate efficacy to slow PD progression because the relationships between progression profiles and their underlying molecular mechanisms remain to be identified. The objective of PRECISE-PD is to propose a mechanisms-based 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 unprecedented opportunity to open the path to the new era of precision and personalized medicine for PD.

9.2. European Initiatives

9.2.1. FP7 & H2020 Projects

9.2.1.1. H2020 - Project EuroPOND

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

Project acronym: EuroPOND

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

Duration: Jan 2016 - Dec 2019

Amount: 6M€

Coordinator: Daniel Alexander

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

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

9.2.1.2. H2020 - Project VirtualBrainCloud

Participant: Stanley Durrleman.

Project acronym: TVBCloud

Project title: Personalized Recommendations for Neurodegenerative Disease

Duration: Jan 2019 - Dec 2022

Amount: 15 M€

Coordinator: Petra Ritter

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

Abstract: The annual worldwide cost of Alzheimer's dementia was 777.81 billion Euro in 2015. This number will rise to 7.41 trillion Euro in 2050. Early diagnosis would save up to \$7.9 trillion in medical and care costs by 2050 in the US alone. However, the emergent pathology is highly variable across people, need highly 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. The VirtualBrainCloud 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.

9.2.1.3. FET Flagship - Human Brain Project

Participants: Olivier Colliot, Stanley Durrleman.

Project acronym: HBP

Project title: Human Brain Project

Sub-project: SP8 - Medical Informatics Platform

Duration: 2016-

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

9.2.1.4. ERC - LEASP

Participant: Stanley Durrleman.

Project acronym: LEASP

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

Duration: 2016-2021

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

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

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

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

9.3. International Initiatives

9.3.1. Informal International Partners

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

9.4. International Research Visitors

9.4.1. Visits of International Scientists

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

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events: Organisation

10.1.1.1. General Chair, Scientific Chair

- S. Durrleman was general chair of the international Neuro Open Science Workshop (ICM, Paris)

10.1.1.2. Member of the Organizing Committees

- N. Burgos organized the international workshop on Simulation and Synthesis in Medical Imaging (SASHIMI) 2019, a satellite workshop of MICCAI 2019.
- N. Burgos organized a PRACE training event (Introduction to machine learning in Python with Scikit-learn)
- F. De Vico Fallani co-organized the Network Neuroscience satellite within the NetSCI conference.
- S. Durrleman co-organized the international workshop on the Mathematical Foundations of Computational Anatomy (MFCA), a satellite workshop of MICCAI 2019.
- S. Durrleman co-organized the workshop GEANT (GEstion et pArtage de données en Neuroinformatique), Marseille Medical School.

10.1.2. Scientific Events: Selection

10.1.2.1. Member of the Conference Program Committees

- O. Colliot served as Program Committee member for the international conference SPIE Medical Imaging (San Diego, USA, 2019) and for the international workshop PatchMI (Shenzen, China, 2019).
- O. Colliot served as Award Committee member for the international conference of the Organization for Human Brain Mapping (OHBM, meeting held in Rome, Italy, 2019).
- F. De Vico Fallani served as Program Committee member for the international conference Netsci, Complemet, Complex networks.
- S. Durrleman served as Program Committee member for the international workshop Medical Imaging meets NeurIPS.

10.1.2.2. 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 international workshop PatchMI.
- N. Burgos acted as a reviewer for the international conference Annual meeting of the Organization for Human Brain Mapping (OHBM), for the international workshop on Simulation and Synthesis in Medical Imaging (SASHIMI), and for the GRETSI symposium of signal and image processing.
- F. De Vico Fallani acted as a reviewer for the international conference on Brain-computer interfaces (Graz BCI) and the international conferences Complemet, Netsci, Complex Networks.
- S. Durrleman acted as a reviewer for Information Processing in Medical Imaging (IPMI) and MIC meets NeurIPS.

10.1.3. Journal

10.1.3.1. Member of the Editorial Boards

- O. Colliot is a member of the Editorial Board of the journal Medical Image Analysis (Elsevier).
- F. De Vico Fallani is a member of the Editorial Board of PLoS One, Brain Topography, IEEE TNSRE.
- S. Epelbaum is member of the editorial board for the Medecine Cognition et Vieillissement Scientific Journal.
- S. Durrleman is member of the editorial board of IEEE Transactions on Medical Imaging (TMI), and Neuron, Behavior and Data Analysis (Scholastica)

10.1.3.2. Reviewer - Reviewing Activities

- O. Colliot acted as a reviewer for Medical Image Analysis, Neuroradiology and Clinical Epidemiology.
- N. Burgos acted as a reviewer for IEEE Transactions on Medical Imaging; Medical Image Analysis; Medical Physics; IEEE Transactions on Computational Imaging; Scientific Reports; Artificial Intelligence in Medicine; Physics in Medicine and Biology; NeuroImage: Clinical; EJNMMI Research; International Journal of Radiation Oncology, Biology, Physics.
- S. Epelbaum acted as a reviewer for Alzheimer's & Dementia, the Journal of Alzheimer's disease, Annals of Neurology and Annals of Clinical and Translational Neurology.
- S. Durrleman acted as a reviewer for Journal of Mathematical Imaging and Vision
- F. De Vico Fallani acted as a reviewer for Brain, PloS Biology, Network Neuroscience, J Neural Engineering, Neuroimage.

10.1.4. Invited Talks

- O. Colliot gave an invited seminar at the University of Southern California (Los Angeles, USA).

- O. Colliot gave an invited seminar at the meeting of the Scientific Council of the Institute of Biology of CNRS.
- O. Colliot gave an invited seminar at CentraleSupélec (Gif-sur-Yvette, France)
- N. Burgos gave an invited seminar at the Université de Tours (Tours, France)
- N. Burgos gave an invited presentation at the MaDICS Symposium (Rennes, France)
- F. De Vico Fallani was invited for a plenary talk at the Institut de neurosciences des systemes INS (Marseille, France)
- F. De Vico Fallani was invited for a plenary talk at the Stem-cell and brain research institute SBRI (Lyon, France)
- F. De Vico Fallani gave an invited seminar at Laboratoire Bordelais de la Recherche en informatique (LABRI), Bordeaux, France
- F. De Vico Fallani gave an invited seminar at the Ecole Polytechnique, Paris, France
- F. De Vico Fallani gave an invited seminar at the Ecole Normale Supérieure, Paris, France
- S. Durrleman gave an invited lecture at the Institute for Pure and Applied Mathematics (IPAM), Los Angeles, USA
- S. Durrleman gave an invited lecture at the Pasadena Workshop, Sorbonne Université, Paris
- S. Durrleman gave an invited lecture at the Disease Progression Modeling workshop in Bonn, Germany
- S. Durrleman gave an invited seminar at CMIC, University College London, UK
- S. Durrleman gave an invited seminar at Bordeaux University, France
- S. Durrleman gave an invited seminar at Ecole Polytechnique, Paris, France

10.1.5. Scientific Expertise

- O. Colliot is a member of the "Commission des emplois scientifiques" of the Inria Paris Center, in charge of evaluating applications for PhD fellowships, postdoc fellowships and secondments.
- O. Colliot acts as an expert for GENCI (the national facility for high-performance computing).
- O. Colliot was a member of the recruitment committee ("jury d'admission") for the national competition for recruitment of permanent researchers at CNRS.
- S. Durrleman is a member of the Commission de Développement Technologique (CDT) of Inria Paris Center.
- S. Durrleman is director of the ICM Center for Neuroinformatics, and scientific manager of the ICM platform for data management and analytics.
- S. Durrleman serves as secretary of the MICCAI Special Interest Group SHAPE.

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

- Master: Olivier Colliot coordinates the course "Methods for medical imaging" of the Master 2 in Computer Science of Sorbonne University and teaches 4.5 hours (eqTD).
- Master: F. De Vico Fallani, 3 hours (eqTD), "Methods for medical imaging" of the Master 2 in Computer Science of Sorbonne University.
- Master: Olivier Colliot coordinates the course "Artificial Intelligence" of the Master 2 Bioentrepreneur of Paris-Descartes University and teaches 30 hours (eqTD).
- Master: S. Epelbaum, Master in Neuroscience, 4 hours (eqTD), Sorbonne University
- Master: S. Durrleman, Master Mathématiques, Vision, Apprentissage (MVA), ENS Paris-Saclay (21 hrs cours magistral)

- Engineering school: Olivier Colliot, 3 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: 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
- Medical school: S. Epelbaum gives lectures in Neurology on the topic of degenerative diseases for medical students of Sorbonne University (10 hours/year) and is regional supervisor of the national Inter University Diploma on Alzheimer’s disease and Related disorders for Paris since 2015.

10.2.2. Supervision

PhD in progress : Juliana Gonzalez-Astudillo, “Network features for brain-computer interfaces”, UPMC, started in 2019, advisor: Fabrizio De Vico Fallani

PhD in progress : Giulia Bassignana, “Identification of driver nodes in biological networks”, Inserm, started in 2017, advisors: Fabrizio De Vico Fallani, Olivier Colliot, Violetta Zujovic

PhD in progress : Tiziana Cattai, “Leveraging brain connectivity networks to detect mental states in brain-computer interfaces”, Inria, started in 2017, advisor: Fabrizio De Vico Fallani

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: Wen Wei, “Learning brain alterations in multiple sclerosis from multimodal neuroimaging data”, Université de Nice Sophia-Antipolis, Started in 2016, advisors: N. Ayache, O. Colliot and S. Durrleman

PhD in progress: Alexandre Bône, “Learning methods for the spatiotemporal analysis of longitudinal image data: application to the diagnosis, prognosis and monitoring of Alzheimer’s disease”, started in 2016, advisors: O. Colliot and S. Durrleman

PhD in progress: Igor Koval, “Construction of disease progression models from multimodal longitudinal data”, started in 2016, advisors: S. Allasonnière and S. Durrleman

PhD in progress: Raphael Couronné, “Spatiotemporal analysis of the progression of the Parkinson’s Disease informed by multimodal longitudinal data”, started in 2018, advisor: S. Durrleman

PhD in progress: Thomas Lartigue, “Mixture Models in Gaussian Graphical Models”, started in 2017, advisors: S. Allasonnière and S. Durrleman

PhD in progress: Vianney Debavelaere, “Analysis of distribution of spatiotemporal trajectories in heterogeneous populations”, started in 2018, advisors: S. Allasonnière and S. Durrleman

PhD in progress: Johann Faouzi, “Machine learning approaches to predict impulse control disorders in Parkinson’s disease”, started in 2018, advisors: O. Colliot and J.-C. Corvol

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: Elina Thibeau-Sutre, “Unsupervised learning from neuroimaging data to identify disease subtypes in Alzheimer’s disease and related disorders”, started in 2018, advisors: D. Dormont and N. Burgos

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: Paul Vernhet, “Learning dynamical systems for disease progression modeling”, started in 2019, advisor: S. Durrleman

PhD in progress: Clément Mantoux, “Statistical analysis of graphs”, started in 2019, advisors: S. Durrleman and S. Allasonnière

10.2.3. *Juries*

- Olivier Colliot participated, as referee, to the PhD committee of Killian Hett (University of Bordeaux).
- Olivier Colliot participated, as referee, to the PhD committee of Florian Tilquin (University of Strasbourg).
- Olivier Colliot participated, as thesis director, to the PhD committee of Jorge Samper-Gonzalez (Sorbonne University).
- Olivier Colliot participated, as thesis director, to the PhD committee of Junhao Wen (Sorbonne University).
- Olivier Colliot participated, as thesis director, to the PhD committee of Pascal Lu (Sorbonne University).
- F. De Vico Fallani participated, as referee, to the PhD committee of Melodie Foullien (University of Lyon).
- F. De Vico Fallani participated, as examiner, to the PhD committee of Sebastien Campeon (Sorbonne University).
- S. Epelbaum participated, as thesis director, to the MD committee of Sinead Gaubert (AP-HP).
- S. Durrleman participated, as referee, to the PhD committee of Razwan Marinescu (University College London)
- S. Durrleman participated, as referee, to the PhD committee of Raphaël Sivera (Université Côte d’Azur)
- S. Durrleman participated, as thesis advisor, to the PhD committee of Maxime Louis (Sorbonne Université)
- S. Durrleman participated, as thesis advisor, to the PhD committee of Manon Ansart (Sorbonne Université)

10.3. Popularization

10.3.1. *Articles and contents*

- Olivier Colliot gave an interview for the popular science magazine "La Recherche".
- Stéphane Epelbaum participated to multiple events dedicated to general audience outreach including: articles in journals (L’Express, AFP, Pourquoi docteur) Radio shows and podcasts (France inter) and TV shows (BFMTV).
- S. Durrleman participated to several events dedicated to general audience outreach including 2 articles in Le Figaro Santé, 2 keynote lectures at AI for Health conference, and Sommet des start-up Challenges, and an article in Médecine, Cerveau et Cognition.

10.3.2. *Interventions*

- N. Burgos gave a presentation for the Rendez-vous des Jeunes Mathématiciennes (Inria Paris).

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Publications of the year

Doctoral Dissertations and Habilitation Theses

- [1] M. ANSART. *Design of data driven decision support systems for the early detection of subjects at risk to develop Alzheimer’s disease*, Sorbonne Université, November 2019, <https://tel.archives-ouvertes.fr/tel-02425735>

- [2] M. LOUIS. *Computational and statistical methods for trajectory analysis in a Riemannian geometry setting*, Sorbonnes universités, October 2019, <https://hal.archives-ouvertes.fr/tel-02430450>
- [3] P. LU. *Statistical Learning from Multimodal Genetic and Neuroimaging data for prediction of Alzheimer's Disease*, Sorbonne Université, November 2019, <https://hal.inria.fr/tel-02433613>
- [4] J. SAMPER-GONZÁLEZ. *Learning from multimodal data for classification and prediction of Alzheimer's disease*, Sorbonne Université, April 2019, <https://tel.archives-ouvertes.fr/tel-02425827>
- [5] J. WEN. *Structural and microstructural neuroimaging for diagnosis and tracking of neurodegenerative diseases*, Sorbonne Universites, UPMC University of Paris 6, July 2019, <https://tel.archives-ouvertes.fr/tel-02425625>

Articles in International Peer-Reviewed Journals

- [6] A. ANDROUIN, Y.-S. K. ABADA, M. LY, M. SANTIN, A. PETIET, S. EPELBAUM, A. BERTRAND, B. DELATOUR. *Activity-induced MEMRI cannot detect functional brain anomalies in the APPxPS1-Ki mouse model of Alzheimer's disease*, in "Scientific Reports", 2019, vol. 9, 1140 p. [DOI : 10.1038/s41598-018-37980-Y], <https://hal.sorbonne-universite.fr/hal-02017552>
- [7] M. ANSART, S. EPELBAUM, G. GAGLIARDI, O. COLLIOT, D. DORMONT, B. DUBOIS, H. HAMPEL, 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", January 2019, 096228021882303 p. [DOI : 10.1177/0962280218823036], <https://hal.archives-ouvertes.fr/hal-01964942>
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