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IN PARTNERSHIP WITH:

CNRS, INSERM, Sorbonne Université (UPMC)

2020 ACTIVITY REPORT

Project-Team ARAMIS

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

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

DOMAIN

Digital Health, Biology and Earth

THEME

Computational Neuroscience and Medicine

Contents

Project-Team ARAMIS

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

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A3.4.4. – Optimization and learning

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B2. – Health

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1 Team members, visitors, external collaborators

Research Scientists

- Olivier Colliot [Team leader, CNRS, Senior Researcher, HDR]
- Ninon Burgos [CNRS, Researcher]
- Stanley Durrleman [Inria, Senior Researcher, HDR]
- Fabrizio de Vico Fallani [Inria, Researcher, HDR]

Faculty Members

- Didier Dormont [Sorbonne Université, Professor]
- Stephane Epelbaum [Assistance publique/Hôpitaux de Paris]
- Daniel Racoceanu [Sorbonne Université, Professor, from Jun 2020, HDR]

Post-Doctoral Fellows

- Marie-Constance Corsi [Institut du Cerveau]
- Baptiste Couvy-Duchesne [Université du Queensland - Australie]
- Vincent Henry [Inria, until Apr 2020]
- Igor Koval [Inria]
- Thomas Nedelec [Institut du Cerveau, from Sep 2020]

PhD Students

- Giulia Bassignana [INSERM, until Oct 2020]
- Remy Ben Messaoud [Inria, from Oct 2020]
- Simona Bottani [Inria]
- Alexandre Bône [Université Pierre et Marie Curie, until Jan 2020]
- Federica Cacciamani [Institut du Cerveau]
- Tiziana Cattai [Inria]
- Raphaël Couronné [Inria]
- Vito Dichio [Inria, from Nov 2020]
- Johann Faouzi [Institut du Cerveau]
- Juliana Gonzalez Astudillo [Sorbonne Université]
- Ravi Hassanaly [CNRS, from Nov 2020]
- Virgilio Kmetzsch Rosa E Silva [Inria]
- Thomas Lartigue [Inria, until Sep 2020]
- Clement Mantoux [Inria]
- Pierre Emmanuel Poulet [Inria, from Oct 2020]

- Charley Presigny [Inria, from Oct 2020]
- Benoit Sauty De Chalon [Inria, from Sep 2020]
- Sophie Skriabine [Inria]
- Elina Thibeau-Sutre [Sorbonne Université]
- Tristan Venot [Inria, from Oct 2020]
- Paul Vernhet [Inria]

Technical Staff

- Arthur Desbois [Inria, Engineer, from Mar 2020]
- Cecile Di Folco [Inria, Engineer, from Sep 2020]
- Mauricio Diaz Melo [Inria, Engineer]
- Etienne Maheux [Inria, Engineer]
- Arnaud Marcoux [Institut du Cerveau et de la Moelle Epinière, Engineer, until Feb 2020]
- Thomas Nedelec [Inria, Engineer, until Feb 2020]
- Juliette Ortholand [Institut du Cerveau, Engineer, from Sep 2020]
- Alexandre Routier [Inria, Engineer, until Oct 2020]
- Arnaud Valladier [Inria, Engineer]
- Mkrtich Vatinyan [Institut du Cerveau, Engineer, from Sep 2020]

Interns and Apprentices

- Valentin Abadie [École Normale Supérieure de Cachan, from Apr 2020 until Aug 2020]
- Baptiste Criniere-Boizet [Inria, from May 2020 until Oct 2020]
- Ravi Hassanaly [Institut du Cerveau, from Apr 2020 until Sep 2020]
- Alban Lemesle-Welti [Inria, from Jun 2020 until Jul 2020]
- Pierre Emmanuel Poulet [Inria, from Apr 2020 until Sep 2020]
- Nessim Richard [Inria, from Feb 2020 until Jul 2020]
- Louis Simon [Sorbonne University, From Oct. 2020 until Dec. 2020]

Administrative Assistant

- Helene Milome [Inria]

2 Overall objectives

2.1 Context

ARAMIS is an Inria project-team within the Paris Brain 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 **Paris Brain Institute (ICM)** gathers all research activities in neuroscience and neurology of the Pitié-Salpêtrière hospital. The ICM is both a private foundation and a public research unit (affiliated to CNRS, Inserm and Sorbonne University). It hosts about 25 research teams as well as various high level technical facilities (neuroimaging, genotyping/sequencing, cell culture, cellular imaging, bioinformatics ...), and gathers over 700 personnel. In addition, the ICM hosts one of the six IHU (*Instituts Hospitalo-Universitaires*), 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: 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, D. Racoceanu) and clinicians (D. Dormont, S. Epelbaum).

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

3 Research program

3.1 From geometrical data to multimodal imaging

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

3.2 Models of brain networks

Functional imaging techniques (EEG, MEG and fMRI) allow characterizing the statistical interactions between the activities of different brain areas, i.e. functional connectivity. Functional integration of

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

3.3 Spatiotemporal modeling from longitudinal data

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

3.4 Decision support systems

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

3.5 Clinical research studies

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

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

4 Application domains

4.1 Introduction

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

- better understanding the pathophysiology of brain disorders;
- designing systems to support clinical decisions such as diagnosis, prognosis and design of clinical trials;
- developing brain computer interfaces for clinical applications.

4.2 Understanding brain disorders

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

4.3 Supporting clinical decisions

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

4.4 Brain computer interfaces for clinical applications

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

5 Highlights of the year

5.1 Awards

- Stanley Durrleman received the Inria-Academy of Sciences Young Researcher award.
- Federica Cacciamani received the Fondation Planiol Young Researcher award.
- Stéphane Epelbaum was granted the Poste d'accueil Inria in collaboration with APHP for the second consecutive year.
- Daniel Racoceanu organised, as General Chair, the 23rd International Conference on Medical Image Computing and Computer Assisted Intervention - MICCAI 2020.

6 New software and platforms

6.1 New software

6.1.1 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.

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

Contacts: Jeremy Guillon, Fabrizio de Vico Fallani, Mario Chavez

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

6.1.2 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!

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

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

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

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

Contact: Stanley Durrleman

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

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

6.1.3 Clinica

Name: Clinica

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

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

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

URL: http://www.clinica.run

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

Contacts: Olivier Colliot, Ninon Burgos

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

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

6.1.4 leaspy

Name: Learning spatiotemporal patterns in python

Keywords: Clinical analysis, Medical applications, Personalized medicine

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

Contacts: Stanley Durrleman, Igor Koval

6.1.5 OpenVIBE

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

Functional Description: OpenViBE is a free and open-source software platform devoted to the design, test and use of Brain-Computer Interfaces (BCI). The platform consists of a set of software modules that can be integrated easily and efficiently to design BCI applications. The key features of OpenViBE software are its modularity, its high-performance, its portability, its multiple-users facilities and its connection with high-end/VR displays. The designer of the platform enables to build complete scenarios based on existing software modules using a dedicated graphical language and a simple Graphical User Interface (GUI). This software is available on the Inria Forge under the terms of the AGPL licence, and it was officially released in June 2009. Since then, the OpenViBE software has already been downloaded more than 60000 times, and it is used by numerous laboratories, projects, or individuals worldwide. More information, downloads, tutorials, videos, documentations are available on the OpenViBE website.

URL: http://openvibe.inria.fr

Authors: Charles Garraud, Jérôme Chabrol, Thierry Gaugry, Cedric Riou, Yann Renard, Anatole Lécuyer, Jozef Legény, Laurent Bonnet, Jussi Tapio Lindgren, Fabien Lotte, Thomas Prampart, Thibaut Monseigne

Contacts: Anatole Lécuyer, Ana Bela Leconte

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

Partners: INSERM, GIPSA-Lab

6.2 New platforms

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 NNIH/ANR and ATTACK Big-brain theory funded projects, as well as experiments by different researchers of the Institute (ANR BETAPARK Project), and the BCINET ERC Consolidator grant are currently being run. To reinforce the impact of the platform we have recently recruited an Inria ADT engineer (A. Desbois)

7 New results

7.1 Convolutional Neural Networks for Classification of Alzheimer's Disease: Overview and Reproducible Evaluation

Participants Junhao Wen, Elina Thibeau-Sutre, Mauricio Diaz-Melo, Jorge Samper-Gonzalez, Alexandre Routier, Simona Bottani, Didier Dormont, Stanley Durrleman, Ninon Burgos, Olivier Colliot *(Correspondant)*.

Numerous machine learning (ML) approaches have been proposed for automatic classification of Alzheimer's disease (AD) from brain imaging data. In particular, over 30 papers have proposed to use convolutional neural networks (CNN) for AD classification from anatomical MRI. However, the classification performance is difficult to compare across studies due to variations in components such as participant selection, image preprocessing or validation procedure. Moreover, these studies are hardly reproducible because their frameworks are not publicly accessible and because implementation details are lacking. Lastly, some of these papers may report a biased performance due to inadequate or unclear validation or model selection procedures. In the present work, we aim to address these

limitations through three main contributions. First, we performed a systematic literature review. We identified four main types of approaches: i) 2D slice-level, ii) 3D patch-level, iii) ROI-based and iv) 3D subject-level CNN. Moreover, we found that more than half of the surveyed papers may have suffered from data leakage and thus reported biased performance. Our second contribution is the extension of our open-source framework for classification of AD using CNN and T1-weighted MRI. The framework comprises previously developed tools to automatically convert ADNI, AIBL and OASIS data into the BIDS standard, and a modular set of image preprocessing procedures, classification architectures and evaluation procedures dedicated to deep learning. Finally, we used this framework to rigorously compare different CNN architectures. The data was split into training/validation/test sets at the very beginning and only the training/validation sets were used for model selection. To avoid any overfitting, the test sets were left untouched until the end of the peer-review process. Overall, the different 3D approaches (3D-subject, 3D-ROI, 3D-patch) achieved similar performances while that of the 2D slice approach was lower. Of note, the different CNN approaches did not perform better than a SVM with voxel-based features. The different approaches generalized well to similar populations but not to datasets with different inclusion criteria or demographical characteristics. All the code of the framework and the experiments is publicly available: general-purpose tools have been integrated into the Clinica software (`http://www.clinica.run`) and the paper-specific code is available at: `https://github.com/aramis-lab/AD-DL`.

More details in [73].

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

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

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

In order to reach precision medicine and improve patients' quality of life, machine learning is increasingly used in medicine. Brain disorders are often complex and heterogeneous, and several modalities such as demographic, clinical, imaging, genetics and environmental data have been studied to improve their understanding. Deep learning, a subpart of machine learning, provides complex algorithms that can learn from such various data. It has become state of the art in numerous fields, including computer vision and natural language processing, and is also growingly applied in medicine. In this article, we review the use of deep learning for brain disorders. More specifically, we identify the main applications, the concerned disorders and the types of architectures and data used. Finally, we provide guidelines to bridge the gap between research studies and clinical routine.

More details in [34].

7.3 Machine learning for classification and prediction of brain diseases: recent advances and upcoming challenges

Participants Ninon Burgos, Olivier Colliot *(Correspondant)*.

We were invited to publish a review paper on machine learning for classification and prediction of brain diseases in the prestigious journal *Current Opinion in Neurology*.

Machine learning (ML) is an artificial intelligence technique that allows computers to perform a task without being explicitly programmed. ML can be used to assist diagnosis and prognosis of brain disorders. While the earliest papers date from more than ten years ago, research increases at a very fast pace. Recent findings. Recent works using ML for diagnosis have moved from classification of a given disease versus controls to differential diagnosis. Intense research has been devoted to the prediction of the future patient state. While a lot of earlier works focused on neuroimaging as data source, the current trend is on the integration of multimodal. In terms of targeted diseases, dementia remains dominant,

but approaches have been developed for a wide variety of neurological and psychiatric diseases. ML is extremely promising for assisting diagnosis and prognosis in brain disorders. Nevertheless, we argue that key challenges remain to be addressed by the community for bringing these tools in clinical routine: good practices regarding validation and reproducible research need to be more widely adopted; extensive generalization studies are required; interpretable models are needed to overcome the limitations of black-box approaches.

More details in [35].

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

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

7-Tesla MRI of the hippocampus enhances the visualization of its internal substructures. Among these substructures, the cornu Ammonis and subiculum form a contiguous folded ribbon of gray matter. We have proposed a method to analyze local thickness measurements of this ribbon. We introduced an original approach based upon the estimation of a diffeomorphic vector field that traverses the ribbon. The method was designed to handle specificities of the hippocampus and corresponding 7-Tesla acquisitions: highly convoluted surface, non closed ribbon, incompletely defined inner/outer boundaries, anisotropic acquisitions. We furthermore proposed to conduct group comparisons using a population template built from the central surfaces of individual subjects. We first assessed the robustness of our approach to anisotropy, as well as to inter-rater variability, on a post-mortem scan and on in vivo acquisitions respectively. We then conducted a group study on a dataset of in vivo MRI from temporal lobe epilepsy (TLE) patients and healthy controls. The method detected local thinning patterns in patients, predominantly ipsilaterally to the seizure focus, which is consistent with medical knowledge. This new technique allows measuring the thickness of the hippocampus from 7-Tesla MRI. It shows good robustness with respect to anisotropy and inter-rater variability and has the potential to detect local atrophy in patients. As 7-Tesla MRI is increasingly available, this new method may become a useful tool to study local alterations of the hippocampus in brain disorders. It is made freely available to the community (code: `https://github.com/aramis-lab/hiplay7-thickness`, postmortem segmentation: `https://doi.org/10.5281/zenodo.3533264`).

More details in [56].

7.5 Genome wide association study of incomplete hippocampal inversion in adolescents

Participants Claire Cury, Maria Scelsi, Roberto toro, André Altmann, Olivier Colliot *(Correspondant)*.

Incomplete hippocampal inversion (IHI), also called hippocampal malrotation,is an atypical presentation of the hippocampuspresent in about 20% of healthy individuals. Here we conducted the first genome-wide association study (GWAS) in IHI to elucidate the genetic underpinnings that may contribute to the incomplete inversion during brain development. A total of 1381 subjects contributed to the discovery cohortobtained from the IMAGEN database. The incidence rate of IHI was 26.1%. Loci with P<1e-5 were followed up in a validation cohort comprising 161 subjects from the PING study. Summary statistics from the discovery cohort were used to compute IHI heritability as well as genetic correlations with other traits. A locus on 18q11.2 (rs9952569; OR=1.999; Z=5.502; P=3.755e-8) showed a significant association with the presence of IHI. A functional annotation of the locusimplicatedgenes AQP4 and

KCTD1. However, neither this locus nor the other 16 suggestive loci reached a significant p-value in the validation cohort. The h2 estimate was 0.54 (sd: 0.30) and was significant (Z=1.8; P=0.036). The top three genetic correlations of IHI were with traits representing either intelligence or education attainment and reached nominal P<=0.013.

More details in [45].

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

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

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

More details in [72].

7.7 Ensemble Learning of Convolutional Neural Network, Support Vector Machine, and Best Linear Unbiased Predictor for Brain Age Prediction: ARAMIS Contribution to the Predictive Analytics Competition 2019 Challenge

Participants Baptiste Couvy-Duchesne *(Correspondant)*, Johann Faouzi, Benoît Martin, Elina Thibeau-Sutre, Adam Wild, Manon Ansart, Stanley Durrleman, Didier Dormont, Ninon Burgos, Olivier Colliot.

We ranked third in the Predictive Analytics Competition (PAC) 2019 challenge by achieving a mean absolute error (MAE) of 3.33 years in predicting age from T1-weighted MRI brain images. Our approach combined seven algorithms that allow generating predictions when the number of features exceeds the number of observations, in particular, two versions of best linear unbiased predictor (BLUP), support vector machine (SVM), two shallow convolutional neural networks (CNNs), and the famous ResNet and Inception V1. Ensemble learning was derived from estimating weights via linear regression in a hold-out subset of the training sample. We further evaluated and identified factors that could influence prediction accuracy: choice of algorithm, ensemble learning, and features used as input/MRI image processing. Our prediction error was correlated with age, and absolute error was greater for older participants, suggesting to increase the training sample for this subgroup. Our results may be used to guide researchers to build

age predictors on healthy individuals, which can be used in research and in the clinics as non-specific predictors of disease status.

More details in [43].

7.8 Plasma microRNA signature in presymptomatic and symptomatic subjects with C9orf72-associated frontotemporal dementia and amyotrophic lateral sclerosis

Participants Virgilio Kmetzsch *(Correspondant)*, Vincent Anquetil, Dario Saracino, Isabelle Le Ber, Olivier Colliot, Emmanuelle Becker.

This study aimed at identifying potential biomarkers of preclinical and clinical progression in chromosome 9 open reading frame 72 gene (C9orf72)-associated disease by assessing the expression levels of plasma microRNAs (miRNAs) in C9orf72 patients and presymptomatic carriers. The PREV-DEMALS study is a prospective study including 22 C9orf72 patients, 45 presymptomatic C9orf72 mutation carriers and 43 controls. We assessed the expression levels of 2576 miRNAs, among which 589 were above noise level, in plasma samples of all participants using RNA sequencing. The expression levels of the differentially expressed miRNAs between patients, presymptomatic carriers and controls were further used to build logistic regression classifiers. Four miRNAs were differentially expressed between patients and controls: miR-34a-5p and miR-345-5p were overexpressed, while miR-200c-3p and miR-10a-3p were underexpressed in patients. MiR-34a-5p was also overexpressed in presymptomatic carriers compared with healthy controls, suggesting that miR-34a-5p expression is deregulated in cases with C9orf72 mutation. Moreover, miR-345-5p was also overexpressed in patients compared with presymptomatic carriers, which supports the correlation of miR-345-5p expression with the progression of C9orf72-associated disease. Together, miR-200c-3p and miR-10a-3p underexpression might be associated with full-blown disease. Four presymptomatic subjects in transitional/prodromal stage, close to the disease conversion, exhibited a stronger similarity with the expression levels of patients. In conclusion, we identified a signature of four miRNAs differentially expressed in plasma between clinical conditions that have potential to represent progression biomarkers for C9orf72-associated frontotemporal dementia and amyotrophic lateral sclerosis. This study suggests that dysregulation of miRNAs is dynamically altered throughout neurodegenerative diseases progression, and can be detectable even long before clinical onset.

More details in [58].

7.9 Visualization approach to assess the robustness of neural networks for medical image classification

Participants Elina Thibeau-Sutre, Olivier Colliot, Didier Dormont, Ninon Burgos.

The use of neural networks for diagnosis classification is becoming more and more prevalent in the medical imaging community. However, deep learning method outputs remain hard to explain. Another difficulty is to choose among the large number of techniques developed to analyze how networks learn, as all present different limitations. In this paper, we extended the framework of Fong and Vedaldi [IEEE International Conference on Computer Vision (ICCV), 2017] to visualize the training of convolutional neural networks (CNNs) on 3D quantitative neuroimaging data. Our application focuses on the detection of Alzheimer's disease with gray matter probability maps extracted from structural MRI. We first assessed the robustness of the visualization method by studying the coherence of the longitudinal patterns and regions identified by the network. We then studied the stability of the CNN training by computing visualization-based similarity indexes between different re-runs of the CNN. We demonstrated that the areas identified by the CNN were consistent with what is known of Alzheimer's disease and that the visualization approach extract coherent longitudinal patterns. We also showed that the CNN training is not stable and that the areas identified mainly depend on the initialization and the training process.

This issue may exist in many other medical studies using deep learning methods on datasets in which the number of samples is too small and the data dimension is high. This means that it may not be possible to rely on deep learning to detect stable regions of interest in this field yet.

More details in [78].

7.10 Influence of diversity on the measurement of functional impairment: An international validation of the Amsterdam IADL Questionnaire in eight countries

Participants Mark Dubbelman, Merike Verrijp, David Facal, Gonzalo Sánchez-benavides, Laura Brown, Wiesje Van der Flier, Hana Jokinen, Athene Lee, Iracema Leroi, Cristina Lojo-seoane, Vuk Milošević, José Molinuevo, Arturo Pereiro Rozas, Craig Ritchie, Stephen Salloway, Gemma Stringer, Stelios Zygouris, Bruno Dubois, Stéphane Epelbaum, Philip Scheltens, Sietske Sikkes.

To understand the potential influence of diversity on the measurement of functional impairment in dementia, we aimed to investigate possible bias caused by age, gender, education, and cultural differences. A total of 3571 individuals (67.1 ± 9.5 years old, 44.7 percents female) from The Netherlands, Spain, France, United States, United Kingdom, Greece, Serbia, and Finland were included. Functional impairment was measured using the Amsterdam Instrumental Activities of Daily Living (IADL) Questionnaire. Item bias was assessed using differential item functioning (DIF) analysis. There were some differences in activity endorsement. A few items showed statistically significant DIF. However, there was no evidence of meaningful item bias: Effect sizes were low (ΔR 2 range 0-0.03). Impact on total scores was minimal. The results imply a limited bias for age, gender, education, and culture in the measurement of functional impairment. This study provides an important step in recognizing the potential influence of diversity on primary outcomes in dementia research.

More details in [49].

7.11 Amyloid beta in Alzheimer's Disease: A Study of Citation Practices of the Amyloid Cascade Hypothesis Between 1992 and 2019

Participants Timothy Daly, Marion Houot, Anouk Barberousse, Yves Agid, Stéphane Epelbaum *(Correspondant)*.

The amyloid cascade hypothesis (ACH) has dominated contemporary biomedical research into Alzheimer's disease (AD) since the 1990 s but still lacks definitive confirmation by successful clinical trials of anti-amyloid medicines in human AD. In this uncertain period regarding the centrality of amyloid-β (Aβ) in AD pathophysiology, and with the community apparently divided about the ACH's validity, we used citation practices as a proxy for measuring how researchers have invested their belief in the hypothesis between 1992 and 2019. We sampled 445 articles citing Hardy and Higgins (1992, "HH92") and classified the polarity of their HH92 citation according to Greenberg (2009)'s citation taxonomy of positive, neutral, and negative citations, and then tested four hypotheses. We identified two major attitudes towards HH92: a majority (62 percents) of neutral attitudes with consistent properties across the time period, and a positive attitude (35 percents), tending to cite HH92 earlier on within the bibliography as time went by, tending to take HH92 as an established authority. Despite the majority of neutral HH92 citations, there was a positive majority of attitudes toward different versions of the ACH and anti-amyloid therapeutic strategies (65 percents), suggesting that the ACH has been dominant and has undergone significant refinement since 1992. Finally, of those 110 original articles within the sample also testing the ACH empirically, an overwhelming majority (89 percents) returned a pro-ACH test result, suggesting that the ACH's central claim is reproducible. Further studies will quantify the extent to which results from

different methods within such original studies convergence to provide a robust conclusion vis-à-vis Aβ's pathogenicity in AD.

More details in [46].

7.12 The meta-memory ratio: a new cohort- independent way to measure cognitive awareness in asymptomatic individuals at risk for Alzheimer's disease

Participants Geoffroy Gagliardi, Marion Houot, Federica Cacciamani, Marie Odile Habert, Bruno Dubois, Stéphane Epelbaum *(Correspondant)*.

Lack of awareness of cognitive decline (ACD) has been described at the preclinical and prodromal stages of Alzheimer's disease (AD). In this study, we introduced a meta-memory ratio (MMR) and explored how it is associated with neuroimaging AD biomarkers in asymptomatic individuals at risk for AD. Four hundred forty-eight cognitively healthy participants from two cohorts of subjective memory complainers (INSIGHT-PreAD and ADNI) were included. Regression models were used to assess the impact of AD biomarkers on the MMR. In both cohorts, there was a significant quadratic effect of cerebral amyloidosis on the MMR value. In particular, participants had a high ACD up to the amyloid positivity threshold, above which a decrease of ACD was eventually observed as the amyloid load increased. This nonlinear evolution of ACD in very early AD must be taken into account in clinical care and for trial enrollment as well.

More details in [53].

7.13 Awareness of cognitive decline trajectories in asymptomatic individuals at risk for AD

Participants Federica Cacciamani, Luisa Sambati, Marion Houot, Marie Odile Habert, Bruno Dubois, Stéphane Epelbaum *(Correspondant)*.

Lack of awareness of cognitive decline (ACD) is common in late-stage Alzheimer's disease (AD). Recent studies showed that ACD can also be reduced in the early stages. Methods: We described different trends of evolution of ACD over 3 years in a cohort of memory-complainers and their association to amyloid burden and brain metabolism. We studied the impact of ACD at baseline on cognitive scores' evolution and the association between longitudinal changes in ACD and in cognitive score. Results: 76.8 percents of subjects constantly had an accurate ACD (reference class). 18.95 percents showed a steadily heightened ACD and were comparable to those with accurate ACD in terms of demographic characteristics and AD biomarkers. 4.25 percents constantly showed low ACD, had significantly higher amyloid burden than the reference class, and were mostly men. We found no overall effect of baseline ACD on cognitive scores' evolution and no association between longitudinal changes in ACD and in cognitive scores. Conclusions: ACD begins to decrease during the preclinical phase in a group of individuals, who are of great interest and need to be further characterized.

More details in [36].

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

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

Identifying the nodes able to drive the state of a network is crucial to understand, and eventually control, biological systems. Despite recent advances, such identification remains difficult because of

the huge number of equivalent controllable configurations, even in relatively simple networks. Based on the evidence that in many applications it is essential to test the ability of individual nodes to control a specific target subset, we develop a fast and principled method to identify controllable driver-target configurations in sparse and directed networks. We demonstrate our approach on simulated networks and experimental gene networks to characterize macrophage dysregulation in human subjects with multiple sclerosis.

More details in [32].

7.15 Network-based brain computer interfaces: principles and applications

Participants Gonzalez-Astudillo Juliana, Cattai Tiziana, Bassignana Giulia, Corsi Marie-Constance, De Vico Fallani Fabrizio *(Correspondant)*.

Brain–computer interfaces (BCIs) make possible to interact with the external environment by decoding the mental intention of individuals. BCIs can therefore be used to address basic neuroscience questions but also to unlock a variety of applications from exoskeleton control to neurofeedback (NFB) rehabilitation. In general, BCI usability critically depends on the ability to comprehensively characterize brain functioning and correctly identify the user's mental state. To this end, much of the efforts have focused on improving the classification algorithms taking into account localized brain activities as input features. Despite considerable improvement BCI performance is still unstable and, as a matter of fact, current features represent oversimplified descriptors of brain functioning. In the last decade, growing evidence has shown that the brain works as a networked system composed of multiple specialized and spatially distributed areas that dynamically integrate information. While more complex, looking at how remote brain regions functionally interact represents a grounded alternative to better describe brain functioning. Thanks to recent advances in network science, i.e. a modern field that draws on graph theory, statistical mechanics, data mining and inferential modelling, scientists have now powerful means to characterize complex brain networks derived from neuroimaging data. Notably, summary features can be extracted from these networks to quantitatively measure specific organizational properties across a variety of topological scales. In this topical review, we aim to provide the state-of-the-art supporting the development of a network theoretic approach as a promising tool for understanding BCIs and improve usability.

More details in [54].

7.16 A Joint Markov Model for Communities, Connectivity and Signals defined over Graphs

Participants Colonnese Stefania *(Correspondant)*, Di Lorenzo Paolo, Cattai Tiziana, Scarano Gaetano, De Vico Fallani Fabrizio.

Real-world networks are typically described in terms of nodes, links, and communities, having signal values often associated with them. The aim of this letter is to introduce a novel Compound Markov random field model (Compound MRF, or CMRF) for signals defined over graphs, encompassing jointly signal values at nodes, edge weights, and community labels. The proposed CMRF generalizes Markovian models previously proposed in the literature, since it accounts for different kinds of interactions between communities and signal smoothness constraints. Finally, the proposed approach is applied to (joint) graph learning and signal recovery. Numerical results on synthetic and real data illustrate the competitive performance of our method with respect to other state-of-the-art approaches.

More details in [40].

7.17 Functional disconnection of associative cortical areas predicts performance during BCI training

Participants Corsi Marie-Constance, Chavez Mario, Hugueville Laurent, George Nathalie, Bassett Danielle, De Vico Fallani Fabrizio *(Correspondant)*.

Brain-computer interfaces (BCIs) have been largely developed to allow communication, control, and neurofeedback in human beings. Despite their great potential, BCIs perform inconsistently across individuals and the neural processes that enable humans to achieve good control remain poorly understood. To address this question, we performed simultaneous high-density electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings in a motor imagery-based BCI training involving a group of healthy subjects. After reconstructing the signals at the cortical level, we showed that the reinforcement of motor-related activity during the BCI skill acquisition is paralleled by a progressive disconnection of associative areas which were not directly targeted during the experiments. Notably, these network connectivity changes reflected growing automaticity associated with BCI performance and predicted future learning rate. Altogether, our findings provide new insights into the large-scale cortical organizational mechanisms underlying BCI learning, which have implications for the improvement of this technology in a broad range of real-life applications.

More details in [41].

7.18 Learning in brain-computer interface control evidenced by joint decomposition of brain and behavior

Participants Stiso Jennifer, Corsi Marie-Constance, De Vico Fallani Fabrizio, Lucas Timothy, Bassett Danielle *(Correspondant)*.

Motor imagery-based brain-computer interfaces (BCIs) use an individual's ability to volitionally modulate localized brain activity, often as a therapy for motor dysfunction or to probe causal relations between brain activity and behavior. However, many individuals cannot learn to successfully modulate their brain activity, greatly limiting the efficacy of BCI for therapy and for basic scientific inquiry. Formal experiments designed to probe the nature of BCI learning have offered initial evidence that coherent activity across spatially distributed and functionally diverse cognitive systems is a hallmark of individuals who can successfully learn to control the BCI. However, little is known about how these distributed networks interact through time to support learning.

More details in [67].

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

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

We performed a systematic review of studies focusing on the automatic prediction of the progression of mild cognitive impairment to Alzheimer's disease (AD) dementia, and a quantitative analysis of the methodological choices impacting performance. This review included 172 articles, from which 234 experiments were extracted. For each of them, we reported the used data set, the feature types, the algorithm type, performance and potential methodological issues. The impact of these characteristics on the performance was evaluated using a multivariate mixed effect linear regressions. We found that using cognitive, fluorodeoxyglucose-positron emission tomography or potentially electroencephalography and magnetoencephalography variables significantly improved predictive performance compared to not including them, whereas including other modalities, in particular T1 magnetic resonance imaging, did not show a significant effect. The good performance of cognitive assessments questions the wide use of imaging for predicting the progression to AD and advocates for exploring further fine domain-specific

cognitive assessments. We also identified several methodological issues, including the absence of a test set, or its use for feature selection or parameter tuning in nearly a fourth of the papers. Other issues, found in 15 percent of the studies, cast doubts on the relevance of the method to clinical practice. We also highlight that short-term predictions are likely not to be better than predicting that subjects stay stable over time. These issues highlight the importance of adhering to good practices for the use of machine learning as a decision support system for the clinical practice.

More details in [29].

7.20 Learning the spatiotemporal variability in longitudinal shape data sets

Participants Alexandre Bône, Olivier Colliot, Stanley Durrleman.

We propose a generative statistical model to learn the spatiotemporal variability in longitudinal shape data sets, which contain repeated observations of a set of objects or individuals over time. From all the short-term sequences of individual data, the method estimates a long-term normative scenario of shape changes and a tubular coordinate system around this trajectory. Each individual data sequence is therefore (i) mapped onto a specific portion of the trajectory accounting for differences in pace of progression across individuals, and (ii) shifted in the shape space to account for intrinsic shape differences across individuals that are independent of the progression of the observed process. The parameters of the model are estimated using a stochastic approximation of the expectation–maximization algorithm. The proposed approach is validated on a simulated data set, illustrated on the analysis of facial expression in video sequences, and applied to the modeling of the progressive atrophy of the hippocampus in Alzheimer's disease patients. These experiments show that one can use the method to reconstruct data at the precision of the noise, to highlight significant factors that may modulate the progression, and to simulate entirely synthetic longitudinal data sets reproducing the variability of the observed process.

More details in [33].

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

Participants Vianney Debavelaere, Stanley Durrleman, Stéphanie Allassonnière.

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 hip-pocampus atrophy in ageing by using an heteregenous population of normal ageing individuals and mild cog-nitive impaired subjects.

More details in [48].

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

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

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

More details in [59].

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

Participants Chao-Hui Huang, Daniel Racoceanu.

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

More details in [14].

7.24 Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part I to VII

Participants Anne LMartel , Purang Abolmaesumi, Danail Stoyanov, Diana Mateus, Maria AZuluaga , S KevinZhou , Leo Joskovicz, Daniel Racoceanu.

The seven-volume set LNCS 12261, 12262, 12263, 12264, 12265, 12266, and 12267 constitutes the refereed proceedings of the 23rd International Conference on Medical Image Computing and Computer-Assisted Intervention, MICCAI 2020, held in Lima, Peru, in October 2020. The conference was held virtually due to the COVID-19 pandemic. The 542 revised full papers presented were carefully reviewed and selected from 1809 submissions in a double-blind review process. The papers are organized in the following topical sections: Part I: machine learning methodologies Part II: image reconstruction; prediction and diagnosis; cross-domain methods and reconstruction; domain adaptation; machine learning applications; generative adversarial networks Part III: CAI applications; image registration; instrumentation and surgical phase detection; navigation and visualization; ultrasound imaging; video image analysis Part IV: segmentation; shape models and landmark detection Part V: biological, optical, microscopic imaging; cell segmentation and stain normalization; histopathology image analysis; opthalmology Part VI: angiography and vessel analysis; breast imaging; colonoscopy; dermatology; fetal imaging; heart and

lung imaging; musculoskeletal imaging Part VII: brain development and atlases; DWI and tractography; functional brain networks; neuroimaging; positron emission tomography

More details in [16, 17, 18, 19, 20, 21, 22]

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.

8.1.2 Sanofi

Participants Stanley Durrleman *(Correspondant)*.

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

9 Partnerships and cooperations

9.1 International initiatives

Informal international partners

- O. Colliot has an enduring collaboration with the Center for Magnetic Resonance Research, University of Minnesota, USA (P-F Van de Moortele, T. Henry).

- O. Colliot has a collaboration with the University of Queensland, Australia (P. Visscher, N. Wray).
- S. Durrleman and O. Colliot have a collaboration with the Center for Medical Image Computing (CMIC) at University College London (UCL), London, UK (D. Alexander, H. Zhang).
- S. Durrleman has collaboration with Portland State University (B. Jedynak)
- D. Racoceanu has a collaboration with the Pontifical Catholic University of Peru (G. Jiménez). Some recent publications have been generated from this collaboration.
- D. Racoceanu has a collaboration with the Bioinformatics Institute, Agency for Science, Technology and Research (BII/A*STAR) Singapore (H.K. Lee) - one PhD (Ms. Oumeima Laifa) was jointly co-supervised and defended her PhD, in 2019.

9.2 European initiatives

9.2.1 FP7 & H2020 Projects

EuroPOND

Title: Data-driven models for Progression Of Neurological Disease

Duration: January 2016 - December 2020

Coordinator: University College London (UCL)

Partners:

- Erasmus Universitair Medisch Centrum Rotterdam (Netherlands)
- Fondazione Irccs Istituto Neurologico Carlo Besta (Italy)
- Icometrix Nv (Belgium)
- Institut National de La Sante et de la Recherche Medicale (Inserm) (France)
- Provincia Lombardo Veneta Ordine Ospedaliero Din Giovanni di Dio - Fatebenefratelli (Italy)
- Stichting Vu-Vumc (Netherlands)
- Universite de Geneve (Switzerland)
- University College London (United Kingdom)

Inria contacts: Stanley Durrleman, Olivier Colliot

Summary: 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.

LEASP

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

Duration: September 2016 - August 2021

Coordinator: Inria

Inria contact: Stanley Durrleman

Summary: Time-series of multimodal medical images offer a unique opportunity to track anatomical and functional alterations of the brain in aging individuals. A collection of such time series for several individuals forms a longitudinal data set, each data being a rich iconic-geometric representation of the brain anatomy and function. These data are already extraordinary complex and variable across individuals. Taking the temporal component into account further adds difficulty, in that each individual follows a different trajectory of changes, and at a different pace. Furthermore, a disease is here a progressive departure from an otherwise normal scenario of aging, so that one could not think of normal and pathologic brain aging as distinct categories, as in the standard case-control paradigm. Bio-statisticians lack a suitable methodological framework to exhibit from these data the typical trajectories and dynamics of brain alterations, and the effects of a disease on these trajectories, thus limiting the investigation of essential clinical questions. To change this situation, we propose to construct virtual dynamical models of brain aging by learning typical spatiotemporal patterns of alterations propagation from longitudinal iconic-geometric data sets. By including concepts of the Riemannian geometry into Bayesian mixed effect models, the project will introduce general principles to average complex individual trajectories of iconic-geometric changes and align the pace at which these trajectories are followed. It will estimate a set of elementary spatiotemporal patterns, which combine to yield a personal aging scenario for each individual. Disease-specific patterns will be detected with an increasing likelihood. This new generation of statistical and computational tools will unveil clusters of patients sharing similar lesion propagation profiles, paving the way to design more specific treatments, and care patients when treatments have the highest chance of success.

VirtualBrainCloud

Title: Personalized Recommendations for Neurodegenerative Disease

Duration: December 2018 - November 2022

Coordinator: CHARITE - UNIVERSITAETSMEDIZIN BERLIN

Partners:

- ALZHEIMER EUROPE (Luxembourg)
- CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE CNRS (France)
- CODEMART SRL (Romania)
- EODYNE SYSTEMS SL (Spain)
- FORSCHUNGSZENTRUM JULICH GMBH (Germany)
- FRAUNHOFER GESELLSCHAFT ZUR FOERDERUNG DER ANGEWANDTEN FORSCHUNG E.V. (Germany)
- FUNDACIO INSTITUT DE BIOENGINYERIA DE CATALUNYA (Spain)

- INSTITUT DU CERVEAU ET DE LA MOELLE EPINIERE (France)
- THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD (UK)
- TP21 GMBH (Germany)
- UNIVERSIDAD COMPLUTENSE DE MADRID (Spain)
- UNIVERSITA DEGLI STUDI DI GENOVA (Italy)
- UNIVERSITAT WIEN (Austria)
- UNIVERSITE D'AIX MARSEILLE (France)

Inria contact: Stanley Durrleman

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

BCINET

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

Duration: October 2020 - September 2025

Coordinator: Inria

Partners:

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

Inria contact: Fabrizio De Vico Fallani

Summary: Human-computer interfaces are increasingly explored to facilitate interaction with the external world. Brain-computer interfaces (BCIs), bypassing the skeletomuscular system, are particularly promising for assisting paralyzed people in control and communication, but also for boosting neuromotor rehabilitation. Despite their potential, the societal impact of BCIs is dramatically limited by the poor usability in real-life applications. While many solutions have been proposed - from the identification of the best classification algorithm to the type of sensory feedback - the accuracy is still highly variable across subjects and BCIs cannot be used by everyone. Critically, these approaches have implicitly assumed that the user's intent could be decoded by examining the activity of single brain areas. Today, we know that this is not true as the brain functioning

essentially depends on a complex network of interactions between differently specialized areas. The grand challenge of this project is to develop a novel generation of BCIs that integrate the user's brain network information for enhancing accuracy and usability. Based on this approach, we will experiment innovative BCI prototypes to restore the lost motor functions in patients suffering from stroke. This project relies on a unifying framework that analyses and models brain networks by means of analytical tools derived from graph theory and complex systems science. By recruiting diverse neuroimaging and experimental methods, within a modern computational framework, we aim to i) identify new control features for enhancing BCI accuracy, ii) study the brain dynamics of human learning for improving adaptive BCI architectures, and iii) optimize brain stimulation techniques for boosting BCI skill acquisition. This project can significantly improve BCI usability as well as determining how brain lesions compromise brain functioning and which solutions are most effective to unlock motor restoration after stroke.

FET Flagship - Human Brain Project

Title: Human Brain Project

Duration: 2016-2026

Coordinator: EPFL, Lausanne, Switzerland

Inria contact: Olivier Colliot, Stanley Durrleman

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

9.2.2 Collaborations in European programs, except FP7 and H2020

E-DADS

Participants Stanley Durrleman.

- Project acronym: E-DADS
- Project title: Early detection of Alzheimer's disease subtypes
- Duration: 2019 - 2022
- Amount: 1.7M€
- funding scheme: Joint Program in Neurodegenerative Diseases (JPND)
- Coordinator: Daniel Alexander
- Other partners: University College London (UK), Stichting VU University Medical Center (VUmc,The Netherlands), IRCCS Fatebenefratelli (Italy), Commonwealth scientific and industrial research organization (CSIRO, Australia)

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

9.3 National initiatives

Health Data Hub

Participants Stanley Durrleman.

- Project acronym: Precise-PD-HDH
- Project title: Modélisation et prédiction de la progression de la maladie de Parkinson
- Duration: 1 year (pilot project)
- Coordinator: Jean-Christophe Corvol
- Other partners: Inserm, réseau NS-PARK, ICM

AVIESAN - ITMO Cancer

Participants Daniel Racoceanu.

- Project acronym: MALMO
- Project title: Mathematical Approaches to Modelling Metabolic Plasticity and Heterogeneity in Melanoma
- Duration: 3 years
- Coordinator: Ovidiu Radulescu
- Other partners: University of Montpellier (LPHI - UMR CNRS 5235, LIRMM - UMR CNRS 5506) and the Institut de Recherche en Cancérologie de Montpellier (IRCM – Inserm U1194), Paris Brain Institute (CNRS UMR 7225 – Inserm U 1127).

- Abstract: Cutaneous melanoma is a highly invasive tumor and despite recent therapeutic advances, most patients with advanced melanoma have a poor clinical outcome. At the molecular level, the most frequent mutations in melanoma affect the BRAF oncogene, a protein kinase of the MAPK pathway. Therapies targeting BRAF/MEK are effective for only 50% of the patients and almost systematically generate resistance. Some non-genetic mechanisms of drug resistance are associated with the strong heterogeneity and the plasticity and melanoma cells that still remain poorly understood. In the proposed project, we will address the importance of metabolic plasticity in melanoma cells in the context of drug resistance. In order to understand the mechanistic origin of the resistance to targeted therapies, we will build a predictive multiscale mathematical model. This model describes intracellular dynamics of the metabolic pathways and the dynamics of the melanoma cell sub- populations in interaction with their micro-environment. The model has spatial extension and takes into account cellular heterogeneity. Model initial conditions and parameters describing the microenvironment are learned from image analysis of tumour sections using deep learning as segmentation approach. In order to validate the model, we use a multiplexed imaging technique applied to the detection of metabolic markers in samples prepared from murine xenografted tumours submitted to treatment. Using the mathematical model and the in situ imaging data, we expect to prove the role of the metabolic reprogramming in generating melanoma heterogeneity and its contribution to resistance to targeted therapies. Our predictive mathematical model will also allow us to investigate in silico the relationship between micro-environment, metabolic/cellular plasticity and drug resistance, as well as the potential of combining several therapies simultaneously or with optimized scheduling.

9.3.1 ANR

ANR-PRC BETPARK

Participants Fabrizio De Vico Fallani *(Correspondant)*.

- Project acronym: BETPARK
- Project title: Neurofeedback for Parkinson's disease
- Duration: Apr 2021 - Mar 2025
- Amount: 712k€
- Coordinator: Nathalie George
- Other partners: CNRS CCLE; ICM
- Abstract: Parkinson's disease (PD) is a complex neurodegenerative disease caused by death of midbrain dopaminergic neurons. This calls for better understanding the pathophysiology of PD in order to pave the way to new non-pharmacological and non-invasive treatment options for PD. We propose to use neurofeedback (NF) to test whether PD patients can learn to self-regulate their brain activity to reduce pathological neural activity and thereby motor symptoms. We will leverage NF to target regulation of pathological beta band (8-35 Hz) oscillations, and we will characterize training-induced changes in cortical network activity and their relationship with symptom severity. Our goal is to provide direct evidence of the functional role of beta rhythms in the pathophysiology of PD while assessing NF as a new non-pharmacological and non-invasive tool for ameliorating PD motor symptoms.

ANR-PRC BRANDY

Participants Fabrizio De Vico Fallani *(Correspondant)*.

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

ANR-NIH-NSF NETBCI

Participants Fabrizio De Vico Fallani *(Correspondant)*, Mario Chavez, Denis Schwartz.

ANR-NIH-NSF CANDT

Participants Fabrizio De Vico Fallani *(Correspondant)*.

- Project acronym: CANDT
- Project title: Advancing neuroscientific discovery and training by lowering the barrier of entry to network neuroscience via open science
- Duration: Oct 2019 - Sep 2023
- Amount: 137k€
- Coordinator: Fabrizio De Vico Fallani
- Other partners: Indiana Univ., US; UPenn, US
- Abstract: This project will use open science methods and cloud-computing, effectively lowering the barrier of entry to network neuroscience and increase the widespread availability of well-maintained and reproducible network neuroscience tools. We will use the platform brainlife.io as a digital marketplace for network neuroscience analysis methods; network neuroscience tools and software will be packaged into self-contained, standardized, reproducible Apps, shared with and modified by a burgeoning community of users, and seamlessly integrated into existing brainlife.io processing and analysis pipelines. This approach will engage both experts in network science, scientists from other domains, and users of the proposed methods. In addition, it will ensure correct implementation, a high level of reproducibility, and maximal reusability of network neuroscience methods. As a requirement, Apps will also be accompanied by links to primary sources, in-depth tutorials, and documentation, and worked-through examples, highlighting their correct usage and

offering solutions for mitigating possible pitfalls. This proposed research lowers the barrier of entry to network neuroscience, standardizes the software sharing process, and provides a cloud-based repository of expertly-maintained network neuroscientific tools and software that is made available to the broader neuroscientific community.

ANR-NIH-NSF 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.

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 2021
- Amount: 770k€
- Coordinator: Olivier Colliot and Pierre-François Van de Moortele
- Other partners: University of Minnesota, Neurospin
- Abstract: The overall goal of this proposal is to develop a coherent mathematical framework for computational anatomy of the internal structures of the hippocampus based on cutting edge MRI acquisition techniques at 7 Tesla. These mathematical and computational approaches are expected to significantly advance the field of computational anatomy of the human brain, breaking down the millimeter barrier of conventional brain morphometry and providing a coherent analysis framework for anatomical data at ultra-high spatial resolution.

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.

9.3.2 Inria Project Labs

IPL Neuromarkers

Participants Stanley Durrleman *(Correspondant)*, Olivier Colliot *(Correspondant)*, Fabrizio De Vico Fallani, Anne Bertrand, Stéphane Epelbaum.

- Project acronym: Neuromarkers

- Project title: Design of imaging biomarkers of neurodegenerative diseases for clinical trials and study of their genetic associations
- Duration: 2017-2021
- Coordinators: Stanley Durrleman and Olivier Colliot
- Other partners: Inria GENSCALE, Inria BONSAI, Inria DYLISS, Inria XPOP, ICM, IHU/ICM iConics
- Abstract: The Inria Project Lab Neuromarkers aims to develop new statistical and computational approaches to integrate multimodal imaging and omics data and to demonstrate their potential to identify early alterations and predict progression of neurodegenerative diseases. To tackle this challenge, the project brings together multidisciplinary expertise from Inria and ICM (Brain and Spine Institute) in the fields of statistical learning, brain imaging, bioinformatics, knowledge modeling, genomics and neurodegenerative diseases.

9.3.3 IHU

General program

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

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

ICM BBT Program - project PredictICD

Participants Olivier Colliot *(Correspondant)*, Jean-Christophe Corvol *(Correspondant)*, Johann Faouzi.

- Project title: Predict impulse control disorders in Parkinson's disease (PREDICT-ICD)
- Started in 2018
- Coordinators: Olivier Colliot and Jean-Christophe Corvol (ICM)
- In Parkinson's disease (PD), the therapeutic strategy is based on the dopamine replacement therapy. Although available since the 1960s', it is only relatively recently that behavioral disorders associated with these drugs have been described. Gathered under the term of "behavioral addiction", they include impulse control disorders (ICDs), dopamine dysregulation syndrome (DDS), and punding. Interestingly, whereas addiction to L-dopa itself occurs quasi exclusively with L-dopa, ICDs appear

electively under dopamine agonist (DA) therapy. The objectives of this project are: i) to elucidate the genetic basis of DA induced ICDs in PD patients from several international cohorts; ii) to develop and validate a machine learning model to predict the occurrence of ICDs from the combination of clinical and genetic data.

ICM BBT Program - project DYNAMO

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

- Project title: Dynamic models of disease progression across Alzheimer's disease stages informed by multimodal neuroimaging and biological data
- Started in 2016
- Coordinator: Stanley Durrleman and Harald Hampel
- Other partners: Institut de la Mémoire et de la maladie d'Alzheimer
- The estimation of data-driven models of disease progression for neurodegenerative diseases, including Alzheimer's disease (AD), is crucial to confirm, refine and extend the current hypothetical models. The estimation of such quantitative models from longitudinal data sets is notably difficult because of the lack of principled methodological frameworks for the analysis of spatiotemporal data.

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

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

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

ICM BBT Program - project SEMAPHORE

Participants Stanley Durrleman *(Correspondant)*, Stéphane Lehéricy *(Correspondant)*, Jean-Christophe Corvol, Marie Vidailhet, Raphael Couronné, Safia Said.

- Project title: Personalized progression model of Parkinson's disease

- Started in 2018
- Coordinator: Stanley Durrleman and Stéphane Lehéricy
- Other partners: Neurology and Neuro-radiology departments, Pitié-Salpêtrière Hospital, AP-HP
- The aim of this project is to build a personalizable model of Parkinson's disease (PD) progression integrating the complex dynamical interplay between phenotypic, imaging, genetic and metabolic alterations. We will identify and validate markers for monitoring of progression of brain damage in early and prodromal PD and identify conversion markers in subjects at risk of PD (idiopathic rapid eye movement sleep behavior disorders iRBD, PD- related mutation carriers). We will describe the appearance, characterize clinical phenotypes of PD, and identify modifier genes of disease phenotype. To this aim, we will relie on a novel statistical learning method using Bayesian non-linear mixed-effects model allowing to combine and realign short term sequence data to estimate a long-term scenario of disease progression. This method is able to estimate individual stages of disease progression and to analyze automatically non-linear spatiotemporal patterns of data change. It estimates both a group-average scenario of PD progression as well as the inter-individual variability of this model in terms of age at onset, pace of disease progression and variability in the spatiotemporal trajectory of data changes. We will analyse the effect of genetic variants in the modulation of these non-linear progression patterns, and assess the statistical power of the individual parameters encoding for these patterns. The method will be applied to two sets of longitudinal data from the local prospective NUCLEIPARK (60 PD patients, 20 patients with iRBD, 60 controls) and ICEBERG studies (200 early idiopathic PD, 50 iRBD, 30 GBA and LRRK2 PD-related mutation carriers, 50 controls). Examinations included clinical, biological, and neurophysiological data, and multimodal 3T MRI, DATScan, and skin and salivary gland biopsies. The models of PD progression for each category of subjects will be released to the community, as well as the software for reproducibility purposes.

ICM BBT Program - project ATTACK

Participants Fabrizio De Vico Fallani *(Correspondant)*, Charlotte Rosso *(Correspondant)*, Marie-Constance Corsi, Laurent Hugueville.

- Project title: ATTACK Brain Network Models Of Motor Recovery After Stroke
- Started in 2018
- Coordinator: Fabrizio De Vico Fallani, Charlotte Rosso
- Other partners: Neurology and Stroke departments, Pitié-Salpêtrière Hospital, AP-HP
- Like in other connected systems, studying the structure of the interactions between different brain regions has profound implications in the comprehension of emergent complex phenomena as, for example, the capability of the human brain to functionally reorganize after cerebrovascular "attacks" or stroke. This dynamic skill, which is known in neuroscience as neural plasticity, is not only interesting from a network science perspective, but it also plays a crucial role in determining the motor/cognitive recovery of patients who survive a stroke. As a critical innovation, this project proposes to develop a systematic and rigorous approach based on neuroimaging techniques, signal processing, and network science for the modeling and analysis of temporally dynamic neural processes that characterize motor recovery after stroke. To achieve these goals, this project is organized around the following objectives: i) acquiring a comprehensive longitudinal dataset of brain and behavioral/clinical data after stroke, ii) developing new analytic tools to characterize and generate temporally dynamic brain networks, iii) building network-based models of motor recovery after stroke, accounting for individual patients. These objectives involve an intensive gathering of heterogeneous mass data, their processing, the subsequent outcome interpretation and statistical simulation, as well as the development of longitudinal models and network-based diagnostics

of the patient's motor recovery progress. Results will be first characterized from pure network-theoretic and neuroscience perspectives, so as to highlight fundamental research challenges, and then validated to clarify the importance and the applicability to the clinical scenario. Our results will unveil multiscale properties of dynamic brain networks and identify predictive neuromarkers for motor recovery after stroke. This project has a two-fold impact on the society. On the one hand, it will provide new methods and robust tools to properly characterize and model temporally dynamic networks in neuroscience. On the other hand, it will provide longitudinal models of motor recovery in stroke patients that can potentially unveil the neural substrate that underpins rehabilitation, improve prognosis, and eventually lower cost of hospitalization time. From a broader perspective this interdisciplinary project proposes a transformative approach to analyze large-scale neural systems.

9.3.4 3IA Institutes - PRAIRIE

Participants Ninon Burgos, Olivier Colliot, Stanley Durrleman.

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

9.3.5 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
- GdR ISIS (Signal and Image Processing) - http://www.gdr-isis.fr/inter-gdr.html

9.3.6 Other National Programs

Fondation Vaincre Alzheimer

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

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

- 2019-2021
- Amount: 100K€
- Coordinator: Olivier Colliot
- Other partners: Frauhofer SCAI (Germany)
- Abstract: Alzheimer's disease (AD) pathophysiology is still imperfectly understood. In particular, we currently lack an integrative view of the disease to interconnect knowledge about the molecular, cellular, clinical and systems levels that remain scattered. Computational knowledge models have the potential to provide such an integrative view. The aim of this project is to provide a multiscale knowledge model of AD pathophysiology by aggregating existing heterogeneous resources (disease maps, ontologies, databases) using Semantic Web standards. The resulting model and associated software tools will be made publicly available to the scientific community.

France Parkinson

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

- Project title: PRECISE-PD - From pathophysiology to precision medicine for Parkinson's disease
- 2019-2024
- Amount: 3M€
- Coordinator: Jean-Christophe Corvol
- Other partners: Inserm CIC-1436, Inserm CIC-P1421, Inserm U1171, Université de Bordeaux (IMN), University of Glasgow, University of Calgary,
- Abstract: Parkinson's disease (PD) is a complex neurodegenerative disease characterized by the progression of motor and non-motor symptoms resulting from the spreading of the disease into dopaminergic and non-dopaminergic areas. Clinical trials have failed to demonstrate efficacy to slow PD progression because the relationships between progression profiles and their underlying molecular mechanisms remain to be identified. The objective of PRECISE-PD is to propose a mechanismsbased progression model of PD by combining genetic and longitudinal clinical data from a large cohort of patients. We will implement a biobank to the NS-PARK/FCRIN cohort collecting motor and non-motor symptoms from >22,000 PD patients followed in the 24 expert centers in France. Genomic data will be generated by using a microarray platform developed for neurodegenerative diseases studies, and brain imaging will be obtained from a subgroup of patients. Computational and machine learning approaches will be developed to address the challenges of analyzing the high dimensionality and the mixture of data necessary to move beyond empirical stratification of patients. Replication will be performed in independent cohorts, and biological validation will combine biomarkers and preclinical research. PRECISE-PD is an unpreceded opportunity to open the path to the new era of precision and personalized medicine for PD.

10 Dissemination

10.1 Promoting scientific activities

10.1.1 Scientific events: organisation

- N. Burgos organized the international workshop on Simulation and Synthesis in Medical Imaging (SASHIMI) 2020, a satellite workshop of MICCAI 2020.

- N. Burgos organized the Hands-on Workshop on Machine Learning Applied to Medical Imaging together with the research group ATLAS of the GdR MADICS at the Paris Brain Institute.

- S. Durrleman organized CompAge 2020, a workshop on computational approaches for ageing and age-related diseases held virtually.

- S. Durrleman organised the 3ème colloque sur l'imagerie médicale à l'heure de l'intelligence artificielle.

- O. Colliot organized the Scientific Workshop of INS2I-CNRS on "Health and Artificial Intelligence".

- D. Racoceanu organized the 23rd International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2020).

General chair, scientific chair

- N. Burgos chaired the international workshop on Simulation and Synthesis in Medical Imaging (SASHIMI) 2020, a satellite workshop of MICCAI 2020.

- D. Racoceanu was the general chair of the 23rd International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2020).

Member of the organizing committees

- N. Burgos and S. Durrleman co-organized CompAge 2020, a workshop on computational approaches for ageing and age-related diseases held virtually.

- S. Durrleman and N. Burgos co-organized the AI4Health winter school of the Health Data Hub, held virtually.

- F. De Vico Fallani organized Network Neuroscience 2020, held virtually.

10.1.2 Scientific events: selection

Member of the conference program committees

- O. Colliot served as Program Committee member for the international conference SPIE Medical Imaging

- O. Colliot served as Program Committee member for the International Joint Conference on Artificial Intelligence (IJCAI)

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

- F. De Vico Fallani served as Program Committee member for the international conference of Complex networks.

- F. De Vico Fallani served as Program Committee member for the Complenet Conference.

- F. De Vico Fallani served as Program Committee member for the NETSCI Conference.

- S. Durrleman served as Area Chair for Medical Imaging Computing and Computer Assisted Intervention (MICCAI).

Reviewer

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

10.1.3 Journal

Member of the editorial boards

- O. Colliot is a member of the Editorial Board of the journal Medical Image Analysis (Elsevier).
- O. Colliot is an Associate Editor of the journal Frontiers in Brain Imaging Methods.
- F. De Vico Fallani is an Associate Editor of the journal PLoS One.
- F. De Vico Fallani is an Associate Editor of the journal IEEE TNSRE.
- F. De Vico Fallani is an Associate Editor of the journal Brain Topography.
- S. Durrleman is editorial board member of the Journal of Imaging

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 and Frontiers in Neuroscience.
- S. Epelbaum acted as a reviewer for Alzheimer's & Dementia, the Journal of Alzheimer's disease, Annals of Neurology and the Lancet Neurology.
- F. De Vico Fallani acted as a reviewer for Brain, PloS Biology, Network Neuroscience, J Neural Engineering, Neuroimage.
- D. Racoceanu acted as reviewer of the Medical Image Analysis journal (MedIA), the IEEE Transactions on Medical Imaging (IEEE TMI), the IEEE Transactions on Biomedical Engineering (IEEE TBME) and Computerized Medical Imaging and Graphics (CMIG).

10.1.4 Invited talks

- O. Colliot gave an invited seminar at the Scientific Workshop of INS2I-CNRS.
- N. Burgos gave an invited talk at the 3e colloque sur l'imagerie médicale à l'heure de l'intelligence artificielle (Paris, France).
- F. De Vico Fallani was invited to give a talk at the Stem cell and Brain Research Institute (SBRI), Inserm, Lyon.
- F. De Vico Fallani was invited to give a talk at the Institute of Systems Neuroscience (INS), AMU Inserm UMR1106, Marseille, France.
- S. Durrleman gave an invited talk at the journées de la société française de radiologie

- D. Racoceanu was invited to give a talk to the 15th European Congress on Digital Pathology (ECDP) organised in Warwick, UK.

- D. Racoceanu was invited to give a talk to the 30th European Congress of Pathology (ECP), Bilbao, Spain.

- D. Racoceanu was invited to give a talk to the Shenzhen Institute of Advanced Technology (SIAT), Shenzhen, China.

- D. Racoceanu was invited to give a talk to the 14th European Congress on Digital Pathology (ECDP) organised in Helsinki, Finland.

- D. Racoceanu gave a presentation as invited speaker at Día Mundial de las Telecomunicaciones, la Sociedad de la Información, y el Internet, Lima, Peru.

10.1.5 Leadership within the scientific community

- F. De Vico Fallani is a member of the Executive Committee of the COmplex Systems Society (CSS)

- D. Racoceanu is member of the Avisory Board of the European Society of Digital and Integrative Pathology (ESDIP), after being its president (2018-2020), its vice-president (2016-2018) and co-funder (2016).

- D. Racoceanu is member of the Board of Directors of the MICCAI Society (Medical Image Computing and Computer Assisted Intervention).

10.1.6 Scientific expertise

- O. Colliot was 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).

- N. Burgos was a member of the recruitment committee ("jury d'admissibilité") for the national competition for recruitment of permanent researchers at Inria Paris.

- N. Burgos acted as reviewer for the Luxembourg National Research Fund.

- S. Epelbaum acted as a member of the national steering committee of the "Fédération des centres mémoire".

- S. Durrleman acted as member of the scientific and ethic committee of the "entrepôt de données de santé" of the APHP.

- D. Racoceanu acted as reviewer for ANRT evaluation (expertise thèse CIFRE).

10.1.7 Research administration

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

- S. Durrleman is the scientific head of the bioinformatics and bio-statistics core-facility at the Paris Brain Institute (ICM)

10.2 Teaching - Supervision - Juries

10.2.1 Teaching

- Master: Olivier Colliot coordinates the course "Deep Learning for Medical Imaging" of the Master 2 MVA (Mathematics, Vision, Learning) of ENS Paris-Saclay, University of Paris, Centrale-Supelec and teaches 15 hours (CM).
- Master: Olivier Colliot coordinates the course "Artificial Intelligence" of the Master 2 Bioentrepreneur of Paris-Descartes University and teaches 20 hours (CM).
- Master: Daniel Racoceanu coordinates the teaching module (UE) "Introduction to Artificial Intelligence" of the Master 1 : Control Sciences and Robotics (AR - Automatique, Robotique) and Electronics, Electrical Energy, Control Sciences (E3A - Électronique, Énergie Électrique, Automatique) at Sorbonne University, Faculty of Science and Engineering (110 students / 3 ECTS) and teaches 30 hours (CM/courses and TP/labs).
- Master: Daniel Racoceanu coordinates the teaching module (UE) "Computer Vision for Biomedical" of the Master 1 : Electronics, Electrical Energy, Control Sciences (E3A - Électronique, Énergie Électrique, Automatique) at Sorbonne University, Faculty of Science and Engineering (50 students / 3 ECTS) and teaches 32 hours (CM/courses and TP/labs).
- Master: Daniel Racoceanu coordinates the teaching module (UE) "Image Processing" of the Master 1 : Control Sciences and Robotics (AR - Automatique, Robotique) at Sorbonne University, Faculty of Science and Engineering (80 students / 3 ECTS) and teaches 36 hours (CM/courses and TP/labs) - courses in English.
- Master: Daniel Racoceanu coordinates the teaching module (UE) "3D Computer Graphics" of the Master 1 : Computer Sciences (Informatique) at Sorbonne University, Faculty of Science and Engineering (20 students / 3 ECTS) and teaches 24 hours (CM/courses and TP/labs) - courses in English (within the european programme EIT Health).
- Engineering school: Olivier Colliot, 5 hours (eqTD), Mines ParisTech
- Medical school: Didier Dormont is the Director of the University Diploma (DIU) “Diagnostic and Therapeutic Neuroradiology", Sorbonne University
- Medical school: Didier Dormont, Courses for Medical Students, Sorbonne University
- Medical school: Stéphane Epelbaum organizes the national teaching course on Alzheimer’s disease and related diseases.
- Medical school: Didier Dormont organizes and participates in the practical teaching of Neuroradiology for Medical Students in the Department of Diagnostic Neuroradiology of Pitié Salpêtrière University Hospital
- Medical school: Didier Dormont organizes and participates in the practical teaching of Neuroradiology for Radiology Specializing Residents in the Department of Diagnostic Neuroradiology of Pitié Salpêtrière University Hospital
- N. Burgos gave lectures on machine learning and deep learning for medical imagong as part of the Educational Courses of the OHBM 2020 conference (30 min., July 2020, Virtual), DIU Neuroradiologie diagnostique et thérapeutique (1h, May 2020, Virtual), the DU Intelligence artificielle IA appliquée en santé (1h, March 2020, Paris Descartes) and the Hands-on Workshop on Machine Learning Applied to Medical Imaging (3h, March 2020, Paris Brain Institute).
- Master: F. De Vico Fallani gave a lecture at UE Closed-loop Neuroscience, Central Supelec)
- Master: Daniel Racoceanu gives lectures / labs (14 hours) in "Visual Perception for Robotics" - Master 2 : Control Science and Robotics (AR - Automatique, Robotique) at Sorbonne University, Faculty of Science and Engineering.

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

10.2.2 Supervision

- PhD in progress : Sophie Skriabine, “Modeling brain vascular networks”, Inria, started in 2019, advisor: Fabrizio De Vico Fallani and Nicolas Renier
- PhD in progress : Juliana Gonzalez-Astudillo, “Network features for brain-computer interfaces”, UPMC, started in 2019, advisor: Fabrizio De Vico Fallani
- 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: 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. Allassonnière and S. Durrleman
- PhD in progress: Vianney Debavelaere, “Analysis of distribution of spatiotemporal trajectories in heterogeneous populations”, started in 2018, advisors: S. Allassonnière and S. Durrleman
- 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. Allassonnière
- PhD in progress: Ravi Hassanaly, “Deep generative models for the detection of anomalies in the brain”, started in 2020, advisors: O. Colliot and N. Burgos
- PhD in progress: Benoît Sauty, Multimodal models of neurodegenerative disease progression, started in 2020, advisor: S. Durrleman
- PhD in progress: Pierre-Emmanuel Poulet, Models of progression of multiple risks, started in 2020, advisor: S. Durrleman

10.2.3 Juries

- Olivier Colliot participated, as president, to the PhD committee of Corentin Mercier (Telecom ParisTech).
- Olivier Colliot participated, as referee, to the HDR committee of Marco Lorenzi (University of Nice-Sophia-Antipolis).
- Olivier Colliot participated, as thesis director, to the PhD committee of Johann Faouzi (Sorbonne University).
- Olivier Colliot participated, as thesis director, to the PhD committee of Giulia Bassignana (Sorbonne University).
- Olivier Colliot participated, as thesis director, to the PhD committee of Alexandre Bône (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. Durrleman participated, as referee, to the PhD committee of Razwan Marinescu (University College London)
- S. Durrleman participated, as reviewer, to the PhD committee of Antoine Legouhy (Université de Rennes)
- S. Durrleman participated, as referee, to the PhD committee of Anuja Sharma (University of Utah)
- S. Durrleman participated, as thesis advisor, to the PhD committee of Wen Wei (Sorbonne Université)
- S. Durrleman participated, as thesis advisor, to the PhD committee of Thomas Lartigue (Université Paris Saclay)
- S. Durrleman participated, as thesis advisor, to the PhD committee of Alexandre Bône (Sorbonne Université)
- S. Durrleman participated, as thesis advisor, to the PhD committee of Igor Koval (Université Paris Saclay)
- D. Racoceanu participated as reviewer to the PhD defense committee of Ms. Lisa CORBAT (University Burgundy Franche-Comté).
- D. Racoceanu participated, as thesis advisor, to the PhD committee of Ms. Oumeima LAIFA Sorbonne University).

- D. Racoceanu participated to the Habilitation (HDR) jury of M. Thomas WALTER, PhD (Sorbonne University).
- D. Racoceanu participated as reviewer to the Habilitation (HDR) jury of M. Julien HENRIET, PhD (University Burgundy Franche-Comté).
- D. Racoceanu participated as reviewer to the Habilitation (HDR) jury of M. Vlad POPOVICI, PhD (Masaryk University, Faculty of Informatics, Czech Republic).

10.3 Popularization

10.3.1 Interventions

- N. Burgos gave a presentation for the "Rendez-vous des Jeunes Mathématiciennes et Informaticiennes".
- N. Burgos gave a presentation at France is AI.
- S. Durrleman took part in the round table AI for Health organised by the French consulate at San Francisco
- S. Durrleman chaired the round table "AI and health : Success stories, best practices and future outlook" at the AI4Health conference organized by the Health Data Hub.

11 Scientific production

11.1 Major publications

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

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

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

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

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

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

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

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

[9] R. Cuingnet, J. A. Glaunès, M. Chupin, H. Benali and O. Colliot. 'Spatial and Anatomical Regularization of SVM: A General Framework for Neuroimaging Data'. In: *IEEE Transactions on Pattern Analysis and Machine Intelligence* 35.3 (2013), pp. 682–696. DOI: 10.1109/TPAMI.2012.142. URL: https://hal.inria.fr/hal-00790079.

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

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

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

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

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

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

[16] *Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part I (machine learning methodologies)*. Oct. 2020. URL: https://hal.archives-ouvertes.fr/hal-03144837.

[17] *Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part II (image reconstruction; prediction and diagnosis; cross-domain methods and reconstruction; domain adaptation; machine learning applications; generative adversarial networks)*. Oct. 2020. URL: https://hal.archives-ouvertes.fr/hal-03144838.

[18] *Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part III (CAI applications; image registration; instrumentation and surgical phase detection; navigation and visualization; ultrasound imaging; video image analysis)*. Oct. 2020. URL: https://hal.archives-ouvertes.fr/hal-03144839.

[19] *Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part IV (segmentation; shape models and landmark detection)*. Oct. 2020. URL: https://hal.archives-ouvertes.fr/hal-03144840.

[20] *Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part V (biological, optical, microscopic imaging; cell segmentation and stain normalization; histopathology image analysis; opthalmology)*. Oct. 2020. URL: https://hal.archives-ouvertes.fr/hal-03144842.

[21] *Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part VI (angiography and vessel analysis; breast imaging; colonoscopy; dermatology; fetal imaging; heart and lung imaging; musculoskeletal imaging)*. Oct. 2020. URL: https://hal.archives-ouvertes.fr/hal-03144844.

[22] *Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part VII (brain development and atlases; DWI and tractography; functional brain networks; neuroimaging; positron emission tomography)*. Oct. 2020. URL: https://hal.archives-ouvertes.fr/hal-03144845.

[23] J. Samper-Gonzalez, N. Burgos, S. Bottani, S. Fontanella, P. Lu, A. Marcoux, A. Routier, J. Guillon, M. Bacci, J. Wen, A. Bertrand, H. Bertin, M.-O. Habert, S. Durrleman, T. Evgeniou and O. Colliot. 'Reproducible evaluation of classification methods in Alzheimer's disease: Framework and application to MRI and PET data'. In: *NeuroImage* 183 (Dec. 2018), pp. 504–521. DOI: 10.1016/j.neuroimage.2018.08.042. URL: https://hal.inria.fr/hal-01858384.

[24] J.-B. Schiratti, S. Allassonniere, O. Colliot and S. Durrleman. 'A Bayesian mixed-effects model to learn trajectories of changes from repeated manifold-valued observations'. In: *Journal of Machine Learning Research* 18 (Dec. 2017), pp. 1–33. URL: https://hal.archives-ouvertes.fr/hal-01540367.

[25] Q. Vanderbecq, E. Xu, S. Stroër, B. Couvy-Duchesne, M. Diaz Melo, D. Dormont and O. Colliot. 'Comparison and validation of seven white matter hyperintensities segmentation software in elderly patients'. In: *Neuroimage-Clinical* 27 (2020), p. 102357. DOI: 10.1016/j.nicl.2020.102357. URL: https://hal.archives-ouvertes.fr/hal-02926474.

[26] W. Wei, E. Poirion, B. Bodini, S. Durrleman, N. Ayache, B. Stankoff and O. Colliot. 'Predicting PET-derived Demyelination from Multimodal MRI using Sketcher-Refiner Adversarial Training for Multiple Sclerosis'. In: *Medical Image Analysis* 58.101546 (Dec. 2019). DOI: 10.1016/j.media.2019.101546. URL: https://hal.archives-ouvertes.fr/hal-02276634.

[27] J. Wen, E. Thibeau-Sutre, M. Diaz-Melo, J. Samper-Gonzalez, A. Routier, S. Bottani, D. Dormont, S. Durrleman, N. Burgos and O. Colliot. 'Convolutional Neural Networks for Classification of Alzheimer's Disease: Overview and Reproducible Evaluation'. In: *Medical Image Analysis* 63 (July 2020), p. 101694. DOI: 10.1016/j.media.2020.101694. URL: https://hal.archives-ouvertes.fr/hal-02562504.

[28] R. Zemouri, N. Zerhouni and D. Racoceanu. 'Deep Learning in the Biomedical Applications: Recent and Future Status'. In: *Applied Sciences* 9.8 (Apr. 2019), p. 1526. DOI: 10.3390/app9081526. URL: https://hal.sorbonne-universite.fr/hal-02170880.

11.2 Publications of the year

International journals

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

[30] A. Aracki-Trenkic, B. Law-Ye, Z. Radovanovic, D. Stojanov, D. Dormont and N. Pyatigorskaya. 'ASL perfusion in acute ischemic stroke: The value of CBF in outcome prediction'. In: *Clinical Neurology and Neurosurgery* 194.4 (July 2020), p. 105908. DOI: 10.1016/j.clineuro.2020.105908. URL: https://hal.archives-ouvertes.fr/hal-03139274.

[31] R. Armignacco, T. Lartigue, A. Jouinot, A. Septier, M. Neou, C. Gaspar, K. Perlemoine, L. Bouys, L. Braun, A. Riester, S. Allassonnière, M. C. Zennaro, M. Reincke, J. Bertherat, F. Beuschlein and G. Assié. 'Identification d'une signature moléculaire d'hypercortisolisme par analyse du methylome du sang total'. In: *Annales d'Endocrinologie* 81.4 (Sept. 2020), p. 180. DOI: 10.1016/j.ando.2020.07.117. URL: https://hal.archives-ouvertes.fr/hal-03035962.

[32] G. Bassignana, J. Fransson, V. Henry, O. Colliot, V. Zujovic and F. De Vico Fallani. 'Step-wise target controllability identifies dysregulated pathways of macrophage networks in multiple sclerosis'. In: *Network Neuroscience* (2020). URL: https://hal.inria.fr/hal-03022314.

[33] A. Bône, O. Colliot and S. Durrleman. 'Learning the spatiotemporal variability in longitudinal shape data sets'. In: *International Journal of Computer Vision* (2nd July 2020). DOI: 10.1007/s11263-020-01343-w. URL: https://hal.inria.fr/hal-02091549.

[34] N. Burgos, S. Bottani, J. Faouzi, E. Thibeau-Sutre and O. Colliot. 'Deep learning for brain disorders: from data processing to disease treatment'. In: *Briefings in Bioinformatics* (15th Dec. 2020). DOI: 10.1093/bib/bbaa310. URL: https://hal.archives-ouvertes.fr/hal-03070554.

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

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