

**UNIVERSITY OF PADOVA**  
**DEPARTMENT OF INFORMATION ENGINEERING (DEI)**

**Ph.D. School in Information Engineering**  
**Section: Bioengineering**

**Ph.D. Candidate:** Erica Silvestri

**Series:** XXX

**Advisor:** Prof. Alessandra Bertoldo

**Three-year report**

**1. Education**

**1.1 Courses organized within the department for PhD students**

- Applied Machine Learning in Biomedicine, Prof. E. Grisan
- Bayesian Machine Learning, Prof. G.M. Di Nunzio
- Mathematical modelling of Cell Biology, Prof. M. Pedersen
- Statistical Methods, Prof. L. Finesso

**1.2 Schools**

- Magnetic Resonance Techniques in Multiple Sclerosis – 18° advanced course. March 19<sup>th</sup>-20<sup>th</sup> 2015, Milano, Italy.
- Statistical Parametric Mapping (SPM) Short Course. May 13<sup>th</sup>-16<sup>th</sup> 2015, UCL Institute of Neurology, London, UK.
- Educational Courses OHBM 2015, Annual meeting, June 13<sup>th</sup>, 2015, Honolulu, Hawaii.
- SPSS course, May 2<sup>nd</sup>-13<sup>th</sup>, 2016, Padova.
- Educational Courses OHBM 2016, Annual meeting, June 26<sup>th</sup>, 2016, Geneva, Switzerland.
- Exploring the Human Connectome, the 2016 Human Connectome Project Course. August 28<sup>th</sup> – September 1<sup>st</sup>, 2016, Boston.
- Educational Courses ECTRIMS 2016, Annual Meeting, September 13<sup>th</sup>, 2016, London, United Kingdom.
- Educational Courses of Brain and Brain PET 2017, Annual Meeting of International society for Cerebral Blood Flow and Metabolism. April 1<sup>st</sup>, 2017, Berlin, Germany.
- Educational Courses OHBM 2017, Annual meeting, June 25<sup>th</sup>, 2017, Vancouver, Canada.

**1.3 Workshops**

- Images of the Mind: new frontiers in brain imaging Advanced (f)MRI statistical methods and their applications. April 9<sup>th</sup> - 10<sup>th</sup> 2015, Milano, Italy.
- La risonanza magnetica 3 Tesla nell'epilessia farmaco-resistente del lobo temporale. December 11, 2015, IRCCS C. Mondino, Pavia.

**1.4 Seminars**

- Brain-Machine-Interface (BMI) in Complete Paralysis, Stroke and Neuropsychiatric Disorders. November 5<sup>th</sup>, 2014, Padova.
- Conference on statistics in neuroimaging. January 15<sup>th</sup>, 2015, Padova.
- Non-linear dynamical analysis of electrophysiological data (EMG and EEG). February 17<sup>th</sup>, 2015, Padova.

- On the geometry of maximum entropy problems. March 13<sup>th</sup>, 2015, Padova.
- Learning with Computational Regularization. March 27<sup>th</sup>, 2015, Padova.
- Computational modelling in cognitive neuroscience: from neurons to robots. April 1<sup>st</sup>, 2015, Padova.
- Oscillations and synchrony in brain dynamics. May 12<sup>th</sup>, 2015, Padova.
- Executive functions: from neural bases to cognitive training. May 19<sup>th</sup>, 2015, Padova.
- New perspectives in multiple testing 80 years after Bonferroni. October 9<sup>th</sup>, 2015, Padova.
- The use of input function in PET kinetics modelling, December 2<sup>nd</sup>, 2016, MD. Paolo Zanotti Fregonara, DEI Padova.
- Neuroscience Day @ DEI, February 2<sup>nd</sup>, 2016, Padova.
- Matching, cat, connectivity: Graph-theoretic solution for biomedical image analysis, May 25<sup>th</sup>, 2016, Prof. Ananda Chowdhury, Padova.
- Long-range functional interactions in the resting state human brain, June 8<sup>th</sup>, 2016, Prof. Dante Mantini, DEI Padova.
- The role of grey matter pathology in clinical progression in MS: new therapeutic targets, June 11<sup>th</sup>, 2016, Prof. Richard Reynolds, Verona.
- Computational Thinking, Inferential Thinking and Data Science, June 21<sup>st</sup>, 2016. Prof. Michael I. Jordan, Padova.
- DTI on skeletal muscle: from simulation to clinical implementation, June 23<sup>rd</sup>, 2016, Dr. Martijn Froeling, Padova.
- Personalized whole brain simulations reveal candidate mechanisms of neural computation, July 7<sup>th</sup>, 2016, Prof. Petra Ritter, Padova.
- Detecting large-scale brain networks using high-density EEG, September 19<sup>th</sup>, 2016, Prof. Dante Mantini, Padova.
- Networks: Brain, Health, and Society. September 29<sup>th</sup>, 2017, Prof. Maurizio Corbetta, Padova.
- Networks cerebrali e comportamento, January 17<sup>th</sup>, 2017, Prof. Maurizio Corbetta, Padova.
- Progressi nel neuroimaging dei tumori cerebrali. May 9<sup>th</sup>, 2017, Prof. Andrea Falini, Padova.
- Consciousness: From Theory to Practice. May 18<sup>th</sup>, 2017, Prof. Giulio Tononi, Padova.
- Il meccanismo specchio, May 30<sup>th</sup>, 2017, Prof. Giacomo Rizzolatti, Padova.
- Learning by Nature: How to Build Soft Robots. June 4<sup>th</sup>, 2017, Prof. Barbara Mazzolai, Padova.
- Efficient Space/Time Learning: Gaussian Regression meets Kalman Filtering, June 23<sup>rd</sup>, 2017, PhD. Marco Todescato, Padova.

### 1.5 International conferences

- 21<sup>st</sup> Annual Meeting of the Organization for Human Brain Mapping (OHBM), June 14<sup>th</sup> - 19<sup>th</sup> 2015, Honolulu, Hawaii.
- 22<sup>nd</sup> Annual Meeting of the Organization for Human Brain Mapping (OHBM), June 26<sup>th</sup> -30<sup>th</sup> 2016, Geneva Switzerland.
- 32<sup>nd</sup> Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) 2016, September 14<sup>th</sup> - 17<sup>th</sup> 2016, London, United Kingdom.
- Updates on Human Brain Connectome: from physiology to disease. Workshop, November 28<sup>th</sup> - 29<sup>th</sup> 2016, Rome, Italy.
- Brain and Brain PET 2017, Annual Meeting of International society for Cerebral Blood Flow and Metabolism: 28<sup>th</sup> Symposium on Cerebral Blood Flow, Metabolism and Function, and 13<sup>th</sup> Conference on Quantification of Brain Function with PET. April 1<sup>st</sup>- 4<sup>th</sup> 2017, Berlin, Germany.
- 23<sup>rd</sup> Annual Meeting of the Organization for Human Brain Mapping (OHBM), June 26<sup>th</sup> -29<sup>th</sup> 2017, Vancouver, Canada.

### 1.6 National conferences

- 6<sup>th</sup> Annual Meeting of International Society for Magnetic Resonance in Medicine (ISMRM)

- Italian Chapter, April 16<sup>th</sup> -17<sup>th</sup> 2015, Verona, Italy.
- 7<sup>th</sup> Annual Meeting of International Society for Magnetic Resonance in Medicine (ISMRM) Italian Chapter, February 4<sup>th</sup> – 5<sup>th</sup> 2016, Bologna, Italy.
- 8<sup>th</sup> Annual Meeting of International Society for Magnetic Resonance in Medicine (ISMRM) Italian Chapter, February 8<sup>th</sup> – 9<sup>th</sup> 2017, Gaeta, Italy.

### 1.7 Teaching activities (as Tutor Junior)

- Providing support and one-to-one assistance in MATLAB laboratories for the classes of:
  - Neuro-engineering course 15/16, Padova, DEI (October 2015 – March 2016)
  - Signals and Systems 16/17, Padova, DEI (January 2017 – July 2017)
- Correlator activity for the master thesis:
  - “Characterization of graph metrics applied to resting state functional connectivity maps” by Francesca Digiacoio

## 2. Research

The research activities carried out in this three-year PhD programme is related to the integration of magnetic resonance imaging (MRI) and positron emission tomography (PET) for the study of resting state connectivity.

As at the beginning of this PhD programme simultaneously acquired PET/MRI data were not yet available, part of the activity was carried out on independent datasets obtained thanks to the collaboration with Prof. Massimiliano Calabrese (Civile Hospital of Verona, Department of Neurological and Movement Sciences, University of Verona) and that with Dr. Maria Lucia Calcagni (Institute of Nuclear Medicine, Università Cattolica del Sacro Cuore, Rome). The goal of this first part of the activity was to acquire and to develop the methodology for the analysis of the MRI data and the quantification of PET data, which would then be useful for the integration of concurrently acquired PET and MRI patients' data.

At first, the PhD programme focused on the analysis of functional magnetic resonance data acquired in resting state, a condition in which the subject within the scanner is not required to perform any task but to stay awake and relaxed. The dataset was made available by Prof. Calabrese and consists of 138 multiple sclerosis (MS) patients with a different degree of impairment, assessed by means of the Expanded Disability Status Scale (EDSS) score (EDSS: median 2, range 1–6.5), and a different phenotype of the pathology (Relapsing Remitting (RR)/Secondary Progressive (SP): 122/16). The acquisition protocol includes structural images such as T1w, T2w and Double Inversion Recovery, and 10 minutes of resting state functional MRI. Aims of the study were to investigate the impact of head motion, a possible confound that has received a lot of attention in recent years, on the functional connectivity, and to assess whether the amount of head motion could depend on EDSS or MS phenotype. During this study, the PhD programme was involved in pre-processing and processing of the structural data, anatomical and functional parcellation included; pre-processing of functional data with state of art approaches, with main focus on techniques aimed at removing the variance of the signal explained by the head displacement; analysis of resting state networks and quantification of functional connectivity with three different approaches: independent component analysis, seed based and atlas based. What was found is that functional connectivity was significantly correlated with head displacement, with some connections made stronger (positively correlated with displacement), whereas other weakened (negatively correlated with displacement), even after the more aggressive post-processing. Moreover, displacement is significantly correlated with impairment and significantly differs between RR and SP patients. On the same dataset were also conducted network analysis and preliminary studies to evaluate the reproducibility of some graph theory network measures as centrality, node degree, etc.

The PhD programme was then devoted to analysis and the quantification of PET data, with particular attention to compartmental modelling. The dataset we worked on, was provided by Prof. Calcagni and consists in 21 patients with histologically proved primary lung tumours and imaging proved metastatic lympho-nodes. In this study, a 55-minute list-mode PET dynamics was acquired with [ $^{18}\text{F}$ ] Fluorodeoxyglucose ([ $^{18}\text{F}$ ]FDG) tracer. This tracer is an analogous of glucose and is frequently used for the study and staging of tumours. Aims of the study were: to identify the compartmental model that best explains [ $^{18}\text{F}$ ]FDG-PET data in primary tumours and metastatic lympho-nodes, and to characterize primary tumours and metastatic lympho-nodes, and tumours histotypes (i.e. adenocarcinoma versus other type of tumours). The work consisted in extraction and fit of image derived input function (IDIF), tumours and lympho-nodes manual segmentation, voxel-wise quantification of metabolic parameters of interest with well-known methodologies in literature (Patlak graphical model and spectral analysis with iterative filtering (SAIF)), and finally, based on SAIF results, compartmental modelling at the voxel level within primary tumours and metastatic Lympho-nodes. The model that best describes the tracer behaviour within primary tumours and metastatic lympho-nodes voxels was identified and macro-parameters compartmental estimates were compared to state of art methods results with excellent results. Statistical analysis, finally revealed significant differences between primary tumours and metastatic lympho-nodes, whereas no significant difference was found between tumours histotypes.

Meanwhile this PhD programme has dealt with the setup of PET-MRI scanner of the University Hospital of Padova (Nuclear Medicine Unit, Department of Medicine) with the aim of bringing the acquisition system from the clinical to the international research level. There has been a collaboration on tuning MRI sequences, with the introduction of multi band acquisition. In particular, the focus was on resting state functional MRI and diffusion tensor imaging acquisition protocols, for which it was possible to reduce respectively TR and voxel size. This PhD programme was also devoted to PET signal reconstruction outside the scanner. The work consisted in integration within e7-tool reconstruction software of state of art attenuation algorithm developed by Izquierdo-Garcia et al. (2014) and in management of software parameter to ensure image reconstruction quality suitable for research study (i.e. optimal time grid, no post-filtering, etc.). The goal of this effort was to obtain qualitatively good images making, at the same time, reconstruction phase independent of the scanner's availability.

Finally, it was possible to obtain a multimodal simultaneously acquired dataset from PET-MRI scanner of the University Hospital of Padova, thanks to a collaboration with Prof. Diego Cecchin and Prof. Angelo Antonini. Ten patients affected by Parkinson's Disease and cognitive impairment were scanned. The MRI protocol included T1w and T2w structural images, single shell diffusion tensor imaging and 15 minutes of resting state functional MRI. While PET protocol consisted in [ $^{18}\text{F}$ ]Flutemetamol (reversible beta-amyloid plaque ligand) injection and two subsequently list-mode dynamic PET scan acquisition: a 20 minutes scan after the injection (*early segment*) and, later, a 20 minutes scan 90 minutes after the injection (*late segment*). Based on static PET reconstruction of the *late segment*, patients were subdivided into positive and negative amyloid load, which means full-blown dementia or not. Aims of the study was to evaluate whether there are differences between amyloid positive and negative patients in terms of resting state connectivity networks, and, if it is so, to determine if these differences could be related to the amyloid load. Additionally, as alterations in the brain blood flow seem to be related to dementia, an evaluation on whether delivery rate constant (a guess of brain blood flow) pattern differs between amyloid positive and negative patients and if these pattern follow specific pattern of graph theory metrics, computed on resting state functional connectivity, was executed. An advanced pre-processing of functional and diffusion MRI data was performed and patients with excessive head displacement during acquisition were discarded. Regional amyloid load was computed as standard uptake value ratio (SUVR) of *late segment* PET activity curve, by using the grey matter cerebellum mean activity as reference region. For the delivery rate constant quantification, analysis was performed on the *early segment*: IDIF has been extracted from internal carotid and fitted with a three-exponential model and a compartmental modelling of the PET signal at region of interest level was performed. As the influence of parameters other than delivery rate constant can be considered negligible during the first minutes of acquisition, the model has been reduced to a single exponential. Functional and structural

network analysis were conducted, and correlation analysis between graph theory measures difference and amyloid load difference between the two groups were performed. What was found is a significant difference between the two groups of patients in ventral-attention, dorsal-attention and fronto-parietal intra- and extra-network functional connectivity, and a significant difference in Node Strength, Clustering Coefficient and Local Efficiency of brain regions within the Ventral Attention Network. No difference was found for the delivery rate constant.

The research activity of this PhD programme was carried out under the supervision of Prof. Alessandra Bertoldo. At closure of the PhD programme, a PhD thesis on the analysis and integration on multimodal PET/MRI data for the study of the resting state network connectivity was composed with title: "Simultaneous PET/MRI for resting state connectivity mapping".

### 3. Publications

#### 3.1 Publications in international journals

- [J1] Cecchin D., Palombit A., Castellaro M., Silvestri E., Bui F., Barthel H., Sabri O., Corbetta M., Bertoldo A. Brain PET and functional MRI: why simultaneously using hybrid PET/MR systems? Quarterly Journal of Nuclear Medicine and Molecular Imaging. 2017 Jul 27. doi: 10.23736/S1824-4785.17.03008-4.
- [J2] Castellaro M., Magliozzi R., Palombit A., Pitteri M., Silvestri E., Camera V., Montemezzi S., Pizzini F.B., Bertoldo A., Reynolds R., Monaco S., Calabrese M. Heterogeneity of Cortical Lesion Susceptibility Mapping in Multiple Sclerosis. American Journal of Neuroradiology. 2017 Jun;38(6):1087-1095. doi: 10.3174/ajnr.A5150

#### 3.2 Manuscripts submitted to international journals

- [MS1] Silvestri E., Scolozzi V., Rizzo G., Indovina L., Castellaro M., Mattoli M.V., Graziano P., Cardillo G., Bertoldo A., Calcagni M.L., The kinetic of 18F-FDG in lung cancer: compartmental models and voxel analysis. Submitted to Journal of Nuclear Medicine

#### 3.3 Manuscripts in preparation

- [MS2] Silvestri E., Tonietto M., Castellaro M., Calabrese M., Bertoldo A. Multiple sclerosis patients with higher disability move more during MR acquisition: effect on resting state functional connectivity. To be submitted to Radiology.

#### 3.4 Publications in international conferences

##### 3.4.1 Abstract

- [C1] Silvestri E., Tonietto M., Castellaro M., Calabrese M., Bertoldo A. (2016). Head motion during resting state fMRI acquisition significantly alter functional connectivity and it depends on patient disability. 32<sup>nd</sup> Congress of the European Committee for Treatment and Research in Multiple Sclerosis 2016, London, United Kingdom.
- [C2] Palombit A., Silvestri E., Castellaro M., De Vita E., Cecchin D., Bertoldo A. Simultaneous PET/MRI for resting-state fMRI: optimized parallel imaging and multiband EPI, a ISMRM-SNMMI Co-Provided Workshop on PET/MRI, Chicago 26-29 October 2017.
- [C3] Castellaro M., Palombit A., Silvestri E., Tonietto M., Gajofatto A., Montemezzi S., Magliozzi R., Howell O.W., Reynolds R., Monaco S., Bertoldo A., Calabrese M. (2015): Heterogeneity of susceptibility mapping of cortical lesions in MS. 31st congress of the European committee for treatment and research in Multiple Sclerosis – ECTRIMS, 2015.

- [C4] Tonietto M., Calabrese M., Silvestri E., Morra A., Castellaro M., Monaco S., Bertoldo A. (2015): Use of cortical thickness to detect localized damage in the somatomotor cortex in MS: relation with clinical disability. 31st congress of the European committee for treatment and research in Multiple Sclerosis – ECTRIMS, 2015.
- [C5] Palombit A., Castellaro M., Tonietto M., Silvestri E., Calabrese M., Bertoldo A. (2015): Comparative Assessment of Methods for Quantitative Susceptibility Mapping on a Clinical Magnetic Resonance Data Set. 37<sup>th</sup> annual international conference of the IEEE Engineering in Medicine and Biology Society, EMBC, Milan, Italy, 2015

Date: 15/09/2017

Signature of PhD student:



Signature of Supervisor: