Presentazione delle attività dei tre anni di dottorato

«Multiscale analysis of brain connectome for the characterization of Alzheimer’s disease»

Dottorato di Ricerca in Fisica, XXXI ciclo
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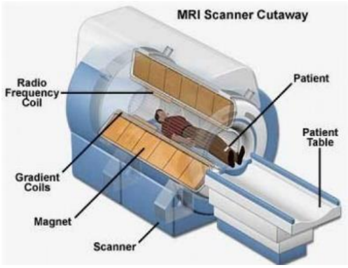
INTRODUCTION

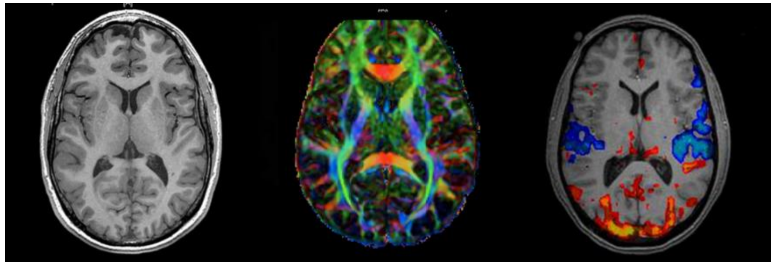
Physics in Neuroscience

Neuroscience is an increasingly important interdisciplinary area of research that aims to understand how the brain works. Physics plays a key role in neuroscience:

- Brain imaging technology

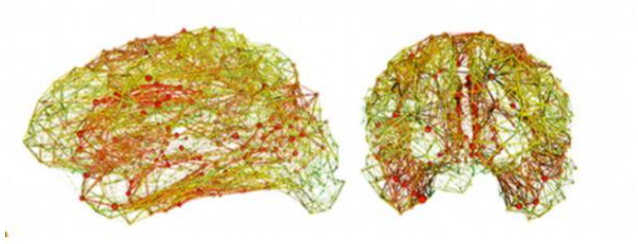


MRI DTI fMRI



- Methodological strategies

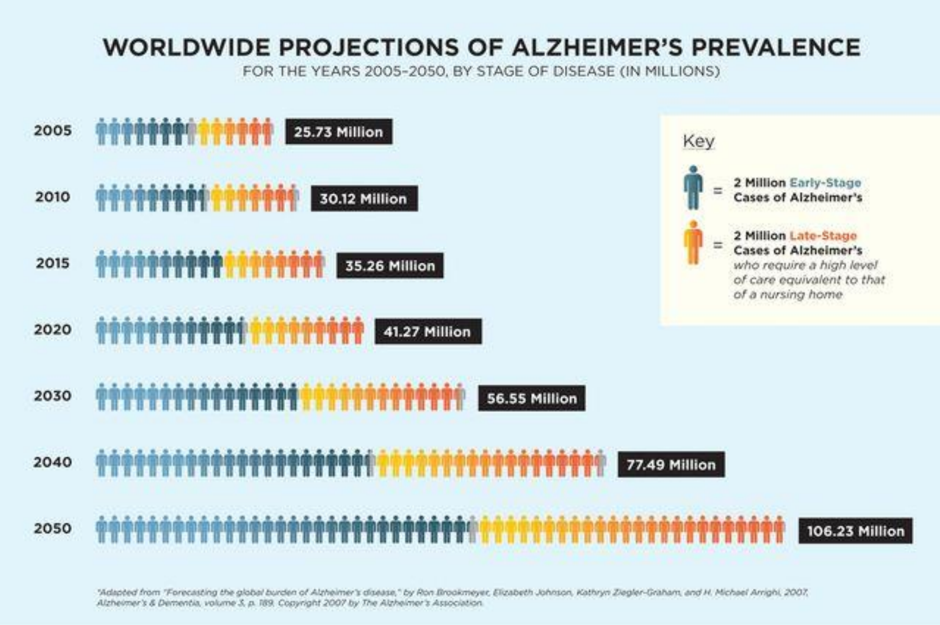
- Brain modelling



INTRODUCTION

Context

In neuroscience, mathematical and statistical-based techniques together with machine learning procedures are aimed to investigate biomarkers and to support the neuropsychological assessments performed by expert clinicians



Alzheimer's disease (AD) is the most common type of neurodegenerative disorder characterized by a progressive cognitive decline

Mild cognitive Impairment (MCI):
early state of abnormal cognitive function

There is evidence supporting the biological hypothesis that this decline is related to a disrupted connectivity among brain regions caused by white matter (WM) degeneration

MULTISCALE ANALYSIS

CONTRIBUTIONS

1. Voxel-wise analysis
2. Graph-based analysis at the cortical level
3. Graph-based analysis at the subcortical level

DATABASE

Alzheimer's Disease Neuroimaging Initiative

ANALYSES

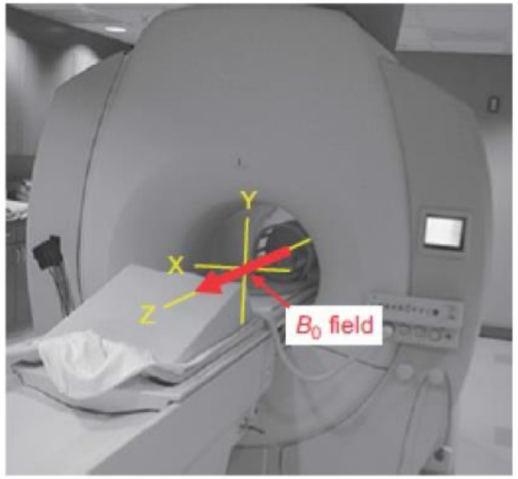
- Group-wise statistical analyses
- Machine learning
- Investigation of **meaningful new features** for AD

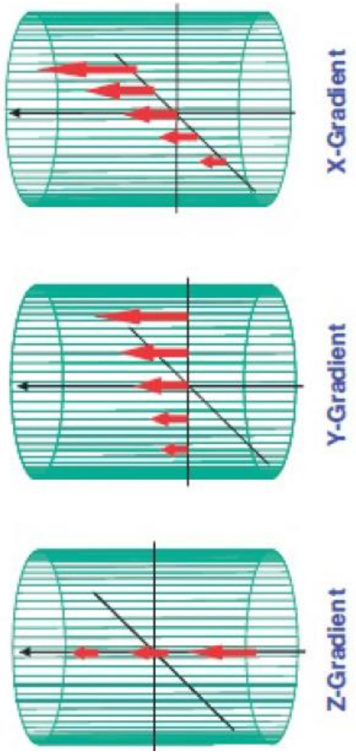
TOOLS AND COMPUTATIONAL INFRASTRUTURES

- MATLAB (MathWorks) computing environment
- Distributed computing infrastructure **ReCaS**-Bari computing farm

DIFFUSION TENSOR IMAGING (DTI)

DTI complements MRI information on brain structural changes by investigating the water diffusion along WM fibers





$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}$$

$$\ln \frac{S}{S_0} = -\boldsymbol{bD}$$

$$\boldsymbol{DE} = \lambda\boldsymbol{E}$$

$$\text{FA} = \frac{1}{\sqrt{2}} \frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{\lambda_1{}^2+\lambda_2{}^2+\lambda_3{}^2}}$$

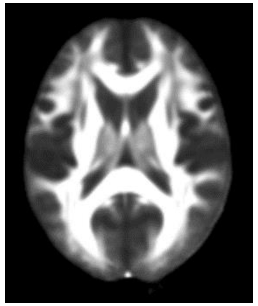
$$\text{MD} = \frac{\lambda_1+\lambda_2+\lambda_3}{3}$$

FA = Fractional Anisotropy
MD = Mean Diffusivity

DIFFUSION TENSOR IMAGING (DTI)

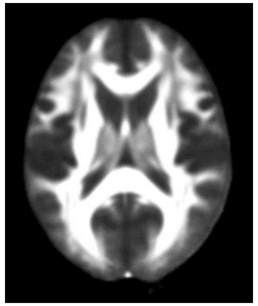
Approaches on DTI data in AD studies

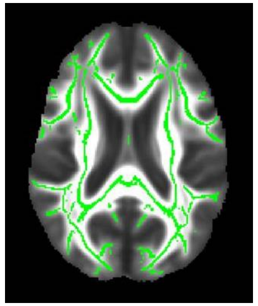
Diffusivity-based measures are used for statistical studies investigating significant microstructural changes in AD and MCI compared to healthy controls (HC) and also as features to train classification models for the automatic diagnosis. In literature, three approaches are used to address these issues:



- Region of interest (ROI)-based approach

The brain is parcelled into ROIs and the DTI scalar indexes averaged over each ROI are used





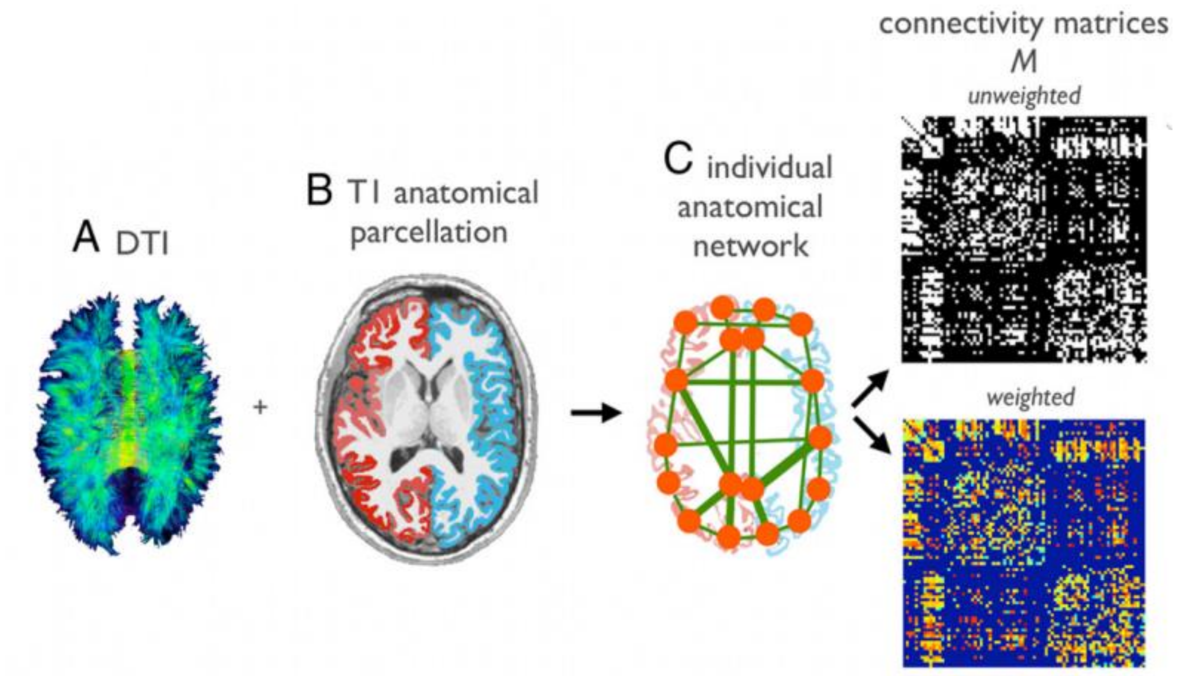
- Voxel-based approach

The FA map of each subject is projected onto the mean FA “skeleton”. The FA or MD (or another index) values of the voxels belonging to the skeleton represent the features used

DIFFUSION TENSOR IMAGING (DTI)

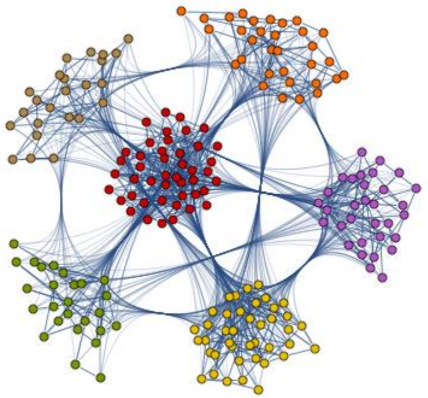
Approaches on DTI data in AD studies

- Network-based approach



The brain can be modeled has a network and its connectivity can be studied applying graph theory

COMPLEX NETWORKS



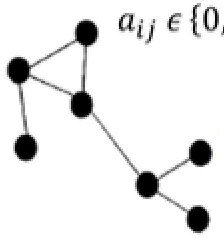
Many real-world systems are composed by a large number of elements characterized by highly dynamic interconnections (e.g., biological and chemical systems, social networks, internet WWW, etc.)

Graph theory is usually considered the most appropriate framework for the mathematical treatment of such complex systems

graph G(*N*, *L*)   *N* = set of nodes *L* = set of unweighted edges
graph G(*N*, *L*, *W*)   *W* = set of weights

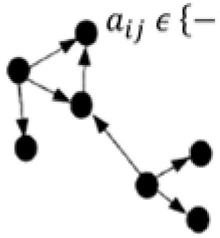
UNDIRECTED

$a_{ij} \epsilon \{0,1\}$



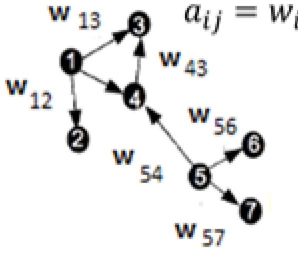
DIRECTED

$a_{ij} \epsilon \{-1,0,1\}$



WEIGHTED

$a_{ij} = w_{ij} \epsilon R$



G(*N*, *L*) can be completely described by the adjacency matrix *A*

G(*N*, *L*, *W*) can be completely described by the weights matrix *W*

Some graph measures:
Nodal: degree, strength, betweenness, clustering coefficient, eigenvector centrality…
Edge: shortest path length, edge betweenness…

ASSESSMENT OF AD LOCAL CHANGES THROUGH VOXEL-BASED APPROACH

Motivations

- Studies using a voxel-based approach with non-nested feature selection on DTI data report higher performance compared with other methods for the HC/MCI classification
  - (O'Dwyer et al., 2011)
  - (Haller et al., 2010)

- Non-nested feature selection chooses the most discriminating voxels by using also the test set, thus introducing a bias (feature selection bias - FSB) in the classification model

- *How far can we rely on these results?*

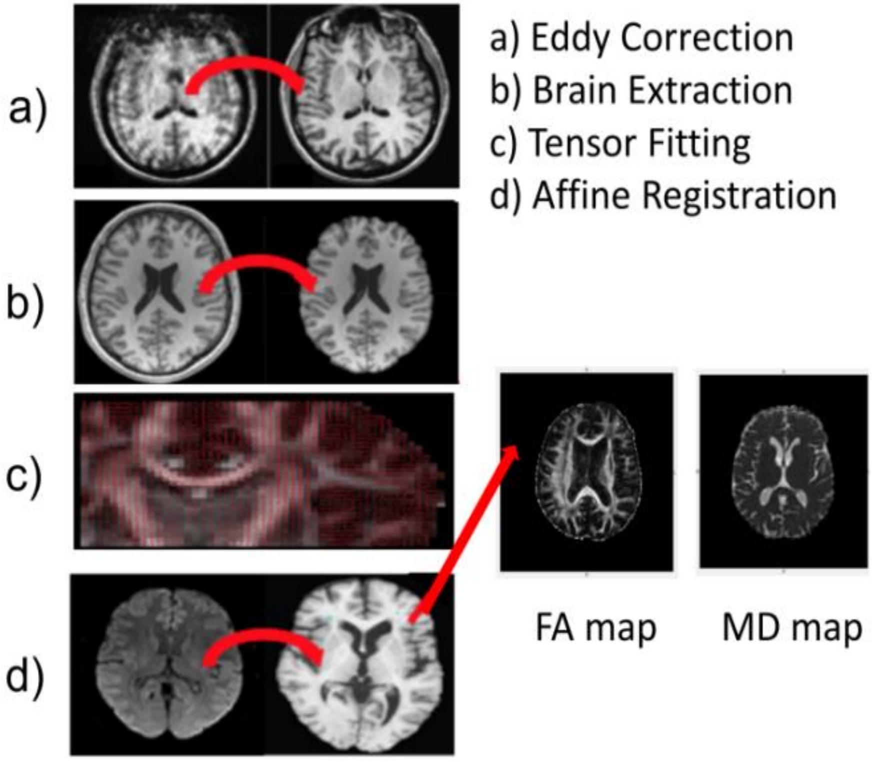
Goals

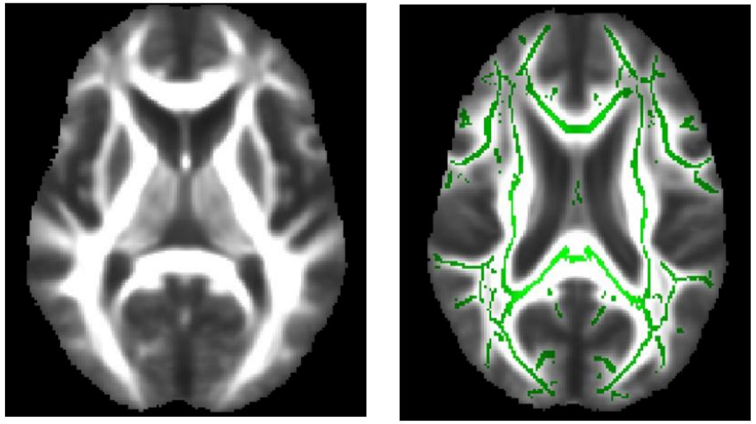
- Measuring the FSB effect, comparing non-nested and nested feature selection on the same data
- Investigating how the FSB impacts our capability to determine which anatomical regions are affected by the disease

ASSESSMENT OF AD LOCAL CHANGES THROUGH VOXEL-BASED APPROACH

Dataset and image processing

Dataset: 50 HC, 50 AD, 50 MCI



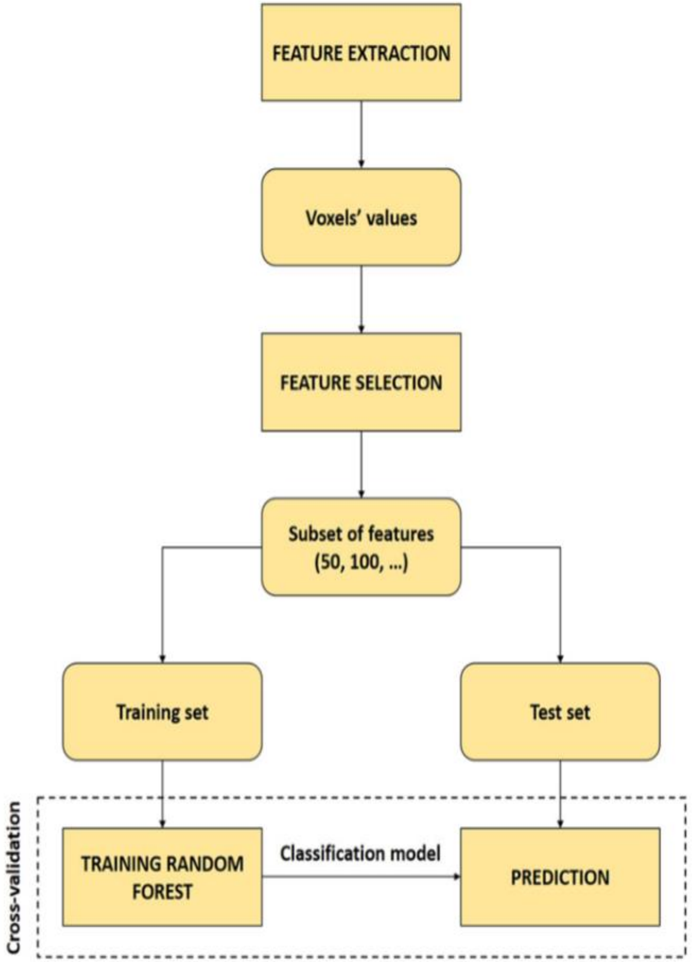


Tract-based Spatial Statistics (TBSS):

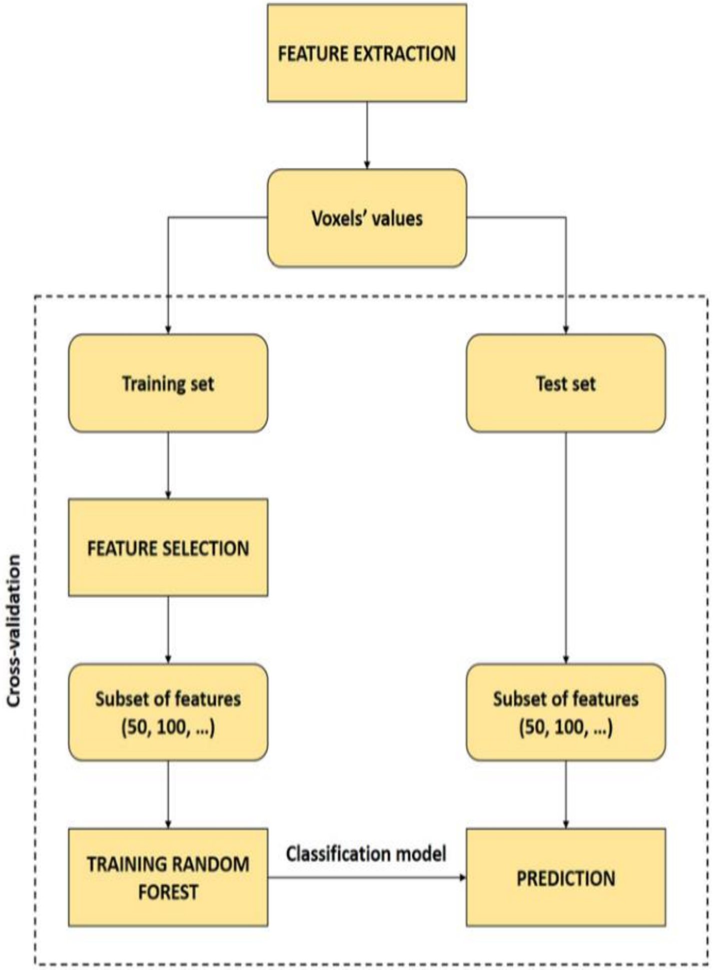
- Registration (nonlinear registration on the FMRIB58_FA template + affine-alignement into 1×1×1 mm MNI152 space
- Calculation of mean FA map and mean FA «skeleton»
- Projection of each subject's map onto the average WM skeleton (this phase returns ~ 120'000 voxels)

ASSESSMENT OF AD LOCAL CHANGES THROUGH VOXEL-BASED APPROACH

Classification comparison



non-nested feature selection



nested feature selection

FEATURE SELECTION:
- Wilkoxon
- ReliefF

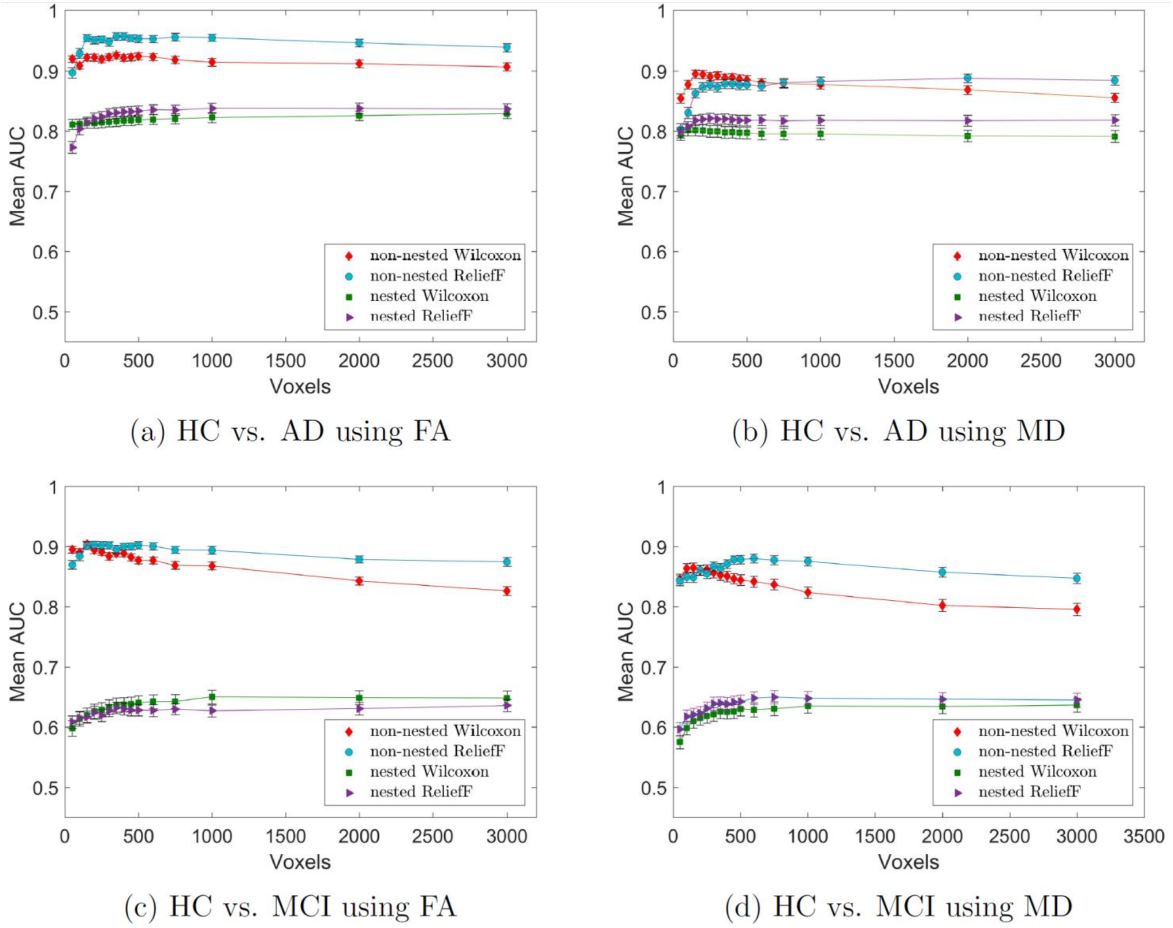
CLASSIFICATION ALGORITHM:
- Random Forest

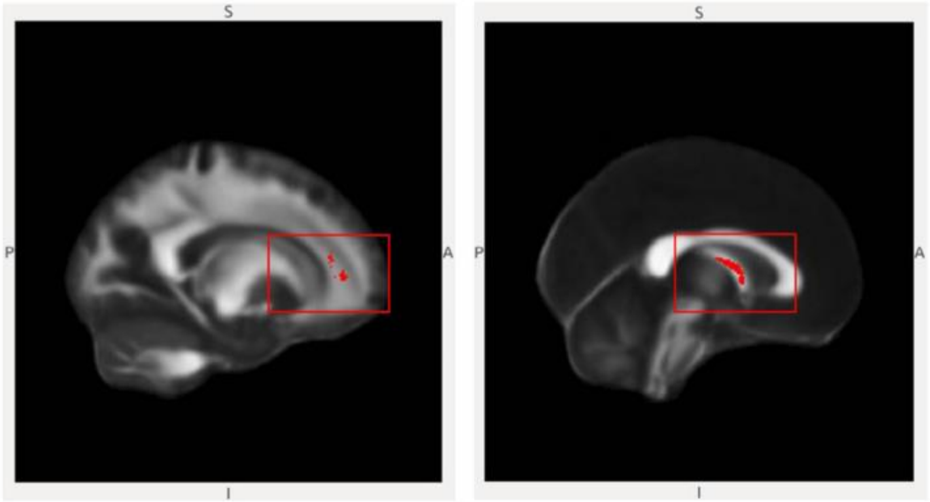
CLASSIFICATION TASKS:
- HC/AD (using FA or MD)
- HC/MCI (using FA or MD)

100 times repeated 5-fold cross-validation

ASSESSMENT OF AD LOCAL CHANGES THROUGH VOXEL-BASED APPROACH

Results





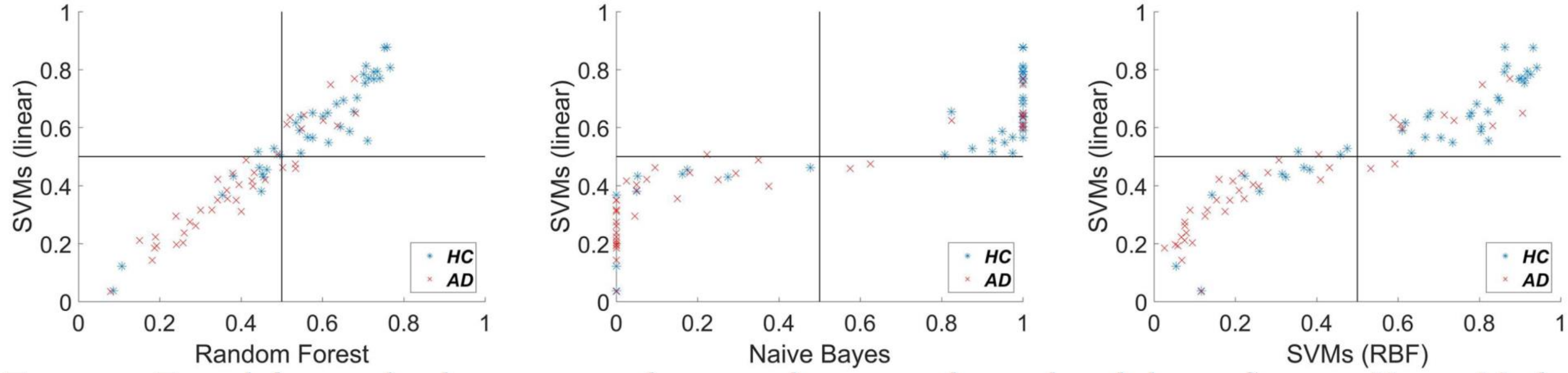
The most discriminating voxels selected during feature selection are localized in the most disease-related brain regions. Our findings are consistent with the existing literature: **Fornix**, **Anterior Corona Radiata** (more in the left hemisphere), **Superior Longitudinal Fasciculus** (more in the left hemisphere), **Cingulum** (Hippocampus), **Forceps major** and **minor**, **Corpus callosum**

Maggipinto, T., Bellotti, R., Amoroso, N., Diacono, D., Donvito, G., **Lella, E.**, Monaco, A., Scelsi, M.A., Tangaro, S., 2017. DTI measurements for Alzheimer’s classification. *Physics in Medicine and Biology*, *62*(6), p.2361.

ASSESSMENT OF AD LOCAL CHANGES THROUGH VOXEL-BASED APPROACH

Models comparison

Task	Classifier	Accuracy	AUC	Sensitivity	Specificity
HC/AD with FA	Random Forest	0.75 ± 0.01	0.84 ± 0.01	0.76 ± 0.02	0.74 ± 0.02
	Naive Bayes	**0.78 ± 0.01**	0.82 ± 0.01	**0.82 ± 0.01**	0.73 ± 0.02
	SVMs (linear)	**0.77 ± 0.01**	**0.87 ± 0.01**	0.76 ± 0.02	**0.77 ± 0.01**
	SVMs (RBF)	0.75 ± 0.01	0.82 ± 0.01	0.79 ± 0.02	0.72 ± 0.03
HC/AD with MD	Random Forest	0.76 ± 0.01	0.82 ± 0.01	0.77 ± 0.02	**0.75 ± 0.02**
	Naive Bayes	**0.77 ± 0.01**	0.81 ± 0.01	**0.83 ± 0.02**	0.72 ± 0.02
	SVMs (linear)	**0.77 ± 0.01**	**0.83 ± 0.01**	**0.83 ± 0.01**	0.72 ± 0.01
	SVMs (RBF)	0.76 ± 0.02	0.82 ± 0.02	0.80 ± 0.02	0.72 ± 0.02



FEATURE SELECTION:
ReliefF (ranking algorithm)

CLASSIFICATION TASKS:
- HC/AD (using FA)
- HC/AD (using MD)

100 times repeated 5-fold cross-validation

- As evidence of the robustness of the method and the content of the selected features, the models show similar results. Even so, SVMs and Naïve Bayes have the best performance
- The results improve the best classification performances of our previous study

Lella, E., Amoroso, N., Bellotti, R., Diacono, D., La Rocca, M., Maggipinto, T., Monaco, A. and Tangaro, S., 2017, September. Machine learning for the assessment of Alzheimer's disease through DTI. In *Applications of Digital Image Processing XL*(Vol. 10396, p. 1039619). International Society for Optics and Photonics.

GRAPH-BASED ANALYSIS AT THE CORTICAL LEVEL

Motivations

- Mostly, the literature applying a network-based approach on DTI data aims at revealing significant differences between the graph measures observed in AD against HC by means of statistical analyses (e.g., Lo et al., 2010; Fischer et al., 2015)
- Very few studies focus on applying DTI tractography, in combination with graph theory, to automatize the AD/HC discrimination through the use of machine learning algorithms (Schouten et al., 2017)

⇩

The potentiality of this approach has not yet been fully investigated

- In addition, all studies use traditional graph measures based on the shortest path length

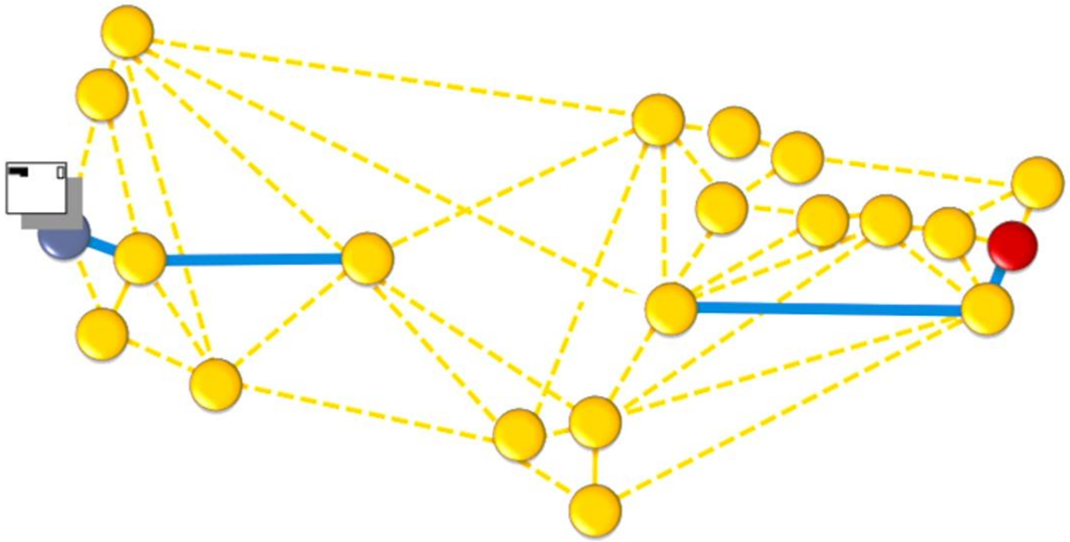
Goal

To investigate the application of new metrics

GRAPH-BASED ANALYSIS AT THE CORTICAL LEVEL

Communication through Traditional Metrics

- It's a common idea that the communication between two nodes in a network occurs via the shortest path connecting them
- But there are two main problems with this approach. The sender may not know the global structure of the network. Thus:
  - Problem 1: The sender does not know which of the many routes connecting it with the destination is the shortest one
  - Problem 2: If the sender knows the shortest path, it does not know *a priori* whether there are damaged edges in it



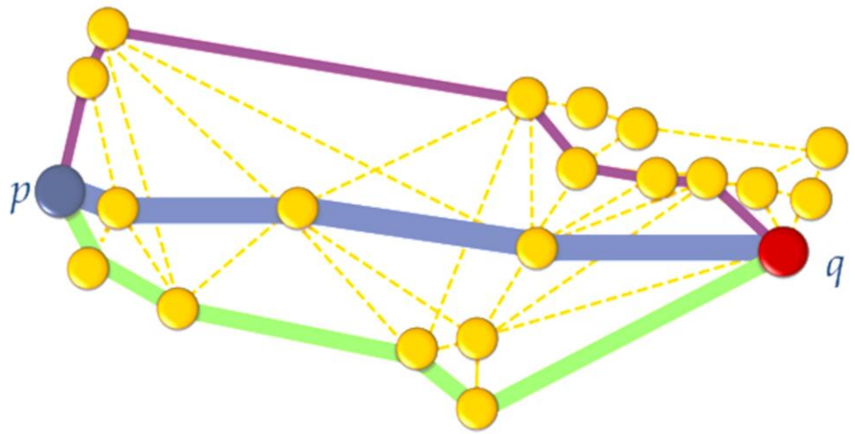
GRAPH-BASED ANALYSIS AT THE CORTICAL LEVEL

Communicability

The communicability G_{pq} between two nodes in a network is defined as a function of the total number of walks connecting them, giving more importance to the shorter than to the longer ones

For a binary graph of N nodes connected by edges where $A = N \times N$ is the adjacency matrix:

$$(A^k)_{pq} = \sum_{r_1=1}^{N} \sum_{r_2=1}^{N} \cdots \sum_{r_{k-1}=1}^{N} a_{p,r_1} a_{r_1,r_2} a_{r_2,r_3} \cdots a_{r_{k-2},r_{k-1}} a_{r_{k-1},q}$$



$$G_{pq} = \sum_{k=0}^{\infty} \frac{(A^k)_{pq}}{k!} = (e^A)_{pq} \qquad G_{pq} = \sum_{j=1}^{N} \varphi_j(p) \varphi_j(q) e^{\lambda_j}$$

For a weighted graph of N nodes $A = N \times N$ is the weighted adjacency matrix.

$$G_{ij} = \left(exp\left(D^{-1/2} A D^{-1/2}\right)\right)_{ij} \qquad D = diag(d_i) \qquad d_i = \sum_{k=1}^{N} a_{ik}$$

Estrada, E. and Hatano, N., 2008. Communicability in complex networks. *Physical Review E*, *77*(3), p.036111.
Crofts, Jonathan J., and Desmond J. Higham. "A weighted communicability measure applied to complex brain networks." Journal of the Royal Society Interface (2009): rsif-2008.

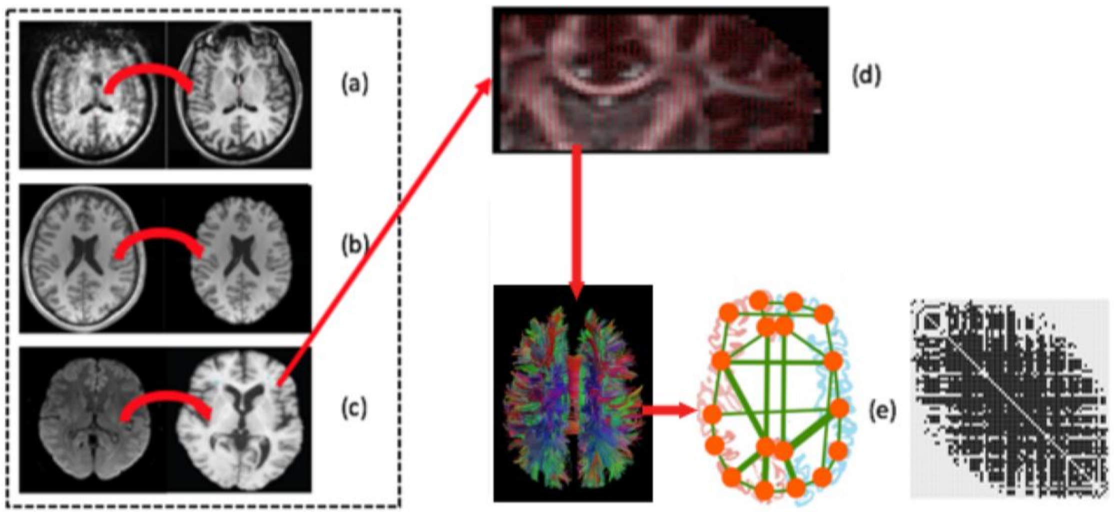
GRAPH-BASED ANALYSIS AT THE CORTICAL LEVEL

Data and methods

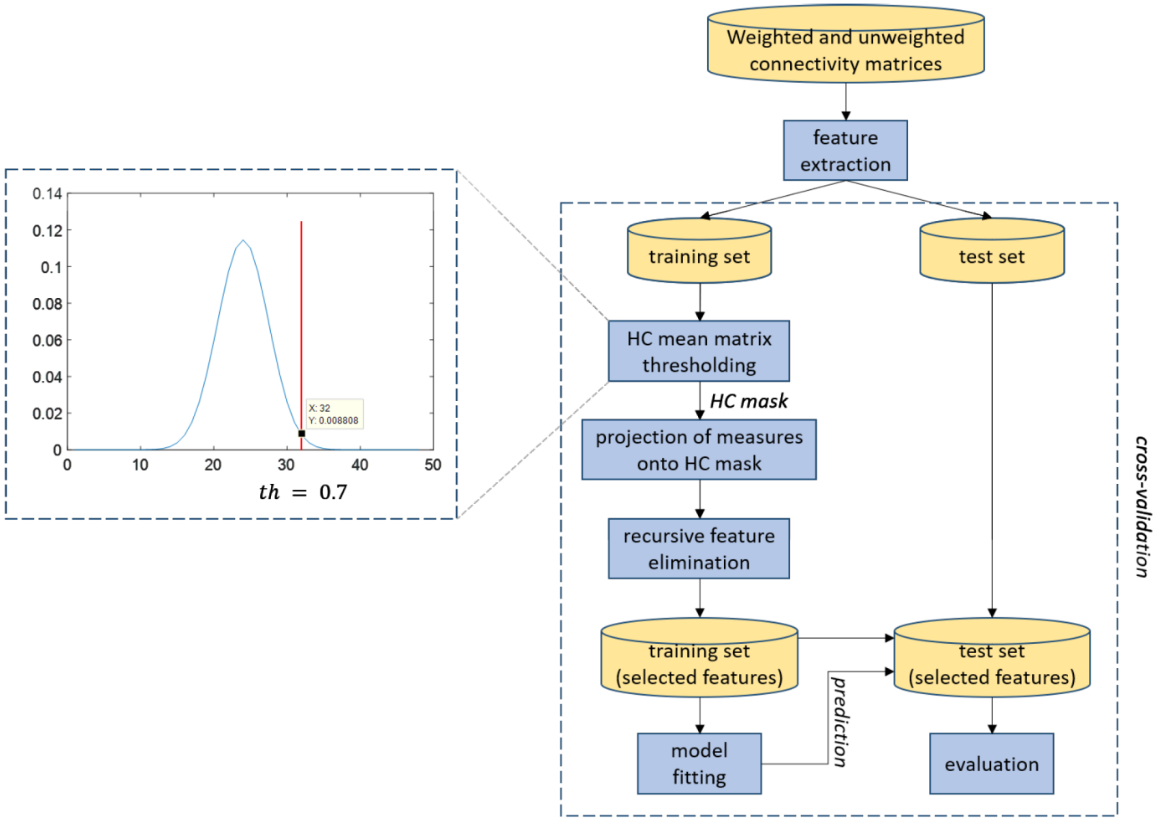
Dataset: 112 subjects, 52 HC and 40 AD, 30 MCI converter from ADNI

Methods:

1. Statistical Analysis: non-parametric statistical test to find node pairs with significantly different communicability
2. Classification HC/AD and HC/AD/MCI: 50-repeated 10-fold cross validation with linear SVMs



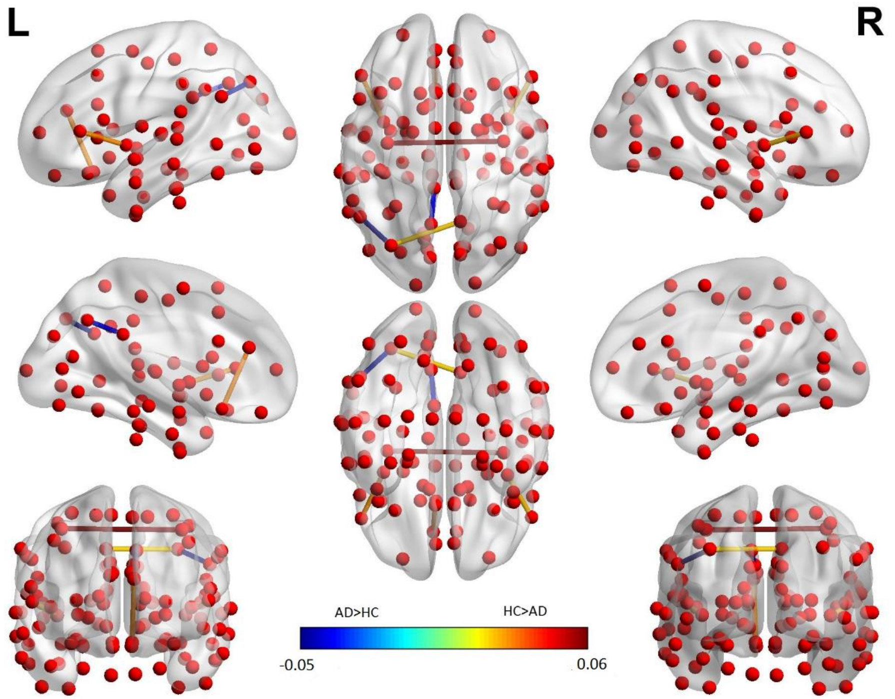
Harvard Oxford cortical Atlas
(96 regions)



GRAPH-BASED ANALYSIS AT THE CORTICAL LEVEL

Statistics on Communicability Group Differences

186 node pairs with statistically significant different communicability, involving regions correlated to AD according to the literature, have been found



- Angular Gyrus (synaptic loss-language function impairment in AD patients)
- Insular Cortex (region of atrophy in AD, related to autonomic instability and to loss of the sense of self)
- Inferior Frontal Gyrus (whose activities protect memory performance against Alzheimer's disease)
- Lateral Occipital Cortex (region of atrophy and hypometabolism in AD)
- Precuneous (involved in self-processing during autobiographical memory retrieval)
- Precentral Gyrus (considered an AD-related brain region)

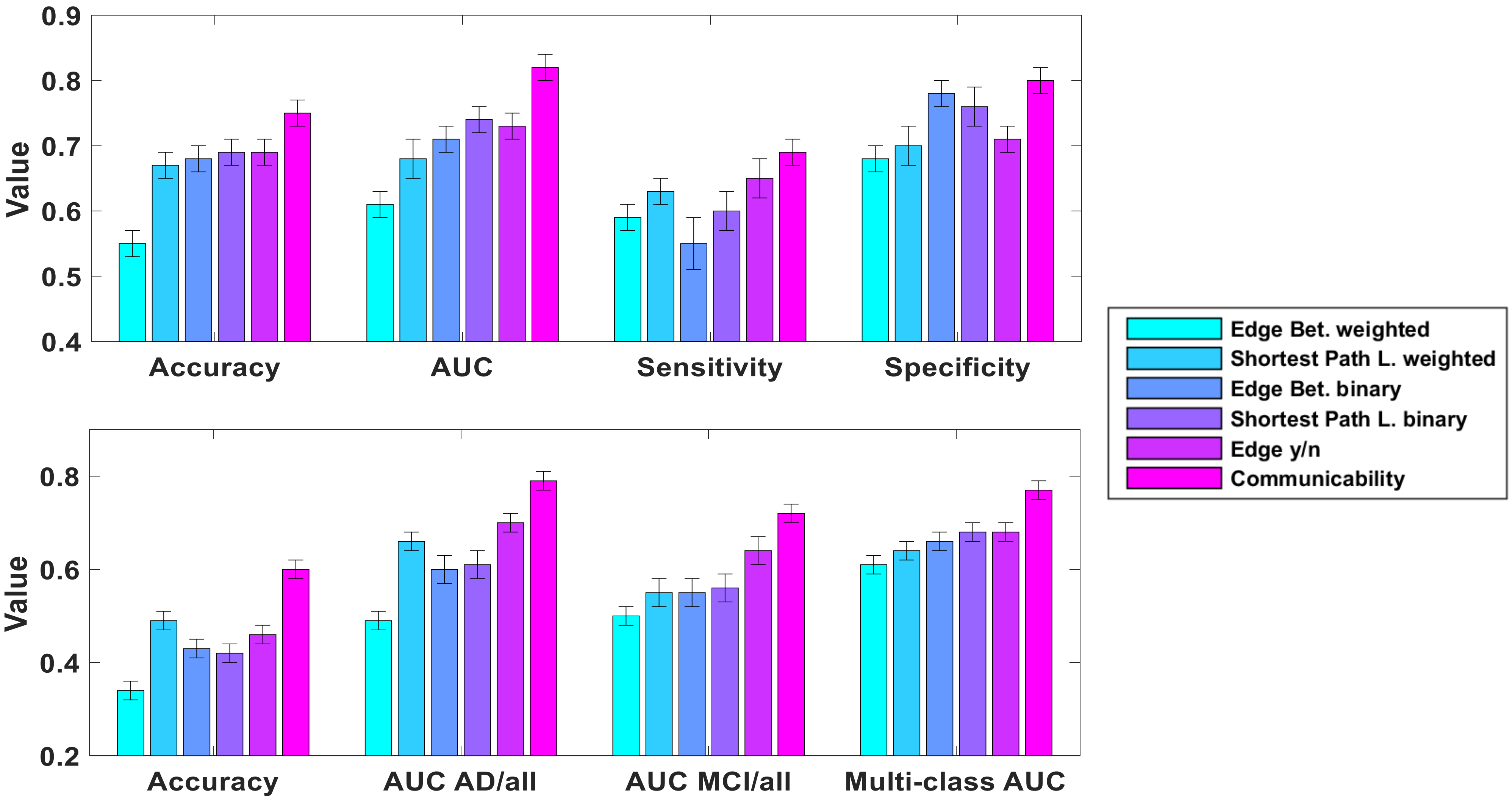
For the three groups (HC, AD and MCI) statistical analysis, 70 node pairs were found to be statistically significant different in communicability, 63 in common with the 186 pairs previously found

Lella, E., Amoroso, N., Lombardi, A., Maggipinto, T., Tangaro, S., Bellotti, R.: Communicability disruption in Alzheimer's disease connectivity networks. Journal of Complex Networks, Oxford University Press (2018)

GRAPH-BASED ANALYSIS AT THE CORTICAL LEVEL

Classification HC/AD

Classification HC/AD/MCI



Lella, E., Amoroso, N., Lombardi, A., Maggipinto, T., Tangaro, S., Bellotti, R.. A Classification Framework for Alzheimer's Disease based on Graph Communicability. Workshop on GRaphs in biomediAl Image anaLysis (GRAIL), in MICCAI 2018

GRAPH-BASED ANALYSIS AT THE SUBCORTICAL LEVEL

Motivations

- Most of the existing literature, regarding AD discrimination using graph theory, focused on AD connectivity abnormalities at a relatively global level such as the whole-brain level and the cortex level
- In literature the crucial role of the subcortical regions is well known

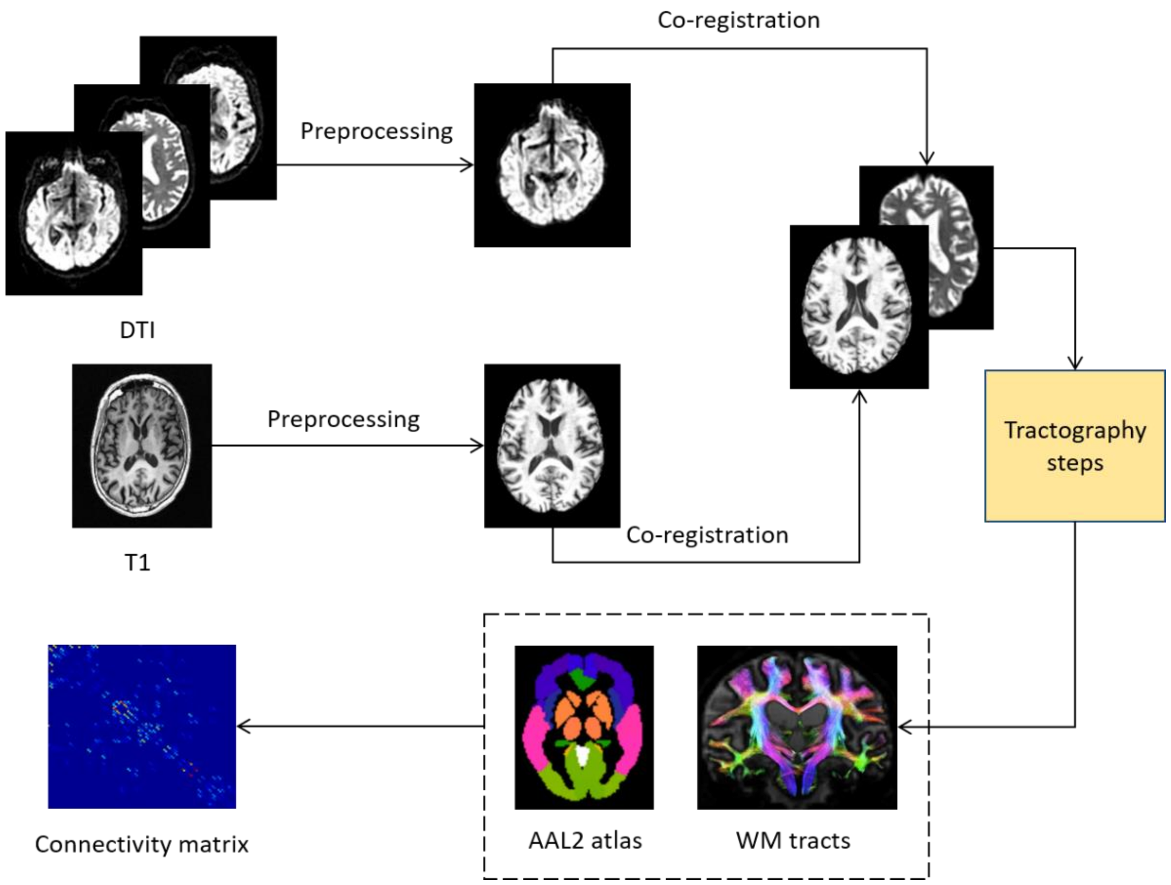
Goals

- Investigating the AD-related network changes at the subcortical structural level in terms of communicability between the subcortical regions and between these regions and the rest of the network
- Measuring the information content of subcortical connections in discriminating AD from normal subjects, in terms of communicability

GRAPH-BASED ANALYSIS AT THE SUBCORTICAL LEVEL

Data and image processing

Dataset: 49 HC and 40 AD from ADNI



Different probabilistic tractography pipeline based on:

- tools provided by the MRtrix3 software package
- Different parcellation scheme (AAL2 atlas involving cortical and subcortical regions)

Output:

120 × 120 weighted symmetric connectivity matrix *W*

Extraction of the 12 × 12 subcortical network including (both left and right):

- Hippocampus
- Amygdala
- Caudate
- Putamen
- Pallidum
- Thalamus

GRAPH-BASED ANALYSIS AT THE SUBCORTICAL LEVEL

Communicability-based measures

$$G_{pq}^{Sub} = \sum_{k=0}^{\infty} \frac{(M^k)_{pq}}{k!} = (e^M)_{pq}$$

the *weighted communicability* for each node pair *p* and *q* of the subcortical network W_s

con $M = D^{-1/2} W_s D^{-1/2}$

$$SC_i^{intra} = \sum_{j \in N_s} G_{ij}^{Sub}$$

the *intra strength communicability* for each node $i \in N_s$
(expresses the intensity of the total node connectivity with the other subcortical regions, in terms of communicability)

$$SC_i^{inter} = \sum_{j \in \{N - \{S - i\}\}} G_{ij}$$

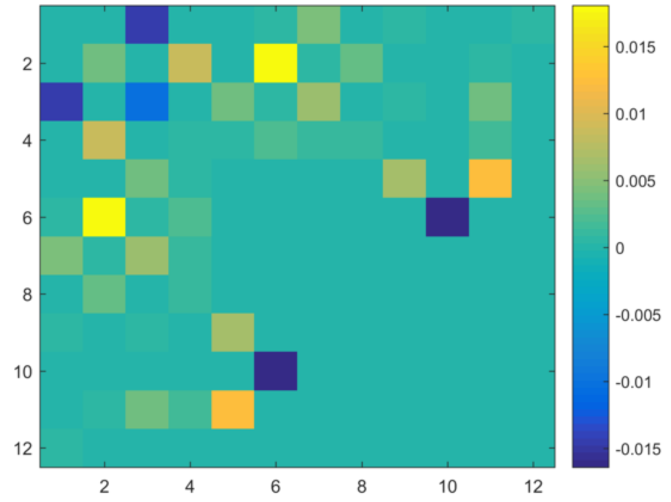
the *inter strength communicability* for each node $i \in S$
(expresses the intensity of the total subcortical node connectivity, in terms of communicability, with the rest of the whole network, excluding the other subcortical regions)

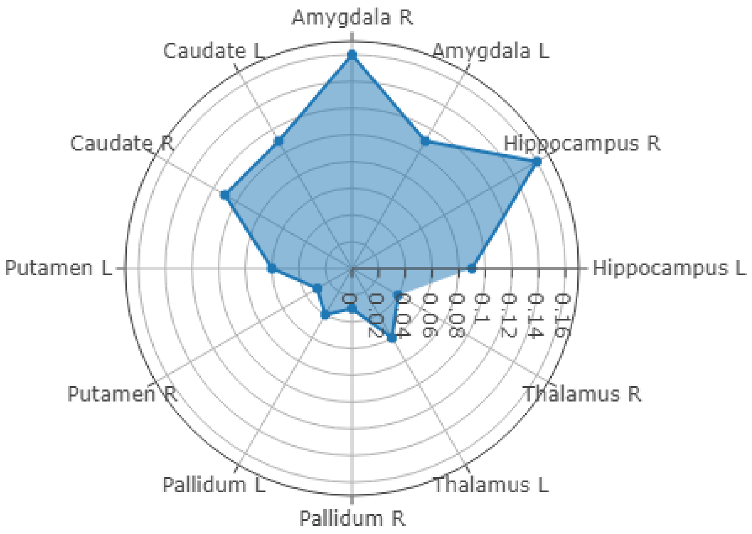
S = subset of the whole matrix indices corresponding to the subcortical regions
G_{ij} = communicability values between the node pairs *ij* in the whole network

GRAPH-BASED ANALYSIS AT THE SUBCORTICAL LEVEL

Results: Subcortical communicability patterns related to AD

1. Hippocampus L
2. Hippocampus R
3. Amygdala L
4. Amygdala R
5. Caudate L
6. Caudate R
7. Putamen L
8. Putamen R
9. Pallidum L
10. Pallidum R
11. Thalamus L
12. Thalamus R





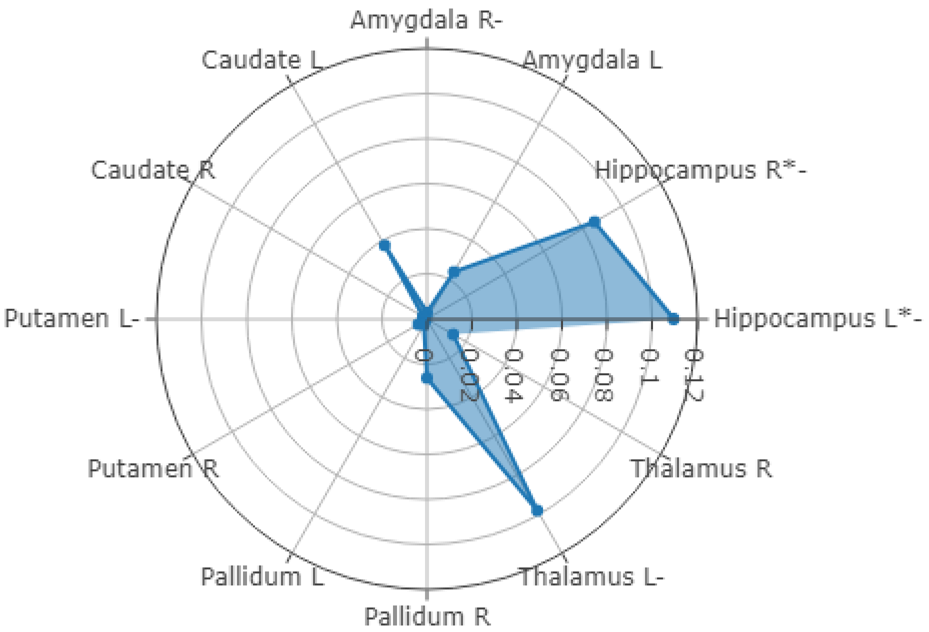
- 35 of 78 subcortical region pairs with statistical significant different communicability (p-value < 0.05)
- average disruption of communicability in most region pairs; nevertheless, the mean communicability is greater in AD than in HC in some node pairs, particularly (left Hippocampus, left Amygdala) and (right Caudate, right Pallidum)

The most involved regions are:

- right and left Hippocampus
- right and left Amygdala
- rigth and left Caudate

GRAPH-BASED ANALYSIS AT THE SUBCORTICAL LEVEL

Results: Subcortical communicability patterns related to AD



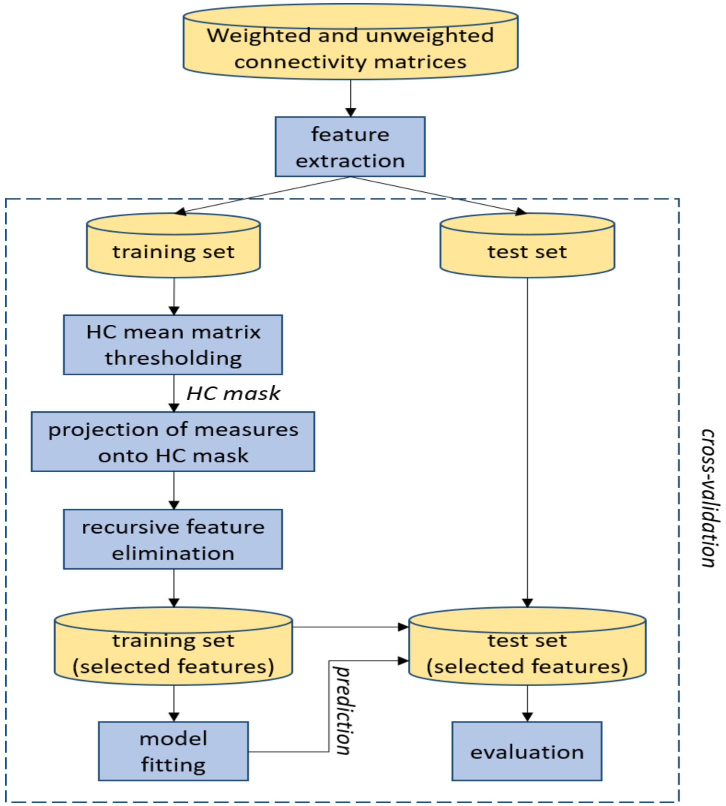
Right and left Hippocampus are statistically significant different in terms of inter strength communicability SC_i^{inter} at the 0.05 significance level

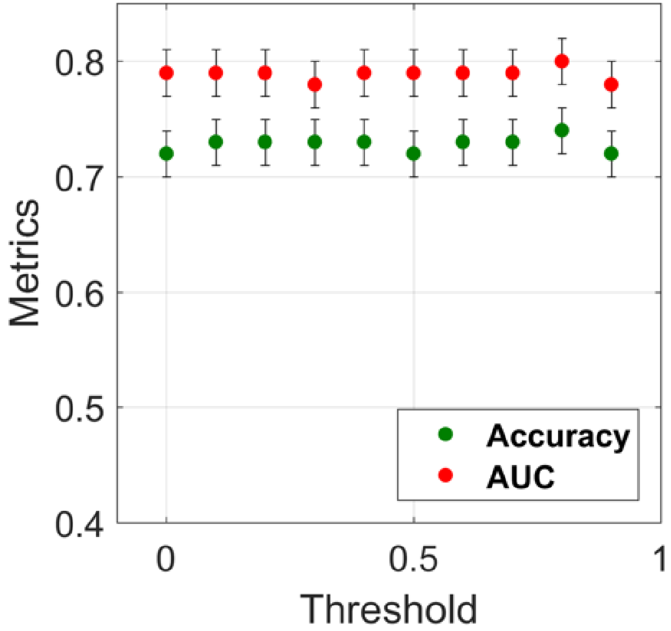
There is evidence in the literature that one of the first events in AD is the disconnection of the hippocampal formation and neocortex and of the isolation of the hippocampal formation in AD

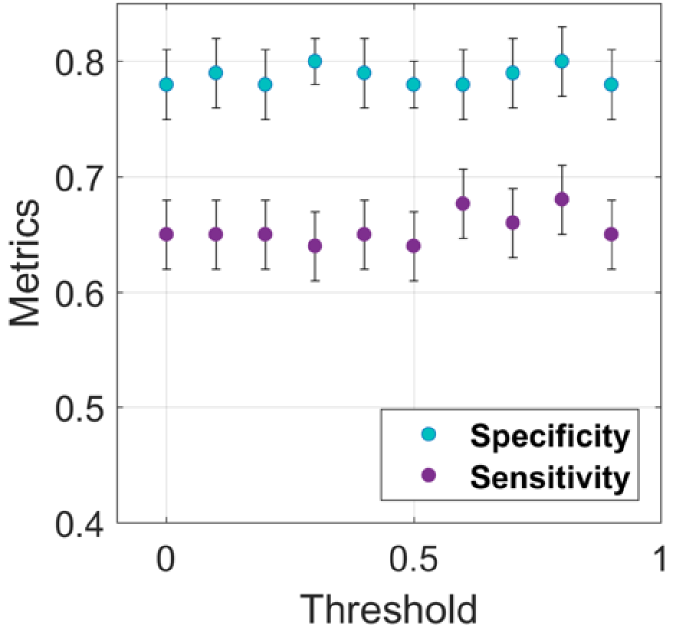
Possible interpretation of results: the increased communicability in AD reflects adaptive changes in the white matter structure that have occurred secondary to the disease

GRAPH-BASED ANALYSIS AT THE SUBCORTICAL LEVEL

Results: Classification performances







These performances, obtained using only the 12 × 12 subcortical network, are quite comparable to those we obtained with the 96 × 96 cortical network in the previous analysis.

CONCLUSIONS

The main results of my PhD activity concerned with:

- The development of a fully-automated and distributed analysis for the processing of DTI brain scans

- The design and implementation of frameworks to investigate the connectome changes due to AD at different scales of investigation and to measure the information content of multiscale DTI-based features for the diagnosis of Alzheimer's disease

- The implementation of a DTI network-based approach based on an uncommon metric used for the first time for the discrimination of AD with very promising results

- The detection of brain regions related to the disease according to connectivity differences at various scales

FUTURE WORK

Some open issues call for future research:

- Deeping into the connectivity pattern involving the hippocampal region and investigating the hypothesis of adaptive changes
- Extending the sub-cortical analysis carried out to a cohort of MCI subjects
- Combining cortical to subcortical
- Combining voxel-based to complex network-based features

CORSI

- Management and knowledge of European research model and promotion of research results, D'Orazio
- How to prepare a technical speech in English, White
- Programming with Python, Diacono
- Complex Systems, Ferraro
- Applications of MATLAB, Dotoli
- Statistical and computational models for data analysis, Tangaro
- Analysis of experimental data, Pompili
- Gaseous Detecrors, Peskov

SCUOLE, CONFERENZE E SEMINARI

- International Summer School on Complex Networks, Bertinoro, 10-14 Luglio 2016
- BigDat 2017 – International winter school on big data, Bari, 13-17 Febbraio 2017
- MSC – Mediterranean summer school on complex networks, Salina, 3-8 Settembre 2017
- Presentazione al 2nd Workshop on GRaphs in biomediAl Image anaLysis (GRAIL), evento satellite di MICCAI 2018, 20 Settembre, Granada, Spagna

- Colloquium: Diario di un viaggio dalle biglie di vetro verso una teoria invariante di scala, Prof. Giorgio Parisi, 2-12-2015, Dipartimento Interateneo di Fisica
- Network Physiology: from complex dynamics of individual systems to networks of organ interactions and the Human Physiolome, Prof. Plamen Ch. Ivanov, 25-05-2016, Dipartimento Interateneo di Fisica
- Onde gravitazionali: la scoperta, le implicazioni, le prospettive, Dott. Losurdo, 19-04-2016, Dipartimento Interateneo di Fisica
- Big Data & Machine Learning, Angelo Mariano, 16/05/2017, Dipartimento Interateneo di Fisica
- Artificial Intelligence: What Lies Beneath, Prof. H. Prosper, 8/06/2017, Dipartimento Interateneo di Fisica
- Learning driven by surprises: Entropic Dynamics of Distrust and Opinions of Social Agents Systems, Nestor Caticha, 27/06/2017, Dipartimento Interateneo di Fisica

DIDATTICA

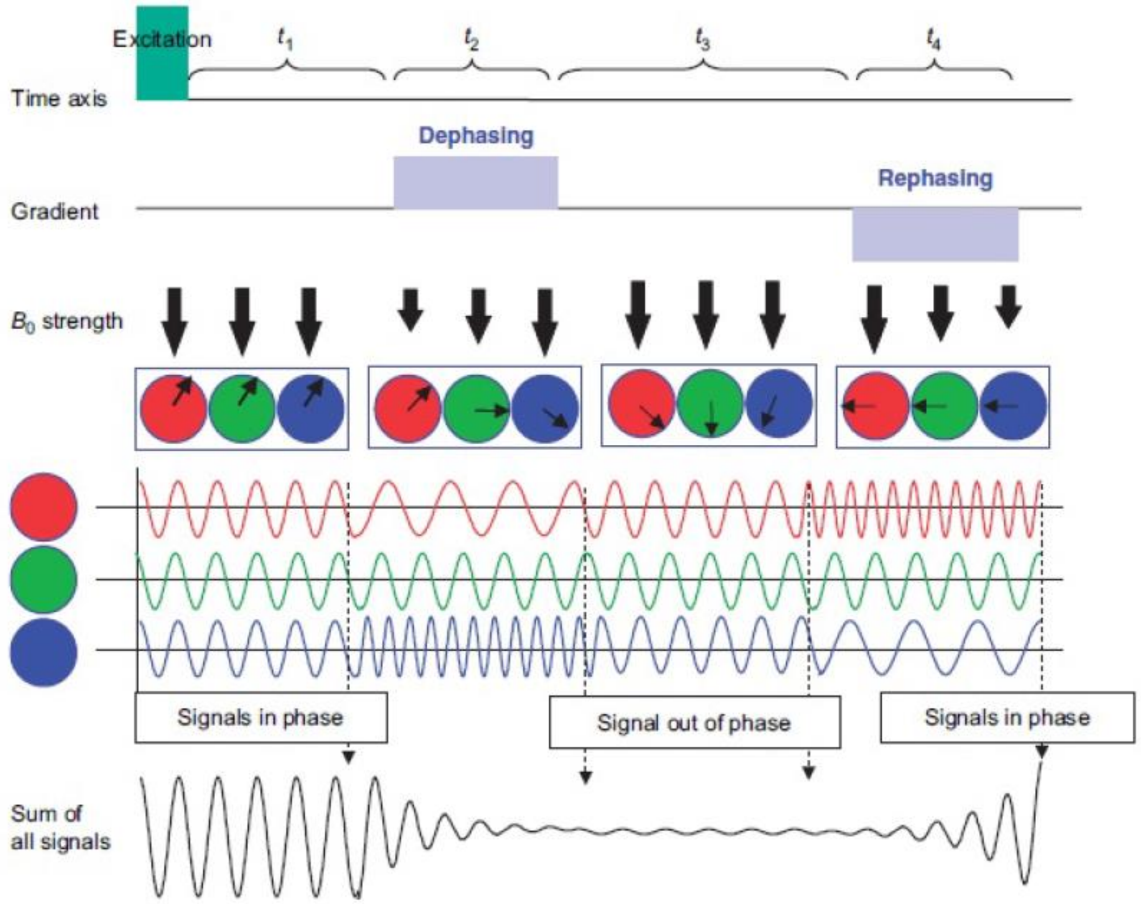
- 40 ore di supporto alla didattica per l’insegnamento di Fisica Generale al Politecnico di Bari
- Seminario didattico dal titolo “Complex networks and applications” all’interno del corso di Elaborazione numerica dei segnali per il corso di laurea in Ingegneria Elettronica, 16 Maggio 2018, Politecnico di Bari

PUBBLICAZIONI

1. T. Maggipinto, R. Bellotti, N. Amoroso, D. Diacono, G. Donvito, E. Lella, A. Monaco, M. A. Scelsi, and S. Tangaro. DTI measurements for Alzheimer’s classification. Physics in Medicine and Biology, 62(6):2361, 2017
2. Lella, E., Amoroso, N., Bellotti, R., Diacono, D., La Rocca, M., Maggipinto, T., ... & Tangaro, S. (2017, September). Machine learning for the assessment of Alzheimer’s disease through DTI. In Applications of Digital Image Pro-cessing XL (Vol. 10396, p. 1039619). International Society for Optics and Photonics
3. La Rocca, M., Amoroso, N., Lella, E., Bellotti, R., & Tangaro, S. A multi-layer MRI description of Parkinson’s disease. In Applications of Digital Image Processing XL (Vol. 10396, p. 1039618). International Society for Optics and Photonics
4. Lella, E., Amoroso, N., Lombardi, A., Maggipinto, T., Tangaro, S., Bellotti, R., edited by Estrada, E. (2018). Com-municability disruption in Alzheimer’s disease connectivity networks. Journal of Complex Networks
5. Lella, E., Amoroso, N., Lombardi, A., Maggipinto, T., Tangaro, S., Bellotti, R.. A Classification Framework for Alzheimer's Disease based on Graph Communicability. Workshop on GRaphs in biomediAl Image anaLysis (GRAIL), in MICCAI 2018
6. Lombardi, A., Amoroso, N., Diacono, D., Lella, E., Bellotti, R., Tangarso, S. Age related topological analysis of sinchronization-based functional connectivity (accepted at the 7th International Conference on Complex Networks and Their Applications, 2018)
7. Lella, E., Amoroso, N., Diacono, D., Lombardi, A., Maggipinto, T., Tangaro, S., Bellotti, R. DTI-based subcortical network analysis in Alzheimer’s Disease (in preparation)

THANK YOU
FOR
YOUR ATTENTION

DIFFUSION TENSOR IMAGING



RESULTS: MEASURING THE FSB

Classification	Non-nested	Nested
HC/AD with FA	Acc = 0.87	Acc = 0.75
	AUC = 0.96	AUC = 0.84
HC/MCI with FA	Acc = 0.81	Acc = 0.59
	AUC = 0.9	AUC = 0.65
HC/AD with MD	Acc = 0.83	Acc = 0.76
	AUC = 0.9	AUC = 0.82
HC/MCI with MD	Acc = 0.79	Acc = 0.6
	AUC = 0.88	AUC = 0.65

SECOND CONTRIBUTION: network-based approach on DTI data

Results: classification HC/AD