Presentazione delle attività del secondo anno di dottorato

«DTI analysis for the diagnosis of Alzheimer's disease»

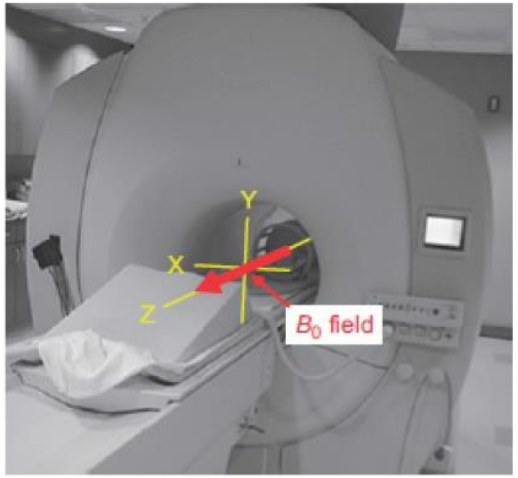
Dottorato di Ricerca in Fisica, XXXI ciclo
Dipartimento Interateneo di Fisica 'M. Merlin'
Dottoranda: Eufemia **Lella**
Tutor: Prof. Roberto **Bellotti**, Prof. Sebastiano **Stramaglia**

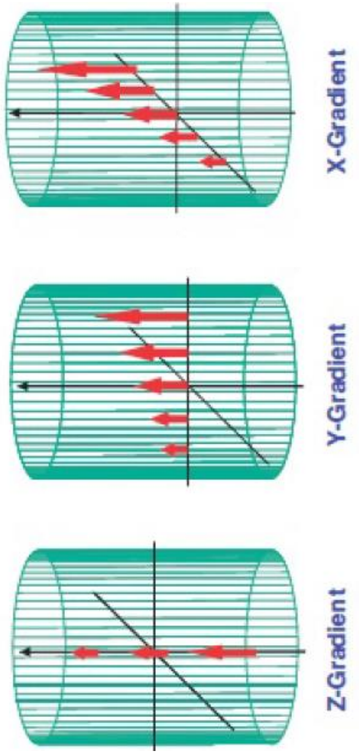
CONTEXT

- In neuroimaging mathematical and statistical-based tecniques togheter with machine learning procedure 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
- 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

DIFFUSION TENSOR IMAGING (DTI)

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





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

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

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

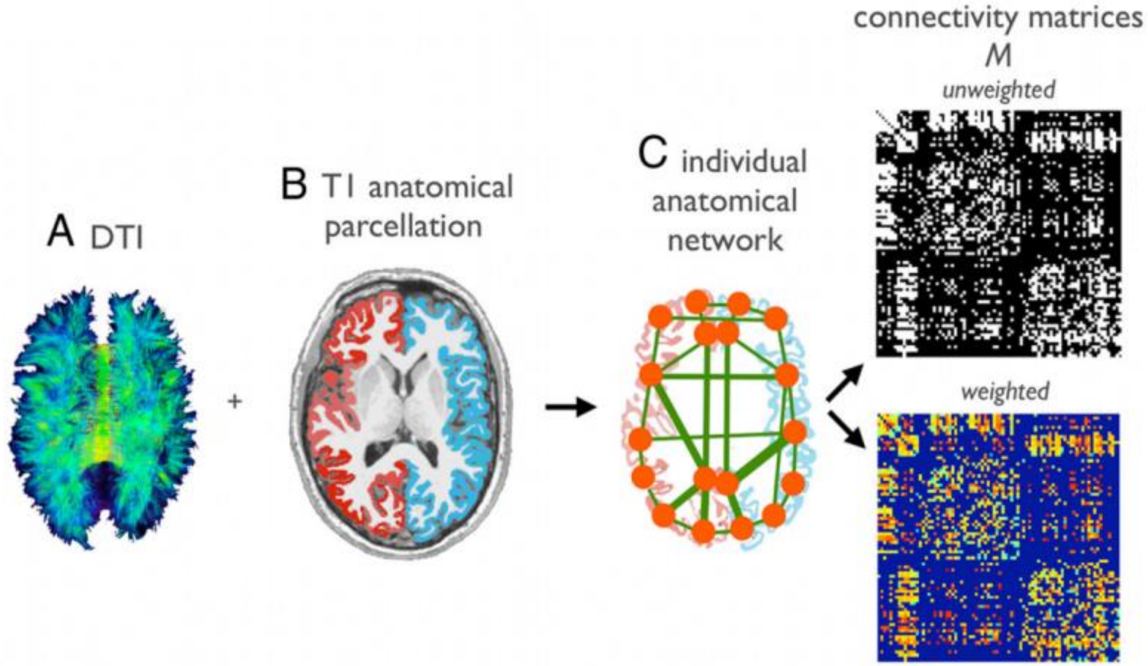
$$\text{FA} = \frac{1}{\sqrt{2}} \frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{{\lambda_1}^2+{\lambda_2}^2+{\lambda_3}^2}}$$

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

FA = Fractional Anisotropy
MD = Mean Diffusivity

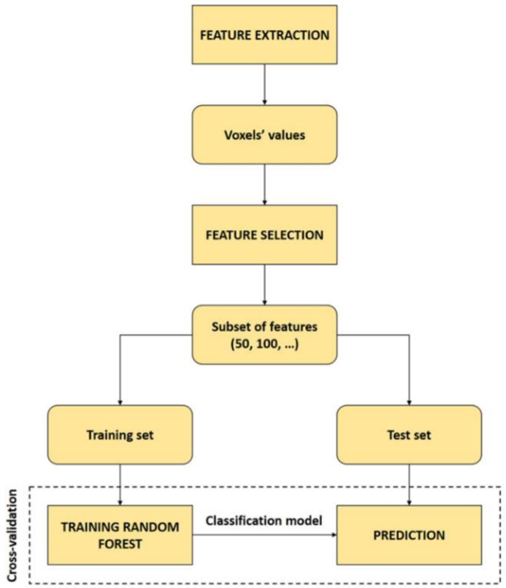
STATE OF THE ART

- Several works use machine learning algorithms based on DTI to automatize the discrimination between AD patients and healty control (HC) subjects
  - Voxel-based approach, e.g. (Maggipinto et al., 2017, O'Dwyer et al., 2011)
  - ROI-based approach, e.g. (Dyrba et al., 2015)
- Some studies use network-based approach: DTI, together with tractography algorithms, provides a way to reconstruct the WM fiber tracts *in vivo*, so obtaining connectivity networks that can be subsequently investigated through the graph theory

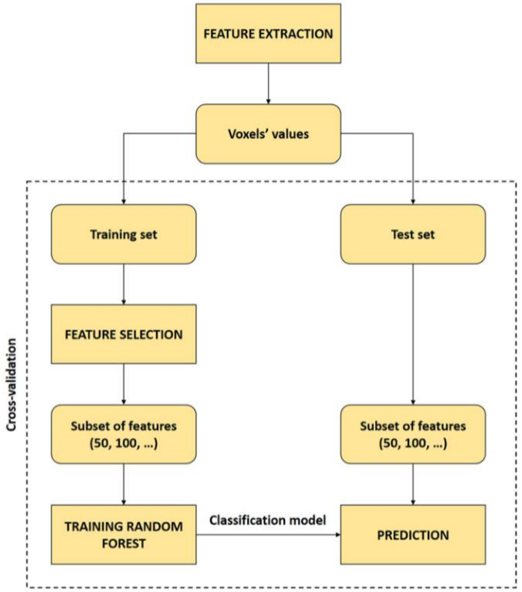


PHD FIRST YEAR: VOXEL-BASED APPROACH

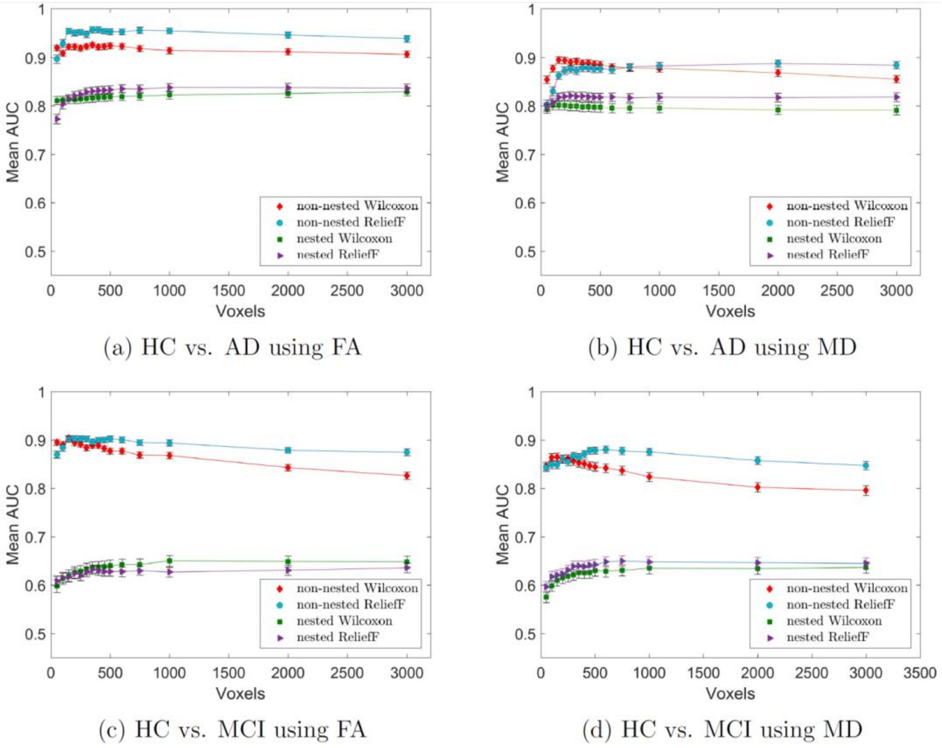
Dataset: 50 HC, 50 AD, 50 MCI (ADNI)

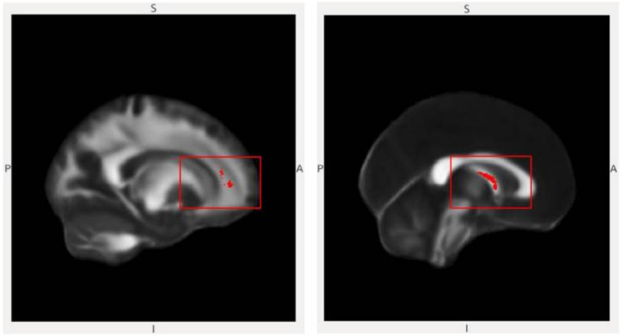


Non-nested feature selection



nested feature selection





- Measurement of the (feature selection bias effect) FSB effect, comparing non-nested and nested feature selection on the same data set
- Investigation of the anatomical regions affected by the disease

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

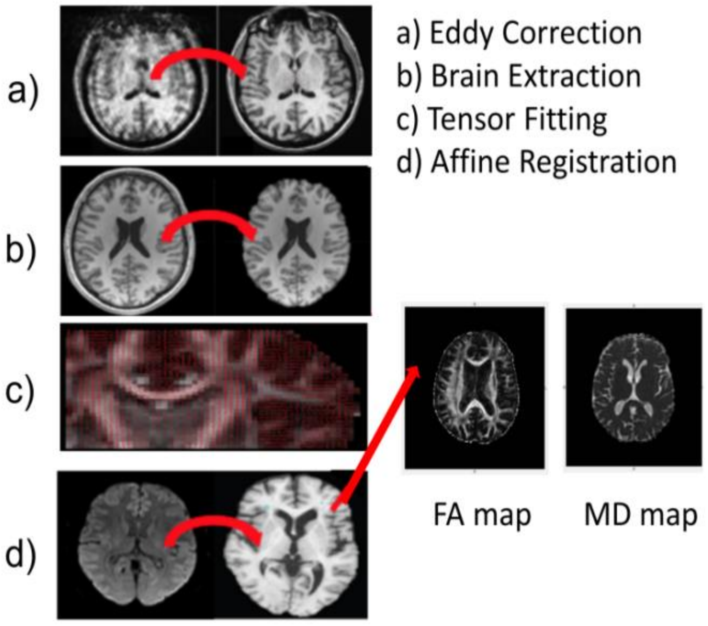
PHD SECOND YEAR, FIRST CONTRIBUTION

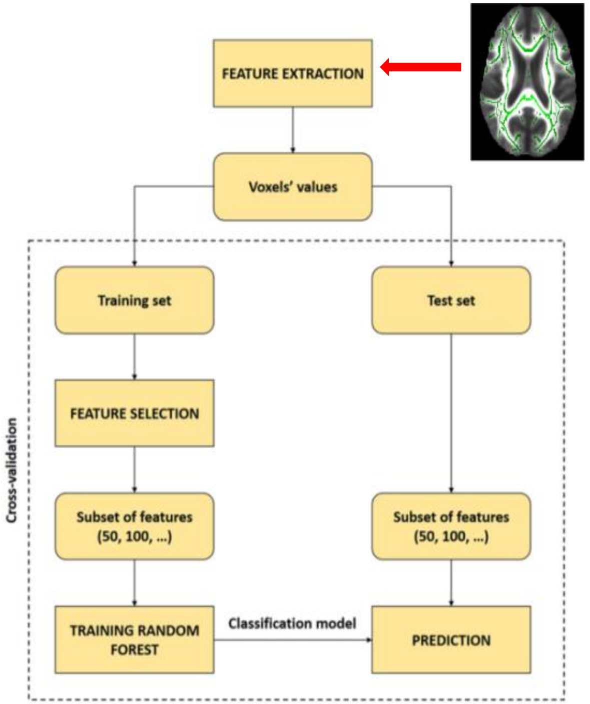
Extending first year results

Goal: exploring how different supervised classification models (Random Forests, Support Vector Machines, Naïve Bayes) provide a robust support to the diagnosis of AD patients

Dataset: diffusion-weighted scans of 80 subjects, 40 HC and 40 AD from ADNI

Methods:





FEATURE SELECTION:
ReliefF (ranking algorithm)

CLASSIFICATION METHODS: Random Forests, (linear and Gaussian) Support Vector Machines, Naïve Bayes

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

Entire procedure validated with a 100 times repeated 5-fold cross-validation

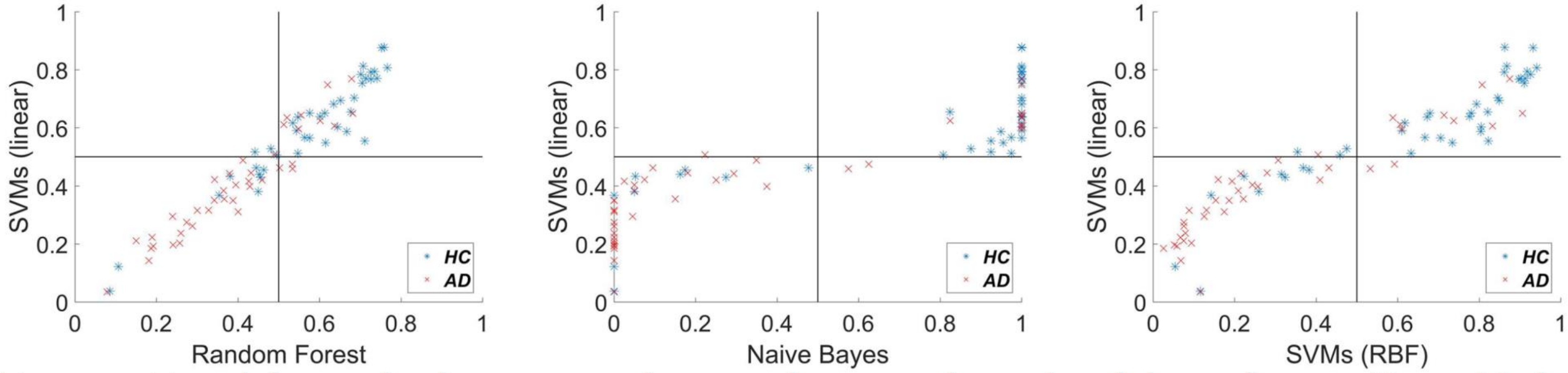
Lella, E., Amoroso, N., Bellotti, R., Diacono, D., La Rocca, M., Maggipinto, T., Monaco, A. and Tangaro, S., 2017, September. Machine learning for the assessment of Alzheimer's disease through DTI. In *Applications of Digital Image Processing XL*(Vol. 10396, p. 1039619). International Society for Optics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

PHD SECOND YEAR, FIRST CONTRIBUTION

Extending first year results

Results

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



- 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 classication 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.

SECOND CONTRIBUTION: network-based approach on DTI data

Motivations of the study

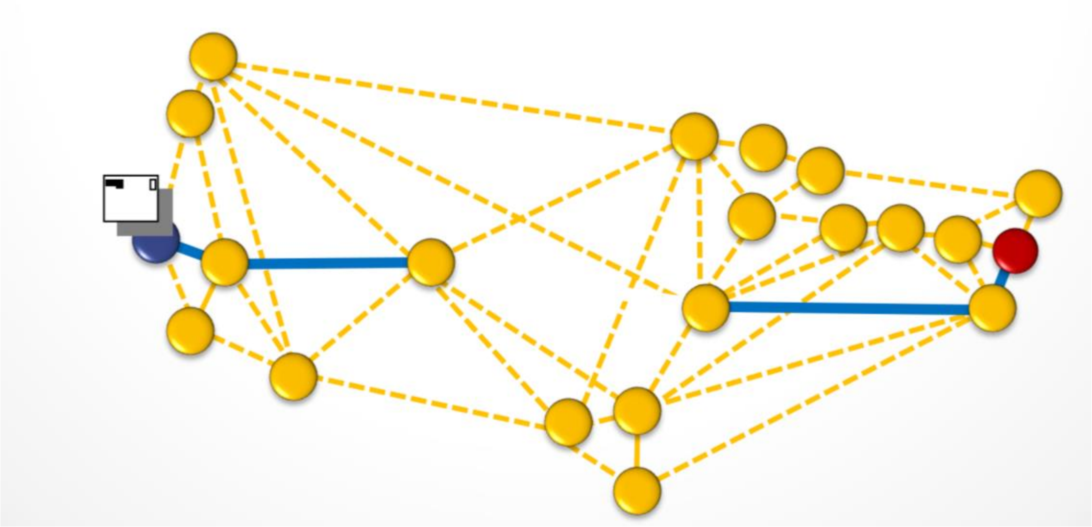
- Mostly, the literature applying a netwok-based approach on DTI data aims at revealing significant differences between the graph measures observed in AD against HC by means of statistical analyses (e.g., Lo et al., 2010; Fischer et al., 2015)
- Very few studies focus on applying DTI tractography, in 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, so we want to investigate the application of new metrics

SECOND CONTRIBUTION: network-based approach on DTI data

- 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, she does not know *a priori* whether there are damaged edges in it



SECOND CONTRIBUTION: network-based approach on DTI data

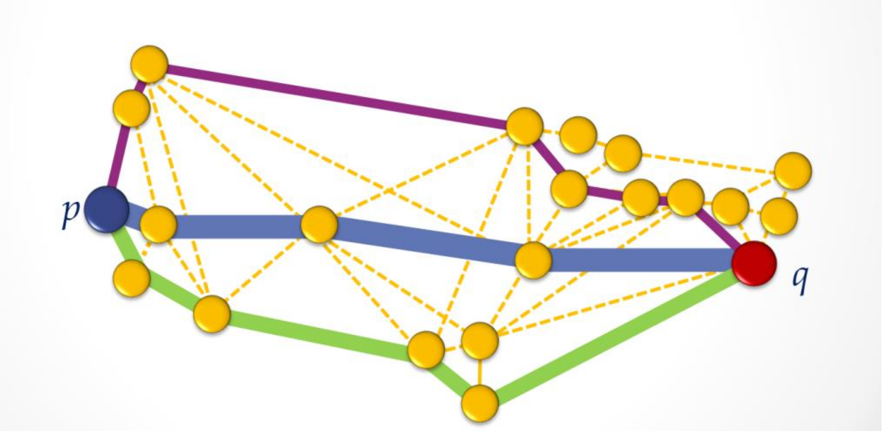
Communicability

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* × *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* × *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.

SECOND CONTRIBUTION: network-based approach on DTI data

Research questions

- Hypothesis: communicability is particularly suitable to emphasize differences between HC and AD in DTI connectivity networks
- Goals:

1. Comparative study, based on a same dataset, between classification models trained with traditional metrics and models trained with communicability
2. Statistical analysis to find edges with statistically significant different communicability between HC and AD
3. Finding out the AD-related brain regions according to communicability differences

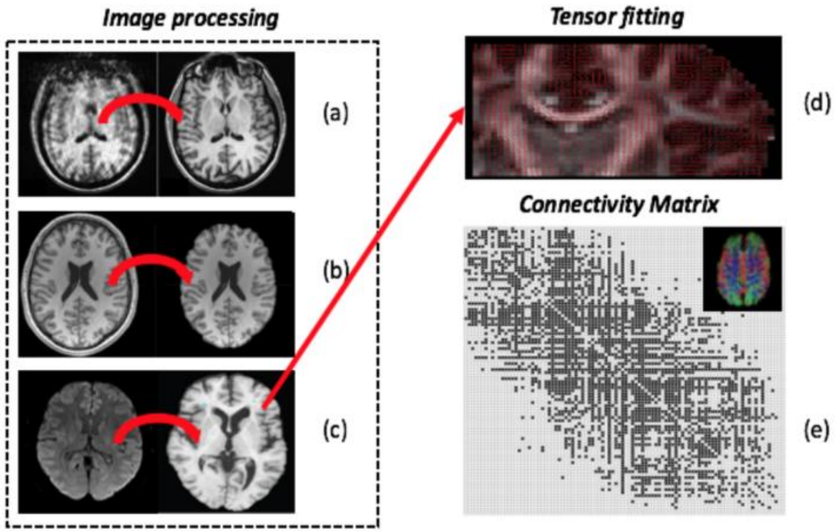
SECOND CONTRIBUTION: network-based approach on DTI data

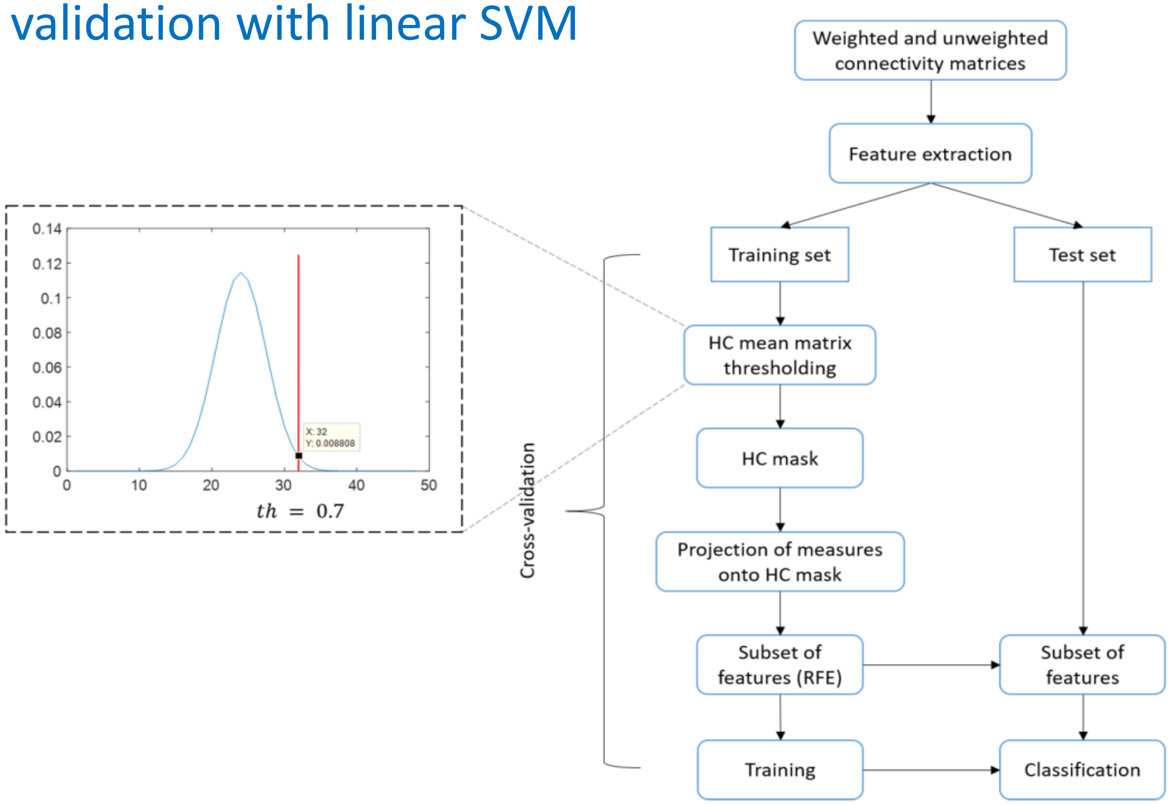
Materials and methods

Dataset: diffusion-weighted scans of 92 subjects, 52 HC and 40 AD from ADNI

Methods:

1. Classification HC/AD: 50-repeated 10-fold cross validation with linear SVM

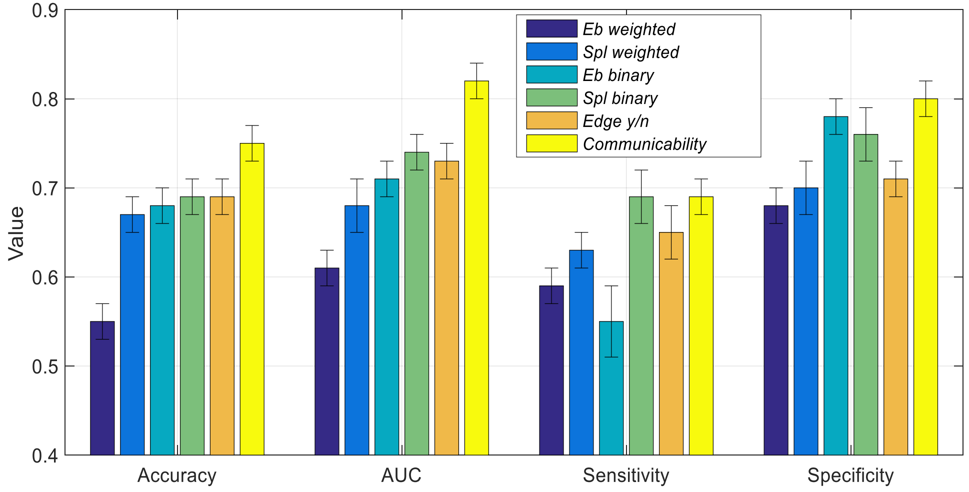


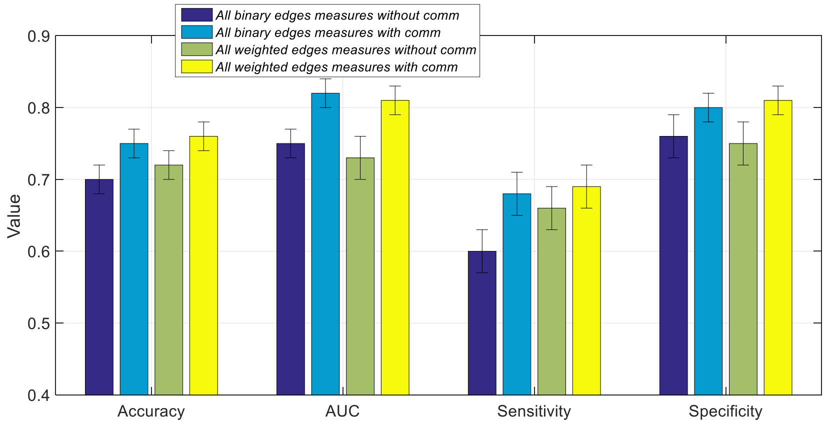


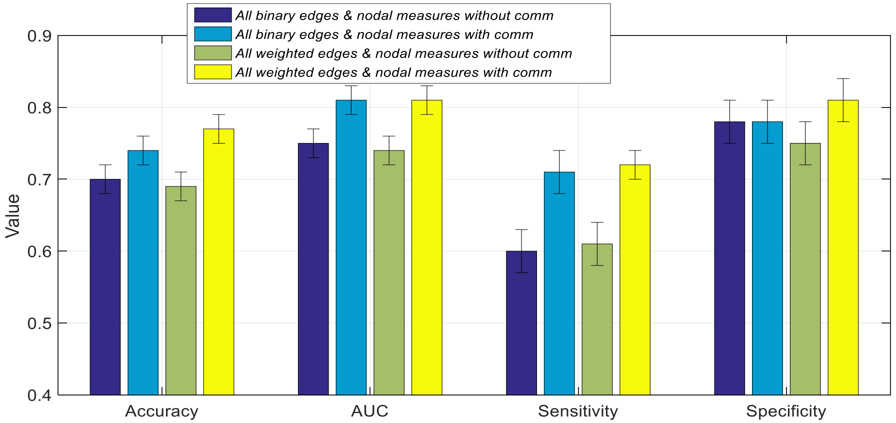
2. Statistical Analysis:
   non-parametric statistical test to find edges with statistical significant different communicability

SECOND CONTRIBUTION: network-based approach on DTI data

Results: classification HC/AD

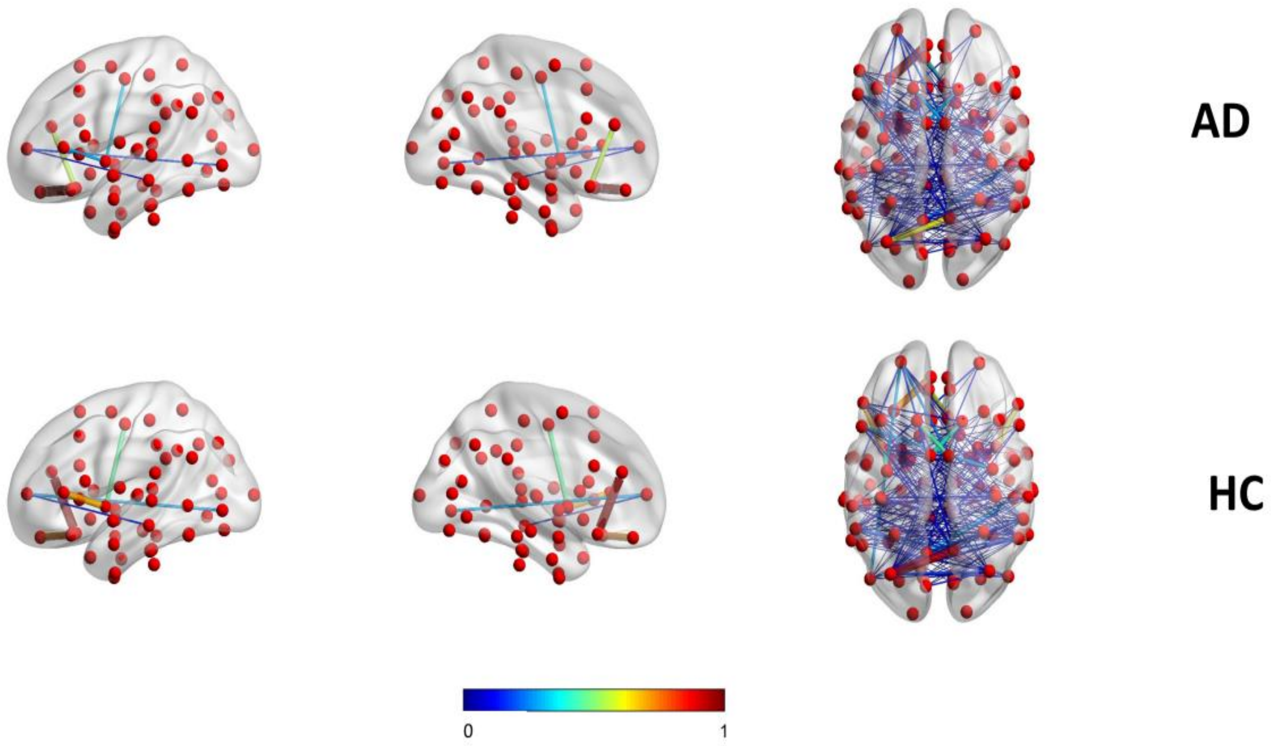






Results: statistical analysis

186 couples of nodes with statistical significant different communicability, involving regions correlated to AD according to the literature



- 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)

FOLLOW UP

- Investigating the advantage to use communicability as feature for the classification between HC and MCI (Mild Cognitive Impairment) and for the 3-class classification (HC/MCI/AD)

- Investigating if this metric can be useful for finding specific patterns in network connectivity discriminating AD from HC brains

- Investigating other measures based on communicability metric (for example using this metric instead of edge betweenness for the community detection)

- Proposing an original metric to better discriminate HC from AD, also in early stages

CONCLUSIONS

The main results of my PhD activity concern:

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

- The design and implementation of a robust methodology for the diagnosis of Alzheimer’s disease with DTI voxel-based features

- The implementation of a DTI network-based approach through the introduction of a metric used for the first time for the discrimination of AD with very promising results;

- The detection of white matter regions related to the disease according to connectivity differences

CORSI

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

SCUOLE E SEMINARI

- 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

- 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

PUBBLICAZIONI

- 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. (*published on February 24, 2017*)

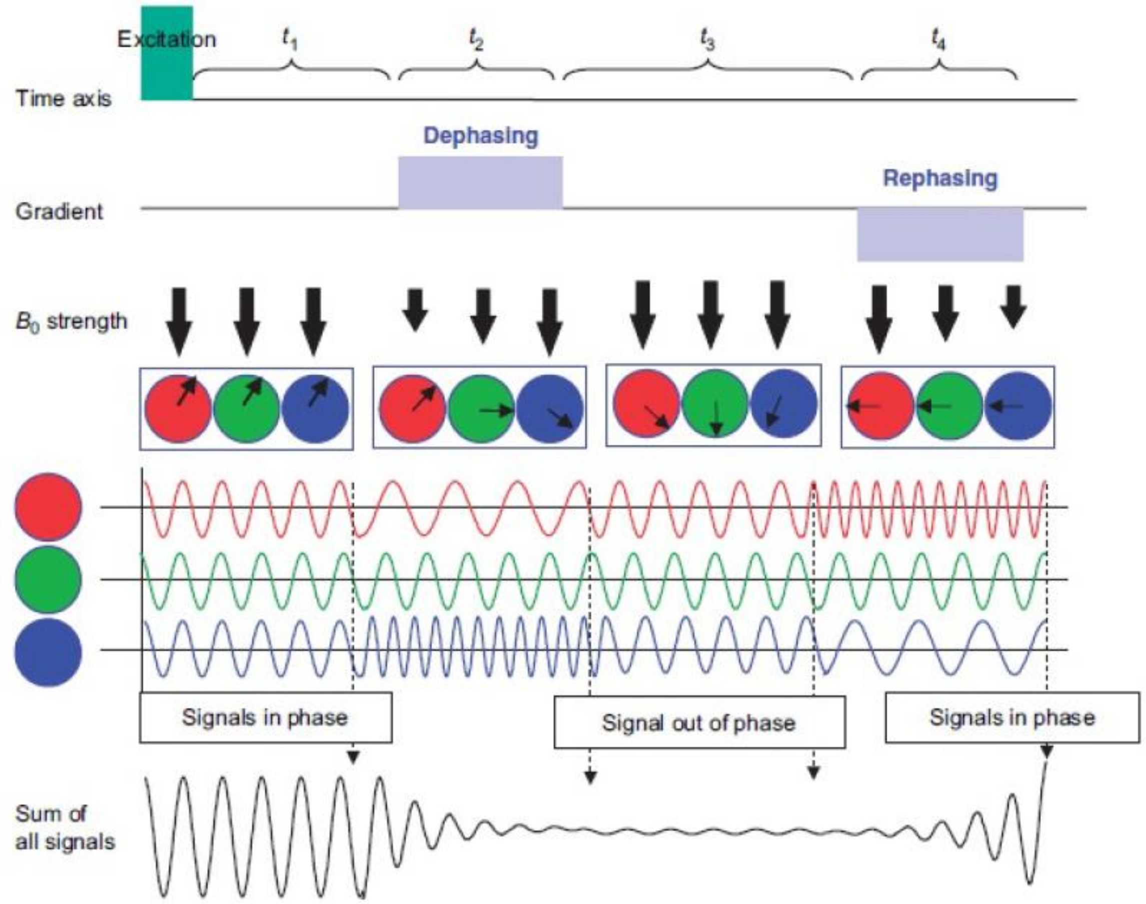
- **Lella, E.**, Amoroso, N., Bellotti, R., Diacono, D., La Rocca, M., Maggipinto, T., ... & Tangaro, S. (2017, September). Machine learning for the assessment of Alzheimer's disease through DTI. In Applications of Digital Image Processing XL (Vol. 10396, p. 1039619). International Society for Optics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

- 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.

- Communicability disruption in Alzheimer's disease connectivity networks (*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

3 CLASS CLASSIFICATION HC/AD/MCI (preliminary results)