Neuroimage analysis

Application to dementia (and brain lesions)
Motivation

**INPUT:**
- High dimensional data
- Multi modal data
- Huge amount of data

**PROCESSING:**
- Machine learning
- Statistics
- Automation
- Complex patterns

**OUTPUT:**
- Observational research
- Interventional research
- Clinical practice
Outline

1. Alzheimer’s disease

2. UPC - FPM research
   a. MRI-based screening: building datasets with subjects at risk.
   b. NeAT: Neuroimaging Analysis Toolbox.
   c. Latent processes governing brain morphology and brain biomarkers.
   d. Longitudinal studies. Relationship between jacobian and biomarkers

3. Conclusions & future work
Alzheimer’s disease

A global epidemic

Clinical diagnosis (probable AD: acc.: 70%):
- Tests: memory, problem solving, etc.
- Questionnaire: daily activities, behavior, personality, etc.

True diagnosis: post-mortem.

Clinical practice: AD defined as a syndrome.
- It gives no clue about its etiology
- Disease modifying therapies must engage biological targets.

Need for a AD continuum definition based on biomarkers that could potentially lead to dementia [1]

Alzheimer’s disease

Biological definition of AD

Using biomarkers for brain state inference. [2]

- **A**: amyloid biomarker (CSF, PET)
- **T**: tau pathology biomarker (CSF, PET)
- **N**: neurodegeneration or neuronal loss (CSF, MRI, FDG-PET)

Cognitive staging:

1. Cognitively normal (CN)
2. Mild cognitive impairment (MCI)
3. Dementia

Alzheimer’s disease

Preclinical stage of AD

Brain alterations appear ~20 years before clinical symptoms appear:
- Better understanding of AD
- Better disease-modifying therapies.

Alterations to the A/T/N profile might occur before clinical and/or cognitive impairment occur.
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MRI-based screening

Goal of the study:

- Devise an MRI-based protocol for screening preclinical subjects:
  - Non-invasive
  - Cost-efficient
- Provide a proof-of-concept study:
  - Use a public dataset to infer the model (ADNI)
  - Apply to private cohorts (HCB)
MRI-based screening

Case study: a proof-of-concept

- Use the publicly available ADNI cohort to build the model
- Use a private cohort to evaluate the model.
MRI-based screening

Results:

- prevalence of preclinical subjects among cognitively impaired subjects (~20%)
- precision
- recall/sensitivity
- \( C_{\text{PET}} \) - cost of a PET scan (~3000€)
- \( C_{\text{MRI}} \) - cost of a MRI scan (~700€)
- \( C_{\text{avg}} \) - average cost of standard screening (~3700€)

\[
\text{Savings}_{CSF/PET} = 1 - \frac{\rho}{P} \\
\text{Savings}_{COST} = 1 - \frac{1}{2C_{\text{avg}}} \left( \frac{C_{\text{PET}}}{P} + \frac{C_{\text{MRI}}}{R} \right)
\]
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Puch et al. VNeAT: Voxelwise neuroimage analysis toolbox. *NIPS Workshop (2016).*

Casamitjana et al. NeAT: Neuroimaging Analysis Toolbox. Application to non-linear modelling of aging and atrophy in Alzheimer's Disease. *MLMI Workshop (Under review).*
NeAT: Neuroimaging Analysis Toolbox

Motivation:

● Standard image analysis softwares include only linear modeling of the brain

Goal:

● Provide the neuroimaging community with non-linear modelling techniques
● Include statistical inference and model comparison
● Work with data preprocessed using different software:
  ○ Voxel-based morphometry VBM (e.g: SPM)
  ○ Surface-based morphometry SBM (e.g: FreeSurfer)
NeAT: Neuroimaging Analysis Toolbox

Toolbox:
- Modular
- Low-memory constraints: batch processing
- Cost-efficient: parallelization of the most demanding tasks.

Usage:
- Command-line interface
- Config file (*.yaml)
- Data loader:
  - Images: *.nii, *.nii.gz, *.thickness
  - Variables: *.csv, *.xls
NeAT: Neuroimaging Analysis Toolbox

Modelling methods:

- **GLM**: General Linear Model
- **PolyGLM**: GLM with polynomial basis expansion.
- **GAM**: Generalized Additive Model
- **PolySVR**: SVR with polynomial kernel
- **Gaussian SVR**: SVR with Gaussian kernel.

Statistical inference:

- **F-test**
- **MSE and R2 coefficient**
- **AIC**: Akaike information criteria
- **PRSS and VNPRSS**: (Variance-normalized) Penalized Residual Sum of Squares.

Model comparison (L statistical maps):

- **ABSdiff / SE maps** \( (L=2) \)
- **Best-fit map** \( (L>1) \)
- **RGB map** \( (L=3) \)
NeAT: Neuroimaging Analysis Toolbox

Validation results: Atrophy patterns across AD continuum.

PolyGLM (magenta), GAM with B-splines (cyan), PolySVR (yellow), GaussianSVR (red) using the ‘Best-fit’ map
NeAT: Neuroimaging Analysis Toolbox

Validation results: Effects of apoE4 in brain aging.

Right Hippocampus
Non-carriers NC (red), heterozygotes HE (green), homozygotes HO (blue)

Right Caudate
HO - 2 copies of ε4 allele
HE - 1 copies of ε4 allele
NC - 0 copies of ε4 allele
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Casamitjana et al. Projection to Latent Spaces Disentangles Specific Cerebral Morphometric Patterns Associated to Aging and Preclinical AD. Abstract accepted in AAIC (2018)

Casamitjana et al. Relationship between CSF biomarkers and structural brain information in the asymptomatic phase of AD. To be submitted.
Latent processes for brain morphology

Goal:

- Disentangle brain aging and brain dementia pattern

Methodology:

- Projection to Latent Structures (PLS)
- Two orthogonal models:
  - Brain aging
  - Brain dementia
Latent processes for brain morphology

**Dataset:**

\[ T_0 := AB \in [230, 295]: N=104, \text{Age}=71.47 \pm 6.07 \]

\[ T_1 := AB \in [175, 230): N=109, \text{Age}=71.49 \pm 5.52 \]

\[ T_2 := AB \in [88,175): N=108, \text{Age}=75.03 \pm 6.36 \]

**Model:**

(A) **PLS - aging**

\[ X \sim \text{age + gender} \rightarrow w_1 \]

\[ Y \sim \text{imaging features (ALL)}. \]

(B) **PLS - dementia**

\[ X \sim \text{biomarkers: AB, PTAU, TTAU} \]

\[ Y_0 \sim \text{imaging features orthogonal to age, computed from PLS-aging} \]

\[ Y_0 = Y - w_1 \cdot w_1^T \cdot Y = (I - w_1 \cdot w_1^T) \cdot Y \]

A single PLS for each ROI (independent).
Latent processes for brain morphology

Relevant regions:

- **Temporal lobe: T0,1,2**
  - Amygdala
  - Inferior temporal
  - Enthorhinal cortex

- **Parietal lobe: T1,2**
  - Postcentral
  - Precentral
  - Paracentral

- **Frontal cortex: T0**
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Petrone et al. Characteristic Brain Volumetric Changes in the AD Preclinical Signature. To be submitted.
Longitudinal studies

Definition:

- For each subject $s_i$ under the study, several visits $L_i \supseteq \{l_{i1}, l_{i2}, ..., l_{iL_i}\}$ are collected. At each visit CSF, MRI and cognitive profile (CP) are collected.

- For each $l_{ij}$ with $j > 1$ quantitative difference is computed for:
  - $d_{CSF} = CSF_{i2} - CSF_{i1}$ → called biomarkers
  - $d_{MRI} = MRI_{i2} - MRI_{i1}$ → called Jacobian features

Goal:

- Show that a preclinical signature is found in jacobian features and they can be used for image classification.
Longitudinal studies

Labels are defined using reference/target Aβ. Analysis is performed at the image level, not in the subject level.

1. A-/A- (Neg)
2. A-/A+ (Conv)
3. A+/A+ without symptoms (Pos)
4. A+(NC)/A+(MCI,AD) (PostMCIAD)
5. A+/A+ with symptoms (Possymp)

Method:
- Correlation between dCSF-A and dMRI
- Statistical maps with relevant correlations through hypothesis testing.
Longitudinal studies

Result 1. Relationship between CSF-MRI.

- Changes in CSF might describe changes in brain morphology in preclinical stages but not in dementia stages.
Longitudinal studies

**Result 2.** Relationship between CSF-MRI.

- There are some regions that experience **atrophy** but others experience **neuro-compensation**.

*Figure 2.* Distribution of jacobian determinant values for each population group (i) normal controls, (ii) preclinical subjects, (iii) MCI/AD, according to brain region of interest (ROIs). Average over significant voxels for each jacobian determinant is provided. Positive values indicate volume expansions and negative values indicate contractions. Units of volume change are arbitrary but consistent throughout the ROIs.
Longitudinal studies

**Result 3.** Group comparison with controls.

- There are some regions that experience **atrophy** but others experience **neuro-compensation**.

Preclinical signature

Dementia signature
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Conclusions

- Dementia = syndrome; **disease = biological continuum.**

- Preclinical stage of AD is key to:
  - Better understanding of the etiology of the disease
  - Design better interventional/therapeutic plan.

- Large scale studies involving Pre-AD subjects might create huge impact on research:
  - Need for cost-effective clinical screening protocols (MRI-based, blood-based).

- Brain morphology follow non-linear patterns along the AD continuum.

- apoE4 is a risk factor for developing AD.
Future directions

- **Observational research:**
  - **Develop and apply multimodal modelling strategies:** design multimodal algorithms that help understanding AD biology and describe brain changes. MRI + fMRI + DWI
  - **Disease progression modelling:** use longitudinal data to model the progression along the AD continuum
  - **Differential diagnosis:** specific patterns for different type of dementia: AD, LBD, FTD

- **Translational research: from the lab to clinic.**
  - **Personalized medicine:** outlier detection for subject specific diagnosis of AD
Contact

Adrià Casamitjana

Image Processing Group (GPI)
ETSETB - TelecomBCN
D5 - 120

adria.casamitjana@upc.edu

@adri_casa (no profesional use, YET)
Outline

- Esquema de la xerrada
- Objectiu: detectar els canvis biològics abans que els clínics
- App 1: necessitem construir bases de dades tant per estudi com per prevenció. Les millors tècniques són cares i invasives. Solucions: machine learning MRI (esmentar blood)
- App 2: nonlinear patterns of atrophy + apoe4 gene.
- App 4: Longitudinal jacobian features: improve classification performance + indicate structural changes.
- Future work:
  - Need for large study cohorts (efforts put in UK biobank, ADNI or Alpha).
  - Translational research.