Imaging biomarkers of neurological disorders: from perfusion imaging to image analysis and machine learning in Multiple Sclerosis

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«Brain Imaging Biomarkers»: From Bench to Bed
General context and challenges in clinical neuroimaging

- **Context:**
  - Expansion of the quantity of data produced and processed in medical imaging (« from the volume to the mass »)
  - Explosion of the ICT available resources

- **Challenges:**
  - To guide the clinician (e.g. a neurologist) within the mass of information to integrate into the medical decision process
  - To guide the surgeon for the exploitation of the different sensors and effectors (e.g. robots) to use in the interventional theater

Focus 1: Imaging markers of grey matter function: Arterial Spin Labelling

- Arterial spin labeling – principles, applications
- Preprocessing the data
  - movement correction
  - coregistration with T1-w
  - denoising and segmentation of T1-w
- Denoising multi-T1 ASL sequence
- Partial volume effects in ASL
- ASL multi parametric estimation (multi-T1)
- Template of normal brain perfusion:
  - Application to functional ASL
  - Application to detect perfusion defect
General consideration about brain function

- Two views about brain functions (Raichle 2010):
  - Event-related activity
  - Intrinsic brain function

Functional ASL

Arterial Spin Labeling (ASL)

- Brain perfusion MRI technique
  - Endogeneous tracer: arterial blood water protons magnetically labelled

1. Magnetic labeling of the arterial blood spins
2. Delay: labelled spins migrate towards the volume of interest
3. Acquisition of the volume of interest: "label image" at time $T_l = inversion time$
   - Acquisition of a 2nd image, without labeling: "control image"
**Arterial Spin Labeling (ASL)**

- **Difference**: perfusion-weighted image
  - Signal depends on the quantity of spins that have perfused the tissue in the volume of interest
  - Proportional to Cerebral Blood Flow (CBF)
  - Acquisition of repeated pairs of label/control images (SNR ↑)
    - Typically 40 to 60 pairs

**ASL – perfusion**

- Difference is around 1-2% of the control image magnitude
- Low SNR - 20-40 pairs necessary
Arterial Spin Labeling

- Endogenous Perfusion MRI technique
- Advantages:
  - Non invasive (no injection, no irradiation)
  - Repeatable, reproducible
  - Quantitative → CBF (ml/100g/min)
- Drawback:
  - Low SNR
- Applications
  - Tumor, epilepsy, dementia [Detre 12]
  - Concordance with FDG-PET
    - Alzheimer’s Disease (AD) [Musiek12, Chen 11]
    - dementia

ASL vs. contrast agent

- Contrast agent
  - injecting agent with different chemical properties than blood
  - need for intervention
  - Contraindications
    + Good SNR

- Arterial spin labeling
  + no intervention
  + using blood as a tracer
  + quantification of the flow in ml/ml.min
  - noisy
ASL - applications

- Completely non-invasive, quantitative -> repetitive studies, healthy patients
- Stroke, neurodegenerative diseases

4h after ischemic Stroke

7 days

Clinical Cases (Stroke)

- 46 years old Women
- Right Facial deficit with aphasia after 2h
ASL Quantification

- Perfusion computed with the knowledge of blood and tissue relaxation [Golay, 99]

• General Kinetic Model [Buxton98]

\[
\Delta M(TI_2) = 2aM_{ob}fTI_1 e^{-TI_2/TI_1} q_p(t)
\]

- ASL Quantification– Mono TI (QUIPSS)

• Without the knowledge of the arrival time \(t_a\) the quantification from a single TI image is not accurate
• Variation of \(t_a\) across brain -> no absolute nor relative comparison of flow

Different flow

Different arrival time

TI 1400ms
ASL – complications

• **Vascular artifacts** – imaging blood in arteries instead of tissue perfusion
• **Transit time** – the arrival of labeled bolus is not instantaneous nor homogeneous around brain
• **SNR**

ASL Arrival time

ASL data processing

ASL series

Motion corr.

Sub. corr.

All PW maps

Mean control

T1-corrig

Normalisation

Smoothing

STATISTICAL ANALYSIS
ASL processing pipeline

- Movement correction
- Co-registration with T1 image
- ASL Denoising of a mono-T1 sequence
- ASL Denoising of a multi-T1 sequence
- Segmentation of T1 image
- Filtering with partial volume correction
- ASL Multi parametric estimation (multi-T1)
- ASL perfusion defect automatic detection

ASL data processing
**Analysis: The template approach**

Petr et al. HBM 2013

- CBF – basal perfusion
- mean std
- Control group
- Template
- Activation detection based on local stats

**Statistical ASL Template**

- Control group
- Patient
Perfusion ASL template: registration

- Template as a mean of all images
- Iterative registration to this template (DARTEL)

DARTEL template – iterations

Template 0  Template 1  Template 2
Template 3  Template 4  Final template
Quantitative identification of voxel-wise patient specific perfusion abnormalities

• Goal: Robust Estimation of the Cerebral Blood Flow in Arterial Spin Labelling

• Method

ROC curves of the homoscedastic and heteroscedastic models

First and second level variance in ASL

• Within-subject variance is not negligible w.r.t. between-subject variance

• Within subject variance can be variable across population

Inter-subject standard deviation (35 healthy subjects)
Detection of perfusion abnormalities

- Model of normal perfusion

\[ \sim N(\mu, \Sigma), \]  

- Detection of perfusion defect with an *a contrario* approach

A contrario approach

- From the computer vision community [Deslnoneux 2003]
**A contrario approach: region-based statistics**

- Rare event count per sphere as region-based statistics

\[ k_v = \begin{cases} 
1, & \text{if } \eta_v^{\text{GLM}} \leq p_{\text{PRE}} \\
0, & \text{otherwise.} 
\end{cases} \]

\[ l_v = \sum_{v \in R} k_v \]

**A contrario approach: Background model**

- From region-based statistics to region-based probabilities

\[ L_v = \sum_{v \in R} K_v \quad \text{with} \quad K_v \sim \text{Bern}(p_{\text{PRE}}) \]

- In MRI, spatial autocorrelation of the noise has been described (e.g. [Chumbley 2009]), independence assumption is therefore not ensured:
  - Rather use a non-independent probability based on the joint distribution of a multivariate Gaussian distribution
**A contrario approach: Thresholding**

- The correction for multiple comparison is usually done by computing the Number of False Alarms (NFA):

  \[ NFA_{(n)} = \text{NumReg} \times \pi_{(n)} \]

- \( \text{NumReg} \) being the number of regions in the images

- Therefore, the detections are outlined with:

  \[ NFA_{(n)} < \epsilon \]

- where \( \epsilon \) is the average number of false detections that can be accepted

- The NFA can be related to Bonferroni correction [Rousseau 2007].

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**A contrario approach: Results**

- Ground Truth
- GLM
- A contrario approach

- Patient 15, FPR = 50%
- Patient 07, FPR = 5%
**A contrario approach: Results**

![Average ROC curves](image)

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**Results: brain tumors perfusion defect detection**

![Images](image)

« Ground Truth » A contrario detection

Patient 020

Patient 006
Application to Semantic Dementia (SD)

- SD: rare subtype of frontotemporal lobar degeneration
  - Loss of word meaning and conceptual knowledge
  - Differentiate AD and SD → imaging techniques

→ Atrophy and hypometabolism in the temporal lobe, left side +++

Preliminary Experiments and Results

- Voxelwise individual statistical analysis on ASL data
  - 1 patient vs healthy template

. p < 0.05 FWE corr. at the cluster level
. cluster defining threshold p < 0.001
Preliminary Experiments and Results

- Voxelwise group analysis
  - Patients vs controls: 10 patients, 12 healthy subjects
  - Age and sex matched

- ASL-PET comparison
Application to functional ASL: motor activation

- Application to functional ASL: motor data

  [Petr et al. HBM 2013]

- Template: 25 subjects
- Tested group: 12 subjects
  - Green: GLM approach (ref)
  - Red: template approach
  - Blue: Anatomical ground truth

fASL vs BOLD: spatial accuracy
Perspective for quantitative perfusion MRI with ASL

- **Major Challenges:**
  - Dynamic imaging with very low SNR: New detection paradigm
  - Estimation of parametric perfusion models (atlases)
  - Brain functional imaging (fMRI vs fASL, towards individual hemodynamic models)
  - Enhance image quality (super resolution, denoising, compressive sensing...)

- **Major Applications**
  - Impact on numerous diseases (markers of disease and of evolution)
    - Stroke, Dementia, Psychiatry, Neuro-developmental, Epilepsy, MS, ...

Focus n°2

Imaging markers in Multiple Sclerosis
Neurological Pathologies:
Neuroimaging in Multiple Sclerosis

**Goal:** To guide the clinician (e.g., a neurologist) within the mass of information to integrate into the medical decision process

- **MS Lesions**
  - Chronic inflammatory-demyelinating CNS disease
  - Lead to acute handicap in young adults (*high prevalence in Brittany*)
  - Most frequent CNS disease in young adults

- **Main Issues and Challenges**
  - Early diagnostic and treatment of the pathology
  - Prevention of disease progression and future handicap
  - Better understanding of the pathology (*new in-vivo classification of MS lesions*)
  - Set-up and evaluate new therapeutic protocols

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**Multiple Sclerosis - a two-stage disease**

**Natural Evolution of Multiple Sclerosis disease**

![Graph showing the natural evolution of MS](chart.png)

*Source: G. Edan, E. Leray, Study on 2054 MS patients, CHU Rennes*
**Segmentation of MS Lesions: a complex workflow**

- **Intensity Normalization**
  - Denoised
  - Inhomogeneity corrected
  - Registered images

- **Robust EM**
  - 3-Class Gaussian Model
  - Robust Expectation
  - Maximization (trimmed likelihood)
  - \( h = n / 10 \)

- **Mean Shift**
  - Non-parametric clustering
  - Joint spatial/intensity domain (\( n+3 \))
  - Bi-weighted kernel (\( b_r = 2.0, b_s = 6 \text{mm} \))

- **Region Fusion**

- **Classification**
  - Each region is assigned to its nearest class
  - Detection of outliers (Mahalanobis dist.)

- **MS Rules**
  - Select lesions from outliers
  - Apply intensity rules
  - MS lesions are contiguous to WM

**Local Processing**

**Global Processing**

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**Results on clinical data**

- Comparative segmentation between Robust EM and regular EM

![Comparative segmentation](image)

- EM (\( \kappa = 0.49 \))
- rEM (\( \kappa = 0.66 \))
- MeS+EM (\( \kappa = 0.43 \))
- rEMMeS (\( \kappa = 0.67 \))
Semi-automatic segmentation of MS lesions using spectral gradient and graph cuts

**Objective:** use multisequence MRI and scale space to end-up with fast and semi-automatic segmentation

**Results:**
- Brain tumor and edema segmentation
- Segmentation of Multiple Sclerosis Lesion (optimal DSC>85% on real data)
- Works on Strokes data

**Results on MS clinical data**

T1-w   Flair   T1-gd

Random decimation   Erosion decimation   "best effort" Result
Magnetic Resonance diffusion biomarkers in Multiple Sclerosis

- **Objective**: Comparative analysis of the normal appearing white matter focal lesions between MS patients and controls from DT-MRI.

- **Method**
  - Definition of the inter hemispheric plane.
  - Computation of the diffusion parameters in lesions (D).
  - Computation of the diffusion parameters in normal appearing contralateral regions (D).
  - Analysis of variance with multiple comparison tests.

**Results**

- FA controls > FA NABT MS patients > FA MS Lesions

**Evolution of neurimaging in MS: USPIO-6 project**

- **Objective**
  - Targeted Patients: CIS (first episode)
  - Cell Labelling with MR imaging using USPIO (Ultra Small superparamagnetic Particles of Iron Oxyde)
  - 8 time points:
    - 1 year follow-up every 3 months with USPIO and Gadolinium
    - 2 years follow-up with quantitative MRI and Gd
    - 16 scalar + 1 tensor volumes per time
  - 36 patients; 20 controls
  - High Dimensional Problem
The novel paradigm

- Investigate the behavior of the disease at onset:
  - Focus on Clinically Isolated Syndrome patients.
- Studying the early deposits of inates macrophages using specific markers is expected to lead to a better understanding of the diffuse pathology and its evolution.
- Ultrasmall Superparamagnetic Iron Oxide Contrast Agent (USPIO) are sensitive to macrophages activity MORE THAN Gadolinium (Gd) that are more related to Brain–Blood Barrier Breakdown

USPIO Contrast Enhancement

T1-w  T1-w / Gd+  T1-w / USPIO+
Longitudinal Study

Pre-USPIO  Post-USPIO

T1 mapping
0-4000 ms

MR Relaxometry
MS lesion detection from MR Relaxation map templates

- **Goal:** Provide a statistical model of Brain structural "fingerprints" from qMRI
- **Challenge:** Built a normal brain template of MR relaxometry maps (T1, T2, T2*, $\rho$)
- **Contribution:**
  - Propose a new pipeline for (T1, T2, T2*, $\rho$) map estimations
  - Generate a 3D qMRI template from probabilistic MR relaxation maps
  - Validate the qMRI template with a true MRI simulator (SimuBloch@VIP)
  - Preliminary applications using the qMRI template (Brain structures « fingerprints », pathology characterization in MS)

MS lesion identification results using qMRI templates. Red outlines representing identified lesion after majority voting on each qMRI map ($P<0.01$, FDR correction)

Lesion pattern and patient classification from USPIO contrast images

1. **Features selection - Spatio-temporal patterns**
2. Lesion representation

Represent the lesions as Tensors of Volumes (voxel)

\[
\sum = \frac{1}{n-1}XX^T = VAV^T
\]

Repeated for two time-points and for Gd and USPIO lesions

\[ f = [\lambda_{x0}, \lambda_{y0}, \lambda_{z0}, \lambda_{x1}, \lambda_{y1}, \lambda_{z1}, \lambda_{x2}, \lambda_{y2}, \lambda_{z2}] \]

Classification framework

1. Classification of lesions
   - Compute sardinality of specific lesion patterns per patient
   - Perform regression at patient level and classify the patients

2. Classification of patients
   - Patient categorization from prediction of severity of evolution

Lesion Classification Layer
Patient Classification Layer
3. FULLY Unsupervised clustering

We devised a two layers classification, first at lesion level and then at patient level: **Nested-Spectral Clustering.**

**Unsupervised clustering:**
- Spectral clustering
- make use of the spectrum (eigenvalues) of a similarity matrix $K$ of the data to perform dimensionality reduction before clustering into fewer dimensions
- $L = D^{-1/2}KD^{-1/2}$
  - $L$: pseudo Laplacien matrix
  - $K$: affinity matrix
  - $D$: Diagonal matrix
- It is repeated twice, once for the lesions and once for the patients

4. Results from USPIO study

- **Classification Layer 1**
  - 3 different groups of early lesions were discovered.
4. Results from USPIO study

- **Classification Layer 2:**
  - Given the lesion pattern classification we use a regression considering the number of lesion pattern in a patient
  - Four different groups of patients were discovered.

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<th>Independent variable</th>
<th>TIL score after 1 year of mild</th>
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- **Conclusion:** Early lesion pattern characterization suggests that belonging to a specific group of patients can have an incidence on the future evolution of the disease.

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