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# Compartments imaging for the characterization of brain diseases from quantitative MRI

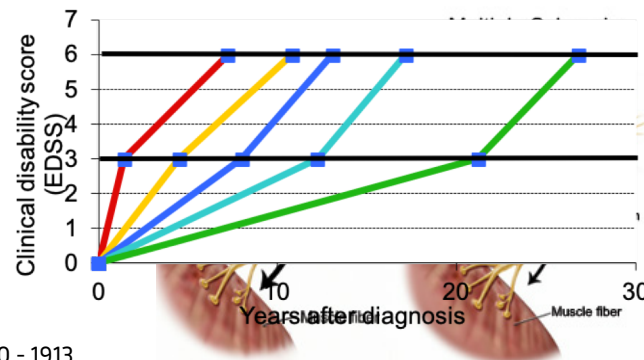
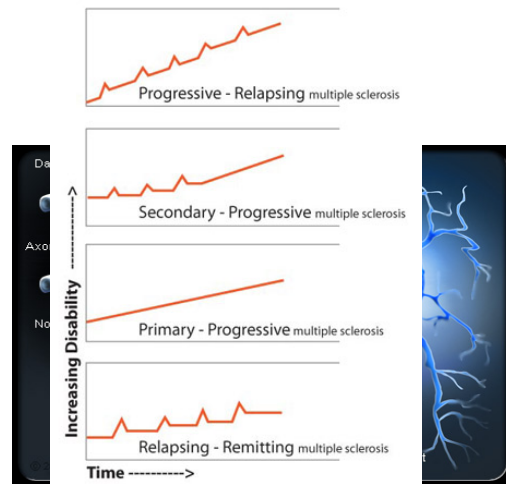
HDR defense - Olivier Commowick  
June 19, 2019

# 01

## General introduction

# Multiple sclerosis

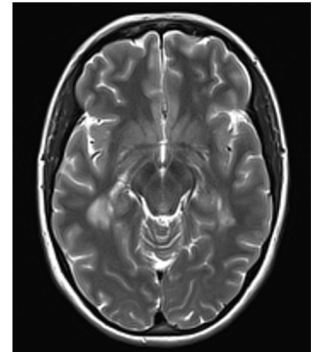
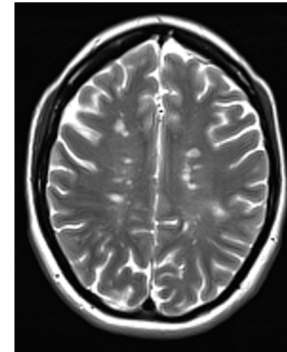
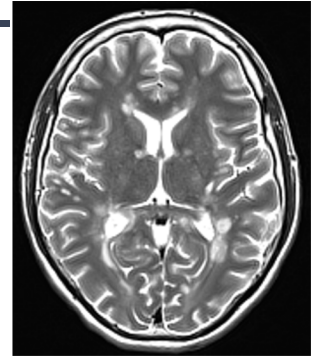
- A central nervous system degenerative disease
  - Auto-immune disease
  - Destructing myelin, leading to increasing handicap
  - ~ 80,000 patients in France
- Highly variable evolution
  - Clinical classification in four types
  - Two main stages
    - Early: variable evolution
    - Later: parallel evolution



Leray, E. et al., 2010. Evidence for a two-stage disability progression in multiple sclerosis. Brain, 133 (7), 1900 - 1913.

# Conventional MRI and the “clinical-radiological paradox”

- Conventional imaging
  - Provides great highlights on tissues
  - Lesion delineation and counting
- Yet not enough
  - No clear link between MRI and clinical scores
- A reason: missing information
  - Lesion position vs fiber tracts
  - Tissue damage

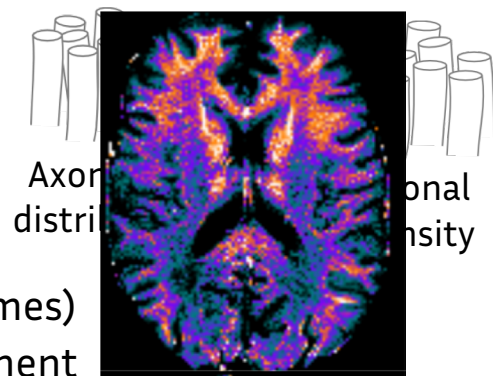
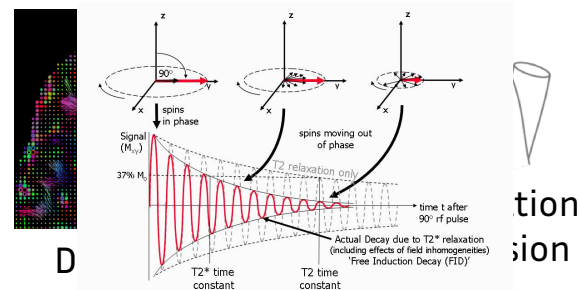


Thompson, A. et al., 2017. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet*, 17 (2), 162 - 173.

Guttmann et al. The evolution of multiple sclerosis lesions on serial MR. *American journal of neuroradiology* 16:1481-1491, 1995.

# Quantitative imaging: a solution?

- Quantitative information on tissue microstructure
  - Much more specific to some properties
  - Can provide interpretable biomarkers of diseases
- Diffusion MRI
  - Characterizes fiber tracts and their properties
  - White matter changes in diseases
- Relaxometry
  - Direct information on tissue properties (relaxation times)
  - Indirect information on myelin content: a key component



# Solving the clinical-radiological paradox

- Quantitative images
  - More specific markers
  - More reproducible between scans (more comparable)
  - Directly interpretable quantities
  - Information invisible in conventional images
    - E.g. position of lesions with respect to fiber tracts
- Put together → could solve the clinical radiological paradox
  - Link between interpretable measures and clinical reality
  - Still many challenges remain

# General challenges (1/2)

- Indirect information
  - 3D water diffusion is not measured directly
  - Neither are T1 and T2 relaxation times
  - Without even talking of fiber tracts or myelin content
- Need for proper models
  - Simple enough to be estimated
  - Able to render microstructure properties
- Need for robust estimation methods
  - Robust enough to artefacts

# General challenges (2/2)

- How to use the obtained models?
  - Compare between patients on meaningful regions
  - Combination for disease understanding
- Need for processing tools
  - Registration between patients
  - Comparison of models
  - Patient to group comparison
  - Longitudinal analysis



# HDR road map

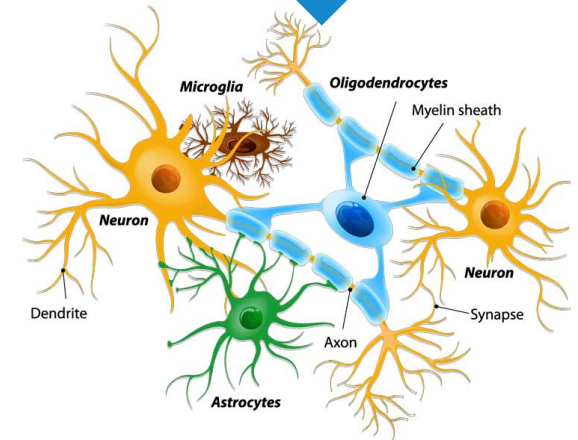
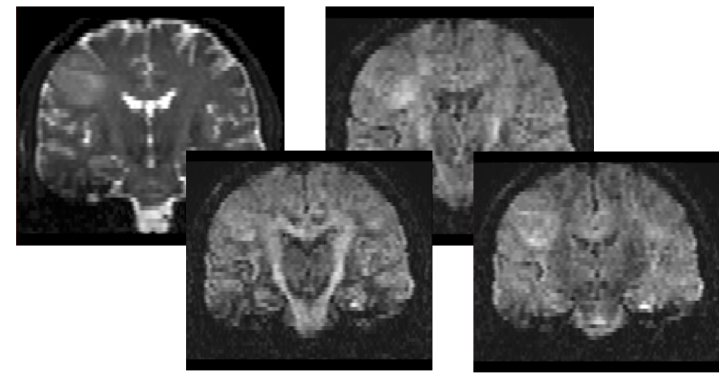
- Diffusion imaging for white matter microstructure imaging
  - Image distortion correction
  - Diffusion compartment models estimation
- Insights on myelin content: relaxometry
  - Modeling relaxation microstructure
  - Model estimation and evaluation on patients
- Quantitative image processing for disease study
  - Patient to group fiber comparison framework
  - Lesion detection from relaxometry and diffusion

# 02

## Diffusion imaging for white matter microstructure imaging

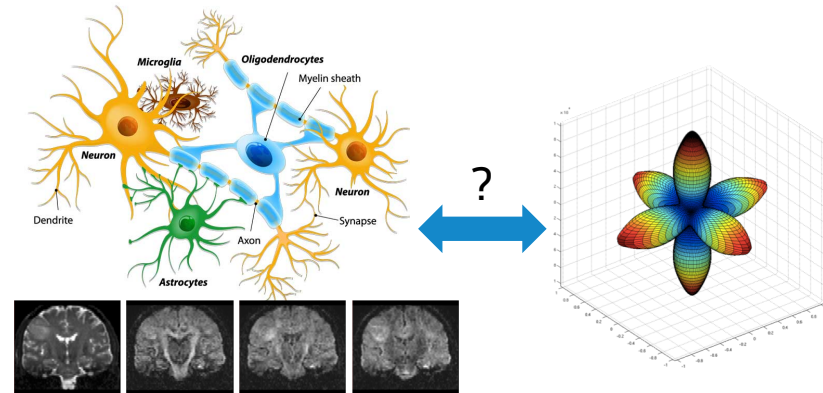
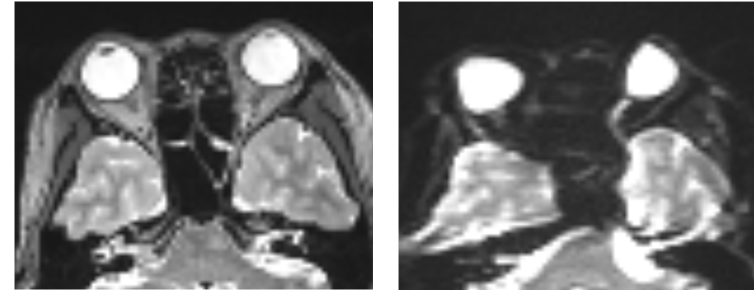
# Diffusion MRI

- Measures constrained water diffusion
  - By underlying tissues
  - Allows imaging white matter microstructure



# Diffusion MRI

- Measures constrained water diffusion
  - By underlying tissues
  - Allows imaging white matter microstructure
- Many challenges are at stake
  - Fast acquisitions: large distortions
  - Which model for diffusion?
    - Simple enough yet meaningful
    - Robust yet generic model estimation



# Signal formation in diffusion

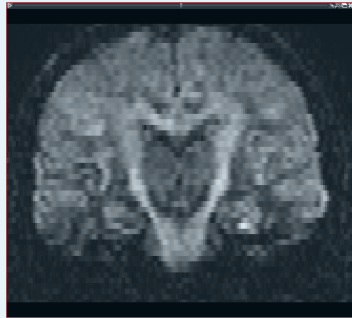
We measure this

Magnetic field gradient

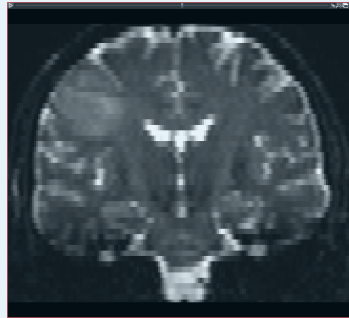
We want to infer that

$$\text{Image} = S_0 \cdot |\text{FT}[p](\mathbf{q})|$$

Image



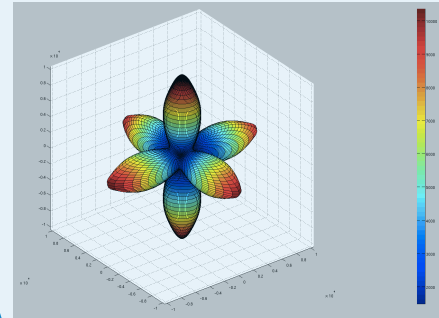
Baseline image



=

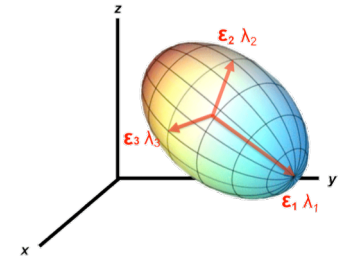
$$\cdot |\text{FT}[p](\mathbf{q})|$$

Diffusion profile



# Limits of simple diffusion models

- Simplest diffusion model: the diffusion tensor
  - Easiest, simple to estimate
  - Able to represent main directions of diffusion
  - Some parameters of microstructure
- Two main problems though
  - Unable to handle fiber crossings
  - Microstructure parameters entangled
    - E.g. free water not differentiated from axonal water

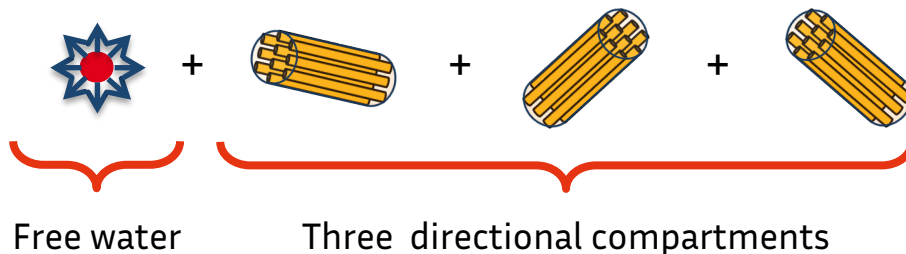


# Diffusion compartment models: going further than DTI

**A simple idea: if one is not enough, use several tensors at each voxel**

- Weighted combination of several compartments
  - Each has a physical meaning → better interpretability
  - Represent diffusion in a given tissue type / fiber bundle

- An example



# Diffusion compartment models: going further than DTI

**A simple idea: if one is not enough, use several tensors at each voxel**

- Weighted combination of several compartments
  - Each has a physical meaning → better interpretability
  - Represent diffusion in a given tissue type / fiber bundle

- A more general formulation  $p = \sum_{j=1}^C w_j p_j \iff S(b_i, g_i) = S_0 \sum_{j=1}^C w_j \varphi_j(b_i, g_i)$

Compartment weight

Compartment model  
(isotropic or anisotropic)

Compartment characteristic  
function



# Diffusion compartment model estimation

- Great potential, however difficult estimation
  - Not an orthogonal basis: highly non linear
  - Not a single compartment model but many
- Our proposition
  - Maximum-likelihood estimation of DCM
  - Generic: agnostic to compartment
  - Based on variable projection for more robustness

Panagiotaki et al, 2012. Compartment models of the diffusion MR signal in brain white matter: A taxonomy and comparison. Neuroimage. 59:2241-2254.

Stamm, A. et al., 2016. Comprehensive Maximum Likelihood Estimation of Diffusion Compartment Models Towards Reliable Mapping of Brain Microstructure. MICCAI, 622 - 630.

# DCM estimation

- General MLE formulation

$$\arg \min_{\mathbf{w}, S_0, \tau^2, \boldsymbol{\theta}} \frac{M}{2} \log \left( \frac{\tau^2}{2\pi} \right) - \frac{\tau^2}{2} \left[ \sum_{i=1}^N \left( S_i - S_0 \underbrace{\sum_{j=1}^C w_j \varphi_j(b_i, g_i)}_{\text{Signal formation model for } (b_i, g_i) \text{ gradient}} \right)^2 \right]$$

Inverse noise variance

Acquired signal

- Variable projection

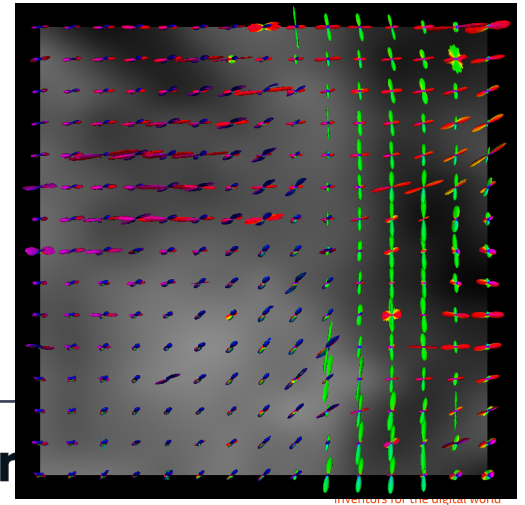
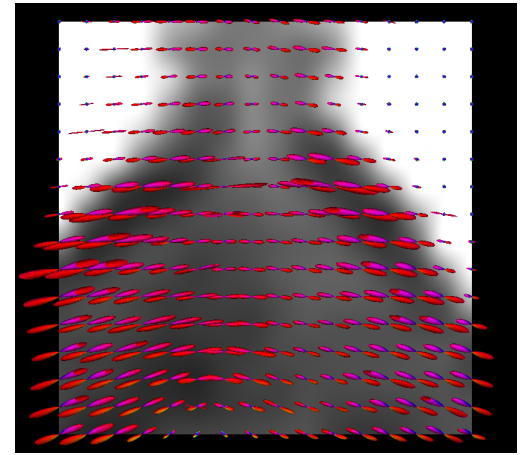
- Replace linear variables by their optimal solution

$$\arg \min_{\boldsymbol{\theta}} \left\| (I_N - \mathbf{F}\mathbf{F}^+) \mathbf{s} \right\|^2$$

- Solving by derivation Matrix composed of patterns  $(b_i, g_i)$  using any optimizer

# DCM estimation evaluation

- Evaluation on simulated data
  - Several configurations (from one to three fibers)
  - In all cases, faster and more robust estimation
- Evaluation on real data
  - HCP data (270 directions on 3 shells)
  - Evaluation on two regions
    - Corpus callosum
    - Centrum semi-ovale
  - More robust estimation



# Summary

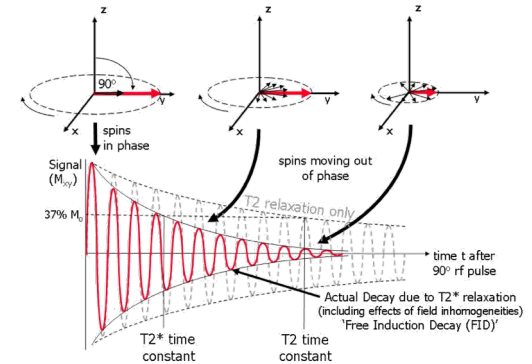
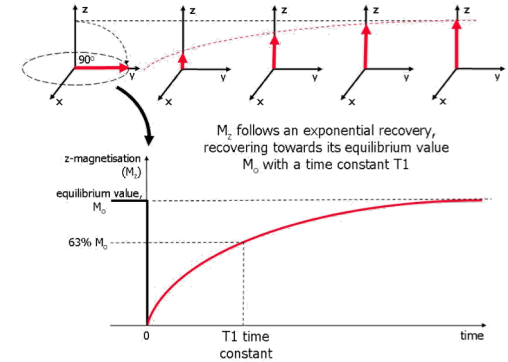
- Diffusion compartment models: great potential for future disease studies
  - Overcomes problems of simpler models
  - Yet simple enough and interpretable
- Many challenges: two explored here by two PhD students
  - Image distortion correction (R. Hédouin)
    - Novel, constrained block-matching approach
  - Model estimation (A. Stamm)
    - Maximum likelihood framework, generic enough to handle any DCM

# 03

## Relaxometry: insights into myelin from MRI

# Why relaxometry?

- Observe quantitative  $T_1$  and  $T_2$  relaxation times
  - Related to tissue contrast in conventional MRI
  - Directly related to tissue properties
- Particular interest in  $T_2$  relaxation
  - Sensitive to myelin (diffusion is not)
  - Insight into its changes due to diseases



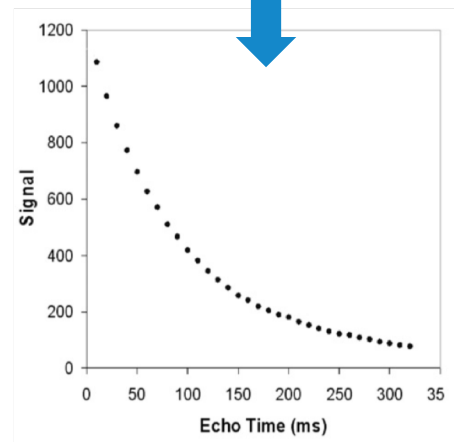
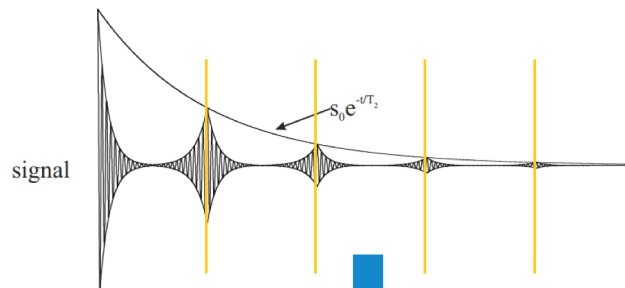
# Measuring $T_2$ relaxation and myelin

- Acquire many signals at a given voxel
  - Each at a different echo time
- Fit a model of  $T_2$  decay along the curve

$$S_i = S_0 \int_{\mathbb{R}^+} p(T_2) A(T_2, e_i) dT_2$$

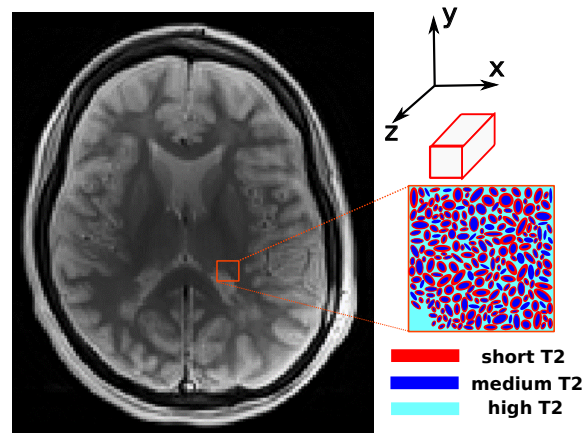
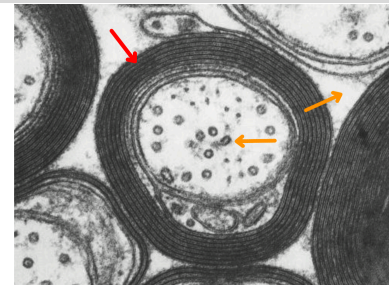
T2 relaxation times PDF

Attenuation function  
at echo time  $e_i$



# Modelling $T_2$ relaxation

- Many different models exist
  - Simplest: mono  $T_2$ , a single peak
  - Most complex: multi  $T_2$ , multiple localized peaks
- Our choice
  - Relaxometry compartment models (RCM)
  - Several compartments each for a  $T_2$  tissue pool
    - Short  $T_2$  e.g. myelin
    - Medium  $T_2$  e.g. cellular water
    - Long  $T_2$  e.g. free water



■ short  $T_2$   
■ medium  $T_2$   
■ high  $T_2$

■  
■ + ■ + ■  
 Short  $T_2$   
 Water Fraction

■  
■ + ■ + ■  
 Medium  $T_2$   
 Water Fraction

■  
■ + ■ + ■  
 High  $T_2$   
 Water Fraction



# RCM definition and estimation

- More precisely:  $p(T_2)$  is a linear combination of three compartments

$$p(T_2) = \sum_{j=1}^3 w_j p_j(T_2) \iff S_i = S_0 \sum_{j=1}^3 w_j \int_{\mathbb{R}^+} p_j(T_2) A(T_2, e_i) dT_2$$

- Challenges
  - Definition of compartment PDFs
  - Signal even less direct than with diffusion
- Positive points
  - Signal formation becomes very similar to DCM
  - Previous estimation methods may be applicable

# RCM estimation

- Our contributions: MLE estimation of RCM
  - Similar to DCM estimation
  - Two proposals
    - Robust estimation: PDF parameters fixed
    - More relaxed estimation: estimate one parameter of a  $T_2$  PDF
- Many evaluations performed
  - Simulated data: robust estimation (to noise and protocol changes)
  - Real data: results robust to test-retest experiments

Chatterjee S. et al, 2017. Gaining Insights Into Multiple Sclerosis Lesion Characteristics from Brain Tissue Microstructure Information: A Multi-Compartment T2 Relaxometry Approach. ISMRM.

Chatterjee S. et al, 2018. Multi-Compartment Model of Brain Tissues from T2 Relaxometry MRI Using Gamma Distribution. ISBI, 141 - 144.

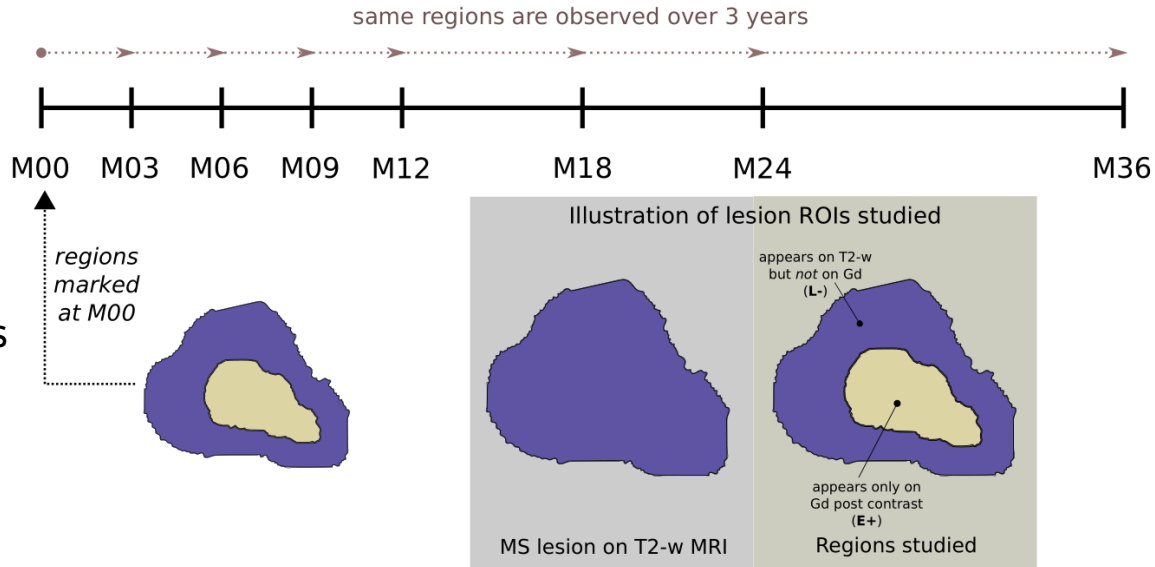
# Longitudinal study of MS patients

- Application study: differences between active and non active MS lesions
  - Mark active and non active lesions at starting point
  - Study of RCM weights evolution at starting point and over time

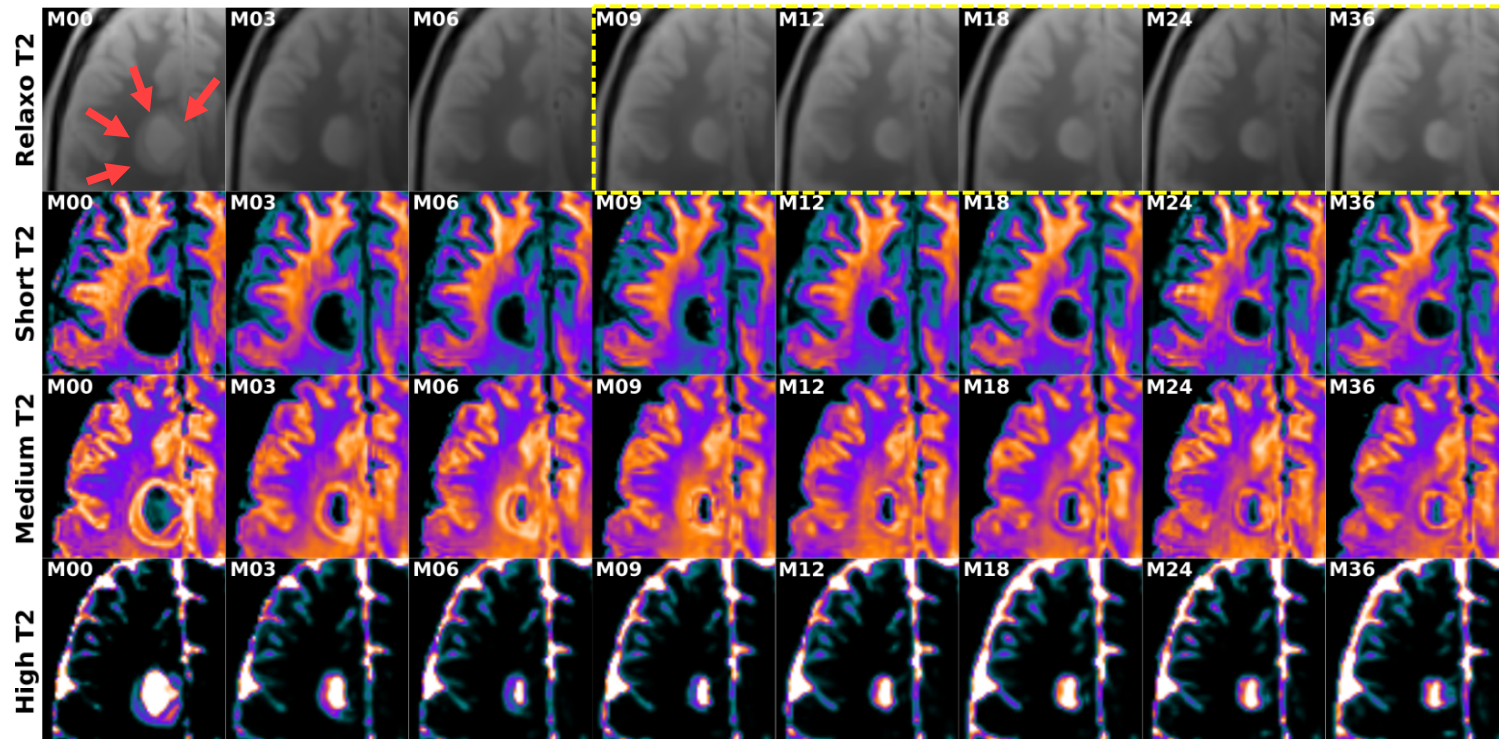
- Protocol

- CPMG sequence
- 7 echoes (13.8ms)
- Resolution:  $1.3 \times 1.3 \times 3.0 \text{mm}^3$

- Estimation with fixed parameters



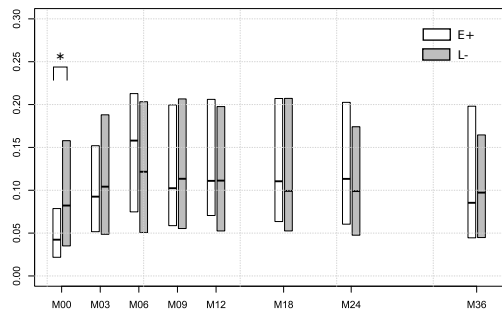
# Illustration of temporal lesion evolution



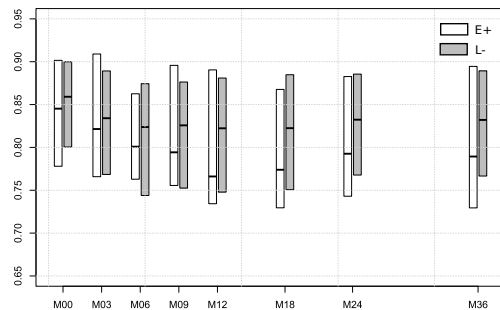
# Quantitative evaluation

- Initial indication of re-myelination in E+ regions
  - Degradation 6 months after baseline
- Higher inflammation in E+ compared to L- at baseline
  - Both subside eventually (< 3 months)

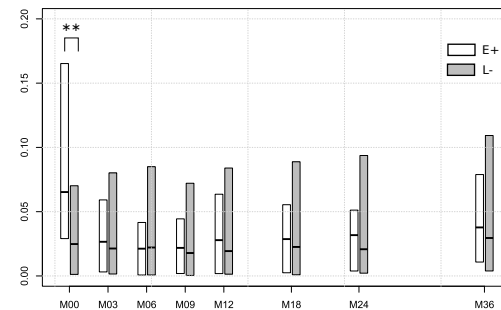
Short-T2 water fraction: E+ vs L-



Medium-T2 water fraction: E+ vs L-



High-T2 water fraction: E+ vs L-



Chatterjee S. et al, 2018. A three year follow-up study of gadolinium enhanced and non-enhanced regions in MS lesions using a MCT2 relaxometry model. *Biorxiv*.

# Summary

- Relaxometry compartment models definition and estimation
  - Explored by one intern and one PhD student
  - Two estimation algorithms proposed
    - One based on fixed PDFs → weights estimation
    - One with one variable PDF → weights and parameters estimation
- Methods have proven their robustness
  - Although PDF parameters estimation is tough
- Initial application on clinical data
  - Ability to distinguish lesion types and evolution
  - Very promising to characterize tissue changes

# 04

## Quantitative image processing for disease study

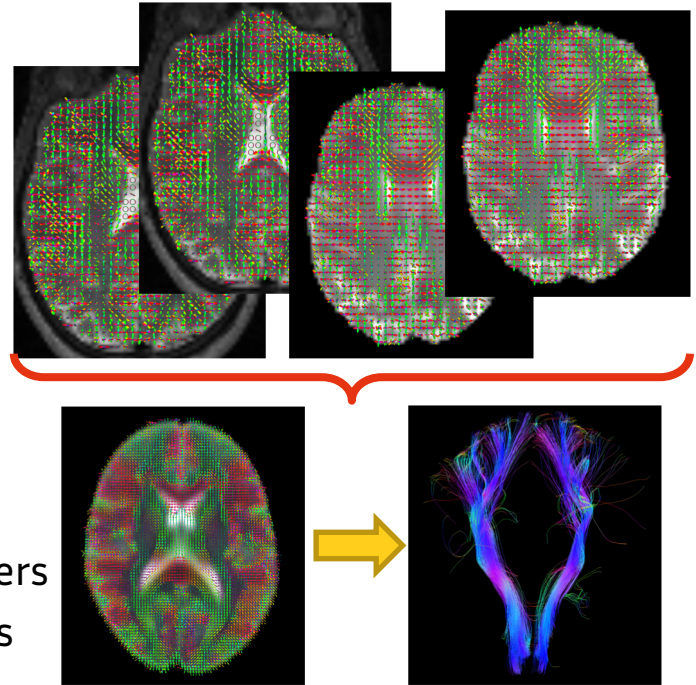
# Quantitative image processing frameworks

- Challenge: how to exploit these new sources of information?
  - Better disease comprehension
  - At the patient and population level
- Two frameworks proposed
  - Atlas-based patient to group comparison
    - Fiber tract based analysis exploiting DCM
  - Joint analysis for active MS lesions detection
    - From DCM and RCM features
    - Without the need of a contrast agent



# Fiber-based patient analysis

- Atlas-based, fiber-based analysis framework
  - Construct atlas from a group of images
    - Reference frame for comparison
    - Extract fibers of interest on atlas
      - Defined at once for all studied patients
  - Register patient on atlas
  - Extract microstructure parameters along fibers
  - Perform appropriate comparison along fibers



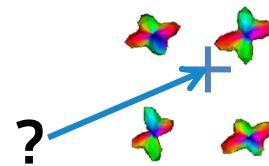
R. Hédouin. *Diffusion MRI processing for multi-compartment characterization of brain pathology*. PhD 2017.

# DCM interpolation

- Atlas construction required
  - Need for interpolation of DCM images
  - Need for DCM averaging technique
- Our proposition: both problems are the same
  - Weighted average of input DCM
  - New framework for DCM interpolation as simplification
    - Builds a huge DCM with all compartments
    - Simplifies it using spectral clustering of compartments
    - Very generic: only needs a distance between compartments

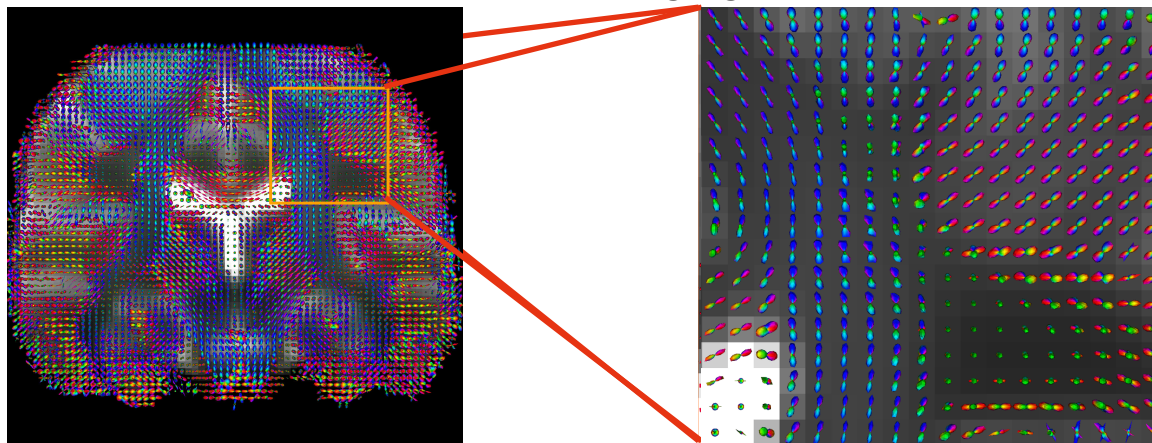


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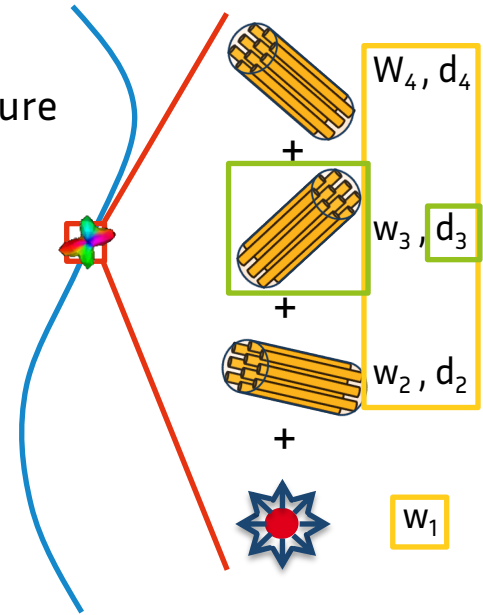
# DCM atlas construction

- Controls atlas construction (from 46 subjects)
  - Atlas built using DT images
  - Application of transformations and averaging of DCM

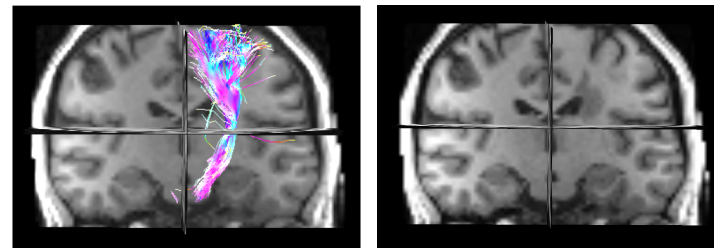


# Fiber-based microstructure information

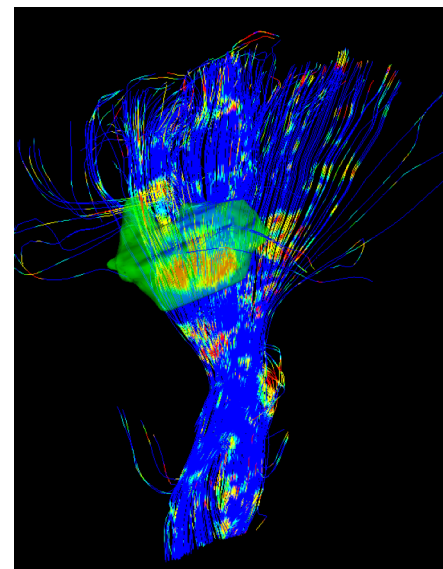
- Two ways to exploit DCM information
  - New, more specific voxelwise parameters of microstructure
    - Directional FA, ADC, ...
    - Isotropic water fractions (free water, glial cells water)
  - Compartment-based microstructure parameters
    - E.g. compartment diffusivity, extra-axonal fraction
    - Great potential: fiber degeneracy evaluation



# Results on an MS patient



- Evaluation on an MS patient
  - Lesions on cortico-spinal tract
  - Diffusion data with 66 directions on 3 b-value shells
- Atlas-based patient analysis on left CST
  - Atlas built from 46 controls
  - Evaluation on compartment ADC and FA
  - Much more specific than lesion count or global ADC



Compartment ADC and FA on left CST

R. Hédouin. *Diffusion MRI processing for multi-compartment characterization of brain pathology*. PhD 2017.

# Detection of active MS lesions from quantitative MRI

- Objective: get rid of contrast agent for MS active lesions detection
  - Gadolinium accumulates in tissues
  - Some counter-indications
- Quantitative images show microstructure changes
  - **Our hypothesis:** DCM and RCM could replace Gd for active lesions detection
- Our method
  - Learn active lesions patterns from a set of quantitative MRI features
  - Apply the learned model to new patient lesions

S. Chatterjee et al. Identification of Gadolinium contrast enhanced regions in MS lesions using brain tissue microstructure information obtained from diffusion and T2 relaxometry MRI. MICCAI 2018, 63 - 71.

# Machine learning scheme

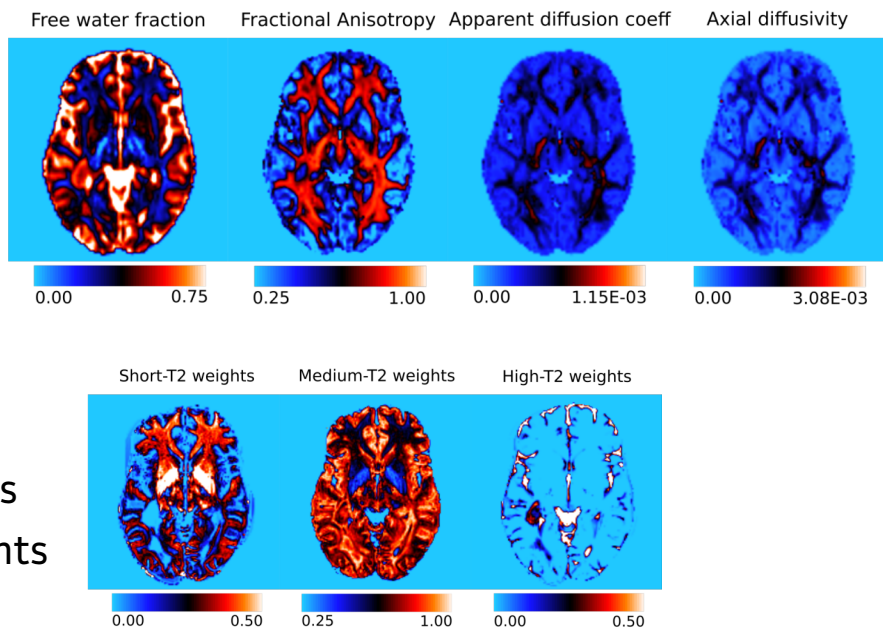
Training Images

15012 (L-)

3904 (E+)

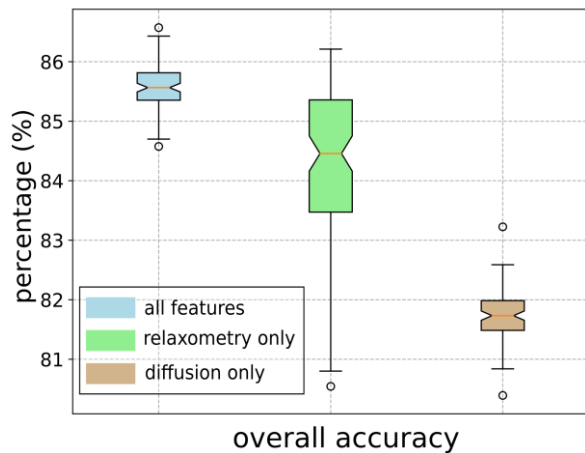
# Quantitative MRI features

- Two sets of features
  - Diffusion MRI features
    - Ball and zeppelin model
    - Directional FA, AD, MD
    - Free water weight
  - Relaxometry
    - Model with fixed PDF parameters
    - Short, medium and high  $T_2$  weights

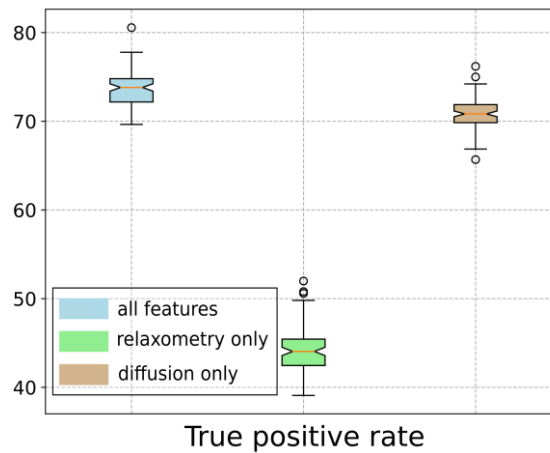




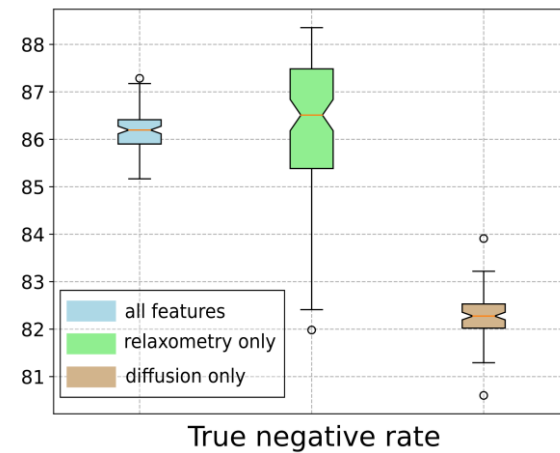
# Detection results



Overall accuracy improves when combining features



Diffusion better at detecting E+ voxels

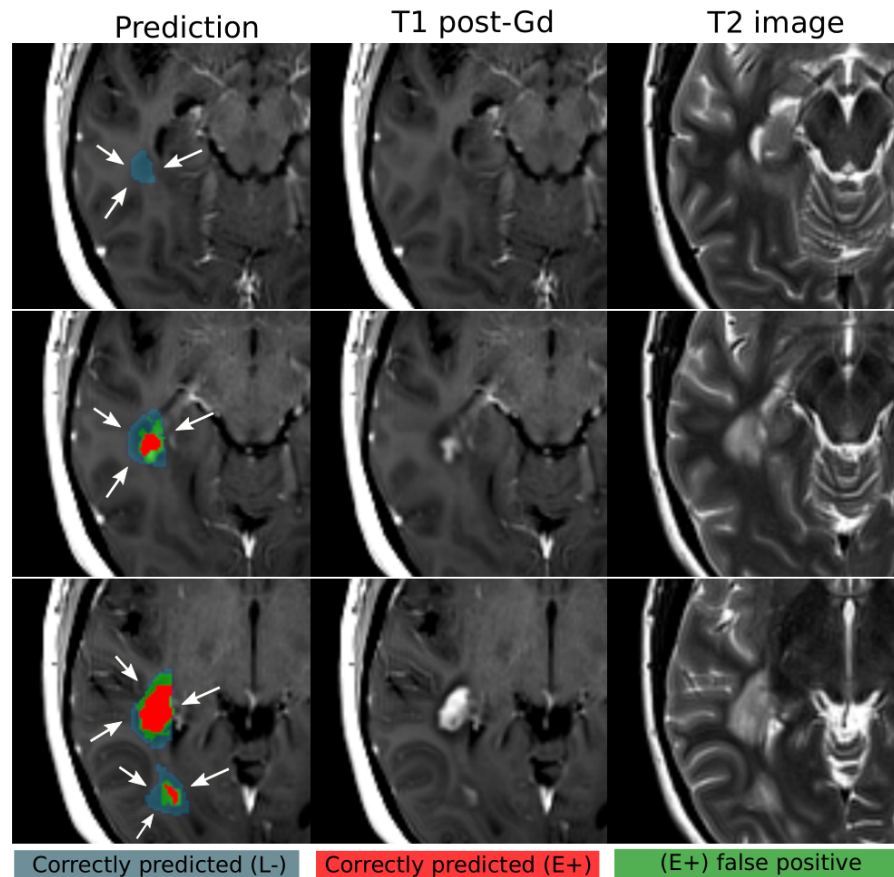


Relaxometry better at detecting L- voxels

# Detection results

## Dice scores

E+	0.64
L-	0.86



# 05

## General conclusion

# General conclusions

- Quantitative MRI: great promises for better disease understanding
  - Diffusion MRI: brain architecture and some of its properties
  - Relaxometry: a great tool for myelin evaluation
- Combined: could lead to great advances
  - Very promising results
  - Specific changes along fibers
  - Combined diffusion and relaxometry to get rid of contrast agents
- Quantitative MRI needs proper tools though

# General conclusions

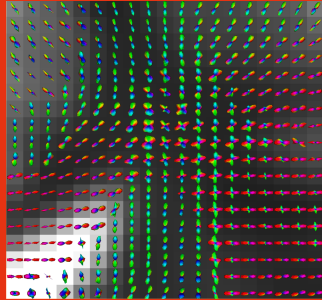
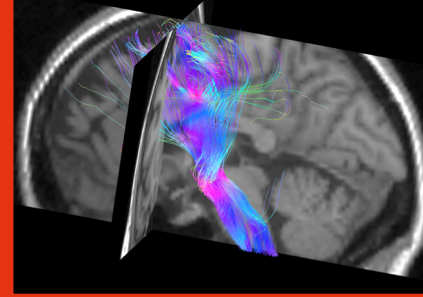
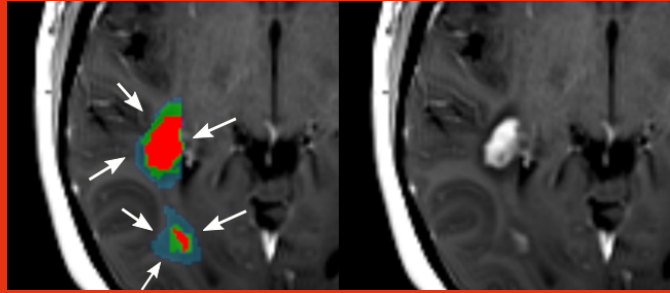
- Diffusion MRI challenges explored
  - Image distortion correction (PhD of R. Hédouin)
  - What model? DCM good for its interpretability
  - Compartment definition (PhD of A. Stamm)
  - Model estimation (collaboration with A. Stamm)
- Relaxometry challenges explored (PhD of S. Chatterjee)
  - Model definition and estimation (including optimization stability)
  - Sequence optimization
  - Combination with other modalities

# General perspectives

- Diffusion MRI
  - More robustness (forbid compartments switching)
  - Making more out of old acquisitions (priors)
  - Registration of DCM images
  - Exploiting new gradient schemes
- Relaxometry
  - Trying to solve estimation instability
  - Combined relaxometry and diffusion estimation
  - Towards faster acquisitions

# General perspectives

- Exploring other quantitative modalities
  - E.g. QSM: opportunity to measure iron
  - Get a full view of brain microstructure
- Need for larger studies
  - Constitute large quantitative MRI databases
  - Longitudinal studies (HCP lifespan like)
  - Atlas construction from quantitative modalities
- Explore other diseases / conditions
  - Applicability to children / preterm-born



# Questions?

