

# Modeling biological water diffusion in complex tissues

Tiago Monteiro Cardoso

Advisor: Prof. Silvia Capuani



SAPIENZA  
UNIVERSITÀ DI ROMA

# 1. Nuclear Magnetic Resonance - NMR

**This thesis consists of simulations of NMR experiments and aims at optimizing its use in biomedical applications**

- NMR measures water diffusion inside biological tissues.
- The exam uses our own bodily water as a contrast to probe micro-structures.
- Two kinds of simulation spaces studied:
  1. Equal-diameter spheres
  2. White matter axons



# NMR / Normal diffusion theory

- The fundamental result of NMR imaging: the **acquired signal** and the **ensemble average propagator** have a Fourier relation:

$$S(\mathbf{q}) = \int P(\mathbf{R}) e^{2\pi i \mathbf{q} \cdot \mathbf{R}} d\mathbf{R} \quad ( \mathbf{q} = (2\pi)^{-1} \gamma \delta \mathbf{g} ) \quad (1)$$

- Since the solution for the diffusion equation (  $\frac{\partial \rho(\mathbf{x},t)}{\partial t} = D \frac{\partial^2 \rho(\mathbf{x},t)}{\partial x^2}$  ) is a Gaussian propagator:

$$\rho(x, t) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{(x-x_0)^2}{4Dt}} \quad (2)$$

- We can derive a simple expression to link the acquired signal and the single parameter D:

$$\frac{S}{S_0} = e^{-bD} \quad (3)$$

# NMR / Anomalous diffusion theory

- Biological tissues are heterogeneous systems. The assumptions underlying normal diffusion theory don't hold.  
(e.g., the PDF of individual displacements must have finite variance)
- Continuous Time Random Walk – CTRW: a more general framework for describing diffusion. It proposes a generalization of the diffusion equation:

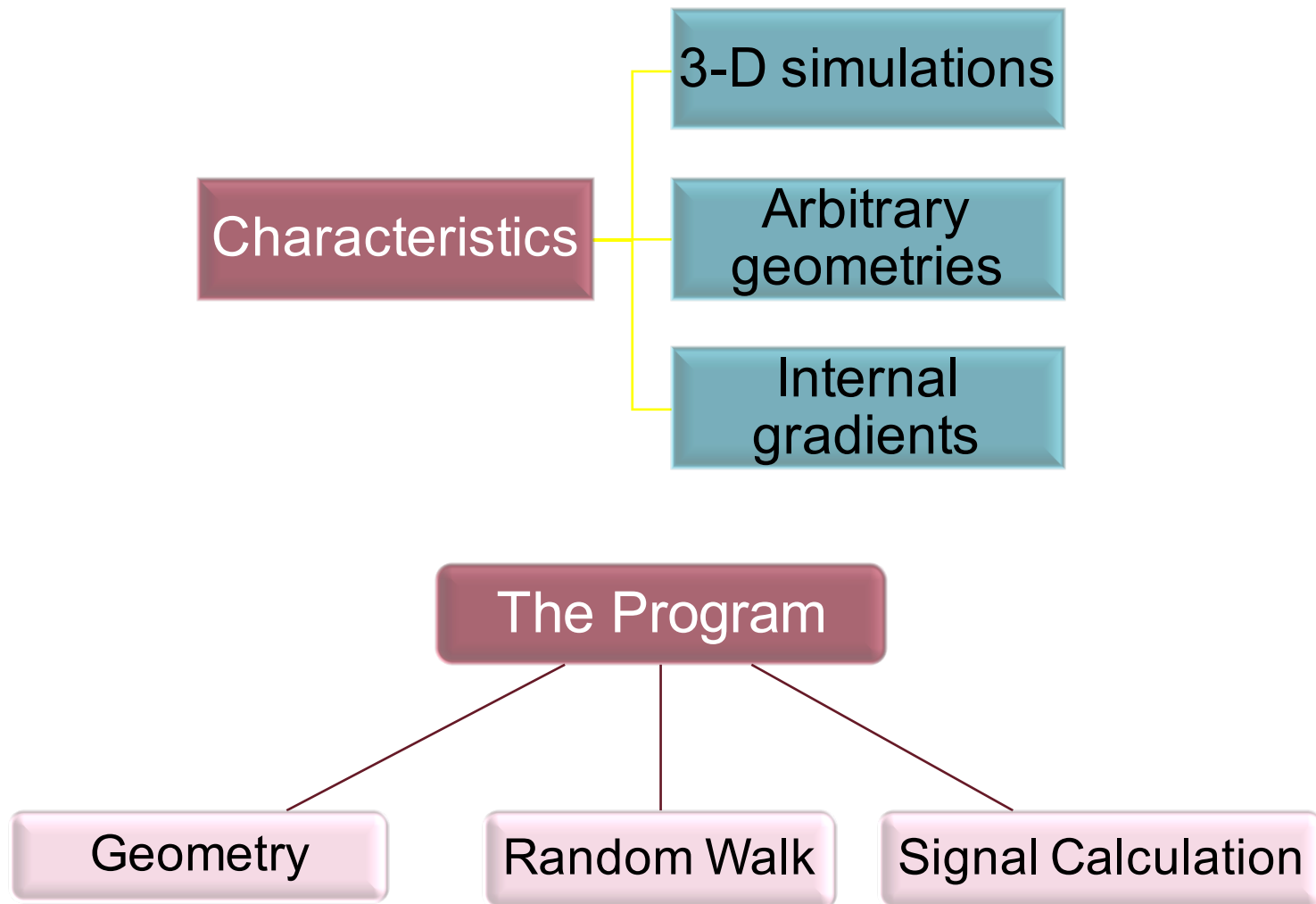
$$\frac{\partial^\alpha \rho}{\partial t^\alpha} = D_{\alpha,\mu} \frac{\partial^\mu \rho(x,t)}{\partial |x|^\mu}, \quad (4)$$

- whose solution propagator is a one-parameter **Mittag-Leffler function**:

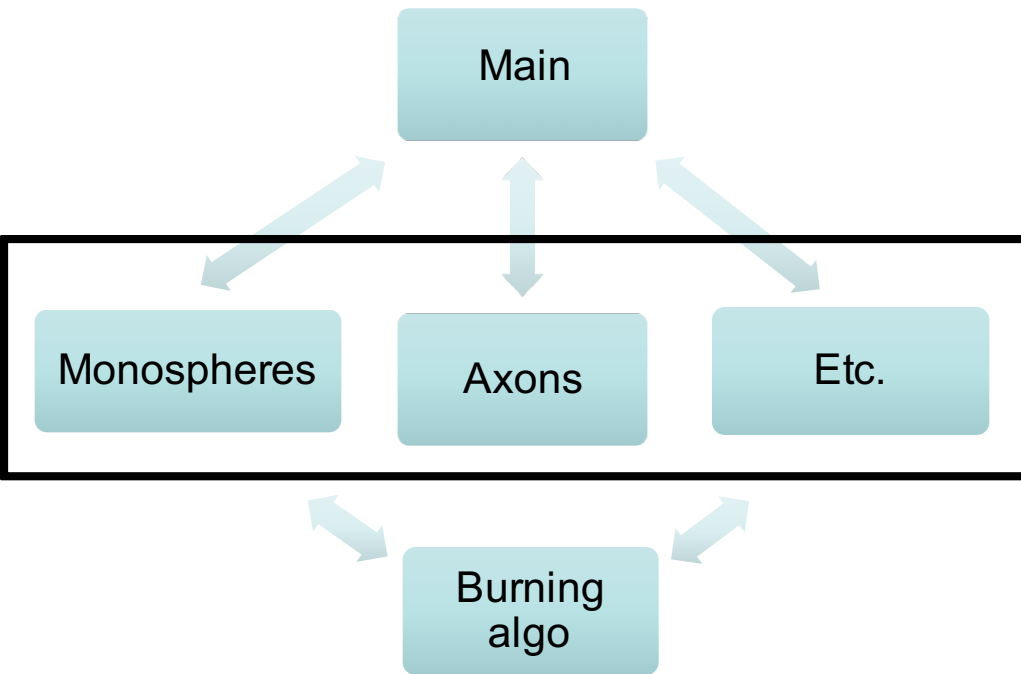
$$\rho(q, t) = E_\alpha (-D_{\alpha,\gamma} |q|^{2\gamma} t^\alpha) \quad (5)$$

$$(E_\alpha(z) = \sum_{i=1}^{\infty} \frac{(z)^i}{\Gamma(\alpha i + 1)})$$

## 2. The Simulation software

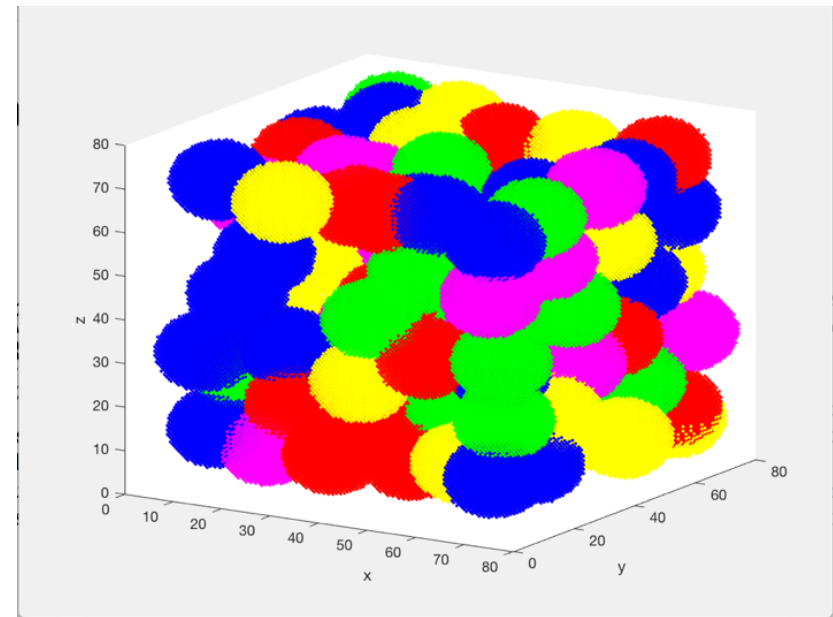


# The Geometry Block



**Modular subroutines:** create the geometry


Ex.: 100 spheres in a 62% packing ratio



**Fixed subroutine:**  
'digitalizes' the  
space (cells) and  
classifies the cells

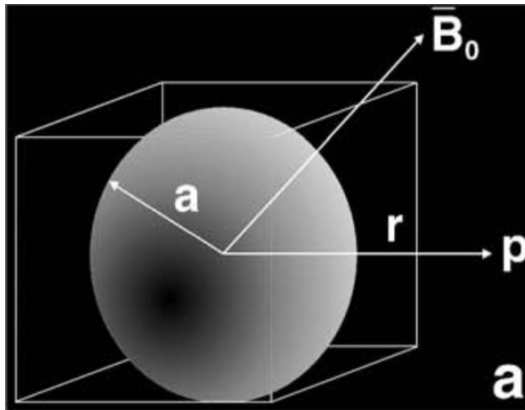
# The Random Walk Block

## Highlights

- Avoidance of wall effects (simulations limited to central region (60% of total space)).
- Avoidance of surface effects (periodic boundary conditions).
- Realistic trajectories: 
  - Normal step
  - Reflecting wall condition
  - Movement retrial

# The Signal Calculation Block

- **Basic Signal Calculation.** Departs from pre-selected range of gradient strength values.
- For each gradient, it calls the Random Walk Block and calculates, for every trajectory, the accumulated phase:  $\Delta\phi = \gamma dt \sum_{j=1}^{numsteps} g \hat{k} \cdot \vec{r}(j)$ .
- Calculates signal attenuation as the ensemble average:  $S/S_0 = \frac{1}{N} \sum_{n=1}^N \cos(\Delta\phi_n)$ .
- **Signal Calculation with the contribution of internal gradients (Finite Perturber Method):**



The solid structure is divided in small spheres (analytical solution for the field is known):

$$\Delta B_{cell}(x, y, z) = \left(\frac{6}{\pi}\right) \frac{\Delta\chi}{3} \frac{a^3}{r^3} (3 \cos^2 \theta - 1) B_0$$

- Fits signal decay to two models:  $\left\{ \begin{array}{l} S/S_0 = E_{\alpha}(-(bD)^{\gamma}) \text{ (Mittag-Leffler model-ML)} \\ S/S_0 = \exp(-(bD)^{\gamma}) \text{ (Stretched Exponential model-STR)} \end{array} \right.$



# 3. Simulations of mono-dispersed spheres

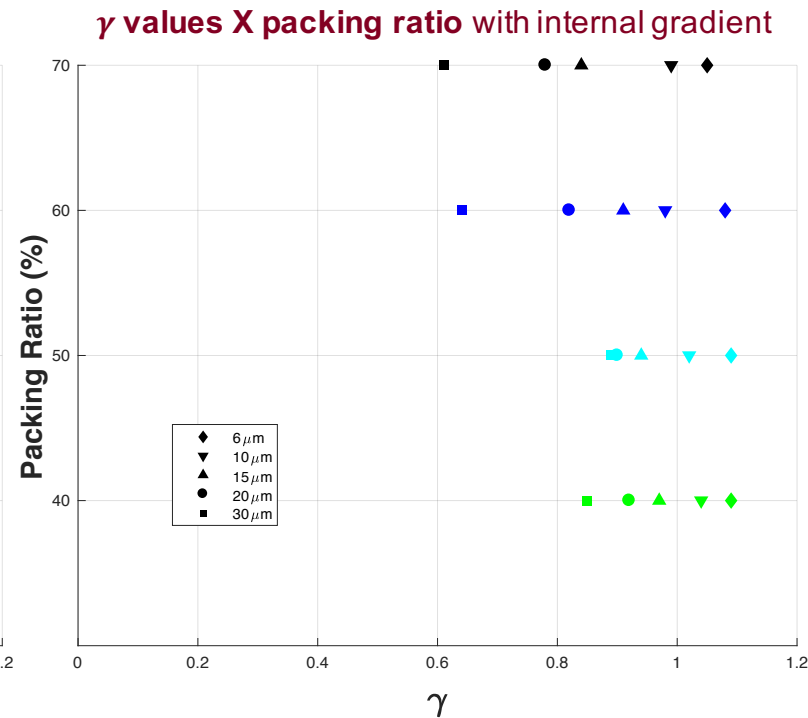
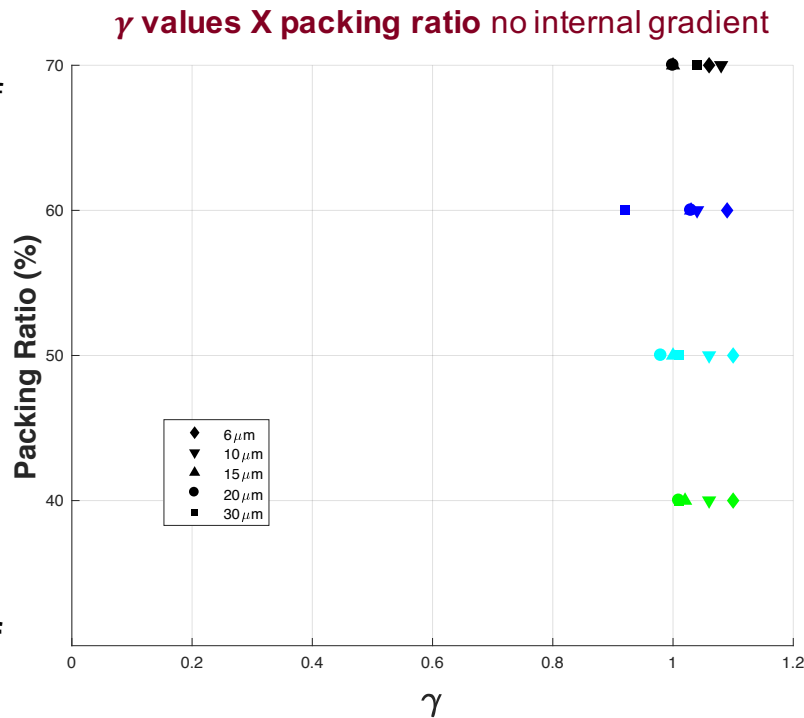
Results: diverse configurations in very high gradients

- Physical systems studied by the Sapienza NMR Group:
  - random dispersed spheres (6, 10, 15, 20 or 30 $\mu\text{m}$ )
  - in 4 packing ratios (40, 50, 60 or 70%)

## Main result

(confirmation of the hypothesis of "pseudo-superdiffusion" (JCP 135, 034504 (2011)))

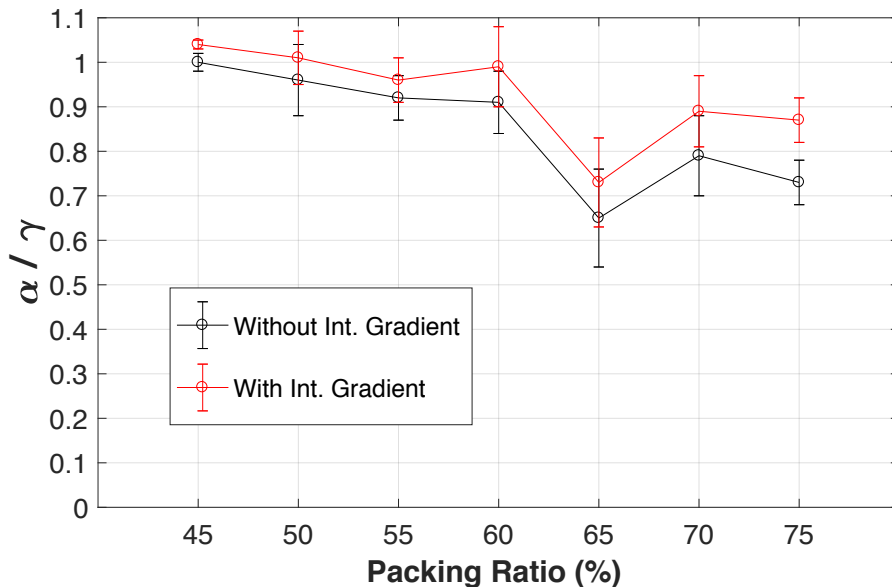
The anomaly of the space parameter -  $\gamma < 1$  - is in practice due to the effect of internal gradients.



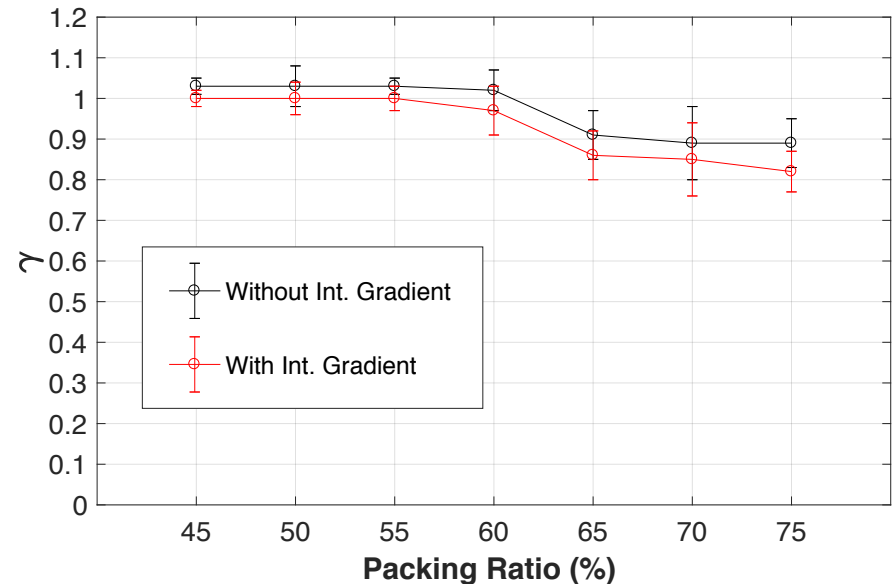
## Results: comparison of 5 and 10 $\mu$ m-spheres in 7 packings (45 - 75%)

- Second result.** Confirmation of a finding by the Sapienza group: **the anomalous diffusion parameter is able to identify structural transition (SPT) in a heterogeneous system** (*Scientific Reports*, 3, 2631 (2013)).

$\alpha/\gamma$  X Packing ratio (ML model / 10-micron-spheres)



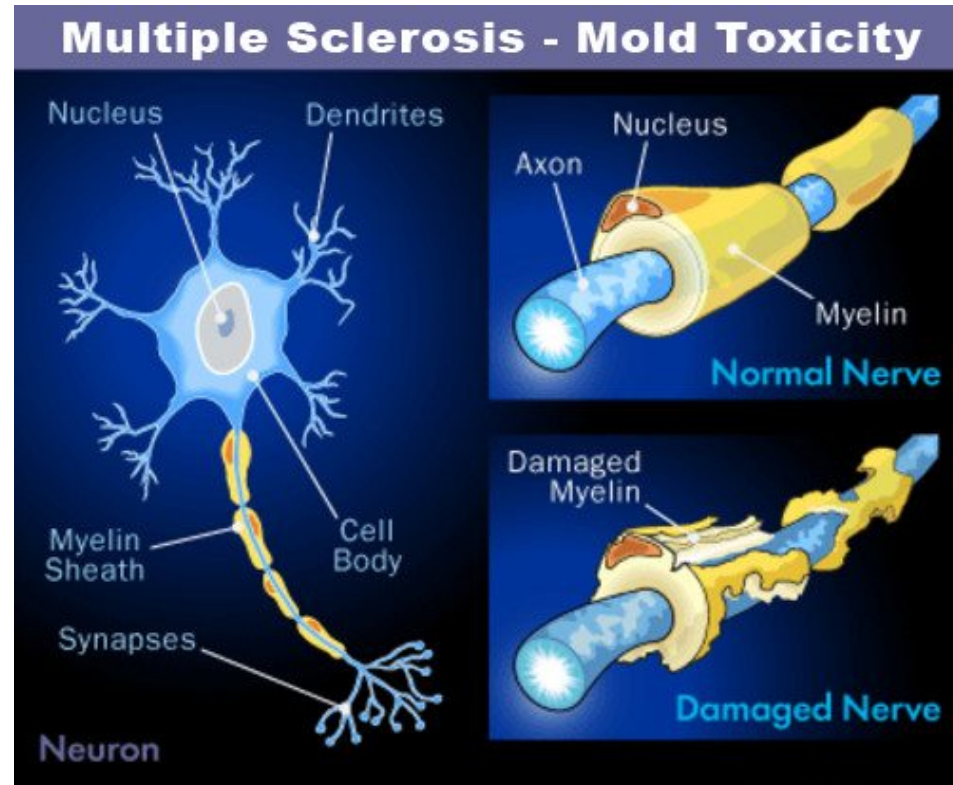
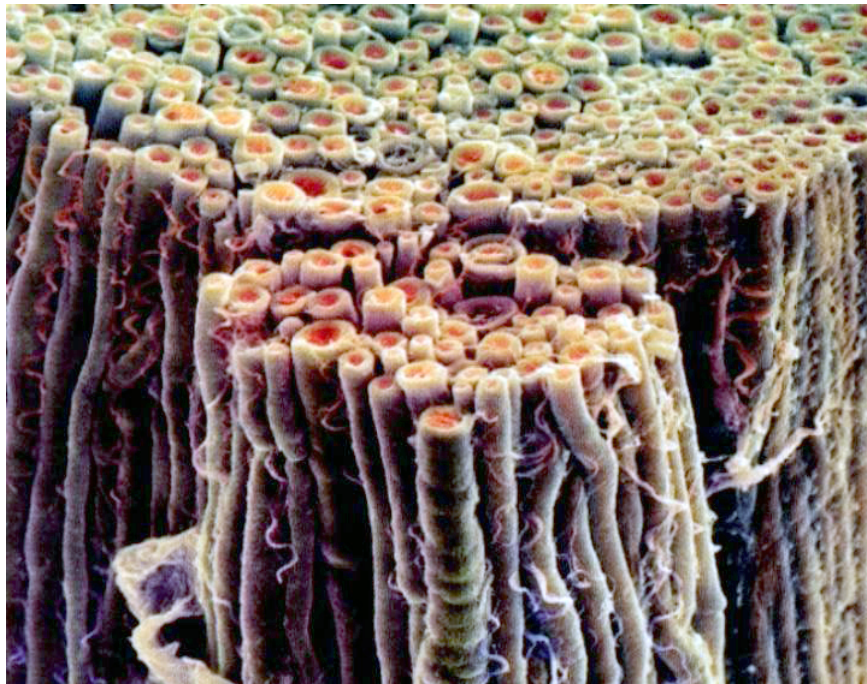
$\gamma$  X Packing ratio (STR model / 10-micron-spheres)



- However, data seem to suggest that this result does not hold in every scale ( cf. 5-micron-spheres).

## 4. Application: detecting demyelination in white matter tracts

- Goal: to search for a new biomarker for the early diagnosis of demyelinating diseases.

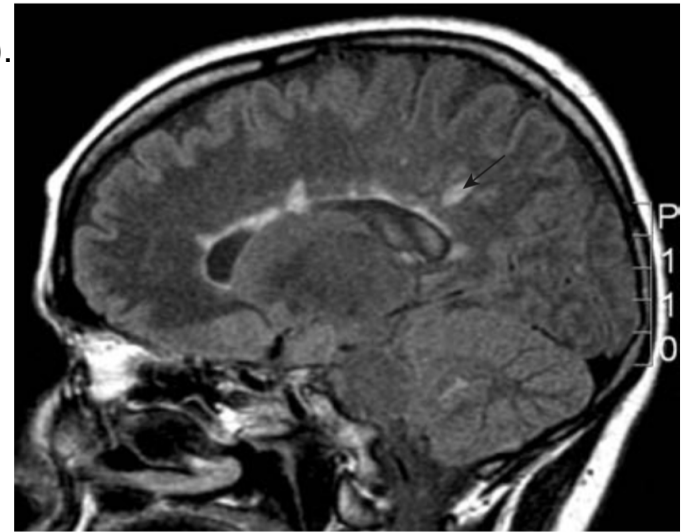
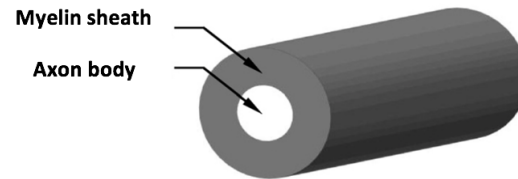
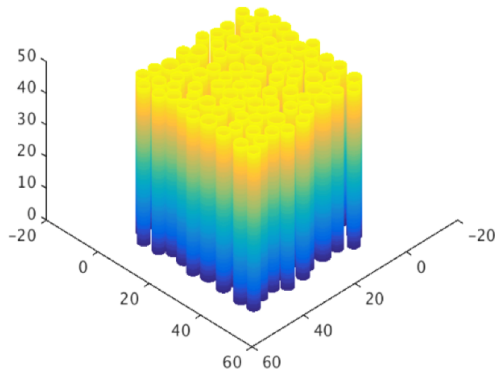


- I decided to model Multiple Sclerosis.

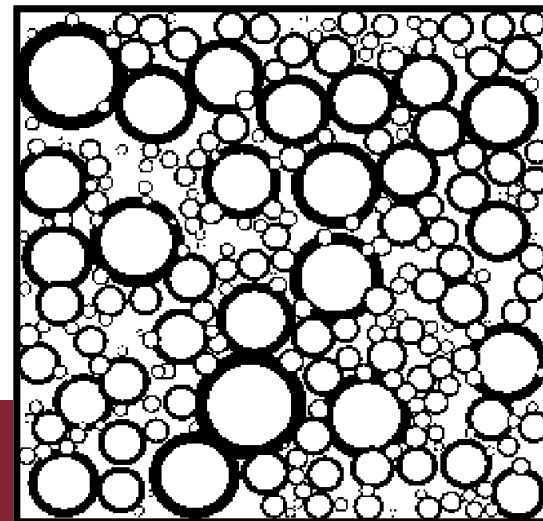
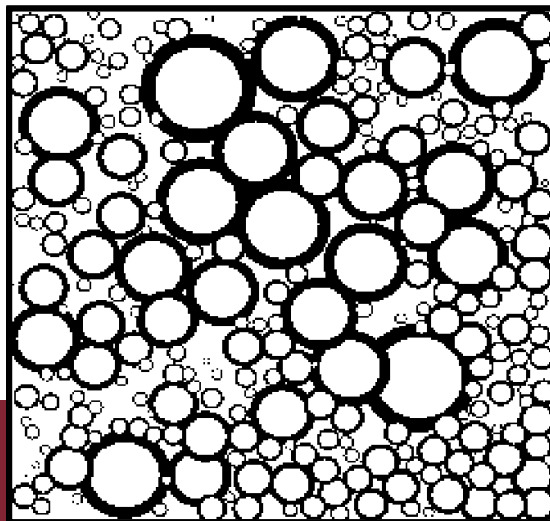
# Modelling the axons

- Choosing a proper ROI. Requirements:
  - 1) Potential for use in diagnosis.
  - 2) Availability of metrics.
  - 3) Potential for NMR detection.
- The corpus callosum fulfills the conditions ("Posterior Body").

## The model:

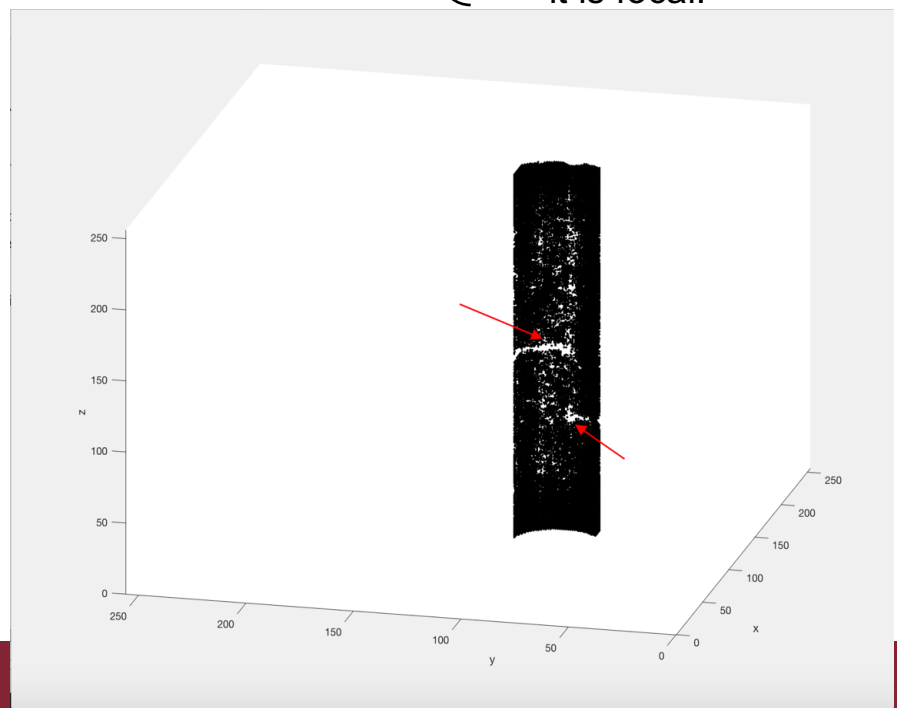
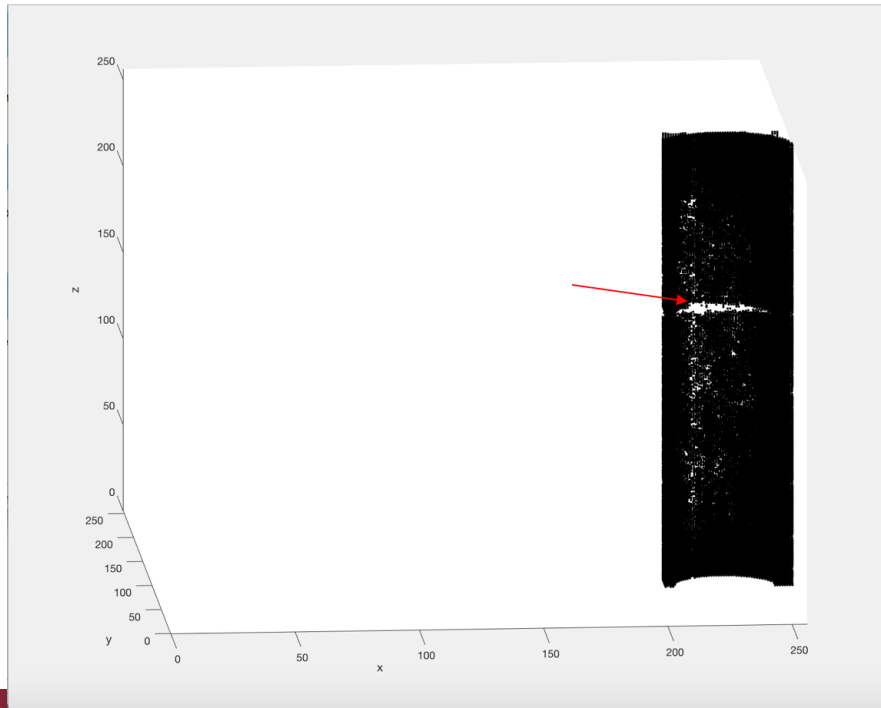
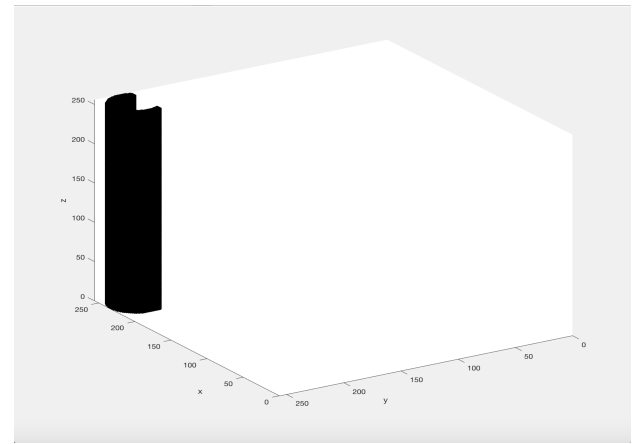


## The outputs:



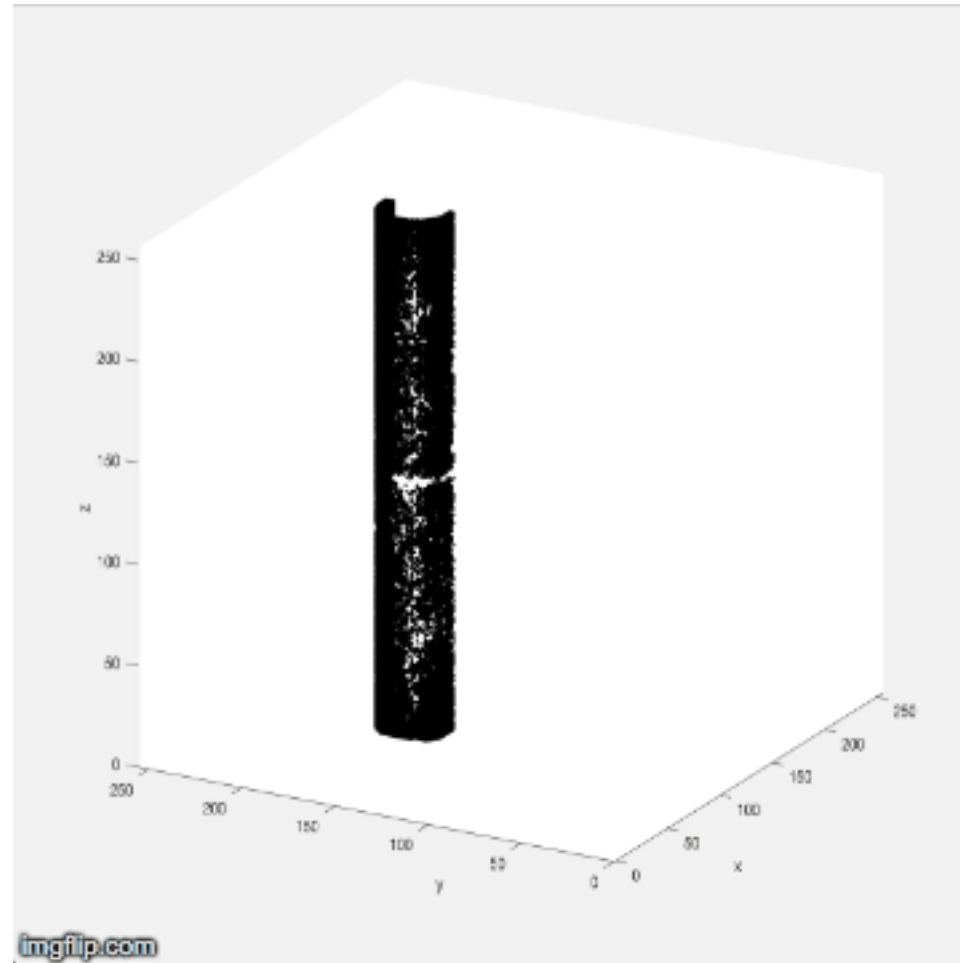
# Modelling demyelination

- Program's first output: **healthy axons**.
- The script emulates the real inflammatory process which is presumably the cause of MS demyelination.
- Characteristics: 1) fibers are attacked to different degrees;  
2) random damage but subject to preferred directions
  - it is mainly external;
  - it is focal.



# Modelling demyelination

## Demyelinated axon



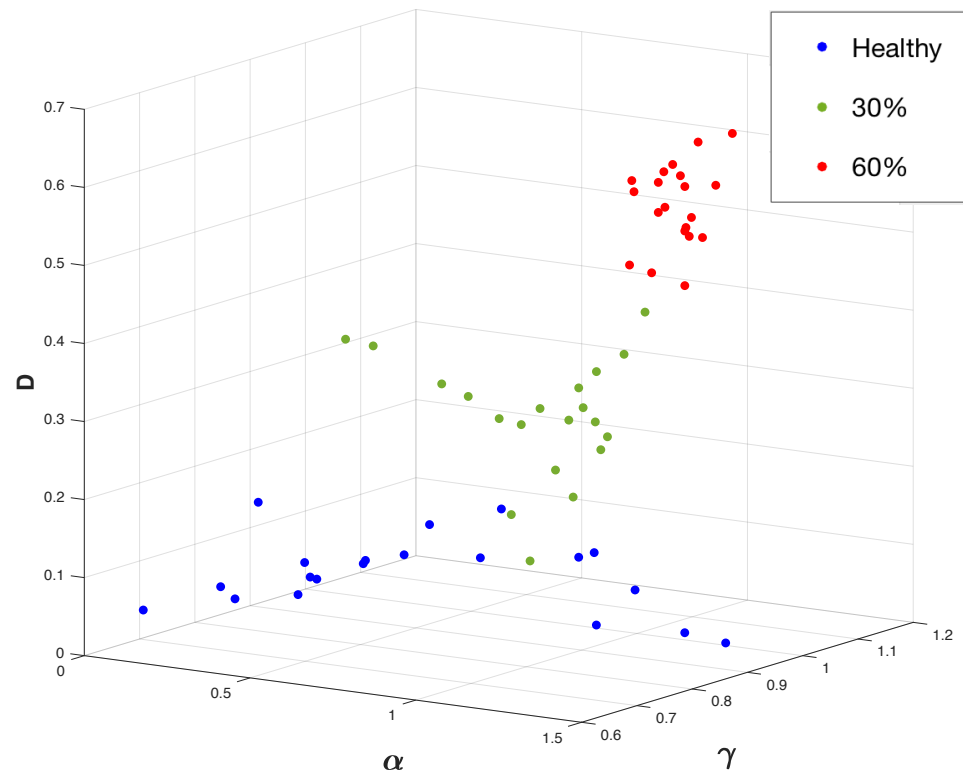
# NMR simulations

## Setup

- 60 simulation spaces (20 **Healthy** / 20 **30% demyelinated** / 20 **60% demyelinated**);
- One NMR experiment (1.000 trajectories) in each;
- Results fitted using two models (ML / STR).

## Mittag-Leffler results

Plot of parameters  
 $\alpha$ ,  $\gamma$  and D



# k-means clustering analysis

- Unsupervised machine learning
- Analyses concerned  $\left\{ \begin{array}{l} \text{parameters } \gamma \text{ and } D \text{ and their 2-D clustering (ML and STR} \\ \text{models);} \\ \text{two groups at a time (Healthy x 60\% demyelinated / Healthy} \\ \text{x 30\% demyelinated).} \end{array} \right.$
- Evaluation  $\left\{ \begin{array}{l} 1. \text{ nonparametric Mann-Whitney-Wilcoxon U-test;} \\ 2. \text{ computation of sensitivity, specificity and accuracy.} \end{array} \right.$



# Results

Healthy  
x  
60% demyelinated

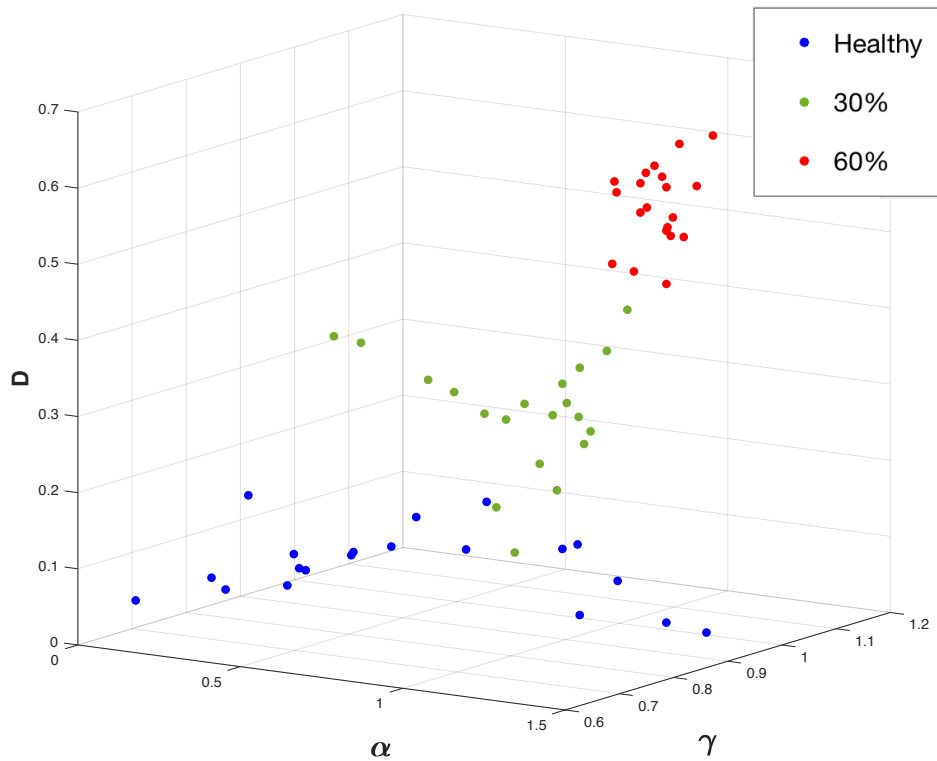
Biomarker	Model	Sensitivity	Specificity	Accuracy
D	ML	1.00	1.00	1.00
	STR	1.00	1.00	1.00
GAMMA	ML	1.00	0.55	0.78
	STR	0.90	0.75	0.83
D + GAMMA	ML	1.00	1.00	1.00
	STR	1.00	1.00	1.00

Healthy  
x  
30% demyelinated

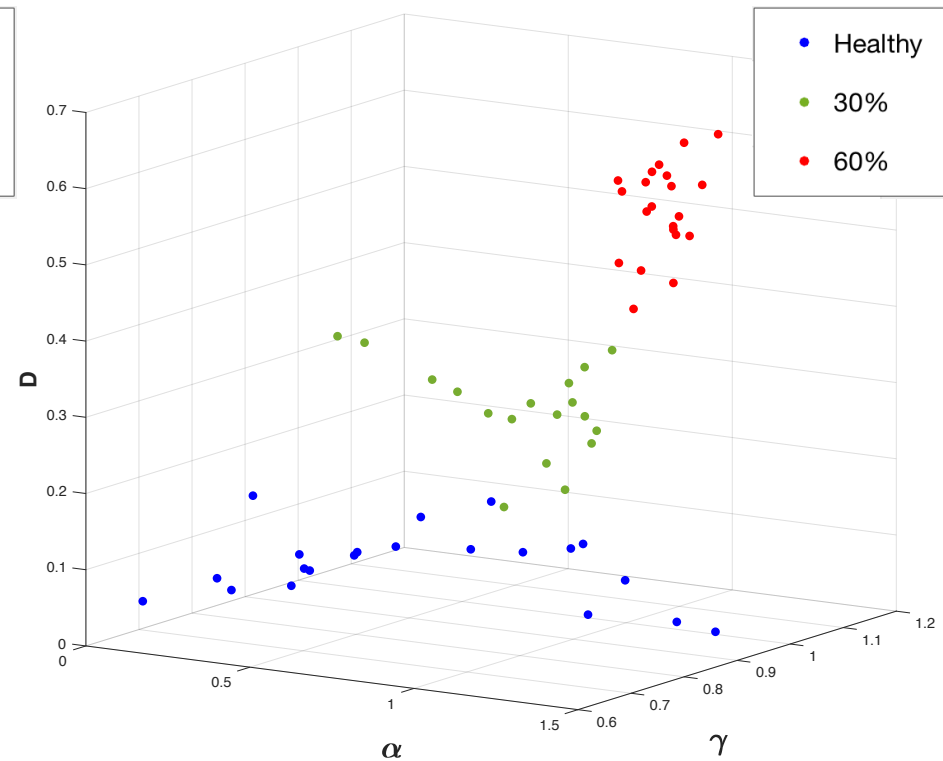
Biomarker	Model	Sensitivity	Specificity	Accuracy
D	ML	0.95	1.00	0.98
	STR	0.95	1.00	0.98
GAMMA	ML	0.75	0.55	0.65
	STR	0.55	0.30	0.43
D + GAMMA	ML	0.85	1.00	0.93
	STR	0.65	1.00	0.83

# Results

True classification



Classification by parameter D



## 5. Conclusions

1. Confirmation of the hypothesis of "pseudo-superdiffusion" (advanced by the Sapienza NMR Group on JCP 135, 034504, 2011).
2. Confirmation that the anomalous diffusion parameter is able to identify structural transition (SPT) in a heterogeneous system (Reported by the Sapienza NMR group on *Scientific Reports*, 3, 2631 (2013)).
3. **Hypothesis advanced on this work:** the ability of the anomalous diffusion parameter to identify structural transition is dependent on the scale of the medium under study and on the diffusive properties of the diffusing fluid / gas.
4. **Original contribution:** the parameters  $D$  and  $\gamma$  (from anomalous diffusion theory) can potentially be employed as biomarkers for demyelination.

# Grazie!