NMR Anomalous Diffusion Measurements to investigate complex systems: experiments

Silvia Capuani

*CNR-ISC UOS Roma
Dipartimento di Fisica
Sapienza Università di Roma
Laboratorio di Risonanza Magnetica Nucleare
Edificio Fermi stanza 319, Edificio Segre’ Laboratorio 5

silvia.capuani@roma1.infn.it
NMR Anomalous diffusion Highlights

Fundamental physics

Molecular diffusion in soft condensed matter: porous heterogeneous, complex systems

Experimental corroboration of simulations and theories

Biophysical applications

Translational longitudinal studies in Humans

Transfer of technology

Clinical application

Anisotropic anomalous diffusion vs age
Why would we want to evaluate the Diffusion parameters of water in materials and biological Tissue?

Because Diffusion parameters and diffusion-weighted NMR signal reflect the micro-structural rearrangement of porous materials and tissues.
We cannot measure the Diffusion Coefficient of water (or of generic ions and molecules) using NMR.

We can measure the displacement of the ensemble of spins in our sample and infer the Diffusion Coefficient.
Diffusion MR images can measure water proton displacements at the cellular level.

Probing motion at microscopic scale (10 μm), orders of magnitude smaller than macroscopic MR resolution (mm).

This has found numerous research and clinical applications.
Can probe diffusion for time scales:

1 ms to seconds

length scales of displacements:

100 nm to 100 μm

NMR diffusion

• Intrinsically multiphase materials
• Pore fluids for NMR detection
Microstructure is important
– Rocks, oil and water reservoirs
– Soils, unconsolidated formation
– Cement and concrete, catalysts
– Food stuff, paper, fabric
– Plant and animal tissues, bone
– Human tissues
– Brain

Conventional diffusion

Anomalous diffusion

Complex systems

Multiscale system constituted by structures at very different levels of hierarchical organization
NMR diffusion

Why anomalous diffusion?

Gaussian diffusion: diameter of the spatial range, \( d \), accessible to a water molecule in a given diffusion time \( t \)

\[ L_D \approx 20 \, \mu m \]

Anomalous diffusion: to make the invisible visible

Invisible structures with conventional Diffusion Magnetic Resonance

\[ L_D \approx d \approx (6Dt)^{1/2} \]
Bone

Trabecular bone marrow

Prostate Cancer staging

100 μm

1. Oligodendrocyte cells
2. Myelinated nerve fibers (transverse orientation)
3. Myelinated nerve fibers (longitudinal orientation)
4. Peroxisomes
5. Axons
6. Myelin
7. Microtubules
8. Ranvier node
9. Myelinic windings
10. Ribosome
11. RNA granules
**NMR principles**

**Nuclear paramagnetism**

NMR signal is an electric signal

f.e.m. induced at the radiofrequency (RF) coil

\[ S(t) = f(N, T_1, T_2, T_2^*, CS, J, D, \ldots) \]

RF pulse sequences
NMR diffusion

Magnetic gradients: inhomogeneity of the instrument

\[ S(t) = f(N, T_1, T_2, T_2^*, CS, J, D, \ldots) \]

RF sequences

\[ \hat{A}_1 \quad \hat{A}_2 \quad \hat{A}_n \]
\[ \tau_1 \quad \tau_2 \quad \tau_n \]

\[ S(t) \propto M(T_E) \approx M_{xy}^0 (1 - e^{-T_1/T_2}) e^{-T_2/T_2} \]
\[ \omega_0 = \gamma H_0 \]

Spectroscopy

\[ \omega(r) = \gamma (H_0 + G \cdot r) \]

Imaging
\[ \omega(\vec{r}) = \omega_0 + \gamma \vec{G} \cdot \vec{r} \]

**RF response**

**MR response**

**G slice selection**

**G frequency enc.**

**G phase enc.**

**Magnetic gradients: imaging**

1. After Slice Selection
2. Phase Encoding
3. After Phase Encoding
4. Frequency Encoding

FT

\[ S(k_x, k_y) \to \rho(x, y) \]
In heterogeneous and complex samples
$\Delta \chi$ at the interface between different tissues or materials

$$M_0 = \frac{N\gamma^2\hbar^2 I(I+1)}{3KT} H_0 = XH_0$$
Conventional Diffusion NMR: Gaussian diffusion

Gaussian Motion Propagator

\[ P(\vec{r} | \vec{r}', t) = \frac{1}{(4\pi D t)^{3/2}} e^{-(\vec{r} - \vec{r}')^2 / 4Dt} \]

\[ < r^2(t) >= 2dDt \]
The diffusion weighted signal is proportional to the characteristic function of the diffusion propagator in time $\Delta$

$$S(\vec{q}, t = \Delta) \propto \int P(\vec{R}, \Delta) e^{i\vec{q} \cdot \vec{R}} \propto W(\vec{q}, t)$$

$$\vec{q} = \gamma \vec{g} \delta$$

$\Delta$ = diffusion time $t$
NMR: how to measure diffusion parameters

\[ \Delta \phi = \vec{q} \cdot \vec{R} = \gamma \delta \tilde{g}(\vec{r}' - \vec{r}) \]
\[ b = (\gamma \delta)^2 \left( \Delta - \frac{\delta}{3} \right) \]

\[ S(b) = S(0) \exp \left( -bD \right) \]

Gaussian propagator

\[ b = \gamma^2 G^2 \delta^2 \left( \Delta - \frac{\delta}{3} \right) \]

\[ \langle x^2(t) \rangle \propto Dt \]
At least six independent parameters are required.

At least six no-complanar

\[
\frac{S(t)}{S_0} = \exp\left(-\sum_{i,j=1}^{3} b_{ij} D_{ij}\right)
\]

\[
D = \begin{pmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{pmatrix}
\]

\[
\nu_1, \nu_2, \nu_3
\]

\[
\sum D_{ij} \nu_i^2 D_{ij} = c
\]

Basser et al., JMR, 1994 (103) 247
MD and FA maps

\[ \overline{D} = MD = \frac{D_1 + D_2 + D_3}{3} \]

FA

\[ FA = \frac{\sqrt{3\left[(D_1 - \overline{D})^2 + (D_2 - \overline{D})^2 + (D_3 - \overline{D})^2\right]}}{\sqrt{2(D_1^2 + D_2^2 + D_3^2)}} \]
NMR diffusion

MD and FA
Quantitative images

Diffusion Tensor Imaging

Mean diffusivity

CSF
GM
WM
Anisotropy

Low sensitivity and specificity
Axon mean diameter \( \approx 7 \mu m \)

Microtubulus \( \approx 20 \text{nm} \)

\[
< r^2 > = 6 D \Delta
\]

\[
(< r^2 >)^{1/2} \approx 30 \mu m
\]

Where: \( D \approx 1 \times 10^{-9} \text{ m}^2/\text{s} \)

\( \Delta = 80 \text{ms} \)
Transient anomalous diffusion can be defined when \( \text{MSD} = T_D^\alpha \) with \( \alpha < 1 \) for \( t \ll T_{CR} \) and \( \text{MSD} = T_D \) for \( t \gg T_{CR} \) where \( T_{CR} \) is the crossover time.

\[
<r^2(t)> \approx t^\nu
\]

\( \nu < 1 \) subdiffusion

\( \nu > 1 \) superdiffusion
How to determine $\alpha$ and $\gamma$

PGSE

$S(q) = S(0)e^{-K\gamma|q|^{2\gamma}{\Delta}}$

$q = \gamma g \delta$

$\langle x^2 \rangle \propto t^\frac{1}{\gamma}$

$q^2 \ll \frac{1}{K\alpha \Delta^\alpha}$

$S(\Delta) = S(0)e^{-K\alpha q^2\Delta^\alpha}$

$\langle x^2 \rangle \propto t^\alpha$
Anomalous diffusion in 3D porous media: experiments

(Bio)-physical interpretation of $\alpha$ and $\gamma$ parameters

Length scale(s) of magnetic heterogeneity

Highly porous polymeric matrices with randomly oriented interconnected pores obtained from a solution of polyvinyl alcohol and ethyltrimethylammonium bromide (PVA scaffolds)

- void size distribution: 10–100 µm
- interconnection size distribution: 4–50 µm
- the three scaffolds differ in the roughness of the walls of their voids and interconnections

<table>
<thead>
<tr>
<th>Sample</th>
<th>Surface area (m²/g)²</th>
<th>$V_p$ (cm³/g)³</th>
<th>$\langle D_p \rangle$ (Å)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVA3</td>
<td>106</td>
<td>0.36</td>
<td>127</td>
</tr>
<tr>
<td>PVA2</td>
<td>68</td>
<td>0.38</td>
<td>215</td>
</tr>
<tr>
<td>PVA1</td>
<td>45</td>
<td>0.20</td>
<td>104</td>
</tr>
</tbody>
</table>

**Imaging:**

*PGSTE sequence*

\[ TR = (5000 - \Delta) \text{ ms} \]

\[ TE = 15 \text{ ms}; \]
\[ \delta = 2 \text{ ms} \]
\[ g = 74 \text{ mT/m} \]
\[ \Delta = (20 \div 520) \text{ ms} \]

\[ S_A = 45 \text{ m}^2/\text{g} \]

\[ S_A = 68 \text{ m}^2/\text{g} \]

\[ S_A = 106 \text{ m}^2/\text{g} \]

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Palombo M., Barbetta A., Cametti C., Dentini M., Capuani S., in preparation
Imaging:
PGSTE sequence
TR = (5000 - Δ) ms
TE = 15 ms;
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g = 74 mT/m
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S_A = 45 m²/g
S_A = 68 m²/g
S_A = 106 m²/g
Application to multiscale porous materials

Fractal dimension of the random path

\[ d_w = 2 / \alpha \]

\( \alpha \) quantifies global structural complexity.

\[ d_w = \frac{A_1 + B_1 x + C_1 x^2}{A_2 + B_2 x + C_2 x^2} \]

M.J. Saxton

*Biophys. J.* 66 (1994)

\( \chi = S / \sigma \)
Anomalous diffusion in 3D porous media: experiments

(Bio)-physical interpretation of $\alpha$ and $\gamma$ parameters

Length scale(s) of magnetic heterogeneity

Disorder Degree

Superdiffusion

Effective ordinary diffusion

Subdiffusion

Internal gradient strength \((\text{T/m}) \propto \Delta \chi_m\)

\[ B_{\text{ind}} \sim \Delta \chi \cdot B \cdot A \cdot \cos \theta \]

Increase of the image contrast
Enhanced interface contrast
intravoxel diffusion heterogeneity in space, i.e., water molecules diffuse with considerably different free lengths.

due to both water multi-compartmentalization and magnetic susceptibility differences ($\Delta\chi$) at the interface between different compartments.

Multi-compartmentalization + magnetic susceptibility differences ($\Delta\chi$)
Superdiffusion process ($\gamma < 1$) is spurious, not real but due to local $\Delta X$ (or $G_i$) at the interface between beads and water.
Phase $\Delta \phi \propto |g|$
Brownian Diffusion
Brownian Diffusion

Phase $\propto |g|$
Spectroscopy, Brownian Diffusion

Intensity (A.U.)

PGSE Echo Signal

$I_{diff}$
With boundary effects: $G_i$
Pseudo-Super Diffusion

$G_i$

Int. (A.U.)

PGSE

Echo Signal

$I_{diff}$

$I_{G_{int}}$

$\Delta I_{diff}$

$\Delta I_{G_{int}}$

$t$

0

PGSE Echo Signal

Intensity (A.U.)

PGSE Echo Signal

$G_i$

$\Delta I_{diff}$

$\Delta I_{G_{int}}$

$t$

0
Pseudo-Super Diffusion Imaging

Voxel 1

Voxel 2

$G_i$
Phase-Contrast Pseudo-Super Diffusion Imaging

Voxel 1

Voxel 2

Phase $\phi_g$
Pseudo-Super Diffusion Imaging

Voxel 1

Voxel 2

PGSE Echo Signal

Intensity (A.U.)

Intensity (A.U.)
Diffusion reflect the micro-structural rearrangement of tissues.

BRAIN AGING

Guerreri M., Caporale A., Palombo M., Bozzali M., Capuani S., submitted
Thank you for your attention

To investigate samples...

To investigate Human subjects...

silvia.capuani@roma1.infn.it
NMR Laboratory

NMR laboratory staff

Alessandra Caporale (PhD student)
Michele Guerreri (PhD student)
Maria Giovanna Di Trani (MS student)
Guglielmo Genovese (MS student)

Physicist collaborators
Andrea Gabrielli, CNR ISC
Vito Servedio, CNR ISC
Marco Palombo, CEA Fontenay-aux-Roses (France)

Chemical collaborators
Felix Wehrli, Penn University (USA)
Andrea Barbetta, Sapienza

Medical collaborators:
Marco Bozzali, Neuorimaging Laboratory,
Fondazione Santa Lucia IRCCS, Rome, Italy.

Department of Diagnostic and Interventional Radiology,
Molecular Imaging and Radiotherapy & Orthopedic and Traumatology Dip.
PTV Foundation, “Tor Vergata” University of Rome,