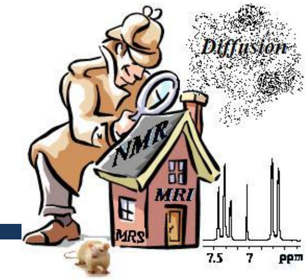
NMR Laboratory



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

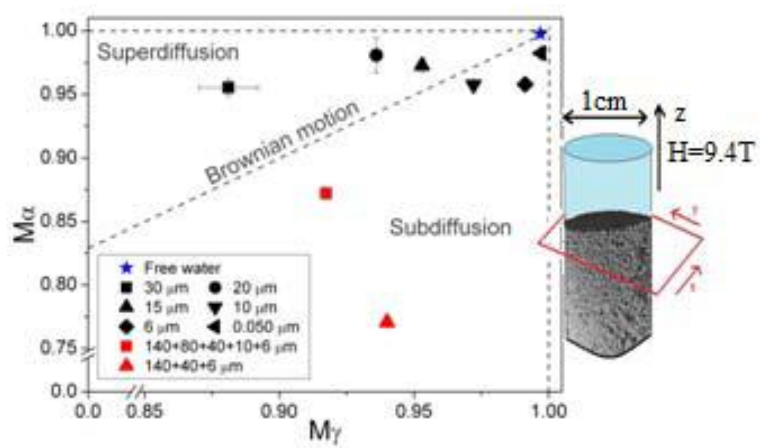
silvia.capuani@roma1.infn.it

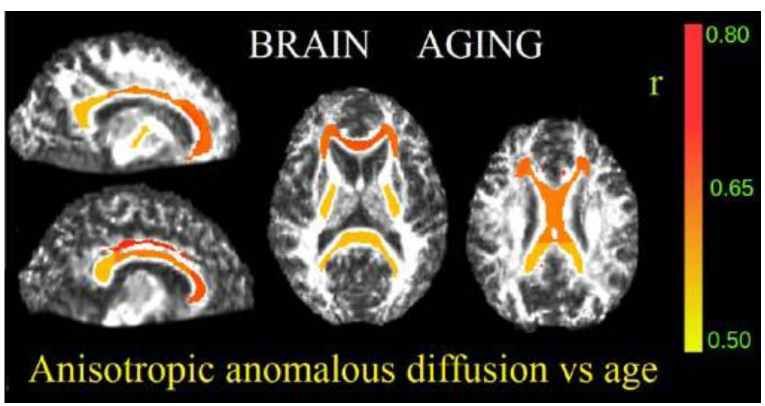
NMR Anomalous diffusion Highlights

Fundamental physics

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

Experimental corroboration of simulations and theories





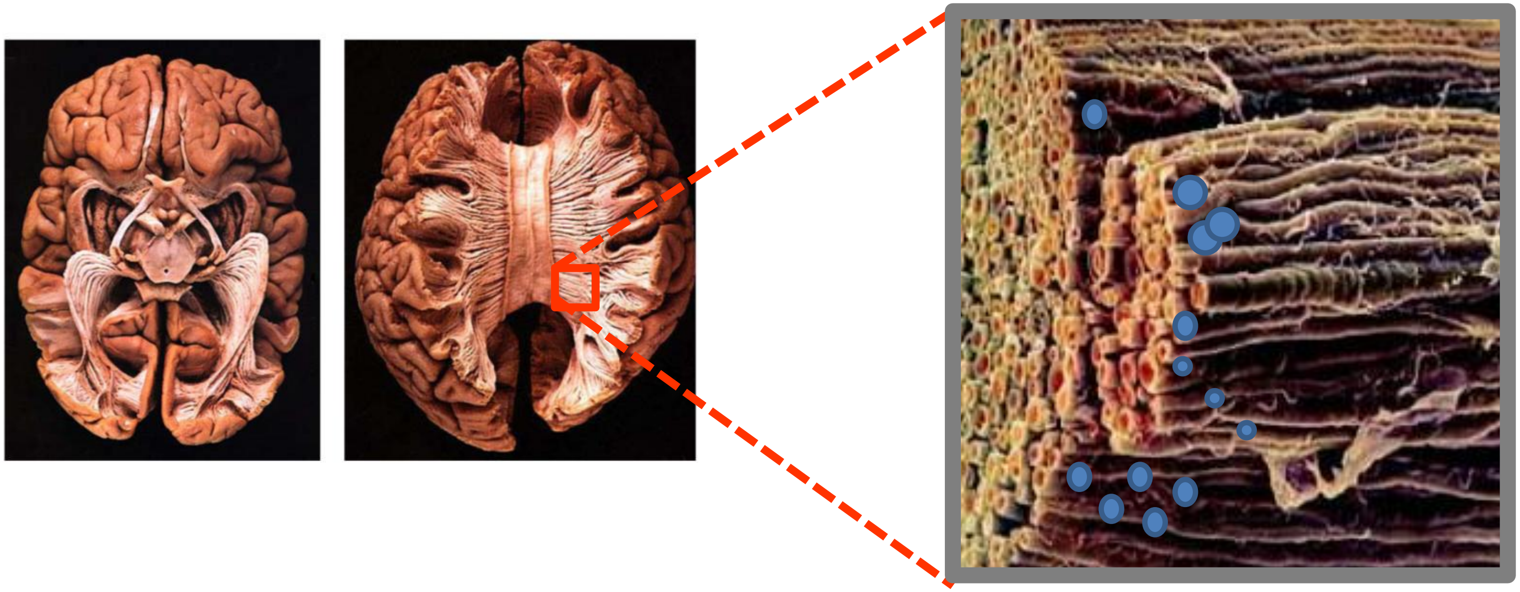
Biophysical applications

Translational longitudinal studies in Humans

Transfer of technology

Clinical application

Why would we want to evaluate the Diffusion parameters of water in materials and biological Tissue?

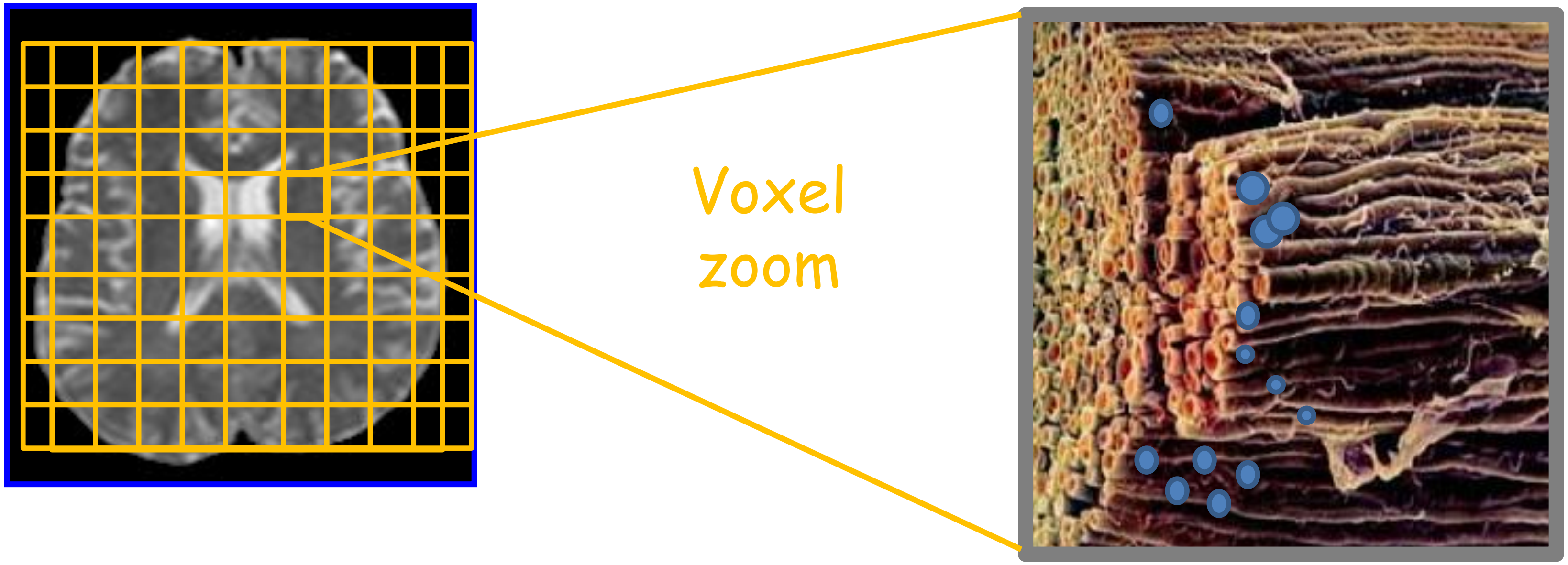


Because Diffusion parameters and diffusion-weighted NMR signal reflect the micro-structural rearrangement of porous materials and tissues

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)

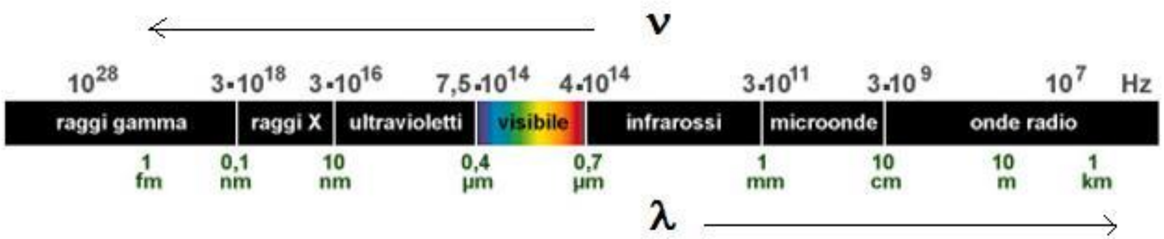
This has found numerous research and clinical applications

Can probe diffusion for time scales:

1 ms to seconds

length scales of displacements:

100 nm to100 μm



Conventional diffusion

Porous Media

- 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

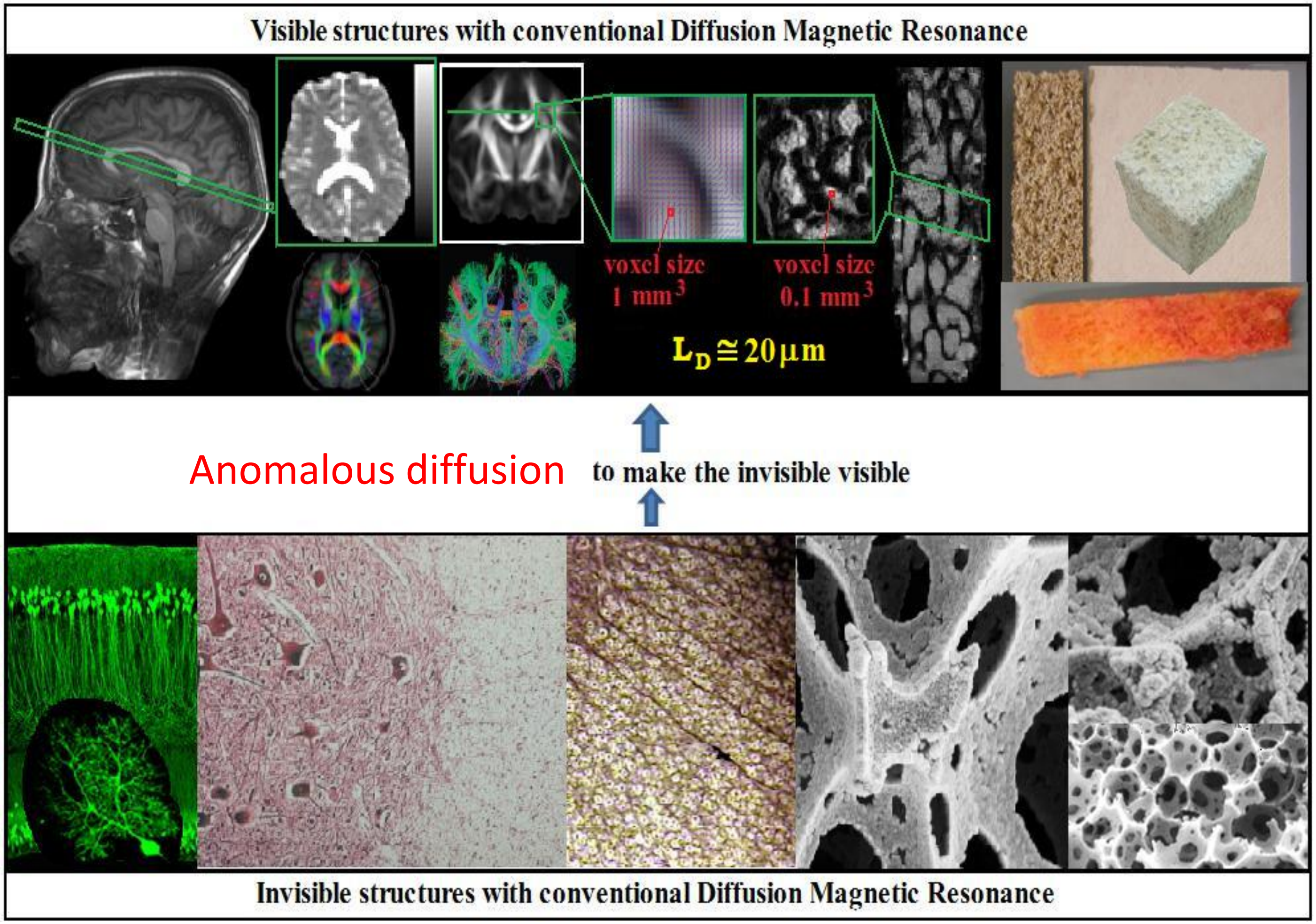
Anomalous diffusion

Complex systems

Multiscale

system constituted by structures at very different levels of hierarchical organization

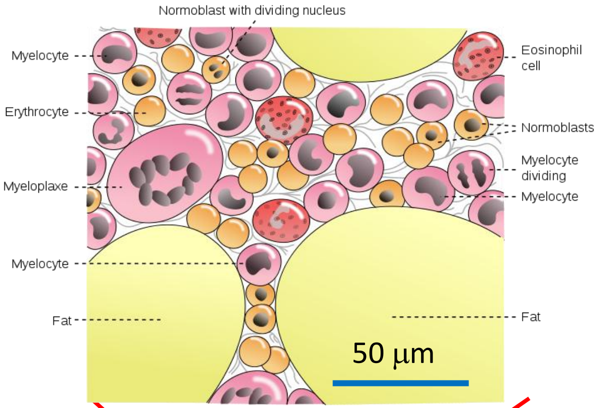
Why anomalous diffusion?



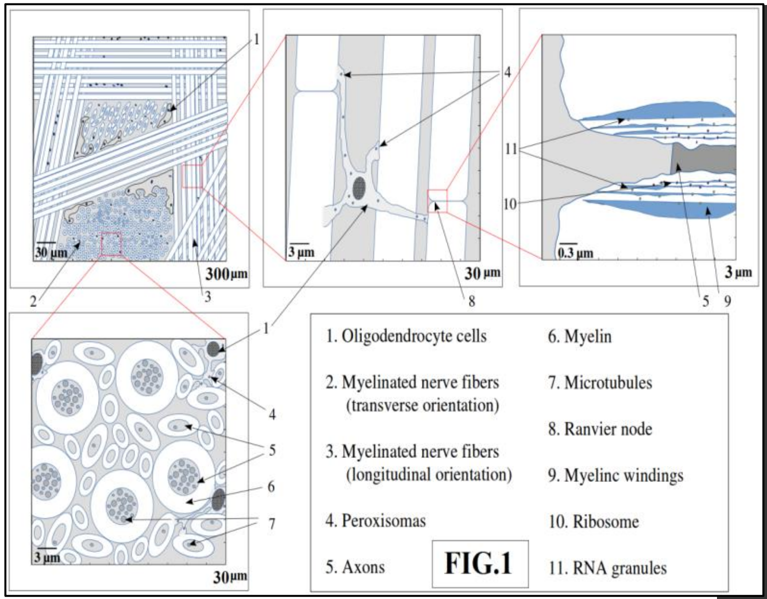
Gaussian diffusion:
diameter of the spatial range, d, accessible to a water molecule in a given diffusion time t

$$L_D = d \cong (6Dt)^{1/2}$$

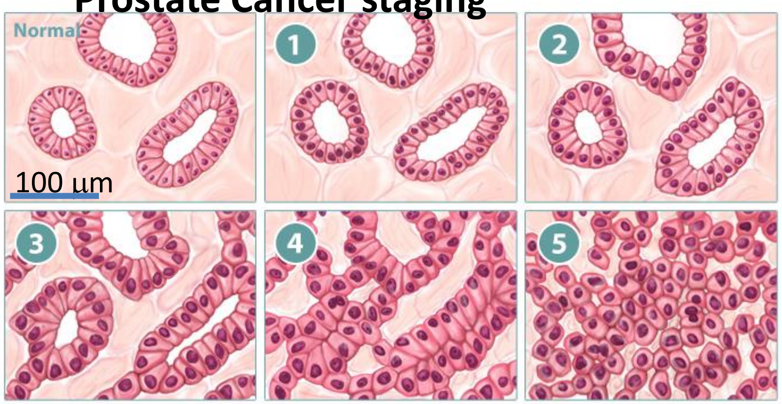
NMR diffusion

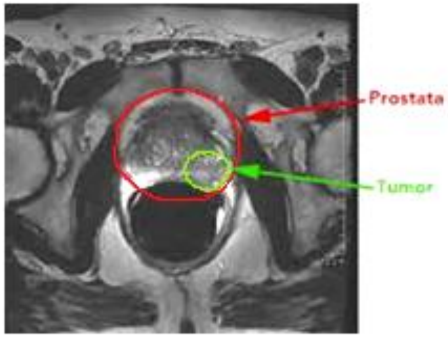


Trabecular bone marrow



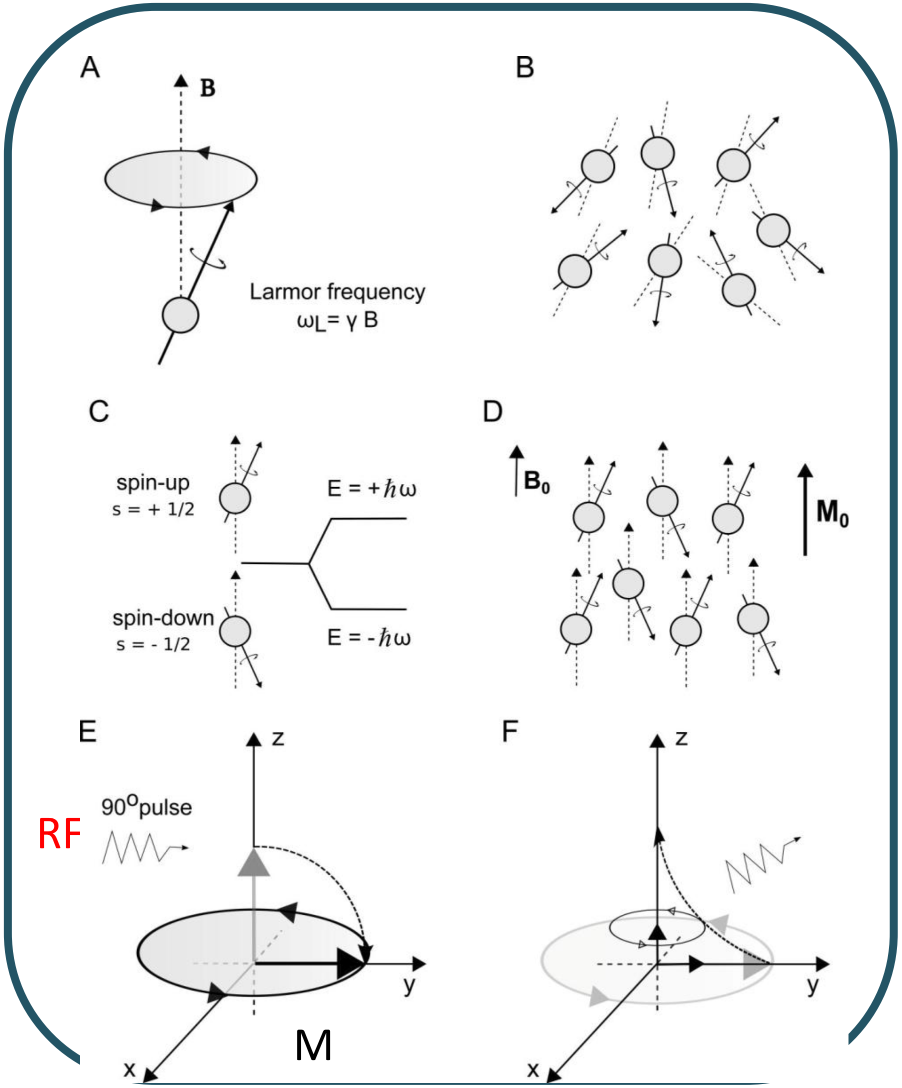
Prostate Cancer staging





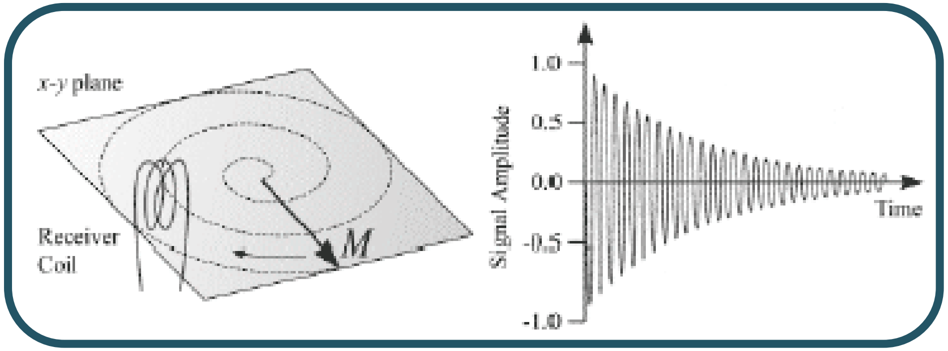
NMR principles

Nuclear paramagnetism



NMR signal is an electric signal

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



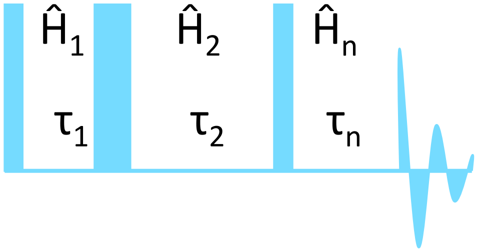
$$S(t) = f(N, T_1, T_2, T_2^*, CS, J, D, ...)$$

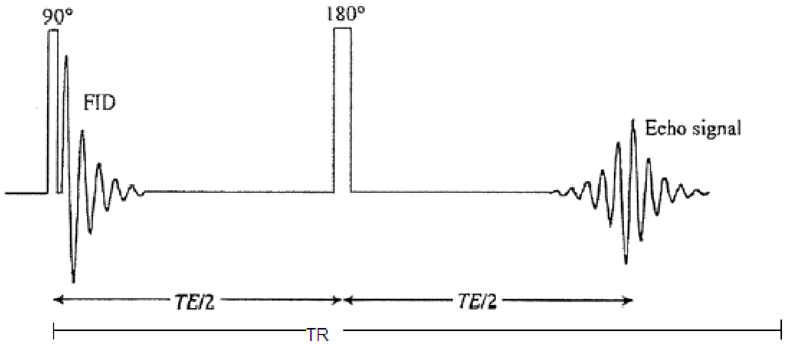
RF pulse sequences

Magnetic gradients: inhomogeneity of the instrument

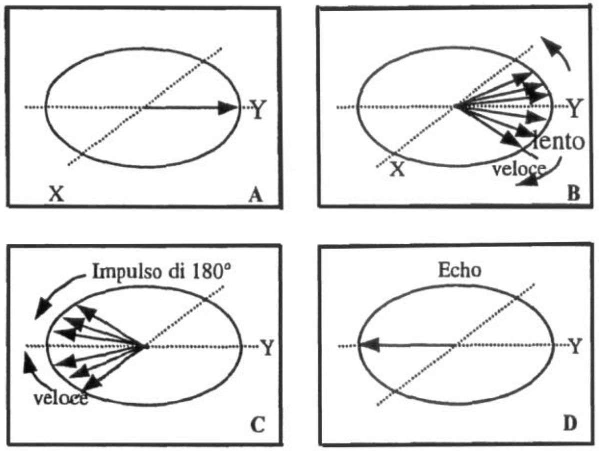
$$S(t) = f(N, T_1, T_2, T_2^*, CS, J, D, ...)$$

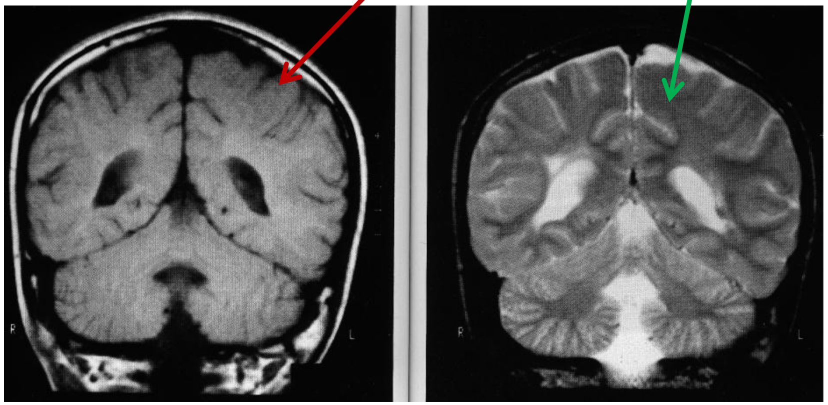
RF sequences



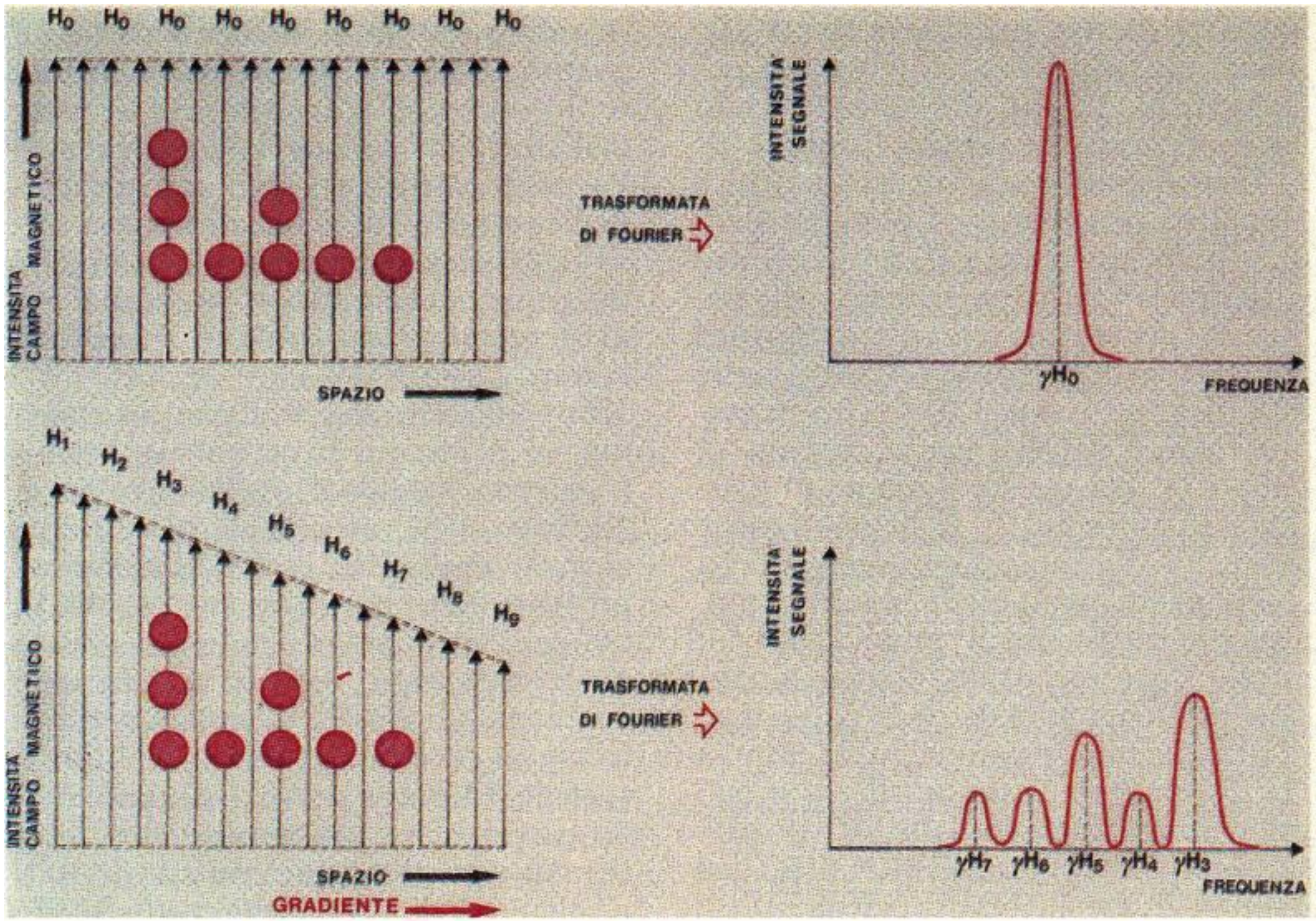


$$S(t) \propto M(T_E) \cong M^0{}_{xy}(1 - e^{-\frac{T_R}{T_1}})e^{-\frac{T_E}{T_2}}$$



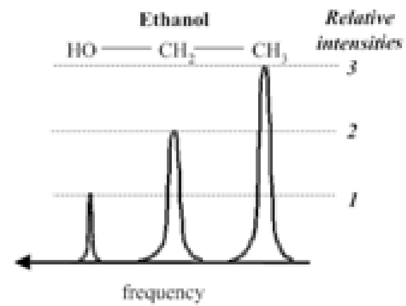


Magnetic field gradients: imaging



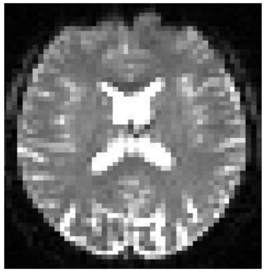
$\omega_0 = \gamma \, H_0$

Spectroscopy



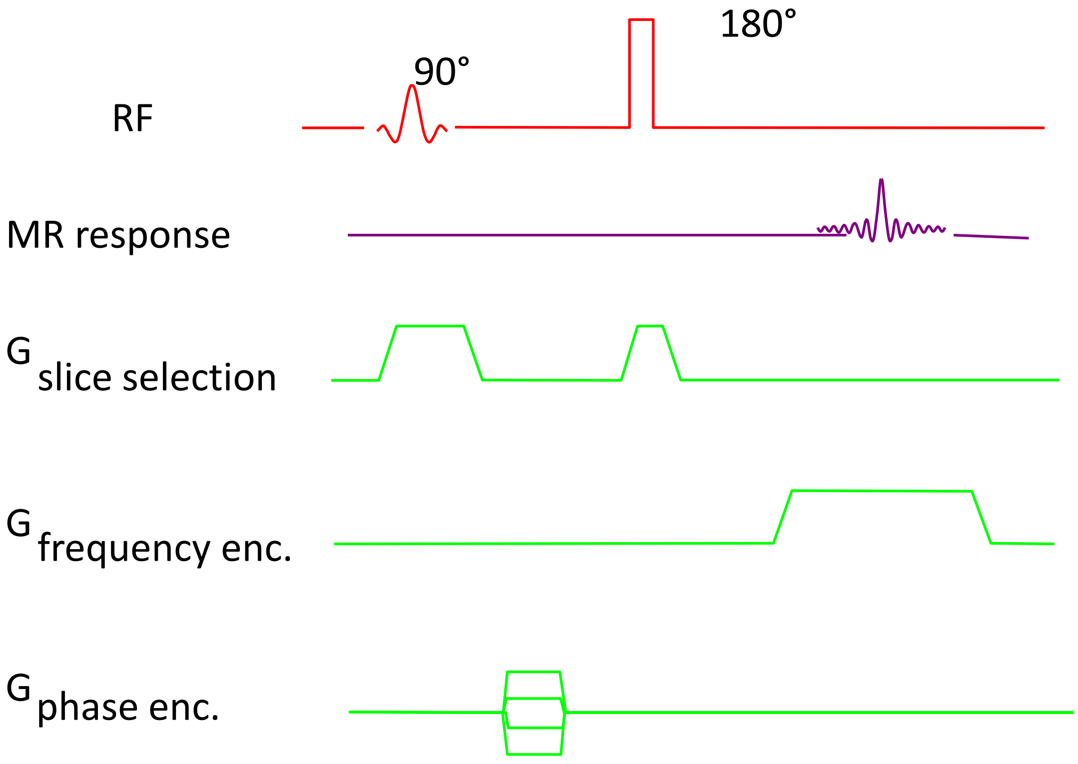
$\omega(r) = \gamma \, (H_0 + G \cdot r)$

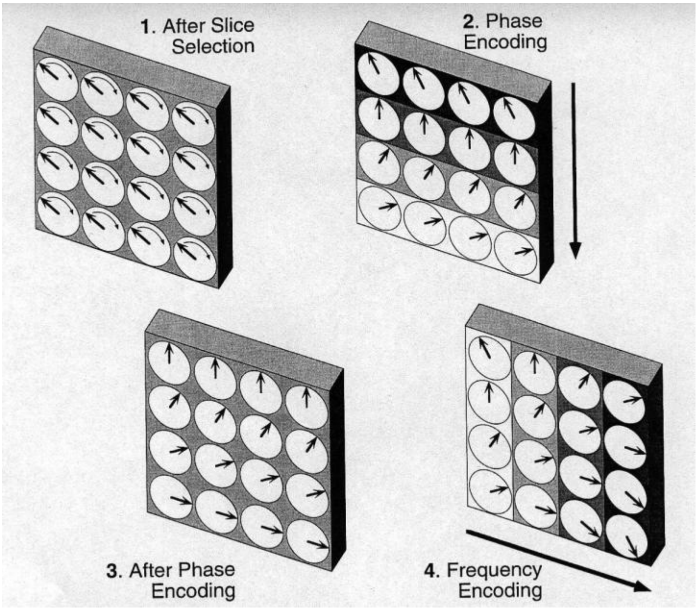
Imaging

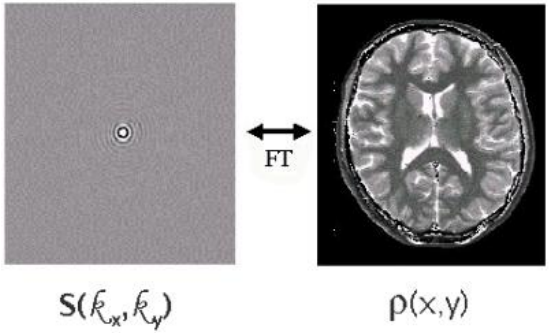


Magnetic gradients: imaging

$$\omega(\vec{r}) = \omega_0 + \gamma\vec{G}\cdot\vec{r}$$

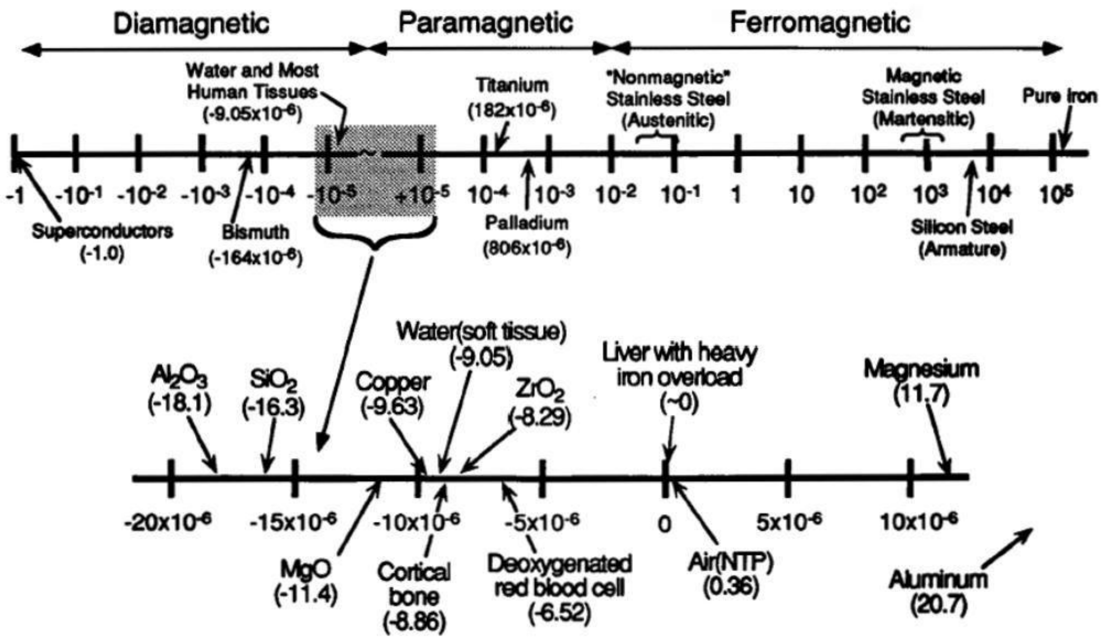


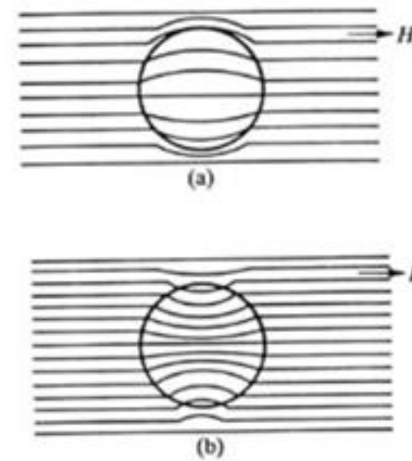




Magnetic field gradients: magnetic susceptibility differences

$$M_0 = \frac{N\gamma^2\hbar^2 I(I+1)}{3KT} H_0 = XH_0$$





In heterogeneous and complex samples

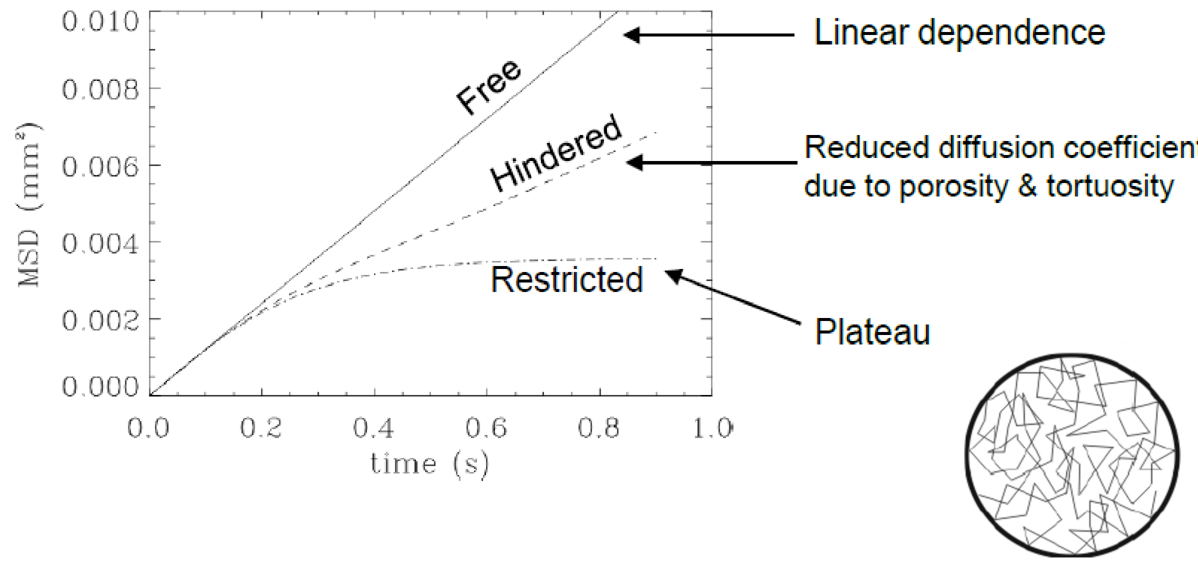
$\Delta\chi$ at the interface between different tissues or materials

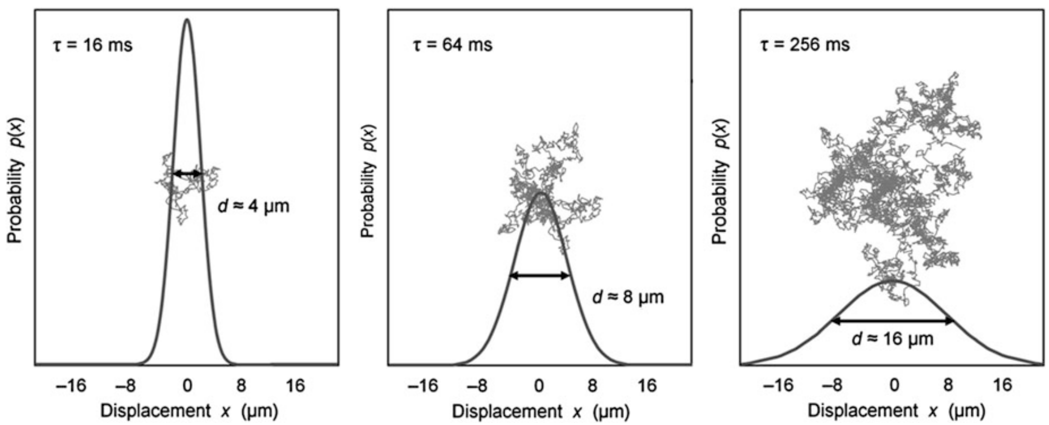
Conventional Diffusion NMR: Gaussian diffusion

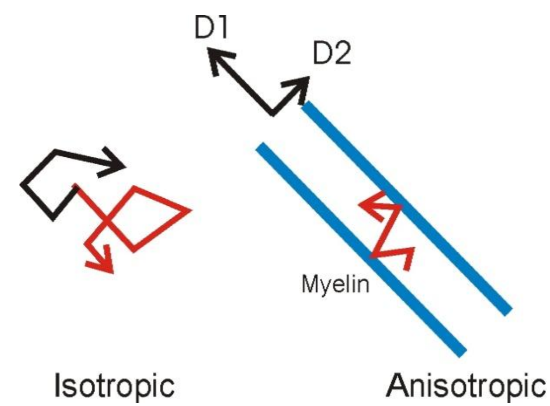
Gaussian Motion Propagator

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

$$\langle r^2(t) \rangle = 2dDt$$







NMR: how to measure diffusion parameters

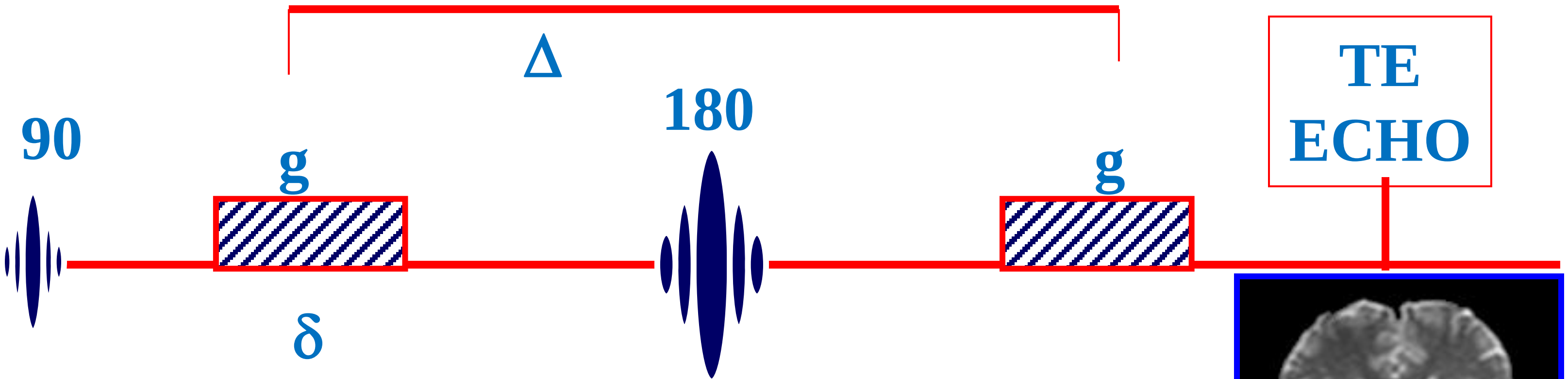
The diffusion weighted signal is proportional to the characteristic function of the diffusion propagator in time Δ

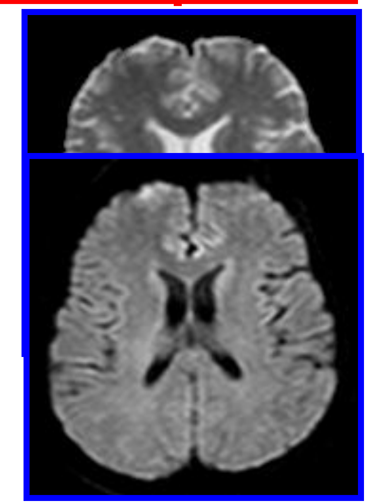
$$S(\vec{q}, t=\Delta) \propto \int P(\vec{R}, \Delta) e^{i\vec{q}\cdot\vec{R}} \propto W(\vec{q}, t)$$

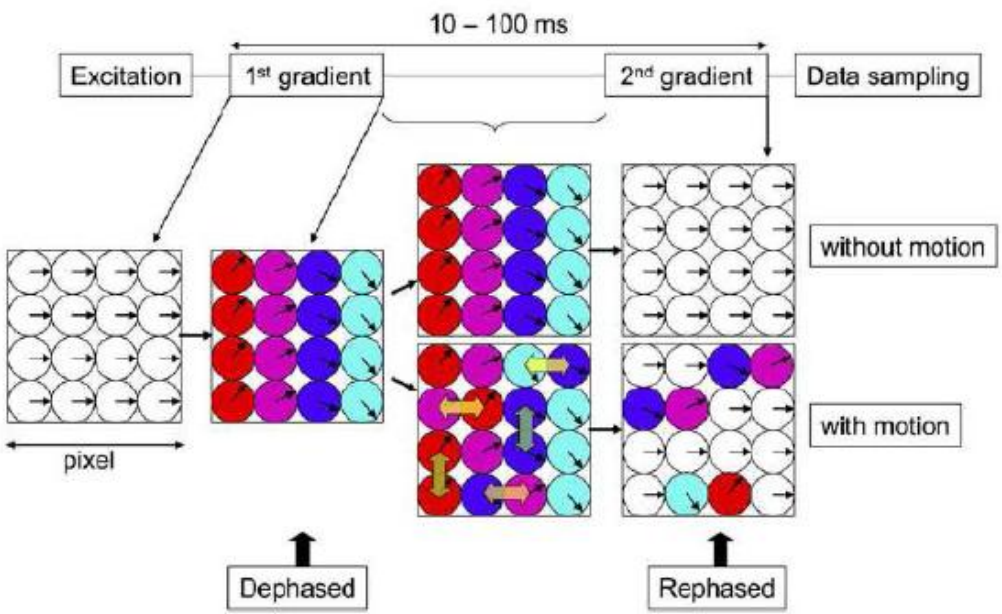
$$\vec{q} = \gamma \vec{g} \delta$$

$$\Delta = \text{diffusion time t}$$

NMR: how to measure diffusion parameters







$$\Delta\phi = \vec{q}\cdot\vec{R} = \gamma\,\delta\vec{g}(\vec{r}\,' - \vec{r})$$

Conventional Diffusion NMR: Gaussian diffusion

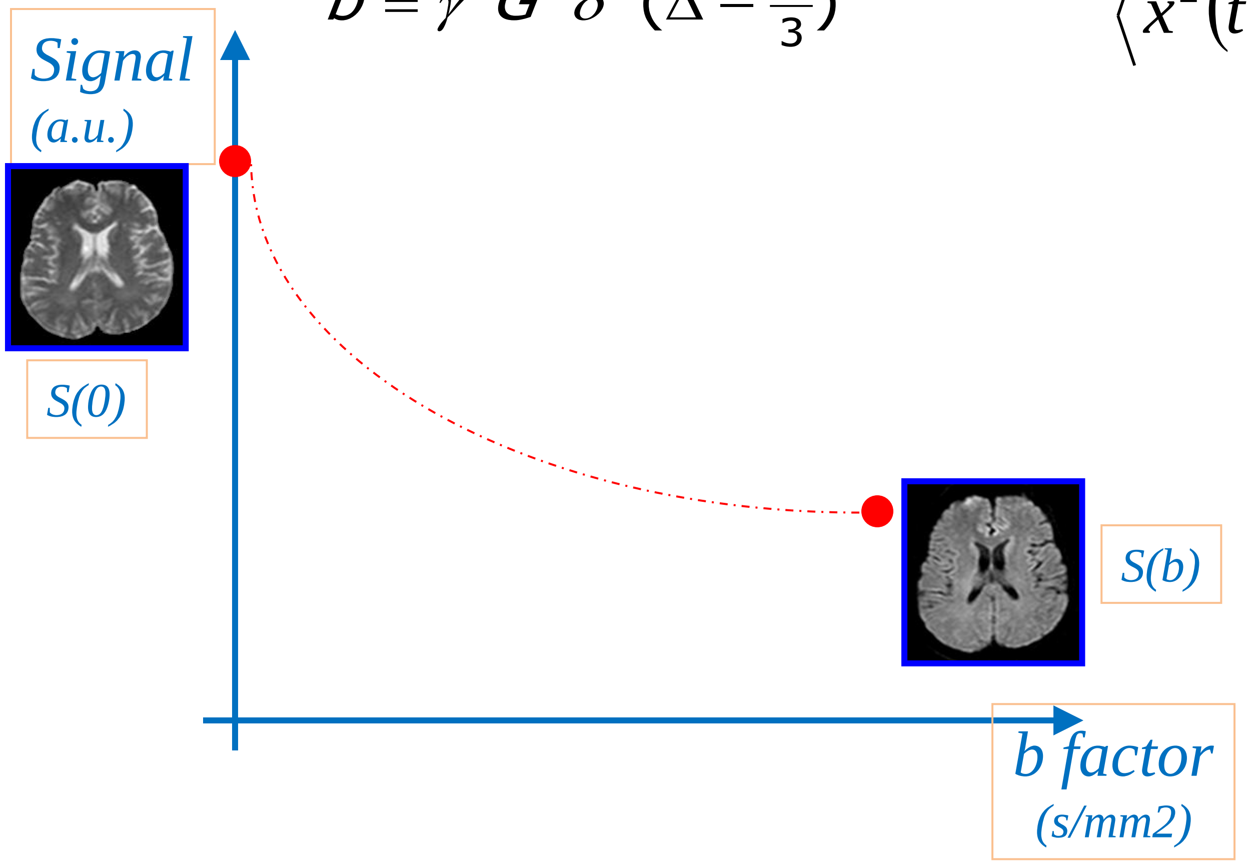
$$b=(\gamma g\delta)^2\left(\Delta-\frac{\delta}{3}\right)$$

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

Gaussian propagator

$$b=\gamma^2G^2\delta^2(\Delta-\frac{\delta}{3})$$

$$\left\langle x^2\left(t\right)\right\rangle \propto Dt$$



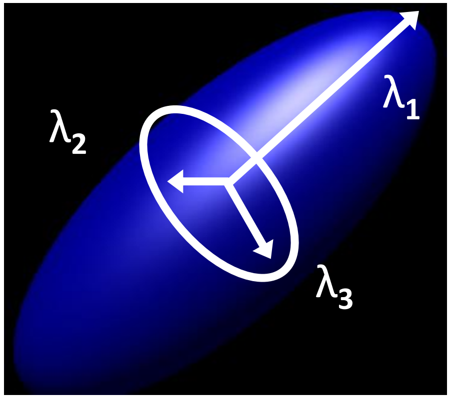
Diffusion tensor Imaging

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

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

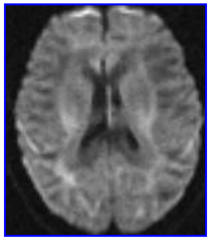
$$\underline{D} = \begin{pmatrix} D_1 & 0 & 0 \\ 0 & D_2 & 0 \\ 0 & 0 & D_3 \end{pmatrix}$$

$$v_1, v_2, v_3$$



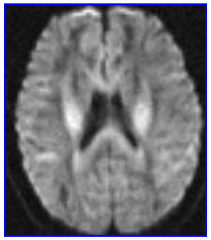
$$D_1 v_1^2 + D_2 v_2^2 + D_3 v_3^2 = c$$

At least six independent parameters are required.
At least six no-complanar



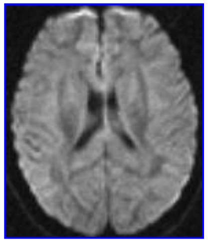
G_x

DWI_x



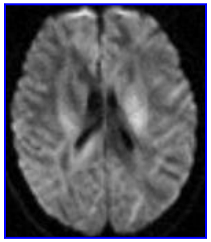
G_y

DWI_y



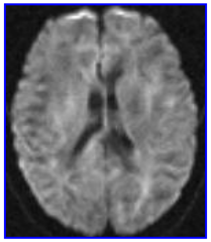
G_z

DWI_z



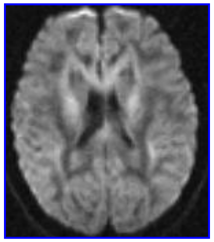
G_{xz}

DWI_{xz}



G_{xy}

DWI_{xy}



G_{yz}

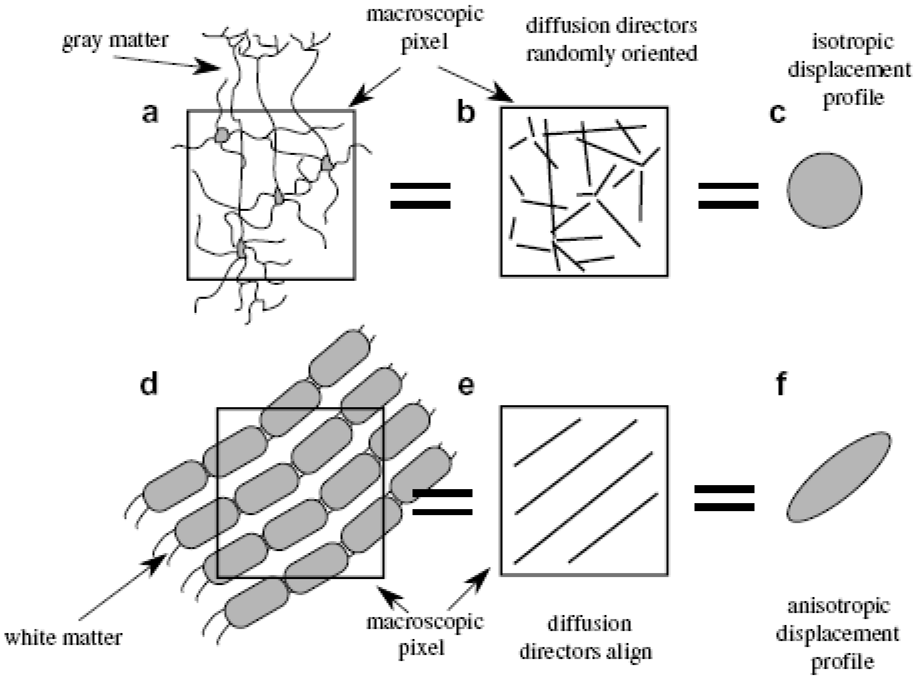
DWI_{yz}

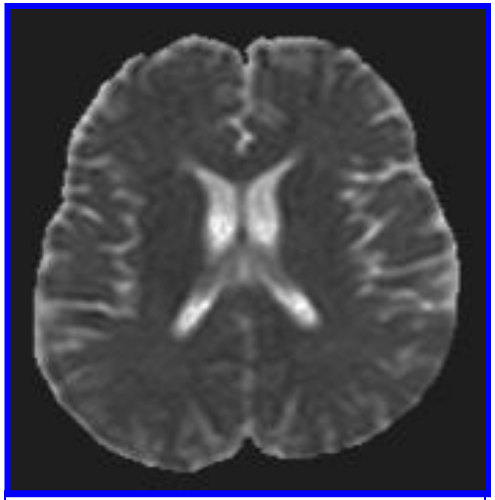
Basser et al., JMR, 1994 (103) 247

Diffusion tensor Imaging

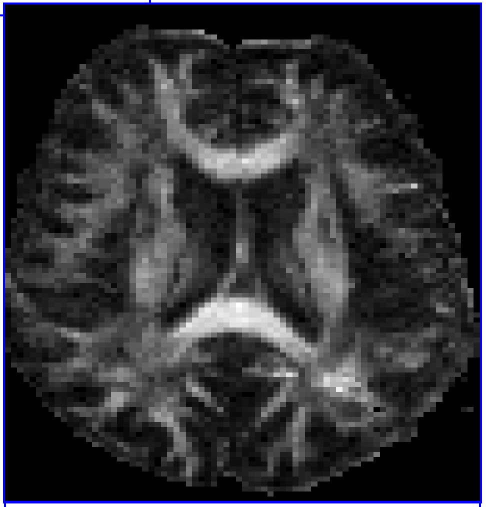
MD and FA maps

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





MD map



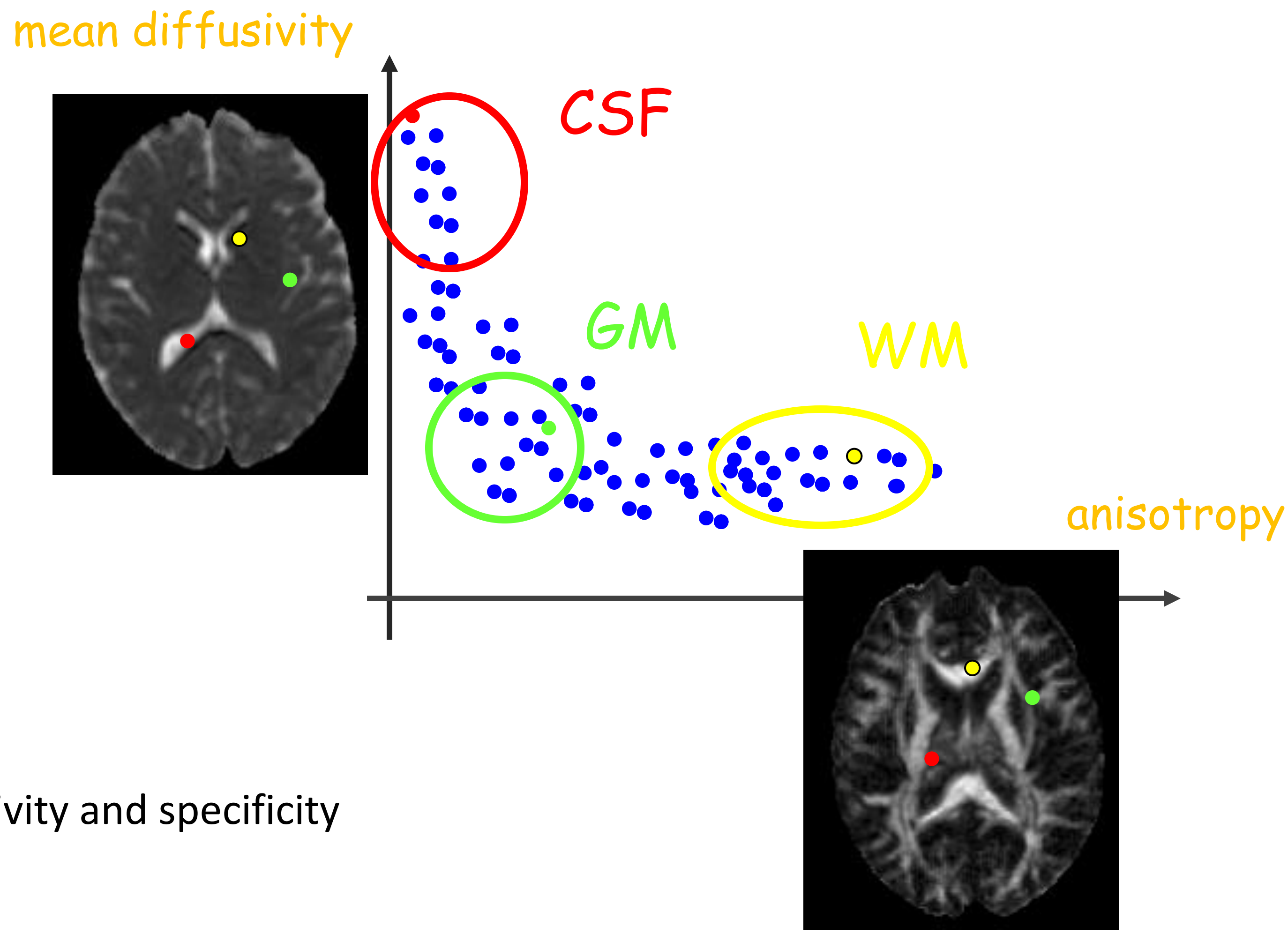
FA map

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

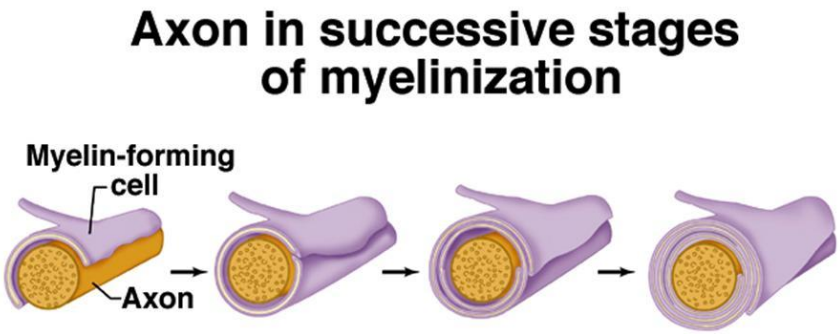
Diffusion tensor Imaging

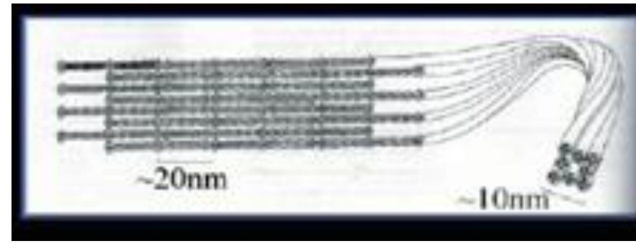
MD and FA
Quantitative images

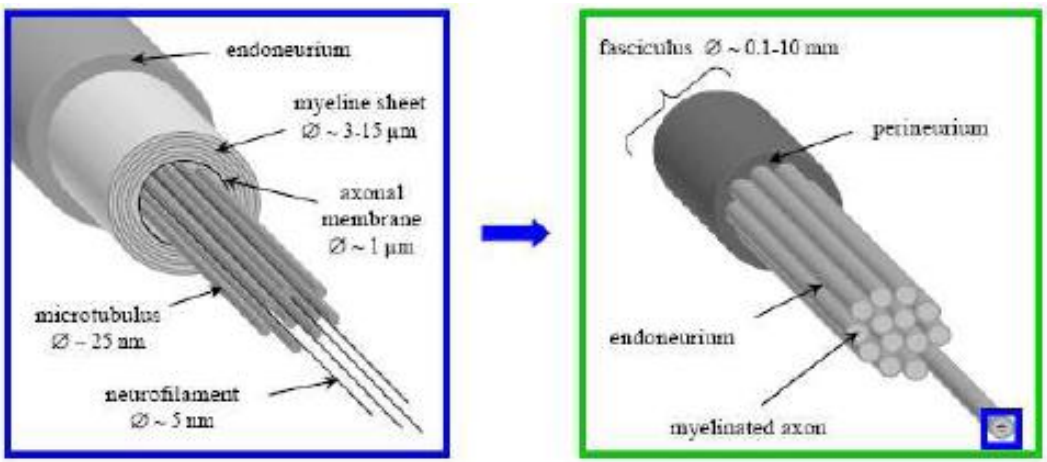
Diffusion Tensor Imaging



Low sensitivity and specificity







Axon mean diameter ≈7µm

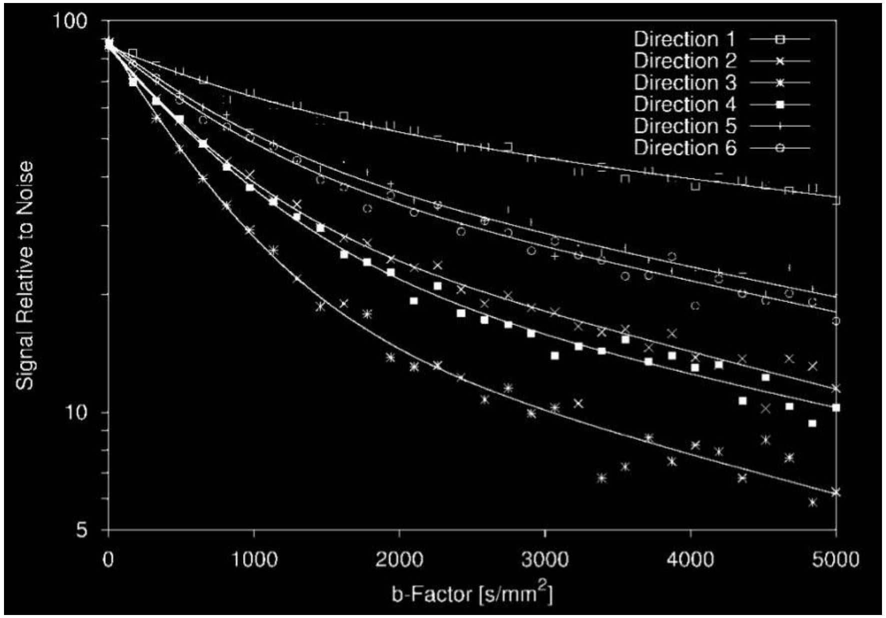
Microtubulus ≈20nm

$$\langle \underline{r}^2 \rangle = 6\,D\Delta$$

$$(\langle \underline{r}^2 \rangle)^{1/2} \approx 30\mu m$$

Where: $D \cong 1\times10^{-9}\ m^2/s$

$\Delta = 80ms$



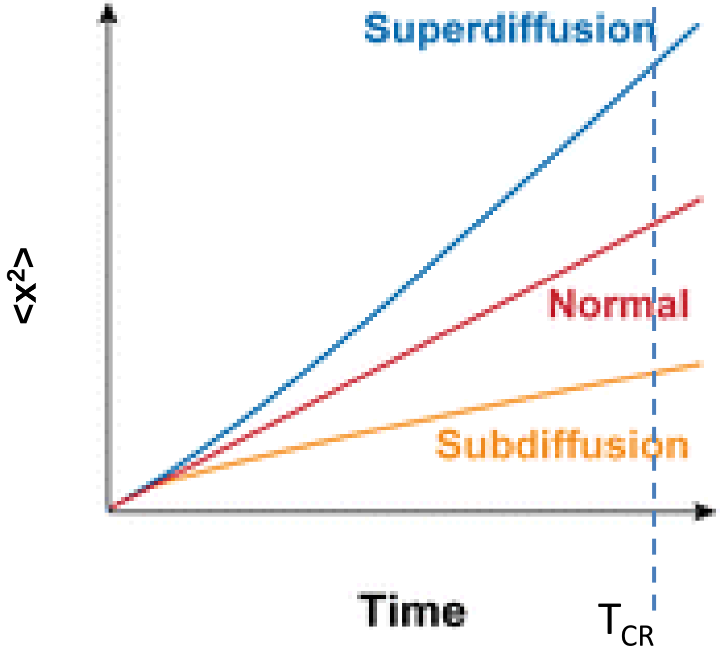
Anomalous Diffusion

$<r^2(t)> \approx t^\nu$

$\nu < 1$ subdiffusion

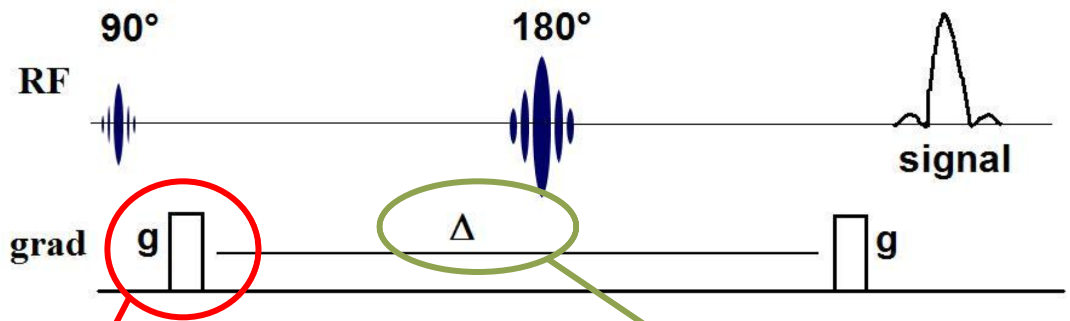
$\nu > 1$ superdiffusion

Transient anomalous diffusion can be defined when MSD $= T_D^{\alpha}$ with $\alpha < 1$ for $t \ll T_{CR}$ and MSD $= T_D$ for $t \gg T_{CR}$ where T_{CR} the crossover time.

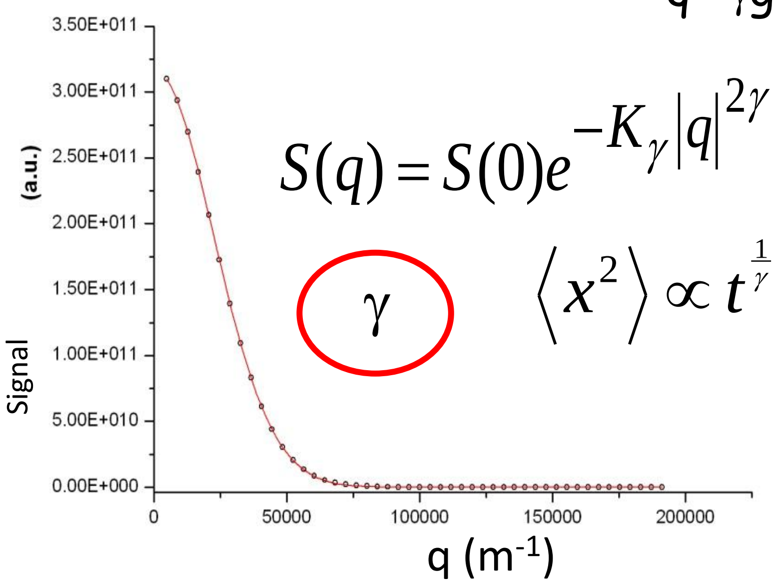


How to determine α and γ

PGSE



$q = \gamma g \delta$

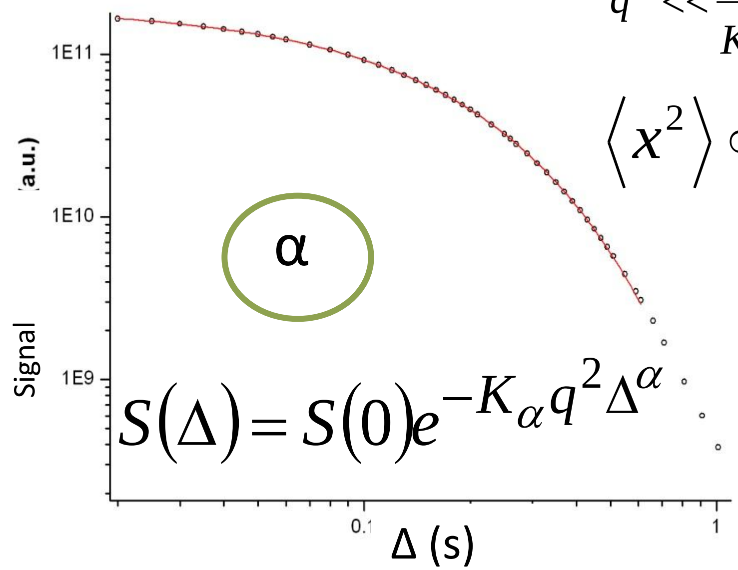


$$S(q) = S(0) e^{-K_\gamma |q|^{2\gamma} \Delta}$$

γ

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

$$q^2 << \frac{1}{K_\alpha \Delta^\alpha}$$

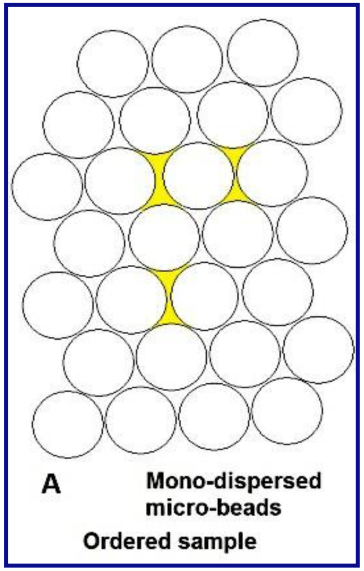


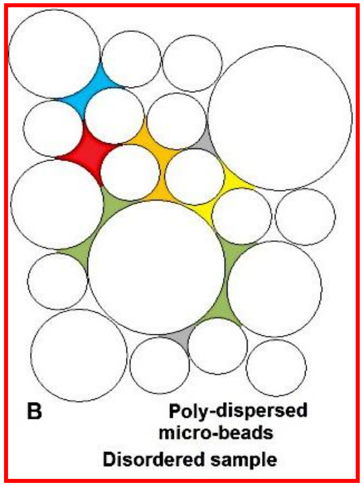
$$\langle x^2 \rangle \propto t^\alpha$$

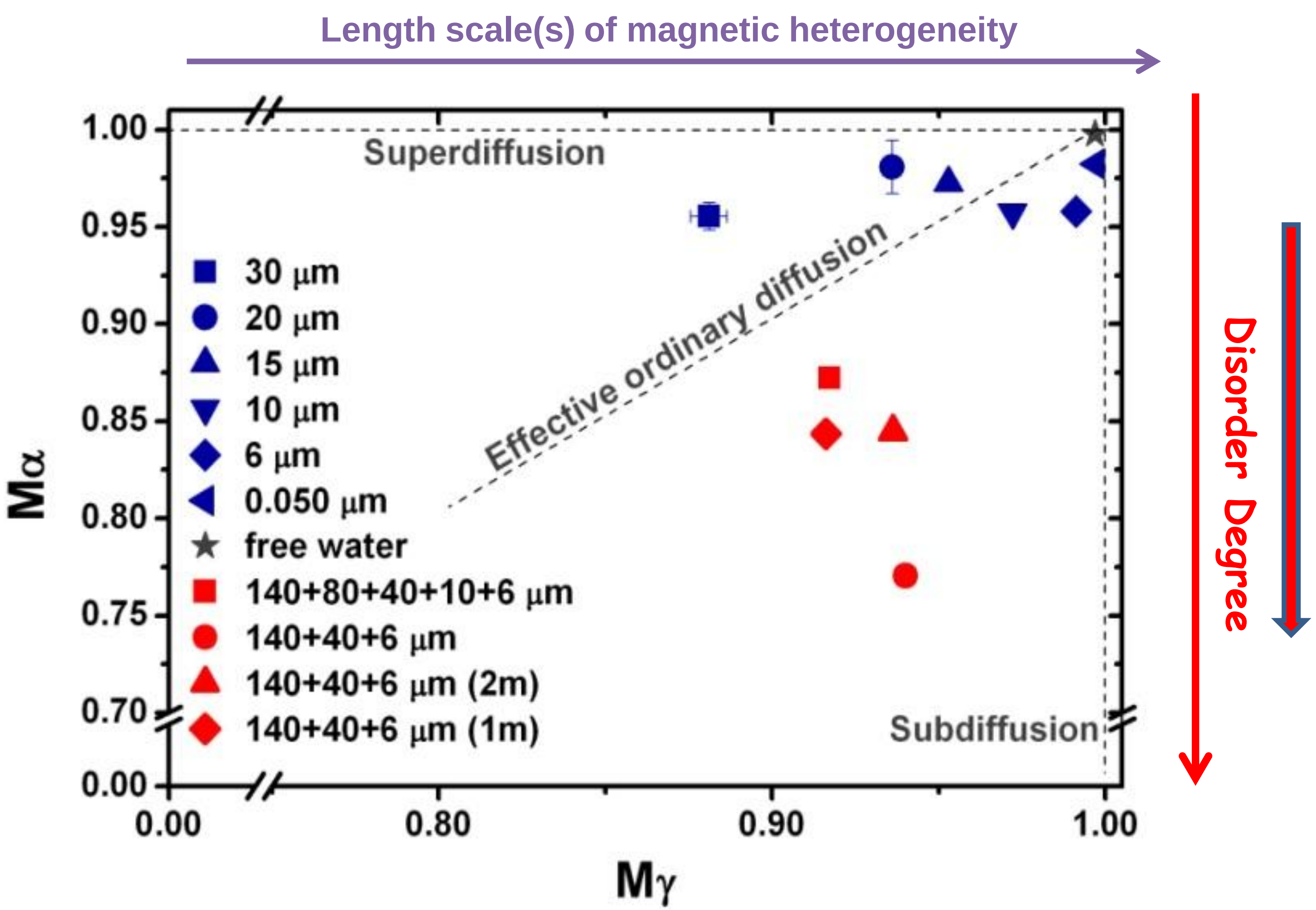
α

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

(Bio)-physical interpretation of α and γ parameters







Palombo M., Gabrielli A., De Santis S., Cametti C., Ruocco G., Capuani S., *J. Chem. Phys.* 135 (2011)

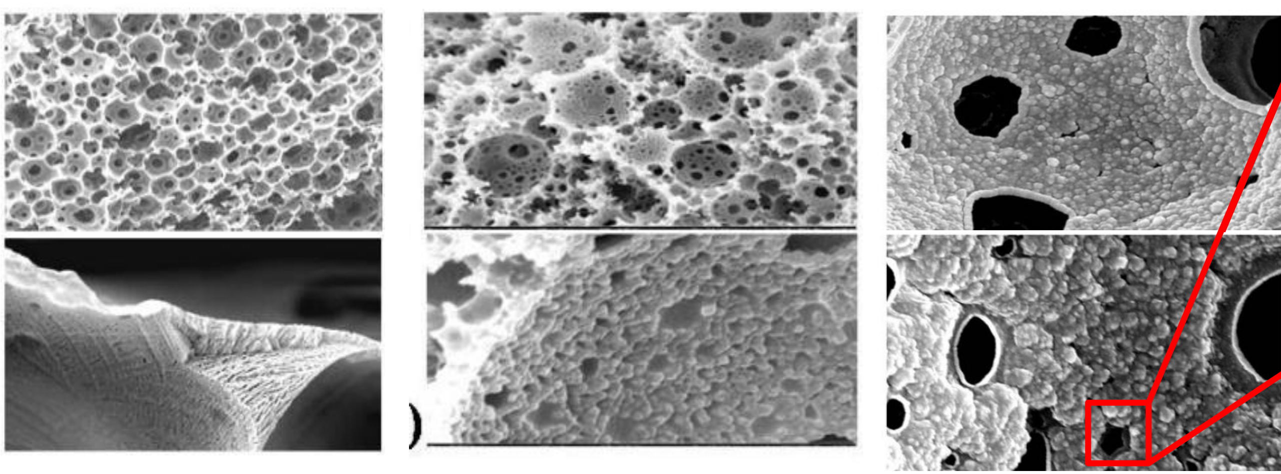
a parameter

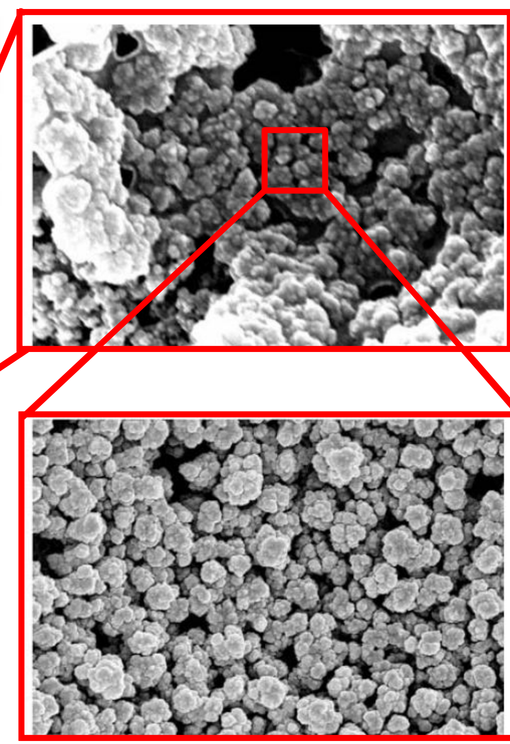
Application to multiscale porous materials

Highly porous polymeric matrices with randomly oriented interconnected pores obtained from a solution of polyvinyl alcohol and etyltrimethylammonium 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**

PVA1 **PVA2** **PVA3**

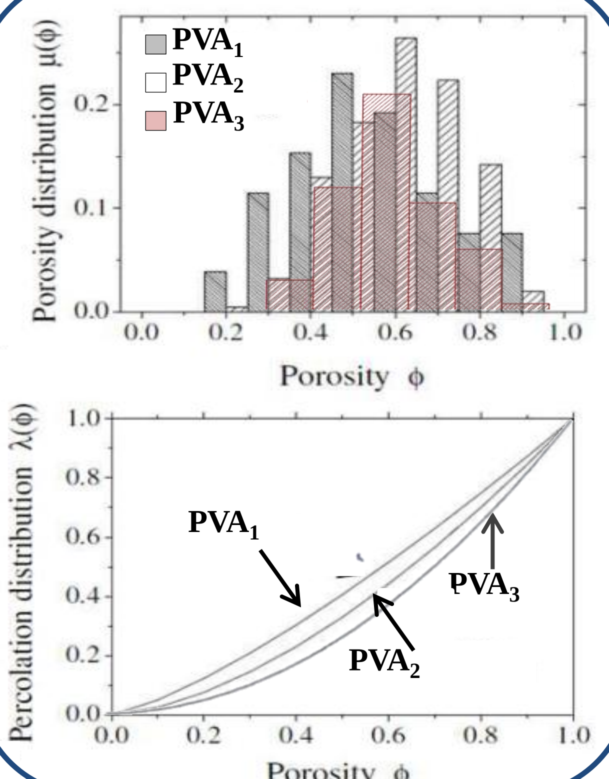


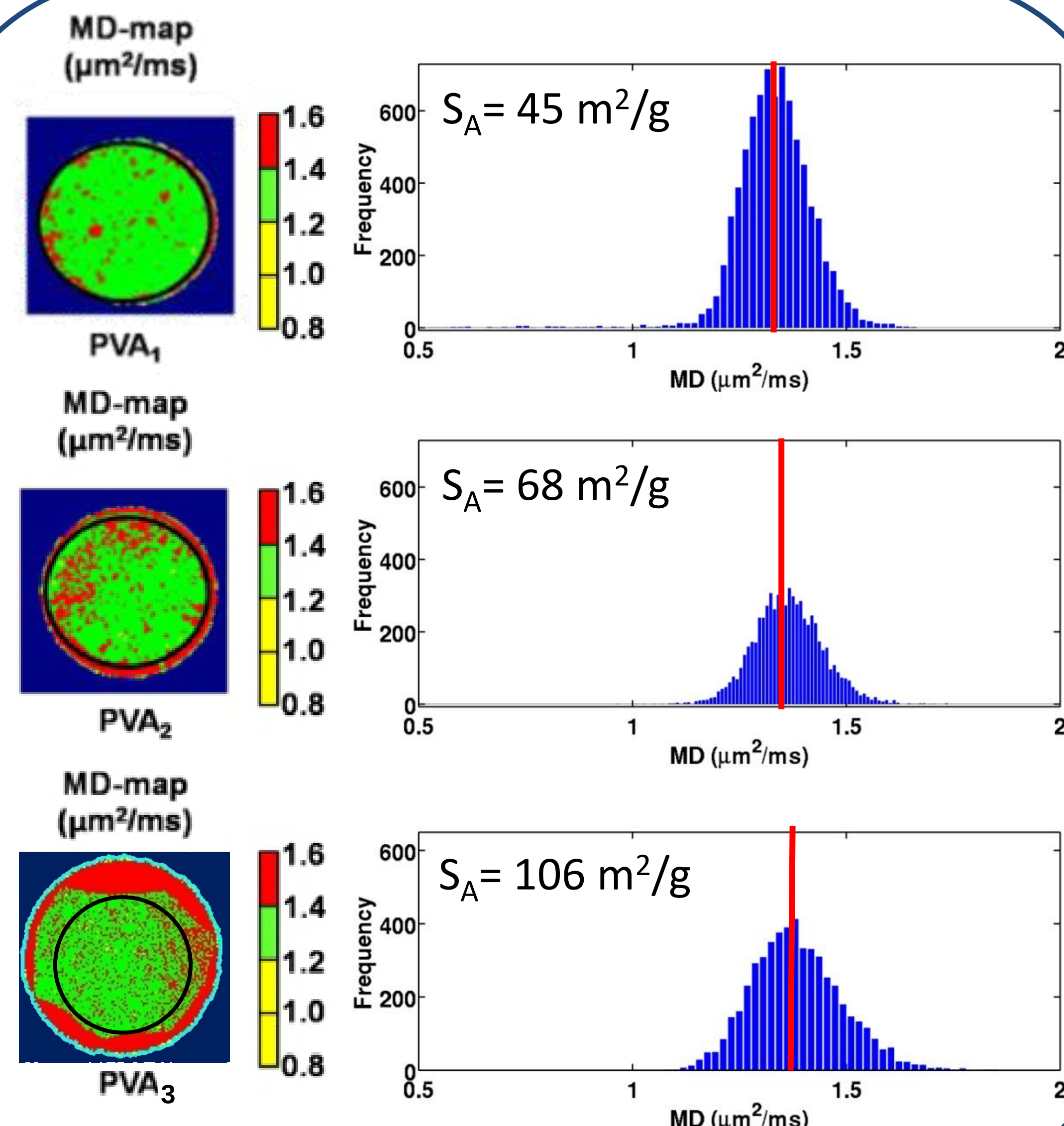


Sample	Surface area (m^2/g)[a]	V_p (cm^3/g)[b]	$\langle D_p \rangle$ (Å)[b]
PVA3	106	0.36	127
PVA2	68	0.38	215
PVA1	45	0.20	104

Gaussian approach

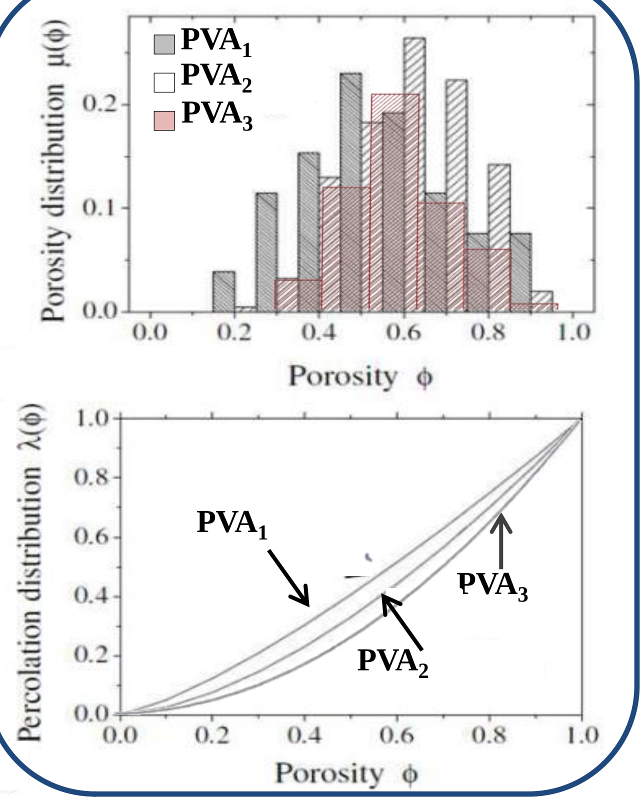
Imaging:
PGSTE sequence
$TR = (5000 - \Delta)$ ms
$TE = 15$ ms;
$\delta = 2$ ms
$g = 74$ mT/m
$\Delta = (20 \div 520)$ ms

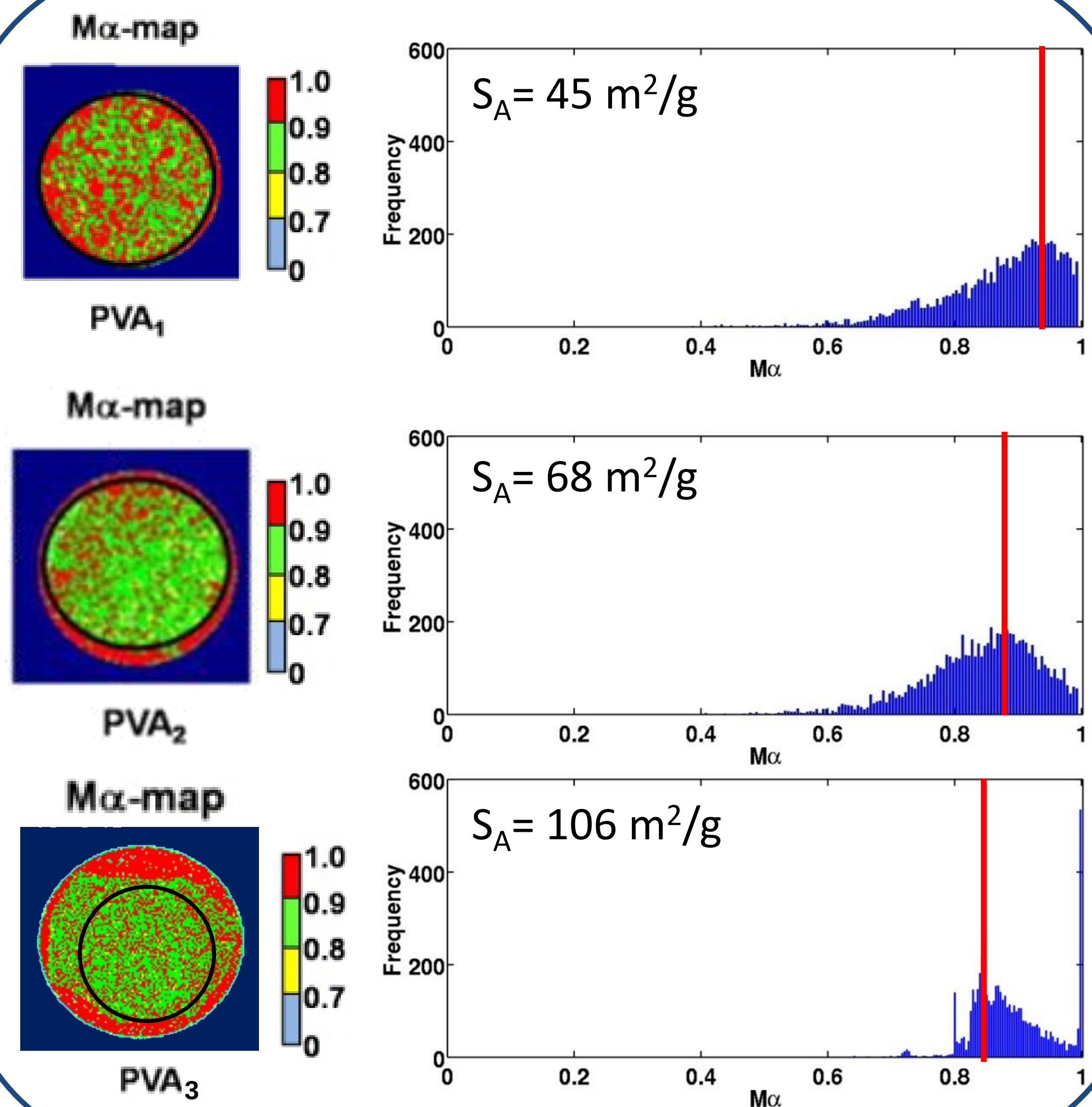




Anomalous diffusion approach

Imaging:
PGSTE sequence
TR = (5000 - Δ) ms
TE = 15 ms;
δ = 2 ms
g = 74 mT/m
Δ = (20 ÷ 520) ms





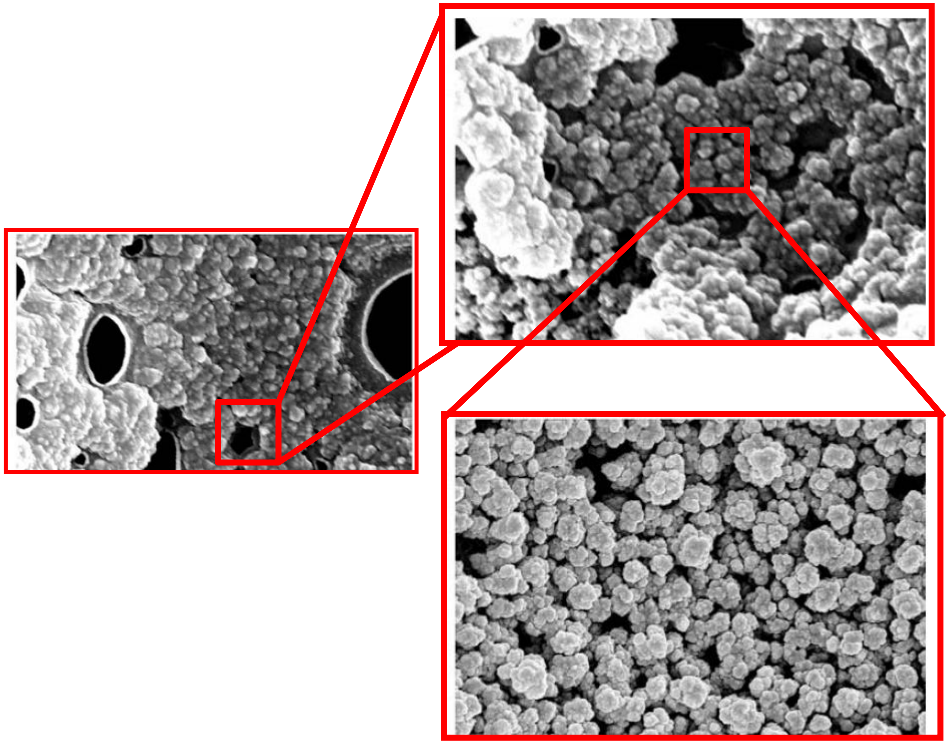
Palombo M., Barbetta A., Cametti C., Dentini M., Capuani S., in preparation

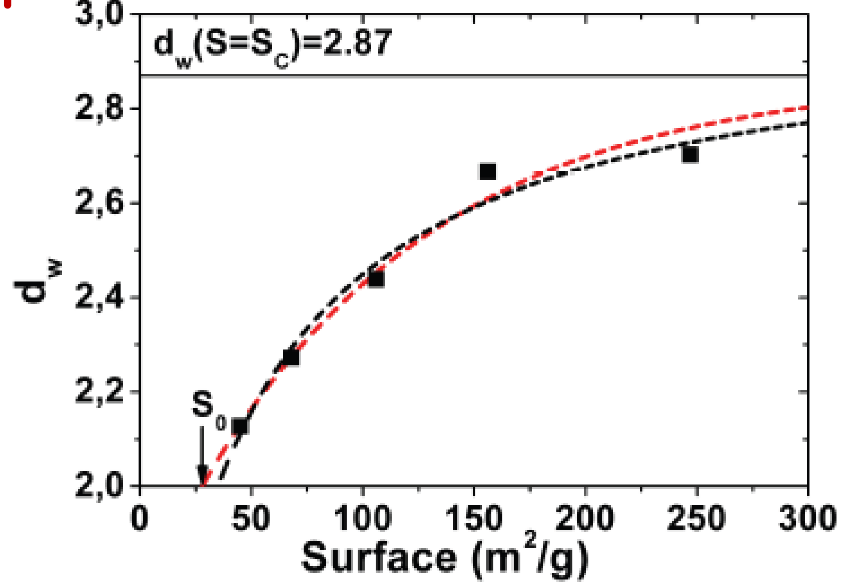
Application to multiscale porous materials

fractal dimension of the random path

$$d_w = 2/a$$

α quantifies global structural complexity



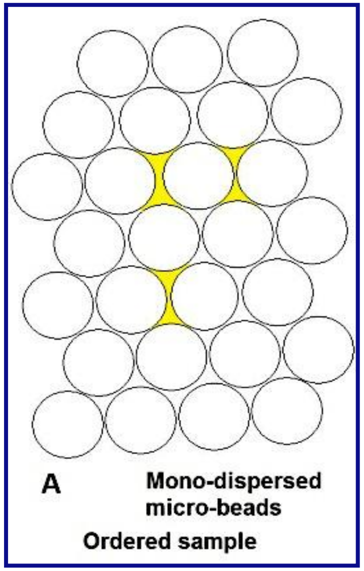


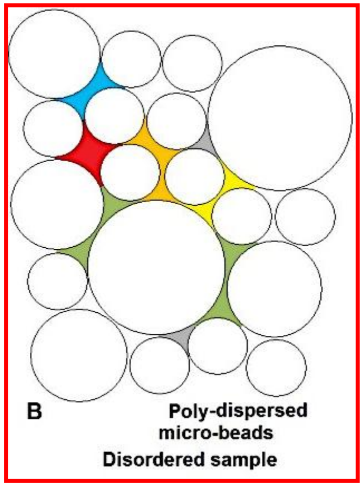
$$d_w = \frac{A1 + B1x + C1x^2}{A2 + B2x + C2x^2}$$

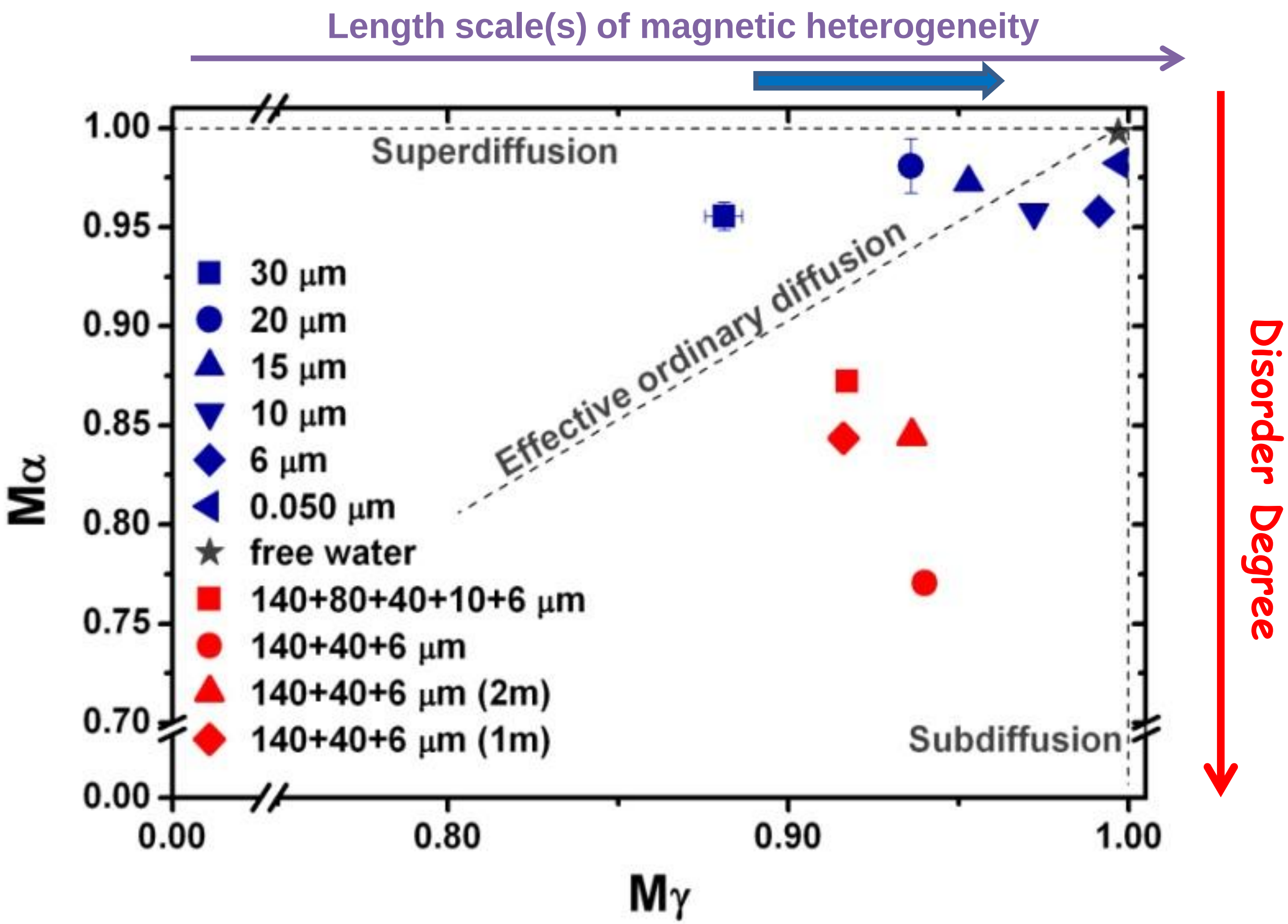
M.J. Saxton
***Biophys, J.* 66 (1994)**

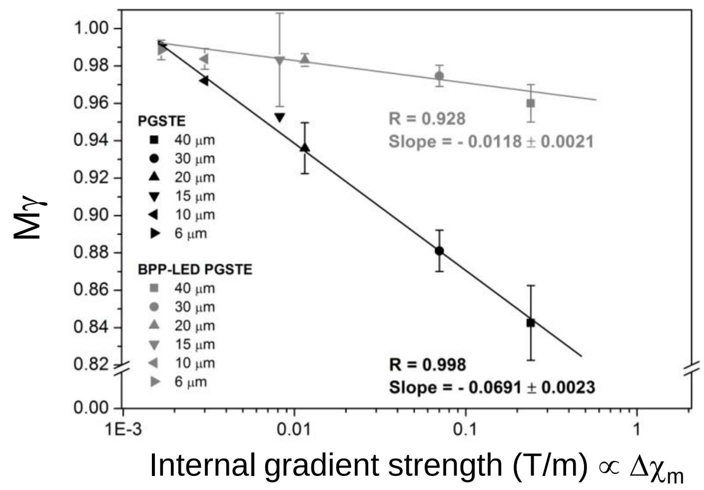
X=S/σ

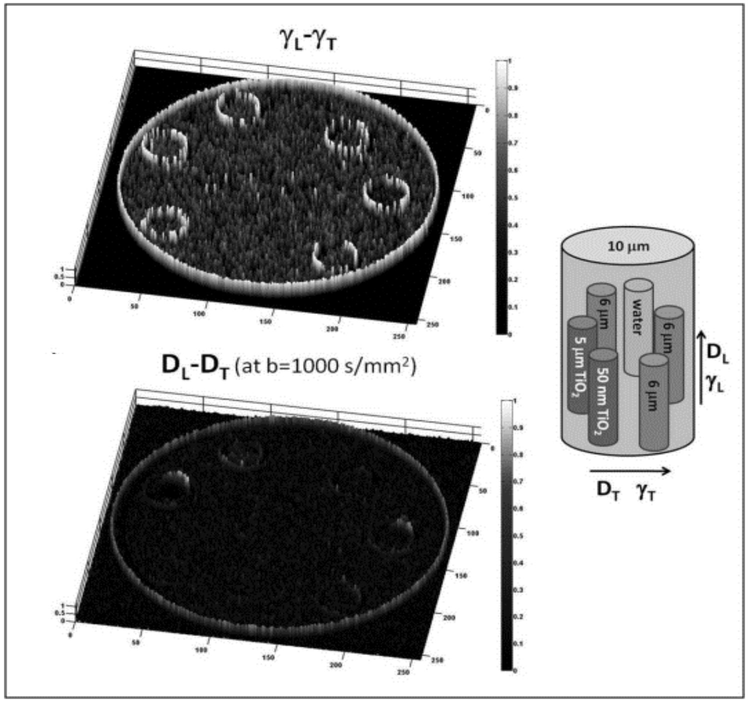
(Bio)-physical interpretation of α and γ parameters









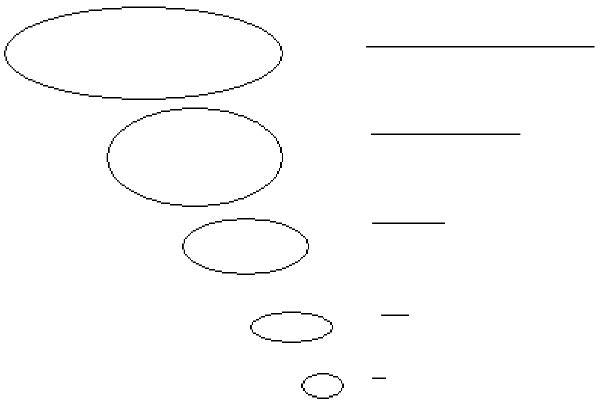


$B_{ind} \sim \Delta\chi * B * A * \cos\theta$

Increase of the image contrast
Enhanced interface contrast

Pseudo-superdiffusion

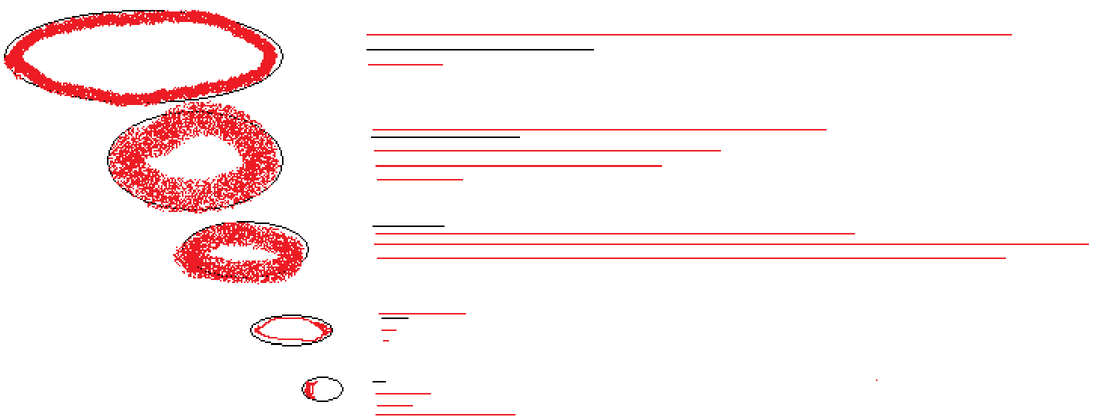
multi-compartmentalization



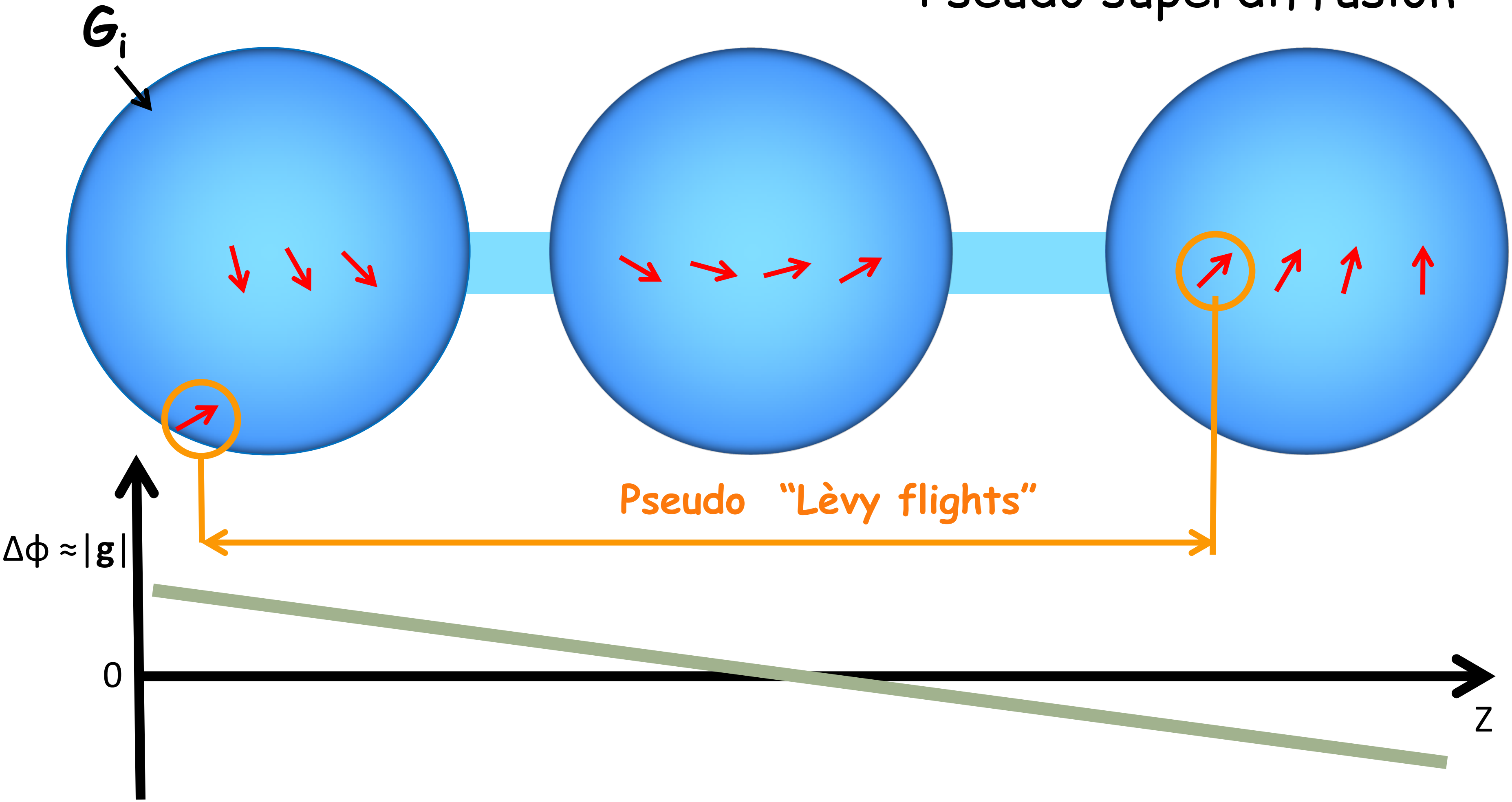
intravoxel diffusion heterogeneity in space, i.e., water molecules diffuse with considerably different free lengths.

due to both water **multi-compartmentalization** and **magnetic susceptibility differences (Δχ)** at the interface between different compartments

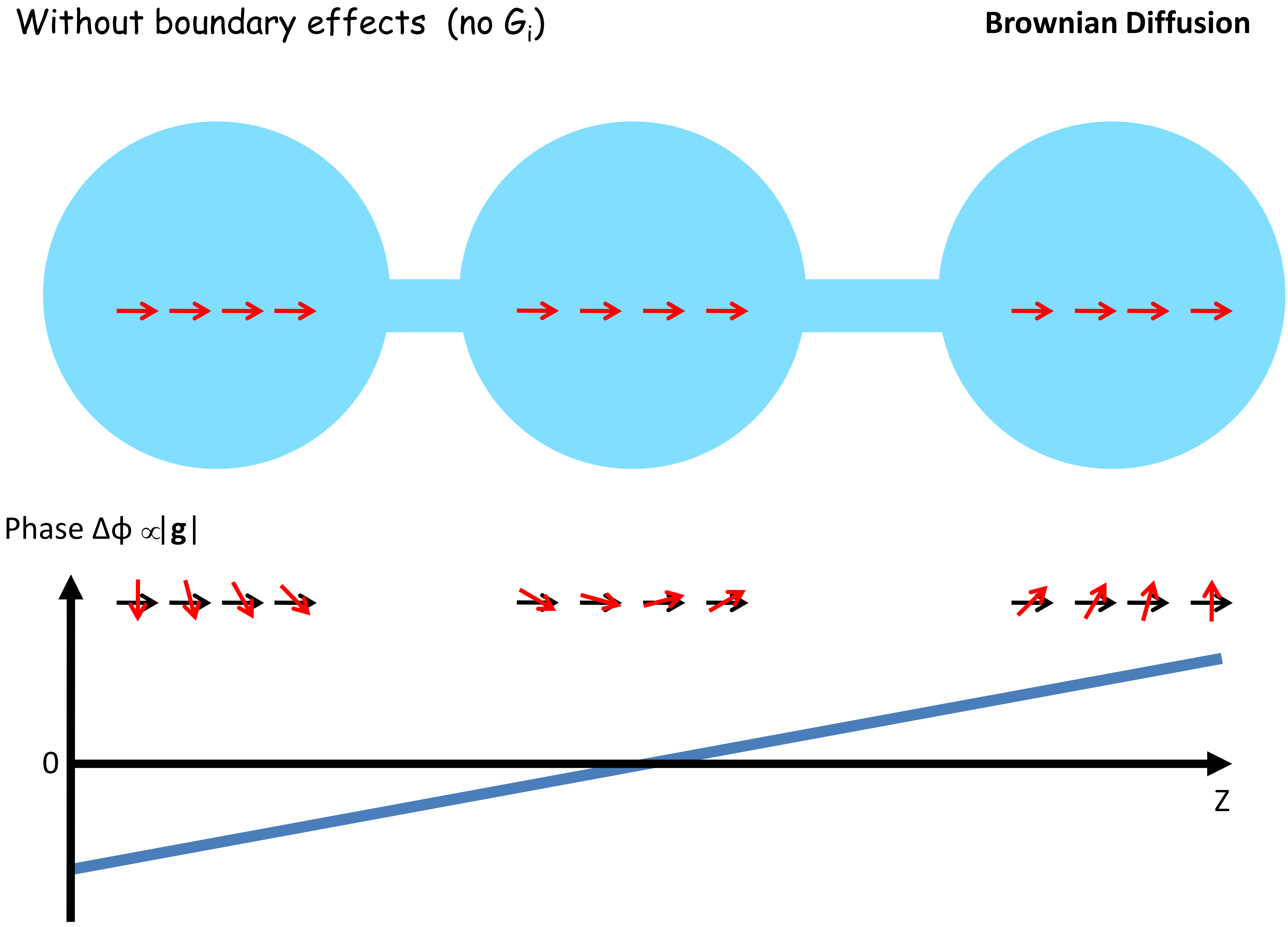
Multi-compartimentalization + magnetic susceptibility differences (Δχ)



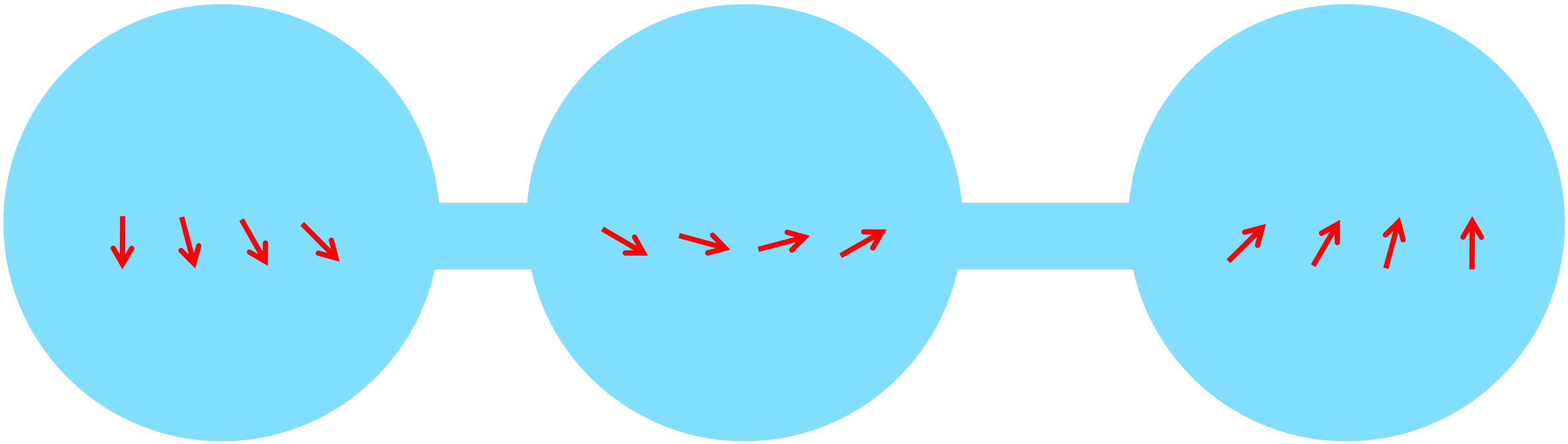
Pseudo superdiffusion



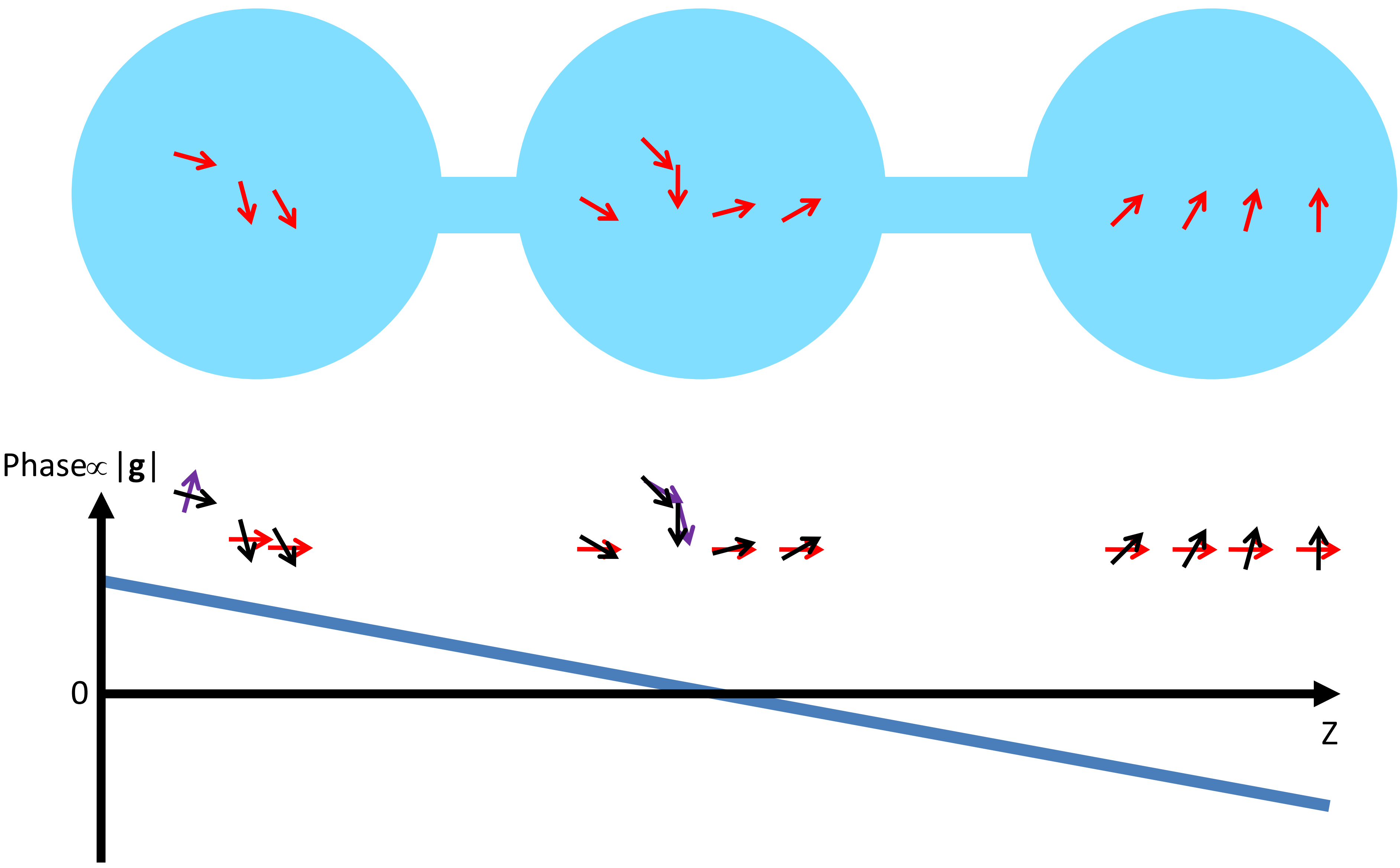
Superdiffusion process (γ <1) is spurious, not real but due to local ΔX (or G_i) at the interface between beads and water


Without boundary effects (no G_i)
Brownian Diffusion
Phase $\Delta\phi \propto |\mathbf{g}|$
0
Z

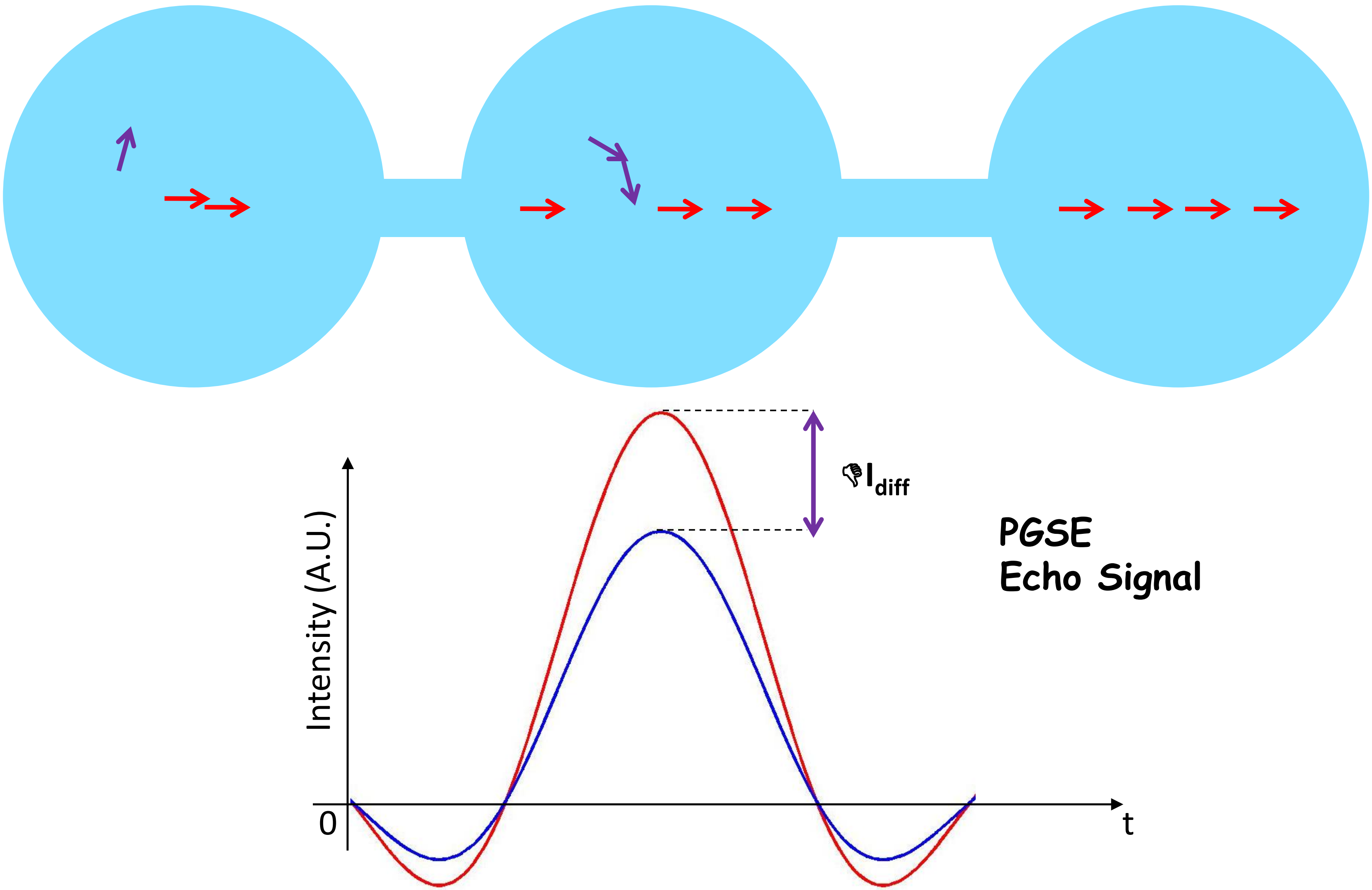
Brownian Diffusion



Brownian Diffusion

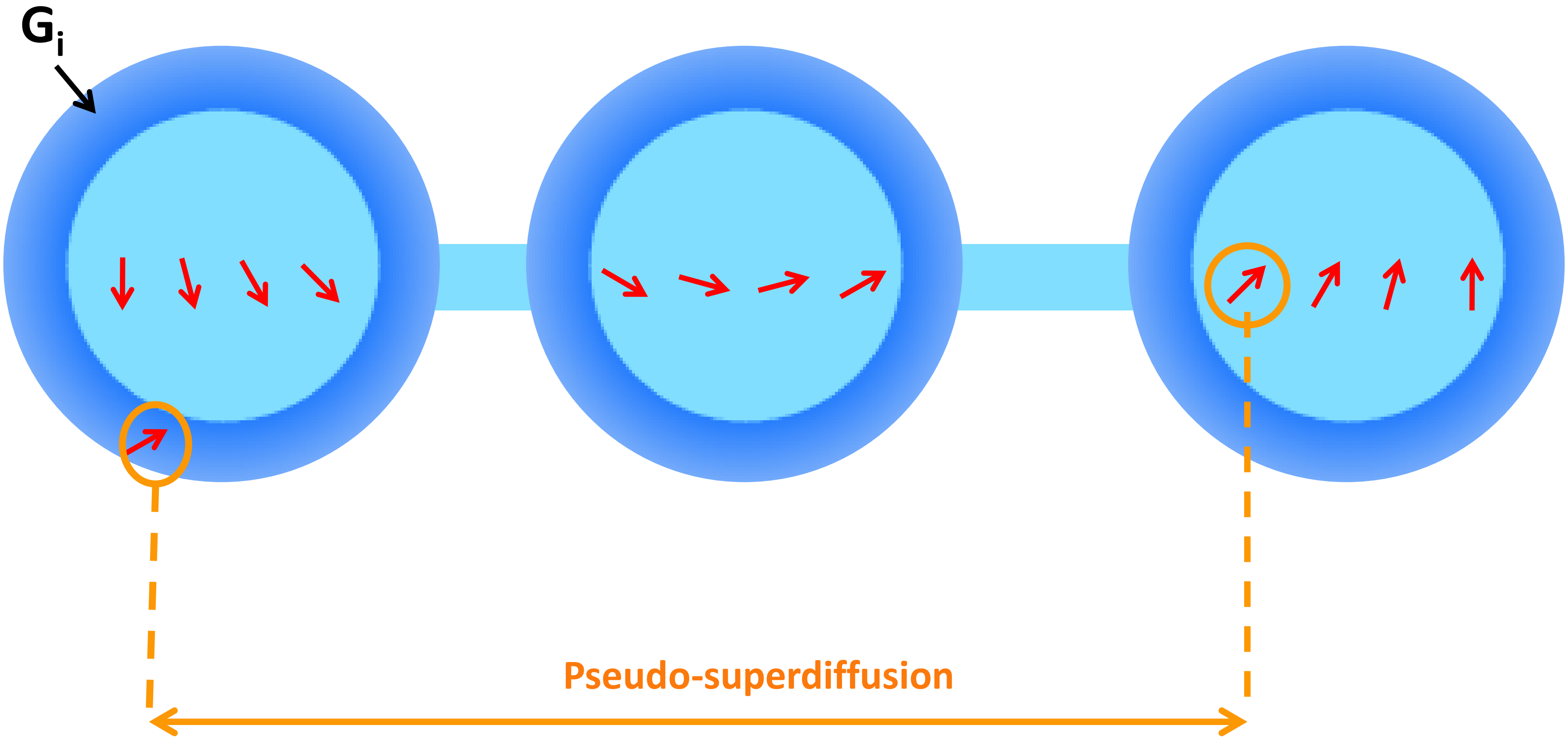


Spectroscopy, Brownian Diffusion

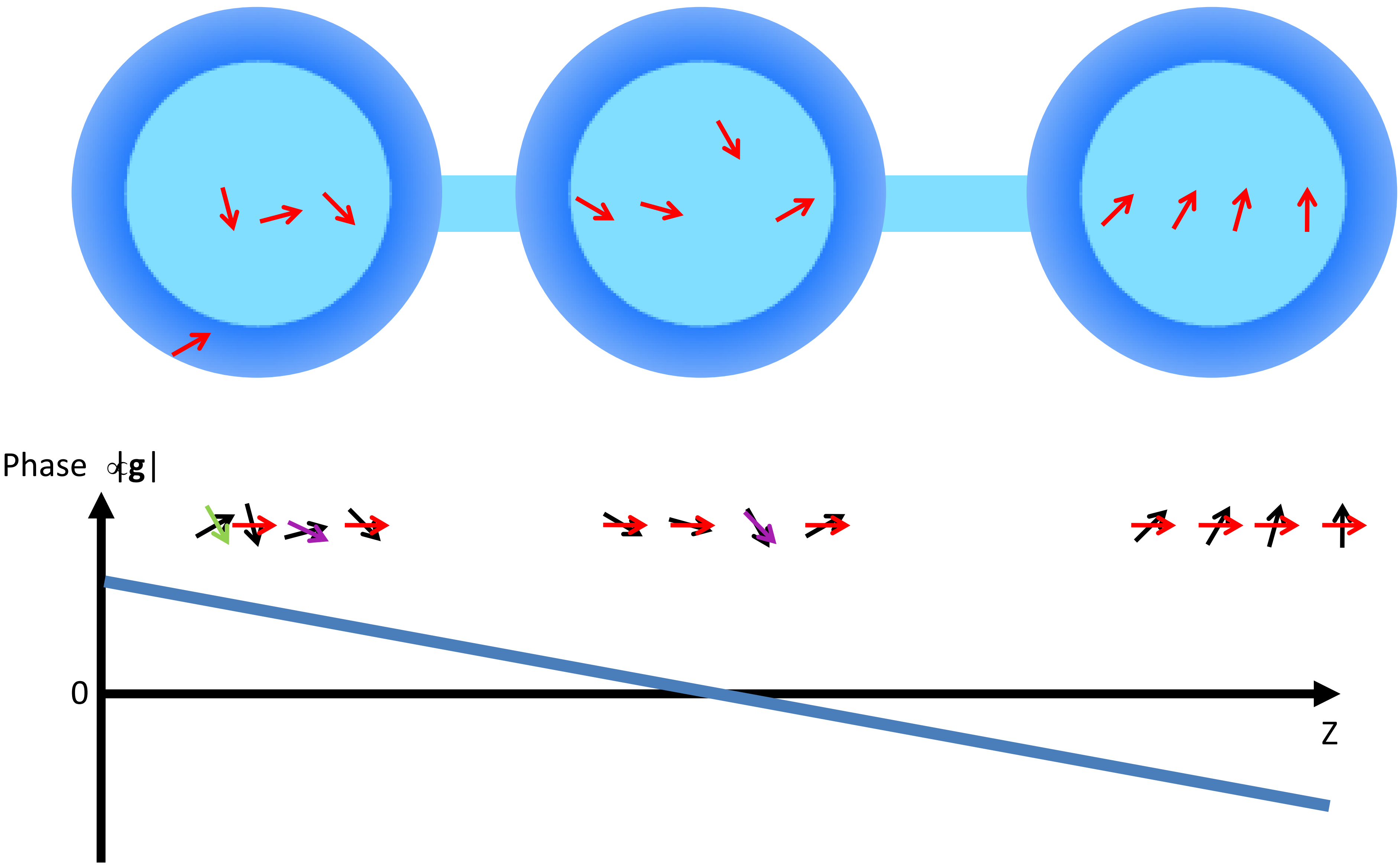


With boundary effects: G_i

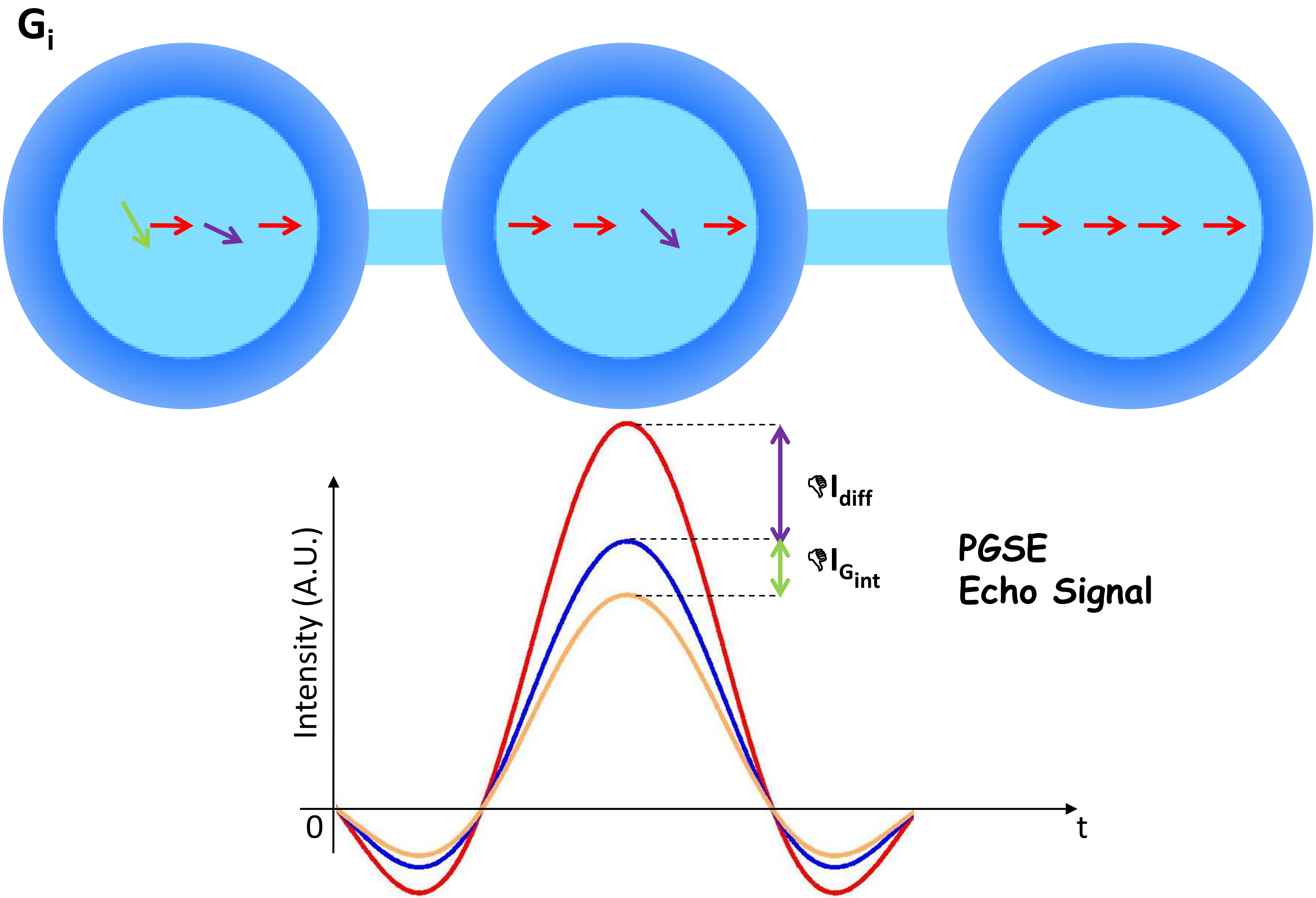
Spectroscopy pseudo-superdiffusion



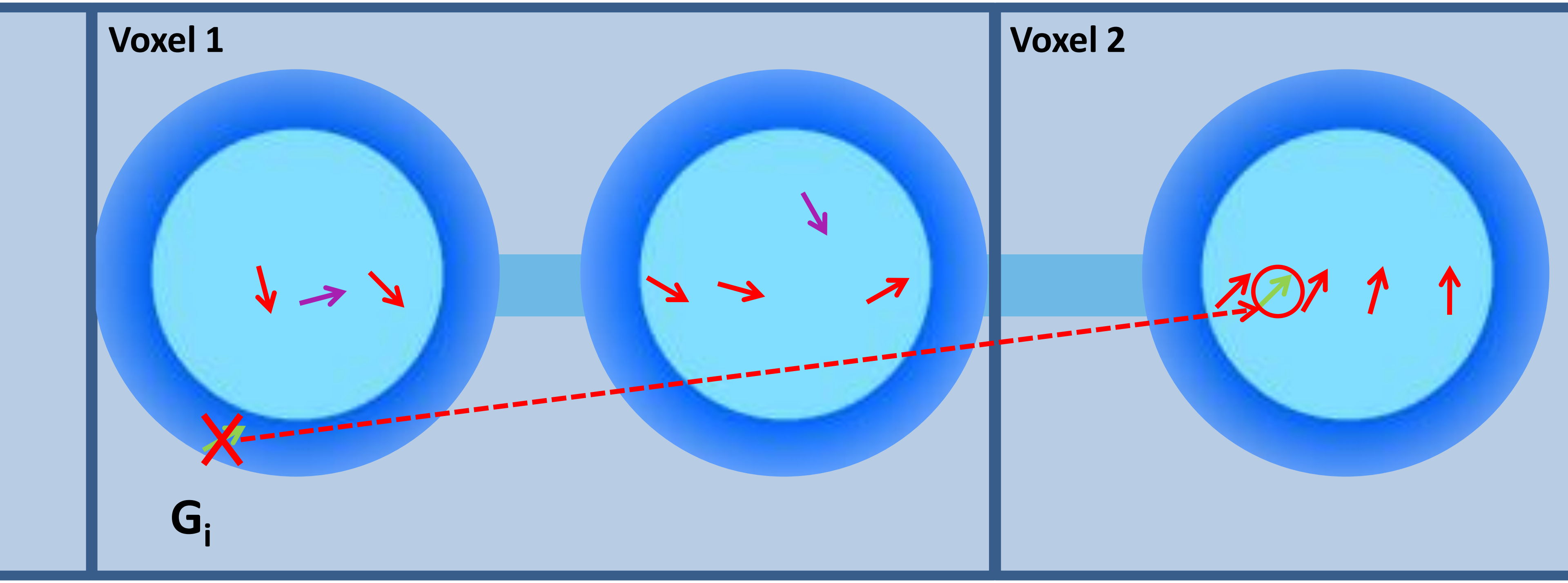
Spectroscopy pseudo-superdiffusion



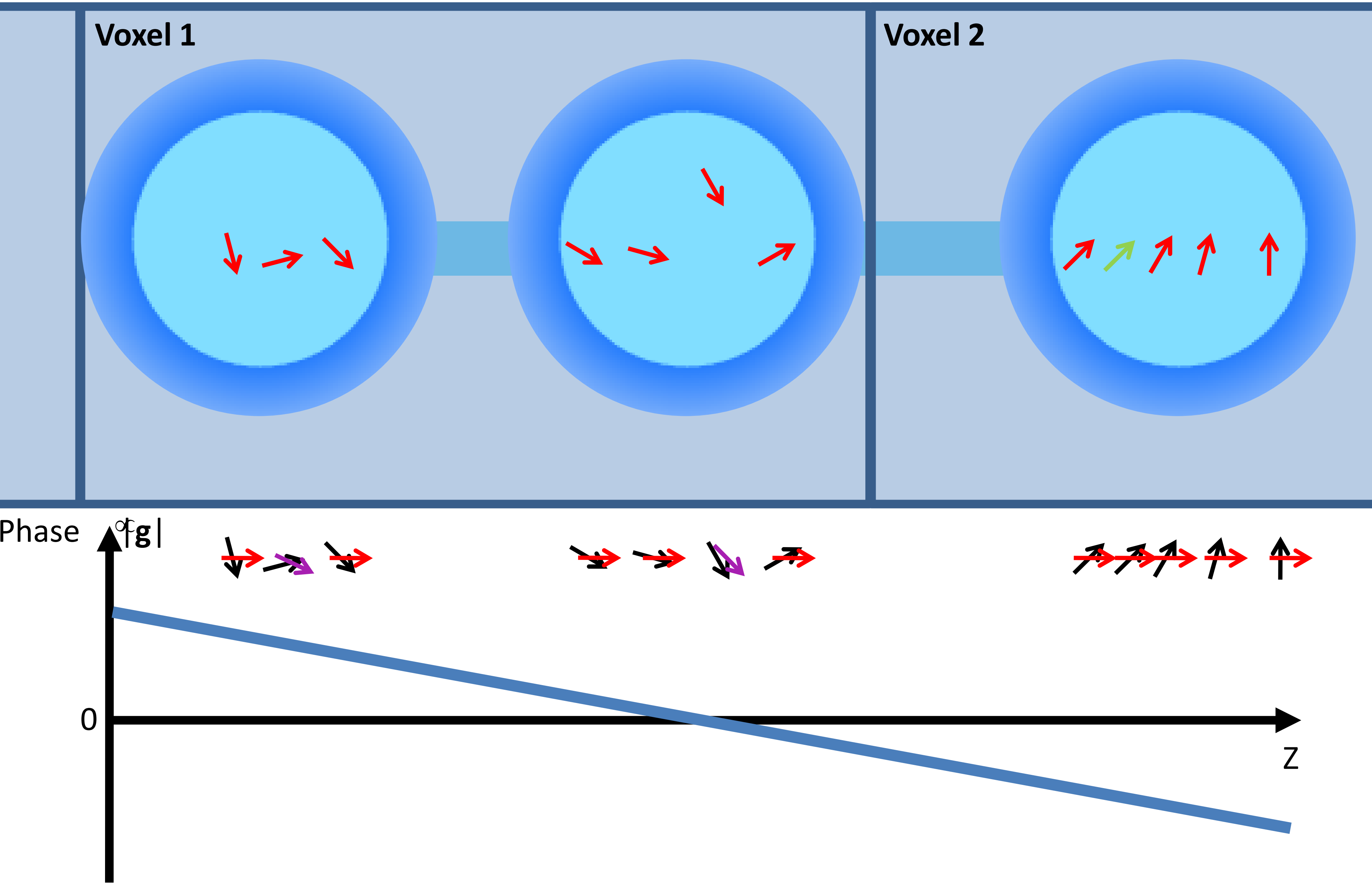
Pseudo-Super Diffusion



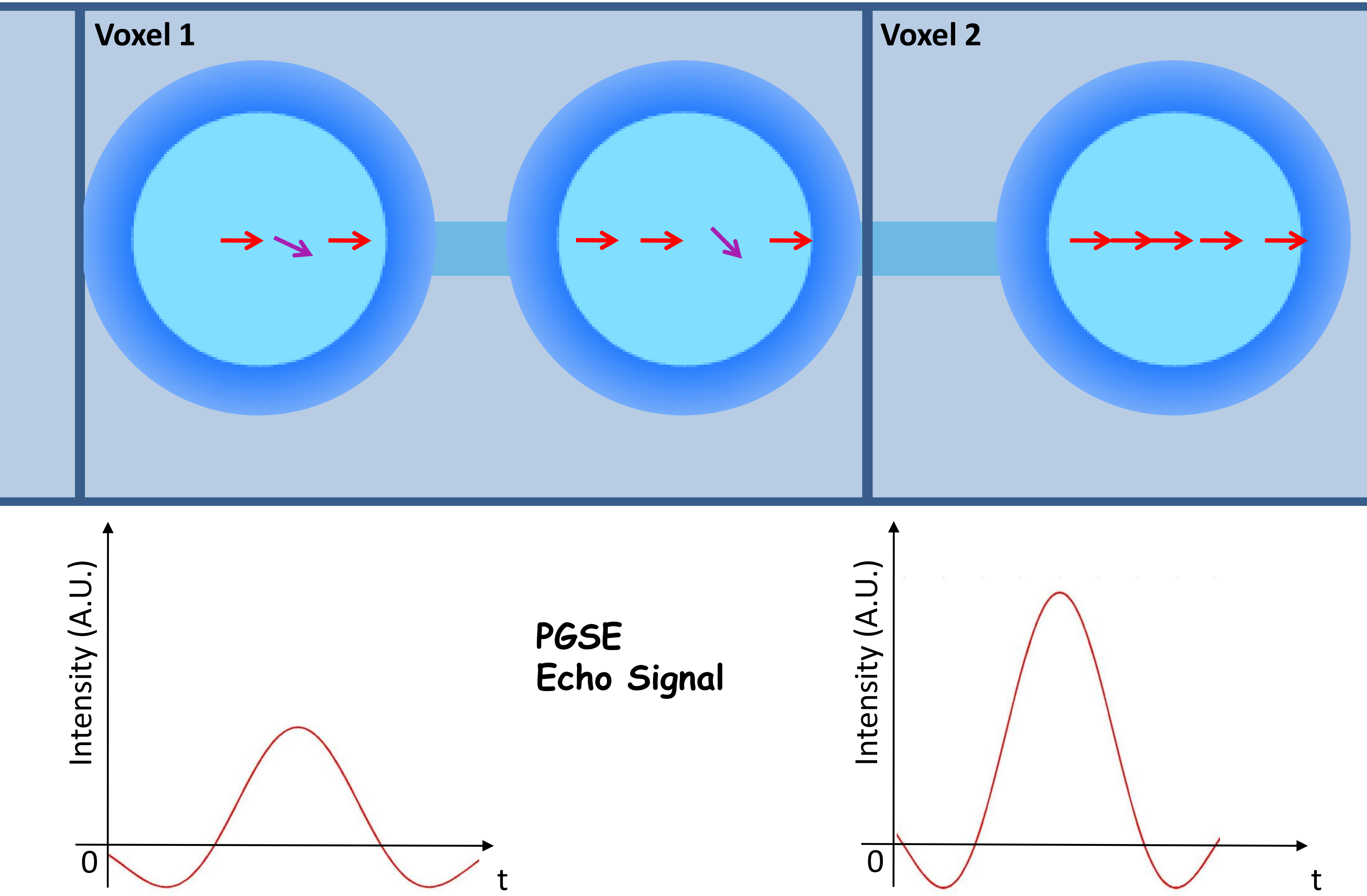
Pseudo-Super Diffusion Imaging



Pseudo-Super Diffusion Imaging



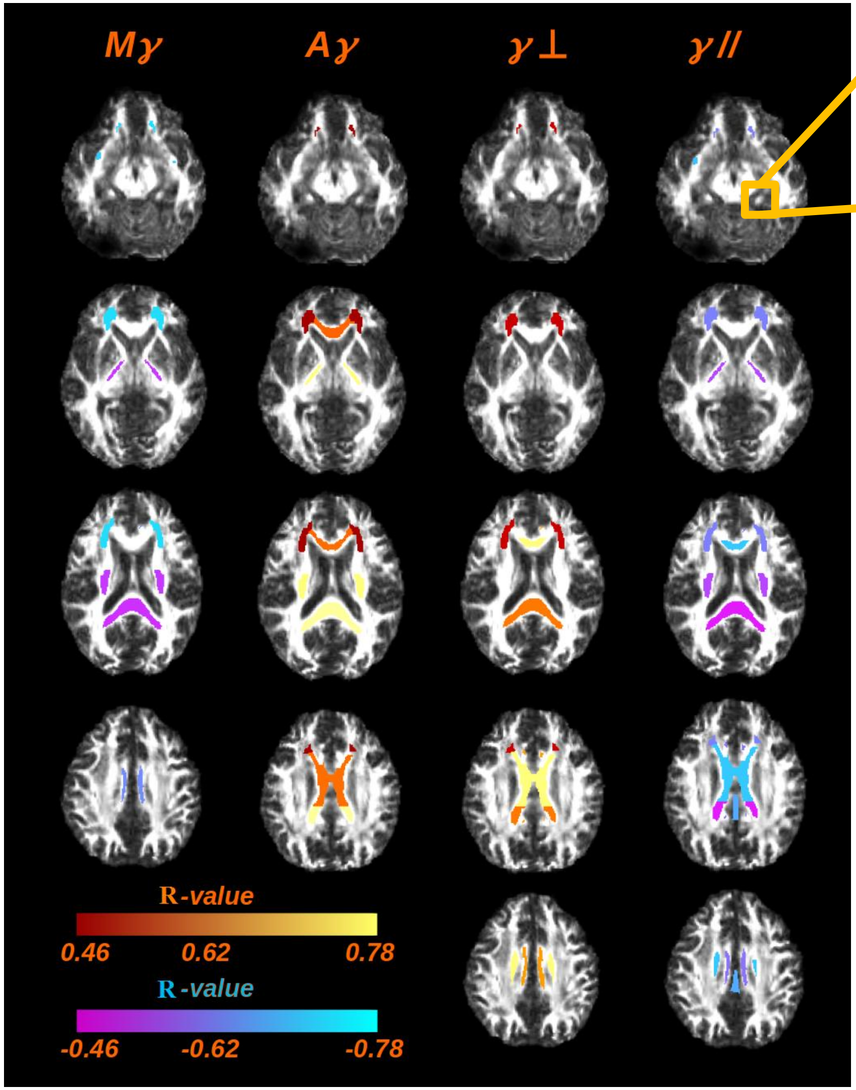
Pseudo-Super Diffusion Imaging

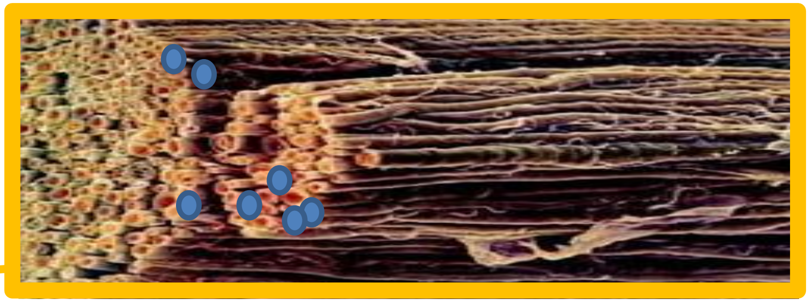


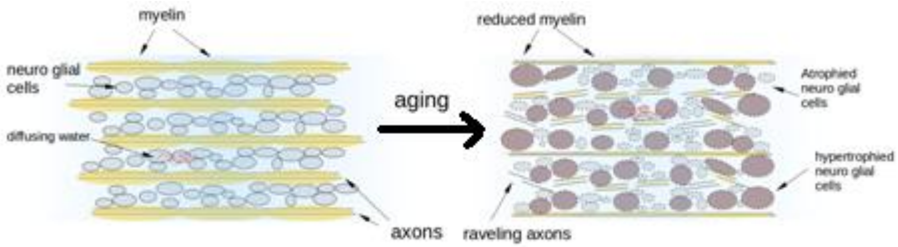
Application to clinical diagnostics

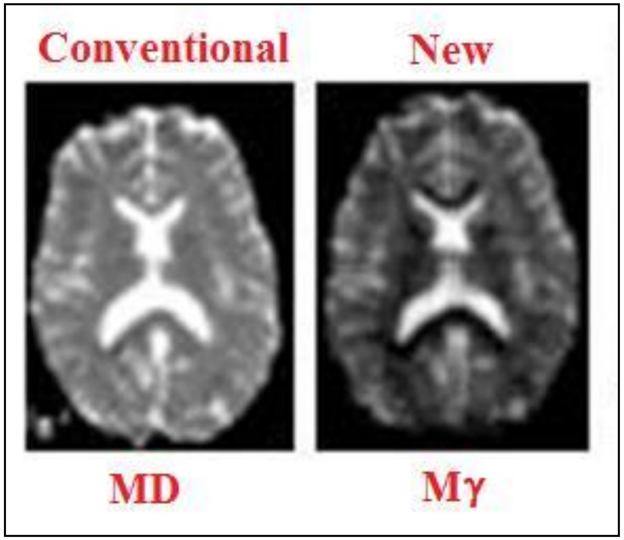
Diffusion reflect the micro-structural rearrangement of tissues

BRAIN AGING





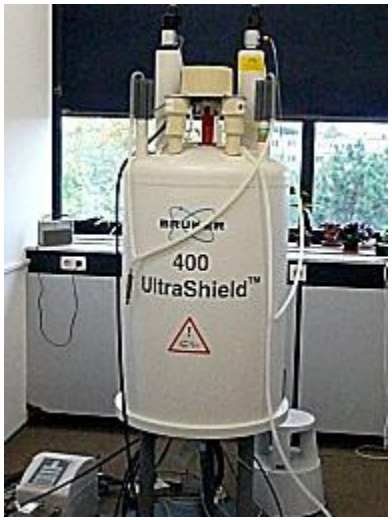


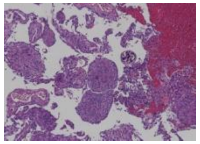


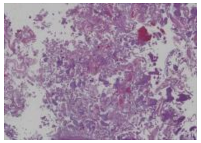
Guerreri M., Caporale A., Palombo M., Bozzali M., Capuani S., submitted

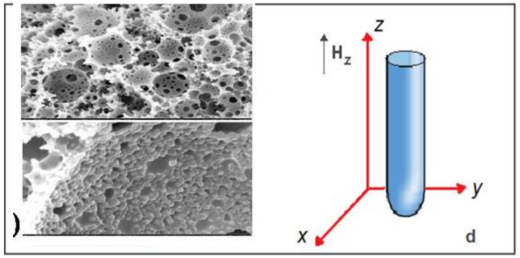
NMR Laboratory

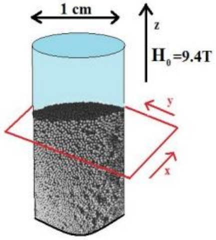
To investigate samples…





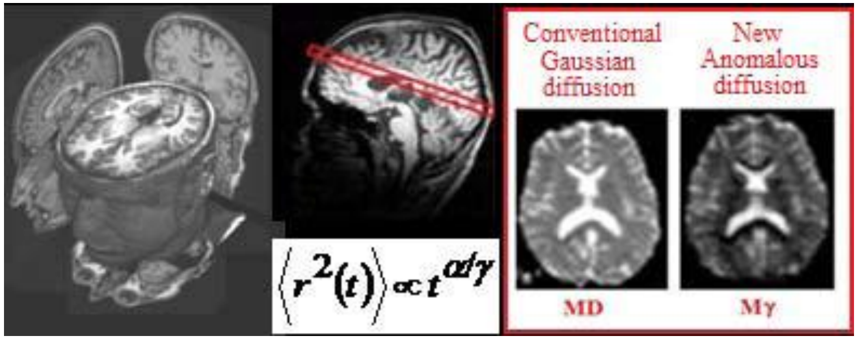






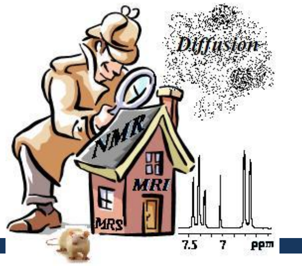
To investigate Human subjects…

Thank you for your attention



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.

UNIVERSITA' degli STUDI di ROMA TOR VERGATA

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