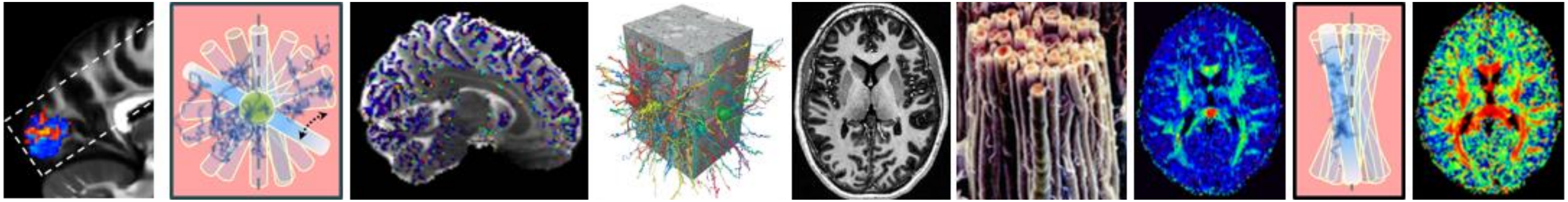
Microstructure Mapping Lab



Principles and applications of diffusion MRI

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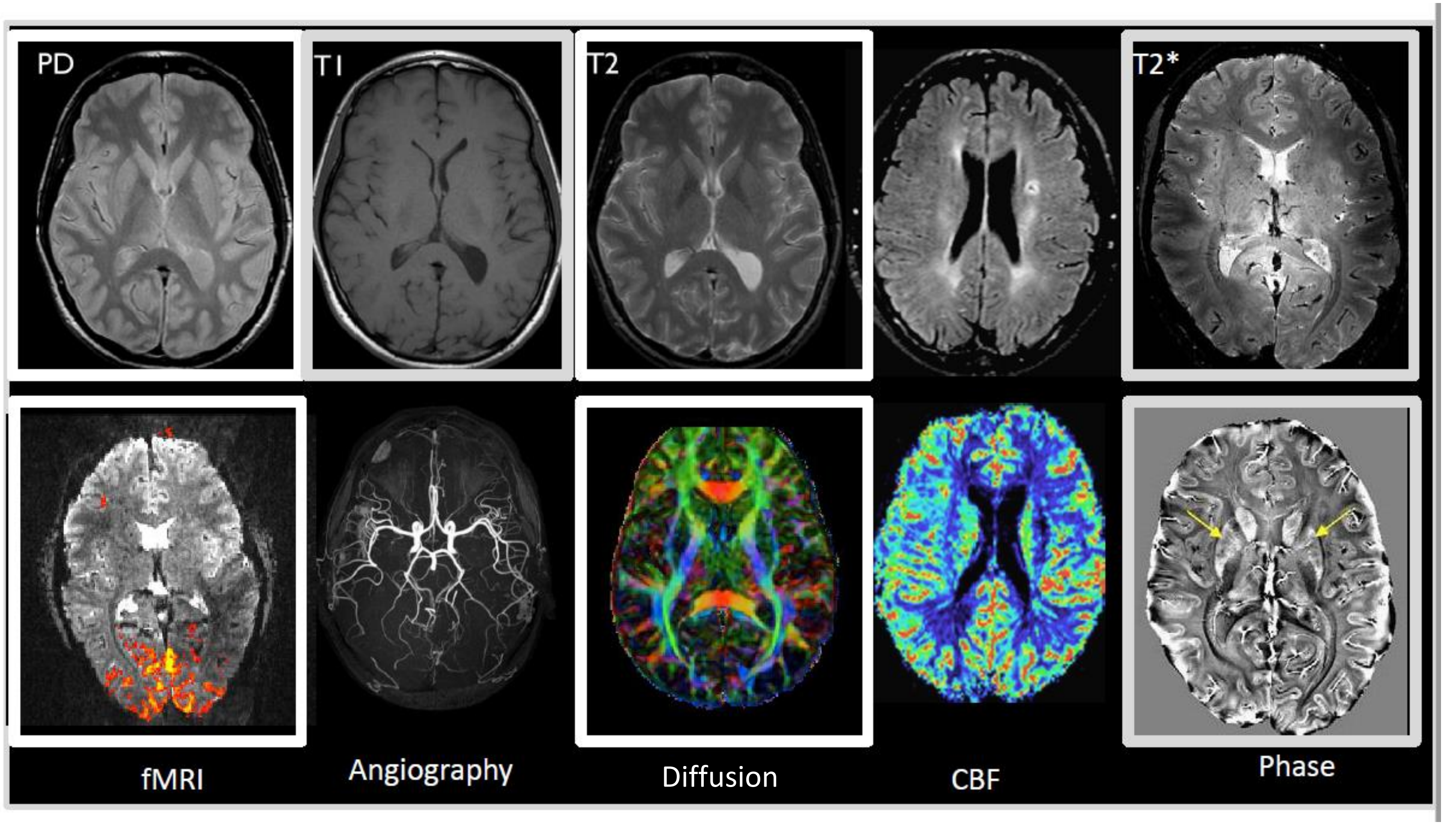
MRI – imaging water

Image contrast can be manipulated to be sensitized to a variety of features

- Depending on: chemical & magnetic properties of immediate environment, mobility of molecules…



Diffusion MRI: sensitizing the signal to the Brownian motion (random walk) of water molecules

Outline

I. Diffusion-weighting

II. Gaussian approximation regime: ADC and DTI

III. Beyond Gaussian:

   i. Signal representations: DKI

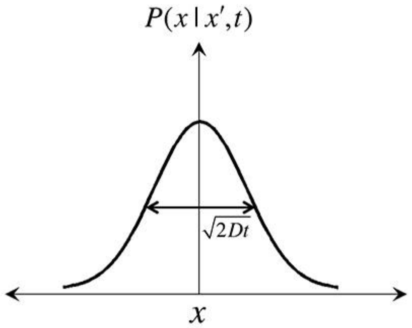
   ii. White matter models & applications

   iii. Gray matter models & applications

   iv. Thinking outside the brain

Diffusion MRI gives access to the mesoscale

➢ **Unrestricted homogeneous medium:**

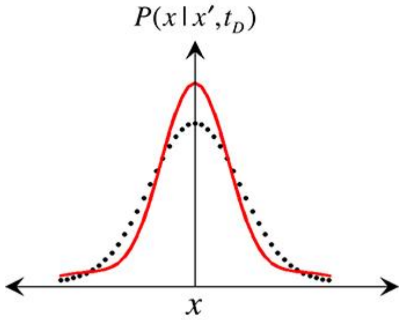


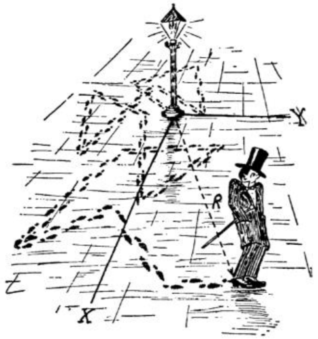
$$\langle x^2 \rangle = 2nDt$$

MRI voxel size:
1 – 2 mm

Typical length scale for
microstructure: 1 – 10 μm

➢ **Biological tissue:**



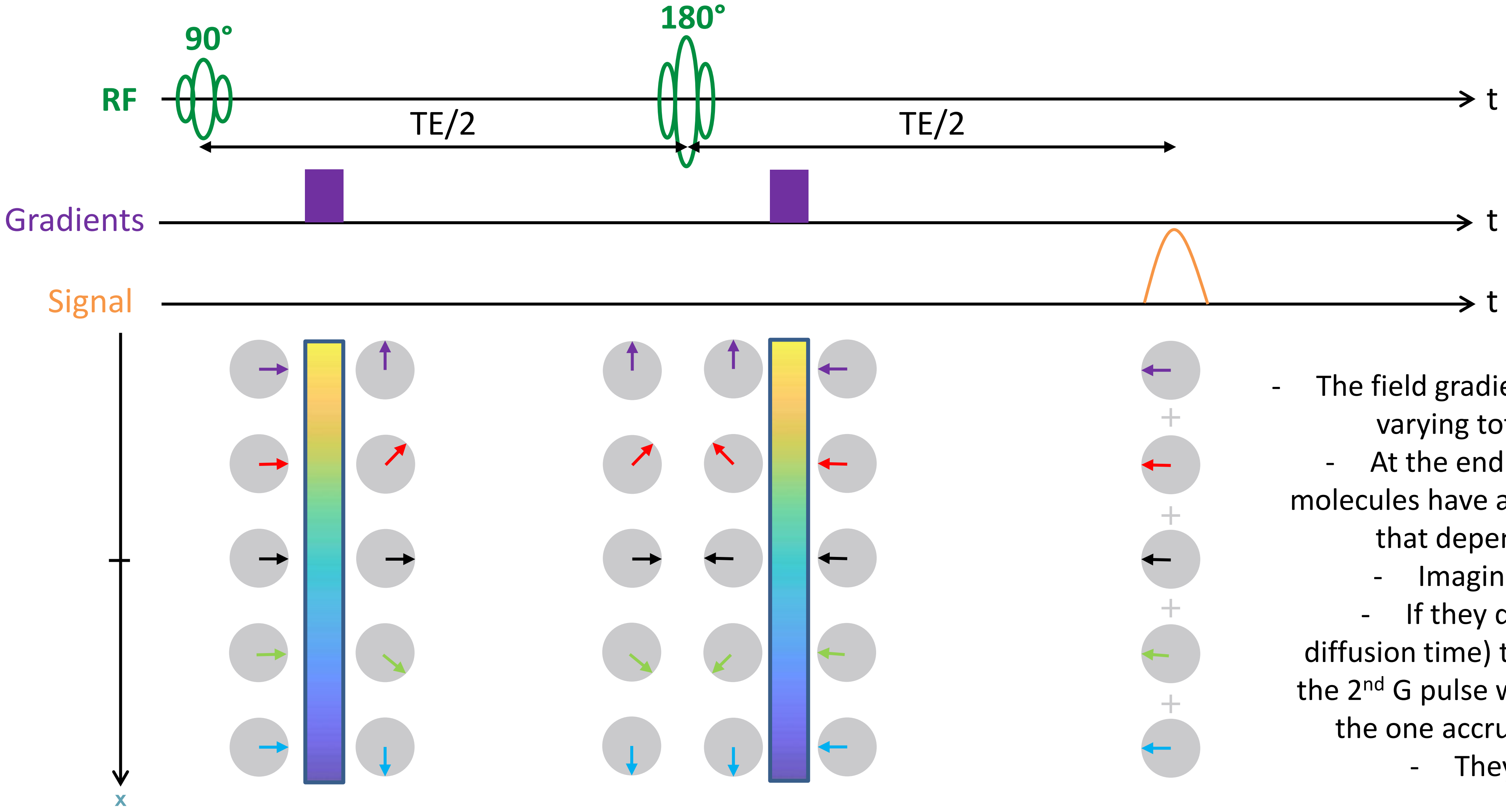


Mean displacement of water molecules :

- **t = 2 – 500 ms** ⟶ $\sqrt{\langle x^2 \rangle} \approx 2 - 50\ \mu m$

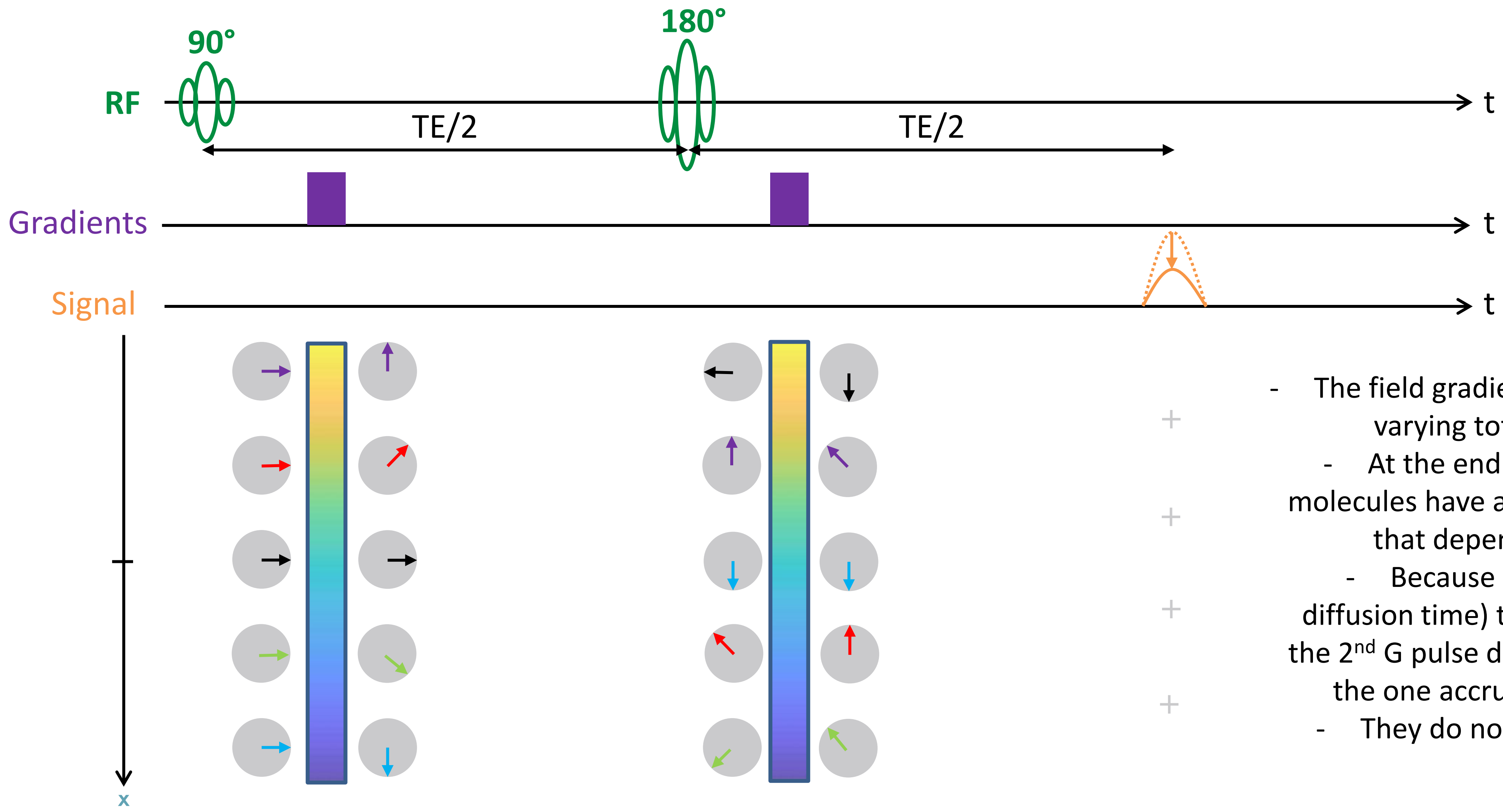
➢ Excellent probe of tissue microstructure

Diffusion weighting in MRI – pulsed gradient spin-echo (PGSE)



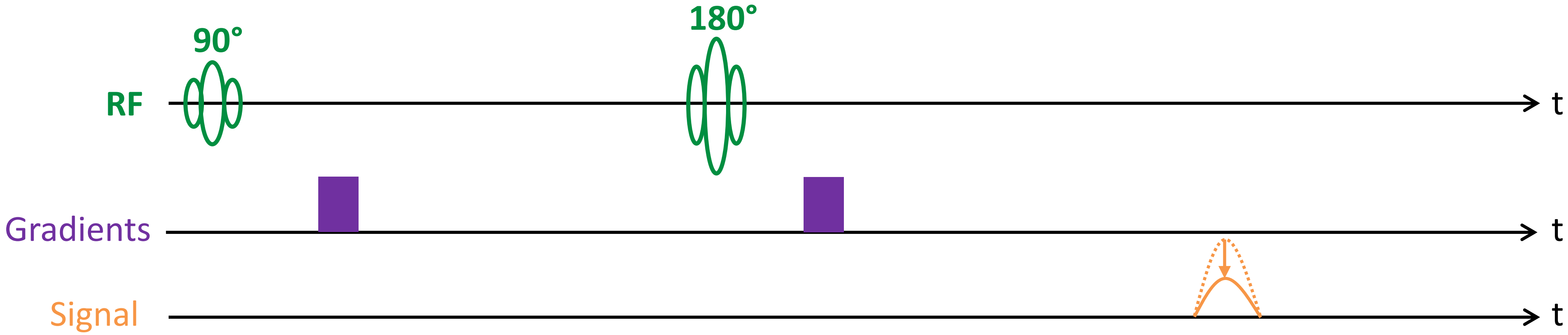
- The field gradient creates a linearly varying total field: $B(x)=B_0+G.x$
- At the end of the (short) pulse, molecules have accumulated a phase that depends on their position
- Imagine: no diffusion (D=0)
- If they don't mix (during the diffusion time) the phase accrued in the 2nd G pulse will fully compensate the one accrued in the 1st G pulse
- They add up coherently!

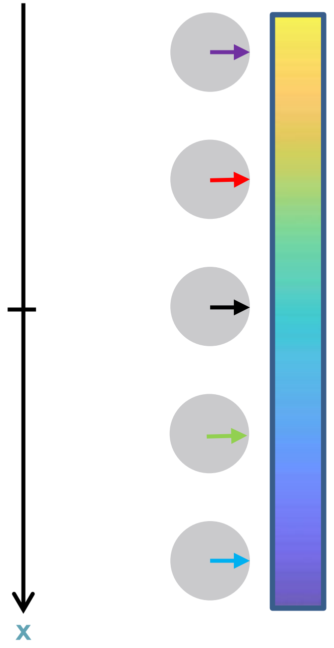
Diffusion weighting in MRI – pulsed gradient spin-echo (PGSE)



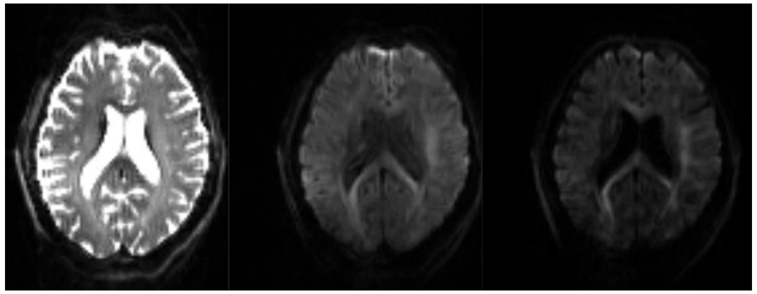
- The field gradient creates a linearly varying total field: $B(x)=B_0+G.x$
- At the end of the (short) pulse, molecules have accumulated a phase that depends on their position
- Because they mix (during the diffusion time) the phase accrued in the 2nd G pulse does not compensate the one accrued in the 1st G pulse
- They do not add up coherently! Signal attenuation

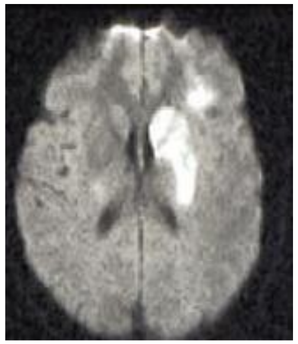
Diffusion weighting: signal attenuation & contrast





Signal attenuation due to diffusion
- Increases with *diffusion-weighting*
- Increases with <u>Diffusivity</u>





Stroke

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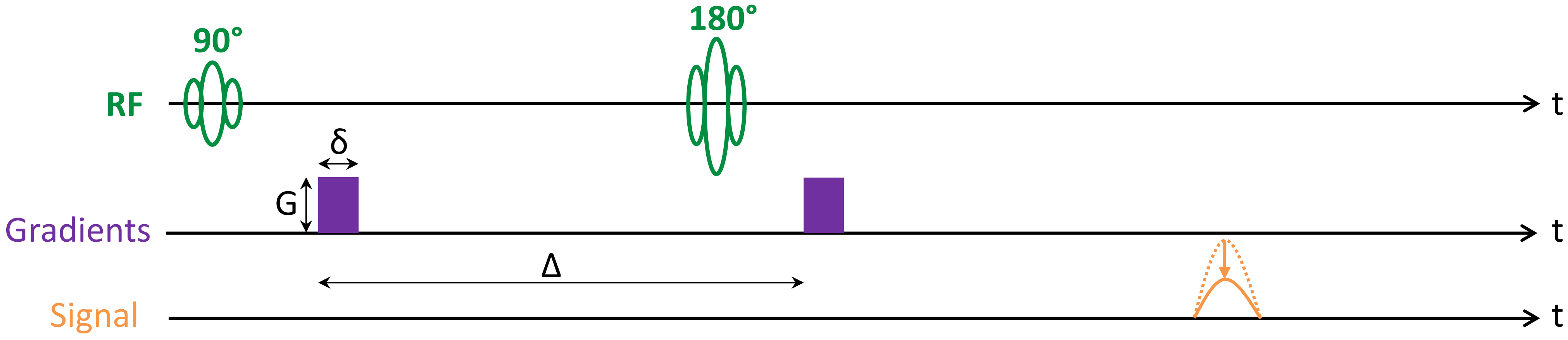
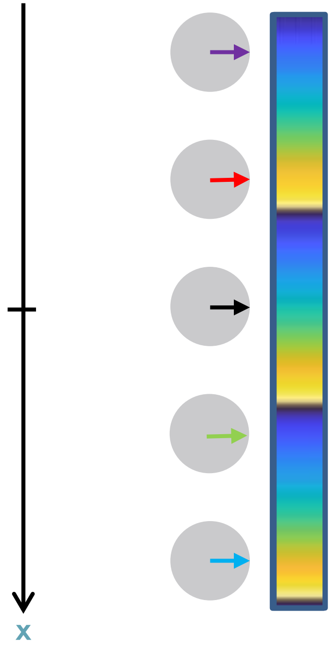
Diffusion weighting in MRI – q, t and the b-value





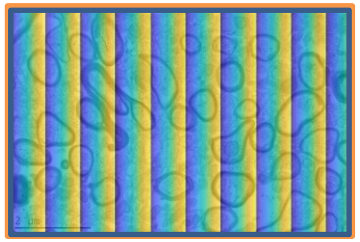
$$b = (\gamma \delta G)^2 \cdot \left(\Delta - \frac{\delta}{3}\right) = q^2 t$$

Phase warp

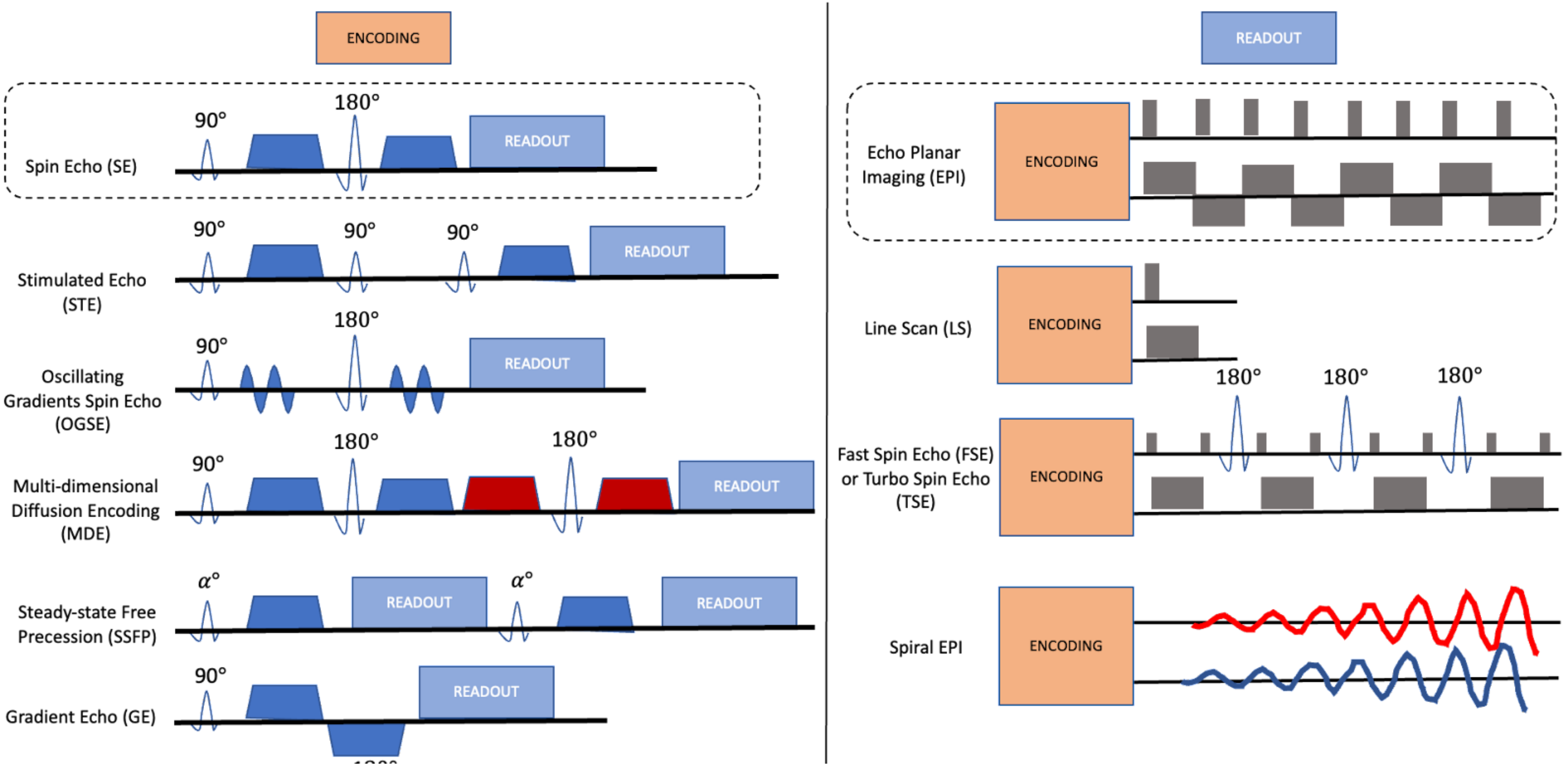
Diffusion time

Low q

High q



Diffusion encoding schemes and image read-out schemes



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Jelescu et al, Magn Reson Med 2025

Summary so far

- Diffusion of water molecules in biological tissue (e.g. brain):
  - Is a stochastic process due to thermal agitation, it is always present
  - Is not free: it is affected by the cellular structures (restriction & hindrance)
  - Can provide information about tissue microstructure below the MR image spatial resolution
- In Diffusion MRI, we sensitize the signal amplitude to the diffusion of water molecules using strong magnetic field gradients G
- The MRI signal attenuation depends on:
  - The diffusion properties of the medium (that we want to measure)
  - The diffusion weighting imparted: $b=q^2.t$ (that we set as acquisition parameter)

Outline

I. Diffusion-weighting

II. Gaussian approximation regime: ADC and DTI

III. Beyond Gaussian:

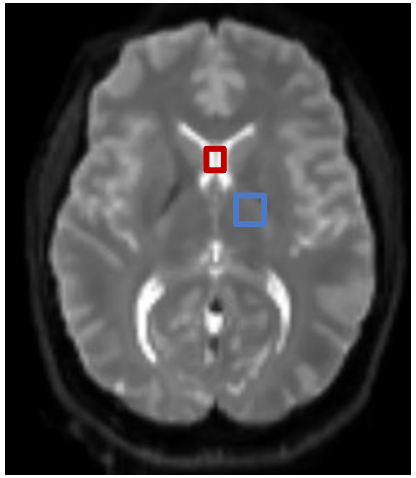
  i. Signal representations: DKI

  ii. White matter models & applications

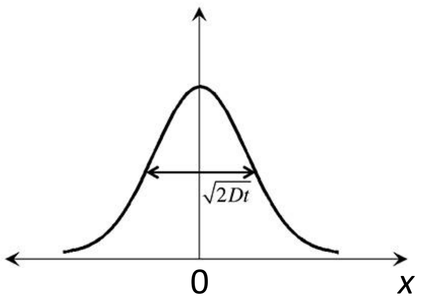
  iii. Gray matter models & applications

  iv. Thinking outside the brain

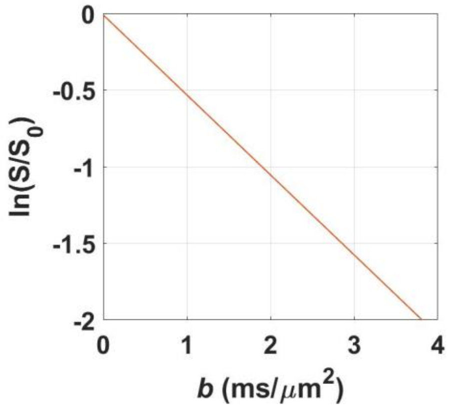
From a free medium to biological tissue (and from D to ADC)



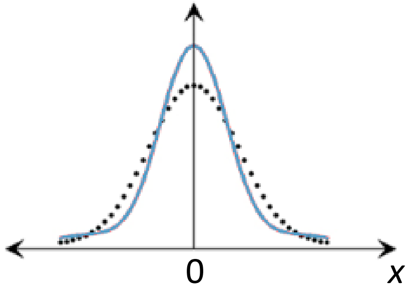
Free homogeneous medium
Gaussian diffusion



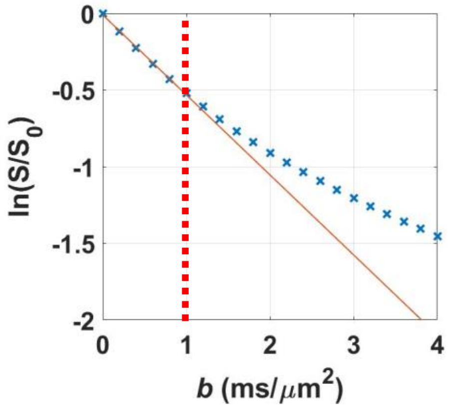
$$\ln\left(\frac{S}{S_0}\right) = -\mathrm{bD}$$



Biological tissue
Non-Gaussian diffusion



$$\ln\left(\frac{S}{S_0}\right) = \mathrm{F(b)}$$



Low b-value regime:
Gaussian approximation
"DTI" regime

$$\ln\left(\frac{S}{S_0}\right) \approx -b \cdot ADC + \mathcal{O}(b^2)$$

Apparent Diffusion Coefficient

Le Bihan, Radiology 1986

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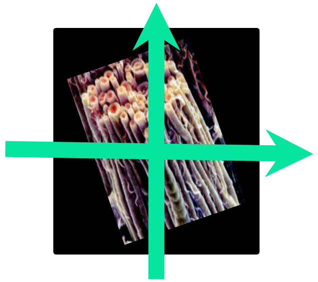
From the ADC to the diffusion tensor (DTI)

Apparent Diffusion Coefficient

…

along a direction $\vec{g}$,

given by $\vec{G} = G \cdot \vec{g}$



$$\ln \frac{S(b,\vec{g})}{S_0} = -b \cdot ADC_{\vec{g}}$$

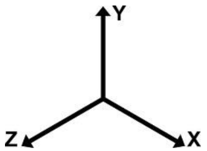
$\vec{g} = [g_1\ g_2\ g_3]$

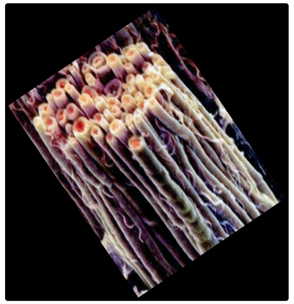
$$\ln \frac{S(b,\vec{g})}{S_0} = -b \sum_{i,j=1}^{3} g_i g_j D_{ij} = -b \vec{g}^T \hat{D} \vec{g}$$

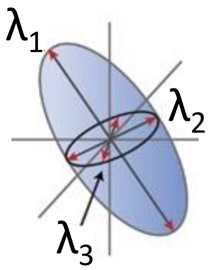
$\vec{g} = [1\ 0\ 0]$

$\vec{g} = [0\ 1\ 0]$

$$\hat{D}_{\{\vec{x},\vec{y},\vec{z}\}} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix}$$







$$\hat{D}_{\{\vec{e}_1,\vec{e}_2,\vec{e}_3\}} = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix}$$

- Symmetric → 6 coefficients to estimate
- Invertible with all eigenvalues real and positive

Minimal data:

- 1 b = 0
- 6 non collinear directions on 1 shell (e.g. b = 1 ms/µm^2)

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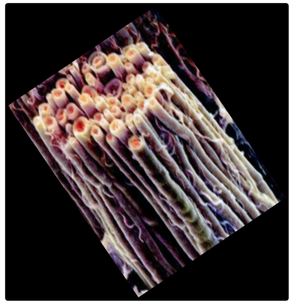
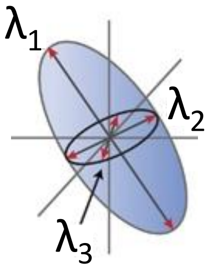
Basser, Biophys J 1994

DTI scalars



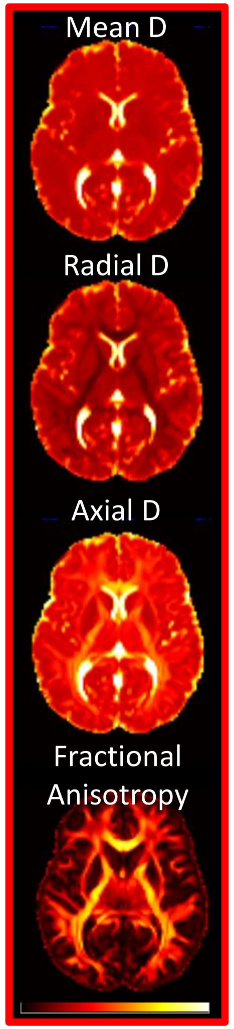


$$\widehat{D}_{\{\vec{e}_1,\vec{e}_2,\vec{e}_3\}} = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix}$$

In white matter in particular:

$\vec{e}_1$: direction of faster diffusion in the voxel (along the axon bundle)

→ Useful in early days of tractography for tracking fiber orientations from voxel to voxel



Mean diffusivity:

$$MD = (\lambda_1 + \lambda_2 + \lambda_3)/3$$
$$MD = \mathrm{Tr}(\widehat{D})/3$$

$MD \sim 1 \frac{\mu m^2}{ms}$ in brain, little GM/WM contrast

Radial diffusivity:

$$RD = (\lambda_2 + \lambda_3)/2$$

Good GM/WM contrast, lowest in WM

Axial diffusivity:

$$AD = \lambda_1$$

Some GM/WM contrast, highest in WM

Fractional anisotropy:

$$FA = \sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{\lambda_1^2+\lambda_2^2+\lambda_3^2}}$$

FA = 0 : isotropic diffusion, FA = 1 : fully anisotropic (1D)

Excellent GM/WM contrast, highest in WM

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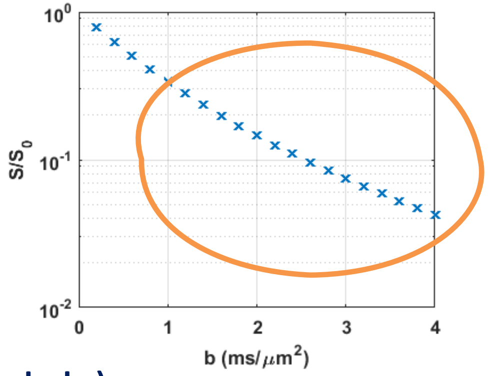
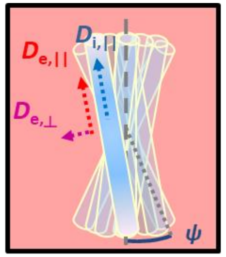
Signal representations vs biophysical models





Signal representations (statistical models)

- "Formulas" to describe signal decay

☺ Applicable to any type of tissue

☺ Provide sensitive biomarkers

☹ Lack specificity: difficult to make inferences about microstructural changes

Biophysical tissue models

- Simplified "pictures" of medium in which water molecules are diffusing

😐 Tissue-specific

☺ Specific biomarkers that characterize microstructure

☹ Assumption validity?

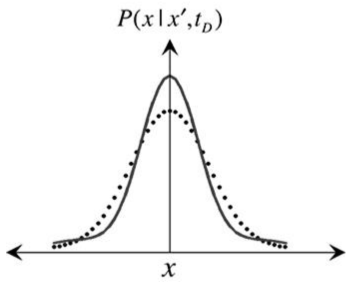
☹ Fit stability?

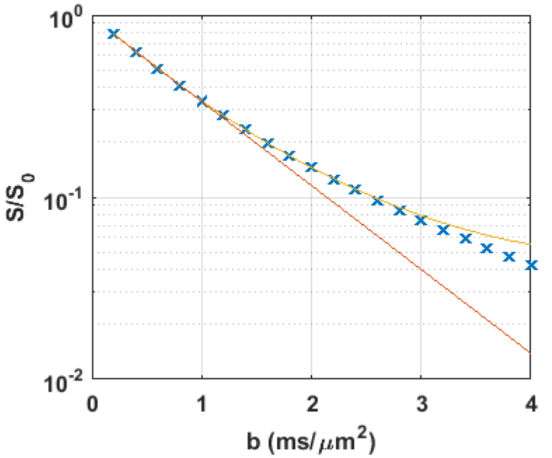
Representations: Diffusion Tensor Imaging (DTI) and Kurtosis (DKI)

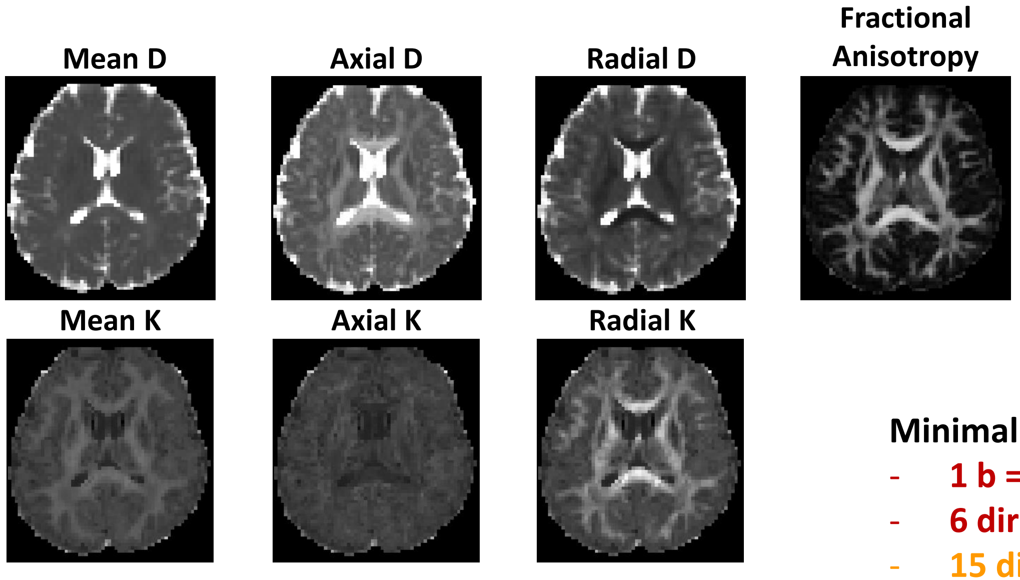
$$\ln\frac{S}{S_0} = -bD + \frac{1}{6}b^2D^2K + \cdots$$

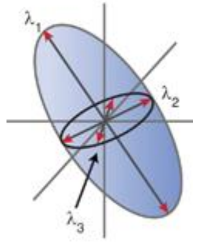
$$\ln\frac{S}{S_0} = -b\sum_{i,j=1}^{3} g_i g_j D_{ij} + \frac{1}{6}b^2\overline{D}^2 \sum_{i,j,k,l=1}^{3} g_i g_j g_k g_l W_{ijkl} + \cdots$$

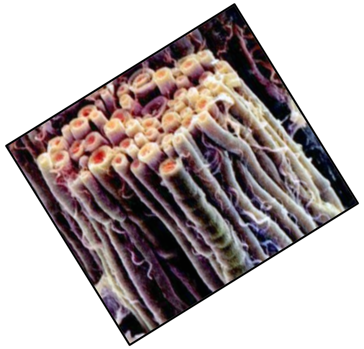
diffusion tensor (DTI) & kurtosis tensor (DKI)







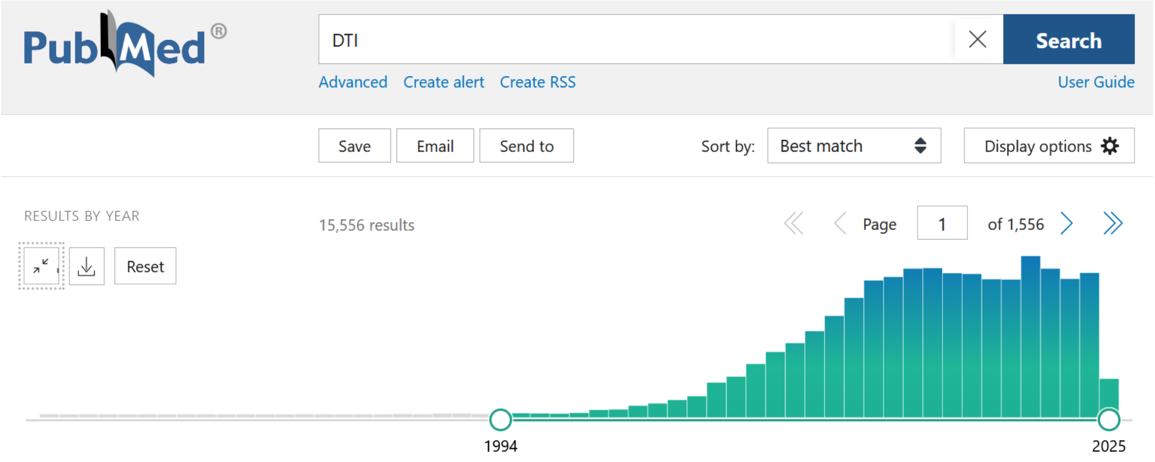


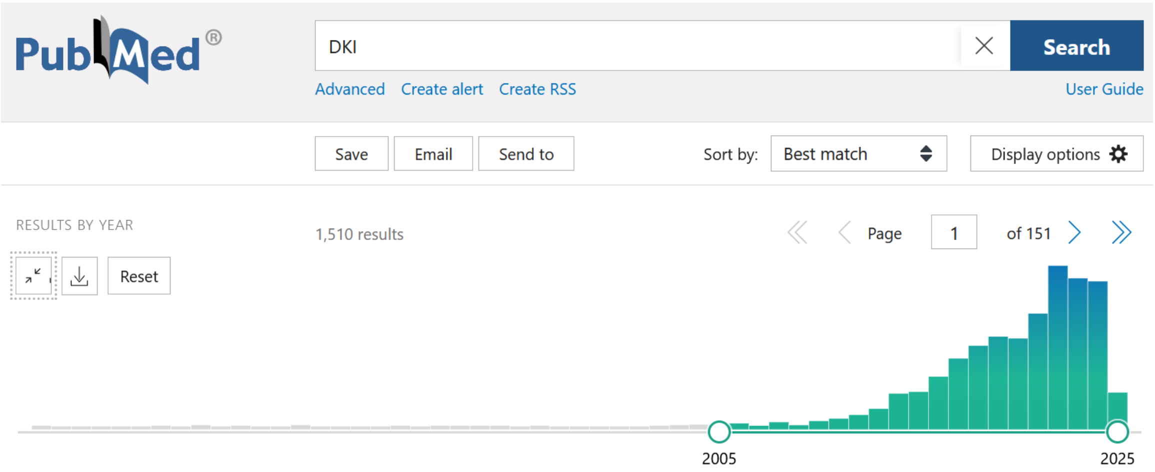


Minimal data:

- **1 b = 0**
- **6 directions on 1 shell (e.g. b = 1 ms/μm²)**
- **15 directions on a 2nd shell (e.g. b = 2/2.5)**

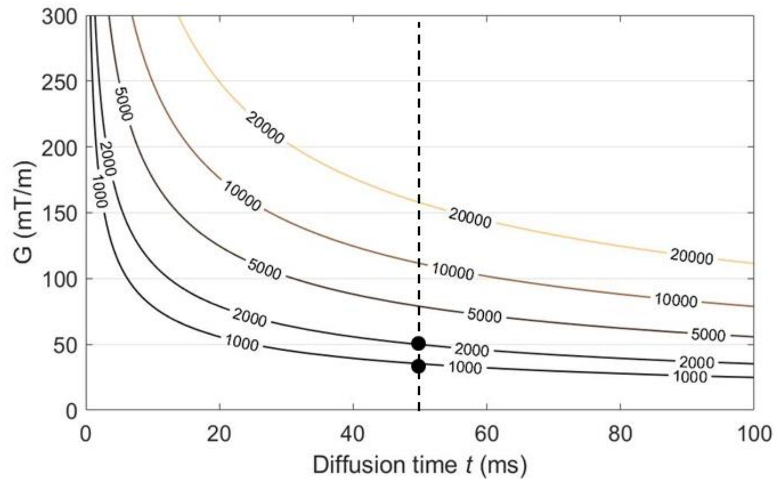
DKI: Valuable





Practicality

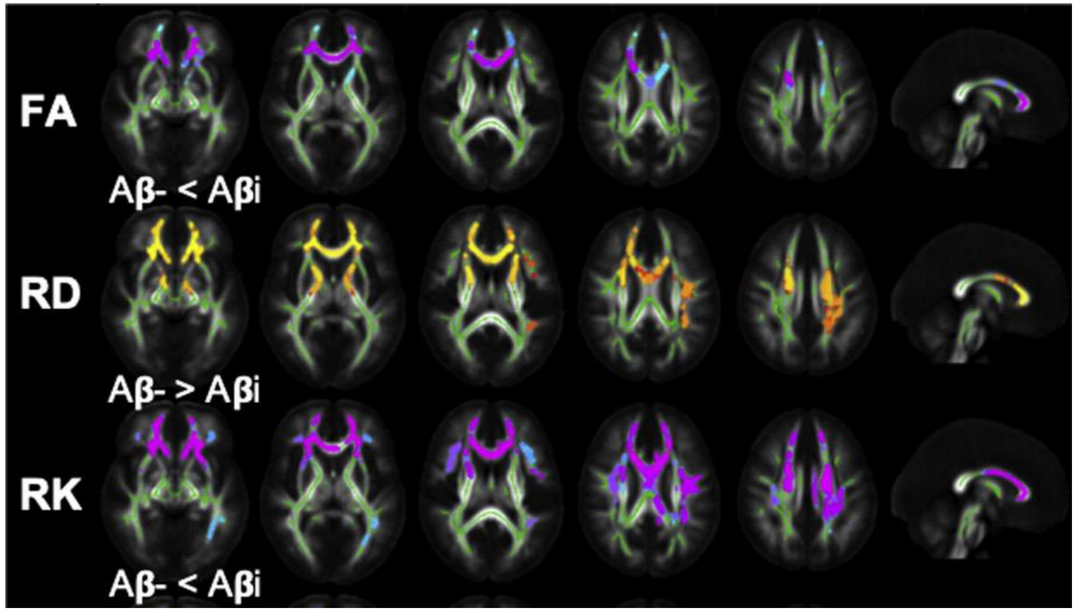
- "Standard" multi-shell acquisition:
  - 1 b = 0, 30 b_1, 60 b_2
  - ➢ ~7-8 min using acceleration (GRAPPA, multiband…)



DKI: Valuable

- Sensitive to tissue complexity
- Complementary information to DTI:
  - Brain development / aging
  - Dementia
  - Stroke
  - Traumatic Brain Injury
  - Glioma
  - Prostate cancer
  - Other body cancers

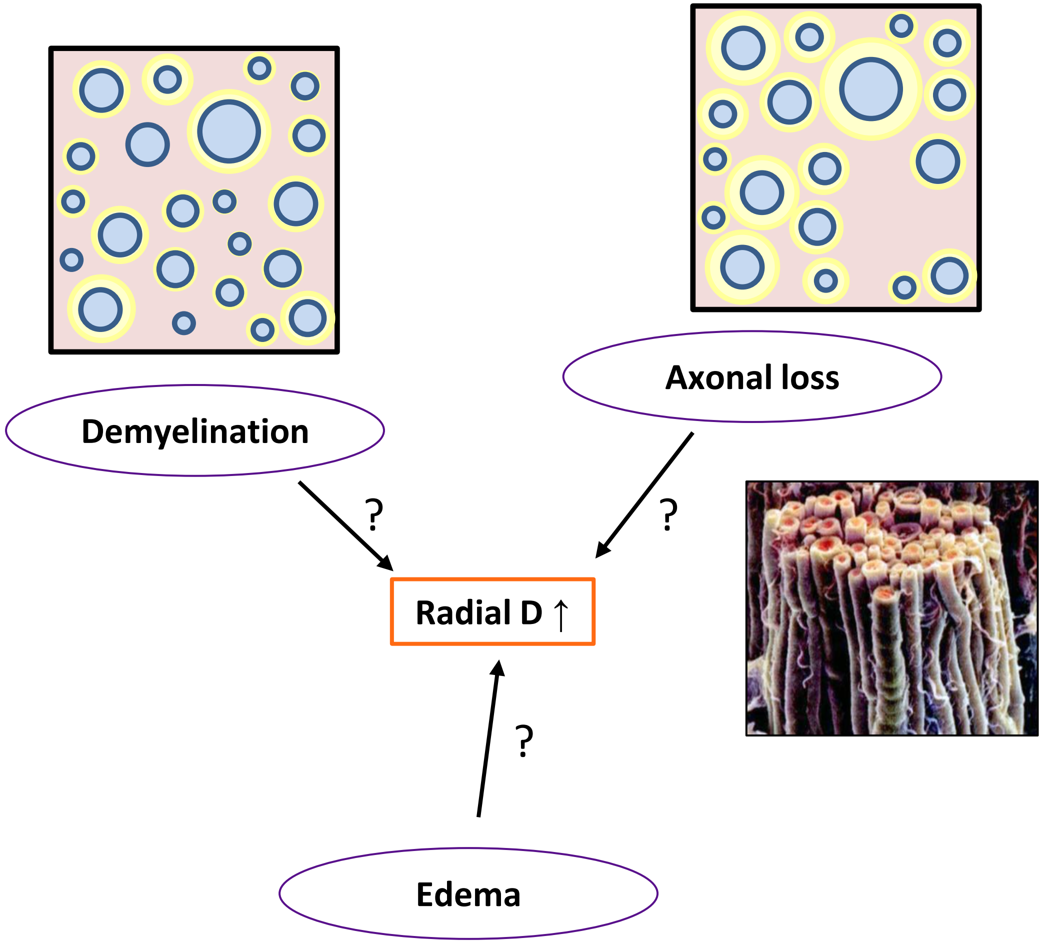
Jensen and Helpern, NMR Biomed 2010
Hui, Stroke 2012
Paydar, AJNR 2014
Rosenkrantz, JMRI 2015
McKenna, Cortex 2019



Relationship between altered WM microstructure & amyloid load in MCI patients

Dong, Neurobiol Aging 2020

Representations: Valuable… but still lack specificity



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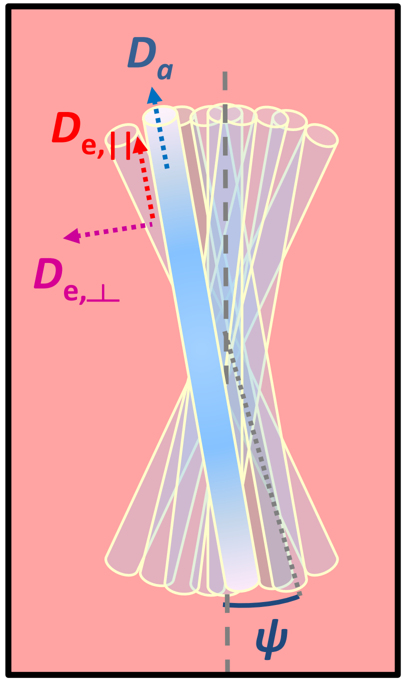
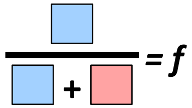
White Matter «Standard Model»



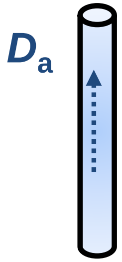


Intra-axonal space

Extra-axonal space

Callaghan, 1979
Jespersen, 2007
Fieremans, 2011
Zhang, 2012
Reisert, 2017
Novikov, 2018

Intra-axonal compartment:
Collection of sticks

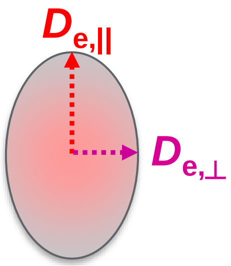


f

Orientation Distribution

$c_2 = \langle \cos^2 \psi \rangle$

Extra-axonal compartment



1-*f*

Markers of:

f: axonal loss

c_2: pruning

D_a : axonal injury

$D_{e,\perp}$: demyelination

$D_{e,||}$: inflammation

"Standard Model" of diffusion in white matter:

$$\mathbf{p} = \left[f, c_2, D_a, D_{e,||}, D_{e,\perp} \right]$$

Jelescu, NMR Biomed 2016 ; Novikov, NeuroImage 2018

Moving away from spurious assumptions

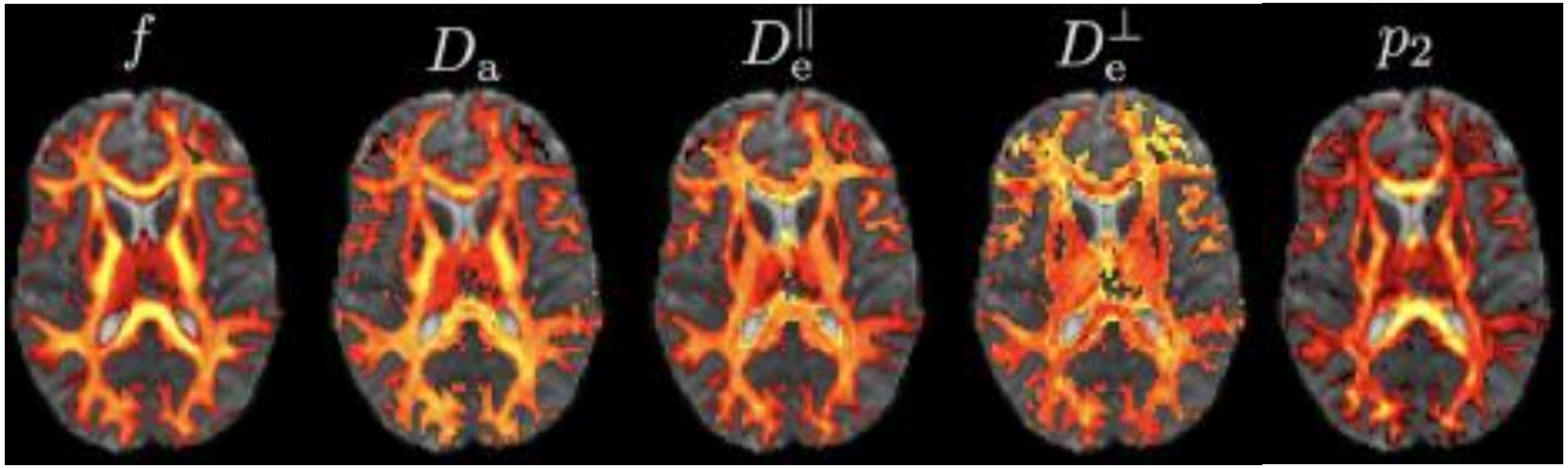
➢ Favor Standard Model frameworks that introduce minimum assumptions

- WMTI-Watson (from DKI)
- SMI (from Rotational Invariants)

https://github.com/Mic-map/WMTI-Watson_DL
https://github.com/NYU-DiffusionMRI/SMI

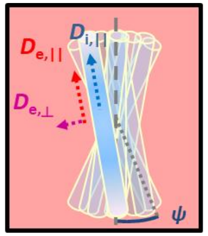
Jespersen, NeuroImage 2018; Novikov, NeuroImage 2018

Axonal fraction	Intra-axonal diffusivity	Extra-axonal parallel & perpendicular diffusivity	Axon bundle alignment



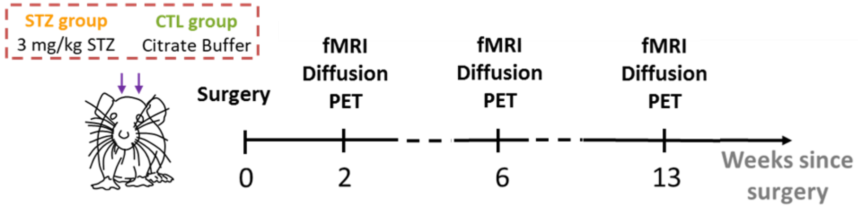
Coelho, NeuroImage 2022

Applications: Rat model of Alzheimer's ("brain diabetes")

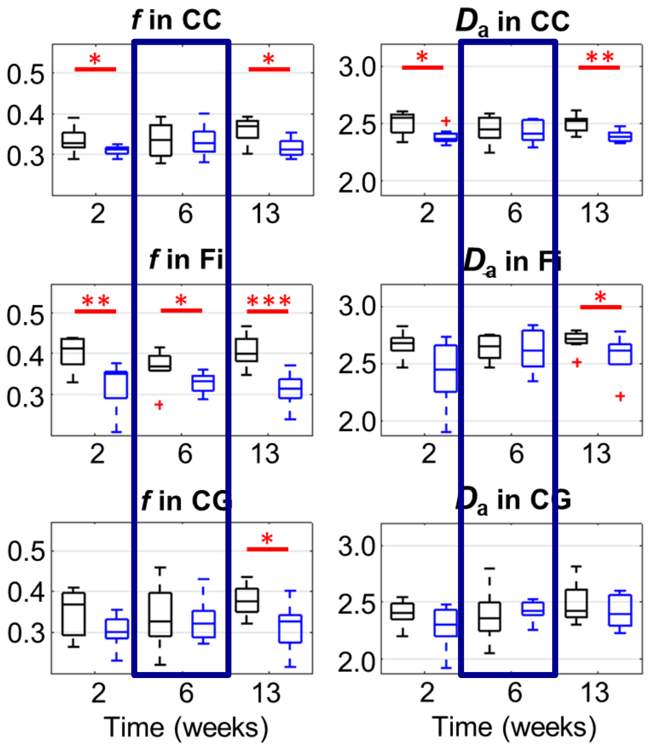


Injection of streptozotocin (STZ) in lateral ventricles

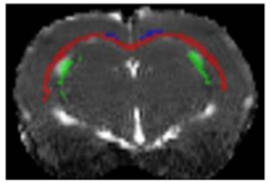
- Insulin-resistant brain state – but <u>no</u> systemic diabetes



WM microstructure



- STZ
- CTL

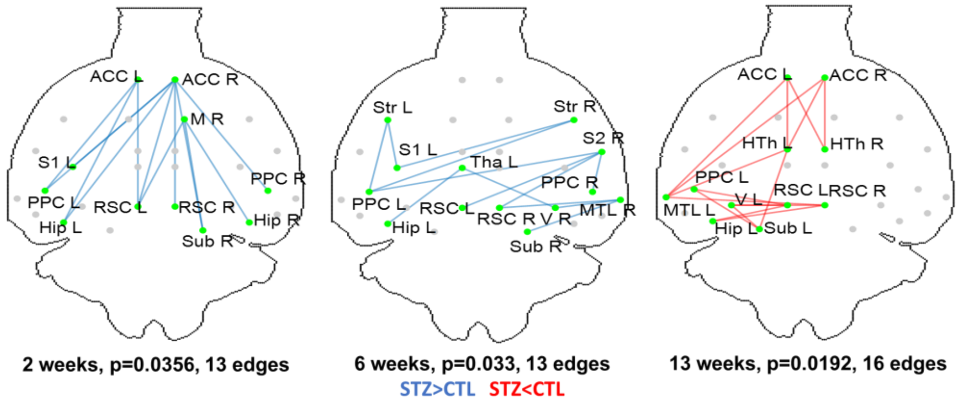


CC: corpus callosum
Fi : fimbria of hippocampus
CG: cingulum

$[\boldsymbol{f}, c_2, \boldsymbol{D}_{\mathbf{a}}, D_{e,\|}, D_{e,\perp}]$

- ➢ Axonal microstructural alterations
- ➢ Inflection point: ~6 weeks (temporary recovery?)

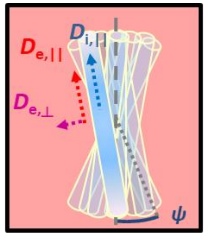
Functional connectivity



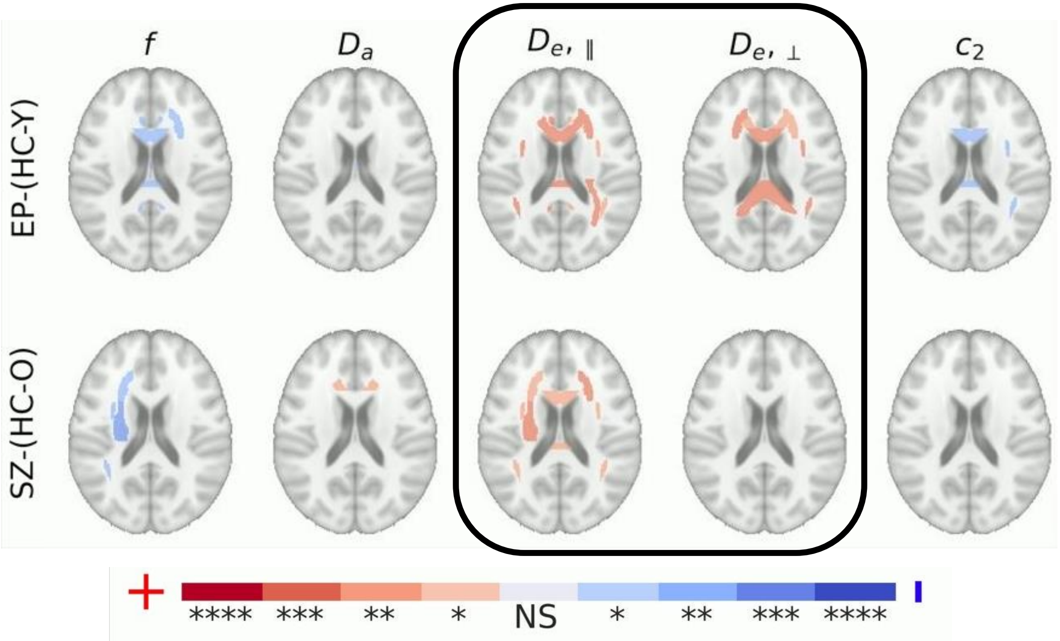
Hyper-connectivity — Hypo-connectivity

Pereira, Diao, et al, NeuroImage 2021; Diao et al, Front Neurosci 2021; Diao et al, Alzheimer's Research & Therapy 2023

Applications of WM Standard Model to patient populations



Early psychosis & schizophrenia

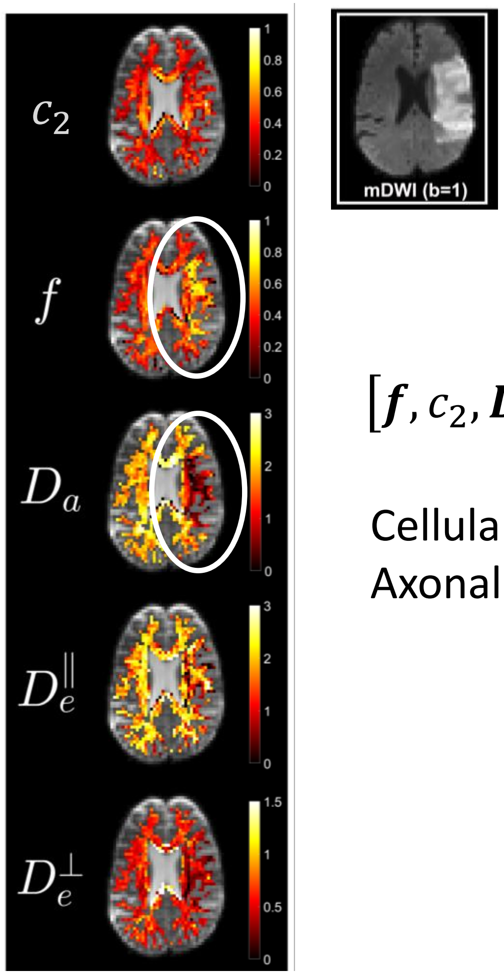


$[\boldsymbol{f}, c_2, D_a, \boldsymbol{D_{e,\parallel}}, \boldsymbol{D_{e,\perp}}]$

Extra-axonal changes
Myelin defects

Pavan et al, medRxiv 2024

Stroke



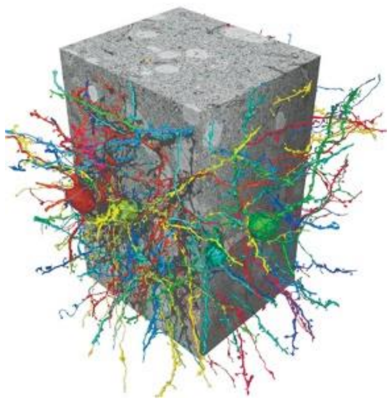
$[\boldsymbol{f}, c_2, \boldsymbol{D_a}, D_{e,\parallel}, D_{e,\perp}]$

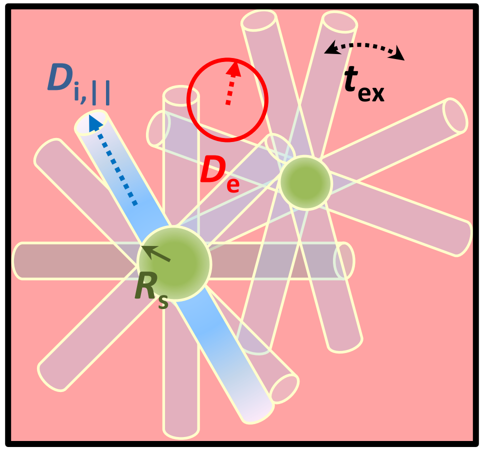
Cellular swelling
Axonal beading

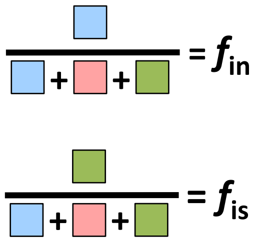
Liao et al, Imaging Neuroscience 2024

Outline

What is a relevant model for gray matter?

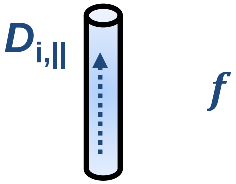






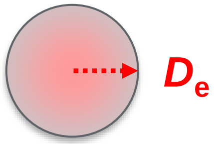
$$\mathbf{p} = [f_{in}, D_{i,\|}, D_e, f_{is}, R_s, t_{ex}]$$

Markers of:

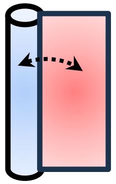


f : loss of cell processes (neurites, …)

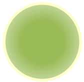
$D_{i,||}$: intra-neurite injury



D_e : inflammation



t_{ex}: membrane permeability: myelination, membrane dysfunction



R_s: soma size, reactivity

f_s: cell proliferation or loss

- Cell bodies: a third compartment?

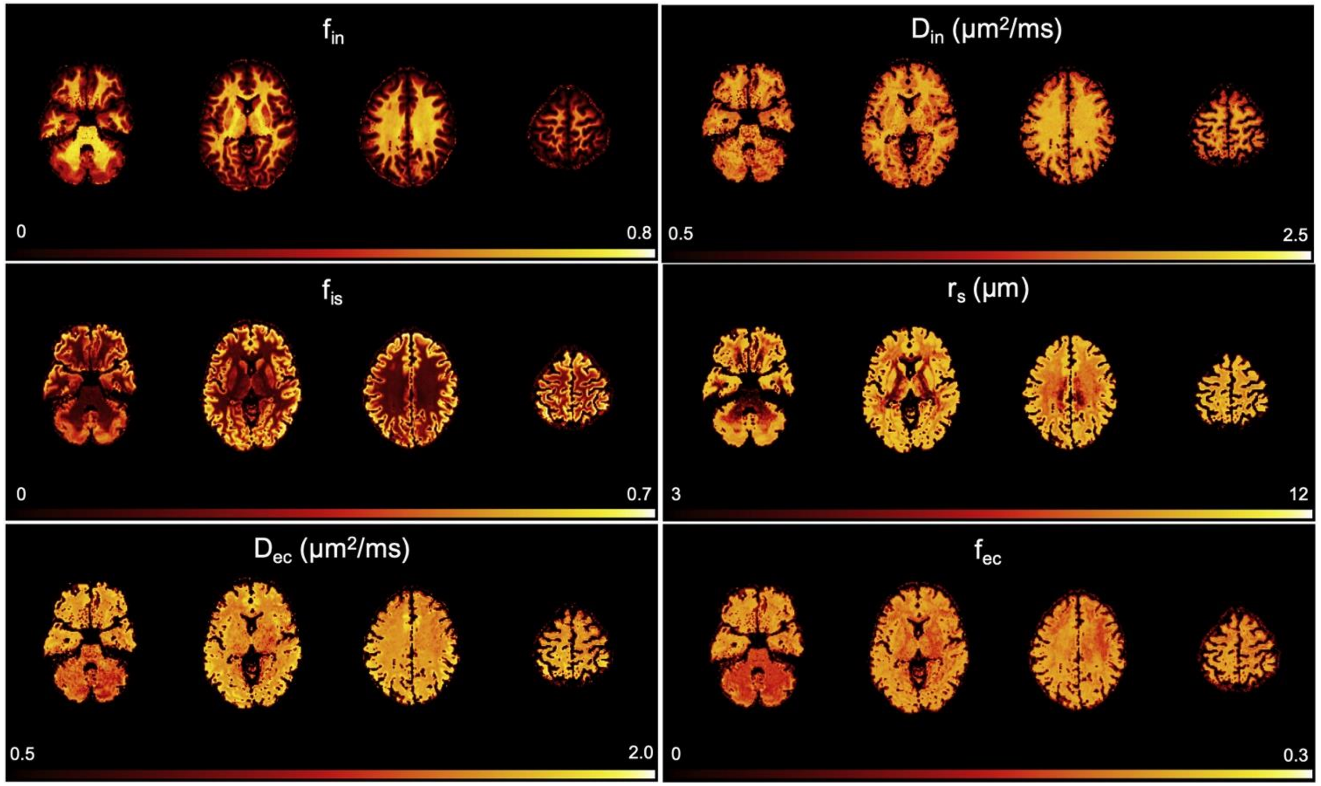
Palombo, NeuroImage 2020

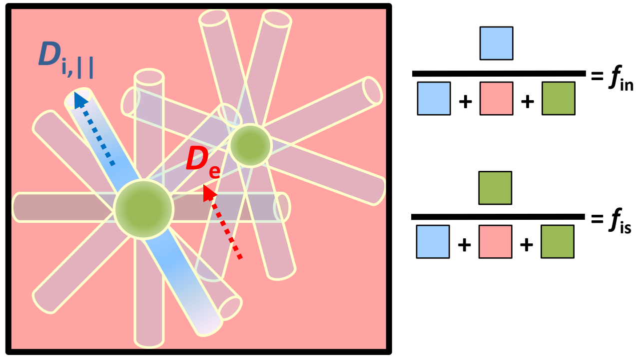
- Little myelin: water exchange between compartments (t_{ex})?

Jelescu, NeuroImage 2022; Olesen NeuroImage 2022

Modeling soma: SANDI – Soma and Neurite Density Imaging

- Assumption: non-exchanging compartments
  - $t_d \leq 20$ ms





$$\mathbf{p} = [f_{in}, D_{i,\|}, D_e, f_{is}, R_s]$$

☺ Reasonable estimate of soma density & size

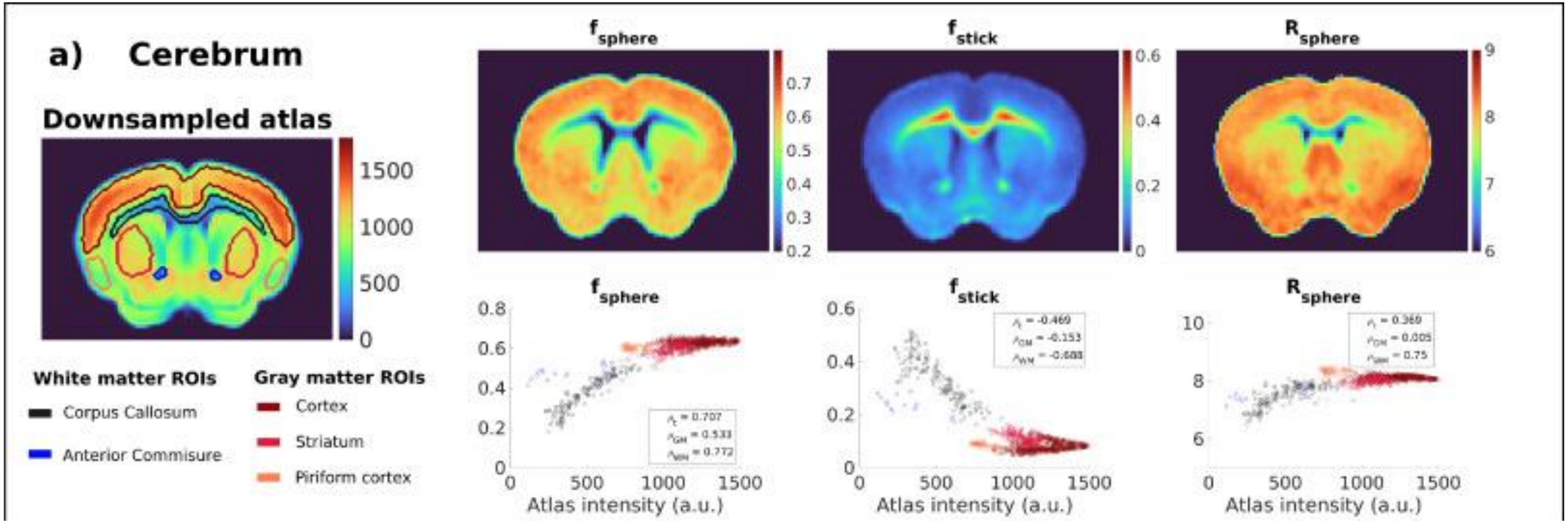
☹ Not feasible on a typical MRI clinical scanner

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

If $\left(\Delta - \frac{\delta}{3}\right)$ is to be kept short,
Need very high G to achieve high b-values (b>5 ms/μm²)

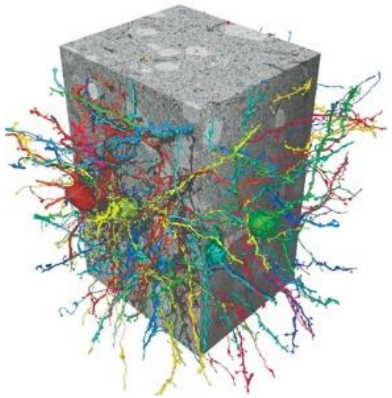
Palombo, NeuroImage 2020

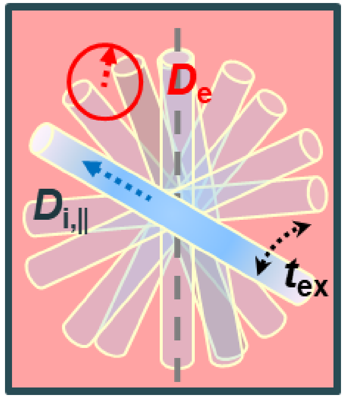
SANDI vs cell density (Allen Brain atlas)

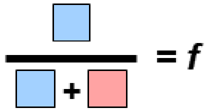


Ianus, NeuroImage 2022

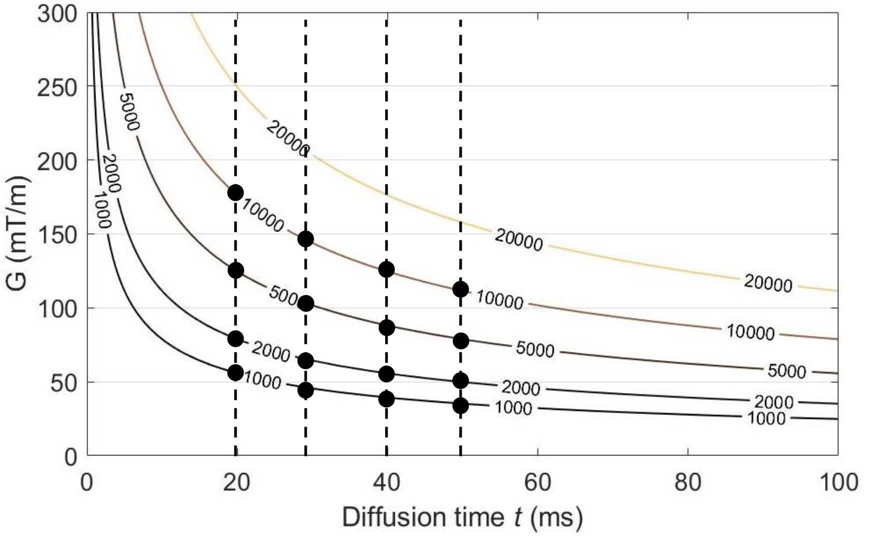
Modeling exchange: NEXI (Neurite EXchange Imaging)



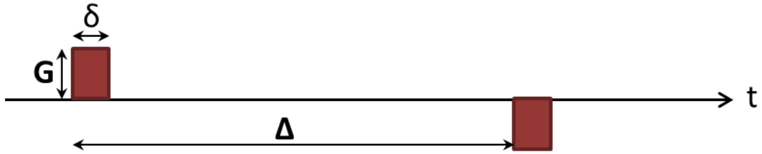




$$\mathbf{p} = [f, D_{i,\|}, D_e, t_{ex}]$$

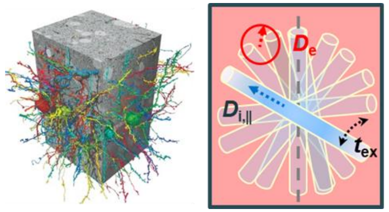


→ Vary G and Δ

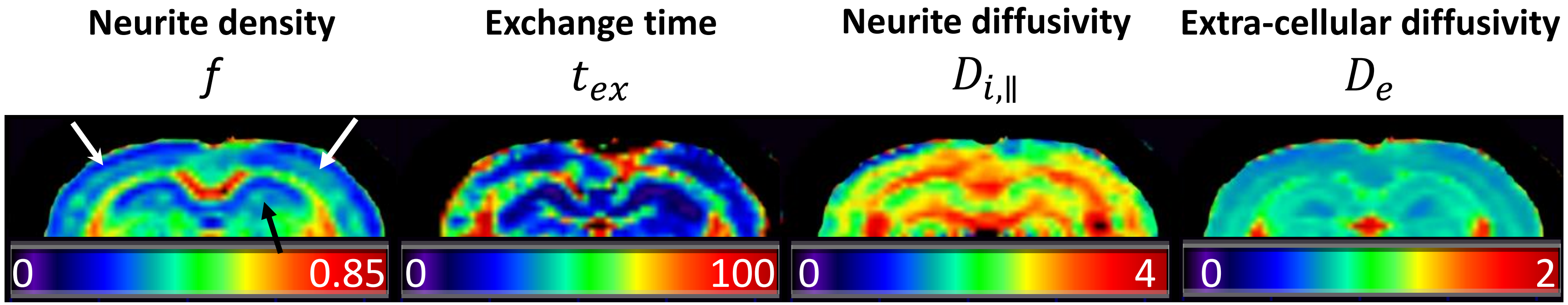


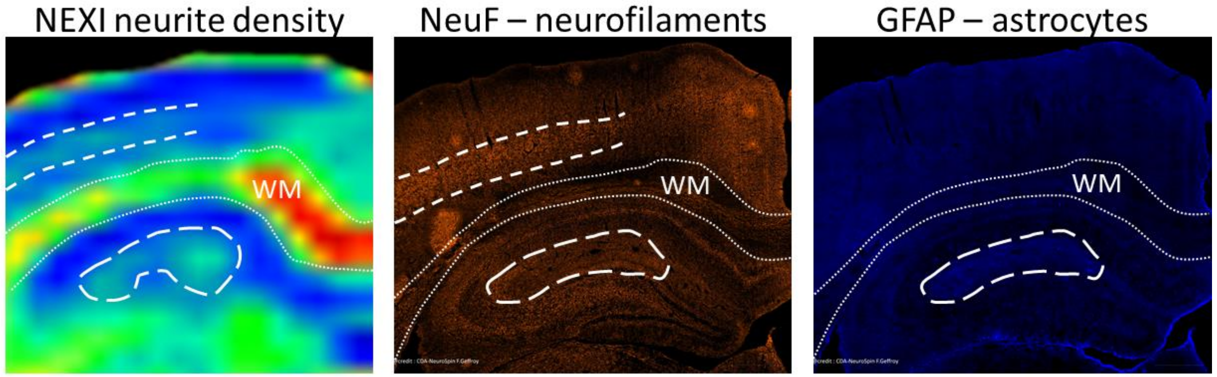
Jelescu, NeuroImage 2022; Olesen NeuroImage 2022

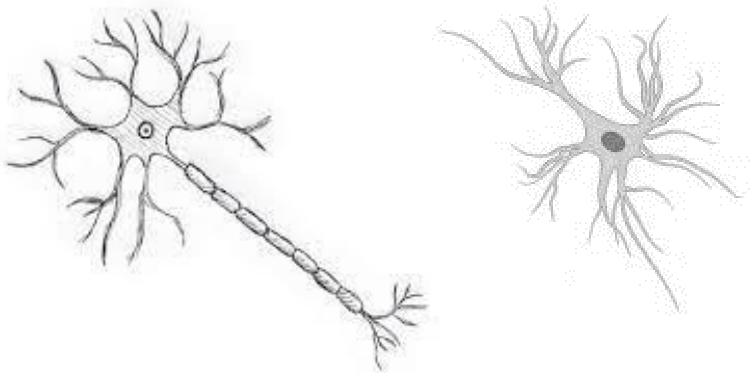
NEXI – rat brain, in vivo



b = 0 – 10’000 s/mm^2
Δ = 10 – 45 ms



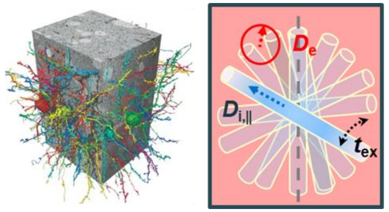




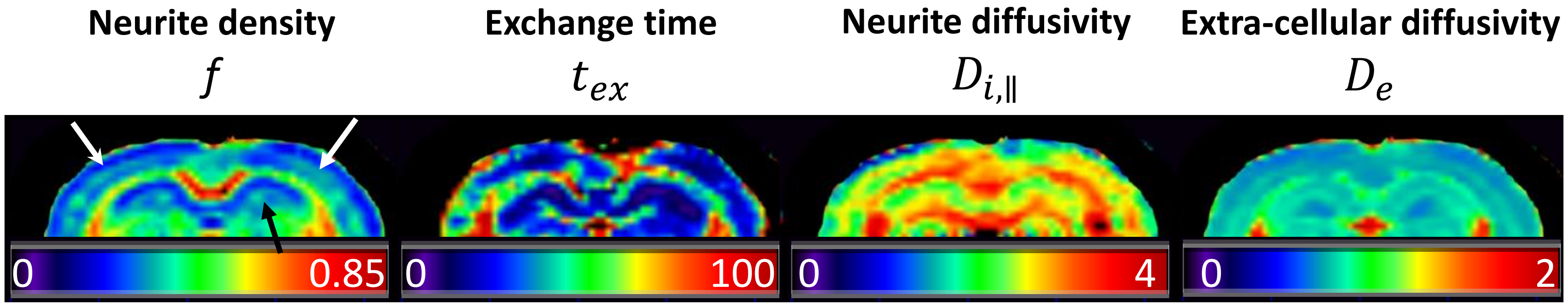
“Neurite density” = “Cell process density”

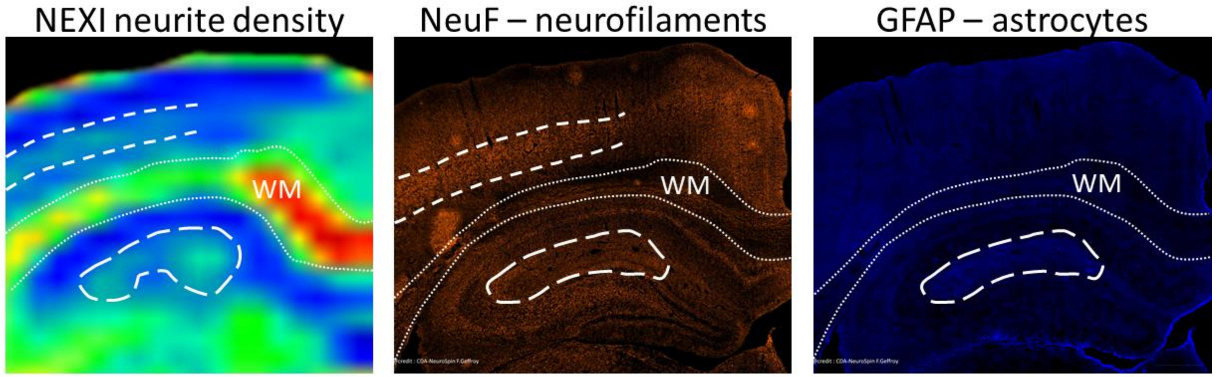
Jelescu, NeuroImage 2022

NEXI – rat brain, in vivo



b = 0 – 10’000 s/mm^2
Δ = 10 – 45 ms





“Neurite density” = “Cell process density”

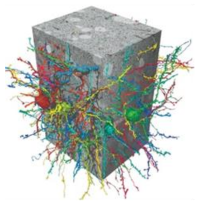
$$t_{ex} \sim 15 - 35 \text{ ms} \cong \frac{d}{4P}$$

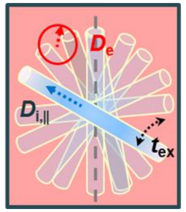
Permeability ~ [2 – 33] x 10^{-3} μm/ms

Vs literature:
Permeability ~ [6 – 30] x 10^{-3} μm/ms

Harkins, 2009; Finkelstein, 1987; Latour, 1994; Stanisz, 1997

Jelescu, NeuroImage 2022





NEXI – human *in vivo*

3T Connectom scanner

G_{max} = 300 mT/m

b = 1000 – 7500 s/mm²
Δ = 20 – 40 ms

Scan time = 40 min

Uhl, Imaging Neuroscience 2024

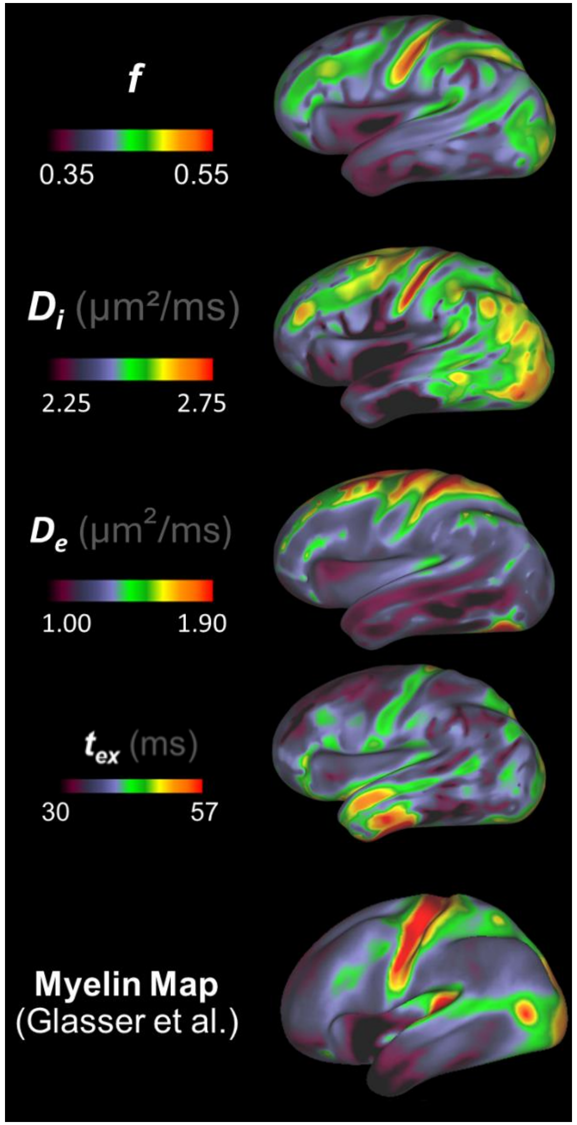
3T Clinical scanner

G_{max} = 80 mT/m

b = 1000 – 5000 s/mm²
Δ = 28 – 65 ms

Scan time = 30 min

Uhl, bioRxiv 2024



https://github.com/Mic-map/graymatter_swissknife

Next steps:
- More with less: reduce scan time
- Model exchange + soma

Olesen, NeuroImage 2022

Applications:
- Multiple sclerosis
- Traumatic Brain Injury
- …

Outline

I. Diffusion-weighting

II. Gaussian approximation regime: ADC and DTI

III. Beyond Gaussian:

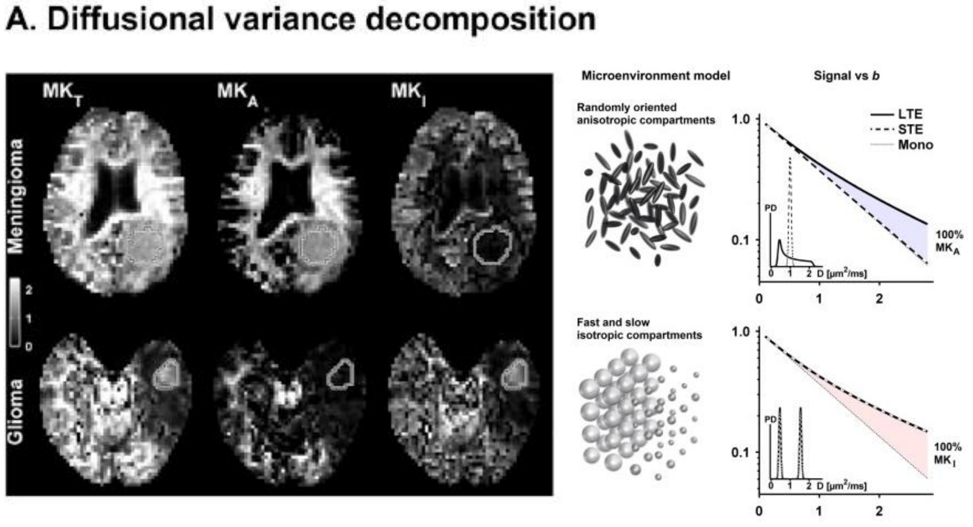
  i. Signal representations: DKI

  ii. White matter models & applications

  iii. Gray matter models & applications

  iv. Thinking outside the brain

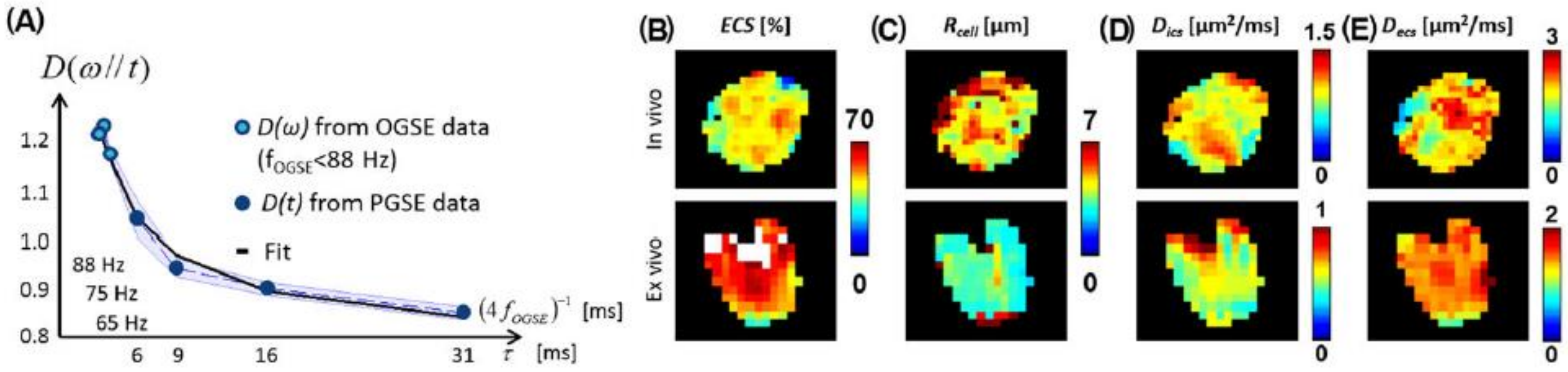
Microstructure models (almost) outside the brain



Szczepankiewicz, NeuroImage 2016

Glioma

Quantification of cell density, radius, and compartment diffusivities



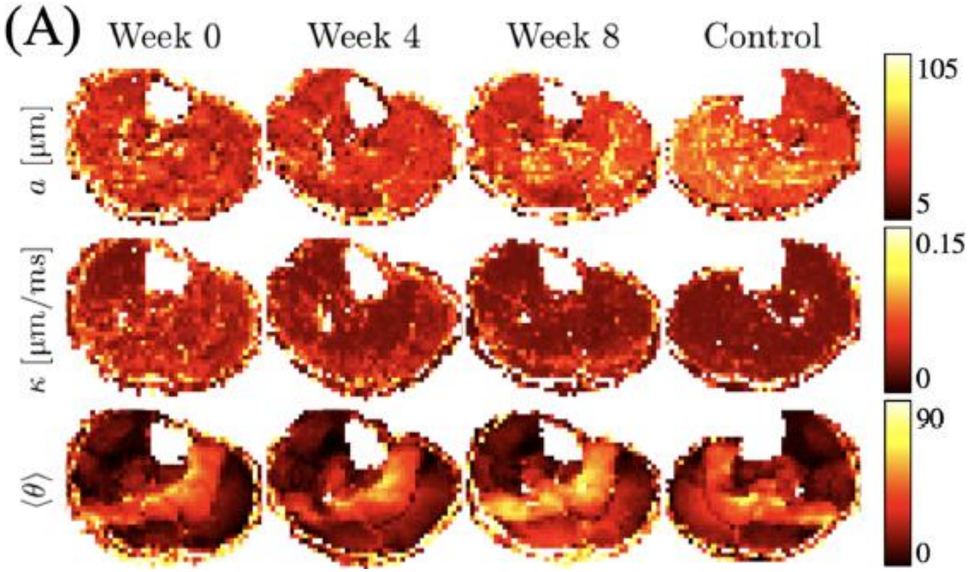
Reynaud, NMR in Biomed 2016

Microstructure models outside the brain

Random Permeable Barrier Model

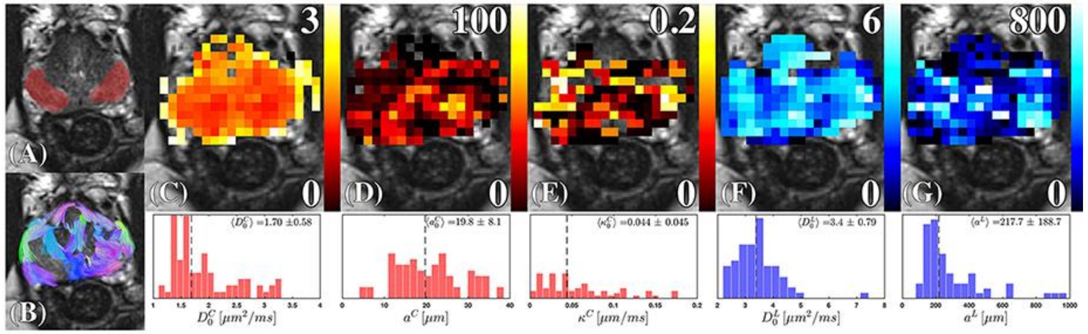
Muscle

Quantification of myofiber size, permeability and orientation



Lemberskiy, NMR in Biomed 2021

Prostate



Cellular diffusivity, fiber diameter, and membrane permeability

Luminal diffusivity and diameter

Lemberskiy, Front Phys 2018

Summary

- Biophysical tissue models:
  - In theory: specific metrics of microstructure
  - In practice: dependent on validity of model assumptions & fitting procedure
    - Interpret output with caution!
- Substantial progress in white matter modeling
  - Estimation of main Standard Model parameters comprehensively
  - Accessible applications and translation to preclinical & clinical studies of disease
- Current focus: gray matter modeling
  - Accounting for inter-compartment exchange appears critical
  - Parameter estimation may require (q-t) coverage
    - Challenge for retrospective studies & prospective clinical studies
  - Eventually: propose a more comprehensive model (exchange + soma + …)
- Other organs / tissue types
  - High interest

Reviews:
Jelescu and Budde, Front Phys 2017
Novikov, MRM 2018
Nilsson, NeuroImage 2018
Alexander, NMR in Biomed 2019
Novikov, NMR in Biomed 2019
Jelescu, J Neurosci Meth 2020

Recommendations Papers:
Jelescu, […], Schilling, MRM 2025
Schilling, […], Jelescu, MRM 2025

Questions?