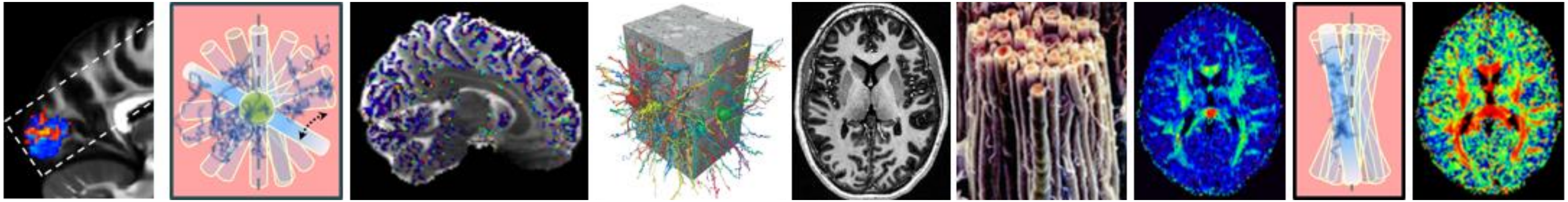
Microstructure Mapping Lab



Principles and applications of diffusion-weighted imaging

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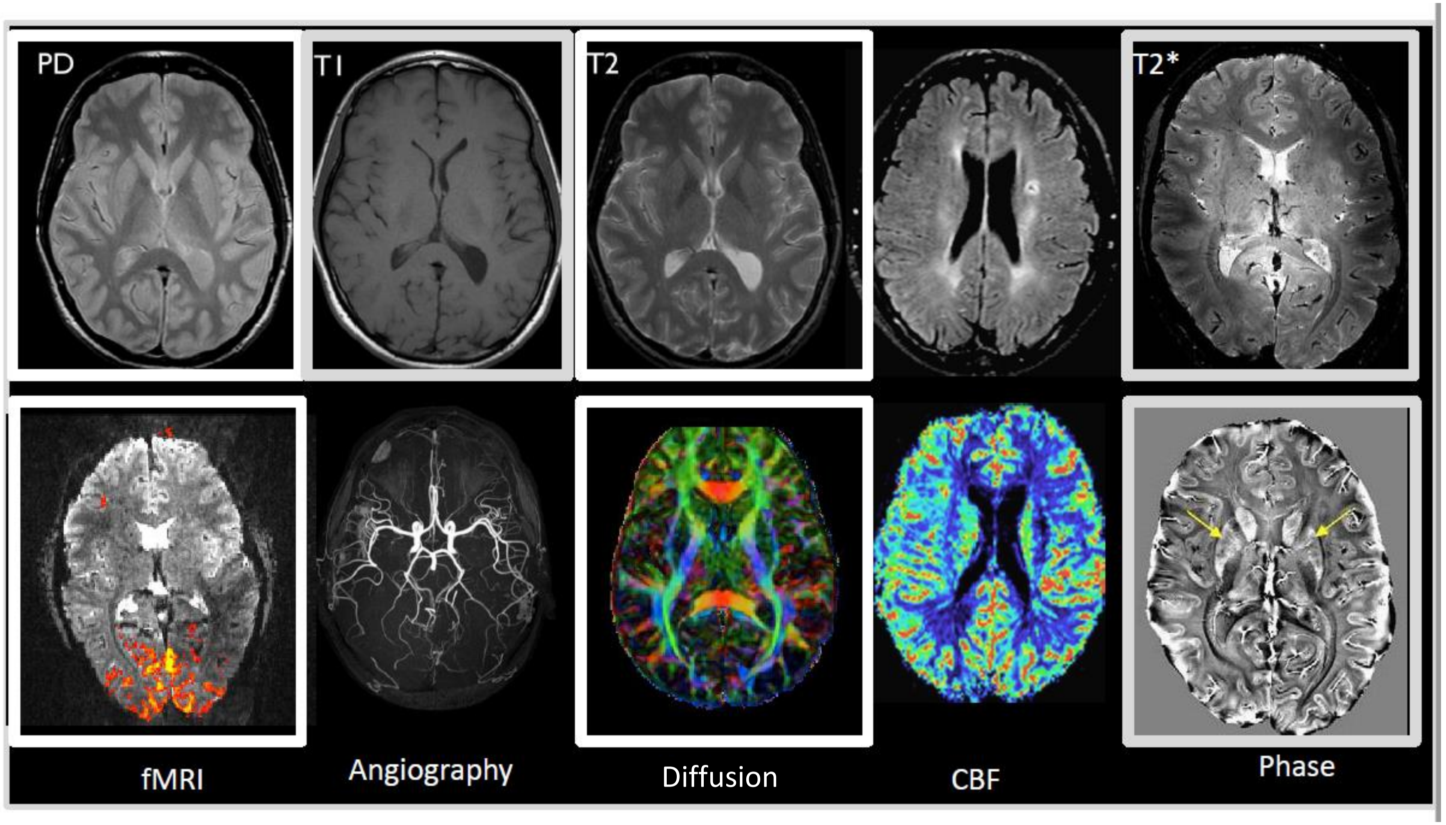
MRI – imaging water

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

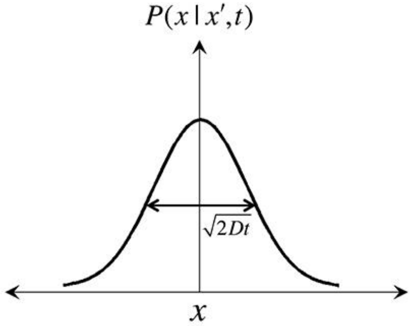
   ii. White matter models & applications

   iii. Gray matter models & applications

   iv. Thinking outside the brain

Diffusion MRI gives access to the mesoscale

- **Unrestricted homogeneous medium:**

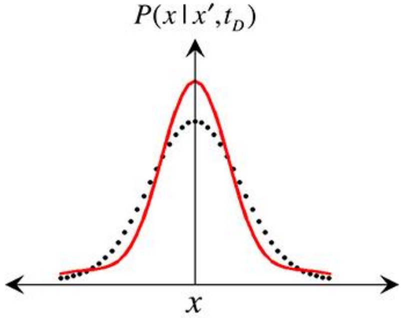


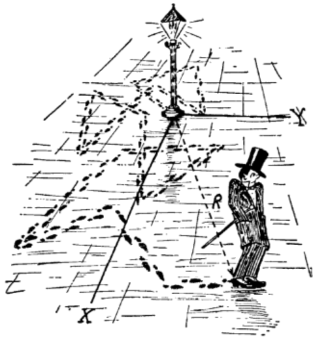
$$\langle x^2 \rangle = 2nDt$$

MRI voxel size:
1 – 2 mm

Typical length scale for
microstructure: 1 – 10 µm

- **Biological tissue:**



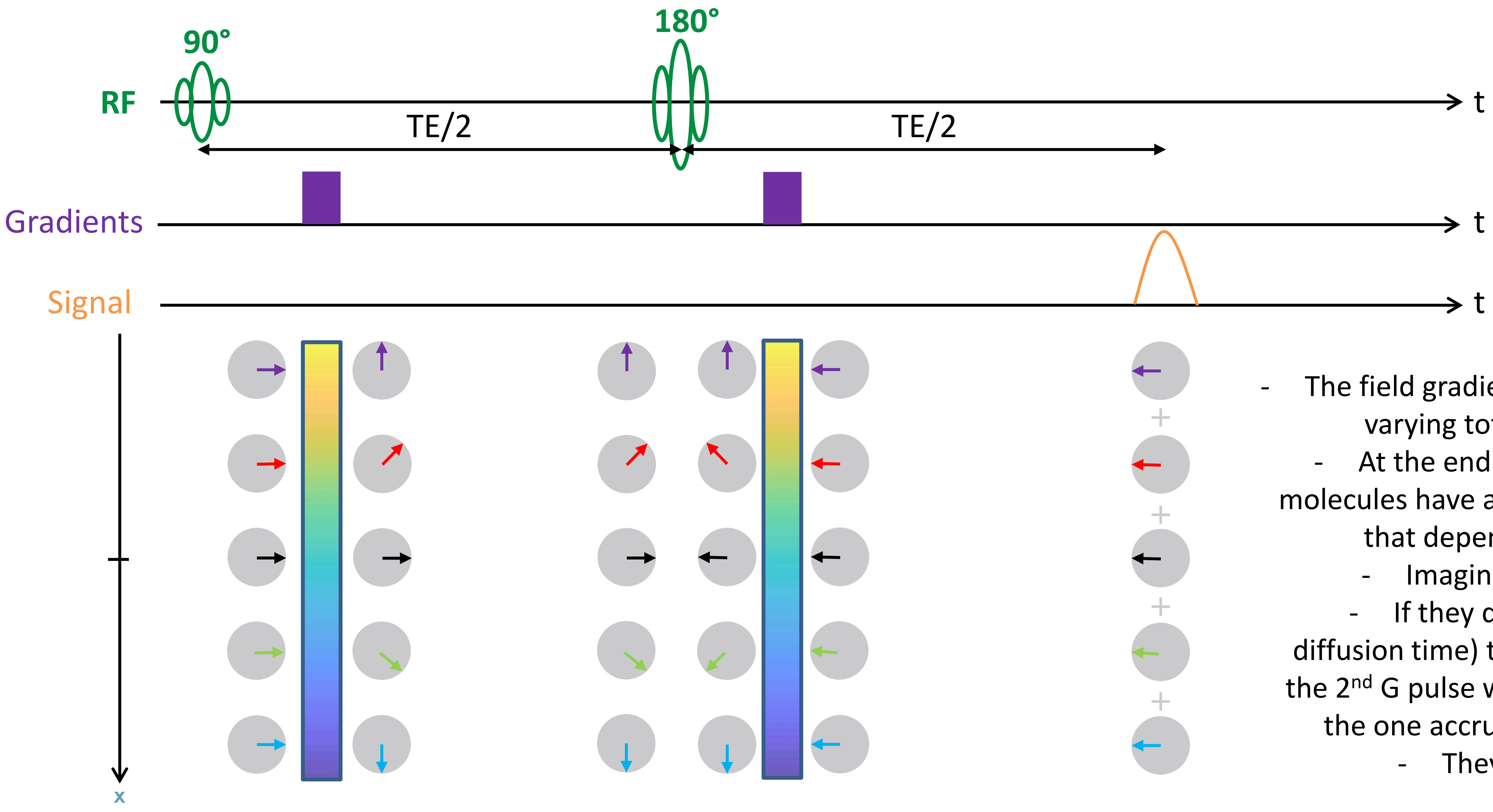


Mean displacement of water molecules :

- **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!

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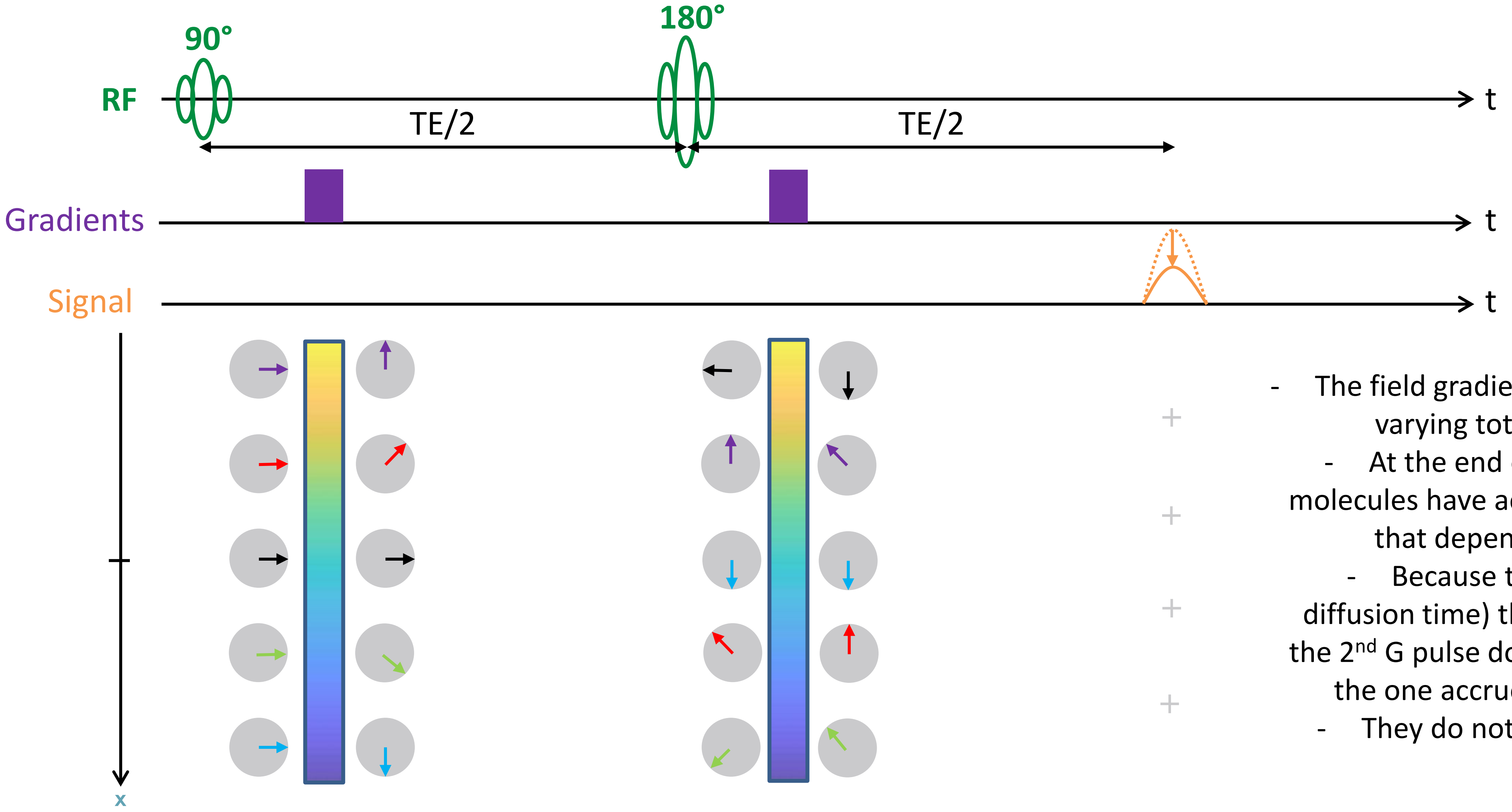
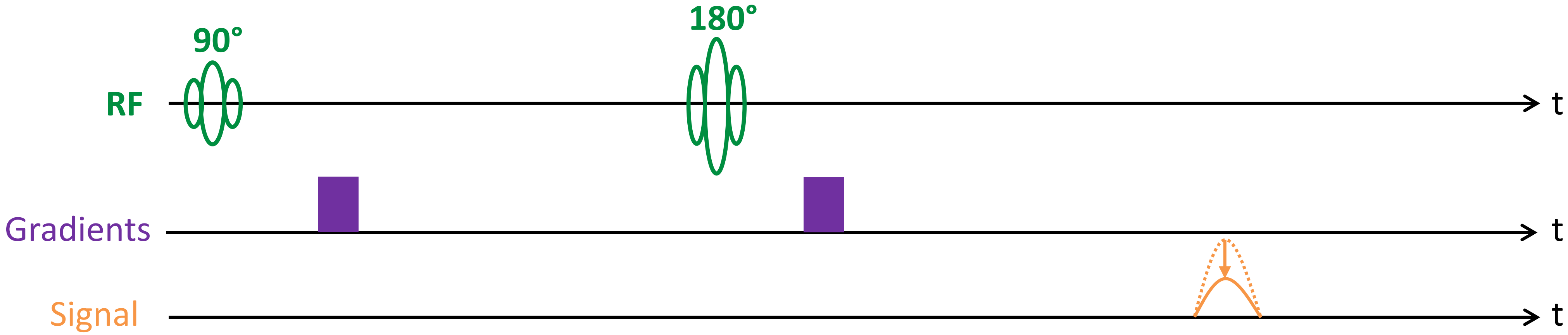
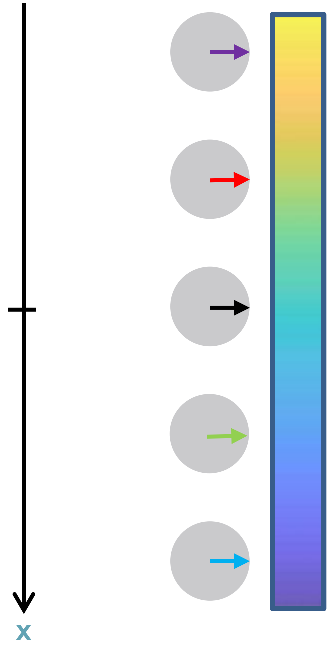
Diffusion weighting in MRI – pulsed gradient spin-echo (PGSE)



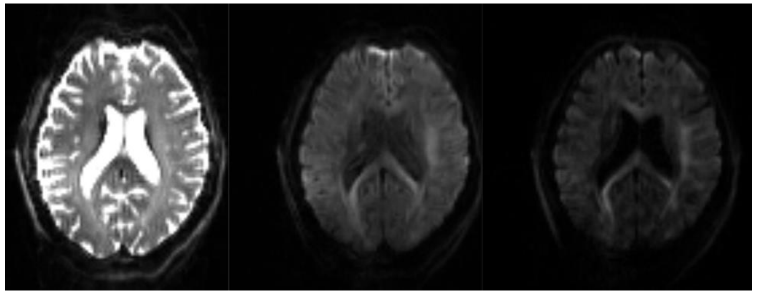
- The field gradient creates a linearly varying total field: $B(x)=B_0+G.x$
- At the end of the (short) pulse, molecules have accumulated a phase that depends on their position
- Because they mix (during the diffusion time) the phase accrued in the 2nd G pulse does not compensate the one accrued in the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

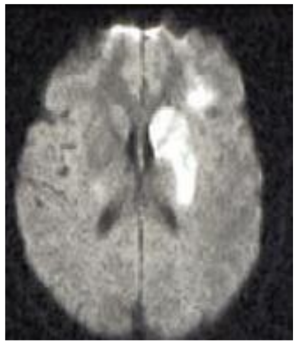
Diffusion weighting: signal attenuation & contrast





Signal attenuation due to diffusion
- Increases with *diffusion-weighting*
- Increases with Diffusivity





Stroke

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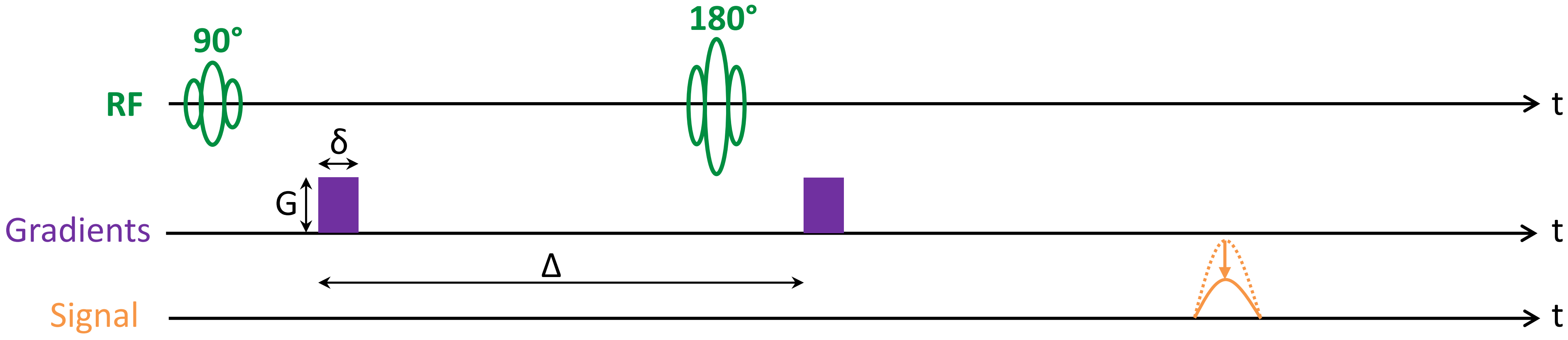
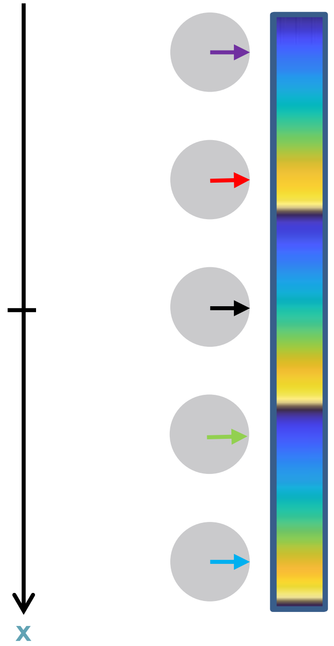
Diffusion weighting in MRI – q, t and the b-value



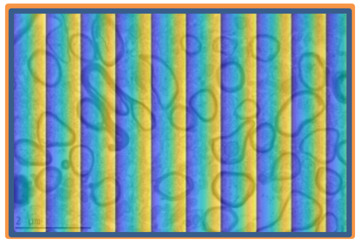


$$b = (\gamma \delta G)^2 \cdot \left(\Delta - \frac{\delta}{3}\right) = q^2 t$$

Phase warp	Diffusion time

Low q

High q



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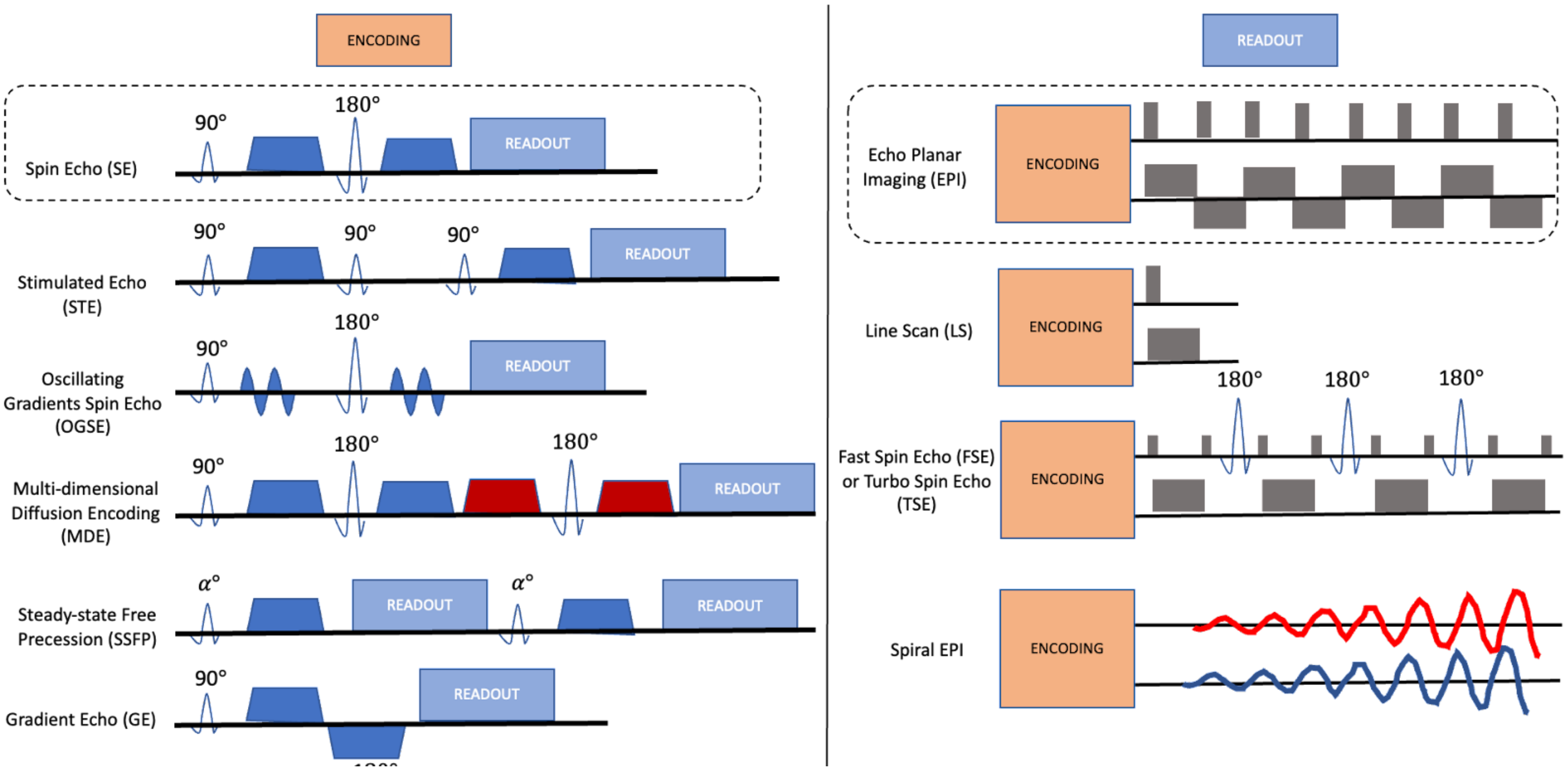
Diffusion encoding schemes and image read-out schemes



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:

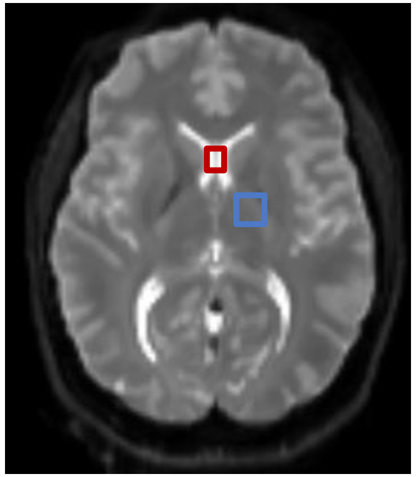
i. Signal representations: DKI

ii. White matter models & applications

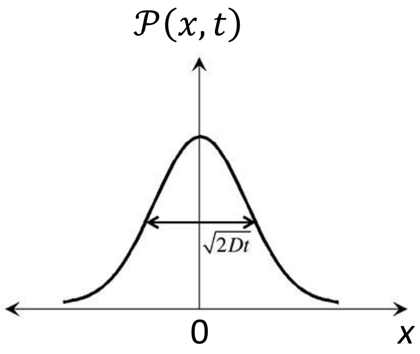
iii. Gray matter models & applications

iv. Thinking outside the brain

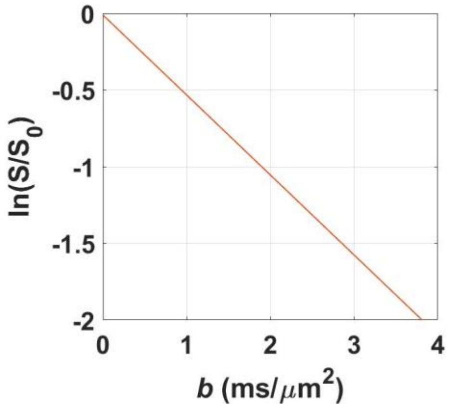
From a free medium to biological tissue (and from D to ADC)



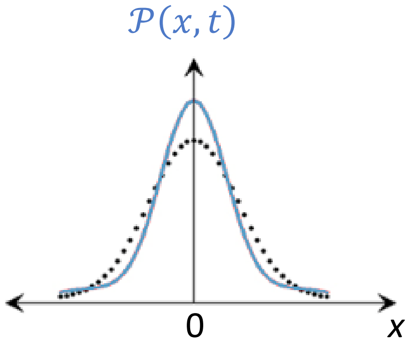
Free homogeneous medium
Gaussian diffusion



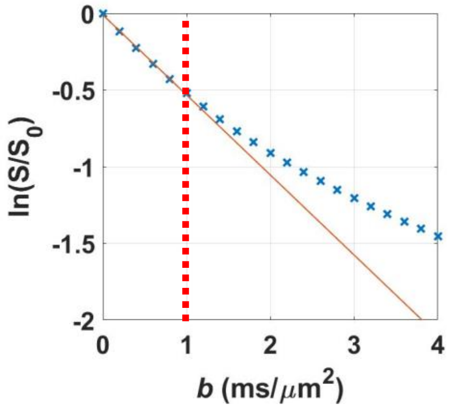
$$\ln\left(\frac{S}{S_0}\right) = -\mathrm{bD}$$



Biological tissue
Non-Gaussian diffusion



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



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

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

<u>Apparent</u> Diffusion Coefficient

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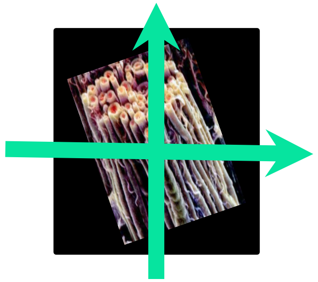
From the ADC to the diffusion tensor (DTI)

Apparent Diffusion Coefficient

…

along a direction $\vec{g}$,

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



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

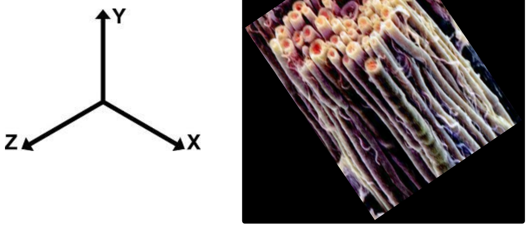
$\vec{g} = [1\ 0\ 0]$

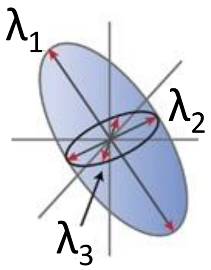
$\vec{g} = [0\ 1\ 0]$

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

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

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





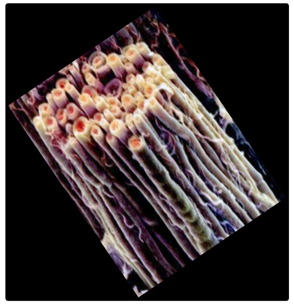
$$\hat{D}_{\{\vec{e}_1,\vec{e}_2,\vec{e}_3\}} = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix}$$

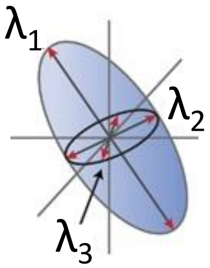
- Symmetric → 6 coefficients to estimate
- Invertible with all eigenvalues real and positive

Minimal data:

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

DTI scalars

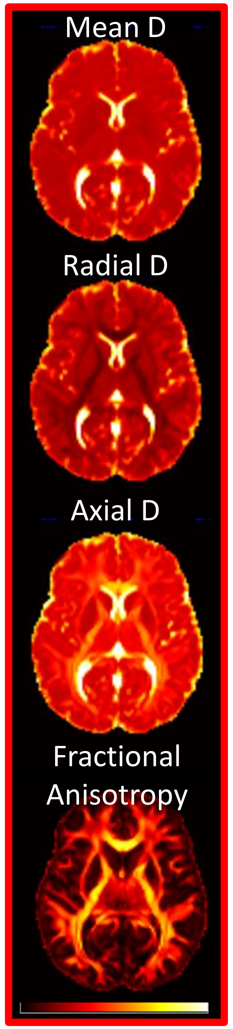




$$\widehat{D}_{\{\vec{e}_1,\vec{e}_2,\vec{e}_3\}} = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix}$$

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:

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

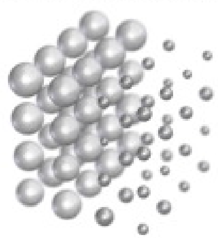
FA = 0 : isotropic diffusion, FA = 1 : fully anisotropic (1D)
Excellent GM/WM contrast, highest in WM

Some important jargon & nuances

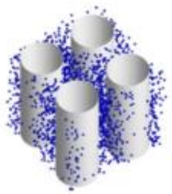
- "Diffusion MRI" ≠ "DTI"
- (Free) Diffusivity ≠ ADC
- In anisotropic tissue: MD ≠ ADC
- Units!

"widespread"		"natural choice"	
Diffusion coefficient	b-value	Diffusion coefficient	b-value
mm^2/s	s/mm^2	$\mu m^2/ms$	$ms/\mu m^2$
3.10^{-3}	1000	3	1
4.10^{-4}	10'000	0.4	10

- Anisotropy ≠ non-Gaussian diffusion



Isotropic diffusion
Non-Gaussian (restricted compartments)



Anisotropic diffusion
yet Gaussian in each direction

Outline

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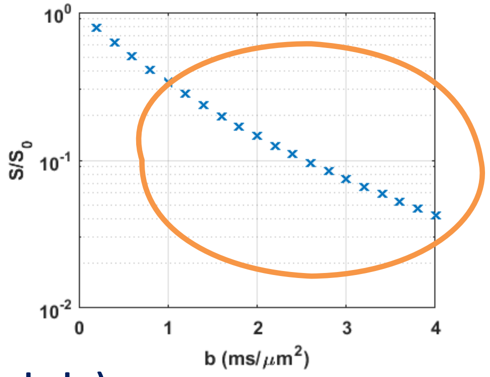
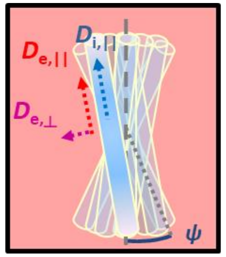
Signal representations vs biophysical models





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

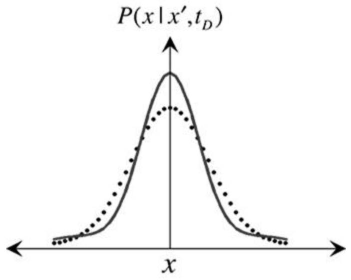
☹ Assumption validity?

☹ Fit stability?

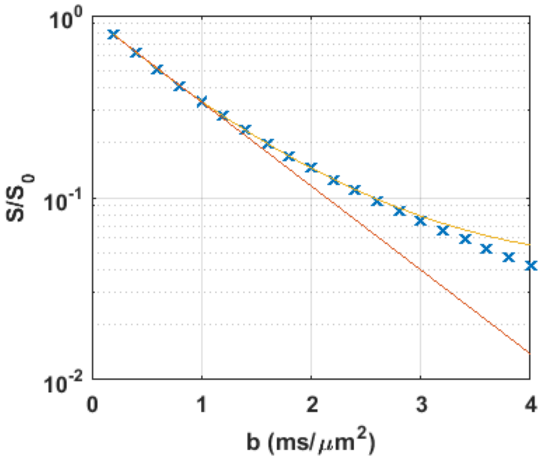
Representations: Diffusion Tensor Imaging (DTI) and Kurtosis (DKI)

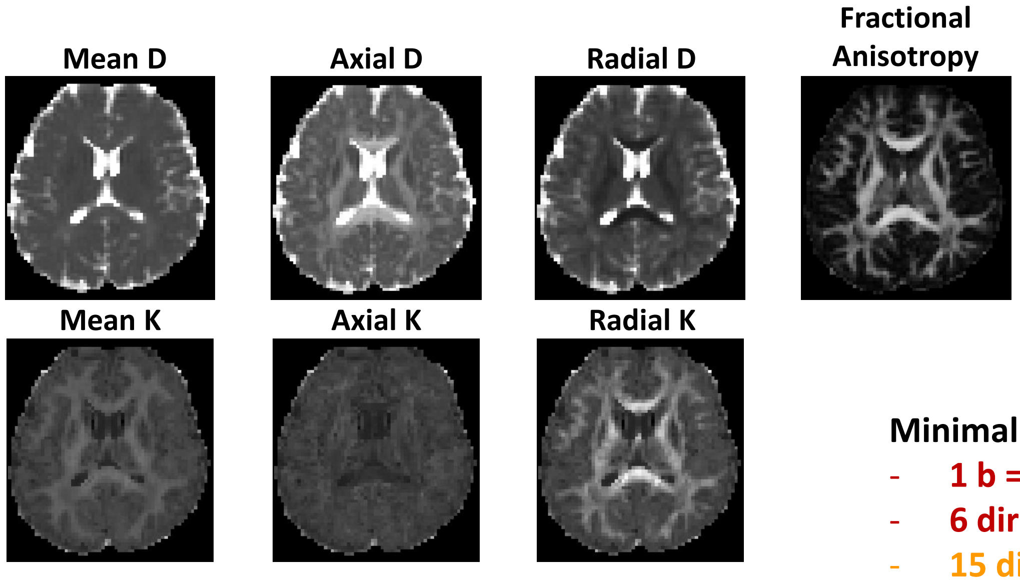
$$\ln\frac{S}{S_0} = -bD + \frac{1}{6}b^2D^2K + \cdots$$

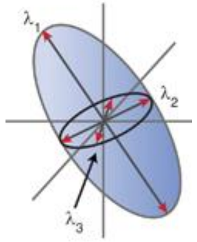
$$\ln\frac{S}{S_0} = -b\sum_{i,j=1}^{3} g_i g_j D_{ij} + \frac{1}{6}b^2\bar{D}^2\sum_{i,j,k,l=1}^{3} g_i g_j g_k g_l W_{ijkl} + \cdots$$

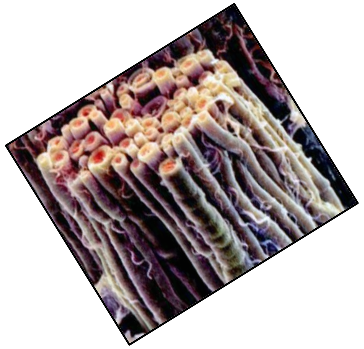


diffusion tensor (DTI) & kurtosis tensor (DKI)









Minimal data:

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

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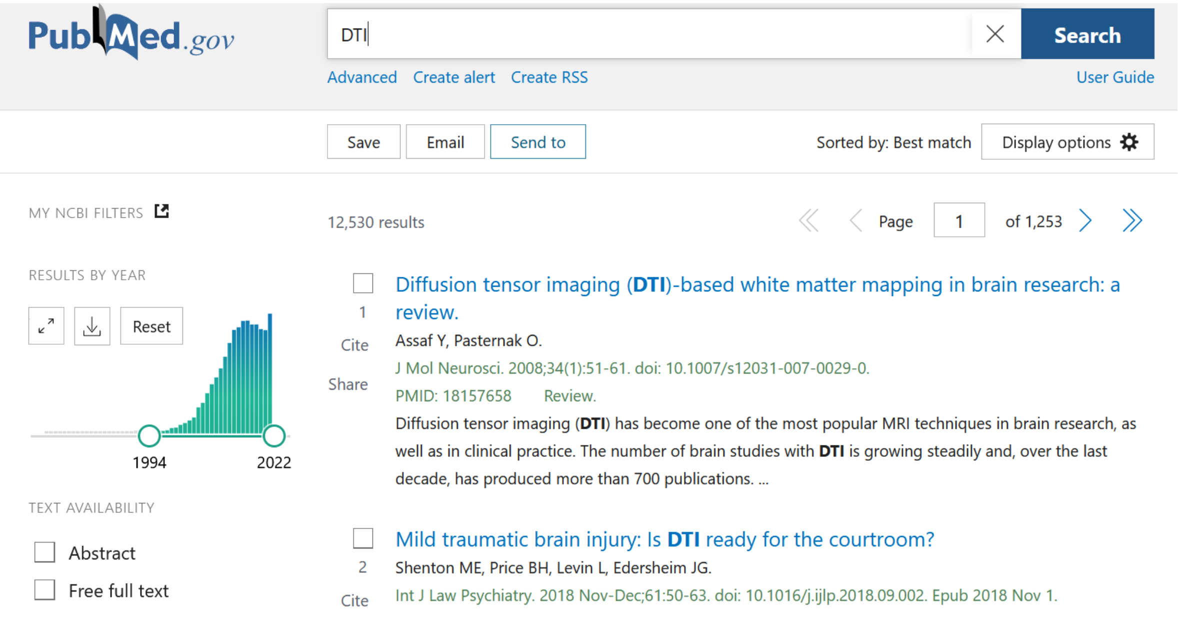
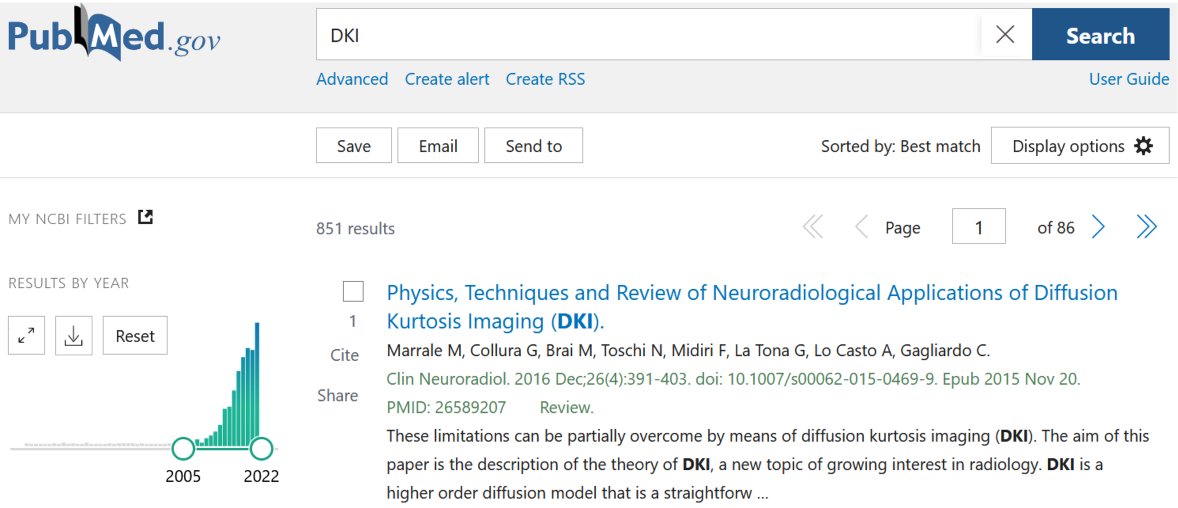
Basser, J Magn Reson 1994; **Jensen**, Magn Reson Med 2005; **Kiselev and Il'yasov**, Magn Reson Med 2007

DKI: Valuable





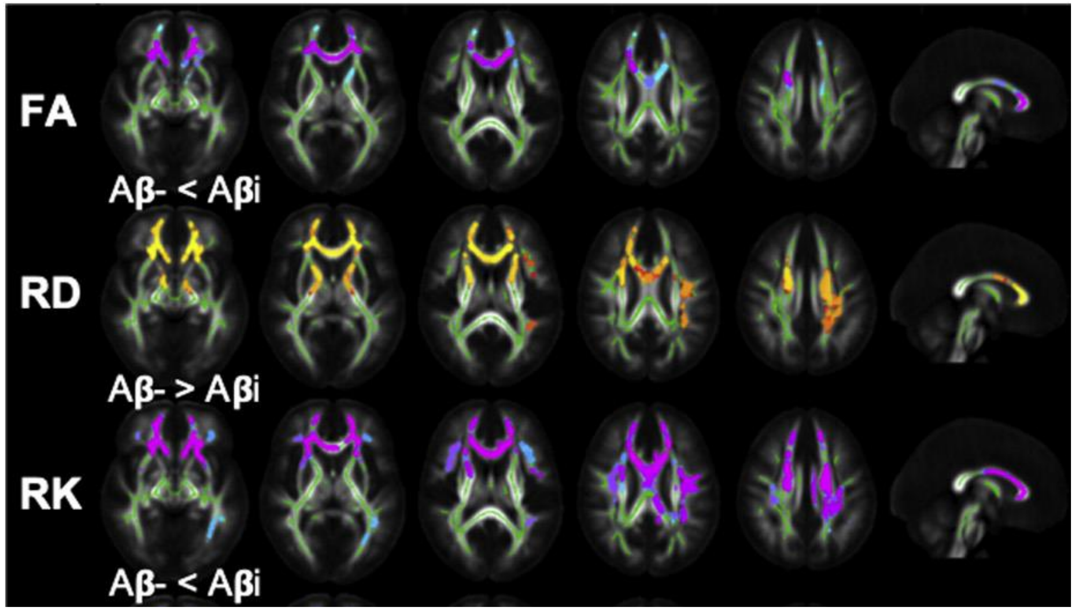
Practicality

- “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
  - Dementia
  - Stroke
  - TBI
  - Glioma
  - Prostate cancer
  - Other body cancers

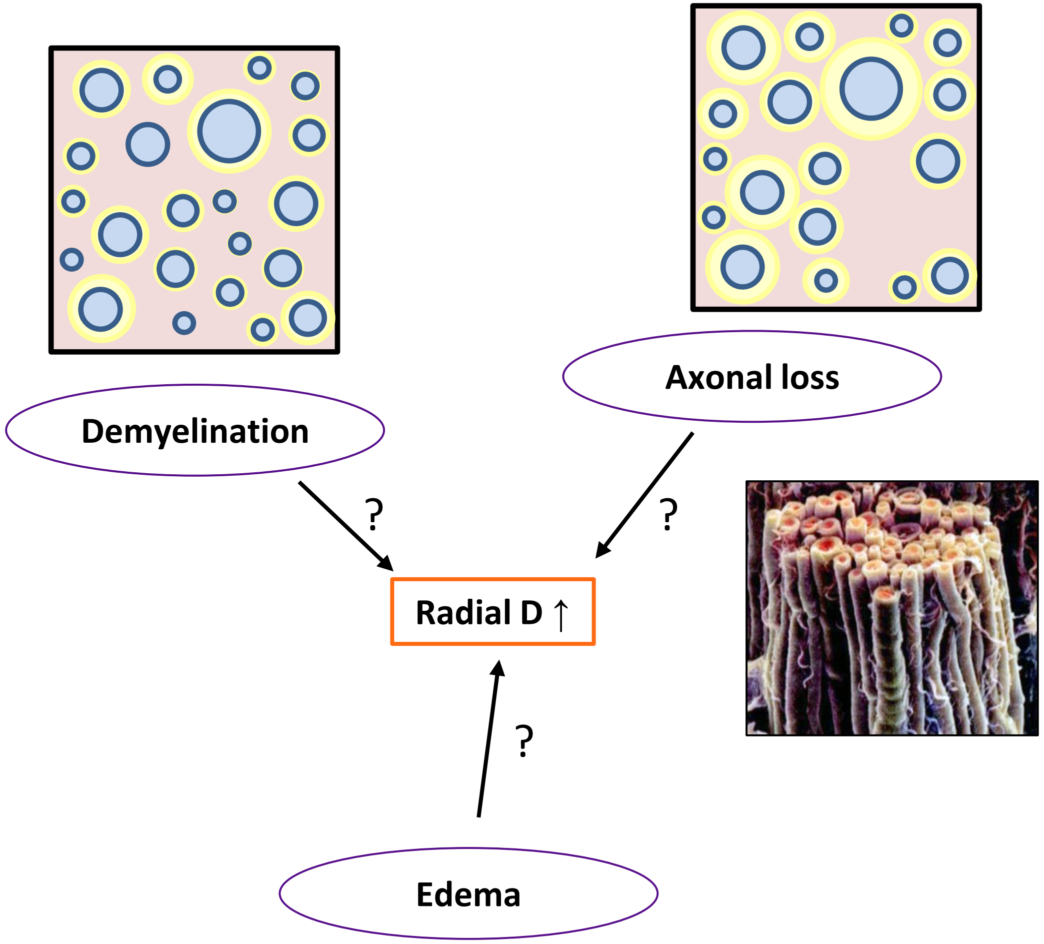
Jensen and Helpern, NMR Biomed 2010
Hui, Stroke 2012
Paydar, AJNR 2014
Rosenkrantz, JMRI 2015



Relationship between altered WM microstructure & amyloid load in MCI patients

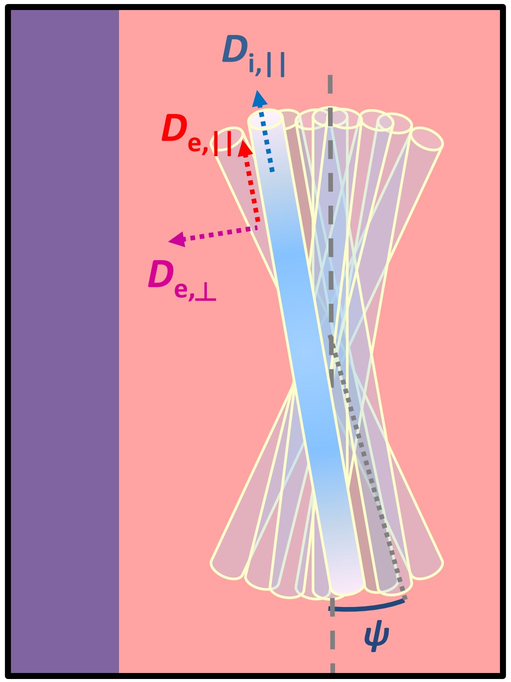
Dong, Neurobiol Aging 2020

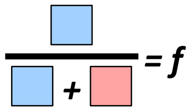
Representations: Valuable… but still lack specificity



Outline

What is a relevant model for white matter?



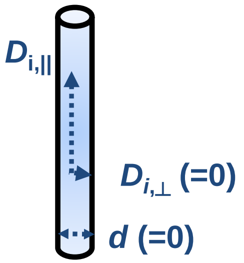


Intra-axonal space

Extra-axonal space

CSF

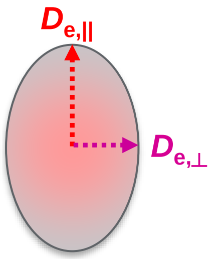
Intra-axonal compartment:
Collection of cylinders (or "sticks")



With some ODF P(**n**)

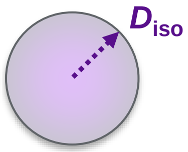
f

Extra-axonal compartment:
(Gaussian) anisotropic connected space



$1\text{-}f\text{-}f_{iso}$

CSF:
Gaussian isotropic



f_{iso}

Markers of:

f: axonal density / loss

ODF: alignment / pruning

d: axon caliber

$D_{i,||}$: axonal injury

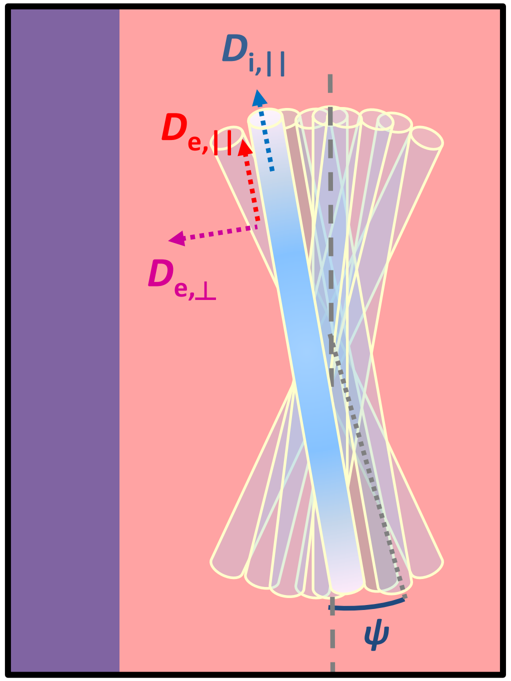
$D_{e,\perp}$: demyelination

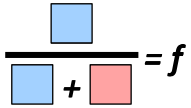
$D_{e,||}$: inflammation

f_{iso}: edema, atrophy

Most cases: “Standard model”

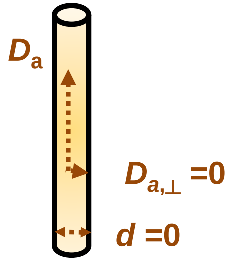
Long-time limit & moderate q





- **Intra-axonal space**
- **Extra-axonal space**
- **CSF**

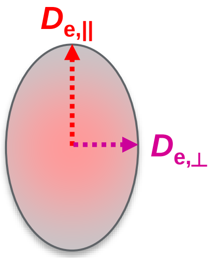
Intra-axonal compartment:
Collection of sticks



With some ODF P(**n**)

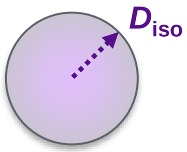
f

Extra-axonal compartment:
Gaussian anisotropic connected space



$1\text{-}f\text{-}f_{iso}$

CSF:
Gaussian isotropic



f_{iso}

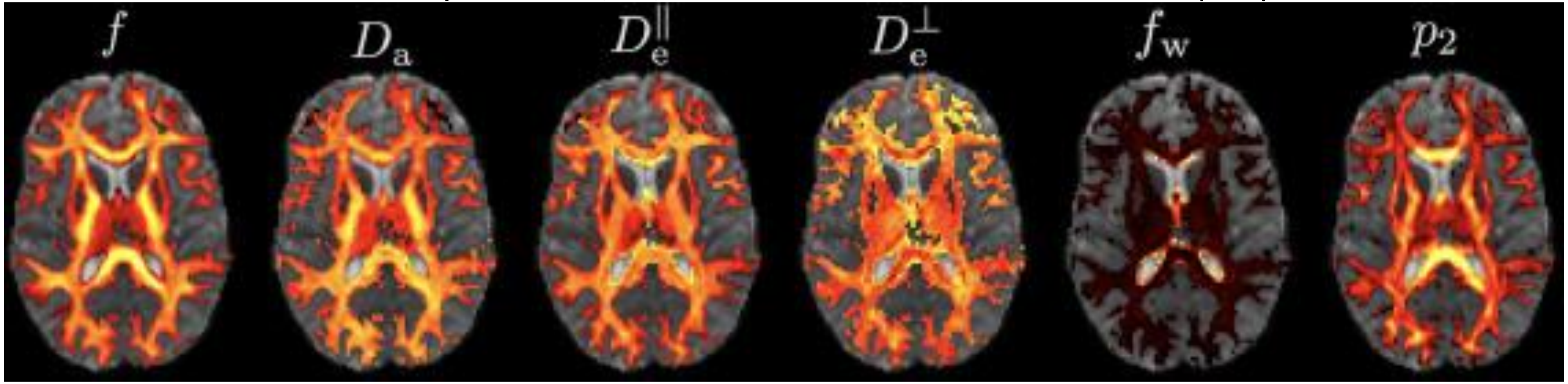
Moving away from spurious assumptions

- Favor Standard Model frameworks that introduce minimum assumptions
  - WMTI-Watson (from DKI)
  - SMI (from Rotational Invariants)
  - Diffusion-relaxometry with tensor encoding

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

Jespersen, NeuroImage 2018; Novikov, NeuroImage 2018; Lampinen, MRM 2020

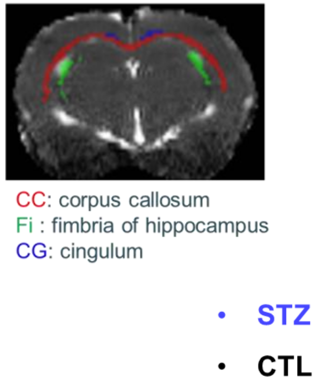
Axonal fraction	Intra-axonal diffusivity	Extra-axonal parallel & perpendicular diffusivity	Free water fraction (CSF)	Axon bundle alignment



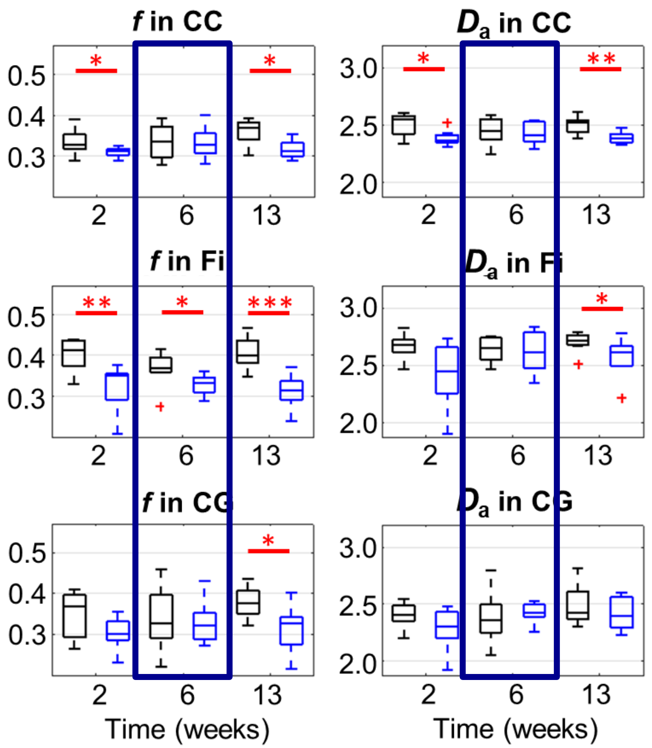
Coelho, NeuroImage 2022

Example applications

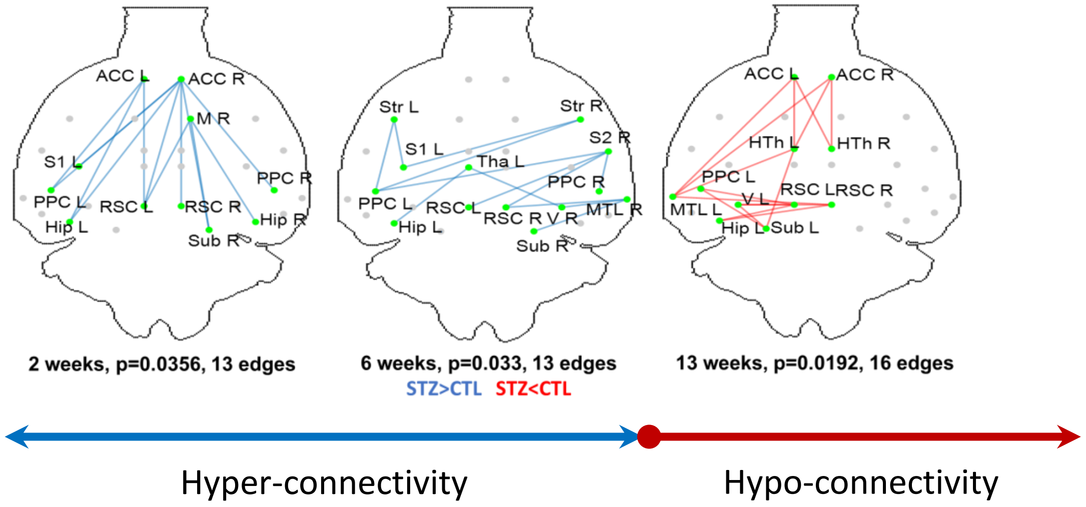
Acute & chronic damage in rat model of AD (“brain diabetes”)



WM microstructure



Functional connectivity



Pereira, NeuroImage 2021; Diao, Front Neurosci 2021

Competition between inflammation & neurodegeneration

WM demyelination and remyelination in cuprizone-fed mice (model for Multiple Sclerosis)

	3W CPZ				6W CPZ			
	Histological analyses	DKI	DTI	WMTI	Histological analyses	DKI	DTI	WMTI
Body	↓ MBP*** ↑ Iba1*** ↑ GFAP*	↑ MK*** ↑ RK** ↑ AK**	↓ MD*** ↓ RD***	↓ D_a*** ↓ $D_{e,\perp}$** ↓ $D_{e,\parallel}$**	↓ MBP* ↑ Iba1** ↑ GFAP***	↓ AK **	↑ MD*** ↑ RD***	↓ AWF*** ?
Splenium	↓ MBP*** ↑ Iba1**	↑ MK*** ↑ RK*** ↑ AK***	↓ MD*** ↓ RD** ↓ AD**	↓ D_a***	↓ MBP*** ↑ Iba1* ↑ GFAP**	↓ MK* ↓ RK** ↓ AK**	↑ MD*** ↑ RD**	↓ AWF**

AWF ≡ f

Competing mechanisms?

- Cellular crowding
- Demyelination

Table 5. Spearman's correlation between diffusion metrics and histological quantitative measures for the cuprizone group (CPZ); correlation coefficient significant (bold) at * $p \leq 0.05$, ** $p \leq 0.01$, and *** $p \leq 0.001$ (two tailed)

		FA	MD	$D_\parallel$	$D_\perp$	MK	$K_\parallel$	$K_\perp$	AWF	D_a	$D_{e\parallel}$	$D_{e\perp}$	α
Myelin	Solochrome	**-0.637*** **	**0.837*** **	**0.518** **	**0.672*** **	**-0.510** **	**-0.495** **	**-0.498** **	**-0.365* **	**0.431* **	0.271	**0.623*** **	-0.276
	Amino	0.035	-0.080	-0.085	0.033	-0.003	-0.258	0.279	-0.239	-0.347	-0.072	0.043	-0.157
	GFAP	0.042	-0.161	**-0.441** **	0.184	0.019	-0.111	0.225	0.175	-0.207	-0.321	0.072	0.018
Microglia	Iba1	-0.340	0.175	**-0.376* **	**0.649*** **	**-0.423* **	**-0.483** **	-0.024	-0.326	-0.316	**-0.435* **	**0.434* **	**-0.365* **

10-week CPZ diet

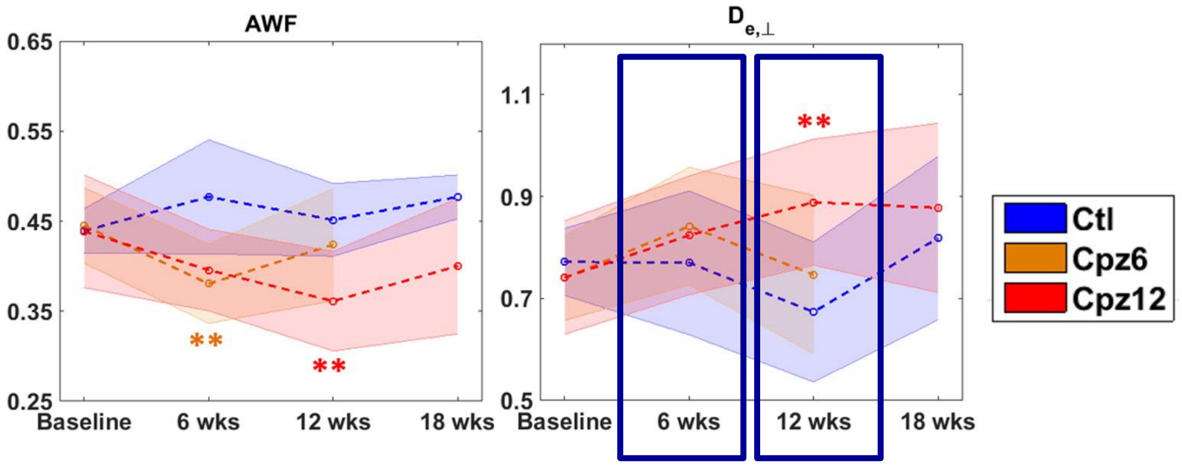
↑ Microglia

↓ $D_{e,\parallel}$ / ↑ $D_{e,\perp}$

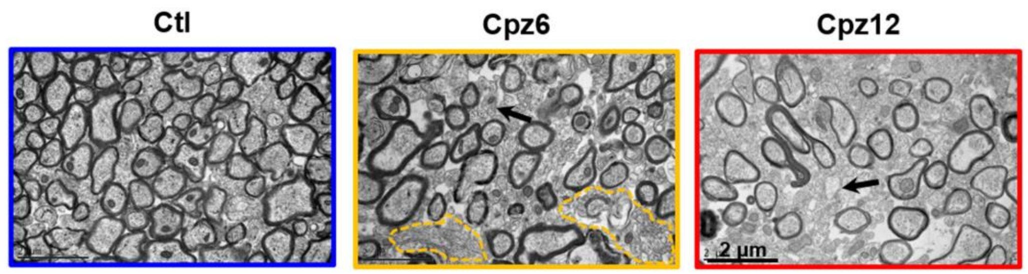
Falangola et al., NMR in Biomed 2014; Guglielmetti et al., NeuroImage 2016

Competition between inflammation & neurodegeneration

WM demyelination and remyelination in cuprizone-fed mice (model for Multiple Sclerosis)



~ $D_{e,\perp}$ ↑ $D_{e,\perp}$



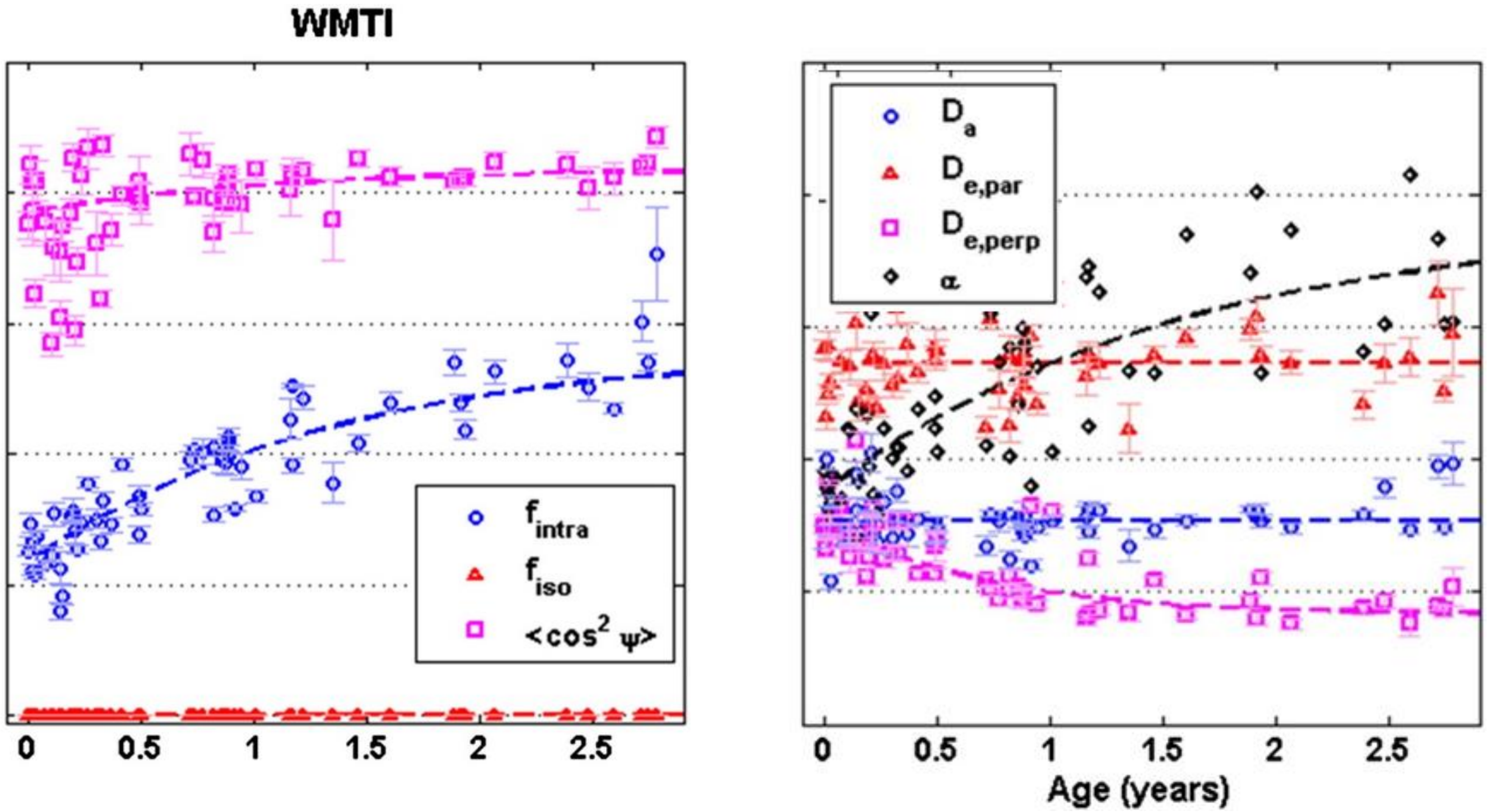
Summary:

3w	6w	10 – 12 w
↓ $D_{e,\perp}$	~ $D_{e,\perp}$	↑ $D_{e,\perp}$
Glia crowding		Heavy demyelination Reduced tortuosity

Jelescu et al., NeuroImage 2016

Example applications

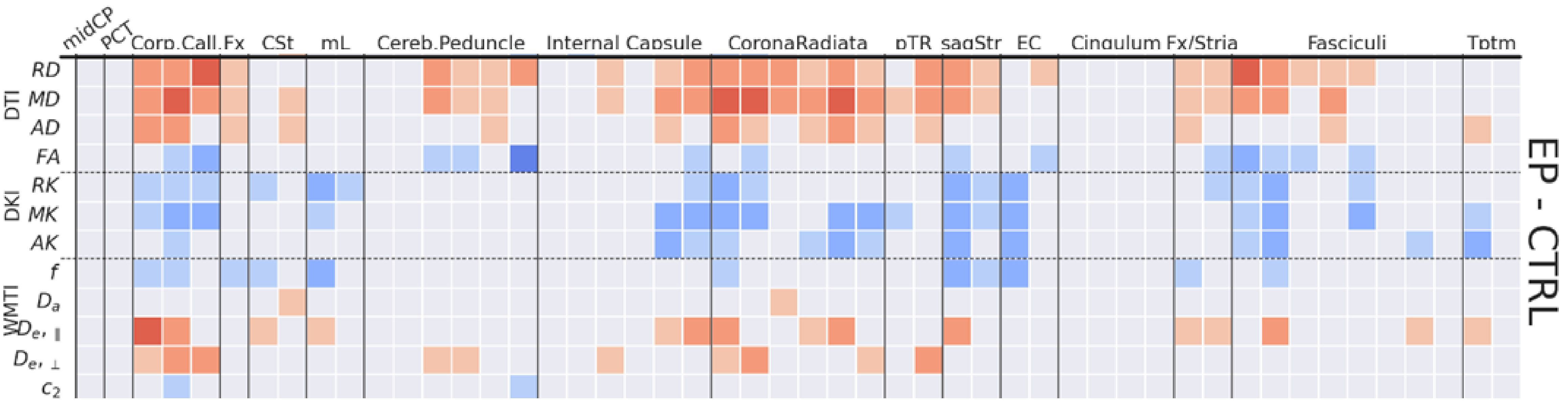
Human WM development



Jelescu, NeuroImage 2015

Example applications

Early Psychosis



Pavan et al., ISMRM 2023

Outline

I. Diffusion-weighting

II. Gaussian approximation regime: ADC and DTI

III. Beyond Gaussian:

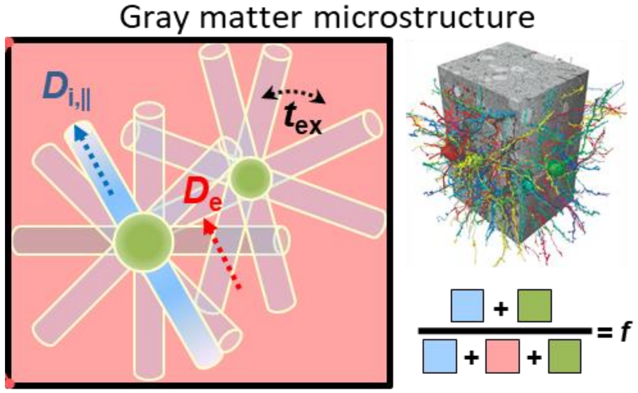
i. Signal representations: DKI

ii. White matter models & applications

iii. Gray matter models & applications

iv. Thinking outside the brain

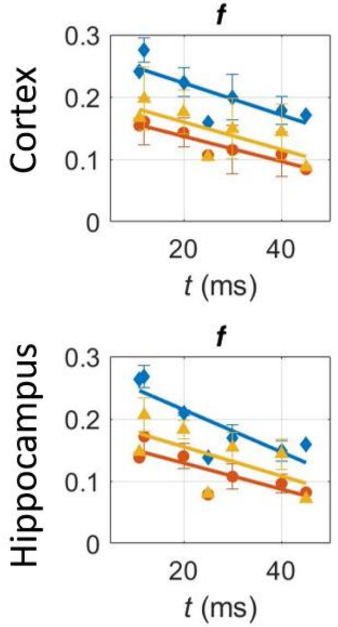
What is a relevant model for gray matter?

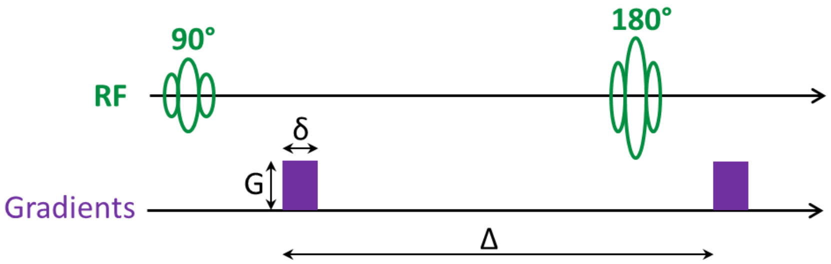


- Cell bodies: a third compartment?
- Little myelin: water exchange between compartments (t_{ex})?
- "Structural disorder", i.e. non-Gaussian diffusion (spines, beading…)?

➡ Exploit both q-t dimensions to probe dynamic processes

- Time-dependent estimates of model parameters
    - Neurite fraction decreases

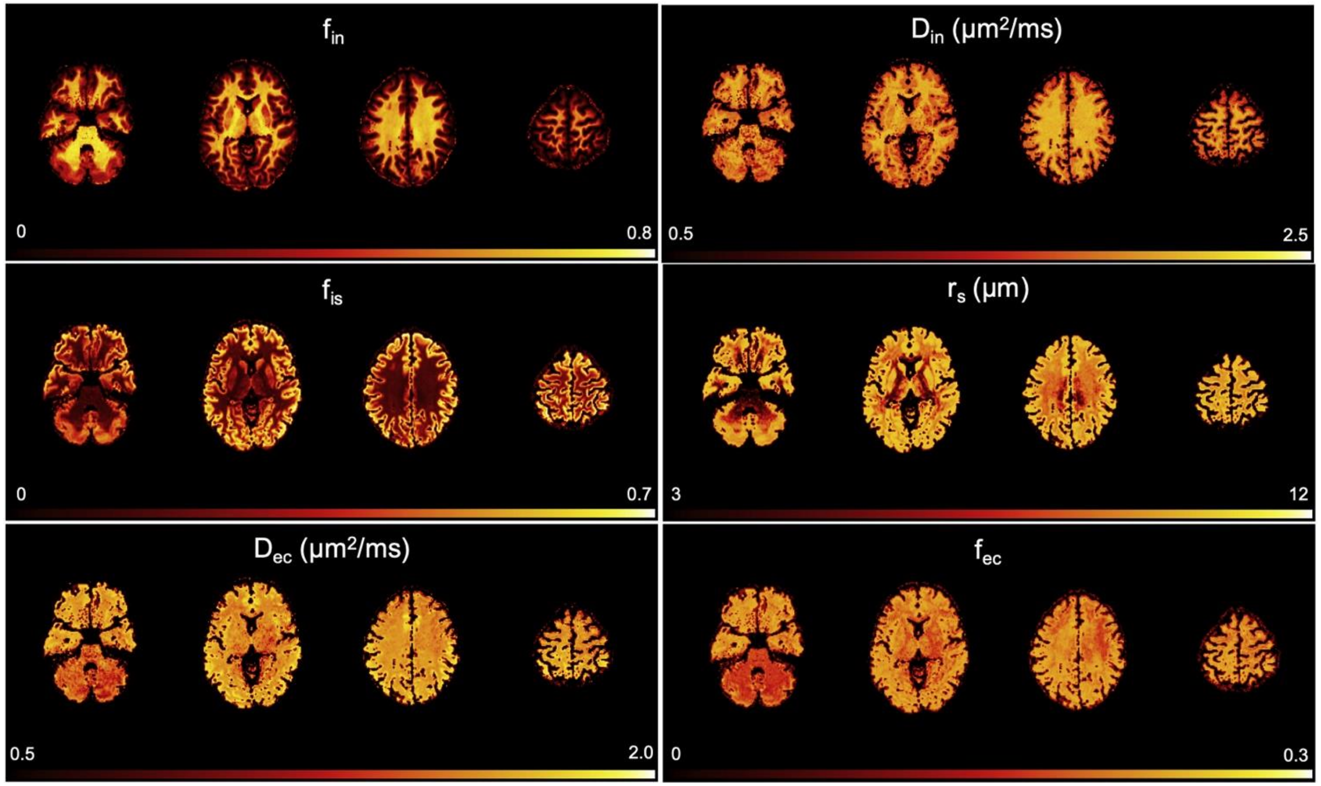


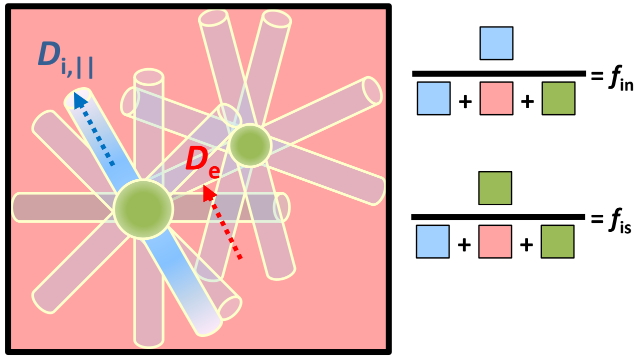


Jelescu, NeuroImage 2022

Modeling soma: SANDI – Soma and Neurite Density Imaging

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





☺ Reasonable estimate of soma density & size

☹ Not feasible on a typical MRI clinical scanner

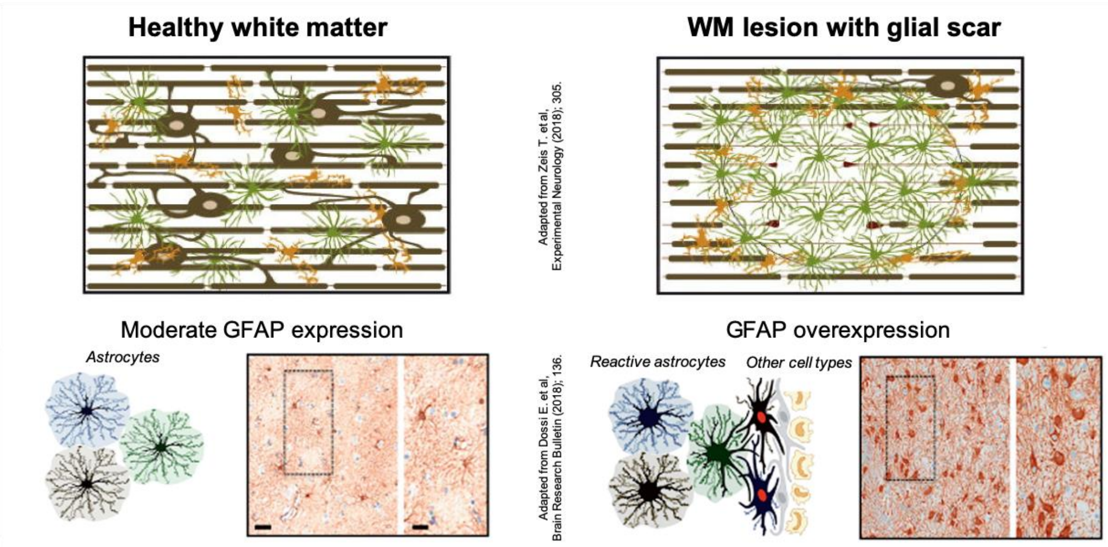
$$b = (\gamma \delta G)^2 \cdot \left(\Delta - \frac{\delta}{3}\right)$$

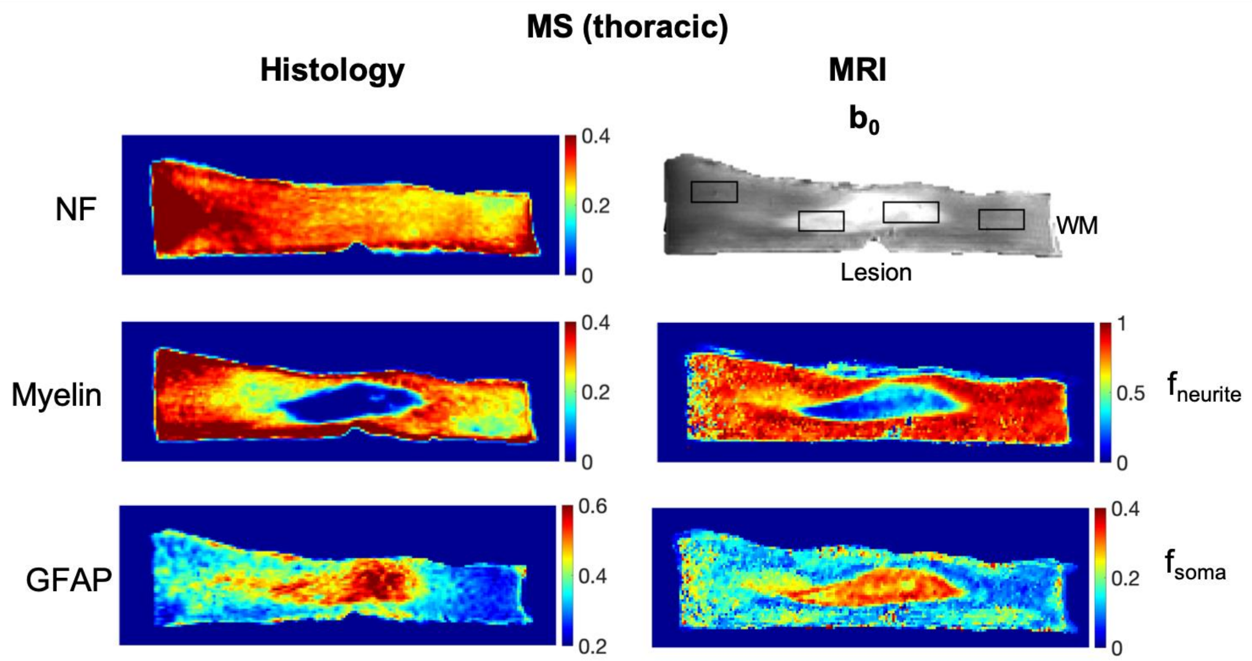
If $\left(\Delta - \frac{\delta}{3}\right)$ is to be kept short,
Need very high G to achieve high b-values ($b > 5$ ms/μm²)

Palombo, NeuroImage 2020; Ianus, NeuroImage 2022

Glial scarring in Multiple Sclerosis

3-compartment SANDI model
Short Diffusion time





- ➢ $f_{neurite}$ captures demyelination and loss of axons?
- ➢ f_{soma} captures increase in astrocyte reactivity?

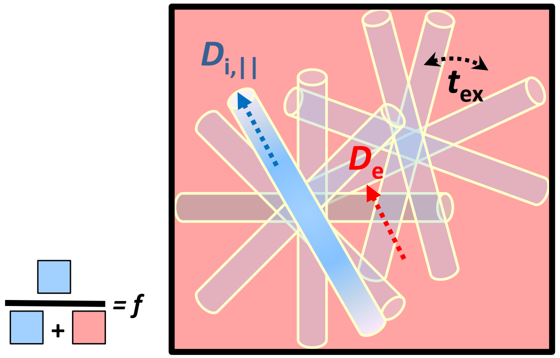
Palombo et al., ISMRM 2020

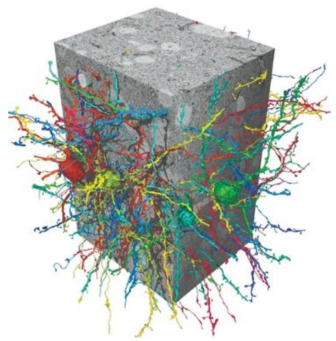
Modeling exchange: 2-compartment anisotropic Kärger model

NEXI – Neurite EXchange Imaging

<u>Kärger Assumption</u>: Barrier-limited exchange

<u>Additionally</u>:
Isotropic distribution of neurites
$D_{e,\parallel} = D_{e,\perp} \equiv D_e$





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

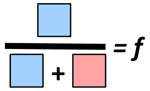
<u>Data acquisition requirements</u>:
Multi-shell (multiple q-values), multi-t (multiple diffusion times)
→ Vary G <u>and</u> Δ

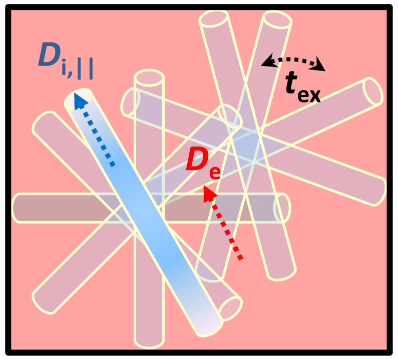
Kärger, 1985; Jelescu, NeuroImage 2022; Olesen, NeuroImage 2022

NEXI (Neurite EXchange Imaging) – preclinical in vivo

Model exchange, ignore soma

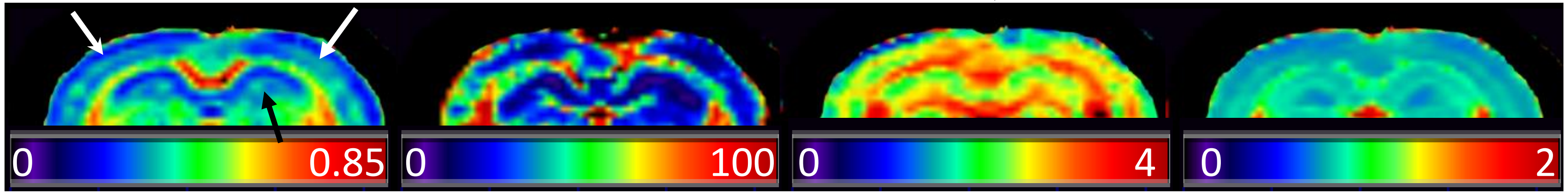
14 Tesla MRI, 1 T/m gradients
b = 0 – 10 ms/um^2
Δ = 10 – 45 ms





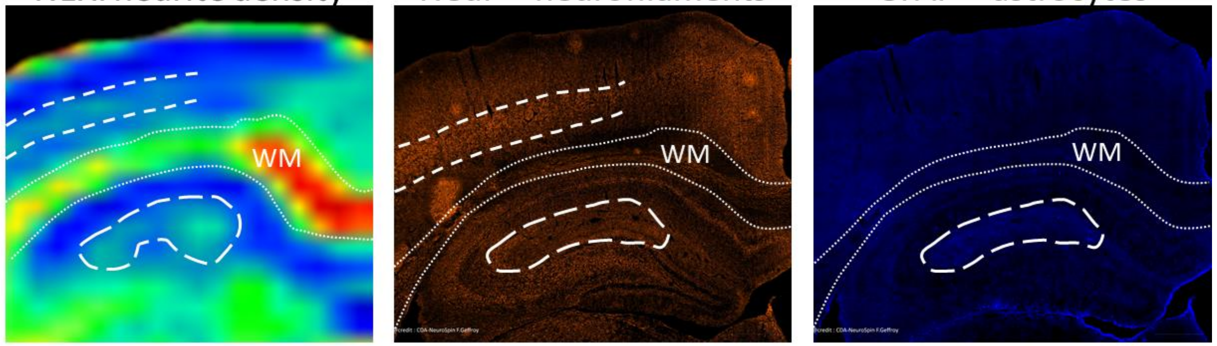
$$\mathbf{p} = [f, D_{i,\parallel}, D_e, t_{ex}]$$

f | t_{ex} | $D_{i,\parallel}$ | D_e



$f \sim 0.25 - 0.5$ | $t_{ex} \sim 15 - 35$ ms | $D_{i,\parallel} \sim 2 - 2.7\ \mu m^2/ms$ | $D_e \sim 0.7 - 0.8\ \mu m^2/ms$

NEXI neurite density | NeuF – neurofilaments | GFAP – astrocytes



$$t_{ex} \cong \frac{d}{4P}$$

P ~ [2 – 33] x 10^{-3} μm/ms

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

Harkins, Magn Reason Med 2009
Finkelstein, 1987
Latour, PNAS 1994
Stanisz, Magn Reason Med 1997

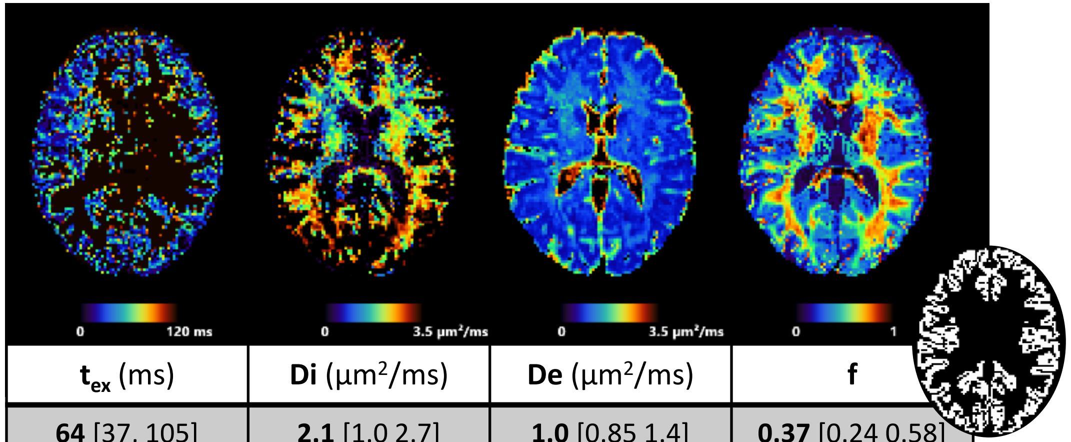
Jelescu et al, NeuroImage 2022

NEXI – human *in vivo*

3T Connectom scanner (G_{max} 300 mT/m)

b = 1 – 7.5 ms/µm^2
Δ = 20 – 40 ms
δ = 9 ms
1.8-mm isotropic resolution
Scan time: 45 min

Estimation: Non-linear least squares

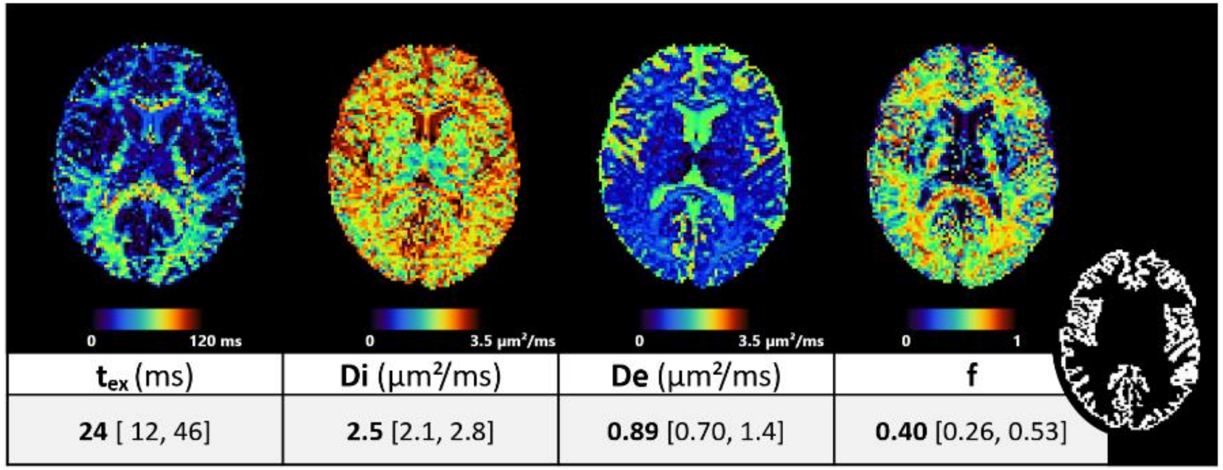


t_{ex} (ms)	**Di** (µm^2/ms)	**De** (µm^2/ms)	**f**
64 [37, 105]	**2.1** [1.0 2.7]	**1.0** [0.85 1.4]	**0.37** [0.24 0.58]

3T Clinical scanner (G_{max} 80 mT/m)

b = 1 – 5 ms/µm^2
Δ = 28 – 65 ms
δ = 16.5 ms
2-mm isotropic resolution
Scan time: 35 min

Estimation: Multi-layer perceptron



t_{ex} (ms)	**Di** (µm^2/ms)	**De** (µm^2/ms)	**f**
24 [12, 46]	**2.5** [2.1, 2.8]	**0.89** [0.70, 1.4]	**0.40** [0.26, 0.53]

Uhl et al, ISMRM 2023

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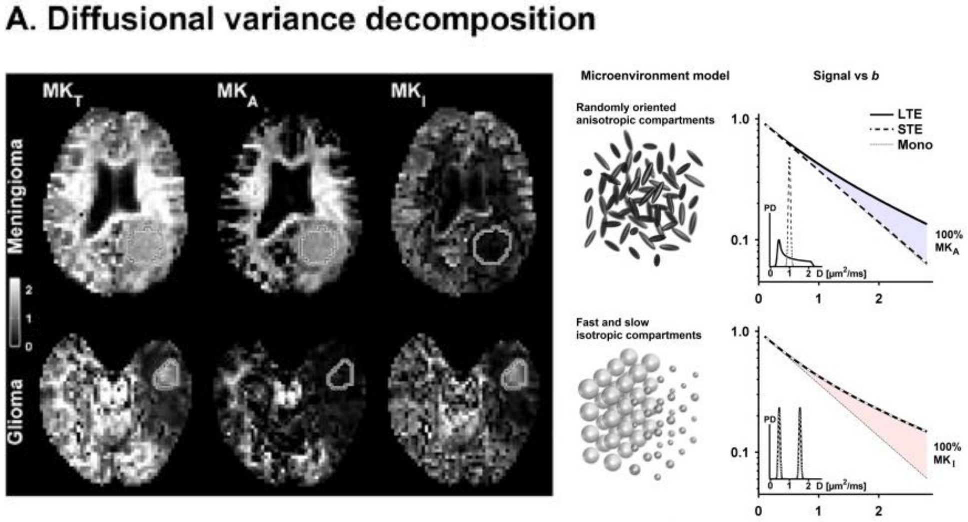
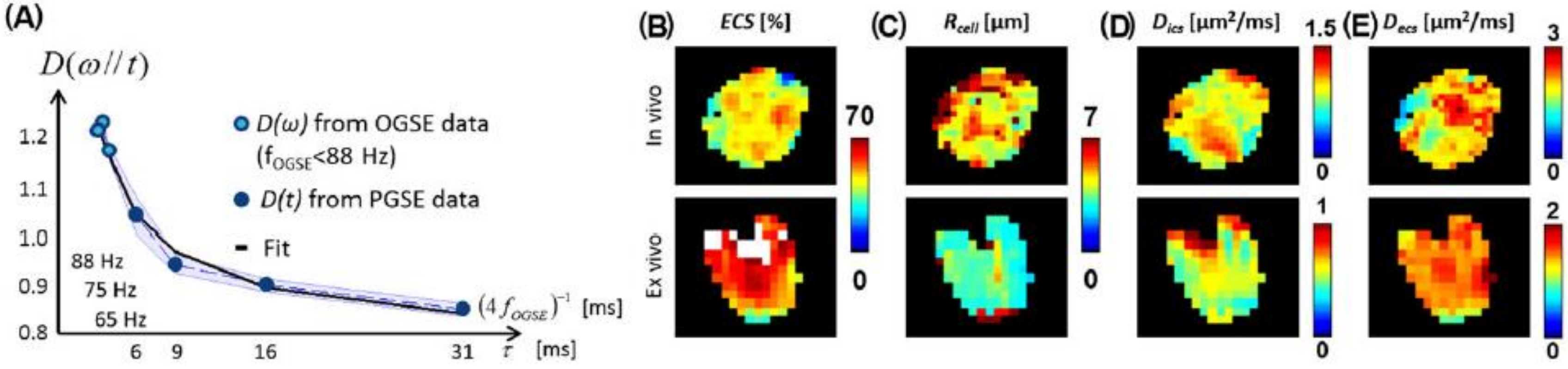
Microstructure models (almost) outside the brain



Szczepankiewicz, NeuroImage 2016

Glioma

Quantification of cell density, radius, and compartment diffusivities



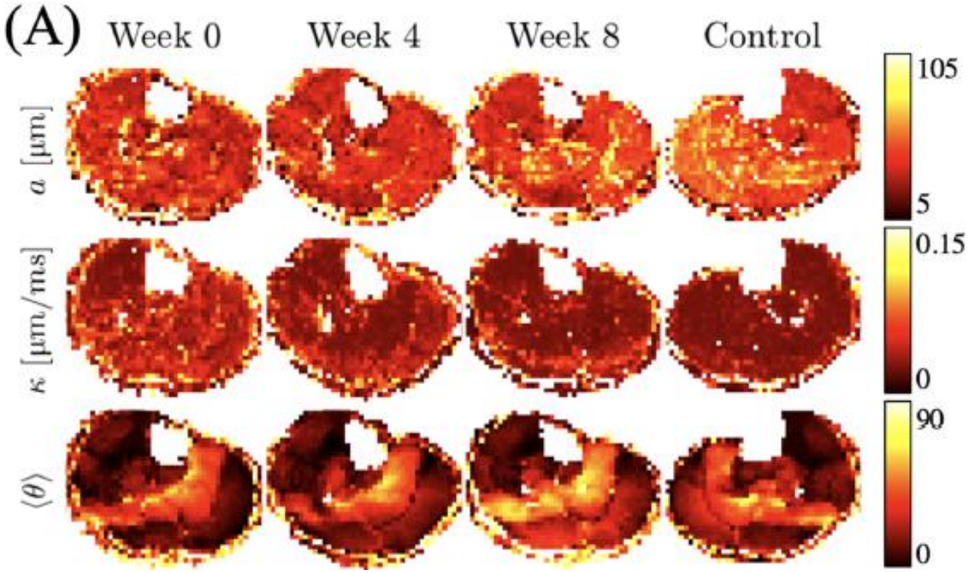
Reynaud, NMR in Biomed 2016

Microstructure models outside the brain

Random Permeable Barrier Model

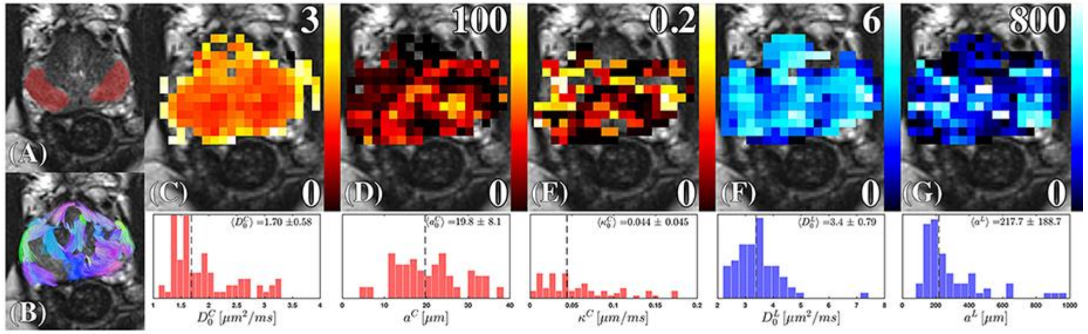
Muscle

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

Guideline Papers:
Jelescu, […], Schilling, arXiv 2022
Schilling, […], Jelescu, arXiv 2022

Questions?