In vivo measurement of inter-hemispheric axon diameters on a clinical scanner using multiple pulsed-field gradient (mPFG) diffusion MRI

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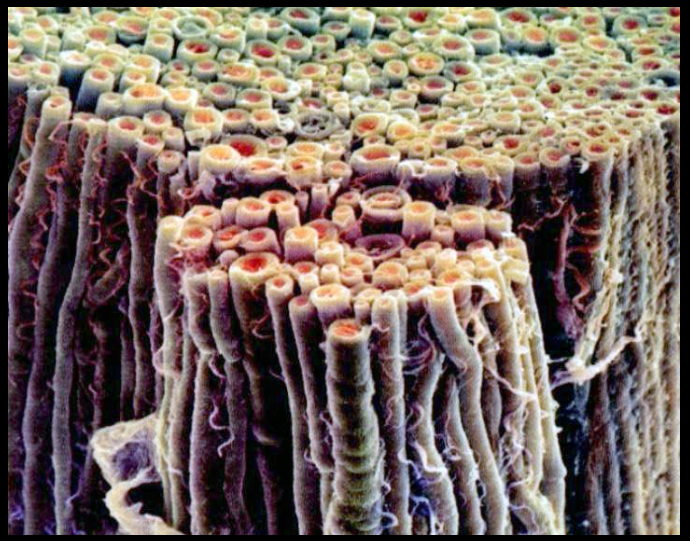
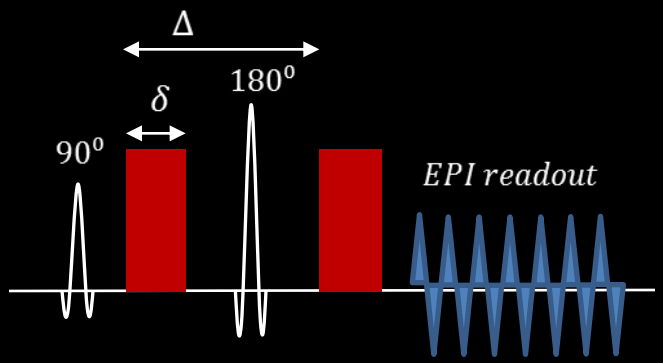
Tissue Microstructue

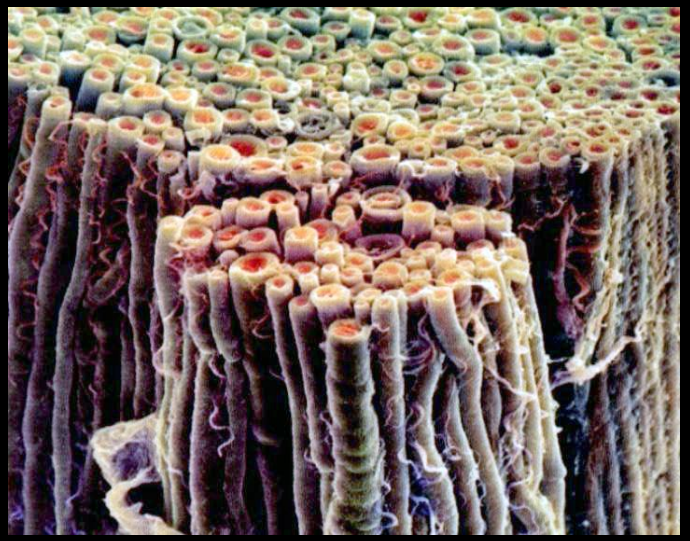
- Quantifying microstructural features of neurons
- Current methods
- Limitations of biopsy-driven histology
- Whole-brain non-invasive histological assessment



Diffusion Tensor Imaging

Single pulsed-field gradient (sPFG) spin echo diffusion MRI



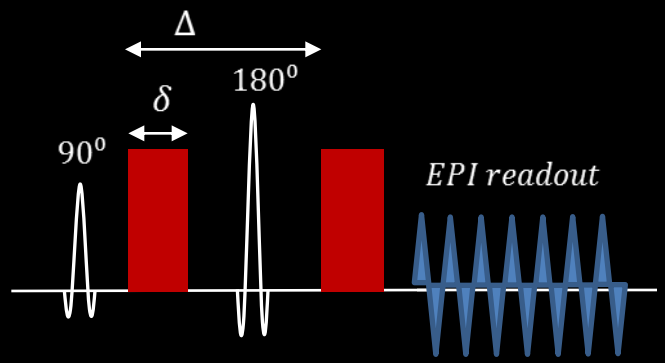


- DTI sensitive clinical tool for imaging white matter microstructural changes and mapping brain connectivity
- The estimated diffusion tensor is modulated by microscopic anisotropy and by macroscopic anisotropy
- Need increased specificity and selectivity
- Clinical application of advanced DTI methods such as CHARMED or AxCaliber is challenging on current whole-body MRI scanners

Assaf et al., Magn Res Med, 2008

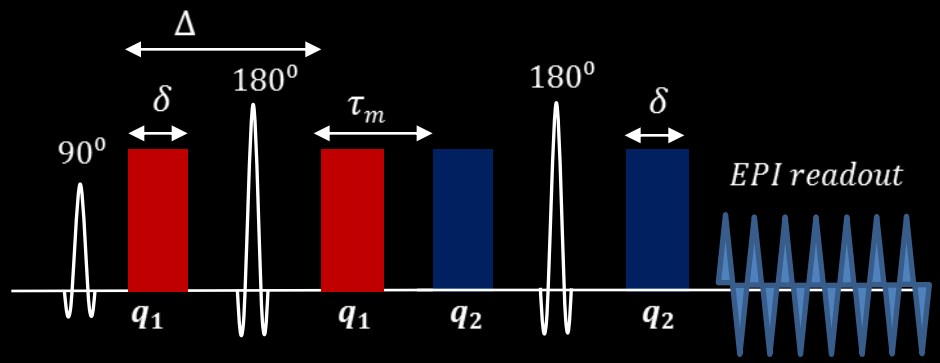
Double PFG diffusion MRI

Single pulsed-field gradient PFG spin echo diffusion MRI



Double PFG diffusion MRI

Double pulsed-field gradient (dPFG) diffusion pulse sequence



Cory et al., *Polym Preprints*, 1990

Double PFG diffusion MRI

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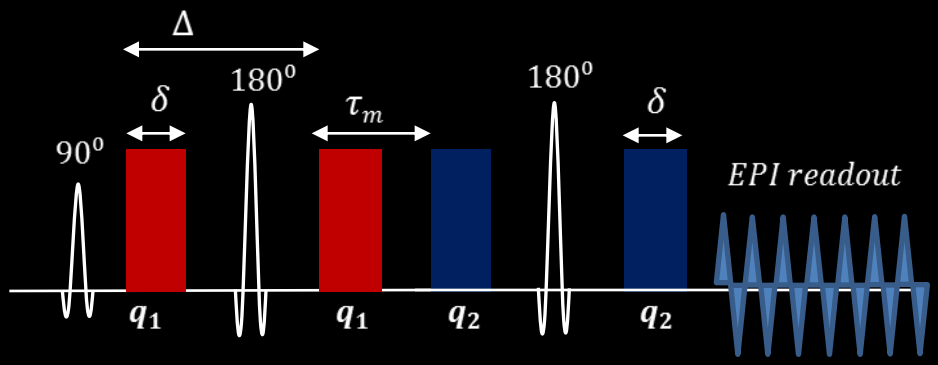
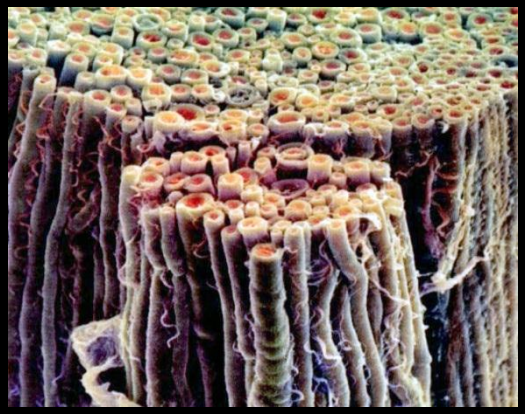
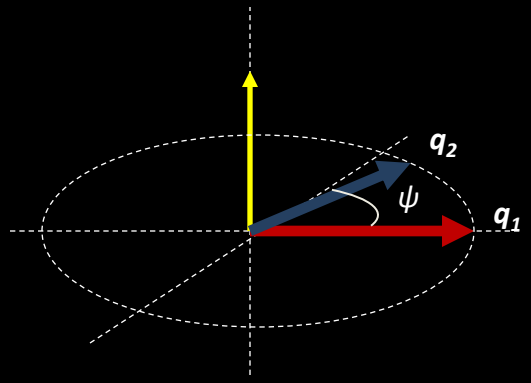
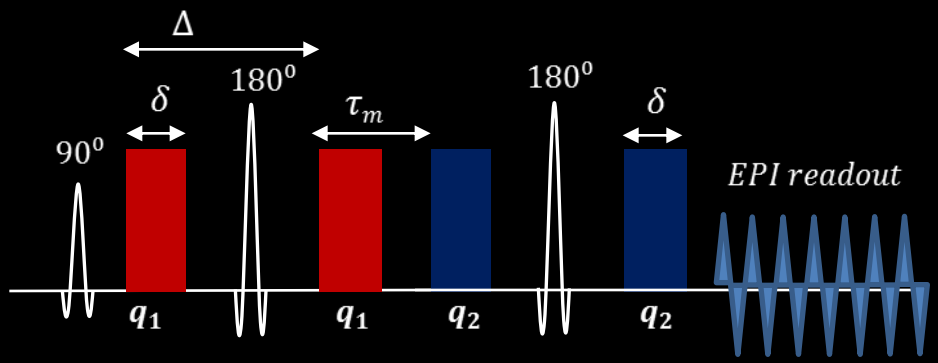


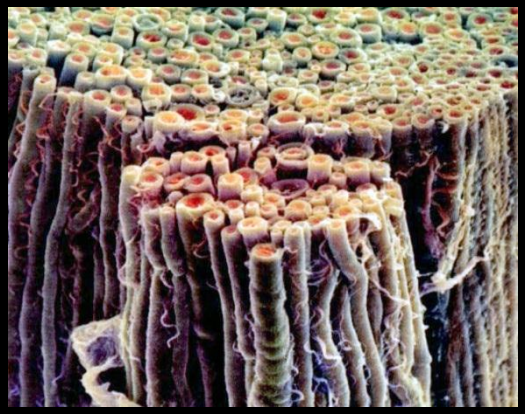


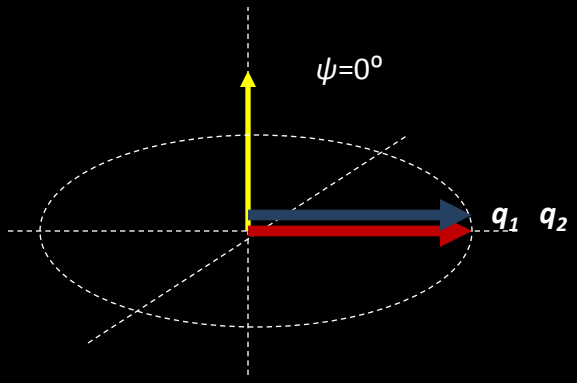


Multiple PFG diffusion MRI

Double pulsed-field gradient (dPFG) diffusion pulse sequence

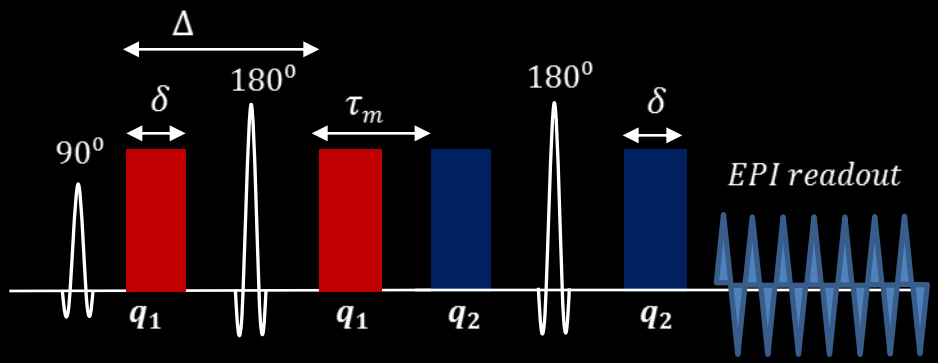


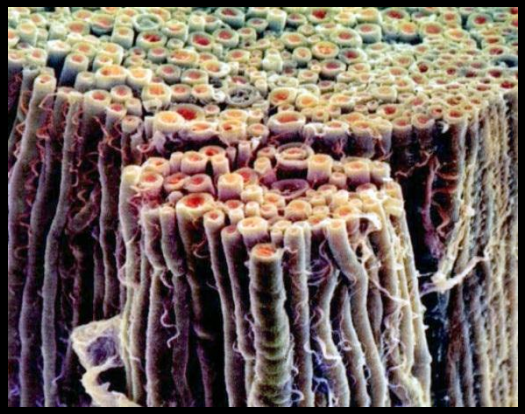


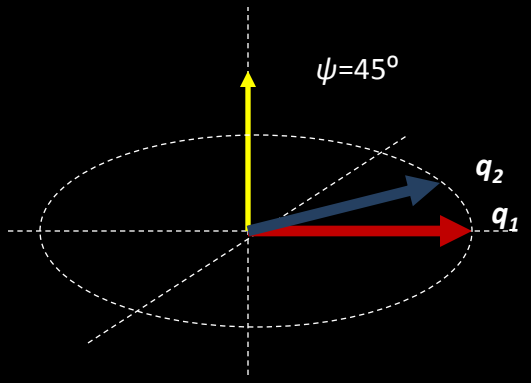


Multiple PFG diffusion MRI

Double pulsed-field gradient (dPFG) diffusion pulse sequence

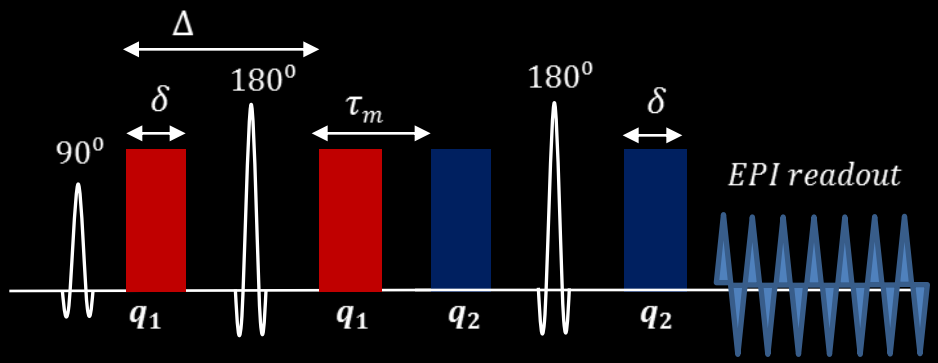


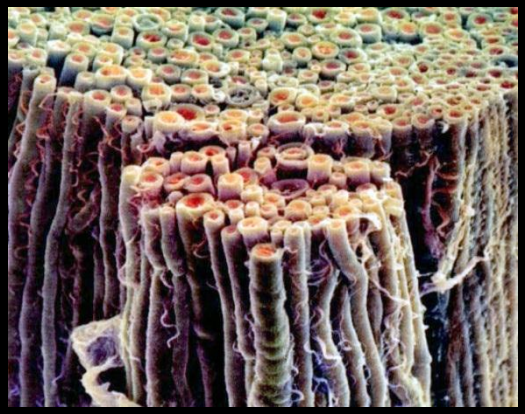


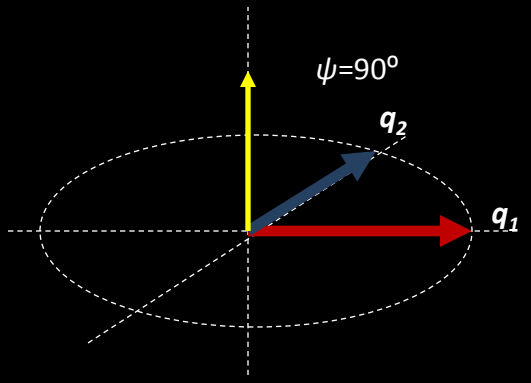


Multiple PFG diffusion MRI

Double pulsed-field gradient (dPFG) diffusion pulse sequence

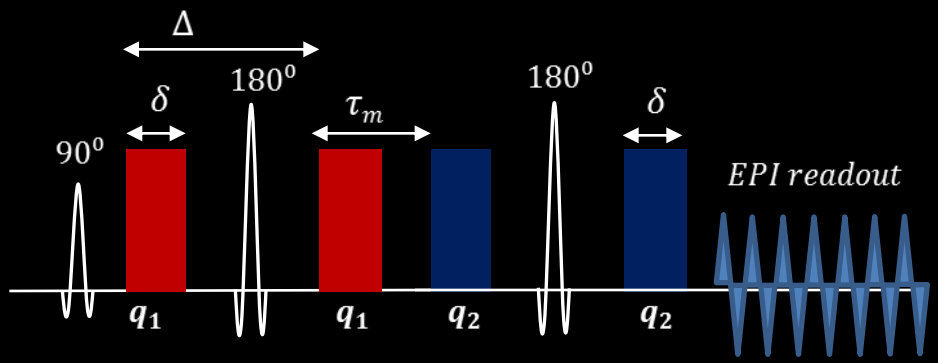


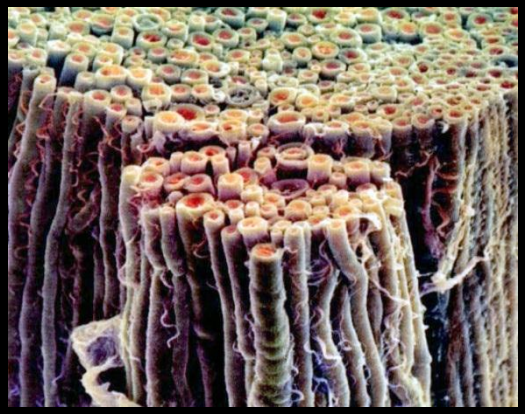


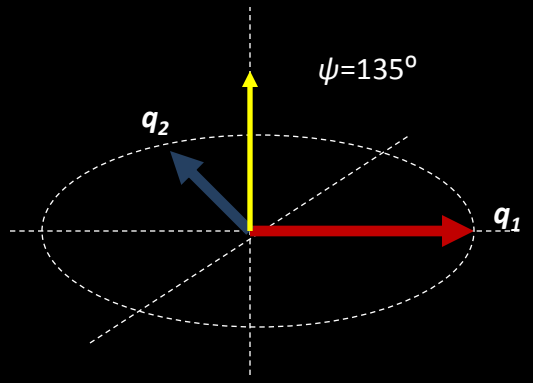


Multiple PFG diffusion MRI

Double pulsed-field gradient (dPFG) diffusion pulse sequence

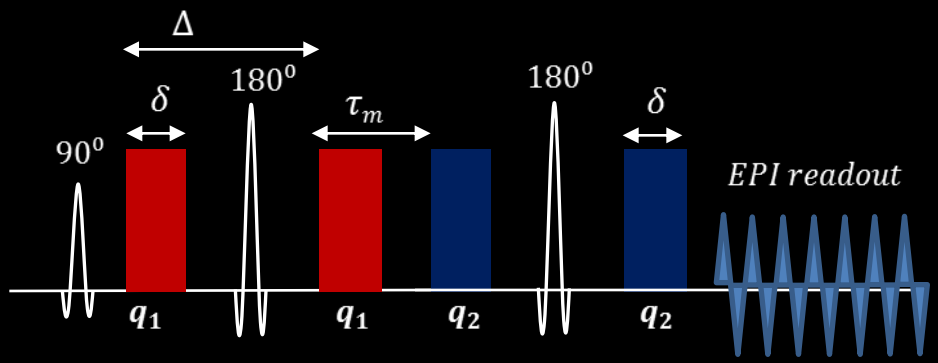


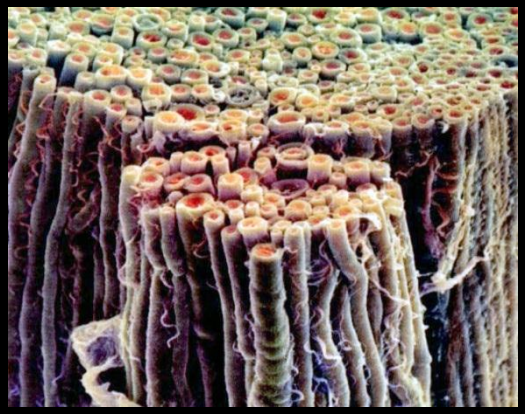


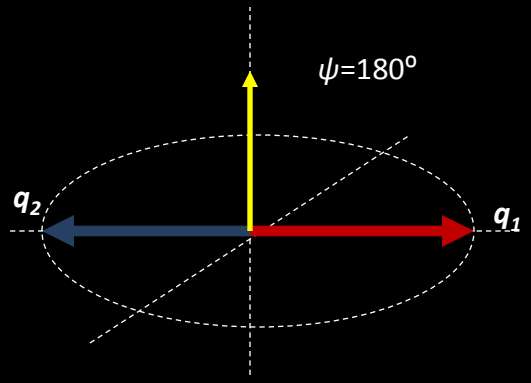


Multiple PFG diffusion MRI

Double pulsed-field gradient (dPFG) diffusion pulse sequence

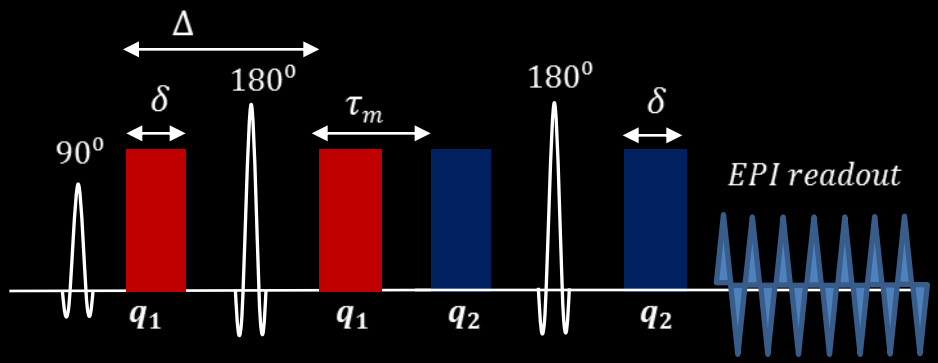


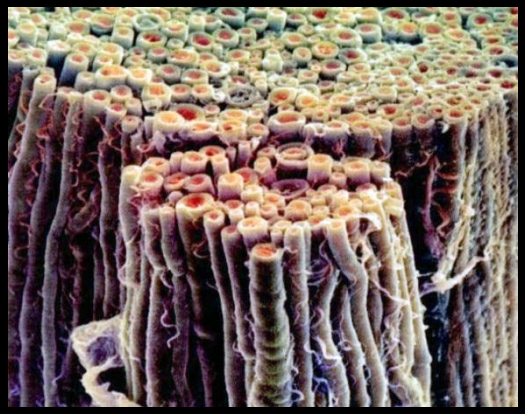


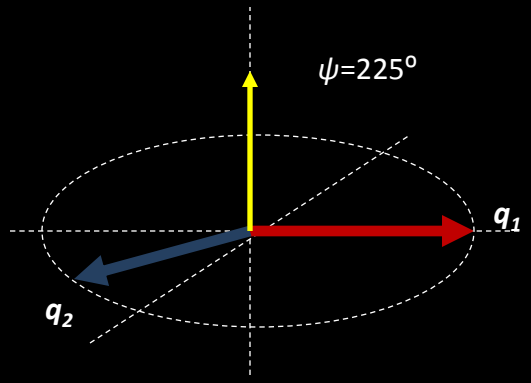


Multiple PFG diffusion MRI

Double pulsed-field gradient (dPFG) diffusion pulse sequence

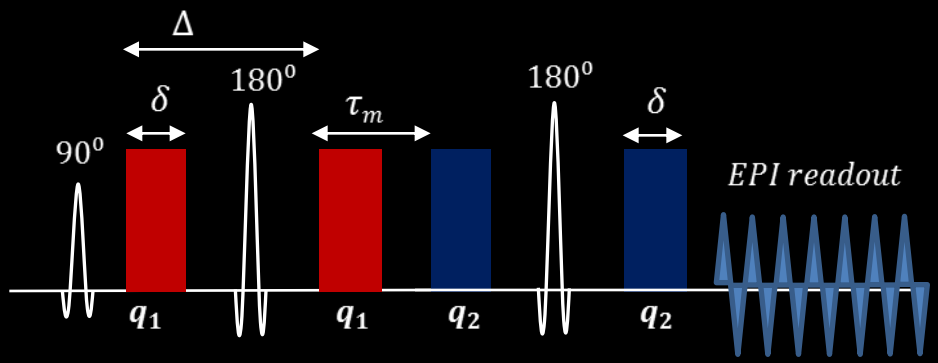


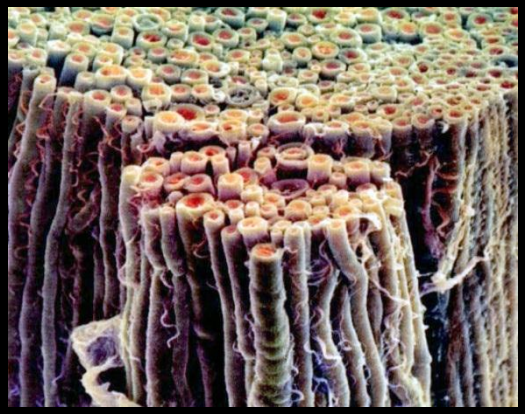


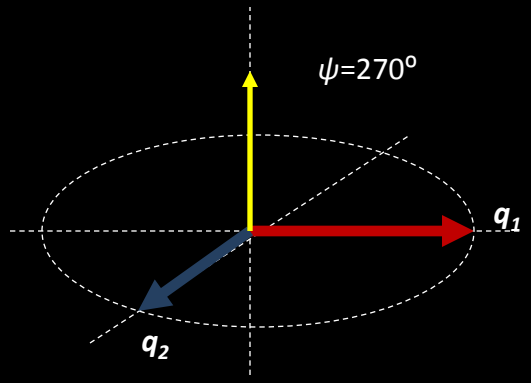


Multiple PFG diffusion MRI

Double pulsed-field gradient (dPFG) diffusion pulse sequence







Multiple PFG diffusion MRI

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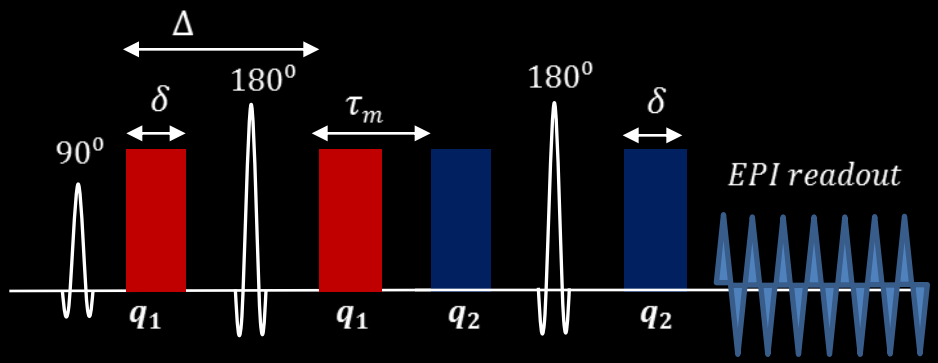
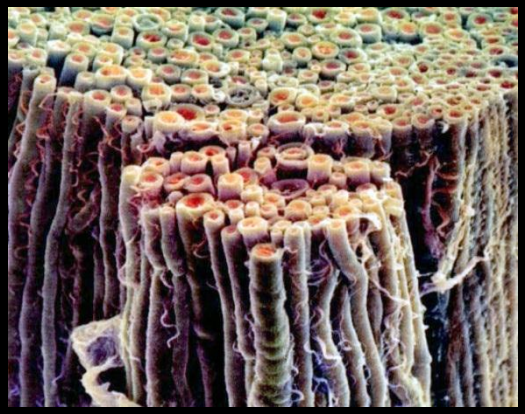
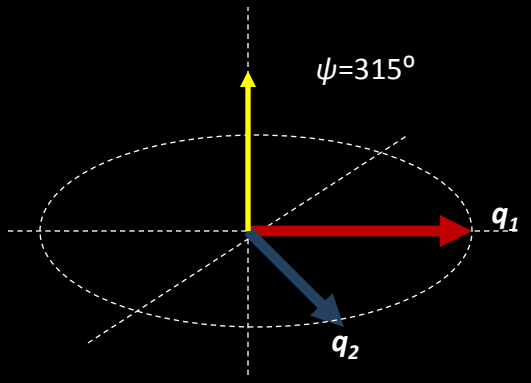
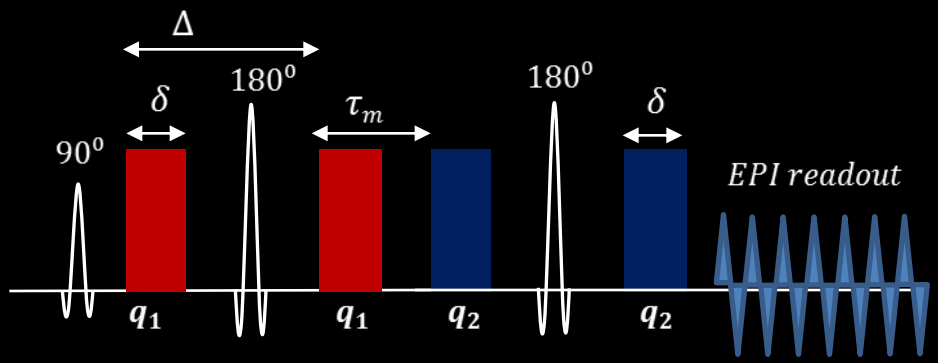


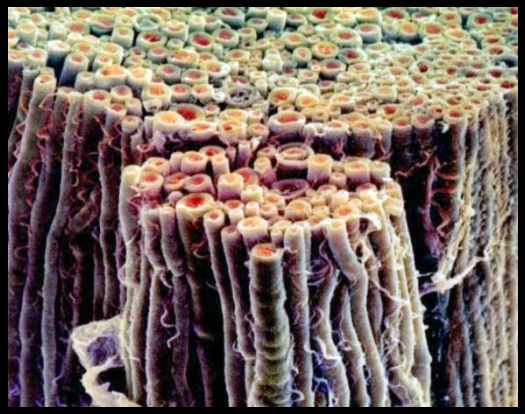


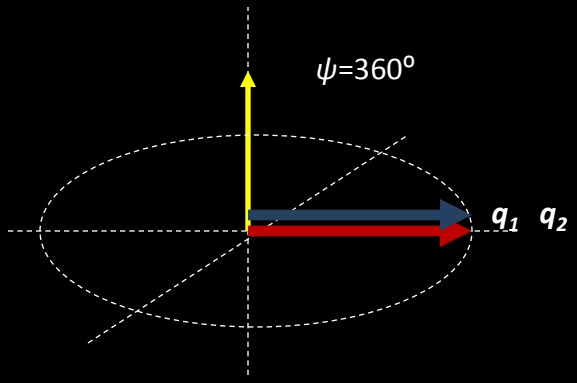


Multiple PFG diffusion MRI

Double pulsed-field gradient (dPFG) diffusion pulse sequence







Multiple PFG diffusion MRI

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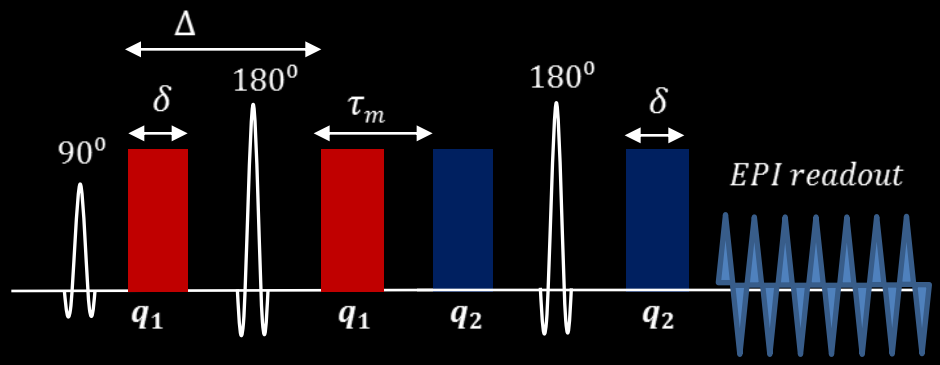
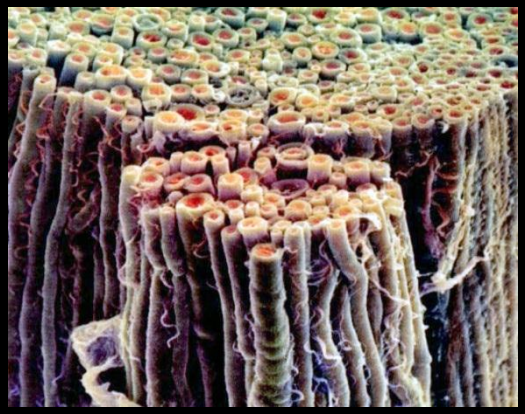
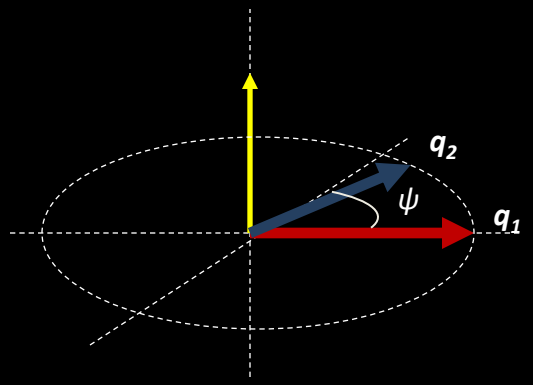
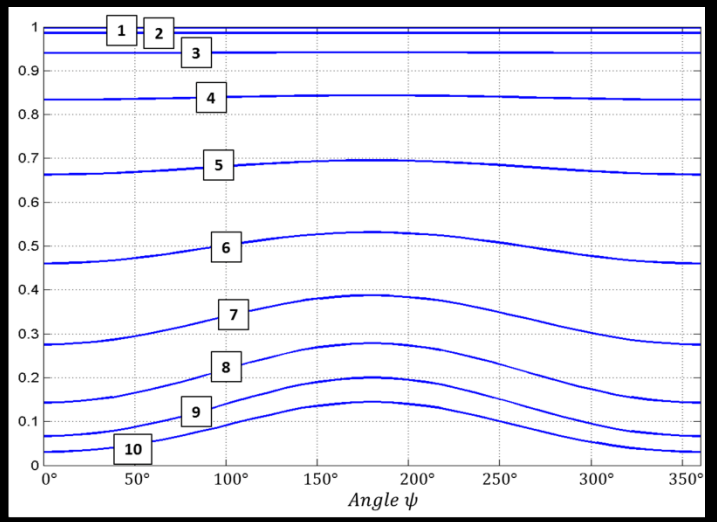


$\delta \to 0;\ \Delta \to \infty$

$$E_0(\psi) = 1 - 8\pi^2 q^2 \langle A \rangle_{iso} - 4\pi^2 q^2 \langle A \rangle_{iso} cos\psi$$

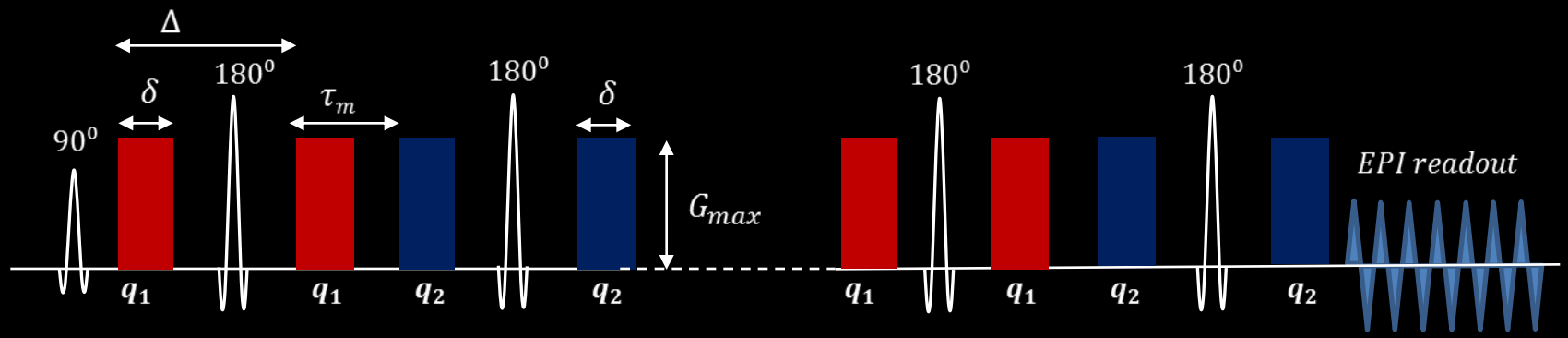






Multiple PFG diffusion MRI

Multiple pulsed-field gradient (mPFG) diffusion pulse sequence with concatenated dPFG blocks



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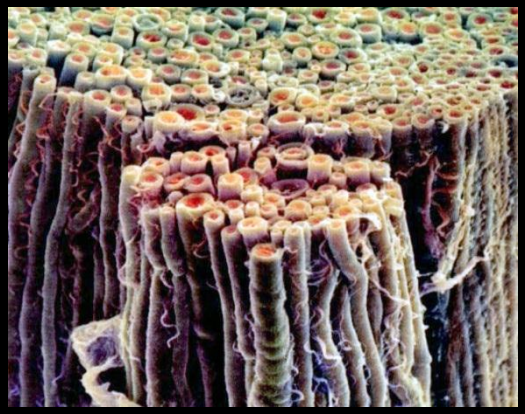
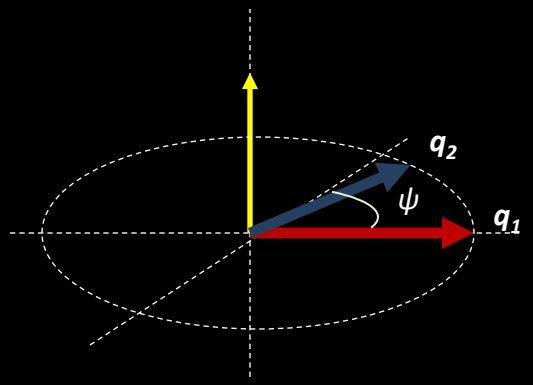
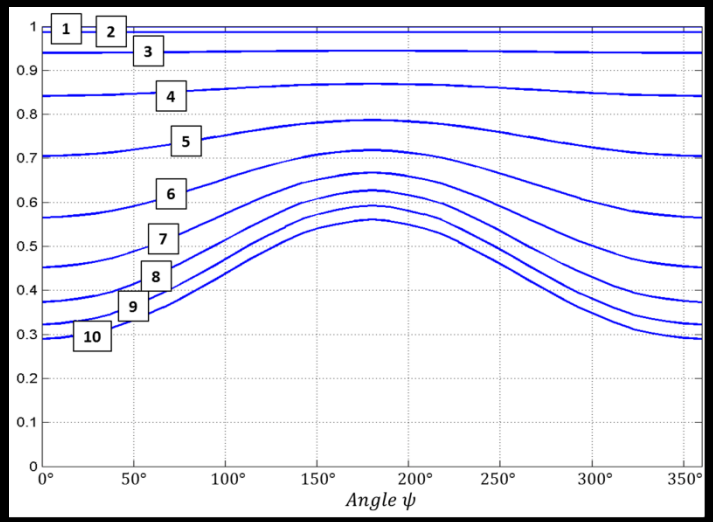




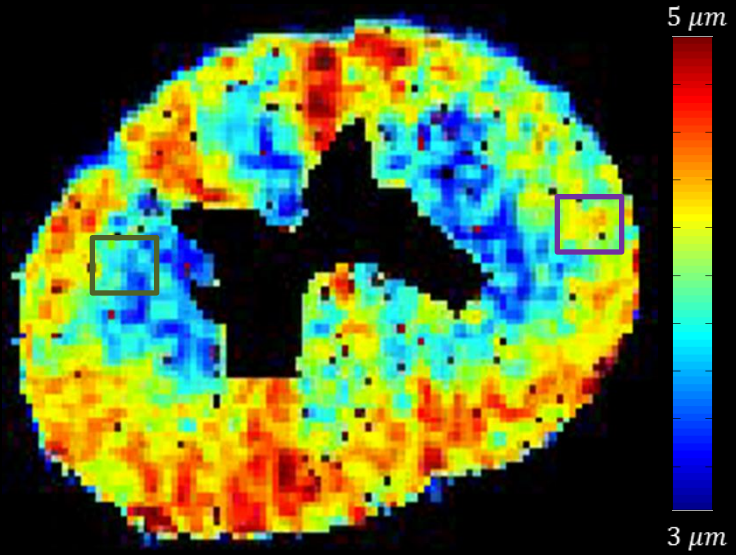


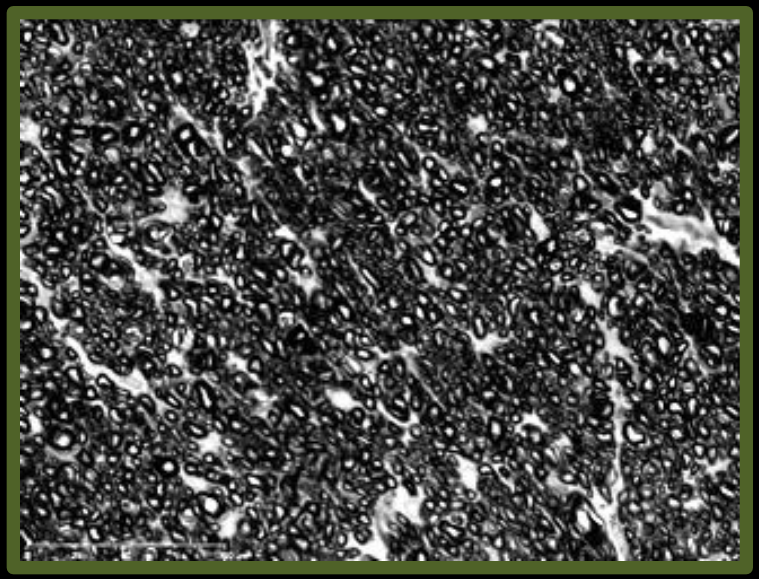
Finsterbusch, *J Magn Res*, 2009

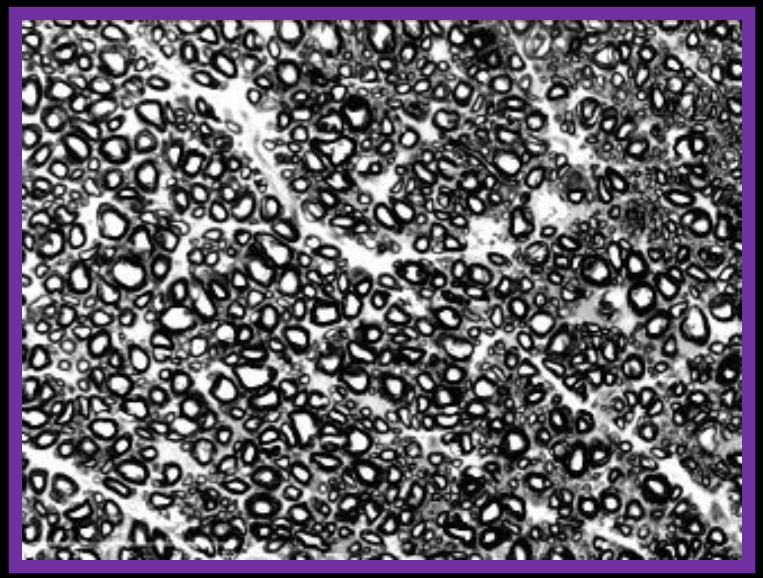
Özarslan and Basser, *J Phys Chem*, 2008

Histological Validation

Map of axon diameters measured using dPFG diffusion MRI in pig spinal cord







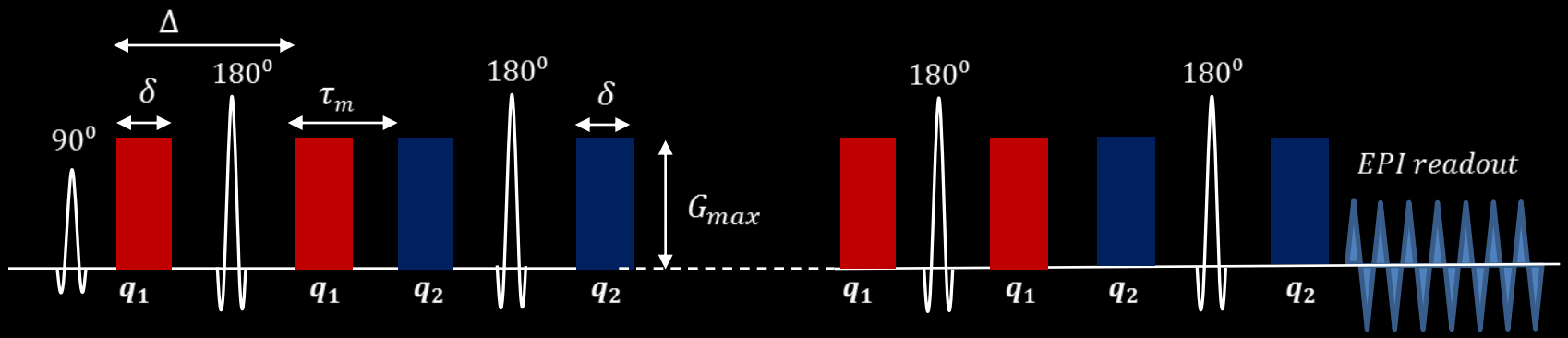
Komlosh et al., *Proc of ISMRM,* 2012

Challenges for *in vivo* human imaging

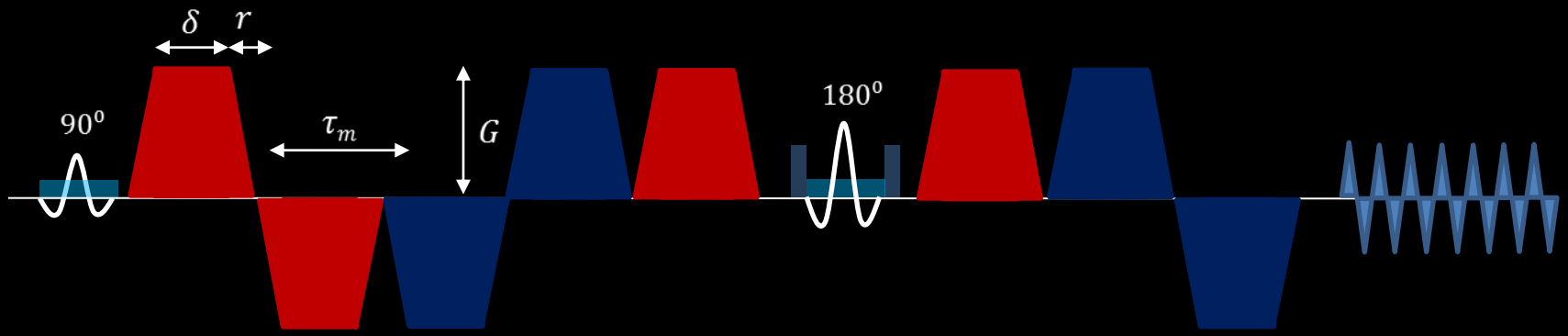
- Limited gradient strength
- Theoretical assumptions
- Need powerful mathematical framework
- Long echo times
- Limited scan duration
- Signal-to-noise ratio (SNR)
- Partial volume effects
- Fiber orientation
- Subject/physiological motion

Clinical Pulse Sequence Design

Multiple pulsed-field gradient (mPFG) diffusion pulse sequence with concatenated dPFG blocks



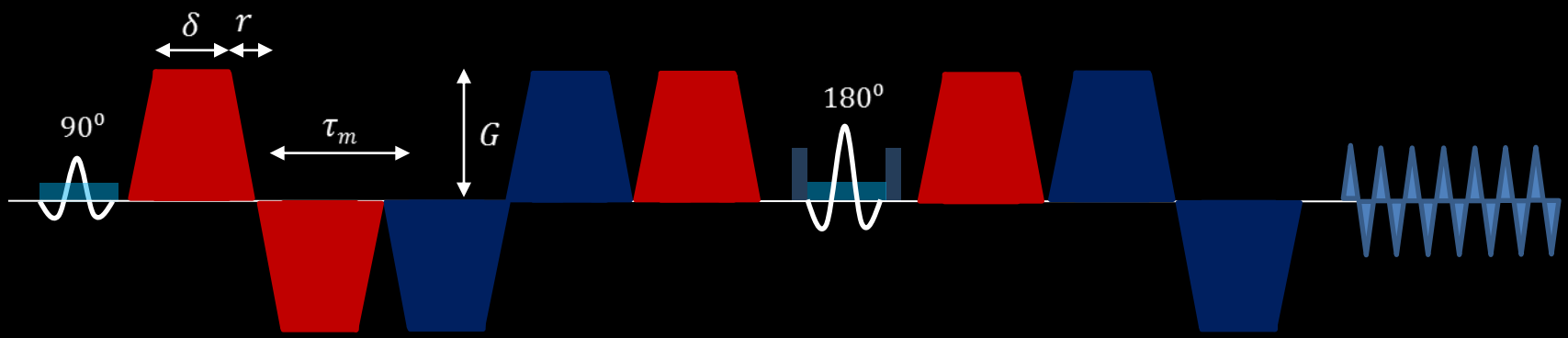
Clinical Implementation of quadruple PFG diffusion MRI with $\tau_m = \delta + 2r$



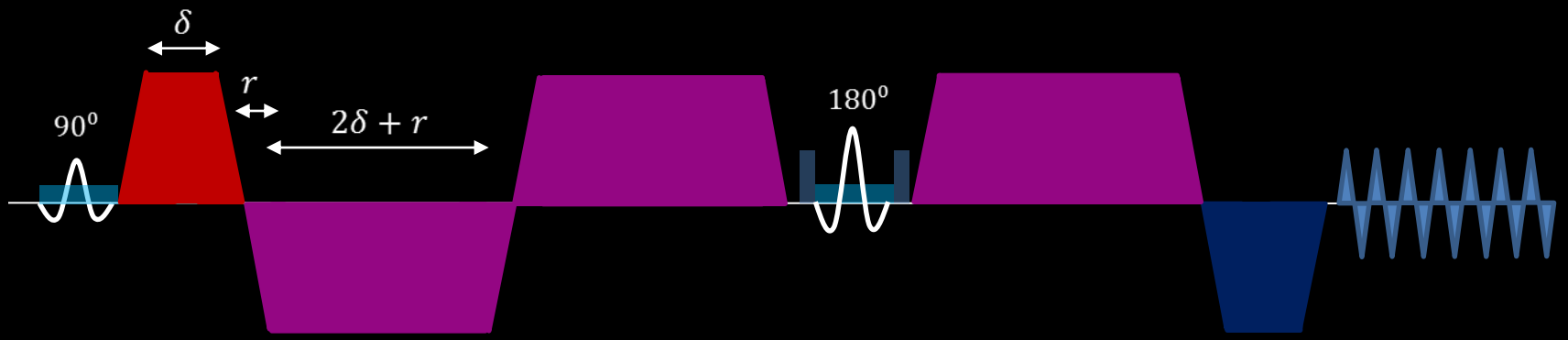
Avram et al., *Neuroimage,* 2012 (submitted)

Clinical Pulse Sequence Design

Clinical Implementation of quadruple PFG diffusion MRI with $\tau_m = \delta + 2r$



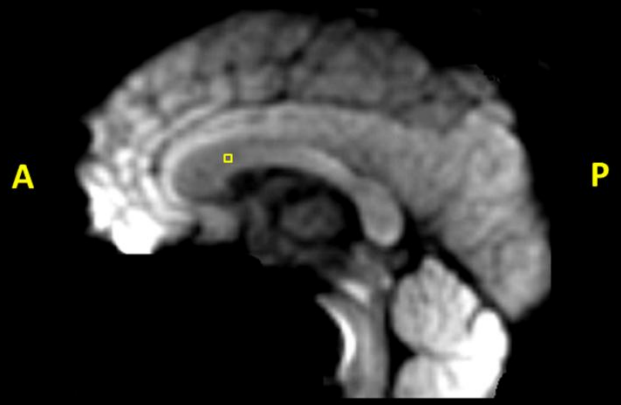
Clinical Implementation of quadruple PFG diffusion MRI with $\tau_m = 0$



Avram et al., *Neuroimage,* 2012 (submitted)

In vivo mPFG diffusion MRI

- Sagittal prescription through the medial corpus callosum with 2x2x6 mm^3 voxel
- Cardiac gating: 7 R-R intervals
- Scan parameters: qPFG diffusion MRI with TE/TR=147/6000 ms, G_{max}=50 mT/m, δ=11.8 ms, r=0.8 ms, $4q$=1,100 cm^{-1}, b=1,200 s/mm^2, 12 angles ψ from 0 to 360^o, τ_m=13.4, 0.0 ms
- High resolution DTI with 2x2x2 mm^3 60 directions



Avram et al., Neuroimage 2012 (submitted)

In vivo mPFG diffusion MRI

- Tissue model

$$E(\psi) = fE^{\mathrm{ax}}(\psi) + (1-f)E^{\mathrm{out}}(\psi)$$

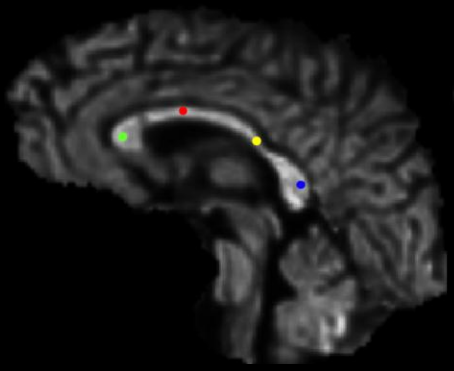
- Incorporating high-resolution DTI to account for the effect of fiber orientation

$$E(\psi) = f\left[\sum_{k=1}^{3} E_k^{\mathrm{ax}}(\psi, \boldsymbol{u_k}, D_k, d)\right] + (1-f)\left[\sum_{k=1}^{3} E_k^{\mathrm{out}}(\psi, D_{k,0})\right]$$

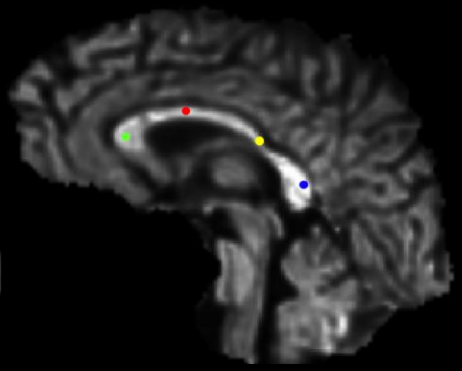
Avram et al., Neuroimage 2012 (submitted)

In vivo detection of microscopic anisotropy

$minE_{13.4}(\psi)$

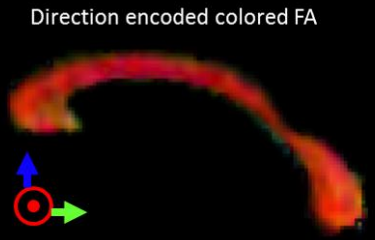


$maxE_{13.4}(\psi)$

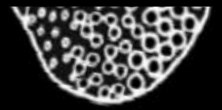


Avram et al., Neuroimage 2012 (submitted)

In vivo estimation of average axon diameters



	Prefrontal	Sensory-Motor	Temporal/Auditory	Visual
Average FA	0.69	0.66	0.66	0.75
Average ADC ($\mu m^2/ms$)	0.71	0.73	0.76	0.68
Intra-axonal Signal Fraction	**0.36**	**0.30**	**0.41**	**0.35**
Mean Axon Diameter (μm)	**3.85**	**6.59**	**4.10**	**4.25**



Avram et al., Neuroimage 2012 (submitted)

Aboitiz et al., *Biol Res*, 2003

Conclusion

- Our results support the clinical feasibility of acquiring qPFG diffusion MRI *in vivo* using a conventional MRI scanners
- Integration of high-resolution DTI data allows the extraction microscopic anisotropy parameters such as average axon diameter
- The good agreement between the measured average axon diameter maps and previous post-mortem studies provides a preliminary validation of our methodology
- qPFG diffusion MRI could provide a histological assessment of brain tissues, enabling a wide range of neuroimaging applications for improved diagnosis of neurodegenerative pathologies (e.g. TBI) and treatment monitoring

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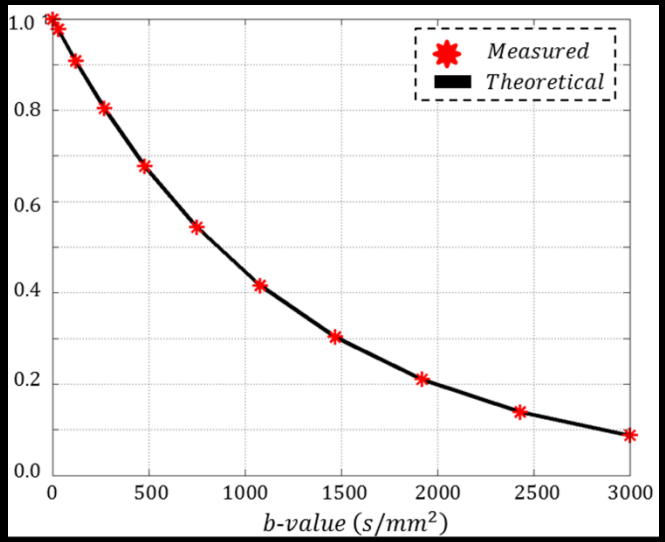
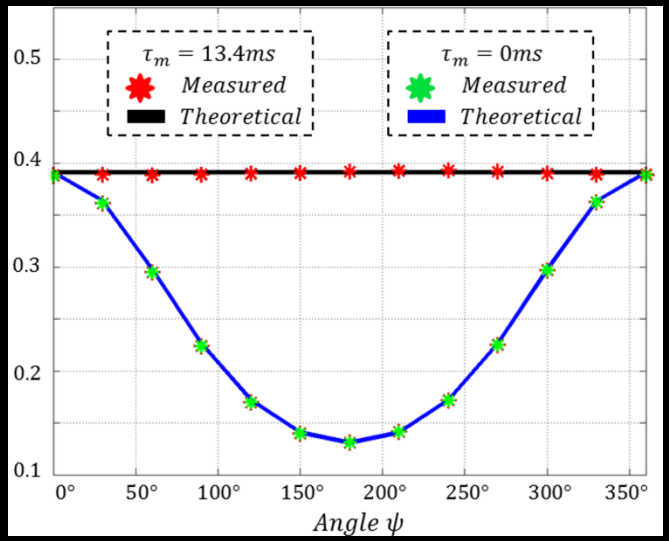
Thank you

- Questions?

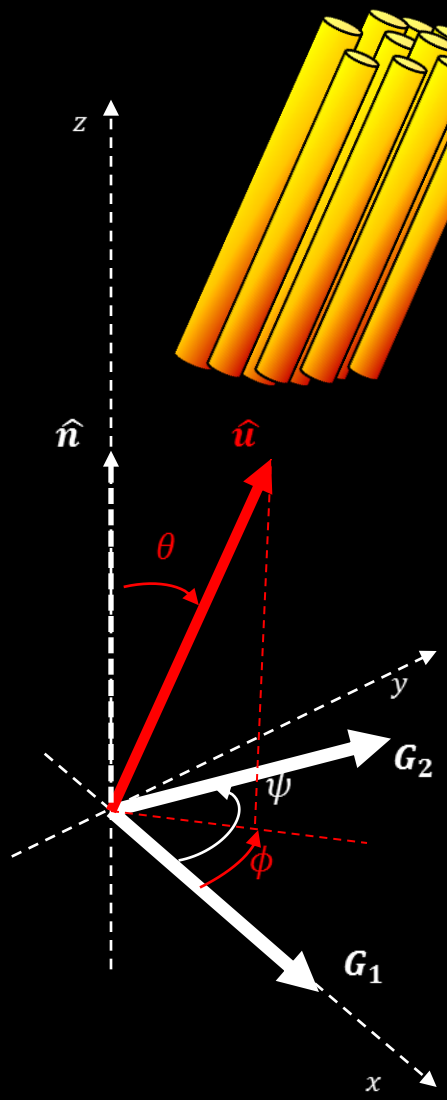
Validation experiment

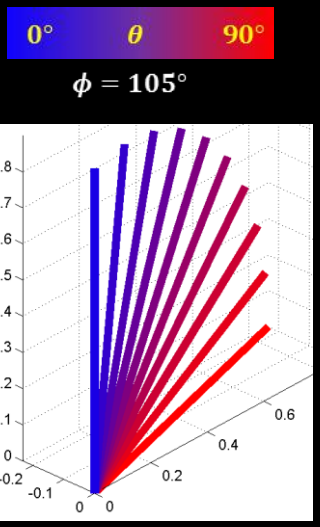
- Calibrated free diffusion phantom 35% Polyvinylpyrrolidone (PVP) polymer solution with water diffusivity D_0=0.81 μm²/ms similar to brain tissue
- Conventional DWI to measure diffusivity: 10 b-values from 300-3,000 s/mm²
- qPFG diffusion MRI with TE/TR=147/6000 ms, G_{max}=50 mT/m, δ=11.8 ms, r=0.8 ms, $4q$=1,100 cm^{-1}, b=1,200 s/mm², 12 angles ψ from 0 to 360^{o}, τ_m=13.4, 0.0 ms

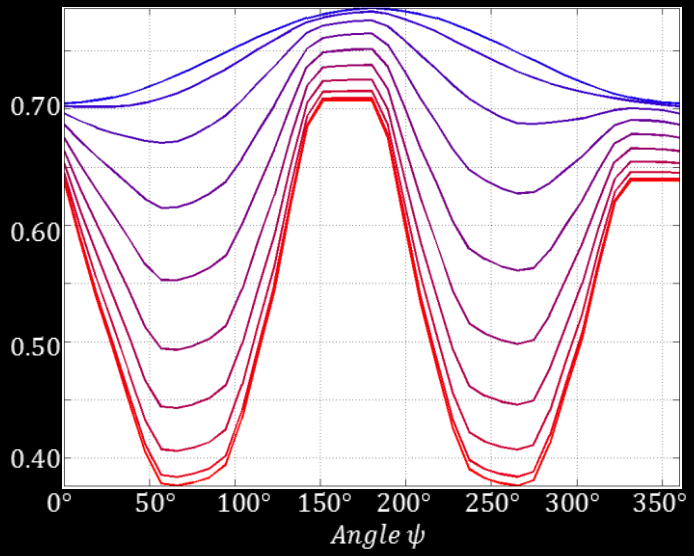


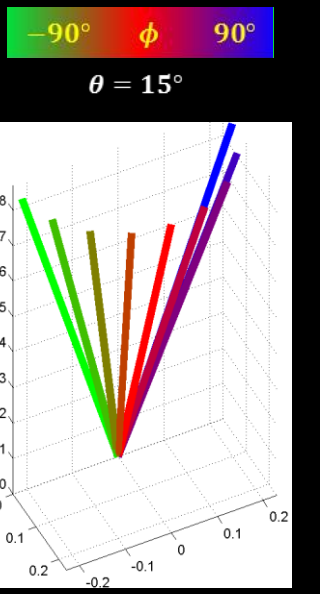


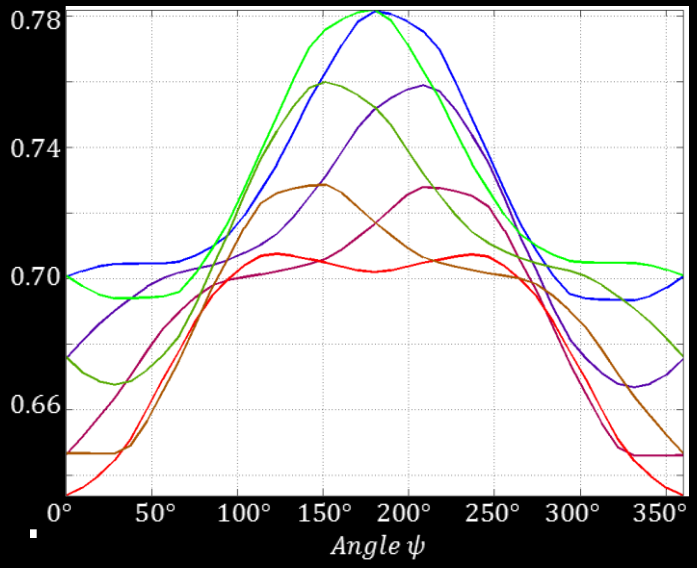
Avram et al., Neuroimage 2012 (submitted)











Avram et al., *Neuroimage,* 2012 (submitted)