Diffusion

What is diffusion?

Basic physics

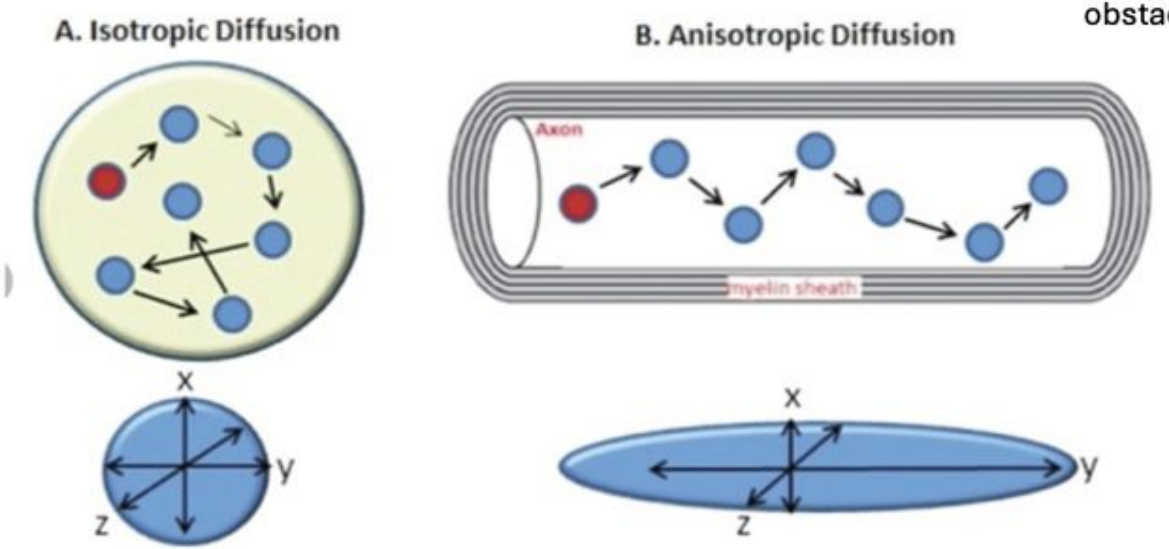
Q-space imaging

Diffusion

Motion of molecules
Totally random

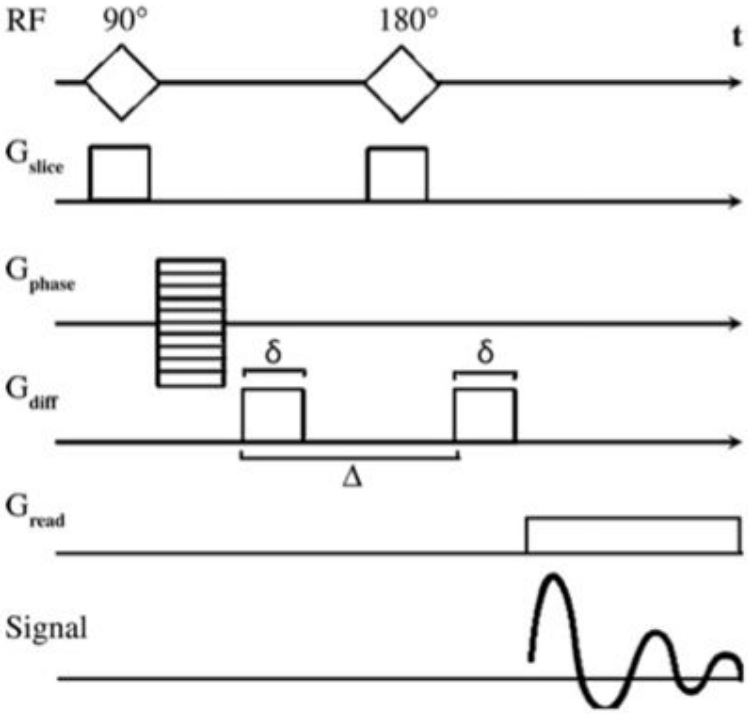
Diffusion and the container

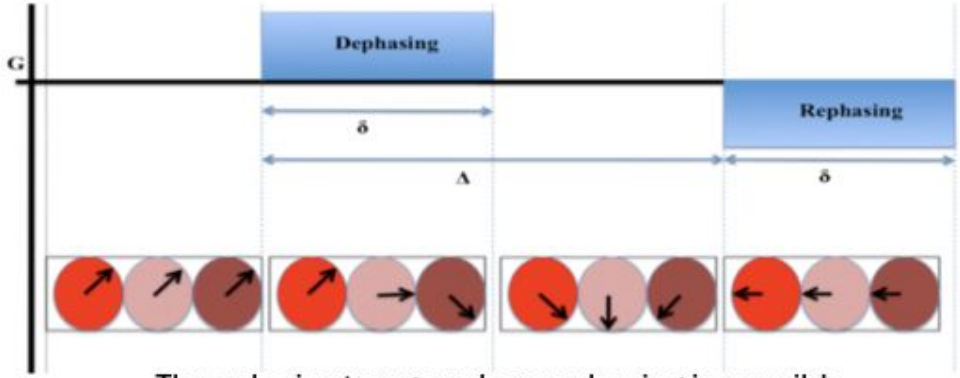
In tissues is no random, because there are obstacles



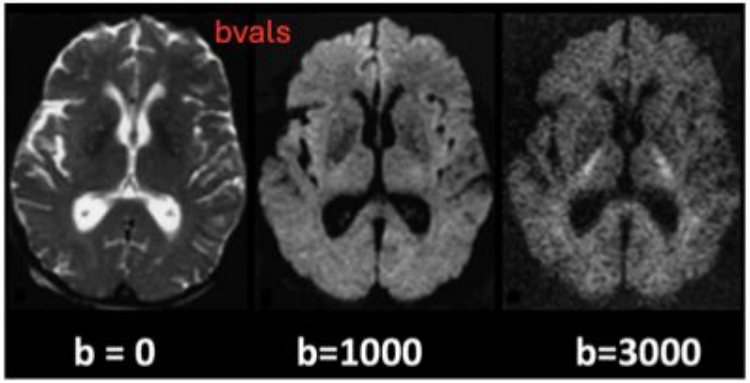
Isotropic and anisotropic diffusion A: Molecular diffusion,

Pulse sequence



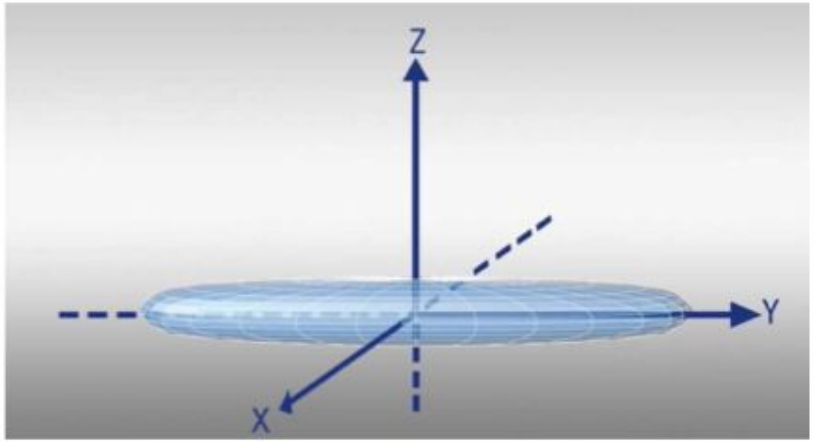


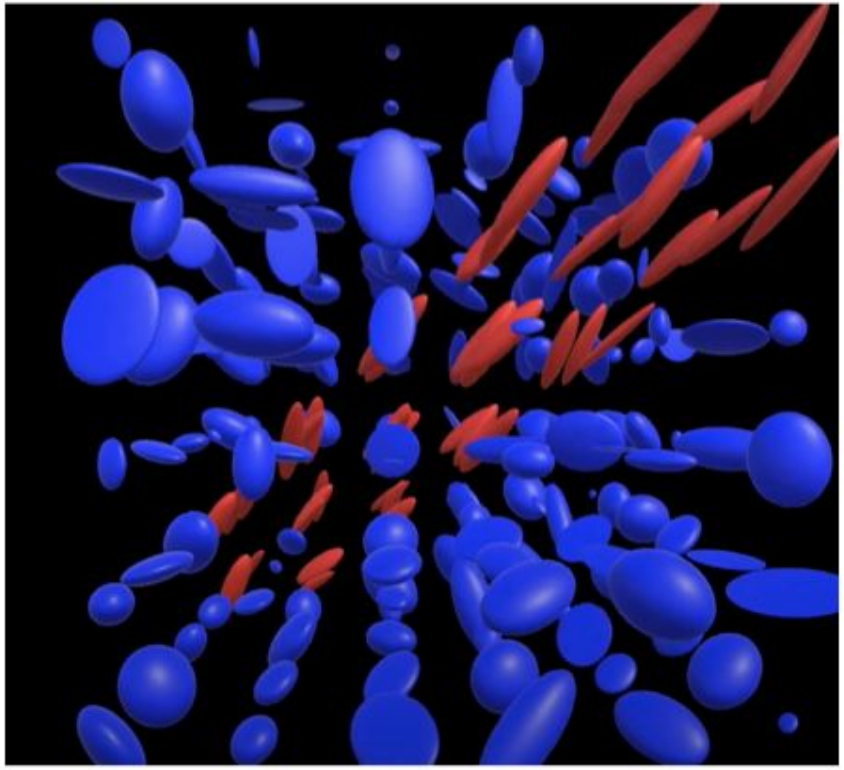
The echo is stronger when rephasing is possible.



bvels (directions)
x, y, z coordinates in one direction

Pulse sequence





DTI vs. DSI

NeuroHackademy | 8.5.24 | Elle Murata

Diffusion Imaging

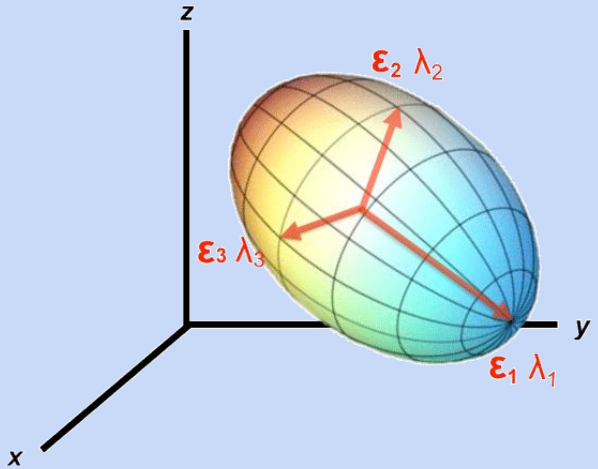
- *Diffusion* of water molecules in the brain
- ‘Structural integrity’ of white matter tracts
- Map direct axonal connections between brain regions

DTI vs. DSI

- Different frameworks for modeling diffusion
  - Different ways of calculating how water moves through the brain!
- DSI is slightly more advanced, more expensive, & less common
- DTI: 4D, DSI: 6D

DTI: Diffusion Tensor Imaging

- Extends from DWI, which cannot measure direction of diffusion
- Measuring **direction & magnitude** of water molecules
- Each ‘tensor’: 3 x 3 matrix of set of eigenvectors & eigenvalues calculated for each voxel
    - Eigenvector: direction of diffusion
    - Eigenvalue: magnitude of diffusion
- …But for each voxel, assumes only one direction
    - Can incorrectly lead to reports of lower white matter integrity



DSI: Diffusion Spectrum Imaging

- Can capture different orientations of fibers, such as crossing, kissing, or branching fibers
- More advanced than DTI
- Samples diffusion in more directions
    - Hundreds of diffusion gradients (vs. DTI, which just uses a handful)
- Provides a more detailed probability map of how water molecules are displaced in each voxel

Why would you choose one over the other?

- Time, money, & complexity
- DTI = less expensive, shorter acquisition time, less data generated
- DSI = more expensive, longer acquisition time, more data generated

Application to NEUROHACKADEMY

- What framework are we using?
  - Human Connectome Project: Diffusion Tensor Imaging (DTI)
  - Can get **direction & magnitude** of water molecules
- What metrics can we calculate?
  - Fractional Anisotropy
  - Mean Diffusivity
- What will we be missing?
  - Difficulty capturing instances of crossing, kissing, branching fibers
  - Overall lower resolution, less detailed, less accurate mapping

DWI vs DTI

Diffusion weighted imaging (DWI)

- Basic diffusion imaging, captures how water molecules move in few directions
- DWI applies strong magnetic gradients to sensitize the MRI signal to water diffusion.
- the intensity value of each voxel (3D pixel) reflects the degree of water diffusion
- Can identify acute stroke, tumors, abscesses, and other conditions where water diffusion is affected.

Diffusion tensor imaging (DTI)

- An advanced form of DWI. DTI collects DWI data in at least six different directions to model the diffusion as a tensor, which describes both the magnitude and direction of diffusion.
- Based on the theory that water molecules diffuse differently within different types of tissue to identify white matter tracts
- Good for detailed mapping of brain white matter and studying brain connectivity.

Data Structure: bvals & bvecs

DWI data are acquired across the whole brain by repeating the acquisition while varying the orientation (bvec) or magnitude (bval) of the diffusion gradients.

Diffusion Weighting (bval):

- how fast the water molecules are moving.
- the amount of diffusion weighting used for each volume.
- Increasing the bval leads to increased contrast and decreased signal-to-noise ratio
- Typical diffusion weighting is b ~ 1000 sec/mm2:
    - 0 0 0 0 0 0 0 0 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 …

Data Structure: bvals & bvecs

Gradient Direction (bvec)

- the direction in which the water molecules are facing/moving in the brain
- predetermined by the scanner protocol depending on how many total directions you choose to collect
  - 0 0 0 0 0 0 0 0 -0.900083 0.0200564 0.617607 0.851959 -0.73575 0.925457 0.969776 0.45729 -0.154832 -0.986917 0.5258 -0.863244 -0.719261 -0.549089 0.275285 0.66294 0.624216 …

The parameters bvals and bvecs are crucial when converting data structure, such as from DICOM to NIfTI

Single Shell vs Multi Shell vs Cartesian

Single Shell:

- collecting dMRI data at a single bval
- All the water molecules are moving at the same speed but different direction
- Simple to acquire, analysis, and modeling with
- Limited in capturing more complex diffusion patterns, may not provide enough detail for advanced modeling techniques

Multi Shell:

- collecting dMRI data at multiple bvals
- All the water molecules are moving at different speeds and in different directions

Single Shell vs Multi Shell vs Cartesian

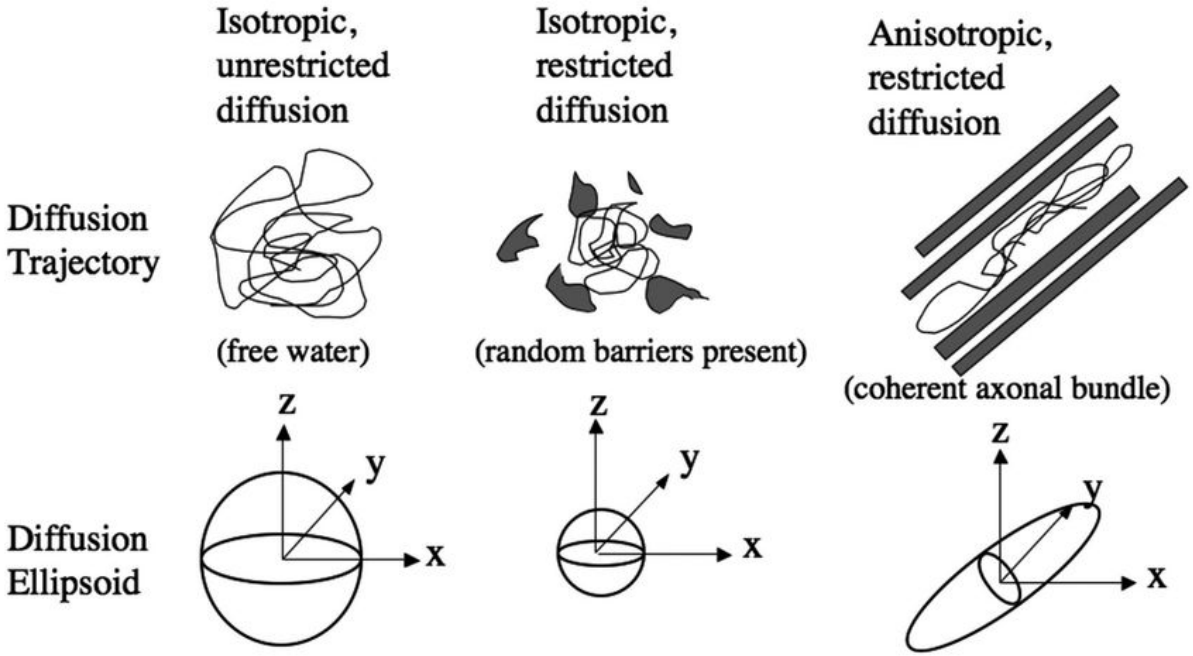
Multi Shell (Cont.):

- Provide richer information about the brain’s microstructure, complex tissue structures, and fiber crossings; Allow advanced modeling techniques.
- More time-consuming and complex to acquire

Cartesian:

- sampling data in a grid-like pattern across different bvec and bval
- Provides comprehensive and evenly distributed data, could construct detailed models of the brain’s diffusion properties. Allow advanced reconstructions and algorithms
- Highly complex and time-consuming to acquire.

Anisotropy vs Isotropy



The tensor model (Basser et al., 1994)

- To quantify diffusion, we typically visualize a three-dimensional ellipsoid (like a rugby ball) of which the shape is described as a symmetric 3x3 matrix (the tensor), where the diagonal elements describe the variance in the X, Y and Z directions; and the off-diagonal elements describe covariance between these elements.
- When we estimate the diffusion coefficient (D), we obtain three apparent diffusion coefficients (ADCs) along the scanner coordinate system (Dx, Dy & Dz)
- It is possible to estimate ADCs at each voxel (which reflect the underlying anatomy) by diagonalizing the tensor matrix
- In the diffusion ellipsoid, the main axis is parallel to the principal diffusion direction within a voxel.The major and minor axes of the diffusion ellipsoid are defined by three orthogonal unit vectors (v1, v2, and v3), known as eigenvectors. The length of each eigenvector (vi) is multiplied by a factor λi, the eigenvalue.

$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

$$\mathbf{D} = [\mathbf{v_1}|\mathbf{v_2}|\mathbf{v_3}]^{\mathrm{T}} \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} [\mathbf{v_1}|\mathbf{v_2}|\mathbf{v_3}]$$

eigenvectors - $\mathbf{v}_1$=direction of max diffusivity

eigenvalues: ADCs along $\mathbf{v}_1,\mathbf{v}_2,\mathbf{v}_3$

Mean diffusivity (MD), Axial diffusivity (AxD) and Radial diffusivity (RD)

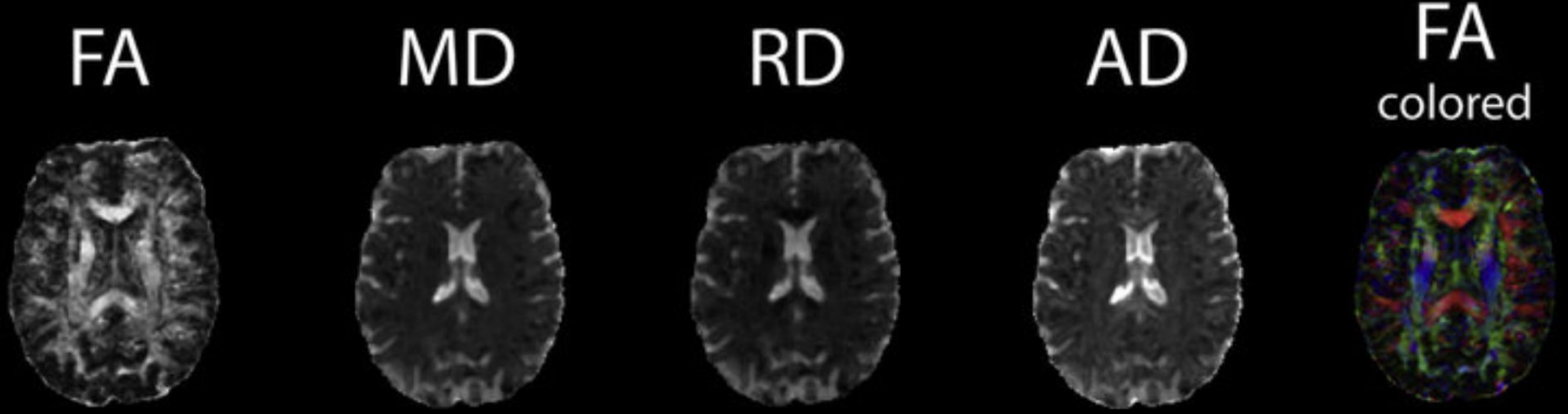
- MD is the average of the eigenvalues and reflects the mean diffusion in a voxel
  - MD = (λ1, λ2 + λ3) / 3
- AxD (parallel diffusivity) measures the diffusion coefficient along the axis of maximal apparent diffusion.
  - AxD = λ1.
- RD (perpendicular diffusivity) is the an average of the two smallest eigenvalues.
  - RD = (λ2 + λ3) / 2
- MD, AxD and RD are expressed in units of mm2/s. There is no unanimity regarding the boundaries of the range of normal diffusion. It depends on tissue and pathology. However, diffusion should be restricted in healthy white matter tracts and increased MD can be an indicator of **abnormal tissue microstructure**.
  - One should be careful when interpreting changes in these metrics: https://doi.org/10.1016/j.neuroimage.2012.06.081

Fractional anisotropy (FA)

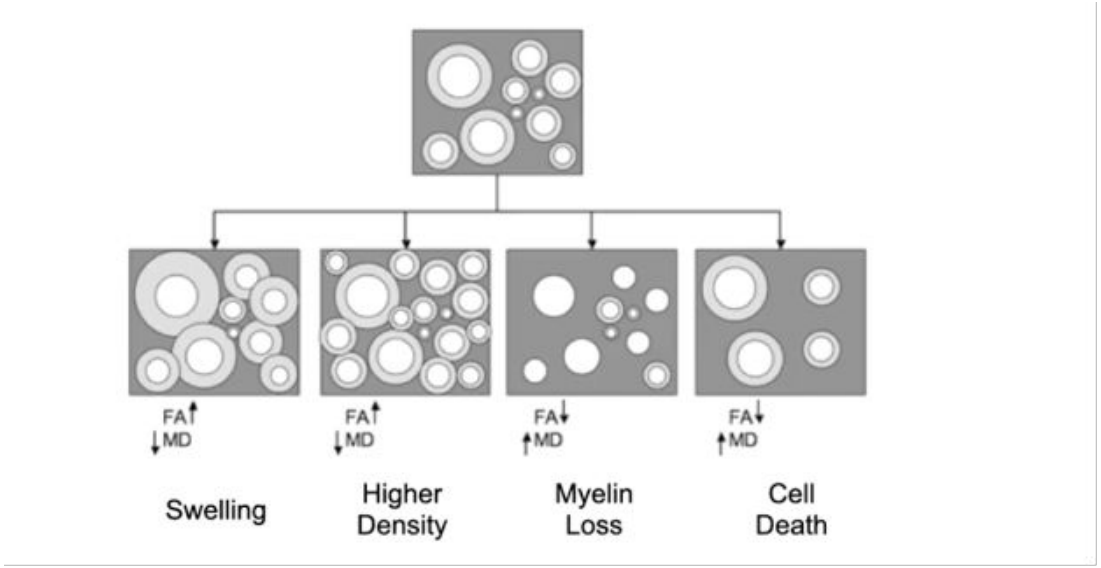
- FA is the most widely used anisotropy measure and it can be thought of as a normalized variance of the eigenvalues.
- It describes the difference of the tensor ellipsoid's shape from that of a perfect sphere (O'Donnell & Westin, 2011).
- FA is quantified from 0 (isotropic) to 1 (restricted to main axis). Values close to 0 (or even negative) are not likely to reflect white matter tissue. Oftentimes, studies exclude voxels where FA < 0.2-0.3 (Smith et al., 2006)

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

Visualization



Biological meaning



- Decreased FA are increased MD are not always reliable indicators of neurodegeneration. These measures are sensitive to other forms of cell damage and they cannot be considered as a biomarker for a specific disease. Moreover, FA is particularly sensitive to the issue of crossing fibers. In healthy subjects, it can be fallacious to conclude that lower FA is equal to lower white matter integrity. DTI scalars reliably reflect underlying tissue microstructure.
- Since these indicators are affected by a number of reasons, it is challenging to infer causality. That being said, some investigations have linked higher MD to tissue necrosis (Alexander et al., 2007); and (in animal models) higher AxD to axonal damage and higher RD to myelin loss (Song et al., 2002)

Intro to QSIPrep

Allesandra Iadipaolo

Neurohackademy 2024

What is QSIPrep and why was it developed?

- A preprocessing and reconstruction pipeline for diffusion MRI data
- Is compatible with nearly all dMRI sampling schemes (e.g., single- and multi-shell as well as non-shelled)
- Developed by Matt Cieslak's group, based on fMRIPrep
- Pulls the best tools from many different software packages (e.g., FSL, DSI Studio, MRtrix3, DIPY, ANTs)
- Allows you to build a customizable workflow

Getting started…

1. Install QSIPrep using a Container: either Docker or Singularity

2. Make sure your data are in valid BIDS format!

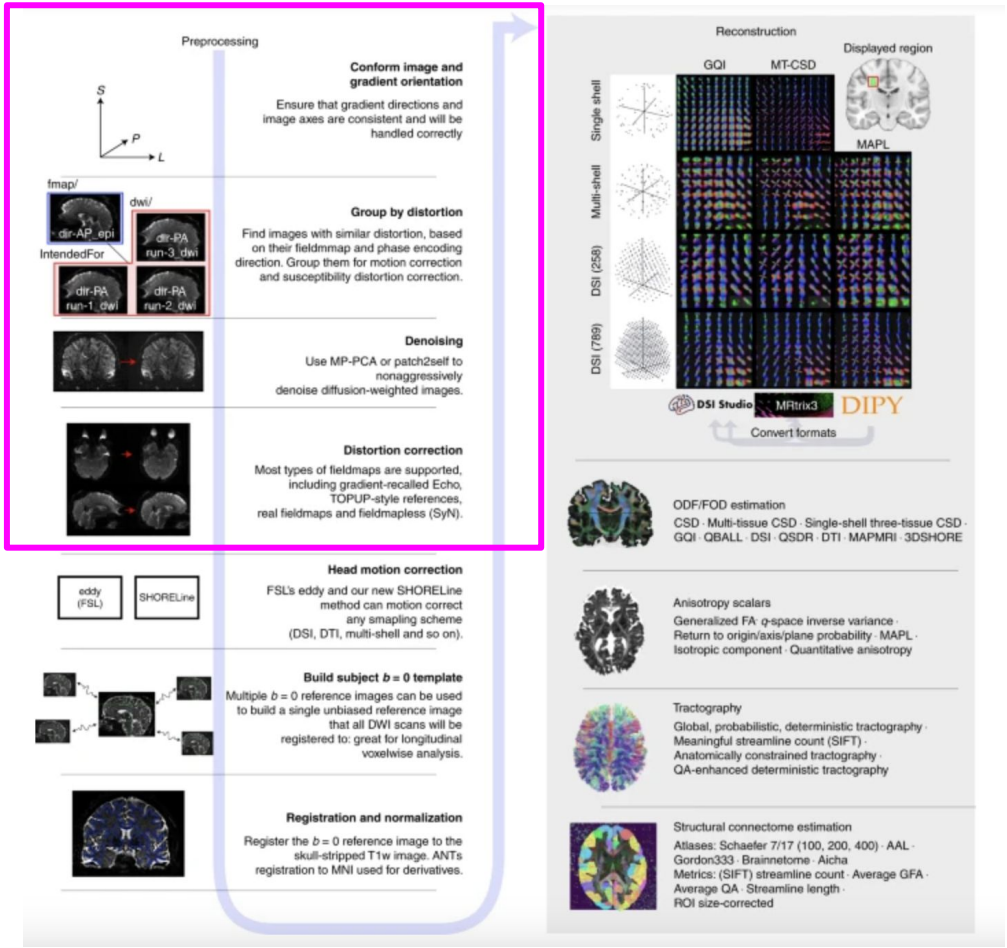
3. Consider when you want to use defaults vs. adjust options. The most common options you'll need to adjust are regarding grouping of scans, specifying outputs, head motion correction, enabling/disabling preprocessing steps

What are the outputs of QSIPrep?

1. Visual quality assessment reports
2. Pre-processed imaging data (*derivatives*)
3. Additional data for subsequent analysis (confounds)
4. Quantitative quality assessment

QSIPrep workflows

Cieslak et. al (2021) *Nature Methods*



Preprocessing steps:

1. Conform image and gradient orientation
2. Group by distortion
3. Denoising
4. Susceptibility distortion correction
5. Head motion correction
6. Build subject *b*=0 template
7. Registration and normalization

Preprocessing steps:

1. **Conform image and gradient orientation**
2. Group by distortion
3. Denoising
4. Susceptibility distortion correction
5. Head motion correction
6. Build subject *b*=0 template
7. Registration and normalization

Conform image and gradient orientation

- FSL-style bvec format required by BIDS specifies gradient directions with respect to image axis, not coordinates

- Spatial transformations performed using ANTs ensures that all images and bvecs conform with LPS+ image orientation

- This allows us to use ANTs for registration and transformation of both the images and gradient vectors

Preprocessing steps:

1. Conform image and gradient orientation
2. **Group by distortion**
3. Denoising
4. Susceptibility distortion correction
5. Head motion correction
6. Build subject *b*=0 template
7. Registration and normalization

Group by distortion

- Groups of scans are often collected with opposite phase-encoding directions so that their *b*=0 images can be used for susceptibility distortion correction

- QSIPrep uses BIDS to divide scans into ‘warped groups’ which share the same susceptibility distortions

- Warped groups undergo denoising separately before being concatenated and sent for motion correction

Preprocessing steps:

1. Conform image and gradient orientation
2. Group by distortion
3. **Denoising**
4. Susceptibility distortion correction
5. Head motion correction
6. Build subject *b*=0 template
7. Registration and normalization

Denoising

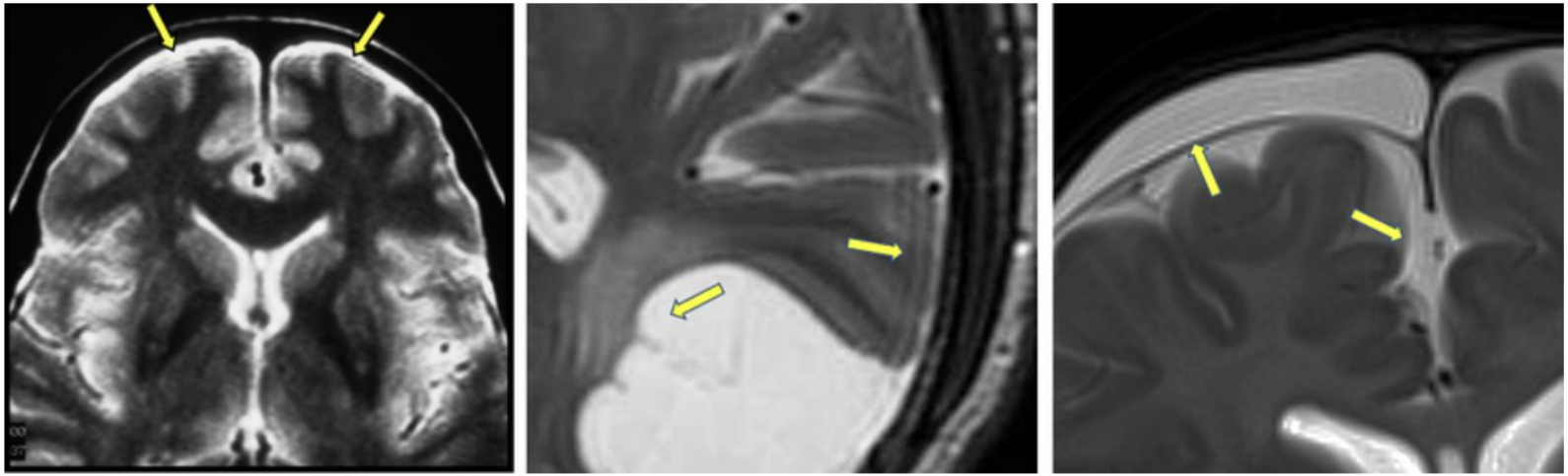
- Denoising steps are important to ensure we get a clean WM/GM boundary

- Denoising operations can be performed on each dMRI input individually or to the concatenated files

- Denoising has four components/operations:
  - Gibbs Unrining (MRtrix3)
  - MP-PCA (MRtrix3; default) or patch2self (DIPY)
  - Bias field correction/regularization (ANTs)
  - *b*=0 intensity normalization (numpy)

Denoising: Gibbs unringing

- Systematic artifacts in areas of high spatial frequency (e.g., contrast, sharp edges) which can hinder GM/WM segmentation and fiber tracking
- Unringing algorithms estimate and remove these artifacts on a voxel level



Denoising: MP-PCA (or Patch2Self)

- Goal is to boost SNR!

- MP-PCA is the default

- You can choose to denoise before or after concatenating
  - Concatenate-then-denoise gives more data for the algorithm to work with, but…
  - Denoise-then-concatenate is the default because if scans are very out of alignment, the MP-PCA may not perform very well

Preprocessing steps:

1. Conform image and gradient orientation
2. Group by distortion
3. Denoising
4. **Susceptibility distortion correction**
5. Head motion correction
6. Build subject *b*=0 template
7. Registration and normalization

Susceptibility distortion correction

- We observe signal distortion along the phase encoding direction especially at air-tissue interfaces

- Three kinds of susceptibility distortion correction available:
  1. Blip-up/blip-down (scd_pepolar)
  2. Use B0map sequence (one magnitude + two phase images) or phasediff image (sdc_phasediff)
  3. Use SyN-based correction (ANTs); average fieldmap in MNI space

- Uses “Best *b*=0” method- you’ll usually get multiple b0 images per scan, so it finds the most representative one(s) from each

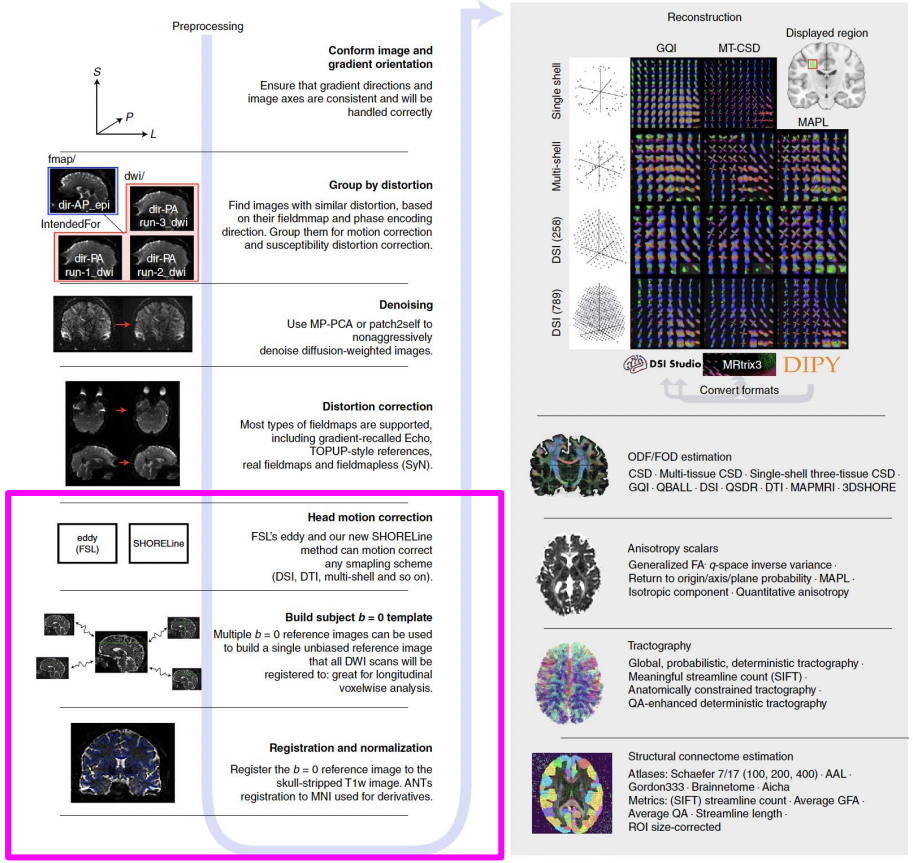
Resources:

- https://qsiprep.readthedocs.io/en/latest/index.html
- https://open.openclass.ai/resource/lesson-63a274afed6b9f57f461ea63?demo=iCukmKNPNWmoTQ
- https://www.nature.com/articles/s41592-021-01185-5

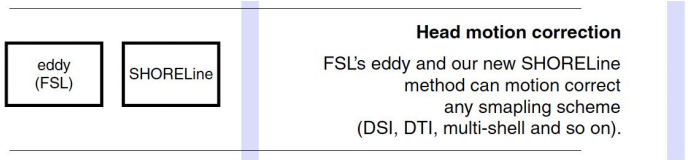
QSIPrep workflows

Lya Paas | 08.06.2024

Cieslak et. al (2021) *Nature Methods*



Head motion correction



Head motion correction (HMC)
Eddy current correction (ECC)
Susceptibility distortion correction (SDC)

} Single workflow

TOPUP, eddy (FSL)

Shelled sampling schemes

A) Reverse-phase-encoding image
→ fieldmap with TOPUP → eddy (FSL)
→ applied to HMC and ECC

B) All other cases
→ fieldmap with fMRIPrep
→ applied to HMC and imputed output from eddy

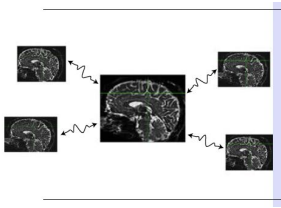
Cartesian and random sampling schemes

→ HMC: QSIPrep's SHORELine algorithm

1. All b0 images are aligned to a midpoint (or first) b0 image and each non-b0 image is transformed along with its nearest b0 image
2. For each non-b0 image, a 3dSHORE or MAPMRI model is fit to all the other images with that image left out
3. Left-out image is registered to the generated target signal image and its vector is rotated accordingly

Susceptibility distortion correction is run as part of this pipeline to be consistent with the TOPUP / eddy workflow

Build subject b = 0 template



Build subject *b* = 0 template

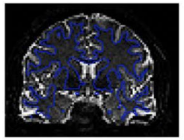
Multiple *b* = 0 reference images can be used to build a single unbiased reference image that all DWI scans will be registered to: great for longitudinal voxelwise analysis.

Reference image: Extracted from the b = 0 images from previous step

- Normalized average (ANTs)
- Histogram equalization (DIPY)

✅ Build a single unbiased reference image that all DWI scans will be registered to
✅ Great for longitudinal voxelwise analysis
✅ Possible to create intramodal templates for multiple sessions

Registration and (optional) normalization



Registration and normalization

Register the *b* = 0 reference image to the skull-stripped T1w image. ANTs registration to MNI used for derivatives.

- Coregistration of *b* = 0 template (ANTs: antsRegistration)
- b0 to T1w registration:
  Rigid transformation to register the skull-stripped T1w image to AC-PC alignment (antsRegistration adapted from fMRIprep)
- Combines all spatial transformations so that only a single resampling can be applied

Some details

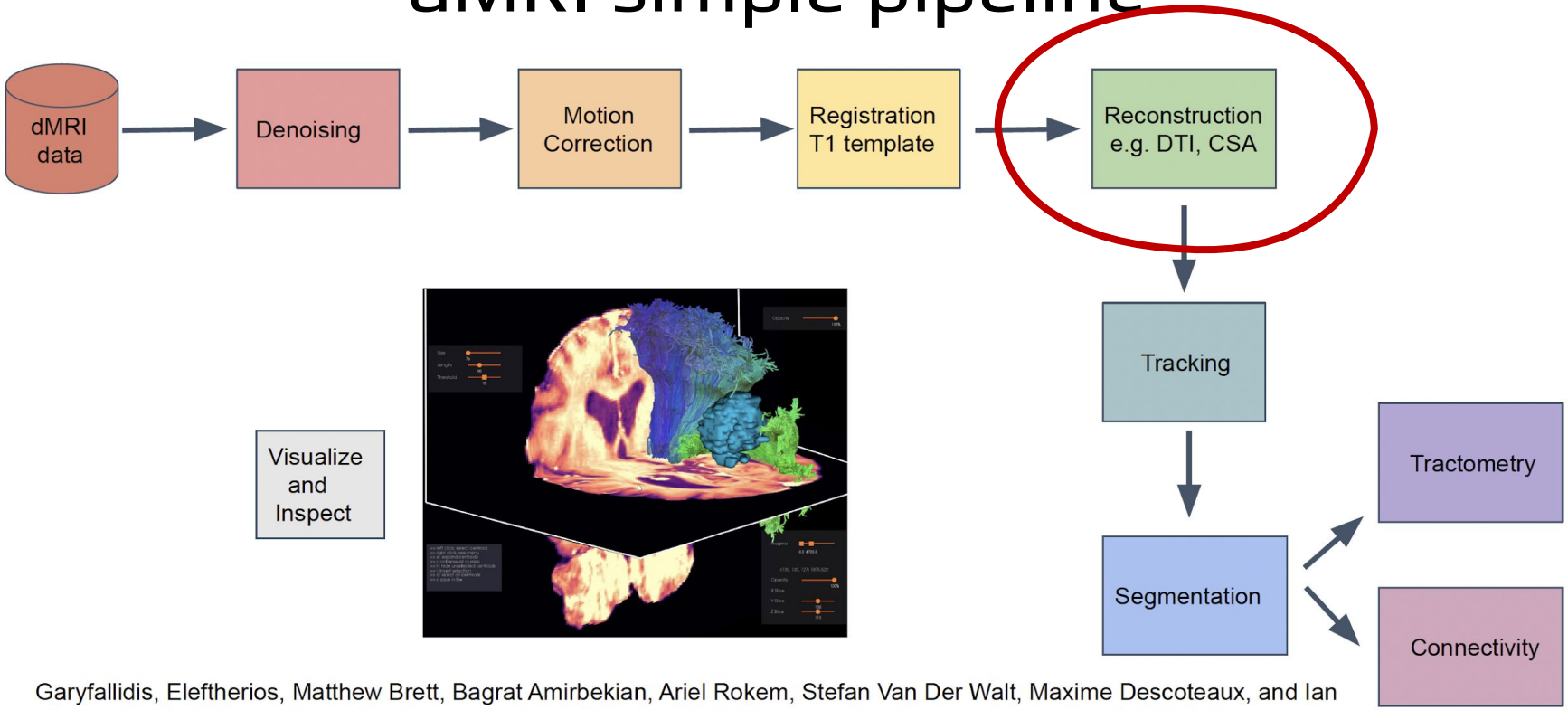
Nipype:
Neuroimaging in Python
Pipelines and Interfaces

Execution of workflow – Managed with nipype (multi-core parallelization)

- ✅ Uniform derived output format → Software interoperability facilitates method comparison
- ✅ Application of standard shelled analytic methods to advanced non-shelled sequences
- ✅ SC: directly comparable between methods and participants
- ✅ Diverse connectivity measurements
- ✅ Reproducibility and quality assurance

- ❗ No double diffusion encoding *q*-space imaging or gradient tensor imaging

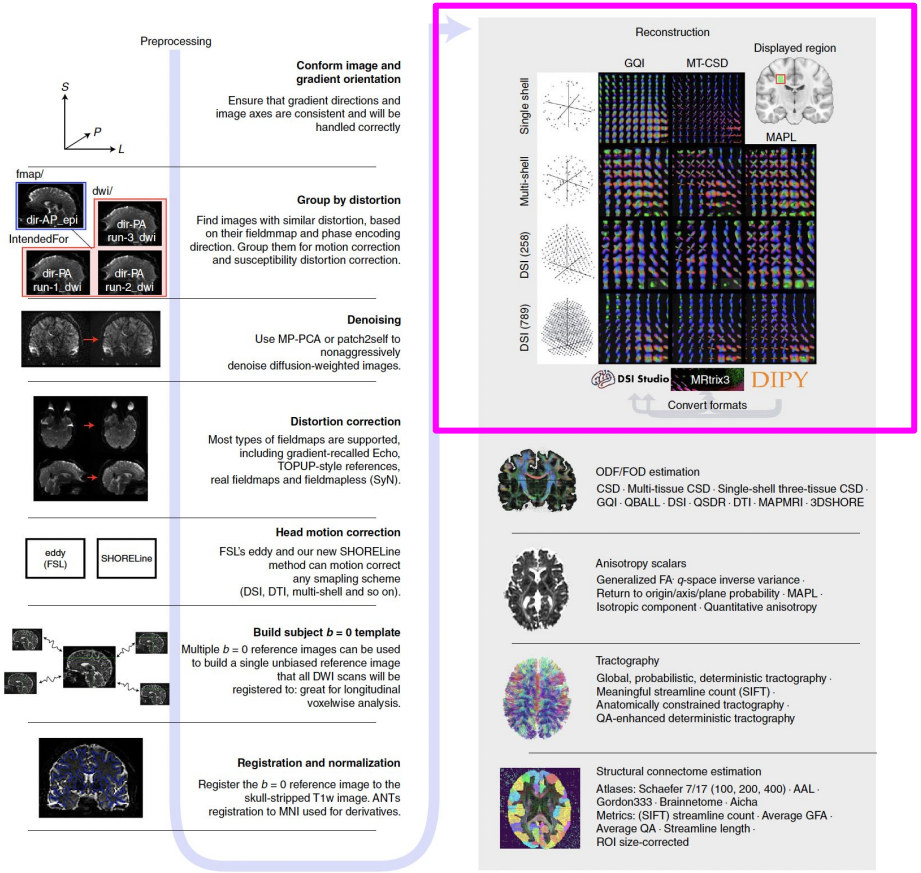
dMRI simple pipeline



Garyfallidis, Eleftherios, Matthew Brett, Bagrat Amirbekian, Ariel Rokem, Stefan Van Der Walt, Maxime Descoteaux, and Ian Nimmo-Smith. **"Dipy, a library for the analysis of diffusion MRI data**." Frontiers in neuroinformatics 8 (2014): 8.

QSIPrep workflows

Cieslak et. al (2021) *Nature Methods*



Reconstruction

What are we reconstructing?

- dMRI probes water motion (aka. diffusion):
  - Spatial specific: microscopic sampling (voxel size)
  - Direction specific: application of directional magnetic gradients.

Methods

A variety of probability displacement distribution (PDF) methods have been developed:

q-space imaging (*QSI*)

↓

diffusion spectrum imaging (*DSI*)

Callaghan *et al.,1988*

Wedeen *et al.,2005*

Reconstruction alternatives

Estimating fibers, alternatives to PDF calculations:

- Reconstructing only an *angular projection* of the 3D PDF:
  - Orientation distribution function (ODF).
- Make *assumptions* about the *distribution* of the PDF:
  - Diffusion tensor imaging (DTI), Gaussian assumptions.

My data, my analysis specs

dMRI preproc, recon, tractography, & connectivity methods should be specific to the acquisition specs, as well as the research/clinical question to address.

Implementation

- MRtrix3, diffusion MRI analyses analysis and tractography methods.
- DSI studio, tractography software.
- DIPY, spatial normalization, signal processing, machine learning, statistical analysis and visualization

Software available:

QSI prep pipelines:

Option	MultiShell	DSI	DTI	Tractography
mrtrix_multishell_msmt_ACT-fast*	Yes	No	No	Probabilistic
mrtrix_multishell_msmt_ACT-hsvs	Yes	No	No	Probabilistic
mrtrix_multishell_msmt_noACT	Yes	No	No	Probabilistic
mrtrix_singleshell_ss3t_noACT	No	No	Yes	Probabilistic
mrtrix_singleshell_ss3t_ACT-hsvs	No	No	Yes	Probabilistic
mrtrix_multishell_msmt_ACT-fast*	No	No	Yes	Probabilistic
pyafq_tractometry	Yes	No	Yes	Both
mrtrix_multishell_msmt_pyafq_tractometry	Yes	No	Yes	Both
amico_noddi	Yes	No	No	None
dsi_studio_gqi	Yes	Yes	Yes*	Deterministic
dsi_studio_autotrack	Yes	Yes	Yes	Deterministic
dipy_mapmri	Yes	Yes	No	Both
dipy_3dshore	Yes	Yes	No	Both
csdsi_3dshore	Yes	Yes	No	Both
reorient_fslstd	Yes	Yes	Yes	None

DIPY pipelines:

Method	Single Shell	Multi Shell	Cartesian	Paper Data Descriptions
DTI (SLS, WLS, NNLS)	Yes	Yes	Yes	Basser 1994
DTI (RESTORE)	Yes	Yes	Yes	Yendiki2013, Chang2005, Chung2006
FwDTI	No	Yes	No	Pasternak 2009, Henriques et al., 2017
DKI - Standard	No	Yes	No	Jensen2005
DKI+ Constraints	No	Yes	No	Tom Dela Haije 2020
DKI - Micro (WMTI)	No	Yes	No	Fieremans 2011, Tabesh 2010
Mean Signal DKI	No	Yes	No	Henriques, 2018
CSA	Yes	No	No	Aganj 2010
Westins CSA	Yes	No	No	
IVIM	No	Yes	No	LeBihan 1984
IVIM Variable Projection	No	Yes	No	Fadnavis 2019
SDT	Yes	No	No	Descoteaux 2009
DSI	No	No	Yes	Wedeen 2008, Sotiropoulos 2013
DSID	No	No	Yes	Canales-Rodriguez 2010
GQI - GQI2	No	Yes	Yes	Yeh 2010
SFM	Yes	Yes	No	Rokem 2015
Q-Ball (OPDT)	Yes	No	No	Tuch 2004, Descoteaux 2007, Tristan-Vega 2010
SHORE	No	Yes	No	Merlet 2013, Özarslan 2009, Özarslan 2008
MAP-MRI	No	Yes	No	Özarslan 2013, Olson 2019
MAP+ Constraints	No	Yes	No	`Tom Dela Haije < https://doi.org/10.1016/j.neuroimage.2019.116405>`__
MAPL	No	Yes	No	Fick 2016
CSD	Yes	No	No	Tournier 2017, Descoteaux 2008, Tournier 2007
SMS/MT CSD	No	Yes	No	Jeurissen 2014
ForeCast	No	Yes	No	Anderson 2005, Alexander 2017
RUMBA-SD	Yes	Yes	Yes	Canales-Rodriguez 2015
QTI	No	Yes	No	Westin 2016
QTI+	No	Yes	No	Herberthson 2021, Morez 2023
Ball & Stick	Yes	Yes	No	Behrens 2003
QTau-MRI	No	Yes	No	Fick 2017
Power Map	Yes	Yes	No	DellAcqua2014
SMT / SMT2	No	Yes	No	NetoHe2019, Kaden2016b
CTI	No	Yes	No	NetoHe2020, NovelloL2022, NetHe2021