Diffusion MRI:
local reconstruction

Outline

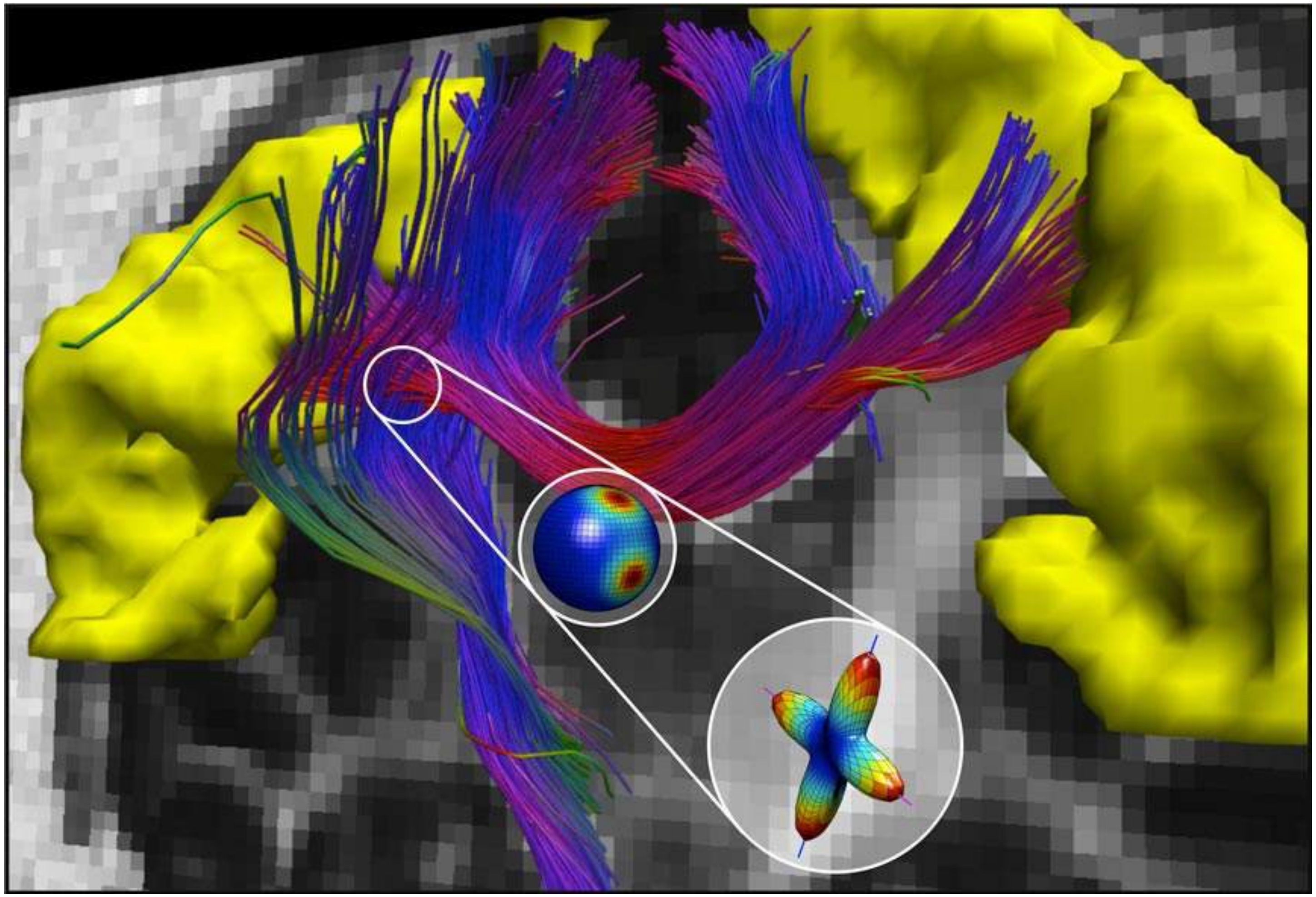
- What is local reconstruction?

- Methods that focus on the **angular information**
  - Diffusion Tensor Imaging
  - Q-Ball Imaging
  - Spherical Deconvolution
  - Spherical Harmonics representation

- Methods to better characterize the **tissue microstructure**
  - Multi-compartment models, e.g. Ball&Stick, CHARMED, NODDI etc
  - Axon density and diameter mapping, e.g. AxCaliber and ActiveAx
  - Accelerated Microstructure Imaging via Convex Optimization (AMICO) framework

What is “local reconstruction”? (1/2)

- Class of algorithms whose aim is to **estimate features of the neural tissue** inside each voxel



What is “local reconstruction”? (1/2)

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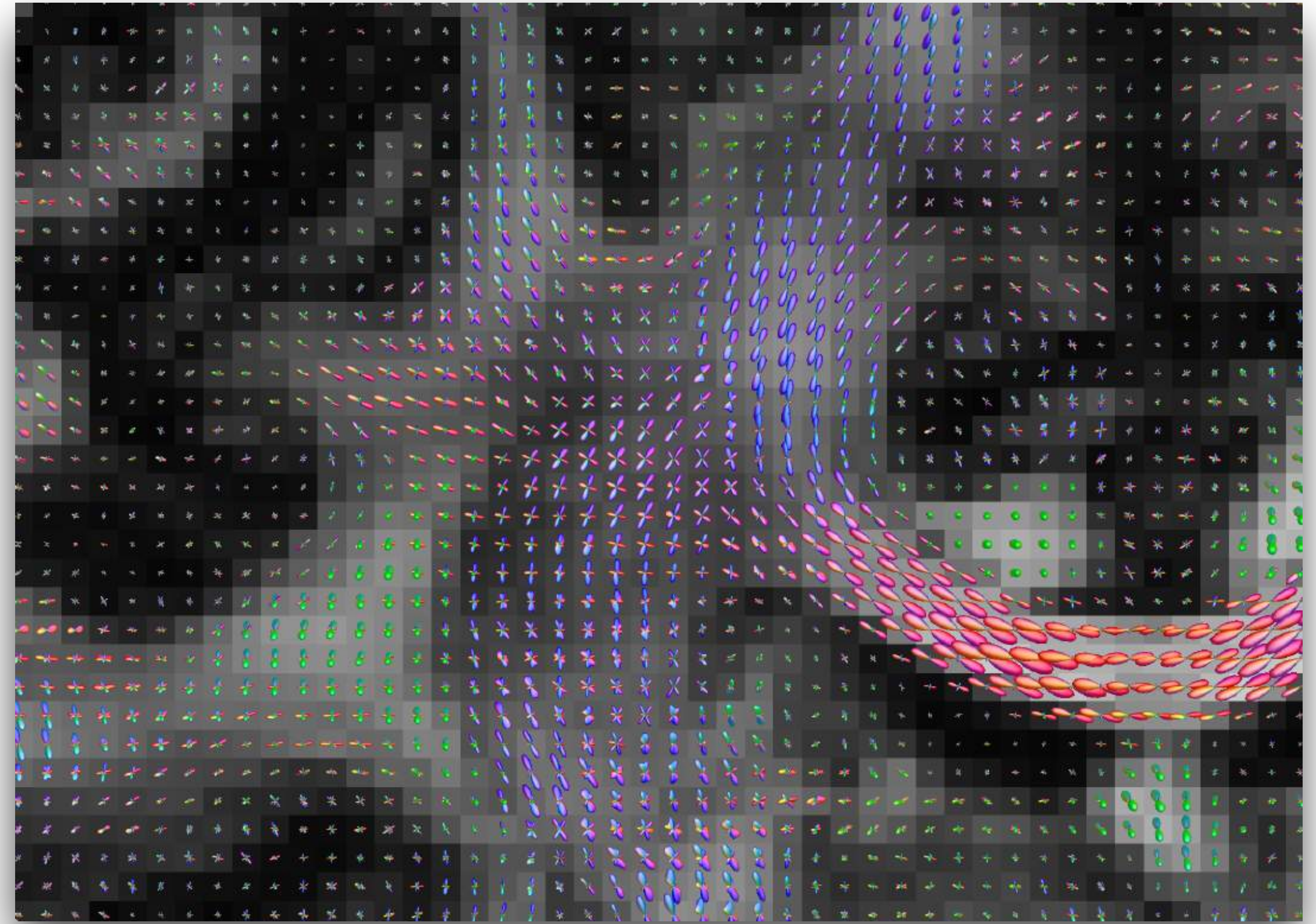
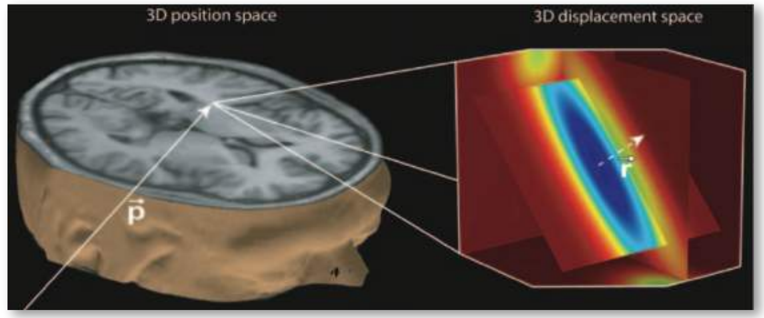


What is “local reconstruction”? (2/2)

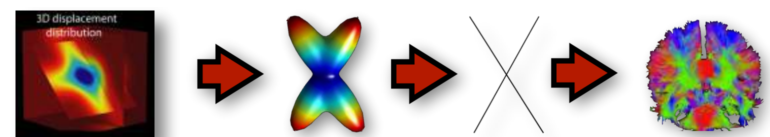
Can be divided in **two main categories**



Diffusion is a 3D process: thus the **signal acquired in each voxel is 3D**

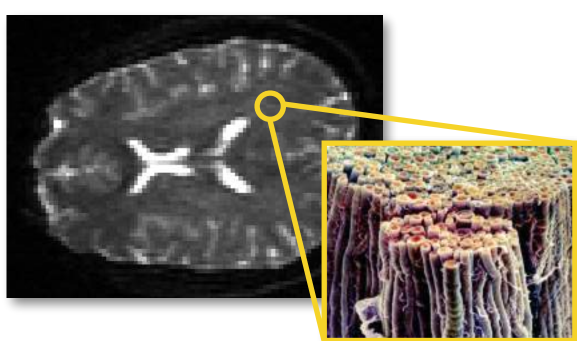
(1) Focus on <u>**angular information**</u> contained in the diffusion signal

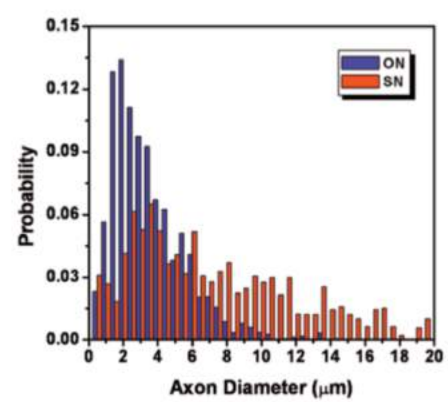
- Reconstruct the **geometry of the fiber bundles** inside a voxel
  e.g. *number of fibers*, their *volume fraction*, *orientation*…
- Tractography, connectivity estimation…

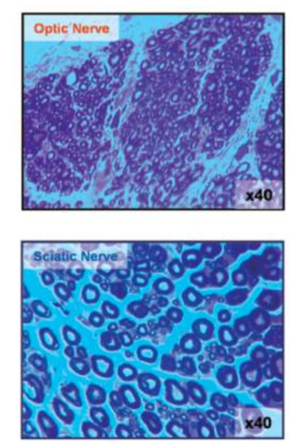


(2) Acquire and use also the <u>**radial component**</u> of the signal

- More advanced features of the **tissue microstructure**
  e.g. *axonal diameter* and *density*







Diffusion MRI:
reconstruction of fiber orientations

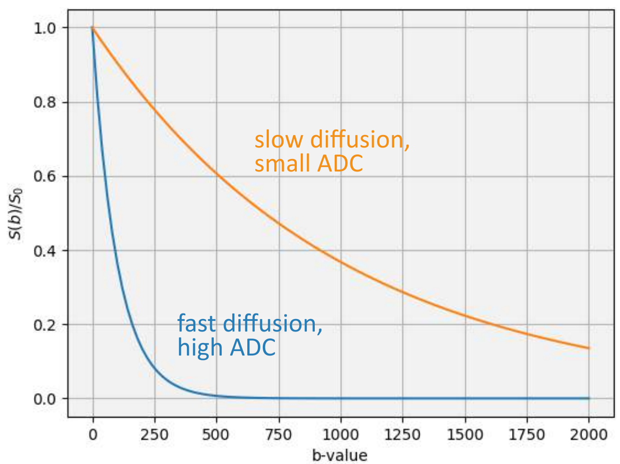
Outline of this part

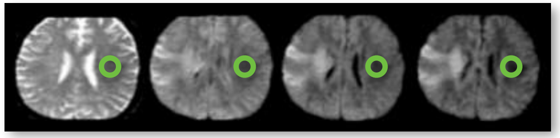
- Diffusion Tensor Imaging (DTI)
  - From *ADC* to the *diffusion tensor*
  - What *information* we get from it
  - How to *measure* it
  - *Multi-tensor* model
- Spherical Harmonics (SH) representation
- Q-Ball Imaging
  - *Numerical* method
  - *Analytical* method
- Spherical Deconvolution
  - Performed in *SH space*
  - Performed in *signal space*

- If **displacement of molecules** is *Gaussian*

$$S(b) = S_0 \exp\left(-b \cdot \mathrm{ADC}\right)$$

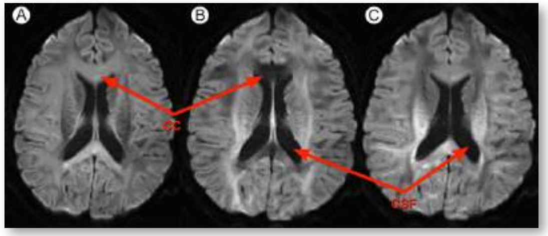
  - ADC : **Apparent Diffusion Coefficient**
  - $b = (\gamma G \delta)^2 \tau$: degree of **diffusion weighting**
    - $\tau = \Delta - \delta/3$ is the *diffusion time*
    - G, Δ and δ define the applied *diffusion sensitizing gradient*
    - γ is the gyromagnetic ratio
  - $S(b)$ and S_0 : **signal** with/without diffusion weighting





- ADC estimated with **two measurements** (at least)

- ADC **strongly depends** on the direction we measure it
  i.e. direction of the sensitizing gradient
  - A single ADC is **inadequate in complex tissue**
  - More **complex models** are needed



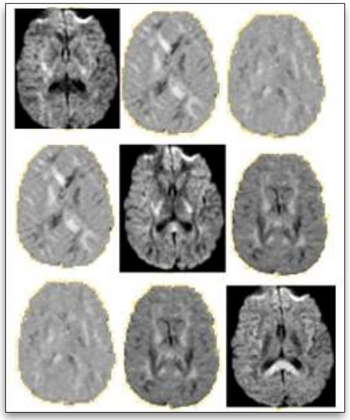
I-S L-R A-P

Diffusion Tensor Imaging (DTI)

- **Anisotropic diffusion coefficients** can be summarized by

(Basser et al., 1994)

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



  - $\mathbf{D}$ is a 3×3 *positive definite symmetric* matrix
  - 6 degrees of freedom (D_{xx}, D_{xy}, D_{xz}, D_{yy}, D_{yz}, D_{zz})
  - Diagonal elements : diffusivities along three orthogonal axes
  - Off-diagonal elements : correlation between displacements along those axes

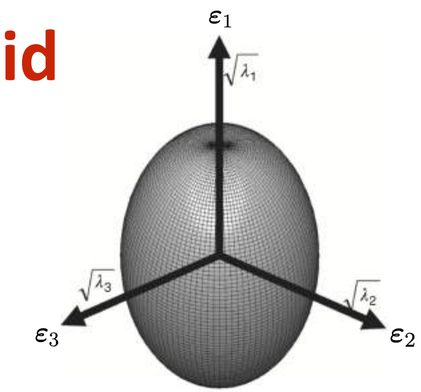
- **Signal decay** as function of gradient direction

$$S(\mathbf{g}_k, b) = S_0 \exp\left(-b\, \mathbf{g}_k^T \mathbf{D} \mathbf{g}_k\right)$$

$$S(\mathbf{q}_k, \tau) = S_0 \exp\left(-\tau\, \mathbf{q}_k^T \mathbf{D} \mathbf{q}_k\right)$$

  - $\mathbf{g}_k$ is the **gradient orientation** on the unit sphere
  - $\mathbf{q}_k = \gamma \delta G \mathbf{g}_k$ is the **diffusion wavevector**
  - $b = q^2 \tau$ with $q = |\mathbf{q}| = \gamma G \delta$

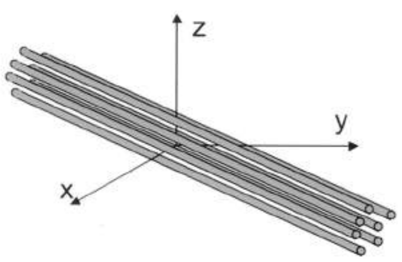
Diffusion tensor usually represented as an **ellipsoid**

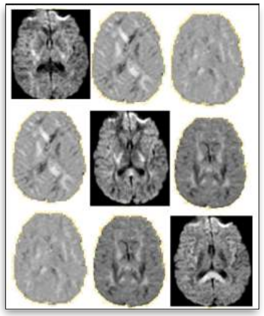


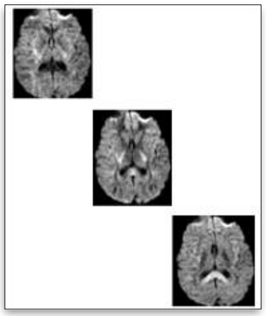
- Computed from the **spectral decomposition** of $\boldsymbol{D}$:
  - **Orientation of the axes** is given by the three *eigenvectors*, i.e. $\boldsymbol{\varepsilon}_1$, $\boldsymbol{\varepsilon}_2$, $\boldsymbol{\varepsilon}_3$
  - The **diffusivity along each axis** is given by the *eigenvalues*, i.e. λ_1, λ_2, λ_3
  - By convention, $\lambda_1 \geq \lambda_2 \geq \lambda_3$
- **Surface** = *distance of a molecule diffusing* from the origin with equal probability
  - *NB: distance/diffusivity relation by* Einstein's equation: $\langle r^2 \rangle = 6Dt$

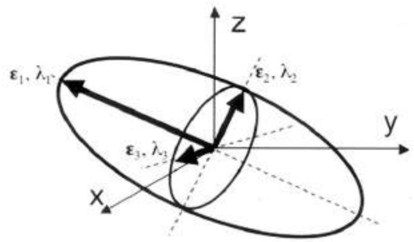
Spectral decomposition = **change of reference frame**

$$\begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ \cdot & D_{yy} & D_{yz} \\ \cdot & \cdot & D_{zz} \end{pmatrix} \xrightarrow[\text{spectral}]{\text{decomposition}} \boldsymbol{\xi}^T \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} \boldsymbol{\xi} \qquad \boldsymbol{\xi} = [\boldsymbol{\varepsilon}_1, \boldsymbol{\varepsilon}_2, \boldsymbol{\varepsilon}_3]^T$$



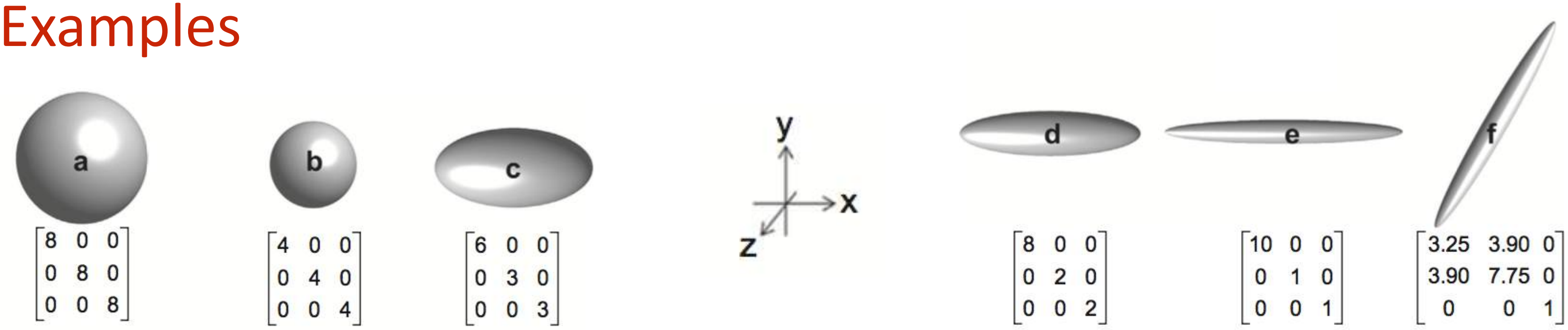




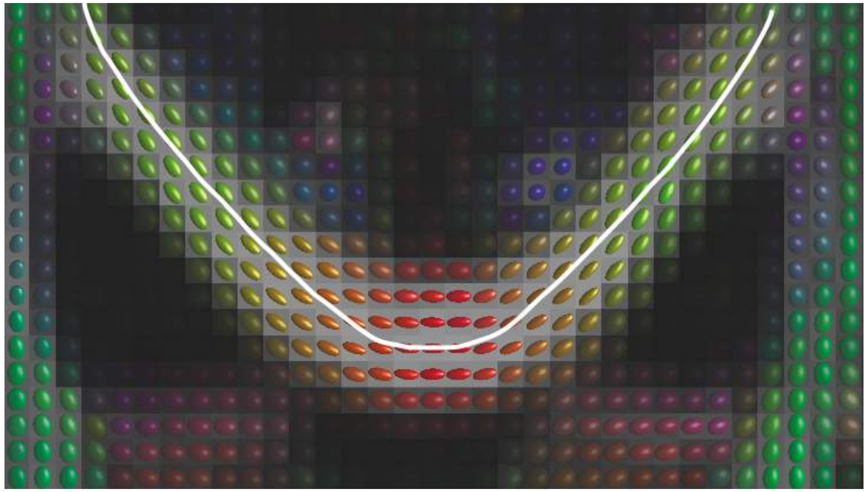


Diffusion Tensor Imaging (DTI) (4/4)

- Examples



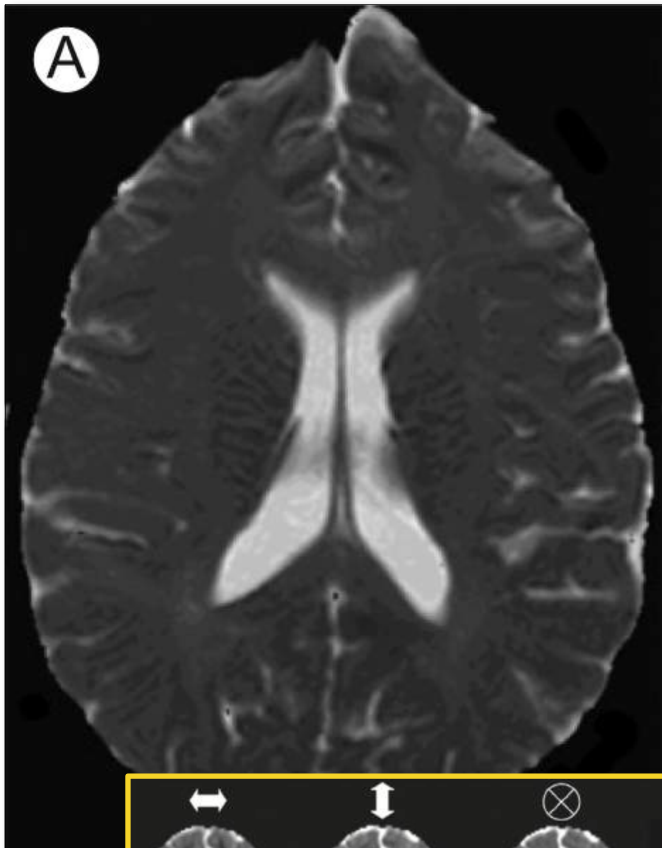
- The *principal eigenvector* ($\boldsymbol{\varepsilon}_1$) is assumed to be co-linear with the **dominant fiber orientation** within the voxel
  - Basic principle that will be used in *tractography*

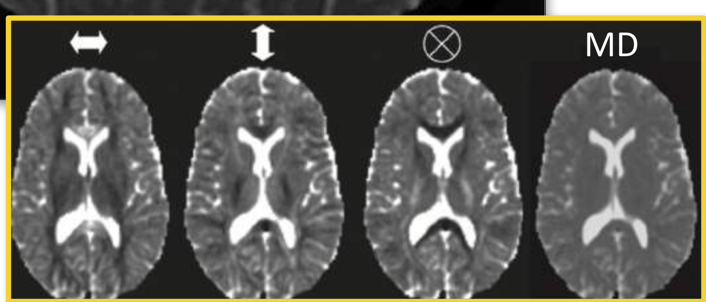


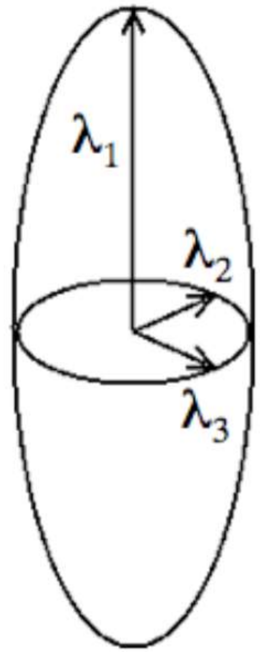
From diffusion tensors to tissue properties (1/2)

Mean Diffusivity (MD)

$$\bar{\lambda} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

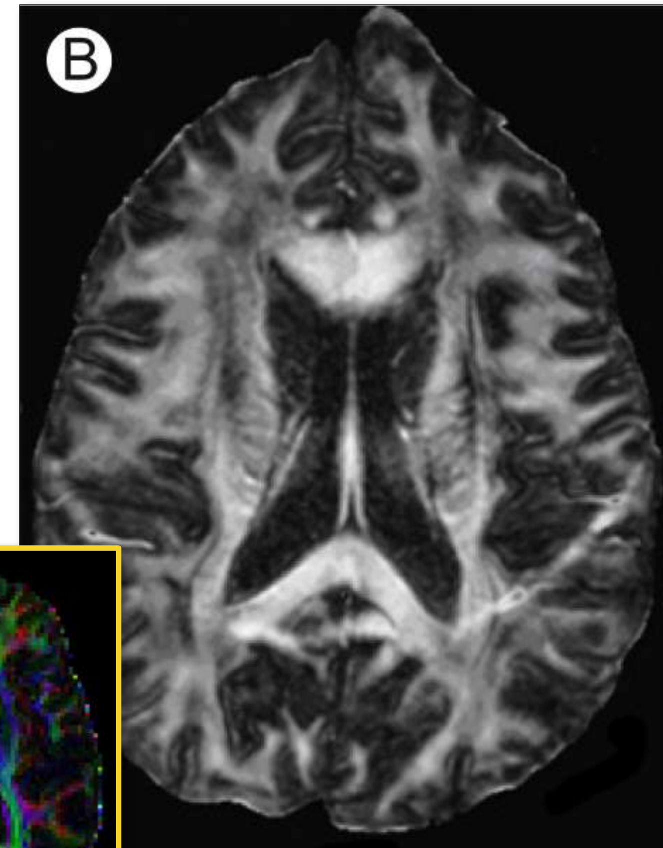


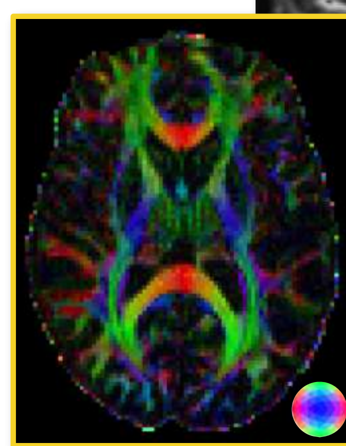




Fractional Anisotropy (FA)

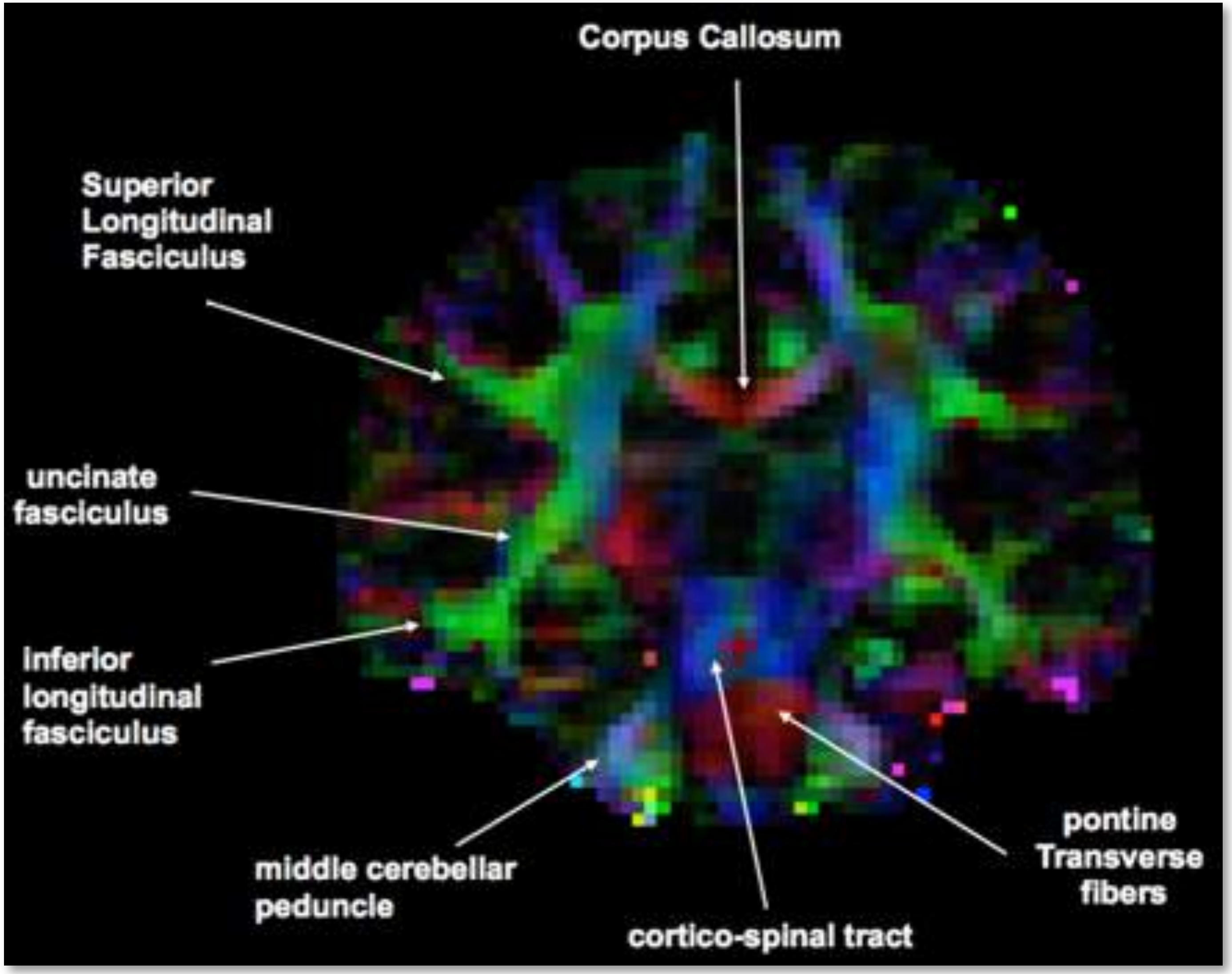
$$\mathrm{FA} = \sqrt{\frac{3}{2}}\sqrt{\frac{(\lambda_1-\bar{\lambda})^2+(\lambda_2-\bar{\lambda})^2+(\lambda_3-\bar{\lambda})^2}{\lambda_1^2+\lambda_2^2+\lambda_3^2}}$$





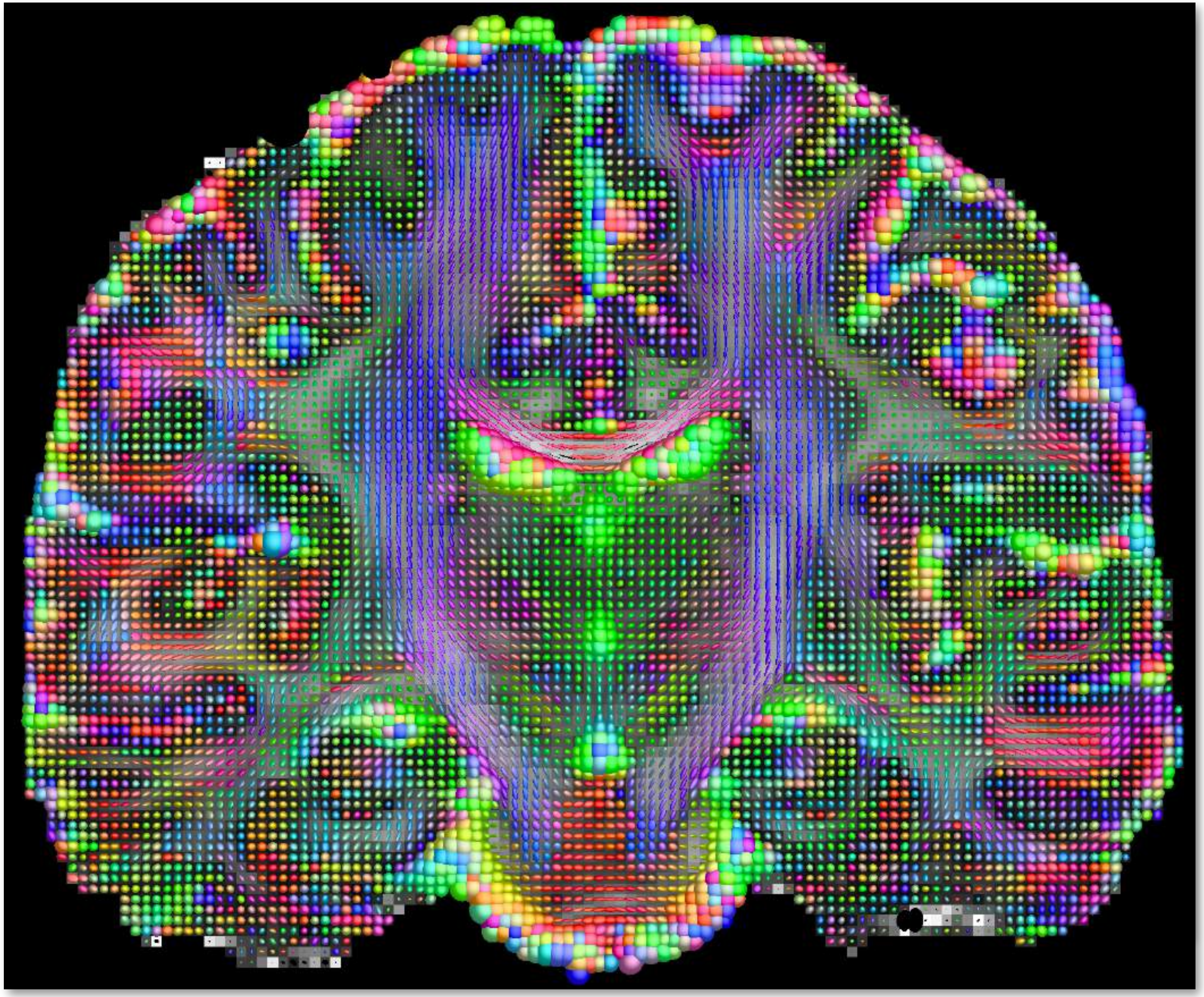
FA map can be **color coded** based on the principal direction, i.e. $\boldsymbol{\varepsilon}_1$

- **New contrast**: possible to delineate major fiber bundles



From diffusion tensors to tissue properties (2/2)

- **New contrast**: possible to delineate major fiber bundles



How to measure a diffusion tensor?

- Signal-Tensor relationship in **matrix form**:

$$\mathbf{Y} = \mathbf{B}\mathbf{D}$$

  - Observed signal : $S(\mathbf{g}_k, b) = S_0 \exp\left(-b\, \mathbf{g}_k^T \mathbf{D} \mathbf{g}_k\right)$
  - Diffusion Tensor : $\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} & D_{yy} & D_{yz} & D_{zz} \end{bmatrix}^T$
  - Log-transformed signal : $\mathbf{Y} = \begin{bmatrix} -\log\left(S(\mathbf{g}_1, b)/S_0\right) & \cdots & -\log\left(S(\mathbf{g}_N, b)/S_0\right) \end{bmatrix}^T$
  - b-matrix :

$$\mathbf{B} = \begin{bmatrix} b_{xx}^1 & 2b_{xy}^1 & 2b_{xz}^1 & b_{yy}^1 & 2b_{yz}^1 & b_{zz}^1 \\ b_{xx}^2 & 2b_{xy}^2 & 2b_{xz}^2 & b_{yy}^2 & 2b_{yz}^2 & b_{zz}^2 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ b_{xx}^N & 2b_{xy}^N & 2b_{xz}^N & b_{yy}^N & 2b_{yz}^N & b_{zz}^N \end{bmatrix}$$

number of measurements ($N \geq 6$)

6 unknowns

$$\mathbf{g}_k = \begin{bmatrix} g_x^k & g_y^k & g_x^k \end{bmatrix}^T$$

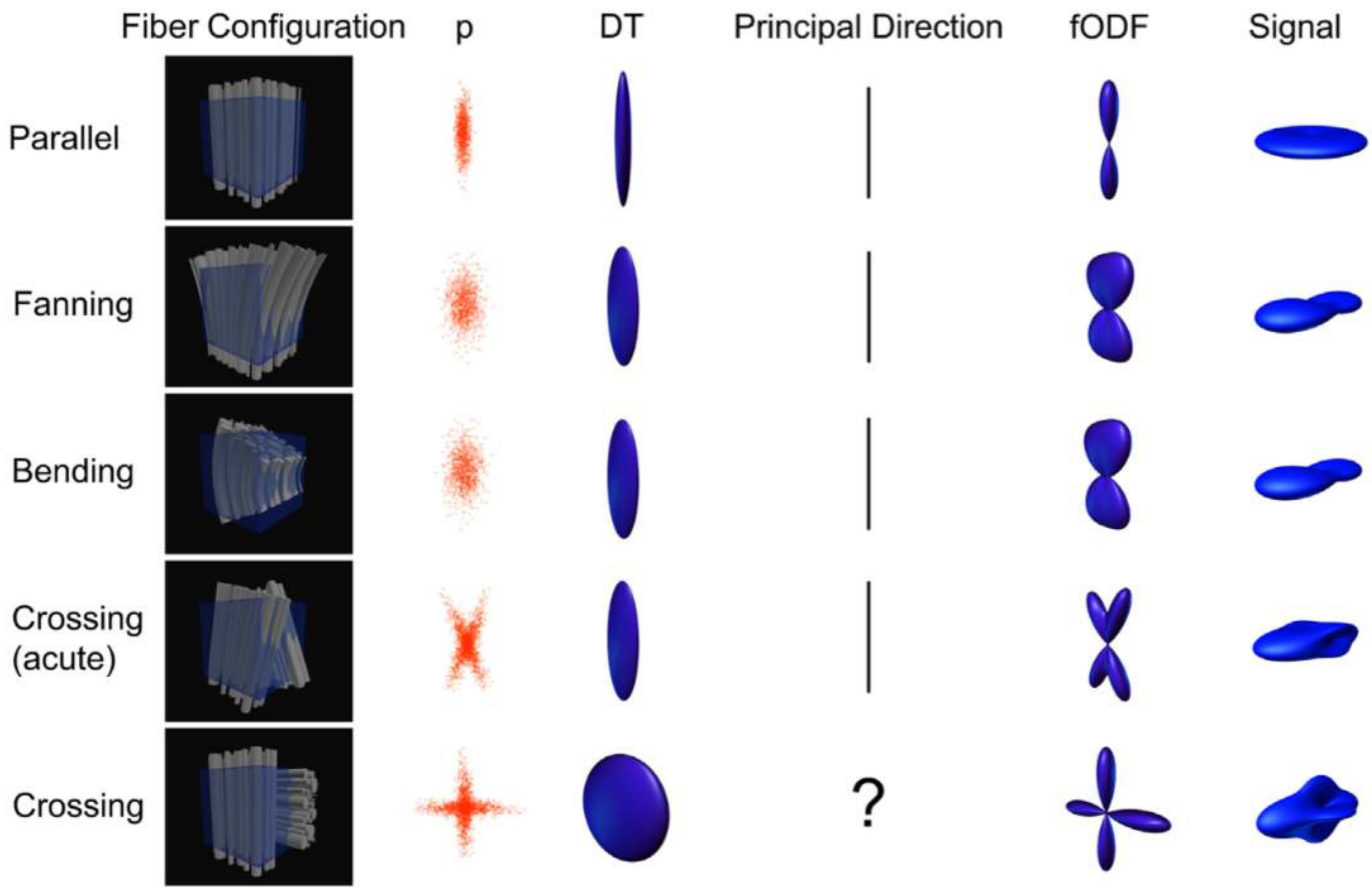
$$b_{xx}^k = b \cdot g_x^k \cdot g_x^k$$
$$b_{xy}^k = b \cdot g_x^k \cdot g_y^k$$
$$\vdots$$
$$b_{zz}^k = b \cdot g_z^k \cdot g_z^k$$

- ***D*** can be estimated using **least squares**

$$\mathbf{D} = \left(\mathbf{B}^T \mathbf{B}\right)^{-1} \mathbf{B}^T \mathbf{Y}$$

Major problem of the Tensor model

- Inability to model **complex fiber configurations**

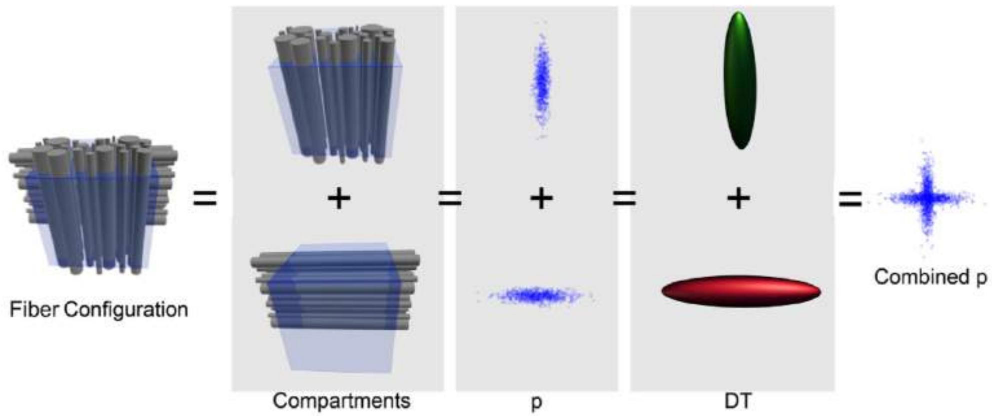


Simple generalization of DTI

- Extends the model to a **mixture of M tensors**

(Tuch et al., 2002)

$$S(\mathbf{g}_k, b) = S_0 \sum_{i=1}^{M} f_i \exp\left(-b\, \mathbf{g}_k^T \mathbf{D}_i \mathbf{g}_k\right)$$

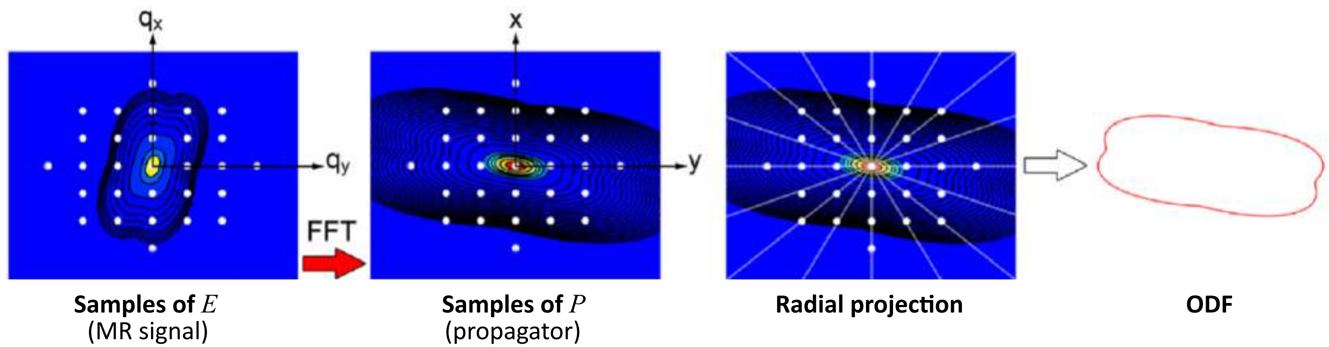


Notes

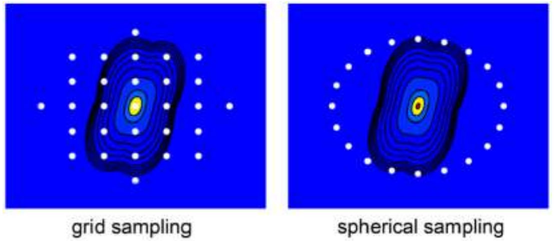
- M=1 ⇒ DTI
- Assumptions:
  - Voxel contains M *distinct populations* of fibers
  - Each population has *Gaussian diffusion* (no exchange)
  - The number M must be known a priori

Numerical Q-Ball Imaging (QBI) (1/2)

- DSI recovers the *full displacement distribution* (EAP)



  - ▶ *Grid sampling* of DSI is very **time consuming**



- QBI **approximates the ODF** sampling the signal only on *spherical shell*

  - ▶ The *approximation* is computed using the **Funk–Radon transform** (FRT)

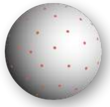
(Tuch et al., 2002)

$$\mathrm{ODF}(\hat{\mathbf{r}}) = \int_{\mathbb{R}+} P(r\hat{\mathbf{r}})r^2 dr \approx \int_{|\mathbf{q}|=1} \delta(\hat{\mathbf{r}}^T\mathbf{q})E(\mathbf{q})d\mathbf{q} = \mathrm{FRT}[E](\hat{\mathbf{r}})$$

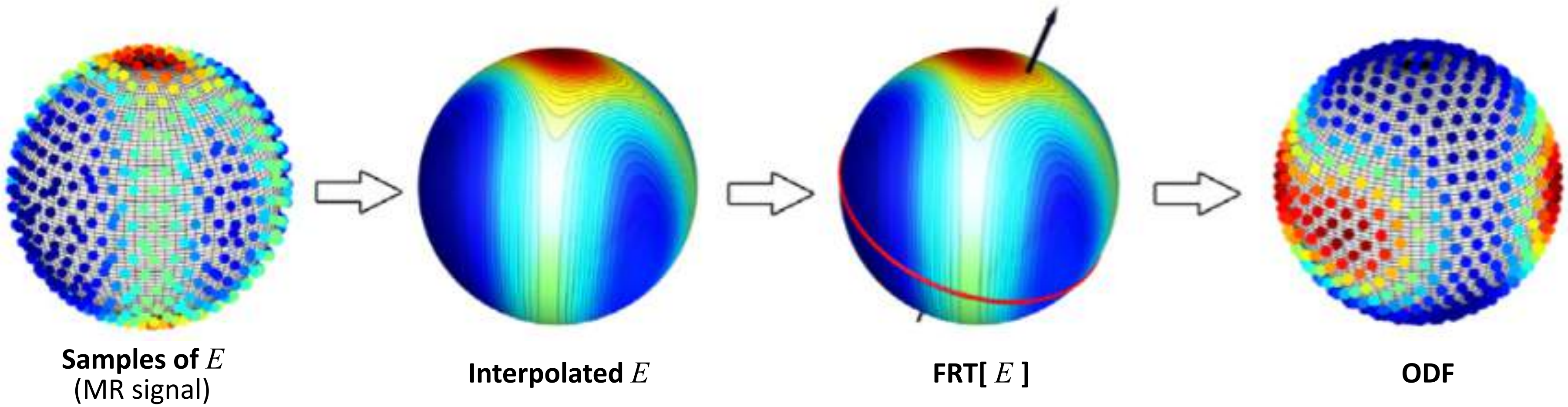
$r = |\mathbf{r}|$ and $\hat{\mathbf{r}} = \mathbf{r}/r$

$E = S/S_0$

  - ▶ Definition : the FRT of a *spherical function* E along orientation $\hat{\mathbf{r}}$ is the *great circle integral of* E *on the sphere* defined by the *plane perpendicular to* $\hat{\mathbf{r}}$ through the origin
  - ▶ NB: signal E sampled with a **single b-value**

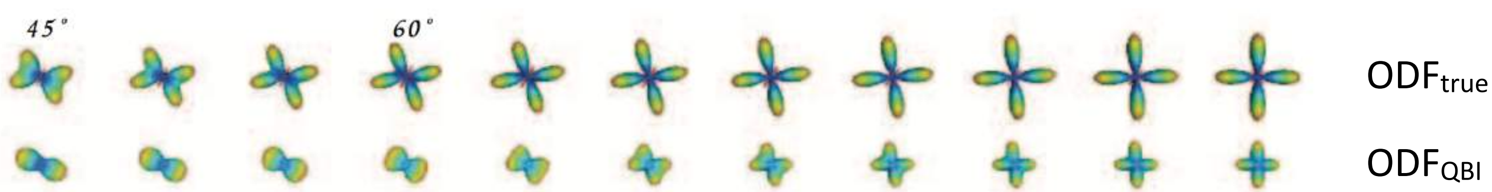


Procedure

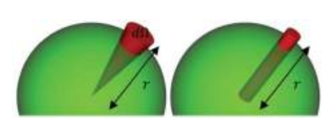


Notes

- The procedure is rather slow
- The approximation <u>does not</u> recover the ODF, but a **blurred version** of it



- This is due to the missing r^2 term in the radial integral
  - The low-frequencies of q-space are weighted more than higher frequency

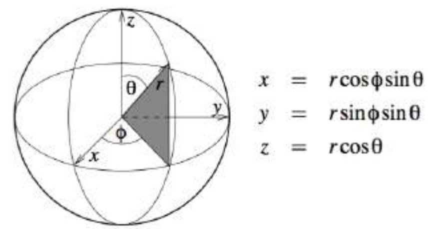


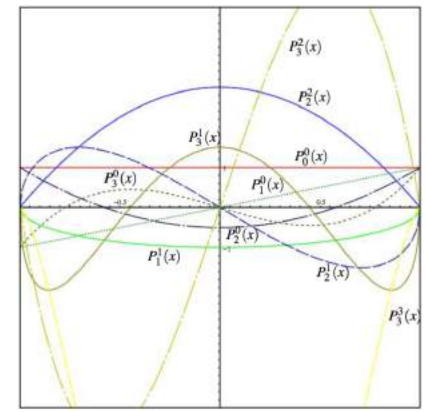
(Aganj et al., 2010)

Orthonormal basis for *complex* functions on the sphere

$$Y_\ell^m(\theta,\phi) = \sqrt{\frac{2\ell+1}{4\pi}\frac{(\ell-m)!}{(\ell+m)!}}\,P_\ell^m(\cos\theta)e^{im\phi}$$

- P_ℓ^m : associated Legendre polynomials
- ℓ : *order* of the SH
- $\forall k \le \ell,\ -k \le m \le k$: *phase factors*





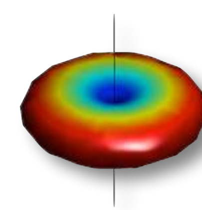
In **diffusion MRI** most objects are *real* and *symmetric*

e.g. signal on one shell, ODF, fDOF

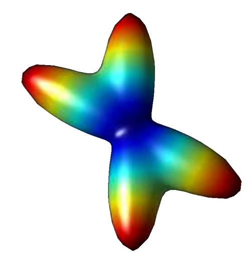
- **Modified basis** for real and symmetric functions

$$Y_j = \begin{cases} \sqrt{2}\cdot \mathrm{Re}(Y_k^m), & \text{if } -k \le m < 0 \\ Y_k^0, & \text{if } m = 0 \\ \sqrt{2}\cdot \mathrm{Img}(Y_k^m), & \text{if } 0 < m \le k \end{cases}$$

- *Index* $j = (k^2 + k + 2)/2 + m$
- Symmetry given by choosing $k = 0, 2, 4, \ldots, \ell$
- If *order* is ℓ, then $R = (\ell+1)(\ell+2)/2$ **basis functions**

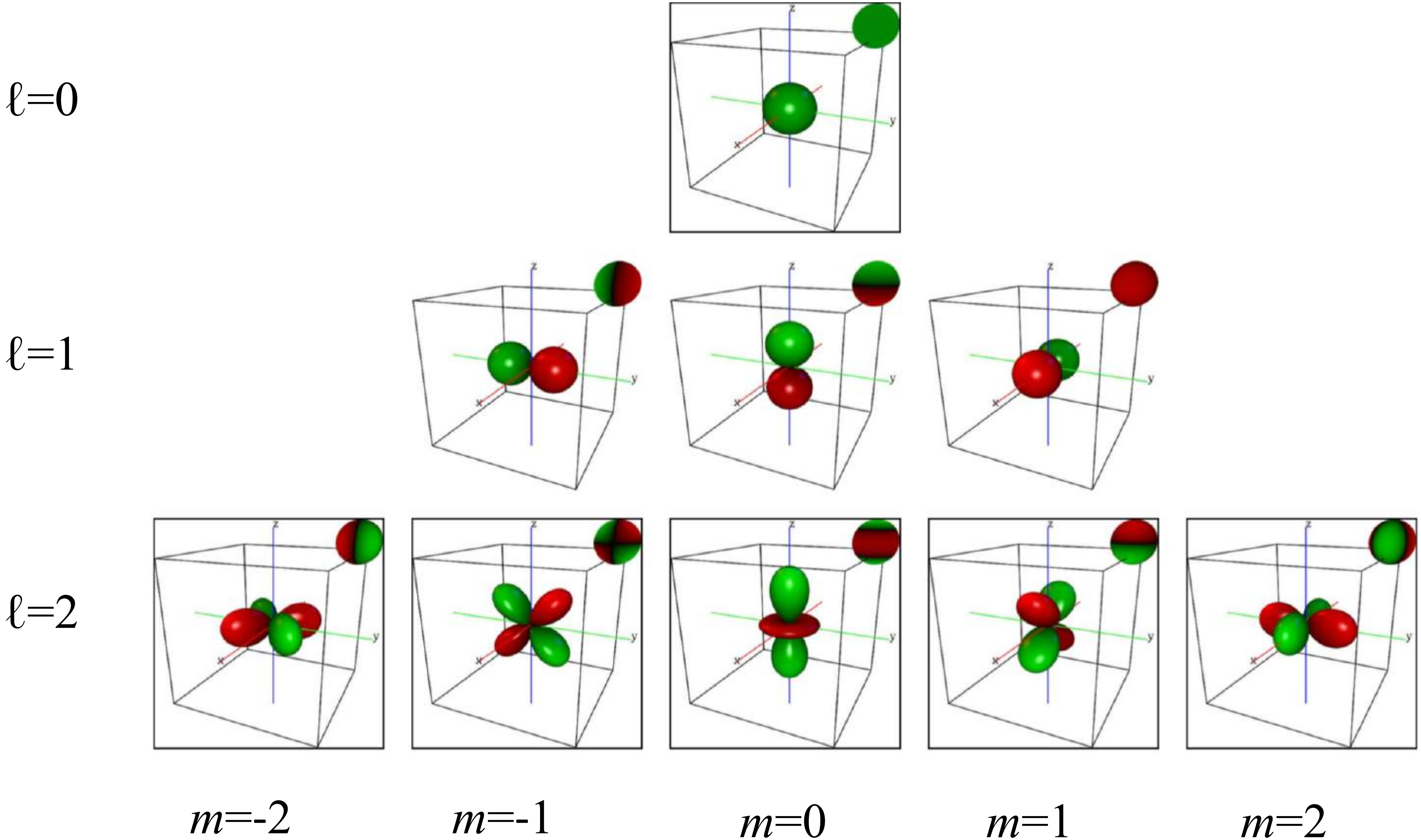


signal on one shell

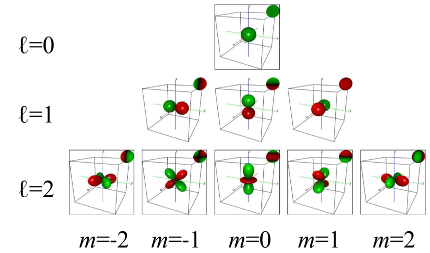


ODF

- How do they look like?



- **How do they look like?**

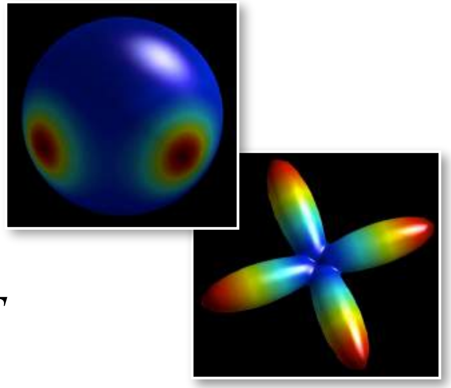


- **Representing a function F in the SH space**

$$F(\theta_i, \phi_i) = \sum_{j=1}^{R} c_j Y_j(\theta_i, \phi_i)$$

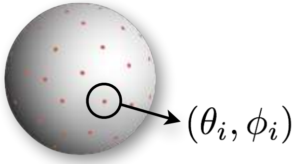
matrix form

$$\mathbf{F} = \mathbf{YC}$$



- $F \in \mathbb{S}^2$ (i.e. function on the sphere) is a *real* and *symmetric*
- $\mathbf{F} = \left[F(\theta_1, \phi_1), \ldots, F(\theta_N, \phi_N)\right]^T$ contains the N *measurements* of F
- $\mathbf{Y}$ contains the R *basis functions* evaluated at the N sampling points:

$$\mathbf{Y} = \begin{pmatrix} Y_1(\theta_1, \phi_1) & Y_2(\theta_1, \phi_1) & \cdots & Y_R(\theta_1, \phi_1) \\ \vdots & \vdots & \ddots & \vdots \\ Y_1(\theta_N, \phi_N) & Y_2(\theta_N, \phi_N) & \cdots & Y_R(\theta_N, \phi_N) \end{pmatrix}$$



- The *coefficients* $\mathbf{C} = \left[c_0, c_1, \ldots, c_R\right]^T$ can be estimated using **least squares**

$$\mathbf{C} = (\mathbf{Y}^T\mathbf{Y})^{-1}\mathbf{Y}^T\mathbf{F}$$

Analytical Q-Ball Imaging (QBI) (1/2)

- Based on the following theorem

(Descoteaux et al., 2007)

Corollary of the Funk-Hecke Theorem: *Let $\delta(t)$ be the Dirac delta function and H_ℓ any SH of order ℓ. Then, given a unit vector* $\mathbf{u}$

$$\int_{|\mathbf{w}|=1} \delta(\mathbf{u}^{\mathrm{T}}\mathbf{w}) H_\ell(\mathbf{w}) d\mathbf{w} = 2\pi P_\ell(0) H_\ell(\mathbf{u}), \qquad [14]$$

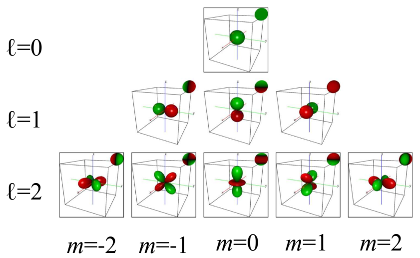
  - $P_\ell(0) = \begin{cases} 0 & \ell \text{ odd} \\ (-1)^{\ell/2} \dfrac{1 \cdot 3 \cdot 5 \cdots (\ell-1)}{2 \cdot 4 \cdot 6 \cdots \ell} & \ell \text{ even} \end{cases}$ are the **Legendre polynomials** of order ℓ (evaluated at 0)
  - The *great circle integral* of SH basis functions can be **computed analytically**

- If we express E in **SH space** ⇒ FRT has **analytical form**

$$E(\theta_i, \phi_i) = \sum_{j=1}^{R} c_j Y_j(\theta_i, \phi_i)$$

(Descoteaux et al., 2007)

$$\mathrm{FRT}[E](\hat{\mathbf{r}}) \equiv \int_{|\mathbf{q}|=1} \delta(\hat{\mathbf{r}}^T \mathbf{q}) E(\mathbf{q}) d\mathbf{q} = \sum_{j=1}^{R} 2\pi P_{\ell_j}(0) c_j Y_j(\hat{\mathbf{r}})$$



  - No need to interpolate, numerically integrate etc… (slow)
  - We then have a **closed form to compute the ODF** (fast)

Analytical Q-Ball Imaging (QBI) (2/2)

Procedure to reconstruct the **ODF in a voxel**

1) **Construct the two $R \times R$ matrices $\mathbf{P}$** and $\mathbf{L}$

$$P = \begin{pmatrix} \ddots & & \\ & 2\pi P_{\ell_j}(0) & \\ & & \ddots \end{pmatrix}$$

Legendre polynomials of order ℓ_j

NB: for $j = 1,2,\ldots,R$
$\ell_j = \{0,2,2,2,2,2,4,4,\ldots\}$

$$L = \begin{pmatrix} \ddots & & \\ & \ell_j^2(\ell_j+1)^2 & \\ & & \ddots \end{pmatrix}$$

Laplace-Beltrami smoothing

2) Express the **signal E with SH**

$$\mathbf{E}_{\ell m} = (\mathbf{Y}^T\mathbf{Y} + \lambda\mathbf{L})^{-1}\mathbf{Y}^T\,\mathbf{E}$$

Used to make the fit more robust
(λ controls regularization strength)

$$\mathbf{Y} = \begin{pmatrix} Y_1(\theta_1,\phi_1) & Y_2(\theta_1,\phi_1) & \cdots & Y_R(\theta_1,\phi_1) \\ \vdots & \vdots & \ddots & \vdots \\ Y_1(\theta_N,\phi_N) & Y_2(\theta_N,\phi_N) & \cdots & Y_R(\theta_N,\phi_N) \end{pmatrix}$$

SH basis functions evaluated at the same N sampling directions of E

$$\mathbf{E}_{\ell m} = [c_1,\ldots,c_j,\ldots,c_R]^T$$

Signal in SH space

3) Compute the **ODF** (in SH space)

$$\mathbf{O}_{\ell m} = \mathbf{P}\mathbf{E}_{\ell m}$$

$$\mathbf{O}_{\ell m} = [c'_1,\ldots,c'_j,\ldots,c'_R]^T$$

ODF in SH space

4) Evaluate the **ODF on the sphere**

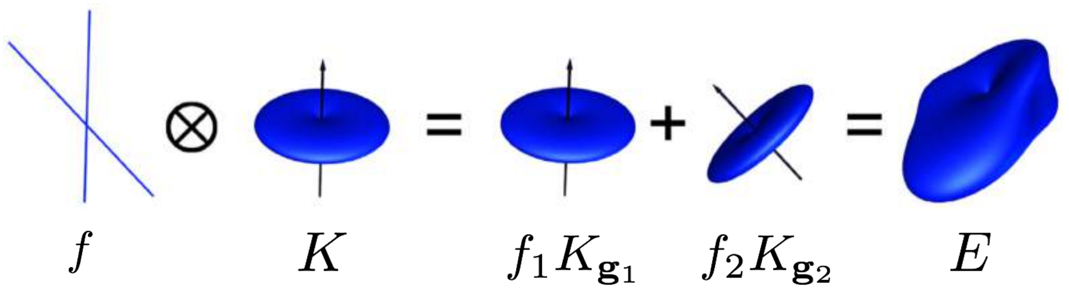
$$\mathbf{O} = \mathbf{Y}'\mathbf{O}_{\ell m}$$

NB: $\mathbf{Y}'$ is **constructed similarly** to $\mathbf{Y}$ but we can change the set of directions where we want to evaluate the ODF

Notes

- All operations are *linear*
- We can *precompute* $\mathbf{T} = \mathbf{P}(\mathbf{Y}^T\mathbf{Y} + \lambda\mathbf{L})^{-1}\mathbf{Y}^T$ and then apply it in each voxel

- **Basic idea**: signal as a convolution on the sphere



  - $K \in \mathbb{S}^2$: signal response (**kernel**) corresponding to a **single fiber population**
  - $f \in \mathbb{S}^2$: **fODF**, i.e. continuous representation of the *volume fractions*
  - Mathematically: $E(\mathbf{g}_k) = \int_{|\mathbf{q}|=1} K_{\mathbf{g}_k}(\mathbf{q}) f(\mathbf{q}) d\mathbf{q}$

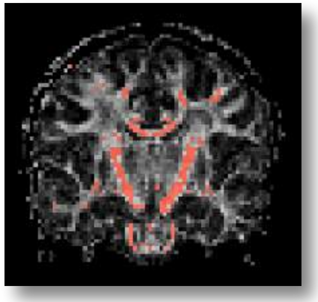
    where $K_{\mathbf{g}_k}$ is the response function *reoriented in direction* $\mathbf{g}_k$

- **Goal**: recover the fODF f by **deconvolving** the signal E with K

- Main assumptions
  - **No exchange** between compartments (contributions are independent)
  - The procedure **requires a model** for diffusion in a fiber population to obtain K

Spherical deconvolution (2/4)

Estimation of the **response function** K



- **Fixed** to a known value, e.g.
  - tensor with $\lambda_1 = 1.7 \cdot 10^{-3}$ mm^2/s and $\lambda_2 = \lambda_3 = 0.3 \cdot 10^{-3}$ mm^2/s (*humans, in vivo)*
- **Estimated** from the data, e.g.
  - Fit DTI to the data and identify areas with single fiber population, e.g. FA > 0.7
  - Average the signal in all those voxels

Reconstruction of the **fODF** by **deconvolution**

- f is usually expressed as a **linear combination** of basis functions

$$f(\hat{\mathbf{p}}) = \sum_j w_j f_j(\hat{\mathbf{p}})$$

e.g. spherical harmonics (SH)

- The **measurement process** can thus be expressed as

$$\mathbf{y} = \Phi \mathbf{x} + \eta$$

  - $\mathbf{y}$ is the vector containing the *samples* of the signal E and η is the acquisition *noise*
  - $\mathbf{\Phi}$ models the *convolution operator* with the response function K
  - $\mathbf{x}$ is the vector containing the *coefficients of the fODF f*

- fODF reconstructed using **(regularized) least squares** of the form

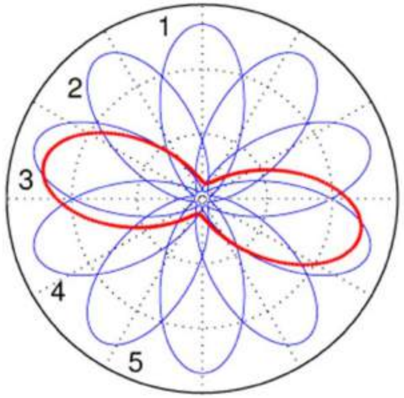
$$\operatorname{argmin} \underbrace{\frac{1}{2}\|\Phi\mathbf{x}-\mathbf{y}\|_2^2}_{\text{data fitness}} + \lambda \underbrace{\Psi(\mathbf{x})}_{\text{regularization}}$$

Optional.
(depends on the specific problem/model)

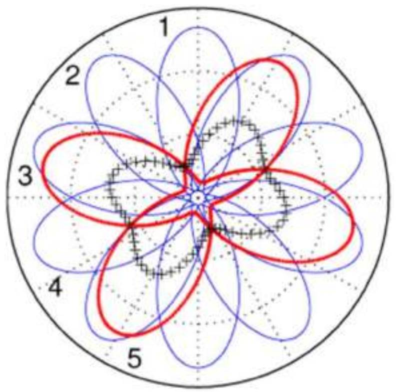
Diffusion Basis Functions (DBF) decomposition

(Ramirez-Manzanares et al., 2007)

- Reconstruction expressed as a **mixture of Gaussians**
  - The *response function* K is a Tensor
  - *Estimate it's diffusivities* (λ_1, λ_2, λ_3) as discussed before
  - *Rotate* K along a given set of orientations
- Can be seen as an **extension of Multi-Tensor**
- Key point
  - These represent the **possible fiber populations** of the voxel…
  - …but **only few of them** will actually correspond to the **actual fiber populations** present the voxel



Only **1 fiber population** is present in the voxel

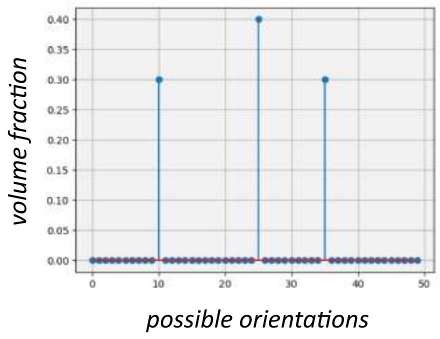


2 fiber populations is present in the voxel

- The fODF is estimated using **non-negative ℓ1-regularized least squares**

$$\arg\min_{\boldsymbol{x}\geqslant 0} \|\boldsymbol{x}\|_1 \text{ subject to } \|\Phi\, \boldsymbol{x} - \boldsymbol{y}\|_2 \leqslant \epsilon$$

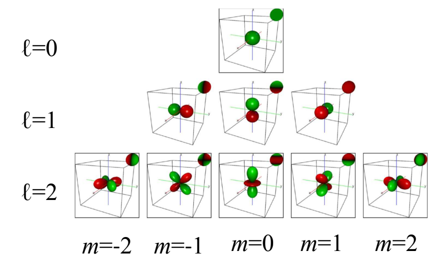
  - $\|\cdot\|_1$ promotes a **sparse solution**, i.e. few nonzero coefficients
  - The **positivity of the fODF** is embedded in the optimization problem
- **Principal diffusion directions** given directly by $\boldsymbol{x}$ coefficients



Constrained Spherical Deconvolution (CSD) *(Tournier et al., 2007)*

- Reconstruction expressed in the **Spherical Harmonics** basis

$$\mathbf{Y} = \begin{pmatrix} Y_1(\theta_1,\phi_1) & Y_2(\theta_1,\phi_1) & \cdots & Y_R(\theta_1,\phi_1) \\ \vdots & \vdots & \ddots & \vdots \\ Y_1(\theta_N,\phi_N) & Y_2(\theta_N,\phi_N) & \cdots & Y_R(\theta_N,\phi_N) \end{pmatrix}$$



- Problem
  - The fODF is a **positive function** (represents volume fractions)
  - With **least squares** and **SH basis** there's nothing to enforce this requirement
  - The **weights** of some SH basis functions **can be negative**

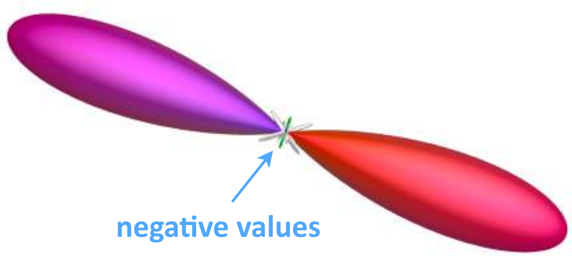
- This issue is *mitigated* by **iteratively refining the estimation** of the fODF

$$f_{i+1} = \arg\min\{\|\mathbf{A}f_i - b\|^2 + \lambda^2\|\mathbf{L}f_i\|^2\}$$

Specific regularization for this particular problem

build from Y **signal samples**

  - f_i is the fODF estimated at iteration i
  - The matrix $\mathbf{L}_{m,n} = \begin{cases} \mathbf{P}_{m,n} & u_m < \tau \\ 0 & u_m \geq \tau \end{cases}$ **penalizes those orientations** in the fODF that fall below a given threshold (τ)
  - The matrix $\mathbf{P}$ maps f_i (SH coefficients of the current FOD estimate) onto the amplitudes $\mathbf{u}$ along a given set of directions



- **Principal diffusion directions** need to be extracted from f (*maxima estimation*)

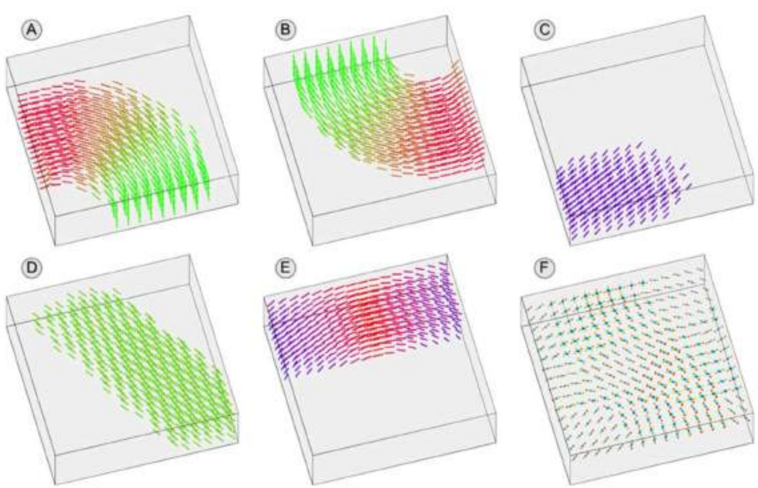
High Angular Diffusion Imaging (HARDI)

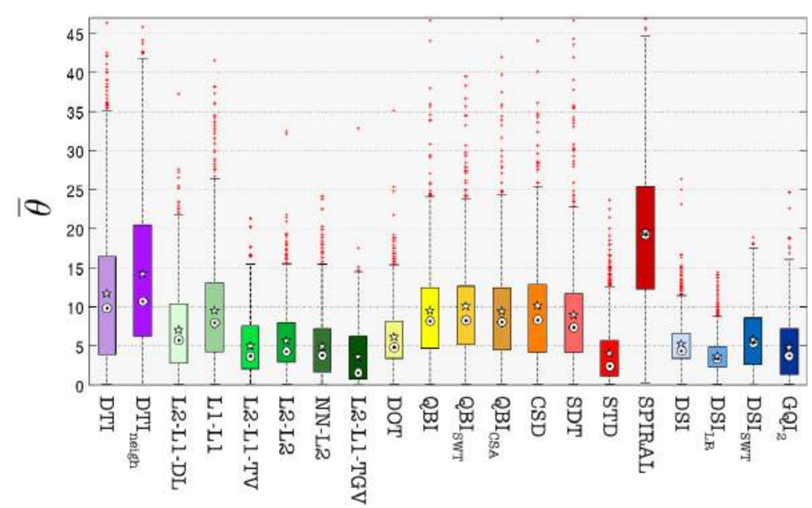
Vast literature of methods

- They <u>differ in a great deal of aspects</u>
  - Target *feature* of interest to estimate, e.g. ODF or fODF
  - *Assumptions* and *requirements*, e.g. cartesian or multiple shells
  - Reconstruction *algorithm* and optimization

Survey and **comparison**: see *(Daducci et al, 2014)*

- **Simulated data** with **known ground truth**
- **Metrics**: accuracy in *number* and *orientation* of fibers





Diffusion MRI: microstructure imaging

Outline of this part

Multi-compartment models

- Ball&Stick
- Composite hindered and restricted model of diffusion (CHARMED)
- Neurite orientation dispersion and density imaging (NODDI)

Axon density and diameter mapping

- AxCaliber
- ActiveAx

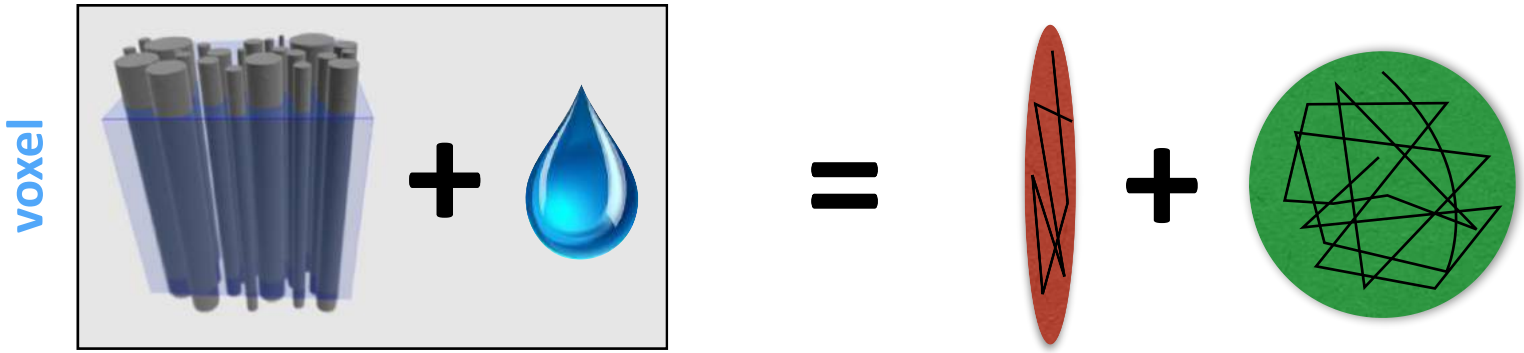
Accelerated Microstructure Imaging via Convex Optimization

- Framework to *accelerate the fit* with previous methods

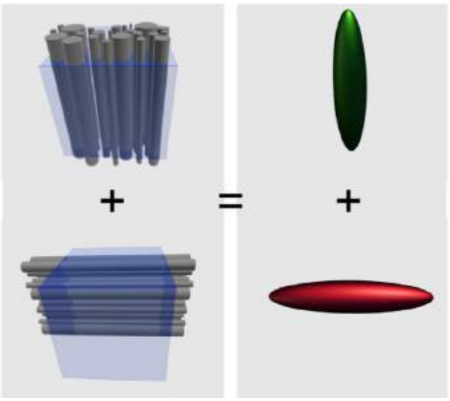
Ball&Stick

- Assumes that water molecules belong to **two populations**
  - A **restricted population** of water molecules in and around axons
  - A **free population** that does not interact with fibers

(Behrens et al., 2003)



- Generalization of the Multi-Tensor (MT) model
  - MT uses tensors to model multiple fiber populations
  - B&S uses tensors to model two distinct compartments
    - Free water is modeled as **isotropic tensor**, i.e. $\mathbf{D}_{\text{ball}} = diag([\lambda_{\text{ball}}, \lambda_{\text{ball}}, \lambda_{\text{ball}}])$
    - Axons modeled as ideal **cylinders with zero radius**, i.e. $\mathbf{D}_{\text{stick}} = diag([\lambda_{\text{stick}}, 0, 0])$

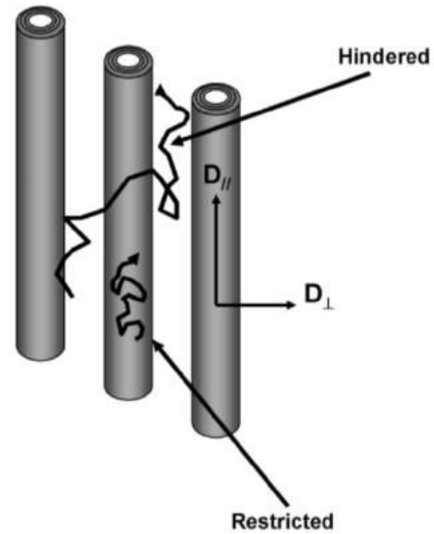


- Oversimplified…but pioneer of **multi-compartment models**

Composite hindered and restricted model of diffusion (CHARMED)

Further distinction between… *(Assaf et al., 2005)*

- Molecules that are **restricted** within the axons
  i.e. **intra-axonal space**
- Those that are **hindered** in the space around them
  i.e. **extra-axonal space**



Model of the signal

- Axons are approximated by **parallel cylinders with a fixed radius**
  (signal given by analytical expressions for *particles diffusing within cylindrical boundaries*)
- **Gaussian process** (anisotropic) assumed in the extra-axonal space
  (anisotropic tensor)
- Signal modeled as

$$E(\mathbf{g}_k, b) = f_h E_h(\mathbf{g}_k, b) + f_r E_r(\mathbf{g}_k, b)$$

relative volume fractions

Radial sampling required to estimate this model's parameters

- **Hindered** model explains the <u>Gaussian</u> signal attenuation observed at **low b-values**
- **Restricted** <u>non-Gaussian</u> model does so at **high b-values**

Composite hindered and restricted model of diffusion (CHARMED)

Further di

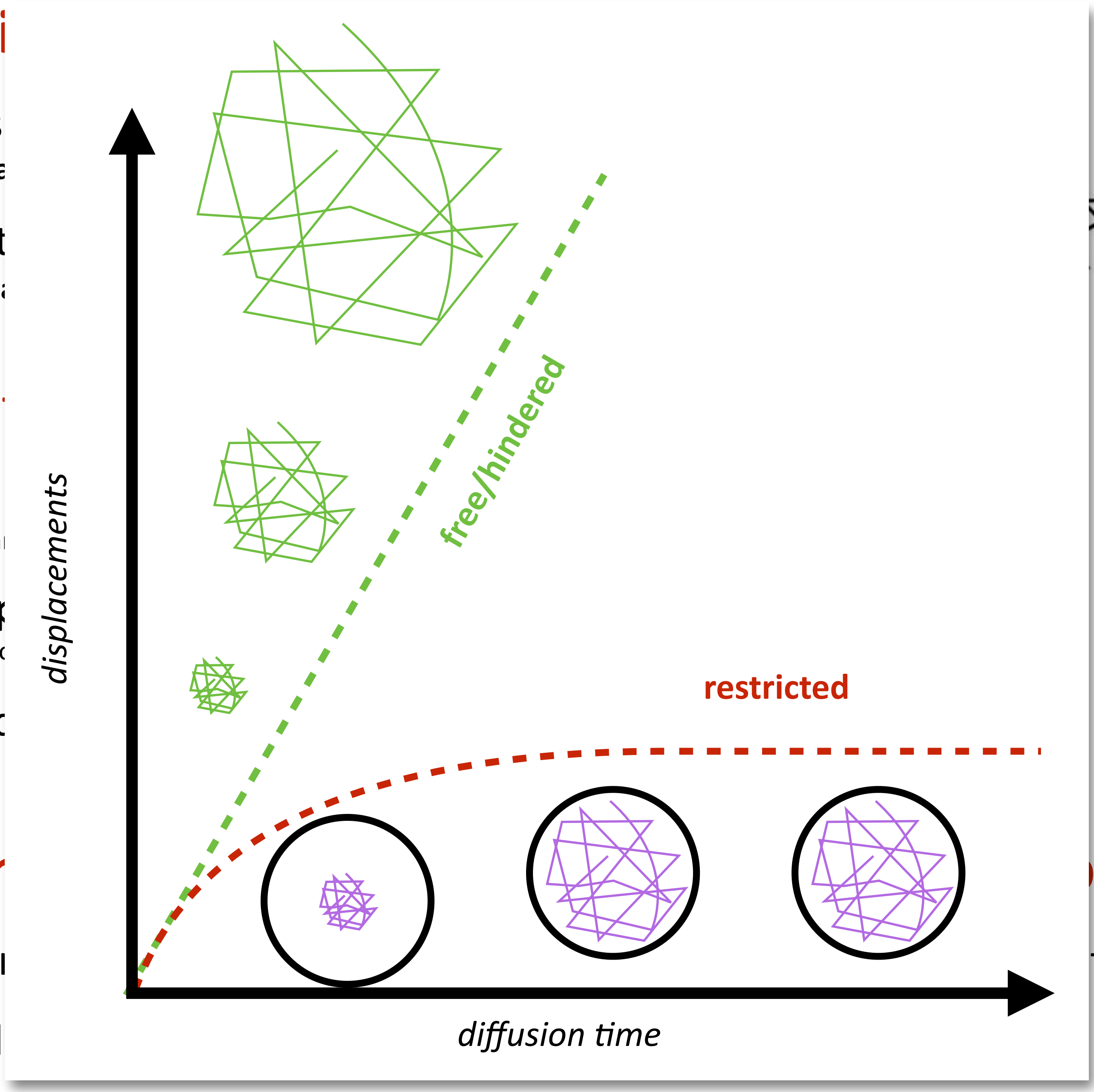
- Molecules
  i.e. **intra-axona**
- Those that
  i.e. **extra-axona**

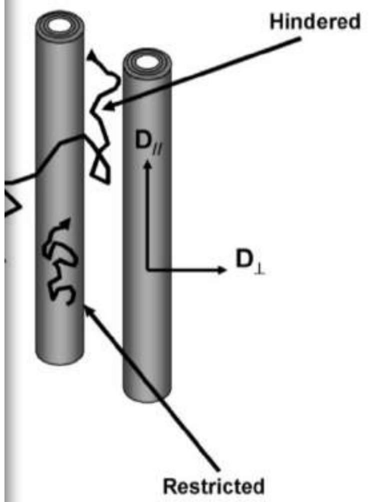
Model of

- Axons are
  (signal given by a
- **Gaussian p**
  (anisotropic tenso
- Signal mod

Radial sar … arameters

- **Hindered … t low b-values**
- **Restricted**

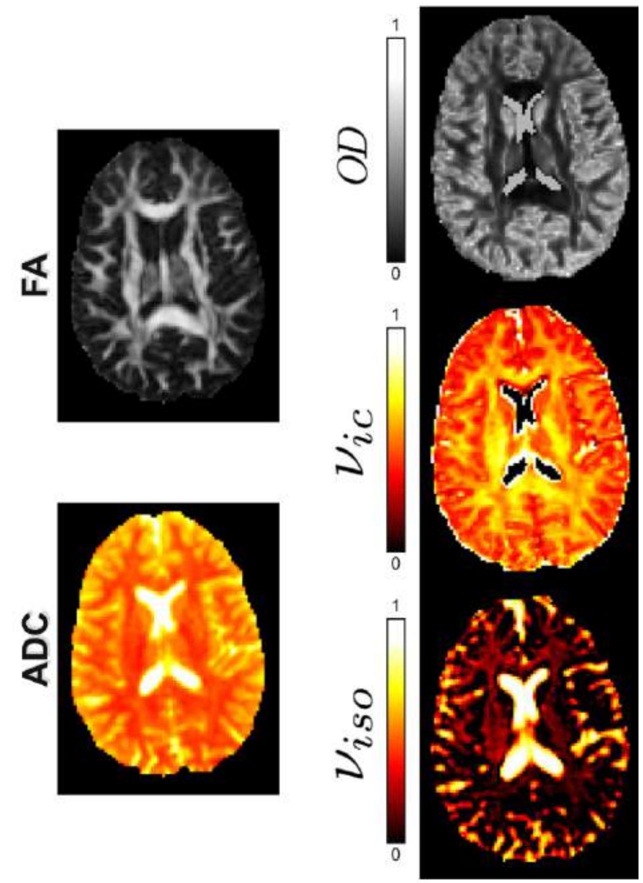




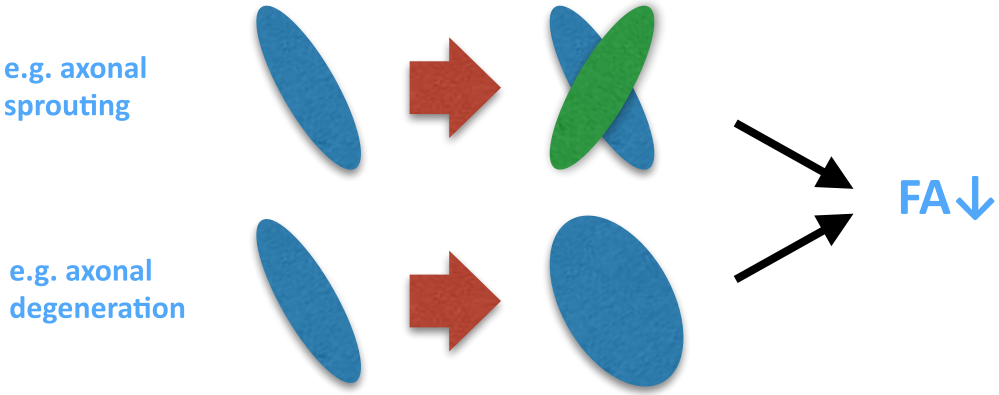
Neurite orientation dispersion and density imaging (NODDI)

- Developed to enable estimation of **useful microstructural information** also in **clinical settings**, e.g. 10–15 min and low G_{max}
  - Axons are assumed as “ideal cylinders” with **null radius**
  - **Model optimized** to describe the signal in terms of
    - *Volume fractions*
    - *Orientation dispersion* of the axons
    - Partial volume with *CSF*

(Zhang et al., 2012)



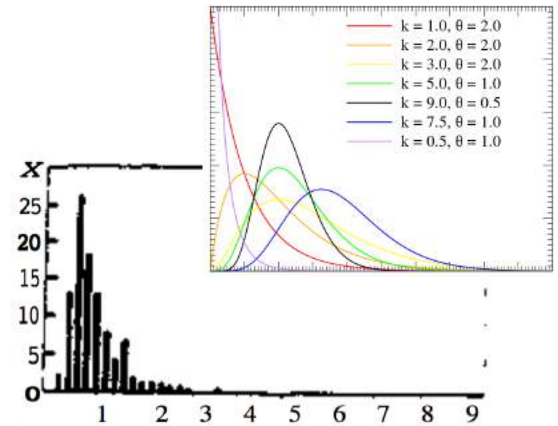
- This model tries to solve some of the **ambiguities of DTI scalar maps**



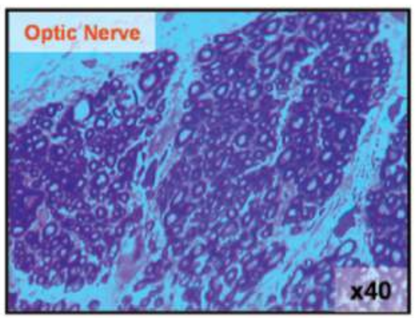
AxCaliber

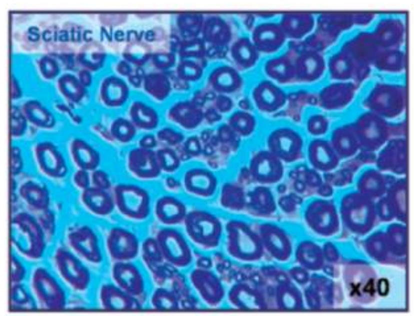
Extension of CHARMED *(Assaf et al., 2008)*

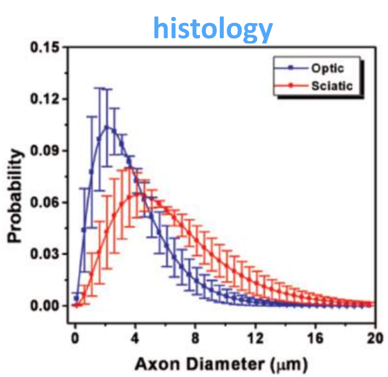
- Axon radii are **not fixed** to a given value as before…
- …but **they are estimated** as well
- Explicitly modeled using *Gamma distributions*
  (as observed from histology)

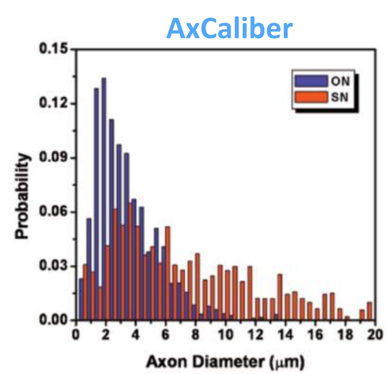


Allows **estimation of the axon diameter** with diffusion MRI







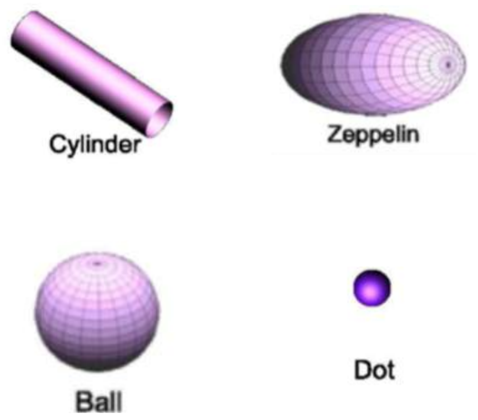


Notes

- Very **long acquisitions**, i.e. need to probe many diffusion times
- Requirements met only in **preclinical scanners**, e.g. G_{max}=1200 mT/m *vs* 40 mT/m in clinics
- Need to know a priori the **orientation of the fascicle** to probe

ActiveAx

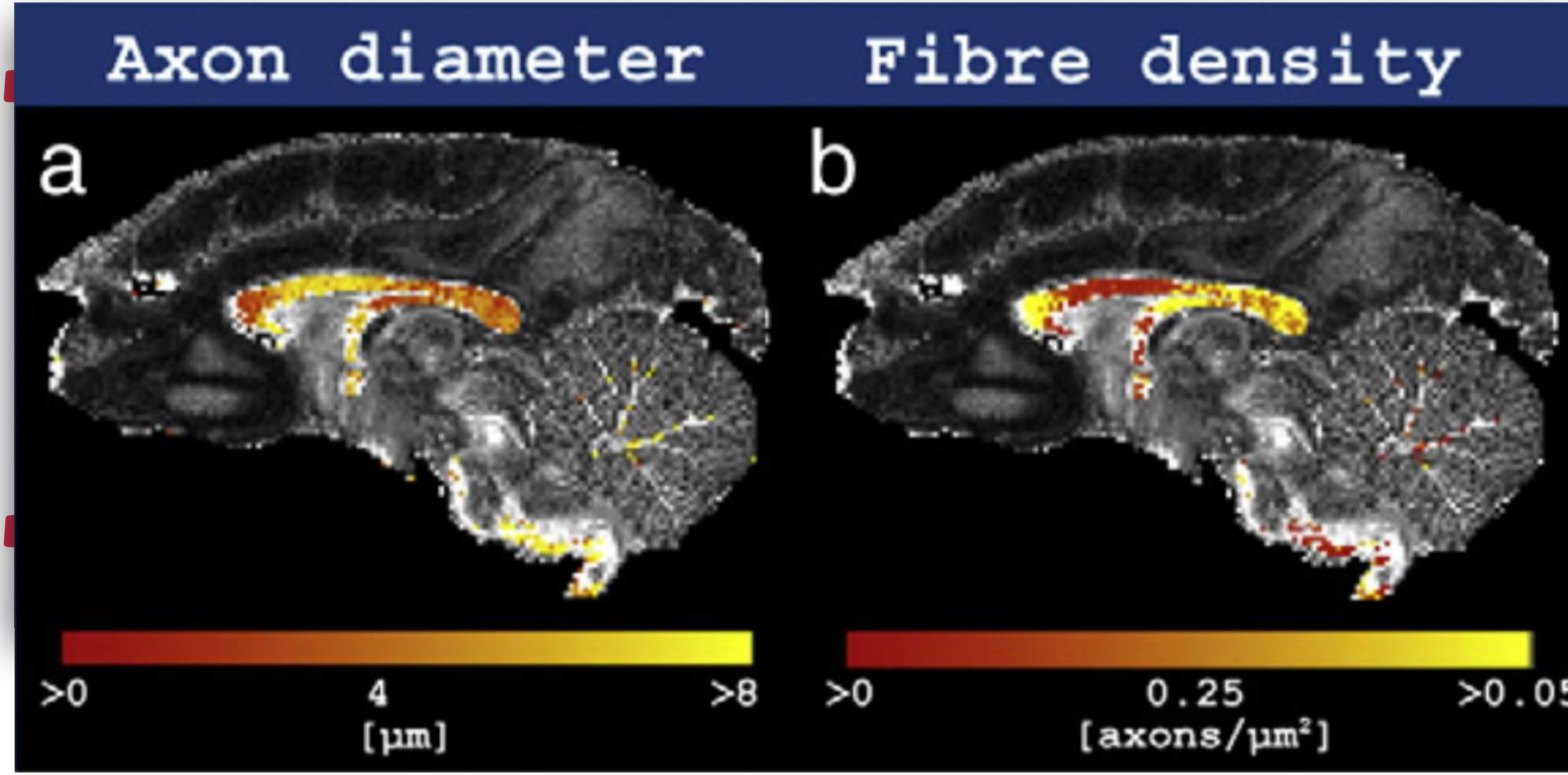
- Specifically designed to **overcome previous limitations**
- **Four compartment** model (Alexander et al., 2010)
  - *Restricted* and *hindered* water pools as CHARMED/AxCaliber but **axons have a diameter to be estimated**
  - *Free water* characterized by isotropic diffusion
  - *Stationary water* trapped within small structures, e.g. glial cells, or in ex-vivo tissue



- Allow **mean axon diameter mapping** in the whole brain
  - **One mean diameter** per voxel, α', *no distributions* of diameters as AxCaliber
  - Index α' is **orientationally invariant**:
    less diffusion times are acquired, but for each value *many directions* are acquired
  - No need to know a priori the direction of the fascicle
  - α' <u>is not</u> the actual axon diameter, but **correlates with histologic estimates**

ActiveAx

- Specifically designed to **overcome previous limitations**



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ActiveAx

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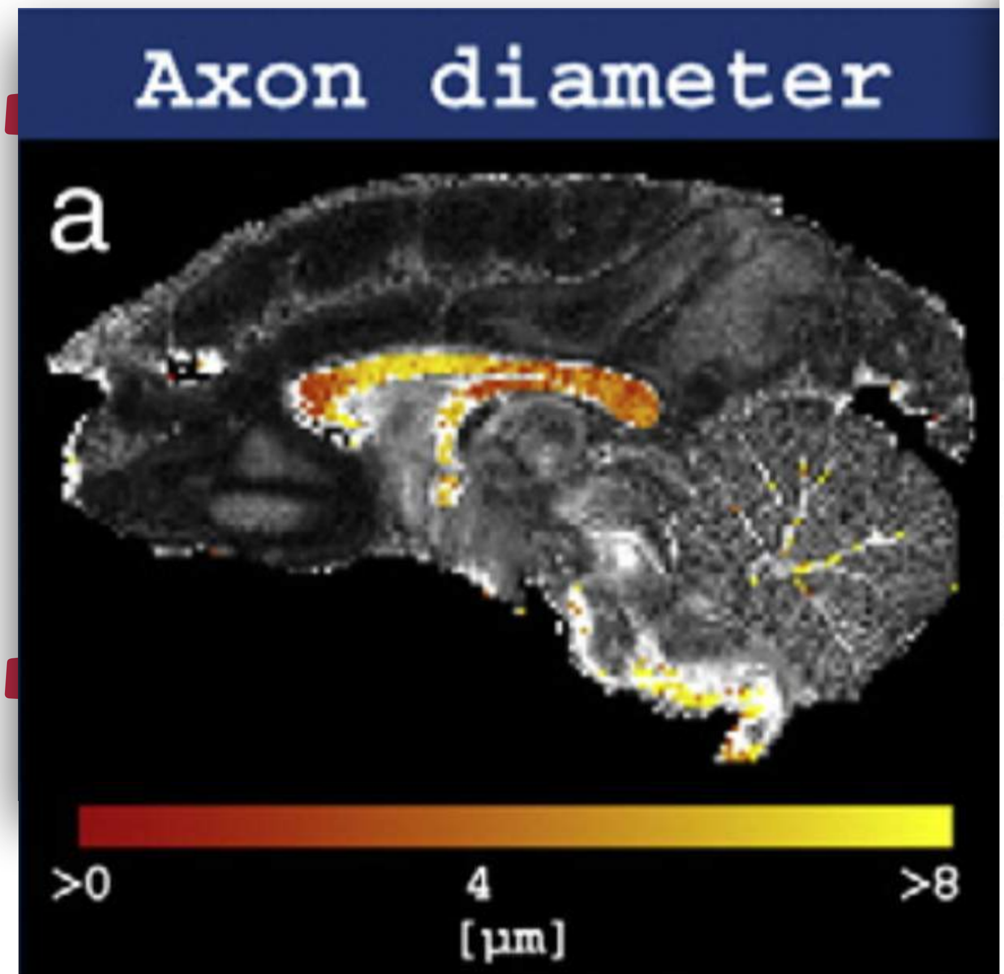

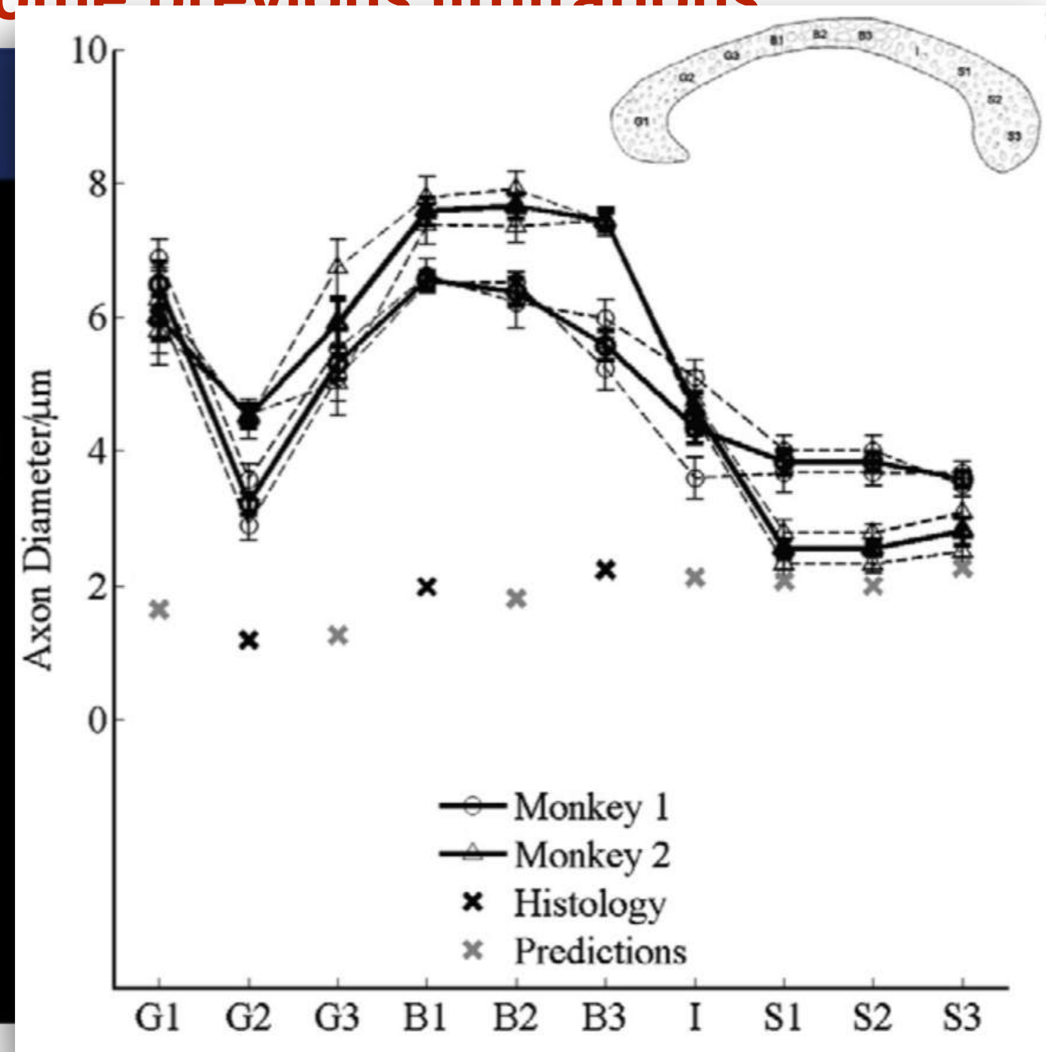

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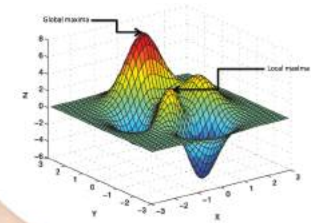
  - α' <u>is not</u> the actual axon diameter, but **correlates with histologic estimates**

The AMICO framework (1/2)

- **Acronym**: Accelerated Microstructure Imaging via Convex Optimization (**AMICO**)

- Common **limitation of previous techniques**: reconstruction uses *nonlinear optimization*
  - Algorithms can be trapped in the **many local minima**
  - **Computationally very expensive**
    e.g. fit NODDI to one brain ≈65 hours

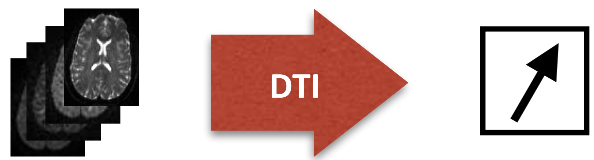


- **Idea**: *accelerate the fit* of previous multi-compartment models by splitting the reconstruction into *two simpler sub-problems*:
  - Estimation of the intra-voxel **fiber geometry**
    i.e. number and orientation of fiber populations
  - Estimation of their **microstructure properties**
    e.g. axon diameter and density

NB: each sub-problem can be **solved independently** and using very efficiently **linear algorithms**

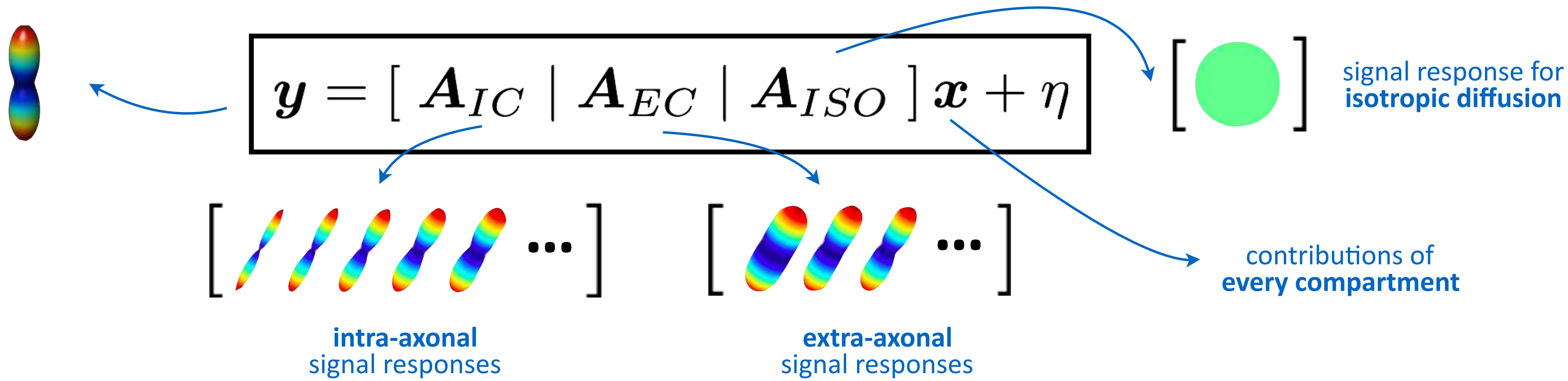
Two-step procedure *(Daducci et al., 2015)*

(1) Identify the **main diffusion direction** in every voxel with *classical algorithms*



(2) Construct a dictionary **along this fixed direction** by varying the signal responses to model **different possible micro-environments** in the voxel

$$y = [\, A_{IC} \mid A_{EC} \mid A_{ISO} \,]\, x + \eta$$

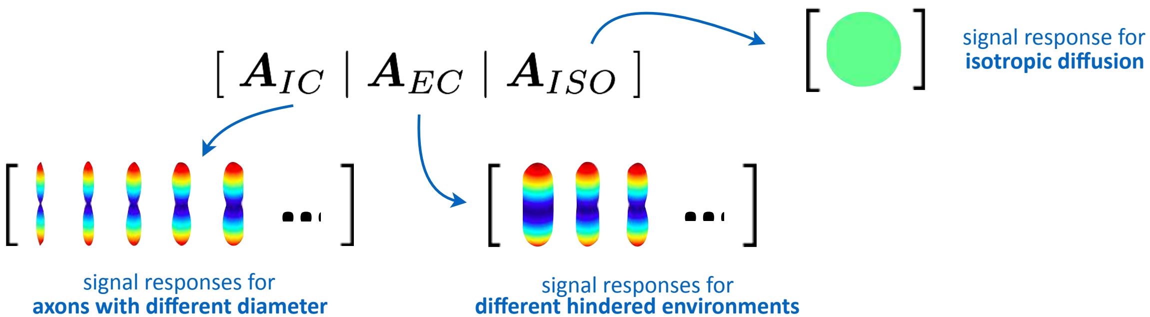


GOAL: find the *contributions of each compartment, x,* (inverse problem) using **convex optimization**

$$\underset{x \geq 0}{\operatorname{argmin}} \underbrace{\frac{1}{2}\|\Phi x - y\|_2^2}_{\text{data fitness}} + \lambda \underbrace{\Psi(x)}_{\text{regularization}}$$

Construction of the **dictionary**

- $\mathbf{A}_{\text{IC}}$ explicitly models *axons with different radii*
- $\mathbf{A}_{\text{EC}}$ explicitly models *distinct environments between the axons* (e.g. packing)
- $\mathbf{A}_{\text{ISO}}$ accounts for *isotropic contributions*



Regularization

- We *tested* several forms of regularization (sparsity, group sparsity etc)
- The most common (***Tikhonov***) was enough to *improve condition number* of $\mathbf{A}$

Formulation

data fit — regularization

$$\underset{\mathbf{x}\geq 0}{\operatorname{argmin}} \frac{1}{2}||\mathbf{A}\mathbf{x}-\mathbf{y}||_2^2 + \frac{\lambda}{2}||\mathbf{x}||_2^2$$

Computation of **microstructure indices**

- Let's partition $\mathbf{x} = [\ \mathbf{x}^{\mathrm{r}} \mid \mathbf{x}^{\mathrm{h}} \mid \mathbf{x}^{\mathrm{i}}\ ]$ into the corresponding compartments
  (r=*restricted*, h=*hindered*, i=*isotropic*)
- Let $N_{\mathrm{r}}, N_{\mathrm{h}}, N_{\mathrm{i}}$ be the number of atoms in $\mathbf{A}_{\mathrm{IC}}, \mathbf{A}_{\mathrm{EC}}, \mathbf{A}_{\mathrm{ISO}}$
- Let R_j be the radius of the axons corresponding to the j^{th} atom in $\mathbf{A}_{\mathrm{IC}}$

intra-axonal volume fraction

$$\nu' = \frac{\sum_{j=1}^{N_r} \mathbf{x}_j^{\mathrm{r}}}{\sum_{j=1}^{N_r} \mathbf{x}_j^{\mathrm{r}} + \sum_{j=1}^{N_h} \mathbf{x}_j^{\mathrm{h}}}$$

mean axonal diameter

$$a' = \frac{\sum_{j=1}^{N_r} 2R_j \mathbf{x}_j^{\mathrm{r}}}{\sum_{j=1}^{N_r} \mathbf{x}_j^{\mathrm{r}}}$$

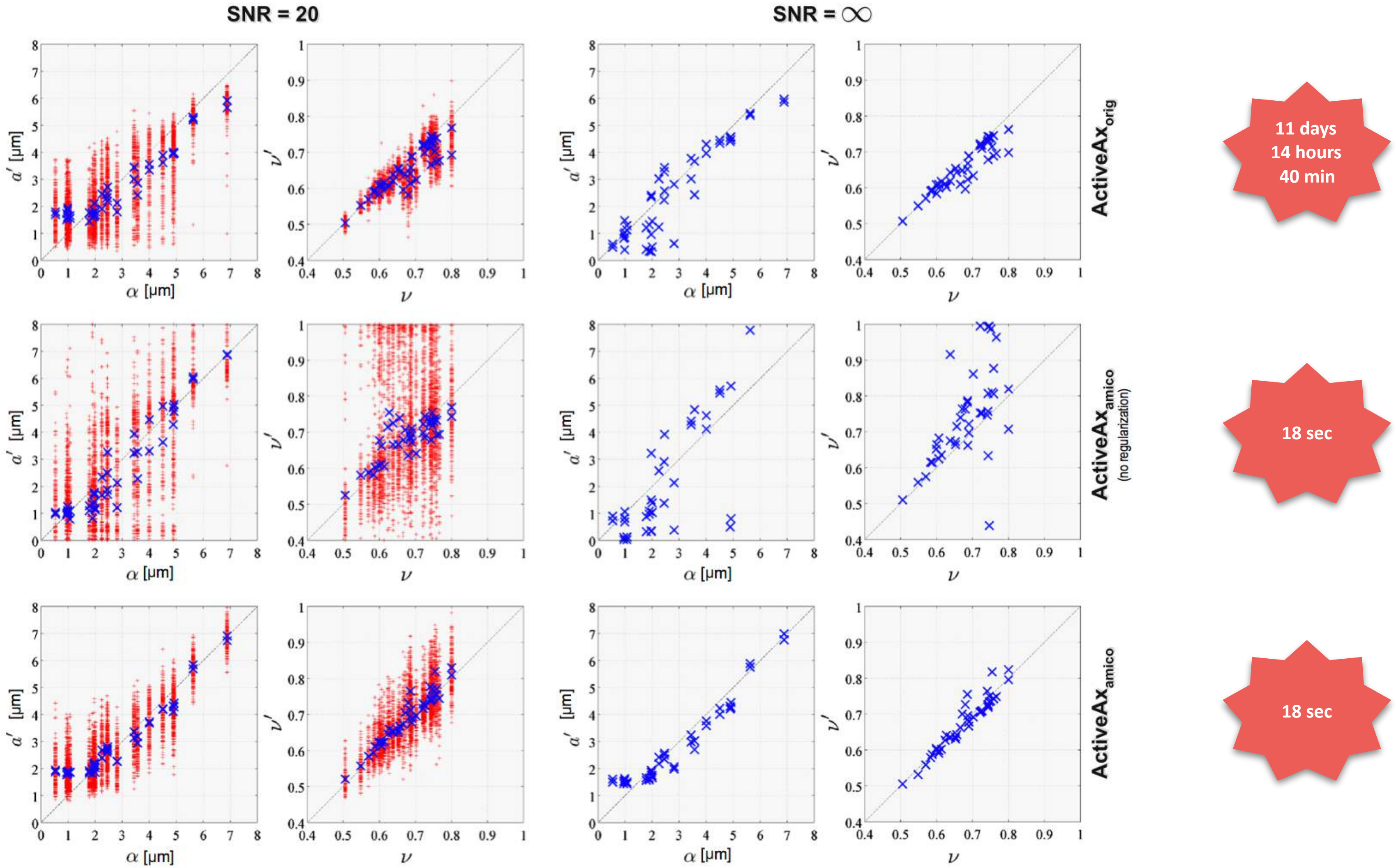
axonal density

$$\rho' = \frac{4\nu'}{\pi a'^2}$$

Example: linearization of ActiveAx (3/4)

Comparison to original implementation

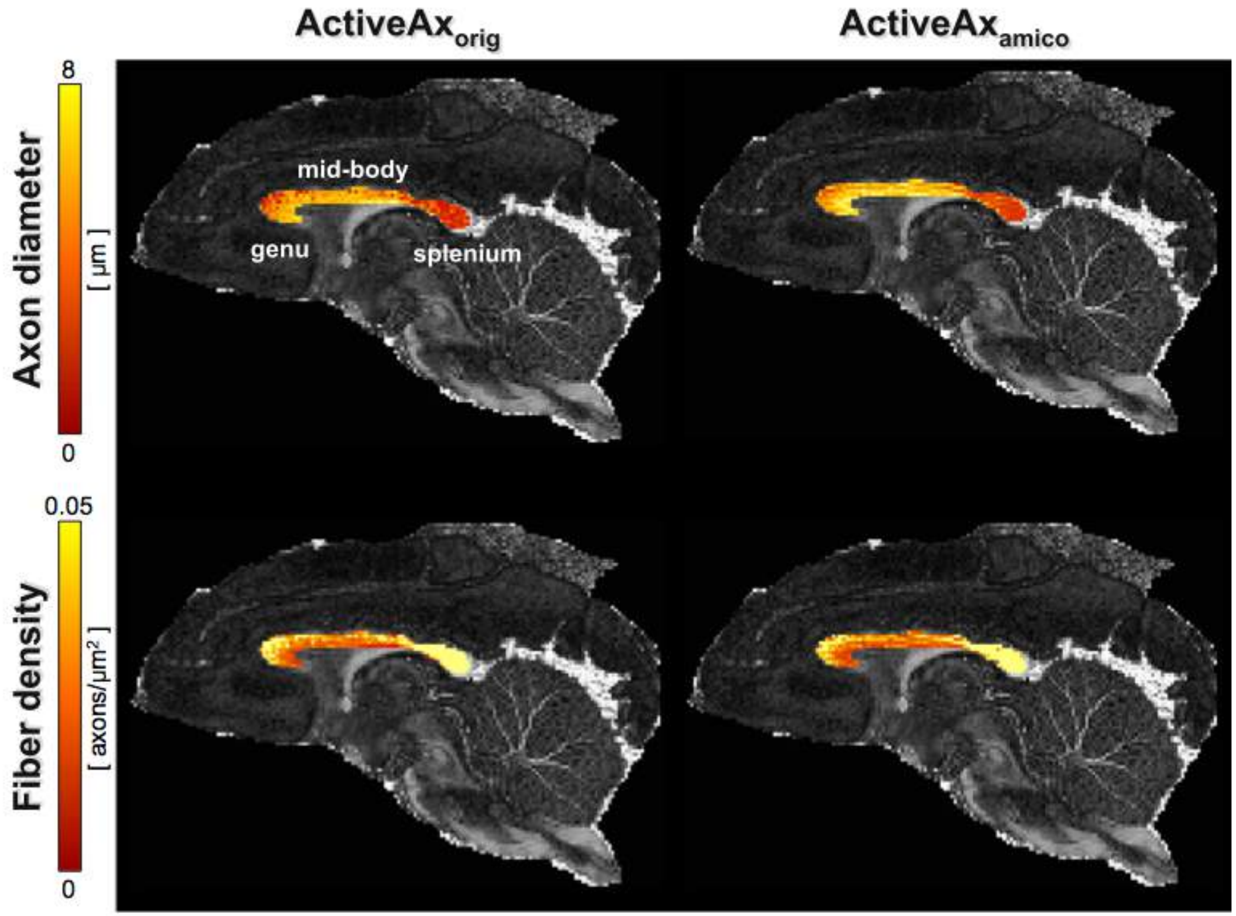
- 44 different substrates used in *(Alexander et al, 2010)*



Example: linearization of ActiveAx

Comparison to original implementation

- Fixed monkey brain, G_{max} = 140 mT/m



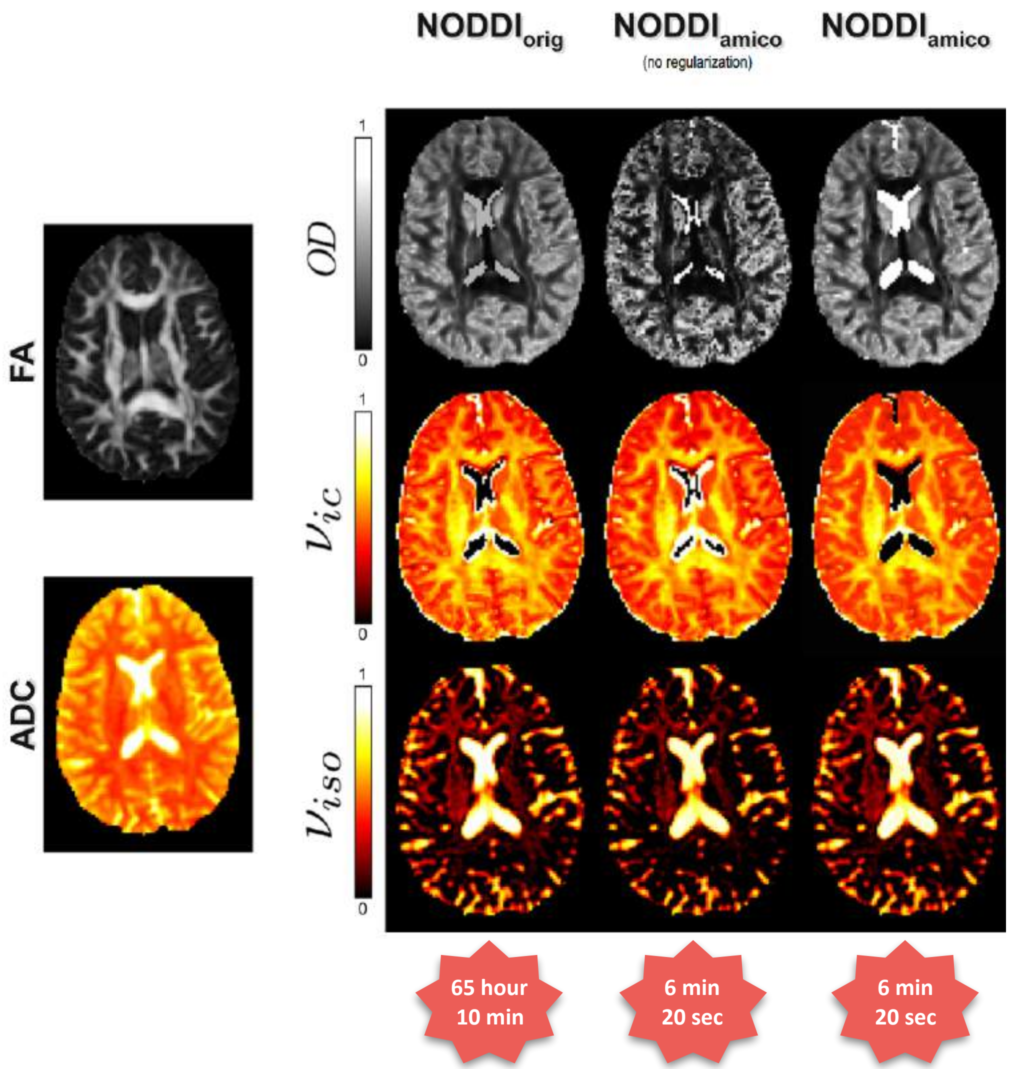
4 hour 30 min

0.3 sec

Example: linearization of NODDI (similar formulation)

Comparison to original implementation

- Human brain, 2 shells (b=700 and b=2000 s/mm^2), G_{max} = 40 mT/m



Questions?

Comments?

Suggestions?