A generalized SMT-based framework for Diffusion MRI microstructural model estimation

Gloria Menegaz[1], Mauro Zucchelli[1]

Maxime Descoteaux[2]

[1]University of Verona, Italy

[2]Universite de Sherbrooke, Canada

UNIVERSITÉ DE SHERBROOKE

Local models of the diffusion signal

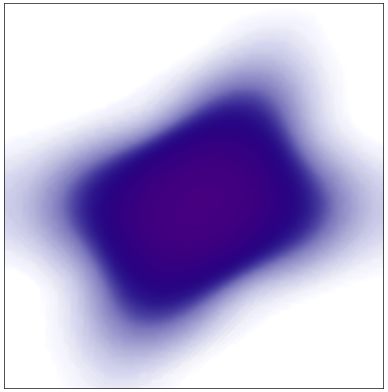
Signal models

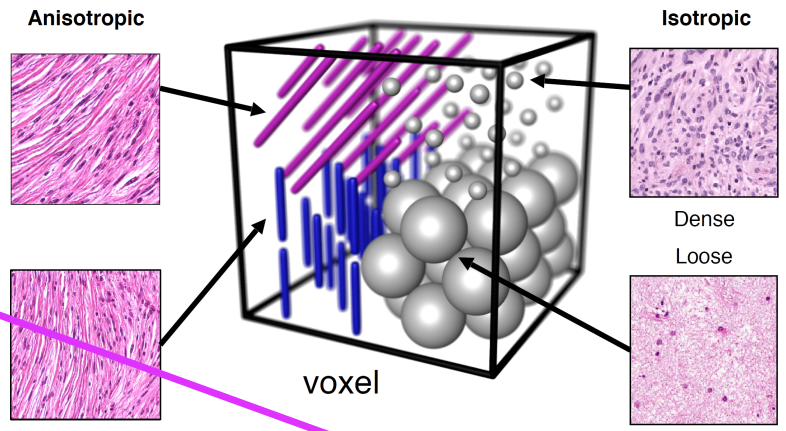
Compartmental models

$$E(\mathbf{q}) = \sum_{n=0}^{N} c_n \Phi_n(q\mathbf{u})$$

$$P(\mathbf{r}) = \int_{\mathbf{q}\in\mathbb{R}^3} E(\mathbf{q}) e^{2\pi i \mathbf{q}\cdot\mathbf{r}} d\mathbf{q}$$

Ensemble Average Propagator (EAP)





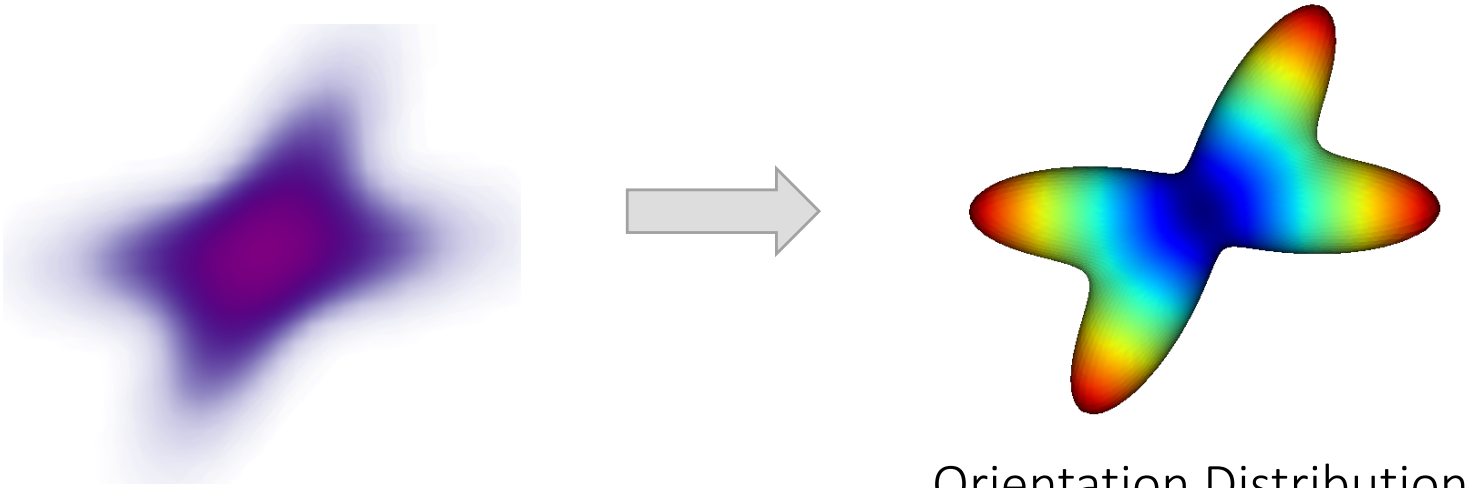
$$E(\mathbf{q}) = \sum_{\mathbf{n}=\mathbf{0}}^{\mathbf{N}} \nu_{\mathbf{n}} \mathbf{F}_{\mathbf{n}}(\mathbf{q})$$

Nilsson, Winter School in Brain Connectomics, Verona, 2017

Signal models

- The signal (and the EAP) shape depend on the underlying microstructural features
- Numerical indices expressing the microstructure can be derived
- Tensor-based (DTI, multi-tensor), MAPMRI[1] …

EAP **ODF**

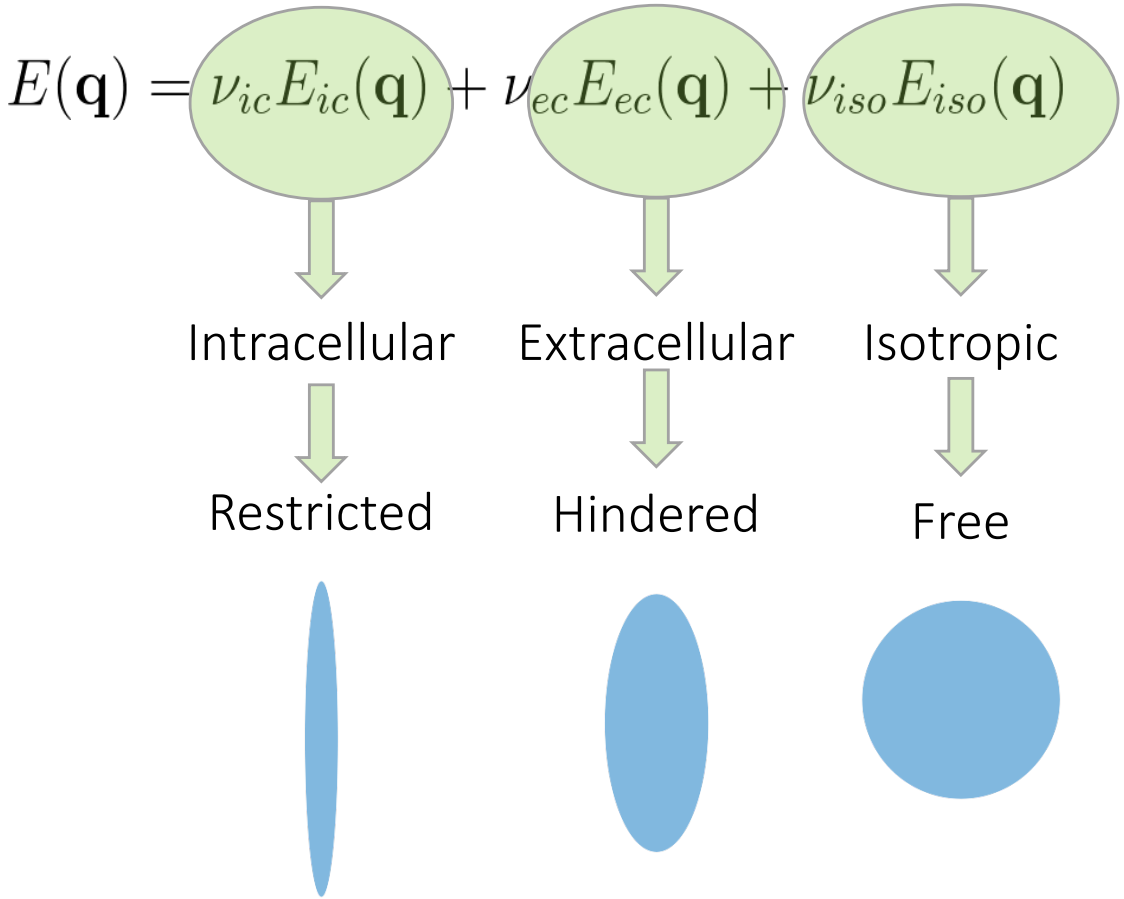


Orientation Distribution Function

[1]Ozarslan et al, *Mean Apparent Propagator (MAP) MRI: A novel Diffusion Imaging Method for Mapping Tissue Microstructure*. NeuroImage 2013

Compartmental models

- Compartmental models represents the signal as a weighted sum of signal components relying on pre-defined biophysical models:



Compartimental models for Diffusion MRI

- Recent years have seen a proliferation of Multi-Compartment (MC) models developed to estimate the brain tissue microstructure from DW-MRI signal
- Each of these models represent the diffusion signal as a weighted sum of some contributions that can be represented by parametric functions (e.g. a 3D Gaussian)
- In order to reduce the number parameters, these models make several assumptions on the physical properties of the diffusion in the brain tissues

The *Standard* Model

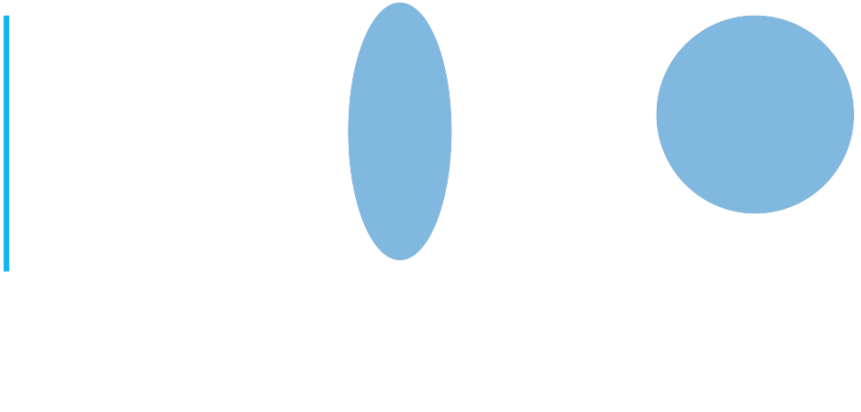
- Global model: multi-compartment model[2], here called *Standard Model* (SM)

$$F(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) = \nu_{ia} F_{ia}(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) + \nu_{ea} F_{ea}(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) + \nu_{csf} F_{csf}(b)$$

stick

Axially symmetric tensor

Isotropic tensor



$\vec{\mathbf{u}}$ is the gradient direction

$\vec{\mathbf{v}}$ is the fiber direction

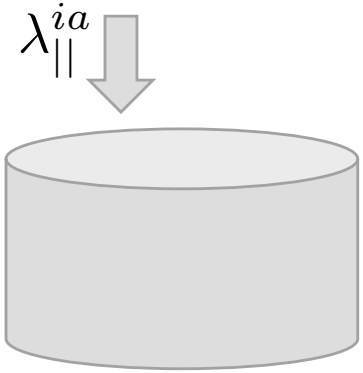
$\nu_{ia} + \nu_{ea} + \nu_{csf} = 1$

[2] Novikov et al (2016). *Quantifying brain microstructure with diffusion MRI: Theory and parameter estimation*. arXiv preprint arXiv:1612.02059.

The Standard Model: intra-axonal compartment

- The intra-axonal model is a simple stick

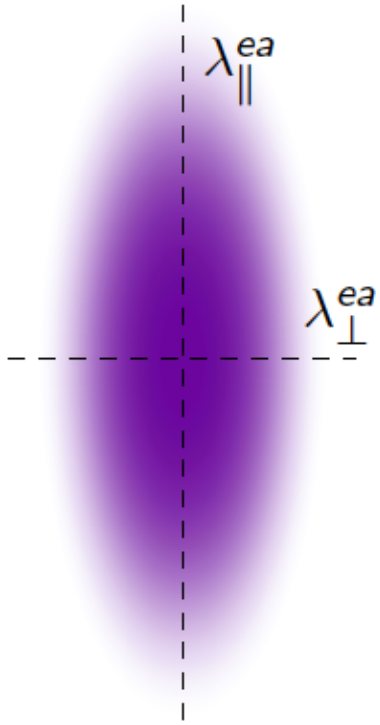
- A stick is a cylinder with radius=0
- The only parameter of the stick is the parallel diffusivity $\lambda_{||}^{ia}$



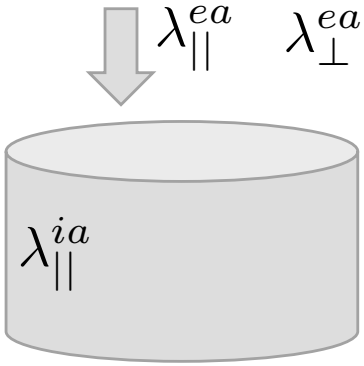
Parameters pool

The Standard Model: extra-axonal compartment

In the SM the extra-axonal contribution of the signal F_{ea} is modeled using an axially symmetric Gaussian

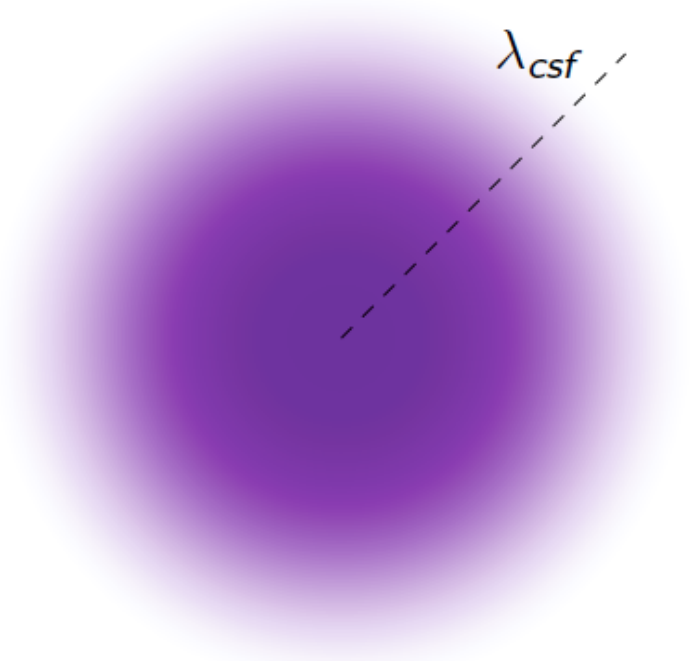


- $\lambda_{\parallel}^{ea}$ is the *extra-cellular* parallel diffusivity
- $\lambda_{\perp}^{ea}$ is the *extra-cellular* perpendicular diffusivity

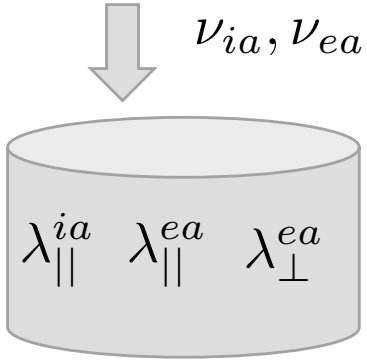


The Standard Model: Fcsf

• In the SM the Cerebrospinal Fluid (CSF) compartment F_{csf} is modeled using an isotropic Gaussian



- λ_{csf} is the free diffusivity
- In-vivo $\lambda_{csf} = 3 \cdot 10^{-3}$ mm^2/s



The Spherical Harmonics representation of the fODF

- This MC representation of the diffusion signal is appropriate only for a single principal diffusion direction
- The general case can be recovered by convolving the single fiber signal to the fiber Orientation Distribution Function (fODF)

$$E(b,\vec{\mathbf{u}}) = \int_{\vec{\mathbf{v}}\in\mathcal{S}^2} \rho(\vec{\mathbf{v}})F(b,\vec{\mathbf{u}},\vec{\mathbf{v}})d\vec{\mathbf{v}} \qquad (2)$$

$$\rho(\vec{\mathbf{v}}) = \sum_{l=0,even}^{\infty}\sum_{m=-l}^{l} c_{lm}Y_l^m(\vec{\mathbf{v}}) \qquad (3)$$

- With $Y_l^m(\vec{\mathbf{v}})$ are the real Spherical Harmonics (SH) functions

The MC signal model

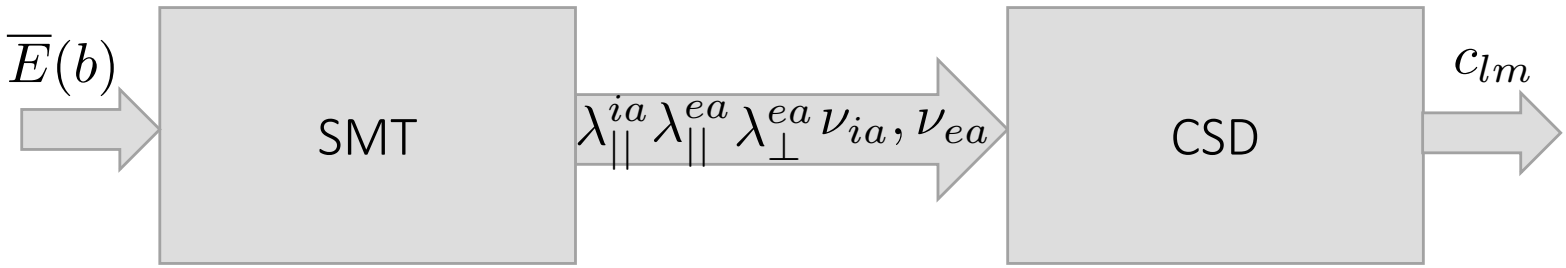
- Solving the integral of Eq. (2) lead us to the complete SM signal approximation
- Ψ_l are functions as in[5]

$$E(b,\vec{\mathbf{u}}) = c_{00}\sqrt{4\pi}\nu_{csf}\exp\left(-b\ \lambda_{csf}\right) + \sum_{l=0,even}^{N}\sum_{m=-l}^{l} c_{lm}2\pi\Big[\nu_{ia}\Psi_l(b\lambda_{\parallel}^{ia}) + \\ + \nu_{ea}\exp\left(-b\lambda_{\perp}^{ea}\right)\Psi_l(b(\lambda_{\parallel}^{ea}-\lambda_{\perp}^{ea}))\Big]Y_l^m(\vec{\mathbf{u}})$$

[5]Jespersen et al, Modeling dendrite density from magnetic resonance diffusion measurements, Neuroimage 2007

Model fitting

- The SM response function has 5 parameters: $\lambda_{||}^{ia}, \lambda_{||}^{ea}, \lambda_{\perp}^{ea}, \nu_{ia}, \nu_{ea}$
- Method: split the estimation of the microstructural parameters from that of the SH coefficients exploiting the Spherical Mean Technique (SMT)[2]
- Given such parameters the SH coefficients c_{lm} can be obtained using the Constrained Spherical Deconvolution (CSD) algorithm



[2]Kaden, E., Kelm, N. D., Carson, R. P., Does, M. D., and Alexander, D. C. (2016). *Multi-compartment microscopic diffusion imaging.* NeuroImage, 139, 346-359.

The Spherical Mean Technique

- Mean signal as a function of *b*

$$\overline{E}(b) = \nu_{csf} \exp\left(-b\lambda_{csf}\right) + \frac{1}{2}\left[\nu_{ia}\Psi_0(b\lambda_{\parallel}^{ia}) + \right.$$
$$\left. + \nu_{ea} \exp\left(-b\lambda_{\perp}^{ea}\right)\Psi_0(b(\lambda_{\parallel}^{ea} - \lambda_{\perp}^{ea}))\right]$$

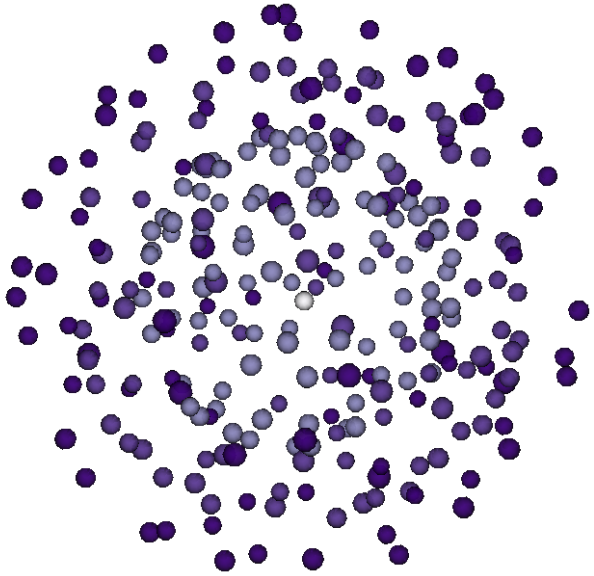
- Using a sufficient number of b-values the model parameters can be estimated from $\overline{E}(b)$

$$q = \frac{\gamma\delta G}{2\pi}$$

$$\tau = \Delta - \delta/3$$

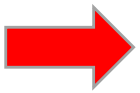
$$b = 4\pi^2\tau q^2$$

$$b = (\Delta - \delta/3)\gamma^2 G^2 \delta^2$$

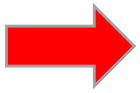


The Spherical Mean Technique: issues

- Constraint: in order to fit 5 parameters using the SMT we need a dataset with at least 5 different *b-values* (shell)
- For each shell a *sufficient* number of directions is needed to estimate the signal mean accurately
- Most of the DW-MRI data do not possess enough samples to use the SMT to estimate the SM parameters



Simplify the model by reducing the number of parameters

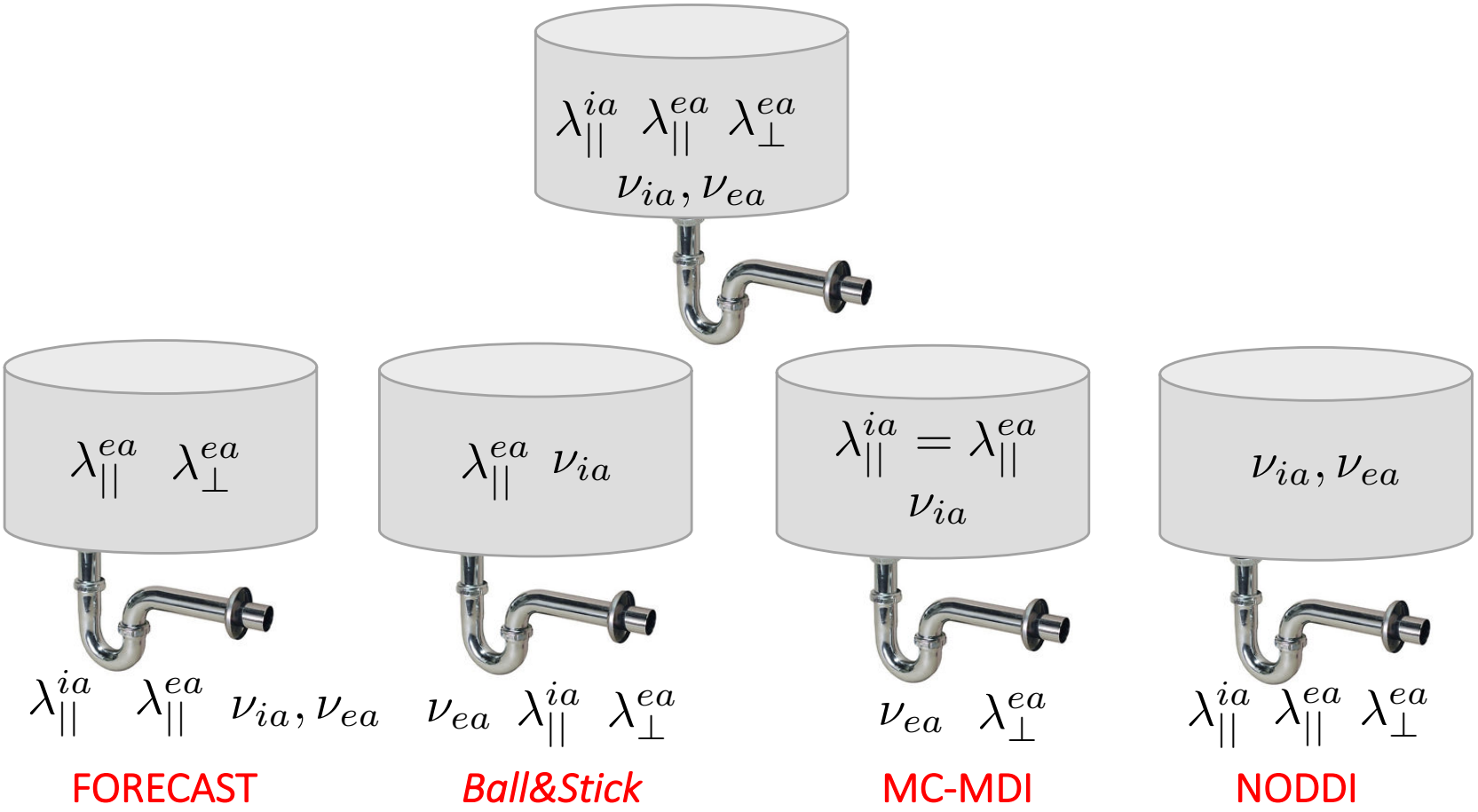


Implies prior assumptions

Two-parameters models

- SM for single dominant direction

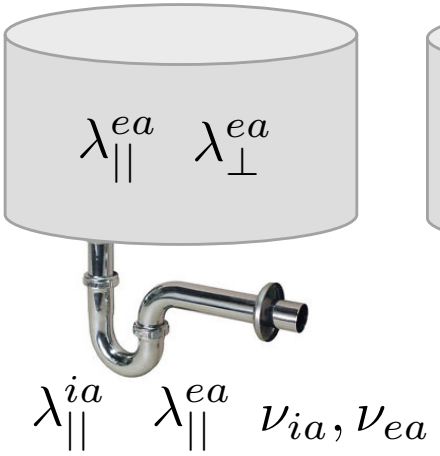
$$F(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) = \nu_{ia}F_{ia}(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) + \nu_{ea}F_{ea}(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) + \nu_{csf}F_{csf}(b)$$



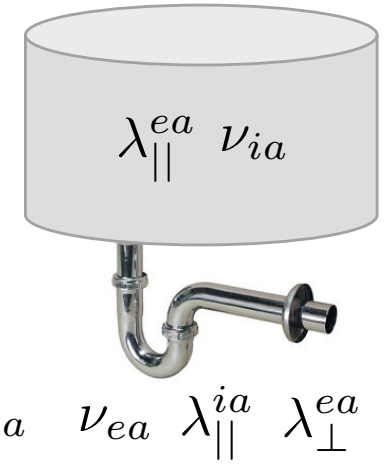
Two-parameters models

- SM for single dominant direction

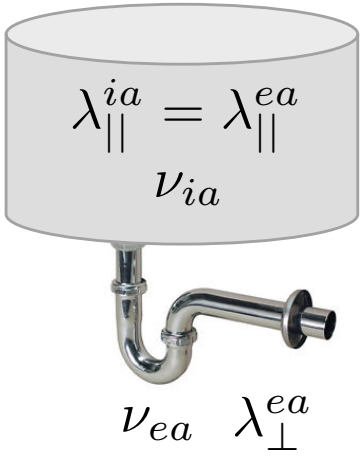
$$F(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) = \nu_{ia}F_{ia}(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) + \nu_{ea}F_{ea}(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) + \nu_{csf}F_{csf}(b)$$



FORECAST



Ball&Stick



MC-MDI

NODDI

BS-SH

- Ball&Stick (BS)[3]

$$F(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) = \nu_{ia}F_{ia}(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) + \nu_{ea}F_{ea}(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) + \nu_{csf}F_{csf}(b)$$

$$\lambda_{\parallel}^{ia} = 1.7 \cdot 10^{-3} mm^2/s$$
$$\lambda_{\parallel}^{ea} = \lambda_{\perp}^{ea}$$

- We call the SH-based formulation of this model BS-SH

[3] Behrens et al (2003). *Characterization and propagation of uncertainty in diffusionweighted MR imaging.* Magnetic resonance in medicine, 50(5), 1077-1088.

FORECAST

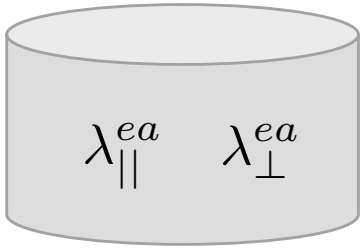
- Fiber ORientation Estimated using Continuous Axially Symmetric Tensors (FORECAST)[4] model
- Single compartment: axially symmetric tensor

$$F(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) = F(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) = \nu_{ia}F_{ia}(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) + \nu_{ea}F_{ea}(b,\vec{\mathbf{u}},\vec{\mathbf{v}}) + \nu_{csf}F_{csf}(b)$$

- Two parameters

$$\lambda_{\|}^{ea}, \lambda_{\perp}^{ea}$$

$$\lambda_{\|}^{ea} \geq \lambda_{\perp}^{ea}$$



[4] Anderson, A. W. (2005). *Measurement of fiber orientation distributions using high angular resolution diffusion imaging.* Magnetic Resonance in Medicine, 54(5), 1194-1206.

NODDI-SH

- Neurite Orientation Dispersion and Density Imaging (NODDI)[5] model
- Three compartments
- We call the SH-based formulation of this model NODDI-SH

$$F(b, \vec{\mathbf{u}}, \vec{\mathbf{v}}) = \nu_{ia} F_{ia}(b, \vec{\mathbf{u}}, \vec{\mathbf{v}}) + \nu_{ea} F_{ea}(b, \vec{\mathbf{u}}, \vec{\mathbf{v}}) + \nu_{csf} F_{csf}(b)$$

$$\lambda_{\parallel}^{ia} = \lambda_{\parallel}^{ea} = 1.7 \cdot 10^{-3} \text{ mm}^2/\text{s}$$

$$\lambda_{\perp}^{ea} = \lambda_{\parallel}^{ea} \frac{\nu_{ea}}{\nu_{ia} + \nu_{ea}}$$

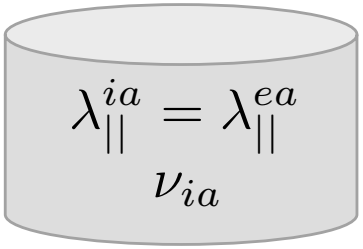
[5] Zhang, H., Schneider, T., Wheeler-Kingshott, C. A., and Alexander, D. C. (2012). *NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain.* Neuroimage, 61(4), 1000-1016.

MC-MDI

- Multi-Compartment Microscopic Diffusion Imaging (MC-MDI)[6] model
- Two compartments

$$F(b, \vec{\mathbf{u}}, \vec{\mathbf{v}}) = \nu_{ia} F_{ia}(b, \vec{\mathbf{u}}, \vec{\mathbf{v}}) + \nu_{ea} F_{ea}(b, \vec{\mathbf{u}}, \vec{\mathbf{v}}) + \nu_{csf} F_{csf}(b)$$

$$\lambda_{\parallel}^{ia} = \lambda_{\parallel}^{ea}$$
$$\lambda_{\perp}^{ea} = \lambda_{\parallel}^{ea}(1 - \nu_{ia})$$



[6] Kaden, E., Kelm, N. D., Carson, R. P., Does, M. D., and Alexander, D. C. (2016). *Multi-compartment microscopic diffusion imaging.* NeuroImage, 139, 346-359.

Synthetic dataset

- Parameters space sampling

$$\lambda_{\parallel}^{ia} = [2, 2.2, 2.5] \cdot 10^{-3} mm^2/s$$
$$\lambda_{\parallel}^{ea} = [1, 1.2, 1.5] \cdot 10^{-3} mm^2/s$$
$$\lambda_{\perp}^{ea} = [0.5, 0.7, 0.9] \cdot 10^{-3} mm^2/s$$
$$\nu_{csf} = [0, 0.1, 0.2]$$
$$\nu_{ia} = [0.5, 0.6, 0.7, 0.8, 0.9, 1.0]$$

- The total number of combinations for the SM parameters is 405
- These parameters were also used to generate a ground-truth microstructural representation (**GT-SH**) to be used for benchmarking excluding the contribution of the error in the estimation of the microstructural parameters

Synthetic dataset

Two populations

1000 different crossing angles

Kent distribution to model dispersion

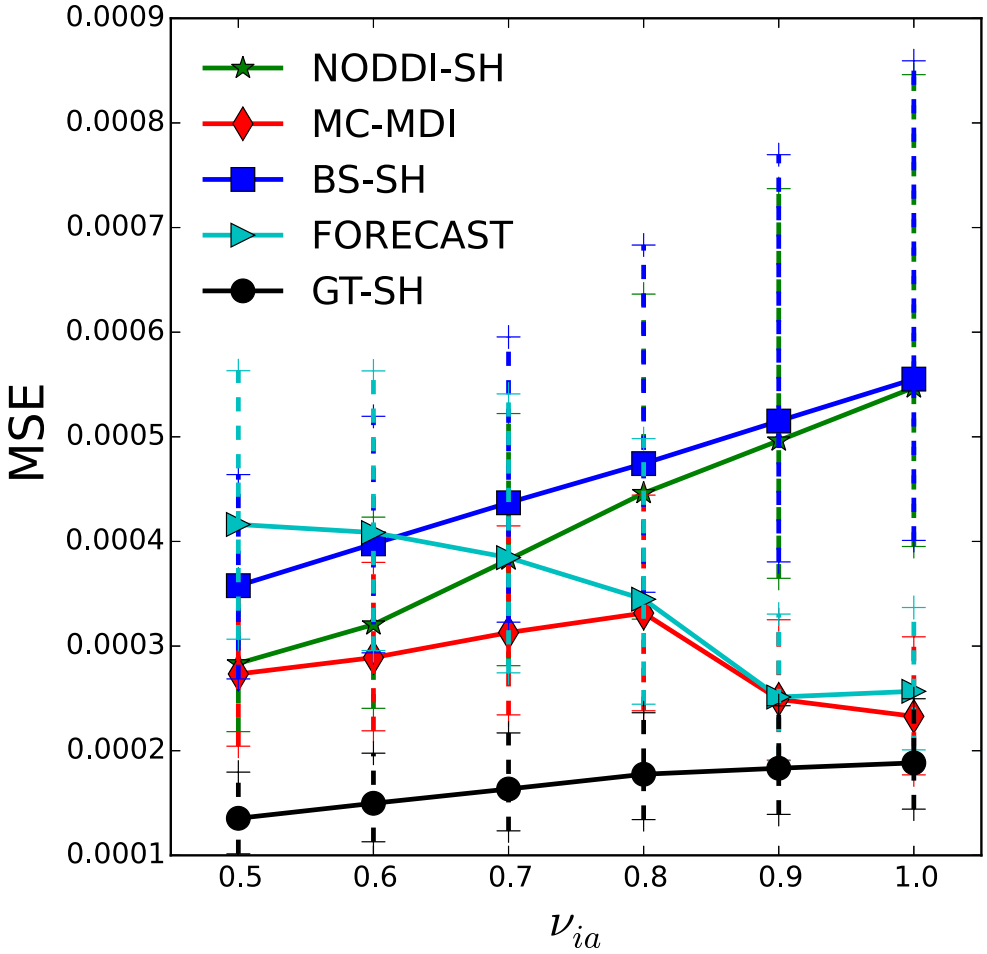
Rician noise with SNR=20

Human Connectome Project sampling scheme:

b=[1000,2000,3000] s/mm2

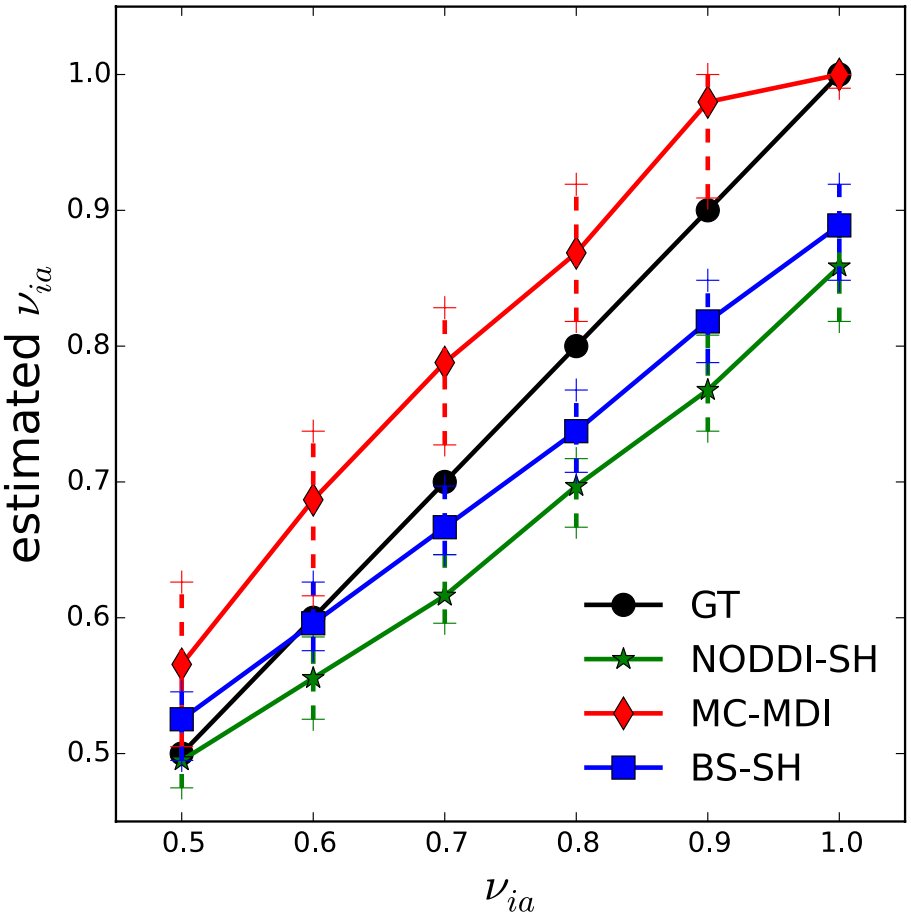
18 b_0 + 90 directions per shell

Mean Square Error (MSE)



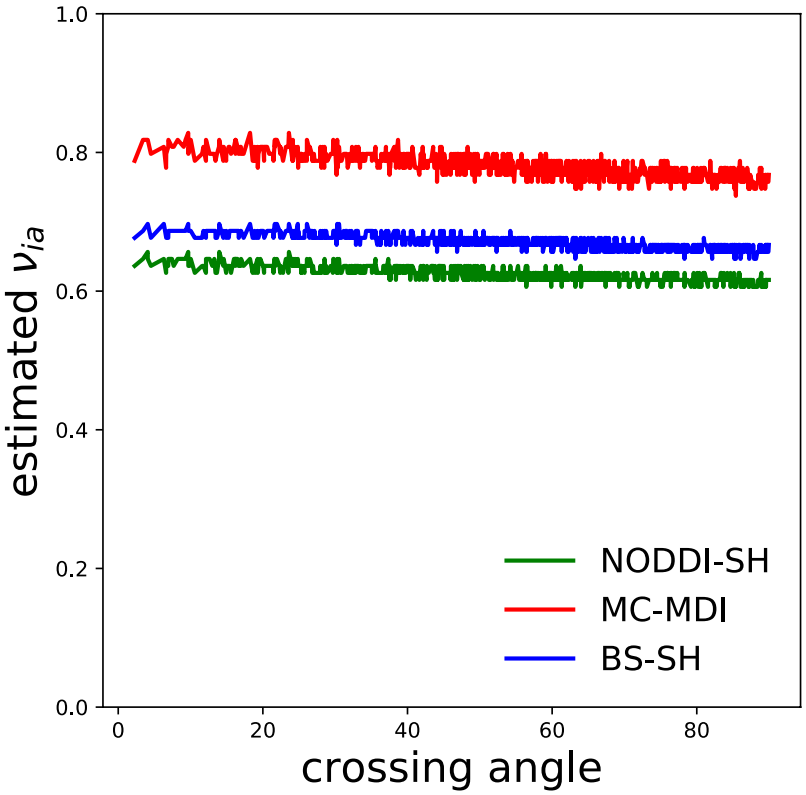
- GT-SH is the MSE theoretical lower bound, where the GT parameters are used for the SH fitting
- MC-MDI is the best model, followed by the FORECAST
- The models for which $\lambda_{||}$ is a free parameter show better performance

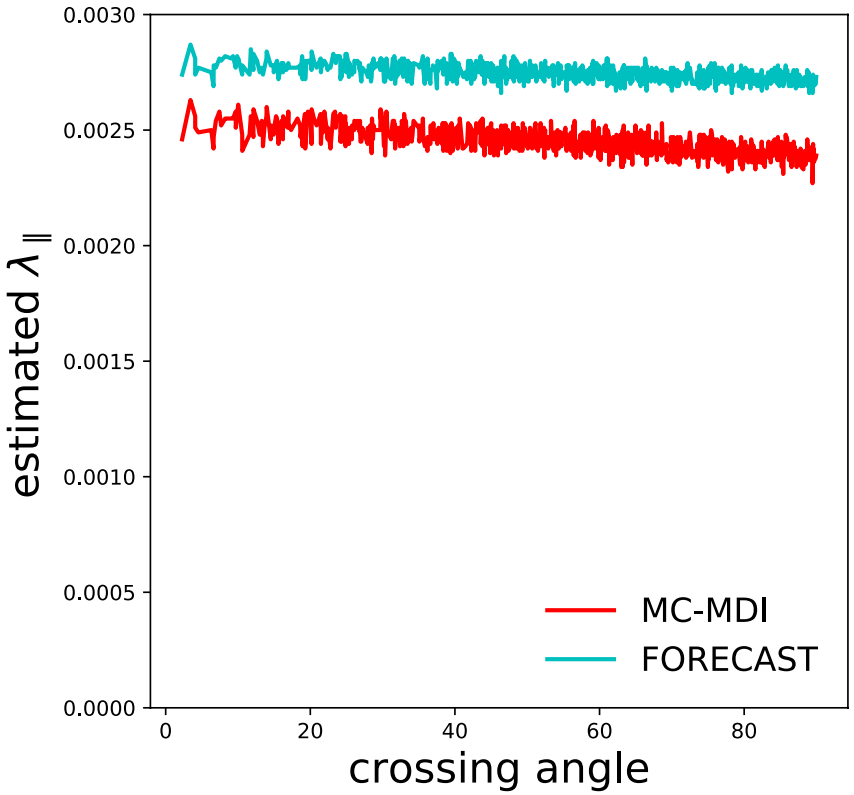
Intra-axonal volume fraction



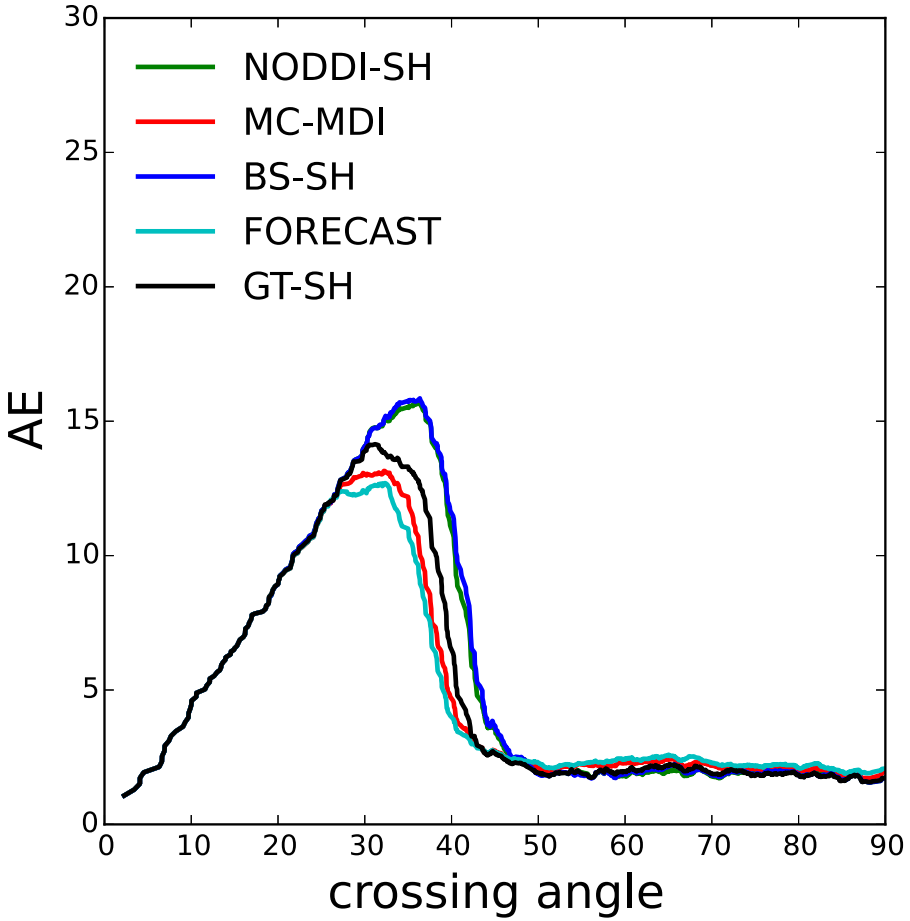
- NODDI-SH and BS-SH tend to underestimate the intra-axonal volume fraction
- MC-MDI tends to overestimate ν_{ia}
- In general MC-MDI trend is more proportional to the Ground Truth (GT) ν_{ia}
- MC-MDI is the only model among the considered with $\lambda_{||}$ as a free parameter

Dependency on the crossing angle



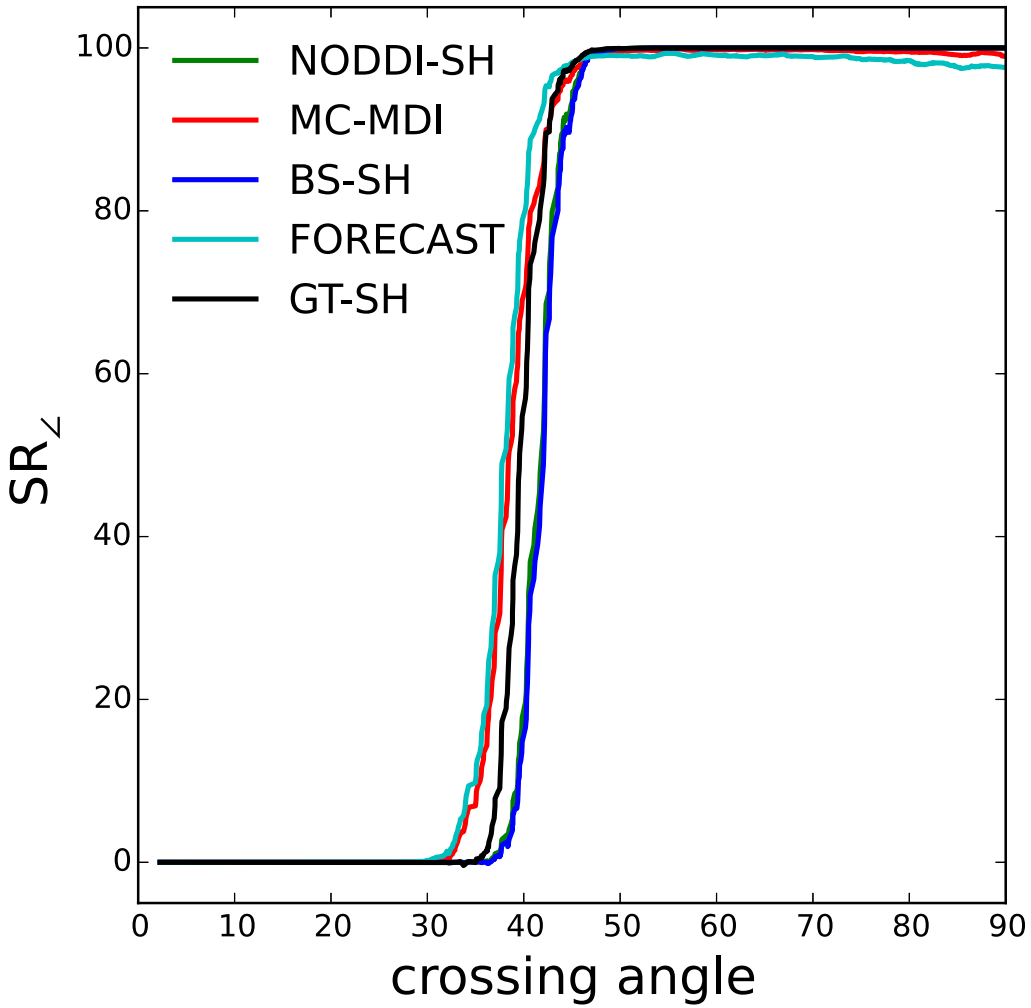


Angular Error (AE)



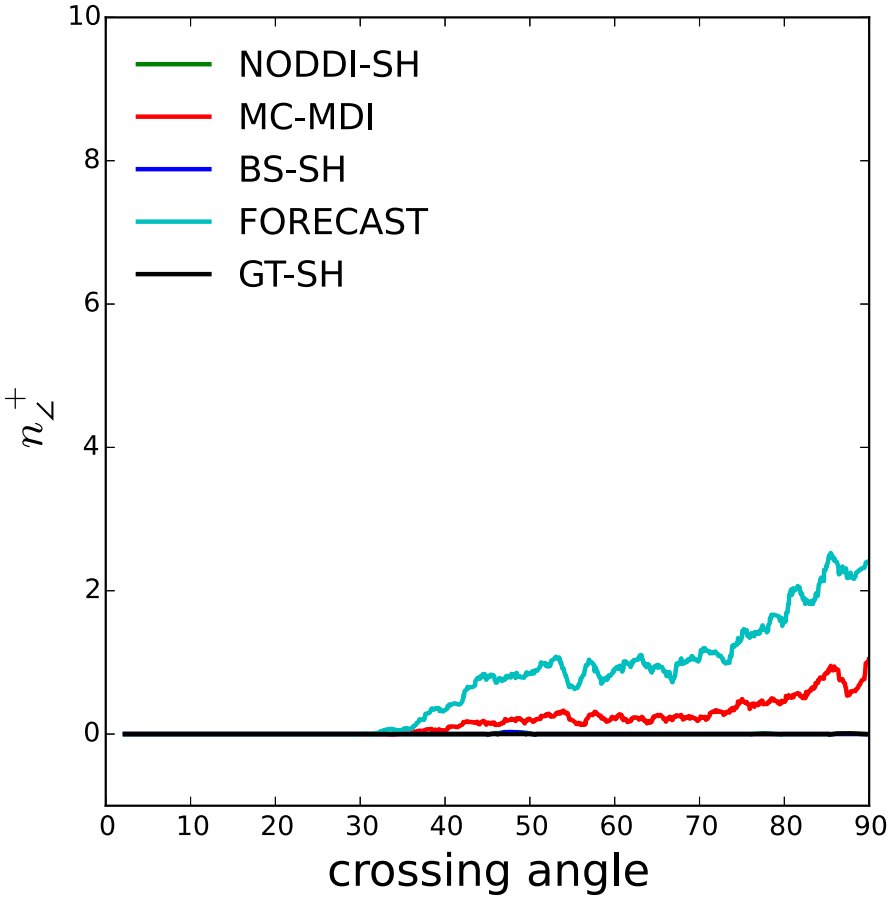
- MC-MDI and FORECAST are the models with an higher angular resolution
- The minimum crossing angle is less than 30 degrees
- For BS-SH and NODDI-SH minimum crossing resolution is ~37 degrees

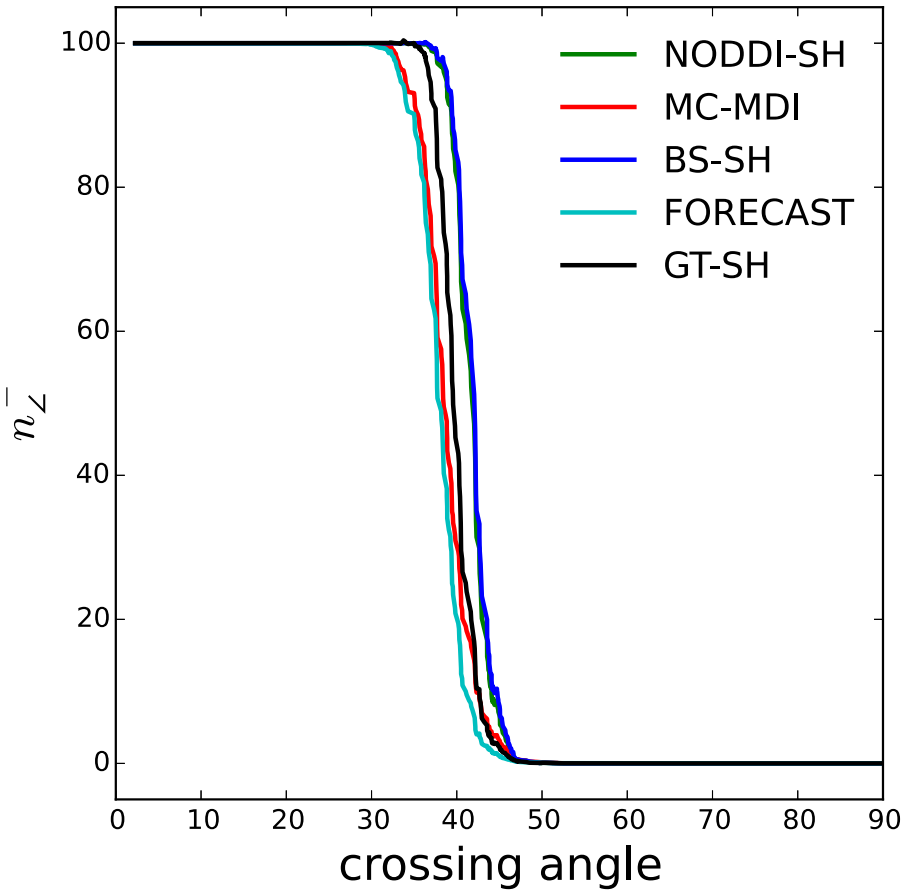
Success Rate (SR)



- The SR indicates the percentage of correctly estimated number of “fibers”
- MC-MDI and FORECAST are the best models at low crossing angles
- But not at 100%
- BS-SH and NODDI-SH appear to be more robust for larger crossing angles

Over Estimation (n^+) and Under Estimation (n^-)





Reminder

MODEL	$\lambda_{\parallel}^{ia}$	$\lambda_{\parallel}^{ea}$	$\lambda_{\perp}^{ea}$	λ_{csf}	ν_{ia}	ν_{ea}	ν_{csf}
FORECAST	-	FREE	FREE*	-	0	1	0
BS-SH	$1.7 \cdot 10^{-3}$	FREE	$\lambda_{\parallel}^{ea}$	-	FREE	1- ν_{ia}	0
MC-MDI	FREE	$\lambda_{\parallel}^{ia}$	$\lambda_{\parallel}^{ia}(1-\nu_{ia})$	-	FREE	1- ν_{ia}	0
NODDI-SH	$1.7 \cdot 10^{-3}$	$\lambda_{\parallel}^{ia}$	$\lambda_{\parallel}^{ia}\frac{\nu_{ea}}{\nu_{ia}+\nu_{ea}})$	$3 \cdot 10^{-3}$	FREE	FREE	$1-\nu_{ia}-\nu_{ea}$

Table 1. Table of free parameters and their relationships for the considered models. All the diffusivities λ are expressed in mm^2/s. * In FORECAST $\lambda_{\parallel}^{ea} \geq \lambda_{\perp}^{ea}$.

$$\lambda_{\parallel}^{ia} = [2, 2.2, 2.5] \cdot 10^{-3} mm^2/s$$

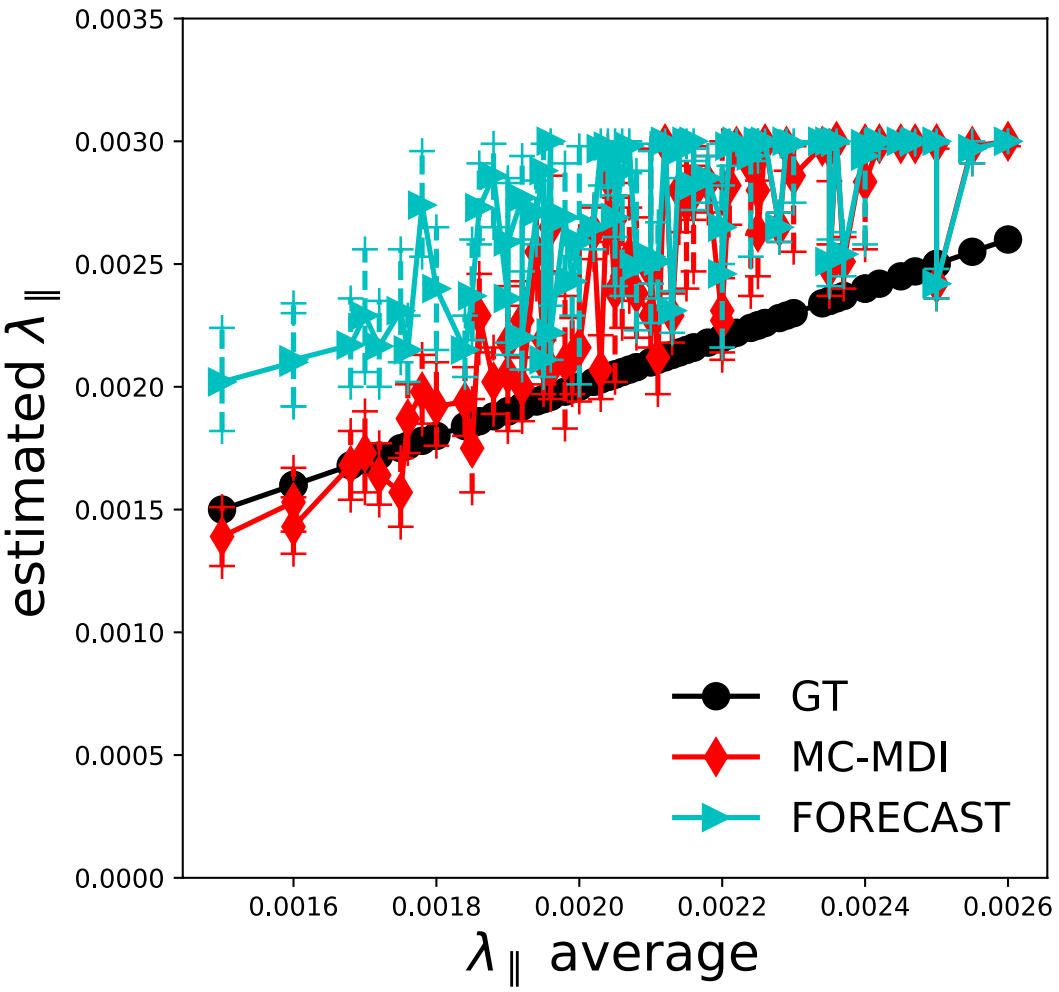
$$\lambda_{\parallel}^{ea} = [1, 1.2, 1.5] \cdot 10^{-3} mm^2/s$$

$$\lambda_{\perp}^{ea} = [0.5, 0.7, 0.9] \cdot 10^{-3} mm^2/s$$

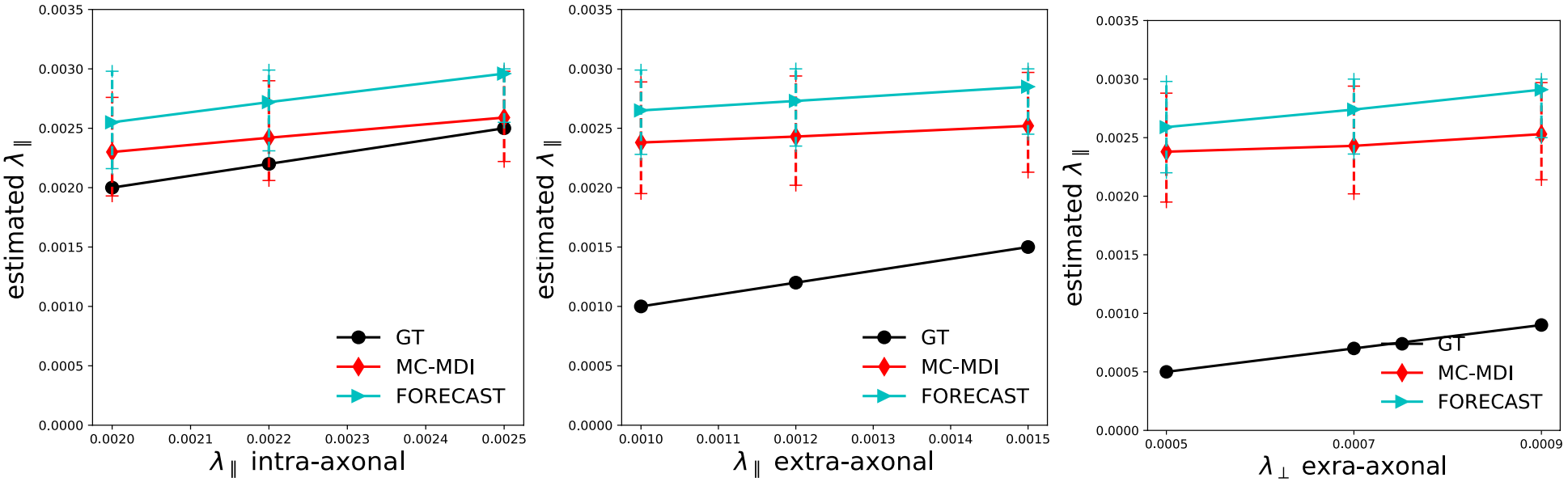
$$\nu_{csf} = [0, 0.1, 0.2]$$

$$\nu_{ia} = [0.5, 0.6, 0.7, 0.8, 0.9, 1.0]$$

Parallel diffusivity

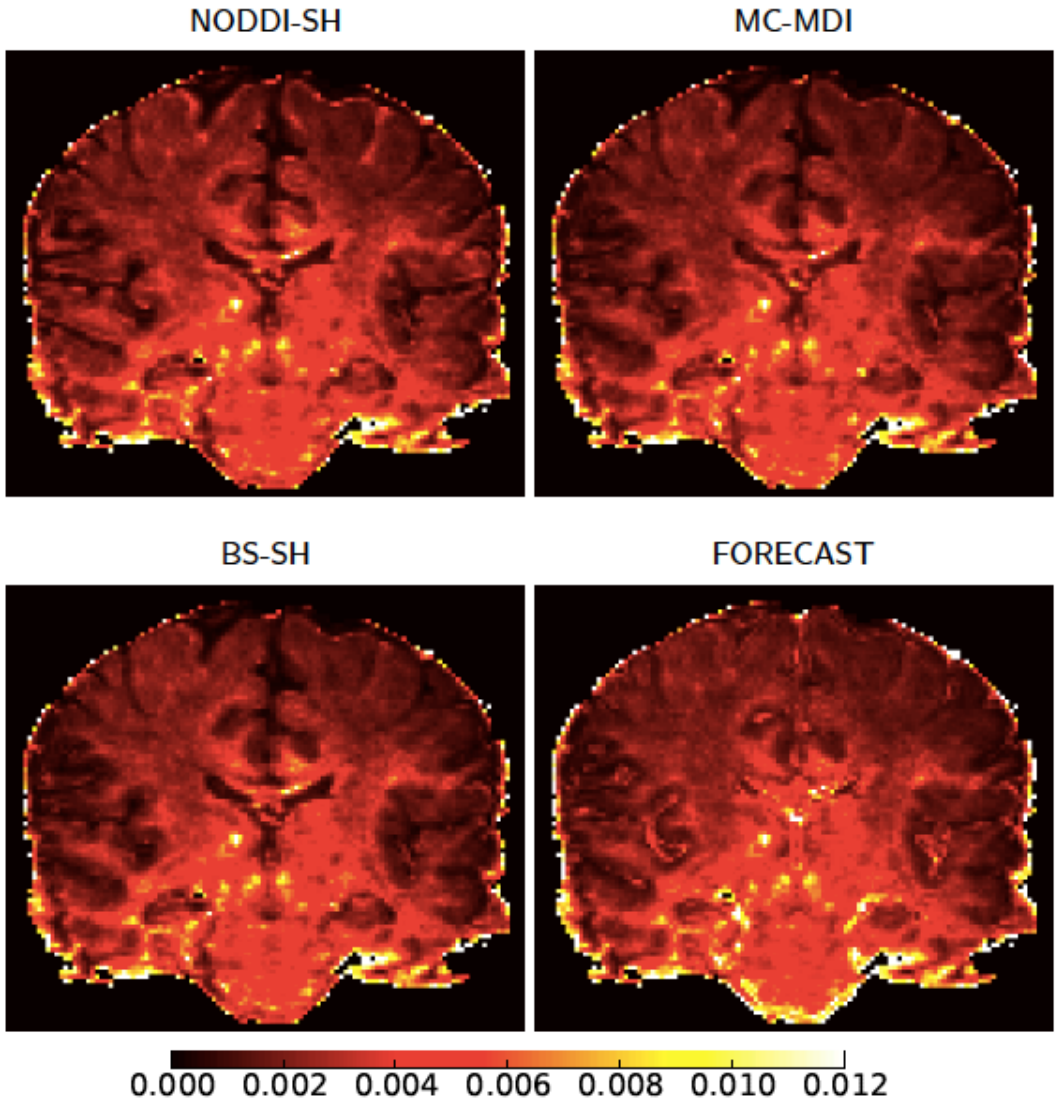


Parallel diffusivity

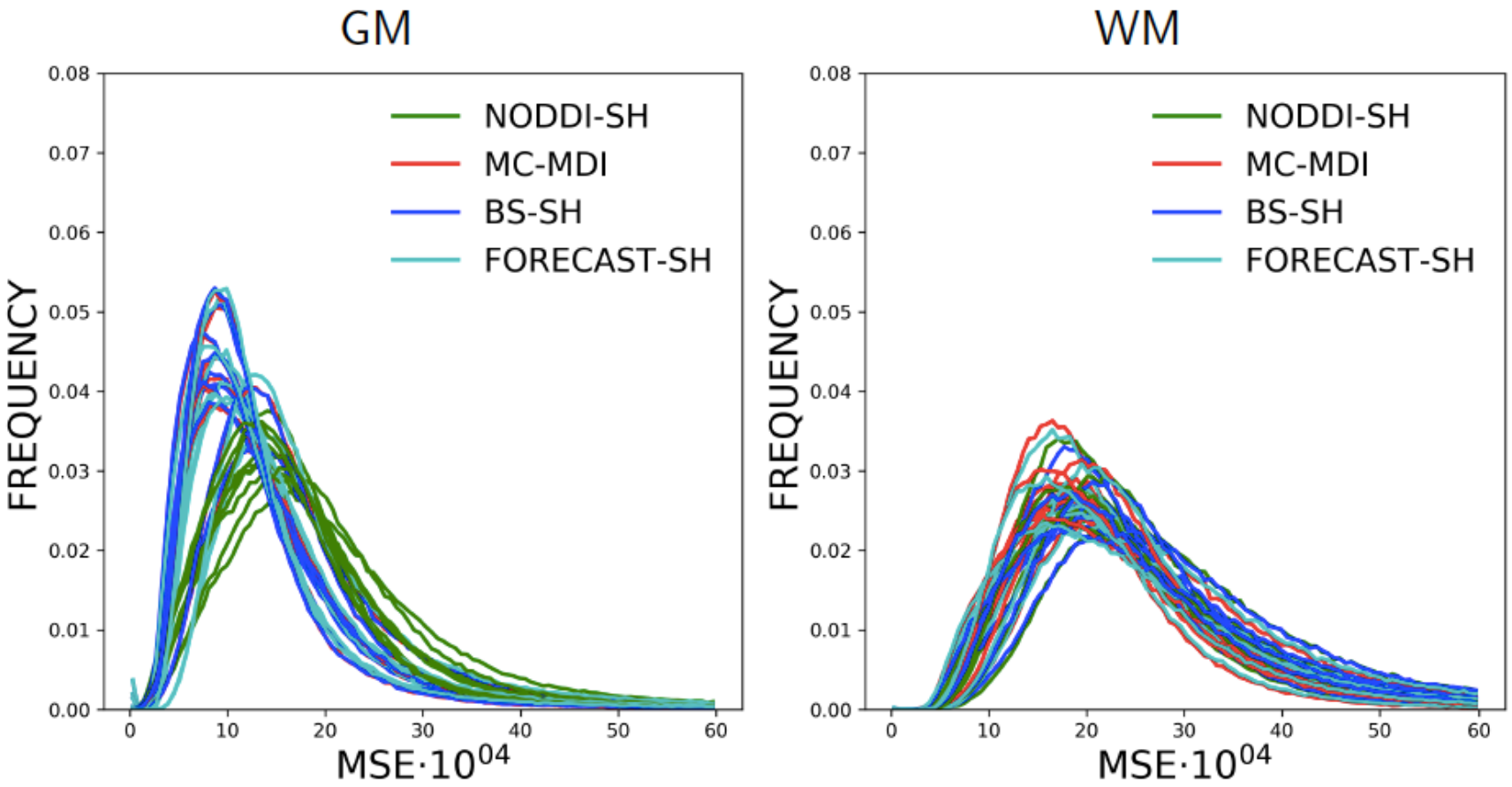


In-vivo: MSE

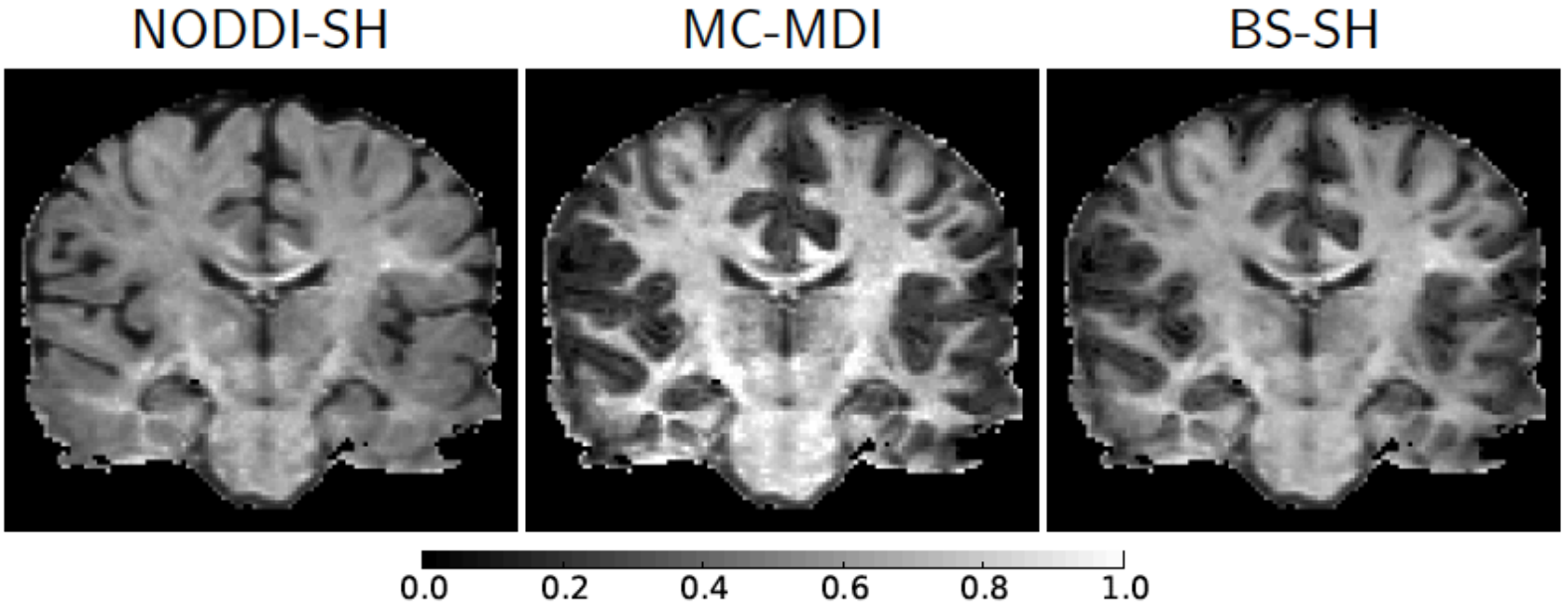
- 10 WU-MINN HCP subjects

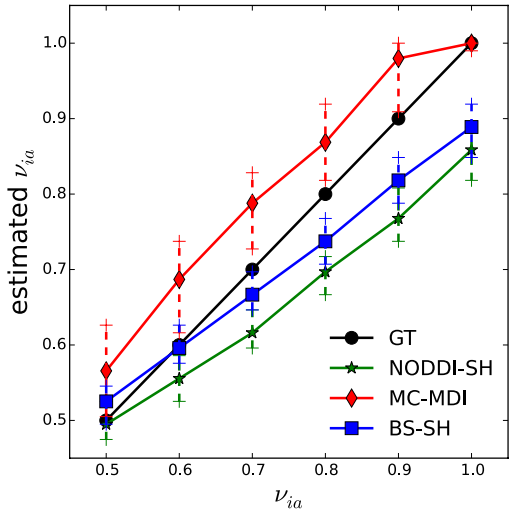


In-vivo: MSE

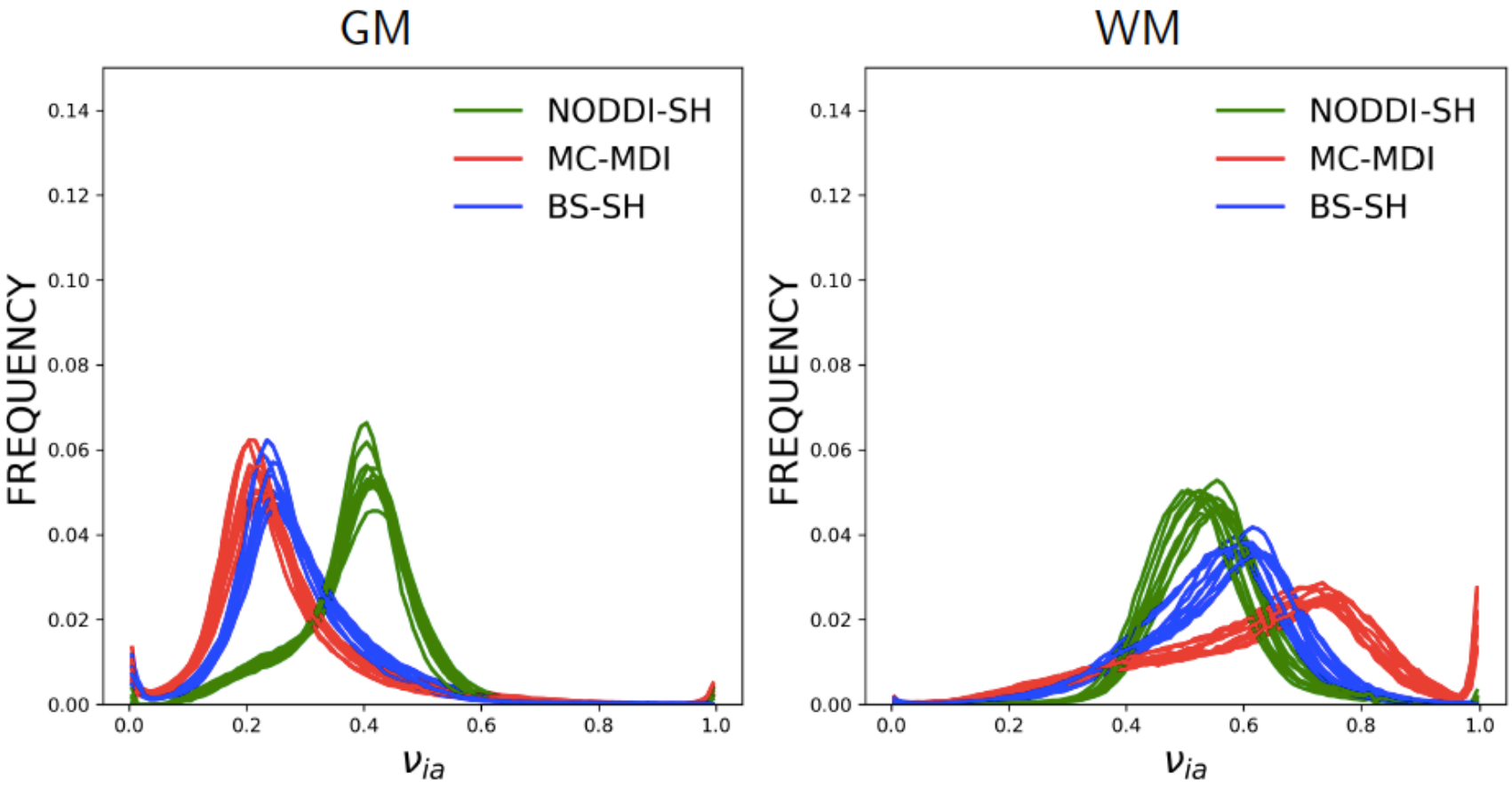

GM
WM
NODDI-SH
MC-MDI
BS-SH
FORECAST-SH
FREQUENCY
MSE·10^04
0.00
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0
10
20
30
40
50
60

In-vivo: intra-axonal volume fraction

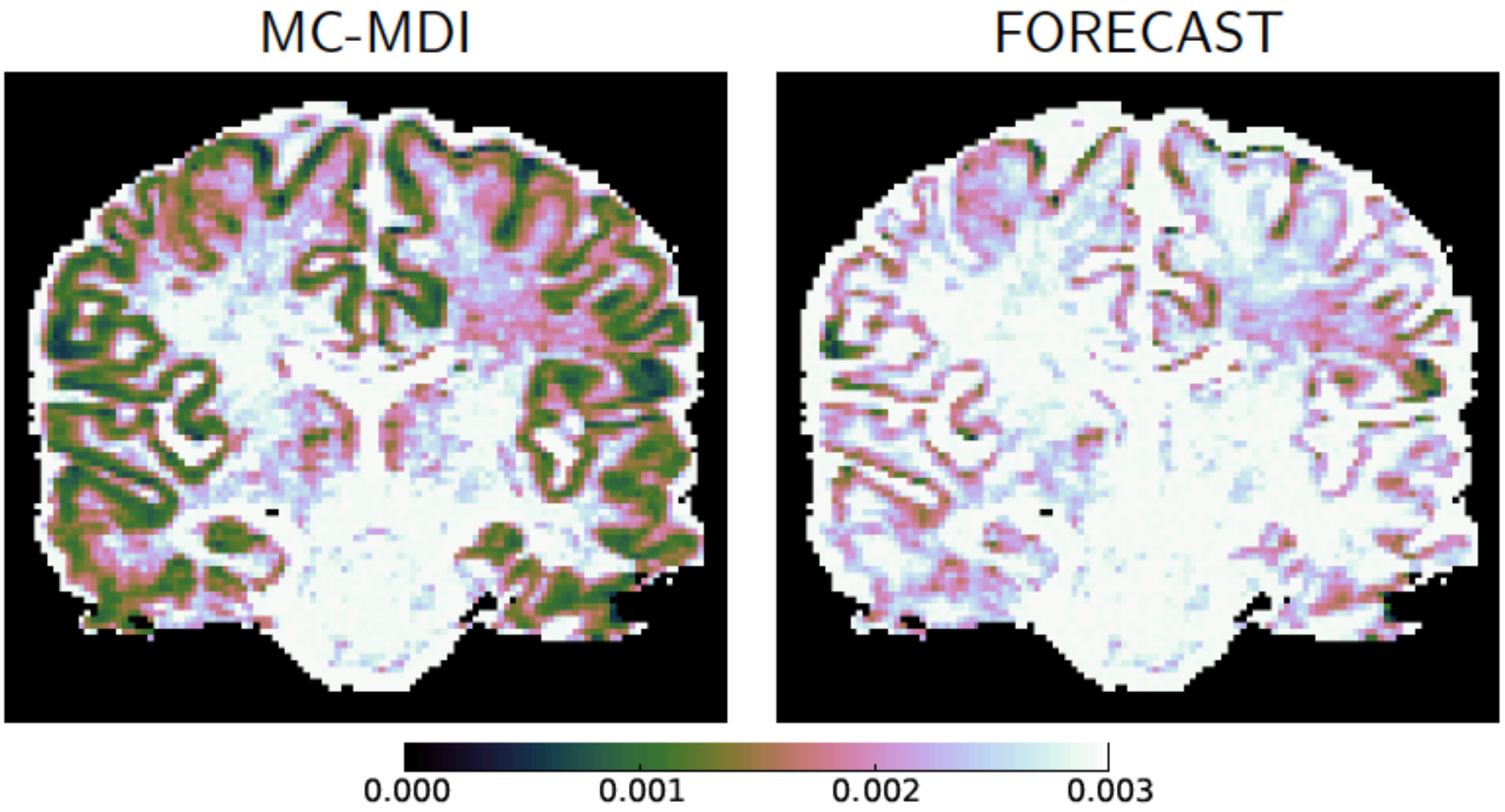




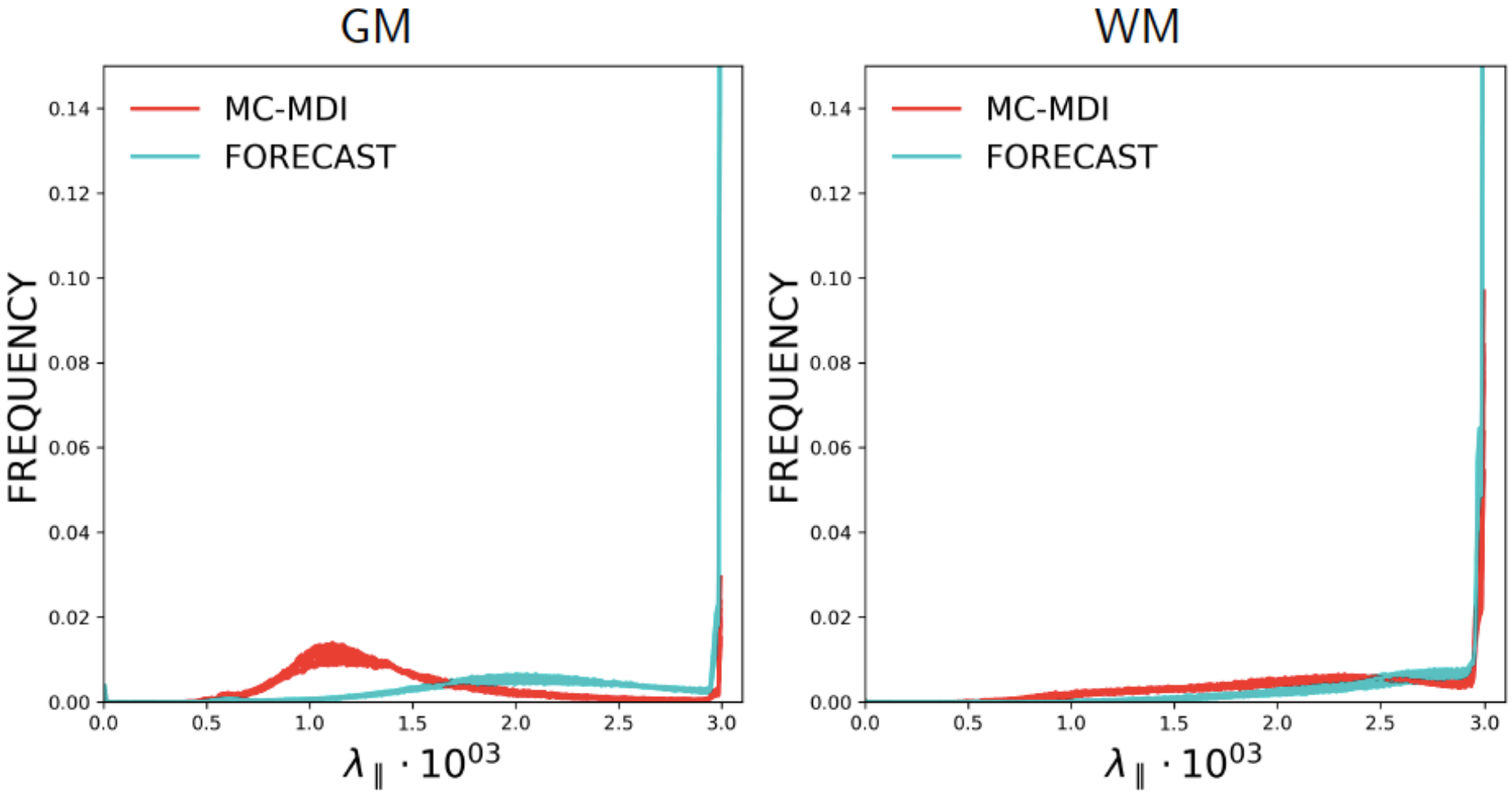
In-vivo: intra-axonal volume fraction



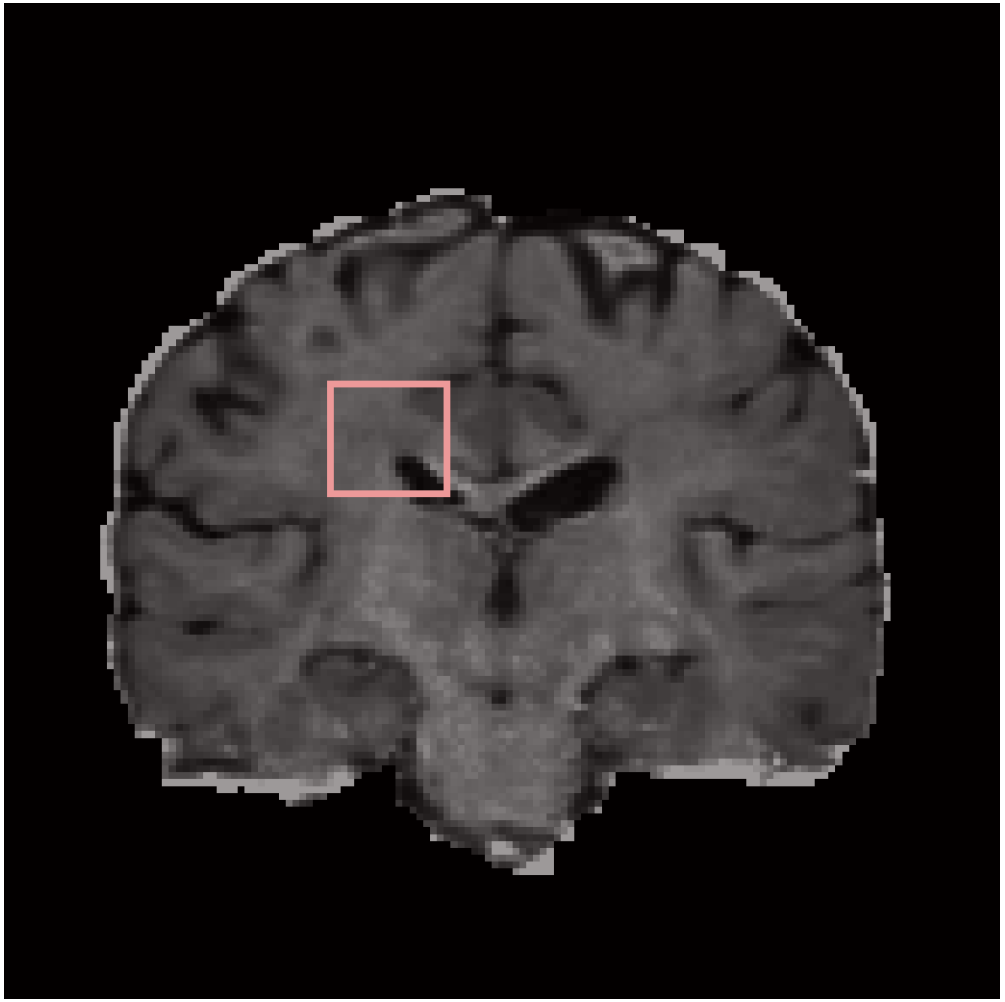
Parallel diffusivity



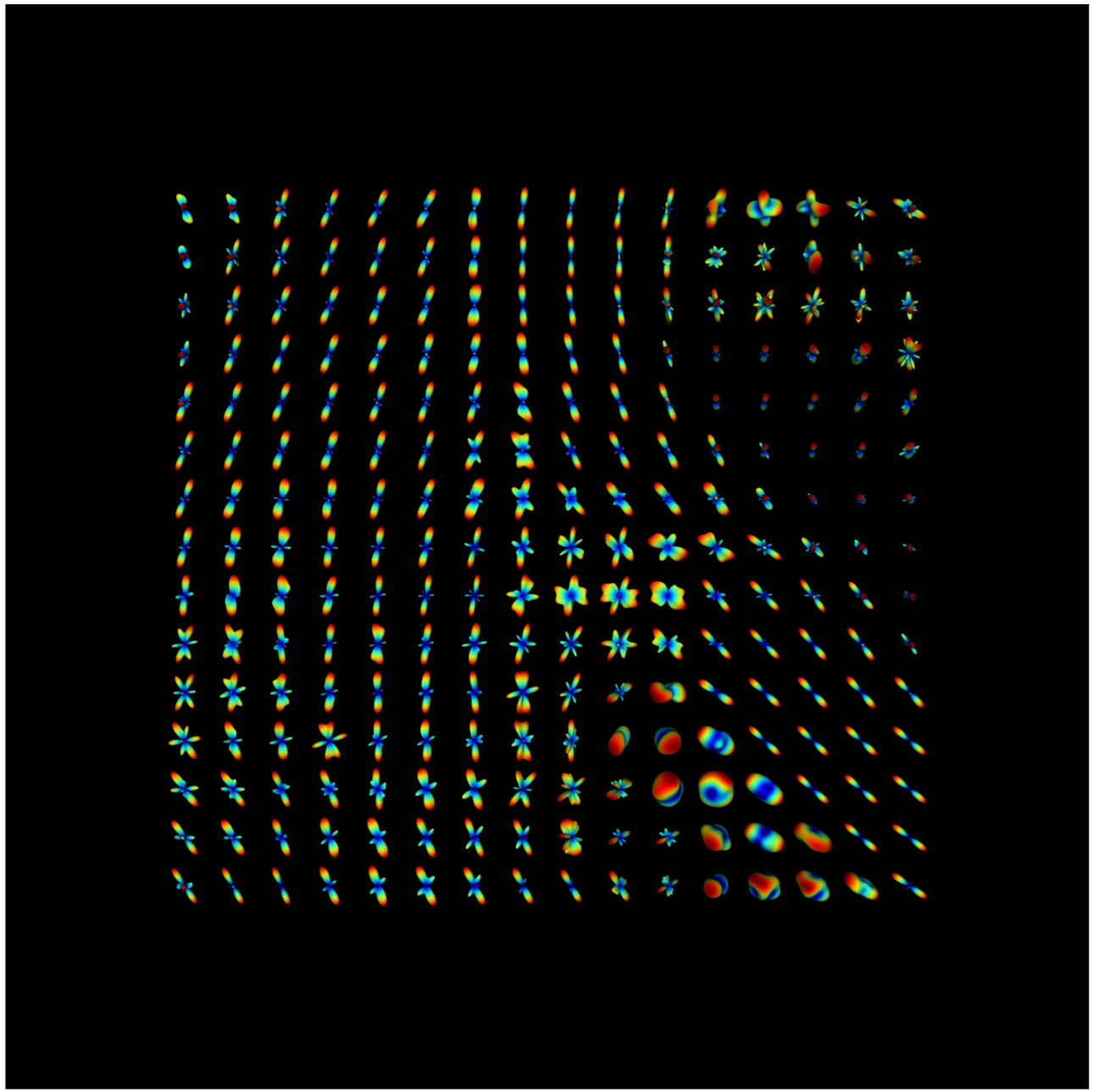
In-vivo: Parallel diffusivity



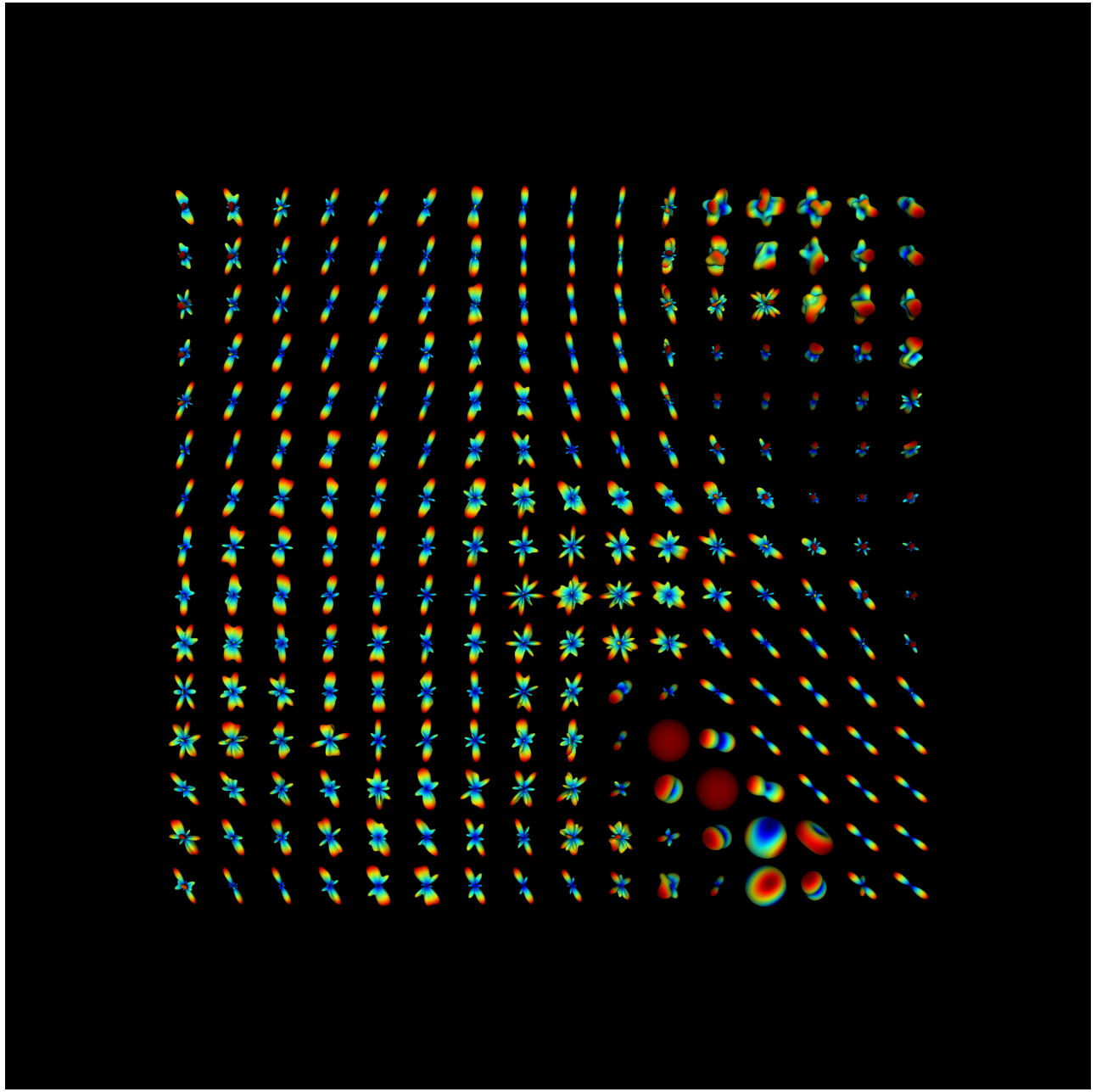
In-vivo: fODF



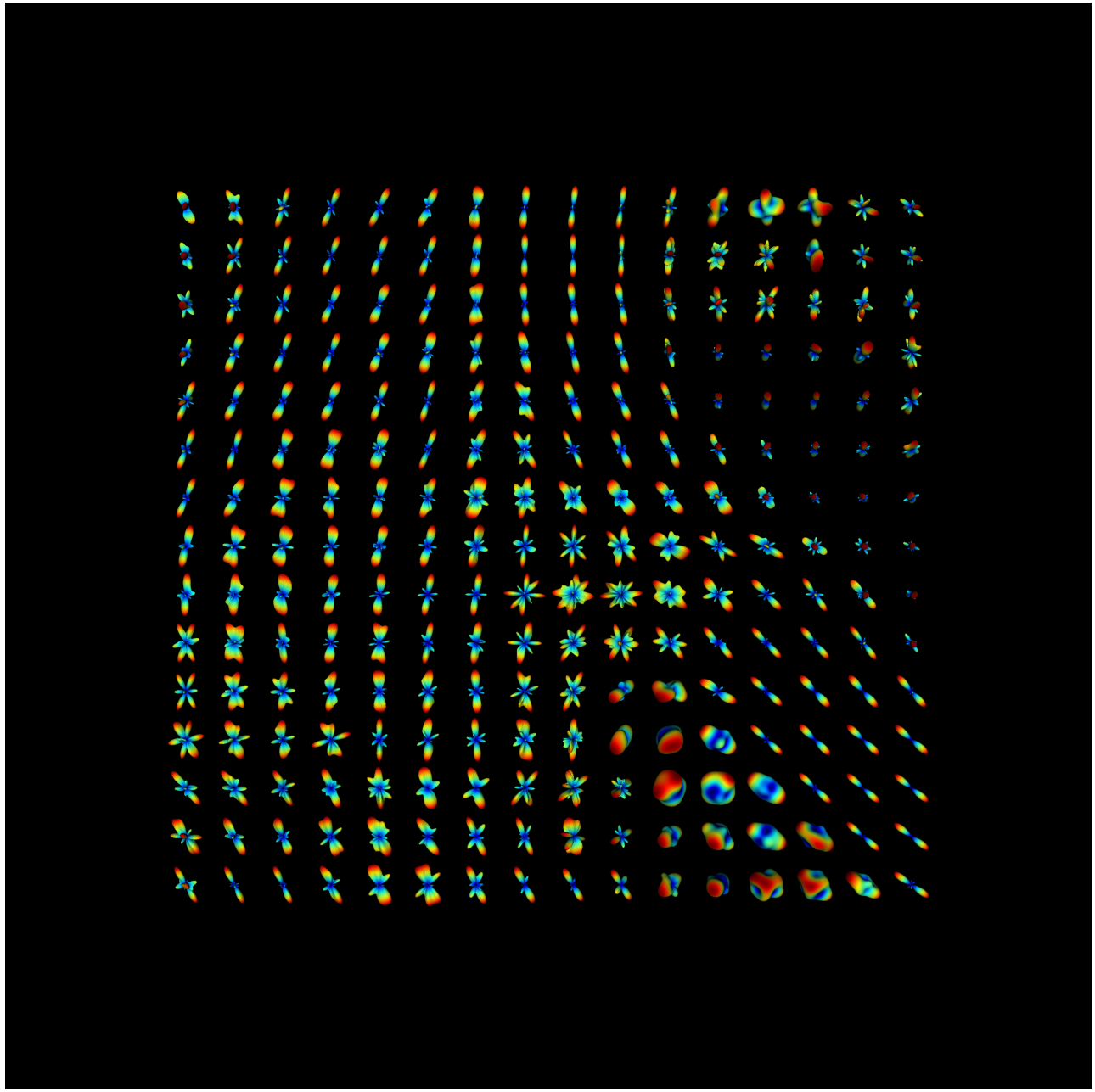
BS-SH



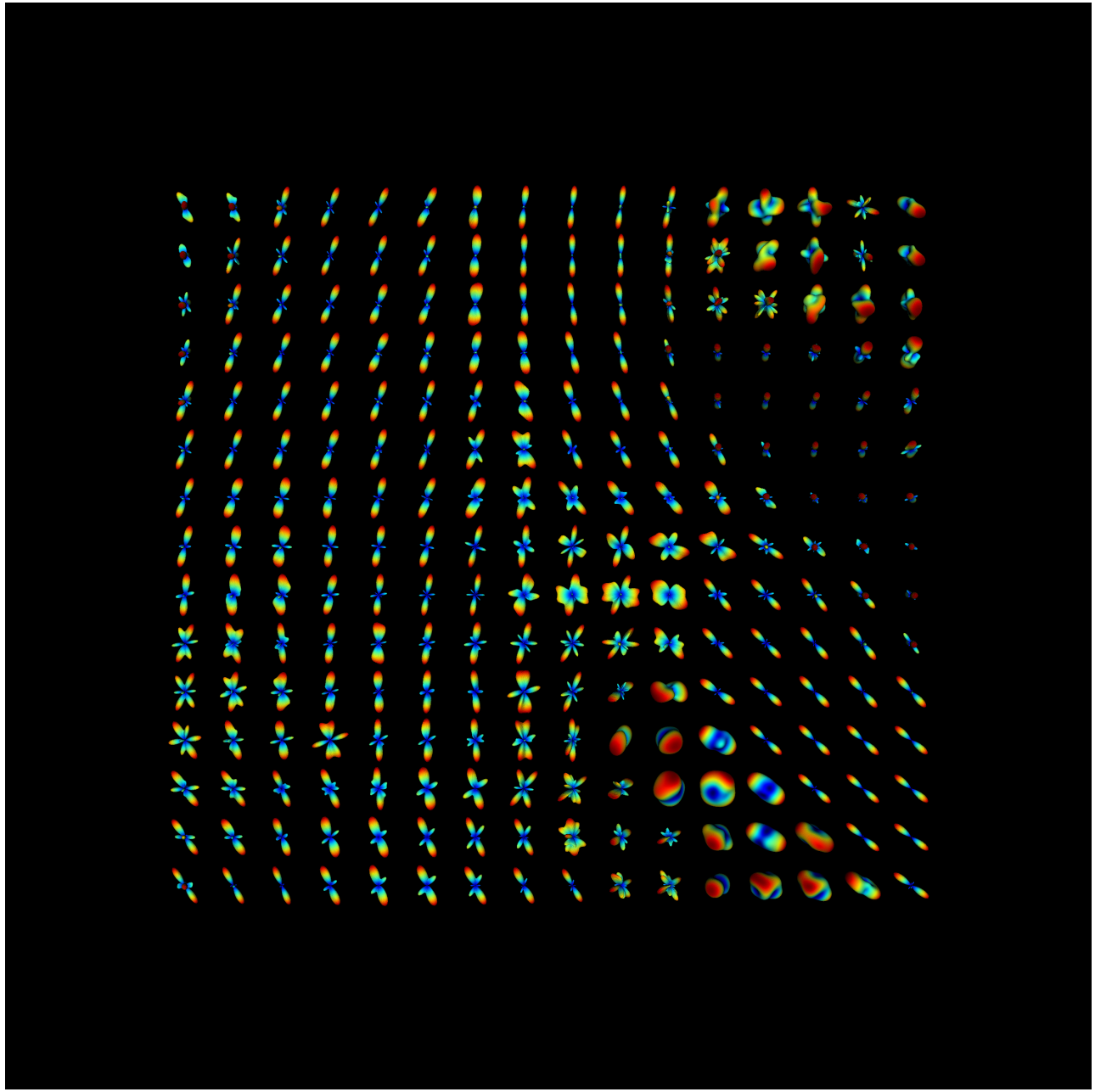
FORECAST



MC-MDI



NODDI-SH



Conclusions

- SMT allowed us to unify several microstructural models under the same mathematical framework
- In-vivo results are coherent with predictions from synthetic data
- Models are consistent across subjects
- Angular features are well represented by all models

- Results highlight that the estimated parameters mirror the microstructural feature, though care must be taken in the interpretation of the results

Thank you!