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Assessing the validity of the approximation of DW-MRI signals from crossing fascicles by sums of signals from single fascicles

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Abstract

Purpose—To assess the validity of the superposition approximation for crossing fascicles, i.e. the assumption that the total diffusion-weighted MRI (DW-MRI) signal is the sum of the signals arising from each fascicle independently, even when the fascicles intermingle in a voxel.

Methods—Monte Carlo simulations were used to study the impact of the approximation on the DW-MRI signal and to assess whether this approximate model allows microstructural features of interwoven fascicles to be accurately estimated, despite signal differences.

Results—Small normalized signal differences were observed, typically 10^{-3} – 10^{-2} . The use of the approximation had little impact on the estimation of the crossing angle, the axonal density index and the radius index in clinically realistic scenarios wherein the acquisition noise was the predominant source of errors. In the absence of noise, large systematic errors due to the superposition approximation only persisted for the radius index, mainly driven by a low sensitivity of DW-MRI signals to small radii in general.

Conclusion—The use of the superposition approximation rather than a model of interwoven fascicles does not adversely impact the estimation of microstructural features of interwoven fascicles in most current clinical settings.

Keywords

Diffusion-weighted MRI; superposition approximation; crossing fascicles; Monte Carlo simulations; tissue microstructure

Introduction

A particularly challenging task in brain microstructure mapping based on diffusion-weighted magnetic resonance imaging (DW-MRI) is to estimate microstructural properties in regions of the white matter where multiple fascicles of axons intersect. The larger the voxel size, the more likely it is for one voxel to contain two or more populations of axons. In (1), authors

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have reported that between 63% and 90% of voxels in the white matter at a resolution of 2.4 mm³ contain more than one fascicle, suggesting that regions of multiple fascicles actually make up the majority of the white matter voxels at common clinical resolutions. At the scale of a voxel, there can be two types of crossing configurations: either each fascicle occupies its own portion of the voxel with axons that do not intermingle with the axons of the other fascicles; or axons from each fascicle abandon their tight, bundle-like organization and instead adopt an interwoven pattern at the intersection, evolving alongside axons from other fascicles (2).

Most models of the microstructure rely on the *superposition approximation*, i.e. they consider that the signal arising from crossing fascicles is equal to the sum of the signals arising from each fascicle independently. This assumption is used in multi-tensor models (3, 4) and their extensions to distributions of tensors (5), in models assuming various restricted water compartments with different directions (6, 7), in dictionary-based methods (8, 9, 10) and also implicitly in spherical deconvolution frameworks (11, 12, 13, 14). This hypothesis is expected to hold reasonably well when fascicles maintain their bundle-like structure and cross along separate pathways in the voxel, even though the interface between the two fascicles is ignored by the approximation. Indeed in a clinical voxel of a few cubic millimeters the diffusion of a vast majority of water molecules will not be affected by this micrometer-scale interface. In contrast the validity of the superposition approximation can be theoretically challenged in voxels where fascicles intersect in *interwoven patterns* since the diffusion of water molecules in the interstitium, or extracellular space, is then simultaneously hindered by all fascicles. Whether the approximation is appropriate and allows microstructural parameters of interest to be reliably estimated in such configurations with common acquisition sequences remains an open question that has so far received little attention in the literature and which we investigate numerically in this paper.

In this work, we assume that the groundtruth is a voxel in which fascicles intersect in interwoven planes, thus sharing the interstitium, and we evaluate the quality of the superposition approximation for fixed, clinically realistic acquisition protocols. Relying on simple yet representative two-compartment phantoms of the microstructure, we first examine the similarity between the DW-MRI signals arising from the groundtruth configuration and the signals arising from the superposition approximation at fixed, matching microstructural parameters. We then conduct a series of experiments to investigate whether microstructural parameters of interwoven fascicles can be accurately estimated from an approximate model consisting in the superposition of independent fascicles. All the DW-MRI signals are obtained using Monte Carlo simulations of the random walk of water molecules, which leverage the well-known physics of diffusion processes.

Methods

This section presents the synthetic phantoms used in this study, a formal definition of the superposition approximation and the Monte Carlo framework for the simulation of DW-MRI signals. It then details how we studied the impact of the superposition approximation on the DW-MRI signal at fixed microstructural configuration. Lastly, it describes the estimation

experiments that were conducted to examine the impact of using the approximation to estimate microstructural parameters of interwoven fascicles.

Synthetic Phantoms of the Microstructure

Single fascicles—We modeled single fascicles of axons by an infinite array of hexagonally-packed straight, parallel and infinitely-long cylinders. A single fascicle is thus characterized by an orientation $\mathbf{u}$, a unique cylinder radius r interpreted as an axonal radius index and by a cylinder packing density f interpreted as an axonal density index (15), which we denote by the quantity $\Omega_{\text{sing}} = (\mathbf{u}, r, f)$. The DW-MRI signal arising from such a configuration for an acquisition sequence of general parameters $\mathbf{p}$ is denoted by $S_{\text{sing}}(\Omega_{\text{sing}}; \mathbf{p})$ and forms the basis of the superposition approximation investigated in this work.

Interwoven fascicles—Interwoven fascicles were modeled by two populations of straight, parallel and infinitely-long cylinders of respective orientations $\mathbf{u}_1$ and $\mathbf{u}_2$, crossing in interleaved layers one cylinder thick with inter-layer spacing e_l in a pattern repeating periodically, as depicted in Fig. 1. All cylinders within Population 1 (Population 2) have the same radius r_1 (r_2), interpreted as an axonal radius index, with inter-cylinder spacing e_1 (e_2). In practice it is often more intuitive to report the populations' intrinsic packing densities f_1 and f_2 , interpreted as axonal density indices, and the populations' volume fractions of occupancy ν_1 and ν_2 rather than the spacing parameters. However, the interstitium is shared by both fascicles and any separation thereof as well as any definition of the quantities f_1 , f_2 , ν_1 and ν_2 is thus arbitrary. In the remainder of this work, we defined them based on a parceling of the extracellular space at a plane located a distance $e/2$ from both populations of axons (see Fig. 1).

In general a interwoven-fascicle environment is thus completely characterized by the set of parameters $\Omega_{\text{intw}} = (\mathbf{u}_1, r_1, f_1, \mathbf{u}_2, r_2, f_2, \nu_1)$. Related useful quantities are readily obtained from Ω_{intw} such as $\nu_2 = 1 - \nu_1$, the crossing angle α as the smallest angle between $\mathbf{u}_1$ and $\mathbf{u}_2$ in the range $[0, 90^\circ]$ and the global axonal density index $f_{\text{tot}} = \nu_1 f_1 + \nu_2 f_2$. The DW-MRI signal arising from such a configuration for an acquisition sequence of general parameters $\mathbf{p}$ is denoted by $S_{\text{intw}}(\Omega_{\text{intw}}; \mathbf{p})$ and was considered as the reference, groundtruth signal throughout this study. A brief discussion on the impact of adding more cylinders to each population's layer in the interwoven configuration can be found in the Supporting Information (Supporting Figures S1 and S2).

Definition of the Superposition Approximation

Given an acquisition sequence of parameters $\mathbf{p}$, we defined the superposition signal $S_{\text{appr}}(\Omega_{\text{appr}}; \mathbf{p})$, supposed to approximate the groundtruth $S_{\text{intw}}(\Omega_{\text{intw}}; \mathbf{p})$, as the linear combination

$$S_{\text{appr}}(\Omega_{\text{appr}}; \mathbf{p}) = \nu_1 S_{\text{sing}}(\mathbf{u}_1, r_1, f_1; \mathbf{p}) + \nu_2 S_{\text{sing}}(\mathbf{u}_2, r_2, f_2; \mathbf{p}), \quad [1]$$

where the weights ν_1 and ν_2 are interpreted as the fractions of the total volume occupied by each fascicle, satisfying $\nu_1 + \nu_2 = 1$. Similarly to fascicles crossing in interleaved planes, the global axonal density index is obtained as $f_{\text{tot}} = \nu_1 f_1 + \nu_2 f_2$.

An approximate interwoven-fascicle environment is fully characterized by the set of parameters $\Omega_{\text{appr}} = (\mathbf{u}_1, r_1, f_1, \mathbf{u}_2, r_2, f_2, \nu_1)$ which all have a straightforward equivalent parameter in Ω_{intw} so that both parameter sets can easily be compared.

Signal Simulations

We relied on Monte Carlo simulations of the random walk of water molecules to obtain DW-MRI signals for the single and interwoven-fascicle configurations described above in order for our study to be as model-independent as possible and because no exact generative formulas exist for interwoven fascicles of axons.

Specifically, we followed the method described in (16) where the exact intracellular signal S_{in} is obtained by the Multiple Correlation Function (MCF) formalism (17) and the extracellular signal S_{ex} is computed from fixed-step Monte Carlo simulations of the random diffusive motion of water molecules in the extracellular space with perfectly elastic reflections at the membranes as described in (18). Compared to Monte Carlo simulations performed in both the intra and extracellular compartments, this provides significant gains in precision at fixed computation time and equivalently, significant computational gains for a set precision (16).

We used the same intrinsic diffusivity D in the intra and extracellular compartments and fixed its value to $D = 2.0 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$, in agreement with values used in similar Monte Carlo settings (18, 19, 20). As noted in (21), we stress that all the results obtained in this study can be obtained for another value of D by appropriately rescaling the spatial lengths L and magnetic gradient intensities G , since the diffusion signal is fully characterized by the two dimensionless parameters $p = DT/L^2$ and $q = \gamma GLT$ (17), where γ is the gyromagnetic ratio of protons and T the characteristic time scale. All the simulations for the extracellular signal of single fascicles were performed using the Camino Diffusion MRI Toolkit (18). The simulations in the extracellular space of interwoven fascicles utilized a new in-house software written in C/C++ and extending the capabilities of the Camino Toolkit to all the interwoven-fascicle configurations considered in this study. Care was taken to ensure that the new code reproduced the results of Camino on the simpler configurations handled by both softwares.

Throughout this study we focused on multi-shell high angular resolution diffusion-weighted imaging (HARDI) protocols (3) based on the widely used pulsed-gradient spin-echo (PGSE) acquisition sequence. Table 1 summarizes the two clinically-realistic protocols that we used in our experiments: the 4-shell, 4-diffusion-times human protocol used with the ActiveAx model (15) and the extended 4-shell protocol proposed with the NODDI estimation framework (22), which we refer to as Protocols A and B, respectively.

It is worth noting that, given the way S_{sing} and S_{intw} were simulated in the absence of membrane permeability, the intracellular signal of the superposition approximation is by

definition exactly identical to that of fascicles crossing in interwoven planes when the radius indices and the fascicles' orientations coincide. In our models, the discrepancies between the reference interwoven-fascicle signals and the approximate signals *at matching microstructural parameters* therefore solely arise from the extracellular signal contribution. The intra- and extracellular contributions are not independent however: as an example, changing the radius index at fixed inter-cylinder spacing directly impacts the intracellular signal but also affects the extracellular geometry and the global axonal density, thereby modifying the extracellular signal and the relative weight of each compartment's contribution. This impact is non-trivial and depends on whether or not the superposition approximation is used.

Impact of the Approximation on the DW-MRI Signal

This section aims at identifying the order of magnitude of the differences between the interwoven-fascicle signal S_{intw} and the approximate signal S_{appr} when the reference parameters Ω_{intw} and the parameters used in the approximation Ω_{appr} match. Without loss of generality, we compared DW-MRI signals of configurations featuring fascicles with identical microstructural properties, i.e. we fixed $r_1 = r_2 = r$, $f_1 = f_2 = f$ and $\nu_1 = \nu_2 = 0.5$. Specifically, we considered 24 microstructural configurations resulting from the combination of 6 radius indices $r = [0.5, 1, 2, 3, 4, 5]\mu\text{m}$ and 4 crossing angles $\alpha = [22.5^\circ, 45^\circ, 67.5^\circ, 90^\circ]$ with density index $f = 0.5$ and we computed the root-mean-square (RMS) signal metric

$$\|S_{\text{appr}}(r, f, \alpha; \wp) - S_{\text{intw}}(r, f, \alpha; \wp)\|_{\text{RMS}} = \frac{1}{\sqrt{P}} \left(\sum_{i=1}^P (S_{\text{appr}}(r, f, \alpha; \mathbf{p}_i) - S_{\text{intw}}(r, f, \alpha; \mathbf{p}_i))^2 \right)^{1/2},$$

over the P sequences of each HARDI shell $\wp$ from Protocols A and B (Table 1).

Impact of the Approximation on Estimated Microstructural Parameters

The previous section seeks the order of magnitude characterizing the differences in DW-MRI signal between reference interwoven fascicles and the superposition approximation but it does not indicate how these signal discrepancies relate to underlying microstructural differences. In this section, we investigated whether we can accurately predict microstructural properties of interest in interwoven fascicles assuming only an approximate model made of the superposition of independent single fascicles, despite the signal differences incurred. Mathematically, for given reference microstructural properties Ω_{intw} and a fixed acquisition protocol $\wp$, this consisted in solving the following microstructural estimation problem

$$\hat{\Omega}_{\text{appr}} = \underset{\Omega_{\text{appr}}}{\text{argmin}} d(S_{\text{intw}}(\Omega_{\text{intw}}; \wp); S_{\text{appr}}(\Omega_{\text{appr}}; \wp)), \quad [2]$$

where $d(\cdot; \cdot)$ is a metric quantifying the discrepancy between the DW-MRI signals. We then examined the microstructural similarity between the reference and the estimated parameters $\hat{\Omega}_{\text{appr}} \approx \Omega_{\text{intw}}$ as an indicator of the quality of the superposition approximation.

Experiments I and II described below consisted in solving Problem [2] within varying subsets of the crossing-fascicle parameter space Ω_{cross} , with and without acquisition noise. Experiment III aimed at comparing the estimation errors due to the use of the superposition approximation to the errors caused by the presence of noise alone.

In our signal simulation framework, the effects of all parameters but ν_1 and ν_2 on the approximated signal S_{appr} are captured by Monte Carlo simulations, which lack a closed-form expression and prevent us from solving Problem [2] continuously. In Experiments I through III, we therefore resorted to a discrete, exhaustive search as illustrated in Fig. 2, using a collection $\mathcal{D}_{\text{sing}}$ of 600 pre-simulated single-fascicle signals combining 20 radius indices r from 0.5 μm to 10 μm by increments of 0.5 μm and 30 density indices f from 0.32 to 0.90 by steps of 0.02 along the fixed direction $\mathbf{u}_1$. Rotated-fascicle signals $S_{\text{sing}}(\mathbf{u}_2) = \mathcal{R}_\alpha[S_{\text{sing}}]$ along any direction $\mathbf{u}_2$ forming an angle α with $\mathbf{u}_1$ could then be obtained by interpolating the pre-computed signals on the inversely-rotated protocol $\mathcal{R}_{-\alpha}[\mathcal{P}]$, which we did for 119 values of α ranging from 1.5° to 178.5° by increments of 1.5°.

The use of Monte Carlo signals and this estimation strategy are however not representative of most current microstructural estimation frameworks in which simplified closed-form formulas are fit to DW-MRI measurements using non-linear optimization, which is subject to pitfalls including the presence of multiple local minima (23) and sensitiveness to the choice of an objective function or the fitting strategy (24, 25). In Experiment IV detailed below, we therefore studied the impact of the superposition approximation on the microstructural estimates of the DIAMOND model (5) which can handle multiple-fascicle configurations.

Experiment I: impact of the approximation on identical fascicles—We considered identical populations of axons both in the reference configurations Ω_{intw} and in the configurations Ω_{appr} over which the minimization in [2] was performed, which simplified the analysis while still providing general trends about the impact of the superposition approximation on the three main microstructural features characterizing crossing fascicles: the radius index, the density index and the crossing angle. This constraint was relaxed in Experiment II.

We selected the 24 reference interwoven-fascicle environments $\Omega_{\text{intw}} = (\mathbf{u}_1, r_{\text{ref}}, f_{\text{ref}}, \mathbf{u}_2 = \mathcal{R}_\alpha[\mathbf{u}_1], r_{\text{ref}}, f_{\text{ref}}, \nu_1 = 0.5)$ described in the previous section and corrupted each interwoven-fascicle signal S_{intw} with Rician noise as $\tilde{S}_{\text{intw}} = \sqrt{(S_{\text{intw}}(\Omega_{\text{intw}}; \mathbf{p}_i) + \varepsilon_{I,i})^2 + \varepsilon_{Q,i}^2}$, where $\varepsilon_{I,i}$ and $\varepsilon_{Q,i}$ are independent, Gaussian variables of zero mean and variance σ^2 , for every acquisition i in the protocol, respectively modeling the acquisition noise in the in-phase (I) and quadrature (Q) channels.

Problem [2] therefore becomes, for a fixed acquisition protocol $\mathcal{P}$,

$$\underset{r, f, \alpha}{\operatorname{argmin}} d \left(\tilde{S}_{\text{intw}}(r_{\text{ref}}, f_{\text{ref}}, \alpha_{\text{ref}}; \varphi) \underbrace{0.5 \cdot S_{\text{sing}}(\mathbf{u}_1, r, f; \varphi) - 0.5 \cdot S_{\text{sing}}(\mathcal{R}_\alpha[\mathbf{u}_1], r, f; \varphi)}_{S_{\text{appr}}(r, f, \alpha; \varphi)} \right),$$

where the metric d is the negative log-likelihood of the Rician distribution. The problem was solved by exhaustive search over the $600 \times 191 = 114\,600$ pre-computed signals (Fig. 2), where $\mathbf{u}_1$ and the plane in which $\mathbf{u}_1$ is rotated were assumed known. We defined the signal-to-noise ratio (SNR) as $1/\sigma$ and recorded the mean absolute error (MAE) on the estimated radius index $|\hat{r} - r_{\text{ref}}|$, density index $|\hat{f} - f_{\text{ref}}|$ and crossing angle $|\hat{\alpha} - \alpha_{\text{ref}}|$ over $N_{\text{reps}} = 100$ noise repetitions at each SNR level. The noise-free estimates corresponding to $\text{SNR} \rightarrow \infty$ were computed using the RMS metric to account for the asymptotic behavior of the Rician distribution (26).

Experiment II: impact of the approximation on dissimilar fascicles—In this experiment we relaxed the constraint that the crossing fascicles should be identical. To keep Problem [2] tractable, we first assumed in Experiment IIa that the crossing angle α was known, leaving 5 parameters to be estimated: $r_1, f_1, r_2, f_2, \nu_1$. In order to more fairly compare the results with Experiment I where the volume fractions were fixed, we then simplified the estimation in Experiment IIb by assuming that ν_1 and ν_2 were known as well.

In both cases, we conducted 8 noiseless microstructural estimation experiments on 8 reference interwoven-fascicle configurations Ω_{intw} in which the crossing angle was fixed to $\alpha = 67.5^\circ$, the first population of axons had fixed parameters $r_1 = 1.0 \mu\text{m}$ and $f_1 = 0.6$ and the microstructural properties of the second population were varied. In the first 4 configurations, we set $f_2 = f_1 = 0.6$ and let r_2 take on values in $[0.5, 1.0, 1.5, 2.0] \mu\text{m}$; in the last 4 configurations we set $r_2 = r_1 = 1.0 \mu\text{m}$ and let f_2 vary in $[0.4, 0.5, 0.6, 0.7]$. The parameters e_1, e_2 and e_f were selected to ensure $f_{\text{tot}} = (f_1 + f_2)/2$ in all 8 reference configurations.

Experiment IIa: Problem [2] was solved by performing continuous optimization over the volume fractions for each possible combination of the 600 pre-computed single-fascicle configurations $\mathcal{D}_{\text{sing}}(k) := S_{\text{sing}}(\mathbf{u}_1, r_k, f_k)$ with their rotated counterparts $\mathcal{R}_\alpha[\mathcal{D}_{\text{sing}}(l)]$,

$$(\hat{k}, \hat{l}) = \underset{1 \leq k, l \leq 600}{\text{argmin}} \min_{x_1 \geq 0} \underbrace{\|x_1 \cdot \mathcal{D}_{\text{sing}}(k) + (1 - x_1) \cdot \mathcal{R}_\alpha[\mathcal{D}_{\text{sing}}(l)] - S_{\text{intw}}(\Omega_{\text{intw}})\|}_{S_{\text{appr}}}, \quad 2 \quad [3]$$

where each of the $600 \times 600 = 360\,000$ sub-problems admits a unique solution obtained with the Matlab (MathWorks, MA, U.S.A.) routine `lsqlin`. We took ν_1 as the minimizer $\hat{x}_1$ of the optimal sub-problem $(\hat{k}, \hat{l})$ giving the lowest objective value and estimated r_1, f_1, r_2, f_2 as the microstructural properties $r_{\hat{k}}, f_{\hat{k}}, r_{\hat{l}}, f_{\hat{l}}$ of the corresponding optimal single-fascicle configurations $\mathcal{D}_{\text{sing}}(\hat{k})$ and $\mathcal{R}_\alpha[\mathcal{D}_{\text{sing}}(\hat{l})]$.

Experiment IIb: With ν_1 fixed, Eq. [3] becomes

$$(\hat{k}, \hat{l}) = \underset{1 \leq k, l \leq 600}{\text{argmin}} \underbrace{\|\nu_1 \mathcal{D}_{\text{sing}}(k) + (1 - \nu_1) \mathcal{R}_\alpha[\mathcal{D}_{\text{sing}}(l)] - S_{\text{intw}}(\Omega_{\text{intw}})\|}_{S_{\text{appr}}}, \quad 2 \quad [4]$$

which was simply solved by exhaustive search over the 600×600 combinations of pre-computed single-fascicle configurations (see Fig. 2).

Experiment III: impact of the approximation with noise compared to the impact of noise alone—Experiment I assessed the *combined* impact of the acquisition noise and of the “approximation noise” on the quality of the microstructural estimates. In this experiment we isolated the impact of acquisition noise alone by performing a similar estimation but using the *true* model of interwoven fascicles for the estimation instead of the approximate model.

We focused on one particular reference interwoven-fascicle configuration with identical populations that led to a non-zero asymptotic error on at least one of the parameters r , f , α in Experiment I and we solved

$$(\hat{r}, \hat{f}, \hat{\alpha}) = \underset{r, f, \alpha}{\operatorname{argmin}} d \left(\tilde{S}_{\text{intw}}(r_{\text{ref}}, f_{\text{ref}}, \alpha_{\text{ref}}; \zeta) - S_{\text{intw}}(r, f, \alpha; \zeta) \right), \quad [5]$$

where d is the negative log-likelihood of the Rician distribution and $\tilde{S}_{\text{intw}}$ is the reference interwoven-fascicle signal corrupted by noise. We compared the microstructural estimates obtained here to those obtained in Experiment I with the superposition approximation.

Similarly to the previous experiments, solving Problem [5] required a discrete, exhaustive search in the space (r, f, α) . Pre-simulating the candidate signals is more computationally demanding than when using the superposition approximation because every new value of crossing angle α requires a complete new signal simulation. For the density index f and the crossing angle α , the same resolutions of 0.02 and 1.5° were kept, the ranges spanned by the exhaustive search were centered around the reference values f_{ref} and α_{ref} and their half-widths were selected to be slightly larger than the worst MAEs observed in Experiment I over all SNR values. For the radius index r we considered candidate values in the range $[0.5 \mu\text{m}, 10 \mu\text{m}]$ every $0.25 \mu\text{m}$ for $|r - r_{\text{ref}}| \leq 0.5 \mu\text{m}$, every $0.50 \mu\text{m}$ for $1.0 \mu\text{m} \leq |r - r_{\text{ref}}| \leq 4.0 \mu\text{m}$ and every $1.0 \mu\text{m}$ elsewhere.

Experiment IV: impact of the approximation on a closed-form model of the microstructure—We studied the impact of the superposition approximation on the DIAMOND model (5) which represents the 3D-diffusivity of each voxel compartment j (e.g. a fascicle of axons) with a peak-shaped statistical distribution of diffusion tensors parameterized by a compartment heterogeneity index cHEI_j and a mean tensor $\mathbf{D}_{0,j}$. The contribution of compartment j to the total signal is weighted by an apparent volume fraction ν_j . Compartment-specific diffusion characteristics such as the axial and radial diffusivities cAD_j and cRD_j are extracted from $\mathbf{D}_{0,j}$.

Specifically, the DIAMOND closed-form, continuous expression $S_{\text{DMD}}(\Omega_{\text{DMD}}; \mathcal{P})$ relating the DW-MRI signal S_{DMD} to the microstructural parameters Ω_{DMD} for a given acquisition protocol $\mathcal{P}$ was fitted to signals $S_{\text{intw}}(\Omega_{\text{cros}}; \mathcal{P})$ arising from reference interwoven configurations Ω_{cros} and to the signals $S_{\text{appr}}(\Omega_{\text{cros}}; \mathcal{P})$ arising from the superposition approximations of matching microstructural parameters. We obtained the model estimates

$\hat{\Omega}_{\text{DMD}}(S_{\text{appr}})$ and $\hat{\Omega}_{\text{DMD}}(S_{\text{intw}})$ by solving, for each of the 24 crossing-fascicle configurations Ω_{cros} previously described,

$$\hat{\Omega}_{\text{DMD}}(S_{\text{appr}}) = \underset{\Omega_{\text{DMD}}}{\operatorname{argmin}} d(S_{\text{appr}}(\Omega_{\text{cros}}; \varphi); S_{\text{DMD}}(\Omega_{\text{DMD}}; \varphi)),$$

$$\hat{\Omega}_{\text{DMD}}(S_{\text{intw}}) = \underset{\Omega_{\text{DMD}}}{\operatorname{argmin}} d(S_{\text{intw}}(\Omega_{\text{cros}}; \varphi); S_{\text{DMD}}(\Omega_{\text{DMD}}; \varphi)),$$

where d is a corrected least-squares metric and where the non-linear minimization was achieved with a customized BOBYQA algorithm (5). The impact of the signal discrepancies caused by the approximation was assessed by comparing $\hat{\Omega}_{\text{DMD}}(S_{\text{appr}})$ to $\hat{\Omega}_{\text{DMD}}(S_{\text{intw}})$ in all 24 cases for Protocols A and B.

Results

This section first reports the observed DW-MRI signal differences between the reference interwoven fascicles and the superposition approximation at matching microstructural parameters. It then provides the results of the four microstructural estimation experiments assessing the impact of those signal differences on the underlying microstructural parameters.

Impact of the Approximation on the DW-MRI Signal

We found that the RMS difference between the approximate and groundtruth signal varied in $[0.0017, 0.024]$ over the 8 considered acquisition shells and 24 microstructural configurations, i.e. an order of magnitude comparable to the standard deviation of Gaussian noise in an MRI acquisition channel with SNR in $[1/0.024, 1/0.0017] \approx [42 - 603]$. The detailed shell-per-shell signal differences are available in Supporting Table S1. Figure 3 shows the DW-MRI signals of the particular scenario that yielded the highest RMS difference as a function of the direction of the applied magnetic gradient. The signal discrepancies seemed largest for gradients perpendicular to $\mathbf{u}_1$ and $\mathbf{u}_2$ but this varied from shell to shell, as illustrated in Supporting Figure S3. Little difference was found between the two protocols: the RMS metric averaged over all 24 microstructural configurations was 6.4×10^{-3} for Protocol A and 6.3×10^{-3} for Protocol B.

Figure 4 shows those same DW-MRI signals as a function of the microstructural parameters for a few selected acquisition sequences with magnetic gradient applied in the plane defined by the orientations of the two fascicles. It suggests that DW-MRI signals (both the reference and the approximation) exhibit heterogeneous degrees of sensitivity to the underlying microstructural parameters. In particular, the signals hardly varied at all in the range of smaller radius indices, which is a well-known limitation of the PGSE sequence (27, 24, 28).

Impact of the Approximation on Estimated Microstructural Parameters

Experiment I: impact of the approximation on identical fascicles—Figure 5 shows the results of 6 of the 24 experiments, corresponding to the reference crossing angle $\alpha_{\text{ref}} = 67.5^\circ$. The results for the other 3 angles were qualitatively similar and are provided in Supporting Figures S4, S5 and S6.

The superposition approximation led to a fast convergence with increasing SNR in the estimation of the crossing angle as the MAE over all 24 experiments consistently remained below 4.8° for all SNR ≥ 5 with Protocol A and below 7.1° with Protocol B, showing no sensitivity to the reference radius index. Given the resolution used in the discrete minimization, we deduced from the apparently zero asymptotic errors that the errors due to the superposition approximation in the absence of noise ($\text{SNR} \rightarrow \infty$) were lower than 1.5° .

The convergence was fast as well for the density index as the worst-case MAE over all 24 reference configurations at SNR = 10 was 0.042 for Protocol A and 0.070 for Protocol B. Asymptotic errors attributable to the superposition approximation could be upper-bounded by 0.08 for reference configurations verifying $r_{\text{ref}} \leq 1 \mu\text{m}$ and by 0.02 elsewhere.

The MAE on the estimated radius index was slower to level off to the asymptotic, noise-free errors. They were slightly larger for Protocol B at smaller radius indices, where they reached between $3.5 \mu\text{m}$ and $4.5 \mu\text{m}$. The non-monotonicity of the red curves in Fig. 5e–f corresponding to a reference radius index $r = 0.5 \mu\text{m}$ is due to both the absence of radius values smaller than $0.5 \mu\text{m}$ in the exhaustive minimization procedure (since the approximated signal hardly varies in that small-radius range) and to the asymptotic bias in the estimation, which artificially improved the estimation error of that parameter at low SNR values.

The variability of the microstructural estimates over the noise repetitions can help reveal the SNR regimes in which the errors due to the noise dominate the errors due to the use of the superposition approximation: a large variability compared to the asymptotic, noise-free error suggests that noise is the predominant source of error. The radius index estimates obtained with the superposition approximation using Protocol A for instance exhibited an interquartile range (IQR), defined as the difference between the 75th and the 25th percentile, that still represented 50% or more of the asymptotic error in 17 of the 18 configurations yielding a non-zero asymptotic error at SNR=50, before dropping to 7 configurations at SNR=100 and 2 at SNR=200. This suggests a prevalence of noise-related errors for SNR levels up to about 50, as illustrated in Fig. 5g–h for one particular experiment.

Experiment II: impact of the approximation on dissimilar fascicles—The results of all 8 estimation experiments on dissimilar populations of axons are presented in Table 2 with (Experiment IIa, in blue) and without (Experiment IIb, in green) the estimation of the volume fractions, in the absence of noise.

Experiment IIa: The errors caused by the approximation without acquisition noise suggest an inter-dependence between the estimation of the volume fraction ν and density index f of a fascicle: when ν was overestimated, f was underestimated and conversely. This conflating

effect seemed exacerbated at small radius index values but slightly less pronounced when the two fascicles occupied similar fractions of the voxel: with Protocol A for instance, the approximation yielded a maximum error on the estimated density index between 0.18 and 0.22 with the smallest radius indices while the largest error over the last 4 cases lied between 0.12 and 0.16 given the 0.02 resolution used in the discrete optimization. In general, the superposition approximation yielded microstructural errors larger than those observed without noise in Experiment I where the volume fractions were equal and known.

Experiment IIb: Fixing the volume fractions v of the fascicles a priori considerably improved the quality of the microstructural estimation using the superposition approximation, containing the error on the estimated density index within 0.04 given our 0.02 discrete resolution, in agreement with the noise-free results of Experiment I.

Experiment III: impact of the approximation with noise compared to the impact of noise alone—Figure 6 presents the results of the microstructural estimation of the reference interwoven-fascicle configuration characterized by $r_{\text{ref}} = 0.5 \mu\text{m}$, $f_{\text{ref}} = 0.5$, $\alpha_{\text{ref}} = 45^\circ$. The exhaustive search over the parameters of the groundtruth interwoven fascicles used 5202 pre-simulated signals and provided an estimate of the errors due to noise alone (green) to be compared to the results from Experiment I obtained using the superposition approximation (blue).

The true model and the approximate model yielded curves that could hardly be distinguished for the estimation of the crossing angle, as could be expected since no asymptotic error caused by the superposition approximation was found in Experiment I. The MAE of the two models on the density index differed by less than 0.022 for all SNR ≥ 5 . The median estimates of the approximation systematically exceeded those of the true model by 0.02 across all SNR levels, consistent with the asymptotic errors detected in Experiment I. For the radius index, the two estimations were very close for SNR values up to 20 with a difference in MAEs representing less than 25% of the asymptotic error. The bias due to the superposition approximation manifested itself after SNR=20 and became clearly apparent at SNR=50, in agreement with the observations made in Experiment I.

Experiment IV: impact of the approximation on a closed-form model of the microstructure—As shown in Fig. 7, the DIAMOND parameters cHEI, cRD and cAD estimated from the superposition approximation were very close to those obtained from the interwoven-fascicle signals, with maximum differences of respectively 1.3×10^{-2} , $6.4 \times 10^{-6} \text{ mm}^2 \text{ s}^{-1}$ and $6.9 \times 10^{-5} \text{ mm}^2 \text{ s}^{-1}$ across all 48 experiments. The estimated apparent volume fraction v_1 differed by less than 0.0575 in 47 of the 48 tested cases and the errors on the crossing angles (not shown) were all below 2° . All the curves in Fig. 7 exhibited similar heights as expected since both crossing-fascicle configurations had identical fascicles, irrespective of the crossing angle. Their relative atness indicated low sensitivity to the reference radius index.

Discussion and Conclusions

This paper examined the validity of approximating the signal arising from fascicles crossing in interwoven planes by the superposition of signals arising from independent single fascicles through the use of Monte Carlo simulations.

The mean normalized signal differences between interwoven fascicles and the superposition approximation were reported in the range $10^{-3} - 10^{-2}$, suggesting that SNRs of the order of 100 would be necessary for those signal differences to become significant and to detect whether fascicles intermingle when they cross, which is not achievable with current MRI technology and clinically acceptable imaging times.

We considered two clinical protocols with b-values lower than 3000 s mm^{-2} which obtained very similar results: the average signal differences were within 1×10^{-4} of each other and the performances were nearly identical in all microstructural estimation experiments with $r > 1 \text{ }\mu\text{m}$. As investigated through Monte Carlo simulations in (29), for larger b-values the signal differences are likely to be *even less* since the extracellular signal, the main source of signal discrepancy in our simulation setting, essentially decays away.

Our experiments have shown that the superposition approximation enables excellent estimation of the crossing angle between two populations of axons even in noisy settings, which supports the results obtained in the estimation of fascicle orientation relying on the superposition hypothesis, such as sums of tensors (3, 4, 5) or tensors with zero radial diffusivity as in most spherical deconvolution frameworks (11, 12, 13, 14).

The use of the superposition approximation generally yielded high accuracy and small systematic biases on the axonal density index, also preserved with noise. Confounding effects were observed when simultaneously estimating the populations' axonal density indices and volume fractions (Experiment II), certainly because very similar signals can be reconstructed by assigning a higher weight ν to a single-fascicle signal with lower intrinsic axonal density index f and conversely. This is reminiscent of the signal equivalence between multi-tensor models at a single b-value when changing the diffusivities of each tensor while correspondingly scaling the volume fractions (4, 30). This mathematical redundancy may be inherent to crossing fascicles in general, whether an approximation is used or not.

Errors in the estimation of the radius index were recurrently observed throughout the experiments, especially at small radius indices. This was mainly driven by the notoriously low sensitivity of DW-MRI signals to small axonal radii (27, 24, 28) which we observed in Fig. 4 with and without the use of the approximation. The results of Experiments I and III suggested that the acquisition noise was the predominant source of error and that the use of the superposition approximation had little impact at low, and thus more realistic, SNR levels. At higher SNR and in noiseless scenarios however, the approximation showed a limitation since the error due to the use of the approximate model persisted while that due to noise alone vanished. Considering a simpler microstructural model without an explicit dependence on the radius in Experiment IV showed uniform estimates across radius indices.

Experiment IV suggested that more phenomenological diffusion models of the microstructure were hardly affected by the use of the superposition approximation, further supporting the quality of the approximation.

Limitations

The synthetic phantoms of the microstructure that we considered in this study did not take axonal membrane permeability into account, which would make the intracellular signal contribution another source of discrepancy between the reference and approximate signal. It is however still unclear whether this strongly affects DW-MRI signals obtained with diffusion times typically no longer than 100 ms, such as used in our analyses. In (31), intracellular exchange times in the brain were reported between 25 and 620 ms while in vivo estimates in (32) lied in 400–600 ms in the genu and splenium of the corpus callosum and in 300–500 ms in the corticospinal tract, for instance.

Another limitation of this work is the simplicity of the two-compartment model adopted at the single-fascicle level. However, this study focused on evaluating the impact of using a *superposition* model rather than selecting the right model at the single-fascicle level. For reasonably simple interweaving patterns of axons in the groundtruth configurations, it should be possible to design a model of single fascicle such that the intracellular compartment of the superposition faithfully mirrors that of interwoven fascicles, as was done in this work. In the absence of membrane permeability, similar conclusions would therefore likely hold for models incorporating more realistic biological features such as myelin sheaths, radius heterogeneity, in-plane and out-of-plane axonal undulation or the presence of glial cells or other cellular compartments in the interstitium.

A myelin compartment in particular should be of limited impact due to rapid T_2 -decay (33) causing a roughly zero signal for the acquisition sequences considered in this work using standard MRI equipment ($B_0 = 3$ T). The reference as well as the approximate signal curves would consequently undergo identical downward translations. Since this would preserve the same signal differences and have little effect on the general sensitivity of signals to microstructural parameters, the conclusions of this study would likely hold.

Likewise, modeling fascicles with a fixed axonal radius index seems physically less realistic than considering a random packing with axonal radius heterogeneity, which would considerably impact the configuration of the extracellular space. However it is known that this index captures important properties of the underlying distribution of radii through its relation with the moments of that distribution (15, 34), simplifying our analyses while still providing meaningful results about the estimation of that microstructural feature. Future studies may have to specifically assess the impact of this simplification.

Conclusion

Overall, we have observed a strong correspondence between DW-MRI signals arising from configurations of interwoven fascicles and DW-MRI signals arising from a weighted sum of independent fascicles for a wide range of realistic microstructural indices and commonly-used acquisition protocols. Even though the approximation might negatively impact the estimation of small radius indices if high imaging SNR becomes available, our experiments

have suggested that using a superposition model enables microstructural properties of interest to be accurately estimated in the presence of clinically-realistic levels of noise corruption, irrespective of the exact configuration of the axons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Jeurissen B, Leemans A, Tournier J, Jones DK, Sijbers J. Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Human brain mapping*. 2013; 34:2747–2766. [PubMed: 22611035]
2. Axer H, Berks G, Keyserlingk DGV. Visualization of nerve fiber orientation in gross histological sections of the human brain. *Microscopy research and technique*. 2000; 51:481–492. [PubMed: 11074619]
3. Tuch DS, Reese TG, Wiegell MR, Makris N, Belliveau JW, Wedeen VJ. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. *Magnetic Resonance in Medicine*. 2002; 48:577–582. [PubMed: 12353272]
4. Scherrer B, Warfield SK. Parametric representation of multiple white matter fascicles from cube and sphere diffusion MRI. *PLoS one*. 2012; 7:e48232. [PubMed: 23189128]
5. Scherrer B, Schwartzman A, Taquet M, Sahin M, Prabhu SP, Warfield SK. Characterizing brain tissue by assessment of the distribution of anisotropic microstructural environments in diffusion-compartment imaging (DIAMOND). *Magnetic resonance in medicine*. 2015
6. Assaf Y, Freidlin RZ, Rohde GK, Basser PJ. New modeling and experimental framework to characterize hindered and restricted water diffusion in brain white matter. *Magnetic Resonance in Medicine*. 2004; 52:965–978. [PubMed: 15508168]
7. Zhang, H., Dyrby, TB., Alexander, DC. Axon diameter mapping in crossing fibers with diffusion MRI. *International Conference on Medical Image Computing and Computer-Assisted Intervention*; 2011. p. 82-89.
8. Ramirez-Manzanares A, Rivera M, Vemuri BC, Carney P, Mareci T. Diffusion basis functions decomposition for estimating white matter intravoxel fiber geometry. *IEEE transactions on medical imaging*. 2007; 26:1091–1102. [PubMed: 17695129]
9. Auria A, Daducci A, Thiran JP, Wiaux Y. Structured sparsity for spatially coherent fibre orientation estimation in diffusion MRI. *NeuroImage*. 2015; 115:245–255. [PubMed: 25944612]
10. Aranda R, Ramirez-Manzanares A, Rivera M. Sparse and Adaptive Diffusion Dictionary (SADD) for recovering intra-voxel white matter structure. *Medical image analysis*. 2015; 26:243–255. [PubMed: 26519793]
11. Tournier J, Calamante F, Gadian DG, Connelly A. Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *NeuroImage*. 2004; 23:1176–1185. [PubMed: 15528117]
12. Tournier J, Calamante F, Connelly A. Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. *NeuroImage*. 2007; 35:1459–1472. [PubMed: 17379540]

13. Jeurissen B, Tournier JD, Dhollander T, Connelly A, Sijbers J. Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion mri data. *NeuroImage*. 2014; 103:411–426. [PubMed: 25109526]
14. Canales-Rodríguez EJ, Daducci A, Sotiropoulos SN, Caruyer E, Aja-Fernández S, Radua J, Mendizabal JMY, Iturria-Medina Y, Melie-García L, Alemán-Gómez Y, et al. Spherical deconvolution of multichannel diffusion MRI data with non-Gaussian noise models and spatial regularization. *PloS one*. 2015; 10:e0138910. [PubMed: 26470024]
15. Alexander DC, Hubbard PL, Hall MG, Moore EA, Ptito M, Parker GJ, Dyrby TB. Orientationally invariant indices of axon diameter and density from diffusion MRI. *Neuroimage*. 2010; 52:1374–1389. [PubMed: 20580932]
16. Rensonnet, G., Jacobs, D., Macq, B., Taquet, M. 11th International Symposium on Medical Information Processing and Analysis. SIPAIM; 2015. A hybrid method for efficient and accurate simulations of diffusion compartment imaging signals; p. 968107-968107.2015
17. Grebenkov DS. Laplacian eigenfunctions in NMR. I. A numerical tool. *Concepts in Magnetic Resonance Part A*. 2008; 32:277–301.
18. Hall MG, Alexander DC. Convergence and parameter choice for Monte-Carlo simulations of diffusion MRI. *IEEE transactions on medical imaging*. 2009; 28:1354–1364. [PubMed: 19273001]
19. Nilsson M, Lätt J, Nordh E, Wirestam R, Ståhlberg F, Brockstedt S. On the effects of a varied diffusion time in vivo: is the diffusion in white matter restricted? *Magnetic resonance imaging*. 2009; 27:176–187. [PubMed: 18657924]
20. Panagiotaki, E., Hall, MG., Zhang, H., Siow, B., Lythgoe, MF., Alexander, DC. High-fidelity meshes from tissue samples for diffusion mri simulations; International Conference on Medical Image Computing and Computer-Assisted Intervention; 2010. p. 404-411.
21. Fieremans E, Novikov DS, Jensen JH, Helpert JA. Monte Carlo study of a two-compartment exchange model of diffusion. *NMR in Biomedicine*. 2010; 23:711–724. [PubMed: 20882537]
22. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. *Neuroimage*. 2012; 61:1000–1016. [PubMed: 22484410]
23. Jelescu IO, Veraart J, Fieremans E, Novikov DS. Degeneracy in model parameter estimation for multi-compartmental diffusion in neuronal tissue. *NMR in Biomedicine*. 2016; 29:33–47. [PubMed: 26615981]
24. Sepehrband F, Alexander DC, Kurniawan ND, Reutens DC, Yang Z. Towards higher sensitivity and stability of axon diameter estimation with diffusion-weighted MRI. *NMR in Biomedicine*. 2016; 29:293–308. [PubMed: 26748471]
25. Harms R, Fritz F, Tobisch A, Goebel R, Roebroek A. Robust and fast nonlinear optimization of diffusion mri microstructure models. *NeuroImage*. 2017
26. Gudbjartsson H, Patz S. The rician distribution of noisy mri data. *Magnetic resonance in medicine*. 1995; 34:910–914. [PubMed: 8598820]
27. Clayden JD, Nagy Z, Weiskopf N, Alexander DC, Clark CA. Microstructural parameter estimation in vivo using diffusion MRI and structured prior information. *Magnetic resonance in medicine*. 2015
28. Drobniak I, Zhang H, Ianu A, Kaden E, Alexander DC. PGSE, OGSE, and sensitivity to axon diameter in diffusion MRI: Insight from a simulation study. *Magnetic resonance in medicine*. 2016; 75:688–700. [PubMed: 25809657]
29. Raffelt D, Tournier JD, Rose S, Ridgway GR, Henderson R, Crozier S, Salvado O, Connelly A. Apparent fibre density: a novel measure for the analysis of diffusion-weighted magnetic resonance images. *Neuroimage*. 2012; 59:3976–3994. [PubMed: 22036682]
30. Taquet M, Scherrer B, Boumal N, Peters JM, Macq B, Warfield SK. Improved fidelity of brain microstructure mapping from single-shell diffusion MRI. *Medical image analysis*. 2015; 26:268–286. [PubMed: 26529580]
31. Nilsson M, van Westen D, Ståhlberg F, Sundgren PC, Lätt J. The role of tissue microstructure and water exchange in biophysical modelling of diffusion in white matter. *Magnetic Resonance Materials in Physics, Biology and Medicine*. 2013; 26:345–370.

32. Nedjati-Gilani, GL., Schneider, T., Hall, MG., Wheeler-Kingshott, CA., Alexander, DC. Machine learning based compartment models with permeability for white matter microstructure imaging; International Conference on Medical Image Computing and Computer-Assisted Intervention; 2014. p. 257-264.
33. Alonso-Ortiz E, Levesque IR, Pike GB. MRI-based myelin water imaging: A technical review. Magnetic resonance in medicine. 2015; 73:70–81. [PubMed: 24604728]
34. Burcaw LM, Fieremans E, Novikov DS. Mesoscopic structure of neuronal tracts from time-dependent diffusion. NeuroImage. 2015; 114:18–37. [PubMed: 25837598]

Figure 1. Synthetic phantom of interwoven fascicles of axons

The total environment is made up of a periodic arrangement where one layer of cylinders with radius r_1 and inter-cylinder spacing e_1 from Population 1 is followed by one layer of cylinders with radius r_2 and inter-cylinder spacing e_2 from Population 2, a distance e_l from the first layer. The green and orange shaded areas show how the water molecules of the interstitium are distributed among the populations, allowing the definition of the respective fractions of occupancy ν_1 and ν_2 and of the population-specific cylinder packing densities f_1 and f_2 .

Figure 2. Performing microstructural estimation with the superposition approximation using a discrete combinatorial search over pre-computed single-fascicle signals

Solving Problem [2] is done by exhaustive search over the parameters $r_1, f_1, r_2, f_2, \alpha$ with constraints imposed at each experiment to reduce the scope of the exhaustive search. At fixed values of the latter parameters, continuous estimation over v_1 and v_2 is possible because they are the only parameters with an explicit, continuous contribution to the approximate signal $\mathcal{S}_{appr}$ via $\mathcal{S}_{sing}$, as noted from Eq. [1]. Note that $\mathbf{u}_1$ is assumed known throughout as well as the plane in which $\mathbf{u}_2$ lies.

Figure 3. DW-MRI signals from the superposition approximation closely match signals from interwoven fascicles

Normalized DW-MRI signal attenuation ((a)–(b)) and differences ((c)–(d)) for the microstructural configuration and the HARDI shell that led to the highest RMS signal difference ($\text{RMS}=2.4 \times 10^{-2}$), plotted on the 3D sphere as a function of the gradient direction $\hat{\mathbf{g}}$. Here the absolute (c) and the relative (d) differences were highest around the direction normal to the plane defined by the fascicles' orientations $\mathbf{u}_1$ and $\mathbf{u}_2$, where DW-MRI signals were highest too.

Figure 4. DW-MRI signals from the superposition approximation closely match signals from interwoven fascicles but exhibit varying degrees of sensitivity to microstructural parameters Normalized DW-MRI signal attenuation of the reference interwoven-fascicle (continuous lines) and the superposition approximation (dashed lines) for one particular sequence extracted from each of the 8 HARDI shells reported in Table 1 with gradient direction $\hat{g}$ selected in the plane defined by $\mathbf{u}_1$ and $\mathbf{u}_2$, parallel (a–b) or perpendicular (c) to $\mathbf{u}_1$. Units of b are in s mm⁻², G in mT m⁻¹ and Δ and δ in ms. We observed: (a) low signal sensitivity at low radius values, (b) generally high sensitivity across the whole range of density values and (c) generally high sensitivity across the whole range of crossing angle values.

Figure 5. The superposition approximation shows fast convergence with increasing SNR and small asymptotic errors for the estimation of the crossing angle and the density index but a slower convergence with larger asymptotic errors for the radius index
Mean absolute error (continuous lines) and standard errors (shaded areas) obtained with Protocol A (left) and B (right) on (a)–(b) the crossing angle α , (c)–(d) the density index f , (e)–(f) the radius index r . The dashed lines are the asymptotic, noise-free errors slightly offset around their true values for visualization purposes. Sub-figures (g) and (h) display box-plots of the radius index estimates corresponding to the blue curve in sub-figures (e)–(f), where large interquartile ranges relative to the asymptotic bias up to SNR=50 suggest

that the acquisition noise is the predominant source of error rather than the use of the superposition approximation.

Figure 6. The use of the superposition approximation has little impact at clinical SNR levels where the errors caused by noise dominate

Mean absolute error (continuous lines) and standard errors (shaded areas) obtained with Protocol A (left) and B (right) on (a)–(b) the crossing angle α , (c)–(d) the density index f , (e)–(f) the radius index r . Sub-figures (g) and (h) display detailed box-plots of the distribution of the radius index estimates over all the noise repetitions at each SNR level suggesting that the errors due to noise alone dominate those due to the use of the superposition approximation at lower SNR levels.

Figure 7. The signal discrepancies of the superposition approximation have a limited impact on DIAMOND parameters

Parameters obtained when fitting the DIAMOND model with 2 voxel compartments (one for each fascicle of axons) to the approximate signal (continuous lines) and the reference interwoven-fascicle signal (dashed lines). (a)–(b) Mean compartment heterogeneity index cHEI. (c)–(d) Mean compartment radial diffusivity cRD. (e)–(f) Mean compartment axial diffusivity cAD. (g)–(h) Normalized apparent volume fraction of occupancy of the first fascicle, where the horizontal dotted line represents the reference axonal density index $f_{\text{ref}} = 0.5$ of the crossing-fascicle configurations.

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Table 1

Multi-shell acquisition protocols

The $\mathbf{\hat{g}}$ column contains the number of gradient directions in each shell (S) characterized by a gradient intensity G , duration δ and diffusion time separating the onsets of the two gradient lobes, combining into a b-value $b \equiv (\gamma G \delta)^2 (\tau - \delta/3)$.

Acquisition protocol	$\mathbf{\hat{g}}$	G [mT m ⁻¹]	δ [ms]	[ms]	b [mm ⁻²]
Protocol A (ActiveAx (15))	S1 : 90	57	5	87	496
	S2 : 90	60	13	20	682
	S3 : 90	46	15	77	2453
	S4 : 90	58	12	80	2635
Protocol B (NODDI (22))	S1 : 30	31.9			711
	S2 : 30	37.8			1000
	S3 : 60	53.4	17.5	37.8	2000
	S4 : 60	63.8			2855

Table 2
Microstructural estimation from the superposition approximation on dissimilar fascicles in the absence of noise

The values in black are the reference values of the interwoven-fascicle configurations. The errors in Experiment IIa (in blue, obtained with the discrete-continuous optimization scheme [3]) are slightly larger than the asymptotic, noise-free errors observed in Experiment I. In Experiment IIb (green, with the volume fractions of the fascicles ν_1 and ν_2 known a priori following Eq. [4]), the estimated parameters are more in line with the asymptotic estimates of Experiment I, where the populations of axons had identical properties.

Protocol A					
r_1 [μm]	f_1	r_2 [μm]	f_2	ν_1	ν_2
Ref	Ref	Ref	Ref	Ref	Ref
1.0	0.60	0.5	0.60	0.65	0.35
1.0	0.60	1.0	0.60	0.50	0.50
1.0	0.60	1.5	0.60	0.41	0.59
1.0	0.60	2.0	0.60	0.35	0.65
1.0	0.60	1.0	0.40	0.50	0.50
1.0	0.60	1.0	0.50	0.50	0.50
1.0	0.60	1.0	0.60	0.50	0.50
1.0	0.60	1.0	0.70	0.50	0.50
Protocol B					
r_1 [μm]	f_1	r_2 [μm]	f_2	ν_1	ν_2
Ref	Ref	Ref	Ref	Ref	Ref
1.0	0.60	0.5	0.60	0.65	0.35
1.0	0.60	1.0	0.60	0.50	0.50
1.0	0.60	1.5	0.60	0.41	0.59
1.0	0.60	2.0	0.60	0.35	0.65
1.0	0.60	1.0	0.40	0.50	0.50
1.0	0.60	1.0	0.50	0.50	0.50
1.0	0.60	1.0	0.60	0.50	0.50
1.0	0.60	1.0	0.70	0.50	0.50