Minimal number of sampling directions for robust measures of the spherical mean diffusion weighted signal: effects of sampling directions, b-value, signal-to-noise ratio, hardware, and fitting strategy

Kurt G Schilling[1,2], Marco Palombo[3,4], Kristin P. O'Grady[1,2], Anna J.E. Combes[1,2], Adam W Anderson[1,2,4], Bennett A Landman[1,2,6], Seth A Smith[1,2]

[1]*Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN, United States*
[2]*Vanderbilt University Institute of Imaging Science, Vanderbilt University Medical Center, Nashville, TN, United States*
[3]*Cardiff University Brain Research Imaging Centre, School of Psychology, Cardiff University, Cardiff, United Kingdom*
[4]*School of Computer Science and Informatics, Cardiff University, Cardiff, United Kingdom*
[5]*Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, United States*
[6]*Electrical Engineering and Computer Engineering, Vanderbilt University, Nashville, TN, United States*
** Corresponding author: kurt.g.schilling.1@vumc.org*

Abstract
Several recent multi-compartment diffusion MRI investigations and modelling strategies have utilized the orientationally-averaged, or spherical mean, diffusion-weighted signal to study tissue microstructure of the central nervous system. Most experimental designs sample a large number of diffusion weighted directions in order to calculate the spherical mean signal, however, sampling a subset of these directions may increase scanning efficiency and enable either a decrease in scan time or the ability to sample more diffusion weightings. Here, we aim to determine the minimum number of gradient directions needed for a robust measurement of the spherical mean signal. We used computer simulations to characterize the variation of the measured spherical mean signal as a function of the number of gradient directions, while also investigating the effects of diffusion weighting (b-value), signal-to-noise ratio (SNR), available hardware, and spherical mean fitting strategy. We then utilize empirically acquired data in the brain and spinal cord to validate simulations, showing experimental results are in good agreement with simulations. We summarize these results by providing an intuitive lookup table to facilitate the determination of the minimal number of sampling directions needed for robust spherical mean measurements, and give recommendations based on SNR and experimental conditions.

Keywords: spherical mean signal, optimal sampling, volume fraction, diffusivity

Introduction

Diffusion MRI is an imaging technique sensitive to the microscopic details of tissue architecture, which is composed of combinations of micro-environments with potentially different cell types, geometries, and diffusion characteristics. Towards this end, multi-compartment diffusion models have been developed that aim to infer biophysical properties of the tissue, for example compartmental volume fractions and diffusivities, in addition to tissue anisotropy or orientation (Assaf and Basser, 2005; Assaf et al., 2008; Dong et al., 2020; Hansen

et al., 2013; Jelescu et al., 2015; Jespersen et al., 2007; Sotiropoulos et al., 2012; Zhang et al., 2012). However, simultaneous estimation of anisotropy and other biophysical properties is challenging due to a large number of unknown parameters and possible degeneracies in the model fitting (Jelescu et al., 2016). Recently, it has been shown that averaging the diffusion weighted signal over all gradient directions factors out the effects of tissue orientation and facilitates analytic derivations of tissue microstructure from this "spherical mean" or "powder averaged" signal.

These spherical mean techniques have been applied in microscopic diffusion anisotropy imaging (Kaden et al., 2016a; Kaden et al., 2016b), fiber ball imaging (McKinnon et al., 2018), apparent fiber density imaging (Raffelt et al., 2012), rotationally invariant modeling (Novikov et al., 2018; Veraart et al., 2018b), power-law scaling (McKinnon et al., 2017; Veraart et al., 2018a), axonal radii estimation (Veraart et al., 2020; Veraart et al., 2021), and soma density imaging (Palombo et al., 2020). Robust model fitting requires an adequate number of directions to ensure an accurate measurement of the orientation-averaged signal. For this reason, most studies employ a large number of gradient directions, with typically 60-200+ directions sampled for each diffusion weighting. However, this is not always feasible for clinical scan protocols with limited scan time, where tradeoffs between scan time and robust measurements must be considered. The aim of the current work is to determine the minimum number of sampling directions for a robust measurement of the spherical mean signal at different b-values and different SNRs.

Few previous studies have investigated the effect of sampling schemes on the spherical mean signal (Afzali et al., 2021; By et al., 2018; Devan et al., 2020; Kaden et al., 2016a; Li et al., 2018; McKinnon et al., 2018). Of particular interest, Li et al. (Li et al., 2018) employed computer simulations of a 2-compartment model to determine the minimum number of gradient directions for robust spherical mean measures, considering both b-values and signal to noise ratio (SNR). They find that the spherical mean signal can be measured accurately with very few gradient directions, and that this required number of directions increases with increasing b-value and decreasing SNR. Here, we extend this work, and generalize the computer simulation framework to different diffusion models and underlying tissue microstructure, different hardware and available gradient strengths, a wider range of SNR, and several spherical mean derivation strategies. We then confirm simulation results on empirically collected diffusion data in the brain and spinal cord, with various diffusion weightings and SNR, and provide recommended minimal sampling directions depending on experimental and biological conditions.

Methods

Theory

We simulated signal using three models of diffusion in tissue (1) the widely used two-compartment model of intra- and extra-axonal spaces (*2-compartment*) typically used in white matter, (2) a compartment model for soma and neurite density imaging (*SANDI*) that may be used for both white and gray matter imaging, and (3) and a model that enables estimating an effective axonal radius within each voxel (*finite-radius*). Below, for each model we give the expressions for the diffusion weighted signal (S) along a gradient direction (**g**), for a fiber population pointing in the direction (**n**), as well as for the signal ($\bar{S}$) averaged over all gradient directions.

2-compartment model

The widely used two compartment model of intra- and extra-axonal spaces can be expressed as a function of b-value (b) and gradient direction (**g**) as:

$$S(b,\boldsymbol{g}) = S_0 \cdot [V_{in} \cdot e^{-bD_{in}^{\perp} - b\left(D_{in}^{\parallel} - D_{in}^{\perp}\right)\cdot(\boldsymbol{n}\cdot\boldsymbol{g})^2} + (1 - V_{in}) \cdot e^{-bD_{ex}^{\perp} - b(D_{ex}^{\parallel} - D_{ex}^{\perp})\cdot(\boldsymbol{n}\cdot\boldsymbol{g})^2}]$$

where S_0 is the signal for b=0, and $D_{in}^{\parallel}$, $D_{in}^{\perp}$, $D_{ex}^{\parallel}$, $D_{ex}^{\perp}$ are intra-axonal axial diffusivity, intra-axonal radial diffusivity, extra-axonal axial diffusivity, and extra-axonal radial diffusivity, respectively. Following previous studies (Kaden et al., 2016a; McKinnon et al., 2018; Szafer et al., 1995) we assumed zero radial diffusivity (i.e., stick-like intra-axonal compartment), $D_{in}^{\perp} = 0$, tortuosity constraints on the extra-axonal compartment, $D_{ex}^{\perp} = (1 - V_{in}) \cdot D_{ex}^{\parallel}$, and equal axial diffusivities, $D_{in}^{\parallel} = D_{ex}^{\parallel} = \lambda$ to constrain the model. From this, the ground truth signal averaged over all directions can be expressed as:

$$\bar{S}(b) = S_0 \cdot [\frac{V_{in}\sqrt{\pi}\,\mathrm{erf}\left(\sqrt{b\lambda}\right)}{2\sqrt{b\lambda}} + \frac{(1 - V_{in}) \cdot \sqrt{\pi} \cdot \mathrm{erf}\left(\sqrt{b\lambda V_{in}}\right)}{2\sqrt{b\lambda V_{in}}} \cdot e^{-b\lambda(1-V_{in})}]$$

Where erf is the error function.

SANDI model

The SANDI model (Palombo et al., 2020) presents a simple addition to the two-compartment model, modeling the intra-axonal compartment as zero-radius sticks (as above), an intra-soma compartment as impermeable spheres, and an extra-axonal compartment. The signal again, can be expressed as a function of b-value (b) and gradient direction (**g**) as:

$$\frac{S(b,\boldsymbol{g})}{S_0} = (1 - f_{ec})\left(f_{in} \cdot e^{-bD_{in}^{\perp} - b(D_{in}^{\parallel} - D_{in}^{\perp})\cdot(\boldsymbol{n}\cdot\boldsymbol{g})^2} + (1 - f_{in}) \cdot exp\left\{-\frac{2(\gamma g)^2}{D_{is}} \sum_{m=1}^{\infty} \frac{\alpha_m^{-4}}{a_m^2 r_s^2 - 2} \times [2\delta] - \frac{2 + e^{-\alpha_m^2 D_{is}(\Delta-\delta)} - 2e^{-\alpha_m^2 D_{is}\delta} - 2e^{-\alpha_m^2 D_{is}\Delta} + e^{-\alpha_m^2 D_{is}(\Delta+\delta)}}{\alpha_m^2 D_{is}}\right\}\right) + f_{ec} e^{-bD_{ec}}$$

where S_0, $D_{in}^{\parallel}$, $D_{in}^{\perp}$, $D_{ex}^{\parallel}$, $D_{ex}^{\perp}$ are the same as above, with an additional two free parameters D_{is} and r_s that describe the intra-soma diffusivity and radius, respectively. Here, δ and Δ are the diffusion gradient pulse width and separation, g the magnitude of diffusion gradient pulse, α_m the mth root of the equation $(\alpha r_s)^{-1} J_{\frac{3}{2}}(\alpha r_s) = J_{\frac{5}{2}}(\alpha r_s)$, with $J_n(x)$ the Bessel function of the first kind. For simplicity, only a single radius, r_s, is considered as representative of all soma in an MRI voxel. It is important to note two things: (1) that intra-soma and extra-axonal signal decay does not depend on orientation, **g**; and (2) the signal attenuation due to soma depends on the diffusion gradient pulse strength, width, and separation, which varies by scanner/hardware. The ground truth, direction averaged signal as a function of b-value becomes:

$$\bar{S}(b) = (1 - f_{ec})\left(f_{in} \cdot \frac{V_{in}\sqrt{\pi}\,\mathrm{erf}\left(\sqrt{bD_{in}}\right)}{2\sqrt{bD_{in}}} + (1 - f_{in}) \right.$$
$$\cdot exp\left\{ -\frac{2(\gamma g)^2}{D_{is}} \sum_{m=1}^{\infty} \frac{\alpha_m^{-4}}{a_m^2 r_s^2 - 2} \times [2\delta] \right.$$
$$\left.\left. - \frac{2 + e^{-\alpha_m^2 D_{is}(\Delta-\delta)} - 2e^{-\alpha_m^2 D_{is}\delta} - 2e^{-\alpha_m^2 D_{is}\Delta} + e^{-\alpha_m^2 D_{is}(\Delta+\delta)}}{\alpha_m^2 D_{is}} \right\} \right) + f_{ec} e^{-bD_{ec}}$$

Finite Radius model

Rather than assuming a zero-radius axonal component, it has recently been shown that the diffusion MRI signal may be sensitive to axon radii, after eliminating confounding factors of orientation dispersion (through spherical averaging) and extra-axonal water (at a high b-value) (Veraart et al., 2018a; Veraart et al., 2020). With a non-zero radius, $D_{in}^{\perp}$ no longer equals zero, and as above, the intra-axonal signal as a function of b-value (b) and gradient direction (g) becomes:

$$S(b, \boldsymbol{g}) = S_0 \cdot [V_{in} \cdot e^{-bD_{in}^{\perp} - b(D_{in}^{\parallel} - D_{in}^{\perp}) \cdot (\boldsymbol{n} \cdot \boldsymbol{g})^2}]$$

As described in detail in (Veraart et al., 2018a; Veraart et al., 2020), the spherical mean signal as a function of b-value (b) is then:

$$\bar{S}(b) = S_0 \cdot [V_{in} \cdot \sqrt{\frac{\pi}{4 \cdot D_{in}^{\parallel}}} \cdot e^{-bD_{in}^{\perp}} b^{-1/2}]$$

From an estimate of $D_{in}^{\parallel}$ from the orientation-averaged signal, the MR-effective radius can be calculated as $r_{MR} = (\frac{48}{7}\delta(\Delta - \delta/3)D_{in}^{\parallel}D_{in}^{\perp})^{1/4}$. Again, the sensitivity to axonal radii depends on diffusion pulse width and separation that is constrained by hardware. Note, finite-radius simulations were performed assuming complete attenuation for extra-axonal signal.

Simulations

Simulations were performed by varying and isolating several experimental and biological factors: (1) the tissue model, (2) tissue microstructure features, (3) the number of sampled gradient directions, (4) b-values, (5) SNR, (6) the spherical mean calculation, and (7) scanner hardware.

For each tissue model, diffusion-weighted signals were simulated with gradient directions **g** approximately evenly distributed on a unit sphere (Jones et al., 1999), varying the number of directions N from 6 to 120. The spherical mean signal $\bar{S}$ was computed in two ways (Afzali et al., 2021), first as the arithmetic mean of the signal over all directions and second as the zeroth-order and zeroth-degree spherical harmonic coefficient. For each value of N, 1,000 different uniformly-oriented directions of a fiber population **n** were simulated, from which the mean and standard deviation of $\bar{S}$ were calculated. Following (Li et al., 2018), the criteria to determine the minimum number of sampling directions N_{min} was based on the relative standard deviation (RSD), defined as the ratio of the standard deviation to the mean, which indicates a measure of precision of the spherical mean measurement. We determine N_{min} as the minimum number of directions to achieve $RSD(\bar{S}) \leq 5\%$ to achieve sufficient spherical sampling.

Simulations were performed in MATLAB with diffusion weighting b-value varied from 1 to 12 ms/um^2. The simulated parameters were varied for each model to cover a wide range of possible central nervous system tissue microstructures. For the 2-compartment model, $V_{in} = [0.4\ 0.6\ 0.8]$, $\lambda = [1.5\ 2\ 2.5]$ um^2/ms, with fixed parameters $S_0 = 1$. For SANDI, $f_{in} = [0.2\ 0.5\ 0.8]$, i.e., $soma\ fraction = 1 - [0.2\ 0.5\ 0.8]$, $r_s = [4\ 8\ 12]$ um, with fixed parameters $S_0 = 1$, $D_{in} = 2.5$ um^2/ms, $D_{is} = 3$ um^2/ms, $f_{ec} = 0.2$, D_{ec}= 1 um^2/ms. For the Finite radius model $r_{MR} = [1\ 3\ 5]$ um, with fixed parameters of $S_0 = 1$, $V_{in} = 1$, $D_{in}^{\parallel} = 2.5$ um^2/ms. For the SANDI and Finite-Radius models, simulations were performed for two potential imaging gradients, an 80mT/m gradient system ($\delta = 25$ ms and $\Delta = 45$ ms) that is common in most scanners, and a 300mT/m system (Jones et al., 2018) ($\delta = 8.5$ ms and $\Delta = 24$ ms).

To investigate the effect of SNR on N_{min}, complex Gaussian noise was added to the simulated signal $S(b, \boldsymbol{g})$, and the magnitude of the noisy signal was considered the measured signal $M(b, \boldsymbol{g})$, from which the mean measured signal $\overline{M}$ was computed. Signal was corrupted for SNR levels of 10, 20, 30, 40, 50, 100, and infinity (no corruption). Rician bias corrected signal was also assessed, with corrected signal amplitude $A(b, \boldsymbol{g}) = \sqrt{M^2(g, \boldsymbol{b}) - 2\sigma^2}$ with $\sigma = 1/SNR$ as the noise level. Unless otherwise noted, primary results focus on the 2-compartment model with common hardware (80mT/m) and SANDI and Finite-Radius results on the connectome scanner (300mT/m), with arithmetic averaging fit of the measured signal. Additional results on the 80mT/m scanner, fitting with spherical harmonic coefficients, and Rician bias corrected signal are given in supplementary figures.

Empirical data

Empirically acquired human data were used to demonstrate the accuracy of subsampling for spherical mean calculation and to confirm simulation results.

The first dataset was high-quality HCP data from the MGH-USC Adult Diffusion Dataset acquired on a customized Siemens 3T Connectom Scanner with 300mT/m gradient system. Diffusion data were acquired with 4 different b-values: 1ms/um^2 (64 directions), 3ms/um^2 (64 directions), 5ms/um^2 (128 directions), and 10ms/um^2 (128 directions). This dataset has previously been used to investigate the SANDI model (Palombo et al., 2020).

The second dataset was the Multiple Acquisitions for Standardization of Structural Imaging Validation and Evaluation (MASSIVE) dataset (Froeling et al., 2017) acquired at UMC Utrecht on a 3T Philips Achieva with an 80mT/m gradient system. While the full acquisition is quite exhaustive with over 8000 volumes over 5 b-values, we selected 2 b-values from a session acquired at 1ms/um^2 (125 directions) and 3ms/um^2 (125 directions), an acquisition typical for fitting the 2-compartment model.

The third dataset was acquired on the cervical spinal cord at Vanderbilt University Medical Center on a 3T Philips Achieva with an 80mT/m gradient system. Diffusion data were acquired with 3 different b-values: 1ms/um^2 (64 directions), 3ms/um^2 (64 directions), and 5ms/um^2 (64 directions). All three datasets were preprocessed for motion, eddy currents, and susceptibility distortions (Jenkinson et al., 2012).

For all datasets, subsamples were chosen based on simulation results, selecting the minimum number of directions for which RSD first falls below 5%. The *dirorder* command from the MRTrix3 software package was used to ensure a near-uniform selection of a subset of gradients. Because subsets cannot be perfectly uniform, spherical mean derivation for empirical datasets was based on spherical harmonic fits. The relative percent difference between $\overline{M}$ from the full dataset and $\overline{M}'$ from the subsampled dataset was calculated as $100 \times |\overline{M} - \overline{M}'|/\overline{M}$.

Results

Diffusion MRI signal decay depends on model, microstructure, and hardware

Figure 1 shows the expected spherical mean diffusion MRI signal as a function of b-value for the 2-compartment model (top), SANDI model (middle), and finite-radius model (bottom), for the range of simulated microstructural configurations, and for both the clinical and connectome gradients. As expected, the signal depends on the assumed model, tissue parameters, and hardware. In all cases, signal decays significantly at high b-values, with a higher non-vanishing signal observed for higher intra-axonal fractions, higher soma fractions with smaller radii, and smaller axon radii.

Figure 1. The expected diffusion MRI signal as a function of b-value (ms/um^2), for a 2-compartment model (A), 3-compartment soma model (B), and finite axonal radius model (C). Different ground truth geometries were simulated in this study, varying the intra-axonal volume fraction (Vin), intra-axonal diffusivity (lambda), soma radius (Rs), and axon radius (R). For the 3-compartment and axonal radius model, a connectome-like acquisition was simulated with 300mT/m gradients and is shown as a solid line, while a clinical-like acquisition with 80mT/m is shown as a dashed line.

Increasing number of gradient directions decreases variability of the spherical mean signal

Figure 2 shows the measured signal magnitude M and its variation over 1000 simulation directions as a function of the number of gradient directions for all 3 models and 3 selected SNR realizations. The solid lines are the ground truth spherical mean signals based on equations 2, 4, and 6. In all cases, the variability of the measured signal decreased with increasing number of directions and takes longer to converge for higher b-values and lower SNR. The measured signal did not always converge to the ground truth value due to Rician noise, and although Rician bias correction reduced bias, variance of the spherical mean signal around the mean is similar (Supplementary Figure 1). Similarly, estimating the spherical mean signal through spherical harmonic basis coefficients did not dramatically change simulations results (Supplementary Figure 2), as the sampling directions are already maximally uniformly sampled. Results for SANDI and Finite-radius models of tissue with clinical gradients (80mT/m) are also shown in supplementary results (Supplementary Figure 3).

The calculated RSD is shown in **Figure 3**, again for all models and 3 noise realizations at selected b-values. In agreement with previous observations, the RSD quickly decreases with increasing number of directions, with higher b-values and lower SNR taking longer to decrease, and converging at a higher RSD. Results for Rician-bias corrected signal, and estimation of spherical mean through spherical harmonic coefficients are given in Supplementary Figure 4 and 5 (with observations in agreement with Figure 3). The RSD is then used to determine the minimal number of N needed for RSD(M)<5%.

Figure 2. Dependence of the measured signal on the number of gradient directions. For the 2-compartment model (top), SANDI model (middle), and finite-radius model (bottom), the ground truth signal is shown as a solid line, while mean +/- standard deviation of the measured noisy signal is shown as box plots. Examples were chosen for select SNRs (Infinity, 30, 10), b-values

(1, 3, 5, and 10 ms/um2), and tissue microstructure (2-COMP: $V_{in} = 0.6, \lambda = 2$ um^2/ms; SANDI: $f_{in} = 0.5,\ r_s = 8$ um; Finite radius model $r_{MR} = 1$ um).

Figure 3. RSD decreases with increasing directions. Dependence of the calculated RSD on the number of gradient directions is shown for the 2-compartment model (top), SANDI model (middle), and finite-radius model (bottom). Examples were chosen for select SNRs (Infinity, 30, 10), b-values (1, 3, 5, and 10 ms/um2), and tissue microstructure (2-COMP: $V_{in} = 0.6, \lambda = 2$ um^2/ms; SANDI: $f_{in} = 0.5,\ r_s = 8$ um; Finite radius model $r_{MR} = 1$ um).

2-compartment model: N_{min} depends on SNR and microstructure

The minimal number of sampling directions, assuming a 2-compartment model of signal decay, is shown in **Figure 4**, shown varying SNR within a plot (top) and varying tissue microstructure within a plot (bottom). In general, sampling requirements increase linearly with b-value. Tissue microstructure also influences the calculated N_{min}, where tissue having smaller intra-axonal signal fraction requires more sampling directions. N_{min} is greater effected by SNR. When SNR>=30, very few sampling directions (N<40) are required, even at high b-value. However, at low SNR, N_{min} very quickly increases, requiring >40 directions even at low to moderate b-values.

Figure 4*. The minimal number of sampling directions for robust spherical mean depends on microstructure and image SNR. The minimal number of directions as a function of b-value are shown for the 2-compartment model, with varying SNR (top), and varying tissue microstructure (bottom).*

SANDI model: varying SNR and microstructure

Figure 5 shows the minimal sampling directions for the SANDI model (300mT/m gradients). Again, N_{min} is influenced by tissue microstructure, and to a greater extent SNR. Larger radii with a larger soma volume fraction (i.e. smaller intra-axonal fraction) require more sampling directions. In most conditions, at high SNR and with moderate volume fractions, N_{min} remains <40.

Figure 5. The minimal number of sampling directions for robust spherical mean depends on microstructure and image SNR. The minimal number of directions as a function of b-value are shown for the SANDI model, with varying SNR (top), and varying tissue microstructure (bottom).

Finite radius model: varying SNR and microstructure

The minimal number of sampling directions for the finite-radius model is shown in **Figure 6**. With MR-derived radii on the order of 1-3um (as expected in the brain), sampling

directions increase with increasing b-value, again requiring <40 directions for high b-value. However, Nmin increases for larger radii, and also at low SNR.

Figure 6. The minimal number of sampling directions for robust spherical mean depends on microstructure and image SNR. The minimal number of directions as a function of b-value are shown for the finite-radius model, with varying SNR (top), and varying tissue microstructure (bottom).

Choosing sampling directions

Table 1 provides the minimal number of sampling directions based on all simulations with all investigated degrees of freedom. Importantly, **Table 1** enables a simple lookup for planning and designing a spherical mean experiment. For example, you would first select your model (i.e., underlying tissue microstructure assumptions). Second, you would determine the expected SNR. Third, you would select the b-values you plan to sample, typically determined in the literature through a sensitivity or optimization procedure. Given these choices, the minimum sampling directions are given in column format, over the range of possible tissue environments. For convenience we have highlighted typical microstructure for in vivo human white matter in blue and gray matter in green. However, a conservative approach would be to select the worst-case scenario, i.e., the largest Nmin appearing in that column. We have also provided example direction sets as supplementary information, generated by using an electrostatic repulsion algorithm described in (Jones et al., 1999) and implemented using the *dirgen* command in MRtrix3 (Tournier et al., 2019).

As an example, with the MGH dataset, we may be interested in performing SANDI analysis with b-values of 1, 3, 5, and 10 ms/um^2 as described in SANDI's initial implementation (Palombo et al., 2020). Given an SNR~50, and an analysis focusing on gray matter only, one would select 6, 10, 30, and 48 directions. As described in detail in the discussion, oversampling is likely necessary due to variation in tissue and non-optimal distributions of sampling directions.

Table 1. The minimal number of sampling directions.

Empirical data: brain

Simulation results were validated on two example human brain datasets, shown in **Figure 7**. For the MGH dataset, we used subsets of 6 directions for b=1 ms/um^2, 12 directions for b=3 ms/um^2, 20 directions at b=5 ms/um^2, and 40 directions for b=10 ms/um^2. Visually, the subsampled spherical mean signal is similar to that from the fully sampled dataset, with whole brain relative differences of 3.5 $\pm$ 3.4%, 4.8 $\pm$ 4.3%, 4.9 $\pm$ 4.0%, and 4.2 $\pm$ 3.2%, respectively (with greater RSD observed in the low SNR center of the brain compared to the periphery given typical patterns of coil sensitivity (Farrell et al., 2007)). Similar results are observed for the MASSIVE selected data, which may be typical of a 2-compartment fit. Here, b-values of 1 ms/um^2 and 3 ms/um^2 were subsampled from 125 and 125 directions to 6 and 14 directions, respectively, resulting in whole brain relative differences of 4.3 $\pm$ 4.0%, 4.1 $\pm$ 3.6%, respectively. Thus, experimental results were in good agreement with simulation results in the brain.

Figure 7. The spherical mean signal can be accurately measured with a subset of the data in the brain. For both an example SANDI acquisition (left; SNR~50) and 2-compartment model acquisition (right; SNR~40), the spherical mean for a full dataset and subset is shown, and relative percent difference calculated.

Empirical data: spinal cord

Similar experiments were performed in the spinal cord, a central nervous system structure that has been much less investigated with multi-compartment modeling than the brain. **Figure 8** shows subsampling of the in vivo human cervical spinal cord. Subsampling was performed at b=1, 3, and 5 ms/um^2 with 8, 26, 32 directions, and evaluated against the full sampling of 64 directions each. Visually, the mean signal shows similar contrast and magnitude as the fully sampled signal, with whole cord relative differences of 4.5 $\pm$ 3.5%, 4.8 $\pm$ 3.5%, and 4.7 $\pm$ 3.5%, respectively. Again, experimental results are in line with expected values of variation from simulations.

Figure 8. The spherical mean signal can be accurately measured with a subset of the data in the spinal cord. For a 2-compartment model acquisition (SNR~20), the spherical mean for a full dataset and subset is shown, and relative percent difference calculated.

Discussion

In this work we have shown that the spherical mean can be measured accurately with a subset of gradient directions, typically much less than what is typically performed in most research studies. Acquiring fewer gradient directions at a given b-value may result in significant scan time reductions or enable acquisition of more b-values that will better condition spherical mean model fitting. Reducing scan time can be particularly beneficial in clinical imaging sessions, or for diffusion MRI that requires cardiac or respiratory gating (e.g., the spinal cord) where acquiring 50-100 images at multiple b-values is infeasible.

Our lookup table provides a convenient way to determine the minimal number of sampling directions that may be required for a particular study. By selecting the assumed tissue compartments (or the model that will be used), and the expected SNR of the scan, one can quickly determine the minimal sampling directions given a wide range of possible tissue features present in the voxel. Because this is the 'minimal' number of directions, some oversampling may be necessary, and we suggest selecting the most conservative estimate of directions from the table, unless analysis is restricted to a specific tissue type. Further, because many scanner direction sets are not perfectly uniformly distributed, it is better to use a slightly larger sampling to guarantee reasonable coverage. Even then, significant scan time savings are possible, reducing acquisitions by 2x-10x from currently used protocols depending on b-value. In agreement with studies on deriving the spherical mean signal (Afzali et al., 2021), we suggest fitting using spherical harmonic based methods, or similar, so that results are not biased by acquired diffusion directions. Finally, if the biology of the tissue in combination with acquisition conditions is expected to decrease the signal, for example larger radii, larger volume fractions of high

diffusivity compartments, and higher b-values, the number of sampling directions should be increased accordingly. We have provided direction sets (Jones et al., 1999), ranging from 6-150 directions, as supplementary resources.

Our results directly reproduce those from Li et al (Li et al., 2018), and expand upon these for different SNR, modeling, spherical mean fitting, and hardware conditions. Moreover, these results nicely parallel other recent works on subsampling for spherical mean. Schiavi et al. (Schiavi et al., 2022) recently showed that the SANDI protocol is feasible on clinical scanners, significantly undersampling those compared to the original SANDI proposal and the use of the MGH Connectom data. Notably, the chosen directions agree with the current suggestions, ranging from as few as 6 to as many as 40 diffusion directions as b-value increases from 0.5 to 6 ms/um^2. The original implementation and description of the 2-compartment spherical mean model also investigated subsets of the data (Kaden et al., 2016a), finding that 50 directions resulted in minimal error and no bias compared to 500+ directions, and we extend this by showing that fewer than 50 are often adequate. Finally, in the spinal cord, work by By et al. (By et al., 2018), showed feasibility of reducing scan time by a factor of 2 (from 64 to 32 directions) with minimal bias in spherical mean measures, saving ~9 minutes of scanning. Studies on efficient and optimal sampling are necessary to enable widespread use and validation of these models, much like the early studies on optimizing diffusion tensor imaging strategies (Farrell et al., 2007; Jones et al., 1999; Landman et al., 2007).

When designing an acquisition scheme, it is important to consider the precision needed. Here, we chose RSD as a summary statistic of variation over expected value, and empirically chose 5% as a baseline (Li et al., 2018). Investigating the effect of variance, and variance at each b-value, is beyond the scope of the current work, and will be specific to the model and assumptions. Different precision may be necessary for different b-values due to higher sensitivity of the signal for different compartments, and RSD<5% may not be enough. We additionally include tables for RSD<2.5% as supplementary material, but note that this is also empirically chosen. Other measures of precision could be chosen, for example normalized to the b=0 signal itself,or normalized by expected change in attenuation at a given b-value. Finally, we chose to present primary results where RSD is calculated based on the noisy measured signal rather than the Rician bias corrected signal. Because Rician bias correction decreases the signal, this will increase RSD and subsequent minimal number of directions, however the variance (with the Rician bias correction used here) remains the same.

Conclusion

In this study, we characterized the variation of the spherical mean diffusion MRI signal as a function of the number of gradient directions. The minimal number of sampling directions for robust measurement was determined, and depends on b-value, underlying tissue microstructure, and SNR. We present an intuitive way to determine the recommended minimal number of directions to ensure robust measurements when designing a spherical mean based diffusion protocol.

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