Magnetic Resonance Imaging 54 (2018) 148–152

Contents lists available at ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.elsevier.com/locate/mri

Original contribution

Minimal number of gradient directions for robust measurement of spherical mean diffusion weighted signal

Hua Li[a,*], Ho Ming Chow[a], Diane C. Chugani[a,b], Harry T. Chugani[a,c]

[a] Katzin Diagnostic & Research PET/MR Center, Nemours – Alfred I. duPont Hospital for Children, Wilmington, DE 19803, USA
[b] College of Health Sciences, University of Delaware, Newark, DE 19716, USA
[c] Department of Neurology, Thomas Jefferson University, Philadelphia, PA 19107, USA

ARTICLE INFO

Keywords:
Diffusion tensor imaging (DTI)
Intra-axonal volume fraction
Spherical mean signal
Spherical mean technique (SMT)

ABSTRACT

Purpose: Determination of the minimum number of gradient directions (N_{min}) for robust measurement of spherical mean diffusion weighted signal ($\bar{S}$).
Methods: Computer simulations were employed to characterize the relative standard deviation (RSD) of the measured spherical mean signal as a function of the number of gradient directions (N). The effects of diffusion weighting *b*-value and signal-to-noise ratio (SNR) were investigated. Multi-shell high angular resolution Human Connectome Project diffusion data were analyzed to support the simulation results.
Results: RSD decreases with increasing N, and the minimum number of N needed for RSD ≤ 5% is referred to as N_{min}. At high SNRs, N_{min} increases with increasing *b*-value to achieve sufficient sampling. Simulations showed that N_{min} is linearly dependent on the *b*-value. At low SNRs, N_{min} increases with increasing *b*-value to reduce the noise. RSD can be estimated as $\frac{\sigma}{\bar{S}\sqrt{N}}$, where $\sigma = 1/\mathrm{SNR}$ is the noise level. The experimental results were in good agreement with the simulation results. The spherical mean signal can be measured accurately with a subset of gradient directions.
Conclusion: As N_{min} is affected by *b*-value and SNR, we recommend using $10 \times b / b_1$ ($b_1 = 1\ \mathrm{ms/\mu m^2}$) uniformly distributed gradient directions for typical human diffusion studies with SNR ~ 20 for robust spherical mean signal measurement.

1. Introduction

Diffusion MRI is a non-invasive tool to detect tissue microstructural information based on restricted water Brownian motion within tissues. The conventional technique measuring tissue microstructure is diffusion tensor imaging (DTI), a technique that models water diffusion in each voxel as a symmetric tensor [1]. The DTI derived mean diffusivity (MD) and fractional anisotropy (FA), measures widely used to quantify tissue microstructure, are rotationally invariant. However, for two voxels with different fiber directions, the measured FA_{voxel1} and FA_{voxel2} cannot be simply averaged to obtain the entire voxel FA. In other words, the single tensor model is inappropriate for quantifying tissue microstructure in situations with complex fiber orientation distribution (FOD). Another diffusion-based approach to quantify tissue microstructure is direct measurement of tissue properties, such as axon size and intra-axonal volume fraction (V_{in}) [2–5]. V_{in} is rotationally invariant, independent of FOD, and can be averaged. The crossing fiber problem still needs to be considered in order to measure V_{in} accurately. Simultaneous fitting of FOD and V_{in} is challenging as the number of unknown parameters increases with increasing the complexity of FOD [6–9]. Recently, it was demonstrated that the FOD information can be factored out by analyzing the spherical mean diffusion weighted signal ($\bar{S}$) averaged over all gradient directions [10–12]. A simple linear relation between V_{in} and $\bar{S}$ was further derived analytically [12]. $\bar{S}$-based analysis has been applied in various recent works, such as apparent fiber density [13–15], spherical mean technique [11,16,17], fiber ball imaging [12,18], power-law scaling [19,20], and rotationally-invariant framework [21–23].

Previous $\bar{S}$-based studies employed a large number of gradient directions, but subsequent sparse sampling analysis demonstrated that the number of gradient directions could be reduced without significant effect on accuracy [16–18]. Clinical diffusion scan protocols are typically < 5 min, which only allows acquiring ~30 different directions. It is undetermined as whether 30 directions is enough for accurate $\bar{S}$ measurement, especially at high *b*-values ($b \geq 3\ \mathrm{ms/\mu m^2}$). Multi-shell acquisition schemes are able to obtain a more comprehensive diffusion

* Corresponding author at: Nemours AI duPont Hospital for Children, 1600 Rockland Road, 1A324, Wilmington, DE 19803, USA.
E-mail address: hua.li@nemours.org (H. Li).

https://doi.org/10.1016/j.mri.2018.08.020
Received 3 July 2018; Received in revised form 28 August 2018; Accepted 28 August 2018
0730-725X/

dataset, and hence, provide greater sensitivity in detecting tissue microstructure than single-shell schemes [11,16,24]. The increased scanning time requires optimal design of number of directions for each shell.

Given the substantial recent interest in using $\overline{S}$ to quantify tissue microstructure, it is worthwhile to determine the minimum number of gradient directions for robust measurement of $\overline{S}$. The current study aims to determine the minimum number of gradient directions for robust measurement of spherical mean signals at different *b*-values. Similar to previous DTI and spherical deconvolution studies [25–27], we employed computer simulations to investigate the effect of signal-to-noise ratio (SNR) on the required number of gradient directions. Multi-shell Human Connectome Project (HCP) diffusion datasets were used to support the simulation results.

2. Materials and methods

2.1. Theory

The results of single fiber analysis can be generalized to crossing fibers as illustrated by Tournier et al. [27] in the determination of the minimum number of directions for spherical deconvolution. The problem of determining the minimum number of directions for spherical mean signal can also be restricted to single fiber analysis. The total spherical mean signal in each voxel is simply the sum of each single fiber's spherical mean signal, and the spherical mean signal of a single fiber is independent of the fiber orientation [10,11]. For this reason, we focus on the analysis of a single fiber pointing in the direction **n**. Based on the widely used two-compartment model of intra- and extra-axonal spaces, the diffusion weighted signal (S) along gradient direction **g** can be expressed as

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

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 multi-compartment modeling studies, we assume $D_{in}^{\perp} = 0$ [16,18,23], $D_{ex}^{\perp} = (1 - V_{in})\cdot D_{ex}^{\parallel}$ [16,28], and $D_{ex}^{\parallel} = D_{in}^{\parallel} =$ the intrinsic diffusivity λ [16]. The ground truth $\overline{S}$ is the signal averaged over all gradient directions, and it can be expressed as

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

where erf is the error function. Due to the exponential decay term, the extra-axonal water contribution can be neglected with sufficiently large *b*-values. In that case, a simple linear relation between $\overline{S}$ and V_{in} can be derived as $\overline{S} = S_0\cdot V_{in}\cdot\frac{\sqrt{\pi}}{2\sqrt{b\lambda}}$ [12,13]. Note that $\mathrm{erf}(\sqrt{b\lambda}) \geq 0.98$ when $b\lambda \geq 3$.

2.2. Simulations

Diffusion-weighted signals were simulated with gradient directions approximately evenly distributed on a unit sphere as proposed by Jones et al. [29]. The number N of gradient directions varied from 6 to 100, and the spherical mean signal $\overline{S}$ was calculated as the signal averaged over N directions. For each value of N, 10,000 different directions of the single fiber **n** (uniformly sampled on a sphere) were simulated, from which the mean and standard deviation of $\overline{S}$ were calculated. The relative standard deviation (RSD), defined as the ratio of the standard deviation to the mean, was used to indicate the precision of $\overline{S}$ measurement. N_{min} was determined as the minimum number of gradient directions for $RSD(\overline{S}) \leq 5\%$. N_{min} is the number of gradient directions needed to achieve sufficient sampling.

Computer simulations were performed in MATLAB with $S_0 = 1$, $V_{in} = 0.6$, and $\lambda = 2\,\mu m^2/ms$ to mimic typical brain white matter parameters [16,18,23]. The diffusion weighting *b*-value varied from 1 to 10 ms/μm². To investigate the effect of SNR on N_{min}, complex Gaussian noise was added to the simulated signal S(*b*,**g**), and the magnitude of the noisy signal was then taken as the measured signal M (*b*,**g**). To correct for Rician bias in the measured signal, here we used the corrected amplitude signal $A(b,\mathbf{g}) = \sqrt{M^2(b,\mathbf{g}) - 2\sigma^2}$, where $\sigma = 1/SNR$ is the noise level. The corresponding $\overline{M}$, $\overline{A}$, $RSD(\overline{M})$, and $RSD(\overline{A})$ were calculated accordingly. Two typical SNRs in the $b = 0$ image of 20 and 40 were used for current study. Two factors are expected to affect $RSD(\overline{M})$ or $RSD(\overline{A})$. The first is the noiseless $RSD(\overline{S})$, and the second is the impact of noise. Since the standard deviation of the mean of N normally distributed random variables is $\frac{\sigma}{\sqrt{N}}$, the noise related RSD is estimated as $\frac{\sigma}{\overline{S}\sqrt{N}}$. Therefore, we used the maximum of $RSD(\overline{S})$ and $\frac{\sigma}{\overline{S}\sqrt{N}}$ to approximate $RSD(\overline{M})$ or $RSD(\overline{A})$.

$$RSD_{app} = \max\left\{RSD(\overline{S}), \frac{\sigma}{\overline{S}\sqrt{N}}\right\} \tag{3}$$

N_{min} was determined as the minimum number of gradient directions for $RSD_{app} \leq 5\%$.

2.3. Human data

High-quality HCP data from 3 healthy adults, as part of the MGH-USC Adult Diffusion Dataset, were downloaded from ConnectomeDB (http://db.humanconnectome.org). Diffusion data were acquired with 4 different *b*-values (i.e., 4 shells): 1 ms/μm² (64 directions), 3 ms/μm² (64 directions), 5 ms/μm² (128 directions), and 10 ms/μm² (256 directions). The gradient direction sets were specifically designed so that a lower shell set is a subset of higher shell set. At each shell, the gradient directions were approximately uniformly distributed [29–31]. One non-diffusion weighted $b = 0$ image was collected for every 13 diffusion weighted images. The signal-to-noise ratio (SNR) was about 20 for white matter in the $b = 0$ image, which was estimated with a maximum-likelihood approach [32].

To demonstrate the accuracy of subsampling for $\overline{M}$ measurement, a subset of gradient directions at each shell were selected: 10 directions for $b = 1$ ms/μm², 30 directions for $b = 3$ ms/μm², 50 directions for $b = 5$ ms/μm², and 100 directions for $b = 10$ ms/μm². Those subsets were determined with the incremental sampling scheme to guarantee reasonably uniform coverage [31]. The numbers of gradient directions in subsets were guided by the simulation results. The relative differences of $\overline{M}$ between full data sets and subsets were calculated.

3. Results

The simulated signal $\overline{S}$, measured magnitude $\overline{M}$, and corrected amplitude $\overline{A}$ were dependent on the number N of gradient directions (Fig. 1). The markers represent the mean values over 10,000 different directions of the single fiber **n**, and the error-bars represent the standard deviations. The solid lines are the ground truth spherical mean signals based on Eq. (2). As shown in Fig. 1(a), the mean $\overline{S}$ is consistent with the ground truth at each *b*-value and the standard deviation decreases with increasing N. The Rician bias is evident in Fig. 1(b), especially at high *b*-values. Increasing N did not help reduce the Rician bias. The corrected amplitude $\overline{A}$ is closer to the ground truth than $\overline{M}$.

$RSD(\overline{S})$ decreases with increasing N, and the minimum number of N needed for $RSD(\overline{S}) \leq 5\%$ is referred to as N_{min}. Fig. 2(a) shows the calculated $RSD(\overline{S})$ as a function of the number of gradient directions. As expected from previous spherical deconvolution work [27], the diffusion signal profile becomes sharp with increasing *b*-value and more gradient directions are needed for accurate measurements of $\overline{S}$. Fig. 2(b) shows the linear dependence of N_{min} on *b*-value.

Our simulations showed that $RSD(\overline{A})$ can be properly fit by Eq. (3).