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Efficient experimental designs for Isotropic Generalized Diffusion Tensor MRI (IGDTI)

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Abstract

Purpose—We propose a new generalized diffusion tensor imaging (GDTI) experimental design and analysis framework for efficiently measuring orientationally-averaged diffusion weighted images (DWI), which remove bulk signal modulations due to diffusion anisotropy and quantify isotropic higher-order diffusion tensors (HOT). We illustrate how this framework accelerates the clinical measurement of rotation-invariant tissue microstructural parameters derived from HOT, such as the HOT-Trace and the mean t-kurtosis.

Theory and Methods—For a large range of b-values, we compare orientationally-averaged DWIs measured with high angular resolution diffusion imaging (HARDI) to those obtained with the proposed isotropic GDTI (IGDTI) experimental design. We compare rotation-invariant microstructural parameters measured with IGDTI to those derived from HOTs measured explicitly with GDTI.

Results—In both fixed-brain micro-imaging and *in vivo* clinical experiments, IGDTI accurately quantifies mean apparent diffusion coefficient (mADC)-weighted DWIs over a wide range of b-values and allows efficient computation of HOT-derived scalar tissue parameters from a small number of DWIs.

Conclusions—IGDTI provides direct and accurate estimates of orientationally-averaged tissue water mobilities over a wide range of b-values. This efficient method may enable new, sensitive and quantitative assessments for clinical applications in which changes in mADC can be observed such as detecting and characterizing stroke, cancers, and neurodegenerative diseases.

Keywords

mean diffusivity; anisotropy; mean apparent diffusion coefficient (mADC); trace; diffusion tensor imaging (DTI); higher-order tensor; HOT

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Introduction

Rotation-invariant parameters, such as the mean apparent diffusion coefficient (mADC) (1), have proven to be sensitive, robust, and reliable quantitative clinical imaging biomarkers for non-invasive detection and characterization of hypoxic ischemic brain injury (2) and other pathologies (3). For a given diffusion sensitization, b , the mADC quantifies the apparent diffusion coefficient averaged uniformly over all orientations $\mathbf{u}$ on the unit sphere

$$mADC(b) = -\frac{1}{4\pi} \int \frac{1}{b} \ln \frac{S_b(\mathbf{u})}{S_0} d\Omega_{\mathbf{u}}$$

, where $S_b(\mathbf{u})$ is the diffusion weighted signal along orientation $\mathbf{u}$, S_0 is the non-diffusion weighted (baseline) signal, and $d\Omega_{\mathbf{u}}$ is the solid angle in the direction of $\mathbf{u}$. For small b -values (i.e., in the Gaussian diffusion regime) the mADC equals one-third the Trace of the diffusion tensor (1), and can be measured from several diffusion weighted images (DWIs) using multiple methods:

Method 1: By taking the geometric mean of multiple DWIs acquired with the diffusion gradient orientations uniformly sampling the unit sphere (4),

Method 2: By estimating the entire diffusion tensor (5) from measured DWI data,

Method 3: By taking the geometric mean of DWIs acquired with diffusion sensitizing gradients applied in three orthogonal directions (most economical).

As a rotation-invariant structural parameter immune to diffusion anisotropy, the mADC provides a robust and eloquent biomarker of tremendous clinical value for detecting and characterizing tissue changes, primarily in stroke and cancer.

Technological advances in radio-frequency (RF) and magnetic field gradient hardware on clinical MRI systems have enabled measurements of mADCs using higher diffusion sensitizations that were previously inaccessible. Clinical studies have shown that the mADC measured at higher b -values improves conspicuity and discrimination in prostate tumors (6), breast lesions (7), and cerebral gliomas (8), and provides a better marker for cell viability (9).

Nevertheless, the ability of the Trace of the diffusion tensor to quantify orientationally-averaged bulk properties of tissue water is limited to low diffusion sensitizations (up to b -values ~ 1000 s/mm²) for which the Gaussian approximation of the signal phase distribution underlying diffusion tensor imaging (DTI) is valid. At higher b -values signal modulations due to diffusion anisotropy become more prominent, especially in regions with complex microstructure (such as crossing white matter fiber pathways), potentially leading to confounds in the interpretation of clinical findings. mADC-weighted signals with higher diffusion sensitization can be obtained by averaging a large number of DWIs acquired with multiple orientations uniformly sampled over the unit sphere (**Method 1**). Alternatively, analogous to **Method 2**, one could analytically approximate the diffusion signal equation using the cumulant expansion and measure the higher order diffusion tensors (HOTs) using an extension of DTI called generalized diffusion tensor imaging (GDTI) (10–12). Both

approaches for measuring orientation-averaged diffusion properties at high b-values require long scan durations to accommodate the acquisition of a large number of DWI data sets with dense orientational sampling (13), rendering these experimental designs impractical for routine clinical use.

A recent paper (14) proposed a more efficient gradient sampling scheme consisting of only 12 DWIs and one baseline non-diffusion weighted ($b=0$ s/mm²) image for estimating the mean kurtosis tensor, i.e., the mean t-kurtosis, $\overline{\mathbb{W}}$. This rotation-invariant parameter is analogous to the mean kurtosis (MK) in diffusion kurtosis imaging (DKI) (15,16), which can be derived from the Traces of the 2nd- and 4th-order diffusion tensors. Similar to the mADC in stroke, it has been claimed that microstructural parameters computed from generalized Traces of HOTs (17), such as the mean t-kurtosis, may provide eloquent (and potentially more biologically specific) clinical markers for many neuropathologies (18–22). Hence, there is a need for extending the clinical quantitation of rotation-invariant diffusion tissue properties to higher b-values and for designing efficient diffusion-encoding schemes to measure intrinsic HOT-derived microstructural parameters.

We propose a novel framework, called isotropic generalized diffusion tensor imaging (IGDTI), and accompanying experimental designs that produce diffusion weightings which are analytically related to the orientational complexity of the bulk diffusion signal as described by HOTs and can efficiently remove modulations due to diffusion anisotropy. We evaluate the potential of IGDTI to measure, within clinically feasible scan durations, mADCs over a wide range of b-values and various rotation-invariant microstructural parameters, such as HOT-Traces (10,17), or the mean t-kurtosis (14). The proposed IGDTI framework may improve and accelerate experimental designs for clinical assessments with advanced diffusion MRI methods (13,23) and encourage the development of new, biologically-specific rotation-invariant parameters for quantifying tissue water mobilities in clinical applications.

Theory

1. Diffusion-weighting by the generalized Traces of HOTs

The diffusion MR signal, $S(\mathbf{G})$, produced by a pulsed-field gradient (PFG) spin-echo diffusion preparation with gradient

$\mathbf{G} = \mathbf{G}\mathbf{u}^T = \mathbf{G}[u_x, u_y, u_z]^T = \mathbf{G}[\sin\theta \cos\phi, \sin\theta \sin\phi, \cos\theta]^T$ can be approximated in terms of HOTs using the cumulant expansion of the MR signal phase (10). Using the Einstein convention for tensor summation we can write the logarithm of the diffusion signal attenuation as:

$$\ln \frac{S(\mathbf{G})}{S_0} = \sum_{n=1}^N i^n b_{i_1 i_2 \dots i_n}^{(n)} D_{i_1 i_2 \dots i_n}^{(n)} \quad (1)$$

where S_0 is the baseline (non-diffusion weighted image), $D_{i_1 i_2 \dots i_n}^{(n)}$ is the HOT of rank n in three-dimensional space ($i_k = x, y, z$) with physical units of mm^n/s , and

$$b_{i_1 i_2 \dots i_n}^{(n)} = \gamma^n \delta^n G^n \left(\Delta - \frac{n-1}{n+1} \delta \right) u_{i_1} u_{i_2} \dots u_{i_n} \quad (2)$$

is the corresponding rank- n b-tensor with units of $(s/mm)^n$. In addition, γ , δ , and Δ , are the magnetogyric ratio, diffusion gradient pulse duration, and pulse separation, respectively.

In the long diffusion-time limit and in the absence of flow, the net displacement probability function of diffusing spins is symmetric with respect to the origin and only tensors with even rank n contribute to the signal expansion in Eq. 1. Moreover, because these tensors are fully symmetric, tensor components with permuted spatial indices are equal. For example, for the 4th-order tensor, $D_{xyz}^{(4)} = D_{zxyz}^{(4)} = \dots = D_{yzxz}^{(4)}$. These assumptions are generally valid for both *in vivo* and fixed-brain imaging (13) and significantly reduce the number of unknown tensor components that need to be estimated with GDTI (10,13).

Moving forward, it is convenient to adopt the so-called “occupation number” notation (24)

by which $D_{n_x n_y n_z}^{(n)}$ denotes all equal (degenerate) tensor elements $D_{i_1 i_2 \dots i_n}^{(n)}$ obtained from all possible permutations in which the spatial indices x , y , and z appear n_x , n_y , and n_z times, respectively. With this notation we can re-write Eq. 1 more compactly for fully symmetric diffusion processes by retaining only HOTs with even rank:

$$\ln \frac{S(G)}{S_0} = \sum_{n=2,4,6 \dots n_x+n_y+n_z=n}^{N_{max}} \sum (-1)^{\frac{n}{2}} \beta_n u_x^{n_x} u_y^{n_y} u_z^{n_z} \mu_{n_x n_y n_z} D_{n_x n_y n_z}^{(n)} \quad (3)$$

where $\mu_{n_x n_y n_z} = \frac{n!}{n_x! n_y! n_z!}$ represents the multiplicity of each unique HOT component

$D_{n_x n_y n_z}^{(n)}$ of rank $n = n_x + n_y + n_z$, and the scalar $\beta_n = \gamma^n \delta^n G^n \left(\Delta - \frac{n-1}{n+1} \delta \right)$ is the orientation-averaged diffusion sensitization factor for order n .

We obtain an orientationally-averaged (isotropic) measurement of the log attenuation,

$\langle \ln \frac{S(G)}{S_0} \rangle_s$, by integrating Eq. 3 over all possible orientations on the unit sphere. Using the following identity derived in Appendix A:

$$\frac{1}{4\pi} \int u_x^{n_x} u_y^{n_y} u_z^{n_z} d\Omega_u = \frac{K_{n_x n_y n_z}}{(n+1)} \frac{\mu_{\frac{n_x}{2} \frac{n_y}{2} \frac{n_z}{2}}}{\mu_{n_x n_y n_z}} \quad (4)$$

where $K_{n_x n_y n_z} = 1$ when n_x , n_y , and n_z are all even, and $K_{n_x n_y n_z} = 0$ otherwise. The integral of Eq. 3 over all orientations on the unit sphere becomes:

$$\langle \ln \frac{S(G)}{S_0} \rangle_S = \sum_{n=2,4,6,\dots}^{N_{max}} \sum_{n_x+n_y+n_z=n} (-1)^{\frac{n}{2}} K_{n_x n_y n_z} \beta_n \frac{\mu_{\frac{n_x}{2} \frac{n_y}{2} \frac{n_z}{2}}}{(n+1)} D_{n_x n_y n_z}^{(n)} \quad (5)$$

Note that, as expected, the orientation-averaged signal is weighted by the generalized traces of HOTs of even ranks, n defined as:

$$Tr D^{(n)} = \sum_{n_x+n_y+n_z=n} K_{n_x n_y n_z} \mu_{\frac{n_x}{2} \frac{n_y}{2} \frac{n_z}{2}} D_{n_x n_y n_z}^{(n)} \quad (6)$$

, which is related to the generalized mean diffusivity (17) of order n : $\overline{D^{(n)}} = \frac{Tr D^{(n)}}{n+1}$. Eq. 5 describes the orientation-averaged signal at arbitrary diffusion sensitization obtained from a very large number of DWIs acquired with orientations uniformly sampling the unit sphere. In practice the acquisition of such large data sets is infeasible for pre-clinical and clinical applications. In the next section we describe a general strategy for designing efficient diffusion gradient sampling schemes that allow fast computation of rotation-invariant diffusion weightings at high b-values from only a few DWIs.

2. Efficient experimental designs for Isotropic GDTI (IGDTI)

The weightings of unique tensor elements $D_{n_x n_y n_z}^{(n)}$ in the expression for the orientation-averaged (i.e., trace-weighted) log signal attenuation in Eq. 5 satisfy two properties:

Condition 1: Only diffusion tensor components with all even indices n_x, n_y, n_z have non-zero weightings (i.e., $K_{n_x n_y n_z} = 0$, unless n_x, n_y, n_z are all even)

Condition 2: The non-zero weightings of $D_{n_x n_y n_z}^{(n)}$ (i.e., $\mu_{\frac{n_x}{2} \frac{n_y}{2} \frac{n_z}{2}}$) do not depend on the order of the spatial indices x, y, and z.

First, we design diffusion gradient sampling schemes that allow us to achieve signal weightings satisfying **Conditions 1** and **2** via linear combinations of the measured log DWIs. Second, we linearly combine multiple signals to obtain the precise weightings for $D_{n_x n_y n_z}^{(n)}$ required for an orientationally-averaged measurement (Eq. 5) and for the computation of the HOT generalized Traces (Eq. 6) from a small total number of DWIs.

Starting with an arbitrary orientation for the applied diffusion gradients $\mathbf{u}^T = [u_x, u_y, u_z]^T$, we can construct an orientationally averaged weighting scheme satisfying both **Conditions 1** and **2** using only 12 DWIs. First, to achieve zero weighting for all HOT components with at least one odd index n_x, n_y, n_z (**Condition 1**) we average the log signal attenuations (Eq. 3) of 4 DWIs acquired with the same b-value and the following gradient orientations $[-u_x, u_y, u_z]^T, [u_x, -u_y, u_z]^T, [u_x, u_y, -u_z]^T$, and $[-u_x, -u_y, -u_z]^T$ to obtain:

$$\left\langle \ln \frac{S(\mathbf{G})}{S_0} \right\rangle_4 = \sum_{n=2,4,6 \dots n_x+n_y+n_z=n}^{N_{max}} \sum_{n_x, n_y, n_z} (-1)^{\frac{n}{2}} K_{n_x n_y n_z} \beta_n u_x^{n_x} u_y^{n_y} u_z^{n_z} \mu_{n_x n_y n_z} D_{n_x n_y n_z}^{(n)} \quad (7)$$

Second, to ensure that all tensor components $D_{n_x n_y n_z}^{(n)}$ have the same weighting in Eq. 7 when the spatial indices x, y, and z are permuted (**Condition 2**), we repeat the first step for three unit vectors $[u_x, u_y, u_z]^T$, $[u_z, u_x, u_y]^T$, and $[u_y, u_z, u_x]^T$ derived from $\mathbf{u}^T$. The general expression for the log signal attenuation averaged over the 12 DWIs is:

$$\left\langle \ln \frac{S(\mathbf{G})}{S_0} \right\rangle_{12} = \frac{1}{3} \sum_{n=2,4,6 \dots n_x+n_y+n_z=n}^{N_{max}} \sum_{n_x, n_y, n_z} (-1)^{\frac{n}{2}} K_{n_x n_y n_z} \beta_n \left(u_x^{n_x} u_y^{n_y} u_z^{n_z} + u_x^{n_z} u_y^{n_x} u_z^{n_y} + u_x^{n_y} u_y^{n_z} u_z^{n_x} \right) \mu_{n_x n_y n_z} D_{n_x n_y n_z}^{(n)} \quad (8)$$

Due to the inherent symmetries of the HOTs, the number of DWIs necessary for computing the average log signal attenuations satisfying **Conditions 1** and **2** in Eq. 8 can be significantly reduced for three special cases of the unit vector $\mathbf{u}$ (see Fig. 1):

1. **Scheme 1:** Starting with $\mathbf{u}=[1, 0, 0]^T$ only three of the twelve measurements are unique. Therefore the average log signal attenuation in Eq. 8, henceforth denoted by $M_3(b)$ for this sampling scheme, can be measured from only three DWIs.
2. **Scheme 2:** Starting with $\mathbf{u}=\left[\frac{1}{\sqrt{3}}, \frac{1}{\sqrt{3}}, \frac{1}{\sqrt{3}}\right]^T$ only four of the twelve measurements are unique. Therefore the average log signal attenuation in Eq. 8, henceforth denoted by $M_4(b)$ for this sampling scheme, can be measured from only four DWIs.
3. **Scheme 3:** Starting with $\mathbf{u}=\left[\frac{1}{\sqrt{2}}, \frac{1}{\sqrt{2}}, 0\right]^T$ only six of the twelve measurements are unique. Therefore the average log signal attenuation in Eq. 8, henceforth denoted by $M_6(b)$ for this sampling scheme, can be measured from only six DWIs.

The average log signal attenuations, $M_3(b)$, $M_4(b)$, and $M_6(b)$ derived from sampling **Schemes 1, 2, and 3**, respectively satisfy **Conditions 1** and **2**, and can be linearly combined to achieve the precise weightings of higher-order tensor elements, $D_{n_x n_y n_z}^{(n)}$ (up to $n=6$) required for an orientationally-averaged (i.e., isotropic or mADC-weighted) measurement with high b-value (Eq. 6). Table 1 summarizes the relative weightings of unique tensor elements $D_{n_x n_y n_z}^{(n)}$ in $M_3(b)$, $M_4(b)$, and $M_6(b)$, as well as in $Tr^{(n)}$ and $\overline{D}^{(n)}$ (up to $n=6$). Table 2 summarizes the linear combinations that achieve orientation-averaged diffusion

weighting in different b-value ranges suggested based on the diffusivities of fixed and live brain tissue.

It is interesting to note that these gradient sampling schemes have been previously proposed for measuring the mADCs in the DTI regime and were discussed by Jones (25). Specifically, **Scheme 1** was originally proposed by (5) as an efficient method for measuring the DTI Trace from a minimum of 3 DWIs and a baseline (non-diffusion weighted image). **Scheme 2** was proposed by Conturo et al. (26), and represents a clever solution for measuring DTI mADCs by efficiently leveraging the limited gradient hardware available on clinical scanners in the early days of diffusion MRI. **Scheme 3** proposed by Davis et al., (27), allows the explicit measurement of the rank-2 (DTI) tensor (28). Finally, combinations of **Schemes 1 and 3** (see row 5 in Table 2) was proposed by Hansen et al., (14,29) to efficiently measure the mean t-kurtosis.

3. IGDTI-derived microstructural parameters

Depending on the b-value and tissue mean diffusivity, we can approximate the diffusion signal by truncating the sum in Eq. 5 and ignoring contributions from generalized diffusion tensors with very high order. With the appropriate truncations (see Table 2), we can combine Schemes 1, 2, and 3 to design very efficient IGDTI experiments that achieve rotation-invariant (i.e., mADC) weighting for a wide range of diffusion sensitizations. The most efficient IGDTI sampling schemes that achieve isotropic HOT weighting up to orders 2, 4, and 6 require 3, 7, and 13 DWIs, respectively, and are highlighted in green in Table 2. Specifically, one can produce mADC-weighted DWIs from only one baseline image and 3 DWIs for low b-values, 3+4=7 DWIs for intermediate b-values, and 3+4+6=13 DWIs for high b-values. Moreover, from at least three mADC-weighted DWIs sampled in different b-value regimes (which can be obtained from one baseline image and 3+7+13=23 DWIs) we can determine the generalized mean diffusivities $\overline{D^{(2)}}$, $\overline{D^{(4)}}$, and $\overline{D^{(6)}}$, respectively (and implicitly HOT Traces, $TrD^{(2)}$, $TrD^{(4)}$, $TrD^{(6)}$) by solving the linear system of equations corresponding to the (green) rows in Table 2. We can also compute other useful rotation-invariant microstructural parameters that are related to these generalized mean diffusivities, such as the mean t-kurtosis:

$$\overline{W} = \frac{6\overline{D^{(4)}} \left(\Delta - \frac{3\delta}{5} \right)}{\overline{D^{(2)}}^2 \left(\Delta - \frac{\delta}{3} \right)^2} \quad (9)$$

Note that $\overline{W}$ is dimensionless (i.e., has no physical units). It is derived from a polynomial expansion of the log signal attenuation (cumulant expansion) with respect to the b-matrix (15), not the q-vector, as in GDTI (10), hence the additional factors related to gradient pulse timings in Eq. 9. In the limit of an infinitely short gradient pulse duration δ , the two expansions are identical for fully symmetric diffusion.

Methods

1. Fixed ferret brain data

A brain specimen from an adult male ferret was prepared for *ex vivo* MRI scanning following cardiac perfusion. The animal was housed and treated at the Uniformed Services University of the Health Sciences (USUHS) according to national guidelines and an approved institutional protocol. On the day of perfusion the animal was deeply anesthetized by isoflurane inhalation (5% in oxygen) and euthanized with an intraperitoneal overdose of Euthasol (50 mg/kg). Upon cessation of reflexes, the ferret was transcardially perfused with 1L of ice-cold phosphate buffered saline (PBS) (pH 7.4) followed by 1L of 4% paraformaldehyde solution in PBS (Santa Cruz Biotechnology) containing 47.6 mg of heparin (Sigma-Aldrich). The brain was harvested, postfixed in 4% paraformaldehyde for 8–10 days, and then transferred to a storage solution containing 0.03% sodium azide in PBS (PBS-NaN₃). Following over one month of rehydration in this solution, the specimen was immersed in Fluorinert (FC-3283, 3M, St. Paul, MN) in a 25mm glass NMR tube for imaging.

The ferret brain specimen was imaged using a 7T Bruker vertical bore micro-imaging scanner with a 25mm linear RF coil. A 3D multi-slice, multi-echo (MSME) pulse sequence was used with TE/TR=30/3000ms, with the following spatial parameters: FOV=26×40×20mm³, matrix=104×160×80 for isotropic voxel dimension of 250μm³. A large GDTI data set containing 278 brain volumes was acquired with multiple b-values: b = 500, 1500, 3000, 4500, 8000, and 13500 mm²/s, and 4, 19, 25, 61, 74, and 95 directions, respectively, uniformly sampling the unit sphere at each b-value. To compute orientation-averaged DWIs efficiently we acquired a separate IGDTI data set at 5 b-values b = 1500, 3000, 4500, 8000, and 13500 s/mm² using the efficient gradient sampling schemes in Table 2, with 3, 3+4, 3+4, 3+4+6, 3+4+6 orientations, respectively. Finally, to assess the rotation-invariance of the proposed method we repeated the aforementioned IGDTI experiment by rotating all gradient sampling orientations using a 3D rotation matrix $R = R_y(54.74^\circ) R_z(45^\circ)$ composed of rotations along the y and z axes by 54.74° (Magic angle) and 45° respectively. All DWIs in this experiment were collected with the same spatial geometry and dimensions as the MSME scan, using a 3D EPI pulse sequence with TE/TR=36/700 ms, NEX=1, 8 segments and 1 repetition and diffusion weighting parameters of $\delta=3.2$ ms and $\Delta=20$ ms.

1. In vivo human data—A healthy volunteer was scanned on a clinical Siemens Prisma 3T MRI scanner, equipped with a maximum gradient strength of 8 G/cm/axis using a 32 channel RF coil under a clinical protocol approved by the IRB of the Intramural Research Program (IRP) of the National Institutes of Neurological Disorders and Stroke (NINDS). Using a conventional single-shot spin-echo diffusion EPI clinical pulse sequence we conducted a series of scans with different diffusion gradient sampling schemes but the same imaging parameters. Whole brain DWIs were acquired with $\delta=34.6$ ms and $\Delta=40.2$ ms, a 21cm field-of-view (FOV), an in-plane resolution of 2.5mm, a 5mm slice thickness, and TE/TR=93/7000ms. The GDTI data set contained 7 baseline images and 278 DWIs with multiple b-values = 500, 1000, 1700, 2500, 4000, and 6000 s/mm², and 4, 19, 25, 61, 74,

and 95 orientations, respectively, uniformly sampling the unit sphere at each b-value. In addition, an IGDTI data sets was acquired (2 averages) with $b = 1000, 2500$, and 6000 s/mm^2 using the efficient gradient sampling schemes in Table 2, with 3, 3+4, 3+4+6 orientations, respectively to achieve isotropic HOT weighting up to orders 2, 4 and 6, respectively. To assess the rotation invariance of IGDTI we repeated this experiment with rotated gradient sampling schemes, as described for the micro-imaging experiment. Finally, in a short clinical IGDTI scan using the 3+4+6 experiment design for high b-values (Table 2) we measured the mADC with $b=8500 \text{ s/mm}^2$ and the same imaging parameters as above, except $TE=100 \text{ ms}$.

2. Post-processing and data analysis—All fixed-brain and clinical diffusion MRI data were processed using the TORTOISE software package (30) to register DWI volumes resampled to isotropic resolution ($250 \mu\text{m}$ and 2.5 mm , respectively) and to remove potential EPI distortions due to eddy currents and other sources of field inhomogeneities. The analysis of GDTI and IGDTI data sets was identical for both micro-imaging and clinical experiments. To derive orientationally-averaged DWIs and measure the mADCs at each b-value in the GDTI averaging the log signal attenuations from the dense gradient orientations uniformly sampling the unit sphere. In addition, we measured the HOTs by fitting the densely sampled GDTI data sets to Eq. 3 using the method described in (10) and computed the HOT Traces and generalized mean diffusivities $\overline{D^{(n)}}$ up to order 6 using Eq. 6, and subsequently, the mean t-kurtosis using Eq. 9. From the IGDTI data sets we measured the orientation-averaged DWIs and mADCs at each diffusion sensitization using the linear combinations of log signal attenuations described in Table 2 for the corresponding b-value range, and compared the results the corresponding images derived from the GDTI data. Subsequently, we computed the HOT Traces, $Tr D^{(n)}$, and generalized mean diffusivities, $\overline{D^{(n)}}$ for $n = 2, 4$, and 6 by fitting the IGDTIs to the polynomial equations in Table 2, and compared the results to those obtained by directly measuring the HOTs with GDTI. The same analysis was applied to the IGDTI data sets acquired with rotated gradient sampling schemes and the results were compared to those of the original sampling scheme (Table 1) to assess the rotation invariance of IGDTI. Finally, from the IGDTI-derived generalized mean diffusivities $\overline{D^{(n)}}$ of order 2 and 4 we computed the mean t-kurtosis using Eq. 9, and compared the results to those obtained from the GDTI analysis.

3. Precision, accuracy, and rotation-invariance—We also conducted numerical simulations to assess the precision, accuracy, and rotation-invariance of estimated microstructural parameters using IGDTI. From the HOT components measured *in vivo* using GDTI analysis (from 278 DWIs) we derived ground-truth values for $Tr D^{(n)}$ and $\overline{W}$. Then we generated DWI signals expected for the proposed gradient sampling scheme using 3, 3+4, and 3+4+6 gradient orientations at b-values 1000 s/mm^2 , 2500 s/mm^2 , and 6000 s/mm^2 , respectively. We added Gaussian noise to the real and imaginary channels to simulate different signal-to-noise ratios (SNR) from 10 to 100 in increments of 10, and computed the mean and standard deviation of the estimated microstructural parameters $Tr D^{(n)}$ and $\overline{W}$ obtained from 200 independent instances of noisy measurements. We evaluated the accuracy as the absolute error of the mean with respect to the ground-truth value and the precision as the standard deviation. To quantitatively assess the rotation invariance of IGDTI-based

measurement of microstructural tissue parameters, from ground-truth HOT values we generated DWI signals with SNR=70 using the proposed gradient sampling scheme re-oriented with 256 different rotations $R=R_x(X) R_y(Y) R_z(0^\circ)$, where Euler angles X , and Y were varied independently between -45° and 45° in 16 steps. Finally, we quantified the means and standard deviations of the microstructural parameters $TrD^{(n)}$ and $\overline{W}$, calculated with different rotations of the gradient sampling scheme.

Results

The accuracy and degree of rotation invariance of IGDTI measured over a large range of b-values is demonstrated in Fig. 2 using data from a ferret brain specimen. Orientationally-averaged (i.e., mADC-weighted) DWIs measured with IGDTI are remarkably consistent with those derived from densely sampled data sets with significantly higher angular resolution, and show virtually no distinguishable anatomical features in difference maps. The same level of agreement can be observed between IGDTI mADC-weighted DWIs acquired with rotated sampling schemes, confirming the rotation invariance of IGDTI in quantifying isotropic bulk diffusion signals in brain tissues.

The unique HOT components measured explicitly from the GDTI data (Fig. S1 in Supplementary Material 1) comprehensively and generally describe diffusion in tissue having complex microstructure including regions of crossing white matter fibers (13). More importantly, from these tensors we can quantify rotation-invariant measures such as the generalized mean diffusivities, $\overline{D^{(n)}}$ (Fig. S1, red boxes), and the generalized HOT-Traces $TrD^{(n)}$ to serve as references for evaluating the performance of IGDTI. Despite requiring significantly fewer DWIs, rotation-invariant microstructural parameters such as $TrD^{(n)}$ and $\overline{W}$ derived with IGDTI were in good agreement (Fig. 3) to those computed by explicitly measuring all HOT components with GDTI. Figure 3 also illustrates the benefit of including a larger number of b-values to stabilize the fit of $\overline{D^{(n)}}$ parameters from orientation-averaged DWIs, in agreement with findings from other studies (29).

The accuracy and rotation invariance of the IGDTI mADC-weighted measurements were replicated in the clinical experiments (Fig. 4). Compared to the fixed brain results in Fig. 2, slightly larger differences between orientation-averaged signals measured with GDTI and IGDTI occurred primarily at tissue boundaries and may be due to subject motion during the two acquisitions. The clinical potential of IGDTI is best illustrated with measurements obtained at very high b-values (Fig. 5) in under two minutes. The *in vivo* mADC-weighted IGDTI signal at $b = 8500 \text{ s/mm}^2$ reveals a tissue contrast that resembles the fractional anisotropy (FA) modulating the direction-encoded colored (DEC) map but may be less affected by architectural features of the tissue, such as crossing fibers (yellow arrows). At the same time, the mADC measured at high b-value (Fig. 5D) shows improved contrast around the putamen and globus pallidus compared to the T2-weighted image (Fig. 5B).

As shown in Fig. 6, $TrD^{(n)}$ and $\overline{W}$ measured with IGDTI in clinically feasible scan durations and with GDTI show a good agreement especially in brain tissue regions that are not affected by partial volume contamination with cerebrospinal fluid (CSF) and are

therefore less prone to quantitation errors due to subject motion. The relatively high apparent $TrD^{(4)}$ and $TrD^{(6)}$ measured *in vivo* in the CSF are likely biased by low SNR in high b-value DWIs as well as CSF partial volume contributions at the tissue interface. Biases in the estimated HOT parameters due to the noise floor may be mitigated with the use of regularization methods (31). Meanwhile biases due to partial volume contributions may require higher-order corrections to the signal model or the use of water elimination (32).

Our numerical simulations results in Fig. 7 show that biases in the estimation of $TrD^{(n)}$ and $\overline{W}$ using the sampling schemes in our experiments are expected for SNR levels <50. For SNR levels higher than 50, the precision of the estimated parameters improves with increasing SNR. These results are consistent with similar findings in the literature (29) and with our empirical results (Figs. 3 and 6). For the *in vivo* experiment, the (“temporal”) SNR level in white matter ranged between 60–75, as computed from six $b = 0 \text{ mm}^2/\text{s}$ images acquired throughout the duration of the experiment. Fig. 8 shows little dependence of the estimated microstructural parameters $TrD^{(n)}$ and $\overline{W}$ on the orientation of the gradient sampling scheme, which is in agreement with our empirical results (Figs. 3 and 6). However, as suggested in (29) increasing orientational sampling at lower b-values may improve the both the accuracy and the rotation-invariance of these estimated parameters.

Errors in the quantitation of diffusion properties may arise from several sources:

1. Inaccurate image registration and correction for distortions due to magnetic field inhomogeneities and gradient eddy currents. These errors are more difficult to correct in DWIs acquired with high b-value (33).
2. Contributions to the diffusion-encoding gradient field due to gradient eddy currents, concomitant fields, gradient non-linearities, as well as from background field gradients in tissue, imaging gradients and magnetic field inhomogeneities. These errors in quantifying the effective diffusion sensitization (b-value) may bias the estimates of higher-order diffusion tensor components, in particular.
3. Physiological and subject motion during *in vivo* experiments, which may require reorientation of the applied diffusion gradients while performing data analysis. These errors are especially problematic in long scans.

Discrepancies between microstructural parameters estimated with GDTI and IGDTI (Figs. 3 and 6) may also be attributed to: 1) Increased effective signal-to-noise ratio (SNR) in the GDTI data set due to the larger number of DWIs, 2) Strong restriction, partial volume and/or noise floor effects along any particular diffusion orientation that may require higher order truncations of the cumulant expansion at high b-values (equations in Table 2); and 3) Asymmetric diffusion (e.g., due to flow or diffusion in asymmetric pores at short diffusion times) violating the assumption that only even orders contribute to the diffusion signal expansion in Eq. 3.

Our results suggest that, given the sensitivities of micro-imaging and clinical experiments, the effects of bulk anisotropy on the MR diffusion signal in tissue can be eliminated using a 6th order tensor model even at high diffusion sensitizations. Nevertheless, for a given experiment, the IGDTI sampling scheme should be chosen based on both the desired

diffusion sensitization (b-value) and the expected average water mobility in the sample. Our experiments confirmed the expected lower tissue water mobility in fixed-brain compared to *in vivo* experiments. This difference in diffusivities is consistent with the literature and may be attributed to: 1) microstructural alterations (e.g., cell shrinkage) in the presence of fixation agents; 2) lower sample temperature (room vs. body), and 3) absence of physiological active transport mechanisms (e.g., cell death), in fixed tissue. The b-value ranges for micro-imaging and clinical experiments suggested in Table 2 are based on the aforementioned considerations.

Discussion

IGDTI measures orientationally-averaged diffusion signals over a wide range of b-values by matching the weightings of all HOT elements in Eq. 6. This is achieved by: 1) generating weightings, such as $M_3(b)$, $M_4(b)$ and $M_6(b)$, with similar symmetry properties (**Conditions 1 and 2**) as the Trace-Weighting in Eq. 6, and 2) forming linear combinations from these weightings to match the weightings for all HOT components in Eq. 6 up to a certain order. Consequently, the gradient sampling scheme design can be analytically related to the complexity of the underlying diffusion signals as described by higher order Cartesian tensors. This strategy yields very efficient solutions for achieving rotation-invariant diffusion weighting and generalizes several classic diffusion gradient sampling schemes (5,14,26).

IGDTI does not capture all orientational information in the diffusion signal. Rather using efficient sampling schemes (with 3, 7 and 13 DWIs) it elegantly removes the effect of diffusion anisotropy based on the complexity of the underlying diffusion signal (as modeled by HOT models of rank 2, 4, and 6, respectively), which usually increases with b-value and tissue diffusivity (Table 2). In general, denser angular sampling is required to capture all orientational information at high b-values.

We can make an argument for the theoretical minimum number of sampling orientations required to obtain orientationally-averaged DWIs (assuming a fully symmetric rank-n HOT signal model) based on the number of unique tensor elements $D_{n_x n_y n_z}^{(n)}$ (n_x, n_y, n_z all even) with non-zero weighting (i.e., number of degrees of freedom) in the expression of the generalized Trace, $Tr D^{(n)}$. For a b-value at which the diffusion signal is described by a

rank-n HOT model, a minimum number of $\frac{(\frac{n}{2}+1)(\frac{n}{2}+2)}{2}$ orientations is needed to obtain a rotation-invariant DWI. Removing modulations due to anisotropy in signals described with rank-2, -4, and -6 HOT models requires at least 3, 6, and 10 DWIs, respectively; while computing rotation-invariant microstructural parameters derived from HOT models of rank-4 (such as $Tr D^{(4)}$ and $\overline{W}$) and rank-6 (such as $Tr D^{(6)}$) requires at least 3+6=9 DWIs and 3+6+9=19 DWIs, respectively, in addition to one baseline image. Approximate gradient sampling schemes using the theoretical minimum number of orientations to remove anisotropy may be obtained with numerical methods (34,35) and have been suggested for measuring $\overline{W}$ (36).

While the measurements of $TrD^{(4)}$ and $\overline{W}$ in Figs. 3 and 6. illustrate how IGDTI sampling schemes may be used to estimate HOT-derived parameters, our work did not specifically aim to improve or optimize existing experimental designs for estimating such parameters (29). Future studies will optimize the number of b-values and gradient orientations to achieve required levels of sensitivity, accuracy, precision, rotation-invariance, robustness, and scan duration for specific clinical applications. The insights from this work will help improve and accelerate experimental designs for many clinical diffusion MRI applications, such as fast diffusion kurtosis imaging (DKI) (14), mean apparent propagator (MAP) MRI (23,37), GDTI (10,13), and may enable new clinical applications, such as isotropic diffusion relaxometry imaging (38,39) at the whole brain level.

IGDTI gradient sampling schemes can provide orientationally-averaged measurements over a wide range of b-values, which can serve in various applications, such as estimating $TrD^{(n)}$ and $\overline{W}$. The parameter $\overline{W}$ defined in (14) represents an approximation to the mean kurtosis (MK) (15) and can be measured from two orientationally-averaged DWIs without the need to explicitly compute the entire kurtosis tensor, W (15). As detailed in Appendix B, for fully symmetric diffusion, we can generalize the definition of W with respect to the HOTs $D^{(n)}$ (10) and define the dimensionless rank-n tensor

$$W^{(n)} = \frac{n! D^{(n)} \left(\Delta - \frac{(n-1)}{(n+1)} \delta \right)}{2^{\frac{n}{2}} D^{(2)}{}^{\frac{n}{2}} \left(\Delta - \frac{\delta}{3} \right)^{\frac{n}{2}}} \quad (10)$$

The mean of tensor $W^{(n)}$, $\overline{W^{(n)}}$, is directly related to the mean of $D^{(n)}$, and implicitly to the generalized trace, $TrD^{(n)}$. Images of $\overline{W^{(6)}}$ derived from both fixed-brain and clinical data sets are shown in Supplemental Figure S2, and reveal significantly larger contrast compared to $\overline{W^{(4)}} = \overline{W}$.

Our experiments were conducted using a conventional spin-echo diffusion sequence without accounting for the ramp durations of the applied diffusion gradient pulses. However, it is interesting to note that the IGDTI sampling schemes can be extended to spin echo diffusion preparations with arbitrary gradient pulse shapes, including trapezoids with finite ramps, twice-refocused spin echo (40), or oscillating diffusion gradient pulses (41). The temporal characteristics only scale β_n in Eqs. 3 and 5, but do not affect the orientational averaging in Eq. 4.

The clinical assessment of orientationally-averaged bulk water diffusion properties in tissues could be further accelerated using advanced diffusion preparation methods (42). Building on the original literature on acquiring single-shot isotropically-weighted diffusion MRI data (43,44), in our recent work (42) we proposed an efficient pulse sequence that leverages the improved capabilities of gradient hardware and RF technologies on state-of-the-art clinical MRI systems to achieve weighting by the DTI-Trace in a single acquisition by applying a series of bipolar diffusion gradient pairs with orientations given by Scheme 2. In principle, this preparation can be adapted with the bipolar gradient pairs applied along the orientations

in Schemes 1 and 3, and extended to larger b-values, yielding estimates of $M_3(b)$, $M_4(b)$, and $M_6(b)$ from single-shot measurements, and enabling computation of orientationally-averaged diffusion signals at high b-values from only 3 DWIs. Such single-shot preparations not only reduce the acquisition time leading to fewer quantitation errors and imaging artifacts in clinical scans, but also have a smaller signal dynamic range due to the partial averaging of anisotropy (Eq. 8). The reduced signal dynamic range extends the quality of orientationally-averaged signals in anisotropic tissues to even higher b-values that are otherwise unobservable with conventional techniques due to noise floor limitations (e.g., along particular directions).

The orientationally-averaged IGDIT weighting of the bulk diffusion signal obtained from linear combinations of log signal attenuations in DWIs acquired using conventional single pulsed-field gradient spin echo (PGSE) diffusion encoding along multiple orientations produces rotation-invariant HOT parameters that can approximate intrinsic isotropic diffusion properties in tissues. The rotation-invariant signal weighting obtained with IGDIT differs from the isotropic weighting that can be obtained with magic angle spinning of the q-vector (45) or q-space trajectory imaging (46), and from other rotation-invariant weightings that can be obtained with single-shot diffusion preparations mentioned above (42–44) or with multiple diffusion encoding MRI (47,48). Such advanced diffusion encoding techniques use complex gradient waveforms to sensitize the signal to diffusion-diffusion correlations but require long echo times that are difficult to achieve on clinical scanners especially at high diffusion sensitizations (46,47,49–51). Distinctions between “isotropic” weightings generated with different diffusion encoding gradient waveforms were originally raised in the classic 1996 paper by de Swiet and Mitra (52).

Conclusions

The ability of IGDIT sampling schemes to assess rotation-invariant diffusion signals with a variety of diffusion sensitizations allows quantitation of a wide range of tissue water mobilities and opens new avenues for clinical translation and adoption of advanced diffusion MRI methods and for the development of new clinical applications with improved biological specificity (53) with the goal of better characterizing stroke, cancer, and neurodegenerative diseases. The short IGDIT scan durations may reduce quantitation errors and imaging artifacts due to subject/physiological motions improving the accuracy and clinical feasibility of isotropic diffusion MRI assessments for a wide range of patient populations, including non-compliant patients (e.g., elderly, agitated, or pediatric).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A

We can compute the orientationally-averaged diffusivity (generalized mean diffusivity) for an HOT of order n , $D^{(n)}$ by evaluating the following integral over the unit sphere:

$$\overline{D^{(n)}} = \frac{1}{4\pi} \int \sum_{n_x+n_y+n_z=n} \mu_{n_x n_y n_z} u_x^{n_x} u_y^{n_y} u_z^{n_z} D_{n_x n_y n_z} d\Omega_{\mathbf{u}} \quad (\text{A1})$$

where

$$\mu_{n_x n_y n_z} = \frac{(n_x+n_y+n_z)!}{n_x! n_y! n_z!} \quad (\text{A2})$$

are the multiplicities (degeneracies) of the equal components $D_{n_x n_y n_z}$ in the fully symmetric tensor of even rank n , $D^{(n)}$ with $n_x+n_y+n_z=n$, and $\mathbf{u}^T = [u_x, u_y, u_z]^T$ is a unit vector.

We note that $\int u_x^{n_x} u_y^{n_y} u_z^{n_z} d\Omega_{\mathbf{u}}$ reduces to 0 if any of the indices n_x , n_y , or n_z is odd. Writing $\mathbf{u}^T = [\sin\theta \cos\phi, \sin\theta \sin\phi, \cos\theta]^T$ in spherical coordinates we have:

$$\int u_x^{n_x} u_y^{n_y} u_z^{n_z} d\Omega_{\mathbf{u}} = K_{n_x n_y n_z} \int_0^\pi (\sin\theta)^{n_1+n_2+1} (\cos\theta)^{n_3} d\theta \int_0^{2\pi} (\sin\phi)^{n_2} (\cos\phi)^{n_1} d\phi \quad (\text{A3})$$

where $K_{n_x n_y n_z} = 1$ when n_x, n_y, n_z are all even, and $K_{n_x n_y n_z} = 0$ otherwise.

Next we use the definition of the Beta function, or the Euler integral of the first kind:

$$B(x, y) = \int_0^1 t^{x-1} (1-t)^{y-1} dt \quad (\text{A4})$$

After a change of variable $t \rightarrow (\sin\theta)^2$ we obtain:

$$B(x, y) = 2 \int_0^{\frac{\pi}{2}} (\sin\theta)^{2x-1} (\cos\theta)^{2y-1} d\theta \quad (\text{A5})$$

Substituting Eq. A5 in A3

$$\int u_x^{n_x} u_y^{n_y} u_z^{n_z} d\Omega_{\mathbf{u}} = 2B\left(\frac{n_1}{2} + \frac{n_2}{2} + 1, \frac{n_3}{2} + \frac{1}{2}\right) B\left(\frac{n_2}{2} + \frac{1}{2}, \frac{n_1}{2} + \frac{1}{2}\right) \quad (\text{A6})$$

and using the relationship between the Beta and Gamma functions

$$B(x, y) = \frac{\Gamma(x) \Gamma(y)}{\Gamma(x+y)} \quad (\text{A7})$$

we obtain

$$\int u_x^{n_x} u_y^{n_y} u_z^{n_z} d\Omega_{\mathbf{u}} = 2 \frac{\Gamma\left(\frac{n_1}{2} + \frac{1}{2}\right) \Gamma\left(\frac{n_2}{2} + \frac{1}{2}\right) \Gamma\left(\frac{n_3}{2} + \frac{1}{2}\right)}{\Gamma\left(\frac{n_1+n_2+n_3}{2} + \frac{3}{2}\right)} \quad (\text{A8})$$

Finally, using the property of the Gamma function

$$\Gamma\left(n + \frac{1}{2}\right) = \frac{(2n)!}{4^n n!} \sqrt{\pi} \quad (\text{A9})$$

for a positive integer n , we obtain

$$\int u_x^{n_x} u_y^{n_y} u_z^{n_z} d\Omega_{\mathbf{u}} = \frac{4\pi}{(n_1+n_2+n_3+1)} \frac{\left(\frac{n_1}{2} + \frac{n_2}{2} + \frac{n_3}{2}\right)!}{\frac{n_1!}{2} \frac{n_2!}{2} \frac{n_3!}{2}} = \frac{4\pi}{n+1} \frac{\mu_{\frac{n_x}{2} \frac{n_y}{2} \frac{n_z}{2}}}{\mu_{n_x n_y n_z}} \quad (\text{A10})$$

Substituting this result back into Eq. A1 gives

$$\overline{D^{(n)}} = \frac{1}{n+1} \sum_{n_x+n_y+n_z=N} K_{n_x n_y n_z} \mu_{\frac{n_x}{2} \frac{n_y}{2} \frac{n_z}{2}} D_{n_x n_y n_z} \quad (\text{A11})$$

Appendix B

The definition of W and $\overline{W}$ can be extended to HOT using the cumulant expansion (10). The 4th- order kurtosis tensor W (15) quantifies the statistical standardized central moment of the probability density function (PDF) of spin displacements, $P(\mathbf{r})$, and can be related to the 4th-order statistical cumulant tensor of $P(\mathbf{r})$

$$W_{ijkl} = 9 \frac{\langle r_i r_j r_k r_l \rangle - \langle r_i r_j \rangle \langle r_m r_n \rangle - \langle r_i r_m \rangle \langle r_j r_n \rangle - \langle r_i r_n \rangle \langle r_j r_m \rangle}{\langle \mathbf{r} \cdot \mathbf{r} \rangle^2} = 9 \frac{Q_{ijkl}^{(4)}}{\langle \mathbf{r} \cdot \mathbf{r} \rangle^2} \quad (\text{B1})$$

In general, assuming fully symmetric diffusion, the cumulant tensor of rank- n $Q_{ijkl}^{(n)}$ is related to the generalized diffusion tensor as described in (12)

$$Q^{(n)} = (-1)^n n! D^{(n)} \left(\Delta - \frac{n-1}{n+1} \delta \right) \quad (\text{B2})$$

We can generalize the definition of W with respect to the HOTs $D^{(n)}$, and define the dimensionless rank- n tensor, $W^{(n)}$, as the standardized statistical cumulants of $P(\mathbf{r})$

$$W^{(n)} = \frac{n! D^{(n)} \left(\Delta - \frac{(n-1)}{(n+1)} \delta \right)}{2^{\frac{n}{2}} \overline{D^{(2)}}^{\frac{n}{2}} \left(\Delta - \frac{\delta}{3} \right)^{\frac{n}{2}}} \quad (\text{B3})$$

The mean of tensor $W^{(n)}$, $\overline{W^{(n)}}$, is directly related to the mean of $D^{(n)}$ and implicitly to the generalized Trace $\text{Tr} D^{(n)}$.

It is important to note that $\overline{W^{(4)}} = \overline{W}$ and $W^{(4)}$ quantifies the apparent diffusional kurtosis along any direction $\mathbf{u}$, $K(\mathbf{u})$, i.e., the 4th-order standardized central moment of $P(\mathbf{r})$, as defined in (16):

$$K(\mathbf{u}) = \frac{\langle (\mathbf{r} \cdot \mathbf{u})^4 \rangle}{\langle (\mathbf{r} \cdot \mathbf{u})^2 \rangle^2} - 3 = \sum_{i,j,k,l} \frac{\overline{D}^2}{[D(\mathbf{u})]^2} u_i u_j u_k u_l W_{ijkl} \quad (\text{B4})$$

Where $\overline{D}$ is the mean diffusivity from DTI (i.e., $\overline{D^{(2)}}$) and $D(\mathbf{u})$ is the apparent diffusivity along $\mathbf{u}$,

$$D(\mathbf{u}) = \frac{\langle (\mathbf{r} \cdot \mathbf{u})^2 \rangle}{2t} = \sum_{i,j} u_i u_j D_{ij} = \sum_{i,j} u_i u_j \frac{\langle r_i r_j \rangle}{2t} \quad (\text{B6})$$

, $D_{ij} = \frac{\langle r_i r_j \rangle}{2t}$ represents the components of the diffusion tensor, $\mathbf{r}$ is the microscopic net spin displacement, t is the diffusion time, and the operation $\langle \cdot \rangle$ represents the ensemble average over the spin population in $P(\mathbf{r})$. For $n > 4$, $W^{(n)}$ depends on the standardized central

moment tensors $\frac{\langle (\mathbf{r} \cdot \mathbf{u})^n \rangle}{\langle (\mathbf{r} \cdot \mathbf{u})^2 \rangle^{\frac{n}{2}}}$ up to order n . For example, if $n=6$ the relation is:

$$\sum_{i,j,k,l} \frac{\overline{D}^3}{[D(\mathbf{u})]^3} u_i u_j u_k u_l u_m u_n W_{ijklmn}^{(6)} = \frac{\langle (\mathbf{r} \cdot \mathbf{u})^6 \rangle}{\langle (\mathbf{r} \cdot \mathbf{u})^2 \rangle^3} - 15 \frac{\langle (\mathbf{r} \cdot \mathbf{u})^4 \rangle}{\langle (\mathbf{r} \cdot \mathbf{u})^2 \rangle^2} + 30 \quad (\text{B7})$$

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Scheme	#DWIs	Diffusion gradient orientations	
1	3	$[1, 0, 0], [0, 1, 0], [0, 0, 1]$	$M_3(b)$
3	4	$\left[\frac{-1}{\sqrt{3}}, \frac{1}{\sqrt{3}}, \frac{1}{\sqrt{3}}\right], \left[\frac{1}{\sqrt{3}}, \frac{-1}{\sqrt{3}}, \frac{1}{\sqrt{3}}\right], \left[\frac{1}{\sqrt{3}}, \frac{1}{\sqrt{3}}, \frac{-1}{\sqrt{3}}\right], \left[\frac{-1}{\sqrt{3}}, \frac{-1}{\sqrt{3}}, \frac{-1}{\sqrt{3}}\right]$	$M_4(b)$
2	6	$\left[\frac{1}{\sqrt{2}}, \frac{1}{\sqrt{2}}, 0\right], \left[\frac{1}{\sqrt{2}}, \frac{-1}{\sqrt{2}}, 0\right], \left[0, \frac{1}{\sqrt{2}}, \frac{1}{\sqrt{2}}\right],$ $\left[0, \frac{1}{\sqrt{2}}, \frac{-1}{\sqrt{2}}\right], \left[\frac{1}{\sqrt{2}}, 0, \frac{1}{\sqrt{2}}\right], \left[\frac{-1}{\sqrt{2}}, 0, \frac{1}{\sqrt{2}}\right]$	$M_6(b)$

Figure 1.

Diffusion gradient orientations for measuring the average log signal attenuations, $M_3(b)$, $M_4(b)$, and $M_6(b)$ satisfying **Conditions 1** and **2**, using the efficient IGDTI sampling **Schemes 1, 2, and 3**.

Figure 2.

Orientationally-averaged (i.e., mADC-weighted) DWIs in a ferret brain specimen at five different b-values generated from a GDTI data set with dense and uniform angular sampling at each b-value, IGDTI using the efficient gradient sampling schemes in Fig. 1 and Table 2, and IGDTI using a rotated gradient sampling scheme. The small values in the difference images, on the order of 2%, demonstrate the rotation-invariance and high accuracy of IGDTI in eliminating anisotropy and generating isotropic diffusion measurements over a wide range of b-values.

Figure 3.

Comparison of Traces of diffusion tensors, $TrD^{(n)}$, for orders 2, 4, and 6, and mean t-kurtosis, $\overline{W}$ in the fixed ferret brain measured with GDTI, IGDTI with 3 b-values, and IGDTI with 5 b-values. Small values in brain tissues in the difference images illustrate the ability of IGDTI to efficiently quantify rotation-invariant higher-order diffusion parameters in fixed-brain tissues. A larger number of b-values improves the stability of measuring these parameters with IGDTI.

Figure 4.

Orientationally-averaged (i.e., mADC-weighted) DWIs in clinical scans at three different b-values generated from a GDTI data set with dense and uniform sampling at each b-value, IGDTI using the efficient gradient sampling schemes in Fig. 1 and Table 2, and IGDTI using a rotated gradient sampling scheme. The small values in the difference images in brain tissue regions illustrate the high accuracy and rotation-invariance of IGDTI in eliminating anisotropy and generating isotropic diffusion measurements over a wide range of b-values in clinical applications. Note that both DWIs and difference images for $b = 2500$ and 6000 s/mm^2 are scaled by factors of 3, and 6 respectively to improve visualization.

Figure 5.

Tissue contrast at high diffusion sensitization measured efficiently with IGDTI acquired in less than 2 minutes. **A.** Direction-encoded color (DEC) map **B.** Baseline (non-diffusion weighted) image **C.** IGDTI with $b = 8500 \text{ s/mm}^2$ (signal scaled by 25) and **D.** mADC at $b = 8500 \text{ s/mm}^2$ computed with clinical IGDTI.

Figure 6.

Comparison of Traces of diffusion tensors, $TrD^{(n)}$, for orders 2, 4, and 6, and mean t-kurtosis, $\overline{MK}$ measured *in vivo* with GDTI and IGDTI with 3 b-values shows ability of IGDTI to quantify rotation-invariant HOT-derived diffusion parameters in brain tissue within a clinically feasible scan duration.

Figure 7.

Numerical simulation of signal-to-noise ratio (SNR) dependence of tissue parameters $TrD^{(n)}$ and $\bar{W}$ estimated using efficient IGDTI sampling schemes. A. Mean and standard deviations maps quantified across 200 simulated experiments with SNR=70. B. SNR dependence (mean – black markers, standard deviation – error bars) in representative gray matter GM (blue) and white matter WM (red) voxels.

Figure 8.

Numerical simulation of rotation invariance of tissue parameters $TrD^{(n)}$ and $\bar{W}$ estimated using efficient IGDTI sampling schemes. The computations assume an SNR=70 and estimate tissue parameters by reorienting the gradient sampling scheme with 256 different rotations $R=R_x(X)R_y(Y)R_z(0^\circ)$, where Euler angles X, and Y were varied between -45° and 45° in 16 steps. **A.** Mean and standard deviations of the measured parameters. **B.** The 256 values of the tissue parameters (means and standard deviations included) in representative GM and WM tissue voxels estimated using different rotations of the gradient sampling scheme.

Table 1

Relative weightings of unique tensor components $D_{n_x n_y n_z}^{(n)}$ in the expressions of for the three log signal attenuation averages, $M_3(b)$, $M_4(b)$, and $M_6(b)$, as well as the generalized HOT Traces and mean diffusivities, computed from Eqs. 8 and 6 respectively (truncated at $n=6$). All quantities in the table columns satisfy the **Conditions 1** and **2**. Consequently, $M_3(b)$, $M_4(b)$, and $M_6(b)$ can be linearly combined to achieve the desired mADC-weighting for a wide range of b-values (see Table 2).

HOT component	M_3 (3 DWIs)	M_4 (4 DWIs)	M_6 (6 DWIs)	$Tr^{(n)}$	$\overline{D^{(n)}}$
D_{200}	1/3	1/3	1/3	1	1/3
D_{400}	1/3	1/9	1/6	1	1/5
D_{220}	0	2/3	1/2	2	2/5
D_{600}	1/3	1/27	1/12	1	1/7
D_{420}	0	5/9	15/24	3	3/7
D_{222}	0	10/3	0	6	6/7

For different b-value regimes, orientation-averaged diffusion signals can be measured very efficiently from linear combinations of the log signal attenuation averages $M_3(b)$, $M_4(b)$, and $M_6(b)$ derived from 3, 4, and 6 DWIs sampled using the orientations in **Schemes 1, 2, and 3** respectively (see Table 1). The most efficient samplings that achieve isotropic HOT weighting for orders 2, 4, and 6 require 3, 7, and 13 DWIs respectively, and are highlighted in green.

Table 2

Order	Schemes	#DWIs	Orientation Averaged Signal	b-value range (s/mm ²)	
				In vivo	Fixed brain
2	1	3	$M_3(b) \cong -\beta_2 \overline{D^{(2)}}$	0-1200	0-2000
	2	4	$M_4(b) \cong -\beta_2 \overline{D^{(2)}}$		
	3	6	$M_6(b) \cong -\beta_2 \overline{D^{(2)}}$		
4	1 and 2	3+4	$\frac{1}{5} (2M_3(b) + 3M_4(b)) \cong -\beta_2 \overline{D^{(2)}} + \beta_4 \overline{D^{(4)}}$	1200-3600	2000-6000
	1 and 3	3+6	$\frac{1}{5} (1M_3(b) + 4M_6(b)) \cong -\beta_2 \overline{D^{(2)}} + \beta_4 \overline{D^{(4)}}$		
6	1, 2, and 3	3+4+6	$\frac{1}{7} \left(\frac{10}{5} M_3(b) + \frac{9}{5} M_4(b) + \frac{16}{5} M_6(b) \right) \cong -\beta_2 \overline{D^{(2)}} + \beta_4 \overline{D^{(4)}} - \beta_6 \overline{D^{(6)}}$	3600-10800	6000-18000