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<u>Precise Inference and Characterization of Structural</u> <u>Organization (PICASO) of tissue from molecular diffusion</u>

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Abstract

Inferring the microstructure of complex media from the diffusive motion of molecules is a challenging problem in diffusion physics. In this paper, we introduce a novel representation of diffusion MRI (dMRI) signal from tissue with spatially-varying diffusivity using a diffusion disturbance function. This disturbance function contains information about the (intra-voxel) spatial fluctuations in diffusivity due to restrictions, hindrances and tissue heterogeneity of the underlying tissue substrate. We derive the short- and long-range disturbance coefficients from this disturbance function to characterize the tissue structure and organization. Moreover, we provide an exact relation between the disturbance coefficients and the time-varying moments of the diffusion propagator, as well as their relation to specific tissue microstructural information such as the intra-axonal volume fraction and the apparent axon radius. The proposed approach is quite general and can model dMRI signal for any type of gradient sequence (rectangular, oscillating, etc.) without using the Gaussian phase approximation. The relevance of the proposed PICASO model is explored using Monte-Carlo simulations and in-vivo dMRI data. The results show that the estimated disturbance coefficients can distinguish different types of microstructural organization of axons.

Keywords

Diffusion MRI; tissue microstructure; Bloch-Torrey equation; structural disorder; diffusion equation; time-dependent diffusion; kurtosis

1. Introduction

Biological tissue contains a complex layout of cells obstructing the diffusive motion of molecules. Molecular movements can be exploited for characterizing complex media, as is done in several fields of scientific investigation (Carslaw and Jaeger, 1959; Altieri et al., 1995; Valentini et al., 2000; Balogh et al., 2008; Martin, 1990) with many neuroimaging

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applications (Van Everdingen et al., 1998; Le Bihan, 2003; Tuch et al., 2003; Le Bihan et al., 1992). Understanding the molecular diffusion in restricted environment has been a major step toward identifying the microstructure of the underlying media. Explicit modeling of restricted diffusion can be obtained from simple geometrical shapes by adding boundary conditions (Carslaw and Jaeger, 1959; Neuman, 1974). Restricted diffusion in arbitrary shapes and complex environments relies on numerical methods such as finite element methods or Monte Carlo simulations (Hagslätt et al., 2003; Hwang et al., 2003; Fichele et al., 2004; Grebenkov, 2007; Jin et al., 2009; Grebenkov, 2010; Grebenkov et al., 2013; Van Nguyen et al., 2014). However, the human brain tissue is neither uniform nor a completely restricted medium. Both, the restricted diffusion from the intra-axonal and intra-cellular space and hindered diffusion from the extra-axonal space contribute to the diffusion magnetic resonance imaging (dMRI) signal at each voxel. The axonal barriers not only determine the restricted diffusion in intra-axonal space but also hindered diffusion in extraaxonal space. Due to anisotropically laid-out axonal structures and crossing and dispersed fiber bundles in brain tissue, the dMRI signal is orientation-dependent. But even in the most basic and simplest arrangement of coherently (without dispersion) laid out fiber bundles oriented in a single direction, the inverse problem of inferring the salient characteristics of the tissue structure from the dMRI measurements has not been completely solved. In other words, the exact relation between the dMRI measurements and the microstructural arrangement of axons is not fully understood. In this paper, we propose one solution to this problem by incorporating the structural information in terms of a disturbance function to represent spatially varying diffusivities and then solving the resulting partial differential equation analytically.

Several groups of methods have been proposed for modeling the dMRI signal acquired using a standard single diffusion encoding (SDE) experiment (Basser et al., 1994; Assaf et al., 2002; Jensen et al., 2005; Schultz et al., 2014; Özarslan et al., 2009; Morozov et al., 2014; Huang et al., 2015). A large family of methods focus on estimating the ensemble average propagator (EAP) of the diffusing spins under the narrow pulse approximation (Cheng et al., 2010; Merlet and Deriche, 2013; Özarslan et al., 2013; Scherrer et al., 2013; Rathi et al., 2014; Ning et al., 2015; Ghosh and Deriche, 2016). These methods provide a probabilistic estimate of the displacement of water molecules, which can then be used to compute properties such as the non-Gaussianity, kurtosis etc. of the diffusion propagators. However, these methods, while being quite sensitive, fail to provide very specific information about the tissue structure. On the other hand, an alternative group of approaches focus on identifying highly specific information about the tissue, such as estimating the axon diameter from dMRI data (Assaf et al., 2008; Alexander et al., 2010; Morozov et al., 2013; Huang et al., 2015; De Santis et al., 2016). However, as mentioned in (Burcaw et al., 2015), the problem of estimating axon diameters may be ill-posed due to the negligible attenuation in signal originating from within axons of diameter smaller than $3 \mu m$, which is the size of an overwhelming majority of axons in the human brain (Aboitiz et al., 1992; Liewald et al., 2014).

Another group of methods focus on understanding tissue microstrucure from the timevarying apparent diffusion coefficient (ADC). Several theories have been proposed to understand the time-dependent ADC in disordered media based on specific assumptions

(Bouchaud and Georges, 1990; Havlin and Ben-Avraham, 1987; Metzler and Klafter, 2000; Topgaard and Söderman, 2003; Åslund and Topgaard, 2009; Novikov et al., 2011). In particular, it was shown in (Mitra et al., 1993) that the surface-to-volume ratio can be estimated from the diffusion signal if the diffusion time is very short. The long-time scale time-varying ADC and other higher order moments of the displacements have been studied in (Özarslan et al., 2006, 2012). Recently, the relation between the time-dependent ADC and the tissue packing structure was explained in (Novikov et al., 2011; Novikov and Kiselev, 2010; Novikov et al., 2014; Burcaw et al., 2015; Fieremas et al., 2016) using the effective medium theory (EMT). In the finite-pulse case, this approach depends on using the Gaussian phase approximation (GPA), which does not account for the non-Gaussian part of the diffusion process. Moreover, the relation between the model parameters and the physical packing structure of tissue is not explicit. Thus, existing models of diffusion, while being very sensitive to tissue changes, do not provide a clear understanding between the structural organization and packing structure of axons and the measured diffusion signal.

Our contributions

In this paper, we propose a novel theory, starting from the first principles, by considering the diffusion equation with spatially varying diffussion coefficients. We introduce a structural disturbance function as the input to the diffusion equation that captures the spatial fluctuations of the diffusion processes. Following the concept of input-output analysis (Banks et al., 1993; Pillai and Shim, 2012; Isakov, 2006; Pintelon and Schoukens, 2012), we obtain an exact relation between diffusion MRI signal and the structural disturbance function. To the best of our knowledge, the proposed theoretical framework presented here is one of the first attempts to use this concept for solving the fundamental diffusion equation with a spatially varying diffusivity term. The salient features of our approach are summarized below:

- The microscopic tissue structure and organization is implicitly captured via the Fourier Transform of a novel disturbance function (i.e., a function that captures the structural disturbances in the diffusion process due to restrictions and hindrances).
- A general relation is derived between the structural disturbance function, the EAP, and the EMT. Further, the proposed approach models the dMRI signal without assuming Gaussian Phase Approximation (GPA).
- We quantify the structural organization of tissue in terms of short- and longrange (short and long length scale) disturbance coefficients derived from the disturbance function. Using Monte-Carlo simulations and in-vivo Human Connectome Project (HCP) dMRI data sets, we show that these indices can be used to identify the microstructural arrangement of axons.
- The proposed approach is quite general and can be used with any type of gradient sequence (i.e., the fundamental concepts developed here are not limited to using the SDE sequence and other types of sequences can potentially be used). In this work however, we show results using SDE experiments only.

The remainder of this paper is organized as follows: In the Theory section, we present an overview of the proposed method based on the modified diffusion equation that contains a spatial disturbance term. More specifically, we derive a relation between the disturbance term and the ensemble average diffusion propagator and its time-varying moments, along with the connection to the effective medium theory. We introduce several methods for estimating the diffusion disturbance function using dMRI measurements. We also provide a more general solution for dMRI signal for any type of pulse sequences based on a modified Bloch-Torrey equation. In the Experiments section, we present details about the Monte-Carlo simulations and the models that are used to characterize the measurements in the invivo HCP data sets. The experimental outcomes are presented in the Results section, which is followed by a section on discussion and conclusions.

2. Theory

2.1. The ensemble-average disturbance function

The diffusion propagator is the Green's function of the following partial differential equation:

$$\partial_{\tau} \hat{G}(\boldsymbol{r}_0, \boldsymbol{r}, \tau) = \nabla_{\boldsymbol{r}} \left[D(\boldsymbol{r}) \nabla_{\boldsymbol{r}} \hat{G}(\boldsymbol{r}_0, \boldsymbol{r}, \tau) \right], \quad (1)$$

where $\hat{G}(\mathbf{r}_0, \mathbf{r}, \tau)$ denotes the probability that the water molecules starting at \mathbf{r}_0 reach a location $\mathbf{r} \in \mathbb{R}^3$ in time τ , where the initial state is $\hat{G}(\mathbf{r}_0, \mathbf{r}, 0) = \delta(\mathbf{r} - \mathbf{r}_0)$ with $\delta(\cdot)$ being the Dirac delta function, and $D(\mathbf{r})$ denotes the diffusivity tensor at \mathbf{r} . We define $\tilde{\mathbf{r}} := \mathbf{r} - \mathbf{r}_0$ as the displacement of the molecules and denote the corresponding Green's function as $G(\mathbf{r}_0, \tilde{\mathbf{r}}, \tau)$. Then Eq. (1) can be equivalently written as:

$$\partial_{\tau} G(\boldsymbol{r}_{0}, \tilde{\boldsymbol{r}}, \tau) = \nabla_{\tilde{\boldsymbol{r}}} [D(\boldsymbol{r}_{0} + \tilde{\boldsymbol{r}}) \nabla_{\tilde{\boldsymbol{r}}} G(\boldsymbol{r}_{0}, \tilde{\boldsymbol{r}}, \tau)], \quad (2)$$

with the initial state $G(\mathbf{r}_0, \tilde{\mathbf{r}}, 0) = \delta(\tilde{\mathbf{r}})$. We decompose the diffusion coefficient $D(\mathbf{r})$ as:

$$D(\mathbf{r}) := D_0 + \tilde{D}(\mathbf{r}),$$
 (3)

where D_0 is the spatial average of the diffusion coefficient and $\tilde{D}(r)$ is the corresponding spatially varying term, i.e. D_0 is the unique value that makes $\int \tilde{D}(r) dr = 0$. Then Eq. (2) can be rewritten as:

$$\partial_{\tau} G\left(\boldsymbol{r}_{0}, \tilde{\boldsymbol{r}}, \tau\right) = \nabla_{\tilde{\boldsymbol{r}}} D_{0} \nabla_{\tilde{\boldsymbol{r}}} G\left(\boldsymbol{r}_{0}, \tilde{\boldsymbol{r}}, \tau\right) + \hat{u}\left(\boldsymbol{r}_{0}, \tilde{\boldsymbol{r}}, \tau\right), \text{ where }$$
(4)

$$\hat{u}\left(\boldsymbol{r}_{0},\tilde{\boldsymbol{r}},\tau\right) := \nabla_{\tilde{\boldsymbol{r}}} \left[\tilde{D}\left(\boldsymbol{r}_{0}+\tilde{\boldsymbol{r}}\right) \nabla_{\tilde{\boldsymbol{r}}} G\left(\boldsymbol{r}_{0},\tilde{\boldsymbol{r}},\tau\right) \right], \quad (5)$$

and $\hat{u}(\mathbf{r}_0, \tilde{\mathbf{r}}, \tau)$ denotes the spatio-temporal disturbances to the evolution of the propagator. We assume that this disturbance does not change the total number of particles in the system,

i.e., $\int_{\tilde{\boldsymbol{r}} \in \mathbb{R}^3} \hat{u}(\boldsymbol{r}_0, \tilde{\boldsymbol{r}}, \tau) d\tilde{\boldsymbol{r}} = 0.$

Let $Prob(r_0)$ denote the density function of the initial distribution of water molecules. Then the ensemble average propagator (EAP) is given by:

$$\rho\left(\tilde{\boldsymbol{r}},\tau\right) = \int \operatorname{Prob}\left(\boldsymbol{r}_{0}\right) G\left(\boldsymbol{r}_{0},\tilde{\boldsymbol{r}},\tau\right) d\boldsymbol{r}_{0}.$$
 (6)

Taking the partial derivative of both sides of Eq. (6) and using Eq. (4), one can derive the following partial differential equation for the evolution of the EAP:

$$\partial_{\tau}\rho\left(\tilde{\boldsymbol{r}},\tau\right) = \nabla_{\tilde{\boldsymbol{r}}}D_{0}\nabla_{\tilde{\boldsymbol{r}}}\rho\left(\tilde{\boldsymbol{r}},\tau\right) + u\left(\tilde{\boldsymbol{r}},\tau\right),\quad(7)$$

where $u(\tilde{r}, \tau) := \int \operatorname{Prob}(r_0) \hat{u}(r_0, \tilde{r}, \tau) dr_0$ denotes the ensemble average disturbance (EAD) function that affects the evolution of the EAP. Moreover, since the EAD does not change the total number of diffusing particles, we have $\int_{\tilde{r} \in \mathbb{R}^3} u(\tilde{r}, t) d\tilde{r} = 0$ for any $\tau = 0$. The solution to Eq. (7) is given by:

$$\rho(\tilde{\boldsymbol{r}},t) = P(\tilde{\boldsymbol{r}}|2D_0t) + \int_0^t \int_{\mathbb{R}^3} P(\tilde{\boldsymbol{r}} - \boldsymbol{r}'|2D_0(t-\tau)) u(\boldsymbol{r}',\tau) d\boldsymbol{r}' d\tau, \quad (8)$$

where $P\left(\tilde{r}|\sum\right)$ denotes a zero-mean Gaussian distribution with covariance Σ . If there is no disturbance to the diffusion of water molecules, i.e., if $u\left(\tilde{r},\tau\right)=0$, then $\rho\left(\tilde{r},t\right)$ is Gaussian and the non-Gaussianity of $\rho\left(\tilde{r},t\right)$ is caused by the disturbance $u\left(\tilde{r},\tau\right)$.

A simpler solution to Eq. (7) can also be obtained using the spatial Fourier transform. To this end, let

$$s\left(\boldsymbol{q},t\right) = \int_{\mathbb{R}^{3}} e^{-i\boldsymbol{q}\cdot\boldsymbol{r}} \rho\left(\tilde{\boldsymbol{r}},t\right) d\tilde{\boldsymbol{r}}, \quad (9)$$

denote the spatial Fourier transform of $\rho(\tilde{r}, t)$, where **q** is the angular wave vector. Let

$$\hat{u}(\boldsymbol{q},t) = \int_{\mathbb{R}^3} u(\tilde{\boldsymbol{r}},t) e^{-i\boldsymbol{q}\cdot\boldsymbol{r}} d\tilde{\boldsymbol{r}}.$$
 (10)

denote the spatial Fourier transform of $u(\tilde{r}, t)$. Henceforth, both $\hat{u}(q, t)$ and $\hat{u}(r, t)$ will be referred to as the ensemble average disturbance function or EAD. Then, the modified diffusion equation (7) can be written as:

$$\partial_{\tau} s\left(\boldsymbol{q},\tau\right) = - \left\|\boldsymbol{q}\right\|_{D_{0}}^{2} s\left(\boldsymbol{q},\tau\right) + \hat{u}\left(\boldsymbol{q},\tau\right), \quad (11)$$

where $\|\boldsymbol{q}\|_{D_0}^2 := \boldsymbol{q}' D_0 \boldsymbol{q}$, and it is equal to $D_0 \|\boldsymbol{q}\|^2$ for isotropic D_0 . The solution of Eq. (11) is given by:

$$s(\boldsymbol{q},t) = e^{-\|\boldsymbol{q}\|_{D_0}^2 t} + \int_0^t \hat{u}(\boldsymbol{q},\tau) e^{-\|\boldsymbol{q}\|_{D_0}^2 (t-\tau)} d\tau, \quad (12)$$

which is the spatial Fourier transform of Eq. (8). Note that, Eq. (12) does not directly provide a solution to the original diffusion equation Eq. (1), but of the modified equation given in Eq. (4). In the case of an SDE experiment, under the narrow-pulse approximation, s(q, t) is also the diffusion MRI signal since it is the Fourier transform of the EAP.

In a uniform medium, there are no restrictions to the diffusing molecules, making $\hat{u}(q, \tau) = 0$, which leads to a Gaussian EAP. In a heterogeneous medium with membranes or restrictions, the disturbances change the evolution of the EAP making it non-Gaussian and

s(q, t) naturally becomes a non-exponential function of $||q||^2_{D_0}$. Thus, our formulation provides a natural explanation for the non-Gaussian signal observed in in-vivo human brain data as well as biological tissue as reported in several works (Chin et al., 2002; Mulkern et al., 2006; Kiselev and Il'yasov, 2007). Note that, characteristic information about the structural organization of the tissue (or medium) is captured by the EAD function, which can be estimated from dMRI measurements to infer the properties of the underlying structure.

2.2. On the time-varying moments of EAP

The relation between the time-varying non-Gaussian EAP and the disturbance function can be elucidated by analyzing the time-varying moments of $\rho(\tilde{r}, t)$. For this purpose, we consider the relation between s(q, t) and $\hat{u}(q, t)$ in the frequency domain using the following Fourier transformations:

$$\begin{split} S\left(\boldsymbol{q},\omega\right) = & \int_{-\infty}^{\infty} s\left(\boldsymbol{q},t\right) e^{i\omega t} dt, \\ U\left(\boldsymbol{q},\omega\right) = & \int_{-\infty}^{\infty} \hat{u}\left(\boldsymbol{q},t\right) e^{i\omega t} dt, \end{split}$$

where we have assumed that s(q, t) = 0 and $\hat{u}(q, t) = 0$ for t < 0. Then Eq. (12) gives:

$$S(\boldsymbol{q},\omega) = \frac{1}{-i\omega + \|\boldsymbol{q}\|_{D_0}^2} + \frac{U(\boldsymbol{q},\omega)}{-i\omega + \|\boldsymbol{q}\|_{D_0}^2},$$
 (13)

where the first term on the right-hand side corresponds to the Gaussian part, while the second term captures the structural organization of the underlying substrate. The expression in Eq. (13) provides a general representation for the diffusion signal assuming narrow gradient pulse.

For a specific disturbance function $U(q, \omega)$, the expression in Eq. (13) can be reduced to the result obtained using EMT in (Novikov and Kiselev, 2010; Burcaw et al., 2015). In (Novikov and Kiselev, 2010), the diffusion signal was represented as:

$$S(\boldsymbol{q},\omega) = \frac{1}{-i\omega + \|\boldsymbol{q}\|_{D_0}^2 - \sum(\boldsymbol{q},\omega)}$$

where $\Sigma(q, \omega)$ was termed as the self-energy term. This expression can be considered as a special case of (13) with:

$$U(\boldsymbol{q},\omega) = \frac{\sum(\boldsymbol{q},\omega)}{-i\omega + \|\boldsymbol{q}\|_{D_0}^2 - \sum(\boldsymbol{q},\omega)},$$

and vise versa. Thus, the results reported in (Novikov and Kiselev, 2010) are equivalent to our formulation for SDE experiments with narrow pulses by using change of variables.

To simplify the analysis and without loss of generality, we only consider a fixed diffusion direction *n* so that s(q, t), $\hat{u}(q, t)$ only depend on the magnitude q := || q || and can be written as s(q, t) and $\hat{u}(q, t)$, respectively. We also consider D_0 as a scalar representing the diffusivity along *n*. We denote $\tilde{r}(t) = n \cdot \tilde{r}(t)$ as the displacement along *n*. Let $\langle \tilde{r}^{2n}(t) \rangle$ denote the $2n^{\text{th}}$ order moment $\tilde{r}(t)$. Using Taylor expansion, we can express the diffusion signal s(q, t) in Eq. (9) in terms of its moments as:

$$s(q,t) = 1 - \frac{\langle \tilde{r}^2(t) \rangle}{2!} q^2 + \frac{\langle \tilde{r}^4(t) \rangle}{4!} q^4 + o(q^4), \quad (14)$$

where we have assumed that the odd order moments $\langle \tilde{r}^{2n+1}(t) \rangle$ for n = 0, 1, ..., vanish due to the macroscopic symmetry of $\rho(\tilde{r}, t)$, i.e. $\rho(\tilde{r}, t) = \rho(-\tilde{r}, t)$. Note that, any asymmetry in $\rho(\tilde{r}, t)$ will lead to complex values for the dMRI signal, which usually cannot be measured reliably in practice. Hence, for all practical purposes, we can safely assume that the odd order moments are zero. The mean-squared displacement $\langle \tilde{r}^2(t) \rangle$ and the fourth-order moment $\langle \tilde{r}^4(t) \rangle$ can also be expressed in terms of the disturbance function EAD. To show this, we use the Taylor expansion of $\hat{u}(q, t)$:

$$\hat{u}(q,t) = \hat{u}_2(t) q^2 + \hat{u}_4(t) q^4 \dots,$$
 (15)

where there is no constant term since $\hat{u}(0, t) = 0$, and the odd terms of q vanish for the same reason as above.

In order to derive the relation between $\langle \tilde{r}^2(t) \rangle$, $\langle \tilde{r}^4(t) \rangle$ and $\hat{u}_2(t)$, $\hat{u}_4(t)$, we denote the timedomain Fourier transform of $\hat{u}(q, t)$ by

$$U(q,\omega) = U_2(\omega) q^2 + U_4(\omega) q^4 + \dots$$

Using the above expansion, we can rewrite Eq. (13) as:

$$S(q,\omega) = \frac{1}{-i\omega_{+}} - \left(\frac{D_{0}}{(-i\omega_{+})^{2}} - \frac{U_{2}(\omega)}{-i\omega_{+}}\right)q^{2} + \left(\frac{D_{0}^{2}}{(-i\omega_{+})^{3}} - \frac{D_{0}U_{2}(\omega)}{(-i\omega_{+})^{2}} + \frac{U_{4}(\omega)}{-i\omega_{+}}\right)q^{4} + o(q^{4})$$

(16)

where $\omega_{+} = \lim_{a \searrow 0} (\omega + ia)$. Comparing the corresponding terms in Eq. (16) and Eq. (14), we obtain the following relations:

$$\langle \tilde{r}^2(t) \rangle = 2! \int e^{-i\omega t} \left(\frac{D_0}{(-i\omega_+)^2} - \frac{U_2(\omega)}{-i\omega_+} \right) \frac{d\omega}{2\pi},$$

= 2 \left(D_0 t - \int_0^t \tilde{u}_2(\tau) d\tau \right), (17)

Other higher order moments can also be derived in a similar way (see the Appendix B for more details on the derivations of the above equations).

2.3. Relation to tissue structure

The connection between the disturbance function and the moments of the EAP in Eq. (17) and Eq. (18) allows us to understand the physical meaning of the time-dependent coefficients $\hat{u}_2(t)$ and $\hat{u}_4(t)$. By taking the time derivative of Eq. (17), we can also obtain the instantaneous diffusion coefficient (see (Burcaw et al., 2015)) given by:

$$D_{\text{inst}}(t) = \frac{\partial}{\partial t} \frac{\langle \tilde{r}^2(t) \rangle}{2} = D_0 - \hat{u}_2(t), \quad (19)$$

which depends on the instantaneous value of $\hat{u}_2(t)$. It was shown in (Novikov and Kiselev, 2010) ([Eq. 39]) that the long-time limit of the instantaneous diffusion coefficient, converges

to a constant value $D_0 - \langle (\delta D)^2 \rangle / (D_0 d)$, where *d* is the dimension of the space and $\langle (\delta D)^2 \rangle$ denotes the variance of $\delta D(r)$. Thus, the connection between the disturbance function and the results obtained using the EMT becomes more apparent implying:

$$\lim_{t \to \infty} \hat{u}_2(t) = \langle (\delta D)^2 \rangle / (D_0 d).$$
 (20)

Thus, the disturbance function $\hat{u}(q, t)$, as expected, depends upon the variance in the diffusivity, which in turn is a function of the structural organization of the underlying tissue substrate.

On the other hand, in the short-time limit, it was shown in (Mitra et al., 1993) that the diffusion coefficient decreases as a function of $t^{1/2}$. Thus, we can assume $\hat{u}_2(t) = ct^{1/2}$ for some constant *c* whose value is related to the surface-to-volume ratio of the pores. Moreover, the short-time analysis of the diffusional kurtosis in (Novikov and Kiselev, 2010) also provides interesting insight for understanding the short-time behavior of the higher order

term $\hat{u}_4(t)$ in (18). In particular, by substituting $\hat{u}_2(t) = ct^{\frac{1}{2}}$ in (17) and (18), the timedependent diffusional kurtosis (Jensen et al., 2005)

$$K(t) := \frac{\langle \tilde{r}^{4}(t) \rangle}{\langle \tilde{r}^{2}(t) \rangle^{2}} - 3$$

is given by:

$$K(t) \simeq \frac{12D_0^2 t^2 - \frac{32}{5}D_0 ct^{\frac{5}{2}} + \int_0^t \hat{u}_4(\tau)d\tau}{4D_0^2 t^2 - \frac{16}{3}D_0 ct^{\frac{5}{2}} + \frac{16}{9}D_0 c^2 t^3} - 3.$$

In the short-time limit, K(t) is given by

$$\lim_{t \searrow 0} K(t) = \frac{1}{(4D_0^2 t^2)} \int_0^t \hat{u}_4(\tau) d\tau.$$

It was also shown using EMT (Novikov and Kiselev, 2010) that the short-time limit of K(t) is given by $3\langle (\delta D)^2 \rangle / D_0^2$. Comparing the two expressions, we obtain $\hat{u}_4(t) \approx 24 \langle (\delta D)^2 \rangle t$ in short-time limit.

Since $\hat{u}(q, t)$ is the spatial Fourier transform of the structural disturbance $\hat{u}(r, t)$, $\hat{u}(q, t)$ consequently captures the spatial variation of the diffusivity. Thus, $\hat{u}(q, t)$ at low q-values is related to the low spatial frequency (long-distance scale) variations in the spatial organization of the tissue, while high spatial frequency (short-distance scale) variations are captured by high q-value terms of $\hat{u}(q, t)$. Moreover, from the expansion in Eq. (10), we note that the value of $\hat{u}(q, t)$ in the low q-value range is dominated by the term $\hat{u}_2 q^2$ while the term $\hat{u}_4 q^2$ becomes non-negligible at high q-values. Thus, \hat{u}_2 and \hat{u}_4 are related to low and

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high spatial frequency of the structural organization of the tissue. In other words, the values of $\hat{u}_2(t)$ and $\hat{u}_4(t)$ are related to the long and short distance disturbance due to the tissue structure. Consequently, we will refer to them as the long and short-range disturbance coefficients, in the remainder of this paper.

2.4. Estimating structural disturbance using dMRI

The dMRI signal obtained from the traditional Stejskal-Tanner experiment with narrow pulses is exactly the Fourier transform of the ensemble-average propagator (EAP) $\rho(\tilde{r}, t)$ (Callaghan, 1991), i.e. s(q, t) in Eq. (9). Both the diffusion time t and the q-value are experimental parameters. Several methods (Özarslan et al., 2009; Merlet and Deriche, 2013; Özarslan et al., 2013; Ning et al., 2015) have been proposed to estimate the EAP using dMRI measurements based on Eq. (9) for a given diffusion time. A limitation of these methods is that the estimated EAP does not provide specific information about the underlying tissue structure. However, this limitation can be addressed if we can obtain information about the EAD from the dMRI measurements.

If the dMRI signal s(q, t) is known explicitly, for all q and t, then the EAD can be deduced from Eq. (12) or written directly from Eq. (11) as follows:

$$\hat{u}\left(\boldsymbol{q},t\right) = \left(\frac{\partial}{\partial t} + \left\|\boldsymbol{q}\right\|_{D_{0}}^{2}\right) \left(s\left(\boldsymbol{q},t\right) - e^{-\left\|\boldsymbol{q}\right\|_{D_{0}}^{2}t}\right),$$
$$= \left(\frac{\partial}{\partial t} + \left\|\boldsymbol{q}\right\|_{D_{0}}^{2}\right) s\left(\boldsymbol{q},t\right),$$
(21)

This equation provides an interesting way of estimating EAD function using the dMRI measurements. However, the differential operator makes it not very useful in practice to use this above equation to estimate $\hat{u}(q, t)$ due to measurement noise and long scan time. To provide insight into the relation between the EAD and tissue structure, in our experiments section, we will use Eq. (21) to estimate the EAD for several synthetic structures based on simulated (Monte-Carlo) diffusion signal.

2.5. Long-diffusion-time model

As shown in Eq. (20), the long-range disturbance $\hat{u}_2(t)$ converges to a constant value in the long-time limit. If the entire function $\hat{u}(q, t)$ converges to a constant value in much shorter time than the diffusion time *t*, then the dMRI signal s(q, t) has a much simpler expression which can be used to estimate the long-time limit of the EAD. Let $\hat{u}(q)$ denote the long-time limit of $\hat{u}(q, t)$. Using $\hat{u}(q, t) = \hat{u}(q)$ in Eq. (12), we obtain the following model for the dMRI signal:

$$s(q,t) = \frac{\hat{u}(q)}{D_0 q^2} + \left(1 - \frac{\hat{u}(q)}{D_0 q^2}\right) e^{-D_0 q^2 t}.$$
(22)

In the Experiments section, we will show that the EAD converges to a stationary state (or a very slowly time-varying state) in a much shorter time than typical diffusion times used on clinical scanners. Thus, Eq. (22) provides a long-time scale dMRI model.

The long-time limit of Eq. (22) also provides insights on understanding the relation between the model parameters \hat{u}_2 , \hat{u}_4 , D_0 and the structural organization. Expanding $\hat{u}(q)$ into its Taylor series, we get:

$$\hat{u}(q) := \hat{u}_2 q^2 + \hat{u}_4 q^4 + o(q^4).$$
 (23)

Taking the limit of Eq. (22), we have

$$\lim_{t \to \infty} s(q, t) = \frac{\hat{u}_2}{D_0} + \frac{\hat{u}_4}{D_0} q^2 o\left(q^2\right).$$
(24)

On the other hand, we may decompose the dMRI signal s(q, t) into two components as in (Assaf et al., 2008; Alexander et al., 2010; Huang et al., 2015) given by:

$$s(q,t) = f_{\text{intra}} s_{\text{intra}}(q,t) + (1 - f_{\text{intra}}) s_{\text{extra}}(q,t),$$

where $s_{intra}(q, t)$, $s_{extra}(q, t)$ denote the dMRI signal contribution from the intra and extraaxonal spaces, respectively. We assume that the displacements of all extra-axonal molecules diverge at long diffusion time, while all the molecules in the intra-axonal space have bounded trajectories. Then, the signal $s_{extra}(q, t)$ decays to zeros at long diffusion time. Thus, the long-time scale dMRI signal is given by:

$$\lim_{t \to \infty} s\left(q, t\right) = f_{\text{intra}} \lim_{t \to \infty} s_{\text{intra}}\left(q, t\right) = f_{\text{intra}}\left(1 - \frac{\langle \tilde{r}_{\text{intra}}^2 \rangle}{2} q^2 + o\left(q^2\right)\right), \quad (25)$$

where $\langle \tilde{r}_{intra}^2 \rangle$ denotes the mean-squared displacement of the intra-axonal molecules and it is equal to $\langle \tilde{r}_{intra}^2 \rangle = \frac{r_{app}^2}{2}$ where r_{app} is the apparent axon radius. The value of r_{app} relates to the distribution of axon sizes (Özarslan et al., 2011), and r_{app}^2 is equal to $\langle r^4 \rangle / \langle r^2 \rangle$ with $\langle r^k \rangle$ being the k-th order moment of the axon-radius distribution (Burcaw et al., 2015).

Comparing (24) and (25), we obtain the following equations:

$$\hat{u}_2 = f_{\text{intra}} D_0, \quad (26)$$

$$\hat{u}_4 = -\frac{1}{4} f_{\text{intra}} D_0 r_{\text{app}}^2,$$
 (27)

which provides direct relation between the short and long-range disturbance coefficients and the tissue structural organization. In particular, under the assumptions made above, Eq. (26) shows that the long-range disturbance coefficient is proportional to the diffusivity with their ratio being the relative intra-axonal volume fraction. In other words, if two structures have the same intra-axonal volume fraction, then the structure with stronger long-range disturbance will have higher diffusivity. Moreover, Eq. (27) shows that the short-range disturbance is closely related to the axon diameter. In particular, Eqs. (26) and (27) imply that $r_{app}^2 = -4\hat{u}_4/\hat{u}_2$. In Appendix C, we provide the exact expression for $\hat{u}_2(t)$ and $\hat{u}_4(t)$ for diffusion in restricted cylinders to show that Eqs. (26) and (27) indeed hold in this standard case.

Having shown the connection between our work and several of existing works, we note that the general representation for the dMRI signal in Eq. (12) was derived without any assumption about the existence of tissue compartments. Hence, it is interesting that the proposed PICASO model provides a direct connection with the multi-compartment models in the long-time scale regime.

In practice, the order of the expansion in Eq. (23) depends on the maximum q-value that can be obtained from MRI scanners. Since q is in the reciprocal space of \tilde{r} , the largest q-value determines the highest spatial-frequency (or the shortest range) of disturbances that can be probed by dMRI measurements. For example, for human brain tissue, the short-range disturbances are primarily caused by the compactly packed intra and extra-axonal space, which is of the order of 1 μ m. But the maximum q-value that can be reached on modern clinical scanners is usually much smaller than 1 rad/ μ m. In this scenario, the diffusion signal only contains information from long-range or longer length scale disturbances. Thus, we can approximate $\hat{u}(q) = \hat{u}_2 q^2$ in the low q-value regime. If the maximum q-value can reach some value near 1 rad/ μ m, then the diffusion signal also contains contributions from short-range structures (small, compactly packed structures), in which case we can assume $\hat{u}(q) = \hat{u}_2 q^2 + \hat{u}_4 q^4$. To this end, we will refer \hat{u}_2 and \hat{u}_4 as the long and short-range disturbance indices, respectively.

2.6. The modified Bloch-Torrey Equation

In the above analysis, we only focused on analyzing the dMRI signal from experiments with narrow pulses and its relation with tissue structures. A more general method for analyzing the relation between the dMRI signal obtained using any type of gradient waveforms and tissue structure is given by the Bloch-Torrey equation (BT) (Torrey, 1956):

$$\partial_{\tau} m\left(\boldsymbol{r},\tau\right) = -i\boldsymbol{g}\left(\tau\right) \cdot \boldsymbol{r}m\left(\boldsymbol{r},\tau\right) + \nabla_{\boldsymbol{r}} \cdot \left[D\left(\boldsymbol{r}\right)\nabla_{\boldsymbol{r}}m\left(\boldsymbol{r},\tau\right)\right], \quad (28)$$

where $r \in \mathbb{R}^3$ denotes the location of the spins in a 3-dimensional space, $m(r, \tau)$ is the complex-valued magnetization density function, g(t) is the product of the gyromagnetic ratio and the vectorial gradient strength, and D(r) is the diffusivity tensor as before. Let *t* denote the instant when the signal is collected. Then, the dMRI signal is the sum of the magnetization of all the protons (Callaghan, 1991) and is given by:

$$s(\boldsymbol{g},t) = \int_{\boldsymbol{r}^3} m(\boldsymbol{r},t) \, d\boldsymbol{r},$$

which is a function of the gradient sequence and the diffusion time.

Proceeding along the lines of Eqs. (1)–(4), we consider a decomposition of the $D(\mathbf{r})$ as in Eq. (3) and denote:

$$u_{m}\left(\boldsymbol{r},\tau\right):=\nabla_{\boldsymbol{r}}\cdot\left[\tilde{D}\left(\boldsymbol{r}\right)\nabla_{\boldsymbol{r}}m\left(\boldsymbol{r},\tau\right)\right],$$

as the disturbance function that depends on the magnetization density $m(r, \tau)$. Then Eq. (28) can be rewritten as:

$$\partial_{\tau} m\left(\boldsymbol{r},\tau\right) = -i\boldsymbol{g}\left(\tau\right) \cdot \boldsymbol{r} m\left(\boldsymbol{r},\tau\right) + \nabla_{\boldsymbol{r}} \cdot D_{0} \nabla_{\boldsymbol{r}} m\left(\boldsymbol{r},\tau\right) + u_{m}\left(\boldsymbol{r},\tau\right). \tag{29}$$

Since $u_m(\mathbf{r}, \tau)$ depends on $m(\mathbf{r}, \tau)$, and $m(\mathbf{r}, \tau)$ depends on the gradient sequence upto time τ , i.e., g(s) for $s \in [0, \tau]$, we can denote $u_m(\mathbf{r}, \tau)$ by:

$$u_{m}(\boldsymbol{r},\tau)=u(\boldsymbol{r},\tau,\boldsymbol{\mathscr{G}}(\tau)),$$

where $\mathscr{G}(\tau) := \{ g(s) : s \in [0, \tau] \}$ denotes the gradient sequence upto time τ . Using $u(r, \tau, \mathscr{G}(\tau))$ in Eq. (29), we obtain the following modified Bloch-Torrey equation:

$$\partial_{\tau} m\left(\boldsymbol{r},\tau\right) = -i\boldsymbol{g}\left(\tau\right) \cdot \boldsymbol{r} m\left(\boldsymbol{r},\tau\right) + \nabla_{\boldsymbol{r}} \cdot D_{0} \nabla_{\boldsymbol{r}} m\left(\boldsymbol{r},\tau\right) + u\left(\boldsymbol{r},\tau,\boldsymbol{\mathscr{G}}\left(\tau\right)\right).$$
(30)

Next, we will derive the exact relation between s(g, t) and the disturbance function $u(r, \tau, \mathcal{G}(\tau))$.

2.7. Solving the modified Bloch-Torrey equation

First, we denote the spatial Fourier transform of *m* and *u* by:

$$\hat{m}(\boldsymbol{k},\tau) = \int_{\mathbb{R}^3} m(\boldsymbol{r},\tau) e^{-\boldsymbol{y}\boldsymbol{k}\cdot\boldsymbol{r}} d\boldsymbol{r}, \\ \hat{u}(\boldsymbol{k},t,\boldsymbol{\mathscr{G}}(\tau)) = \int_{\mathbb{R}^3} u(\boldsymbol{r},\tau,\boldsymbol{\mathscr{G}}(\tau)) e^{-\boldsymbol{y}\boldsymbol{k}\cdot\boldsymbol{r}} d\boldsymbol{r}.$$

By taking the spatial Fourier transform of Eq. (30), we obtain the following PDE:

$$\partial_{\tau}\hat{m}\left(\boldsymbol{k},\tau\right) = \boldsymbol{g}\left(\tau\right) \cdot \nabla_{\boldsymbol{k}}\hat{m}\left(\boldsymbol{k},\tau\right) - \left\|\boldsymbol{k}\right\|_{D_{0}}^{2}\hat{m}\left(\boldsymbol{k},\tau\right) + u\left(\boldsymbol{k},\tau,\boldsymbol{\mathscr{G}}\left(\tau\right)\right).$$
(31)

Let $q(\tau) := \int_{\tau}^{t} g(s) ds$. If the gradient satisfies the echo condition so that q(0) = 0 and assuming s(0, t) = 1, the diffusion signal $s(q, t) = \hat{m}(0, t)$ is given by:

$$s(\boldsymbol{g},t) = e^{-\int_{0}^{t} \|\boldsymbol{q}(\tau)\|_{D_{0}}^{2} d\tau} + \int_{0}^{t} \hat{u}(\boldsymbol{q}(\tau),\tau,\boldsymbol{\mathscr{G}}(\tau)) e^{-\int_{\tau}^{t} \|\boldsymbol{q}(\tau')\|_{D_{0}}^{2} d\tau'} d\tau.$$
(32)

Note that, Eq. (32) is not a direct solution to the original equation Eq. (28) but of its modified form in terms of the EAD function. A detailed derivation of Eq. (32) is given in Appendix A. Note that, the difference between Eq. (32) and the expression in Eq. (12) is the time dependence of the $q(\tau)$ and the dependence of $\hat{u}(q, \tau, \mathcal{G}(\tau))$ on the gradient sequence. In order to gain insight about the gradient-dependence of $\hat{u}(q, \tau, \mathcal{G}(\tau))$, we will discuss in detail the models for the disturbance function in the case of SDE experiments with finite pulse width and double diffusion encoding (DDE) experiments.

2.8. On the dependence of the disturbance function on gradient sequences

In the case of SDE experiments, a single gradient direction is used during the entire diffusion experiment. Consequently, all the elements of the gradient sequence $g(\tau)$ and the trajectory $q(\tau)$ in the q-space can be represented as linear functions of the maximum q-value q_{\max} as: $g(\tau) = q_{\max}c_g(\tau)$ and $q(\tau) = q_{\max}c_q(\tau)$ for some scalar function $c_g(\tau)$ and $c_q(\tau)$, respectively. In SDE experiments, the functions $c_g(\tau)$ and $c_q(\tau)$ only depend on the pulse width and diffusion time¹. Thus, if the pulse width and diffusion time are fixed, the function $\hat{u}(q(\tau), \tau, \mathcal{G}(\tau))$ only depends on q_{\max} and τ . Consequently, the disturbance function can be simplified to $\hat{u}(q_{\max}, \tau) := \hat{u}(q(\tau), \tau, \mathcal{G}(\tau))$, which has a similar form as the disturbance function in Eq. (10) in the narrow-pulse case.

In the case of DDE experiments, the gradient directions may not be collinear with each other (Özarslan and Basser, 2008; Shemesh et al., 2010). Since the elements in $\mathscr{G}(\tau)$ and $q(\tau)$ are related to the gradient waveform before and after the time instant τ , the functions $g(\tau)$ and $q(\tau)$ cannot be represented by scaling of a single vector q_{max} as in the SDE experiments. Nevertheless, the functions $g(\tau)$ and $q(\tau)$ in DDE experiments can be represented as a linear combination of two vectors, i.e., $q_{1,\text{max}}$ and $q_{2,\text{max}}$, which are the maximum q-values for the two pairs of pulses, respectively. Thus, the disturbance function can be written in the form $\hat{u}(q_{1,\text{max}}, q_{2,\text{max}}, \tau)$, which is different from the simplified model in SDE experiments. The dependence of the disturbance function on the gradient sequence indicates that the DDE experiments may provide additional information about the microscopic structure of the tissue that cannot be probed by SDE experiments, as has already been pointed out in (Özarslan and Basser, 2007; Özarslan, 2009; Lawrenz et al., 2010; Jespersen, 2012).

$$c_{g}(\tau) = \begin{cases} 1/\delta, & \text{for } \tau \in (0, \delta], \\ 0, & \text{for } \tau \in (\delta, \Delta], \\ -1/\delta, & \text{for } \tau \in (\Delta, \Delta + \delta], \end{cases}, \quad c_{q}(\tau) = \begin{cases} \tau/\delta, & \text{for } \tau \in (0, \delta], \\ 1, & \text{for } \tau \in (\delta, \Delta], \\ (\Delta + \delta - \tau)/\delta, & \text{for } \tau \in (\Delta, \Delta + \delta]. \end{cases}$$

¹In SDE experiments, $q_{\text{max}} = g\delta$ and the function $c_g(\tau)$ and $c_q(\tau)$ are given by:

In the rest of this paper, we will only focus on the SDE experiments and analyze the biophysical meaning of the model parameters in the disturbance function $\hat{u}(q_{\max}, \tau)$. The time dependent $q(\tau)$ in SDE experiments is given by:

 $\boldsymbol{q}\left(\tau\right) = \begin{cases} \boldsymbol{g}\tau, & \text{for } 0 < \tau \leq \delta, \\ \boldsymbol{g}\delta, & \text{for } \delta < \tau \leq \Delta, \\ \boldsymbol{g}\left(\Delta + \delta - t\right), & \text{for } \Delta < \tau \leq \Delta + \delta, \end{cases}$

We clarify a few notations that we use in the next section; $q(\tau)$ denotes the q-value at a particular time instant τ , while writing it without the argument τ implies $q := q_{\text{max}} = g\delta$ which denotes the maximum q-value in SDE experiments. Hence, in the rest of this section, $\hat{u}(q_{\text{max}}, \tau)$ is written as $\hat{u}(q, \tau)$.

3. Methods and Modelling

We demonstrate the performance of the proposed approach using both Monte-Carlo simulations and in-vivo data sets. In the simulations, we first compared diffusion MRI signals and the estimated disturbance functions from three synthetic tissue structures mimicking the intra-axonal, myelin, extra-axonal spaces. Moreover, we also examined the differences in diffusion signals and disturbance functions due to the partial-volume effect using an additional pair of synthetic structures. In the in-vivo data experiments, we tested the proposed approach using two data sets that were acquired from the WU-Minn HCP and MGH HCP connectome scanner (Van Essen et al., 2013; Setsompop et al., 2013), respectively. The experimental results demonstrate how the PICASO model can be used to understand the tissue microstructural organization and how it changes with diffusion time and gradient strength.

3.1. Comparing axonal packing structures using Monte-Carlo simulations

We generated synthetic diffusion data using Monte-Carlo simulations on three types of cellular and axonal packing in a two-dimensional substrate. The simulated field of view of these structures was $100 \times 100 \,\mu \text{m}^2$. Figs. 1a, 1b and 1c illustrate a partial field of view with size $30 \times 30 \,\mu \text{m}^2$ for the three types of packing, which are denoted by Structure 1, Structure 2 and Structure 3, respectively. The green circles (regions) are the myelin sheaths that surround the axons shown in red. The g-ratio (the ratio between the inner and outer radii of each green circle) for all axons was set to 0.6, which is based on result from Rushton (1951) and Basser (2004). Structure 1 has small and more densely packed axons. Structure 3 has relatively loosely packed large axons. The intra-axonal volume fraction, myelin volume fraction and extra-axonal volume fraction for the three structures are {0.24, 0.43, 0.33}, {0.23, 0.40, 0.37} and {0.23, 0.41, 0.36}, respectively. The extra-axonal volume fraction is close to the histology results from monkey brain in (Lamantia and Rakic, 1990). The average axon radius weighted by the intra-axonal areas for the three structures was 0.31, 0.50, 0.68 μ m, respectively.

In our Monte-Carlo simulations, a total of 10^5 particles were randomly selected from a uniform distribution within the extra axonal space (no particles were initialized in the myelin

areas since the MRI signal decays quickly due to very short T_2 of myelin water (Laule et al., 2007) and long TE of clinical acquisitions). During a time step of dt = 0.005 ms, each particle moved a distance of $2\sqrt{Ddt} \mu m$ along a randomly selected direction with $D = 2 \mu m^2/ms$. The boundaries were considered impermeable, so that the particles would reflect off the myelin sheaths. Then the dMRI signal from the extra-axonal space was computed from the simulated trajectories of the particles. The dMRI signal within each synthetic axon was computed using the explicit expressions proposed in (McCall et al., 1963) and (Neuman, 1974) for SDE experiments with narrow and finite pulses, respectively. The ensemble dMRI signal was computed as the average of intra and extra-axonal signal weighted by the corresponding volume fractions.

3.1.1. SDE simulations with narrow pulses—In this simulations, we sampled the

dMRI signals s(q, t) for the three structures at a dense set of time points in the interval 0 t80 ms with 0 q 3 rad/ μ m. The baseline diffusion coefficients D_0 for the three structures was estimated by fitting the signal s(q, t) in the interval 0 q 0.1 rad/ μ m and 0 t 1 ms using the DTI model $e^{-q^2 D_0 t}$. Using Eq. (21), we computed the two-dimensional EAD function $\hat{u}(q, t)$ in the interval 1 t 80 ms for the three structures. The disturbance function $u(q, \tau)$ in the interval $\tau \in [t_0, t]$ can still be estimated from s(q, t) using Eq. (21). We assume that $s(q, t_0)$ is Gaussian for a presumed small $t_0 = 1$ ms, and estimate the corresponding diffusivity as the baseline D_0 . The EAD function at high q-values and its evolution process with time was also estimated to understand the nature of the disturbance function. From the estimated u(q, t) at t = 80 ms, we also computed the corresponding \hat{u}_2 and \hat{u}_4 coefficients using Eq. (15).

3.1.2. Finite-pulsed SDE simulations—Based on the collected particle trajectories, we computed two sets of diffusion data with different experimental parameters. In the first set, we set the pulse width to $\delta = 10.6$ ms, diffusion time of = 43.1 ms and gradient strength of $g = 20, 40, \dots, 100$ mT/m, while the experimental parameters for the second set were: $\delta = 12.9$ ms, = 21.8 ms and $g = 30, 60, \dots, 300$ mT/m. The pulse width, diffusion time and maximum gradient strength of the two sets of signals were chosen according to the parameters in the WU-Minn HCP and MGH HCP diffusion data sets, respectively.

The maximum q-value for the first data set (WU-Minn HCP) is $q_{max,1} = 0.2836$ rad/ μ m while for the second data set (MGH HCP) is $q_{max,2} = 1.0353$ rad/ μ m. The different q_{max} -values allow assessment of different types of microstructural information about the tissue. Given the low q-values in the first data set, we expect that the signal contribution is primarily from the long-range disturbances, while, both the short and long-range perturbations can be measured from the second data set (due to large q-values). To this end, we assume that the disturbance function for the first data set is modeled by $\hat{u}(q, t) = \hat{u}_2 q^2$, while the disturbance function for the second data set is given by $\hat{u}(q, t) = \hat{u}_2 q^2 + \hat{u}_4 q^4$. Since the gradient pulse length is finite (and not narrow), we used the following signal model for the two data sets:

$$s_1(q) = \frac{\hat{u}_2}{D_0} + (1 - \frac{\hat{u}_2}{D_0})e^{-q^2 D_0(\Delta - \delta/3)},$$
 (33)

$$s_2(q) = \frac{\hat{u}_2 + \hat{u}_4 q^2}{D_0} + (1 - \frac{\hat{u}_2 + \hat{u}_4 q^2}{D_0})e^{-q^2 D_0(\Delta - \delta/3)}.$$
 (34)

Eq. (33) and Eq. (34) are derived from Eq. (32) with disturbance function being $\hat{u}(q, \tau) = \hat{u}_2 q(\tau)^2$ and $\hat{u}(q, \tau) = (\hat{u}_2 + \hat{u}_4 q^2)q(\tau)^2$, respectively. The model parameters \hat{u}_2 , \hat{u}_4 , D_0 were estimated using the *lsqnonlin.m* routine in Matlab (The MathWorks Inc., Natick, MA) for all the simulations.

3.2. Sensitivity to partial-volume effects

In-vivo diffusion MRI data sets are typically plagued with partial-volume effects, especially close to white matter-CSF boundaries, due to the relatively large voxel sizes. To understand the impact of partial voluming, we estimated the disturbance function in two synthetic structures shown in Fig. 2. The blue region at the bottom of Fig. 2b represents CSF area, which is separated from the axonal fiber bundles by an impermeable membrane. The intra-axonal volume fraction, myelin volume fraction and extra-axonal volume fractions for the structure illustrated in Fig. 2a are {0.23, 0.37, 0.40}. The volume fraction of the CSF area in Fig. 2b is 0.3. We used the same configuration as in the previous simulations to collect the diffusion trajectories within the two types of synthetic structures (using Monte-Carlo simulations). Then, we generated two sets of diffusion MRI signals with finite pulse width using the same parameter as in the previous WU-Minn and MGH HCP simulations. From the simulated signals, we used Eq. (33) and (34) to estimate the disturbance functions from the two structures, respectively. Results from this experiment are discussed in the Results section.

3.3. WU-Minn HCP data set

We tested the performance of our method using the in-vivo WU-Minn HCP dMRI data set. The spatial resolution of the diffusion-weighted image was $1.25 \times 1.25 \times 1.25 \times 1.25 \text{ mm}^3$. The experimental parameters were TR/TE = 5500/89 ms, $\delta = 10.6 \text{ ms}$ and = 43.1 ms. The data set consisted of three b-values with b = 1000, 2000 and 3000 s/mm² with $b = \gamma^2 g^2 \delta^2 (-\delta/3)$. The maximum gradient strength was $g_{\text{max}} = 97.4 \text{ mT/m}$. At each b-shell, the diffusion signal was acquired along 90 gradient directions. More detailed information about data acquisition and pre-processing steps are given in (Sotiropoulos et al., 2013).

Since the maximum q-value for this data set is about $0.2762 \text{ rad}/\mu m$, we expect that the primary contribution to the diffusion signal is only from long-range disturbance. For a full three-dimensional analysis, we generalized the scalar model (33) to include the full diffusion tensor as follows:

$$s(q, \boldsymbol{u}) = \boldsymbol{u}^T M_2 \boldsymbol{u} + (1 - \boldsymbol{u}^T M_2 \boldsymbol{u}) e^{-q^2 (\Delta - \delta/3) \boldsymbol{u}^T D \boldsymbol{u}}$$

where M_2 and D are both 3×3 positive semidefinite tensors. For model simplicity, we assume that M_2 and D have the same set of eigenvectors. Similar to DTI, we consider the eigenvector corresponding to the largest eigenvalue of D as the dominant diffusion direction and the corresponding eigenvalue is denoted by d_{\parallel} . We assume a cylindrical model of diffusion, with the two smaller eigenvalues being the same and denoted by d_{\perp} . The two eigenvalues of M_2 corresponding to the same eigenvectors as d_{\perp} are assumed to have the same value. From the estimated values for M_2 and D, we compute $\hat{U}_2 := M_2 D$. Similarly, the corresponding eigenvalues of \hat{U}_2 are denoted by $\hat{u}_{2,\parallel}$, $\hat{u}_{2,\perp}$, which represent the long length scale disturbance (organization) in the parallel and perpendicular direction of the fiber orientation.

3.4. MGH HCP data set

We also tested our method using the MGH HCP data set acquired on the Siemens 3T Connectome scanner with maximum gradient strength of 300 mT/m. The spatial resolution of this data set was $1.5 \times 1.5 \times 1.5$ mm³. The experimental parameters were *TR/TE* = 8800/57 ms, $\delta = 12.9$ ms and = 21.8 ms. The data set consisted of four b-values with b =1000, 3000, 5000 and 10000 s/mm². The number of gradient directions at each b-shell were 64, 64, 128 and 256, respectively. More detailed information about data acquisition and preprocessing steps can be found in (Setsompop et al., 2013).

The maximum q-value that can be reached in this data set is about 0.7559 rad/ μ m, which allows for probing short-range disturbances as well. In order to incorporate short-range disturbances, we extend the model (34) to the three-dimensional case as follows:

$$s(q, \boldsymbol{u}) = \boldsymbol{u}^T M_2 \boldsymbol{u} + q^2 \boldsymbol{u}^T M_4 \boldsymbol{u} + (1 - \boldsymbol{u}^T M_2 \boldsymbol{u} - q^2 \boldsymbol{u}^T M_4 \boldsymbol{u}) e^{-q^2 (\Delta - \delta/3) \boldsymbol{u}^T D \boldsymbol{u}},$$

where M_2 and D are both 3 × 3 positive semidefinite tensors as before. Similar to the previous experiment, we assume that \hat{U}_2 , \hat{U}_4 and D_0 all have the same set of eigenvectors. From M_2 and M_4 , we define $\hat{U}_2 := M_2 D$ and $\hat{U}_4 = M_4 D$. The eigenvalues for the three tensors are denoted by $\{\hat{u}_{2,\parallel}, \hat{u}_{2,\perp}\}, \{\hat{u}_{4,\parallel}, \hat{u}_{4,\perp}, \hat{u}_{2,\perp}\}$ and $\{d_{\parallel}, d_{\perp}, d_{\perp}\}$, respectively.

4. Results

4.1. Comparing axonal packing structures using Monte-Carlo simulations

4.1.1. Narrow-pulse SDE experiments—As mentioned earlier, we used Eq. (21) to estimate the EAD funciton. The first row of Figure 3 shows the simulated dMRI signals s(q, t) for the three structures at a selected set of time points. The estimated diffusion coefficients using the dMRI signal s(q, t) for 0 t 1 ms and $0 q 0.1 \text{ rad/}\mu\text{m}$ are shown in the first row of Table 1. Note that the estimated diffusivity, \hat{D}_0 , for all the three structures is the apparent diffusivity and not the intrinsic diffusivity (the true spatially averaged diffusivity devoid of the effect of restrictions). This is because the axon sizes used in the simulation are

very small, making the effect of restriction quite apparent even at short time scales of 1 ms. Thus, an exact estimation of the intrinsic diffusivity would require the use of diffusion signal within an ultra short diffusion time $\ll 1$ ms or use of correct time-varying model for the diffusion process (Mitra et al., 1993). Nevertheless, the estimated u(q, t) still captures the structural disturbance due to the underlying structural organization of the tissue. The second row of Figure 3 shows the estimated EAD $\hat{u}(q, t)$ at the same set of time points as in the figures in the first row. For each structure, the estimated EAD functions $\hat{u}(q, t)$ at different time points have a similar pattern in q-space, i.e., they are all monotonically increasing in the interval 0 q 2.6 rad/ μ m. The functions $\hat{u}(q, t)$ corresponding to Structure 3 reach their maximum value at about $q = 2.6 \text{ rad}/\mu\text{m}$. The last row of Figure 3 also shows the same EAD functions in the time domain at a selected set of points in q-space. These functions show a sharp change during the first 1–2 ms, which corresponds to the change of D_{inst} at a rate of $t^{\frac{1}{2}}$ shown in (Mitra et al., 1993). The functions then gradually transition to stationary values around 10 20 ms. This implies that the coefficients $\hat{u}_2(t)$ and $\hat{u}_4(t)$ from Eq. (15) for the three structures also transition to stationary values after a certain diffusion time.

The blue, green and red dots in Figure 4 show the estimated values of $\hat{u}(q, t)$ at t = 80 ms for the three structures, respectively. The solid lines show the plot using the 4th-order approximation $\hat{u}(q) = \hat{u}_2 q^2 + \hat{u}_4 q^4$ as in Eq. (15) with \hat{u}_2 and \hat{u}_4 estimated using the leastsquares fitting method, whose values are shown in Table 1. We notice that the Structure 3 has the highest apparent diffusivity, which is consistent with its strongest long-range disturbance. On the other hand, the Structure 1 has the weakest long-range disturbance due to the densely packed small axons, which leads to the smallest value for the apparent diffusion coefficient. From Eq. (26), we also estimated the relative intra-axonal volume

fractions \hat{u}_2/\hat{D}_0 for the three structures as 0.44, 0.36 and 0.35, respectively, which is very

close to the corresponding true values: $\frac{0.24}{0.24+0.33}\approx 0.42, \frac{0.23}{0.23+0.37}\approx 0.38$ and

 $\frac{0.23}{0.23+0.36} \approx 0.39$. Thus, the estimated parameters \hat{D}_0 , \hat{u}_2 , \hat{u}_4 correctly reflect the microscopic packing of axons in the tissue.

4.1.2. Finite-pulse SDE experiments—The blue, green and red curves in Figure 5a show the estimated signal for the Structures 1, 2 and 3 with the diffusion signal simulated using the first set of parameters (low-q-value regime). The signal obtained using the PICASO model perfectly matches the monte-carlo simulated measurements that are shown as the black star markers. The model parameters corresponding to the three structures are shown in Table 2. The estimated EAD, $\hat{u}_2 q^2$, is illustrated in Figure 5b in blue, green and red curves, respectively. We note that the Structure 1 has the most densely packed axons with very small diameters, resulting in lower values for the estimated \hat{u}_2 (long-range disturbance) and \hat{D}_0 , as expected. With larger axon sizes (among all the three tissue substrates) which are more uniformly distributed, Structure 3 has stronger long-range disturbance and higher apparent diffusivity. With axon sizes and packing structure lying in between that of Structures 1 and 3 substrates, the estimated long-range disturbance \hat{u}_2 and apparent diffusivity \hat{D}_0 for Structure 2 lie in between that of the other two structures, as expected.

The blue, green and red curves in Figure 6a show the estimated signal for the three substrates with the diffusion signal simulated according to the second set of parameters, i.e. $\delta = 12.9$ ms, = 21.8 ms and g = 30, 60, ..., 300 mT/m. The signal fitting using the PICASO model perfectly matches the Monte-Carlo simulated measurements, which are shown as the black star markers in Figure 6a. The estimated model parameters are given in Table 3. Similar to the previous result, the Structure 2 still has the lowest values for \hat{u}_2 and

 \hat{D}_0 while the Structure 1 has the highest values. But the estimated value for \hat{u}_4 for Structure 1 is highest, while the lowest value is for Structure3, indicating that Structure 1 has the strongest short-range disturbance, as expected. The estimated disturbance functions $\hat{u}(q) = \hat{u}_2 q^2 + \hat{u}_4 q^4$ for the three structures are illustrated in Figure 6b.

We note that the model for $\hat{u}(q)$ used in this example is assumed to be time-invariant. However, even with fixed diffusion time and varying gradient strength, the estimated model parameters show differences for the different tissue types. Note that, these structures have similar intra-cellular, extra-cellular and myelin volume fractions and the average axon diameter is less than $1\mu m$ for all the substrates. At-least in the noiseless simulations, the proposed method is capable of detecting such subtle differences in the tissue structural organization.

4.2. Sensitivity to partial-volume effects

The simulated diffusion signals from the two synthetic structures using the Wu-Minn and MGH HCP sequences are shown as the solid lines in Figs. 7a and 7c, respectively. Since the structure in Fig. 2b is not macroscopically symmetric, the diffusion MRI signal is complex valued, i.e.. The blue plots in Figs. 7a and 7c were taken as the absolute value of the simulated signals. We note that the analytic expression for the diffusion signal from the CSF area with a single restrict barrier is available in (Özarslan et al., 2008). The estimated signals using the PICASO model is indicated by the star markers in Figs. 7a and 7c. We note minor fitting errors at very high q-values in Fig. (7c), which may have be caused by the truncated expansion of $\hat{u}(q)$ to order 4. The estimated EAD functions using the Wu-Minn experiment are shown in Fig. 7b. The \hat{u}_2 values for the two structures with and without the partialvolume effect are 0.3674 $\mu m^2/ms$ and 0.1745 $\mu m^2/ms$, respectively. Fig. 7d shows the corresponding EAD functions for the MGH acquisition parameters where (\hat{u}_2, \hat{u}_4) values for the two structures with and without the partial volume effects are $(0.3493 \,\mu m^2/ms, -0.1042)$ $\mu m^4/ms$) and (0.1991 $\mu m^2/ms$, $-0.0213 \mu m^4/ms$), respectively. We note that the partialvolume effect leads to increased long-range disturbance coefficient and decreased shortrange coefficient, as expected. Very interestingly, we also found similar observations from our in-vivo experimental results (the boundary of corpus callosum and vecntricles).

4.3. Estimation results for the WU-Minn HCP data set (low q-value regime)

Figures 8a to 8d show the estimated model parameters $\hat{u}_{2\perp}$ (long range disturbance in the direction orthogonal to the fiber orientation), $\hat{u}_{2\parallel}$ (long range disturbance along the fiber orientation), d_{\perp} and d_{\parallel} (diffusivities perpendicular and parallel to fiber orientation) for a coronal slice of the WU-Minn HCP data set. For comparison, we also show the perpendicular and parallel diffusivities estimated from the standard DTI model; see Figures 8e and 8f. We note that the contrasts in the images for $\hat{u}_{2\perp}$ and d_{\perp} are substantially different

than those for DTI. The $\hat{u}_{2\perp}$ image in Figure 8a shows a similar dark contrast in the ventricles and the corpus callosum (CC) area. Since the CC area contains densely packed small axons (Aboitiz et al., 1992), it leads to very little long-range disturbance (as expected). On the other hand, ventricles are regions with very little structure to hinder water diffusion and primarily contain freely diffusing water. Thus, we do not expect any short or long-range disturbance in this area, as is clear from Figs. 9a and 14a. Quite interestingly though, due to partial volume effect as well as the biological difference between the tissue types at the interface of white matter and ventricles, Figure 8a shows a clear boundary between the CC and the ventricle area as indicated by the yellow arrow. Though the CC and CSF area both have weak long-range disturbances, the mixing of the two structures leads to strong longrange disturbance, which is consistent with the simulation results in Section 4.2. We note that the white-matter region indicated by the yellow arrow in Fig. 8b has lower perpendicular disturbance $\hat{u}_{2\perp}$ and higher parallel disturbance $\hat{u}_{2\parallel}$. The much stronger parallel disturbance may be caused by orientation dispersion in the underlying fiber bundles, while the lower $\hat{u}_{2\perp}$ may indicate that the axons are very densely packed. This demonstrates the potential of the disturbance coefficients in distinguishing different tissue microstructures. For clarity, we show a close-up of the estimated long-range disturbance $\hat{u}_{2\perp}$ and the FA values in Figures 9a and 9b, for the brain region indicated by the yellow arrow in Figure 8a.

Figures 10a to 10f show the same set of model parameters for a sagittal slice of the same data set. Figure 10c still shows distinct and clear contrast between CSF and white-gray matter areas. To show the difference in the packing structure (and fiber dispersion) as captured by \hat{u}_2 within the different regions of the corpus callosum as indicated by the yellow arrow in Figure 10a, we plot in Figure 11b the estimated value of $\hat{u}_{2\perp}$ at a few manually selected set of voxels in the corpus callosum; see 11a. Higher values of $\hat{u}_{2\perp}$ in the midbody could be caused by loosely packed large axons as shown in (Aboitiz et al., 1992). We also note that the genu has slightly lower value for $\hat{u}_{2\perp}$ than splenium, implying that the axons in the genu are more densely packed and/or less dispersed. Thus, the packing structure as captured by \hat{u}_2 is strikingly similar to the schematic of the axon density and size of CC shown in (Aboitiz et al., 1992).

Figures 12c to 12d illustrate the estimated disturbance function $\hat{u}_2 q^2$ perpendicular to the estimated fiber orientation at several different locations in the brain (background is standard DTI FA image). From figure 12c it is clear that the genu has the weakest long-range disturbance (or very tightly packed axons) compared to the midbody and splenium areas. Figure 12d shows clear differentiation between the organizational structure of tissue in the cortical and sub-cortical areas, as is also known from histology studies.

To illustrate the robustness of the PICASO model in fitting the measurements, we show the estimated signal in 5 representative voxels in Figures 13a to 13e, respectively. The blue, red and green curves in Figure 13 show the estimated signal for b = 1000, 2000 and 3000 s/ mm², respectively, while scanner measurements are shown by the star makers. In these plots, the horizontal axis is the cosine of the angle between fiber orientation and the gradient directions. The location of the voxels are indicated by the arrows in Figures 12a and 12b, respectively, where the background is the FA image from DTI. The estimated model accurately fits the measurements especially in the white matter voxels. We expect that using

the fourth order term \hat{u}_4 will improve the fit, particularly for the results in Figs. 13d and 13e, as will be shown for the MGH-HCP data. Moreover, since the disturbance coefficients are sensitive to partial volume effects, the estimated disturbance maps in Fig. 8a and 8b may look noisier than the diffusivity maps.

4.4. Results from the MGH HCP data set (high q-value regime)

Figures 14a to 14f illustrate the estimated model parameters for a coronal slice of the MGH HCP data set with the perpendicular and parallel diffusivity from DTI shown in Figures 14g and 14h, respectively. The $\hat{u}_{2\perp}$ and $\hat{u}_{2\parallel}$ images show similar contrast between different brain tissue as in the previous data set. Note that, we see some hindrance to parallel diffusion along the fiber orientation as well, which is captured by $\hat{u}_{2\parallel}$. In particular, the yellow arrow in Figure 14a points to the boundary between the CC and the cingulum. Note that, although visually, the images appear noisier, it is primarily because of two reasons: First, the estimated disturbance function is sensitive to changes in tissue types or composition leading to higher values of \hat{u}_2 and \hat{u}_4 at the boundaries and in the subcortical gray matter areas which has several types of cell nuclei within each voxel. Second, we did not enforce any kind of spatial regularization in our estimation algorithm, leading to a bit noisier parameter estimate due to the lower signal-to-noise ratio from the high b-value measurements.

Figures 14c and 14d show the estimated short-range disturbance $\hat{u}_{4\perp}$ and $\hat{u}_{4\parallel}$ in the perpendicular and parallel direction of the fiber orientation, respectively. As seen in Figure 14c, most single-fiber white matter regions have strong short-range disturbance along the perpendicular direction indicating these areas are more densely packed.

Figures 15a to 15h show the estimated map of the disturbance and diffusivity parameters for a sagittal slice. As indicated by the yellow arrow in Figure 15a, the midbody of the CC has higher long-range disturbances compared to the genu and splenium areas, as expected. Figure 16 shows the estimated $\hat{u}_{2\perp}$ and $\hat{u}_{4\perp}$ at a manually selected set of voxels shown in Figures 16a and 16b, respectively. More negative values indicate less short range disturbance, while values of $\hat{u}_{4\perp}$ closer to 0 indicate dense packing of axons, as is seen in the genu and splenium of the CC (but not in the mid-body). We also note that Figure 15a shows interesting features in the cortical areas, specifically at the boundaries of tissue types.

Figures 18a to 18e illustrate the estimated and the measured signal in 5 representative voxels of the brain. The blue, red, green and magenta curves represent the estimated signal at b = 1000, 3000, 5000 and 10000 s/mm², respectively, while the star markers are the measurements. The location of the voxels are indicated by the arrows shown in Figures 17a and 17b. We note that including the 4th-order term ensures a better fit to the data even at b = 10000 s/mm². Figures 17c and 17d show the estimated disturbance functions $\hat{u}_{2\perp}q^2 + \hat{u}_{4\perp}q^4$ perpendicular to fiber orientation. The midbody shows stronger long-range disturbance than the genu and splenium areas, as expected. The disturbance function estimated at a couple of voxels in the cortical and sub-cortical gray matter areas are shown in Figure 17d. We should note that the range of *q*-values is different in Figures 17 and 12, and hence the disturbance function looks different, but in the low q-value range, they are consistent.

From these experiments, it is clear that novel features of structural organization of brain tissue can be extracted not only from theoretical predictions and Monte-Carlo simulations, but also from in-vivo human brain data.

5. Discussion and conclusions

In this paper, we proposed a novel PICASO model for investigating the biophysical cellular and axonal architecture of biological tissue using diffusion MRI. We used the Diffusion equation and the Bloch-Torrey equation with spatial variability of the diffusion coefficient to incorporate the structural organization of the underlying media. We introduced a novel representation of the diffusion MRI signal in terms of a structural disturbance function, which contains information about the underlying structural organization of the medium. Moreover, we also proposed novel measures termed as the short- and long-range disturbance coefficients derived from the disturbance function using dMRI measurements to infer specific properties of the tissue structure. We also derived the relation between the disturbance function and the EAP, and its connection with the effective medium theory of (Novikov and Kiselev, 2010). The relevance of the proposed method was examined using Monte-Carlo simulations and in-vivo experiments. The main conclusions from the experimental results are summarized below:

- The Monte-Carlo simulation results showed that the proposed method is capable of identifying and quantifying different types of packing structure of axons with SDE signal acquired at fixed diffusion-time and varying gradient strengths. The theory we developed is quite general and models the structural organization using a function $\hat{u}(q, t)$ of both q and t. For simplicity, even if this disturbance function is assumed to be time-invariant, the estimated model parameters still capture different short and long length scale disturbances associated with the structural organization of cells and axons.
- The experimental results using the WU-Minn HCP dMRI data set showed that, for diffusion signal acquired at low q-values, the PICASO model can be used to estimate long-range disturbance in microstructural arrangement of axons. The results show that the long-range disturbance is different for different segments of the corpus callosum. Further, several novel contrasts between tissue types, tissue boundaries and the corresponding diffusivities were seen, which further reveal the packing structure of axons in brain tissue obtained from in-vivo dMRI data.
- The experimental results using the MGH HCP dMRI data set showed that high qvalues can provide information about short-range or short-length scale disturbances in the microstructural arrangement of axons. Different types of tissue can be distinguished by the estimated disturbance function. However, since the SNR is low at high q-values, the estimated model parameters show larger variance within the same type of tissue. Hence, an important goal of our future work is to investigate a robust estimation method that is not as sensitive to measurement noise.
- In this initial work, we developed a general theory to understand the relation between the structural organization of brain tissue and the dMRI measurements.

Our experiments and simulations were limited to assuming a predominant single fiber bundle at each voxel in the brain. Note that, this is a first step towards getting a deeper insight into the biophysical properties of the tissue organization in the simple case of coherently organized single fiber region, which is still a challenging problem and an area of active research as seen with several other specific models proposed in the literature (DTI, CHARMED, NODDI, etc.). Moreover, we note that a polynomial expansion for the disturbance function may not be the most appropriate model for investigating the dependence of the dMRI signal on gradient strength. Furthermore, we also assumed that the disturbance is cylindrically symmetric to reduce model complexity. Generalizing the dependence of the disturbance function on fiber orientation, gradient strength, direction and time will be part of our future work.

To conclude, the proposed theory provides a general framework for analyzing microstructural organization of brain tissue from in-vivo diffusion signal acquired using the standard single pulse experiment. We proposed several novel indices with specific biophysical meaning and which have the potential to be used in clinical settings to study neuronal abnormalities.

Appendix A. Solving the modified Bloch-Torrey equation

The expression in Eq. (32) can be obtained from Eq. (31) as described below. To re-iterate, the PDE in Eq. (32) is given by:

$$\partial_t \hat{m}(\mathbf{k},t) = \mathbf{g}(t) \cdot \nabla_{\mathbf{k}} \hat{m}(\mathbf{k},t) - \|\mathbf{k}\|_{D_0}^2 \hat{m}(\mathbf{k},t) + \hat{u}(\mathbf{k},t,\mathbf{\mathscr{G}}(t)).$$
(A.1)

First, we define

$$\boldsymbol{q}(t_1, t_2) := \int_{t_1}^{t_2} \boldsymbol{g}(s) \, ds.$$

Next, we show that the solution for $\hat{m}(\mathbf{k}, t)$ is given by the following:

$$\hat{m}(\mathbf{k},t) = \hat{m}(\mathbf{k}+\mathbf{q}(0,t),0) e^{\left(-\int_{0}^{t} \|\mathbf{k}+\mathbf{q}(s,t)\|_{D_{0}}^{2} ds\right)} + \int_{0}^{t} \hat{u}(\mathbf{k}+\mathbf{q}(\tau,t),\tau,\mathscr{G}(\tau)) e^{\left(-\int_{\tau}^{t} \|\mathbf{k}+\mathbf{q}(s,t)\|_{D_{0}}^{2} ds\right)} d\tau.$$
(A.2)

Note that, the first term in the right-hand side of Eq. (A.2) depends on $\hat{m}(\mathbf{k}, 0)$ which is the initial condition. To verify that Eq. (A.2) satisfies Eq. (31), we first take the partial derivative of $\hat{m}(\mathbf{k}, t)$ with respect to t

$$\begin{aligned} \partial_{t}\hat{m}\left(\boldsymbol{k},t\right) = & \boldsymbol{g}\left(t\right) \cdot \nabla_{\boldsymbol{k}}\hat{m}\left(\boldsymbol{k}\!+\!\boldsymbol{q}\left(0,t\right),0\right) e^{\left(-\int_{0}^{t} \left\|\boldsymbol{k}\!+\!\boldsymbol{q}\left(s,t\right)\right\|_{D_{0}}^{2} ds\right)} \\ & + \hat{m}\left(\boldsymbol{k}\!+\!\boldsymbol{q}\left(0,t\right),0\right) e^{\left(-\int_{0}^{t} \left\|\boldsymbol{k}\!+\!\boldsymbol{q}\left(s,t\right)\right\|_{D_{0}}^{2} ds\right)} \times \\ & \left(-\left\|\boldsymbol{k}\right\|_{D_{0}}^{2} - 2\boldsymbol{g}\left(t\right) \cdot D_{0}\int_{0}^{t}\left(\boldsymbol{k}\!+\!\boldsymbol{q}\left(s,t\right)\right) ds\right) \\ & + \int_{0}^{t} \boldsymbol{g}\left(t\right) \cdot \nabla_{\boldsymbol{k}}\hat{u}\left(\boldsymbol{k}\!+\!\boldsymbol{q}\left(\tau,t\right),\tau,\boldsymbol{\mathcal{G}}\left(\tau\right)\right) e^{\left(-\int_{\tau}^{t} \left\|\boldsymbol{k}\!+\!\boldsymbol{q}\left(s,t\right)\right\|_{D_{0}}^{2} ds\right)} d\tau \\ & + \int_{0}^{t} \hat{u}\left(\boldsymbol{k}\!+\!\boldsymbol{q}\left(\tau,t\right),\tau,\boldsymbol{\mathcal{G}}\left(\tau\right)\right) e^{\left(-\int_{\tau}^{t} \left\|\boldsymbol{k}\!+\!\boldsymbol{q}\left(s,t\right)\right\|_{D_{0}}^{2} ds\right)} \times \\ & \left(-\left\|\boldsymbol{k}\right\|_{D_{0}}^{2} - 2\boldsymbol{g}\left(t\right) \cdot D_{0}\int_{\tau}^{t}\left(\boldsymbol{k}\!+\!\boldsymbol{q}\left(s,t\right)\right) ds\right) d\tau \\ & + \hat{u}\left(\boldsymbol{k},t,\boldsymbol{\mathcal{G}}\left(t\right)\right) \end{aligned}$$

where we have used the chain rule and the following Leibniz integral rule

$$\frac{d}{dx}\left(\int_{a}^{x} f\left(x, y\right) dy\right) = \int_{a}^{x} \partial_{x} f\left(x, y\right) dy + f\left(x, x\right).$$

Similarly, we can derive the partial derivative of $\hat{m}(\mathbf{k}, t)$ with respect to \mathbf{k} as

$$\begin{split} \nabla_{\boldsymbol{k}} \hat{\boldsymbol{m}} \left(\boldsymbol{k}, t \right) = & \nabla_{\boldsymbol{k}} \hat{\boldsymbol{m}} \left(\boldsymbol{k} + \boldsymbol{q} \left(0, t \right), 0 \right) e \left(-\int_{0}^{t} \| \boldsymbol{k} + \boldsymbol{q} \left(s, t \right) \|_{D_{0}}^{2} ds \right) \\ & + \hat{\boldsymbol{m}} \left(\boldsymbol{k} + \boldsymbol{q} \left(0, t \right), 0 \right) e^{\left(-\int_{0}^{t} \| \boldsymbol{k} + \boldsymbol{q} \left(s, t \right) \|_{D_{0}}^{2} ds \right)} \left(-2D_{0} \int_{0}^{t} \left(\boldsymbol{k} + \boldsymbol{q} \left(s, t \right) \right) ds \right) \\ & + \int_{0}^{t} \nabla_{\boldsymbol{k}} \hat{\boldsymbol{u}} \left(\boldsymbol{k} + \boldsymbol{q} \left(\tau, t \right), \tau, \boldsymbol{\mathscr{G}} \left(\tau \right) \right) e^{\left(-\int_{\tau}^{t} \| \boldsymbol{k} + \boldsymbol{q} \left(s, t \right) \|_{D_{0}}^{2} ds \right)} d\tau \\ & + \int_{0}^{t} \hat{\boldsymbol{u}} \left(\boldsymbol{k} + \boldsymbol{q} \left(\tau, t \right), \tau, \boldsymbol{\mathscr{G}} \left(\tau \right) \right) e^{\left(-\int_{\tau}^{t} \| \boldsymbol{k} + \boldsymbol{q} \left(s, t \right) \|_{D_{0}}^{2} ds \right)} \times \\ & \left(-2D_{0} \int_{\tau}^{t} \left(\boldsymbol{k} + \boldsymbol{q} \left(s, t \right) \right) ds \right) d\tau. \end{split}$$

Then, it is straightforward to verify that $\hat{m}(\mathbf{k}, t)$ satisfies Eq. (31). By setting $\mathbf{k} = 0$ in Eq. (A.2), we obtain the expression in Eq. (32) for the diffusion signal $s(t) = \hat{m}(0, t)$.

An alternative derivation follows from the techniques developed in the field of control theory. Consider the following dynamical system:

$$\partial_t x(t) = A x(t) + u(t)$$
, (A.3)

where u(t) is the input that changes the evolution of x(t). In control theory, the solution to this problem is well studied and is given by (Isakov, 2006):

$$x(t) = e^{At}x(0) + \int_0^t e^{A(t-\tau)}u(\tau) d\tau.$$
 (A.4)

The infinite-dimensional dynamical system (31) is just a more complex version of (A.3) with the system matrix A replaced by the time-dependent and commutative operator

 $(g(t) \cdot \nabla_k - ||k||^2_{D_0})$. Thus, the solution Eq. (A.2) also has a similar form as the solution in Eq. (A.4).

We also note that the solution (A.4) still holds even if u(t) depends on x(t). For example, let us consider u(t) = Bx(t). Then, Eq. (A.3) reduces to tx(t) = (A + B)x(t) whose solution is simply given by:

$$x(t) = e^{(A+B)t} x(0)$$
. (A.5)

One can also verify that Eq. (A.5) also satisfies the general solution Eq. (A.4) by replacing u(t) with $Be^{(A+B)t}x(0)$. Thus, in the original problem Eq. (31), though the value of $\hat{u}(\mathbf{k}, t, \mathcal{G}(t))$ may depend on $\hat{m}(\mathbf{k}, t)$, Eq. (A.2) still provides a general solution for analyzing the relation between the diffusion signal and the structural disturbance.

Appendix B. Note on computing the time-varying moments of EAP

We provide more detailed information on computing the time-varying moments given in Eqs. (17) and (18). First, we note that the following inverse Fourier transforms:

$$\begin{aligned} \mathscr{F}^{-1}\left(\frac{1}{-i\omega_{+}}\right) &= \lim_{a \searrow 0} \mathscr{F}^{-1}\left(\frac{1}{-i\omega_{+}a}\right) = \lim_{a \searrow 0} e^{-at}h\left(t\right) = h\left(t\right), \\ \mathscr{F}^{-1}\left(\frac{1}{(-i\omega_{+})^{2}}\right) &= \lim_{a \searrow 0} \left(h\left(t\right)e^{-at}\right) * \left(h\left(t\right)e^{-at}\right) = h\left(t\right)t, \\ \mathscr{F}^{-1}\left(\frac{1}{(-i\omega_{+})^{3}}\right) &= \left(h\left(t\right)t\right) * \left(h\left(t\right)e^{-at}\right) = h\left(t\right)t^{2}, \end{aligned}$$

where h(t) is the Heaviside function, i.e. h(t) = 1 for t = 0 and h(t) = 0 for t = 0. Then, the

inverse Fourier transform of $\frac{U_2(\omega)}{(-i\omega_+)^2}$ and $\frac{U_4(\omega)}{-i\omega_+}$ can be obtained using the Convolution Theorem of the Fourier transform.

Appendix C. The disturbance function for restricted diffusion in cylinders

In this appendix, we derive an expression for the ensemble average disturbance (EAD) function for diffusion in restricted cylinders. The main purpose is to show that the proposed method is also able to model restricted diffusion, where the the EAD has a specific form. The diffusion propagator for a perfectly reflecting cylinder with radius *a* has been derived in (Neuman, 1974; Stepišnik, 1993; Callaghan, 1991) and the corresponding diffusion signal is given by:

$$s(q,t) = \sum_{k=1}^{\infty} 4e^{-\beta_{0k}^2 D_0 t/a^2} \left[\frac{(qa)J_0'(qa)}{(qa)^2 - \beta_{0k}^2} \right]^2 + \sum_{n,k=1}^{\infty} \frac{8\beta_{nk}^2}{\beta_{nk}^2 - n^2} e^{-\beta_{nk}^2 D_0 t/a^2} \left[\frac{(qa)J_n'(qa)}{(qa)^2 - \beta_{nk}^2} \right]^2$$
(C.1)

where J_n and J'_n are Bessel functions of the first kind and their derivatives, respectively, and β_{nk} is the *k*th root of $J'_n(x)$.

Using Eq. (21), we derived the expression for the corresponding EAD:

$$\begin{split} \hat{u}\left(q,t\right) = &\sum_{k=1}^{\infty} 4\left(q^2 D_0 - \frac{\beta_{0k}^2 D_0}{a^2}\right) e^{-\beta_{0k}^2 D_0 t/a^2} \left[\frac{(qa)J_0'(qa)}{(qa)^2 - \beta_{0k}^2}\right]^2, \\ &+ \sum_{n,k=1}^{\infty} 8\left(q^2 D_0 - \frac{\beta_{nk}^4 D_0}{a^2 \left(\beta_{nk}^2 - n^2\right)}\right) e^{-\beta_{nk}^2 D_0 t/a^2} \left[\frac{(qa)J_n'(qa)}{(qa)^2 - \beta_{nk}^2}\right]^2. \end{split}$$

Using $J_{0}^{'}(x) \simeq -\frac{1}{2}x$, $J_{1}^{'}(x) \simeq \frac{1}{2} - \frac{3}{16}x^{2}$, and $J_{2}^{'}(x) \simeq -\frac{1}{4}x$ for $x \ll 1$, the Taylor expansion of $\hat{u}(q, t)$ can be written as:

$$\hat{u}(q,t) \simeq \hat{u}_2(t) q^2 + \hat{u}_4(t) q^4$$

with

$$\begin{aligned} \hat{u}_{2}\left(t\right) = & D_{0} - \sum_{k=1}^{\infty} \frac{2D_{0}}{\beta_{1k}^{2} - 1} e^{-\beta_{1k}^{2} D_{0}t/a^{2}}, \\ \hat{u}_{4}\left(t\right) = & -\frac{D_{0}a^{2}}{4} + \sum_{k=1}^{\infty} \left[\frac{\left(-4 + 3\beta_{1k}^{2}\right) D_{0}a^{2}}{2\beta_{1k}^{2} \left(\beta_{1k}^{2} - 1\right)} e^{-\beta_{1k}^{2} D_{0}t/a^{2}} - \frac{D_{0}a^{2}}{2\left(\beta_{2k}^{2} - 1\right)} e^{-\beta_{2k}^{2} D_{0}t/a^{2}} \right]. \end{aligned}$$

The higher order functions J'_n with n = 3 do not contribute to the q^2 and q^4 terms in $\hat{u}(q, t)$. We note that

$$\lim_{t \to \infty} \hat{u}_2(t) = D_0, \text{ and } \lim_{t \to \infty} \hat{u}_4(t) = -\frac{D_0 a^2}{4}.$$
 (C.2)

Using in Eqs. (26) and (27), the above equation implies $f_{intra} = 1$ and the axon radius is equal to *a*.

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Figure 1.

Figs. (a) (b) and (c) show partial field of views of the three simulated tissue structures.



Figure 2.

Illustration of two tissue structures used in testing the partial volume effects. The blue region at the bottom of Fig. 2b represents the CSF area which is separated from the axonal bundles by an impermeable membrane.



Figure 3.

The first row shows the narrow-pulse dMRI signal s(q, t) in the q-space at a selected set of time points for the three structures. The second row shows the corresponding EAD $\hat{u}(q, t)$ at the same time points. The third row shows the same $\hat{u}(q, t)$ function in the time domain at a selected set of q-values.



Figure 4.

The dots are the estimated values of the EAD $\hat{u}(q, t)$ for the three structures at t = 80 ms. The solid lines are the corresponding functions fitted using the model in Eq. (15) with the coefficients \hat{u}_2 and \hat{u}_4 shown in Table 1.



Figure 5.

The blue, green and red curves in (a) show the simulated signal for $\delta = 10.6$ ms, = 43.1 ms and g = 20, 40, ..., 100 mT/m corresponds to Structures 1, 2 and 3, respectively. The black star markers represent the estimated signal. The blue, green and red curves in (b) show the disturbance function $\hat{u}_2 q^2$ corresponding to the three structures.



Figure 6.

The blue, green and red plots in (a) show the Monte-Carlo simulated signals with $\delta = 12.9$ ms, = 21.8 ms and g = 30, 60, ..., 300 mT/m corresponding to Structures 1, 2 and 3, respectively. The black star markers represent the estimated signal using the PICASO model. The blue, green and red curves in (b) show the estimated disturbance function $\hat{u}_2 q^2 + \hat{u}_4 q^4$ corresponding to the three structures.



(a) Simulated and estimated signal using Wu-Minn sequence





 $q (rad/\mu m)$

0.2

0.25

0.1

0.05

(c) Simulated and estimated signal using MGH sequence

Figure 7.

Figs. 7a and 7c illustrate the simulated (solid lines) and the estimated (star markers) diffusion MRI signals from the two structures in Fig. 2 using the Wu-Minn and MGH HCP sequences, respectively. Fig. 7b shows estimated disturbance functions using the Wu-Minn signals and Eq. (33). Fig. 7d shows the estimated disturbance functions using the MGH signals and Eq. (34).



(e) Perpendicular diffusivity d_{\perp} from (f) Parallel diffusivity d_{\parallel} from DTI DTI

Figure 8.

Estimated model parameters for a coronal slice of the HCP data set with all units shown in $\mu m^2/ms$.



(a) Long-range disturbance $\hat{u}_{2\perp}$

Figure 9.

Figs. (a) and (b) show the estimated long-range disturbance coefficient $\hat{u}_{2\perp}$ and the FA value for the brain region pointed by the arrow in Fig. 8a. Fig. (a) highlights the partial-volume effect between corpus callosum and ventricle.



(e) Perpendicular diffusivity d_{\perp} from (f) Parallel diffusivity d_{\parallel} from DTI DTI

Figure 10.

Estimated model parameters for a sagittal slice of the WU-Minn HCP data set with all units shown in $\mu m^2/ms$.



Figure 11.

Fig. (b) shows the estimated long-range disturbance coefficient $\hat{u}_{2\perp}$ with unit shown in $\mu m^2/ms$ at a selected set of voxels in the corpus callosum shown in Fig. (a).





Figure 12.

Fig. (c) shows the estimated disturbance functions $\hat{u}_2 q^2$ at three representative voxels, indicated in Fig. (a), in the genu (the bottom line, colored in blue), splenium (the middle line, colored in red), and the midbody (the top line, colored in green), respectively. Fig. (d) shows the estimated \hat{u}_{2q}^2 in two voxels, indicated in Fig. (b), in the cortical gray matter (the lower line, colored in green), and the subcortical gray matter (the upper line, colored in red), respectively.



Figure 13.

The solid plots and star markers in Figs. (a) to (e) show the estimated and the measured diffusion signal for the voxels indicated in Figures 12a and 12b versus the inner product between gradient direction and the dominant eigenvector of the diffusion tensors. The blue, red and green plots and markers correspond to the diffusion signal at b-shells with b = 1000, 2000 and 3000 s/mm², respectively.



Figure 14.

Estimated model parameters for a coronal slice of the MGH HCP data set, where the units for $\hat{u}_{2\perp}$, $\hat{u}_2 \parallel$, d_{\perp} , d_{\parallel} are shown in $\mu m^2/ms$ and the units for $\hat{u}_{4\perp}$, $\hat{u}_4 \parallel$ are shown in $\mu m^4/ms$.



Figure 15.

Estimated model parameters for a sagittal slice of the MGH HCP data set, where the units for $\hat{u}_{2\perp}$, $\hat{u}_2 \parallel$, d_{\perp} , d_{\parallel} are shown in $\mu m^2/ms$ and the units for $\hat{u}_{4\perp}$, $\hat{u}_4 \parallel$ are shown in $\mu m^4/ms$.



Figure 16.

Figs. (c) and (d) show the estimated long- and short-range disturbances, i.e. $\hat{u}_{2\perp}$ (in $\mu m^2/ms$) and $\hat{u}_{4\perp}$ (in $\mu m^4/ms$), for the set of voxels illustrated in Figs. (a) and (b), respectively.



Figure 17.

(c)

Fig. (c) shows the estimated disturbance functions $\hat{u}_2 q^2 + \hat{u}_4 q^4$ at three representative voxels, indicated in Fig. (a), in the genu (the middle line, colored in blue), splenium (the bottom line, colored in red), and the midbody (the top line, colored in green), respectively. Fig. (d) shows the estimated $\hat{u}_2 q^2 + \hat{u}_4 q^4$ in two voxels, indicated in Fig. (b), in the cortical gray matter (the lower line, colored in green), and the subcortical gray matter (the upper line, colored in red), respectively.

(d)



Figure 18.

The solid plots and star markers in Figs. (a) to (e) show the estimated and the measured signal for the voxels indicated in Figures 17c and 17d, respectively, versus the inner product between gradient direction and the dominant eigenvector of the diffusion tensors. The blue, red, green and magenta plots (and markers) correspond to diffusion signal at b-shells with b = 1000, 3000, 5000 and 10000 s/mm^2 , respectively.

Table 1

The estimated parameters for the three structures using dMRI signals with narrow pulses.

	Structure 1	Structure 2	Structure 3
$\hat{D}_0(\mu \mathrm{m}^2/\mathrm{ms})$	0.2803	0.5058	0.6903
$\hat{u}_2 (\mu \mathrm{m}^2/\mathrm{ms})$	0.1220	0.1832	0.2423
$\hat{u}_4 (\mu \mathrm{m}^4/\mathrm{ms})$	-0.0030	-0.0086	-0.0178

Table 2

The estimated model parameters for the three structures with $\delta = 10.6$ ms, = 43.1 ms and g = 20, 40, ..., 100 mT/m.

	Structure 1	Structure 2	Structure 3
$\hat{D}_0(\mu \mathrm{m}^2/\mathrm{ms})$	0.2650	0.3260	0.4776
$\hat{u}_2 (\mu \mathrm{m}^2/\mathrm{ms})$	0.1257	0.1499	0.2213

Table 3

The estimated model parameters for the three structures with $\delta = 12.9$ ms, = 21.8 ms and g = 30, 60, ..., 300 mT/m.

	Structure 1	Structure 2	Structure 3
$\hat{D}_0(\mu \mathrm{m}^2/\mathrm{ms})$	0.2868	0.3593	0.5179
$\hat{u}_2 (\mu m^2/ms)$	0.1443	0.1762	0.2501
$\hat{u}_4 \ (\mu m^2/ms)$	-0.0115	-0.0200	-0.0276