Bessel Fourier Orientation Reconstruction (BFOR): An analytical diffusion propagator reconstruction for hybrid diffusion imaging and computation of q-space indices

A. Pasha Hosseinbor a,b,⁎, Moo K. Chung b,c, Yu-Chien Wu b,d,e, Andrew L. Alexander a,b,f

⁎ Corresponding author at: Department of Medical Physics, University of Wisconsin-Madison, Madison, WI, USA.
E-mail address: hosseinbor@wisc.edu (A.P. Hosseinbor).

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Introduction

The aim of diffusion-weighted imaging (DWI) is to non-invasively recover information about the diffusion of water molecules in biological tissues. The most common form of DWI is diffusion tensor imaging (DTI) [Basser et al., 1994], which is a good model of diffusion-weighted signal behavior at low levels of diffusion weighting. However, DTI is limited by the Gaussian assumption, which is invalid at higher levels of diffusion weighting (b > 2000 s/mm²) and its inability to resolve multiple fiber orientations within a voxel [Alexander et al., 2001; Frank, 2001; Wiegell et al., 2000]. In order to recover complex white matter (WM) geometry, high angular resolution diffusion imaging (HARDI) [Tuch et al., 2002], which reduces the diffusion signal sampling to a single sphere (i.e. single level of diffusion weighting) within q-space, was proposed. Many HARDI techniques [Aganj et al., 2010; Canales-Rodriguez et al., 2009; Descoteaux et al., 2007; Hess et al., 2006; Tuch, 2004] seek to extract the orientation distribution function (ODF), a probability density function describing the angular distribution of water molecules during diffusion. Unlike apparent diffusion coefficient (ADC) profiles, the maxima of the ODF are aligned with the fiber directions, making it useful in fiber tractography applications. However, the ODF only retrieves the angular content of the diffusion process.

The ensemble average propagator (EAP) describes the 3D average diffusion process of water molecules, capturing both its radial and angular contents. The EAP can thus provide richer information about complex tissue microstructure properties than the orientation distribution function (ODF), an angular feature of the EAP. Recently, several analytical EAP reconstruction schemes for multiple q-shell acquisitions have been proposed, such as diffusion propagator imaging (DPI) and spherical polar Fourier imaging (SPFI). In this study, a new analytical EAP reconstruction method is proposed, called Bessel Fourier Orientation Reconstruction (BFOR), whose solution is based on heat equation estimation of the diffusion signal for each shell acquisition, and is validated on both synthetic and real datasets. A significant portion of the paper is dedicated to comparing BFOR, SPFI, and DPI using hybrid, non-Cartesian sampling for multiple b-value acquisitions. Ways to mitigate the effects of Gibbs ringing on EAP reconstruction are also explored. In addition to analytical EAP reconstruction, the aforementioned modeling bases can be used to obtain rotationally invariant q-space indices of potential clinical value, an avenue which has not yet been thoroughly explored. Three such measures are computed: zero-displacement probability (P0), mean squared displacement (MSD), and generalized fractional anisotropy (GFA).

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where \( E(\mathbf{q}) = S(\mathbf{q})/S_0 \) is the normalized q-space diffusion signal, \( S(\mathbf{q}) \)

is the diffusion signal measured at position \( \mathbf{q} \) in q-space, and \( S_0 \)

is the baseline image acquired without any diffusion gradients (\( q = 0 \)).

We denote \( q = u \theta \), where \( u \) and \( \theta \) are 3D unit vectors. The wave vector \( \mathbf{q} = q \mathbf{u} \), where \( q \) is the nuclear

gyromagnetic ratio and \( \mathbf{G} = \mathbf{gu} \) is the applied diffusion gradient direction.

The norm of the wave vector, \( q \), is related to the diffusion weighting level (\( b \)-value) via \( b = 4\pi^2 q^2(\Delta - \delta/3) \) (Basser, 2002),

where \( \delta \) is the duration of the applied diffusion gradients and \( \Delta \) the time between the two pulses. Eq. (1) is valid only if the narrow

pulse condition is met, which is rarely the case for q-space diffusion

MRI performed under experimental conditions. Several studies

(Bar-Shir et al., 2008; Mair et al., 2002; Weeden et al., 2005) however,

have shown that even when these assumptions do not hold, the

Fourier relationship in Eq. (3) is still a reasonable approximation of

the microstructural features. The diffusion dispersions, however,

will be consistently underestimated (Weeden et al., 2005).

Various methods already exist to reconstruct the EAP. Using the

diffusion tensor framework, the EAP is simply described by a multi-

variate Gaussian function (Basser et al., 1994). The authors in Gosh

and Deriche (2010) presented a closed-form approximation of the

EAP using higher order tensors, specifically the 4th order diffusion
tensor. The diffusion orientation transform (DOT) (Ozarslan et al.,

2006) is a HARDI technique that computes the iso-radius of the EAP.

DOT assumes the radial diffusion follows a mono-exponential decay,

which allows the radial integration in Eq. (1) to be solved analytically.

The spherical integration is then solved numerically. The application

of this technique, however, is limited by its mono-Gaussian assump-
tion of the radial diffusion decay. In addition, the single shell

approach of DOT gives an incomplete picture of the EAP, whose esti-
mation requires signal measurements along all of q-space.

EAP reconstruction techniques using multiple diffusion weighting

acquisitions can be divided into two strategies: Fast Fourier Trans-

form (FFT) based and analytical. FFT based methods include diffusion

spectrum imaging (DSI) (Canales-Rodriguez et al., 2010; Weeden

et al., 2005) and hybrid diffusion imaging (HYDI) (Rathi et al., 2011;

Wu and Alexander, 2007). DSI is based on direct sampling of the dif-

fusion signal on a Cartesian q-space lattice. The FT in Eq. (1) is then

numerically evaluated via FFT to obtain the EAP. A major advantage

of DSI is that the EAP is estimated without any prior assumptions

of behavior of the diffusion signal. However, DSI requires dense sam-

pling of the Cartesian lattice, resulting in very long acquisition

times. HYDI samples the diffusion signal along concentric spherical

shells in q-space, with the measurements then being interpolated

and regridded onto a 9 x 9 x 9 Cartesian lattice so that the EAP can

be similarly reconstructed as in DSI. HYDI uses much fewer samples

than DSI, making it more clinically feasible. However, the HYDI prop-

agator reconstruction may suffer from the ad hoc signal interpolation

and regridding.

The FFT is impractical for methods employing spherical q-space

sampling schemes, such as HYDI, since the FFT requires data to lie

on a Cartesian grid. It is also quite computationally expensive. Solving

the FT in spherical coordinates (i.e. spherical Fourier Transform) in-

stead, obviates the need for FFT and ad hoc processing. Analytic

methods, seeking to obtain a closed-form solution of the EAP, pursue

such a route. Currently, the two main analytical EAP reconstruction

schemes are diffusion propagator imaging (DPI) (Descoteaux et al.,

2011) and spherical polar Fourier imaging (SPFI) (Assemlal et al.,

2009a; Cheng et al., 2010a, 2010b).

DPI assumes that \( E(\mathbf{q}) \) is a solution to the 3D Laplace's equation

\( \nabla^2 E = 0 \), which results in the signal basis being composed of the reg-

ular and irregular solid harmonics. It is fast, and seems to work well

with only a small number of samples. However, the DPI signal basis

is an unrealistic model of \( E(\mathbf{q}) \) because Laplacian modeling of diffusion

signal entails that (1) \( E(\mathbf{0}) \) does not exist, which arises from the

irregular solid harmonic term, and (2) MSD of water molecules

is zero, which will be proved in the Theory section. In addition, the

DPI signal basis lacks orthornormality, and hence does not possess

the robust numerical stability that would otherwise feature in an

orthonormal basis.

SPFI models the diffusion signal in terms of an orthonormal basis

comprising the spherical harmonics (SH) and Gaussian–Laguerre

polynomials. The SPFI signal basis is, in fact, a modified solution of

the 3D quantum mechanical simple harmonic oscillator problem. It

is robust to noise and low anisotropy, and works well with just a

few number of samples. However, SPFI has not been tested at

\( b > 3000 \) s/mm². A slightly modified version of the SPFI signal basis

was proposed just recently by the authors in Caruyer and Deriche

(2012). This paper, however, will only be concerned with the original

SPFI basis.

A closely related basis to SPFI was proposed in Ozarslan et al.

(2008, 2009), which use the Hermite polynomials to estimate the

1D q-space diffusion signal. In addition to forming a complete ortho-

gonal basis, the Hermite polynomials are also eigenfunctions of the

Fourier transform. However, the 3D EAP solution has yet to be derived

using this basis.

With respect to analytical EAP reconstruction methods, one valu-

able though overlooked use is in extracting rotationally invariant

quantitative measures from them. Recently, the authors in Assemlal

et al. (2011) used the SPFI signal basis to compute the novel fiber

population dispersion (FPD), an index which assess the presence of

crossing fibers within a voxel. The FPD, however, is a relatively

new measure that has not yet been computed for an actual human

brain. More well-established q-space metrics include generalized

fractional anisotropy (GFA) (Tuch, 2004), mean squared displace-

ment (MSD) (Assaf et al., 2000; Wu and Alexander, 2007), and

zero-displacement probability (Po) (Assaf et al., 2000). All three are

simply scalar features of the EAP, the GFA and the MSD can be viewed

as high angular resolution analogues of the DTI indices fractional an-

isotropy (FA) and mean diffusivity (MD) (Basser and Pierpaoli, 1996),

respectively. An analytical representation of the EAP (and hence

diffusion signal) can facilitate either analytic computation of such

features or numerical efficiency in estimating them.

In this paper, we present Bessel Fourier Orientation Reconstruction

(BFOR) (Hosseinbor et al., 2011). Rather than assuming the sig-

nal satisfies Laplace’s equation, we reformulate the problem into a

Cauchy problem and assume \( E(\mathbf{q}) \) satisfies the heat equation.

The heat equation is a generalization of Laplace’s equation, which

the latter approaches at the steady state (i.e. \( t \rightarrow \infty \)). BFOR provides

an analytical reconstruction of the EAP profile from diffusion signal

and models the diffusion signal in terms of an orthonormal basis. In addi-

tion, it contains an intrinsic exponential smoothing term that allows

one to control the amount of smoothing in the EAP estimation.

The last point is significant because, although the Laplacian modeling

intrinsically smooths the diffusion signal, the amount of smoothing

cannot be controlled, and hence it may oversmooth the signal. In addi-

tion to heat diffusion smoothing, we also look at linear signal ex-

trapolation as a potential means to mitigate the effects of common

artifacts afflicting the reconstructed EAP profile, such as Gibbs ringing

and signal truncation. Employing a hybrid, non-Cartesian encoding

scheme in both synthetic and in vivo datasets, we reconstruct the

EAP using BFOR, SPFI, and DPI and assess their performances. Lastly, we

use BFOR to compute GFA, Po, and MSD, and compare BFOR’s

accuracy in estimating such indices to that of DPI and SPFI.

The paper is organized as follows: in Theory section, we develop

BFOR, first by describing how to estimate the diffusion signal, and

then deriving the analytical solution for the EAP using Eq. (1). Scalar

features of the EAP are also introduced in this section. The Appendix

carefully details the derivations of the BFOR signal basis, EAP, and

q-space indices. In Materials and methods section, we describe the

implementation details of BFOR and present the synthetic and

in vivo human brain datasets that will be used to validate and
The assumption of a Laplacian operator results in Eq. (3) becoming posed in Descoteaux et al. (2011) to re

where

orthonormal basis, which we show in Appendix A:

Assuming that smoothing being applied.

and SPFI, it significantly differs from them due to its inclusion of a smoothing term.

Consider the eigenvalue/boundary condition problem

which we use to solve the Cauchy problem

where \( f(q) \) is simply the acquired signal and \( \Im \) is some self-adjoint linear operator. We require \( \lambda > 0 \). Chung et al. (2007) derived a unique solution for Eq. (3):

where \( e^{-\lambda t} \) is a smoothing term controlled by parameter \( t \geq 0 \) and the coefficients are given by \( a_i = \langle f \phi_i \rangle \). The implication of Eq. (4) is that the solution decreases exponentially as \( t \) increases and smooths out high spatial frequency noise much faster than low-frequency noise. In DPI, however, the steady state assumption permanently removes any temporal term, which governs the extent of smoothing, so there is no smoothing control mechanism. Note that \( t = 0 \) corresponds to no smoothing being applied.

Assuming that \( \nabla = \nabla^2 \), where \( \nabla^2 \) is the 3D Laplacian operator in spherical coordinates, Eq. (2) becomes

Eq. (5) can be solved via separation of variables to obtain an orthonormal basis, which we show in Appendix A:

where \( \alpha_{nl} \) is the \( n \)th root of \( l \)th order spherical Bessel function of first kind \( j_l \) and \( \tau \) is the radial distance in \( q \)-space at which the Bessel function goes to zero. \( Y_l \) are a modified real and symmetric SH basis proposed in Descoteaux et al. (2011) to reflect the symmetry and rea

Within the context of our problem, \( g(q,t) \) is the diffusion signal. The assumption of a Laplacian operator results in Eq. (3) becoming the heat equation: \( \nabla^2 E(q,t) = \frac{\partial E}{\partial t} \). From Eq. (4) then, the diffusion signal can be expanded in terms of the spherical orthonormal basis \( \psi_n \) given in Eq. (6):

where \( C_n \) are the expansion coefficients, \( R = \frac{\ell + 1}{2} \) is the number of terms in the modified SH basis of truncation order \( \ell \), and \( N \) is the number of roots for any spherical Bessel function of order \( \ell \).

The total number of coefficients in the expansion is \( W = \frac{\ell + 1}{2} (\ell + 2) \). Note that the actual acquired signal from scanner is given at \( t=0 \). In DWI, \( E(0) = 1 \), and so for our basis, we obtain the following identity (derived in Appendix B):

which holds for any \( u \) within the unit sphere \( S^2 \) (i.e. \( u \in S^2 \)).

An important property of the diffusion signal is that it asymptotically approaches zero as \( q \to \infty \). However, the spherical Bessel functions infinitely oscillate about zero, as shown in Fig. 1, so a finite upper bound \( \tau \) is needed at which the BFOR signal model becomes zero. The fact that the radial basis in BFOR does not radically decay to zero but becomes zero at some point in \( q \)-space is the main limitation of the BFOR algorithm.

In deriving the EAP, the spherical integration of Eq. (1) is made easier by expressing the Fourier kernel as a plane wave expansion:

Substituting Eqs. (7) and (9) into Eq. (1), we obtain

Spherical Bessel Function of 1st Kind

Fig. 1. Plots of spherical Bessel functions of first kind, which form the radial basis of the BFOR signal solution, for different orders \( I \). As \( q \) approaches infinity, they infinitely oscillate about zero.
The task is to estimate coefficients $C_{0i}$ in Eq. (12) from the observed signal $E(q, u, t = 0)$. We achieve this by carrying out a linear least squares (LLS) fitting with regularization in the radial and angular parts. We let $S = [E(q, t = 0)]$ be the $M \times 1$ vector representing the diffusion signal measurements across all shells. We also let $C$ represent the $W \times 1$ vector of unknown expansion coefficients $C_{0i}$, where

$$W = \frac{N_{\text{sh}} \times 4 + 3}{2}.\$$

Defining $Z_{0i}(q, u) = \langle Y_{j}(\alpha_{0i} q) q / \tau \rangle Y_{j}(u)$, we let $Z$ denote our $M \times 1$ design matrix:

$$Z = \left( \begin{array}{cccccccc} Z_{11}(q, u_1) & Z_{12}(q, u_1) & \cdots & Z_{N_{\text{sh}}1}(q, u_1) & Z_{11}(q, u_2) & Z_{12}(q, u_2) & \cdots & Z_{N_{\text{sh}}1}(q, u_2) \\ Z_{11}(q, u_3) & Z_{12}(q, u_3) & \cdots & Z_{N_{\text{sh}}1}(q, u_3) & Z_{11}(q, u_4) & Z_{12}(q, u_4) & \cdots & Z_{N_{\text{sh}}1}(q, u_4) \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ Z_{11}(q, u_M) & Z_{12}(q, u_M) & \cdots & Z_{N_{\text{sh}}1}(q, u_M) & Z_{11}(q, u_M) & Z_{12}(q, u_M) & \cdots & Z_{N_{\text{sh}}1}(q, u_M) \end{array} \right) \left( \begin{array}{c} C_{01} \\ C_{02} \\ \vdots \\ C_{0M} \end{array} \right)$$

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Thus, we have a simple linear model of the form \( S = ZC \). This system of over-determined equations is solved with a regularized LLS solution yielding vector \( \hat{C} \) given by

\[
\hat{C} = \left( Z^T Z + \lambda_l L_{\text{reg}} + \lambda_n N_{\text{reg}} \right)^{-1} Z^T S,
\]

where \( L_{\text{reg}} \) is the Laplace–Beltrami regularization diagonal matrix with \( l^2(l+1)^2 \) entries on the diagonal and \( N_{\text{reg}} \) is the regularization diagonal matrix for the radial basis, with entries \( n^2(n+1)^2 \) on the diagonal. The angular and radial regularization matrices penalize, respectively, high degrees of the angular and radial parts of Eq. (7) in the estimation under the assumption that they are likely to capture noise (Assemlal et al., 2009a). They also serve to reinforce the positivity constraint of the EAP. \( \lambda_l \) and \( \lambda_n \) are the regularization terms for angular and radial bases, respectively.

Visualization of EAP

Lastly, from the estimated vector \( \hat{C} \), we can extract the \( C_{nj} \) coefficients needed to compute the EAP, Po, MSD, and GFA. The spherical function \( P(p.r,t) \) is the iso-probability profile at some instant of smoothening \( t \) for a given \( p \)—that is, the probability density that a water molecule, initially at the origin, diffuses a distance \( p \) along the direction \( r \). It is computed by generating 800 equidistant points along the equator of a sphere of radius \( p \) i.e. the polar angle \( \theta \) is fixed at \( \pi/2 \) and the azimuthal angle \( \phi \) is uniformly varied from 0 to \( 2\pi \). The EAP profile \( P(p.r,t) \) is then interpolated along these 800 points. Thus, the resulting profiles are 2D with the equator perpendicular to the \( z \)-axis. It is important to note that in this paper smoothening was applied only to the EAP, itself, and not on the diffusion signal.

Value of \( \tau \) parameter

An important point to consider in the implementation is how to determine the parameter \( \tau \) in the signal basis. In practice, the diffusion signal is bounded by the maximal \( q \)-value \( q_{\text{max}} \) achievable by the imaging system. The authors in Assaf and Cohen (1998) have shown that, depending
on the length of diffusion time, the amount of signal present at $b$-values near 30,000 s/mm$^2$ varies from about half a percent to about 5%, which means that the signal does not approach zero at $q_{\text{max}}$ unless the diffusion weighting/diffusion time are very high/long. Thus, we conclude $\tau \geq q_{\text{max}}$. Based on numerical simulations, we find the value of $\tau$ that best reconstructs the EAP to be $\tau_{\text{optimal}} = q_{\text{max}} + \Delta q$, where $\Delta q$ is the (uniform) $q$-space sampling interval.

### Diffusion MRI data acquisitions for synthetic and human brain data

The synthetic and in vivo datasets use a hybrid, non-Cartesian sampling scheme (Wu and Alexander, 2007), shown in Table 1. Since EAP reconstruction is sensitive to angular resolution, the number of encoding directions is increased with each shell to increase the angular resolution with the level of diffusion weighting. The number of directions in the outer shells was increased to better characterize complex tissue organization. Diffusion tensor elements for measurements in the second shell were calculated using non-linear least squares estimation with the Camino software package (Cook et al., 2006), which were then used to obtain the FA and principal eigenvector.

### Synthetic data

The mono-exponential (also referred to as mono-Gaussian) mixture model (Tuch et al., 2002) is frequently used to generate synthetic data to validate a given EAP reconstruction, such as in Assemal et al. (2009a), Cheng et al. (2010b), where the maximum $b$-value used was 3000 s/mm$^2$. However, diffusion MR imaging experiments using high $b$-values (>2000 s/mm$^2$) have shown that the diffusion signal decay is no longer mono-exponential. Studies in normal human brain, with $b$-values over an extended range of up to 6000 s/mm$^2$, have shown that the signal decay is better described with a bi-exponential i.e. bi-Gaussian curve (Clark and Le Bihan, 2000; Mulkern et al., 1999). Similar findings were made for rat brain, using multiple $b$-values of up to 10,000 s/mm$^2$ (Niendorf et al., 1996). According to Assaf and Cohen (1998), a bi-exponential fit gives very good agreement with the observed water signal attenuation in excised brain tissue from rats for $b$-values of up to $2 - 3 \times 10^4$ s/mm$^2$. Thus, BFOR, SPFI, and DPI were applied to simulations of crossing fiber configurations generated by a bi-Gaussian mixture model. Fig. 2 illustrates mono-exponential and bi-exponential decay curves, where the latter has a pronounced tail at high $q$ values, indicating that it takes longer for the signal to decay to zero than under the mono-exponential assumption. The head and tail of the bi-exponential decay curve can be viewed as the fast and slow diffusion components, respectively (Clark and Le Bihan, 2000; Maier et al., 2004).

In bi-Gaussian mixture,

$$E(q, u) = \sum_{k=1}^{N_b} \left[ f_k e^{-b u^T D_k u} + f_k e^{-b u^T D_k u} \right],$$

(18)

**BFOR Signal Fit**

(a) $b=375$

(b) $b=1500$

(c) $b=3375$

(d) $b=6000$

(e) $b=9375$

**SPFI Signal Fit**

(f) $b=375$

(g) $b=1500$

(h) $b=3375$

(i) $b=6000$

(j) $b=9375$

**DPI Signal Fit**

(k) $b=375$

(l) $b=1500$

(m) $b=3375$

(n) $b=6000$

(o) $b=9375$

Fig. 3. The ground truth diffusion signal (green) and estimated signal (red) using BFOR, SPFI, and DPI when noise was absent. Two equally weighted WM fibers were simulated crossing at 60°. Measurements from all 5 shells were used. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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\[ N_b \] is the total number of simulated fibers, \( f_{k\text{f}} \) the volume fraction of the fast component of the \( k^{th} \) fiber, and \( f_{k\text{s}} \) the volume fraction of the slow component. The summation of all volume fractions is 1, i.e., \( \sum_{k} f_{k\text{f}} + f_{k\text{s}} = 1 \). \( D_{k\text{f}} \) and \( D_{k\text{s}} \) describe the diffusion tensor for the fast and slow components, respectively, of the \( k^{th} \) fiber assuming no exchange between the fast- and slow-diffusion compartments. It should be noted

\[ \text{BFOR Slow EAP reconstruction at } t = 0 \]

\[ \begin{align*}
(a) & \quad p=1 \, \mu\text{m} \\
(b) & \quad p=5 \, \mu\text{m} \\
(c) & \quad p=10 \, \mu\text{m} \\
(d) & \quad p=15 \, \mu\text{m}
\end{align*} \]

\[ \text{SPFI Slow EAP reconstruction} \]

\[ \begin{align*}
(e) & \quad p=1 \, \mu\text{m} \\
(f) & \quad p=5 \, \mu\text{m} \\
(g) & \quad p=10 \, \mu\text{m} \\
(h) & \quad p=15 \, \mu\text{m}
\end{align*} \]

\[ \text{DPI Slow EAP reconstruction} \]

\[ \begin{align*}
(i) & \quad p=1 \, \mu\text{m} \\
(j) & \quad p=5 \, \mu\text{m} \\
(k) & \quad p=10 \, \mu\text{m} \\
(l) & \quad p=15 \, \mu\text{m}
\end{align*} \]
that there is controversy over the assignment of these components and whether the bi-Gaussian model should take into account exchange between compartments (Mulkern et al., 1999). The ground truth of EAP is then

\[
p_{\mathbf{p}}(\mathbf{p}, \mathbf{r}) = \sum_{k=1}^{N_b} \left[ \frac{f_{\mathbf{k}}}{\sqrt{4\pi \tau}} e^{-\frac{p^2 \mathbf{r}^2}{4\tau}} + \frac{f_{\mathbf{s}}}{\sqrt{4\pi \tau}} e^{-\frac{p^2 \mathbf{r}^2}{4\tau}} \right], \tag{19}
\]

where \(= \Delta - \delta/3\). For the synthetic data, the diffusion gradient duration is \(\delta = 45 \text{ ms}\) and diffusion gradient separation \(\Delta = 56 \text{ ms}\).

In reconstructing the EAP, we look at two equally weighed fibers crossing at 60°, and set eigenvalues of each diffusion tensor to be \([1.6, 0.4, 0.4] \cdot e^{-3}\), which gives an FA value of 0.7071. The values of the fast and slow Gaussian diffusion functions were taken from Maier et al. (2004) and are shown in Table 2. Monte Carlo noise simulations were then performed to investigate the effect of SNR on the estimation of Po, MSD, and GFA for a single voxel for each EAP method. Seven SNR levels \([10, 20, 30, 40, 50, 60, 100]\) for the \(b=0\) image were simulated, 1000 times each, by adding Rician noise in a similar manner as in Descoteaux et al. (2007) for four different scenarios: a fast isotropic component \((D = 0.00115 \text{ mm}^2/\text{s})\); a slow isotropic component \((D = 0.00045 \text{ mm}^2/\text{s})\); fast anisotropic components of a corpus callosum fiber and internal capsule fiber crossing at 60°; and the slow anisotropic components for the previous scenario. The BFOR parameters are \(\{L = 4, N = 6, \tau = 91.2 \text{ mm}^{-1}\}\), \(\lambda_l = 10^{-6}\), \(\lambda_n = 10^{-6}\), DPI parameters \((L = 4, \lambda_l = 0 \text{ (no noise)}/\lambda_l = 0.006 \text{ (with noise)})\), and SPFI parameters \((L = 4, N = 3, \zeta = 500, \lambda_l = 10^{-8}, \lambda_n = 10^{-8}\) \). For each method, model parameters were chosen based on giving the optimal EAP reconstruction when no noise was present.

Human brain data

HYDI was performed on a healthy, adult human using a 3.0T GE-SIGNA scanner with an 8-channel head coil and ASSET parallel imaging. The DW pulse sequence was a single-shot, spin-echo, echo-planar imaging (SS-SE-EPI) with pulse-oximeter gating. The MR parameters were as

BFOR Fast EAP Reconstruction at \( t = 0 \) with Linear Extrapolation

\[(a) \quad p = 1 \mu m \quad (b) \quad p = 5 \mu m \quad (c) \quad p = 10 \mu m \quad (d) \quad p = 15 \mu m\]

SPFI Fast EAP Reconstruction with Linear Extrapolation

\[(e) \quad p = 1 \mu m \quad (f) \quad p = 5 \mu m \quad (g) \quad p = 10 \mu m \quad (h) \quad p = 15 \mu m\]

BFOR Slow EAP Reconstruction at \( t = 0 \) with Linear Extrapolation

\[(i) \quad p = 1 \mu m \quad (j) \quad p = 5 \mu m \quad (k) \quad p = 10 \mu m \quad (l) \quad p = 15 \mu m\]

SPFI Slow EAP Reconstruction with Linear Extrapolation

\[(m) \quad p = 1 \mu m \quad (n) \quad p = 5 \mu m \quad (o) \quad p = 10 \mu m \quad (p) \quad p = 15 \mu m\]

Fig. 6. Extrapolated samples were acquired by linearly damping the signal measurements in the outermost shell. Reconstruction of the EAP (red) using BFOR and SPFI compared with the ground truth (green). Two equally weighted WM fibers were simulated crossing at 60°. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
follows: \(\text{TE} = 122\, \text{ms}, \text{TR} = 12\, \text{s}, \text{FOV} = 256\, \text{mm}, \text{matrix} = 128 \times 128, \text{voxel size} = 2 \times 2\, \text{mm}^2, 30 \text{ slices} \text{ with slice thickness} = 3\, \text{mm}, \text{and a total scan time of about 30 min.} \)

Diffusion parameters were maximum \(b\)-value \(b_{\max} = 9375\, \text{s/mm}^2, \text{diffusion gradient duration} \delta = 45\, \text{ms, diffusion gradient separation} \Delta = 56\, \text{ms, q-space sampling interval} \Delta q = 15.2\, \text{mm}^{-1}, \text{maximum length of the q-space wave vector} q_{\max} = 76\, \text{mm}^{-1}, \text{field of view of the diffusion displacement space} \text{FOV}_p = (1/\Delta q) = 65\, \mu\text{m, and resolution of the diffusion displacement space} \Delta p = (1/2q_{\max}) = 6.6\, \mu\text{m (Callaghan, 1991).} \) The same BFOR, DPI, and SPFI modeling parameters utilized for synthetic data were also used for \textit{in vivo} data.

**Results**

BFOR, DPI, and SPFI are first applied to the numerical phantom and then on the real dataset. The numerical phantom is used to validate BFOR, compare its performance to those of DPI and SPFI, assess all three methods’ robustness in estimating the scalar measures \(p_0\), MSD, and GFA, and answer the following questions: (1) Can these methods properly reconstruct a diffusion signal acquired via hybrid sampling? (2) How does the slow diffusion component affect the EAP reconstruction and the estimations of the scalar quantities? (3) What can be done to reduce the effects of Gibbs ringing on the EAP reconstructions? It is also important to note that the EAP and quantitative scalar measures were reconstructed using only 125 diffusion measurements, while those presented in Descoteaux et al. (2011) used 256.

![Monte Carlo simulation investigating the effect of noise on estimation of \(p_0\) using fast/slow anisotropic components and fast/slow isotropic components. Error bars denote one standard deviation across 1000 trials.](http://dx.doi.org/10.1016/j.neuroimage.2012.08.072)
only six measurements were acquired in this shell (see Table 1), which may be inadequate for their respective radial bases.

Performances of BFOR, DPI, and SPI in reconstructing EAP. Fig. 4 shows the EAP reconstruction for the fast diffusion component across propagator space using each method. Modeling the fast component (i.e. head of the bi-exponential in Fig. 2) is tantamount to fitting a mono-exponential curve, and so the EAP reconstruction for the fast diffusion component can be viewed as if the diffusion signal decay was mono-exponential. Both BFOR and SPI model the fast component EAP very well, accurately capturing the geometry and orientation of the EAP profile, and the BFOR reconstruction is nearly identical to that of SPI. DPI performs reasonably well, but tends to overestimate the EAP.

Fig. 5 shows the EAP reconstruction for the slow diffusion component, which can be viewed as modeling the tail of the bi-exponential curve in Fig. 2. Note that the BFOR and SPI reconstructions are quite alike. At \( p = 1 \mu m \), all three methods capture the correct geometry of the ground truth EAP profile, but underestimate it, DPI more so. At \( p = 5 \mu m \), all three methods are unsuccessful in capturing the correct geometry, in particular failing to capture the peaks of the ground truth EAP profile. However, they do capture the correct orientation. At \( p = 10 \) and especially \( p = 15 \mu m \), the BFOR and SPI EAP reconstructions of the slow diffusion component begin to suffer from Gibbs ringing, which arise from the truncation of the signal bases at high \( q \). The DPI reconstruction at \( p = 15 \mu m \) benefits from the inherent smoothing of Laplacian signal modeling, with no spurious peaks present. Although oversmoothened and overestimated, it does a much better job than BFOR and SPI in resolving the correct fiber orientation at \( p = 15 \mu m \). The difficulty in reconstructing the EAP for the slow diffusion component is due to the slow diffusion component being sensitive to truncation effects. The reality of finite sampling makes it challenging to capture the tail of the bi-exponential curve. How then should one combat the effects of truncation artifacts?

Signal extrapolation. Extrapolating the diffusion signal to higher \( q \)-values so that \( q \)-space is more thoroughly explored could mitigate the truncation effects. Signal extrapolation can increase the spatial resolution of the EAP (Cohen and Assaf, 2002), and in the case of DSI, significantly reduce the cumbersome \( q \)-space sampling (Yeh et al., 2008). By linearly damping the signal measurements in the outermost shell (\( b = 9375 \) shell), we were able to (linearly) extrapolate samples onto three new ‘pseudo-shells.’ Specifically, the outermost signal measurements were attenuated by a factor of 0.7, 0.4, and 0.1 to form the three ‘pseudo-shells.’ The BFOR and SPI scaling factors, \( \tau \) and \( \zeta \), respectively, were changed for the extrapolation to

Fig. 8. Monte Carlo simulation investigating the effect of noise on estimation of MSD using fast/slow anisotropic components and fast/slow isotropic components. Error bars denote one standard deviation across 1000 trials.

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τ = 136.8 mm$^{-1}$ and ζ = 1100. Note that the q-space sampling interval Δq was not changed for the extrapolation.

Fig. 6 shows that signal extrapolation improves the reconstruction of the slow EAP component for both BFOR and SPFI. At $p = 10\, \mu m$, the BFOR and SPFI slow EAP reconstructions with signal extrapolation, although not perfectly capturing the ground truth geometry, better capture the angular features of the ground truth than those without signal extrapolation. The biggest improvement, however, is seen at $p = 15\, \mu m$, where the pronounced Gibbs ringing is greatly reduced by the signal extrapolation. In particular, the BFOR slow EAP reconstruction with signal extrapolation at $p = 15\, \mu m$ is not spiky and much closer to the ground truth, although their orientations are slightly off, than those without extrapolation (Fig. 5). Note that both the BFOR and SPFI slow EAP reconstructions with extrapolation are quite alike. The BFOR fast EAP reconstruction was not affected by extrapolation, being nearly identical to its counterpart without extrapolation. However, the SPFI fast EAP reconstruction with extrapolation was moderately less accurate than that without extrapolation. In general, signal extrapolation can significantly improve EAP reconstructions at larger diffusion displacements (i.e., $p = 15\, \mu m$).

Estimation of q-space indices. Fig. 7 shows the results for the Po measurements. Without signal extrapolation, BFOR and SPFI asymptotically approach the ground truth fast anisotropic Po, whereas DPI overestimates it. All three methods, without signal extrapolation, severely underestimate slow anisotropic Po, which is due to the truncation of the signal bases at high q. Both BFOR and SPFI asymptotically approach the ground truth fast/slow isotropic Po, while DPI overestimates both. At low levels of SNR (e.g., 10 and 20), which is quite common in diffusion MRI, all three methods (without signal extrapolation) have biased estimates of Po, though the variance is fairly small.

When signal extrapolation is applied, the estimation of the slow anisotropic Po by BFOR and SPFI significantly improves, as shown in Fig. 7b. According to Fig. 7a, signal extrapolation does not asymptotically affect SPFI’s estimation of fast anisotropic Po, but slightly worsens that of BFOR’s. At low levels of SNR, however, signal extrapolation results in more severe overestimation of fast anisotropic Po than without signal extrapolation for both BFOR and SPFI.

Fig. 8 shows the results for the MSD measurements. BFOR estimates both the fast and slow anisotropic/isotropic MSD very well across SNR levels. However, at low levels of SNR, the variability (given by the standard deviation) of the BFOR estimation of MSD is biased (given by the standard deviation) of the BFOR estimation of MSD is

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quite large, indicating strong sensitivity to noise. SPFI without signal extrapolation severely underestimates anisotropic MSD, giving negative values for slow anisotropic MSD, which indicates that it will give inaccurate measurements of the MSD of WM. SPFI also underestimates fast isotropic MSD, but asymptotically approaches ground truth slow isotropic MSD. Interestingly, there is less variability in SPFI's estimation of MSD than BFOR.

When signal extrapolation is applied to the MSD measurements, SPFI's estimations of slow anisotropic and slow isotropic MSD significantly improve, well-estimating them across SNR levels, as shown in Figs. 8b and d, respectively. Specifically, the SPFI slow anisotropic MSD estimation is no longer negative with signal extrapolation. BFOR's estimations of slow anisotropic and slow isotropic MSD with extrapolation are nearly identical to those without it. However, the variability of the BFOR and SPFI MSD measurements is much less than those without extrapolation. A negative consequence of signal extrapolation is that it increases the inaccuracy (i.e. asymptotically worsening) of the BFOR/SPFI fast anisotropic and fast isotropic MSD estimations, all of which are greatly underestimated. The simulations indicate signal extrapolation may be more beneficial to SPFI's estimation of MSD than that of BFOR's.

Fig. 9 shows the results for the GFA measurements. Asymptotically, BFOR and SPFI without signal extrapolation approach the ground truth fast anisotropic GFA, while DPI underestimates it. Across SNR levels, DPI severely underestimates slow anisotropic GFA, while both BFOR and SPFI greatly overestimate it. For the case of isotropic diffusion, where GFA=0, the GFA estimated by each method approaches zero at high SNR. However, at SNR=10, both SPFI and BFOR severely overestimate the isotropic GFA, giving values comparable to the GFA of WM. DPI's estimation of the isotropic component is much more robust to noise than BFOR and SPFI.

SPFI with signal extrapolation still overestimates slow anisotropic GFA, though slightly less so than without it, but the extrapolation increases the estimation's variability at the same time. Signal extrapolation has negligible effects on BFOR's estimation of slow anisotropic GFA. Both BFOR's and SPFI's estimation of fast anisotropic GFA are not asymptotically affected by signal extrapolation, having similar convergences as those without signal extrapolation, but the extrapolation causes both methods to overestimate fast anisotropic GFA to a larger degree at SNR = 10, 20, and 30 than without it. Based on Fig. 9c, both SPFI and BFOR with signal extrapolation overestimate isotropic GFA, across SNR levels, to a larger extent than without extrapolation, implying that extrapolation is quite sensitive to noise in CSF regions.

Results of human brain data

Resolving single fibers. In Fig. 10, a 4 × 4 ROI was drawn on the splenium of corpus callosum. The EAP profiles reconstructed at $p = 10 \mu m$ by each method have the fundamental peanut shape of a single fiber. Note that the BFOR and SPFI reconstructions in both cases are very similar. We see that application of smoothing $t = 550$ removes the center peaks of the BFOR EAP profiles, While these center peaks in the EAP profiles are the result of Gibbs ringing (i.e. artificial peaks) or describe some underlying biological process is an open question.

Resolving crossing fibers. In Fig. 11, a 4 × 4 ROI was drawn in a region of fiber crossing, where the EAP profiles were reconstructed at $p = 10 \mu m$. Although not identical, the BFOR and SPFI reconstructions are quite similar, and they recover and well discriminate crossing fiber configurations in the EAP. DPI, however, tends to oversmooth the EAP profiles of crossing WM fibers, resulting in spherical/oblate shapes that give the impression of isotropic diffusion. Based on Fig. 11d, the application of smoothing $t = 60$ to BFOR removes the center peaks from several voxels, but at the expense of slight angular smoothing of EAP profiles themselves.

Fig. 12 shows the reconstructed EAP profiles for the same crossing fiber region, but at $p = 15 \mu m$. Fiber crossing configurations are recovered and well discriminated in the EAP for each method. Unlike at $p = 10 \mu m$, the DPI EAP reconstruction at $p = 15 \mu m$ is sharper and does not suffer from oversmoothing. In fact, as the propagator radius $p$ increases, the angular resolution improves, at the expense of the EAP profiles becoming spiky, as is evident in Figs. 12a, e, and g. When a smoothing of $t = 60$ is applied to the BFOR EAP reconstruction...

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(without signal extrapolation), the subsequent EAP profiles are still spiky. At $t=350$, the spikiness is smoothed out, but many of the WM voxels have EAP reconstructions significantly differing, with respect to orientation and geometry, from those at $t=0$. Figs. 12d and $f$ show the BFOR and SPFI EAP profiles reconstructed at $p=15 \mu m$ with signal extrapolation, respectively, which are much less spiky than the corresponding ones without signal extrapolation, which is consistent with the synthetic results shown in Fig. 6. The signal extrapolation also smoothes the reconstructed EAP profiles, but unlike BFOR at $t=350$, none of the WM voxels are oversmoothed to such a degree that their EAP profiles have oblate shapes. Unlike BFOR at $t=350$, the underlying EAP geometry and orientation of the BFOR/SPFI reconstructions with signal extrapolation are fairly consistent to those without extrapolation (at $t=0$). As observed at $p=10 \mu m$, the BFOR and SPFI EAP reconstructions at $p=15 \mu m$ are quite similar, which is consistent with the synthetic data results.

Q-space indices. Table 3 shows the mean index value and corresponding standard deviation for genu and splenium of corpus callosum (WM) and putamen (GM). Three $4 \times 4$ ROIs were drawn on both the genu and splenium and one such ROI on both the left and right putamen, across several slices. The table shows that the SPFI MSD (without signal extrapolation) erroneously gives negative values for the MSD of genu and splenium. With extrapolation, the SPFI MSD of genu and splenium are positive.

Based on the numerical simulations, signal extrapolation was applied to both BFOR’s and SPFI’s estimation of $P_o$. Fig. 13 displays an axial slice of $P_o$ generated by each method. In the first row, we show $P_o$ computed from BFOR, SPFI, DPI, and numerically (Wu et al., 2008). The BFOR, SPFI, and numerical $P_o$ maps are quite similar, exhibiting rich GM/WM and tissue/CSF contrasts while the DPI $P_o$ map has less GM/WM contrast. In particular, based on Table 3, the $P_o$ ratio of WM to GM is slightly above 2 for BFOR and SPFI, while less than 2 for DPI.

The MSD maps computed from BFOR, SPFI, DPI, and numerically (Wu et al., 2008) are shown in Fig. 14. Both the BFOR and numerical MSD maps exhibit rich tissue/CSF contrast, but have little WM/GM contrast, which is similar to the DTI MD. Table 3 shows that the BFOR MSD values for WM and GM are quite similar. In the SPFI (without signal extrapolation) MSD map, WM regions are completely dark, having negative MSD values. This is consistent with the results of the noise simulations, which showed that SPFI severely underestimates the MSD of WM. Signal extrapolation has the effect of enforcing the positivity constraint on the MSD for SPFI. However, both the BFOR and SPFI MSD maps with signal extrapolation have poor tissue/CSF contrast because of the noise induced by the signal extrapolation. With regards to BFOR, both the synthetic and in vivo data suggest that it’s best not to use signal extrapolation in estimating MSD. SPFI, however, does not generate reliable MSD maps either with or without signal extrapolation. Although DPI predicts the MSD to be zero, an MSD map was computed for it by numerically estimating the second moment of the diffusion propagator. The contrast of the MSD DPI map is completely inverted, with WM appearing bright and CSF dark.

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Fig. 16 displays axial slices of the GFA computed at $p = 5, 10, \text{ and } 15 \mu m$ for each method, illustrating how the anisotropy of different WM regions, such as the corpus callosum and capsules, varies with diffusion displacement $p$. According to Table 3, at $p = 5 \mu m$, the anisotropy of corpus callosum is lower with respect to levels seen in DTI. At $p = 10 \mu m$, the corpus callosum is very anisotropic, as can be seen from Table 3, indicating that $p = 10 \mu m$ is a diffusion displacement worth reconstructing the EAP at. The GFA at $p = 15 \mu m$ is more noisy, which is due to truncation of signal basis at high $q$-values and 15 $\mu m$ being well beyond the resolvable resolution (of diffusion displacement) limit. The BFOR and SPFI GFA maps without signal extrapolation are very similar, while WM regions in the DPI computed GFA maps at $p = 5$ and $10 \mu m$ have lower intensity than those of BFOR and SPFI, which is consistent with the underestimation of GFA(10) by DPI observed in the Monte Carlo noise simulations (Fig. 9). CSF regions in the BFOR GFA(10) map with signal extrapolation are more noisy than without it, which is consistent with the simulation results shown in Fig. 9c. In the case of SPFI, however, the noise level is very severe in CSF regions in the GFA(5) and GFA(10) maps with signal extrapolation than those without it.

Discussion

The three analytical EAP reconstruction schemes examined in this paper possess both certain advantages and disadvantages. Among the three, the DPI reconstruction uses the least number of expansion coefficients. According to both synthetic and in vivo data, DPI tends to greatly oversmoothen the EAP, especially $p = 10 \mu m$, but performs well at $p = 15 \mu m$ where it did not make use of signal extrapolation. DPI’s assumption of Laplacian signal modeling, however, entails that the MSD is zero (refer to Eq. (14)). Fig. 9 indicates that DPI greatly underestimates GFA(10), which is reflected in Fig. 16 and Table 3. In addition, the DPI signal basis is only applicable at $q > 0$, which is unrealistic since the diffusion signal is defined at $q = 0$.

The SPFI signal basis possesses several advantages in that it radially decays to zero and has no singularity at $q = 0$. In addition, the EAP...
is derived via integration over the entire q-space, unlike BFOR and DPI, where the q-space integration is up to a certain bound that is related to $q_{\text{max}}$. Interestingly, however, the SPFI EAP reconstructions for both synthetic and real datasets are quite similar to those of BFOR, suggesting the two methods may be inherently related. According to the synthetic data, signal extrapolation greatly improves the SPFI EAP reconstruction at $p = 15 \, \mu m$. Although not shown in this paper, heat diffusion smoothening can be applied to SPFI. SPFI’s estimation of $P_G$ and $GFA$, either with or without signal extrapolation, is quite comparable to those of BFOR’s. However, it poorly estimates the MSD, which recalling Eq. (14), may be due to, from a computational standpoint, SPFI’s signal basis not being an eigenfunction of the Laplacian operator. The main limitation of the BFOR signal model, as mentioned in the Theory section, is that it infinitely oscillates about zero, which entails a finite integration of the signal over q-space ($\tau$ being the upperbound) to retrieve the EAP. However, based on Fig. 3, BFOR outperforms DPI and SPFI in modeling the diffusion signal. Heat diffusion smoothening helps in removing potentially spurious peaks, and signal extrapolation.

### Table 3

<table>
<thead>
<tr>
<th>Index</th>
<th>Splenium</th>
<th>Genu</th>
<th>Putamen</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFOR GFA(5)</td>
<td>0.212 ± 0.0162</td>
<td>0.188 ± 0.0153</td>
<td>0.593 ± 0.0103</td>
</tr>
<tr>
<td>BFOR GFA(5) Extrap</td>
<td>0.416 ± 0.0310</td>
<td>0.370 ± 0.0235</td>
<td>0.879 ± 0.0296</td>
</tr>
<tr>
<td>SPI GFA(5)</td>
<td>0.234 ± 0.0178</td>
<td>0.209 ± 0.0179</td>
<td>0.402 ± 0.0155</td>
</tr>
<tr>
<td>SPI GFA(5) Extrap</td>
<td>0.461 ± 0.0342</td>
<td>0.402 ± 0.0308</td>
<td>0.103 ± 0.0342</td>
</tr>
<tr>
<td>BFOR GFA(10)</td>
<td>0.998 ± 0.00310</td>
<td>0.991 ± 0.0184</td>
<td>0.254 ± 0.0068</td>
</tr>
<tr>
<td>BFOR GFA(10) Extrap</td>
<td>0.999 ± 0.00270</td>
<td>0.991 ± 0.0187</td>
<td>0.360 ± 0.0075</td>
</tr>
<tr>
<td>SPI GFA(10)</td>
<td>0.999 ± 0.00246</td>
<td>0.994 ± 0.0156</td>
<td>0.263 ± 0.00735</td>
</tr>
<tr>
<td>SPI GFA(10) Extrap</td>
<td>0.996 ± 0.00335</td>
<td>0.988 ± 0.0243</td>
<td>0.339 ± 0.0072</td>
</tr>
<tr>
<td>DFI GFA(10)</td>
<td>0.831 ± 0.0280</td>
<td>0.766 ± 0.0533</td>
<td>0.123 ± 0.0038</td>
</tr>
<tr>
<td>SPI GFA(15)</td>
<td>0.527 ± 0.0424</td>
<td>0.857 ± 0.0736</td>
<td>0.397 ± 0.0830</td>
</tr>
<tr>
<td>SPI GFA(15) Extrap</td>
<td>0.859 ± 0.0782</td>
<td>0.753 ± 0.104</td>
<td>0.349 ± 0.0737</td>
</tr>
<tr>
<td>SPI GFA(15)</td>
<td>0.957 ± 0.0346</td>
<td>0.875 ± 0.0849</td>
<td>0.380 ± 0.0797</td>
</tr>
<tr>
<td>SPI GFA(15) Extrap</td>
<td>0.858 ± 0.0838</td>
<td>0.730 ± 0.104</td>
<td>0.318 ± 0.0722</td>
</tr>
<tr>
<td>DFI GFA(15)</td>
<td>0.952 ± 0.0253</td>
<td>0.906 ± 0.0566</td>
<td>0.286 ± 0.0068</td>
</tr>
<tr>
<td>BFOR MSD (10$^{-3}$ mm$^2$)</td>
<td>0.207 ± 0.0860</td>
<td>0.219 ± 0.0980</td>
<td>0.211 ± 0.0820</td>
</tr>
<tr>
<td>BFOR MSD Extrap (10$^{-3}$ mm$^2$)</td>
<td>0.137 ± 0.0300</td>
<td>0.162 ± 0.0333</td>
<td>0.158 ± 0.0164</td>
</tr>
<tr>
<td>SPI MSD (10$^{-3}$ mm$^2$)</td>
<td>0.1060 ± 0.0770</td>
<td>0.0202 ± 0.0365</td>
<td>0.0700 ± 0.0150</td>
</tr>
<tr>
<td>SPI MSD Extrap (10$^{-3}$ mm$^2$)</td>
<td>0.0830 ± 0.0210</td>
<td>0.103 ± 0.0210</td>
<td>0.137 ± 0.0150</td>
</tr>
<tr>
<td>DFI MSD (10$^{-4}$ mm$^2$)</td>
<td>4.60 ± 0.430</td>
<td>4.27 ± 0.460</td>
<td>4.28 ± 0.361</td>
</tr>
<tr>
<td>SPI GFA(10$^{-3}$ mm$^{-2}$)</td>
<td>6.63 ± 0.729</td>
<td>5.65 ± 0.630</td>
<td>2.95 ± 0.263</td>
</tr>
<tr>
<td>BFOR Po Extrapol (10$^{-2}$ mm$^{-3}$)</td>
<td>10.8 ± 1.17</td>
<td>9.24 ± 1.07</td>
<td>4.41 ± 0.396</td>
</tr>
<tr>
<td>SPI Po (10$^6$ mm$^{-3}$)</td>
<td>7.00 ± 0.757</td>
<td>6.06 ± 0.649</td>
<td>3.12 ± 0.258</td>
</tr>
<tr>
<td>SPI Po Extrapol (10$^6$ mm$^{-3}$)</td>
<td>11.2 ± 1.33</td>
<td>9.37 ± 1.22</td>
<td>4.33 ± 0.449</td>
</tr>
<tr>
<td>DFI Po (10$^6$ mm$^{-3}$)</td>
<td>5.00 ± 0.514</td>
<td>4.38 ± 0.435</td>
<td>2.99 ± 0.231</td>
</tr>
<tr>
<td>BFOR QIV (10$^{-10}$ mm$^5$)</td>
<td>4.04 ± 0.447</td>
<td>4.78 ± 0.563</td>
<td>11.1 ± 1.28</td>
</tr>
</tbody>
</table>

**Fig. 13.** Axial slice of $P_o$ generated by each method.
significantly improves the EAP reconstruction at $p = 15 \mu m$. According to both the synthetic and real data, BFOR gives reasonable estimates of all three q-space indices.

The slow component of diffusion is the most sensitive to truncation artifacts, which can induce severe Gibbs ringing and adversely affect the orientation of reconstructed EAP. In this paper, signal extrapolation was proposed as a means to mitigate the effects of such artifacts, and was observed to be most effective at higher radii (i.e. $p = 15 \mu m$), where the effects of signal truncation artifacts are most pronounced. The significant improvement in the BFOR/SPFI EAP reconstruction at $p = 15 \mu m$ via linear signal extrapolation hence suggests that extrapolation may be a useful preprocessing step for EAP reconstruction at large diffusion displacements. Signal extrapolation also greatly improves the accuracy of the BFOR/SPFI Po estimation, according to the synthetic data. However, signal extrapolation increases the severity of noise in CSF regions in the GFA and MSD maps for both BFOR and SPFI, as evidenced by the synthetic and real datasets, reducing tissue/CSF contrast. Hence, extrapolation may not be desirable for GFA and MSD estimation. Future work includes optimizing the signal extrapolation for a given signal basis.

The degree of heat diffusion smoothing desired depends on the propagator radius and whether the fibers are single or crossing. Based on Fig. 10, a smoothing of $t = 550$ was applied to splenium at $p = 10 \mu m$ to remove the center peaks. However, for a crossing fiber region at $p = 10 \mu m$, a smoothing of $t = 60$ was only applied because the EAP profiles of crossing fibers can easily become oversmoothed, resulting in oblate shapes. The fact that the smoothing factor is different for different brain regions poses a problem for whole brain EAP processing. One way to address this issue is to use an optimal bandwidth selection framework from statistics to estimate the optimal $t$. Specifically, the bandwidth $t$ is selected to minimize a certain cost function. In a spline setting, the cost function will be a generalized cross-validation (GCV) criterion (Katkovnik, 1999). In a more simple setting like ours, we can choose the $t$ that minimizes the sum of the squared residuals, where the residual is simply the difference between the actual data and model fit.

Although the encoding scheme in this study consisted of equally spaced concentric spherical shells, the BFOR framework does not require such a scheme. BFOR only requires a minimum of two diffusion weightings and use of a spherical coordinate system. Random sampling along q-space or even the use of unequally spaced concentric shells is perfectly valid. This, however, leads to the important question of what is the best way to sample $N$ diffusion measurements in q-space, which have started to be addressed (Assemlal et al., 2009b; Caruyer et al., 2011; Merlet et al., 2011). Future work includes optimizing the q-space sampling and applying compressed sensing to BFOR.

Both the ODF and EAP profiles are not sharp enough to extract the true fiber orientation. Rather, the fiber orientation is given by the fiber orientation distribution function (FODF), which can be computed via spherical deconvolution of some assumed kernel (i.e. response

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**Fig. 14.** Axial slice of MSD generated by each method.

**Fig. 15.** Axial slice of BFOR QIV. Within the CSF regions, some voxels were zeroed out because they blew up upon the division operation in computing QIV.

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Fig. 16. GFA maps computed at $p = 5$, 10, and 15 μm.
function) from q-space diffusion signal (Tournier et al., 2004). Mathematically, the angular convolution is given by

\[ E(q, \mathbf{u}) = \int F(r)K(q, \mathbf{u}, r)d^3r, \tag{20} \]

where \( F(r) \) is the IODF and \( K \) the kernel. The derivation of the IODF using the BFOR, SPFI, and DPI signal bases is worth exploring in the future.

In any future clinical study employing HYDI to examine brain pathology, where rotationally invariant indices like GFA and Po can be used to assess changes between diseased and normal subjects, voxel-wise analysis is desired. However, spatial normalization of multiple b-value datasets is no easy task. Recently, the authors in Du et al. (2012) proposed a registration algorithm to align HARDI datasets using the ODFs. Specifically, the algorithm seeks an optimal diffeomorphism of large deformation between two ODF fields across a spatial volume domain and at the same time, locally reorients an ODF in a manner consistent with the underlying anatomical structure. HYDI images could be aligned using the same algorithm, except replacing the ODF with the EAP.

The MSD measure is quite sensitive to noise (Assaf and Cohen, 1999; Wu and Alexander, 2007). The authors in Wu et al. (2008) proposed an alternative measure to MSD called the q-space inverse variance (QIV), which is a pseudo-diffusivity measure. Mathematically, the QIV is defined as

\[ \text{QIV} = \left[ \int q^2 E(q) d^3q \right]^{-1} \tag{21} \]

The QIV can thus be interpreted as the inverse of the “variance” of \( q \) (i.e., \( \text{QIV} = 1/(\langle q^2 \rangle) \)). It is not a real variance in the statistical sense because \( E(q) \) does not constitute a probability density function. The QIV is not an arbitrary measure, but related to the EAP in a manner analogous to which the MSD is related to the diffusion signal—see Appendix F, we will show that \( \text{QIV}^{-1} = \frac{1}{\sqrt{2\pi} \tau} \frac{1}{\text{SD}^2} \). The QIV within the BFOR framework is (see Appendix F for derivation)

\[ \text{QIV}_{\text{BFOR}} = \frac{1}{2\sqrt{\pi}^5 \sum_{n=1}^{N} (-1)^n C_n} \left( \frac{6 - \alpha_0}{\alpha_0} \right)^2 \tag{22} \]

Fig. 15 displays an axial slice of the BFOR QIV, illustrating rich tissue/CSF contrast. The tissue/CSF contrast in the QIV is more enhanced than that of the MSD, and unlike the MSD, the QIV map also exhibits WM/GM contrast (the right and left putamen are visible in Fig. 15 but not in the MSD maps). According to Table 3, the QIV of the corpus callosum is about a third of that of the putamen.

Conclusion

We have introduced a new orthonormal basis to model the q-space diffusion signal and from which the EAP can be analytically reconstructed using hybrid, non-Cartesian sampling with multiple q-shell measurements. BFOR is a linear and efficient reconstruction based on heat equation estimation of the diffusion signal. Compared to DSI, BFOR employs much fewer diffusion measurements. Rotationally invariant q-space indices such as GFA, Po, and MSD can then be obtained using the derived EAP.

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Appendix A. Derivation of BFOR signal basis

We want to solve the following boundary value partial differential equation:

\[ \frac{1}{q^2} \frac{\partial}{\partial t} \left( q^2 \frac{\partial}{\partial q} \right) \left( \sin \frac{\partial}{\partial q} \right) + \frac{1}{q^2} \frac{\partial^2}{\partial q^2} \psi(q) = -\lambda \psi(q), \quad \psi(q = \tau, \theta, \phi) = 0 \]  

where we require \( \lambda > 0 \). Substituting the separable solution of the form

\[ \psi(q, \theta, \phi) = f(q) h(\theta, \phi) \tag{A.2} \]

into Eq. (A.1), we obtain

\[ q^2 \frac{d^2 f}{dq^2} + 2q \frac{df}{dq} + q^2 \lambda = -\lambda h = l(l + 1), \tag{A.3} \]

where \( \lambda_h = \frac{\sin^2 \theta}{2} \left( \frac{\sin^2 \theta}{2} + \frac{\sin^2 \theta}{2} \right) \) is the Laplace–Bertrami operator and \( l \) is some real-valued constant.

We first solve for the second equation in Eq. (A.3):

\[ \Delta_h h + (l + 1) h = 0 \tag{A.4} \]

The solutions to Eq. (A.4) are the spherical harmonics \( \langle \text{SH} \rangle Y^m_l(\theta, \phi) \tag{847} \). The second equation in (A.3) can be written as

\[ q^2 \frac{d^2 f}{dq^2} + 2q \frac{df}{dq} + \left[ q^2 \lambda - (l + 1)^2 \right] f = 0 \tag{848} \]

Defining a new variable \( f(q) = \sqrt{q^2} \tau F(q) \), we can transform Eq. (A.5) to

\[ q^2 \frac{d^2 F}{dq^2} + q \frac{dF}{dq} + \left[ q^2 \lambda - (l + 1)^2 \right] F = 0, \tag{A.6} \]

which is simply a scaled version of the Bessel differential equation. The only bounded solution at the origin is given in terms of the Bessel function of the first kind as \( f(q) = j_{l+1} \sqrt{\lambda q} \). The solution to Eq. (A.5) is then \( f(q) = \sqrt{\frac{\pi}{2 \lambda q}} j_{l+1} \sqrt{\lambda q} = j_{l} \sqrt{\lambda q} \), where \( j_l \) is the spherical Bessel function of the first kind and we invoke the relation

\[ j_l(\alpha) = \sqrt{\frac{\pi}{2 \alpha}} j_{1,2} \sqrt{\alpha} \tag{859} \]

Imposing the boundary condition from Eq. (A.1), we have

\[ j_l(\sqrt{\lambda q}) = 0 \tag{860} \]. Defining \( \alpha_0 \) as the \( n \)th root of the \( n \)th order spherical Bessel function of first kind, then the eigenvalues are found to be \( \alpha_0 = \frac{n \pi}{2} \). Note that for \( l = 0 \), the roots are simply \( \alpha_n = n \pi \). Multiplying the spherical Bessel functions and the spherical harmonics together, we obtain the eigenfunctions (i.e. our orthonormal basis) to Eq. (A.1):

\[ Z_{\alpha_0}(q, \theta, \phi) = \frac{1}{\sqrt{2 \pi}} Y^m_l(\theta, \phi). \tag{666} \]

The complete set of solutions to Eq. (A.1) is

\[ \psi(q, \theta, \phi) \approx \sum_{n=1}^{N} \sum_{l=0}^{L} \sum_{m=-l}^{l} C_{\alpha_0}(q) Y^m_l(\theta, \phi). \tag{A.7} \]

where \( N \) is the truncation order of the number of roots of spherical Bessel function and \( L \) the truncation order of the SH.

Now, to derive the diffusion signal, we make two important assumptions. First, we assume the diffusion signal \( E(q) \) is a solution to the heat equation:

\[ \nabla^2 E(q, t) = \frac{\partial E}{\partial t}, \quad E(q, t = 0) = H(q). \tag{A.8} \]
where $H(q)$ is simply the acquired signal. Second, we assume that the diffusion signal can be expressed as a linear combination of the orthonormal basis derived in Eq. (A.7):

$$E(q, u, t) = \sum_{n=1}^{N} \sum_{l=0}^{\infty} \sum_{m=-l}^{l} C_{nlm}(t) Y_{nl}(u)$$

(A.9)

Substituting Eq. (A.9) back into Eq. (A.8), we obtain

$$\sum_{n=1}^{N} \sum_{l=0}^{\infty} \sum_{m=-l}^{l} C_{nlm}(t) Y_{nl}(u) \left[ -\frac{\alpha^2}{\tau^2} g_{nl}(t) - \frac{d}{dq} g_{nl}(t) \right] = 0$$

(A.10)

A unique solution exists if and only if $g_{nl}(t) = b_{nl} e^{-\frac{\alpha}{\tau}}$ (Chung et al., 2008), and so

$$E(q, u, t) = \sum_{n=1}^{N} \sum_{l=0}^{\infty} \sum_{m=-l}^{l} C_{nlm}(t) Y_{nl}(u)$$

(A.11)

Note that all constants are absorbed into $C_{nlm}$. In the following sections, we will use the SH basis $Y_{nl}$ proposed in Descoteaux et al. (2011).

Appendix B. Diffusion signal at origin

In diffusion weighted imaging (DWI), $E(0) = 1$. Thus, for our basis, we obtain the following identity:

$$E(0, t = 0) = \sum_{n=1}^{N} \sum_{l=0}^{\infty} \sum_{m=-l}^{l} C_{nlm}(0) Y_{nl}(u) = \frac{1}{\sqrt{2\pi}} \sum_{n=1}^{N} C_{n1} = 1,$$

(B.1)

which holds for any $u$ within the unit sphere $S^2$ (i.e. $u \in S^2$). In deriving Eq. (B.1), we invoked a basic property of the spherical Bessel function that

$$j_0(0) = \begin{cases} 1, & \text{if } l = 0 \\ 0, & \text{if } l \neq 0 \end{cases}$$

and the identity $Y_{0}^0 = \frac{1}{\sqrt{\pi}}$.

Appendix C. Derivation of analytical BFOR EAP solution

In the Theory section, we showed that

$$P(p, r, t) = 4\pi \sum_{n=1}^{N} \sum_{l=0}^{\infty} (-1)^{l+1} C_{nl} e^{-\frac{\alpha}{\tau} \chi} Y_{nl}(l_{nlm}(p),$$

(C.1)

where $l_{nlm}(p) = \int q^2 j_{l}^{(0,0)}(\alpha \tau) j_{l}(2\nu \tau \rho) dq$. We rewrite $l_{nlm}(p)$ in terms of the Bessel function of the first kind

$$l_{nlm}(p) = \frac{1}{2} \int \frac{4\pi \tau}{2\alpha p} \tilde{q} j_{l}^{(0,0)}(\alpha \tau) j_{l}(2\nu \tau \rho) dq$$

(C.2)

Recall the Bessel function of first kind $J_k(\alpha \chi)$, where $k$ is some real-valued constant, satisfies

$$\left( \frac{d^2}{d\chi^2} + \frac{d}{d\chi} + \alpha^2 \chi^2 - k^2 \right) J_k(\alpha \chi) = 0$$

(C.3)

Thus, by definition of the Bessel function, $J_{l+1/2}(\alpha \tau) \mu$ and $J_{l+1/2}(2\nu \tau \rho)$ satisfy

$$\left( \frac{d^2}{dq^2} + \frac{d}{dq} + \alpha^2 \frac{q^2}{\tau^2} - \frac{1}{4} \left( l + 1/2 \right)^2 \right) J_{l+1/2}(\alpha \tau) \mu = 0.$$

$$\left( \frac{d^2}{dq^2} + \frac{d}{dq} + \alpha^2 \frac{\tau^2}{q^2} - \frac{1}{4} \left( l - 1/2 \right)^2 \right) \mu J_{l+1/2}(2\nu \tau \rho) = 0,$$

(C.4)

respectively. Multiplying Eq. (C.4) by $J_{l+1/2}(2\nu \tau \rho)$ and Eq. (C.5) by $J_{l+1/2}(\alpha \tau)$ and then subtracting, we obtain

$$J_{l+1/2}(2\nu \tau \rho) \frac{d}{dq} \left[ \int q^2 j_{l}^{(0,0)}(\alpha \tau) \mu - J_{l+1/2}(\alpha \tau) \right] = \frac{q}{4\nu \tau \rho} \left( \nu \tau - \frac{\alpha}{\tau} \right) J_{l+1/2}(\alpha \tau)$$

Integrating the above from $q = 0$ to $q = \pi$ via integration by parts and noting that $J_{l+1/2}(\alpha \tau) = 0$, we have

$$\int q^2 j_{l}^{(0,0)}(\alpha \tau) \mu J_{l+1/2}(2\nu \tau \rho) dq = \frac{q}{4\nu \tau \rho} \left( \nu \tau - \frac{\alpha}{\tau} \right) J_{l+1/2}(\alpha \tau)$$

(C.6)

The right side of Eq. (C.6) can be simplified via the Bessel recurrence relations, so

$$J_{l+1/2}(2\nu \tau \rho) \frac{d}{dq} \left[ \int q^2 j_{l}^{(0,0)}(\alpha \tau) \mu - J_{l+1/2}(\alpha \tau) \right] = \frac{q}{4\nu \tau \rho} \left( \nu \tau - \frac{\alpha}{\tau} \right) J_{l+1/2}(\alpha \tau)$$

(C.7)

Using the Bessel recurrence relation $J_{l+1/2}(x) = \frac{1}{\nu} J_{l+1}(x)$, we obtain

$$J_{l+1/2}(\alpha \tau) = \frac{1}{\nu} \left[ J_{l+1}(\alpha \tau) J_{l+1/2}(2\nu \tau \rho) - J_{l+1/2}(\alpha \tau) J_{l+1/2}(2\nu \tau \rho) \right],$$

(C.8)

Thus, substituting Eq. (C.8) back into Eq. (C.2), we obtain

$$l_{nlm}(p) = \frac{1}{\sqrt{2\pi}} \frac{\sqrt{\alpha \tau} \mu}{\nu} J_{l+1/2}(\alpha \tau) \mu J_{l+1/2}(2\nu \tau \rho)$$

(C.9)

and so the diffusion propagator is then

$$P(p, r, t) = 2\sqrt{\nu \tau} \sum_{n=1}^{N} \sum_{l=0}^{\infty} (-1)^{l+1} C_{nl} e^{-\frac{\alpha}{\tau} \chi} Y_{nl}(r) \sqrt{\alpha \tau} \mu J_{l+1/2}(\alpha \tau) \mu J_{l+1/2}(2\nu \tau \rho) \left( \frac{4\nu \tau \rho - \alpha}{\nu \tau} \right)^{1/2},$$

(C.9)

Appendix D. Derivation of BFOR zero-displacement probability

We can derive $P_0$ by evaluating Eq. (C.9) at $p = 0$:

$$P_0 = P(p = 0, r) = 2\sqrt{\nu \tau} \sum_{n=1}^{N} C_{n1} Y_{1}(r) \sqrt{\alpha \tau} \mu J_{1/2}(\alpha \tau) \mu J_{1/2}(2\nu \tau \rho) \left( \frac{4\nu \tau \rho - \alpha}{\nu \tau} \right)^{1/2}$$

(D.1)

where we used the relation $J_{1/2}(x) = \frac{1}{\sqrt{x}} \sin(x)$.
Appendix E. Relationship between MSD and diffusion signal in q-space

We define the wave vector \( \mathbf{q} \) as \( \mathbf{q} = q_x \mathbf{i} + q_y \mathbf{j} + q_z \mathbf{k} \) and the radius vector in propagator space \( \mathbf{p} \) as \( \mathbf{p} = p_x \mathbf{i} + p_y \mathbf{j} + p_z \mathbf{k} \). The norm of \( \mathbf{p} \) is \( p = \sqrt{p_x^2 + p_y^2 + p_z^2} \).

Since the diffusion signal and EAP are FT pairs, then the inversion of Eq. (1) gives

\[
E(\mathbf{q}) = \int \mathcal{P}(\mathbf{p}) e^{2\pi i \mathbf{q} \cdot \mathbf{p}} d^3 \mathbf{p} = \int \mathcal{P}(\mathbf{p}) e^{2\pi i (q_x p_x + q_y p_y + q_z p_z)} d^3 \mathbf{p}
\]

(E.1)

Taking the second derivative of \( E(\mathbf{q}) \) with respect to \( q_x, q_y, \) and \( q_z \) gives

\[
\frac{\partial^2 E(\mathbf{q})}{\partial q_x^2} = (2\pi i)^2 \int \mathcal{P}(\mathbf{p}) e^{2\pi i q_x p_x} d^3 \mathbf{p}
\]

\[
\frac{\partial^2 E(\mathbf{q})}{\partial q_y^2} = (2\pi i)^2 \int \mathcal{P}(\mathbf{p}) e^{2\pi i q_y p_y} d^3 \mathbf{p}
\]

\[
\frac{\partial^2 E(\mathbf{q})}{\partial q_z^2} = (2\pi i)^2 \int \mathcal{P}(\mathbf{p}) e^{2\pi i q_z p_z} d^3 \mathbf{p}
\]

(E.2)

The sum of the derivatives is simply the Laplacian of the operator acting on \( E(\mathbf{q}) \): \( V^2 E(\mathbf{q}) \). \( \nabla^2 E(\mathbf{q}) = \frac{\partial^2 E(\mathbf{q})}{\partial q_x^2} + \frac{\partial^2 E(\mathbf{q})}{\partial q_y^2} + \frac{\partial^2 E(\mathbf{q})}{\partial q_z^2} = (2\pi i)^2 \int \mathcal{P}(\mathbf{p}) e^{2\pi i q \cdot \mathbf{p}} d^3 \mathbf{p} \)

(E.3)

Note that the Laplacian of \( E(\mathbf{q}) \) evaluated at \( \mathbf{q} = 0 \) is related to the second moment of the EAP. Thus, the MSD is

\[ \left< P^2 \right> = \frac{1}{4\pi^2} \nabla^2 E(\mathbf{q}) \bigg|_{\mathbf{q}=0} \]

(E.4)

For the case of DTI, where \( E(\mathbf{q}, \mathbf{u}) = e^{-4\pi^2 \mathbf{q}^2 (\Delta - \delta/3) \mathbf{u} \cdot \mathbf{Du}} \), Eq. (E.3) simplifies to the Einstein relation

\[ \left< P^2 \right> = 6(\Delta - \delta/3) MD \]

(E.5)

E.1. Derivation of BFOR MSD

The BFOR signal basis is an eigenfunction of the Laplacian operator, with eigenvalues \( -\frac{\alpha^2}{\lambda^2} \). Hence

\[
V^2 E(\mathbf{q}) = \sum_{n=1}^{N} \sum_{i=1}^{R} C_n (\frac{\alpha_{n,i} q}{\tau})^2 e^{-\alpha_{n,i} q^2 \tau^2} j_0 \left( \frac{\alpha_{n,i} q}{\tau} \right) Y_j(\mathbf{u})
\]

(E.6)

(E.7)

Substituting Eq. (E.6) into Eq. (E.3), we obtain

\[ \left< P^2 \right>_{\text{BFOR}} = \frac{1}{8\pi^2} \sum_{n=1}^{N} C_n \alpha^2_{n,0} \]

where we dropped the smoothing term.

Appendix F. Relationship between QIV and EAP in q-space

Using the definition of QIV, we have

\[
QIV^{-1} = \int q^2 E(\mathbf{q}) d^3 \mathbf{q} = \int q^2 \left[ \mathcal{P}(\mathbf{p}) e^{2\pi i q \cdot \mathbf{p}} \right] d^3 \mathbf{p}
\]

(E.1)

The Dirac delta function is defined as

\[
\delta(\mathbf{p}) = e^{2\pi i \mathbf{q} \cdot \mathbf{p}} d^3 \mathbf{q}
\]

Taking the second derivative of \( \delta(\mathbf{p}) \) with respect to \( p_x, p_y, p_z \), we obtain

\[
\frac{\partial^2 \delta(\mathbf{p})}{\partial p_x^2} = (2\pi i)^2 \int e^{2\pi i q \cdot \mathbf{p}} d^3 \mathbf{p}
\]

\[
\frac{\partial^2 \delta(\mathbf{p})}{\partial p_y^2} = (2\pi i)^2 \int e^{2\pi i q \cdot \mathbf{p}} d^3 \mathbf{p}
\]

\[
\frac{\partial^2 \delta(\mathbf{p})}{\partial p_z^2} = (2\pi i)^2 \int e^{2\pi i q \cdot \mathbf{p}} d^3 \mathbf{p}
\]

(E.2)

The sum of the derivatives is simply the Laplacian of the operator acting on \( \delta(\mathbf{p}) \): \( V^2 \delta(\mathbf{p}) \). Hence

\[
V^2 \delta(\mathbf{p}) = \frac{\partial^2 \delta(\mathbf{p})}{\partial p_x^2} + \frac{\partial^2 \delta(\mathbf{p})}{\partial p_y^2} + \frac{\partial^2 \delta(\mathbf{p})}{\partial p_z^2} = (2\pi i)^2 \int e^{2\pi i q \cdot \mathbf{p}} d^3 \mathbf{p}
\]

(E.3)

Thus, Eq. (F.1) becomes

\[
QIV^{-1} = \frac{1}{4\pi^2} \int \mathcal{P}(\mathbf{p}) \left[ V^2 \delta(\mathbf{p}) \right] d^3 \mathbf{p}
\]

(E.4)

Since the Laplacian operator \( V^2 \) is Hermitian and the EAP and \( \delta(\mathbf{p}) \) are real-valued, Eq. (F.4) can be equivalently stated as

\[
QIV^{-1} = \frac{1}{4\pi^2} \left[ \int \mathcal{P}(\mathbf{p}) \left[ V^2 \delta(\mathbf{p}) \right] d^3 \mathbf{p} = \int \mathcal{P}(\mathbf{p}) \left[ V^2 \delta(\mathbf{p}) \right] d^3 \mathbf{p} \right]
\]

(E.5)

Exploiting the property of the Dirac delta function that \( \int e^{-\alpha x} \delta(x) dx = f(0) \), we have

\[
QIV^{-1} = \frac{-\nabla^2 \mathcal{P}(\mathbf{p}) |_{\mathbf{p}=0}}{4\pi^2}
\]

(E.6)

which is very similar in form to Eq. (E.3). This, whereas the MSD directly varies with the Laplacian of the diffusion signal evaluated at the origin, \( QIV \) inversely varies with the Laplacian of the EAP evaluated at the origin.

F.1. Derivation of BFOR QIV

\[
QIV^{-1} = \int q^2 E(\mathbf{q}) d^3 \mathbf{q} \approx \sum_n \sum_i C_n j_0(\alpha_{n,i} q) \int \frac{\alpha_{n,i} q}{\tau} \sin \frac{\alpha_{n,i} q}{\tau} dq = \sqrt{4\pi^2} \sum_n \sum_i C_n j_0(\alpha_{n,i} q) \int \frac{\alpha_{n,i} q}{\tau} \sin \frac{\alpha_{n,i} q}{\tau} dq
\]

(E.7)

The last integral can easily be solved via integration by parts, and so the QIV is

\[
QIV_{\text{BFOR}} = \frac{1}{2\sqrt{\pi^2 \sum_{n=1}^{N} (-1)^{n-1} C_n (\frac{\alpha_{n,0}}{\tau})}^2}
\]

(E.8)
References