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A new methodology for the estimation of fiber populations in the white matter of the brain with the Funk-Radon transform

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Abstract

The Funk-Radon Transform (FRT) is a powerful tool for the estimation of fiber populations with High Angular Resolution Diffusion Imaging (HARDI). It is used in Q-Ball imaging (QBI), and other HARDI techniques such as the recent Orientation Probability Density Transform (OPDT), to estimate fiber populations with very few restrictions on the diffusion model. The FRT consists in the integration of the attenuation signal, sampled by the MRI scanner on the unit sphere, along equators orthogonal to the directions of interest. It is easily proved that this calculation is equivalent to the integration of the diffusion propagator along such directions, although a characteristic blurring with a Bessel kernel is introduced. Under a different point of view, the FRT can be seen as an efficient way to compute the angular part of the integral of the attenuation signal in the plane orthogonal to each direction of the diffusion propagator. In this paper, Stoke's theorem is used to prove that the FRT can in fact be used to compute accurate estimates of the true integrals defining the functions of interest in HARDI, keeping the diffusion model as little restrictive as possible. Varying the assumptions on the attenuation signal, we derive new estimators of fiber orientations, generalizing both Q-Balls and the OPDT. Extensive experiments with both synthetic and real data have been intended to show that the new techniques improve existing ones in many situations.

Keywords

HARDI; Funk-Radon transform; Q-Balls; OPDT

1 Introduction

Diffusion Tensor Imaging (DTI) has allowed the study of nerve fibers and their connectivity in the white matter *in vivo* (Basser et al., 1994; Basser and Pierpaoli, 1996). This technique, however, is intended to track the principal diffusion direction at each voxel of the image, so

it may fail to describe the actual underlying neural architecture in the presence of fibers crossing, bending, or kissing (Tuch et al., 2003; Wedeen et al., 2005). In these cases, it is necessary to consider the more general Fourier relation between the probability density function (PDF) of the displacements of water molecules, $P(R)$, and the attenuation signal acquired by the scanner, $E(q)$, see Callaghan (1991):

$$P(R) = \mathcal{F}\{E(q)\}(R) = \int \int \int_{\mathbb{R}^3} E(q) \exp(-2\pi j q^T R) dq, \quad (1)$$

where R is the displacement of water molecules in a time δ , and $q = \gamma \delta G / 2\pi$ is its dual variable in the Fourier domain, with γ the gyromagnetic ratio, G the gradient applied to the magnetic field in the scanner, and δ its duration; the Short Gradient Pulse (SGP) condition, i.e. $\delta \ll \tau$, is necessarily assumed for eq. (1) to hold. These parameters are related to the b -value of the acquisition as: $b = 4\pi^2 \tau q^2$, for $q = \|q\|$ and $\tau = \delta / 3$. With DTI, the diffusion propagator $P(R)$ is assumed to be a Gaussian process, so that eq. (1) can be solved analytically, and only six degrees of freedom have to be fitted. When this premise does not hold, $E(q)$ may be sampled in the whole space, and $P(R)$ recovered by means of Fourier transform. This is the principle of Diffusion Spectrum Imaging (Wedeen et al., 2005, DSI), whose main limitation is the need to sample $E(q)$ for all $q \in \mathbb{R}^3$, which is unpractical for clinical purposes.

This problem can be overcome by means of High Angular Resolution Diffusion Imaging (HARDI) techniques, based on sampling $E(q)$ only in a sphere $S \subset \mathbb{R}^3$ with fixed radius $q = q_0$. As a consequence, the information provided by $E(q)$ is partially lost, and has to be somehow recovered. Withal, the whole $P(R)$ has not to be characterized, but only some orientation information related to the presence of a fiber bundle in a given unit direction $r = R/\|R\|$. For example, the following functions are usually computed:

$$\Phi(r) = \int_0^\infty R^2 P(Rr) dR = \frac{1}{2} \int_{-\infty}^\infty R^2 P(Rr) dR; \quad (2)$$

$$\Psi(r) = \int_0^\infty P(Rr) dR = \frac{1}{2} \int_{-\infty}^\infty P(Rr) dR, \quad (3)$$

where the axial symmetry of $P(R)$ has been exploited. The Orientation Probability Density Function (OPDF), $\Phi(r)$, has been previously used by Aganj et al. (2009a); Tristán-Vega et al. (2009b); Wedeen et al. (2005), and its main advantage is that it represents a true PDF thanks to the inclusion of the Jacobian R^2 in the integration, as opposed to the Orientation Distribution Function (ODF), $\Psi(r)$, first introduced by Tuch et al. (2003).

HARDI approaches include generalizations of the tensor model, such as mixtures of Gaussians (Kreher et al., 2005), continuous mixtures of Gaussians (Jian et al., 2007), higher order tensors (Descoteaux et al., 2006; Özarslan et al., 2003), or spherical deconvolution (Alexander, 2005; Anderson, 2005; Descoteaux et al., 2009; Jian and Vemuri, 2007; Tournier et al., 2007, 2004). Other techniques have also been proposed that get rid of the Gaussian model, such as the Diffusion Orientation Transform (Özarslan et al., 2006, DOT), or Persistent Angular Structures (Jansons and Alexander, 2003, PAS).

With these approaches, the only information available is the sampling of $E(q)$ at S , so either a prior model or some unrealistic assumptions are often imposed. On the other hand, other recent works propose an intermediate solution between DSI and HARDI: the attenuation signal is sampled at a number of shells with different b -values, giving rise to the so-called Hybrid Diffusion Imaging (Wu et al., 2008, HYDI). This technique may be used either to perform numerical integration in the direction of q (Canales-Rodríguez et al., 2009; Wu et al., 2008), or to fit more accurate diffusion models such as multi-exponential (Aganj et al., 2009b; Özarslan et al., 2006) or Laplace's equation basis (Descoteaux et al., 2009). Finally, in Khachaturian et al. (2007), it is proposed to combine multiple shells to improve the signal to noise ratio (SNR) of the reconstructed ODF.

Our work is centered on conventional, single-shell HARDI data sets, which can be easily acquired in clinical times with current machinery. Hence, we have to deal with the modeling of the diffusion signal from one single b -value. The starting point is Q-Ball Imaging (QBI), that allows to obviate the need for any model or assumption (obviously, the SGP condition is still required) by directly estimating the integral in eq. (3) only from available data, without considering $P(R)$ (Tuch, 2004; Tuch et al., 2003). The Funk-Radon Transform (FRT) is at the heart of QBI: for each direction r , $E(q)$ is integrated along the equator of S orthogonal to r , so $\Psi(r)$ is estimated without the need of any additional information outside S . This nice property has been exploited to derive other related estimators such as the Orientation Probability Density Transform (Tristán-Vega et al., 2009b, OPDT) or the spherical deconvolution approach by Descoteaux et al. (2009), allowing to highly relax the assumptions on $E(q)$. On the other hand, the FRT does not provide the exact integral in eq. (3) along R , but instead it estimates a Bessel kernel-weighted integral inside tubes along R , which is its main source of error. Moreover, with the OPDT, this limitation supposes an inherent theoretical restriction: it is demonstrated in Tristán-Vega et al. (2009b) that for arbitrarily large b -values the FRT necessarily drives to negative estimates of the OPDF.

The aim in our previous work (Tristán-Vega et al., 2009b) was to include the Jacobian of the spherical coordinates system in the radial integration to estimate true probabilities. On the contrary, the present paper is focused on the study of the intrinsic blurring due to the use of the FRT. The analysis is performed both for estimators of the ODF and the OPDF, i.e. with or without the Jacobian, and it is carried out using an alternative representation of eqs. (2) and (3) in the Fourier domain. It is demonstrated that the error in the radial integration can be reduced in different degrees, depending on the restrictions assumed for the diffusion model. This result is used to propose a new methodology, based on differential geometry, which allows to drastically reduce the integration error while keeping the main advantage of the FRT, since it only needs a weak condition on the attenuation signal. Yet, varying the restrictions on the diffusion model, the same methodology leads to an alternative derivation of some known estimators (Aganj et al., 2009a; Canales-Rodríguez et al., 2009), together with some new ones.

2 Theory

2.1 Radial integrals as circulations in the q-space

We aim to estimate the integrals in eqs. (2) and (3) with an alternative representation in the Fourier domain. To that end, the methodology is as follows:

1. Deduce the expression relating the integral of $P(R)$ (or $R^2P(R)$) along r with $E(q)$. It translates to an integral in the plane Π orthogonal to r .
2. Approximate this calculation by the integral in a bounded domain, i.e. the disk Ω delimited in Π by the sphere S .
3. Relate the latter integral to a line integral along the equator of S described by its intersection with Π (i.e., along the boundary Γ of Ω).

In what follows, each of these steps is motivated and discussed.

2.1.1 Representation of radial integrals in the Fourier domain—Consider the auxiliary cylindrical coordinates system in Fig. 1 (left), for which the ‘z’ axis is aligned with the direction of interest, r . The calculation of the orientation functions described in eqs. (2) and (3) requires the integration of the (weighted) diffusion propagator along the direction r . Given the Fourier relation between $P(R)$ and the attenuation signal, described in eq. (1), the central section theorem can be used to show the equivalence with the integral of $E(q)$ in the plane Π orthogonal to r containing Γ , as it has been previously noted by Aganj et al. (2009a); Canales-Rodríguez et al. (2009); Tristán-Vega et al. (2009a); Wu et al. (2008). For the sake of completeness, this result is demonstrated in Appendix A. Hence, the following equalities hold:

$$\Phi(r) = \frac{-1}{8\pi^2} \iint_{\Pi} \Delta E(q) d\Pi. \quad (4)$$

$$\Psi(r) = \frac{1}{2} \iint_{\Pi} E(q) d\Pi. \quad (5)$$

The Laplacian operator Δ , and the constant $-1/4\pi^2$ in eq. (4), are used to include the term R^2 in the Fourier transform of $E(q)$, i.e. $P(R)$, see Aganj et al. (2009a); Tristán-Vega et al. (2009b). Eq. (5) may be used to compute the exact ODF, without any error. Unfortunately, conventional HARDI techniques do not allow the characterization of $E(q)$ in the whole plane Π , but only in its intersection with the sphere S , i.e. in the curve Γ . The work-around with the FRT (i.e., in QBI) is to integrate the corresponding function only along this equator, replacing eq. (5) with the integral in the circumference Γ in Fig. 1. Obviously, this is a coarse approximation which may induce large errors in the estimation. Instead, an alternative approach is derived in what follows to overcome the problems of this technique.

2.1.2 Approximation of line integrals as integrals in a disk—The integrals in eqs. (4) and (5) cannot be explicitly computed from the values sampled at Γ . Instead, the integral inside the disk Ω , whose boundary $\Gamma = \partial\Omega$ is the intersection of S with Π , may be thought of. Consider now the spherical coordinates system depicted in Fig. 1, right. The direction of

interest corresponds to the colatitude angle $\xi = 0$, so the disk Ω is easily parametrized as: $\Omega = \{(q, \xi, \nu) | 0 \leq q \leq q_0, \xi = \pi/2, 0 \leq \nu \leq 2\pi\}$, and:

$$\Phi(r) \simeq \frac{-1}{8\pi^2} \int \int_{\Omega} \Delta E(q) d\Omega = \frac{-1}{8\pi^2} \int_0^{q_0} \int_0^{2\pi} \widetilde{\Delta E}\left(q, \frac{\pi}{2}, \nu\right) q d\nu dq. \quad (6)$$

$$\Psi(r) \simeq \frac{1}{2} \int \int_{\Omega} E(q) d\Omega = \frac{1}{2} \int_0^{q_0} \int_0^{2\pi} \widetilde{E}\left(q, \frac{\pi}{2}, \nu\right) q d\nu dq. \quad (7)$$

In general, the decay of the attenuation signal follows an exponential law, so the most of the energy of $E(q)$ (or $\widetilde{E}(q)$) is concentrated inside Ω . For this assumption to hold, it is not necessary to assume a mono-exponential decay of $E(q)$. It has been shown that, in most situations, the attenuation signal is accurately described by a multi-exponential model (Niendorf et al., 1996; Özarslan et al., 2006; Shinmoto et al., 2009), so it may be assumed that the error committed neglecting the integral outside Ω is small enough compared to the integral inside this subset. Of course, the error in the computation decreases as q_0 (or, alternatively, the b -value) increases, since the subset of Π for which the integral is neglected is smaller. Still, there is a side problem in using the integral inside Ω : a multi-exponential model ensures that only a small fraction of the actual value of the integral is neglected; but the exponential law, and consequently the error, is different for each direction $\mathbf{g} = \mathbf{G}/\|\mathbf{G}\|$. In case this error is not negligible (for example, for those directions of minimum diffusion), a certain distortion in the estimated orientation function may be induced. Apart from these considerations, it remains to compute the integrals inside Ω , and for this task only the values sampled at Γ (those available in the HARDI data set) may be used. The next Section is centered on this topic.

2.1.3 Flux integrals in the Fourier domain and Stokes' theorem—Stokes' theorem arises naturally when relating the integral inside a bounded surface Ω to the integral along its boundary Γ . It states that the circulation of a vector field $\mathbf{F}$ along a closed curve Γ in $\mathbb{R}^3$ equals the flux integral of the projection of its curl $\mathbf{H}$ on the unit vector normal to the surface Ω enclosed by Γ . For the particular situation depicted in Fig. 1, Stokes' theorem reads:

$$\int_{\Gamma} \mathbf{F} \cdot \mathbf{t} \, d\Gamma = \int \int_{\Omega} (\nabla \times \mathbf{F}) \cdot \mathbf{n} \, d\Omega = \int \int_{\Omega} \mathbf{H} \cdot \mathbf{n} \, d\Omega, \quad (8)$$

where $\mathbf{t}$ is a unit vector tangent to Γ at each point and $\mathbf{n}$ is a unit vector normal to Ω ; the orientations of $\mathbf{t}$ and $\mathbf{n}$ are related through the *right-hand-rule*. $\nabla \times \mathbf{F}$ is the conventional notation for the curl of a vector field. Using the auxiliary spherical coordinates system in Fig. 1 (right), the domains of integration, the tangent and normal unit vectors, and the Jacobian determinants for the integration may be explicitly computed:

$$\int_{\Gamma} \mathbf{F} \cdot \mathbf{t} \, d\Gamma = \int_0^{2\pi} \widetilde{F}_{\nu}\left(q_0, \frac{\pi}{2}, \nu\right) q_0 d\nu; \quad (9)$$

$$\int \int_{\Omega} \mathbf{H} \cdot \mathbf{n} \, d\Omega = - \int_0^{q_0} \int_0^{2\pi} \widetilde{H}_{\xi}\left(q, \frac{\pi}{2}, \nu\right) q d\nu dq, \quad (10)$$

where $\tilde{F}$ and $\tilde{H}$ are the representations of F and H in this system, and $\tilde{F}_\nu$ and $\tilde{H}_\xi$ their projections in the unit directions e_ν and e_ξ orthogonal to the isosurfaces of ν and ξ . The minus sign in eq. (10) is necessary since e_ξ follows the opposite direction to the normal vector n . Identifying corresponding terms in eqs. (7) (or (6)) and (10), it is clear that the attenuation signal E (or its Laplacian) has to be related to the component of H in the direction of e_ξ . The other components of H (H_q and H_ν) are orthogonal to e_ξ , and therefore do not contribute to the flux integral in eq. (8). The estimates in eqs. (6) and (7) may thus be written as the flux across Ω of the following vector fields:

$$\widetilde{H^\Phi} = \widetilde{H^\Phi}_\xi e_\xi = \frac{1}{8\pi^2} \widetilde{\Delta E}(q, \xi, \nu) e_\xi. \quad (11)$$

$$\widetilde{H^\Psi} = \widetilde{H^\Psi}_\xi e_\xi = -\frac{1}{2} \tilde{E}(q, \xi, \nu) e_\xi. \quad (12)$$

For each direction of interest r , the auxiliary system, and thus e_ξ , changes. As a consequence, H is different for each r , and has to be expressed in terms of the curl of a given field F to be computed using the expression of this differential operator in spherical coordinates. Since H follows the direction of e_ξ at each point, only this component has to be considered, yielding:

$$\nabla \times \tilde{F} = \tilde{H} \Rightarrow \frac{1}{q \sin(\xi)} \left(\frac{\partial \tilde{F}_q}{\partial \nu} - \sin \xi \frac{\partial q \tilde{F}_\nu}{\partial q} \right) = \tilde{H}_\xi. \quad (13)$$

The boundary Γ of Ω is tangent at each point to the unit vector e_ν (see Fig. 1). From eq. (9), it is evident that the components of F orthogonal to e_ν (i.e., F_q and F_ξ) are perpendicular to the trajectory of integration, and they do not contribute to the circulation along Γ . Consequently, the term F_q may be dropped down and eq. (13) is equivalent to:

$$\tilde{H}_\xi(q, \xi, \nu) = -\frac{1}{q} \frac{\partial q \tilde{F}_\nu(q, \xi, \nu)}{\partial q}. \quad (14)$$

For each H_ξ in eqs. (11) or (12), eq. (14) has to be solved for F_ν . The corresponding estimators may be easily computed using eq. (9):

$$\Phi(r) \simeq \frac{1}{2} \int \int_\Omega \frac{-\Delta E(q)}{4\pi^2} d\Omega = \int_\Gamma \tilde{F}^\Phi \cdot t \quad d\Gamma = \int_0^{2\pi} \tilde{F}_\nu^\Phi(q_0, \frac{\pi}{2}, \nu) q_0 d\nu, \quad (15)$$

where $\tilde{F}_\nu^\Phi$ is the result of solving eq. (14) for $\tilde{F}_\nu$, with $\tilde{H}_\xi$ corresponding to $\tilde{H}^\Phi$ in eq. (11). Accordingly, for $\Psi(r)$:

$$\Psi(r) \simeq \int_0^{2\pi} \tilde{F}_\nu^\Psi \left(q_0, \frac{\pi}{2}, \nu \right) q_0 d\nu. \quad (16)$$

Both estimators can now be written in terms of integrals along Γ , where $E(q)$ may be characterized from the HARDI data set. To this point, the only source of error in the estimators is the part of the integral over Π which is neglected (the subset outside the disk

Ω), since the line integrals in eqs. (15) and (16) are identical to their bi-dimensional counterparts in eqs. (6) and (7). It only remains to solve eq. (14) for F_v to explicitly evaluate the estimators. The following Sections give particular solutions to this problem for known estimators.

2.2 Circulation-based OPDT

The OPDT is based on the integration of the Laplacian of the attenuation signal. Integrating E in the plane Π orthogonal to the direction of interest r , the true marginal probability of diffusion along this direction (the OPDF) is computed. In spherical coordinates, the Laplacian may be represented as:

$$\Delta E(q) = \frac{1}{q^2} \Delta_q E(q) + \frac{1}{q^2} \Delta_b E(q) = \frac{1}{q^2} \frac{\partial}{\partial q} \left(q^2 \frac{\partial E(q)}{\partial q} \right) + \frac{1}{q^2} \Delta_b E(q), \quad (17)$$

where Δ_b is the Laplace-Beltrami operator. The first term in eq. (17) is the radial part, whose representation in the auxiliary system of Fig. 1 is exactly the same, since the radial coordinate q is the same in both systems. Its integral over the plane Π may be explicitly computed integrating by parts, and it equals -2π (Aganj et al., 2009a). This result is demonstrated in Appendix B. The integral related to the Laplace-Beltrami operator cannot be explicitly computed, so the methodology proposed in the previous Section has to be used. In this case, eq. (14) particularizes to the following expression:

$$\frac{\widetilde{\Delta_b E}(q, \xi, \nu)}{8\pi^2 q^2} = -\frac{1}{q} \frac{\partial q \widetilde{F_\nu^\Phi}(q, \xi, \nu)}{\partial q} \Rightarrow \frac{-\widetilde{\Delta_b E}(q, \xi, \nu)}{8\pi^2 q} = \frac{\partial q \widetilde{F_\nu^\Phi}(q, \xi, \nu)}{\partial q}. \quad (18)$$

The previous equation involves radial derivatives of $\widetilde{F_\nu^\Phi}$. Obviously, they cannot be characterized from the HARDI data set, since it is sampled in an isosurface tangent to e_q . The solution proposed by Tristán-Vega et al. (2009b) is to assume a slow variation of the Apparent Diffusion Coefficient (ADC) in an environment of q_0 . Note that this condition is far less restrictive than the mono-exponential decay assumed by Aganj et al. (2009a). Yet, it allows to analytically find a closed form solution for eq. (18). In particular, it is demonstrated in Appendix C that the following approximation holds whenever the ADC slowly varies near q_0 :

$$\widetilde{F_\nu^\Phi}(q_0, \xi, \nu) \simeq \frac{-1}{16\pi^2 q_0} \Delta_b E_{in} \left(4\pi^2 \tau q_0^2 \widetilde{D}(q_0, \xi, \nu) \right), \quad (19)$$

where E_{in} is the non-singular exponential integral described in Appendix E. Eq. (19) may be casted into eq. (15) to compute the estimate of the integral of the angular Laplacian. Finally, the OPDF is estimated joining this result with that in Appendix B for the integral of the radial Laplacian:

$$\begin{aligned} \Phi(r) &\simeq \int_0^{2\pi} \frac{-1}{16\pi^2 q_0} \Delta_b E_{in} \left(4\pi^2 \tau q_0^2 \widetilde{D}(q_0, \frac{\pi}{2}, \nu) \right) q_0 d\nu + \frac{-1}{8\pi^2} (-2\pi) \\ &= \frac{-1}{16\pi^2} \int_0^{2\pi} \Delta_b E_{in} \left(4\pi^2 \tau q_0^2 \widetilde{D}(q_0, \frac{\pi}{2}, \nu) \right) d\nu + \frac{1}{4\pi} \\ &= \frac{-1}{16\pi^2} \int_0^{2\pi} \Delta_b E_{in} \left(-\log \left(\widetilde{E}(q_0, \frac{\pi}{2}, \nu) \right) \right) d\nu + \frac{1}{4\pi}. \end{aligned} \quad (20)$$

This estimator is an alternative to the OPDT intended to reduce the blurring due to the computation of the FRT. It has two main sources of error: first, the angular part of the Laplacian is not integrated in the whole plane Π , but only over the subset $\Omega \subset \Pi$. This distortion may be reduced increasing the b -value (i.e., increasing the radius q_0 of the sampling sphere). Compared to the OPDT, this is a clear advantage, since the problems of the OPDT are especially noticeable for larger b -values. Second, the ADC has to be supposed constant in a local sense in an environment of q_0 . Since this is the same assumption required to compute the OPDT, the new approach does not introduce a new source of error in this sense.

2.3 Circulation-based Q-Balls

Q-Balls is an estimator of the ODF, $\Psi(r)$. It may be generalized particularizing eq. (14) for the $\widetilde{H\Psi}$ in eq. (12):

$$-\frac{1}{2}\tilde{E}(q, \xi, \nu) = -\frac{1}{q} \frac{\partial q \widetilde{F_{\nu}^{\Psi}}(q, \xi, \nu)}{\partial q} \Rightarrow \frac{q}{2}\tilde{E}(q, \xi, \nu) = \frac{\partial q \widetilde{F_{\nu}^{\Psi}}(q, \xi, \nu)}{\partial q}. \quad (21)$$

Once again, the presence of a radial derivative imposes the weak assumption of a locally constant ADC. The same procedure described in Appendix C applies here. Yet, the integration of the partial derivatives equation is much easier, so that the following result can be easily proved (Tristán-Vega et al., 2009a):

$$\Psi(r) \simeq \frac{q_0^2}{4} \int_0^{2\pi} \frac{1 - \tilde{E}(q_0, \frac{\pi}{2}, \nu)}{-\log(\tilde{E}(q_0, \frac{\pi}{2}, \nu))} d\nu. \quad (22)$$

This estimator shares the two drawbacks of that in eq. (20). In this case, it indeed needs an extra assumption with respect to Q-Balls, which is the slow variation of the ADC.

2.4 Alternative estimators of orientation information

A keystone in our methodology is to avoid hard restrictions on the behavior of the diffusion signal. As opposed to the works by Aganj et al. (2009a); Canales-Rodríguez et al. (2009), where a global mono-exponential behavior is assumed as a working hypothesis, we only impose a very weak restriction, the local slow variation of the ADC. This assumption has been shown very realistic in practical scenarios (Tristán-Vega et al., 2009b). If our general model is particularized to the case of mono-exponential attenuation signals, the methodology presented naturally leads to the derivation of the estimators for the OPDF and the ODF proposed, respectively, by Aganj et al. (2009a) and Canales-Rodríguez et al. (2009):

$$\Phi(r) \simeq \frac{1}{16\pi^2} \int_0^{2\pi} \Delta_b \log \left(-\log \left(\tilde{E} \left(q_0, \frac{\pi}{2}, \nu \right) \right) \right) d\nu + \frac{1}{4\pi}; \quad (23)$$

$$\Psi(r) \simeq \frac{q_0^2}{4} \int_0^{2\pi} \frac{-d\nu}{\log\left(\tilde{E}\left(q_0, \frac{\pi}{2}, \nu\right)\right)}. \quad (24)$$

The key is to realize that, with the mono-exponential model, the solutions for $\widetilde{F}_\nu^\Phi$ and $\widetilde{F}_\nu^\Psi$ are valid for all q , and not only q_0 . Then, Stokes' theorem may be used for an equator Γ with arbitrary radius q . Taking the limit when q approaches infinity, the disk Ω tends to the plane Π , and the resulting integral tends to the exact value of the radial integral in the domain of the diffusion propagator. This methodology is used in Appendix D to derive the main result by Aganj et al. (2009a), i.e. eq. (23), under our own framework.

3 Methods

3.1 Practical implementation of the estimators. Relation with the FRT

Four estimators have been discussed, corresponding to eqs. (20), (22), (23), and (24). The first two are based on the circulation of a vector field along Γ , so they will be referred to as cOPDT and cQ-Balls, where 'c' stands for 'circulation'. The other two estimators are based on the integration of a given function in the whole plane Π , and will be referred to as pOPDT and pQ-Balls, where now 'p' stands for 'plane'. All these estimators can be reduced to the integral of a given function, somehow related to $E(q)$, in an equator perpendicular to the direction of interest, r . Therefore, they can be computed as the FRT, $\mathcal{G}\{f(q)\}(r)$, of such function. Table 1 shows a summary of these estimators.

The interpretation in terms of the FRT allows to use the Spherical Harmonics (SH) implementation proposed by Anderson (2005); Descoteaux et al. (2007); Hess et al. (2006), and to compute the FRT of a function sampled at S by means of simple matrix operations. The application of the Laplace-Beltrami operator Δ_b is equally simple, as described in Tristán-Vega et al. (2009b). For the sake of brevity, only a representative example is given in the next Section for the OPDT, which may be easily extrapolated to the remaining techniques.

3.2 A short comment on the implementation of the OPDT

Given the $N \times 1$ vector of sampled values of $E(q)$, E , the $H \times 1$ vector of SH coefficients ($H < N$), C , is computed by means of Least Squares (LS):

$$C = (B^T B + \lambda L^2)^{-1} B^T E, \quad (25)$$

where B is an $N \times H$ matrix whose $\{n, h\}$ element is the evaluation of the h -th SH basis function at the n -th gradient direction. L is an $H \times H$ diagonal matrix whose entries are the eigenvalues of the SH basis functions associated to the Laplace-Beltrami operator; λ is a Tikhonov regularization term. Thus, the SH coefficients of the angular part of the Laplacian can be computed as:

$$C_{\Delta_b} = L (B^T B + \lambda L^2)^{-1} B^T E. \quad (26)$$

The radial part is directly estimated from E assuming a slow-varying ADC, and then expressed in the basis of SH:

$$C_{\Delta_q} = \left(B^T B + \lambda L^2 \right)^{-1} B^T [-2D (3 - 2D) E], \quad (27)$$

where brackets $[\cdot]$ denote element-wise operations and $D = [-\log E]$. Next, the property of SH being eigenfunctions for the FRT is exploited: the vector of SH coefficients is multiplied by the $H \times H$ diagonal matrix F whose entries are the eigenvalues associated to the FRT, see Descoteaux et al. (2007):

$$\begin{aligned} C_{OPDT} &= \mathcal{F} \left(C_{\Delta_b} + C_{\Delta_q} \right) \\ &= \mathcal{F} L \left(B^T B + \lambda L^2 \right)^{-1} B^T E - \mathcal{F} \left(B^T B + \lambda L^2 \right)^{-1} B^T [2D (3 - 2D) E]. \end{aligned} \quad (28)$$

It remains to evaluate the OPDF at the directions of interest by simply taking:

$$P_{OPDT} = \frac{-1}{4^2 \pi q_0^2} B' \mathcal{F} \left(C_{\Delta_b} + C_{\Delta_q} \right), \quad (29)$$

where B' is an $N' \times H$ matrix with the evaluations of the OPDF at the desired directions. Further details on these developments may be found in Tristán-Vega et al. (2009b). Table 2 describes the corresponding implementations for the other estimators previously discussed.

As a final remark, there is an error in our previous work (Tristán-Vega et al., 2009b) we would like to point out¹. For the first term in eq. (28), it is said that L and $(B^T B + \lambda L^2)^{-1}$ are symmetric and *therefore they commute*. This is obviously not true. The condition for two matrices to commute is that they share the same eigenspace, which for L^2 is the canonical basis since it is diagonal. For the LS matrix, in general this is not the case. Yet, it is usually a well conditioned matrix; in the ideal scenario, all its eigenvalues would be equal, and so its eigenspace would be the same as that of L^2 . In practice, the eigenvalues are not equal but only similar, so this condition is not strictly met, and eq. (B.11) in Tristán-Vega et al. (2009b) is only a good approximation.

3.3 Setting-up of the experiments

The methodology for numerical validation is the same carried out in Tristán-Vega et al. (2009b). We study the capability to resolve crossing fibers in different scenarios, which are characterized by the b -value, the number of sampling gradients N , and the noise power σ_n^2 (or, alternatively, the Peak Signal to Noise Ratio, PSNR) as described in Table 3. Two synthetic tensors are generated, with eigenvalues $[1.8, 0.2, 0.2] \cdot 10^{-3} \text{mm}^2/\text{s}$, partial volume fractions 1/2 each, and principal eigenvectors in the XY plane forming an angle of α degrees. The ground-truth $E(q)$ is generated directly from eq. (1). The local maxima of the orientation functions are computed with arbitrary precision, from the continuous representation provided by SH coefficients, in the following way:

¹The authors would like to express their gratitude to Iman Aganj for reporting this error and discussing its implications.

1. A regular grid in the (θ, φ) plane is created with enough resolution so that the ground-truth maxima cannot be mixed-up, and the corresponding orientation function is exactly evaluated at the nodes of such grid by means of SH expansions.
2. The local maxima are found in that grid, and a local grid with higher resolution is centered at each detected maximum.
3. The previous step is repeated for each new local maxima, until the resolution of the grids allows to find their positions with a predefined angular error (we have chosen 10^{-3} degrees).

These maxima are compared to ground-truth directions whenever both of them are detected. If more than two maxima are detected, we keep those corresponding to the largest two values. The angular errors reported refer to mean values among the two fibers and all Montecarlo trials (for noisy scenarios).

For comparison purposes, all the estimators reviewed in Table 1, plus the DOT by Özarslan et al. (2006), are included in the analysis. To better organize such large amount of information, results have been split in two groups: on one hand, those related with the estimation of the ODF, $\Psi(r)$; on the other, the ones related to the estimation of the OPDF, $\Phi(r)$. Regarding the DOT, it is intended to estimate the probability profile at a given distance R_0 , $Y(r) = P(R_0r)$. Since the performance of the DOT is closer to that of the OPDT than it is to Q-Balls, its results are grouped in this second category.

SH expansions up to order $L = 6$ ($H = 28$ SH coefficients) have been taken, with $\lambda = 0.006$ (see Descoteaux et al. (2007) for details). For the DOT, we use $R_0 = 12\mu m$. Although higher values can yield a better resolution accuracy, they result in a little robustness to noise, as it has been pointed out by Pr kowska et al. (2008). Hence, $R_0 = 12\mu m$ is preferable in real-world scenarios (Özarslan et al., 2006), and it is the trade-off used in all our experiments. For the noisy scenarios, we introduce a Rician distributed distortion (Gudbjartsson and Patz, 1995). This is done by adding a complex Gaussian process with variance σ_n^2 to $E(q)$ and taking its real envelope.

4 Results

4.1 Capability of resolving two crossing fibers

4.1.1 ODF estimators—Fig. 2 illustrates the angular error in the detected fibers compared to the ground-truth directions, as a function of the initial angle between them. The performance for all the estimators compared is very similar, as previously reported in our preliminary work (Tristán-Vega et al., 2009a). Nevertheless, pQ-Balls shows a greater error for low b -values, and its resolution capability is poorer than that of the other two estimators: it fails to correctly recover the two crossing fibers for larger angles than Q-Balls or cQ-Balls. For higher b -values, the resolution capability is practically the same for all the estimators, although the error committed by pQ-Balls is still slightly higher. Comparing cQ-Balls with Q-Balls, the former performs better practically in all situations. Although its advantage is only slightly noticeable, cQ-Balls shows a better resolution capability and lower detection errors. Fig. 3 shows glyph representations of the three estimators for

scenario S-4. The differences in the shapes of the estimations are completely negligible, corresponding to the behavior observed in Fig. 2. This first experiment allows to conclude that the error introduced by the computation of the FRT in fact is not so relevant: the reduction in the radial blurring achieved by cQ-Balls with the integration inside Ω is almost compensated by the need to assume a locally constant ADC, so that the overall advantage is only marginal. On the other hand, pQ-Balls allows to completely remove the radial blurring, but at the expense of imposing a much more restrictive model, i.e. a constant ADC for all q ; the performance of pQ-Balls is noticeably worsened for this reason, especially for lower b -values. Therefore, and at least for the estimation of $\Psi(r)$, it follows that the error due to the FRT is comparable to the error in the assumption of a slowly varying ADC, but lower than the error due to the assumption of an absolutely constant ADC.

4.1.2 OPDF estimators—The counterpart of Fig. 2 for the estimators of the OPDF is shown in Fig. 4. In this case, the results are more difficult to interpret. For low b -values, the advantage of the cOPDT is clear. The resolution capability is drastically improved, and the detection errors, especially with few gradient directions, are also reduced. For scenario S-2, however, the OPDT and the pOPDT may be preferable to resolve fiber crossings in large angles. Now, the pOPDT based on the assumption of a constant ADC yields a very similar behavior to the OPDT (contrary to Q-Balls, the OPDT needs a weak assumption on the ADC, so the pOPDT introduces a lighter change in the model with respect to the OPDT than pQ-Balls does with respect to Q-Balls). With regard to the DOT, it shows a poorer accuracy, which is especially noticeable for low b -values. Note that using a higher value of R_0 in this noiseless scenario would improve the estimates (at the expense of not being so representative of a practical situation), but the difference with OPDT-like estimators is still quite important. The pOPDT and the DOT share the same model for the attenuation signal and almost the same numerical implementation, so it becomes evident that the different behavior comes from the different orientation functions estimated. The importance of estimating true probabilistic information is demonstrated by this comparison. For larger b -values, the situation is different. First, both the pOPDT and the cOPDT show a very well differentiated local minimum for low input crossing angles. This artifact, although quite subtle, is appreciated as well in the OPDT, and can be explained in terms of the error in the estimation of the radial Laplacian (Tristán-Vega et al., 2009b). With the other estimators, the effect for high b -values is even more obtrusive. Yet, the peak for the cOPDT is more noticeable, appearing even for low b -values, contrary to the other estimators compared. As discussed later, the possible origin of this artifact is the error committed when approximating the integral in the plane by the integral in the disk Ω ; it will be shown that the error (and, what is more important, the variability of this error among all possible orientations) is reduced when the orientations of both fibers get closer. This effect, together with the higher accuracy of the locally constant ADC model for small angles, could explain the fast decay of the angular error, before the estimator is finally unable to resolve the fiber crossing. Comparing the performance of the estimators, the cOPDT is still the one resolving lower crossing angles, followed by the pOPDT. However, for larger crossing angles, the OPDT is preferable due to its higher accuracy. Even the DOT can yield better results for nearly orthogonal fiber crossings. Nevertheless, neither the cOPDT nor the pOPDT show the theoretical limitation of the OPDT for arbitrarily high b -values, so they are still an

interesting choice. In particular, the pOPDT shows a good trade-off between the resolution capability of the cOPDT and the accuracy of the OPDT. To finish this discussion, Fig. 5 shows glyph representations of the estimators compared in this Section. The shape of the estimate by the OPDT is sharper, although both the cOPDT and the pOPDT yield also well defined lobes.

4.2 Behavior in the presence of noise

4.2.1 ODF estimators—Fig. 6 shows the angular errors in a noisy environment (see Table 3), averaged for 100 Montecarlo trials. The first conclusion is that Q-Balls and cQ-Balls behave practically the same. Although cQ-Balls is slightly more accurate for low b -values, Q-Balls seems to perform better for higher b -values (although for S-5 cQ-Balls shows a better resolution capability). But concerning pQ-Balls, it is clearly less robust to noise, with much higher angular errors and, in general, a worse capability to resolve crossing fibers (except for scenario S-4; however, this result seems not very conclusive). To give a deeper insight into the effect of noise for the estimators of the ODF, Fig. 7 shows glyphs for S-2, for an angle of 90° . While the shapes of the ODF recovered by both Q-Balls and cQ-Balls are very similar, pQ-Balls clearly fails to recover the orientation information, yielding an inadequate estimation. The conclusion is that pQ-Balls is far more sensitive to noise than the other estimators.

4.2.2 OPDF estimators—Fig. 8 is the counterpart for the corresponding estimators of the ODF in Fig. 6. The obvious conclusion is that the OPDT is more robust to noise than both the cOPDT and the pOPDT. But for low b -values (and for scenario S-5), the cOPDT has still an important advantage recovering small crossing angles. For high b -values, the cOPDT and the pOPDT have a similar behavior (the pOPDT yields more accurate estimates but the cOPDT has a slightly better resolution capability): the estimation accuracy is worsened so that it gets close to that of the DOT, losing in part the advantage of the OPDT over this estimator. Note, however, that the DOT fails to recover the fiber crossing before the cOPDT and the pOPDT do. In these cases, the OPDT shows a very similar resolution capability, but it is notably more accurate. Generally speaking, the FRT-based estimators are more robust to noise than their ‘circulation’ and ‘plain’ counterparts. This observation may be explained by the averaging inherent to the FRT: the integration inside the Bessel-shaped tubes blurs the orientation information yielding poorer estimates, but at the same time averages the radial information, partially palliating the effect of noise. Finally, Fig. 9 shows glyphs for scenario S-2 and PSNR=13.33. Although not so evident as it is for pQ-Balls, the higher sensitivity to noise of the pOPDT is still noticeable. This estimator yields unnatural shapes for the OPDF, with flattened surfaces and a large blurring (and thus a greater uncertainty) in the direction of local maxima. Comparing the OPDT and the cOPDT, the former is almost unaltered by the presence of such large amount of noise, while the latter shows a certain distortion in the recovered OPDF. This is consistent with the higher angular errors measured for the cOPDT in Fig. 8.

4.3 Accuracy of the integrals in the disk Ω

This Section is focused on the study of the error committed in the approximation of the integrals in the plane Π as integrals in the disk $\Omega \subset \Pi$. This analysis allows to partially

justify the non-monotonic behavior of the curves in Fig. 4. The same tensor configuration as in the previous experiments has been used. For each input angle between the fibers, 51 gradient directions $\mathbf{r}$ uniformly distributed on the surface of the sphere have been chosen. For each of them, the integral of the Laplacian of the attenuation signal is computed in the whole plane Π (this integral is denoted I_p), and inside the disk Ω (denoted I_c), for a range of values of q_0 . The relative error is defined as:

$$\epsilon = \frac{I_p - I_c}{I_p} > 0, \quad (30)$$

where I_p is negative (it is the opposite of a probability density), but I_c is not necessarily. The most representative results are depicted in Fig. 10. The following conclusions can be drawn from this experiment:

- Even when the relative errors are large, the disk approximation is far more accurate than the approximation as the integral along the boundary of Ω , and it avoids the theoretical limitations of the OPDT.
- The relative error ϵ decreases as the fibers get closer. Moreover, the difference in the relative error among the directions $\mathbf{r}$ (and hence the angular distortion) becomes smaller with decreasing crossing angles.

The second point is a possible explanation of the non-monotonic behavior of the error curves presented in Fig. 4. One important source of error with the cOPDT is the approximation of the plane integral. As it is suggested by the previous result, this error is notably reduced as the input angle decreases, which justifies that the error in the detected fibers is also smaller. When the input angle is excessively small, other sources of error, such as the inherent blurring of the orientation information, or the finite resolution capability of SH basis functions, become more important, and the error rapidly increases until it is impossible to distinguish between the two fibers.

Together with the error in the integration, there is another side effect which partially justifies the non-monotonic behavior of OPDT-like estimators. As it has been reported by Tristán-Vega et al. (2009b), the local (for the OPDT and the cOPDT) or global (for the pOPDT) assumption on the slow variation of the ADC introduces an error which is also less important if the fiber bundles are close enough.

4.4 In vivo experiments

We use a HARDI volume of an informed volunteer, scanned in a 1.5 Tesla GE Echospeed system (Scanning Sequence: Max. gradient amplitudes: 40 mT/M. Rectangular FOV 220×165 mm. 128×96 scan matrix (256×192 image matrix); 4 mm slice thickness, 1 mm interslice distance. Receiver bandwidth 6kHz. TE 70 ms; TR 80 ms (effective TR 2500 ms). Scan time 60 seconds/slice). It comprises 8 non-weighted baseline images and 51 independent gradient directions with diffusion weighting parameter $b = 700 \text{ s/mm}^2$. Like in Tristán-Vega et al. (2009b), we deliberately choose such a small b -value to test the proposed estimators in very extreme conditions. The data set has been denoised with the filter proposed by Tristán-Vega and Aja-Fernández (2008). It has been shown that the presence of

noise notably worsens the resolution accuracy of all fiber populations estimators, especially those based on the OPDT and the DOT. Given that DWI data sets usually show a poor SNR due to the attenuation induced by the sensitizing gradients, this step is of great importance.

Two sample slices of this volume are represented in Fig. 11. Accordingly, the Regions of Interest (ROI) marked in the figure are analyzed in Fig. 12, with glyph representations similar to Fig. 5 for the cOPDT. This estimator is able to correctly resolve the architectures of fiber bundles even for such small b -value. Multiple crossing structures are well resolved: for slice 15, the mcp and the pct on the lateral sides are perfectly distinguishable (see in particular the selected ROI). For slice 23, the red structure which is hardly visible in Fig. 11 is well noticeable in Fig. 12: the scp bends over itself forming the fiber crossings appreciated in the center of the image. In the small ROI selected on Fig. 12, right, the color-coding image suggests that the scp, once again, is rapidly bending where the dominant color changes from green to blue. For convenience, the small ROI in Fig. 12 are detailed in Fig. 13, comparing all OPDT-based techniques. As it was predicted in the previous Sections, the pOPDT shows an overall poorer performance than the other estimators. For slice 15, the lobes are more blurred and difficult to interpret, and yet the spatial coherence of the glyphs is not so obvious. For slice 23, the smaller robustness to noise of this technique becomes evident. Most of the voxels show incoherent representations which are completely unintelligible. Comparing now the OPDT and the cOPDT, their behavior is virtually the same for the ROI in slice 15. For slice 23, however, some differences may be appreciated: the cOPDT is able to resolve the bending of fibers for most of voxels, while the OPDT is not. All these comments are completely consistent with the results obtained for synthetic data. As a final result, Fig. 14 shows analogous results to those in Fig. 13, for slice 15, without the denoising stage. The spatial coherence of the estimated fibers is almost lost. According to the experiments with synthetic data, the estimates are greatly prejudiced by a poor SNR. Besides, more spurious lobes appear in all the glyphs, so that it results difficult to interpret them. Nonetheless, there are some regions (like that highlighted in the image) for which the glyphs show now a better angular contrast, so it may be concluded that the filtering stage introduces a certain blurring. Even so, it remains evident comparing Figs. 13 and 14 that the preconditioning of the DWI signals is necessary to achieve adequate estimates. Note, however, that this is an extreme case with a very low b -value; in a practical situation, OPDT-like estimators will be still less robust to noise than Q-Balls, but, according to our experience, the effect of noise will not be as severe as it is suggested by Fig. 14.

5 Discussion

The FRT has been proved an extremely valuable mathematical tool for HARDI estimators, beyond its direct use as an estimator of orientation information. This kind of information is computed as (weighted) line integrals of $P(R)$ along the directions of interest, whose calculation has to be carried out in the dual Fourier domain (the q -space). A line integral in the R -space is equivalent to an integral in the orthogonal plane of the q -space. Due to the symmetry of the problem, this plane has to be parametrized using polar coordinates: the FRT represents the integration on the angular coordinate of such system, which explains the ubiquitousness of this operator in the techniques presented.

With Q-Balls and the OPDT, the FRT is used directly as an estimator, so the radial integral in the aforementioned polar coordinates system is ignored. Obviously, this is an important source of error, but at the same time it allows to get rid of any assumption on the behavior of the attenuation signal (for Q-Balls) or at least of strong assumptions (for the OPDT). A number of techniques to minimize the effect of this source of error have been discussed, varying the modeling assumptions of $E(q)$. For the estimators of $\Psi(r)$ (based on Q-Balls), it has been shown that the error introduced by unrealistic models may be more important than the blurring due to the FRT: cQ-Balls is only marginally better than Q-Balls, and pQ-Balls performs worse and is more sensitive to noise. For the estimators of $\Phi(r)$, on the contrary, the advantage of reducing the FRT blurring has been evidenced. The novel cOPDT shows a better resolution capability and higher accuracy than the OPDT for low b -values; for high b -values, its accuracy is worse than that of the OPDT, but its resolution capability is still better. The cOPDT does not require additional assumptions with respect to the OPDT, so alleviating one of its sources of error may drive to better results. Yet, the pOPDT may perform similar to the OPDT for low b -values (for high b -values, it shows a better resolution capability, although its accuracy is poorer), even when the modeling of the attenuation signal for the pOPDT is far more restrictive.

Generally speaking, there are two fundamental sources of error in the estimation: the error in the estimation of radial integrals (which is reduced with the cOPDT and completely removed with the pOPDT), and the error due to the incorrect modeling of the attenuation signal (which is more severe for the pOPDT; although the OPDT and the cOPDT share the same model, at the sight of Fig. 4 it seems that the integration of such model to apply Stokes' theorem is more sensitive to the error than its derivation to compute the radial Laplacian). The reduction of one of these errors has to be done at the expense of increasing the other, and therefore a trade-off has to be achieved.

The estimation techniques not directly using the FRT yield results which are less robust to noise than those obtained by the direct application of the FRT. This fact may be explained by the elimination of the FRT averaging. Nevertheless, the noisy scenarios tested in the numerical simulations are extreme cases, with a very poor SNR. Moreover, the use of filtering techniques may drastically improve the quality of the HARDI data-sets, so the new estimators may indeed prove advantageous in many situations. Their adequacy is justified by the experiments performed over real data sets.

In particular, the results in Fig. 4 suggest very useful guidelines to choose the appropriate estimator for a particular situation, assuming that the denoising step allows to consider a high enough SNR. These guidelines may be seen as an heuristic to determine the aforementioned trade-off between the contributions of each source of error. For low b -values, it seems clear that the cOPDT is the best choice. For high b -values, the OPDT should be used unless very small crossing angles need to be detected (this could be the case for particular regions of the brain like the cerebellar peduncle). In this case, the pOPDT may be more appropriate, but if a high enough SNR cannot be assumed, the cOPDT is preferable (see for example Fig. 9). Additionally, it is important to stress that neither the cOPDT nor the pOPDT show the theoretical limitation of the OPDT for arbitrarily high b -values, so they can be used regardless of the scanning parameters. Besides, the cOPDT does not require any

additional assumption on $E(q)$ with respect to the OPDT, as opposed to the pOPDT, which is an important advantage. Finally, Q-Balls-related estimators, and above all cQ-Balls, can be very interesting in case only large angles have to be detected, due to their higher robustness to noise. On the other hand, they have the additional drawback of a reduced angular contrast, and as a result the estimated ODF has to be further processed (min-max normalization) to achieve a convenient visualization, see Figs. 3 and 7. A brief summary of this discussion is sketched in Table 4.

Additionally, the usefulness of the estimation of true probabilistic information remains evident from the presented results. In general terms, the pOPDT shows an overall worse accuracy than the OPDT and the cOPDT, but yet it is more accurate and has a better resolution capability than the DOT. Except for very wide crossing angles, its robustness to noise is also higher. The modeling of the attenuation signal, based on a constant ADC for all q , is exactly the same for the pOPDT and the DOT. Their numerical implementations, based on SH expansions and analytical integration, are also very similar. Consequently, the origin of their different performances has to be the different orientation information estimated by each of them: only the pOPDT estimates a true marginal probability density.

As a final remark, it is interesting to discuss the recent methodologies based on multiple-shells sampling, such as those by Aganj et al. (2009b); Descoteaux et al. (2009). If more than one b -value are available, multi-exponential models can be easily fitted (Özarslan et al., 2006). The attenuation signal can then be expressed as the linear superposition of several mono-exponential signals without any significant error. In that case, the methodology proposed in the present paper is not so useful: since the modeling error is almost null, the pOPDT first proposed by Aganj et al. (2009a) is more appropriate, since the exact integral in the orthogonal plane is analytically computed, and hence the two sources of error are fully avoided (Aganj et al., 2009b). Therefore, our methodology is restricted to HARDI (and not DSI or HYDI) data sets.

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Appendix

A The central section theorem

The integral of $P(R)$ (resp. $R^2P(R)$) along r may be easily computed from eq. (3) (resp. eq. (2)) using the auxiliary coordinates system of Fig. 1, left:

$$\begin{aligned}
\Psi(\mathbf{r}) &= \frac{1}{2} \int_{-\infty}^{\infty} P(R\mathbf{r}) dR = \frac{1}{2} \int_{-\infty}^{\infty} \tilde{P}(u, \beta, \vartheta) d\vartheta|_{u=0} \\
&= \frac{1}{2} \int_{-\infty}^{\infty} \left(\int_0^{\infty} \int_0^{2\pi} \int_{-\infty}^{\infty} \tilde{E}(t, \alpha, z) \exp(-j2\pi(0+z\vartheta)) t dz d\alpha dt \right) d\vartheta \\
&= \frac{1}{2} \int_0^{\infty} \int_0^{2\pi} \int_{-\infty}^{\infty} \tilde{E}(t, \alpha, z) \left(\int_{-\infty}^{\infty} \exp(-j2\pi z\vartheta) d\vartheta \right) t dz d\alpha dt \quad (\text{A.1}) \\
&= \frac{1}{2} \int_0^{\infty} \int_0^{2\pi} \left(\int_{-\infty}^{\infty} \tilde{E}(t, \alpha, z) \delta(z) dz \right) t d\alpha dt \\
&= \frac{1}{2} \int_0^{\infty} \int_0^{2\pi} \tilde{E}(t, \alpha, 0) t d\alpha dt,
\end{aligned}$$

where $\tilde{P}$ and $\tilde{E}$ are respectively the cylindrical coordinates representations of P and E in the system of Fig. 1, left, and δ stands for Dirac's delta distribution. The last term in eq. (A.1) is obviously the integral of the attenuation signal in the 'xy' plane of the auxiliary system (note the presence of the Jacobian of polar coordinates, t). Translated to real-world coordinates, this plane Π is that orthogonal to $\mathbf{r}$ and intersecting the origin.

B Integration of the radial projection of the Laplacian

For the first term in eq. (17), and integrating by parts in q :

$$\begin{aligned}
&\int \int_{\Pi} \frac{1}{q^2} \widetilde{\Delta_q E}(q, \xi, \nu) d\Pi = \int_0^{2\pi} \int_0^{\infty} \frac{1}{q^2} \frac{\partial}{\partial q} \left(q^2 \frac{\partial \tilde{E}(q, \frac{\pi}{2}, \nu)}{\partial q} \right) q dq d\nu \\
&= \int_0^{2\pi} \left(\left[q \frac{\partial \tilde{E}(q, \frac{\pi}{2}, \nu)}{\partial q} \right]_0^{\infty} + \int_0^{\infty} \frac{\partial \tilde{E}(q, \frac{\pi}{2}, \nu)}{\partial q} dq \right) d\nu \quad (\text{B.1}) \\
&= \int_0^{2\pi} \left(\lim_{q \rightarrow \infty} q \frac{\partial \tilde{E}(q, \frac{\pi}{2}, \nu)}{\partial q} + \lim_{q \rightarrow 0} \tilde{E}(q, \frac{\pi}{2}, \nu) - \tilde{E}(0, \frac{\pi}{2}, \nu) \right) d\nu \\
&= \int_0^{2\pi} (0+0-1) d\nu = -2\pi,
\end{aligned}$$

where the limits for $q \rightarrow \infty$ and $q = 0$ are computed taking into account only the physics of diffusion: for $q = 0$, no diffusion gradient is applied, so that there is no attenuation. For $q \rightarrow \infty$, the exponential decay of $E(q)$ guarantees that the corresponding limits are 0, so eq. (B.1) has general validity independently on the mono-exponential model used by Aganj et al. (2009a).

C Inverse curl for the circulation-based OPDT

The assumption of a slowly varying ADC means that the attenuation signal may be approximated, in an environment of q_0 , as (Tristán-Vega et al., 2009b):

$$\tilde{E}(q, \xi, \nu) \Big|_{q \simeq q_0} \simeq \exp\left(-4\pi^2 \tau q^2 \tilde{D}(q_0, \xi, \nu)\right). \quad (\text{C.1})$$

We can find the value of the field whose curl approximates the angular Laplacian of E in an environment of q_0 . For other values, the estimated field is not necessarily equal to the actual solution, but we only need to know its value at q_0 to integrate in the boundary Γ of the disk Ω . From eq. (18), it follows:

$$\begin{aligned}
\widetilde{F_{\nu}^{\Phi}}(q, \xi, \nu) &= \frac{-1}{8\pi^2 q} \int_0^q \frac{1}{u} \widetilde{\Delta_b E}(u, \xi, \nu) du \\
&\simeq \frac{-1}{8\pi^2 q} \int_0^q \Delta_b \exp\left(-4\pi^2 \tau u^2 \tilde{D}(q_0, \xi, \nu)\right) du. \quad (\text{C.2})
\end{aligned}$$

The integration has been performed between 0 and q because Stokes' theorem needs certain regularity conditions on F to hold. In particular, a singularity at $q = 0$ is not allowed. Since q appears in the denominator, it is necessary to ensure that the numerator tends to 0 for $q = 0$ to avoid a pole in the function. It is important to stress that this is not equivalent to assume that the ADC is constant between 0 and q_0 . Eq. (C.2) represents an approximation to the primitive of the function to integrate only for $q = q_0$. Amongst the infinite number of primitives of such function, the one whose value at $q = 0$ is 0 is chosen. If the ADC is assumed constant for all q , the solution of eq. (C.2) holds for every q (not only q_0). On the contrary, if the ADC is only assumed to vary slowly near q_0 , the solution of eq. (C.2) is only valid for a neighborhood of q_0 . Since the computation of the circulation of F_v requires to know its value only for q_0 , the latter assumption is enough. It is exactly the same premise used with the OPDT, so the new technique does not introduce new sources of error *per se*. The computation of the integral in eq. (C.2) is not trivial, since the division by u introduces a pole which is not integrable for $u = 0$. It is shown in Appendix E that in fact the integral in eq. (C.2) is always convergent due to the presence of the Laplace-Beltrami operator, which assures that a zero of a greater order than the pole is present. Indeed, eq. (C.2) can be written:

$$\widetilde{F}_v^\Phi(q, \xi, \nu) \simeq \frac{-1}{8\pi^2 q} \Delta_b \int_0^q \frac{\exp(-4\pi^2 \tau u^2 \tilde{D}(q_0, \xi, \nu)) - 1}{u} du, \quad (C.3)$$

where the order of the Laplace-Beltrami operator and the radial integral may be exchanged since the new integral is convergent. Although the integral in eq. (C.3) is not trivial either, it may be written in terms of the exponential integral E_i (Abramowitz and Stegun, 1972), which is reviewed in Appendix E:

$$\begin{aligned} \widetilde{F}_v^\Phi(q, \xi, \nu) &\simeq \frac{-1}{8\pi^2 q} \Delta_b \left[\frac{1}{2} E_i \left(-4\pi^2 \tau u^2 \tilde{D}(q_0, \xi, \nu) - \log(u) \right) \right]_0^q \\ &= \frac{-1}{16\pi^2 q} \Delta_b E_{in} \left(4\pi^2 \tau q^2 \tilde{D}(q_0, \xi, \nu) \right), \end{aligned} \quad (C.4)$$

where E_{in} is the non-singular exponential integral, whose definition, together with some asymptotic properties, is given in Appendix E.

D Particularization of eq. (20) to the mono-exponential model

If the ADC is assumed to be constant for all q , eq. (20) is an approximation of the true integral in Π for any disk Ω with an arbitrary radius q . Hence, the limit when q approaches infinity has to be the true integral in Π :

$$\begin{aligned} \Phi(r) &\simeq \lim_{q \rightarrow \infty} \left(\frac{-1}{16\pi^2} \int_0^{2\pi} \Delta_b E_{in} \left(4\pi^2 \tau q^2 \tilde{D}(q_0, \frac{\pi}{2}, \nu) \right) d\nu + \frac{1}{4\pi} \right) \\ &= \frac{-1}{16\pi^2} \int_0^{2\pi} \lim_{q \rightarrow \infty} \Delta_b \left(E_{in} \left(4\pi^2 \tau q^2 \tilde{D}(q_0, \frac{\pi}{2}, \nu) \right) \right) d\nu + \frac{1}{4\pi} \\ &= \frac{-1}{16\pi^2} \int_0^{2\pi} \lim_{q \rightarrow \infty} \Delta_b \left(-\log \left(4\pi^2 \tau \tilde{D}(q_0, \frac{\pi}{2}, \nu) \right) - \log(q^2) - \gamma \right) d\nu + \frac{1}{4\pi} \\ &= \frac{1}{16\pi^2} \int_0^{2\pi} \Delta_b \log \left(-\tilde{E} \left(q_0, \frac{\pi}{2}, \nu \right) \right) d\nu + \frac{1}{4\pi}, \end{aligned} \quad (D.1)$$

where γ is the Euler-Mascheroni constant (see Appendix E for details on the asymptotic behavior of E_{in}). Note that, although eq. (D.1) computes the true integral in the orthogonal plane Π , it is still an approximation due to the unrealistic modeling of the attenuation signal.

E The non-singular exponential integral

Consider the integral in eq. (C.2), where the exponential term in the numerator is simply 1 for $u = 0$. Without the Laplace-Beltrami operator, the resulting function has a pole of the form u^{-1} , so it is not integrable at $u = 0$. To overcome this problem, this equation may be re-written in the form:

$$\begin{aligned}\widetilde{F}_\nu^\Phi(q, \xi, \nu) &\simeq \frac{-1}{8\pi^2 q} \int_0^q \frac{\Delta_b \left(\exp(-4\pi^2 \tau u^2 \widetilde{D}(q_0, \xi, \nu)) - 1 + 1 \right)}{u} du \\ &= \frac{-1}{8\pi^2 q} \int_0^q \frac{\Delta_b \left(\exp(-4\pi^2 \tau u^2 \widetilde{D}(q_0, \xi, \nu)) - 1 \right) + \Delta_b 1}{u} du \quad (\text{E.1}) \\ &= \frac{-1}{8\pi^2 q} \int_0^q \frac{\Delta_b \left(\exp(-4\pi^2 \tau u^2 \widetilde{D}(q_0, \xi, \nu)) - 1 \right)}{u} du;\end{aligned}$$

Δ_b is a linear differential operator, so applying it to a constant yields simply 0. Besides, this operator does not depend on the radial coordinate u , since it represents precisely the angular Laplacian. Consequently, we may write:

$$\widetilde{F}_\nu^\Phi(q, \xi, \nu) \simeq \frac{-1}{8\pi^2 q} \Delta_b \int_0^q \frac{\exp(-4\pi^2 \tau u^2 \widetilde{D}(q_0, \xi, \nu)) - 1}{u} du. \quad (\text{E.2})$$

This step is possible because the resulting integral is now convergent. To prove it, consider the power series expansion of the numerator, which is trivially related to the expansion of the exponential function:

$$\exp(-4\pi^2 \tau u^2 \widetilde{D}(q_0, \xi, \nu)) - 1 = \sum_{k=1}^{\infty} \frac{1}{k!} \left(-4\pi^2 \tau u^2 \widetilde{D}(q_0, \xi, \nu) \right)^k. \quad (\text{E.3})$$

From the previous expression, it is trivial to show that the numerator in eq. (E.2) has a zero of order 2 in $u = 0$, so the u^{-1} pole is compensated and the integral is always convergent. Operating in eq. (E.2), we have:

$$\begin{aligned}&\int_0^q \frac{\exp(-4\pi^2 \tau u^2 \widetilde{D}) - 1}{u} du = \int_0^q \frac{\exp(-4\pi^2 \tau u^2 \widetilde{D})}{u} du - \int_0^q \frac{du}{u} \quad (\text{E.4}) \\ &= \frac{1}{2} \int_0^{4\pi^2 \tau q^2 \widetilde{D}(q_0, \xi, \nu)} \frac{\exp(-u)}{u} du - \int_0^q \frac{du}{u},\end{aligned}$$

where the change of variable $u' = 4\pi^2 \tau u^2 \widetilde{D}(q_0, \xi, \nu)$ has been used in the first term. Note that the equality in the previous equation cannot be stated strictly speaking, since none of the resulting integrals is convergent. However, from the previous discussion it follows that eq. (E.4) must hold as an equality between finite real numbers when the limit for $u \rightarrow 0$ is taken. A primitive for the second integral is obviously the logarithm function. The first one is related to the definition of the exponential integral $E_i \left(4\pi^2 \tau q^2 \widetilde{D}(q_0, \xi, \nu) \right)$ (Abramowitz and Stegun, 1972):

$$E_i(x) \triangleq \int_x^\infty \frac{\exp(-u)}{u} du \Rightarrow \int_0^x \frac{\exp(-u)}{u} du = \lim_{x \rightarrow 0^+} E_i(x) - E_i(x). \quad (E.5)$$

Fig. E.1 sketches the behavior of the exponential integral for real-valued arguments.

Moreover, since $\tilde{D}(q_0, \xi, \nu)$ is always positive, the argument of E_i is always greater than 0, and the interesting properties of this function are

Fig. E.1.

The real-valued exponential integral $E_i(x)$. For negative arguments, the value of the function is not unique, so the principal (real) branch has been depicted.

those corresponding to $\mathbb{R}_+$. In particular, the following equivalence holds:

$$E_i(x) = -\gamma - \log(x) - \sum_{k=1}^{\infty} \frac{(-x)^k}{k \cdot k!}, \text{ if } x > 0, \quad (E.6)$$

where $\gamma \simeq 0.5772$ is the Euler-Mascheroni constant. $E_i(x)$ shows a logarithmic singularity for $x = 0$, according to the behavior shown in Fig. E.1. Casting the expression in eq. (E.6) into eq. (E.4), the integral can be explicitly evaluated:

$$\begin{aligned} & \int_0^q \frac{\exp(-4\pi^2 \tau u^2 \tilde{D}(q_0, \xi, \nu)) - 1}{u} du \\ &= \lim_{q \rightarrow 0^+} \left(\frac{1}{2} E_i \left(4\pi^2 \tau q^2 \tilde{D} \right) + \log q \right) - \frac{1}{2} E_i \left(4\pi^2 \tau q^2 \tilde{D} \right) - \log q \\ &= \lim_{q \rightarrow 0^+} \left(\frac{1}{2} \left(-\gamma - \log \left(4\pi^2 \tau \tilde{D} \right) - 2 \log q - \sum_{k=1}^{\infty} \frac{1}{k \cdot k!} \left(-4\pi^2 \tau q^2 \tilde{D} \right)^k \right) + \log q \right) \\ & \quad - \frac{1}{2} \left(-\gamma - \log \left(4\pi^2 \tau \tilde{D} \right) - 2 \log q - \sum_{k=1}^{\infty} \frac{1}{k \cdot k!} \left(-4\pi^2 \tau q^2 \tilde{D} \right)^k \right) - \log q \\ &= \frac{1}{2} \sum_{k=1}^{\infty} \frac{1}{k \cdot k!} \left(-4\pi^2 \tau q^2 \tilde{D}(q_0, \xi, \nu) \right)^k. \end{aligned} \quad (E.7)$$

The final series expansion in eq. (E.7) is, by definition, the non-singular exponential integral $E_{in}(4\pi^2\tau q^2\tilde{D}(q_0, \xi, \nu))$:

$$E_{in}(x) \triangleq \sum_{k=1}^{\infty} \frac{(-x)^k}{k \cdot k!}. \quad (\text{E.8})$$

Fig. E.2.

The non-singular exponential integral $E_{in}(x)$. For a large enough x , E_{in} rapidly converges to minus the logarithm of x (minus the constant γ).

The non-singular exponential integral is depicted in Fig. E.2. Its representation in terms of the exponential integral allows to derive the asymptotic behavior of $E_{in}(x)$ for large x in a very easy way. Identifying corresponding terms in eqs. (E.6) and (E.8), the following relation remains evident:

$$E_{in}(x) = -\gamma - E_i(x) - \log(x). \quad (\text{E.9})$$

Since the exponential integral $E_i(x)$ vanishes to 0 very fast as x increases (see Fig. E.1), $E_{in}(x)$ shows a similar behavior to minus the logarithm for relatively high x ; in fact, Fig. E.1 suggests that the approximation:

$$E_{in}(x) \simeq -\gamma - \log(x) \quad (\text{E.10})$$

holds for values of x above 3.

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Fig. 1. Auxiliary coordinates systems (left: cylindrical coordinates; right: spherical coordinates) for the computation of the integrals in the plane Π , the disk Ω , or the curve Γ . The plane Π is orthogonal to the direction of interest, $\mathbf{r}$.

Fig. 2.

Angular errors in the estimation of two crossing fibers, as a function of the initial angle between the ground-truth directions, for the estimators of the ODF, $\Psi(r)$. Together with Q-Balls, the results for cQ-Balls and pQ-Balls are presented.

Fig. 3. Glyph representations of the estimators of $\Psi(r)$ in a noise-free environment (S-4), for two fibers crossing in an angle of 80° . The glyphs are min-max normalized for visualization purposes.

Fig. 4.

Angular errors in the estimation of two crossing fibers, as a function of the initial angle between the ground-truth directions, for the estimators of the OPDF $\Phi(r)$. Together with the OPDT, the cOPDT and the pOPDT are tested. Additionally, the DOT is included for comparison purposes, though it is an estimator of $Y(r)$ and not $\Phi(r)$.

Fig. 5.

Glyph representations of the estimators of $\Phi(r)$ (and $Y(r)$, in the last row) in a noise-free environment (S-4), for two fibers crossing in an angle of 55° . Min-max normalization is not necessary in this case.

Fig. 6.

Angular errors in the estimation of two crossing fibers, as a function of the initial angle between the ground-truth directions, for the estimators of the ODF, $\Psi(r)$. Noisy scenario with PSNR=13.33 (top), and PSNR=5 (bottom).

Fig. 7.

Glyph representations of the estimators of the ODF in a noisy scenario: S-2 with PSNR=13.3. The ground-truth angle between the fibers is 90° . The glyphs are min-max normalized for visualization purposes.

Fig. 8.

Angular errors in the estimation of two crossing fibers, as a function of the initial angle between the ground-truth directions, for the estimators of the OPDF, $\Phi(r)$. Noisy scenario with PSNR=13.33 (top), and PSNR=5 (bottom).

Fig. 9.

Glyph representations of the estimators of the OPDF in a noisy scenario: S-2 with PSNR=13.3. The ground-truth angle between the fibers is 70° , and no min-max normalization is performed.

Fig. 10.

Relative errors in the estimation of the integral in the plane Π as the integral in the disk ω , as a function of the b -value, for crossing angles of 90° (left), 65° (center) and 50° right. Each curve represents the relative error ε for an arbitrary spatial direction r (including those yielding maximum and minimum errors) as a function of the b -value.

Fig. 11.

Sample axial slices (15 and 23 of 78, respectively) of the real data set used, following usual color-coding conventions: red for the 'x' axis, green for the 'y' axis, and blue for the 'z' axis. For convenience, some tracts of interest have been highlighted: the cerebellar peduncle (cp), the corticopontine tract (cpt), the corticospinal tract (cst), the middle cerebellar peduncle (mcp), the medial lemniscus (ml), the pontine crossing tract (pct), and the superior cerebellar peduncle (scp).

Fig. 12.

Glyphs obtained with the cOPDT for the corresponding ROI marked in Fig. 11. The ROI for slice 15 has been down-sampled for visual convenience. The gray levels in the background correspond to the Fractional Anisotropy (FA) of the voxels.

Fig. 13. Glyphs obtained for the small ROI marked in Fig. 12, for slice 15 (top) and 23 (bottom). In both cases, the OPDT (left), the pOPDT (center), and the cOPDT (right) are compared.

Fig. 14. Glyphs obtained for the small ROI marked in Fig. 12 for slice 15, without applying the denoising filter. The OPDT (left), the pOPDT (center), and the cOPDT (right) are compared.

Table 1

Summary of some HARDI estimators considered in this paper.

Name	Implementation	Function
OPDT	$\frac{-1}{4\pi^2} G \left\{ E(q) \right\} (r)$	$\Phi(r)$
cOPDT, eq. (20)	$\frac{-1}{16\pi^2} G \left\{ {}_bE_{in} \left(-\log E(q) \right) \right\} (r) + \frac{1}{4\pi}$	$\Phi(r)$
pOPDT, eq. (23)	$\frac{1}{16\pi^2} G \left\{ {}_b\log \left(-\log E(q) \right) \right\} (r) + \frac{1}{4\pi}$	$\Phi(r)$
Q-Balls	$G \{ E(q) \} (r)$	$\Psi(r)$
cQ-Balls, eq. (22)	$\frac{-q_0^2}{4} G \left\{ \frac{1-E(q)}{\log E(q)} \right\} (r)$	$\Psi(r)$
pQ-Balls, eq. (24)	$\frac{-q_0^2}{4} G \left\{ (\log E(q))^{-1} \right\} (r)$	$\Psi(r)$

Table 2

Matrix implementations of the estimators presented in this paper.

$$P_{\text{cOPDT}} = \frac{-1}{16\pi^2} \mathbf{B}' \mathbf{F} \mathbf{L} (\mathbf{B}^T \mathbf{B} + \lambda \mathbf{L}^2)^{-1} \mathbf{B}^T \left[\mathbf{E}_{in}(\mathbf{D}) \right] + \frac{1}{4\pi}$$

$$P_{\text{pOPDT}} = \frac{1}{16\pi^2} \mathbf{B}' \mathbf{F} \mathbf{L} (\mathbf{B}^T \mathbf{B} + \lambda \mathbf{L}^2)^{-1} \mathbf{B}^T \left[\log(\mathbf{D}) \right] + \frac{1}{4\pi}$$

$$P_{\text{cQ-Balls}} = \frac{q_0^2}{4} \mathbf{B}' \mathbf{F} (\mathbf{B}^T \mathbf{B} + \lambda \mathbf{L}^2)^{-1} \mathbf{B}^T \left[\frac{1 - \mathbf{E}}{\mathbf{D}} \right]$$

$$P_{\text{pQ-Balls}} = \frac{q_0^2}{4} \mathbf{B}' \mathbf{F} (\mathbf{B}^T \mathbf{B} + \lambda \mathbf{L}^2)^{-1} \mathbf{B}^T \left[\frac{1}{\mathbf{D}} \right]$$

Table 3

Characteristics of the scenarios used for the testing of the estimators. The PSNR refers only to the noisy scenarios.

	S-1	S-2	S-3	S-4	S-5
<i>b</i> -value (s/mm ²)	1000	1000	3000	3000	3000
<i>N</i>	50	100	50	100	200
PSNR	13.3	13.3	—	5.0	5.0

Table 4

Properties of some HARDI estimators discussed in this paper.

Name	Adequate <i>b</i> -values	Robustness to noise	Constant ADC	Integration error	Angular contrast	Probabilistic information
OPDT	medium	medium	Local	High (FRT)	Good	Yes
cOPDT	medium	low	Local	Low (disk)	Good	Yes
pOPDT	medium	low	Global	No	Good	Yes
Q-Balls	high	high	No	High (FRT)	Poor	No
cQ-Balls	high	high	Local	Low (disk)	Poor	No
pQ-Balls	high	very low	Global	No	Poor	No