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SR-HARDI: Spatially Regularizing High Angular Resolution Diffusion Imaging

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Abstract

High angular resolution diffusion imaging (HARDI) has recently been of great interest in mapping the orientation of intra-voxel crossing fibers, and such orientation information allows one to infer the connectivity patterns prevalent among different brain regions and possible changes in such connectivity over time for various neurodegenerative and neuropsychiatric diseases. The aim of this paper is to propose a penalized multi-scale adaptive regression model (PMARM) framework to spatially and adaptively infer the orientation distribution function (ODF) of water diffusion in regions with complex fiber configurations. In PMARM, we reformulate the HARDI imaging reconstruction as a weighted regularized least-squares regression (WRLSR) problem. Similarity and distance weights are introduced to account for spatial smoothness of HARDI, while preserving the unknown discontinuities (e.g., edges between white matter and grey matter) of HARDI. The L_1 penalty function is introduced to ensure the sparse solutions of ODFs, while a scaled L_1 weighted estimator is calculated to correct the bias introduced by the L_1 penalty at each voxel. In PMARM, we integrate the multiscale adaptive regression models (Li et al., 2011), the propagation-separation method (Polzehl and Spokoiny, 2000), and Lasso (least absolute shrinkage and selection operator) (Tibshirani, 1996) to adaptively estimate ODFs across voxels. Experimental results indicate that PMARM can reduce the angle detection errors on fiber crossing area and provide more accurate reconstruction than standard voxel-wise methods.

Keywords

Ensemble Average Propagator; High angular resolution diffusion imaging; Orientation distribution function; Penalized multiscale adaptive regression model; Propagation-separation

1 Introduction

Diffusion magnetic resonance imaging (dMRI) is a popular imaging technique for tracking the effective diffusion of water molecules, which is constrained by the surrounding structures, such as nerves or cells, in the human brain *in vivo*. Because water molecules tend to diffuse fast along the pathways of white matter fibers and slow cross fibers, tracking its diffusion with dMRI allows one to map the microstructure and organization of those pathways (Basser and Pierpaoli, 1996). Measuring the diffusion process quantitatively is

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critical for a quantitative assessment of the integrity of anatomical connectivity in white matter. A reconstruction step to dMRI is to estimate the normalized signal attenuation $E(\mathbf{q}; \mathbf{v})$, the Orientation Distribution Function (ODF) $\mathcal{O}(\mathbf{r}; \mathbf{v})$, and Ensemble Average Propagator (EAP) $p(\mathbf{R}; \mathbf{v})$ at each voxel $\mathbf{v}$ in a common space $\mathcal{V}$, where $\mathbf{q} = q\mathbf{u} \in R^3$ and $\mathbf{R} = R\mathbf{r} \in R^3$, respectively, represent the effective gradient direction and displacement direction. Examples of $E(\mathbf{q}; \mathbf{v})$, $\mathcal{O}(\mathbf{r}; \mathbf{v})$, and $p(\mathbf{R}; \mathbf{v})$ will be discussed below.

A standard dMRI, diffusion tensor Imaging (DTI), is based on $E(\mathbf{q}; \mathbf{v}) = \exp(-b\mathbf{u}^T D(\mathbf{v})\mathbf{u})$, where b is the diffusion weighting factor associated with $\mathbf{q}$. This yields that $p(\mathbf{R}; \mathbf{v})$ is the density of a multivariate Gaussian distribution parametrized by a 3×3 covariance matrix $D(\mathbf{v})$, called a diffusion tensor. The principal directions of the diffusion tensors can be used to reconstruct major fiber pathways in regions of the brain and spinal cord with strong white-matter coherence, and it has enabled the mapping of anatomical connections in the central nervous system. However, a major limitation of DTI is that it fails to accurately model complex fiber architectures other than one single fiber bundle at each image voxel, such as crossing, bending, or kissing fibers. With the advent of high angular resolution diffusion imaging (HARDI) in dMRI, it is possible to characterize more complex fiber architectures in order to address such limitations of DTI.

Various HARDIs in dMRI have been developed to accurately model complex fiber architectures across voxels. Examples of HARDI include mixture of tensor models (Tuch et al., 1999, 2002), generalized DTI (Liu et al., 2004), high order tensors (HOT) (Özarslan and Mareci, 2003), diffusion spectrum imaging (DSI) (Wedeen et al., 2005), hybrid diffusion imaging (HYDI) (Wu and Alexander, 2007), Q-ball imaging (QBI) (Tuch, 2004; Anderson, 2005; Descoteaux et al., 2007), diffusion orientation transforms (DOT) (Özarslan et al., 2006), spherical deconvolution, diffusion propagator imaging, simple harmonic oscillator reconstruction and estimation, and spherical polar Fourier imaging, among others. Most reconstruction methods focus on computing the orientation distribution function (ODF), which is the angular profile of the diffusion probability density function of water molecules, from the HARDI measures.

Many existing methods for reconstructing HARDI images perform reconstruction independently at each voxel, which essentially ignores the functional nature of the HARDI data at different voxels in space. Most of these methods model $E(\mathbf{q}; \mathbf{v})$ or $\mathcal{O}(\mathbf{r}; \mathbf{v})$ as a linear combination of some known or unknown basis functions and then compute the model parameters by using a regularized linear least-squares optimization. Recently, there has been a great interest in incorporating spatial smoothness constraints into the HARDI reconstruction algorithm. The key assumption of this approach is that the orientation and anisotropy of any single fiber population are expected to vary smoothly along the dominant fiber orientation, except at the boundaries between tracts and interfaces with gray matter structures and cerebrospinal fluid spaces. Until recently, a few number of different approaches have been developed starting from smoothing raw HARDI images (Descoteaux et al., 2008; Becker et al., 2012, 2014), smoothing procedures in ODF space (Kim et al., 2009; Goh et al., 2011), spatial DTI (Tabelow et al., 2008; Yu et al., 2013; Yu and Li, 2013; Liu et al., 2013), to spatial HARDI, which reconstructs and denoises all ODFs simultaneously (Raj et al., 2011).

The aim of this paper is to develop a penalized multi-scale adaptive regression model (PMARM) framework to spatially and adaptively infer ODFs across all voxels. The PMARM procedure can be regarded as a natural extension of the propagation-separation method developed for DTI (Tabelow et al., 2008). Similar to (Raj et al., 2011), PMARM is also a simultaneous reconstruction and denoising procedure. However, PMARM differs significantly from the method in (Raj et al., 2011) in two major ways. First, we use similarity and distance weights to account for local spatial smoothness of HARDI, while preserving the unknown local discontinuities. In contrast, the spatial HARDI method uses a single smoothness regularization term to control global smoothness. Thus, PMARM should be more robust to heterogeneous noise levels across different locations. Second, PMARM is a general framework that incorporates the L_1 regularization and other regularization terms to ensure the sparse solutions of ODFs, whereas the spatial HARDI enforces Tikhonov regularization with several global tuning parameters in order to stabilize the estimated ODFs.

Section 2 presents PMARM for HARDI reconstruction. In Section 3, we conduct simulation studies with the known ground truth to examine the finite sample performance of PMARM. Section 4 illustrates an application of the proposed methods in a real HARDI dataset. We present concluding remarks in Section 5. Additional examples, simulations, and a real data analysis can be found in the Appendix.

2 Methods

2.1 Model Formulation

We usually acquire n normalized HARDI data with each image containing N voxels for each subject. Thus, we observe n normalized HARDI measurements $\{(E(\mathbf{q}_i; \mathbf{v}), \mathbf{q}_i, b_i) : i = 1, \dots, n\}$ at voxel $\mathbf{v} \in \mathcal{V}$, where $\mathbf{q}_i$ is associated with the gradient vector $\mathbf{r}_i = (r_{i,1}, r_{i,2}, r_{i,3})^T$ and the b factor, b_i , for each i . Most HARDIs assume that

$$f(E(\mathbf{q}_i; \mathbf{v})) = \mathbf{x}_i^T \boldsymbol{\beta}(\mathbf{v}) + \varepsilon_i(\mathbf{v}), \quad (1)$$

where $f(\cdot)$ is a given transformation function (e.g., $f(s) = s$ or $f(s) = \log(s)$), $\mathbf{x}_i$ is a $p \times 1$ vector of covariates, which depends on $\mathbf{q}_i$ (or $(\mathbf{r}_i, b_i)$), $\boldsymbol{\beta}(\mathbf{v})$ is a $p \times 1$ vector of regression coefficients, and $\varepsilon_i(\mathbf{v})$ is an error term with mean zero and variance $\sigma_i^2(\mathbf{v})$. In practice, $E(\mathbf{q}_i; \mathbf{v})$ equals the ratio of magnetic resonance signal measured at $\mathbf{q}_i$, denoted by $S(\mathbf{q}_i; \mathbf{v})$, to the magnetic resonance signal measured at $\mathbf{0}$, denoted by $S(\mathbf{0}; \mathbf{v})$. Since the signal-to-noise ratio in $S(\mathbf{0}; \mathbf{v})$ is very high, we may ignore the noise component of $S(\mathbf{0}; \mathbf{v})$. Moreover, it is well known that the noise in an HARDI measurement approximately follows Rician or non-central Chi-distribution in case of parallel acquisitions (Zhu et al., 2009, 2007; Becker et al., 2012, 2014), and thus model (1) implicitly uses an approximation to the distribution of HARDI measurements. Model (1) is general enough to cover many existing HARDIs. In the literature, for generalized DTI and high order tensors (HOT), it is common to set $f(E(\mathbf{q}_i; \mathbf{v})) = \log(E(\mathbf{q}_i; \mathbf{v}))$ and represent $\log(E(\mathbf{q}_i; \mathbf{v}))$ as a polynomial function of $\mathbf{q}_i$, whereas for most other HARDIs, such as Q-ball imaging (QBI) or diffusion orientation transforms (DOT), it is

common to set $f(E(\mathbf{q}_i; \mathbf{v})) = E(\mathbf{q}_i; \mathbf{v})$ and approximate $E(\mathbf{q}_i; \mathbf{v})$ by a linear combination of some basis functions, such as spherical harmonics. For the purpose of illustration, we include two theoretical examples in the Appendix.

2.2 Estimation Procedures

Most HARDI methods focus on reconstructing $\beta(\mathbf{v})$ by solving a regularized linear least-squares optimization problem

$$\hat{\beta}(\mathbf{v}) = \underset{\beta(\mathbf{v})}{\text{minimize}} \|\mathbf{y}(\mathbf{v}) - \mathbf{X}\beta(\mathbf{v})\|^2 + \rho(\beta(\mathbf{v}); \lambda(\mathbf{v})), \quad (2)$$

where $\mathbf{y}(\mathbf{v}) = (f(E(\mathbf{q}_1; \mathbf{v})), \dots, f(E(\mathbf{q}_n; \mathbf{v})))^T$, $\mathbf{X}$ is an $n \times p$ matrix with the i -th row being $\mathbf{x}_i$, and $\rho(\beta(\mathbf{v}); \lambda(\mathbf{v}))$ is a penalty function with $\lambda(\mathbf{v})$ being a tuning parameter. Different penalty functions have been proposed in the literature. For instance, for analytical Q-ball imaging, the Laplacian-Beltrami regularization assumes

$$\rho(\beta(\mathbf{v}); \lambda(\mathbf{v})) = \lambda(\mathbf{v}) \sum_{l=0}^L \sum_{m=-l}^l l^2(l+1)^2 \beta_{lm}^2 = \lambda(\mathbf{v}) \beta(\mathbf{v})^T \Lambda \beta(\mathbf{v}), \quad (3)$$

where $\Lambda = \text{diag}(0, 4, 4, 4, \dots, L^2(L+1)^2, \dots, L^2(L+1)^2)$. Alternatively, we may consider other penalty functions, such as LASSO, adaptive LASSO, generalized LASSO, or smoothly clipped absolute deviation (SCAD) (Fan and Li, 2001; Tibshirani and Taylor, 2011; Zou, 2006; Tibshirani, 1996). Specifically, the penalty function of the generalized LASSO (Tibshirani and Taylor, 2011) is given by

$$\rho(\beta(\mathbf{v}); \lambda(\mathbf{v})) = \lambda(\mathbf{v}) \|D\beta(\mathbf{v})\|_1, \quad (4)$$

where $\|\cdot\|_1$ is the L_1 norm and D is a pre-specified $p_1 \times p$ filter matrix. For instance, the standard LASSO assumes D to be an identity matrix. Following the Laplacian-Beltrami regularization, we may set $D = \Lambda^{1/2}$ in order to give different weights to the coefficients at different orders for Q-ball imaging.

Many estimation methods have been developed to solve the regularized linear least-squares optimization (2). For instance, it is computationally easy to compute $\hat{\beta}_{LB}(\mathbf{v}) = (\mathbf{X}^T \mathbf{X} + \lambda(\mathbf{v}) \Lambda)^{-1} \mathbf{X}^T \mathbf{y}(\mathbf{v})$ for the Laplacian-Beltrami regularization (Descoteaux et al., 2007), but it is very sensitive to noise. As shown in the second row of (Figure 1), there are many false maxima in ODF based on $\hat{\beta}_{LB}(\mathbf{v})$. Although the LASSO method has been widely used and yields a sparse estimate of $\beta(\mathbf{v})$, denoted by $\hat{\beta}_{LO}(\mathbf{v})$, LASSO can introduce substantial bias in the estimation of $\beta(\mathbf{v})$ (Figure 1), even though the estimated ODF from LASSO seems to be slightly better than the one based on $\hat{\beta}_{LB}(\mathbf{v})$. In Zhang and Zhang (2014), a low-dimensional projection estimator (LDPE), denoted by $\hat{\beta}_{LE}(\mathbf{v})$, is developed to address such bias issue

(Figure 1). The LDPE estimator is included in Appendix. From here on, we primarily consider the three estimation methods including the Laplace-Beltrami regularization, LASSO, and LDPE, even though extension to other cases is definitely feasible. After calculating $\hat{\beta}(\mathbf{v})$, we can calculate ODFs and infer their maxima.

A key feature in HARDI is its spatial constraint. Specifically, the orientation and anisotropy of any single fiber bundles change smoothly from one voxel to the next, particularly along the dominant fiber orientation, whereas it may change dramatically at the boundaries between tracts and interfaces with gray matter structures and cerebrospinal fluid (CSF) spaces. Moreover, the ODF is expected to change smoothly from one voxel to the next in the same fiber crossing region, whereas it may change dramatically at the boundaries of fiber crossing regions and surrounding fiber bundles. This is a very important and powerful constraint that can be exploited to improve the reconstruction in HARDI. However, the methods in (2) of estimating ODF are voxel-wise methods and do not make use of the spatial constraint of HARDI.

To explicitly exploit such a spatial constraint, we develop a penalized multiscale adaptive regression model (PMARM) to spatially and adaptively update $\{\beta(\mathbf{v}) : \mathbf{v} \in \mathcal{V}\}$ by integrating various penalization methods (Fan and Li, 2001; Tibshirani and Taylor, 2011; Zou, 2006; Tibshirani, 1996; Zhang and Zhang, 2014), multiscale adaptive regression models (Li et al., 2011), and the propagation-separation method (Polzehl and Spokoyny, 2000). The key idea of PMARM is to combine HARDI signals in a neighboring sphere of voxel $\mathbf{v}$ to make inference on $\beta(\mathbf{v})$ at voxel $\mathbf{v}$. Specifically, let $B(\mathbf{v}, h)$ be a sphere with radius h centered at voxel $\mathbf{v}$ and $\omega(\mathbf{v}, \mathbf{v}'; h)$ be a weight function of triple $(\mathbf{v}, \mathbf{v}', h)$ such that

$$\sum_{\mathbf{v}' \in B(\mathbf{v}, h)} \omega(\mathbf{v}, \mathbf{v}'; h) = 1 \text{ and } \omega(\mathbf{v}, \mathbf{v}'; h) \geq 0 \text{ for all } h \geq 0.$$

PMARM is based on a set of weighted penalization functions, denoted by $P_n(\beta(\mathbf{v}); \omega, h)$, which is defined as follows:

$$\begin{aligned} P_n(\beta(\mathbf{v}); \omega, h) &= \sum_{\mathbf{v}' \in B(\mathbf{v}, h)} \omega(\mathbf{v}, \mathbf{v}'; h) \|\mathbf{y}(\mathbf{v}') - \mathbf{X}\beta(\mathbf{v})\|^2 + \rho(\beta(\mathbf{v}); \lambda(\mathbf{v})) \\ &= \|\mathbf{y}_w(\mathbf{v}; h) - \mathbf{X}\beta(\mathbf{v})\|^2 + \rho(\beta(\mathbf{v}); \lambda(\mathbf{v})) + \text{constant}, \end{aligned} \quad (5)$$

where $\mathbf{y}_w(\mathbf{v}; h) = \sum_{\mathbf{v}' \in B(\mathbf{v}, h)} \omega(\mathbf{v}, \mathbf{v}'; h) \mathbf{y}(\mathbf{v}')$. Given the current weights $\{\omega(\mathbf{v}, \mathbf{v}'; h) : \mathbf{v}, \mathbf{v}' \in \mathcal{V}\}$, we consider the weighted generalized estimation equation (GEE) estimator of $\beta(\mathbf{v})$, denoted by $\hat{\beta}(\mathbf{v}, h)$, which satisfies

$$\hat{\beta}(\mathbf{v}, h) = \arg\min_{\beta(\mathbf{v})} P_n(\beta(\mathbf{v}); \omega, h). \quad (6)$$

It is critical to choose a good $\omega(\mathbf{v}, \mathbf{v}'; h)$ in preventing oversmoothing the estimates of $\beta(\mathbf{v})$ across voxels, while preserving the edges between different structures, such as fiber bundles, crossing fibers, or gray matter regions. A good $\omega(\mathbf{v}, \mathbf{v}'; h)$ should quantify the similarity between $\beta(\mathbf{v})$ and $\beta(\mathbf{v}')$ or their corresponding ODFs. Specifically, if $\beta(\mathbf{v})$ and $\beta(\mathbf{v}')$ substantially differ from each other, then the HARDI signals in voxel $\mathbf{v}'$ do not contain too much information on $\beta(\mathbf{v})$ and thus $\omega(\mathbf{v}, \mathbf{v}'; h)$ should be close to 0. However, if $\beta(\mathbf{v})$ and $\beta(\mathbf{v}')$ are close to each other indicating that the HARDI signals in voxel $\mathbf{v}'$ contain useful information on $\beta(\mathbf{v})$, then $\omega(\mathbf{v}, \mathbf{v}'; h)$ should be significantly larger than zero. See the explicit expression of $\omega(\mathbf{v}, \mathbf{v}'; h)$ in Section 2.3.

2.3 PMARM

We develop the PMARM procedure to adaptively determine $\{w(\mathbf{v}, \mathbf{v}'; h)\}$ and estimate $\beta(\mathbf{v})$ across all voxels $\mathbf{v} \in \mathcal{V}$. Our multiscale adaptive strategy starts with building a sequence of nested spheres with increasing radii $h_0 = 0 < h_1 < \dots < h_S = r$ ranging from the smallest scale $h_0 = 0$ to the largest scale $h_S = r$ at each voxel $\mathbf{v}$. At the scale $h_0 = 0$, we just calculate $\hat{\beta}(\mathbf{v}; h_0) = \hat{\beta}(\mathbf{v})$ voxel-wisely without using any spatial information. This corresponds to setting $w(\mathbf{v}, \mathbf{v}'; h_0) = 1$ if $\mathbf{v} = \mathbf{v}'$ and 0 otherwise. Then, based on the signals contained in voxels $\mathbf{v}$ and $\mathbf{v}'$, we use methods as detailed below to calculate the weights $w(\mathbf{v}, \mathbf{v}'; h_1)$ at scale h_1 for all voxels $\mathbf{v}$. After getting the new weights $w(\mathbf{v}, \mathbf{v}'; h_1)$, we can update $\hat{\beta}(\mathbf{v}; h_1)$. Then we can sequentially determine $w(\mathbf{v}, \mathbf{v}'; h_s)$ and then adaptively estimate $\hat{\beta}(\mathbf{v}; h_s)$. From $h_0 = 0$ to $h_S = r$, a path diagram of the multiscale adaptive strategy is given below:

$$\begin{array}{ccccccc}
 w(\mathbf{v}, \mathbf{v}'; h_0) & & w(\mathbf{v}, \mathbf{v}'; h_1) & & \dots & w(\mathbf{v}, \mathbf{v}'; h_S=r) \\
 \downarrow & \nearrow & \downarrow & \nearrow & \dots & \downarrow \\
 \hat{\beta}(\mathbf{v}; h_0) & & \hat{\beta}(\mathbf{v}; h_1) & & \dots & \hat{\beta}(\mathbf{v}; h_S)
 \end{array}$$

PMARM consists of three key steps: (I) an initialization step, (II) a weighted estimation step, and (III) a stop checking step. In the initialization step, we prefix a geometric series $\{h_s = c_h^s; s = 1, \dots, S\}$ of radii with $h_0 = 0$, where $c_h \in (1, 2)$, say $c_h = 1.15$ and $S = 10$. We use a small c_h in order to prevent incorporating too many neighboring voxels at the beginning, and this improves the robustness of the procedure and the accuracy of the parameter estimation. At $h_0 = 0$, we solve the regularized linear least-squares optimization problem (2) for a given penalty function to obtain $\hat{\beta}(\mathbf{v}; h_0) = \hat{\beta}(\mathbf{v})$ across all voxels $\mathbf{v}$. We then set $s = 1$ and $h_1 = c_h$.

In the weighted estimation step, we first compute $\text{Dist}(\mathbf{v}, \mathbf{v}'; h_{s-1})$ to characterize the similarity between the two estimated ODFs based on $\hat{\beta}(\mathbf{v}; h_s)$ and $\hat{\beta}(\mathbf{v}'; h_s)$ at voxels $\mathbf{v}$ and $\mathbf{v}'$ and the adaptive weights $\omega(\mathbf{v}, \mathbf{v}'; h_s)$, which are defined as

$$\omega(\mathbf{v}, \mathbf{v}'; h_s) = \frac{K_{loc}(\|\mathbf{v} - \mathbf{v}'\|_2 / h_s) K_{st}(\text{Dist}(\mathbf{v}, \mathbf{v}'; h_{s-1}))}{\sum_{\mathbf{v}' \in B(\mathbf{v}, h_s)} K_{loc}(\|\mathbf{v} - \mathbf{v}'\|_2 / h_s) K_{st}(\text{Dist}(\mathbf{v}, \mathbf{v}'; h_{s-1}))}, \quad (7)$$

where $K_{loc}(u)$ and $K_{st}(u)$ are two nonnegative kernel functions with compact support.

We compute $\text{Dist}(\mathbf{v}, \mathbf{v}'; h_{s-1})$ as the similarity between the estimated ODFs in voxels $\mathbf{v}$ and $\mathbf{v}'$ for HARDI as follows. For instance, for QBI in Example 1, we transform $\hat{\beta}(\mathbf{v}; h_{s-1})$ to its corresponding ODF representation, denoted as $\widehat{ODF}(\mathbf{v}; h_{s-1})$, which is a linear combination of the SH basis functions. Since the spherical harmonic basis is orthonormal,

$$\text{Dist}(\mathbf{v}, \mathbf{v}'; h_{s-1}) = \|\widehat{ODF}(\mathbf{v}; h_{s-1}) - \widehat{ODF}(\mathbf{v}'; h_{s-1})\|_2 \text{ can be written as } \|\hat{\beta}(\mathbf{v}; h_{s-1}) - \hat{\beta}(\mathbf{v}'; h_{s-1})\|_2.$$

The weights $K_{loc}(\|\mathbf{v} - \mathbf{v}'\|_2/h_s)$ give less weight to the voxel $\mathbf{v}' \in B(\mathbf{v}, h_s)$, whose location is far from the voxel $\mathbf{v}$. The $K_{loc}(\cdot)$ is a regular kernel function for smoothing the smoothed curves or surfaces. Some common choices of $K_{loc}(\cdot)$ include the Gaussian kernel and Epanechnikov kernel (Tabelow et al., 2006, 2008; Polzehl and Spokoiny, 2000). We use $K_{loc} = (1 - u^2)_+$ throughout this paper. The weights $K_{st}(\cdot)$ downweight the voxels that are dissimilar to voxel $\mathbf{v}$. The $\text{Dist}(\mathbf{v}, \mathbf{v}'; h_{s-1})$ takes large values if ODF in voxel $\mathbf{v}$ differ significantly from those in voxel $\mathbf{v}'$. We set $K_{st} = \exp(-u^2/a)$, where a is a positive scalar.

After the calculation of $\omega(\mathbf{v}, \mathbf{v}'; h_s)$, we calculate the weighted HARDI signals of voxel $\mathbf{v}$, denoted by $\mathbf{y}_w(\mathbf{v}; h_s) = \sum_{\mathbf{v}' \in B(\mathbf{v}, h_s)} \omega(\mathbf{v}, \mathbf{v}'; h_s) \mathbf{y}(\mathbf{v}')$. Then, we use (6) to compute $\hat{\beta}(\mathbf{v}; h_s)$ and $\widehat{ODF}(\mathbf{v}; h_s)$ at voxel $\mathbf{v}$. The computation of PMARM at each iteration is of the same order as that for the voxel-wise approach. Thus, this multiscale adaptive method provides an efficient method for adaptively exploring the neighboring voxels of each voxel. Since PMARM sequentially includes more data at each iteration, it will adaptively increase the statistical efficiency in estimating $\beta(\mathbf{v})$ in a homogenous region, while decreasing the variation of the weights $w(\mathbf{v}, \mathbf{v}'; h_s)$.

In the stop checking step, after the first iteration, we start to calculate a stopping criterion based on the L_2 distance between $\widehat{ODF}(\mathbf{v}; h_s)$ and $\widehat{ODF}(\mathbf{v}; h_{s-1})$, denoted by $\text{Dist}_s(\mathbf{v})$. Since the spherical harmonic basis is orthonormal, we have $\text{Dist}_s(\mathbf{v}) = \|\hat{\beta}(\mathbf{v}; h_{s-1}) - \hat{\beta}(\mathbf{v}; h_s)\|_2$. We use $\text{Dist}_s(\mathbf{v})$ to determine whether 'bad' HARDI signals from neighboring voxels lead to a dramatic change in the estimated $\widehat{ODF}(\mathbf{v}; h_{s-1})$. If $\text{Dist}_s(\mathbf{v}) > C_s$, where C_s is a positive scalar, then we set $\widehat{ODF}(\mathbf{v}; h_s) = \widehat{ODF}(\mathbf{v}; h_{s-1})$ and $s = S$ for voxel $\mathbf{v}$. If $s = S$ for all voxels, we stop. If $\text{Dist}_s(\mathbf{v}) \leq C_s$, then we set $h_{s+1} = c_h h_s$, increase s by 1, and continue with the weighted estimation step. In practice, different voxels may stop at different bandwidths, indicating that different degrees of smoothness are used to reconstruct HARDI.

We suggest choosing a relatively small c_h . Small c_h prevents incorporating too many neighboring voxels at the beginning of PMARM, and thus it can improve the robustness of PMARM for those voxels that are near or on the edge of regions with distinct features. Based on our previous experiences in Li et al. (2011), the choice of $c_h = 1.15$ and the use of the stop checking step can improve the robustness of PMARM and the accuracy of parameter estimation across all voxels.

We set $C_s = \chi^2(1)^{0.6/s} \bar{D}_{med}$ to prevent oversmoothing, where $\chi^2(1)^a$ is the upper $1-a$ percentile of the $\chi^2(1)$ distribution. As s increases, C_s decreases to zero. Moreover, $\bar{D}_{med}$ is chosen to be the median of $\{\text{Dist}(\mathbf{v}, \mathbf{v}'; h_0) : \mathbf{v} \neq \mathbf{v}'\}$, where $\mathbf{v}$ and $\mathbf{v}'$ are M preselected

voxels $\{\mathbf{v}_i\}_{i=1}^M$ from HARDI. Specifically, we select these M voxels from regions with different Generalized Fractional Anisotropy (GFA) values. For instance, for QBI, if the ODF $\Phi(\mathbf{r})$ is represented by the SH basis with coefficients $\{c_{lm}\}$, it is shown in Özarslan et al. (2005) that the GFA can be represented by

$$\text{GFA}\{\Phi_t(\mathbf{r})\} = \sqrt{1 - \frac{\beta_{00}^2}{\sum_{l=0}^L \sum_{m=-l}^l \beta_{lm}^2}}. \quad (8)$$

Determining a good C_s can be very difficult. Large C_s can increase estimation error near or on the edge of regions with distinct features, whereas small C_s may reduce the accuracy of parameter estimation in the interior of homogeneous regions. The most challenging issue is that a small difference in $\text{Dist}_s(\mathbf{v})$ can lead to a big change in ODF shape and its associated maximum directions. The term $\chi^2(1)^{0.6/s}$ in C_s decreases very fast as s increases and can prevent oversmoothing, while $\bar{D}_{med}$ that is estimated from the target dataset can prevent the substantial shape change in estimated ODF. By noting that the spherical harmonic basis is orthonormal, $\text{Dist}_s(\mathbf{v}) = \bar{D}_{med}$ can be regarded as a scaled L^2 distance between $\hat{\beta}(\mathbf{v}; h_s)$ and $\hat{\beta}(\mathbf{v}; h_{s-1})$. An intuition of selecting $\chi^2(1)$ is that the distribution of $\text{Dist}_s(\mathbf{v})/\bar{D}_{med}$ at least for small s may be roughly approximated by $\chi^2(1)$.

- Estimate $\hat{\beta}(\mathbf{v})$ from (2), in which we set $\lambda_{LB} = 0.006$ and λ_{I_1} is chosen using 10-fold Cross Validation.
- For $s \leftarrow 1$ to S
 - calculate the weights $w(\mathbf{v}, \mathbf{v}'; h_s)$ for $\mathbf{d}' \in B(d, h_s)$ by (7);
 - calculate the weighted signals of voxel $\mathbf{v}$ by using $\mathbf{y}_w(\mathbf{v}; h_s) = \sum_{\mathbf{v}' \in B(\mathbf{v}, h_s)} w(\mathbf{v}, \mathbf{v}'; h_s) \mathbf{y}(\mathbf{v}')$;
 - calculate $\hat{\beta}(\mathbf{v}; h_s)$ based on (6);
 - calculate $\widehat{ODF}(\mathbf{v}; h_s)$.
 - If $\text{Dist}_s(\mathbf{v}) > C_s$,
 - $\widehat{ODF}(\mathbf{v}; h_s) = \widehat{ODF}(\mathbf{v}; h_{s-1})$, and $s = S$,
 - else $h_{s+1} = c_h h_s$.
- End.
- Return $\hat{\beta}(\mathbf{v}; h_S)$ and $\widehat{ODF}(\mathbf{v}; h_S)$.

Ideally, we might use some criterion (e.g., cross-validation or AIC) to determine $\lambda(\mathbf{v})$ at each $\mathbf{v}$. However, for computational efficiency, we set $\lambda(\mathbf{v}) = \lambda_{LB} = 0.006$ in cQBI across all voxels. The choice of $\lambda_{LB} = 0.006$ was discussed in Descoteaux et al. (2007) and choice of $\lambda_{I_1} = 0.02$ is selected based on our experiments. We also chose $\lambda(\mathbf{v}) = \lambda_{I_1}$ in LASSO by the 10-fold cross validation.

2.4 Maxima Extraction

Based on $\widehat{ODF}(\mathbf{v}; h_s)$ at voxel $\mathbf{v}$, we need to extract its maxima in order to infer fiber directions. Although there are other more complicated methods for extracting ODF maxima, such as the method presented in Hlawitschka and Scheuermann (2005), spherical Newton's method (Tuch, 2004), and Powell's method (Jansons and Alexander, 2003), we take a simple thresholding approach in this paper. Specifically, we project the estimated ODF onto the sphere tessellated with a triangle mesh, which has 2562 points on the unit sphere. If the estimated ODF value at a mesh point is greater than the corresponding value at all of its neighboring mesh points and this estimated ODF value is greater than $\max(\text{ODF})/2$, then the direction at this mesh point is regarded as a maximum. This thresholding method avoids selecting small peaks that may appear due to noise.

3 Simulation Studies

In this section, we use Monte Carlo simulations based on four phantoms to evaluate the finite-sample performance of PMARM and compare PMARM with other estimation methods. All computations for these numerical examples were done in Matlab on an IBM ThinkCentre M50 workstation. The computation for PMARM is relatively efficient. The computational time for PMARM can be further reduced by using other computer languages, such as C++.

3.1 Simulation Setup

We examined the finite sample performance of our PMARM on detecting crossing fibers by using synthetic HARDI data generated from the multi-tensor model (Alexander et al., 2002; Tuch, 2004). We simulated the diffusion-weighted signals according to

$$E(\mathbf{q}_i; \mathbf{v}) = \sqrt{\left(\sum_{k=1}^K p_k e^{-b_i \mathbf{u}_i^T \mathbf{D}_k(\mathbf{v}) \mathbf{u}_i + \sigma \varepsilon_{i1}} \right)^2 + (\sigma \varepsilon_{i2})^2} \quad (9)$$

for $i = 1, \dots, n$, where $\mathbf{q}_i = q_i \mathbf{u}_i$ with $\mathbf{u}_i$ being a unit vector, K is the number of fibers, p_k is the weight for k -th fiber, b is the b-value and $\mathbf{D}_k(\mathbf{v})$ is the tensor matrix for the k -th fiber, $\text{SNR} = 1/\sigma$, and ε_{i1} and ε_{i2} are independently simulated from a standard normal distribution. We used the multi-tensor model (9) to generate different phantoms with different regions of interest (ROIs) with 81 sampling directions on the hemisphere for the 3rd order tessellation of the icosahedron and $b = 1000, 2000 \text{ s/mm}^2$. Specifically, voxels with a single fiber were generated from a single tensor model using diffusion tensor profiles with eigenvalues $[1.7, 0.3, 0.3] \times 10^{-3} \text{ mm}^2/\text{s}$, voxels with two fiber directions were generated by a two-tensor model $E(\mathbf{q}_i; \mathbf{v}) = e^{-b_i \mathbf{u}_i^T \mathbf{D}_1(\mathbf{v}) \mathbf{u}_i} / 2 + e^{-b_i \mathbf{u}_i^T \mathbf{D}_2(\mathbf{v}) \mathbf{u}_i} / 2$, and voxels isotropic tensors were generated by a single tensor model using diffusion tensor profiles with eigenvalues $[1, 1, 1] \times 10^{-3} \text{ mm}^2/\text{s}$. We estimated ODF at each voxel by using the three voxel-wise estimation methods including cQBI, LASSO and LDPE, and their corresponding three PMARMs

including p-cQBI, p-LASSO, and p-LDPE. For PMARM, we set $K_{st} = \exp(-u^2/4)$ and then we extracted the ODF maxima aligned with fiber directions.

Although we consider four phantoms, we include the simulation results for the second and third phantoms in the Appendix for the sake of space.

3.1.1 Angle Detection in the First Phantom with 90° crossing fibers—In the first 10×10 phantom with voxel size 1×1 , we included four different ROIs including isotropic ROIs, two single fiber ROIs with its direction going either along the x axis (ROI1) or along the y axis (ROI2), and the 90° crossing fiber ROIs (ROI3). Figure 2 presents the estimated ODF images for this type of phantom. The left panel on the top row presents the recovered ODF from noise free data, whereas the other three panels on the top row present those from the data with SNR/10 by using cQBI, LASSO, and LDPE, respectively. Three panels on the bottom row present the recovered ODFs from the same dataset by using p-cQBI, p-LASSO and p-LDPE. Generally, PMARMs outperform the voxel-wise methods in terms of detecting the isotropic regions and consistently recovering the ODFs with fiber crossing.

To quantify the accuracy of detection angle, we generated 1,000 data sets for three different SNRs including 10, 15, and 20. We estimated the ODFs by using voxel-wise cQBI, LASSO and LDPE and their corresponding three PMARMs. Then we extracted the ODF maxima aligned with fiber directions. For voxels with a single fiber, we calculated angle detection errors by comparing recovered fiber directions with the ground truth. For voxels with two crossing fibers, we calculated angle detection errors by comparing recovered crossing angles with the ground truth. Mean angle detection errors at each voxel are calculated based on the 1000 simulations using each estimation method. The average values of these detection errors for each ROI are presented in Table 1. Moreover, the computational time of 1000 simulations for cQBI, LASSO, LDPE, p-cQBI, p-LASSO, and p-LDPE are around 8, 16, 10, 12, 25, and 13 minutes, respectively.

Table 1 reveals that the mean angle errors are substantially reduced for the three PMARM methods. It may indicate that PMARM can efficiently exploit spatial smoothness for reconstructing ODFs, while reducing noise leading to better angle detection. Among the three methods, LASSO and LDPE outperform cQBI in terms of the mean angle error, since LASSO and LDPE force smaller ODF coefficients to be zero, leading to a more stable recovery of ODFs. Moreover, LDPE outperforms LASSO in terms of the mean angle error, since non-zero coefficients of LDPE are unbiased compared with LASSO estimators (Zhang and Zhang, 2014). Among the three methods with PMARM, p-LASSO performs the best. The reason is that these simulated ODFs can be indeed represented as the sparse linear combination of order 4 spherical harmonic basis, see Appendix for the figures of order 4 SH basis. Together with the de-noising effect of PMARM, the recovered ODFs are very close to the ground truth.

When using the same order of SH basis, the results from b value 2000s/mm² are better than those from 1000s/mm². This indicates that stronger signal would lead to better ODF recovery. When b values are the same, the results from using order 4 SH basis are better. This is because higher order terms of SH basis in this setting contribute more to the noise.

3.1.2 Angle Detection in the Fourth Phantom with Twisted Crossing—In the fourth 17×13 phantom with voxel size 1×1 , we included a twisted crossing region in the middle, one fiber along x axis (ROI1), and the other fiber with changing angles with x axis from 45° , 60° , 75° , to 90° and then from 90° , 75° , 60° , to 45° . We marked all region with single fiber, which is not along x axis as ROI2, and all regions with crossing fibers as ROI3. We used the same setting as the previous phantom simulations. Figure 3 presents the estimated ODF images. Table 2 includes the average values of these detection errors for each ROI, indicating reduction in mean angle errors by using PMARM. The computational time of 1000 simulations for cQBI, LASSO, LDPE, p-cQBI, p-LASSO, and p-LDPE are around 16, 30, 12, 21, 42, and 30 minutes, respectively.

3.2 Summary of Simulations

We have the following findings. First, the three PMARM methods outperform the three voxel-wise methods in all ROIs, especially in ROIs with crossing fibers. Second, the estimated ODFs in the single fiber ROIs are sharper and it is easier to detect the maxima. Third, the L_1 penalty based methods outperform the methods based on the Laplacian-Beltrami regularization in the isotropic ROIs, since in the isotropic regions, the ODF coefficients are small and tend to be suppressed to zero. Fourth, the improvement in Simulation 3 is much less than those in Simulations 1 and 2. This may be due to the fact that the simulated phantoms in Simulations 1 and 2 are geometrically simpler compared with that in Simulation 3. Fifth, when using the same order of SH basis, the results from b value 2000s/mm^2 are better than those from 1000s/mm^2 . It may indicate that stronger signal would lead to better ODF recovery. Sixth, the results based on the order 4 SH basis are better than those based on the order 6 SH basis, since the higher order terms of SH basis contribute more to the noise.

4 Pig Brain

The pig brain data set comes from a post-mortem porcine brain and was kindly provided by Tim Dyrby from The Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital, Hvidovre, Denmark (Dyrby et al., 2011). The acquisition uses a spherical acquisition scheme with 61 unique gradient directions with the b -value of 4009 s/mm^2 and three baseline images with $b = -\text{s/mm}^2$. Imaging protocol included: image size: $256 \times 128 \times 35$, voxel size: $0.51 \times 0.51 \times 0.5\text{ mm}^3$, TR= 6500ms, TE=67.1ms, and gap= 0.5 mm .

We used analytical QBI, in which $E(\mathbf{q}; \nu)$ is represented as a linear combination of spherical harmonic basis functions, to estimate the ODF by using voxel-wise cQBI, LASSO and LDPE and their corresponding three PMARMs. We set $K_{st} = \exp(-u^2/4)$ and λ in LASSO is chosen by 10-fold cross validation. The results are shown in (Figure 4). All PMARM methods lead to better ODF reconstruction results, in terms of smoother ODFs along the fiber tract. In the isotropic regions, i.e. regions with low GFA values, PMARM can get more isotropic results. The mean GFA values of isotropic ROIs in the red boxes from p-cQBI (0.083), p-LASSO (<0.001), and p-LDPE (0.084) are less than those from cQBI (0.128), LASSO (0.091) and LDPE (0.098). In the regions with fiber crossings, the main fibers are

easier to detect than less small noisy fibers. Since in PMARM, we exploit the spatial constraints to estimate ODFs, PMARM can reduce the noise level in HARDI, while improving the ODF reconstruction, especially in some ROIs. Generally, PMARM can improve the recovery of crossing fibers.

5 Conclusion

We have introduced a penalized multiscale adaptive model (PMARM) framework to adaptively reconstruct the ODF across all voxels from HARDI signals. PMARM reconstructs the ODF at each voxel by adaptively borrowing the spatial information from the neighboring voxels. We have shown in the real and simulated data sets that PMARM can substantially reduce the noise level, while improving the ODF reconstruction. We have shown that the L_1 penalty function outperforms the Laplacian-Beltrami regularization and leads to sparse ODF solution in isotropic regions, and can better detect the these regions when the sparse ODF solution exists. However, such sparse solution does not always exist, this is because the SH basis is not a complete basis, not all ODF can be represented by the linear combination of these basis functions.

Many important issues need to be addressed in future research. First, we use a homogeneous linear model in (2), but such approximation can introduce substantial bias even for DTI when the signal-to-noise ratio is relatively low (Zhu et al., 2009). Thus, it is interesting to appropriately model noise components in HARDI for relatively low signal-to-noise ratio. Second, we have not investigated the theoretical properties of PMARM, such as the convergence rate of $\hat{\beta}(\mathbf{v}; h_s)$ and $\widehat{ODF}(\mathbf{v}; h_s)$. Third, it is interesting to consider other locally adaptive smoothing methods, such as nonlocal means, in the literature (Qiu and Mukherjee, 2010; Mukherjee and Qiu, 2011). Fourth, it is critically important to develop computationally efficient algorithms for the implementation of PMARM for real HARDI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Simulation results: in the first row, ODF reconstruction of noise-free data; in the second row, ODFs of the data with noise (SNR=10) using cQBI, Lasso and LDPE, respectively.

Figure 2.

Simulation results for the first phantom: ODF reconstruction results of simulated data with 90 degree crossing.

Figure 3.

Simulation results for the fourth phantom: ODF reconstruction results on simulated data with twisted crossing.

Figure 4.

ODF reconstruction results for the pig dataset: The first shows the GFA maps from cQBI, LASSO and LDPE methods; the second row shows the GFA maps from three corresponding PMARM methods; the third row shows the ODF 24 in the selected ROI without PMARM; the fourth row shows the ODF with PMARM. All the ODF's are min-max normalized.

Table 1

Mean angle errors of different ROIs in the first phantom. 1,000 simulated data sets were used.

ROI1: fibers along x axis								
<i>b</i> value (s/mm ²)	SH order	SNR	cQBI	p-cQBI	LASSO	p-LASSO	LDPE	p-LDPE
1000	4	10	4.73	2.35	2.49	0.40	0.75	0.32
1000	4	15	3.09	1.03	1.62	0.15	0.40	0.21
1000	4	20	2.13	0.40	1.03	0.05	0.26	0.10
1000	6	10	6.91	3.74	4.98	1.23	2.31	1.72
1000	6	15	4.48	2.10	3.23	0.42	1.04	0.58
1000	6	20	3.26	1.16	2.28	0.22	0.65	0.36
2000	4	10	3.48	1.47	1.99	0.27	0.58	0.31
2000	4	15	2.46	0.68	1.36	0.12	0.42	0.24
2000	4	20	1.92	0.34	1.03	0.07	0.41	0.13
2000	6	10	4.94	2.55	4.00	0.75	1.53	1.04
2000	6	15	3.69	1.64	2.98	0.41	1.02	0.63
2000	6	20	2.9	1.01	2.42	0.27	0.89	0.51
ROI2: fibers along y axis								
<i>b</i> value (s/mm ²)	SH order	SNR	cQBI	p-cQBI	LASSO	p-LASSO	LDPE	p-LDPE
1000	4	10	4.72	2.14	2.46	0.32	0.73	0.31
1000	4	15	3.09	0.85	1.57	0.12	0.43	0.17
1000	4	20	2.11	0.30	0.99	0.04	0.28	0.06
1000	6	10	6.97	3.56	5.08	1.20	2.42	1.75
1000	6	15	4.51	1.87	3.27	0.33	1.15	0.56
1000	6	20	3.31	0.96	2.29	0.16	0.73	0.34
2000	4	10	3.48	1.28	1.95	0.21	0.62	0.26
2000	4	15	2.47	0.55	1.32	0.08	0.45	0.16
2000	4	20	1.93	0.26	1.01	0.04	0.39	0.11
2000	6	10	4.95	2.34	4.05	0.67	1.56	1.02

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ROI2: fibers along y axis										
<i>b</i> value (s/mm ²)	SH order	SNR	cQBI	p-cQBI	LASSO	p-LASSO	LDPE	p-LDPE		
2000	6	15	3.7	1.43	3.03	0.33	1.09	0.6		
2000	6	20	2.92	0.84	2.40	0.21	0.92	0.49		

ROI3: 90° crossing										
<i>b</i> value (s/mm ²)	SH order	SNR	cQBI	p-cQBI	LASSO	p-LASSO	LDPE	p-LDPE		
1000	4	10	7.94	2.74	11.26	7.07	9.33	5.28		
1000	4	15	4.56	1.69	3.69	0.17	3.69	0.27		
1000	4	20	3.24	1.07	1.50	0.04	0.95	0.12		
1000	6	10	15.24	8.19	15.59	13.12	10.83	8.95		
1000	6	15	11.90	5.03	9.09	1.07	5.37	0.91		
1000	6	20	9.38	3.59	5.66	0.23	2.30	0.59		
2000	4	10	3.61	1.63	2.25	0.10	2.14	0.19		
2000	4	15	2.29	0.88	0.80	0.03	0.23	0.1		
2000	4	20	1.78	0.41	0.57	0.01	0.12	0.07		
2000	6	10	10.56	4.76	7.25	0.58	3.95	1.59		
2000	6	15	7.12	2.99	4.20	0.25	1.66	0.66		
2000	6	20	5.26	2.04	2.99	0.16	1.14	0.47		

Table 2

Mean angle errors of different ROIs in the fourth phantom. 1,000 simulated data sets were used.

ROI1: fibers along x axis								
<i>b</i> value (s/mm ²)	SH order	SNR	cQBI	p-cQBI	LASSO	p-LASSO	LDPE	p-LDPE
1000	4	10	4.71	1.94	2.43	0.29	0.73	0.32
1000	4	15	3.08	0.65	1.57	0.09	0.42	0.15
1000	4	20	2.10	0.26	0.98	0.03	0.27	0.07
1000	6	10	6.93	3.40	5.04	1.22	2.36	1.81
1000	6	15	4.50	1.66	3.26	0.32	1.09	0.57
1000	6	20	3.29	0.93	2.29	0.14	0.68	0.34
2000	4	10	3.47	1.01	1.95	0.19	0.62	0.25
2000	4	15	2.47	0.37	1.31	0.07	0.45	0.16
2000	4	20	1.92	0.18	1.01	0.04	0.38	0.12
2000	6	10	4.96	2.15	4.05	0.67	1.54	1.05
2000	6	15	3.71	1.12	3.06	0.31	1.07	0.61
2000	6	20	2.92	0.69	2.43	0.18	0.91	0.50
ROI2: single fibers except the ones from x axis								
<i>b</i> value (s/mm ²)	SH order	SNR	cQBI	p-cQBI	LASSO	p-LASSO	LDPE	p-LDPE
1000	4	10	4.77	3.16	3.75	2.22	3.09	2.75
1000	4	15	3.25	2.44	2.57	1.85	2.44	1.96
1000	4	20	2.40	2.15	1.87	1.72	1.88	1.52
1000	6	10	6.93	4.27	6.40	3.24	4.23	4.14
1000	6	15	4.58	2.99	4.24	2.14	3.19	2.45
1000	6	20	3.45	2.52	3.13	1.79	2.40	1.80
2000	4	10	3.61	2.53	2.91	1.84	2.73	1.96
2000	4	15	2.71	2.16	2.15	1.59	2.04	1.46
2000	4	20	2.26	2.00	1.80	1.53	1.67	1.32
2000	6	10	5.00	3.26	4.94	2.49	3.68	2.89

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ROI2: single fibers except the ones from x axis										
<i>b</i> value (s/mm ²)	SH order	SNR	cQBI	p-cQBI	LASSO	p-LASSO	LDPE	p-LDPE		
2000	6	15	3.83	2.64	3.78	1.88	2.75	1.90		
2000	6	20	3.11	2.35	3.10	1.66	2.26	1.64		

ROI3: two crossing fibers										
<i>b</i> value (s/mm ²)	SH order	SNR	cQBI	p-cQBI	LASSO	p-LASSO	LDPE	p-LDPE		
1000	4	10	11.02	7.60	18.74	15.11	24.17	15.36		
1000	4	15	7.50	7.27	9.38	4.81	17.66	5.17		
1000	4	20	5.18	3.36	4.71	3.62	8.45	5.86		
1000	6	10	13.56	11.16	19.73	23.32	23.30	19.40		
1000	6	15	11.48	9.67	13.21	7.19	20.01	5.19		
1000	6	20	9.66	7.98	8.72	3.80	11.31	4.44		
2000	4	10	5.32	3.95	6.32	4.00	10.97	4.21		
2000	4	15	3.71	3.59	3.50	3.62	4.11	3.95		
2000	4	20	3.30	3.44	3.33	3.53	3.49	3.82		
2000	6	10	9.33	5.45	9.22	4.75	12.10	5.41		
2000	6	15	6.61	4.39	5.47	3.47	5.32	4.20		
2000	6	20	5.11	22 3.37	4.39	3.27	4.06	3.96		