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A Unified Computational Framework for Deconvolution to Reconstruct Multiple Fibers From Diffusion Weighted MRI

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Abstract

Diffusion magnetic resonance imaging (MRI) is a relatively new imaging modality which is capable of measuring the diffusion of water molecules in biological systems noninvasively. The measurements from diffusion MRI provide unique clues for extracting orientation information of brain white matter fibers and can be potentially used to infer the brain connectivity *in vivo* using tractography techniques. Diffusion tensor imaging (DTI), currently the most widely used technique, fails to extract multiple fiber orientations in regions with complex microstructure. In order to overcome this limitation of DTI, a variety of reconstruction algorithms have been introduced in the recent past. One of the key ingredients in several model-based approaches is deconvolution operation which is presented in a unified deconvolution framework in this paper. Additionally, some important computational issues in solving the deconvolution problem that are not addressed adequately in previous studies are described in detail here. Further, we investigate several deconvolution schemes towards achieving stable, sparse, and accurate solutions. Experimental results on both simulations and real data are presented. The comparisons empirically suggest that nonnegative least squares method is the technique of choice for the multifiber reconstruction problem in the presence of intravoxel orientational heterogeneity.

Index Terms

Deconvolution; diffusion-weighted magnetic resonance imaging (DW-MRI); multifiber reconstruction; nonnegative least squares (NNLS)

I. Introduction

Diffusion-weighted magnetic resonance imaging (DW-MRI or DWI) is a noninvasive technique exploiting the directional sensitivity of the MR signal to the diffusion of water molecules [1]. The directional dependence of water diffusion in fibrous tissues, like muscle and white-matter in the brain, provides an indirect but powerful means to study the microstructure of these tissues and probe neuronal connections between different regions of the central nervous system.

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Assuming a local 3-D Gaussian diffusion profile, diffusion tensor MRI (DTI or DT-MRI) provides a relatively simple way of quantifying diffusion anisotropy as well as extracting fiber directions locally from DW-MRI data [2]. The DTI model has been shown to be quite successful in regions of the brain and spinal cord with significant white-matter coherence and has enabled the mapping of anatomical connections in the central nervous system [3]. However, the major drawback of diffusion tensor MRI is that it can only reveal a single fiber orientation in each voxel and fails in regions containing multiple fiber orientations [4]–[6]. In a recent study, it was estimated that this intravoxel orientational heterogeneity (IVOH) problem affects one third of white matter voxels where tractography applications relying on the diffusion tensor model will provide unreliable results [7].

To overcome this limitation of diffusion tensor model, a number of advanced image acquisition strategies and sophisticated mathematical models have been proposed. With the multidirectional measurements from the high angular resolution diffusion weighted imaging (HARDI) [6] method, both the spherical harmonic transformation [4], [5] and the equivalent generalized diffusion tensor model [8] have been employed to represent the apparent diffusivity profiles in the presence of multiple fiber populations. There are two limitations in these methods. First, both methods assume mono-exponential signal decay model, which has been shown to be not valid for high diffusion-weighting values *in vivo* [9]. Second, it has been demonstrated [10] that the peaks of the diffusivity profile do not necessarily correspond to the orientations of the distinct fiber populations.

Q-ball imaging (QBI) [11] reconstructs the so called diffusion orientation distribution function (ODF) by using the spherical Funk-Radon transform to approximate the radial projection of the diffusion probability density function (pdf). More recent studies have expressed QBI's funk-radon transform in a spherical harmonic basis [12]–[14]. One problem with QBI is that the measured diffusion ODF is modulated by a zeroth-order Bessel function that induces spectral broadening of the diffusion peaks. Diffusion spectrum imaging (DSI) [15] computes the microscopic diffusion function directly based on the Fourier relation between the diffusion signal and the diffusion function, but is limited by the time-intensive q -space sampling burden. The recently proposed diffusion orientation transform (DOT) [10] is able to transform the diffusivity profiles into probability profiles by explicitly expressing the Fourier relation in spherical coordinates and evaluating the radial part of the integral analytically. However, DOT also assumes mono-exponential signal decay. The extension to the bi-exponential signal decay would then require acquiring data acquisition over two concentric spheres in the q -space.

Tuch [6] proposed to model the diffusion signal using a discrete mixture of Gaussians. Other similar multiple tensor models include [7], [16], [17]. Two problems accompany the use of multicompartment models. First, the number of such compartments has to be prespecified, presenting a model-selection problem. Second, the parameter estimation requires a nonlinear fitting which tends to perform poorly when more than two fiber orientations are present. To avoid the problems of the multicompartment models, Tournier *et al.* [18] employed a spherical deconvolution method to estimate the underlying arrangement and orientations of fiber populations. The key idea of the spherical deconvolution method is to assume that there is a distribution, rather than a discrete number, of fiber orientations in each voxel. Under this assumption, the diffusion MR signal is the convolution of the fiber orientation distribution (FOD), which is a real-valued function on the unit sphere, with some kernel function representing the response derived from a single fiber bundle. Compared to the multicompartment models, the spherical deconvolution framework has two significant advantages. First, it does not require the specification of the number of underlying fibers before computing the FOD. Second, the spherical deconvolution methods often lead to a

linear system which can be solved efficiently while the multicompartment models usually involve a computationally expensive nonlinear fitting.

Recognizing these merits of the spherical deconvolution framework, recently many researchers have proposed a number of variants of the spherical deconvolution approaches [12], [19]–[21]. Although the deconvolution as an elegant tool has now been used widely for the multifiber reconstruction from diffusion weighted MRI, some important computational issues that arise in application of the deconvolution framework have not been addressed adequately in literature. The key issues of concern are the stability of the deconvolution in the presence of noise and the ability to accurately recover multiple fiber orientations from relatively low angular resolution imaging data. In this paper, we will systematically investigate each of these issues. The remainder of the paper is organized as follows. First, we present a unified deconvolution framework in the context of multifiber reconstruction and compare several existing reconstruction algorithms in this framework in terms of their choices of FOD parameterizations, deconvolution kernels, and regularization schemes. Then in the subsequent sections, we address the importance of regularization as well as the nonnegativity and sparsity constraints. A few representative computational methods are explored in depth towards achieving stable recovery of multiple fiber orientations. Finally, we present experimental results on both simulations and real data sets followed by comparisons and discussions.

II. Unified Deconvolution Framework

In this section, we formulate a general deconvolution framework which unifies several aforementioned DW-MRI reconstruction approaches. For convenience, the major notation and symbols used in this paper are summarized in Table I. It is interesting to observe that many model-dependent DW-MRI reconstruction methods can be cast into the following unified deconvolution framework:

$$S(\mathbf{q})/S_0 = \int_{\mathcal{M}} R(\mathbf{q}, \mathbf{x}) f(\mathbf{x}) d\mathbf{x}. \quad (1)$$

In (1), the signal is expressed as the convolution of a probability density function $f(\mathbf{x})$ and a kernel function $R(\mathbf{q}, \mathbf{x})$. The integration is over a manifold $\mathcal{M}$, each point, $\mathbf{x}$, of which contains information about fiber orientation and anisotropy. In order to handle the intravoxel orientational heterogeneity, a fiber orientation distribution $f(\mathbf{x}) : \mathcal{M} \mapsto \mathbb{R}$ is assumed to give a continuous representation of the volume fractions. The convolution kernel, $R(\mathbf{q}, \mathbf{x}) : \mathbb{R}^3 \times \mathcal{M} \mapsto \mathbb{R}$ represents the response derived from a single fiber. The deconvolution problem involves estimating $f(\mathbf{x})$ given $R(\mathbf{q}, \mathbf{x})$ and the measurement $E(\mathbf{q})$. We can now cast the existing multifiber reconstruction methods into the above described general deconvolution framework thereby interpreting these methods as specializations of a unified deconvolution framework. Table II summarizes some of the existing multifiber reconstruction methods in the above described unified deconvolution framework. The first approach listed in Table II corresponds to the traditional diffusion tensor imaging method when the mixing distribution in the convolution integral is taken to be a single Dirac distribution. Note that in all the other listed methods in the table, the fiber orientation distribution $f(\mathbf{x})$ is expressed as a linear

combination of K basis functions $f(\mathbf{x}) = \sum_{k=1}^K \omega_k f_k(\mathbf{x})$. The listed methods include the use of radial basis functions in [19], spherical harmonics in [12], and the mixture of Wishart (matrix-variate Gamma) distributions in [23]. It is important to note that with the exception of work reported in [24] where K is set to a fixed number (usually 2), the number K only reflects the resolution of the discretization on the manifold $\mathcal{M}$ and should not be interpreted as the number of expected fiber populations. Moreover, except for the method described in

[24] where both the volume fraction ω_k and the parameter of basis functions (D_k) are unknown, all the other methods lead to a problem that can be expressed in the general form of

$$A\omega = s + \eta \quad (2)$$

where, on the right-hand side, s is a column vector containing N multidirectional measurements, $\{s_i\} = \{S(\mathbf{q}_i)/S_0\}$, and η represents the noise; while on the left-hand side, $A = \{a_{ik}\}$ is an $N \times K$ matrix given by $a_{ik} = \int_M R(\mathbf{q}_i, x) f_k(x) dx$ and ω is the unknown weight vector. Note that the integral to compute the entries of A may have an analytical solution as in [23] or needs to be numerically approximated as in [19], depending on the choices of convolution kernels and basis functions. But once the response kernel $R(\mathbf{q}, x)$ and the basis function are specified, the matrix A can be fully computed (or approximated) and only ω , a column vector containing K unknown coefficients, remains to be estimated. It is worth noting that a further spherical harmonics (SH) expansion on ω in [12], [18], [20] leads to a parametric deconvolution of ω in terms of SH coefficients. However, it is straightforward to change this parametric deconvolution back to the direct nonparametric deconvolution of ω . In our opinion, it is more natural and easier to interpret and handle the weight vector than the SH coefficients vector. For this reason, we will only discuss the nonparametric deconvolution of ω in this paper.

After obtaining the vector ω , the diffusion weighed MR signal attenuation model $E(\mathbf{q}) = S(\mathbf{q})/S_0$ can be analytically expressed using the general form as in (2). As a result, the displacement probability $P(\mathbf{r})$ can then be computed by the Fourier transform $P(\mathbf{r}) = \int (S(\mathbf{q})/S_0) \exp(-i\mathbf{q} \cdot \mathbf{r}) d\mathbf{q}$ where $\mathbf{r}$ is the displacement vector. The $P(\mathbf{r})$ function defined above describes the probability for water molecules to move a fixed distance and has been employed in the DOT method [10]. Note that when a tensor based response kernel $R(\mathbf{q}, x)$ is used, the resulting $P(\mathbf{r})$ can be approximated as a mixture of oriented Gaussians. In this case, many of the quantities produced by other methods including the radial integral of $P(\mathbf{r})$ in QBI [11] and the integral of $P(\mathbf{r})r^2$ in DSI [15] are analytically computable. This fact provides us the opportunity to understand these quantities and evaluate their performances in resolving complicated local fiber geometries.

Solving the problem in (2) is central to many fiber reconstruction methods and it requires a suite of well designed algorithms. In the following, we briefly discuss several issues which are not addressed adequately in previous studies. With regards to the matrix A , two numerical issues arise. First, A can be ill conditioned which leads to the stability issue. We noticed that most deconvolution models used in literature ([19]) result in extremely ill conditioned linear systems. Second, A can be under-determined when $K > N$. Actually, in practice, N , the number of diffusion MRI imaging acquisition sequence, is rarely greater than 100. On the other hand, in order to obtain a high resolution reconstruction, K is usually set to a large number greater than 100. As a result, there is no unique solution to (2) even in the least-squares sense. The aforementioned issues reveal the fact that the deconvolution problems in our application domain are often ill posed. A disturbing consequence of this ill posedness is that, if the data are even slightly inaccurate, the solution obtained by the standard least squares method will be staggeringly unstable. This can be a real concern as was shown in [12].

Regarding the unknown vector ω , it is natural to impose some useful prior information based on the following considerations: Since the weights $\omega = \{\omega_i\}_{i=1}^K$ correspond to volume fractions, they are expected to be nonnegative. Negative weights are not physically meaningful and should be penalized by adding a regularization term or excluded by imposing an explicit nonnegativity constraint. In addition, it is reasonable to assume that

most white matter voxels only contain contributions from relatively few fiber bundles. Therefore, apart from a few significant peaks, we expect ω has a sparse support, i.e., most entries of ω are expected to be zero (or very small). It is important to note that the sparsity property also has advantages in the optimization process required to find the maxima of the water molecule displacement probability function, which represent the fiber orientations in the multifiber reconstruction problem.

III. Computational Issues

A. Regularization and Stability

To set up the computational model for solving the deconvolution problem, we need to first select a measure of discrepancy between $A\omega$ and s . Under the assumption that the measurement errors η are independent and follow identical normal distributions, the maximum likelihood estimate of ω naturally leads to the L_2 norm as a goodness measure. Without inequality constraints, the corresponding quadratic programming (QP) problem of minimizing the residual sum of squares

$$(P_1) \quad \min \|A\omega - s\|^2 \quad (3)$$

can be efficiently solved by seeking a solution to a linear system using direct methods when the size of the linear system in (3) is not large as in our application. The solution in the least squares sense is given by $\omega = A^+s$ where $A^+ = (A^T A)^{-1} A^T$ is the pseudo-inverse of the A . The advantage of applying the pseudo-inverse is in its light computational burden since the matrix A is identical in each voxel and its pseudo-inverse only needs to be computed once. However, this simplicity and efficiency comes at the cost of higher susceptibility to noise, especially when A is ill conditioned, which occurs very often in practice and raises serious numerical issues. This ill conditioning phenomena is clearly illustrated in Fig. 1.

Tikhonov regularization [25] is a very popular technique for solving ill posed inverse problems. In the general framework of Tikhonov regularization, the original problem in (2) can be formulated as finding the ω that solves

$$(P_2) \quad \min \|A\omega - s\|^2 + \alpha \|T\omega\|^2 \quad (4)$$

where α is a regularization parameter and T is a regularization operator. In order to penalize the magnitude of the estimates, a zeroth-order Tikhonov regularization with the matrix operator T being set to the identity operator $\mathbf{I}$ is commonly used. Minimization of the objective function in (4) with $T = \mathbf{I}$ yields the equation $A^T s = (A^T A + \alpha \mathbf{I}) \omega$ whose solution is given by

$$\omega = (A^T A + \alpha \mathbf{I})^{-1} A^T s. \quad (5)$$

In (5), $(A^T A + \alpha \mathbf{I})^{-1} A^T$ is called the damped least squares (DLS) inverse of A and can be computed using the singular value decomposition (SVD).

Since the nonnegative damping factor α controls a trade-off between accuracy and stability, it is important to choose α in order to avoid the under-regularization or the over-regularization. Recently, [26] used the DLS method to regularize the fiber orientation distribution combined with generalized cross validation (GCV) [27] to select the optimal damping factor. The GCV function is a one-dimensional function of the regularization parameter (damping factor α) and can be efficiently evaluated by taking the compact SVD of the system matrix A . The cost to minimize the GCV is hence small. However, GCV may have trouble when dealing with perfect data because practically the numerical calculations

with the theoretically right $\alpha = 0$ or α near machine 0 can cause numerical instabilities and yield an unsatisfactory solution. Moreover, as discussed in [27], “the theory justifying the use of GCV is an asymptotic one. Good results cannot be expected for very small sample sizes when there is not enough information in the data to separate signal from noise.”

B. Nonnegativity and Sparsity Constraints

From our experience, we found that Tikhonov regularization is able to suppress the large spurious negative spikes in the deconvolved vector ω as expected but there are still many negative components in ω when Tikhonov regularization was applied with practical regularization parameters. Obviously, such negative weights are not physically meaningful. A recently proposed spherical deconvolution technique [20] places a nonnegativity constrain on the estimated FOD which eliminates the need for previously suggested low-pass filtering [18]. It is important to understand that the appearance of negative weights is partially caused by the under-determined configuration in our deconvolution problem. In practice, N , the number of diffusion MRI image acquisition sequence, is rarely greater than 100. On the other hand, in order to obtain an accurate reconstruction, a high resolution tessellation with $K > 100$ is usually taken. This gives a “fat” rectangular matrix A in (2) and hence results in an under-determined system of equations with infinitely many solutions.

Now consider the $N \times K$ matrix A in (2) as a collection of vectors $\mathbf{a}_i \in \mathbb{R}^N$, $i = 1 \dots K$. In the terminology of signal representation theory, such collections (A) are usually called “*dictionaries*,” and their elements ($\mathbf{a}_i$) are called “*atoms*.” The deconvolution problem then is equivalent to finding a meaningful representation for the signal $\mathbf{s} = \sum_i \omega_i \mathbf{a}_i$ as a linear combination of atoms in the dictionary A . When the nonnegativity constraint is imposed on ω_i , the linear combination is restricted to a conic combination. In addition, a compressed and sparse representation for signal is very often preferred especially when the dictionary A is *overcomplete* with $K > N$, which is the exact case in our problem.

1) L_1 Minimization Methods—Stable recovery of sparse overcomplete representations in the presence of noise has been widely studied in signal processing literature. A number of interesting arguments, both heuristic and theoretical, have been proposed (see [28] and references therein). Sparsity measured as the number of nonzero entries and expressed as the so-called L_0 norm. However, the naive exhaustive search for the sparsest solution with smallest L_0 norm is known to be NP-hard. Over the last few years it has been both observed experimentally and shown theoretically that, under appropriate conditions on A and $\mathbf{s}$, minimizing L_1 norm of the solution often recovers the sparsest solution. This phenomenon is referred to as L_1/L_0 equivalence. The concept of *mutual coherence* (defined in [28]) of the dictionary A plays a major role in these results. It has been shown in [28], that when the dictionary A has a property of *mutual incoherence*, and when the ideal noiseless signal $\mathbf{s}$ does have a sufficiently sparse representation with respect to A , the L_1 minimization based reconstruction is locally stable, i.e., under addition of small amounts of noise, the result has an error which is at worst proportional to the input noise level. Unfortunately, it turns out that our dictionaries always have very high mutual coherence values, ranging from 0.95 to 1, which makes these nice theoretical bounds inapplicable to our problem. To investigate the performance of L_1 minimization based methods in the context of our problem, we experimentally tested the L_1 -MAGIC package, a collection of MATLAB routines for solving the convex optimization problems central to sparse signal recovery [29]. Among the several programs implemented in L_1 -MAGIC package, we are particularly interested in the following two programs.

¹<http://www.l1-magic.org>.

- **Min- L_1 with equality constraints.** The program can be mathematically stated as

$$(P_3) \quad \min \|\omega\|_1 \quad \text{subject to} \quad A\omega = s. \quad (6)$$

- **Min- L_1 with quadratic constraints.** In this formulation, one finds the vector with minimum L_1 norm that comes close to explaining the measurements s , i.e.,

$$(P_4) \quad \min \|\omega\|_1 \quad \text{subject to} \quad \|A\omega - s\|_2 \leq \varepsilon \quad (7)$$

where ε is a user specified parameter.

It has also been shown that (P_3) can be recast as an linear-programming (LP) problem while (P_4) can be recast as a second order cone programming (SOCP) problem. The experimental results for these two programs are reported in Section IV.

2) Nonnegative Least Squares (NNLS)—The above L_1 minimization methods (P_3) and (P_4) do not explicitly enforce the nonnegativity constraints. Constraining the solution to the nonnegative space could drastically reduce the ambiguity of the solution and hence improve the final reconstruction results. The reconstruction problem incorporating a nonnegativity constraint can be expressed as

$$(P_5) \quad \min \|A\omega - s\|^2 \quad \text{subject to} \quad \omega \geq 0. \quad (8)$$

This nonnegative-constrained optimization is precisely a quadratic programming problem stated as follows. Find the minimum point of a concave quadratic function in a linearly bounded convex feasible hyperspace. An algorithm for solving this nonnegative least-squares problem was developed in [30] where the optimal solution was found by an *active set* strategy. In this algorithm, a series of least squares problems without constraints are solved sequentially according to the tentative status of an active set S , which contains only positive components and is initialized to an empty set. A positive component is added to S in the main loop, followed by a possible deletion of some components from S in the inner loop, and the loop is terminated when the Kuhn–Tucker condition is satisfied. Though the algorithm provided by Lawson and Hanson finds the solution to (P_5) iteratively, it has been proved that the iteration always converges and terminates in a finite number of steps. Hence, there is no cutoff in iteration required and the dependence on the initial guess is minimal. Noise in the measurements, as expected, increases the number of iterations required to reach the solution. In such cases, one can stop the iteration before the full convergence and still achieves a fairly satisfactory solution, since the solution improves smoothly with iteration.

IV. Experimental Results

A. Numerical Simulations

Prior to performing the experiments on real diffusion MRI data, we first apply the methods described in the previous section to simulated data. Throughout this section, we use the HARDI simulations of 1-, 2-, and 3-fiber geometries with known fiber orientations. The signals were simulated by using the exact form of the MR signal attenuation from particles diffusing inside cylindrical boundaries [31] with b -value 1500 s/mm². The gradient directions were chosen to point toward 81 vertices sampled on a unit hemisphere from the second-order icosahedral tessellation. The orientations in our 1-, 2-, and 3-fiber configurations are specified by the azimuthal angles of $\phi_1 = 30^\circ$, $\phi_2 = \{20^\circ, 100^\circ\}$, and $\phi_3 = \{20^\circ, 75^\circ, 135^\circ\}$, respectively. Polar angles for all fibers were taken to be $\theta = 90^\circ$, so that a view from the z axis will clearly depict the individual fiber orientations. Fig. 2 shows the

corresponding orientation distribution function profiles computed from a model-independent Q-ball ODF formula developed in [12, eq. (21)] with spherical harmonics expansion terminated after $l = 8$.

1) A Comparison of Deconvolution Methods in the Noiseless Case—In order to compare the performance of the deconvolution methods described before, in the noiseless case, we first apply all of them to the 1-fiber HARDI simulation data shown in Fig. 2. The matrix A is constructed by using the Wishart model with $p = \infty$ and the tessellation contains 321 unit vectors sampled from a hemisphere.

The DLS method as a solver of the Tikhonov regularization problem (P_2) was implemented using the MATLAB regularization toolbox developed by [32]. To solve (P_3) and (P_4), we used the L_1 -MAGIC MATLAB package. For the nonnegative least squares solver, we used the MATLAB optimization toolbox function, *lsqnonneg* which implements the Lawson and Hanson's algorithm [30]. The initial guess for ω was set to the zero vector for all the iterative methods (P_3), (P_4) and (P_5).

The results of ω obtained from these methods are plotted in Fig. 3. From Fig. 3, we can see that the least squares solution to (P_1) contains a large number of negative weights and hence has a relatively large magnitude. A zeroth-order Tikhonov regularization is able to reduce the magnitude significantly. By minimizing the L_1 norm with equality or quadratic constraints, (P_3) and (P_4) yield better sparsity and nonnegativity in the results. Evidently, the best result is obtained by solving (P_5) using the nonnegative linear least squares. Among the 321 components, there are only two nonzero and significant spikes both of which lie in the neighborhood of true fiber orientation (30° , 90°). Although all of these different results of ω actually lead to very similar displacement probability functions $P(r)$ after taking the Fourier transform, a sparse positive representation of ω obviously offers a great advantage in setting the initial guess in the optimization procedure used to find the fiber orientations by estimating the extrema of $P(r)$.

2) A Comparison of Deconvolution Methods in the Presence of Noise—To provide a more realistic comparison, we chose the 2-fiber simulation shown in Fig. 2 and created the noisy profiles by adding Rician-distributed noise with increasing noise levels ($\sigma = 0.01, 0.02, \dots, 10$). For each noise level, the noisy profile contains 100 samples. The deconvolution formulation is derived from the mixture of Wisharts model [23] with $p = 2$ and $K = 321$. To recover the weight vector ω , we tested the following methods:

- a. the pseudo-inverse method as in (P_1);
- b. the damped least squares as in (P_2) (the damping factor is empirically chosen to be 5σ which gives quite satisfactory results);
- c. the damped least squares method with the damping factor determined using the GCV criterion;
- d. the Min- L_1 norm with equality constraints as in (P_3);
- e. the Min- L_1 norm with quadratic constraints as in (P_4) ($\epsilon = 1.0$);
- f. the nonnegative least squares as in (P_5).

Following [26], we implemented the GCV method using the MATLAB regularization toolbox [32]. The GCV solution was also used as the initial guess in both the methods (d) and (e). When the NNLS approach, the initial guess for ω was always set to the zero vector.

As discussed in Section II, once the deconvolution problem is solved, quantities including the probability displacement function restricted on a sphere, $P(|\mathbf{r}| = r)$ in DOT [10], radial integral of $P(\mathbf{r})$ in QBI [11], and the integral of $P(\mathbf{r})r^2$ in DSI [15] are analytically computable when the mixture of Wisharts model is used. In the following, we chose to compare the resulting quantity $\int P(\mathbf{r})r^2 d\mathbf{r}$. For the purposes of visualization and the follow-up numerical computation of fiber orientations by finding the peaks, all the resulting spherical functions were represented by smooth surfaces using spherical harmonics expansions up to order $l = 8$. To gain a global assessment of these methods in terms of stability, we estimated the fiber orientations of each system by numerically finding the maxima of the spherical functions with a quasi-Newton numerical optimization algorithm and computed the deviation angles between the estimated and the true fiber orientations. As expected, the results of method (a), the pseudo-inverse method (P_1), degrades quickly as the noise level increases. It has also been observed that method (e), Min- L_1 with quadratic constraints (P_4), produces much worse results than the other four methods (b), (c), (d), (f). In general, the results of method (d), Min- L_1 with equality constraints (P_3), are very close to the results of method (c), the Damped Least Squares method with damping factor determined by GCV, due to the fact that method (d) starts with the solution of method (c).

Fig. 4 shows the mean and standard deviation of deviation angles in the two-fiber experiment. The results of the pseudo-inverse method (P_1) and the results of Min- L_1 with quadratic constraints (P_4) were not included since both methods seem extremely sensitive to the noise. It is evident from Fig. 4 that the NNLS method gives the most accurate results consistently. While there is no significant difference between the other three methods. Note that in all the cases, Min- L_1 methods with both equality and quadratic constraints were started with the solution returned by the GCV method. For the nonnegative least squares, we always used the zero vector as the initialization.

B. Real Data Experiments

We tested aforementioned reconstruction methods on a dataset acquired from a perfusion-fixed excised rat optic chiasm. Due to its distinct myelinated structure with both parallel and decussating (crossing) optic nerve fibers, the rat optic chiasm provides an excellent “testbed” to experimentally validate our approach. DWI data were collected at 14.1 T using a Bruker Avance imaging system with a diffusion-weighted spin echo pulse sequence. There are 46 directions with a b -value of 1250 s/mm² and six directions with $b \approx 0$ s/mm². Echo time and repetition time were 23 ms and 0.5 s, respectively; Δ and δ values were set to 12.4 ms and 1.2 ms, respectively; bandwidth was set to 35 kHz; signal average was 10; a volume size of $128 \times 128 \times 5$ and a resolution of $33.6 \times 33.6 \times 200 \mu\text{m}^3$ was used. The optic chiasm images were signal averaged to $67.2 \times 67.2 \times 200 \mu\text{m}^3$ resolution prior to computation of the water molecule displacement probability field.

Four methods were used to generate the probability surfaces at each voxel in the optic chiasm image, a slice of which is shown in Fig. 5. For the sake of clarity, we excluded every other voxel and overlaid the probability surfaces on the generalized anisotropy (GA) maps [33]. GA is the variance of normalized diffusivity function. Higher values of GA (brighter regions) indicate higher anisotropy. The GCV method used to automatically estimate the regularization parameter, is not always able to predict the “correct” regularization factors. The Min- L_1 with quadratic constraints does yield satisfactory results but only in regions mostly populated with single fibers, which is not surprising according to the previous observation on the 2-fiber simulation. As seen from the figure, the fiber-crossing in the optic chiasm region is not identifiable in either Fig. 5(a) or (b). Note that both the DLS method used in [23] and the NNLS method used in this paper are able to demonstrate the distinct fiber orientations in the central region of the optic chiasm where ipsilateral myelinated axons

from the two optic nerves cross and form the contralateral optic tracts. It is evident from this figure that compared to all other solutions, the NNLS scheme yields significantly sharper displacement probability profiles.

Note that validating the precise angle of the fiber crossing in this real data set is nontrivial as it will need a histology stack to be created and then fiber directions estimated from this stack to be validated against those obtained from the HARDI data. This will be the focus of our future work.

V. Discussion and Conclusion

In this paper, we addressed the important problem of multiple fiber reconstruction from the diffusion MRI signal. After a state-of-the-art review, we showed that under proper mathematical formulation, several previously published research works in this field can be reformulated in a unified deconvolution framework. The discretized version naturally leads to the familiar linear system model $A\omega = s$. The central topic of this paper is to investigate several different deconvolution methods in the context of multifiber reconstruction in diffusion MRI.

Like most deconvolution problems in other application domains, our deconvolution model here is ill posed and susceptible to noise. First, to cope with the originally ill posed problem, the immediate modification to the direct least squares is the well known Tikhonov regularization. A naive zeroth-order Tikhonov regularization still yields a linear system and allows for an efficient solution. However, one should pay attention to the choice of the regularization parameter in order to avoid the under-regularization or the over-regularization. Usually, the “optimal” regularization factor is obtained by minimizing the so-called generalized cross validation (GCV) [27] function. Though the GCV method provides a simple and objective method for choosing the regularization parameter, the real optimal solution is never guaranteed due to the theoretical limits of the GCV method [27].

Additionally, our deconvolution framework often leads to an under-determined system when the angular resolution of the DWI data is relatively low compared to the overcomplete basis required by a high resolution deconvolution. In this situation, nonnegativity and the sparsity are the two most desired properties which we expect from the unknown ω vector. A recent strand of research [28], [29] has established that certain under-determined systems can be solved robustly with efficient algorithms based on the minimization of L_1 norm, provided that the solution is sparse. Two typical techniques are studied in this work, namely, the Min- L_1 with equality constraints and the Min- L_1 with quadratic constraints. However, these L_1 minimization formulations do not explicitly enforce the nonnegativity constraints and highly rely on the setting of the initial guess in the optimization. Some theoretical bounds do not hold here either due to the fact that our underdetermined systems do not have the property of mutual incoherence.

Lawson and Hanson [30] developed a classic nonnegative least squares (NNLS) algorithm and proved its finite convergence. Additionally, NNLS requires no arbitrary cutoff parameter and hence the output is not susceptible to mistuning of the input parameters. It has been empirically shown in [34] and [35] that the nonnegative least-squares method by [30] is superior to several other deconvolution methods in various applications. Our experimental results on both simulation and real DW-MRI data have demonstrated that NNLS is also a powerful deconvolution algorithm when applied to the multifiber reconstruction problem. In terms of both accuracy and stability, it outperformed several other methods including the pseudo-inverse method, damped least squares, Tikhonov regularization with GCV and the

L_1 minimization methods which have been employed in published articles [18], [19], [23], [26] on multi-fiber reconstruction using a deconvolution formulation.

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Fig. 1.

Ill conditioning problem in the deconvolution. Left plot shows the case where the A matrices are constructed from the radial basis function and the tensor kernel model as in [19]. Right plot shows the case with a standard diffusion tensor kernel weighted by a mixture of Wisharts [23]. Both assume 81 diffusion gradient directions. The x axis shows the associated parameters used in each model while the y axis shows the corresponding condition numbers of the resulting A matrices. Two tessellation schemes (81 and 321 directions) are considered for each model.

Fig. 2.

Simulations of 1-, 2- and 3-fibers ($b = 1500 \text{ s/mm}^2$) HARDI profiles visualized in Q-ball ODF surfaces computed from the formula in [12] with spherical harmonics expansion terminated after $l = 8$. Orientation configurations: azimuthal angles $\phi_1 = 30^\circ$, $\phi_2 = \{20^\circ, 100^\circ\}$, $\phi_3 = \{20^\circ, 75^\circ, 135^\circ\}$; polar angles were all 90° .

Fig. 3.

Results of ω on 1-fiber HARDI simulation data using different deconvolution methods. The x -axis shows the indices of ω while the y -axis presents the corresponding numerical values of ω . The matrix A is of size 81×321 and is built from the tensor kernel model and Wishart basis with $p \rightarrow \infty$, $\lambda = \{0.0015, 0.0004, 0.0004\}$.

Fig. 4.

Mean and standard deviation of error angles for the two-fiber simulation. At each noise level, from left to right, the four methods compared are (1) the DLS method as in (P_2) (the damping factor is empirically chosen to be 5σ); (2) the DLS method with the damping factor determined using the GCV criterion; (3) the Min- L_1 norm with equality constraints as in (P_3) (initialized with the solution obtained by DLS+GCV); (4) the NNLS method as in (P_5). The displayed values for error angles are averaged over the two fiber orientations.

Fig. 5. Probability maps computed using (a) damped least squares with GCV; (b) Min- L_1 with quadratic constraints ($\epsilon = 1$) initialized from (a); (c) damped least squares with fixed regularization parameter ($\alpha = 0.6$); (d) nonnegative least squares from a rat optic chiasm data set overlaid on axially oriented GA [8] maps. The decussations of myelinated axons from the two optic nerves at the center of the optic chiasm are readily apparent. In all the plates, the corresponding reference (S_0) image is shown in the upper left corner.

TABLE I
A List of Major Notation and Symbols Used in This Paper

Notation	Description
$\mathcal{M}, x$	$\mathcal{M}$ is a smooth manifold and x is a point on $\mathcal{M}$.
$\delta(x; x_0)$	Dirac delta function on manifold $\mathcal{M}$ centered at point x_0
$\mathbb{R}^3, \mathbf{r}$	$\mathbb{R}^3$ is the 3-d Euclidean space and $\mathbf{r}$ is an element in $\mathbb{R}^3$.
$S^2, \mathbf{v}$	S^2 denotes a unit sphere in $\mathbb{R}^3$ and $\mathbf{v}$ is an unit vector.
$\mathcal{P}_n$	The manifold of 3×3 positive definite matrices.
$\mathbf{D}$	Diffusion tensor represented by a 3×3 positive definite matrix.
$\mathbf{q}$	$\mathbf{q}$ diffusion gradient represented by a vector in $\mathbb{R}^3$.
$\{\mathbf{q}_{i=1}^N\}$	A diffusion imaging scheme with N diffusion gradient directions.
$P(\mathbf{r})$	Average water molecule displacement probability density function.
$\{\mathbf{v}_{i=k}^K\}$	A sphere tessellation containing K sample directions.
λ	Eigenvalues of $\mathbf{D}$ ($\lambda_1 \geq \lambda_2 \geq \lambda_3 > 0$)
$\mathbf{D}_\lambda^{\mathbf{v}}$	Prolate tensor with $\lambda_1 > \lambda_2 = \lambda_3$ and dominant eigenvector $\mathbf{v}$
Y_l^m	Spherical harmonic function of degree l and order m
$\{\mathbf{c}_l^m\}$	Coefficients in the spherical harmonics expansion
γ_p, Σ	A matrix-variate Gamma distribution [22] over $\mathcal{P}_n$ with shape parameter $p > 0$ and scale parameter $\Sigma \in \mathcal{P}_n$
$\boldsymbol{\omega}$	$\boldsymbol{\omega} = \{\omega_k^K\}$ is a vector of nonnegative weights, i.e. $\omega_k \geq 0$.
$S(\mathbf{q}), S_0$	$S(\mathbf{q})$ is the MR signal with diffusion gradient $\mathbf{q}$ and S_0 is the MR signal in the absence of any gradient.

TABLE II
A List of Previously Published Fiber Reconstruction Methods Expressed in the Proposed Unified Deconvolution Framework

Method	$\mathcal{M}$	x	$f(x)$	$R(q, x)$	unknown
Basser et al. [2]	$\mathcal{P}_n$	D	$\mathcal{Q}(D; D_0)$	$\exp(-q^T D q)$	D_0
Tuch [6]	$\mathcal{P}_n$	D	$\omega_k \mathcal{Q}(D; D_k)$	$\exp(-q^T D q)$	$\{\omega_k, D_k\}$
Tournier et al. [18,20]	$\mathcal{S}^c$	$\mathbf{v}$	$\mathbf{c}_l^m \mathbf{Y}_l^m$	$\exp(-(\mathbf{v} \cdot \mathbf{q})^2)$	$\{\mathbf{c}_l^m\}$
Anderson [12]	$\mathcal{S}^c$	$\mathbf{v}$	$\mathbf{c}_l^m \mathbf{Y}_l^m$	$\exp(-\mathbf{q}^T D_\lambda^v \mathbf{q})$	$\{\mathbf{c}_l^m\}$
Alexander [19]	$\mathcal{S}^c$	$\mathbf{v}$	$\omega_k \exp(-\frac{\arccos(\mathbf{v} \cdot \mathbf{v}_k)^2}{\sigma^2})$	$\exp(-(\mathbf{v} \cdot \mathbf{q})^2)$	$\boldsymbol{\omega} = \{\omega_k\}$
Jian et al. [23]	$\mathcal{P}_n$	D	$\omega_k \gamma_{p,D}^{v_k}$	$\exp(-q^T D q)$	$\boldsymbol{\omega} = \{\omega_k\}$
Ramirez-Manzanares et al. [21]	$\mathcal{S}^c$	$\mathbf{v}$	$\omega_k \mathcal{Q}(\mathbf{v}; \mathbf{v}_k)$	$\exp(-\mathbf{q}^T D_\lambda^v \mathbf{q})$	$\boldsymbol{\omega} = \{\omega_k\}$