CHAPTER 4
NEIGHBOURHOOD BASED EXTENSION OF LINEAR DKI RECONSTRUCTION FRAMEWORK

4.1 Introduction

DW-MRI has gained more importance in with the development of advanced models such as DTI and DKI. The significance and reliability of clinical studies depend on the accuracy and precision of DTI and DKI reconstruction. The main drawback in achieving such an efficient diffusion MRI reconstruction is the physiological noise associated with DW-MRI acquisition such as head motion. Conventional linear and non-linear reconstruction methods are incapable of overcoming such artifacts. This leads to development of robust estimation of DTI and DKI to address signal drop outs and perturbations. DKI reconstruction deals with the estimation of the kurtosis tensor from which kurtosis derived parameters are computed. A desirable tensor estimation technique would achieve the following,

1. low computational cost

2. overcome data outliers due to inherent characterization of DW-MRI technique such as signal perturbations, low signal to noise ratio, motion and eddy current distortions
3. avoid implausible values

4. reduced noise bias

Several reconstruction methods were reported in the past that aimed to achieve these desirable characteristics [40, 44, 46, 49, 51, 53, 54]. In principle, the DKI reconstruction framework is based on a non-linear model. The main drawback of this model is the prolonged computation time, of the order of hours for a whole brain volume, which limits the clinical application of DKI [13]. To achieve quicker reconstruction, linear framework was proposed for DKI reconstruction. The diffusion tensors for the widely used models such as DTI and DKI are estimated by linearizing using natural log transformation. Linear least squares method [40] has been widely used for DKI reconstruction. Variants of LLS methods such as WLLS and CLLS were also reported in-order to overcome the limitations of LLS method such as noise bias and implausible values [46, 49, 54]. DW-MRI is more prone to signal perturbations caused by various artifacts and outliers [42, 72]. Different approaches for reconstruction of DKI have been reported that deal with the robustness of the reconstruction to noise and outliers [40, 44, 51, 53]. The 2 general approaches for obtaining robust DTI estimates are,

1. process the data separately before or after the DTI or DKI reconstruction using denoising or smoothing operations

2. include the smoothing during tensor estimation by incorporating a correlation measure from the neighbourhood voxels

The first approach has been followed in various methods [73–75] in order to reduce noise in DW-MRI data. In this approach, the original DW-MRI data is processed for denoising. This denoised data is later used for tensor estimation. Alternatively, denoising is applied as a post-processing step after the tensor estimation on the diffusion parametric maps [76, 77]. The second category of these approaches wherein the noise
reduction is done along with tensor estimation in a single step has been reported in [78] in the context of DTI. Additionally, the approach used in [78] assigns a weighting factor for including the neighbourhood voxels.

In the proposed method, we adapt the approach in the second category in the context of DKI. Low computational cost and quick execution make LLS and the corresponding weighted and constrained variants of LLS, widely used approaches for DKI reconstruction as compared to the computationally expensive non-linear reconstruction [49]. In the proposed method, we provide an extension for the linear method of DKI reconstruction and hence is named as Extended Linear Framework (ELF) which could be applied on any variant from the class of LLS estimators to improve the robustness and the performance of the reconstruction. Unlike the class of LLS estimators, where a single independent voxel is considered for the estimation of the parameter, we incorporate the advantage of spatial correlation available in DW-MRI data. This has been achieved by using the neighbouring voxels in the voxel-wise estimation of DKI parameter. In the older DW-MRI technique that only utilizes the tensor estimates, DTI, a reported work [78] utilizes the neighbourhood information. The images are smoothed during estimation while assigning a weighting factor for each of the neighbouring pixels. In contrast, in the present context of DKI, in the proposed method the entire neighbourhood is considered as a single system. This has been achieved by using the neighbouring voxels in the voxel-wise estimation of DKI parameter. The experiments performed on simulated and real datasets illustrate the robustness of the method to noise and also improvement in reconstruction. The workflow comprising of the proposed method along with the experimental validation is shown in Figure FC4.1.
Figure FC4.1: Workflow depicting the proposed method along with the experimental validation carried out (a) Ordinary Linear Least Squares method (b) Extended Linear Framework (c) Simulation Experiments (d) Real Data Experiments (e) Flowchart for the generation of simulated whole brain data.
4.2 Materials and methods

4.2.1 DKI formulation

The diffusion kurtosis model is an extension of the diffusion tensor model which describes the non-Gaussian diffusion displacement. In DTI, the signal attenuation is given by the following Stejskal-Tanner equation

$$\ln \left[ \frac{S(b,g)}{S(0)} \right] = -bD_{\text{app}}(g)$$  \hspace{1cm} (Eqn 4.1)

where

$$D_{\text{app}}(g) = \sum_{i,j=1}^{3} D_{ij} g_i g_j$$  \hspace{1cm} (Eqn 4.2)

with $S(b,g)$ the noise-free DW signal along gradient direction $g = (g_1, g_2, g_3)$, $b$ the diffusion weighting, $S(0)$ the non-DW signal, $D$ the diffusion tensor which is a 3x3 symmetric tensor $D_{ij}$ for $(i, j = 1, 2, 3)$.

In DKI, the signal attenuation equation given in Eqn 4.1 is expanded to include higher order $b^2$ term. Both $(D_{\text{app}}(g))$ and $(K_{\text{app}}(g))$ along each applied diffusion gradient direction, $g$ are estimated by fitting the following equation with multiple DW signals:

$$\ln \left[ \frac{S(b,g)}{S(0)} \right] = -bD_{\text{app}}(g) + \frac{1}{6} b^2 D_{\text{app}}(g)^2 K_{\text{app}}(g)$$  \hspace{1cm} (Eqn 4.3)

where

$$D_{\text{app}}^2 K_{\text{app}} = \sum_{i=1}^{3} D_{ii}^2 \sum_{i=1}^{3} \sum_{j=1}^{3} \sum_{k=1}^{3} \sum_{l=1}^{3} g_i g_j g_k g_l W_{ijkl}$$  \hspace{1cm} (Eqn 4.4)

with $W$, the kurtosis tensor which is a 4th order symmetric tensor $W_{ijkl}$ for $(i, j, k, l = 1, 2, 3)$. Since both tensors are fully symmetric, $D$ and $W$ have 6 and 15 degrees of freedom, respectively.
4.2.2 Linear Least Squares

The diffusion weighted signal equation (Eqn 4.3) can be solved for unknowns $D$ and $W$ using:

$$
\ln \left[ \frac{S(b,g)}{S(0)} \right] = \left[ \begin{array}{c}
-b, \\
\frac{1}{6} b^2
\end{array} \right] \cdot \begin{bmatrix}
D_{app}(g) \\
D_{app}(g)^2 K_{app}(g)
\end{bmatrix}
$$

(Eqn 4.5)

Thus Eqn 4.3 is transformed to a set of linear equations which can be solved directly using OLLS method by minimizing the sum of squared differences to fit the tensors to each voxel of the DW-MRI data [13].

4.2.3 Weighted Linear Least Squares

Eqn 4.3 can be reformulated as,

$$
y = Ax
$$

(Eqn 4.6)

where $y$ is the n x 1 column vector of the measured log transformed signal intensities, $n$ being the number of measurements, $A$ is the $b$ matrix containing all the combinations of the gradient orientations and $b$ values and $x$ being the unknown parameter vector containing 6 diffusion and 15 kurtosis parameters, altogether forming a 21 x 1 vector. The unknown parameters are estimated in LLS framework as,

$$
\hat{x} = [A^T A]^{-1} A^T y
$$

(Eqn 4.7)

Basically, LLS approach minimizes the sum of the squared differences between the measured and the predicted signals. In the solution obtained using Eqn 4.7, the variance of the log-transformed diffusion signals is not uniform and in order to correct for the differences in the variance, weights are introduced in LLS framework leading to the WLLS solution [46]. The weights are defined as the squares of the noisy DW-MRI
signals as explained in [46],

\[ W = \text{diag}(S^2(b_i, g_i)) \]  

(Eqn 4.8)

Thus in weighted LLS(WLLS) the unknown parameter estimator of \( x \) is,

\[ \hat{x} = [A^T W A]^{-1} A^T W y \]  

(Eqn 4.9)

### 4.2.4 Constrained Linear Least Squares

It is well known that in DW-MRI the diffusivity of water is taken as a positive quantity. This property is essential since negative diffusion coefficients are non-physical. However there is no guarantee that the coefficients \( D_{i,j,k} \) estimated by the above process, will form a positive semi-definite tensor. Moreover, kurtosis should also be in the plausible range. A robust estimation of DKI where the implementation of three different constraints such as positive diffusivity function, positive rank-2 diffusion tensor, and constrained apparent kurtosis explicitly as a set of linear systems with non-negative least squares solutions is demonstrated in the work reported in [79].

### 4.2.5 Extended Linear Framework

We propose an extension of the linear DKI reconstruction based on the correlation existing between spatially proximal voxels in a slice of a brain volume. As seen in the previous section, the reconstruction of DKI involves estimation of 6 diffusion tensor and 15 kurtosis tensor elements which totals to 21 unknowns for every voxel in a volume. In all the estimators based on LLS fitting, the estimation is done voxelwise and is independent to every single voxel without including any spatial interactions between neighbouring voxels (Figure FC4.1(a)). As is well known that the spatial correlation is greater among voxels within same slice of a brain volume and hence we utilize this correlation information to enhance the class of LLS estimators. This is carried out by
considering a window of specific size surrounding the voxel for which the tensor has to be estimated at the center as shown in Figure FC4.1(b). In Figure FC4.1(b), a window of size 5x5 is utilized, taking into account the 24-neighbourhood voxels (marked in yellow) for estimation of the center voxel tensor (marked in red).

In the linear reconstruction framework, the signal measurements from the voxel to be estimated is used. Thus the number of linear equations available to estimate tensor elements for a voxel is based on the number of b-values and the number of gradient directions used in the acquisition for every b-value. In the proposed ELF method, for every voxel, information from N-Neighbourhood voxels are incorporated for the estimation. The user can decide upon the size of the neighbourhood (kernel), N. As shown in Figure FC4.2, for estimating DKI for the voxel at position(i,j), only the single voxel is considered in LLS (voxel shaded in Figure FC4.2(a)) whereas in ELF, in addition to the voxel at position (i,j), the 8 neighbouring voxels are also included in case of 8-neighbourhood ELF (voxels shaded in Figure FC4.2(b)).

In the case of LLS method, the tensors are fitted to each voxel by using the least square estimator as given below,

$$\hat{x} = [A^T A]^{-1} A^T y$$

(Eqn 4.10)

where y is the n x 1 column vector of the measured log transformed signal intensities,
$n$ being the number of measurements.

$$y = \begin{bmatrix}
\ln\left[\frac{S_{1,i,j}(b,g)}{S_{1,i,j}(0)}\right] \\
\ln\left[\frac{S_{2,i,j}(b,g)}{S_{2,i,j}(0)}\right] \\
\vdots \\
\ln\left[\frac{S_{n,i,j}(b,g)}{S_{n,i,j}(0)}\right]
\end{bmatrix}$$

(Eqn 4.11)

and

$$A = \begin{bmatrix}
-b_{1,i,j}(g_{1}^{1,i,j})^2 & \cdots & -b_{1,i,j} & g_{1}^{1,i,j} & g_{2}^{1,i,j} & \cdots & \frac{1}{6}(b_{1,i,j})^2 & (g_{1}^{1,i,j})^4 & \frac{12}{6}(b_{1,i,j})^2 & g_{1}^{1,i,j} & g_{2}^{1,i,j} & (g_{3}^{1,i,j})^2 \\
\vdots & \cdots & \cdots & \cdots & \cdots & \cdots & \vdots & \cdots & \cdots & \cdots & \cdots & \cdots \\
-b_{n,i,j}(g_{1}^{n,i,j})^2 & \cdots & -b_{n,i,j} & g_{1}^{n,i,j} & g_{2}^{n,i,j} & \cdots & \frac{1}{6}(b_{n,i,j})^2 & (g_{1}^{n,i,j})^4 & \frac{12}{6}(b_{n,i,j})^2 & g_{1}^{n,i,j} & g_{2}^{n,i,j} & (g_{3}^{n,i,j})^2
\end{bmatrix}$$

(Eqn 4.12)

In the above equations (Eqn 4.12 and Eqn 4.13), the indices $(i,j)$ denotes the spatial location of the voxel belonging to a particular slice of a volume for which the tensor is to be estimated. $x$ is the unknown parameter vector of 21 tensor elements. In case of the proposed ELF, the size of $y$ and $A$ increases, as the signal measurements of the neighbouring voxels are also included. For realizing the proposed ELF with $N$-neighbourhood, the size of $y$ and $A$ increases $N$ times. The number of linear equations to be solved for a single voxel increases $N$ fold resulting in a correlation incorporated estimate of the tensors. The ELF estimator is thus given as,

$$\hat{x} = [A_{\text{modified}}^{T}A_{\text{modified}}]^{-1}A_{\text{modified}}^{T}y_{\text{modified}}$$

(Eqn 4.13)
where the size of $A_{modified}$ and $y_{modified}$ increases N-fold as given below. The size of the window is $\sqrt{N+1}$ for N-neighbourhood.

\[
y = \begin{bmatrix}
\ln \left[ \frac{S_{1,i-M,j-M}(b, g)}{S_{1,i-M,j-M}(0)} \right] \\
\vdots \\
\ln \left[ \frac{S_{n,i+M,j+M}(b, g)}{S_{n,i+M,j+M}(0)} \right]
\end{bmatrix}
\]  
(Eqn 4.14)

and

\[
A = \begin{bmatrix}
-b_{1,i-M,j-M}^1(g_1^{i-M,j-M})^2 & \cdots & -b_{1,i-M,j-M}^1g_1^{i-M,j-M} & \cdots & \frac{1}{6}(b_{1,i-M,j-M})^2g_1^{i-M,j-M} & \cdots \\
\vdots & \ddots & \vdots & \ddots & \vdots & \ddots \\
-b_{n,i+M,j+M}^n(g_1^{n+i+M,j+M})^2 & \cdots & -b_{n,i+M,j+M}^ng_1^{n+i+M,j+M} & \cdots & \frac{1}{6}(b_{n,i+M,j+M})^2g_1^{n+i+M,j+M} & \cdots \\
\vdots & \ddots & \vdots & \ddots & \vdots & \ddots \\
\frac{12}{6}(b_{1,i-M,j-M})^2g_1^{1,i-M,j-M}g_2^{1,i-M,j-M} & \cdots & \frac{12}{6}(b_{n,i+M,j+M})^2g_1^{n,i+M,j+M}g_2^{n,i+M,j+M}
\end{bmatrix}
\]  
(Eqn 4.15)

where $M = \frac{(size\ of\ window)}{2} - 1$.

Figure FC4.2: Voxels considered for DKI estimation in (a)LLS method and (b)ELF method
4.2.6 Simulations

The performance of the proposed method is evaluated in terms of accuracy, reliability, parameter validity, precision and robustness by conducting experiments on both simulated and real data. In Figure FC4.1(d-e) the details of these experiments along with the tests and the corresponding validation measures are listed. Monte Carlo simulations of 100 repetitions for whole brain data were performed under different conditions. In all simulations, we have extended the three linear estimators LLS, WLLS and CLLS using the proposed ELF reconstruction and compared the results with conventional LLS, WLLS and CLLS methods. The ELF method was implemented for 8-neighbourhood case where the window has a size of $3 \times 3$. All these reconstruction techniques were implemented using in-house MATLAB (MathWorks, Natick, MA, USA) programs based on the theory described in sections 2.1-2.5 on a Windows machine with 3.2 GHz Intel Xeon Processor and 8 GB RAM. The following convention for the reconstruction methods is followed in the forthcoming sections of this report:

1. Ordinary Linear Least Squares reconstruction (QLLS)
2. Weighted Linear Least Squares reconstruction (WLLS)
3. Constrained Linear Least Squares reconstruction (CLLS)
4. ELF extension on OLLS (ELF-OLLS)
5. ELF extension on WLLS (ELF-WLLS)
6. ELF extension on CLLS (ELF-CLLS)

The proposed method was evaluated in terms of commonly used DTI and DKI parameters such as FA, MK and RK. Different experiments were performed to assess ELF for various factors which are listed below,
1. Experiment 1: Assess for plausible parametric values

2. Experiment 2: Robustness to noise

3. Experiment 3: Accuracy

4. Experiment 4: Precision

4.2.6.1 Generation of Simulated Data

The procedure carried out for generating whole brain simulated dataset is shown in Figure FC4.1(c). Initially, a real dataset from a normal subject was used as the reference for the simulated data generation and the dataset, numbered 1 (Table TC4.1) for our simulation study. The acquisition details of this dataset is given in section 2.7.1. The diffusion and kurtosis tensors estimated for this real data using OLLS is considered to be the reference ground truth tensors and the corresponding parameter maps as the reference maps. The simulated data were computed from these ground truth tensors by using the signal equation given in Eqn 4.3. The simulated data were noise corrupted by adding Rician noise of varying noise levels in the image domain, which is given as,

\[ V_{\text{noise}} = \sqrt{(\frac{S}{\sqrt{2}} + \text{Gaussian}_{\text{Real}})^2 + (\frac{S}{\sqrt{2}} + \text{Gaussian}_{\text{Imag}})^2} \quad \text{(Eqn 4.16)} \]

where \( V_{\text{noise}} \) is the noisy voxel intensity with \( \text{Gaussian}_{\text{Real}} \) and \( \text{Gaussian}_{\text{Imag}} \) as the real and imaginary parts of corresponding Gaussian noise and \( S \) is the input DW-MRI signal intensity.

4.2.6.2 Experiment 1: Assess for plausible parametric values

In experiments, voxels from four different brain regions were picked up from three selected axial slices. These ROIs are shown in Figure FC4.3. Two ROIs corresponding to WM such as Corpus Callosum (CC) and Corona Radiata (CR) and two ROIs
corresponding to GM such as putamen and thalamus were identified. The ROIs were manually marked by an expert. The diffusion kurtosis parameters MK and RK were estimated for noise free simulated data using all the three linear reconstruction and the corresponding proposed ELF methods. The values of the parameters were evaluated to be in the plausible range by comparing the values reported in [4] for all the chosen ROIs in the brain.

![Figure FC4.3: 4 ROIs considered for experimental validation; Red-CC; Blue-CR; Green-Putamen; Pink-Thalamus](image)

### 4.2.6.3 Experiment 2: Accuracy

In this experiment, the accuracy and precision were evaluated in terms of the relative percentage error between the reference and the noise free simulated data fitted using the considered reconstruction methods. The relative percentage error calculated voxelwise is given as below,

$$\% \text{Relative Error} = \left| \frac{\hat{P} - P}{P} \right| \times 100\% \quad \text{(Eqn 4.17)}$$

where P and \( \hat{P} \) are the parameter estimates for reference and simulated data for a voxel. The estimate for simulated data is computed using any one of the reconstruction methods. The median relative error from a sample of all voxels in a specific ROI was analyzed.
4.2.6.4 Experiment 3: Robustness to noise

In this experiment, the effects of noise on the parameter estimates were evaluated by comparing the estimates across different levels of Rician noise. The error in mean, standard deviation and the root mean square error (RMSE) of parametric maps MK and RK between the reference data and the noisy simulated data were analyzed as a function of the noise level.

4.2.6.5 Experiment 4: Precision

100 noisy DW-MRI datasets were simulated, for a fixed Rician noise level to validate precision. The estimates for the 100 datasets computed using various reconstruction methods were compared for evaluating accuracy and precision.

4.2.7 Real Data Experiments

4.2.7.1 Data Acquisition

The studies were performed on datasets from 10 healthy subjects in the age range of 14-56 years with informed consent. Nine datasets were acquired using a Philips Achieva 3 Tesla (T) scanner (Philips Medical Systems, Best, The Netherlands) and one dataset was acquired using 3T Trio system (Siemens Medical Solutions, Erlangen, Germany). DKI image acquisition was performed using a pulsed gradient spin echo (PGSE) sequence with echoplanar imaging (EPI). The scanning parameters of the acquisitions are given in Table TC4.1. The details about the subjects such as age and gender and the diffusion scheme including the b-values and the number of gradient orientation used are given in Table TC4.2.
Table TC4.1: MRI Scanning Parameters for the 10 datasets

<table>
<thead>
<tr>
<th>Subject</th>
<th>TR/TE (ms)</th>
<th>Acquisition Matrix</th>
<th>Image Resolution (mm³)</th>
<th>Acquisition Duration (sec)</th>
<th>Slice Thickness (mm)</th>
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<td>530</td>
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<td>3</td>
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Table TC4.2: Details of age, gender and diffusion scheme of the 10 datasets

<table>
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<tr>
<th>Subject</th>
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<th>Gender</th>
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<td>3</td>
<td>Philips</td>
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<td>F</td>
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<td>4</td>
<td>Philips</td>
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<td>42</td>
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4.2.7.2 Data Preprocessing

The datasets acquired were preprocessed using [80] for correcting motion and eddy current induced distortions followed by Gaussian smoothing with a FWHM of 2mm and aligned to the standard space, Montreal Neurological Institute (MNI) is used. The preprocessed images were then given as input for DKI estimation. All the non-zero b-values are used for the estimation of diffusion metrics.
4.3 Results

4.3.1 Simulation Experiments

4.3.1.1 Experiment 1: Assess for plausible parametric values

The results of the first simulation experiment are shown in Table TC4.3. The diffusion parameters MK, RK and FA were computed for the voxels belonging to the 4 different ROIs (Figure FC4.3) using the 3 linear estimators, LLS, WLLS and CLLS and their corresponding ELF extensions. The mean parameter values taken over the voxels for every ROI are listed in Table TC4.3 with unique color coded to differentiate the reconstruction method implemented. Additionally, the distribution of MK and RK values taken from voxels of 4 regions are shown in Figure FC4.4.

Table TC4.3: Mean FA, MK and RK values taken over all voxels for each of the 4 regions in a specific slice for noise-free simulated data; Color conventions used for various reconstruction methods: Yellow - OLLS, Green - WLLS, Blue - CLLS, Red - ELF-OLLS, Pink - ELF-WLLS, Orange - ELF-CLLS

<table>
<thead>
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<th>Diffusion Parameters</th>
<th>CC FA</th>
<th>CR MK</th>
<th>Putamen MK</th>
<th>Thalamus MK</th>
<th>CC FA</th>
<th>CR MK</th>
<th>Putamen MK</th>
<th>Thalamus MK</th>
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<td>0.501</td>
<td>0.158</td>
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<td>0.497</td>
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<td>1.112</td>
<td>0.738</td>
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<td>1.113</td>
<td>0.744</td>
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</tr>
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<td>0.998</td>
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<td>1.000</td>
</tr>
<tr>
<td>FA</td>
<td>0.754</td>
<td>0.564</td>
<td>0.169</td>
<td>0.352</td>
<td>0.771</td>
<td>0.546</td>
<td>0.171</td>
<td>0.349</td>
</tr>
<tr>
<td>MK</td>
<td>1.251</td>
<td>1.075</td>
<td>0.627</td>
<td>0.872</td>
<td>1.236</td>
<td>1.079</td>
<td>0.654</td>
<td>0.888</td>
</tr>
<tr>
<td>RK</td>
<td>2.798</td>
<td>1.470</td>
<td>0.679</td>
<td>1.009</td>
<td>2.812</td>
<td>1.497</td>
<td>0.688</td>
<td>0.998</td>
</tr>
<tr>
<td>FA</td>
<td>0.815</td>
<td>0.546</td>
<td>0.132</td>
<td>0.347</td>
<td>0.794</td>
<td>0.552</td>
<td>0.154</td>
<td>0.338</td>
</tr>
<tr>
<td>MK</td>
<td>1.189</td>
<td>1.134</td>
<td>0.723</td>
<td>0.892</td>
<td>1.221</td>
<td>1.124</td>
<td>0.734</td>
<td>0.891</td>
</tr>
<tr>
<td>RK</td>
<td>2.230</td>
<td>1.582</td>
<td>0.682</td>
<td>0.996</td>
<td>2.436</td>
<td>1.580</td>
<td>0.688</td>
<td>1.001</td>
</tr>
</tbody>
</table>
4.3.1.2 Experiment 2: Accuracy

The percentage error in the parameter estimates were calculated between the reference and the noise-free simulated datasets using OLLS, WLLS, CLLS, ELFOLLS, ELFWLLS and ELFCLLS for voxels in WM ROIs. The median error for each of the reconstruction methods is given in Table TC4.4.

Table TC4.4: Comparison of median of the percentage relative error computed from voxels of WM ROIs for all the considered reconstruction methods

<table>
<thead>
<tr>
<th></th>
<th>OLLS</th>
<th>ELF-OLLs</th>
<th>WLLS</th>
<th>ELF-WLLs</th>
<th>CLLS</th>
<th>ELF-CLLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK</td>
<td>15.09</td>
<td>8.97</td>
<td>11.75</td>
<td>9.97</td>
<td>12.84</td>
<td>9.40</td>
</tr>
<tr>
<td>RK</td>
<td>12.93</td>
<td>9.54</td>
<td>9.36</td>
<td>8.54</td>
<td>10.65</td>
<td>8.32</td>
</tr>
</tbody>
</table>

4.3.1.3 Experiment 3: Robustness to noise

The performance of the proposed reconstruction method is evaluated for different levels of noise in terms of the error in mean of MK values and RMSE between the reference MK and the estimated MK. The mean MK and RMSE were computed for voxels selected from the brain volume. The corresponding plots are shown in Figure
4.3.1.4 Experiment 4: Precision

The accuracy and precision of ELF method is validated by conducting Monte-Carlo simulations for the generation of Gaussian noise for a fixed noise level of 5 over 100 repetitions and the MK values are averaged voxelwise for the first 50 repetitions and the second 50 repetitions. The MK values for the noisy simulated data are plotted against the corresponding MK values for noise free reference data voxelwise for both OLLS and ELF-OLLS (Figure FC4.6).

4.3.2 Real Data Experiments

Experiments are performed on the 10 real datasets in terms of the following validations,

1. Parameter Validity
Figure FC4.6: Results of Simulation Experiment 4: Repetition 1 and 2 indicates the first 50 trials and the next 50 trials for the generation of noise level of 5

2. Stability

3. Performance

4. Robustness

4.3.2.1 Parameter Validity

The correctness of the proposed reconstruction is evaluated by comparing parameter estimates with those of known healthy anatomy. ROIs are marked on brain volume corresponding to 2 brain regions such as WM and GM (Figure FC4.7). The OLLS and ELF-OLLS estimation of MK and RK for WM and GM regions are compared with the
MK and RK values reported in [4] for these 2 regions. The representative MK and RK values for a single dataset is shown in Table TC4.5. These values correspond to the mean MK value computed for all ROIs of a specific region (WM or GM) for all slices of a single volume.

![Image of ROIs selected for WM and GM](image)

**Table TC4.5: Representative MK and RK values for a dataset (Subject=3) computed using OLLS and ELF-OLLS**

<table>
<thead>
<tr>
<th>Brain Regions</th>
<th>OLLS</th>
<th>ELF-OLLS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MK</td>
<td>RK</td>
</tr>
<tr>
<td>WM</td>
<td>0.7912</td>
<td>1.0012</td>
</tr>
<tr>
<td>GM</td>
<td>0.5437</td>
<td>0.6314</td>
</tr>
</tbody>
</table>

### 4.3.2.2 Stability

The proposed method has been validated for stability of the estimated DKI parameter by the following ways,

1. Validating across subjects based on differences in gender
2. Validating across subjects of different age groups
3. Analyzing the effects of changes in MR acquisition parameters

The diffusion parameters such as MK, RK and AK were estimated using ELF-OLLS for the voxels from CC and the mean values of these parameters were plotted against
the corresponding subjects as shown in Figure FC4.8. The reconstructions were iterated on subjects of 4 different age groups such as 14 to 19, 20 to 35, 36 to 50 and 51 to 56. The MK values were consistent across all subjects for both OLLS and ELF-OLLS and mean MK values for an entire volume clearly showed an increase with respect to age for WM (Table TC4.6). In order to illustrate the performance of the proposed method for different diffusion acquisition schemes, the DKI model was fitted using ELF-OLLS for data from 2 different schemes. The first scheme had 20 slices per volume, 3 b-values and 20 gradient directions, while the second scheme had 25 slices per volume, 5 b-values and 15 gradient directions (Subjects 1 and 2 given in Table TC4.2). The MK maps for the 2 subjects are shown in Figure FC4.9.

Figure FC4.8: Validation across subjects based on differences in gender. (a)MK, RK and AK values of 5 male subjects (b)MK, RK and AK values of 3 female subjects

Table TC4.6: Mean MK values for WM regions computed agewise using OLLS and ELF-OLLS

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No. of Subjects</th>
<th>Age of subjects used for the study</th>
<th>MK (OLLS)</th>
<th>MK (ELF-OLLS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 19</td>
<td>2</td>
<td>14 and 16</td>
<td>0.6625</td>
<td>0.7237</td>
</tr>
<tr>
<td>20 - 35</td>
<td>2</td>
<td>27 and 31</td>
<td>0.6802</td>
<td>0.7821</td>
</tr>
<tr>
<td>36 - 50</td>
<td>2</td>
<td>38 and 45</td>
<td>0.7600</td>
<td>0.8533</td>
</tr>
<tr>
<td>51 - 56</td>
<td>2</td>
<td>53 and 56</td>
<td>0.7987</td>
<td>0.9107</td>
</tr>
</tbody>
</table>

4.3.2.3 Performance

The performance of ELF has been validated by comparing the diffusion parametric maps estimated using all the 6 reconstruction methods(Figure FC4.10). The improve-
Figure FC4.9: Validation across subjects based on differences in MR Acquisition Parameters. (a)MK map for Subject 1 (b)MK map for Subject 2

A critical validation related to the proof of robustness to noise has been performed by adding Gaussian noise to the preprocessed real data and compared between OLLS

4.3.2.4 Robustness

A critical validation related to the proof of robustness to noise has been performed by adding Gaussian noise to the preprocessed real data and compared between OLLS
and ELF-OLLS. An unit noise level of 1 and 3 were added to the real data for evaluation of MK. The improvement in visual details are illustrated for ELF-OLLS as compared to OLLS in Figure FC4.12.

4.4 Discussion

The proposed method utilizes information from the neighbouring voxels for DKI parameter estimation. The conventional method is to obtain the voxel-wise estimate of the tensor, using signal equations pertaining to the same voxel. In the current work, we define an extended system of linear equations by putting together the signal intensities
from the neighbouring voxels. This extended system of linear equations is solved to obtain the tensor estimate only at the central voxel. The objective of solving this extended system of equations is to obtain a more accurate least square estimate. To consider an entire neighbourhood instead of a single voxel for the estimation has the following advantages,

1. For a neighbourhood of \( N \) voxels, \( N \) measurements are available for estimating the central voxel. This makes the estimation less vulnerable to noise pockets.

2. Equal distribution of weights to the entire neighbourhood allows no-bias in the estimation.

3. Smoothing in log space rather than native space allows the advantage of linearity.

4.4.1 Simulation Experiments

The MK values reported in literature clearly shows that the MK values are higher for WM as compared to GM which accounts for the high anisotropic structures of WM as compared to that of GM. The values estimated using in-house implementation of conventional linear methods and proposed ELF framework also followed this pattern for WM and GM as shown in Table TC4.3. The kurtosis parameter values vary for different brain regions with a range of plausible values for each of the regions. The proposed method showed the diffusion parameters such as MK and RK lying well within the plausible range which is shown from the distribution of parameter values in Figure FC4.4.

The accuracy of ELF method, assessed in terms of the percentage relative errors, showed reduced errors for ELF methods as compared to the conventional methods (Table TC4.4). Hence the ELF extension implemented on any of the linear reconstruction methods would help improve the accuracy of the DKI investigations.

In validating the robustness of ELF, the plots shown in Figure FC4.5 clearly illustrate
that ELF outperforms the conventional linear methods such as OLLS, WLLS and CLLS. There is a visible improvement when one compares each of the conventional linear methods independently with its corresponding ELF implementation. For instance, from the error mean MK plots (Figure FC4.5), it is evident that ELF-OLLS has reduced error as compared to OLLS and this holds for other methods like WLLS and CLLS. The RMSE plots for MK values also suggest improvement of ELF methods compared to its conventional counterparts.

The precision of the proposed extension technique is well demonstrated from the scatterplots between the noisy simulated data and the noise free reference data (Figure FC4.6). In both the set of repetitions, the OLLS method showed outliers as the values are deviated from the reference values. In case of ELF-OLLS, most of the voxels were found inline with the reference values.

4.4.2 Real Data Experiments

The validity of the estimated parameters using ELF method was proved for real data and the results were in line with the simulation data results. A sample MK value for WM and GM is shown in Table TC4.5. The stability of the proposed method which was illustrated using validations across datasets of varying age groups, gender and diffusion acquisition parameters, strengthened the performance of the proposed extension (Figures FC4.8 and FC4.9). Moreover, the aging analysis conducted using DKI, showed significant increase in the values of MK as age increases (Table TC4.6). This significant difference is more prominent in MK values computed from ELF-OLLS than MK values from OLLS. Figure FC4.11 shows the MK maps compared between OLLS and ELF-OLLS and ELF-OLLS reveals better visual structures as compared to OLLS which is again zoomed for a smaller region to illustrate the visual improvement. The added noise to the preprocessed real data distorted the details of the DW-MRI data which is given as input for DKI reconstruction using OLLS and ELF-OLLS to validate the robust
behaviour of the proposed method to distortions. The improved performance of ELF-OLLS can be seen in Figure FC4.12, where more details are preserved in ELF-OLLS reconstruction as compared to that using OLLS. In the proposed ELF reconstruction, the voxels of the whole neighbourhood is considered equally as a single system without assigning any weighting factors for the individual neighbourhood voxels. This is also due to various reasons like, not to have a very extended neighbourhood and on incorporating weighting, the error in the strategy to determine weights will propagate errors in reconstruction as well.

4.4.3 Comparing ELF with Conventional DKI Post-processing

ELF incorporates the neighbourhood voxels during the estimation stage, thereby avoiding the conventional DKI postprocessing involving smoothing of the reconstructed DKI maps. The advantages and disadvantages of the 2 approaches - 1. ELF framework and 2. Conventional DKI postprocessing where smoothing is performed on the reconstructed DKI parameters are listed as below,

4.4.3.1 Conventional DKI Postprocessing

In the conventional approach, the isolated regions where signal values are very different are ignored, it is engulfed by its neighbourhood due to smoothing. The main advantages of this approach being easy implementation and moreover, ensures smoothness and uniformity in the parametric maps.

4.4.3.2 ELF Approach

The proposed method may not be the best way of incorporating spatial correlation. However, the benefit is even isolated regions of very different values will not be lost
though it considers neighbourhood. Figure FC4.13 compares the MK maps from ELF and the conventional post-smoothing approach. The map obtained from latter method shows an overall smoothed appearance losing finer details as compared to the proposed ELF method.

![Figure FC4.13: Representative MK Maps shown for a single slice(Slice=24) for subject=4 (a)ELF-OLLS;(b) DKI reconstruction followed by Smoothing;(c)Difference between the 2 approaches (a) and (b);(d)Zoomed region inside yellow box shown for case (a);(e)Zoomed region inside yellow box shown for case (b)]](image)

4.5 Conclusion

In this work, we propose a novel framework called ”Extended Linear Framework” for robust reconstruction of DKI. The focus is on utilizing the spatial correlations existing in DW-MRI data to enhance the class of linear estimators. Diffusion weighted images obtained on 10 healthy subjects are reported in this study. Kurtosis parameters are estimated for the entire brain volume using the proposed ELF method and compared against the conventional linear methods. The performance of ELF in terms of accuracy, precision and robustness to noise are evaluated by comparing the parameter values with the state of the art reconstruction methods. The results obtained using the proposed ELF framework seem promising.