Robust Variability Analysis Using Diffusion Tensor Imaging

DISSERTATION

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* * * * *

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Understanding the anatomical changes in the connectional network of the human brain is an important research problem in cognitive and clinical neuroscience that could give improved insights onto human development, progression of neurological diseases and effects of traumatic injuries over time. Modeling the variability of human brain “connectivity” over a population can also help understand the effects of demographic or genetic variables on human anatomy and enable early diagnosis of possible anomalies. In the past two decades, diffusion tensor imaging (DTI) has been widely used to understand the neuroanatomy of human brain, mostly in terms of tensor-derived scalar maps such as fractional anisotropy (FA) or apparent diffusion coefficient (ADC) providing additional quantitative information about the tissue structures; or fiber tractography, a DTI based methodology aiming to represent a symbolic version of neuro-connectivity. Due to the lack of mathematical tools able to cope with the complex nature of DTI data and numerous challenges involved in diffusion weighted image processing, population and longitudinal studies based on DTI acquisitions classically simplify the problem onto a simpler domains. However, it is widely acknowledged that the bias in diffusion data introduced by the acquisition and post–processing steps renders different analysis approaches incompatible, and possibly inaccurate.

In this thesis, I present new paradigms and an accompanying suite of tools to realize a robust approach to DTI analysis from groupwise variability modeling perspective. The
first part of the thesis describes the problems involved in diffusion weighted image and diffusion tensor image processing and why DTI data can not be directly used in a statistical analysis framework performing as a black box. These problems include different types of distortions involved in data acquisitions, unification and assessment of a variety of DTI acquisition protocols, problems involved in diffusion weighted data interpolation, the bias introduced by physiological noise and the data bias. In the second part, these challenges are analyzed in detail and either processing solutions are methodologies to incorporate their effects into statistical frameworks are provided. Efficient and robust algorithms required for multi-data DTI analysis have been developed in the following sections, focusing on spatial alignment of tensor data and computation of tensorial statistics enabling voxel or region-wise variability analysis using DTI data.

The complete DTI processing and variability analysis framework developed here was applied to DTI studies for understanding the differences in human brain due to demographic variables.
This thesis is dedicated to my family, without whom this journey would not have ended.
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INTRODUCTION

There are two mistakes one can make along the road to truth...not going all the way, and not starting.

Gautama Buddha (563BC–483BC)

This dissertation describes a complete framework for variability and change analysis using diffusion tensor imaging (DTI) data. This chapter opens by presenting the background of the problem in Section 1 followed by a specific research statement in Section 2 and the proposed solutions in Section 3. Finally, the organization of the rest of this book is laid out in Section 4.

1 Background of Problem

1.1 Neuro-Connectivity and DTI

Even though the human mind has been the subject of scientific studies dating back to ancient Greek philosophical texts [61], many aspects of brain function and interactions of different brain regions are still unknown. Perception, information processing and memory are only a few of the cognitive capacities intensively investigated in today’s neuroscience, which seeks to understand the relationship between the mind and the brain. Therefore understanding the brain not only requires a comprehension of the workings of low–level
neural networks but also demands a detailed map of the brain’s architecture and a description of the large-scale connections between populations of neurons [57].

Human central nervous system mainly includes two components: gray matter which consists of computational units and white matter, the tissue through which messages pass between different areas of gray matter within the nervous system. Using computers as an analogy, gray matter represents the computational units such as the central processing unit (CPU), the graphics processing unit (GPU) and the sound card whereas the white matter represents the connectional architecture on the motherboard consisting of metallic wires for messaging system.

When applied to the brain, the term connectivity refers to several different and interrelated aspects of brain organization [52]. Brain connectivity refers to a pattern of anatomical links, the anatomical connectivity, or of statistical dependencies, the functional connectivity, between distinct units within a nervous system. The units correspond to individual neurons, neuronal populations, or anatomically segregated brain regions. Connectivity patterns are formed by structural links such as synapses or fiber pathways, or it represents statistical or causal relationships measured as cross-correlations, coherence, or information flow. Neural activity are constrained by connectivity. Brain connectivity is thus crucial to elucidating how neurons and neural networks process information.

Anatomical (structural) connectivity refers to a network of physical synaptic connections linking sets of neuronal elements, as well as their associated structural biophysical attributes encapsulated in parameters such as synaptic strength or effectiveness. The development of non-invasive neuroimaging technologies opened new possibilities to study structural brain connectivity in vivo at macroscopic level.
Since its development in 1994, Diffusion tensor imaging (DTI) [9] has become a popular neuroimaging tool due to its ability to model macro-level tissue orientation non-invasively in vivo based on the properties of water diffusion. The method is based on nuclear magnetic resonance (NMR) signal changes due to the strength and directionality of the diffusion of water molecules within the tissue [106]. Diffusion MRI is a magnetic resonance imaging (MRI) method that produces in vivo images of biological tissues weighted with the local microstructural characteristics of water diffusion. The field of diffusion imaging can be understood in terms of two distinct applications: diffusion weighted MRI and the diffusion model. Diffusion weighted MRI provides information about the amount of diffusion taking place at a specific location as a function of the experimental setup and can provide insights about the damage to parts of the nervous system. The diffusion model, such as the diffusion tensor model, fourth order tensor model, or diffusion propagators are mathematical models that try to describe the diffusion process independent of the experimental setup and can provide information about connections among brain regions.

In diffusion weighted imaging (DWI), each image voxel (three dimensional pixel) has an image intensity that reflects a single best measurement of the rate of water diffusion at that location. This measurement is more sensitive to early changes after a stroke than more traditional MRI measurements such as $T_1$ or $T_2$ relaxation rates. DWI is most applicable when the tissue of interest is dominated by isotropic water movement, e.g. grey matter in the cerebral cortex where the diffusion rate appears to be the same when measured along any axis.
In traditional DWI, only three gradient-directions were applied, sufficient to estimate the trace of the diffusion tensor or 'average diffusivity', a putative measure of edema. Clinically, trace-weighted images have proven to be very useful to diagnose vascular strokes in the brain. Diffusion tensor imaging (DTI) is important when a tissue such as the neural axons of white matter in the brain or muscle fibers in the heart, has an internal fibrous structure. Water will then diffuse more rapidly along the direction aligned with the internal structure, and more slowly as it moves perpendicular to the preferred direction. This also means that the measured rate of diffusion will differ depending on the direction from which an observer is looking. Estimation of the diffusion tensors from diffusion weighted images is a "model fitting" or "regression" process where six or more diffusion weighted images acquired with non-collinear gradients are used to compute the diffusion tensor components, which can be used to derive neural tract directional information from the data. The "hindered" diffusion modeled by diffusion tensors is a rather simple model of the diffusion process, assuming homogeneity and linearity of the diffusion within each image voxel. From the diffusion tensor, diffusion anisotropy measures such as the fractional anisotropy (FA), can be computed. Moreover, the principal direction of the diffusion tensor can be used to infer the white-matter connectivity of the brain, which is the foundation for the family of mathematical tracing algorithms called fiber tractography.

1.2 Requirements for Robust DTI

Most of the diffusion tensor imaging based analysis initially used the diffusion weighted images directly, as acquired with an MRI scanner. This approach that will be referred as
black-box DTI analysis has been shown to suffer from several artifacts involved in diffusion weighted MRI [8, 70, 97]. These artifacts have a profound effect on the DTI analysis outcomes including the tensor components, tensor-derived scalar maps and tractography. Among these, motion artifacts i.e. patient motion is the largest physiological effect that causes artifacts, often resulting from involuntary movements (e.g. respiration, cardiac motion and blood flow, eye movements and swallowing) and minor subject movements. In traditional MRI, movement of the subject being imaged during the sequence results in inconsistencies in phase and amplitude, which lead to blurring and ghosting. In modalities such as DTI or fMRI, which require several volumes for the same subject, motion artifacts causes misalignments among acquisition volumes, hence voxel-wise correspondence required for each modality can not be initially established. Correction of these artifacts has been the subject of numerous research efforts and presently a common approach for the problem is to employ rigid registration based techniques to align the images [70, 97].

Eddy currents related distortions are another sources of imperfection in diffusion imaging. These are electric currents induced in a conductor by a changing magnetic field or by motion of the conductor through a magnetic field [101]. Eddy currents cause artifacts in images and may seriously degrade overall magnet performance. Common means to reduce the influence of eddy currents on gradient fields include eddy current compensation and shielded gradient coils (active or passive) [35, 95]. In diffusion weighted imaging, eddy currents manifest themselves in a different manner for each diffusion weighted volume due to different directions of diffusion synthesizing gradients employed to generate them. Such distortions have similar effects on acquired images to motion artifacts in the sense that voxel-wise correspondence among different volumes can no longer be established directly. Additionally, due to compression and expansion of some local regions of the images, the
signal intensity distribution is altered and signal pile-ups occur. Several correction approaches for eddy currents distortions from research groups have been proposed. These include hardware based techniques, pulse sequence based techniques and image processing/registration based techniques.

Another source of artifacts in diffusion weighted imaging is due to the Echo-Planar Imaging (EPI) protocol. In DTI, as well as other diffusion based modalities such as diffusion spectrum imaging (DSI) \cite{114} or Q-Ball imaging \cite{115}, diffusion weighted measurements are used to quantify the signal loss due to the Brownian motion of water molecules hindered by anatomical barriers. These measurements are typically spin-echo EPI acquisitions due to the necessity for fast gradient switches and imaging. A well-known problem with EPI is the geometrical and intensity distortions caused by field inhomogeneities along with poor bandwidth in the phase-encode direction. Geometrical distortions manifest themselves as displacements along the phase-encode direction whereas intensity distortions are due to local convolutions of the point spread functions (PSF). These field inhomogeneities are generally caused by magnetic susceptibility differences \cite{52} among local features as well as the concomitant fields \cite{25}. It should be noted that these EPI distortions are different from the eddy current distortions, which are global distortions typically corrected in DWI processing. Correction of susceptibility-related distortion requires the acquisition of additional data, either $B_0$ mapping \cite{52} or T2 weighted (T2W) dedicated structural targets for non-linear elastic registration, and it is generally not performed.

Correction of issues previously mentioned in this section mostly involves image registration based techniques. Successive application of image registration to diffusion weighted image series raises another challenge for DTI quality: interpolation artifacts. This issue is very
rarely investigated in diffusion imaging community [98] but can have profound effects on outcomes even when the successive interpolation steps are combined into a single one. An interpolation scheme specialized for diffusion weighted imaging is required for robust processing of diffusion tensor images.

In order to analyze the variability of human brain using diffusion tensor imaging, previously mentioned sources of uncertainty have to be eliminated from the data. Additionally, a robust methodology to align inter-subject diffusion tensor fields is required to enable voxel-wise or region-wise correspondences among the population of interest. The field of diffusion tensor image registration or tensor field registration is a relatively new branch of registration technique, which differs from the traditional approaches primarily in the similarity metric and interpolation methods [43, 44]. These techniques, once the tensor field is computed from DWIs with "tensor fitting" generally disregards the information in DWIs and only considers the information present in the tensor field.

1.3 Variability in Human Brain

There is considerable interest in medical community for extracting the most relevant information to characterize normal anatomical variability within a group of subjects as well as between different groups, to detect anatomical abnormalities, to classify new images according to their pathologies, and for understanding disease progression. However, modeling the individual anatomy and its normal variability across a population is difficult as there are no physical models for comparing different subjects, and anatomical shapes are complex and require large number of degrees of freedom to model adequately.
Moreover, anatomical landmarks such as curves or surfaces as well as deformations do not exhibit vector space properties \cite{26}, hence defining statistical models is therefore difficult and specific tools have to be developed to accurately measure anatomical variations. If anatomic variations were better understood, tools encoding variations could have a significant impact in neuroscience to minimize the influence of the anatomical variability in functional group analysis, and in clinical medical image analysis to better drive the personalization of generic models of the anatomy. Variability analysis using DTI data generally relies on features derived from tensor fields \cite{29, 46, 103} or tractography \cite{26} and a methodology to combine the strengths of both approaches is needed.

2 Research Statement

The purpose of this dissertation is to provide the foundations to enable a robust and reliable diffusion tensor imaging based analysis by providing methodologies to remove the external factors such as image distortions and imaging and processing artifacts from the data and using the proposed robust framework to understand the structural variability within the human brain. The questions aimed to be answered in this document are:

**Diffusion Variability** Does the diffusion MRI provide more information about the variability of human brain than conventional methods? How can such variability be modeled and understood within a population? Can we better understand the change in a human brain over time due to progression of disease or aging? What should the properties of such models be?
Foundations for Robust DTI Analysis  What challenges lie in diffusion imaging to perform a robust variability analysis? How much uncertainty is involved in "black-box" DTI analysis and how reliable can these experiments be? How much of an effect do typical diffusion processing methods, commonly taken for granted, have on variability and uncertainty? What additional robust methodologies are needed to perform such an analysis?

3 Outline of Solution

In order to study and understand the variability of the human brain with diffusion MRI, one either has to either eliminate artificial sources of variability/uncertainty in the data or include them as (hidden) model variables in the model. I developed a complete set of processing tools to account for most of these artifacts and provide analysis approaches to robustly understand the concept of variability.

i Diffusion imaging processing tools for robust DTI analysis:

i.i A practical but robust correction method for susceptibility distortions, which are generally disregarded in typical diffusion based analysis. First the effects of these distortions were analyzed and then a correction methodology is posed as a non-linear image registration where the deformation flexibility is constrained by initial estimates of the real distortions [37].

i.ii An image noise variance transformation scheme to correct for the second order statistical artifacts introduced to the diffusion data by typical diffusion MRI processing pipelines. The output of this approach is a spatial noise map, which
can be used during the tensor fitting operation to eliminate the second order spatial bias in the tensor-derived quantities such scalar maps or tractography outcomes \[48\].

i.iii A partial differential equations (PDE) based image interpolation methodology specifically for diffusion weighted image interpolation. This interpolation methodology is not solely signal based but considers the relationships among different diffusion weighted images through the diffusion model, such as the diffusion tensor. Due to its PDE-based nature, it is suitable for scenarios where the partial volume effects at tissue interfaces are magnified by convolution based interpolants.

ii Diffusion tensor field alignment tools:

   ii.i A robust diffusion tensor field registration methodology that non-rigidly aligns diffusion tensor data from a group of subjects. This approach considers the uncertainty introduced by the experimental design and image noise to the tensors and prefers to align regions with more ”certain” information than regions corrupted by noise or artifacts. \[43\].

   ii.ii A metric warping tool that can be used for faster diffusion tensor field registration, when the diffusion tensor similarity metric is rather complex, or for extracting the statistical properties of the diffusion tensor fields with respect to the similarity metric \[45\].

iii Variability analysis tools:
A global variability analysis approach that captures the main modes of variations within data from a population of subjects. This approach, which operates on the Log-Euclidean manifold, aims to capture the locations of largest variations within the entire brain and extract differences between different segments of populations.

A local variability analysis approach that considers the relationships of different voxels and that models the local variability in terms of shape and diffusion tensor characteristics within a population of subjects.

A longitudinal regression based model that captures changes over-time.

4 Organization of Thesis

This book is organized into four self-contained parts.

Part I sets the context for the research problems dealt with in this thesis. Section 1.1 provides a brief background on the principles of NMR and MRI. Section 1.4 presents the basic concepts of diffusion MRI, including modalities such as standard diffusion imaging. Chapter 2 provides an overview of DTI processing pipelines and the challenges involved in terms of acquisition and image analysis. Chapter 3 concludes the background section by providing an overview of the interpolation techniques employed in image processing.

Part II describes the requirements for robust variability analysis using diffusion imaging data. Chapter 6 presents my analysis on the effects of EPI distortions on DTI features quality and introduces a novel EPI distortion correction technique. Chapter 7 presents the
effects of cumulative interpolation during distortion correction steps and proposes a PDE based interpolation scheme specialized for diffusion image processing. Chapter 8 addresses the problem of diffusion tensor field registration to align DTI data from a population of subjects.

Part III introduces my variability analysis approach with Chapter 10 providing a framework to model the global tensor variability and Chapter 11 focusing on local spatial variations respectively.

Finally, the Epilogue concludes this book with a summary of the research presented here and shares some thoughts on future directions.
PART I

Background
CHAPTER 1

BACKGROUND: DTI PRINCIPLES

Watch the sparrow falling. Gives new meaning to it all. If not today nor yet tomorrow then some other day.

Dream Theater,
Pull me Under.

The physical principle behind diffusion tensor imaging is nuclear magnetic resonance (NMR), which in turn depends on the Zeeman effect [124]. The physics underlying this phenomenon were refined in the 1920s and 1930s and practical instruments for measuring it were developed by Felix Bloch and Edward Purcell with coworkers in the 1940s. For these developments, Bloch and Purcell shared the Nobel prize in 1952. In work pioneered by Paul Lauterbur in the 1970s, methods for generating tomographic images of objects based on the NMR phenomenon were developed [67] leading to the development of magnetic resonance imaging (MRI). In the 1980s, MRI was established as an indispensable diagnostic clinical tool due to its ability to non-invasively produce high quality anatomical images of the human body. During the 1990s, an array of MRI techniques for studying human physiology were developed. Examples of such techniques now available are MR angiography and arterial spin labeling (ASL) for imaging blood vessels and blood flow,
real-time cardiac imaging and perfusion measurements, diffusion tensor MRI for tracing white matter fibres [9] and functional MRI for mapping brain activity [51].

This chapter begins with a brief description of the theory of NMR in Section 1.2. The principles behind diffusion tensor MRI are then explained in Section 1.4, starting with a brief note on Brownian motion in Section 1.3. Section 1.4.1 gives an overview of the theory behind DTI and Section 1.4.2 describes the advantages and disadvantages of different tensor fitting approaches. The tensor eigensystem is reviewed in Section 1.4.3 and the chapter is concluded with a very brief overview of different diffusion models in Section 1.5.

1.1 Nuclear Magnetic Resonance

The sub-atomic particles in an atom nucleus, viz. protons, neutrons, possess a magnetic moment of $\pm 1/2$ arising from the spin of the these particles, imparting it a net magnetic moment. Of interest to NMR is hydrogen ($^1$H) with one unpaired proton and a total nuclear spin $= 1/2$. Tomographic images are generated by measuring the spatial distribution of the magnetic moment of $^1$H, abundantly present in living tissue in the form of water.

When placed in a large external magnetic field (the $B_0$ field), hydrogen nuclei align either parallel or anti-parallel with the direction of the magnetic field (cf. Fig. 1.1). The detectable signal that is produced at room temperature depends on the manipulation of the few parts per million protons aligned with the magnetic field (in the $z$ direction of the $B_0$ field). At the same time, the magnetization vector of the proton precesses at a frequency $\omega_0$ which depends upon its gyromagnetic ratio $\gamma$, given by the Larmor equation $\omega_0 = \gamma B_0$. The gyromagnetic ratio is a nucleus specific constant and for hydrogen, $\gamma = 42.6$ MHz/Tesla.
Figure 1.1: **Precession of the Nuclear Magnetic Moment.** Hydrogen nuclei attain one of two different energy states when placed in a static magnetic field $B_0$. The nucleus can be seen as a small bar magnet and in the lower energy state the bar magnet is aligned with $B_0$ while the higher energy state corresponds to a counter–aligned magnet.

A pulse of radiation resonant with the precession frequency is applied to turn the small fraction of the $z$-aligned protons by an angle of $\pi/2$, to align in the direction perpendicular to the magnetic field. This rotating magnetic moment now experiences a torque tending it along the $B_0$ field, as per the equations derived by Felix Bloch:

\[
\frac{dM_z}{dt} = -\frac{M_z - M_0}{T_1} - \gamma (M \times B)_z \quad \text{and} \quad \frac{dM_{x,y}}{dt} = -\frac{M_{x,y}}{T_2} - \gamma (M \times B)_{x,y}, \quad (1.1.1)
\]

where $M$ is the nuclear magnetization as a function of time, and $M_0$ is the equilibrium magnetization in a steady and uniform field $B_0$ in the $z$ direction. The *longitudinal relaxation time* $T_1$ gives the time it takes for the magnetization in the $z$ direction to relax back to its equilibrium value $M_0$, while the *transverse relaxation time* $T_2$ gives the time for the azimuthal angles of the spins to get out of phase with one another. As the polarized protons precess together and relax to their initial alignment, they produce electromagnetic radiation of frequency proportional to the strength of the magnetic field and is called the *free induction decay* (FID) signal.
Figure 1.2: Radio Frequency (RF) Excitation. There will be a small excess of hydrogen nuclei in the lower energy state and therefore a resultant magnetic vector pointing in the direction of $B_0$. Energy can be supplied to the nuclei by applying a Radio Frequency (RF) pulse. The resultant magnetic vector is then tilted into the $xy$-plane and a current is induced in the receiver coil. Due to different relaxation processes, the $xy$-component of the magnetic vector, as well as the induced current in the receiver coil, will decay.

Variations in the molecular structure of biological substances can cause field inhomogeneities causing the spins to experience different local magnetic fields, and they go out of phase as they precess, reducing the net free induction decay (FID) signal. The time constant $T^*_2$ measures the combined effect of random nuclei interactions and magnetic field inhomogeneities. It holds that $T_1 >> T_2 > T^*_2$.

1.2 Magnetic Resonance Imaging

The main concept of MRI is the spatial selection and localization of the NMR signal through the use of magnetic gradients. As seen in the previous section, the resonant frequency $\omega$ of the nuclear spin system is dependent on its gyromagnetic ratio $\gamma$ and the magnetic field strength $B$ experienced by it. The use of spatially varying magnetic gradient fields $\mathbf{G} = (G_x, G_y, G_z)$ creates a different net magnetic field at every spatial location in the sample, thereby changing its intrinsic Larmor frequency. When this frequency changes
linearly with position then the net measured signal becomes the Fourier transform of the spin density of the sample.

Slice selection is achieved by applying a strong linear gradient in the slice direction $z$ during excitation with the $B_1$ RF pulse. The slice select gradient $G_z$ changes the Larmor frequency as a function of $z$ coordinate. The RF pulse has a finite bandwidth and thereby excites only the $z$-extent with Larmor frequency within its bandwidth.

The phase–encode gradient is then switched on for a period of time $\tau_y$, causing a phase warping of the protons in the selected slice as a function of $y$ position in space $k_y = \gamma G_y \tau_y$. After some time this gradient is switched off and the frequency encode gradients $G_x$ are applied and the signal is sampled. The gradient activity as a function of time on each orthogonal axis is typically represented, along with RF activity, in a pulse sequence diagram of Figure 1.3. The final image is obtained by an inverse Fourier transform of the $k$-space data.

The time constants $T_1$, $T_2$ and $T_2^*$ are tissue type dependent, allowing delineation of different tissues, and are the main cause of different types of contrasts in clinical MRI. This effect comes from the governing equation of spin-echo MRI (derived from eqn. 1.1.1)

$$S = S_0 \left(1 - e^{-\frac{TR}{T_1}}\right) e^{-\frac{TE}{T_2}}$$

(1.2.1)

where $S$ is the signal detected, $S_0$ is the maximum detectable signal, proportional to $B = B_0 + \langle G, x \rangle$ and to the spin density $\rho(x)$. Here $TE$ is the echo time between the $B_1$ excitation and readout, and $TR$ is the repeat time between one $B_1$ excitation and the next.
1.3 A Note on the History of Brownian Motion and Diffusion MRI

In 1828 the Scottish Naturalist Robert Brown published a pamphlet entitled "A Brief account of microscopical observations". In this pamphlet Brown recorded that pollen grains of Clarkia pulchella suspended in water under a microscope exhibited a peculiar rapid oscillatory motion [17]. Brown initially believed that such motion was particular to the male sexual cells of plants, but was later startled to observe that pollen of plants suspended in alcohol for almost eleven months exhibited the same erratic motion: a very unexpected fact of seeming vitality being retained by these molecules so long after the death of the plant. The erratic particle motion observed by Brown would remain unexplained until the dawn of the kinetic theory of matter in the third quarter of the nineteenth century. Pioneered
by Maxwell, Boltzmann, and Claussius, the kinetic theory of matter introduced the radical concept that the heat of a liquid or gas is mediated by the constant random thermal motion of the molecules in the medium.

Shortly after the initial discovery of the NMR phenomenon by Bloch \cite{Bloch} and Purcell \cite{Purcell}, Hahn published his seminal paper \cite{Hahn} on NMR spin echo in which he noted that the random thermal motion of the spins would reduce the amplitude of the observed spin echo signal in the presence of a magnetic field inhomogeneity. In their classic paper on the spin diffusion experiment, Stejskal and Tanner \cite{Stejskal} developed the methodology and theory of the pulsed gradient spin echo experiment which made possible direct measurement of the diffusion function and opened the window for quantitative measurements of molecular diffusion coefficients. Shortly following the first description of diffusion imaging by Taylor and Bushell \cite{Taylor} LeBihan obtained the first diffusion images on a whole-body system.

In 1994, Peter J. Basser \cite{Basser} introduced the diffusion tensor model to diffusion imaging. The tensor model provided a systematic analytical framework for describing diffusion anisotropy in tissue and entrenched Gaussian diffusion as the dominant model for diffusion imaging of anisotropy. In particular, the identification of the diffusion tensor major eigenvector with the dominant fiber orientation enabled the fiber orientation mapping program.

1.4 Diffusion Tensor MRI Principles

Diffusion tensor images are acquired using a novel MR imaging technique known as diffusion tensor MRI (DT-MRI) pioneered by Basser et al. \cite{Basser}. DT-MRI enables us to probe
certain microscopic features of the imaged tissue, particularly the presence of fibrous structures, that are not previously possible with other imaging modalities. It achieves this unique capability by measuring, at each voxel location, a tensor that quantifies aspects of water diffusion found to be sensitive to tissue composition and microarchitecture. The technique is non-invasive, requires no contrast agents and can be done in clinically acceptable time. As a consequence, it has established itself as a requisite imaging protocol for white matter related studies and is also routinely used for explorative brain imaging studies.

1.4.1 Diffusion Tensor MRI Theory

The notations, equations and figures in this section are borrowed from the original work of Basser et al. [9]. As stated in this work, one can observe significantly different diffusion constants in anisotropic media in contrast to isotropic ones, when the diffusion gradients are applied in different directions. The orientation dependence of diffusion can be characterized by \( D \), an effective self-diffusion tensor. For anisotropic media, the effective diffusion tensor, \( D \), inherently contains more information than a scalar apparent diffusivity, some of which can be represented graphically by an effective diffusion ellipsoid. To motivate its use and interpret its meaning, it is helpful to represent molecular diffusion in an anisotropic medium as a Brownian random process characterized by a macroscopic Gaussian conditional probability density function, \( \rho(x|x_0, t) \) [9] the probability that the spin-labeled species initially at \( x_0 \) and \( t = 0 \) reaches position \( x \) at time \( t \):

\[
\rho(x|x_0, \tau) = \frac{1}{\sqrt{|D(\tau)|(4\pi\tau)^3}} \exp\left(\frac{-(x-x_0)^T D^{-1}(\tau)(x-x_0)}{4\tau}\right) \tag{1.4.1}
\]
where $\tau$ is the diffusion time as will be explained in detail later. In this equation, $D$, which is assumed to be uniform within a voxel, can be interpreted as a covariance matrix of this translational displacement distribution $\rho(x|x_0, \tau)$. In tissue, we would expect $D(\tau)$ to be isotropic for very short diffusion times, until a significant number of protons encounter permeable barriers. For longer diffusion times, we would expect the ellipsoids to become more prolate. However, for media with impermeable barriers, or for very long diffusion times the Gaussian displacement distribution assumed above may not adequately represent the observed displacement distribution.

The effective second order self–diffusion tensor $D$ relates the macroscopic concentration gradient, $\nabla C$, and macroscopic diffusive flux, $J$ in an anisotropic medium with $J = -D \nabla C$, or:

$$
\begin{bmatrix}
J_x \\
J_y \\
J_z
\end{bmatrix} = -
\begin{bmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{bmatrix}
\begin{bmatrix}
\partial C/\partial x \\
\partial C/\partial y \\
\partial C/\partial z
\end{bmatrix}
$$

(1.4.2)

Diagonal elements of $D$ scale fluxes and concentration gradients in the same direction; off-diagonal elements couple fluxes and concentration gradients in orthogonal directions.

### 1.4.1.1 Relating Echo Intensity and $D$

Stejskal [106] related the applied magnetic-field gradient vector $G(t), G(t) = [G_x(t), G_y(t), G_z(t)]$ and its time integral,

$$
F(t) = \int_0^t G(t')dt'
$$

(1.4.3)

to the echo intensity, $A(TE)$ in a spin echo experiment according to:
\[
\frac{A(TE)}{A(0)} = \exp\left(-\gamma^2 \int_0^{TE} \left[ F(t') - 2H(t' - \frac{TE}{2})f \right]^T D \times \left[ F(t') - 2H(t' - \frac{TE}{2})f \right] dt' \right)
\]

(1.4.4)

where \( \gamma \) is the gyromagnetic ratio of protons, \( A(0) \) is the echo intensity with no applied gradients, \( H(t') \) is the unit heaviside function, \( TE \) is the echo time and \( f = F(TE/2) \). In equation (1.4.4), \( D \) is the diffusivity constant and not the diffusion tensor itself. The version with the effective diffusivity tensor \( D \), as a mean value of the exponent over the time interval \([0, TE]\) can be written as:

\[
-\gamma^2 \int_0^{TE} \left[ F(t') - 2H(t' - \frac{TE}{2})f \right]^T D \left[ F(t') - 2H(t' - \frac{TE}{2})f \right] dt' : D
\]

(1.4.5)

where ":\" is the generalized dot product. In matrix multiplication form:

\[
-\gamma^2 \int_0^{TE} \left[ F(t') - 2H(t' - \frac{TE}{2})f \right]^T D \left[ F(t') - 2H(t' - \frac{TE}{2})f \right]
\]

(1.4.6)

Taking the logarithm of Equation (1.4.4) with the definition in Equation (1.4.6), we obtain:

\[
\log \left( \frac{A(TE)}{A(0)} \right) = -\sum_{i=1}^{3} \sum_{j=1}^{3} b_{ij} D_{ij} = -b : D
\]

(1.4.7)

In this equation, \( b_{ij} \) is the \( ij \)th component of the symmetric \( b \)–matrix, \( b \), is defined as:

\[
b = -\gamma^2 \int_0^{TE} \left[ F(t') - 2H(t' - \frac{TE}{2})f \right]^T D \left[ F(t') - 2H(t' - \frac{TE}{2})f \right] dt'
\]

(1.4.8)
The $B$–matrix performs the role in anisotropic diffusion that the scalar $b$ factor performs in isotropic diffusion. Equation 1.4.7 suggests that to observe different linear combinations of the components of $D$, one can design experiments by applying diffusion gradients along various directions. For example, to observe the echo attenuation caused only by $D_{xx}$:

$$\log \left( \frac{A(b)}{A(0)} \right) = -b_{xx}D_{xx}$$  (1.4.9)

Figure 1.4 depicts a typical pulsed gradient spin-echo (PGSE) experiment. Assuming a symmetric trapezoidal pulse, an analytical model for the $b$-matrix can be described as:

$$b_{ij} = \gamma^2 G_i G_j \left[ \delta^2 \left( \Delta - \frac{\delta}{3} \right) + \frac{\epsilon^3}{30} - \frac{\delta \epsilon^2}{6} \right]$$  (1.4.10)

**Figure 1.4:** Waveforms in a pulsed gradient spin echo experiment. (a) 90° and 180° RF stimulating pulses from the surface coil; the magnetic field gradients (g/cm) applied in the (b) x, (c) y, and (d) z directions; (e) the time. Gradients applied in different directions must be applied simultaneously.
1.4.2 Tensor Fitting

With \( N \) diffusion weighted images acquired with \( N \) corresponding diffusion gradients, the set of diffusion equations can be described as:

\[
\{ A_i = A_0 \cdot e^{-b_i \cdot D} \} \quad i = 1, \ldots, N \tag{1.4.11}
\]

This equation is written in compact tensor form. For ease of notation, let \( \gamma \) be the vectorized version of the diffusion tensor (not to be confused with gyromagnetic ratio) as:

\[
\gamma = [D_{xx}, D_{xy}, D_{xz}, D_{yy}, D_{yz}, D_{zz}, \log(A_0)] \tag{1.4.12}
\]

and the overall \( B \)–matrix, an \( N \times 6 \) matrix, whose rows contain the entries of the original \( b \)–matrix for each gradient as:

\[
B_{i,:} = [b_{xx}, b_{xy}, b_{xz}, b_{yy}, b_{yz}, b_{zz}, -1] \quad \text{for} \quad G_i \tag{1.4.13}
\]

Then Equation 1.4.11 can be rewritten as a system of equations as:

\[
\vec{A} = A_0 \cdot e^{-B \cdot D} \tag{1.4.14}
\]

where \( \vec{A} \) is the vector of length \( N \) containing the signal values from the diffusion experiments.

1.4.2.1 Linear Fitting

If there were no error in measuring the echo intensity, we could in principle, determine the six components of the diffusion tensor \( D \) and \( A_0 \) using only seven independent trials with non-collinear gradient directions by simply inverting the \( 7 \times 7 \) \( B \)–matrix as:
\[
\gamma = -B^{-1} \log \left( \frac{A}{A_0} \right)
\] (1.4.15)

Since signal measurements are noisy, this approach provides poor estimates of \( D \) and has to be avoided. Instead \( N \gg 7 \) is generally suggested, meaning much larger number of trials than seven are required along with a multivariate regression approach to estimate the diffusion tensor. In regression analysis, the goal is to estimate the diffusion tensor that yields the minimum amount of error (residual) between the estimated signal from Equation (1.4.15) and the real signal. The reader is referred to the work from Jones [55] for a thorough study on the requirements for number of gradients.

The simplest regression type for tensor computation is multivariate linear least squares. This form is expressed as:

\[
f_{LLS}(\gamma) = \frac{1}{2} \sum_{i=1}^{N} \left( \log(A_i) + \sum_{j=1}^{7} B_{ij} \gamma_j \right)^2
\] (1.4.16)

This equation is the standard least-squares formulation for an over-determined system. The linearization is performed by applying to \( \log \) transform to Equation (1.4.15). The solution to Equation (1.4.16) can be written in terms of pseudo-matrix inverse as:

\[
\gamma = (B^T B)^{-1} B^T \left( -\log \left( \frac{A}{A_0} \right) \right)
\] (1.4.17)

This methodology for computing the diffusion tensor is relatively fast, however less accurate than the proceeding methods. The \( \log \) transform performed to linearize the system also diminishes the magnitudes of very large residuals, rendering them with less effect on
the outcome. An alternative approach is the weighted linear least squares methodology expressed as:

\[ f_{WLLS}(\gamma) = \frac{1}{2} \sum_{i=1}^{N} \omega_i^2 \left[ \log(A_i) + \sum_{j=1}^{7} B_{ij} \gamma_j \right]^2 \]  

(1.4.18)

In this version, the residual from each diffusion experiment is weighted with a term \( \omega_i \) to counteract the effects previously described. Let \( W \) be a diagonal matrix whose rows consist of \( \omega_i \), then the solution to this system can be written as:

\[ \gamma = (B^T WB)^{-1} B^T W \left( -\log \left( \frac{A}{A_0} \right) \right) \]  

(1.4.19)

Generally the weights are chosen to be the signal values \( A_i \), such that \( \omega_i = A_i \). The reader is referred to [62] for a detailed explanation of this reasoning.

The weighted least squares approach is considered to yield outcomes with quality in between the linear least squares and non–linear least squares approaches.

1.4.2.2 Non–Linear Fitting

Non-linear least-squares regression (NLS) approach to estimate the diffusion tensor components is considered to be the most accurate methodology. In this form, the signals are not transformed with the logarithm operation, hence the residuals are unaltered. This form can be described as:

\[ f_{NLS}(\gamma) = \frac{1}{2} \sum_{i=1}^{N} \left( A_i - \exp \left[ \sum_{j=1}^{7} -B_{ij} \gamma_j \right] \right)^2 \]  

(1.4.20)

Even though it is the most accurate formulation, non–linear regression based diffusion tensor estimation is computationally the most expensive and does not have a closed form
solution. There are several numerical methods for solving the NLS problem in DTI. Yet, the Levenberg-Marquardts (LM) \cite{71, 74} approach has been the method of choice, perhaps, due to its simple implementation. This simplicity is due in part to its approximation to the Hessian matrix of the NLS objective function. Another approach is Newton’s method (or full Newton-type method) where the complete Hessian matrix is required in the estimation process. It is well known that Newton’s method is more robust than the LM method and can speed up convergence in NLS problems \cite{76, 90}, but the complete Hessian matrix is often not available or known for a given problem.

1.4.3 Tensor Eigensystem

In this section, the diffusion tensor eigensystem and the tensor–derived scalar maps are discussed. The $3 \times 3$ diffusion tensor can be decomposed into its eigensystem as:

$$D = RAR^T \quad (1.4.21)$$

where $R = (e_1, e_2, e_3)$ is a column matrix of the orthonormal diffusion tensor eigenvectors $e_v$ and $\Lambda = \text{diag}(\lambda_1, \lambda_2, \lambda_3)$ is a diagonal matrix of the diffusion tensor eigenvalues $\lambda_v$.

The diffusion tensor eigensystem can be conceptualized in terms of the diffusion iso-probability surface which represents the surface on which a spin at the origin will diffuse to with equal probability. For a Gaussian diffusion process the isoprobability surface is a three-dimensional ellipsoid. The isoprobability ellipsoid represents the surface on which the Gaussian diffusion function has a constant value, i.e., $x^T Dx = \text{const.}$
The axes of the isoprobability ellipsoid are oriented in the direction of the tensor eigenvectors and have lengths proportional to the diffusion distance along the corresponding eigenvectors (Figure 1.5). Since the diffusion distance is proportional to the square root of the diffusion eigenvalues this is equivalent to scaling by the square root of the diffusion tensor eigenvalues.

![Figure 1.5: Isoprobability ellipsoid for a Gaussian diffusion function.](image)

While the ellipsoidal representation has a convenient physical interpretation in terms of the isoprobability surface, for visualization purposes it is sometimes desirable to display the diffusion tensor as another geometric glyph, such as lines for principal eigenvectors, cylinders, cuboids, super-quadrics. Figure 1.6 displays some of these visualization techniques.

### 1.4.4 Tensor–derived Scalar fields

Various rotationally invariant scalar measures of the diffusion tensor can be extracted in order to summarize the geometric properties of the tensor eigensystem, facilitate visualization on a two-dimensional plane or, enable univariate statistical comparisons between subjects or groups of subjects. For inter-subject comparisons, the scalar maps have the additional
Figure 1.6: Glyph Visualization. Different Glyph visualizations of the same diffusion tensor field. The glyphs are visualized in the region indicated in the right image.

The advantage of not requiring registration of the diffusion tensors which requires some care. While many such scalar measures have been defined in the literature, three important ones will be defined here: trace, fractional anisotropy and prolateness/oblateness.

The trace $Tr$ of the diffusion tensor is imply the sum of the eigenvalues or the tensor’s diagonal entries. The term Apparent Diffusion Coefficient (ADC) describes the average
diffusion amount and therefore \( Tr = 3 \times ADC \).

\[
Tr(D) = \sum_{i=1}^{3} \lambda_i = \sum_{i=1}^{3} D_{ii} \tag{1.4.22}
\]

where \( \lambda_i \) is the \( i^{th} \) eigenvalue. The trace provides a measure of the total diffusion within a voxel. The trace of the diffusion tensor is observed to be constant across normal brain tissue [83].

The fractional anisotropy (FA) metric is a measure of the orientational coherence of the diffusion compartments within a voxel [83]. Fibers that are strongly aligned, such as corpus callosum, exhibit high FA whereas fibers that are more weakly aligned (for example, in regions of fiber intersection) exhibit a relatively lower FA. Additionally, the FA metric can be effected by the degree of diffusion restriction perpendicular to the fiber direction. The FA metric is defined as:

\[
FA(D) = \sqrt{\frac{3}{2}} \sqrt{\frac{\sum_{i=1}^{3}(\lambda_i - Tr(D)/3)^2}{\sum_{i=1}^{3} \lambda_i^2}} \tag{1.4.23}
\]

The FA metric has the advantage of being automatically normalized to the unit interval and not requiring any sorting of the eigenvalues. Additionally, the FA metric is relatively insensitive to noise compared to other anisotropy metrics [83]. For these reasons, the FA metric has become the most widely used measure of diffusion anisotropy in biological tissues.

Prolate geometry refers to an elongated tensor eigensystem with a high difference between the first and second eigenvalues. The prolate metric is defined as \( \delta_{12} = \lambda_1 - \lambda_2 \). In comparison, oblate geometry refers to a planar, sheet-like eigensystem which is captured by the oblateness metric \( \delta_{23} = \lambda_2 - \lambda_3 \) (19). The sheet metric is higher in regions of fiber
crossing within a plane, and is helpful for identifying regions of intravoxel orientational heterogeneity [121].

### 1.5 Some Other Diffusion Models

One of the advantages of using the single effective diffusion tensor formalism in tissue is that it provides new information without making many explicit assumptions about the underlying tissue architecture and microstructure except that the diffusion characteristics can be represented by a single symmetric gaussian displacement distribution. DTI is currently considered to be one of the simpler diffusion models and several new and more complicated models have been proposed since its proposal. Inferring the microstructure and the underlying architectural organization of tissue using diffusion imaging data is complicated by several factors. First, homogeneity within each voxel cannot be assured. Numerous microscopic compartments exist within brain parenchyma. A priori, we must assume that gray matter, white matter and cerebrospinal fluid (CSF); and several fiber bundles with differing orientations could occupy the same macroscopic voxel.

The diffusion tensor model was one of the earlier models for tissue diffusion. Due to its simplicity it gained popularity in the neuroscience and computer sciences communities but its deficits were uncovered shortly including its inability to model complex tissue structures containing a population of fiber bundles [72, 84, 121]. Several new and more complex diffusion models have been proposed since, differing in their acquisition requirements and their models. These include but not limited to two compartment models [85], High Angular Resolution Diffusion Imaging (HARDI) with spherical harmonics model [34], Q-Ball
imaging [115], diffusion spectrum imaging (DSI) [114] and diffusion kurtosis imaging [50].

Table 1.1 presents in a simple fashion the evolution of diffusion models.
<table>
<thead>
<tr>
<th>Purpose</th>
<th>Model</th>
<th>Presentation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>• D (scalar)</td>
<td></td>
<td>• PGSE sequence</td>
</tr>
<tr>
<td></td>
<td>• $A_i = A_0 e^{-bD}$</td>
<td></td>
<td>• 1 $b$–value.</td>
</tr>
<tr>
<td>Single Fiber</td>
<td>• D (tensor)</td>
<td></td>
<td>• PGSE sequence</td>
</tr>
<tr>
<td></td>
<td>• $A_i = A_0 e^{-bG^T_i D_{G_i}}$</td>
<td></td>
<td>• 1 $b$–value.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• 6 gradients reqrd.</td>
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<tr>
<td>Parenchyma (nerve cells and glia)</td>
<td>• 1 isotropic and 1 diffusion tensor</td>
<td></td>
<td>• PGSE sequence</td>
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<tr>
<td></td>
<td>• $A_i = A_0(\alpha e^{-bG^T_i D_{1,G_i}} + (1 - \alpha)e^{-3b})$</td>
<td></td>
<td>• Multiple $b$–values.</td>
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<td></td>
<td>• 7 gradients reqrd.</td>
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<td></td>
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<td></td>
<td>• More needed practically.</td>
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<td></td>
<td>• 2 sets of fibers.</td>
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<td>• Multiple $b$–values.</td>
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<td>• Optic Chiasm, centrum semiovale.</td>
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<td>• 15 gradients reqrd.</td>
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<tr>
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<td>• High Angular Resolution is practically needed.</td>
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<td></td>
<td>• Multiple fibers.</td>
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<td>• Multiple high $b$–values.</td>
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<td></td>
<td>• No exchange.</td>
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<td>• 15 gradients reqrd.</td>
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<td>• HARDI.</td>
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<td>• Mixture of tensors.</td>
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<td></td>
<td>• Spherical Harmonics.</td>
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</tr>
<tr>
<td></td>
<td>• $A_i = A_0(\sum_{k=1}^{n} \alpha_k e^{-bG^T_i D_{k,G_i}})$</td>
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<tr>
<td></td>
<td>• or $4^{th}$ order tensors.</td>
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<td></td>
<td>• Complex fiber architecture.</td>
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<td>• Non-parametric displacement pdf.</td>
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<td></td>
<td>• $P(r_2, \triangle</td>
<td>r_1, 0)$</td>
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<td></td>
<td>• Orientation distribution functions (ODF).</td>
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<td>• Cell imaging.</td>
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<td>• Restricted diffusion.</td>
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<td>• Composite hindered and restricted model of diffusion (CHARMED).</td>
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**Table 1.1: Diffusion Models with Increasing Complexity.** The requirements for tissue analysis, diffusion model and acquisition experimental designs are interrelated. Depending on the tissue of interest, a simple experiment with a simple model might be sufficient whereas for complex architectures, more involved acquisition schemes and diffusion models might be necessary. More complex models can represent the architectures of the simpler models but they can suffer from overfitting problems.
CHAPTER 2

BACKGROUND: DTI PROCESSING PIPELINES

The creative process is a process of surrender, not control.

Julia Cameron

Data obtained with a diffusion tensor MRI acquisitions are not equivalent to scalar image data, in the sense that diffusion data can not be directly used for clinical or analysis purposes but have to undergo some processing before interpretations can be made. The outcomes of DTI data based analysis can vary significantly depending on the processing methodologies considered. In this chapter, various challenges posed by diffusion weighted data processing will be briefly reviewed and the processing pipeline model will be gradually improved to account for these challenges.

Section 2.1 opens the chapter with the simplest processing model. Section 2.2 introduces the motion–artifact correction step and describes its effects. Section 2.3 describes artifacts induced by eddy–currents and how their correction can be included in a DTI processing pipeline. In Section 2.4 EPI distortions are described and several models are proposed for their solutions. Section 2.6 describes the spatial noise alteration problem introduced by all these correction steps.
2.1 Black Box DTI processing

In this book, the direct use of raw diffusion weighted data is called *black box* DTI processing because the results can be completely unreliable. Even though this approach was the most commonly followed methodology in the early years of DTI, the deficits involved with this approach were apparent [8]. The pipeline of this simpler methodology is depicted in Figure 2.1.

**Figure 2.1:** Black-box DTI processing pipeline. In this methodology, the raw diffusion data is directly fed into a tensor fitting routine without any processing. The computed diffusion tensors are used to extract the desired features.

In the remainder of this chapter, the tensor processing steps of the pipelines will be very similar to those in Figure 2.1, therefore will be omitted. In each proceeding section, a type of artifact or distortion that needs to be considered in the processing pipelines will be briefly described and the pipelines will be modified to account for these challenges.
2.2 Motion Artifacts

The patient’s movements are the most common source of image artifacts. In standard structural MRI, random patient movements might produce a blurry and noisy image, mainly in the phase-encode direction while periodic motion can create ghost images. In the context of diffusion imaging (or any times-series based imaging, motion artifacts cause misalignments among the diffusion weighted volumes [77], hence tensors computed from non–corresponding diffusion signals will not reflect the underlying tissue characteristics. Figure 2.2 displays the difference in FA maps between motion corrected data and the black-box version.

![Figure 2.2: Difference in FA between original and motion artifacts corrected data.](image)

After motion correction, the noise-like artifacts in the FA maps of the raw data are clean. Additionally, the motion corrected data have higher FA values in homogeneous white matter regions.
The pipeline of this processing methodology is illustrated in Figure 2.3. Motion correction step indicated in the pipeline generally employs a "rigid image registration" framework and all the diffusion weighted images are aligned with a pre-chosen image in the dataset, typically a $b = 0s/mm^2$, diffusion-free image.

![Motion correction processing pipeline](image)

**Figure 2.3:** Motion correction processing pipeline. In this methodology, the raw diffusion data is first corrected for motion artifacts and the newly generated "motion-free" dataset is provided to tensor fitting routines.

### 2.3 Eddy–currents Artifacts

Eddy-currents cause different spatial distortions for each diffusion weighted volumes, resulting in misalignment of DWIs. Eddy currents are significantly reduced, but not eliminated, by actively shielded gradients [95] and preemphasis correction schemes [35] in modern magnets.

Image distortions from eddy currents depends on the time and space dependence of $b_{eddy}(y, t)$, the component parallel to $B_0$ of the magnetic field generated by the eddy currents. The shifts in the readout, phase-encode, and slice-select directions are:

$$
\delta_{\text{read}} \approx \frac{b_{eddy}}{gau ss}, \quad \delta_{\text{phase}} \approx \frac{b_{eddy}}{0.07gau ss}, \quad \delta_{\text{slice}} \approx \frac{b_{eddy}}{2.5gau ss} \tag{2.3.1}
$$
The reader is referred to [97] for details of these equations. These equations state that the dominant distortions due to eddy-currents are along the phase-encoding direction.

Rohde et al. [97] provided an elegant solution to eddy-currents transformations using an image registration based framework. They combined motion distortion correction step and the eddy current distortion correction step into a single optimization problem, where they optimized each transform parameter simultaneously.

The philosophy behind this approach, which I employ throughout the rest of this book as the primary method for eddy currents distortions, is that since fields due to eddy currents induced in the subjects head can be neglected, \( b_{\text{eddy}}(y, t) \) must obey the Laplace equation [105] as follows:

\[
\nabla^2 b_{\text{eddy}} = 0
\]

(2.3.2)

The Laplace equation in Cartesian coordinates has well-known solutions with arbitrary polynomial orders. The second order solution in conformance with eddy currents induced distortions can be written as:

\[
\beta b_{\text{eddy}}(y) = c_0 + c_1 y_1 + c_2 y_2 + c_3 y_3 + c_4 y_1 y_2 + c_5 y_1 y_3 + c_6 y_2 y_3 + c_7 (y_1^2 - y_2^2) + c_8 (2y_3^2 - y_1^2 - y_2^2)
\]

(2.3.3)

where \( c_0 - c_8 \) are parameters to be determined from the optimization procedure. Once the optimal parameters are computed that maps a distorted image onto a distortion-free image, new distortion-free coordinates can be found with:

\[
y' = y - \beta b_{\text{eddy}} e_2
\]

(2.3.4)

with \( e_2 = (0, 1, 0) \) representing the phase encoding direction.
Non-linear deformations such as eddy currents distortions can cause expansion or contraction in local regions of images, where the total energy is preserved. This signal transformation is generally computed using the Jacobian of the deformation in elastic image registration community and the same principal applies to this transformation, yielding a signal transform term $\Gamma$ as:

$$\Gamma = 1 + c_2 + c_4 y_1 + c_6 y_3 + 2(c_7 + c_8)y_2$$  \hspace{1cm} (2.3.5)

### 2.3.1 Eddy–currents Artifacts Pipeline

Two processing pipelines accounting for eddy-currents distortions can be proposed (Figure 2.4 and 2.5).

**Figure 2.4:** Sequential motion and eddy distortions correction processing pipeline. In this pipeline, motion distortion correction and eddy-currents distortion correction steps are performed consecutively generating intermediate sets of data.

**Figure 2.5:** Combined motion and eddy distortions correction processing pipeline 2. In this pipeline, motion distortion correction and eddy-currents distortion correction steps are performed as a single step as proposed by [97]
The second pipeline is preferred to the first one for several reasons. First of all, it does not generate additional intermediate sets of data and is computationally less intensive. However, more importantly, as stated in this section, eddy currents cause displacements along the phase encoding direction. If the images are first corrected for motion, the phase encoding direction of the original images become an oblique direction in the motion corrected data, hence the correction scheme is not entirely accurate. Combining these two steps resolve these issues and is employed used in this work. With the combined framework, the motion and eddy currents transformation parameters are solved for within a single optimization framework, which improves robustness and an additional interpolation step to generate the final images. Additionally, it provides better alignment especially around the border regions because the eddy currents corrections are performed in the original image space, not the intermediate images with altered phase encoding directions.

2.4 EPI Artifacts

In most diffusion weighted MRI experiments, diffusion weighted measurements are typically spin-echo planar imaging acquisitions due to the necessity for fast imaging (Section 1). A well-known problem with EPI is the geometrical and intensity distortions in the phase-encode direction caused by field inhomogeneities [52] and concomitant fields [25]. It should be noted that these EPI distortions are different from the eddy current distortions, caused by the rapid switching of the diffusion sensitizing gradients. Eddy current distortions affect only the diffusion weighted images, and are typically corrected in DWI processing. Correction of EPI distortion generally requires acquisition of additional data,
such as $B_0$ mapping [52], advanced pulse sequences or dedicated $T1$ or $T2$ weighted structural targets, and it is generally not performed in a standard diffusion processing pipeline.

The effect is most severe in regions where air–filled sinuses border with bone or tissue such as the frontal lobes, occipital and temporal lobes, but it is also apparent to a lesser extent in other regions and arise along the direction in which the acquisition time between adjacent points is greatest. This is the phase encoding direction, often along the anterior–posterior axis (and also along the inferior–superior axis for 3D-EPI). Distortions along the read–out direction (left–right axis) are negligible because the acquisition time between adjacent points is small [58].

EPI distortions and their effects on scalar images is a well investigated problem [122] and several classes of correction algorithms have been proposed. In their pioneering work, Jezzard et al. [52] employed a $B_0$ inhomogeneity map, or fieldmap, which was computed from two gradient–echo scans with different echo times. They showed that the distortions are significant along the phase-encoding direction and are linear functions of such fieldmaps. Several other works followed, which employ the fieldmapping strategy [93][69].

Other approaches to the problem involve using “distortion–free” pulse sequences such as the works of Techavipoo [109], Gui [37] and Embleton [28] and non-linear registration of the distorted $B0$ EPI image to a structural anatomically correct MR image. The work of Kybic et al. [66] was the pioneer in this class of techniques. They used a multi–resolution uniform B–Splines transform with increasing grid resolutions to correct for the distortion transformations. Several other deformable registration approaches or transformations have been employed, such as the variational method from Tao et al. [107] and optic flow registration from Ardekani et al. [6].
2.4.1 EPI Artifacts Pipeline

Similarly, two pipelines can be devised for EPI distortion corrections with sequential and combined processing strategies. Figure 2.6 depicts the first version.

![Figure 2.6: Motion, Eddy and EPI distortions correction processing pipeline 1.](image)

In this pipeline, the distorted $b = 0 \text{s/mm}^2$ image is elastically registered to a distortion-free structural image. The computed deformation field is subsequently applied to all diffusion weighted images in the dataset.

This pipeline assumes that the EPI distortion correction scheme is based on an elastic image registration framework, therefore an additional structural, distortion–free $T1_w$ or $T2_w$ image is required. In this version, while the motion & eddy distortion correction is performed, the $b = 0 \text{s/mm}^2$ image is non-linearly registered to the structural image and the deformation field modeling the EPI distortion is computed. This registration takes place in the $b = 0 \text{s/mm}^2$ image’s native space. Afterwards, the deformation field is applied to every diffusion weighted volume in the dataset to unwarp the distortions. This correction scheme suffers from similar problems. It generates intermediate datasets and might not be completely accurate due to the inconsistency of phase encoding direction with the image.
axis after motion & eddy distortion correction. However, due to its simplicity and relatively less computational requirements, it is the model employed in this work.

![Diagram](image)

**Figure 2.7: Motion, Eddy and EPI distortions correction processing pipeline 2.** In this pipeline, the motion, eddy and EPI distortion correction steps are interleaved.

The pipeline displayed in Figure 2.7 interleaves all the distortion correction steps. Each diffusion weighted volume is processed independently in its native space with either fieldmapping or elastic registration. This approach is more accurate but computationally more intensive.

### 2.5 Interpolation Combination

Sometimes it is desired to have the diffusion weighted data in the native space of another image, such as a structural image or and fMRI data. This introduces an additional transformation at the final stage of the pipeline and the entire framework includes two intermediary (and temporary) datasets and a final dataset obtained through the use of three interpolation steps. The cumulative effects of these interpolation steps become non-negligible after a point and interpolation becomes a significant source of uncertainty/variability in the data. Therefore, the use of only one interpolation step to generate the final images is suggested in this context, as displayed in Figure 2.8.
2.6 Noise & Interpolation related Artifacts

If parallel imaging techniques, such as SENSE [91] are not employed in the image acquisition process, the noise in the images is spatially uncorrelated and follow a Rician distribution [94]. However, when a spatial transformation is applies to the images and the resulting new set of images are generated through interpolation, noise becomes spatially correlated and follow certain characteristics. Rohde et al. were the first ones to observe this phenomenon [98]. These noise characteristics, if not accounted for, can significantly alter the properties of diffusion tensor derived features, such as tractography, uncertainty estimation and voxel based morphometry. In this section Rohde’s solution will be first reviewed and an alternate pipeline will be proposed. In Chapter 7, a complete solution set to this problem will be presented.
In their work, Rohde et al. deployed the diffusion processing pipeline of Figure \ref{fig:2.5}, therefore only the motion & eddy currents distortions were corrected in a single step. They employed a "trilinear" interpolation methodology to generate the final images and their proposed solution only covers these cases.

Let \( w_i \) be integer grid index locations in the original image, \( x \) the continuous physical coordinates and \( f(x) \) be the transformation that maps \( x \) onto new coordinates. The image signal value at \( f(x) \) can be estimated using trilinear interpolation as:

\[
A(f(x)) = \sum_{w_i \in \Theta} \alpha_i A(w_i)
\]

(2.6.1)

where \( \Theta \) defines a set of sampling coordinates that surround \( f(x) \) and includes eight voxels in the case of trilinear interpolation. The coefficients \( \alpha_i \) are weights for each signal at integer grid locations and can be found from linear distances. The noise variance at the new location \( f(x) \) is:

\[
Var(A(f(x))) = \left( \sum_{w_i \in \Theta} \alpha_i^2 Var(A(w_i)) \right) + 2 \left( \sum_{w_i, w_j \in \Theta, i < j} \alpha_i \alpha_j Cov(A(w_i), A(w_j)) \right)
\]

(2.6.2)

The noise variance at integer grid locations can be assumed to be constant, i.e. \( Var(A(w_i)) = \lambda^2 \) when parallel imaging techniques are not used, in which case the noise would be spatially varying. Additionally, from the definition of covariance, one can state \( Cov(A(w_i), A(w_j)) = \lambda^2 Corr(A(w_i), A(w_j)) \) where \( Corr \) indicates the correlation operator. Then the variance equation can be written as:
\[ Var(A(f(x))) = \lambda^2 \left( \left( \sum_{w_i \in \Theta} \alpha_i^2 \right) + 2 \left( \sum_{w_i, w_j \in \Theta, i < j} \alpha_i \alpha_j \text{Corr}(A(w_i), A(w_j)) \right) \right) \]  

(2.6.3)

This equation states that the new noise variance is less than or equal to the original noise variance due to the fact that the first summation term maximizes at one. Additionally, the noise variance becomes a spatial function of the original variance \( \lambda^2 \) and the transformation \( f(x) \). For typical image registration schemes, the weights \( \alpha_i \) will repeat themselves in a pattern, especially if \( f(x) \) models a rotation transformation. This causes striped patterns in the noise maps, and the \( \chi^2 \) error maps of tensor fitting operation if the original noise variance is used in the fitting. If these newly estimated noise variances are used in the estimation of tensors as the \( \chi^2 \) denominator term, the striations should be eliminated. This behavior is depicted in Figure 2.9.

The correlation operator in Equation. 2.6.3 has to be defined in an intelligent way. Rohde et al. proposes an \( 8 \times 8 \) correlation matrix for trilinear interpolation, that considers the physical correlation between voxels adjacent on slice encoding direction (which should be almost zero), on phase-encoding direction and read-out direction. This model however can not be generalized for general use with other interpolants.

### 2.6.1 Noise & Interpolation related Artifacts Pipeline

This is the final pipeline demonstrated in this book and is the one used for experimentation. Figure 2.10 displays its flowchart layout. It includes processing methodologies for all known types of distortions and artifacts and provides data free of external sources of
Figure 2.9: $\chi^2$ map from tensor fitting with and without the spatial noise estimation. Demonstration of bias in $\chi^2$ between the DT model and registered DWI data. Part (a) shows the $\chi^2$ map computed using a single value for the variance in the data. Part (b) shows the non-uniform variance estimated using Equation. 2.6.3. Part (c) shows the same $\chi^2$ map, however, this time computed using the variance values displayed in part (b).

data corruption and enables the possibility of a robust DTI analysis. The effects of this processing scheme will be detailed and illustrated in Sections 6 and 7.
Figure 2.10: The complete diffusion image processing pipeline accounting also for noise variance. In this pipeline, another process is added to estimate the spatial noise variance, which is fed into the tensor estimation routines. These routines are internally altered to account for this noise variance change.
CHAPTER 3

BACKGROUND: INTERPOLATION STRATEGIES

*If that enabled us to predict the succeeding situation with the same approximation, that is all we require, and we should say that the phenomenon had been predicted, that it is governed by the laws.*

Henri Poincare, 1903

In mathematics, interpolation is the process of constructing new data points within the range of discrete set of known data points and has many applications in computer vision and medical image analysis. Interpolation is required for a large set of operations manipulating discrete images, such as upsampling/resampling, geometric alignment and registration and improving image quality.

Therefore, image interpolation methods have occupied a peculiar position in medical image processing. They are required for image acquisition as well as in image post-processing. In magnetic resonance imaging (MRI), image reconstruction requires interpolation to approximate the discrete functions to be back projected for inverse Fourier transform. In the context of diffusion weighted imaging, image interpolation plays an important role at various stages, from acquisition when the final image and k-space acquisition matrices differ in size, to post-processing to realize motion & distortion correction.
In signal processing community, interpolation methodologies are known to introduce artifacts to final images [88, 110]. In the context of medical imaging, interpolation methods can significantly affect registration outcomes [96] and can introduce structured patterns in the second order statistics of images due to the noise present in the acquired images [98]. Therefore, cumulative effects of "interpolation" during acquisition and processing is a non-negligible source of undesired variation in any diffusion weighted imaging data and these variations need to be either considered in a robust population or longitudinal study model, or need to be removed from data.

In this section, background information on different interpolation methodologies will be presented under two categories from a diffusion imaging point of view: 1) Linear (convolution based) interpolators and 2) Non–linear (partial differential equations (PDE) based) operators. Evaluation and analysis on these interpolants will be performed in Section [7] in terms of their effects on the image quality and tensor statistics based on $\chi^2$ maps of tensor-fitting operations.

### 3.1 Linear (Convolution based) Interpolation

Convolution based interpolation operators are the most commonly used interpolation strategies and primarily focus on frequency domain attributes or $C^n$ continuity of the interpolated images. Simple algorithms such as nearest neighbors and bi/tri–linear interpolation were historically succeeded by sinc function approximations as a direct impact of the burgeoning field of information theory introduced by [102]. For convolution based interpolators, the sinc function is accepted as the interpolation function of choice but this ideal interpolator has an infinite impulse response (IIR) and is not suitable for local interpolation. For
this reason, several interpolation kernels of finite size have been introduced, including but not limited to polynomial kernels, spline based kernels, truncated/windowed sinc kernels, Gaussian kernels.

For image resampling, the interpolation step must reconstruct a 3D continuous signal $s(x, y, z)$ from its discrete samples $z[i, j, k]$ with $s, x, y, z \in \mathbb{R}$ and $i, j, k \in \mathbb{N}$. In linear interpolation methods, the signal at the position $(x, y, z)$ are estimated from its discrete neighbors, mathematically described as the convolution of the discrete image samples with the continuous 3D impulse response of an interpolation kernel $h$:

$$s(x, y, z) = \sum_{i} \sum_{j} \sum_{k} z[i, j, k] h(x - i, y - j, z - k)$$ (3.1.1)

Please note that the interpolation kernels described in this section are separable, i.e. $h(x, y, z) = h_1(x)h_2(y)h_3(z)$ and for simplicity reasons, only the 1D versions of the kernels will be visualized. Additionally, only the kernels employed in the analysis will be reviewed.

### 3.1.1 Nearest Neighbor Interpolation

Nearest neighbor (NN) interpolation is the simplest and fastest interpolation methodology. The value $s(x)$ at location $x$ is chosen as the next known value $z[i]$. Therefore only one support point is required for NN interpolation and the kernel and its Fourier transform are visualized in Figure 3.1 with the kernel equation as:

$$h(x) = \left\{ \begin{array}{cl} 1, & 0 \leq |x| < 0.5 \\ 0, & o/w \end{array} \right\}$$ (3.1.2)

**Pros and cons in DWI interpolation:** For interpolation during motion and distortion correction of diffusion weighted images, the choice of nearest neighbor interpolation has the
advantage of being fast and not introducing new signal values to the images. With non-
convoluted diffusion signals, the anisotropy of the computed tensors stay larger compared
to other convolution based interpolants. However, the disadvantages outweighs the advan-
tages since this interpolation yields very noisy and aliased images in terms of signal values.

### 3.1.2 Trilinear Interpolation

For trilinear interpolation, the values of neighbors are weighted by their distance to the
opposite point of interpolation. Therefore in $3D$, this interpolation method requires eight
supporting points. Therefore, the kernel follows a triangular shape (Figure 3.2).

$$h(x) = \begin{cases} 
1 - |x|, & 0 \leq |x| < 1 \\
0, & o/w
\end{cases}$$

(3.1.3)
Pros and cons in DWI interpolation: Trilinear interpolation is relatively fast. It introduces new values into images, however because these values are convex combinations of existing image values, which are norms of complex valued signals, the new image values are guaranteed to be non-negative. The main disadvantages of trilinear interpolation during DWI postprocessing is still its inability to accurately filter out high frequency components. Additionally, a slight amount of blurring occurs at tissue interfaces.

3.1.3 Cubic Interpolation

Cubic polynomials are frequently used as interpolators due to their ability to generate $C^2$ continuous images. Cubic interpolators require four points per dimension, therefore for three-dimensional images, 64 support points are necessary. The generic form of a cubic interpolation kernel $C$ is described in Equation (3.1.4).

$$C = \sum_{i=0}^{3} \sum_{j=0}^{3} \sum_{k=0}^{3} a_{ijk} x^i y^j z^k$$  \hspace{1cm} (3.1.4)
In this equation, the weights $a_{ijk}$ for the 64 neighbors are determined based on $C^0$, $C^1$ and $C^2$ continuity constraints with respect to the image values. The kernel of these interpolators is visualized in Figure 3.3.

![Cubic polynomial kernel](image1.png) ![Cubic Fourier transform](image2.png)

(a) Cubic polynomial kernel  (b) Cubic Fourier transform

Figure 3.3: Cubic interpolation. Cubic kernel and its Fourier spectrum.

**Pros and cons in DWI interpolation:** Cubic polynomials are the ones that best represent the sinc function among the interpolators reviewed so far. However, to achieve this they require a larger kernel size, which renders them slower than their lower order counterparts. Additionally, cubic polynomials can introduce negative values to the diffusion weighted images. Another challenge arising from large kernels is the blurring of edges at tissue interfaces such as white matter (WM) v.s. Cortico Spinal Fluid (CSF), which introduces additional partial volume effects to the data not originating from acquisition (Section 7).

### 3.1.4 Gaussian Interpolation 1

Gaussian function is a relevant choice for the proposed method in this work. In its original form visualized in Figure 3.4, the Gaussian kernel does not act as an interpolator but as an
approximator because it does not intersect the zero line at integer grid points. Therefore, even when the convolution is applied at integer grid locations, a smoothed version of the original signal is yielded instead of the unchanged value. This form of Gaussian function is very frequently used in image smoothing and image restoration (intrinsically) but not as an interpolation kernel.

![Gaussian function](image.png)

**Figure 3.4:** Gaussian function. The Fourier transform is again a Gaussian function and is not visualized.

### 3.1.5 Gaussian Interpolation 2

Appledorn has proposed modified versions of typical Gaussian kernels [5] that are both locally compact and almost band limited. In his formalization, a 1D Gaussian function with zero mean and variance $\beta$ is defined as:

$$G^0(x, \beta) = \frac{1}{\sqrt{2\pi \beta}} e^{-x^2/2\beta}$$  \hspace{1cm} (3.1.5)

and the $N^{th}$ order derivative of this function is defined as:

$$G^M(x, \beta) = \frac{\partial^M}{\partial x^M} G^0(x, \beta)$$  \hspace{1cm} (3.1.6)
Then the interpolation kernel is defined as:

\[
h^M(x) = \left\{ \sum_{m=0}^{M} \alpha_M G^m(x, \beta_m), \quad 0 \leq |x| < \text{support} \right\}
\]  
(3.1.7)

The weights \( \alpha \) and the variances \( \beta \) are computed from a set of three constraints for each degree of the kernel.

For 1D interpolation, the second degree interpolation kernel with pixel spacing \( \triangle x \) is defined as:

\[
D_2(x, \triangle x) = \triangle xG^0(x, k_1\triangle x^2) - k_2G^2(x, k_3\triangle x^2)
\]  
(3.1.8)

The parameters \( k_1, k_2 \) and \( k_3 \) are determined based on a set of three constraints as:

i \[ \int_{-\infty}^{\infty} D_2(x, \triangle x)dx = \triangle x \]

ii \[ \frac{d^n}{dw^n} \hat{D}_2(w, \triangle x)|_{w=0} = 0 \text{, for } n \text{ even} \]

iii \[ D_2(x, \triangle x)|_{x=0} = 1 \]

The first constraint states that the area under the interpolation kernel should be equal to pixel spacing. The second constraint states that the Fourier transform of the kernel \( (\hat{D}(w, \triangle x)) \) should be flat with no curvature at zero frequency. The last constraint states that when convolved at an integer grid location, the original signal value should be returned. Solving for these constraints yields a set of three equations as:

\[
k_2 = 1/2k_1\triangle x^2
\]

\[
k_3 = 1/2k_1
\]

\[
k_1 = \left( \frac{1}{\sqrt{2\pi}} + \frac{1}{\sqrt{\pi}} \right)^2 \quad \text{(with } \triangle x = 1) \]
This second order kernel and its Fourier transform are visualized in Figure 3.5.

(a) Gaussian interpolation kernel  
(b) Fourier transform

Figure 3.5: Second order Gaussian interpolator.

### 3.1.6 3D Anisotropic Gaussian Kernel

The Gaussian function based kernel proposed by Appledorn has very desirable compactness properties in both spatial and frequency domain. It is of special interest to this work because convolution with a Gaussian function intrinsically manifests itself in a variety of image processing applications such as partial differential equations based image filtering or image restoration.

For multi-dimensional case, the Appledorn kernel can be directly extended to the desired number of dimensions using the outer products due to the separability of Gaussian kernels. However, for spatially equal voxel spacing, the computed kernels would be spatially isotropic, hence not directional.

*Pros and cons in DWI interpolation:* In terms of disadvantages, the Gaussian interpolator suffers from the same problems as the cubic interpolator. However, computation of the
Gaussian interpolator is relatively fast due to its recursive nature. Additionally, this interpolator has a very compact frequency response. The main advantage of this approach will be described in Section Chapter 7, where the intrinsic Gaussian convolution behavior of PDE processing will be employed to propose a novel interpolator.

3.2 Non–Linear (PDE based) Interpolation

PDE based interpolation schemes are generally used not for general interpolation purposes but upsampling images [99, 113]. Their power lies in their ability to preserve and improve local structures such as edges and corners while retaining noise reduction and scale-space properties. The philosophy behind PDE based filtering relies on the fact that the 3D heat equation displayed in Equation (3.2.1) is equivalent to convolution with an oriented Gaussian filter. Let \( I \) be the 3D image in consideration, \( x, y, z \) be spatial dimensions and \( t \) be the time parameter, the Laplacian version of the heat equation can be written as:

\[
\frac{\partial I(x, y, z, t)}{\partial t} = c \left( \frac{\partial^2 I}{\partial x^2} + \frac{\partial^2 I}{\partial y^2} + \frac{\partial^2 I}{\partial z^2} \right)
\]  

(3.2.1)

By setting the initial condition \( I_0 \) to the original image and using this update equation with corresponding weights \( c \) for the spatial second derivatives, one can obtain the exact results of Gaussian interpolation with unmodified kernel of Figure 3.4. PDE based filtering has been gaining popularity in image processing community for its ability to give local control over the directionality and amount of filtering. Instead of an isotropic, spatially constant Gaussian kernel, one can intrinsically employ anisotropic kernels of different length scales along the principal axes by slightly modifying the equation to:

\[
\frac{\partial I(x, y, z, t)}{\partial t} = c_1 \frac{\partial^2 I}{\partial \xi^2} + c_2 \frac{\partial^2 I}{\partial \eta^2} + c_3 \frac{\partial^2 I}{\partial \zeta^2}
\]  

(3.2.2)
where $\xi$, $\varrho$, and $\varsigma$ are the directions of the principal axes of the 3D Gaussian kernel and $c_i$ are the length scales along these dimensions. This equation can further be rewritten as:

$$\frac{\partial I(x, y, z, t)}{\partial t} = \text{trace}(TH)$$

(3.2.3)

where $H$ is the spatial Hessian matrix of the image and $T$ is the "anisotropic diffusion tensor" (not to be confused with the diffusion tensor model of DTI), which rotates and scales the Gaussian kernel. In 3D both matrices are $3 \times 3$ and are spatially varying to account for homogeneity of the filtered regions and discontinuities such as edges and corners. Therefore, the eigenvectors $\xi$, $\varrho$, $\varsigma$ of the anisotropic diffusion tensor $T$ are computed from a locally smoothed version of the structure tensor field $G$ s.t.:

$$G = G_s \ast (\nabla I)(\nabla I)^T$$

(3.2.4)

with

$$G = \lambda_1 \varsigma\varsigma^T + \lambda_2 \varrho\varrho^T + \lambda_3 \xi\xi^T$$

(3.2.5)

The weights $c_i$ are also functions of the eigenvalues $\lambda_i$ as follows:

$$s = \sqrt{\sum_{i=1}^{3} \lambda_i}$$

(3.2.6)

$$c_1 = \frac{1}{(1 + s^2)^{-1/2}}$$

(3.2.7)

$$c_2 = \frac{1}{(1 + s^2)^{-1}}$$

(3.2.8)

$$c_3 = \frac{1}{(1 + s^2)^{-4}}$$

(3.2.9)
In this setting, the weight of the principal direction, the direction with highest image gradient, is set to be a relatively low value to prevent filtering along edges. Please refer to [113] for a detailed explanation of the choice for these functions.

**Pros and cons in DWI interpolation:** The main advantage of PDE based filtering is its ability to minimize partial volume effects due to interpolation. Even though frequency response of these filters are not obvious due to their spatially varying nature, their scale space properties are well analyzed in the literature [82, 118, 119, 120]. PDE based interpolation schemes are considerably slower than any convolution based approaches and additionally they do not meet the ”interpolation function space” criteria [38, 99], i.e. intrinsically the local Gaussian kernels do not intersect the zero line at discrete voxel locations and hence the process is not reversible, i.e successive interpolation with an inverse process do not yield the original signal.
In order to perform a voxel-wise morphometry analysis using population or longitudinal datasets, all the images in the data have to be spatially aligned. Spatial normalization of groups of diffusion tensor images acquired from different subjects enables accurate mapping of characteristics of the diffusion tensor, such as diffusion anisotropy and orientation, within these images. It has important applications in assisting clinical studies into the variation of measurements derived from the diffusion tensor over normal and patient population groups [80].

Compared to registering scalar images, the registration of diffusion tensor images is particularly challenging not only due to the multi-dimensionality of the data, but also because one must ensure that the tensor orientations remain consistent with the anatomy after image transformations [2]. Earlier diffusion tensor image registration techniques circumvent tensor reorientation by registering tensor–derived scalar images [59, 56], thus discarding the orientation component of the data. Some other methods register actual tensor images but not reorienting the tensors during registration [1, 100], thus introducing inaccuracies in image matching. Later Park et al. [79] showed that using diffusion tensors as a whole
improved the quality of registration by better matching the diffusion tensors orientation information; but their method only applied tensor reorientation iteratively and tensor reorientation was not explicitly optimized. Curran et al. [24] then demonstrated that explicitly optimizing tensor reorientation during affine registration of synthetic images improved image matching. Zhang et al. proposed a locally affine registration algorithm that both explicitly optimizes tensor reorientation and has a novel derivative-based formulation in [125]. Most recently, Cao et al. [18] developed a large deformation diffeomorphic registration algorithm for vector fields. The algorithm was applied to register diffusion tensor images by matching their corresponding principal eigenvectors.

In this chapter, the concept of image registration is first presented in Section 4.1. The reasons why DTI based registration outperforms scalar based registration is described in 4.2 and the challenges involved in DTI registration are presented in Section 4.3.

4.1 Scalar Image Registration

Image registration is the process of spatially aligning the moving image $I_m$ to the fixed image $I_f$ with the goal of having voxel-wise correspondence (Figure 4.1). The first row of this figure displays two anatomical images with different modalities and their overlay on the same image. Due to different image coordinate spaces, the images are initially not aligned. The second row depicts an illustration of the iterations of a registration process, where the images are gradually aligned better after each iteration.

Registration is an optimization process, where the optimization variables are the parameters $\Theta$ of the spatial transformation $T_\Theta$ [73]. The generic registration optimization formulation
can be written as:

$$\varepsilon = \arg_{\Theta} \min f(I_f, I_m(T_{\Theta}))$$

(4.1.1)

where $\varepsilon$ is the registration error, $f$ is the image similarity function and $I_m(T_{\Theta})$ is the moving image transformed with $T_{\Theta}$ and generated using an interpolation routine.

• The image similarity metric $f$ should be chosen based on the modalities of $I_f$ and $I_m$. Numerous similarity metrics have been proposed including but not limited to the Mean Squares Error metric (MSE), Normalized Cross Correlation (NCC) and Mutual Information (MI).

• The transformations $T_{\Theta}$ should be chosen based on the deformation in consideration. Rigid transformations (6 parameters) are suitable for aligning data form the same subject, affine transformations (7-12 parameters) can represent scaling and shearing

\[64\]
in addition to rotation and translation described by rigid transformations and elastic (or deformable or non-linear) transformations can cope with alignments from different subjects and can include a couple of thousands of parameters.

- The interpolation employed to resample the moving image based on the transformation $T_\Theta$ can play a crucial role in the outcome. Interpolation techniques can depend on the chosen transformation and can be as simple as linear interpolation or be as complex as $n^{th}$ order polynomial interpolation.

4.2 Why Register Diffusion Tensor Images?

The primary motivation for registering diffusion tensor images is the belief that this approach can enable better alignment of white matter (WM) structures than what is possible with the registration of standard anatomical images. It can be argued that this is the result of the additional features of WM that are uniquely captured in diffusion tensor images but absent in standard anatomical images. While there is sufficient contrast for separating the three brain tissue types from one another in $T1w$ images, the WM appears entirely homogeneous. As a consequence, the only features available to a registration algorithm for aligning WM structures are the interfaces between the WM and the two other tissue types, the gray matter (GM) and cerebro-spinal fluid (CSF). The resulting WM alignment can be unsatisfactory for two reasons.

Firstly, since the interfaces between adjacent WM structures are invisible in this modality, their alignment can not be driven by image features and therefore can not be guaranteed. Secondly, since the basic feature of WM structures, their fibrous organization at the cellular
level, are also absent from the images, the alignment based on boundary matching can not guarantee that the interior of the WM structures are aligned appropriately with respect to their internal organization. In contrast, diffusion tensor images can not only distinguish the WM from the GM and the CSF but also enable the differentiation of different WM structures based on their differences in FA and, more importantly, orientations. It can be observed that leveraging these additional features can help remedy the issues challenging the WM alignment using anatomical images. Firstly, although not all, many adjacent WM tracts can be distinguished from one another based on their individual characteristic FA values or orientations. Secondly, the fibrous internal organization of the WM is captured in terms of the fiber orientation at each voxel. Hence, by matching diffusion tensor images directly, registration routines can now have access to such features and exploit them to improve the alignment of adjacent WM tracts. In doing so, such methods have the potential to align WM in a manner that is consistent with its internal organization. In summary, the development of diffusion tensor image registration algorithms can potentially provide the community superior alternatives that will produce more accurate mapping of WM tracts across subject populations which in turn will make it possible to generate more reliable comparison of WM tissue properties.

### 4.3 Challenges in Diffusion Tensor Image Registration

Registration of diffusion tensor images presents several unique challenges. In this section, these challenges will be discussed along with the ones that are common to all registration problems.
Similar to any other registration task, diffusion tensor image registration can be formulated as an optimization problem. Just as other registration task, to implement this optimization routine, the following elements are required:

i A method to compute the warped image $I_m(T_\Theta)$ from $I_m$ and $T_\Theta$;

ii An appropriate tensor similarity criteria such that $f(I_f, I_m(T_\Theta))$ can be computed;

iii A suitable transformation $T_\Theta$.

iv A tensor interpolation routine.

v A numerical optimization algorithm.

4.3.1 Image Warping

For scalar-valued images, an image transformation $\Theta$ merely changes the location of each point $x$, i.e., mapping $x$ to $T_\Theta(x)$. The image value at the warped location should be identical to the one at the original location. Therefore, if $I$ and $I'$ denote the original and the warped images, then

$$I'(T_\Theta(x)) = I(x) \quad (4.3.1)$$

This process, however, is more complex for diffusion tensor images as depicted in Figure 4.2.

Figure 4.2(a) shows schematically the axial slice view of an anisotropic region in a diffusion tensor image. Figure 4.2(b) shows the same slice after a 30° rotation about z-axis.
Figure 4.2: Diffusion tensor reorientation. Panel (a) shows schematically an axial slice in an anisotropic region of a diffusion tensor image. Panel (b) shows the same slice after a 30° rotation about the z-axis with no reorientation of the diffusion tensors. Panel (c) shows the slice after the same rotation, but with each tensor transformed by the same rotation.

(perpendicular to the axial slice) and the tensor values at the warped locations are prescribed according to Equation 4.3.1, i.e., they are simply copied from the corresponding locations in the original image. It is evident that the internal organization of the region is entirely disrupted, making this approach undesirable. Figure 4.2(c) shows the same slice again after a 30° rotation about z-axis but after copying the tensor-values from the corresponding locations in the original image, a 30° rotation to the tensors themselves was applied. Hence, transformations of diffusion tensor images also requires changing the orientation of diffusion tensors accordingly [2] and the relation between the template $I_t$ and the warped template $I'_t$ should instead be formulated as:

$$I'_t(T_\Theta(x)) = R_{T_\Theta(x)}[I(x)] \quad (4.3.2)$$

where $R_{T_\Theta(x)}$ denotes some operator that accounts for the changes in orientation of diffusion tensors induced by the transformation $T_\Theta$ at spatial location $x$. The reorientation operator $R_{T_\Theta(x)}$ needs to ensure that the orientation of diffusion tensors remains consistent
with the anatomy after an image transformation. The general scheme of this procedure, known as the tensor reorientation, was originally described in [2].

4.3.2 Similarity Criterion

Finding suitable similarity measures for diffusion tensors is another unique challenge for diffusion tensor image registration. A numerical estimate of the image similarity function $f$ is typically computed by comparing the data values at corresponding points in the two images $I_f$ and $I_m$. In the case of diffusion tensor images, a comparative measure of similarity between diffusion tensors is required. To fully exploit the information in diffusion tensor images, similarity measures that are sensitive to all aspects of the diffusion tensor including size, shape and, most importantly, orientation are needed. Illustration of this problem with the sum-of-squared distances (SSD) metric with three diffusion tensors is visualized in Figure 4.3. This example shows that unsuitable selection of a diffusion tensor similarity metric can yield incorrect results. The SSD metric between the first and second tensor, i.e. $||D_1 - D_2||$ yields exactly the same similarity metric of $||D_1 - D_3||$ even though tensorial shapes are very different.
The first two diffusion tensors have the exact same shape but different orientations. The last diffusion tensor is completely isotropic. If the Frobenius norm of tensor differences is used as a similarity metric in between diffusion tensors, the SSD between $D_1$ and $D_2$ becomes 1024 and the SSD between $D_1$ and $D_3$ becomes exactly 1024 as well. This shows that specialized similarity metrics are required for diffusion tensors.

**4.3.3 Tensor Interpolation**

As in the case of tensor similarity metric, scalar image interpolation techniques are not suitable for diffusion tensor images to generate the transformed moving image $I_m(T_\theta)$. Linear
interpolation on tensor components is known to increase the volume of the tensor ellip-
soids and linear extrapolation does not guarantee the positive definiteness of the diffusion
tensors. Arsigny et al. [7] proposed the Log-Euclidean metric for diffusion tensor inter-
polation, which operates on the Riemannian manifold of positive definite matrices and has
been shown to interpolate the shape and orientation properties of diffusion tensors better
than simple linear interpolation.
PART II

Requirements for Robust Variability Analysis
CHAPTER 5

ROBUST DTI ANALYSIS

In order to perform a thorough analysis using diffusion MRI data, all the sources of external uncertainty or variability have to be either eliminated or incorporated in the model. Additionally, all data have to be in the same coordinate framework, i.e. voxel-wise correspondence has to be established beforehand in order to attempt voxel-wise morphometry analysis.

In this part I will address several problems that I consider crucial for robust diffusion weighted image processing as well as alignment of tensors. These problems have mostly been unsolved or even disregarded in the medical imaging community but can have a considerable effect on the outcomes. My provided methodologies will primarily focus on providing robust solutions by considering the uncertainties and practicalities involved with the challenges.

- EPI distortions: Echo Planar distortions are known to cause distortions that affect tensor field quality. In this chapter, the effects of such distortions on scalar images and tractography images will be examined and analyzed.
• DWI interpolation: Interpolation of diffusion weighted images during correction steps is mainly a disregarded problem. However, it can introduce new artifacts to the data. I shall examine these artifacts and provide solutions to rectify them.

• DTI Registration: While performing an analysis using population or longitudinal data, misalignments among images can affect the outcomes of the analysis procedures. Tensor image registration methodologies are needed to robustly align images acquired with different protocols from different sites. In this chapter, novel tensor registration algorithms will be proposed that employ the uncertainty information inherent in tensor data due to image noise, experimental design and tissue characteristics to provide better alignment in reliable regions.

5.1 Datasets

In my experiments and analysis procedures to analyze the effects of external factors and to describe variability within human brain, several datasets were employed with different properties throughout this book. In this section, a brief overview of these datasets will be given.

5.1.1 Dataset 1: EPI Dataset

To analyze the effects of EPI distortions (primarily), five healthy volunteers aged 32 to 55 years, two males, three females, were scanned on a 3.0T GE Excite scanner using an eight channel coil (GE Medical Systems, Milwaukee, WI). All participants provided written informed consent before taking part in the study, which was approved by NIH. Whole
brain single-shot echo-planar (EPI) DWI datasets were acquired with a field of view (FOV) $\text{FOV} = 24 \times 24 \text{ cm}$, slice thickness= 2.5 mm, matrix size= 128 $\times$ 128, 66 axial slices, parallel imaging factor 2. No cardiac gating was performed. The DWI data set consisted of ten images with $b = 0 \text{ s/mm}^2$ and ten images with $b = 300 \text{ s/mm}^2$ and 60 images with $b = 1100 \text{ s/mm}^2$. For all subjects, two DTI scans were acquired with different phase encode direction Anterior-Posterior (AP) and Right-Left (RL) to analyze the effect of different distortions on the various fiber bundles. Structural T2 weighted anatomical images ($T_2W$) were also acquired with a fast spin echo sequence with the same FOV and matrix size=256 $\times$ 256.

Throughout this book, this dataset will be referred as ”dataset 1” or ”EPI dataset”.

5.1.2 Dataset 2: DTI Registration Dataset

To test the performances of the proposed DTI registration algorithms, a new dataset, that will be referred as ”dataset 2” or ”DTI registration dataset”, was collected. Data from six healthy subjects were acquired with an 8–channel head coil in a 1.5T MR system. Diffusion tensor imaging (DTI) was performed using a single shot EPI sequence ($b = 1000s/mm^2$, 72 diffusion gradient directions). Matrix sizes for all images were $128 \times 157$ with 114 axial slices and 1.5mm isotropic voxel resolution.

5.1.3 Dataset 3: Variability Dataset

To observe the variability within human brain, a larger number of individuals were required for analysis. For this reason, two additional datasets were collected. For the first dataset,
data from ten healthy subjects were acquired with an 8–channel head coil in a 3T MR system (Achieva, Philips Medical Systems). Diffusion tensor imaging (DTI) was performed using a single shot EPI sequence (SENSE factor = 3, b = 1000s/mm2, 6 diffusion gradient directions). Images were resampled to have size 153 × 153 × 80. One of the images was chosen to be the fixed image and the other nine were used as moving images. The diffusion tensors were extracted by imposing the constraint of positive-definiteness on the tensors. The methodology presented in Section 8.2 was used to register the diffusion tensor images.

### 5.1.4 Dataset 4: Gender Dataset

The second dataset acquired for variability analysis was employed to understand the differences between the male and the female brains. For this experiment, data from forty healthy subjects were acquired from twenty male and twenty female volunteers. Diffusion tensor imaging (DTI) was performed using a single shot EPI sequence using an e-DTI sequence with ten b=0s/mm², ten b=100s/mm², ten b=300s/mm², ten b=500s/mm², thirty b=800s/mm² and fifty b=1100s/mm² images. Images were resampled to have size 153 × 153 × 80. The diffusion tensors were extracted by imposing the constraint of positive-definiteness on the tensors. The registration of tensor images was performed with the tool provided in [125].
EPI distortions are the types of distortions that are generally disregarded in diffusion weighted image processing even though they can have a considerable effect on tensor-derived features such as scalar maps or tractography. The effects of these distortions have been previously analyzed by Wu et al. [122]. However, the effects of EPI distortions on the “correctness” and consistency of fiber tractography is a problem that has not thoroughly been investigated to my knowledge. In this chapter I address this problem and analyze how these distortions alter the connectivity maps obtained through tractography. The chapter is concluded by proposing a novel elastic image registration based EPI distortion correction scheme, which is more robust in local convergence than known methods due its lower requirements for transformation parameter space. Even with its lower dimensional parameter space, this approach can model very large deformations in magnitude that would normally require a very large parameter degrees of freedom.

Previous works on the relationship between DTI and EPI distortions focused either on showing improvements on global tract behavior obtained with $B_0$–mapping type corrections, such as the works of Lee et al.[69], Andersson et al. [3], and Pintjens et al. [87] or on improvements in tensor-derived scalar maps [122]. Another approach to the problem
involved using “distortion–free” pulse sequences as presented by Techavipoo et al. [109], Gui et al. [37] and the work from Embleton et al. [28]. In their work Lee et al. [69] employed a field-mapping based EPI distortion correction scheme to investigate for improvements in voxel-wise correspondences among FA images computed from DT-EPI of human and monkey brains acquired using a 3T scanner and their corresponding distortion free anatomical $T1_W$ images. They also showed improvements in continuity and symmetry of prefrontal tracts of one subject using streamline tractography. In a similar work Andersson et al. [3] used their previously published susceptibility distortion correction scheme [4] and showed that probabilistic tract accuracy was improved for the medio-dorsal thalamic nucleus. Embleton [28] investigated the effects of eddy currents and susceptibility induced distortions on tractography and functional MRI (fMRI) by employing a distortion correction scheme that is a variant of reversed direction k–space traversal method [16]. They showed improvements on both streamline and probabilistic tractography, as well as fMRI statistics. Pintjens [87] showed that susceptibility distortion correction with their proposed $B_0$ map acquisition improves streamline tractography on a synthetic fiber dataset. Techavipoo et al. [109] showed that with field inhomogeneity based EPI geometric distortion correction, tractography on optic nerves was feasible with healthy volunteers and multiple sclerosis patients. Gui et al. followed a different approach in their work [37] and proposed a ”distortion–free” pulse sequence, namely Turboprop, to show the improvements on streamline tractography of several anatomical fiber bundles.
6.1 Effects of EPI distortions on Tractography

In this chapter, I propose a simple framework to enable clinical investigators to assess the presence and severity of EPI distortions on their tractography and connectivity studies. I apply the framework to data acquired on a population of healthy subjects with typical acquisition parameters on a 3T clinical scanner (dataset 1). Finally, I show improvements produced by a freely available image–based distortion correction algorithm that does not require collection of additional data to operate.

6.1.1 General Analysis Framework

I follow a systematic analysis scheme to understand the extents of the effects EPI distortions on fiber tractography and deduce if EPI distortion correction has a crucial affect on the computed tracts. Acquisition of additional information for EPI distortion correction, such as the fieldmaps or dwell times, might not be plausible in every situation due to increased scan times or other technical difficulties, such as unknown dwell times, however, most diffusion scans are acquired along with an anatomical structural image. Therefore, a registration based EPI distortion correction scheme was employed due to its applicability to most scenarios.

The displacements due to EPI distortions take place along the phase encode direction. Therefore, the level of effect of the distortions on tracts might be significantly different depending on the direction of the distortions as well as the directions of the tracts in consideration. For this reason, instead of one fiber bundle from a single data, my analysis procedure tries to uncover the sensitivity and robustness of several specific fiber bundles
with distinct behaviors, to distortions in a population of subjects. The selected fiber bundles’ behaviors were observed under distortions in Anterior–Posterior (AP) or Right–Left (RL) directions, in an attempt to determine the “robust” tracts, tracts with anatomically plausible pathways, and “sensitive” tracts, as a function of the distortion direction. It can be hypothesized that if EPI distortions had minimal effects on tractography, regardless of the employed phase encode direction, AP or RL, fiber tracking images would be similar and EPI distortion correction would not have a great impact on the outcomes. If the distortion effects were non–negligible, these two versions of tractography would differ significantly even with a small population. Assuming that the distortion effects are important, after distortion correction:

- Dissimilarities in tracts in between DT-EPI data with different phase encoding should be reduced,

- Asymmetries between left and right homologous tracts in both AP and RL datasets should be reduced,

- Overall anatomical accuracy of connectivity maps should be improved.

To verify these hypotheses, all the acquired diffusion weighted images first underwent motion and eddy current distortion correction. Subsequently, for each AP and RL dataset, an additional EPI distortion correction step was either performed, producing the “corrected data”, or not, yielding the original distorted, or “uncorrected data” (Section 6.1.1.1). Diffusion tensors were computed from both dataset versions, which were then used to compute the transformations that mapped each data onto a common coordinate framework via tensor field registration (Section 6.1.1.4).
A total of five representative anatomical pathways (Section 6.1.1.2) were chosen from association, projection and commissural fibers and the same anatomical ROIs for these bundles were used as seed regions for probabilistic tractography (Section 6.1.1.3). The resulting tract images were subsequently transformed onto a common space using the tensor field deformations. For each tract of interest, an average tract image was derived over the population for both the corrected and uncorrected images with phase encoding in both AP and RL directions. These average tract images were visually and statistically analyzed to determine the robustness of each bundle under distortion and the improvements after EPI distortion correction (Section 6.1.2).

6.1.1.1 DTI processing

Processing of DWIs was performed with algorithms included in the TORTOISE software package [86]. Processing pipeline in Figure 2.10 was used. The diffusion weighted images for all subjects, for both the AP and RL datasets were corrected for motion and eddy-current distortions with the method proposed by Rohde et al. [97], which includes proper reorientation of the $B$–matrix to account for rotational differences among the diffusion weighted volumes, and intensity correction based on transformation Jacobians. The next step in the processing pipeline was the application of EPI distortion correction, which produced the “corrected” version of the data, in addition to the “uncorrected” version, which did not undergo this step. This correction was performed by elastically registering the first $b = 0$ $s/mm^2$ image in each DWI set to its corresponding undistorted $T2_W$ structural image, with a cubic B–Splines transformation of knot grid size $10 \times 10 \times 10$. The computed deformation field was applied to all DWIs belonging to that DWI dataset, yielding four datasets for each subject ($AP_{corr}$, $AP_{uncorr}$, $RL_{corr}$, $RL_{uncorr}$). All corrections were performed in the native
space of the DWI images. For consistency, all images were reoriented onto a common space defined by the mid-sagittal plane, the anterior commissure and the posterior commissure (ACPC) \[12\]. Tensor fitting on all data was performed using non–linear optimization \[62\]. Figure 6.1 displays the $T_2W$ and the fractional anisotropy (FA) images computed from the corrected and uncorrected versions of the AP and RL datasets of a single subject. The boundary of the T2W image is overlayed onto the FA images to emphasize the shape differences due to phase encode direction. For both uncorrected cases, the subject’s brain extends out of the contour region in the direction of phase encoding whereas this issue is minimized after elastic registration based correction \[122\].

6.1.1.2 Anatomical Pathways

Five anatomical pathways were chosen for analysis: corpus callosum (CC), cortical spinal tracts (CST), inferior cerebellar peduncles (ICP), superior cerebellar peduncles (SCP), and the cingulum bundle (CB). This set of representative pathways were selected due to:

• Their well–known anatomical trajectories to visually ensure anatomical correctness.

• Their proximity to region interfaces with large susceptibility differences to observe distortions effects.

• Their directional coverage, i.e. CST for projection fibers (mostly Inferior–Superior direction), CB for association fibers (mostly Anterior–Posterior direction), CC for commissural fibers (focusing on the body for Right–Left direction) and inferior and superior cerebellar peduncles, to analyze the effects of different distortion directions on different directional fibers.
**Figure 6.1: Outputs of registration for EPI distortion correction.** The image on the left is the T2W structural image used as a target with boundaries indicated with a contour. Images on the right are the FA maps computed from data with different phase encode and correction schemes, with the same contour overlayed.

For the CST and ICP pathways, a one voxel size ROI is placed deep in brain stem (MNI coordinate $\approx -40$ [19]) on both lateral hemispheres, exactly at the same anatomical location for each subject data. For the SCP bundle, three voxel size ROIs were placed on both hemispheres on an axial slice (MNI coordinate $\approx -22$). For CB, two large ROIs including the partially affected voxels were chosen, one on an axial slice and one on coronal. These ROIs for this set of bundles were used for seed regions for the probabilistic tractography scheme. An illustration of these ROIs is shown in Figure 6.2. For CC, small ROIs at the
edge of the genu and splenium were manually placed and then used in streamline tractography to observe the local tract stabilities, such as determining the likelihood of tracts getting “lost” or joining other tract bundles.

![ROIs](image)

**Figure 6.2:** ROIs illustrated for the pathways chosen for analysis. One voxel size ROIs for ICP and CST are displayed in (a). For SCP, three voxel size ROIs were chosen on both hemispheres (b). The size of the two ROIs for cingulum bundle o a single hemisphere varied based on the data and all voxels were included to account for partial volume interference.

### 6.1.1.3 Fiber Tractography

Four of the five selected pathways were used to analyze the global “connectivity” for which the tract images were obtained with probabilistic tractography. Probabilistic tractography as proposed by Behrens *et al.* ([13]) is a tool for quantitative analysis of DTI based “connectivity” for its ability to provide information on expected reproducibility within a scan, which can be combined within a population. For this reason, to investigate for the improvements of EPI distortion correction and the effects of phase encode direction on tract reproducibility, a probabilistic tractography framework was employed using the FSL software package ([104]). Ten thousand tracts were casted from each voxel in ICP, SCP, CST, CB ROIs (Section 6.1.1.2) with a curvature threshold of 0.2. This fiber tracking procedure
was performed in native space for each data and the left and right hemisphere connectivity images for the same anatomical structure were combined to yield a single image to be used for assessing symmetry improvements. Additionally, for each tract image, voxels with number of visitations less than 1% of maximum attained number were thresholded out to avoid noise tracts.

Probabilistic tractography produces 3D tract images with visitation counts as voxel values, and hence do not contain any local directional information unless further reprocessed. For this reason, streamline tractography was carried out using the Trackvis [117] software package using small ROIs on the brain stem and genu and splenium of CC pathway. This allowed the visual assessment of local directional consistency, such as the presence of off-tracts and lost–tracts near tissue interfaces.

6.1.1.4 Coordinate Transformations & Average Tract Images

The probabilistic tract images of each subject resided in their native space, thus were not directly comparable. For this reason, the diffusion tensor images for every subject, for each phase encode direction and correction scheme, were fed into a tensor field based elastic registration routine to compute a population average tensor image and the transformations that mapped each data onto this average brain space. This registration was performed using the DTI-TK software package [125]. The transformations were subsequently applied to the corresponding tract images in such a way that every single tract image resided in the same coordinate framework, that of the mean tensor image. Tract images of the same class (i.e. anatomical pathways, phase encode direction and application of distortion correction) for each subject were then combined to yield population averaged connectivity images.
6.1.2 Visual & Statistical Analysis

The effects of EPI distortions and their corrections on tractography were analyzed from several perspectives such as fidelity to the underlying anatomy, continuity, improvements in bilateral symmetry and stability/consistency.

6.1.2.1 Visual Analysis

Glyphs and streamline tracts from a single subject data were first visually inspected to verify the hypotheses stated in Section 6.1.1, i.e. local mismatch of tensor orientations and tensors’ voxel-wise relative locations; magnification of this behavior in streamline tractography due to accumulated errors in line integrals affecting continuity or at tissue peripheries, resulting in spurious or lost tracts.

Population average probabilistic tract images were first visually inspected as well to determine any global abnormalities, such as anatomically incorrect pathways and extreme bilateral asymmetries. Additionally, due to the fact that DTI can not cope with crossing fiber regions, such as cerebellum fiber decussation, the resulting spurious tracts were visually determined to be flagged for quantitative analysis. For visual assessment of the quality of probabilistic tractography, the tract images were rendered using volume rendering with composite shading with ray casting. For the sake of clarity on the underlying anatomy, the tracts were rendered on the average $T1_W$ image again visualized with volume rendering.

For the cingulum bundle, the number of voxels in ROIs vary from data to data because these ROIs cover the entire CB pathway region on their slice, including the partially contaminated voxels. Due to this difference in the size of the seed ROIs, the number of casted tracts and
thus intensity levels in the produced tract images differ among different data. However, theoretically, the size of the cingulum ROI should be the same for each image of the same subject and any differences can be attributed to the only acquisition difference, i.e. phase encode direction. This study also aims to uncover any tractography differences due to phase encoding effect, therefore tract images are rendered with the same colormap table, with the maximum visitation number for all four versions of data is mapped to “white”. This makes visual comparison of different tractography images possible.

### 6.1.2.2 Quantitative Analysis

Voxel values in probabilistic tract images indicate visitation counts, thus higher values on the entire image indicate a more stable or reproducible tract pathway. For quantitative examination, three different analysis were carried out using features derived from population average probabilistic tract images to quantitatively assess the stability of the tracts, bilateral asymmetry and their spatial variance.

- **Tract stability/reproducibility**: This analysis aimed to determine the presence of an increase in tract stability between corrected and uncorrected bundles by statistically comparing the visitation counts of the average tract images. A difference on the median of these visitation counts would indicate increased intra and inter-reproducibility of the tracts, i.e. the spatial variance of the tracts would be decreased among different experiments. For this analysis, tracts with complete disagreement with the anatomy were first visually identified and left out of the analysis. For semi-plausible tracts, region of tracts, which are known to disagree with the anatomy were also eliminated to yield only tracts “similar” to the underlying fiber bundles.
For ICP, SCP and CST pathways values in voxels of the entire tract images satisfying the conditions were statistically compared with a non-parametric test, Wilcoxon Rank-Sum test to check the equality of the medians of number of visitation distributions and to deduce consistency differences between AP and RL; and corrected and uncorrected data. This test was chosen because the underlying distributions do not follow a specific distribution. For the cingulum bundle, there is no anatomical evidence that the initial fibers connect one end of the structure to the other but instead, initial fibers might deviate from the main bundle along the superior direction towards the cortical region and might disappear where new fibers might join the main bundle. For this reason, for the CB pathway, the entire tract images were not used for statistical comparison but 3D tube-shaped ROIs were placed along the pathway, which fibers from the seed ROIs should anatomically be able to reach. Only the visitation values in these 3D ROIs were used for statistical analysis. For all these four pathways, similar to the work by Ciccarelli et al. [21], only the upper half of the visitation counts were used in the statistical tests.

• **Spatial Variance:** My first statistical analysis only considered the distributions of visitations but not their spatial properties. To analyze the spatial stability of tracts, I followed an approach derived from the work of Lazar et al. [68]. In essence, I took all voxels from a particular distance from the seed ROI, weighted each voxel’s spatial coordinate by the visitation number for that voxel, and computed a covariance matrix. The primary eigenvalue of the covariance matrix represents the variance along the main mode at that distance from the seed. This is repeated for all distances from the seed until there are no more voxels with visitations. The spatial variance is plotted against distance from the seed ROI in order to create a spatial variance signature.
for each tract, which can be compared before and after correction. These signatures can be interpreted to measure the tract similarities before and after correction; the presence of lost tracts in case of sudden jumps in the signature and the spatial spread of the tracts.

- **Bilateral Symmetry**: Differences are anatomically expected in the pathways of right and left hemisphere fibers but not at drastic levels. To quantitatively assess dramatic changes in bilateral symmetry, a heuristic symmetry measure based on probabilistic tract images was used. The symmetry plane of the average structural image was initially extracted manually. This symmetry plane can be used as the symmetry plane of tract images thanks to the registration process described in Section 6.1.1.3. Each tract image $I$ was flipped along the RL direction using this symmetry plane, to generate the flipped images, $I^F$. The symmetry measure is described as:

$$\text{sym} = \frac{\sum_{x \in \Omega} ||I_x - I^F_x||/2}{\sum_{x \in \Omega} I_x} \quad (6.1.1)$$

where $x$ signifies the voxel in question and $\Omega$ represents the image domain. This measure takes the value zero when there is no mirror–overlap in between bilateral tract bundles and takes the value 1 when the tracts in both hemispheres are completely identical with respect to mirroring around the symmetry plane. It should be noted that small variations in this metric might be caused by several reasons, including anatomy and might not be fully intuitive. However, dramatic changes indicate considerable improvements in bilateral symmetry, thus increase in fidelity to underlying anatomy.
6.1.3 Results

6.1.4 Streamline Tractography Visual Inspection

Figure 6.3 is an example that depicts the problems that arise due to EPI distortions. The glyphs displayed on this figure are computed from diffusion tensor data of a single subject, acquired with AP phase encode direction. The data on the left column (a) is the original, distorted version whereas the one on the right has gone through EPI distortion correction scheme before computation of tensors, as described in Section 6.1.1.1. From these two versions of the same data, it can be observed that the region of the brain stem between the medulla and the pons is deformed in the anterior-posterior direction. The orientation of this anatomical structure indicated with the colored rectangles is significantly different between the original distorted data and its distortion free counterpart. When the tensor orientations are examined, as displayed in the bottom, it can clearly be seen that the tensors in both cases are very similar and that the tensor directions in the distorted case do not follow the shape of the underlying structure.

This behavior is magnified in fiber tractography due to the accumulated effects along the tracts. Figure 6.4 displays streamline tractography results on the cingulum bundle from two ROIs again using the original distorted data and its EPI distortion corrected version acquired with RL phase encode direction. Due to the displacement of the anatomical location on the coronal ROIs, the two tract sets remain disconnected in the distorted data whereas continuity is achieved when EPI distortions are eliminated.

An observed behavior at the periphery of tissue structures is displayed in Figure 6.5. Every tract, the length of which is exceeding a certain threshold is displayed in both images. With
Figure 6.3: **Tensor Glyphs.** Tensor glyphs visualized as lines for clarity on the Fractional Anisotropy (FA) images computed from a) distorted, b) distortion corrected data of the same subject. Top row displays the shape of the underlying anatomy and the images on the second row zoom in to the indicated rectangles for glyphs clarity.

the one voxel size ROI at the edge of the genu of CC, streamline tractography outcomes are significantly different with this subject. Only one tract can traced using the distorted data, with the one voxel-wide sphere ROI at the edge of the genu of the *corpus callosum*. Additionally, this tract is anatomically erroneous and does not follow the expected pathway. Using the tensor field computed after correcting for the distortions on DWIs, denser, longer and anatomically more accurate tracts can be obtained with the same ROI.
Figure 6.4: **Cingulum Streamline tractography.** Streamline fiber tractography of cingulum bundle using the two ROIs displayed in (a). Tracts are visualized on Directionally Encoded Color (DEC) maps of an axial and coronal slice. Tracts from the two ROIs do not connect when the original distorted data is used for tractography (b). After distortion correction continuity is achieved with ROIs at exact same anatomical locations.

### 6.1.5 Population Average Tract Images

The population average tract images provide both quantitative and visual information on the effects of distortions. In this section, all the fiber bundles will be examined under different directions and with or without the EPI distortion corrections applied.

#### 6.1.5.1 Projection Fibers

Figure 6.6 displays the population averaged CST probabilistic tracts for both AP and RL data, corrected and uncorrected versions. The effect of phase encode direction is prominent when the uncorrected data is examined. In the presence of different directions of distortions, bilateral tracts of CST reached different regions of the brain. This set of tracts were particularly sensitive to distortions in RL direction, which caused the majority of CST become spurious and reach anatomically incorrect brain regions. This behavior was not
observed with AP distortion. This can be attributed to the fact that fibers on the inferior aspect of the pons have a large orientational variability along the RL direction and in the presence of distortions in this direction, they are more likely to go off-track. Additionally, right and left tracts in the population are affected differently from the RL distortion, which resulted in a complete loss of tract symmetry. The corrected RL data did not have most of these problems, indicating that EPI distortion correction reduced the off-track and spurious tracts. The average CST tracts in the corrected RL data reach the cortical regions of the brain, which shows the importance of correction for this case. Distortion correction also improves consistency: the uncorrected AP and RL data have significantly different trajectory signatures, whereas after correction, the shapes of these average tracts get more similar. Additionally, another improvement with the correction for the AP data is the increase in probability of reaching the cortical regions of the brain. This can be observed from higher number of visitations as indicated by the colormap legend, in the cortical regions in the corrected versions of the AP data compared to the lighter tones in the undistorted case.
Table 6.1 summarizes the $p$–values of NULL hypothesis tests for tract stability. The uncorrected data acquired with RL encoding, i.e. $RL_{uncorr}$, was left out of the analysis due to its disagreement with anatomy. The $p$–values show that $AP_{corr}$ has a significantly higher visitation median than $AP_{uncorr}$, stating that for CST, EPI distortion correction improves connectivity probabilities of the bundle. Additionally, the corrected version of the RL data had interestingly more visitation numbers than AP.
Figure 6.6: **Population average probabilistic CST tracts.** Population average CST tracts for RL and AP data for both corrected and uncorrected cases displayed in three main views. The Asymmetry of right and left tract of $AP_{uncorr}$ are improved after distortion correction in $AP_{corr}$. Both corrected versions have a higher probability of reaching the cortex. Colormap on the right indicates the number of visitations of tract voxels.
<table>
<thead>
<tr>
<th>$H_0$</th>
<th>$p$–value</th>
<th>$\mu$</th>
<th>$\mu$</th>
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<td>$RL_{corr}$</td>
<td>3522</td>
</tr>
</tbody>
</table>

Table 6.1:  Statistics on equality of the mean of CST visitation distributions.

The spatial variance signature is displayed in Figure 6.7, where the top plot illustrates the signatures of tracts obtained from data with RL phase encode direction and the bottom plot for AP distortion.

As implied visually by Figure 6.5, the distorted and corrected tracts with AP direction have very similar spatial variability. Some amount of tracts are lost in $AP_{uncorr}$ bundle 15 voxels away, where this behavior is delayed to 17 voxels in corrected version. However, the effect of correction on the signatures of the RL encoded data is significant. The $AP_{uncorr}$ data looses a significant amount of (spurious) tracts from 15 to 20 units away from the seed ROI, where this is not observed in the corrected version. Additionally, the monotonically increasing behavior of the spatial variance of the uncorrected data means a very high spatial spread of tracts at large distances, indicating instability of the tracts. Another point to note is that EPI correction increased consistency of AP and RL data tracts, which can be observed from the increased similarity of the corrected tracts compared to the original distorted versions.
6.1.5.2 Association Fibers

When cingulum bundle tractography images are examined, the most striking observation is the increase in continuity with RL data after distortion correction, which can be clearly observed from the axial slices (Figure 6.8). This also resulted in the lowest bilateral symmetry (Section 6.1.5.4). An increase in connectivity probability can also be observed in AP data on both axial and sagittal slices. Additionally, the maximum number of visitations...
in a voxel took place for $RL_{corr}$ data with $1.3 \times 10^5$ and the other tract colors are scaled w.r.t. this maximum value. The maximum visitation for $AP_{uncorr}$, $RL_{uncorr}$, $AP_{corr}$ are 25%, 45%, and 9% less than $RL_{corr}$’s, which is apparent from the shades of reds for in tract overlays.
Figure 6.8: Population average probabilistic cingulum bundle tracts. Population average CB tract for RL and AP data for both corrected and uncorrected cases displayed in three main views.
The region where cingulum bundle turns around the genu of the *corpus callosum* is expected to be greatly affected by distortions. Even when ROIs in close proximity to this region (Figure 6.2) were used for tract seeding, improvements were observed in connectivity and curvature of this turn. This effect is clearly visible on the sagittal slices of AP data where the corrected version stays more on-track and results in higher connection probabilities to the lower regions. This behavior is present but is minimal in the RL data. However, when ROIs with larger separation are used for tracking, a drastic drop in connectivity occurs as indicated by the streamline tractography images of Figure 6.4. Another interesting observation about cingulum bundle is that with the data acquired with AP direction, the tracts on the left brain hemisphere (radiological convention) were more robust and provided better connectivity than right brain tracts whereas the opposite behavior was observed with RL data where the right tracts were more stable.

<table>
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**Table 6.2:** Statistics on equality of the median of cingulum visitation distributions.

Statistically, every single test that was run on the cingulum bundle turned out to be significantly different (Table 6.6). This also suggests that CB is very sensitive to both distortion direction, and distortion correction schemes.

In terms of spatial variances, the signatures for both $RL$ and $AP$ are similar, with slightly less variance in $RL$ distortion (Figure 6.9). Additionally, the distortion correction improved
the spatial variance for \textit{RL} distorted data whereas it did not contribute much in the case of \textit{AP}.

6.1.5.3 Cerebellar Fibers

Figure 6.10 displays the population averaged inferior cerebellar peduncles probabilistic tracts for all data versions. Due to the proximity of the ICP ROIs to other anatomical structures such as sensory or motor fibers, the challenge while tracing these bundle is avoidance of spurious tracts. Among four versions of the data, only \textit{RL}_{uncorr} tracts got erroneously mixed up with sensory tracts and reached superior cortical regions. Distortion correction
solved this problem and $RL_{corr}$ only generated plausible tracts. Additionally, tracts in the left hemispheres for $RL_{uncorr}$ data correctly reached cerebellum but the bundle in the right hemisphere turned towards the anterior direction. This also drastically altered bilateral symmetry (Table 6.5) even when the erroneous tracts reaching the cortex are excluded. This behavior is visible in the axial and coronal slices of Figure 6.10 when regions inferior to cerebellum are examined. From a consistency standpoint, when the shapes of the anatomically feasible parts of ICP tracts are examined in all data, it can be observed that the curvature of the $AP_{uncorr}$ tracts while turning towards cerebellum is relatively larger than the curvatures in the other three data versions for the same location, i.e. $RL_{uncorr}$ tracts bends sharper into cerebellum. With the distortion correction, the curvature of this tract bending is similar to both versions of the data acquired with AP phase encoding. Anatomically, it might be very hard to assess the correctness of these two types of curvatures, however increase in similarity of the corrected tract images w.r.t. the uncorrected ones indicates an improvement on conformance of the tracts to the anatomy.

Table 6.3 summarizes the $p$–values for ICP statistics. Even though there are anatomical inaccuracies in some of the generated tracts, the observations assert that connection–wise, all the four version of data have statistically indifferent visitations medians.

<table>
<thead>
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<th>$H_0$</th>
<th>$p$–value</th>
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Table 6.3: Statistics on equality of the median of ICP visitation distributions.
Figure 6.10: Population average probabilistic ICP tracts. Population average ICP tract for RL and AP data for both corrected and uncorrected cases displayed in three main views.
Figure 6.11: **ICP tract signatures.** Right hemisphere ICP bundle tract signatures displaying the spatial variance of the tract voxels as a function of distance from the seed ROI. The top plot displays the signatures of the corrected and uncorrected data acquired with RL phase encode direction whereas the bottom plot is for AP direction.

The spatial variance signature for ICP in Figure 6.11 indicates that the spatial behavior of ICP before and after correction is very similar with AP distortion direction. However, for RL direction, the spurious tracts in the uncorrected data version increases the spatial variance significantly compared to the corrected version. After the anatomically correct part of the uncorrected bundle terminates around 18 distance units away from the seed ROI, the variance of the uncorrected data decreases but it is zero for the corrected version because of the lack of tracts.
Figure 6.12 displays the tractography outputs for the superior cerebellar peduncles. SCP anatomically connects the cerebellum to the decussation in the midbrain, where right and left tracts cross towards the lateral hemisphere. However, the tensor model in DTI is not able to capture this behavior and tractography results in “kissing” fibers instead of “crossing” fibers. For this reason, I only focus on anatomically plausible pathways up to the decussation in midbrain and consider more superior tracts as DTI artifacts and disregard them.

SCP turned out to be a tract bundle robust to distortions and their directions. The plausible part of the anatomy is captured in all four data and abnormal lateral asymmetries between the hemispheres do not exist in any versions.

Table 6.4 summarizes the p–values for SCP statistics. An interesting observation from SCP is that the median of the distributions of the original data $AP_{uncorr}$ and $RL_{uncorr}$ are statistically significantly different but after distortion correction, differences vanish.

<table>
<thead>
<tr>
<th>$H_0$</th>
<th>p–value</th>
<th>$\mu$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_{AP_{corr}} = \mu_{AP_{uncorr}}$</td>
<td>0.168</td>
<td>$AP_{uncorr}$</td>
</tr>
<tr>
<td>$\mu_{RL_{corr}} = \mu_{RL_{uncorr}}$</td>
<td>0.127</td>
<td>$RL_{uncorr}$</td>
</tr>
<tr>
<td>$\mu_{AP_{corr}} = \mu_{RL_{corr}}$</td>
<td>0.129</td>
<td>$AP_{corr}$</td>
</tr>
<tr>
<td>$\mu_{AP_{uncorr}} = \mu_{RL_{uncorr}}$</td>
<td>$5.8 \times 10^{-4}$</td>
<td>$RL_{corr}$</td>
</tr>
</tbody>
</table>

Table 6.4: Statistics on equality of the median of SCP visitation distributions.
Figure 6.12: Population average probabilistic SCP tracts. Population average SCP tract for RL and AP data for both corrected and uncorrected cases displayed in three main views.
For the spatial variance signature of SCP (Figure 6.13), only the regions of SCP before the decussation should be considered, at around 18 distance units from the ROI. For both the *AP* and *RL* distortion, with or without correction, the tract signatures before this threshold are very similar, indicating that SCP is a robust tract bundle under both types of distortions. However, after the decussation, the behavior is completely erratic, which is expected in single tensor model based DTI.

**Figure 6.13:** SCP tract signatures. SCP bundle tract signatures displaying the spatial variance of the tract voxels as a function of distance from the seed ROI. The top plot displays the signatures of the corrected and uncorrected data acquired with RL phase encode direction whereas the bottom plot is for AP direction.
6.1.5.4 Symmetry Results

Table 6.5 displays the values of symmetry metrics for each fiber bundle and each data version. It should be noted that small variations in this metric might be caused by several reasons, including anatomy and might not be fully intuitive. However, dramatic changes indicate considerable improvements in bilateral symmetry, thus increase in fidelity to underlying anatomy. An interesting observation that can be made from the metrics is that all of the three drastic increases in symmetry (CST, ICP, CB) took place when using data acquired with RL phase encode direction. This is an intuitive finding because distortions in AP direction affect all bilateral tracts in a similar way and therefore under such distortions, anatomical symmetry is preserved. However, with RL distortions, structures in one hemisphere are pushed towards the medial plane whereas the structures in the lateral hemisphere are pushed away. Therefore, tracts in different hemispheres get affected differently by these distortions and become artifactual resulting in a complete loss of bilateral symmetry. For all three tract bundles, the distortion correction scheme was able to improve bilateral symmetry both visually and in terms of the metric, to the levels obtained with AP acquisition.

<table>
<thead>
<tr>
<th></th>
<th>(AP_{uncorr})</th>
<th>(AP_{corr})</th>
<th>(RL_{uncorr})</th>
<th>(RL_{corr})</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST</td>
<td>0.352</td>
<td>0.441</td>
<td>0.244</td>
<td>0.475</td>
</tr>
<tr>
<td>ICP</td>
<td>0.586</td>
<td>0.511</td>
<td>0.181</td>
<td>0.554</td>
</tr>
<tr>
<td>SCP</td>
<td>0.550</td>
<td>0.559</td>
<td>0.586</td>
<td>0.544</td>
</tr>
<tr>
<td>CB</td>
<td>0.541</td>
<td>0.508</td>
<td>0.292</td>
<td>0.504</td>
</tr>
</tbody>
</table>

Table 6.5: Symmetry measures for bilateral tracts. Zero (0) means no symmetry whereas one (1) indicates complete bilateral symmetry.
6.1.6 Discussion

In this chapter, the effects of echo planar imaging distortions caused by magnetic susceptibility differences and concomitant fields on diffusion tensor imaging based fiber tractography were examined. These distortions manifest themselves as displacements along the phase encode directions therefore data acquired with different phase encoding were hypothesized to produce significantly different tract pathways. In such a case, the application of even a simple distortion correction methodology would render such tracts more similar, increasing tract consistency and thus reducing artifactual tract bundles originating from distortion effects. This EPI distortion correction step is most generally not performed in DTI processing pipelines unlike eddy–currents induced distortions and their effects are considered inherent properties of data. The goal of this section was to assess the effects of the presence and directionalities of these distortions by closely examining the behaviors of five tract bundles, which were selected due to their well–known anatomical pathways, their directional spread and vulnerability to displacements.

The primary finding of this study was that the effects of EPI distortions on the examined tracts were quite significant and that correction methodologies should be included in diffusion imaging processing pipelines, especially for “tractography accuracy” sensitive clinical applications such as neuro–surgical planning. The effects of such distortions will become more profound when high and ultra–high magnetic field strength acquisitions become more common. Additionally, other diffusion imaging based protocols such as high angular resolution diffusion imaging or diffusion spectrum imaging are at least as prone to these distortions as DTI.
One observation that can be made from this analysis is that all selected fibers, except superior cerebellar peduncles were very sensitive to distortions in Right–Left directions. Using Anterior–Posterior direction for phase encoding reduces bilateral asymmetry but suffers from other systematic problems, such as decreased stability and reproducibility. Additionally, among the examined pathways, projection fibers and association fibers suffered the most from these distortions, independent of distortion directionality. Inferior cerebellar peduncles are observed to be very likely to get mixed with other brain stem structures such as cortical spinal tracts in the presence of strong distortions and for all these structures a form of EPI distortion correction is strongly advised.

Another very interesting point about inter-session or population reproducibility of the tracts and bias. In their work, Techavipoo et al. \cite{109} stated that the variance of the tracts is lower with spin–echo EPI (SE-EPI) for inter–session studies, in other words tractography experiments were more reproducible with SE-EPI. However, the anatomical correctness of the tracts obtained with propeller sequence in inter–session studies was superior to SE-EPI. With intra-session studies, both the variance and anatomical conformance was better with propeller. In this study, I observed a similar behavior. The cortical spinal tracts for example were very consistent and reproducible among most of the population with distorted data but the generated anatomical pathways were inconsistent with the underlying anatomy, especially with RL distortion in all subjects. This low variability and high reproducibility among subjects can be very dangerous in statistical analysis, which are designed to deal with variance but not bias. The systematical bias introduced by distortions are reduced by correction schemes to a degree, which I think is mandatory for any type of statistical analysis on tractography.
6.2 A Novel Robust EPI distortions Correction Framework

Fieldmapping based methods, or in other words, $B_0$ inhomogeneity map estimation based methods [52] suffer from the difficulty of calculating the phase maps near edges, in spite of their physical intuitiveness. They also require additional scans and precise measurements, such as dwell time. Additionally Wu et al. and Tao et al. [107, 122] respectively showed that elastic registration based correction schemes usually outperform fieldmapping approaches. However, elastic registration based approaches usually suffer from the "curse of dimensionality" due to their large parametric space and result in distortion of salient anatomical locations. If the parametric space is reduced to deal with this problem, large distortions at high and ultra–high fields can not be corrected.

In this section, I propose a novel fast and robust algorithm for EPI distortion correction, which combines the strengths of fieldmap approaches and elastic registration. A non-uniform B-Splines control grid is constructed, where the image is densely sampled with grid knots at locations with large expected distortions and sparsely sampled at locations where the distortions are homogenous. The expected distortions are obtained by synthesizing an artificial fieldmap based on tissue segmentation maps and tissue susceptibility models. My methods are physically–based due to their relationship to fieldmaps; however, they overcome the shortcomings of fieldmap based techniques given the increased adaptivity. Section 6.2.1 describes the main steps of the proposed pipeline, where the fieldmap estimation process is briefly reviewed in Section 6.2.1.1 and B–Splines knot sampling is described in Section 6.2.1.2. The experimental setup and validation procedures are described in Section 6.2.1.3. The results are presented in Section 6.2.2.
6.2.1 Methodology

The proposed EPI distortion correction framework is demonstrated in Figure 6.14. After motion and distortion correction of the DWI data \([97]\), the distortion-free structural \((T_2)\) image is rigidly registered to the specific \(b = 0\) \(s/mm^2\) image. It is then segmented into four classes, white matter, gray matter, cerebro–spinal fluid (CSF) and air in the \(b = 0\) \(s/mm^2\) image’s native space. The tissue label image is subsequently fed into a fieldmap estimation routine first proposed in \([49]\), later employed in \([89]\). The estimated fieldmaps are transformed into deformation fields and these deformation fields are used to determine the non-uniform sampling regimen of B–Splines knot points. The resulting transformation is used during elastic registration and the final deformation field is applied to each diffusion weighted volume.

![Figure 6.14: The flow of the proposed EPI distortion correction framework.](image)
6.2.1.1 Fieldmap Estimation

The fieldmap estimation process is based on the work of Jenkinson et al. [49], which models the first order perturbations in the main magnetic field \( B_{z}^{(0)} \). The notations and equations are borrowed from this work.

Let the susceptibility, \( \chi \), be expanded as: \( \chi = \chi_0 + \delta \chi_1 \), where \( \chi_0 \) is the susceptibility of air \( (4 \times 10^{-7}) \), \( \delta \) is the susceptibility difference between tissue and air \( (-9.5 \times 10^{-6}) \) and \( \chi_1 \) is a binary variable describing the tissue type. Then the first order perturbations in the magnetic field \( B_{z}^{(1)} \) can be written in terms of the main magnetic field \( B_{z}^{(0)} \) as (assuming \( z \) is the primary direction):

\[
B_{z}^{(1)} = \frac{\chi_1}{3 + \chi_0} B_{z}^{(0)} - \frac{1}{1 + \chi_0} \left( \frac{\partial^2 G}{\partial z^2} * (\chi_1 B_{z}^{(0)}) \right)
\]

(6.2.1)

where \( G \) is the Green’s function with \( G(x) = (4\pi r)^{-1} \) with \( r = \sqrt{x^2 + y^2 + z^2} \). The solution to the convolution operation for a single voxel of resolution \( (a, b, c) \):

\[
H(x) = \left( \frac{\partial^2 G}{\partial z^2} \right) * (\chi_1 B_{z}^{(0)}) = \sum_{i,j,k \in \{-1,1\}} (ijk) F(x + ia/2, y + jb/2, z + kc/2)
\]

(6.2.2)

where \( F(x) = \frac{1}{4\pi} \text{atan}(\frac{x}{2r}) \).

For a set of voxels, due to the linearity of convolution operation, the perturbation field becomes: \( B_{z}^{(1)}(x) = \sum_{x'} \chi_1(x') H(x - x') \)

Assuming the phase encoding direction along the \( y \) axis, the deformation due to this fieldmap can be obtained with:

\[
\Delta y = \frac{\gamma B_{z}^{(1)}(x) N_y t_{dwell}}{2\pi}
\]

(6.2.3)

where \( \gamma \) is the gyromagnetic ratio, \( \Delta y \) is the pixel shift, \( N_y \) is the number of voxels along the phase encoding direction and \( t_{dwell} \) is the dwell time. As pointed out in [49], this model
does not account for the shimming process applied around the edges and might not be adequate for direct use in EPI distortion correction with the above equation. It also directly depends on the quality of the initial segmentation $\chi_1$. However, it can serve as a good initial estimate for the displacements field due to EPI distortions. Figure 6.15 (a) displays a slice from a structural image and (b) the estimated fieldmap.

![Structural image](image1)
![Unmasked fieldmap](image2)
![Knot point distribution](image3)

Figure 6.15: Examples slices for fieldmap estimation from a structural image and the sampling of a B–Splines grid points.

6.2.1.2 Adaptive B–Splines Sampling using Fieldmaps

The power of the proposed approach is its ability to model and improve the complex deformations estimated with fieldmaps in a robust manner through a sophisticated physically-based transformation model. This is achieved by nonuniform sampling of B–Splines grid locations as a function of the estimated displacements. The sampling of the knot points is performed algorithmically in a multi–resolution fashion as follows: let $\mathcal{D}_f$ be the deformation field estimated using the fieldmaps.
i Place a B–Splines grid of $m \times m \times m$ onto $\mathcal{D}_f$. This partitions the image onto $(m-1)^3$ cubes. Typically, $m = 7$.

ii Generate $\mathcal{D}_e$ by only using values of $\mathcal{D}_f$ on grid locations and interpolating the other voxel displacements using cubic B–Splines kernels.

iii For each cube $\Omega$:

- Temporarily place a control point $p$ at the center of $\Omega$.
- Recompute $\mathcal{D}_e(\Omega)$ for the given cube within the cube $\Omega$.
- If $||\mathcal{D}_f(\Omega) - \mathcal{D}_e(\Omega)|| > \varepsilon$ (a user–defined threshold),
  - Set $p$ as a new control point.
  - Replace $\Omega$ with eight new cubes within itself.
  - Activate the new cubes.
- Else deactivate $\Omega$.

iv Repeat until no active cubes are present.

This strategy generates a multi-resolution pyramid of B–Splines grids, with the initial level containing fully active $7 \times 7 \times 7$ control points (if $m = 7$), the second level containing partially active $15 \times 15 \times 15$ control points, and so on. Figure 6.15 (c) displays the knot sampling obtained with this procedure with the displacements computed from the fieldmap in (b). Non–brain tissue is masked out in this image for visual illustration purposes.
6.2.1.3 Elastic Registration & Experimental Setup

During elastic registration, the deformation field obtained in the previous level of the pyramid is used to initialize the coefficients of the B–Splines at the current level. The optimizer used in the registration is a variant of limited memory Broyden-Fletcher-Goldfarb-Shanno (BFGS) method [33], which allows the user to set lower and upper bounds for the coefficients. At current level of the pyramid, the active grid points are allowed to move freely, whereas the inactive nodes were constrained to move only within 10% of the value obtained from the previous level. Additionally, control points were only allowed to move along the phase encoding direction. Up to four levels of the B–Splines coefficient pyramid was employed for registration in practice.

The ”EPI dataset” (Section 5.1.1) was again used for testing. Tissue segmentation for the structural images was realized by using the segmentation tools of FSL package [104]. Motion and eddy current distortion of the diffusion weighted images and tensor fitting was performed using the TORTOISE package [86]. Elastic registration was implemented using the ITK library.

6.2.1.4 Validation

For comparison purposes, another elastic registration algorithm with B–Splines transformation of uniform grid sampling (e.g., $10 \times 10 \times 10$) was implemented as reference. The performance of such a registration scheme has been previously shown to outperform that of a fieldmap based approach in most cases [122].
The validation of the proposed correction framework was two-folds: First, the overlap of the structural image, the distorted image, image corrected with the reference algorithm and the image corrected with the proposed algorithm were visually assessed. Second, to quantify the overall improvements in diffusion tensor image quality, probabilistic tractography was carried out on cingulum bundle. The tensor images for every subject, for each phase encode direction and correction scheme, were then fed into a tensor field-based elastic registration routine to compute a population average tensor image and the transformations that mapped each data onto this average brain space. The transformations were subsequently applied to the corresponding tract images in such a way that every single tract image resided in the same coordinate framework. These population connectivity images were first visually analyzed. For these tract images, voxel values were subsequently statistically compared with Wilcoxon Rank test to check for the equality of the medians of number of visitations and to deduce consistency differences between AP and RL; and reference v.s proposed method.

6.2.2 Results

Figure 6.16 displays the results for the scalar images. The first column of the figure depicts the original undistorted $T2_w$ structural image, the second column displays slices from the distorted $b = 0 \text{ s/mm}^2$ image, third column shows the output of the proposed correction scheme and the last column is for the reference algorithm. The distortion is along the RL direction. In the lower brain, where the distortion is significant, the proposed algorithm performs significantly better than the reference method in the right temporal lobe and left limbic lobe. Both approaches can correct for global displacements but the proposed approach
can cope with large local displacements due to its transformation model. For mid-level slices (bottom row), both approaches perform well, with the proposed method showing a slightly better performance around middle frontal gyrus (top left portion of images).

### 6.2.2.1 Tractography Results

The average population tracts for the cingulum bundle over 5 subjects, for data acquired with RL and AP distortion are displayed in Figure 6.17. In this figure, brightness of tracts indicate the probability of reaching the voxel from the seed ROI. Following conclusions can be drawn from this figure:
• Both correction schemes improve the continuity of the tracts indicated by brighter shades along the tracts. Therefore, one can conclude that EPI distortion correction is an often neglected but crucial step in DTI processing.

• Continuities are also improved with the proposed method compared to the reference.

• The proposed method also increases the consistency between data acquired with different distortion directions as the similarity of tracts increases with the reference method compared to the distorted data and with the proposed method compared to the reference approach.

<table>
<thead>
<tr>
<th></th>
<th>AP</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dist.</td>
<td></td>
<td><img src="image" alt="AP Distortion" /></td>
<td><img src="image" alt="RL Distortion" /></td>
</tr>
<tr>
<td>Ref.</td>
<td><img src="image" alt="AP Reference" /></td>
<td><img src="image" alt="RL Reference" /></td>
<td></td>
</tr>
<tr>
<td>Prop.</td>
<td><img src="image" alt="AP Proposed" /></td>
<td><img src="image" alt="RL Proposed" /></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 6.17:** Tractography results with the new EPI distortion correction scheme. Population tract averages. Left column displays the results for data acquired with AP distortion and the right column RL distortion. Top column tracts are computed with distorted data, middle column with the reference correction and the bottom row with the proposed correction.
Table 6.6 displays the results of the statistical tests. These statistics indicate that the proposed correction algorithm results in improved continuity along the tracts. Even though tracts obtained from RL distorted data and AP distorted data are still not statistically significantly similar, a considerable improvement can be observed in their consistency behavior.

<table>
<thead>
<tr>
<th>$H_0$</th>
<th>$p$–value</th>
<th>$\mu$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_{RL\text{ref}} = \mu_{AP\text{ref}}$</td>
<td>$1.19 \times 10^{-8}$</td>
<td>$AP_{\text{ref}}$</td>
</tr>
<tr>
<td>$\mu_{RL\text{prop}} = \mu_{AP\text{prop}}$</td>
<td>$8.37 \times 10^{-3}$</td>
<td>$RL_{\text{ref}}$</td>
</tr>
<tr>
<td>$\mu_{RL\text{prop}} = \mu_{RL\text{ref}}$</td>
<td>$1.81 \times 10^{-7}$</td>
<td>$AP_{\text{prop}}$</td>
</tr>
<tr>
<td>$\mu_{AP\text{prop}} = \mu_{AP\text{ref}}$</td>
<td>$0$</td>
<td>$RL_{\text{prop}}$</td>
</tr>
</tbody>
</table>

Table 6.6: Statistics on equality of the median of cingulum visitation distributions. The mean values indicate the average number of visitations per voxels along the tracts. 10,000 tracts were initially casted per seed voxel.

### 6.2.3 Discussion

In this section, I proposed a novel EPI distortion correction approach that combines the strengths of fieldmap based and elastic registration based correction approaches and minimizes their pitfalls. The algorithm has been shown to perform better than a typical elastic registration based approach both in terms of overlaps of single images and tracts computed from a set of diffusion weighted images of a population. The advantages of the proposed algorithm is its robustness around the non-distorted regions and its ability to cope with very large deformations. However, the biggest advantage is its simplicity and practicality. Most diffusion weighted data are accompanied with a structural image in clinical settings and this correction approach can be directly applied to existing clinical data without the need for any additional acquisition related information.
In this book, the distinction between only tissue and air was made to estimate the inhomogeneity maps. However, this model can be further improved to account for bone as well as the differences among the tissue types to better estimate the susceptibility maps. If distortions that are not sufficiently corrected by the proposed method are encountered, it might be advantageous to make these further distinctions while automatically estimating the fieldmaps.
CHAPTER 7

DIFFUSION WEIGHTED IMAGE INTERPOLATION

In this chapter, the effects of several convolution based interpolation schemes employed during motion and distortion correction process of diffusion weighted images will be analyzed in detail. Interpolation methods used in the pipeline of Figure 2.8 can affect the final DWIs both due to their differences in computing the continuous signal values (Section 7.1.9) and due to their effects on the convergence of registration transformation as described in [96] (Section 7.1.10). Additionally, a solution to the frequently disregarded problem with interpolation used in registration of noisy images, previously described in Section 2.6 will be presented in Section 7.1.4. This chapter will be concluded with a generic, PDE based solution to the diffusion weighted image interpolation in Section 7.3.

7.1 Illustration of Problems due to DWI interpolation

Artifacts and signal alterations introduced by interpolation to the diffusion weighted images during motion and correction pipelines are generally disregarded in further analysis. However, they can have a non–negligible impact on the outcomes. In this section, these problems will be stated without discussing methodologies to understand or improve them.
7.1.1 Partial Volume Effects magnified by Interpolation

Tissue interfaces such as white matter – CSF boundaries, the original data acquired from an MRI scanner generally includes some signal convolutions, for which the signals originate from a mixture of different tensorial shapes. With convolution based interpolation, the scales and amount of these partial volume affected voxels increase due to further spatial averaging of the signals. Figure 7.1 illustrates this problem. It is important to note that after interpolation, the width of the partially affected voxels around CSF increase to 3–4 voxels compared to the original data where this width is around 1-2 voxels. The reader should note that because the interpolated data is transformed during motion and distortion correction, exact anatomical slices can not be extracted.

Figure 7.1: Illustration of magnification of partial volume effects after interpolation.
7.1.2 Changes in Scalar Distributions

In addition to the partial volume effects, interpolation on diffusion weighted images affect the computed tensors and more specifically the shape of the tensor fitting functions. Therefore, the derived scalar fields exhibit different statistical properties. In the experiments, an image interpolated with trilinear and tricubic interpolation showed a difference of 120 voxels in the voxel segment with fractional anisotropy larger than 0.8. These regions with very high anisotropy are of specific importance in DTI and such a difference is not negligible. Behaviors of different interpolation kernels will be analyzed in detail in Section 7.1.8.

7.1.3 Oversmoothing of Data

Small brain structures get affected more by interpolation due to the relative sizes of the structures and the convolution kernels. Smoothing effect of convolution operation might render these regions fuzzier than the original data. This can be observed in Figure 7.2.

7.1.4 Patterns in Chi-Squared Error maps

Diffusion tensors are computed from diffusion weighted images with a regression processed, called tensor fitting. The $\chi^2$ maps [9] from this error fitting process are indicators of correctness and robustness of the tensor fitting process. As previously described by Rohde et al. [96], interpolation of diffusion weighted images introduce patterns and striations to these maps, therefore affecting the second order statistics of the derived scalar maps from the tensor fields. This problem occurs due to inadvertent interpolation of image noise and is illustrated in Figure 7.3.
7.1.5 Physical Plausibility of Interpolation

Interpolation is a solely image based procedure and does not consider the underlying tissue characteristics, i.e. shape or orientation of tensors. Along with the underlying diffusion tensors, the diffusion synthesizing gradient has a direct impact on the image contrast. For the sake of illustration, let us consider this case with an example 1D diffusion signal for 3D tensors. This case is illustrated in Figure 7.4.

For this illustration of the problem, consider an image consisting of five pixels, for which the signal in the diffusion free image is constant and set to 1000. For illustration purposes the contrast for this value is set to white. I assume specific orientations for the underlying diffusion tensors where the first pixel corresponds to an anatomical location with eigenvectors corresponding to the axes of the image with the principal eigenvector is oriented along the $y$ axis with an eigenvalue of $2000 \times 10^{-6} \text{mm}^2/\text{s}$ and the two other eigenvalues are set
to $200 \times 10^{-6} \text{mm}^2/s$. The diffusion tensors are rotated by $45^\circ$ along the $z$ (in-plane) axis consecutively for the other pixels. With a constant diffusion synthesizing gradient along the $x$ axis and an assumed $b$–value equal to 1000 $s/mm^2$, the diffusion weighted signals can be estimated by using the Stejskal–Tanner equation [106], as displayed in the last two rows of the figure.

Consider the case where the diffusion weighted signal in the third voxel needs to be estimated through interpolation by using the other four voxel's signals. Linear interpolation in this case would yield the same value as the neighboring pixels, i.e. 332.87 and cubic interpolation would yield a value of 170.91. If the diffusion tensor at this location was assumed to be the one indicated in the third row, corresponding pixel, the diffusion signal decay equation would yield a value of 135. In this case, the linear interpolation overestimates the value (332.87 v.s. 135) and cubic interpolation gives a more reasonable estimate (170.91 v.s. 135) solely due to the choice of the diffusion tensor for this pixel. For example, if
the diffusion tensor was vertical such as the one in the first pixel but not horizontal, the estimation error (170.91 v.s. 818.73) would have been increased.

This example had the purpose of illustrating the discrepancies in between image based interpolation of diffusion weighted signals and its anatomical/physical plausibility. The constructed example was an extreme case due to the discrete nature of the tensor field however such situations occur in human brain data especially near tissue interfaces and crossing fiber regions. In these regions convolution based interpolators can result in large signal estimation errors, hence significantly affect image statistics or tract continuities.

The reader should note that during the interpolation phase of the diffusion weighted images, the underlying diffusion tensors are generally not known, otherwise in the presence of a continuous tensor field, the interpolation process would be redundant. However, in iterative interpolation processes such as PDE based interpolation schemes, estimates of the diffusion
tensors can be incorporated into the interpolation process. This concept is the focus of Section 7.3.1.

7.1.6 Experimental Setup to Observe Interpolation problems

In this section, the effects of problems described in the previous on real data will be systematically analyzed. The pipeline of Figure 2.8 reduces the cumulative effects of interpolation and helps us focus on the effects of a single interpolation step and its problems for DWI processing. The reader should note that internal interpolation routines are employed in each registration process and they affect the output transformations from registration but not directly the final DWIs.

The dataset for these experiments consisted of data from five healthy subjects of the "EPI dataset" and a synthetic continuous diffusion tensor phantom, where the underlying diffusion tensors at continuous locations are analytically generated. These data underwent the modified diffusion image processing pipeline of Figure 2.8. Three different convolution kernels were used for both the internals of each registration process and the final resampling step: nearest neighbor kernel, trilinear interpolation kernel and tricubic interpolation kernel. To differentiate the effects of interpolation on the final images, two separate experiments were conducted:

- For each interpolation kernel, the entire pipeline is used for each data. Therefore, the selected interpolation kernel affects both the resampling step and the transformations output by each registration step. Differences in final DWIs are attributed to the effects of kernel on the overall pipeline.
• Only the resampling step is carried out with fixed transformations for each interpolation kernel. The selected transformations are the ones obtained with cubic polynomial kernel of the previous experiment.

7.1.7 Synthetic Tensor Data

In addition to the real subject data, a synthetic, analytical phantom was created to quantitatively assess interpolation performance and amount of artifacts. The phantom was generated from several spatially continuous analytical functions for the diffusion tensors themselves, which divided the image space into four regions with different diffusion properties to emulate real data. For each continuous location within the final image, a diffusion tensor was first synthesized to yield a DTI image. This tensor field was then used along with the experimental design of the data from healthy subjects to generate the diffusion weighted images for a given SNR with Rician noise model. For tensors falling into the same voxel regions, the multi-compartment tensor model was used to synthesize the data. For illustration purposes, a tensor image of size $64 \times 64 \times 64$ with one tensor per voxel was generated whereas during the analysis, a tensor field of size $128 \times 128 \times 128$ with 64 tensors per voxel was used. Axial slices from the $b = 0 \text{s/mm}^2$ image and a diffusion weighted image of the phantom are displayed in Figure 7.5.

The four regions of the synthetic phantom served as ground truth data simulating the properties of different regions of the brain. With the use of this data, the errors introduced by successive interpolation operations could be measured by examining the interpolated data and the ground truth version. Different regions of the phantom exhibit different properties:
**Region 1:** This region’s purpose was to emulate the behavior of crossing fiber thus two sets of completely intervened fibers were generated. The first set of fibers were similar to projectional fibers along the Inferior-Superior direction and the second set was Right-Left directional. For the first set, the tensor trace was set to $2100 \text{ mm}^2/\text{s}$ with decreasing FA near region edges and for the second set, the trace was set to $2800 \text{ mm}^2/\text{s}$ with a constant FA of 0.7.

**Region 2:** This region contained mostly isotropic tensors simulating CSF.

**Region 3:** This region contained an infinite amount of helix with smaller radii closer to the center. With constant trace, the fractional anisotropy of helix tensors was inversely proportional with to the distance from the center of the region. FA and trace distributions were designed to simulate those of corpus callosum.
**Region 4:** This region had the purpose of emulating the white matter fiber bundles at the interface with CSF. The sphere at the center consists of isotropic tensors with trace around 3000 $mm^2/s$. Voxels outside the sphere consists of tracts forming circles with higher anisotropy near the sphere and lower towards the edges.

Figure 7.6 displays these tracts from two different angles.

![Figure 7.6: Tracts of the artificial data with 2 planar ROIs.](image)

**7.1.8 Analysis**

To understand the differences of data obtained with the use of different interpolators, I analyzed the overall brain distributions of fractional anisotropy (FA) and trace maps of data both by fixing the transformations of registrations and having them flexible. After diffusion weighted image processing steps, the tensors were computed using non-linear regression and the scalar maps were derived. While analyzing FA, statistics of voxels with
FA larger than 0.8 were also computed and these voxels localized because these high FA regions highly anisotropic white matter regions, which most studies are interested in. In addition to global analysis, properties of voxels at tissue interfaces were also examined to observe the effects of partial volume effects.

### 7.1.9 Fixed Transformation

In order to eliminate the effects of interpolation kernel on the output transformation of registration of motion & distortion steps of DWI processing pipeline, the transformations obtained with cubic interpolators were directly used in the "resampling" step of Figure 2.8 for trilinear and nearest neighbors interpolants. Figure 7.7 displays the FA and ADC maps of slice from a single subject data interpolated with these three kernels. The version interpolated with the nearest neighbor kernel suffers as predicted from extreme jagginess that results in discontinuities in CSF regions (ADC) and the body of corpus callosum (FA). The data interpolated with trilinear and cubic kernels show a smoother behavior and do not suffer from the discontinuities, but still differ significantly. In the trilinear case, the FA in the body of CC is significantly higher than that of the cubic version. On the contrary, the FA in the extremity white matter regions in the cubic data is higher than the corresponding regions in the trilinear version. When ADC maps are examined, the ghost-like artifact just above the CSF region is visually standing in the cubic data. This artifact is not observed at such a significant level in the trilinear version.

Figure 7.8 displays the histograms of FA and trace averaged over the population for the three interpolants. The areas under the curves are normalized to one to be compatible with probability distribution functions. Even with fixed transformations, the differences in FA
Figure 7.7: A slice from data with three different interpolators employed in motion & distortion correction step. The transformations are fixed to be the same for all cases.

distributions are significant. Due to its property of not introducing new values to the data, preventing signal mixing, the nearest neighbor interpolant yields a distribution with significantly higher probabilities for high FA values. This also suggests that the anisotropy is reduced when trilinear and tricubic interpolants are used due to signal mixing in DWI level especially around highly anisotropic white matter regions at gray matter or CSF interfaces. Trilinear interpolation significantly increases the probabilities of lower FA values and hence decreases the anisotropy of high FA regions, whereas the tricubic interpolation stands in between due to its ability to model sharper edges. For high ADC regions, the three interpolants yield similar results whereas they differ in low trace regions with a similar behavior by the different kernels to the FA case.
To understand the effects of partial voluming due to interpolation, I semi-automatically segmented the CSF and corpus callosum of all data. After applying a set of dilation morphological operations to the segmented masks and taking their intersections, I built a mask for voxels that are possibly affected by partial volume effects. Figure 7.8 illustrates the histogram of FA using the three interpolants by only considering the voxels in this intersection mask.

These distributions exhibit an interesting behavior with the cubic interpolant increasing the frequencies of low FA values. Nearest neighbor interpolation and trilinear interpolation yield high mid-range FA frequencies while the trilinear causes in the lowest high FA probabilities. Another observation that can be drawn from these plots is that the effects of interpolation are magnified when voxels with possible contaminations are examined.
7.1.10 Variable Transformation

Images obtained by letting the transformation in the motion & correction step be flexible are illustrated in Figure 7.10. The reader should note that exact same slices can not be displayed due to different orientations of images in different cases.

The images in this Figure 7.10 are different than those of Figure 7.7 (except the cubic one, which is set to be the same), due to interpolants effecting the registration, and causing different transformations. Table 7.1 displays the mean squares metric computed from the variable and fixed transformation FA images to emphasize the effects.

These metrics suggest that the images obtained with cubic interpolant are non-negligibly different than those of trilinear and NN interpolants due to the large differences in the images. Linear interpolation is very consistent with or without imposing the transformations.
Figure 7.10: A slice from data with three different interpolators employed in motion & distortion correction step. The transformations are flexible for all cases to observe the overall effects of interpolants.

but the nearest neighbor yields very different images in this case, as can be observed from the high metric equal to 0.0031.

7.1.11 Phantom Data

For synthetic data experiments, data with $256 \times 256 \times 256$ image dimensions with 64 sub-samples per voxel was first generated to serve as ground truth. For testing purposes, data with $128 \times 128 \times 128$ dimensions with one sample per voxel was also generated using the experimental design matrix of the healthy subject. Each volume of this test data was rigidly transformed to simulate head motion by analytically sampling the spatially continuous tensor field and generating the corresponding the diffusion weighted signals, hence
no interpolation was involved in this transformation. This motion distorted synthetic data then underwent the same pipeline of correction, yielding registered data obtained through interpolation.

To observe regional behaviors between the ground truth and the interpolated data, the differences are summed over sagittal slices and plotted as signatures, i.e.

\[ G(x) = \sum_y \sum_z (g_{\text{ground}}(x, y, z) - g_{\text{interp}}(x, y, z))^2 \]  

(7.1.1)

where for function \( g \), I chose to analyze again FA, trace and the angular differences between the primary eigenvectors.

Figure displays the spatial experiment results with the synthetic data. The top left image is the rotated image to simulate head motion, sampled from the continuous image, rotated back to its original space with tricubic interpolation. The image on the top right is the difference in FA produced by the ground truth and the images obtained with different interpolations, computed with the above equation. The bottom images are for trace and angular differences of primary eigenvectors of computed tensors.

When the FA signature is examined, it can be observed that the error in FA increases significantly in Region 2 where the tensors are mostly isotropic and noisy. This behavior is

<table>
<thead>
<tr>
<th></th>
<th>Cubic</th>
<th>Linear&lt;sub&gt;fixed&lt;/sub&gt;</th>
<th>NN&lt;sub&gt;fixed&lt;/sub&gt;</th>
<th>Linear&lt;sub&gt;free&lt;/sub&gt;</th>
<th>NN&lt;sub&gt;free&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.0090</td>
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<tr>
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<td>0.0118</td>
<td>0.00009</td>
<td>0.0023</td>
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<tr>
<td>NN&lt;sub&gt;fixed&lt;/sub&gt;</td>
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<td>0.0119</td>
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<tr>
<td>Linear&lt;sub&gt;free&lt;/sub&gt;</td>
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<td>NN&lt;sub&gt;free&lt;/sub&gt;</td>
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<td>0</td>
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</tr>
</tbody>
</table>

Table 7.1: Mean Squares metrics among different images.
expected but even for this region the cubic interpolant performs significantly better than the trilinear and Nearest Neighbor interpolants, which yield very similar error patterns. Another point to note is for Region 1 which models crossing fibers as intersecting planes. In this region, the reconstruction errors are significantly lower, interestingly with the linear interpolant yielding the best reconstruction and NN producing the worst results. Region 3, which consists of an infinite amount of helixes with constant FA, all interpolants produce the same result. Region 4 causes an interesting reconstruction error pattern in FA. This region which aims to model tight white matter tracts closely surrounded by CSF, yields
high reconstruction errors with cubic interpolation giving the best results. A very important observation that should be drawn from the FA reconstruction error signature is that the error signature starts to increase significantly in the partially affected voxels not completely in the corresponding regions. This supports my hypothesis that tightly packed tissues and partially affected voxels get affected from the chosen interpolation method significantly and alter image characteristics the most.

When the angular reconstruction error is examined, it can be observed that the errors are at their lowest in Region 3, which only consists of high FA regions with rapidly varying tract directionality towards the center. All interpolants are able to capture this orientation variations well, hence yielding the lowest errors.

### 7.2 Practical Solution to the Noise Variance Interpolation

In Section 2.6 and in Section 7.1.4, I defined the problem introduced by interpolation to the noise characteristics of diffusion weighted images. Rohde et al. [98] proposed a solution for the simple case of single interpolation step trilinear interpolation kernel. However, a practical solution that is suitable for successive interpolation steps and arbitrary kernels is required to enable a thorough analysis approach. In this section, I propose a method for accounting for signal variance changes in diffusion weighted images that underwent a series of distortion correction steps. I show the effects on images of the $\chi^2$ statistics of tensor fitting.
7.3 A novel PDE based interpolation method for diffusion weighted image processing

Convolution based interpolation schemes are not suitable for DWI interpolation as described in Section 7.1.6. Therefore, in this work I propose a PDE based interpolation scheme to overcome the stated problems. In this section the proposed PDE will be systematically constructed while often alluding to the aforementioned objectives of Section 7.1.6.

My proposed PDE is mainly based on Equation 3.2.3, where the values at continuous index locations $X = (x, y, z)$ are sought. Direct application of these non-linear PDE filters to 3D data is not straightforward due to the fact that smoothing remains isotropic on the tangent plane of the gradient. In this section, I adopt the weighting formulation of Hossain et al. [41]. In their work, the authors chose the directions of smoothing $\varsigma$, $\varrho$ and $\xi$, to be the directions of minimum curvature $\kappa_1$, maximum curvature $\kappa_2$ and the image gradient respectively. They define the weighting functions as:

$$\frac{\partial I(x, y, z, t)}{\partial t} = g \left( \frac{\partial^2 I}{\partial \varsigma^2} \right) \left( \frac{\partial^2 I}{\partial \xi^2} + \tau_\rho \frac{\partial^2 I}{\partial \varrho^2} + \eta \frac{\partial^2 I}{\partial \varsigma^2} \right)$$

(7.3.1)

where $g(\alpha) = 1 - (0.9)^{(\frac{\alpha}{\sigma})^2}$, with $\sigma$ a prechosen parameter. Also, $\eta$ is set to 0 and $\tau_\rho$ is defined as:

$$\tau_\rho = \begin{cases} \left( \frac{\kappa_1,\rho}{\kappa_2,\rho} \right)^4 & \text{where } |\kappa_{2,\rho}| > 0 \\ 1, & |\kappa_{2,\rho}| = 0 \end{cases}$$

(7.3.2)

where $\kappa_{1,\rho}$ and $\kappa_{2,\rho}$ are computed from a smoothed version of the image $I_\rho$ with a Gaussian filter of variance $\rho^2$. The anisotropic filtering diffusion tensor $T$ is constructed from these eigenvalues and eigenvectors of the diffusion tensor. The PDE-based interpolation brings the following advantages to the underlying applications:
• Nonlinear PDE filtering reduces the impact of the partial volume effects described in Section 7.1.1. This is inherently achieved in the PDE formulation wherein Gaussian kernels are oriented along edges. Therefore, signals from different tissue types are not mixed during interpolation.

• The formulation of [41] also improves the oversmoothing of small structures problem described in Section 7.1.3.

• Additionally, the striations in $\chi^2$ maps of tensor fitting operation occurs due to the presence of noise and repeated use of similar convolution weights repeatedly in a pattern. PDE-based interpolation can automatically cope with these issues by filtering out the noise components. Spatially varying nature of Gaussian kernels originating from PDE evolution will not yield an equivalent set of repeated weighting functions. Therefore, PDE-based filtering minimally suffers from these problems even if the more basic version described in Equation 3.2.3 is used.

### 7.3.1 Anatomical Plausibility

Partial differential equations based image filtering is equivalent to filtering with spatially varying Gaussian kernels as described in Section 3.2. Therefore, Equation 3.2.3 yields the solution at time $t$:

$$I^{t+1} = I^t \ast G^{(T,1)}$$

(7.3.3)

where $\ast$ stands for the convolution operator and $G^{(T,1)}$ is an oriented Gaussian kernel defined by:

$$G^{(T,1)}(X) = \frac{1}{4\pi} \exp \left( -\frac{X^T T^{-1} X}{4} \right) \quad \text{with} \quad X = (x, y, z)^T$$

(7.3.4)
The convolution in Equation (7.3.3) is simply a weighted sum of the signals of neighboring voxels. In Section 7.1.5, I state that this approach will not be very suitable for diffusion weighted images where a tensor or non-parametric probability models describe the underlying tissue structures. For this reason, I propose a modified version of this convolution operation, in the form of a novel PDE. Let us first write Equation (7.3.3) in its original form:

\[
I^{t+1}(X) = \int_{\Omega} I^t(X') G^{(T,1)}(X - X') dX', \quad X = (x, y, z)^T, \quad X' = (x', y', z')^T
\]  

(7.3.5)

where \( \Omega \) is the domain of the Gaussian kernel. I propose to include another term to balance the signal weighting in order to counteract the discrepancies due to underlying diffusion tensor and gradient orientations. Let \( f(X, X') : \mathbb{R}^6 \rightarrow \mathbb{R} \) be a function that relates the decay at voxel \( X \) to the decay at voxel \( X' \). If such a function was known, the weighting in convolution could be modified as follows:

\[
I^{t+1}(X) = \int_{\Omega} I^t(X') G^{(T,1)}(X - X') f^t(X, X') dX'
\]  

(7.3.6)

The function \( f \) can be considered as a function which generates another 3D image \( I_X \) for each voxel \( X \) where the values in the image are relative signal decays due to diffusion with respect to voxel \( X \). In other words, the function \( f \) converts the diffusion weighted image onto a diffusion-free image relative to voxel \( X \). The PDE update equation which generates Equation (7.3.5) as its solution is:

\[
I^{t+1}(X) = I^t(X) + g \left( \frac{\partial^2 I_X^t}{\partial \xi^2} \right) \left( \frac{\partial^2 I_X^t}{\partial \eta^2} + \tau_p \frac{\partial^2 I_X^t}{\partial \rho^2} + \eta \frac{\partial^2 I_X^t}{\partial \xi^2} \right)
\]  

(7.3.7)

\[
I_X^t = I^t \times f^t(X)
\]  

(7.3.8)

\[
I^0(X) = I_0 \times f^0(X)
\]  

(7.3.9)
where $\Omega$ represents the image domain, $I_0$ the original diffusion weighted image, $f^t(X) = f^t(X, \Omega)$ the decay relation function of the entire image at time $t$ relative to voxel $X$, and the operator $\times$ indicates voxel-wise multiplication. In an iterative framework such as the one described in this section, the signal decay function $f$ can be estimated at each iteration by first computing the tensors (or any diffusion model employed) within the support of the Gaussian kernel and can be expressed as:

$$f(X, X') = \exp \left( -bg^T(D(X) - D(X'))g \right)$$

(7.3.10)

where $D(X)$ and $D(X')$ are the estimated diffusion tensors at the corresponding voxel locations and $g$ is the diffusion synthesizing gradient.

### 7.3.2 Frequency Domain Properties

Gaussian convolution implicitly employed during PDE filtering acts as a low pass filter that does not intersect the zero level set at integer index locations and its’ primary purpose is to selectively smooth out image noise. However, in this work, this filtering is used as an interpolator. Previous work on using PDEs for interpolation project the PDE update function onto the interpolation function space \[99\] and guarantee that after successive upsampling and downsampling the original signal on integer index locations are conserved.

In this work, I follow a different approach and make use of the analogy between PDE filtering and Gaussian convolution. As described in Section \[5.4.8\], Appledorn proposed an interpolation kernel solely based on Gaussian convolution. The kernel proposed by Appledorn in Equation \[5.4.8\] only employs 1D Gaussian functions and its second order derivatives. For the PDE-based interpolation, the orientation and the shape of the Gaussian
function implicitly employed during the PDE evolution depends on $T$ (Equation 3.2.3), therefore, this Gaussian function is not isotropic or unoriented as in the function of 3.1.8.

To demonstrate the proposed method that combines both approaches, consider a case of anisotropic filtering diffusion tensor $T$ that is anisotropic in shape but not oriented. In this case, the PDE-based filtering inherently behaves as dictated by Equation 7.3.3. However, along an eigenvector dimension, I will aim to achieve:

$$I_{t+1} = I_t \ast \left( \triangle x G(k_1 \triangle x^2) - k_2 \triangle x \frac{\partial^2 G(k_3 \triangle x^2)}{\partial x^2} \right)$$

(7.3.11)

From the linearity of convolution, this equation is identical to:

$$I_{t+1} = \triangle x I_t \ast G(k_1 \triangle x^2) - \triangle x I_t \ast k_2 \frac{\partial^2 G(k_3 \triangle x^2)}{\partial x^2}$$

(7.3.12)

due to the linearity of both convolution and differentiation:

$$I_{t+1} = \triangle x I_t \ast G(k_1 \triangle x^2) - \triangle x \frac{\partial^2 I_t}{\partial x^2} \ast G(k_3 \triangle x^2)$$

(7.3.13)

In the above equation the two Gaussian functions on the right hand side of the equation have different variances, with the first one having half the variance of the second one. Using the fact that a Gaussian function can be expressed as a product of two other Gaussian functions, let: $G(k_3 \triangle x^2) = G(k_1 \triangle x^2).G(\sigma^2)$, where $\sigma^2$ is the variance of the ”converted” Gaussian and can easily be computed. Then, Equation 7.3.13 can be rewritten as:

$$I_{t+1} = G(k_1 \triangle x^2) \ast (\triangle x I_t - k_2 \triangle x.G(\sigma^2).\frac{\partial^2 I_t}{\partial x^2})$$

(7.3.14)
This equation has the form of Equation 7.3.13. I demonstrate its’ efficacy for 1D signals; in 3D, the Gaussian function \( G(k_1 \Delta x^2) \) can be considered as the Gaussian function parameterized with the covariance matrix \( T \). Therefore, by setting \( k_1 \Delta x^2 \) to a multiple of the corresponding eigenvalue of \( T \), one can convert one filter to the other. In this work, to cover the entire support of the Gaussian functions, \( \Delta x \) was computed as: \( \Delta x^2 = \frac{9 \lambda_i}{k_1} \) where \( \lambda_i \)s are the eigenvalues. Therefore, by combining Equation 7.3.13, Equation 7.3.7, and Equation 7.3.8, the final version of the proposed PDE can be written as:

\[
I^{t+1} = I^t + g \left( \frac{\partial^2 I^t_{\text{final}}}{\partial \xi^2} \right) \left( \frac{\partial^2 I^t_{\text{final}}}{\partial \xi^2} + \tau \frac{\partial^2 I^t_{\text{final}}}{\partial \eta^2} + \eta \frac{\partial^2 I^t_{\text{final}}}{\partial \rho^2} \right) \quad (7.3.15)
\]

\[
I^t_{\text{final}}(X) = \Delta X I^t_X - k_2 \Delta X G(\sigma^2) \frac{\partial^2 I^t_X}{\partial X^2} \quad (7.3.16)
\]

\[
I^t_X = I^t \times f^t(X) \quad (7.3.17)
\]

\[
I^0(X) = I^0_0 \times f^0(X) \quad (7.3.18)
\]

### 7.3.3 Experimental Setup

The reader should note that internal interpolation routines are employed in each registration step and they affect the output transformations from registration but not directly the final DWIs.

The dataset for these experiments consisted of data from five healthy subject and a synthetic continuous diffusion tensor phantom, where the underlying diffusion tensors at continuous locations are analytically generated. Two different convolution kernels were used for both
the internals of each registration process and the final resampling step: trilinear interpolation and tricubic interpolation kernels. To differentiate the effects of interpolation on the final images the transformations were fixed for each experiment.

7.3.4 Materials

For the real brain data, the “EPI dataset” described in Section 5.1.1 was used. In addition to the real subject data, the same synthetic, analytical phantom was used to quantitatively assess interpolation performance and amount of artifacts. This tensor field was then used along with the experimental design of the data from healthy subjects to generate the diffusion weighted images for a given signal-to-noise-ration (SNR) with Rician noise model.

To understand the differences of data obtained with the use of different interpolators, I analyzed the overall distributions of fractional anisotropy (FA) and trace maps by fixing the transformations of registrations and also using a flexible set of parameters. After diffusion weighted image processing steps, the tensors were computed using non-linear regression and the scalar maps were derived. While analyzing the FA maps, statistics of voxels with FA larger than 0.8 were also computed and these voxels localized. In addition to global analysis, properties of voxels at tissue interfaces were also examined to observe the effects of partial volume effects.

For synthetic data experiments, data with $256 \times 256 \times 256$ image dimensions with 64 subsamples per voxel was first generated to serve as ground truth. Each volume of this test data was rigidly transformed to simulate head motion by analytically sampling the spatially continuous tensor field and generating the corresponding the diffusion weighted

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signals, hence no interpolation was involved in this transformation. This motion distorted synthetic data then underwent the same pipeline of correction, yielding registered data obtained through interpolation. The same metric of Equation 7.1.1 was used to observe the deviations from the ground truth. This metric is reiterated here for the reader.

\[ G(x) = \sum_y \sum_z (g_{\text{ground}}(x, y, z) - g_{\text{interp}}(x, y, z))^2 \]  

\hspace{1cm} (7.3.19)

### 7.3.5 Results

Figure 7.12 displays images from the phantom data. The first image depicts the rotated phantom analytically transformed, the second image is obtained with rotation with linear interpolation and the last image is obtained with the proposed interpolant. Linear interpolation results in an image with deteriorated small structures whereas the continuity of the planes in the first region is preserved with the proposed method.

![Images](image_url)

(a) Original phantom  
(b) Linear interpolation.  
(c) PDE interpolation

**Figure 7.12:** Rotation experiment with trilinear and the proposed PDE based interpolants. Fine structures are preserved with the proposed method.
Angular differences of tracts between the ground truth data and the interpolated versions are displayed in Figure 7.13. The signatures are overlayed on the a slice from the phantom data. With this synthetic data, the linear and nearest neighbor interpolants perform very similarly. Among the convolution based interpolants, the tricubic filter yields the lowest reconstruction error. The PDE based scheme performs significantly better than all convolution based approaches on regions with small structures, as well the regions consisting mostly of noise.

![Image](image_url)

**Figure 7.13:** Angular differences of tracts between the ground truth data and the interpolated versions summed over the $x$ and $z$ dimensions and plotted as a function of $y$ coordinate. Tricubic interpolation yields the best error among convolution based approaches. The proposed PDE-based method performs better at region interfaces. The signatures are overlayed on a sagittal slice of the phantom.

Figure 7.15 displays diffusion weighted images in their original form and after being interpolated with Equation 5.2.3 and the proposed method. The standard PDE-based filtering oversmooths the image and emphasizes some structures incorrectly, such as the magnification of internal capsule regions (bilateral dark regions by CSF). Due to the diffusion tensor weighting scheme employed by the proposed method, this region is slightly smoothed but
Figure 7.14: Histograms of the FA values obtained with different interpolation methods, averaged over the population. The proposed method yields a high likelihood for high FA values.

the primary shape described by the original data is preserved. Additionally, regions such as the genu of the corpus callosum is more homogenous with the proposed method compared to its counterpart, which is in conformance with the anatomy.

Figure 7.14 displays the distributions of the FA values, only from regions susceptible to partial volume interference. The histograms are generated using a population of five subjects. This figure suggests that convolution based interpolants have an undesired effect of reducing the frequencies of high FA regions. This occurs due to intermixing of signals at tissue interfaces and both linear interpolation and tricubic interpolation cause FA values to reduce for very anisotropic regions. The proposed method increases the likelihood of high FA values even to a higher level than that of the nearest neighbor interpolation. This can be attributed to the decrease in partial volume effects and sub-voxel contamination introduced to the original data during image acquisition.
Figure 7.15: Comparison of the proposed interpolation method with basic PDE filtering based interpolation.

Figure 7.16 displays the isosurface models of FA maps at an isovalue of 0.2 for the proposed method, tricubic interpolation and nearest neighbor interpolation. The NN interpolation results in a very noisy surface and disconnected islands. The tricubic interpolation and the PDE method yield very similar surfaces, with the proposed method yielding a slightly thicker interface.

To illustrate the differences in tractography, a very small ROI in low brain stem region encapsulating only the cortical spinal tracts was chosen for each case. Tractography results obtained with exact same parameter set are displayed in Figure 7.17. Tractography results from such an ROI are known to be unreliable due to the effects of distortions and tight packing of structures in a small area. In fiber tractography experiments, assessing the correctness of tracts is a very challenging problem due to the lack of ground truth as well as the unknown anatomy, therefore, the purpose of this experiment was to analyze the stability of the tracts. Tractography from linearly interpolated data results in relatively fewer
Figure 7.16: Isosurfaces of FA extracted from data obtained through different interpolation schemes. Tricubic and proposed scheme yield similar results with the latter one resulting in slightly thicker cortical interface.

number of tracts due to the lack of continuity of the anterior tracts. Cubically interpolated data result in tracts with a wider spread. The tracts computed after interpolating with the proposed method results in very compact and consistent tracts. Even though the anatomical correctness of these tracts are unclear, compactness and stability achieved with the PDE method are generally desirable features in tractography experiments.

7.3.6 Discussions

In this chapter, I first analyzed the weaknesses of the convolution based interpolation for diffusion weighted image processing and then proposed a novel method for diffusion weighted image interpolation to be used in image registration based motion and distortion correction frameworks. My approach was based on a partial differential equations (PDE)
based scheme specifically modified for diffusion imaging. The analogy between PDE filtering and Gaussian convolution was used to improve the frequency response of the proposed filter, which also eliminated the need for projecting the PDE updates onto the interpolation function space.

Results indicated that the proposed scheme significantly improves data quality especially around tissue interfaces, improves tissue relations with respect to convolution based operators, and provides coherent fiber tractography. As future research direction, the improvements provided by the proposed algorithm on partially contaminated voxels will be thoroughly investigated. Additionally, in this work, the relationship among different diffusion weighted volumes was established through diffusion tensors. The use of more complex diffusion models such as DSI non-parametric probability distribution functions or spherical harmonics should further enhance the capabilities and tissue discrimination of the methodology.
CHAPTER 8

DIFFUSION TENSOR FIELD REGISTRATION

In Chapter 4.3.3, the concepts of image registration and diffusion tensor field registration were reviewed and their importance for a population based or longitudinal study was described. In this chapter, two novel diffusion tensor image registration frameworks are proposed. In Section 8.1 I propose a robust diffusion tensor field registration algorithm that not only considers the tensorial properties but includes the uncertainty information involved with them. Section 8.2 concludes this chapter with another approach that can be individually used for registration, to make other registration approaches faster or just for statistical analysis purposes.

8.1 Diffusion Tensor Image Registration in the Presence of Uncertainty

The use of full tensor information for registration, along with metrics powerful enough to acknowledge shape and direction information, has been shown to lead to better registration accuracy [53]. However, all these approaches consider diffusion tensors as independent from the original diffusion weighted images. It is crucial to note that diffusion tensors are obtained through an optimization process on the DWIs and do not reflect the underlying
diffusion properties within the brain, but also depend on the noise in the signal of DWIs and the experimental design, i.e., gradient directions and $b$-values. In this thesis, I propose a method that uses a dissimilarity metric that not only makes use of the full tensor, but also uses the uncertainty present in DWIs to cause the registration to favor directionally more informative, inherently more anisotropic and less noisy regions. To my knowledge, this property of diffusion tensors has never been investigated and employed in a registration procedure. For each voxel, a Gaussian tensor–variate distribution is constructed with a mean and a covariance tensor obtained from the tensor fitting function; the mean tensor provides the best estimate of the diffusion tensor in each voxel while the covariance matrix gives an insight into how well the estimated mean diffusion tensors reflect the underlying diffusion properties. The main contributions of this work are:

- using the uncertainty information present in the diffusion weighted images as tensor distributions along with diffusion tensor properties to automatically favor brain regions, with high diffusion anisotropy and fiber coherence that form an internal skeleton with which to guide the registration.

- incorporating an initial segmentation for a tissue adaptive registration.

- providing analytically derived error differentials for accurate and fast convergence.

In this section, I propose a novel registration framework for DTI registration based on a probabilistic tensor dissimilarity metric, which is able to capture the inherent uncertainty in the diffusion weighted images and tensorial changes due to tissue type, as well as the differences in tensor orientations and shapes.
The Kullback-Leibler (KL) divergence dissimilarity for tensor–variate Gaussian distributions is used as a voxel-wise dissimilarity metric in a hierarchical registration framework that starts with a coarse, rigid registration, continues with affine and finishes with a finely resolved B–Splines deformable registration. A $6 \times 6$ covariance tensor is computed from the invariant Hessian of the non–linear tensor fitting optimization function along with each mean estimated diffusion tensor to construct a Gaussian tensor–variate distribution. The covariance matrix provides additional information that intrinsically weights brain regions with higher diffusion anisotropy and diffusion tensor fit with higher confidence.

Figure 8.1 depicts the workflow of the proposed framework. There exists three main parts, namely: i) pre–processing, ii) generation of salient white matter maps iii) registration. I list some salient components of the flow while simultaneously sketching the road map for my work.
• **Tensor fitting:** The registration framework starts by estimating the tensors from the diffusion weighted images, where the covariance of each diffusion tensor is also computed using the non-linear fitting function (Section 8.1.1.1).

• **Covariance dimensionality reduction:** The $6 \times 6$ covariance matrix has 21 independent components. The dimensionality of independent components is reduced to two by exploiting the covariance isotropy assumption (Section 8.1.1.5).

• **Tissue segmentation:** With the dimensionality reduction, each voxel includes a diffusion tensor and a tensor covariance matrix represented with two parameters. The moving image is segmented with an Expectation–Maximization algorithm (Section 8.1.2), where label–maps are produced along with white matter probabilities. A hierarchical, non-uniform support grid is employed during the B–Splines elastic registration where the grid size is a rule–based function of the expected tissue type obtained from the segmentation.

• **Dissimilarity metric:** The diffusion tensors, covariance matrices and segmentation outputs are then fed into the registration pipeline where the KL tensor dissimilarity metric, is used to compute the fitness values for the registration optimization function (Section 8.1.1.3).

• **Metric and finite strain differentials:** Formulations for metric and finite strain differentials are provided to the optimizer for faster and more accurate error gradient computations (Section 8.1.1.4).

• **Interpolation:** For a complete registration, the framework uses rigid, affine and B–Splines transformations where tensor and covariance matrix interpolations are achieved through a continuous B–Splines approximations (Section 8.1.1.6).
8.1.1 Methodology

The main principle in the proposed DTI registration methodology is the concept of tensor-variate distributions. In Section 8.1.1.1, methods to compute tensor covariances will be described and Section 8.1.1.3 will present the framework for using this distribution information for registration purposes.

8.1.1.1 Tensor Fitting and Covariance Tensor Estimation

As described in Chapter 1 in a typical DTI experiment, the measured signal in a single voxel has the following form:

\[ S_i = S_0 \exp(-bg_i^T D g_i) \] (8.1.1)

where the measured signal, \( S_i \), depends on the diffusion encoding vector, \( g_i \), of unit length, the diffusion weight, \( b \), the reference signal, \( S_0 \), and the diffusion tensor \( D \). Given \( n \geq 7 \) sampled signals derived from six non–collinear gradient directions and at least one sampled reference signal, the diffusion tensor estimate can be found with non–linear regression by minimizing the following objective function (with \( \gamma \) represents the vectorized version of diffusion tensor entries):

\[ f_{NLS}(\gamma) = \frac{1}{2} \sum_{i=1}^{n} \left( s_i - \exp \left[ \sum_{j=1}^{7} W_{ij} \gamma_j \right] \right)^2 \] (8.1.2)

where \( s_i \) is the measured diffusion weighted signal corrupted with noise, \( \hat{s}_i(\gamma) = e^{\sum_{j=1}^{7} (W_{ij} \gamma_j)} \) is the predicted diffusion weighted signal evaluated at \( \gamma \), and \( W \) the experimental design
The function in Equation 8.1.2 introduces the variability in the signal as explained in the design matrix $W$. In [63], it is shown that the diffusion tensors at each voxel can be considered as a normally distributed random variable with the covariance matrix being a function of the Hessian matrix at the optimum solution. Thus according to [63], the Hessian matrix can be computed from:

$$\nabla^2 f_{NLS}(\hat{\gamma}) = W^T(\hat{S}^2 - \hat{S})W$$  \hspace{1cm} (8.1.3)

where $S$ and $\hat{S}$ are diagonal matrices whose diagonal elements are the observed and the estimated weighted signals, respectively, and $R = S - \hat{S}$. Then the covariance matrix of a diffusion tensor can be estimated as in [63]:

$$\Sigma_{\gamma} = \sigma_{DW}^2 \left[\nabla^2 f_{NLS}(\hat{\gamma})\right]^{-1}$$  \hspace{1cm} (8.1.4)

where $\sigma_{DW}^2$ represents the variance of the noise in the diffusion weighted images. Please refer to [63] for derivations and details.

The covariance matrix is therefore a function of the noise in the images, $\sigma_{DW}^2$, the gradient magnitudes and directions (embodied in the design matrix, $W$) and the underlying tissue properties. The anisotropy, the norm and the shape of this $6 \times 6$ matrix all provide insights on the reliability of the optimum diffusion tensor solution and the tissue properties. Figure 8.4 b) and c) display maps of the deviations from these matrices from the pure isotropic designs of Section 8.1.1.5, thus displaying a measure of the shape of these matrices with respect to tissue type.
With the diffusion tensor, $\hat{\gamma}$, and the associated covariance tensor, $\Sigma_{\hat{\gamma}}$, the data in each voxel can be used to construct a tensor-variate Gaussian distribution function with diffusion tensors as random variables. This fact is used to drive the registration process.

### 8.1.1.2 Positive Definiteness and Distributions of Diffusion Tensors

Diffusion tensors are predicted to have non-negative eigenvalues, representing the real molecular water diffusion. However, in DTI, the diffusion tensors are obtained through a physical setup not only affected by real water diffusion but also the scan parameters. This results in generally non positive-definite tensors in typical DTI scans (unconstrained fitting), especially in highly anisotropic regions such as corpus callosum. In their work, Pasternak et al. considers diffusion tensors as Cartesian physical quantities and shows that the Euclidean space is better suited for diffusion tensors than affine–invariant Riemannian manifolds [81]. Pajevic et al. also shows through the use of Monte–Carlo simulations mimicking physical imaging setups, that tensor coefficients can be modeled with a Gaussian distribution over a wide range of SNR and the number of DWIs acquired. [10]. Aiming to cope with uncertainties such as noise and artifacts in practical settings, it was preferable to use a tensor–variate Gaussian distribution in this framework, instead of a Wishart distribution, which conserve positive definiteness.

### 8.1.1.3 Dissimilarity Metric

In this work, I propose using a new metric function, $F$, for diffusion tensor field registration. This metric uses the distribution of diffusion tensors obtained in each voxel, arising from
noise and tissue properties. The error metric is based on the symmetric KL divergence and can be described as:

\[
F(I_f, I_m, \Theta) = \frac{1}{N} \sum_{p \in \Omega} w_p(I_f, I_m) \left( \frac{1}{2} \left( tr(\Sigma^{-1}_m \Sigma_f) + (\gamma'_m - \gamma_f)^T \Sigma^{-1}_m (\gamma'_m - \gamma_f) \right) + tr(\Sigma^{-1}_f \Sigma_m) + (\gamma_f - \gamma'_m)^T \Sigma^{-1}_f (\gamma_f - \gamma'_m) \right) \tag{8.1.5}
\]

In Equation 8.1.5, \( \gamma_f \) signifies \( \gamma_f(p) \), the diffusion tensor on the fixed image at physical voxel location \( p \); similarly \( \Sigma_f \) signifies the covariance at voxel location \( p \), i.e., \( \Sigma_f(p) \). For the moving image, the covariance tensor is obtained through interpolation as in Section 8.1.1.6 so \( \Sigma_m \) corresponds to \( \Sigma_m(T(p, \Theta)) \). Deforming a diffusion tensor, \( \gamma_m(p) \), with a (locally) affine transformation matrix, \( A \), involves tensor interpolation followed by reorientation. In this work, the Finite Strain model proposed in [2] is followed and the interpolated and rotated diffusion tensor \( \gamma'_m(p) \) can be found to be \( \gamma'_m(p) = R^T \gamma_m(T(p, \Theta)) R \). \( R \) is the rotation component extracted from the affine matrix, \( A \), and can be found to be \( R = (AA^T)^{-1/2} A \). For the elastic registration case, \( A \) is not constant throughout the image and can be locally estimated from the displacement field, \( u \), as \( A(p) = I + J(u(p)) \) where \( I \) is the identity matrix and \( J(u(p)) \) is the Jacobian of the deformation field at \( p \).

Equation 8.1.5 is the Kullback-Leibler (KL) divergence symmetrized with respect to both distributions. When the first part of the equation is examined, \( \frac{1}{2}(tr(\Sigma^{-1}_m \Sigma_f) + (\gamma'_m - \gamma_f)^T \Sigma^{-1}_m (\gamma'_m - \gamma_f)) \), it can be seen that the first term in the summation, \( tr(\Sigma^{-1}_m \Sigma_f) \), is a measure for the similarities of the two covariance matrices and the second term is the standard Mahalanobis distance. The overall metric for the registration is the weighted \((w_p(I_f, I_m)) \) summation over the KL metrics on all voxels, normalized by the number of voxels used.
8.1.1.4 Error Metric Differentials

Registration is mainly an optimization procedure, where the optimizers generally require partial differentials of the error metric with respect to the transformation parameters. Most of the DTI registration frameworks suffer from using numerical approximations to these gradients. One strategy for computing the differential is to use the centered differences: \( \frac{\partial \xi}{\partial \Theta_i} = \frac{F(\Theta_1, \ldots, \Theta_i + s, \ldots, \Theta_m) - F(\Theta_1, \ldots, \Theta_i - s, \ldots, \Theta_m)}{2s} \). The problem with this approach is that it requires two metric computations per transform parameter. For deformable registrations with very large parameter space dimensionality, such as B–Splines or finite elements based registration, this approach is infeasible and an analytical solution for the differential is required. In this section, I will analytically derive the error metric gradient so that each partial differential involved has a simple form, easy to compute numerically at most once per iteration, instead of once per transformation parameter. This way the metric evaluations are minimized and the gradient computations are more accurate and faster. Let us have a closer look on the first terms of the error metric:

\[
F = \frac{1}{2} (tr(\Sigma_m^{-1}(T(p, \Theta))) \Sigma_f(p)) + (\gamma'_m(p) - \gamma_f(p))^T \Sigma_m(T(p, \Theta))^{-1} (\gamma'_m(p) - \gamma_f(p))
\]

(8.1.6)

Let \( f \) be the trace term, \( f = tr(\Sigma_m^{-1}(T(p, \Theta))) \Sigma_f(p) \), and \( g \) be the Mahalanobis term, \( g = (\gamma'_m(p) - \gamma_f(p))^T \Sigma_m(T(p, \Theta))^{-1} (\gamma'_m(p) - \gamma_f(p)) \). The differential can be expressed as \( \partial F/\Theta_i = \partial f/\Theta_i + \partial g/\Theta_i \). From the chain rule, it follows that:

\[
\frac{\partial f}{\partial \Theta_i} = \sum_{j=1}^{6} \sum_{k=1}^{6} \frac{\partial tr(\Sigma_f \Sigma_m^{-1}(T(p, \Theta)))}{\partial \Sigma_m(k_j)} \sum_{x,y,z} \frac{\partial \Sigma_m^{-1}(T(p, \Theta))}{\partial T_{x,y,z}} \frac{\partial T_{x,y,z}}{\partial \Theta_i}
\]

(8.1.7)
• The first differential term, \( \frac{\partial \text{tr}(\Sigma f^{-1}(T(p, \Theta)))}{\partial \Sigma f^{-1}(p)} \), is just \( \Sigma f^{-1}_{kj} \) from the symmetry of covariance tensors and the derivative of traces w.r.t the matrices. Also note that the inverses of the covariance matrices are stored and used as images, canceling the need for the inverse operation for the differential. Additionally, as explained in Section 8.1.1.5 the isotropic covariance matrix \( \Sigma m^{-1}(T(p, \Theta)) \) is obtained only using interpolation but not reorientation due to rotational invariance assumption, yielding a simpler formula [10].

• The second partial in Equation 8.1.7 represents the image gradient of the maps of each covariance components with respect to imaging directions. These gradients need to be computed once at the beginning of the registration.

• The last term \( \frac{\partial T_{x,y,z}}{\partial \Theta_i} \) corresponds to the Jacobian of the transformation and needs to be computed once per iteration.

The Mahalanobis term of the function \( F \), i.e., the function \( g \), has a more complicated differential due to the rotation of diffusion tensors \( \gamma m(T(p, \Theta)) \) into \( \gamma'(p) \) if an affine or deformable registration scheme is employed. Let \( a = \gamma' - \gamma f \), then the Mahalanobis part \( g \) can be rewritten as \( g = \sum_j \sum_k a_j a_k \Sigma m^{-1}_{jk} \). Then the differential can be rewritten as:

\[
\frac{\partial g}{\partial \Theta_i} = \sum_j \sum_k \frac{\partial a_j}{\partial \Theta_i} \Sigma m^{-1}_{jk} + \sum_j \sum_k a_j \frac{\partial a_k}{\partial \Theta_i} \Sigma m^{-1}_{jk} + \sum_j \sum_k \frac{\partial}{\partial \Theta_i} \frac{\partial \Sigma m^{-1}_{jk}}{\partial \Theta_i}
\]

(8.1.8)

The differential in the last term, \( \frac{\partial \Sigma m^{-1}_{jk}}{\partial \Theta_i} \) is the same as the one used in Equation 8.1.7, i.e.,

\[
\sum x,z \frac{\partial \Sigma m^{-1}(T(p, \Theta))}{\partial \Theta_i} \frac{\partial T_{x,y,z}}{\partial \Theta_i}
\]

With the finite strain model, \( a \) is realized as \( a = R^T \gamma m(T(p, \Theta)) R - \gamma f \). Then the first differential can be expressed as:

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\[
\frac{\partial a_i}{\partial \Theta_z} = \frac{\partial R^T}{\partial \Theta_z} \gamma_m(T(p, \Theta)) R + R^T \frac{\partial \gamma_m(T(p, \Theta))}{\partial \Theta_z} + R \gamma_m(T(p, \Theta)) \frac{\partial R}{\partial \Theta_z} \quad (8.1.9)
\]

The second partial on the right hand side of Equation 8.1.9 can be found similarly to the covariance matrix case and is \( \sum_{x,y,z} \frac{\partial \gamma_m(T(p, \Theta))}{\partial T_{x,y,z}} \frac{\partial T_{x,y,z}}{\partial \Theta_i} \). In the case of an affine transformation, where the parameters \( \Theta_i \) corresponds to the entries in the affine matrix, \( A \), the partial derivative of the rotation matrix, \( R \), with respect to the transformation parameter, \( \Theta_z \), becomes from the application of the chain rule, \( \frac{\partial R}{\partial \Theta} = \frac{\partial R}{\partial A} \). For the elastic registration case, the local affine matrix is estimated from the displacement field, \( u \), and the differential becomes:

\[
\frac{\partial R}{\partial \Theta_z} = \sum_j \sum_k \frac{\partial R}{\partial u_{jk}} \frac{\partial u_{jk}}{\partial \Theta_z} \quad (8.1.10)
\]

For B–Splines registration of order 3, the displacement field can be written as, \( u(p, \beta) = \sum_i \sum_j \sum_k \beta_{ijk} b_{i,3}(p_x)b_{j,3}(p_y)b_{k,3}(p_z) \), where \( \beta_{ijk} \) are B–Splines weights corresponding to parameters \( \Theta \) and \( b_{r,3} \) are 3rd order spline basis functions. Then the second partial derivative, \( \frac{\partial u_{jk}}{\partial \Theta_z} \), is just \( \beta_{ijk} b_{i,3}(p_x)b_{j,3}(p_y)b_{k,3}(p_z) \) for \( \Theta_z = \beta_{ijk} \). The first term, \( \frac{\partial R}{\partial A} \), is the most complex derivative among all these partials and in [123], it has been shown by letting \( S = (AA^T)^{\frac{1}{2}} \):

\[
dR = -R[R^T(tr(S)I - D)^{-1}R \sum_i (R^T)_i \otimes (dA^T)_i]^\oplus \quad (8.1.11)
\]

where \( \otimes \) denotes 3D cross product, \((.)_i\) denotes the \( i^{th} \) column of \((.)\) and \( \oplus \) is the operator that converts any \( 3 \times 1 \) vector \( m = [m_1, m_2, m_3]^T \) into the skew symmetric matrix

\[
\begin{pmatrix}
0 & -m_3 & m_2 \\
m_3 & 0 & m_1 \\
-m_2 & m_1 & 0
\end{pmatrix}.
\]

\( \frac{\partial R}{\partial A_{ij}} \) can be found by setting all elements of \( dA \) to zero, except for \( dA_{ij} = 1 \).
These differentials complete the required set to compute the gradient of the error metric w.r.t to the transformation parameters. This differential framework provides an accurate and fast scheme for the registration.

8.1.1.5 Covariance Matrix Dimensionality Reduction

In Section 8.1.1.4, the error metric gradient equations were derived to make the registration faster and more accurate. In this section, I will motivate simplifications of the form of the covariance matrix to reduce the dimensionality of the data space. Independent components of diffusion tensors (6) and covariance matrices (21) yield a total of 27 dimensions for the feature vectors. This fact poses problems in terms of memory allocation and speed during elastic registration.

In Section 8.1.1.1, the covariance matrix was shown to be a function of the design matrix, \( W \), therefore its form depends on the number of gradients and the direction of gradients used. In [10], it is shown that with sufficient number of diffusion gradients sampling the unit icosahedron densely enough, the 4D covariance tensor \((3 \times 3 \times 3 \times 3)\) corresponding to the 2D covariance matrix tends to be isotropic and rotationally invariant. These isotropic covariance tensors yield a specific 2D, \(6 \times 6\) covariance matrix structure. They result in \(6 \times 6\) covariance matrices with the block matrix form shown in Figure 8.1.1.5.

This type of isotropic covariance matrix can be fully described with only two parameters, \( \lambda \) and \( \mu \) [10]. Therefore with the isotropy and rotational invariance assumption, the dimensionality of the covariance matrices can be reduced from 21 to two. However the covariance matrices obtained with Equation 8.1.4, which are based on the invariant Hessian of the \( f_{NLS} \) function, generally do not have this exact isotropic form. For this reason, for
Figure 8.2: Isotropic covariance matrix structure, which only requires 2 parameters, \( \lambda \) and \( \mu \).

Each covariance tensor \( \Sigma \), the most similar isotropic matrix \( \Sigma^* \) is found by minimizing the Frobenius norm of the differences, w.r.t the parameters \( \lambda \) and \( \gamma \) as

\[
\min_{\lambda, \gamma} \| \Sigma - \Sigma^* \|.
\]

This approach yields the isotropic matrix \( \Sigma^* \), closest to the original covariance matrix \( \Sigma \):

\[
\lambda = \frac{1}{21} (2\Sigma_{0,0} + 2\Sigma_{1,1} + 2\Sigma_{2,2} + 5\Sigma_{0,1} + 5\Sigma_{0,2} + 5\Sigma_{1,2} - \Sigma_{3,3} - \Sigma_{4,4} - \Sigma_{5,5}) \quad (8.1.12)
\]

\[
\mu = \frac{1}{42} (\Sigma_{0,0} + \Sigma_{1,1} + \Sigma_{2,2} - \Sigma_{0,1} - \Sigma_{0,2} - \Sigma_{1,2} + 3\Sigma_{3,3} + 3\Sigma_{4,4} + 3\Sigma_{5,5}) \quad (8.1.13)
\]

Figure 8.3 displays \( \lambda \) and \( \lambda/\mu \) maps.

Figure 8.4 displays the maps for deviations from the isotropic design, i.e. \( \| \Sigma - \Sigma^* \| \) maps. These maps very much look like an anisotropy map, therefore stating that the covariance matrix has information about the tissue characteristics to discriminate white matter regions.

8.1.1.6 Interpolation

The proposed registration framework requires interpolation of the diffusion tensors as well as the covariance matrices at subvoxel levels. The interpolation of diffusion tensors is a well-studied problem; the Log–Euclidean interpolation framework [7] and continuous
Figure 8.3: $\lambda$ and $\mu$ maps. The left two images display two slices from the $\lambda$ map and the right two images show the map for the ratio of $\lambda$ and $\mu$. It can be said that $\lambda$ and $\mu$ are very similar for most brain regions except very anisotropic regions.

B–Splines approximation framework [78] for DTI interpolation are employed. For the covariance matrices, the B–Splines interpolation scheme is employed on the reduced dimensionality space over the parameters $\lambda$ and $\mu$.

### 8.1.2 Tissue Segmentation

The main strength of this approach is that the error metric behaves differently according to the tissue type. With the information desired from the entire tensor distributions. To illustrate this point, and to also make the registration framework more robust and faster, a classical Expectation–Maximization (EM) segmentation was performed, initialized with $K$-means clustering, with the distance function originating from the KL-metric and tensor–variate distributions derived from the mean and covariance matrices. For the illustrations of this section, a brain image was segmented by using three different levels of information: the isotropic covariance tensors only with no contribution from the diffusion tensors (trace part of the error metric), the full covariance tensors only, and full covariance tensors along with
Figure 8.4: Deviations of the original covariance matrices from the isotropic form are displayed in b) and c). The latter two images clearly depict that the covariance matrices tend to be more anisotropic in WM regions.

The diffusion tensors as described by the error metric. Note that for the registration initialization, segmentation results obtained by using the diffusion tensors along with isotropic covariance tensors, is employed. Figure 8.5 displays the result of these segmentations on an axial slice.

The images in Figure 8.5 clearly show that the tensor covariance information brings additional crucial information about the tissue type. Figure 8.5 (b) displays the segmentation results of a brain DTI image using only the simplified isotropic version of the covariance. The image indicates that the isotropic covariance information is perfectly able to capture the differences in diffusion properties between WM and cerebrospinal fluid (CSF). However, the isotropy simplification of the covariances removes the anisotropic information and this information alone can not capture the difference between WM and GM regions. When
Figure 8.5: Segmentation results. Segmentation with only isotropic covariance matrix (b) can perfectly capture the difference between WM and CSF but cannot discriminate for white matter. Using full covariance tensor and diffusion tensor information (d), the segmentation of white matter improves. Blue indicates CSF, yellow WM, red GM.

The full covariance tensors are used in, as in Figure 8.5 (b), WM regions can be discriminated from the rest. The discrimination is improved when the diffusion tensors are used along with the covariance matrices.

The segmentation procedure described here is also used in the initialization of the registration procedure. For each moving image to be registered, first a segmentation procedure is carried out. The probability of a voxel being a WM voxel obtained from the EM segmentation is used as the weighting factor $w_p(I_f, I_m)$ in Equation 8.15. Additionally, the segmentation labels are used to build a multi-level grid for B–Splines registration. A coarser B–Splines transformation grid is placed on CSF locations to decrease the computational complexity, whereas a denser grid is used for WM. This placement is achieved through hierarchical B-Splines grids where the deformation on denser grid levels on CSF are constrained to be the solutions obtained from the coarser grid.
8.1.3 Experiments & Results

One of the images in "dataset 2" was chosen to be the fixed image and the other five were used as moving images. For comparison, I implemented a reference multi–channel registration algorithm with *six* channels for tensor components, including one channel for FA and one channel for ADC. The reference method followed the same vector image registration steps. Standard deviation maps of the FA maps were also computed from the registered images and compared to the standard deviation maps of the benchmark algorithm to illustrate the quality of the registration.

For the described dataset, the proposed registration pipeline with rigid, affine, and B–Splines transformations, where the maximum splines grid size is $20 \times 20 \times 20$, takes on the average 20 minutes per image on a modern computer.

Figure 8.6 displays the output of the registration algorithm. The rows depict different slice views whereas the columns display pictures from different images. The metric proves to perform well on white matter regions, as can be observed from the similarity of the images in the first column and third column. The difference image of the registered moving image (with the proposed method) and the fixed image is displayed on the fourth column, where it is visible that the metric performs significantly better than the reference method on *corpus callosum* regions. The difference image for the reference method is displayed in the last column.

Figure 8.7 displays the standard deviation of the FA maps of the five images registered with the proposed method. Note that the performance of the algorithm on white matter is clearly visible and that the deviations are within the acceptable range.
8.1.4 Discussion

In this section, I proposed a novel, robust and fast approach for tensor–to–tensor registration for Diffusion Tensor Image data, which is very suitable for group analysis and tensor atlas-ing problems. The proposed metric captures the uncertainty of the diffusion tensors with a tensor-variate Gaussian distribution resulting in a faster and more accurate registration. My future research directions include the analysis of the shape and isotropy characteristics of the distribution of covariance tensors for optimization of the registration, testing of the algorithm with a larger population, as well as the use of these distributions in a probabilistic fiber tracking methodology.
8.2 Manifold Unfolding for Diffusion Tensor Similarity Metrics

In this section, I propose a method that exploits the salient statistics of tensors. My method uses a dissimilarity metric between tensors, namely the geodesic–loxodrome distance [59], so it does not disregard any tensor information. However, the strength of this approach is that it can be used with any diffusion tensor similarity metric, even one as complex as the one derived in Section 8.1.1.3. The proposed method vectorizes the tensor field using a version of Multi Dimensional Scaling (MDS) algorithm to yield multi–channel vector images. The channels used in the registration process come from the eigen–modes of the MDS algorithm so the entire tensor information is encoded in these channels without the need for extraneous dimensions for tensor shape or orientation. In essence, it identifies the most salient tensors and describes a lower–dimensional vector subspace wherein meaningful measurements are conducted. This vector space allows for faster and more intuitive computations than what a typical tensor manifold can. The registration process for vector
images starts with a coarse, rigid registration, continues with affine and is concluded with a fine B–Splines deformable registration. The deformation fields from each step are used to reorient the original tensor field.

### 8.2.1 Methodology

![Diagram of the algorithm](image)

**Figure 8.8**: Illustration of the algorithm. Rectangular boxes represent input, generated and output data and elliptic boxes represent algorithm operators.

#### 8.2.1.1 Distance Metric

The registration algorithm’s flow is described in Figure 8.8. The most important operators in this flow are the metrics and interpolators. The biggest challenge in tensor field

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registration is the need to operate on a manifold, which fully characterizes clinically significant shape and orientation information. Multi–channel registration approaches heuristically try to achieve this by padding extra channels for diffusion norm and anisotropy. Riemannian geodesics get one step closer by implicitly (monotonically) interpolating tensor determinants but anisotropy strength and type of anisotropy are not considered. Geodesic–loxodromes proposed by Kindlmann et al. introduce an intuitive way to compute the distance in between two tensors, which monotonically interpolates all basis shape parameters and orientation [59]. The shape of the tensor \( D \) is modeled with three orthonormal invariant bases \( R_i \) chosen as:

\[
\begin{align*}
R_1(D) &= ||D|| \\
R_2(D) &= FA(D) \\
R_3(D) &= \text{mode}(D)
\end{align*}
\]  

(8.2.1)

Geodesic–loxodrome \( \gamma(t) \), the curve connecting tensor \( A \) and \( B \) is defined as:

\[
\begin{align*}
\gamma(0) = A, & \quad \gamma(l) = B, & \quad ||\gamma'(t)|| = 1 \\
\gamma'(t) : \nabla R_i(\gamma(t)) = \alpha_i & \quad \text{for all } t \in [0,1], \ i \in 1, 2, 3
\end{align*}
\]

where the operator \( : \) signifies tensor contraction, \( l \) and \( \alpha_i \) are constants that characterize the path of the curve, \( \nabla R_i(\gamma(t)) \) is the gradient of the invariant \( i \) on the tensor space. The curve \( \gamma(t) \) connects the tensors \( A \) and \( B \) while monotonically interpolating, in a controlled manner, the invariants \( R_i \). The distance in between tensors \( A \) and \( B \) is defined as:

\[
d(A, B) = \int_0^1 ||\gamma'(t)||. \]

This way of computing dissimilarity accords ample importance to clinically significant shape parameters as well as orientation.
8.2.1.2 Tensor Vectorization

Geodesic–Loxodromes (GL) provide a clinically intuitive way to do tensor interpolation and distance measurement but cannot directly be used to compute tensor population statistics. An ideal way to achieve this would be to unfold the GL manifold (if any) onto a planar one, in such a way that the statistics and distances are preserved on the new plane. Then it would be possible to just consider the vector coordinates of the points on the projected space.

The main goal of pre–processing is to convert the tensor images into vector images, with independent channels, with GL pairwise dissimilarities in between the voxels of all DT images. Multi Dimensional Scaling \[64\] is a statistical dimensionality reduction tool used to extract the coordinates of data points on a lower dimensional manifold, when only pairwise dissimilarities among the data points are available. In my case, the goal is to compute the dissimilarity matrix in between the voxels of two diffusion tensor images, from the tensor data and unfold this symmetric matrix onto vectorial coordinates using MDS.

8.2.1.3 Tensor Sampling

Theoretically, it is possible to use the tensors from every voxel of the DT image, build the dissimilarity matrix to be used in MDS, and extract the coordinates of each voxel in the lower dimensional space. However, the dissimilarity matrix for two regular size DT images would require about 10000GB of memory. Instead, both DT images are sampled in such a way that the sampled tensors are the best representatives for the entire tensor sets in the images. I employ the $K$–means clustering algorithm on the tensors of both images with the
GL distance metric, to select the best tensor representatives. \( K \) was empirically chosen to be 100 based on experiments with a validation set with values ranging from 10 to 1000. The mean tensors obtained with clustering are fed into the MDS algorithm. Figure 8.9 displays the mean tensors when \( K = 10 \) based on the data described in 8.2.2. In this figure, the tensor \( a) \) is the zero–tensor that represents background. Please note that only one tensor, tensor \( h \), is completely isotropic and \textit{eight} tensors are needed to describe the anisotropic behavior. Please also note that three tensors (\textit{tensors} \( e), \( f \) \textit{and} \( j) \) have similar directions but different determinants and modes, which is due to special importance assigned to these invariants by GL metric.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.9.png}
\caption{Mean tensors obtained with clustering displayed with ellipsoids.}
\end{figure}
8.2.1.4 Multi Dimensional Scaling

Let the mean tensor from K–means be $M_i$ for the first image and $L_i$ for the second image where $i \in [1,K]$. The mean tensors are concatenated and the pairwise distances to obtain the symmetric dissimilarity matrix $A$ is computed, where $A_{ij} = d(M_i, M_j)$ when $i, j < K$, $A_{ij} = d(M_i, L_j)$ when $i < K, K \leq j < 2K$ and $A_{ij} = d(L_i, L_j)$ when $K \leq i, j < 2K$.

In classical metric MDS, the Euclidean distances are tried to be preserved. Let $I_{2K \times 2K}$ be an identity matrix and $1_{2K \times 2K}$ be a matrix full of ones, define:

$$P = I_{2K \times 2K} - 1_{2K \times 2K}$$
$$B = P(-\frac{1}{2}A \odot A)P$$

where $\odot$ signifies component by component multiplication. The matrix $B$ is equal to $B = XX^T$ where the matrix $X$ contains the coordinates of the data.

I used this classical MDS approach just to understand the intrinsic dimensionality of the data by examining the eigenvalues. The first six eigenvalues after spectral decomposition were on the order of $1 \times 10^{10}$ where the remaining eigenvalues were on the order of $1 \times 10^{-2}$ except the last six ones which were negative with order $-1 \times 10^3$. This fact suggested that the intrinsic dimensionality of the data is six. With this in consideration, the non–classical, non–metric version of MDS was utilized to extract the final coordinates of the data points.

8.2.1.5 DTI projection onto MDS space

MDS vectorizes only the mean tensors computed with the clustering algorithm. However, for registration purposes, every tensor in both DTI images has to be projected on to this
vector space. Here the protocol to project the distances for unobserved tensor points to the MDS space is described. Let $X_i^t$ be the $i^{th}$ coordinate of the $t^{th}$ data point in the salient MDS space, $Y_i$ be the corresponding coordinate of the unobserved point, where $i \in [1,6]$ and $t \in [1,2K]$. Let $d^t$ be the distance of $Y$ to mean point $X^t$. Then $Y$ lies on the sphere defined as $\sum_{i=1}^{6} (Y_i - X_i^t)^2 = (d^t)^2$. At least six different points $X^t$ need to be used in order to have a non–infinite number of solutions for $Y_i$. Because of the imperfections in distance computations and in MDS, this system of equations might not have a solution. Therefore, slack variables $\xi^t$ are introduced for distances $d^t$ and setup up a minimization problem over the slack variables:

$$\min \sum_{i=1}^{6} (\xi^t)^2$$

$$s.t. \sum_{i=1}^{6} (Y_i - X_i^t)^2 - (d^t - \xi^t)^2 = 0 \quad \text{for all } t \in [1, 6]$$

This non–linear optimization problem was solved for each voxel in each image with a sequential quadratic programming (SQP) method [15]. The mean points, $X^t$, used in the constraints are chosen to be the closest six points to $Y$ and the optimization is initialized with the closest point’s coordinates. This optimization procedure is inexpensive and requires a few seconds to project both images onto the MDS space with a modern computer. To test its accuracy, I also implemented the Log–Euclidean metric [7], which has a closed–form expression, and were able to recover the exact point coordinates after the projection operator. Figure 8.10 displays the corresponding slices for each of six dimensions from the vector images produced with this method.
8.2.1.6 Vector Image Registration

Once the diffusion tensors in all images are converted to vector images as described in Section 8.2.1.2, the images are registered with well–known registration algorithms, using the following steps:

i The moving image is translated so that its center of mass matches that of the fixed image.

ii The moving image is registered to the fixed image with rigid transformation, vector mean squares metric, linear interpolation, and evolutionary optimization. The parameters are set to perform the search in a coarse manner.

iii The moving image is registered to the fixed image with an affine transformation initialized with a rigid transformation of Step ii. The vector mean squares metric and linear interpolation are used in conjunction with a regular step gradient descent optimizer. After this fine-scale registration, the moving image is resampled and transformed to match the fixed image.

iv The output image of Step iii is registered to the fixed image with a B–Splines transformation with $15 \times 15 \times 15$ B–Splines grid resolution.

Figure 8.10 (c) displays the output of the registration on the $B = 0$ image along with the fixed image.
8.2.1.7 Tensor Reorientation

The tensors are reoriented based on the transformation matrix from affine registration and the deformation field from B–Splines registration, with Preservation of Principal Direction (PPD) method [2]. Let $\mathcal{D}$ be the tensor to be transformed and $\mathcal{D'}$ be the resulting tensor.

i When the transformation is rigid, the new coordinates and the resulting tensors can be found as $T(x) = Rx + t$, $\mathcal{D}' = \mathcal{D}RRT$, where $x$ is the coordinate vector, $R$ is the rotation matrix, $t$ the translation vector.

ii When the transformation is affine the coordinates can be found with $T(x) = Fx + t$ where $F$ is the affine transformation matrix. $F$ can be decomposed as $F = UR$, where $R = (FF^T)^{-1/2}F$ is the rotation matrix and $U$ is the strain matrix. The
simple approach for tensor reorientation would be to rotate the tensor with $\mathbf{R}$ but $\mathbf{U}$ also affects the orientation of the tensors so it needs to be included in a detailed reorientation strategy.

iii When B–Splines registration is employed, there is no closed linear form for the transformation. Since every transformation is locally affine if the underlying deformation field $u(x)$ is continuous and smooth, the affine transformation matrix can be locally estimated for each point. Let the local coordinate transformation be $T(x) = x + u(x)$ and $T(x) = Fx + t$. Equating the two equations and differentiating w.r.t. $x$ yields $F = I + J_u$, where $J_u$ is the Jacobian of the deformation field.

8.2.2 Experiments and Results

DTI registration dataset ("dataset 2") was again used for the experiments. One of the images was chosen to be the fixed image and the other five were used as moving images. The diffusion tensors were extracted by imposing the constraint of positive-definiteness on the tensors. For comparison, I implemented a reference multi–channel registration algorithm with six channels for tensor components, including one channel for FA and one channel for ADC. The reference method had the same vector image registration steps. Figure 8.11 shows the principal eigenvectors of the moving tensors generated with the proposed method and the reference method on the FA map of the fixed image to signify the conformance. Please also note that the Euclidean Frobenius difference norm in between the fixed tensor field and registered moving tensor field was on the average $1.259 \times 10^9$ with the proposed method, whereas that quantity was $1.751 \times 10^9$ with the reference method. Additionally, the proposed method take about two hours on a modern PC, whereas the reference method
took 3 hours on the average because of the extra channels. About 90% of computations for both methods were for B–Splines registration.

**Figure 8.11:** Moving images’ eigenvectors plotted on fixed image’s FA map. a) Full FA slice with ROI in rectangle. b) Proposed method. c) Reference method. Reference method’s vectors are correct on sides but there is a mismatch on regions indicated by the arrow.

**Figure 8.12** (a) shows the corresponding fiber set from the fixed image (blue colored fibers) and registered moving image (skin colored fibers). The fiber differences are mostly due to anatomy and imperfections in the fiber tracking algorithm. Please note the fully corresponding fibers on the right picture.

For statistical purpose, an ROI was chosen and statistics of the tensors and the projected vectors were computed. The corpus callosum was automatically segmented within the algorithm by selecting $K = 2$ and compared the mean values of the variables from the method with mean tensors from Log-Euclidean.

The mean vector computed from CC with the proposed method was:

$[6.91, 0.15, -0.21, 5.62, 0.035, 5.7]^T$
Figure 8.12: a) Corresponding fibers from fixed and registered moving images. b) Zoomed in version of a. Arrows indicate the fully corresponding fibers.

where the matrix produced with Log–Euclidean was

$$\begin{bmatrix} 6.8694, 0.1464, -0.2083; 0.1464, 5.6471, 0.0338; -0.2083, 0.0338, 5.6081 \end{bmatrix}^T$$

These results indicate that the proposed method yield similar outputs for tensor statistics to Log-Euclidean approach.

8.2.3 Discussions

In this section, I proposed a novel, robust and fast approach for tensor–to–tensor registration for Diffusion Tensor Images, which is very suitable for fiber correspondence matching problem. The method can operate with any tensor similarity metric of choice and is based on vectorization of tensors in such a way to conserve all shape and orientation properties. The registration was done on vector image space and the resulting deformation fields were used to reorient the tensors.
PART III

Variability Analysis
CHAPTER 9

VARIABILITY AND CHANGE

The analysis and visualization of the variability of human brains (size, morphology, architecture, etc.) is an important and challenging problem for neuroanatomy. Different functional and structural brain organizations across subjects prevents the direct use of statistical models for clinical purposes such as understanding the patterns of abnormalities for patients suffering from Alzheimer’s and other degenerative diseases. Visualization provides intuitive feedback to assess the variability in the given data and for ways to interpret and manipulate data. In this work, I propose a method for analyzing and visualizing variability of brain morphology as measured by diffusion tensor fields. There has been much work that has addressed the variability of shapes of human and animal organs. The work of D’Arcy Thompson is perhaps the most classical and seminal [111]. More recent work includes [23] and [75]. Diffusion Tensor Imaging has opened new avenue for analysis and visualization of brain morphometry given its capability to non–invasively capture the architecture and geometrical properties of brain white matter (WM) neuronal fibers in vivo. Due to the complexity inherent in describing properties of diffusion tensors, a method to compute and visualize variability is not straightforward. A vexing problem pertaining to population and/or longitudinal studies is that the tensors extracted from DTI scans of different subjects
do not generally lie in the same coordinate frame given different head orientations and motion artifacts that occur during patient scans. Robust registration is therefore an essential step towards capturing and characterizing the inherent variability of data.

Variability analysis and visualization have been studied for scalar–valued anatomical images. A promising approach relies on statistical analysis of deformation field that can be derived from the registration of images that uses geometrical primitives like cortex surfaces, sulcal lines as landmarks. Kindlmann et al. [60] proposed a method to analyze brain variability based on the covariance matrices of the displacement vector fields originating from elastic registration and visualized these matrices with superquadric tensor glyphs. In [20], Chung et al. employed a statistical deformation-based morphometry model on the Jacobian of the displacement fields from the moving image to an atlas, to detect local volume changes. In [27, 30] methods were proposed to use the sulcal lines as shape descriptors and model these lines with B–Splines. A mean curve is computed to extract the covariance tensors with respect to 72 other sulcal curves. They use Riemannian tensor interpolation to densely estimate the brain variability. An extension of this work [31] also considered the correlations of spatial anatomical locations with each other. Toews et al. [112] employ generic scale–invariant features and statistical part–based models along with machine learning approaches to describe the space of human brains. Still, variability among diffusion tensor images has not been investigated deeply. In [8] Basser and Jones analyzed the variability of DT images from the same subject using bootstrap analysis and displayed the differences using fiber tractography. Fletcher and Joshi [32] used Riemannian geometry on the manifold of positive definite tensors to compute the statistics of diffusion tensors. However, variability among DT images was not analyzed. Arsigny et al. analyzed the tensor
properties again using Riemannian geometry with the Log–Euclidean metric [7]. Durrleman et al. [26] proposed a generic framework for registration and variability analysis of white matter fiber bundles using metric currents.

9.1 Variability with DTI

Diffusion tensor imaging has been widely used for clinical applications. Kubicki et al. [65] reported 14 different clinical uses for DTI. Most of these diseases reveal themselves as abnormal variations from a known normal brain template. Therefore, the pre-knowledge of deviation from the normal will aid diagnosis immensely. Due to its specific modality properties, DTI not only defines the shape of the important structures in the brain but also contains other crucial information, which might be very useful when shape characteristics are not sufficient for diagnosis. Therefore, a variation analysis on DTI should consider the full tensorial information instead of focusing only on derived scalar fields such as fractional anisotropy (FA) or Apparent Diffusion Coefficients (ADC).

Consider Figure 9.1. This figure displays the volume rendering of the FA map of the tensor field describing the most important variations of the brain morphology of a healthy population subjects (based on the used dataset). This variation tensor image delineates the regions of largest variability, namely, the corpus callosum and the brain stem, as well as the magnitude (brightness) and directions (color code) of the most dominant changes. Along with other change modes, this tensor is suitable to be used in a statistical model to understand the space of healthy subject DTI, and to detect anomalies.
In this part of this book, the concept of variability using DTI data will be analyzed in three ways:

i  *Spatial Variability based on Deformations:* The deformation fields that map each subject’s diffusion tensor image data onto a template (commonly population average) image can be used as a feature to understand the deviations within a population and to detect abnormalities. This approach only considers the tensorial information for registration and hence is not complete.

ii  *Global Tensor Variability:* My second approach to analyze tensor field variability considers a tensor image as an ensemble. The global tensor variability is extracted from a population, either considering the overall population variability or global variability with respect to a discrete *parameter of change*.
iii Local Tensor Variability: If a diffusion tensor image is not considered as an ensemble but a combination of local regions, a more detailed analysis of tensor variability can be carried out. These local regions, assumed to be homogeneous in some property have to be either manually selected or automatically computed from the images.

The remainder of this book will describe the models to understand the variability within human brain. Chapter 10 will describe a method to analyze and visualize global variability of diffusion tensors and shall aim to identify regions of large variability within a population and how this variability manifest itself. Chapter 11 will describe models to understand variability locally, where local deviations could be indications of abnormal behaviors.
CHAPTER 10

GROUPWISE GLOBAL TENSOR VARIABILITY

In this chapter, the proposed models for analyzing the global tensor variability will be presented. First in Section 10.1.1 the mathematical tools used in the models will be described. In Section 10.2 a linear dimensionality reduction based method to capture the overall variability of the tensor field will be presented. Section 10.3 extends the variability analysis concept presented in the previous chapter to include a parameter of change for which the variability will be measured on.

10.1 Mathematical Tools

The mathematical methodologies presented in this section are only pertinent to the models of this chapter. They describe various ways to perform linear and multi-linear dimensionality reductions.

10.1.1 Principal Components Analysis

Principal Components Analysis (PCA) is the most commonly used linear dimensionality reduction technique. Its principle assumes that a linear transformation of the data onto a
new coordinate framework can yield a new representation of the data where the importance of the dimensions with respect to the variance of the data along them can be enumerated.

Let $X$ be a data matrix of size $M \times N$ whose columns $x^j$ are the instances of data as $M$ dimensional vectors. Therefore, $x^j_i$ signifies the $j^{th}$ data instance and $i^{th}$ component of the vector. Let $\bar{x}$ be the mean feature vector as:

$$\bar{x} = \frac{1}{N} \sum_{j=1}^{N} x^j$$ \hspace{1cm} (10.1.1)

Let $\tilde{X}$ be the mean subtracted data matrix, i.e. $\tilde{X} = X - \bar{x}1^{1 \times N}$.

Then the covariance matrix of the data can be written as:

$$\text{Cov}(x) = \Sigma_x = \frac{1}{N-1} \tilde{X} \tilde{X}^T$$ \hspace{1cm} (10.1.2)

The eigen–decomposition of this covariance matrix yields:

$$\Sigma_x = U\lambda U^T$$ \hspace{1cm} (10.1.3)

where $U$ is the eigenvector matrix whose columns are the individual eigenvectors of $\Sigma_x$ and $\lambda$ is the diagonal eigenvalue matrix.

The principal eigenvector corresponding to the largest eigenvalue describes a dimension vector for which the data spread is the largest. Therefore, for dimensionality reduction purposes, it is the dominant dimension. The eigenvector corresponding to the second largest eigenvalue describes the second most important dimension, orthonormal to the first one. Any number of dimensions (with eigenvectors as bases) can be chosen to represent the data
or a pre-chosen amount of the original variance can be kept by determining the $K$ amount of dimensions to describe it. For example, to keep the 95% of the original variance, choose $k$ such that:

$$\sum_{i=1}^{K} \frac{1}{N} > 0.95$$

(10.1.4)

Let $\hat{U}$ be the reduced dimensional eigenvector matrix of size $M \times K$. When a new data instance $x$ is encountered, its projection onto the new lower dimensional space can be found as:

$$x' = \hat{U}^T(x - \bar{x})$$

(10.1.5)

where $x'$ is a $K$ dimensional vector that represents the coordinates of $x$ in the new coordinate space.

Just like the eigenvectors of a diffusion tensor, the eigenvectors obtained with PCA describe an ellipsoid. This ellipsoid defines the space of plausible data instances, even unencountered ones based on the properties of the training dataset.

10.1.1.1 PCA v.s. Singular Value Decomposition

In general, the number of instances $N$ is much less than the dimensionality of the feature vectors $M$, i.e. $N << M$. In this case, operating on the $M \times M$ covariance matrix is computationally very expensive and redundant given that the maximum number of attainable dimensions is $N - 1$. In this case the problem can be solved more efficiently with reduced singular value decomposition (SVD). SVD decomposition of a matrix $F$ asserts that:

$$F = USV^T$$

(10.1.6)
If the SVD operator is applied to the mean subtracted data matrix \( \tilde{X} \), we get:

\[
\tilde{X} = U_1 S V_1^T
\]  

(10.1.7)

In Section [10.1.1], it was shown that for PCA the covariance matrix can be written as:

\[
\frac{1}{N - 1} \tilde{X} \tilde{X}^T = U_2 \lambda U_2^T
\]  

(10.1.8)

When Equation [10.1.7] is inserted into Equation [10.1.8] we get:

\[
\frac{1}{N - 1} U_1 S V_1^T V_1 S^T U_1^T = U_2 \lambda U_2^T
\]  

(10.1.9)

Therefore from the orthonormality of eigenvectors:

\[
\frac{1}{N - 1} U_1 S^2 U_1^T = U_2 \lambda U_2^T
\]  

(10.1.10)

This states that the eigenvectors computed with SVD and covariance eigenvector decomposition are equal, i.e. \( U_1 = U_2 \). However, the eigenvalues need to be transformed as:

\[
\lambda = \frac{1}{N - 1} S^2
\]  

(10.1.11)

### 10.1.2 Higher Order Singular Value Decomposition

Higher Order Singular Value Decomposition (HoSVD) is a multi-linear dimensionality reduction model where the relationships between different modes come into play to generate the data.

A matrix \( D \in \mathbb{R}^{I_1 \times I_2} \) is a two-mode mathematical object that has associated vector spaces, a row space and a column space. SVD orthogonalizes these two spaces and decomposes...
the matrix as \( D = U_1 S U_2^T \), the product of an orthogonal column space represented by the left matrix \( U_1 \in \mathbb{R}^{I_1 \times J_1} \), a diagonal singular value matrix \( S \in \mathbb{R}^{J_1 \times J_2} \), and an orthogonal row space represented by the right matrix \( U_2 \in \mathbb{R}^{I_2 \times J_2} \).

The \( \text{mode} - n \) product of a tensor and a matrix is a special case of the inner product in multilinear algebra and tensor analysis. In the literature, it is often denoted using Einstein summation notation. The \( \text{mode} - n \) product notation for SVD can be written as:

\[
D = \Sigma \times_1 U_1 \times_2 U_2 \quad (10.1.12)
\]

This notation states that the core matrix \( \Sigma \) operates on the row space of \( U_1 \) and the column space of \( U_2 \) as the standard matrix multiplication would.

By extension, an order \( N > 2 \) tensor or \( n \)-way array \( D \) is an \( N \)-dimensional matrix comprising \( N \) spaces. ”\( N \)-mode SVD is an extension of SVD that orthogonalizes these \( N \) spaces and expresses the tensor as the mode-\( n \) product of \( N \)-orthogonal spaces [116].

\[
D = Z \times_1 U_1 \times_2 U_2 \ldots \times_n U_n \ldots \times_N U_N \quad (10.1.13)
\]

This process is illustrated in Figure [10.1] for three modes. Tensor \( Z \) known as the core tensor is analogous to the diagonal singular value matrix in conventional matrix SVD. It is important to realize, however, that the core tensor does not have a diagonal structure; rather, \( Z \) is in general a full tensor. The core tensor governs the interaction between the mode matrices \( U_n \), for \( n = 1, \ldots, N \). Mode matrix \( U_n \) contains the orthonormal vectors spanning the column space of the matrix \( D \) that results from the mode-\( n \) flattening of \( D \). Please refer to [116] for details.

The \( N \)-mode SVD algorithm for decomposing \( D \) is as follows:
For $n = 1, \ldots, N$, compute matrix $U_n$ by computing the SVD of the flattened matrix $D_n$ with respect to the mode $n$ and setting $U_n$ to be the left matrix of the SVD.

ii Solve the core tensor with Equation 10.1.14.

$$Z = D \times_1 U_1^T \times_2 U_2^T \times_3 \ldots \times_n U_n^T \times_{N+1} U_N^T$$ (10.1.14)

Let us clarify the use of HoSVD with an example. Consider DTI data from two different genders and this gender differences need to be analyzed. Applying PCA to both data types separately would summarize the information solely contained in each data type and each data mode’s mean and deviations can provide crucial information. However, in this type of analysis these two modes stay disjoint and no information that connect the two can be extracted. HoSVD additionally captures this information can build the bridge that connects the two modes.
10.2 Global Variability Visualization based on a Population

In all the variability analysis related chapters it will be assumed that the elastic registration of the tensor fields was performed [83, 85, 125] and that voxel-wise correspondence among images of the population was established. Once the voxel-wise correspondence is established, it is possible to compute statistics on the images. I achieve this with a tensor manifold version of appearance models [22].

To extract the main modes of variations in DT images, the Log–Euclidean tensor manifold version of PCA is applied to the DT images. Let $N_X$, $N_Y$ and $N_Z$ be the sizes of the images. First the volumes are vectorized, such that the number of entries in the vectors is $N = N_X \times N_Y \times N_Z$. Let $I^j_i$ be the vector entry containing the matrix logarithm of $T^j_i$, the $i^{th}$ tensor in image $j$. The matrix logarithm can be computed as follows. Let the singular value decomposition of $T_i$ be $T_i = U_i S_i V_i^T$, where $U_i$ is the matrix containing the eigenvectors of $T_i$ and $S_i$ is a diagonal matrix containing the singular values. Then matrix logarithm is:

$$\log_M(T_i) = U_i \log(S_i) V_i^T$$

$I^j$ is then a vector version of DT image $j$ where each entry contains the matrix logarithm of tensor $T^j_i$. With $L$ datasets in the training set, the mean tensor–logarithm image $\mathcal{M}$ contains the mean tensor $\mu_i$ of the tensors $T_i$ in the corresponding voxel $i$ from all images $j \in [1..L]$. Figure 10.2 displays the FA maps and the results of fiber tracking of the mean image and another reference image from the training set near the corpus callosum. Figure 10.3 displays the isosurfaces obtained from FA maps, with an isovalue of 0.8 for both the mean image and a regular image from the training set. Please note that the mean image
is smoother on low FA regions but edges are preserved due to the non-elastic approach employed during registration.

\[ \Sigma \] be the data matrix of size \( N \times L \), where \( \Sigma(i, j) \) contains the tensor logarithm \( T^j_i \) of the \( i^{th} \) voxel in image \( j \). Let \( \hat{\Sigma} \) be the mean centered version of \( \Sigma \) where \( \mathcal{M} \) is subtracted from every columns of \( \Sigma \). The singular value decomposition of this matrix gives us the following PCA decomposition: \( \hat{\Sigma} = WSV \). This decomposition renders the space of DT images a Gaussian ellipsoid, with axes oriented along the eigenvectors of \( W \) with scales.
described in $S$. Any diffusion tensor image $I_{\text{new}}$ (within the space of DT images used in the training set), can then be generated as:

$$I_{\text{new}} = W.d\text{iag}(zS) + M \quad (10.2.1)$$

where $d\text{iag}$ is the operator that extracts the diagonal entries of a matrix. This generative model along with the eigenvectors of $W$ is used to understand the global variability present in the training set.
10.2.1 Experiments

For tensor image SVD, eight of the dimensions accounting for $\approx 91\%$ of the variance were kept. The visualization of the eigenvectors indicate the main locations of variability and their directions. Figure 10.4 displays a volume rendering of the FA map of the eigenvector corresponding to the largest eigenvalue. This figure indicates that the most important change locations in terms of diffusion tensor properties are corpus callosum and brain stem regions. The region of the eye is also an important area with much variation; however, the variability in this area is mostly due to the misregistrations in the training set. This can be verified from examining the deformation maps and validating the registration process.

![Volume rendering of the FA map of the eigenvector corresponding to the largest eigenvalue. The main locations of variability are corpus callosum and brain stem](image)

**Figure 10.4:** Volume rendering of the FA map of the eigenvector corresponding to the largest eigenvalue. The main locations of variability are corpus callosum and brain stem.

When we use the generative model of Equation 10.6 and select free variable $z$ as $z \in -2.5\sigma, -1.5\sigma, -0.5\sigma, 0.5\sigma, 1.5\sigma, 2.5\sigma$, images along the main axis of variation can be generated. Figure 10.5 and Figure 10.6 displays these images. Figure 10.5 displays

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the progression of the change along the main eigenvector (displayed as the $X$ axis of the Gaussian ellipsoid symbolizing the space of DTI) and Figure 10.6 shows a more clear view of the images.

Figure 10.5: Variability along the main eigenvector. The ellipsoid symbolizes the Gaussian space of DTI. Scales of axes are proportional to eigenvalues.
Figure 10.6: Images generated along the main eigenvector. Please note that the main changes are along CC and brain stem.

10.3 Global Variability Visualization based on a Population with a Parameter of Change

For a complete analysis, one needs to consider every possible factor contributing to the variability in the images. In several studies, one might need to analyze the variability of the tensor field within a population with respect to a parameter of change, such as gender, age and disease progression stage. Understanding the change within the human brain as a function of such a variable is an important research problem. In this section, I will apply
the HoSVD based multi-linear model to comprehend the variability within a population considering two parameters of change: EPI distortions and gender. HoSVD has several advantages over standard linear dimensionality reduction techniques such as PCA; it is very suitable for type of data with several contributing modes; it can linearly model the interaction among several modes, which can be used to separate the contributing variances; it yields more compact data structures for analysis; and it subsumes PCA.

10.3.1 Understanding Tensor Variability due to EPI protocol

The effects of EPI distortions and their corrections on tractography was analyzed in Section 6.1. In this section, the application of an EPI correction scheme, and the direction of phase-encoding will be considered as variables, for which the effects will be included in the analysis framework. The same dataset (“dataset 1”) was used for the purposes of this section. After performing the tensor registration to establish voxel-wise correspondences, the log-tensor images computed from the dataset, were assembled to build the 5–mode data tensor $\mathcal{D}$, with the first mode for subjects, the second mode for data repetitions, the third mode for phase encode direction, the fourth mode for the application of EPI correction step, and finally the fifth mode for log-tensors. Figure 10.7 displays this procedure.

As described in Section 10.1.2, this multi-mode data structure can be decomposed as:

$$
\mathcal{D} = \mathcal{Z} \times_1 U_{\text{subjects}}^{5 \times 5} \times_2 U_{\text{reps}}^{2 \times 2} \times_3 U_{\text{phase}}^{2 \times 2} \times_4 U_{\text{corr}}^{2 \times 2} \times_5 U_{\text{tensors}}^{9664512 \times 40} \tag{10.3.1}
$$

where the $5 \times 2 \times 2 \times 2 \times 40$ core tensor $\mathcal{Z}$ governs the interaction between the 5 mode matrices: The $5 \times 5$ mode matrix $U_{\text{subjects}}$ spans the space of anatomical differences among subjects, the $2 \times 2$ mode matrix $U_{\text{reps}}$ covers the variability between multiple scans of the
same subject with the same parameters, the $2 \times 2$ mode matrix $U_{phase}$ spans the space of EPI distortions due to different phase encoding directions, the $2 \times 2$ mode matrix $U_{corr}$ spans the space of changes after EPI correction. The $9664512 \times 40$ mode matrix $U_{tensors}$ is the Principal Components Analysis (PCA) analog of HoSVD and orthonormally spans the space of tensors. Figure 10.8 displays these principal axes of variation over all the images.

The big advantage of multilinear analysis beyond linear PCA is that this approach explicitly represents how the various factors interact to produce the diffusion tensor images. Please refer to [116] for the details on computation of the $Z$ core tensor and the $U$ matrices.
My DTI variability analysis and visualization is two fold: The analysis on the eigenmodes of the $U_{tensors}$ matrix which correspond to the PCA eigenvectors and synthesizing artificial data with the generative model by keeping four factors constant and varying the independent mode to observe its effects. Figure 10.8 and Figure 10.5 display the visualizations of analysis on eigenmodes with tensor components such as $D_{xx}$, $D_{yy}$ or scalar maps such as FA are used to visualize the inherent variations present in the data. These figures show the amount of variability and the anatomical locations of largest variations. Common regions that is sensitive to all inter–subject, distortion direction and correction modes, are especially genu and splenium of corpus callosum and the inferior regions of brain stem. Upper
portions of cortical spinal tracts also have a large variation among subjects but they turn out to be less sensitive to distortions and their corrections.

Figure 10.9 displays a volume rendering of the principal variation axis. The first image displays a rendering of the variation of the $D_{xx}$ component where most of the variability is around the border of the ventricles and corpus callosum and upper cortical spinal tracts. The second image displays a volume rendering of the $D_{xy}$ components and the variation is mostly around the genu and splenium of corpus callosum where the fibers are very dependent on $x - y$ correlations.
Figure 10.9: Volume renderings of the principal eigenvector image. The variability on the $D_{xx}$ and $D_{xy}$ components are displayed. The biggest variability on the $D_{xx}$ image occurs around the ventricles, especially around the border of ventricles and genu of *corpus callosum*. Upper cortical spinal tracts have some level of inherent deviations as well. For the $D_{xy}$ component image, the most important variations are around the tracts where there is a strong correlation between the $x$ and $y$ directions of the tracts such as splenium.
10.3.1.1 Generative Model

The strength of the multi–linear analysis is its ability to provide a framework that lets users adjust separately, the factors contributing to the variability in the data. My second approach to analyze the data in addition to the eigenmodes, is to create a generative model that can synthesize data with the desired attributes. Note that the row vectors of the $U$ matrices in Equation [10.3.1] can be considered as the coordinates of the given mode variable in a lower dimensional manifold. Therefore, any points within the Gaussian space created by these coordinates is a valid tensor image point that has not yet been seen. Let the generative tensor $T$ be:

$$T = Z \times_2 U_{reps} \times_5 U_{tensors}$$

Then an unseen instance can be generated with:

$$d = T \times_1 s^T \times_3 p^T \times_4 c^T$$

where $s$ is a five dimensional vector describing the anatomical properties, $p$ is a two dimensional vector describing the phase–encoding direction and $c$ is a two dimensional vector indicating whether or not the data has been corrected for the distortions. For example, if a distortion–free data with different anatomical features, with phase encoding direction as AP, is to be generated, $p^T$ becomes the first row of $U_{phase}$, $s^T$ becomes the second row of $U_{corr}$ and the coefficients in $s$ can be freely chosen within the limits. Another example might be the case where data obtained with a lesser magnetic field strength is to be simulated. In this case, the lesser distortions can be obtained with a linear combination of the rows of the $U_{corr}$ matrix.
Figure 10.10 is an interesting case of using the generative model. The fibers in Figure 10.10 (a) correspond to the same anatomical fiber with the same seed point but they are generated by synthesizing DTI data by varying the subject mode parameters and keeping the other modes constant (distortion=AP, correction=on). The set of fibers span the set of spatial places where the fiber in of interest can reach within the brain (based on the information of the data). Figure 10.10 (b) displays again the same anatomical fiber synthesized by varying only the distortion mode. As can be observed, the likelihood for the fiber to deviate along the AP direction gets less and less when the parameter is closer to the RL case.

In case "subjects" are considered separately, the descriptive vector for subject mode has five dimensions, each having different effects on the created data. Figure 10.11 displays the FA maps of the synthetic DTI data generated by varying each component.
Figure 10.10: The same fiber tracked based on different variability sources. The fibers in a) are tracked from synthesized data different only in anatomy. The fibers in b) are again tracked from synthesized data based on the space of distortion learnt from the training set. As can be seen from the fibers, when the distortion parameter is continuously moved from AP to RL, the fibers tend to deviate less in the AP direction but becomes more sensitive to RL effects. Blue colored fibers are obtained from a real subject data with no distortion.
10.3.2 Understanding Tensor Variability due to Gender Differences

In this section, I will apply the model built in Section 10.3.1 to another problem and try to visualize and understand the differences between the male brain and the female brain. For this experiment, the “gender dataset” described in Section 5.1.4 was used.

The data tensor $D$ consisted therefore of three modes: data instance, gender and tensor images. The corresponding higher order tensor decomposition then yields:

**Figure** 10.11: Variations created by the parameters individually. Each parameter has different effects on the FA maps.
\( \mathcal{D} = \mathcal{Z} \times_1 U_{\text{subjects}}^{20 \times 20} \times_2 U_{\text{gender}}^{2 \times 2} \times_3 U_{\text{tensors}}^{11236320 \times 40} \) (10.3.2)

Figure 10.12 displays the outputs of the generative model on the subject mode. The first four parameters out of twenty were changed between the minimum and maximum allowable values to generate these artificial tensors, for which the computed FA maps are displayed. In the figure, \( \rho_i \) signify these four parameters and \( v^j_i \) are the monotonically increasing values they take to generate the \( i^{\text{th}} \) row, \( j^{\text{th}} \) column image. The very high FA noise around the edges of the brains are due to minimal registration errors of the tensor fields.

The artificial data generated from the subject mode displayed in Figure 10.12 is not very informative. Figure 10.13 displays instead the difference of these images from the FA image computed from the mean tensor. Only the parameters \( \rho_2 \), \( \rho_3 \) and \( \rho_4 \) and the four \( v^j \)s away from the center (zero as the value) are considered for this figure as the first mode’s purpose is to represent the mean tensor field.

This figure shows that the principal dimension along the subject mode mainly captures the differences around cortical regions. The second dimension still has an effect on the cortex but more importantly it affects the high FA regions such as corpus callosum more than the first one. This states that the tensor variability in the cortical regions are more prominent than corpus callosum variability. The third parameter has a lesser effect on the cortex. This behavior can also be observed from Figure 10.14 which visualizes these three eigenvector dimensions.

A more interesting analysis in this experiment involves the gender mode instead of the subject mode. Figure 10.15 displays the differences in FA between the mean female brain
Figure 10.12: Variations created by the parameters $\rho$ individually. Each parameter is varied between $-3\sigma$ and $3\sigma$ based on its standard deviations and five new artificial data is synthesized to visualize the variability.

and artificially generated brains using the HoSVD model. The generated brains linearly transitions between the female brain and the male brain and hence the figure aims to give an intuition on how the FA maps of average female brains transitions into a brain and what the changes are.
Figure 10.13: Variations created by the parameters $\rho$ individually. Each parameter is varied between $-3\sigma$ and $3\sigma$ based on its standard deviations and five new artificial data is synthesized to visualize the variability.

Figure 10.15: The difference between the female mean brain FA map and the FA maps artificially generated with the model representing in-between gender brains.
Let $\rho_{\text{female}}$ be the two dimensional vector representing the female gender and $\rho_{\text{male}}$ represent the male gender in $U_{\text{gender}}$. In the experiments, based on the data:

$$
\rho_{\text{female}} = [-0.7137, 0.7005], \quad \rho_{\text{male}} = [-0.7005, -0.7137]
$$

To generate the images in Figure 10.15 artificial brains were generated using the HoSVD the model by varying these two gender parameters from pure female to pure male. The FA map of the pure female is displayed as the first image and four difference images between the mean female FA and the synthetically generated images linearly spanning the gender mode, are displayed to visualize the transition. The reader should note that this transition is not linear in FA maps and that the scale of the colorbar in the last image is twice the previous ones.

The difference images in Figure 10.15 do not exhibit a strong structure. Differences can be observed again in the cortical regions between the two genders but do not yield conclusive
information. To derive more information from this analysis, the properties of the core tensor $Z$ can be analyzed. Even though it does not have a diagonal structure, the core tensor in HoSVD is the analogue of the singular value matrix in SVD or the eigenvalue matrix in PCA and it includes information about the variance contained in each mode that can be used for dimensionality reduction purposes.

In my experiments, the total variance along the first dimension of the gender mode, i.e. $\sigma_{gender_1}^2 = \sum_i \sum_k Z(i, 1, k)^2$ was on the order of $4 \times 10^7$ whereas the variance along the second dimension, $\sigma_{gender_2}^2 = \sum_i \sum_k Z(i, 2, k)^2$ was on the order of $4 \times 10^4$. In other words, the first dimension of the gender mode accounted for about 850 times more variance than the second mode. In terms of dimensionality reduction, this states that the second dimension of the gender mode can be safely omitted and be represented with one scalar, yielding:

$$\rho_{female} = [-0.7137], \quad \rho_{male} = [-0.7005]$$

After reducing the dimensionality, the representation of male and female genders in this model almost yields identical feature vectors and statistical analysis on the equality of these parameters states that these two genders are significantly not different in terms of their diffusion tensor properties.
CHAPTER 11

GROUPWISE LOCAL TENSOR VARIABILITY

In Chapter 10, the variability of the diffusion tensor images was analyzed considering the diffusion tensor images as an ensemble, i.e. the spatial positioning and ordering of voxels did not play a role in PCA or HoSVD models as long as voxels contained anatomically corresponding data from all considered images. In this chapter, the local variations in the brain shape will be analyzed. My strategy is based on modeling the local deformations and it provides a framework to detect abnormal spatial deviations.

11.1 Spatial Variability using Deformation Fields

As described in Chapter 8, the diffusion tensor images from every subject need to be spatially aligned to enable the different analysis procedures. These registration methodologies output the aligned images as well as deformation fields that map the original images onto the final ones. Traditionally, analyzing these deformation fields to capture population variability or to detect abnormalities has been a popular approach. This approach does not consider the modality of the underlying data and once the deformation fields are computed, the additional information inherent in DTI is disregarded. However, using the diffusion
tensor images for registration purposes can yield better quality deformation fields that can result in better analysis.

### 11.1.1 Methodology

Figure 11.1 displays the $D_{xx}$ component of the mean image computed from the gender data described in Section 10.3.2, the $D_{xx}$ map of an instance of the original data, the $D_{xx}$ map of the registered data and the $x$-component of the deformation field that maps the original image to the final one.

The deformation field displayed in Figure 11.1 was computed using the DTITK toolkit [125]. The algorithm employed in this toolkit divides the image space into hierarchical regular grids and performs a locally affine registration with continuity constraints of the regions in these grids. To analyze the variability using the deformation fields, I follow a similar strategy and divide the deformation field image space into hierarchical regular grids as employed by the registration algorithm (Figure 11.2).

The image in Figure 11.2 is an illustration of the deformation grid. In my implementation, the image is split into four grid levels consisting of rectangular grid sizes of $8 \times 8 \times 4$, $16 \times 16 \times 8$, $32 \times 32 \times 16$ and $64 \times 64 \times 32$.

#### 11.1.1.1 Local Shape Variation Modeling

PCA was again applied to each grid patch of the deformation field data separately at each hierarchy level. Let the deformation field of patch $i, j, k$ at level $\alpha$ of image $s$ be $Df_{i,j,k}^s(s)$, where $\alpha$ represents the grid density level with $\alpha = 1$ representing the grid of size $64 \times 64 \times$
Figure 11.1: Example of a deformation field. The deformation field in (d) maps the original image in (b) to the image in (c) which is aligned with the image in (a).

32 and $\alpha = 4$ representing the grid of size $8 \times 8 \times 4$. Therefore, the number of patches at a given level is a function of the level and the image size. PCA is applied to each patch at each level over the image mode to model the variability within each patch. Therefore, if we let the mean deformation image in patch be: $\tilde{D}_{ef}^{\alpha}_{i,j,k} = \frac{1}{N} \sum_s D_{ef}^{\alpha}_{i,j,k}(s)$, each patch can be decomposed as:
The eigenvectors and eigenvalues of each deformation field patch can be used again to separate the “normal” deviations from the unexpected ones.

Figure 11.3 displays the mean deformation patches $\overline{De f}_{i,j,k}^\alpha$ for $32 \times 32 \times 16$ patch size at the mid level of the brain and Figure 11.4 displays the principal mode of deviation for the same patches. Because the patches are discontinuous, very local and represent deformation field components instead of the actual brains, the images in these figures are not very intuitive.

Figure 11.4 displays the principal mode of deviation for the same patches. Quantitatively these models describe the local variations in shape of the human brain with respect to the training.
The mean deformations for local patches at mid brain level. Each patch is retrieved from a single slice and is of size $32 \times 32$ data and can be utilized to detect abnormal shape deviations. The algorithm for the training step and testing step for this approach, assuming $N$ deformation fields in the training set is presented below:

**Training:**

1. Register $N$ training images, compute the mean image $I_\mu$ and the deformation fields $Def(s)$ that map each image to $I_\mu$
ii Set $\alpha = 1$

iii iii.i Construct the grid for corresponding to level $\alpha$.

iii ii i Construct the deformation patch data matrix $Def^{\alpha}_{i,j,k}(s)$.

iii iii Apply PCA to $Def^{\alpha}_{i,j,k}(s)$ to compute $U^{\alpha}_{i,j,k}$ and $S^{\alpha}_{i,j,k}$.

iii iv Set $\alpha = \alpha + 1$
iii.v Repeat at the next level.

Testing for abnormal local spatial shape of an unseen test image $I_t$:

i Register $I_t$ to $I_\mu$ to compute the deformation field $Def(t)$.

ii Apply the same patch decomposition.

iii Set $\alpha = 1$

iv For each patch $(i, j, k)$ at $\alpha$ level

v v.i Project $Def_{i,j,k}^\alpha(t)$ onto the corresponding PCA space to compute lower dimensional coefficients $c$ with:

\[
c = U_{i,j,k}^\alpha T (Def(t) - \overline{Def}_{i,j,k}^\alpha)
\]

v.ii Check if the coefficients $c$ are within tolerable limits based on the variance described by $S_{i,j,k}^\alpha$.

v.iii If more than three standard deviations apart, flag the region.

vi Set $\alpha = \alpha + 1$ and repeat at the next level.

11.2 Local Variability of Diffusion Tensors

The variability modeling and abnormal behavior detection of Section 11.1.1.1 only deals with shape properties. However, if unexpected local tensor field variations exist in data that do not affect the elastic registration outcome, the detection and modeling of these abnormal regions might not be possible. Additionally, the regular grid structure employed in Section 11.1.1.1 might not be suitable because homogeneity assumption on tensor distributions...
can not be made. In this section, I will provide a framework to detect any local deviation from normal tensor field behavior of healthy subject DTI data. To accomplish this goal, the distributions of the second order diffusion tensors will modeled with a Gaussian distribution as proposed in [11] and a distribution similarity metric, specifically the KL metric, will be employed to compare training ROI regions and test ROI regions.

### 11.2.1 Diffusion Tensor Distributions

In Section 8.1 I utilized the fact that a diffusion tensor can be considered as a random variable describing an uncertainty in the estimation process, to guide an elastic registration. Similarly, the distributions of diffusion tensors can also be estimated within a region of interest. In [10] and [11] Basser and Pajevic showed that the distributions of the diffusion tensors can be modeled with a Gaussian distribution with either a fourth order covariance matrix or its corresponding second order counterpart. In a homogeneous region, the probability density function of a second order diffusion tensor can be expressed as:

\[
p(\mathbf{D}) = \sqrt{\frac{|\Sigma|^{-1}}{8\pi^6}} e^{-\frac{1}{2}(\mathbf{D}-\overline{\mathbf{D}}):\Sigma^{-1}(\mathbf{D}-\overline{\mathbf{D}})}
\]  

(11.2.1)

where \(\overline{\mathbf{D}}\) is the mean tensor, \(\Sigma\) is a fourth order covariance tensor, \((\mathbf{D} - \overline{\mathbf{D}}):\Sigma^{-1}(\mathbf{D} - \overline{\mathbf{D}})\) is a scalar contraction of the inverse of the three dimensional fourth order covariance tensor \(\Sigma\) and the three dimensional second order tensor \((\mathbf{D} - \overline{\mathbf{D}})\).

Due to the symmetry constraints \(\Sigma\) has 21 independent components just as a 6-dimensional symmetric second order covariance matrix would. In fact a diffusion tensor can be vectorized with:
\[
\tilde{D} = (D_{xx}, D_{yy}, D_{zz}, \sqrt{2}D_{xy}, \sqrt{2}D_{xz}, \sqrt{2}D_{yz})^T
\]  

(11.2.2)

and the fourth order covariance tensor can be converted to a matrix with:

\[
S = \begin{pmatrix}
\Sigma_{xxxx} & \Sigma_{xxyy} & \Sigma_{xxzz} & \sqrt{2}\Sigma_{xxyy} & \sqrt{2}\Sigma_{xxzz} & \sqrt{2}\Sigma_{xyyz} \\
\Sigma_{xxyy} & \Sigma_{yyyy} & \Sigma_{yyzz} & \sqrt{2}\Sigma_{yyxy} & \sqrt{2}\Sigma_{yyxz} & \sqrt{2}\Sigma_{yyyy} \\
\Sigma_{xxzz} & \Sigma_{yyzz} & \Sigma_{zzzz} & \sqrt{2}\Sigma_{zzxy} & \sqrt{2}\Sigma_{zzxz} & \sqrt{2}\Sigma_{zzyz} \\
\sqrt{2}\Sigma_{xxyy} & \sqrt{2}\Sigma_{yyxy} & \sqrt{2}\Sigma_{zzxy} & 2\Sigma_{xyxy} & 2\Sigma_{xyxz} & 2\Sigma_{xyyz} \\
\sqrt{2}\Sigma_{xxzz} & \sqrt{2}\Sigma_{yyzz} & \sqrt{2}\Sigma_{zzxz} & 2\Sigma_{xyzx} & 2\Sigma_{xxyz} & 2\Sigma_{xyzz} \\
\sqrt{2}\Sigma_{xxyy} & \sqrt{2}\Sigma_{yyyz} & \sqrt{2}\Sigma_{zzyz} & 2\Sigma_{xyyz} & 2\Sigma_{xxyz} & 2\Sigma_{xyzz}
\end{pmatrix}
\]  

(11.2.3)

The pairs \((D, \Sigma)\) and \((\tilde{D}, S)\) are analogous can be interchanged for computational and analysis purposes.

As proposed in [11], spectral decomposition with PCA can be utilized to analyze variability within a region similar to the methods of Section 11.1.1.1. However, in this section, a different strategy for abnormality detection will be followed.

### 11.2.2 Spatial Grids and ROIs

In order to perform statistical tests on tensor distributions, regions where the tensors are distributed primarily with a single distribution have to be identified first in order to avoid mixture modeling. This can be achieved with a segmentation based approach as I proposed in [46], or an atlas-based approach can be followed. For this purpose, the "International
Consortium for Brain Mapping” (ICBM) white matter atlas was employed. The label map itself and its overlayed version on a $T2_w$ image are displayed in Figure 11.5.

The atlas contains 48 white matter labels. To realize the use of these regions in variability training, the diffusion tensor image corresponding to the atlas was first elastically registered to the mean tensor image frequently used for this document. The deformation field obtained from this registration was subsequently applied to the atlas label map to have it aligned with the mean image, therefore with all the images in the training set.

To test the distributions on a new unseen image, the image is first registered to the mean image’s space again. Assuming registration errors are minimal, the ROI should correspond to the anatomical structures of the new image. To eliminate the outliers at the ROI interface,
the ROI was fed to a morphological erosion operator and the remaining voxels were used to build the distributions.

11.2.3 Training and Testing

The gender data described in Section 10.3.2 was used to build the distributions. Fifteen of the forty subjects were used for training, i.e. computing the mean and covariance tensors for each ROI and twenty five subject’s data were used for validation. The validation phase consisted of computing the symmetric version of the KL divergence of each of the validation subject with respect to the pre-learnt distributions. Figures 11.6 – 11.9 display the KL metrics for each ROI with a fitted 1D normal distribution to indicate their probability densities.

These plots in 11.6 give an insight on the expected variability within each selected white matter region. Even though outliers exist, such as the single data point in left cingulum bundle, most distributions can be represented with a Gaussian distribution. Although this is not a typical use of KL metric, it gives valuable information on tensor distribution similarities. An abnormal local behavior arising from the presence of a multiple sclerosis lesion, a tumor, or a trauma would cause the local distributions to deviate and the KL metric would fall outside the tolerable range [46].
Figure 11.6: The distributions of KL metrics for each ROI. Part 1. The star symbols indicate the actual KL values on the $x$ axis. For visual clarity, these values are not displayed on the zero line but instead are slightly elevated. These distributions can be used to discriminate healthy regions from abnormal ones.
Figure 11.7: The distributions of KL metrics for each ROI. Part 2.
Figure 11.8: The distributions of KL metrics for each ROI. Part 3.
Figure 11.9: The distributions of KL metrics for each ROI. Part 4.
PART IV

Conclusions
CHAPTER 12

EPILOGUE

In this thesis I have attempted to address the pressing need for solutions to the problem of studying the structural variability of human brain using diffusion tensor imaging (DTI) while dealing with the unsolved challenges involved that introduce additional sources of uncertainty. In pursuit of this, the first part of the problem was to either comprehend or eliminate these artifactual sources of uncertainty inherently present in diffusion data.

The first part of this document focused on giving the background information and described the different challenges involved in diffusion weighted image processing. These challenges included the distortions arising from the image acquisition processes and additional artifacts introduced during the processing steps.

Part II presented my analysis approaches and solutions to the challenges described in the background section. One of the pressing problem analyzed in this Section was the echo-planar imaging (EPI) related distortions that included the susceptibility and concomitant field distortions. This is a challenging problem in the diffusion community that is frequently disregarded in diffusion processing pipelines. In the community, several efforts on the effects of such distortions on the tensor-derived scalar maps had been proposed. In
my analysis approach, I first focused on the effects of these distortions on vector-valued data, namely fiber tractography. The analysis procedure uncovered that depending on the direction of the phase-encoding direction and depending on the fiber bundles of interest, these distortions and their corrections can have a profound effect on the analysis outcomes. The main findings of this analysis was that the image scanning protocol and the processing steps have to be designed based on a target of interest. If for example, the fiber bundles of interest are superior or inferior cerebellar peduncles, the direction of the phase encoding or the application of an EPI correction step does not matter as much as the case where cortico-spinal tracts or cingulum bundles are of interest. In the latter, phase encoding direction plays a crucial role on the spatial distribution and consistency of the tracts and I have shown that the application of even a simple registration based correction scheme improves the results considerably.

My analysis on EPI distortions indicated to us that no correction algorithm is perfect. Fieldmapping based correction schemes suffer from the inaccurate estimation of the homogeneity maps especially around the interfaces. Additionally, they require either an explicit pulse sequence to compute the fieldmaps or two additional scans with different echo times, with measured dwell times. Elastic registration based methods require a large degree of freedom for the transformation parameters to model the extent of possible distortions. This leads to local extremas in the optimization procedure and can introduce additional synthetic distortions to the data. In the second part of the distortion chapter, I proposed a simple but novel elastic registration based EPI distortion correction scheme that combines the strengths of fieldmapping and registration approaches. The methodology relied on an initial estimate of a fieldmap from an undistorted structural image, which was subsequently
utilized to estimate the complexities and magnitudes of local distortions. With such an estimate of where large or small distortions are expected, the registration parameter space was distributed accordingly. This approach was then able to model large local distortions where needed with a much less parameter space to avoid local extremas and the results showed that it performs faster and more robustly than other registration based techniques, which are known to surpass the fieldmap approaches [122]. A future version of the proposed correction methodology will also consider the signal convolution besides the geometric distortions by estimating the point spread function causing the distortions and utilizing this estimate to deconvolve the data.

EPI distortions were one type of artifactual source in diffusion processing. They originate during the image acquisition process. However, processing of diffusion data for correction can actually introduce unexpected sources of artifacts as well. These artifacts are caused by the interpolation methodologies used during the correction steps and interpolation has not been considered as an artifact source in diffusion community to my knowledge except the work of Rohde et al. [98]. To analyze interpolation in the context of diffusion weighted image processing, a similar approach was followed: first, the effects of traditional convolution based interpolation on the outcomes were analyzed to determine if the selection of interpolation kernel can affect the tensor statistics. In the analysis, three kernels were tested: nearest neighbor, linear and tricubic. All these kernels resulted in statistically significant differences in tensor derived scalar map distributions such as fractional anisotropy (FA) and apparent diffusion coefficients (ADC), which prompted us for a need for an interpolation scheme specialized for diffusion weighted image processing.
Diffusion is a physical process. In more complex models than DTI, the distributions of individual water molecules can be modeled to determine the resulting signal decay. However, diffusion weighted image correction steps, a signal processing based philosophy is generally followed, which might not provide the special needs involved in this context. For this reason, I aimed to propose an interpolation methodology, which is physically based to counter the artifacts originating from kernel based methods. The proposed interpolation scheme involved the use of partial differential equations (PDEs) instead of kernels to minimize the partial volume effects magnified with traditional kernels. The Gaussian convolution assumption underlying the PDE iterations was further exploited to provide a method that is also band-limited in the signal domain. Results indicated that such an interpolation scheme can greatly improve the diffusion weighted image quality after processing, while the drawback being the extreme computational complexity relative to the kernel-based methods.

While the artifacts both from the acquisition and processing introduce additional uncertainty to diffusion data, their effects might be relatively smaller if data from different images are not perfectly aligned, for a population or longitudinal study. Therefore, once foundations to eliminate the undesired sources of variations were built, my next objective was to provide a robust tensor image alignment methodology, which not only considered the tensor data itself but their uncertainty as well. My first proposed methodology for tensor image registration included the uncertainty information from the tensor estimation itself using error propagation methods and considered the diffusion tensors not as single points in the space of symmetric $3 \times 3$ positive-definite tensors, $\text{Sym}_3$, but random variables having a Gaussian distribution in $\text{Sym}_3$. This distributions were functions of several factors
including the image noise, the experimental design and the tissue types and therefore provided a robust way to register data acquired from different sites. The tensor dissimilarity metric computed the divergence in between tensor distributions to provide a more robust framework.

Tensor image registration is generally a computationally expensive process, as was the case with my first proposed method. The second approach to the problem was based on metric manifold unfolding. Given any tensor dissimilarity metric, a methodology to unwarp the space defined by the metric was proposed in such a way that statistical computations on registration properties could be performed as if the space was Euclidean. This approach can be employed to fasten tensor image registration or for easier statistical computations on tensor features.

Based on the two proposed registration approaches, one of my future objectives is to assess the applicability of these schemes onto more complex diffusion models such as HARDI or DSI. Due to expensive requirements of such modalities, the uncertainty information obtained from the model estimation processes can play a crucial role in the performances of registration algorithms and the proposed methods can significantly improve the outcome quality.

Part III of this document provided a framework for variability analysis. Once the additional sources of artifacts were eliminated and the data were aligned, it is possible to perform robust analysis with DTI data. My first approach was to apply the principal components analysis dimensionality reduction method to capture the global tensor variations present in the data. This relatively simple approach yields a picture of regions of large and small variabilities within a population. Several regions, including low brain stem and corpus
callosum were determined to be the largest varying white matter regions of the human brain.

Capturing the global tensor variability from a population can provide useful information in cases. However, a more interesting question is the variability with respect to a parameter of change, i.e. how a parameter such as age, gender, disease stage affect the variability. To accomplish this analysis, a multi-linear higher order singular value decomposition (HoSVD) based model was proposed, which served to delineate the parameters of interest. This model was test with two experiments: to model the EPI distortions and to analyze the gender effects.

As stated before frequently in this document, in order to perform a robust DTI analysis, one has to either eliminate or understand external uncertainty sources. The first experiment included the effects of EPI distortions in the model in case their corrections are not possible in practical scenarios. This experiment mostly focused on the visual aspects of the model and provided artificially generated images from the model to point out the effects. My second experiment aimed to discover the differences in the human brain due to gender differences. The outcomes obtained with the same model could not find any statistically significant differences between the male and female brain even though it could point out some local differences especially on cortical regions. The last framework for variability analysis focused on local variations. A spatial model to account for shape differences and an ROI based tensor distribution model to detect abnormalities were provided.

A missing ingredient in the variability analysis is for longitudinal models. Such models could explain the variability due to a continuous variable such as age or disease stage instead of a discrete variable, such as gender or distortion direction (RL/AP) or correction
application (on/off). These models, which are generally based on some form of regression analysis should consider not only the ROIs themselves but the relationships between different regions of the brain and how they effect another spatially distant but functionally or structurally connected region. Unfortunately, such a study could not have been performed due to the unavailability of longitudinal DTI data densely sampled over the time dimension.
REFERENCES


