

From Diffusion MRI to Brain Connectomics

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³¹ Chapter 1 ³² From Diffusion MRI to Brain Connectomics

33 Aurobrata Ghosh and Rachid Deriche

commentaire # 1
 commentaire # 2
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34 35

Abstract Diffusion MRI (dMRI) is a unique modality of MRI which allows one to indirectly examine the 36 microstructure and integrity of the cerebral white matter in vivo and non-invasively. Its success lies in 37 its capacity to reconstruct the axonal connectivity of the neurons, albeit at a coarser resolution, without 38 having to operate on the patient, which can cause radical alterations to the patient's cognition. Thus dMRI 39 is beginning to assume a central role in studying and diagnosing important pathologies of the cerebral 40 white matter, such as Alzheimer's and Parkinson's diseases, as well as in studying its physical structure 41 in vivo. In this chapter we present an overview of the mathematical tools that form the framework of 42 dMRI – from modelling the MRI signal and measuring diffusion properties, to reconstructing the axonal 43 connectivity of the cerebral white matter, i.e., from Diffusion Weighted Images (DWIs) to the human 44 connectome. 45

46 1.1 Introduction

The main objective of this chapter is to present some mathematical models and computational tools for 47 analyzing and modeling the complex central nervous system's (brain and spinal cord) neural connectivity. 48 These models and tools will help to better understand the white matter architecture of the human *central* 49 *nervous system* (CNS) and in a long term, will also help in addressing important and challenging clinical 50 and neuroscience questions. Indeed, due to our aging society, diseases like Alzheimer's, Parkinson's disease 51 (PD) and depression will affect a large population. These examples of CNS diseases as well as others, 52 like multiple sclerosis have characteristic abnormalities in the microstructure of brain's tissues such as its 53 white matter, which are not apparent and cannot be revealed reliably by standard imaging techniques. 54 Diffusion Magnetic Resonance Imaging (dMRI), a recent imaging modality based on the measurement 55 of the random thermal movement (diffusion) of water molecules within samples, can make visible these 56 co-lateral damages to the fibers of the CNS white matter that connect different brain regions. This is 57 why in this chapter, dMRI is the major anatomical imaging modality that will be considered to recover 58 the neural connectivity in the CNS. 59

We begin this chapter by presenting the CNS, in particular the brain, before delving into the mathematical framework for dMRI. Section 1.1 is dedicated to a perusal of its general structure and organization, the tissues constituting it, and in highlight, the brain's major neuronal pathways interconnecting its various regions. It aims to provide a context for understanding the general physical problem dMRI attempts to solve.

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65 1.1.1 The Central Nervous System

The human nervous system can be divided into the CNS, which consists of the brain and spinal cord and the *peripheral nervous system* (PNS) which consists of the cranial and spinal nerves and their ganglia.

The CNS is the largest part of the nervous system and is composed of the spinal cord and the brain which comprises a lower part, the brainstem, and an upper part, the prosencephalon or forebrain composed of two main units. One is known as the diencephalon. It is located in the midline of the brain and contains the thalamus and the hypothalamus. The other is called the telencephalon or cerebrum and holds the lateral ventricles, the basal ganglia and the cerebral cortex. The brainstem is also composed of two units: the mesencephalon or midbrain and the rhombencephalon or hindbrain which connects the forebrain and midbrain to the spinal cord.

The nervous system is made of about 100 billion nerve cells, or neurons, able to generate and propagate 75 electrical signals to process and transmit neural information. Neurons can receive electrical stimulation 76 from other neurons on their soma, through their multiple dentrities. They can integrate this information 77 and propagate it to more or less distant locations of the cerebrum by an extension called an axon. Nerve 78 signal communication is performed at specialized loci called synapses. Each neuron has on average 1000 79 synaptic connections with other neurons. This yields about 100 trillion connections within a human brain. 80 All these synapses result in an impressively dense and complex network between functional areas, which 81 can be understood as aggregates of nerve cells' soma and dendrites. They are essentially located in the 82 grey matter while the underlying wiring constitutes the white matter. According to the connectionist 83 point of view, the human brain is organized into distinct processing regions interconnected by a network 84 of anatomical relays. Processing units handle the execution of primary cognitive functions, and higher 85 cognitive tasks arise from a global coordination between these processing units. Neural signal is processed 86 in the cerebral cortex and transmitted to various regions of the brain through the white matter. So we 87 distinguish: 88

- The *grey matter* essentially forms the outer part of the cerebrum, some nuclei within the brain, as well as the deeper part of the spinal cord. It is made of neurons and their unmyelinated fibers. The cerebral cortex is the most important structure of the grey matter and plays a major role in various functions such as memory, attention and language.
- White matter is composed of axonal nerve fibers, covered by a myelin sheath giving its distinctive colour in MRI. It is found in the inner layer of the cortex, the optic nerves, the central and lower areas of the brain and surrounding the central shaft of grey matter in the spinal cord.

The CNS white matter axons can be distributed diffusely or concentrated in bundles, also referred to as tracts or fiber pathways. The brain's white matter pathways are generally categorized into commissural, association and projection fibers, depending on the areas they connect (see Fig. 1.1).

- The commissural tracts connect a region in one hemisphere to another region of the opposite hemi sphere.
- The association tracts connect various cortical areas within a given hemisphere.
- The *projection tracts* connect the cortex to deep brain regions such as the thalamus or the spinal cord.

In the spinal cord, it is the grey matter that is located in the center with a typical H-shaped appearance
 in transverse sections. It is surrounded by white matter which contains long ascending and descending
 pathways.

106 1.1.2 In Vivo CNS Connectivity

Compared to the understanding of neural circuitry in animals as cats or mice where the use of invasive 107 tracers is possible [59], the knowledge of the human brain organization is relatively poor. Therefore, 108 how to study the connectivity information about the CNS anatomy, in particular, about the cerebral 109 and spinal cord white matter? Anatomical MRI allows us to distinguish and classify grey matter and 110 white matter. However, with this contrast, white matter retains a homogeneous aspect, preventing any 111 observation of neural fibers and thus of neuronal connectivity. Cerebral and spinal dissection used to be 112 the only means of accessing the neural architecture [22, 30, 74]. Then, anatomists started using chemical 113 markers to do neuronography [55, 59]. More recently, neural fiber tractography based on local injection of 114

chemical markers and subsequent observation of the induced propagation yielded high-quality connectivity mapping in the cat and monkey cerebral cortices [75, 59].

The relatively recent development of dMRI, which uses the orientational preference of water molecules 117 in diffusing along the directions of the fibers has brought in the last twenty years great hopes for the 118 non-invasive exploration of the neural anatomy of the CNS. Indeed dMRI provides a non-invasive way 119 of estimating in vivo CNS fiber structures using the average random thermal movement (diffusion) of 120 water molecules as a probe. Diffusion MRI is a field of research with a history of roughly three decades. 121 It was introduced in the mid 80's by Le Bihan et al. [39], Merboldt et al. [43] and Taylor et al. [63]. As 122 of today, it is the unique non-invasive technique capable of describing the neural connectivity in vivo by 123 quantifying the anisotropic diffusion of water molecules in biological tissues. The great success of dMRI 124 comes from its ability to accurately describe the geometry of the underlying microstructure and to probe 125 the structure of the biological tissue at scales much smaller than the imaging resolution. 126

The diffusion of water molecules is Gaussian in an isotropic medium and under normal unhindered conditions, but in fibrous structure such as white matter, the diffusion is very often directionally biased or anisotropic and water molecules tend to diffuse along fibers. For example, a molecule inside the axon of a neuron has a low probability to cross a myelin membrane. Therefore the molecule will move principally along the axis of the neural fiber. Conversely if we know that molecules diffuse locally principally in one direction, we can infer that this corresponds to a set of fibers.

133 1.1.3 Organization of the Chapter:

Section 1.2 briefly covers the historical development of Nuclear Magnetic Resonance (NMR) and MRI to 134 set the stage. We explore the physics of the signal generation in NMR and how diffusion properties can be 135 measured non-invasively from NMR in Sect. 1.3. Section 1.3 begins by presenting the fundamental ideas 136 of NMR. Section 1.3.1 then presents the crucial spin echo experiment proposed by Hahn, which is a corner 137 stone experiment that led to the development of diffusion NMR. Next in Sect. 1.3.2 we describe diffusion 138 in considerable detail. Section 1.3.3 then presents the pulse-field-spin-echo (PGSE) experiment that was 139 proposed by Stejskal and Tanner. This important experiment is the modern and practical approach for 140 measuring diffusion from NMR. The Stejskal-Tanner model for the diffusion NMR signal is based on 141 Fick's laws of diffusion. Section 1.3.4 presents next the q-space approach for modelling the diffusion 142 NMR signal, which is based on Einstein's random walk approach to Brownian motion. 143

Section 1.4 is dedicated to dMRI reconstruction algorithms that allow to go beyond simply measuring intrinsic diffusion properties from NMR/MRI to inferring the microstructure of the underlying tissue noninvasively. Section 1.4.1 presents diffusion tensor imaging (DTI), the most widely used dMRI algorithm with the simplest experimental requirements, but with powerful applications. DTI is however limited under certain microstructure configurations. Section 1.4.2.1 presents diffusion spectrum imaging (DSI), which allows to overcome these limitations. Finally Sect. 1.4.2.2 presents Q-Ball imaging, which can recover complex microstructures like DSI, but isn't limited by the latter's lengthy acquisition schemes.



Fig. 1.1 Major white matter fiber pathways in the brain. (a) Commissural tracts – the Corpus Callosum (CC). (b) Association tracts – short "U"-fibers connecting neighbouring gyri, the Superior Longitudinal Fasciculus (SLF), the Cingulum and the Inferior Longitudinal Fasciculus (ILF). (c) Projection tracts – the Corona Radiata (CR) and the Corticospinal Tract (CST). Adapted from [74].

Section 1.5 introduces briefly the computational framework consisting of sophisticated mathematical tools that have been developed for processing dMRI data and images, since these represent complex mathematical objects. In particular we present various metrics for a field of diffusion tensors in Sect. 1.5.1, an algorithm that ensures that the estimated diffusion tensors are in the proper space of symmetric positive definite matrices using a Riemannian metric in Sect. 1.5.2, and a segmentation algorithm for segmenting fields or images of diffusion tensors in Sect. 1.5.3.

Section 1.6 is dedicated to tractography – algorithms that integrate local microstructure information to
 reconstruct white matter fiber pathways. Section 1.6.1 presents deterministic approaches while Sect. 1.6.2
 presents probabilistic approaches. The penultimate section – Sect. 1.7, is dedicated to applications. It
 presents the impacts of dMRI in both clinical and neuroscientific scenarios, and highlights its usefulness.
 The chapter concludes with a summary in Sect. 1.8. In Sect. 1.9 we provide an incomplete list of

¹⁶² important internet resources in terms of available softwares and database for processing dMRI data.

163 1.2 A Brief History of NMR and MRI

The scientific heritage of NMR and MRI is reflected in the list of Nobel laureates who contributed to 164 their developments. The theoretical underpinnings that made NMR possible were proposed in 1924 by 165 Wolfgang Pauli who suggested a new quantum degree of freedom that later came to be known as spin. He 166 formulated the mathematical theory by 1927, and was awarded the Nobel prize in physics in 1945 for his 167 contributions. The concept of spin implies that atomic nuclei bearing spins exhibit magnetic moments. 168 The fact that protons exhibit magnetic moments had already been discovered in 1922 by Otto Stern prior 169 to the concept of spin. Stern was awarded the Nobel prize in physics in 1943. Pauli's theory was verified 170 in 1938 by Isidor Rabi in molecular beams. From his experiments Rabi was able to both detect the effects 171 of spin and measure the gyromagnetic ratio that is the characteristic signature of an atomic nucleus due 172 to its spin. His experiments also established the concept and the technique of NMR for manipulating 173 spins. Rabi was awarded the Nobel prize in physics in 1944. 174

In 1946 Felix Bloch [12] and Edward Mills Purcell [56] independently extended the techniques estab-175 lished by Rabi. They successfully demonstrated the magnetic resonance effect in liquids and solids. Bloch 176 and Purcell shared the Nobel prize of 1952 in physics, and NMR was established. In his seminal paper 177 of 1950 [31] Erwin Hahn proposed the spin echo experiment, which used a combination of 90° and 180° 178 electromagnetic or radio frequency pulses to filter out effects of magnetic field inhomogeneities in the 179 measurement of the transverse signal. Further works of Herman Carr and Purcell in 1954 [14] led to the 180 full development of the radio frequency pulse technique introduced by Hahn. This formed the foundations 181 of NMR. 182

It must be noted at this point that both the papers of Hahn [31] and Carr & Purcell [14] critically point out the observed effects of diffusion of the spin bearing nuclei in magnetic resonance experiments with a succession of radio frequency pulses. Although these papers generally perceive the diffusion effect as an unfortunate phenomenon resulting in a loss of signal, Carr & Purcell [14] in fact demonstrate that diffusion can be directly measured from NMR and go on to actually measure the diffusion constant of water at 25°C. This forms the corner-stone of diffusion NMR.

Although NMR became a well established technique for studying various materials, it took almost 189 three decades since the experiments of Bloch and Purcell in 1946, for MRI to be invented. NMR by itself 190 is capable of examining a single spin ensemble or a tiny region of a sample, but it can't image the whole 191 sample to recreate a 2D slice or a 3D volumetric image necessary to study entire biological samples like 192 the human body. Paul Lauterbur in 1973 [37] proposed the use of magnetic gradient fields to spatially 193 encode the positions or voxel regions of the spin ensembles. This was a remarkable invention, which 194 made it possible to reconstruct entire slice or volumetric images from NMR data. Spatial encoding was 195 improved in terms of frequency encoding by Richard Ernst in 1978, and phase encoding by Bill Edelstein 196 in 1980 using pulsed gradients. In 1977 Peter Mansfield [42] developed the mathematical framework for 197 rapidly switching gradients for spatial encoding, greatly speeding up the process of reconstructing images 198 of an entire biological sample. This is known as echo planar imaging (EPI). Lauterbur and Mansfield 199 were jointly awarded the Nobel prize in medicine in 2003 for making MRI possible. Thus modern MRI 200 was developed from the phenomenon of NMR coupled with the method of spatial encoding. 201

²⁰² 1.3 Nuclear Magnetic Resonance & Diffusion

The principles of NMR are based on *spin*, a fundamental quantum characteristic possessed by electrons, 203 protons, and neutrons, like electrical charge and mass. Spins come in multiples of 1/2 and can be positive 204 or negative. In grouped particles, e.g. atomic nuclei, opposite spin-signs can pair up to eliminate the 205 total spin of the group. But the net spin of unpaired particles or atomic nuclei imparts a magnetic dipole 206 moment. In other words such particles or such atomic nuclei can be influenced by an external magnetic 207 field. In the presence of a strong magnetic field \mathbf{B}_0 with magnitude B_0 , the magnetic dipole moment 208 vector or the spin vector of the particle or nucleus aligns itself with ${\bf B_0}$ and precesses around it with 209 an angular frequency known as the Larmor frequency $\omega_0 = \gamma B_0$, where γ is the gyromagnetic ratio, 210 characteristic of the particle or the nucleus. The effect is detectable when it becomes pronounced in the 211 presence of an ample collection of spin bearing particles or nuclei with the same gyromagnetic ratio. 212 From a macroscopic perspective, when such a collection is subjected to a magnetic field, the randomly 213 oriented individual magnetic dipole moment vectors align themselves along $\mathbf{B}_{\mathbf{0}}$. Laws of thermodynamics 214 ensure that a greater number of spins point along the magnetic field (low energy configuration) than 215 opposite to it (high energy configuration). This forms a resultant ensemble magnetic dipole moment 216 vector \mathbf{M} . Conventionally the external magnetic field \mathbf{B}_0 is considered to be aligned with the Z-axis. The 217 XY-plane is then known as the transverse plane, and the net magnetization vector \mathbf{M} can be separated 218 into the longitudinal component \mathbf{M}_z , along the Z-axis (or \mathbf{B}_0), and the transverse component \mathbf{M}_{xy} , in 219 220 the transverse plane (Fig. 1.2).

Of particular interest is the hydrogen nucleus ${}^{1}H$, which is found abundantly in nature, accounting for 99.98% of all hydrogen atoms, and also constituting water. 60% of the human body and 78% of the brain is water. Therefore, ${}^{1}H$ is a natural spin bearing nucleus of choice for MRI. ${}^{1}H$ is an unpaired proton with a net spin of 1/2, and has a gyromagnetic ratio of $\gamma = 42.58$ MHz/T.

The NMR signal is generated by exposing the ensemble of spins precessing along B_0 to an oscillating 225 magnetic field or an electro-magnetic (radio-frequency: RF) pulse. This is known as the excitation phase. 226 The energy absorbed by the low energy configuration spins from this pulse tilts the magnetization vector 227 \mathbf{M} away from \mathbf{B}_0 towards the high energy configuration. The oscillation of the secondary magnetic 228 field ensures that the spins (and hence \mathbf{M}) continue to precess around \mathbf{B}_0 even tilted away from it – 229 along the surface of a cone (Fig. 1.2). Once the RF pulse is switched off, the spins begin to recover 230 their alignment with the main magnetic field \mathbf{B}_0 , and to return to their low energy configuration or the 231 thermal equilibrium. This is known as the relaxation phase. The signal is created as the spins precess 232 tilted away from \mathbf{B}_0 , and it decays as the spins relax, dissipating the absorbed energy. The longitudinal 233 relaxation and the transverse relaxation of \mathbf{M} are governed by different phenomena and are characterized 234 by different time signatures. 235

The *longitudinal relaxation* is known as the T1 relaxation since it is described using a time signature denoted T1. The T1 relaxation occurs as the spin ensemble radiates the energy it had absorbed from the RF pulse to the surrounding thermal reservoir or lattice and regains its thermal equilibrium with the lattice. Therefore, the T1 relaxation is also known as the *spin-lattice* relaxation. In this process the



Fig. 1.2 Nuclear Magnetic Resonance. (a) A net magnetization dipole moment vector \mathbf{M} forms when spins are exposed to an external magnetic field \mathbf{B}_0 . (b) The NMR signal is generated by exciting the ensemble of spins precessing along \mathbf{B}_0 by exposing them to a radio-frequency pulse – the magnetization vector \mathbf{M} spirals down to the transverse plane in the fixed frame of reference.

spins realign themselves with \mathbf{B}_0 . In terms of the net magnetization vector \mathbf{M} , this implies that the longitudinal component \mathbf{M}_z progressively regains its initial magnitude, while the transverse component \mathbf{M}_{xy} progressively becomes null again.

The transverse relaxation involves the phenomenon of the spins regaining their thermal equilibrium 243 amongst themselves, and is characterized by the time signature T2. Therefore it is also known as the 244 spin-spin relaxation or the T2 relaxation. In the transverse plane this is interpreted by the spins losing 245 their initial coherence. From an initial coherent transverse magnetization vector \mathbf{M}_{xy} , they progressively 246 dephase as they radiate the energy they had absorbed to neighbouring spins. Transverse relaxation is, 247 however, a complex phenomenon. Although theoretically \mathbf{B}_0 is supposed homogeneous, in reality minor 248 inhomogeneities exist. These inhomogeneities are relevant enough to also contribute to spins dephasing in 249 the transverse plane, though this is not a true relaxation. Transverse relaxation is therefore a combination 250 of spin-spin relaxation and field inhomogeneity dephasing. The pure spin-spin relaxation time is known 251 as T2. The combined transverse relaxation time is known as $T2^*$. 252

The *Bloch equations* are a coupled set of three differential equations that combine the effects of NMR and describe the evolution of the net magnetization vector **M** over time. These are macroscopic and phenomenological equations that include the effects of Larmor precession and T1 and T2 relaxations. They are written in the fixed frame of reference in terms of the relaxation time constants as:

$$\frac{d\mathbf{M}(t)}{dt} = \gamma \mathbf{M}(t) \times \mathbf{B}(t) + \begin{pmatrix} -\frac{1}{T_2} & 0 & 0\\ 0 & -\frac{1}{T_2} & 0\\ 0 & 0 & -\frac{1}{T_1} \end{pmatrix} \mathbf{M}(t) + \begin{pmatrix} 0\\ 0\\ \frac{M_0}{T_1} \end{pmatrix},$$
(1.1)

where $\mathbf{B}(t)$ is the total external magnetic field.

258 1.3.1 The Hahn Spin Echo Experiment

Erwin L Hahn was the first to notice the effects of diffusion when he conceived the *spin echo* experiment to remove the effects of field inhomogeneities or T2^{*} from the signal [31]. Diffusion NMR is derived from Hahn's original spin echo experiment of 1950. Hahn put forth the idea that following a 90° RF pulse that tilts the net magnetization vector to the transverse plane, the dephasing that follows caused by the field inhomogeneities, could be refocused using a second RF pulse of 180°, thus removing the effects of the field inhomogeneities.

After the 90° RF pulse, the spins precessing in the transverse plane should appear static in a frame of reference rotating at the Larmor frequency. However, due to field inhomogeneities, as the spins begin to



Fig. 1.3 The Hahn Spin Echo experiment. (a) Pulse sequence with Free Induction Decay & signal echo. Adapted from Wikipedia. (b) Concept of spin echo refocussing in the rotating frame of reference. (A) The net magnetization vector \mathbf{M} (green vector), initially aligned with the Z-axis under the influence of \mathbf{B}_0 . (B) 90° RF pulse tilts (orange arrow) \mathbf{M} on to the transverse plane. (C) & (D) Spins dephasing due to local field inhomogeneities. Slow spins fall back, while the fast spins move ahead in the transverse plane. (E) 180° RF pulse (orange arrow) flips the spins around such that now the slow spins are ahead and the fast spins are behind. (F) Refocussing begins as the fast spins begin to catch up the slow spins from behind. The echo begins to form. (G) The spins are completely refocussed. This is the centre of the echo and the signal is free of the effects of field inhomogeneities. Drawing by A.G. Filler, image source Wikipedia.

dephase, some would appear to speed up (or move ahead clockwise in the rotating frame of reference), 267 while some would slow down (or fall back anti-clockwise in the rotating frame of reference). This transverse 268 dephasing is known as the *free induction decay* (FID) and causes the signal to decay faster than pure T2 269 effects. However the application of a second RF pulse of 180° has the effect of flipping the individual spins 270 in the transverse plane such that the "slow" spins that had fallen behind the rotating frame of reference 271 are flipped ahead of it, while the "fast" spins that had moved ahead are flipped behind the rotating frame 272 of reference. Indeed, the 180° RF pulse causes the spins to refocus after a certain length of time as the 273 fast spins catch up with the slow spins, which regenerates the signal. This is known as the *echo* and it is 274 free of the $T2^*$ effects due to field inhomogeneities (Fig. 1.3). 275

It must be noted, however, that the echo regenerates the signal completely only under the assumption that none of the spins in the ensemble have moved. If they move then the 180° RF pulse doesn't completely invert the spin and this results again in signal decay. However, this is not due to field inhomogeneities. As noted by Hahn [31] and Carr & Purcell [14], this is due to the translational motion of diffusion. This forms the basis of diffusion NMR.

281 1.3.2 Diffusion

Diffusion NMR (dNMR) is a modality of NMR that is sensitive to the Brownian motion of the particles in a sample. The dNMR experiment can therefore be used to measure the diffusion properties of the underlying sample. This makes dNMR central to diffusion MRI. At the heart of dNMR is the diffusion process, and understanding diffusion helps to understand how it can be measured from NMR. It leads to the critical improvements that were made by Stejskal & Tanner to the original spin echo experiments of Hahn and Carr & Purcell that opened up the domain of dNMR.

Diffusion is a process of mass transport that describes the random spreading of molecules or particles 288 generally in the presence of a concentration gradient. The process of diffusion was observed, studied and 289 mathematically described over the entire 19th century. It was initially observed in three different forms, 290 namely heat diffusion in the presence of a temperature gradient, molecular diffusion in the presence of a 291 concentration gradient, and Brownian motion, which occurs even in the absence of any gradients. These, 292 apparently very different phenomena – the first, concerning the spreading of energy in a solid medium, 293 the second, concerning the spreading of molecules from a region of high concentration to a region of 294 low concentration in fluids, and the third, concerning the random motion of molecules and particles in 295 fluids due to the ambient temperature - can all be described by the same diffusion equation. However, 296 while today their correspondence is widely accepted, establishing this connection wasn't always an easily 297 demonstrable task. 298

Fick's Laws of Diffusion: The phenomenological equations of diffusion were proposed by Joseph Fourier in 1822 to describe the diffusion of heat in solids, and then adapted by Adolf Fick in 1855 to describe the diffusion of molecules in fluids in the presence of a concentration gradient [21]. Fick derived his "laws of diffusion" from Fourier's laws by analogy, while attempting to describe the experiments conducted by Thomas Graham in 1831 on the diffusion of gases. These laws describe the molecular transfer or diffusion that takes place in a system from regions of high concentration to regions of low concentration due to the concentration gradient.

Fick's first law relates the rate of transfer of the diffusing substance per unit area, or flux \mathbf{J} , to the concentration gradient \mathbf{C} causing the diffusion:

$$\mathbf{J} = -D\nabla\mathbf{C},\tag{1.2}$$

where D is the diffusion coefficient. Conservation of mass during the diffusion process implies $-\nabla \mathbf{J} = \frac{\partial \mathbf{C}}{\partial t}$. This leads to Fick's second law of diffusion:

$$\frac{\partial \mathbf{C}}{\partial t} = D\nabla^2 \mathbf{C}.$$
(1.3)

Fick's second law describes the change of the concentration field over time due to the diffusion process. Eq. (1.3), which relates the time derivative of the concentration to the second order spatial derivative of the concentration is known as the *diffusion equation* – it describes diffusion phenomenologically.

D being a scalar quantity in Eqs. (1.2 - 1.3) is an indication that diffusion is equal in all directions. This is known as *isotropic* diffusion. However, certain media such as crystals, textile fibers, etc. can be inherently anisotropic and can favour diffusion in a certain spatial direction while hindering it in others. This results in *anisotropic* diffusion, which is described by replacing the scalar diffusion coefficient D by

a generalized diffusion tensor **D** $(3 \times 3 \text{ matrix})$ in Fick's laws [21]:

$$\mathbf{J} = -\mathbf{D}\nabla\mathbf{C},\tag{1.4}$$

$$\frac{\partial \mathbf{C}}{\partial t} = \nabla \cdot (\mathbf{D} \nabla \mathbf{C}). \tag{1.5}$$

Diagonalizing the diffusion tensor **D** into its eigenvalues and eigenvectors provides a local orthogonal coordinate system that indicates the preferential diffusion direction favoured by the anisotropy of the underlying material. This is the budding idea that indicates that diffusion can be considered as a probe of the underlying medium's microstructure. Isotropic diffusion can be understood as a special case of anisotropic diffusion when $\mathbf{D} = D\mathbf{I}$, where \mathbf{I} is the identity matrix. The idea of the diffusion tensor is central to dMRI, since the fibrous quality of the cerebral white matter also exhibits directional anisotropy.

Brownian Motion & Einstein's Random Walk Approach: Although Fick's laws are concerned 324 with the diffusion of molecules from regions of high concentration to regions of low concentration, they 325 essentially describe the evolution of the concentration gradient over time and space, and aren't concerned 326 with the movements of the molecules themselves. The molecular description of diffusion emerged with 327 Albert Einstein in 1905 when he related the molecular-kinetic theory of heat to the observations made 328 by Robert Brown in 1828. Brown had noted the perpetual erratic motion of pollen grains suspended 329 in water while observing them under a microscope. This erratic movement came to be known by his 330 name as Brownian motion. When Einstein proposed [28] that due to the thermal kinetic energy of 331 molecules, particles suspended in a liquid large enough to be observed under a microscope would exhibit 332 random movements governed by the probabilistic law he derived, his idea was quickly recognized to be 333 the theoretical description of Brownian motion. It turned out that the probabilistic law of Brownian 334 motion derived by Einstein also satisfied the diffusion equation. This provided the final link and showed 335 that diffusion was driven by the thermal kinetic energy of molecules due to the ambient temperature, 336 implying that diffusion, in the form of Brownian motion also occurred in the absence of a temperature or 337 a concentration gradient. The special case of diffusion when the suspended particles belong to the liquid 338 is known as *self diffusion*. 339

To describe the erratic movement of a large number of particles undergoing Brownian motion, Einstein adopted the probabilistic approach of a random walk model [28]. He modelled diffusion using two Probability Density Functions (PDF)s – $f(\mathbf{x}, t)$, the probability of finding a particle at the position \mathbf{x} at a time t, and $P(\Delta \mathbf{x}, \Delta t)$, the transition probability or the probability of finding a particle at a distance $\Delta \mathbf{x}$ from its initial position after a time Δt . Considering $P(\Delta \mathbf{x}, \Delta t)$ symmetric, such that $P(\Delta \mathbf{x}, \Delta t) = P(-\Delta \mathbf{x}, \Delta t)$, Einstein proposed the relation between $f(\mathbf{x}, t)$ and $P(\Delta \mathbf{x}, \Delta t)$:

$$f(\mathbf{x}, t + \Delta t) = \int_{-\infty}^{\infty} f(\mathbf{x} - \Delta \mathbf{x}, t) P(\Delta \mathbf{x}, \Delta t) d\Delta \mathbf{x}.$$
 (1.6)

He then showed that $f(\mathbf{x}, t)$, which can also be considered as the local particle concentration, satisfies the diffusion equation:

$$\frac{\partial f(\mathbf{x},t)}{\partial t} = D\nabla^2 f(\mathbf{x},t),\tag{1.7}$$

which introduces the diffusion coefficient D, showing that the random walk approach can model diffusion. In the isotropic case discussed by Einstein, he further showed that the diffusion coefficient is directly proportional to the variance of the particle displacement $\langle (\Delta x)^2 \rangle = 2\Delta t D$, where without loss of generality x is any chosen spatial direction. A similar development in the anisotropic case along the lines proposed by Einstein results in the anisotropic diffusion equation and connects the diffusion tensor to the covariance tensor:

$$\frac{\partial f(\mathbf{x},t)}{\partial t} = \nabla \cdot (\mathbf{D} \nabla f(\mathbf{x},t)), \tag{1.8}$$

$$\mathbf{D} := \frac{1}{2\Delta t} \begin{pmatrix} \langle (\Delta x)^2 \rangle & \langle \Delta x \Delta y \rangle & \langle \Delta x \Delta z \rangle \\ \langle \Delta y \Delta x \rangle & \langle (\Delta y)^2 \rangle & \langle \Delta y \Delta z \rangle \\ \langle \Delta z \Delta x \rangle & \langle \Delta z \Delta y \rangle & \langle (\Delta z)^2 \rangle \end{pmatrix}.$$
(1.9)

Finally Einstein also derived that under the initial condition $f(\mathbf{x}, 0) = \delta(\mathbf{x})$, which corresponds to free

diffusion, the local particle concentration $f(\mathbf{x},t)$ is a Gaussian function with the derived variance 2tD.

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This, however, implies that the Green's function of the diffusion equation, or the transition probability is also a Gaussian in the case of free diffusion:

$$P(\Delta \mathbf{x}, \Delta t) = \frac{1}{(4\pi\Delta t)^{3/2} |\mathbf{D}|^{1/2}} \exp\left(-\frac{\Delta \mathbf{x}^T \mathbf{D}^{-1} \Delta \mathbf{x}}{4\Delta t}\right).$$
(1.10)

³⁵⁸ In the anisotropic case it is an oriented Gaussian parameterized by the covariance tensor.

³⁵⁹ 1.3.3 The Stejskal-Tanner PGSE Experiment

After Hahn who first noticed the effects of diffusion in NMR in his spin echo experiment [31], Carr & Purcell measured the diffusion coefficient for the first time from NMR. In their modification to Hahn's experiment they employed a temporally constant magnetic gradient field and modelled the diffusion of spin bearing particles with discrete jumps [14]. However, the continuous description was formulated by Torrey in 1956. He modified the phenomenological Bloch equations by adding to it Fick's diffusion equation (Eq. 1.3) [64]. This came to be known as the Bloch-Torrey equation for describing the net magnetization vector **M** (without flow):

$$\frac{\partial \mathbf{M}}{\partial t} = \gamma \mathbf{M} \times \mathbf{B} + \begin{pmatrix} -\frac{1}{T_2} & 0 & 0\\ 0 & -\frac{1}{T_2} & 0\\ 0 & 0 & -\frac{1}{T_1} \end{pmatrix} \mathbf{M} + \begin{pmatrix} 0\\ 0\\ \frac{M_0}{T_1} \end{pmatrix} + D\nabla^2 \mathbf{M}, \tag{1.11}$$

³⁶⁷ where Fick's law is employed to describe the self diffusion of the net magnetization.

About a decade later, in 1965, Stejskal & Tanner designed the *pulsed gradient spin echo* (PGSE) experiment by modifying Hahn's spin echo experiment with two identical magnetic gradients around the 180° RF pulse to encode the transverse phase of the diffusing spin bearing particles [62, 61] (Fig. 1.4). This made it easier to measure the decay in the transverse signal due to diffusion, and from there the diffusion coefficient. The PGSE experiment established the field of dNMR.

In the PGSE experiment the first gradient **G** of duration δ spatially encodes the phase of the individual 373 spins (by dephasing them by an amount dependent on their position), and the effects of this gradient are 374 undone by the second identical gradient after the 180° RF pulse which flips the spins around (implying 375 an effect $-\mathbf{G}$ from the second gradient). This results in a complete recovery of the signal since the 376 magnitude of transverse magnetization vector \mathbf{M}_{xy} depends on the phase coherence of the individual 377 spins. However, if the individual spins move due to diffusion during the period Δ , between the two pulsed 378 gradients, then the effects of the second gradient isn't the exact opposite of the first gradient (-G)379 that was used to encode their phases. This leads to a partial phase incoherence – resulting in a reduced 380 transverse magnetization \mathbf{M}_{xy} , implying a loss in the spin echo signal. Since the signal decay is related to 381 the rate of diffusion or the diffusion coefficient, measuring the signal decay makes it possible to measure 382 the diffusion coefficient. 383



Fig. 1.4 The pulsed gradient spin echo (PGSE) sequence. Two identical gradients are applied around the 180° RF pulse of Hahn's spin echo experiment. This encodes the transverse phase of the diffusing spin bearing particles. It then becomes easier to measure the decay of the signal due to diffusion.

Stejskal and Tanner provided the mathematical solution to the Bloch-Torrey differential equation for their PGSE experiment, which became the corner stone equation for dNMR as the Stejskal-Tanner

³⁸⁶ equation for the signal:

$$S = S_0 \exp\left(-\gamma^2 \delta^2 g^2 \left(\Delta - \frac{\delta}{3}\right) D\right) = S_0 \exp\left(-bD\right), \qquad (1.12)$$

where S is the magnitude of the signal decay due to diffusion, S_0 is the magnitude of the signal in the absence of a diffusion encoding gradient, Δ is the time between the two gradients, δ is the application time of each gradient, and $b = \gamma^2 \delta^2 g^2 \left(\Delta - \frac{\delta}{3}\right)$ is the b-value. The modifications introduced by Stejskal and Tanner in the PGSE experiment, therefore, makes it possible to measure the diffusion coefficient Da regular spin-echo experiment in NMR.

In the same year, Stejskal further considered diffusion in anisotropic media by employing the anisotropic Fick's law (Eq. 1.5) instead of the isotropic law (Eq. 1.3), in the Bloch-Torrey equation, which introduces the diffusion tensor **D** [61]. He was able to derive the modified Stejskal-Tanner equation incorporating the diffusion tensor in anisotropic media [61]:

$$S = S_0 \exp\left(-\gamma^2 \delta^2 g^2 \left(\Delta - \frac{\delta}{3}\right) \mathbf{g}^T \mathbf{D} \mathbf{g}\right) = S_0 \exp\left(-b \mathbf{g}^T \mathbf{D} \mathbf{g}\right).$$
(1.13)

³⁹⁶ However, Stejskal in this seminal paper fell short of providing a method for measuring the diffusion tensor

³⁹⁷ from NMR, which could have preempted diffusion tensor imaging by almost three decades. But he did

 $_{\tt 398}$ $\,$ lay the foundations of the q-space formalism with the "pulsed" gradient assumption.

³⁹⁹ 1.3.4 Narrow Gradient Pulse PGSE: q-space Formalism

Diffusion in the PGSE experiment can also be modelled from a probabilistic or random-walk model 400 driven by the thermal kinetic energy of the spin bearing particles. The PGSE experiment (Fig. 1.4) 401 spatially encodes or labels the transverse phase of the spins using the first gradient, which results in a 402 deliberate dephasing of the transverse magnetization. The purpose of the second gradient after the 180° 403 RF pulse is to undo the effects of the first gradient and rephase the transverse magnetization. However, if 404 the spins diffuse away from their position between the two gradients, then the transverse magnetization 405 isn't entirely rephased after the second gradient, resulting in a loss of the transverse signal. This can be 406 described by using a random-walk approach for the spin bearing particles. 407

⁴⁰⁸ Under the assumption $\delta \ll \Delta$, which is known as the *narrow gradient pulse* (NGP) condition, which ⁴⁰⁹ implies that the spins are static during the application of the diffusion encoding gradients $\mathbf{G}(t)$, the ⁴¹⁰ dephasing accrued by a spin in the initial position \mathbf{r}_0 during the first gradient is [44] $\phi_1 = \gamma \int_0^{\delta} \mathbf{G}(t) \cdot \mathbf{r}_0 dt =$ ⁴¹¹ $\gamma \delta \mathbf{G} \cdot \mathbf{r}_0$, when $\mathbf{G}(t) = \mathbf{G} = g\mathbf{g}$. Similarly the dephasing accrued by the spin, now in the position \mathbf{r} due ⁴¹² to diffusion, during the second gradient is $\phi_2 = \gamma \int_{\Delta}^{\Delta+\delta} \mathbf{G}(t) \cdot \mathbf{r} dt = \gamma \delta \mathbf{G} \cdot \mathbf{r}$. Since the second gradient ⁴¹³ is applied after the 180° RF pulse, which flips the spins around, the net phase shift accrued by a spin is ⁴¹⁴ $\phi = \phi_2 - \phi_1 = \gamma \delta \mathbf{G} \cdot (\mathbf{r} - \mathbf{r}_0)$. Of course, if the spins hadn't diffused and had remained static during the ⁴¹⁵ period Δ (between the gradients), then the net phase shift would have cancelled out. In other words the ⁴¹⁶ amount of net phase shift is proportional to the diffused distance $(\mathbf{r} - \mathbf{r}_0)$.

⁴¹⁷ The NGP condition $\delta \ll \Delta$ can also be interpreted in the way Stejskal proposed it $\delta \to 0$, with $\delta \mathbf{G}$ ⁴¹⁸ finite. Although in practice the NGP condition can never be achieved, it provides a powerful insight into ⁴¹⁹ the process of measuring diffusion from NMR.

The complex signal generated by individual spins with a net phase shift ϕ is $\exp(i\phi) = \exp[i\gamma\delta\mathbf{G}\cdot(\mathbf{r}-\mathbf{r}_0)]$ [13, 44]. However, the spin echo signal $E(\mathbf{G}, \Delta)$ is the averaged net signal from the spin ensemble, or it is the expected value of the complex signal given the probability of spins starting at \mathbf{r}_0 and diffusing to \mathbf{r} in the time Δ . This probability is the product of the probabilities $f(\mathbf{r}_0, 0)$, of finding a spin initially at \mathbf{r}_0 , and $P(\mathbf{r}|\mathbf{r}_0, \Delta)$, of a single spin starting at \mathbf{r}_0 and diffusing to \mathbf{r} in time Δ . The product $f(\mathbf{r}_0, 0)P(\mathbf{r}|\mathbf{r}_0, \Delta)$ introduces the random-walk model for the spin bearing particles diffusing from \mathbf{r}_0 to \mathbf{r} , and [13]:

$$E(\mathbf{G}, \Delta) = \int f(\mathbf{r}_0, 0) \int \exp\left[i\gamma\delta\mathbf{G} \cdot (\mathbf{r} - \mathbf{r}_0)\right] P(\mathbf{r}|\mathbf{r}_0, \Delta) d\mathbf{r} d\mathbf{r}_0.$$
(1.14)

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This indicates that in the absence of diffusion encoding gradients $E(\mathbf{0}, t) = 1$. In practice $E(\mathbf{G}, \Delta)$ is obtained by dividing the echo signal amplitude from a PGSE experiment with diffusion gradients by the echo signal amplitude from a Hahn spin echo experiment without gradients $E(\mathbf{G}, \Delta) = S(\mathbf{G})/S_0$.

This leads to the q-space formalism by defining a reciprocal space q where [13] $\mathbf{q} := \gamma \delta \mathbf{G}/2\pi$. Inserting q in Eq. (1.14) gives the q-space signal:

$$E(\mathbf{q},\Delta) = \int f(\mathbf{r}_0,0) \int \exp\left[i2\pi\mathbf{q}\cdot(\mathbf{r}-\mathbf{r}_0)\right] P(\mathbf{r}|\mathbf{r}_0,\Delta) d\mathbf{r} d\mathbf{r}_0.$$
(1.15)

Assuming the transition probability $P(\mathbf{r}|\mathbf{r}_0, \Delta)$ to be translationally invariant or that the movement of a spin is independent of the movements of the other spins and also of its own position and movements in the past – as in a random-walk, implies that $P(\mathbf{r}|\mathbf{r}_0, \Delta) = P(\Delta \mathbf{r}, \Delta)$, which is the diffusion propagator. Also since in a random-walk the movements of all the particles are independent and identical, and since the complex signal and the diffusion propagator for a spin only depend on the spin displacement $\Delta \mathbf{r} = (\mathbf{r} - \mathbf{r}_0)$, it is useful to consider the *ensemble average propagator* (EAP), which describes the average probability of any spin in the ensemble diffusing by $\Delta \mathbf{r}$ during the time Δt [13]:

$$\overline{P}(\Delta \mathbf{r}, \Delta t) = \int P(\Delta \mathbf{r}, \Delta t) f(\mathbf{r}_0, 0) d\mathbf{r}_0.$$
(1.16)

438 Combining Eqs. (1.15 - 1.16) gives the main result of the q-space formalism [13]:

$$E(\mathbf{q},t) = \int \overline{P}(\Delta \mathbf{r},t) \exp\left(i2\pi \mathbf{q} \cdot \Delta \mathbf{r}\right) d\Delta \mathbf{r}, \qquad (1.17)$$

which establishes an inverse Fourier Transform relationship between the EAP, henceforth denoted $P(\mathbf{r})$, and the normalized echo signal, henceforth denoted $E(\mathbf{q})$.

This Fourier relationship between the ensemble average diffusion propagator and the diffusion NMR signal ushers in the paradigm change that diffusion can be viewed more than just an intrinsic property, but also as a probe of the microstructure of the underlying medium. This becomes apparent when the medium is anisotropic and has a complex microstructure, which is the case in cerebral white matter where numerous fiber bundles criss-cross at a resolution much finer than that of dMRI.

⁴⁴⁶ 1.4 From Diffusion MRI to Tissue Microstructure

Although Stejskal in Eq. (1.13) formulated the signal for anisotropic diffusion using a *diffusion tensor* (DT), the reason he fell short of providing a method for estimating the DT is perhaps because he was involved with dNMR. In such experiments it was generally possible to re-orient the experimental setup to align the primary anisotropy direction with the laboratory frame, sufficing it to measure the diffusion coefficient in only three directions [34].



Fig. 1.5 Diffusion Weighted Images of the brain acquired along different gradient encoding directions showing different contrasts.

This however changed with MRI and dMRI, when large anisotropic specimen that couldn't be rotated in the scanner began to be imaged. Imaging such specimen, e.g. cerebral white matter tissue, or the entire brain, revealed that the diffusion coefficient measured in such specimen depended upon the direction of the diffusion encoding gradient. In other words the dMRI signal decay was different along different gradient

directions; or again such dMRI images revealed different contrasts as the diffusion encoding gradient was
 rotated. These dMRI images were called Diffusion Weighted Images (DWIs). DWIs were at first cryptic

⁴⁵⁸ because while they revealed the diffusion coefficient, they clearly also indicated that the underlying tissue

459 was highly anisotropic, but they did not provide a method for inferring the preferential directions of this

⁴⁶⁰ anisotropy. The diffusion coefficients computed from these DWIs using Stejskal-Tanner's isotropic signal

decay formulation $S = S_0 \exp(-bD)$ (Eq. 1.12) were called the *apparent diffusion coefficient* (ADC), since these changed in the highly anisotropic tissue depending on the direction of the diffusion encoding gradient (Fig. 1.5). This limitation of the DWI's, and of Stejskal-Tanner's isotropic signal formulation,

⁴⁶⁴ shifted the interest from measuring only the diffusion coefficient to inferring the preferential diffusion ⁴⁶⁵ anisotropy directions, or to using diffusion as a probe to infer the tissue's microstructure. This brought ⁴⁶⁶ forth a whole new meaning to Stejskal's DT formulation, and it's measurement from dMRI, since its

diagonalisation provided a local coordinate system that was a good indicator of the preferential diffusion
 anisotropy directions or the underlying medium's microstructure.

469 1.4.1 Diffusion Tensor Imaging: The Simplest Model

Diffusion tensor imaging (DTI) was introduced by Basser et al. [5, 6] in 1994, which for the first time
provided a method for measuring the DT from dMRI and for inferring the local tissue microstructure
from the DT. Starting from Stejskal's equation, Basser et al. defined the b-matrix, which also accounted
for the imaging gradients in addition to the pure diffusion encoding gradients [5, 6]. They formulated the
PGSE echo signal to be:

$$S = S_0 \exp\left(-tr(\mathbf{b}\mathbf{D})\right),\tag{1.18}$$

where $tr(\mathbf{A})$ represents the trace of the matrix \mathbf{A} . This simplifies to Stejskal's formulation (Eq. 1.13) 475 $S = S_0 \exp\left(-b \mathbf{g}^T \mathbf{D} \mathbf{g}\right)$ in the absence of the imaging gradients, or under the consideration that the 476 imaging gradients are small compared to the diffusion encoding gradients, which is mostly true. Otherwise, 477 the **b**-matrix has to be computed from the dynamics of the imaging and the diffusion encoding gradients. 478 **DTI Estimation: D** is a covariance tensor, therefore, it is symmetric and positive definite. This 479 implies that there are six unknowns to be estimated from the DTI signal in Eq. (1.18). Therefore, at least 480 six DWIs, acquired along linearly independent and non-coplanar gradient directions, and a non diffusion 481 weighted or Hahn spin echo (S_0) image is required to measure the six unknown coefficients of **D**. The 482 linearized version of Eq. (1.18) provides the simplest scheme for doing this [5, 6]: 483

$$\ln\left(\frac{S}{S_0}\right) = -b_{ij}D_{ij}.\tag{1.19}$$

In practice, often more than six DWIs are used to account for acquisition noise. In the case of N DWIs, the linearized equation for the signal is written in a matrix form:

$$\begin{bmatrix} -\ln(S_{1}/S_{0}) \\ -\ln(S_{2}/S_{0}) \\ -\ln(S_{3}/S_{0}) \\ \vdots \\ -\ln(S_{N}/S_{0}) \end{bmatrix} = \begin{bmatrix} b_{11}^{11} 2b_{12}^{11} 2b_{13}^{11} b_{22}^{11} 2b_{23}^{11} b_{33}^{11} \\ b_{11}^{21} 2b_{12}^{21} 2b_{13}^{21} b_{22}^{22} 2b_{23}^{22} b_{33}^{23} \\ \vdots \\ \vdots \\ b_{11}^{N} 2b_{12}^{N} 2b_{13}^{N} b_{22}^{N} 2b_{33}^{N} b_{33}^{N} \end{bmatrix} \begin{bmatrix} D_{11} \\ D_{12} \\ D_{13} \\ D_{22} \\ D_{23} \\ D_{33} \end{bmatrix},$$
(1.20)
$$\mathbf{X} = \mathbf{Bd}.$$
(1.21)

The easiest option for solving this is to use the least squares optimization $\mathbf{d}_{opt} = argmin_{\mathbf{d}} ||\mathbf{X} - \mathbf{Bd}||^2$, which translates to the Moore-Penrose pseudo-inverse solution:

$$\mathbf{d} = (\mathbf{B}^T \mathbf{B})^{-1} \mathbf{B}^T \mathbf{X}.$$

488 Due to its linear form which only involves matrix manipulations, this solution is extremely rapid. However,

489 it doesn't account for the signal noise or of the distortion to the noise it introduces while taking the

⁴⁹⁰ logarithms of the signal in the linearization process. Due to DTI's popularity and maturity as a technique of probing tique microstructures a number of conditions out for measuring **D** from the

 $_{491}$ of probing tissue microstructures, a number of sophisticated solutions exist for measuring **D** from the

xviii

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Fig. 1.6 Microstructure from DTI. Coherent fibers (a) can be inferred from the ellipsoid of the diffusion tensor (DT) (b). The DT also provides a local coordinate system (c) that indicates the preferential diffusion anisotropy directions.

dMRI signal. These range from Basser's original weighted least squares approach [5] which accounts for the logarithmic distortion of the signal noise, to non-linear optimization approaches that account for signal noise, spatial smoothing, and also for constraining the DT to be positive definite [18, 19, 70, 29, 45, 51, 40].

Microstructure from DTI: The consistency between the phenomenological approach and the q-495 space formalism, under the NGP condition, implies that the propagator describing the diffusion measured 496 by DTI is the Gaussian PDF (Eq. 1.10). This is an oriented Gaussian parameterized by the DT D, or 497 its inverse. The orientation of the PDF can be deduced from the eigen-decomposition of the DT. The 498 eigenvalues and eigenvectors of \mathbf{D} form a local coordinate system that indicates the preferential diffusion 499 direction orienting the Gaussian PDF. In other words it indicates the diffusion direction favoured by 500 the microstructure of the medium. This preferential orientation of the microstructure can be visually 501 represented by the ellipsoid represented by \mathbf{D} whose implicit quadratic form is [6]: 502

$$\frac{\mathbf{x}^T \mathbf{D}^{-1} \mathbf{x}}{2t} = 1. \tag{1.22}$$

Since **D** is symmetric it can be diagonalized $\mathbf{D} = \mathbf{W}^{T} \mathbf{\Lambda} \mathbf{W}$, where **W** are its orthonormal eigenvectors and $\mathbf{\Lambda}$ is a diagonal matrix whose diagonal elements are its eigenvalues. The canonical form of the diffusion ellipsoid defined by \mathbf{D}^{-1} emerges in the coordinate frame of its eigenvectors:

$$\left(\frac{x'}{\sqrt{2\lambda_1 t}}\right)^2 + \left(\frac{y'}{\sqrt{2\lambda_2 t}}\right)^2 + \left(\frac{z'}{\sqrt{2\lambda_3 t}}\right)^2 = 1.$$

To infer the microstructure of the cerebral white matter from DTI, the fundamental assumption is that the coherent fiber bundle structures formed by the axons hinder the perpendicular diffusion of water molecules (spin bearing ${}^{1}H$ atoms) more than the parallel diffusion. Therefore, the elongation and orientation of the DT are good indicators of these coherent structures or fiber bundles locally. The eigenvector corresponding to the largest eigenvalue, the major eigenvector, indicates the main fiber direction, while the other eigenvectors and eigenvalues indicate diffusion anisotropy in the perpendicular plane (Fig. 1.7).

Scalar Measures: The microstructure of the medium or the white matter can be further characterized from a number of rotationally invariant scalar measures derived from the DT that reveal diffusive properties of the underlying tissue. A number of such scalar measures are of primary importance since they are often used as bio-markers.

• The first is mean diffusivity (MD) [4]:

$$\overline{\lambda} = tr(\mathbf{D})/3.$$

• Fractional anisotropy (FA) is the other measure which describes the amount of anisotropy presented by the microstructure. It too is derived from the eigenvalues of \mathbf{D} ($\lambda_1 \ge \lambda_2 \ge \lambda_3$) [4]:

$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \overline{\lambda})^2 + (\lambda_2 - \overline{\lambda})^2 + (\lambda_3 - \overline{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}},$$

• The *Relative anisotropy* (RA) is given by [4]:

$$RA = \frac{1}{\sqrt{3}} \frac{\sqrt{(\lambda_1 - \overline{\lambda})^2 + (\lambda_2 - \overline{\lambda})^2 + (\lambda_3 - \overline{\lambda})^2}}{\overline{\lambda}}$$



Fig. 1.7 Diffusion Tensor Imaging (DTI). (a) DTI ellipsoids from an axial slice of the brain. (b) Zoom of highlighted box in (a). (c) Fractional Anisotropy (FA). (d) Colour FA where the colour components RGB represent the unit major eigenvector of the diffusion tensor $\mathbf{e}_1 = [r, g, b]^T$ weighted by FA, or the colours indicate the preferential diffusion anisotropy directions.

• Westin et al. [73] proposed anisotropy measures to discern *linear* c_l , *planar* c_p and *spherical* c_s diffusion tensor shapes:

$$c_l = \frac{\lambda_1 - \lambda_2}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}; \quad c_p = \frac{2(\lambda_2 - \lambda_3)}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}; \quad c_s = \frac{3\lambda_3}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

523 1.4.2 Beyond DTI

In DTI, the Gaussian assumption over-simplifies the diffusion of water molecules. While it is adequate 524 for voxels in which there is only a single fiber orientation (or none), it breaks down for voxels in which 525 there are more complex internal structures. This is an important limitation, since the resolution of dMRI 526 acquisitions is between 1mm^3 and 3mm^3 while the physical diameter of fibers can be between $1 \mu \text{m}$ and 527 $30 \ \mu m$ [54, 8]. Research groups currently agree that there is complex fiber architecture in most fiber 528 regions of the brain [53]. In fact, it is currently thought that between one third to two thirds of imaging 529 voxels in the human brain white matter contain multiple fiber bundle crossings [9]. This has led to the 530 development of various High Angular Resolution Diffusion Imaging (HARDI) techniques [69] such as 531 Q-Ball Imaging or Diffusion Spectrum Imaging for exploring the microstructure of biological tissues with 532 greater accuracy. 533

HARDI samples q-space along as many directions as possible in order to reconstruct estimates of the true diffusion PDF – also referred as the EAP – of water molecules. This true diffusion PDF is model-free and can recover the diffusion of water molecules in any underlying fiber population. HARDI depends on the number of measurements N and the gradient strength (*b*-value), which directly affects acquisition time and signal to noise ratio in the signal.

⁵³⁹ 1.4.2.1 Diffusion Spectrum Imaging: Recovering the Diffusion EAP

Diffusion spectrum imaging (DSI) introduced by Wedeen et al. [71, 67] in 2000, was the first dMRI 540 method that applied the q-space formalism to measure or estimate the EAP in biological tissue. The 541 forte of the q-space formalism, where diffusion could reveal more than just the intrinsic properties like 542 the diffusion coefficient, and show how it could probe the complex microstructure of the underlying 543 tissue, became quickly apparent. Crossing fiber microstructures were clearly revealed by the geometric 544 forms of the measured EAPs, or their characteristics. Such EAPs clearly represented non-free diffusion 545 and were non-Gaussian. DSI was based on the Fourier Transform relationship between the signal and 546 the EAP described in Eq. (1.17). Although in practice it couldn't satisfy the NGP condition required by 547 the q-space formalism, DSI essentially imaged the q-space densely and reconstructed the EAP via a fast 548 Fourier Transform (FFT). In fact, $\delta \approx \Delta$ in the DSI experiments conducted in [71, 67, 72]. Nonetheless, 549

the angular results produced by such DSI experiments clearly spoke in favour of q-space imaging – as seen in [58].

⁵⁵² DSI, however, considered the modulus Fourier Transform:

$$P(\mathbf{r}) = \int |E(\mathbf{q})| \exp\left(-i2\pi\mathbf{q}\cdot\mathbf{r}\right) d\mathbf{q},$$

⁵⁵³ in place of the true Fourier Transform, justifying that in the case of pure diffusion the modulus Fourier ⁵⁵⁴ Transform is equal to the true Fourier Transform. This was done to counter biological motion such as ⁵⁵⁵ cardiac pulsation, which tended to contaminate the phase of the signal.

Initially visualizing iso-surfaces of the estimated EAP [71], DSI techniques later introduced the *orientation distribution function* (ODF), to emphasize the angular results, which indicated underlying fibers. Two ODFs were used, namely [72] (Fig. 1.8):

$$\Psi_{SA}(\mathbf{u}) = \int_{\mathbf{R}^+} P(r\mathbf{u}) r^2 dr, \quad \mathbf{u} = \mathbf{r}/|\mathbf{r}|, \qquad (1.23)$$

and the one introduced by Tuch [67]:

$$\Psi_T(\mathbf{u}) = \int_{\mathbf{R}^+} P(r\mathbf{u}) dr, \quad \mathbf{u} = \mathbf{r}/|\mathbf{r}|.$$
(1.24)

However, DSI had severe acquisition setbacks. To correctly estimate the EAP, the q-space had to be 560 densely sampled, and also at very high b-values. The DSI sampling scheme was a Cartesian grid inside a 561 sphere in q-space, where both the radius of the sphere – the maximum b-value, and the number of grid-562 points – the number of acquisitions played important roles in determining the accuracy of the estimated 563 EAP. For example in [71, 72], the maximum b-value was in the range of $20,000 \text{ s/mm}^2$, and the number 564 of acquisitions were more than 500. In comparison, DTI acquisitions are done for b-values of 1000 s/mm², 565 and only require a minimum of 6 acquisitions. These demanding requirements played unfavourably for 566 DSI, since its clinical viability was near impossible. 567

However, DSI was the proof of concept for q-space imaging, which quickly became the popular approach
 for dMRI, and gave rise to a plethora of techniques for estimating complex EAPs or their characteristics
 like the ODF. These q-space techniques were developed to overcome the acquisition limitations of DSI.

571 1.4.2.2 Q-Ball Imaging: Emphasizing the Anisotropic Diffusion Orientation Information

Q-Ball Imaging (QBI) was proposed by Tuch [67, 68] spurred by the facts that DSI had severe acquisition
requirements, and that the DSI result of interest wasn't the estimated EAP itself, but rather its radial
projection – the ODF, which emphasized angular details. His idea was to retrieve the same angular result
with reduced acquisition requirements. His initial attempt was the model based multi-tensor approach
which was stricken with instabilities induced by the assumed model. Therefore, he proposed QBI, a



Fig. 1.8 Diffusion Spectrum Imaging & Q-Ball Imaging. (a) DSI diffusion PDFs from [71]. Corticospinal tract (orientations sup.-inf.) and pontine decussation (left-right). (b) ODFs, estimated from an analytical q-ball approach, such that they represent the angular marginal distributions of the true and unknown EAPs (biological rat phantom).

⁵⁷⁷ model free method that sampled q-space only on a sphere or q-shell with fixed q-radius with high angular ⁵⁷⁸ resolution.

⁵⁷⁹ QBI like DSI is based on the q-space formalism and shows promising results, although like DSI, in ⁵⁸⁰ practice it cannot satisfy the NGP condition [67]. However, QBI became a forerunner to a plethora of ⁵⁸¹ q-space methods that attempted to reconstruct the EAP or its characteristics from partial sampling of ⁵⁸² the q-space. QBI, itself maps spherical acquisitions in q-space to the ODF – a spherical function in real ⁵⁸³ space.

QBI is based on the *Funk Radon transform* (FRT), which is a mapping from a sphere to a sphere $\mathcal{G}: S^2 \to S^2$. To a point on the sphere, called the pole, the FRT of a spherical function f, assigns the value of the integral of the spherical function along the equator on the plane that has for normal the vector connecting the centre of the sphere to the pole:

$$\mathcal{G}[f(\mathbf{u})](\mathbf{u}) = \int_{S^2} f(\mathbf{u}) \delta(\mathbf{u}^T \mathbf{w}) d\mathbf{w},$$

where $\mathbf{u}, \mathbf{w} \in S^2$. Using the Fourier slice theorem, Tuch was able to show that the FRT of the signal acquired on a q-sphere was equal to the ODF in Eq. (1.24) blurred by a zeroth-order Bessel function, where the blurring or the width of the Bessel function was inversely proportional to the radius of the acquisition q-sphere.

⁵⁹² QBI, therefore, made it possible to reconstruct the angular result of DSI, i.e. the ODF, with fewer ⁵⁹³ acquisitions and without assuming any models. QBI was further boosted by [2, 32, 24], where an analytical ⁵⁹⁴ solution was proposed, by using the *spherical harmonic* (SH) basis. It was shown that the SHs are the ⁵⁹⁵ eigenfunctions of the FRT [24]. Letting Y_l^m denote the SH of order l and degree m ($m = -l, \dots, l$), a ⁵⁹⁶ modified real and symmetric SH basis is defined. For even order l, a single index j in terms of l and m⁵⁹⁷ is used such that $j(l,m) = (l^2 + l + 2)/2 + m$. The modified basis is given by:

$$Y_{j} = \begin{cases} \sqrt{2} \cdot \operatorname{Re}(Y_{l}^{|m|}), & \text{if } m < 0\\ Y_{l}^{m}, & \text{if } m = 0, \\ \sqrt{2} \cdot (-1)^{m+1} \cdot \operatorname{Im}(Y_{l}^{m}), & \text{if } m > 0 \end{cases}$$
(1.25)

where $\operatorname{Re}(Y_l^m)$ and $\operatorname{Im}(Y_l^m)$ represent the real and imaginary parts of Y_l^m respectively. This modified basis is designed to be real, symmetric and orthonormal, and it is then possible to obtain an analytical estimate of the ODF in Eq. (1.24) with [24]:

$$\Psi_T(\mathbf{u}) = \sum_{j=1}^L \underbrace{2\pi P_{l(j)}(0)c_j}_{c'_j} Y_j(\mathbf{u}), \qquad (1.26)$$

where L = (l+1)(l+2)/2 is the number of elements in the modified SH basis, c_j are the SH coefficients describing the input HARDI signal, $P_{l(j)}$ is the Legendre polynomial of order l that is associated with *j*th element of the modified SH basis and c'_j are the SH coefficients describing the ODF Ψ_T .

Aganj et al. [1] recently proposed an analytical solution to QBI using SHs to compute the ODF in Eq. (1.23), under a mono-exponential assumption of the signal. The ODF in Eq. (1.23) takes into account the solid angle factor during the radial integration, therefore, it is a true marginal density function of the EAP. This solution was also proposed by Vega et al. in [66]. The ODF in Eq. (1.24) proposed by Tuch on the other hand doesn't account for this solid angle, and therefore needs to be numerically normalized after estimation [68] (Fig. 1.8).

⁶¹⁰ 1.5 Computational Framework for Processing Diffusion MR Images

⁶¹¹ Diffusion MRI is a rich source of complex data in the form of images. Processing dMRI data poses a ⁶¹² challenging problem since diffusion images can range from scalar images such as DWIs, where each voxel ⁶¹³ contains a scalar grey-level value, to tensor images such as in DTI, where each voxel contains a 2nd order ⁶¹⁴ tensor, to more complex and generic function images such as in DSI or QBI, where each voxel contains a ⁶¹⁵ diffusion function such as the EAP in DSI or a spherical function such as the ODF in QBI, represented

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as coefficients in a particular basis of choice – such as the SH basis. Therefore, processing such higher
 dimensional images requires sophisticated mathematical and computational tools.

Processing diffusion images also forms an important part of the dMRI pipeline from acquisition to ex-618 traction of meaningful physical and medical information from the data. Operations such as regularization 619 are important for denoising diffusion images as they render the tensor field in DTI or ODF field in QBI 620 more coherent and therefore greatly improve the results of post-processing algorithms such as tractog-621 raphy. A rich body of literature for regularizing tensor fields in DTI can be found in [51, 3, 15, 50, 46]. 622 The capacity to segment tensor images or ODF images makes it possible to identify and reconstruct 623 white matter structures in the brain such as the corpus callosum, which is not possible from simple scalar 624 MR images. However, the extension of such operations from scalar images to tensor fields or ODF fields 625 requires the correct mathematical definitions for spaces of tensors (or EAPs or ODFs) with the appropri-626 ate metric. In this section we will present the tools required to process tensor images (DTI), which has 627 seen extensive mathematical development recently. In particular we will present appropriate metrics for 628 the space of symmetric positive definite matrices (or diffusion tensors) Sym_n^+ , an estimation algorithm 629 for DTI that ensures that the DT is estimated in Sym_n^+ using the Riemannian metric of Sym_n^+ and a 630 segmentation algorithm that uses the Riemannian metric of Sym_n^+ to segment regions in a tensor field. 631

⁶³² 1.5.1 The Affine Invariant Riemannian Metric for Diffusion Tensors

⁶³³ Diffusion tensors are 3×3 symmetric matrices. However, since negative diffusion is non-physical these ⁶³⁴ matrices are also required to be positive definite. In other words DTs belong to the space Sym_3^+ of 3×3 ⁶³⁵ symmetric positive definite matrices, which is a non-Euclidean space. Therefore an appropriate metric ⁶³⁶ needs to be defined on this space which would render it into a Riemannian manifold and which would ⁶³⁷ permit to constrain all operations naturally to Sym_3^+ by using Riemannian geometry. Sym_3^+ naturally ⁶³⁸ inherits the Euclidean and the Frobenius metrics from the space of all matrices, however, Sym_3^+ is neither ⁶³⁹ complete nor closed under these metrics.

A number of works have recently proposed the affine invariant Riemannian metric for Sym_n^+ which has been used extensively to compute on DTs [45, 51, 40]. In [51] the Riemannian metric is derived to be $g_{ij} = g(X,Y) = \langle X,Y \rangle_{\mathbf{S}} = tr\left(\mathbf{S}^{-\frac{1}{2}}X\mathbf{S}^{-1}Y\mathbf{S}^{-\frac{1}{2}}\right), \forall \mathbf{S} \in Sym_3^+ \text{ and with } X, Y \in T_{\mathbf{S}}Sym_3^+ = Sym_3 \text{ the}$ tangent space at **S**. The geodesic distance between DTs induced by this metric can be computed to be:

$$\mathcal{D}_{Rm}(\mathbf{S}_1, \mathbf{S}_2) = \sqrt{\frac{1}{2} tr\left(\ln^2\left(\mathbf{S}_1^{-1/2} \mathbf{S}_2 \mathbf{S}_1^{-1/2}\right)\right)}.$$
(1.27)

An equally well known metric for Sym_n^+ is the Log-Euclidean metric [3]. Although it isn't affine invariant and only similarity invariant, computationally it is more efficient than the affine invariant Riemannian metric and resembles closely the latter. The distance between DTs induced by this metric is:

$$\mathcal{D}_{LE}(\mathbf{S}_1, \mathbf{S}_2) = \sqrt{\frac{1}{2} tr\left(\left(\ln(\mathbf{S}_1) - \ln(\mathbf{S}_2)\right)^2\right)}.$$
(1.28)

⁶⁴⁷ 1.5.2 Estimation of DTs in Sym_3^+ Using the Riemannian Metric

⁶⁴⁸ Using the appropriate Riemannian metric and geometry for Sym_3^+ can constrain all operations to Sym_3^+ . ⁶⁴⁹ For example using the Riemannian metric for DTI estimation can ensure that the DTs are positive definite ⁶⁵⁰ or that no negative diffusion will be estimated even in the presence of noisy DWIs. This can be done by ⁶⁵¹ using the logarithmically transformed version of the Stejskal-Tanner equation (Eq. 1.13) and considering ⁶⁵² its explicit least square minimization $E(\mathbf{D}) = \frac{1}{2} \sum_{i=1}^{N} \left(\frac{1}{b} \ln \left(\frac{S_i}{S_0}\right) + \mathbf{g}_i^T \mathbf{D} \mathbf{g}_i\right)^2$. The gradient of this least ⁶⁵³ square functional using the affine invariant Riemannian metric can be shown to be [40]:

$$\nabla E(\mathbf{D}) = \sum_{i=1}^{N} \left(\frac{1}{b} \ln \left(\frac{S_i}{S_0} \right) + \mathbf{g}_i^T \mathbf{D} \mathbf{g}_i \right) \cdot (\mathbf{D} \mathbf{g}_i) (\mathbf{D} \mathbf{g}_i)^T.$$
(1.29)

⁶⁵⁴ Furthermore the Euclidean gradient descent algorithm required for optimization has to be appropriately ⁶⁵⁵ replaced by a Riemannian geodesic descent algorithm to respect the Riemannian geometry of Sym_3^+ .

⁶⁵⁶ 1.5.3 Segmentation of a Tensor Field

The goal of segmenting a tensor field or an image of DTs is to compute the optimal 3D surface separating an anatomical structure of interest from the rest of the tensor image (see Fig. 1.9). To do this we follow the method proposed in [23]. The idea will be to treat the tensor field as a field of Gaussian probability density functions and to utilize the affine invariant Riemannian metric on Sym_3^+ , which also forms a Riemannian metric in the space of Gaussian density functions, to compute the segmentation boundary. Therefore, a DT at the point x in the image corresponds to the 3D Gaussian distribution N(x, r).

Using the level-set approach and the optimal boundary Γ between the object of interest Ω_1 and the background Ω_2 , the level-set $\phi : \Omega_1 \cup \Omega_2 \to \mathbb{R}$ can be defined as:

$$\begin{cases} \phi(x) = 0, & \text{if } x \in \Gamma \\ \phi(x) = \mathcal{D}_E(x, \Gamma), & \text{if } x \in \Omega_1 \\ \phi(x) = -\mathcal{D}_E(x, \Gamma), & \text{if } x \in \Omega_2 \end{cases}$$
(1.30)

where $\mathcal{D}_E(x,\Gamma)$ represents the Euclidean distance between x and Γ . Then according to the geodesic active regions model along with a regularity constraint on the interface, the optimal boundary Γ or the segmentation of the tensor field is obtained by minimizing the functional:

$$E(\phi, P_1, P_2) = \nu \int_{\Omega = \Omega_1 \cup \Omega_2} |\nabla H_{\varepsilon}(\phi)| dx - \int_{\Omega} H_{\varepsilon}(\phi) \ln(P_1(N(x, r))) dx - \int_{\Omega} (1 - H_{\varepsilon}(\phi)) \ln(P_2(N(x, r))) dx,$$
(1.31)

where $H_{\varepsilon}(\cdot)$ is a regularized version of the Heaviside function [23], and P_1 and P_2 are the probability distributions of the set of Gaussian distributions N(x, r) in Ω_1 and Ω_2 respectively.

Equation (1.31) can be solved computationally by assuming the distributions P_1 and P_2 themselves to be Gaussians distributions. However, that would require the computation of the mean and the standard deviation of the set of 3D Gaussian distributions N(x, r) constituting Ω_1 and Ω_2 . This mean and standard deviation of a set of Gaussian distributions would require a metric to be defined on the space of Gaussian distributions. A number of examples are provided in [23] – the Euclidean metric, the Kullback-Leibler divergence, and the Riemannian metric. We reproduce here only the final example.

Using the affine invariant Riemannian metric on Sym_3^+ , which also forms a Riemannian metric on the space of 3D Gaussian distributions N(x, r), it is possible to compute the mean distribution $\overline{N}(X, r)$ of a set of Gaussian distributions by a process of Riemannian geodesic descent – a modified gradi-



Fig. 1.9 Tensor field segmentation on a synthetic dataset simulating DTI [41].

ent descent process. Similarly the empirical covariance matrix relative to the mean \overline{N} is defined to be $\Lambda_{Rm} = \frac{1}{n-1} \sum_{i=1}^{n} \beta_i \beta_i^T$, with $\beta_i = \overline{N} \ln(N_i^{-1}\overline{N})$ which is the gradient of the squared geodesic distance $\nabla \mathcal{D}_{Rm}^2(N_i, \overline{N})$ in vector form. Using these it is possible to define a generalized Gaussian distribution over the space of 3D Gaussian distributions with a covariance matrix Λ_{Rm} of small variance $\sigma^2 = tr(\Lambda_{Rm})$:

$$P_{Rm}(N \mid \overline{N}, \Lambda_{Rm}) = \frac{1 + O(\sigma^3) + \varepsilon(\sigma/\eta)}{\sqrt{(2\pi)^{m(m+1)/2} |\Lambda_{Rm}|}} \exp\left(\frac{-\beta^T \gamma \beta}{2}\right) \quad \forall N \in \mathcal{S}ym_3^+, \tag{1.32}$$

where $\gamma = \Lambda_{Rm}^{-1} - \mathcal{R}/3 + O(\sigma) + \varepsilon(\sigma/\eta)$ with \mathcal{R} as the Ricci curvature tensor at \overline{N} , η as the injection radius at \overline{N} and ε such that $\lim_{0^+} x^{-\beta} \varepsilon(x) = 0 \forall \beta \in \mathbb{R}^+$.

⁶⁸⁵ 1.6 Tractography: Inferring the Connectivity

When DTI/DSI/QBI is performed on the brain, the DT/EAP/ODF – hereafter referred to as the spherical 686 diffusion function (SDF), is a local indicator of coherent structures or fiber bundles in the cerebral 687 white matter. However, the process of reconstructing the global structures of fiber bundles by connecting 688 the local information is known as fiber tracing or *tractography*. Tractography graphically reconstructs 689 the connectivity of the cerebral white matter by integrating along the direction indicated by the local 690 geometry of the SDF. It is a modern tool that is unique in the sense that it permits an indirect dissected 691 visualization of the brain in vivo and non-invasively [16]. The underpinnings of tractography are also 692 based on the fundamental assumption of dMRI – the diffusion of water molecules is hindered to a greater 693 extent perpendicular to coherent fiber bundle structures than parallel to these. Therefore, following the 694 geometry of the local diffusion function and integrating along reveals the continuous dominant structure 695 of the fiber bundle. However, in spite of the gain due to its non-invasive nature, tractography can only 696 infer such structures indirectly. Therefore, tractography is acutely sensitive to the local geometry and the 697 error is cumulative. The correct estimation of the local geometry is crucial. 698

Deterministic tractography is a well established tool that has seen considerable success in researching 699 neurological disorders [20]. Deterministic tractography begins from a seed point and traces along the 700 dominant fiber direction by locally connecting the "fiber" vectors or mathematically becoming tangent 701 to these. Classically the major eigenvector of the diffusion tensor in DTI represented these "fiber" vectors 702 [47, 7, 38]. However, since DTI is ambiguous and cannot accurately describe the fiber directions in regions 703 with complex fiber configurations, DTI tractography, in spite of its successful usage, is known to be prone 704 to errors. Hence the trend in recent years to extend tractography to complex shaped SDFs that describe 705 the underlying fiber directions more accurately [67, 72, 25]. 706

Probabilistic tractography was proposed to address the reliability of deterministic tractography which 707 remains sensitive to a number of parameters. The concept and output of probabilistic tractography is, 708 however, subtly different from determinist tractography. While the latter attempts to find the connectivity 709 between two regions, the former measures the likelihood that two regions are connected, or it provides a 710 connectivity confidence. Given the capabilities and ambiguities of dMRI acquisition and reconstruction 711 schemes of today, due to partial voluming, noise, etc., probabilistic tractography provides a more complete 712 statement. However, probabilistic tractography is also computationally more expensive than deterministic 713 tractography. 714

715 1.6.1 Deterministic Tractography

Of the many deterministic tractography algorithms, the continuous *streamline tractography* is a widely used scheme. The continuous version of streamline tractography [7] defined for DTI, considers a fiber tract as a 3D space curve parametrized by its arc-length, $\mathbf{r}(s)$, and describes it by its Frenet equation:

$$\frac{d\mathbf{r}(s)}{ds} = \mathbf{t}(s) = \varepsilon_1(\mathbf{r}(s)), \tag{1.33}$$

where $\mathbf{t}(s)$ the tangent vector to $\mathbf{r}(s)$ at s is equal to the unit major eigenvector $\varepsilon_1(\mathbf{r}(s))$ of the diffusion tensor at $\mathbf{r}(s)$. This implies that fiber tracts are locally tangent to the dominant eigenvector of the

diffusion tensor at every spatial position. The differential equation Eq. (1.33) along with the initial 721 condition $\mathbf{r}(0) = \mathbf{r}_0$ means that starting from \mathbf{r}_0 , a fiber can be traced by continuously integrating Eq. 722 (1.33) along the direction indicated locally by the major eigenvector of the diffusion tensor at that point. 723 However, integrating Eq. (1.33) requires two things – first, a spatially continuous tensor (or SDF) field, 724 and second, a numerical integration scheme. In [7], the authors proposed two approaches for estimating a 725 spatially continuous tensor field from a discrete DTI tensor field, namely approximation and interpolation. 726 They also proposed the Euler's method, the 2nd order Runge-Kutta method, and the adaptive 4th order 727 Runge Kutta method as numerical integration schemes. Finally, for stopping they proposed four criteria 728 - the tracts are within the image volume, the tracts are in regions with FA value higher than a threshold, 729

the curvature of a tract is smaller than a threshold, and that a tract is better aligned with the major ran eigenvector in the next spatial location than any of the two other eigenvectors.

The streamline tractography algorithm can be adapted to SDFs with multiple maxima (EAP/ODF etc.) by modifying Eq. (1.33) to:

$$\frac{d\mathbf{r}(s)}{ds} = \eta_{\theta_{min}}(\mathbf{r}(s)), \quad \mathbf{r}(0) = \eta_{max}(0) \tag{1.34}$$

where $\eta_i(\mathbf{r}(s))$ are all the unit maxima vectors of the SDF at $\mathbf{r}(s)$, η_{max} is the unit maximum vector whose function value is the largest amongst all the η_i , and $\eta_{\theta_{min}}$ is the unit maximum vector in the current step that is most collinear to the unit maximum vector followed by the integration in the previous step. Equation (1.34) and the initial condition state that at the starting point the integrating begins along the dominant maximum direction, and at each consecutive step first all the maxima of the SDF are detected and the maximum direction most collinear to the maximum direction from the previous integration step is chosen to move forward in the integration.

The maximum direction most collinear to the previously chosen maximum direction can be chosen by computing the dot product between the previously chosen maximum direction and all the maxima of the current step, and by considering the absolute values of the dot products. Hence, the maximum chosen for the next integration direction is the maximum whose absolute value of its dot product with the previously chosen maximum direction is the largest. Also to avoid erratic forward and backward steps during the integration, if the value of the dot product is negative, it is necessary to flip the unit maximum direction to point it consistently along the fiber direction, just like in [7].

⁷⁴⁸ Since streamline tractography requires a continuous field of SDFs for integrating Eq. (1.34), a contin-⁷⁴⁹ uous field of SDFs can be computed from a simple Euclidean interpolation of the SDFs when the SDFs

uous held of SDF's can be computed from a simple Euclidean interpolation of the SDF's when the SDF's
 are expressed in the SH basis. The Euclidean interpolation in the SH basis is equivalent to the L2-norm
 interpolation of the SDFs, since the SHs form an orthonormal basis [26].



Fig. 1.10 Deterministic Tractography on ODFs. (a) Three fiber bundles are traced, starting from different seed regions. Red: seeds in the CC (left-right). Blue: seeds in the CST (superio-inferior). Green: seeds in the SLF (anterio-posterior). (b) Zoom into crossing region.

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752 1.6.2 Probabilistic Tractography

General SDF-based (ODF etc.) probabilistic tractography have recently been published in the litera-753 ture [52, 48, 9, 33, 57, 35, 60, 17] to generalize several existing DT-based methods. First, in [35] para-754 metric spherical deconvolution is used as the SDF [65] and in [9] a mixture of Gaussian model is used 755 to extend the probabilistic Bayesian DT-based tracking [10]. Related to these techniques, [33] uses a 756 Bayesian framework to do global tractography instead of tracking through local orientations. In [52], 757 Monte Carlo particles move inside the continuous field of q-ball diffusion ODF and are subject to a tra-758 jectory regularization scheme. In [48], an extension to their DT-based approach [49] is also proposed using 759 a Monte Carlo estimation of the white matter geometry and recently, a Bingham distribution is used to 760 model the peak anisotropy in the fiber distributions [60]. Finally, in [17], large number of M-FACT QBI 761 streamlines are reconstructed and all pathways are reversed-traced from their end points to generate of 762 map of connection probability. In this chapter, a new probabilistic algorithm is presented based on the 763 ODF using a Monte Carlo random walk algorithm. 764

The new algorithm is an extension of the random walk method proposed in [36] to use the distribution profile of the fiber ODF. It starts off a large number of particles from the same seed point and lets the particles move randomly according to the local ODF estimate, F, and counts the number of times a voxel is reached by the path of a particle. This yields higher transitional probabilities along the main fiber directions. The random walk is stopped when the particle leaves the white matter mask.

For each elementary transition of the particle, the probability for a movement from the seed point xto the target point y in direction \mathbf{u}_{xy} is computed as the product of the local ODFs in direction \mathbf{u}_{xy} , i.e.

$$P(x \to y) = F(\mathbf{u}_{xy})_x \cdot F(\mathbf{u}_{xy})_y \tag{1.35}$$

where $P(x \to y)$ is the probability for a transition from point x to point y, $F(\mathbf{u}_{xy})_x$ is the ODF at point x in direction xy (by symmetry, direction xy and yx are the same).

The transition directions in the local model are limited to 120 discrete directions corresponding to the angular sampling resolution of the acquired brain data and the step size of the particle step was fixed to 0.5 times the voxel size. A trilinear interpolation of the ODF was used for the subvoxel position and a white matter mask computed from a minimum FA value of 0.1 and a maximum ADC value of 0.0015 was used. A total of 100000 particles were tested for each seed voxel. The connectivity of any given voxel with the seed voxel is estimated by the number of particles that reach the respective voxel, called a *tractogram*.

⁷⁸¹ 1.7 Clinical Applications

Diffusion MRI has now proved to be extremely useful for studying the normal and pathological human 782 brain [11, 27] and for improving diagnosis and therapy of brain diseases. It has led to many applications in 783 clinical diagnosis of neurological diseases and disorders, neuroscience applications in assessing connectivity 784 785 of different brain regions and more recently, therapeutic applications, primarily in neurosurgical planning. Indeed, the sensitivity of diffusion measures to changes in the white matter have led to a wealth of clinical 786 studies using second order diffusion tensor imaging as an in vivo clinical marker and dMRI has opened 787 up a landscape of discoveries for neuroscience and medicine through research and clinical exploration of 788 fiber connectivity and CNS diseases. 789

The dMRI models and tools presented in this chapter are at the heart of what is strongly needed to better recover, study and understand the anatomical connectivity of the normal and pathological human CNS. These dMRI methodological developments have already been applied in many places to better describe, characterize and quantify abnormalities within the CNS white matter and develop in vivo markers for diseases in clinical neuroscience.

The first and most successful application of dMRI since the early 1990s has been in acute brain ischemia, that emerged from the discovery of Moseley et al. that water diffusion immediately drops after the onset of an ischemic event, when brain cells undergo swelling through cytotoxic edema. This result was later confirmed by different groups using animal models and human patients with stroke.

Since then, many important CNS diseases have attracted the interest of dMRI researchers. Hence, DTI
 has appeared as a promising tool to look at brain maturation and development, especially to monitor
 the myelination process, as well as changes in connectivity in relation to functional disorders. Indeed, it

has been shown by many studies that the degree of diffusion anisotropy in white matter increases during the myelination process, so that dMRI could be used to assess brain maturation in children, newborns or premature babies, as well as to characterize white matter disorders in children. DTI has now been used for more than ten years to look, in vivo, at the disorganization of white matter in schizophrenia, which is thought to come from myelin abnormalities. Most neuroimaging studies of schizophrenia have used second order DTI so far, as a means to quantify the integrity of the white matter.

Alzheimer's and Parkinson's diseases, two of the most important neurodegenerative diseases, as well as others like multiple sclerosis have characteristic abnormalities in the microstructure of brain tissues that are not apparent and cannot be revealed reliably by standard imaging techniques. Diffusion MRI can reveal these co-lateral damages to the fibers of the CNS white matter that connect different brain regions.

We in the Athena Project Team, INRIA, France, are currently focusing on the use of ultra high field 813 MRI (3T and 7T) techniques for investigating the structural disorders of the brain stem and of the 814 central deep nuclei in the field of Parkinson's syndrome. This work aims to identify the biomarkers of the 815 pathology by benefitting from the latest developments in the domain of ultra high fields and from the latest 816 image processing innovations in the field of diffusion imaging based on high angular resolution models. 817 Determining the biomarkers for the various forms of Parkinson's disease using high field systems will surely 818 open the way for developing new diagnosis tools at lower field strengths and thus make them available to 819 a clinical environment. Deep brain nuclei are important structures that are involved in a large array of 820 behaviors, such as locomotion, eye-movement, or sleep. Damage to these structures leads to movement 821 disorders such as Parkinson's disease. To date, except for the larger striato-pallidal complex, there are 822 no reliable imaging markers of small deep nuclei. With dMRI and refinements of neuroimaging methods 823 and higher field magnets, imaging of these nuclei has become possible. Together with our collaborators at 824 the Center of Neuroimaging Research (CENIR, Paris, France) and CEA Neurospin (Saclay, France), we 825 are currently conducting a series of experiments in normal volunteers and in patients with basal ganglia 826 pathology to characterize deep brain structures and study the structural disorders of the brainstem in 827 the case of Parkinsonian syndromes. More precisely, we are involved in the data analysis part with the 828 objective to detect the anatomical connectivity of the brainstem structures and their connectivity to 829 the brain and we hope to find new neuroimaging markers of deep brain nuclei that could be used for 830 the diagnosis of Parkinsonian syndromes at an early stage. Possible extension and improvements of the 831 tractography algorithms presented here would be necessary to obtain a satisfactory spatial resolution for 832 identifying the anatomical network involved in Parkinson's disease and improve the characterization of 833 lesions of deep brain structures. 834

An important application where dMRI is expected to significantly impact in the close future is Traumatic Brain Injury (TBI), which is the damage caused to the brain due to external mechanical force, such as rapid acceleration or deceleration, falls, motor vehicle accidents, impact or penetration by a projectile. The worst injuries can lead to permanent brain damage or death. Because a sudden and violent trauma to the head can cause injury to and shearing of the white matter fibers, it's indeed possible to use dMRI to examine the integrity of white matter that is especially vulnerable to TBI. This opens the way to exciting and challenging problems to quantify and qualify structural changes in white matter.

To this date, a large number of dMRI clinical studies of TBI only uses simple scalar diffusion measurements such as FA and/or MD to characterize the structural abnormalities present along a given fiber pathway to identify pathologies and compare patients with healthy controls. This clearly opens the road to many exciting and challenging problems to examine with more elaborate diffusion models the white matter's integrity and to better quantify and qualify structural changes in white matter.

Through our collaborations with clinical partners and our development of innovative tensor and HARDI processing methods, we are convinced that we can advance further our ability to better understand the architecture of the CNS and help to prove that dMRI can provide a relevant source of useful information, such as in vivo markers of diseases in clinical neuroscience.

Efficient and better tools are therefore more than welcome for undertaking a more systematic study of these abnormalities. For instance, HARDI's improved signal-to-noise ratio can image fiber paths with extraordinary angular detail, identifying more relevant anatomical features, connections and disease biomarkers not seen with conventional MRI.

Moving from quantitative comparisons of scalar values derived from second order diffusion tensors in voxels or along existing pathways, to more relevant measures based on higher order diffusion models and demonstration of qualitative changes in white matter anatomy is extremely challenging.

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Therefore, key challenges to tackle include defining new biomarkers related to the quantities, scalar or not, that could be retrieved from High Order Tensors, HARDI, Q-Ball or the EAP to better describe and characterize the biological tissue being analyzed.

Overall, one of the main objectives now is to apply the new methodological developments to improve dMRI as a clinical tool and make it more apt in characterizing and quantifying abnormalities within CNS white matter and to develop better neuroimaging markers for the diagnosis of CNS neurodegenerative diseases. There is a consensus in the neuroimaging field that more elaborate models and HARDI measures will certainly advance research in a large number of CNS diseases.

We are confident that the recent development of novel mathematical analysis tools for dMRI and HARDI will certainly result in fundamental advances for research on stroke, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's and Parkinson's diseases, HIV/AIDS, neurosurgery, tumor growth modeling or neuropsychiatric disorders like schizophrenia. Moreover, our understanding of the development of the human brain, the effect of aging or the organization of anatomo-functional networks has already started to greatly benefit from the unprecedented insight that dMRI provides into the brain's microstructure.

1.8 Conclusion

In this chapter we presented an overview of the mathematical tool and framework of dMRI. Diffusion 874 MRI is unique in its capacity at inferring the microstructure of the cerebral white matter in vivo and 875 non-invasively, albeit in an indirect fashion. We first presented a quick perusal of the brain its general 876 structure and organization, the tissues constituting it, and in highlight, its major neuronal pathways 877 interconnecting its various regions. These are central for understanding the diffusion of water molecules 878 in the brain, and for understanding the usefulness of dMRI in studying the brain. The Brownian motion 879 of the water molecules contained in the brain is hindered in the white matter by its fibrous structures 880 in a particular fashion. While the diffusion of water molecules is greatly hindered perpendicular to these 881 structures, the diffusion parallel to these structures is relatively less affected. In other words the diffusing 882 water molecules probe the white matters microstructure. Therefore, since dMRI is sensitive to the diffusion 883 of water molecules, it is used to measure the constrained or anisotropic diffusion of water molecules in 884 the white matter, to infer its major axon fiber bundles non-invasively. 885

Next we presented the fundamentals of the NMR phenomenon, the diffusion NMR experiment, and 886 reviewed three important diffusion MRI reconstruction algorithms. The NMR experiment can recover 887 several different physical properties from samples which contain spin bearing particles by simply applying 888 a set of magnetic fields and gradients. This forms the core of the non-invasive nature of MRI. However, 889 NMR can only examine a tiny region of a sample or a single spin ensemble and cannot image an entire 890 biological specimen. This is made possible by the spatial encoding technique of MRI, which allows to 891 spatially encode various juxtaposed regions or spin ensembles where NMR can be applied independently. 892 This is done in MRI again using magnetic gradients. Therefore, this allows MRI to examine entire 893 biological specimen, like the brain or the body, in vivo and non-invasively. 894

One of the properties that NMR can be sensitized to is the Brownian motion of the spin bearing particles in a sample. Therefore, NMR can be used to measure the diffusion properties of a sample by modelling the diffusion of the spin bearing particles in the sample. Since diffusion has been historically modelled in two different ways, namely the Ficks phenomenological laws of diffusion and Einsteins random walk model of Brownian motion, the diffusion NMR signal is also modelled in two ways, namely the Stejskal-Tanner formulation and the q-space formalism.

DTI was the first dMRI technique that was proposed to infer the tissue microstructure. It is the most commonly used technique since its mathematical framework is simple, it has few acquisition requirements and has a number of powerful and practical applications. However, it is limited in regions with microstructural heterogeneity. Many higher order techniques have been therefore proposed recently in dMRI to overcome this limitation of DTI. Of these we presented DSI and QBI, and in particular the ODF.

⁹⁰⁷ Diffusion MRI data represents images that contain complex mathematical objects. Recently the com-⁹⁰⁸ putational framework of mathematical tools required to process such images has been vastly improved. ⁹⁰⁹ We presented the appropriate metrics, in particular the Riemannian metric for Sym_n^+ , an estimation ⁹¹⁰ algorithm and a segmentation framework using this metric for DTI. DTI, ODFs and other general SDFs represent the local microstructure of the cerebral white matter in each voxel. As the final mathematical tools we presented tractography algorithms which spatially integrate anisotropy information to reconstruct more global structures such as white matter fiber tracts. Tractography is a unique tool which permits one to indirectly dissect and visualize the brain's white matter in vivo and non-invasively

Finally we concluded the chapter with an overview of major clinical applications to highlight and emphasize the usefulness and strengths of dMRI.

⁹¹⁸ 1.9 Online Resources: Softwares and Databases

919 <u>medINRIA</u> http://www-sop.inria.fr/asclepios/software/MedINRIA/

medINRIA is a multi-platform medical image processing and visualization software, and it's free. Through an intuitive user interface, medINRIA offers from standard to cutting-edge processing functionalities for your medical images such as 2D/3D/4D image visualization, image registration, or dMRI

⁹²³ processing and tractography. medINRIA was initially developed by the Asclepios Project Team, IN-

RIA, France. A new version of medINRIA is being jointly developed by the Asclepios, Athena, Parietal

and the Visages INRIA Project Teams. It also has a new website at http://med.inria.fr/

⁹²⁶ Key Features: Log-Euclidean metric, HARDI/ODF, Fiber Tracking.

928 BrainVISA/Anatomist http://brainvisa.info/

⁹²⁹ BrainVISA/Anatomist is developed by the Institut Fédératif de Recherche no.49, France.

- BrainVISA is a software, which embodies an image processing factory. A simple control panel allows the user to trigger sequences of treatments on series of images. These treatments are performed by calls to command lines provided by different laboratories. These command lines, hence, are the building blocks on which are built the assembly lines of the factory.
- Anatomist is a visualization software, which main originality is a generic module dedicated to 934 structural data, namely sets of objects linked one another into a graph structure. These objects 935 may be cortical folds inferred from T1 weighted MR data, fiber bundles inferred from MR diffusion 936 weighted data, activated clusters inferred from Statistical Parametric Maps, etc... This module 937 includes a nomenclature control panel, which can drive several brains simultaneously. Anatomist 938 provides also some tools to easily map Statistical Parametric Maps on 3D renderings of the brain, 939 inflated meshes of the cortical surface, etc... Finally, a manual drawing toolbox can be used for 940 various purpose. 941
- ⁹⁴² Key Features: toolboxes for T1-MRI, dMRI (DTI, QBI), fMRI, MEG/EEG, etc.

944 FMRIB Software Library (FSL) http://www.fmrib.ox.ac.uk/fsl/index.html

FSL is a comprehensive library of analysis tools for fMRI, MRI and DTI brain imaging data. FSL
is written mainly by members of the Analysis Group, fMRIB, Oxford, UK. FSL runs on Apple and
PCs (Linux and Windows), and is very easy to install. Most of the tools can be run both from the
command line and as GUIs ("point-and-click" graphical user interfaces).

- Key Features: Diffusion toolbox contains tools for low-level diffusion parameter reconstruction and
 probabilistic tractography, including crossing-fiber modelling. It is also capable of tract-based spatial
- statistics voxel-wise analysis of multi-subject diffusion data.
- 953 Camino Diffusion MRI Toolkit http://web4.cs.ucl.ac.uk/research/medic/camino/pmwiki/pmwiki.php
- Camino is a free, open-source, object-oriented software package for analysis and reconstruction of
 dMRI data, tractography and connectivity mapping. It is developed by the Microstructure Imaging
 Group, University College London, UK.
- Key Features: DTI, multi-tensor model, QBI, MESD/PAS-MRI, deterministic/probabilistic tractog raphy, synthetic data generation and more.
- 960 MRI Studio An Image Processing Program https://www.mristudio.org/
- MRI Studio is an image processing program running under Windows. It is suitable for such tasks as tensor calculation, color mapping, fiber tracking, and 3D visualization. Most of operations can be done
- tensor calculation, color mapping, fiber tracking, and 3D visualization. Most of operations can be done with only a few clicks. DTI Studio is being developed through the support of the Laboratory of Brain

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- 1 From Diffusion MRI to Brain Connectomics
- Anatomical MRI and Center for Imaging Science at Johns Hopkins University, USA.
- Key Features: DTI, Fiber-tracking and editing, 3D visualization, Region of Interesting (ROI) draw ing and statistics, image registration.

3D Slicer http://www.slicer.org/

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- ⁹⁶⁹ Slicer, or 3D Slicer, is a free, open source software package for visualization and image analysis. 3D
- Slicer is natively designed to be available on multiple platforms, including Windows, Linux and Mac
 Os X. 3D Slicer provides image registration, processing of DTI (diffusion tractography), an interface
 to external devices for image guidance support, and GPU-enabled volume rendering, among other
 capabilities. It is developed by the Surgical Planning Laboratory, Brigham and Women's Hospital and
 the Harvard Medical School, USA.
- **Key Features:** Functionality for segmentation, registration and 3D visualization of multi-modal image data, advanced image analysis algorithms for DTI and fMRI, supports standard image file formats.

978 MRtrix: MR tractography including crossing fibers http://www.nitrc.org/projects/mrtrix/

- MRtrix provides a set of tools to perform diffusion-weighted MRI white matter tractography in the presence of crossing fibers, using Constrained Spherical Deconvolution, and a probabilistic streamlines algorithm. These applications have been written from scratch in C++, using the functionality provided by the GNU Scientific Library, and gtkmm. The software is currently capable of handling DICOM and AnalyseAVW image formats, amongst others. The source code is distributed under the GNU General Public License. MRtrix is being developed by the Brain Research Institute (BRI), Melbourne, Australia.
- Key Features: Detection of crossing fibers using Constrained Spherical Deconvolution, probabilistic
 streamline fiber tracking.

989The Fiber Cup Phantom Databasehttp://www.lnao.fr/spip.php?rubrique79

- The Fiber Cup was originally intended to be a tractography contest at the MICCAI conference help in London in 2009. Today, the Fiber Cup is still open and is intended to provide a common dataset with known ground truth along with an evaluation methodology to compare and challenge tractography algorithms. It was developed at Neurospin, CEA, France.
- Key Features: Provides a MR phantom containing a plethora of crossing, kissing, splitting and
 bending fiber configurations, acquisitions done at three b-values providing dMRI data on three q-ball
 shells.

997 List of Acronyms

- 998 ADC Apparent Diffusion Coefficient
- 999 CC Corpus Callosum
- 1000 **CNS** Central Nervous System
- 1001 **CR** Corona Radiata
- 1002 **CST** Corticospinal Tract
- $_{1003}$ $\,$ dMRI Diffusion Magnetic Resonance Imaging
- 1004 **dNMR** Diffusion Nuclear Magnetic Resonance
- $_{1005}$ $\ \mbox{DT}$ Diffusion Tensor
- 1006 **DTI** Diffusion Tensor Imaging
- 1007 **DSI** Diffusion Spectrum Imaging
- 1008 **DWI** Diffusion Weighted Image
- 1009 **EAP** Ensemble Average Propagator
- 1010 **EPI** Echo Planar Imaging
- ¹⁰¹¹ **FA** Fractional Anisotropy
- ¹⁰¹² **FRT** Funk Radon Transform
- 1013 HARDI High Angular Resolution Diffusion Imaging
- $_{1014}$ $\,$ ILF Inferior Longitudinal Fasciculus
- 1015 **MD** Mean Diffusivity
- 1016 **NGP** Narrow Gradient Pulse
- 1017 **NMR** Nuclear Magnetic Resonance

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- 1018 **ODF** Orientation Distribution Function
- 1019 **PD** Parkinson's disease
- 1020 **PDF** Probability Density Function
- ¹⁰²¹ **PGSE** Pulsed Gradient Spin Echo
- ¹⁰²² **PNS** Peripheral Nervous System
- 1023 **QBI** Q-Ball Imaging
- 1024 **RA** Relative Anisotropy
- ¹⁰²⁵ **SDF** Spherical Diffusion Function
- 1026 **SH** Spherical Harmonics
- 1027 **SLF** Superior Longitudinal Fasciculus
- 1028 **TBI** Traumatic Brain Injury

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