

École polytechnique de Louvain

Advanced methodologies in multi-shell diffusion-weighted MRI: Integrating Spherical Mean Technique with NODDI and improving noise estimation in Microstructure Fingerprinting

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Academic year 2023–2024

Master [120] in Mathematical Engineering

Abstract

This thesis explores advanced methodologies in Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) to enhance the analysis and characterization of brain microstructure. In DW-MRI, the processing of DW-MRI signal by complex analytical or numerical models allows the interpretation of the DW-MRI signal into biophysical models that can be related to actual histological compartments in vivo. However, the use of models and the assumptions associated with them introduces biases and errors in the final estimation. This work aims to improve parameter estimations in Neurite Orientation Dispersion and Density Imaging (NODDI) and Microstructure Fingerprinting (MF) by reducing assumptions and biases. The study is divided into two parts: integrating the NODDI model with the Spherical Mean Technique (SMT) for Multiple Sclerosis (MS) analysis and incorporating noise estimation techniques into the MF model.

In the first part of this study, we combine NODDI and SMT to enhance microstructural parameter estimation in MS. A key limitation of NODDI is its assumption of fixed parallel diffusivity across voxels. By leveraging SMT for voxel-wise diffusivity estimation, we refine NODDI parameter fitting. Our synthetic experiments demonstrate reduced absolute errors in parameter estimates at higher Signal-to-Noise Ratio (SNR) values (25+). In vivo analysis further shows improved model fit and clear distinctions between white and gray matter regions. Importantly, this method reveals significant differences between the normal-appearing white matter of healthy controls and MS subjects, indicating increased sensitivity to subtle disease-related microstructural changes.

The second part of this study aims to enhance the robustness of the MF model by integrating noise estimation techniques. Recognizing that preprocessing alone cannot fully eliminate noise, we introduced a noise parameter to the MF model to prevent diffusion parameters from compensating for noise. Our synthetic experiments show significantly improved fit quality and reduced errors across all SNR levels. In higher SNR settings, our model matches or surpasses ML-enhanced MF models in accurately estimating parameters. Moreover, in vivo data experiments reveal that our method produces parameter estimates more consistent with known brain anatomy and improves the quality of fit, as indicated by higher R^2 scores, despite an observed increase in MSE in central brain regions.

Overall, this thesis contributes to the field of DW-MRI by proposing innovative approaches to enhance microstructural imaging. The combined NODDI-SMT method offers a promising tool for MS research, while the noise-estimation-enhanced MF model shows potential for broader clinical applications. Future research should focus on optimizing the speed of the fitting process and further improving noise estimation techniques to fully realize the benefits of these methods.

Acknowledgements

I would like to express my deepest gratitude to my supervisor, Professor Benoît Macq, for giving me the opportunity to work on this fascinating topic. I have always wanted to apply mathematics to research with the potential to make a positive social impact, and the medical field felt like the perfect avenue for this pursuit. I am especially grateful to him for trusting me and believing in my ability to undertake this project, despite my lack of prior knowledge in biomedical engineering

I am also immensely thankful to Colin Vanden Bulcke and Quentin Dessain for their invaluable support throughout the course of my thesis work. Their patience and guidance in navigating this complex field were instrumental to my progress. I am particularly grateful for the insightful feedback they provided during the writing process, as well as their readiness to answer questions and offer assistance whenever needed.

Additionally, I would like to thank Clément Fuchs for his active involvement throughout this work. His ideas and insights contributed significantly to the development of my research, and I greatly appreciate his dedication and support.

Finally, I would like to express my heartfelt thanks to my parents for their unwavering support and encouragement throughout my studies and during the research and writing of this thesis. Their belief in me has been a constant source of motivation.

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List of Acronyms

A Atomic Mass.

AD Axial Diffusivity.

AUC Area Under the Curve.

CNS Central Nervous System.

CSF Cerebrospinal Fluid.

DTI Diffusion Tensor Imaging.

DW Diffusion-Weighted.

DWI Diffusion Weighted Imaging.

DW-MRI Diffusion-Weighted Magnetic Resonance Imaging.

EPI Echo Planar Imaging.

FA Fractional Anisotropy.

FID Free Induction Decay.

FLAIR Fluid Attenuated Inversion Recovery.

FOV Field of View.

Gad Contrast-Enhancing Lesion.

GM Gray Matter.

HC Healthy Control.

MAE Mean Absolute Error.

MD Mean Diffusivity.

MF Microstructure Fingerprinting.

ML Machine Learning.

MLP Multi-Layer Perceptron.

MR Magnetic Resonance.

MRF Magnetic Resonance Fingerprinting.

MRI Magnetic Resonance Imaging.

MS Multiple Sclerosis.

MSE Mean Squared Error.

NABT Normal-Appearing Brain Tissue.

NAGM Normal-Appearing Gray Matter.

NAWM Normal-Appearing White Matter.

NDI Neurite Density Index.

NLLS Non-Linear Least Squares.

NMR Nuclear Magnetic Resonance.

NNLS Non-Negative Least Squares.

NODDI Neurite Orientation Dispersion and Density Imaging.

ODI Orientation Dispersion Index.

PGSE Pulse Gradient Spin Echo.

PP Primary-Progressive.

PPMS Primary-Progressive Multiple Sclerosis.

PRL Paramagnetic Rim Lesion.

PRLs Paramagnetic Rim Lesions.

RD Radial Diffusivity.

RF Radio Frequency.

ROC Receiving Operator Curve.

ROI Regions of Interest.

RR Relapsing-Remitting.

RRMS Relapsing-Remitting Multiple Sclerosis.

SE Spin Echo.

SLSQP Sequential Least Squares Programming.

SMT Spherical Mean Technique.

SNR Signal-to-Noise Ratio.

SP Secondary-Progressive.

SPMS Secondary-Progressive Multiple Sclerosis.

SVM Support Vector Machine.

TE Echo Time.

TR Repetition Time.

tSNR Temporal Signal-to-Noise Ratio.

WM white Matter.

Z Atomic Number.

Introduction

Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) has become a crucial tool in neuroimaging, providing valuable insights into the microstructural organization of brain tissue. By measuring the diffusion of water molecules in biological tissues, DW-MRI enables the characterization of white matter pathways, tissue integrity, and microstructural alterations associated with various neurological conditions. However, accurately estimating microstructural parameters from DW-MRI data remains a challenging task due to the complex nature of brain tissue and the presence of noise in the acquired signals.

This thesis aims to advance the field of DW-MRI by investigating two distinct approaches: the application of the Neurite Orientation Dispersion and Density Imaging (NODDI) [1] model combined with the Spherical Mean Technique (SMT) for studying Multiple Sclerosis (MS), and the integration of noise estimation techniques into the Microstructure Fingerprinting (MF) [2] model to enhance its robustness.

MS is a chronic inflammatory disease characterized by the degradation of myelin sheaths and axonal damage in the central nervous system. Traditional diffusion imaging techniques, such as Diffusion Tensor Imaging (DTI) [3], often fall short in detecting the subtle microstructural changes associated with MS. The NODDI model has shown promises in analyzing MS pathology [4]. NODDI relies on the assumption of fixed parallel diffusivity (i.e., the diffusivity of water molecules along the direction of the axons) to a typical in vivo value across all brain voxels. Recent studies [5] have challenged this assumption. Building on the work by Cabeen et al. [6], who proposed a method to estimate and fix the volume fractions of the NODDI model using the Spherical Mean Technique (SMT), and the framework proposed by Kaden et al. [7], [8] for estimating parallel diffusivities, we propose a new SMT-based NODDI model. This model uses SMT to estimate and fix the parallel diffusivity value voxel-wise in the NODDI model before fitting the remaining parameters. We anticipate that this approach will yield parameters that more accurately reflect the underlying microstructures of the brain.

This thesis is structured into three main parts. The first part provides the theoretical foundations necessary to understand the methods and results presented in the subsequent sections. It covers the theory behind Magnetic Resonance Imaging (MRI) and DW-MRI and offers a detailed description of the microstructural models which are explored in the following parts.

The second part investigates the application of the NODDI-SMT framework in an MS

application. It begins with a brief theoretical explanation of MS pathology and the SMT, followed by a literature review of NODDI applications in MS studies. Finally, we explore the practical application of our model in the context of MS, aiming to gain a deeper understanding of the disease's impact on brain tissue and to identify reliable biomarkers for MS.

In the third and final part, we shift our focus to the MF model. One of the primary challenges of this model is its sensitivity to noise, which can significantly affect the accuracy of parameter estimation. To address this issue, we incorporate noise estimation techniques into the MF model. By explicitly modeling the noise in the diffusion signal, we aim to enhance the robustness and accuracy of the parameter estimates.

Throughout this thesis, we aim to demonstrate the potential of these advanced modeling techniques to enhance our understanding of brain microstructure and to improve the diagnostic capabilities of DW-MRI. The results presented here highlight the strengths and limitations of the NODDI-SMT and MF models, providing a comprehensive evaluation of their performance in both synthetic and in vivo settings.

Part I

Theoretical Background

Chapter 1

Magnetic Resonance Imaging

In this first chapter, we establish the theoretical foundations necessary to understand the advanced diffusion Magnetic Resonance Imaging (MRI) techniques explored later in this thesis. We begin by covering the fundamental principles of MRI and Diffusion Weighted Imaging (DWI), followed by an in-depth discussion of the microstructural models that serve as the basis for our subsequent analyses.

1.1 Magnetic Resonance Imaging

MRI is a non-invasive technology that produces anatomical images, widely used for detecting diseases, diagnosing conditions, and monitoring treatments.

1.1.1 Nuclear Magnetic Resonance

MRI operates on the principle of Nuclear Magnetic Resonance (NMR). Every atomic nucleus possesses a characteristic angular momentum known as spin. The quantum number I , associated with nuclear spin, is determined by the Atomic Mass (A) and Atomic Number (Z).

For MRI applications, the primary element of interest is hydrogen (^1H) because it is abundant in the human body and has a significant magnetic moment. Hydrogen (^1H) has a spin quantum number $I = 1/2$.

A nucleus with spin behaves like a tiny magnet due to its angular momentum. In the absence of an external magnetic field, the nuclear spins are randomly oriented, leading to no net macroscopic magnetization as can be seen in Figure 1.1A:

$$\mathbf{M} = \frac{1}{V} \sum_i \boldsymbol{\mu}_i = 0, \quad (1.1)$$

where V represents the volume under consideration and $\boldsymbol{\mu}_i$ denotes the magnetic moments of the nuclei.

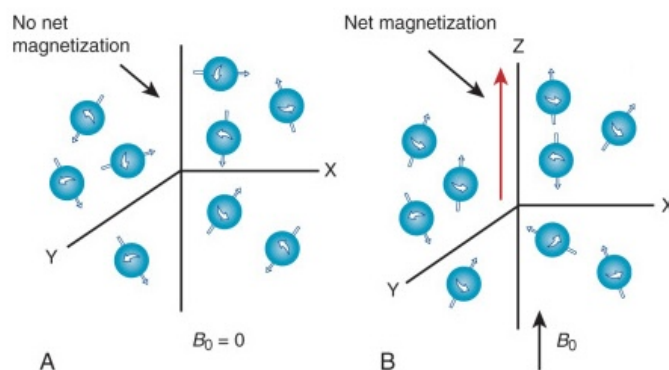


Figure 1.1: **Illustration of the behavior of nuclear spins in the absence of (A) and in the presence of (B) an external magnetic field (B_0).** In the absence of an external magnetic field ($B_0 = 0$), the nuclear spins are randomly oriented, resulting in no net macroscopic magnetization. When exposed to an external magnetic field ($B_0 = B_0 \mathbf{1}_z$), the spins tend to align with the field, resulting in net magnetization along the direction of the field. (Adapted from [9]).

When exposed to an external magnetic field $\mathbf{B}_0 = B_0 \mathbf{1}_z$, the spins tend to align with the field (See Figure 1.1B). Quantum mechanics dictates that each spin can only align in discrete orientations, determined by $2I + 1$. For hydrogen (^1H), this results in two possible alignments: parallel (spin-up) or anti-parallel (spin-down).

Furthermore, a magnetic moment in a magnetic field experiences a torque, which induces a precessional motion around the field direction at the Larmor frequency f_0 :

$$f_0 = \gamma B_0, \quad (1.2)$$

where γ is the gyromagnetic ratio (42.58 MHz/T for ^1H). This precession movement is illustrated in figure 1.2

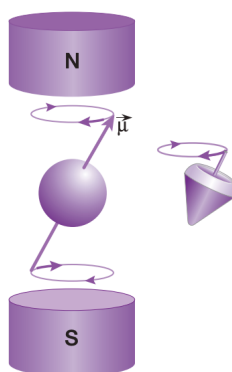


Figure 1.2: **Illustration of precession motion.** A magnetic moment in an external magnetic field experiences a torque, resulting in precessional motion around the field direction at the Larmor frequency, $f_0 = \gamma B_0$. The gyromagnetic ratio γ is 42.58 MHz/T for ^1H . This precession motion is depicted with the magnetic moment (represented by the vector $\vec{\mu}$) tracing out a cone-shaped path as it precesses around the axis of the magnetic field. (Adapted from [10]).

The macroscopic magnetization that results from applying an external magnetic field primarily aligns along the z-axis:

$$\mathbf{M} = M_z \mathbf{1}_z. \quad (1.3)$$

The difference in energy between the spin-up and spin-down states is given by:

$$\Delta E = E_\downarrow - E_\uparrow = hf_0, \quad (1.4)$$

where h is the Planck constant. The parallel orientation is at a lower energy level and is hence more populated. The ratio of populations in the two energy states is given by:

$$\frac{N_\uparrow}{N_\downarrow} = \exp\left(\frac{\Delta E}{kT}\right), \quad (1.5)$$

with k being the Boltzmann constant. The longitudinal magnetization, M_z , can be expressed as:

$$M_z = M_0 = \frac{\gamma^2 h^2 \rho B_0 I(I+1)}{3kT}, \quad (1.6)$$

where ρ is the spin density.

1.1.2 Magnetic Resonance Imaging

In the presence of an external magnetic field, the magnetization $\mathbf{M} = M_0 \mathbf{1}_z$ is relatively small compared to the external field, making direct measurement challenging. To facilitate measurement, the magnetization must be disturbed from the direction of the external magnetic field using a Radio Frequency (RF) pulse. RF pulses oscillating at the Larmor frequency are the most effective for energy transfer and hence often used, though other frequencies may be used for specific applications. In this context, we will consider RF pulses oscillating at the Larmor frequency. The magnetic field perturbed by an RF pulse oscillating at this frequency is expressed as:

$$\mathbf{B}_1(t) = 2B_1(t) \cos(2\pi f_{RF}t + \phi) \mathbf{1}_{xy}, \quad (1.7)$$

where $f_{RF} = f_0$. Since the RF pulse oscillates at the Larmor frequency, it carries an energy of ΔE , leading to a resonance phenomenon. This RF pulse induces transitions from the lower energy state $E_\uparrow$ to the higher energy state $E_\downarrow$, causing a reorientation of the longitudinal magnetization. Additionally, these state transitions cause the spins to synchronize, resulting in the development of transverse magnetization.

The angle the net magnetization is rotated through by the RF pulse is called the *flip-angle* and is defined by:

$$\alpha = \gamma \int_{T_{RF}} B_1(t) dt \stackrel{B_1(t) \text{ cst}}{=} \gamma B_1 T_{RF}, \quad (1.8)$$

with T_{RF} the duration of the RF pulse.

The commonly used RF pulses are those of 90° and 180° .

- The 90° RF pulse is used to rotate the net magnetization into the transverse plane. It is often called the *excitation pulse* as its primary role is flipping the net magnetization of the protons from its equilibrium position aligned with the external magnetic field into the transverse plane.
- The 180° RF pulse is used to invert the net magnetization. When used after a 90° RF pulse, it is often called a *refocusing pulse* as it is used to reverse the loss of coherence caused by magnetic field inhomogeneities. Magnetic field inhomogeneities are variations in the magnetic field strength within the imaging volume, which can cause the spins to dephase and lead to signal loss. The 180° RF pulse effectively reverses these dephasing effects, re-aligning the spins and restoring signal coherence.

The impact of these RF pulses is illustrated in Figure 1.3.

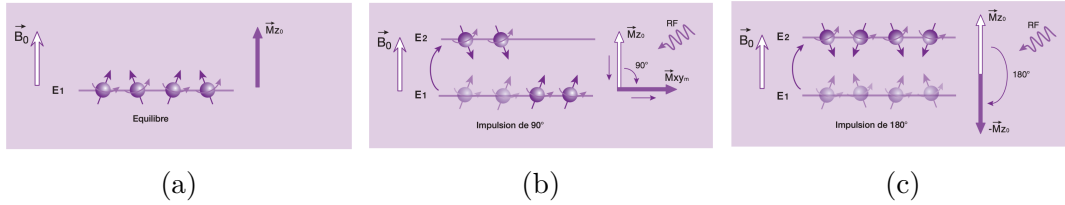


Figure 1.3: **Impact of Radio Frequency pulses on the net macroscopic magnetization.** (a) Resting state; (b) System after a 90° Radio Frequency pulse; (c) System after a 180° Radio Frequency pulse. (Adapted from [10])

1.1.3 Relaxation

After excitation, the spin system tends towards its equilibrium state, denoted $\mathbf{M}_0$. This process involves two primary mechanisms. The first one is called T_1 relaxation (see Figure 1.4) and the second T_2 relaxation (see Figure 1.6).

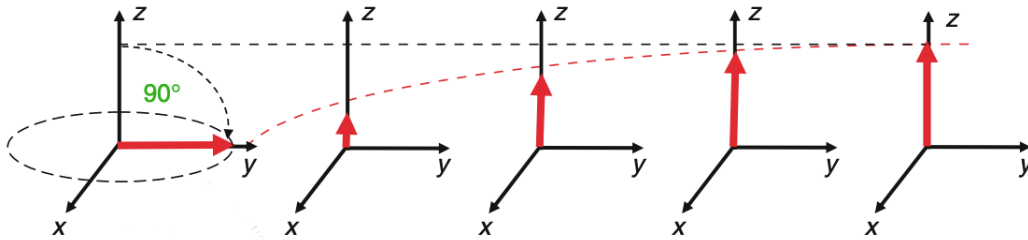


Figure 1.4: **T_1 relaxation after a 90° RF pulse.** This diagram illustrates the process of T_1 relaxation, where the net magnetization vector (red arrow) returns to its equilibrium state along the z-axis after being flipped into the transverse plane (y-axis) by a 90° RF pulse. The sequence shows the gradual recovery of the longitudinal magnetization over time. (Adapted from [11]).

T_1 relaxation (spin-lattice relaxation): After the RF pulse, through energy exchanges between the spins and the surrounding 'lattice' (thermic exchange, i.e.

collisions), the spins go back to their original energy level preceding the RF pulse excitation. As a result, the longitudinal magnetization M_z goes back to its equilibrium M_0 . This is described by the following mathematical expression:

$$M_z(t) = M_0 + (M_z(0) - M_0)e^{-\frac{t}{T_1}}, \quad (1.9)$$

where $M_z(0)$ is the longitudinal magnetization right after the RF pulse and T_1 is the time constant that describes the time needed to recover 63% of the equilibrium magnetization.

The efficiency of the energy transfer depends on the frequency of the molecular collision f_c . The closer it is to the Larmor frequency, the faster the recovery rate is. As the frequency f_c changes depending on the tissue, different responses will be observed for each tissues. This is illustrated in Figure 1.5.

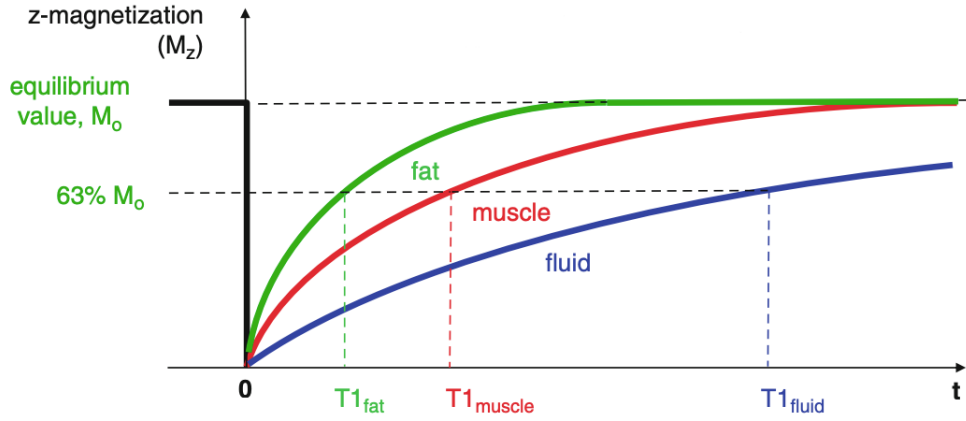


Figure 1.5: **Impact of tissue type on T1 relaxation.** The graph shows the z-magnetization (M_z) as a function of time (t) for different tissue types: fat, muscle, and fluid. The equilibrium magnetization value M_0 and the point at which the magnetization reaches 63% of M_0 are indicated. The T1 relaxation times ($T1_{fat}$, $T1_{muscle}$, $T1_{fluid}$) for each tissue type are also marked. (Adapted from [11]).

T2 relaxation (spin-spin relaxation): After the RF pulse, a phase shift occurs on the spins. Since they do not stay in phase, it results in the disappearance of the transverse magnetization M_{xy} . This phenomenon is the consequence of the interactions of the spins with each other and is thus called spin-spin relaxation. Protons progress in different molecular environments where small magnetic fields superpose with B_0 . Due to these inhomogeneities, the spins precess at different speeds and lose their phase coherence. This is described by the following mathematical expression:

$$M_{xy}(t) = M_{xy}(0)e^{-\frac{t}{T_2}}, \quad (1.10)$$

where $M_{xy}(0)$ is the transverse magnetization right after the RF pulse and T_2 is the time constant that describes the time needed for M_{xy} to lose 63% of its initial value. The T_2 time is also characteristic of the tissue and different responses are obtained depending on the environment.

In practice, the transverse magnetization decays faster than what is expressed previously. This is mainly due to inhomogeneities in the external magnetic field B_0 . This can be accounted for by introducing an effective relaxation time $T2^*$.

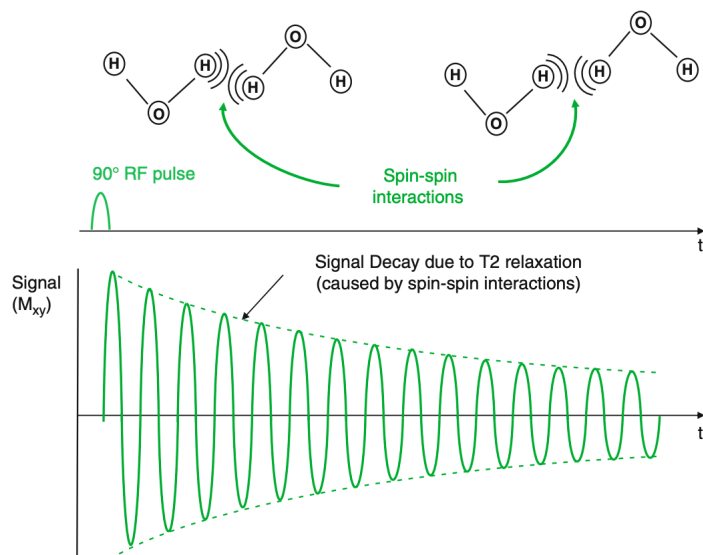


Figure 1.6: **T2 relaxation after a 90° Radio Frequency pulse.** This figure illustrates the T2 relaxation process, where the signal decays due to spin-spin interactions following a 90° RF pulse. The top section depicts molecular interactions that contribute to T2 relaxation. The bottom graph shows the exponential decay of the transverse magnetization signal (M_{xy}) over time, characterized by a decreasing amplitude of the oscillating signal. (Adapted from [11]).

The oscillating behavior of the transverse magnetization induces a signal known as the Free Induction Decay (FID). This signal is sinusoidal with an envelope decreasing exponentially according to the $T2^*$ constant as shown in Figure 1.7.

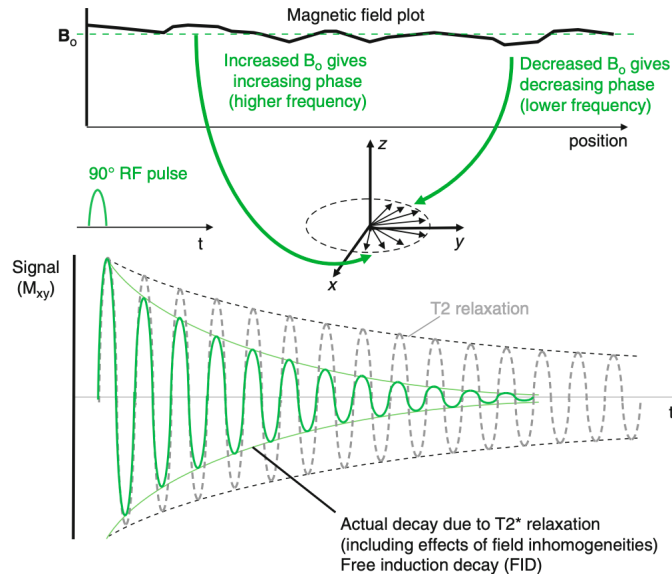


Figure 1.7: **Free Induction Decay (FID) signal.** This figure illustrates the FID process following a 90° RF pulse. The top section shows a magnetic field plot indicating how variations in B_0 cause changes in phase and frequency. The middle section depicts the precessional motion of the magnetization vector in the transverse plane (xy -plane) under the influence of field inhomogeneities. The bottom graph displays the resulting signal decay (M_{xy}) over time, combining effects of $T2^*$ relaxation (which includes field inhomogeneities) and $T2$ relaxation. The exponential decay of the transverse magnetization is represented by the diminishing amplitude of the oscillating signal. (Adapted from [11]).

1.1.4 Spin Echo sequence

The Spin Echo (SE) sequence, one of the earliest MRI sequences, consists of a 90° RF pulse followed by a 180° RF pulse. The 90° RF pulse is used to convert the longitudinal magnetization into a transverse one. Due to the field inhomogeneities, the spins rotate at different speeds and lose their coherence. At time $t = \tau$, a 180° RF pulse is applied to inverse the phase, causing the spins to progressively rephase. Finally, at time $t = 2\tau$, they fully refocus, causing a "spin echo". The sequence is illustrated in Figure 1.8.

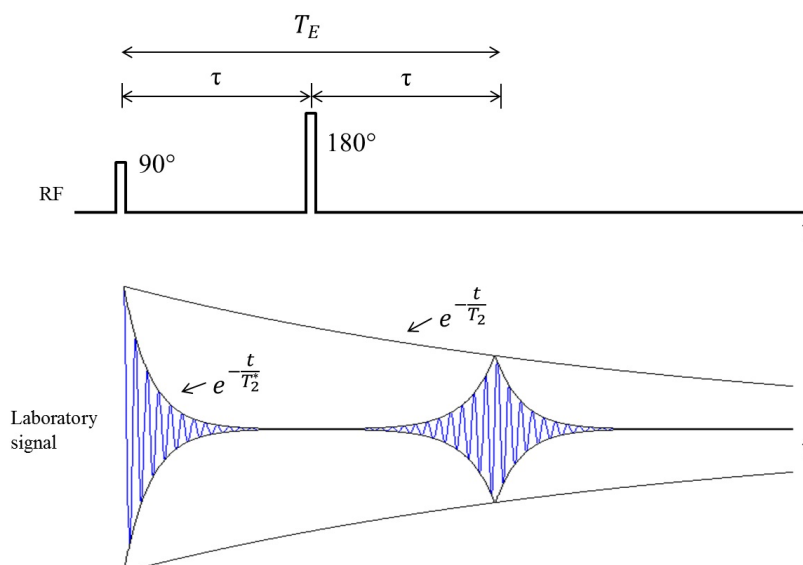


Figure 1.8: **Spin-Echo sequence.** This figure illustrates the Spin-Echo sequence used in MRI. The top section shows the timing diagram of the sequence, with a 90° RF pulse followed by a 180° RF pulse separated by a time interval τ , resulting in an echo at time T_E . The bottom section depicts the signal, showing the decay and subsequent refocusing of the transverse magnetization. The signal decay follows an exponential function $e^{-\frac{t}{T_2}}$, with the echo peak occurring at T_E .

This sequence is sensitive to variations in T_2 relaxation times and is used to generate different image contrasts by varying the Echo Time (TE) and the Repetition Time (TR). Specifically:

- Short TE and TR settings enhance T_1 -weighted contrast, useful for distinguishing between white and gray matter.
- Long TE and TR settings enhance T_2 -weighted contrast, which are advantageous for imaging fluid-filled spaces and detecting edema.

1.1.5 Spatial localization

In MRI, it is essential to selectively excite a specific region of the patient and accurately localize the MR signals within that region. This is accomplished using magnetic field gradients produced by gradient coils. A magnetic field gradient is a magnetic field whose strength varies linearly along a particular axis.

Slice selection gradient (G_{ss})

This magnetic gradient varies linearly along the z -direction, resulting in a Larmor frequency given by:

$$f(z) = \gamma(B_0 + G_{ss}z). \quad (1.11)$$

By using a RF pulse with a bandwidth $\Delta f = \gamma G_{ss} \Delta z$ and a center frequency $f_c = f_0 + \gamma G_{ss} z_0$, it is possible to excite only the spins within a slice of thickness

Δz located at z_0 .

The application of the gradient also induces a phase shift, necessitating a second gradient with an opposite slope and half the duration of the slice selection gradient. This compensates for the dephasing that occurs during the second half of the slice selection gradient, as transverse magnetization is generated halfway through the RF pulse.

During the 180° pulse, the same G_{ss} gradient must be applied to ensure that the pulse affects the protons that underwent the 90° pulse, i.e., the protons in the selected slice. This process is illustrated in Figure 1.9.

Frequency encoding gradient (G_ω)

To encode spatial information along the x -direction during acquisition, a gradient G_ω is applied along this axis. Consequently, the Larmor frequency becomes position-dependent along the x -direction, resulting in a signal composed of various frequencies. Each frequency corresponds to a unique location along the frequency encoding gradient. Additionally, the transverse magnetization acquires a phase shift given by:

$$\phi(x) = -\gamma G_\omega x t. \quad (1.12)$$

To prevent a net phase shift at the center of the echo, a focusing gradient is applied before the 180° pulse to compensate for this effect (see Figure 1.9).

Phase encoding gradient (G_ϕ)

To encode spatial information along the y -direction, a gradient G_ϕ is applied along this axis for a duration T_y following the 90° pulse. Consequently, the transverse magnetization acquires a phase shift given by:

$$\phi(y) = -\gamma G_\phi T_y. \quad (1.13)$$

Through frequency and phase encoding, the spins are uniquely defined by a frequency (along the x -direction) and a phase (along the y -direction), enabling their localization.

The MR signal is given by:

$$S(k_x, k_y) = \iint \rho(x, y) e^{-i2\pi(k_x x + k_y y)} dx dy, \quad (1.14)$$

where $\rho(x, y)$ represents the imaged spin density, and k_x and k_y are the indices of the k -space (the frequency domain used in MRI reconstruction). For an SE sequence, these are defined as:

$$\begin{cases} k_x = \gamma G_\omega t, \\ k_y = \gamma G_\phi T_y. \end{cases} \quad (1.15)$$

Equation 1.14 shows the relationship to the 2D Fourier transform. Each experiment with a specific phase encoding gradient fills one line of the k -space $S(k_x, k_y)$. The experiment is repeated multiple times with different phase encoding gradient values (see Figure 1.10), and the spatial image $\rho(x, y)$ is reconstructed using an inverse 2D Fourier transform.

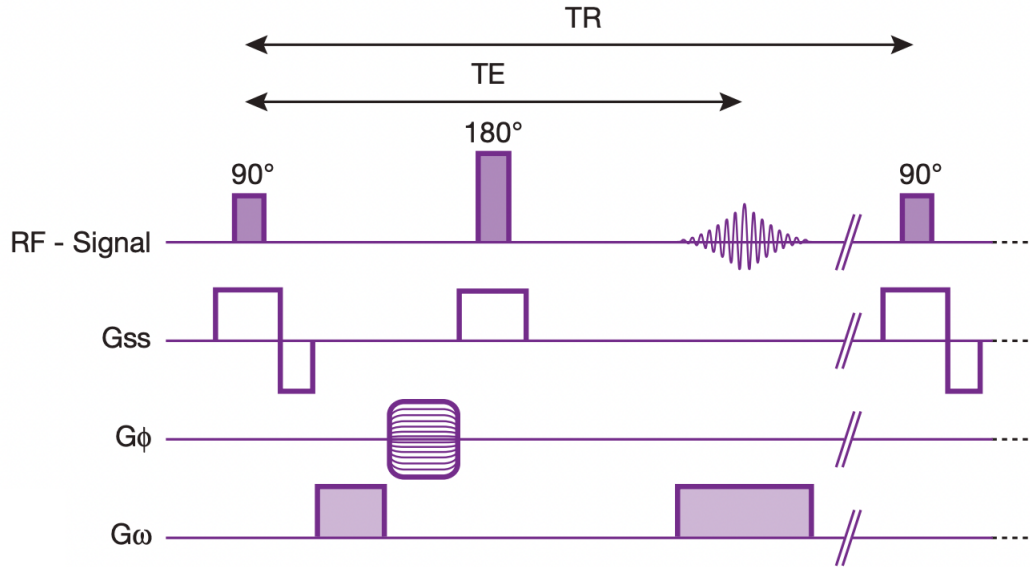


Figure 1.9: **Timeline of the events (RF pulses and three gradients) in a SE sequence.** (Adapted from [10]).

1. 90° RF pulse that must coincide with the slice selection gradient G_{ss} .
2. Phase encoding gradient G_ϕ (encoding of the lines of the k-space).
3. 180° RF pulse (which also coincides with a slice selection gradient: the 90° and 180° RF pulses have to select the same slice).
4. Frequency encoding gradient G_ω (encoding of the columns of the k-space) with the refocusing gradient turned on before the 180° RF pulse and the measurement gradient coinciding with the echo signal.

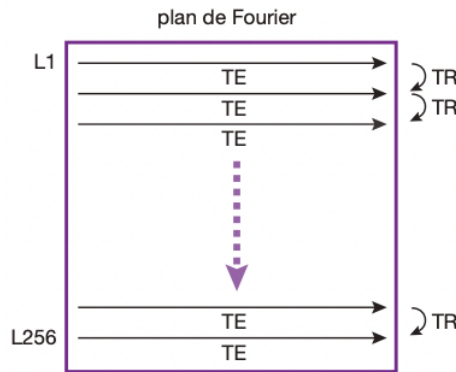


Figure 1.10: **Filling the k-space.** This diagram illustrates the process of filling k-space in MRI. Each line corresponds to a Spin Echo (SE) sequence with a different phase encoding gradient, resulting in a different line in the Fourier plane. In this example, there are 256 different phase encoding gradients in total, indicated by the lines labeled from L1 to L256. The Repetition Time (TR) and Echo Time (TE) are shown for each sequence. (Adapted from [10]).

For N_p different phase encoding gradients, the acquisition time is therefore given by

$$T_{acq} = N_p \times TR \times N_{ex}, \quad (1.16)$$

where N_{ex} is the number of excitations, that is, the number of measures of a same echo signal.

1.2 Diffusion-Weighted MRI

Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) is a technique that leverages the Brownian motion of water molecules to generate image contrast. This method is particularly sensitive to microstructural changes in tissues, offering superior specificity compared to conventional MRI by highlighting the impact of cellular structures on water molecule movement.

1.2.1 Pulse Gradient Spin Echo sequence

The Pulse Gradient Spin Echo (PGSE) sequence, commonly used in DW-MRI, incorporates two diffusion gradients (see Figure 1.11). The first gradient, applied after the 90° pulse, dephases the spins, while the second gradient, following the 180° pulse, rephases them.

The PGSE sequence is characterized by several parameters:

- Δ : time between the two diffusion gradients
- δ : duration of the diffusion gradients
- G : magnitude of the diffusion gradients.

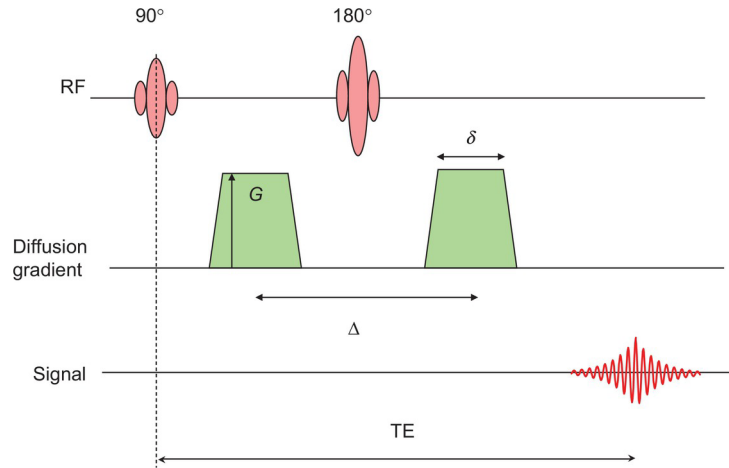


Figure 1.11: **Illustration of Pulse Gradient Spin Echo (PGSE).** This diagram shows the PGSE sequence, highlighting the key components of the RF pulses, diffusion gradients, and resulting signal. The 90° and 180° RF pulses are shown at the top, followed by the application of diffusion gradients (G) with a separation of Δ and duration δ . The bottom section depicts the signal and the Echo Time (TE). Gradients G_{ss} , G_ϕ , and G_ω are omitted for clarity. (Adapted from [12]).

These parameters can be summarized by a single scalar that characterizes the PGSE sequence, called the b-value [13] and defined as

$$b_{PGSE} = (\gamma G \delta)^2 (\Delta - \frac{\delta}{3}) \text{ [s/mm}^2\text{]}. \quad (1.17)$$

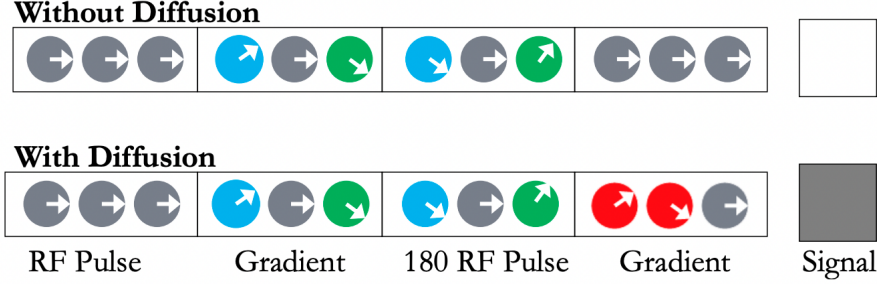


Figure 1.12: **Illustration of diffusion weighting.** This figure compares the effects of diffusion on the MR signal. The top row represents a scenario without diffusion, where water molecules do not diffuse. In this case, when the second diffusion gradient is applied, the spins refocus perfectly, resulting in a more intense signal. The bottom row represents a scenario with diffusion, where water molecules diffuse (e.g., in Cerebrospinal Fluid (CSF) or along an axon). In this case, the spins do not refocus perfectly due to the diffusion of the molecules, leading to signal attenuation. (Adapted from [14]).

The effect of the diffusion gradients on the spins is illustrated in Figure 1.12. The first diffusion gradient dephases the spins proportionally to their position along the axis of the gradient. After a time Δ , the second diffusion gradient rephases them accordingly. Therefore, if spins have moved due to diffusion along the direction of the diffusion gradients, they will not be correctly rephased and the signal will be attenuated (as the net magnetization will be smaller due to reduced phase coherence). In order to gather information about the diffusion along different directions, the experience has to be repeated multiple times with diffusion gradients pointing in different directions. These directions are known as the b-vectors.

1.2.2 Single and multi-shell acquisitions

Multi-shell acquisition of diffusion-weighted images is an advanced imaging technique that allows for the detailed analysis of brain tissue microstructure by varying the diffusion weighting (b-values) during image acquisition. Unlike single-shell DW-MRI, which uses a constant b-value, multi-shell DW-MRI employs multiple b-values, enabling the capture of more comprehensive information about the diffusion properties of water molecules in different tissue compartments.

The use of multiple shells allows for better results because it captures a wider range of diffusion behaviors, which improves the accuracy of microstructural models. Each b-value is sensitive to different aspects of water diffusion: lower b-values capture more general diffusion properties, while higher b-values provide information about more restricted diffusion environments. This multi-faceted approach helps in constructing a

comprehensive picture of tissue microstructure, leading to improved diagnostic capabilities and more precise characterizations of diseases such as multiple sclerosis [15].

However, using higher b-values comes with trade-offs. While higher b-values are more sensitive to detecting diffusion in tightly packed tissues and smaller cellular environments, they also increase the risk of noise and susceptibility to artifacts such as vibration. Higher b-values lead to a lower Signal-to-Noise Ratio (SNR), which can result in noisier images and reduced image quality. Additionally, these higher b-values make the images more susceptible to motion artifacts and distortions due to vibrations during the scanning process [16] (see Figure 1.13). Therefore, the choice of b-values in multi-shell DW-MRI involves balancing the need for detailed diffusion information against the potential increase in noise and artifacts.

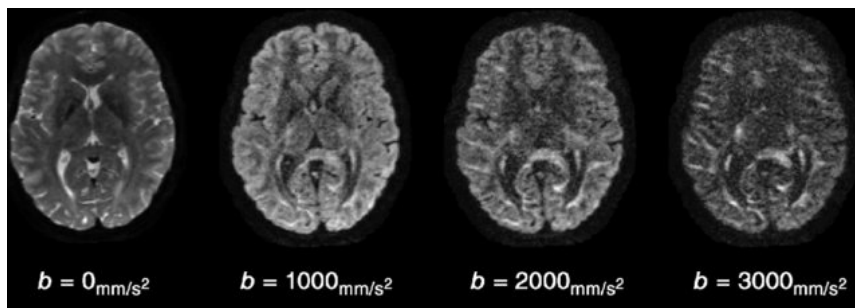


Figure 1.13: **Impact of the b-value on the diffusion signal.** Higher b-values will be more sensitive to detecting diffusion, but at the risk of more noise and more susceptibility to vibration artifacts. (Adapted from [7]).

1.2.3 Echo Planar Imaging

Echo Planar Imaging (EPI) [17] is a rapid MRI acquisition technique that significantly reduces scan times by capturing an entire 2D plane of data following a single RF excitation pulse. Unlike the classical SE sequence, which acquires one line of k-space per RF excitation and requires multiple excitations to fill k-space, EPI fills k-space in a single shot or in a few segmented shots (see Figure 1.15).

In EPI, the readout gradient rapidly alternates between positive and negative, generating multiple gradient echoes. This rapid switching allows for the entire k-space to be traversed in a zigzag pattern within a single acquisition period. The "blipped" single-shot EPI sequence further refines this process by briefly applying phase encoding gradients at each readout gradient zero crossing, reducing artifacts and improving spatial encoding efficiency. This acquisition scheme is represented in Figure 1.14.

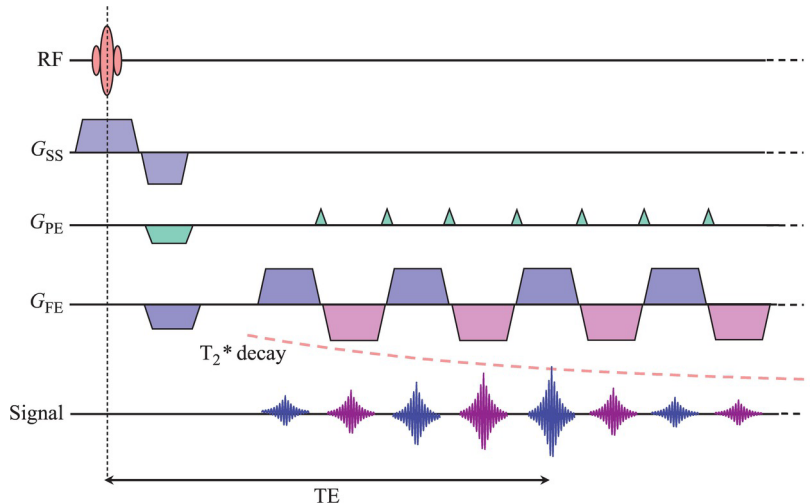


Figure 1.14: **Illustration of the "Blipped" single-shot Echo Planar Imaging (EPI) sequence.** This diagram illustrates the EPI sequence, including RF pulses, slice selection gradient (G_{SS}), phase encoding gradient (G_{PE}), and frequency encoding gradient (G_{FE}). The alternating readout gradient generates multiple echoes, filling k-space in a zigzag pattern. Phase encoding blips reduce artifacts and improve spatial encoding. (Adapted from [18]).

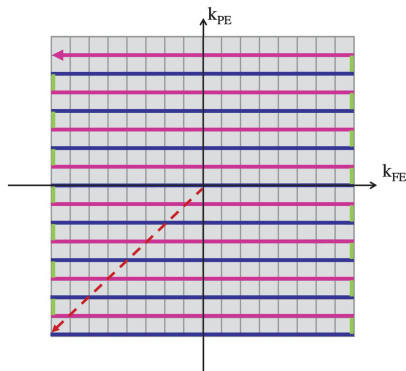


Figure 1.15: **Illustration of the k-space trajectory of a "blipped" single-shot Echo Planar Imaging (EPI) sequence.** This figure shows the zigzag k-space trajectory of the sequence, with blips in the phase encoding direction (k_{PE}) between readout lines in the frequency encoding direction (k_{FE}). (Adapted from [18]).

However, this speed comes with trade-offs, including increased sensitivity to magnetic susceptibility artifacts and often provides less spatial resolution than conventional sequences due to gradient limitations [19].

1.2.4 Diffusion Tensor Imaging

Diffusion Tensor Imaging (DTI) [3] models water diffusion in each voxel using a 3×3 diffusion tensor $\mathbf{D}$. This tensor describes how water diffuses along three orthogonal

axes and is used to infer tissue microstructure:

$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}, \quad (1.18)$$

which can be diagonalized to determine principal diffusion directions and magnitudes. The resulting eigenvalues and eigenvectors of $\mathbf{D}$ provide insights into the anisotropic or isotropic nature of the tissue microstructure. The diffusion tensors can be represented using an ellipsoid representation, as shown in Figure 1.16, where the shape of the ellipsoid indicates the degree of anisotropy and the direction of diffusion.

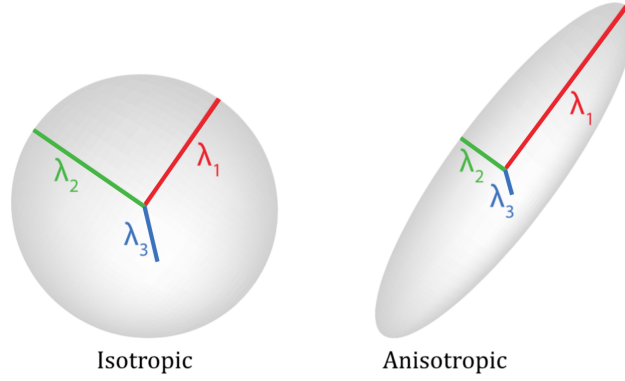


Figure 1.16: **Illustration of ellipsoid representation in Diffusion Tensor Imaging.** The isotropic case (left) shows equal diffusion along all three axes ($\lambda_1 = \lambda_2 = \lambda_3$), represented by a sphere. The anisotropic case (right) shows unequal diffusion along different axes ($\lambda_1 \neq \lambda_2 \neq \lambda_3$), represented by an ellipsoid. The lengths of the axes correspond to the eigenvalues of the diffusion tensor, indicating the magnitude of diffusion in each direction.

The relationship between the diffusion tensor $\mathbf{D}$ and the signal attenuation in a PGSE sequence with a specific b-value, b_{PGSE} , is described by the Stejskal-Tanner equation:

$$\frac{S(b_{PGSE}, \hat{\mathbf{g}})}{S_0} = e^{-b_{PGSE} \hat{\mathbf{g}}^T \mathbf{D} \hat{\mathbf{g}}}, \quad (1.19)$$

where $S(b_{PGSE}, \hat{\mathbf{g}})$ is the signal intensity measured with a diffusion gradient along the unit vector $\hat{\mathbf{g}}$ and S_0 is the baseline signal intensity obtained without any diffusion gradients. This fundamental equation allows for the quantification of diffusivities along different directions in the tissue.

To reliably estimate the diffusion tensor, which is symmetric, a minimum of six different gradient directions are necessary, in addition to a baseline measurement without diffusion weighting (referred to as the b_0 image) which has a b-value of $b = 0$ [s/mm^2].

1.2.4.1 Metrics derived from DTI

DTI provides several quantitative metrics that reflect different aspects of tissue microstructure:

- **Mean Diffusivity (MD)** is the average of the diffusion tensor's eigenvalues, representing the general mobility of water molecules within a voxel:

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \quad (1.20)$$

- **Axial Diffusivity (AD) and Radial Diffusivity (RD)** are measures of diffusivity along the primary diffusion direction and the average diffusivity perpendicular to it, respectively:

$$AD = \lambda_1 \quad (1.21)$$

$$RD = \frac{\lambda_2 + \lambda_3}{2} \quad (1.22)$$

- **Fractional Anisotropy (FA)** quantifies the degree of anisotropy in a voxel's diffusion properties. FA values range from 0 to 1, where 0 indicates isotropic diffusion (equal diffusivities in all directions), and 1 indicates highly anisotropic diffusion (diffusion predominantly along one direction):

$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad (1.23)$$

1.2.4.2 Advantages and limitations of DTI

Advantages:

- DTI is a straightforward and quick-to-implement model that yields valuable clinical metrics related to tissue architecture and myelination.
- DTI can be computed with a very light acquisition sequence which is ideal for clinical applications.

Limitations:

- DTI's interpretation can be challenging as it does not provide a direct measure of microstructural properties but rather an indirect phenomenological indication. The same DTI metrics could result from multiple different underlying tissue structures.
- A significant limitation is DTI's inability to resolve fiber crossings, which are present in approximately 60% to 90% of brain voxels [20], potentially leading to ambiguous or misleading interpretations in areas with complex fiber architectures.

1.3 Microstructural models

Due to the limitations of DTI outlined in Section 1.2.4.2, more sophisticated models have been developed to better capture the intricate microstructure of dendrites and axons. This section introduces two advanced multicompartment models, Neurite Orientation Dispersion and Density Imaging (NODDI) [1] and Microstructure Fingerprinting (MF) [2], which are designed to overcome DTI's shortcomings. These models employ the superposition principle, which posits that the observable MR signal is the sum of signals from distinct, non-interacting microstructural compartments.

1.3.1 Neurite Orientation Dispersion and Density Imaging

NODDI is a comprehensive model that distinguishes three specific compartments within each voxel (see Figure 1.17):

- **Intra-cellular compartment:** Enclosed by neurite membranes.
- **Extra-cellular compartment:** The space surrounding neurites, filled with various glial cells.
- **CSF compartment:** Regions occupied by cerebrospinal fluid.

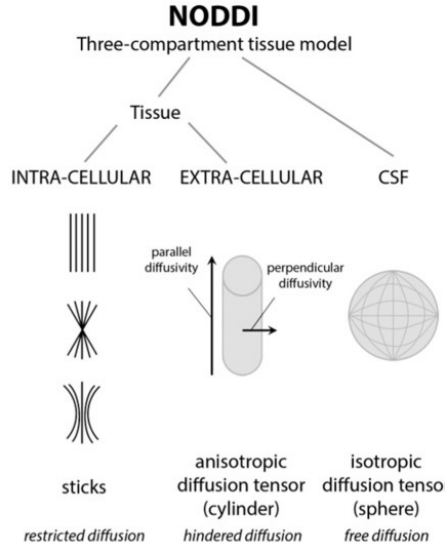


Figure 1.17: **Models of diffusion for NODDI.** (Adapted from [21]).

NODDI models these compartments independently to delineate their distinct contributions to water diffusion, subsequently integrating these using the superposition principle to compute the overall signal A :

$$A = (1 - \nu_{iso})(\nu_{ic}A_{ic} + (1 - \nu_{ic})A_{ec}) + \nu_{iso}A_{iso}, \quad (1.24)$$

where A_{ic} , A_{ec} , and A_{iso} represent the normalized signals from the intra-cellular, extra-cellular, and CSF compartments, respectively, with ν_{ic} and ν_{iso} denoting their respective volume fractions.

1.3.1.1 Intra-cellular model

The intra-cellular compartment is modeled as a collection of infinitely narrow cylinders (sticks), which restrict diffusion perpendicular to their orientation while allowing free diffusion along their length. The aggregate signal from this compartment, A_{ic} , is calculated as:

$$A_{ic} = \int_{\mathbb{S}^2} f(\mathbf{n}) e^{-bd_{\parallel}(\mathbf{q} \cdot \mathbf{n})^2} d\mathbf{n}, \quad (1.25)$$

where $\mathbf{q}$ represents the diffusion gradient vector, b the b-value, and $d_{||}$ the axial diffusivity. The distribution function $f(\mathbf{n})$, modeled by a Watson distribution, describes the orientation dispersion of the sticks:

$$f(\mathbf{n}) = M \left(\frac{1}{2}, \frac{3}{2}, \kappa \right)^{-1} e^{\kappa(\boldsymbol{\mu} \cdot \mathbf{n})^2}, \quad (1.26)$$

where κ is the concentration parameter, and $\boldsymbol{\mu}$ represents the mean orientation of the neurites.

1.3.1.2 Extra-cellular model

The extra-cellular space is modeled with a Gaussian anisotropic diffusion process, influenced by the proximity of neurites, which does not completely restrict water movement:

$$A_{ec} = e^{-b\mathbf{q}^\top \left(\int_{\mathbb{S}^2} f(\mathbf{n}) D(\mathbf{n}) d\mathbf{n} \right) \mathbf{q}}. \quad (1.27)$$

Here, $D(\mathbf{n})$ is a diffusion tensor reflecting the anisotropic nature of this compartment, influenced by the distribution and orientation of the neurites.

1.3.1.3 Cerebrospinal Fluid model

The CSF compartment is characterized by isotropic Gaussian diffusion, reflecting the free movement of water molecules within this fluid:

$$A_{iso} = e^{-bd_{iso}}, \quad (1.28)$$

where d_{iso} is the isotropic diffusivity of the CSF.

1.3.1.4 Parameters of the NODDI model

Key parameters of the NODDI model include:

- ν_{ic} : Volume fraction of the intra-cellular space.
- ν_{iso} : Volume fraction of isotropic diffusion regions, primarily CSF.
- κ : Concentration parameter governing the dispersion of neurite orientations.
- $\boldsymbol{\mu}$: Principal orientation of the neurites.
- d_{iso} and $d_{||}$: Isotropic and axial diffusivities, respectively, fixed based on in vivo measurements to $d_{||} = 1.7 \times 10^{-3} [mm^2/s]$ and $d_{iso} = 3.0 \times 10^{-3} [mm^2/s]$.

These parameters are estimated from MR data using maximum likelihood estimation techniques.

1.3.1.5 Metrics derived from NODDI

The main metrics that are used to interpret NODDI results are:

- The extra-cellular volume fraction ν_{ec} , also known as f_{extra} .
- The intra-cellular volume fraction ν_{ic} , also known as f_{intra} , or Neurite Density Index (NDI).
- The Orientation Dispersion Index (ODI), defined as $ODI = \frac{2}{\pi} \arctan\left(\frac{1}{\kappa}\right)$.

1.3.1.6 Advantages and limitations of NODDI

Advantages:

- Provides detailed metrics of the microstructure relevant to clinical assessments, such as neurite density and orientation.
- Offers deeper insights into brain tissue structure than DTI.

Limitations:

- Does not account for radial diffusivity variations within axons.
- Relies on fixed parameters which may introduce biases in estimates.
- Cannot resolve crossing fibers, which occur in a significant portion of brain voxels.

1.3.2 Microstructure Fingerprinting

MF is a novel approach that integrates Monte Carlo simulations of water diffusion with advanced signal decomposition techniques to uncover the microstructure within each voxel. This model conceptualizes each voxel as comprising multiple independent microstructural fascicles and potentially a CSF space, each contributing uniquely to the observed diffusion signal.

1.3.2.1 Model formulation

For a voxel containing K fascicles and a CSF component, the diffusion-weighted signal S is modeled as:

$$S = M_0 \left[\sum_{k=1}^K \nu_k A_{fasc}(\Omega_k, \mathbf{T}_k, \mathbf{u}_k; \mathbf{g}) + \nu_{csf} A_{csf}(D_{csf}, \mathbf{T}_{csf}; \mathbf{g}) \right], \quad (1.29)$$

$$= \sum_{k=1}^K w_k A_k + w_{csf} A_{csf}, \quad (1.30)$$

where each fascicle's contribution A_{fasc} is determined through Monte Carlo simulations that account for its unique orientation $\mathbf{u}_k$, microstructural parameters Ω_k , and relaxation properties $\mathbf{T}_k$. The CSF's contribution, A_{csf} , assumes free diffusion with a diffusivity D_{csf} .

1.3.2.2 Precomputing and runtime steps

The fingerprinting process involves extensive precomputation of potential signal profiles (fingerprints) for various microstructural configurations, followed by a runtime optimization to match these precomputed fingerprints to the observed signal, thus identifying the most probable microstructural configuration for each voxel. These steps are detailed below:

1. **Fascicle number and orientation estimation:**

An external routine estimates the number of fascicles, K , within each voxel and their respective orientations.

2. **Dictionary calculation for each fascicle:**

From the initial dictionary $\mathbf{F}^0$ along direction $\mathbf{u}_0$, single fascicle dictionaries $\mathbf{F}^k$ are computed for directions $\mathbf{u}_k$ for each fascicle, where $1 \leq k \leq K$ (with K determined in the previous step).

3. **Optimization with sparsity constraints:**

The optimization problem is solved under constraints that ensure only one configuration per fascicle dictionary $\mathbf{F}^k$ significantly contributes to the signal $\mathbf{y}$. The objective is to minimize the following function:

$$(\hat{j}_1, \dots, \hat{j}_K) = \underset{1 \leq j_1, \dots, j_K \leq N}{\operatorname{argmin}} \min_{w \geq 0, \sigma \geq 0} \left\| \mathbf{y} - [\mathbf{A}_{j_1}^1 \mid \dots \mid \mathbf{A}_{j_K}^K \mid \mathbf{A}_{csf}] \cdot \begin{bmatrix} w_1 \\ \vdots \\ w_K \\ w_{csf} \end{bmatrix} \right\|_2^2.$$

Here, the solution provides the optimal indices $(\hat{j}_k)$ for each dictionary $\mathbf{F}^k$, which best represent the measured signal.

4. **Estimation of volume fractions:**

The fractions of occupation ν_k are estimated using the optimal weights w_k :

$$\nu_k = \frac{w_k}{\sum_{k=1}^{K+1} w_k}.$$

The fiber volume fractions (fvf_k) and extra-axonal diffusivities ($D_{ex,k}$) are retrieved from the dictionaries using the optimal indices $\hat{j}_k$.

1.3.2.3 Advantages and limitations of MF

Advantages:

- Can handle complex fiber architectures, including crossing fibers.
- Provides a near ground-truth simulation of DW-MRI signals, leading to highly specific and interpretable results.
- Generates physically meaningful microstructural parameters across diverse experimental conditions.

- MF is a framework and is based on a precomputed dictionary. More dictionaries can be computed in the future, potentially compensating for some of the shortcomings of MF.

Limitations:

- High computational cost due to the extensive simulations required.
- Some biological factors such as membrane permeability and axonal undulation are not yet modeled, potentially affecting accuracy.
- Estimations are voxel-specific, which may lead to inconsistencies in microstructural labeling across different scans or adjacent voxels.
- Does not directly estimate the impact of noise on the diffusion measurements, potentially affecting the robustness of the results.

Part II

Combining NODDI and the Spherical Mean Technique for microstructure imaging in Multiple Sclerosis

Chapter 2

State of the Art

In this chapter, we begin with an overview of Multiple Sclerosis (MS) pathology, followed by a literature review of studies that have utilized the NODDI model in the context of MS. Next, we introduce the theoretical basis of the Spherical Mean Technique (SMT) for estimating parallel diffusivities and review an alternative SMT-based NODDI model. Finally, we conclude the chapter by outlining the objectives of our study.

2.1 Pathology of Multiple Sclerosis

MS is a chronic inflammatory demyelinating and neurodegenerative disease of the Central Nervous System (CNS). It is characterized by areas of demyelinated plaques scattered throughout the CNS, with a predilection for the optic nerves, spinal cord, periventricular white Matter (WM), corpus callosum, and cortical and sub-cortical Gray Matter (GM) [22], [23].

MS lesions reveal significant heterogeneity concerning the presence and extent of inflammation, demyelination, axonal injury, gliosis, and remyelination. These pathological features are also present, albeit to a lesser extent, in Normal-Appearing Brain Tissue (NABT), including Normal-Appearing White Matter (NAWM) and Normal-Appearing Gray Matter (NAGM) [22].

Lesions in MS can appear throughout the CNS and are most easily recognized in the white matter as focal areas of demyelination, inflammation, and glial reaction. Early active white-matter lesions are heterogeneous and evolve over months. These lesions can be classified into different patterns based on the immunologic and histopathologic features, such as the presence of mononuclear phagocytes, T-cell infiltration, and complement deposition [23].

In MS, active lesions mark the early stages of disease, characterized by acute inflammation and blood-brain barrier disruption. This phase, lasting 4–8 weeks, shows contrast enhancement on gadolinium-based MRI due to high inflammatory activity [24]. After the acute phase, lesions can become either chronic inactive or chronic active. Chronic inactive lesions show resolved inflammation and may have some remyelination. Chronic active lesions, however, continue with persistent inflammation at their edges. These le-

sions have an inactive core and a rim of activated microglia and macrophages containing iron, visible as Paramagnetic Rim Lesions (PRLs) on susceptibility-based MRI [25], [26]. Chronic active lesions are linked to significant tissue damage, increased neurofilament light chain levels in the blood, and lower brain volumes, indicating greater brain atrophy. These lesions correlate with more severe disease progression and underscore the need for early, effective treatment [27]–[30].

While conventional MRI (including T2-weighted, pre- and post-contrast T1-weighted scans) is instrumental in diagnosing MS and monitoring treatment response, it has low sensitivity to diffuse damage in NAWM and NAGM. DWI overcomes these limitations by providing markers that are more specific to underlying pathologic substrates and more sensitive to occult brain tissue damage [22].

Demyelination in MS also affects gray matter, where lesions are often less inflammatory than those in white matter. Spinal cord lesions are a significant source of clinical disability in MS, and they are often highly inflammatory. The optic nerve is another major target in MS, with loss of retinal ganglion cells leading to thinning of the retinal nerve-fiber and ganglion-cell layers [23].

The clinical course of MS varies, with approximately 85% of patients experiencing a Relapsing-Relmitting (RR) course, followed by a transition to Secondary-Progressive (SP) MS in most cases. A smaller proportion of patients experience Primary-Progressive (PP) MS from the onset, without relapses. The heterogeneity in lesion pathology and the varying clinical courses highlight the need for personalized therapeutic strategies to manage this complex disease [22], [23].

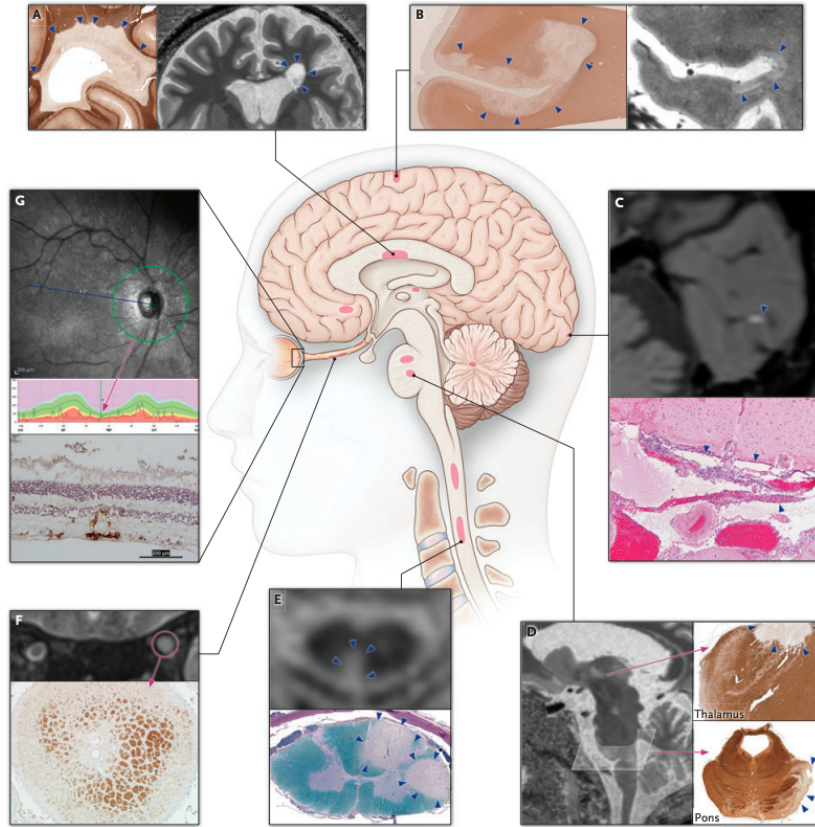


Figure 2.1: **Topography of Multiple Sclerosis lesions.** This schematic illustrates lesion locations with imaging and pathological examples in various CNS regions including the periventricular white matter, subpial cortex, leptomeninges, thalamus, pons, spinal cord, optic nerve, and retina. In all insets, the lesions are marked with circles or arrowheads. (Adapted from [23]).

2.2 NODDI in MS

NODDI is an advanced diffusion MRI technique that provides detailed characterization of tissue microstructures by modeling the diffusion signal in relation to neurite (axon and dendrite) properties (see subsection 1.3.1 for more details). Unlike DTI, which is a representation of the diffusion images without specific assumptions about the tissue structure, NODDI is a mathematical diffusion model that aims to capture the actual biophysical properties of the tissue. This distinction is crucial, as DTI primarily offers a statistical description of diffusion anisotropy, whereas NODDI provides a more accurate depiction of the underlying tissue architecture by explicitly modeling factors such as neurite density and orientation dispersion [31].

NODDI has proven particularly useful in clinical research on MS, where it offers insights beyond those provided by traditional DTI (see subsection 1.2.4). By accurately modeling the diffusion process within the brain's microstructure, NODDI allows for a more precise understanding of the microstructural changes occurring in MS.

2.2.1 Clinical applications of NODDI in MS

NODDI has been used to investigate the microstructural changes in white matter in MS patients. This technique is advantageous over DTI because it can capture more detailed features of tissue microstructures, such as neurite density and orientation dispersion, which are critical in understanding the pathophysiology of MS [32].

2.2.2 Microstructural characterization

Studies have shown that NODDI can effectively characterize the microstructural damage within various types of MS lesions, including active, chronic active, and chronic inactive lesions. NODDI parameters can differentiate between these lesion types and provide insights into their evolution. For instance, active lesions exhibit distinct microstructural patterns that can be tracked over time to assess their progression into chronic stages [4].

Moreover, NODDI has been used to analyze the periplaque WM and NAWM in MS patients. The findings suggest that microstructural damage extends beyond the visible lesion edges into the surrounding WM, which is not apparent on conventional MRI scans. This highlights the utility of NODDI in detecting subtle changes in brain tissue that are crucial for a comprehensive assessment of MS pathology [4].

2.2.3 Comparative performance

When compared to other diffusion models, NODDI has shown superior performance in characterizing the microstructural complexities of MS lesions. Multi-compartment models based on NODDI metrics (e.g., neurite density and orientation dispersion) are better suited for MS applications, providing more accurate and biophysically interpretable data compared to simpler models like DTI [4].

2.2.4 Findings from meta-analysis

A systematic review and meta-analysis of NODDI studies in MS revealed significant findings regarding NDI and ODI values. The primary outcome measure, NDI, was used to quantify microstructural abnormalities in neuroaxonal pathology. The meta-analysis showed that NDI was significantly reduced in WM MS lesions and NAWM compared to healthy WM, indicating a loss of axonal density or integrity [33]. The secondary outcome measure, ODI, quantified the loss of fiber coherence (increase in fiber dispersion). However, there was no statistically significant difference in ODI between MS patients and healthy controls, suggesting variability in fiber coherence changes across different brain regions and stages of MS [33].

2.3 Per-axon diffusivities estimation

The NODDI-Watson model, proposed by Zhang et al. (2012) [1], estimates the dispersion of neurites (i.e., axons and dendrites) using a Watson distribution to model the orientation dispersion of a single axon bundle. This model separates the signal

contributions from CSF, restricted and hindered diffusion. The key hypotheses of the NODDI-Watson model include the use of an isotropic diffusivity for CSF fixed at $3 \times 10^{-9} \text{ m}^2/\text{s}$, and a parallel diffusivity ($\lambda_{\parallel}$) fixed at $1.7 \times 10^{-9} \text{ m}^2/\text{s}$. Additionally, a tortuosity model links the perpendicular diffusivity ($\lambda_{\perp}$) to the intra- and extra-axonal volume fractions (f_r and f_h) and the parallel diffusivity ($\lambda_{\parallel}$).

The precision of the NODDI model can potentially be improved by computing voxel-wise estimates of the parallel diffusivity ($\lambda_{\parallel}$) or the volume fractions. This section presents the key computations and results from Kaden et al. [7], who developed a method based on spherical means of diffusion signals to obtain more accurate measurements of microstructural parameters within each voxel. Additionally, Section 2.4 details a method by Cabeen et al. [6], which also uses the spherical means technique to estimate the volume fractions of the compartments in the NODDI model.

2.3.1 Spherical mean theoretical background

In the context of diffusion MRI, the signal originating from a small axonal segment within a voxel can be characterized by its orientation, described by a tangent vector $\omega \in \mathbb{S}^2$, where $\mathbb{S}^2$ represents the two-dimensional unit sphere in $\mathbb{R}^3$. The diffusion process around this segment and its immediate environment is modeled using an impulse response function $h_b(g, \omega)$, dependent on the diffusion weighting factor $b \geq 0$ and the normalized gradient direction $g \in \mathbb{S}^2$.

Key properties of the impulse response h_b include:

- **Voxel averaging effect:** The diffusion signal h_b remains independent of the precise spatial location within the voxel due to the averaging effect over the voxel volume.
- **Rotational invariance:** The function $h_b(g, \omega)$ depends only on the dot product $\langle g, \omega \rangle$, which measures the spherical distance between g and ω , and is invariant under any orientation-preserving rotation $R \in SO(3)$.
- **Antipodal symmetry:** The impulse response exhibits symmetry such that $h_b(g, \omega) = h_b(-g, \omega)$ for all $g, \omega \in \mathbb{S}^2$.

Given the impulse response h_b for a known fiber orientation ω , the macroscopic MR signal observable at the voxel level is obtained by convolving h_b with the distribution of fiber orientations $p(\omega)$:

$$e_b(g) = \frac{E_b(g)}{E_0} = \int_{\mathbb{S}^2} h_b(g, \omega) p(\omega) d\omega, \quad (2.1)$$

where $E_b(g)$ denotes the diffusion-encoded signal, and E_0 represents the baseline signal without diffusion weighting, normalized to account for T2 contrast.

2.3.2 Spherical Mean Technique

The actual diffusion signal from a fiber segment is not directly observable and must be estimated. The spherical mean technique provides a method to estimate the average diffusion signal across all gradient directions. The spherical mean of the diffusion signal is defined as:

$$\bar{e}_b = \frac{1}{4\pi} \int_{\mathbb{S}^2} e_b(g) dg. \quad (2.2)$$

Kaden et al. [7] demonstrated that $\bar{e}_b$ is invariant to the distribution of fiber orientations within the voxel, making it a robust measure for parameter estimation.

2.3.3 Modeling the diffusion signal

2.3.3.1 Single compartment microscopic model

Following the model proposed by Kaden et al. [7], the per-axon diffusion signal can be approximated using a second-order expansion:

$$h_b(g, \omega) = \underbrace{\exp(-b\langle g, \omega \rangle^2 \lambda_{\parallel})}_{\text{longitudinal}} \underbrace{\exp(-b(1 - \langle g, \omega \rangle^2) \lambda_{\perp})}_{\text{transverse}}. \quad (2.3)$$

This approximation allows the expression of the spherical mean of the diffusion signal in terms of the parallel and perpendicular diffusion coefficients:

$$\bar{e}_b(\lambda_{\parallel}, \lambda_{\perp}) = \exp(-b\lambda_{\perp}) \frac{\sqrt{\pi} \operatorname{erf}(\sqrt{b(\lambda_{\parallel} - \lambda_{\perp})})}{2\sqrt{b(\lambda_{\parallel} - \lambda_{\perp})}}. \quad (2.4)$$

2.3.3.2 Multi-compartment microscopic model

In [8], Kaden et al. extend their previously developed model to a multi-compartment framework, dividing brain tissue into intra-neurite and extra-neurite compartments.

The diffusion signal for a microscopic environment of brain tissue with orientation $\omega \in \mathbb{S}^2$ is then modeled as

$$h_b(g, \omega) = \underbrace{\nu_{int} h_b^{int}(g, \omega)}_{\text{intra-neurite}} + \underbrace{(1 - \nu_{int}) h_b^{ext}(g, \omega)}_{\text{extra-neurite}}, \quad (2.5)$$

where $\nu_{int} \in [0, 1]$ is the intra-neurite volume fraction, and h_b^{int} (respectively h_b^{ext}) denotes the signal from the intra-neurite (respectively extra-neurite) compartment. The diffusion signal of the extra-neurite compartment is given by Eq.2.3. Based on the assumption that the attenuation of the signal component perpendicular to the neurites is negligible, the diffusion signal of the intra-neurite compartment is modeled similarly to the extra-neurite compartment but with the transverse microscopic diffusivity set to zero.

The mean diffusion signal for the multi-compartment microscopic model is then given by

$$\bar{e}_b = \nu_{int} \bar{e}_b^{int} + (1 - \nu_{int}) \bar{e}_b^{ext}. \quad (2.6)$$

2.3.4 Fitting the parametric impulse response

To estimate the spherical mean signal $\bar{e}_b$, the average of the Rician-noise adjusted diffusion signals acquired under various gradient directions for each b -value is computed, normalized by the T2 contrast. The following optimization is performed to fit the model:

$$\min_{0 \leq \lambda_{\perp} \leq \lambda_{\parallel} \leq \lambda_{free}} \sum_{i=1}^n (\hat{e}_{b_i} - \bar{e}_{b_i}(\lambda_{\parallel}, \lambda_{\perp}))^2, \quad (2.7)$$

where λ_{free} denotes the diffusivity of free water. This minimization is constrained to ensure the physical plausibility of the diffusion coefficients.

2.4 NODDI-SMT

The NODDI-SMT model developed by Cabeen et al. [6] uses a two-step approach:

1. The volume fractions of the NODDI model (ν_{iso} , ν_{ic} and ν_{ec}) are estimated by casting the NODDI model in the spherical mean framework.
2. Then, fixing the volume fractions to the values computed in the previous step, the other parameters of the NODDI model are fitted in the standard modeling framework described in Subsection 1.3.1.

The main hypothesis of the NODDI-SMT model is that integrating the SMT into the NODDI framework enhances the accuracy and efficiency of parameter estimation. This approach addresses the high computational cost of traditional NODDI fitting methods by using SMT to obtain orientationally-invariant parameters through signal averaging, simplifying the fitting process.

Cabeen et al. demonstrated through various analyses that the SMT-based fitting significantly reduces runtime while maintaining high accuracy and robustness to noise compared to Non-Linear Least Squares (NLLS) and AMICO methods [34]. Their conclusions highlight that the NODDI-SMT model provides reliable estimates of neurite density and orientation dispersion with an 82% reduction in runtime compared to NLLS, making it a practical and efficient method for in vivo neurite imaging.

2.5 Objective of the study

Recent studies [5] have challenged the assumption that fixing the parallel diffusivity to a typical in vivo value of $1.7 [\mu m/ms]$ in the NODDI model is an adequate approximation, particularly in GM regions, where this value has been shown to be suboptimal. These studies also demonstrated that variations in the parallel diffusivity significantly impact the estimated NODDI parameters. Motivated by these findings, the primary objective of the study is to leverage the SMT-based estimation method developed by Kaden et al. [7], [8] to enhance the NODDI model. Specifically, the study aims to use voxel-wise estimates of parallel diffusivities ($\lambda_{\parallel}$) in the tortuosity model, rather than applying a fixed in vivo value across all voxels.

By obtaining more precise, localized estimates of the NODDI diffusivities, we seek to improve the accuracy and reliability of the NODDI model's microstructural parameter estimates. This approach is intended to address the inherent variability and heterogeneity within brain tissue, offering a more nuanced and detailed characterization of neurite properties.

Chapter 3

Methods

3.1 Synthetic data

3.1.1 Data generation

The synthetic data was generated using the Dmipy library [35]. The process involves creating a NODDI-Watson multi-compartment model, as detailed in Section 1.3.1. This model includes three compartments:

- The isotropic compartment: modeled as a Ball.
- The intra-cellular compartment: modeled as a Stick.
- The extra-cellular compartment: modeled as a Zeppelin.

The signal of the multi-compartment model, shown schematically in Figure 3.1, is given by:

$$E_{Watson}^{NODDI} = \nu_{iso} \overbrace{E_{iso}(\cdot|\lambda_{iso})}^{\text{Ball}} + \overbrace{W(\kappa, \boldsymbol{\mu})}^{\text{Watson}} *_{\mathbb{S}^2} \left[\nu_{ec} \overbrace{E_{ec}(\cdot|\lambda_{\perp}^{tort}, \lambda_{\parallel})}^{\text{Zeppelin}} + \nu_{ic} \overbrace{E_{ic}(\cdot|\lambda_{\parallel})}^{\text{Stick}} \right], \quad (3.1)$$

where the isotropic diffusivity (λ_{iso}) is set to $3 \times 10^{-9} [m^2/s]$ and a tortuosity model is used to link the perpendicular diffusivity ($\lambda_{\perp}^{tort}$) to the intra- and extra-cellular volume fractions ν_{ic} , ν_{ec} , and the parallel diffusivity ($\lambda_{\parallel}$).

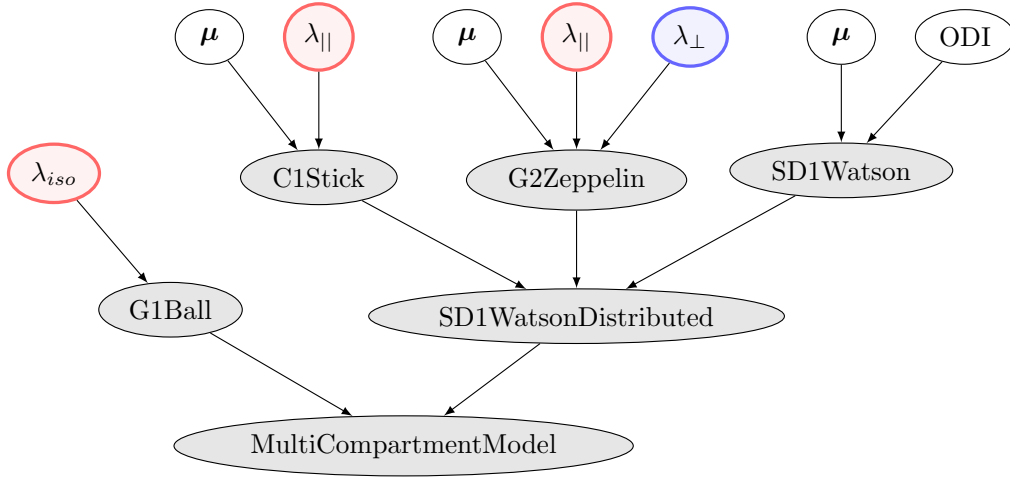


Figure 3.1: **Schematical representation of the NODDI-Watson multi-compartment model and its parameters.** The parameters in red ($\lambda_{||}$ and λ_{iso}) are set to typical in vivo values across all voxels. The parameter in blue ($\lambda_{\perp}$) is constrained by a tortuosity model. All other parameters are fitted voxel-wise to the data.

To generate the synthetic data, the following parameter ranges were used:

- $\mu \in [-\frac{\pi}{2}, \frac{\pi}{2}] \times [-\frac{\pi}{2}, \frac{\pi}{2}]$
- $ODI \in [0.1, 0.7]$
- $\nu_{iso} \in [0, 0.3]$
- $\nu_{ic} \in [0.3, 0.9]$
- $\lambda_{||} \in [0.5 \times 10^{-9}, 3 \times 10^{-9}] [m^2/s]$

3.1.2 Noise addition

To simulate noise in the synthetic data, a Sum-of-Squares MRI signal was used for phased array systems. The noisy signal was computed as:

$$E_{noisy} = \sqrt{\sum_{i=1}^N (E_i + \epsilon_1)^2 + \epsilon_2^2}, \quad (3.2)$$

where N is the number of coils, and ϵ_1 and ϵ_2 are two independent zero-mean Gaussian variables with standard deviation σ_g . The resulting noisy signal follows a non-central Chi distribution, which is typical for MRI data [36].

The standard deviation parameter σ_g is computed based on the desired SNR level as:

$$\sigma_g = \frac{E_{max}}{SNR}, \quad (3.3)$$

where E_{max} is the maximum value reached by the MRI signal.

3.2 In vivo DWI data

3.2.1 Participants

The study involved a total of 83 MS participants and 23 age and gender-matched healthy controls (HC). The MS participants included 56 with Relapsing-Remitting Multiple Sclerosis (RRMS), 18 with Secondary-Progressive Multiple Sclerosis (SPMS), and 9 with Primary-Progressive Multiple Sclerosis (PPMS). All participants were aged 18 years or older, and the diagnosis of MS was based on the 2017 McDonald criteria [4].

3.2.2 MRI acquisition protocol

MRI acquisition was performed on a 3T whole-body MR scanner equipped with a 48-channel head coil. The specific protocol to obtain the DWI data included a multi-shell diffusion-weighted sequence with the following parameters [4]:

- **TR:** 4842 *ms*
- **TE:** 77 *ms*
- **Diffusion time (Δ):** 35.7 *ms*
- **Diffusion gradient duration (δ):** 22.9 *ms*
- **b-values and gradients:**
 - 64 gradients at $b = 1000 \text{ s/mm}^2$
 - 32 gradients at $b = 2000 \text{ s/mm}^2$
 - 32 gradients at $b = 3000 \text{ s/mm}^2$
 - 32 gradients at $b = 5000 \text{ s/mm}^2$
 - 7 b_0 images
- **Field of View (FOV):** 220 *mm*
- **Voxel size:** 2 *mm* isotropic
- **Number of slices:** 68

Figure 3.2 shows a graphical representation of the shells.

3.2.3 Preprocessing

The multi-shell diffusion data were preprocessed through several steps: denoising [37], top-up correction [38], motion and eddy-current correction [39], and skull-stripping using FSL BET [40].

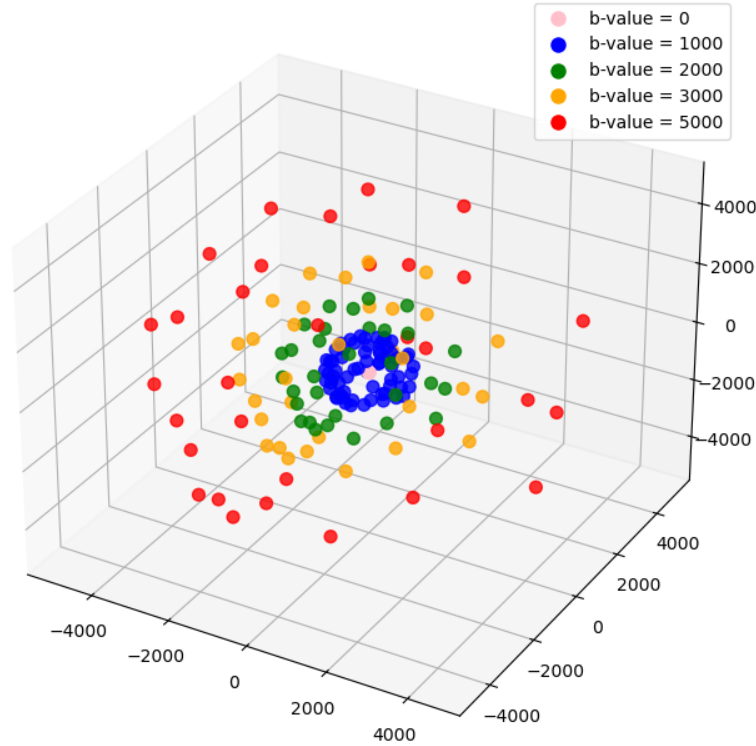


Figure 3.2: **Gradient shells represented on a 3D sphere.** The radius of the spheres are scaled by the b-value and the orientation of the points corresponds to the directions of the gradients

3.3 Implementation of NODDI with SMT based diffusivity coefficients estimation

NODDI with SMT-based diffusivity coefficients estimation is a two-step algorithm designed for advanced diffusion MRI analysis. In the first step, voxel-wise parallel diffusivities ($\lambda_{||}$) are estimated using the SMT implemented in a C++ routine [41]. Subsequently, a NODDI-Watson model is fitted voxel-wise, with the parallel diffusivity fixed to the values computed in the first step. This fitting is performed using the Dmipy library [35].

We implemented two versions of NODDI with SMT-based diffusivity coefficients estimation. The first version, referred to as NODDI-SMT, uses parallel diffusivities estimated with the single-compartment model described in Section 2.3.3.1. The second version, called NODDI-SMT-MICRO, uses parallel diffusivities estimated with the multi-compartment model described in Section 2.3.3.2.

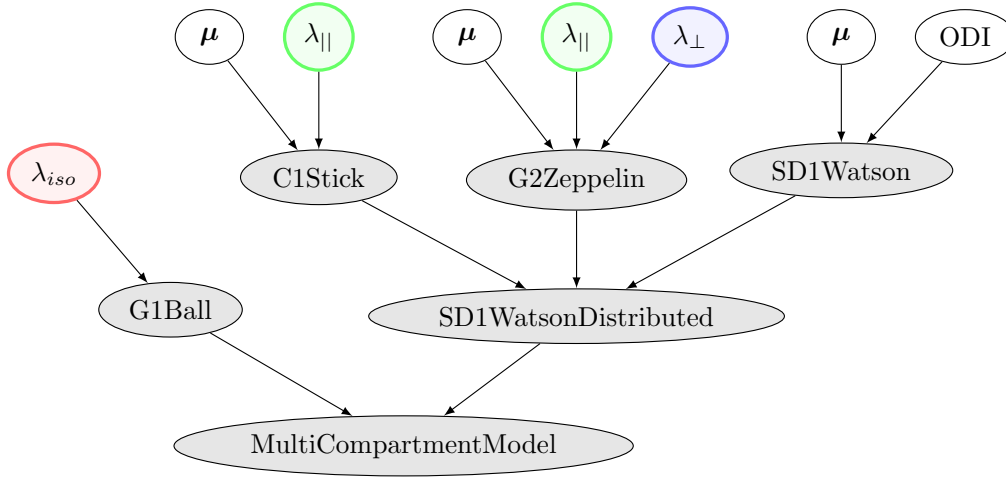


Figure 3.3: **Schematic representation of the NODDI-SMT multi-compartment model and its parameters.** The parameter in red (λ_{iso}) is set to typical in vivo values across all voxels. The parameter in green ($\lambda_{||}$) is set voxel-wise to values obtained using the SMT-based diffusivity coefficient estimation developed by Kaden et al. [7]. The parameter in blue ($\lambda_{\perp}$) is constrained by a tortuosity model. All other parameters are fitted voxel-wise to the data.

By employing these techniques, we aim to achieve a more nuanced understanding of microstructural variations within brain tissue, enhancing the diagnostic power of MRI data.

3.3.1 Fast version of the algorithm

To accelerate the model fitting process, the algorithm includes a thresholding step applied to the computed parallel diffusivity values. This step limits the number of unique diffusivity values, allowing the fitting to be performed in batches of voxels that share the same thresholded parallel diffusivity value.

3.4 Validation methods

3.4.1 Synthetic data validation

3.4.1.1 Performance metrics

To evaluate the performance of NODDI-SMT and NODDI-SMT-MICRO on synthetic data, several key metrics were used.

Mean Squared Error (MSE):

$$\text{MSE} = \frac{1}{n} \sum_{i=1}^n (y_i - y_{rec,i})^2,$$

where $\bar{y} = \frac{1}{n} \sum_{i=1}^n y$. This metric measures the average magnitude of the errors between the reconstructed signal and the measured signal.

Coefficient of Determination (R^2):

$$R^2 = \frac{(\sum_{i=1}^n (y_i - \bar{y})(y_{rec,i} - \bar{y}_{rec}))^2}{\sum_{i=1}^n (y_i - \bar{y})^2 \sum_{i=1}^n (y_{rec,i} - \bar{y}_{rec})^2}.$$

This metric assesses the goodness of fit of the reconstructed signal.

Absolute Error: To assess the quality of the estimated parameters, the absolute errors between the estimated model parameters and their respective ground truths were computed.

3.4.2 In vivo data validation

The performance of the NODDI-SMT and NODDI-SMT-MICRO models on in vivo data was evaluated using the following methods:

First, we conducted a visual comparison of the models based on MSE and R^2 maps, as well as parameter maps.

Next, we assessed the models in the context of MS pathology by examining the values within known areas of specific pathological damage (active, chronic active, and chronic inactive lesions), using histopathological priors to inform these pathological processes. Specifically, we investigated the following WM ROI: acute contrast-enhancing lesions (Gad), non-enhancing lesions bearing or not a paramagnetic rim (respectively, PRL+ and PRL-), the periplaque of the above-mentioned lesions (respectively, peri-Gad, peri-PRL+, peri-PRL-), the NAWM of MS participants and HC (respectively, NAWM-MS and NAWM-HC). Figure 3.4 illustrates every ROI and their segmentation.

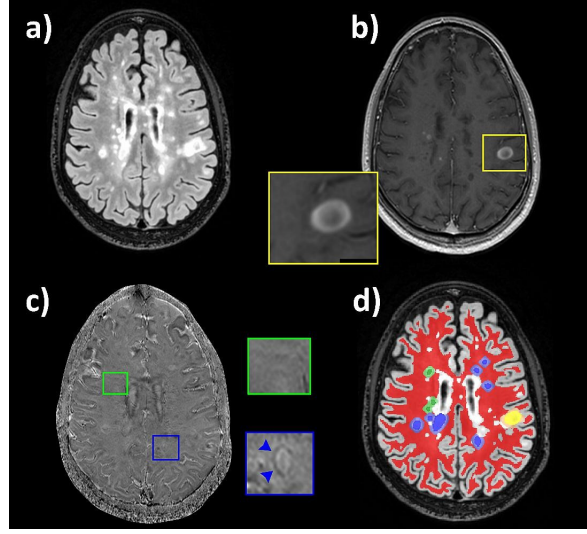


Figure 3.4: **Axial Fluid Attenuated Inversion Recovery (FLAIR) and post-gadolinium T1-weighted spoiled gradient recalled echo (CE-SPGR) images highlighting various white-matter lesions in a Relapsing-Remitting MS subject.** (a) and (d) Axial FLAIR images showing different types of white-matter lesions, including their periplaques and Normal-Appearing White Matter (NAWM). (b) CE-SPGR image highlighting a contrast-enhancing lesion (Gad, yellow box). (c) Axial filtered unwrapped-phase image showing chronic non-enhancing paramagnetic rim lesions (PRL+, blue box) and non-paramagnetic rim lesions (PRL-, green box). In (d), NAWM is segmented in red, while Gad, PRL+, and PRL- are segmented in yellow, blue, and green, respectively. Lesions' periplaques are shown with similar desaturated colors. (Adapted from [4]).

Finally, we evaluated the models in control subjects by analyzing the values within ROI derived from the aseg atlas provided by FreeSurfer [42].

3.4.3 Statistical analysis

3.4.3.1 Receiver Operating Characteristic analysis

The ability of the different models to differentiate microstructural tissue was assessed using a Support Vector Machine (SVM) classifier to compute Receiving Operator Curve (ROC) curves. Metrics evaluated included:

- **Area Under the Curve (AUC):** A measure of the model's ability to distinguish between different ROI.
- **Accuracy, sensitivity, and specificity:** These metrics were calculated to evaluate the overall performance of the models.
- **Mean and variance of AUC:** The mean AUC and the variance of AUC were used as proxies for the model's stability across different differentiation tasks.

3.4.3.2 Statistical tests

To compare the performance metrics across different ROI, Welch's ANOVA and Games-Howell post-hoc tests were employed. The significance levels were reported as

- (*) for $p < 0.05$ (significant),
- (**) for $p < 0.01$ (very significant),
- (***) for $p < 0.001$ (strongly significant).

3.4.4 Comparison with existing models

To benchmark the performance of NODDI-SMT and NODDI-SMT-MICRO against existing models, the aforementioned metrics and statistical tests were compared to those of the NODDI model.

Chapter 4

Results

4.1 Synthetic data results

4.1.1 Comparison of the methods

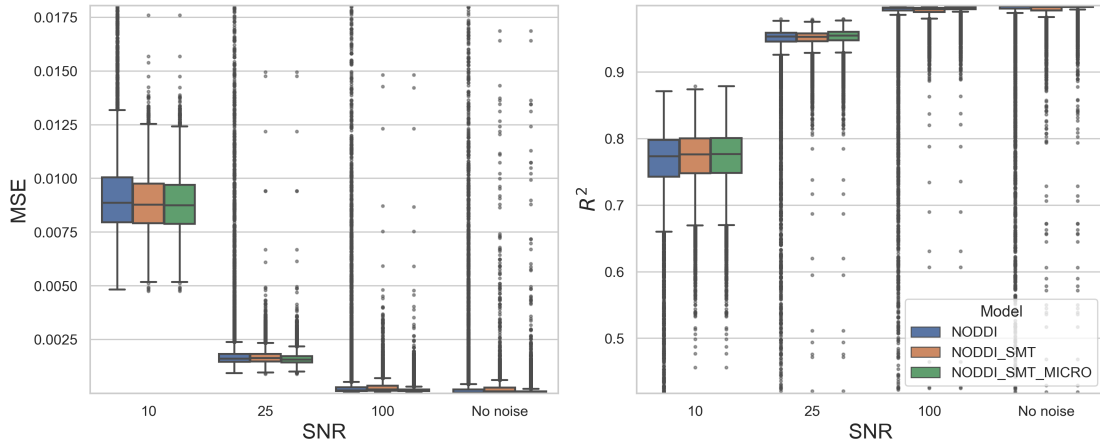


Figure 4.1: **Comparison of MSE and R^2 values across different models under varying SNR levels.** The boxplots illustrate the performance of three models (NODDI, NODDI-SMT, NODDI-SMT-MICRO) across SNR levels of 10, 25, 100, and no noise. The dataset consists of 10,000 samples per SNR level.

The boxplots in Figure 4.1 compare the performance of the three models at different SNR levels. The boxplot on the left shows the distribution of MSE values, indicating that as the SNR increases, the MSE decreases, reflecting improved model performance with less noise. Among the models, NODDI-SMT-MICRO consistently exhibits lower MSE values across all SNR levels, suggesting it is the most robust to noise. The boxplot on the right presents the R^2 values for the models, with higher R^2 values indicating better performance. Similar to the MSE results, NODDI-SMT-MICRO generally achieves higher R^2 values, particularly at higher SNR levels. An ANOVA test was conducted for both MSE and R^2 at each SNR level, revealing statistically significant differences across all comparisons ($p < 0.05$). Detailed p-values for these statistical tests are provided in the appendix (see Table C.5).

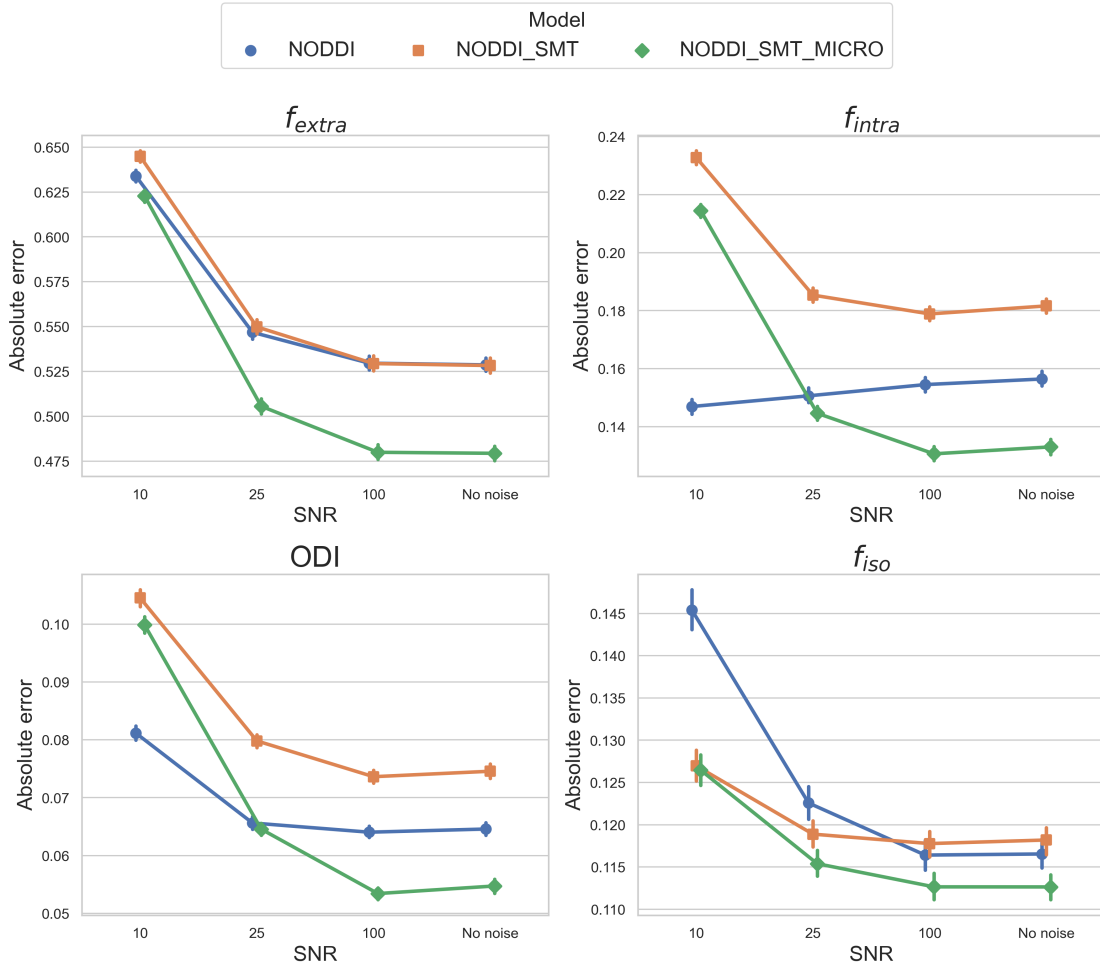


Figure 4.2: **Average absolute error comparison for different parameters (f_{extra} , f_{intra} , ODI, f_{iso}) across models (NODDI, NODDI-SMT, NODDI-SMT-MICRO) under varying SNR levels.** The dataset consists of 10,000 samples per SNR level. NODDI-SMT-MICRO generally exhibits lower absolute errors at higher SNR levels, while differences among models are less pronounced at lower SNR levels.

In Figure 4.2, we can see that for higher SNR values, NODDI-SMT-MICRO generally performs better than NODDI and NODDI-SMT, exhibiting lower absolute errors across all parameters. However, this trend does not hold for lower SNR values (10-25). Specifically, for f_{intra} and odi , NODDI outperforms NODDI-SMT-MICRO at an SNR of 10 and performs similarly to NODDI-SMT-MICRO at an SNR of 25. In contrast, for f_{iso} , both NODDI-SMT and NODDI-SMT-MICRO outperform NODDI at an SNR of 10. For f_{extra} , all models show a trend of decreasing error with increasing SNR, with NODDI-SMT-MICRO maintaining a consistently lower error rate.

General observations:

The NODDI-SMT-MICRO model consistently outperforms the NODDI and NODDI-SMT models across all metrics (MSE, R^2 , and absolute error for f_{extra} , f_{intra} , ODI, and f_{iso}) at higher SNR levels. However, at the lower SNR level of 10, the results are more

nuanced: while NODDI-SMT-MICRO still performs better in terms of MSE and R^2 , NODDI outperforms it in terms of absolute error for certain parameters. As expected, the performance of all models improves with increasing SNR, reflecting the reduced impact of noise across all parameters and metrics.

However, it is important to note that these results are obtained on synthetic data and should therefore be interpreted with caution as they may not necessarily translate to in-vivo data.

4.1.2 Fast versions of NODDI-SMT and NODDI-SMT-MICRO

4.1.2.1 Error comparison

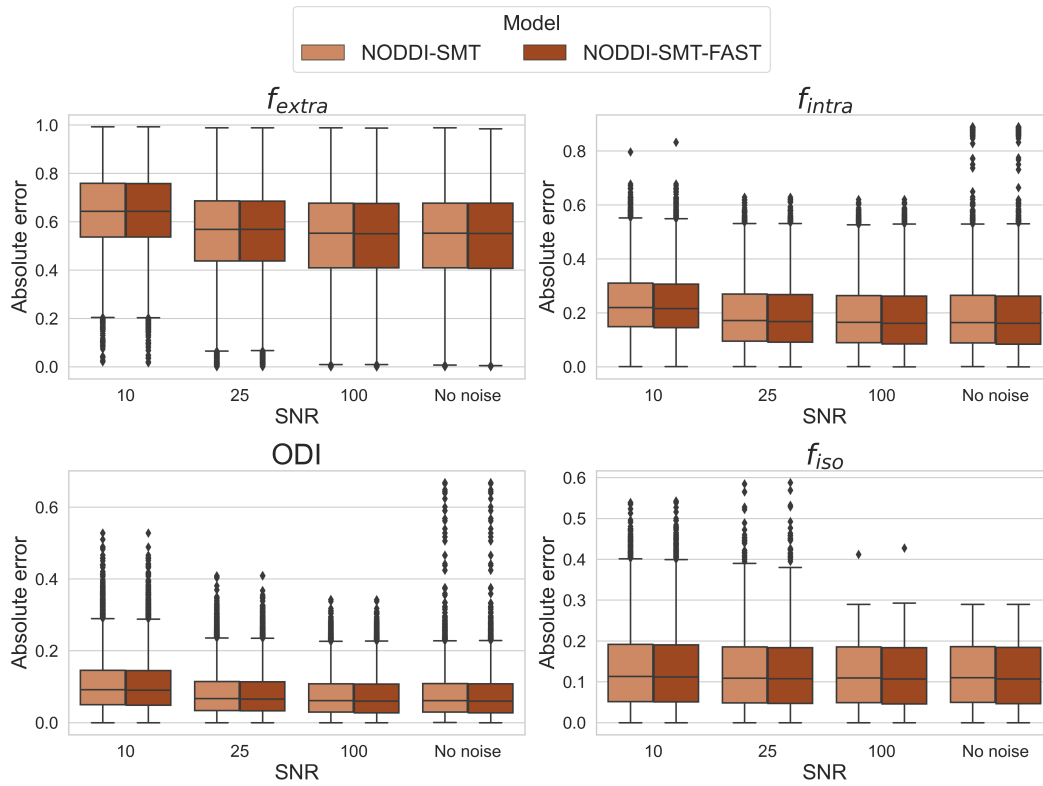


Figure 4.3: Comparison of absolute error for different parameters (f_{extra} , f_{intra} , ODI, f_{iso}) between the regular and fast versions of NODDI-SMT under varying SNR levels. The dataset consists of 10,000 samples per SNR level. The fast version of NODDI-SMT demonstrates comparable performance to the regular version across all SNR levels, maintaining similar absolute error values.

Analyzing Figures 4.3, it is evident that the fast version of the NODDI-SMT model generally exhibits comparable performance to its regular counterparts across different SNR levels. Specifically, the absolute error for parameters such as f_{extra} , f_{intra} , ODI, and f_{iso} remains similar between the regular and fast versions, indicating that the accelerated models maintain accuracy while significantly reducing computation time. This performance consistency across varying noise levels underscores the robustness of

the fast models. The result for NODDI-SMT-MICRO displays the same behavior and can be found in Section B.1

4.1.2.2 Runtime comparison

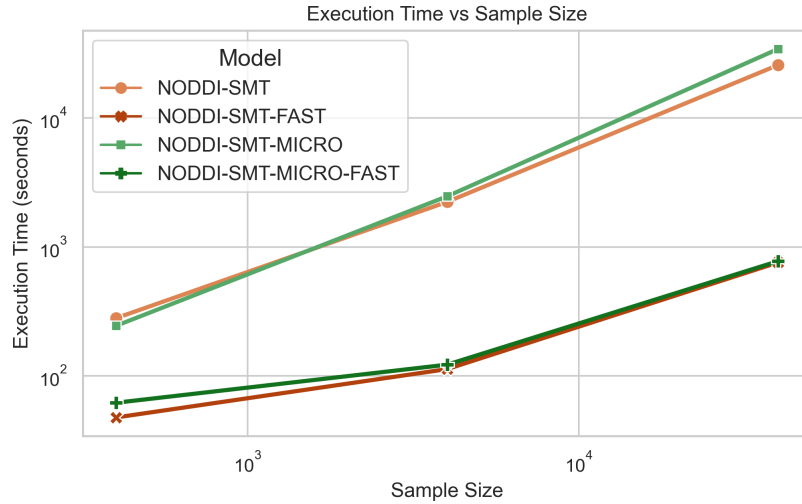


Figure 4.4: **Comparison of execution times for the regular and fast version of NODDI-SMT-MICRO depending on the sample size.** The sample sizes used were 400, 4000, and 40000. The fast versions significantly reduce computational time, particularly as the sample size increases.

Figure 4.4 shows the comparison of execution times for the regular and fast versions of NODDI-SMT and NODDI-SMT-MICRO models across different sample sizes. As expected, the fast versions significantly reduce the computational burden, especially as the sample size increases. This reduction in execution time without a substantial loss in accuracy, as shown in Figures 4.3 and B.1, highlights the efficiency and practicality of the fast models for large-scale applications.

4.2 In vivo data results

4.2.1 Visual results

4.2.1.1 MSE and R^2 maps

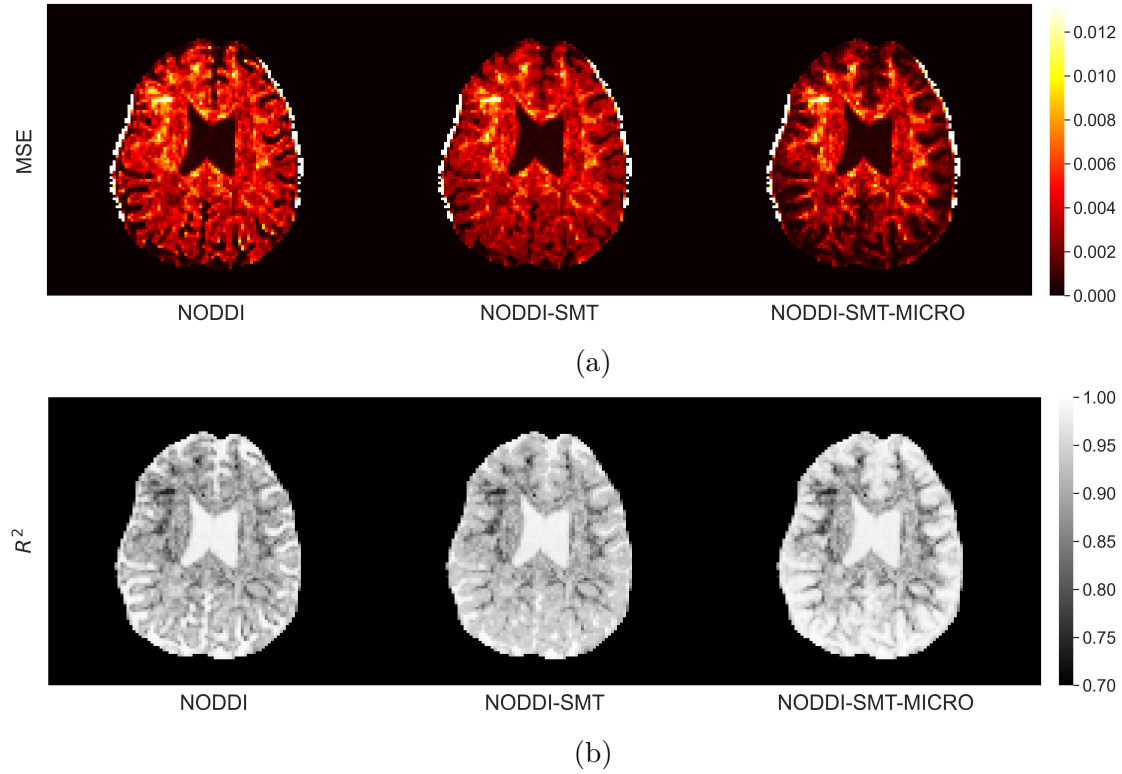


Figure 4.5: Comparison of (a) MSE and (b) R^2 maps for the different models (NODDI, NODDI-SMT, NODDI-SMT-MICRO) in a transverse slice of subject 005. The MSE maps highlight areas with higher errors, while the R^2 maps show how well each model fits the data. Across both metrics, NODDI-SMT-MICRO demonstrates superior performance, particularly in regions with complex fiber structures, such as the cerebral cortex.

Figures 4.5a and 4.5b provide a visual comparison of the performance of different models on in vivo data. The MSE maps reveal areas where the models exhibit higher errors, while the R^2 maps show how well each model fits the data. From the MSE maps, it can be observed that the NODDI-SMT and NODDI-SMT-MICRO models generally exhibit lower errors compared to the traditional NODDI model, especially in regions with complex fiber structures. The NODDI-SMT-MICRO model, in particular, shows reduced errors in the cerebral cortex. Additionally, the R^2 maps consistently present higher values for the NODDI-SMT-MICRO model, indicating a better fit to the data.

It is important to interpret these results with caution, as they are derived from a single subject and may not be representative of all in vivo data. Further validation with a larger cohort is necessary to confirm these findings.

4.2.1.2 Parameter maps

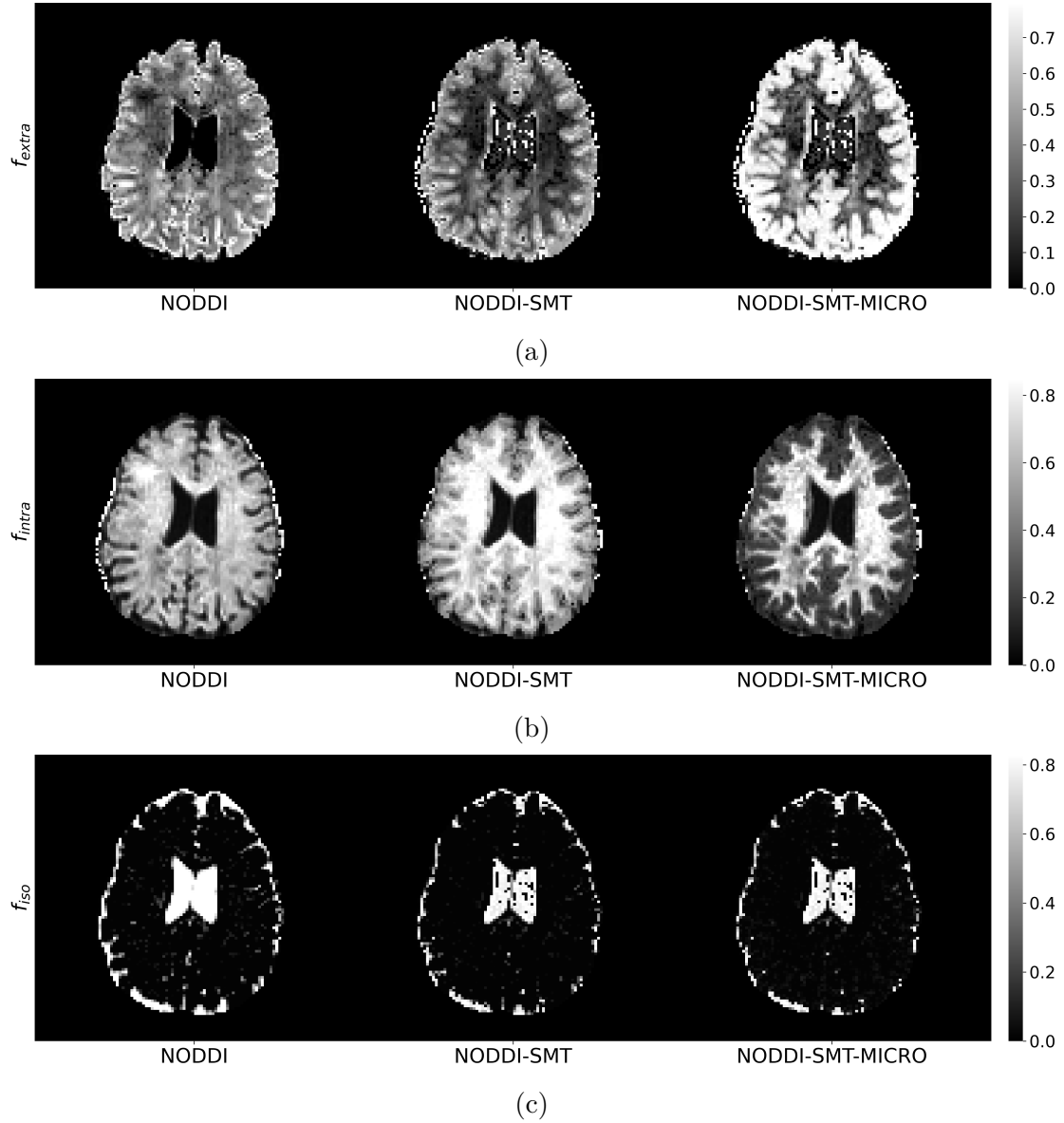


Figure 4.6: **Comparison of (a) f_{extra} , (b) f_{intra} , and (c) f_{iso} maps for the different models (NODDI, NODDI-SMT, NODDI-SMT-MICRO) in a transverse slice of subject 005.** The f_{extra} maps show the extra-cellular volume fraction. However, the SMT and SMT-MICRO models include regions of the CSF, as seen from the "holes" in the f_{iso} maps. The f_{intra} maps indicate the intra-cellular volume fraction. Specifically, the f_{intra} map for the SMT-MICRO model shows good distinction between gray matter and white matter regions.

Figures 4.6a, 4.6b, and 4.6c provide a comparative visualization of parameter maps for the different models. The f_{extra} maps (Figure 4.6a) show the extra-cellular volume fraction, but the SMT and SMT-MICRO models include regions of the CSF. This is corroborated by the f_{iso} maps (Figure 4.6c), where there are missing "spots" in the CSF

regions for SMT and SMT-MICRO models. The f_{intra} maps (Figure 4.6b) illustrate the intra-cellular volume fraction, with the SMT-MICRO model specifically showing good distinction between gray matter and white matter regions. The heatmaps for the ODI parameter can be found in Appendix B.

4.2.2 Comparison of the diffusion models

		PRL+~PRL-	pPRL+~pPRL-	PRL+~Gad	pPRL+~pGad	Gad~PRL-	pGad~pPRL-	mean	variance
NODDI	AUC	0.7942	0.7550	0.7939	0.7066	0.7887	0.7494	0.7647	0.0010
	accuracy	0.7229	0.6533	0.7664	0.7305	0.7358	0.6985	0.7179	-
	sensitivity	0.7903	0.6167	0.7504	0.7143	0.7869	0.7143	0.6752	-
	specificity	0.7053	0.7381	0.6456	0.6000	0.7628	0.6999	0.6919	-
SMT	AUC	0.7104	0.6613	0.7864	0.7117	0.7512	0.4201	0.6735	0.0143
	accuracy	0.6404	0.5907	0.8054	0.6568	0.7574	0.6549	0.6850	-
	sensitivity	0.5484	0.4167	0.7869	0.7049	0.5455	0.7143	0.6194	-
	specificity	0.6849	0.7871	0.6256	0.6200	0.7976	0.6815	0.6994	-
SMT-MICRO	AUC	0.7990	0.7183	0.8008	0.7056	0.7534	0.6635	0.7342	0.0024
	accuracy	0.7093	0.6316	0.7245	0.6431	0.7574	0.6843	0.6921	-
	sensitivity	0.7097	0.5167	0.7377	0.5738	0.7544	0.7143	0.6678	-
	specificity	0.7070	0.6800	0.7534	0.7080	0.6800	0.6671	0.7075	-

Table 4.1: **Receiver operating characteristic (ROC) curve analysis comparing the ability of different diffusion models to differentiate between different Regions of Interest (ROI).** The table displays a summary of the full performance (Area Under the Curve (AUC), accuracy, sensitivity, specificity) of each model for differentiating ROI between one another and their mean performance across all applications. *Abbreviations:* periplaque of Paramagnetic Rim Lesion (pPRL+); periplaque of non-Paramagnetic Rim Lesion (pPRL-); periplaque of Gadolinium contrast enhanced lesion (pGad); NODDI-SMT (SMT); NODDI-SMT-MICRO (SMT-MICRO).

Table 4.1 presents a comparison of the performance metrics for different diffusion models (NODDI, SMT, SMT-MICRO) in differentiating various MS lesions and their periplaque. The NODDI model achieves the highest mean AUC of 0.7647 with the lowest variance of 0.0010, indicating consistent and reliable performance across different ROI. SMT-MICRO also performs well, especially in PRL+ vs. Gad and PRL+ vs. PRL- comparisons, achieving the highest individual AUC values. However, it shows slightly higher variability compared to NODDI. The SMT model, while effective in some comparisons, generally shows lower mean auc and higher variance, suggesting less consistent performance. These results highlight the robustness of NODDI in differentiating between various ROI, although SMT-MICRO also shows promises with certain applications.

4.2.3 MRI analysis of MS lesions' microstructural damage

Figure 4.7 compares the extracellular volume fraction (f_{extra}), intracellular volume fraction (f_{intra}) and isotropic volume fraction (f_{iso}) parameter values across different regions of interest (ROI) in the brain for NODDI, NODDI-SMT, and NODDI-SMT-MICRO models. The ROI are ordered by the extent of microstructural damage, providing a comprehensive overview of how each model captures microstructural changes. The figure illustrating the comparison of ODI values across the ROI, along with the complete list of p-values from Welch's ANOVA statistical test, can be found in the appendix (refer to Figure B.3) and Tables C.1-C.4).

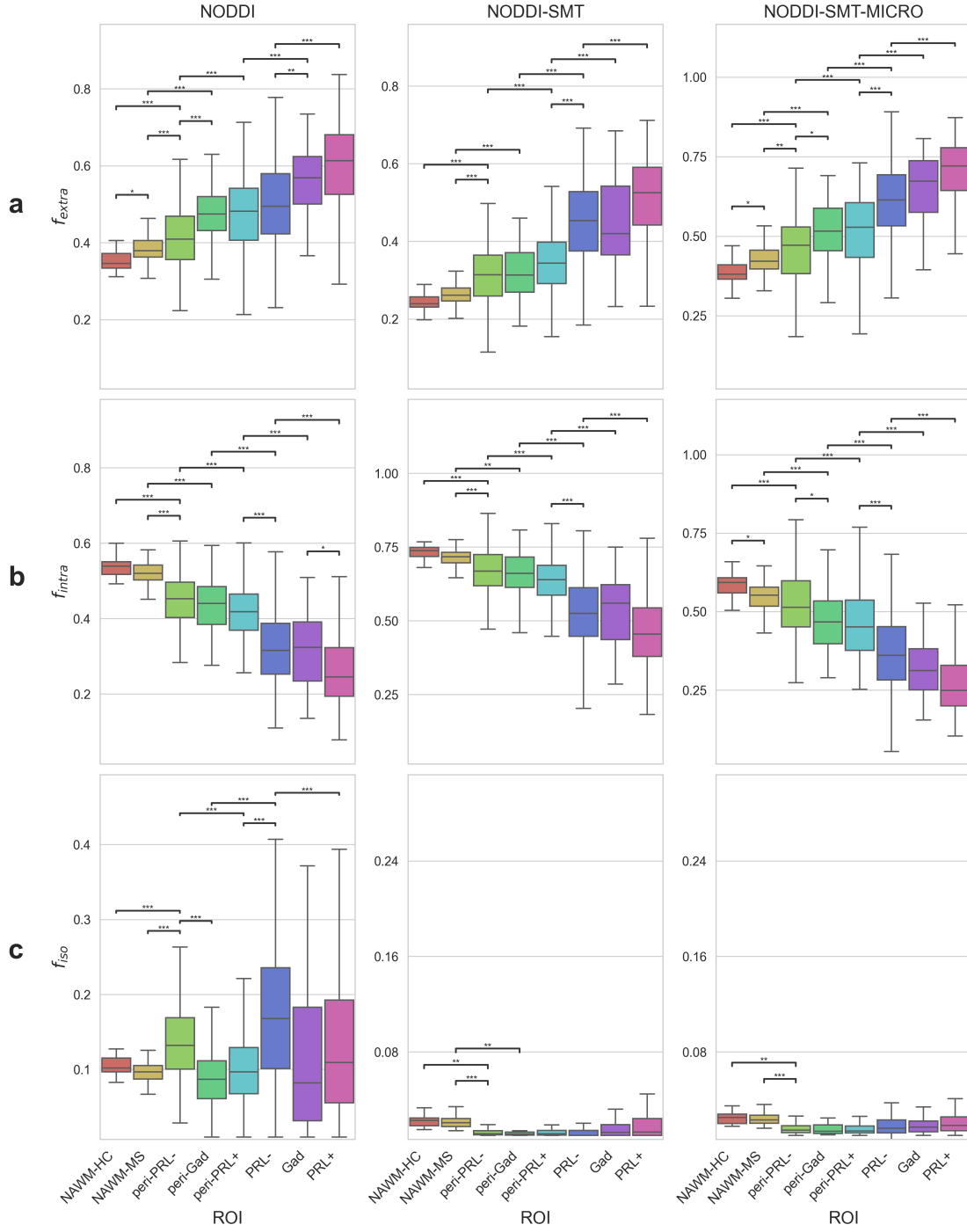


Figure 4.7: **Comparison of parameter values across different ROI for NODDI, NODDI-SMT, and NODDI-SMT-MICRO models.** Panels a, b, c show the extra-cellular volume fraction (f_{extra}), intra-cellular volume fraction (f_{intra}), and isotropic volume fraction (f_{iso}) parameter values, respectively. The ROI are ordered by the extent of microstructural damage based on histopathological analysis [4]. Statistical differences are noted between ROI with a range of 2, with * ($p < 0.05$), ** ($p < 0.01$), *** ($p < 0.001$).

In Figure 4.7 a, the NODDI-SMT-MICRO model exhibits overall higher f_{extra} values compared to NODDI. This difference is particularly pronounced in regions with more

significant damage, such as PRL-, Gad, and PRL+. While NODDI-SMT shows overall lower f_{extra} values, it still highlights a noticeable difference in scale between the ROI with higher damage and the others. Moreover, NODDI-SMT-MICRO demonstrates a broader range of f_{extra} values (0.35-0.74) compared to NODDI (0.375-0.61), indicating a greater contrast in the values observed.

Figure 4.7 **b** demonstrates that NODDI-SMT-MICRO behaves similarly to NODDI in terms of f_{intra} values. However, a consistent decrease in f_{intra} values is observed in more severely damaged ROI within the NODDI-SMT-MICRO model. NODDI-SMT shows slightly higher f_{intra} values compared to NODDI, which aligns with its lower f_{extra} values. Notably, NODDI-SMT-MICRO is the only model showing a significant difference between the values in NAWM-HC and NAWM-MS.

Finally, Figure 4.7 **c** compares the f_{iso} parameter values. The behavior of NODDI differs significantly from that of NODDI-SMT and NODDI-SMT-MICRO. NODDI shows substantially higher f_{iso} values across all studied ROI compared to the other models, suggesting potential overestimation in NODDI.

4.2.4 Comparison of the models in gray matter regions of control subjects

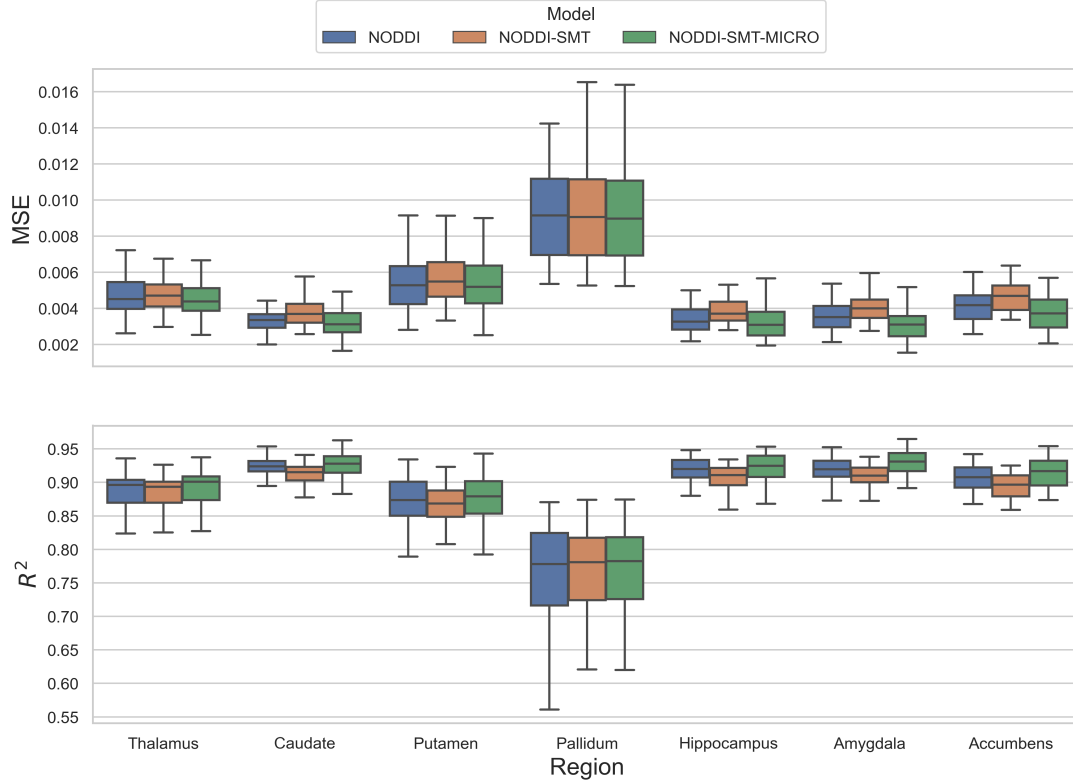


Figure 4.8: Comparison of the MSE and R^2 metrics for the different NODDI models (NODDI, NODDI-SMT, NODDI-SMT-MICRO) in gray matter regions of control subjects. The boxplots show the performance of these models across various gray matter regions, including the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens. NODDI-SMT-MICRO consistently achieves lower MSE and higher R^2 values, indicating better model accuracy and fit quality.

Figure 4.8 demonstrates that NODDI-SMT-MICRO consistently shows lower MSE and higher R^2 values across all examined GM regions compared to the other models. This suggests that the inclusion of microstructural information in NODDI-SMT-MICRO enhances the model's accuracy and fit quality.

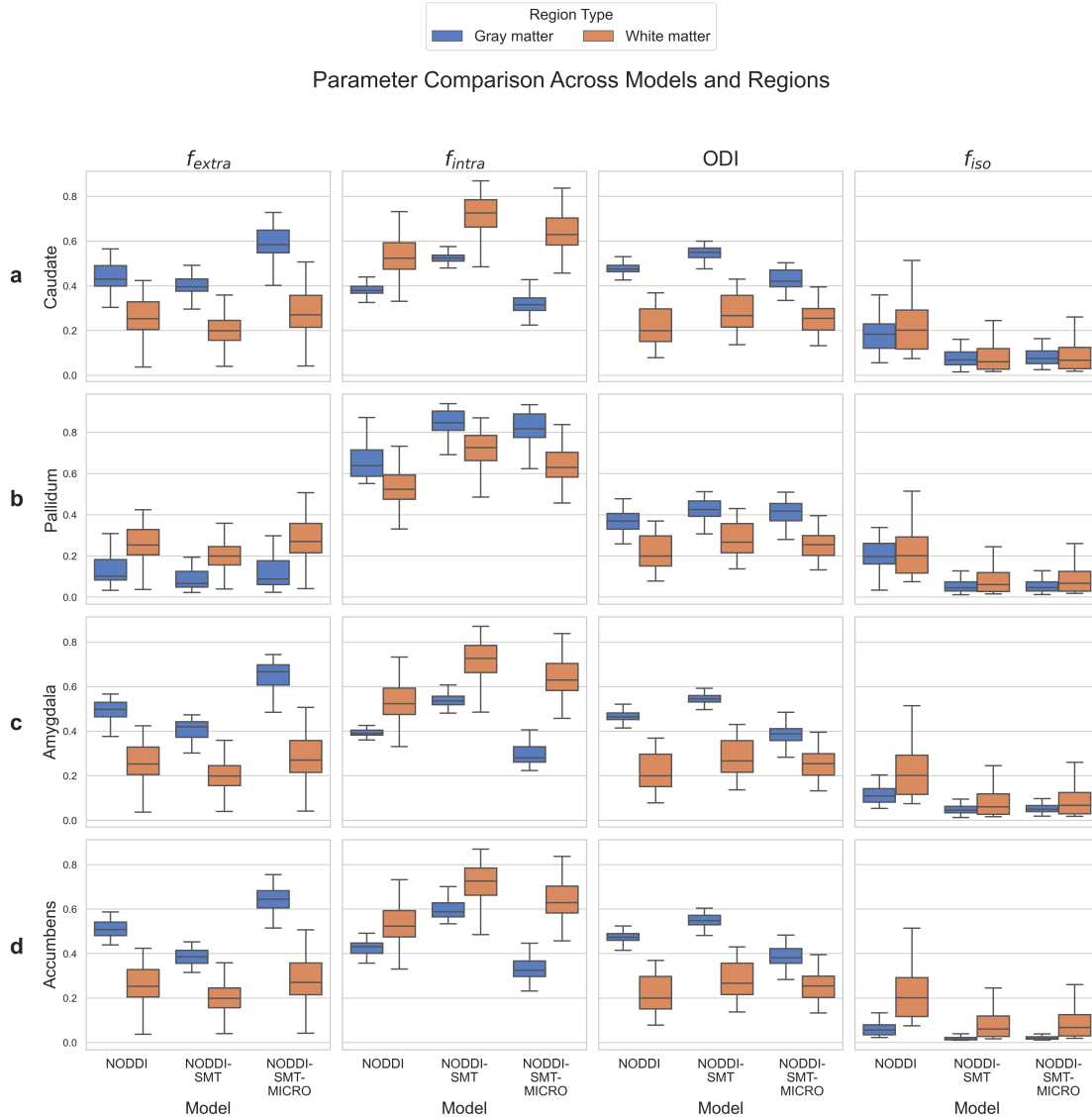


Figure 4.9: Boxplots depicting the values of f_{extra} , f_{intra} , ODI, and f_{iso} for different models (NODDI, NODDI-SMT, NODDI-SMT-MICRO) across various subcortical GM regions. The boxplots compare these values with those obtained from NAWM regions, serving as a baseline for comparison. The plots are organized by region: **a** Caudate, **b** Pallidum, **c** Amygdala, and **d** Accumbens.

The following observations based on Figure 4.9 highlight the differences in model parameters across the analyzed regions and models:

- **f_{intra} :** There is a pronounced contrast between subcortical GM and WM regions in the f_{intra} parameter, particularly with the NODDI-SMT-MICRO model. This model shows more pronounced differences, indicating its sensitivity to variations in tissue microstructure.
- **f_{extra} :** Similar to f_{intra} , the f_{extra} parameter also shows a significant contrast between subcortical GM and WM with the NODDI-SMT-MICRO model. The similarity between NODDI and NODDI-SMT-MICRO values in WM suggests a

consistent representation of extracellular components in these models, whereas NODDI-SMT tends to show lower values in subcortical GM.

- **ODI:** The distinction between subcortical GM and WM is more pronounced with NODDI and NODDI-SMT models than with NODDI-SMT-MICRO. This suggests that the latter model may capture less variability in fiber orientation within these regions.
- **f_{iso} :** There are notable differences in the f_{iso} parameter within subcortical GM regions, especially in the Pallidum, Amygdala, and Accumbens. NODDI-SMT and NODDI-SMT-MICRO consistently show lower f_{iso} values compared to NODDI.

The boxplots of the Thalamus, Putamen, and Hippocampus region can be found in the appendix (see Figure B.4).

Chapter 5

Discussion

The primary objective of this study was to enhance the interpretability of NODDI parameters, aiming to provide a more nuanced and detailed characterization of neurite properties. To achieve this, we employed a voxel-wise estimation of parallel diffusivities, hypothesizing that this approach would improve model fitting and yield more informative contrasts in parameter values, particularly when comparing MS lesions to healthy controls. This chapter presents the key findings, followed by an interpretation of the results and a discussion of the model’s limitations, along with potential avenues for improvement in future research.

5.1 Key findings

Our analyses on synthetic data showed that the SMT-based NODDI models, particularly NODDI-SMT-MICRO, achieved slightly lower MSE values and better parameter estimation at higher SNR levels (25+). Similarly, in vivo data also indicated improved model fitting; however, some issues emerged, notably the overestimation of the f_{extra} parameter with both NODDI-SMT and NODDI-SMT-MICRO models. This was particularly evident in the lateral ventricles, where high f_{extra} and low f_{iso} values suggested inaccuracies ("holes" in the f_{iso} maps). Despite these challenges, NODDI-SMT-MICRO provided notable contrast distinctions between GM and WM regions based on the f_{intra} parameter. Additionally, both SMT-based models consistently showed lower f_{iso} values compared to the traditional NODDI model, which is known to overestimate this parameter [43].

5.2 Interpretation of the results

The discrepancies between synthetic and in vivo data indicate that the expected improvements in parameter estimation were not fully realized, particularly in regions such as the lateral ventricles. This discrepancy is likely attributable to the inherent noise in in vivo DW-MRI data (i.e., low SNR), which undermines the benefits of per-axon diffusivity estimation as seen in the results on synthetic data.

In the context of characterizing the microstructure of MS lesions and periplaques, ROC

curve analysis suggested that the traditional NODDI model remains the most effective. Nevertheless, NODDI-SMT-MICRO demonstrated promising results, particularly in distinguishing MS subjects' NAWM from that of healthy controls, based on f_{extra} and f_{intra} . This differentiation could indicate that these parameters are sensitive to microstructural differences related to disease pathology.

Furthermore, the f_{intra} parameter (i.e., NDI) from the NODDI-SMT-MICRO model was significantly reduced in the NAWM of MS subjects compared to healthy controls, aligning with previous findings [33]. Interestingly, this significant difference was not observed with NODDI or NODDI-SMT, highlighting the potential added value of NODDI-SMT-MICRO in capturing subtle microstructural changes.

When evaluating model performance in GM of healthy control subjects, NODDI-SMT-MICRO provided the best distinction between WM and various GM regions (Figures 4.6b and 4.9), suggesting that its parameters may more accurately reflect underlying microstructures.

5.3 Limitations

A major limitation identified in SMT-based models is the tendency to overestimate parallel diffusivities, frequently hitting the maximum allowed value ($\lambda_{||} = 3 \times 10^{-9} [m^2/s]$). This behavior is illustrated in Figure 5.1.

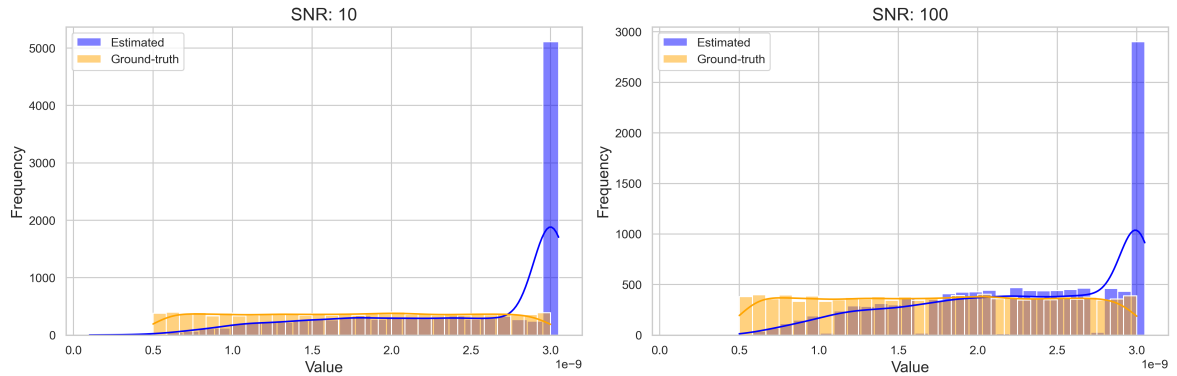


Figure 5.1: Illustration of the overestimation in multicompartiment SMT-based parallel diffusivity estimates. The plot shows that, for a uniform distribution of ground-truth parallel diffusivities, the estimated parallel diffusivity values obtained using the multicompartiment SMT model frequently reach the maximum allowed diffusivity value. This overestimation is even more pronounced in the single compartment SMT model, as demonstrated in Figure B.5.

This issue is particularly pronounced in low SNR settings, typical of in vivo data, leading to an underestimation of the extra-cellular volume fraction and an overestimation of the intra-cellular volume fraction (f_{intra}). This discrepancy is clearly visible in Figures 4.7 and 4.9.

Another significant limitation is the computational speed of fitting SMT-based models, which is constrained by the need for voxel-wise or batch-wise processing due to the varying values of parallel diffusivity. This poses a challenge for clinical applications where speed is crucial.

5.4 Future research

Future research should focus on improving the estimation of SMT-based per-axon diffusion coefficients, particularly in understanding how to avoid the overestimation of parallel diffusivities. This includes investigating the impact of acquisition schemes (e.g., b-values, number of gradient directions) and considering whether constraints on parallel diffusivity should be adjusted based on preliminary data analysis.

Additionally, optimizing the fitting algorithms to achieve runtimes comparable to the NODDI model is essential to enhance clinical feasibility. This could involve algorithmic innovations or more efficient computational approaches.

Part III

Improving the robustness of Microstructure Fingerprinting by including noise estimation

Chapter 6

State of the Art

In this chapter, we begin with an overview of Magnetic Resonance Fingerprinting (MRF), a groundbreaking MRI technique that introduced a new paradigm for MRI analysis through the concept of *fingerprinting*. This method inspired the Microstructure Fingerprinting (MF) model, which we will build upon in this part of the thesis. We then review two key methods developed to enhance the speed and accuracy of the MF model. Finally, we explore the theoretical principles of noise modeling in MRI, which are essential for our study, as we aim to incorporate noise estimation into the MF model.

6.1 Magnetic Resonance Fingerprinting

MRF is an innovative MRI technique introduced by Ma et al. in 2013 that enables rapid, quantitative imaging of multiple tissue properties simultaneously [44]. Unlike traditional MRI, which typically provides qualitative images, MRF leverages a pseudorandom variation of acquisition parameters to create unique signal evolutions for different tissue types.

6.1.1 Core concepts

6.1.1.1 Pseudorandom acquisition

MRF varies acquisition parameters such as flip angle, TR, and TE in a pseudorandom manner. This approach generates unique signal trajectories for different tissues, known as *fingerprints*, facilitating comprehensive tissue characterization.

6.1.1.2 Dictionary matching

A precomputed dictionary of signal evolutions corresponding to known tissue properties is created. The acquired signals are then matched to this dictionary to identify the best matches, allowing for the extraction of quantitative tissue properties.

6.1.2 Advantages and drawbacks

6.1.2.1 Advantages

MRF provides quantitative maps of tissue properties, such as T1 and T2 relaxation times and proton density, enabling:

- Enhanced diagnostic accuracy through detailed tissue characterization.
- Rapid acquisition, reducing scan times compared to traditional methods.

6.1.2.2 Drawbacks

The main drawbacks of MRF include:

- High computational burden for dictionary creation and matching.
- Potential for discretization errors in dictionary-based methods.

6.1.3 Advances in dictionary matching

Several approaches have been proposed to improve the efficiency and accuracy of dictionary matching in MRF:

- **Accelerated iterative reconstruction:** AIR-MRF integrates temporal compression and approximate nearest neighbor search for faster and more accurate MRF reconstructions [45].
- **Machine learning techniques:** Fully convolutional networks and hybrid deep learning models reduce computational burdens and improve matching accuracy [46], [47].
- **Efficient search algorithms:** MRF-ZOOM breaks down computational complexity, enabling scalable multi-resolution dictionary searching [48].

6.2 Fast MF

Several methods have been developed to enhance the efficiency and accuracy of the dictionary matching step in MF, which is the most time-consuming component of the algorithm. In the MF algorithm (see Section 1.3.2), dictionary matching is performed by solving NNLS problems for all atom combinations in the dictionary. The following two methods aim to optimize this critical step.

6.2.1 Hybrid method

The initial version of fast-MF [49] introduces an efficient two-step approach. Instead of solving the optimization problem for all combinations of atoms in the dictionary (a necessity to enforce the sparsity constraint on the weight vectors, ensuring that only one microstructure contributes, i.e., $\|w\|_0 = 1$), a single NNLS problem is solved

initially. Subsequently, a split Multi-Layer Perceptron (MLP) neural network is utilized to perform the final inference of the microstructural parameters (ν , D_{ex} , and fvf). This approach is illustrated in Figure 6.1.

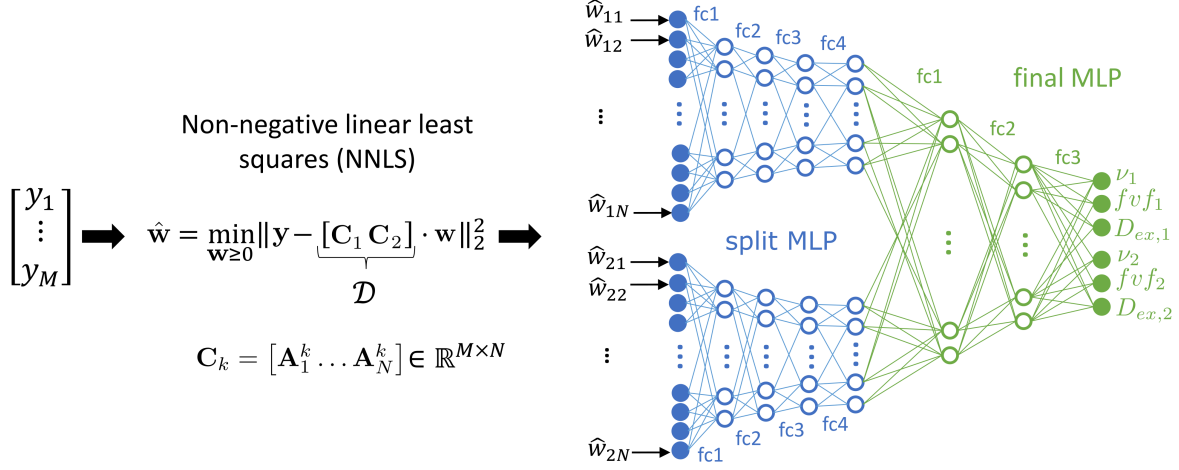


Figure 6.1: **Illustration of the hybrid fast-MF method.** Initially, a single NNLS problem is solved to reduce computational complexity. Then, a split-MLP neural network is used to infer the microstructural parameters (ν , D_{ex} , and fvf), enhancing the overall efficiency of the process. (Adapted from [49]).

In the case of in vivo data, where the number of fascicles (K) and their orientation ($\mathbf{u}_k$, $1 \leq k \leq K$) is not known, an external routine is used to estimate them. Then, from the pre-computed dictionary $\mathbf{F}^0$ along direction $\mathbf{u}_0$, single fascicle dictionaries $\mathbf{F}^k$ are computed for the estimated directions $\mathbf{u}_k$.

6.2.2 Fully-learned method

The latest version of fast-MF [50] advances further by eliminating the NNLS solving step entirely. Instead, for each shell with a fixed b-value, a spherical harmonics representation is computed. The resulting coefficients are then used as inputs for a deep neural network. This method is depicted in Figure 6.2.

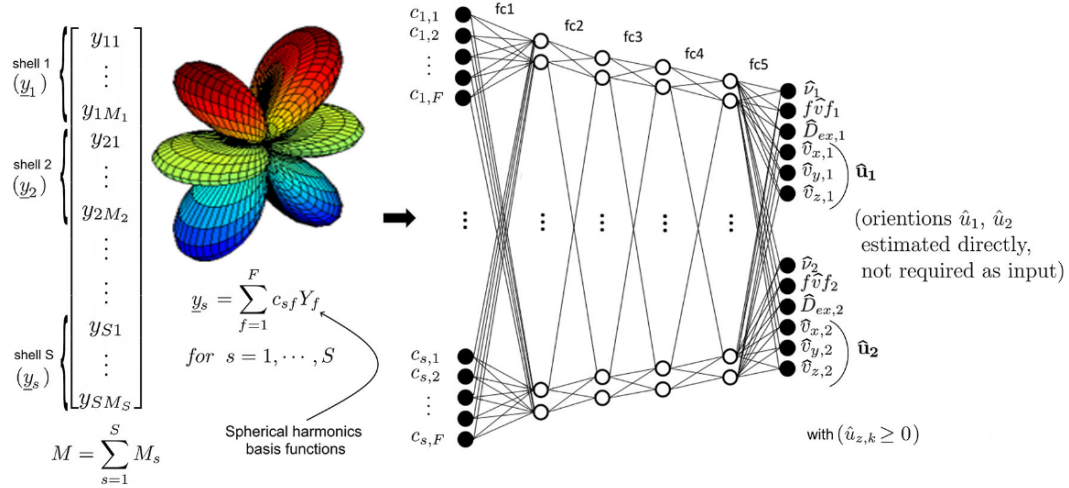


Figure 6.2: **Illustration of the fully-learned fast-MF method.** This approach computes a spherical harmonics representation for each shell, using the resulting coefficients as inputs for a deep neural network, thereby eliminating the need for NNLS solving. (Adapted from [50]).

A significant difference between this method and the previously discussed hybrid method is that it does not require an external routine to estimate the directions of the fascicles. Instead, the deep neural network is trained to infer these directions directly from the spherical harmonics representation coefficients.

6.3 Rician noise estimation

In MRI imaging, the noise present in the acquired images is typically non-Gaussian due to the process of calculating magnitude images from the complex signal data. Indeed, supposing we have independent Gaussian noise on the real and imaginary parts of the signal

$$\hat{y}_c = (\Re(y) + \epsilon_1) + j(\Im(y) + \epsilon_2), \quad (6.1)$$

where y is the noiseless signal and $\epsilon_1, \epsilon_2 \sim \mathcal{N}(0, \sigma)$, the magnitude

$$\hat{y} = \sqrt{(\Re(y) + \epsilon_1)^2 + (\Im(y) + \epsilon_2)^2} \quad (6.2)$$

is no longer Gaussian. It can be shown [51] that the probability density function of $\hat{y}$ is given by

$$p_{\hat{y}}(\hat{y}) = \frac{\hat{y}}{\sigma} \exp\left(-\frac{\hat{y}^2 + y^2}{2\sigma^2}\right) I_0\left(\frac{\hat{y}y}{\sigma^2}\right), \quad (6.3)$$

where I_0 is the modified zeroth order Bessel function of the first kind.

To utilize this probability density function in model fitting, one can derive an objective function by taking the log-likelihood of the data. The log-likelihood for a single measurement is the log of the Rician distribution, which can be summed over all measurements to form the objective function for fitting, as outlined in [52]. This

approach adjusts for the Rician noise bias and can be represented for a single voxel with N pairs of b-values and b-vectors as

$$J(\tilde{y}, \sigma) = \sum_{k=1}^N 2 \log \sigma - \log I_0 \left(\frac{\hat{y} \tilde{y}}{\sigma^2} \right) + \frac{\hat{y}^2 + \tilde{y}^2}{2\sigma^2}, \quad (6.4)$$

where $\tilde{y}$ is the model to be fitted.

However, to simplify the optimization process, an alternative objective function can be derived by incorporating an offset Gaussian noise model [53]. This model, as described in [54], involves minimizing a chi-squared objective function that accounts for the expected offset from the Rician noise bias:

$$J(\tilde{y}, \sigma) = \left\| \hat{y} - \sqrt{\tilde{y}^2 + \sigma^2} \right\|_2^2. \quad (6.5)$$

This simplified objective function facilitates more efficient fitting of diffusion-weighted data, enabling robust parameter estimation even in the presence of complex noise characteristics typical of DW-MRI data.

Chapter 7

Methods

To validate our model, we used two types of datasets: in vivo and simulated diffusion-weighted images. The details of these datasets and their acquisition methods are described in the following sections.

7.1 Data

7.1.1 Simulated DW data

The simulated DW datasets were generated using the synthesizer from the Fast-MF module [55]. This tool allows for the creation of data based on specified b-values, b-vectors, and scheme files, with customizable SNR ranges. The synthesizer simulates the diffusion signals by modeling the PGSE signal of single-fascicles for given directions and atoms according to the provided scheme. These individual signals are then combined using their respective volume fractions to generate the final diffusion-weighted images.

We used a multi-shell diffusion scheme with each voxel made of 532 volumes:

- 40 baseline volumes with a b-value of 0 [s/mm^2]
- 64 volumes with direction gradients and a b-value of 2000 [s/mm^2]
- 64 volumes with direction gradients and a b-value of 3000 [s/mm^2]
- 128 volumes with direction gradients and a b-value of 5000 [s/mm^2]
- 9 volumes with direction gradients and a b-value of 9950 [s/mm^2]
- 236 volumes with direction gradients and a b-value of 10000 [s/mm^2]
- 11 volumes with direction gradients and a b-value of 10050 [s/mm^2].

The shells are represented in Figure 7.1.

7.1.2 In vivo DW data

The in vivo DW dataset used in this study is sourced from the Human Connectome Project [56], specifically the MGH Adult Diffusion dataset. The data was acquired using a PGSE EPI sequence with $TR = 8800\text{ ms}$ and $TE = 57\text{ ms}$. The matrix size is $140 \times 140 \times 96$ with voxels of size $1.5 \times 1.5 \times 1.5\text{ mm}^3$ and no inter-slice gaps (resulting in a $210 \times 210 \times 140\text{ mm}^3$ FOV). The same multi-shell diffusion scheme was used as for the synthetic DW data. The shells are represented in Figure 7.1.

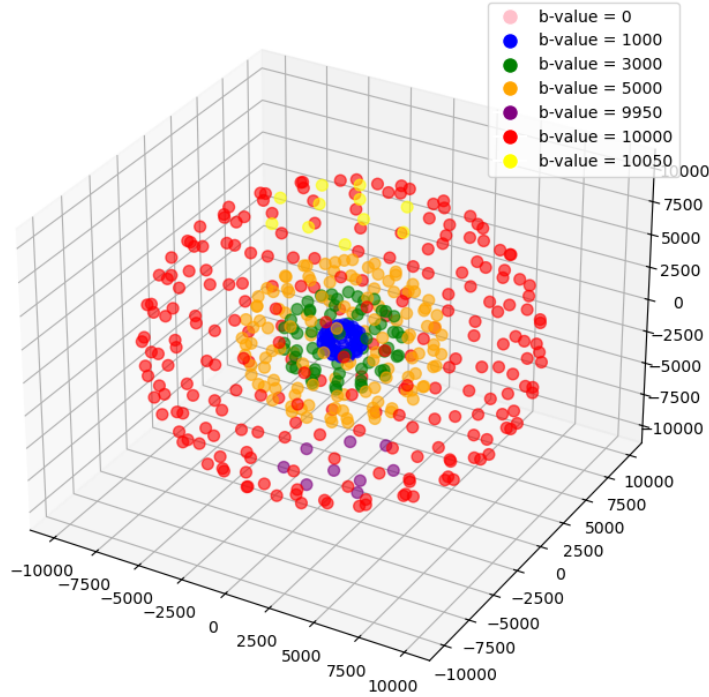


Figure 7.1: **Gradient shells represented on a 3D sphere.** The radius of the spheres are scaled by the b-value and the orientation of the points corresponds to the directions of the gradients

7.2 MF with noise estimation

The method for MF with noise estimation follows the same procedural steps as standard MF [2], with the primary difference being in the objective function used during the optimization process.

Consider a single fascicle dictionary $\mathbf{F}^0 \in \mathbb{R}^{M \times N}$ containing the fingerprints of N microstructural configurations for a fascicle aligned along a fixed direction $\mathbf{u}_0$

$$\mathbf{F}^0 = [\mathbf{A}_1^0, \dots, \mathbf{A}_N^0], \quad \text{where} \quad \mathbf{A}_j^0 = [A_{fasc}(\Omega_j, \mathbf{T}_0, \mathbf{u}_0, \mathbf{g}_i)]_{i=1}^M.$$

The algorithm proceeds through the following steps:

1. **Fascicle number and orientation estimation:**

An external routine estimates the number of fascicles, K , within each voxel and their respective orientations.

2. **Dictionary calculation for each fascicle:**

From the initial dictionary $\mathbf{F}^0$ along direction $\mathbf{u}_0$, single fascicle dictionaries $\mathbf{F}^k$ are computed for directions $\mathbf{u}_k$ for each fascicle, where $1 \leq k \leq K$ (with K determined in the previous step).

3. **Optimization with sparsity constraints:**

The optimization problem is solved under constraints that ensure only one configuration per fascicle dictionary $\mathbf{F}^k$ significantly contributes to the signal $\mathbf{y}$. The objective is to minimize the following function:

$$(\hat{j}_1, \dots, \hat{j}_K) = \underset{1 \leq j_1, \dots, j_K \leq N}{\operatorname{argmin}} \min_{w \geq 0, \sigma \geq 0} \left\| \mathbf{y} - \sqrt{\left(\left[\mathbf{A}_{j_1}^1 \mid \dots \mid \mathbf{A}_{j_K}^K \mid \mathbf{A}_{csf} \right] \cdot \begin{bmatrix} w_1 \\ \vdots \\ w_K \\ w_{csf} \end{bmatrix} \right)^2 + \sigma^2} \right\|_2.$$

Here, the solution provides the optimal indices $(\hat{j}_k)$ for each dictionary $\mathbf{F}^k$, which best represent the measured signal.

4. **Estimation of volume fractions:**

The fractions of occupation ν_k are estimated using the optimal weights w_k :

$$\nu_k = \frac{w_k}{\sum_{k=1}^{K+1} w_k}.$$

The fiber volume fractions (fvf_k) and extra-axonal diffusivities ($D_{ex,k}$) are retrieved from the dictionaries using the optimal indices $\hat{j}_k$.

To perform the optimization, the `scipy.optimize.minimize` function was employed using the Sequential Least Squares Programming (SLSQP) algorithm.

7.3 Validation methods

7.3.1 Validation on synthetic data

The validation of the model using simulated data involves comparing the estimated parameters with the ground truth values used to generate the synthetic DWI datasets. Key metrics for evaluation include the MSE and Mean Absolute Error (MAE) of the reconstructed signals, as well as the accuracy of the estimated microstructural parameters such as ν_1 , ν_2 , $D_{ex,1}$, $D_{ex,2}$, fvf_1 , and fvf_2 .

7.3.2 Validation on in vivo data

For in vivo data, validation is conducted by assessing the quality of the reconstructed signal and the reliability of the estimated microstructural parameters. Metrics such as the MSE and coefficient of determination (R^2) are used to evaluate the fit between the observed and predicted signals. Additionally, the consistency and plausibility of the estimated parameters are examined across different regions of the brain.

7.3.3 Statistical analysis

Statistical tests, such as the Mann-Whitney U test, are employed to determine the significance of differences between the standard MF and MF with noise estimation models. The p-values from these tests are reported to establish the statistical validity of the observed improvements in signal reconstruction and parameter estimation.

7.3.4 Robustness to starting point perturbations

The robustness of the model to variations in the initial guess is evaluated by perturbing the initial guesses for w_1 and w_2 by $\pm 10\%$ and $\pm 1000\%$ from the optimal values. The impact on the reconstructed signal quality, parameter estimation accuracy, and convergence behavior is analyzed.

7.3.5 Evaluation of computational efficiency

The computational efficiency of the MF with noise estimation model is assessed by measuring the number of iterations required for convergence and the overall computation time. This evaluation helps to ensure that the method is feasible for practical applications.

Chapter 8

Results

8.1 Comparison of the fitted parameters with the ground-truth values

Using the simulated data, we compare the fitted parameters obtained with MF and MF with noise estimation to the ground-truth values. Figure 8.1 presents the results for ν_1 , $D_{ex,1}$, fvf_1 , while Figure 8.2 shows the results for ν_2 , $D_{ex,2}$, fvf_2 . Each figure illustrates the relationship between the estimated and true values, along with the R^2 score indicating the goodness of fit. The dataset contains 1000 voxels with SNR values ranging from 20 to 100.

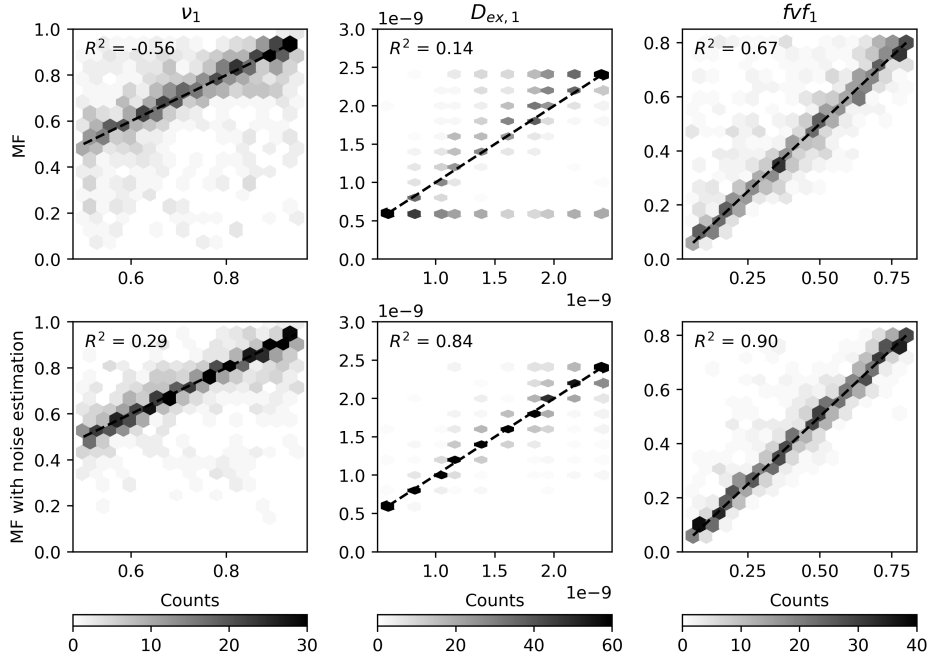


Figure 8.1: **Comparison of fitted parameters ν_1 , $D_{ex,1}$, fvf_1 to ground-truth values.** The subplots display the estimated vs. true values for MF (top row) and MF with noise estimation (bottom row), with R^2 scores indicating the goodness of fit. The dataset contains 1000 voxels with SNR values ranging from 20 to 100.

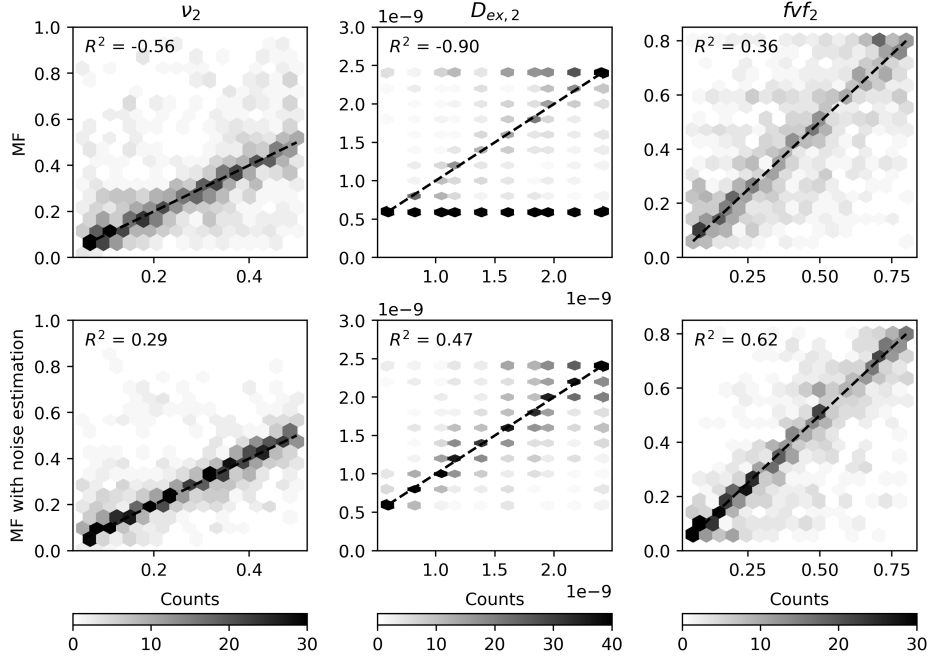


Figure 8.2: **Comparison of fitted parameters ν_2 , $D_{ex,2}$, fvf_2 to ground-truth values.** The subplots display the estimated vs. true values for MF (top row) and MF with noise estimation (bottom row), with R^2 scores indicating the goodness of fit. The dataset contains 1000 voxels with SNR values ranging from 20 to 100.

The results presented in Figures 8.1 and 8.2 demonstrate the performance of MF and MF with noise estimation in fitting the parameters ν_1 , $D_{ex,1}$, fvf_1 , ν_2 , $D_{ex,2}$, and fvf_2 to their ground-truth values. The R^2 scores indicate a generally better fit for the MF with noise estimation method across most parameters, particularly for $D_{ex,1}$ and $D_{ex,2}$, where the improvement is most pronounced. This suggests that incorporating noise estimation significantly enhances the model's ability to accurately capture the underlying parameter values. These findings highlight the effectiveness of the noise estimation approach in improving model accuracy, thus demonstrating its potential utility in various applications requiring precise parameter estimation.

8.2 Impact of the Signal-to-Noise Ratio

To assess the impact of SNR on the quality of the reconstructed signal and parameter fitting, we ran MF and MF with noise estimation on three datasets of 500 voxels each, with SNR values of 10, 25, and 100. Figure 8.3 compares the MSE and MAE of the reconstructed signal for MF and MF with noise estimation. Figures 8.4 and 8.5 compare the errors of the fitted parameters for MF and MF with noise estimation.

8.2.1 Impact on the reconstructed signal

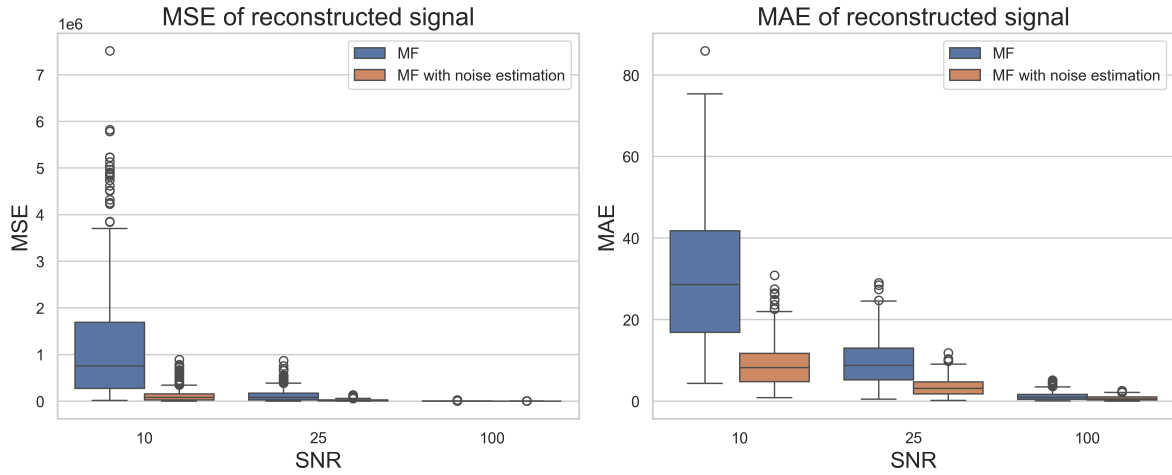


Figure 8.3: **MSE and MAE boxplots of reconstructed signals for SNR values 10, 25, and 100.** The boxplots compare the MSE and MAE of the reconstructed signals obtained using MF and MF with noise estimation across all voxels.

SNR	MSE p-value	MAE p-value
10	1.0531×10^{-102}	5.8927×10^{-111}
25	1.3184×10^{-79}	1.2350×10^{-86}
100	3.0950×10^{-11}	1.0588×10^{-12}

Table 8.1: **Mann-Whitney U test results for MSE and MAE.** The table shows the p-values for the Mann-Whitney U test comparing the performance of the MF and MF with noise estimation models across different SNR levels.

The boxplots in Figure 8.3 highlight the impact of SNR on the MSE and MAE of the reconstructed signals. Both MSE and MAE decrease as the SNR increases, indicating improved reconstruction quality with higher SNR values. MF with noise estimation consistently outperforms MF across all SNR levels, with significantly lower MSE and MAE values. This is supported by the extremely low p-values obtained from the Mann-Whitney U test (Table 8.1), which indicate that the differences in MSE and MAE between the two methods are highly significant across all tested SNR levels.

8.2.2 Impact on the fitted parameters

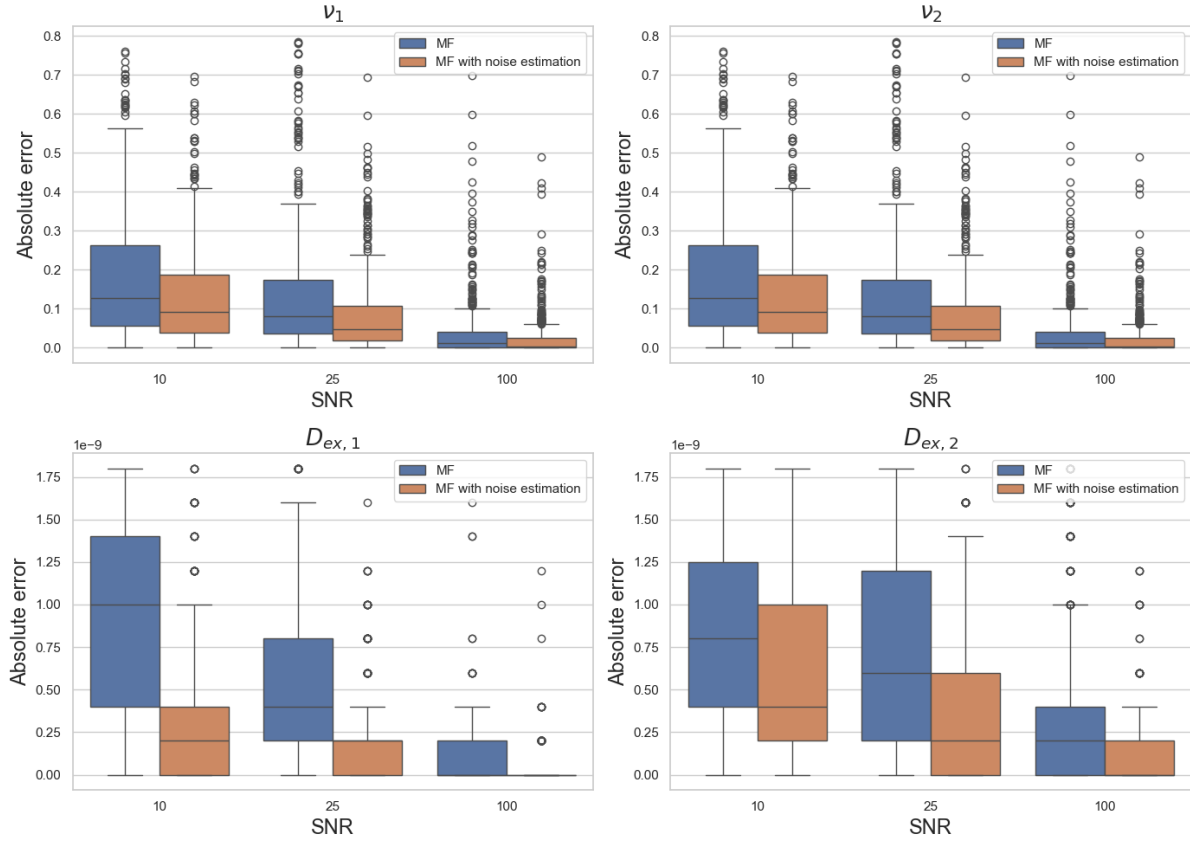


Figure 8.4: **Error boxplots of volume fractions ν_1 and ν_2 , and extra-axonal diffusivities $D_{ex,1}$ and $D_{ex,2}$ for SNR values 10, 25, and 100.** The boxplots compare the error of the volume fractions ν_1 , ν_2 and the extra-axonal diffusivities $D_{ex,1}$, $D_{ex,2}$ obtained using MF and MF with noise estimation across all voxels.

SNR	ν_1 p-value	ν_2 p-value	$D_{ex,1}$ p-value	$D_{ex,2}$ p-value
10	4.3679×10^{-7}	4.3678×10^{-7}	2.5537×10^{-54}	2.4762×10^{-12}
25	9.3616×10^{-10}	9.3616×10^{-10}	9.0897×10^{-45}	1.3370×10^{-22}
100	5.0569×10^{-5}	5.0569×10^{-5}	1.2938×10^{-12}	2.5888×10^{-12}

Table 8.2: **Mann-Whitney U test results for ν_1 , ν_2 , $D_{ex,1}$ and $D_{ex,2}$.** The table shows the p-values for the Mann-Whitney U test comparing the performance of the MF and MF with noise estimation models across different SNR levels.

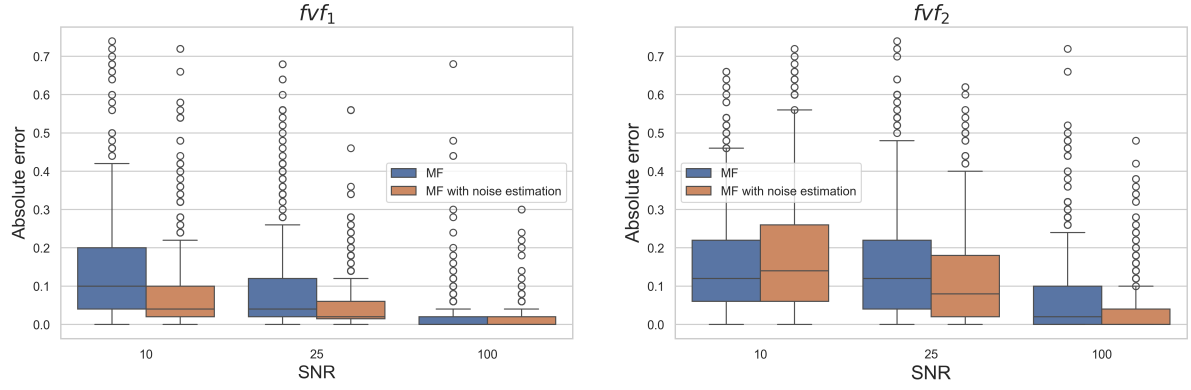


Figure 8.5: **Error boxplots of fiber volume fractions fvf_1 and fvf_2 for SNR values 10, 25, and 100.** The boxplots compare the error of the fiber volume fractions fvf_1 and fvf_2 obtained using MF and MF with noise estimation across all voxels.

SNR	fvf_1 p-value	fvf_2 p-value
10	4.2835×10^{-16}	0.2568
25	3.8763×10^{-9}	9.7324×10^{-7}
100	1.1812×10^{-4}	5.5970×10^{-9}

Table 8.3: **Mann-Whitney U test results for fvf_1 and fvf_2 .** The table shows the p-values for the Mann-Whitney U test comparing the performance of the MF and MF with noise estimation models across different SNR levels.

Figures 8.4 and 8.5 present the absolute error boxplots for the fitted parameters ν_1 , ν_2 , $D_{ex,1}$, $D_{ex,2}$, fvf_1 , and fvf_2 across different SNR values. The results show that the absolute error generally decreases as the SNR increases, reflecting better parameter fitting at higher SNR levels. MF with noise estimation consistently achieves lower absolute errors compared to MF alone, particularly for the diffusivity parameters $D_{ex,1}$ and $D_{ex,2}$.

This improvement is statistically significant, as highlighted by the p-values in Tables 8.2 and 8.3. For instance, for ν_1 and ν_2 , the p-values are extremely low (4.3679×10^{-7} at SNR 10, 9.3616×10^{-10} at SNR 25, and 5.0569×10^{-5} at SNR 100), indicating a significant difference in performance between MF and MF with noise estimation. Similar trends are observed for $D_{ex,1}$ and $D_{ex,2}$, with p-values further underscoring the statistical significance of the improvements.

For the fiber volume fractions fvf_1 and fvf_2 , the p-values also reflect significant differences for fvf_1 , particularly at lower SNR levels, where the p-values are 4.2835×10^{-16} at SNR 10, 3.8763×10^{-9} at SNR 25, and 1.1812×10^{-4} at SNR 100, indicating highly significant improvements. However, for fvf_2 , the p-value at SNR 10 is 0.2568, which is not statistically significant (typically a p-value > 0.05), suggesting that the difference in performance between MF and MF with noise estimation is not significant for fvf_2 at this SNR level.

8.2.3 Summary

The results presented in this section provide an overview of the performance of MF and MF with noise estimation across different SNR levels. The clear reduction in error and significant improvements in parameter estimation highlight the benefits of incorporating noise estimation techniques. A more detailed analysis and interpretation of these results will be provided in the discussion chapter.

8.3 Impact of the starting point

As the optimization procedure requires an initial guess as a starting point, we decided to study its impact on the quality of the fit. We ran MF with noise estimation on a dataset of 500 voxels, with initial guesses for w_1 and w_2 perturbed by $\pm 10\%$ and $\pm 1000\%$ from the optimal values. Tables 8.4 and 8.5 present the results for the reconstructed signal and the fitted parameters, respectively. Table 8.6 shows the impact of the starting point on the number of iterations required to converge.

8.3.1 Impact on the reconstructed signal

Method	Perturbation	Min MAE	Max MAE	Mean MAE	Median MAE
MF with noise estimation	$\pm 10\%$	10.5616	0.0215	1.6396	1.2253
	$\pm 1000\%$	14.0567	0.0215	1.6894	1.2518

Table 8.4: **Summary of MAE statistics for reconstructed signals with different starting point perturbations.** The table shows the minimum, maximum, mean, and median MAE of the reconstructed signals when the starting point is perturbed by $\pm 10\%$ and $\pm 1000\%$ from the optimal value.

Table 8.4 presents the MAE statistics for the reconstructed signals with different perturbations of the starting point. The results indicate that the MAE remains relatively low even with large perturbations ($\pm 1000\%$), suggesting that the reconstruction quality is robust to changes in the starting point.

8.3.2 Impact on the fitted parameters

Parameter	Perturbation	Max error	Mean error	Median error	Std error
ν_1	$\pm 10\%$	0.6446	0.0494	0.02	0.0826
	$\pm 1000\%$	0.6446	0.0521	0.0212	0.0884
ν_2	$\pm 10\%$	0.6446	0.0494	0.02	0.0826
	$\pm 1000\%$	0.6446	0.0521	0.0212	0.0884
$D_{ex,1}$	$\pm 10\%$	1.2×10^{-9}	8.2×10^{-11}	0	1.71×10^{-10}
	$\pm 1000\%$	1.2×10^{-9}	8.56×10^{-11}	0	1.75×10^{-10}
$D_{ex,2}$	$\pm 10\%$	1.6×10^{-9}	2.18×10^{-10}	2.0×10^{-9}	3.03×10^{-10}
	$\pm 1000\%$	1.6×10^{-9}	2.26×10^{-10}	2.0×10^{-10}	3.02×10^{-10}
fvf_1	$\pm 10\%$	0.4600	0.0283	0.0198	0.0522
	$\pm 1000\%$	0.4600	0.0292	0.02	0.0526
fvf_2	$\pm 10\%$	0.68	0.0680	0.04	0.0934
	$\pm 1000\%$	0.68	0.0721	0.04	0.0989

Table 8.5: **Summary of absolute error statistics for fitted parameters of MF with noise estimation for different starting point perturbations.** The table shows the maximum, mean, median, and standard deviation of absolute errors of the fitted parameters when the starting point is perturbed by $\pm 10\%$ and $\pm 1000\%$ from the optimal value.

Table 8.5 summarizes the absolute error statistics for the fitted parameters under different perturbations. The maximum absolute errors remain consistent across perturbations for all parameters. The mean and median absolute errors increase slightly with larger perturbations but remain within a reasonable range, demonstrating the method's robustness. The standard deviation of the errors also increases slightly with larger perturbations, indicating a marginal rise in variability. For instance, the standard deviation for ν_1 increases from 0.0826 to 0.0884, and for $D_{ex,1}$, it increases from 1.71×10^{-10} to 1.75×10^{-10} .

Overall, these results show that MF with noise estimation exhibits robustness to variations in the starting point, maintaining accurate parameter estimates and manageable variability even under significant perturbations.

8.3.3 Impact on the speed of convergence

Perturbation	Min iterations	Max iterations	Mean iterations	Median iterations
$\pm 10\%$	12	32	19.02	19.0
$\pm 1000\%$	18	46	29.234	29.0

Table 8.6: **Summary of iteration statistics of MF with noise estimation for different starting point perturbations.** The table shows the minimum, maximum, mean, and median number of iterations required for convergence when the starting point is perturbed by $\pm 10\%$ and $\pm 1000\%$ from the optimal value.

Table 8.6 displays the iteration statistics for different starting point perturbations. The results show that a higher perturbation leads to an increased number of iterations required for convergence. Specifically, the mean number of iterations increases by approximately 1.5 times when the perturbation changes from $\pm 10\%$ to $\pm 1000\%$, indicating that larger deviations from the optimal starting point can slow down the convergence.

8.3.4 Summary

The results presented in this section demonstrate the robustness of the MF with noise estimation method to variations in the starting point. Despite large perturbations, the MAE of the reconstructed signals remains low, and the errors in the fitted parameters are generally small. Although larger perturbations increase the number of iterations required for convergence, the optimization process remains efficient. These findings highlight the method's reliability and robustness, making it suitable for practical applications where the optimal starting point may not be known. A more detailed analysis and interpretation of these results will be discussed in the subsequent chapter.

8.4 Comparison with other models

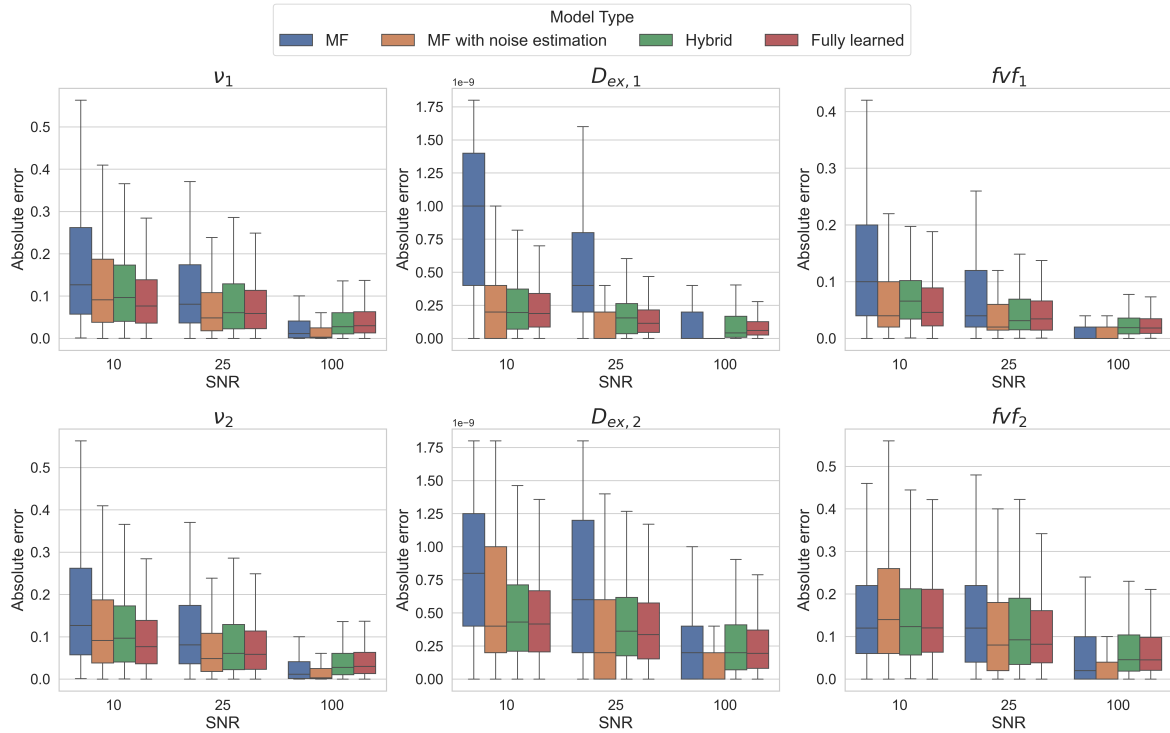


Figure 8.6: **Error boxplots of model parameters.** The boxplots illustrate the absolute errors in estimating the volume fractions (ν_1, ν_2), extra-axonal diffusivities ($D_{ex,1}, D_{ex,2}$), and fiber volume fractions (fvf_1, fvf_2) using four different models: MF, MF with noise estimation, the hybrid model, and the fully learned model.

In Figure 8.6, the performance of various models is compared across different SNR levels. At an SNR of 10, the MF with noise estimation model shows a wider spread in error values compared to the hybrid and fully learned models, indicating greater variability in its estimates. However, it does achieve a slightly lower median absolute error for the parameters fvf_1 and $D_{ex,2}$. At an SNR of 25, MF with noise estimation generally performs better, showing lower median absolute errors and less variability, although it has a higher spread for $D_{ex,2}$. Finally, at an SNR of 100, both MF and MF with noise estimation outperform the hybrid and fully learned models.

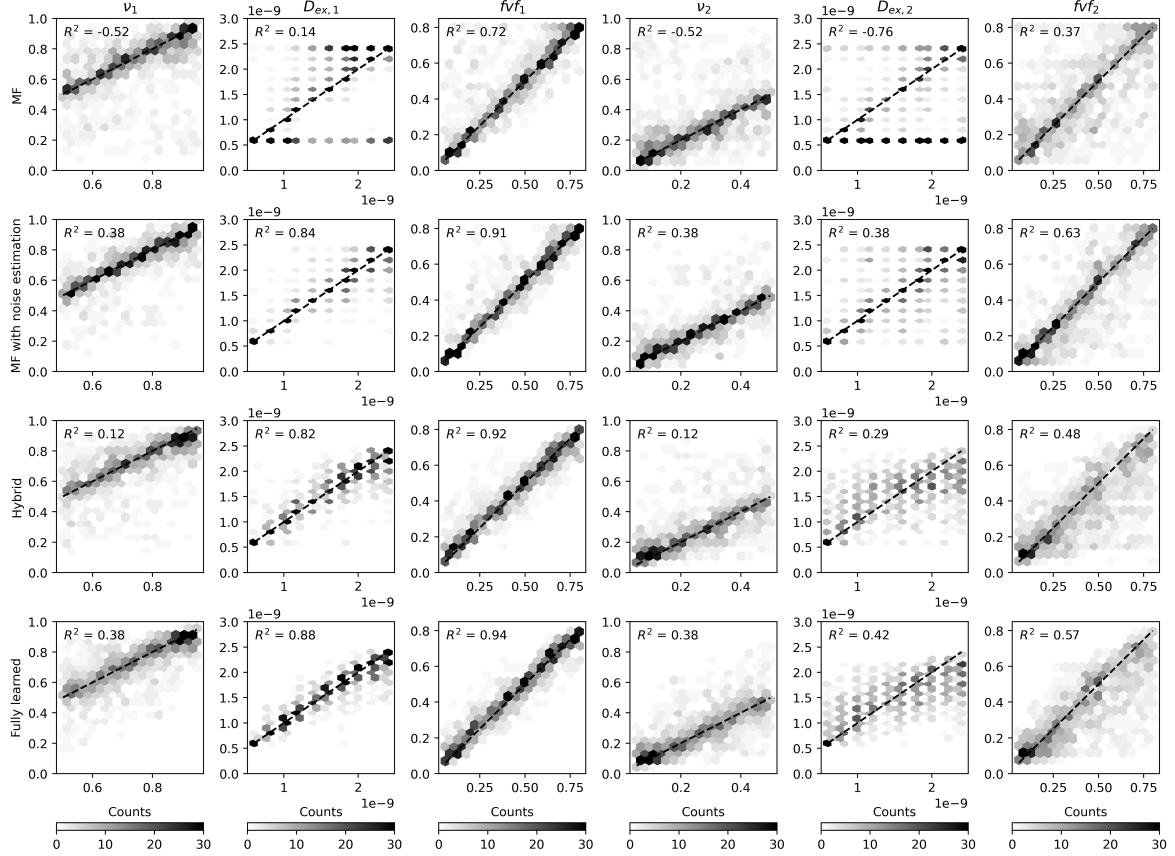


Figure 8.7: **Comparison of fitted parameters to ground-truth values in high SNR setting.** The subplots display the estimated versus true values for MF (top row), MF with noise estimation (second row), the hybrid model (third row), and the fully learned model (bottom row), with R^2 scores indicating the goodness of fit. The dataset consists of 1000 voxels, with 500 voxels at an SNR of 25 and 500 voxels at an SNR of 100.

Figure 8.7 provides a visual comparison of the fitted parameters against ground-truth values for high SNR levels (25-100). Here, the MF with noise estimation model demonstrates performance comparable to the hybrid and fully learned models, occasionally outperforming or underperforming depending on the specific parameter being estimated. This observation aligns with the trends noted in Figure 8.6, particularly in the high-SNR range.

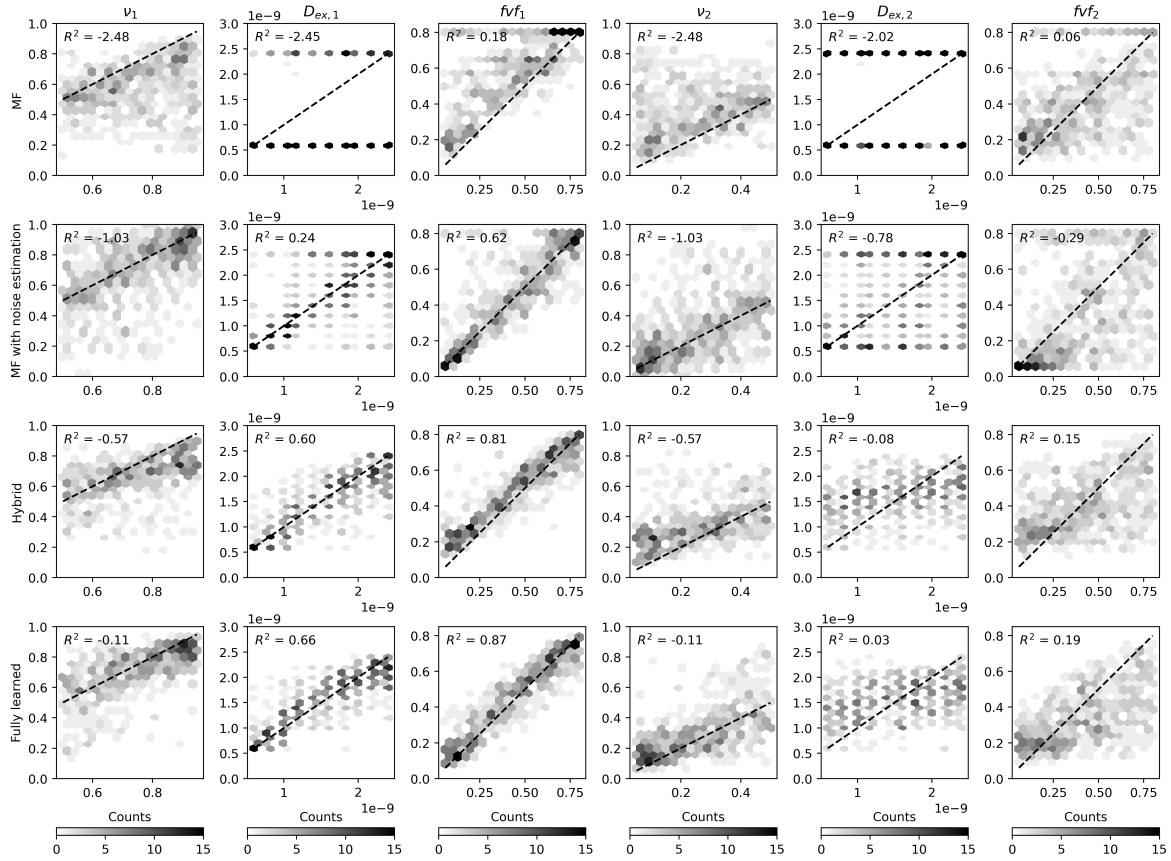


Figure 8.8: **Comparison of fitted parameters to ground-truth values in low SNR setting.** The subplots show estimated versus true values for MF (top row), MF with noise estimation (second row), the hybrid model (third row), and the fully learned model (bottom row), with R^2 scores indicating the goodness of fit. The dataset contains 500 voxels with an SNR of 10.

Conversely, Figure 8.8 illustrates the performance at a low SNR of 10, where the MF with noise estimation model performs significantly worse than the hybrid and fully learned models. The boxplots in Figure 8.6 suggested some differences in performance; however, the hexbin plots in Figure 8.8 reveal a more pronounced discrepancy. This indicates that while MF with noise estimation can be effective at higher SNRs, its reliability decreases substantially at lower SNRs, where it struggles to provide accurate parameter estimates compared to the other models.

8.5 Parameter map of slice of in-vivo data

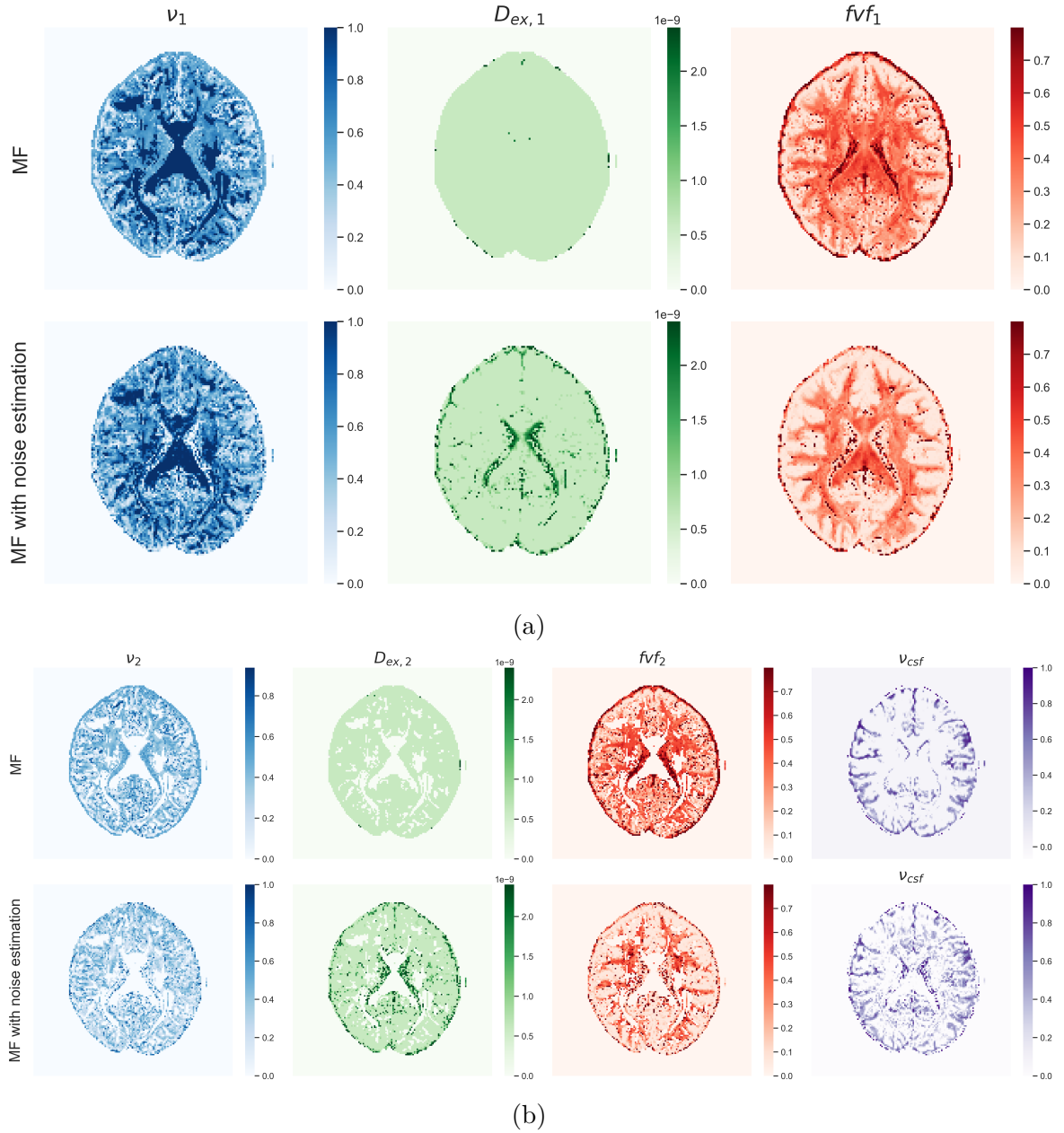


Figure 8.9: Maps of parameters ν_1 , ν_2 , $D_{ex,1}$, $D_{ex,2}$, fvf_1 , and fvf_2 obtained by fitting MF and MF with noise estimation on a transversal slice of the DW of subject 1007. Subfigure (a) compares the maps for parameters ν_1 , $D_{ex,1}$, and fvf_1 , while subfigure (b) compares the maps for parameters ν_2 , $D_{ex,2}$, and fvf_2 . Each subfigure shows the results from the MF model on the top and the MF model with noise estimation on the bottom.

Figures 8.9a and 8.9b present the maps of various microstructural parameters obtained by fitting MF and MF with noise estimation on a transversal slice of in vivo data. These figures display the intra-axonal volume fractions (ν_1 and ν_2), the extra-axonal

diffusivities ($D_{ex,1}$ and $D_{ex,2}$), the fiber volume fractions (fvf_1 and fvf_2), and the CSF volume fraction (ν_{CSF}) for two distinct fascicles within the brain.

Based on these figures, we can make the following observations:

- **Extra-axonal diffusivity:** The MF model shows limited variability in extra-axonal diffusivity (D_{ex}) values. In contrast, the MF with noise estimation model exhibits greater variability, which aligns better with expected biological heterogeneity.
- **Fiber volume fractions:** The MF model indicates high fiber volume fraction (fvf) values in the ventricles region, which is unexpected since this area is primarily filled with CSF. The MF with noise estimation model reduces this overestimation, presenting more realistic values.
- **CSF volume fraction:** The MF model underestimates the CSF volume fraction (ν_{CSF}) in the ventricles, showing very low values where high values are expected. The MF with noise estimation model provides higher and more accurate CSF volume fractions in this region.

Overall, the MF with noise estimation model seems to deliver parameter values that are more consistent with known brain anatomy, particularly in the ventricles region. This model demonstrates higher extra-axonal diffusivity values, appropriate fiber volume fractions, and accurate CSF fractions, highlighting its improved performance over the standard MF model.

These observations set the stage for a more detailed analysis and interpretation, which will be thoroughly discussed in the subsequent chapter dedicated to the discussion of results.

8.6 MSE and coefficient of determination maps of in vivo data

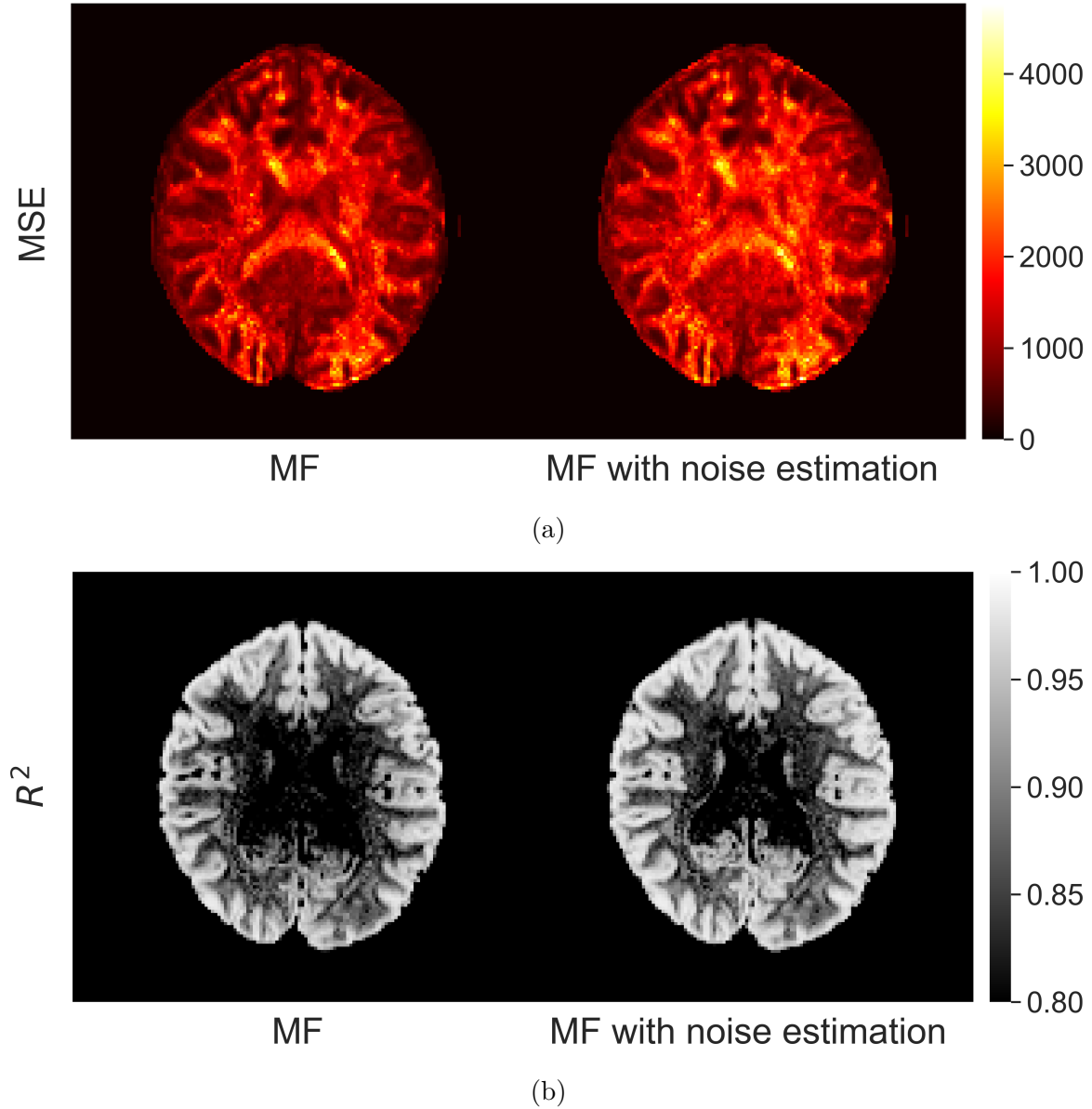


Figure 8.10: **MSE and R^2 maps of subject 1007 for the diffusion models MF and MF with noise estimation.** (a) MSE maps show the error distribution across the brain, with the MF model with noise estimation exhibiting higher MSE values in central regions such as the ventricles and corpus callosum. (b) R^2 maps indicate the goodness of fit, where the MF model with noise estimation generally provides a better fit across most regions of the brain compared to the standard MF model.

Based on Figure 8.10a, we observe that the MF with noise estimation method exhibits noticeably higher MSE values than the standard MF method in central brain regions such as the ventricles, caudate, thalamus, fornix, corpus callosum, and cuneus. This

indicates that the noise estimation model introduces some degree of error in these regions. However, when considering the R^2 maps shown in Figure 8.10b, it is evident that, while the fit is not improved in the ventricles and corpus callosum, the MF with noise estimation method provides a better fit in almost all other regions of the brain. This suggests that the noise estimation enhances the model's overall performance despite the higher MSE in specific areas.

Chapter 9

Discussion

The objective of this section was to explore the integration of noise estimation techniques to enhance the robustness of the MF model. While preprocessing methods are effective at reducing noise, residual noise often persists. By incorporating noise estimation directly into the model, we aim to further mitigate the influence of this remaining noise. Our hypothesis is that adding a noise parameter that accurately reflects the noise distribution will prevent core diffusion parameters from being erroneously adjusted to compensate for noise. Consequently, we anticipate that the model will yield parameter estimates that more faithfully represent the underlying microstructures, thereby improving the overall accuracy of microstructural characterization. The following sections will discuss the key findings and provide interpretations of the results.

9.1 Key findings

In synthetic data experiments, incorporating noise estimation into the MF model significantly enhances its robustness, resulting in improved overall fit and more accurate parameter estimation compared to the standard MF model. Additionally, this approach demonstrates stability with respect to the choice of starting points in the optimization process. When compared to models employing machine learning techniques, such as the hybrid model (Section 6.2.1) and the fully-learned model (Section 6.2.2), MF with noise estimation performs comparably, if not better, at higher SNR values (25+). However, at lower SNR values (10), its performance is notably inferior.

For the *in vivo* data, the parameters estimated using MF with noise estimation align more closely with the known anatomy of the brain. Specifically, there are higher extra-axonal diffusivities observed in regions like the ventricles and subarachnoid space, reduced overestimation of fiber volume fractions, and increased volume fractions of CSF—consistent with these areas being filled with CSF. Despite higher MSE values in central brain regions (ventricles, caudate, thalamus, fornix, corpus callosum, and cuneus), the overall goodness of fit improves in most brain regions, except for the ventricles and corpus callosum. The fit is generally better in GM regions compared to WM regions.

9.2 Interpretation of the results

The improved accuracy observed in our synthetic data experiments indicates that the MF model with noise estimation is more effective at capturing the microstructural features of white matter across various noise configurations, demonstrating its superiority over the standard MF model in synthetic settings. This finding suggests that incorporating noise estimation allows for a more nuanced interpretation of the diffusion signal, effectively disentangling the effects of noise from the underlying tissue properties.

However, the benefits of noise estimation are not fully realized at a low SNR of 10. One possible explanation is that at very low SNR levels, the noise component overwhelms the signal, making it challenging for the noise estimation mechanism to accurately separate noise from the signal. This limitation may prevent the model from achieving the desired level of robustness. Additionally, on synthetic data, machine learning-based methods tend to perform better in low SNR settings due to extensive training on datasets that cover a wide range of SNR values, enabling these models to better handle the variability and complexity of noisy data. However, it is difficult to determine if the fast methods remain superior on in vivo data since ground-truths are not available.

Temporal Signal-to-Noise Ratio (tSNR) analysis [57] shows (see Figure 9.1) that the regions with poor fitting coincide with regions where the tSNR is low across most or all shells. Given that MF and MF with noise estimation perform poorly in low SNR settings, it is therefore not surprising that those regions exhibit a worse fit. However, it remains unclear why MF with noise estimation shows higher MSE values than MF in the central regions of the brain, as this behavior was not observed in our synthetic data experiments.

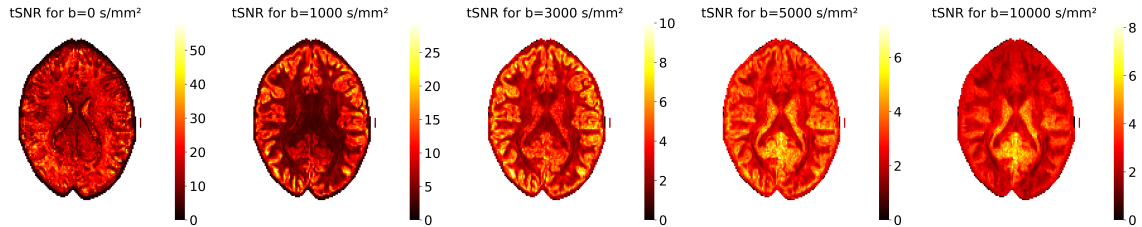


Figure 9.1: **Temporal Signal-to-Noise Ratio (tSNR) maps for different b-values.** (a) $b = 0, \text{s/mm}^2$, (b) $b = 1000, \text{s/mm}^2$, (c) $b = 3000, \text{s/mm}^2$, (d) $b = 5000, \text{s/mm}^2$, and (e) $b = 10000, \text{s/mm}^2$. The tSNR is computed as $\text{tSNR} = \frac{\mu}{\sigma}$, where μ is the mean signal intensity and σ is the standard deviation of the signal intensity across multiple acquisitions. These maps highlight the spatial distribution of tSNR across different diffusion weightings.

Despite this anomaly, the fit appears to be improved in most other brain regions, even in some where the MSE was higher. This indicates that MF with noise estimation still offers advantages over the standard MF model for in vivo data, though the improvements are less pronounced than those observed with synthetic data. The discrepancy in performance between synthetic and in vivo data likely stems from the greater complexity and variability of real brain tissue, which may not be fully replicated

in synthetic models. Additionally, the noise distribution in in vivo data may differ from the theoretical one, due to factors such as multi-coil reconstruction and preprocessing with denoising algorithms.

9.3 Limitations

The proposed method, while effective, has several notable limitations. First, it is computationally slow, which can be a significant drawback in practical applications where time efficiency is critical. Second, the method's performance deteriorates at low SNR values, limiting its robustness and accuracy in conditions where noise is prevalent, a common scenario in diffusion-weighted MRI.

9.4 Future research

Future research should focus on two main areas for improvement. Enhancing the speed of the fitting process is crucial. One promising approach involves interpolating the dictionary entries to move away from the discrete framework. The goal is to avoid exhaustive solving of all subproblems by directly optimizing over the continuous parameter space made possible through interpolation. However, this presents challenges as the optimization domain is likely non-convex, necessitating the use of advanced non-convex optimization methods such as genetic algorithms or simulated annealing [58], [59]. Additionally, the current noise estimation model does not show significant improvements at lower SNR values, which is crucial for diffusion-weighted MRI, known for its inherently low SNR [60], [61]. Future research should aim to refine these models to enhance performance under these challenging conditions. This could involve developing more sophisticated noise models or integrating machine learning techniques to better handle low SNR scenarios. By addressing these areas, future iterations of the MF model can be made more robust, efficient, and applicable to a broader range of MRI data scenarios.

9.5 Perspectives

While the results obtained so far are promising, there remains significant work to be done, as outlined in the limitations section. One of the key advantages of MF with noise estimation over machine learning methods is its robust generalization capability. Machine learning models are often at risk of overfitting, especially when trained exclusively on synthetic data. Although improvements in the quality of synthetic datasets can mitigate some biases, inherent biases will always persist to some extent.

Our model, on the other hand, is fully general and does not rely on pre-learned weights or parameters. This characteristic inherently reduces the risk of overfitting and enhances its potential applicability across diverse datasets. If the current limitations, particularly regarding computational speed and performance at low SNR values, can be addressed, MF with noise estimation could become a powerful and reliable tool in medical settings. Its ability to provide accurate parameter estimates without extensive

reliance on training data makes it particularly valuable for clinical applications where robustness and adaptability are crucial.

In conclusion, overcoming the discussed limitations and further refining the model could significantly enhance its utility and effectiveness, paving the way for broader adoption in medical imaging and diagnostics.

Conclusion

This thesis has investigated two distinct approaches to advance the field of diffusion-weighted MRI for more accurate and robust microstructural parameter estimation: the application of the NODDI-SMT model for multiple sclerosis and the integration of noise estimation techniques into the MF model.

In the first part of this study, we applied the NODDI-SMT and NODDI-SMT-MICRO models to evaluate their effectiveness in capturing microstructural changes associated with MS pathology. Although not all results suggested that SMT-based NODDI models outperform the original NODDI model for MS microstructure imaging, the NODDI-SMT-MICRO model showed promising results. It significantly distinguished between Normal-Appearing White Matter (NAWM) of MS patients and healthy controls, eliminated the overestimation of the isotropic volume fraction (f_{iso}), and effectively differentiated white Matter (WM) from Gray Matter (GM) regions. Furthermore, key parameters correlated well with the extent of damage observed in ROI analysis, indicating a closer relationship to underlying microstructures. However, the primary limitation of the SMT-based models is the overestimation of diffusivities, which leads to inconsistencies in parameter estimation in certain regions. Additionally, while fast algorithm versions significantly improve fitting run time, the computational complexity remains an issue for clinical use, where efficiency is crucial.

In the second part of this study, we focused on enhancing the MF model by incorporating noise estimation techniques to improve its robustness to noise. Our synthetic data experiments showed that MF with noise estimation significantly improves parameter estimation accuracy at higher SNR levels, making it comparable to machine learning-based methods. However, the benefits were less pronounced at low SNR values, indicating that the noise estimation model needs further refinement. For in vivo data, the enhanced model provided parameter maps that better aligned with known anatomical structures, particularly in differentiating regions with high extra-axonal diffusivities and CSF volumes. Despite these improvements, the method exhibited higher MSE in certain brain regions, suggesting that additional work is needed to optimize the model for diverse in vivo conditions.

Both parts of this thesis highlight the importance of robust and accurate microstructural parameter estimation in advancing neuroimaging techniques. The NODDI-SMT model provides valuable insights into disease-specific changes in MS, while the MF model with noise estimation shows promise in generalization and reducing the impact of noise on parameter estimates.

Future research should focus on enhancing the speed and computational efficiency of both models. For NODDI-SMT, developing faster fitting algorithms and optimizing the model for clinical data will be crucial. For the MF model, exploring innovative approaches such as dictionary interpolation to enable continuous parameter optimization and improving the noise estimation model to ensure significant improvements across all SNR levels are key areas of interest.

This thesis has demonstrated that both the NODDI-SMT and MF models offer significant advancements in the field of diffusion-weighted MRI, providing detailed and accurate microstructural insights. Addressing the identified limitations and further refining these models could position them as powerful tools for clinical applications, ultimately contributing to better diagnosis and monitoring of neurological conditions.

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Declaration

I acknowledge the use of ChatGPT-4 and 4o to assist in the writing process of this thesis, specifically to improve language, flow, and readability. After using these tools, I reviewed and edited the content as necessary, and I take full responsibility for all aspects of this thesis.

The types of prompts used included, for example:

> Improve the wording and flow of the following paragraph: [paragraph].

Appendix A

Additional data

A.1 MS in vivo dataset

A.1.1 b-values

```
0 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000
  1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000
  1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000
  1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 0 2000 2000 2000
  2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 0 2000 2000
  2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 0 3000 3000
  3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 0 3000
  3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 3000 0 5000
  5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 0
  5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 5000 5000
```

A.1.2 b-vectors

```
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  -0.3461830542 -0.4569160416 0.4869383345 0.6178089223 -0.5769204481 0.8266819892
  -0.8936770921 -0.2900360864 -0.1159256906 0.8002142901 -0.5140012675
  0.7885942974 -0.9492945385 -0.2330150364 -0.02092002666 -0.2169402921
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  -0.5840764131 0.08793777843 0.5522478065 -0.8381318736 -0.3630502942
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  -0.3850594189 0.7130522449 -0.259899467 -0.0009223291753 -0.03703018955
  -0.5702585575 0.2821781002 -0.7211274113 -0.2669846606 0 -0.9999999747
  -0.494347754 0.1197899266 -0.9189497957 0.1119674689 0.9142976183 -0.6809920467
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  -0.3896599911 -0.1718406143 0.609631183 -0.598937561 0.7278847807 -0.8829262953
  -0.3204161075 -0.04383210269 -0.1888091215 -0.7320206327 -0.3089936618
  -0.286043829 -0.8592534214 0.107076466 0.2978459856 0 -0.9999999858
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 -0.876553478 -0.333160701 -0.5500160688 0.8578474467 0.503973155 0.2149803552
 -0.1779514023 0 1.854832571e-05 0.869358282 0.641028814 -0.3309912638
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 0.7678133452 0.3292421965 0.666748881 -0.0130055969 0.3667161686 0.1029899611
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 -0.648738484 0.2488524447 0.7724746943 -0.9623959739 0.4427082323 -0.59424671
 0.7758814391 -0.426958026 0.08790553918 -0.9707294932 0.9378824806

A.2 MGH Adult Diffusion dataset

A.2.1 b-values

0 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 0 1000 1000
 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 0 1000 1000 1000 1000
 1000 1000 1000 1000 1000 1000 1000 1000 1000 0 1000 1000 1000 1000 1000 1000 1000
 1000 1000 1000 1000 1000 1000 1000 1000 0 1000 1000 1000 1000 1000 1000 1000 1000
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 10000 10050 10000 10000 10000 10000 10000 10050 10000 10000 10000 10000 0
 10000 10000 10000 10000 10000 10000 10000 10000 10000 10000 10000 10000 10050 9950

0 10000 10000 10000 10000 10000 10000 10000 10000 10000 10000 10000 10000
10000 0 10000 10000 10000 10000 10000 10050 10000 10000 10000 10000 10000

A.2.2 b-vectors

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 -0.02043525551 0 -0.5285295806 0.5950394258 0.3521210672 -0.5335073708
 -0.3960881534 0.4267062397 0.4942639958 -0.281669962 0.9839562227 -0.9463742021
 -0.9533314881 0.8719585365 -0.7357175027 0 0.5055494749 -0.9790988149
 0.9340616905 0.05323536994 0.03735406269 0.3829554418 -0.2889525743 0.2170826866
 0.1036211974 -0.8612228509 0.5339473121 0 -0.1157250762 -0.005377479428
 -0.3722401413 0.4334080504 -0.6310185061 0.5858158351 0.504249236 -0.4129200307
 0.003497059608 -0.0576159187 0.04557439036 -0.1007093222 0.417938519 0
 -0.3840595988 -0.5329766926 0.4997912393 -0.6786275235 0.6034074809 -0.546480017
 0.5531562728 0.2088874509 -0.3161039343 0.6813436684 -0.621327246 -0.3374598995
 0.2337627097 0 0.5556891141 -0.4692565788 -0.6676917514 0.7000997518
 0.877829351 -0.888231725 0.8120486198 -0.8418932315 0.9513373782 -0.8775687941
 0.4970003097 -0.3775522526 0.8623753463 0 -0.8962340416 -0.8359288757
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 0.724818622 -0.9316547118 0.9621133202 0.1481839999 -0.07411220856 0
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 0.1643015115 -0.0738115164 -0.3164836326 0.212692096 -0.7353820165 0.7692636189
 0.4699136425 0 -0.5998516138 -0.682498838 0.5073540488 -0.9184613588
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 -0.01550746521 0.3219965684 0.002673085849 0 0.2095555633 -0.09458073529
 -0.383335552 0.4198944555 -0.6469666242 0.7265159926 0.3700774045 -0.1687332266
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 0.3070101571 -0.7812990525 0.9968857463 -0.3537443408 0.1846655249 0.2379437273
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 -0.296744225 0.2441687199 -0.579552599 0.5875369351 0.7350477106 -0.7217387242
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 -0.6865118156 -0.0885771148 0.3586260855 -0.2017820594 0.735678361 0
 -0.8474962462 0.7949442152 -0.198130563 -0.3366714727 -0.8906019723 0.8737911167
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 -0.419798177 -0.3825747471 0 0.3270272615 -0.1537525745 -0.2650588183
 -0.8806418108 0.818377217 0.7753749843 -0.8142282321 0.6681332436 -0.5012421804
 0.404423636 -0.5087072794 0 -0.5888858498 0.6611940531 -0.6590942204
 0.5547978851 -0.3927821044 0.5883181562 -0.5131730655 0.615465324 -0.06841712191
 0.1176352644 0.5769348338 -0.3774808099 -0.3282315264 0 0.4168423118
 0.7378742578 -0.7776356078 -0.2540842012 0.1311499966 -0.7913516558 0.7296518758
 -0.03499034985 0.2538297346 0.68676406 -0.7802645593 -0.8263793701 0.8438896245
 0 -0.04474069561 -0.08945562707 0.2454298567 -0.358367552 -0.01836730314

0.03706311427 0.5823083286 -0.5334558026 -0.09689224978 0.2422877443 0.867668315
 -0.9234844882 0.1739290341 0 -0.2819171735 0.4288620296 -0.5160316689
 -0.5096268197 0.399342963 -0.2602432099 0.2680383369 -0.4742447257 0.5189179031
 -0.3587302642 0.2719316754 -0.9377671763 0.9062308042 0 0.7840543107
 -0.7455736621 0.8085500348 -0.7191869817 0.6823795969 -0.7555536671 0.7375251228
 -0.8186736722 -0.9799457201 0.9576975333 -0.7267188793 0.7121142015
 0.5057681747 0 -0.5437331418 0.4264871426 -0.5586329782 0.412568984 -0.461962044
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 0.8253613647 -0.9143885986 0.8920191307 0 0.3868689262 -0.4052094624
 0.9505238835 -0.9315940352 0.1995473147 -0.08888091966 0.7840590275
 -0.7939698629 0.9403535731 -0.9209694056 0.5088106447 -0.4167437237
 -0.6841007864 0 0.5454283087 0.7024198787 -0.8611364715 0.2095632469
 -0.2544623916 -0.582875142 0.5239899831 0.1069684917 -0.05923534443
 -0.0483473972 0.3049237647 0.9461962761 -0.9765168912 0 -0.649338926
 0.5016033718 0.2810042689 -0.1959962751 0.1816111761 -0.2820208006 -0.5100454097
 0.8372041498 -0.00360945768 0.1702586064 0.03890561254 -0.04181289026
 -0.3870845791 0 0.3142130404 0.08574403321 0.01746072788 -0.2469318978
 -0.4508578939 0.9580332666 -0.7463717995 -0.3109068968 0.5672494999
 0.07695789696 -0.2704155437

Appendix B

Supplementary figures

B.1 Comparison of NODDI-SMT-MICRO and NODDI-SMT-MICRO-FAST

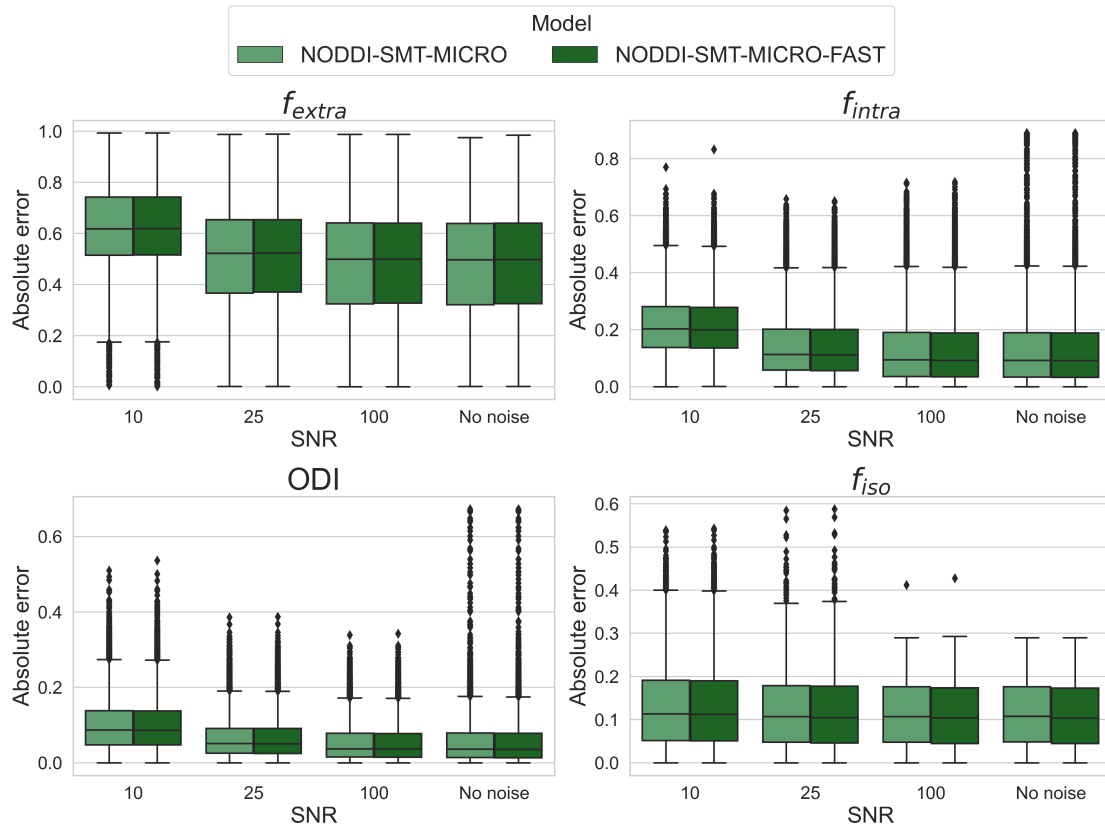


Figure B.1: Comparison of absolute error for different parameters (f_{extra} , f_{intra} , ODI, f_{iso}) between the regular and fast versions of NODDI-SMT-MICRO under varying SNR levels. The dataset consists of 10,000 samples per SNR level. The fast version of NODDI-SMT-MICRO demonstrates comparable performance to the regular version across all SNR levels, maintaining similar absolute error values.

B.2 Orientation Diffusion Index graphs

B.2.1 Parameter map

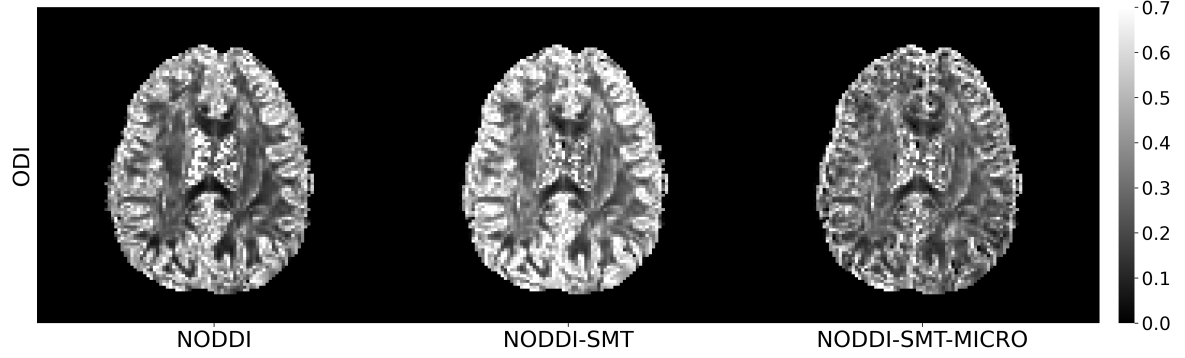


Figure B.2: Comparison of ODI maps for the different models (NODDI, NODDI-SMT, NODDI-SMT-MICRO) in a transverse slice of subject 005.

B.2.2 Boxplots of ODI values across different regions of the brain

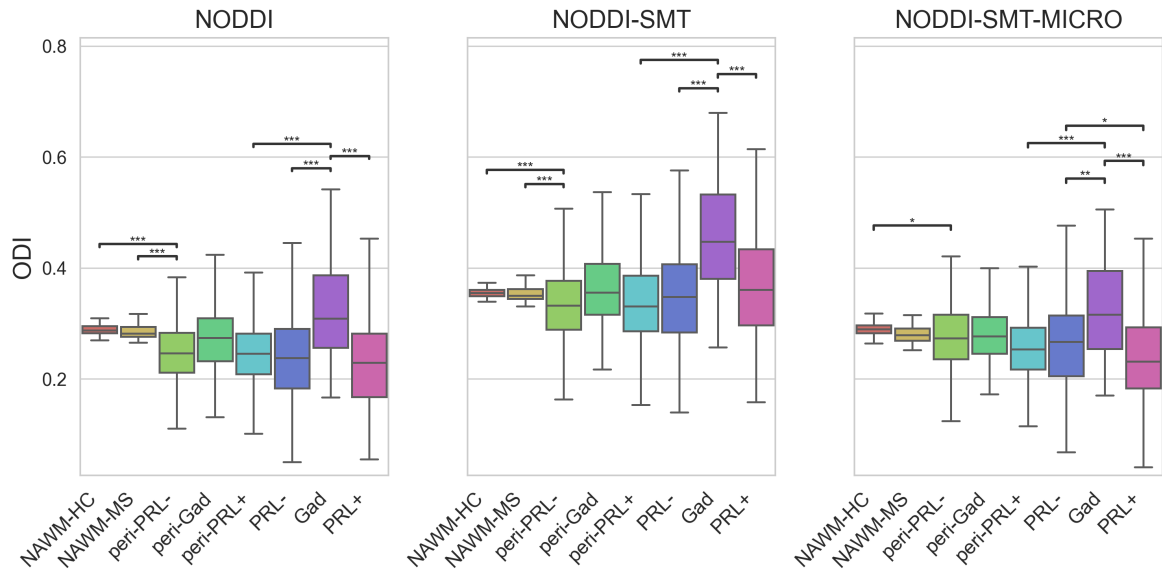


Figure B.3: Comparison of ODI values across different ROI for NODDI, NODDI-SMT, and NODDI-SMT-MICRO models. The ROI are ordered by the extent of microstructural damage based on histopathological analysis [4]. Statistical differences are noted between ROI with a range of 2, with * ($p < 0.05$), ** ($p < 0.01$), *** ($p < 0.001$).

B.3 Comparison of the NODDI models in the Thalamus, Putamen, and Hippocampus region of control subjects

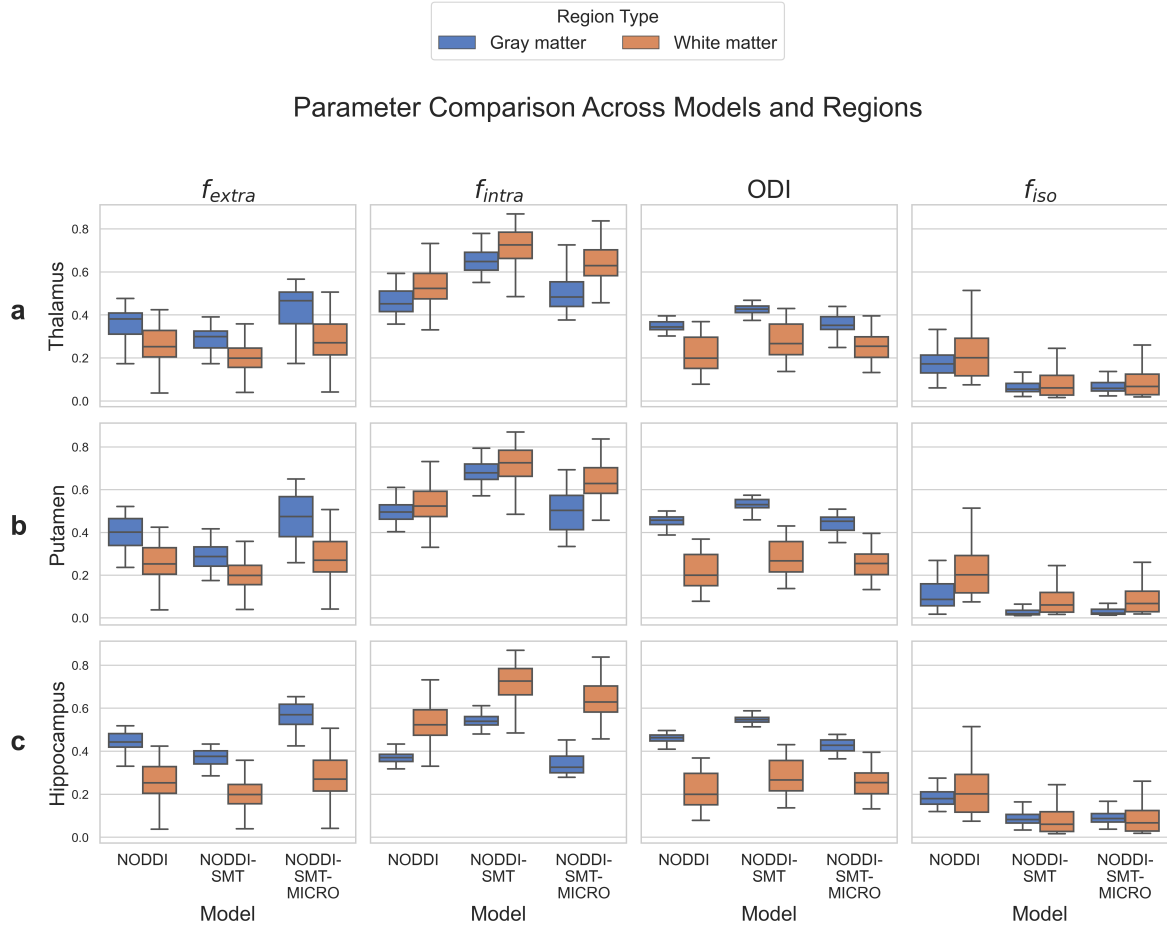


Figure B.4: Boxplots depicting the values of f_{extra} , f_{intra} , ODI, and f_{iso} for different models (NODDI, NODDI-SMT, NODDI-SMT-MICRO) across various subcortical GM regions. The boxplots compare these values with those obtained from NAWM regions, serving as a baseline for comparison. The plots are organized by region: **a** Thalamus, **b** Putamen, and **c** Hippocampus.

B.4 Overestimation of parallel diffusivities with the single compartment SMT model

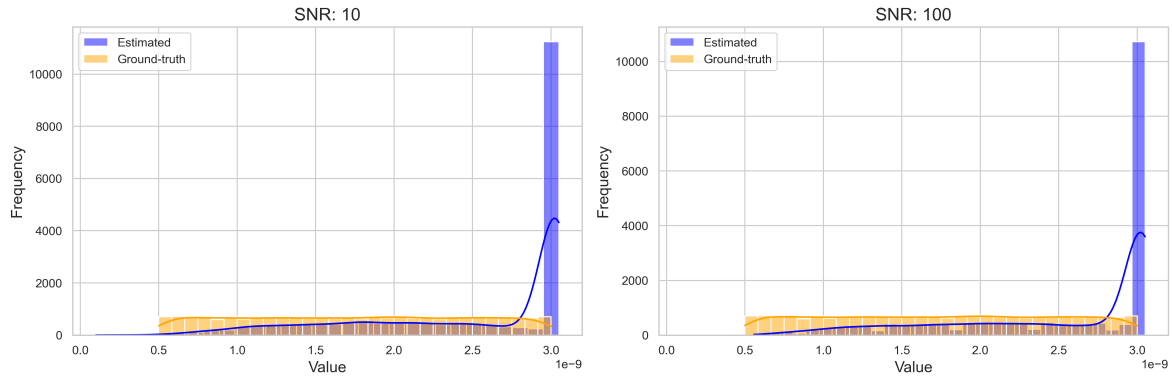


Figure B.5: **Illustration of the overestimation in single compartment SMT-based parallel diffusivity estimates.** The plot shows that, for a uniform distribution of ground-truth parallel diffusivities, the estimated parallel diffusivity values obtained using the single compartment SMT model very frequently reach the maximum allowed diffusivity value.

Appendix C

Supplementary tables

C.1 P-value tables from Welch’s ANOVA and Games-Howell post-hoc tests

ROI1	ROI2	NODDI	NODDI-SMT	NODDI-SMT-MICRO
NAWM-MS	Gad	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	PRL+	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	PRL-	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	peri-Gad	1.00e-07	2.64e-04	1.08e-04
NAWM-MS	peri-PRL+	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	peri-PRL-	1.62e-04	0.00e+00	3.03e-03
NAWM-MS	NAWM-HC	2.19e-02	5.80e-02	2.18e-02
Gad	PRL+	3.02e-01	7.84e-02	2.68e-01
Gad	PRL-	3.01e-03	1.00e+00	7.01e-02
Gad	peri-Gad	4.77e-04	7.45e-05	2.70e-06
Gad	peri-PRL+	3.57e-05	1.22e-04	1.00e-07
Gad	peri-PRL-	0.00e+00	1.40e-06	0.00e+00
Gad	NAWM-HC	0.00e+00	0.00e+00	0.00e+00
PRL+	PRL-	0.00e+00	0.00e+00	0.00e+00
PRL+	peri-Gad	0.00e+00	0.00e+00	0.00e+00
PRL+	peri-PRL+	0.00e+00	0.00e+00	0.00e+00
PRL+	peri-PRL-	0.00e+00	0.00e+00	0.00e+00
PRL+	NAWM-HC	0.00e+00	0.00e+00	0.00e+00
PRL-	peri-Gad	9.05e-01	0.00e+00	6.96e-04
PRL-	peri-PRL+	5.75e-01	0.00e+00	0.00e+00
PRL-	peri-PRL-	0.00e+00	0.00e+00	0.00e+00
PRL-	NAWM-HC	0.00e+00	0.00e+00	0.00e+00
peri-Gad	peri-PRL+	1.00e+00	9.71e-01	1.00e+00
peri-Gad	peri-PRL-	5.50e-04	9.49e-01	4.50e-02
peri-Gad	NAWM-HC	0.00e+00	2.60e-06	2.00e-07
peri-PRL+	peri-PRL-	0.00e+00	4.42e-04	0.00e+00
peri-PRL+	NAWM-HC	0.00e+00	0.00e+00	0.00e+00
peri-PRL-	NAWM-HC	6.00e-07	0.00e+00	3.20e-06

Table C.1: P-values from Welch’s ANOVA and Games-Howell post-hoc tests for f_{extra} , comparing the performance across different ROIs for the models NODDI, NODDI-SMT, and NODDI-SMT-MICRO.

ROI1	ROI2	NODDI	NODDI-SMT	NODDI-SMT-MICRO
NAWM-MS	Gad	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	PRL+	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	PRL-	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	peri-Gad	2.00e-07	2.35e-03	5.35e-04
NAWM-MS	peri-PRL+	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	peri-PRL-	1.68e-03	0.00e+00	2.68e-02
NAWM-MS	NAWM-HC	4.60e-03	3.97e-02	1.03e-01
Gad	PRL+	2.93e-01	2.66e-01	2.59e-01
Gad	PRL-	7.37e-01	9.82e-01	7.17e-01
Gad	peri-Gad	1.47e-01	6.17e-01	8.06e-01
Gad	peri-PRL+	9.91e-01	1.00e+00	9.84e-01
Gad	peri-PRL-	3.56e-02	9.49e-01	5.72e-01
Gad	NAWM-HC	0.00e+00	0.00e+00	4.26e-04
PRL+	PRL-	7.00e-03	5.94e-02	3.95e-02
PRL+	peri-Gad	2.53e-01	1.68e-01	3.32e-02
PRL+	peri-PRL+	3.37e-01	1.67e-01	1.00e-02
PRL+	peri-PRL-	0.00e+00	1.98e-02	0.00e+00
PRL+	NAWM-HC	0.00e+00	0.00e+00	1.23e-06
PRL-	peri-Gad	8.32e-01	9.89e-01	8.21e-01
PRL-	peri-PRL+	9.60e-01	9.74e-01	5.80e-01
PRL-	peri-PRL-	5.22e-03	9.94e-01	3.24e-02
PRL-	NAWM-HC	0.00e+00	2.00e-04	0.00e+00
peri-Gad	peri-PRL+	2.91e-01	7.14e-01	9.12e-01
peri-Gad	peri-PRL-	6.23e-04	8.29e-01	1.22e-01
peri-Gad	NAWM-HC	1.88e-05	4.08e-04	0.00e+00
peri-PRL+	peri-PRL-	1.12e-01	2.66e-01	5.30e-01
peri-PRL+	NAWM-HC	2.64e-01	9.91e-01	9.81e-01
peri-PRL-	NAWM-HC	2.00e-07	1.33e-03	4.96e-02

Table C.2: P-values from Welch’s ANOVA and Games-Howell post-hoc tests for f_{intra} , comparing the performance across different ROIs for the models NODDI, NODDI-SMT, and NODDI-SMT-MICRO.

ROI1	ROI2	NODDI	NODDI-SMT	NODDI-SMT-MICRO
NAWM-MS	Gad	1.48e-01	1.00e+00	1.00e+00
NAWM-MS	PRL+	0.00e+00	5.79e-01	9.71e-01
NAWM-MS	PRL-	0.00e+00	1.00e+00	1.00e+00
NAWM-MS	peri-Gad	1.00e+00	7.06e-03	6.78e-02
NAWM-MS	peri-PRL+	1.57e-01	1.00e+00	1.00e+00
NAWM-MS	peri-PRL-	0.00e+00	5.03e-04	7.02e-04
NAWM-MS	NAWM-HC	4.02e-01	9.99e-01	1.00e+00
Gad	PRL+	9.86e-01	9.80e-01	8.31e-01
Gad	PRL-	6.96e-02	1.00e+00	9.90e-01
Gad	peri-Gad	8.29e-01	6.63e-01	9.79e-01
Gad	peri-PRL+	9.97e-01	1.00e+00	9.98e-01
Gad	peri-PRL-	9.97e-01	8.43e-01	9.88e-01
Gad	NAWM-HC	9.87e-01	1.00e+00	9.55e-01
PRL+	PRL-	7.24e-04	9.88e-01	9.96e-01
PRL+	peri-Gad	2.72e-04	8.84e-04	3.61e-02
PRL+	peri-PRL+	1.83e-03	9.93e-01	9.99e-01
PRL+	peri-PRL-	9.99e-01	7.50e-04	5.13e-03
PRL+	NAWM-HC	1.48e-04	8.91e-01	9.98e-01
PRL-	peri-Gad	0.00e+00	1.91e-01	3.16e-01
PRL-	peri-PRL+	0.00e+00	1.41e-02	3.51e-02
PRL-	peri-PRL-	3.02e-01	4.37e-02	3.02e-01
PRL-	NAWM-HC	2.79e-02	8.19e-01	7.55e-01
peri-Gad	peri-PRL+	9.91e-01	1.00e+00	8.43e-01
peri-Gad	peri-PRL-	9.76e-01	8.31e-01	5.21e-01
peri-Gad	NAWM-HC	6.03e-02	1.00e+00	9.79e-01
peri-PRL+	peri-PRL-	1.88e-01	8.75e-01	9.79e-01
peri-PRL+	NAWM-HC	1.97e-01	9.98e-01	8.79e-01
peri-PRL-	NAWM-HC	8.75e-02	1.00e+00	1.00e+00

Table C.3: **P-values from Welch’s ANOVA and Games-Howell post-hoc tests for ODI, comparing the performance across different ROIs for the models NODDI, NODDI-SMT, and NODDI-SMT-MICRO.**

ROI1	ROI2	NODDI	NODDI-SMT	NODDI-SMT-MICRO
NAWM-MS	Gad	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	PRL+	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	PRL-	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	peri-Gad	3.25e-04	2.25e-02	1.02e-01
NAWM-MS	peri-PRL+	0.00e+00	0.00e+00	0.00e+00
NAWM-MS	peri-PRL-	1.00e-02	1.03e-01	2.32e-02
NAWM-MS	NAWM-HC	1.87e-01	5.87e-01	1.56e-01
Gad	PRL+	5.20e-01	9.79e-01	9.71e-01
Gad	PRL-	1.20e-02	1.00e+00	1.00e+00
Gad	peri-Gad	2.09e-01	3.71e-01	9.78e-01
Gad	peri-PRL+	8.79e-01	9.99e-01	9.87e-01
Gad	peri-PRL-	9.89e-01	9.55e-01	1.00e+00
Gad	NAWM-HC	9.85e-01	9.90e-01	9.98e-01
PRL+	PRL-	9.78e-01	1.00e+00	9.99e-01
PRL+	peri-Gad	9.67e-01	9.56e-01	1.00e+00
PRL+	peri-PRL+	7.79e-01	9.98e-01	9.99e-01
PRL+	peri-PRL-	8.01e-01	1.00e+00	9.88e-01
PRL+	NAWM-HC	9.79e-01	9.88e-01	9.98e-01
PRL-	peri-Gad	3.09e-01	3.78e-01	9.90e-01
PRL-	peri-PRL+	5.67e-01	8.99e-01	9.78e-01
PRL-	peri-PRL-	9.67e-01	9.98e-01	9.99e-01
PRL-	NAWM-HC	8.79e-01	9.87e-01	9.99e-01
peri-Gad	peri-PRL+	9.87e-01	1.00e+00	8.99e-01
peri-Gad	peri-PRL-	8.99e-01	9.98e-01	9.77e-01
peri-Gad	NAWM-HC	9.90e-01	1.00e+00	9.56e-01
peri-PRL+	peri-PRL-	9.88e-01	9.87e-01	9.98e-01
peri-PRL+	NAWM-HC	8.79e-01	9.78e-01	9.88e-01
peri-PRL-	NAWM-HC	9.99e-01	9.99e-01	9.79e-01

Table C.4: P-values from Welch’s ANOVA and Games-Howell post-hoc tests for f_{iso} , comparing the performance across different ROIs for the models NODDI, NODDI-SMT, and NODDI-SMT-MICRO.

C.2 P-value tables from ANOVA test across SNR levels

SNR	MSE p-value	R^2 p-value
10	3.75×10^{-23}	1.22×10^{-137}
25	3.95×10^{-16}	3.50×10^{-161}
100	5.59×10^{-15}	7.67×10^{-163}
No noise	1.91×10^{-9}	1.75×10^{-179}

Table C.5: ANOVA p-values for MSE and R^2 across different SNR levels.

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