Quantitative diffusion MRI with application to multiple sclerosis

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I, Elizabeth Powell, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.
Abstract

Diffusion MRI (dMRI) is a uniquely non-invasive probe of biological tissue properties, increasingly able to provide access to ever more intricate structural and microstructural tissue information. Imaging biomarkers that reveal pathological alterations can help advance our knowledge of complex neurological disorders such as multiple sclerosis (MS), but depend on both high quality image data and robust post-processing pipelines. The overarching aim of this thesis was to develop methods to improve the characterisation of brain tissue structure and microstructure using dMRI.

Two distinct avenues were explored. In the first approach, network science and graph theory were used to identify core human brain networks with improved sensitivity to subtle pathological damage. A novel consensus subnetwork was derived using graph partitioning techniques to select nodes based on independent measures of centrality, and was better able to explain cognitive impairment in relapsing-remitting MS patients than either full brain or default mode networks. The influence of edge weighting scheme on graph characteristics was explored in a separate study, which contributes to the connectomics field by demonstrating how study outcomes can be affected by an aspect of network design often overlooked.

The second avenue investigated the influence of image artefacts and noise on the accuracy and precision of microstructural tissue parameters. Correction methods for the echo planar imaging (EPI) Nyquist ghost artefact were systematically evaluated for the first time in high $b$-value dMRI, and the outcomes were used to develop a new 2D phase-corrected reconstruction framework with simultaneous channel-wise noise reduction appropriate for dMRI. The technique was demonstrated to alleviate biases associated with Nyquist ghosting and image noise in dMRI biomarkers, but has broader applications in other imaging protocols that utilise the EPI readout.

I truly hope the research in this thesis will influence and inspire future work in the wider MR community.
Abstract
**Impact statement**

Multiple sclerosis (MS) is an inflammatory autoimmune disease characterised by focal and diffuse damage to the brain and spinal cord. A leading cause of disability in young adults, MS is a lifelong condition with no cure. Disease mechanisms in MS are not fully understood, so the development of robust, accurate and precise imaging biomarkers is an attractive and non-invasive means by which we can advance our knowledge - and by extension the diagnosis, prognosis and treatment - of the condition.

Biomarkers derived from network science and graph theory are able to capture diffuse disease aspects not evident in conventional MRI biomarkers; however, they often lack specificity or sensitivity to subtle pathological damage. The first experiments in this thesis introduced a novel consensus network that demonstrated improved sensitivity to damage in MS. Different components of this research have been presented at 3 national and international conferences, and have contributed to a paper recently accepted into *Scientific Reports* (2020). The second connectivity experiment highlighted the influence of edge weighting scheme on study outcomes, and was published as a book chapter in *Computational Diffusion MRI* (2019). Together, these studies reveal how effective network construction can improve sensitivity to disease mechanisms and reduce confounding factors; the findings are anticipated to help inform future connectivity work, in MS and neurological conditions more widely.

Ultimately, though, imaging biomarkers are only as informative as the underlying data quality allows. Subsequent experiments therefore shifted towards fundamental physics investigations of data acquisition and reconstruction strategies, and the confounding effects of artefacts and noise on biomarkers. A systematic comparison of correction techniques for the Nyquist ghost artefact prominent in echo planar images (EPI) demonstrated for the first time how strong diffusion weighting (DW) can adversely affect their efficacy, revealing the need for alternative strategies in DW-EPI. Results have been presented at an interna-
This research also provided the foundation for development of a new phase-corrected reconstruction framework with simultaneous channel-wise noise reduction (coined SPECTRE), which demonstrated superior performance in DW-EPI over existing methods. Results will be presented at an international conference this year (2020) and are being prepared for publication as a paper in *Magnetic Resonance in Medicine* (*MRM*). Although demonstrated in DW-EPI, SPECTRE has applications in any acquisition that utilises the EPI-readout, for example intra-voxel incoherent motion imaging, arterial spin labelling, functional MRI and multi-contrast relaxometry acquisitions. The generalisability increases its impact on future studies, either in the context of clinical research (even trials) or technical methods development. Indeed, as it resolves a common technical issue, collaboration has already been proposed by an external group at NIH (USA). Beyond academia, the work has received corporate interest from Philips: results have been presented at global internal meetings and technical discussions are underway regarding a more practical deployment of the method.

I hope the translational research in this thesis will continue to spark and shape future technical methods development, as well as clinical studies in MS and across neuroimaging.
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Abbreviations

ADC  Apparent diffusion coefficient
AP   Artefact power
BBB  Blood brain barrier
CI   Confidence interval
CIS  Clinically isolated syndrome
CM   Classical mechanics
CN   Consensus network
CNS  Central nervous system
CSF  Cerebrospinal fluid
DKI  Diffusion kurtosis imaging
DKT  Diffusion kurtosis tensor
DMN  Default mode network
dMRI Diffusion MRI
DSEPI Double-sampled echo planar imaging
DT   Diffusion tensor
DTI  Diffusion tensor imaging
DWI  Diffusion weighted imaging
EDSS Expanded disability status scale
EPI  Echo planar image
FA   Fractional anisotropy
FBN  Full brain network
FFE  Fast field echo
FID  Free induction decay
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>FLAIR</td>
<td>Fluid attenuated inversion recovery</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>FOV</td>
<td>Field-of-view</td>
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<tr>
<td>FT</td>
<td>Fourier transform</td>
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<tr>
<td>GE</td>
<td>Gradient echo</td>
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<tr>
<td>GM</td>
<td>Grey matter</td>
</tr>
<tr>
<td>GRAPPA</td>
<td>Generalised autocalibrating partial parallel acquisition</td>
</tr>
<tr>
<td>HARDI</td>
<td>High angular resolution imaging</td>
</tr>
<tr>
<td>HC</td>
<td>Healthy controls</td>
</tr>
<tr>
<td>iid</td>
<td>Independent and identically distributed</td>
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<tr>
<td>MB</td>
<td>Multi-band</td>
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<tr>
<td>MD</td>
<td>Mean diffusivity</td>
</tr>
<tr>
<td>MPPCA</td>
<td>Marchenko-Pastur principal component analysis</td>
</tr>
<tr>
<td>MRI</td>
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<tr>
<td>MS</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NAGM</td>
<td>Normal appearing grey matter</td>
</tr>
<tr>
<td>NAWM</td>
<td>Normal appearing white matter</td>
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<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
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<td>NODDI</td>
<td>Neurite orientation dispersion and density imaging</td>
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<td>NSL</td>
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<td>ODI</td>
<td>Orientation distribution index</td>
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<td>PAGE</td>
<td>Phased array ghost elimination</td>
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<td>Phase error correction with sensitivity encoding</td>
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<td>PGSE</td>
<td>Pulsed gradient spin echo</td>
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<td>PN</td>
<td>Principal network</td>
</tr>
<tr>
<td>PNA</td>
<td>Principal network analysis</td>
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<tr>
<td>PNS</td>
<td>Peripheral nerve stimulation</td>
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<tr>
<td>POCS</td>
<td>Projection onto convex sets</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>-------------</td>
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<tr>
<td>PPE</td>
<td>Pulse programming environment</td>
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<td>PPMS</td>
<td>Primary progressive multiple sclerosis</td>
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<td>PRMS</td>
<td>Progressive relapsing multiple sclerosis</td>
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<tr>
<td>QM</td>
<td>Quantum mechanics</td>
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<td>Rich-club</td>
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<td>RF</td>
<td>Radio-frequency</td>
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<td>RMT</td>
<td>Random matrix theory</td>
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<td>RRMS</td>
<td>Relapsing-remitting MS</td>
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<td>Spin echo</td>
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<td>SMS</td>
<td>Simultaneous multi-slice</td>
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<td>Signal-to-noise ratio</td>
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<tr>
<td>SPMS</td>
<td>Secondary progressive multiple sclerosis</td>
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<tr>
<td>TE</td>
<td>Echo time</td>
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<tr>
<td>TR</td>
<td>Repetition time</td>
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<tr>
<td>WM</td>
<td>White matter</td>
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Chapter 1

Introduction

1.1 Background

Magnetic resonance imaging (MRI) is uniquely able to probe biological tissue properties non-invasively. Precise sequence design can alter the sensitivity of the acquisition to different tissue characteristics, providing information from proton density to tissue perfusion and oxygenation levels. Diffusion MRI (dMRI) can further characterise microstructural tissue properties: biological barriers such as cell walls restrict or hinder the Brownian motion of protons, so intricate information regarding cell structures can be inferred in deviations from free Gaussian diffusion. Image biomarkers derived from quantitative MRI are subsequently able to reveal pathological alterations in biological tissues.

Imaging biomarkers are particularly attractive as a non-invasive means of advancing our knowledge of complex neurological conditions in which disease mechanisms are still not fully understood, such as multiple sclerosis (MS); however, detecting the early effects can be challenging, as imaging biomarkers may be insensitive to subtle disease effects or biased by poor image quality.

The research in this thesis explores two avenues for improving the characterisation of brain tissue structure and microstructure using dMRI. Firstly, alternative representations of core human brain networks are developed to facilitate biomarkers with improved sensitivity to subtle pathological damage. Secondly, the influence of image artefacts and noise on the accuracy and precision of microstructural tissue parameters is investigated, and reconstruction methods are developed to alleviate associated biases in quantitative imaging biomarkers.
1.2 Brain graphs

The human brain is a complex network of cortical grey matter nuclei densely interconnected by white matter tracts. Communication between cortical regions is the foundation of brain function, and damage to the connecting axons occurs in a range of neurological disorders including MS [1, 2]. Techniques for estimating axonal damage and characterising grey matter interactions could therefore offer considerable opportunities in advancing our understanding of brain structure and function in neurological diseases.

Modelling brain networks as graphs is an effective means for assessing structural or functional connections between anatomical regions. Cortical regions and their pairwise interactions can be considered as abstract nodes (vertices) and edges, with edge weights describing some property of the connection between regions. Network behaviour can be characterised on different scales - for example at local (nodal) or global (whole network) levels - using graph theory, and pathologically relevant alterations in network behaviour have been demonstrated in a range of diseases using this model [3–8]. Particularly for diffuse diseases such as MS, where conventional imaging biomarkers do not correlate well with clinical disability [9, 10], improving sensitivity to regional pathological changes using network science remains an important avenue of research.

A key challenge in the analysis of brain graphs is the choice of vertices, edges and edge weights. Naturally, the arrangement of nodes and edges in a graph define its fundamental characteristics, such as the efficiency with which information is transferred between vertex pairs. For brain networks, the flexibility of the model enables similar graphs to be constructed using different underlying data, including functional, diffusion-weighted (DW) or structural MRI, but there is no consensus on how nodes and edges should be defined. Comparisons between study outcomes are therefore challenging. A further consideration is the inclusion of nodes unaffected by the pathology of interest: owing to the modular structure of the brain it is reasonable to assume that only a subset of regions and connections will be of importance for a given study, meaning that significant local changes could be masked in a global analysis of brain network topology.

The first part of this thesis aims to address two objectives in the construction and analysis of brain networks. Firstly, the role of subnetworks in facilitating improved sensitivity to subtle disease effects in MS is explored. A novel consensus network identifying the brain regions most influential to overall network function is derived using independent clustering
techniques and evaluated against conventional structurally- and functionally-defined networks. Secondly, the influence of edge weighting scheme on study outcomes is explicitly demonstrated in a comparative analysis between healthy controls and MS patients.

1.3 Noise and Nyquist sampling errors

The foundation of any quantification of tissue structure or microstructure is an unbiased representation of the MR signal. In addition to mapping connections between cortical regions, dMRI has been used to estimate a variety of tissue properties from the anisotropy and orientation of cellular structures [11–15] to distributions of cell size, shape and permeability [16–21] and even pseudo-diffusion effects from microscopic perfusion [22–24]. Changes in these tissue characteristics have been detected in MS [25–27], neurodegeneration [28, 29], tumours [30–32] and ischaemia [33, 34]; however, the use of such biomarkers in routine clinical use is limited. Primarily, this is because robust, accurate and precise estimations of quantitative tissue parameters are difficult to obtain.

Nyquist sampling errors and high noise levels are ubiquitous in dMRI, and are key limitations in the robust characterisation of tissue properties. Fast acquisition requirements combined with imperfections in the gradient system used for spatial encoding can produce ghost images superimposed on the true data, while the strong gradients used to provide diffusion weighting are highly attenuating and result in a low signal-to-noise ratio (SNR). Current methods for correcting Nyquist sampling errors typically acquire additional reference data or exploit parallel imaging methods to estimate the error from the data itself. Crucially, they are demonstrated in non-DW images only. The methods are therefore limited in dMRI owing to a lack of validation and either additional scan time requirements or noise amplification from increased parallel imaging acceleration, which, for an acquisition scheme that is already time-consuming with poor SNR, are infeasible conditions. Left uncorrected, though, Nyquist sampling errors can introduce signal biases that cause artefactual changes in estimated parameter maps and result in the misinterpretation of findings [35, 36].

The second part of this thesis considers techniques for providing robust Nyquist ghost correction with minimal noise amplification and without the requirement for additional reference scans. A systematic evaluation of existing phase error correction methods is first performed to provide the foundation on which a method for simultaneous ghost correction and channel-wise noise removal during reconstruction is developed.
1.4 Aims

The aim of this thesis was to develop methods to improve the sensitivity, accuracy and precision of imaging biomarkers in subtle pathology, from large scale network properties to microstructural tissue characteristics. Key objectives were to:

i Develop methods for defining core human brain subnetworks that provide improved sensitivity to subtle MS pathology.

ii Investigate the influence of edge weighting schemes on the interpretation of brain connectivity study outcomes.

iii Explore data quality and Nyquist phase error correction techniques, and validate the efficacy of existing ghost correction schemes in high $b$-value dMRI.

iv Develop reconstruction methods for improving dMRI data quality that incorporate robust Nyquist phase error correction with noise level reduction.

1.5 Structure

This thesis covers two distinct topics, which are best presented as a chronological account of the research performed. An initial review of the MR theory and MS pathology overarching the entire work is provided, while background literature and theory pertaining to individual chapters are self-contained for readability. The structure of this thesis is therefore as follows:

- **Chapter 2** introduces the basic principles of MRI and graph theory.

- **Chapter 3** provides an overview of MS pathology.

- **Chapter 4** proposes a novel consensus network based on influential nodes in order to improve sensitivity to subtle disease pathology. Structural connectivity alterations are evaluated in healthy controls and MS patients in the consensus network and compared against whole brain and default mode networks.

- **Chapter 5** demonstrates the biases and pitfalls that can be encountered when interpreting network properties without considering different edge weighting schemes (material published in [37]).
• **Chapter 6** moves towards considering the effects of acquisition and reconstruction strategies on data quality. A simulation framework is developed to characterise artefacts arising from Nyquist sampling errors and their interplay with parallel imaging, which are then confirmed in a small cohort of healthy controls. A systematic evaluation of 2D phase-correction techniques is performed in high $b$-value dMRI, in-silico and in-vivo.

• **Chapter 7** presents a proof of concept study for denoising aliased images from individual channels during reconstruction. Experiments are performed in-silico and in-vivo.

• **Chapter 8** proposes and implements a method for simultaneous 2D phase error correction and channel-wise noise reduction for SENSE-based parallel imaging data. The method is validated in phantom and human data.

• **Chapter 9** concludes this thesis and considers the wider impact of the research presented as well as avenues for future work.

### 1.6 Scientific contributions

The research in this thesis has resulted in papers and conference presentations at national and international level. Two manuscripts are also currently in preparation (not listed). Specific contributions are listed below.


Chapter 2

Theory

This chapter introduces the basic principles of MR physics and graph theory. Particular focus is given to signal sampling, image reconstruction and noise characteristics to provide a foundation for the research presented in this thesis.

2.1 Signal origins

Nuclear spin and its interaction with an applied magnetic field forms the basis of all nuclear magnetic resonance (NMR) experiments. Magnetic fields can be used to encode the spatial positions, densities and interactions of nuclei in the body. Most MRI experiments are conducted using hydrogen nuclei (protons), primarily owing to a high signal strength, a high natural abundance (99.98% relative to other isotopes), and a high concentration in the body in both water and fat. Other nuclei, for example sodium $^{23}$Na, carbon $^{13}$C and phosphorous $^{31}$P, may be used to study different tissue properties, but are less sensitive relative to $^1$H.

This section provides an overview of the origin of the $^1$H MR signal.

2.1.1 Precession

The precession of a single nucleus around the axis of an external magnetic field is considered in both the classical and quantum frameworks, and its equation of motion is derived.

Classical mechanics

Nuclei with unpaired nucleons possess an intrinsic angular momentum, or spin, which gives rise to a magnetic dipole moment $\mu$. The angular momentum $J$ is related to the magnetic moment through the gyromagnetic ratio $\gamma$ (Eq. 2.1), which is an intrinsic property of a nucleus dependent on its mass $m$ and charge $q$. The proton gyromagnetic ratio is typically expressed as the reduced constant $\gamma/2\pi = 42.58$ MHz/T.

$$\mu = \gamma J, \quad \text{with } \gamma = \frac{q}{2m}$$ (2.1)
Figure 2.1. Precession. A spin magnetic moment $\mathbf{\mu}$ undergoes clockwise precession about the axis of an applied magnetic field $\mathbf{B}_0$.

Dipole moments are randomly oriented in the absence of an applied magnetic field; however, an applied magnetic field $\mathbf{B}_0$ will exert a torque $\mathbf{\tau}$ - equivalent to the rate of change of total angular momentum - which acts to align the dipole moments with the field axis (parallel or anti-parallel). The torque is calculated as the cross product between the magnetic moment and the field itself, and gives rise to the precessional motion of a spin in a field (Fig. 2.1).

$$\mathbf{\tau} \equiv |\frac{d\mathbf{J}}{dt}| = \mathbf{\mu} \times \mathbf{B}_0$$

(2.2)

The rate of precession $\omega_0$ - equivalent to the instantaneous angular velocity - is governed by the gyromagnetic ratio and magnetic field magnitude (Eq. 2.3).

$$\omega_0 \equiv \left| \frac{d\phi}{dt} \right| = \gamma B_0$$

(2.3)

Quantum mechanics

The spin quantum number $s$ of a nucleus parameterises its intrinsic spin angular momentum $\mathbf{S}$ such that the magnitude is given by $S = \hbar [s(s+1)]^{\frac{1}{2}}$; similarly, the azimuthal quantum number $l$ parameterises its orbital angular momentum $\mathbf{L}$, with $L = \hbar [l(l+1)]^{\frac{1}{2}}$. The total angular momentum of a nucleus is the sum of its orbital and spin components ($\mathbf{J} = \mathbf{S} + \mathbf{L}$). The quantisation of spin means that its angular momentum, and subsequently magnetic dipole moment, are also quantised (Eq. 2.4).

$$J^2 = S^2 = s(s+1)\hbar^2, \quad \text{for } ^1H \text{ with } l = 0$$

(2.4)

Owing to the fact that simultaneous measurements of multiple angular momentum components cannot be made it is conventional to only consider the component of the dipole
2.1. Signal origins

Figure 2.2. Energy levels. A nucleus with two spins states \( s = \pm 1/2 \) in a magnetic field has two possible energy levels.

The moment along the magnetic field axis, typically the \( z \)-axis. This component of the magnetic dipole moment, \( \mu_z \), is parameterised by the magnetic quantum number \( m_s \).

\[
\mu_z = \gamma \hbar m_s \quad \text{where} \quad m_s = \{-s, -s+1, \ldots, s-1, s\} \tag{2.5}
\]

For nuclei with two spin states \( s = \pm 1/2 \) the magnetic moment may be parallel (‘spin up’) or anti-parallel (‘spin down’) to the magnetic field. In this quantum mechanical (QM) framework the spin state of any given nucleus is a linear combination of all possible spin states; it is the superposition of spin states that leads to an expectation, or average, magnetic moment value which corresponds to a clockwise precession around the magnetic field axis.

The precession frequency in the classical mechanical (CM) framework is related to the energy of the spin states in the QM framework. Each spin state has an associated energy \( E \) (Eq. 2.6). In the absence of a magnetic field the energy states are degenerate; in a non-zero magnetic field, the spin up state for protons - and any other isotope with a positive gyromagnetic ratio - is the lower energy level.

\[
E = -\mu \cdot B_0 = -\mu_z B_z = -\gamma \hbar m_s B_z \tag{2.6}
\]

\[
E = \pm \frac{1}{2} \gamma \hbar B_z, \quad \text{for} \quad s = \frac{1}{2} \tag{2.7}
\]

The energy required to transition between states is then none other than the Larmor frequency (Fig. 2.2).

\[
\Delta E = \gamma \hbar B_0 = \omega B_0 \tag{2.8}
\]
**Equation of motion**

The equation of motion for a spin in an external field $\mathbf{B} = B_0 \hat{z}$ can be derived from Eqs. 2.1 and 2.2, and is provided in Eq. 2.9.

$$\frac{d\mathbf{\mu}}{dt} = \gamma \frac{d\mathbf{J}}{dt} = \gamma \mathbf{\mu} \times \mathbf{B}_0 = \gamma \mathbf{\mu} B \sin \theta$$

where

$$\frac{d\mu_x}{dt} = \gamma \omega_y B_0, \quad \frac{d\mu_y}{dt} = -\gamma \omega_x B_0, \quad \frac{d\mu_z}{dt} = 0$$

From Eq. 2.9 it can be seen that the differential change in direction $|d\mathbf{\mu}|$ is equivalent to a clockwise rotation in the plane perpendicular to that defined by $\mathbf{\mu}$ and $\mathbf{B}$; it is therefore useful to define the precession of a nucleus using the complex notation in which $\mu_{xy}(t) = \mu_x(t) + i\mu_y(t)$. This yields the equation of motion in Eq. 2.10 and its solution in Eq. 2.11.

$$\frac{d\mu_{xy}}{dt} = -i \omega_0 \mu_{xy}$$

$$\mu_{xy}(t) = \mu_{xy}(0) e^{-i\omega_0 t} = |\mu_{xy}(t)| e^{-i\phi(t)}$$

### 2.1.2 Magnetisation, resonance and relaxation

The previous section considered the behaviour of a single, isolated nucleus. In this section, the interaction of nuclei with each other and their environment is considered and used to derive the equation of motion for interacting spins - the Bloch equation.

**Bulk magnetisation**

The splitting of energy states in an applied magnetic field gives rise to a bulk magnetisation, denoted $M_0$ or $M_z$, owing to the small excess of spins preferentially existing in the lower energy state. The population in each energy state is governed by the Boltzmann distribution in Eq. 2.12, where $N_\uparrow$ and $N_\downarrow$ denote the number of protons in the spin up and spin down state respectively, $k_B$ is Boltzmann’s constant and $T$ is the temperature.

$$\frac{N_\uparrow}{N_\downarrow} = \exp \left( \frac{\Delta E}{k_B T} \right)$$

The bulk magnetisation $\mathbf{M}$ is simply the sum over all $N$ individual magnetic moments.

Utilising the approximation in Eq. 2.13, an expression for the bulk magnetisation is given in Eq. 2.14; incoherent precession of the magnetic moments means there is no transverse component ($M_{xy} = 0$).

$$\exp \left( \frac{\Delta E}{k_B T} \right) \approx 1 + \frac{\Delta E}{k_B T} \quad \text{for} \quad \Delta E \ll k_B T$$

$$\mathbf{M} = \sum_{n=1}^{N} \mu_n = \sum_{n=1}^{N} \mu_n \hat{z} = (N_\uparrow - N_\downarrow) \mu_z \hat{z} \approx \frac{(\gamma \hbar)^2}{4 k_B T} B_0 \hat{z}$$
Neglecting proton interactions, the equations of motion in Eqs. 2.9 and 2.10 are directly applicable to the bulk magnetisation vector $M$.

$$\frac{dM_{xy}}{dt} = \gamma M_{xy} \times B, \quad \frac{dM_z}{dt} = 0 \quad (2.15)$$

**Resonance and excitation**

The NMR signal derives from the coherent precession of the bulk magnetisation in the transverse plane (i.e. perpendicular to $B_0$). Transverse magnetisation is achieved by applying an RF pulse, $B_1$, perpendicular to $B_0$. Classically, a $90^\circ$ pulse is analogous to ‘tipping’ the magnetisation fully into the transverse plane (Fig. 2.3). In the QM framework, a $90^\circ$ pulse is equivalent to exciting spins from the ground state into the higher energy state such that the number of nuclei in the spin up and spin down states is equal (i.e. $M_z = 0$). From both the CM and QM frameworks it is clear that, in order to excite spins into the higher energy state, the applied RF pulse must contain their resonant frequency: the Larmor frequency.

**Rotating reference frame**

The additional torque experienced by nuclei owing to $B_1$ results in a rotation in two planes, as in Eq. 2.16.

$$\frac{dM}{dt} = \gamma M \times (B_0 + B_1) \quad (2.16)$$

A rotating frame of reference can therefore be useful to simplify the mathematical description of spin dynamics. In a primed reference frame rotating about the $z = z'$ axis with frequency $\Omega$, the static field $B_0$ is described by the effective field $B_{\text{eff}}$ (Eq. 2.17).

$$B_{\text{eff}} = B_0 + \frac{\Omega}{\gamma} = \frac{\Omega - \omega_0}{\gamma} \quad (2.17)$$
If the reference frame is rotating at the Larmor frequency (ie. \( \Omega = \omega_0 \)), then \( B_{\text{eff}} = 0 \) and the precession of spins around \( B_0 \) can be ignored. The resulting equation of motion in the rotating (primed) reference frame is given in Eq. 2.18.

\[
\left( \frac{dM}{dt} \right)' = \gamma M \times (B_{\text{eff}} + B_1) = \gamma M \times B_1 \tag{2.18}
\]

**Relaxation and the Bloch equation**

Following the application of a temporary RF pulse \( B_1 \), and in the continued presence of a static field \( B_0 \), the return of the longitudinal and transverse components of the magnetisation to their equilibrium states is governed by the relaxation parameters \( T_1 \) (longitudinal) and \( T_2 \) (transverse).

Transverse (spin-spin) relaxation is a result of the loss of phase coherence between interacting spins. Interacting nuclei experience the magnetic fields of neighbouring spins in addition to the external field \( B_0 \), and the resulting energy transfer between spins causes slightly faster or slower rates of precession. This leads to a gradual decrease in phase coherence and thus \( M_{xy} \). Additional transverse relaxation is caused by local magnetic field inhomogeneities, but can be recovered by re-phasing the spins as described in Section 2.3.2. Without re-phasing, though, \( T_2^* \) relaxation is observed, where \( T_2^* < T_2 \). Transverse relaxation essentially acts as a dampener to the MR signal and results in the exponentially decaying free induction decay (FID) signal (Fig. 2.4a).

Longitudinal (spin-lattice) relaxation occurs when spins lose the energy absorbed by the RF pulse and return to their lower energy state (Fig. 2.4b). Energy lost to the lattice represents the transfer of heat, and occurs through collisions and rotations, or electromagnetic interactions.

Relaxation rates are empirically determined, and are related to the thermal tumbling of molecules as described by Bloembergen, Purcell and Pound [38]. The decay constants are used to modify the equation of motion in Eq. 2.15 to describe interacting protons, giving the Bloch equation in Eq. 2.19.

\[
\frac{dM}{dt} = \gamma M \times B - \frac{1}{T_2} M_{xy} + \frac{1}{T_1} (M_0 - M_z) \hat{z} \tag{2.19}
\]

Evolution of the longitudinal and transverse magnetisation is found by solving the partial differential equations in Eqs. 2.20, 2.21 and 2.22, which describe the magnetisation in the static and rotating (primed) reference frames.

\[
\frac{dM_z}{dt} = \omega_0 M_y - \frac{M_z}{T_2} \quad \text{or} \quad \left( \frac{dM_z}{dt} \right)' = -\frac{M_z}{T_2} \tag{2.20}
\]
2.1. Signal origins

Figure 2.4. Relaxation. a. Transverse relaxation damps the FID signal as viewed in the lab (black line) and rotating (blue line) frames. b. Longitudinal relaxation leads to the recovery of the bulk magnetisation back to its equilibrium state ($M_z = M_0$).

\[
\frac{dM_y}{dt} = -\omega_0 M_x - \frac{M_x}{T_2} \quad \text{or} \quad \left(\frac{dM_y}{dt}\right)' = -\frac{M_y}{T_2}
\]

Utilising the complex representation described in Eq. 2.11 for the transverse magnetisation, the static field solutions are given in Eqs. 2.24 and 2.23.

\[
M_z(t) = M_z(0) e^{-t/T_1} + M_0 \left(1 - e^{-t/T_1}\right)
\]

\[
M_{xy}(t) = M_{xy}(0) e^{-t/T_2}
\]

The Bloch-Torrey equation

The Brownian motion of spins in a medium also affects the evolution of the magnetisation. Random-walk fluctuations in the position of a spin affect its phase owing to the different magnetic fields it experiences during its interactions with other spins. To include the effects of random walks, the equation of motion is modified to include a diffusion term as in Eq. 2.25, where $D$ is the diffusion coefficient of the medium at a particular location $r$; this is known as the Bloch-Torrey equation [39].

\[
\frac{\partial M(r,t)}{\partial t} = \gamma M(r,t) \times B(r,t) - \frac{1}{T_2} M_{\perp} + \frac{1}{T_1} (M_0 - M) \hat{z} + D \nabla^2 M(r,t)
\]
2.1.3 Signal detection

By Faraday’s law of induction, a time-varying magnetic flux $\Phi$ (induced, for example, by a rotating magnetic dipole or the rotating transverse bulk magnetisation) induces an electro-motive force ($emf$) in a coil according to Eq. 2.26; Lenz’s law states that the induced current generates a field that opposes the initial field, explaining the negative sign in Faraday’s law.

$$emf = -\frac{d\Phi}{dt}$$  (2.26)

From Lenz’s law and the principle of reciprocity, which states that the $emf$ induced in coil 1 is proportional to the flux change $d\Phi_{1,2}/dt$ induced by coil 2 (Eq. 2.27), the flux $\Phi_M$ from a rotating magnetisation source $M(r,t)$ can be represented by the flux that would be induced by a detection coil with ‘receive field’ $B$.

$$emf_1 = -\frac{d\Phi_{1,2}}{dt}$$  (2.27)

$$\Phi_M = \int d^3r B(r) \cdot M(r,t)$$  (2.28)

The signal arising from magnetisation precessing in an external field, then, is proportional to the $emf$ induced in the coil, where the proportionality is dependent on the electronic measurement system.

$$s \propto -\frac{d}{dt} \int_{sample} d^3r M(r,t) \cdot B(r)$$  (2.29)

2.2 Signal sampling and aliasing

The NMR signal is a continuous function arising from the $emf$ induced in detection coils by the rotating bulk magnetisation. Measurement of spin density and dynamics must, then, necessarily involve discretisation of the signal.

This section describes basic signal sampling concepts, including the Nyquist sampling criterion required to avoid aliasing. The relationship between the signal measured in the spatial frequency domain ($k$-space) and image domain ($x$-space) through the Fourier transform (FT) is also considered. For simplicity, the continuous FT in 1D and the concept of infinite sampling is used throughout: truncation of the signal in $k$-space (i.e. finite data collection) corresponds to a convolution in image space of the ‘true’ spin density with a blurring function, the effects of which can be considered independently from the effects of discretisation owing to the associative nature of the convolution operator.
2.2. Signal sampling and aliasing

2.2.1 Sampling function

If the MR signal $s(k)$ was known for all $k$, the spin density $S(x)$ could be obtained simply through the inverse Fourier transform (iFT) of $s(k)$ (Eq. 2.30).

$$S(x) = \int_{-\infty}^{\infty} dk s_m(k) e^{i2\pi kx}$$  \hspace{1cm} (2.30)

Despite the requirement for finite sampling in practice, the concept of infinite sampling is useful for simplicity in the derivation of the sampling function. Infinite sampling can be interpreted as the discretisation of a signal with no limit placed on the number of measurements; that is, no truncation of the signal.

Signal sampling in general can be considered as the multiplication of the signal with a sampling, or ‘comb’, function (Fig. 2.5a). In the case of infinite sampling, the sampling function $u(k)$ is defined as an infinite series of periodically spaced delta functions (Eq. 2.31). If measurements in $k$-space are made at intervals of $\Delta k$, the location of the delta functions is given by $p\Delta k$, with $p$ an integer. The product of these impulse functions with the continuous MR signal subsequently returns the signal value at the sampled locations $p\Delta k$ and null everywhere else (Eq. 2.32).

$$u(k) = \Delta k \sum_{p=-\infty}^{\infty} \delta(k - p\Delta k)$$  \hspace{1cm} (2.31)

$$s_\infty(k) \equiv s(k) \cdot u(k)$$

$$= \Delta k \sum_{p=-\infty}^{\infty} s(p\Delta k) \delta(k - p\Delta k)$$  \hspace{1cm} (2.32)

The equivalent sampling function in image space $U(x)$ is obtained through the iFT of $u(k)$ (Eq. 2.33).

$$U(x) \equiv F^{-1}(u(k)) = \Delta k \sum_{p=-\infty}^{\infty} \int_{-\infty}^{\infty} dk \delta(k - p\Delta k) e^{i2\pi kx}$$  \hspace{1cm} (2.33)

Representing the delta function by an infinite series of complex exponential functions (Eq. 2.34), the FT of which is well-defined (Eq. 2.35), and multiplying Eq. 2.33 by $e^{i2\pi p\Delta k} e^{-i2\pi p\Delta k} = 1$ enables $U(x)$ to be similarly represented as an infinite series of delta functions (Eq. 2.36).

$$\Delta k \sum_{p=-\infty}^{\infty} e^{i2\pi p\Delta k} = \sum_{q=-\infty}^{\infty} \delta \left( x - \frac{q}{\Delta k} \right)$$  \hspace{1cm} (2.34)

$$\int_{-\infty}^{\infty} dx \delta(x - x_0) e^{-i2\pi k(x-x_0)} = 1$$  \hspace{1cm} (2.35)
Chapter 2. Theory

Figure 2.5. Sampling functions. **a.** Signal and sampling functions in \( k \)-space. Left: the sampling function in \( k \)-space is a series of delta functions periodically spaced by \( \Delta k \). Centre: the continuous signal \( s(k) \). Right: infinite sampling of the signal in \( k \)-space is equivalent to the product of the true signal with the sampling function. **b.** Signal and sampling functions in image space. Left: the equivalent sampling function in image space is a periodic series of delta functions spaced by the FOV. Centre: the image space function \( S(x) \) generating the signal \( s(k) \) in \( k \)-space. Right: infinite sampling in image space yields infinite replicas of the true function.

\[
U(x) = \Delta k \sum_{p=-\infty}^{\infty} e^{i2\pi p\Delta kx} \int_{-\infty}^{\infty} dk \delta(k-p\Delta k) e^{i2\pi(k-p\Delta k)x}
\]

\[
= \Delta k \sum_{p=-\infty}^{\infty} e^{i2\pi p\Delta kx}
\]

\[
= \sum_{q=-\infty}^{\infty} \delta(x-q/\Delta k)
\]

(2.36)

Convolution of the sampling function \( U(x) \) with the spin density \( S(x) \) yields the \( x \)-domain equivalent of the sampling relationship given in Eq. 2.32: using the convolution theorem in Eq. 2.37, then, the infinitely sampled reconstructed spin density \( S_\infty(x) \) can be expressed by Eq. 2.38, in which \( L \equiv FOV \equiv 1/\Delta k \).

\[
S(x) \ast \delta(x-x_0) = \int_{-\infty}^{\infty} dx' S(x') \delta(x-x'-x_0) = S(x-x_0)
\]

(2.37)
2.2. Signal sampling and aliasing

In essence, Eq. 2.38 is an infinite series with periodicity $L$ such that $S(x) = S(x - qL)$; in other words, each term is a copy of the spin density $S(x)$ displaced by the sampling interval $L$, of which only one is needed for the reconstructed image (Fig. 2.5b).

### 2.2.2 Aliasing and the Nyquist sampling criterion

Aliasing occurs when the spatial interval over which the image is repeated, $L$, is smaller than the extent of the imaged object (denoted here as $A$). In the case where $L < A$, the copies of the reconstructed image overlap and result in substantial differences between the true and reconstructed images (Fig. 2.6). This leads to the Nyquist criterion in Eq. 2.39.

$$L > A \quad \text{or} \quad \Delta k < \frac{1}{A}$$

(2.39)

Aliasing from undersampling can be demonstrated by considering image reconstruction using the even and odd lines of $k$-space separately. In this instance the interval between samples becomes $2\Delta k$ and the Nyquist criterion is no longer satisfied.

The sampling function defined in Eq. 2.31 can be reformulated as the sum of two separate functions representing the even and odd lines respectively as in Eqs. 2.41 and 2.42; multiplication of the continuous signal by these functions subsequently produces the
corresponding sub-sampled signals \( s_e(2p\Delta k) \) and \( s_o((2p+1)\Delta k) \).

\[
    u(k) = u_e(k) + u_o(k) \tag{2.40}
\]

\[
    u_e(k) = \Delta k \sum_{p=-\infty}^{\infty} \delta(k - 2p\Delta k) \tag{2.41}
\]

\[
    u_o(k) = \Delta k \sum_{p=-\infty}^{\infty} \delta(k - (2p+1)\Delta k) \tag{2.42}
\]

As before, the iFT of \( u_e(2p\Delta k) \) and \( u_o(2p\Delta k) \) yield the corresponding \( x \)-domain sampling functions \( U_e(x) \) and \( U_o(x) \) (Eqs. 2.44 and 2.45).

\[
    U(x) = U_e(x) + U_o(x) \tag{2.43}
\]

\[
    U_e(x) \equiv \mathcal{F}^{-1}(u_e(k)) = \Delta k \sum_{q=-\infty}^{\infty} \delta(2\Delta kx - q) = \frac{1}{2} \sum_{q=-\infty}^{\infty} \delta \left(x - q\frac{L}{2}\right) \tag{2.44}
\]

\[
    U_o(x) \equiv \mathcal{F}^{-1}(u_o(k)) = \mathcal{F}^{-1}(u_e(k - \Delta k)) = e^{i2\pi k_0x} \mathcal{F}^{-1}u_e(k) = \frac{1}{2} \sum_{q=-\infty}^{\infty} \delta \left(x - q\frac{L}{2}\right) e^{iq\pi} \tag{2.45}
\]

The derivation of the odd sampling function \( U_o(x) \) utilises the Fourier shift theorem in Eq. 2.48, which describes how a shift in the origin of \( k \)-space \( s(k) \rightarrow s(k - k_0) \) produces a linear phase shift in image space.

\[
    S(x) \equiv \mathcal{F}^{-1}(s(k - k_0)) = \int_{-\infty}^{\infty} dk s(k - k_0) e^{i2\pi kx} = e^{i2\pi k_0x} \int_{-\infty}^{\infty} dk' s(k') e^{i2\pi k'x} = e^{i2\pi k_0x} S_{\text{expected}}(x) \tag{2.46}
\]

Convolution of \( S(x) \) with the respective sampling functions yields the even and odd images (Eqs. 2.49 and 2.50).

\[
    S_e(x) \equiv S(x) * U_e(x) = \frac{1}{2} \sum_{q=-\infty}^{\infty} S \left(x - q\frac{L}{2}\right) \tag{2.49}
\]

\[
    S_o(x) \equiv S(x) * U_o(x) = \frac{1}{2} \sum_{q=-\infty}^{\infty} S \left(x - q\frac{L}{2}\right) e^{iq\pi} \tag{2.50}
\]

Given that the convolution produces an infinite series of Nyquist copies of \( S_e(x) \) and \( S_o(x) \) with periodicity \( L \), only the interval given by \(-L/2 < x < L/2\) need be considered; this
2.3. Image formation

corresponds to the terms given by \( q = [-1,0,1] \). Aliasing in the sub-sampled images is demonstrated in Eqs. 2.51 and 2.52, where it is evident from the separate contribution of these three terms that the true image is replicated three times in each reconstruction, offset from each other by \( L/2 \).

\[
S_e(x) = \frac{1}{2} \left[ S\left(x + \frac{L}{2}\right) + S(x) + S\left(x - \frac{L}{2}\right) \right] \quad (2.51)
\]

\[
S_o(x) = \frac{1}{2} \left[ -S\left(x + \frac{L}{2}\right) + S(x) - S\left(x - \frac{L}{2}\right) \right] \quad (2.52)
\]

In this example, the odd terms of the two series (i.e. \( q = [-1,1] \)) cancel and the fully sampled image can be recovered by summing \( S_e(x) \) and \( S_o(x) \) (Eq. 2.53). Image artefacts resulting from phase errors between \( S_e(x) \) and \( S_o(x) \) are discussed in Chapter 6.

\[
S(x) = S_e(x) + S_o(x) \quad (2.53)
\]

2.3 Image formation

Previous sections have considered MR experiments in terms of single spins or 1D spin systems; this section extends the 1D imaging equation in Eq. 2.30 to 3D and addresses the fundamentals of image acquisition. Basic pulse sequence design, including spatial encoding and the generation of image contrast, is introduced.

2.3.1 Spatial encoding

Spatial information is encoded into the signal using the orthogonal magnetic field gradients \( G_x, G_y \) and \( G_z \) to vary the phase and frequency of spin precession as a function of position within the gradient fields. The spatial frequency interrogated in any direction depends on the amplitude and duration of the spatial encoding gradients (Eq. 2.54); high frequencies (edge details) are therefore stored at the edges of \( k \)-space while low frequencies (signal-to-noise and contrast details) are stored at the centre of \( k \)-space (Fig. 2.7). This information can be used practically to determine the coverage and sampling order of \( k \)-space.

\[
k_x(t) = \frac{\gamma}{2\pi} \int_0^t G_x(t') dt', \quad k_y(t) = \frac{\gamma}{2\pi} \int_0^t G_y(t') dt', \quad k_z(t) = \frac{\gamma}{2\pi} \int_0^t G_z(t') dt' \quad (2.54)
\]

The FT pair for imaging in multiple dimensions is provided in Eq. 2.55, where \( \mathbf{k} = [k_x, k_y, k_z] \) and \( \mathbf{r} = [x, y, z] \).

\[
s(\mathbf{k}) = \int d^3r S(\mathbf{r}) e^{-2\pi i \mathbf{k} \cdot \mathbf{r}}, \quad S(\mathbf{r}) = \int d^3k s(\mathbf{k}) e^{+2\pi i \mathbf{k} \cdot \mathbf{r}} \quad (2.55)
\]
Figure 2.7. Spatial encoding in k-space. a. k-space is traversed using the imaging gradients $G_x$ and $G_y$ ($\Delta k_{x,y} = \gamma G_{x,y} \Delta t$). b. Example k-space. The centre of the signal echo is stored at the centre of k-space.

**Slice selection**

Acquisitions of 3D volumes are often acquired as a stack of 2D slices so that spatial encoding is only required in 2D (i.e. $k_x$ and $k_y$). For this approach, the slice selective gradient $G_z$ induces an initial precession frequency variation across the imaging volume. An RF pulse, applied simultaneously with a central frequency corresponding to the precession frequency in the desired slice, selectively excites spins in a narrow band. The resulting band of transverse magnetisation is dependent on the RF pulse bandwidth, magnitude and duration.

**Phase and frequency encoding**

The phase encoding (PE) gradient $G_y$ introduces a spatially varying phase shift across the selected slice: during the PE gradient the precession frequency varies as a function of position such that when the gradient is turned off the spins, which return to precessing at the Larmor frequency, have acquired a phase shift dependent on gradient field.

Frequency encoding (FE), performed using $G_x$ during readout, ensures that spin phase and frequency correspond to unique locations in the imaging volume.

**2.3.2 Signal echoes**

A FID signal is generated immediately after the initial RF excitation pulse, but to sample the signal an echo is usually created. Gradient echoes, spin echoes and stimulated echoes are all possible; however, stimulated echoes are not discussed here.
2.3. Image formation

Gradient echo (GE) and spin echo (SE) sequences form the basis of many acquisitions (Fig. 2.8). In the simplest sequences, spatial information is encoded into the signal using the imaging gradients and one echo (one \( k \)-space line) is acquired for each excitation pulse. The time between excitation pulses is the repetition time \( T_R \); the time at which an echo is generated following the excitation pulse is the echo time \( T_E \).

Gradient echoes are generated by inverting the FE gradient (Fig. 2.8a). Effects of \( B_0 \) inhomogeneities are not accounted for in this approach, so GE images are inherently \( T_2^* \)-weighted. However, the method allows for fast imaging owing to minimal additional time requirements for echo generation.

Spin echoes are formed following an additional 180° RF pulse (Fig. 2.8b). This refocusses the additional de-phasing caused by field inhomogeneities, so images acquired using SE sequences are less sensitive to \( B_0 \) inhomogeneities and are \( T_2 \)-weighted.

2.3.3 Echo planar imaging

Echo planar imaging (EPI) is one of several methods designed to reduce imaging times. Rapid FE gradient switching is used to acquire a train of gradient echoes for each excitation pulse, with the PE gradient ‘blipped’ between each echo to traverse \( k \)-space (Fig. 2.9). The time to fully sample \( k \)-space is greatly reduced, but EPI are prone to several artefacts.

Susceptibility artefacts around the sinuses are particularly prominent owing to the use of gradient echoes: magnetic field inhomogeneities from magnetic susceptibility differences between air and tissue create variations in precession frequency that are not reversed, which results in signal loss and distortions. Nyquist ghosting is also inherent in EPI. Owing to the alternating readout gradient polarities, gradient system imperfections cause a phase shift between opposing \( k \)-space trajectories which produces a ghost image offset by half the FOV.

The susceptibility-induced off-resonance field can be corrected using two images acquired with opposing polarities of the PE gradient blips. In each case the distortion will be equal but opposite, so the susceptibility field can be estimated as that which maximises the similarity between the images once ‘unwarped’. To a first approximation, the susceptibility field is constant for all acquired images, so only one image in a dynamic series needs acquiring twice. Nyquist ghosting, however, can be more challenging to correct, and is the focus of Chapters 6 and 8 of this thesis.

Finally, rapid gradient switching can lead to peripheral nerve stimulation (PNS) in patients, so gradient slew rates must be limited to avoid adverse effects.
Gradient echo pulse sequence

Spin echo pulse sequence

**Figure 2.8. Basic pulse sequence diagrams.** The RF pulse, applied in conjunction with the slice select gradient, excites spins in a narrow band. The phase encoding gradient induces a phase variation in the spin precession as a function of spatial location; the frequency encoding gradient induces a variation in the precession frequency such that the spins in the slice have a unique phase and frequency dependent on their location within the spatial encoding gradients. All gradients applied cause the spins to de-phase; therefore each spatially-encoding gradient is accompanied by an opposing gradient designed to re-phase the spins.
2.3. Image formation

2.3.4 Contrast

Image contrast is dependent on differences between tissue relaxation times and the sequence timing parameters. \( T_1 \) weighting is achieved when \( T_R \) and \( T_E \) are short. Tissues with short \( T_1 \) relaxation times are hyper-intense as there is enough time for the magnetisation to fully recover. A long \( T_R \) and long \( T_E \) produces \( T_2 \) weighting, in which tissues with long \( T_2 \) relaxation times are hyper-intense. Proton density imaging is obtained using a long \( T_R \) and short \( T_E \).

2.3.5 Eddy currents

Faraday’s law of induction (Section 2.1.3) states that a changing magnetic field induces a current in an electric conductor; from Lenz’s law, the direction of the induced current gen-
erates a magnetic field to oppose the initial field. In MR imaging, then, any gradient or RF pulse used for signal encoding generates eddy currents in nearby conducting components of the MR scanner (for example, the main magnet, gradient coils, shim coils or liquid helium vessel) or the patient.

As the induced $emf$ is dependent on the rate of change of magnetic flux, fast imaging sequences that use rapid gradient switching, such as EPI, are most affected. Techniques such as pre-emphasis (modifying gradient waveforms to compensate for expected eddy currents) or active shielding of gradient coils (secondary coils to constrain flux changes induced by the primary gradients) can reduce the impact of eddy currents, but there are often residual effects.

Eddy currents induced in components of the MR scanner affect the main magnetic field and cause either frequency shifts or time-varying gradients; this can translate into geometric distortions or Nyquist ghosting in acquired images.

2.3.6 Multi-band imaging

Multi-band (MB) - or simultaneous multi-slice (SMS) - imaging uses composite RF pulses to excite multiple slices together [40]. The detected image is a superposition of both slices, which can be unfolded using coil sensitivity profiles in a manner similar to parallel imaging reconstruction (Section 2.5). A phase shift between the excited slices can be induced using the RF pulse, thereby aiding the separation of adjacent slices where coil sensitivity profiles may be similar [41]. Unlike parallel imaging, MB-imaging does not suffer the same SNR penalties, meaning that acquisition times can be reduced proportional to the number of simultaneously excited slices.

2.4 Partial Fourier encoding

Partial Fourier encoding exploits the conjugate symmetry of $k$-space in order to acquire fewer phase-encoding lines for a given image resolution. This has the primary benefit of reducing acquisition times, but also allows echo times to be reduced which can have signal-to-noise ratio benefits. In EPI, for instance, an asymmetric acquisition of $k$-space means that the centre of $k$-space can be sampled much earlier.

In practice, phase errors in the sampled data mean that conjugate symmetry no longer holds. In addition to synthesising the missing data, then, phase correction must also be performed. There are several approaches to partial $k$-space reconstruction. The most trivial approach is to simply fill the uncollected lines with zeros. While acceptable results can
be obtained for partial Fourier factors close to unity, blurring and ringing artefacts become increasingly prominent as the fraction of $k$-space acquired approaches one half: zero-filling is akin to multiplying $k$-space by a step function, the iFT of which is an impulse function that distorts the data.

**2.4.1 Homodyne filtering**

Phase correction of the partial $k$-space data is performed using the phase of a low resolution image $\phi_c(x)$; this is obtained from a narrow, symmetrically sampled region at the centre of $k$-space. The iFT of the partial $k$-space data $S_{pf}(x)$ is then corrected as in Eq. 2.56.

To avoid the artefacts associated with weighting a partially filled $k$-space by the effective step function (described above in the zero-filling approach), a ramp filter $W(k)$ is used to pre-weight the partial $k$-space data prior to phase correction. The key idea is that the real component of the phase corrected data in image space corresponds to a uniform weighting by the filter in $k$-space [42].

$$S(x) = \Re \left\{ S_{pf}(x) e^{-i\phi_c(x)} \right\}, \quad \text{with} \quad S_{pf}(x) = \mathcal{F}^{-1} \left( s(k) W(k) \right) \quad (2.56)$$

**2.4.2 Projection onto convex sets**

Projection onto convex sets (POCS) [43] iteratively transforms the data between $k$-space and image space. On the first iteration, the partial $k$-space is zero-filled, transformed to image space, and corrected using a phase estimate $\phi_c(x)$ from the low resolution image obtained from the symmetrically sampled centre of $k$-space. Transformation back to $k$-space fills the uncollected entries. The final step updates the estimates of the collected lines with the actual data. The algorithm converges when: (i) the phase of the filled $k$-space conforms to the phase of the low resolution image $\phi_c(x)$, and (ii) the estimate of the missing $k$-space data best represents the acquired data.

Iterative methods tend to offer improved local phase recovery over direct methods such as homodyne filtering.

**2.5 Parallel imaging and reconstruction**

Parallel imaging is the technique of reducing acquisition time by acquiring fewer phase-encoding steps in $k$-space and substituting information from multiple RF coils (receiving in parallel) to recover the true image. There are two primary approaches: GRAPPA (Gen-erAlized Autocalibrating Partial Parallel Acquisition) and SENSE (SENSitivity Encoding). The key difference is that GRAPPA recovers the missing data in $k$-space prior to channel
combination in the image domain, while SENSE unfolds the aliased channel data in image space during reconstruction.

The basic principles of parallel imaging and reconstruction using SENSE are described here, once more using the test case of a 1D spin distribution with complex magnetisation $M(y)$ for simplicity. The convention $k \equiv k_y$ is adopted to signify phase encoding in the $y$-dimension. Matrix formulations for signal encoding and image reconstruction are introduced for a more compact description of the forward and inverse problems; the discrete FT is introduced to allow for finite sampling.

### 2.5.1 Matrix formulation

Given a set of $N_c$ coils and the fully sampled case where the $N_y$ phase encoding steps in $k$-space is equal to the $N_p$ pixels in image space, the discrete FT pair describing the signal detected by the $n$th coil is given in Eqs. 2.57 and 2.58, where $B_n(y)$ is again the coil receive field, or sensitivity profile.

$$ s_n(k) = \sum_{j=1}^{N_c} \Delta y e^{-i2\pi k y_j} B_n(y_j) M(y_j) $$ (2.57)

$$ n = 1, 2, \cdots, N_c, \quad m = 1, 2, \cdots, N_p $$

$$ S_n(y_j) = B_n(y_j) M(y_j) = \sum_{m=1}^{N_p} \Delta k e^{i2\pi k y_j} s_n(k) $$ (2.58)

$$ n = 1, 2, \cdots, N_c, \quad j = 1, 2, \cdots, N_p $$

The $e^{i2\pi k y_j}$ phase factors in Eq. 2.57 can be used to construct a set of $N_y$ linearly independent basis vectors $v$ for the matrix representation in Eq. 2.59. In the fully sampled case, the basis set is simply the $N_y k$-space lines; when RF coil data replaces some gradient data the basis set is defined by $N_y \times N_c$ vectors (Eq. 2.59) made sufficiently independent through coil design. Using the basis set $v$, the signal can be compactly described as in Eq. 2.60. If $N_y N_c = N_p$, then $v$ is square and can be inverted (assuming a non-zero determinant) to obtain the image ($M = v^{-1} s$).

$$ v_{n \times m, j} \equiv \Delta y e^{-i2\pi k y_j} B_n(y_j) $$ (2.59)

$$ n = 1, 2, \cdots, N_c, \quad m = 1, 2, \cdots, N_y, \quad j = 1, 2, \cdots, N_p $$

$$ s_n(k_m) \equiv s_{n \times m} = v_{n \times m, j} M(y_j) \quad \text{or} \quad s = vM $$ (2.60)
2.5.2 Acceleration and aliasing

While the FT pair in Eqs. 2.57 and 2.58 holds for the general case where $N_y = N_p$, in parallel imaging $N_y$ is reduced and the missing data provided by coil sensitivity maps. Subsequently, $N_y$ no longer directly corresponds to the final image resolution $\Delta y$. The reduction in $N_y$ breaks the Nyquist sampling criterion and leads to aliasing.

The amount of aliasing is determined by the degree of $k$-space under-sampling, represented by the acceleration factor $R$. For $R > 1$, the number of $k$-space lines is reduced by $N_y/R$ and the spacing $\Delta k$ is increased by $R\Delta k$; in turn the acquisition time is reduced by $1/R$. To maintain the same extent of $k$-space sampling in parallel imaging, it is required that $N_{y,full} = N_y R \times N_c$; however, it is usually the case that data in parallel imaging is overdetermined, with $N_{y,full} < N_y R \times N_c$ and $R < N_c$.

The number of image replicates $N_r$ in an aliased data set is determined by the FOV $L$, object size $A$, and acceleration factor $R$. The number of replicates is given by Eq. 2.61, where the brackets $\lceil ... \rceil$ denote the ceiling function. $N_r = 1$ corresponds to no aliasing.

$$N_r = 2 \left\lceil \frac{1}{2} \left( \frac{AR}{L} - 1 \right) \right\rceil + 1 \quad (2.61)$$

2.5.3 Sensitivity encoding

The first stage of a SENSE-based reconstruction is to generate the $N_c$ aliased data sets from separate channels in the image domain through the discrete iFT. The full FOV image is then formed using knowledge of the coil sensitivity profiles to reverse the signal superposition, the key being that each superposed signal has a different weighting depending on its local coil sensitivities.

For a given pixel $\rho$, a $N_c \times 1$ column matrix $S$ containing the complex signal from each channel can be constructed. Supposing this pixel contains $N_r$ superimposed signals from pixels located at $r_\rho$ in the full FOV, the $N_c \times N_r$ matrix $B$ describes the spatial sensitivity of each coil at the superimposed pixel locations. If $N_r = N_c$, then $B$ is square and can be inverted - assuming a non-zero determinant - to obtain the $N_r$ intensity values $M$ of the unfolded pixels in the full FOV (Eq. 2.62).

$$S = BM, \quad M = B^{-1}S \quad (2.62)$$

When $M$ is overdetermined, i.e. $N_c N_y > N_p$ and $N_r < N_c$, $B$ is no longer square and the
pseudo-inverse solution in Eq. 2.63 must be used instead.

$$M = (B^H B)^{-1} B^H S$$ (2.63)

### 2.6 Noise

Noise is an important consideration for signal detection, as random signal fluctuations can affect both the accuracy and precision of the measurement. This section describes common noise sources in MRI and introduces the signal-to-noise ratio (SNR), which quantifies the influence of noise on signal measurements. The impact of signal rectification and parallel imaging on noise characteristics is also discussed.

#### 2.6.1 Noise sources

Noise arises from random thermal fluctuations in the MR signal, which originate in both the imaged sample and the coil electronics. The magnitude of these signal fluctuations is governed by the thermal entropy of the system $k_B T$ and its effective resistance $R_{\text{eff}}$, which is the resistance in the sample, coil and electronics combined Eq. 2.64. As these processes are independent their contributions are additive, but sample resistance is generally dominant.

$$R_{\text{eff}} = R_{\text{coil}} + R_{\text{sample}} + R_{\text{electronics}} \approx R_{\text{sample}}$$ (2.64)

Equal noise power is expected at all frequencies - it is ‘white’ noise - so bandwidth also influences the overall noise level: higher bandwidths contain more noise. An expression for the overall variance in the measured voltage is given in Eq. 2.65, where the receive bandwidth $\Delta f$ is the only parameter that can be controlled.

$$\sigma^2 (k) \propto 4k_B T \Delta f R_{\text{eff}}$$ (2.65)

Noise in $k$-space is additive: the measured noisy signal $s_m(k)$ is the sum of the true signal $s(k)$ and the Gaussian distributed noise $\varepsilon(k)$ (Eq. 2.66). Through the linearity of the FT, noise $\eta(r)$ in complex-valued MRI is similarly additive and normally distributed.

$$s_m (k) = s (k) + \varepsilon (k), \quad S_m (r) = S (r) + \eta (r)$$ (2.66)

#### 2.6.2 Signal rectification and Rician bias

MR data are usually displayed as magnitude images to avoid artefacts from phase errors. However, as signal rectification is a non-linear transformation, noise in magnitude images
2.6. Noise

is no longer normally distributed and instead follows the Rician distribution in Eq. 2.67, where $I_0$ is the modified Bessel function of the first kind with order zero [44] (Fig. 2.10b).

$$f(S_m|S, \sigma) = \frac{S_m}{\sigma^2} \exp\left(\frac{-S^2_m + S^2}{2\sigma^2}\right) I_0\left(\frac{S_m S}{\sigma^2}\right)$$

(2.67)

For low SNR measurements, then, signal rectification gives rise to a minimum measurable signal, or noise floor - the so-called Rician bias (Fig. 2.10c). Given a noise-only signal, the mean $\eta$ and standard deviation (SD) $\sigma_\eta$ of the magnitude signal are related to the SD of the complex signal $\sigma$ as in Eq. 2.68.

$$\eta = \sigma \sqrt{\frac{\pi}{2}}, \quad \sigma_\eta = \sigma \sqrt{\frac{2 - \pi}{2}}$$

(2.68)

For SNR > 3, however, which holds for most MR images, the signal magnitude is unbiased and the variance is equal to that of either the real or imaginary component of the complex signal.

2.6.3 Signal-to-noise ratio

The SNR describes how well a signal $S$ can be detected given a noise level $\sigma$ (Eq. 2.69). In MR experiments, the influence of noise in the image is governed by a number of imaging parameters, including voxel size ($\Delta x, \Delta y, \Delta z$), $k$-space samples ($N_x, N_y, N_z$), detection bandwidth ($\Delta f$) and number of signal averages (NSA).

$$\text{SNR} = \frac{S}{\sigma} \propto \frac{\Delta x \Delta y \Delta z \sqrt{N_x N_y N_z \text{NSA}}}{\sqrt{\Delta f}}$$

(2.69)

2.6.4 Noise in parallel imaging

Noise correlation and the $g$-factor

The reduction of phase encoding steps in parallel imaging by the acceleration factor $R$ reduces the SNR by a factor of $1/\sqrt{R}$; however, coil noise correlation and image aliasing introduce an additional coil-specific reduction in SNR. This additional SNR reduction is captured by the geometry factor, or $g$-factor (Eq. 2.70).

$$\text{SNR}_R = \frac{\text{SNR}_{R=1}}{g\sqrt{R}}$$

(2.70)

Noise correlation between channels is induced by electromagnetic coupling and overlapping sensitivity profiles. Coil noise covariance in image space is described by the square $N_c \times N_c$ matrix $\Psi$ in Eq. 2.71, where $\eta$ is the $N_c \times N_p$ image noise matrix ($S = BM + \eta$). The off-diagonal elements of $\Psi$ correspond to the noise correlation between coils while the diagonal
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Figure 2.10. Noise in MRI. a. A simple 2D phantom was simulated using $D = 1 \times 10^{-3} \text{mm}^2/\text{s}$, $b = [0 : 200 : 6000]\text{s/mm}^2$ and $\text{SNR} = [20, \infty]$ to demonstrate the effects of signal rectification and Rician bias on noise characteristics. For brevity, only a selection of the (magnitude) images are shown for $\text{SNR} = 20$ and the $b$-values indicated. b. The real component of the complex noise distribution added to the data (across all $b$-values) is shown in black; after signal rectification the noise becomes Rician distributed (blue). c. The mean signal at each $b$-value normalised by signal at $b=0$ is plotted, with and without noise (blue and black lines respectively). With noise, a minimum measurable signal equal to the theoretical noise floor in (Eq. 2.68) is evident.

The generalisation of Eq. 2.63 to include noise covariance is given by Eq. 2.72, where $\sigma^2 = (B^H \Psi^{-1} B)^{-1}$ describes the variance of the reconstructed image $M$.

$$M = (B^H \Psi^{-1} B)^{-1} B^H \Psi^{-1} S$$  \hspace{1cm} (2.72)
2.7 Diffusion weighted imaging

Figure 2.11. Noise decorrelation. a. The noise correlation matrix $\Psi$ of the real signal component before noise decorrelation. The off-diagonal elements represent noise correlation between coils and the diagonal elements depict the noise variance in each channel $\sigma_n^2$. b. After noise whitening, there is no longer any correlation between coils and $\Psi$ is reduced to the identity matrix.

Noise decorrelation

Noise correlation and inconsistent noise levels between coils can adversely affect image reconstruction. Noise decorrelation, or pre-whitening, alters the noise distribution of the measurement (described by the noise covariance matrix $\Psi$) such that it is independent and identically-distributed (iid) Gaussian (Fig. 2.11). The $N_c \times N_c$ noise decorrelation matrix $D$ is obtained from the inverse of the Cholesky decomposition of $\Psi$ as in Eq. 2.74, where $\Psi_L$ is the lower triangle of $\Psi$.

$$D = (\Psi_L \Psi_H^L)^{-1}$$  \hspace{1cm} (2.74)

Prior to SENSE reconstruction, the data $S$ and coil sensitivity profiles $B$ are modified by the decorrelation matrix (2.75).

$$S_{\text{whitened}} = DS, \quad B_{\text{whitened}} = DB$$  \hspace{1cm} (2.75)

This operation is equivalent to weighting the set of linear equations by the inverse square root of the noise covariance; channels with higher noise levels subsequently receive a lower weighting and are thus less influential in the final reconstruction.

2.7 Diffusion weighted imaging

Diffusion weighted imaging (DWI) uses the Brownian motion of spins to generate a contrast based on their bulk-averaged mobility. The mobility of spins varies based on their environment: spins in free water have few microstructural barriers and are free to diffuse relatively
large distances isotropically; biological barriers in GM, such as cell membranes, hinder diffusion in all directions, leading spins to diffuse isotropically but along shorter length scales; finally, spins in WM diffuse anisotropically because axons restrict motion perpendicular to the fibre orientation. The degree and direction of spin displacements therefore provide microstructural information.

This section describes the pulsed gradient spin echo (PGSE) experiment used to encode the diffusive motion of spins into the MR signal, as well as some common signal models used to estimate parameters relating to microstructural tissue organisation.

### 2.7.1 Diffusion encoding

Spin displacement is encoded into the MR signal using diffusion encoding gradients applied prior to the imaging gradients; Fig. 2.12 illustrates the classic Stejskal-Tanner PGSE sequence [45]. A diffusion gradient applied along one axis, with amplitude $G$ and duration $\delta$, introduces a location-dependent phase shift across the gradient field. The spins are then allowed to diffuse for a time $\Delta$, after which a refocussing diffusion gradient is applied. Spins diffusing along the gradient field experience a refocussing gradient that is different to the initial sensitising gradient owing to their change in position, so are subsequently not fully re-phased. The resulting lack of phase coherence attenuates the MR signal and provides the diffusion weighting.

The mechanism for signal loss is related to $T_2$ relaxation. As previously described in Section 2.1.2, spin-spin interactions produce local fluctuations in the magnetic field that arise from both the random motion of spins and the spins themselves, and ultimately cause dephasing to occur. In diffusion sensitising experiments, additional gradients enhance the signal loss arising from Brownian motion. The amount by which the signal is reduced is dependent on the mean-squared displacement of the spins $\langle x^2 \rangle$, which is related to the diffusion time $\Delta$ through the diffusion coefficient $D$ (Eq. 2.76).

$$\langle r^2 \rangle = 6D\Delta \quad \text{(in 3D)}$$

The $b$-value expresses the sensitivity of a given PGSE sequence to the diffusion length scale; it is determined by the diffusion gradient timings and amplitudes (Eq. 2.77). Assuming square gradient waveforms in 1D, the solution to Eq. 2.77 is given in Eq. 2.78.

$$b = \int_0^{T_E} q(t) q^T(t) \, dt, \quad q = \gamma \int_0^{\tau} G(t') \, dt'$$

$$b = (\gamma \delta G)^2 \left( \Delta - \frac{\delta}{3} \right)$$
Figure 2.12. PGSE pulse sequence. Large diffusion gradients (shaded) are used to sensitise the signal to the Brownian motion of protons. An EPI readout is typically used in order to rapidly acquire multiple volumes with different diffusion gradients.

Signal loss is subsequently exponential, characterised by both the $b$-value and the diffusivity of the medium as in Eq. 2.79, where $S_0$ is the signal measured without diffusion weighting.

Diffusion in most biological substances is hindered by cell membranes and macromolecules, so the measured diffusivity is lower than that observed in free water; diffusivity measured using MRI is therefore typically referred to as the apparent diffusion coefficient, or ADC.

$$S(b) = S_0 \exp(-b \cdot \text{ADC}) \quad (2.79)$$

### 2.7.2 Signal models

**The diffusion tensor**

Biological tissues are often anisotropic, meaning that the measured ADC is dependent on the diffusion gradient axis. The diffusion tensor (DT) model [11] provides a more general description of diffusion in a voxel: a symmetric $3 \times 3$ matrix describes the parameters of a trivariate Gaussian distribution which models spin displacement probabilities in 3D (Eq. 2.80). Unique elements of the DT are quantified from a weighted multivariate linear regression of signals acquired with diffusion gradients along at least six non-collinear directions.

$$S(b) = S_0 \exp(-b \cdot D), \quad D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \quad (2.80)$$
Figure 2.13. The diffusion tensor. a. The DT represents the probability of spin displacement in 3D. Axes correspond to the eigenvectors and are scaled by the eigenvalues; the shape and volume represent FA and MD respectively. b. Spherical (left), prolate (centre) and oblate (right) DTs.

The eigenvectors \( \mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3 \) and eigenvalues \( \lambda_1 \geq \lambda_2 \geq \lambda_3 \) of the DT parameterise the diffusion properties in any given voxel (Fig. 2.13a): the principal eigenvector \( \mathbf{e}_1 \) represents the primary diffusion direction and its corresponding eigenvalue \( \lambda_1 \) is the ADC. The mean diffusivity (MD) in a voxel - given by the trace of the DT as in Eq. 2.81 - quantifies the average rate of diffusion in all directions.

\[
MD = \frac{1}{3} \text{Trace}(\mathbf{D}) = \frac{1}{3} \sum_{i=1}^{3} \lambda_i \quad (2.81)
\]

Diffusion anisotropy is represented by the DT shape (Fig. 2.13b). Fractional anisotropy (FA) is a measure of the variance in eigenvalues, and characterises how much the DT deviates from a sphere and isotropic diffusion.

\[
FA = \left[ \frac{3 \sum_{i=1}^{3} (\lambda_i - \langle \lambda \rangle)^2}{2 \sum_{i=1}^{3} \lambda_i^2} \right]^{\frac{1}{2}} \quad (2.82)
\]

A limitation of diffusion tensor imaging (DTI) is the assumption of mono-exponential signal decay; in other words that a unimodal Gaussian distribution can fully describe spin diffusion within a voxel [46]. This approximation is appropriate only if the voxel contains homogeneous tissues with high orientation coherence and the diffusion time is short relative to the time required for the spins to experience restrictions (i.e. spins do not coincide with biological barriers during the observation time). Generally these conditions are not satisfied, as the resolution of DTI is such that different tissue and cell types and orientations in a single voxel are likely. Inferences of tissue microstructure based on a voxel scale average therefore have two major constraints: (i) multiple rates of diffusion arising from heterogeneous tissue...
within a voxel cannot be modelled; (ii) multiple fibre directions within voxel (i.e. crossing, kissing and bending fibres) cannot be resolved.

These limitations impact the interpretation of the commonly reported MD and FA metrics. Changes in these parameters are regularly reported as signs of pathology, but, while it is clear that MD and FA are sensitive to a range of pathologies, they are non-specific as to the cause of the alteration. FA, for instance, can be reduced as a result of axonal loss (i.e. a decrease in axon density), demyelination, or an increase in the orientation distribution of axons. Measures of MD may be increased owing to an increase in the tissue cellularity index or to the cells swelling.

The kurtosis tensor

Diffusion kurtosis imaging (DKI) aims to capture the extent to which diffusion in biological tissues deviates from the Gaussian distribution. It is therefore seen as a measure of tissue heterogeneity. A common approach is to use the Taylor expansion of the exponent in Eq. 2.80 to give the bi-exponential model in Eq. 2.83 [47].

\[
S(b) = S_0 \exp \left( -bD + \frac{1}{6}b^2D^2K \right)
\]

As with the ADC, the measured kurtosis depends on the orientation of the diffusion gradient, so a diffusion kurtosis tensor (DKT) is constructed that is analogous to the DT but with 15 independent components. To obtain the DKT, then, the signal along an additional 15 different directions must be measured using at least 3 unique \(b\)-values. Larger \(b\)-values (\(b > 1500 \text{s/mm}^2\)) are also required to provide enough signal variation for the higher order term to be measurable and not overly sensitive to noise (Fig. 2.14).

Despite the ability to characterise restricted diffusion, though, DKI is also limited by the inability to resolve crossing fibres.

Neurite orientation dispersion and density imaging

Neurite orientation dispersion and density imaging (NODDI) [15] is an imaging protocol and biophysical model that separates the contribution of three key microstructural compartments - that is intra-neurite, extra-neurite and cerebrospinal fluid (CSF) - on the MR signal. The primary aim is to disentangle the confounding factors of neurite density and their orientation dispersion on measures of FA. The signal model adopted in NODDI is given in Eq. 2.84, in which \(S_{ic}, S_{ec}\) and \(S_{iso}\) are the normalised signals from the intra-neurite, extra-neurite and CSF (isotropic) compartments, and \(\nu_{ic}\) and \(\nu_{iso}\) are the volume fractions of the intra-neurite and CSF compartments.
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Figure 2.14. Diffusional kurtosis. Signal decay curves simulated analytically using the DT (Eq. 2.80) and DKT models (Eq. 2.83), with $D = 1 \times 10^{-3}$ mm$^2$/s, $b = [0 : 200 : 2500]$ s/mm$^2$, and $K = 1$ (DKT only). Restricted diffusion in-vivo results in higher than expected signal values and the subsequent deviation from Gaussian diffusion and mono-exponential signal decay.

NODDI has two key limitations: (i) diffusivities of the different compartments must be fixed in order to provide more accurate estimates of the volume fractions; (ii) the tortuosity constraint $D_{e,\perp} = D_{e,\parallel} (1 - f_{ic})$ is not applicable to myelinated axons as the $g$-ratio (the ratio between the inner and outer axon diameters) is not considered.

$$S = (1 - v_{iso}) (v_{ic} S_{ic} + (1 - v_{ic}) S_{ec}) + v_{iso} S_{iso}$$  \hspace{1cm} (2.84)

2.7.3 Probabilistic tractography

Tractography is the process of identifying white matter fibres in the brain. Firstly, an orientation density function - describing the probability distribution of the principle diffusion direction - is generated in each voxel by fitting a model to the diffusion weighted signal that can estimate axon orientation (the ‘ball-and-sticks’ model [48], for example). Then, a set of streamlines is generated by sampling from the distribution of possible fibre orientations in each voxel multiple times and plotting a path probability map.

Tractography algorithms are highly prone to errors [49]. A major source of error arises from modelling assumptions, in particular the treatment of crossing or fanning fibres. Image noise can also affect the estimation of the principle fibre direction, while tractography algorithms themselves can produce physically infeasible tracts owing to the accumulation of errors along the streamline. False-positive and false-negative tracts can have major consequences in the interpretation of graph theoretic measures of brain connectivity derived from tractography data, for example.


2.8 Graph theory

Graphs are a mathematical representation of a set of discrete variables (vertices or nodes) and their pairwise relationships (edges). In connectomics, brain regions are depicted by nodes with patterns of association between regions (see Section 2.8.7) modelled by edges.

A graph $G$ is represented by the set of vertices $V$ and set of edges $E$ such that $G = (V,E)$. The number of nodes in $G$, or the order of $G$, is denoted by $n$; the number of edges, or size, of $G$ is denoted by $m$. $G' = (V',E')$ is a subgraph of $G$ - that is $G' \subset G$ - if $V' \subset V$ and $E' \subset E$. An induced subgraph is one in which all the edges in $E$ that join any two vertices in $V'$ are contained in $E'$.

A fully connected group of nodes is referred to as a clique; a cluster is simply a highly interconnected group of nodes.

These basic concepts are illustrated in Fig. 2.15.

2.8.1 Adjacency matrices

Graphs may be represented using an adjacency, or association, matrix $A$, in which any element $A_{ij}$ represents the edge between nodes $i$ and $j$. The adjacency matrix of an undirected graph is symmetric such that $A_{ij} = A_{ji}$. Only undirected graphs will be considered in this thesis as the directionality of edges cannot be resolved using measures of connectivity based on functional, diffusional or structural MRI.

Edges may be binary or weighted. In the binary case, $A_{ij} = 1$ depicts an edge while

![Figure 2.15. Example graphs. a. A simple graph $G$. Each node is connected to 6 neighbours, so the degree of each node is $k = 6$. There are many cliques within $G$: nodes $\{1,4,6\}$, for example, are all interconnected and so form a clique. b. A subgraph $G'_1$ of $G$; c) An induced subgraph $G'_2$ of $G$; d) A subgraph $G'_3$ of $G$ that displays modular topology: nodes $\{1,2,8\}$ and $\{3,4,5,6,7\}$ form highly interconnected clusters, and few edges connect the clusters.](image-url)
$A_{ij} = 0$ denotes the absence of an edge. An edge in a weighted graph is given by $A_{ij} = w$, where $w$ is the weight of the edge between nodes $i$ and $j$.

### 2.8.2 Degree matrices

A degree matrix $D$ is a diagonal matrix containing the degree of each node, where the degree of a node $k_i$ is defined as its number of neighbours (Eq. 2.85).

$$k_i = \sum_{j=1}^{n} A_{ij} \quad (2.85)$$

### 2.8.3 Laplacian matrices

The Laplacian of a graph is defined as the adjacency matrix subtracted from the degree matrix (Eq. 2.86). It is regularly used in spectral graph theory, which studies the relationship between the properties of a graph and its set of eigenvalues, or spectrum.

$$L = D - A \quad (2.86)$$

The eigensystem of the Laplacian enables a graph to be partitioned (see Section 2.8.4) as it relates to the number of connected components: if there are $k$ zero eigenvalues then there are $k$ connected components in $L$, disconnected from each other [50]. By construction the sum of elements in each row of the Laplacian is zero, so at least one eigenvalue of $L$ is zero.

### 2.8.4 Graph partitioning and modularity

Partitioning is the process of dividing a graph into clusters (modules). A modular graph is one that can be partitioned into clusters that are maximally connected within groups and minimally connected between groups [51]; a modular structure is illustrated in Fig. 2.15d. The modularity of a graph is therefore high if it can be partitioned such that the clusters are more densely interconnected than would be expected given a comparable random graph.

Modularity is representative of the functional segregation within a network, as densely interconnected clusters are able to perform specialised processing tasks.

### 2.8.5 Random and complex graphs

The Erdős-Rényi model of a random graph is one in which, for a given order and size, all edges are equally likely [52]. A complex graph is one that displays non-random characteristics. Random graphs are often used as a benchmark for network properties of real systems, for example to satisfy that a property is feature of a particular network and not simply expected by chance. Graphs, random or complex, are comparable only if their order, size and degree distribution are equal.
2.8.6 Complex graph properties

Edge density

The edge density $\rho$ is defined as the proportion of edges present out of the total number of possible edges; as such, it is a measure of the physical ‘wiring cost’ of a network.

$$\rho = \frac{m}{n(n-1)/2} \quad (2.87)$$

Global efficiency and path length

Global efficiency and characteristic path length are related properties that reflect the functional integration of a network. Paths (the number of edges that connect any two nodes) are of interest because they can represent communication patterns in the cortex: shorter, or ‘stronger’, paths provide faster information transfer between regions and are hence more ‘efficient’.

The distance along any path between nodes $i$ and $j$ is simply the sum of the edges on the path. If the shortest path is denoted $g_{i\rightarrow j}$, then the shortest path length $d_{ij}$ is given by the sum over all edges $A_{uv}$ in the path $g_{i\rightarrow j}$ (Eq. 2.88). Path length in weighted graphs is inversely proportional to edge weight: larger weights represent stronger connectivity and therefore shorter paths.

$$d_{ij} = \sum_{A_{uv} \in g_{i\rightarrow j}} A_{uv} \quad (2.88)$$

The characteristic path length $L$ is the mean shortest path length in the network (Eq. 2.89).

$$L = \frac{1}{n} \sum_{i \in n} \frac{\sum_{j \in n, j \neq i} d_{ij}}{n-1} \quad (2.89)$$

Characteristic path length is disproportionately affected by disconnected nodes: the path to a disconnected node is, in essence, infinite (i.e. not possible), so the mean path length in a graph with disconnected nodes is also infinite. Global efficiency $E$ (Eq. 2.90) is inversely related to path length, and as such is not adversely affected as the contribution of a disconnected node to the total efficiency is zero instead of infinity.

$$E = \frac{1}{n} \sum_{i \in n} \frac{\sum_{j \in n, j \neq i} d_{ij}^{-1}}{n-1} \quad (2.90)$$

Local efficiency and mean clustering coefficient

Local efficiency and mean clustering coefficient are indicative of network resilience. For a given node $i$ the local efficiency $E_{loc}$ is defined as the efficiency of the subgraph created
from all the neighbours of \( i \) but not \( i \) itself (Eq. 2.91); local efficiency therefore reflects the ability of a network to function after the loss of a node, as the loss will have less of an impact on overall network efficiency if its neighbours are also interconnected.

\[
E_{\text{loc}} = \frac{1}{n} \sum_{i \in n} \sum_{j, h \in n, j \neq i} \frac{a_{ij} a_{ih} [d_{jh}(n)]^{-1}}{k_i (k_i - 1)}
\]  

(2.91)

The fraction of a node’s neighbours that are interconnected is given by the mean clustering coefficient \( C \) (Eq. 2.92).

\[
C = \frac{1}{n} \sum_{i \in n} \sum_{j, h \in n} \frac{a_{ij} a_{ih} a_{jh}}{k_i (k_i - 1)}
\]  

(2.92)

**Small worlds**

A high clustering coefficient in combination with high global efficiency describes a network that has ‘small world’ properties: segregated clusters connected together via a small number of ‘hub’ nodes sufficient to retain short average path lengths throughout the network. Small-world networks are therefore modular networks that can support high levels of both functional segregation and integration: efficiency is maximised whilst wiring cost is minimised.

**Centrality**

Centrality measures identify important nodes within a network. Degree centrality, for example, uses the degree of a node to index its importance to the network as a whole. Node strength is a related concept for weighted graphs: influential nodes are those for which the sum over all connected edge weights is highest. Betweenness centrality quantifies the number of shortest paths between all other node pairs that it belongs to.

**2.8.7 Graph theory and brain networks**

Graphs depicting brain networks can be constructed in a variety of ways. Common measures of association include: (i) functional connectivity obtained from functional MRI, defined using temporal correlations of the blood oxygenation level dependent (BOLD) signal between regions; (ii) structural connectivity obtained using diffusion tractography, and defined as some property of the tracts representing WM fibres; (iii) structural connectivity obtained using structural \( T_1 \)-weighted imaging, and defined using group-level correlations between regional cortical thickness.
Chapter 3

Multiple Sclerosis

3.1 Pathogenesis and epidemiology

MS is an inflammatory autoimmune disease that affects the central nervous system (CNS). Immune cells infiltrate across the blood-brain-barrier (BBB) and cause inflammation and demyelination with subsequent neuro-axonal degeneration and gliosis. Remyelination also occurs to some degree. Inflammatory, demyelinating episodes tend to localise in foci, especially in white matter (WM), resulting in visible lesions on conventional MR images. More subtle damage occurs in the so-called ‘normal appearing white matter’ (NAWM) and ‘normal appearing grey matter’ (NAGM) owing to neuro-axonal loss and chronic low grade inflammation. Consequently, neural transmission is impaired in MS patients and causes a range of symptoms including vision, speech, mobility and cognitive impediments.

The progression of disability in MS is dependent on the phenotype. Clinically isolated syndrome (CIS) refers to the first symptom caused by the first attack of the immune system on the CNS. For a diagnosis of clinically definite MS at least two attacks disseminated in time and space must be observed [53]. Relapsing-remitting MS (RRMS) is the most common form of clinically definite MS: around 85% of MS patients start as the RRMS phenotype. Disease activity in RRMS is characterised by acute relapses followed by periods of remission as the myelin recovers. Approximately 50% of RRMS patients will develop secondary progressive MS (SPMS) within 10-15 years [54]. SPMS is characterised by more progressive clinical disability with a decrease in the frequency of acute attacks. Primary progressive MS (PPMS) occurs in around 10% of patients from disease onset. PPMS is characterised by progressive disability without periods of remission. Progressive-relapsing MS (PRMS) is the most aggressive but also most rare phenotype, affecting just 5% of patients. Patients with PRMS experience a progressive decline in ability interspersed with
periods of acute relapses without remission.

The onset of MS typically occurs in young adults, with the average age at diagnosis around 30 years. MS is most prevalent in the northern hemisphere, and affects twice as many women as men. Its exact causes are unclear, although a range of genetic and environmental factors have been proposed.

### 3.2 Diagnosis and imaging

The McDonald criteria [53] outline a range of clinical and imaging tests that are recommended for the differential diagnosis of MS. The imaging criteria are briefly discussed here, along with common clinical measures used to quantify disability. Advanced imaging methods with the potential to offer additional information are also introduced.

#### 3.2.1 Clinical disability measures

The expanded disability status scale (EDSS) largely quantifies motor ability on a scale of 1-10. A number of functions are assessed, including ambulatory function, muscle weakness, speech, vision, balance, and bowel and bladder control. A low score indicates minimal disability; a score of 10 is death due to MS. There are a number of limitations with using the EDSS score; for example, the scale is not linearly related to a patient’s disability due to MS, and the upper end of the scale (> 4.0) is heavily focused on walking ability.

The symbol digit modalities test (SDMT) aims to capture cognitive ability. Subjects are presented with a reference key and given 90 seconds to pair geometric symbols with numbers using the key. SDMT performance may be affected by a variety of demographic factors, including age and education, so appropriate statistical corrections may be necessary in clinical studies.

#### 3.2.2 Structural imaging

Structural imaging is one of the primary diagnostic tests for MS outlined in the McDonald criteria. MS lesions (Fig. 3.1a) are identified on \( T_2 \)-weighted fluid attenuation inversion recovery (FLAIR) images as hyper-intense regions relative to normal WM, while gadolinium contrast agents are used to distinguish active lesions: damage to the BBB resulting from inflammation enables the gadolinium chelate to permeate into new lesions, thus reducing \( T_1 \) relaxation times and generating contrast. Measures of atrophy (Fig. 3.1b) are derived from \( T_1 \)-weighted images.

Despite advances in the ability to determine clinically definite MS, correlations between biomarkers obtained using conventional imaging - such as lesion load or atrophy -
3.2. Diagnosis and imaging

3.2.3 Diffusion-weighted imaging

Abnormalities in parameters derived from dMRI are frequently reported in MS patients. Lesions, for example, demonstrate reduced FA and increased MD relative to both NAWM and healthy controls (HC), a finding which is consistent with demyelination, neuroaxonal loss, gliosis and increased water content. NAWM also displays reduced FA relative to HC [25, 55]. Correlations between altered FA and MD values and clinical disability have also been published [56]; however, the relationship is weak to moderate at best. Moreover, the exact causes of the parameter changes are unclear.

Paradoxically, studies in GM have demonstrated increased FA and decreased MD parameters in MS patients, with moderate correlations with clinical disability [27, 57]. The authors attributed these findings to axonal degeneration in focal lesions, but again the exact causes were uncertain.

DTI metrics, then, can be sensitive to structural damage in MS but lack specificity. Alternative strategies, such as $q$-space imaging (QSI) and DKI, have been proposed to overcome the limitations of DTI-derived indices [47, 58]. Such approaches are not restricted by the assumption of Gaussian diffusion, and have subsequently demonstrated increased sensitivity to pathological changes in NAWM compared to DTI [26, 59]. QSI and DKI are more demanding sequences though, requiring multiple high $b$-values and long scan times.
so their application clinically has been limited.

3.2.4 Connectivity

The network approach to modelling brain function in MS has generated great interest. On the mesoscopic (subnetwork) scale, many studies have explored alterations of specific functional networks in MS patients. The default mode network (DMN) in particular has received much focus owing to its intrinsic link to cognition [60], which is affected in 40-65% of MS patients [61]. DMN functional connectivity has therefore been linked to cognitive impairment [62–69], depression [64, 70] and fatigue [70, 71] in MS patients. Structural connectivity within the DMN has also shown sensitivity to MS pathology on an individual tract basis [72] as well as more generally across the subnetwork [68]. The motor network has also demonstrated disruption in MS, with correlations between reduced efficiency and increased motor disability [73].

Correlations between clinical disability and network properties at the macroscopic (whole network) level, such as reduced efficiency, increased path length and altered hub nodes in MS patients compared to HC subjects, have also been demonstrated [8, 74, 75].

Network-based approaches offer information complementary to specific microstructural tissue properties, such as how resilient network function is to injury; however, there is a degree of subjectivity in the results as the choice of cortex parcellation, tractography algorithm and edge weighting scheme are highly influential [76, 77].
Chapter 4

Subnetworks and the detection of subtle MS pathology

4.1 Introduction

The concept of subnetworks in the network model of the human brain is well established, both structurally and functionally. Subsets of nodes densely interconnected by white matter fibres are reported to establish structural hubs employed in multiple functional tasks [5], while structurally disjoint nodes are known to form subsets that perform functionally similar tasks [78, 79]. While many approaches to community detection in brain networks have been proposed, the decomposition of a network into clusters that are meaningful for a given study is non-trivial; consequently, graph theoretical analysis is typically performed across full networks or functionally-specific subnetworks. Both approaches may limit the sensitivity of derived graph properties to significant local changes, either by attenuating effects through the inclusion of unaffected nodes or by excluding relevant nodes because they do not all feature in the same task-specific network as defined by fMRI.

The abstract nature of graphs both aids and confounds the challenge of selecting salient nodes and edges. Networks constructed using different modalities for defining connectivity - such as white matter fibre pathways, correlations in functional activity, or even group-level correlations in cortical thickness - may be analysed in the same way, but the flexibility in this framework imposes no constraints on the chosen set of nodes and edges. It is therefore necessary to identify the set of nodes and edges that are pivotal to the mechanisms of a pathology in order for graph theoretical biomarkers to accurately reflect and predict disease severity.

Data-driven approaches can be used to select nodes based on a measure of their centrality in the network; in other words, nodes to which damage will have a disproportionate effect on the network as a whole. Rich-club networks and principal networks, for example,
both consist of highly influential nodes, but their selection criteria are inherently different. A consensus network (CN) consisting of nodes in both subnetworks would provide strong evidence of high nodal centrality irrespective of how influence is characterised, and could lead to the generation of a robust subnetwork sensitive to subtle pathology. The generation of CNs and their sensitivity to subtle multiple sclerosis (MS) pathology underpins the work here.

The chapter is divided into three sections. The selection of salient nodes is an interesting and critical problem that has received much attention; the first section therefore provides an overview of community detection algorithms that have been employed in brain connectivity analyses, with a more detailed discussion of principal networks and rich-clubs. An extension to the method of extracting principal networks - with the aim of providing a more robust approach to the nodal selection criteria - is proposed and implemented in R. In the second section, a data-driven CN of central nodes based on principal networks and rich-clubs is generated. Networks are derived using cortical thickness data from a cohort of healthy subjects, both of which are independent of the final sensitivity analysis to ensure that outcomes are not influenced by the initial subnetwork derivation. The third and final section performs a multi-level analysis of topological graph properties in healthy controls and MS patients using diffusion tractography data. Specifically, the sensitivity of network measures calculated across full brain, default mode, and consensus networks to pathological alterations is assessed through the ability to predict cognitive impairment in early relapsing-remitting (RRMS) patients. Connectivity in the default mode network (DMN) is known to be altered both functionally and structurally by MS [66, 68, 70, 72], so in comparing the CN against the DMN it may be possible to elucidate between any additional sensitivity gained from the identification of a set of influential nodes and the use of subnetworks more generally.

### 4.2 Community detection in brain networks

Many community detection algorithms used in connectomics are based on modularity maximisation [51, 80, 81]. A graph arbitrarily partitioned into $k$ non-overlapping clusters is considered to have high modularity if the identified communities are more densely interconnected than in a comparable random graph (Section 2.8.5. Various systematic approaches to maximising the modularity of the partitions have been proposed, but are largely heuristic [82]. As such, an exhaustive search of all possible partitions is intractable and so only
approximations of the near-optimal partitions are possible. Moreover, the number of near-optimal partitions grows exponentially with network size, meaning that the true solution can become impossible to distinguish if the partitions are structurally dissimilar. Modularity optimisation also has a resolution limit determined by the size of the original graph: clusters that are small relative to the graph may not be detected [50].

Hierarchical clustering assumes multiple levels of clustering within a graph - that is, clusters within clusters - where communities are identified based on some chosen measure of similarity between nodes. Clustered nodes are not necessarily connected. Agglomerative algorithms form iteratively larger clusters in which clusters are merged based on their mutual similarity; conversely, divisive algorithms iteratively split clusters by removing nodes with low similarity. It is unclear, then, at what level the partitions best represent the modular structure of the graph. Despite this, hierarchical clustering has been utilised in some studies, demonstrating, for example, changes in the modularity of fMRI connectivity during non-rapid eye movement sleep [83, 84].

Partitional clustering assigns each node a point in space and a distance measure, with the objective of grouping nodes such that a cost function based on distances between the points and a set of centroids is minimised; \(k\)-means clustering is an example of a partitional clustering algorithm. However, the number of clusters (centroids) present in the graph must be predetermined.

Spectral clustering refers to any technique that partitions a graph using the eigenvectors of some matrix representation, typically the Laplacian matrix (Section 2.8.3). Such algorithms have not been widely adopted in connectomics, although some studies have used the method to obtain parcellations in fMRI data [85, 86].

Finally, machine learning algorithms are emerging for graph partitioning purposes, and have demonstrated potential for extracting reliable subnetworks that can discriminate between populations [87].

Evidently there are several approaches for identifying important nodes and subnetworks. Ultimately, though, these methods tend to offer disjoint partitions with no indication of the relative importance of the derived subnetworks.

4.2.1 Rich-club analysis
Subnetworks created from hub nodes (Section 2.8.6) can be considered influential within the original network. Hubs play a central role in network architecture as they exhibit high
degree properties, which are important for overall network integration; subsequently, local
damage to a hub node may have a disproportionate effect on network resilience to injury.
The ‘rich-club’ phenomenon proposes a description in which hub nodes are densely in-
terconnected with fewer connections to lower degree nodes. The regions that form these
rich-clubs can be classified as a subnetwork, offering high communication efficiency and
some level of network resilience to the failure of a hub node [5]. A rich-club is therefore
defined as a set of hubs that are more interconnected than expected given a comparable
random graph.

For a given degree level \( k \), an induced subgraph containing the \( n' \) nodes connected by
a number of edges greater than \( k \) is created. The rich-club coefficient \( \phi (k) \) of this subgraph
is computed as the proportion of edges remaining, \( m' \), out of all possible connections (Eq.
4.1) [5].

\[
\phi (k) = \frac{2m'}{n'(n' - 1)}
\]  

(4.1)

For the equivalent weighted rich-club coefficient, \( \phi^w (k) \), a vector containing all edges in the
full graph ranked by their weight is first constructed (\( w^{\text{ranked}} \)). The collective weight of the
\( m' \) edges in the induced subgraph is then computed, along with the weight of the strongest
\( m' \) edges in the full network (Eq. 4.2).

\[
\phi^w (k) = \frac{\sum_{l=1}^{m'} w'_l}{\sum_{l=1}^{m'} w'^{\text{ranked}}_l}
\]  

(4.2)

Owing to the fact that higher degree nodes have a greater probability of being intercon-
connected than lower degree nodes, rich-club coefficients must be normalised relative to a set
of comparable random networks (Eq. 4.3). Practically, the set of random graphs at each
degree level is generated by randomly reorganising the connections of the subgraph while
maintaining the degree distribution [88].

\[
\phi_{\text{norm}} (k) = \frac{\phi (k)}{\phi_{\text{random}} (k)}
\]  

(4.3)

Here, \( \phi_{\text{random}} (k) \) is the average rich-club coefficient of \( N \) randomised networks. For brevity,
\( \phi_{\text{norm}} (k) \) and \( \phi_{\text{norm}}^w (k) \) will be referred to as \( \phi (k) \) and \( \phi^w (k) \) from here on.

To fully identify rich-club behaviour, then, it must be observed that \( \phi_{\text{norm}} > 1 \) and
increases over a range of \( k \).

4.2.2 Principal network analysis

Principal network analysis (PNA), a spectral clustering technique, was recently introduced
as an alternative graph partitioning method that identifies influential subnetworks [89].
4.2. Community detection in brain networks

Eigendecomposition of the association matrix extracts ‘principal networks’ (PN), composed of nodes with similar connectivity patterns, that can be ranked in terms of their importance in the original network. Nodes may feature in multiple subnetworks and can be rated within each subnetwork based on their degree of influence. The eigendecomposition of an association matrix $\mathbf{A}$ into its canonical form is given in Eq. 4.4.

$$\mathbf{A} = \mathbf{Q}\boldsymbol{\Lambda}\mathbf{Q}^{-1}$$  

(4.4)

For a square $n \times n$ association matrix, whose elements $A_{ij}$ quantify some measure of connectivity between regions $i$ and $j$, the eigenvalues are given by the diagonal matrix $\boldsymbol{\Lambda}$ and the $n$ eigenvectors are contained in the columns of $\mathbf{Q}$. The eigenvalue magnitude $\lambda_k$ signifies the influence of component $k$ in $\mathbf{A}$; in other words it is a measure of the importance of subnetwork $k$ in the original network $\mathbf{A}$. To form a subnetwork, or principal network, partial association matrices are computed for all components by setting all but the relevant eigenvalue to zero.

$$\tilde{\mathbf{A}}_k^{ij} = \lambda_k Q_{ik} Q_{jk}; \quad \mathbf{A} = \sum_k \tilde{\mathbf{A}}^k$$  

(4.5)

The eigenvector element $Q_{ik}$, or loading, represents the influence of node $i$ on the $k$th PN; a threshold applied to each eigenvector element $Q_{ik}$ may therefore differentiate the nodes to retain within a given subnetwork. In the original method, thresholds were set at $|Q_{ik}| > 0.1$.

**Extension of principal network analysis**

A more rigorous approach to node retention was developed here using bootstrap confidence intervals and implemented in R; in a Monte Carlo simulation study, this technique demonstrated greater reliability than eigenvalue thresholds for retaining significant loadings [90]. Bootstrapping, by design, requires data from a sample population, so the extension is only applicable to group-based networks. This could include group-wise average networks based on diffusion data or networks derived from correlations in cortical thickness.

The procedure is as follows. Given an association matrix $\mathbf{A}$ derived from the connectivity information of $N_s$ subjects, $N_b$ bootstrapped association matrices $\mathbf{A}'$ are created by sampling the subjects with replacement. PNA performed on the original association matrix and on the bootstrapped samples produces the original loadings $\mathbf{Q}$ and the set of $N_b$ bootstrapped loading matrices $\mathbf{Q}'$ respectively. Retention of node $i$ in principal network $j$ is then based on confidence intervals obtained from the distribution of bootstrapped loading matrices: if the 95% confidence interval does not span zero then the loading magnitude $|Q_{ij}|$ can be considered significantly non-zero and the node is retained.
4.3 Defining consensus networks

This section describes the generation of the CN. Firstly, rich-club analysis (RCA) and the modified PNA method were used to identify influential subnetworks; correlations in the cortical thickness measurements of healthy controls (HC) were used as the underlying connectivity data. A CN was then derived using nodes in the intersection of the rich-club and principal networks. The resulting rich-club, principal and consensus networks were evaluated in terms of order, size, laterality and edge weight attributes to discern key shared characteristics of the participating nodes.

As the final aim was to analyse the topology of this CN in relapsing-remitting multiple sclerosis (RRMS) patients using diffusion tractography connectivity graphs (Section 4.4), it is perhaps pertinent to consider here whether correlations in cortical thickness should ultimately reveal nodes that are central to white matter structural connectivity. While the relationship is not naturally obvious, convergence between cortical thickness correlations and diffusion tractography have been reported [91]. Moreover, graph topology in cortical thickness covariance networks has demonstrated alterations in MS [92] as well as other neurological disorders such as depression [93] and synaesthesia [94]. A cortical thickness correlation network was also convenient in this instance as it provided another degree of separation (in addition to different cohorts) between the derived CN and its application to detect pathological alterations in the diffusion tractography networks of MS patients.

4.3.1 Methods

Participants

Data from 46 HCs (26 females; mean age 34.0 ± 8.6 years) were analysed; all subjects were recruited at the Queen Square MS Centre, UCL, and written informed consent was obtained. Handedness was available for 26 subjects; of these, 22 were right-handed.

Image acquisition and pre-processing

A 3D $T_1$-weighted fast field echo (FFE) image was acquired for each participant on a 3T MR system (Philips Healthcare, Best, Netherlands) using a 32-channel head coil, with TR/TE = 6.9/3.1 ms, inversion time $TI = 824$ ms and resolution $1 \times 1 \times 1$ mm$^3$. The images were parcellated into $n = 98$ structurally-defined sub-regions using NiftyWeb’s geodesical information flows (GIF) algorithm [95]. For brevity, nodes will generally be referred to by number; a full list of correspondences between node number and anatomical region is provided in Table 4.1. Cortical thickness measurements were obtained using the GIF GM
### 4.3. Defining consensus networks

<table>
<thead>
<tr>
<th>Region</th>
<th>Index (right)</th>
<th>Index (left)</th>
</tr>
</thead>
<tbody>
<tr>
<td>anterior cingulate gyrus</td>
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<td>2</td>
</tr>
<tr>
<td>anterior insula</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>anterior orbitofrontal cortex</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>angular gyrus</td>
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<td>8</td>
</tr>
<tr>
<td>calcarine cortex</td>
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<td>10</td>
</tr>
<tr>
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<td>12</td>
</tr>
<tr>
<td>cuneus</td>
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<td>14</td>
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<tr>
<td>entorhinal cortex</td>
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<td>16</td>
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<tr>
<td>frontal operculum</td>
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<tr>
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</tr>
<tr>
<td>fusiform gyrus</td>
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<td>22</td>
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<td>24</td>
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<tr>
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<tr>
<td>inferior temporal gyrus</td>
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<td>28</td>
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<tr>
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<td>32</td>
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<tr>
<td>middle cingulate gyrus</td>
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<td>middle occipital gyrus</td>
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<tr>
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<td>82</td>
</tr>
<tr>
<td>supplementary motor cortex</td>
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<td>84</td>
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<tr>
<td>supramarginal gyrus</td>
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<tr>
<td>superior occipital gyrus</td>
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</tr>
<tr>
<td>inferior frontal gyrus pars triangularis</td>
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</tr>
<tr>
<td>transverse temporal gyrus</td>
<td>97</td>
<td>98</td>
</tr>
</tbody>
</table>

**Table 4.1. Full brain network nodes.** Correspondences between node number and anatomical region.
mask and the pipeline described in [96].

Cross-subject correlations between regional cortical thickness were used to define a structural connectivity network; edge weights were therefore the Pearson correlation coefficient between regions. Edges were thresholded at 0.2 (absolute value).

**Network construction**

Normalised weighted rich-club coefficients $\phi^w(k)$ were generated over the degree range $1 < k < k_{\text{max}}$, where $k_{\text{max}}$ was the maximum nodal degree in the cortical thickness correlation network. Normalisation was performed using the rich-club coefficient averaged over $N = 1000$ randomly generated networks [88]. The rich club subnetwork (RCN) was defined from the nodes that formed the most selective rich-club (greatest possible degree threshold) within the rich-club regime, defined by the range of $k$ in which $\phi^w(k) > 1$ and was increasing.

Using the extended bootstrap ($N_b = 1000$) method to select significant loadings, PNA was used to derive the top three PNs; these will be denoted PN$_1$, PN$_2$ and PN$_3$ respectively. By definition, PN$_1$ extracts the nodes with the greatest internal connectivity [89], so the inclusion of PN$_2$ and PN$_3$ should additionally capture important but more subtle connectivity characteristics. Using the nodes in the top three PNs, a combined network, PN$_c$, was also created.

**4.3.2 Results**

**Graph topology of rich-club and principal networks**

Example data showing the cortical parcellation is given in Fig. 4.1; the full association matrix derived from cortical thickness correlations in the 46 HCs is shown in Fig. 4.2. Moderate to strong positive correlations dominate the network. Graphical representations of the RCN and PNs are provided in Fig. 4.3; Table 4.2 provides an overview of subnetwork topologies, including order and edge density.

The RCN identified in this cohort was relatively inclusive, with 66 nodes retained. Edges were primarily weighted by moderately positive correlations (Fig. 4.3e). No obvious bias was evident in the anatomical distribution of nodes towards one region or hemisphere: each hemisphere featured 33 nodes and there were 25 bilateral pairs.

The first PN - that is PN$_1$ - retained only positive edges, and was the largest of the three with 30 nodes (Fig. 4.3a). The laterality of PN$_1$ was strongly weighted towards the left hemisphere (21 nodes), and only 7 bilateral pairs were present.
4.3. Defining consensus networks

Figure 4.1. Cortical parcellation. Each cortical region is labelled using a unique colour.

Figure 4.2. Full structural network. Edge weights represent Pearson’s correlation coefficient between regional cortical thicknesses in a cohort of 46 HCs; the network is thresholded at $|R| = 0.2$.

Table 4.2. Network properties. Characteristics for the full brain network (FBN), rich-club network (RCN) and principal networks (PN) are provided; PN$_c$ represents the network of edges and nodes that feature in the top three PNs.
Figure 4.3. Anatomical arrangement of subnetworks. Edge weights represent Pearson’s correlation coefficient between regional cortical thickness measurements. a-c. The first 3 principal networks, PN\textsubscript{1}, PN\textsubscript{2} and PN\textsubscript{3} respectively. d. The combined principal network, PN\textsubscript{c}. e. The rich-club network. f. The consensus network, defined as the intersection between the RCN and PN\textsubscript{c}. 

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The laterality of PN\textsubscript{2} was, conversely, heavily biased towards the right hemisphere: 11 of the 14 nodes were right hemisphere regions. The structure of PN\textsubscript{2} was notably defined by two anatomically distinct clusters located anteriorally and posteriorally (Fig. 4.3b). Intra-cluster connectivity was characterised by positively weighted edges while inter-cluster edges were negatively weighted.

PN\textsubscript{3} was the smallest PN with just 9 nodes, and was also dominated by right hemisphere regions (6 nodes) (Fig. 4.3c). Anatomically distinct clusters were again apparent, with one posterior cluster and one central. Intra- and inter-cluster connectivity showed patterns similar to those observed in PN\textsubscript{2}: edges within clusters were primarily positively weighted, and edges between clusters were negatively weighted.

Considered together, the spatial distribution of nodes in the top three PNs was balanced, with 24 and 26 nodes in the right- and left-hemispheres respectively (Fig. 4.3d). However, only a modest number of bilateral pairs - that is 16 - were observed. There was minimal correspondence between the different PNs: only 3 nodes appeared in more than 1 PN.

**Graph topology of the consensus network**

Nodes in the intersection between the RCN and PNs - and so forming the CN - are presented in Fig. 4.3f and Table 4.3. Notably, every node in PN\textsubscript{1} also featured in the RCN; this proportion decreased to 86% in PN\textsubscript{2} and 66% in PN\textsubscript{3}. Combined, 68% of all PN nodes belonged to the RCN. The laterality of the CN was relatively even, with 21 and 24 nodes in the right- and left-hemispheres respectively.

It was observed that nodes of the DMN featured heavily in the CN: of the 45 nodes, 25 belonged to the DMN. This is highlighted in Table 4.3. The remaining regions were primarily located in the sensory-motor cortex, including the temporal lobes, postcentral gyrus and precentral gyrus.

**4.3.3 Discussion**

In any given study it is reasonable to assume that a subnetwork will be of more relevance than the full network, but community detection in brain networks is a complex task and it is difficult to establish important subnetworks. The graph partitioning approaches utilised in this section can be beneficial in several ways: (i) subnetworks can be derived based on some measure of node centrality; (ii) subnetworks and nodes within the subnetworks can be ranked according to their relative influence; (iii) partitions need not be disjoint. As node
### Table 4.3. Anatomical regions of the consensus network.

Regions belonging to the DMN are highlighted in grey.

<table>
<thead>
<tr>
<th>Region name</th>
<th>Index (right)</th>
<th>Index (left)</th>
</tr>
</thead>
<tbody>
<tr>
<td>anterior cingulate gyrus</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>anterior orbitofrontal cortex</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>angular gyrus</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>central operculum</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>frontal operculum</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>gyrus rectus</td>
<td>-</td>
<td>24</td>
</tr>
<tr>
<td>inferior occipital gyrus</td>
<td>-</td>
<td>26</td>
</tr>
<tr>
<td>inferior temporal gyrus</td>
<td>-</td>
<td>28</td>
</tr>
<tr>
<td>medial orbitofrontal gyrus</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>medial precentral gyrus</td>
<td>-</td>
<td>46</td>
</tr>
<tr>
<td>medial superior frontal gyrus</td>
<td>-</td>
<td>48</td>
</tr>
<tr>
<td>middle temporal gyrus</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>precuneus</td>
<td>-</td>
<td>62</td>
</tr>
<tr>
<td>parietal operculum</td>
<td>-</td>
<td>68</td>
</tr>
<tr>
<td>postcentral gyrus</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>planum polare</td>
<td>-</td>
<td>74</td>
</tr>
<tr>
<td>precentral gyrus</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>supplementary motor cortex</td>
<td>-</td>
<td>84</td>
</tr>
<tr>
<td>supramarginal gyrus</td>
<td>-</td>
<td>86</td>
</tr>
<tr>
<td>superior parietal lobule</td>
<td>-</td>
<td>90</td>
</tr>
<tr>
<td>temporal pole</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>inferior frontal gyrus pars triangularis</td>
<td>95</td>
<td>-</td>
</tr>
<tr>
<td>transverse temporal gyrus</td>
<td>-</td>
<td>98</td>
</tr>
<tr>
<td>calcarine cortex</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>cuneus</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>frontal pole</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>gyrus rectus</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>inferior occipital gyrus</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>lingual gyrus</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>middle frontal gyrus</td>
<td>37</td>
<td>-</td>
</tr>
<tr>
<td>medial orbitofrontal gyrus</td>
<td>41</td>
<td>-</td>
</tr>
<tr>
<td>superior frontal gyrus</td>
<td>81</td>
<td>82</td>
</tr>
<tr>
<td>superior occipital gyrus</td>
<td>87</td>
<td>-</td>
</tr>
<tr>
<td>entorhinal cortex</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>middle occipital gyrus</td>
<td>39</td>
<td>-</td>
</tr>
<tr>
<td>parahippocampal gyrus</td>
<td>63</td>
<td>-</td>
</tr>
<tr>
<td>superior occipital gyrus</td>
<td>87</td>
<td>-</td>
</tr>
<tr>
<td>superior parietal lobule</td>
<td>89</td>
<td>90</td>
</tr>
</tbody>
</table>
centrality can be defined in a number of ways, a CN defined as the intersection between two independent methods provides an opportunity to further refine the set of nodes that are critical to overall network function, irrespective of the measure of influence.

The CN derived in this section featured nodes prominent in the DMN and sensory-motor cortex. As these are regions that have independently demonstrated disrupted connectivity in MS [68, 71–73] there is good potential for this subnetwork to offer increased sensitivity to subtle pathological damage; this is explored in the next experiment (Section 4.4).

The following discussion considers the graph topology of the derived subnetworks and the potential relevance of participating nodes.

Laterality
A strong laterality bias was observed in all PNs, but was absent in the RCN. This is likely related to the inherent behaviour of PNA to decompose the data into clusters of densely interconnected nodes. As such, cortical thickness correlations between regions in the dominant hemisphere of this primarily right-handed cohort could account for the greatest variance in the data, and would therefore drive the left hemisphere bias in PN\(_1\). Such biases are not present in the identification of hub regions in RCA; however, the participation of 100\% of PN\(_1\) nodes in the RCN suggests that PNA and RCA at least partially capture the same variability in the data - that is, hub nodes that are densely interconnected with few connections to outside regions. It would be interesting to establish whether biases in the PNs are preserved in either a cohort of left-handed subjects or in a cohort with matched handedness.

Spatially-distinct communities
The clustering of nodes into two anatomically distinct communities in PN\(_1\) and PN\(_2\) was an unexpected and intriguing feature, in particular owing to the positive edge weights within clusters and negative edges between clusters. In the context of regional cortical thickness correlations across subjects, this implies a positive association of thickness within clusters and an inverse association between clusters.

In PN\(_2\), the anterior cluster contained regions of the frontal pole and the posterior cluster featured regions in the visual cortex, suggesting the existence of an opposing interplay between high-order cognitive functions - such as decision making and emotional expression [97–100] - and visual processing. This finding has also been observed in a recent fMRI study [101].
The posterior cluster of PN\textsubscript{3} similarly contained regions in the visual cortex while the central cluster contained parahippocampal regions associated with memory [102–105], once more suggesting a trade-off between visual processing and high-order cognitive function. This subtle but important variability captured by the lower PNs validates their role in the derivation of a CN in addition to PN\textsubscript{1}.

**Consensus network**

The CN was largely dominated by nodes of the DMN - substantiating their importance to overall network function - with nodes of the sensory-motor cortex also featuring heavily. Both the DMN and sensory-motor cortex have consistently demonstrated disrupted connectivity in MS [8, 92, 106–108], but are typically analysed as functionally separate systems. Graph theoretical analysis of this subnetwork of central nodes spanning the DMN and sensory-motor cortex therefore has promising potential to improve the characterisation of pathology in MS patients.

**Limitations**

In both RCA and PNA, a decision is required on how to define the inclusion criteria for nodes. The bootstrapped eigenvector confidence intervals implemented here in the PNA method should provide more meaningful PNs in comparison to eigenvector thresholding, as it is not implicit in the magnitude of a loading whether it is truly non-zero; however, the width of the confidence interval still influences which nodes are retained. In RCA it is the degree threshold applied that affects the subnetwork size: by construction a higher threshold produces smaller rich-clubs. In this work the most exclusive rich-club was selected, but this still generated a rich-club containing 66 nodes. The intersection between RC and PN nodes was thus largely driven by the size of the RCN. An evaluation of the subnetworks generated over a range of degree thresholds within the rich-club regime would be valuable future work, but was out of the scope of this work.

A further issue is the threshold applied to the original correlation matrix: owing to the large number of multiple comparisons it is necessary to remove insignificant correlations. There are several approaches to correcting correlation networks, and both the absolute threshold used here and a threshold based on corrected \( p \)-values have precedent [89, 109]. The applied threshold will inevitably affect the absolute value of any graph property calculated on the resulting network, but, despite this, measures such as small-worldness have demonstrated insensitivity to the choice of threshold [109].
4.4 Topological alterations of brain networks in multiple sclerosis

A multi-level analysis of graph topology in full brain, default mode and consensus networks was performed in a cohort of HCs and RRMS patients using diffusion tractography data. Global and mean local efficiency, characteristic path length and mean clustering coefficient were evaluated to provide an overall indication of network integrity. Node strength was assessed to establish the regions most affected by pathology within the networks: as these regions may be pivotal in disease mechanisms, their identification is important. Individual edges were not analysed as the state of the overall network was considered more important than the integrity of specific connections; however, general trends in edge weight behaviour were examined.

The ability of graph properties to predict clinical disability in RRMS patients was then explored in each network. Cognitive ability was quantified using the symbol digit modalities test (SDMT) and motor skills were scored using the expanded disability status scale (EDSS).

4.4.1 Methods

Participants

Data from 27 HCs and 33 RRMS patients were analysed. All subjects were recruited at the Queen Square MS Centre, UCL, and written informed consent was obtained from each participant. Demographic and clinical data are given in Table 4.4.

Image acquisition and pre-processing

Images were acquired on the same 3T MRI system specified in Section 4.3.1. All participants underwent a cardiac-gated SE EPI sequence with TR/TE = 24000/68 ms, resolution $2 \times 2 \times 2$ and high angular resolution diffusion weighting in 61 volumes with $b = 1200$ s/mm$^2$; an additional 7 volumes were acquired with $b = 0$. The same 3D $T_1$

<table>
<thead>
<tr>
<th></th>
<th>HC subjects</th>
<th>RRMS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>($n = 27$)</td>
<td>($n = 33$)</td>
</tr>
<tr>
<td>Mean (SD) age [years]</td>
<td>37.0 (11.8)</td>
<td>40.2 (10.0)</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>11/16</td>
<td>9/24</td>
</tr>
<tr>
<td>Median (range) EDSS score</td>
<td>-</td>
<td>2.0 (1-6.5)</td>
</tr>
<tr>
<td>Mean (SD) SMDT†</td>
<td>-</td>
<td>54.6 (13.2)</td>
</tr>
</tbody>
</table>

Table 4.4. Demographic and clinical subject data. †SDMT scores only available for 20 patients.
weighted FFE sequence described in Section 4.3.1 was also acquired for each subject.

DWI were corrected for eddy current distortion using FSL [110] and for motion and susceptibility distortion using BrainSuite [111]. The DT model was fitted to each DWI using FSL’s *dtifit* to generate maps of FA and MD; estimates of fibre orientations were obtained by fitting the ball-and-sticks model to the data (FSL’s *bedpostx*; [112]) with a maximum of 3 fibres modelled per voxel. The $T_1$-weighted images were registered to the distortion-corrected DWI using BrainSuite, then parcellated into $n = 98$ structurally-defined sub-regions using NiftyWeb GIF (Fig. 4.4a).

A probability map of DMN regions was obtained in standard MNI (Montreal Institute of Neurology) space from published data [113] and thresholded at $Z = 3$ as recommended. The map was registered to each subject’s DWI in native space by registering the MNI $T_1$-weighted average brain atlas with 2mm resolution to the $T_1$-weighted image in DWI space and using this transform to propagate the DMN mask (NiftyReg; [114]) (Figure 4.4b).

**Full brain network construction**

Streamlines originating from WM voxels and terminating in GM voxels were generated using probabilistic tractography (FSL’s *probtrackx*; [112]) with 1000 seeds per WM voxel. Weighted association matrices were created for each subject using TractoR (Tractography with R; [115]), with edge weights defined as the mean tract FA. Group-wise average full brain networks (FBN) for HC and RRMS cohorts were constructed for statistical analysis. Missing tracts were replaced with 0.

Nodes are once again referred to by number for brevity; correspondences between node number and anatomical region name are consistent with Section 4.3 (Table 4.1).

**Default mode network construction**

The DMN masks in native space were dilated once using a $3 \times 3 \times 3$ box kernel so that they extended into WM (Figure 4.4b). Target regions were defined as the intersection between the GM and dilated DMN masks (Figure 4.4d). Small target regions (< 10 voxels) were removed. The intersection between the target regions (dilated once to extend into WM), WM tissue and dilated DMN mask determined the seed regions (Figure 4.4c).

Owing to the reduced number of seed voxels relative to whole brain tractography, a streamline sensitivity analysis was performed to find the minimum number of seeds for which the edge density of the resulting graph was stable: below a certain threshold the edge density increases with the number of seeds. Based on the outcome of these validation
4.4. Topological alterations of brain networks in multiple sclerosis

**Figure 4.4. Image pre-processing.**

- **a.** Parcellated $T_1$
- **b.** DMN mask
- **c.** Seed regions
- **d.** Target regions

**Figure 4.4. Image pre-processing.**

- **a.** Anatomical $T_1$ parcellation.
- **b.** DMN mask registered to the subject’s native space.
- **c-d.** Seed and target regions used for tractography between DMN regions.

<table>
<thead>
<tr>
<th>Region</th>
<th>Index (right)</th>
<th>Index (left)</th>
</tr>
</thead>
<tbody>
<tr>
<td>anterior cingulate gyrus</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>angular gyrus</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>calcarine cortex</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>cuneus</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>frontal pole</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>gyrus rectus</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>inferior occipital gyrus</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>lingual gyrus</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>middle cingulate gyrus</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>medial frontal cortex</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>middle frontal gyrus</td>
<td>37</td>
<td>-</td>
</tr>
<tr>
<td>middle occipital gyrus</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>medial postcentral gyrus</td>
<td>-</td>
<td>44</td>
</tr>
<tr>
<td>medial superior frontal gyrus</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>middle temporal gyrus</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>posterior cingulate gyrus</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td>precuneus</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>planum temporale</td>
<td>77</td>
<td>-</td>
</tr>
<tr>
<td>superior frontal gyrus</td>
<td>81</td>
<td>82</td>
</tr>
<tr>
<td>supramarginal gyrus</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td>superior occipital gyrus</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>superior parietal lobule</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>superior temporal gyrus</td>
<td>91</td>
<td>92</td>
</tr>
</tbody>
</table>

**Table 4.5. Default mode network nodes.** Correspondences between node number and anatomical region.
experiments (results not shown), probabilistic tractography was run using 5000 streamlines per seed voxel.

As with the FBN, individual weighted association matrices were generated using mean tract FA as edge weights. The anatomical regions corresponding to the 43 nodes in this subnetwork are indicated in Table 4.5. Note that nodes may represent partial anatomical regions owing to the method of generating the seed regions. Group-wise average networks were again constructed for HC and RRMS cohorts.

**Consensus network construction**

A subgraph induced from the FBN by the nodes in the CN was created for each subject. Edges were weighted using the mean tract FA, and average group-wise graphs were constructed for HC and RRMS subjects.

**4.4.2 Statistical analyses**

**Topological network alterations between HC and RRMS**

Global efficiency, local efficiency, characteristic path length, mean clustering coefficient and nodal strength were calculated for each average graph and compared between groups using TractoR. Group-wise average networks were used to evaluate topological alterations between groups to ensure that graph properties were calculated on comparable graphs - that is, graphs with the same set of nodes and edges. This was particularly relevant for the more sparse DMN networks, for which an averaging approach should reduce the influence of false-positive or false-negative tracts that may otherwise dominate.

The statistical significance of inter-group differences was obtained using non-parametric permutation testing. Group labels (‘HC’ or ‘RRMS’) were randomly reassigned to subjects to build 1000 permuted group-wise average graphs (preserving initial group sizes) and the null distributions of group-wise mean edge weights, node strengths and graph properties. In an approach akin to obtaining confidence intervals, *p*-values for the original group differences were calculated using their quantile within the null distribution. A false discovery rate (FDR) correction was applied to all *p*-values to account for multiple comparisons; edge weights, node strengths and global graph properties were treated as separate families.

**Network properties as a marker for clinical disability**

As global efficiency best captures overall network integration, this metric was computed for individual patients in the FBN, DMN and CN and correlated with SDMT and EDSS scores.
using Pearson’s correlation coefficient. Global efficiency was also evaluated over just the set of nodes with significantly altered strength between groups and correlated with disability scores. SDMT scores were adjusted for IQ, fatigue and education level. No effects from age and gender were observed in the clinical scores. Significance was set at $p < 0.05$. All statistical analysis was performed in R [116].

### 4.4.3 Results

Example data in Fig. 4.5 shows the principle fibre directions obtained from DTI and used for the tractography.

**Global graph properties**

Global graph properties of the FBN, DMN and CN are summarised in Table 4.6. Global efficiency, mean local efficiency and mean edge weight were decreased while mean shortest path was increased in the FBN of RRMS patients ($p < 0.05$, FDR-corrected).

In the DMN, although a trend towards decreased efficiency and increased path length was observed in patients, global network organisation was not significantly altered between groups.

In the CN, global efficiency and mean local efficiency were significantly reduced and characteristic path length was significantly increased in patients ($p < 0.01$, FDR-corrected). Trends towards decreased mean edge weight (FA) and clustering coefficient in patients were detected in the DMN and CN, but did not reach significance.

![Figure 4.5. Principle fibre directions.](image)

Red indicates fibres are oriented left-right, green indicates anterior-posterior and blue indicates superior-inferior.
<table>
<thead>
<tr>
<th></th>
<th>Full brain network</th>
<th>Default mode network</th>
<th>Consensus network</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC</td>
<td>RRMS</td>
<td>p</td>
</tr>
<tr>
<td>Order</td>
<td>98</td>
<td>98</td>
<td>-</td>
</tr>
<tr>
<td>Size</td>
<td>4800</td>
<td>4836</td>
<td>-</td>
</tr>
<tr>
<td>Edge density (%)</td>
<td>99</td>
<td>99</td>
<td>-</td>
</tr>
<tr>
<td>Mean edge weight (FA)</td>
<td>0.34</td>
<td>0.32</td>
<td>0.39*</td>
</tr>
<tr>
<td>Global efficiency</td>
<td>0.37</td>
<td>0.35</td>
<td>0.008**</td>
</tr>
<tr>
<td>Mean local efficiency</td>
<td>0.37</td>
<td>0.35</td>
<td>0.008**</td>
</tr>
<tr>
<td>Mean shortest path (steps)</td>
<td>2.91</td>
<td>3.09</td>
<td>0.012*</td>
</tr>
<tr>
<td>Mean clustering coefficient</td>
<td>0.32</td>
<td>0.30</td>
<td>0.062</td>
</tr>
</tbody>
</table>

Table 4.6. Group comparison of global graph properties. Properties are calculated over the group-wise average FA-weighted networks for HC and RRMS subjects.

Mean edge weights are lower than may be expected given the FA of WM owing to the inclusion of absent tracts as 0’s during the averaging operation.

* $p < 0.05$, FDR-corrected.

** $p < 0.01$, FDR-corrected.
4.4. Topological alterations of brain networks in multiple sclerosis

Node strength

Node strength differences between groups are represented graphically in Fig. 4.6. Twenty-eight nodes (out of 98) in the FBN demonstrated reduced strength in patients \((p < 0.05, \text{ FDR-corrected})\); no strength increases were observed in patients (Fig. 4.6a). Of the 28 altered nodes, 19 corresponded to core regions of the DMN, including the precuneus, posterior cingulate gyrus and angular gyrus.

Analysis of nodal strength within the DMN alone, however, revealed reductions in patients in just 5 of the 43 nodes and an increase in 1 node \((p < 0.05, \text{ FDR-corrected})\). With the exception of the planum temporale (which, incidentally, showed the increase in centrality in patients), all nodes with reduced strength in patients in the DMN also showed significantly lower strength in the FBN (Fig. 4.6c).

Reduced strength was observed in 12 nodes (out of 45) in the CN (Fig. 4.6f), while 1 node showed increased strength in patients \((p < 0.01, \text{ FDR-corrected})\). Of the nodes with significantly altered strength properties, approximately half (6) belonged to the DMN.

Global efficiency as a predictor of clinical disability

Decreased global efficiency was correlated with worse cognitive ability in the FBN \((R^2 = 0.40, p = 0.003)\) and in the subgraph induced on the FBN by the set of altered nodes \((R^2 = 0.39, p = 0.003)\) (Figs. 4.7a and 4.7b). No correlations were observed between global efficiency in the DMN and cognitive scores (Figs. 4.7c and 4.7d). Global efficiency in the subject-specific CNs was most highly correlated with SDMT scores \((R^2 = 0.43, p = 0.002)\) (Fig. 4.7e); significant associations were also observed when global efficiency across the altered nodes alone was considered \((R^2 = 0.35, p = 0.006)\) (Fig. 4.7f).

No correlations with the EDSS score were observed.

4.4.4 Discussion

A multi-level analysis of network topology in RRMS patients revealed disruptions on both global (network) and local (nodal) scales. Global efficiency in the CN - defined using highly central nodes - provided the best correlation with SDMT scores, indicating a greater ability to capture subtle pathological damage than FBNs. This finding demonstrates that the inclusion of unaffected nodes in a FBN analysis can attenuate the effects of localised damage, and highlights both the relevance and importance of selecting salient subnetworks when performing a graph theoretical analysis of brain connectivity.

The impact of subnetwork selection was also highlighted in the negative findings asso-
Chapter 4. Subnetworks and the detection of subtle MS pathology

Figure 4.6. Group comparison of nodal strength in each network and sub-network. a,c,e. Complete node sets for the full brain, default mode and consensus networks (FBN, DMN and CN respectively). b,d,f. Only nodes with significant strength differences between groups are shown. Nodes with significantly reduced strength ($p < 0.05$, FDR-corrected) in MS patients are shown in red; blue indicates increased strength in patients. Only edges with significant weight differences (i.e. FA) between groups ($p < 0.05$, FDR-corrected) are shown for brevity.
4.4. Topological alterations of brain networks in multiple sclerosis

Figure 4.7. Global efficiency as a predictor of clinical disability. Patient-specific global efficiency scores in each network and subnetwork are correlated with SDMT scores. Correlation coefficients and their statistical significance are indicated in each plot.
associated with the DMN. Given that over two-thirds of nodes with significantly altered strength in the FBN belonged to the DMN, this was a surprising result. Two possible conclusions can be drawn here: (i) nodes and edges of the DMN in isolation were not altered enough to generate significant inter-group differences in global graph properties; (ii) the result was an artefact of the processing pipeline. A post-hoc analysis was therefore conducted to investigate the effect of running tractography between specific DMN regions (which may then include full or partial regions depending on the intersection between DMN and GM masks), as opposed taking the subgraph induced from the FBN by full GM regions associated with the DMN (even if only partially intersecting the DMN mask). These results are presented and discussed in the next section, prior to discussion of the primary results.

**Post-hoc analysis of structural DMN construction**

As with the CN, a subgraph induced from the FBN by the nodes in the DMN was created for each subject, with edges weighted by mean tract FA. Note that the node set is the same as in the original DMN. Average group-wise graphs were again utilised to explore differences in global network properties. Significant differences in the strength of 27 out of 43 nodes were observed between groups (Fig. 4.8a); this is in stark contrast to the 6 nodes reported for the original DMN. Global efficiency across subject-specific DMN nodes in this instance

![Figure 4.8. DMN† obtained from full brain tractography. In a post-hoc analysis the DMN was derived from full brain tractography. a. The anatomical configuration of nodes (note this is the same as in the original DMN illustrated in Fig. 4.6c). Nodes with significantly reduced strength ($p < 0.05$, FDR corrected) in RRMS patients are indicated in red; blue indicates strength increases in patients. b. Correlations between patient-specific global efficiency measures in the DMN† and SDMT scores.](image)
correlated with SDMT scores \( R^2 = 0.4, p = 0.003 \), in contradiction to the original finding (for which \( R^2 = 0.11, p = 0.170 \) (Fig. 4.8b).

It is striking from these results how significantly the construction of a network can affect outcomes. The original motivation for tracking between specific regions was two-fold: (i) as the DMN is a functional network the exact set of regions resulting from the structural parcellation in this work was not obvious, so it was felt that the inclusion of partial regions was justified; (ii) tracking between specific regions could in theory reduce the false-positives known to dominate whole brain tractography [49]. However, for very small seed regions, as some were in this case, then it is possible that false-negatives may become influential. Whether one approach is more valid or accurate than another is not straightforward, though, and a deeper exploration of tractography approaches was out of scope in this work.

As the results presented here are more in line with expected outcomes, results from this network will also be included in subsequent discussions, denoted DMN↑ for clarity.

**Graph topology**

Global network alterations in RRMS patients were generally characterised by reductions in efficiency and increases in path length, as has been previously reported [8, 72]. Given the equivalent edge sets of the average graphs in this work, these changes can be attributed to global changes in edge weight as opposed to the organisation or density of edges. A decrease in edge weight, corresponding here to a reduction in mean tract FA, may be attributed to demyelination, axonal damage or inflammation [117, 118]; however, determining the exact underlying cause is not possible without histological validation or diffusion models that can capture microstructural properties such as neurite density or myelination.

Reductions in tract FA can also explain the local network changes observed in RRMS patients, which were largely characterised by decreased node strength. Increased node strength was reported in one node - the frontal operculum - in the CN, though. Increases in FA have previously been linked to axonal alterations (for example number, diameter or packing density) as well as increases in glial cell numbers and sizes [119], but, again, the true cause can only be inferred using connectivity data and there is ongoing debate whether such changes are causal or compensatory. It is interesting to note, though, that the frontal operculum did not display any significant alterations in the FBN. It may be that the effect of highly localised changes, particularly those that oppose general trends within the full graph,
may be diluted by the inclusion of all nodes in a FBN analysis.

A curious feature of the node strength analysis was the observation that 68% of altered nodes in the FBN belonged to the DMN. This could be explained by the fact that they are densely connected regions with high probability to be connected by several damaged tracts: several of the altered nodes, including the precuneus, superior parietal lobule and insula, are known to be display hub properties in both HC and MS patients [8].

**Global efficiency as a predictor of clinical disability**

Global efficiency across the FBN was alone able to explain 40% of the variation in SDMT score among RRMS patients; however, efficiency calculated over the subgraph of damaged nodes was similarly able to account for 39% of the SDMT variation. This result supports the hypothesis that there exists a subnetwork that best captures disability in MS patients: assuming every region and connection were affected in MS then efficiency across the FBN should be more highly correlated with clinical scores than efficiency across the subnetwork of damaged nodes. Conversely, the subgraph of only those nodes with altered strength is evidently not the salient network. Global efficiency across the DMN† also did not improve correlations with clinical scores, equally explaining 40% of SDMT variance.

Global efficiency across the CN provided a better correlation with clinical disability; however, the improvement over the FBN and DMN† was only modest with 43% of SDMT variance explained. The clinical metric used in the correlation analysis may become influential here. Correlations of network topology with clinical disability scores are generally performed on FBNs, which by definition capture global alterations, or on networks that are functionally related to the clinical disability metric; for example, the topology of the motor network with motor skills [73], or the DMN with cognitive ability [68]. Given that the CN contained both DMN and sensory-motor nodes, then, the SDMT as a solo measure of disability may not provide the best correlation with network topology. Analysis of additional clinical disability scores in future work, or even a multiple linear regression across several, could explain additional variability in overall patient disability.

The absence of any relation between EDSS score and global efficiency in the DMN† and CN may similarly be explained by a lack of affinity between the clinical measure (relating to motor skills) and node function (primarily relating to cognitive ability). It may also be that network measures in any of the networks were insensitive to the minimal disability of the cohort, as the median EDSS was just 2.0.
4.5. Conclusions

Limitations
White matter lesions are an inherent limitation of any MS connectivity study. Reductions in FA, for example, can arbitrarily stop tractography algorithms, but it is not straightforward to compensate for such effects. More generally, the influence of false-positive tracts from tractography itself also cannot be ignored. In this study, average graphs were utilised in an attempt to partially compensate for the effects of false-positive tracts.

The choice of edge weight may be another limiting factor. FA was chosen as it has been related to demyelination in MS, however FA as a biomarker for disease is confounded for a number of reasons: crossing, kissing or fanning fibres can artificially reduce the value, while the true biological basis for other changes in FA are not always obvious [25, 27, 57]. However, it is useful as a biomarker for simply identifying regions of damage or change.

4.5 Conclusions

Identifying imaging biomarkers sensitive to mild or early pathology remains an important topic in MS: the clinico-radiological paradox makes diagnosis and treatment particularly challenging, and motivates the search for new biomarkers. This chapter introduces an alternative data-driven approach to classifying subnetworks based on nodes that are central to overall network integration, and demonstrates that a subnetwork consisting exclusively of highly central nodes can improve sensitivity to subtle pathology.

Indeed, a consensus network derived using principal network analysis and rich-club analysis revealed a set of 45 nodes out of an initial 98 that featured in the intersection of both subnetworks and was best able to capture global and local disruptions in RRMS patients with respect to HCs: decreased global efficiency the in individual CNs of patients was more highly associated with cognitive decline than efficiency in either the FBN or DMN†. This supports the hypothesis that there exist subnetworks that best capture pathological processes.

A primary aim of the study was to be objective in selecting subnetworks. It is remarkable that, despite defining the subnetwork in this work using structural cortical thickness data, a coherent set of nodes involved primarily in the (functionally-defined) DMN and sensory-motor system were extracted, whose network of structural white matter connections related to clinical disability. This demonstrates a link between structural covariance, structural diffusion and functional networks; moreover, it confirms the importance of DMN nodes to overall network integration.
However, as revealed by the construction of the DMN, defining and utilising salient subnetworks remains challenging and, naturally, graph analysis over different networks will alter study conclusions. It is imperative to ultimately select networks that maximise sensitivity to pathology in any given study, not only in terms of node and edge sets but also in regard to edge weighting schemes.
Chapter 5

On the influence of edge weighting scheme

5.1 Introduction

The construction of graphs for the assessment of brain network structure and function is a much debated topic. Naturally, the selection of nodes, edges and edge weights will determine any topological measures calculated, but there is no consensus on how to generate graphs that produce robust and accurate measures that relate to a given pathology or condition. Other components of the network construction pipeline - for example the parcellation strategy used to extract brain nodes or the tractography algorithm used to generate white matter (WM) fibre ‘connections’ - have already demonstrated significant influence on derived network measures [77, 120].

Appropriate edge weighting strategies are also widely discussed [121, 122]. For the structural connectome - defined here as spatially distinct cortical regions connected by axon bundles reconstructed using diffusion tensor imaging (DTI) - typical edge weights include the number of streamlines (NSL) connecting pairwise regions, the mean fractional anisotropy (FA) of the tract, and binary values. All are valid weighting schemes: the NSL and FA offer some suggestion of connection ‘integrity’ or ‘efficiency’, while binary graphs provide analytic simplicity. Network parameters will depend on the chosen weighting scheme [123], but whether or not outcomes in a comparative analysis of brain networks between healthy control (HC) and patient groups are consistent across edge weighting schemes cannot be assumed.

This chapter evaluates the impact of the edge weighting scheme on the network alterations detected in a relapsing-remitting multiple sclerosis (RRMS) patient cohort with respect to HC.
5.2 Methods

5.2.1 Network construction

Data from 27 HC and 33 RRMS patients were used, as described in Section 4.4.1. No effects of age and gender were observed ($p = 0.27$ and $p = 0.27$ respectively). Image acquisition, pre-processing stages, and diffusion tractography details can be found in Section 4.4.1. Correspondences between the 98 nodes of the full brain network (FBN) and anatomical regions are given in Table 4.1.

Association matrices were generated using TractoR [115] for each subject and masked to remove any edges absent in more than $N$ subjects, where $N = \max(N_{HC}, N_{RRMS}) + 2$ and $N_{HC}$, $N_{RRMS}$ denote HC and RRMS group sizes respectively. Masking in this way ensured that any given edge was present in at least two subjects within a group and aided the statistical analysis. All vertices remained connected for all subjects.

Edges were weighted using four different metrics commonly reported: the NSL, the NSL corrected for tract length (NSL$_{cor}$), the mean tract FA, and a simple binary weight. The correction for tract length was implemented as the product of the NSL connecting two regions and the average length of those streamlines. An example of each association matrix generated for a single representative subject is provided in Fig. 5.1.

5.2.2 Statistical analysis

Global and local network properties were calculated for each subject and edge weighting scheme. The global metrics evaluated were efficiency, mean shortest path and modularity; the local properties were efficiency, clustering coefficient, node strength and betweenness centrality.

Significant differences in global network properties between HC and RRMS groups were identified using a t-test with significance set at $p < 0.05$.

Significant intergroup differences in local network properties were determined using a permutation-based approach. This strategy enabled the null distribution of $p$ values to be empirically derived whilst taking multiple comparisons into consideration, from which a corrected $p$ value could be estimated. Separate null distributions of $p$ values were generated for each network type and property. The procedure was as follows. First, at each permutation, group labels were randomly reallocated to create new ‘HC’ and ‘RRMS’ groups with original group sizes preserved in each of the 1000 samples generated. Then, at each node the mean local network properties were compared between sample groups using a t-test.
5.3. Results

5.3.1 Global network properties

Global network properties are summarised in Table 5.1. Global efficiency was significantly lower ($p < 0.05$) in RRMS patients relative to HC subjects in networks weighted using FA, NSL$_{cor}$ and NSL edge properties; the mean shortest path was correspondingly greater.
Table 5.1. Group comparison of global graph properties. Properties are calculated over the group-wise average networks for HC and RRMS subjects, using FA, NSL, NSL\(_{\text{cor}}\) and binary values as edge weights.

\* \( p < 0.05 \).

\** \( p < 0.01 \).

\( (p < 0.05) \) in the RRMS population across the same networks. Binary networks exhibited no intergroup differences in global efficiency and mean shortest path; however modularity was significantly greater in the HC group \( (p < 0.05) \).

These results are consistent with published findings [8, 75]. Of note here is that inferences of intergroup differences in global network properties were unaffected by the choice of edge property for weighted networks, but were substantially different between weighted and binary networks.

5.3.2 Local network properties

Local efficiency

Lower local efficiencies were observed in the RRMS cohort across all weighted networks, which is consistent with published reports [75]; no alterations were detected in binary networks (Fig. 5.2a). However, the set of vertices with different efficiency properties between groups was highly inconsistent across the weighted network types. FA-weighted networks exhibited the greatest intergroup differences, with lower efficiency in 97 out of 98 nodes in the RRMS cohort \( (p < 0.05, \text{corrected}) \). In NSL\(_{\text{cor}}\)-weighted networks only 78 nodes demonstrated alterations between groups \( (p < 0.05, \text{corrected}) \), while in NSL-weighted networks the proportion was lower still at just 10 nodes \( (p < 0.05, \text{corrected}) \).

Clustering coefficient

Lower clustering coefficients were observed in the RRMS group in all weighted networks (Fig. 5.2b), in line with previous studies [75]. The extent of the alterations was again highly variable between the weighted network types: substantially more intergroup differences
5.3. Results

a. Local efficiency
b. Clustering coefficient
c. Node strength
d. Betweenness centrality

Figure 5.2. Group comparison of local network properties. Significant intergroup differences ($p < 0.05$, corrected) in: a. local efficiency; b. clustering coefficient; c. node strength, and; d. betweenness centrality. Red represents a decrease in RRMS patients and blue an increase. Each numbered segment corresponds to a node, as specified in Table 4.1. In each sub-figure the concentric rings correspond to specific network types: the outermost ring (ring 1) corresponds FA-weighted graphs; ring 2 to NSL$_{cor}$-weighted networks; ring 3 to NSL-weighted networks; ring 4 (innermost ring) to binary networks.
were identified in FA-weighted networks (54 out of 98 nodes; \( p < 0.05 \), corrected) than in NSL_{cor}^- and NSL-weighted networks (5 and 3 nodes respectively; \( p < 0.05 \), corrected). No differences were observed in binary networks.

**Nodal strength**

Lower nodal strengths were found in the RRMS group in FA-weighted, NSL_{cor}^-weighted and binary networks (Fig. 5.2c), consistent with published findings [75]. The proportion of nodes exhibiting different strength properties between the HC and RRMS groups once more varied across the network types, with 17 out of 98 nodes (\( p < 0.05 \), corrected) identified in FA-weighted networks, 4 nodes (\( p < 0.05 \), corrected) in NSL_{cor}^-weighted networks and 1 node (\( p < 0.05 \), corrected) in binary networks. No intergroup differences were observed in NSL-weighted networks.

**Betweenness centrality**

Minimal intergroup differences were observed in betweenness centrality: only 2 nodes in FA-weighted networks displayed significantly greater (\( p < 0.05 \), corrected) betweenness centrality in the RRMS group (Fig. 5.2d). No other networks indicated any differences.

### 5.4 Discussion

The impact of edge weighting scheme on a comparative analysis of network properties is explicitly demonstrated using HC subjects and RRMS patients with very mild disease severity as example data sets. While graph theoretic analyses performed over different network types will naturally be incongruent to a degree, the disparities presented here are striking. Given any one of the network types in isolation, as is common in connectivity studies, the assessment of damage to the structural connectome of these RRMS patients would be substantially different, with potential conclusions ranging from ‘intact connectivity’ to ‘complete disruption despite the mild disability’.

In FA-weighted networks, for example, reductions were observed in the local efficiency of almost every node and in the clustering coefficient of more than half the nodes. Further, regions of the default mode network (DMN) - which is important for high level function and prone to impairment in MS [125] - such as the precuneus and posterior cingulate gyrus displayed significantly reduced nodal strength. From these findings it may be inferred that the networks of these RRMS patients were substantially damaged despite the relatively mild disability levels - the median EDSS was just 2.0, indicating no major motor, visual, sensory or cognitive disabilities - and that the graph properties were in fact sensitive
5.4. Discussion

In NSL_cor-weighted networks, on the other hand, the clustering coefficient, node strength and betweenness centrality were unaffected in the majority of nodes, and core DMN nodes in particular showed no changes; only local efficiency appeared to indicate any alterations. It may be concluded here, then, that networks in this RRMS cohort were only moderately disrupted, and potentially reflected their relative lack of clinical disability.

The variation in findings between the NSL_cor- and NSL-weighted networks was also particularly marked, with the NSL_cor-weighted networks typically demonstrating greater differences between groups. It is possible here that additional uncertainties in NSL-weighted networks, perhaps resulting from inherent biases in probabilistic tractography towards tract length [126], could be driving the discrepancies.

The relative absence of intergroup differences both locally and globally in binary networks is likely to reflect the similarity in edge set between groups, and the applied edge threshold is likely to be influential here. A complete analysis of individual edges was beyond the scope of this work, but could be considered in future work.

Ultimately, the choice of edge weight is largely dependent on the study design in question. For example, it could be interesting to compare edge weighting schemes and local network properties in alternative subject populations, such as those with more severe pathology: substantial microstructural changes may then outweigh confounding factors and result in more consistent outcomes. It is important to consider, though, that the nuances of each weighting scheme influence derived network parameters, which may in turn substantially impact outcomes in intergroup comparative studies.

5.4.1 Limitations

It is noted here that the statistics used in any analysis of group-wise comparisons can also significantly influence results. This is apparent in the node strength analysis on FA-weighted graphs: in this chapter only 17 nodes presented with reduced strength in RRMS patients compared to the 28 nodes identified in Chapter 4. Partially, this is because the edge set over which the analysis was performed was different: average graphs were used in Chapter 4, whereas here subject specific graphs were used for which edges were discarded if they did not feature in a majority of subjects. The corrections for multiple comparisons were also different, although both were appropriate for the study in question. For example, the ‘minimum \( p \)’ approach was not feasible in Chapter 4 as it required an initial t-test in global
network properties between the original groups, which was not possible owing to the use of average graphs; however, it is a more stringent correction, and so was used here.

The specificity of local network properties to biological alterations may be improved in general by including additional confounding variables - for example estimates of head motion [127] - as covariates in the statistical analysis. Typically, though, connectivity studies tend to correct only for demographic parameters such as age and gender (for which no effects were observed in this cohort), so to make results more generalisable this approach was adopted here.

5.5 Conclusions
Network-based approaches offer important contributions towards analysing the connections that form the basis of brain structure and function; however the interpretation of graph theoretic properties remains challenging. This study highlighted for the first time how outcomes in intergroup comparative studies across different network types may be affected by the combined influence of biological alterations and factors unrelated to inter-regional connectivity. Specifically, comparisons of local network properties between groups may be particularly prone to variations across network types. The global metrics evaluated here were comparatively less sensitive to weighting scheme, but the utility of global properties can be limited by a lack of specificity to potentially more meaningful local alterations.

Evidently, interpretations of network analyses must be made with caution: graph theoretic metrics may be sensitive to subtle alterations between groups but they lack biological specificity. Factors known to systematically bias estimates of structural connectivity range from head motion [127] and low signal-to-noise ratio [46] during acquisition to the parcellation strategy and tractography algorithm adopted during image processing [77, 120], but other unwanted artefacts - for example from image aliasing - are also likely to affect results. Ultimately, to obtain reliable measures of brain connectivity, the robustness of the analysis pipeline and quality of the underlying data are critical.
Chapter 6

Giving up the ghost: correcting DW-EPI phase errors

6.1 Introduction

Echo planar imaging (EPI) suffers from inherent aliasing artefacts owing to the acquisition of $k$-space in both readout polarities (Section 2.3.3). System imperfections, such as timing delays and eddy currents (Section 2.3.5), can cause a misalignment between opposing $k$-space trajectories, which manifests as a ghost image offset by half the field-of-view (FOV) along the phase-encoding axis. Without correction, fluctuating image intensities introduced by Nyquist ghosting have the potential to influence quantitative parameter maps derived from the data at the local level [35, 36] and could transfer to the outcomes of brain network analyses at the whole-brain or subnetwork level. Moreover, diffusion-weighted imaging (DWI) may be uniquely prone to such errors: eddy currents from both the imaging and diffusion gradients [128–130] can induce phase errors (Section 2.2.2), while low SNR and additional phase errors from physiological motion in high $b$-value data may hinder ghost correction methods. Crucially, existing correction schemes are demonstrated in non-diffusion weighted EPI, meaning their efficacy in high $b$-value data is not explicitly validated.

The body of literature proposing ghost correction methods is vast and so choosing an appropriate technique is not straightforward, particularly for the unique challenges presented by DWI. Some approaches - including those implemented in clinical sequences - neglect to correct high $b$-value data at all: ghosting artefacts are not immediately apparent by eye given the low SNR while physiologically-induced phase errors can be problematic. For these reasons only $b=0$ images are corrected. It is important to note, though, that any ghosting visible in the $b=0$ data is still present in the DWI.

Another factor potentially confounding the choice of correction method is that the min-
imisation of ghost intensity is typically used as the objective measure by which correction efficacy is judged. Each correction method has some limiting factor, and it may be that a limitation affecting image quality - for example g-noise amplification (Section 2.6.4) - incurs greater biases in parameter estimations than the ghosting artefact itself. Indeed, few studies have explored the effect of Nyquist ghosting on quantitative parameter maps, while those that have primarily explored ADC values calculated from low diffusion weighting ($b_{\text{max}} = 800 \text{ s/mm}^2$) [131, 132].

This work performs a systematic comparison of reference-based and reference-free (Section 6.3) 2D correction methods in DW-EPI. A formal description of Nyquist phase errors is provided, along with an overview of phase correction methods. Four correction methods are implemented in this work, chosen pragmatically based on: (i) compatibility with a SENSE-based reconstruction (Section 2.5.3) [133]; (ii) ability to extend to higher acceleration factors and multi-band imaging (Section 2.3.6) [40, 41]; (iii) computational cost; (iv) ease of implementation and integration into existing reconstruction pipelines. The correction techniques are investigated in-silico and in-vivo, and evaluated based on artefact suppression, noise amplification, and accuracy of derived quantitative parameter maps.

6.2 Theory

This section builds on the sampling theory introduced in Section 2.2 to provide a formal description of Nyquist phase errors.

6.2.1 Nyquist phase errors

The EPI Nyquist ghost arises when data in $k$-space are not correctly interleaved; that is, when the echo centres of odd and even $k$-space lines are not aligned. The net effect in image space is a relative phase shift between the odd and even data.

To understand the effects of incorrect interleaving, it is useful to re-consider a simple 1D spin system $s(k)$, where $k$ is the spatial frequency, and to treat the sampling of this system as the product of its continuous signal with an infinite ‘comb’ function, i.e. $s_c(k) = s(k) \cdot u(k)$ (Section 2.2.1). If the comb, or sampling, function $u(k)$ is once again modelled as a series of Dirac delta functions periodically spaced by $p\Delta k$ such that $u(k) = \Delta k \sum_{p=-\infty}^{\infty} \delta (k - p\Delta k)$, with $p$ an integer, the result of this operation is the signal value at the sampled locations $p\Delta k$ and null everywhere else. Representing the sampling function as the sum of two separate series - now periodically spaced by $2p\Delta k$ - allows the odd and even $k$-space lines to be considered independently.
6.2. Theory

A relative time shift between odd and even lines, as in the case of incorrect interleaving, can be modelled by the introduction of an offset into the odd and even sampling functions $u_e(k)$ and $u_o(k)$ as in Eqs. 6.1 and 6.2. Here, the subscript $i$ indicates ‘incorrect’ interleaving and $\varepsilon, \alpha$ are the respective offsets.

\[
u_{e,i}(k) = \Delta k \sum_{p=-\infty}^{\infty} \delta(k-(2p-\varepsilon)\Delta k) \tag{6.1}\]
\[
u_{o,i}(k) = \Delta k \sum_{p=-\infty}^{\infty} \delta(k-(2p+1-\alpha)\Delta k) \tag{6.2}\]

\[-1 < \varepsilon < 1, \quad -1 < \alpha < 1\]

The effect in image space of incorrect interleaving in $k$-space is demonstrated by convolving the true image $S(x)$ with the Fourier transform (FT) of the odd and even sampling functions $U_{e,i}(x)$ and $U_{o,i}(x)$ (Eqs. 6.3 and 6.4).

\[
U_{e,i}(x) \equiv \mathcal{F}^{-1}(\nu_{e,i}(k)) = \mathcal{F}^{-1}(u_e(k-\varepsilon\Delta k)) = \frac{1}{2} \sum_{q=-\infty}^{\infty} \delta\left(x-\frac{L}{2}q\right) e^{iq\pi\varepsilon} \tag{6.3}\]
\[
U_{o,i}(x) \equiv \mathcal{F}^{-1}(\nu_{o,i}(k)) = \frac{1}{2} \sum_{q=-\infty}^{\infty} \delta\left(x-\frac{L}{2}q\right) e^{iq\pi(1-\alpha)} \tag{6.4}\]

In the interval $-L/2 < x < L/2$, where $L$ is the FOV, the resulting convolutions are given by the expressions in Eqs. 6.5 and 6.6.

\[
S_{e,i}(x) = \frac{1}{2} \left[ S\left(x+\frac{L}{2}\right) e^{-i\pi\varepsilon} + S(\delta) + S\left(x-\frac{L}{2}\right) e^{i\pi\varepsilon}\right] \tag{6.5}\]
\[
S_{o,i}(x) = \frac{1}{2} \left[ -S\left(x+\frac{L}{2}\right) e^{-i\pi(1-\alpha)} + S(\delta) - S\left(x-\frac{L}{2}\right) e^{i\pi(1-\alpha)}\right] \tag{6.6}\]

\[-L/2 < x < L/2\]

Aliasing from under-sampling in $S_{e,i}(x)$ and $S_{o,i}(x)$ is apparent in the contribution of the odd series terms $q = [-1, 1]$: separating the odd and even lines is equivalent to sampling at half the Nyquist rate, meaning that a component of the signal is offset by $\pm L/2$ in both (Section 2.2.2). The fully sampled image is obtained by summing over both series (Eq. 6.7). In the case of correct interleaving - that is for $\varepsilon = 1 - \alpha$ or $\varepsilon = \alpha = 0$ - the aliasing terms (gathered in square brackets in Eq. 6.7) cancel. For all other cases, though, the aliasing terms do not cancel, meaning that a residual ghost is present in the final reconstruction.

\[
S(x) = S(x) + \frac{e^{-i\pi\varepsilon} - e^{-i\pi(1-\alpha)}}{2}S\left(x+\frac{L}{2}\right) + \frac{e^{i\pi\varepsilon} - e^{i\pi(1-\alpha)}}{2}S\left(x-\frac{L}{2}\right) \tag{6.7}\]

\[-L/2 < x < L/2\]
Corrections for EPI Nyquist ghost artefacts aim to estimate and correct this phase difference.

### 6.2.2 Simulating phase errors

The effect in image space of a constant echo offset in \( k \)-space is evident from the Fourier shift theorem (Section 2.2.2): a modulation in the origin of \( k \)-space from \( s(k) \to s(k - \delta k) \) produces a linear phase shift in the associated image \( S(x) \). Phase errors can therefore be introduced into the data after transformation into the \((x,k_y)\) domain \[134\], where \( x \) indexes pixels along the \( x \)-axis in image space and \( k_y \) indexes \( k \)-space samples along the \( y \)-axis.

Given an original ghost-free complex image \( S(x,k_y) = |S(x,k_y)|e^{i\phi(x,k_y)} \), the phase can be modulated according to Eqs. 6.8 and 6.9 such that the total phase change across the FOV along the readout axis is \( \Delta \phi = N_p \delta \), where \( N_p \) is the number of pixels in image space and \( \delta \) the incremental phase shift.

\[
\phi_{e,i}(x,k_y) = \phi_e(x,k_y) - \delta x \tag{6.8}
\]

\[
\phi_{o,i}(x,k_y) = \phi_o(x,k_y) + \delta x \tag{6.9}
\]

\( x = 1,2,\ldots,N_p \)

The effect of this phase accrual in image space is a non-uniform ghost with intensity banding along the readout axis, offset from the true image along the phase encoding axis by \( L/2 \) (see Section 6.3.3 and Fig. 6.1)

### 6.3 2D phase correction methods

Phase errors are typically estimated by the scanner manufacturer using a fast calibration scan with no phase-encoding and few readout lobes \[130, 135\]. This navigator, performed either once at the beginning of a time-series or before each EPI volume, is then used for a line-by-line correction of each subsequent readout. While the approach is generally effective for 1D errors, residual ghosting from higher order phase errors is often present. Several 2D phase correction methods have been proposed, but, despite significant reductions in ghosting levels, a range of factors has prevented their widespread use.

Corrections techniques can be broadly divided into those that are reference-based or reference-free. Similar to the manufacturers’ 1D phase correction, 2D reference-based corrections can be implemented using phase encoded navigator scans for a point-by-point correction of errors \[136–139\]; however, the additional time required for phase encoding means that the reference cannot be updated for each acquisition in a time-series. Consequently, reference-based methods are sensitive to dynamic error variations.
Reference-free methods are an attractive alternative: each EPI volume can be independently corrected and so sensitivity to dynamic errors is mitigated. A number of reference-free methods have been proposed, including image-based approaches, pulse sequence compensation techniques, structured low-rank matrix completion approaches, and parallel imaging-based methods.

Image-based corrections are a post-processing approach which define a cost function that is minimised when the ghost image is suppressed [36, 137, 140–143]. These techniques tend to rely on the ability to define regions in the reconstructed data containing only ghost or parent signal, and often require user input to delineate such ROIs. High acceleration factors, where ghost and parent images significantly overlap, and low SNR data, for example high $b$-value or high resolution images, can therefore limit the efficacy of image-based methods.

Pulse sequence compensation techniques instead aim to account for misalignments by sampling each acquired $k$-space line with both readout polarities. The challenge here is to maintain similar scan times and image quality. One approach is to oversample and acquire the full $k$-space twice by doubling the readout gradient strength [144]; however hardware and $dB/dt$ safety constraints restrict wide adoption of this method. Another fully-sampled option is to alternate the readout polarity between EPI volumes and correct the data in pairs [145], but dynamic errors between subsequent scans can again be problematic. It is also possible to sample half the required $k$-space lines but with both readout polarities and then separately unfold the wrapped positive and negative lines using parallel imaging [129], but the limitation here is the $g$-noise penalty.

Parallel imaging can also be exploited during reconstruction to correct for phase errors. These methods similarly incur a $g$-factor penalty, but don’t require sequence modifications. Coil sensitivity profiles are instead used to reconstruct positive and negative $k$-space lines into separate ghost-free images, which are either directly combined or utilised to generate a phase correction map that is used to inform the final reconstruction [129, 146–151].

Structured low-rank matrix completion approaches [132, 152–155] similarly reconstruct odd and even lines separately, but, instead of unwrapping folded data with coil sensitivity profiles, use matrix recovery techniques to fill the undersampled positive and negative $k$-spaces. Inverse Fourier transformation (iFT) of the two filled $k$-spaces produces full FOV images that are combined to produce the final image. These methods are more tolerant to high acceleration factors, but are computationally expensive and can be less successful for
images with rapidly varying phase or small FOV [152]. The four methods evaluated in this chapter are described in more detail below.

6.3.1 Method 1: phased array ghost elimination (PAGE)

PAGE [146] generates two ghost-free images from the odd and even \(k\)-space lines by exploiting the coil sensitivity profiles. After de-interleaving \(k\)-space, the iFT of odd and even echoes separately contain aliasing due to undersampling but not due to phase errors. The data are reconstructed using SENSE to produce two full FOV ghost-free images with opposing phase offset, which are combined to produce the final reconstruction as in Eq. 6.10.

\[
S = (S_e \cdot S_o)^{\frac{1}{2}} \quad (6.10)
\]

The major limitation of PAGE is the reduction in SNR by the \(g\)-factor. This is a consequence of separately reconstructing the odd and even images, which effectively doubles the acceleration factor.

6.3.2 Method 2: phase error correction with SENSE (PEC-SENSE)

The concept of PEC-SENSE [151] is similar to that of PAGE; the primary difference is that a 2D correction map is generated from the phase difference between the odd and even echo reconstructions (Eq. 6.11) and used to modify the coil sensitivity maps \((B)\) for the odd echoes (Eq. 6.12) in the final joint SENSE reconstruction (Eqs. 6.13 and 6.14).

\[
\Delta \phi (x,y) = \text{Arg}(S_e \cdot S_o) \quad (6.11)
\]

\[
B' (x,y) = B(x,y) e^{-i \Delta \phi} \quad (6.12)
\]

\[
S_e (x) = \frac{1}{2} \left[ B \left( x + \frac{L}{2} \right) S \left( x + \frac{L}{2} \right) + B(x) S(x) + B \left( x - \frac{L}{2} \right) S \left( x - \frac{L}{2} \right) \right] \quad (6.13)
\]

\[
S_o (x) = \frac{1}{2} \left[ -B' \left( x + \frac{L}{2} \right) S \left( x + \frac{L}{2} \right) + B' (x) S(x) - B' \left( x - \frac{L}{2} \right) S \left( x - \frac{L}{2} \right) \right] \quad (6.14)
\]

PEC-SENSE still suffers from \(g\)-noise amplification owing to the separate reconstruction of odd and even echoes; however, by smoothing the phase map and jointly solving the set of equations in Eqs. 6.13 and 6.14, the conditioning of the problem is improved relative to PAGE and leads to better SNR preservation.

6.3.3 Method 3: double sampled EPI (DSEPI)

The DSEPI method [144] samples each \(k\)-space line using both polarity readout gradients. In practice, this is achieved by acquiring two EPIs with the readout gradient polarity reversed between them. The data can be reconstructed in one of two ways (see also Fig. 6.1):
6.3. 2D phase correction methods

Figure 6.1. Nyquist ghost simulations. Phase errors are demonstrated schematically and in a noise-free, binary phantom simulated using Matlab. Phase errors were introduced into the toy phantom using Eqns. 6.8 and 6.9 with $\Delta \phi = \pi/2$. **a-b.** Schematic demonstration of $k$-space acquisition in both readout polarities with a misalignment between interleaved lines. **c-d.** Collecting the positive and negative $k$-space lines into separate datasets matches the offset between interleaved lines. **e-f.** Introducing a misalignment between the positive and negative $k$-space lines of the toy phantom produces a ghost image offset by $L/2$. **g-h.** De-interleaving the $k$-space data and collecting the positive and negative lines as per (c) and (d) mitigates the phase error and ghost artefact in image space. **i.** Complex average of the data with opposing phase errors - i.e. (e) and (f) - nulls the ghost through phase cancellation. **j.** The sum-of-squares (SOS) difference between the complex averaged data in (i) and the ground truth demonstrates marginal signal loss owing to phase cancellation. **k.** Magnitude average of the de-interleaved data, i.e. (g) and (h). **l.** The SOS difference between the magnitude averaged data in (k) and the ground truth shows perfect ghost correction.
1. Two fully sampled and artefact-free data sets are created by de-interleaving the \( k \)-space of each EPI and collecting the positive and negative \( k \)-space lines into separate datasets. The final image is produce by a simple average of the magnitude images, and image SNR is subsequently increased by a factor of \( \sqrt{2} \).

2. The complex average of the original EPI is performed after inverse Fourier transformation along the readout axis (i.e. in \( xk_y \)-space). The Nyquist ghost is nulled as a consequence of the opposing phase errors between the datasets; however, owing to this phase cancellation, the final image SNR is marginally reduced compared to the previous approch of averaging magnitude images. The amount of signal reduction is proportional to the phase misalignment.

DSEPI has two major limitations: (i) twice the data of a standard EPI sequence is required, so scan time is doubled; (ii) additional phase differences between DW-EPI shots resulting from physiological motion during the diffusion gradients mean that the method is incompatible with DWI.

### 6.3.4 Method 4: double sampled non-DW EPI (DSb0)

In a variation of the DSEPI method, only the non-DW volumes are sampled using both readout polarities. Imaging time is significantly reduced relative to the DSEPI method, but is slightly longer than a standard DW-EPI experiment.

This correction is implemented by default on the Philips 3T MR system: obvious ghosting in high SNR \( b = 0 \) data is corrected, while additional data for the DWI (which are not visibly corrupted and cannot be corrected using this method regardless) is not unnecessarily acquired.

### 6.4 Methods

#### 6.4.1 In-silico data generation

Simulations were performed in Matlab 2017b (The MathWorks, Natick, MA, USA) using the noise-free digital D-BRAIN phantom [156]; this was obtained from Figshare (https://dx.doi.org/10.6084/m9.figshare.2199001.v3) under the Creative Commons Attribution License. The phantom data utilised here consisted of 12 volumes with \( b = 0 \) and 60 DW volumes each for \( b \)-values of 1000 and 2500 s/mm\(^2\), with 1.4 mm\(^3\) isotropic spatial resolution. Images were magnitude only. Phased array data, parallel imaging acceleration, noise and Nyquist ghost artefacts were introduced into the phantom images through a se-
ries of image- and $k$-space transformations. The pipeline is described in detail below and graphically represented in Fig. 6.2.

**Phased array image generation**

Phased array images were emulated by weighting the phantom with simulated coil sensitivity profiles in image space; this is the forward model of the inverse problem solved using SENSE. Complex sensitivity profiles representing a 32-channel head coil were generated using the Michigan Image Reconstruction Toolbox (MIRT; [157]), and optimised empirically to maximise image uniformity and minimise $g$-noise amplification (validation experiments not shown).

**Noise corruption**

Following a 2D FT of the (now complex) images into $k$-space, Gaussian noise was added in quadrature to each ‘channel’ independently. Adding noise to $k$-space ensured appropriate SNR-dependent noise statistics were obtained in the final magnitude data - that is, with Rician bias at low SNR. The noise level added to the $k$-space data generated an average SNR of 25 in WM at $b=0$ after the standard SENSE reconstruction; the SNR of the phase-corrected reconstructions varied owing to differing noise propagation through the algorithms.

**Parallel imaging acceleration**

A SENSE acceleration factor of 2 was simulated by sampling alternate $k_y$ lines in each channel.

**Nyquist phase errors**

A 1D iFT was applied along the $x$-axis to obtain data in the $(x,k_y)$ domain. Nyquist ghosting was introduced by adding a 1st order phase error to the read-out axis of each channel according to Eqs. 6.8 and 6.9 [134]. A phase variation of $\delta = \pi/8$ rad introduced along the readout axis corresponded to a ghost-to-signal ratio (GSR) of 0.5% (determined empirically through simulations). Acquisitions with reversed readout polarity were simulated by reversing the polarity of the phase shift $\delta$.

**Final pre-reconstruction data**

The data were transformed by a 1D iFT along the $y$-axis into the full image domain. The resultant data was representative of complex images obtained from each individual channel of a 32-channel coil, complete with noise, aliasing from parallel imaging acceleration, and ghosting from Nyquist phase errors. Corresponding ground truth reference images were created using the same pipeline but without introducing phase errors.
Figure 6.2. Schematic overview of synthetic data generation.
6.4.2 In-vivo data acquisition

Multi-shell DW-EPI were acquired on five healthy volunteers (age 35 ± 12 years); written informed consent was obtained and imaging was approved by the local ethics committee. Data were acquired at 3T (Philips Ingenia CX; maximum gradient strength 62 mT/m) using the vendor’s 32-channel head coil. Nine volumes were acquired without diffusion weighting followed by 90 DW volumes with \( b = [1000, 2000, 3000] \text{ s/mm}^2 \) (30 diffusion directions in each shell). A SENSE acceleration factor of 2 was used, with resolution \( 2 \times 2 \times 2 \text{ mm}^3 \), \( \text{TR/TE} = 6848/85 \text{ ms} \), and bandwidth = 3281 Hz/px. Each volume was acquired twice using opposing readout gradient trajectories so that each \( k \)-space line was sampled in both readout directions. Image reconstruction was performed off-line in Matlab on the vendor’s 1D-phase corrected raw \( k \)-space data. The data were inspected (post-reconstruction) for motion and any other artefacts; no corrections for motion and eddy current distortions or Gibbs ringing were applied in order to avoid confounding the effects of post-processing with the 2D phase-correction. One \( b = 0 \) volume in each in-vivo dataset was discarded owing to severe artefacts: at the time of acquisition, collection of multiple true \( b = 0 \) images within a DW-EPI sequence was not possible, necessitating the use of small diffusion gradients \( (b = 1 \text{ s/mm}^2) \) to acquire effectively non-DW data. One orientation of the small diffusion gradients subsequently interfered with the imaging gradients and caused significant signal drop out.

6.4.3 Reconstruction

An overview of each reconstruction is provided in Table 6.1; each method was implemented in Matlab using in-house modifications of the SENSE algorithm in the MIRT. All in-silico and in-vivo data were reconstructed using SENSE (no phase correction), PAGE, PEC-SENSE and DSb0. In-silico data were additionally reconstructed using the DSEPI method, while a variant of the DSEPI method (referred to as pseudo DSEPI, or pDSEPI) was used for the in-vivo DWI. The pDSEPI method was required in-vivo to control for additional phase differences between EPI shots resulting from physiological motion; as such, it was necessary to magnitude average DW-data and complex average only the non-DW data.

Reference data

The simulation framework provided ground truth reference images for the in-silico data. These were standard SENSE reconstructions of the data without phase errors and with matched baseline SNR; that is, to account for the \( \sqrt{2} \) increase in SNR introduced by refer-
ence images in the DSb0 and DSEPI methods. Reference images with SNR representative of the underlying ‘acquired’ data enabled the effects of g-noise amplification to be separated from imperfect phase correction.

The pDSEPI method provided the reference ‘ghost-free’ data in-vivo; however, it is noted that the pDSEPI method is only a silver standard as perfect ghost cancellation is not achieved by magnitude averaging in the DW-EPI. Moreover, with the exception of the $b = 0$ data in the DSb0 reconstruction, SNR was a factor of $\sqrt{2}$ greater owing to the dual acquisition.

6.4.4 Analysis

Signal-to-noise ratio

The signal-to-noise ratio (SNR) at each pixel location was defined as the mean signal intensity $s(x, y)$ divided by the standard deviation $\sigma(x, y)$ measured across repetitions of the $b = 0$ data (Eq. 6.15). There were 12 $b = 0$ volumes in the digital phantom and 8 in-vivo.

$$\text{SNR}(x, y) = \frac{s(x, y)}{\sigma(x, y)} \quad (6.15)$$

Artefact suppression

Artefact power (AP) maps were created using the absolute relative error between the phase-corrected and references images (Eq. 6.16).

$$\text{AP}(x, y) = \left| \frac{S(x, y) - S_{\text{ref}}(x, y)}{S_{\text{ref}}(x, y)} \right| \quad (6.16)$$

The AP therefore provides an indication of overall reconstruction performance, encompassing both errors introduced by residual Nyquist ghosting and as well as g-noise amplification; however, the measure is slightly confounded in-vivo owing to SNR differences in the reference data.

Model parameter accuracy and precision

The DT, DK and NODDI models (Section 2.7.2) were fitted to all in-silico and in-vivo reconstructions. The DT and DKI tensors were fitted using an iteratively re-weighted linear least squares estimator [158, 159], with the DT fitting limited to data with $b \leq 1000 \text{ s/mm}^2$. The NODDI model was fitted using the NODDI Matlab toolbox [15]. These models encompass common parametric and non-parametric approaches; however the influence of Nyquist ghost artefacts on microstructural tissue parameters is not specific or limited to these models. For brevity, only results for FA and MD from the DT model, MK from the DK model and ODI from the NODDI model are reported here.
<table>
<thead>
<tr>
<th>Reconstruction</th>
<th>Reference data</th>
<th>Phase correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENSE [133]</td>
<td>None.</td>
<td>None</td>
</tr>
<tr>
<td>PAGE [160]</td>
<td>None.</td>
<td>Parallel imaging exploited to separately reconstruct positive and negative echoes. The two resulting non-aliased ghost-free images were summed to produce a phase-corrected image.</td>
</tr>
<tr>
<td>PEC-SENSE [151]</td>
<td>None</td>
<td>Parallel imaging exploited to separately reconstruct positive and negative echoes, from which a phase correction map was generated. The map was used to modify coil sensitivity weights for the negative echoes during a final joint reconstruction of all echoes.</td>
</tr>
<tr>
<td>DSb0</td>
<td>Dual acquisition of $b=0$ data with opposing readout polarities.</td>
<td>Complex average of dual $b=0$ data only.</td>
</tr>
<tr>
<td>DSEPI (in-silico reference data) [161]</td>
<td>Dual acquisition of all data with opposing readout polarities.</td>
<td>Complex average of all dual sampled data.</td>
</tr>
<tr>
<td>pDSEPI (in-vivo reference data)</td>
<td>Dual acquisition of all data with opposing readout polarities.</td>
<td>Complex average of dual $b=0$ data; magnitude average of dual DW-data.</td>
</tr>
</tbody>
</table>

Table 6.1. Phase correction methods.
Chapter 6. Giving up the ghost: correcting DW-EPI phase errors

The accuracy and precision of parameter estimates was assessed using the relative error between the parameter fit in the phase-corrected data $p_i$ and reference data $p_{i,\text{ref}}$ (Eq. 6.17); the subscript $i$ here denotes a different parameter $p$.

$$
\epsilon_i(x,y) = \frac{p_i(x,y) - p_{i,\text{ref}}(x,y)}{p_{i,\text{ref}}(x,y)}
$$

(6.17)

6.5 Results

6.5.1 Qualitative assessment

Digital phantom

Representative images of each digital phantom reconstruction are shown in Fig. 6.3. Without phase correction, ghosting was clearly apparent in the $b = [0, 1000]$ s/mm$^2$ data. Notably, the ghost was also visible in the $b = 1000$ s/mm$^2$ images of the DSb0 method while suppressed in the $b=0$ volumes. Nyquist ghosting artefacts appeared corrected in the PAGE and PEC-SENSE methods; however SNR degradation from $g$-noise amplification was evident, and particularly severe in the $b = 2500$ s/mm$^2$ volumes. As expected, the DSEPI reconstruction was superior: ghost artefacts were suppressed and SNR was improved.

In-vivo

Fig. 6.4 shows a sample of in-vivo data for each reconstruction. Without 2D phase correction (note that 1D phase correction had been performed), Nyquist ghost artefacts were visible in the $b=0$ data only. Qualitatively, the ghost appeared suppressed by each phase-correction method, and, although SNR degradation was still apparent in the PAGE and PEC-SENSE methods at higher $b$-values, the effects of $g$-noise amplification were not as prominent as in-silico.

6.5.2 Signal-to-noise ratio

Digital phantom

SNR maps calculated across repetitions of $b=0$ data in-silico demonstrated the spatial noise variation introduced by each 2D phase-correction method (Fig. 6.5). In particular, the $g$-noise penalty was a dominating feature in the PAGE SNR map: relative to the standard SENSE reconstruction, SNR was reduced by 56%. SNR in PEC-SENSE was minimally reduced by just 8% relative to the standard SENSE reconstruction. SNR increases of 36% - that is a factor of $\sqrt{2}$ - were observed in the DSb0 and DSEPI methods, as expected.

These results are applicable only to the $b=0$ data, however. Due consideration must be given to the fact that for the DSb0 method the SNR increase is only true for the $b=0$
Figure 6.3. Digital phantom reconstructions. Representative images at each $b$-value are displayed for a central slice; windowing has been optimised for each $b$-value but is consistent across reconstructions. Images in the leftmost column (SENSE) have not undergone any phase error correction. Nyquist ghost artefacts are highlighted in yellow, g-noise amplification in red.
Figure 6.4. In-vivo reconstructions. Representative images at each $b$-value are displayed for a central slice; windowing has been optimised for each $b$-value but is consistent across reconstructions. Note that all data from individual channels were corrected using the vendor’s 1D phase-correction prior to reconstruction. The leftmost column (SENSE) displays images corrected only using this 1D phase-correction (no 2D phase-correction). Nyquist ghost artefacts are highlighted in yellow, g-noise amplification in red.
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Figure 6.5. Digital phantom SNR maps. SNR is calculated using the multiple replica method in $b=0$ data for each 2D phase-correction method; the leftmost image has not been phase-corrected. The average SNR in WM for the displayed slice is also provided.

Figure 6.6. SNR performance across $b$-values. SNR is calculated using the multiple replica method for a randomly chose DW volume for each $b$-value and averaged across WM. Data is simulated using the digital phantom.

Figure 6.7. In-vivo SNR maps. SNR is calculated using the multiple replica method in $b=0$ data for each 2D phase-correction method; the leftmost image has been corrected using the vendor’s 1D phase-correction method only. The average SNR in WM for the displayed slice is also provided.
data, whereas for the DSEPI method the SNR is increased across all volumes. Crucially, the SNR performance of PAGE and PEC-SENSE in the DW volumes is less straightforward to predict. Multiple replicas of a randomly chosen DW volume for each $b$-value were therefore simulated using the digital phantom to assess SNR performance across $b$-values (Fig. 6.6). PEC-SENSE achieved relatively good SNR preservation for $b \leq 1000$ s/mm$^2$ with reductions under 10%; however, at $b = 2500$ s/mm$^2$, given the much lower signal, the effect of $g$-noise amplification reduced the SNR by 20%. The greatest SNR reductions were observed at $b = 2500$ s/mm$^2$ in PAGE, at 38%.

**In-vivo**

SNR maps calculated using multiple $b = 0$ replicas in-vivo showed similar trends to the phantom data (Fig. 6.7). SNR reductions in the PAGE reconstruction corresponded spatially to regions with increased $g$-factor, but the overall penalty was less severe than in-silico with an average reduction across WM of 29%. SNR was reduced in PEC-SENSE by 10%, and increased in the DSb0 method by 38% (factor of $\sim \sqrt{2}$).

### 6.5.3 Artefact suppression

**Digital phantom**

The residual error following phase correction is demonstrated in-silico in Fig. 6.8. Without phase correction, a sinusoidal error variation corresponding to the simulated ghost intensity (Section 6.2.2) was observed across all $b$-values. Also evident was a large, localised error in the $b = 0$ data (AP $\sim 70\%$) corresponding to the narrow region of aliased CSF; this was notably absent in the DW images owing to suppression of the CSF signal by the diffusion gradients (AP $\sim 1.8\%$ in the same region).

The ghost was almost fully suppressed by the DSEPI correction, although a residual artefact was observed owing to phase cancellation during averaging (Section 6.3.3). The error magnitude in these lateral regions was minimal, though, with a mean AP of 1.7% across WM at $b = 2500$ s/mm$^2$. Given the identical correction method, ghosting in $b = 0$ volumes of the DSb0 method was equally well suppressed; conversely, with no correction applied to the DW volumes, AP maps for these retained biases from Nyquist ghosting.

Mean errors in PAGE ranged from $\langle AP \rangle = 3.8\%$ at $b = 0$ to $\langle AP \rangle = 43\%$ at $b = 2500$ s/mm$^2$. PEC-SENSE performed relatively well at $b = 0$ with $\langle AP \rangle = 0.7\%$, but performance similarly deteriorated at high $b$-values, with $\langle AP \rangle = 33\%$ at $b = 2500$ s/mm$^2$.

To better characterise the residual artefacts in PAGE and PEC-SENSE - that is to eluci-
6.5. Results

a. Single, randomly chosen DW direction

b. Powder average of all DW directions

Figure 6.8. Digital phantom AP maps. a. AP maps for a single, randomly chosen DW image. b. AP maps averaged over all volumes. Note that images in the leftmost column (SENSE) of each figure have not undergone any phase error correction.
Figure 6.9. Digital phantom AP noise dependence. The mean AP in WM is presented separately for each $b$-value; the error bars indicate the variation (standard deviation) in mean AP across the volumes. a Noisy data (SNR=25). b. Noise-free data.
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Date between incomplete phase correction and g-noise amplification - the same analysis was performed on noise-free simulations. Ghost and ground-truth datasets were subsequently created without adding noise and reconstructed using each phase-correction technique. An analysis of the average AP in each EPI volume (Fig. 6.9a) demonstrates the progressive degradation in image quality (increase in AP) with increasing $b$-value in PAGE and PEC-SENSE. In the noise-free PAGE and PEC-SENSE reconstructions, however, $\langle AP \rangle = 0$ for all $b$-values and diffusion directions (Fig. 6.9b). Similar mean AP values were observed in the noisy and noise-free SENSE, DSb0 and DSEPI reconstructions at $b \leq 1000$ s/mm$^2$ with only marginal increases observed in noisy data at $b = 2500$ s/mm$^2$; the implication here is that these reconstructions were only minimally affected by noise.

In-vivo

Although there was no ground truth data in-vivo, similarities in spatial biases were observed in the AP maps generated with respect to the pseudo ground truth pDSEPI reconstruction (Fig. 6.10). Without 2D phase correction, aliasing from CSF generated large, localised errors ($AP \sim 24\%$) in the $b=0$ data, although no sinusoidal variations in AP were observed. No errors were observed in the $b=0$ data of the DSb0 reconstruction as the correction was identical to that of the reference pDSEPI dataset. Evidence of residual ghosting was apparent in the SENSE and DSb0 AP maps for $b = [1000, 2000, 3000]$ s/mm$^2$. A plot of the average AP per EPI volume (Fig. 6.11) shows that errors increased with $b$-values, with $\langle AP \rangle = 15\%$ at $b = 3000$ s/mm$^2$.

PAGE and PEC-SENSE both showed signs of bias from g-noise amplification: $\langle AP \rangle = 45\%$ was observed in PAGE and $\langle AP \rangle = 40\%$ in PEC-SENSE at $b = 2500$ s/mm$^2$. The average AP per EPI volume (Fig. 6.11) once again demonstrated a significant and progressive degradation of image quality in PAGE and PEC-SENSE with increasing $b$-value. Additional artefacts not characteristic of the Nyquist ghost artefact were observed anteriorally in the AP maps for PAGE and PEC-SENSE.

6.5.4 Model parameter accuracy and precision

Digital phantom

Biases from ghosting and reconstruction artefacts were directly evident in the raw parameter maps obtained from fitting the DT, DK and NODDI models in-silico (Fig. 6.12). Voxel-wise error maps in Fig. 6.13, calculated relative to artefact-free ground truth simulated data, elucidate these findings.
Figure 6.10. **In-vivo AP maps.** a. AP maps for a single, randomly chosen DW image. b. AP maps are averaged over all volumes. Note that images in the leftmost column (SENSE) of each plot have been corrected with the vendor’s 1D phase correction only (no 2D phase correction).
Figure 6.11. In-vivo AP dependence. The mean AP in WM in all five subjects is presented separately for each $b$-value; the error bars indicate the variation (standard deviation) in mean AP across the volumes.

Errors in parameter estimates generally displayed a similar spatial distribution to the AP. Without phase correction, this manifested as localised regions of high error magnitude corresponding to the aliased CSF signal - local errors of $|\epsilon| \sim 40\%$ were observed in FA, for example - accompanied by more subtle but global sinusoidal errors. No errors were observed in the FA and MD maps of the DSEPI reconstruction, although small error spikes were visible in the MK and OD maps. For the PAGE and PEC-SENSE reconstructions, error maps were once more dominated by the effects of $g$-noise amplification, with MK and OD particularly affected. Parameter maps in the DSb0 reconstruction were also notably corrupted, with significant global sinusoidal variations visible in all parameter estimates.

The accuracy and precision of parameter estimates is illustrated in Fig. 6.14a, which shows box plots of the voxel-wise error for each reconstruction. Without phase correction, the error median (denoted $\bar{\epsilon}$) was close to zero and the interquartile range (IQR) was narrow despite the localised regions with high error magnitude: $\bar{\epsilon}_{FA} = -0.9\%$ (IQR = 5.0\%), $\bar{\epsilon}_{MD} = 0.1\%$ (1.2\%), $\bar{\epsilon}_{MK} = 0.2\%$ (5.3\%) and $\bar{\epsilon}_{OD} = 0.1\%$ (5.3\%). The performance of the DSb0 correction was comparable for FA, MD and OD with $\bar{\epsilon}_{FA} = -0.1\%$ (1.9\%), $\bar{\epsilon}_{MD} = -0.4\%$ (3.6\%), $\bar{\epsilon}_{OD} = 0.3\%$ (5.2\%), but MK accuracy and precision was worse with $\bar{\epsilon}_{MK} = -0.7\%$ (9.5\%). PEC-SENSE errors were marginally greater for FA and MD, but demonstrated significant overestimations for MK and OD: $\bar{\epsilon}_{FA} = -1.2\%$ (4.8\%), $\bar{\epsilon}_{MD} = -1.6\%$ (3.7\%), $\bar{\epsilon}_{MK} = 27\%$ (41\%) and $\bar{\epsilon}_{OD} = 11\%$ (33\%). Parameter estimates
Figure 6.12. Digital phantom parameter maps. Representative FA, MD, MK and OD maps are shown for each reconstruction. Note that the leftmost column (SENSE) has not undergone any phase correction. Nyquist ghost artefacts are highlighted in yellow, g-noise amplification in red.

Figure 6.13. Digital phantom voxel-wise parameter errors. Errors calculated relative to ground truth artefact-free simulated data are displayed for each parameter and reconstruction; note that the leftmost column (SENSE) has not undergone any phase correction.
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Figure 6.14. Digital phantom global parameter errors. Box plots of voxel-wise errors in WM for each parameter and reconstruction. a. Noisy data (SNR = 25). b. Noise-free data. Note that the leftmost group of error distributions (SENSE) have not undergone any phase correction.
derived from the PAGE reconstruction were all heavily biased by g-noise amplification: with the exception of MD, all parameters were overestimated, with $\tilde{\varepsilon}_{FA} = 1.4\% (13.6\%)$, $\tilde{\varepsilon}_{MD} = -0.3\% (5.0\%)$, $\tilde{\varepsilon}_{MK} = 30\% (60\%)$ and $\tilde{\varepsilon}_{OD} = 10\% (50\%)$.

The influence of noise on the accuracy and precision of parameter estimates is illustrated in Fig. 6.14b, which provides box-plots of the voxel-wise error for equivalent noise-free simulated data. Errors persisting in SENSE and DSb0 reconstructions show that parameter accuracy and precision of these methods were primarily affected by incomplete phase correction, while the absence of errors observed in PAGE and PEC-SENSE reconstructions confirm that parameter estimates were primarily biased by g-noise amplification for these corrections.

**In-vivo**

Without 2D phase correction, Nyquist ghosting was evident in both the raw parameter maps (Fig. 6.15) and in maps of the error computed relative to the pseudo ground truth pDSEPI data (Fig. 6.16). Evidence of a residual Nyquist ghost was also present in the MD error map for the DSb0 correction, and a trend towards overestimation of FA and underestimation of MD was observed. Parameter maps derived from PAGE and PEC-SENSE reconstructions were not visibly corrupted by g-noise amplification in the image centre; however, OD was globally overestimated in both. An additional anteriorly localised artefact - initially detected in the AP maps for PAGE and PEC-SENSE - was also present in the error maps for FA and MD.

Box plots of the voxel-wise error across all subjects in Fig. 6.17 illustrate the effects of the spatially-varying residual ghosts and g-noise amplification on the accuracy and precision of parameter estimates globally. Without 2D phase correction, parameter estimates were generally accurate (errors were approximately centred on zero), although the precision was considerably worse than in-silico: $\tilde{\varepsilon}_{FA} = 1.9\% (18\%)$, $\tilde{\varepsilon}_{MD} = 0.4\% (9.2\%)$, $\tilde{\varepsilon}_{MK} = -1.2\% (11\%)$ and $\tilde{\varepsilon}_{OD} = 0.0\% (10\%)$. Errors in the DSb0 correction were arguably worse owing to the overestimation of FA ($\tilde{\varepsilon}_{FA} = 4.5\% (14\%)$) and underestimation of MD ($\tilde{\varepsilon}_{MD} = -2.6\% (6.3\%)$); however precision was improved relative to the standard SENSE reconstruction. No improvements relative to the standard SENSE reconstruction were seen in the MK and OD estimates using the DSb0 correction method: $\tilde{\varepsilon}_{MK} = -1.1\% (10\%)$, $\tilde{\varepsilon}_{OD} = 0.2\% (10\%)$.

The accuracy and precision of FA and MD estimated using the PEC-SENSE recon-
Figure 6.15. In-vivo parameter maps. A representative map of FA, MD, MK and ODI estimates from a single subject are shown for each reconstruction. Note that the leftmost column (SENSE) has been corrected with the vendor’s 1D phase correction only (no 2D phase correction).

Figure 6.16. In-vivo voxel-wise parameter errors. Errors calculated relative to the silver-standard pDSEPI reference data are shown for each parameter and reconstruction in a single representative subject. Note that the leftmost column (SENSE) has been corrected with the vendor’s 1D phase correction only (no 2D phase correction).
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Figure 6.17. In-vivo global parameter errors. Box plots of the voxel-wise errors across all subjects in WM are shown for each parameter and reconstruction. Note that the leftmost group of error distributions (SENSE) have been corrected with the vendor’s 1D phase correction only (no 2D phase correction).

Construction were comparable to the standard SENSE reconstruction, with $\tilde{\epsilon}_{\text{FA}} = 0.7\% (22\%)$, $\tilde{\epsilon}_{\text{MD}} = 0.2\% (11\%)$; however, overestimations of MK and OD were apparent with $\tilde{\epsilon}_{\text{MK}} = 6.3\% (29\%)$, $\tilde{\epsilon}_{\text{OD}} = 6.4\% (20\%)$. Parameter precision was low for all parameters derived from the PAGE reconstruction, and, with the exception of MD, there was a tendency for overestimation: $\tilde{\epsilon}_{\text{FA}} = 4.1\% (28\%)$, $\tilde{\epsilon}_{\text{MD}} = 0.1\% (12\%)$, $\tilde{\epsilon}_{\text{MK}} = 5.7\% (37\%)$ and $\tilde{\epsilon}_{\text{OD}} = 5.8\% (25\%)$.

6.6 Discussion

Nyquist ghost artefacts are prevalent in EPI, but high b-value DW-data are often left uncorrected owing to a lack of appropriate correction methods that can account for low SNR and additional phase errors arising from physiological motion. Simulated data in this chapter characterised the effects of uncorrected Nyquist phase errors observable in derived parameter maps; these biases were corroborated in-vivo even after 1D phase correction, confirming the need for robust 2D phase error correction in DW-EPI. However, the systematic evaluation of 2D phase correction techniques performed here - both in-silico and in-vivo - demonstrated varying degrees of success in artefact correction. PAGE and PEC-SENSE both resolved the phase error but introduced secondary artefacts into parameter estimates from g-noise amplification and reconstruction errors. Conversely, the DSb0 correction did not suffer from noise or reconstruction artefacts, but incomplete phase error correction led to biases in the derived parameter maps.

Phase errors may vary considerably depending on a number of imaging factors, including slice orientation and diffusion weighting [130, 134]; the degree of ghosting may subse-
6.6. Discussion

Consequently vary between subjects and lead to erroneous conclusions regarding microstructural tissue integrity, particularly if there are biases in positioning between patients and healthy subjects, or subjects of different age and gender for example. Implementing a robust phase correction procedure for DW data is therefore imperative, but, as is demonstrated in this chapter, compromises between ghost suppression and reconstruction artefacts are currently inevitable.

6.6.1 Method 1: PAGE

The benefits of PEC-SENSE over PAGE in SE EPI (i.e. no DW) have been previously discussed [151]; the motivation for including PAGE in this analysis was to provide a baseline for comparison in high $b$-value data, where there was the potential for low SNR to adversely affect the phase error map estimation in PEC-SENSE. However, PAGE was outperformed by PEC-SENSE at all $b$-values in terms of SNR preservation, AP, and parameter accuracy. Consequently, and owing to similarities between the methods, the subsequent discussion will focus primarily on PEC-SENSE.

6.6.2 Method 2: PEC-SENSE

In noise-free simulations, PEC-SENSE provided perfect artefact correction for the phase error modelled in this work. Practically, though, the efficacy of the method was dependent on two key features of the underlying data quality. Firstly, generation of an accurate phase correction map was contingent upon SNR high enough that the already ill-conditioned SENSE problem was not overtly affected by the doubled acceleration factor required to calculate the map. Consequently, $g$-noise amplification in the phase correction map introduced substantive artefacts into reconstructions both in-silico and in-vivo, even after smoothing the phase map; moreover, the influence of $g$-noise amplification became progressively greater in higher $b$-value data owing to stronger signal attenuation. This potentially explains the disproportionately large errors observed in MK and OD. These parameters rely on high $b$-value (low SNR) data to fit the respective DKT and NODDI models, whereas the DT model (from which FA and MD are derived and for which errors were comparable to the standard SENSE reconstruction) is fitted to data with $b \leq 1000 \text{ s/mm}^2$ and so relatively well preserved SNR.

Secondly, accurate estimates of coil sensitivity maps were crucial for optimal performance. Slight mismatches between the estimated coil profiles and the true sensitivity encoding of the data can arise from a number of factors, such as differing distortions (coilmaps
are always fully sampled) or subject motion between the coilmap and DW-EPI acquisitions. The doubled SENSE acceleration factor inherent in the method renders PEC-SENSE more sensitive to small discrepancies in the coilmap estimation, so this could explain the additional artefacts seen anteriorly in-vivo - which manifested in a manner similar to the Nyquist ghost - but not in-silico.

6.6.3 Method 3: DSb0

By design, the DSb0 method does not fully correct the phase error. Under the assumption that a lack of power in ghost artefacts in DW images minimally affects the data, these volumes are not corrected. However, while this is a common correction scheme, the impact of this assumption on derived parameter maps has not been considered before.

It was demonstrated here that the disparity between a corrected \( b = 0 \) signal and uncorrected DW signal can significantly bias parameter estimates. The effect was most apparent in estimates of MD and MK in-silico: errors were observed globally, and were introduced to regions that were unbiased without phase correction. In-vivo, the discrepancy led to a global overestimation of FA and underestimation of MD. The reason for these biases is not easy to identify: it is likely dependent on the exact phase error that produces the ghost image, which, if fully known, could be trivially corrected.

6.6.4 Method 4: DSEPI and pDSEPI

The pDSEPI method was implemented in-vivo to provide a reference ‘ghost-free’ dataset. Experiments in-silico verified that the DSEPI method accurately corrects Nyquist ghost artefacts in the absence of any other phase errors; however, additional shot-to-shot phase variation in-vivo, arising, for example, from physiological noise, prohibited the complex averaging of DW-volumes. This is illustrated in Fig. 6.18a: severe signal drop out is introduced if two volumes with random phase errors from physiological noise are averaged using complex data. Simulations of such shot-to-shot phase variation - achieved by shifting the centre of \( k \)-space, corresponding in turn to a rotation in image-space [162] - corroborate the artefacts observed in-vivo (Fig. 6.18b). This necessitated the pDSEPI correction in-vivo, which by design is an imperfect solution. Associated limitations are discussed in Section 6.6.6.

6.6.5 Implications and potential solutions for phase correction in DW-EPI

There is a clear need for robust 2D phase correction in DW-EPI: the manufacturer’s 1D phase correction was not sufficient to remove the ghost image in-vivo, which was evident
6.6. Discussion

a. In-vivo

b. In-silico

Figure 6.18. Shot-to-shot phase variation. a. The complex average of two volumes in-vivo acquired consecutively with opposing $k$-space trajectories is shown. Random phase variations between the images (arising from physiological noise) result in phase cancellation and severe signal drop out. b. Shot-to-shot phase variation was simulated in the digital phantom by randomly shifting the centre of $k$-space. This corresponds to a rotation in image-space, which is the movement likely to arise from physiological noise [162].

in all 5 subjects and propagated into derived parameter maps. However, each correction method implemented here demanded some compromise between robust ghost correction and reconstruction-related artefacts. The key finding was that, while the DSb0 method was demonstrably not a correct solution, reconstruction-related artefacts in PAGE and PEC-SENSE resulted in some parameter estimates that were both less accurate and less precise than the DSb0 correction. However, the DSb0 method is undesirable as a permanent solution owing to its fundamental flaws. Provided a solution to the $g$-noise amplification could be found, PEC-SENSE may be a viable alternative candidate: no additional acquisition time is needed and temporal variability in ghosting artefacts is addressed by correcting each volume independently.

Acquisition-based approaches could also be implemented to reduce the accrued phase error, but there are also inevitable trade-offs here. Lower bandwidths, for example, can reduce the intensity and temporal variation of ghosting artefacts [163]: readout bandwidth is linearly related to readout gradient strength, and so reducing the bandwidth lowers the readout gradient, its associated eddy currents, and the subsequent phase errors. However,
this comes at the price of increased geometric distortions, as the effects of magnetic field inhomogeneities are accentuated owing to longer sampling times.

6.6.6 Limitations

A confounding factor in the interpretation of in-vivo results was the lack of a ground truth data set. The silver standard pDSEPI acquisition suppresses the ghost but does not fully correct it, making interpretations of AP and parameter accuracy difficult. Assuming that some degree of ghosting remained in the reference data, though, it is likely that errors were underestimated: residual ghosting in both the reference and test data, for example, could explain the lack of sinusoidal intensity variation observed in-silico. However, this could also be explained by the 1D phase error correction performed in-vivo but not in-silico.

In this work, a relatively simple phase error was implemented for the in-silico experiments. More complexity could be introduced with additional 1D phase errors or shot-to-shot phase variations representing physiological noise and would offer a more comprehensive analysis of the methods; however, for the purposes of method comparison, the phase error implemented here was considered sufficient.

PAGE and PEC-SENSE were both disproportionately affected by experimental design. In-silico, simulated coil sensitivity profiles were relatively inhomogeneous even after optimisation experiments; this, combined with the effective doubling of the acceleration factor inherent in the methods, caused excessive g-noise amplification. In-vivo, minor errors in coil map estimation together with a non-optimal in-house SENSE implementation transpired to produce significant SENSE artefacts in the reconstructions. Tikhonov regularisation was used to improve the conditioning of the problem; however, a more in-depth exploration into SENSE implementations was out of the scope of this comparison. Iterative SENSE and regularisation using a body coil image, for example, could greatly improve image quality and should be explored in future work. Alternative ways of obtaining coil sensitivity profiles could also be explored: data-driven approaches to coil map estimation such as ESPIRiT [164], for example, could provide a more robust result. Ultimately, a worst case scenario for PAGE and PEC-SENSE, both in-silico and in-vivo, was examined here.

Corrections for Gibbs ringing, motion and eddy current distortion were not applied before computation of parameter maps. This is likely to affect the accuracy of the parameter estimates, and could explain the large error spikes in MK and OD. However, as errors will be systematic in each of the phase-correction methods tested, the comparative analysis is
6.7 Conclusions

A key motivation for this work was to assess the applicability of phase-correction methods in high $b$-value, low SNR data. The methods implemented here were chosen as they represented plausible solutions for our MR facility. Crucial properties included compatibility with SENSE reconstruction, parallel imaging and multi-band imaging. The findings showed that a trade-off is currently unavoidable with each of the methods as they stand. Ultimately, whether the trade-off was with insufficient artefact suppression, $g$-noise amplification or acceleration-based reconstruction artefacts, the net effects were unpredictable biases in the estimation of quantitative tissue parameters. Imaging biomarkers not explicitly evaluated in this chapter are also likely to be affected by uncorrected Nyquist ghosting; greater uncertainties or biases in fibre orientation estimates, for example, could affect tractography algorithms and subsequent analyses of brain networks. Development of the PEC-SENSE approach via mitigation of $g$-noise amplification could provide a solution with robust phase correction and limited reconstruction-related artefacts.
Chapter 6. Giving up the ghost: correcting DW-EPI phase errors
Chapter 7

Denoising complex channel data: proof of concept

7.1 Introduction

MR images are inherently noisy, meaning that compromises between SNR, acquisition times and image quality are common. SNR can be improved by acquiring more data points (for example by increasing signal averages or the \( k \)-space sampling density) or reducing image resolution; however, owing to the high angular resolution requirements typical in dMRI, standard acquisition times are already long and resolution is correspondingly coarse. A further complication for dMRI is the rectification of the complex signal, which introduces a minimum measurable signal, or ‘noise floor’. This is particularly limiting for highly attenuated data acquired with large \( b \)-values, and overestimations of signals close to the noise floor are concomitant [165]. Post-processing approaches for reducing noise in dMRI are therefore desirable.

Denoising magnitude data after image reconstruction can alleviate some of the effects of noise in DWI. Principal component analysis (PCA), for example, can help improve image quality by exploiting the redundancies in high dimensional DWI to identify and remove noise-only components [166–171] (Section 7.2.1). Reductions in the noise floor, though, can only be achieved by denoising complex data prior to rectification (Section 2.6.2).

Denoising complex data from individual channels prior to reconstruction has the potential to both reduce the noise floor and increase image SNR owing to increased data redundancy compared to magnitude denoising. While this approach has been demonstrated using GRAPPA for parallel image reconstruction [172], it has never before been validated for SENSE-based parallel image reconstruction. The extension to a SENSE-based reconstruction is non-trivial: in GRAPPA, the missing \( k \)-space lines are filled in \( k \)-space prior to the inverse Fourier transformation (iFT) into image space, meaning that full field-of-view
(FOV) images are generated for individual coils prior to image reconstruction; in SENSE, the correction is made in the image domain after the iFT, so data from individual channels are aliased.

For a PCA-based denoising approach, image aliasing has the potential to introduce confounding factors. For example, associated increases in significant signal components per voxel relative to noise-only components may alter expectations regarding the bulk distribution of eigenvalues and reduce the efficacy of the method. Moreover, any non-linear transformation - such as SENSE, GRAPPA, partial Fourier encoding, re-gridding, or other imaging filter - distorts the original independent and identically distributed (iid) Gaussian noise statistics and so violates the fundamental assumption of a PCA-based denoising strategy.

This chapter therefore presents a proof-of-concept study for PCA-based denoising of images from individual channels that are under-sampled from partial Fourier encoding and parallel image acceleration using SENSE. The impact of partial Fourier encoding and SENSE-based aliasing are first separately considered using synthetic DW data. The method is then validated in-vivo for the first time using a high resolution DW data set acquired with both partial Fourier encoding and SENSE acceleration. This acquisition provides the opportunity to verify the applicability of the method in a challenging data set that encompasses low SNR from high resolution and under-sampling along with distorted noise statistics from non-linear transformations.

7.2 Theory

A successful denoising technique is one that can (i) remove noise without introducing blurring or partial volume effects, both of which can result in the removal of small anatomical details (potentially reducing sensitivity to subtle pathological alterations), and (ii) cope with spatially varying noise levels. Spectral filtering methods, for example, decompose the data into low frequency (image) and high frequency (noise) components - typically using wavelets [173–175] - but can remove small anatomical details if sharp edges contribute to the filtered high frequency band. Many image-domain techniques, though, such as the Gaussian filter [176], non-local means (NLM) filter [177, 178] or anisotropic diffusion filter (ADF) [179, 180], can suffer from blurring and partial volume effects. PCA-based denoising (Section 7.2.1) is in principle more robust to these limitations, assuming appropriate elimination of noise-only eigenvectors (Section 7.2.2).
Denoising methods are typically applied to magnitude MR data after reconstruction. While signal fluctuations may be significantly reduced, the underlying noise floor remains unchanged as the noise floor is created during signal rectification. Using the method of moments correction [181] it is possible to mitigate some of this bias; however, it cannot be completely removed and signals at high $b$-values remain artificially inflated owing to the presence of the noise floor. This in turn can affect estimates of microstructural tissue parameters.

Denoising complex data therefore offers the opportunity of noise floor reductions, as signal fluctuations are reduced prior to the magnitude operation. This has the potential for increased contrast at lower SNR levels, either from higher $b$-values or higher resolution. Beyond this, the extra redundancy offered by denoising complex data from individual channel prior to image reconstruction could further reduce the noise floor.

### 7.2.1 Principal component analysis

PCA is a linear transformation that projects some measured data onto a new set of orthogonal basis vectors such that the greatest variance is described by the first coordinate of the new system and the smallest variance by the last component. Dimensionality reduction is achieved by suppressing the smallest components, which contain little information, and representing the data using a few principal components only.

DWI lends itself to PCA owing to high redundancy in the data: the multiple DW measurements are correlated because each acquisition is measuring the same underlying processes, meaning that the signal can be efficiently represented by a small number of linearly independent parameters $P$. Redundancy is further enforced by denoising small local patches on the order of $3 \times 3 \times 3$ pixels as opposed to the whole image.

Given an $M \times N$ measurement matrix $\mathbf{X}$, with each row one of the $M$ DW measurements and each column one of the $N$ voxels in the local patch, PCA linearly transforms the data into a set of uncorrelated variables $\mathbf{T}$ (Eq. 7.1). The projection matrix $\mathbf{U}$ is described by an $M \times M$ orthonormal matrix whose columns are the eigenvectors of the covariance matrix $\mathbf{XX}^T$ (Eq. 7.2).

\[
\mathbf{T} = \mathbf{XU} \tag{7.1}
\]
\[
\mathbf{Q} = \frac{1}{N} \mathbf{XX}^T = \mathbf{U} \Lambda^2 \mathbf{U}^T \tag{7.2}
\]

For numerical precision $\mathbf{U}$ and $\Lambda$ are obtained from the singular value decomposition of $\mathbf{X}$ (Eq. 7.3), where $\mathbf{U}$ and $\mathbf{V}$ are the left and right singular vectors of $\mathbf{X}$, and $\Lambda$ are the singular values.
values of $X$, the square root of which are equal to the eigenvalues of the covariance matrix $Q$.

$$X = \sqrt{N} U \Lambda V^T$$  \hspace{1cm} (7.3)

Dimensionality reduction is achieved by selecting an eigenvalue threshold, $\lambda_+$, to nullify all components for which $\lambda < \lambda_+ (\Lambda \rightarrow \tilde{\Lambda})$ and reconstructing the matrix to return $\tilde{X}$ (Eq. 7.4).

$$\tilde{X} = \sqrt{N} U \tilde{\Lambda} V^T$$  \hspace{1cm} (7.4)

### 7.2.2 Random matrix theory

Random matrix theory (RMT) has been recently proposed as a method for selecting the eigenvalue threshold $\lambda_+$ [171]. RMT states that for a random matrix $X$ - for example a noise-only matrix composed of iid Gaussian variables with zero mean and variance $\sigma^2$ - its eigenvalues are described by the Marchenko-Pastur (MP) distribution [182] (Fig. 7.1). This states that the probability of observing some eigenvalue $\lambda$ given a variance $\sigma$ and matrix size ratio $\gamma = M/N$ is given by $p(\lambda|\sigma, \gamma)$, with eigenvalue limits $\lambda_{\pm} = \sigma^2 \left( \sigma^2 \pm \sqrt{\gamma} \right)^2$ (Eq. 7.5). Note that the maximum number of eigenvalues is given by $O \equiv \min\{M,N\}$, so for $M < N$ only the first $M$ eigenvectors are obtained.

$$p(\lambda|\sigma, \gamma) = \begin{cases} \frac{\sqrt{(\lambda_+-\lambda)(\lambda-\lambda_-)}}{2\pi\gamma\sigma^2}, & \lambda_- \leq \lambda \leq \lambda_+ \\ 0, & \text{otherwise} \end{cases} \hspace{1cm} (7.5)$$

The expectation and width of the MP spectrum are given in Eqs. 7.6 and 7.7 respectively.

$$\int_{\lambda_-}^{\lambda_+} p(\lambda|\sigma, \gamma) \lambda d\lambda = \sigma^2 \hspace{1cm} (7.6)$$

$$\lambda_+ - \lambda_- = 4\sqrt{\gamma}\sigma^2 \hspace{1cm} (7.7)$$

If $X$ is now derived from noisy DW data with $P$ significant components (described by the $P$ largest PCA eigenvalues), the MP distribution still holds for the $\bar{O} = O - P$ noise-only eigenvalues so long as $P \ll \bar{O}$: a few signal-carrying components do not significantly distort the bulk distribution.

The upper edge of the MP distribution $\lambda_+$ can be estimated by iteratively computing the mean of the $O - P_i$ smallest eigenvalues, where $P_i$ indexes the $i$th eigenvalue. In principle, the mean will exceed the expectation value of the MP distribution $p(\lambda|\sigma, \gamma_i)$ (with $\gamma = (O - P_i) / N$) if one of the eigenvalues represents a significant component, so the number of
Figure 7.1. Marchenko Pastur distribution. This example distribution was generated using DW intensities over a range of $b$-values estimated using simulations of noisy diffusion tensors with isotropic diffusivity (ADC = $2 \times 10^{-3}$ mm$^2$/s, $b = 0 - 5000$ s/mm$^2$, $M = N = 1000$. One significant principal component representing the single ADC value (blue arrow) is visible an an outlier of the MP distribution containing the noise-only eigenvalues (red arrow indicates the upper edge).

significant components $P$ can be estimated by increasing $i$ until Eq. 7.8 holds.

$$\sum_{i=1}^{O} \lambda_{i+1} \geq (O - P) \hat{\sigma}^2 (P)$$  \hspace{1cm} (7.8)

The estimated variance can then be updated for each $i$ as in Eq. 7.9, taking $\lambda_+ \sim \lambda_{i+1}$ and $\lambda_- \sim \lambda_{M}$.

$$\hat{\sigma}^2 = \frac{\lambda_{i+1} - \lambda_{O}}{4 \sqrt{p}}$$  \hspace{1cm} (7.9)

Solving Eqs. 7.8 and 7.9 for $\hat{P} = P$ provides the final estimate of $\hat{\sigma}^2$ (Eq. 7.10).

$$\hat{\sigma}^2 = \frac{\sum_{i=1}^{O} \lambda_i}{O - \hat{P}}$$  \hspace{1cm} (7.10)

Naturally, full noise suppression is unobtainable. Given a variance $\sigma_{\lambda_0}^2$ in the omitted eigenvalues, the variance of residual noise in the $P$ retained eigenvalues, $\sigma_{\lambda_r}^2$, is given by Eq. 7.11.

$$\sigma_{\lambda_r}^2 = \sigma^2 - \sigma_{\lambda_0}^2 \approx \frac{P}{O} \sigma^2$$  \hspace{1cm} (7.11)

PCA denoising of MR data using RMT has been coined MPPCA [170, 171].

7.3 Methods

7.3.1 Simulations I: partial Fourier encoding

To control the exact number of components in a voxel and to avoid any other confounding factors, a simple digital phantom was used for this experiment. The Shepp-Logan digital
phantom was generated in Matlab 2017b (The MathWorks, Natick, MA, USA) with a resolution of $128 \times 128$ pixels in-plane and 11 slices. Isotropic diffusion tensors were simulated in each ellipse with ADC values ranging between $1 - 5 \times 10^{-3}$ mm$^2$/s (constant within an ellipse). Diffusion weighting intensities were computed for 21 $b$-values distributed equidistantly between $b = [0, 2000]$ s/mm$^2$ using Eq. 7.12; each shell was replicated 6 times to give $M = 126$. Gaussian noise was added in quadrature to $k$-space to achieve SNR$_{base} = 15$ (as measured across the 6 replicas of the $b=0$ images) in the fully sampled data.

\[ S(b) = S_0 \exp(-b \cdot \text{ADC}) \] (7.12)

Partial Fourier encoding was simulated by removing 51 lines of $k$-space along the $x$-axis, corresponding to a partial Fourier factor of 0.6 (the highest level used in-vivo). Three reconstruction algorithms were implemented in Matlab: zero-filling, homodyne detection [42], and projection onto convex sets (POCS) [43] (Section 2.4). The SNR gain in each data set was then evaluated using three denoising kernels whose geometry was chosen to investigate any spatial correlations introduced by partial Fourier reconstruction:

i. Isotropic $5 \times 5 \times 5$ voxels ($N = 125$) (kernel axes spanning all spatial axes)

ii. Plate $11 \times 1 \times 11$ voxels ($N = 121$) (kernel axes spanning the partial Fourier encoded $x$-axis and one orthogonal axis, $z$)

iii. Plate $1 \times 11 \times 11$ voxels ($N = 121$) (kernel axes not spanning the partial Fourier encoded $x$-axis)

Denoising was performed on complex images in all cases.

### 7.3.2 Simulations II: parallel imaging

In order to assess the effects of potential distortions to the bulk distribution of eigenvalues arising from parallel image aliasing, a digital phantom in which the DW signal was represented by multiple principal components reflective of in-vivo acquisitions was required; the D-BRAIN digital phantom [156] (described in detail in Section 6.4) was therefore used for these experiments. Noise was added in quadrature to $k$-space in each of the 132 volumes ($12 b=0$, $60 b=1000$ s/mm$^2$, $60 b=2500$ s/mm$^2$) to give SNR = 25 in the $b=0$ data. Aliasing corresponding to acceleration factors of $R = [1.0, 1.5, 2.0, 2.5]$ was simulated by removing equidistant lines of $k$-space along the $y$-axis. Each data set was denoised using the $5 \times 5 \times 5$ isotropic kernel and the $11 \times 1 \times 11$ plate kernel.

As with any operation involving sliding kernels, image edges typically require different
7.3. Methods

treatment. Here, a wrapped kernel is proposed for edges where image data is continuous owing to aliasing (i.e. along the phase-encoding axis).

Kernel performance in the folded data was evaluated by analysing the distribution of residuals between the noisy and denoised data ($S$ and $\tilde{S}$ respectively), normalised using the estimated standard deviation $\hat{\sigma}$.

$$r(x,y) = \frac{S(x,y) - \tilde{S}(x,y)}{\hat{\sigma}(x,y)}$$  \hspace{1cm} (7.13)

7.3.3 In-vivo experiments

Data acquisition

One healthy volunteer (30 years; female) was imaged after providing written informed consent. Single shot spin echo DW-EPI were acquired with TR/TE = 5000/73 ms, SENSE acceleration factor $R = 2$, partial Fourier factor $f = 0.6$, resolution $= 1.2 \times 1.2 \times 1.2 \text{ mm}^3$ and FOV $= 224 \times 224 \times 24 \text{ mm}$ with no slice gap. Diffusion weighting was applied along 30 isotropically distributed directions for $b = 1000, 2000$ and $3000 \text{ s/mm}^2$, with 9 interleaved $b = 0$ volumes. An additional $b = 0$ volume was acquired with opposing phase encoding blips to enable susceptibility-induced distortion correction. Total scan time was 13 min.

Complex data was exported at the earliest practical stage in the reconstruction pipeline to minimise the distortion of noise characteristics from data filtering; complex data from individual channels was thus obtained after 1D iFT along the readout axis and the vendor’s 1D phase correction. Data were therefore in the $(x,k_y)$ domain. All subsequent data processing was performed off-line using Matlab.

Image reconstruction and denoising

Data from each coil were obtained in the image domain following a 1D iFT along the phase-encoding $y$-axis; partial Fourier reconstruction was then performed using POCS (informed from simulation experiments). Decorrelation of the signals from each channel was achieved using a covariance matrix estimated using the same noise-only region in each coil; this ensured that noise statistics in each channel were iid Gaussian (Section 2.6.4). Complex channel data were independently denoised using MPPCA and an isotropic $5 \times 5 \times 5$ kernel (informed from simulation experiments). Finally, the aliased images from each channel were unwrapped and combined using SENSE.

Results of the proposed complex channel denoising method were compared with standard (no denoising) and magnitude MPPCA denoised SENSE reconstructions.
Image post-processing

After partial Fourier reconstruction, channel-wise denoising and SENSE combination, each data set was corrected for Gibbs ringing artefacts using the method of local subvoxel-shifts [183]. Susceptibility distortions, eddy currents and motion were then corrected using FSL’s topup and eddy tools [110, 184, 185]. Finally, $B_1$ field inhomogeneities were estimated using the mean $b=0$ image and FSL’s FAST tool [185], and propagated to all DW volumes.

The DT and DKT were estimated in each dataset using an iteratively re-weighted linear least squares estimator [158, 159]; a maximum of $b = 1000 \text{s/mm}^2$ was used for the DT estimation. FA and MD were derived from the DT model and MK from the DKT model.

Denoising performance was evaluated in terms of the distribution of $\sigma$-normalised residuals (Eq. 7.13) and the distributions of parameter estimates.

7.4 Results

7.4.1 Simulations I: partial Fourier encoding

Fig. 7.2 shows the results of denoising partial Fourier data using varying kernel shapes for zero-filling, homodyne filtering, and POCS reconstructions. Results for full $k$-space data are also shown for comparison. A visual inspection revealed higher residual noise levels for all reconstructions using the $5 \times 5 \times 5$ and $11 \times 1 \times 11$ kernels; in other words, the kernels that sampled multiple voxels along the direction of partial Fourier encoding. The $1 \times 11 \times 11$ kernel performed much better: for POCS, a 9-fold SNR increase was observed relative to a 4-fold increase using either the $5 \times 5 \times 5$ kernel or $11 \times 1 \times 11$ kernels. Significant benefits were also noted for the $1 \times 11 \times 11$ kernel in the zero-filled data, in which SNR gains of almost $11 \times \text{SNR}_{\text{base}}$ were seen compared to under 2 for the $5 \times 5 \times 5$ and $11 \times 1 \times 11$ kernels. The $1 \times 11 \times 11$ plate kernel was less effective for the homodyne reconstruction, although SNR was still increased by a factor of 8 compared to the $4 \times \text{SNR}_{\text{base}}$ seen in the $5 \times 5 \times 5$ kernel or $11 \times 1 \times 11$ kernels. In the full $k$-space data, SNR gains were marginally lower for both plate kernels than for the isotropic kernel; however, all kernels performed well with SNR gains at $\sim 16 \times \text{SNR}_{\text{base}}$. All SNR results are given in Table 7.1.

The SNR dependence on kernel can be elucidated by the number of retained eigenvectors $\hat{P}$ (Fig. 7.3). The full $k$-space example was almost perfectly representative of the underlying ground truth data: no significant components were detected in the majority of noise-only voxels, and only voxels at phantom boundaries required $\hat{P} > 1$ to explain the signal variance (recall that a different diffusivity was modelled in each ellipse, so owing
7.4. Results

Figure 7.2. Noise reduction in partial Fourier encoded data. The top row shows the Shepp-Logan phantom reconstructed using zero-filling, homodyne and POCS solutions; the second row is the same data windowed to better visualise background noise. The bottom three rows show results for denoising using the three kernels. Full $k$-space data is shown in the leftmost column for reference.

Figure 7.3. Significant principal components $\hat{P}$ in partial Fourier encoded data. The colourbar indicates the number of significant eigenvectors detected by the three kernels in partial Fourier encoded data reconstructed using zero-filling, homodyne and POCS solutions. The leftmost column shows full $k$-space data for comparison.
Table 7.1. SNR of partial Fourier encoded data. Baseline SNR values (calculated using repetitions of the $b=0$ data) are provided for each partial Fourier reconstruction of the Shepp-Logan phantom, along with the SNR computed after denoising the data with $5 \times 5 \times 5$, $11 \times 1 \times 11$ and $1 \times 11 \times 11$ kernels. SNR gains ($\times \text{SNR}_{\text{base}}$), calculated as the ratio between the SNR pre- and post-denoising, are also reported.
to the spatial extent of the kernel both were sampled simultaneously at boundaries). As SNR scales with $\sqrt{O/P}$, the full k-space data for this toy phantom essentially demonstrated maximal noise reduction. Fig. 7.3 shows that the number of retained eigenvectors was considerably larger in the partial Fourier data. Specifically, the kernels that sampled data along the partial Fourier encoding direction displayed increased number of significant eigenvectors and correspondingly lower SNR as compared to the $1 \times 11 \times 11$ kernel.

### 7.4.2 Simulations II: parallel imaging

Fig. 7.4 shows the results of denoising aliased images using $5 \times 5 \times 5$ and $11 \times 1 \times 11$ kernels. Examples of the folded, noisy, images are provided for a randomly chosen DWI ($b = 1000 \text{s/mm}^2$) alongside the same image denoised with each kernel. Qualitatively, both kernels denoised the images well; however, a slight ‘striping’ artefact was apparent in data denoised using the $11 \times 1 \times 11$ kernel when viewed orthogonal to the kernel plane.

Maps of residuals relative to noise-free ground truth data (the unsuppressed noise) are provided in Fig. 7.5. More quantitatively, box plots in Fig. 7.6 of the relative errors (residuals normalised using the ground truth noise-free data) were centred on zero, indicating a lack of bias in denoised data irrespective of acceleration factor and denoising kernel. Error distributions were marginally wider for the $11 \times 1 \times 11$ kernel for all acceleration factors; this was reflected in an SNR gain $\sim 20\%$ lower relative to the $5 \times 5 \times 5$ kernel (Table 7.2).

Also shown in Fig. 7.5 are maps of the number of retained eigenvectors $\hat{P}$ required to describe the DW signal in each voxel. No obvious bias from acceleration factor was present: the spatial distributions of $\hat{P}$ varied to reflect the folded images, but a visual inspection suggested that signal components were not substantially increased by image aliasing. A weak dependence on kernel was apparent, though: the $11 \times 1 \times 11$ kernel retained more

<table>
<thead>
<tr>
<th>$R$</th>
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<th>plate kernel</th>
</tr>
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<tr>
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<td>$11 \times 1 \times 11$</td>
</tr>
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</tr>
<tr>
<td>2.5</td>
<td>5.6</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Table 7.2. SNR gains in denoised SENSE-aliased data. SNR gains ($\times \text{SNR}_{\text{base}}$) are computed as the ratio between the SNR pre- and post-denoising.
Figure 7.4. Noise reduction in aliased data. A randomly selected $b = 1000 \text{s/mm}^2$ volume is shown denoised using a $5 \times 5 \times 5$ and $11 \times 1 \times 11$ kernel; the leftmost column shows the original noisy data. Windowing has been optimised for each acceleration factor. Note the ‘striping’ artefacts introduced by the $11 \times 1 \times 11$ kernel - this is perhaps best visualised by the ratio between the two denoised datasets (rightmost column).

Figure 7.5. Residual noise and significant principal components $\hat{P}$ in denoised aliased data. Residuals between the denoised and noise-free ground truth data for a randomly selected $b = 1000 \text{s/mm}^2$ are shown on the left. On the right are the number of significant eigenvectors retained by each denoising kernel. Note the slight dependence of $\hat{P}$ on kernel but not acceleration factor.
Figure 7.6. Relative errors in denoised aliased data. Distributions of relative errors between the denoised and noise-free ground truth data (i.e. residuals normalised by the ground truth) are shown for each acceleration factor; results for the $5 \times 5 \times 5$ kernel are shown on the left, and for the $11 \times 1 \times 11$ kernel on the right. Residuals have been computed across all $b$-values for a central slice.

Properties of the removed noise are captured in the $\sigma$-normalised residuals $r$ between the noisy and denoised data. In the case where all noise (and only noise) has been removed, the normalised residuals should be represented by the standard normal distribution $\mathcal{N}(0,1)$. Plotting the logarithm of the distribution $p(r)$ against $r^2$, then, should yield a straight line with gradient $= -0.5$. Standard deviations greater than unity (gradient $> -0.5$) indicate that signal components have been removed from the data: there is more variance in the suppressed eigenvectors than can be explained by noise alone. Plots of the error distributions are shown in Fig. 7.7 for each aliased image denoised using both kernels. In all cases the residuals were well represented by a normal distribution across all $b$-values, with standard deviations between 0.66-0.69.

7.4.3 Validation in-vivo

Fig. 7.8a shows a representative selection of images from individual channels before and after complex denoising. Noise suppression was evident, but stripe-like patterns in the background noise indicated the presence of spatial noise correlations from the partial Fourier encoding. Analysis of the $\sigma$-normalised residuals showed a corresponding deviation from Gaussianity in the tails of the removed noise distribution (Fig. 7.8b).

Example DWI and parameter maps are shown in Figs. 7.9a and 7.9b for a qualitative
Figure 7.7. Suppressed noise properties. Logarithms of the distributions of $\sigma$-normalised residuals between denoised and noisy data (the suppressed noise), $p(r)$, are plotted against $r^2$. Real and imaginary components of the residuals have been combined. Distributions are perfectly Gaussian (straight lines); standard deviations range between 0.66-0.69. The normal distribution is shown for reference (black line).
Figure 7.8. Demonstration of complex channel denoising in-vivo. a. Example channel images pre and post denoising with the $\sigma$-normalised residuals. b. Distributions of the normalised residuals (blue circles) demonstrate non-Gaussian behaviour in the deviation of the tails away from the equivalent normal distributions (solid blue lines; the standard normal distribution is in black for reference.)
Figure 7.9. Reconstructions and parameter maps in-vivo. a. A representative slice is shown for each reconstruction and $b$-value. Windowing is consistent across reconstructions but is optimised for each $b$-value. Maps of FA, MD and MK estimates are also shown. b. Distributions of parameter values within the blue ROI indicated in the MD map (top row).
comparison. The SNR measured across repetitions of the $b=0$ images was 6.6, 6.9, and 9.0 respectively for the standard, magnitude MPPCA, and complex channel MPPCA reconstructions. Diffusion parameters showed decreased contrast in the standard reconstruction (without denoising); this was particularly notable in the FA map. Distributions of parameter estimates in an ROI placed manually in the corpus callosum (Fig. 7.9b) suggested that the proposed complex channel denoising method reduced biases in parameter estimates: mean FA and MK values were shifted down towards more biologically meaningful values [186].

7.5 Discussion

Standard reconstruction and post-processing techniques involve non-linear transformations that can distort the perfect iid Gaussian noise statistics on which many denoising methods rely. Denoising complex channel data is therefore beneficial in several ways: (i) the data has been minimally processed, so noise statistics are preserved as far as acquisition methods allow; (ii) denoising complex data prior to the magnitude operation allows for noise floor reductions; (iii) the added redundancy from denoising individual channels offers additional SNR gains. However, two confounds remain applicable to denoising complex channel data acquired using SENSE-based parallel imaging: image aliasing from parallel imaging acceleration and noise correlation introduced by partial Fourier reconstruction. Experiments using synthetic and in-vivo data in this chapter provide a proof-of-concept for denoising undersampled, partial FOV, complex channel data, and demonstrate that the method outperforms conventional magnitude MPPCA.

7.5.1 Noise and spatial correlations

Partial Fourier encoding affects the data in two relevant ways. Firstly, reconstructing data from fewer measurements increases the variance and thus the underlying noise level (SNR $\sim \sqrt{N_y}$, where $N_y$ is the number of phase encoding steps). The homodyne reconstruction showed the lowest baseline SNR, as iterations in POCS allowed for better SNR preservation [43]. Zero-filling in $k$-space is equivalent to smoothing in image space with a sinc function, which explains the higher SNR of this reconstruction and potentially the superior noise removal in noise-only regions; however, unacceptable Gibbs ringing was also introduced.

The second, and more important, consideration is that the interpolation of $k$-space necessarily means that observations in $k$-space are correlated [187]. As the FT is a linear operator, these correlations persist in image space, where in a SVD of the data they are liable to constitute principal components whose eigenvalues exceed the threshold $\lambda_+$. Lower
SNR gains in the denoised partial Fourier data in simulations indicated that such principal components contained little information about the underlying data and primarily contributed to the noise level. It was demonstrated in the Shepp-Logan phantom that a denoising kernel with no component along the spatially correlated partial Fourier axis can boost noise removal by a factor of 2.

7.5.2 Kernel geometry

Experiments with the D-BRAIN phantom revealed that, despite good noise reduction, stripe-like artefacts were introduced by the plate kernel. Analysis of residuals confirmed that no anatomy was removed during denoising, so the artefact most likely represents a spatially dependent performance using the 2D 11 × 1 × 11 kernel. Considering that the plate kernel samples an area 4 times larger than the 3D kernel this is not surprising: heterogeneity in large areas of tissue (even in the synthetic brain phantom used here) is likely to be greater and more spatially varying than in a more compact volumetric tissue sample. Reduced spatial redundancy was also indicated in the analysis of significant eigenvectors: a greater number were retained using the plate kernel than the 3D kernel.

A smaller 2D kernel could potentially improve performance by limiting the sampled tissue heterogeneity, but SNR gains are also limited by \( \sim \min(M,N)/P \). Optimisation of kernel size and shape was beyond the scope of this chapter, though.

7.5.3 Accuracy

In extreme cases, increased tissue heterogeneity arising from image aliasing within a denoising kernel could break the assumption that \( P \ll \bar{M} \) such that the bulk distribution no longer follows the MP distribution; the eigenvalue threshold \( \lambda_+ \) estimated using RMT may subsequently lead to the exclusion of signal-carrying principal components (i.e. poor accuracy). Distributions of the \( \sigma \)-normalised residuals (the suppressed noise) showed a consistent variance for all acceleration factors that was less than unity, indicating stable performance irrespective of image aliasing without the removal of true signal fluctuations. Accuracy was likewise demonstrated in maps of the unsuppressed noise: no anatomical structures were visible and noise distributions were centred on zero.

It is noted here that physiological motion in-vivo could contribute heavily to the number of significant principal components. The primary goal of this chapter, however, was a proof-of-concept demonstration that PCA-based denoising can be utilised for data aliased owing to SENSE acceleration, so an absence of additional confounding factors introduced
into the simulations was preferential.

### 7.5.4 Validation in-vivo

Analysis of residuals demonstrated that accurate noise suppression was also obtained using the proposed complex channel denoising method in-vivo: despite the deviation of the removed noise distribution from Gaussianity the variance did not exceed unity, so it can be assumed that no significant signal carrying components were removed. The skewness of the distribution was attributed to noise correlations resulting from partial Fourier encoding.

Superior noise removal was observed in the higher SNR of the complex channel MP-PCA reconstructions relative to the standard and magnitude MPPCA reconstructions. More biologically realistic FA and MK values were also observed in the corpus callosum ROI of the complex channel MPPCA reconstruction: for example, both standard and magnitude denoised MPPCA reconstructions produced estimates of FA > 1, which was not observed in the complex channel MPPCA reconstructions. The higher MD values in the complex channel MPPCA reconstructions could be attributed to an underestimation in the standard and magnitude MPPCA reconstructions owing to influence of the noise floor at $b = 1000 \, \text{s/mm}^2$; however, it is noted that the estimation is higher than expected in a healthy subject [186]. It may be that uncorrected Nyquist ghosting is introducing a bias, the effect of which is masked by the higher noise floor of the standard and magnitude MPPCA reconstructions, but this requires further investigation.

### 7.6 Conclusions

The feasibility and practicality of denoising complex channel data acquired with standard acceleration methods - namely partial Fourier encoding and SENSE-based parallel imaging - was demonstrated here for the first time in both synthetic and real data. In the absence of physiological noise in the D-BRAIN phantom, image aliasing did not alter the data redundancy and limit the dimensionality reduction achieved using MPPCA. Robust and accurate noise removal was uniformly obtained across clinically relevant acceleration factors up to $R = 2.5$.

Spatial correlations introduced by partial Fourier reconstruction naturally proved detrimental to the efficacy of the denoising; however substantial SNR gains were still demonstrated in the Shepp-Logan phantom. Plate-like kernels with no spatial component along the partial Fourier axis may potentially improve performance, but increased and spatially-varying tissue heterogeneity in a 2D kernel over a more compact 3D kernel could introduce
undesirable striping artefacts into the data.

Finally, complex channel MPPCA denoising was validated in a challenging data set in-vivo; that is low SNR, high $b$-value data, with both partial Fourier encoding and SENSE aliasing. Other challenging data sets could potentially benefit from this denoising strategy; data reconstructed using PEC-SENSE, for example, would a good candidate as the reconstruction can introduce considerable noise amplification into low SNR data. Based on the results presented here, complex channel MPPCA in SENSE-accelerated data could realistically be generalised for noise suppression in a range of acquisitions.
Chapter 8

SENSE reconstruction with simultaneous 2D phase correction and channel-wise noise removal

8.1 Introduction

Nyquist sampling errors in EPI often require 2D phase correction during reconstruction to remove unwanted ghost artefacts; however, phase corrections can be challenging to translate to high b-value DWI owing to associated noise amplification (Chapter 6). Noise amplification is particularly undesirable in DWI, where the drive for ever higher b-values often means that signals are lost to the noise floor. In this chapter, SENSE with 2D Phase Correction and channel-wise noise Removal - termed SPECTRE - is proposed. It is demonstrated that by denoising complex channel data (Chapter 7) prior to reconstruction using phase error correction with sensitivity encoding (PEC-SENSE [151]), the geometry factor dependent noise (g-noise) amplification in high b-value DWI can be mitigated to simultaneously produce robust Nyquist ghost correction and remove associated biases in parametric maps.

The efficacy of the method is first quantified in phantom data, using measures of the rectified noise floor level as well as the accuracy and precision of derived parametric maps for evaluation. In-plane resolution is varied to characterise potential image quality improvements at different SNR levels. SPECTRE is then used to reconstruct high b-value DWI in a small cohort of 4 healthy controls. The method is compared against denoising both magnitude and complex data after image reconstruction using PEC-SENSE. SENSE reconstructions are included to provide a baseline for both residual ghosting and expected noise levels in the DWI.
8.2  Methods

8.2.1  Data acquisition, denoising, and reconstruction

All data (phantom and human) were acquired using a 3T Philips Ingenia CX and the vendor’s 32-channel headcoil. The FUNSTAR phantom [188, 189] and 4 healthy volunteers (35 ± 5 years; 1 female) were imaged using single shot DW-EPI; written informed consent was obtained from all subjects prior to imaging. Key acquisition parameters for all protocols are summarised in Table 8.1. An additional \( b = 0 \) volume was acquired with opposing phase encoding blips so as to perform susceptibility-induced distortion correction in-vivo.

Data were exported after 1D inverse Fourier transformation (iFT) along the readout axis and after the vendor’s 1D phase correction, prior to any filtering; the obtained data were therefore minimally processed and in the \((x, k_y)\) domain. All subsequent data processing was performed off-line using Matlab 2017b (The MathWorks, Na tick, MA, USA).

A 1D iFT was first performed along the \( y \)-direction to obtain image space data for each coil. To ensure that noise was independent and identically distributed (iid) Gaussian in each channel, signals from each coil were decorrelated using a covariance matrix estimated using the same noise-only region in each coil (Section 2.6.4).

Denoising was performed using MPPCA and an isotropic \(5 \times 5 \times 5\) kernel. Images were denoised at three separate stages of the reconstruction pipeline in order to separate between the effects of increased data redundancy and operating on complex data; these are summarised in Table 8.2. A dataset with no denoising was also created. Reconstruction was performed using PEC-SENSE, as well as with standard SENSE in order to obtain baseline measures of Nyquist ghosting and SNR. Reconstruction algorithms were in-house modifications of the SENSE algorithm in the Michigan Image Reconstruction Toolbox (MIRT; [157]). Together with the different denoising strategies this yielded a total of 8 reconstructions per acquisition.

The FUNSTAR phantom was additionally imaged using a DW-SE sequence to provide a verification of its diffusivity that was unbiased by EPI distortions or ghosting and independent of the proposed reconstruction methods. The manufacturer’s reconstruction was used and no denoising was performed.

8.2.2  Phantom analysis

Signal attenuation curves were plotted to characterise the noise floor in each dataset (3 acquired resolutions, 8 reconstructions each) after signal rectification: at each \( b \)-value, the
# Methods

readout TR/TE [ms] \( b \) [s/mm\(^2\)] # dirs. \( b_0/b \) M resolution [mm] matrix [vox] # slices

<table>
<thead>
<tr>
<th>Phantom</th>
<th>SE</th>
<th>4000/81</th>
<th>[0,500,1000]</th>
<th>1/6</th>
<th>13</th>
<th>( 3.0 \times 3.0 \times 3.0 )</th>
<th>64 × 64</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
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<td>[0:200:4000]</td>
<td>7/6</td>
<td>127</td>
<td>( 2.0 \times 2.0 \times 2.0 )</td>
<td>120 × 118</td>
<td>10</td>
</tr>
<tr>
<td>In-vivo</td>
<td>EPI</td>
<td>5000/88</td>
<td>[0,1000,2000,3000]</td>
<td>9/30</td>
<td>99</td>
<td>( 2.0 \times 2.0 \times 2.0 )</td>
<td>112 × 110</td>
<td>20</td>
</tr>
</tbody>
</table>

**Table 8.1. Acquisition parameters.** All images were acquired with SENSE acceleration factor \( R = 2 \), no partial Fourier encoding, and no slice gap. Diffusion gradient directions were isotropically distributed in each case; \( M \) denotes the total number of volumes per acquisition. Total scan time in-vivo was 13 min.

<table>
<thead>
<tr>
<th>Denoising strategy</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Complex channel MPPCA / SPECTRE</td>
<td>Reduced FOV (aliased) complex channel data denoised prior to image reconstruction</td>
</tr>
<tr>
<td>Complex MPPCA</td>
<td>Full FOV complex data denoised after reconstruction using original channel data</td>
</tr>
<tr>
<td>Magnitude MPPCA</td>
<td>Full FOV magnitude data denoised after reconstruction using original channel data</td>
</tr>
<tr>
<td>Standard</td>
<td>No denoising performed</td>
</tr>
</tbody>
</table>

**Table 8.2. Denoising strategies.**
average signal $S(b)$ per volume was computed and normalised using the mean signal at $b=0$. DT estimation was performed in each dataset using an iteratively re-weighted linear least squares estimator [158, 159] in volumes with $b \leq 1000$ s/mm$^2$ and the MD computed.

8.2.3 In-vivo analysis

After image reconstruction and denoising, Gibbs ringing artefacts were corrected using the method of local subvoxel-shifts [183]. FSL’s topup and eddy tools [110, 184, 185] were used to correct for susceptibility distortions, eddy currents and motion, and a $B_1$ bias field correction was estimated from the mean $b=0$ image using FSL’s FAST tool [185] and propagated to all DW volumes.

Without loss of generality, only FA and MD from the DT model and MK from the DKT model were considered. Each tensor was fitted using an iteratively re-weighted linear least squares estimator [158, 159]; only data acquired with a maximum of $b = 1000$ s/mm$^2$ was used for the DT model.

8.3 Results

8.3.1 Phantom experiments

Fig. 8.1 shows a representative selection of phantom reconstructions from the highest resolution data set. Noise floor reductions in both the complex MPPCA and complex channel MPPCA denoising strategies were visually apparent in the reduced background noise. The effects of operating on complex-valued data and of increased data redundancy (arising from denoising channels independently) on the minimum measurable signal can be elucidated from the signal attenuation curves in Fig. 8.2: denoising complex-valued data reduced the noise floor up to a factor of 1.8 over magnitude data, while the added redundancy in denoising complex channel data provided a further $\sim 2$-fold reduction in noise floor. This equated to noise floor decreases of up to 3.6-fold for complex channel denoising relative to standard reconstructions or magnitude denoising.

The lower noise floors obtained by complex and complex channel MPPCA increased the range of $b$-values over which perfectly Gaussian diffusion was observed. For example, high noise floors in the standard and magnitude MPPCA PEC-SENSE reconstruction at 1.5 mm$^2$ in-plane resolution limited the dynamic range to below $b = 200$ s/mm$^2$; following complex MPPCA, Gaussian diffusion was observed up to $b = 600$ s/mm$^2$, while after complex channel denoising (i.e. in SPECTRE) the dynamic range was further increased to $b = 0−800$ s/mm$^2$. The noise floor increase brought about by the phase error correction in
8.3. Results

Figure 8.1. Phantom reconstructions. A selection of images is shown for each denoising strategy, for a. SENSE, and; b. PEC-SENSE reconstructions. For brevity, only the highest resolution data are displayed up to $b = 2000 \text{s/mm}^2$. Each data set is normalised relative to the $b = 0$ image.

Figure 8.2. Phantom signal decay curves. Normalised signal decay curves are shown for the 3 image resolutions, for SENSE (top row) and PEC-SENSE (bottom row) reconstructions.
PEC-SENSE was thus effectively mitigated, considering that the noise floor of the equivalent SENSE reconstruction without denoising was reached at approximately \( b = 400 \text{ s/mm}^2 \). Similar trends were observed across the acquisitions (i.e. different image resolutions).

Fig. 8.3 shows the distribution of MD estimates obtained in each acquisition (i.e. at each image resolution) for all denoising strategies, and Table 8.3 reports the corresponding mean and standard deviation of parameter estimates. For reference, the MD as measured in the SE-DWI acquisition was \( \text{MD} = 2.04 \pm 0.09 \text{ mm}^2/\text{s} \). Noise floor reductions were seen to directly translate into improved accuracy and precision in diffusion parameter estimates. The effects were most striking in the PEC-SENSE reconstructions of the highest in-plane resolution data (1.5 mm²). At \( b = 1000 \text{ s/mm}^2 \), the high noise floor without complex denoising artificially inflated the DW-signal, which, because the signal at \( b = 0 \) was much greater the noise floor and so unaffected, lead to a gross underestimation of MD; in magnitude MPPCA, for example, the average diffusivity across the phantom was \( \text{MD} = 1.23 \pm 0.37 \text{ mm}^2/\text{s} \).

Moreover, a bi-modal distribution was observed owing to a spatial variability in noise levels across the phantom: noise levels were highest at the phantom centre owing to the effective \( g \)-factor increase in PEC-SENSE, and so further reduced MD estimates. Complex MPPCA produced more accurate MD estimates which tended towards a more normal distribution, but estimates were less precise: \( \text{MD} = 2.06 \pm 1.28 \text{ mm}^2/\text{s} \). In the SPECTRE reconstruction, MD estimates were largely uniform across the phantom and only marginally biased by the noise floor, reflecting the increased dynamic range (\( \text{MD} = 1.93 \pm 0.13 \text{ mm}^2/\text{s} \)).

All denoising strategies improved image SNR across the acquisitions; Table 8.4 reports SNR values for each resolution and denoising strategy. Complex MPPCA achieved SNR improvements between \( 1.5 - 1.9 \times \text{SNR}_{\text{base}} \) (i.e. no denoising) across the acquisitions for both SENSE and PEC-SENSE reconstructions, while increases up to \( 3.6 \times \text{SNR}_{\text{base}} \) were observed in SPECTRE and complex channel MPPCA in SENSE. In SENSE reconstructions, magnitude MPPCA performed comparably to complex MPPCA \( (1.5 - 1.9 \times \text{SNR}_{\text{base}}) \); however, in PEC-SENSE reconstructions, magnitude MPPCA outperformed complex MPPCA and achieved results comparable to SPECTRE with up to \( 3 \times \text{SNR}_{\text{base}} \).

### 8.3.2 In-vivo experiments

A representative selection of individual channel images from a single subject is shown before and after complex channel MPPCA in Fig. 8.4a. Substantial noise removal following complex channel MPPCA denoising was qualitatively evident. Residuals showed no
Figure 8.3. Phantom MD distributions. MD distributions, calculated using $b \leq 1000 \text{s/mm}^2$ data, are shown for the 3 image resolutions, for SENSE (top row) and PEC-SENSE (bottom row) reconstructions. Note that the y-axis varies across the plots to best appreciate the detail of the distributions.

<table>
<thead>
<tr>
<th></th>
<th>SENSE</th>
<th>PEC-SENSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5 mm$^2$ 2 mm$^2$ 2.5 mm$^2$</td>
<td>1.5 mm$^2$ 2 mm$^2$ 2.5 mm$^2$</td>
</tr>
<tr>
<td>standard</td>
<td>1.91 (1.35) 1.95 (0.37) 1.97 (0.13)</td>
<td>1.41 (0.83) 1.63 (0.54) 1.80 (0.23)</td>
</tr>
<tr>
<td>magnitude MPPCA</td>
<td>1.74 (0.40) 1.87 (0.14) 1.93 (0.09)</td>
<td>1.23 (0.37) 1.50 (0.31) 1.72 (0.21)</td>
</tr>
<tr>
<td>complex MPPCA</td>
<td>1.97 (0.16) 1.97 (0.13) 1.98 (0.08)</td>
<td>2.06 (1.28) 1.99 (0.72) 2.00 (0.12)</td>
</tr>
<tr>
<td>SPECTRE</td>
<td>1.99 (0.08) 1.98 (0.08) 1.98 (0.05)</td>
<td>1.93 (0.13) 1.91 (0.13) 1.97 (0.06)</td>
</tr>
</tbody>
</table>

Table 8.3. Phantom MD. The mean (standard deviation) diffusivity [$\times 10^{-3} \text{mm}^2/\text{s}$] for each acquisition (image resolution) and denoising strategy is reported.
Table 8.4. Phantom SNR. SNR values calculated using the multiple replica method in the $b=0$ volumes are reported for each acquisition (image resolution) and denoising strategy.

<table>
<thead>
<tr>
<th></th>
<th>SENSE 1.5 mm$^2$</th>
<th>SENSE 2 mm$^2$</th>
<th>SENSE 2.5 mm$^2$</th>
<th>PEC-SENSE 1.5 mm$^2$</th>
<th>PEC-SENSE 2 mm$^2$</th>
<th>PEC-SENSE 2.5 mm$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>standard</td>
<td>8.7</td>
<td>12.2</td>
<td>17.9</td>
<td>6.9</td>
<td>9.7</td>
<td>14.2</td>
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<td>magnitude MPPCA</td>
<td>14.5</td>
<td>18.6</td>
<td>28.3</td>
<td>23.0</td>
<td>25.1</td>
<td>38.1</td>
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<tr>
<td>complex MPPCA</td>
<td>15.7</td>
<td>18.1</td>
<td>29.8</td>
<td>13.6</td>
<td>16.0</td>
<td>27.1</td>
</tr>
<tr>
<td>SPECTRE</td>
<td>31.6</td>
<td>29.5</td>
<td>57.3</td>
<td>23.7</td>
<td>22.5</td>
<td>43.2</td>
</tr>
</tbody>
</table>

The CME and SENSE reconstructions were validated using a simulated phantom. Each acquisition was denoised using different strategies and parameters, and the SNR was calculated for each denoising strategy. The results are reported in Table 8.4.

The anatomical features and exhibited perfectly Gaussian behaviour (Fig. 8.4b), indicating a high level of accuracy in the noise removal.

Reconstructions and parameter maps for all denoising strategies are shown for a representative subject in Figs. 8.5 and 8.6. As reported in Chapter 6, EPI ghosting was visible in the $b=0$ volumes of the SENSE reconstructions - irrespective of denoising strategy - and translated into local biases in parameter estimates. Likewise, although artefacts were well corrected in PEC-SENSE reconstructions, the familiar $g$-noise amplification was evident, particularly in the $b=3000$ s/mm$^2$ volumes of standard and magnitude MPPCA reconstructions. Effects of noise were also qualitatively evident in the marginal global increase of MK estimates in PEC-SENSE reconstructions without complex channel MPPCA relative to the equivalent SENSE reconstructions. The SPECTRE reconstruction was qualitatively less affected by $g$-noise amplifications and the MK estimates appeared less artificially inflated.

A reduction of $g$-noise bias in SPECTRE-derived parametric maps was observed quantitatively in distributions of parameter estimates in WM across all subjects (Fig. 8.7). Lower values were observed in both MK and FA estimates across subjects consistent with literature [165, 190], and an increase in the precision of FA values was exhibited in the narrower distributions obtained using SPECTRE. Notably, while MK was over-estimated in the standard and magnitude MPPCA PEC-SENSE reconstructions relative to the equivalent SENSE reconstructions, parameter estimates using SPECTRE were in line with the complex channel MPPCA in SENSE. Complex MPPCA after image formation using PEC-SENSE partially removed the MK bias; however, biases in FA remained. MD values demonstrated less susceptibility to noise level changes above the noise floor as has been previously reported [165]; this could explain the minimal variation in MD estimates across denoising strategies.

Fig. 8.8 shows, for the same representative subject, the normalised root-mean-square-
Figure 8.4. Complex channel denoising in-vivo. a. Four representative channel images are shown before and after denoising, together with the σ-normalised residuals. b. Distributions of the σ-normalised residuals demonstrate Gaussian behaviour in the close correlation with equivalent normal distributions (blue line); the standard normal distribution is shown for reference (black line).
Figure 8.5. In-vivo reconstructions. A representative slice is shown from a single subject for each denoising and reconstruction strategy.
Figure 8.6. **In-vivo parameter maps.** Representative FA, MD and MK parameter maps are displayed for a single subject. Note the ghost artefact in SENSE reconstructions, which is removed in the SPECTRE reconstruction.
Figure 8.7. In-vivo model parameter distributions. Distributions of model parameters (FA, MD and MK) for all subjects in MW are displayed. Each denoising and reconstruction strategy is represented by a different line colour and fill.
8.4 Discussion

Nyquist ghost correction is important in order to minimise biases in quantitative parameter maps, but many corrections based on parallel imaging do not translate well to DWI owing to noise amplification that disproportionately affects high b-value data. It was demonstrated here that performing MPPCA denoising on complex channel data prior to reconstruction with 2D phase error correction was more effective than after image production, as redundancies present in the data were better exploited. By operating on complex data and utilising the redundancy in individual channel images, the lowered noise floor and increased SNR was used to enable PEC-SENSE ghost correction without incurring major biases in the accuracy and precision of parameter estimates.

8.4.1 Denoising complex-valued data

The phantom data shown here demonstrated a clear reduction in noise floor levels when denoising complex data (before or after image formation) over magnitude data; however, the SNR analysis suggested the amount of noise suppression achieved by complex MPPCA after image formation was comparable to or lower than that achieved by denoising magnitude data. Higher noise levels in complex denoising relative to magnitude denoising after image formation were also indicated in the less precise DKI model fit in-vivo. The effect could be a consequence of phase information contributing additional significant components to the PCA. For example, additional phase correlations introduced during phase error correction in PEC-SENSE reconstructions may be spuriously detected as significant signal components and so limit the efficiency of noise removal. This could also explain why, in both phantom

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Figure 8.8. In-vivo NRMSD. The accuracy of the DKT model fit is shown in the normalised root mean squared deviation (NRMSD) between the measured data and predicted signal.

deviation (NRMSD) between the measured signal and the signal predicted from the DKT model fit. Denoising both magnitude reconstructions or complex channel data improved the precision of the DKT model fit, as observed in the lower NRMSD. Denoising complex data after image formation afforded less improvement in the accuracy of the model fit.
and in-vivo data, the effects were more pronounced in PEC-SENSE over SENSE reconstructions. In other words, although complex denoising after image formation reduces the noise floor to a degree, the amount of noise removal is comparable to (or potentially worse than) magnitude denoising. Denoising complex channel data prior to image formation (as in SPECTRE, for example) mitigates this potential confound.

8.4.2 Accuracy and precision of parametric maps

Biases in FA at moderate $b$-values and their dependence on SNR level are well documented [165]. Eigenvalue repulsion leads to the systematic overestimation of the largest eigenvector $\lambda_1$ and underestimation of the smallest eigenvector $\lambda_3$, leaving $\lambda_2$ largely unaffected; these effects become more pronounced at lower SNR levels. FA is subsequently overestimated, while the biases cancel to leave MD relatively unaffected. The systematic lowering of FA estimates observed here in-vivo using SPECTRE therefore indicate that superior SNR levels achieved by denoising complex channel data removed this bias. As the signal at $b = 1000 \text{s/mm}^2$ was above the noise floor, consistent MD estimates in-vivo were exhibited across the reconstructions in line with expectations.

In phantom data, though, noise floor effects could be directly observed in MD estimates owing to the choice of acquisition parameters and range of $b$-values used to fit the DT. Here, the benefits of SPECTRE in lowering the noise floor resulted in substantially improved precision and accuracy in parameter estimates when using $b_{\text{max}} \leq 1000$ for the DT fitting.

Noise floor effects were observed in-vivo in the MK parameter maps. Highly attenuated signals at $b = 3000 \text{s/mm}^2$ were artificially inflated by the noise floor in standard and magnitude MPPCA reconstructions while lower $b$-value data remained unaffected, resulting in an overestimation of MK. Biases were present in both SENSE and PEC-SENSE reconstructions; however, biases were noticeably worse using PEC-SENSE owing to the elevated noise levels. Denoising complex channel data in SPECTRE corrected this additional bias and brought MK estimates in line with the equivalently denoised SENSE reconstructions.

Improved accuracy and precision in parametric maps using SPECTRE were reproducible across the different resolutions in phantom data and across all subjects in-vivo.

8.4.3 Limitations and future work

While phantom experiments confirmed that SPECTRE reduced biases in MD estimates (both higher accuracy and precision were achieved), ground truth data were not available for quantifying the accuracy of parameter estimates in-vivo. One approach to obtaining an
in-vivo reference would be to create a high SNR group-wise average data set. In the experiments in this chapter, however, registration between subjects was not feasible owing to the small FOV acquisitions, which were necessary owing to file size limits enforced in the Philips pulse programming environment (PPE) used to export the raw \( k \)-space data. Future work should consider solutions to this limitation. One possibility would be to modify the reconstruction code on the scanner, thus eliminating the need for the PPE for data export.

There are two primary avenues of research for future work. Firstly, phase correlations and their effects on denoising complex data warrant a more detailed investigation. After image formation, it is possible that background phase elimination - for example using total variation \([191, 192]\) - prior to complex image denoising could aid the detection of noise-only components; however, this approach would be more complicated to apply to complex channel MPPCA, for which coil phase information needs retaining for SENSE reconstruction.

The second avenue should explore the possibility of denoising a joint voxels \( \times \) q-space \( \times \) coils data matrix. This would offer two key benefits: (i) increased data redundancy in the denoising matrix should improve the detection of noise-only components, while (ii) denoising the coil data jointly would reduce processing time.

### 8.5 Conclusions

MPPCA denoising applied to partial FOV (i.e. aliased) EPI from individual channels and incorporated into a 2D phase-corrected reconstruction pipeline was demonstrated to mitigate Nyquist ghost artefacts and alleviate associated \( g \)-noise amplification. The improvement in image quality obtained using the proposed SPECTRE method is of particular benefit for complex, higher order diffusion models such as DKI, which rely on high \( b \)-value (low SNR) data. Connectivity studies could also profit: fewer artefacts and lower noise levels should result in more reliable tractography outcomes.

The proposed method could also benefit applications other than DWI that utilise the EPI readout, such as fMRI, intravoxel incoherent motion (IVIM) imaging \([22, 23]\), arterial spin labelling \([193]\) and magnetisation transfer imaging with EPI readout \([194]\), and could help the translation of these techniques into clinical practice.
Chapter 9

Concluding remarks

This thesis was an exploration and development of quantitative diffusion MRI, approached from two distinct angles; the overarching aim was to improve the characterisation of tissue structure and microstructure in the brain in order to increase sensitivity to pathological alterations in complex neurological diseases such as MS.

The first approach used network science in combination with graph theory to investigate alterations in brain structure - and its subsequent relation to function - as a result of subtle MS pathology. The primary contributions of this thesis were:

1. The definition of a novel data-driven subnetwork, incorporating only the nodes most central to overall network function. The subnetwork demonstrated increased sensitivity to subtle MS pathology in a study of 33 minimally-disabled relapsing-remitting (RRMS) patients and 27 HCs, as compared to full brain and default mode networks.

2. Explicit demonstration that the choice of edge weighing scheme can dramatically influence the interpretation of results, thus providing awareness of potential pitfalls and confounding factors in connectivity studies.

Major unanswered questions in the field of brain connectomics surround the issue of specificity. What do our results truly reflect? Are the mechanisms of network reorganisation adaptive or maladaptive, compensatory or causal? How can we validate our findings? Most crucially, how can we translate brain connectivity metrics into clinical practice in a manner that assists in the diagnosis and treatment of complex, diffuse pathologies? A key limitation in answering these questions is the lack of consensus in designing and interpreting connectivity studies. Data-driven approaches to network structure should be implemented in the absence of well-defined models, and a novel solution to this is proposed in Chapter
4. Reporting the same core set of connectivity metrics is also essential for reproducibility and comparability between studies, but this requires an awareness of how metrics can be affected by image pre-processing and network construction; Chapter 5 elucidates one of these factors.

The question of casual or compensatory mechanisms could be addressed in future longitudinal studies. Evaluation of network metrics over time could offer insight into network reorganisation as a function of disease progression, but the majority of connectivity studies to date are cross-sectional. Data mining and machine learning could assist in the translation of connectivity metrics into clinical practice. These are fields currently experiencing explosive expansion, finding applications across medical imaging from reconstruction of highly undersampled data to enhancement of low-quality images. Combining connectivity metrics with other imaging and clinical biomarkers into a data mining tool could aid in the classification and staging of neurological disorders.

The robustness and reliability of any quantitative parameter derived from MR images, though, is inherently dependent on the underlying data quality. The second part of this thesis investigated the impact of uncorrected EPI Nyquist phase errors on quantitative microstructural tissue parameters, together with potential correction methods. Specific contributions were:

1. A systematic evaluation of 2D Nyquist phase correction algorithms in multi-shell high angular dMRI. The study showed for the first time that, while many correction methods are highly effective in non-DW EPI, their efficacy can be limited by low SNR and additional phase errors in DW-EPI. These outcomes could provide guidance for the design of future acquisition and post-processing pipelines in dMRI studies.

2. Proof-of-concept demonstration of the ability to denoise complex, aliased data from individual coil channels prior to image formation using a PCA-based approach to removing noise-only components. The method was validated in simulations and in a single healthy volunteer for the first time.

3. Development of a reconstruction framework with simultaneous Nyquist ghost correction and channel-wise noise removal, affectionately coined SPECTRE. The proposed method demonstrated improved accuracy and precision in quantitative parameter estimates in both phantom data and in a pilot study of 4 healthy volunteers.
SPECTRE was developed in Chapters 7 and 8 of this thesis to overcome noise amplification in phase-corrected EPI without demanding extra scanning time; however, the implemented framework could be utilised for several other applications. Functional MRI, intravoxel incoherent motion imaging (IVIM), arterial spin labelling (ASL) and multi-contrast relaxometry acquisitions, for example, all generate sequential EPI whose redundancy could be exploited for denoising using PCA. Noise reductions could be utilised to offer improved SNR for the same amount of acquired data, to reduce scan times by replacing the need for multiple signal averages, to increase resolution, or, specifically for dMRI, to enable the acquisition of higher $b$-values than previously attainable on clinical scanners. There may also be potential benefits for clinical studies in terms of statistical power: improvements in the accuracy and precision of quantitative parameter estimates - achieved through robust ghost removal and SNR gains - could reduce the number of recruits required to see a given effect size.

An interesting future development would be to explore alternative sources of data redundancy. So far, redundancy in PCA-based denoising methods has only been achieved through multiple acquisitions of the same object, using either dMRI or multi-exponential relaxometry data. The work in this thesis, though, demonstrated that images from individual channels can be denoised even in the presence of aliasing, so a potential source of redundancy could be the channel data itself; in other words, it may be possible to denoise single acquisitions of an object by exploiting only the redundancy in complex channel images. This could potentially apply to any image type, not only those with the EPI readout; even structural scans, for example, could be improved by increasing SNR or resolution.

Pragmatically, considerable technical development is required to make SPECTRE routinely operational. The current offline reconstruction is a major limitation, in terms of speed, practicality, and its ability to cope with small mismatches between coil sensitivity profiles and acquired data. There are a several potential solutions to the latter issue, including estimating coil maps from the data itself or integrating the phase error correction into the online reconstruction pipeline, but both options need implementation and validation. A further issue surrounding the offline reconstruction involves the maximum data size that can be transferred from the scanner. Currently, the Recon2.0 emulator in the Philips pulse programming environment places a 4GB limit on file size, thus restricting acquisition resolution in either image- or $q$-space. Ultimately, the whole framework needs translating into an easy-to-use reconstruction pipeline accessed from the scanner console to offer a truly
practical solution.

Deriving clinically relevant imaging biomarkers remains an important component in the pursuit of a deeper understanding into brain structure and function and its connection to neurological disorders. More accurate imaging biomarkers offer the potential to not only aid in non-invasively characterising the mechanisms of early disease stages, but also to observe changes related to treatment and even stratify patients in-line with the move towards personalised medicine.

This thesis has explored and developed two different avenues in order to improve the accuracy, precision and sensitivity of imaging biomarkers to pathology, but many alternative paths exist. I hope that the research here provides a stepping stone that can help others traverse the vast sea that is quantitative diffusion MRI.
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