Functional and Diffusion
Magnetic Resonance Imaging at
Ultra-high Magnetic Field Strengths

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Diese Dissertation ist auf den Internetseiten der Universitätsbibliothek online verfügbar.
This dissertation is devoted to the exploration of novel imaging methods for functional and diffusion magnetic resonance imaging at ultra-high field strengths, particularly targeting at human in vivo applications at 9.4 Tesla.

In the first part of this work the principles of nuclear magnetic resonance (NMR) and the basics of magnetic resonance imaging (MRI) are introduced. This is followed by a brief overview of two specialised imaging methods that nowadays find wide application in clinical and research routine: functional magnetic resonance imaging (fMRI) and diffusion magnetic resonance imaging (dMRI), specifically diffusion tensor imaging (DTI) and q-ball imaging (QBI).

Part two and three of this work give a comprehensive overview of the self-contained implementations, simulations, experiments and findings carried out and made in the context of this work. Part two has a very close focus on the yet unsolved problem of analytically defining an isotropic distribution of direction vectors. Among various scientific disciplines this problem is common to DTI, QBI and other high angular resolution diffusion imaging (HARDI) methods, which today still greatly rely on numerically precomputed look-up tables. To provide more experimental flexibility a novel deterministic sampling scheme is developed and shown to achieve results as isotropic as the numerical gold standard. To prove this, exhaustive DTI Monte Carlo simulations as well as single- and multi-fibre QBI simulations are performed. The systematic analysis of DTI and QBI estimation errors made as a function of simulated fibre direction provides novel insights into the importance of sampling isotropy in QBI.

The third and final part of this work is devoted to the development and implementation of suitable MRI pulse sequences for ultra-high field (UHF) applications, in particular for fMRI and dMRI. Latest findings and considerations with regard to an alternative single-shot dMRI technique based on stimulated echoes are discussed and the applicability at UHF is debated. With regard to the topical field of high-resolution fMRI at UHF, the implementation of various extensions to the common two-dimensional echo planar imaging (EPI) sequence are explained and experimentally validated. In this context, a novel and simple water excitation method is proposed, which is particularly fast and reduces specific absorption rate significantly. Results showing unique contrast and resolution at 3 and 9.4 Tesla are presented.

A few final words on the structure of this work: all parts are subdivided into chapters. Each chapter is opened with a brief introduction. The chapters of part two and three are explicitly closed by a concluding section followed by a collection of related, peer reviewed journal or conference papers that have been published in preparation to this work, during this work, or following the conclusion of this work. Hereby, pending papers are indicated by "(Prospective)". A final conclusions part summarises and closes this work.
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Part I.

Introduction to MRI
Chapter 1.

Principles of Nuclear Magnetic Resonance

Many Nuclear Magnetic Resonance (NMR) phenomena can be described (semi-)classically on a macroscopic level. One nucleus alone, however, is solely described by quantum mechanical properties from which the macroscopic ensemble phenomena derive. The essential basics of NMR shall thus be covered in a brief quantum mechanical introduction. A more detailed discussion of the motion of nuclear magnetisation follows by means of the classical Bloch-equation. The main physical mechanisms underlying many typical NMR and Magnetic Resonance Imaging (MRI) experiments are briefly discussed and the generation of spin and stimulated echoes is described. Finally, phase graphs are discussed as a preparation for the extended phase graph concept introduced in the following chapter.
1.1. Quantum Mechanical Description of NMR

1.1.1. Nuclear Spins

Single atomic nuclei are characterised by quantum numbers associated to a corresponding quantum mechanical operator such as the spin angular momentum, \( \hat{S} = \hbar \hat{I} \). Here \( \hat{I} \) is the spin operator and \( \hbar = \hbar / 2\pi \) is Planck’s constant. Nuclei with an even number of both neutrons and protons have a nuclear spin quantum number, \( I \), equal to zero. All other nuclei have an integer or half-integer \( I \). Via the spin angular momentum the spin is associated with a nuclear magnetic dipole moment,

\[
\hat{\mu} = \gamma \hat{S} = \gamma \hbar \hat{I}
\]

The constant of proportionality, \( \gamma \), is known as the gyromagnetic ratio, which is specific for different nuclei. For NMR, and explicitly for the application of Magnetic Resonance Imaging (MRI), the most important gyromagnetic ratio is that of the the proton, \( \gamma_{1H} \approx 2.675 \cdot 10^8 \text{ rad s}^{-1} \text{ T}^{-1} \), which is the nucleus of hydrogen. Hydrogen is the most prevalent element in the universe, e.g. the human body consists of more than 70% water (\( \text{H}_2\text{O} \)).

Magnetic dipoles interact with external magnetic fields. The Hamilton operator (Hamiltonian) is given by

\[
\hat{H} = -\hat{\mu}B_0 = -\hat{\mu}_zB_0 = -\gamma \hbar \hat{I}_zB_0 \quad ,
\]

where \( B_0 \) is the external magnetic field, which is, by convention and without loss of generality, assumed parallel to the \( z \)-axis. \( \hat{I}_z \) represents the (longitudinal) projection of the spin operator on the \( z \)-axis. According to Eq. (1.1), it commutes with the Hamiltonian, \( [\hat{H}, \hat{I}_z] = 0 \). Hence, the eigenstates of the Hamiltonian probed in NMR are eigenstates of the spin projection,

\[
\hat{I}_z|m\rangle = m|m\rangle \quad , \text{where} \quad m = -I, -I+1, \ldots, I-1, I \quad ,
\]

and accordingly we observe a Zeeman splitting of energy levels, \( E_m = m \hbar \gamma B_0 \). The gyromagnetic ratio embodies the direct proportionality of the “Larmor frequency” to the static magnetic field:

\[
\omega_0 := \gamma B_0 = \frac{\Delta E}{\hbar} \quad ,
\]

where \( \Delta E \) is the energy difference between two adjacent energy levels.
1.1.2. Nuclear Magnetisation

The actual spin of a single nucleus is described by the general spin state \( |\Psi\rangle = \sum_m a_m |m\rangle \) with complex coefficients, \( a_m \). The observable spin angular momentum is given by the expectation value. As an example, the longitudinal projection observable is discussed here. Due to the eigenvalue equation (1.2) the matrix representation of \( \hat{I}_z \) is diagonal and consequently

\[
\langle \hat{I}_z \rangle = \langle \Psi | \hat{I}_z | \Psi \rangle = \sum_{m,m'} a_m a_{m'}^* \langle m' | \hat{I}_z | m \rangle = \sum_m |a_m|^2 .
\]

The real number \( |a_m|^2 \) can be interpreted as the probability to detect the eigenvalue \( m \) in a quantum mechanical measurement of a single spin. For a spin 1/2 nucleus, such as the proton, the equation assumes the explicit shape

\[
\langle \hat{I}_z \rangle = \frac{1}{2} \left( |a_\uparrow|^2 - |a_\downarrow|^2 \right) ,
\]

where \( \uparrow \) and \( \downarrow \) stand for the eigenvalues \( m = \pm \frac{1}{2} \), respectively.

In an actual macroscopic NMR experiment ensemble averages of a mixture of different sub-ensembles, \( |\Psi\rangle \), are measured. May each of the sub-ensembles have the classical probability, \( p_\Psi \), the ensemble average is then

\[
\overline{\langle \hat{I}_z \rangle} = \sum_\Psi p_\Psi \langle \Psi | \hat{I}_z | \Psi \rangle = \sum_\Psi p_\Psi \sum_m m |a_\Psi^m|^2 = \sum_m m \overline{|a_m|^2} .
\]

The averaged coefficients \( \overline{|a_m|^2} = \sum_\Psi p_\Psi |a_\Psi^m|^2 \) represent the normalised populations of the energy-levels associated to the spin states \( |m\rangle \). For a spin 1/2 nucleus the ensemble averaged expectation value, \( \overline{\langle \hat{I}_z \rangle} = \frac{1}{2} \left( |a_\uparrow|^2 - |a_\downarrow|^2 \right) \), hence represents the population difference between lower and higher energy level, i.e. the polarisation of the ensemble [1].

The discrete probability distribution of such canonical ensemble is given by Boltzmann statistics: \( |a_\uparrow|^2/|a_\uparrow|^2 = e^{-\Delta E/k_B T} \). Here, \( k_B \approx 1.381 \cdot 10^{-23} \) J K\(^{-1} \) denotes the Boltzmann constant and \( T \) denotes the temperature. At room temperature and for common field strengths the thermal energy, \( k_B T \), exceeds the Zeeman gap, \( \Delta E = \hbar \gamma B_0 \), by several orders of magnitude such that the population difference is close to zero. After all, a population excess in the lower, more favourable energy state in the order of only 0.001% amounts in a detectable macroscopic magnetisation using nuclear magnetic resonance.

The spin components perpendicular to \( \hat{I}_z \) are not diagonal in the basis of \( |m\rangle \). For a spin 1/2 nucleus the ensemble averaged expectation value, for example of \( \hat{I}_x \), is given by \( \overline{\langle \hat{I}_x \rangle} = \frac{1}{2} \left( a_\uparrow^* a_\downarrow + a_\downarrow a_\uparrow^* \right) \), which expresses the state of dephasing of the ensemble. These coefficients
stand for the phase coherence between $|\uparrow\rangle$ and $|\downarrow\rangle$ [1].

The entire magnetisation vector is expressed in terms of all ensemble averaged spin components:

$$M = N \langle \mu \rangle = N\gamma \hbar \begin{pmatrix} \langle I_x \rangle \\ \langle I_y \rangle \\ \langle I_z \rangle \end{pmatrix}. \quad (1.4)$$

Here, $N$ denotes the number of nuclear spins in the sample volume. One can show that the equilibrium magnetisation aligned with an external magnetic field of strength $B_0$ is given by Curie’s law [1, 2]:

$$M_0 = N \frac{\hbar^2 \gamma^2 I(I+1)}{3k_B} \frac{B_0}{T} \quad (I=\frac{1}{2}) \quad \frac{\hbar^2 \gamma^2 B_0}{4k_BT}.$$

To summarise, when placed into an external magnetic field, $B_0$, a spin ensemble is polarised but has no a priori phase coherence in thermal equilibrium. The corresponding magnetisation vector is static as long as it is not perturbed: $M \propto \langle I_z \rangle e_z \parallel B_0$.

1.1.3. Excitation in the Quantum Mechanical Picture

By resonant absorption of photons with energy $\hbar \omega_0$ single spins from the spin ensemble can be excited (from lower to higher energy levels). For hydrogen and a magnetic field strength in the order of 1 Tesla ($\omega_0(B_0 = 1T) \approx 42.6$ MHz) such photons correspond to radio-frequency (RF) electromagnetic waves. Note that photons of the same energy are emitted for each spin “falling back” to the ground state. If many spins are excited coherently, the corresponding magnetisation vector is deflected about an axis determined by the well defined phase of the RF wave.

1.1.4. Precession in the Quantum Mechanical Picture

In order to describe the equation of motion of a single spin or an ensemble of spins it is made use of the density operator description. Be $|\Psi\rangle$ a general spin state, then $\rho = |\Psi\rangle\langle\Psi|$ is the corresponding density operator. The expectation value of an observable, such as $\hat{I}_x$, is given by $\langle \hat{I}_x \rangle = \text{Tr}(\rho \hat{I}_x)$, where $\text{Tr}$ denotes the trace. The equation of motion (evolution) under the influence of the Hamiltonian $\hat{H}$ is given by the Liouville-von-Neumann (LvN) equation, $i\hbar \frac{\partial \rho(t)}{\partial t} = [\hat{H}, \rho(t)]$, which can be interpreted as the density operator analogue of the Schrödinger equation [1]. If the Hamiltonian is not explicitly time dependent (such as Eq. 1.1),
1.1. Quantum Mechanical Description of NMR

The solution of the LvN equation is given by

$$\rho(t) = \hat{U}(t)\rho(0)\hat{U}^{-1}(t) = e^{-i\hat{H}t/\hbar}\rho(0)e^{i\hat{H}t/\hbar},$$  \hspace{1cm} (1.5)

where $\hat{U}$ is known as the propagation or evolution operator [1]. The latter follows from the time-dependent Schrödinger equation, $i\hbar\frac{\partial|\Psi(t)\rangle}{\partial t} = \hat{H}|\Psi(t)\rangle$, which is solved by $|\Psi(t)\rangle = \hat{U}(t)|\Psi(0)\rangle$ with $\hat{U}(t) = e^{-i\hat{H}t/\hbar}$.

In case of the (not explicitly time dependent) Zeeman Hamiltonian, $\hat{H} = -\hbar\gamma \hat{I}_z B_0$ (Eq. 1.1; spin in a static magnetic field, $B_0$, along $z$-direction), and with the definition of the Larmor frequency, $\omega_0 = \gamma B_0$ (Eq. (1.3)), the evolution operator becomes

$$\hat{U}(t) = \exp\left(\frac{\hat{H}t}{\hbar}\right) = \exp\left(\frac{\hbar}{2}\hat{I}_z\omega_0 t\right) = \frac{1}{2} \begin{pmatrix} e^{\Omega_0 t} & 0 \\ 0 & e^{-\Omega_0 t} \end{pmatrix}.$$  \hspace{1cm} (1.6)

Here, the matrix representation of $\hat{I}_z$ in the basis of spin up and spin down states was used. The complete set of matrices for all spin components are known as Pauli matrices:

$$\hat{I}_x = \frac{1}{2} \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}, \quad \hat{I}_y = \frac{1}{2} \begin{pmatrix} 0 & -i \\ i & 0 \end{pmatrix}, \quad \hat{I}_z = \frac{1}{2} \begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix}.$$  \hspace{1cm} (1.7)

To evaluate the solution of the LvN equation (1.5) for a spin $1/2$ system in a static magnetic field, let us assume, for simplicity, an initial state of the density operator along the $x$-axis, $\rho(0) = \hat{I}_x$. Using Eqs. (1.5) through (1.7) we find

$$\rho(t) = \frac{1}{2} \begin{pmatrix} e^{\Omega_0 t} & 0 \\ 0 & e^{-\Omega_0 t} \end{pmatrix} \frac{1}{2} \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix} \begin{pmatrix} e^{-\Omega_0 t} & 0 \\ 0 & e^{\Omega_0 t} \end{pmatrix} = \frac{1}{2} \begin{pmatrix} 0 & e^{2\Omega_0 t} \\ e^{-2\Omega_0 t} & 0 \end{pmatrix}.$$  \hspace{1cm} (1.8)

Calculating the expectation value $\langle \hat{I}_{x,y,z} \rangle = \text{Tr} \left( \rho(t)\hat{I}_{x,y,z} \right)$ by inserting in Eq. (1.8) the pauli matrices for all spin components we finally find that the nuclear magnetic moment performs a clockwise precession in the transverse plane:

$$\langle \hat{\mu} \rangle = \hbar\gamma \langle \hat{I} \rangle = \frac{\hbar\gamma}{2} \begin{pmatrix} \cos \omega_0 t \\ -\sin \omega_0 t \\ 0 \end{pmatrix}.$$  \hspace{1cm} (1.9)
Chapter 1. Principles of Nuclear Magnetic Resonance

1.2. Classical Description of Spin-Dynamics

1.2.1. Precession in the Classical Picture

The magnetization equation of motion can be derived by equating the torque of a magnetic dipole moment, \( \mu = \hbar \gamma I \), in a magnetic field, \( B \), with the time rate of change of the spin angular momentum, \( S = \hbar I \):

\[
\mu \times B = \frac{dS}{dt} = \frac{1}{\gamma} \frac{d\mu}{dt} \quad \iff \quad \frac{dM}{dt} = M \times \gamma B = -\gamma B \times M ,
\]

We find that the equation of motion (1.10) is solved by a left-handed precessional motion with the precession frequency \( \omega = \gamma B \) about the unit vector \( B/|B| \). The following example makes this more clear: suppose, for the sake of simplicity, that \( B = B_0 \) is static and defines the \( z \)-axis of our frame of reference, then Eq. (1.10) simplifies to

\[
\frac{dM_x}{dt} = \gamma B_0 M_y , \quad \frac{dM_y}{dt} = -\gamma B_0 M_x , \quad \frac{dM_z}{dt} = 0 .
\]

This is solved by:

\[
M_x(t) = M_x(0) \cos \omega_0 t + M_y(0) \sin \omega_0 t \\
M_y(t) = -M_x(0) \sin \omega_0 t + M_y(0) \cos \omega_0 t \\
M_z(t) = M_z(0).
\]

The magnetisation vector performs a left-handed precessional motion in the transverse plane with the Larmor-frequency \( \omega_0 = \gamma B_0 \). Note that this is equivalent to the quantum mechanical finding, Eq. (1.9), if we assume identical starting conditions, i.e. \( M_x(0) = M_0 \) and \( M_y(0) = M_z(0) = 0 \).

1.2.2. Excitation in the Classical Picture

In a rotating frame of reference (performing a left-handed rotation with the angular frequency \( \omega \) about the \( z \)-axis), the magnetisation precesses only with \( \omega_0 - \omega \), which corresponds to a reduced external, longitudinal magnetic field strength, \( (\omega_0 - \omega)/\gamma \).

Suppose that the actual external magnetic field, \( B \), has additional, time-varying components perpendicular to a longitudinal static component, \( B_0 \). This is achieved by an additional, left-
handed, circularly polarised (electro-magnetic) wave,

\[ B_1(t) = B_1(t) \begin{pmatrix} \cos(\omega t + \Phi_0) \\ -\sin(\omega t + \Phi_0) \\ 0 \end{pmatrix}, \] (1.12)

characterised by an envelope function, \( B_1(t) \), a frequency, \( \omega \), and an arbitrary phase, \( \Phi_0 \). In the frame of reference rotating with the same frequency (and reference phase), the magnetisation is exposed to an effective magnetic field given by

\[ B_{\text{eff}} = \begin{pmatrix} B_1(t) & 0 \\ 0 & B_0 - \omega/\gamma \end{pmatrix}. \] (1.13)

For a resonant RF wave, i.e. \( \omega = \omega_0 \), the equation of motion, Eq. (1.10) – now with \( B = B_{\text{eff}} = (B_1(t)\cos\Phi_0, B_1(t)\sin\Phi_0, 0)^T \) – is solved by a precessional motion about a transverse axis defined by the phase \( \Phi \) with the frequency, \( \omega_1(t) := \gamma B_1(t) \). We note that the additional field \( B_1(t) \) enables us to deflect magnetisation from its equilibrium about an arbitrarily chosen flip angle, \( \alpha \). Usually this is accomplished by employing a pulsed, resonant RF wave of duration \( \tau \) according to \( \alpha = \gamma \int_0^\tau B_1(t) dt \). For a most simple rectangular RF pulse shape this yields \( \alpha = \gamma B_1 \tau \).

### 1.2.3. Relaxation

Following excitation an immediate ‘decay’ of the transverse magnetisation and a ‘recovery’ of the longitudinal magnetisation is observed. Both the longitudinal (spin-lattice) relaxation and the transverse (spin-spin) relaxation are phenomenologically described by exponential decay rates \( 1/T_1 \) and \( 1/T_2 \), respectively. On a microscopic level one can show that these relaxation effects are driven by spin–magnetic dipole–interactions and that always \( T_2 < T_1 \).

The spin-lattice relaxation describes the return to, or the approach of thermal equilibrium polarisation. After spins have been excited or after the probe was just placed in the \( B \)-field, thermal equilibrium is established driven by resonant oscillations of the surrounding magnetic dipoles in the transverse plane (energy exchange with the surrounding thermal energy reservoir known as ‘lattice’ [1]). Note that, as the Zeeman-gap increases with higher field strengths, greater thermal energy is required for energy exchange, and thus \( T_1 \) increases with higher field strengths [3].

The same field fluctuations determine the transverse spin-spin relaxation but here the z-
component of the surrounding field fluctuation has an additional, dominant influence (hence, \(T_2 \leq T_1\)): the \(z\)-component spin-interactions lead to a peak-broadening of the spin resonance frequencies and hence to a loss of (single quantum) coherence. The amount of the peak-broadening is defined by the low-frequency contribution of the \(z\)-field fluctuations (near zero). Hence, \(T_2\) is almost independent of the field strength [3].

### 1.3. Bloch Equation

The relaxation of magnetisation after perturbation has to be considered additionally in the equation of motion (1.10). As indicated above, it is found heuristically that the change of time rate during both relaxation processes is inversely proportionally to the time-constants \(T_1\) and \(T_2\). This leads to the Bloch-equation:

\[
\frac{dM}{dt} = M \times \gamma B - \begin{pmatrix} \frac{M_x}{T_2} \\ \frac{M_y}{T_2} \\ \frac{(M_z - M_0)}{T_1} \end{pmatrix}, \tag{1.14}
\]

where \(M_0\) denotes the equilibrium magnetisation. For a static magnetic field along the \(z\)-axis, \(B = B_0(0, 0, 1)^T\), the equations of motion can be simplified by mapping the real transverse plane onto a complex plane by the definition \(M =: M_x + iM_y\) (cf. Eq. (1.11)):

\[
\begin{align*}
\frac{dM}{dt} &= \gamma B_0 (M_y - iM_x) = -i\gamma B_0 M = -M(1/T_2 + i\omega_0) \tag{1.15} \\
\frac{dM_z}{dt} &= -(M_z - M_0)/T_1 \tag{1.16}
\end{align*}
\]

Now, the solution for the transverse magnetisation is a left-handed precession about the \(z\)-axis with the Larmor-frequency, multiplied by an exponential decaying transverse relaxation term:

\[
M(t) = M(0)e^{-t/T_2}e^{-i\omega_0 t}. \tag{1.17}
\]

The \(z\)-component slowly recovers exponentially according to

\[
M_z(t) = M_z(0)e^{-t/T_1} + M_0(1 - e^{-t/T_1}). \tag{1.18}
\]

The magnetisation vector follows a funnel-shaped trajectory (the vector norm is not constant).
1.4. Echoes in MRI

1.4.1. Free Induction Decay

According to Faraday’s law we can pick up a signal induced by the time varying transverse magnetisation in a nearby conductor loop (a coil non-parallel to the transverse plane): the electromotive force (EMF) induced in the conductor corresponds to the time rate of change of the magnetic flux. The measured signal of the entire sample is determined by the integral over the magnetisation in the sample volume and hence it follows the signal-equation

\[ S(t) \propto \int \int \int_{\text{Vol}} M(x,y,z, t = 0) e^{-t/T_2} e^{-i\omega_0(x,y,z)t} \, dx \, dy \, dz . \] (1.19)

We observe the Free Induction Decay (FID).

**Effective Transverse Relaxation** Consider a signal according to Eq. (1.19) from one small voxel. Only if the relaxation times and the Larmor-frequencies are constant over the entire voxel, the effective FID decay time equals $T_2$. Otherwise, the overall signal will decay faster with a relaxation time $T_2^* < T_2$ due to the integral over the voxel. The effective decay can be approximated by a decomposition according to

\[ \frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'} , \]

where the first term reflects the irreversible loss of phase coherence as described before (spin-spin-relaxation), and the second term a loss of phase coherence due to field inhomogeneities in the volume (“dephasing” of isochromats\(^1\)), which is reversible. Such field inhomogeneities can be caused, for example, by micro-gradients within the magnetic field due to susceptibility changes between different tissues.

1.4.2. Spin Echo

At time $t = TE/2$ following excitation of initial transverse magnetisation, $M_0$, spin-spin interactions as well as field inhomogeneities will have caused a decay of the transverse magnetisation to $M_0 e^{-TE/2T_2^*}$. If a second RF pulse is then applied, which flips all isochromats by 180° about the RF phase axis (e.g. the $x$-axis), the individual isochromat phases accumulated until $TE/2$

---

\(^1\)An ensemble of spins resonating at the same frequency is called “isochromat” – a distribution of spins with different resonance frequencies are commonly discussed as a group of isochromats.
are inverted. Since their resonance-frequencies have not been altered, exactly the same amount of phase change with the same sign will have accumulated from $TE/2$ until $TE$: all isochromats are rephased at time $t = TE$ and thus the vector sum in the transverse plane – the transverse magnetisation – is maximised. The loss of phase coherence due to field inhomogeneities has been reversed. The irreversible loss due to spin-spin interactions cannot be undone and thus the transverse magnetisation is reduced compared to the initial magnetisation by the factor $e^{-TE/T_2}$.

An RF pulse, which is applied in order to invert the spin phases at $t = TE/2$, is called refo-cussing pulse. The following peak of transverse magnetisation occurring at the echo time, $t = TE$, is called Spin echo (SE) or Hahn echo [4]. If the refocussing pulse was not an ideal $180^\circ$ pulse, at $TE$ the isochromats would have approached the so-called ‘eight ball’ distribution on the sphere (cf. Fig. 1.1 (D)) [4]. From the bulk rephased magnetisation in the transverse plane there is still a spin echo arising with a reduced amplitude compared to the maximal spin echo amplitude induced by a $180^\circ$ pulse.

### 1.4.3. Stimulated Echo

Consider the before mentioned ‘eight ball’ distribution of isochromats that occurs at the spin echo time, $TE$, following a non-ideal $180^\circ$ refocussing pulse. Suppose that, after continuous dephasing to a cone-like distribution of isochromats as shown in Fig. 1.1 (E), a third RF pulse at time $t = TE/2 + \tau$, flips all isochromats again about a defined axis. As a consequence, a certain partition of the isochromats will rephase to form a further echo at the echo time $t = TE + \tau$. This echo was prepared by the preceding two pulses and stimulated by the third pulse.

The spin phase distribution at $TE/2$ has been stored in the form of longitudinal magnetisation by the second pulse, i.e. the isochromat phases have been converted into different vector magnitudes along the positive and negative $z$-axis. This effect is commonly referred to as phase memory. The stored longitudinal magnetisation then decays according to $e^{-(t-TE/2)/T_1}$ and is finally (after mixing time $\tau$) converted back to transverse magnetisation by the third pulse (the vector magnitudes remain). The transverse magnetisation forms a stimulated echo at $TE + \tau$ when the isochromats are maximally rephased (cf. Fig. 1.1 (G)). The stimulated echo amplitude is maximal if the second and third pulses are $90^\circ$ pulses.

### 1.4.4. Phase Graphs

In a phase graph the phase evolution of one representative isochromat is plotted versus time. With the help of phase graphs the occurrence of echoes in the course of a pulse sequence can be predicted easily: an echo always occurs when a phasegraph path crosses the zero line. Figure
1.4. Echoes in MRI

![Diagram of pulse sequence and isochromatic depiction](image)

**Figure 1.1.** Pulse sequence and isochromatic depiction of the formation of a spin echo and stimulated echo, adapted from Ref. [4]. The SE according to the 'eight ball' isochromat distribution (D) is formed by a 2nd pulse not equal to 180°. A maximum of 50% of the initial magnetisation can form a stimulated echo (ignoring transverse relaxation during intervals [A,B] and [EG] and longitudinal relaxation during [C, F]), if all pulses are 90°. The (extended) phase graph concept provides a simplified means to understand the formation (and to calculate signal amplitudes) of echoes compared to an isochromatic depiction.

![Diagram of phase graphs for spin echo, stimulated echo, and general 3-pulse sequence](image)

**Figure 1.2.** Phase graphs for an ideal spin echo, stimulated echo, and a general three pulse sequence in accordance with the examples discussed before. In the first two examples only the phase graph path ways relevant for the ideal spin echo or stimulated echo formation are depicted. For the general example all possible path ways are depicted, five of which lead to an echo. Here, the subscript numbers denote the RF pulses involved in the echo formation.

1.2a shows the phase graph of a spin echo sequence using an ideal 90° excitation and an ideal 180° refocussing pulse. Figure 1.2b shows the phase graph of a stimulated echo sequence using ideal 90° excitation, tip-up and tip-down pulses as discussed above.

In a general three pulse sequence employing arbitrary flip angles several echoes can be observed as demonstrated in Fig. 1.2c. In addition to the primary spin echo and the stimulated echo, a secondary spin echo, “SE<sub>2/3</sub>”, occurs at TE/2+2τ (formed by α<sub>3</sub> from the magnetisation originally excited by α<sub>2</sub>), another spin echo, “SE<sub>1/2/3</sub>”, at time 2τ − TE/2 formed by twice refocussing (α<sub>2</sub> and α<sub>3</sub>) and a much later, higher order spin echo, “SE<sub>1/3</sub>”, formed at time TE+2τ by α<sub>3</sub> from the initial transverse magnetisation. The actual echo amplitudes depend on the series of flip angles and relaxation periods. The extended phase graph formalism introduced in section 2.5 is a quantitative, mathematical analysis of the magnetisation based on phase graphs.
Chapter 2.

Magnetic Resonance Imaging

In this chapter the principle of spatial encoding in Magnetic Resonance Imaging (MRI) using magnetic field gradients is described. The common k-space concept of discrete and finitely sampled spatial frequencies as well as the most relevant related imaging parameters are introduced. With these tools basic MRI pulse sequences are discussed. Finally, the Extended Phase Graph concept (EPG) is introduced providing a valuable tool for the analysis of signal evolution in the course of MR imaging pulse sequences.
2.1. Magnetic Field Gradients

In section 1.4 it was described how transverse magnetisation in the presence of field inhomogeneities dephases faster than in a perfectly uniform magnetic field ($T_2^* < T_2$). In the following sections it is described how a targeted spin dephasing can be achieved using well defined, switchable magnetic fields superimposed to the default static field. Such additional field variations are usually generated using an extra set of coils arranged in a way that they produce a linearly varying longitudinal field along the three orthogonal scanner $x, y, z$-directions such that $G = \nabla B_z(x, y, z) = \text{const} \neq (0, 0, 0)^T$. Therefore, such additional fields are often referred to as field gradients or, for reasons described below, imaging gradients.

2.1.1. Gradient Echo

Consider spins distributed in a homogeneous, static magnetic field: after excitation all spins precess with the Larmor-frequency and thus remain coherent. Now consider a linearly varying field (a constant field gradient) – say, along the $x$-axis – is superimposed to the static field such that spins at places $x_1 < x_2$ will precess faster than spins at places $x_2$ and the spin coherence is quickly lost. Inverting the linear field polarity at a certain time $TE/2$ after gradient onset makes the spins at $x_1$ precess slower than at $x_2$ so that at time $TE$ all spins are largely rephased. Such recall of magnetisation induced by switchable field gradients is called gradient (recalled) echo.

As indicated above, the default static field is usually not completely homogeneous, for example due to unavoidable susceptibility differences between tissues. Unlike spin echo (SE) spin rephasing induced by a refocussing pulse, which can be performed in the presence of gradients as well, gradient echo (GRE) spin rephasing is not capable of reversing the loss of coherence due to susceptibility differences. The GRE-magnetisation peak is therefore smaller than a corresponding SE-magnetisation peak, $e^{-TE/T_2^*} < e^{-TE/T_2}$. On the other hand, $T_2^*$ contrast between tissues, which is exclusively obtainable using gradient echoes, is often more valuable than $T_2$ contrast depending on the application (cf. section 3.1). Furthermore, gradient echoes can be created much more rapid than spin echoes.

2.2. Spatial Encoding in MRI

Making use of imaging gradients to impress a defined spatial dependence of the spin Larmor frequency is the common basis for standard spatial encoding methods in MRI. Multiple techniques are commonly combined in order to obtain data for an entire image as described in this section. The most relevant spatial encoding techniques are briefly discussed in the following.
2.2. Spatial Encoding in MRI

2.2.1. Slice-selective Excitation

One very common and intuitive method to employ spatial encoding using field gradients is called slice-selective excitation. For the sake of simplicity we may assume an RF pulse with a strictly defined bandwidth, $\Delta \omega$. In fact, very common excitation pulses are apodised (i.e. smoothly windowed) Sinc pulses. According to Eq. (2.1), the (non-apodised) infinite Sinc function corresponds to a continuous summation over oscillations with frequencies within $[\omega_0 - \Delta \omega/2, \omega_0 + \Delta \omega/2]$.

By employing a linear field gradient during excitation with such a superposition of equally weighted oscillations, only spins with resonance frequencies within the pulse bandwidth – i.e. only spins within a defined slice perpendicular to the slice-selection gradient axes – are excitable, whereas spins outside this slice are non-resonant. In other words, the spin off-resonance with respect to the excitation centre-frequency (the latter determines the slice shift in slice-select gradient direction) is defined by the slice-selection gradient amplitude. This impressed off-resonance is usually larger than other off-resonance effects.

Small Tip-Angle Approximation

Slice profiles are in general computed by solving the Bloch equations with an effective field in the rotating frame according to Eq. (1.13). One can show that, by approximating $\sin(\alpha) \approx \alpha$ with $\alpha = \gamma \int_0^t B_1(t) \, dt$, the slice profile is given by the Fourier transform of the excitation pulse envelope, $B_1(t)$ [5]. This small tip-angle approximation usually holds reasonably well for flip angles up to 90 degrees. However, for larger flip angles the deviations from the target slice profile become severe.

2.2.2. Frequency Encoding

Due to the linearity of applied field gradients, the precession frequencies of spins across the object are directly proportional to the spin location with respect to the axis defined by the gradient direction. The Fourier transform of the MR signal obtained in the presence of such a field gradient hence yields a temporal frequency spectrum, which directly corresponds to the spatial spin distribution along the applied field gradient direction. Such spatial encoding method is called
**frequency encoding.** The constant gradient during signal acquisition is called readout gradient. The Fourier transform of the acquired signal specifically is the projection of the complex spin distribution on the axis of the readout gradient (complex because the spins at different places may have different phases). As shown below the actual Fourier transform is performed with respect to a new spatial frequency variable as a function of time (Eq. (2.3)) and thus directly yields spatial units.

### 2.2.3. Phase Encoding

As an alternative to frequency encoding, which takes place during signal acquisition, an equivalent form of spatial encoding can be performed in a step-by-step manner by playing out changing preparation gradient pulses preceding repeated signal acquisitions. In this case the spin phases in the direction of the gradients are altered step-wise before the readout. This method referred to as phase encoding is usually applied to complement frequency encoding in a perpendicular direction. Together with preceding slice selection in the third perpendicular direction an entire three-dimensional spatial encoding can be accomplished. We refer to such experiment as a slice-selective MR experiment (two-dimensional Fourier encoding). Alternatively, one phase encode direction can be combined with an additional phase encode direction in slice-direction (three-dimensional Fourier encoding). Both methods can be combined in a way such that, instead of thin slices, thicker “slabs” are individually phase encoded in slice direction and finally combined in image space (“multi-slab acquisition”).

### 2.3. The $k$-space

Without loss of generality, the following section consider two-dimensional Fourier encoding only. In accordance with Eq. (1.19) the signal equation for a slice-selective experiment with phase encoding performed along $y$-direction and frequency encoding performed along $x$-direction can be written as

$$S(t) = C(t) \int \int_{\text{Slice}} dx \, dy \, M(x, y) e^{-i \omega_0 t} e^{-i y \left[ \int_0^T G_y(t') \, dt' \right]} y e^{-i x \left[ \int_0^T G_x(t') \, dt' \right]} x,$$  \hspace{1cm} (2.2)
whereby relaxation and and further factors have now been integrated into \( C(t) \). It is convenient to define new spatial frequency variables,

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

such that Eq. (2.2) can be rewritten as

\[
S(t) = C(t) \int_{\text{Slice}} \text{d}x \text{d}y \, M(x, y) e^{-i\omega_0 t} e^{-i2\pi k_y y} e^{-i2\pi k_x x} = S(k_x, k_y)
\]

Note that the actual spatial encoding axes do not have to coincide with the physical scanner gradient axes\(^1\). In the above example, \( x \) would be the “readout axis” and \( y \) would be the “phase encode axis” defined by the respective linear field gradient directions. The oscillating factor \( e^{-i\omega_0 t} \) corresponds to the Larmor-Frequency in the default static field (off-resonances are neglected for the sake of simplicity) and is usually omitted. In practice, such demodulation is achieved by mixing the imaginary and real part of the received signal with \( \cos(i\omega_0 t) \) and \( \sin(i\omega_0 t) \), respectively. Hence, one effectively measures the signal in the rotating frame of reference (cf. section 1.2).

It is crucial to realise that, following demodulation, Eq. (2.4) resembles the two-dimensional Fourier transform of the transverse magnetisation distribution in the selected slice. Thus, the complementary coordinates, \((x, y)\) and \((k_x, k_y)\) are in fact Fourier-pairs. This means that the distribution of the transverse magnetisation in real space (or rather image space), \( M(x, y) \), is obtainable by computing the inverse 2D-Fourier transform of the \( k \)-space signal. Likewise, from a three-dimensional experiment (acquire all combinations of “primary” \( k_y \) and “secondary” \( k_z \) phase encode lines successively), the inverse 3D-Fourier transform of the corresponding three-dimensional \( k \)-space would yield the entire spatial distribution of the transverse magnetisation, \( M(x, y, z) \).

### 2.3.1. Total Acquisition Time, Bandwidth and Signal-to-noise Ratio

In a real experiment, the received MR signals are first digitised using an analogue-to-digital converter (ADC) and then assigned to discrete \( k \)-space data matrices, which finally enables one to apply a discrete fast Fourier transform, (D)FFT. The low signal-to-noise ratio (SNR) inherent to MRI is a major reason to acquire relatively small data matrices, typically in the order of \( 64 \times 64 \) to \( 256 \times 256 \) in-plane. The total acquisition time of a general three-dimensional MRI experiment

\(^1\)Arbitrary (“double oblique”) axes can always be defined by a superposition of all three imaging gradients.
is directly proportional to the number of step-by-step primary \((N_{pe})\) and secondary \((N_{3d})\) phase encode steps and the number of readout pixels \((N_{ro})\) times the receiver dwell time (the interval between the ADC sampling time points). For a final image matrix of \(N_{ro} \times N_{pe} \times N_{3d}\) voxels, the total acquisition time – i.e. the cumulated duration of signal acquisition, not considering durations for gradient and RF pulses and “empty” fill times – amounts

\[
T_{acq} = N_{av} N_{pe} N_{3d} \cdot \frac{N_{ro}}{Δν}, \quad (2.5)
\]

where \(N_{av}\) denotes the number of averages and \(Δν/N_{ro}\) denotes the receiver bandwidth per pixel. The receiver bandwidth, \(Δν\) is equal to the inverse of the ADC dwell time.

The SNR is proportional to the square root of the total acquisition time, \(SNR \propto \sqrt{T_{acq}}\). Practical implications are, for example, that the SNR of an MR image increases with the square root of the number of averages or that it decreases with one over the square root of the bandwidth per pixel. Note, however, that also the applied flip angle (cf. section 2.4.2 or chapter 7) or the kind of RF excitation (cf. section 8.2) and further contrast generating sequence modules usually have a significant impact on the image SNR. Furthermore, note that the number of slices or slabs do not appear in the simplified formula stated above, which does not consider fill times and is hence not suited to describe multi-slice/multi-slab experiments. Such effects are partially covered by section 2.4.2.

### 2.3.2. Spatial Resolution and Field of View

According to the fundamental Nyquist-Shannon sampling theorem the discrete nature and the finite boundaries of \(k\)-space matrices are directly related to important imaging parameters such as the spatial resolution and the field-of-view (FOV) in the image space (using the \(k\)-space coordinate definition (2.3) in one dimension, without loss of generality):

1. The spatial resolution is determined by the extent of the acquired \(k\)-space:

\[
δ = \frac{1}{2k_{max}} \quad \text{(2.6)}
\]

2. The field-of-view is determined by the \(k\)-space sampling intervals:

\[
\text{FOV} = \frac{1}{Δk} \quad \text{(2.7)}
\]

Eq. (2.6) and Eq. (2.7) are equivalent expressions if one considers that \(\text{FOV} = Nδ\) and \(2k_{max} = NΔk\) where \(N\) is the number of pixels (and therefore also the number of \(k\)-space samples).
2.3. The k-space

**Aliasing**

Due to the Nyquist-Shannon theorem the FOV has to be adjusted such that complete extent of the object to be imaged lies within the FOV. According to Eq. (2.7) this is equivalent to choosing the \( k \)-space intervals sufficiently small. Violating the Nyquist-Shannon theorem results in aliasing artefacts. Aliasing in frequency encoding direction, for example, means that the temporal frequencies are not uniquely defined over the object any more. If \( \Delta \nu \) is the receiver bandwidth, only temporal frequencies (= spatial locations) within \([- \Delta \nu / 4, \Delta \nu / 4]\) respectively, can be correctly resolved in the rotating frame of reference. Higher temporal frequencies are erroneously assigned to the lower part of the resolvable spectrum: in MRI locations beyond one end of the FOV are assigned to the opposite end of the FOV. Such artefacts are also referred to as fold-in or fold-over artefacts.

**Point Spread Function and Convolution Theorem**

As shown below, aliasing artefacts reflect only one aspect of the point spread function (PSF) in imaging space which is characteristic for the utilised imaging experiment. Further properties of the PSF are related to the extent and the frequency-dependent weighting of the acquisition. The modulation transfer function (MTF), related to the PSF via the Fourier transform, characterises the (spatial-) spectral characteristics of the experiment in \( k \)-space. As it was already indicated in the context of the slice-selective excitation, the Fourier transform of a Heaviside (“boxcar”) MTF, i.e. the finite \( k \)-space, is a Sinc PSF. Since the boxcar MTF is an even function, the Sinc PSF is purely real. However, asymmetric MTFs are common in MRI as well, which generally lead to complex PSFs.

Due to the fundamental convolution theorem the Fourier transform of \( k \)-space signal, \( S(k) \), weighted by \( MTF(k) \) corresponds to the convolution of the actual image, \( I(x) \), convolved with the PSF:

\[
\text{FT}\{S(k) \cdot MTF(k)\} = \text{FT}\{S(k)\} \otimes \text{FT}\{MTF(k)\} = I(x) \otimes PSF(x)
\] (2.8)

For example, the sidelobes of the Sinc-PSF, corresponding to the usual \( k \)-space truncation, are most prominently expressed near edges and strong contrast in the final image, which is known as Gibbs-ringing. One common method to suppress Gibbs-ringing is to enforce smoother transitions between the fully weighted, low frequencies and the non-weighted, high frequencies. This is commonly referred to as apodisation.
Partial Fourier and Asymmetric Echo

Prominent examples for an asymmetric MTF are so-called Partial-Fourier (PF) or Asymmetric echo (AE) acquisitions where the $k$-space is not acquired from $-k_{\text{max}}, \ldots, k_{\text{max}}$ but from $-k_{\text{PF}}, \ldots, k_{\text{max}}$ instead, where $k_{\text{PF}} < k_{\text{max}}$. Sparing a distant part of the $k$-space either in phase encode directions (PF) or readout direction (AE) reduces imaging time and/or facilitates short echo times. However, two main drawbacks concur with typical truncated $k$-space reconstructions: a reduced SNR (proportional to the square-root of the total acquisition time) and degradation of the PSF (either increased Gibbs-ringing or reconstruction errors). Increased Gibbs-ringing results from simply zero-padding the asymmetrically truncated $k$-space prior to the FFT. More elaborate PF reconstruction methods exploit the Hermitian symmetry of $k$-space data under the ideal condition of a purely real image, in which case the missing part of the $k$-space data could just be copied from the available half. However, as indicated above many reasons may cause phase variations over the imaged object, for instance inhomogeneities of the main magnetic field. Typically, PF reconstruction algorithms aim to reduce such reconstruction errors by – mostly iteratively – approximating the actual phase. The amount of residual reconstruction errors strongly depends on the amount of the omitted $k$-space and the complexity of the image phase.

2.3.3. Parallel Imaging

The aliasing artefacts introduced above, are one further, very important manifestation of the convolution theorem to MRI. Due to the discrete sampling of the $k$-space signal, the continuous MTF is additionally multiplied with a regular distribution of Kronecker-delta functions with an interval of $\Delta k$ (comb- or Shah-function). The PSF (Fourier transform) of such an MTF is a regular, infinite repetition of the actual PSF (e.g. the Sinc) with a distance of $1\text{FOV} = \frac{\pi}{\Delta k}$ (cf. Eq. (2.7)) as a consequence of the Nyquist-sampling theorem.

The use of phased-array receive antennas (a combined “mesh” of receive coils) allows one to violate the Nyquist-Shannon sampling theorem with minimal sacrifices in the final image by employing (partial) parallel imaging techniques [6]. Here, the missing information due to $R$-fold $k$-space undersampling (acquire only every $R$th line = $R$-fold smaller FOV) is recovered from the “known” spatial distribution of the phased-array receive sensitivities. Usually this sensitivity information is estimated from a prescan. The most prevalent parallel imaging techniques are SENSE (Sensitivity Encoding) [7] and GRAPPA (Generalized Autocalibrating Partially Parallel Acquisitions) [8]. The first operates in image space by deterministically “disentangling” the aliased pixels of a complete, complex-valued image, whereas the latter operates in $k$-space where, for each receive channel separately, the missing $k$-space lines are interpolated prior to FFT.
For both methods the coil sensitivity information is gained from one or more low resolution calibration scan(s), which are used to compute the weights for pixel disentangling (SENSE) or for k-space interpolation (GRAPPA). From the SENSE theory directly follows the so-called g-factor map \([7]\), which describes the spatially varying signal-to-noise ratio (SNR) after SENSE reconstruction compared to unaccelerated image acquisition,

\[
\frac{\text{SNR}}{\text{SNR}_0} = \frac{1}{\sqrt{R \cdot g(r)}} .
\]  

(2.9)

For GRAPPA an equivalent g-factor expression follows more deep analysis of noise propagation due to the different regimes and due to additional coil combination applied in GRAPPA \([9]\). The main advantages of the GRAPPA technique are, first, that the coil sensitivity information is gained from a single autocalibration scan (ACS), and second, that individual images are available for each receive channel following GRAPPA reconstruction. The latter enables the application of near-optimal sum-of-squares coil combination \([10]\).

### 2.4. MRI Pulse Sequences

It was already indicated that different spatial encoding techniques are usually combined simultaneously or sequentially (e.g.: slice-selective excitation → phase encoding → frequency encoding) to acquire parts of the k-space data required for image reconstruction. Since typically only a minor part of the entire k-space (e.g. a single readout) is acquired following excitation, a block of RF and gradient pulses are usually repeated many times to successively fill the entire k-space data matrix. These combinations of RF pulses and gradient pulses are generally referred to as pulse sequences. Besides the echo time, \(TE\), already introduced above, the repetition time, \(TR\), between repeated pulse sequence blocks is an important timing parameter. Depending on the pulse combination and the sequence timing very different image contrasts are generated such as \(T_1\)-, \(T_2\)-, \(T_2^*\)-contrast, or, for instance, diffusion weighted contrast (cf. chapter 4) and blood-oxygen level dependent (BOLD) contrast (cf. chapter 3).

#### 2.4.1. MRI Contrasts

Consider repetition times shorter than the characteristic time for longitudinal magnetisation recovery, \(T_1\). If the magnetisation is continuously excited after partial longitudinal recovery only, the original equilibrium magnetisation is not re-established. However, a new, smaller steady state magnetisation with a corresponding steady state signal is eventually reached. The steady state strongly depends on the excitation flip angle, the repetition time and the \(T_1\) of the sample. The
contrast between samples (tissues) with different $T_1$ is largest if $TR$ is chosen in the order of a typical $T_1$ value which is referred to as “$T_1$ weighting”. Depending on the MRI pulse sequence type, such a $TR$ is comparably short. Increasing $TR$ to achieve (almost) full recovery avoids $T_1$ contrast and weighs the signal with the relative proton-density instead (“PD weighting”). Finally, let $TE$ be in the range of typical $T_2$ or $T_2^*$ values for a corresponding “$T_2$ or $T_2^*$ weighting”. For typical MRI pulse sequences such echo times are comparably long.

### 2.4.2. Ernst Angle

Besides the acquired echo type and the chosen timing parameters, the excitation flip angle is one further parameter with large impact on the image contrast as can be seen from the steady state signal equation: to calculate the steady state signal, reached after several “dummy repetitions”, the signals (magnitudes of transverse magnetisation) corresponding to the $n$th $TR$ and the $(n + 1)$th $TR$ are equated. Assuming non-contributing transverse magnetisation from the $n$th $TR$ to the actual $(n + 1)$th signal, e.g. for $TR \gg T_2$, the steady state signal is [5]

$$S(\alpha) = M \frac{\sin \alpha \left(1 - e^{-TR/T_1}\right) e^{-TE/T_2^*}}{1 - e^{-TR/T_1 \cos \alpha}}.$$  \hspace{1cm} (2.10)

The flip angle, $\alpha$, that maximises the steady state signal for the given experimental timing parameters is called Ernst angle:

$$\alpha_E = \arccos \left(e^{-TR/T_1}\right)$$  \hspace{1cm} (2.11)

In case of full recovery the Ernst angle is $90^\circ$, whereas for decreasing $TR$s the Ernst angle gets smaller.

### 2.4.3. Fundamental MRI Pulse Sequences

**Gradient Echo Imaging Sequences**

Figs. 2.1 and 2.2 show sequence diagrams of typical GRE sequences in a two-dimensional and a three-dimensional variant. Echo times and repetition times strongly depend on the targeted contrast. Lower limits are often determined by acquisition parameters such as the minimum readout bandwidth for sufficient SNR or by hardware limitations such as minimum gradient rise times (maximum “slew rate”) or maximum gradient amplitudes. Usually, only one $k$-space line is acquired following excitation. All slices/slabs of the volume to be imaged are excited (and read out) one after another before the initial slice is excited again. For a large number of slices this
corresponds to rather long effective TRs and large Ernst angles. Selecting only a few slices or exchanging the slice- and line-loop order results in considerably shorter effective TRs and thus typically small Ernst angles. The same effect is achieved when performing a three-dimensional experiment with a non-selective (or slab-selective) excitation pulse such that the entire volume is excited with every pulse. Generally, such fast GRE sequences are also known as fast low angle shot (FLASH) sequences.

In order to minimise the recurrence of “spurious echoes” from preceding repetitions usually the remaining transverse magnetisation is “spoiled” after signal acquisition: using gradients (on one, two or three scanner axes) the post readout transverse magnetisation is strongly dephased (gradient spoiling). Furthermore, a phase offset is usually added to the transmitter and receiver phase between two consecutive repetitions (RF spoiling) – mostly a quadratic phase increment, \( \varphi_n = \Delta \varphi \cdot n(n - 1)/2 \) with established values of \( \Delta \varphi = 50^\circ \) or \( \Delta \varphi = 117^\circ \) is selected. Note that such RF spoiling approximates the condition of non-contributing transverse magnetisation from previous TRs and therefore the Ernst signal and Ernst angle, Eqs. (2.10) and (2.11), are valid expressions, even if TR is not much larger than \( T_2 \).

Spin-Echo Imaging Sequences

Fig. 2.3 shows a typical two-dimensional (single) SE sequence diagram. The readout “dephaser” prior to the 180° refocussing pulse has the same polarity as the subsequent readout gradient since all magnetisation is inverted by the refocussing pulse. The empty fill times are adjusted such that the central \( k \)-space column is acquired at the exact echo time, i.e. after twice the time from excitation to refocussing pulse\(^2\). Usually the refocussing pulse is surrounded by “crusher gradients” of which the second one is supposed to spoil undesired new FID signal, whereas the first one assures that the refocussed magnetisation is still rephased appropriately .

Generally, spin echo sequences generate pure \( T_2 \) contrast. However, the single spin echo is often also used as a basis for different contrast mechanisms. For instance, introducing large gradient pulses into the excitation–refocussing interval and the refocussing–readout interval leads to a strong diffusion weighting of the signal as discussed in detail in chapter 4.

2.5. Extended Phase Graph Formalism

Solving the Bloch equations (1.14) of the magnetisation undergoing an imaging sequence is one option to calculate the signal course during acquisition. In fact, solving the Bloch equations is

\(^2\)Otherwise the signal would have additional \( T_2^* \)-weighting due to non-refocussed contributions at \( TE \).
Figure 2.1. Slice-selective, two-dimensional gradient echo sequence diagram. "SL" = slice-selection, "PE" = phase encode, "RO" = readout gradient axis. Time evolves from left to right. Black shading of subsequent gradients with opposite polarity indicates equal gradient moments. Superimposed trapezoids with a grey arrow indicate the PE gradient table and reordering scheme. Post-ADC gradients serve as spoilers of the transverse magnetisation. Dotted lines indicate how successive gradient pulses with equal polarity are merged. Note that the SL loop is inside the PE loop. This allows for longer effective TRs between excitations of the same slice.

Figure 2.2. Volume-selective, three-dimensional gradient echo sequence diagram. Compared to Fig. 2.1 the limited bandwidth RF pulse was replaced by a non-selective hard pulse. Spatial encoding in SL direction is achieved by replacing the slice loop by a secondary phase encoding ("partition") loop. Since the entire volume is excited with each RF pulse TR is much shorter compared to 2D-GRE, i.e. the Ernst angle is smaller. The loop order of primary and secondary phase encoding can be interchanged.

Figure 2.3. Slice-selective, two-dimensional ideal spin-echo sequence diagram. Again, post-ADC gradients serve as spoilers of the transverse magnetisation. The gradients labelled with "c" indicate the crusher gradients surrounding the 180 degree refocussing pulse, which are applied to spoil FID signals (excited by the refocussing pulse) as described in the text.
the only option if all magnetisation components need to be known at any point in time. For instance, this is required when explicitly studying the trajectory of the magnetisation vector during the application of an RF pulse. However, even if instantaneous RF pulses are assumed and efficient numerical computation methods are used [11], Bloch simulation of entire MRI pulse sequences are often too expensive. The Extended Phase Graph (EPG) concept provides a very efficient description of the magnetisation if global signal properties over time, such as the envelope of the signal of a specific voxel (i.e. spatial encoding is neglected), are investigated. In the following the basic EPG theory is derived and the calculus is explained.

### 2.5.1. Woessner-Decomposition and Kaiser-Coefficients

In section 1.4 phase graphs have been introduced as a pictorial representation of the magnetisation phase. In order to extend the information content of such a graph use is made of the Woessner decomposition proposed by Jaynes and Woessner in 1955 and 1961, respectively [12, 13].

Both real, orthogonal components of the transverse magnetisation are expressed by a single complex magnetisation as introduced in section 1.3, now denoted by

\[ F = M_x + iM_y \]

Conversely, the classical magnetisation vector components are expressed by \( F \) and the complex conjugate \( F^* \):

\[
M_x = \frac{1}{2}(F + F^*) \quad , \quad M_y = -\frac{i}{2}(F - F^*) \quad .
\]

The longitudinal magnetisation remains real and is expressed by \( Z = M_z \). The bulk magnetisation is decomposed into states of multiple amounts of dephasing and expressed as a Fourier series as proposed by Kaiser et al. [14]:

\[
F = \int_{\text{Vol}} F(r) \, dr = \int_{\text{Vol}} \sum_{n=-\infty}^{\infty} F_n e^{in\Phi_G r} \, dr = \sum_{n=-\infty}^{\infty} F_n \int_{\text{Vol}} e^{in\Phi_G r} \, dr \quad \quad (2.13)
\]

\[
Z = \int_{\text{Vol}} Z(r) \, dr = \int_{\text{Vol}} \sum_{n=-\infty}^{\infty} Z_n e^{in\Phi_G r} \, dr = \sum_{n=-\infty}^{\infty} Z_n \int_{\text{Vol}} e^{in\Phi_G r} \, dr \quad \quad (2.14)
\]

where \( \Phi_G r \) denotes the phase accumulated during one TR at a certain place, \( r \), in the sam-
ple. $\Phi_G = \gamma \int_0^T G(t) \, dt$ represents the gradient moment introduced by the pulsed field gradient (imaging gradient) of duration $T$, $\gamma$ denotes the gyromagnetic ratio. The integration in Eqs. (2.13) and (2.14) is performed over the entire volume of the sample which could be one imaging voxel for example [15]. The regular phases $n \Phi_G r$ are the discrete phase steps that the phase graph (of the regular imaging sequence) can assume. The Fourier coefficients, $F_n$ and $Z_n$, correspond to the (complex) “populations” of the phase graph paths or “states” (cf. Fig. 2.4). For simulation of signal amplitude and phase over the course of an imaging sequence it is sufficient to track the discrete set of states, which undergo transitions upon application of an RF pulse and evolution (shift and relaxation) between RF pulses.

Most remarkably, the integrals in Eqs. (2.13) and (2.14) result in a Sinc function with roots at all integer $n$ except $n = 0$ provided a dephasing of (multiples of) $2\pi$ over the volume is assured by properly adjusted spoiling gradients within each $TR$. As a consequence the zeroth transverse state, $F_0$, at the echo time reflects the entire echo magnetisation (all other states are dephased by $2\pi, 4\pi, \ldots$ and thus do not contribute to the echo signal).

**Transition Operation**

Let an RF pulse with flip angle $\alpha$ be applied along the $x$-axis. The resulting magnetisation components after the pulse are:

\begin{align*}
M_x &= M_x^- \\
M_y &= M_y^- \cos \alpha - M_x^- \sin \alpha \\
M_z &= M_z^- \sin \alpha + M_x^- \cos \alpha
\end{align*}

(2.15)  (2.16)  (2.17)

where the superscript “-” indicates the pre-pulse magnetisation. In terms of the Fourier expansion (2.13) and (2.14) equations (2.15) through (2.17) become

\begin{align*}
F_n &= M_{n,x} + i M_{n,y} \\
&= M_{n,x}^- + i(M_{n,y}^- \cos \alpha - M_{n,z}^- \sin \alpha) \\
&= \frac{1}{2} F_n^- (1 + \cos \alpha) + \frac{1}{2} F_{-n}^- (1 - \cos \alpha) - i Z_n^- \sin \alpha \\
&= F_n^- \cos^2 \left(\frac{\alpha}{2}\right) + F_{-n}^- \sin^2 \left(\frac{\alpha}{2}\right) - i Z_n^- \sin \alpha
\end{align*}

(2.18)

\begin{align*}
Z_n &= M_{n,y}^- \sin \alpha + M_{n,z}^- \cos \alpha \\
&= Z_n^- \cos \alpha - i \frac{1}{2} (F_n^- - F_{-n}^-) \sin \alpha
\end{align*}
Here, Eq. (2.12) and trigonometric relations have been used. The term $\sin^2 \left( \frac{a}{2} \right)$ reflects the fraction of the transverse magnetisation that is unchanged, as if acted upon an $0^\circ$-pulse (no transition), and $\cos^2 \left( \frac{a}{2} \right)$ reflects the fraction whose phase is inverted, as if acted upon a refocussing pulse (cf. Fig. 2.4). At the same time, a fraction of $\sin \alpha$ is converted from transverse to longitudinal states (phase memory) and vice versa. Generally, for an RF pulse with the arbitrary phase $\varphi$ the corresponding equations are compactly written in matrix-vector form [15]:

\[
\begin{pmatrix}
F_n \\
F_{-n} \\
Z_n
\end{pmatrix}
= 
\begin{pmatrix}
\cos^2 \left( \frac{a}{2} \right) & e^{2i\varphi} \sin^2 \left( \frac{a}{2} \right) & -ie^{i\varphi} \sin \alpha \\
e^{-2i\varphi} \sin^2 \left( \frac{a}{2} \right) & \cos^2 \left( \frac{a}{2} \right) & ie^{-i\varphi} \sin \alpha \\
-\frac{i}{2}e^{-i\varphi} \sin \alpha & \frac{i}{2}e^{i\varphi} \sin \alpha & \cos \alpha
\end{pmatrix}
\begin{pmatrix}
F_n \\
F_{-n} \\
Z_n
\end{pmatrix},
\]  

(2.19)

**Evolution Operation**

For the evolution between RF pulses the spin-lattice and spin-spin relaxation need to be accounted for. Diffusion weighting effects could be considered as well [16]. Most of all, the *dephasing and rephasing* of the transverse states, $F_{-n,...,+n}$, must be considered. As Fig. 2.4 suggests, for the case of a three-pulse-experiment with gradients whose moments are integer multiples of the first one, the state-index, $n$, displays the *order of dephasing* that is changed from pulse to pulse. The inter-pulse evolution with a pulse spacing of $T$ is characterised by the transitions [15]

\[
F_n \rightarrow F_{n+1} = e^{-T/T_2}F_n
\]  

(2.20)
\[ Z_n \rightarrow Z_n^- = e^{-T/T_1} Z_n + \begin{cases} M_0(1 - e^{-T/T_1}) , & \text{for } n = 0 \\ 0 , & \text{else} \end{cases} \] (2.21)

The first describes $T_2$-decay as well as dephasing (increase of the index) whereas the latter only describes $T_1$-relaxation and recovery in case of $n = 0$.

Solely by means of the transition-equations (2.19), (2.20) and (2.21), the state evolution for an arbitrary MR experiment may be computed without the need to solve Bloch-equations numerically for a large amount of virtual isochromats [17]. An echo thereby always occurs when a transverse state crosses the null-dephasing axis. This allows one to determine the exact signal train in a multi-pulse experiment by observing only the the post RF pulse states $F_0$ (in case of a gradient echo sequences) or $F_{-1}$ (in the simplest case of spin echo or stimulated echo sequences), at the beginning of each TR.
Chapter 3.

Functional Magnetic Resonance Imaging (fMRI)

Since the discovery of the Blood Oxygenation Level-Dependent (BOLD) contrast in the early 1990s it has been utilised in countless functional MRI (fMRI) studies to measure brain activation. Although not undisputed, today fMRI is certainly one of the most important MR imaging techniques for Neuroscientists. This chapter starts with a brief introduction to the BOLD effect and a coarse overview over the formal basis of fMRI. Then the basics of the fundamental fast Echo Planar Imaging (EPI) technique are introduced. Finally, typical image artefacts related to EPI in the presence of susceptibility inhomogeneities are discussed.
3.1. Blood Oxygenation Level-dependent Functional MRI

In the early 1990’s Ogawa et al. discovered the blood oxygenation level-dependent (BOLD) MRI contrast – a signal change which could be observed upon functional stimulation of the brain [18]. Since then the BOLD effect has been utilised in countless functional MRI studies, not only to investigate brain responses upon various task related activation paradigms but also recently to investigate the ‘resting state’ hemodynamics of the brain. Although the complex physiological mechanisms underlying the BOLD effect are not yet fully understood, a basic introduction can be given here.

3.1.1. The BOLD Effect

The BOLD signal change following a specific functional stimulus is traditionally detected using GRE based imaging techniques which are sensitive to $T_2^*$ changes. The specific change in $T_2^*$ is related to a change of the magnetic susceptibility, $\chi$, of blood from its oxygenated to its deoxygenated state when passing through the capillary bed. This is due the paramagnetism of deoxyhemoglobin ($\chi_{dHb} > 0$) as opposed to the diamagnetism ($\chi < 0$) of most other components of biological tissues such as water, lipids, proteins [19] and oxyhemoglobin. Theoretical derivations as well as experimental measurements have shown a total susceptibility difference of $\Delta \chi_0 = 0.27$ ppm between completely deoxygenated and oxygenated red blood cells [19]. As a consequence, the total susceptibility of blood (here, the red blood cell susceptibility has to be multiplied with the hematocrit level, a relative parameter between 0 and 1), which is always diamagnetic, becomes more diamagnetic the higher the blood oxygenation level is. The more diamagnetic the blood is, the longer is the $T_2^*$ relaxation time in the neighbourhood of blood vessels and thus the higher is the received MR signal at a given echo time. To sum up, an oxygenation level overshoot leads to a signal increase in $T_2^*$ sensitive MR sequences.

3.1.2. The Hemodynamic Response Function

It is today well understood that neuronal activation leads to at least two compensating actions which finally result in: (a) an increase of the cerebral metabolic rate of oxygen consumption (CMRO$_2$), and (b) an increase of the cerebral blood flow (CBF). The CBF increase hereby surpasses the oxygen consumption. In total all involved physiological mechanisms lead to a characteristic hemodynamic response function (HRF) as schematically illustrated in Fig. 3.1a: delayed by several seconds after stimulation a positive HRF peak (representing the oxygenation excess) is followed by a negative “undershoot” (reflecting the oxygen consumption). The baseline is
reached only after several tens of seconds. The BOLD response to an arbitrary stimulation pattern corresponds to the convolution of this pattern with the HRF (cf. Fig. 3.1b).

3.1.3. The General Linear Model

The BOLD response to the known stimulus pattern represents one column\(^1\) of what is commonly referred to as the design matrix, \(X\) for the general linear model (GLM). Additional columns of the design matrix describe further known input factors, which affect the MRI data, such as motion or respiration (explanatory variables). The dimensions of \(X\) are \(T \times M\), where \(T\) is the number of time points and \(M\) is the number of explanatory variables (e.g. one columns for the BOLD response, six columns for rigid motion, etc.). According to the GLM the \(T \times N\) fMRI data matrix \(Y\) is described by

\[
Y = X\beta + \epsilon, \tag{3.1}
\]

where \(\beta\) is a \(M \times N\) coefficient matrix and \(\epsilon\) is an additional \(T \times N\) error matrix. \(N\) is the number of voxels. The goal of any fMRI experiment is to find the best estimates of the coefficients in \(\beta\) that quantify the strength of the BOLD response resulting in a statistical parameter map (SPM).

To adequately model the BOLD signal the shape of the HRF is commonly approximated as two gamma functions (“canonical HRF”) with fixed parameters, e.g. by the SPM software package (http://www.fil.ion.ucl.ac.uk/spm/). However, there exist also approaches that individually estimate the HRF from the fMRI data together with or prior to the statistical tests for fMRI (e.g. in Ref. [20]).

\(^1\)one column per modelled condition of the fMRI paradigm
3.1.4. Typical fMRI Paradigms

The BOLD response to a single stimulus is rather slow. Although event-related fMRI, which is based on the BOLD response that follows from carefully distributed single stimuli in time (cf. Fig. 3.1b), is today well established, blocked paradigms are often more favourable due to a higher BOLD contrast (cumulative BOLD signal to block-wise presented stimuli). Here, stimuli are presented in blocks of 20 - 30 seconds, for example in the form 'ABABAB', where 'A' and 'B' represent the two contrasting conditions such as finger tapping and rest. Each epoch (AB) is usually repeated three to five times at least. Visual or auditory cues can be given to indicate the blocks to the subject.

3.2. Conventional Single-shot Echo Planar Imaging

From the temporal dynamics of the HRF it is clear that BOLD fMRI potentially offers the appropriate intermediate temporal resolution on a second time scale with high spatial resolution as compared to electroencephalography (EEG, high temporal resolution, low spatial resolution) and functional positron emission tomography (PET, low spatial resolution, high functional specificity). However, fast MR imaging techniques are required to sample the BOLD response to the input stimulus pattern sufficiently dense. Here, gradient echo (GRE) single-shot echo planar imaging (EPI) is the common technique of choice.

The concept of single-shot echo planar imaging (EPI) was already published in 1977 by Sir Peter Mansfield [22]. The essential idea was to acquire the entire spatial frequency information according to a two-dimensional image following a single excitation pulse. With this “snap shot” technique images could be acquired rapidly in succession resulting in a continuous time series of images.

3.2.1. Sequence Diagram and k-space Trajectory

In its simplest form the original GRE-EPI consisted of an oscillating readout gradient together with a constant, small phase encode gradient following slice-selective excitation and adequate pre-dephasing [22]. In the k-space domain this corresponds to a “zig-zag” trajectory. With continuous acquisition of the MR signal this results in non-uniformly distributed sampling points

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2Finger tapping refers to a gold standard motor task where the subject continuously taps with the finger tips of one or both hands against the thumb of the respective hand in a periodical manner for the entire duration of the block, e.g. (1) index finger (2) middle finger (3) ring finger (4) little finger (3) ring finger (2) middle finger (1) index finger (2) middle finger, etc.
according to cf. Fig. 3.2a. However, following k-space regridding and Fast Fourier transform (FFT) an entire image is obtained.

Various readout gradient waveforms have been proposed, among others sinusoidal and trapezoidal waveforms. However, the greatest modification from the original sequence was to replace the constant phase encoding gradient by short “blips” between two readout gradient polarities (“BEST” sequence [22]). Signal acquisition is then only performed when no phase encoding gradient is active. K-space data are thus sampled on parallel k-space lines according to Fig. 3.2b. Finally, k-space regridding becomes completely obsolete when acquiring the signal at constant rate only during the flat top times of a trapezoidal readout gradient waveform (according to the dotted acquisition window in Fig. 3.2b). Today the before mentioned variant with trapezoidal readouts and ramp sampling is routinely preferred. Modern computational power facilitates to include the regridding process into the standard image reconstruction pipeline easily. Furthermore, ramp sampling allows for speeding up the EPI acquisition. This can be beneficial for various reasons as discussed in detail in chapter 8.

For the sake of completeness, it is mentioned here that, besides GRE-EPI, there exist other EPI flavours. For instance, spin echo EPI (SE-EPI) is the basis for standard diffusion weighted EPI (DW-EPI, cf. chapter 4). The latter results in $T_2$ (and diffusion) contrast while GRE-EPI generates $T_2^*$ contrast. As indicated above, this is highly beneficial in the context of conventional BOLD functional MRI (fMRI). Furthermore, the high temporal rate of complete image acquisition
makes GRE-EPI an ideal sequence for fMRI.

### 3.2.2. Typical EPI Artefacts

The speed benefit of single-shot EPI is accompanied by a row of negative side effects. Most of them can, however, be handled reasonably well by an appropriate sequence implementation or by an appropriate choice of sequence parameters. Typically, such negative side effects are visible in EPI images as “ghost” images or as artefacts, which will be discussed briefly in the following. Example images are given in Fig. 3.3.

### 3.2.3. Susceptibility-Induced Artefacts

Usually, the object to be imaged – the human head for example – consists of multiple adjacent compartments of different tissues possessing different electric and magnetic properties. Local differences between tissue-specific magnetic susceptibilities introduce magnetic micro-gradients within the object if placed in an external magnetic field. The static magnetic field-inhomogeneities due to these local gradients cause a row of typical image artefacts in EPI, and most severely in GRE-EPI images. General means to manipulate such artefacts can be changing the voxel size, the readout bandwidth, the echo time, the slice angulation and/or flipping the EPI phase encode direction.

**Geometric Distortions**

As discussed in chapter 2, basic magnetic resonance imaging relies on the assumption that spin precession frequencies are solely determined by deliberately controllable external imaging gradients. This assumption is not valid if the magnitudes of susceptibility-induced micro-gradients, which are per definition proportional to the external field strength, become comparable to the imaging gradient magnitude. More specific, susceptibility effects cannot be neglected if the precessional frequency modulation and phase accumulation induced by micro-gradients and imaging gradients are of comparable magnitude. In case of frequency encoding with a relatively low readout bandwidth, for example, the linear mapping between precessional frequency and spatial location breaks down and manifests itself in severe geometrical distortions in readout direction (misplaced signal intensities).

For EPI, employed readout bandwidths are typically rather large. However, due to the continuous $k$-space-traversal the effective bandwidth in phase encode direction is very small: while negligible in readout direction, susceptibility-induced geometric distortions are very prominent
in phase encode direction. This is in particular the case near cavities and close to the skull base for usual head-first supine positioning in human MR scanners. As discussed in the appendix (D), common means to reduce geometric distortions in EPI are based on an increase of the effective phase encode bandwidth, for example by employing parallel imaging techniques, by using ramp sampling or by acquiring complete $k$-space data using multiple, interleaved shots with coarser echo planar readout trajectories.

**Intra-voxel Dephasing/ Through-Slice Dephasing**

Susceptibility-induced micro-gradients can have another disadvantageous effect, in particular on GRE-EPI images where the corresponding spin dephasing is never unwound and has typically become quite large by the time the $k$-space centre is acquired. Spin dephasing within a voxel, or across several voxels, is proportional to the local micro-gradients and accumulates over time. In GRE images the corresponding decrease of the $T_2^*$ relaxation time can lead to significant signal drop outs depending on imaging parameters. Reducing the voxel size is one effective means to reduce intra-voxel dephasing.

For two-dimensional, slice-selective acquisitions the spin distribution in slice direction is not Fourier encoded but integrated over the slice profile such that any net dephasing can only lead to signal reduction. Again, reducing the slice thickness reduces the amount of dephasing across the slice. Alternatively, the dephasing may partially be compensated for by so-called $z$-shimming techniques, where small slice gradient blips are applied prior to acquisition to prephase the spins such that they are in phase by the echo time. The moment of the respective slice gradient blip needs to be determined by means of a more or less time consuming prescan calibration.

**3.2.4. Chemical-shift Artefact**

A typical artefact related to the low phase encode bandwidth in EPI is the spatial misregistration of signal from tissue with a systematically shifted resonance frequency. A prominent example relevant for EPI is the signal from lipids (fat) which has a chemical (frequency) shift compared to free water of approximately -3.5 parts per million (ppm) on average. Without going too deep into details, chemical shift is caused by electrical shielding of the protons within specific molecules such as lipids (containing many $\text{CH}_2$ groups). When utilising a low signal acquisition bandwidth, the constant frequency offset leads to a constant spatial displacement of the lipid signal relative to the free-water ($\text{H}_2\text{O}$) signal. In EPI sequences with a high readout bandwidth but very low phase encode bandwidth this displacement occurs in the phase encode direction. Usually, the superposition of target water signal by displaced fat-signal is avoided by employing
so-called fat suppression techniques (cf. section 8.2).

3.2.5. N/2 Ghost

A specific EPI artefact is the so called N/2 ghost caused by a misregistration between odd and even lines acquired. The N/2 ghost is a rather faint duplicate of the imaged object shifted by half the field-of-view. The intensity of the N/2 ghost is usually modulated by a sinusoidal signal profile in readout direction which reflects the phase difference corresponding to the shift between the k-space lines. Various methods have been proposed to correct for these ghosts, some of which do not even require a separate calibration scan. The most prevalent calibration method relies on the acquisition of two non-phase-encoded projections using a very short echo train immediately following excitation (and slice rewinding). Assuming, without loss of generality, the first readout is positive, the second, negative readout is usually followed by an additional third positive readout resulting in three projections with extremely short echo time and thus very little phase evolution (almost no signal drop-outs, etc.). The first and the third projection, i.e. the Fourier transformed odd numbered signals, are averaged and the complex phase is compared to the complex phase of the second projection. The systematic phase difference can then be corrected for in the following imaging scans. Unless stated otherwise, for all results shown in this work a linear approximation of the phase (constant offset and slope) is used for phase correction. This leads to reasonable N/2 ghost reduction, at least at moderate field strengths of 3 Tesla. Alternative methods include non-linear phase correction and a pixel-by-pixel phase correction which can be computed from standard phase correction scans as well. A detailed discussion of these fundamental phase correction methods can be found in Ref. [23].
Figure 3.3. Example EPI images demonstrating typical artefacts. Two axial slices from a whole brain scan with 2.5 mm isotropic resolution are shown. Images (a) and (b) were acquired under identical conditions, except for the readout bandwidth that was increased in (b). Accordingly, the bandwidth in PE direction (vertical direction) was increased, hence the geometric distortions are reduced in (b). Images (b) and (c) were acquired under identical conditions, except for the echo time that was decreased in (c). The TE reduction results in less intra-voxel dephasing, which is apparent in the proximity of the ear canals (indicated by arrows). Images (c) and (d) were acquired under identical conditions, except for the fat suppression that was disabled in (d). In the top slice of (d) the chemical-shift artefact is particularly prominent (subcutaneous fat signal shifted by several pixels in PE direction). Image (e) shows similar slices as in (a-d), but here the EPI phase correction was not operating properly, hence quite strong N/2 ghosts become visible in the image background (intensity scaled by a factor of four). Images (a-d) were acquired with a custom EPI implementation (cf. chapter 8), image (e) was acquired with a vendor-provided EPI sequence.
Chapter 4.

Diffusion Magnetic Resonance Imaging (dMRI)

At the beginning of the following chapter, the sensitivity of specific MR pulse sequences to the diffusion of proton spins is explained and briefly developed to the concept of diffusion MRI (dMRI), which has become an indispensable tool for clinical diagnosis and neuroscientific research. A summary over the physical background of dMRI is given using the ensemble average propagator (EAP) description which relates the diffusion MR signal to the microscopic Brownian proton spin displacements. From the EAP the rather simplistic diffusion tensor as well as the orientation density function is mathematically derived. Accordingly, an introduction to diffusion tensor imaging (DTI) and q-ball imaging (QBI) is given. For both DTI and QBI the advantages and disadvantages are briefly discussed.
4.1. The MR Signal with Proton Spin Diffusion

The sensitivity of spin echo MRI pulse sequences to the diffusion of proton spins was already observed by Erwin Hahn in 1950 [4]. The NMR spectrometers of these times did not yet have the capabilities to homogenise the main magnetic field (shimming) as precise as it is nowadays the case. Thus, the proton spins within the NMR probes were permanently exposed to non-negligible field gradients. In the presence of “[...] self diffusion of ‘spin-containing liquid molecules’ [...]” [4] signal attenuation in addition to the expected $T_2$ decay was observed.

The simplified, qualitative explanation is as follows: the spin phases evolve as a function of the spin location within magnetic field gradients. At the spin echo time only those spins are refocussed whose phase accumulation between excitation and refocussing pulse, on the one hand, and refocussing pulse and spin echo time, on the other hand, are identical. The phase accumulation primarily depends on the location within the field gradient. While for coherent motion, such as flow, a net phase shift is measured, incoherent, Brownian motion is irreversible and thus leads to a signal attenuation due to destructive interference in the ensemble average. An early approach to account both effects led to the Bloch-Torrey equations [24] where a specific spin-flow velocity and a second order diffusion tensor were introduced.

Today, a typical diffusion weighting NMR experiment makes use of the pulsed gradient spin echo (PGSE) sequence (or derivatives) as originally proposed by Stejskal and Tanner in 1965 [25]. According to Fig. 4.1 it consists of two identical diffusion weighting or diffusion encoding gradient pulses of duration $\delta$ and amplitude $g = |g|$ usually surrounding one refocussing pulse. The two DW gradients are separated in time by $\Delta > \delta$. By substitution of the varying field into the Bloch-Torrey equation a signal dependence is obtained which is today referred to as the Stejskal Tanner equation [25],

$$E(b) = \frac{S(b)}{S(0)} = e^{-b \cdot ADC} = e^{-\beta^2 |g|^2 \left(\Delta - \frac{\delta}{2}\right) u^T D u}.$$  \hspace{1cm} (4.1)

Here, the apparent diffusion coefficient (ADC) describes the observed signal attenuation due to
4.1. The MR Signal with Proton Spin Diffusion

diffusion along the actual diffusion weighting direction \( u = g/|g| \). The \( b \)-value,
\[
    b = \gamma^2 \delta^2 |g|^2 \left( \Delta - \frac{\delta}{3} \right)
\]
contains the relevant pulse sequence parameters for diffusion weighting: a higher \( b \)-value can be obtained through either prolongation of the diffusion time, \( \Delta \), or by using a higher gradient moment, \( \delta |g| \).

The diffusion tensor model is widely utilised. However, it describes only the very special case of unhindered, Gaussian diffusion as specified in section 4.2.1. A more general formulation of diffusion makes use of the diffusion propagator formalism which essentially covers all modern diffusion MRI (dMRI) flavours [26].

4.1.1. The Ensemble Average Propagator

Let \( P(p_0|p_\Delta) \) be the diffusion propagator which describes the conditional probability that proton spins at position \( p_0 \) immediately after excitation have moved to \( p_\Delta \) after a time \( \Delta \). In practice this is the diffusion time between the diffusion weighting (DW) gradients of the PGSE sequence shown in Fig. 4.1. If \( \rho(p_0) \) denotes the initial proton spin density then the normalised diffusion MR signal at the spin echo time (i.e. the DW signal relative to the non-DW signal) is given by
\[
    E(q) = \frac{S(q)}{S(0)} = \int_{\text{Vol}} \rho(p_0) \int_{\text{Vol}} P(p_0|p_\Delta) e^{i\gamma \int_{t_0}^{t} g(t') dt'} e^{i2\pi q(p_0-p_\Delta)} dp_\Delta dp_0
\]
\[
    = \int_{\text{Vol}} \rho(p_0) \int_{\text{Vol}} P(p_0|p_\Delta) e^{i2\pi q(p_0-p_\Delta)} dp_\Delta dp_0
\]
(4.3)
(4.4)

Here, the narrow pulse approximation (NPA), \( \delta \ll \Delta \), was assumed so that the DW gradients can be considered as delta peaks with area \( \delta |g| \) [27]. In this scenario the proton spins are hence static during the application of the DW gradients. Furthermore, the substituted diffusion wave-vector,
\[
    q = \frac{\gamma}{2\pi} g \delta
\]
where \( \gamma \) is the gyromagnetic ratio, is thus explicitly not a function of time.
If the ensemble average propagator (EAP) defined over the net displacement, $p = p_\Delta - p_0$, 

$$P(p) = \int_{\text{Vol}} \rho(p_0) P(p_0 | p_0 + p) d\phi_0,$$  

(4.6)

is substituted, Eq.(4.4) simplifies to 

$$E(q) = \int_{\text{Vol}} P(p) e^{i2\pi p \cdot q} d\phi.$$

(4.7)

Equation (4.7) clearly reflects a Fourier relationship between the diffusion signal in “q-space” and the EAP defined in “spin displacement space”, i.e.

$$E = \mathcal{F}^{-1}[P(q)] \iff P = \mathcal{F}[E](p).$$

(4.8)

Usually the EAP is in fact reconstructed from the diffusion signal using the modulus Fourier transform in order to avoid artefacts caused by biologically induced phase errors in the signal:

$$P = \mathcal{F}[|E|](q).$$

(4.9)

This operation is equivalent to the full complex Fourier transform since the error-free diffusion signal is real (due to the symmetry of the EAP) and positive (due to the positive definiteness of the EAP) [28].

### 4.1.2. Diffusion Spectrum Imaging

In analogy to the familiar k-space formalism in MRI it would be convenient to successively acquire q-space signals on a Cartesian grid and finally reconstruct the ensemble average propagator via discrete Fast Fourier transform. While this may be possible for ex vivo probes utilising a gradient-equipped spectrometer with large maximum gradient amplitudes in the order of $\sim 200 - 800$ mT/m$^{-1}$ such an exact “diffusion propagator imaging” solution for human in vivo applications is still infeasible. If no specific hardware for diffusion weighting is installed, gradient amplitudes of a human MR scanner are usually limited to a maximum that ranges between 40 mT/m (whole body gradient coils) and 80 mT/m (special head gradient coils) in order to prevent peripheral nerve stimulation$^2$.

Very recently, the human connectome project, explores dedicated hardware with maximum

$^1$e.g. pore size estimation in porous media using such “q-space diffraction” techniques [29]

$^2$Motoneuronal activation induced by rapid gradient switching
4.1. The MR Signal with Proton Spin Diffusion

Gradient strengths between 100 – 300 mT/m for this purpose [30]. But even with such large gradient strengths the narrow pulse approximation can in general not be fulfilled. For example, if a specific EAP resolution (the resolution of the diffusion spectrum), e.g. \( p_{\text{min}} \sim 5 \, \mu\text{m} \) is desired:

\[
q_{\text{max}} = \frac{1}{2p_{\text{min}}} \sim 100 \, \text{mm}^{-1}
\]

\[
\Rightarrow \delta |g| \sim 2.35 \cdot 10^3 \, \text{ms} \cdot \text{mT/m} \quad \text{if} \quad \gamma \approx 2.675 \cdot 10^8 \, \text{s}^{-1} \cdot \text{T}^{-1}
\]

\[
\Rightarrow \delta \gtrsim 60 \, \text{ms} \quad \text{if} \quad |g| \lesssim 40 \, \text{mT/m}
\]

\[
\Rightarrow b \gtrsim 18000 \, \text{s/mm}^2 \quad \text{if} \quad \Delta \gtrsim 65 \, \text{ms} .
\]

(4.10)

In order to minimise the echo time of the diffusion weighted acquisition, typically \( \Delta \gtrsim \delta \) is selected instead of \( \Delta \gg \delta \). It has however been shown that the violation of the NPA only leads to a modified interpretation from the EAP towards a “centre-of-mass propagator”, which rather represents the mean of the spin positions during the first gradient pulse (\( t \in [0, \delta] \)) and the second gradient pulse (\( t \in [\Delta, \Delta + \delta] \)) [29]. This essentially leads to a slight underestimation of the diffusion displacements and EAP blurring but it does not alter the global propagator characteristics [31].

Acquisition and reconstruction of six-dimensional DSI data (3 image dimensions \( \times 3 \) q-space dimensions) while neglecting the NPA is commonly referred to as diffusion spectrum imaging (DSI) [31]. It is a very general diffusion MRI modality that contains all essential diffusion metrics such as the expected diffusion displacement, diffusion anisotropy and the diffusion orientation density function (dODF) of multiple non-parallel fibres. The latter, described in detail in section 4.3, is of particular interest for resolving neuronal fibre bundle tracts (“fibre-tracking”). Fig. 4.2 shows an example of fibre tracts derived from DSI performed at 3 Tesla in collaboration with Dr. Dr. Svenja Caspers. A spherically truncated Cartesian grid of 257 q-space samples with \( q_{\text{max}} = 65 \, \text{mm}^{-1} \) were used. Unfortunately, DSI acquisitions usually require up to 45-75 minutes, even if classical rapid imaging methods are employed, which is infeasible for many research applications and certainly unacceptable in a clinical scenario. Recently, more and more DSI methods are developed that save a lot of acquisition time by undersampling the q-space heavily and then performing “compressed sensing” [33] based EAP reconstruction [34]. However, the focus of clinical and most research applications still lies on classic “diffusion tensor imaging” or high angular resolution imaging methods such as “Q-Ball Imaging”, which are introduced next.

\[\text{As a matter of fact, it is common practice to define a minimum ‘pore diameter’, } a_{\text{min}} = 2p_{\text{min}}, \text{ of the structures one aims to resolve according to ref. [1] such that } q_{\text{max}} = 1/a_{\text{min}}. \text{ Unfortunately, the difference between displacement, } p \text{ and diameter, } a, \text{ is not made very clear in the prevalent DSI literature [31, 32].} \]
Chapter 4. Diffusion Magnetic Resonance Imaging (dMRI)

4.2. Diffusion Tensor Imaging

In contrast to DSI, diffusion tensor imaging (DTI) is a very widespread and robust, but also highly simplified diffusion MRI modality. DTI has numerous clinical applications from stroke diagnosis to neuroanatomical surgery planning.

4.2.1. The Diffusion Tensor

The second order diffusion tensor, $D$, is typically used to model the anisotropy of the apparent diffusion coefficient as a function of DW gradient direction in a rather simplistic way (cf. Eq. (4.1)) [26]. From the diffusion propagator perspective, one can show that, in the large-displacement-limit, $p \to \infty$, the diffusion tensor corresponds to the mean squared displacement tensor,

$$ H = \langle pp^\top \rangle = \begin{pmatrix} \langle x^2 \rangle & \langle xy \rangle & \langle xz \rangle \\ \langle xy \rangle & \langle y^2 \rangle & \langle yz \rangle \\ \langle xz \rangle & \langle yz \rangle & \langle z^2 \rangle \end{pmatrix} $$

divided by twice the diffusion time, $\Delta$ [27]. It is thus consistent with the Einstein equation describing Brownian motion in three dimensions [27]:

$$ D = \frac{H}{2\Delta} \iff \text{trace}(H) = \langle p^2 \rangle = 2 \cdot \text{trace}(D) = 6\langle D \rangle \Delta \ . $$
Using the Fourier relationship between the diffusion signal and the EAP Peter Basser showed by Tailor expansion of the logarithm of the normalised diffusion signal about \( q = 0 \) [27] that the EAP in the large-displacement-limit is a Gaussian distribution:

\[
\lim_{p \to \infty} P(p) = \frac{1}{\sqrt{|D|(4\pi\Delta)^3}} \exp \left( -\frac{p^T D^{-1} p}{4\Delta} \right). \tag{4.11}
\]

Due to the large-displacement limit, the Gaussian EAP is strictly valid for unrestricted diffusion only. In brain tissue, diffusivity is often classified as hindered instead of restricted, e.g. in white matter where protons can diffuse rather freely in the inter-axonal space, hower not without hitting the axonal (permeable) walls in the radial direction. Via the Stejskal-Tanner equation (4.1) the six independent diffusion tensor elements can be fitted rather robustly to properly diffusion encoded signals. In principle only six DW images (six non-coplanar DW encoding directions) and one non-weighted image [35] are required to reconstruct the diffusion tensor.

Optimal parameters for DTI, such as the optimal \( b \)-value (\( b \sim 1000 \text{ s/mm} \sim \langle D \rangle^{-1} \)) and the optimal number of isotropically distributed encoding directions (\( N \sim 30 \)), are well studied (e.g. [35–38]). DTI data acquisition is feasible in clinically acceptable times below 10 minutes and provides a number of clinically useful scalar indices and vectorial parameters as briefly introduced in the following.

### 4.2.2. Important DTI Parameters

#### Mean Diffusivity

The diffusion tensor trace is rotationally invariant and defines the mean diffusivity according to

\[
MD = \langle D \rangle = \frac{1}{3} \text{trace}(D) = \frac{1}{3} (\lambda_1 + \lambda_2 + \lambda_3).
\]

Here, \( \lambda_{1,2,3} \) are the three eigenvalues of the diffusion tensor. By convention, the eigenvalues are usually sorted according to \( \lambda_1 \geq \lambda_2 \geq \lambda_3 \), without loss of generality. While in the healthy brain, for instance, the mean diffusivity provides only little contrast (cf. Fig. 4.3b) it is strongly altered in case of a stroke within comparably short time after onset.

#### Axial and Radial Diffusivity

Recently, axial and radial diffusivity are often discussed as biomarkers, e.g. for neurodegenerative diseases (for example, see Ref. [39]). Axial diffusivity corresponds to the largest eigenvalue
of the diffusion tensor, $D_\parallel = \lambda_1$, whereas the radial diffusivity corresponds to the orthogonal magnitude of diffusion, $D_\perp = \sqrt{\lambda_2^2 + \lambda_3^2}$.

**Principal Eigenvector**

The eigenvector corresponding to the largest eigenvalue is referred to as the principal eigenvector (PEV), $e_1$, of the diffusion tensor. It defines the direction of largest mean-square displacement of the spins. Generally, one distinguishes between spheroidal ($\lambda_1 \approx \lambda_2 \approx \lambda_3$), prolate ($\lambda_1 \gg \lambda_2 \approx \lambda_3$) and oblate ($\lambda_1 \approx \lambda_2 \gg \lambda_3$) diffusivity [40]. The PEV is uniquely defined (except for spheroidal diffusion tensors) and most relevant for DTI fibre tracking, which assumes that only one dominating diffusion direction is present in each imaging voxel. Conventionally, PEV maps are displayed by using the three spatial PEV components as red, green and blue (RGB) image colour channels.

**Fractional Anisotropy (FA)**

Various indices of diffusion tensor anisotropy have been defined to account for the variety of tensor shapes. The fractional anisotropy is the most robust and wide spread anisotropy index and is defined via the ratio of the eigenvalue standard deviation and the root mean squared eigenvalue according to

$$FA = \frac{\text{std}(\lambda_i)}{\text{rms}(\lambda_i)} = \sqrt{\frac{3}{2} \frac{(\lambda_1 - \langle D \rangle)^2 + (\lambda_2 - \langle D \rangle)^2 + (\lambda_3 - \langle D \rangle)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}.$$  

As demonstrated in Fig. 4.3c, $FA$ maps reflect very well those main white matter fibre bundles that have a single main direction. $FA$ ranges between 0 (isotropic diffusion) and 1 (totally anisotropic diffusion) whereby low diffusion tensor anisotropy can also occur where the diffusion is in fact strongly directed along multiple non-parallel fibres. Furthermore, $FA$ is typically used as a weighting factor multiplied to PEV maps as illustrated in Fig. 4.3d.

**4.2.3. DTI Downsides**

Besides the assumption of unrestricted diffusion, which is very often not true, the second order diffusion tensor model is not able to adequately describe diffusion in multiple non-parallel main directions such as crossing, “kissing”, bending fibres within one imaging voxel. Hence, DTI
based fibre tracking is particularly problematic in areas where these assumptions are violated. In particular the latter has motivated the recent development of various parametric and non-parametric methods based on high angular resolution diffusion imaging (HARDI) which are able to discriminate multiple fibres [26].

4.3. Q-Ball Imaging

For many diffusion MRI applications such as fibre tracking only the EAP information with respect to fibre orientation is of interest (the mean diffusivity or mean diffusion displacement, for instance, are of minor interest). Reconstructing an “orientation density function” (ODF) instead of the entire displacement probability function (the EAP) can be expected to require fewer q-space samples than diffusion spectrum imaging, for instance. In 2004 Tuch proposed the “q-ball imaging” framework where an ODF is obtained from sampling only a single spherical shell in q-space (HARDI) followed by ODF reconstruction based on the Funk-Radon transform [28]. Almost at the same time Tournier proposed a related technique based on spherical deconvolution of HARDI data [41]. Although both have gained similar popularity and both have exclusive advantages and disadvantages, we focus here on q-ball imaging (QBI).

4.3.1. The Orientation Density Function

The ODF definition by Tuch is the radial integral over the EAP,

$$\Psi(\theta, \varphi) = \frac{1}{Z} \int_0^\infty P(p, \theta, \varphi) dp$$

(4.14)
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(a) Fibre orientations  
(b) Marginal dODF, Eq. (4.17)  
(c) ODF according to Tuch [28], Eq. (4.16)  
(d) min-max norm. ODF

Figure 4.4. Orientation density functions according to a Gaussian multi-tensor model (cf. section 6.2.2). Each tensor corresponds to $FA = 0.8$. One of three orthogonal fibres has been assigned half the weight of the remaining fibres. Fig. 4.4b corresponds to the true fibre ODF whereas Fig. 4.4c corresponds to the ODF definition by Tuch without ‘solid angle consideration’ [44]. The latter can be min-max normalised [28] for a better fibre distinction. Besides all apparent disadvantages only the ODF definition by Tuch allows for the closed mathematical QBI framework without specifying a model of diffusion. (Figures created using MATLAB (The MathWorks, Natick, MA))

where $Z$ is a normalisation constant so that $\int_0^{2\pi} \int_0^\pi \Psi(\theta, \Phi) \sin \theta \, d\theta \, d\Phi = 1$. This is the most trivial way to sacrifice the radial EAP information. It is also one of the largest criticisms drawn on QBI since it generally leads to rather smooth instead of distinct ODF features [42, 43]. This is due to the fact that $\Psi$ is not a “true” probability density function as would be the correct spherical integral over the EAP* that considers the Jacobian, $p^2$, in the integration [43]:

$$\Phi(\theta, \varphi) = \frac{1}{Z} \int_0^{\infty} P(p, \theta, \varphi) p^2 \, dp,$$  \hspace{1cm} (4.15)

Eq. (4.15) is also called marginal ODF or second order diffusion orientation density function (dODF) [26] and usually yields sharper estimates of the fibre orientation distribution.

Figure 4.4 displays the ODF and dODF according to Eq. (4.14) and (4.15) for a configuration of three orthogonal fibres. A Gaussian linear multi-tensor signal model according to ref. [45] (cf. section 6.2.2) has been used for ODF synthesis (one of the fibres was assigned half the weight of the others), whereby $FA = 0.8$ was assumed for each tensor. A corresponding multi-tensor EAP formula can be gained via the Fourier transform of the signal, as discussed above. The ODF can then be calculated algebraically as a sum of single-tensor ODFs due to the linearity of both the Fourier transform and the subsequent integration using Eq. (4.14) or (4.15). For a single tensor

*the marginal probability density function [42]
Tuch gives the expression
\[ \Psi(u) = \frac{1}{Z'} \left( u^T D^{-1} u \right)^{-\frac{1}{2}} \] (4.16)
according to his ODF definition [28]. Here, \( Z' \) is a new normalisation constant and \( u = p / |p| \) is the unit vector indicating the diffusion direction. Likewise, by inserting the diffusion tensor EAP, Eq. (4.11), into Eq. (4.15), one can derive the true single-fibre ODF,
\[ \Phi(u) = \frac{1}{Z} \int_0^\infty \frac{\exp \left( - \frac{u^T D^{-1} u}{4\Delta} p^2 \right)}{\sqrt{|D|(4\pi\Delta)^3}} p^2 \phi \]
\[ = \frac{1}{Z''} \left( u^T D_f^{-1} u \right)^{-3/2}. \] (4.17)

According to Fig. 4.4 the marginal dODF seems clearly more useful in terms of fibre distinction and tracking. A min-max normalisation of the smooth ODF, as proposed by Tuch [28], is only suggestive of being equivalent to the dODF (cf. Fig. 4.4d), as it introduces sharpness but also a loss of small features compared to the dODF.

However, the ODF definition by Tuch has one major advantage: it allows for a mathematically closed QBI framework which does not rely on a particular diffusion model. This is briefly described in the following.

4.3.2. The Funk-Radon Transform and QBI

The **Funk-Radon transform** (FRT) [46] is the spherical extension of the planar Radon transform [28] known from radial image reconstruction in MRI and Computed Tomography (CT) (e.g. [5]). It maps from the sphere to the sphere (\( S^2 \)). The FRT of a function on the unit sphere, \( f(u) \), is defined as the great circle integral over the function values on the perpendicular equator \( w \in \{ S^2 \mid w \perp u \} \) (cf. Fig. 4.5a):
\[ \text{FRT}[f](u) = \int_{S^2} f(w) \delta(w^T u) dw. \]
Here, \( \delta \) is the Dirac-delta. Tuch introduced a generalised version of the FRT evaluated at a specific radius, hence it maps from \( \mathbb{R}^3 \) to the sphere:
\[ \text{FRT}_q[f](u) = \int_{\mathbb{R}^3} f(x) \delta(x^T u) \delta(|x| - q) dx. \]
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Figure 4.5. The FRT of a spherical function at the unit vector \( u \) (red arrow) is defined as the integral along the perpendicular great circle (a). (b) “Bessel-beam projection” in displacement space, which approximates the radial EAP integration along \( u \) according to Eq. (4.14). The blue and red dots (size modulated by the magnitude) visualise the negative and positive lobes of the radial Bessel function which is additionally plotted below the sample cube. (Figures created using MATLAB (The MathWorks, Natick, MA))

By moving to cylindrical coordinates, \((r, \varphi, z)\), and assuming, without loss of generality, that the unit vector of interest, \( u = (0, 0, 1) \), is along the cylinder \( z \)-axis, Tuch proved that the ODF is approximated by the generalised FRT of the diffusion signal at radius \( q' \) [28]. That means, the ODF at direction \( u \) is approximated by the integral over the diffusion signal along the great circle perpendicular to \( u \):

\[
\text{FRT}_{q'}[E](u) = \int E(q'w)\delta(w^Tu)dw \\
= 2\pi q' \int_{p \in \mathbb{R}^3} P(r, \varphi, z)J_0(2\pi q'r)r\,dr\,d\varphi\,dz \\
\approx \Psi(u) .
\]

Sampling at the specific \( q \)-value \( q' \) results in the zeroth order Bessel function of the first kind, \( J_0 \), within the integral in Eq. (4.18) [28]. The Bessel function resembles a delta function in \( z \)-direction for large \( q' \). According to fig. 4.5b it hence approximates a “projection beam” along which the EAP is integrated to yield the ODF at \( u \). The central peak width and the side lobes depend on \( q' \). Analogue to the sinc function in \( k \)-space-based MR imaging the Bessel function can thus be interpreted as a truncation artefact leading to both limited angular resolution and side lobes [47].
Two facts can be noted here. First, the integration along \( z \), to which the triple integral in Eq. (4.18) collapses if the delta approximation is valid, is essentially over \( P(z) \) (and not over \( z^2 P(z) \), for instance). Thus, the Funk-Radon transform leads to the ODF defined by Tuch (4.14) and not to the true dODF according to Eq. (4.15). Second, the “Bessel-beam” approximation of the delta function becomes more accurate as \( q' \), the radius of the \( q \)-space sampling shell, increases. However, at the same time, the signal-to-noise ratio of realistic diffusion MR images decreases significantly. A \( b \)-value of \( b = 3000 \text{s/mm} \) has found wide acceptance as a good compromise. According to Eqs. (4.2) and (4.5) the \( b \)-value is related to the \( q \)-value via

\[
b = \frac{|q|^2}{(2\pi)^2} \left( \Delta - \frac{\delta}{3} \right).
\]

4.3.3. Generalised Fractional Anisotropy (GFA)

From the ODF different parametric maps can be derived, such as maps of the main fibre directions or ODF anisotropy maps. These parameters can generally be obtained by sampling the ODF at a sufficiently large number of unit directions (e.g. the reconstructed ODF values according to the encoding scheme or at interpolated directions). While ODF maxima detection is a topic on its own, the estimation of the ODF anisotropy as originally proposed by Tuch will be described briefly.

In analogy to the fractional anisotropy in DTI (Eq. (4.13)), Tuch defined the generalised fractional anisotropy [28] as the ratio of ODF standard deviation and root mean squared ODF,

\[
\text{GFA}_T = \frac{\text{std}(\Psi)}{\text{rms}(\Psi)} = \sqrt{\frac{n \sum_{i=1}^{n} (\Psi(u_i) - \text{mean}(\Psi))^2}{(n-1) \sum_{i=1}^{n} \Psi(u_i)^2}}, \tag{4.19}
\]

where \( u_1, \ldots, u_n \) denote ODF sampling directions. Fig. 4.6 shows an axial brain FA map compared to a GFA \( T \) map of the same slice based on identical HARDI data (\( N = 120 \) isotropically distributed diffusion encoding directions and \( b = 3000 \text{s/mm}^2 \) typical for QBI) obtained at 3 Tesla. There is a clear match between both maps where FA and GFA are quite strong. This corresponds to regions with single main diffusion directions where the diffusion tensor is a good model. More differences become visible in the background of the GFA map. Here, multiple crossing, bending, “kissing”, etc., fibres are resolved reasonably well whereas, on the DTI side, FA is artificially reduced due to simplified spheroidal diffusion tensors (= isotropic diffusion).
4.3.4. Analytical QBI

QBI, in contrast to DTI, is a model-free technique. This implies that ODFs are per se not described by an analytical expression equivalent to the diffusion tensor. While the diffusion tensor anisotropy is fully characterised by exactly three eigenvalues, the ODF is defined only on a set of samples specified during QBI reconstruction. Thus, Tuch and others had to perform ODF reconstruction explicitly and numerically on the basis of interpolated HARDI data \cite{28}.

In 2007 Descoteaux introduced a robust and particularly fast QBI algorithm on the basis of the Funk-Hecke Theorem \cite{45}. It exploits the fact that the Funk-Radon transform can be performed analytically if the diffusion signal is expressed in spherical harmonics\(^5\). In order to account for the reality and symmetry of the diffusion signals, a real and symmetric spherical harmonics basis is used:

\[
S(\theta, \varphi) = \sum_{j=1}^{R} c_j Y_j(\theta, \varphi)
\]

\[
Y_j(\theta, \varphi) = \begin{cases} 
\sqrt{2} \text{ Re}\{ Y_j^m \}, & \text{if } -\ell \leq m < 0 \\
Y_0^0, & \text{if } m = 0 \\
\sqrt{2} \text{ Im}\{ Y_j^m \}, & \text{if } 0 < m \leq \ell 
\end{cases}
\]

Here, Re\{\( Y_j^m \)\} and Im\{\( Y_j^m \)\} respectively denote the real and imaginary part of the conventional spherical harmonics functions,

\[
Y_j^m(\theta, \varphi) = \sqrt{\frac{2\ell + 1}{4\pi} \frac{(\ell - m)!}{(\ell + m)!}} P^m_\ell(\cos \theta)e^{im\varphi}
\]

where \( P^m_\ell \) are the associated Legendre polynomials. The \( c_j \) in Eq.(4.21) are the coefficients of the SH signal expansion of degree \( L \). The mapping between the modified basis indices, \( j = \)

\(^5\)A spherical harmonics expansion can be regarded as a spherical analogy to the usual discrete Cartesian Fourier synthesis.
4.3. Q-Ball Imaging

1, \ldots, R = \frac{1}{2}(L + 1)(L + 2), and the conventional SH basis indices, \( \ell = 0, 2, \ldots, L \) (degree) and \( m = -\ell, -\ell + 1, \ldots, \ell - 1, \ell \) (order), is bijective [45]. Such series will be denoted as “Lth order spherical harmonics expansion” throughout this work.

Descoteaux [45], and before him Anderson and Hess [48, 49], showed that the ODF could be expressed in the same SH basis just by rescaling the signal SH coefficients \( c_j \):

\[
\Psi(\theta, \varphi) = \sum_{j=1}^{R} 2\pi P_{\ell(j)}(0) c_j Y_j(\theta, \varphi) \equiv \sum_{j=1}^{R} a_j Y_j(\theta, \varphi)
\]  

(4.22)

Here, \( P_{\ell(j)}(0) \) denotes the \( \ell \)th Legendre polynomial at the origin. If one further requires the ODF to be normalised, one can easily derive that the coefficients should rather be

\[
a_j = \frac{P_{\ell(j)}(0) c_j}{2\sqrt{\pi} c_1}
\]  

(4.23)

since with Eq. (4.22)

\[
\int_0^{2\pi} \int_0^{\pi} \Psi(\theta, \varphi) \sin \theta \, d\theta \, d\varphi = 2\pi \sum_{j=1}^{R} \int_0^{2\pi} \int_0^{\pi} P_{\ell(j)}(0) c_j Y_j(\theta, \varphi) \sin \theta \, d\theta \, d\varphi = 4\sqrt{\pi^3 c_1}.
\]

The essential step in the ODF reconstruction algorithm by Descoteaux is the computation of the signal coefficients, \( c_j \). This is conveniently done by solving the corresponding system of linear equations (simultaneously for all imaging voxels and encoding directions) using a Moore-Penrose pseudo inversion, for instance. A regularisation term can be incorporated here in order to make the algorithm more robust against noise. Descoteaux proposed a Laplace-Beltrami regularisation since SH terms of higher degree, \( \ell \), will thus rather naturally be penalised by the eigenvalues of the eigenvalue equation \( \triangle_b Y^m_\ell = -\ell(\ell + 1)Y^m_\ell \). Here, \( \triangle_b \) is the Laplace-Beltrami operator on the sphere. For the implementation used in this work the rescaled ODF coefficients, \( a_j \), according to Eq. (4.23) are finally obtained using the MATLAB (The MathWorks, Natick, MA) implementation of the Moore-Penrose pseudo inverse.

To summarise, the fast algorithm by Descoteaux allows for ODF reconstruction without numerical interpolation of the HARDI data. The signal and ODF expansion can be evaluated at arbitrary angles. Nevertheless, the angular resolution of the ODF reconstruction is not only limited by the angular resolution of the HARDI encoding scheme but also by the SH truncation order, \( L \), the strength of the Laplace-Beltrami regularisation and by ODF blurring due to the “Bessel-beam” approximation in QBI (see above).
4.3.5. QBI Downsides

Despite the beauty of the closed mathematical q-space derivation, QBI clearly has some deficits. For example, the QBI orientation density function is not the true fibre ODF but a smoothed version. Therefore, fibres crossing at small angles can usually not be distinguished or lead to comparably large fibre estimation errors. This is due to the missing Jacobian in the integral of Eq. (4.14) \[ 43 \]. The (constrained) spherical deconvolution technique by Tournier \[ 41, 50 \] is frequently preferred over QBI because it results in more distinct ODFs. However, here a single-fibre response “prototype” must either be modelled or extracted from the data prior to deconvolution. As a consequence the results are not as reproducible \[ 26 \].

Recently, QBI methods that adequately consider the “solid angle effect” and thus deliver ODFs according to Eq. (4.15) have been proposed \[ 42 \]. However, specific assumptions about the diffusion are therefore reintroduced, e.g. a multi-Gaussian diffusion signal approximation \[ 26 \]. The algorithm by Descoteaux can be adapted to perform these kinds of reconstructions \[ 42 \]. Alternative techniques based on q-space sampling on multiple shells with different radii have become more popular recently. Here, the integration along the radius can be performed numerically \[ 47, 51 \] or by fitting the signal to a more or less adequate three-dimensional basis such as the solid spherical harmonics \[ 52 \]. The entire EAP is then approximated analytically. In analogy to Eq. (4.22), trivial true fibre ODF formulae, just as a function of series coefficients, can then be derived \[ 52 \].

Nevertheless, QBI is still one of the most popular and widely used HARDI techniques \[ 26 \]. It requires a comparably low number of diffusion weighted images (40-120) and is thus feasible even in a clinical scenario. The minimum number of isotropically distributed encoding directions for accurate ODF estimation has already been studied (e.g. \[ 53, 54 \]). However, as the next chapter will show, distributing directions isotropically is not trivial and there exist various approaches to find approximate solutions. Systematic errors as introduced by the encoding scheme will be investigated. This was previously done for DTI parameters but little is yet know for the QBI case, which will be studied more carefully.
Part II.

Anisotropic Errors in Diffusion MRI
Chapter 5.

Isotropic DISCOBALL Diffusion Encoding

The problem of distributing directions isotropically in space is encountered in numerous scientific disciplines. It is related to the generally unsolved but well studied spherical packing problem (Thomson’s problem, Tammes’s problem). In diffusion tensor imaging isotropic encoding directions are particularly important to minimise the dependence of accuracy and precision on a priori unknown diffusion orientations. As will be shown in chapter 6 this applies even more to high angular resolution diffusion imaging (HARDI) techniques. A variety of encoding scheme types has already been developed, which all approximate an isotropic distribution of directions by following different strategies. So far, however, these schemes are either numerically expensive, only available for a very limited number of directions or provide only an insufficient degree of uniformity for application in diffusion MRI. In this chapter, a novel deterministic scheme type is presented, which largely overcomes the limitations of previous deterministic approximations.
5.1. Deterministic Schemes

A representative list of icosahedral, numerically optimised and analytical spiral encoding scheme types, which are commonly used in dMRI, can be found in appendix A. The reader may refer to this list when specific schemes are utilised in the following chapter. A fourth deterministic type of encoding schemes has recently also found application in dMRI. As a matter of fact, two such scheme types have been proposed in 2009 and 2011 by Stirnberg et al. [55] and Koay et al. [56, 57], respectively. Both are based on comparable geometric strategies: a regular partitioning of the sphere by several latitudinal circles is suggested, on which points can be distributed evenly. To provide approximately consistent isotropy for varying direction numbers these methods require appropriate latitudinal discretisation “rules” (how many latitudinal circles needed and how many points on each?).

Koay and co-workers reported that discontinuities in the Riesz s2-energy according to the electrostatic repulsion model (see appendix A, Eq. (A.1)) associated with their discretisation rules were negligible for \( N > 60 \) by comparison to tabulated CFmin gold standard schemes [56]. In the current work an optimised algorithm based on our recently proposed DIrection SChemes Obtained By ALigning points on Latitudes (DISCOBALL) [55] is developed, which is shown to overcome the limitations of the Koay schemes for all numbers of directions. It will be used as a deterministic scheme type reference, specifically denoted ‘Disco\( N \)’ throughout the following chapters.

5.2. A Novel Deterministic Method for Isotropic Diffusion Encoding

A sketch of the DISCOBALL model is presented in Fig. 5.1. The Euclidean distances between adjacent points on the same latitude, \( d_{1,...,n/2} \), are denoted “intra-latitudinal next-neighbour distances”; the expected Euclidean distance between the two closest points on adjacent latitudes, \( d \), is denoted “inter-latitudinal next-neighbour distance”. The aim of the novel DISCOBALL algorithm is to minimise the mean squared error between the inter-latitudinal and the intra-latitudinal next-neighbour distances. Thus, in accordance with the Jones model (Coulomb repulsion depending on Euclidean distances) an approximately isotropic distribution of next-neighbour distances over the unit sphere is enforced. Previous methods for isotropic directions, just as the first version of the DISCOBALL algorithm [55], relied on comparably trivial rounding operations or heuristic rules targeting at similar arc lengths\(^1\) between next-neighbours over the sphere [56–60].

\(^1\)Knowing the Euclidean distance instead of the arc length is relevant for minimisation of the repulsive Coulomb force between two charged particles on the sphere.
5.2.1. Mathematical Foundation of the DISCOBALL Algorithm

Determination of the best configuration of $N$ directions according to the novel DISCOBALL model starts with setting the required number of latitudes, $n(N)$. An analytical expression can be found by means of basic trigonometric relations as follows.

The intra-latitudinal next-neighbour distance on the $m$th latitude populated with $k_m$ evenly distributed points is given by

$$d_m(n, k_m) = 2 \sin \left( \frac{m \pi}{n} \right) \sin \left( \frac{\pi}{k_m} \right). \tag{5.1}$$

The expected inter-latitudinal distance is

$$d(n) = 2\epsilon \cdot \sin \left( \frac{\pi}{2n} \right), \tag{5.2}$$

whereby the geometrical factor, $\epsilon$, is specified below. Then the optimal number of points on the $m$th latitude can be obtained by equating the intra- and inter-latitudinal distances, Eq. (5.1) and (5.2):

$$k_m(n) = \pi \cdot \arcsin \left( \epsilon \cdot \frac{\sin(\pi/(2n))}{\sin(m \pi/n)} \right). \tag{5.3}$$

The geometrical factor

$$\epsilon = \cos^{-1}(\pi/12) \tag{5.4}$$

expresses about how much $d = \text{mean}(d_{\text{inter}})$ is greater than the well known closest possible inter-latitudinal distance, $\min(d_{\text{inter}}) = 2\sin(\pi/(2n))$. This is the case if two points have equal azimuth. According to Fig. 5.1 the largest angle enclosed between this line and the line of the largest inter-latitudinal next-neighbour distance, $\max(d_{\text{inter}})$, is approximately $\pi/6$. On average
the angle is thus $\pi/12$, and hence Eq. (5.2) with $\epsilon$ according to Eq. (5.4).

For $n \geq 3$ the argument of the arcsine in Eq. (5.3) is very small and can thus be approximated linearly for all relevant cases ($N \geq 6$). The total number of directions is then well approximated by

$$N(n) = 1 + \frac{1}{2} \sum_{m=1}^{n} k_m(n) \approx \frac{\pi}{\epsilon \sin(\pi/(2n))} \sum_{m=1}^{n} \sin \left( \frac{m \pi}{n} \right)$$

$$= \frac{\pi \cos(\pi/(2n))}{\epsilon \cdot (1 - \cos^2(\pi/(2n)))}$$

(5.5) \hspace{1cm} (5.6)

Here, the following relation was used (employing the geometric series):

$$\sum_{m=1}^{n} \sin(mx) = \frac{i}{2} \sum_{m=0}^{n} \left[ (e^{-ix})^m - (e^{ix})^m \right]$$

$$= \frac{i}{2} \left( e^{-i(n+1)x} - 1 - e^{i(n+1)x} - 1 \right)$$

$$= \frac{i}{2} \left( e^{-i(n+1)x} - e^{i(n+1)x} \right) \cdot \left( e^{-i(n+1)x/2} - e^{i(n+1)x/2} \right)$$

$$= \frac{\sin(nx/2) \cdot \sin((n+1)x/2)}{\sin(x/2)}$$

which, applied to Eq. (5.5) yields

$$N(n) = \frac{\pi}{\epsilon \sin(\pi/(2n))} \cdot \frac{\sin(\pi/2) \cdot \sin(\pi/2 + \pi/(2n))}{\sin(\pi/(2n))} = \frac{\pi \cdot \cos(\pi/(2n))}{\epsilon \sin^2(\pi/(2n))}$$

and hence Eq. (5.6).

Equation (5.6), which is cubic in $\cos(\pi/(2n))$, can be solved and rearranged to the required number of latitudes given a total number of directions:

$$n(N) = \pi \cdot 2 \cdot \arccos \left( \frac{\pi}{\epsilon(N-1)} + \sqrt{\left( \frac{\pi}{\epsilon(N-1)} \right)^2 + 1} \right)^{-1}$$

(5.7)

The floating point number $n$ can be rounded up or down to yield an integer number of latitudinal circles, $\hat{n}$, each of which (on the upper hemisphere, $m = 1, \ldots, \hat{n}/2$) can now be populated with $k_m$ points. As these latitude populations are integer numbers they are very likely differing.
5.2. A Novel Deterministic Method for Isotropic Diffusion Encoding

from the optimal numbers according to Eq. (5.3). They thus lead to a characteristic squared distance error on each latitude, \((d_m(\hat{n}, k_m) - d(\hat{n}))^2\) with Eqs. (5.1) and (5.2). To maintain antipodal symmetry if the last latitude coincides with the equator (if \(\hat{n}/2\) is an integer number) only one half of the equator is populated, thus

\[
d_m(\hat{n}, k_m) = \begin{cases} 
2 \sin \left( \frac{m \pi}{\hat{n}} \right) \sin \left( \frac{\pi}{k_m} \right), & \text{if } m < \frac{\hat{n}}{2} \\
2 \sin \left( \frac{m \pi}{\hat{n}} \right) \sin \left( \frac{\pi}{2k_m} \right), & \text{if } m = \frac{\hat{n}}{2}
\end{cases}
\]

In the following, specific sets of latitude populations on the upper hemisphere, \(k_m\) with \(m = 1, \ldots, \hat{n}/2\), will be referred to as configurations. The well defined “optimal configuration” for the given number of latitudes, \(\hat{n}\), is defined by the minimum squared distance error on each latitude. Ideally, i.e. if no rounding operations were involved, the optimal configuration should be given by Eq. (5.3) in accordance to the previous derivation. It is, however, unlikely that for the specified \(N\) there exist such an optimal configuration. Instead, summation over the optimal configuration for the given \(\hat{n}\) probably yields a differing number of directions. Nevertheless, by ascending sorting of the squared distance errors, also the “least disadvantageous” \(k_m\) with \(\sum_{m=1}^{\hat{n}/2} k_m = N\) can be unambiguously determined.

The least disadvantageous configuration is determined twice - once for \(n\) being rounded down and once for \(n\) being rounded up (Eq. (5.7)). The one with the lower mean squared error,

\[
MSE(\hat{n}) = \frac{1}{\hat{n}} \sum_{m=1}^{\hat{n}/2} (k_m - 1)(d_m(\hat{n}, k_m) - d(\hat{n}))^2
\]

is considered the “best configuration” for \(N\) directions.

5.2.2. Performance of the DISCOBALL Algorithm

In practice, the novel DISCOBALL algorithm requires an initial definition of a reasonable range of populations per latitude which are subsequently ruled out by the least squared error sorting. This can be a considerable computational overhead. However, such an algorithm is expected to perform much faster than any numerical algorithm for CFmin schemes: neither a single explicit evaluation of the s2-energy nor a single numerical minimisation step (such as a downhill simplex iteration) is required. On the other hand the DISCOBALL algorithm requires more operations and more memory for storing distance errors and corresponding vector indices compared to a simplistic spiral algorithms or the recent Koay algorithm, for example. In the following, a brief comparison of computation speeds and the respective s2-energies as an objective measure for
scheme performance is presented.

**Computation Speed**

A MATLAB (The MathWorks, Natick, MA) implementation of the DISCOBALL algorithm (see appendix C) is compared to a MATLAB implementation of the Koay algorithm [57] and a freely available and efficient CFmin scheme algorithm implemented in c++ as part of the MRtrix software package (J-D Tournier, Brain Research Institute, Melbourne, Australia, http://www.brain.org.au/software/). Schemes for several small and larger direction numbers are generated. While the Disco and Koay schemes were generated repeatedly for accurate computation speed estimation, the CFmin schemes were generated only once due to computational costs.

**S2-Energies**

DISCOBALL schemes, Koay schemes and Spiral schemes (MATLAB implementation) are generated for all numbers of directions between six and 360. Jones schemes are generated only for a subset of directions due to the computational costs for larger numbers of directions. In addition, first to fourth order Icosahedral schemes corresponding to $N = 6, 21, 81, 321$ are generated using a MATLAB implementation kindly provided by Chung et al. (http://brainimaging.waisman.wisc.edu/~{}chung/lb) [61]. Fig. 5.2 illustrates for each scheme type the $N = 21, 81, 321$ schemes. For all generated schemes, the s2-energies are computed according to Eq. (A.1).

**5.2.3. Results and Discussion**

Tab. 5.1 lists computation times and residual relative s2-energy differences for deterministic Koay and DISCOBALL schemes compared to numerically optimised CFmin schemes. The latter are considered as optimal solution. The computation times for the Koay and the DISCOBALL schemes are in the range of milliseconds compared to minutes, hours or even days required for large numbered CFmin schemes. They can hence be neglected in all practical scenarios. The relative residual s2-energies are computed as the scheme-specific s2-energy minus the respective CFmin s2-energy divided by the latter. The s2-energies of the Koay schemes seem to fluctuate more heavily compared to the DISCOBALL schemes although both tend towards the optimum.

Fig. 5.3 shows plots of the s2-energies for all encoding scheme types discussed over a large range of direction numbers. The reasonably constant residual CF difference between the Disco and the CFmin schemes may be attributed to the restriction to latitudinal circles mainly. Note
Figure 5.2. Graphical comparison of different scheme types. Black dots indicate the directions. Scheme-specific s2-energies are given explicitly; the CFmin schemes are considered as the reference. The shown DISCOBALL schemes achieve lower s2-energies as the corresponding Koay schemes. According to the s2-energies Disco321 already corresponds to more isotropic distribution of directions than fourth order icosahedron subdivision.

Table 5.1. Computation times and s2-energies for the generation of various Koay (left), Disco (middle) and CFmin schemes (right) relative to the respective CFmin s2-energies.

<table>
<thead>
<tr>
<th>N</th>
<th>Koay Computation time</th>
<th>rel. CF difference [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Koay</td>
<td>Disco</td>
</tr>
<tr>
<td>30</td>
<td>0.1 ms</td>
<td>0.6 ms</td>
</tr>
<tr>
<td>40</td>
<td>0.1 ms</td>
<td>0.6 ms</td>
</tr>
<tr>
<td>60</td>
<td>0.1 ms</td>
<td>0.9 ms</td>
</tr>
<tr>
<td>81</td>
<td>0.1 ms</td>
<td>0.9 ms</td>
</tr>
<tr>
<td>120</td>
<td>0.2 ms</td>
<td>1.1 ms</td>
</tr>
<tr>
<td>240</td>
<td>0.3 ms</td>
<td>1.6 ms</td>
</tr>
<tr>
<td>321</td>
<td>0.2 ms</td>
<td>1.8 ms</td>
</tr>
<tr>
<td>500</td>
<td>0.3 ms</td>
<td>2.3 ms</td>
</tr>
<tr>
<td>1284</td>
<td>0.5 ms</td>
<td>4.5 ms</td>
</tr>
<tr>
<td>5124</td>
<td>1.4 ms</td>
<td>16.5 ms</td>
</tr>
</tbody>
</table>
that, according to Fig. 5.3, none of the selected direction numbers in Tab. 5.1 corresponds to unfavourable Koay schemes (no local CF maxima but rather local CF minima). Nevertheless, the Disco schemes outperform them with respect to minimal s2-energy. The considerable irregularities accompanying the Koay schemes are clearly “flattened” using the DISCOBALL algorithm.

5.3. Conclusions

A novel deterministic diffusion encoding scheme type has been proposed which offers near-optimal solutions to the problem of distributing directions isotropically in space. Compared to related deterministic scheme types the derivation of the DISCOBALL algorithm is based very closely on the Jones model. Thus, taking the related s2-energies as a proximate measure for scheme uniformity, the DISCOBALL schemes are most close to the numerically optimised schemes, at least over a range of 6 to 5124 directions tested here, and very likely also beyond \( N = 360 \). A continuously high degree of scheme isotropy with varying numbers of directions is guaranteed by the demonstrated monotony of s2-energies compared to other analytical and deterministic scheme types.

As a preliminary conclusion, judging from the computation times and the s2-energies only, the DISCOBALL schemes are most qualified for applications requiring a flexible number of isotropic directions in space such as diffusion tensor MRI (DTI) or q-ball imaging (QBI). In contrast to numerically optimised schemes they are computed online within milliseconds which allows for more flexible experimental planning in clinical routine, i.e. selecting exactly the maximum number of directions which fit into the available time scheduled for DTI or QBI. As a matter of fact, the vendor supplied schemes often only provide a very limited set of directions. Filling the gaps near-instantaneously with a negligible difference to numerically optimised solutions is where the potential of the DISCOBALL approximation lies.
5.3. Conclusions

The following chapter will investigate sampling-induced anisotropy in DTI and QBI by performing various simulations using numerically optimised schemes, analytical spiral schemes and DISCOBALL schemes.

Related Publications


Chapter 6.

Anisotropy in DTI vs. Anisotropy in QBI

The effect of anisotropic diffusion encoding has so far been studied for diffusion tensor imaging (DTI) only. In this chapter sampling-induced anisotropies in q-ball imaging (QBI) are systematically investigated for the first time. Therefore, extensive DTI and QBI single- and multi-fibre simulations are performed. The novel deterministic scheme type introduced in the previous chapter as well as some common scheme types defined in the appendix are utilised for diffusion encoding in both modalities. To allow for an adequate, unbiased analysis of the simulation data, the common method for response anisotropy estimation is completed by the introduction of a spherical “density weighting” functionality. It will be shown that residual response anisotropies in DTI and in QBI are very similar in magnitude if an optimised diffusion encoding scheme is employed. Compared to DTI, however, QBI turns out to be clearly more sensitive to non-optimal diffusion encoding. Further simulations are performed to investigate the degree of anisotropy that is additionally introduced in QBI by systematic ODF sampling. For both, diffusion encoding and ODF sampling, the novel DISCOBALL scheme type proves to satisfy the DTI and QBI demands very well.
The isotropy of DTI encoding schemes explicitly determines the accuracy and precision of reconstructed DTI parameters as a function of diffusion (fibre) orientation. This has been shown repeatedly by means of systematic DTI Monte Carlo simulations. For a convenient analysis of such DTI simulations the concept of DTI parameter “response surfaces” was used \[36, 37, 63\]. In appendix B a generalisation of the response concept is presented, which will be applied to single-fibre DTI simulations as well as to single- and multi-fibre QBI simulations in this chapter. The particular aim is to determine the direction scheme type and the minimum number of directions that minimise the anisotropy of the respective parameter response, which is calculated from the standard deviation and the mean of the response (cf. section B.3).

### 6.1. Anisotropic Errors in Diffusion Tensor Imaging

DTI error anisotropy has already been studied extensively. The aim of the present study is to compare the DTI performance of the novel deterministic “Disco” scheme type introduced in section 5.2 to the performance of numerically optimised “CPmin” schemes (Jones schemes) – the gold standard in this field. This is done for varying numbers of diffusion weighting directions.

#### 6.1.1. Materials and Methods

**Simulations**

To investigate noise propagation properties related to each encoding scheme type, an extensive DTI Monte Carlo simulation according to Skare \[63\], Batchelor \[36\] and Jones \[37\] and colleagues is carried out with \(N = 6, 10, 12, 15, 20, 30, 60\) directions per encoding scheme type realistic noise added to the diffusion signals. In accordance with these earlier studies 484 prolate diffusion tensors, their principal eigenvector (PEV) orientations distributed over a regularly spaced polar grid with \(N_\Theta = 11\) values of inclination angle,

\[
\Theta_m \in \left\{ \frac{m \cdot \pi}{2(N_\Theta - 1)} \right\}, \quad m = 0, 1, \ldots, N_\Theta - 1 \in [0, \pi/2],
\]

and \(N_\Phi = 44\) values of azimuth angle,

\[
\Phi_n \in \left\{ \frac{n \cdot 2\pi}{N_\Phi} \right\}, \quad n = 0, 1, \ldots, N_\Phi - 1 \in [0, 2\pi],
\]
are synthetically generated such that

\[ D_{mn} = \lambda_1 e_{1,mn}^T (e_{1,mn}) + \lambda_2 e_{2,mn}^T (e_{2,mn}) + \lambda_3 e_{3,mn}^T (e_{3,mn}) \]  

(6.1)

Here, \( T \) denotes the transpose. The eigenvectors are defined as

\[
\begin{align*}
e_{1,mn} &= \left( \begin{array}{c} \sin \Theta_m \cos \Phi_n \\ \sin \Theta_m \sin \Phi_n \\ \cos \Theta_m 
\end{array} \right), \\
e_{2,mn} &= \left( \begin{array}{c} \sin(\Theta_m + \pi/2) \cos \Phi_n \\ \sin(\Theta_m + \pi/2) \sin \Phi_n \\ \cos(\Theta_m + \pi/2) 
\end{array} \right), \\
e_{3,mn} &= e_{1,mn} \times e_{2,mn}.
\end{align*}
\]

The diffusion tensor eigenvalues, \( \lambda_{1,2,3} \), are calculated such that the tensor trace corresponds to a biologically relevant mean diffusivity of \( 0.7 \cdot 10^{-3} \text{mm}^2 \text{s}^{-1} \) and their ratio, \( \lambda_1 : \lambda_2 : \lambda_3 \), corresponds to three different fractional anisotropy values, \( FA = 0.7, 0.8, 0.9 \). With each diffusion tensor, the Stejskal-Tanner equation is computed 60 times with a \( b \)-value of \( b = 1000 \text{s mm}^{-2} \) and once with \( b = 0 \):

\[
\left( \frac{S(u_k)}{S_0} \right)_{mn} = e^{-b u_k^T D_{mn} u_k + \eta}.
\]  

(6.2)

Here, \( u_k \) denotes the \( k \)th normalised encoding direction from the scheme averaged so as to yield 60 measurements in total (e.g. 2x30 directions) and \( \eta \) is additional complex Gaussian pseudo random noise according to a typical signal-to-noise ratio (SNR) of 15 in the non-weighted signal. Due to the magnitude operation this results in Rician noise in the final signals. From the 61 signals, each diffusion tensor is reconstructed using the Moore-Penrose pseudo inverse least squares solution in MATLAB and finally FA is calculated.

Signal simulations, reconstructions and parameter estimations are repeated 10000 times followed by computation of the mean and the standard deviation of FA, \( \mu FA(x_{mn}) \) and \( \sigma FA(x_{mn}) \), for each response sampling point, \( x_{mn} = (\Theta_m, \Phi_n) \).

Analysis accounting for non-isotropic response sampling

Fig. 6.1 shows two examples of typical \( \sigma FA \) responses obtained for identical schemes. Only the orientation relative to the simulated fibre directions was altered. It is obvious that the non-isotropic response sampling must be considered when numerically integrating over such a response. Response integration or summation, respectively, is required for computing the mean or the standard deviation over all sampling points according to Eqs. (6.3) and (6.4), for instance.

\[
\text{mean}_w(f) = \frac{\sum_{m,n} w_{mn} f(x_{mn})}{w_{mn}}
\]  

(6.3)
Figure 6.1. Typical $\sigma FA$ responses obtained with identical encoding schemes (Disco6, indicated by the black arrows) rotated differently with respect to the simulated fibre directions (response samples, indicated by the mesh grid). The central ticks on the vertical axis indicate the conventional mean ± standard deviation over the respective response.

\[
\text{std}_w(f) = \sqrt{\frac{\sum_{m,n} w_{mn}}{\left(\sum_{m,n} w_{mn}\right)^2} \cdot \sum_{m,n} w_{mn}(f(x_{mn}) - \text{mean}_w(f))^2}
\]  \hspace{1cm} (6.4)

Analogue to the Jacobian determinant for coordinate transformation, weights, $w_{mn}$, are introduced which are proportional to the surface elements on the sphere associated with each diffusion tensor orientation, $x_{mn} = (\Theta_m, \Phi_n)$. For the present case of a regular polar grid the weights (the spherical Voronoi cell areas [64]) can be computed analytically as a function of the inclination angle (latitude):

\[
w_{mn} = \frac{2\pi}{m}\frac{(m+1)\Delta \Theta}{\frac{1}{2}N_\Theta} \sin \theta d\theta d\varphi = 2\pi \left( \cos \left( \frac{(m - \frac{1}{2})\pi}{(N_\Theta - 1)2} \right) - \cos \left( \frac{(m + \frac{1}{2})\pi}{(N_\Theta - 1)2} \right) \right), \hspace{1cm} (6.5)
\]

for $\Theta_m = m\Delta \Theta$, where $m = 1, 2, \ldots, N_\Theta - 1$

\[
w_{0n} = \frac{2\pi}{\frac{1}{2}N_\Theta} \sin \theta d\theta d\varphi = 2\pi \left( 1 - \cos \left( \frac{\pi}{(N_\Theta - 1)4} \right) \right), \hspace{1cm} (6.6)
\]

Here, $\Delta \Theta = \frac{\pi}{2(N_\Theta - 1)}$ denotes the constant latitudinal increment. Fig. 6.2b illustrates the weights used here.
6.1. Anisotropic Errors in Diffusion Tensor Imaging

![Image of two spheres representing inadequate and adequate weighting](image)

**(a) Inadequate weighting**  
**(b) Adequate weighting**

**Figure 6.2.** Equal (inadequate) and analytically determined (adequate) weighting of non-isotropically distributed response samples according to the regular polar grid used within the present DTI Monte Carlo simulations. The numbers next to Fig. 6.2b denote the explicit weights computed via Eqs. (6.5) and (6.6).

6.1.2. Results

Figures 6.3 and 6.4 show $\mu FA$ and $\sigma FA$ responses obtained from the $FA = 0.9$ DTI simulations employing Disco and CFmin schemes with $N = 6, 10$ and 15 directions (averaged 10, 6 and 4 times, respectively).

Already from the responses in Figs. 6.3a, 6.3d and 6.4a, 6.4d one can appreciate that CFmin6 schemes clearly reduce response variations compared to Disco6. However, the DISCOBALL approximation becomes more accurate as $N$ grows so that the responses actually become almost indistinguishable from the corresponding CFmin responses. At the same time the numerical optimisation for the CFmin schemes according to Jones [35] becomes extremely time consuming (cf. Tab. 5.1), though still providing most isotropic responses.

The corresponding response mean and response anisotropy indices summarised in Figs. 6.5a through 6.5c confirm this impression. The CFmin anisotropy curves for both FA estimate and FA imprecision responses approach a minimum at approximately 30 directions. This is in total agreement with earlier findings [37, 63]. It is noteworthy that the Disco anisotropy curves are almost congruent with the CFmin curves while Spiral responses are consistently more anisotropic (although only slightly). A zoomed version of the anisotropy plot in Fig. 6.5b can be found in section 6.2 (Fig. 6.9).

Compared to the response anisotropies the mean of the FA estimate and imprecision responses appear more noisy and quickly approach a common level. However, note that the Spiral mean curves show a systematic FA overestimation as well as increased standard deviation for low direction numbers as opposed to the Disco and CFmin mean curves.
Figure 6.3. Fractional anisotropy estimate responses for several encoding schemes (true $FA=0.9$). Each data point on the surface plots represents the mean over 10000 $FA$ estimates for that particular fibre orientation. Here, the three ticks on the vertical axis indicate the weighted mean ± the weighted standard deviation over the entire $\mu FA$ response.

Figure 6.4. Fractional anisotropy imprecision responses for the same schemes as in Fig. 6.3. Each data point represents the standard deviation over 10000 $FA$ estimates for that particular fibre orientation. Here, the three ticks on the vertical axis indicate the weighted mean ± the weighted standard deviation over the entire $\sigma FA$ response.
6.1. Anisotropic Errors in Diffusion Tensor Imaging

![Graphs showing mean(µFA) and mean(σFA) for different FA values](image)

(a) $FA=0.7$

(b) $FA=0.8$

(c) $FA=0.9$

Figure 6.5. Fractional anisotropy estimate and imprecision response mean and anisotropy plotted versus number of encoding directions. Results for Disco, Spiral and CFmin scheme DTI simulations with three degrees of diffusion tensor anisotropy (a) - (c). Note that the number of excitation was NEX=60 for each data point.
6.1.3. Discussion

The simulations performed yield equal overall fractional anisotropy estimates and precisions for both the numerically optimised CFmin and the DISCOBALL schemes if ten or more encoding directions are employed – not an unusual but rather a routine scenario. More importantly, the residual response anisotropies are larger when using a simplistic spiral scheme compared to CFmin or Disco schemes. The results thus confirm the preliminary conclusions drawn at the end of chapter 5: Disco schemes are equivalent to CFmin schemes with respect to isotropic DTI diffusion encoding.

Overall, also results from earlier DTI simulation studies have been confirmed: both the $\mu FA$ and $\sigma FA$ response anisotropies summarised in Fig. 6.5 are minimised for $N = 30$ directions and there is no clear advantage in terms of response isotropy by using, for example, 60 directions instead of averaging the 30 directions measurements twice. It has been shown elsewhere that similar conclusions can be drawn from analyses of the estimate and imprecision responses of the mean diffusivity (MD) or the cone of uncertainty (CU) of the estimated principal eigenvector \cite{37}. Although not shown here, the present simulations have also confirmed these findings.

While in previous, comparable publications the problem of anisotropic response sampling has not been mentioned \cite{36,37,63} it has been addressed here by introducing weighted statistics with weights being proportional to the sphere surface elements associated to the points.

The generalised definition of response functions, given at the beginning of this chapter, will prove useful throughout the following chapter in which sampling-induced anisotropies in $q$-ball imaging are discussed.

6.2. Anisotropic Errors in Q-Ball Imaging

This section characterises the main factors for anisotropy in standard QBI by quantifying typical QBI parameter estimation and imprecision anisotropies for realistic experimental scenarios. Monte Carlo simulations as well as noise-free simulations are performed with single-, two- and three-fibre configurations. To avoid under-sampling of the respective responses the orientations of these fibre configurations are distributed uniformly with a high angular resolution. Comparable investigations of QBI anisotropy have not been carried out before.

Anisotropic errors in QBI may have a variety of sources and characteristics. Here, we focus on two different categories. The first category – even in a noise-free scenario – results from the diffusion encoding ($b$-value, encoding scheme) in combination with intrinsic QBI approximations (e.g. that the ODF equals the Funk-Radon transform of the signal \cite{28,45,47}) and
6.2. Anisotropic Errors in Q-Ball Imaging

various reconstruction parameters such as spherical interpolation [28] or spherical harmonics expansion parameters (series truncation order, regularisation parameter) [45]. In this section, the anisotropic effects of conventional and alternative encoding scheme types on the generalised fractional anisotropy (GFA) [28] are compared under typical experimental conditions by means of single- and multi-fibre simulations in analogy to the DTI studies carried out before [36, 37, 63]. Due to the spherical harmonics ODF expansion used here, the GFA can be evaluated analytically and thus an additional source of anisotropy, as discussed next, is avoided.

The second category of systematic QBI bias is introduced during post processing. For example, many ODF maxima detection algorithms, essential for fibre tracking, rely on a uniform sampling of the reconstructed ODFs. The numerical calculation of GFA, as originally proposed by Tuch [28], also relies on a uniform ODF sampling. Any ODF sampling anisotropy can be expected to directly propagate to derived parameters. This effect is first demonstrated on in vivo GFA error maps by using different ODF sampling schemes followed by a quantitative discussion of GFA estimate response anisotropies derived from systematic single-fibre simulations employing the same ODF sampling schemes. In both cases the analytical GFA serves as an unbiased reference.

6.2.1. Analytical GFA Using Spherical Harmonics

The generalised fractional anisotropy is today still largely computed according to the formula (4.19) proposed by Tuch in 2004, i.e. on the basis of ODF samples. This is even done if, for instance, the ODF was already reconstructed terms of spherical harmonics (SH),

\[ \Psi(u) = \sum_{l=0}^{L} \sum_{m=-l}^{l} a_{l,m} Y_{l}^{m}(u), \quad (6.7) \]

by using the analytical QBI algorithm by Descoteaux. In his original paper [45], for example, Descoteaux used Icosa81 and Icosa321 sampling schemes to compute voxel-wise GFA according to the formula given by Tuch.

An analytical expression for the GFA can be found in the literature [26, 65, 66] that makes use of the continuous representation of the ODF in SHs. For the sake of completeness a derivation of the analytical solution is presented here, which is unfortunately lacking in the respective references. Therefore, the integrals needed for the root mean square ODF and the ODF standard deviation entering the definition of the GFA, Eq. (4.19), are solved algebraically. The notation \( E[.] \) for the expected value is used as well as the fact that \( Y_{0}^{0} = 1/\sqrt{4\pi} \) and the orthonormality property of spherical harmonics, \( \int \int Y_{l}^{m} Y_{l'}^{m'} \sin \theta d\theta d\phi = \delta_{ll'} \delta_{mm'} \). The symbol \( \delta_{ij} \) denotes the
Kronecker delta.

\[ GFA = \frac{\text{std}(\Psi)}{\text{rms}(\Psi)} = \sqrt{\frac{\mathbb{E}[(\Psi - \mathbb{E}[\Psi])^2]}{\mathbb{E}[\Psi^2]}} = \sqrt{1 - \frac{\mathbb{E}[\Psi]^2}{\mathbb{E}[\Psi^2]}} \]  

(6.8)

\[ E[\Psi] = \frac{1}{4\pi} \sum_{l=0}^{L} \sum_{m=-l}^{l} a_{l,m} \int_{0}^{\pi} \int_{0}^{2\pi} Y_{l,m}(\theta, \varphi) \sin \theta \, d\theta \, d\varphi = \frac{a_{0,0}}{\sqrt{4\pi}} \]  

(6.9)

\[ E[\Psi^2] = \frac{1}{4\pi} \int_{0}^{\pi} \int_{0}^{2\pi} \left( a_{0,0} Y_{0,0}^0 + \cdots + a_{l,l} Y_{l,l}^l \right)^2 \sin \theta \, d\theta \, d\varphi = \frac{1}{4\pi} \sum_{l=0}^{L} \sum_{m=-l}^{l} a_{l,m}^2 \]  

(6.10)

Thus, by inserting Eq. (6.9) and (6.10) into Eq. (6.8) the analytical GFA expression is obtained just as a function of the ODF spherical harmonics series coefficients:

\[ GFA = \sqrt{1 - \frac{\sum_{l=0}^{L} \sum_{m=-l}^{l} a_{l,m}^2}{\sum_{l=0}^{L} \sum_{m=-l}^{l} a_{0,0}^2}}. \]  

(6.11)

It allows for quicker and – most importantly – unbiased GFA computation compared to the sampling based expression. In this context “unbiased” refers to the avoidance of yet another sampling scheme introducing potential anisotropy of GFA accuracy or precision.

One goal of the simulations discussed next is to investigate GFA response anisotropy introduced by ODF sampling, on the one hand, and to compare it to the GFA response anisotropy introduced by the choice of encoding scheme, on the other hand. Therefore, the analytical GFA is an indispensable reference measure for the actual GFA.

### 6.2.2. Materials and Methods

An experimental verification of encoding scheme-induced anisotropies in QBI is even more unfeasible than it is the case for DTI due to the shear number of repetitions for statistical robustness and, not least, the exact arrangement of fibre orientations. Therefore, the analysis of encoding scheme-induced anisotropies is here solely based on simulations. As described below, however, the effect of different ODF sampling schemes will be investigated by means of simulation and experimental in vivo data.

For QBI signal synthesis, a multi-tensor model according to ref. [45] is assumed as an exten-
6.2. Anisotropic Errors in Q-Ball Imaging

Anisotropic errors in Q-ball imaging can be assessed by comparing the response of the Q-ball model to the single-fibre model used for the DTI simulations (Eq. (6.2)): 

\[
\frac{S(v_i)}{S_0} = \left| \left( \sum_{j=1}^{n_F} c_j e^{-b u_k^T (D_j) u_k} \right) + \eta \right|.
\]  

(6.12)

Here, \( c_j \) are fibre weights for the case of \( n_F \) (here \( n_F \leq 3 \)) non-parallel diffusion tensors, \( D_j \). The index \( m \) denotes the \( m \)th orientation of the simulated fibre configuration drawn from a predefined set of orientations as discussed below. Each tensor trace is again set to a biologically relevant \( 2.1 \cdot 10^{-3} \text{ mm}^2/\text{s} \) and the eigenvectors correspond to prolate diffusion ellipsoids with high fractional anisotropy of 0.8 (not varied here in contrast to the DTI simulations).

The \( b \)-value is set to \( b = 3000 \text{ s/mm}^2 \). The encoding directions, \( u_k \), are drawn from the CFmin, Disco and Spiral encoding scheme types introduced in chapter 5 with \( N \in \{30, 40, 60, 120\} \). Again, \( \eta \) denotes complex Gaussian noise, either corresponding to an SNR=15 in a non-weighted image (taking the magnitude again results in Rician noise) or SNR=\( \infty \) (no noise). In the noisy case the signals are averaged \{4, 3, 2, 1\} times, respectively, resulting in a constant number of excitations, NEX=120, for a fair comparison of imprecision measures, such as the standard deviation. A scenario without averaging is realised as well to be more close to a realistic experimental planning situation.

**Single-fibre encoding simulations**

According to the “near-isotropic” distribution of fibre orientations as discussed above, at least four times more fibres (isotropically distributed response samples) than the number of encoding directions should be simulated. The principal eigenvectors of the diffusion tensors simulated here are thus aligned along the directions defined by a CFmin500 scheme. Rician distributed noise corresponding to an SNR=15 in a non-weighted image is added to each signal repeated 10000 times for sufficient statistical power. For each of the 500 orientations 10000 ODFs are reconstructed using a self-written implementation of the SH method by Descoteaux once without Laplace-Beltrami (LB) regularisation and once with a recommended regularisation weight of \( \lambda = 0.006 \) [45]. In all cases the analytical GFA is computed according to Eq. (6.11).

GFA estimate and imprecision responses are obtained by computing the mean and standard deviation over 10000 GFA values for each fibre orientation. The two-dimensional responses (as a function of principal eigenvector inclination and azimuth angle) are denoted \( \mu_{GFA} \) (mean) and \( \sigma_{GFA} \) (standard deviation). In addition, estimate responses, denoted \( GFA^\infty \), are obtained with only one signal simulation per fibre orientation and encoding direction for a noise-free scenario.

For each response the response anisotropy index is calculated by inserting the weighted mean
and standard deviation over all response sampling points into Eq. (B.2). The respective spherical Voronoi cell areas are used as as response sample weights as discussed above.

**Multi-fibre encoding simulations**

For the previous single-fibre simulations only a limited range of encoding directions have been used which allowed for a response comparison with equal numbers of excitation (NEX). This excluded icosahedral encoding schemes. Finally, in a series of noise-free multi-fibre simulations with variable NEX, icosahedral schemes up to the fourth tessellation order are compared to CFmin, Disco and Spiral schemes with a broader range of direction numbers. For signal synthesis one, two and three perpendicular, equally weighted, prolate diffusion tensors are assumed (all other parameters as described above).

To realise all possible fibre orientations with two or more non-parallel fibres, the respective configuration are rotated successively by three Euler angles about three axes (here: \(z/y/z\)-axis of a fixed frame of reference), i.e. a third rotation about the fixed \(z\)-axis is performed prior to the usual inclination and azimuth rotation. Only a discrete set of initial rotations with constant angle increment is necessary to provide sufficiently dense response sampling. This increment, \(\Delta \alpha\), is chosen such that the number of rotations for a whole turn, \(2\pi/\Delta \alpha\), is an integer and such that

\[
\Delta \alpha \approx \sqrt{\frac{4\pi}{N\sqrt{3}}}.
\]

The latter represents the angular resolution of the inclination and azimuth rotation (2nd and 3rd Euler angles) given here by CFmin1284. This corresponds to an angular resolution of 4.3 degrees and thus to an initial Euler angle raster with \(360^\circ/4.3^\circ \approx 84\) steps for arbitrary multi-fibre constellations. In the current study performing sufficient Monte Carlo repetitions (10000) for stable statistics has been found to be computationally unmanageable. \(1284\times 84=107856\) fibre orientations yield \(\sim 10^9\) individual ODFs to be reconstructed on the basis of \(N\) times as many signals per scheme type. Even if additional symmetries in case of identical, orthogonal fibres were exploited, the number of simulated signals could not be reduced sufficiently.

Instead of Monte Carlo simulations, a single noise-free simulation per fibre orientation and encoding direction is thus performed here. As will be shown this is sufficient if one focuses on the systematic bias only (corresponding to the “bias-only” example given Fig. B.1). The ODF reconstruction is performed as described above.
6.2. Anisotropic Errors in Q-Ball Imaging

Single-fibre ODF sampling simulations

Sampling based GFA is estimated according to Eq. (4.19) employing CFmin, Spiral, Disco and Icosa sampling schemes with 21, 81, 321 and 1281 directions. The ODFs are obtained from QBI simulations using a CFmin120 encoding scheme as described. No noise is added and ODF reconstruction is performed without LB regularisation. Since all other parameters remain unchanged the analytical reference GFA is taken from the previous single-fibre simulations with CFmin120. For adequate response sampling, single-fibre inclination and azimuth angles corresponding to a CFmin5124 direction scheme are realised.

ODF sampling of experimental data

For experimental demonstration of ODF sampling-induced GFA anisotropy it is sufficient to perform repeated analysis on one single in vivo data set using different ODF sampling schemes. The analytical GFA is regarded as the ground truth reference. The error dependence on fibre orientation is probed sufficiently by the natural distribution of single-fibre tracks and multi-fibre crossings within the brain.

HARDI data (Disco120 at $b = 3000 \text{s/mm}^2$ interleaved with 14 $b = 0$ weighted images) of one healthy volunteer are acquired using a standard double-refocused spin echo diffusion weighted EPI sequence on a 3 Tesla scanner (TIM Trio, Siemens, Erlangen, Germany). A 32-channel phased array head coil is used for signal reception. Twofold GRAPPA imaging acceleration [8] and oblique slice orientations are chosen to maximise the imaging volume per acquisition time (90 × 90 × 55 matrix, 2.4 mm isotropic resolution). Using the same analytical QBI reconstruction as for the simulations, the ODFs in each voxel are reconstructed and the analytical GFA is computed. Sampling based $GFA_T$ maps are computed using CFmin, Spiral, Disco and Icosa ODF sampling schemes with 21, 81 and 321 sampling directions to create difference maps to the analytical reference ($GFA_T - GFA$). In addition to GFA maps a “primary-ODF-maxima” direction map is computed using a CFmin321 sampling scheme.

6.2.3. Results

Single-Fibre Encoding Simulations

Fig. 6.6 shows typical single-fibre GFA responses on the example of CFmin40, Spiral40 and Disco40 without averaging (NEX=40) reconstructed (a) with and (b) without moderate LB regularisation. For each response the colour range is scaled individually to fit the entire dynamic response range. Please note the correlation between response pattern and encoding scheme.
Figure 6.6. Typical GFA estimate and imprecision responses for $\text{NEX}=N=40$ obtained with (a) and without (b) moderate Laplace-Beltrami regularisation. For each of the 500 single-fibre orientations, which define the response inclination and azimuth angle, 40000 diffusion-weighted signals have been simulated and 10000 ODFs reconstructed.

(indicated by small circles) on the one hand, and the correlation between the estimate ($\mu GFA$)/imprecision ($\sigma GFA$) response patterns and the noise-free $GFA^{\infty}$ patterns on the other hand. The latter is particularly obvious for Spiral responses where the systematic anisotropy correlated to the scheme directions is consistently larger than the response uncertainty background (denoted as “response noise” in the following analysis as it exhibits no obvious directional preference).

Figs. 6.7 and 6.8 summarise the respective response means and anisotropies plotted versus number of diffusion directions for the single fibre simulations (reconstruction performed without LB regularisation). Note that only the mean $\mu GFA$ and $\sigma GFA$ curves show a significant difference between the simulations with varying NEX (Fig. 6.7) and constant NEX=120 (Fig. 6.7) whereas the anisotropy curves as well as the noise-free mean estimate curves (mean($GFA^{\infty}$)) are practically identical. From the mean imprecision curves one can appreciate that the overall GFA uncertainty is at the NEX=120 specific minimum using either CFmin or Disco schemes already with $N \geq 30$ but clearly not using Spiral schemes. Similar conclusions can be drawn from the final, noisy NEX=120 GFA estimate to which the CFmin and Disco responses converge rather quickly but which is not even achieved with Spiral120. The “true” mean GFA in 6th order SH expansion can be approximated as 0.361 from the noise-free simulations. Note that GFA values in the order of only 0.3-0.4 – even for high diffusion tensor anisotropies as simulated here – are
not unusual \[67\] for standard QBI reconstruction without “solid angle consideration” \[44\].

The response anisotropy index (\(\sim\) coefficient of variation) reveals larger differences between encoding schemes than the response mean. Generally, the estimate anisotropies, aniso(\(G\text{FA}^\infty\)), aniso(\(\mu\text{GFA}\)), and imprecision anisotropies, aniso(\(\sigma\text{GFA}\)), range between \(\sim 0\%-0.5\%, 0.05\%-0.5\%\) and \(0.8\%-5\%\), respectively. The imprecision responses are most isotropic when using CFmin encoding (aniso(\(\sigma\text{GFA}\))). Again, the corresponding, minimum anisotropy index of approximately \(0.8\%\) is solely determined by residual response noise. The Disco schemes achieve comparable imprecision isotropy for \(N \geq 40\). A similar behaviour is observed for the estimate anisotropies which are again minimised by CFmin. Here, the convergence to \(\sim 0.01\%\) and \(0.5\%\) in the noise-free (aniso(\(G\text{FA}^\infty\))) and noisy (aniso(\(\mu\text{GFA}\))) simulations occurs later for \(N\) between 60 and 120. The difference between the two is again given by the additional response noise in \(\mu\text{GFA}\).

However, larger anisotropy values for smaller \(N\) or inadequate scheme types, such as Spirals, obviously result from systematic response variation as demonstrated in Fig. 6.6.

It is now very interesting to relate the QBI results shown in Fig. 6.8 to the DTI results discussed above (aniso(\(\mu\text{GFA}\)) and aniso(\(\sigma\text{GFA}\)) vs. aniso(\(\mu\text{FA}\)) and aniso(\(\sigma\text{FA}\)) for \(\text{FA}=0.8, \text{SNR}=15\)). Fig. 6.9 shows a zoomed excerpt from the \(\text{FA}=0.8\) response anisotropy curves in Fig. 6.5b with the same scaling of the vertical anisotropy axes. It is noteworthy that the aniso(\(\mu\text{GFA}\)) and the aniso(\(\mu\text{FA}\)) curves converge to a similar lowest level of \(\sim 0.05\%\) anisotropy. Also the aniso(\(\sigma\text{GFA}\)) and aniso(\(\sigma\text{FA}\)) curves converge to the same value of \(\sim 1\%\) anisotropy.

Despite this general accordance it is striking that the isotropy of the FA estimate and imprecision responses is rather similar amongst all scheme types whereas in QBI the isotropy of the corresponding GFA responses depends more strongly on the actual scheme: in QBI the Spiral schemes clearly perform worse than CFmin and Disco schemes.

**Multi-fibre Encoding Simulations**

The following multi-fibre analysis is exclusively based on noise-free simulations with varying NEX. Therefore, conclusions about imprecision responses cannot be drawn. This can however be tolerated as the single-fibre simulations suggest that the systematic anisotropy patterns related to the encoding schemes are reflected in the estimate responses – with or without noise. Monte Carlo simulations primarily seem to add scheme independent “response noise” (a constant anisotropy offset). Furthermore, the relative anisotropy differences for different encoding schemes seem to be just as well characterised by simulations with varying NEX as with constant NEX (cf. Fig. 6.7 and 6.8).

Fig. 6.10 displays noise-free single- and multi-fibre GFA estimate responses obtained with CFmin321, Spiral321, Disco321 and Icosa321 diffusion encoding and reconstructed without LB
Figure 6.7. Summary statistics for single-fibre responses obtained with varying NEX (without LB regularisation).

Figure 6.8. Summary statistics for single-fibre responses obtained with constant NEX (without LB regularisation). The GFA estimates averaged over the entire response (top rows in Figs. 6.7 and 6.8) do not differ much for different scheme types. The anisotropy plots (bottom rows in Figs. 6.7 and 6.8) allow for a more distinct comparison. Generally, the numerically optimised CFmin schemes perform best with respect to isotropy and estimation stability for varying numbers of directions; the Spiral schemes perform worst.

Figure 6.9. Zoomed excerpt from the FA=0.8 (DTI) response anisotropy curves shown in Fig. 6.5b. The same scaling is applied to the vertical anisotropy axes as in the corresponding two QBI graphs on the bottom right of Fig. 6.8. Note that the imperfect isotropy of the Spiral scheme compared to Disco or CFmin is even more detrimental to the QBI than to the DTI reconstruction.
regularisation as an example. The top row corresponds to single-fibre responses as a function of fibre inclination and azimuth angle, the other rows correspond to the two- and three-fibre responses as a function of second and third Euler angle (about y- and z-axis) whereby any preceding initial rotation about the z-axis was omitted.

Fig. 6.11 summarises the respective response anisotropies for a large range of directions. The GFA anisotropies increase with additional fibres, in particular from two to three fibres. This is, however, rather associated to decreasing mean GFA, not shown here, than to increasing, absolute response variation: the “true” GFA reference values (noise-free, without regularisation) for one, two and three crossing fibres are approximately 0.361, 0.205 and 0.091. These GFA estimates are already achieved with CFmin60 or Disco60 (not displayed here). The fact that response anisotropies still continuously decrease with larger N indicates an actual reduction of absolute response variation. CFmin240 finally seems to minimise the anisotropy.

Finally, we note that the relative performance of the icosahedral schemes decreases substan-
Figure 6.11. GFA° anisotropy summary for single- and multi-fibre simulations with varying NEX. The numerically optimised CFmin schemes perform best, closely followed by DISCOBALL schemes. GFA anisotropy seems to be ultimately minimised with CFmin240 diffusion encoding directions. Icosahedral schemes with N > 81 perform rather comparable to the deficient Spiral schemes.

Initially with increasing orders of icosahedron subdivision (Icosa81 and Icosa321). For fourth order subdivision (N=321) the anisotropy is even larger than with Spiral321.

ODF Sampling Experiments and Simulations

Fig. 6.12 demonstrates the ODF sampling effect on GFA by applying different ODF sampling schemes on the same in vivo data. Fig. 6.12 (a) shows DTI-based fractional anisotropy (FA) and colour-coded FA (principal eigenvector) for comparison to QBI based analytical GFA and colour-coded GFA (b). Fig. 6.12 (c) shows difference maps of sampling based GFA and analytical GFA. The meshgrids of the min-max normalised ODF [28] insets demonstrate the respective ODF sampling schemes for the voxel indicated by the white arrow in (b). The numbers indicate the GFA difference mean ± standard deviation in the shown slice in 10⁻⁴.

On average, sampling based GFA leads to scheme-specific, systematic overestimation and decreased precision depending on fibre orientation and diffusion anisotropy (not investigated further in the present work). There also exist areas where GFAF systematically underestimates the unbiased GFA (e.g. those denoted by the black arrows).

According to the examples shown, numerically optimised schemes generally result in minimal ODF sampling bias with the smallest standard deviation closely followed by Disco sampling. In particular, the standard deviation seems to converge slower for Spiral and Icosa sampling.

Fig. 6.13 depicts GFAF responses from single-fibre simulations obtained with the same ODF sampling schemes. The subplots show the exact directional dependence of GFA estimation. For each row (constant number of samples) the colour range is scaled to cover the mean GFA ± twice the respective standard deviation over all responses with equal sampling numbers. The respective range is exceeded by certain response extremes (Disco21 and Spiral21, 81, 321). The similarity between Icosa21 and CFmin21 responses indicates that the first order of icosahedron
Figure 6.12. In vivo fractional anisotropy (a) vs. analytical GFA (b) accompanied by directional information obtained from the diffusion tensor principal eigenvectors and primary ODF maxima, respectively (red=left-right, green=anterior-posterior, blue=inferior-superior). Difference maps of sampling based $GFA_r$ and analytical $GFA$ are shown in (c). The min-max normalised ODF insets demonstrate the respective ODF sampling for the pixel indicated by the white arrow in (b). The numbers indicate the GFA difference mean ± standard deviation in the shown slice in $10^{-4}$. The black arrows in the Spiral difference maps indicate prominent regions in which $GFA_r$ underestimates the unbiased GFA – a relatively rare case. CFmin schemes generally minimise the errors made by ODF sampling closely followed by Disco schemes.
Figure 6.13. \( \text{GFA}_r \) responses for different ODF sampling schemes obtained by noise-free QBI simulations with 5124 uniformly distributed single-fibre orientations. Interestingly, the Icosa responses maintain their icosahedral symmetry with higher scheme tessellation. The large outliers in the equatorial region of the Spiral responses are presumably responsible for the systematic errors in the corresponding in vivo maps of Fig. 6.12.
subdivision still yields the an optimised scheme. However, with increasing orders the subdivision becomes more and more anisotropic while the icosahedral symmetry of the response pattern is maintained. As a consequence, even Disco81 is better suited for sampling based GFA estimation than Icosa81.

This can be well appreciated from Fig. 6.14 which quantitatively summarises the anisotropies of all $GFA_T$ responses. There is even no significant reduction in $GFA_T$ anisotropy when using Icosa1281 instead of Icosa321 sampling whereas Disco and CFmin anisotropies decrease to a common minimal level one order of magnitude smaller. All equal numbered CFmin and Disco schemes are thus clearly superior to the corresponding Icosa schemes. On the other hand, the global accuracy according to the left graph in Fig. 6.14 generally improves with increasing direction numbers, irrespective of the scheme type used. Generally, residual anisotropy due to ODF sampling is one to two orders of magnitude larger than encoding scheme-induced anisotropies.

6.2.4. Discussion

The QBI encoding scheme simulations showed, first of all, that the numerically optimised CFmin scheme type generally results in most stable GFA estimates and minimised imprecision. It was demonstrated that the systematic anisotropy effect induced by encoding schemes is rather reflected in the estimate responses than in the imprecision responses although employing non-optimal schemes, such as Spirals or higher-order Icosahedrals, boosts both the overall uncertainty and anisotropy. With this regard, the novel DISCOBALL schemes ('Disco') may be assigned to the class of optimal schemes – also for q-ball imaging.

It was shown that generally the order of magnitude of residual GFA anisotropy ($\text{aniso}(\mu GFA) \sim 0.05 - 0.1\%$) with optimal schemes is comparable to typical residual FA anisotropy encountered in DTI [37]. The corresponding absolute GFA variation over all fibre orientations ($\text{std}(\mu GFA) \sim$
0.0003) would be one to two orders of magnitude below the overall GFA imprecision level (mean(σ_{GFA}) \sim 0.01) which is also comparable to DTI [37, 63]. These response anisotropy values are rather small, though – as the extensive discussion in the field of diffusion tensor imaging has taught us – not negligible. Hence, it was also shown that, with non-optimal schemes, GFA estimate anisotropy becomes significantly more pronounced. Consequently, CFmin or Disco schemes should be preferred over less isotropic schemes such as spiral and higher-order icosahedral schemes.

A comparison of the QBI results to the DTI results presented earlier in this chapter in fact suggests that the encoding scheme isotropy is even more critical in q-ball imaging than it is in diffusion tensor imaging. This can be considered quite surprising. A reasonable a priori assumption could as well have been that, for increasing direction numbers, the impact of the differences between encoding scheme types on response anisotropy would become negligible. This is clearly not the case. The larger b-value used in QBI compared to DTI (here 3000 s/mm² vs. 1000 s/mm²) may explain the increased sensitivity to scheme isotropy since QBI signal profiles generally have more variations within equal solid angles than DTI signal profiles.

As an addition to the QBI results discussed above, it has been observed that employing Laplace-Beltrami regularisation for a robust signal fit can have an increasing effect on response anisotropies which may however be explained by decreased mean GFA estimates. With more crossing fibres per voxel, estimation anisotropies are generally increased. In particular the ratio of response anisotropy with non-optimal schemes compared to anisotropy with optimal schemes is emphasised in the presence of three orthogonal fibres compared to one fibre. Such multi-fibre conclusions were not previously drawn for DTI. Finally, it was observed that GFA estimates from typical icosahedral HARDI data can be up to ten times more anisotropic than with CFmin or Disco schemes for a typical range of encoding directions.

Similar conclusions can be drawn from the ODF sampling simulations for realistic parameters as assumed throughout this work. These simulations suggest that GFA approximated by icosahedral ODF sampling will never show significantly less than 0.4% anisotropy, not even with high orders of icosahedron subdivision. GFA approximation by numerically optimised ODF sampling or DISCOBALL ODF sampling are up to one order of magnitude smaller. They become thus comparable to encoding scheme-induced anisotropies. The ODF sampling analysis on experimental data point into the same direction: for 321 directions, for example, the numerically optimised scheme results in small systematic bias and minimised dispersion about the ground truth at the same time, closely followed by the DISCOBALL scheme. Icosa321 and Spiral321 sampling results in considerably larger dispersion about the ground truth. Both ODF sampling simulations and experiments do also demonstrate that, whenever it is possible and reasonable, analytical exact solutions should be preferred over sampling-based solutions. For example, ODF
maxima extraction, essential for QBI fibre tracking, has been shown to be feasible analytically on the basis of ODF expansion in spherical harmonics [68, 69]. If analytical solutions are not available, the ODF sampling used should at least provide excellent response isotropy such as the DISCOBALL schemes.

6.3. Conclusions

In summary, the error distribution in diffusion tensor imaging and in q-ball imaging has been compared in this chapter for several well-known diffusion encoding schemes. The novel deterministic scheme type introduced in chapter 5 has been shown to perform similarly well as the computationally expensive, Coulomb-Force-optimised schemes for both diffusion imaging methods. By means of QBI simulations, which have been systematically performed for the first time, it was demonstrated that single- and multi-fibre GFA anisotropies introduced by different encoding and/or post processing sampling schemes are comparable in magnitude to the well-studied FA anisotropies introduced in diffusion tensor imaging. An inadequate scheme can however result in considerably larger estimate or imprecision variation as a function of fibre orientation. A careful encoding scheme choice in QBI seems thus even more important than it is in DTI. Considering that (constrained) spherical deconvolution [41, 50] results in more distinct ODF estimates than QBI, it can be expected that this HARDI technique is even more sensitive to an improper scheme choice. It was furthermore shown that higher-order icosahedral schemes, which are commonly employed for diffusion encoding in HARDI imaging (such as QBI) and post processing (such as ODF sampling), provide considerably less isotropic GFA estimation and precision than optimal schemes do, which is a relevant finding. The analytical expression of the generalised fractional anisotropy formally derived here was essential for the separation of sampling-based error contributions from encoding scheme errors.

Related Publications


Part III.

Development of Rapid Pulse Sequences for Diffusion MRI and Functional MRI at Ultra-high Fields
Chapter 7.

Diffusion Weighted Single-shot Stimulated Echo Acquisition Mode (DW Ss-STEAM)

While the previous chapters have been focused on appropriate encoding of the diffusion signal, the following chapter deals with appropriate acquisition of the diffusion signal. A specific imaging sequence entitled Diffusion Weighted Single-Shot Stimulated Echo Acquisition Mode (DW Ss-STEAM) is discussed, which has previously been developed to overcome typical image artefacts associated Echo Planar Imaging (EPI), the commonly used sequence for diffusion imaging. A brief review over the recent development of DW Ss-STEAM will be given before novel modifications will be introduced. These modifications are tailored to reduce typical artefacts encountered with previous DW Ss-STEAM versions, the cause of which are explored by means of the phase graph concept and by comparison to the related, very well-studied Turbo-Spin-Echo imaging sequence. Finally, the novel modifications will be investigated experimentally by means of phantom and in vivo measurements performed at 3 Tesla.
7.1. The Origins: RF spoiled DW Ss-STEAM

In the year 2000 a novel diffusion weighted single-shot Stimulated Echo Acquisition Mode (DW Ss-STEAM) sequence has been proposed [70] to overcome typical artefacts associated to single-shot spin echo EPI (geometric distortions, signal drop outs, etc.). The schematic sequence diagram and phase graph in Fig. 7.1 help to understand the principle of this original sequence version. First, standard Stejskal-Tanner (see chapter 4) diffusion weighting is applied. Then, instead of acquiring the diffusion encoded spin echo at $t = T_{SE}$, the magnetisation is dephased by a specific amount before half of it is transferred to longitudinal magnetisation (“phase memory”) at $t = T_{SE} + TE/2$ by means of a 90° “tip-up” pulse. Within the following delay time, $TM$, the residual transverse magnetisation is dephased heavily by means of large crusher gradient pulses on all three gradient axes. Within the STEAM readout module, the stored magnetisation is then successively “tipped down” by small flip angles over several readout periods, in each of which a differently phase encoded stimulated echo is acquired. Hence, the entire $k$-space data of one slice is collected following a single initial excitation (“Single-shot”).

In the basic sequence version a train of constant flip angles (cFA) is utilised within the STEAM readout module. In order to prevent destructive interference of the stimulated echoes with spin echoes, etc., which originate from previous stimulated echo path ways (“spurious echoes”), gradient spoiling and RF spoiling is performed. The use of constant flip angles leads to an exponential reduction of the stored longitudinal magnetisation and thus to strong image blurring in the phase encoding direction. Though compared to standard EPI-based acquisitions this basic DW Ss-STEAM sequence is less efficient in terms of acquisition times and SNR, it results in images free from typical off-resonance-related artifacts (geometrical distortions, signal drop outs, eddy current-induced distortions, etc.) [70].

To optimise the SNR efficiency $(SNR / \sqrt{\text{acquisition time}})$ a sequence version capable of par-
7.2. DW Ss-STEAM Utilising All Transverse Coherences

Partial Fourier acquisition and image reconstruction based on Projection onto Convex Sets (POCS) [71] was later proposed [72]. Here, also a variable flip angle (vFA) train was introduced to optimise the point-spread-function (PSF) in image space by controlled shaping of the modulation-transfer-function (MTF) in $k$-space: by assuming perfect RF spoiling a simple recursive vFA formula (starting with small flip angles and terminating in a final 90° pulse) assures a constant signal envelope and thus a Sinc-shaped PSF for tissue with a specific $T_1$. In the following, this sequence version is referred to as the original sequence version.

7.2. DW Ss-STEAM Utilising All Transverse Coherences

A lot of the available diffusion weighted magnetisation remains unused in the original DW Ss-STEAM sequences: a specific stimulated echo phase graph path way would never contribute to any of the following echoes, neither as a primary or higher-order spin echo nor as a higher-order stimulated echo. In 2009 a sequence modification according to the phase graph depicted in Fig. 7.2 was thus proposed, which makes use of all transverse coherences by omitting RF spoiling [73]. Appropriate vFA trains are computed by using an extended phase graph (EPG) algorithm (see section 2.5) that considers all generated coherence pathways and incorporates them into constant or exponentially decaying signal shapes. A significant SNR increase is thus achieved and it was shown that deviations from the modelled relaxation time parameters (here, $T_1$ and $T_2$) or from the ideal flip angles results in negligible PSF deterioration. Still all coherence pathways utilised for signal generation originate from the initially diffusion weighted magnetisation and not from any freshly excited magnetisation.
7.2.1. Signal Shaping

In the latest DW Ss-STEAM reference [73] the flip angle trains are tailored according to constant or exponentially decaying target signal shapes. A centric view ordering results in most efficient vFA trains: the image SNR is essentially proportional to the sine of the initial flip angle of the vFA train. It becomes larger the more rapidly the exponential target signal shape is chosen to decay. This, however, also introduces more blurring.

Alternative parametric and non-parametric signal shapes with less negative effects on the point spread function (PSF) were investigated within the exploratory work for this thesis [74, 75]. In Refs. [74, 76] we have shown that a Hanning \((c = 0)\) or a Hamming \((c = 0.08)\) filter function according to Eq. (7.1) is well realisable and can approximately lead to an SNR increase by a factor of two compared to constant signal shaping [74]. The broadening of the PSF is acceptable and the sidelobes are reduced compared to moderate exponential shapes according to Eq. (7.2) with a similar SNR gain \((\lambda \geq 0.5)\).

\[
\begin{align*}
  w_{H,c}(k) &= \frac{1 - c}{2} \cos \left( \frac{\pi k}{k_{\text{max}}} \right) + \frac{1 + c}{2} \\
  w_{E,\lambda}(k) &= \exp \left( -\pi \lambda \frac{|k|}{k_{\text{max}}} \right)
\end{align*}
\]  

(7.1)  
(7.2)

The vFA trains according to these target shapes are rather different (cf. Fig. 7.3). In the present context it is important to note that with the Hanning shape (as well as with Hamming or Gaussian shapes [74]) a large amount of RF energy (with many flip angles being close to 90°) is applied during the initial segment of the vFA train. While this improves the SNR efficiency, the image acquisition becomes particularly sensitive to phase errors, as will be discussed next.

7.2.2. Violation of the CPMG Condition

The phase graph of the DW Ss-STEAM readout module (starting with the first DW spin echo, \(TE_{SE}\) in Fig. 7.2) is essentially identical to the phase graph of the well-studied Turbo-Spin-Echo (TSE) sequence, also known under the acronym RARE (Rapid Acquisition with Relaxation Enhancement) [77]. Instead of “storing” the dephased magnetisation longitudinally for subsequent access of stimulated echoes via small flip angles, the magnetisation is refocused repeatedly after excitation. If perfect 180° refocusing pulses are used, the excited magnetisation stays purely transverse during the entire readout. Usually, however, refocusing pulses are not ideal – either intentionally (smaller flip angles for SAR reduction or signal shaping [78]) or due to experimental imperfections (non-uniform excitation field or slice profile). Hence, also FIDs, primary spin echoes and stimulated echoes are generated in analogy to the STEAM sequence. However,
7.2. DW 8s-STEAM Utilising All Transverse Coherences

![Graphs showing normalized MTF and PSF](image)

**Figure 7.3.** Several normalised modulation-transfer-functions (MTF) and the corresponding point spread functions (PSF). The Hann shape leads to a clear broadening of the central PSF peak while it suppresses side lobes effectively compared to the exponential shape according to Eq. (7.2) with \( \lambda = 0.5 \). The corresponding variable flip angles (vFA) on the right have been computed based on DW 8s-STEAM utilising all transverse coherences as discussed in Ref. [73]. Typical sequence parameters and white matter relaxation times at 3 Tesla have been assumed.

with the TSE sequence, the acquired signal is usually dominated by spin echoes while with the STEAM sequence, the signal is dominated by stimulated echoes, provided that the flip angles are relatively small (<90°).

It is well known that the TSE sequence has to fulfil the so-called **CPMG condition** (Carr, Purcell, Meiboom and Gill) in order to avoid destructive interference of primary spin echoes and stimulated echoes [79]: only if, first, the RF phase of the refocusing pulses is orthogonal to the initial excitation RF phase and, second, it is guaranteed that the spin isochromats accumulate the same phase between any two consecutive refocussing pulses, the transverse magnetisation will always refocus exactly at the midpoint between two consecutive refocussing pulses with the same phase. Hence, spin echoes and stimulated echoes superimpose constructively [5].

The fixed phase advance within one echo spacing (ESP) period must exactly be twice the phase advance between the initial excitation and the first refocusing pulse. This phase relation must not change throughout the entire CPMG readout train. The sequence developer has to account for the CPMG condition by implementing correct RF pulse phases and sequence timing and by providing identical imaging gradient integrals within each ESP.

**Phase Alterations in Diffusion Imaging**

There are basically two factors in the context of diffusion imaging that may cause a violation of the CPMG condition. Both are related to the large amplitudes of diffusion weighting gradients. The first and usually minor source are eddy currents which may generate a complex, time-varying magnetic field superimposed to the DW and imaging gradients. In that case a constant
phase advance throughout all ESPs may not be guaranteed.

The second, non-negligible source of phase alteration is coherent spin motion during diffusion weighting. While incoherent motion of spins leads to a signal decrease due to the ensemble average of all statistically distributed spin vectors (the principle of diffusion MRI) coherent motion leads to a systematic phase variation depending on the spin trajectory. According to Ref. [80] already sub-voxel rigid-body translations during non-zero DW gradients introduce a significant constant phase offset to the k-space signal or to the object in image space. Rigid-body rotations during non-zero DW gradients, on the other hand, introduce a linear shift of the k-space signal (maximum not at DC anymore) and thus result in a strong linear phase variation over the object in image space compared to the static case. Nonrigid-body motion, such as brain pulsation (synchronized to the heart beat) additionally induces more complex, non-linear phase alterations, even though the physical distortions are well below typical voxel sizes.

**General Consequences for Diffusion Imaging Sequences**

Diffusion weighting and TSE sequences are mutually incompatible as long as no correction techniques are employed. The PROPELLER technique [81], where with each new excitation a radial segment is acquired, is one of the few TSE-based approaches which provides inherent capabilities to correct for intershot phase inconsistencies\(^1\). However, this does not solve the problem of interfering spin echoes and stimulated echoes during the CPMG readout. To minimize stimulated echoes, large refocusing pulses must thus be used for PROPELLER imaging, which increases SAR considerably. In contrast to the established EPI-based sequences, however, no geometric distortions are observed with PROPELLER.

Nevertheless, single-shot spin echo EPI, so far, remains the method of choice for in vivo diffusion imaging, although very recently also multi-shot EPI sequences have found more and more application in high-resolution diffusion imaging (“readout-segmented EPI”) [82]. In this EPI flavour, one extra navigator EPI train is acquired following each acquired segment (one extra refocusing pulse and a repeated EPI readout covering the k-space centre). The navigator data is then used to apply phase correction and thus to make the k-space data consistent between segments. Since no repetitive spin echo refocusing is applied here, the CPMG condition is of no concern.

\(^1\)Each segment ideally covers a sufficiently large part of the central k-space to compute a low resolution phase map used for phase correction
Figure 7.4. Corrupted phantom and in vivo data obtained at 4 Tesla with DW Ss-STEAM utilising all transverse coherences. From left to right: varying DW directions with $b = 1000 \text{s/mm}^2$. The “high-SNR” Hann signal shape leads to SE and STE contributions of comparable magnitude in the centre of $k$-space. The phase errors induced by movement (e.g. table vibration, c.f. section 7.5.3) during DW cause destructive interferences, most apparent for low spatial frequencies.

Consequences for DW Ss-STEAM

As indicted above, the most recently proposed DW Ss-STEAM sequence [73] and a DW TSE sequence are very similar, with the only major difference (besides minor alteration of the pulse sequence following diffusion weighting) being the scaling of the flip angles employed (STEs vs. SEs as the primary source of echo signals). The CPMG condition is thus also relevant for DW Ss-STEAM utilising all transverse coherences, especially if vFA trains with high SNR efficiency are applied. Then the amount of refocussing, and thus the contribution of SE signals to the STE signals is relatively large. In case of DW-induced phase errors the superposition of such incoherent pathways thus inevitably leads to interferences. In particular for centric view ordering with large initial flip angles for maximised SNR the corresponding low spatial frequency interferences are severe, as demonstrated in Fig. 7.4 on the example of a “high SNR” Hann signal shape at 4 Tesla. The phase graph depicted in Fig. 7.5 illustrates the incoherent pathways in such a case.

In the most recent DW Ss-STEAM publication based on work at 4 Tesla strong artefacts as observed in Fig. 7.4 have not been reported [73]. The vFA trains utilised there for exclusively constant or moderate exponential signal shaping (predominantly STEs in the central $k$-space region) would in any case lead to less pronounced interferences in the image. However, in the exploratory work for this thesis based on the original sequence source code of Ref. [73], it was found that the gradient moments were in fact not exactly balanced as demanded by the CPMG condition. As a consequence, the phase graph was accidentally altered in a similar way as discussed next. The mistake remained undetected since the vFA trains for constant or moderate exponential signal shaping do not differ much, as Figs. 7.11 (b) and (c) demonstrate.
Figure 7.5. Phase graph for DW Ss-STEAM utilising all transverse coherences in case of an an initial phase error (*): the dephasing following the DW module is, for example, larger than expected. Consequently, all “primary” STEs are delayed (→) and start to mix with SEs (and later also STEs) which are shifted in the opposite direction in time (←). Starting with the second readout period all signals have contributions from positively and negatively shifted echoes (opposed phase = incoherent). Red lines represent the part of the signal that is acquired during readout (solid = positively shifted, dotted = negatively shifted). Curved and straight blue arrows are added to assist retracing the incoherent mixing of the first relevant coherent path ways.

Figure 7.6. Phase graph with the novel gradient spoiling scheme: an additional spoil moment following each readout (indicated by blue-shaded gradient pulses with increased amplitude) prevents mixing of SE signal during the 2nd readout period (originating from the 1st STE pathway) with the 2nd STE signal. However, as indicated by the blue arrows, it adds again to the 3rd echo. The part of the first STE pathway that has been stored longitudinally over the 2nd readout period will, in a similar fashion, add to the 4th echo. The echo contributions become manifold very quickly. Note that only coherence path ways shifted in the same direction in time add up (same phase = coherent).
7.3. Novel DW Ss-STEAM Modifications

In order to overcome the limitations of the previous DW Ss-STEAM sequence several DW Ss-STEAM modifications have been implemented and refined. The explicit aim of this part of the work was to establish an artefact-free DW Ss-STEAM sequence with the SNR kept at least as large as previously reported [73]. For illustrative purposes the flip angle trains and the corresponding images shown in Fig. 7.11 at the end of this chapter reveal the effects of each novel modification in the order discussed next.

7.3.1. Adapted Gradient Spoiling for Partial Usage of Transverse Coherences

The fact, that the primary source of image signal is supposed to be provided by stored magnetisation allows one to modify the sequence in such a way that it is not as strictly bound to the CPMG condition as a TSE sequence. As shown in [74] and as illustrated by the phase graph in Fig. 7.6 this can be achieved by increasing the readout gradient spoilers. Following the \((n-1)\)th signal readout, for example, this additional moment shifts the respective path way beyond the amount of dephasing that the stored magnetisation has experienced. Hence, the corresponding spin echo path way refocused by the next RF pulse will not interfere with the \(n\)th echo generat-
ing stimulated echo path way since refocusing occurs outside the acquisition window. However, by the end of the \( n \)th readout period the spin echo path way will have accumulated the exact initial amount of dephasing. The SE signal following the subsequent pulse will coherently mix with the excited STE signal and thus contribute to the \((n + 1)\)th echo. A corresponding stimulated echo path way (stored longitudinally during the \( n \)th readout period and refocused outside the acquisition window during the \((n + 1)\)th readout period), which will add coherently to the \((n + 2)\)th echo, can also be identified in Fig. 7.6.

Reviewing the new phase graph one can conclude that the sequence was manipulated in such a way that it does provide balanced gradient moments, as dictated by the CPMG condition, from one to the next readout period, which do however not match to the initial amount of dephasing. Consequently, one echo generating path way always skips the following readout period. Thereby, the sequence has been made insensitive to any phase errors that have been introduced prior to the “tip-up” pulse. A similar strategy was first proposed by Norris et al. for TSE-type sequences in 1992 [83]. In that particular “displaced U-RARE” implementation, however, the additional spoil moment was inserted before the readout gradient in order to always shift the “odd echo” out of the following acquisition window. Implementation of the manipulated phase graph into the iterative vFA computation for DW Ss-STEAM is straight-forward. As a consequence of the prolonged effective spin echo spacing \((2 \times ESP)\) and higher order stimulated echo spacing \((3 \times ESP)\) the resulting vFA trains exhibit corresponding subharmonic oscillations as shown in Figs. 7.10 and 7.11 (c)-(f), depending on the actual flip angle amplitudes. Also note that, due to filtering out the disturbing spin echo pathways and due to the prolonged effective spin echo spacing (more \( T_2 \) decay), the vFA trains are not as SNR efficient as the vFA trains which do utilise all transverse coherences (cf. Fig. 7.11 (b) and (c)). On the other hand, the proposed decoupling of one readout period from its predecessor allows for minimal echo spacings since \( ESP \) does not have to match \( TE \) any more. This approach to gain back some SNR efficiency is particularly useful if the duration needed for the post ADC gradient spoilers is small compared to the readout time (e.g. small readout bandwidths, low or moderate spatial resolutions, etc.).

### 7.3.2. Incorporation of the Initial Transverse Coherence Path Ways

Comparing the phase graphs in Fig. 7.5 and 7.6 it is apparent that with the novel gradient spoiling scheme the first two echoes used for imaging are pure stimulated echoes. Before having introduced the new gradient spoiling scheme, already the second echo had STE and SE contributions (Fig. 7.5 or 7.2, respectively). As an attempt to regain some of the related SNR efficiency, the \( TM \) period can be replaced by one “dummy” readout period\(^2\) as illustrated in Fig.

\(^2\)The “dummy” readout might just as well be replaced by a navigator readout, for example, to correct for motion or phase errors in multishot experiments.
7.3. Novel DW Sr-STEAM Modifications

Figure 7.8. Extended phase graph according to the DW Sr-STEAM version with adapted gradient spoiling. The excerpt shows four arbitrary echoes (circles on k = 0 axis, where k quantifies the amount of dephasing). Highlighted (blue) are the three coherence path ways of the (n − 1)th readout period that contribute to the nth echo coherence pathway (red) according to Eq. (7.4). The red labels with superscript “−” denote the relevant $F_{-k}$ and $Z_{-k}$ states immediately before the nth pulse equal (aside from relaxation) to the states labelled in blue by the time of the (n − 1)th echo.

7.7. Note that now also the transverse coherence path ways, that have previously been spoiled within the TM period, are incorporated into the echo formation. After all, this is one half of the initial transverse magnetisation (following DW and and the first TE/2 period). A fraction of $\sin^2(\frac{\alpha_1}{2})$ of this magnetisation can now contribute to the first echo. This option was already discussed in Ref. [73]. It was rejected there because the authors rightly suspected non-negligible destructive interferences due to motion. Due to the novel gradient spoiling, however, phase errors induced by motion during the DW period is not an issue any more. Note that still no freshly excited or differently diffusion encoded magnetisation contributes to the signal.

7.3.3. Acceleration of Variable Flip Angle Computation: 1-Ahead-Solution

As a final step the vFA algorithm was made more efficient by introducing an analytical “1-ahead-solution” similar to what has previously been proposed for signal shaping in TSE sequences [78, 84]. The basic idea of the previous vFA algorithm as used in Refs. [73–75] was to start with a specific flip angle and a corresponding initial signal magnitude. Then the second flip angle was searched such that the corresponding second signal magnitude in relation to the first magnitude matched the second sampling point of the desired signal shape. If no solution could be found, the entire search was started anew with a reduced initial flip angle. If a solution could be found, the entire search was started anew with an increased initial flip angle. The vFA with the highest SNR efficiency could hence be determined iteratively. The outer loop of the algorithm (defining the new initial flip angle) was performed via a bisectioning algorithm. The inner part (determining the subsequent flip angle to achieve the next sampling point of the signal shape) was executed by means of a numerically efficient, but still iterative root finding procedure [73].

According to the extended phase graph theory (cf. section 2.5) each signal within the DW
Ss-STEAM readout train, for example following the \(n\)th pulse, is composed of exactly three coherence pathways prior to the pulse, as indicated in Fig. 7.8. Thus, the numerical search for the next flip angle can be replaced by an analytical solution as derived in the following. The \(n\)th signal is given by

\[
S_n = F_{-1}(n)e^{-\frac{TE}{2T_2}} ,
\]  

(7.3)

whereby, according to the extended phase graph concept, the respective transverse coherence pathway is given by

\[
F_{-1}(n) = \sin \alpha_n \cdot Z_1(n) + \cos^2 \frac{\alpha_n}{2} \cdot F_{-1}(n) + \sin^2 \frac{\alpha_n}{2} \cdot F_1(n) \\
= \sin \alpha_n Z_1(n-1)e^{-\left(\frac{ESP-TE/2}{T_1}\right)} \\
+ \cos^2 \frac{\alpha_n}{2} F_{-3}(n-1)e^{-\left(\frac{ESP-TE/2}{T_2}\right)} \\
+ \sin^2 \frac{\alpha_n}{2} F_{-1}(n-1)e^{-\left(\frac{ESP-TE/2}{T_2}\right)} .
\]  

(7.4)

In the last equation the three contributing states by the time of the \(n\)th pulse (denoted by the \((-1)\) superscript) have been expressed in terms of the states of the previous \(ESP\) period, more specifically, by the time of the \((n-1)\)th echo according to Fig. 7.8. Equations (7.3) and (7.4) thus relate the actual signal (known sampling point of the target signal shape), exclusively to the previous states (also known at this point in time within the vFA algorithm) and the actual flip angle (the quantity that we are looking for). Substituting the constants \(E_1 \equiv e^{-\frac{ESP}{T_1}}\), \(E_2 \equiv e^{-\frac{ESP}{T_2}}\), \(E_{12} \equiv e^{-\frac{ESP}{2T_2}} (1\frac{1}{T_2} - 1\frac{1}{T_1})\), omitting the pulse identifier \((n-1)\) for brevity and combining Eqs. (7.3) and (7.4) yields the equation

\[
S_n = \sin \alpha_n Z_1 E_{12} E_1 + \cos^2 \frac{\alpha_n}{2} F_{-3} E_2 + \sin^2 \frac{\alpha_n}{2} F_{-1} E_2 ,
\]

which can be solved for the required flip angle:

\[
\alpha_n = 2 \arctan \left[ -Z_1 E_{12} E_1 \pm \sqrt{Z_1^2 E_{12}^2 E_1^2 - E_{-3} F_{-1} E_2^2 + F_{-3} E_2 S_n + F_{-1} E_2 S_n - S_n^2} \over F_{-1} E_2 - S_n \right].
\]  

(7.5)

The two solutions (Eq. (7.5) modulo \(2\pi\)) are real as long as the radicand is equal or greater than zero. The smaller absolute flip angle is selected in order to reduce the specific absorption rate. Imaginary solutions are not valid and hence trigger the outer bisectioning loop for the initial flip angle again.
7.4. Phase Compensation for DW Ss-STEAM Utilising All Transverse Coherences

Evidently, combining DW Ss-STEAM utilising all transverse coherences [73] and some of the novel modifications (SNR-efficient signal shapes, incorporation of the initial transverse coherences, etc.) would render a significant additional SNR increase possible [74] – if only the CPMG condition was not violated by motion during diffusion weighting. It was thus investigated whether it is possible to achieve this goal by means of a phase compensation approach.

As indicated above, it would be possible to obtain a phase map from a navigator scan during the “dummy” readout period. With the corresponding phase map one could, hypothetically, adopt the following STEAM readout module according to the measured phase error and thus fulfill the CPMG condition. This requires several implementations such as a (non-Cartesian) navigator acquisition followed by an online image reconstruction, a robust real-time feedback to the pulse sequence program, and, not least, adequate techniques to correct for the phase errors. The implementation of such a complete prospective phase compensation framework was beyond the scope of this work. However, for objects that move reproducibly (such that phase error mapping and compensation can be employed in two separate scans) a basic prescan calibration and correction technique was explored in this work.

7.4.1. Prescan Calibration

The phase error that impedes artefact-free DW Ss-STEAM acquisition utilising all transverse coherences can be mapped without artefacts by means of the modified DW Ss-STEAM version with adapted gradient spoiling. While the DW module of the prescan must be identical to the actual scan it is sufficient to acquire the prescan data at low resolution. Such a prescan does not take more than 5 seconds per DW direction for a typical whole brain DTI field-of-view (multiple slices).

The phase error map according to the $m$th DW direction is obtained from the product of the respective complex conjugate prescan data, $S^*_m(r)$, and the non-weighted reference data, $S_{\text{ref}}(r)$,

$$ \Delta \Phi(r) = \arg \left( |S_m(r)||S_{\text{ref}}(r)|e^{(\Phi_m(r)-\Phi_{\text{ref}}(r))} \right), $$

where $r$ shall denote the image coordinate with respect to the scanner isocentre and $\Phi_m(r)$ and $\Phi_{\text{ref}}(r)$ denote the respective image phases. Following preliminary phase wrap removal using the autocorrelation method by Ahn and Cho [85] a linear fit to the phase error map is performed.
such that

$$\Delta \Phi(r) = \varphi_0 + g^T r + \epsilon(r) .$$

Here, $\varphi_0$ denotes a constant phase offset (due to rigid body translations during DW, cf. section 7.2.2) and $g$ denotes the linear slopes of the phase error map (due to rigid body rotations during DW, cf. section 7.2.2) such that the residual error, $\epsilon(r)$ (due to nonrigid motion), is minimised in the least squares sense.

### 7.4.2. Phase Compensation

The adaption of the DW Ss-STEAM sequence for constant and linear phase error compensation is demonstrated schematically in Fig. 7.9. The linear phase term is compensated by means of very small correction gradient blips on the readout, phase encode and slice select axis. Their respective gradient moments are given by

$$M = \left( M_{ro}, M_{pe}, M_{sl} \right) = \frac{g}{\gamma} ,$$

where $\gamma$ is the gyromagnetic ratio of the proton spin. The gradient blips of negligible duration are here incorporated before and after each readout gradient pulse. The constant phase offset is compensated by subtracting the fitted constant phase term from the variable flip angle RF pulse phases.

Although the proposed approach is not suitable for in vivo applications (non-reproducible motion, nonrigid brain deformation with each heart beat) it was investigated, as described below, whether it may be suitable for imaging of phantoms or tissue samples. Such samples only move due to table vibrations, which are strongly correlated to the direction and the kind of diffusion
encoding and are thus robustly reproducible.

7.5. Experiments Performed at 3 Tesla

Despite the fact that DW Ss-STEAM was originally proposed for applications at ultra-high fields, three main factors currently prevent the sequence from being employed successfully at 9.4 Tesla: first, the extremely short transverse relaxation times result in a signal that corresponds to only a quarter or a fifth of the initial magnetisation already at the time of the DW spin echo (for common \(b\)-values); second, strong transmit field inhomogeneities result in insufficient refocusing and a large bias in the following variable flip angle train in most parts of the brain; third, the specific absorption rate (SAR) safety limits enforce the application of either unreasonably long RF pulses (prolongation of the echo spacing), or only rather small flip angles below 20\(^\circ\), for example. Hence, all experiments discussed next were conducted at 3 Tesla. The absence of ultra-high field related experimental problems thus allowed for a detailed investigation of all the before-mentioned DW Ss-STEAM specific problems. For RF transmission the body-coil was used while for signal reception either a 32 channel head coil array or a 12 channel head coil array was used. Unless stated otherwise parallel imaging acceleration was performed along the phase encoding direction. On the one hand, an acceleration factor of two corresponds to only moderate \(g\)-factor penalty (noise amplification; see [7, 9]), and on the other hand leads to a sufficiently reduced echo train length (ETL). A reduced ETL generally allows for more SNR-efficient \(vFA\) trains in DW Ss-STEAM, i.e. noise amplification due to parallel imaging with low acceleration factors is usually overcompensated by larger initial flip angles [74].

7.5.1. Materials and Methods

Novel DW Ss-STEAM Modifications

A DW Ss-STEAM phantom experiment was performed such that all sequence modifications as introduced above were employed under identical conditions. Two cylindrical gel phantoms with relaxation times matched to grey matter and white matter at 3 Tesla and an additional smaller tube filled with a liquid simulating cerebrospinal fluid (CSF) were placed into a 32 channel head coil array. A single-slice protocol with a slice thickness of 4 mm was prepared, which, for consistency reasons, allowed to keep the timing parameters, in particular the echo spacing, \(ESP = 10\) ms, constant throughout all sequence variants. A readout bandwidth of 210 Hz/pixel was therefore selected. The matrix size of \(108 \times 84\) with an in-plane voxel size of \(2\times2\text{mm}^2\) corresponds to a typical field-of-view for \textit{in vivo} applications. A parallel imaging acceleration
factor of 2 resulted in an ETL of 42. One non-weighted and three orthogonal DW acquisitions with $b = 1000\ s/mm^2$ were performed. A repetition time of 10 seconds was selected between successive slice excitations. For all sequence variants the vFA trains were computed according to a constant signal shape assuming $T_1 = 1000\ ms$ and $T_2 = 80\ ms$ (approximating white matter relaxation times at 3 Tesla). For the final acquisition, which included both the adapted gradient spoiling and the “dummy” readout in place of the TM period, an exponentially decaying signal shape (according to Eq. (7.2) with $\lambda = 0.5$) and a Hamming signal shape (according to Eq. (7.1) with $c = 0.08$) were selected in addition to the constant signal shape.

For comparison between DW Ss-STEAM and a standard EPI-based diffusion acquisition under realistic conditions, a brief in vivo DTI experiment was performed. To ensure sufficiently high SNR of the STEAM acquisition an exponentially decaying target signal shape according to Eq. (7.2) with a relatively large decaying rate of $\lambda = 0.75$ was selected for vFA computation (cf. Fig. 7.10). Again, $T_1 = 1000\ ms$ and $T_2 = 80\ ms$ were assumed. Further sequence parameters were: $TE=8.8\ ms$, echo spacing, $ESP=9.4\ ms$, $TR=11791\ ms$ between excitation of identical slices (minimum), 200 Hz/Pixel readout bandwidth, 2 mm isotropic voxel size, 25 slices without gap, $256\ mm \times 176\ mm$ in-plane field-of-view with centric phase encode view ordering in the left–right direction, two-fold parallel imaging acceleration (yielding an ETL of 43) with 24 reference lines acquired externally using a constant signal shape. Image reconstruction was performed utilising GRAPPA [8]. For the STEAM acquisition a standard Stejskal-Tanner diffusion weighting was performed for 15 isotropically distributed DISCOBALL diffusion directions [55] with $b = 800\ s/mm^2$ and 6 additional non-weighted images. The EPI protocol was performed with identical diffusion encoding, however, as commonly done, a twice-refocused spin echo diffusion weighting module [86] had to be employed to reduce eddy-current-related geometric image shearing at the expense of a prolonged DW echo time. Further EPI-specific sequence parameters that deviated from the STEAM protocol were: $TE=85\ ms$, $TR=5000\ ms$ between excitation of identical slices, 1860 Hz/Pixel readout bandwidth, Partial Fourier 6/8 in phase encode direction, $256\ mm \times 256\ mm$ in-plane field-of-view with linear phase encode view ordering in the anterior–posterior direction. The total acquisition times of the STEAM and the EPI protocol were: 5:18 min and 2:00 min, respectively. Following diffusion tensor reconstruction using FSL [87] the non-weighted image average (from six single images), the trace weighted image (the geometric mean of the weighted images), the fractional anisotropy map and the colour-coded principal eigenvector map was computed for STEAM and EPI.
DW Ss-STEAM with Prospective Phase Compensation

A two-compartment white matter (inner cylinder)/gray matter (outer ring) gel phantom\(^3\) was placed into a 12 channel head coil array such that the cylinder axes was aligned along the left–right direction. As described in section 7.4 a low resolution phase map was first acquired for three DW encoding directions \((b = 1000 \text{ s/mm}^2)\) along orthogonal scanner axes) and one non-weighted reference utilising the DW Ss-STEAM version with adapted gradient spoiling. A slice thickness of 2 mm and a slice distance factor of 300% according to a slice gap of 6 mm were selected. The in-plane voxel size was \(8 \times 8 \text{ mm}^2\) such that the complete \(32 \times 22 \times 15\) low-resolution data matrix exactly corresponds to the field-of-view of the final \(128 \times 88 \times 60\) high-resolution matrix with an isotropic voxel size of 2 mm (no slice gap). For the calibration scan a constant signal shape and typical WM relaxation times were assumed for vPA train computation. For the high-resolution scan utilising all transverse coherences (original sequence version including initial TM period according to Fig.7.9 [73]) a Hamming signal shape was assumed.

From the prescan data a linear fit of the phase was performed offline for each DW direction using MATLAB (MathWorks, Natick, Massachusetts). The corresponding fit parameters were written into a text-file that was copied back to the host computer of the MR scanner. The actual high-resolution imaging sequence, which included the compensation gradient blips and extra RF phases, looked up the corresponding values in that file and computed the compensation gradient moments and extra RF phases. With these values the high-resolution data were acquired. One additional high-resolution acquisition without compensation gradient blips and RF phases was performed for comparison as well as one low-resolution phase map with compensation gradient blips and RF phases. From the phase compensated high-resolution data a mean diffusivity (MD) map was computed from the DW image magnitudes, \(|S_{1,2,3}|\) (orthogonal DW directions), and the non weighted image magnitude \(|S_0|\) according to

\[
MD = \frac{1}{3} \text{Tr}[D] = \frac{1}{3b} \ln \left( \prod_{m=1}^{3} \frac{|S_m|}{|S_0|} \right) = \frac{\ln |S_0|}{b} - \frac{\ln \left( \prod_{m=1}^{3} |S_m| \right)}{3b}
\]

\(^3\)Courtesy of Daniel Brenner
Figure 7.11. Non-weighted (middle) and DW (bottom) phantom images (WM, GM, CSF) along with the respective vFA trains used for image acquisition (top). The image intensities are scaled equally among all non-weighted and among all DW images, respectively. “PE” indicates the phase encode direction. From left to right: (a) RF spoiled (original) DW Ss-STEAM [72], (b) utilising all transverse coherences [73], (c) adapted gradient spoiling [74], (d)-(f): as (c) with the initial delay time replaced by a “dummy” readout (no TM). All signal shapes except (e) and (f) were constant. Note the artefacts in (b) due to the violation of the CPMG condition. By employing all sequence modifications and by using elaborate signal shapes such as an exponential decay (e) or a Hamming window (f) a considerable SNR increase is finally achieved compared to (b) with minor residual artefacts in the DW image.

7.5.2. Results

Figure 7.11 shows representative phantom images (non-weighted and diffusion weighted) along with the respective flip angle trains demonstrating the progress of DW Ss-STEAM with the novel implementations (from left to right). The first two steps, (a) and (b), display the status prior to this work. The novel gradient spoiling scheme (c) solved the problem of interfering stimulated echoes and spin echoes (visible in the DW image in (b) despite the low flip angles employed), however the SNR has dropped to a level almost identical to the original RF spoiled sequence (a). With the replacement of the TM period by a “dummy” readout (d), more SNR is regained. With more SNR efficient signal shapes (e,f) the SNR is finally higher than in (b) without observing the strong artefacts related to the violation of the CPMG conditions. However, minor artefacts pointed out by the arrows do appear.

Figure 7.12 shows, as examples of the in vivo experiment (from left to right): the non-weighted (average of six b=0 acquisitions) and the trace-weighted image, example DW images according to the first and the 15th DW direction, the fractional anisotropy (FA) and the principal eigenvector map (PEV) of a representative slice obtained with the DW Ss-STEAM sequence (top) and a standard EPI sequence (bottom). The respective phase encode directions are indicated by white arrows. First, note that the strong geometric distortions visible in the EPI images do not
Figure 7.12. Representative slices from the in vivo DTI experiment comparing the performance of DW St-STEAM with adapted gradient spoiling and incorporation of the initial transverse coherence path ways (top) vs. standard EPI-based acquisition (bottom). The white arrows indicate the respective phase encode direction. From left to right: Non-weighted average image, trace-weighted image, example DW images (1st and 15th direction), fractional anisotropy (FA) map, principal eigenvector map (PEV). Note the unspecific blur of the trace-weighted STEAM image and the corresponding noise in the FA and PEV maps.

occur in the STEAM images. Second, despite the strong exponential signal shaping, the b=0 STEAM image clearly appears sharper than the EPI image, which is blurred in the phase encode direction due to $T_2^*$ decay. This confirms adequate application of the signal shaping technique. On the contrary, the trace-weighted STEAM image is much more blurred, apparently without any specific direction. One can observe this blurring in the individual example DW images as well. The FA map exhibits very strong noise that appears to be larger in the central brain region. Accordingly, the PEV map is as noisy with respect to the pixel intensities and, in addition, with respect to the pixel colour values.

Figure 7.13 shows high-resolution magnitude and low-resolution phase data from the phase compensation experiment. The images shown here correspond to diffusion weighting along the readout direction (a,b: uncorrected; c,d: linear phase error compensation). The mean diffusivity map (e) reveals a relatively homogeneous distribution of MD values ($MD = (2.2 \pm 0.3) \ mm^2/s$) within the WM and GM phantom compartment despite residual errors in the shown DW image (indicated by the yellow arrow). The histograms in Fig. 7.13 reflect the phase dispersion for all DW directions before (pre) and after (post) phase error compensation.
Figure 7.13. High-resolution magnitude images (a,c) and corresponding low-resolution phase images (b,d) according to strong diffusion weighting along the readout direction. Images (c) and (d) show results following linear phase error compensation. Despite residual magnitude artefacts (yellow arrow in (c)) due to non-linear phase terms still present (d) the mean diffusivity map (e) shows relatively homogeneous $MD = (2.2 \pm 0.3)$ mm$^2$/s. The phase histograms suggest that the example images shown here (green line) correspond to the strongest phase alteration and the largest residual phase dispersion after phase compensation.

### 7.5.3. Discussion

The decoupling of one readout period from its preceding readout period by means of the novel gradient spoiling scheme has made DW Ss-STEAM insensitive to strong phase errors induced by motion during the diffusion weighting period. Unfortunately this comes at the expense of less SNR-efficient recovery of transverse coherences for signal generation. If only constant signal shaping was employed, only little SNR gain could be achieved compared to the original DW Ss-STEAM version. However, the flexible signal-shaping capability results in improved PSFs and allows for increased SNR. The less obvious advantage of the novel gradient spoiling scheme is that it facilitates the incorporation of the initial transverse coherence path ways into the signal generation that had to be spoiled previously [73]. With more SNR-efficient signal shapes, such as exponentially decaying or Hamming shapes as opposed to constant shapes, a considerably larger part of the respective coherence path ways can be refocused right at the beginning of the readout train. This finally yields an SNR level that was initially aimed at. Unfortunately, with larger initial flip angles some PSF artefacts reappear that can only be attributed to diffusion weighting as they are not visible in the non-weighted images. The reason is most certainly found in the fact that the object phase is apparently not static, as assumed throughout this discussion, but evolves
slightly during the readout period (ongoing table vibrations in the presence of strong imaging/motion sensitising gradients, decaying eddy currents, etc.). As before, the artefacts related to such kind of violation of the CPMG condition unfortunately become notable when employing vFA trains with higher SNR-efficiency. Compared to the status prior to this work, the intensity and the extent of these artefacts are however significantly reduced.

Nevertheless, the in vivo experiments have revealed major remaining problems, if applied under realistic conditions, even with the modified sequence version. Although the artefacts in the individual DW images have been drastically reduced (compare example images in Fig. 7.4 and 7.12), they still obscure appropriate DTI reconstruction if “high-SNR” signal shapes are selected. This is indicated by the strong noise of the diffusion tensor parameter maps, in particular the intensity and colour noise in the PEV map. This noise supposedly results from both low SNR in central brain regions and raw data inconsistencies (direction/intensity of the blurring and signal voids depending on DW direction). Such specific artefacts in the DW images are very likely induced by continuous motion during signal readout. Unfortunately, more acquisitions (DW directions or averages) would hence not significantly improve the results with the STEAM protocol. If one could show that nonrigid brain pulsation is a negligible factor with this regard, mechanical decoupling of the patient table from the scanner could be a promising solution to reduce these artefacts. One further, not yet investigated option to improve SNR in case of GRAPPA parallel imaging reconstruction would be an alternative acquisition technique (for example fast low angle shot [88]) for the external auto calibration scans. Here as well as in Ref. [73] a non-weighted STEAM acquisition with a reduced number of lines has been employed.

The reasons, why interferences as shown in Fig. 7.4 and 7.12 (as a consequence of CPMG violation) and significant noise amplification in DTI parameter maps as shown in Fig. 7.12 have not been observed or discussed in the original publication that proposed utilising all transverse coherences for DW Ss-STEAM [73] may be manifold. First, as indicated above, the data discussed there were accidentally obtained using a pulse sequence that rather resembled the gradient spoiling scheme proposed here. Hence, direct interference of stimulated and spin echo coherence pathways has automatically been avoided. Second, rather moderate exponential signal shaping has been used for the in vivo examples shown in Ref. [73]. The corresponding vFA trains do not differ much for the sequence versions proposed here and in Ref. [73] (except for slightly larger initial flip angles and the absence of small flip angle oscillations for the same signal shape, as demonstrated in Fig. 7.11 (b) vs. Fig. 7.11 (c)). On the one hand, this explains why the accidental pulse sequence alteration in Ref. [73] has remained unnoticed. On the other hand, this resulted in initial flip angles of only approximately 25°-30° as compared to 35°-60° due to stronger exponential signal shaping used for the results shown in Fig. 7.10. The observed data inconsistencies might as well have been reduced here, if less SNR-efficient signal shapes
had been chosen. Lastly, besides residual sequence parameter differences (e.g. the signal shaping strength used for GRAPPA auto calibration scans), it is noteworthy that the results of Ref. [73] have been obtained at 4 Tesla, which can be expected to be beneficial for the comparison of DW Ss-STEAM vs. DW SE-EPI: on the one hand, compared to 3 Tesla a prolonged $T_1$ and reduced $T_2^*$ is observed; on the other hand, compared to ultra-high fields such as 9.4 Tesla excitation field inhomogeneities are not yet too strong such that spin echo refocusing and signal shaping are still possible.

Finally, as a proof of principal, the histograms in Fig. 7.13 summarise the attempt to facilitate DW Ss-STEAM imaging utilising all transverse coherences on a phantom by prospective linear phase compensation. According to the histograms the example magnitude images displayed in Fig. 7.13 (DW along the readout direction) corresponded to comparably strong phase alterations with significant non-linear residual phases after correction (cf. Fig. 7.13 (d)). The residual artefacts in the magnitude image after correction might even suggest an (artificial) increase of the apparent diffusivity. However, in the MD map such an effect was not observed. The large diffusivity that was estimated, by the way, explains very well the low SNR of the raw DW images: the $b$-value that was employed is typically used for in vivo DTI where mean diffusivities are a factor of three smaller. For adequate MD mapping of this phantom, a $b$-value of $b \approx 300 - 400 \text{s/mm}^2$ would have been more appropriate. With the selected $b$-value, however, the induced table vibrations, and hence the phase errors, do correspond to realistic scenarios.

### 7.6. Conclusions

The presented modifications, in particular the new gradient spoiling scheme, have made DW Ss-STEAM insensitive to static phase errors. A high SNR level with considerably reduced artefacts could thus be achieved in phantom experiments. However, continuous motion in the presence of quite large imaging gradients (in particular the increased spoiler gradients involuntarily acting as motion sensitising gradients) does lead to continuous alterations of the magnetisation phase. Furthermore, decaying eddy current fields certainly also have a small dynamic impact on the object phase. Though negligible compared to the phase errors introduced by motion during DW, these dynamic phase alterations effectively spoil the designed PSF non-negligibly – even with the adapted gradient spoiling. This is indicated by the artefacts visible in the high-SNR phantom images in Fig. 7.11 and the in vivo images shown in Fig. 7.12. Employing signal shaping with only moderate SNR-efficiency (only little exponentially decaying or broad Gaussian shapes) may be one realistic means to suppress the artefacts, on the one hand, and to maintain a notable SNR and PSF advantage over RF spoiled constant signal shaping at the same time.

In the presence of dynamic phase alterations obviously also the proposed prospective phase
compensation collapses as it is based on a static phase error map as a reference. But even with non-dynamic phase errors, it can be concluded from the experiments performed here, that the linear approach alone is not sufficient for serious application of DW Ss-STEAM utilising all transverse coherences. As a proof of principle, however, the approach showed that manipulation of the object phase is possible by relatively simple means and implementation into the DW Ss-STEAM sequence is trivial. The presence of compensatory gradient blips and extra phases in each readout period hypothetically even allows for the dynamic adaption of the phase compensation, if only the dynamics of the phase errors were known. As one further step the non-linear phase terms could be accounted for by tailored RF pulses that result in a spatially dependent excitation phase [89].

To sum up, at 3 Tesla DW Ss-STEAM is not comparable to conventional DW-EPI in terms of SNR-efficiency. However, it remains a diffusion weighting sequence with non of the off-resonance-related artefacts known from EPI, though it is more vulnerable to motion. The amount of destructively interfering spin echoes and stimulated echoes can be minimised by an appropriate choice of “SNR-inefficient” signal shapes. “High-SNR” signal shapes unfortunately even obviate in vivo application of the more robust sequence modifications proposed here on standard clinical MR scanners. One yet unexplored possibility would be the implementation of “high-SNR” signal shapes, such as proposed here, into the original RF spoiled sequence version [72], thus combining the strengths of both sequence generations: the original robustness and the improved signal shaping capabilities.

Related Publications


High-resolution Functional Imaging

Functional MR imaging (fMRI) is almost exclusively based on whole-brain single-shot EPI time series data with an isotropic resolution of approximately 3 millimetres. This allows for unaccelerated signal acquisitions with optimal echo times at 1.5 to 3 Tesla and sufficiently short volume repetition times of approximately two seconds. Some applications, however, require higher resolutions, for example surgery planning on individual fMRI data but also in the field of neuroscientific research. This chapter evaluates several sequence modifications that facilitate an increase of spatial resolution without leading to an unacceptable loss of temporal resolution. Amongst others, asymmetric EPI acquisition is proposed as one yet rarely investigated means to increase acquisition speed and to minimise achievable echo times. A particular focus of this chapter lies on three-dimensional EPI acquisitions, segmented in one or two dimensions. In this context a reduced field-of-view method based on slab-selective excitation is introduced. Whole-brain fMRI results obtained at 3 and 9.4 Tesla at 1.5 millimetres isotropic resolution are presented that were acquired with volume repetition times as short as two seconds. For such high temporal resolutions a fast and simple lipid-suppression technique, which is proposed and investigated as part of this work, is essential.
Chapter 8. High-resolution Functional Imaging

8.1. Tailored High-Resolution EPI for Ultra-high Fields

Functional MRI at ultra-high fields benefits from an increase of the blood oxygenation level dependent (BOLD) contrast (cf. section 3.1). Furthermore, higher spatial resolutions can be achieved at higher field strengths without sacrificing image signal-to-noise ratio (SNR) due to the larger equilibrium magnetisation available. At the same time a thermal noise dominated regime can be sustained by decreasing the voxel volume: physiologically induced signal fluctuations are minimised (physiological noise < thermal noise) such that the temporal SNR (tSNR), which is critical for fMRI, is not disproportionally decreased compared to the image SNR in the hypothetical absence of physiological signal fluctuations [90].

However, there are also several aspects, in which EPI suffers from the increased magnetic field strength, most of which can be counteracted by employing extremely rapid EPI acquisitions. For instance, susceptibility-induced geometric distortions are reduced by increasing the bandwidth in blipped phase encode (PE) direction, i.e. by realising shorter echo spacings (ESP)\(^1\). Furthermore, rapid EPI acquisitions counteract pronounced image blurring and allow for shorter echo times (TE), which are required for optimal BOLD contrast at ultra-high fields due to a general reduction of \(T_2^*\) relaxation times [91]. Acceleration methods gain even more relevance for three-dimensional EPI (3D-EPI), which was implemented as part of this work. An overview over the technical details and the particular implementation of established standard acceleration techniques are given in appendix D. In this section, in addition to parallel imaging acceleration, segmented (interleaved multi-shot) acquisitions [92] for 2D- and 3D-EPI as well as asymmetric EPI acquisitions are discussed as optional means to reduce ESPs.

The results presented in the following are exclusively based on custom sequences, which have been derived from a self-written two-dimensional EPI sequence template, in which several standard and advanced acceleration methods have been implemented. In the following, each of the discussed subtopics are accompanied by experimental demonstrations. In the concluding section 8.2, which features a novel method for increased temporal resolution of 3D-EPI with reduced specific absorption rate and RF peak power, several of the described methods are combined for the experiments performed under realistic functional MRI conditions \(in vivo\).

\(^1\)Traversing the \(k\)-space at a faster pace in PE direction (due to a shortened ESP) corresponds to an increased bandwidth in PE direction, which reduces susceptibility-induced geometric distortions in PE direction. This is analogous to the effect a shortened readout dwell time (increased readout bandwidth) has on susceptibility-induced geometric distortions in readout direction.
8.1.1. Multi-shot Acquisition and Echo Time Shifting

As discussed in appendix D one favourable effect of parallel imaging in EPI is the increased bandwidth in phase encode direction. Essentially the same effect can be achieved without parallel imaging by employing interleaved multi-shot EPI acquisitions, whereby the PE lines are distributed over multiple excitations, \( N_s \), followed by an \( N_s \)-fold undersampled EPI readout train. Note that this results in a rather uniform \( k \)-space segmentation along the PE direction. Each of the successive shots (each interleaf) is assigned a different PE pre-dephaser gradient pulse such that the superposed trajectories cover the complete \( k \)-space. For minimised ghosting artefacts in multi-shot EPI image reconstruction it is required to employ *echo time shifting* [93, 94]: each interleaf is assigned a small time delay – the echo time shift (ETS) – such that the central \( k \)-space column experiences a virtually continuous phase evolution as illustrated by Fig. D.3c in appendix D. Classic multi-shot acquisition can be – and is in this work – combined with parallel imaging to increase the PE bandwidth even more.

8.1.2. Appropriate Reference Scan Acquisition for Parallel Imaging

As detailed in appendix D, the acquisition of EPI reference scan data for parallel imaging reconstruction should be carried out with a bandwidth in blipped PE direction identical to that of the subsequent, \( R \)-fold undersampled imaging scans. This requires an \( (N_s \times R) \)-shot reference scan EPI acquisition, where \( N_s \) denotes the number of shots utilised for the imaging scans. Usually, the reference echo trains are significantly shorter than the imaging echo trains since only the central \( k \)-space section is acquired. As the image contrast for reference and imaging scans do not need to match, using the reduced echo train length to minimise the echo time for the reference scans is hypothesised to improve the robustness of parallel imaging reconstruction: the SNR is increased and signal drop outs are minimised during reference scan acquisition.

Figure 8.1 demonstrates the effect of different reference scan acquisitions (with and without segmentation) on the final GRAPPA reconstruction quality. Therefore, 2D-EPI phantom images were obtained with \( R = 2 \) and \( R = 4 \)-fold under sampling at 3 Tesla using a 12 channel head coil (Siemens). 22 reference scans were either acquired in a single shot or using two or four shots. The multi-shot reference scans were once acquired at the same echo time as the imaging scans, \( TE = 70 \text{ ms} \), and once at the minimum echo time possible (13 and 7ms for two and four shots, respectively). The results are displayed together with the differences to the corresponding, fully sampled multi-shot images, which show identical distortions\(^2\). Clearly, the GRAPPA reconstruction errors are maximal for the single-shot reference scan acquisition and minimal for

\(^2\)As a matter of fact, each multi-shot acquisition contains one trajectory – the one that includes the \( k_{pe} = 0 \) line – that exactly matches the respective GRAPPA imaging trajectory employed here.
the multi-shot reference acquisition at minimal \( TE \).

A typical \textit{in vivo} example shows that, for practical acceleration factors such as \( R = 2 \), GRAPPA reconstruction is particularly sensitive to reconstruction errors in regions of large magnetic susceptibility differences, e.g. in the proximity of cavities (cf. Fig. 8.2a). In these regions, the receive coil sensitivities are not well represented, and consequently GRAPPA reconstruction suffers. This is due to the fact that the receive sensitivities, as captured by the single-shot or long echo time reference scan acquisitions, are either geometrically more distorted or contain more severe signal drop-outs compared to the final imaging scan acquisition. Hence, the \( k \)-space interpolation kernel for GRAPPA reconstruction is not appropriately estimated. The left image depicts the mean over ten volumes obtained with single-shot reference scans; the right image shows the corresponding standard deviation and thus reflects the \( g \)-factor map (in addition to the rather dominating physiological noise). The coefficient of variation (std/mean) is summarised in the histograms plotted in Fig. 8.2b for single-shot, two-shot and two-shot with minimal echo time reference scan acquisition.

\textbf{8.1.3. Asymmetric EPI}

Significant drawbacks of high-resolution EPI trajectories are first, increased echo spacings (ESP) and second, increased echo train lengths (ETL) due to greater \( k \)-limits and larger matrix sizes to be filled. While partial Fourier imaging, parallel imaging and interleaved multi-shot acquisition reduce the ETL and the \textit{effective} ESP (except for partial Fourier) – i.e. the time that has virtually passed between adjacent PE lines in the final, completely filled \( k \)-space – asymmetric EPI acquisition is considered in this work in addition to standard ramp sampling in order to reduce the actual ESP \cite{95}.

If, for the sake of simplicity, the time required for phase encode gradient blips is ignored, the actual ESP essentially consists of the readout sampling time, \( T \) (cf. appendix D). This duration is a product of the readout dwell time, \((\Delta v)^{-1}\), the inverse of the readout bandwidth; cf. section 2.3.1), and the number of readout columns, \( N \) (see Fig. 8.3). Hence, \( ESP \gtrsim N/\Delta v \), is approximately proportional to the number of sampled readout columns. Reducing the number of readout columns (without changing the readout bandwidth) thus displays an effective means to reduce the actual ESP as long as the phase encode gradient blip duration is in fact short compared to the readout sampling time. Note, that with the same motivation, a remotely related “readout-segmented EPI” technique has recently been employed successfully for high-resolution diffusion weighted imaging at 7 Tesla \cite{82}\footnote{In addition the diffusion weighted spin echo \( TE \) is considerably decreased with readout-segmented EPI}. Furthermore, note that with partial Fourier acquisition, which results in an equivalent asymmetry of \( k \)-space coverage in phase encode instead
Figure 8.1. Fully sampled two- and four-shot 2D-EPI acquisitions of a single phantom slice (column 1) and GRAPPA reconstructions of two- and four-fold undersampled 2D-EPI acquisitions (columns 2-4) of the same slice using different strategies for the acquisition of 22 reference lines (phase encode direction: left–right). Clearly, the single-shot reference scan acquisition causes most severe artefacts mainly related to areas with critical susceptibility gradients. These are minimised by using an R-shot reference acquisition at the shortest echo time possible. This finding is supported by minimised noise penalty (g-factor) and artefacts appreciable from the difference images (bottom), which take the unaccelerated two- and four-fold segmented images displayed on the top left as a reference.
Figure 8.2. (a) Mean (left) and standard deviation (right) over 10 two-fold accelerated brain images (2D-EPI) in arbitrary signal units. (b) Histogram of the coefficient of variation (std/mean). In particular around the eyes and nose, where susceptibility gradients are critical, the standard deviation is large. This is indicated by the asterisk “*” within the logarithmic histogram sub plot of the coefficient of variation. The grey arrows indicate the minor difference between the two-shot reference scan acquisitions using normal and minimal echo time. The latter tends towards smaller coefficients of variation.
of the readout direction, an ESP reduction, and hence reduction of geometric distortions, is not possible.

In general, asymmetric echo acquisitions are realised by reducing the number of \( k \)-space columns and placing them asymmetrically in \( k \)-space such that the \( k \)-space edges (depending on resolution) are only hit one-sidedly. This requires shorter readout gradient durations and optionally a reduced prephaser gradient if acquisition should start at some \( k_0 > k_{\text{min}} \). In single-line gradient echo imaging, this is usually done to achieve minimal echo times\(^4\). As discussed above the particular potential of asymmetric EPI is to facilitate high-resolution acquisitions with increased bandwidth in blipped phase encode direction and, additionally, reduced \( T_2^* \) decay during acquisition. On the downside, asymmetric echo reconstruction typically corresponds to one-sided \( k \)-space-filtering and thus to a loss in actual resolution (increase of Gibbs-ringing) and signal-to-noise ratio depending on the actual amount of asymmetry, as known from partial Fourier reconstructions.

The gain in acquisition speed of asymmetric EPI depends critically on the base resolution, \( N_0 \), and the readout bandwidth per pixel, \( \Delta v / N_0 \) (which stays constant since only \( N \), the number of actually sampled readout columns, and not the base resolution is changed). No significant timing benefit is expected at common, low spatial resolutions such as 3 millimetres isotropic voxels, which are easily achieved using very large readout bandwidths per pixel without hitting gradient amplitude limits. In this work, asymmetric EPI is introduced for high-resolution application, where ESP can increase drastically as readout gradients are permanently driven at their hardware limits and thus only comparably low bandwidths per pixel are possible. In such cases the phase encode gradient blip times become short compared to long readout sampling times, and hence asymmetric EPI is more efficient to reduce ESP.

\(^4\)Radial imaging, starting at \( k_0 = 0 \), corresponds to an extreme case of asymmetric echo acquisition.
Figure 8.4. Mean (top) and standard deviation (bottom) over ten repetitions of a 3D-EPI head scan using increasing degrees of EPI anisotropy (from left to right). Readout direction is inferior–superior. There is no notable degradation of image quality up to $AE = 0.40$ but rather a moderate suppression of high frequency Gibb's ringing. Also changes of the (temporal) noise are not observed.

According to Fig. 8.3 the asymmetry of asymmetric EPI acquisition is here defined as

$$AE = \frac{N_c}{N} \leq \frac{1}{2}.$$ \hspace{1cm} (8.1)

That is, the asymmetry is determined by the actual number of $k$-space columns, $N$, and the $k$-space centre column, $N_c$. If $AE = 0.5$, the latter equals to half the base resolution, $N_c = N_0/2$. In particular

$$N = N_c + \frac{N_0}{2}$$

and thus

$$N_c = \frac{N_0}{2} \cdot \frac{AE}{1 - AE}.$$ \hspace{1cm} (8.1)

which is the essential equation from the implementation point of view.

Figure 8.4 shows representative orthogonal cross sections of a whole-brain acquisitions using a symmetric EPI readout as well as three acquisitions with varying degrees of EPI asymmetry, $AE = 0.45, 0.40, 0.35$. A 3D-EPI sequence, as discussed next, was used to achieve these high resolution images with a voxel size of $(1.5\text{mm})^3$. GRAPPA $R = 4$ was achieved by two-fold acceleration in both phase encode directions. Additionally, partial Fourier $6/8$ was employed in both phase encode directions. The readout direction is inferior-superior (foot–head). Further
8.1. Tailored High-Resolution EPI for Ultra-high Fields

![Graph and images](image)

**Figure 8.5.** Mean over ten repetitions of a 3D-EPI phantom scan at (1.5 mm) isotropic resolution (top) using increasing degrees of EPI anisotropy (from left to right). The profile plots (bottom), which show image intensities for $AE = 0.5$ and $AE = 0.35$ along the white line in the top-left image (indicating the readout direction), confirm a non-negligible degree of smoothing for $AE < 0.4$.

Imaging parameters were: $TE/TR = 30\, ms/60\, ms$, volume $TR = 2.34 \, s$, flip angle = $20^\circ$, bandwidth (symmetric/asymmetric) = $1488\, Hz/px/1429\, Hz/px$. The actual echo spacings were, respectively, $760\, \mu s$, $710\, \mu s$, $660\, \mu s$ and $620\, \mu s$. The top row shows the mean over ten repetitions, the bottom row the standard deviation. The intensity of the bottom row is scaled by a factor of ten compared to the top row. Note that changes of the actual resolution compared to symmetric acquisition seem to be negligible up to $AE = 0.40$. In fact, a slight apodising effect that reduces high frequency Gibb’s ringing in RO direction can even be considered beneficial.

Corresponding resolution phantom images as well as the representative magnitude profile plots, shown in Fig. 8.5, indicate that $AE \leq 0.35$ in fact leads to a notable loss of resolution. The horizontal white arrows indicate increased Gibb’s ringing artefacts that are prominent in the $AE = 0.35$ image. Furthermore, slightly increased image artefacts in regions of strong magnetic field distortions indicate that image reconstruction can become critically affected by too much missing k-space information in particular in the presence of a non-constant spatial phase distribution (diagonal white arrow in Fig. 8.5).
8.1.4. Three-dimensional EPI

The term “3D-EPI” as used in the following refers to multi-shot EPI acquisitions in the sense of stacked Cartesian k-space planes, each acquired following separate excitation RF pulses, as depicted in the top graphs of Fig. 8.6. As discussed in ref. [96] such a 3D-EPI acquisition provides several advantages over 2D-EPI acquisitions for fMRI at ultra high fields:

- It requires much smaller Ernst angles (SAR reduction)
- It provides higher signal sensitivity compared to slice-selective EPI due to signal contributions from the entire magnetisation for each shot
- It allows for the application of parallel imaging techniques in two dimensions
- It allows for asymmetrically truncated k-space acquisition and reconstruction in two (partial Fourier) or even three dimensions (asymmetric EPI, see above)
- It does not suffer from lost signal due to through-slice dephasing
- It allows for real isotropic, small voxel sizes (no slice gap required to avoid slice crosstalk)
- Further unique features not available to 2D-EPI may be applicable (see Ref. [97])

The application at ultra-high fields suggests to apply k-space segmentation not only along the partition direction but also along the blipped phase encode direction in order to increase the bandwidth (cf. bottom graphs in Fig. 8.6), which was investigated as part of this work [98]. However, one should keep in mind that, as opposed to single-shot 2D-EPI acquisitions, object motion during segmented volumetric MRI acquisitions is not captured per slice (in a “snap shot” fashion) but instead affects the entire imaging volume. The amount and type of motion artefacts typically depends on the number and the temporal ordering of segments, the acquisition time per volume and, not least, the kind of motion [5].
Physiological Noise

One major disadvantage of multi-shot 3D-EPI is an increased susceptibility to physiological noise compared to 2D-EPI if coarse image resolutions are selected [99]. During the acquisition of three dimensional \( k \)-space data physiological processes such as pulsation of cerebrospinal fluid (CSF), dynamic changes of the static field due to breathing, blood pulsation and motion, etc. as well as system instabilities introduce small variations of the spin dynamics between shots [100]. These inconsistencies lead to a reduction of the temporal signal-to-noise ratio (tSNR)\(^5\) of a time series compared to the actual image SNR (SNR\(_0\)). The exact tSNR-SNR\(_0\) behaviour for both 2D- and 3D-EPI is characterised by

\[
tSNR = \frac{SNR_0}{\sqrt{1 + \lambda^2 \cdot SNR_0^2}},
\]

whereby \( \lambda \) is a system (sequence/parameter) dependent constant. In fact, tSNR approaches a plateau for large image SNR\(_0\). This plateau has been shown to be lower the more shots have been performed for image acquisition [99].

However, as SNR\(_0\) decreases, tSNR assumes a direct proportionality to SNR\(_0\). This almost linear behaviour is referred to as the thermal noise dominated regime [90]. Thus, with small voxel sizes (or small Ernst signal magnitudes, etc.) tSNR is not significantly reduced compared to SNR\(_0\). Consequently, 3D-EPI displays an appropriate choice for high-field fMRI as long as voxel sizes are not too large. With larger voxels (physiological noise dominated regime), on the other hand, 2D-EPI using as few shots as possible (single-shot) would be an appropriate sequence choice to maximise the tSNR. This preference does, however, not consider that 3D-EPI has more degrees of freedom for imaging acceleration compared to conventional 2D-EPI. More sampling points per time interval may thus still increase statistical robustness of 3D-EPI fMRI data even if tSNR was reduced compared to 2D-EPI [101].

For the sake of completeness it should be mentioned that a number of strategies have been developed to reduce the effect of physiological noise in functional data (e.g. [102]). The general approach is to incorporate additional physiological information, such as heart beat and respiration as additional regressors into the general linear model analysis for fMRI. The physiological data can be acquired and logged easily using an MR compatible pulse oxymeter and a respiratory belt, for example. The required modifications have been implemented and physiological data has been recorded during several 9.4 Tesla experiments performed for this work. However, the respective fMRI corrections have not been performed for the results presented in the following since a comprehensive discussion of physiological noise reduction is beyond the scope of this

\(^5\)tSNR = ratio of mean and standard deviation of time series data with respect to the time dimension.
work.

### 8.1.5. A Slab-selective 3D-EPI Approach for Reduced-field-of-view fMRI

Reduced-field-of-view (rFOV) imaging denotes an MRI technique that allows choosing an imaging FOV smaller than the actual object size. The signal from areas outside the rFOV must therefore be suppressed in order to avoid fold-in artefacts according to the Nyquist-Shannon theorem. Smaller rFOV imaging matrix sizes are in particular beneficial in EPI where the reduced FOV dimension is typically defined as the blipped PE direction. The shortened echo train length results in less severe geometric distortions in addition to reduced total scan times \[^{103}\].

Generally, reduced-field-of-view (rFOV) imaging either relies on outer volume suppression (OVS) or on inner volume imaging (IVI), i.e. direct spatially selective excitation of the rFOV only. The first kind is usually accomplished by means of a set of preparation RF pulses. A specific variant has recently been shown to perform very well for accelerated, sub-millimetre fMRI using 2D-EPI, in particular when combined with parallel imaging \[^{103}\]. The latter kind, on the other hand, has the potential to be more versatile since almost arbitrary shapes can hypothetically be excited within acceptable times using parallel excitation techniques.

Unfortunately, typical OVS and IVI techniques are both time demanding and SAR intensive. In this work a simple low-SAR variant of IVI is implemented via slab-selective excitation in the blipped EPI direction. This corresponds to changing the phase encode loop orders from “blipped PE = inner loop/ 3D = outer loop” to “blipped 3D = inner loop/ PE = outer loop”. A rather well defined slab-profile can be achieved by utilising a standard Hamming-apodised sinc excitation pulse.

Figure 8.7 illustrates different acceleration strategies for rFOV imaging as recently discussed in ref. \[^{103}\]. Here, the proposed slab-selective rFOV approach was employed instead of using outer volume suppression. GRAPPA acceleration was only performed in the blipped EPI direction (vertical). The images highlighted with a blue frame correspond to equal (four-fold) effective imaging acceleration. Compared to the full FOV acquisition with GRAPPA R=4 (left bottom image) the rFOV strategy I according to \[^{103}\] (rFOV excitation but unchanged FOV with high GRAPPA acceleration factor) already reduces GRAPPA reconstruction artefacts clearly. Strategy II (rFOV excitation and rFOV acquisition + moderate GRAPPA acceleration), however, even outperforms strategy I for the same effective acceleration factor, which is in accordance with the findings in ref. \[^{103}\].

Figure 8.8 demonstrates a useful rFOV set-up for high spatial and high temporal resolution fMRI of the occipital lobe (visual activation) at 3 Tesla. In this case, slab-selective excitation and blipped partition encoding was performed along the anterior–posterior direction (readout was
inferior–superior, phase encode was left–right). At an isotropic resolution of 1.5 mm the rFOV of only $104 \times 96 \times 104 \text{mm}^3$ facilitates a temporal resolution of 1566 ms per volume. To achieve this, $2 \times 2$ parallel imaging acceleration and partial Fourier factors of 6/8 in both phase encode directions was performed.

### 8.1.6. Discussion

A custom 2D-EPI sequence has been implemented including several techniques that make this implementation suited for ultra-high field application. In the first place, this covers established techniques such as ramp sampling, in-plane segmentation and parallel imaging acceleration. For the latter, it was found that, first, segmenting the reference scan acquisition into $R$ times more shots than the $R$-fold undersampled imaging scans and, second, minimising the echo time yields the least GRAPPA reconstruction artefacts. Note that this experimental comparison did not consider a simple FLASH (Fast Low Angle SHOt) readout [88] as yet another alternative for reference scan acquisition. This would again be expected to yield a representation of the receive channel sensitivities with deviating geometrical distortions compared to the imaging scans. However, this drawback might be counterbalanced by the least signal drop outs thus achievable due to ultimately minimised echo times. Beyond established techniques, asymmetric EPI ac-
Figure 8.8. Mean image from an rFOV 3D-EPI in vivo experiment (colour-scale) overlaid on the anatomical reference image (gray-scale). On the transverse section the fold-ins in the PE direction (left-right) are visible. There are no fold-ins in the blipped partition direction (anterior–posterior), which was the rFOV dimension in this example.

Acquisition was investigated. Due to the effective loss of spatial resolution with large asymmetry factors on the one hand and a comparably small increase of bandwidth in blipped phase encode direction on the other hand, only moderate asymmetries, $0.4 \leq AE \leq 0.5$, were found to be advisable.

Finally, to increase signal sensitivity at high spatial resolutions the 2D-EPI implementation was turned into a segmented 3D-EPI implementation, which hence inherited all before mentioned features including in-plane segmentation. In the following section the latter will be shown to prove particularly useful for application at 9.4 Tesla with minimal geometric distortions. For 3D-EPI a convenient reduced field-of-view (rFOV) method based on slab selective volume excitation was proposed and used to reproduce earlier findings [103] that showed improved parallel imaging reconstruction with rFOV compared to full field-of-view imaging. The rFOV method proposed here is much less time- and SAR-intensive than rFOV based on outer volume suppression.

For the sake of completeness, it is worth mentioning that, alongside classic parallel imaging methods implemented here, there exist alternative methods to reconstruct spatially undersampled data, which have not been considered in this work. Some of them explicitly utilise temporal correlations between $k$-space data points, such as UNFOLD$^6$ [104] or $k$-$t$-BLAST/$k$-$t$-SENSE$^7$ [105]. These require dedicated reconstruction algorithms and it is yet unclear whether they are suited for fMRI analysis as they rely on prior knowledge, for example from training data as dis-

$^6$UNFOLD = “UNaliasing by Fourier-encoding the Overlaps using the temporal Dimension”

$^7$BLAST = “Broad-use Linear Acquisition Speed-up Technique”, SENSE = “SENsitivitv Encoding”
8.2. A Simple, Low SAR Lipid-suppression Technique for Fast Whole-brain 3D-EPI

Volumetric MRI acquisitions, such as 3D-EPI, can be performed based on volume excitation of a confined region (e.g. slab-selection) or spatially non-selective excitation (only confined by transmit and receive coil sensitivity profiles). The latter facilitates the application of spectrally-selective excitation pulses instead. The objective of the method proposed in the following is to achieve – with minimal time and SAR costs – full excitation of brain-water-magnetisation and

8a condition that is fulfilled by most fMRI studies, which in any event conduct spatial smoothing within the process of GLM analysis (cf. section 3.1) and spatial registration to a group or standard template
minimal excitation of subcutaneous fat magnetisation at the same time. A rectangular RF pulse shape is discussed as the most simplistic spectrally selective pulse example, for which an analytic pulse duration formula independent of the small tip angle approximation will be derived.

8.2.1. Introduction

Lipid- or “fat-suppression” is essential for typical echo planar imaging (EPI) applications such as functional MRI as explained in section 3.2.4. A conventional fat-suppression technique in standard two-dimensional EPI consists of chemical shift selective excitation (CHESS [109]) of the lipid proton spins (usually by means of a Gaussian shaped RF pulse) followed by large crusher gradients that spoil the transverse lipid signal. Such fat-saturation is performed before the actual, spatially-selective proton spin excitation.

While conventional fat-saturation methods are quite effective in suppressing the fat signal [109] they imply at least two major drawbacks for functional imaging in general and for ultra-high field MRI in particular. First, as rapid image acquisition times decrease, the fixed time required for fat-saturation becomes disproportionally long, which limits the temporal resolution of the fMRI time series. Second, the specific-absorption-rate (SAR) is comparably large due to the extra spectrally-selective lipid excitation. This makes the application impracticable at ultra-high fields where SAR estimation has to be performed very conservatively to prevent local tissue heating [110]. In contrast to fat-saturation the solution proposed here can be classified as a water excitation method. It will be shown to be particularly useful for high-resolution whole-brain fMRI using multi-shot three-dimensional EPI [96]. Due to considerable SAR and time savings, and due to minimal implementation costs, the proposed method may be considered a key step to improve temporal resolution of high-resolution fMRI time series at ultra-high fields.

8.2.2. Theory

Fat-suppression Condition

Let $\omega_0 = \gamma |B_0|$ denote the proton Larmor frequency in a nominal constant magnetic field, $B_0$. Here, $\gamma$ denotes the gyromagnetic ratio of protons. Let further $\omega = \omega_0 + \Delta \omega$ be the resonance frequency of chemically shifted lipid-protons (or water-protons in a poorly shimmed region), for instance. Typical chemical shifts of lipids are in the range of $\Delta \omega/\omega_0 = 3.1 - 3.7 \text{ ppm (parts per million)}$ [5].

For a water-resonant RF pulse assume that, without loss of generality, in the rotating frame of reference (rotation frequency $\omega_0$) the RF pulse vector is aligned along the $x$-axis. On-resonant
spins experience an effective magnetic field identical to this RF pulse vector, \( (B_1(t),0,0)^T \), while off-resonant spins experience an effective field with non-vanishing longitudinal component,

\[
B_{\text{eff}}(t) = \begin{pmatrix}
B_1(t) \\
0 \\
\Delta \omega / \gamma
\end{pmatrix} .
\]  

(8.3)

As a consequence, off-resonant spin-magnetisation, \( M_{\text{off}} \), starts nutating about an effective field vector that is tilted from the \( x \)-axis towards the \( z \)-axis according to Fig. 8.9. The corresponding nutation frequency,

\[
\Omega_{\text{eff}}(t) = \gamma \cdot \left| B_{\text{eff}}(t) \right| \\
= \sqrt{\Delta \omega^2 + (\gamma B_1(t))^2} ,
\]  

(8.4)

is larger than the (Rabi-)nutation frequency, \( \gamma B_1(t) \), of on-resonant spin-magnetisation.

The requirement, that off-resonant spins must not be deflected by the end of the RF pulse, corresponds to the following geometrically motivated condition:

\[
\int_0^\tau \Omega_{\text{eff}}(t)dt = 2\pi n
\]  

(8.5)

Here, \( \tau \) is the total RF pulse duration and \( n \) is a natural integer number such that the total nutation angle is an integer multiple of \( 2\pi \). The trivial case of \( n = 0 \) will be neglected here. Eq. (8.5) can be evaluated by inserting Eq. (8.4) and assuming a specific RF pulse envelope function ("pulse shape"), \( B_1(t) \).
Rectangular Pulse Shape

So far, no assumptions about the pulse shape have been made. By considering a very trivial rectangular pulse shape,

\[
B_1(t) = \begin{cases} 
B_1, & \text{if } 0 \leq t \leq \tau \\
0, & \text{else}
\end{cases}
\]  

(8.6)

Eq. (8.5) simplifies to \(2\pi n = \tau \sqrt{\Delta \omega^2 + (\gamma B_1)^2}\). This is easily rearranged to the required pulse duration for optimal fat-suppression:

\[
\tau_n = \frac{2\pi n}{\sqrt{\Delta \omega^2 + (\gamma B_1)^2}}.
\]  

(8.7)

The subscript \(n\) indicates that the duration is specific for what is here denoted as “nth order fat-suppression”. This refers to the number of entire turns the off-resonance magnetisation has nutated by the end of the pulse, according to Eq. (8.5).

Finally, by introducing the condition \(\alpha = \gamma B_1 \tau_n\), the optimal pulse duration for off-resonant signal suppression as a function of on-resonance flip angle, \(\alpha\), is obtained:

\[
\tau_n = \frac{\sqrt{(2\pi n)^2 - \alpha^2}}{|\Delta \omega|}.
\]  

(8.8)

Note that Eq. (8.8) is not restricted to small flip angles (no such assumptions have been made). However, the optimal pulse duration in fact approaches the small tip angle solution, \(2\pi n/\Delta \omega\), for \(\alpha \rightarrow 0\).

Effective Flip Angle for Heterogeneous Off-resonances

Equation (8.8) yields the optimal pulse duration for a specific off-resonance, \(\Delta \omega\). In a realistic experiment, however, the dispersion of resonance frequencies can be rather wide. This width is on the one hand mainly determined by the natural distribution of off-resonance frequencies (different lipids with different chemical shifts, for instance), and on the other hand by non-perfect shimming of the static magnetic field, \(B_0\) (or susceptibility-induced micro-gradients). To estimate how off-resonance variability affects the proposed fat-suppression method a formalism recently proposed in ref. [111] is used. According to Freed et al. off-resonant pulse sequences can be treated just like on-resonant pulse sequences if the nominal RF pulse flip angles and phases (valid for on-resonant spins) are replaced by effective flip angles and phases, \(\alpha_{\text{eff}}\) and \(\phi_{\text{eff}}\).
(valid for the off-resonant spins), respectively. For rectangular pulses these are given by

\[
\cos(\alpha_{\text{eff}}) = \cos(\Omega_{\text{eff}}\tau) + \left(\frac{\Delta \omega}{\Omega_{\text{eff}}}\right)^2 \cdot (1 - \cos(\Omega_{\text{eff}}\tau)) \tag{8.9}
\]

\[
\tan(\varphi_{\text{eff}}) = \frac{\Delta \omega}{\Omega_{\text{eff}}} \tan\left(\frac{\Omega_{\text{eff}}\tau}{2}\right) \tag{8.10}
\]

As a remark, the geometrically derived fat-suppression condition (8.8) formally also follows from equating Eq. (8.9) with identity.

### 8.2.3. Materials and Methods

**Phantom Experiment**

A cylindrical plastic bottle filled with an aqueous nickel sulphate solution (NiSO\(_4\)·6H\(_2\)O) and a smaller plastic bottle filled with transformer oil were placed next to each other in a clinical Tim Trio 3 Tesla MR scanner (Siemens, Erlangen) such that the cylinder axes were approximately aligned with the main magnetic field. A commercially available single-channel birdcage coil (Siemens) was used for signal transmission and reception. The various interfaces between air, plastic, nickel sulphate solution and oil make automatic shimming challenging compared to a typical *in vivo* situation, which is hence performed manually.

For the computation of a \(B_0\) map two spatially non-selective gradient echo (GRE) sequences were performed with two different echo times, \(TE_1 = 4.92\) ms and \(TE_2 = 5.67\) ms. To ensure sufficient oil-signal a comparably short rectangular pulse duration of \(\tau = 100\) \(\mu\)s was chosen for excitation using a flip angle of 11 degrees. Other imaging parameters were: \(TR = 20\) ms, \(FOV = 210 \times 218 \times 156\) mm\(^3\), 3 mm isotropic voxels. \(B_1\) mapping was performed using a Bloch Siegert shift gradient echo sequence [112] with the field-of-view and matrix size as for the \(B_0\) map.

**In Vivo Experiments**

**Variable pulse durations.** An RF-spoiled segmented 3D-EPI sequence [96], which allows for repeated volume acquisitions with linearly increasing rectangular pulse durations, was implemented for a Siemens 3 Tesla and 9.4 Tesla MR system. The variable pulse duration feature was utilised here to successively acquire 60 whole-brain EPI volumes with RF pulse durations ranging from 100 to 6000 \(\mu\)s with 100 \(\mu\)s increment. A volunteer was positioned head first supine in the Tim Trion 3 Tesla scanner. A field-of-view of \(210 \times 210 \times 180\) mm\(^3\) and a matrix size of \(70 \times 70 \times 60\) resulted in 3 mm isotropic voxels. A sagittal slice orientation was selected such that
the readout direction is inferior–superior, partition encode direction is left–right and blipped phase encode direction is anterior–posterior. A commercial 32 channel head coil (Siemens) is used for signal reception, which provides a limited receive sensitivity in inferior–superior direction. Combined with an oversampling factor of two this ensures no aliasing in readout-direction. RF pulse transmission was performed with the body coil. A readout bandwidth of \( 2551 \text{ Hz/px} \) and ramp sampling resulted in a minimal echo time of \( TE = 21.5 \text{ ms} \) limited by the echo train length and the longest RF pulse duration of 6 ms. The corresponding minimal repetition time, \( TR = 42 \text{ ms} \), resulted in an effective volume \( TR \) of \( 2.53 \text{ s} \). This leads to a total acquisition time of 2:35 minutes including 100 preparation \( TRs \) prior to the imaging scans. A steady increase of the pulse duration (per complete imaging volume) ensures that each new lipid steady-state is quickly established following a few excitations. A nominal flip-angle of 15 degrees was applied which approximates the (on-resonant) Ernst angle. A similar protocol was performed \textit{in vivo} at 9.4 Tesla.

**Comparison to conventional fat-saturation.** The main imaging parameters were adopted from the previous experiment. However, an echo time of \( TE = 30 \text{ ms} \), typical for fMRI at 3 Tesla, is now used and the repetition time is increased to \( TR = 65 \text{ ms} \) such that it allows the inclusion of the conventional fat-saturation module (\( \sim 12 \text{ ms} \)) prior to each excitation pulse. The duration for the latter was set to \( \tau = 100 \mu s \) when performed in combination with conventional fat-saturation and to \( \tau_1 = 2400 \mu s \) for fat-suppression exclusively based on the proposed method. According to Eq. (8.8) this approximates the optimal first-order fat-suppression duration at 3 Tesla for a nominal flip angle of 17 degrees if a chemical shift of 3.3ppm is assumed. A hypothetical combination of both methods to optimise general fat-suppression efficiency is mentioned here only for the sake of completeness but will not be further discussed. For each method, only five repetitions were acquired to ensure minimal motion of the volunteer between scans.

**High-resolution fMRI at 3 Tesla.** The previous protocol was modified such that a nominal isotropic resolution of 1.5 mm is achieved with a reasonably large field-of-view of \( 210 \times 210 \times 168 \text{ mm}^3 \) (140 \( \times \) 140 \( \times \) 112 matrix). The 32 channel head coil and the sagittal slice orientation provide excellent conditions to utilise the full parallel imaging potential of the 3D-EPI implementation. Two-fold acceleration in phase encode and partition encode direction employed here yields a total GRAPPA acceleration factor of four. The vendor-provided image reconstruction was performed using GRAPPA \( k \)-space interpolation kernels obtained from 24 reference scans in phase encode times 24 reference scans in partition direction. To ensure matching bandwidths in the blipped phase encode direction, the reference scans were acquired in a segmented EPI.
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fashion (cf. section 8.1.2). Reference scan acquisition was carried out once following 100 initial preparation TRs and immediately before the imaging scans start (TR is constant throughout the entire experiment9). Generally, parallel imaging acceleration saves a considerable amount of time and helps reducing geometrical distortions in EPI. Here, it furthermore permits a minimum echo time of $TE = 32\,\text{ms}$ in combination with a maximum readout bandwidth of $1488\,\text{Hz/px}$ and ramp sampling. The actual repetition time was set to a minimum of $TR = 62\,\text{ms}$. In addition to the four-fold GRAPPA acceleration, $6/8$ partial Fourier acquisition is employed in partition direction thus yielding a total effective repetition time of $2.6\,\text{s}$. Partial Fourier acquisition in phase encode direction would not have gained a timing advantage in the present context and was thus avoided. A nominal flip angle of 16 degrees and a rectangular pulse duration of $2.4\,\text{ms}$ was again selected.

A continuous 3D-EPI time series of 54 volumes was acquired while a simple fMRI experiment was performed with a paradigm consisting of 3 periods of rest (baseline) followed by bilateral finger tapping (9 volume TRs = 23.4 s each block). The respective onset times were indicated by acoustic cues. In addition, the same experiment is repeated with a conventional 2D-EPI protocol: 3mm isotropic voxel size, 40% gap between 37 transverse slices to avoid crosstalk, bandwidth=2232 Hz/px, $TE = 30\,\text{ms}$, total repetition time $2.34\,\text{s}$ (10 volume TRs = 23.4 s each block). Both data sets were analysed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) starting with motion parameter estimation, realignment (to the mean) and reslicing. No smoothing was performed prior to the general linear model analysis which used, in addition to the relevant finger-tapping periods, the six motion parameter estimates as regressors (three translational and three rotational degrees of freedom).

High-resolution fMRI at 9.4 Tesla employing additional in-plane segmentation. A similar protocol was set up for fMRI measurements with a 9.4 Tesla human MR scanner (Siemens): matrix size $= 140 \times 140 \times 96$, 1.5 mm isotropic voxels, four-fold GRAPPA acceleration with 48 reference scans in each dimension, no partial Fourier. RF pulse transmission and signal reception were performed using a home-built, cylindrical eight-channel transceiver coil with transparent casing to facilitate visual cueing. The duration of the rectangular excitation pulses was set to $\tau_1 = 0.71\,\text{ms}$. According to Eq. (8.8) this corresponds to the first order fat-suppression duration for a chemical shift of 3.5ppm at 9.4T if a nominal flip angle of 11 degrees is assumed. The eight transmit channels are driven with individually adjusted amplitudes and phases to perform RF shimming. The 16 RF shimming coefficients were computed on the basis of relative and absolute $B_1$ maps (actual flip angle mapping [113, 114]) obtained within approximately six minutes at

9Here, $TR$ refers to the duration per shot as opposed to $TR_{\text{vol}}$, which is the duration needed to acquire one entire imaging volume. They are related by $TR_{\text{vol}} = N_{\text{shots}} \cdot TR$, where, $N_{\text{shots}}$ is the number of shots per imaging volume.
the beginning of the session.

Here, three-fold in-plane segmentation was employed such that retrospective geometric distortion correction is obsolete (cf. section 8.1.1) [98]. The much shorter echo time thus achieved, $TE = 13.5\,\text{ms}$, is presumably below the yet unknown echo time providing optimal BOLD contrast at 9.4 Tesla. On the other hand, it allows for a very short repetition time of $TR = 26\,\text{ms}$. Nevertheless, due to the in-plane segmentation the effective volume repetition time increases to $TR = 3.75\,\text{s}$. To achieve an fMRI paradigm comparable to the 3 T experiment, 3 periods of rest (baseline) and bilateral finger tapping were performed with 6 volume $TRs = 22.5\,\text{s}$ each block. This time, a visual cue is presented to indicate the respective onset times via a screen mounted approximately 2.5 meters behind the MRI scanner bore and visible via a mirror mounted on top of the head coil.

Subsequent to the bilateral finger-tapping experiment the same setup is used for visual “flickering checker-board” stimulation. The fMRI block paradigm consisted of six alternating epochs of rest (fixation cross in the center of the screen) and flickering checkerboard stimulation (a black and white checkerboard pattern and its negative image flickering with a frequency of 8 Hz), each for $22.5\,\text{s} = 6TR_{\text{vol}}$.

8.2.4. Results

Phantom Experiments

Figure 8.10a and 8.10b show a representative slice of the off-resonance map and the transmit sensitivity map obtained from the phantom experiments. Using these maps, the recommended rectangular pulse duration for $n$th order signal suppression can be computed voxel-wise using Eq. (8.7) or – equivalently – by first computing the actual on-resonant flip angle, $\alpha$, which is then inserted into Eq. (8.8). The result of this operation is shown in Fig. 8.10c for $n = 1$. In the water bottle the recommended pulse durations go towards infinity as expected (suppressing on-resonant signal is impossible using the proposed method). The values within the oil bottle, however, are distributed fairly narrow about approximately 2.4 milliseconds except at the bottom of the bottle. Here the required durations increase up to approximately 5 ms due to large gradients in the main field (inadequate shim).

The voxel-wise effective flip angles that can be achieved using a rectangular pulse of $\tau = 0.1\,\text{ms}$, $\tau = 2.4\,\text{ms}$ and $\tau = 4.8\,\text{ms}$ duration are shown in Figs. 8.10d, 8.10e and 8.10f. The maps were simulated via Eq. (8.9) whereby the inserted nutation frequency was computed according to Eq. (8.4) using the off-resonance and transmit sensitivity maps shown in Figs. 8.10a and 8.10b. Aside from the expected “centre brightening effect”, a reasonably homogeneous flip angle
distribution is achieved in both oil and water for the short pulse duration. For the recommended first order fat-suppression pulse duration Fig. 8.10e shows that the effective flip angle is clearly not negligible in the badly shimmed region at the bottom of the oil bottle. However, in the remaining part the flip angles are, as desired, very low compared to the average flip angle in water.

The spectral bandwidth of the second order fat-suppression pulse is clearly reduced such that one spot in the water bottle, with roughly -200 Hz off-resonance, yields a reduced flip angle compared to the previous map. The signal suppression in the major part of the oil bottle is as good as with half the pulse length, but now the critical spot at the bottom is suppressed as well. In fact the first minimum is achieved there, according to Fig. 8.10c. A pulse duration of 4.8 milliseconds may be considered impractically long.

This changes when operating at higher fields such as 9.4 Tesla. Here, the recommended second order fat-suppression pulse duration would be approximately 1.4 milliseconds only. Also the spectral peak-suppression is increased at higher fields so that the water peak is less affected provided that a reasonable shim is possible.
Figure 8.11. Representative sagittal slices according to every tenth pulse duration step. In the first magnitude image (top row) the shifted “fat-image” is very clear but looses intensity from the first to the second to the third image. The bottom row shows the change in magnitude signal (fat mainly) due to the varied pulse duration. The image intensity range is identical in all images.

Figure 8.12. Signal magnitude as a function of pulse duration for voxels indicated in Fig. 8.11 containing only brain tissue signal, fat tissue signal and a superposition of brain tissue and fat signal (mix).

In Vivo Experiments

Variable pulse duration. Figure 8.11 shows six representative sagittal 3D-EPI slices according to every tenth pulse duration step performed at 3T. In the first magnitude image (top row) the spatially shifted fat signal is pronounced but clearly loses intensity from the first to the second to the third image. The bottom row depicts magnitude differences to the first volume ($\tau = 0.1\text{ ms}$) to show the changing fat signal. Only for $\tau \gtrsim 4.1\text{ ms}$ there is a faint increase in the difference-signal from water near the skull base where changes in the resonance frequencies are large.

For each RF pulse duration the signal magnitudes of three specific voxels are plotted versus pulse duration in Fig. 8.12: the circle, square and triangle symbols indicate arbitrarily selected voxels according to fat signal only, brain tissue signal only and a mixture of (shifted) fat and brain signal (ignoring partial volume effects). The fat signal has a sinc-like behaviour as can be expected from the Fourier transform of the rectangular pulse shape according to the small
8.2. A Simple, Low SAR Lipid-suppression Technique for Fast Whole-brain 3D-EPI

tip angle approximation. The brain tissue signal does not oscillate while the mixture signal oscillates and has a minimum where the fat *magnitude* curve has the second maximum (the *real part* of the fat signal in fact also has a minimum). The fat component at that particular voxel is minimised at approximately $\tau = 2.1$ ms or $\tau = 4.2$ ms. This indicates a rather large chemical shift mean of $\gtrsim 3.6$ ppm with respect to the centre frequency for that specific voxel (probably due to a non-perfect shim). According to the fat curve a signal reduction of approximately 97% at $\tau = 2.1$ ms compared to $\tau = 0.1$ ms is achieved ($\sim 3\%$ residual fat signal). At $\tau = 2.4$ ms, which was assumed for the following comparison of fat suppression methods, the signal reduction is still about 85% in the same voxel.

Figure 8.13 shows images from a corresponding experiment at 9.4 Tesla with an isotropic resolution of 1.5 mm. Here, the first order fat suppression pulse duration is expected at approximately $\tau_1 = 0.71$ ms. During that particular session the static field shim was insufficient, which resulted in a rather broad distribution of water and fat off resonances. It was thus expected that about the first order pulse duration a lot of fat signal with resonance frequencies closer to the calibrated (water) Larmor frequency\(^{10}\) would still be visible. In Fig. 8.13 one can in fact observe that only for pulse durations around the third order estimate $\tau_3 \approx 2.1$ ms reasonable fat suppression is achieved. Brain water signal is not yet compromised. For longer durations, however, the latter also approaches the first signal minimum in specific areas typically characterised by large susceptibility gradients (indicated by diagonal arrows). Not surprisingly, also a general signal reduction can be observed for $\tau \gtrsim 3.0$ ms as the spectral bandwidth of the excitation becomes narrower and more and more off-resonant water signal is suppressed. From the inhomogeneity of the excitation RF field (which is conceivable in particular from the first images of Fig. 8.13 where the pulse bandwidth is still very large) and in accordance with Eq. (8.7), with $\gamma B_1$ being much smaller than $\Delta \omega$, the proposed method is quite insensitive to variations of $B_1$.

It can be concluded that, even though not one defined optimum pulse duration can be identified in a badly shimmed scenario, at least a reasonable range of well performing pulse durations can be estimated. According to the 9.4 Tesla *in vivo* example, about the third order pulse duration most fat signal is either suppressed or is at least scaled down according to one of the small sidelobes of the sinc-like function depicted in Fig. 8.12.

**Comparison to conventional fat-saturation.** The grey scale images in Fig. 8.14 show representative orthogonal cross sections of 3D-EPI magnitude images obtained at 3 Tesla with different combinations of rectangular pulse durations and extra fat-saturation: “optimal pulse without extra fat-saturation” (top left), “short pulse with conventional fat-saturation prior to excitation” (bottom left), and “short pulse without fat-saturation”. The latter serves as a reference image

\(^{10}\)and thus still far away from the first root of the sinc-like function depicted in Fig. 8.12

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for the two different fat-suppression approaches (proposed and conventional). The colour scale images show difference images, which facilitate the following observations: (a) the proposed method suppresses fat signal effectively, (b) conventional fat-saturation suppresses not only fat but also water signal to some extent so that (c) the difference between both methods almost exclusively shows a water-signal excess with the proposed method. Only a very faint (but still positive) ring in the coronal view of the last difference image suggests that the suppression efficiency compared to the conventional method is slightly reduced.

Overall, both methods suppress the fat signal comparably well but the proposed method leaves a significant amount of water magnetisation unaffected. The brain water signal decrease with the conventional method is very likely due to the magnetisation transfer contrast [115] induced by the fat-saturation pulse. This effect is known for 2D-EPI applications [116] and seems to have a larger effect on 3D-EPI, where the volume repetition times are one to two orders of magnitude shorter. A rough temporal SNR estimation (tSNR) with the five repetitions acquired for each method confirms this finding: the mean tSNR values in brain-only voxels have an approximate ratio of 69 : 59 : 70 (Reference : Conventional : Proposed). The corresponding SAR estimates reported from the scanner software were 6% : 11% : 1%. These numbers furthermore demonstrate the twofold SAR reduction mechanism of the proposed method: first, by omitting fat-saturation SAR is already approximately halved (from 11 to 6%). Then, by prolonging the
excitation pulse (reducing the RF amplitude to maintain the effective on-resonant flip angle), SAR is ultimately reduced (from 6 to 1%). The latter effect has even more impact when utilising longer pulses ($\tau_2, \tau_3, \ldots$).

**High-resolution fMRI at 3 Tesla.** The whole-brain images in Fig. 8.15 show activation from the 3D-EPI experiment ($p$-threshold 0.001, 8 voxel minimum cluster size) overlaid on three cross sections of the mean 1.5 mm isotropic 3D-EPI data. The zoomed excerpts show the results in detail and allow for a comparison to the corresponding 2D-EPI activation ($p$-threshold 0.001, 1 voxel minimum cluster size – cluster volume thus comparable with the 1.5 mm example). Notably, the 3D-EPI and 2D-EPI top three cluster $t$-scores are $\{9.7, 16.5, 18.20\}$ and $\{8.0, 8.5, 10.0\}$, respectively. This and the distinct activation patterns aligned with the central sulcus highlights the increased specificity with 3D high-resolution fMRI compared to 3mm 2D-EPI very well.

Note that no fat signal is visible in the 3D-EPI data which were acquired with a rectangular, water-selective (and fat-minimising) excitation pulse of $\tau = 2.4$ ms duration instead of conventional fat-suppression. This allowed for a comparably short total repetition time and lead to an SAR estimate (as reported form the scanner software) of only one percent. The SAR estimate for the standard 2D-EPI reported from the scanner software was 25%.
Figure 8.15. Finger tapping results at 3 Tesla overlaid on axial, coronal and sagittal mean magnitude 3D-EPI images. Red: activation detected using the 1.5 mm isotropic 3D-EPI protocol employing the proposed fat-suppression method (phase encode direction: anterior–posterior, readout: inferior–superior, SAR~1%). Green: activation detected using the 3 mm isotropic 2D-EPI protocol with 40% slice gap and conventional fat-saturation (phase encode direction: anterior–posterior, readout: left–right, SAR~25%).

High-resolution fMRI at 9.4 Tesla. Figure 8.16 shows cross sections of the 9.4 Tesla mean 3D-EPI data corresponding to the 3 Tesla results shown in Fig. 8.15 overlaid with the activation patterns detected (p-threshold 0.001, 2 voxel minimum cluster size). From the magnitude data the short wavelength problems at 9.4 Tesla and the imperfect RF shimming are apparent\(^{11}\). Interference effects due to the segmented EPI readout are visible on the sagittal images (eye movement). As expected, the anatomical contrast is greater at 9.4 Tesla than at 3 Tesla (differing relaxation rates, adjusted timing parameters and flip angle).

Despite the very short echo time neuronal activation was detected rather robustly. The patterns again delineate the central sulcus and some surrounding gyri quite well. The top three cluster t-scores are [9.4, 10.8, 12.5] and are thus comparable to the 3 Tesla results. Note that none of the raw images has been smoothed prior to fMRI analysis. Again, the fat signal was efficiently suppressed using the proposed method with a pulse duration of $\tau = 0.71 \text{ ms} \approx \tau_1$.

Figure 8.17 shows activation patterns (t-scores) for the visual stimulation experiment overlaid on the mean magnitude 3D-EPI image. The zoomed excerpts (bottom) show that the activation accurately follows occipital grey matter as expected for a visual stimulation experiment.

\(^{11}\)Not until conclusion of this work a malfunctioning of the used eight channel transmit coil was detected and corrected.
Figure 8.16. Finger tapping results at 9.4 Tesla (TE = 13.5 ms) overlaid on axial, coronal and sagittal mean magnitude images acquired using 1.5 mm isotropic 3D-EPI with the proposed fat-suppression method (phase encode direction: anterior–posterior, readout: inferior–superior).

Figure 8.17. Neuronal activation (colour coded t-scores) as a result of a visual stimulation experiment at 9.4 Tesla overlaid on the mean magnitude image (grey scale). From left to right: sagittal, axial and coronal view. Bottom row: zoomed excerpts. Spatial resolution was 1.5 mm isotropic.
8.2.5. Discussion

A simple, time-efficient and and low-SAR fat-suppression technique for 3D-EPI imaging has been proposed. The method is based on spectrally selective water excitation, which was discussed here on the example of a very simple rectangular pulse shape. The free parameter, the pulse duration, is adjusted such that the lipid resonance frequency matches the frequency of the \( n \)th minimum of a sinc-like frequency response function (in fact the frequency spectrum in the small tip angle approximation). A generalised expression for the “\( n \)th order pulse duration”, which makes no assumptions about the on-resonant flip angle whatsoever (independent of the small tip angle approximation), was derived here based on geometrical magnetisation vector considerations.

The proposed method makes conventional fat-saturation prior to excitation in three dimensional whole-brain imaging sequences obsolete and is thus particularly suited for ultra-high field MRI: first, it allows for higher resolution within comparable acquisition times and second, SAR is reduced significantly due to the omission of fat-saturation, on the one hand, and due to prolonged RF pulses, on the other hand. The increased fat and water peak separation at high fields is furthermore advantageous for the proposed solution (decreased \( n \)th order pulse durations), provided a good shim can be established. Even under imperfect circumstances a reasonable range of well performing, longer pulse durations can be identified, as has been demonstrated in vivo at 9.4 Tesla.

Following varying pulse duration experiments and comparison to the conventional fat-suppression technique at 3 Tesla, which both validated the applicability of the proposed method in vivo, it was amongst others applied to high resolution finger tapping fMRI at 3 and 9.4 Tesla. The expected increase of specificity with high-resolution fMRI (1.5mm isotropic voxels at 3 Tesla = thermal noise dominated regime) was demonstrated by comparison to results from a conventional 3 mm isotropic 2D fMRI protocol. Despite the technical difficulties at 9.4 Tesla, similar activation patterns with comparable significance level were achieved. Here, additional in-plane segmentation made exceptionally short echo times and minimised geometric distortions possible.

Due to its timing and SAR benefit the proposed fat-suppression method displays a valuable tool to achieve high-resolution whole-brain fMRI at temporal resolutions comparable to standard low-resolution fMRI. Using advanced spectrally selective single pulses, such as Gaussian or apodised sinc pulses, may be one means to make the method less vulnerable to an insufficient shim. Employing established spatio-spectral water excitation methods, such as binomial pulses [117, 118], would render the combination of not using fat-saturation and slab-selective reduced field-of-view (rFOV) imaging (cf. section 8.1.5) possible, albeit at the cost of increased
SAR and longer excitation times compared to the proposed method. With respect to spectral selectivity, the simplest form of binomial pulses \(^{12}\), which have a total duration comparable to the proposed first order pulse duration, are in fact expected to perform similar or even worse than the the proposed method. The single rectangular pulse method can easily be employed to any other whole-brain application based on volumetric imaging sequences. It can of course be combined with advanced acquisition or temporal undersampling techniques such as recently discussed \([119, 120]\). Further sequence parameter optimisation, development of new coils and, in particular, incorporation of physiological data into the fMRI analysis are promising for fMRI at 9.4 Tesla.

### 8.3. Conclusions

Several ultra-high field specific techniques for acceleration of 2D- and 3D-EPI have been proposed and implemented on a 3 Tesla and a 9.4 Tesla human MRI scanner. At both field strengths the custom sequences have achieved higher acceleration factors or less geometric distortions or highly reduced specific absorption rates compared to what the vendor provided sequence for BOLD functional imaging is capable of. In particular the proposed fat suppression method by means of a single on-resonant rectangular pulse opened up new opportunities for high resolution whole-brain functional MRI at ultra-high fields such as 7 or 9.4 Tesla. By omitting the conventional fat-saturation module prior to each excitation the specific gain with the proposed method is threefold: first, a “dead time” of more than 10 milliseconds per shot with the conventional method is eliminated; second, SAR is reduced from unacceptable levels preventing the scanner to run a BOLD fMRI protocol under realistic conditions to exceptionally low values without losing fat-suppression efficiency; third, additional water signal suppression due to an unwanted magnetisation transfer effect with the conventional method, that appears to be quite large when utilised in 3D-EPI sequences, is completely avoided. Overall, an exemplary increase of sensitivity (\(tSNR/\sqrt{\text{acquisition time}}\)) has been achieved. Utilising additional physiological information (respiration, heart beat) is expected to even more improve 3D-EPI raw data and/or functional data.

Unmentioned thus far are the recently emerged and increasingly utilised simultaneous multislice (SMS) 2D-EPI methods for functional and diffusion MRI. In particular the so called slice-blipped CAIPI technique \([121]\) displays a promising alternative for slice-acceleration to the 3D-EPI sequence proposed here. In particular it utilises a virtual field-of-view shift between simultaneously acquired slice signals to reduce the noise penalty (“g-factor”) during reconstruction of

\(^{12}\)a composition of two short pulses with half the desired flip angle separated by a 180 degrees free precession period of the fat isochromat
separate slice signals, which is in principle easily implemented to volumetric imaging sequence as well. Beyond that, slice-blipped CAIPI should be more robust against physiological noise compared to segmented 3D-EPI since the slice signals are acquired within a single shot (as long as no in-plane segmentation is employed). On the other hand, this method leads to even higher SAR than single-slice 2D-EPI due to the transmission of significantly higher RF power for simultaneous slice excitation plus the conventional fat-saturation. It may thus be necessary to introduce unacceptably long fill times compared to accelerated 3D-EPI with the proposed fat-suppression method to stay within the SAR safety limits at 9.4 Tesla. Accelerated 3D-EPI may thus remain more time- and tSNR-efficient depending on image resolution and other protocol parameters as long as the SAR issues with SMS excitation are not solved satisfactory.

Related Publications


Part IV.

Conclusions
Aim of this work was the investigation of novel rapid imaging methods for diffusion MRI and functional MRI at ultra-high field (UHF) strengths.

**Anisotropic Errors in Diffusion MRI:** The first self-contained part of this work introduced and investigated a novel, isotropic encoding scheme type for diffusion imaging, termed “DISCOBALL” (direction scheme obtained by aligning points on latitudes), which has a particular potential for high angular diffusion imaging (HARDI) – not only at UHF. The ability to instantly generate an arbitrary number of isotropic directions deterministically (for instance “online” at the scanner console) provides an increased degree of flexibility with respect to the optimisation of clinical or preclinical diffusion imaging protocols compared to today’s limited sets of pre-computed look-up tables. With DISCOBALL schemes the available acquisition time can be used most efficiently by employing as many isotropic diffusion weighting directions as possible in the given time. Thereby diffusion parameter accuracy and precision is increased over all possible diffusion directions, which are usually unknown a priori. This has been demonstrated using classic diffusion tensor imaging (DTI) simulations based on single fibre directions as well as single- and multi-fibre q-ball imaging (QBI) simulations.

To the best of the author’s knowledge such detailed QBI simulations, focused on the anisotropy of reconstruction accuracy and precision made in the presence and absence of noise, have been performed systematically for the first time. The results revealed that for standard reconstruction parameters at least 60 to 120 directions distributed as isotropic as possible are required for a minimised error level and – more importantly – for a minimised reconstruction dependence of fibre orientation. In fact the isotropy of QBI response functions turned out to be even more critically depending on the isotropy of the employed encoding scheme than it is the case for DTI. One consequence is that quite frequently utilised schemes based on icosahedral subdivision are performing significantly worse with regard to response isotropy than numerically optimized schemes (in the literature often referred to as “Jones schemes” and should hence be avoided in favour of the latter or, for example, DISCOBALL schemes. Even more, simulations as well as in vivo data showed that response anisotropy introduced by inadequate sampling of orientation density functions during HARDI post processing can be reduced by one order of magnitude when utilising DISCOBALL or numerically optimised schemes with, for example, 1281 directions instead of the corresponding icosahedral scheme (five-fold triangular subdivision of the icosahedron faces). This result once more highlights the value of the introduced deterministic DISCOBALL scheme type.

**Diffusion Weighted Single-shot Stimulated Echo Acquisition Mode (DW Ss-STEAM):** With regard to diffusion weighted image acquisition several aspects of MR physics at UHF (short
transverse relaxation times, long longitudinal relaxation times, large susceptibility-induced field distortions, etc.) gave rise to the question whether it was worthwhile to move away from the standard sequence for diffusion imaging, namely spin echo EPI (echo planar imaging), to a rarely used alternative fast imaging method based on stimulated echoes. In contrast to EPI such a single-shot STEAM (stimulated echo acquisition mode) sequence, investigated in chapter seven of this work, benefits from prolonged longitudinal relaxation times and is immune to off-resonance artefacts. However, it comes at the expense of an inherent loss of 50 per cent of the available signal and increased specific absorption rate (SAR). Several modifications have been implemented to the sequence in order to counteract the intrinsic low signal-to-noise ratio (SNR) of DW Ss-STEAM by means of an efficient use of more of the generated coherent pathways (adapted spoiling scheme and signal shaping).

As discussed in this work, the proposed modifications are in fact able to boost SNR significantly while maintaining good resolution properties. However, they also make the sequence more prone to dynamic phase changes during signal acquisitions (motion sensitisation, eddy currents, etc.). This renders the adapted spoiling scheme, which introduces a mixing between spin echo and stimulated echo pathways compared to the original, RF-spoiled sequence version, inappropriate for diffusion weighting applications. The novel signal shaping capabilities (more efficient flip angle algorithm and target shapes with a good trade-off between SNR increase and point spread function broadening) on the other hand are hypothesised to find their future applications in diffusion imaging, if pathway mixing is again avoided. To be successfully applied at UHF, however, more effort has first to be put into current research topics such as flip angle homogenisation and reduction of RF power deposition in order to counteract UHF specific excitation field inhomogeneities and tissue heating. Novel parallel transmission techniques are promising developments with this regard. To the current state, however, DW Ss-STEAM is not an alternative to DW spin echo EPI for whole brain diffusion imaging at ultra high fields.

**High-resolution Functional Imaging:** In the final, self-contained chapter eight of this work the use of gradient echo EPI – in particular a self-implemented volumetric, multi-shot variant with segmentation capabilities in secondary and primary phase encoding direction – has been discussed for the application of high-resolution functional imaging. One of the main advantages of segmented 3D-EPI over conventional 2D-EPI is the ability to accelerate acquisition in slice direction by means of parallel imaging techniques and/or partial Fourier acquisition. In contrast to recent developments that enable slice-acceleration in combination with a 2D-EPI readout by means of simultaneous excitation of multiple slices, 3D-EPI requires no dedicated image reconstruction and no specialised excitation RF pulses and is hence easily applicable on every modern MRI scanner. Additionally, specific absorption rate limits are no critical issue for in vivo
applications at UHF due to the use of low Ernst flip angles exciting either a rather large slab or the entire magnetisation (the subject) contained in the excitation RF coil.

The possibility to acquire 3D-EPI images following purely spectrally selective (and spatially unconstrained) excitation was utilised in this work in order to increase the sensitivity of 3D-EPI by two means: primarily by saving the conventional, time-intensive fat-suppression module prior to every volume excitation, and secondly by avoiding an unwanted suppression of water signal apparently caused by magnetisation transfer effects related to the chemical shift selective RF pulse tuned to the fat resonance frequency in conventional fat suppression. This is achieved by replacing fat saturation by a water excitation pulse based on a single rectangular RF pulse. As a by-product the RF power deposition is decreased massively. For the required pulse duration a geometrically motivated, analytical formula was derived as a function of flip angle and off-resonance frequency to tune the first or higher order stop bands of the pulse frequency response to the lipid frequency. Since no use was made of the small tip angle approximation, the formula is hypothetically valid for all flip angles. One should however be aware of the very specific fat frequency the formula assumes, similar to the widely used, so-called binomial 1-1 water excitation method. While not observed for on-resonant Ernst angles below 20 degrees, as used throughout this work, lipid magnetisation with slightly offset frequencies may experience a non-negligible effective flip angle for larger on-resonant flip angles.

To give a final outlook, the combination of the proposed segmented 3D-EPI sequence with a non-cubic parallel imaging sampling pattern (e.g. hexagonal) would introduce the same improved image reconstruction quality to 3D-EPI as it is currently utilised in modern simultaneous multi-slice (SMS) 2D-EPI methods (so-called slice-blipped CAIPI). This would open up the possibility for a fair comparison between these two different techniques. Since the SAR advantage of 3D-EPI is currently out of reach for SMS techniques it can be expected that segmented 3D-EPI may become more attractive for neuroscientists interested in high-resolution functional imaging at UHF than SMS-EPI.
Part V.

Appendix
Appendix A.

Common Diffusion Encoding Scheme Types

A.1. Icosahedral schemes (“Icosa”)

Many standard DTI encoding schemes are defined by the vertices, faces or edges of the five Platonic solids (regular polyhedra): tetrahedron, cube, octahedron, dodecahedron and icosahedron [122]. Only a limited set of perfectly uniform Platonic solid schemes can thus be obtained. The most prominent and most isotropic six-direction scheme, ‘Icosa6’, is defined by lines through the twelve vertices of the icosahedron and the origin. Lines through the vertices of subdivided versions of the icosahedron, denoted as higher order icosahedrals, provide larger numbers of directions, \( N = 5n^2 + 1 \), where \( n = 2, 3, 4 \ldots \) [123].

At the beginning of icosahedron subdivision each of the 20 equal-sided triangles – the faces of the icosahedron – is subdivided into four new triangles by adding new vertices at the triangle halve lengths. This is illustrated in Fig. A.1a. The new vertices are then projected onto the unit-sphere to ensure a spherical mesh as depicted in Fig. A.1b. Thereby the sub-triangles undergo subtle geometric distortions. Fig. A.1c gives examples of the different side lengths and angles that develop already during the first two icosahedron subdivision iterations.

The Icosa81 and Icosa321 schemes are regularly utilised in QBI (e.g. in Refs. [28, 45]). It will be shown in chapter 6 how much the increasing deviation from ideal uniformity with each level of icosahedron subdivision in fact reduces the reliability of QBI.

A.2. The Jones Schemes (“CFmin”)

Several direction scheme types originally proposed for DTI diffusion encoding are based on extensive numerical optimisation which makes the generation of HARDI schemes, as required for QBI, computationally challenging. For example, the popular schemes proposed by Jones [35] are based on an electrostatic model: each of \( N \) diffusion encoding directions is represented
Appendix A. Common Diffusion Encoding Scheme Types

Figure A.1. (Adapted from ref. [124]) Each face of the icosahedron is subdivided into four new triangles. The new triangles are not equal-sided due to a projection onto the unit sphere. This corresponds to a definition of the new vertices as the normalised vector sum of two neighbouring vertices as illustrated in Fig. A.1b). Fig. A.1c illustrates the different triangle side lengths and angles developing during the first (top) and second (bottom) level of icosahedron subdivision already.

by a pair of point charges on the unit sphere connected by a “rigid rod” through the origin. In equilibrium the sum of repulsive Coulomb forces, the Riesz s-energy with \( s = 2 \) (“\( s_2 \)-energy”) [62],

\[
C_F = \sum_{i=1}^{2N} \sum_{j>i}^{2N} |\mathbf{u}_i - \mathbf{u}_j|^{-3}, \quad s = 2,
\]  

(A.1)
is minimised. The unit directions, \( \mathbf{u}_{1,...,N} \), are finally distributed as uniformly as possible with the given boundary conditions (minimisation algorithm, random initialisation, max. number of iterations, etc.). These schemes will be referred to as ‘CFminN’ schemes in the following. Note that due to the double sum in Eq. (A.1) the computation of \( s_2 \)-energies becomes increasingly challenging with respect to memory and computation speed if \( N \) grows (cf. Table 5.1).

A.3. Analytical Schemes (“Spiral”)

In particular, the latest advances of diffusion imaging techniques that require multiple q-shell HARDI acquisitions such as “Hybrid Diffusion Imaging”, “Exact Q-ball Imaging”, “Generalized Q-Sampling Imaging”, “Multiple q-shell diffusion propagator imaging”, “Bessel Fourier Orientation Reconstruction”, “Model-based analysis of multishell diffusion MR data for tractography”, etc. [47, 51, 125–128] – optionally with adapted angular resolution [129] – make the use of
analytical or deterministic direction schemes very appealing. These scheme types offer valuable flexibility in experimental planning because they instantaneously provide exactly the maximum number of directions that makes the best use of available scan time. Comparable flexibility using CFmin schemes would require the preparation and storage of lookup tables for all reasonable natural numbers. Unfortunately, just as the related spherical packing problem\(^1\), distributing directions isotropically in space is a mathematical problem that has still not been solved analytically \([62]\). In this work an approximately uniform, analytical spherical spiral algorithm \([131]\) was modified to enforce antipodal symmetry, as required for diffusion weighting \([132]\), by using only points of the upper hemisphere as described in ref. \([133]\). The simplicity of this spiral scheme comes at the expense of slightly inhomogeneous point density over the sphere in particular at the poles and the equator (cf. Fig. 5.2). Such schemes will be referred to as ‘SpiralN’.

\(^1\)Thomson’s “plum pudding problem” \([130]\) or Tammes’s “hard-spheres” problem of maximising the minimum distance between pairs of points on a sphere \([62]\)
Appendix B.

Generalisation of Diffusion Parameter Responses for Anisotropy Analysis

Previously, two-dimensional response surfaces have been utilised to study encoding scheme dependent DTI error anisotropy (e.g. [36, 37, 63]). Such response surfaces usually displayed the mean, the standard deviation or a certain percentile of the rotationally invariant diffusion parameter under investigation (e.g. fractional anisotropy or angular error) as a function of diffusion orientation. Generally, DTI accuracy and precision depend on diffusion orientation with respect to the employed encoding scheme. Figure 6.1 shows, as an example, two-dimensional $FA$ standard deviation responses as a function of fibre azimuth and inclination. Utilising the response concept well performing DTI scheme types and the optimal number of diffusion encoding directions that minimise the response variance over all fibre orientations have been identified [36, 37, 63].

For diffusion MRI methods that are sensitive to multiple non-parallel fibres, such as spherical deconvolution [41] or $q$-ball imaging [28], three-dimensional responses are required due one extra rotational degree of freedom. In the following, a generalised definition for $n$-dimensional response functions is given. Details on how to adequately asses and analyse such responses will then follow.

B.1. Definition: Response Function

Scheme specific$^1$ functions, $f : X \rightarrow \mathbb{R}$, that map an estimate or precision metric such as the standard deviation or the expected value of $A$ on the space of all possible diffusion (fibre) orientations, $X$, will be referred to as “responses”. Here, $A$ denotes a rotationally invariant diffusion parameter such as the fractional anisotropy index ($FA$) or the generalised fractional anisotropy index ($GFA$).
anisotropy (GFA). In that sense, the response \( f(x) \) characterises the probability distribution of \( A \) as a function of \( x \in X \). These fibre orientations (relative to the scheme) could be determined by inclination and azimuth, \( x = (\theta, \varphi) \), or three Euler angles, \( x = (\alpha, \beta, \gamma) \in X \), for instance. Assuming arbitrary fibre constellations, this would correspond to \( X = [0, \pi/2] \times [0, 2\pi) \) or \( X = [0, 2\pi) \times [0, \pi/2] \times [0, 2\pi) \), respectively\(^3\). Since \( A \) is supposed to be rotationally invariant, any observed response variation is definitely caused by the underlying scheme geometry. As already indicated, conventional response examples are the standard deviation, \( f(x) = \sqrt{\text{Var}[A](x)} = \sigma(x) \), or the expected value, \( f(x) = \mathbb{E}[A](x) = \mu(x) \). However, the response could as well refer to the median or alternative measures of statistical dispersion such as the “cone of uncertainty” [41, 134].

### B.2. Ideal, Biased and Realistic Responses

Fig. B.1 illustrates the variability of a hypothetical two-dimensional response on three examples: a noise-free experiment without systematic errors (“ideal”), a noise-free experiment including intrinsic systematic errors (“biased”) and a noisy experiment including both systematic and statistical errors (“realistic”).

An ideal experiment, in which all observations correspond to the ground truth, no matter how the fibre structure is oriented (\( \mu = a_0 \) and \( \sigma = 0 \) for all \( x \in X \)), is represented by the distribution

\(^2\text{synonym for “probability density function” in this context}

\(^3\text{Due to the symmetry of diffusion \( \pi/2 \) rotation for inclination or second Euler angle in \( z/y/z \)-convention suffices.}
B.2. Ideal, Biased and Realistic Responses

illustrated in Fig. B.1(a) top. Any noise-free DTI simulation with pure Gaussian diffusion using any adequate encoding scheme (six noncoplanar directions or more) would correspond to such case because the modelled diffusion tensor can be fitted exactly for all diffusion orientations. The system of linear equations for diffusion tensor estimation is well-posed in such a noise-free scenario.

If an intrinsic error is already made within the measurement or basic data processing, on the other hand, the estimates can be systematically biased depending on fibre orientation, \( \mu = a_0 + \delta(x) \), even without noise, as illustrated in Fig. B.1(b). For example, noise-free QBI simulations, will not be able to exactly reproduce the well defined ground truth orientation density function (ODF). The reconstructed ODF is, amongst others, intrinsically dependent on the choice of \( b \)-value and on the encoding scheme, as demonstrated in chapter 6. Also, the set of directions used to sample the reconstructed ODF for maxima detection or conventional computation of the generalised fractional anisotropy (GFA) displays a considerable source of orientation dependent bias introduced during post processing, as shown in section 6.2.3.

Finally, Fig. B.1(c) illustrates the most general, realistic case in which noisy raw signals result in observations with varying mean, \( \mu = a_0 + \Delta(x) \), and varying standard deviation, \( \sigma(x) > 0 \). Noisy DTI and QBI simulations as performed below are represented by this scenario. However, as opposed to systematic DTI bias, which results from numerically solving an overdetermined system of linear equations, the QBI bias is generally a mixture of the noise effect and the intrinsic bias discussed before. In general, minimal variation of estimate and imprecision responses is desired in diffusion MRI methods.

The DTI and QBI simulations presented in this work focus on estimating the mean and the standard deviation of a diffusion measure, e.g. FA or GFA, as a function of fibre orientation. In previous DTI studies Monte Carlo simulations with 10000 sample repetitions were usually performed to approach the realistic scenario from a statistical view point and to yield good estimators for \( \mu \text{FA} \) or \( \sigma \text{FA} \) responses, for instance [36, 37, 63]. The QBI simulations performed in this work focus on both the realistic and the systematically biased-only scenarios in order to separate both effects from each other. The particular focus is on minimising the respective response anisotropy.
B.3. Definition: Response Anisotropy

A common definition of diffusion anisotropy, such as the fractional anisotropy index in DTI, is given by

\[ FA = \frac{\text{std}(\lambda)}{\text{rms}(\lambda)} \]  \hspace{1cm} (B.1)

where \(\text{std}(\lambda)\) denotes the unbiased estimator of the standard deviation over the diffusion tensor eigenvalues, \(\lambda_{1,2,3}\), and \(\text{rms}(\lambda)\) denotes the root mean squared eigenvalue. For q-ball imaging the generalised fractional anisotropy index (GFA) is defined correspondingly (cf. Eq. (4.19)). It relates the standard deviation of the ODF to the root mean square ODF [28]. These anisotropy indices range between 0 (totally isotropic) and 1 (totally anisotropic)\(^4\). A corresponding definition for the anisotropy index, \(\text{aniso}(f)\), of a general response function \(f(x)\) suggests itself:

\[ \text{aniso}(f) \equiv \frac{\text{std}(f)}{\text{rms}(f)} = \sqrt{\frac{\text{Var}[f(X)]}{\text{Var}[f(X)] + \text{E}[f(X)]^2}} = \left( 1 + \frac{1}{\text{CV}(f)^2} \right)^{-\frac{1}{2}}. \]  \hspace{1cm} (B.2)

Here, \(\text{E}[Y]\) and \(\text{Var}[Y]\) denote the expected value and the variance of a random function \(Y = f(X)\) where \(X\) denotes the random variable “fibre direction”. The definition \(\text{rms}(Y) = \sqrt{\text{E}[Y^2]}\) and the identity \(\text{Var}(Y) = \text{E}[Y^2] - \text{E}[Y]^2\) have been used. \(\text{CV}(f) = \text{std}(f)/|\text{mean}(f)|\) denotes the coefficient of variation of \(f\) over all unique fibre orientations. By rearranging one easily shows that response anisotropy and coefficient of variation are equivalent for very small anisotropies:

\[ \text{CV}(f) = \frac{\text{aniso}(f)}{\sqrt{1 - \text{aniso}(f)}} \approx \text{aniso}(f) , \quad \text{if } \text{aniso}(f) \ll 1 . \]  \hspace{1cm} (B.3)

B.4. Response Sampling

The computation of the response coefficient of variation, \(\text{CV}(f)\), entering Eq. (B.2) implies the computation of the mean and the standard deviation of the parameter \(f\) over all simulated fibre orientations. A dilemma is encountered here: if the simulated fibre orientations, \(x_i\), were not distributed isotropically and the varying sampling density was ignored, the rather arbitrary orientation between tested encoding schemes and simulated diffusion orientations would clearly bias the resulting index of scheme anisotropy\(^5\).

It is sensible to review some options on how to minimise the effect of response sampling\(^4\) e.g. if the diffusion tensor resembles one delta peak or the ODF resembles one or more delta peaks

\(^4\)Recall that distributing directions isotropically is the central problem discussed here.
B.4. Response Sampling

Table B.1. Fibre distribution strategies considered to appropriately deal with non-isotropic response sampling. The response samples are the simulated fibre orientations with respect to the employed encoding scheme.

<table>
<thead>
<tr>
<th>Option</th>
<th>Con</th>
<th>Pro</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Regular polar grid of fibre angles [36, 37, 63]</td>
<td>High oversampling of north pole region; Weighted statistics mandatory.</td>
<td>Simple implementation; Analytical weighting function; More samples than required.</td>
</tr>
<tr>
<td>(b) “Near-isotropic” distribution of fibre orientations by numerical optimisation</td>
<td>Computation of directions time consuming; Residual anisotropy depending on termination condition.</td>
<td>No more and no less samples than required; Weighting factors for residual anisotropy numerically accessible using spherical Voronoi cells [64].</td>
</tr>
<tr>
<td>(c) Monte Carlo distribution of fibre orientations</td>
<td>A posteriori definition of sampling grid required; Multiple assignment of the same samples to different, overlapping bins (cones about directions); Varying numbers of samples per final bin.</td>
<td>No bias due to non-isotropic response sampling.</td>
</tr>
</tbody>
</table>

first. An overview over the advantages and disadvantages of three obvious strategies considered for this work is provided by table B.1: (a) regular polar grid of response samples, (b) “Near-isotropic” distribution of fibre orientations by numerical optimisation, and (c) Monte Carlo distribution of fibre orientations.

Here, option (a) and (b) are selected for the DTI and QBI simulations presented in chapter 6, respectively. Thereby the amount of data storage and memory is kept under a reasonable level. Furthermore, response blurring due to overlapping, conical response sampling bins accompanying option (c) is prevented. Option (a) and (b) correspond to a manageable number of predefined fibre orientations, say $N_F$, with $N_{MC}$ repeated signal simulations per encoding directions, whereas with option (c) one would have to deal with at least $N_F \times N_{MC}$ different fibre orientations for comparable statistical robustness – however, the disadvantages listed in table B.1 would remain. Furthermore, it appeared useful to restrict the Monte Carlo component to the noise added to each signal. Throughout this work we consider 10000 signal simulations per predefined fibre orientation to be sufficient for reliable statistics.

The number of fibre orientations required to sufficiently sample the scheme specific responses depends on the response sampling strategy, (a) or (b), and on the angular resolution of the employed encoding schemes. DTI and QBI responses can be expected to vary at worst at the angular resolution that corresponds to the largest number of encoding directions used. In order not to undersample these responses the angular resolution of a hypothetical, perfectly isotropic...
scheme with $N$ directions is first approximated.

From ref. [62] one finds an estimate for the expected “maximised minimal distance” between the vertices of an isotropic distribution of $2N$ points on the unit sphere ($\sim N$ directions according to the Jones model of directions): $\delta_{2N} = \sqrt{\frac{4\pi}{N\sqrt{3}}}$. By utilising the relation $\delta_{2N} = 2\sin(\alpha/2)$ between a chord length and the corresponding angle on the unit sphere and by assuming large $N$ the average angle between the scheme directions is

$$\alpha = 2\arcsin\left(\sqrt{\frac{\pi}{N\sqrt{3}}}\right) \approx \sqrt{\frac{4\pi}{N\sqrt{3}}} = \delta_{2N}. \quad \text{(B.4)}$$

As a consequence, response sampling must at least be performed with an average angle of $\alpha/2$ between sampling points. For option (a) “Regular polar grid of fibre axngles” the maximum regular angle increment is thus:

$$\Delta\Theta = \Delta\Phi \leq \frac{\alpha}{2} = \sqrt{\frac{\pi}{N\sqrt{3}}}. \quad \text{(B.4)}$$

This corresponds to sufficient sampling in the equatorial region (with the lowest sampling density) and oversampling at the poles (cf. Fig. 6.2a). Due to the symmetry of diffusion signals the distribution of fibre orientations over one hemisphere is sufficient. The minimum number of response samples with option (a) can thus be approximated as

$$N_{F}^{(a)} \geq \frac{2\pi}{\Delta\Phi} \cdot \frac{\pi}{2\Delta\Theta} = \sqrt{3}\pi N \approx 5.441N. \quad \text{(B.4)}$$

For option (b) “Near-isotropic, numerical fibre orientations” Eq. (B.4) (as well as simple geometrical considerations) require an isotropic distribution of at least four times more fibres than the encoding scheme, thus:

$$N_{F}^{(b)} \geq 4N. \quad \text{(B.4)}$$

In conclusion, both oversampling the polar region by choosing a regular polar grid and not oversampling the polar region by choosing numerically optimised fibre directions can be beneficial. The first allows for a simple simulation design whereby the inherent sampling density variation can be compensated for analytically. The latter is computationally advantageous, in particular when investigating response anisotropies for schemes with large $N$, because more than 25% of fibre orientations can be saved. Furthermore, the computation of the coefficient of variation does not necessarily require a sampling density compensation as the samples are already distributed as isotropically as possible. However, as shown in section 6.1.1, residual sampling anisotropy can be considered by numerically computing the spherical areas of the
Voronoi cells [64] surrounding each response sampling point (these areas are proportional to the respective solid angles and thus display an adequate weighting factor for each sampling point).
Appendix C.

DISCOBALL Implementation in MATLAB

```matlab
% USAGE: scheme = DISCO(N[, tag]);
% 
% Input args:  [N]
%  Requested number of isotropically distributed coordinates
%  on the unit sphere (in default mode).
%  [tag]
%  (optional) string
%   - 'total' (default): DISCOBALL scheme with N directions or
%   - 'polar': DISCOBALL scheme with n=N latitudes. The final
%     number of directions corresponds to the optimal
%     configuration with n latitudes.
% Output args: [scheme]
%  N x 3 matrix with Cartesian direction coordinates on the
%  unit sphere, where N is the number of directions.

% Copyright (C) 2012 Ruediger Stirnberg

function s = DISCO(N, tag)
    % if nargin<2
    %   bNisNtheta=false;
    % else
    %   if strcmpi(tag,'polar')
    %     bNisNtheta=true;
    %   elseif isempty(tag) || strcmpi(tag, 'total')
    %     bNisNtheta=false;
    %   else
    %     error('tag must be either ''polar'' or ''total''');
    % end
    % end
    % geometry factor
    alpha=30;
    epsilon = 1/cosd(alpha/2) - 1;
```
if bNisNtheta
  \% The specified N is actually the number of latitudes, 
  \% so distribute the coordinates as good as possible.
  n0 = N;
  N = []; 
  k_ = zeros([1 floor(n0*0.5)]);
  n_ = n0;
  for i=1:floor(n0*0.5)
    \% Determine the number of points per latitudinal circle
    if i==n0*0.5
      k_(i) = round(0.5*pi/asin(sin(pi/n0/2)/sin(i*pi/n0)));
    else
      k_(i) = round(pi/asin(sin(pi/n0/2)/sin(i*pi/n0)));
    end
  end
  \% This is the more common case, where N specifies the final number
  \% of coordinates. Here, the best number of latitudinal circles has
  \% yet to be found. This also depends on the actual distribution of
  \% points on all latitudinal circles.
  tmp= pi / ( 4 * (1+epsilon) * (N-1) );
  n0 = pi / ( 2 * acos(-tmp + sqrt(tmp^2+1) ) );
  n0 = [floor(n0), ceil(n0)];
  \% init. final parameters
  m_=inf; \% best mean squared distance error (1 x 1)
  n_-[]; \% best number of latitudinal circles (1 x 1)
  k_-[]; \% best population of lat. circles (n_- x 1)
  s=zeros([N 3]); \% coordinates computed finally (N x 1 each)
  for n=n0
    \% n/2 (max. lat. circle in upper hemisphere)
    nhalf = floor(n*0.5);
    \% mean n.n. distance
    d0 = 2*(1+epsilon)*sin(pi/2/n);
    \% reasonable population range per latitude
    k = repmat((1:4*n),[nhalf 1]);
    \% latitude index matrix of same size
    i = repmat((1:nhalf)',[1 size(k,2)]);
    \% corresponding distances
    d = 2*sin(i*pi/n).*sin(pi./k);
    if ~mod(n,2) \% equator
      d(end,:) = 2*sin(i(end,:)*pi/n).*sin(pi./k(end,:)/2);
    end
    \% corresponding squared errors
    e = (d0-d).^2;
    [e ind] = sort(e,2);
    \% sort population per lat. circle according to least error
    for i=1:nhalf
      k(i,:) = k(i,ind(i,:));
end

% optimal parameters for given n(l):
E = e(:,1);
K = k(:,1);
N0 = 1 + sum(K);

% optimal population for given n -> best population for given N:
i2 = []; e2 = []; k2 = [];
Ndiff = N0 - N; % if actual - desired number is zero, we’re done!
if Ndiff == 0
  % if difference is not zero, we have to modify the configuration.
  for i=1:nhalf
    if Ndiff > 0
      % indices available for population reduction
      tmpj = find(k(i,:) < K(i));
    else
      % indices available for population increase
      tmpj = find(k(i,:) > K(i));
    end
    i2 = cat(2, i2, i * ones(size(tmpj)));
    e2 = cat(2, e2, e(i, tmpj));
    k2 = cat(2, k2, k(i, tmpj));
  end

  % change total number by Ndiff, but only on those lat. circles, % where the corresponding error made is least.
  [e2, ind] = sort(e2);
  k2 = k2(ind);
  i2 = i2(ind);

  % update best parameters for given n and N
  E(i2(1:abs(Ndiff))) = e2(1:abs(Ndiff));
  K(i2(1:abs(Ndiff))) = k2(1:abs(Ndiff));
end

% mean squared error
m = sum(E .* (K - 1)) / N;

% update final parameters for given N
if m < m_
  m_ = m;
  n_ = n;
  k_ = K;
end

% Final computation of coordinates according to defined configuration.
s(1,:) = [0 0 1];
o = 1;
for i=1:floor(n_*0.5)
  j = (1:k_(i))';
  s(i,:) = [0 0 1];
end

end
theta = i*pi/n_; 
if i<n_*.5 
    phi = (i/2+j)*2*pi/k_(i); 
else % equator 
    phi = (i/2+j)*pi/k_(i); 
end 
st = sin(theta); ct = cos(theta); 
sp = sin(phi); cp = cos(phi); 
s曜日:o:曜日(1),1 = st*cp; 
s曜日:o:曜日(1),2 = st*sp; 
s曜日:o:曜日(1),3 = ct; 
o=o+k_(i); 
end 
end
Appendix D.

Established Methods for Accelerated Echo Planar Imaging

In this section, three established EPI techniques are summarised, which were fundamental for the implementation of tailored EPI for ultra-high fields in this work: ramp sampling, parallel imaging and echo time shifting for multi-shot interleaved EPI trajectories.

D.1. Ramp Sampling

As indicated in chapter 3, ramp sampling can be employed to reduce the ESP. This is useful in particular when RO gradient amplitude limits are not yet hit. With ramp sampling the sampling period as well as the readout (RO) bandwidth per pixel (dwell time of the receiver analogue-to-digital converter) are typically unchanged. The total gradient duration is however reduced symmetrically with respect to the sampling window. Thus, parts of the signal are acquired during the end of the ramp up and the beginning of the ramp down which enclose the RO flat-top (cf. Fig. D.1). Here, these durations are denoted ramp sampling time, \( \tau \). In order to still yield the correct RO gradient moment during sampling under the non-rectangular gradient shape (identical to the moment without ramp sampling) the gradient amplitude must be increased. The physical limits of the scanner hardware and safety regulations display strong restrictions in this context. In the following, analytic expressions are derived for the maximum available ramp sampling time.

First, a fixed readout sampling time, \( T \), and RO gradient slew rate (rate of gradient amplitude change), \( s \), are assumed. For maximum time efficiency the latter is generally chosen as large as possible without hitting the gradient limits (typically \( s = s_{\text{max}} = 200 \text{ mT/m/ms} \)) and without causing peripheral nerve stimulation. The original flat-top moment of the RO gradient, i.e. the exact moment during signal acquisition, corresponds to the correct \( k \)-space trajectory for the
actual voxel size,

\[ M = \frac{2\pi}{\gamma} \cdot (k_{\text{max}} - k_{\text{min}}) = G \cdot T \quad . \tag{D.1} \]

With ramp sampling the area under the non-rectangular gradient shape with a larger gradient amplitude, \( G' \), is

\[ M' = G' \cdot T - \tau^2 s \quad . \tag{D.2} \]

according to Fig. D.1. Here, the ramp sampling time, \( \tau \), was used to express the gradient amplitude difference from ramp sampling start to flat-top start, \( \tau s \), via the fixed slew rate. Equating Eqs. (D.1) and (D.2) yields the required gradient amplitude as a function of ramp sampling time

\[ G'(\tau) = G + \frac{\tau^2 s}{T} \quad . \tag{D.3} \]

From the gradient limitation, \( G \leq G_{\text{max}} \) (typically \( G_{\text{max}} = 40/\sqrt{3} \text{mT/m} \)) follows an upper limit for realisable ramp sampling times, \( \tau \leq \sqrt{(G_{\text{max}} - G) T/s} \). This proves that only little benefit can be gained from ramp sampling if the prepared RO amplitude is already close to the gradient amplitude limit.

If a given (minimum) blip gradient ramp time, \( t_b \), is additionally considered, the ramp sampling time is further restricted. The sum of both must equal the ramp time of the new RO gradient,

\[ t_b + \tau = \frac{G'}{s} = \frac{G}{s} + \frac{\tau^2}{T} \quad , \]
whereby Eq. (D.3) has been used. This is easily rearranged to

$$\tau(t_b) = \frac{T}{2} \pm \sqrt{\frac{T^2}{4} + \left(t_b - \frac{G}{s}\right)T}.$$  \hspace{1cm} (D.4)

Here, only the solution with the minus sign is considered since ramp times larger than half of the total sampling time are unphysical. Since also imaginary solutions are invalid, a lower limit for blip durations with ramp sampling is given by: \(t_b \geq G/s - T/4\). Inserted into Eq. (D.4) this yields a second upper limit for the ramp sampling time, \(\tau \leq T/2\). The rather unconventional case \(\tau = T/2\) corresponds to a triangular RO gradient shape. Compared to the echo spacing without ramp sampling, \(ESP(\tau = 0) = T + 2G/s\), the echo spacing with such extreme ramp sampling, \(ESP(\tau_{\text{max}} = T/2) = T/2 + 2G/s\) would in fact correspond to a maximal time saving of half the signal acquisition time. However, this is usually prevented by the gradient amplitude limitations.

### D.2. Parallel Imaging

As discussed in chapter 2, the image- or \(k\)-space-based parallel imaging techniques SENSE [7] and GRAPPA [8] can facilitate considerable imaging acceleration. In particular for EPI, parallel imaging is extremely valuable: if \(R\) denotes the nominal “acceleration factor” (only every \(R\)th line is acquired) the bandwidth in blipped phase encode (PE) direction approximately equals the bandwidth without imaging acceleration multiplied by \(R\). Thus, susceptibility-induced geometric distortions are reduced by the same factor. Of course, also the total imaging time reduces considerably. Here, only the considerations for GRAPPA are discussed as only this method has been implemented in this work. While partial Fourier acquisition is readily compatible to EPI without requiring any significant sequence modifications (shortened EPI trajectory from \(k_{\text{min}}\) to \(k_{\text{PF}} < k_{\text{max}}\)), the introduction of parallel imaging capability requires a few additional implementations.

First, the acquisition of a reduced number of parallel imaging (blipped PE) lines with increased gaps requires a larger blipped PE gradient moment. The triangular gradient pulse has to be prolonged if the increased gradient moment cannot be obtained by (only) increasing the pulse amplitude. This is restricted by the system capabilities (typically \(G_{\text{max}} = 40/\sqrt{3} \text{ mT/m}\)) and peripheral nerve stimulation limits. The latter in particular also limits the maximum slew rate (typically \(s_{\text{max}} = 200 \text{ mT/(m\cdot ms)}\)). A prolonged blip duration affects the available time for ramp sampling or generally results in increased echo spacing (ESP). This ESP prolongation is however negligible compared to the valuable increase of the effective blipped PE bandwidth.
Appendix D. Established Methods for Accelerated Echo Planar Imaging

Figure D.2. Illustration of EPI $k$-space trajectories for GRAPPA imaging acceleration by a factor of $R = 2$. The fully sampled GRAPPA reference scans are acquired prior to the undersampled imaging scans. (a) depicts the case of a single-shot imaging scan (1) which requires a two-shot reference scan (1,2). (b) depicts the case of a two-shot imaging scan (1,1) which requires a four-shot reference scan (1,2,3,4). For details on multi-shot EPI cf. Fig. D.3.

Second, the quality of the GRAPPA $k$-space interpolation kernel has a direct influence on the reconstructed image quality. Large SNR for the GRAPPA reference (autocalibration) scans can, for instance, be ensured by acquisition at minimum echo time (cf. section 8.1.2). This also minimises the amount of signal drop outs in regions with critical susceptibility gradients. While different image contrast in reference scans is not relevant, it is crucial that these are acquired on the basis of the same imaged object (the receive sensitivities within the entire object must be obtainable). To guarantee identical image distortions for the undersampled imaging scans and the reference scans, the latter have to be performed with the same effective bandwidth in blipped PE direction. This can be achieved by segmenting the fully sampled, central reference scans into $R$ interleaved shots as depicted in Fig. D.2a. If already the imaging scans are segmented into $N_i$ interleaves, as discussed in section 8.1.1, the reference scans have to be segmented into $R \times N_i$ interleaves, as illustrated in Fig. D.2b for $R = 2$ and $N_i = 2$. In section 8.1.2 this aspect is investigated in more detail.

D.3. Echo Time Shifting for Multi-Shot EPI

A requirement to avoid ghosting artefacts in interleaved EPI acquisitions such as multi-shot reference scans for parallel image reconstruction is a technique called echo time shifting (ETS) [94]. The three-dimensional $k$-$t$-diagrams in Fig. D.3 display different EPI trajectories that illustrate the idea of echo time shifting. Let $t_{ESP}$ denote the echo spacing between the acquisition of two subsequent lines in PE direction. With ETS the gradient course of the $n$th of $N_i$ total shots is delayed by $(n-1) t_{ESP}/N_i$ to ensure a continuous signal magnitude and phase evolution along the central $k$-space column for all phase encode coordinates (cf. Fig. D.3c). Without ETS signal discontinuities in the $k$-space centre every $N_i$th line (cf. Fig. D.3b) would result in repeated
image ghosting artefacts with a spatial frequency of \( \text{FOV}_{PE}/N_s \) in PE direction. Note that ETS cannot prevent discontinuities at the \( k \)-space edges. This, however, only leads to high frequency ghosting artefacts, which are usually considered negligible [94].

Figure D.3 indicates that, apart from reducing geometric image distortions due to shorter effective ESP (increased PE bandwidth), multi-shot EPI also facilitates shorter echo times due to an \( N_s \)-fold reduction of the echo train length (ETL). Both is valuable for ultra-high field applications. It should however be mentioned that the total acquisition time increases with a larger number of shots. This is due to an overhead of time spent on fat-saturation, excitation, phase correction scans, phase encoding, fill times and spoil times attached to each EPI readout.

Figure D.4 demonstrates, by means of representative 2D-EPI resolution phantom images acquired with an increasing number of shots for varying voxel sizes (varying ETL), the effective reduction of geometric distortions by using \( N_s > 1 \) shots. Adequate echo time shifting was employed in all cases. From top to bottom: single-shot, two and four shots. From left to right: 1 mm, 1.5 mm, 2 mm and 3 mm in-plane resolution. All other parameters, mainly determined by the most demanding 1 mm acquisition, were kept constant: 3 mm slice-thickness, bandwidth = 977 Hz/px, \( TE/TR = 140 \text{ ms}/2000 \text{ ms} \), FOV = 240 × 240 mm\(^2\), flip angle = 90°. For the lower spatial resolutions larger readout bandwidths could hypothetically be realised which would then lead to reduced geometrical distortions. For the sake of comparability, however, this parameter was fixed throughout the experiment. Note that the actual, spatial pixel shifts decrease disproportionally to the actual pixel size. Hence, the actual deformation in real space units (mm) is the same for constant \( N_s \) and constant FOV. The grey scale is identical for all images.
Figure D.4. Experimental demonstration of the reduction of geometric distortions by means of multi-shot EPI acquisitions (1, 2, 4 shots from top to bottom) for varying spatial resolutions (1, 1.5, 2, 3 mm in-plane resolution from left to right). With larger voxel sizes increasing signal drop outs become very obvious, in particular when comparing the 3 mm images with the 1 mm images with the same (rather long) echo time. The drop outs are minimised when choosing short echo times (rightmost column). shown except for the right-most 3 mm data, which was obtained with a reasonably short echo time of $TE = 35\,$ms and thus provides considerably higher SNR. Compared to the corresponding $TE = 140\,$ms images, signal drop outs are significantly reduced. All data were obtained at 3 Tesla. Ramp sampling was enabled but neither partial Fourier nor parallel imaging was employed.
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