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Mapping of T1, MT saturation and local flip angle

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# Gradient echo-based quantitative MRI of human brain at 7T

Mapping of T1, MT saturation and local flip angle

HAMPUS OLSSON DEPARTMENT OF MEDICAL RADIATION PHYSICS | LUND UNIVERSITY



## Gradient echo-based quantitative MRI of human brain at 7T

In this thesis, the process of implementing and optimizing quantitative magnetic resonance imaging (qMRI) methodologies based on spoiled gradient-recalled echo (GRE) pulse sequences for whole brain imaging at 7T is described. The thesis tackles 7T-specific challenges in qMRI, especially the increased inhomogeneities of the radio frequency (RF) field (B1) and increased specific absorption rate (SAR). Special attention is given to the mapping of two structural MR parameters linked to longitudinal magnetization, namely T1 and the semi-quantitative magnetization transfer saturation (MTsat) metric. The mapping is performed using either standard spoiled GRE sequences or MPRAGE-based techniques. Emphasis is also put on mapping of the local flip angle, critical for many qMRI methodologies.



Hampus Olsson is a licensed medical physicist and received his M.Sc. in medical radiation physics in 2014.



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Gradient echo-based quantitative MRI of human brain at 7T

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## Mapping of T1, MT saturation and local flip angle

Hampus Olsson



### DOCTORAL DISSERTATION

by due permission of the Faculty of Science, Lund University, Sweden. To be defended at Lundmarksalen, Astronomihuset, Sölvegatan 27, Lund, Friday the 29<sup>th</sup> of October 2021 at 9:00 a.m.

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Gradient echo-based quantitative MRI of human brain at 7T: Mapping of T1, MT saturation and local flip angle

#### Abstract

Quantitative MRI (gMRI) refers to the process of deriving maps of MR contrast parameters, such as relaxation times, from conventional images. If the qMRI maps have a high degree of precision and a low degree of bias, they can be compared longitudinally, across subjects, and (ideally) between measurement protocols and research sites. They also provide a more direct biophysical interpretation of the pixel intensities.

The increased magnetization of spins at ultra-high field (UHF) strengths of 7T and above could potentially be translated into higher spatial resolution and/or reduced scan time. This thesis tackles UHF-related challenges in qMRI, namely the increased inhomogeneity of the radio frequency (RF) field (B1) and increased specific absorption rate (SAR). The changing relaxation times (i.e. prolonged T1 and shortened T2) also needs to be accounted for.

Here, spoiled gradient-recalled echo (GRE) techniques are employed to map (primarily) two structural MR parameters, i.e. the longitudinal relaxation time (T1) and the magnetization transfer (MT) saturation (MTsat). Because of its influence at UHF, emphasis is also put on mapping of the local flip angle. Primarily, gMRI is performed by the inversion of analytical signal equations, as opposed to numerical approaches.

The process of implementing and modifying the dual flip angle (DFA) technique in conjunction with an MTweighted GRE for 7T is described. Implementation is performed within the well-established multi-parameter mapping (MPM) framework and special attention is afforded to the reduction of biases as well as overcoming saftey restrictions imposed by SAR. An approach to obtain high-SNR low-bias flip angle maps at 7T, using the dual refocusing echo acquisition mode (DREAM) technique is also presented. This is important since high fidelity flip angle maps are a prerequisite in DFA-based T1-mapping and recommended for correcting MTsat at UHF. Furthermore, MPRAGE-based techniques are discussed. Firstly, it is demonstrated how to most effectively obtain B1-corrected MPRAGE images of "pure" T1 contrast using a sequential protocol This is followed by a description of T1-mapping using MP2RAGE. Finally, an innovative technique for simultaneous mapping of T1 and the local flip angle is introduced, dubbed "MP3RAGE".

Key words: T1, MT, Ultra-high field, 7T, spoiled gradient echo, human brain, B1 mapping, dual flip angle, MPRAGE, longitudinal relaxation

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Hampus Olsson



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## Abstract

Quantitative MRI (qMRI) refers to the process of deriving maps of MR contrast parameters, such as relaxation times, from conventional images. If the qMRI maps have a high degree of precision and a low degree of bias, they can be compared longitudinally, across subjects, and (ideally) between measurement protocols and research sites. They also provide a more direct biophysical interpretation of the pixel intensities.

The increased magnetization of spins at ultra-high field (UHF) strengths of 7T and above could potentially be translated into higher spatial resolution and/or reduced scan time. This thesis tackles UHF-related challenges in qMRI, namely the increased inhomogeneity of the radio frequency (RF) field (B1) and increased specific absorption rate (SAR). The changing relaxation times (i.e. prolonged T1 and shortened T2) also needs to be accounted for.

Here, spoiled gradient-recalled echo (GRE) techniques are employed to map (primarily) two structural MR parameters, i.e. the longitudinal relaxation time (T1) and the magnetization transfer (MT) saturation (MTsat). Because of its influence at UHF, emphasis is also put on mapping of the local flip angle. Primarily, qMRI is performed by the inversion of analytical signal equations, as opposed to numerical approaches.

The process of implementing and modifying the dual flip angle (DFA) technique in conjunction with an MT-weighted GRE for 7T is described. Implementation is performed within the well-established multi-parameter mapping (MPM) framework and special attention is afforded to the reduction of biases as well as overcoming safety restrictions imposed by SAR. An approach to obtain high-SNR low-bias flip angle maps at 7T, using the dual refocusing echo acquisition mode (DREAM) technique is also described. This is important since high fidelity flip angle maps are a prerequisite in DFA-based T1-mapping and recommended for correcting MTsat at UHF. Furthermore, MPRAGE-based techniques are discussed. Firstly, it is demonstrated how to most effectively obtain B1-corrected MPRAGE images of "pure" T1 contrast using a sequential protocol This is followed by a description of T1-mapping using MP2RAGE. Finally, an innovative technique for simultaneous mapping of T1 and the local flip angle is introduced, dubbed "MP3RAGE".

# Populärvetenskaplig sammanfattning

Största delen av den mänskliga kroppen består av vatten. Vattnets kärnmagnetiska egenskaper utnyttjas inom magnetresonanstomografi (MRT) till att avbilda kroppens insida. Jämfört med till exempel röntgen är MRT mycket bra på att urskilja olika sorters mjukvävnad såsom vit och grå hjärnsubstans. I konventionell MRT är pixelvärdena i den digitala bilden av en arbiträr natur och kan vara svåra att tolka. Utöver detta är konventionella MRT-bilder generellt sett inte jämförbara när de har upptagits vid olika tillfällen eller med olika magnetkameror. Detta är ett problem både inom forskning och i kliniska tillämpningar, exempelvis när en läkare vill följa hur en patient svarar på en viss behandling.

Kvantitativ MRT använder matematiska samband mellan den uppmätta signalen, inställningar på magnetkameran, och underliggande egenskaper hos den avbildade vävnaden till att beräkna dessa vävnadsspecifika egenskaper. De olika "MRparametrarna" är känsliga för olika förhållanden i kroppen, till exempel mängden järn eller hur friska nervtrådarna är. Genom kvantitativ MRT omvandlas magnetkameran från att vara "bara en kamera" till ett vetenskapligt mätinstrument från vilket "kartor" över vävnadsspecifika parametrar kan erhållas. Två centrala MR-parametrar i denna avhandling är den "longitudinella relaxationstiden,  $T_1$ " samt "magnetization transfer saturation".

Alla magnetkameror genererar ett statiskt magnetiskt fält som alltid är aktivt. Styrkan på detta fält anges i enheten tesla (T) och är på kliniska kameror vanligtvis 1.5 T eller 3.0 T. Ett starkare magnetiskt fält betyder generellt en högre signal vilket kan användas till att öka detaljskärpan (upplösningen) och/eller minska undersökningstiden. En högre fältstyrka kan dock även innebära svårigheter eftersom den uppmätta signalen tenderar att bli olika stark på olika ställen i kroppen. Ett annat potentiellt problem är att uppvärmningen av kroppen under undersökningen ökar.

I denna avhandling har olika kvantitativa MRT-metoder implementerats på en magnetkamera med fältstyrkan 7 T i syfte att kartlägga de två ovanstående MRparametrarna i den mänskliga hjärnan. Arbetet har resulterat i att metoderna levererat mer exakta resultat, genom att korrigera för, eller helt undvika, olika sorters felkällor. De implementerade metoderna innefattar beprövade tekniker som modifierats utefter förutsättningarna på 7 Tesla såväl som en helt ny teknik som kan kartlägga två parametrar samtidigt.

# Original papers

The thesis is based on the following publications and manuscripts, referred to by their roman numerals:

- I. Olsson H, Novén M, Lätt J, Wirestam R, Helms G. Radiofrequency bias correction of magnetization prepared rapid gradient echo MRI at 7.0 Tesla using an external reference in a sequential protocol. Tomography 2021;7(3). doi: 10.3390/tomography7030038.
- II. Olsson H, Andersen M, Lätt J, Wirestam R, Helms G. Reducing bias in dual flip angle T1-mapping in human brain at 7T. Magn Reson Med 2020;84(3):1347-1358. doi: 10.1002/mrm.28206.
- III. Olsson H, Andersen M, Helms G. Reducing bias in DREAM flip angle mapping in human brain at 7T by multiple preparation flip angles. Magn Reson Imaging 2020;72:71-77. doi: 10.1016/j.mri.2020.07.002.
- IV. Olsson H, Andersen M, Wirestam R, Helms G. Mapping magnetization transfer saturation (MTsat) in human brain at 7T: Protocol optimization under specific absorption rate constraints. Magn Reson Med. 2021; 00: 1-15 (Early View). doi:10.1002/mrm.28899.
- V. Olsson H, Andersen M, Kadhim M, Helms G. MP3RAGE Simultaneous mapping of T1 and B1+ in human brain at 7T. Submitted to Magn Reson Med. Under revision.

## List of contributions

This is a summary of my contributions to each paper in this thesis.

- I. I participated in the experimental setup and acquisition of the data. I evaluated the data, prepared the figures and developed the lookup table approach for  $T_1$  quantification. I was the main author of the paper.
- II. I participated in the experimental setup, sequence programming and acquisition of the data. I evaluated the data, prepared the figures and developed methods for validation. I was the main author of the paper.
- III. I participated in the experimental setup and acquisition of the data. I evaluated the data and prepared the figures. I was the main author of the paper.
- IV. I participated in the experimental setup, sequence programming and acquisition of data. I evaluated the data, prepared the figures and calibrated the  $B_1^+$  correction for 7T. I was the main author of the paper.
- V. I participated in the conceptualization of the idea and took initiative to ensure its realization. I participated in the experimental setup, sequence programming and data collection. I was the main author of the manuscript.

## Papers not included in this thesis

- I. Novén M, Olsson H, Helms G, Horne M, Nilsson M, and Roll M. Cortical and white matter correlates of language-learning aptitudes. Human Brain Mapping, 2021;42(15):5037-5050. doi:10.1002/hbm.25598.
- II. Helms G, Lätt J, and Olsson H. 2020. Cross-vendor transfer and RF coil comparison of high-resolution MP2RAGE protocol for brain imaging at 7T, Acta Scientiarum Lundensia, 2020: 1-12.
- III. Lundberg A, Lind E, Olsson H, Helms G, Knutsson L, Wirestam R. Comparison of MRI methods for measuring whole brain oxygen extraction fraction under different geometric conditions at 7T. Unpublished manuscript.

# **Common Abbreviations**

BSB	Binary spin bath
CNR	Contrast to noise ratio
DFA	Dual flip angle
DREAM	Dual refocusing echo acquisition mode
EPI	Echo-planar imaging
GM	Gray matter
GRE	Gradient-recalled echo
hMRI	In vivo histology using magnetic resonance imaging
IR	Inversion recovery
LUT	Lookup table
MPM	Multi-parameter mapping
MPRAGE	Magnetization prepared rapid gradient echo
MP2RAGE	Magnetization prepared 2 rapid gradient echoes
MT	Magnetization transfer
MTR	Magnetization transfer ratio
MT <sub>sat</sub>	Manetization transfer saturation
PD	Proton density
PSF	Point spread function
qMRI	Quantitative MRI
qMT	Quantitative magnetization transfer
SAR	Specific absorption rate
SNR	Signal to noise ratio
UHF	Ultra-high field
VFA	Variable flip angle
WM	White matter

### Mathematical symbols

Mz	Longitudinal magnetization
$M_0$	Longitudinal magnetization at thermal equilibrium
$M_0^*$	Longitudinal magnetization at driven equilibrium
S	Signal amplitude
Α	Maximum signal amplitude
$A_{\mathrm{app}}$	Apparent maximum signal amplitude
$T_1$	Longitudinal relaxation time
<i>T</i> <sub>1,app</sub>	Apparent longitudinal relaxation time
$T_{1}^{*}$	Time constant with which $M_z$ approaches $M_0^*$
$T_{1.s}$	Longitudinal relaxation time biased by incomplete spoiling
$T_2$	Transverse relaxation time
$T_{2}^{*}$	Effective transverse relaxation time
TI	Inversion time
TR	Repetition time
TE	Echo time
TD	Time from last excitation to next inversion
ТС	Cycle duration
TF	Turbo factor
$\omega_1$	Amplitude of RF pulse
α	Nominal flip angle
$\alpha_{loc}$	Local flip angle
$f_{\mathrm{T}}$	Transmit field bias
$f_{\rm R}$	Receive field bias
$f_{ m inv}$	Inversion efficiency
$\delta_{ m MT}$	MT <sub>sat</sub> calculated using local flip angles
$\delta_{ m MT,app}$	MT <sub>sat</sub> calculated using nominal flip angles
$\delta_{ m MT, corr}$	MT <sub>sat</sub> corrected for residual transmit field bias
$\delta_{ m MT,inc}$	Incidental MT <sub>sat</sub> caused by excitation pulse
$\delta_{\mathrm{b}}$	Instantaneous saturation of bound pool
$\delta_{ m f}$	Instantaneous saturation of free pool
F <sub>b</sub>	Bound pool fraction
$g_{\rm b}(\Delta,T_{\rm 2b})$	Bound pool absorption lineshape
Δ	MT pulse offset frequency
$t_{ m RF}$	Duration of excitation pulse
t <sub>sat</sub>	Duration of MT pulse
Q	Pulse shape factor

## 1 - Introduction and aims

Magnetic resonance imaging (MRI) utilizes the interactions between the magnetic moments of hydrogen nuclei and externally applied electromagnetic fields to produce anatomical images of high resolution, wide coverage, and excellent soft tissue contrast. Different types of contrast can be obtained by careful tailoring of the externally applied electromagnetic fields to emphasize a particular biophysical MR parameter. Such parameters include, for instance, the longitudinal relaxation time,  $T_1$ , the transverse and effective transverse relaxation times,  $T_2$  and  $T_2^*$ , proton density (PD), magnetization transfer (MT) and diffusion. In conventional MRI, the image results from a mixture of MR parameters, but is said to be "weighted" by whichever parameter dominates the contrast. The measured signal depends nonlinearly on the MR parameters, as well as on imaging protocol, subject positioning and scanner hardware. The values of individual pixels, that collectively make up the image, thus lacks strict physical meaning and are generally not comparable across scanning sessions, subjects or research sites.

Quantitative MRI (qMRI) addresses this issue by converting the arbitrary pixel intensities into physical units to obtain a "map" of a specific MR parameter, thus transforming the MR scanner from merely an imaging device to a scientific measurement instrument. Performing qMRI generally requires the acquisition of more than one image. The images are then used to solve an inverse problem (either numerically or analytically) on a pixelwise level, thus obtaining a quantitative map (Nikolaus Weiskopf, Edwards, Helms, Mohammadi, & Kirilina, 2021). This is often followed up by some form of correction for expected biases, such as deviations from the nominal flip angle. Given that the bias is sufficiently low, and that the precision is sufficiently high, these maps can be compared in longitudinal studies, across large cohorts and (ideally) between different scanners and imaging protocols (Stikov et al., 2015; Voelker et al., 2021). Bias refers to a systematic error not accounted for in the qMRI methodology and can be estimated by comparison to a gold-standard reference technique. Precision refers to a random variability, either in a scan-rescan experiment performed during the same session and under identical conditions (repeatability) or under differing conditions such as different MRI scanners and/or separated by long-time intervals (reproducibility) (Kessler et al., 2015). It can be important to consider what degree of precision is needed for a certain purpose, and what amount of bias can be tolerated since improvements often entail an increase in scan time which is very precious in MRI.

A semi-quantitative technique refers to when the MR signal is normalized to some reference and denoted by a fraction or in percent units (p.u.). It pertains to obtain a "pure" contrast, i.e. dependent on only one MR parameter. Although it lacks a direct biophysical interpretation, and will vary based on pulse sequence parameters, it shares the improved reproducibility of a fully quantitative parameter in contrast to conventional MRI. A semi-quantitative approach is typically less time consuming than a fully quantitative one. The importance of achieving low bias and high repeatability applies to a semi-quantitative methodology as much as a fully quantitative one, and it is therefore considered a subset of qMRI in this thesis.

MRI scanners come with different strengths of the static magnetic field,  $B_0$ . Clinical MRI scanners typically operate at 1.5T or 3T. Ultra-high field (UHF) strengths refer to  $B_0$  values of 7T or above and have become increasingly prevalent in recent years (Barisano et al., 2019). Increasing  $B_0$  enhances the magnetization of the hydrogen nuclei in thermal equilibrium which generally translates into a higher signal to noise ratio (SNR) (Balchandani & Naidich, 2015). The higher SNR can alternatively be traded for either higher resolution or decreased scan time by alterations to the pulse sequence. Relaxation times change at higher  $B_0$  as  $T_1$  is prolonged while  $T_2$  and  $T_2^*$ are shortened (Oros-Peusquens, Laurila, & Shah, 2008; Rooney et al., 2007). Depending on pulse sequence and application, this can be either a benefit or a detriment. Other effects are an increased sensitivity to susceptibility effects as well as an increased separation between metabolic peaks (Ugurbil et al., 2003). Further, the spatial inhomogeneities of both the  $B_0$  field and the radio frequency (RF)  $B_1$  field increases (Stockmann & Wald, 2018; Vaughan et al., 2001). Especially the inhomogeneity of the  $B_1$  field, which governs both the local flip angle through the transmit  $(B_1^+)$  component as well as the receiver sensitivity, poses a great challenge for qMRI at 7T. Lastly, the specific absorption rate (SAR) increases quadratically with  $B_0$  which acts as a bottle neck when frequent high-power pulses are used, as in MT experiments.

In this thesis, the process of implementing and optimizing qMRI methodologies based on spoiled gradient recalled echo (GRE) pulse sequences for whole brain imaging at 7T is described. Methodologies based on both the standard spoiled GRE sequence, acquired entirely in the steady state, as well as the magnetization prepared rapid gradient echo (MPRAGE) sequence is treated. Special attention is given to the mapping of two MR parameters linked to structural MRI, namely  $T_1$  and the semiquantitative magnetization transfer saturation (MT<sub>sat</sub>) metric. Emphasis is also put on mapping of the local flip angle, critical for most qMRI methodologies at 7T.

The aims of the projects included in this thesis were to

- I. Implement and evaluate a reference GRE for normalization in MPRAGE imaging, to obtain semi-quantitative  $T_1$ -weighted images
- II. Implement and reduce bias in a dual flip angle (DFA)  $T_1$ -mapping protocol

- III. Introduce a methodology to reduce bias in dual refocusing echo acquisition mode (DREAM) flip angle mapping
- IV. Maximize MT under SAR constraints in an MT<sub>sat</sub>-mapping protocol while avoiding bias
- V. Introduce and implement a novel "MP3RAGE" approach for simultaneous mapping of  $T_1$  and the local flip angle

## 2 – Background

This chapter serves as a review of the theoretical concepts on which the work of this thesis is based. The basics of MR physics, including  $T_1$ -relaxation, is explained through the phenomenological Bloch equations (Bloch, 1946). To explain the phenomenon of MT, the Bloch equations are expanded to include exchange with a second pool of motionally restricted spins, forming the Bloch-McConnel equations (McConnell, 1958). The biophysical origin of  $T_1$  and MT is discussed, as well as some common applications in neuroscientific research. Lastly, some of the most well-established techniques used to measure  $T_1$  and MT are briefly described.

### **Bloch** equations

Hydrogen nuclei (protons) possess a spin angular momentum, **J**, which gives them a magnetic moment,  $\boldsymbol{\mu} = \gamma \mathbf{J}$ , where  $\gamma = 2\pi \times 42.58 \text{ MHz/T}$  is the gyromagnetic ratio. For an ensemble of spin isochromats, the net magnetization is denoted  $\mathbf{M} = (M_x, M_y, M_z)$ . If an external magnetic field,  $\mathbf{B} = (B_x, B_y, B_z)$ , is applied, **M** experiences a torque,  $\boldsymbol{\tau} = \mathbf{M} \times \mathbf{B}$ , causing precession around **B**. This is described by the equation of motion (Bloch, 1946):

$$d\mathbf{M}/dt = \mathbf{M} \times \gamma \mathbf{B},\tag{2.1}$$

where the angular frequency of precession is given by the Larmor equation as  $\omega = \gamma |\mathbf{B}|$ . Replacing the generic **B** by the static magnetic field  $\mathbf{B}_0 = (0,0,B_0)$  (by definition in the longitudinal direction) where  $B_0 = 7$  T, the Larmor frequency of water is obtained:

$$v_0 = \frac{\omega_0}{2\pi} = \frac{\gamma}{2\pi} B_0 = 298.06 \text{ MHz.}$$
 (2.2)

To achieve resonance, a time-varying RF field,  $\mathbf{B}_1$ , with carrier frequency  $\omega$  close to  $\omega_0$  and amplitude  $\omega_1$ , is applied perpendicular to  $\mathbf{B}_0$ . To simplify the behaviour of **M**, the rotating frame of reference is introduced which rotates like  $\mathbf{B}_1$  with  $\omega$  around  $\mathbf{B}_0$ . In this frame,  $\mathbf{B}_1 = (B_1, 0, 0)$  is fixed and **M** precesses around the oblique effective field  $\mathbf{B}_{e} = \mathbf{B}_{1} \times (\mathbf{B}_{0} - \hat{\mathbf{z}} \,\omega/\gamma)$  instead of  $\mathbf{B}_{0}$ , where  $\hat{\mathbf{z}} = (0,0,1)$  is a unit vector. Deriving the three components of **M** from Eq. (2.1) and transforming them to the rotating frame yields:

$$dM_{\rm x}/dt = (\omega_0 - \omega)M_{\rm y}, \tag{2.3a}$$

$$dM_{\rm y}/dt = -(\omega_0 - \omega)M_{\rm x} + \omega_1 M_z, \qquad (2.3b)$$

$$dM_{\rm z}/dt = -\omega_1 M_{\rm y}.$$
 (2.3c)

The precession of **M** around **B**<sub>e</sub> rotates (or nutates) **M** towards the transverse plane where a signal magnitude proportional to  $|\mathbf{M}_{xy}| = \sqrt{M_x^2 + M_y^2}$  is induced in a receiver coil. The phase  $\phi = \tan^{-1}(M_y/M_x)$  of  $\mathbf{M}_{xy}$  can also be obtained if the signal is measured in quadrature mode. In this case, the signal is complex, where the real part of the signal denotes the x-axis and the imaginary part denotes the yaxis.

The magnetization will also undergo two forms of relaxation governed by two phenomenological time constants. First, there is the longitudinal or "spin-lattice" relaxation which governs the return of  $M_z$  to its thermal equilibrium value,  $M_0$ , by  $T_1$ . Secondly, there is the transverse or "spin-spin" relaxation which describes the dephasing of the spin isochromats and subsequent decay of  $M_x$  and  $M_y$  by  $T_2 \leq T_1$ . Adding relaxation terms to Eq. (2.3) yields the full Bloch equations in the rotating frame (de Graaf, 2018):

$$dM_{\rm x}/dt = (\omega_0 - \omega)M_{\rm v} - M_{\rm x}/T_2, \qquad (2.4a)$$

$$dM_{\rm y}/dt = -(\omega_0 - \omega)M_{\rm x} + \omega_1 M_z - M_{\rm y}/T_2,$$
 (2.4b)

$$dM_{\rm z}/dt = -\omega_1 M_{\rm y} + \frac{M_0 - M_{\rm z}}{T_1}.$$
 (2.4c)

In the special case of perfect on-resonance, i.e.  $\omega = \omega_0$  and  $\mathbf{B}_{e}(t) = \mathbf{B}_{1}(t)$ , the Bloch equations simplify to:

$$dM_{\rm x}/dt = 0, \tag{2.5a}$$

$$dM_{\rm v}/dt = \omega_1 M_{\rm z} - M_{\rm v}/T_2, \qquad (2.5b)$$

$$dM_{\rm z}/dt = -\omega_1 M_{\rm y} + \frac{M_0 - M_{\rm z}}{T_1}.$$
 (2.5c)

After  $B_1$  has been applied on-resonance for a certain duration,  $t_{\rm RF}$ , there exists a fixed angle which **M** has been tilted away from the longitudinal z-axis. This angle is referred to as the flip angle:

$$\alpha = \gamma \int_0^{t_{\rm RF}} B_1(t) = \int_0^{t_{\rm RF}} \omega_1(t) dt.$$
(2.6)

Eq. (2.6) implies that  $\omega_1(t)$  can be time-dependent during  $t_{\rm RF}$ , described by the pulse shape envelope of  $B_1(t)$ . However, since  $t_{\rm RF} \ll T_2$  for many pulse sequences (hence the term RF "pulse"), the Bloch equations can often be separated into periods of instantaneous irradiation followed by periods of free relaxation. In this way, the Bloch equations can be numerically simulated using matrix operators applied to **M**. These operators are for irradiation (Yarnykh, 2010):

$$\mathbf{R} = \begin{bmatrix} 1 & 0 & 0\\ 0 & \cos \alpha & \sin \alpha\\ 0 & -\sin \alpha & \cos \alpha \end{bmatrix},$$
(2.7)

and for relaxation:

$$\mathbf{E} = \begin{bmatrix} E_2 \cos\psi_1 & E_2 \sin\psi_1 & 0\\ -E_2 \sin\psi_1 & E_2 \cos\psi_1 & 0\\ 0 & 0 & E_1 \end{bmatrix},$$
(2.8)

where  $E_1 = \exp(-TR/T_1)$ ,  $E_2 = \exp(-TR/T_2)$ , TR is the repetition time (time between excitation RF pulses) and  $\psi_1 = l \cdot 2\pi/(N-1)$  with index l = 0, 1, ..., N denoting a spatially unique phase for each of the N spin isochromats (needed to simulate  $T_2$  decay).

Under the assumption of instantaneous irradiation interspersed by intervals of relaxation, it is often possible to derive analytical signal equations from the more fundamental Bloch equations. A famous example is the Ernst equation, describing spoiled gradient echoes (Ernst & Anderson, 1966). In this thesis, qMRI was based

mainly on such signal equations. In particular, the rational approximation for small flip angles and short TR was used to facilitate the calculation of, for example,  $T_1$ , by analytical inversion (Helms, Dathe, & Dechent, 2008).

### The longitudinal relaxation time: $T_1$

#### Definition and biophysical origin

The longitudinal relaxation time,  $T_1$ , describes how rapidly the longitudinal magnetization,  $M_z(t)$ , of an ensemble of spins return to  $M_0$  after absorption of energy through RF irradiation. Relaxation is facilitated by transfer of excess energy from the spins to a "lattice" of surrounding molecules, and it is thus sometimes referred to as spin-lattice relaxation. The process is exponential and the time constant  $T_1$  is of the order of a second. Solving the longitudinal relaxation part of equations (2.4c) and (2.5c),  $dM_z/dt = (M_0 - M_z)/T_1$ , yields:

$$M_{z}(t) = M_{0} + (M_{z}(0) - M_{0})\exp(-t/T_{1}).$$
(2.9)

The presence of macromolecules as well as iron has a shortening effect on  $T_1$  (Callaghan, Helms, Lutti, Mohammadi, & Weiskopf, 2015). In vivo, myelin forms sheaths around the axons while iron is stored inside ferritin proteins or in the blood (Schenck & Zimmerman, 2004). Consequently,  $T_1$  in CSF is much longer than in tissue while white matter (WM) experiences a shorter  $T_1$  than gray matter (GM) due to its higher concentration of myelinated axons and overall macromolecular content. In cortical GM,  $T_1$  has been used as a surrogate parameter of myelination (Lutti, Dick, Sereno, & Weiskopf, 2014). Further, increased iron concentration results in slightly shorter  $T_1$  in deep brain GM compared to cortical GM (Vymazal et al., 1999). Likewise, blood shows a shorter  $T_1$  than CSF albeit not as short as tissue (Rooney et al., 2007).

#### Applications in neuroscience

Mapping of  $T_1$  can be useful in the study of demyelinating disorders such as multiple sclerosis (MS) where WM and GM that appear normal on conventional MRI have shown prolonged  $T_1$  in relapsing-remitting patients (Davies et al., 2007; Griffin et al., 2002). The connection to iron, makes  $T_1$ -mapping suitable to study Parkinson's disease (Vymazal et al., 1999) where excess iron (outside the ferritin) is prevalent (Dexter, Jenner, Schapira, & Marsden, 1992). Changes in  $T_1$  are, however, not as specific to iron as  $T_2^*$  or quantitative susceptibility mapping (QSM). It has been suggested that  $T_1$  could be more useful to study progression of Parkinson's disease in the form of general neuronal loss (Baudrexel et al., 2010), while  $T_2^*$  or QSM could be used to measure iron accumulation in the basal ganglia, specifically the substantia nigra (Baudrexel et al., 2010; Langkammer et al., 2016; Loureiro et al., 2018; Nurnberger et al., 2017). Similarly, tumor progression in glioblastoma patients has been detected earlier compared to conventional MRI by using  $T_1$ -mapping to measure the spread of malignant cells outside the gross tumor volume (Lescher et al., 2015).

### Inversion recovery (IR)

The gold-standard method for measuring  $T_1$  is a single-slice inversion recovery (IR) experiment where after inversion and a subsequent waiting period, TI, magnetization is excited into the transverse plane and measured. This is repeated for n = 1, 2, ..., N different values of TI and the acquired signal,  $S_n$ , is fitted (e.g. using the Levenberg-Marquardt algorithm) to a three-parameter model:

$$|S_{n}| = |A(1 - 2f_{inv}\exp(-TI_{n}/T_{1}))|, \qquad (2.10)$$

where A is the hypothetical signal maximum at  $M_0$  ( $TI_n \rightarrow \infty$ ) and  $f_{inv}$  is the efficiency of the, likely imperfect, inversion pulse. Here, the modulus of the signal equation is used to denote that the polarity of  $M_z$  is unknown. In the experiments pertaining to Papers II and V, Eq. (2.10) was used to validate the respective  $T_1$ -mapping protocols suggested.

A common rule-of-thumb is to allow a period of free relaxation of  $TD = 5 \times T_1$  between excitation and the next inversion to allow  $M_z$  to return to equilibrium (Kingsley, 1999). However, it has been claimed that setting *TR* significantly longer than the longest *TI* improves neither accuracy nor precision, provided a three-parameter model is used (Kingsley & Monahan, 2001). Because of this, the reference phantom measurements reported in Paper II were performed with TR = 10 s and a maximum  $TI_N = 4000$  ms which would only allow full relaxation for  $T_1$  values up to 1200 ms.

Another important aspect to consider, is the choice of minimum TI. It is common and sometimes recommended that the minimum TI is set as short as possible to maximize precision (Kingsley & Monahan, 2001). However, the monoexponential behaviour hitherto implied by the Bloch equations is an oversimplification of the multi-compartment environment typically present within a voxel. In the two-pool bi-exponential model, this environment is described by a free pool with long  $T_1$  ( $T_{1f}$ ) and a macromolecular pool with short  $T_1$  ( $T_{1b}$ ) as well as MT between the two pools in either direction. Assuming a monoexponential behaviour immediately after inversion will lead to a reduction in the observed  $T_1$  as magnetization returns more quickly to equilibrium through MT. This is especially noticeable in WM where the macromolecular fraction (short  $T_1$  component) is larger. Such "inverse MT" (from the free to the macromolecular pool) is induced because of the low power of the inversion pulse. It has, for instance, been observed that adiabatic pulses does not saturate non-aqueous signal (Reynolds et al., 2021). The issue is circumvented by choosing a minimum  $TI \ge 200$  ms. From this time point and onwards, equilibrium between the two pools has been re-established at 7T and MT effects can be ignored (Rioux, Levesque, & Rutt, 2016). Such a minimum TI was thus set for the in vivo reference IR measurements in Papers II and V.

To save time when TR is long, phase encoding is often performed using a turbo spin echo (TSE) sequence where, following an inversion, a number of refocusing pulses are applied which result in an equal number of spin echoes (Hennig, Nauerth, & Friedburg, 1986). Scan time is reduced compared to a classic spin-echo sequence by the number of echoes acquired in each cycle, i.e. the echo train length (ETL). Alternatively, an echo planar imaging (EPI) sequence which can be either GRE- or spin echo-based, can be used (Stehling, Ordidge, Coxon, & Mansfield, 1990). In spin echo-based EPI, only one refocusing pulse is applied before the echo train. Consequently, there is no risk of unwanted stimulated echo pathways forming due to non-180° refocusing pulses (Hinks & Constable, 1994). In "single-shot" encoding, the whole of k-space is sampled within one echo train. This manifests as chemical shift artifacts in the phase encoding direction, governed by the phase encoding bandwidth. Such artifacts can be suppressed by a spectrally selective inversion pulse applied at such a time that the fat signal is saturated during readout (i.e. "fat suppression") (Kaldoudi, Williams, Barker, & Tofts, 1993). Also because of the very low phase encoding bandwidth, spatial distortions in the form of elongation/contractions occurs in the presence of  $B_0$  inhomogeneities causing susceptibility differences (Zhou et al., 1998). An effective way to limit such distortions is to reduce the ETL through parallel imaging techniques such as SENSE (Pruessmann, Weiger, Scheidegger, & Boesiger, 1999) or to use a "multi-shot" acquisition. If a separately acquired  $B_0$  map is acquired, distortions can be "unwarped" with post-processing tools such as FSL FUGUE (FMRIB's Utility for Geometrically Unwarping EPIs). Blurring in the phase encoding direction due to different  $T_2$ -weightings for different k-space lines may occur. The blurring is not as severe as in TSE or 3D imaging because of the shorter effective TE, but more severe than in multi-shot imaging. It can similarly be reduced by increasing the SENSE factor. For the phantom reference measurement described in Paper II, a multi-shot 2D IR-EPI with a SENSE reduction factor of 2.5 was used. For the in vivo reference measurements described in Paper II and V, a single-shot sequence was used to reduce motion sensitivity. The EPI distortions were then corrected for during post processing using FSL FUGUE.

Variable flip angle method (VFA)

The gold-standard IR experiment is much too slow to allow for high-resolution  $T_1$ mapping in 3D. A more effective approach is to determine  $T_1$  by varying the flip angle, first introduced in a non-clinical nuclear magnetic resonance (NMR) setting by Christensen, Grant, Schulman, & Walling) (1974). The VFA principle is favorably combined with the 3D spoiled GRE sequence, known as either FLASH, SPGR or T1-FFE depending on vendor (Haase, Frahm, Matthaei, Hanicke, & Merboldt, 1986). In this context, the VFA technique has been named drivenequilibrium single-pulse observation of  $T_1$  relaxation (DESPOT) (Homer & Beevers, 1985). It was later popularized as DESPOT1 when used to obtain  $T_1$  maps with whole-brain coverage at 1 mm isotropic resolution (Deoni, Rutt, & Peters, 2003).

The signal, *S*, of the spoiled GRE is primarily governed by  $M_z$ , which after a sufficient number of *TR* periods is in a steady state. The steady state signal is in turn determined by  $T_1$ , *TR* and the local flip angle,  $f_T \alpha$ , where  $f_T$  is the ratio of the local to the nominal ( $\alpha$ ) flip angle and thus represents the local transmit ( $B_1^+$ ) field bias. From here on,  $f_T$  will be inserted in all signal equations to emphasize the large deviations from the nominal flip angle experienced at UHF. Using these variables, the spoiled GRE steady state signal is analytically described by the Ernst equation (Ernst & Anderson, 1966):

$$S(f_{\rm T}\alpha) = A\sin(f_{\rm T}\alpha)\frac{1 - \exp(-TR/T_1)}{1 - \cos(f_{\rm T}\alpha)\exp(-TR/T_1)}$$
(2.11)

where A is the signal amplitude acquired with  $f_T \alpha = 90^\circ$  at thermal equilibrium  $(TR \gg T_1)$ . The signal is maximized for a certain  $f_T$  and tissue  $T_1$  at the Ernst angle:

$$\alpha_{\rm E}(f_{\rm T}) = \cos^{-1} \left( \exp(-TR/T_1) \right) / f_{\rm T}.$$
(2.12)

To obtain a function of the form y = mx + b from which  $T_1$  can be determined through linear regression, Eq. (2.11) is rearranged as:

$$\frac{S}{\sin(f_{\rm T}\alpha)} = \exp\left(-\frac{TR}{T_1}\right)\frac{S}{\tan(f_{\rm T}\alpha)} + A\left(1 - \exp\left(-\frac{TR}{T_1}\right)\right),\tag{2.13}$$

where  $T_1$  is determined from the slope *m* as  $T_1 = -TR/\ln(m)$  and *A* from the intercept *b* as A = b/(1 - m).

If the VFA experiment consists of only two flip angles, i.e. a dual flip angle (DFA) experiment,  $T_1$  can be solved for analytically through the elementary slope equation

although the derived expressions are rather unwieldly and not very intuitive. In Chapter 3, the rational approximation for small flip angles and short TR will be introduced which yields simple intuitive expressions for  $T_1$  and A (Helms, Dathe, & Dechent, 2008).

The VFA technique is popular because of its simplicity, speed, high SNR per unit time and potential whole-brain coverage. A problem is the inherent quadratic  $f_T$ dependence, making accurate and precise external flip angle mapping mandatory even at non-UHF strengths. The precision of the flip angle map will greatly affect the precision of the  $T_1$  map (Lee, Callaghan, & Nagy, 2017). It is not unlikely that the increased sensitivity to variations in the RF coil setup leads to the somewhat worse reproducibility observed for VFA-derived  $T_1$  maps compared to the interleaved MP2RAGE (Voelker et al., 2021). It has further been shown to result in higher  $T_1$  estimates compared to inversion recovery (Stikov et al., 2015). This could either be due to imperfect spoiling or incidental MT effects (A. G. Teixeira et al., 2020; Preibisch & Deichmann, 2009), both of which will be treated in Chapter 3.

### MP2RAGE

Mapping of  $T_1$  through the magnetization prepared 2 rapid acquisition gradient echoes (MP2RAGE) sequence (Marques et al., 2010) has become very popular and has shown a very high degree of reproducibility across sites (Voelker et al., 2021). As the signal dependence is more complicated than in the spoiled GRE, it becomes difficult to obtain an analytical solution for  $T_1$ . Thus, a lookup table- (LUT-) based approach facilitated by forward signal modeling is the method of choice. MP2RAGE will be covered in more detail in Chapter 5.

## Magnetization transfer (MT)

### Definition and biophysical origin

MT is a unique contrast mechanism inherent to tissue where magnetization is transferred from protons in rotationally restricted water bound to macromolecules, to protons in rotationally free water (Henkelman, Stanisz, & Graham, 2001; Wolff & Balaban, 1989). A macromolecule is characterized by its reduced mobility, e.g. due to its size or being part of a membrane. It includes, for instance, proteins and phospholipids which comprise the dry mass in myelin. The strong coupling of neighbouring protons leads to almost instant dephasing of signal and a very broad absorption lineshape. To induce MT, a high-energy RF pulse is applied off-resonance, targeting this broad absorption lineshape. Through cross-relaxation, the magnetization is dispersed within the macromolecule (spin diffusion), transferred to

the bound water and then to the free water. Macromolecular content can thus be indirectly detected as a decrease in signal amplitude. Since the transverse magnetization of the bound pool dephases during the MT pulse itself, the concepts of "excitation" and "flip angle" does not apply. Hence, the MT is always in the form of a saturation and cannot result in echo formation. MT between bound and free water can also manifest through the exchange of the protons themselves, i.e. chemical exchange saturation transfer (CEST). CEST resonances are much narrower and relate to specific macromolecular groups, unlike the broad lineshape of the "general" macromolecular resonance. Due to the longer  $T_2$ , CEST can result in transfer of transverse magnetization and not just saturation transfer (van Zijl, Lam, Xu, Knutsson, & Stanisz, 2018). Cross-relaxation is, however, believed to be the dominant mechanism in a standard MT experiment where the general macromolecular lineshape is targeted, as was done in the experiments pertaining to Paper IV.

### Applications in neuroscience

MT is more sensitive to demyelination than  $T_1$  (Janve et al., 2013). It is therefore often used in studies of multiple sclerosis (Filippi & Agosta, 2007). Particularly remitting-relapsing multiple sclerosis where each relapse is often accompanied by a new WM lesion (De Stefano et al., 2006; York, Thrippleton, Meijboom, Hunt, & Waldman, 2021).

### Experimental considerations

MT techniques were traditionally developed in non-clinical NMR settings. In such environments, MT is often induced using long periods (0.1-1.0 s) of continuous wave irradiation. This produces a very narrow frequency response which heavily saturates the macromolecules while leaving free water unaffected (Hajnal, Baudouin, Oatridge, Young, & Bydder, 1992). This is not feasible in a clinical MRI setting, since data cannot be collected during irradiation and the RF coils are designed for pulsed irradiation (Pike, 1996). Instead, pulsed saturation techniques with pulses of a couple of milliseconds are employed (Graham & Henkelman, 1997). Due to the limited  $B_1$  amplitude and safety restrictions regarding SAR, the macromolecular water can only be partially saturated and some degree of direct saturation of the free water is likely to occur. The most common pulse sequence for imaging and mapping MT is the spoiled GRE, in either 2D or 3D (York et al., 2021).

#### The magnetization transfer ratio

The most common, and simplest, metric to map MT is the semi-quantitative magnetization transfer ratio (MTR) (Dousset et al., 1992; York et al., 2021). In MTR, the relative difference (in percent) between an MT-weighted image,  $S_{\rm MT}$ , and a reference image,  $S_{\rm ref}$ , with identical sequence parameters but no MT pulse is calculated as:

$$MTR = 100 \left(\frac{S_{\rm ref} - S_{\rm MT}}{S_{\rm ref}}\right). \tag{2.14}$$

Such an experiment will, however, be biased by both  $T_1$  and  $B_1^+$  inhomogeneities and has exhibited rather poor inter-site comparability (York et al., 2021).

#### Quantitative magnetization transfer

MT can be described by a two-pool model, where pool f represents the liquid/free spins and pool b represents the macromolecular/bound spins. This model is referred to as the binary spin bath (BSB) model. The BSB model is described by the longitudinal relaxation rates  $R_{1f} = 1/T_{1f}$  and  $R_{1b} = 1/T_{1b}$ , (rates are used here to follow the convention in MT literature), the longitudinal magnetizations at thermal equilibrium  $M_{0f}$  and  $M_{0b}$ , as well as the rate of transfer in either direction,  $k_{bf}$  and  $k_{fb}$ . From these parameters the bound pool fraction is obtained as:

$$F_{\rm b} = M_{\rm 0b} / (M_{\rm 0f} + M_{\rm 0b}) \equiv k_{\rm fb} / (k_{\rm fb} + k_{\rm bf}).$$
(2.15)

The Bloch-McConnell equations modify the standard Bloch equations to include two coupled pools of spins (McConnell, 1958). To describe MT, the Bloch-McConnell equations are expressed as (Graham & Henkelman, 1997):

$$\frac{dM_{\rm xf}}{dt} = -2\pi\Delta M_{\rm yf} - \frac{M_{\rm xf}}{T_{\rm 2f}},\tag{2.16a}$$

$$\frac{dM_{\rm yf}}{dt} = 2\pi\Delta M_{\rm xf} - \omega_1(t)M_{zf} - \frac{M_{\rm yf}}{T_{\rm 2f}},$$
(2.16b)

$$\frac{dM_{\rm zf}}{dt} = \omega_1(t)M_{\rm yf} + R_{\rm 1f}(M_{\rm 0f} - M_{\rm zf}) - k_{\rm fb}M_{\rm zf} + k_{\rm bf}M_{\rm zb}, \qquad (2.16c)$$

$$\frac{dM_{\rm zb}}{dt} = R_{\rm 1b}(M_{\rm 0b} - M_{\rm zb}) - (\pi g_{\rm b}(\Delta, T_{\rm 2b})\omega_1^2(t) + k_{\rm bf})M_{\rm zb}$$
(2.16d)  
+  $k_{\rm fb}M_{\rm 0b}M_{\rm zf}$ .

Here,  $M_{0f}$  can be normalized to 1 in the Henkelman model (Henkelman et al., 1993),  $g_{\rm b}(\Delta, T_{2\rm b})$  is the bound pool absorption lineshape and  $\Delta = (\omega - \omega_0)/2\pi$  is the MT pulse offset frequency in Hz. For an MT pulse of duration of  $t_{\rm sat}$ , the differential absorption law in Eq. (2.16d) can also be expressed using the average saturation rate of  $M_{\rm zb}$ :

$$W_{\rm b} = \pi g_{\rm b}(\Delta, T_{\rm 2b}) \frac{1}{t_{\rm sat}} \int_0^{t_{\rm sat}} \omega_1^2(t) dt, \qquad (2.17)$$

where the integral is referred to as the "power integral".

Similarly as for a spoiled GRE sequence, a pulsed MT experiment can be separated into periods of free cross-relaxation between the two pools (no RF irradiation) interspersed with instantaneous events of saturation (Pike, 1996). The instantaneous saturation of the bound pool can then be described by a unitless factor:

$$\delta_b = \frac{M_b(0) - M_b(t_{sat})}{M_b(0)} \propto F_b W_b.$$
(2.18)

In fully quantitative MT (qMT), the MR parameters  $k_{\rm bf}$ ,  $F_{\rm b}$ ,  $R_{1\rm f}$ ,  $T_{2\rm f}$  and  $T_{2\rm b}$  can all be solved for numerically by performing a set of MT-weighted measurements with varying  $\int_0^{t_{\rm sat}} \omega_1^2(t) dt$  (typically through the flip angle) and  $\Delta$  (Sled & Pike, 2001). The bound pool relaxation rate,  $R_{1\rm b}$ , is often set arbitrarily to 1 s<sup>-1</sup> since it has a limited effect on the other parameters (Henkelman et al., 1993). In vivo,  $R_{1\rm b} =$ 1 s<sup>-1</sup> could be an underestimation by a more than a factor of 5, however, which could lead to a systematic underestimation of  $F_{\rm b}$  (Helms & Hagberg, 2009). Modelling is preferentially performed after reaching a steady state between the two pools has been reached (Helms & Hagberg, 2004). Since qMT requires a fair number of separate scans (~10-20), it is rather time consuming and thus mostly performed in a single slice. It is, however, highly reproducible and more specific to macromolecular content than MTR (York et al., 2021). The long acquisition time of full qMT and the poor reproducibility/specificity of MTR motivates the use of the semi-quantitative magnetization transfer saturation (MT<sub>sat</sub>) metric (Helms, Dathe, Kallenberg, & Dechent, 2008), covered in detail in Chapter 3.

### Ultra-high field strengths

The move to UHF strengths is often motivated by the increase in magnetization and consequently, the MR signal. This implies an increase in SNR and contrast to noise ratio (CNR). The induced signal in a receiver coil will increase by the square of  $B_0$ while the dominant subject-related noise increases linearly. Theoretically, the increase in SNR with  $B_0$  should thus be linear. However, the actual increase in SNR also depends on the pulse sequence, the properties of the imaged objects (such as relaxation times) as well as the decreased transmit  $(B_1^+)$  and receive sensitivity  $(B_1^-)$ ) homogeneity (the  $B_1$  inhomogeneity at UHF is elaborated on in Chapter 4). The SNR is difficult to quantify in absolute terms because, at UHF strengths, the receive sensitivity cannot feasibly be derived from the transmit field through the principle of reciprocity (Hoult, 2000) (described below). Thus, the SNR increase at UHF has often been reported as a relative increase compared to lower fields. In a comparison between 4T and 7T, where full relaxation was allowed, the average SNR in a slice increased linearly (Ugurbil et al., 2003). The increase was spatially varying, however, with the periphery (low  $B_1^+$ ) experiencing a smaller increase. A review article suggested an increase by  $\sqrt{B_0}$  as a lower limit due to  $T_1$  saturation effects and increased  $T_2^*$  decay (Duyn, 2012). A third study using spoiled GREs at 3T, 7T, and 9.4T reported an overall increase in the intrinsic SNR (corrected for relaxation and transmit field effects) across the cerebrum by  $\sim B_0^{1.65}$  (Pohmann et al., 2016).

The CNR is, of course, dependent on the main contrast mechanism. In the case of  $T_1$ , the increase with  $B_0$  has been determined as a power law up to 100 MHz (~2.3 T) (Bottomley, Foster, Argersinger, & Pfeifer, 1984):

$$T_1 = aB_0^{\ b}, (2.19)$$

where *a* and *b* are tissue-specific constants to be empirically determined. For  $B_0 = 0.2/1.0/1.5/4.0/7.0$  T, these parameters were determined as a = 583/867 ms and b = 0.382/0.376 for WM and GM in the putamen respectively (Rooney et al., 2007). The  $T_1$  in CSF was constant at  $4.3\pm0.2$  s. The exponential behaviour of  $T_1$  indicates a decrease in the relative  $T_1$  difference across tissues and thus implies a convergence and subsequent decrease in CNR. However, a study in rat brain using spoiled GREs showed an increase in CNR per unit time between WM and cortical GM even at 16.4 T (Pohmann, Shajan, & Balla, 2011). The observed CNR increase thus occurred despite the decrease in relative  $T_1$  difference, and the authors expected improved image quality in  $T_1$ -weighted images up to 20 T.

On average,  $T_2^*$  in the cerebrum drops by approximately 50% when going from 3T to 7T (Pohmann et al., 2016). This influences obtainable signal but can be beneficial in multi-echo spoiled GRE measurements (Peters et al., 2007). The decrease is exponential as:

$$T_2^* = ae^{-bB_0}, (2.20)$$

where the tissue specific parameters have been empirically determined to be a = 64/90 ms and b = 0.132/0.142 T<sup>-1</sup> for WM and GM respectively (Pohmann, Speck, & Scheffler, 2016). A plot of the  $B_0$  dependences of  $T_1$  and  $T_2^*$  is shown in Figure 2.1.



**Figure 2.1.** Increase in  $T_1$  (a) and decrease in  $T_2^*$  (b) as a function of  $B_0$ . The  $T_1$  was plotted using Eq. (2.19) and the fitted parameters as obtained by Rooney et al. (2007) while  $T_2^*$  was plotted using Eq. (2.20) and the fited parameters as obtained by Pohmann, Speck, & Scheffler (2016).

In steady state imaging, longitudinal relaxation and MT are two competing processes constituting alternative pathways for the spin system to restore equilibrium magnetization (Henkelman et al., 2001). A longer  $T_1$  thus means more MT-weighting in conventional imaging although the absolute MT does not necessarily increase. As both MT and SAR are governed by the square of the time-varying RF field, obtainable MT at UHF is curtailed by safety limits regarding tissue heating. SAR is governed by the induced electrical current of the applied field as well as local tissue conductivity and density, thus local "hot spots" of SAR deposition can arise that are difficult to predict.

The inhomogeneity of the  $B_0$  field increases at UHF due to susceptibility effects and is most severe close to the nasal sinuses between diamagnetic tissue and paramagnetic air (Juchem & de Graaf, 2017). The choice of RF pulse shape is thus important to ensure a homogenous non-selective excitation and this issue was considered in an experiment pertaining to Paper II and is elaborated on in Chapter 3.

A benefit of the decreased homogeneity of the receive sensitivity is an increased performance of parallel imaging techniques (Wiesinger et al., 2004). The geometry (g) factor is a spatially dependent measure denoting the noise enhancement for a certain receive coil array (Pruessmann et al., 1999). Past a certain reduction factor, the *g*-factor will be lower at UHF compared to lower field strengths. This is because the sensitivity profiles of individual receive elements overlap less and noise correlation is reduced.

The separation of metabolic peaks increases at UHF which can be beneficial in MR spectroscopy as well as in CEST imaging. An interesting consequence of this is the increasing shift of the macromolecular absorption lineshape relative the free water resonance (Hua et al., 2007). This was exploited for Paper IV and will be elaborated on in Chapter 3.

Phase differences due to susceptibility effects increase at UHF which is beneficial in QSM (Acosta-Cabronero et al., 2018). The increased susceptibility effects are also beneficial for the blood oxygenation level dependent (BOLD) contrast used in functional MRI (Yacoub et al., 2001).

Table 2.1 shows a summary of parameters and whether they increase/decrease at increasing  $B_0$ .

Parameter	Increase/Decrease (+/-)
SNR	+
CNR	+
SAR	+
<b>T</b> 1	+
<b>T</b> <sub>2</sub>	_*
$T_2^*$	-
MT	+
B <sub>0</sub> homogene	ity –
B1 homogene	ity –
Susceptibility effects	+
Chemical shif	`t +
<i>g</i> factor	-

Table 2.1 Decemptor dependence on increasing R

*g* factor – \* The actual *T*<sub>2</sub> relaxation is theoretically independent of *B*<sub>0</sub> but there is an apparent decrease due to increasing microscopic susceptibility gradients caused by diffusion.

### Hardware and signal combination

A hardware specific peculiarity of UHF is the lack of an integral RF transmit body coil within the bore. Instead, a dedicated transmit head coil is used for transmission. To improve SNR and/or allow for parallel imaging, reception should be performed using a phased array consisting of multiple receive elements (Larkman & Nunes, 2007; Roemer, Edelstein, Hayes, Souza, & Mueller, 1990). Each receive element is connected to its own channel (receiver pathway) and preamplifier to minimize noise correlation. The signals measured by each element will have a local sensitivity field distribution as well as a spatially dependent phase. This receiver phase needs to be corrected to avoid signal cancellation and to preserve phase changes during *TE* due to susceptibilities in the imaged object (Robinson et al., 2017). To this end, complex
sensitivity maps of each element needs to be obtained from a separate reference scan. These sensitivity maps should be free of anatomical information and, on a clinical system, the anatomical information is thus removed through division by an image acquired with the homogeneous body coil (when used for reception). On the UHF system used here, the sensitivity maps are instead divided by the sum of squares of the phased array signals. For a phased array with *N* elements, a combined, SNR-optimized, and phase-corrected signal is obtained as:

$$S_{\text{opt}} = \sum_{i=1}^{N} w_i \frac{S_i}{C_i}$$
, (2.21)

where  $S_i$  is the measured signal of element *i*,  $C_i$  is the respective sensitivity and  $w_i = C_i^* C_i / \sum_{j=1}^N C_j^* C_j$  is the weighting (index *j* also denotes individual coil elements and the asterisk denotes the complex conjugate). The process is analogous to a SENSE reconstruction with a reduction factor of 1 (Pruessmann et al., 1999). The experimental parts of this thesis were all conducted on an actively shielded 7T Achieva scanner, (Philips Healthcare, Best, NL), using a head coil with two transmit channels at fixed phase settings (Nova Medical, Wilmington, MA) and a 32-channel phased array for reception.

#### Principle of reciprocity

According to the principle of reciprocity, the receive sensitivity and transmit field of a coil are identical in the non-radiative near field region, i.e. when the phase of the RF irradiation is constant across the imaged object (Hoult & Richards, 1976; Ilott & Jerschow, 2018). Theoretically, this allows for direct sensitivity mapping of individual receive coil elements by flip angle mapping if the receive coil elements were used for transmission. Thus, the receive field bias  $(f_{\rm R})$  is determined from the transmit field bias  $(f_{\rm T})$ . Strictly speaking, it is the complex conjugate of the negatively rotating field (i.e.  $B_1^* \approx \hat{B}_1^+$ ) that determines receive sensitivity, and not  $B_1$  as is more commonly referred to. The seemingly simple principle quickly becomes complicated as spatially dependent phase changes need to be accounted for, i.e. in the intermediate region of 3T and above, and in a sample with varying conductivity (Hoult, 2000). Often, errors arise as complex numbers are used to denote both the direction of rotation of  $B_1^+$  and  $B_1^-$  in the laboratory frame, as well as spatially dependent phase changes across the sample in the rotating frame (Ilott & Jerschow, 2018). Although theoretically sound, the principle of reciprocity becomes unfeasible to apply in a practical imaging experiment at UHF. Since normalized sensitivity mapping is also not an option (no homogenous body coil),  $f_{\rm R}$ must be modeled through numerical approaches such as the unified segmentation approach (Ashburner & Friston, 2005).

# 3 – Multi-parameter mapping (MPM) using spoiled gradient echoes

Multi-parameter mapping (MPM) refers to the process of simultaneously deriving maps of more than one MR contrast parameter. The versatile 3D spoiled GRE sequence lends itself well to this purpose (Weiskopf et al., 2013). Simple changes in the pulse sequence result in image contrast being dominated by a different tissuespecific MR parameter. For instance, increasing the flip angle leads to a more  $T_1$ weighted, as opposed to PD-weighted, image (the concept behind VFA-based  $T_1$ mapping). MT-weighting can be induced by a high-energy, off-resonance RF pulse, applied prior to each *TR* cycle. The  $T_2$ \*-weighting is governed by *TE*, which can be varied in a single sequence through a multi-echo readout and, provided that phase data are available, also facilitates QSM. Thus, from only three multi-echo spoiled GRE sequences, maps of  $T_1$ , PD, MT<sub>sat</sub>,  $T_2$ \* and magnetic susceptibility,  $\chi$ , can be derived. In this chapter, special attention will be given to the mapping of  $T_1$  and MT<sub>sat</sub> using a spoiled GRE-based MPM protocol.

This chapter will explain:

- 1. How to derive simple expressions for  $T_1$  and  $MT_{sat}$  through a rational approximation and inversion of the Ernst signal equation.
- 2. Aspects of reducing bias in derived  $T_1$  and MT<sub>sat</sub> estimates
- 3. How to increase the obtainable  $MT_{sat}$  under the SAR constraints present at 7T

# Rational approximation of the Ernst equation

For sufficiently small flip angles and short TR, the Ernst equation can be approximated as a rational function of  $f_{\rm T}\alpha$  and TR (Dathe & Helms, 2010). To derive this, the linear approximation  $\exp(-TR/T_1) \approx 1 - TR/T_1$  (i.e. a first-order Taylor polynomial) valid for  $TR/T_1 \ll 1$  must be introduced. The Ernst equation (Eq. 2.11) then becomes:

$$S(f_{\rm T}\alpha) \approx A\sin(f_{\rm T}\alpha) \frac{TR/T_1}{1 - \cos(f_{\rm T}\alpha)(1 - TR/T_1)}.$$
(3.1)

After removing the exponential terms, the trigonometric terms are dealt with through the tangent half-angle substitution:

$$t = \tan(f_{\rm T}\alpha/2). \tag{3.2}$$

This allows to substitute the trigonometric functions in Eq. (3.1) using the doubleangle formulas and then some other trigonometric identities as:  $\sin(f_{\rm T}\alpha) = 2\sin(f_{\rm T}\alpha/2)\cos(f_{\rm T}\alpha/2) = 2\tan(f_{\rm T}\alpha/2)\cos^2(f_{\rm T}\alpha/2) = 2\tan(f_{\rm T}\alpha/2)/(1 + \tan^2(f_{\rm T}\alpha/2)) = 2t/(1 + t^2)$ and  $\cos(f_{\rm T}\alpha) = 2\cos^2(f_{\rm T}\alpha/2) - 1 = 2/\sec^2(f_{\rm T}\alpha/2) - 1 = 2/(1 + \tan^2(f_{\rm T}\alpha/2)) - 1 = (1 - \tan^2(f_{\rm T}\alpha/2))/(1 + \tan^2(f_{\rm T}\alpha/2)) = (1 - t^2)/(1 + t^2)$ . The Ernst equation now becomes a rational function of t:

$$S(t) \approx A \frac{2t TR/T_1}{[1+t^2][1-(1-t^2/1+t^2)(1-TR/T_1)]'}$$
(3.3)

where simplification of the denominator yields:

$$S(t) \approx A \frac{2t TR/T_1}{2t^2 + (1 - t^2) TR/T_1}.$$
(3.4)

Applying a linear approximation also to Eq. (3.2), this time with regard to the flip angle, yields  $t \approx f_T \alpha/2$ , valid for  $f_T \alpha/2 \ll 1$ . The Ernst equation is now regained as a function of  $f_T \alpha$ :

$$S(f_{\rm T}\alpha) \approx A f_{\rm T} \alpha \frac{T R / T_1}{(f_{\rm T}\alpha)^2 / 2 + (1 - (f_{\rm T}\alpha)^2 / 4) T R / T_1}.$$
 (3.5)

Note that if the linear approximation for small flip angles were to be performed without the tangent half-angle substitution, i.e.  $\sin(f_T\alpha) \approx f_T\alpha$  and  $\cos(f_T\alpha) \approx 1$ , then  $f_T\alpha$  would cancel out from the equation which would make for a poor approximation. The final approximation is  $TR/T_1 \cdot (f_T\alpha)^2/4 \approx 0$ . This yields the final rational approximation of the Ernst equation for small flip angles and short *TR* as:

$$S(f_{\rm T}\alpha) \approx A f_{\rm T} \alpha \frac{TR/T_1}{(f_{\rm T}\alpha)^2/2 + TR/T_1}.$$
(3.6)

Interestingly, since this last approximation can only lead to an overestimation of  $S(f_T\alpha)$ , Eq (3.6) is closer to the exact solution than Eq. (3.5). From here, the Ernst angle is solved for as:

$$\alpha_E \approx \frac{\sqrt{2 TR/T_1}}{f_{\rm T}}.$$
(3.7)

Figure 3.1 shows the spoiled GRE steady state signal as a function of  $f_T \alpha$  for the sequence parameters used in the experiments pertaining to Paper II ( $\alpha = 16^\circ$ , TR = 18 ms) and 7T specific conditions, i.e.  $0 \le f_T \le 2.0$  and  $T_1 = 1300$ , 1900 and 4300 ms. It also shows the slight deviation of the rational approximation compared to the exact equation at moderately high local flip angles and/or short  $T_1$ .

Eq. (3.6) has a pedagogical value in that the influence of  $f_T \alpha$  on  $S(f_T \alpha)$  and thus the contrast of the resulting image becomes very clear. At very small  $f_T \alpha$ , the righthand quotient approaches unity and  $S(f_T \alpha)$  is dominated by A, resulting in a PDweighted image. Vice versa, if  $f_T \alpha$  is large,  $S(f_T \alpha)$  is dominated by the ratio containing  $T_1$ , resulting in a  $T_1$ -weighted image. As  $f_T$  varies across the brain, so does the local contrast. Nevertheless, a small  $\alpha$  results in a predominant PDweighting while a large  $\alpha$  results in predominant  $T_1$ -weighting. Thus, the lower nominal flip angles in a DFA experiment is referred to as  $\alpha_{PD}$  and the higher  $\alpha_{T1}$ . The resulting signals are referred to as  $S_{T1}$  and  $S_{PD}$ .

Rearranging Eq. (3.6) to form a linear equation (y = mx + b) yields:

$$\frac{S}{f_{\rm T}\alpha} \approx -\frac{T_1}{2TR} S f_{\rm T}\alpha + A. \tag{3.8}$$

Solving for  $T_1$  and the signal amplitude through linear regression yields  $T_1 \approx -2mTR$  and  $A \approx b$ . In a DFA experiment, using  $S_{T1}$ ,  $S_{PD}$  and the elementary slope equations for slope and intercept, the rational equations for  $T_1$  and A become:

$$T_{1} = \frac{2TR}{f_{T}^{2}} \cdot \frac{S_{PD}/\alpha_{PD} - S_{T1}/\alpha_{T1}}{S_{T1}\alpha_{T1} - S_{PD}\alpha_{PD}},$$
(3.9)

$$A = \frac{S_{\rm PD}S_{\rm T1}}{f_{\rm T}} \cdot \frac{\alpha_{\rm T1}/\alpha_{\rm PD} - \alpha_{\rm PD}/\alpha_{\rm T1}}{S_{\rm T1}\alpha_{\rm T1} - S_{\rm PD}\alpha_{\rm PD}}.$$
(3.10)

Equations (3.9) and (3.10) expose the respective quadratic and linear  $f_{\rm T}$  bias imposed on the  $T_1$  and A calculations when using nominal flip angles. In other words, it is instead the apparent counterparts of  $T_1$  and A ( $T_{1,{\rm app}}$  and  $A_{{\rm app}}$ ) that will be obtained when using nominal flip angles. Their relationships to the true estimates are written as

$$T_1 = T_{1,\text{app}} / f_T^2,$$
 (3.11)

$$A = A_{\rm app} / f_{\rm T}. \tag{3.12}$$

The appearance of these biases is not evident when using the traditional VFA linearization in Eq. (2.13).



**Figure 3.1.** The spoiled GRE steady state signal as a function of the local flip angle for TR = 18 ms and three typical values of  $T_1$  representing WM, GM and CSF. The flip angle for which the signal maximum is reached at each  $T_1$  is referred to as the Ernst angle,  $\alpha_E$ . Dotted lines represent the rational approximation which result in a slight overestimation at high local flip angles and short  $T_1$ .

## Magnetization transfer saturation (MT<sub>sat</sub>)

Magnetization transfer saturation (MT<sub>sat</sub>) is a semiquantitative metric denoting the fraction of  $M_{zf}$  saturated by a single MT pulse during TR as introduced by Helms & Piringer (2005). MT<sub>sat</sub> is inherently corrected for  $T_1$  and (in the absence of direct saturation) directly proportional to  $\delta_b$  (Eq. (2.18)) and consequently to  $F_b$  (Eq. (2.15)). It is derived by adding an MT-weighted spoiled GRE to the previously described DFA experiment. By virtue of being independent of the already estimated  $R_1 = 1/T_1$ , it is more directly representative of  $F_b$  than the MTR (as before, rates are used as is the convention in MT literature). Expanding on the rational approximation of the Ernst equation (Eq. (3.6)), an MT saturation event,  $\delta_{MT}$ , separate from the saturation due to the readout excitation,  $(f_T \alpha)^2/2$ , can be added in the denominator to describe the steady state signal in an MT-weighted spoiled GRE sequence (Helms, Dathe, Kallenberg, et al., 2008):

$$S_{\rm MT} \approx A f_{\rm T} \alpha \frac{R_1 T R}{(f_{\rm T} \alpha)^2 / 2 + \delta_{\rm MT} + R_1 T R}.$$
(3.13)

Solving for  $\delta_{MT}$  yields:

$$\delta_{\rm MT} = (A f_{\rm T} \alpha / S_{\rm MT} - 1) R_1 T R + (f_{\rm T} \alpha)^2 / 2. \tag{3.14}$$

Note that since  $R_1$  and A are determined from the DFA experiment, any biases will carry over when calculating  $\delta_{MT}$ . Eq. (3.14) serves as the definition of  $\delta_{MT}$  and the "approximately equal to" sign is thus dropped. Since  $\delta_{MT}$  is directly related to  $\delta_b$ , it is approximately proportional to the power integral and thus  $f_T^2$  (equations (2.17) and (2.18)).

By substituting  $R_1$  and A with their apparent counterparts, obtained when using nominal flip angles (equations (3.11) and (3.12)),  $f_T$  cancels out from Eq. (3.14):

$$\delta_{\rm MT,app} = (A_{\rm app} \alpha / S_{\rm MT} - 1) R_{1,\rm app} TR + \alpha^2 / 2. \tag{3.15}$$

Thus,  $\delta_{MT,app}$  is corrected for the primary influence of  $f_T^2$ . Albeit the somewhat confusing terminology, this implies that  $\delta_{MT,app}$ , not  $\delta_{MT}$ , is inherently corrected for  $B_1^+$  inhomogeneities. There is still a residual transmit field related bias, however, and it will be shown later that correction through external flip angle mapping is still necessary, at least at UHF strengths.

In a recent review study of MT in relapsing-remitting MS it was suggested to use MT<sub>sat</sub> instead of MTR to increase comparability between different studies and

research sites (York et al., 2021). Also recently, it has been used to determine the inner to outer myelinated axon diameter (g-ratio), which in turn was used to study disease progression in MS through brain network topologies (Kamagata et al., 2019). Further,  $MT_{sat}$  is not sensitive to iron and has thus been used for improved automated segmentation of deep brain structures compared to conventional  $T_1$ -weighted images (Helms, Draganski, Frackowiak, Ashburner, & Weiskopf, 2009).

# Spoiling

The Ernst equation assumes perfect spoiling of transverse magnetization before each new excitation. If this condition is not fulfilled, alternative echo pathways will form, and full Bloch equation simulations become necessary to model the signal. It follows that the subsequent DFA-based  $T_1$ -mapping will be biased (Preibisch & Deichmann, 2009). A very straightforward way to achieve complete spoiling would be to set  $TR \ge 5 \times T_2$  so that all transverse magnetization has decayed before the next TR period. This is, however, not a feasible solution because of the long acquisition times this would entail. Another way is to apply a spoiler gradient at the end of the TR period. Spoiling gradients are by themselves unsuitable since gradients are spatially varying and thus the effectiveness of the spoiling will also show a spatial dependence. The third option is to use RF spoiling where the phase of the excitation pulse is varied according to a phase-cycling scheme (Crawley, Wood, & Henkelman, 1988; Zur, Wood, & Neuringer, 1991):

$$\phi_j = \phi_{j-1} + j\phi_0, \qquad j = 1, 2, 3, \dots$$
 (3.16)

where  $\phi_j$  denotes the phase of the *j*th pulse and the starting value,  $\phi_0$ , is referred to as the *phase difference increment*. Eq. (3.16) can be solved for to reveal a quadratic dependence of index *j*:

$$\phi_j = \frac{1}{2}\phi_0(j^2 + j + 2), \qquad j = 1, 2, 3, \dots$$
 (3.17)

The net transverse magnetization vector,  $\vec{M}_j$ , produced by the *j*th pulse will thus have a different phase than the net magnetization,  $\vec{M}_{j-1}$ , remaining from the previous pulse. The resulting transverse magnetization,  $\vec{M}_{xy}$ , that is measured will be a superposition of all residual magnetizations that have not yet completely decayed and is thus generally somewhat smaller than what would be expected from the Ernst equation.

The phase cycling scheme complicates the Bloch equations as  $\mathbf{B}_1$  is applied solely in the x-direction only for  $\phi_j = 0$ . For numerical simulations, the rotation matrix must thus be modified to account for  $\phi_i$  (Yarnykh, 2010):

$$\mathbf{R}(\alpha,\phi_j) = \begin{bmatrix} \cos\alpha + (1-\cos\alpha)\cos^2\phi_j & (1-\cos\alpha)\sin\phi_j\cos\phi_j & -\sin\alpha\sin\phi_j \\ (1-\cos\alpha)\sin\phi_j\cos\phi_j & \cos\alpha + (1-\cos\alpha)\sin^2\phi_j & \sin\alpha\cos\phi_j \\ \sin\alpha\sin\phi_j & -\sin\alpha\cos\phi_j & \cos\alpha \\ & & & & & & \\ \end{bmatrix}$$

which is equal to Eq. (2.7) for  $\phi_i = 0$ .

The length of the phase cycle,  $N_{\phi}$ , refers to the number of *TR* periods until an RF pulse with  $\phi_j = \phi_0$  is produced again. For instance,  $\phi_0 = 120^{\circ}$  yields a phase cycle of  $N_{\phi} = 3$  and would thus be a poor choice as  $\phi_0$  should pertain to yielding  $N_{\phi} \gg T_2/TR$ . The poorness of  $\phi_0 = 120^{\circ}$  in particular is interesting since phase difference increments that yields very long phase cycles, such as  $\phi_0 = 117^{\circ}$  (Zur et al., 1991) or  $\phi_0 = 123^{\circ}$  (both yielding  $N_{\phi} = 16$ ) become somewhat sensitive to instabilities in the assigned phase. Some typical values of  $\phi_0$  include 117° ( $N_{\phi} = 16$ , GE), 50° ( $N_{\phi} = 9$ , Siemens) and 150° ( $N_{\phi} = 9$ , Philips).

Typically, spoiling gradients and RF phase cycling are combined to increase spoiling efficiency. In the spoiled GRE experiments used for this thesis, the phase difference increment was  $\phi_0 = 150^\circ$  and spoiling gradients were applied in the readout and slice directions with areas of ~13 mT·ms/m each.



**Figure 3.2.** Steady state signal derived from the Bloch simulations (solid) or the Ernst equation (dashed=exact, dotted=rational approximation) as a function of  $\phi_0$  for  $\alpha_{PD} = 4^\circ$  and  $\alpha_{T1} = 16^\circ$ . The signal is generally well-represented by the Ernst equation for  $\alpha_{PD} = 4^\circ$  but at  $\alpha_{T1} = 16^\circ$  the signal is systematically ~1% lower than predicted. Some values of  $\phi_0$ , like 118.2° and 121.9°, result in perfect agreement but are situated on steep slopes (arrows) close to 120° and therefore sensitive to instabilities. A phase difference increment situated on a plateu such as  $\phi_0 = 150^\circ$  is more stable although it will lead to a consistent bias if not corrected for. Simulation details: Number of isochromats = 360,  $T_1 = 1300$  ms,  $T_2 = 50$  ms, TR = 18 ms,  $f_T = 1$ . The "Reference" plot was simulated with the parameters given by Preibisch & Deichmann (2009), i.e.  $\alpha = 30^\circ$ ,  $T_1 = T_2 = 1000$  ms, TR = 50 ms, and served as validation of the other simulations. Note the difference in vertical scales.

Most spoiling schemes will result in at least some deviation from the Ernst equation. The deviation often becomes substantial past a certain upper threshold of the local flip angle, where it will result in an increasing overestimation of the signal (Ganter, 2006). This upper threshold can be determined experimentally and is most sensitively identified visually by the linear Eq. (3.8) (Helms, Dathe, Weiskopf, & Dechent, 2011). By performing a VFA experiment and determining for which flip angle the measurement deviates from the expected linear relationship, the upper limit of  $\alpha_{T1}$  for the expected conditions (range of  $f_T$ ,  $T_1$ ,  $T_2$ , TR) can be determined. Figure 3.3 shows a simulation of this deviation corresponding to the experiment performed in Paper II. Here, the measured signal is replaced by simulations of the Bloch equations. Noticeable deviations from the Ernst equation occur beyond a local flip angle of  $f_T \alpha \approx 20^\circ$ .



**Figure 3.3.** Deviations of the exact and approximated Ernst equation from the simulated steady state signal. The linear form of the Ernst equation (right-hand panel) more readily shows the deviation from the simulated signal at a local flip angle of approximately 20° (arrows). This is in accordance with the experimental results described in Paper II. Simulation details: TR = 18 ms,  $T_1 = 1300 \text{ ms}$ ,  $T_2 = 50 \text{ ms}$ ,  $\phi_0 = 150^\circ$ , 1000 spin isochromats where each spin was rotated by different increments between 0 and  $2\pi$  at the end of each TR to simulate full gradient spoiling.

The effect of incomplete spoiling in a DFA  $T_1$ -mapping experiment can also be corrected for post hoc by protocol-specific ( $\alpha_{T1}$ ,  $\alpha_{PD}$  and TR) correction factors derived from Bloch equation simulations (Preibisch & Deichmann, 2009). Unless separate  $T_2$ -mapping is performed, it becomes necessary to assume a fixed  $T_2$  in the simulations. This is justified since  $T_2$  does not vary much between WM and GM. Since  $T_2$  is shorter at higher field strengths, the correction factors will, however, still be field strength dependent. For 7T measurements of  $T_2$ , see Oros-Peusquens et al. (2008) and Wiggermann, MacKay, Rauscher, & Helms (2021).

The relationship between the true  $T_1$  and the biased  $T_{1,sp}$  is linear (Preibisch & Deichmann, 2009):

$$T_1 = m(f_{\rm T})T_{1.\rm sp} + b(f_{\rm T}), \tag{3.19}$$

where the slope,  $m(f_T)$ , and intercept,  $b(f_T)$ , must be determined through protocoland field strength-specific simulations. Accordingly, simulations were performed for protocol- and 7T-specific conditions over a range of  $T_1$  values between 1100 ms and 2200 ms in increments of 100 ms,  $f_T$  values between 0.2 and 2.0 in increments of 0.1 and  $T_2 = 50$  ms. The results can be seen in Figure 3.4. The parameters  $m(f_T)$ and  $b(f_T)$  can both be described by respective cubic polynomials that, after curve fitting, yields the following equations:

$$m = 0.0437 f_{\rm T}^3 - 0.0673 f_{\rm T}^2 + 0.0505 f_{\rm T} + 0.9905, \qquad (3.20)$$

$$b = -33.1972f_{\rm T}^3 + 59.8589f_{\rm T}^2 - 34.2340f_{\rm T} - 1.8759$$
 ms. (3.21)



**Figure 3.4.** Bias in  $T_1$  estimation due to incomplete spoiling and how to correct it for a specific 7T DFA protocol. (A) The relative difference between the true  $T_1$  and  $T_{1,sp}$  increases strongly with  $f_T$  and weakly with  $T_1$ . (B) The relationship between the true  $T_1$  and  $T_{1,sp}$  is linear where the slope, m, and intercept, b, depends on  $f_T$ . (C) The slope m is very well described by a cubic function and less so by a quadratic one. (D). The same as in (C) applies to the intercept, b.

In the original work, two quadratic polynomials for m and b were proposed (Preibisch & Deichmann, 2009). Because the simulation behind this correction also accounts for differences between the rational and exact solutions of the Ernst equation, and because of the wider range of  $f_T$  ( $0.2 \le f_T \le 2.0 \text{ vs } 0.7 \le f_T \le 1.3$ ), two cubic polynomials resulted in much better fits,  $r_2 = 0.988 \text{ vs } r_2 = 1.000$  for m and  $r_2 = 0.973 \text{ vs } r_2 = 0.999$  for b.

To circumvent protocol-specific simulations, separately acquired flip angle maps can be modified by a factor (Baudrexel, Noth, Schure, & Deichmann, 2018):

$$C_{\phi 0} = \sum_{k,l=0}^{k+l \le 5} P_{k,l} \cdot \alpha_{T1}^k \cdot TR^l$$
(3.22)

where  $\alpha_{T1}$  should be given in degrees and *TR* in ms. The 2D set of polynomial parameters,  $P_{k,l}$ , was obtained for the three most common values of  $\phi_0$  (50°, 117° and 150°) and provided to allow calculation of  $C_{\phi 0}$ . The underlying assumption is

that deviations in the  $T_1$  estimation will stem solely from inefficient spoiling of the highest flip angle,  $\alpha_{T1}$ , and that the bias will be largely unaffected by  $T_1$  (supported by Figure 3.4, panel A, for  $f_T < \sim 1.5$ ). In practice, the procedure is done as follows: (1) Scale the flip angle map to  $f_T\alpha_{T1}$ . (2) Calculate a map of  $C_{\phi 0}$  from Eq. (3.22). (3) Multiply  $f_T\alpha_{T1}$  by  $C_{\phi 0}$ . (4) Divide by  $\alpha_{T1}$  to obtain  $f_{T,mod}$ . The modified  $f_{T,mod}$ is then used to correct the  $T_{1,app}$  map. Since the protocol-specific simulation was not available at the time, this approach was implemented for the experiments pertaining to Paper II. Note that the simulations were originally performed with 3T in mind and hence for a rather long  $T_2 = 85$  ms and a somewhat lower range of  $T_1$ (700 ms – 1800 ms). Furthermore, CSF has much longer  $T_1$  and  $T_2$  than brain tissue and the correction may thus not be valid in those pixels. Since  $\alpha_{T1}$  had already been experimentally restricted (Figure 3.3), this was deemed a sufficient correction at the time. Note also that the shorter  $T_2$  of 7T benefits spoiling (Corbin & Callaghan, 2021).

Lastly, it should be noted that spoiler gradients induce diffusion which will effectively increase spoiling efficiency (Yarnykh, 2010). In the strong spoiling regimen, with gradient areas between 280-450 mT·ms/m, spatial averaging of spin isochromats due to diffusion leads to very effective spoiling in combination with RF phase cycling. However, this strong spoiling feature will require prolonged *TR* (or removal of the multi-echo readout) and was therefore not implemented. Note also that the above simulations (Figure 3.4) did not account for diffusion effects.

# Shape of excitation pulse

VFA-based  $T_1$ -mapping is mostly performed with 3D encoding and nonselective excitation rather than by multislice excitation. This increases SNR and reduces slice profile effects since there is no risk of crosstalk between overlapping nonrectangular slice profiles (Helms et al., 2011). However, the frequency response profile of the nonselective excitation must be sufficiently constant across the range of Larmor frequencies resulting from  $B_0$  inhomogeneities at 7T. The deviation in Larmor frequency,  $\Delta v_0$ , is usually within  $\pm 500$  Hz at 7T after second order gradient shimming. If the response profile is not sufficiently flat, areas with a high  $|\Delta v_0|$  will experience deviating (likely smaller) local flip angles. This effect is not monitored by independent flip angle mapping unless the same RF pulse is applied in both techniques. Increasing the bandwidth of the pulse by reducing its duration,  $t_{\rm RF}$ , is not appropriate because of subsequent increase of the power integral (Eq. (2.17)) and ensuing MT effects (covered later in this Chapter). Instead, the shape of the excitation pulse should be considered. Figure 3.5 shows four different RF pulse shapes with three different  $t_{\rm RF}$  and their frequency responses. All the pulses yields a flip angle of 16° at  $\Delta v_0 = 0$  Hz. Three of the shapes (block, sinc main lobe and sinc) show a narrow frequency response profile within  $-500 \le \Delta v_0 \le +500$  Hz unless the pulse duration is short ( $t_{\rm RF} = 211 \ \mu s$ ). Even at  $t_{\rm RF} = 211 \ \mu s$ , the block-shaped pulse saturates  $M_z$  slightly less close to  $\Delta v_0 = \pm 500$  Hz. The fourth shape, an asymmetric sinc with a single sidelobe on the negative side, yields a flat frequency response even at a moderately long  $t_{\rm RF} = 698 \ \mu s$ . The peak  $B_1$  value also needs to be considered. A sinc-shaped pulse with  $t_{\rm RF} = 211 \ \mu s$  for instance, requires a peak  $B_1$  of 21.2  $\mu$ T to produce a flip angle of 16° which exceeds the limit of 20  $\mu$ T deliverable by the RF coil. To summarize, four out of the 4×3 = 12 RF pulse options presented in Figure 3.5, show a sufficiently narrow frequency response. In the study reported in Paper II, incidental MT effects were minimized using the asymmetric sinc-shaped pulse with duration  $t_{\rm RF} = 698 \ \mu s$ . The same pulse was then also applied for readout excitation in Papers IV and V. The other three pulses (sinc main lobe/sinc/asymmetric sinc with  $t_{\rm RF} = 211 \ \mu s$ ) have a higher power integral and will thus result in incidental MT effects.



**Figure 3.5.** Four RF pulse shapes, each with three different durations ( $t_{RF}$ =211, 698 and 2003 µs), (left column) and their corresponding frequency responses (right column). Each RF pulse yields a flip angle of 16° at the center frequency. Unless the pulse duration is short ( $t_{RF}$ =211 µs), all shapes except the asymmetric sinc with a single side lobe (bottom row) result in uneven profiles within the expected range of Larmor frequencies, i.e.  $\Delta v_0 = \pm 500$  Hz (highlighted white area). This will lead to varying local flip angles across the imaged object which cannot be corrected for by flip angle mapping. A short pulse duration entails a high power integral which is undesirable due to incidental MT effects. Simulations were performed using the PulseWizard tool available from de Graaf (2018).

## MT pulse

The purpose of the MT pulse is to maximize the saturation of the bound pool ( $\delta_b$  in Eq. (2.18)) without directly saturating the free pool (i.e. the "direct effect"), while also keeping within SAR limits. The parameters of the MT pulse that can be controlled experimentally through the user interface on the scanner are (1) the nominal flip angle,  $\alpha_{sat}$ , (2) the duration,  $t_{sat}$ , (3) the shape of the pulse and (4) the offset frequency,  $\Delta$ .

To derive a relation between  $\alpha_{sat}$ ,  $t_{sat}$  and pulse shape to the power integral in Eq. (2.17) (and thus  $\delta_b$ ), the local flip angle is first re-written as:

$$f_{\rm T}\alpha_{\rm sat} = \int_0^{t_{\rm sat}} \omega_1(t)dt = \omega_{1,\max}t_{\rm sat}\int_0^1 \dot{\omega}_1(t)dt = \omega_{1,\max}t_{\rm sat}q_1, \quad (3.23)$$

where  $\omega_{1,\max}$  is the maximum amplitude of the RF pulse and the unitless shape factor  $q_1 = \int_0^1 \dot{\omega}_1(t) dt \le 1$  describes the shape of the pulse.

Secondly, performing the analogous operation on the power integral yields:

$$\int_{0}^{t_{\text{sat}}} \omega_{1}^{2}(t)dt = \omega_{1,\max}^{2} t_{\text{sat}} \int_{0}^{1} \omega_{1}^{2}(t)dt = \omega_{1,\max}^{2} t_{\text{sat}} q_{2}, \qquad (3.24)$$

where the next shape factor  $q_2 = \int_0^1 \dot{\omega}_1^2(t) dt \leq 1$  describes the shape of the RF power integral. The substitutions  $\omega_{1,\max}t_{\text{sat}} = f_T \alpha/q_1$  and  $\omega_{1,\max} = f_T \alpha_{\text{sat}}/q_1 t_{\text{sat}}$  in Eq. (3.24) yields:

$$\int_{0}^{t_{sat}} \omega_{1}^{2}(t)dt = Q (f_{T}\alpha_{sat})^{2}/t_{sat},$$
(3.25)

where Q is the final shape factor. Eq. (3.25) relates the power integral to pulse parameters that can be defined at the console. For a given pulse shape:

$$Q = \frac{q_2}{q_1^2} = \frac{\int_0^1 \dot{\omega}_1^2(t) dt}{\left(\int_0^1 \dot{\omega}_1(t) dt\right)^2} \ge 1,$$
(3.26)

describes the normalized energy. A lower Q translates to a higher normalized energy where a rectangular pulse has the lowest Q = 1. In other words, Q describes the

time efficiency of a certain pulse shape, with a rectangular shape being the most efficient. The upper limit of the MT pulse power will be set by SAR restrictions and can only be further increased by increasing *TR*. Although the pulse power is thus set, the question of how to trade-off Q,  $\alpha_{sat}$  and  $t_{sat}$  can make for an interesting optimization problem since these parameters affect the frequency response profile of the MT pulse. If the frequency response of the MT pulse overlaps with the free water resonance, the direct saturation will bias the MT<sub>sat</sub> estimate. An MT pulse with low Q and short  $t_{sat}$  will generally have a wider frequency response. Thus, care must be taken so that a time-efficient MT pulse still has a sufficiently narrow response so as not to induce direct saturation. This is the opposite rationale to the readout pulse of the non-selective excitation, where the frequency response should be as wide as possible.

Furthermore, the MT pulse offset frequency,  $\Delta$ , is important to consider both with regard to the direct effect and induced  $\delta_b$ . Obviously, the risk of direct saturation decreases at higher values of  $\Delta$ . However, a larger  $\Delta$  also entails a smaller  $\delta_b$  through the absorption lineshape of the bound pool,  $g_b(\Delta, T_{2b})$ . How much smaller it will become depends on which function best describes  $g_b(\Delta, T_{2b})$ . In the BSB model,  $g_b(\Delta, T_{2b})$  has been described by several different functions. These include (among others) Lorentzian (like the free water lineshape,  $(g_f(\Delta, T_{2f}))$  (Grad & Bryant, 1990), Gaussian (Henkelman et al., 1993) and super-Lorentzian (Morrison & Henkelman, 1995). In textbook literature, the lineshape is often illustrated as being Gaussian, i.e. with a rather flat top. However, in a clinical setting (i.e. for brain tissue and  $\Delta < 20$  kHz) the super-Lorentzian line shape has been shown to give the best fit to experimental data (Li, Graham, & Henkelman, 1997).

The free pool Lorentzian lineshape is expressed as:

$$g_{\rm f}(\Delta, T_{\rm 2f}) = \frac{T_{\rm 2f}}{\pi} \cdot \frac{1}{1 + (2\pi\Delta \cdot T_{\rm 2f})^2},\tag{3.27}$$

while the super-Lorentzian bound pool lineshape (Wennerström, 1973) is given by:

$$g_{\rm b}(\Delta, T_{\rm 2b}) = \sqrt{\frac{2}{\pi}} \int_0^{\pi/2} \frac{T_{\rm 2b}}{|3\cos^2 \theta - 1|} \exp\left(-2\left(\frac{2\pi\Delta T_{\rm 2b}}{3\cos^2 \theta - 1}\right)^2\right) \sin \theta \, d\theta. \quad (3.28)$$

The super-Lorentzian shape of  $g_b$  means that  $\delta_b$  increases somewhat faster with decreasing  $\Delta$  than one would expect for a Gaussian shape (Figure 3.6). It follows that  $\Delta$  should be set as small as is allowed by the frequency response. Such a minimum  $\Delta$  was experimentally identified in an experiment described in Paper IV by varying  $\Delta$  and examining the estimated  $\delta_{MT}$  in GM relative to WM. In the absence of a direct effect,  $\delta_{MT}$  should increase solely due to  $g_b(\Delta, T_{2b})$  as  $\Delta$  is decreased, i.e. the ratio  $\delta_{MT}(GM)/\delta_{MT}(WM)$  should be approximately constant and

independent of  $\Delta$  as can be seen in Figure 3.6. However, in the presence of a direct effect there will be a  $\Delta$ -dependent "shift" in both  $\delta_{MT}(GM)$  and  $\delta_{MT}(WM)$  which depends on  $g_f(\Delta, T_{2f})$ . Note that  $T_{2f}$  is similar in GM and WM (Wiggermann, MacKay, Rauscher, & Helms, 2021). Thus, the above ratio increases by decreasing  $\Delta$  in the presence of a direct effect. In this way, the onset of the direct effect and thus the minimum  $\Delta$  for a particular MT pulse can be determined. An observed  $\delta_{MT}(CSF) > 0$  is also a sign of direct saturation since the CSF should be practically devoid of macromolecular content and consist only of a free pool. Lastly, it should be noted that the above rationale assumes identical  $g_b(\Delta, T_{2b})$  and thus identical  $T_{2b}$  in WM and GM which is not strictly the case as  $T_{2b}$  in GM is very slightly shorter (~1 µs). This should have a very minor, and also opposite effect, on the  $\Delta$ -dependency of  $\delta_{MT}(GM)/\delta_{MT}(WM)$ , i.e. the ratio should decrease at decreasing  $\Delta$ .

Another important aspect of  $\Delta$  is its sign, i.e. whether the MT pulse should be applied on the negative (lower frequency, upfield in NMR terminology) or the positive (higher frequency, downfield in NMR terminology) side of the free water resonance. In the traditional MT literature, this issue is not considered and only positive offsets have been studied at 1.5T (Henkelman et al., 1993; Morrison & Henkelman, 1995; Sled & Pike, 2000). It has been shown that  $g_{\rm b}(\Delta, T_{\rm 2b})$  is not centered at the water resonance but is instead shifted towards lower frequencies (Hua et al., 2007). In human WM, this shift was measured to be  $-2.34\pm0.17$  ppm. This means that a rather substantial increase in  $\delta_{\rm h}$  is obtained simply by changing the sign of  $\Delta$  from "+" to "-" on the console. Further, this means that, as the absolute shift in Hz is field dependent, the increase in  $\delta_{\rm b}$  obtainable in this way is quite a bit higher at 7T compared to 3T or 1.5T. At absolute shifts of -697±51 Hz, -299±22 Hz and  $-149\pm11$  Hz, the relative increase in  $g_b(\Delta = \pm 2 \text{ kHz}, T_{2b} = 10.4 \text{ }\mu\text{s})$ , and thus  $\delta_{\rm h}$ , should be about 8%, 16% and 39%. Most of the classical MT literature was conducted at 1.5T, and this may explain why this shift was not recognized. As described in Paper IV, an increase of 45% of  $\delta_{MT}$  in WM was indeed observed when altering the sign as  $\Delta = \pm 2$  kHz. Figure 3.6 illustrates the shift of the super-Lorentzian  $g_{\rm b}$  at 7T for two different values of  $T_{\rm 2b}$ , representing WM and GM, as well as the Lorentzian line shape of free water. Note that there is no data on the shift in GM available, so identical shifts were assumed in the figure to facilitate comparison of  $g_{\rm b}(\Delta, T_{\rm 2b})$ .



**Figure 3.6.** Super-Lorentzian absorption line shapes of the bound pool,  $g_b(\Delta, T_{2b})$ , as a function of offset frequency ( $\Delta$ ) for WM (blue,  $T_{2b}$ =10.4 µs) and GM (red,  $T_{2b}$ =9.2 µs). The Lorentzian free pool line shape  $g_t(\Delta, T_{2t})$  at  $T_{2t}$ =50 ms is shown in black. The arrows indicate the increase in  $g_b(\Delta, T_{2b})$  and thus  $\delta_b$  that can be obtained when changing the sign of the applied MT pulse. The  $T_{2b}$  values were obtained from Morrison & Henkelman (1995).

# Incidental MT effects caused by the excitation pulse

When an excitation pulse with duration  $t_{\rm RF}$  is applied on-resonance to a two-pool spin system, it acts on both the free and the bound pool, resulting in partial saturation of both  $M_{\rm zf}$  and  $M_{\rm zb}$ . The degree to which the bound pool is saturated is determined by the power integral while the saturation of the free pool is determined by the local flip angle as  $\delta_{\rm f} = 1 - \cos(f_{\rm T}\alpha)$ , which after second order Taylor expansion (valid for small flip angles) is approximated by:

$$\delta_{\rm f} \approx (f_{\rm T} \alpha)^2 / 2. \tag{3.29}$$

If the proportion between  $M_z$  in the two pools is disturbed by the excitation pulse so that it no longer conform to the original pool size ratio (i.e.  $M_{zb}/M_{zf} \neq M_{0b}/M_{0f}$ ), MT is induced in addition to  $T_1$  relaxation. These MT effects lead to deviations from the single pool Ernst equation (Ou & Gochberg, 2008). The incidental MT observed on the free pool ( $\delta_{MT,inc}$ ) can be described in analogy to the  $\delta_{MT}$  imposed by offresonance irradiation in Eq. (3.13). Conventional MT (as in an MT experiment) is directed from the bound to the free pool and typically occurs when using high power pulses whereas "inverse" MT (from the free to the bound pool) occurs for low power "soft" pulses. The direction of MT can be described by the sign of  $\delta_{MT,inc}$  which is governed by the initial difference in partial saturation, i.e.  $\delta_b - \delta_f$  (Helms, 2021). Looking at the Ernst equation in the presence of MT (Eq. (3.13)), it can be seen that a positive  $\delta_{\text{MT,inc}}$  (conventional MT,  $\delta_{\text{b}} > \delta_{\text{f}}$ ) will decrease the steady state signal while a negative  $\delta_{\text{MT,inc}}$  (inverse MT,  $\delta_{\text{f}} > \delta_{\text{b}}$ ) entails an increase in the steady state signal. If the readout excitation pulse induces MT in either direction, the single pool Ernst equation is no longer valid and any subsequent estimation of  $T_1$  (and consequently  $\delta_{\text{MT}}$ ) will be biased.

To express  $\delta_b - \delta_f$  in parameters that can readily be defined on the console, the previously introduced shape factor Q (Eq. (3.26)) is used to obtain:

$$\delta_{\rm b} - \delta_f = A \int_0^{t_{\rm RF}} \omega_1^2(t) dt - (f_{\rm T}\alpha)^2 / 2 = \left(A \frac{Q}{t_{\rm RF}} - \frac{1}{2}\right) (f_{\rm T}\alpha)^2 (3.30)$$

where A is an unknown proportionality factor. Since both  $\delta_b$  and  $\delta_f$  are functions of  $(f_T \alpha)^2$  and Q is a pulse shape-specific constant, there should exist a value of  $t_{RF}$ which result in a balance between the two pools, i.e.  $\delta_b - \delta_f = 0$  and hence  $\delta_{MT,inc} = 0$  for all values of  $f_T \alpha$ . Since the above derivation assumes that the RF pulses producing  $f_T \alpha_{T1}$  and  $f_T \alpha_{PD}$  in a DFA experiment have the same  $t_{RF}$  and Q, the following is valid:

$$\delta_{\mathrm{MT,inc}}(f_{\mathrm{T}}\alpha_{\mathrm{T1}}) = (\alpha_{\mathrm{T1}}/\alpha_{\mathrm{PD}})^2 \delta_{\mathrm{MT,inc}}(f_{\mathrm{T}}\alpha_{\mathrm{PD}}).$$
(3.31)



**Figure 3.7** Simulation of how incidental MT can influence  $T_1$ -mapping in a DFA experiment with  $\alpha_{PD}=4^{\circ}$  and  $\alpha_{T1}=16^{\circ}$ . (A) The saturation of the free pool (dashed black line) is independent of  $t_{RF}$  but the saturation of the bound pool will decrease as the energy of the pulse decreases. This means that there should be a common "balanced"  $t_{RF}$  where  $\delta_{b}=\delta_{T}$  regardless of  $\alpha$ . (B) The incidental MT saturation becomes negative past this "balanced" value of  $t_{RF}$ =698 µs where "inverse" MT is induced. (C) The steady state signals (Sr1 and SPD) are decreased by conventional MT (short  $t_{RF}$ , high power) and increased by "inverse" MT (long  $t_{RF}$ , low power). Black dashed lines denote the steady state signals when  $\delta_{MT,inc}=0$ . (D) Since  $\alpha_{T1}$  will disturb the equilibrium more than  $\alpha_{PD}$ , the  $T_1$  calculation is dominated by  $S_{T1}$ . When  $S_{T1}$  is decreased due to conventional MT,  $T_1$  is underestimated. When  $S_{T1}$  is increased due to inverse MT,  $T_1$  is overestimated. Black solid line denotes the true  $T_1=1253$  ms obtained when  $\delta_{MT,inc}=0$ . Note that this simulation is entirely for illustrative purposes and that the proportionality factor was set as  $A=1.46\cdot10^4$  s<sup>-1</sup> for Q=2.39 so that  $t_{RF}=698$  µs yielded  $\delta_{MT,inc}=0$  to match the empirical results reported in in Paper II. For simplicity,  $f_T=1$ .

This means that the bias in the  $T_1$  calculation is dominated by  $S_{T1}$  where conventional MT ( $\delta_{MT,inc}(f_T\alpha_{T1}) > 0$ ) leads to an overestimation while inverse MT ( $\delta_{MT,inc}(f_T\alpha_{T1}) < 0$ ) leads to an underestimation. The MT<sub>sat</sub> that is created by an MT pulse (i.e.  $\delta_{MT}$  in Eq. (3.14)) is based on the  $T_1$  map, so this parameter will also be biased by incidental MT in the underlying DFA experiment, albeit in the opposite direction (overestimated at long  $t_{RF}$  and vice versa). To test the above hypothesis regarding  $T_1$ -mapping and to attempt to determine a "balanced"  $t_{RF}$ , measurements were performed in the study relating to Paper II in which  $t_{RF}$  was kept fixed between  $\alpha_{PD}$  and  $\alpha_{T1}$  (instead varying the peak  $B_1$ ) but changed in between different DFA experiments. The resulting  $T_1$  maps did indeed show the expected dependence on  $t_{RF}$  (shorter estimated  $T_1$  at longer  $t_{RF}$ ). A value of  $t_{RF} =$ 698 µs yielded the  $T_1$  map most comparable with an IR-derived reference as well as with literature values of the three durations examined (211, 698 and 2003 µs), and was thus deemed the most "balanced". Figure 3.7 shows an illustrative sketch of the above rationale, using  $\delta_{MT}(t_{RF} = 698 \,\mu s) = 0$  from the experimental results as the ground-truth.

### Residual transmit field bias on MT<sub>sat</sub>

As shown in equations (3.14) and (3.15), MT<sub>sat</sub> is approximately compensated for transmit field  $(f_{\rm T})$  inhomogeneities when using nominal flip angles in the calculation  $(\delta_{\rm MT,app})$ . However, the assumption of instantaneous saturation (Eq. (2.18)) is only an approximation and there will, in fact, be a moderate decrease in  $M_{\rm zb}$  during the MT pulse itself (Eq. (2.24)). Induced  $\delta_{\rm b}$  will thus increase slightly less than by  $f_{\rm T}^2$ , and the observed  $\delta_{\rm MT,app}$  will consequently be somewhat overcompensated. In other words,  $\delta_{\rm MT,app}$  will be overestimated in low  $B_1^+$  areas and vice versa. At 3T, this residual transmit field bias on  $\delta_{\rm MT,app}$  has been empirically shown to follow a linear dependence (Helms, 2015):

$$\delta_{\mathrm{MT,app}}(f_{\mathrm{T}}) = A_{\mathrm{c}} \alpha_{\mathrm{sat}}^2 (1 - B \alpha_{\mathrm{sat}} f_{\mathrm{T}}), \qquad (3.32)$$

where  $A_c$  and B are phenomenological parameters, specific to the shape (Q), offset ( $\Delta$ ) and duration ( $t_{sat}$ ) of the MT pulse. Re-writing Eq. (3.32) on the form:

$$\delta_{\rm MT,app}/\alpha_{\rm sat}^2 = -A_{\rm c}Bf_{\rm T}\alpha_{\rm sat} + A_{\rm c}, \qquad (3.33)$$

reveals that  $A_c$  and B can be obtained by varying the nominal  $\alpha_{sat}$  and performing a linear regression of  $\delta_{MT,app}/\alpha_{sat}^2$  versus  $f_T\alpha_{sat}$ , where  $f_T$  is obtained from a separate flip angle map. After  $A_c$  has been obtained as the intercept, B is calculated from the slope ( $m = -A_cB$ ) as:

$$B = -m/A_{\rm c}.\tag{3.34}$$

The transmit field-corrected estimate,  $\delta_{MT,corr}$ , represents  $\delta_{MT,app}$  in the absence of flip angle bias (i.e.  $f_T = 1$ ):

$$\delta_{\text{MT,corr}} = \delta_{\text{MT,app}}(f_{\text{T}} = 1) = A_{\text{c}}\alpha_{\text{sat}}^2(1 - B\alpha_{\text{sat}}).$$
(3.35)

Dividing Eq. (3.35) by Eq. (3.32) to remove the tissue-specific parameter  $A_c$  and solving for  $\delta_{MT,corr}$  yields:

$$\delta_{\text{MT,corr}} = (1 - B\alpha_{\text{sat}}) / (1 - B\alpha_{\text{sat}} f_{\text{T}}).$$
(3.36)

where  $B\alpha_{sat} = C$  forms a pulse-specific linear correction factor. For the sake of completeness, the final post-hoc transmit field correction formula is as follows:

$$\delta_{\text{MT.corr}} = (1 - C) / (1 - f_{\text{T}}C).$$
 (3.37)

If a pixelwise linear regression is performed, maps of  $A_c$  and B are obtained. In the original 3T work, B was independent of tissue type and only moderately varying across the brain. This motivated a global correction factor of C = 0.4 for a  $t_{sat} = 4$  ms Gaussian pulse with  $\alpha_{sat} = 220^{\circ}$  and  $\Delta = +2.0$  kHz.

In the work relating to Paper IV, it was of interest to assess whether the linear  $f_{\rm T}$ -dependence observed at 3T, was indeed valid also for the wider range of local flip angles encountered at 7T. Furthermore, if the dependence was linear, it was relevant to resolve whether *C* needed to be adjusted for the slightly different MT pulse  $(t_{\rm sat} = 4 \text{ ms sinc main lobe with } \alpha_{\rm sat} = 180^{\circ} \text{ and } \Delta = -2.0 \text{ kHz}).$ 

In the subsequent 7T experiments, derived maps of *A* and *B* were quite noisy. At small local flip angles, it becomes very difficult to discern any potential non-linear behaviour, as noise becomes completely dominant (Figure 3.8). At the higher end of local flip angles, the residual bias does indeed appear to be linear. However, at the lower end, the true dependence remains obscure. As for *C*, it varied rather strongly between subjects and between different areas within the same subject. This is also visualized in Figure 3.8, where two similar linear fits result in either C = 0.20 or C = 0.34. In the end, a linear correction with C = 0.34 was settled for after calculating the mean value from multiple subjects and ROIs. In this context, it should be noted that the linear correction considerably improved homogeneity in the MT<sub>sat</sub> maps, as demonstrated in Paper IV.



**Figure 3.8.** Normalized apparent MT<sub>sat</sub> as a function of local flip angle. Data points were acquired from segmented WM in a subject where  $\alpha_{sat}$  was varied as 45, 60, 80, 90, 100, 120, 135, 140, 160, and 180 degrees. There is a weak negative dependence, indicating the residual transmit field bias. The magnitude and exact behaviour of this residual bias is, however, difficult to determine due to the very low SNR at small local flip angles. Note that *x* in the equations denote the horizontal axis in radians. The blue fit with was weighted by the inverse of the SD at each local flip angle while the red fit was obtained by determining the slope and intercept from a fixed *C*=0.34.

# Concluding remarks on MPM

The MPM-related research in this thesis focused almost exclusively on the derivation of  $T_1$  and MT<sub>sat</sub> maps. However, the MPM approach also facilitates mapping of PD through A and (if a multi-echo readout is employed)  $T_2^*$  (N. Weiskopf et al., 2013). Here, maps of the magnetic susceptibility ( $\chi$ ) from the phase data of the  $T_1$ -weighted scan were also derived. Recently, the hMRI toolbox was introduced which streamlines the process of DICOM to NIfTI conversion, coregistration, deriving the qMRI maps, as well as nonlinear registration to MNI space for multi-subject studies (Tabelow et al., 2019).

The A map derived from the DFA experiment is the product of PD and the RF receive sensitivity bias,  $f_R$ . The hMRI toolbox allows for correction of  $f_R$  through a separately acquired scan, scaled by a reference obtained by a homogenous body coil. Since a homogenous body coil is not available at 7T, this is not an option. The toolbox also provides the option to remove spatial intensity bias through the *Unified Segmentation* algorithm (Ashburner & Friston, 2005). In brief, *Unified Segmentation* assumes smoothly varying pixel intensities due to  $f_R$ , distinct from the

sharp pixel intensity gradients that arise close to tissue borders. The algorithm uses this assumption to perform simultaneous tissue segmentation and bias field correction. When  $f_{\rm R}$  has been separated from A, the latter is scaled to obtain an assumed mean PD value of 69 p.u. in normal appearing WM as determined in (Volz et al., 2012).

Eight equidistant echoes with multiples of TE = 1.97 ms were routinely acquired when performing MPM. This approach allowed for an increase in SNR by averaging the echoes (Helms & Dechent, 2009) and facilitated calculation of both  $T_2^*$  and  $\chi$ . By employing a log-linear fit over TE, performed simultaneously (using an approach named ESTATICS (N. Weiskopf, Callaghan, Josephs, Lutti, & Mohammadi, 2014)) for all three different weightings ( $T_1$ , PD, MT), calculation of  $T_2^*$  was again facilitated by the hMRI toolbox. ESTATICS has been shown to reduce the effects of subject motion on derived maps, assuming constant  $T_2^*$  across the different weightings. The phase data of the  $T_1$ -weighted echo train was used to perform QSM with either the MSDI (Acosta-Cabronero et al., 2018) or the MEDI algorithm (Liu et al., 2012).

The entire MPM approach is visualized in Figure 3.9, showing the same axial slice of a subject.



Figure 3.9. Flowchart of the MPM approach showing data from a representative subject. Note the increased spatial homogeneity after  $B_1^+$  correction.

# 4 – Flip angle mapping and DREAM

The inhomogeneity of the  $B_1$  field increases at higher  $B_0$  due to the shortening of the RF wavelength at higher Larmor frequencies (Eq. (2.2)). At 7T, the wavelength in tissue is approximately 11-12 cm and thus somewhat smaller than the width of an average human head (15-18 cm). This means that the MRI experiment is no longer performed in the near field region, but instead in the intermediate region, where run time effects start to affect the phase of  $B_1$ . The  $B_1$  inhomogeneity can be improved by using coils with several RF transmit channels that are driven with adapted phases and amplitudes ("RF shimming"). For a dual-channel setup, the degrees of freedom will increase from 0 to 2 compared to a single-channel coil transmitting in quadrature mode (identical amplitude of the two ports and a fixed phase difference of  $90^{\circ}$ ). The resulting interferences are, however, difficult to predict and large inhomogeneities will likely remain. With the dual-transmit head coil used here,  $B_1$ can vary from approximately 20% up to 170% of the prescribed amplitude, depending on subject head size and positioning (Figure 4.1). As the amplitude of  $B_1$ governs the flip angle according to Eq. (2.6), the variation in local flip angle to the nominally prescribed value (as set in the user interface) is the same. For any qMRI technique based on the local flip angle being known, it thus becomes necessary to perform a correction based on a separately acquired flip angle map, and this requirement includes most techniques that are based on changes of  $M_{z}$ . At non-UHF strengths, it is not strictly necessary to correct qMRI maps obtained with techniques that are only moderately biased by flip angle inhomogeneities, such as MT<sub>sat</sub> or MP2RAGE-based  $T_1$ -mapping. Strongly biased techniques such as DFA-based  $T_1$ mapping will still require correction. At 7T however, inhomogeneities are so pronounced that even techniques with only a weak dependence on the local flip angle may show a visually appreciable spatially varying bias.

It is customary to use the terms "flip angle map" and " $B_1^+$  map" interchangeably. The latter term stems from the concept that the linearly polarized  $B_1$  can be separated into two counter-rotating components denoted  $B_1^+$  and  $B_1^-$ . The  $B_1^+$  component rotates in the same direction as the rotating frame of reference and is the component related to the flip angle. The  $B_1^+$  component is thus referred to as the transmit field of a coil. The  $B_1^-$  component rotates in the other direction (against the precession of the spin isochromats) and is thus far off resonance but relates to receive sensitivity (see *Principle of Reciprocity*, Chapter 2)). In practice, the final  $B_1$  field is a superposition of all the fields created by each of the coils and different coils are used

for transmission and reception. Thus, the term "flip angle map" would be the more correct wording for the topic treated in this chapter.

When used to correct qMRI maps, it is convenient to denote the flip angle map by the transmit field bias  $(f_T)$  defined as the ratio of the local flip angle  $(\alpha_{loc})$  to the nominal flip angle  $(\alpha)$ :

$$f_{\rm T} = \alpha_{\rm loc} / \alpha, \tag{4.1}$$

which can alternatively be expressed in percent.



**Figure 4.1.** Example flip angle maps from two subjects using a dual channel transmit coil. The maps are shown in percent of the nominal flip angle. The central areas, particularly around the basal ganglia, exhibits larger local flip angles while peripheral areas such as the temporal lobess and cerebellum show smaller ones. Subject #2 has a larger and more elongated head in the anterior-posterior direction compared to Subject #1. This results in lower flip angles in the center for Subject #2 (~130% vs. ~170%). On the other hand, Subject #2 shows smaller local flip angles in the temporal lobes compared to subject #1 (~40%~~60% vs. ~70%). Note also the stronger right-left asymmetry of Subject #2.

# Dual Refocusing Echo Acquisition Mode (DREAM)

Dual refocusing echo acquisition mode (DREAM) is a very fast flip angle mapping sequence, able to map the whole brain in a few seconds (Nehrke & Bornert, 2012). The multislice DREAM pulse sequence consists of a stimulated echo acquisition mode (STEAM) preparation module with preparation flip angle  $\alpha$  (Frahm, Merboldt, Hänicke, & Haase, 1985), followed by a train of GRE modules with readout flip angle  $\beta$ . This produces a GRE signal of the free induction decay (FID),  $S_{\text{FID}}$ , and a stimulated echo (STE) signal,  $S_{\text{STE}}$ . Dividing the signal equations:

$$S_{\rm STE} = \sin(f_{\rm T}\beta) \frac{1}{2} \sin^2(\alpha_{\rm loc}) M_0, \qquad (4.2)$$

and

$$S_{\rm FID} = \sin(f_{\rm T}\beta)\cos^2(\alpha_{\rm loc})\,M_0,\tag{4.3}$$

and solving for  $\alpha_{loc}$  yields:

$$\alpha_{\rm loc} = \tan^{-1} \sqrt{2 S_{\rm STE} / 2 S_{\rm FID}}.$$
(4.4)

From here,  $f_{\rm T}$  is obtained from Eq. (4.1). The STEAM preparation module consists of two preparation  $\alpha$  pulses separated by time interval  $T_{\rm S}$  and dephaser gradient  $G_{\rm m2}$ . The first  $\alpha$  pulse excites magnetization into the transverse plane where it is dephased ("prepared") by  $G_{\rm m2}$  and then returned ("stored") to the longitudinal plane by the second  $\alpha$  pulse. If  $\alpha_{\rm loc} \neq 90^{\circ}$ , transverse magnetization will remain and is subsequently spoiled by gradient  $G_{\rm spoil}$  (a spoiler gradient is simply a dephaser gradient with a larger area). The imaging module starts with a  $\beta$  pulse that excites "fresh" magnetization into the transverse plane as well as inverting a small portion of the longitudinally stored magnetization. This is followed by dephaser gradient  $G_{\rm m1}$  and then readout gradient  $G_{\rm m}$  (standard GRE sequence) under which the echo constituting  $S_{\rm FID}$  is formed first, followed by  $S_{\rm STE}$ .

The process of different echoes being formed during the same pulse sequence through alternative "echo pathways" is nicely illustrated by the concept of extended phase graphs (Weigel, 2015). In brief, magnetization is described as being partitioned into "configuration states" that describe the degree and direction of dephasing, as well as in which plane (longitudinal/transverse) the magnetization resides. Figure 4.2 visualizes the DREAM sequence using the extended phase graph concept. When a pathway crosses the horizontal axis, an echo is formed. The echo

classification (FID, spin echo or STE) is determined by the pathway of the magnetization prior to echo formation.



**Figure 4.2.** Extended phase graph visualization and pulse sequence diagram showing a simplified version of a DREAM sequence. Black lines show different pathways of the magnetization created by RF excitation. Dashed lines denote magnetization that is "stored" in the longitudinal plane and therefor not dephased/rephased by gradients. When a pathway crosses the bold horizontal line at  $\tilde{F}_0, \tilde{Z}_0$ , the spin isochromats are rephased and an echo is formed. The pathway of the STE is denoted in blue and the pathway of the FID is denoted in red. There is also a spin echo formed during the STEAM preparatory module but it is not acquired. Note also the pathway (arrow) that will form the *next* STE during the second imaging module within the GRE train.

The periodicity of the tangent function sets the theoretical limit of the DREAM approach to  $0^{\circ} \leq \alpha_{loc} \leq 90^{\circ}$ . At  $\alpha_{loc} > 90^{\circ}$ , DREAM will return underestimated values as  $180^{\circ} - \alpha_{loc}$ . Effects from the Rician noise floor can affect the estimation at the lower end of the theoretical range (Figure 4.3). At the lower end,  $S_{STE}$  will approach the noise floor faster than  $S_{FID}$  and thus dominate imposed bias which manifests as an overestimation of  $\alpha_{loc}$ . At the upper end, this dynamic is reversed as  $S_{FID}$  will be very low while  $S_{STE}$  is high, and  $\alpha_{loc}$  could be consequently underestimated. In the experiments pertaining to Paper III, an underestimation was observed at high local flip angles although this was attributed to slice profile effects, and Rician noise effects was not considered in this regard. The observed overestimation at the lower end was, however, attributed to Rician noise which will lead to a stronger bias than at the upper end.

Relaxation will generally affect  $S_{\text{FID}}$  and  $S_{\text{STE}}$  differently. From Figure 4.2, it is clear that spin isochromats associated with  $S_{\text{STE}}$  will experience more  $T_2$  decay due to being in the transverse plane longer than the  $S_{\text{FID}}$  components (×2 in the figure). Ideally,  $TE_{\text{STE}}$  should be set as short as possible, since a long  $TE_{\text{STE}}$  (relative  $TE_{\text{FID}}$ ) in combination with a short  $T_2$  will result in an underestimation of  $\alpha_{\text{loc}}$  (Figure 4.4). A shorter  $TE_{\text{STE}}$  can be obtained by inverting the polarity of  $G_{\text{m2}}$  as this will result



**Figure 4.3.** (A) The S<sub>STE</sub> (blue) and S<sub>FID</sub> (red) signal as a function of the local preparatory flip angle (α). (B) The calculated local flip angle with/without (dashed/solid) additive noise from the noise floor in panel A. The arrows denote when either S<sub>STE</sub> or S<sub>FID</sub> approaches the noise floor, resulting in bias. Note the steep decline in calculated αloc passed 90°. Simulation details:  $\alpha/\beta=40^{\circ}/12^{\circ}$ ,  $0 \le f_T \le 2$ . Noise floor set to 1% of the maximum of S<sub>FID</sub>.

in the  $S_{\text{STE}}$  echo forming before the  $S_{\text{FID}}$  echo (not done in the experiments pertaining to Paper III). Furthermore, the  $S_{\text{STE}}$  signal will undergo  $T_1$  relaxation when stored in the longitudinal plane which may result in a small underestimation of  $\alpha_{\text{loc}}$  at short  $T_1$ . Finally,  $T_{\text{S}}$  can be modified so that the  $T_2^*$  decay of  $S_{\text{STE}}$  is matched to the  $T_2^*$  decay of  $S_{\text{FID}}$ . At  $T_{\text{S}} = TE_{\text{STE}}$ ,  $S_{\text{STE}}$  will be fully compensated for  $T_2^*$  decay, which introduces a bias in the flip angle map since  $S_{\text{FID}}$  will always have a  $T_2^*$  decay governed by  $TE_{\text{FID}}$ . By setting  $T_{\text{S}} = TE_{\text{STE}} + TE_{\text{FID}}$  (as done in the experiments pertaining to Paper III), both  $S_{\text{STE}}$  and  $S_{\text{FID}}$  experience the same  $T_2^*$ decay which thus factors out when applying Eq. (4.4). The simplified diagram in Figure 4.2 would also be compensated for  $T_2^*$  effects at  $T_{\text{S}} = TE_{\text{STE}} - TE_{\text{FID}}$ . The practical implication of this timing would be either a very long  $TE_{\text{STE}}$  (suboptimal with respect to SNR) or a very high amplitude of  $G_{\text{m2}}$ .

Since DREAM is commonly a multislice sequence, it may suffer from slice profile related bias caused by crosstalk between neighbouring slices. Acquiring slices in an interleaved manner (odd slices first and then the even slices) is a prerequisite to obtain unbiased flip angle maps. Slice profile bias in Eq. (4.4) is further alleviated by using a broader slice thickness in the STEAM module relative the GRE imaging module. The ratio of the slice thickness ratio. Lastly, the time between excitation of two neighbouring slices ( $T_{shot}$ ) can be increased to allow for full relaxation (5 ×  $T_1$ ). In the original work, this was done by increasing the number of slices

beyond the imaged object, but the current implementation allows to set  $T_{\text{shot}}$  independently of the FOV. Slice profile bias relates to  $T_1$  but is separate from the negligible  $T_1$  bias in Figure 4.4.



**Figure 4.4.** Bias in DREAM flip angle mapping due to  $T_1$  or  $T_2$  relaxation. Left column shows the  $S_{STE}$  (blue) and  $S_{FID}$  (red) relative signal as a function of either  $T_1$  (A) or  $T_2$  (C). The  $T_1$  bias is quite negigible (B) while the  $T_2$  bias of this ("FID" first pulse sequence) becomes quite serious at short  $T_2$  values (D). At the 7T average of  $T_2 = 50$  ms the bias is, however, <1°. Simulation details:  $\alpha/\beta=40^\circ/12^\circ$ ,  $TE_{STE}/TE_{FID}/TS/TD = 1.39/0.99/2.38/6.08$  ms. The  $T_2$  was set infiniteley long when simulating  $T_1$ -related bias and vice versa.

As  $T_1$  increases at 7T, sensitivity to slice crosstalk increases, demanding a longer  $T_{\text{shot}}$ . The increased range of  $\alpha_{\text{loc}}$  due to  $B_1$  inhomogeneities compared to 3T will increase sensitivity to bias from Rician noise and slice profile effects.

#### The use of several preparation flip angles

In Paper III, a small underestimation of the local flip angle at  $\alpha_{loc} > 50^{\circ}$  in a phantom and in vivo is demonstrated. In the paper, this is tentatively explained by deviations in the slice profiles, not represented by the signal equations (4.2) and (4.3). This claim was supported by simulations of the STEAM pulse shape at various  $\alpha_{loc}$ , indicating that the deviations were relevant even at a slice thickness ratio of 2.0. At the lower end of the  $f_{\rm T}$  range, an overestimation was observed at  $\alpha_{loc} < 20^{\circ}$  which was likely due to Rician noise. Here, it is worth noting that the upper limit of 50° should be independent of research site, while the lower limit of 20° will depend

on other factors of the pulse sequence, such as  $\beta$ ,  $TE_{FID}$ ,  $TE_{STE}$ , voxel size, and also on receiver equipment since it pertains to low SNR.

The work described in Paper III was initially motivated by observed blurring artifacts, appearing in the temporal lobes and cerebellum (areas with low  $f_{\rm T}$ ) of DFA-derived  $T_1$  maps. It was determined that the cause of these artifacts was the low SNR of the DREAM flip angle map used for correction. Increasing the preparation flip angle  $\alpha$  resulted in signal voids in the center of the brain as  $\alpha_{loc}$ approached 90°. Thus, more than one DREAM sequence was acquired with different  $\alpha$ . It was then revealed that the DREAM flip angle maps systematically varied in estimated  $\alpha_{loc}$  based on the nominal  $\alpha$ . To solve this problem, three DREAM sequences with nominal  $\alpha = 25^{\circ}$ ,  $40^{\circ}$ , and  $60^{\circ}$  were acquired. The obtained  $100 \times f_{\rm T}$  maps (calculated directly on the scanner in %) were scaled to  $\alpha_{\rm loc}$  whereafter pixels where  $\alpha_{\rm loc} < 20^{\circ}$  and  $\alpha_{\rm loc} > 50^{\circ}$  were masked. The three masked maps were then combined into a single high-SNR map free of bias from Rician noise and slice profile effects. In pixels where there are more than one nonzero value, the average is calculated. Since the  $\alpha = 60^{\circ}$  map will contain a signal void in the center, it is important to perform the combination prior to coregistration to any high-resolution image volume, as this procedure will interpolate between finite-valued and zero-valued pixels, creating artificially underestimated local flip angles. The steps of the combination process are visualized in Figure 4.5.



**Figure 4.5.** Flowchart showing the process of combining separately acquired DREAM flip angle maps with nominal preparation flip angles of  $\alpha$  = 25, 40 and 60°. The flip angle maps ( $f_T$ ) are first scaled to the local flip angle,  $\alpha_{loc}$ , separately masked in pixels with  $\alpha_{loc} < 20^\circ$  or  $\alpha_{loc} > 50^\circ$ , scaled back to  $f_T$  and then combined through non-zero averaging into a high-SNR bias-free map. Note the central signal void in the  $\alpha$  = 60° map.

# 5 – MPRAGE-based qMRI

The MPRAGE sequence was introduced to obtain  $T_1$ -weighted 3D images with a high WM-GM contrast and short scan time (Mugler & Brookeman, 1990, 1991). It has since become a standard for structural imaging  $T_1$ -weighted imaging (Deichmann, Good, Josephs, Ashburner, & Turner, 2000). The sequence consists of three modules within an encompassing cycle, TC (Figure 5.1). Enhanced tissue contrast is obtained by a magnetization preparation (MP) module consisting of an inversion pulse and a subsequent period of free  $T_1$  relaxation. This is followed up by a train of  $TF = N_y$  spoiled GREs with a varying inner loop phase encoding gradient, sampling a 2D plane of the 3D k-space. The last module consists of a recovery period, TD, before the magnetization is inverted again and a new cycle (with a different outer loop phase encoding) starts. The process is repeated  $N_z$  times until the desired 3D k-space has been sampled. The  $M_z$  reaches a steady state *between* sequential cycles after only a few iterations. The default acquisition time is:

$$T_{\rm acg} = N_{\rm z} \times TC. \tag{5.1}$$

The readout train, referred to as a rapid acquisition gradient echo (RAGE), has a duration of  $TF \times TR$ . The inversion time, TI, is defined as the time from inversion to the center of the 2D k-space plane. Note that the definitions of TI, TD etc. tend to vary in the literature.

For three typical Cartesian phase encoding orders, TC is calculated as:

Linear: 
$$TC = TI - \frac{TF \times TR}{2} + TF \times TR + TD,$$
 (5.2a)

Centric: 
$$TC = TI + TF \times TR + TD$$
, (5.2b)

Reverse centric: TC = TI + TD. (5.2c)

The  $T_1$  contrast is governed by these sequence timings as well as the flip angle. The *TE* is typically very short and  $T_2^*$ -weighting can thus be ignored. Unlike the ordinary spoiled GRE, the RAGE is acquired under transient conditions, i.e. a changing  $M_z$  and thus a changing WM-GM contrast. This means that the phase encoding order

also influences the overall contrast, which is dominated by  $M_z$  at the center of k-space. During the RAGE,  $M_z$  approaches an inner loop steady state ( $M_0^* < M_0$ ) with time constant ( $T_1^* < T_1$ ) (Deichmann et al., 2000; Deichmann & Haase, 1992):

$$T_1^* = [1/T_1 - 1/TR \cdot \ln(\cos(f_{\mathrm{T}}\alpha))]^{-1}, \tag{5.3}$$

$$M_0^* = M_0 \cdot \frac{1 - \exp(-TR/T_1)}{1 - \exp(-TR/T_1^*)}.$$
(5.4)

For  $f_T \alpha \to 0$  it follows that  $T_1^* \to T_1$  and  $M_0^* \to M_0$ . This steady state can be referred to as a driven equilibrium to distinguish it from the outer loop steady state between sequential cycles. The transition in  $M_z$  leads to a signal weighting across k-space which manifests as a distortion of the point spread function (PSF). This distortion is exacerbated if the polarity of  $M_z$  changes sign close to acquisition of (Deichmann et al., 2000). The *TR* is typically kept short to reduce the duration of the RAGE. In summary, an MPRAGE image has the benefit of enhanced WM-GM contrast, compared to a standard spoiled GRE, by the use of inversion and a corresponding increase in the dynamic range of  $M_z$ . However, MPRAGE may suffer from PSF distortions as well as a longer scan time.



**Figure 5.1.** Summary of a single-shot MPRAGE sequence with linear phase encoding and full k-space sampling.(A) Development of  $M_z$  during *TC* for WM (blue,  $T_1 = 1300 \text{ ms}$ ,  $\rho = 0.65$ ), GM (red,  $T_1 = 1900 \text{ ms}$ ,  $\rho = 0.75$ ) and CSF (green,  $T_1 = 4300 \text{ ms}$ ,  $\rho = 1.0$ ). The MP leads to a larger separation of WM and GM at *TI* (solid black vertical line) compared to the steady state acquired by the end of the RAGE (the RAGE is encompassed by the dashed lines). (B) Sampling of a plane in k-space during *TR*×*TF*. When *TF* lines have been sampled, the next inversion pulse is applied and the process is repeated  $N_z$  times. (C) Applied RF pulses during *TC*. The cycle begins with an inversion pulse, followed by a delay and then a readout train of excitation pulses (RAGE). Lastly, there is another delay, *TD*, until the next inversion pulse at the beginning of the next cycle. Simulation details: *TCITITDITR* = 3500/1200/808/8 ms, *TF* = 256,  $f_{T\alpha} = 8^\circ$ ,  $f_{mv} = 0.96$ , 3 cycles to obtain an outer loop steady state. The *TF* was reduced to 12 in (B) and (C) for visual clarity.

# Partial k-space sampling

Other acquisition considerations pertain to partial k-space sampling techniques such as partial Fourier, parallel imaging and elliptical k-space sampling. The common purpose of all these techniques is to reduce scan time by sampling less k-space lines. In partial Fourier, asymmetric sampling is employed so that only one half of k-space is fully sampled (Feinberg, Hale, Watts, Kaufman, & Mark, 1986). Unmeasured kspace data is then substituted through zero-filling or homodyne processing. In parallel imaging, the distance between k-space lines are increased while the maximal extent in k-space is maintained. If a phased array is used, ensuing aliasing due to the reduced FOV can be either removed or prevented by the individual sensitivity of the coil elements. One such technique is SENSE, where the aliased images are unfolded in image space (Pruessmann et al., 1999). Elliptical k-space sampling pertains to omitting the low-SNR diagonal corners of k-space. In 3D, the sampled portion forms an elliptic cylinder inside the cuboid k-space. To maintain a constant *TI*, a zigzag *k*-space trajectory is employed, alternating between the inner and outer phase encoding directions ( $k_y$  and  $k_z$ ) during the RAGE. Trajectories in the periphery have a larger variation in the outer loop phase encoding direction to maintain the same number of sampled k-space lines (Figure 5.2), and *TF* can thus be chosen independently of  $N_y$ . The trajectories are optimized in such a way that the contrast is unaffected. An analogous concept for TSE-imaging has been introduced as "view orders" (Busse et al., 2008). On the system used here, it is referred to as the "3D free factor".



**Figure 5.2.** Ellipitcal phase encoding, showing zigzag k-space trajectories during individual RAGE trains (color coded). Since  $k_y$  denotes the inner loop, variation during each RAGE is primarily in this direction. However, there is also some variation in the outer loop ( $k_z$ ) direction, ensuring that each RAGE contains the same number of k-space lines (denoted as dots since the readout  $k_x$  direction is through plane). Thus, trajectories far from  $k_z$ =0 (black and light green), varies more in the  $k_z$  direction.

Some partial k-space sampling settings may have an influence on the pulse sequence timing parameters. For instance, a varying *TI* between RAGE trains was observed when using partial Fourier in the inner loop phase encoding direction in conjunction with an elliptical phase encoding.

# Correction of $B_1$ -induced spatial bias in MPRAGE

In a standard spoiled GRE,  $M_z$  is always in a driven equilibrium in all voxels of the acquired volume as the central k-space line is acquired. Only the value of  $M_0^*$  and the amount of magnetization flipped into the transverse plane by  $f_T \alpha$  will vary and lead to a  $B_1$ -dependent spatial bias. For MPRAGE on the other hand, signal homogeneity is affected by a third factor in the form of  $T_1^*$  (Eq. (5.3)). Whether  $M_z$  is in a steady state (as well as the closeness to that steady state) depends on  $T_1^*$  and will be spatially dependent. This further implies that the phase encoding order may have an influence on the spatial signal homogeneity. An ordinary  $T_1$ -weighted spoiled GRE may still show a stronger spatial bias depending on coil setup, however, since it typically employs a higher flip angle than MPRAGE.

Sensitivity to  $B_1$  inhomogeneity in MPRAGE can be reduced by a separately acquired spoiled GRE with a predominantly PD-weighted contrast (Van de Moortele et al., 2009). If  $S_{MP}$  is the magnetization prepared signal and  $S_{GRE}$  is the reference GRE signal, the corrected signal is obtained by a simple ratio:

$$S_{\text{MP/GRE}} = \frac{S_{\text{MP}}}{S_{\text{GRE}}} = \frac{f_{\text{R}}\rho M_{\text{z,MP}}(T_1^*)\sin(f_{\text{T}}\alpha_{\text{MP}})\exp(-TE/T_2^*)}{f_{\text{R}}\rho M_{\text{z,GRE}}\sin(f_{\text{T}}\alpha_{\text{GRE}})\exp(-TE/T_2^*)} = \frac{M_{\text{z,MP}}(T_1^*)\sin(f_{\text{T}}\alpha_{\text{MP}})}{M_{\text{z,GRE}}\sin(f_{\text{T}}\alpha_{\text{GRE}})}$$
(5.5)

where  $f_{\rm R}$  denotes the receive sensitivity after combination of channels and  $\rho$  is the PD. The underlying idea is that  $S_{MP}$  and  $S_{GRE}$  are affected by the same sensitivity and transmit fields and that the influence of those fields can be "divided out" in the corrected image. Further, since  $S_{\text{GRE}}$  lacks the MP-induced  $T_1$ -contrast of  $S_{\text{MP}}$ ,  $T_1$ weighting is not reduced by the division. On the contrary, given that both acquisition voxels are the same size, they will also share the same spin system so that influence of PD and  $T_2^*$  is removed from the normalized image to create a "pure"  $T_1$  contrast. Removal of PD influence will, in fact, increase the WM-GM contrast as  $\rho$  is typically higher in GM than in WM. This was successfully demonstrated in Paper I. Both acquisitions should further have identical bandwidths per pixel so that the fat signal displacement does not vary. As previously mentioned,  $M_{z,MP}$  experiences an additional influence from  $f_{\rm T}$  in the form of  $T_1^*$ . Thus, the transmit component of  $B_1$ is partly compensated for by the division, but not removed entirely (even for  $\alpha_{MP}$  =  $\alpha_{\rm GRE}$ ) as is the case for  $f_{\rm R}$ . Careful choice of  $\alpha_{\rm MP}$  and  $\alpha_{\rm GRE}$  will minimize the residual  $f_{\rm T}$  dependence. To this end,  $\alpha_{\rm GRE}$  should be kept small. A small  $\alpha_{\rm GRE}$  also means that the  $T_1$  contrast in  $S_{MP/GRE}$  is not reduced.

As in the MPM-technique, algebraic operations applied to the raw images will lead to noise propagation into the resulting image or map. Compared to the SNR of  $S_{MP}$  (SNR<sub>MP</sub>), the SNR of  $S_{MP/GRE}$  (SNR<sub>MP/GRE</sub>) will be (Van de Moortele et al., 2009):
$$SNR_{\rm MP/GRE} = \frac{SNR_{\rm MP}}{\sqrt{1 + S_{\rm MP/GRE}^2}}.$$
(5.6)

A benefit of Eq. (5.6) is that the reduction in SNR is larger for high values of  $S_{\rm MP/GRE}$ , so that pixels with low  $S_{\rm MP}$  and thus low inherent SNR are less affected by the noise progression. For some typical normalized pixel intensities of  $SNR_{\rm MP/GRE} = 0.97/0.60/0.39$  in WM/GM/CSF respectively (acquired by the 0.7 mm isotropic protocol described in Paper I) the decrease in SNR would be 28/14/6.8% compared to the initial  $SNR_{\rm MP}$ . The previously described increase in WM-GM contrast will counteract this decrease in SNR and the CNR may actually be higher in  $S_{\rm MP/GRE}$ .

As the spatial variation of  $B_1$  is dominated by low spatial frequencies, the voxel size of the reference GRE could be increased to reduce scan time (van Gelderen, Koretsy, de Zwart, & Duyn, 2006), although this can potentially blur the "pure"  $T_1$ contrast as the above rationale regarding identical spin systems is no longer strictly true. The sequential acquisition of  $S_{\rm MP}$  and  $S_{\rm GRE}$  is suboptimal since it is likely to require offline post-processing in the form of rigid (6 parameters) co-registration. Perhaps more importantly, it cannot exploit the negative dynamic range of  $M_z$  to increase conventional WM-GM contrast (bright WM, darker GM), as the polarity of  $M_z$  cannot be determined from two separate scans. A sequential approach is, however, less sensitive to intra-scan subject motion.

### Inversion pulse

It is suboptimal to employ standard RF pulses for inversion as the inversion efficiency (the proportion of  $M_z$  that is inverted at the end of the cycle) will vary due to  $B_1$  inhomogeneities. This is of course especially true at UHF strengths. Hence; an adiabatic RF pulse is normally employed instead. An adiabatic pulse is both amplitude and frequency modulated and very insensitive to  $B_1$  inhomogeneities above a certain threshold amplitude, referred to as the adiabatic condition. As the duration of an adiabatic inversion pulse is typically of the same order of magnitude as the  $T_2$  in tissue, local inversion efficiency could potentially be biased as observed at 9.4T (Hagberg et al., 2017). Due to the  $B_0$ -dependency of  $T_2$ , this spatially imposed bias should be smaller at 7T compared to 9.4T although larger than at 3T. In the experiments relating to Paper V, an adiabatic 13 ms inversion pulse, tailored for UHF, was used (Hurley et al., 2010).

### MP2RAGE

The reference GRE can also be acquired in an interleaved fashion to reduce interscan subject motion and facilitate inherent coregistration of the two image volumes (Van de Moortele et al., 2009). The MPRAGE and reference GRE are acquired within the same *TC* at two different *TI* values:  $S_1$  at  $TI_1$  and  $S_2$  at  $TI_2$  (Figure 5.3). The two RAGE trains may be separated by an additional short delay. The MP2RAGE approach expanded on this concept by replacing  $S_{MP/GRE}$  in the standard ratio of Eq. (5.4) with the complex combination (Marques et al., 2010):

$$S_{\text{MP2RAGE}} = \text{Re}\left(\frac{S_1 \cdot S_2^*}{|S_1|^2 + |S_2|^2}\right),$$
 (5.7)

where the asterisk denotes the complex conjugate. As opposed to their respective counterparts (the magnitude signals  $S_{MP}$  and  $S_{GRE}$  in Eq (5.5)),  $S_1$  and  $S_2$  here denotes complex signals with  $|S_1|$  and  $|S_2|$  being the respective magnitudes. Eq. (5.7) implies the same benefits as Eq. (5.5), i.e. removal of influence from PD,  $T_2^*$  and  $f_R$  as well as a reduction of  $f_T$  bias. The added benefit comes from the preservation of the relative phase information, i.e. any change in sign in the polarity of  $M_z$  between  $TI_1$  and  $TI_2$  can be identified. This becomes clear if Eq. (5.7) is first expanded as (Helms, Lätt, & Olsson, 2020):

$$S_{\text{MP2RAGE}} = \frac{\text{Re}(S_1)\text{Re}(S_2) + \text{Im}(S_1)\text{Im}(S_2)}{\text{Re}(S_1)^2 + \text{Im}(S_1)^2 + \text{Re}(S_2)^2 + \text{Im}(S_2)^2}.$$
(5.8)

An identical result is obtained if the numerator in Eq. (5.7) is instead  $S_1^*S_2$ . Thus, both versions can be found in the literature (Marques & Gruetter, 2013; Marques et al., 2010). If Eq. (5.8) is instead expressed in terms of magnitude

$$|S_{1,2}| = \sqrt{\operatorname{Re}(S_{1,2})^2 + \operatorname{Im}(S_{1,2})^2},$$
 (5.9a)

and phase

$$\phi_{1,2} = \tan^{-1}(\operatorname{Im}(S_{1,2})/\operatorname{Re}(S_{1,2})),$$
 (5.9b)

the following expression is obtained:

$$S_{\rm MP2RAGE} = \frac{|S_1| / |S_2| \cos(\phi_1 - \phi_2)}{|S_1|^2 / |S_2|^2 + 1}.$$
(5.10)

Here, the removal of  $f_{\rm R}$  bias and the semi-quantitative nature of MP2RAGE becomes evident by the ratio  $|S_1|/|S_2|$ . The change in polarity is identified by the cosine function, where  $\phi_2$  serves as a reference which is assumed to be of positive polarity. This means that the central k-space line no longer needs to be acquired after the zero-crossing. Thus,  $TI_1$  can be shortened to better utilize the dynamic range obtained after the inversion. This can considerably increase WM-GM contrast. Other benefits of Eq. (5.7) includes the fact that  $S_{MP2RAGE}$  will be limited to values between -0.5 and +0.5. This increases comparability between different research sites and protocols since this range of possible values determines the display window range. It also conveniently limits the values of background noise pixels. A potential drawback of such a constriction is that pixel intensities may become "saturated" for a certain protocol after, for example, injection of a contrast agent, which would strongly reduce contrast. Further, the SNR in the case described by Eq. (5.7) is increased compared to the one in Eq. (5.5). The MP2AGE protocol used as a comparison in Paper I yielded pixel intensities in WM/GM/CSF of approximately +0.36/-0.15/-0.47, an increase in the WM-GM pixel intensity difference by 38% compared to the protocol for sequential normalization.



**Figure 5.3.** Development of  $M_z$  during *TC* in an MP2RAGE experiment, analogous to panel A in Figure 5.1 for MPRAGE. The colored lines denote WM (blue,  $T_1 = 1300$  ms,  $\rho = 0.65$ ), GM (red,  $T_1 = 1900$  ms,  $\rho = 0.75$ ) and CSF (green,  $T_1 = 4300$  ms,  $\rho = 1.0$ ). The first RAGE is marked by a light gray background with a vertical line denoting  $TI_1$  and starts almost instantly after the inversion. The second RAGE is marked by a darker gray background with  $TI_2$  denoted by a second vertical line. Note the larger dynamic range of  $M_z$  compared to the standard MPRAGE in Figure 5.1. Note also that the  $M_z$  of CSF has a negative polarity at  $TI_1$ . Simulation details:  $TCITI_1/TI_2/TDITR = 5000/900/2750/6.8$  ms, TF = 256,  $f_r\alpha_{TI1}/f_r\alpha_{TI2} = 5^\circ/3^\circ$ ,  $f_{inv} = 0.96$ , 3 cycles to obtain an outer loop steady state.

### MP2RAGE T<sub>1</sub>-mapping

The restriction of  $-0.5 \leq S_{\text{MP2RAGE}} \leq +0.5$  and semi-quantitative nature of the MP2RAGE technique allows for conversion of  $S_{\text{MP2RAGE}}$  into  $T_1$  by forward signal modeling (Figure 5.4). If mono-exponential relaxation is assumed,  $M_z$  and hence  $S_{\text{MP2RAGE}}$  can be rather easily simulated as the MP2RAGE cycle alternates between free  $T_1$  relaxation towards  $M_0$ , and a driven progression during the readout train towards  $M_0^*$  with time constant  $T_1^*$ , as described by equations (5.3) and (5.4). To simulate  $M_z$  requires stating the flip angles ( $\alpha_1$  and  $\alpha_2$ ), TF, TR,  $TI_1$ ,  $TI_2$  as well as TC. For a more accurate simulation, a separate flip angle map can be added to obtain the local flip angles  $f_T\alpha_1$  and  $f_T\alpha_2$  (Marques & Gruetter, 2013).



**Figure 5.4.** Complex MP2RAGE raw data at  $Tl_1$  and  $Tl_2$ . The "MP2RAGE image" ( $S_{MP2RAGE}$ ) is derived using Eq. (5.7) and the  $T_1$  map is derived from forward signal modeling of  $S_{MP2RAGE}$  ( $f_{ITV} = 0.96$ ). The  $T_1$  map also used a separetley acquired flip angle map for  $f_T$  bias correction. Note the lack of tissue contrast at  $Tl_2$  as  $M_z$  has passed the zero-crossing for all  $T_1$  values. Acquisition details:  $TC/Tl_1/Tl_2/TD/TR = 5000/900/2750/6.8$  ms, TF = 256,  $\alpha_{TI1}/\alpha_{TI12} = 5^{\circ}/3^{\circ}$ .

## MP3RAGE

The residual  $f_T$  bias in MP2RAGE-derived  $T_1$  maps served as a motivation for introducing the MP3RAGE sequence in Paper V. The purpose of this technique is to quantify both  $T_1$  and  $f_T$  simultaneously, thereby obtaining inherently coregistered whole brain maps of both these MR parameters at the same high spatial resolution. As the name implies, a third RAGE is appended to the end of the MP2RAGE cycle (Figure 5.5). This third RAGE is applied with a relatively high flip angle ( $\alpha_{high}$ ) compared to what is typically used in MP2RAGE sequences. The high flip angle quickly forces the spin system into a  $T_1$ -weighted driven equilibrium



**Figure 5.5.** Development of  $M_z$  (solid colored lines) during *TC* in an MP3RAGE sequence, analogous to Figure 5.3 for MP2RAGE. The colored lines denote WM (blue,  $T_1 = 1300$  ms,  $\rho = 0.65$ ), GM (red,  $T_1 = 1900$  ms,  $\rho = 0.75$ ) and CSF (green,  $T_1 = 4300$  ms,  $\rho = 1.0$ ). The three readout trains are denoted by different shades of gray background. The cycle contains no "dead time" of free relaxation (no white background). The first two readout trains are acquired using the same low flip angle ( $\alpha_{low}$ ) so that  $M_z$  can progress undisturbed towards a PD-weighted driven equilibrium (DE) (upper dashed lines). The third RAGE is acquired with a higher flip angle ( $\alpha_{high}$ ) and is quickly forced into a  $T_1$ -weighted driven equilibrium (lower dashed lines) before  $TI_3 = TC$  and the next inversion. Note the smaller dynamic range compared to MP2RAGE in Figure 5.3 which affects precision. The three readout trains are acquired using a linear/reverse centric phase encoding order. Simulation details:  $TC/TI_1/TI_2/TI_2/TR = 5721/954/3814/5721/7.45$  ms, TF = 256,  $f_r\alpha_{low}/f_r\alpha_{high} = 3^\circ/16^\circ$ ,  $f_{Inv} = 0.96$ , 3 cycles to obtain an outer loop steady state.

(very short  $T_1^*$  and a low  $M_0^*$ ). Note that there is no free  $T_1$  relaxation after the third RAGE. Thus, if the driven equilibrium is reached during the cycle, the outer loop steady state is automatically enforced. Immediately after inversion, the first and second readout trains are acquired at a lower flip angle ( $\alpha_{low}$ ) and identical *TR* under transient conditions towards a PD-weighted (high  $M_0^*$ ) driven equilibrium with a longer  $T_1^*$ . The three resulting images, acquired at  $TI_1$ ,  $TI_2$  and  $TI_3$ , respectively, are referred to as  $S_1$ ,  $S_2$  and  $S_3$ . The  $S_1$  image obtains a  $T_1$ -weighting from the inversion recovery with moderate  $f_T$  bias and resembles a typical MPRAGE image. The  $S_2$  image is PD-weighted with moderate  $f_T$  bias and

resembles the  $S_{PD}$  image in a DFA experiment. The  $S_3$  image is  $T_1$ -weighted with a heavy  $f_T$  bias and should be completely analogous to the  $S_{T1}$  image in a DFA experiment (but the  $S_3$  nomenclature will be used in the context of MP3RAGE).

The idea is to combine a DFA experiment with an MP2RAGE sequence and to exploit the  $f_T$  dependence of both  $T_{1,app}$  and  $T_1^*$  to solve for  $T_1$  and  $f_T$  simultaneously. The first step is to perform a fit of the progressive partial saturation towards  $M_0^*$  under  $\alpha_{PD}$  during the first two RAGE trains, based on  $S_1$  and  $S_2$ , thus, determining the longer  $T_1^*$  as well as the hypothetical signal acquired at the PD-weighted driven equilibrium ( $S_{PD}$ ) at  $TI \rightarrow \infty$  as:

$$S_{1,2} = S_{\rm PD} + (S_0 - S_{\rm PD}) \exp(-TI_{1,2}/T_1^*).$$
(5.11)

where  $S_0$  is the hypothetical signal that would have been acquired at TI = 0 ms,  $\alpha_{low}$  and the same TR as  $S_1$  and  $S_2$ . As  $S_{PD}$  here is analogous to  $S_{PD}$  in the DFA experiment (but different from  $S_2$ ) it will be referred to by that same nomenclature. This is analogous to a standard inversion recovery experiment (Eq. (2.10)) albeit with  $T_1^*$  instead of  $T_1$ . The problem is ill-posed with three unknown parameters and only two data points. However, if a global  $f_{inv}$  can be assumed (and TD = 0 ms),  $S_0$  can be approximated from  $S_3$  as:

$$S_0 = -f_{\rm inv} S_3 \frac{\sin(f_{\rm T} \alpha_{\rm low})}{\sin(f_{\rm T} \alpha_{\rm high})} \approx -f_{\rm inv} S_3 \frac{\sin(\alpha_{\rm low})}{\sin(\alpha_{\rm high})}.$$
 (5.12)

The right-hand approximation is necessary to eliminate  $f_{\rm T}$ , which is yet unknown. The highly saturated driven equilibrium of  $S_3$  ensures that this error has only a limited effect on the absolute value of the calculated  $S_0$ . The same applies to any moderate deviation of the assumed global  $f_{\rm inv}$  from the local, actual, efficiency.

The fitted  $S_{PD}$  and acquired  $S_3 = S_{T1}$  constitutes the DFA experiment. Using the rational approximation and nominal flip angles, the apparent  $T_1$  is obtained as:

$$T_{1,\text{app}} = 2TR \frac{S_{\text{PD}}/\alpha_{\text{low}} - S_3/\alpha_{\text{high}}}{S_3\alpha_{\text{high}} - S_{\text{PD}}\alpha_{\text{low}}},$$
(5.13)

with a quadratic  $f_{\rm T}$  dependence (Eq. (3.11)):

$$T_{1,\text{app}} = f_{\text{T}}^2 T_1. \tag{5.14}$$

The next step is to exploit the  $f_{\rm T}$  dependencies of the calculated  $T_{1,\rm app}$  and the fitted  $T_1^*$  to obtain closed-form solutions for both  $T_1$  and  $f_{\rm T}$ . To do this,  $T_1^*$  (Eq. (5.3)) is

re-written as a rational function like  $T_{1,app}$ , valid for small flip angles and short *TR*. This is done first by the linear approximation  $\ln(\cos(f_T\alpha_{low})) \approx \cos(f_T\alpha_{low}) - 1$  and then by the rational approximation  $\cos(f_T\alpha_{low}) - 1 \approx -(f_T\alpha_{low})^2/2$ . This yields:

$$T_1^* = \left(\frac{1}{T_1} + \frac{f_T^2 \alpha_{\text{low}}^2}{2TR}\right)^{-1}.$$
 (5.15)

By the substitution:

$$f_{\rm T} = \sqrt{T_{1,\rm app}/T_1},$$
 (5.16)

and solving for  $T_1$ , a rational expression for  $T_1$  is obtained as follows:

$$T_{1} = T_{1}^{*} \left( 1 + T_{1,\text{app}} \frac{\alpha_{\text{low}}^{2}}{2TR} \right).$$
(5.17)

Once  $T_1$  has been calculated,  $f_T$  can be obtained from Eq. (5.16).



**Figure 5.6.** Simulation of bias in MP3RAGE, caused by the rational approximation. Deviation in  $S_0$  due to the omission of  $f_T$  in Eq. (5.12) is very small (A) and leads to negligible bias in the fitting of  $T_1^*$  (B) and  $S_{PD}$  (C). Likewise, deviation in  $T_1^*$  caused by the rational approximation is very small due to both the small  $\alpha_{low} = 3^\circ$  and short TR = 7.45 ms. Due to the higher  $\alpha_{high} = 16^\circ$ , the bias in  $T_{1,app}$  is larger (D). At  $f_T = 1.7$ , there is a deviation of +130 ms (arrow) compared to +3 ms for  $T_1^*$ . This bias is reduced in the estimated  $T_1$  (E) to +13 ms (arrow) and +0.017 in estimated  $f_T$  (F). This simulation assumes that the  $T_1$ -weighted driven equilibrium has been reached by the end of TC and that  $f_{frv} = 0.96$  is known.

The rational approximation of Eq. (5.15) is very accurate because of the small  $\alpha_{low} = 3^{\circ}$  and short TR = 7.45 ms (Figure 5.6). The rational approximation of  $T_{1,app}$  is not as accurate due to the higher  $\alpha_{high} = 16^{\circ}$ . This will translate to a small overestimation of estimated  $T_1$  and  $f_T$  at high  $B_1^+$ . It is possible to solve for  $f_T$  (and thus  $T_1$ ) numerically without using the rational approximation although this will yield a quite complicated expression considered to be beyond the scope of this text. A flowchart of the MP3RAGE approach can be seen in Figure 5.7.



**Figure 5.7.** Flowchart of the MP3RAGE calculations. Note the lack of contrast in the basal ganglia of the  $T_1^*$  map compared to the  $T_1$  map and the high resolution of the flip angle map ( $f_1$ ).

#### Phase encoding order

The MP3RAGE cycle contains no period of free relaxation and the three *TI* values are therefore restricted by the phase encoding order. The encoding order determines where in the RAGE the central k-space line ( $k_0$ ) is acquired (Figure 5.5). The three Cartesian encoding orders treated here are centric ( $k_0$  acquired in the beginning), linear ( $k_0$  acquired in the middle) and reverse centric ( $k_0$  acquired in the end).

Regarding signal fitting to obtain  $T_1^*$  and  $S_{PD}$ , the encoding orders of  $S_1$  and  $S_2$  are important to increase precision as the orders determine  $TI_1$  and  $TI_2$ . The issue of optimizing precision in an IR experiment with *N* TI values has been treated by (Ogg & Kingsley, 2004). The longest TI ( $TI_{N-1}$ ) should be set as close to full relaxation (5 ×  $T_1$ ) as possible (in practice, as long as possible) while the shortest TI ( $TI_0$ ) should be set as short as possible. The remaining TI values should be geometrically spaced between  $TI_0$  and  $TI_{N-1}$  (Labadie, Gounot, Mauss, & Dumitresco, 1994):

$$TI_{n} = TI_{0} + (TI_{N-1} - TI_{0})[(2^{n} - 1)/(2^{N-1} - 1)].$$
(5.18)

In MP3RAGE, N is limited to 3 and  $TI_0$  is fixed at 0 ms. The value of  $TI_2 = TI_{N-1}$  is maximized by a reverse centric order which for  $TF \times TR = 7.45 \times 256$  ms (as in the experiments pertaining to Paper V) amounts to 3821 ms. This leaves only  $TI_n = TI_1$  left to be determined, and it should then be set as close to 1274 ms as possible. Out of the three encoding orders, a linear order with  $TI_1 = 960$  ms yields the closest value ( $TI_1 = TI_0$  for centric and  $TI_1 = 1914$  ms for reverse centric). The increase in precision was experimentally confirmed in an experiment pertaining to Paper V.

The encoding order of  $S_3$  is only relevant to ensure that  $M_z$  is fully in the  $T_1$ -weighted driven equilibrium by  $TI_3$ . This is essential to reduce bias when calculating  $T_{1,app}$ . For the third RAGE, a reverse centric order should thus be chosen. Figure 5.5 depicts the optimal combination of encoding orders, i.e. linear/reverse centric/reverse centric.

#### Solving for $T_1^*$ and $S_{PD}$ analytically

It is possible to forego the curve fitting of Eq. (5.11) and instead obtain  $T_1^*$  and  $S_{PD}$  analytically. First, consider the simplest scenario when the three *TI* values of  $S_0$ ,  $S_1$  and  $S_2$  are equidistantly spaced by the time constant  $\tau$ , i.e.  $TI_0/TI_1/TI_2 = 0/\tau/2\tau$ . This corresponds to a reverse centric (or high-low) phase encoding order of both  $S_1$  and  $S_2$ . The signal equation is re-written as:

$$S_{i} = F - DE^{i}, \tag{5.19}$$

where  $i = 0, 1, 2, E = \exp(-\tau/T_1^*), D = (S_0 - S_{PD})$ , and  $F = S_{PD}$ . To eliminate D and F, P is introduced as:

$$P = \frac{S_0 - S_2}{S_0 - S_1} = \frac{(F - D) - (F - DE^2)}{(F - D) - (F - DE)} = \frac{1 - E^2}{1 - E} = \frac{(1 - E)(1 + E)}{(1 - E)} = 1 + E,$$
(5.20)

which yields:

$$E = \frac{S_0 - S_2 - S_0 - S_1}{S_0 - S_1} = \frac{S_1 - S_2}{S_0 - S_1}.$$
(5.21)

Now  $T_1^*$  can be solved for in closed form:

$$T_1^* = -\tau / \ln(E). \tag{5.22}$$

Setting up the difference  $S_1 - S_0$  yields *D* as:

$$S_1 - S_0 = D(1 - E) \Rightarrow D = \frac{S_1 - S_0}{1 - E},$$
 (5.23)

from which  $F = S_{PD}$  is finally obtained:

$$F = S_0 + D.$$
 (5.24)

If the *TI* values are not equidistantly spaced, it becomes necessary to introduce "fictitious" evenly spaced time points on the  $T_1^*$  curve, which can be treated algebraically. Consider five points on the  $T_1^*$  curve during the 1st and 2nd RAGE trains, all equidistantly spaced with time interval  $\tau/2$  (Figure 5.8). Each point represents possible values of  $TI_1$  and  $TI_2$  when using either a centric, linear, or reverse centric phase encoding order. With the new time interval, *E* becomes  $E = \exp\left(-\frac{\tau/2}{T_1^*}\right)$ . The signal equation is again re-written as:

$$S_{j} = F - DE^{j}, \qquad (5.25)$$

where j = 0,1,2,3,4. For a linear order of the 1<sup>st</sup> and 2<sup>nd</sup> RAGE (j = 0,1,3), *P* becomes:

$$P = \frac{S_0 - S_3}{S_0 - S_1} = \frac{(1 - E)(E^2 + E + 1)}{(1 - E)} = E^2 + E + 1.$$
(5.26)

Note that the index of *S* now denotes *j* and no longer a particular RAGE train. The positive root of *E* is obtained from the quadratic formula:

$$E = -1/2 + \sqrt{(1/2)^2 + P - 1}.$$
 (5.27)

To obtain  $T_1^*$ , the correct time interval must be used:

$$T_1^* = -\frac{\tau/2}{\ln(E)}.$$
 (5.28)

Lastly, *D* and *F* are solved for as above (equations (5.23) and (5.24)).

For a linear-reverse centric order (j = 0,1,4), solving for *E* requires finding the roots of the cubic polynomial:

$$P = \frac{S_0 - S_4}{S_0 - S_1} = \frac{1 - E^4}{1 - E} = E^3 + E^2 + E + 1.$$
(5.29)

A fully analytical approach would be beneficial compared to signal fitting with regards to processing time. The effect on noise progression has not yet been evaluated, however.



**Figure 5.8.** Illustration of how to analytically solve for  $T_1^*$  and  $S_{PD}$  if  $T_0/T_1/T_2$  are not equidistantly spaced. Each point on the  $T_1^*$  curve during RAGE#1 and RAGE#2 represents possible values of  $T_1$  and  $T_2$  using either centric, linear or reverse centric phase encoding order. The points on the  $T_1^*$  curve during RAGE#1 and RAGE#2 are equidistantly spaced by  $T_2$  and represent possible values of  $T_0/T_1/T_2$  for any combination of the three phase encoding orders. All combinations must have three values of *j*, where the first must be *j* = 0.

# High spatial frequency artifacts and the $T_1$ -weighted driven equilibrium

When the third RAGE ( $S_3$ ) is acquired, there is an initial steep decline in  $M_z$  as the magnetization is forced into the  $T_1$ -weighted driven equilibrium (cf. Figure 5.5 and 5.8). This leads to a strong weighting of the signal across k-space. If  $S_3$  is acquired with a reverse centric encoding order, it is the high spatial frequencies at the edge of k-space that receive the highest weighting. In the image, this manifests as strong ringing artifacts near the border between the brain and the dura mater. This is basically the opposite effect of the broadening of the PSF typically experienced in MPRAGE imaging. In the experiments pertaining to Paper V, these artifacts were successfully suppressed by an adiabatic saturation pulse, applied immediately before acquisition of  $S_3$  (Figure 5.9). In most of the brain, this prepares  $M_z$  so that the distance between the starting point and  $M_0^*$  is decreased. The saturation pulse could thus also aid in ensuring that the driven equilibrium is reached. However, if  $f_{\rm T}$  is low,  $M_0^*$  will increase by the increased  $T_1^*$  (see equations (5.3) and (5.4)). This means that in areas of low  $f_{\rm T}$  and long  $T_1$ , the distance between the starting point of  $M_z$  and  $M_0^*$  could instead be increased by the saturation pulse. How to ensure that the driven equilibrium is reached in the entirety of the brain is still an unresolved issue with the MP3RAGE technique.



**Figure 5.9.** An RF saturation pulse is applied prior to RAGE#3. At  $f_T = 1.0$  (red),  $M_z$  is prepared much closer to  $M_0^*$  (dashed line) compared to when the pulse is not applied (dotted line). This eliminates ringing artifacts in  $S_3$  and the system reaches a driven equilibrium earlier. At low  $B_1^*$  (blue),  $M_0^*$  is elevated elevated away from the starting point of  $M_z$  when a saturation pulse is applied. Thus, the driven equilibrium is not reached at  $T_{13}$  neither with nor without the saturation pulse (arrow). Simulation details:  $T_1 = 1900$  ms,  $\rho = 0.75$  (GM),  $\sigma_{high} = 16^\circ$ , TR = 7.45 ms, TF = 256.

#### **Concluding remarks on MP3RAGE**

Other uses of the nomenclature "MP3RAGE" exists in the literature (conference abstracts) (Hung, Chen, Chuang, Chang, & Wu, 2013; Rioux, Saranathan, & Rutt, 2014). However, the concept of incorporating a DFA experiment within an MP3RAGE cycle and solving for  $T_1$  and  $f_T$  analytically appears to be new. Ideally, the technique should be fully analytical, without the need for a signal fit to acquire  $T_1^*$  and  $S_{PD}$ . For Paper V, a signal fit was, however, used to acquire  $T_1^*$  and  $S_{PD}$  instead of trying to find the roots of the cubic polynomial in Eq. (5.29), although this should be solvable using the well-established cubic formula (Guilbeau, 1930). Such an approach would make post-processing virtually instantaneous as no coregistration is required. It is possible to obtain  $T_1$  and  $f_T$  through a LUT-based approach as with MP2RAGE, and this was shown in a preliminary report (Olsson, Andersen, Kadhim, & Helms, 2021). This method would remove the necessity to force the system into a driven equilibrium by the end of the cycle. The increased dimensionality would, however, increase the processing time dramatically.

It is possible that using a non-adiabatic saturation pulse that scales with  $f_{\rm T}$  would be beneficial, to prepare  $M_{\rm z}$  closer to  $M_0^*$  also in low  $f_{\rm T}$  areas, while also avoiding edge enhancement artifacts.

The inherently coregistered flip angle map will be of an unusually high spatial resolution (1 mm isotropic was used in Paper V). Conventionally, flip angle maps are acquired at low spatial resolution, justified by the supposedly smoothly varying  $B_1$  field. However, flip angle mapping based on DREAM, dual *TR* (Yarnykh, 2007), and the Bloch-Siegert shift (Sacolick, Wiesinger, Hancu, & Vogel, 2010), all show elevated  $B_1^+$  estimates in the CSF of the ventricles (Brink, Bornert, Nehrke, & Webb, 2014). Simulations of the electromagnetic field have indicated that this could be caused by the higher electrical conductivity of CSF. The sharp edge at the border between the ventricles and surrounding tissue could thus result in PVEs when a flip angle map of low spatial resolution is used to correct a quantitative map, and the same concern should apply to sulcal CSF close to cortical GM.

The  $T_1$  maps acquired with MP3RAGE show generally higher  $T_1$  estimates compared to the DFA technique, and substantially higher than the MP2RAGE LUTbased approach. This overestimation is larger than expected based on the rational approximation (Figure 5.6) and does not appear to be  $B_1^+$  related (not spatially dependent). The adiabatic inversion pulse should introduce an MT-related bias in the  $T_1^*$  calculation as in MP2RAGE (Rioux et al., 2016). However, due to the  $T_1^$ weighted driven equilibrium at the end of the cycle, the difference in magnetization between the free and the bound pool  $(M_{0b}/M_{0f} - M_{zb}/M_{zf})$  should be considerably less than in MP2RAGE. The MP3RAGE technique should thus be less sensitive to incidental MT effects than MP2RAGE, albeit more sensitive than DFA.

# 6 – Concluding remarks

The work presented in this thesis has aimed at implementing existing and novel qMRI techniques and optimizing them for 7T-specific conditions. Efforts have been made to identify and correct biases in derived parameter maps, as well as forming an understanding of the underlying physical origin of these biases. The strong inhomogeneity of the  $B_1$  field at 7T is the primary source of bias and well-established techniques such as MPM requires more care to control or exclude different biases compared to 3T. On this note, it would be interesting to evaluate the performance of the MP3RAGE technique at 3T, as the reduced  $B_1^+$  inhomogeneity would allow to more reliable reach the driven equilibrium across the whole brain. Similarly, the performance of MP3RAGE using a more advanced parallel transmit array at 7T would also be interesting to explore.

The scope of this thesis has been rather broad, as the parameter mapping has focused on both  $T_1$ , MT<sub>sat</sub>, and the local flip angle (Figure 6.1). Regarding pulse sequences, they have ranged from the standard spoiled GRE, to variations of the MPRAGE sequence, to the STEAM-prepared DREAM sequence. A common theme amongst the pulse sequence protocols treated here is that they can all be considered to be rather fast, which is a critical aspect for any clinical application. More research regarding the variability of especially  $T_1$ -mapping techniques is needed. This statement is valid not only for the techniques used in this thesis and for UHF, but for  $T_1$ -mapping in general, as noted by Stikov et al. (2015). It is my personal hope that the findings presented in this thesis can be useful to other researchers pursuing increased robustness and reproducibility within the qMRI field.



**Figure 6.1.** Maps of the three main parameters in this thesis: The longitudinal relaxation time ( $T_1$ ), the magnetization transfer saturation ( $\delta_{MT,corr}$ ), and the local flip angle ( $f_T$ ).

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