

Development of spoiled gradient echo sequences for MRI relaxometry

Thesis submitted for the degree of Doctor of Biomedical Sciences at the University of Antwerp to be defended by

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Antwerp, 2024

Faculty of Pharmaceutical, Biomedical and Veterinary Sciences

Department of Biomedical Sciences





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Summary

Magnetic Resonance Imaging (MRI) is a noninvasive, non-ionizing technique that allows both anatomical and functional imaging with tunable contrast among soft tissues. Although MRI is a significant source of data, providing knowledge about the physical parameters that define image contrast, images are being interpreted qualitatively in the clinical practice for the vast majority of applications. Quantitative MRI (qMRI) is an umbrella term that encompasses quantification of the parameters specifying signal intensity, including relaxation, magnetic susceptibility, and diffusion properties, as well as chemical composition and concentration, just to name a few. Relaxometry is the specific qMRI aiming to quantify the MR relaxation parameters which are dependent on the biochemical tissue environment. Relaxometry remains a main research topic in qMRI as the relaxation times have been used as biomarkers for tissue characterization and differentiation and can be of great radiological support. A major disadvantage of qMRI is the necessity of acquiring multiple contrast-weighted images from which the parameters can be estimated. This requires additional scanning time.

Several methods for fast relaxometry have been proposed, but there is yet no general consensus on a fast multiparametric mapping technique that allows good image quality within clinically acceptable time and with good reproducibility and repeatability.

This PhD thesis discloses developments in this direction.

Chapter 1 reports a short history of the concept of Nuclear Magnetic Resonance and the development of the Magnetic Resonance Imaging technique. The main MRI hardware components are briefly introduced to then describe the MR signal generation and acquisition. A detectable signal is first generated via RF excitation, after which it experiences relaxation processes through T_1 and T_2 relaxation. The signal is then spatially encoded by the application of magnetic field gradients. This Chapter describes the main types of RF excitation pulses and the three imaging encoding gradients principles (frequency encoding, phase encoding, and slice selection), as well as the principle of Spin Echo and Gradient Echo sequences, and the k-space acquisition techniques. Part of the Chapter is dedicated to Extended Phase Graphs simulations, a powerful tool for MR sequence development that can provide a thorough description of the signal. We then present an overview of the main qMRI techniques dedicated to relaxometry. A few of the most common T_1 mapping techniques are reported, including Inversion Recovery, Look Locker, Variable Flip Angle, Magnetization Prepared 2 Rapid Acquisition Gradient Echoes, and Variable flip angle with Actual Flip angle Imaging (VAFI). Lastly, T_2 and T_2^* mapping techniques are discussed, and the main brain applications for T_1 , T_2 , and T_2^* are reported. The Chapter ends with an introduction of simultaneous multiparametric mapping protocols and the confounding factors in relaxometry.

Chapter 2 describes the contributions presented in this PhD thesis, with a quick overview of the relaxometry methods that were developed and tested.

Chapter 3 reports the research study on the optimization of a preparation module for a faster steady-state approach and sampling of Actual Flip angle Imaging (AFI), a B_1 mapping technique. In order to achieve a fast steady-state signal, we studied the spoiling characteristics for a prepared AFI together with the number of dummy pulses that would be needed in a AFI sequence without any preparation. We report and describe the features of the preparation module and we validate them against B_1 inhomogeneities to show the robustness of the approach. The use of the preparation pulse is also tested for the (center-outwards) k-space acquisition scheme, showing how the module can provide both a time benefit and higher accuracy to the parameter estimation.

Chapter 4 introduces a slice profile correction for VAFI – a T_1 and B_1 mapping technique using AFI and spoiled gradient echo acquisitions – as well as a 2D multislice stacking approach for AFI, which respectively provide a more accurate and faster way to acquire parametric maps. These two new approaches were used together to improve AFI and VAFI as fast 2D quantitative approaches: the two contributions indeed allow the computation of B_1 -corrected T_1 maps to be reconstructed from a fast 2D multislice scans while retaining the accuracy and precision of the original 3D technique. The stacking approach can be extended to other sequences that use multiple repetition times and is of easy implementation, while the slice correction method is based on a look-up table of values generated via fitting of Bloch simulations.

Chapter 5 illustrates a newly developed sequence, Relaxation Alternate Mapping of Spoiled Echo Signals (RAMSES) for multiparametric mapping of T_1 , B_1 , and T_2^* parameters. This was achieved by adding a bipolar multi-gradient-echo readout to the second repetition time of AFI, without lengthening the scanning time. The RF spoiling features were analyzed to find the optimal RF spoiling increment. The method used for B_1 -corrected T_1 mapping is identical to the one used in VAFI, while T_2^* mapping was achieved from the data within the exponential signal decay. RAMSES was tested for an array of T_1 and T_2^* values, and while it is meant to be used as a 3D technique, we also provided an example of a 2D implementation.

Chapter 6 illustrates the newly developed sequence, Echo Planar Imaging Fast Actual

Nutation Imaging (EPIFANI) for ultrafast B_1 -corrected T_1 mapping. This sequence is an EPI version of AFI, which can be used to provide high time efficiency to a multiparametric acquisition, and represents one of the very few attempts to acquire multiparametric maps with EPI. We reported the T_2^* decay effects on the signal as well as on the estimated B_1 and T_1 parameters. A slice profile correction was also integrated for B_1 computation, while the correction presented in Chapter 4 was applied to correct for slice profile effects in T_1 maps.

For the research studies presented in Chapter 3, 4, 5, and 6, we report simulations, as well as phantom, ex vivo and in vivo analyses for sequence testing, while validation is performed against literature gold standard techniques and shows the potential of the proposed techniques as new methods for mapping in qMRI, with the aim to acquire faster and more accurate relaxometry maps.

Chapter 7 reports a summary of the contributions as well as a list of expected future developments for all the techniques and methods presented in this manuscript. Conclusive thoughts and reflection are then reported on the contributions to the field and their place in the context of the general direction and meaning of qMRI as a bioimaging approach.

Chapter 8 concludes the thesis with an overview of the author's CV including the academic experiences and publications.

Samenvatting

Magnetic Resonance Imaging (MRI) is een niet-invasieve, niet-ioniserende techniek die zowel anatomische als functionele beeldvorming mogelijk maakt waarbij er verschillende beeldcontrasten tussen de weefsels kunnen gebruikt worden. Hoewel MRI een belangrijke bron van gegevens is en kennis biedt over de fysieke parameters die het beeldcontrast bepalen, worden beelden in de klinische praktijk voor de meeste toepassingen kwalitatief geïnterpreteerd.

Kwantitatieve MRI (qMRI) is een overkoepelende term die de kwantificering omvat van parameters die in de conventionele MRI beelden de signaalintensiteit bepalen, waaronder relaxatie, magnetische susceptibiliteit en diffusie-eigenschappen, evenals chemische samenstelling en concentratie, om er maar een paar te noemen. Reeds meerdere decennia is het bepalen van de MR relaxatietijden (relaxometrie) een belangrijk onderzoeksonderwerp in qMRI. De relaxatietijden worden gebruikt als biomarkers voor weefselkarakterisering en -differentiatie en zijn van groot radiologisch belang. Een nadeel van qMRI is de noodzaak van de opname van meerdere contrast-gewogen beelden op basis waarvan de parameters kunnen geschat worden. Dus dit vraagt extra scantijd.

Verschillende methoden voor snelle relaxometrie zijn voorgesteld, maar er is nog geen algemeen consensus over een snelle multiparametrische mappingtechniek die een goede beeldkwaliteit biedt binnen klinisch aanvaardbare tijd, met een goede reproduceerbaarheid en herhaalbaarheid.

Dit proefschrift draagt bij tot ontwikkelingen in deze richting.

Hoofdstuk 1 geeft een korte geschiedenis van het concept van Nucleaire Magnetische Resonantie en de ontwikkeling van de Magnetic Resonance Imaging-techniek. De belangrijkste MRI hardwarecomponenten worden kort geïntroduceerd om vervolgens het MR-signaalte beschrijven. Een detecteerbaar signaal wordt eerst gegenereerd via RF-excitatie, en ondergaat vervolgens relaxatieprocessen via T₁- en T₂-relaxatie. Het signaal wordt vervolgens spatiaal gecodeerd door het specifiek aansturen van magnetische veldgradiënten. Dit hoofdstuk beschrijft de belangrijkste soorten RF-excitatiepulsen en de drie ruimtelijke codering principes gebruikmakend van de beeldvormingsgradiënten (frequentiecodering, fasecodering en snede selectie), evenals het principe van Spin Echo- en Gradient Echo-sequenties, en de k-ruimte-acquisitietechnieken. Een deel van het hoofdstuk is gewijd aan de simulaties van Extended Phase Graphs, een krachtig hulpmiddel voor MR-sequentieontwikkeling dat een grondige beschrijving van het signaal kan bieden. Vervolgens presenteren we een overzicht van de belangrijkste qMRItechnieken die gewijd zijn aan relaxometrie. Enkele van de meest voorkomende T₁mappingtechnieken worden besproken, waaronder *Inversion Recovery, Look Locker, Variable Flip Angle, Magnetization Prepared 2 Rapid Acquisition Gradient Echoes* en *Variable Flip Angle met Actual Flip angle Imaging* (VAFI). Vervolgens worden T₂- en T₂^{*} mappingtechnieken besproken, en de belangrijkste hersentoepassingen worden gerapporteerd. Het hoofdstuk eindigt met een introductie van gelijktijdige multiparametrische mapping protocols en de verstorende factoren in relaxometrie.

Hoofdstuk 2 beschrijft kort de bijdragen gepresenteerd in dit proefschrift, met een overzicht van de ontwikkelde en geteste relaxometrie methoden.

Hoofdstuk 3 rapporteert het onderzoek naar de optimalisatie van een voorbereidingsmodule in de Actual Flip angle Imaging (AFI) - een B₁-mappingtechniek- sequentie waardoor de steady-state sneller bekomen wordt ten voordele van een snellere sampling van AFI. Voor deze optimalisatie werden de *spoiling*-eigenschappen bestudeerd van de voorbereidingsmodule in AFI, evenals het aantal dummy-pulsen dat nodig zou zijn in een AFI-sequentie zonder voorbereidingsmodule. We rapporteren en beschrijven de kenmerken van de voorbereidingsmodule en valideren deze tegen B₁-inhomogeniteiten om de robuustheid van de aanpak aan te tonen. Het gebruik van de voorbereidingsmodule wordt ook getest voor een (van centrum naar buiten gericht) k-ruimteacquisitieschema, waarbij wordt aangetoond hoe de module zowel een ijdswinst als een hogere nauwkeurigheid in de parameterschatting kan bieden.

Hoofdstuk 4 introduceert een snedeprofielcorrectie voor VAFI - een T_1 - en B_1 -mappingtechniek die gebruik maakt van AFI en *spoiling* gradient echo-acquisities - evenals een 2D multisnede-sequentiële aanpak voor AFI, die respectievelijk een nauwkeurigere en snellere manier biedt om parametrische kaarten te verkrijgen. Deze twee nieuwe strategieën werden samen gebruikt om AFI en VAFI te verbeteren als snelle 2D-kwantitatieve methode. Het gecombineerde protocol laat toe om B_1 -gecorrigeerde T_1 -mappen te reconstrueren uit snelle 2D-multisnede-scans terwijl de nauwkeurigheid en precisie van de parameterschatting van de oorspronkelijke 3D-techniek behouden blijven. De sequentiële aanpak kan worden uitgebreid naar andere sequenties met meerdere repetitietijden en is eenvoudig te implementeren. Dee snedecorrectiemethode is gebaseerd op een look-up tabel van waarden die zijn gegenereerd via fitten van Bloch-simulaties.

Hoofdstuk 5 illustreert een nieuw ontwikkelde sequentie, *Relaxation Alternate Mapping of Spoiled Echo Signals* (RAMSES) voor multiparametrische mapping van T_1 , B_1 en T_2^* -parameters. Dit werd bereikt door het toevoegen van een bipolaire multi-gradient-

echo readout binnen de tweede repetitietijd in de AFI sequentie. Deze modulatie vraagt geen extra scantijdDe RF-*spoiling* eigenschappen werden geanalyseerd om de optimale stapgrootte van de RF-*spoiling* te vinden. De methode die werd gebruikt voor B₁-gecorrigeerde T₁-mapping is identiek aan die in VAFI, terwijl T₂*-parameters geschat werden uit de data tijdens het exponentieel signaal verval. RAMSES werd getest voor een reeks van T₁- en T₂*-waarden, en hoewel het bedoeld is om te worden gebruikt als een 3D-techniek, hebben we ook een voorbeeld van een 2D-implementatie ontwikkeld.

Hoofdstuk 6 illustreert de nieuw ontwikkelde sequentie, Echo Planar Imaging Fast Actual Nutation Imaging (EPIFANI) voor ultrasnelle B₁-gecorrigeerde T₁-mapping. Deze sequentie is een EPI-versie van AFI, die als voordeel heeft een hoge tijdefficiëntie te bieden voor de multiparametrische acquisitie. We rapporteren de invloed van T^{*}₂-verval zowel op het signaalals op de B₁ en T₁ parameter schattingen. Een snedeprofielcorrectie werd ook geïntegreerd voor B₁-schatting, terwijl de snedeprofielcorrectie gepresenteerd in Hoofdstuk 4 werd toegepast om snedeprofieleffecten te corrigeren in T₁mappen.

Voor de onderzoeksstudies gepresenteerd in Hoofdstuk 3, 4, 5, en 6, rapporteren we simulaties, evenals fantoom-, ex vivo- en in vivo-analyses voor het testen van sequenties. Validatie wordt uitgevoerd ten opzichte van de gouden standaardtechnieken uit de literatuur en toont de potentiële waarde van de voorgestelde technieken als nieuwe methoden voor relaxometrie, met snellere en nauwkeurigere parameter schattingen.

Hoofdstuk 7 rapporteert een samenvatting van de bijdragen evenals een lijst van verwachte toekomstige ontwikkelingen voor alle technieken en methoden gepresenteerd in dit manuscript. Concluderende visies en reflecties worden vervolgens gerapporteerd over de bijdragen aan het vakgebied en hun positie in de context van de algemene onderzoeksdomein van qMRI als een bio-imaging methode.

Hoofdstuk 8 sluit het proefschrift af met de CV met een overzicht van de academische ervaringen en publicaties van de auteur.

Chapter 1 Magnetic Resonance Imaging- an introduction

Magnetic Resonance Imaging (MRI) is a noninvasive and non-ionizing imaging technique that allows the acquisition of both anatomical and functional imaging with tunable contrast among soft tissues. The core of MRI systems is represented by scanners that generate a strong magnetic field and employ magnetic field gradients and radiofrequency waves to elicit and acquire signals which are then processed to provide images. Although a relatively young technique, MRI made its way into the clinical practice and its use has been constantly increasing over the years, with a plethora of clinical and research applications for imaging of all body parts. Applications for MRI span from neuroimaging to angiography, from musculoskeletal to cardiac MR, for analysis of several properties via diffusion, perfusion, functional imaging, elastography, and spectroscopy MR. It is the de facto standard for monitoring iron overload [1] and soft tissue imaging including brain, for neuroimaging, breast, cardiac, abdominal/pelvic, and musculoskeletal imaging [2] as well as for imaging major joints, the spine, and soft tissues (muscles, tendons, and ligaments) of the extremities. The impressive versatility of this technique has contributed to making MRI a thriving research field, with a myriad of ongoing active threads in all of the topics - a look at the topics and the proceedings of the annual meeting of the International Society for Magnetic Resonance in Medicine will clear any skepticism about the liveliness of MRI research.

It is estimated that during 2022 in OECD countries, an average of 84.4 MRI exams every 1000 inhabitants were performed – with a minimum of 5.1 and a maximum of 163.4 among the OECD countries [3] – with an increasing trend in the mean number over the last few years, as shown in Figure 1.1.



Figure 1.1: Average number of MRI exams every 1000 inhabitants for the OECD countries. A dip in 2020 – during the zenith of the COVID-19 pandemic – can be observed.

Due to the high cost of purchasing the MRI system, as well as maintenance costs, direct costs (technician and electricity), departmental and allocated overhead, MRI is commonly associated with high costs [4]. The expensiveness of this imaging technique is also associated with the long scanning time required in the clinical practice, as well as to many other factors: in the United States, for example, factors such as rural location, number of contracted insurance plans, and Medicare patient proportion were found to be positively associated with commercial prices for brain MRI on a sample of 2630 hospitals, with a national median cost of \$1,900 (interquartile range: \$1,024-\$3,197) for brain MRI [5] and a Medicare cost of \$471 [6]. The reduction of costs, the proneness to artifacts (especially related to motion) and the increasing research on new MRI modalities for the simultaneous investigations of several parameters (multiparametric MRI) have attracted studies for faster scans. Indeed, faster MRI acquisitions allow to optimize machine time use while reducing cost per capita and increasing scanner throughput. However, the MR images acquired and analyzed in clinical practice remain qualitative, often based on mixed contrast due to the large number of parameters to be fine-tuned in MRI, and the variability in its images can lead to interpretations that may be unreliable, uncertain, or ambiguous. One of the applications that has been gaining land in this attempt is guantitative MRI (gMRI), which relies on the calculations of maps for tissue parameters that could serve as biomarkers. Nowadays, qMRI represents a fervid research area contributing to a more standardized and objective image analysis and interpretation, but several issues still need to be tackled before qMRI becomes a clinically reliable imaging approach.

1.1 From NMR to MRI - a short history

It's 1938 when Isidor Isaac Rabi at Columbia University describes how lithium chloride can be induced to change its principal magnetic orientation through the application of an oscillating magnetic field within the radio frequency range and a varying main magnetic field produced by an electromagnet [7]. Rabi named this phenomenon "Nuclear Magnetic Resonance" (NMR) and was awarded the 1944 Nobel Prize in Physics. One year later, the team led by Felix Bloch at Stanford University [8] and the one led by Edward Mills Purcell at the Massachusetts Institute of Technology [9] simultaneously and independently demonstrated NMR in condensed matter (water and paraffin, respectively). Purcell then extended this work to solids and liquids and Bloch formally reports the equation of the nuclear induction experiment, granting them a joint Nobel Prize in Physics in 1952.



Figure 1.2: Nuclear Magnetic Resonance as first observed by Rabi in 1938. The figure shows the refocused beam intensity at various fields (frequency of oscillation was held constant at $3.518 \cdot 10^6$ cycles/second). Image obtained with permission from Rabi et al. 1938 [7].

In 1959, Singer at the University of California, Berkeley, proposes NMR as a noninvasive tool to measure in vivo blood flow. In 1971, Raymond Damadian discovers a difference in the relaxation times of certain mouse tumors with respect to normal tissues [10]. Paul Lauterbur demonstrated in 1973 the use of NMR to create an image by the application of magnetic field gradients for frequency encoding [11]. In 1974, the sensitization of tomographic image slices – the selective excitation – was published by Sir Peter Mansfield; while in 1977, he first described the echo-planar imaging technique, for acquiring such 2D images in only a few seconds [12]. By taking advantages of the developments in cryogenics, Damadian and his colleagues at the State University of New York designed and built a superconducting magnet operating at 0.508 T. The first human body image by NMR is acquired in 1977 (see 1.3b) [13], 6 years after the first human CT images [14], but only Lauterbur and Mansfield will be awarded with the Nobel Prize "for their discoveries concerning magnetic resonance imaging", arising a controversy regarding the paternity of the idea of NMR as an imaging technique.





(a)

(b)

Figure 1.3: (a): Dr. Damadian and his colleague Dr. Minkoff in front of the first human NMR 0.508 T scanner. (b): First human scan, performed on Dr. Minkoff, which required 4.5 hours of scanning. Resolution is 4-6 mm. Image obtained with permission from Damadian 1980 [15].

In 1975, Richard Ernst's group in Zurich invented the two-dimensional Fourier transform imaging (2D FT), while Clow and Young produced the first published human head image with MRI in 1978. Since then, commercial clinical systems in hospitals have started to be introduced and the technique developed rapidly through the late 1980s to become the method of choice for non-trauma neurological scanning. Norman Ramsey was then awarded in 1989 a Nobel prize for developing the theory of the chemical shift, while Kurt Wührich was awarded the Nobel Prize in Chemistry in 2002 for his development of NMR spectroscopy for the determination of the three-dimensional structure of biological macromolecules in solution.

Since its discovery, NMR has become an even more powerful tool, employed in spectroscopy for the study of molecular physics and for the determination and identification of the structure of organic molecules in solution. When Lauterbur published the principle of frequency encoding, which instead allows the generation of images, he baptized the technique as 'zeugmatography' (meaning "imaging from a joining together" – of the main field and the gradients), but was then shortened to simply 'Magnetic Resonance'. Switching the name of the technique from NMR to MRI helped in its acceptance as an imaging technique by society, as the term 'nuclear' needed to be dropped as it implied a connection with nuclear energy and nuclear medicine which uses ionizing electromagnetic waves with high energy. Nevertheless, the term NMR still remains employed to distinguish the spectroscopy use of MR from the imaging one, which instead is unanimously called MRI.

1.2 MR hardware - an overview

As the name MRI suggests, the principle behind the acquisition of scans relies on the application of a static magnetic field, the B_0 field, to the tissue of interest, which is generated by either room-temperature or - most often - superconducting, electromagnets or permanent magnets.

Superconducting magnets are by far the most common ones, as they provide the best homogeneity and stability over time, and have a typical tunnel shape. They are made of Niobium-Titanium (NbTi) alloy filaments embedded in a copper matrix and coated with an insulator. The metal is cooled down under the superconducting transition temperature (7.7 K for NbTi filaments) by liquid Helium, which allows exploiting their superconductive property of near zero electric resistance at temperatures close to absolute zero. Thus, the current runs in a loop of superconductive wire without resistive losses. In order to maintain the temperature low, these coils are immersed in a cryostat containing liquid Helium and surrounded by a cold shield and a vacuum chamber. To limit the amount of He evaporation in the Helium vessel, pressure is maintained above the liquid surface pressure by a heater. When heat is generated (e.g. by gradient activity), the pressure increases and helps to limit the amount of evaporation. Pressure is controlled and kept within the 'thermal margin' with the possibility to be released by the system in case of malfunction. The cryocooler or 'cold head' uses controlled gas expansion to keep the heat shield at 40 K within the magnet cryostat. Some new systems also use cryogen-free magnets, which contain Helium gas at around 40 K instead of liquid and rely on efficient cold-head units. If the superconducting transition temperature is exceeded, the wire becomes resistive and the stored electrical energy will be dissipated as heat, propagating the effect and resulting in a 'quench', a collapse of the magnetic field together with very rapid boiling off of the Helium. High-pressure gas will then be released in exhaust or quench pipes, venting the gas outside the imaging room.

On the other hand, dipolar electromagnets systems use regular resistive coils wound around iron pole pieces to generate low magnetic field. When an electric current flows through the coils, the iron becomes magnetized. These systems tend to have lower costs but are heavier than superconductive systems.

Permanent magnets, with fields up to 0.3 T, are cheap and offer the advantage of very low running costs since neither He nor electrical power is needed to maintain the field. They are heavier than other magnets, may require extra floor strength and the field is often orientated vertically.

While clinical scanners operate in the range of 1.5-3 T, some vendors offer low cost

systems with fields under 1 T, while others offer systems with 7-9.4 T fields. Preclinical scanners are instead characterized by much smaller bores and coils, allowing an optimized signal reception, and can reach challenging high magnetic fields. All magnets produce a static magnetic field that is non-uniform and its homogeneity over the imaging volume needs to be optimized by a process known as shimming: while passive shimming, upon system installation, involves adding small iron plates into special rails in the magnet bore, active shimming is done with up to 18 in-built specialized roomtemperature shimming coils in addition to the main magnet coils. Although passive shimming is performed during the system installation, any object introduced into the system will generate relatively large inhomogeneities, requiring active shimming on a per-patient basis. This relies on the acquisition of a map of the magnetic field to set the electric current for the shimming coils to then maximize the homogeneity of the magnetic field within a volume of interest. An additional active dynamic shimming modulating the current in the shimming coils for each slice excitation can also be used for even higher local field homogeneity.

Besides the magnet, three orthogonal linear magnetic field gradients are needed for spatial localization and the creation of images: the gradient subsystem comprises the set of gradient coils inside the bore of the magnet, and the gradient amplifiers which drive electrical current through them. Also, the radio frequency (RF) system generates a (preferentially) homogeneous B_1 field over the imaging volume, at the Larmor frequency. This comprises an RF synthesizer, an RF waveform generator, an RF modulator, an RF amplifier, and an RF transmit coil. The receiver subsystem consists of receive coils, preamplifiers, RF demodulator, amplifier, A/D converters that are used for detecting, amplifying, and digitizing the MR signal before it gets transmitted and eventually reconstructed.

1.3 Signal generation

NMR is a physical phenomenon in which nuclei in a strong constant magnetic field B_0 are perturbed by a weak oscillating magnetic field (in the near field) and respond by producing an electromagnetic signal with a frequency characteristic of the magnetic field at the nucleus. This process occurs near resonance when the oscillation frequency matches the intrinsic frequency of the nuclei, which depends on a few factors, including B_0 , the magnetic properties of the nucleus and the surrounding chemical environment. In practical applications with static magnetic fields up to ~ 18 T, the frequency is found within the radio frequency range (20 kHz - 766 MHz).

All atomic nuclei with an odd number of protons or neutrons possess an intrinsic nuclear spin angular momentum **J**, as they spin on their own axes. The angular momentum is given by

$$\mathbf{J} = \hbar \mathbf{I} \tag{1.1}$$

where \hbar is the reduced Planck constant (1.05457 \times 10⁻³⁴ J·s) and I is the spin quantum number (dimensionless), an intrinsic property of the nucleus, which is an integer or a half-integer, and the spin angular momentum operator J has eigenvalues \hbar I(I + 1).

For the Ampère-Maxwell's law, as the nucleus is charged, this is associated to a magnetic field, so the angular momentum is coupled with a magnetic dipole moment μ by means of the nucleus-dependent gyromagnetic ratio γ :

$$\mu = \gamma \mathbf{J}$$
 (1.2)

When an external magnetic field is applied, this tries to align the magnetic moment with the main field as μ will experiences a torque and precess about the magnetic field axis, customarily referred to as the z axis. The frequency of the precession is known as Larmor frequency ω_L , which is proportional to both γ and the magnetic field intensity B₀, so that

$$\omega_L = \gamma B_0$$
 . (1.3)

 ω_L defines a clockwise rotation about the z axis. So the magnetic moment precesses clockwise about B₀ at an angular frequency of ω_L (or a scalar frequency of f₀ = γ B₀, with $\gamma = \gamma/(2\pi)$). So, nuclei with non-zero nuclear spin have an intrinsic nuclear magnetic moment and angular momentum. Indeed, while nuclei with even numbers of both protons and neutrons have a total spin of zero (and are therefore NMR-inactive), odd mass number nuclei and nuclei with odd/odd number of protons/neutrons exhibit nuclear magnetic resonance. The most commonly used nuclei are ¹H and ¹³C, but application of ¹⁹F, ²³Na and ³¹P are not rare.

The most common nucleus considered in clinical MRI exams is the hydrogen proton ¹H, because of its abundance in the human body as water molecules as well as in other molecules – hydrogen makes up approximately 10% of the body mass. For ¹H, the gyromagnetic ratio is $\gamma = 2.675 \cdot 10^8$ rad/s/T, corresponding to $\gamma = \gamma/(2\pi) = 42.574$ MHz/T, and its spin quantum number I = 1/2.

In an external magnetic field, the angular moment can have 2I + 1 orientations, ranging from I to -I. Hence, for ¹H these are +1/2 and -1/2, which correspond to two values of the magnetic dipole moment, $-1/2\gamma\hbar$ and $+1/2\gamma\hbar$. These, in turn, correspond to two opposite energy levels $E = -\mu_0 \cdot \mathbf{B}_0 = \pm 1/2\gamma\hbar B_0$, a phenomenon known as Zeeman effect, where the higher energy level is referred to as the 'spin down' (anti-parallel with B_0) and the lower energy level as 'spin up' (parallel with B_0). Transitions between these two energy levels are possible by absorption or emission of a photon with energy corresponding to the energy gap between the levels

$$\Delta E = \gamma \hbar \mathsf{B}_0 = \omega_L \hbar \quad . \tag{1.4}$$

An ensemble of nuclei subjected to an external magnetic field shows a slightly higher prevalence of the spin-up state (lower energy) as the occupation of the energy states follows a Boltzmann distribution:

$$\frac{N_{\uparrow}}{N_{\downarrow}} = \exp\left(\frac{\Delta E}{k_B T}\right) \tag{1.5}$$

with N_{\uparrow} and N_{\downarrow} being the number of spin-up and spin-down states, respectively, k_B the Boltzmann constant (1.380 × 10⁻²³ m²kg²/(s²K)) and T the absolute temperature. The difference in occupation of both states at body temperature and in a magnetic field of clinical strength (3 T) is in the order of 10 ppm. MRI is thus a very insensitive technique and needs a high concentration of molecules to make a significant population difference, which is made up by the large number of ¹H protons.

At equilibrium conditions, the protons are all out of phase with each other although precessing at the same frequency, so the tips of the magnetic moment vectors are evenly spread out around the circular precession trajectory of the magnetic moment. On a macroscopic scale, the magnetic dipoles can be grouped in spin ensembles, called 'isochromat'. The vector sum of the magnetic moments of an isochromat is called the net magnetization M, and at equilibrium M is aligned with the main field B₀. Also, in an isochromat, the magnetic moments add up to a macroscopic nuclear magnetic momentum $M = [M_x, M_y, M_z]$, which at equilibrium becomes $M = [0, 0, M_0]$. In case of $^1\mathrm{H},$ the macroscopic magnetic moment at equilibrium becomes

$$M_0 = \chi \mathsf{B}_0 \tag{1.6}$$

with χ being the magnetic susceptibility of the isochromat. In equilibrium conditions, when B₀ is applied along the z direction and the transverse component of the magnetization is null ($M_x^2 + M_y^2 = 0$) and considering that $k_B T \gg \Delta E$, the z component can be approximated to

$$M_0 = \rho (N_{\uparrow} - N_{\downarrow}) = \frac{\rho \gamma^2 \hbar^2 B_0}{4k_B T}$$
(1.7)

which is normally in the orders of tens of μ T, roughly around the magnitude of the Earth's magnetic field at its surface.

1.3.1 RF excitation

The NMR signal can not be acquired when the magnetization lies along the direction of the main static magnetic field. In order to generate a detectable signal, the magnetization needs to be perturbed from its equilibrium state. The magnetization vector should have a non-null rotating component, which is achieved by the application of a much weaker magnetic field (B₁), perpendicular to B₀ and oscillating at ω_L . The application of such B₁-field is performed via short RF pulses (with duration of hundreds of microseconds or milliseconds). The magnetization is tilted of an amount – the flip angle α – which is directly related to the duration *T* and power B₁ of the RF pulse, so that on-resonance (i.e. when the RF frequency matches the Larmor frequency)

$$\alpha(T) = \gamma \int_0^T \mathbf{B}_1(t') dt'$$
(1.8)

and, in the ideal case of a B_1 pulse with a rectangular profile,

$$\alpha = \gamma \mathsf{B}_1 T \quad . \tag{1.9}$$

When the population of protons is irradiated by an RF field, protons can flip between energy levels: while spin-up protons can absorb energy to jump into the spin-down position, the spin-down protons are stimulated into giving up energy to drop into the spin-up state. Both phenomena have an equal probability of each transition but due to the slightly higher number of spin-down protons at equilibrium, the net effect will be the absorption of energy. Besides, the RF pulse also synchronizes the phase of the spins, which makes them all point towards the same direction for a 90 degrees RF pulse.

1.3.2 MR signal

When choosing a reference frame that rotates at the Larmor frequency around the z axis (the 'rotating frame' with axis x'y'z', with z and z' aligned), spins that precess with ω_L are stationary, while spins with $\omega \neq \omega_L$ contribute with a fictitious magnetic field expressed by ω/γ , so that the effective magnetic field experienced by the spins in the rotating frame is represented by $B_0 + \omega/\gamma$.

While in the rotating the application of RF pulses is observed as a rotation around the application of the B_1 field, in the laboratory frame M moves along the surface of a sphere while maintaining the precession (the resulting motion is the trajectory of a spherical spiral).

Firing an RF pulse in a resonance condition with the isochromat will cause the magnetization to tilt from the z axis and gain a component in the transverse (xy) plane, which induces a voltage in the receiver coil placed perpendicularly to the transverse plane.

The torque that the magnetization vector M experiences when placed in an external magnetic field B₀ (see Figure 1.4) can be expressed as

$$\frac{dM}{dt} = \gamma M \times \mathbf{B_0} \quad . \tag{1.10}$$



Figure 1.4: The magnetization vector M experiences a torque due to the external magnetic field B_0 , which makes it precess with angular frequency ω_L .

An RF pulse promotes protons from the low-energy state to the high-energy state, causing a net absorption of energy. However, the high-energy state is a stable non-equilibrium position for the proton and leads to precession of the magnetization vector in the transverse plane of the laboratory frame, which induces a voltage at the Larmor frequency in the receiver coil that experiences an oscillating magnetic flux. When the RF pulse is switched off, the system and its magnetization will gradually return to its

equilibrium state along the z axis, losing energy due to the influence of the magnetic moments of neighboring protons, nuclei, or molecules.

1.3.3 Relaxation

Most of the understanding about the interactions between protons and their environment which cause spin-spin and spin-lattice relaxation is based on the theory published in 1948 by Bloembergen, Purcell and Pound. The BPP theory, from the acronym of its authors, states that every atom or molecule is characterized by a rotational, vibrational, and translation motion happening in random directions and this motion changes rapidly thanks to atomic reciprocal collisions. The time that an atom spends in a particular state of motion before a collision is known as the correlation time τ_c and is mainly affected by the state of the matter and by temperature. Solids have a higher correlation time than liquids, which in turn have a higher correlation time than gases.

In biological systems, water molecules closely bind to macromolecules such as proteins and polysaccharides to form hydration layers, while water is found in free form in cerebrospinal fluid (CSF), blood, or cysts. A free exchange of protons between the hydration layer and free water exists, with protons freely exchanging between molecules, so that the measured signal results from a mixture of water molecules in different states.

Statistical methods can be used to show that a collection of molecules with an average correlation time will have a range of motional frequencies described by a spectral density function $J(\omega)$. Long τ_c corresponds to low motional frequencies, meaning that such molecules spend a relatively long time in a particular motional state before suffering a collision as the movements are modeled with a narrow range of frequencies. The Larmor frequency of most clinical MR systems, around tens of MHz, is in the middle of the frequency range.

The spectral density function $J(\omega)$ represents the "amount of fluctuations at the right frequency" and is related to the correlation time τ_c as follows:

$$J(\omega) = \frac{2\tau_c}{1 + \omega^2 \tau_c} \tag{1.11}$$

Figure 1.5 reports an example of the spectral density function of three example substances. Longer correlation times correspond to smaller mean frequencies.



Figure 1.5: Example of the spectral density function $J(\omega)$ for three substances. Image obtained with permission from McRobbie et al. 2017 [16].

The energy absorbed from the RF pulse is thus dispersed during relaxation mechanisms. Additionally, the system loses the phase coherence due to small differences in the spin precessional frequencies caused by random fluctuations, thus determining the signal decay. These relaxation mechanisms can be subdivided into a longitudinal and a transverse component:

The T₁, longitudinal or spin-lattice relaxation stems from the redistribution of the spin states in order to reach thermal equilibrium. The energy released during this redistribution is transferred from the spins to their surrounding environment (the lattice) by molecular vibrations. Thus, the magnetization vector tends to return to its equilibrium state, aligned along the z axis.

 T_1 relaxation results in a growth of M_z , modeled by an exponential behavior with a time constant T_1 , the longitudinal relaxation time. After an RF pulse with a flip angle β applied to the equilibrium magnetization M_0 , the longitudinal magnetization can be expressed as

$$M_z(t) = M_0 [1 - (1 - \cos \beta) \exp(-t/T_1)] \quad . \tag{1.12}$$

In a single water molecule, for example, the magnetic moments of the hydrogen atoms influence each other so that relaxation arises as an intra-molecular dipole-dipole interaction. In order to induce the transitions needed for T_1 relax-

ation, the fluctuations have to be at the Larmor frequency, so the more protons tumbling near the Larmor frequency the more efficient the T_1 relaxation will be. Both bound and free protons have long T_1 s, while more protons with intermediate binding tumble at the Larmor frequency than protons in either free fluids or bound in hydration layers. The spectral density function also explains why T_1 depends on the magnetic field as a decrease in the strength of the static magnetic field will result in a decrease of the excess spins in the spin-up state, leading to a faster equilibrium approach and a decrease of the Larmor frequency.

The T₂, transverse or spin-spin relaxation is due to the loss in phase coherence of the spins. Thus, T₂ relaxation arises from intrinsic inhomogeneities in the magnetic field. When molecules such as free protons are tumbling rapidly, dipoles will see the local magnetic field as rapidly fluctuating, effectively averaging out over a few milliseconds. This results in a relatively homogeneous local field and little dephasing ('motional averaging'). Conversely, a slowly tumbling molecule such as bound protons will see a relatively static magnetic field inhomogeneity and will be more effectively dephased with respect to other protons. T₂, the time constant of the decay, is affected by low-frequency motions as well as those at the Larmor frequency while T₁ is only affected by Larmor frequency fluctuations. For example, bound protons in bulk fluids have the longest T₂s while those with intermediate binding have medium T₂ relaxation times.

Indeed, the magnetic moment of the spins in an isochromat adds or subtracts from the main field, and these random fluctuations slightly change the precessional frequency to follow the variation in the magnetic field, so that each spin will dephase with respect to the Larmor frequency but the total transversal component M_{xy} keeps precessing around the z-axis at ω_L . As the phase angles acquired during the interaction are irreversible, the signal gradually decays with a time constant T₂. Imperfect shimming or heterogeneous samples with differences in magnetic susceptibility cause inhomogeneities in the magnetic field, which fasten the dephasing process. This can be modeled with an additional time-independent relaxation constant T'₂ so that the total relaxation time can be written as

$$\frac{1}{\mathsf{T}_2^*} = \frac{1}{\mathsf{T}_2} + \frac{1}{\mathsf{T}_2'} \tag{1.13}$$

thus allowing the relaxation of the transverse magnetization M_{xy} to be modelled

as an exponential decay:



$$M_{xy}(t) = M_{xy}(0) \exp(-t/\mathsf{T}_2^*)$$
 (1.14)

Figure 1.6: Sketch reporting T_1 and T_2 as a function of the correlation time τ_c .

To summarize the excitation and relaxation phenomena, Bloch derived a set of phenomenological differential equations completely based on classical mechanics describing the behavior of the magnetization vector during its excitation and relaxation. The magnetization is modeled as

$$\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B} = \gamma \begin{bmatrix} (M_y B_z - M_z B_y) \mathbf{i} \\ (M_z B_x - M_x B_z) \mathbf{j} \\ (M_x B_y - M_y B_x) \mathbf{k} \end{bmatrix}$$
(1.15)

where **B** includes both the static field (or flux density, measured in Tesla) **B**₀ along the z direction and a rotating field **B**₁ in the transverse plane ($B_x = B_1 \cos(\omega t), B_y = -B_1 \sin(\omega t), B_z = B_0$). When accounting for the relaxation of the signal and diffusion phenomena as well, the Bloch equations can be expressed in a compact way as

$$\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B} = \gamma \mathbf{M} \times \mathbf{B} - \frac{M_x \mathbf{i} + M_y \mathbf{j}}{\mathsf{T}_2} - \frac{(M_0 - M_z)\mathbf{k}}{\mathsf{T}_1} + D\nabla^2 \mathbf{M} \quad .$$
(1.16)

1.4 Image formation - anatomy of MRI pulse sequences

The signal from a bulk volume or a single voxel is given by the transverse component of the magnetization, which can be detected via a receiver placed around the subject in the transverse plane. This time-varying magnetic field of the rotating magnetization will induce an electromotive force (potential) in the receiver coil. Due to the transverse relaxation, the voltage amplitude will decay exponentially. This signal is the so-called free induction decay (FID).

In order to assign the signal to specific spatial locations and perform imaging, the resonance signal needs to be encoded. This is done via spatial localization, which is achieved by the superimposition of three orthogonal imaging gradients to the main magnetic field B₀. The application of the imaging gradients encodes the NMR signal into a 2D or 3D frequency space, called the k-space, from which an MRI image can be reconstructed via inverse Fourier Transforms. The finite time resolution of the MR receiver quantizes the signals which will be represented by voxels. Data can be directly encoded in three dimensions (3D imaging), two dimensions (2D imaging), or via a series of 2D slices (2D multislice imaging). Depending on the way the echo is generated, which is based on how imaging gradients and RF pulses are played, conventional MRI sequences can be subdivided into two main categories: spin echo and gradient echo sequences.

• In spin echo (SE) sequences, a 90° pulse flips the magnetization onto the transverse plane and after TE/2 a 180° pulse is applied so that the local M_{xy} component spins will be flipped. This will reverse the order of spins that are precessing: spins that were precessing faster will rephase exactly with spins that were precessing slower, thus generating a spin echo that builds up until the time TE (echo time) and then fades again over time. Symmetrically with respect to the refocusing 180° pulse, after TE/2, a measurable echo signal is created. The TE in SE sequences should still be kept short to avoid complete transverse relaxation of the signal. A SE sequence can be used to generate a pure T₂-weighted image with long TE and TR, but can also be used to generate proton density or T₁-weighted signals by using a short TE and a long or short TR, respectively.

	Short TE	Long TE
Short TR	T1w	poor contrast
Long TR	PDw	T2w

• Gradient echo (GE) is a class of pulse sequences primarily used for fast scanning and widely used in fast 3D volume imaging such as for angiography and cardiac imaging, breath-holding abdominal scans, as well as for functional MRI for the study of highly T^{*}₂ sensitive oxygenation changes (BOLD MRI). GE pulse sequences employ gradient reversal on the frequency encoding axis to form an echo, as opposed to the 180° RF refocusing pulse in SE sequences: first, a readout dephasing gradient lobe dephases the spin isochromats, and then these are rephased with a readout gradient with opposite polarity so that the peak of the signal occurs when the area under the two gradient lobes matches. Partial-echo acquisition and reconstruction are commonly used in GE and are implemented in the pulse sequence by reducing the gradient area of the readout dephasing lobe. GE acquisitions can be fast because the excitation flip angle α is typically $\alpha < 90^{\circ}$. Therefore, no lengthy T₁ recovery is required, and GE pulse sequences can use short TR (e.g., 2-50 ms).

A noteworthy property of GE sequences is that the flip angle that maximizes the steady-state signal, called Ernst angle, is dependent on the tissue T_1 and sequence repetition time TR and is analytically expressed as

$$\alpha_{Ernst} = \arccos(e^{-\mathsf{TR}/\mathsf{T}_1}) \tag{1.17}$$

which lies between 0° and 90° and monotonically increases as TR/T₁ increases since the arccos function is monotonically decreasing. Figure 1.7 shows an example of the signal intensity of different tissues for increasing flip angle.



Figure 1.7: Dependency of the SPGR steady state signal over the provided flip angle. The signal for tissues with different T_1 is maximized with different angles, namely at the Ernst angle - whose respective signal is represented by a star for each example tissue.

Some GE sequences employ gradients after signal acquisition and variation of the phase of the RF pulses for spoiling, the process of removing coherence in the transverse magnetization that may persist in sequence cycles. For this reason, these are called Spoiled Gradient echo sequences (SPGR). Spoiling ensures that the steady-state magnetization has negligible or no residual transverse component, which is fundamental as even small transverse magnetization components can lead to inaccuracies of the steady-state signal intensity and different degrees of spoiling can result in different dephasing of the transverse magnetization.

The phase of the spin isochromats in the transverse plane continues to accumulate during the entire TE so GE images are contrast weighted by a factor of $exp(-TE/T_2^*)$, where T_2^* is the 'apparent' T_2 and $1/T_2^* = 1/T_2 + 1/T_2'$, with $T_2' \sim 1/(\gamma \Delta B)$ is inversely proportional to the magnetic field inhomogeneity. For this reason, GE images are much more prone to signal loss than their RF SE counterparts in regions near interfaces of materials with significantly different susceptibility, as close to air cavities (nose/ear) and metallic implants.

Regardless of the type of sequences used, MRI employs two main classes of com-
ponents to excite and acquire the magnetic resonance signal: RF pulses and imaging gradients.

1.4.1 RF excitation pulse

Excitation pulses tip the magnetization vector away from the direction of the main magnetic field B₀ by switching on the RF field modulation envelope, denoted by B₁(t), for a short time, typically 200 μ s to 5 ms - short enough so that T₁ and T₂ relaxation during the pulse typically can be neglected for proton MRI.

Modulating the RF envelope with a predetermined shape, such as the sinc waveform, generates a selective RF pulse and selective excitation pulses are played concurrently with a slice selection gradient. By definition, the on-resonance condition is always met at the center of the slice profile, but the flip angle produced by an excitation pulse can vary across the selected slice. This results in a distribution of transverse magnetization, the slice profile, when plotted versus either position or frequency. For small α , the slice profile is approximated by the Fourier transform (FT) of the RF pulse. Except at the center of the selected slice profile, we cannot assume that the spins are exactly on-resonance. For small α , the slice profile is approximately equal to the modulus of the inverse FT of the RF envelope. The FT approximation (also called the 'linear approximation' or the 'small flip angle approximation') generally holds quite well for flip angles up to $\alpha = 30^{\circ}$ and breaks down only when $\alpha > 90^{\circ}$. Deviations from it are known as nonlinearity in the Bloch equations, for which Shinnar-Le Roux or iterative numerical methods rather than Fourier methods are usually used for RF pulse design when high-quality slice profiles are needed.

After the selective RF pulse is played along the x axis, the transverse magnetization at different spatial locations will generally not lie exactly along the y axis in the rotating frame because of precession caused by the slice selection gradient. This generates phase dispersion across the slice, which needs to be refocused and thus corrected by the application of a slice rephasing gradient pulse. The isodelay parameter Δt_I is used to calculate the optimal area of the slice-rephasing gradient, and generally, the isodelay corresponds to the period from the peak of the RF excitation pulse to the end of the slice selective gradient.

1.4.1.1 Hard pulses

A rectangular or hard pulse is simply a pulse shaped like a rectangular function in the time domain. Hard pulses can be used when no spatial or spectral selection is required

and are time-convenient as their length can be very short. These pulses are played without a concurrent gradient, and they have a broad bandwidth, which means that the spins with a wide range of resonant frequencies are affected. In the small flip angle approximation, the frequency profile corresponding to a hard pulse is a sinc function whose first zero-crossing is the inverse of the corresponding rect width. This means that a longer pulse will have a narrower pulse width.

Hard pulses can also be grouped together to form spectrally selective composite pulses, simulating long RF pulses with narrow bandwidth.

1.4.1.2 Soft pulses

As opposed to hard pulses, time-varying or shaped pulses are sometimes called soft pulses. Examples of this category are sinc pulses, widely used for selective excitation, saturation, and refocusing. A sinc pulse consists of several adjacent lobes of alternating polarity. The central lobe has the highest amplitude and is also twice as wide as every other lobe and the amplitude of the other lobes progressively decreases on either side of the central lobe, as their polarity alternates. The time dependence of the RF envelope of a sinc pulse (without windowing) is given by:

$$B_{1}(t) = A \cdot \operatorname{sinc}(\pi t/t_{0}) = At_{0} \frac{\sin(\pi t/t_{0})}{\pi t}$$
(1.18)

and to a good approximation, the bandwidth of the sinc pulse (the full width at half maximum of the slice profile) is given by $\Delta f \approx 1/t_0$ where t_0 is one half the width of the central lobe.

The FT of an infinitely long sinc pulse is the rect function, which represents the ideal slice profile. As such, a sinc pulse has been a natural choice when a uniform slice profile is desired. However, a real sinc pulse has a finite duration and is obtained by truncating all but the central lobe and a few side lobes. In general, the greater the number of lobes that are included in the sinc pulse, the better the approximation to the ideal rect frequency profile is, but the longer the duration of the pulse is. This can lead to an increase of the minimum TE and TR of a sequence as well as to an increased sensitivity to flow and off-resonance effects. An apodizing window is usually applied to the sinc pulse to ease the effects caused by truncation and to smooth its slice profile.

1.4.1.3 Adiabatic pulses

Adiabatic pulses are a class of amplitude- and frequency-modulated RF pulses that are relatively insensitive to B_1 inhomogeneity and frequency offset effects. They use the

adiabatic principle wherein magnetization is manipulated by a slow passage of the B_1 field through resonance. While an amplitude-modulated pulse affects spins simultaneously, with an adiabatic pulses spins having different resonant frequencies are inverted or manipulated at different times.

The frequency of an adiabatic RF pulse is slightly off-resonance, which causes the transverse and longitudinal components of B₁ to create an effective field B_{eff}, a non-null component of B₁ at an angle ψ to the z' axis. When the amplitude of B₁ is small or RF frequency is off-resonance, B_{eff} is very close to the z₀ axis but as the amplitude is increased and the frequency is exactly on resonance, B_{eff} is exactly in the transverse plane. The precessional frequency about B_{eff} needs to be much greater than the rate of ψ change $\gamma B_{eff} \gg d\psi/dt$ which requires either strong effective field B₁ or a slow frequency modulation.

With respect to non-adiabatic pulses, in adiabatic pulses, the flip angle produced is not simply proportional to B_1 magnitude and pulse length, but depends on how the B_1 field varies in amplitude and phase throughout the pulse. Likewise, adiabatic pulses cannot be scaled or stretched to change their effect (e.g. doubling a 90° adiabatic pulse does not produce a 180° inversion pulse). Besides, no energy is absorbed from the RF pulse, so the spin temperature does not change.

Adiabatic pulses show some advantages with respect to nonadiabatic pulses, such as being less sensitive to RF miscalibration and hence having a high tolerance to field inhomogeneity, making them particularly useful at high field strengths. They allow accurate spin manipulation over a large range of RF power levels and minimization of energy deposition in terms of SAR and sample heating.

The design of adiabatic pulses is often based on hyperbolic tangent or secant functions, with independent amplitude and frequency (or phase) modulation. In addition to the simpler adiabatic inversion pulses used for fat or water suppression, a more modern class of plane rotation pulses is now becoming popular, especially the BIR-4 (B₁-Insensitive Rotation) pulse.

1.4.2 k-space

The acquired MR signal is proportional to the transverse magnetization resulting from the sum of all precessing magnetization vectors. The time domain signal generated by the transverse magnetization in the rotating frame is

$$S(t) = \int M_{xy}(\vec{r}) B_{\perp}(\vec{r}) e^{-i\phi(\vec{r},t)} d^3r$$
(1.19)

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where $M_{xy}(\vec{r})$ is the transverse magnetization at position \vec{r} , $B_{\perp}(\vec{r})$ is the transverse component of the B₁ field at position \vec{r} , and $\phi(\vec{r}, t)$ is the accumulated phase

$$\phi(\vec{r},t) = \gamma \int_0^t \vec{r} \cdot \vec{G}(\tau) d\tau$$
(1.20)

where G is the amplitude of the gradients. By defining the spatial frequency, the k-space vector \vec{k} , as

$$\vec{k}(t) = \frac{\gamma}{2\pi} \int_0^t \vec{G}(\tau) d\tau$$
(1.21)

we can also define the 'k-space' as the spatial frequency domain representing the raw data matrix in MR, where the shortest sampled interval Δt represents the sampling time per complex point (the time between two acquired data points, called dwell time), providing every digitized sample point its own unique location in the k-space.

The application of gradients allows to spatially encode the MR signal, stepping through and sampling the whole desired k-space. In particular, the accumulated phase – hence the acquired k frequencies – depends on both the gradient strength and the time point Δt . The application of different gradient strengths G with a fixed Δt corresponds to the phase encoding, applied before the acquisition, while the application of different Δt values for a fixed G corresponds to a frequency encoding applied during the acquisition. The selection of the specific k-space frequency or frequencies is performed by the application of one or two phase encoding gradients and a frequency encoding (readout) gradient. When only a phase encoding gradient is used, the plane on which the phase and readout gradients are encoded is defined by the application of a slice selection gradient. Data in the middle of k-space define the SNR and contrast of an image as they represent the lowest spatial frequencies, while data around the outside contains the information about the image edges. After the acquisition of all k frequencies, an inverse Fourier transformation is used to reconstruct the image from the acquired k-space.

Many k-space sampling schemes have been proposed, but the most common ones rely on Cartesian acquisitions – acquiring k-space lines one at a time – multishot Echo Planar Imaging (EPI) acquisitions – acquiring groups of phase encoding lines in the k-space after each RF excitation – or single shot EPI – where the whole k-space is obtained after one RF excitation.

1.4.3 Imaging gradients

1.4.3.1 Slice selection gradient

The slice selection gradient is typically a constant gradient played concurrently with the selective RF pulse and, if the RF pulse performs excitation, then a slice rephasing lobe usually follows the slice selection gradient. The slice-selection gradient translates the band of frequencies of an RF pulse into the desired band of locations corresponding to the slice, and the slice position and the strength of the slice selection gradient at that location determine the central frequency of the RF pulse.

Increasing the amplitude of the slice selection gradient decreases the thickness of the slice for a fixed RF bandwidth. The gradient direction determines the normal, perpendicular direction to the slice plane.

Usually, the desired slice plane does not pass through the point where all three gradient coils produce zero magnetic fields (the isocenter of the gradients), which typically is the same point as the isocenter of the magnet. So the desired slice offset δz is obtained by shifting the carrier frequency of the RF by an amount δf .

If the slice selection gradient is not spatially uniform, the offset δz will also vary and the selected slice will not be planar and hyperbolic paraboloid (potato-chip) shaped slice can result. This effect often occurs for large values of δz due to gradient nonlinearity and whenever local gradient fields induced by magnetic susceptibility variations perturb the slice-selection gradient. The slice selection gradient typically results in some phase dispersion of transverse magnetization across the slice: when a linear phase RF excitation pulse is used in conjunction with a constant slice selection gradient, the resultant slice is linearly phase modulated across the slice. A slice refocusing or rephasing lobe is associated with the slice selection gradient of an excitation pulse. The slice rephasing gradient lobe has opposite polarity compared to the slice selection gradient and is used to compensate for the phase dispersion caused by the slice selection gradient. Without the slice rephasing gradient lobe, there is intravoxel phase dispersion across the slice which is approximately given by the product of the RF bandwidth and the isodelay. This would result in signal loss, as the slice selection gradient after the isodelay point of an excitation RF pulse functions as a spoiler gradient. The gradient area of the slice rephasing lobe is calculated based on the isodelay value of the excitation pulse. While spatially selective refocusing pulses generally do not require rephasing lobes, the majority of RF excitation pulses require the rephasing lobe.

1.4.3.2 Frequency encoding gradient

Frequency encoding is a common spatial encoding method used by many MRI pulse sequences. This gradient spatially encodes MR signals by assigning a unique precession frequency to each spin isochromat at a distinct spatial location along the gradient direction so that time-domain MR signals will consist of a range of frequencies, each corresponding and linearly related to a different spatial location.

A FT of the time-domain signal produces a spectrum that reveals the density of spins at these frequencies, thereby producing a projection of the objects. Spatial information is encoded into the MR signal by the frequency encoding gradient, and then decoded by a subsequent FT.

A frequency encoding gradient waveform typically consists of two portions, a prephasing gradient lobe (dephasing gradient lobe) and a readout gradient lobe (played during acquisition). For the SE case, the 180° RF pulse refocuses phase accumulation from chemical shift, B₀-field inhomogeneity, and susceptibility variations, collectively known as off-resonance effects. Because GE sequences do not employ a refocusing RF pulse, the off-resonance effects continue to cause phase accumulation throughout the frequency encoding process. This difference between SE and GE gives rise to different contrast mechanisms (T₂ vs. T^{*}₂) and artifacts in MR images.

During the application of the frequency encoding gradient (while τ is increasing), different points in k-space are sampled at the same phase encoding position. The range of sampled frequencies depends on the Field of View (FOV) and the amplitude of the frequency encoding gradient. The range of precession frequencies, or bandwidth, across the object in the x direction is

$$\Delta f = \gamma G_x L_x \tag{1.22}$$

where G_x is the gradient strength along the x direction and L_x is the length of the FOV in the same direction. These frequencies are sampled at intervals $2\Delta f$ corresponding to $\Delta t/2$ to satisfy the Nyquist theorem. The interval between readout points in k-space is then defined as

$$\Delta k_x = \gamma G_x \Delta t \tag{1.23}$$

corresponding to the inverse of L_x .

The echo time TE defines the time point when the center of the k-space is sampled. If k-space is sampled symmetrically with respect to its center, then the readout gradient must be on for a time period $T_{acq}/2$, prior to TE. As the area under the prephasing gradient lobe determines the time at which the echo peak forms, the echo signal reaches its maximum when the area under the readout lobe is equal to the area of the

prephasing lobe. During the time period [TE - $T_{acq}/2$, TE], data points on the negative k_x axis are sampled. To sample the k-space points on the positive k_x axis, the readout gradient remains active for an additional time period $T_{acq}/2$ after TE, which produces a symmetric k-space line spanning. Specifically in GE acquisitions, the k-space can also be applied asymmetrically to acquire fewer data points before TE. This acquisition technique, known as partial or fractional echo, can considerably reduce the minimum TE and the gradient moments.

Although a smaller FOV can also be achieved by reducing the receiver BW, this leads to a longer data acquisition time and makes the image more susceptible to flow effects and off-resonance artifacts.

The maximal gradient amplitude can be used to minimize the TE for applications such as MR angiography. Alternatively, a smaller gradient amplitude with a longer duration can be employed to reduce the effects of eddy currents and concomitant magnetic fields (particularly important in fast imaging at low magnetic field).

Although the readout gradient is typically held constant during data acquisition, time-varying gradients can also be used during readout. Examples of time-varying readout gradients can be found in spiral scans, echo planar imaging with sinusoidal gradients, sampling during the gradient ramps, twisted projection imaging, and concentric circular sampling. With a time-varying readout gradient, the k-space sampling often becomes nonuniform, which requires data resampling prior to image reconstruction using fast FT.

1.4.3.3 Phase encoding gradient

The idea behind phase encoding is to create a linear spatial variation of the magnetization phase. This is implemented by applying a gradient lobe before the readout while the magnetization is in the transverse plane. Phase encoding (Fourier encoding) is used to spatially encode information orthogonal to the frequency-encoded direction. 3D volume acquisitions use phase encoding in the slice direction (sometimes called slice encoding or secondary phase encoding) as well as in-plane along the primary phase encoding direction. In some applications, such as in spectroscopic imaging (or chemical-shift imaging) techniques, spatial localization is achieved without frequency encoding, and only phase encoding is used. Non-Cartesian k-space trajectories, such as spirals, do not use phase encoding, except sometimes in the slice direction for 3D scans.

The phase encoding gradient may occur any time after the RF excitation pulse and before the readout. For practical implementation, the phase encoding gradient lobe usually has the same shape and time duration for each phase encoding step and the amplitude is scaled to give the desired k-space step size k_y .

Figure 1.8 reports an example of a gradient echo and a spin echo sequence, as well as a representation of Cartesian readout.



Figure 1.8: Pulse sequence diagram for gradient echo (left) and spin echo (center) sequences. The principle of Cartesian readout is also reported (right), with the phase gradient selecting the k-space line via phase encoding and the readout gradient providing the frequency encoding of that line of k-space.

1.4.4 k-space sampling

Pulse sequences that collect a single Cartesian line of k-space for each k_y excitation typically collect the lines starting at one edge of k-space and moving continuously to the other edge (sequential/top-down method). Echo train pulse sequences that collect multiple k_y lines for each excitation (EPI/RARE) may collect the lines in a different order. The reverse-centric view order start the acquisition from the k-space edge and end at the central k-space lines, while other acquisitions may start to sample data from the center of the k-space (center-out). In some 3D acquisitions, the view orders for both phase encoding axes are sometimes sorted to start at the center of the $k_y - k_z$ plane and then to move radially outward based on the distance to the center of k-space (elliptical centric view order).

In full Fourier encoding, lines are collected symmetrically around the $k_y = 0$ line, while when using partial Fourier encoding, one-half of k-space is fully filled and the other half is only partially filled and the missing data are either replaced with zeros or restored using an algorithm based on Hermitian conjugate symmetry or another consistency criterion.

1.4.4.1 Echo Planar Imaging

Echo Planar Imaging (EPI) is one of the fastest MRI readout methods and represents one of the first approaches for ultrafast imaging. As such, it has had an important role in a number of applications, including diffusion, perfusion, and cardiac imaging, as well as neurofunctional and dynamic studies [17]. With respect to conventional SE and GE sequences, EPI employs a series of switching readout gradients to generate a gradient echo train separated by phase-encoding blips so that each echo is distinctively spatially encoded and cover multiple k-space lines. This allows a full 2D slice to be acquired after a single RF excitation (single-shot) or multiple excitation (multi-shot). An EPI acquisition results in a 'snake-like' trajectory made of straight lines with a jump in k-space at the end of each readout k-space line and inversion of the k-space direction due to the bipolar readout, which requires additional pre-processing of the data prior to image reconstruction: first, the even-numbered lines need to be reversed as these are acquired with opposite polarity (row-flipping). Then, a number of artifacts need to be addressed in EPI images, including ghosting and banding along the phase-encoded direction due to phase inconsistency or displacement of k-space data. The ghosts along the phase encoding direction are also called (Nyquist ghosts or N-over-two ghosts), and because a shift in k-space corresponds to a linear phase error in the image domain, they are also called linear-phase ghost, or linear ghost. Many techniques have been developed to remove the Nyquist ghosts: for example, a common method is to acquire a reference scan without phase-encoding, which is then inverse Fourier-transformed along the readout direction. The phase among the projections is then computed and the constant and linear phase errors are removed. EPI images can also show geometric distortions and chemical shift artifacts, which can be severe along the phase-encoded direction due to the smaller phase-encoding bandwidth, requiring fat suppression to be applied [18]. Using segmented EPI can reduce the blurring and off-resonance artifacts (such as geometric distortion) of single-shot EPI [19]. Off-resonance effects from magnetic susceptibility variations, B_0 inhomogeneities, and eddy currents can also cause signal distortion, which can be mitigated with parameter optimization and careful shimming. Non-linear effects should also be corrected via re-gridding when data acquisition is performed during both the gradient plateau and the gradient ramp (ramp-sampling). On top of this, T_2^* decay takes place during EPI signal acquisition, which can cause blurring and underrepresentation of the k-space lines acquired later.

1.4.4.2 Non-Cartesian sampling

Other non-Cartesian k-space sampling patterns, such as radial and spiral, can also be used for fast MR data acquisition. Radial sampling collects k-space using radial k-space lines or spokes passing and overlapping around the center of k-space, often employing trajectory profiles based on golden ratio, in which radial spokes are rotated by a 'golden angle' (e.g. 111.25° for 2D radial sampling) [20]. Reconstructing of radial k-space data typically involves an interpolation step, as the points must be gridded into a Cartesian format to be reconstructed via inverse Fourier transform.

Figure 1.9 illustrates some of the most commonly used k-space trajectories.



Figure 1.9: Examples of k-space trajectories: (top left) Cartesian - conventional line-by-line, (top right) Cartesian - EPI (single shot and multishot), (bottom row) Non-Cartesian - Radial and Spiral.

1.4.4.3 Parallel imaging

Parallel imaging is a technique for accelerated MR imaging and works by acquiring a reduced amount of k-space data with an array of independent receiver channels instead of using a large homogeneous volume receive coil [21], where each receiver coil is more sensitive to the nearest tissue volume. Since the Nyquist criterion is not met in parallel imaging, the individual scans are undersampled and aliased images. Artifact-free and unaliased images are reconstructed via an algorithm that requires some knowledge of the individual coil sensitivities. The k-space is undersampled in the phaseencoding direction, and the acceleration (reduction) factor represents the ratio between the amount of k-space lines acquired over the total amount of lines for a fully sampled image, with the number of receiver channels being the limiting factor for the maximum acceleration factor. Two main types of reconstruction algorithms are used for parallel imaging: one works with aliased images (SENSE-type reconstruction), and the other reconstructs the missing k-space data (GRAPPA-type reconstruction).

- SENsitivity Encoding (SENSE) [22] also called ASSET (Array coil Spatial Sensitivity Encoding) – is a widely used parallel imaging method, that includes the generation of coil sensitivity maps, the acquisition of partial k-space data, the individual coil reconstruction of partial FOV images by multiplication of the coil sensitivity value and the pixel value, and the combination of images by matrix inversion. The main drawback of SENSE is that errors in the coil sensitivity map will cause artifacts in the form of residual aliasing in the reconstructed full FOV image.
- GeneRalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) [23] is another widely used method for parallel imaging that works via the acquisition of images, estimation of missing phase-encoding lines, individual coil images generation, and combination of images via sum of squares method. As the signal intensity is weighted by the coil sensitivity profile, k-space experiences a smearing of information across neighboring k-space points, which leads to a spread of information of any given k-space point to neighboring k-space points. GRAPPA requires the acquisition of the autocalibration signal, a low resolution patch of k-space (mainly the central lines) frequently collected during the scan, which is used to determine the GRAPPA weighting factors by the application of a sliding kernel to both the autocalibration signal and the undersampled k-space data. The autocalibration signal lines are interspersed with the image acquisition itself, hence the term "autocalibrating".

1.5 MR Simulations - Extended Phase Graphs

MRI simulations are needed in many cases to reduce the complexity and costs of MRI prior to the implementation on MRI scanners. Simulators could be used with different aims, spanning from educational purposes for the understanding of MRI physics, to sequence and protocol optimization. Other aims include the design of new pulse sequences, the prototyping of new ideas, data fitting to solve for unknown parameters as well as for test/training data for image reconstruction and analysis and validation of sequences to test physical models.

In the past few decades, a list of MR simulators have been published and made available, including many MATLAB and Python-based code snippets. Among the most commonly known MR image simulators there are POSSUM (fsl.fmrib.ox.ac.uk/fsl/fslwiki/POS-SUM), ODIN (od1n.sourceforge.net/index.html), SpinBench (heartvista.com/SpinBench), PSUdoMRI (pennstatehershey.org /web/nmrlab/resources/software/PSUdoMRI), MRI-SIMUL (mri.dib.uth.gr), JEMRIS (jemris.org/) and MRI Lab (mrilab.sourceforge.net). Also, spin simulations have been developed as well, such as the web-based Bloch simulator developed by Lars Hansson (drcmr.dk/BlochSimulator).

The majority of these simulators are focused on image simulation and sequence development based on the analytical solution of Bloch equations. They compute the general magnetization response to a series of RF pulses and gradients via the rotation operator algorithm [24], which represents the direct algorithmic conversion of the Bloch equation [8] into rotations of isochromats as classical magnetization vectors. Nevertheless, typically thousands of isochromats and their evolutions need to be defined over time to compute their sum, which is not computationally efficient.

The Extended Phase Graph (EPG) concept represents a powerful tool for depicting and understanding the magnetization response of several MR sequences. EPG is an especially useful tool to predict the timings for echo formation and their amplitude with respect to the ideal signal. This can be greatly beneficial for gradient echo sequences as different degrees of spoiling can result in a different dephasing of transverse magnetization and thus lead to inaccuracies of the steady state signal intensity.

The effects of RF pulses were first modeled with "phase graphing" which was originally published as the partition state method [25, 26], defined as

$$M_{+}(r) = M_{x}(r) + iM_{y}(r) = Me^{i\theta(r)} = Me^{ikr} = (M_{-})^{*}$$

$$M_{-}(r) = M_{x}(r) - iM_{y}(r) = Me^{-i\theta(r)} = Me^{-ikr} = (M_{+})^{*}$$

given $k(t) = \gamma \int_{0}^{t} G(t')dt'$
(1.24)

where the symbol '*' denotes the complex conjugate operator with $(M_+)^* = M_-$, and this describes the magnetization in the physical space. The solution for general RF pulses with initial RF phase angle $\Phi \neq 0$ (not rotating around the x-axis) can be described by the Woessner decomposition (or "partitioning effect" of an RF pulse), and it was proven to be true for spin 1/2 particles:

$$\begin{bmatrix} M_+\\ M_-\\ M_z \end{bmatrix}^+ = \begin{bmatrix} \cos^2\frac{\alpha}{2} & e^{2i\Phi}\sin^2\frac{\alpha}{2} & -ie^{i\Phi}\sin\alpha\\ e^{-2i\Phi}\sin^2\frac{\alpha}{2} & \cos^2\frac{\alpha}{2} & ie^{-i\Phi}\sin\alpha\\ -\frac{i}{2}e^{-i\Phi}\sin\alpha & \frac{i}{2}e^{i\Phi}\sin\alpha & \cos\alpha \end{bmatrix} \cdot \begin{bmatrix} M_+\\ M_-\\ M_z \end{bmatrix}^-$$
(1.25)

which can be written as $M^+ = T_{\Phi}(\alpha) \cdot M^-$, where superscript + and - refer to after and before the application of the RF pulse. The model shows how an isochromat with initial magnetization M^- is split into three parts after an RF pulse. One part is the dephasing transverse magnetization M_+ , one part is the rephasing transverse magnetization M_- able to produce an echo, and the last one is the longitudinal M_z component.

According to the "partition state model", a sequence of RF pulses splits all partitions into three further partitions each. This method can be illustrated by diagrams and represents the original phase graph approach. The phase graph approach allows the characterization of echo generation, the calculation of echo times and the quantitation of the corresponding echo intensities. However, this method starts with only one representative isochromat/magnetization vector. The combination of RF pulse partitioning and Fourier based configuration states can be summarized in the Extended Phase Graph (EPG) framework, which allows us to depict a phase graph approach representing the evolution of a complete isochromat ensemble.

In EPG, the full complex system of reference system is expressed using the concept of configuration states (via Fourier decompositions and transforms) as a new system of reference $[\tilde{F}_+, \tilde{F}_-, \tilde{Z}]^T$ of all magnetization components. While \tilde{F}_+ denotes the dephasing transverse magnetization and can be illustrated by a right-handed helix, \tilde{F}_- represents the rephasing part and corresponds to a helix of opposite chirality (left-handed helix), as represented in Figure 1.10 and described by:

$$\tilde{F}_{+}(k) = \int_{V} M_{+}(r) e^{-ikr} d^{3}r \iff M_{+}(r) = \int_{V} \tilde{F}_{+}(k) e^{ikr} d^{3}k$$

$$\tilde{F}_{-}(k) = \int_{V} M_{-}(r) e^{-ikr} d^{3}r \iff M_{+}(r) = \int_{V} \tilde{F}_{-}(k) e^{ikr} d^{3}k$$

$$\tilde{Z}(k) = \int_{V} M_{z}(r) e^{-ikr} d^{3}r \iff M_{z}(r) = \int_{V} \tilde{Z}(k) e^{ikr} d^{3}k$$
(1.26)

which contains a redundancy explained by the relationships between the configuration

states:

$$(\tilde{F}_{+}(k))^{*} = \tilde{F}_{-}(-k) , \quad (\tilde{Z}(k))^{*} = \tilde{Z}(-k) .$$
 (1.27)

These equations use a full 3D representation with 3D space and dephasing coordinates. However, a 1D dephasing coordinate is normally sufficient for understanding the magnetization response of multi-pulse sequences so scientific literature almost exclusively deals with a 1D approach using the read/frequency encoding direction, and the vectors **k** and **r** reduce to the scalars k and r, respectively.



Figure 1.10: Graphical interpretation of an RF pulse affecting the EPG configuration states: each RF pulse causes an exchange of magnetization between equal dephasing orders only. While conversion from $\tilde{Z}(0)$ to $\tilde{F}(0)$ represents a FID, conversion for $k \neq 0$ exchanging magnetization between \tilde{F}_+, \tilde{F}_- and \tilde{Z} is usually called storing. Image obtained with permission from Weigel 2015 [27].

1.5.0.1 EPG - RF effects

RF pulses convert longitudinal magnetization into a transverse component and vice versa, so the effect of an RF pulse on the configuration states is:

$$\begin{bmatrix} \tilde{F}_{+}(k) \\ \tilde{F}_{-}(-k) \\ \tilde{Z}(k) \end{bmatrix}^{+} = T_{\Phi}(\alpha) \cdot \begin{bmatrix} \tilde{F}_{+}(k) \\ \tilde{F}_{-}(-k) \\ \tilde{Z}(k) \end{bmatrix}^{-}$$
(1.28)

where the center $T_{\Phi}(\alpha)$ matrix-operator is the same of Equation 1.25 as Fourier transform is linear and T does not explicitly depend on k. This means that RF pulse exchanges or mixes fractions of magnetization among configuration states of equal dephasing order |k|, and that non-coherent ($k \neq 0$) transverse magnetization components converted into longitudinal $\tilde{Z}(k)$ states remain constant, not experiencing any phase evolution or dephasing.

Coherent, not modulated configuration states with k = 0 represent the equilibrium magnetization (corresponding to $\tilde{Z}(0)$) and the freshly excited coherent transverse magnetization $\tilde{F}(0)$, i.e., a free induction decay (FID) and echoes. The quantification of the population of such $\tilde{F}(0)$ state allows to estimate both magnitude and phase of the complex-valued population while, frequently, measured echoes result as a superposition of echoes of different configuration states.

1.5.0.2 EPG - Gradient dephasing

Gradients cause harmonic wave patterns of transverse magnetization $\tilde{F}_+(k)$ and $\tilde{F}_-(-k)$. Dephasing effects caused by gradients are implemented using the shift operator S:

$$S(\Delta k): \quad \tilde{F}_k \to \tilde{F}_{k+\Delta k} \text{ and } \tilde{Z}_k \to \tilde{Z}_k$$
 (1.29)

where the gradient has the 0th moment of $\Delta k = \gamma \int_0^t G(t') dt'$, which shows that only transverse $\tilde{F}_{\pm}(k)$ states experience phase evolution, while longitudinal $\tilde{Z}(k)$ states do not.

When considering the rotating reference frame introduced by Rabi et al [28], constant gradients cause a linearly position-dependent off-resonance Larmor frequency along their axis. If we consider the transverse magnetization as a helix of coherent isochromat, the longer the gradient is turned on, the more turns the helix will have. When magnetization is interpreted in terms of "configuration states" directly linked to the dephasing coordinate k, a change of k means a change of dephasing of the transverse magnetization of the isochromat ensemble $\tilde{F}_+(k)$, and a gradient dephasing can then be described as a sum of helices of isochromats, as shown in Figure 1.11.



Figure 1.11: Partitioning effect of an RF pulse as described by Kaiser et al. [26] as then presented by Scheffler [29] (the components M_+ and M_- are complex conjugates), and example of the representation of the configuration state \tilde{F}_+ depicting the configuration of transverse magnetization with time when a constant gradient is applied. Image adapted with permission from Weigel 2015 [27].

1.5.0.3 EPG - Relaxation effects

Relaxation, dephasing, and diffusion phenomena maintain the anisotropy between longitudinal and transverse magnetization in EPG, so relaxation is included by a matrixoperator of relaxation terms for $k \neq 0$ states:

$$E(\tau, \mathsf{T}_1, \mathsf{T}_2) = \begin{bmatrix} E_2 & 0 & 0\\ 0 & E_2 & 0\\ 0 & 0 & E_1 \end{bmatrix}$$
(1.30)

with $E_1 = \exp(-\tau/T_1)$ and $E_2 = \exp(-\tau/T_2)$, being T_1 and T_2 the relaxation times and τ the time interval. For k = 0, $\tilde{Z}(0)$ has an additional term for T_1 recovery toward thermal equilibrium magnetization M₀:

$$\begin{bmatrix} \tilde{F}_{+}(k) \\ \tilde{F}_{-}(-k) \\ \tilde{Z}(k) \end{bmatrix}^{+} = E(\tau, T_{1}, T_{2}) \cdot \begin{bmatrix} \tilde{F}_{+}(k) \\ \tilde{F}_{-}(-k) \\ \tilde{Z}(k) \end{bmatrix}^{-} + \begin{bmatrix} 0 \\ 0 \\ M_{0}(1-E_{1}) \end{bmatrix}$$
(1.31)

1.5.0.4 EPG - Diffusion effects

The most general EPG solution in regard to diffusion was published by Weigel et al [27], and considers a general pulse sequence with arbitrary time intervals and gradient shapes as well as anisotropic diffusion in a 3D space. As each isochromat acquires an individual phase shift – destroying the harmonic wave patterns – this leads to a decay of macroscopic magnetization, equivalent to the attenuation of the populations of the configuration states. The common propagator for isotropic free diffusion in 1D and its Fourier representation are

$$P(r,\Delta t) = \frac{1}{\sqrt{4\pi D\Delta t}} \exp\left(-\frac{r^2}{4D\Delta t}\right) \quad \Longleftrightarrow \quad \tilde{P}(k,\Delta t) = \exp(-Dk^2\Delta t) \quad .$$
(1.32)

As diffusion sensitivity is proportional to k^2 , higher order k configuration states are more sensitive to diffusion and higher spatial frequencies are more affected than low modulation frequencies, as shown in Figure 1.12. For isotropic diffusion, the diffusion integral operator can then be expressed as

$$D(k(t), D, \tau) = \exp\left(-\int_{t=0}^{\tau} k^2(t) dt D\right) = \exp(-b_{\tau} D)$$
(1.33)

so that two isotropic diffusion operators can be derived when evaluating the boundary condition of a constant background gradient, which are the diffusion operator for the transverse \tilde{F} states and for the longitudinal \tilde{Z} states, respectively:

$$D^{T} = \exp(-((k_{1} + \frac{\Delta k}{2})^{2}\tau + \frac{(\Delta k)^{2}}{12}\tau)D) = \exp(-b_{\tau}^{T})$$

$$D^{L} = \exp(-((k_{1})^{2}\tau)D) = \exp(-b_{\tau}^{L}D)$$
(1.34)

combined in the matrix operator

$$D = \begin{bmatrix} D^T & 0 & 0\\ 0 & D^T & 0\\ 0 & 0 & D^L \end{bmatrix}$$
(1.35)

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and where in a regular, periodic sequence, $\Delta k = k_2 - k_1$ is constant (as k_1 and k_2 are multiples of Δk).



Figure 1.12: All configuration states representing spatial harmonic patterns of magnetization are affected by the incoherent diffusion motion of the isochromats, leading to information loss of all the EPG states with $k \neq 0$ due to the stochastic nature of diffusion. Image obtained with permission from Weigel 2015 [27].

1.5.0.5 EPG - Framework

In practice, the magnetization vector as the result on an isochromat ensemble is described as the sum of different configuration states at any time during the MR sequence. This set of defining configuration states is usually stored in a state matrix

$$\Omega = \begin{bmatrix} \tilde{F}_{0} & \tilde{F}_{1} & \tilde{F}_{2} & \tilde{F}_{3} & \tilde{F}_{4} & \dots \\ \tilde{F}_{0}^{*} & \tilde{F}_{-1}^{*} & \tilde{F}_{-2}^{*} & \tilde{F}_{-3}^{*} & \tilde{F}_{-4}^{*} & \dots \\ \tilde{Z}_{0} & \tilde{Z}_{1} & \tilde{Z}_{2} & \tilde{Z}_{3} & \tilde{Z}_{4} & \dots \end{bmatrix}$$
(1.36)

which corresponds to a sequencing of the 3 base states along an increasing dephasing order k. Indeed, during a sequence, the state matrix will increase in size as the EPG

evolution occupies states of higher k order, where the sum of the square of the absolute value of each configuration state is equal to the equilibrium magnetization $M_0 = 1$.

Although scientific literature uses the terms "state" and "pathway" interchangeably, it should be noted that a set of configuration states characterizes the isochromat ensemble at a given time, while magnetization pathways connect these configuration states to illustrate how these states evolve over time as a result of RF pulses and gradients

1.5.0.6 EPG - Limitations

The EPG concept has some limitations, including:

- RF pulses are usually treated as impulses (delta functions) under the hard pulse approximation and provide instantaneous rotations thus neglecting relaxation, diffusion, and off-resonance effects. The isodelay can be used as a time reference for the application of the RF pulse, but more sophisticated solutions have also been used [30];
- EPG is a Fourier representation of an uncoupled spin 1/2 spin system, but coupling effects should be taken into account [30];
- EPG assumes the voxel to be a cuboid homogeneous in the dephasing coordinate direction, with properly dephased configuration states except for \tilde{F}_0 . The object should be represented by a continuous spectrum with a finite width of $\delta k \approx 2\pi/\Delta x$ in frequency space, which leads to a broadening of the EPG states and pathways.

1.6 Quantitative MRI

The onset of non-invasive or minimally invasive exploration of the human body as a radiological exam can be traced back to the late 19th century with the discovery of X-rays by Wilhelm Röntgen. From its beginning, the technological advancements and the new imaging modalities in terms of contrast possibilities have prospered in both research and clinical environments. The workflow of a radiology exam is based on image acquisition, after which the radiologist looks for potential abnormalities, and a diagnosis or a clinical suggestion for further assessments is made. Currently, pathophysiological features in MRI images are identified based on their contrast differences or enhancement patterns and the interpretation of radiological evidence is largely qualitative. For example, anatomical structures are assessed by means of a visual inspection and comparison with normal-appearing counterparts, carefully seeking for relative hyper- or hypo-intensity of anatomical structures. The contrast-weighted approach remains the most widespread and this is used to highlight contrast differences between tissues on a single image. However, when multiple contrast mechanisms are involved, this approach may not result in optimal contrast, thus not optimally separating the appearance of tissues [31]. Moreover, specific protocols and the degree of weighting applied can considerably change the appearance of qualitative images. As such, the lack of quantitative measurements, the qualitative nature of image contrast, and the variability in MR images may lead to unreliable, uncertain or ambiguous radiological interpretation. Conversely, the computation of the physical and magnetic properties of a tissue to isolate single components of the image variability from confounding factors might help to characterize tissues, and could be considered as a 'Principal Component Analysis' of MR imaging as this is about the extraction of the features that rule image contrast. Few quantitative considerations are performed - mainly related to size, volume, and distance evaluation [32] - although MRI could be employed to measure several properties: among the tissue properties that can be computed we acknowledge relaxation times $\mathsf{T}_1,\,\mathsf{T}_2$ and T_2^* (via relaxometry), magnetic susceptibility and iron concentration, diffusion and perfusion properties as the apparent diffusion coefficient ADC, the diffusion coefficient D, the pseudodiffusion coefficient D* and perfusion fraction f (via diffusion and perfusion MRI), fat and water fraction, myelin fraction, complex shear moduli (via elastography), temperature (via thermometry), chemical composition and chemical exchange (via spectroscopy).

The acquisition of images for the computation of all of these parametric maps represents the principle of quantitative MRI (qMRI). This allows a quantitative tissue characterization that could lead to several advantages:

- Enabling early detection and quantitative differentiation of diseases, improving diagnosis by complementing or replacing biopsy stage as well as providing rich datasets for artificial intelligence [33]. Indeed, provided that consistency within and among scanners (inter- and intra-scanner) can be proved and that confound-ing factors can be pointed out, maps from patients could be pooled to perform radiomic analyses.
- The ability to compute probability maps from imaging and non-imaging data for various diseases to be used in support of the clinical decision.
- Unhealthy tissue characterization and identification when the discriminant feature can be probed and then sensitized with MRI. Anatomical abnormalities and loss/regain of function could also be of assistance during surgeries and in clinical practice, where currently anatomy-driven images are used (eg: for surgical, procedural, or function-driven specialties such as endocrinology and nephrology).
- The ability to study multiple parameters independently and jointly from each other, as in complex systems a single parameter may not always be sufficient for a comprehensive assessment of the underlying tissue pathophysiology. This should, ideally, serve as actionable information parallel to standard clinical practice.

Ideally, MRI scans should be used as a diagnostic tool able to provide quantitative information for reproducible tissue property maps to allow tissue health characterization, with less need for diagnosis via histopathological approach. Currently the main diagnostic gold standard for oncology, in particular, remains a histological examination, while

if the goal of imaging is diagnosis without invasive interrogation, then every biopsy is an imaging failure.

This is the opening statement in the book "Quantitative Magnetic Resonance Imaging" by Vikas Gulani and Nicole Seiberlich, which implicitly states the ultimate goal of noninvasive diagnosis in bioimaging.

The barriers to the adoption of quantitative tissue property mapping via MRI images in the clinical routine, as of today, can be traced back to three main facts:

• the inherent speed limitations of MRI. At least two images have to be acquired, and each image may require a lengthy acquisition. This has made the collection of quantitative information not feasible in many clinical settings.

- the lack of reproducibility and repeatability. Both features are key for clinical translation as the goal of the clinical use of qMRI is the objective comparison between pathophysiological states or patient groups. Inter-scanner reproducibility could and should be reached to remove the dependency of signal intensity over user-controllable settings, software versions, and vendors.
- the clinical use of qualitative MRI images. The ability of qualitative MRI images to provide enough anatomical information for a diagnosis (eg: vessel stenosis, ischemic tissues) is one of the reasons for reluctance to change and an obstacle for qMRI which leaves a large amount of information unused. Indeed, physicians and surgeons already obtain anatomical information from conventional MRI and are able to identify pathologies and characteristic imaging appearance (eg: vessel stenoses, duct strictures, ischemic tissues) to drive clinical care in the appropriate direction.

Quantitative measurements of pathophysiological features need to satisfy characteristics in terms of closeness to the true value, range of possible values, and reliability. Accuracy and precision loosely correspond to systematic and random source of errors. A systematic error represents an offset/bias in the measurement: software version, hardware features, as well as non-uniformity in the excitation field B_1 , partial volume errors, parameter fitting via incomplete models, and imperfections in k-space sampling (as for EPI acquisitions) are found among the major contributors to systematic errors. Also, it is important to be aware that the accuracy of some relaxometry parameters such as T_1 times have been correlated to the measurement technique: Stikov et al. found that Look-Locker and Variable Flip Angle techniques report different values, overestimating T_1 with respect to the gold-standard Inversion Recovery spin-echo sequence [34]. Precision is often referred to as measurement reproducibility or repeatability and can be checked via test-retest performances, carried out within a time interval for which the underlying quantity can be considered constant. This is normally caused by random error due to image noise, patient movement, and normal variation in physiology, which contribute to the uncertainty, the spread of estimated true values in repeated measurements.

A convenient way to test measurement accuracy and stability is through imaging of phantoms. Phantoms are physical (and virtual) models that can be used to mimic tissues and sources of error. These can be used to track back problems in all the steps of the imaging pipeline, from acquisition to post-processing, and can then serve as a baseline reference for further in vivo testing. Ideally, any error-free measurement should result in a value that perfectly represents the underlying pathophysiology. In the book "Quantitative MRI of the Brain" edited by Cercignani, Dowell and Tofts, a perfect qMRI machine is theorized as

one that, in making a measurement, contributes no significant extra variation to that which already exists from biological variation [35].

Various grades of performance can be expected and separated, depending on the purpose of the measurement. For example, the most demanding and clinically relevant discrimination should be between a variation defining a pathological state as opposed to the normal variation of the parameter under investigation. A medal system proposal was made identifying three levels based on the required sample size and power and reached performances of the machine in terms of parameter variance sample. Medals are awarded based on requirements in terms of total deviation within the group (GSD), computed as a function of the instrumental standard deviation (ISD) and the biological standard deviation (BSD), where $GSD^2 = ISD^2 + BSD^2$. Other parameters considered are also the inter-centre standard deviation (BCSD) and the within-subject biological changes (WSSD).

- Bronze medal: awarded in group comparison when the instrumental standard deviation makes an insignificant contribution to the total deviation within the group with respect to the biological standard deviation. The bronze medal would be awarded for ISD < 0.3GSD. As BSD depends intrinsically on the kind of subjects considered, this would need to be untangled from confounding variables, such as age and gender.
- Silver medal: awarded in multicenter studies when the inter-centre standard deviation (BCSD) is smaller than the total group standard deviation, BCSD < GSD. This would guarantee that the measurements performed in different centers are free from variations strictly related to the specific research center, thus enabling parallel studies.
- Gold medal: awarded in a serial study when instrumental variation can be considered negligible with respect to within-subject biological changes (WSSD), so that ISD < 0.3WSSD. As this biological variation can limit the power of a serial study, this makes the gold medals the hardest to obtain.

1.7 Relaxometry

The term 'relaxometry' refers to the study and quantification of magnetic resonance relaxation parameters such as T_1 , $T_{1,\rho}$, T_2 and T_2^* in NMR and (q)MRI. This quantification can be performed to reconstruct parametric images (maps) with a one-to-one correspondence between voxel and parameter intensity, which is called "mapping".

1.7.1 T₁ mapping

Since the development of the first techniques for T_1 mapping, this has mostly been limited to research applications, and it has been infrequently exploited as part of clinical imaging protocols. While early T_1 mapping implementations were characterized by long acquisition times and the requirement of additional calibration steps, recent technological developments made both clinicians and MRI manufacturers more interested in adopting rapid mapping techniques as standard sequences for their scanners. The possibility to obtain T₁ maps in clinically feasible times consequently led to growing interest in mapping as a clinical tool. Yet, over the years, a wide range of published T_1 values for the same tissue and pathology have become available and a standardization step among different methods, scanners, parameter setups is still needed for a true validation of T_1 as a biomarker [34, 36], which makes the paradigm shift from T_1 -weighted to T_1 -maps far from being reached. Three fundamental approaches are currently undertaken for T_1 mapping, namely a signal recovery, a steady-state, and a dictionary-based approach, from which most other techniques developed. Although multiexponential T_1 mapping has been investigated, this has not gained the same level of interest as multiexponential T₂ mapping.

1.7.1.1 Inversion Recovery (IR)

The Inversion Recovery (IR) technique was first developed for NMR in the 1940s [37, 38], and it is widely considered the gold-standard for T_1 mapping in MRI as it provides accurate T_1 estimates by means of a simple monoexponential fit, and has some notable advantages such as being partially insensitive to pulse sequence parameter imperfections and imperfect spoiling. In IR, the signal is acquired after a 180° inversion pulse and a 90° pulse which, for different runs of the sequence, is applied at several delays after the 180° pulse, called inversion times (TI), to bring the magnetization vector from the z axis to the transverse plane. The recovery curve is thus sampled in multiple points while reaching thermal equilibrium via a spin echo or gradient echo readout.

Variations of the IR technique based on modifications of the flip angle used during the inversion phase can be useful for faster acquisition. For example, a common implementation of IR is the partial saturation recovery sequence, which was used to acquire the first T_1 map ever computed [39]. This sequence uses a saturation pulse (flip angle of 90°) rather than fully inverting (flip angle of 180°) the magnetization with the preparation pulse. Despite IR techniques show great robustness at measuring T₁, they require long acquisition times, as the longitudinal magnetization needs to be back at at equilibrium before every inversion pulse on the same slice. This requires repetition times on the order of 3-5 times the longest T_1 of the analyzed tissue, which in neuroimaging can typically be white, gray matter, or CSF, with T_1 times around 0.7-1.7, 1.0-1.8, and 4 seconds at 3 T, respectively [40, 41]. For example, supposing that in a 2D multislice acquisition with a 128x128x36 matrix size a k-space line for each slice would be acquired in a Cartesian fashion in around 5 seconds, this would lead to 10.7 minutes of acquisition time for a slice for each TI. For a reference 3D acquisition, this would lead to a single full acquisition of a prohibitive 6.4 hours for each TI, to be repeated at least for another TI to obtain two points for model fitting. This makes it challenging (if not impossible) to acquire whole-organ multislice 2D or 3D T_1 maps in a clinically feasible time. These considerations apply to standard SE or GE readout acquiring a single line in k-space per TR. However, in 2D scans, the acquisition of multiple slices can be stacked in a single TR, and IR can also be followed by EPI or RARE readout to shorten the acquisition time. IR is used as a gold standard and is a useful bulk measurement technique as it establishes a reference measurement for the development and comparison of T_1 techniques, including several variations of the IR technique with an EPI readout [42, 43].

The steady-state longitudinal magnetization of an IR experiment can be derived from the Bloch equations for the pulse sequence (symbolically represented by θ_{180} - TI - θ_{90} - (TR-TI)):

$$M_{z}(\mathrm{TI}) = M_{0} \frac{1 - \cos \alpha e^{-\frac{\mathrm{TR}}{\mathrm{T}_{1}}} - [1 - \cos \alpha] e^{-\frac{\mathrm{TI}}{\mathrm{T}_{1}}}}{1 - \cos \alpha \cos \beta e^{-\frac{\mathrm{TR}}{\mathrm{T}_{1}}}}$$

=
$$A(1 - 2e^{-\frac{\mathrm{TI}}{\mathrm{T}_{1}}} + e^{-\frac{\mathrm{TR}}{\mathrm{T}_{1}}}) \quad (1.37)$$

where M_z is the longitudinal magnetization prior to the β pulse that creates a transverse magnetization, α is the inversion pulse and A is a constant which encompasses constant terms (TI, TE, α). The first expression of the equation represents the general form of the signal model, while the second expression generated assuming $\alpha = 180^{\circ}$ and $\beta = 90^{\circ}$ represents its approximate form. In case TR is long enough to allow for full relaxation

of the tissue (which requires TR in the order of at least 3-5 T₁) and TR is also longer than the longest TI, the $e^{-\frac{\text{TR}}{\text{T}_1}}$ term becomes negligible.

Stable fitting via IR is typically reached via acquiring signals at multiple inversion times in the [0, TR] interval. Also, acquiring data at $TI = T_1 \ln 2$ (called TI_{null}) where the signal for the tissue of interest is nulled should be avoided as the magnitude images at this TI time will be dominated by Rician noise that can impair the fitting procedure. Early implementations of IR fitting algorithms included the "null method" [44], which assumes that each recovery curve has a unique zero-crossing at TI_{null} , but now algorithms such as nonlinear least-squares fittings can be applied to model the signal. It was demonstrated that a simplified equation is sufficient for accurate T_1 mapping when the provided flip angle is accurate and $e^{-\frac{TR}{T_1}} \approx 1$ (long TR approximation):

$$S(\mathsf{TI}) = a + be^{-\frac{\Pi}{\mathsf{T}_1}} \tag{1.38}$$

where a and b can either be complex values (5-parameter fitting) or real values (3parameter fitting - used when magnitude-only data are available). As no assumptions about TR are made, this model is as robust as the general model as long as the pulse sequence parameters are consistent among measurements. A further simplification of the model using only a single free parameter is used as well, with $S(TI) = 1 - 2e^{-TI/T_1}$. Figure 1.13 reports an example of recovery curves from the general model and the long TR approximation.



Figure 1.13: Signal recovery curves from general model and long TR approximation ($\alpha = \pi$, $\beta = \pi/2$, TR = 9 s, T₁ = 4 s). The difference between the two curves becomes negligible as TR \gg T₁.

1.7.1.2 Look Locker (LL)

A method stemming out as a variation of the IR sequence, the Look-Locker (LL) sequence (also called Inversion-Recovery Fast Low Angle SHot - IR-FLASH), was developed with the intent to measure T_1 during a single relaxation process. This was originally designed and used for NMR spectroscopy [45] and then adapted for imaging [46] as SNAPSHOT-FLASH and only then used as a mapping technique [47]. This technique employs a series of low flip angle (α) pulses after an inversion pulse while keeping most of the longitudinal magnetization along the z axis. Each α pulse tips the magnetization, creating a transverse magnetization and thus generating a detectable signal that is proportional to the current longitudinal magnetization, so that the collection of the signals acquired at each repetition time during the sequence reflects the recovery of the magnetization that takes place with a modified relaxation time T_1^* constant. The magnitude of α is non-trivial and represents the trade-off in the estimation of T_1 , as a noise floor may dominate the signal when α is too small, or it could interfere with the relaxation process (accelerating the recovery and leading to T_1 underestimation) when α is too large. This is shown in Figure 1.14, where the development of the longitudinal relaxation is reported for T₁ = 1.5 s, α = 5° and TR = 5 ms, and the unperturbed exponential and effective (non-exponential) relaxation curves do not overlap. Also, the steady-state value for the longitudinal magnetization differs from M_0 : indeed, M_z approaches an effective longitudinal magnetization value $M_0^* < M_0$ with a modified relaxation time $T_1^* < T_1$ [48], where

$$T_1 = \frac{TI}{TI/T_1^* + \log(\cos \alpha)} \quad . \tag{1.39}$$



Figure 1.14: Magnetization behavior for an ideal/unperturbed and Look-Locker (perturbed) acquisition.

The signal evolution has been previously derived [19, 49, 50], and the behavior of the longitudinal magnetization can be described by

$$M_{z}(n) = M_{z}^{*} - (M_{z}^{*} - M_{0})) \exp\left(-\frac{n\mathrm{TI}}{\mathrm{T}_{1}^{*}}\right)$$
(1.40)

where $M_z(n)$ represents the longitudinal magnetization before the n-th excitation pulse, and M₀ is the equilibrium magnetization corresponding to the close-to-zero longitudinal magnetization immediately after the inversion pulse. M_z^* is related to the equilibrium longitudinal magnetization by

$$M_z^* = M_0 \frac{1 - \exp(-\tau/T_1)}{1 - \exp(-\tau/T_1^*)}$$
(1.41)

and its first-order Taylor expansion leads to the following relationship between T_1 , T_1^* , M_z^* , and M_0 [51]:

$$T_1 = T_1^* \frac{M_0}{M_z^*} \quad . \tag{1.42}$$

In this way, the acquired signal can be fitted to the model of Equation 1.40 via a threeparameter (M_0 , M_z^* and T_1^*) fitting procedure and T_1 can be determined from Equation 1.42. Similarly, Equation 1.40 can be re-written as

$$M_z(n) = A - B \exp\left(-\frac{n\mathsf{TI}}{\mathsf{T}_1^*}\right) \tag{1.43}$$

and T_1 can be retrieved after fitting A, B and T_1^* as

$$T_{1} = T_{1}^{*} \left(\frac{B}{A} - 1\right)$$
(1.44)

which holds for small flip angles ($\alpha < 10^{\circ}$) [47]).

Look-Locker relaxometry is the basis for quantitative breath-hold ECG-triggered cardiac T₁ mapping using LL variants known as MOLLI (MOdified Look-Locker Imaging), ShMOLLI (Shortened MOLLI), and SASHA (SAturation recovery Single sHot Acquisition) [42, 43, 52]. MOLLI uses single-shot balanced steady-state free precession (bSSFP) readouts after each α excitation pulse. The original MOLLI implementation – one of the many available – uses 3 inversion pulses for 11 readouts over 17 heartbeats (Figure 1.15) and data acquisition is performed after inversion pulse fired at inversion times of TI, TI + RR and TI + 2 × RR, where RR represents the heartbeat interval.



Figure 1.15: MOLLI pulse sequence implementation. Adapted with permission from Messroghli et al. [42].

With respect to the inversion recovery sequence, LL samples the inversion time relaxation curve much more efficiently, but with a lower SNR. However, with respect to inversion recovery, B_1 inhomogeneities and imperfect spoiling impact on a greater extent on T_1 quantification, as the magnetization of each measurement depends on the previous series of RF excitations [53].

1.7.1.3 Variable Flip Angle (VFA)

Variable flip angle (VFA) T_1 mapping [54, 55, 56, 57, 58] is a rapid quantitative T_1 measurement technique used to acquire maps in a clinically feasible time. VFA is also known as Driven Equilibrium Single Pulse Observation of T_1 (DESPOT1) [59] and employs multiple (at least two) SPGR signals acquired with different excitation flip angles. SPGR acquisitions use very short TRs (around 10-50 ms) and the technique is based on the readout of a steady-state regime of the signal.

Because of its widespread availability, speed, and short processing times, VFA remains one of the most widely used T_1 mapping methods in research, employed either in a 3D or 2D single slice or multislice fashion. However, the VFA method is very sensitive to inaccuracies in the flip angle value, since the actual flip angle experienced by the spins can present position-dependent bias compared to the nominal flip angle set by the scanner and this difference worsens with increasing field strength, with variations reaching 20-30% at 3 T [34, 60, 61] and 50-60% at 7 T [62]. This bias can impact the T_1 estimates resulting in reconstructed T_1 values with a spatially varying bias [63, 64]. For example, Liberman reported a mean absolute difference in T_1 of 235 ms in the brain at 3 T when information from the B_1 map was omitted [65]. In order to scale the actual flip angle back to the nominal one, VFA typically requires the acquisition of additional images for the computation of the $B_1^{(+)}$ field map which represents the spatial variations of the transmit RF amplitude in the field of view. Typically, B1 field maps are computed as a map of the κ factor, where κ represents the ratio between the nominal and the acquired flip angle. Voxel-wise values of κ then impact the accuracy and precision of the corrected T_1 maps themselves, so the computation of reliable B_1 maps is pivotal and adds an additional time requirement, potentially hindering the time advantage over the saturation recovery techniques [61, 66]. As rapid B_1 mapping pulse sequences are not commonly widely available, alternative ways of removing the bias from the quantitative - especially T₁ - maps have been explored by modeling or computing a synthetic/artificial B_1 map (for example, generating an artificial B_1 map through the use of image processing techniques [65]). Also, when slice profile effects are not taken into account, these could impact signal intensity as a distribution of flip angles will be present in the slice and, ultimately, T₁ maps will be computed encompassing the effect of a generalized apparent low-flip angle. For this reason, 3D acquisitions or longer selective pulses (with a slice profile closer to an ideal rectangular profile) can be used to help reduce

slice profile effects.

As the VFA method is based on the acquisition and fitting of SPGR signals, it is fundamental to understand the origin of SPGR signals. Starting from Bloch equations, we can obtain the steady-state magnetization for an SPGR sequence. Assuming perfect spoiling for a sequence of SPGR pulses, the transverse magnetization is zero just before each new RF pulse, which then converts longitudinal magnetization into transverse magnetization. In a non-equilibrium state ($M_z \neq M_0$, if M_z is M_{zA} , then after the RF pulse with flip angle α this will be $M_{zB} = M_{zA} \cos \alpha$. Relaxation would then occur according to the Bloch equations and after a time TR the magnetization would become $M_{zC} = M_{zB}e^{-\text{TR/T}_1} + \text{M}_0(1 - e^{-\text{TR/T}_1}) = M_{zA} \cos \alpha E_1 + \text{M}_0(1 - E_1)$ where $E_1 = e^{-\text{TR/T}_1}$. The steady-state condition is reached for longitudinal magnetization when $M_{zA} = M_{zC}$, which yields

$$\frac{M_{zA}}{M_0} = \frac{1 - E_1}{1 - \cos \alpha E_1} = f_{z,ss}$$
(1.45)

so that the approach to steady state (transient state) at the j-th pulse of an SPGR sequence can be expressed as

$$S_j = \mathsf{M}_0 \sin \alpha e^{-\mathsf{TE}/\mathsf{T}_2^*} [f_{z,ss} + (\cos \alpha E_1)^{j-1} (1 - f_{z,ss})]$$
(1.46)

while the steady state signal is given by

$$S_{SPGR} = \mathsf{M}_0 \sin \alpha f_{z,ss} e^{-\mathsf{TE}/\mathsf{T}_2^*} = \mathsf{M}_0 \sin \alpha \frac{1 - E_1}{1 - \cos \alpha E_1} e^{-\mathsf{TE}/\mathsf{T}_2^*} \quad . \tag{1.47}$$

An example of the transient state and the approach to steady state using the analytic formula is reported in Figure 1.16: it can be appreciated how larger flip angles and shorter relaxation times (or longer repetition times) can sometimes increase the speed of the approach.



Figure 1.16: The approach to steady state for the signal of SPGR sequences (here represented as normalized over the steady state value) varies based on the sequence parameters, mainly flip angle, TR, and T_1 .

The main assumption underlying the closed-form solution of Equation 1.47 is that the transverse magnetization is perfectly spoiled (meaning that there is no residual signal left in the transverse plane) and at steady state at the end of each repetition time. Normally, an arbitrary number of RF pulses (dummies) is provided and discarded before reaching the regime condition provided by the steady-state value.

Figure 1.17 also shows the number of dummy pulses needed for an ideal (noise-free) approach to steady-state for α up to 40°, T₁ in the 0.5-4 s range, and TR = 30 ms, which can be generalized reporting a general TR/T₁ ratio. The contour lines show that the number of dummy pulses for 5% accuracy depends on the sequence parameters and the tissue properties. The approach to steady state for several sequence parameters and common tissue T₁s is reached in tens of pulses, but can also require hundreds of pulses in case of tissues with long T₁ – such as for CSF or parenchymatous tissues at high magnetic field.



Figure 1.17: Contour map reporting the dependency of the SPGR steady state signal over the provided flip angle and underlying T_1 for TR = 30 ms. Contour lines represent the number of dummy pulses required for reaching an accuracy within the 5% of the steady state value.

Preparation pulses or an inward k-space acquisition pattern is typically sufficient to allow the magnetization to reach a steady state before the center of k-space is acquired, avoiding any major deterioration and artifacts caused by signal stabilization on image quality. Ideally, a preparation module would make the magnetization vector reach its steady-state value with just one RF pulse and a subsequent recovery time whose duration is defined by an analytical expression that is not a function of imaged tissue properties. A preparation module consisting of a saturation pulse was proposed for SPGR sequences [67], but this remains rarely employed in practice, although advantages of using a magnetization preparation pulse would include lower energy deposition (as SAR \propto B₁²) and an almost immediate SS approach, which can help with fast and ultra-fast acquisitions. For this reason, 3D sequences have a time benefit over multislice 2D acquisitions as every RF pulse flips the magnetization vectors of the whole volume of interest and the whole sample would reach steady-state conditions within the first tens/hundreds of RF pulses with no need to repeat the preparation for every slice. However, multislice 2D sequences can be played in an interleaved fashion, exciting multiple slices in a single repetition time.

It should also be noted that the ideal, steady state signal can be approached only with a combination of gradient and RF spoiling, while the lack of at least one type of spoiling will result in non-accurate signals in SPGR acquisitions. The application of suboptimal spoiling will indeed result in spurious signal coherences that can impact and deteriorate signal accuracy, as reported in Figure 1.18, thus impacting the T₁ value computed via VFA estimation.



Figure 1.18: SPGR signal simulated in different spoiling conditions with an EPG approach. While ideal spoiling would allow to reach the ideal steady state of Equation 1.47, the amount of spoiling greatly impacts the steady state signal and, eventually, the T_1 computation via the VFA approach. Signals were simulated with $T_1 = 2$ s, $T_2 = 0.1$ s, diffusion coefficient $D = 2*10^{-9}$ mm²/s, TR = 20 ms, TE = 2.8 ms.

In order to estimate T_1 from SPGR signals via VFA, a linear least squares fitting algorithm can be used and that comes with a net reduction of the processing time with respect to a nonlinear least square fitting algorithm, as a linear expression of the y = mx + b form can be obtained [55]:

$$\frac{S_{SPGR}}{\sin\alpha} = E_1 \frac{S_{SPGR}}{\tan\alpha} + C(1 - E_1)$$
(1.48)

where the last term, constant between measurements, represents the y-axis intercept, so that T₁ can be estimated from the slope of the regression line from $S_{SPGR}/\sin \alpha$ and $S_{SPGR}/\tan \alpha$ values:

$$\mathsf{T}_1 = -\frac{\mathsf{TR}}{\mathsf{ln}(m)} \quad . \tag{1.49}$$

The precision in T_1 estimation would benefit from the acquisition of images at several flip angles. As different flip angles result in different noise weighting and low SNR data might be acquired, weighted linear least-square approaches, as well as nonlinear approaches, can be used to avoid biased T_1 estimates [68]. Moreover, it has been shown that the best precision for a single-tissue T_1 estimate via VFA with acquisitions with only two flip angles is obtained with the two flip angles α that provide a $0.71 \cdot S_{SPGR,Ernst}$ signal, found on the sides of the skewed curve of the SPGR signal [59, 69]. As the information about the provided flip angle is needed for the computation of T_1 via VFA method, the intensity of the B_1 field should be known and used to correct for possible inhomogeneities. Nevertheless, the selection and use of a B_1 mapping technique needs careful consideration as this can introduce an additional source of error.

1.7.1.4 Magnetization Prepared 2 Rapid Acquisition Gradient Echoes (MP2RAGE)

Dictionary-based qMRI techniques use numerical dictionaries for both image reconstruction and post-processing. Dictionaries can be considered as databases of pre-calculated (pre-simulated as well as pre-acquired) and pre-processed data in a wide range of tissue and protocol combinations. As the dictionaries are available in advance prior to scanning sessions and interpolation is fast and not computationally expensive, the use of dictionary-based techniques results in shorter post-processing times than most current fitting algorithms, which allows quantitative maps to be displayed directly on the MRI scanner console. Short acquisition times and fast post-processing computation time ease the use of dictionary-based MRI for T_1 mapping. Popular examples of dictionary-based techniques that have been applied to T_1 mapping are MR Fingerprinting (MRF) [70], some Compressed Sensing (CS) techniques [71, 72], and Magnetization Prepared 2 Rapid Acquisition Gradient Echoes (MP2RAGE) [73].

MP2RAGE, in particular, is becoming increasingly available as a standard 3D pulse sequence on many MRI systems. This has been developed as an extension of the Magnetization Prepared Rapid Gradient Echo Imaging (MPRAGE) sequence [74], a 3D sequence that uses a magnetization preparation via a non-selective inversion pulse followed by a collection of rapidly acquired gradient echoes. MPRAGE and MP2RAGE both have the advantage of not requiring a steady state, as the signal is acquired while T₁ relaxation takes place during the readout. MP2RAGE corrects both the static (B₀) and dynamic/pulsing (B₁) RF field. Typically T₁ maps from MP2RAGE can be reconstructed online with software made available from the vendor, but alternatively, several open source packages with post-processing tweaks to handle parallel imaging acceleration and partial Fourier are available online [75, 76].

Having one of the fastest acquisitions and post-processing times among quantitative T_1 mapping techniques (1 mm isotropic maps at 3 T and submillimeter maps at 7 T can both be acquired in under 10 min [77]), MP2RAGE has been proved to be highly reproducible in both inter- and intra-site studies [78], and this has further contributed to increasing the interest for T_1 mapping in neuroscience and clinical practice. Nevertheless, the reproducibility of the maps depends on the pre-calculated dictionaries, so the same data, when interpolated with different dictionaries, might show differences in T_1 estimates due to the differences in dictionary interpolations. Lastly, the assumption in MP2RAGE is that the totality of signal variability can be explained by a monoexponential relaxation, yielding suboptimal T_1 estimates for biexponential relaxation model, especially at high magnetic fields [79].

MP2RAGE pulse sequence can be seen as a hybrid between VFA and IR: a 180° pulse inverts the magnetization and then two gradient echo images are acquired using both a different flip angle and different inversion times, as shown in Figure 1.19.



Figure 1.19: MP2RAGE pulse sequence diagram. Each excitation pulse is followed by a constant in-plane phase encode weighting (G_{pe}) for the dimension with highest resolution and a variable phase encode weighting ($G_{sl pe}$) along the second phase encoding direction, which replaces the slice direction in a 3D acquisition. The center of k-space for the 3D phase encoding direction is acquired at the TI time for each GE imaging block. A delay is introduced at the end of the first block, then the acquisition is repeated with a different flip angle. This is repeated while changing the gradient amplitude in the second phase encoding direction to sample the k-space in the third dimension. Image obtained with permission from Marques et al. 2010 [73].

Complex data are needed to reconstruct the MP2RAGE signal, which is calculated
from the images acquired at two inversion times (TI_1 and TI_2):

$$S_{MP2RAGE} = \Re\left(\frac{S_1 * S_2}{|S_1|^2 + |S_2|^2}\right)$$
(1.50)

where $S_{1,2}$ refer to the gradient echo data collected in TI₁ and TI₂.

As the steady-state is not achieved during the short train of GE imaging blocks, the number of phase-encoding steps will determine the amplitude of the signal at the k-space center and the contrast for each readout and the analytical formula for $S_{1,2}$ signals is:

$$S_{1} = \mathbf{B}_{1}^{-}\mathbf{M}_{0}\sin(\alpha_{1}) \left[\left(\frac{-\eta m_{ss}}{\mathbf{M}_{0}} E_{A} + (1 - E_{A}) \right) (\cos \alpha_{1} E_{R})^{n/2 - 1} + \left(1 - E_{R} \right) \frac{1 - (\cos \alpha_{1} E_{R})^{n/2 - 1}}{1 - \cos \alpha_{1} E_{R}} \right]$$

$$S_{2} = B_{1}^{-} e^{\frac{TE}{\tau_{2}^{*}}} \mathbf{M}_{0} \sin \alpha_{2} \left[\frac{m_{ss} - \mathbf{M}_{0} (1 - E_{C})}{\mathbf{M}_{0} E_{C} (\cos \alpha_{2} E_{R})^{n/2}} - \left(1 - E_{R} \right) \frac{(\cos \alpha_{2} E_{R})^{-n/2} - 1}{1 - \cos \alpha_{2} E_{R}} \right]$$
(1.51)

where B_1^- is the receive field sensitivity, η is the inversion pulse efficiency, E_R corresponds to $\exp(-\text{TR}/\text{T}_1)$ and E_X (where X = A, B, C) refers to $\exp(-T_X/\text{T}_1)$ where T_A corresponds to the time between inversion pulse and beginning of the gradient echo block, T_B corresponds to the time between the end of the acquisition with α_1 and beginning of the acquisition with α_2 , while T_C is the time between the end of the second gradient echo acquisition and the end of the TR. If no k-space acceleration is used (no partial Fourier or parallel imaging acceleration), then $T_A = TI_1 - (n/2)TR$, $T_B = TI_2 - TI_1 + (n/2)TR$, $T_C = TR - TI_2 + (n/2)TR$ where n is the matrix size in the second phase encoding direction through-plane. The value m_{ss} is the steady-state longitudinal magnetization prior to the inversion pulse, and is given by:

$$m_{ss} = \frac{\mathsf{M}_{0} \Big[\beta (\cos \theta_{2} E_{R})^{n} + (1 - E_{R}) \frac{1 - (\cos \alpha_{2} E_{R})^{n}}{1 - \cos \alpha_{2} E_{R}} \Big] E_{C} + (1 - E_{C})}{1 + \eta [\cos \alpha_{1} \cos_{2}]^{n} e^{-\mathsf{TR}/\mathsf{T}_{1}}}$$
(1.52)
$$\beta = \Big[(1 - E_{A}) (\cos \theta_{1} E_{R})^{n} + (1 - E_{R}) \frac{1 - (\cos \alpha_{2} E_{R})^{n}}{1 - \cos \alpha_{2} E_{R}} \Big] E_{B} + (1 - E_{B})$$

The B_1^- sensitivity can be reduced with protocol optimization as well as with the acquisition of a B_1 map to be included as one of the dictionary dimensions $[T_1, B_1, S_{1,2}]$ with an increase in total scanning time.

1.7.1.5 Variable flip angle with Actual Flip angle Imaging (VAFI)

To face the inhomogeneities in B_1 , both B_1 correction methods and joint estimation approaches have been proposed. While the former usually require additional acquisitions of stand-alone scans providing separate B_1 information [80], the latter perform multiparameter fitting from a set of acquisitions, thus providing a B_1 map as an output along with other quantitative parameters. Examples of methods for T_1 mapping with an integrated B_1 correction are DESPOT1-HIFI [63], MP2RAGE [73], MP(n)RAGE [81], and VAFI [82]. Among them, VAFI (Variable flip angle - Actual Flip angle Imaging) stands out as a fast 3D spoiled gradient echo based method which performs the joint estimation of T_1 , B_1 and the equilibrium magnetization (proportional to net magnetization). The VAFI method exploits a single Actual Flip angle Imaging (AFI) acquisition and at least an SPGR acquisition. AFI is characterized by a low Specific Absorption Rate (SAR) as compared with the commonly used B_1 mapping techniques [80] and SPGR volumes are typically acquired fast and with low energy deposition as well which makes VAFI a candidate for accurate, fast, low-SAR T_1 mapping.

Actual Flip angle Imaging (AFI): AFI is a 3D SPGR-based sequence originally proposed by Yarnykh [83] for simultaneous B_1 and T_1 mapping. Figure 1.20 reports the AFI pulse sequence diagram: the phase encoding gradients are played and rewound so that each crossed k-space segment – each line in Cartesian sampling – is sampled in two steady-state conditions created by alternating repetition times TR₁ and TR₂, where $TR_2 = n \cdot TR_1$ and n is chosen to provide contrast between the two acquired AFI images.

Transverse magnetization needs to be spoiled after signal sampling to avoid possible coherence build-up which would lead to deviations from model signal (ideally perfectly spoiled) [84, 85, 86]. Increasing n allows for the introduction of long spoiling gradients as well as for longer T₂ relaxation effects, which contribute to a sharper contrast between AFI images, while affecting the total acquisition time.

As for many steady-state sequences, the first few samples in an AFI sequence can be discarded to acquire data close to the steady-state. AFI steady-state signal is then reached and the analytical form of the signals can be derived by solving the Bloch equations, which provide [83]

$$S_{AFI1,2} = S_0 \sin \alpha \cdot \frac{1 - E_{2,1} + (1 - E_{1,2})E_{2,1}\cos \alpha}{1 - E_1 E_2 \cos^2 \alpha} \exp(-\mathsf{TE}/\mathsf{T}_2^*)$$
(1.53)

where S_0 represents the net magnetization signal (directly proportional to the proton density ρ), $E_{1,2} = \exp(-TR_{1,2}/T_1)$ and the subscripts 1 and 2 represent the respective repetition times. n appears to be the main parameter for contrasting AFI images, and the choice of *n* close to 5 provides sufficient sensitivity to FA variations ($S_{AFI,2}/S_{AFI,1}$ = 15–65%). Examples of the variation of the main AFI parameters are reported in Figure 1.21.



Figure 1.20: The pulse sequence diagram for AFI, a dual-TR 3D spoiled gradient sequence, is reported. This starts by playing the RF pulse and the phase encoding in the slice direction, after which phase encoding and read encoding take place. Eventually, the signal is acquired while the readout gradient is played. The sequence ends by refocusing the phase in both phase encoding directions. Gradient spoiling is performed at the end of the TR by playing a gradient in the readout direction, while RF spoiling takes place by cycling the RF phase.

AFI has been used as a fast and low SAR [80] B_1 mapping module for RF inhomogeneity correction in T_1 maps when $TR \ll T_1$ applies. With this assumption, $E_{1,2}$ can be approximated by 1, so that

$$r = \frac{S_{AFI2}}{S_{AFI1}} = \frac{1 - E_1 + (1 - E_2)E_1 \cos \alpha}{1 - E_2 + (1 - E_2)E_1 \cos \alpha} \approx \frac{1 + n \cos \alpha}{n + \cos \alpha}$$
(1.54)

and, thus, the values for B_1 can be computed as

$$\alpha \approx \arccos\left(\frac{rn-1}{n-r}\right)$$
 . (1.55)



Figure 1.21: Effects of parameter selection on the contrast of S_{AFI1} and S_{AFI2} images in terms of the signal ratio r as a function of the FA for the AFI sequence. a: Effect of T_1 ($TR_1/TR_2 = 20/100$ ms, meaning n = 5). b: Effect of TR_1 ($T_1 = 500$ ms, n = 5). c: Effect of n ($T_1 = 500$ ms, $TR_1 = 20$ ms). Image obtained with permission from Yarnykh 2007 [83].

When sequence and RF properties such as RF bandwidth, echo time, and spoiling pattern guarantee a perfectly spoiled signal, AFI and SPGR can be assumed to have a consistent net magnetization signal S_0 . As such, SPGR images are convenient for parameter fitting in combination with AFI images.

From AFI to VAFI: Acquiring multiple SPGR volumes and assuming the linearity of the errors in the B₁ transmit field for different flip angles, Hurley described the VAFI method for the joint estimation of B_1 , T_1 and T_2^* -reduced net magnetization M_0^* by a least-square fit of one AFI and an arbitrary number of SPGR acquisitions [82]. The dependency over the effective transverse relaxation T_2^* - minimized by using very short echo times - and additional factors such as coil sensitivity and receiver gain were encompassed and jointly estimated in the M₀^{*} term. The simultaneous voxel-wise fitting of the unknown parameters requires a minimum of 3 values, provided by S_{AFI1} , S_{AFI2} and SPGR signal(s), and allows overcoming the intrinsic T_1/TR dependency of the original AFI method for B_1 estimation. In particular, B_1 is estimated through the computation of a map of κ values, where κ represents the proportionality constant between the voxelwise actual and nominal flip angle, whose linearity has been demonstrated in a wide range of flip angles, with higher uncertainties for low values [87, 88]. In a second stage, the flip angle map is smoothed to better model the behavior of the real B₁ field, and a second fitting is performed for T_1 and M_0^* estimation only. At both stages, the figure of merit for parameter fitting established in the literature and then commonly used for the method is the residual sum of squares of AFI signals and M > 1 SPGR signals:

$$[\mathsf{T}_{1},\rho,\kappa] = \underset{\mathsf{T}_{1},\rho,\kappa}{\arg\min} \Big(\sum_{i=1}^{2} \Big(S_{AFIi} - \hat{S}_{AFIi} \Big)^{2} + \sum_{i=1}^{M} \Big(S_{SPGR,i} - \hat{S}_{SPGR,i} \Big)^{2} \Big) \quad (1.56)$$

1.7.2 Ultrafast T₁ mapping

The need for fast diagnostic imaging techniques has promoted the development of T_1 mapping techniques with shorter and shorter acquisition times. The investigation of ultrafast T_1 mapping has mainly relied on a few approaches including the use of parallel imaging, the development of new k-space sampling strategies, as well as the design of new sequences.

1.7.2.1 Parallel imaging

SENSE reconstructions have been applied for silent rotating ultrafast imaging sequence (RUFIS), combining an effective echo time of zero (ZTE) with short TRs, for a total acquisition time of 4 minutes [89]. Examples of applications of GRAPPA for ultrafast T_1 mapping is a LL method combined with a stack-of-spirals accelerated acquisition for abdominal imaging using a 3D spiral GRAPPA reconstruction [90].

1.7.2.2 New sequences and acquisition strategies - Cartesian

The main area of interest for quantitative ultrafast T_1 mapping has been lung imaging, as the ability to image multiple slices during a breath-hold can lead to robustness against motion and pulsation artifacts. For example, ultrafast T_1 mapping has been studied for ventilation and diffusion: an implementation of the inversion recovery ultra-fast steadystate free precession (IR-ufSSFP) technique [91] was used for oxygen-enhanced proton MRI of the lungs, as balanced steady-state free precession sequences offer the highest SNR per unit of time amongst all MRI techniques [92]. Most of the oxygen-enhanced MRI relaxometric techniques are based on either cardiac-triggered IR-FLASH [93] or an IR half-Fourier fast spin echo (HASTE) [92] method.

However, ultrafast T₁ mapping techniques remain of interest for any anatomical regions to provide faster mapping and higher patient throughput. For example, TAPIR (T₁ mapping with Partial Inversion Recovery) represents another technique based on a magnetization-prepared LL method and a segmented k-space data collection scheme [94]. Full brain coverage is reached within 8 minutes for a 256x256 matrix size and 25 slices. The method uses an optimized interleaved scheme of slices and time points, and its accuracy in phantom measurements is <3% for slow-relaxing compartments (T₁ > 2000 ms) and around 1% for faster-relaxing species (T₁ < 1200 ms). The method has also been improved with a spiral readout, which reduces the mean fitting error from -2.5% to -0.1% over a wide range of T₁s, as well as with the application of compress sensing making imaging up to 3.3 times faster [95].

Another approach based on VFA with a single 3D SPGR data set per each time point was implemented for the dynamic T_1 computation with the acquisition of an AFI B_1 map for accuracy with a total scan time of 6:08 minutes and a 128x128x48 matrix size [96].

Stemming from the MP2RAGE sequence, a few other ones such as ME - MP2RAGE were developed to extend the capabilities of MP2RAGE [97] by acquiring multiple gradient echo echoes at two inversion time points, which demonstrated robustness against inhomogeneities in both the static magnetic field B₀ and transmit field B₁. Full brain coverage was achieved in around 19 minutes for a 320×280×224 matrix, and enabled the extraction of maps about T₁, T^{*}₂, and magnetic susceptibility χ . Nevertheless, this approach tends to underestimate T₁ values. To overcome this limitation, the MPnRAGE sequence was introduced combining a high number of inversion time points [81] and allowing full brain coverage in 7.5 minutes. ME-MPnRAGE and QRAGE further build upon this by incorporating the acquisition of multiple inversion and echo times, and allowing matrix size of 256×256×160 and full brain coverage in 7:15 minutes [98].

Other techniques for ultrafast T_1 mapping have focused on the optimization of gradient echo based, MR fingerprinting and VFA-based methods to include the corrections for slice effects and B_1 inhomogeneties [61, 99, 100, 101].

FSE-based, such as zoomed U-FLARE [102], are also used, and exploit the fact that the signal follows a T_2 rather than a T_2^* decay, allowing for a longer imaging readout time and a higher SNR (smaller reduced spectral width).

1.7.2.3 New sequences and acquisition strategies - EPI-based

Although EPI is an established and common sampling pattern found transversely in all the scanners commonly as part of the readout portion of diffusion or fMRI sequences, EPI-based T₁ methods still represent a niche topic due to the main drawbacks associated with this k-space traveling approach. Sequences based on EPI readout have been developed in the last two decades, including EPI LL techniques, first studied for neuronal tract tracing after stereotaxic Mn²⁺ injection into the olfactory bulb of rats [103, 104]. An IR sequence with zonally oblique-magnified multislice (ZOOM) EPI readout [105] was developed for a time-efficient single-shot T₁ mapping of the spinal cord [106]. Multishot multi-slice inversion-recovery EPI (MS-IR-EPI) is another example of EPI-based sequences with fast whole brain coverage (matrix size 192x192x192, acquisition time 3:45 minutes) [107].

1.7.2.4 New sequences and acquisition strategies - Non Cartesian

Non cartesian k-space readout scanning trajectories, including 2D and 3D radial and spiral, both 2D multislice (stack-of-stars) and 3D versions have been employed for relaxometry. For example, a radial acquisition technique with improved SNR has been introduced for simultaneous T_1 and T_2^* mapping in the lungs with an inversion recovery sequence with half-sinc pulses, ultra-short echo times (UTE) and a Look-Locker multiecho scheme [108]. Another example of T_1 mapping techniques with radial sampling is the Triggered RAdial Single-Shot Inversion recovery sequence (TRASSI) [109], a sequence that uses a slice-selective inversion pulse followed by radial imaging blocks. Magnetization-Prepared Golden-angle RAdial Sparse Parallel (MP-GRASP) has also been used as a T₁ mapping sequence with stack-of-stars trajectory for free-breathing acquisitions and high resolution scans (matrix size 320x320x32 and acquisition time 2:49 minutes) [110]. Spiral sampling has been implemented with LL [111], in which a variabledensity spiral read-out trajectory was used to sample 400 SPGR echoes for each slice, resulting in an acquisition of 3:30 minutes for full brain coverage. Another spiral readout has been applied to Inversion Recovery sequences for cardiac manganese-enhanced MRI (MEMRI) in mice, with a total scan time of 10-12 minutes [112]. Similarly, an IR-FLASH with highly undersampled radial data [113] was developed and its fast and parallel online calculation enables its use in clinically feasible times, with a possible clinical value in a large spectrum of diseases [114].

1.7.2.5 T₁ mapping - brain applications and limitations

The determination of the factors affecting the longitudinal relaxation time in brain tissues has been investigated thoroughly: T_1 in brain tissues has been modeled by assuming a fast exchange, two-pool model, with rapid exchange between "free" water molecules and "bound" water molecules restricted by proximity to macromolecules [115]. This model was then supported by empirical evidence showing a linear relationship between the relaxation rate $(1/T_1)$ and the inverse of the water content [116]. Since then, many studies have shown a relationship between brain T_1 and tissue water content [117]. Nevertheless, the mentioned linear relationship is not necessarily reliable in the presence of iron, contrast agents, or in complex pathology like tumors which may exhibit changes in biochemical composition.

Relaxation times have been demonstrated to be affected by magnetic field strength, age, temperature, macromolecular composition - including myelin, and iron content - as well as fiber orientation [118, 119]. T_1 times in the brain range from around 650 ms

to 1200 ms at 1.5 T, from 800 ms to 1300 ms at 3 T, and from 1200 ms to 2200 ms at 7 T for example, with the lowest values of the interval representing white matter values and the highest ones representing gray matter values [120].

Inter-site T_1 mapping studies of healthy brain tissues are in approximate agreement, although T_1 times may depend upon the measurement technique, and reproducibility studies of VFA, IR, and MP2RAGE T_1 measurements at 3 T have reported coefficients of variation of less than 5% in brain tissues [73, 121, 122]. The assessment of cortical myelin is a growing research trend, and T_1 contrast is currently the best MR technique for mapping it. Cortical myelin has recently been studied using T_1 -weighted images, T_1 mapping, and the ratio between T_1 -weighted to T_2 weighted images [123], but the T_1 myelin relationship does not hold for white matter as neither T_1 nor T_2 weighted images correlate with myelin water fraction from T_2 measurements and histological validation.

A few examples of the clinical application of T_1 relaxometry include the study of the following:

• Development and aging

T₁-weighted imaging is often used to assess brain maturation in infants [124], but there is also substantial research on changes in T₁ values in normal brain during life. The development of white matter tracts in young children and the breakdown of brain cells during senescence can be correlated to the dynamics of the histogram of T₁ values, as shown in Figure 1.24: at 1.5 T, whole brain T₁ histograms before the age of 1 year contain a single peak ~1200-1500 ms. A transition from a monomodal to a bimodal histogram begins by age of 2 years when a peak representing white matter starts to grow at around 750 ms, while between 2 and 50 years the histogram then returns to distribution with a single peak at ~700 ms [125]. This can also be seen with T₁ values in white matter tracts decreasing until 40-50 years and then increasing with age [126], changes that were attributed to a decrease in water content and increase in iron, although no consensus on this has yet been reached [127].



Figure 1.22: Whole brain T_1 values histograms at 1.5 T during development and aging showing white matter and gray matter peaks. Image obtained with permission from Saito et al. 2009 [125]

Multiple sclerosis

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system and has been the largest clinical application of T₁ and T₂ relaxometry. Scientific literature reports increased T₁ values in enhancing and black hole lesions [128, 129], but studies also focused on the investigation of normal appearing white matter (NAWM) and normal appearing gray matter (NAGM) in patients with primary progressive MS (PPMS), relapsing remitting MS (RRMS), and secondary progressive MS (SPMS), finding association with increasing T_1 values for both white matter and gray matter, which was also associated with MS phenotypes: T₁ in PPMS was higher than the healthy control white matter, but lower than in NAWM for RRMS, which in turn is lower than NAWM for SPMS, and similar changes were found in NAGM [130, 131, 132], where the differences in T_1 could be related to pronounced differences in tissue degeneration and reparative processes such as remyelination and gliosis, as well as in differences in iron deposition in the cortex [133]. In PPMS, it was also found that increased NAWM T₁ values at baseline predicted the MS functional composite score, a disability measure, 2 years later [134]. Increased T₁ in NAWM is most likely due to increases in water content, presumably from inflammation or edema, while increased T₁ inhomogeneity was also associated with longer disease duration [135]. Recent studies have also shown how apparently non-enhancing lesions (demyelinating plaques showing no visible post-contrast enhancement) exhibiting differences in T₁ values that deviate from control patients and may indicate persistent, subtle, blood-brain barrier disruption [136]. Also, MS pathology is not homogenously distributed, and a recent study has shown that structures adjacent to CSF (periventricular areas) are more severely affected and gradients correlate with clinical disability, which is detectable via T₁ and is present at clinical disease onset [137]. T₁ mapping has been found sensitive to disability-relevant microstructural changes over 1 year following RRMS diagnosis, as the number of thresholded white matter lesions increased significantly – indicating increasing microstructural damage – which are significantly associated with clinical disability [138]. All these findings and the information provided by qMRI – also reported in Figure 1.23 – are promoting quantitative MRI techniques, including T₁ mapping, as a clinical application and clinical decision support tool [139].



Figure 1.23: Information provided by quantitative MRI about key features of multiple sclerosis pathology for clinical applications in patients with multiple sclerosis. Image obtained with permission from Granziera et al. 2021 [139].

• Parkinson's disease

Parkinson's disease (PD) is a long-term degenerative disorder of the central ner-

vous system mainly affecting the motor system, associated with an age-dependent cortical thinning [140]. Deep grey matter regions such as the substantia nigra are early affected by PD and show shorter T_1s [141] – likely reflecting gray matter loss found contralateral to the most affected body side – while cortex T_1 was found to be 3 times shorter in PD subjects than controls in an interval of 6.5 years for a cohort of patients with an average age of 63 years [142]. This makes T_1 a potential biomarker for the differentiation of PD more powerful than the evaluation of cortical thinning.

• Brain cancer and radiation

The interpretation of T_1 maps can allow the detection of tumor enhancement earlier than conventional contrast-enhanced T_1 -weighted images [143], and it has been used for tumor subtype differentiation, such as for the identification of differences between peritumoral regions of low-grade gliomas versus glioblastomas [144]. Another potential application of T_1 mapping is the differentiation between tumor recurrence and radiation necrosis in gamma knife radiosurgery [145], and the use of T_1 maps for the quantification of tumor permeability following contrast injection.

• Other applications

Other T₁ brain mapping applications have been reported in clinical research.

- Sickle cell disease demonstrated an abnormal trajectory of brain maturation from birth to 4 years, which has been associated with high gray and white matter T₁ values in infant patients and low values by year 4 [146];
- Manganese toxicity has been studied and associated with shorter T₁ values in the globus pallidus, substantia nigra, caudate nucleus, and the anterior prefrontal lobe [147];
- Repeated gadobutrol exposure has been associated with reduced globus pallidus T₁ [148];
- Patients with psychiatric diseases including schizophrenia, and psychosis have shown elevated brain T₁s [149, 150], while women with anorexia nervosa show reduced T₁ in white and gray matter [151];
- Mild traumatic brain injury, HIV, and dementia have been associated with elevated brain T₁ values [152, 153, 154].

1.7.3 T_2 and T_2^* mapping

The transverse relaxation time provides a measure that is sensitive to changes in the biochemical environment and microanatomical composition such as myelination [155], iron content [156], and water content in edema and inflammation processes [157], and can also be used for the study of articular cartilage composition often altered in pathological tissues [158]. Although variations in T_2 are not specific for a single disease, they reflect changes in tissue composition and can be used to gather valuable information about disease processes.

1.7.3.1 T₂ mapping: spin echo sequences

The gold standard and most straightforward method for T₂ mapping is to acquire at least two spin echo signals at two different echo times (TE) generated from the excitation of the magnetization at thermal equilibrium (achieved when TR \gg 5T₁). The resulting decay of transverse magnetization M_{\perp} can be expressed from the transverse component of the Bloch equations

$$M_{\perp}(\text{TE}) = M_{\perp}(0^+) \exp(-\text{TE}/\text{T}_2)$$
 (1.57)

where $M_{\perp}(0^+)$ is the transverse magnetization immediately after each 90° excitation pulse. T₂ and the magnetization vector amplitude (proportional to the proton density) can then be estimated by fitting the signal to a monoexponential decay.

For faster sequences and clinical feasibility, shorter TRs (TR<5T₁) are normally employed, which leads to M_{\perp} to be a function of both TE and TR as determined via Bloch equations:

$$M_{\perp}(\text{TE}, \text{TR}) = M_0\{1 - 2\exp[-(\text{TR} - \text{TE}/2)/\text{T}_1] + \exp(-\text{TR}/\text{T}_1)\}\exp(-\text{TE}/\text{T}_2) \quad . \tag{1.58}$$

This variability can be overcome by either assuming TR \gg TE for which Eq. 1.58 which can be approximated as

$$M_{\perp}(\mathrm{TE},\mathrm{TR}) \approx \mathrm{M}_{\mathrm{0}}[1 - \exp(-\mathrm{TR}/\mathrm{T}_{\mathrm{1}})]\exp(-\mathrm{TE}/\mathrm{T}_{\mathrm{2}}) \tag{1.59}$$

or by assuming that the longitudinal magnetization is negligible at TE, which leads to

$$M_{\perp}(\mathsf{TE},\mathsf{TR}) \approx \mathsf{M}_{0}[1 - \exp(-TD/\mathsf{T}_{1})]\exp(-\mathsf{TE}/\mathsf{T}_{2}) \tag{1.60}$$

where TD is the delay time TD = TR - TE, which is of particular interest for short-TR spin echo sequences. The optimal delay time can be determined by first assuming that the total rate of acquisitions (number of acquisitions per unit-time) is inversely proportional to TD. Under this assumption, the SNR per unit acquisition time (SNR efficiency) is optimized for a specific T₁ when $TD \approx 1.26$ T₁, or for the worst SNR efficiency in the case of a large range of T₁s [117]. Methods for the optimization of T₂ estimates have been proposed by setting a lower limit on the variance of the estimated parameters by Cramer-Rao Lower Bound (CRLNB) theory, but the general recommendation is to acquire images over a large range of logarithmically spaces TEs [159]. Confounding factors affecting single SE acquisitions and T₂ mapping accuracy include water diffusion through susceptibility-induced magnetic field gradients and chemical exchange between frequency-shifted environments or tissue compartments, which result in an apparent T₂ decrease.

Multiecho spin echo sequences are currently used for T_2 mapping, and generally involve the application of a series of refocusing 180° pulses played at odd integers of a given delay, with the signal acquisition taking place at even integers of the same delay, which generates a series of exponentially decaying spin echoes. The Carr-Purcell-Meiboom Gill (CPMG) sequence [160, 161] is often employed in spectroscopy because the relative phase of the excitation and refocusing pulses minimizes the bias due to B_0 and B_1 imperfections. As signal contributions from stimulated echoes (non-SE pathways) can contaminate the signal decay and bias T_2 , the use of decay models including all the pathways or non-CPMG approaches can be used [162, 163]. In multiecho spin echo sequences, TR can be shortened to increase SNR efficiency, and multiple lines of k-space can be acquired around each echo via a gradient and spin echo (GRASE) acquisition, which have allowed whole-brain T_2 mapping in 15 minutes [164]. Also, the use of the shortest and constant echo spacing can reduce diffusion and chemical exchange effects, that is of interest in multiecho SE sequences with a high number of echoes for multiexponential and multi-compartmental T_2 mapping.

1.7.3.2 T^{*}₂ mapping: single and multiecho SPGR sequences

Both single and multiecho SPGR sequences can be used to quantify T_2^* . Multiecho SPGR sequences are generally preferred for multicompartmental T_2^* estimations applications where a wide range of T_2^* values is expected. Important confounding factors in the determination of T_2^* are susceptibility effects: these generate macroscopic magnetic field gradients which cause an additional signal loss that is a function of the magnitude of the gradients relative to the voxel dimensions, normally typically larger in the slice thickness

axis. For an accurate T_2^* estimation, susceptibility-induced field effects must either be corrected either prospectively or accounted for retrospectively.

- Prospective correction: shimming should always be the first method used to minimize susceptibility-induced field gradients. Nevertheless, complete removal of these magnetic field gradients is not possible in many cases due to their nonlinear nature, especially at high magnetic field. As such, additional techniques are often required, including the use of:
 - excitation pulses with inverted phase profile with respect to the gradients, which can only be tailored for a single TE and gradient amplitude, making it difficult to implement in the presence of spatially varying susceptibilityinduced field gradients.
 - modulated slice refocusing gradient amplitudes ('z-shimming'), which requires a series of images with different slice refocusing amplitudes [165].
 - 3D sequences (alternatively) typically have much smaller through-plane dimensions than 2D sequences, which can minimize the susceptibility induced signal loss.
- Retrospective correction: this can be performed via
 - The estimation of the main magnetic field offset, which can be determined from two gradient echo phase images acquired at different TEs [166]. The gradients of the magnetic field offset are numerically estimated and then used to estimate the phase accrual at TE as well as the corresponding fractional signal loss [167].
 - The fractional signal loss from susceptibility-induced field gradients as additional free parameter in the signal model, which may require additional model constraints [168].

1.7.3.3 Approaches for estimating T_2 and T_2^*

Assuming perfect refocusing and perfect spoiling conditions, the observed signal S at different echo times TE_i values – for a voxel that can be described by a single T_2 (or T_2^*) component – can be expressed as

$$S_i = S_0 \exp(-\mathsf{TE}_i/\mathsf{T}_2^{(*)}) + \nu_i$$
 (1.61)

where S_0 is the apparent relative proton density and ν is additive noise. Both $T_2^{(*)}$ and S_0 can be estimated by fitting observations at multiple TEs via nonlinear least-squares fit or via a linear least-square method after model linearization through log-transformation. While nonlinear approaches are recommended because they yield maximum likelihood parameter estimates in the presence of Gaussian noise (since this is no longer additive following log-transformation), linear methods eliminate the need to provide initial parameter guesses reducing complexity, but on the other hand may produce biased parameter estimates. Indeed, at longer TEs and for datasets acquired with low SNR – for which the distribution of magnitude data is better approximated by a Rician distribution rather than a Gaussian distribution – $T_2^{(*)}$ estimates are biased towards longer values. This can be avoided by truncation of the signal decay at long TEs (low SNRs). Alternatively, maximum likelihood estimates can be used [169], or an additional baseline offset term can be added empirically to the model.

When the assumption of perfect refocusing and spoiling is not guaranteed, the signal in multiecho sequences can show oscillations between odd and even echoes and thus deviate from the simple exponential decay model. Also, fitting signals from multiecho sequences using a bipolar readout have been shown to provide higher precision than the use of monopolar readout [170]. A-posteriori correction methods can be applied by selecting echoes to be discarded increasing sensitivity to T₁ and B₁, or using models that either include B₁ as a free parameter or estimate it using field mapping approaches.

If different intrinsic $T_2^{(*)}$ values may arise from multiple components within each tissue compartment (e.g., intra/extracellular water) and slow inter-compartmental exchange, the signal model can include N decaying exponentials (assuming perfect spoiling and refocusing):

$$S_i = \sum_{j=1}^{N} S_{0,j} \exp(-\mathsf{TE}_i/\mathsf{T}_{2,j}^{(*)}) + \nu_i \quad . \tag{1.62}$$

Such multi-exponential models come with two major disadvantages: the number of tissue components N is not known a priori, and the estimation of the parameters can result in ill-conditioned matrices and thus variable estimates based on the initial guesses. An alternative approach is to rewrite the summation as a linear system of decaying exponentials A and apparent proton densities ($T_2^{(*)}$ spectrums) d as in

$$s = Ad + \nu \tag{1.63}$$

where s is a vector of observed signal intensities and ν is a corresponding vector of additive noise and inversion methods are generally applied for images with high SNR.

Conventional linear least-squares methods could be used to invert this system but nonnegative least square (NNLS) algorithm and regularization methods that reduce sensitivity to noise are commonly used being A rank-deficient [171]. Also, NNLS algorithms do not require a priori knowledge about N.

Specifically for T_2^* measurement, concomitant influences of T_2 relaxation and magnetic susceptibility (orientation-dependent frequency shifts) [172] can make the analysis complex. Also, B_0 inhomogeneities impact the quantification of T_2^* , but these can be corrected a posteriori via postprocessing [173] or a priori by z-shimming [174]. Myelin water maps can also be reconstructed starting from T_2^* fitting [175, 176] using models with 2 or 3 exponential components at 3 and 7 T, respectively, optionally including susceptibility-driven frequency shifts [177]. Robust myelin water mapping is also possible by fitting the three pool model to complex data [178], although T_2^* myelin water fraction values are slightly larger than those from T_2 measurements, possibly due to exchange effects [179].

1.7.3.4 T₂ and T^{*}₂ - brain applications and limitations

Values for T_2 in the white matter of human brains need to be estimated by multiexponential fit. Histological validation in both healthy animal models and human tissues supports the identification of two components: a short component – assigned to 'myelin water', i.e. water trapped within the myelin bilayers – and a long component – assigned to water in the intra/extra-cellular spaces [180, 181]. The same is not true in pathological brain tissues, as there can be more than two T_2 peaks in the T_2 white matter distribution [182]. Because of the multicomponent nature of T_2 in the brain and B_1 inhomogeneities, the acquisition of images at more than two echo times is necessary.

In vivo brain T_2 mapping is mainly performed via 3D multiple SE as well as multiple SE and GE sequences, but 2D multislice approaches have also been proposed [183, 184], with TE ranging from the minimum possible TE to a few hundreds of milliseconds. In particular, a number of different approaches for brain T_2 analysis exist [185, 186, 187]. NNLS provides a T_2 distribution and normally, the myelin water fraction (MWF) and the geometric mean T_2 time (mean T_2 on a log scale 40-200 ms for clinical systems) of the intra/extracellular water T_2 peak are computed from that, which has led to the concept of myelin water imaging and myelin water fraction (MWF) mapping [188].



Figure 1.24: T_2 distribution in healthy human white matter at 1.5 T and classification into two pools as the principle of myelin water fraction mapping. Image obtained with permission from MacKay et al. 2016 [189]

Edema, inflammations, axonal swelling, and increased water content can lead to a decrease of MWF. For example, MS patients report a 16% reduction in MWF in NAWM due to global edema or cellular infiltrates. Confounding factors in MWF include the impossibility to separate debris from intact myelin [190], as well as the effects of magnetization exchange, which causes a movement of water between the two compartments and leads to an underestimation of MWF [191].

Clinical applications of T_2 and T_2^* mapping include multiple sclerosis, Alzheimer's disease, epilepsy, as well as the study of development, aging, and cancer, with T_2^* being used as an iron marker:

• Multiple sclerosis (MS)

T₂ is typically increased in MS lesions, and MWF is decreased on average by 50% [192, 193]. MWF is able to differentiate black holes and separate lesions based on their temporal evolution, as well as to separate contrast enhancing lesions and T₂ lesion subtypes [194]: in particular, it was found that MWF can delineate lesions less than a year old from older lesions [122]. MWF has been used to differentiate T₂ lesions from NAWM with a higher sensitivity when compared to other MR quantitative parameters including magnetization transfer ratio and diffusion parameters [193]. Diffusely abnormal white matter and NAWM also show widespread reductions in MWF, while GM and water content are globally increased [157, 183, 195, 192]. A correlation between basal ganglia T^{*}₂ with age and disease duration was also found, which suggests an association between MS morbidity and iron accumulation [196]. As lesions develop and resolve over months,

new lesions show decreased and subsequent increases in MWF [195, 197, 198]. Also, T_2 -based myelin mapping techniques such as MWF could be used to assess treatments designed to promote remyelination [199].

• Alzheimer's disease (AD)

Healthy controls, mild cognitive impairment and AD patients can be separated based on brain T_2 and MWF values, with the healthy controls being associated to higher MWF than AD and vascular dementia patients [200].

• Development and aging

The dependency of brain T₂ values on age can be fit to a single or double exponential, with a very rapid decrease occurring over the first year of life and a slower rate in adolescence and adulthood [201]. On the other hand, MWF varies following a quadratic behavior throughout life [202], thus making age a confounding factor for studies. Also, while prenatal stress has been associated with lower corpus callosum MWF in adulthood, Cesarean delivery is thought to influence infant MWF brain development [203]. Genetic variations in the gene PLP1 – encoding for the main myelin protein (proteolipid protein 1), and thought to affect WM myelination – have been associated to significant asymmetries in MWF [204].

Cancer

Several studies have characterized brain tumors using T_2 , such as meningiomas, which report shorter T_2 values than astrocytomas [205] and gliomas [206]. Glioblastomas show a single or two T_2 components depending on their histology (solid tissue, or a mix of solid and necrotic tissue) [207]. Glioblastoma, oligodendroglioma and meningioma tumors have different T_2 distribution profiles [208]. T_2 has also been used in the study of neurofibromatosis 1, where T_2 intra/extracellular water value is increased while MWF does not show any significant difference [209].

• Other applications:

Other clinical applications of T_2 , T_2^* mapping and MWF include:

- Neuromyelitis optica, which can be differentiated from multiple sclerosis by MWF and show diffusely elevated T₂ in patients with an old onset of the disease (20+ years) [197, 210].
- Progressive solitary sclerosis (proposed as a possible MS variant), where MWF demonstrates diffuse myelin reductions through NAWM [211].

- Amyotrophic lateral sclerosis (ALS), where T₂ is elevated in both brain and muscle tissues and this can be used to differentiate it from primary lateral sclerosis [212].
- Concussion and traumatic brain injury, where reduced MWF may be a sign of a transient myelin disruption [213].
- Schizophrenia, where increased T₂ and reduced MWF provide evidence of white matter abnormalities. Also, unlike healthy controls, people with schizophrenia show no relationship between white matter MWF and age or years of education [214, 215].
- Ischemic stroke, where T₂ is higher and WM MWF is reduced [216].
- Intracranial hemorrhage, where T^{*}₂ changes were indicative of iron overload in rodents' brains [217];
- Parkinson's disease, where MWF was linked to clinical subtypes as well as disease severity, daily levodopa equivalent dose, and disease duration [218, 219].
- Autism, where T₂ was found to be longer in both WM and GM, and MWF show differences compared to controls [220].
- Phenylketonuria, where MWF is generally decreased and T₂ is elevated and where an additional long T₂ component – possibly attributed to vacuoles in myelin – has been investigated [221].
- β-thalassemia major, where T^{*}₂ measurements were used for the evaluation of brain iron overload [222];

1.7.4 Simultaneous multiparametric mapping

While relaxation parameters are sensitive, they are not necessarily specific to a given feature and wide ranges of values are often reported for a tissue. This complicates the relation between a relaxometry parameter and pathophysiological processes, limiting the clinical impact of qMRI. For example, multiple sclerosis white matter lesions are characterized by several phenomena occurring simultaneously and affecting the transverse relaxation time, including inflammation, edema, demyelination, remyelination processes, and iron accumulation [223]. A few different approaches including the application of multicompartment and multiparametric models have been proposed to address the lack of specificity of qMRI: while multicompartment models are used to describe the effects that several components have on the acquired signal, multiparametric models are based on the extraction of rich information from multiple parameters. In particular, multiparametric acquisition methods in MRI can be based on the processing of parameters coming from different acquisitions (sequential multiparametric mapping) or from a single acquisition able to provide multiple parameter maps (simultaneous multiparametric mapping). The latter approach removes coregistration needs and represents a hot research topic, as there is a clinical interest in reducing scan times while obtaining a spectrum of parameters. Also, simultaneous multiparametric imaging and mapping can rely on complex signal models, although many of the published methods assume single-component signals. When the heterogeneous biochemical and microstructural environment of voxels is of interest, multicompartment models might be more desirable instead.

1.7.4.1 Simultaneous T₁ and T₂ mapping

Among multiparametric techniques, simultaneous mapping of T_1 and T_2 has been one of the most studied application.

The SIMPLE sequence was developed for T_1 and T_2 mapping of carotid plaque in 8 minutes [224], and uses an interleaved 3D golden angle radial trajectory [225] with variable T_2 preparation modules and inversion recovery pulses.

Another technique uses a multishot spin-echo EPI (ms-SDEPI-T12) with varying repetition times and echo times for dynamic contrast enhanced MRI, where T_1 was used to estimate contrast agent concentration [226].

A myocardial T_1 and T_2 mapping method using a radial FLASH sequence with inversion recovery and T_2 preparation modules was developed and proved to generate accurate T_1 maps [227]. A similar ECG-triggered, 2D single-shot bSSFP sequence acquired

across 10 cardiac cycles named Multimapping was studied for cardiovascular disease as well [228]. Another cardiac T_1 and T_2 3-parameter model was also developed for mSASHA (multiparametric SAturation-recovery single-SHot Acquisition), which uses 9 saturation recovery images in 11 heartbeats, for a total acquisition of 8 minutes for a 256x144 matrix size and 8 mm slice thickness [229].

Other approaches include MR Multitasking, a technique that captures and resolves motion, relaxation and other dynamical phenomena conceptualizing them as different time dimensions and solving this 'tasks' using a low-rank tensor imaging method [230]. For example, a MR Multitasking framework was developed to provide co-registered, distortion-free images and maps in a single 9.3 minutes scan for 100 mm brain coverage by concatenating a series of T_2 preparation modules and 3D segmented FLASH acquisitions [231].

An alternate approach uses multicomponent-driven equilibrium single pulse observation of T_1/T_2 (mcDESPOT) [232] which estimates T_1 and T_2 times of the tissue components in brain via stochastic regional contraction method [233]. This approach can provide volume fraction of myelin (VFM) values in brain [234] fast and with high spatial resolution.

1.7.4.2 Simultaneous T₁ and T^{*}₂ mapping

The investigation of both T_1 and T_2^* relaxation times can provide insights into brain composition, specifically about iron content and myelin [235], as well as the assessment of tumor oxygenation and the differentiation between the blood oxygen level dependent (BOLD) and the tissue oxygen level dependent (TOLD) effect [236]. When monitoring dynamic relaxation time changes during contrast agent bolus injection and respiratory challenges, only T_1 changes with respect to a baseline status are of interest. However, a spoiled multi-gradient echo sequence can be easily integrated to provide simultaneous T_2^* quantification. In this case, the ideal signal of a spoiled gradient echo sequence at time *t* is given by

$$S(t, TE) = M_0 \cdot \sin \alpha \frac{1 - E_1(t)}{1 - E_1(t) \cos \alpha} \exp(-TE/T_2^*(t))$$
(1.64)

with $E_1(t) = \exp(-\text{TR}/\text{T}_1(t))$ and being both T_1 and T_2^* time-dependent. $\text{T}_2^*(t)$ can be computed via exponential fit of the multiecho data and, if relative changes are of interest, ΔT_2^* can be determined from S(t)/S(0), avoiding the impact of large-scale field gradients [236]. ΔT_1 can be computed using $S(\text{TE}_{min})$ or via a weighted average over all measured echo times. The combination of a LL sequence with a multigradient echo acquisition (multiecho LL) is a straightforward approach for this multiparametric mapping, and QRAPTEST [237] and MP2RAGE [97] represent two examples. The QRAPTEST technique is a 3D saturation-recovery turbo-field echo with an intrinsic B₁ field correction, and can be used for whole brain 1.5 mm³ isotropic mapping in less than 8 minutes. On the other hand, MP2RAGE is based on a LL sequence and a gradient echo readout after adiabatic inversion, and is relatively insensitive to B₁ variations [97].

Recently, a new sequence exploiting parallel imaging for the acquisition of a multiecho multi-flip angle gradient echo dataset has been proposed. Joint MAPLE (MRaccelerated parameter mapping with cyclic loss and unsupervised scan-specific networks) makes use of zero-shot self-supervised learning with a physics-guided scan-specific self-supervised network for improved joint parameter estimation [238].

1.7.4.3 Simultaneous T₂ and T^{*}₂ mapping

Simultaneous measurement of T_2 and T_2^* can be performed via combined spin and gradient echo (SAGE) methods [239], which are of particular interest in susceptibility contrast MRI where hemodynamic status and tissue perfusion are characterized by dynamic measurements. The SAGE sequence includes the acquisition of a series of echoes with EPI: a 90 degrees pulse is followed by 2 GE-EPI acquisitions, then a 180 degrees refocusing pulse is used to acquire two asymmetric SE and a symmetrical SE. A similar approach used for non-dynamic studies is the GESFIDE method (gradient echo sampling of the free induction decay and echo) [240].

1.7.4.4 Simultaneous T₁, T₂ and T₂^{*} mapping

Only a handful of sequences with the capability to map all the main relaxometry parameters have been proposed. SIMPLE^{*} is an interleaved single-echo and multiecho method originally developed to distinguish carotid atherosclerotic plaque components [241]. This uses three modules with different T₂ inversion recovery preparation modules with adiabatic pulses and acquisition schemes with 3D golden angle radial acquisitions. This sequence is able to provide accurate maps with 0.8 mm isotropic resolution over a field of view of 100x100x100 mm³ in 10 minutes.

3D Echo Planar Time-resolved Imaging (3D-EPTI) is another technique that acquires highly-accelerated k-t data using continuous highly time efficient readouts with minimal dead time [242]. This is able to provide 1 mm isotropic maps for T_1 , T_2 and T_2^* in 3 minutes, exploiting VFA-GRASE and acceleration via CAIPI pattern (Controlled Aliasing

in Parallel Imaging) that uses the coil sensitivity information.

Other techniques for simultaneous mapping of T_1 , T_2 and T_2^* are based on MR fingerprinting and MR multitasking. These include a nine-echo MRF sequence used for the study of non-alcoholic fatty liver disease that relies on the reconstruction of a transient signal then used for MRF dictionary matching [243]. Another technique is used for cardiovascular MR and uses hybrid T_2 -IR modules with five different preparation durations followed by FLASH excitations to acquire training and imaging data [244, 245].

1.7.4.5 Confounding factors in relaxometry

Signal models often represent a simplification of the complexity involved in biophysical phenomena. This can be the result of a lack of a complete theoretical description as well as an intentional omission of terms in a model. As such, the quantification of the parameter through model fitting can result inaccurate. Common factors known to confound relaxometry mapping are B_1 inhomogeneities, magnetization transfer, partial volume, slice profile, flow and motion, and magic angle effects.

- As already discussed, the quantification of B₁ is necessary for accurate relaxometry mapping in particular for T₁ and at high magnetic field. As B₁ variations can reach up to $\pm 30\%$ at 3 T [246] and up to $\pm 35\%$ at 7 T [247], for quantitative T₁ results, B₁ inhomogeneities need to be taken into account as these directly translate into signal inhomogeneities and, thus, variations in the apparent T₁.
- Magnetization Transfer effects are caused by cross-relaxation or chemical exchange leading to a spurious transfer of magnetization between the macromolecular pool and the free water pool [248]. The macromolecular pool has a wide spectral resonance, and it can be indirectly excited by RF pulses targeted at other slices. The protons in the macromolecular pool then interact with the observable water signal, causing its attenuation. This effect is particularly apparent when shifting to sequences rich in RF pulses, such as in multislice acquisitions.
- Partial volume effects arise when more than one tissue is found in a voxel, causing the voxel intensity to depend also on the proportion of each tissue type [249].
- Slice profile effects are caused by the imperfect slice profile of the RF pulses which leads to a partial excitation of neighboring slices. Selective RF pulses with a slice profile approaching a step function can help mitigate this effect at the expense of longer minimum echo times and repetition times. 3D acquisitions are also less susceptible to this slice profile effects [250].

- Flow and motion effects are caused by the excitation of moving a tissue that changes its relative position with respect to the FOV. These have a relatively small effect on relaxation times unless specifically encoded during signal acquisition [251].
- Magic angle effects are caused by an actual (physical) change of the value of T₁ or T₂ as a function of the angle of the external static magnetic field and the orientation in tissues with hydrophilic surface area and high internal order (such as cartilage, tendons, and highly ordered nerve bundles) [252].

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Chapter 2 Contributions

In MRI, the relaxation constants rule both the recovery of the longitudinal magnetization and the decay of the transverse magnetization and, thus, the signal acquired. Relaxometry is the branch of quantitative MRI that deals with the computation of the relaxation constants and can provide meaningful information for the study of a plethora of pathophysiological conditions. The main interest in research is the development of techniques for fast, accurate, precise, and reproducible mapping techniques, i.e. methods that are able to associate a parameter value to each voxel. However, the main issues for the translation of relaxometry parameters as clinically useful biomarkers can be found in the long acquisition times required for high resolution and accurate relaxometry maps, as well as in the current lack of specificity, which is a common issue for many qMRI approaches. This is further exacerbated by the inter- and intra-scanner variability, as well as parameter and sequence sensitivity which undermine reproducibility and repeatability of quantitative measurements. On top of that, simultaneous multiparametric approaches are used for a more comprehensive characterization of tissues as well as for the potential correction and separation of confounding factors. For example, the RF excitation field B_1 is a well-known confounding factor for T_1 estimation for all the models that require some knowledge of the provided flip angle.

Although the applications for MRI relaxometry span a variety of tissues and organs, one of the main focuses in research is brain analysis, where white matter consists of myelinated axons, while grey matter is primarily made up of the cell bodies of the neurons, as well as glial cells. As the majority of the mass of our brains is water (\approx 70% for white matter, \approx 82% for grey matter), we are able to detect good MRI signal from it. Also, the differences in biochemical environment and the interactions between water and the nonaqueous molecules generate a spectrum of T₁ and T₂ relaxation times, which can be used as biomarkers to investigate pathological changes.

An important step for the development and future translation of novel qMRI protocols to the clinical practice is their application in preclinical and animal studies. Indeed, the relevance of preclinical studies remains high as information could be used for comparative anatomy and functional studies to establish relationships between structures and properties in animals and humans. A thorough relaxometry study on the (in)dependence of relaxometry values among species is challenging to realize due to the multitude of contributing and confounding factors implied in the measurement of T_1 and T_2 . However, standardization of parameters should be performed when possible, especially when they can be checked, monitored, and potentially adjusted, such as for temperature, age, and analyzed tissue. Also, more hidden and treacherous factors could influence relaxometry parameters with relatively minor fluctuations, such as for circadian rhythm, which has been found to impact T_1 but not T_2 or water content, or time after excision for ex vivo data collection [1]. A remarkable feature of the relaxation data is its apparent independence of species although showing changes in different histological environments [2]. This was demonstrated in fields up to 2.3 T [1] and the independence of relaxation parameters over the analyzed species should also be confirmed at higher magnetic field intensities.

Once the confounding factors have been identified and isolated, qMRI can help assess and characterize pathophysiological conditions, using relaxation times as versatile biomarkers. However, the current methods employed for parameter mapping suffer from limitations, the main ones being the slowness of the sequences used - that make the application of qMRI techniques not feasible in the clinical practice - as well as the dependency of many common T_1 mapping techniques on the excitation field B_1 that needs to be estimated and corrected for a-posteriori. Undoubtedly, the acquisition of qMRI data should be sufficiently fast not to pose an obstacle in the current clinical imaging routine while not sacrificing qMRI maps accuracy, precision, nor reliability in the broadest sense. Indeed, it could be argued that the slow speed and inter-observer variability of qMRI measurements are the main reasons behind the inertia in the paradigm shift from qualitative to quantitative MRI. Faster and reliable qMRI techniques could promote a wide distribution of quantitative imaging, first in a clinical research environment and then as diagnostic aid tools, since promising results have been obtained for the use of relaxometry parameters as differentiation and characterization biomarkers, and nowadays qMRI research is a fervid research area. This paradigm shift would directly translate into a reduced need for diagnosis via histopathological approach - as histological examination currently remains the gold standard in oncology - with the added benefit of improving patient safety via a non-invasive and conservative procedure. Additionally, qMRI could be used as an approach for more standardized, objective, and reproducible interpretation of bioimages, removing the mixed contrast nature of qualitative MR images.

Gradient echo sequences are ubiquitous on MR scanners and represent an interesting and straightforward choice for the development of fast scans. In particular, spoiled gradient echo (SPGR) sequences use gradients to spoil the signal, removing possible coherences of the transverse magnetization, hence better approaching the ideal steady state, and the Actual Flip angle Imaging (AFI) is based on the use of SPGR sequences for mapping B₁. However, AFI and SPGR sequences are based on the acquisition of the signal at steady-state conditions, which might not always be met then jeopardizing map accuracy. The use of Variable flip angle with AFI (VAFI) then relies on AFI to provide accurate B₁-corrected T₁ maps, but this method remains slow, as it employs a 3D sequence with a relatively long total repetition time (TR₁-TR₂ interval) where most of TR₂ represents idle time for the scanner. The goal of this thesis is to provide new and fast approaches for accurate quantitative MRI based on developments of spoiled gradient echo sequences, and in particular, adaptations and optimization of AFI and VAFI.

The next few chapters of this thesis will cover the contributions presented throughout my Doctoral education. The projects have been developed in the context of fast and accurate quantitative MRI for the B-Q MINDED Innovative Training Network Marie Skłodowska-Curie Actions (ITN-MSCA).

Chapter 3 reports the development of a new approach to fast steady state of AFI. The application of a preparation pulse avoids possible artifacts arising from the transient state of the signal, which can impact B_1 estimation in AFI. To test this, we study the characteristics of the preparation module and describe the features for B_1 inhomogeneities robustness via EPG simulations. We validate the use of the preparation pulse via AFI signal comparisons and B_1 map estimation in phantoms, and ex vivo on a mouse brain.

Chapter 4 is the introduction to an efficient slice stacking technique for AFI and sliceprofile correction for VAFI, which directly translates into faster acquisitions for both approaches. This allows B₁-corrected T₁ maps to be reconstructed from a fast 2D multislice acquisition while retaining the accuracy and precision of the original 3D technique. The RF pulse profile of each signal included in the VAFI estimation was reconstructed via Bloch simulations, and these signals were then fitted to a VAFI model to create a lookup table of B₁ values and of T₁ values. A correction factor is then computed from these to retrieve both B₁ and the B₁-corrected T₁ value from the VAFI approach.

Chapter 5 analyzes RAMSES (Relaxation Alternate Mapping of Spoiled Echo Signals), a new simultaneous B_1 -corrected T_1 and T_2^* mapping technique based on VAFI. This was achieved by adding a bipolar multi-gradient echo readout to the second repetition time of AFI, with no additional scan time with respect to VAFI method as this part of the pulse sequence is otherwise unused and hosts relaxation-induced signal decay. EPG simulations, gelatin phantom, Gd-DOTA water solutions, and ex vivo rat head phantom were analyzed with RAMSES and compared to gold standard methods for validation of the sequence in terms of accuracy and precision. Lastly, Chapter 6 presents the development of a novel B_1 -corrected T_1 mapping based on EPI readout or dual-TR and SPGR signals. EPIFANI (Echo Planar Imaging Fast Actual Nutation Imaging) allows the acquisition of ultrafast images, providing high acquisition efficiency to a multiparametric acquisition. A slice profile correction was also integrated for B_1 computation and a slice profile correction for T_1 maps was based on the one presented in Chapter 4. The effect of T_2^* decay was studied and results on phantoms and in vivo at high magnetic field are reported. Although EPI represents a powerful and fast acquisition method in MR, EPIFANI is one of the very few attempts at acquiring multiparametric maps with EPI readout because of EPI susceptibility to artifacts.

These represent the novelty of the contributions, previously unpublished. These projects have been designed in the context of this PhD thesis, and thus the respective sequences have been installed and tested in MR Solutions scanners (Guildford, United Kingdom).

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Chapter 3 A preparation pulse for fast steady state approach in Actual Flip angle Imaging

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3.1 Introduction

The longitudinal relaxation time T_1 has been in the spotlight for being a promising and versatile biomarker for dementia, multiple sclerosis [2], epilepsy [3], and for tumor identification and characterization [4, 5, 6, 7]. On top of biological and pathophysiological variability, T_1 mapping techniques report a wide range of T_1 values in tissues, raising the issue of protocols reproducibility and standardization [8, 9, 10, 11, 12, 13, 14]. As accuracy is a requirement for using quantitative MRI in clinical applications, one needs to investigate and isolate confounding factors of signal variability: for example, T_1 mapping can not overlook knowledge of the excitation field B_1 , with B_1 inhomogeneity affecting T_1 accuracy especially at high magnetic field [15]. As a result, a standardization step as well as a thorough study of the confounding factors [16, 17] is still needed for a true validation of T_1 as a biomarker [15].

Actual Flip angle Imaging (AFI) is a gradient echo based sequence employed for fast B_1 mapping [18] with a low Specific Absorption Rate (SAR) [19]. The excitation field is estimated by a robust and simple approximation based on the negligible ratio between the repetition times of the sequence and the T_1 (TR \ll T_1) of commonly scanned tissues, which warrant the method validity for a broad range of T_1 values.

AFI is commonly used as a stand-alone module, but it was also embedded in the VAFI (Variable flip angle with Actual Flip angle Imaging) method, which relies on the acquisition of an AFI and at least one SPoiled GRadient echo (SPGR) acquisition to perform the joint estimation of T_1 , B_1 and equilibrium magnetization [20]. Indeed, as AFI is characterized by a low SAR and SPGR volumes are typically acquired fast and with

low energy deposition, VAFI can be employed for accurate, fast, low-SAR T_1 mapping at high magnetic field. Both AFI and SPGR acquisitions require the signal to be acquired at steady state (SS), so the spoiling properties and the transient approach need to be investigated.

As for many SS sequences, samples at the beginning of an AFI sequence are usually discarded to acquire a signal close to SS. However, to our knowledge, the approach to SS for an AFI sequence has not been discussed and no alternatives have been published so far. As a result, the number of discarded acquisitions (or dummy pulses) is chosen arbitrarily, ranging from as little as 8 to 600 dummy pulses [18, 21]. A high number of dummy pulses can impact negatively the length of the acquisition overhead time, while an insufficient number or discarded pulses can result in artifacts in the image due to clipping or to an incorrect weighting of k-space lines. These artifacts can be detrimental and impair parameter mapping, especially in centric ordering acquisitions, EPI-based acquisitions, and in highly accelerated sequences. A preparation pulse has been proposed for fast SS approach for SPGR acquisitions [22] relying on a single saturation pulse, but possible flip angle deviations due to B₁ field inhomogeneity could invalidate the benefit of using a preparation pulse, keeping the approach to SS long. A more efficient preparation pulse for SPGR and AFI acquisitions would be useful for a new, fast approach to SS and to avoid possible artifacts arising from signal transient-state.

Here we propose a new preparation pulse for the AFI sequence, we study its characteristics and describe the features for B_1 inhomogeneities robustness. We validate the use of the preparation pulse via AFI signal comparisons and B_1 map estimation in phantoms, and ex vivo on a mouse brain.

3.2 Materials and Methods

3.2.1 Actual Flip angle Imaging

Actual Flip angle Imaging (AFI) was originally proposed by Yarnykh as a method for a fast and low-SAR B_1 computation and is also employed in the inhomogeneity correction for accurate T_1 mapping [21, 23, 24, 25, 26, 27, 28].

AFI steady-state signals can be derived by solving the Bloch equations for a sequence with asymmetric repetition times, which provides [18]

$$\begin{split} S_{AFI1,2} &= \mathsf{M}_{0} \sin \alpha \cdot \frac{1 - E_{2,1} + (1 - E_{1,2})E_{2,1} \cos \alpha}{1 - E_{1}E_{2} \cos^{2} \alpha} \exp(-\mathsf{TE}/\mathsf{T}_{2}^{*}) = \\ &= \mathsf{M}_{0} \sin \alpha \cdot \exp(-\mathsf{TE}/\mathsf{T}_{2}^{*})A_{1,2} \quad \text{(3.1)} \end{split}$$

where M_0 represents the net magnetization signal, α represents the flip angle, $E_{1,2} = \exp(-TR_{1,2}/T_1)$, n represent the ratio between TR_2 and TR_1 , $A_{1,2}$ represents a dimensionless measure of the SS longitudinal magnetization, and the subscripts 1 and 2 represent the respective repetition times.

The computation of B₁ maps in AFI assumes that $TR_{1,2} \ll T_1$ applies for the scanned tissues, for which $E_{1,2}$ can be approximated by 1, so that the flip angle can be computed as

$$\alpha \approx \arccos \frac{S_{AFI2}/S_{AFI1} \cdot n - 1}{n - S_{AFI2}/S_{AFI1}} \quad . \tag{3.2}$$

Although originally used as a 3D technique, AFI has been used for 2D data acquisition and can be adapted to acquire multislice 2D data. As 2D encoding leads to systematic errors in the computation of the transmit field B_1 values, accurate mapping can be achieved by using RF pulses with adequate spatial excitation profile, and reducing the slice cross-talk, as well as by the implementation of slice profile correction strategies [29]. These help in mitigating measurement errors and in producing reliable B_1 maps for arbitrarily chosen slice selective RF pulses, opening the possibility to implement the technique in an interleaved or distributed fashion [30] while improving time efficiency.

SPGR-based sequences are sampled at SS to match the model expression and to avoid artifacts caused by signal approach to stabilization. Normally, an arbitrary number of RF pulses (dummies) is provided and discarded before reaching the regime condition at SS. Ideally, a preparation module would make the magnetization vector reach its SS value with just one RF pulse and a subsequent recovery time whose duration is analytically defined and independent of imaged tissue properties. While a preparation module consisting of a saturation pulse was proposed for SPGR sequences [22], this remains rarely employed in practice, and, to our knowledge, no preparation module has been proposed for AFI yet. Advantages of the application of a magnetization preparation pulse include lower energy deposition (as SAR $\propto B_1^2$) and an almost immediate SS approach, which can help with fast and ultra-fast SPGR-based acquisitions.

3.2.2 Preparation pulse

In AFI sequences, the number of dummy pulses for SS approach is relatively low. However, a preparation pulse would make the approach faster, irrespective of the tissue characteristics, which can be of special interest for multi-slab and multi-slice acquisitions, as well as when a centric or radial k-space acquisition scheme is utilized, and for AFI sequences acquired with an EPI readout. Indeed, centric acquisitions first sample the central region of the k-space to then move outwards (center-out), while EPI acquisitions travel through the central region of the k-space at every shot, which could result in signal artifacts and distortions if the magnetization has not reached SS yet. Preparation in center-out acquisitions is normally achieved by the application of dummy pulses. Nevertheless, highly accelerated and time-critical fast and ultra-fast acquisitions would benefit from the application of a preparation pulse.

Signal simulations are needed for the analysis and determination of the preparation pulse features. These also need to include RF phase effects for the study of the time evolution of the magnetization vector: the analysis of echoes and their generation can be studied via Extended Phase Graph (EPG) model [31, 32, 33]. This powerful model generates the signal from an isochromat ensemble and uses matrix operations to describe the effects of the sequence components and sequence-related effects such as gradients, RF pulses, motion, relaxation and diffusion on configuration states representing the magnetization dephasing coordinates.

The signal for the j-th AFI pulse can be described analytically by the solution of Bloch equations, by recursively exploiting the expression for the SS approach of SPGR sequences, assuming the signal is perfectly spoiled. Analytically, for $j \ge 1$ each pulse has an offset from SS value of $(\cos \alpha E_{1,2})^{j-1}(1-A)$ so that when the magnetization has experienced a total of 2j - 2 + i pulses and i = 1, 2 for AFI_{1,2}, respectively, the signal in this ideally spoiled scenario is

$$S_{j,i} = \mathsf{M}_0 \sin \alpha [A_i + (\cos \alpha E_1)^j (\cos \alpha E_2)^{j-1} (1 - A_i)] \exp(-\mathsf{TE}/\mathsf{T}_2^*) \quad .$$
 (3.3)

SS longitudinal magnetization of the AFI sequence ($M_0A_1 = S_{AFI1,2}/(\sin \alpha \exp(-TE/T_2^*))$) can be matched to the magnetization value after an arbitrary β pulse and a free relaxation period T_{rec} :

$$M_z(T_{rec}) = M_0[1 - (1 - \cos\beta)\exp(-T_{rec}/T_1)]$$
(3.4)

which cancels out the magnetization term M_0 from the equation and provides the expression of the recovery times required to reach the SS of AFI₁ signal, which should be reached after the preparation pulse (although an analogous expression can be similarly derived for AFI₂):

$$T_{rec} = \mathsf{T}_1 \log \left(\frac{1 - \cos \beta}{1 - A_1} \right) \quad . \tag{3.5}$$

3.2.3 Simulations

To show the duration of AFI without any preparation, the effects of repetition time, n and the error threshold defined as $\epsilon = 100 \cdot |S_{j,1} - S_{AFI1}|/S_{AFI1}$ on the signal variability as a function of the flip angle α and T₁ was studied for a TR₁/T₁ ratio from 0.005 to 0.05.

To ensure a spatially homogeneous excitation with the preparation β pulse, we employed an adiabatic pulse with a hyperbolic secant profile as a preparation pulse because of its high tolerance to B₁ field variations over the excitation volume that could be significant, especially for 3D acquisitions at high field [30, 34]. However, due to the higher pulse amplitude (and SAR) and longer duration, adiabatic RF pulses are rarely employed as imaging (α) pulses. We report T_{rec} for AFI after an application of the β pulse with an amplitude of 86 to 94° for α = 60° and T₁ values increasing from 0 to 5 s, computed from Equation 3.5. Also, we investigated the effects of T₂ on the approach to SS for a prepared and a non-prepared AFI sequence for T₁ = 1.5 s, T₂ \in [0.01, 0.2] s, α = 40°, $D = 1 \cdot 10^{-3}$ mm²/s.

As the time employed by the preparation time T_{rec} will depend exclusively on tunable parameters, we report a plot of T_{rec} in AFI units corresponding to TR₁(*n*+1) as a function of the flip angle for n = 4, 5, 6.

Simulations to check the effects of the β pulse amplitude on AFI₁ were performed via an EPG approach with analogous parameters and with T₁ = 2.52 s, T₂ = 0.01 s, gradient spoiling = 327 and 1415 mT·ms/m for TR₁ and TR₂, respectively, and diffusion coefficient $D = 1 \cdot 10^{-3}$ mm²/s for flip angles of 30° and 60°. β was set as an equispaced array of flip angles ranging from 84 to 96°. Values around 90° are reported to simulate the effect of possible imperfections in the flip angle of the preparation RF pulse on the recovery time T_{rec} , while the value n = 5 was chosen within the range of n values from the original publication with sufficient sensitivity to flip angle variations. Simulation TR values were chosen under 100 ms, also in agreement to the original AFI publication, to better exploit the speed of SPGR-based sequences. We also report the behavior of AFI₁ signal following a non-adiabatic preparation pulse, which was simulated by scaling the saturation pulse by the empirically computed scaling factor or normalized B₁ value $\kappa = B_1/\alpha$, and the simulated behavior for the respective B₁ relative percent difference values, where B₁ was computed via Equation 6.2 and the difference values were computed as $100 \cdot |B_1 - \alpha_{nominal}|/\alpha_{nominal}$.

A slice profile correction was implemented for the computation of B_1 values following the approach of Malik [29]. Numerical integration of Bloch simulations solved for a 3 lobes sinc pulse, for the relevant gradient waveforms parameters and for an array of B₁ values was used to obtain the flip angle distribution and the signal received with 2D spatial encoding, estimated by integration over the slice thickness. T₁ and T₂ values were matched to those computed from experimental values when available, else T₁ = 1000 ms was used and the effects of transverse relaxation were neglected according to the original slice profile correction method. The simulated values for the ratio S_{AFI2}/S_{AFI1} were used to create a lookup table and B₁ values were retrospectively linearly interpolated from it.

The main sequence parameters for AFI acquisitions and physiological values used for the simulations are also summarized in Table 3.1.

Simulations	TE/TR ₁ [ms/ms]	α [°]	ϕ_0 [°]	κ [-]	n	T ₁ [s]	T ₂ [s] [s]	$\frac{D}{[\cdot 10^{-3}\mathrm{mm^2/s}]}$	$\begin{bmatrix} T_{rec} \\ [ms] \end{bmatrix}$
Fig. 3.1	3/20	0 - 90	-	1	5	0.4 - 4	-	-	-
Fig. 3.3a	3/50	60	-	1	5	0 - 5	-	-	366
Fig. 3.4, 3.5	3/20	60, 30	25	1	5	2.52	0.01	1	147, 469
Fig. 3.6	3/20	40	25	1	5	1.5	0.01 - 0.2	1	279

Table 3.1: Parameters used for AFI simulations reported in this study. The rows of parameters have been used in the referenced Figures of the first column.

3.2.4 Experiments

Experiments were performed on 4.7 T and 7 T MR Solutions (MR Solutions Ltd, Guildford, United Kingdom) preclinical scanners with 38 mm ID quadrature coils. The prepared AFI sequence was developed starting from a SPGR sequence by adding a hyperbolic secant adiabatic pulse for B_1 insensitivity (BW = 3 kHz) followed by a spoiler gradient in the read and slice direction to crush the remaining transverse signal in a preparation module occurring only once at the beginning of the acquisition.

A homogeneous gelatin phantom at 16°C was used to validate the use of the proposed preparation module on a 4.7 T system, testing the approach to SS for the AFI sequence with and without the use of the described preparation pulse. T₁ ground truth values were computed through a 3-parameter fit of 22 points Inversion Recovery Spin Echo data to allow for deviations of the inversion angle [35, 36] (TR = 10000 ms, TE = 16 ms, slice thickness = 2 mm, FOV = (20x20) mm², matrix size = [64x64], 22 TI \in [5, 3500] ms). AFI acquisitions on the gelatin phantom were run with TR₁ = 20 ms, TE = 3 ms, *n* = 5, $\alpha_{AFI} = 60^{\circ}$. A 2D AFI was performed on a gelatin phantom in order to evaluate the effect of the preparation pulse on RF cycling (slice thickness = 2 mm, FOV = (20x20) mm², matrix size = [64x64]) and to investigate the impact of β amplitude and pulse features

on the SS. We compared the effects of using an adiabatic (hyperbolic secant pulse, $\beta \in$ [84, 96]°), non-adiabatic (3 lobe sinc pulse) preparation pulses both with BW = 3 kHz and no preparation on the approach to SS (slice thickness = 2 mm, FOV = (20x20) mm², NEX = 20).

A phosphate-buffered saline phantom with 5 different Gadolinium contrast concentrations in tubes was used to acquire B₁ values and compare the central slice of a 3D dataset used as a reference (TR₁ = 200 ms, n = 4, TE = 3 ms, slab thickness = 16 mm, FOV = (40x40x16) mm², matrix size = [128x128x16]) with 2D data acquired with a centerout k-space linear trajectory with no dummies, with 1 and 2 dummies, with the proposed preparation pulse, and with a conventional linear out-center k-space trajectory (TR₁ = 200 ms, n = 4, TE = 3 ms, slice thickness = 1 mm, FOV = (40x40) mm², matrix size = [128x128]). T₁ ground truth values were computed through a 4-parameter fit of Look-Locker data (TR = 10 ms, TE = 50-5130 ms, slice thickness = 2 mm, FOV = (40x40) mm², matrix size = [138x138]), while T₂ ground truth values were computed via a mono-exponential fit of Multi-Echo Multi-Shot (MEMS) data (TR = 1400 ms, TE = 15-150 ms, slice thickness = 1 mm, FOV = (40x40) mm², matrix size = 1 mm, FOV = (40x40) mm², matrix size = 1 mm, FOV = (40x40) mm², matrix size = 1 mm, FOV = (40x40) mm², matrix size = 1 mm, FOV = (40x40) mm², matrix size = [128x128]). The S_{AF12}/S_{AF11} ratio values were then linearly interpolated from those found in the lookup table of values simulated from the respective T₁ values, and B₁ values were then subsequently computed via Equation 6.2.

A 2D ex vivo validation of the preparation pulse was performed on a mouse brain (TR₁ = 100 ms, n = 5, TE = 3 ms - 3D: slab thickness = 16 mm, FOV = (40x40x16) mm², matrix size = [128x128x16]; 2D: slice thickness = 1 mm, FOV = (40x40) mm², matrix size = [128x128]), acquiring images with the same protocol used for the phosphate-buffered saline phantom.

No assumptions on T_1 were made and T_2 relaxation effects were ignored for the generation of the lookup table used for the slice profile correction, to test the generalization power of the correction method according to the original slice correction method publication [29].

We report Bland-Altman plots of the distribution of the κ map, namely the B₁ map normalized by the nominal flip angle $\kappa = B_1/\alpha$, for specific Regions of Interest in both the phosphate-buffered saline phantom and the ex vivo mouse brain. In the former, we provide an example of the κ line profile for all the acquisitions performed.

The experiments were run with the application of a spoiling gradient along the readout and slice direction. The RF pulse phase characteristic ϕ_0 was selected as 25° (see Section 3.6.3) and gradient moments were chosen as 327/1415 mT·ms/m (for TR₁ and TR₂, respectively), in order to reach high signal spoiling [37]. The main sequence parameters for AFI acquisitions and physiological values used for the experiments are also summarized in Table 3.2.

Experiments	TE/TR ₁	α	ϕ_0	n	T ₁	B_0	T_{rec}
	[ms/ms]	[°]	[°]		[s]	[T]	[ms]
Fig. 3.4, 3.5	3/20	60	25	5	2.52	4.7	147
Fig. 3.7a, 3.7b, 3.7c	3/200	60	25	4	2.52	7	1200
Fig. 3.7d	3/200	60	25	4	1.11 - 2.59	7	1200
Fig. 3.8	3/100	60	37	5		7	733

Table 3.2: Parameters used for the AFI experiments reported in this study.

3.3 Results

3.3.1 Preparation pulse features

The number of discarded acquisitions to reach SS with a good approximation is a function of the sequence parameters. The level plot in Figure 3.1 shows the number of AFI pulses required for a relative error $\epsilon < 5\%$ for an AFI sequence without preparation, where the signal was simulated via Equation 3.3 and ϵ is defined as the absolute normalized distance from the SS signal. The selection of the flip angle greatly impacts the approach to SS, as already demonstrated for SPGR sequences (refer to Supplementary Materials 3.9 for the corresponding behavior in SPGR acquisitions). Increase in the repetition time and in n, as well as a larger admissible error ϵ reduce the number of discarded acquisitions required for signal accuracy, shifting the level lines of the plot towards lower TR₁/T₁ values, which is indicated by the black arrow.



Figure 3.1: Level plot of the number of pulses required for a relative error $\epsilon < 5\%$ for an AFI sequence without preparation. Flip angle, the TR₁/T₁, *n* and the error threshold ϵ have an effect on the minimum number of dummies required, shifting the level lines towards the left of the plot, as indicated by the black arrow.



The sequence pulse diagram for a prepared AFI acquisition is reported in Figure 3.2.

Figure 3.2: Pulse sequence diagram for an AFI acquisition with the preparation module.

Dependency of the recovery time T_{rec} over T_1 is shown in Figure 3.3a, where the flip angle β of the preparation pulse determines the curve slope for the long T_1 s. This T_1 dependency becomes negligible for $\beta = 90^\circ$ in the range of T_1 commonly found in physiological tissues ($T_1 > 0.5$ s). Thus, for the considered interval the following applies

(refer to Supplementary Materials 3.6.2 for the formula derivation):

$$T_{rec}(\beta = \pi/2, \mathsf{T}_1 \to \infty) = \mathsf{TR}_1 \frac{n + \cos \alpha}{1 - \cos^2 \alpha} \quad . \tag{3.6}$$

The relative change of T_{rec} for $T_1 > 0.5$ s reduces to below 2.1% and asymptotically approaches zero when $\beta = 90^{\circ}$ – the analysis of the partial derivative $\partial T_{rec}/\partial T_1$ is reported in the Supplementary Materials 3.6.2. In case of $\beta \neq 90^{\circ}$, the curve diverges and hence no unique T_{rec} can be defined for a range of T_1 values.

For $\beta=90^\circ,$ the total acquisition time T_{tot} for a prepared 3D AFI will then correspond to

$$T_{tot} = T_{rec} + T_{AFI} = \mathsf{TR}_1 \frac{n + \cos \alpha}{1 - \cos^2 \alpha} + \mathsf{TR}_1 (n+1) n_{pe,1} n_{pe,2}$$
(3.7)

where T_{AFI} is the total acquisition time for a single AFI scan (NEX = 1) and $n_{pe,1}$ and $n_{pe,2}$ represent the number of gradient steps (hence k-space lines) in the first and the second phase encoding direction, respectively. As T_{AFI} is usually much larger than T_{rec} , T_{tot} can also be approximated to T_{AFI} .

Figure 3.3b shows the duration of the recovery time following the preparation pulse T_{rec} in terms of full AFI acquisitions (or AFI units, defined as $TR_1(n + 1)$), so to compare the duration of the preparation module with respect to that of dummy pulses. For flip angles within the 30-80° range and for n = 4, 5, 6, the recovery time T_{rec} of the preparation module is shorter than 4 repetitions of the AFI sequence, with increasing sensitivity for smaller flip angles. Thus, the duration of the preparation module T_{rec} is shorter than a preparation achieved with dummies, as at least 5 dummies are required for SS approach according to the level plot for flip angles in the 30-80° range.





Figure 3.3: a: Dependency of the recovery time T_{rec} and flip angle for AFI₁ (continuous line) signal following the adiabatic preparation pulse over T₁, for different β values ranging from 86° to 94°, with α = 60°, TR₁ = 50 ms, n = 5. Asymptotic value for T₁ $\rightarrow \infty$ is shown in red (dashed line at T_{rec} = 366.6 ms, compared to a single AFI dummy cycle of TR₁(n + 1) = 300 ms). b: T_{rec} time normalized by the duration of an AFI sequence for increasing flip angle. An AFI unit corresponds to the duration of a full AFI acquisition, namely TR₁(n + 1). The recovery time following the described preparation module is shorter than 4 full AFI units.

Using the β values around the nominal value of 90° considerably reduces signal variability in the first RF pulses, and reduces the time required to reach SS as compared to not applying the preparation pulse. An example of the dependency of the preparation pulse efficiency over a range of β values, in both simulations and experiments, is presented in Figure 3.4. The lowest mean signal variability in terms of signal range is reached for $\beta = 90^\circ$ – a saturation pulse – but applying a preparation pulse with an amplitude close to the optimal flip angle is still more effective in approaching the SS with respect to the application of dummy pulses. Simulation results (on the left column of Figure 3.4) are in agreement with the experimental data (right column), which show the signal of AFI₁ after the application of the preparation pulse approaching SS values (reported as a dashed gray line) faster than without any preparation.

Figure 3.4 also reports the signal behavior for AFI₁ following the application of nonadiabatic and adiabatic preparation pulses. Signal intensity values are reported in arbitrary units 'a.u.' which represent fractions of the equilibrium magnetization multiplied by several factors including the transverse relaxation decay, receiver gain, and coil sensitivity profiles. The adiabatic pulse allows to sample the SS signal immediately after the preparation pulse, reproducing the attended behavior of the simulations, while a non-adiabatic pulse can show deviations in the effective flip angle due to the inhomogeneity of the B₁ field. Also, the values of the non-adiabatic preparation pulse match the experimental values for a preparation pulse provided with a flip angle of around 81°. The different length of the transient state for $\alpha = 60^{\circ}$ (top row) and 30° (bottom row) is shown, with $\beta = 90^{\circ}$ providing the closest signal to SS in both cases. Row (a) shows $\alpha = 60^{\circ}$, for which T_{rec} takes 146.6 ms, while a single AFI cycle takes 120 ms. The SS is reached after approximately 6-9 cycles taking 720-1080 ms in total. Row (b) shows $\alpha =$ 30°, for which T_{rec} takes 469.3 ms, and SS is reached after more than 15 cycles (> 1.8 s).

B₁ relative percent difference values follow a similar trend with respect to the absolute AFI signals: Figure 3.5 report simulations (left column) for $\alpha = 60^{\circ}$ (top) and $\alpha = 30^{\circ}$ (bottom), and data simulated without any preparation module (black line) show the highest difference with respect to the nominal B₁, while the non-adiabatic 90° pulse (green line) allows a faster approach to the SS value. The adiabatic pulse (purple line) reaches SS B₁ values almost immediately after T_{rec}. This is also confirmed by experimental data (right column), which follows the same relative trend, with the applications of dummies being the slowest approach.



Figure 3.4: EPG simulations (left) and experimental results (right) on the variation of β amplitude for AFI with $\alpha = 60^{\circ}$ (a) and 30° (b). The upper right boxes show a magnification of the signal for the first RF pulses. Graphs on the right also show a comparison between the signal behavior when prepared via adiabatic RF pulses (β ranging from 84° to 96°) and a non-adiabatic RF pulse ($\beta = 90^{\circ}$) – the amplitude of the non-adiabatic pulses was scaled by the κ factor computed via AFI for simulations. Median SS value is reported as gray dashed lines. The values of the parameters used for both simulations and experiments are found in Table 3.1 and 3.2, respectively.



Figure 3.5: B₁ relative percent difference computed for both simulations (left column) and experimental data (right column), for $\alpha = 60^{\circ}$ (top) and 30° (bottom). Black lines refer to data acquired without any preparation module, green lines refer to data acquired with a 90° non-adiabatic preparation pulse, and purple ones refer to data acquired with a preparation pulse featuring an adiabatic pulse with $\beta = 90^{\circ}$.

EPG simulations also demonstrate how the preparation module allows a faster sampling of the SS with respect to the signal achieved without preparation. A similar behavior is followed by both AFI_1 and AFI_2 (not shown). For increasing T_2 values, the lack of the preparation module or dummy pulses results in a prolonged oscillation around SS (Figure 3.6).



Figure 3.6: Simulated approach to steady state without (dashed line) and with (continuous line) preparation pulse for AFI₁ for T₁ = 1.5 s, α = 40°, $D = 1 \cdot 10^{-3}$ mm²/s, T₂ ranging from 0.01 to 0.2 s (increasing T₂ values are represented by a shift from red to blue color and are indicated by the black arrow).

A comparison on a phantom containing a phosphate-buffered saline solution is reported in Figure 3.7: the κ values (B₁ normalized by the nominal flip angle) computed from an acquisition performed with no preparation pulse and no dummies show are inaccurate with a mean systematic difference of -39.2% with respect to the reference values from a 3D AFI acquisition. As shown in the dotted values along the line profile in Figure 3.7a and the reconstructed κ maps of Figure 3.7b, some values can not be interpolated from the lookup table used for slice profile correction. This results in unreliable and unusable maps for the data acquired with no preparation and no dummies. All other acquisitions show fewer values that can not be matched with the lookup table and can be attributed to noise fluctuations. By selecting a region of interest at the center of the phantom (Figure 3.7c), the highest accuracy with respect to the reference B₁ values from a 3D AFI is reached with the preparation pulse (mean difference -6.0%), while

values in the case of an out-center acquisition scheme, center-out with one dummy, and two dummies are -9.2%, -14.2%, and -6.6%, respectively. Similarly, when compared to the average of the κ values in the Gadolinium solutions, the systematic difference is -5.6% for an out-center acquisition, -32.9% with no preparation, -10.9% and -7.6% with one and two dummies, and -6.4% with the preparation module, respectively (Figure 3.7d). The preparation with dummies took 1000 ms and 2000 ms for one and two dummies, respectively, while the proposed preparation module required 1200 ms.







Figure 3.7: Phosphate-buffered saline solution phantom. a: Example for κ (normalized B₁) profile along the yellow line for values uncorrected and corrected for the slice profile effects. b: Slice profile corrected normalized B₁ maps for acquisitions performed with an out-center scheme, with no preparation, with a single dummy scan, with two dummy scans, with the proposed preparation pulse, and from a 3D reference acquisition. Pixels belonging to the background and whose values that can not be mapped based on the slice correction are black. Colors found under the image refer to the respective colors in the other plots. c, d: Bland-Altman plots for the normalized B₁ values found (c) in the central area of the sample reported as a yellow rectangle and (d) in the 5 Gadolinium solutions reported as a yellow rectangle. Values are compared against the 3D reference. Mean (dashed line) and values at 2 standard deviations from the mean (dotted lines) refer to the B₁ values for a prepared acquisition.

The analysis of images acquired on an ex vivo mouse brain phantom in Figure 3.8 further confirms what was found for the phosphate-buffered saline phantom. Presenting the images with the same intensity scale shows that the images acquired before the stabilization of the signal around SS (images with no preparation, one and two dummies) have a higher signal intensity, which results in systematic errors in the computed B₁ and, thus, κ values. The Bland-Altman plot referring to the brain report mean κ difference values of 2.0% (out-center), -21.4% (no preparation), -6.2% (one dummy), -3.1% (two dummies) and 2.2% (preparation module) with respect to the conventional 3D version of AFI. Analogously, mean difference value in the agar were 10.3% (out-center), -19.4% (no preparation), -5.7% (one dummy), -1.5% (two dummies), and 4.1% (preparation module)

ule). The preparation with dummies in this AFI example took 600 ms for each dummy, while the proposed preparation module required 733 ms.



Figure 3.8: Examples of AFI₁ images (a) and corresponding κ maps of data acquired on an ex vivo mouse brain with a conventional 2D out-center k-space trajectory, and for center-out trajectories with no preparation, one and two dummy pulses, with the proposed preparation module, and with a 3D acquisition. Bland-Altman plots (b) referring to both the mouse brain (left) and the agar (right) are reported.

3.4 Discussion

We demonstrated the rationale for the use and efficiency of a preparation module for fast SS approach in AFI sequence. Experimental results validate theoretical findings, which confirm the robustness of the preparation pulse.

We presented the characteristics of a preparation pulse and the analytical expres-

sion for the subsequent recovery time to reach SS without using discarded acquisitions. The preparation module is composed of an adiabatic 90° RF pulse, spoiler gradients in non-encoding directions, and a recovery time T_{rec} . We found that for short repetition times, tissues with $T_1 > 0.5$ s require the same amount of time T_{rec} to allow longitudinal magnetization to recover to steady-state levels and that T_{rec} depends exclusively on the tunable sequence parameters (TR_1 , n and flip angle). The fundamental independence of T_{rec} on T₁ has been demonstrated analytically for a saturation pulse: indeed, by choosing the T_{rec} value that is reached asymptotically for increasing T₁s, this preparation pulse can be applied to achieve steady-state in the majority of biological tissues of interest in neuroimaging at high magnetic field minimizing the dependency over the actual relaxation time of the imaged specimen. Due to the sensitivity of T_{rec} and, consequently, of $M_z(T_{rec})$, to the flip angle, the preparation pulse should deliver a flip angle as close as possible to 90°, which is easily ensured by the RF pulse calibration, as this represents a widespread amplitude reference [38]. Nevertheless, the use of an adiabatic pulse is robust to variations of the β amplitude and better allows SS to be reached faster than with the application of dummy pulses or in the case of B₁ inhomogeneities, which are a main drawback when scanning at high magnetic field. Further studies could focus on the impact on the signal of multiple consecutive saturation pulses in a WETlike approach [39], which could provide further $B_0/B_1/T_1$ robustness in the elimination of the transverse magnetization.

The application of such preparation module both speeds up the approach to SS and allows an accurate computation of B_1 values right after its application, without the need to provide further dummy pulses, as demonstrated in both simulations and experimental results. Also, it can be particularly advantageous for tissues with short T_2 and for acquisition methods that sample the center of the k-space early in the sequence. We have shown that imaging CSF mimicking tissues with long T_2 such as phosphate-buffer saline solution and agar still benefits from the application of the preparation module as the signal from a prepared sequence has a faster approach to SS conditions, leading to lower signal offsets within the first RF pulse excitations.

The time benefit of the application of a preparation pulse could be majorly appreciated when employing parallel imaging with acceleration factor R > 1, for 2D multislice imaging, for acquisitions with a center-out k-space trajectory (spiral, radial, linear), especially at high field where long tissue T_1 values are expected (such as CSF [40], with $T_1 > 4$ s). Further applications could be found in fast breath-hold AFI acquisitions, which could be used to avoid the many dummy pulses needed to ensure operation at SS [41] and serve as both a SAR-efficient static and dynamic way to map RF transmission, thus allowing T₁ mapping correction for cardiac and abdominal imaging. Simulations show that in the range of flip angles commonly used for AFI, the preparation pulse allows reaching the SS in less than the time needed for 4 full dummy acquisitions for any repetition time employed and for any tissue analyzed (around 1.25 AFI units for $\alpha = 60^{\circ}$), resulting in a faster SS approach which otherwise would take at least 5 dummies. Also, the recovery time T_{rec}, when expressed in times of AFI units, does not fundamentally dependent on the parameter *n*.

When compared to a conventional 3D AFI acquisition, we have shown that the use of the proposed preparation module for 2D AFI helps in increasing the accuracy of κ , thus B₁ values, with respect to acquisitions performed without any preparation or with dummy acquisitions with a fundamentally equivalent duration. This was shown in both a uniform phosphate-buffered saline solution with multiple Gadolinium concentrations and with an anatomical model provided by an ex vivo mouse brain, where solution and tissues with different T₁ also show the fundamental T₁-independence of the preparation module.

It should be noted that a slice profile correction needs to be performed for both 2D cartesian AFI, taking into account the physiological parameter, specific RF pulse excitation, and the employed sequence parameters to produce reliable and accurate B_1 maps. Nevertheless, the use of a fixed value for the T_1 and neglecting the transverse relaxation – as suggested in the original slice profile correction method [29] – still provides reliable values that closely approach those computed from the reference 3D AFI acquisition.

AFI represents one of the choices for B_1 mapping, but other fast techniques have been proposed in the last decades, including methods based on adiabatic phase imaging [42], orthogonal- α [43], stimulated echo/spin echo imaging [44], saturated Turbo FLASH [45], Bloch-Siegert shift imaging [46]. AFI, nevertheless, remains one of the most commonly employed B_1 mapping reference sequences [21, 26, 27, 47, 48, 49] due to its rapidity and robustness in B_1 mapping. For possible EPI applications of AFI, it has been shown that 2D EPI readouts have only a small influence on the flip angle uncertainties thanks to the preceding preparation and/or long repetition times [19]. Further studies on the 2D applications of B_1 methods should focus on possible effects of outof-bandwidth magnetization and signal pollution from distal regions to the imaged slice [50].

In center-out, radial and small matrix-size acquisitions, artifacts given by an incorrect weighting of k-space lines appear when the signal is sampled before it reaches SS conditions and where signal oscillations affect the image contrast. Data clipping artifacts are an extreme example of this effect, which could appear in center-out acquisitions when
no sequence preparation is performed. The use of the preparation pulse or dummy pulses mitigates the effects of these artifacts, thus enabling fast center-out acquisitions for both gualitative and accurate guantitative assessments. We demonstrated potential impact of the preparation pulse on parametric maps computed with an AFI approach. Although centric-view ordering schemes are typically used for reduction of motion artifacts [51] either within the context of rapidly changing (dynamic) contrast or to capture transient effects [52] rather than SS effects, the application of a preparation pulse can find an application in both ultrafast EPI-based AFI sequences and centric-view ordering sequences: the former ones could be used for dynamic B₁ mapping in order to reduce artifacts of single-shot EPI such as blurring due to the T^{*}₂ decay and geometric distortion due to off-resonance effects [53]. Centric-view ordering sequences instead could use only the central part of the k-space of poor SNR AFI acquisitions: as B1 profiles are usually smooth, acquiring only the central lines of the k-space - taking care of the ringing artifacts caused by k-space truncation - could reduce the total acquisition time while increasing the SNR [54]. Furthermore, the computation of B_1 -corrected T_1 maps via VAFI can benefit from the use of the preparation pulse, when both 2D multislice or 3D maps are computed starting from AFI and SPGR acquisitions. As a final note, the features of the preparation module have been described for AFI, however, they can be applied without loss of generality to any SS dual-TR sequence when used on tissues with a longitudinal relaxation time that respects the AFI assumption ($T_1 \gg TR_{1,2}$) [55].

3.5 Conclusion

A preparation module composed of an adiabatic pulse, spoiler gradients and a recovery time was proposed for a fast steady-state approach of signal for the AFI sequence, which represents a steady-state method for B_1 mapping. The approach is robust to variations of the pulse amplitude, the analytical expression of the recovery time is T_1 -independent and all tissues require approximately the same amount of time to recover to steady-state levels of longitudinal magnetization. The advantages of using a preparation module include the elimination of discarded acquisitions and artifacts that occur at the beginning of an acquisition with sampling the center of the k-space early, such as EPI readout or center-out k-space trajectories.

3.6 Supplementary materials

3.6.1 Steady-state approach with dummy pulses in SPGR

A perfectly spoiled SPGR signal follows the well-known expression

$$S_{SPGR} = M_0 \sin \alpha \cdot \frac{1 - E_1}{1 - E_1 \cos \alpha} \exp(-\text{TE}/\text{T}_2^*)$$
 (3.8)

Starting from Bloch equations and assuming perfect spoiling, the steady-state magnetization for an SPGR sequence can be retrieved. The transverse magnetization is zero just before each new pulse, which then converts longitudinal magnetization into transverse magnetization. If M_z is M_{zA} , then after the RF pulse $M_{zB} = M_{zA} \cos \alpha$ and, after relaxation, magnetization would become $M_{zC} = M_{zB}e^{-\mathrm{TR}/\mathrm{T}_1} + \mathrm{M}_0(1 - e^{-\mathrm{TR}/\mathrm{T}_1}) = M_{zA} \cos \alpha E_1 + \mathrm{M}_0(1 - E_1)$ where $E_1 = e^{-\mathrm{TR}/\mathrm{T}_1}$. The steady-state condition is reached for longitudinal magnetization when $M_{zA} = M_{zC}$, which yields

$$\frac{M_{zA}}{M_0} = \frac{1 - E_1}{1 - \cos \alpha E_1} = f_{z,ss}$$
(3.9)

so that the approach to steady state (transient state) at the j-th pulse of an SPGR sequence can be expressed as

$$S_j = \mathsf{M}_0 \sin \alpha e^{-\mathsf{TE}/\mathsf{T}_2^*} [f_{z,ss} + (\cos \alpha E_1)^{j-1} (1 - f_{z,ss})] \quad . \tag{3.10}$$

In Figure 3.9 we report a level plot of the number of pulses required for a relative error $\epsilon < 5\%$ for a SPGR sequence without preparation, where the signal was simulated via Equation 3.10. Counter-intuitively, the smaller the flip angle is, the higher the amount of dummy pulses/discarded acquisitions is required to approach reliably the SS in SPGR-based sequences, which may require hundreds of dummy pulses for a 5-10% accuracy in terms of absolute distance between the signal intensity and the SS value.



Figure 3.9: Level plot of the minimum number of pulses required for a relative error $\epsilon < 5\%$ for an SPGR sequence without preparation.

For AFI (shown in Figure 3.1), flip angle, TR_1/T_1 , and the error threshold ϵ have significant effect on the number of dummies required. The black arrow shows the shift direction of the level lines towards the left of the plot. With respect to an AFI acquisition with analogous parameters (and n > 1), the number of dummy pulses for reaching signal accuracy is higher, and can reach hundreds for low flip angle amplitudes and long T_1 values.

3.6.2 Derivation of Equation 3.6

Matching the magnetization after an arbitrary β pulse and a free relaxation period T_{rec} to the SS magnetization of the AFI sequence we get Equation 3.5:

$$T_{rec} = \mathsf{T}_1 \log \left(\frac{1 - \cos \beta}{1 - A_1} \right) \stackrel{\beta = \pi/2}{=} -\mathsf{T}_1 \log(1 - A_1)$$
(3.11)

which, for $T_1 \to +\infty$, brings to an indeterminate form of the type $\infty \cdot 0$. With a first order approximation via Taylor series, this becomes

$$T_{rec} \approx \mathsf{T}_1 A_1 = \mathsf{T}_1 \frac{1 - E_2 + (1 - E_1)E_2\cos\alpha}{1 - E_1 E_2\cos^2\alpha} \tag{3.12}$$

and expanding $E_{1,2}$ as $1 - TR_{1,2}/T_1$, this leads to

$$T_{rec} \approx \frac{\mathsf{TR}_2 + \mathsf{TR}_1 \cos \alpha}{1 - \cos^2 \alpha} = \mathsf{TR}_1 \frac{n + \cos \alpha}{1 - \cos^2 \alpha}$$
(3.13)

Also, the partial derivative of T_{rec} in ∂T_1 from Equation 3.5 is

$$\frac{\partial T_{rec}}{\partial \mathsf{T}_1} = \frac{N_1 A_1 + N_2}{T_1^2 D_1 (1 - A_1)} - \log(1 - A_1) \tag{3.14}$$

with $N_1 = \cos^2 \alpha E_1 E_2 \cdot \text{TR}_1(n+1)$, $N_2 = \text{TR}_1(-\cos \alpha E_1 E_2 + n \cos \alpha (1-E_1)E_2 - nE_2)$, and $D_1 = (1 - \cos^2 \alpha E_1 E_2)$.

The plot for $\alpha = 60^{\circ}$, TR₁ = 50 ms, and n = 5 (matching the values for Figure 3.3a) is reported in Figure 3.10a. This shows the approach to a T₁-independent T_{rec} for increasing T₁ values. The minimum T₁ value that leads to a partial derivative smaller than $\epsilon =$ 10% (arbitrarily chosen) for TR₁ \in [0.001, 0.1], $\alpha \in$ [30, 80]°, and n = 4, 5, 6 is reported in Figure 3.10b. For increasing flip angle and ϵ , and smaller n factors, the minimum T₁ decreases, while longer TR₁ values come with longer minimum T₁s.



Figure 3.10: a: Partial derivative $\partial T_{rec}/\partial T_1$ for $\alpha = 60^\circ$, TR₁ = 50 ms, n = 5. b: Minimum T₁ value for $\partial T_{rec}/\partial T_1 < 0.05$ for TR₁ $\in [0.02, 0.1]$, $\alpha \in [30, 80]^\circ$, n = 4 (black), 5 (blue), 6 (red).

3.6.3 Signal spoiling

The pivotal Equations 6.1 and 3.8 are only valid for complete spoiling of transverse magnetization before each excitation pulse, which can be reached by gradient and RF spoiling. RF spoiling, in particular, requires a model for cycling the RF phase to avoid coherence build-up that spoils the transverse magnetization, and in a popular method [56, 57, 58], the phase of the k-th RF pulse is cycled as

$$\phi_k = \phi_{k-1} + k\phi_0 \quad k = 1, 2, 3, \dots$$
(3.15)

with ϕ_0 being the phase-cycling characteristic. Nevertheless, standard RF spoiling is generally insufficient both in VFA and in AFI, which may yield systematic errors in parameter quantification, so several methods for efficient signal spoiling have been proposed, such as corrections to T₁ maps [59], the use of effective excitation angles [60] or the introduction of very strong spoiling gradients [37]. We selected the last approach, and investigated the influence of RF pulse phase characteristic ϕ_0 on the behavior of the signal after the application of the preparation pulse.

The spoiling features for a prepared AFI sequence were obtained via Extended Phase Graph simulations. The signal from AFI sequence with the implementation of the preparation module was simulated to check spoiling characteristics including the effects of $T_1 \in [0.5, 4.5]$ s, $T_2 \in [0.01, 1.0]$ s, gradient spoiling = 327 and 1415 mT·ms/m (high spoiling

regime) for TR₁ and TR₂, respectively, TE = 5 ms and diffusion coefficient $D \in [0, 2] \cdot 10^{-3}$ mm²/s following the approach of Hargreaves [61] and Weigel [33]. TR₁ = 20 ms, n = TR₂/TR₁ = 5 and α = 60° were chosen from literature values [20, 18] for simulations and then used during scanning.

3.6.4 Results

The RF pulse spoiling phase characteristic for both AFI₁ and AFI₂ signals for a range of physiological values with the preparation module shows the same features as the signals in a not-prepared AFI sequence. As shown in Figure 3.11, the periodicity of the original AFI signals is maintained (the symmetry around 90° and 180° period). The minimum distance between the median values and the perfectly spoiled SS value for AFI₁ and AFI₂ are found in the different locations along the RF increment range. Nevertheless, the common minimum distance to the steady-state values (represented by the zero horizontal line) for median values is observed in the region of $\phi_0 = 20-25^\circ$ for all *n* values investigated. This RF phase increment for the AFI sequence also corresponds to a local minimum of the sum of the absolute distances from the steady state for the whole range of T₁, T₂ and *D* considered. For both simulations and experiments with AFI sequences, we used an RF pulse with spoiling phase characteristic ϕ_0 of 25°.



Figure 3.11: Left: Using a RF pulse phase characteristic ϕ_0 can result in a bias of AFI signals with respect to SS signal, and this bias also depends on the sample properties. Upper and lower lighter lines represent the maximum and the minimum of the distributions for TR₁ = 20 ms, T₁ \in [0.5,4.5] s, T₂ \in [0.01,1.0] s, gradient spoiling = 327/1415 mT·ms/m (for TR₁ and TR₂, respectively, corresponding to a high spoiling regime), $D \in$ [0,2]·10⁻³ mm²/s, n = 5 and $\alpha = 60^{\circ}$. Crosses represent experimental data for a water phantom (T₁ = 2.09 s, T₂ = 1.08 s). Right: Median (blue), interquartile range (dark shaded area) and range (light shaded area) values also show a variation over the common sequence and tissue parameters with respect to the SS value (black dashed line). Minimum values for AFI₁ and AFI₂ can be found for different RF increment values, but a range characterized by small ranges and minimum bias is common for both signals around 25°.

3.6.5 Discussion

An RF phase increment for a wide range of physiological parameters (T₁, T₂ and *D*) in the high gradient spoiling regime was reported. The $\phi_0 = 25^\circ$ appears to minimize the variability of AFI₁ around the steady state and matches the region of small AFI₂ variability as well. This RF increment indeed minimizes both the overall median difference and range to the ideal steady-state value for a range of *n* values. Nevertheless, this is specific to the sequence parameters we used (TR₁ = 20 ms, α = 60°, high spoiling regime) and users are advised to run simulations with their own system and sequence specifics.

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Chapter 4 Time-efficient multislice 2D and slice profile correction for T_1 and B_1 mapping with VAFI

Parts of the work in this chapter are in preparation for submission as a research paper to Magnetic Resonance in Medicine.

4.1 Introduction

Mapping of relaxometry parameters has been gaining popularity for its clinical application as potential biomarkers. The longitudinal relaxation time T_1 has been quantified and analyzed in tissues and pathologies as an iron concentration marker [1, 2], differentiation tool for brain conditions [3], and used as a tool for contrast agent development and delivery studies [4, 5], blood perfusion studies [6, 7] and manganese- and oxygenenhanced functional MRI [8, 9], as well as an anatomical reference [10]. However, different MR sequences, T_1 estimation methods, parameters, and setups are being used in the context of T_1 relaxometry, with no clinical standard for fast and accurate mapping. A standardization step and a thorough study of the confounding factors [11, 12] is still needed for a validation of T_1 as a biomarker [13] as relaxation times have been demonstrated to be affected by several subject-dependent parameters including age and temperature, system-specific variables such as magnetic field strength and the acquisition method. Macromolecular composition - including myelin, and iron content together with fiber orientation [14, 15, 16] also affect T_1 , making it a tissue-dependent parameter.

The Variable Flip Angle (VFA) method [17, 18, 19], also known as Driven Equilibrium Single Pulse Observation of T_1 (DESPOT1), is a widely employed T_1 mapping method that requires the acquisition of at least two Spoiled Gradient echo (SPGR) images acquired with two different flip angles and same repetition time. Although popular and broadly available in commercial scanners, this method is very sensitive to inaccuracies in the provided flip angle amplitude [20, 21, 22]. T_1 mapping methods are indeed sensitive to inaccuracies of the RF excitation field B_1 , as any relaxometry method needs to make assumptions on the provided flip angle and B_1 maps are thus required to calibrate the nominal flip angle to the actual value [13, 23, 24, 25]. Since the RF excitation within the body is not uniform and shows inhomogeneities in the B_1 map – more pronounced at high magnetic field [26, 27, 28] – tissue contrast can be affected resulting in intensity distortion and causing issues in the analysis of structural information in the reconstructed maps [29].

The Actual Flip angle Imaging (AFI) method has been widely used as an efficient tool for B₁ mapping due to its low Specific Absorption Rate and easy implementation. Originally developed as a method with 3D spatial encoding [24, 30, 31, 32, 33], AFI has been integrated into the Variable flip angle with AFI (VAFI) approach for a joint B_1 , T_1 , and equilibrium magnetization estimation. While AFI can not reliably map B₁ values when T_1 is close to the used repetition time, VAFI overcomes this limitation by fitting an AFI and at least a SPGR signal jointly against their signal models. Nevertheless, 3D AFI acquisitions still require long scan time due to the asymmetric dual-repetition time fashion of the sequence. Also, long repetition times should be used to increase the B_1 sensitivity, which makes the application of both 3D AFI, and therefore 3D VAFI, not feasible from a clinical standpoint. A few 2D implementations for B_1 mapping have been published for AFI [34, 35], but a 2D multislice acquisition scheme for AFI would be greatly beneficial, especially if it was possible to exploit the idle time in the longest of the repetition times of AFI. However, the acquisition of different slices in multi-TR sequences can not be stacked in a simple sequential interleaved fashion due to the asymmetrical TRs. Also, 2D quantitative mapping with VAFI is subject to slice imperfection errors, which propagate in the estimations of parameters. While a careful selection and calibration of RF pulses can be used to mitigate slice profile effects, correction methods have also been proposed to either include a priori knowledge of the pulses or introduce correction terms in the signal equations [13, 36, 37, 38]. An approach for slice profile correction in 2D AFI has been proposed by Malik and can reliably reconstruct B₁ maps [35, 39], but no correction has been applied or proposed for 2D single- or multi-slice VAFI acquisitions and the respective B_1 and T_1 mapping.

Here we introduce a new strategy for time-optimized 2D multislice acquisitions with AFI as well as a new slice profile correction method for VAFI which provides faster and more accurate B_1 and T_1 maps. The slice profile correction employs Bloch simulations of each signal included in the VAFI estimation by simulating the RF pulse profile and the relevant gradient waveforms, fitting these signals to a VAFI model to create lookup tables of B_1 and T_1 values. A correction factor is then computed from these to retrieve both B_1 and the B_1 -corrected T_1 value with a VAFI approach.

4.2 Methods

AFI is a 3D gradient-echo sequence used in relaxometry for the computation of the B_1 field. It uses a dual and asymmetrical repetition time scheme, hence two SPGR units of different duration, to provide two different steady-state values [30] defined as

$$S_{AFI1,2} = S_0 \sin \alpha \cdot \frac{1 - E_{2,1} + (1 - E_{1,2})E_{2,1}\cos \alpha}{1 - E_1 E_2 \cos^2 \alpha} \exp(-\mathsf{TE}/\mathsf{T}_2^*)$$
(4.1)

where S_0 represents the net magnetization signal, α represents the flip angle, $E_{1,2} = \exp(-TR_{1,2}/T_1)$, with $TR_2 = nTR_1$, and the subscripts 1 and 2 represent the respective repetition times.

The SPGR signals used in the VFA method as well as for VAFI fitting are modeled by the well-known expression

$$S_{SPGR} = S_0 \sin \alpha \cdot \frac{1 - E_1}{1 - E_1 \cos \alpha} \exp(-\text{TE}/\text{T}_2^*)$$
, (4.2)

which reaches a maximum with respect to the provided flip angle at the so-called Ernst angle [40] $\alpha_{Ernst} = \arccos E_1$.

Both Equation 4.1 and 4.2 are valid assuming a perfectly spoiled signal, which can be approximated by the application of high-amplitude spoiling gradients as well as by the use of an optimized RF phase increment [41].

Acquiring an AFI and multiple SPGR volumes and assuming the linearity of the errors in the B₁ transmit field for different flip angles, Hurley described the VAFI method for the joint estimation of B₁, T₁ and an equilibrium magnetization term M_0^* by means of a nonlinear least-square fit [42]. When sequence properties such as RF bandwidth, echo time, and spoiling pattern guarantee a perfectly spoiled signal, AFI and SPGR signals can indeed be assumed to have a consistent net magnetization signal S_0 , thus SPGR images can then be conveniently fitted jointly with AFI images. The equilibrium magnetization and the dependency over the effective transverse relaxation T_2^* – minimized by using very short echo times – and additional factors such as coil sensitivity and receiver gain – is encompassed in the M_0^* term. The joint estimation is performed by the minimization of the residual sum of squares using the L-BFGS-B algorithm [43] where the figure of merit is computed as:

$$[\mathsf{T}_{1},\rho,\mathsf{B}_{1}] = \arg\min_{\mathsf{T}_{1},\mathsf{M}_{0}^{*},\kappa} \left(\sum_{i=1}^{2} \left(S_{AFIi} - \hat{S}_{AFIi} \right)^{2} + \sum_{j=1}^{M} \left(S_{SPGR,j} - \hat{S}_{SPGR,j} \right)^{2} \right)$$
(4.3)

and where S and \hat{S} represent the voxel-wise model and observed signal intensity, respectively. This approach allows to overcome the intrinsic limit provided by TR/T₁ of the original AFI method for B₁ estimation, which requires TR to be much shorter than T₁. B₁ is estimated through the computation of a map of κ values, where κ represents the proportionality constant between the provided and nominal flip angle on a voxel-wise level, whose linearity has been demonstrated in a wide range of flip angles, with higher uncertainties for low values [44, 45].

4.2.1 2D multislice AFI

AFI is a dual-TR SPGR sequence with asymmetrical TRs where the ratio *n* between TR_2 and TR_1 is normally between 3 and 6 to provide enough contrast between AFI_1 and AFI_2 signals [30]. Thus, a non-negligible part of the AFI sequence is used for T_1 relaxation and represents idle time for a 3D sequence. When used in a 2D fashion, AFI time efficiency can be optimized by acquiring multiple slices during this interval. The number of slices that can be acquired in a single repetition time depends on sequence parameters that define the shortest TR (TR_{min}), a parameter that is necessary for the design of SPGR sequences as it includes all the RF, gradient, and acquisition parts of the pulse sequence. Also, in 3D MRI scans, only spoiler gradients in the read directions can be applied as the slice direction is effectively a phase encoding direction. The implementation and use of a 2D multislice VAFI also allows to apply spoiler gradients in the slice direction. This is the most effective direction for spoiling as slice thickness is usually the biggest voxel dimension and its phase distribution is maximized [46], and the applications of spoiler gradients along this direction can make the signal to better approach the ideal steady-state value for a perfectly spoiled sequence.

To acquire multiple slices in the same batch (i.e. in the same TR_1-TR_2 time), the repetition times should be increased, with an increase of the S_{AFI1} and S_{AFI2} signals, hence leading to an improvement in terms of SNR. Then, the RF pulse and gradients for each slice in the same batch are acquired consecutively for S_{AFI1} until TR_1 is filled. S_{AFI2} for the same slices is then acquired, and a new iteration of S_{AFI1} for a new slice group is acquired only if the respective S_{AFI2} can be acquired within the end of TR_2 .

4.2.2 Slice corrected VAFI

To take into account the slice profile effects, sequence parameters and timings are used to simulate the RF and gradient profiles for AFI signals as well as for SPGR signals via numerical integration of Bloch equations. The echo time TE is assumed to be negligible with respect to T_2^* to remove the dependency of $S_{AFI1,2}$ and S_{SPGR} on the transverse relaxation. The flip angle distribution over the slice thickness is obtained and integration of the simulated profile provides an estimation for the signals received with 2D spatial encoding for AFI and SPGR. These signals are then fitted with a VAFI approach using the joint estimation of Equation 4.3 for an array of B₁ with $\kappa \in [0.70, 1.30]$ with step 0.02 and T₁ values for T₁ $\in [0.1, 5.0]$ s with step of 0.1 s, to generate a reference lookup table of simulated κ and T₁ values that reflect the effects of the slice profile ('table A'). Another table is computed as the ratio between the simulated and true T₁s ('table B') as well as the ratio between the simulated and true κ values ('table C').

The absolute difference between the voxel T_1 value and table A is computed, and the array of the positions of the minimum T_1 residuals is calculated. Then, the value of κ closest to the array of B_1 s is used together with the mean T_1 index to pinpoint the value of the correction factors in tables B and C (the mean was heuristically found to be a parameter able to provide low post-correction biases). These are then applied to the voxel T_1 and κ for slice profile correction. We report examples for κ and T_1 estimation bias as a function of the κ and T_1 arrays for $TR_1 = [100, 200]$ ms.

4.2.3 Experiments

Simulation parameters were set to TR₁ = [100, 200] ms, n = 5, TE = 3 ms, FA_{AFI} = 60°, FA_{SPGR} = [10, 20, 30, 40, 50, 60, 70, 80]°, slice thickness = 1 mm, T₁ \in [0.1, 5.0] s with step of 0.1 s, $\kappa \in$ [0.70, 1.30] with step 0.02, 3 lobes sinc pulse (bandwidth = 50 kHz). To show the robustness of the correction, an array of TR = [10, 20, 50, 100, 200, 300] ms and an array of n = [3, 4, 5, 6] for FA_{AFI} 60° and FA_{SPGR} matching the Ernst angle $\alpha_{Ernst} = \arccos(e^{-\text{TR/T}_1})$ [40] was also applied to resemble a noise-free ideal sampling case.

Experiments were performed on a 7 T MR Solutions (MR Solutions Ltd, Guildford, United Kingdom) preclinical scanner. For the study of the optimized 2D multislice AFI scheme and the VAFI slice correction, images were acquired on an ex vivo fixed rabbit brain (TR₁ = 200 ms, n = 5, TE = 3 ms, FA_{AFI} = 60°, FA_{SPGR} = [10, 20, 30, 40, 50, 60, 70, 80]°, slice thickness = 1 mm, FOV = (50x50) mm², matrix size = [128x128], 16 slices) and compared to a 3D acquisition with analogous parameters (FOV = (50x50x16) mm³, matrix size = [128x128x16]). To reduce slice cross-talk effects, an interleaved pattern for 2D multislice acquisitions was used by first acquiring odd-numbered slices and then even-numbered slices.

In order to test slice profile correction on an array of T_1 values, a 'revolver' 50 mL falcon containing vials (NMR tubes of 5 mm outer diameter) filled with aqueous cupric

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sulfate (CuSO₄) solutions of increasing concentrations (0.2, 0.4, 0.5, 0.6, 0.8, 1.0 mM and no CuSO₄ in the surrounding water) arranged in a circle was designed and made based on a previous validation study [47]. This was scanned with the gold standard Spin Echo Inversion Recovery (IRSE) with TR = 10000 ms, matrix size = [64x64], FOV = (40x40) mm², 1 slice with slice thickness = 1 mm, TI array = [50, 100, 250, 500, 750, 1000, 1250, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000] ms, as well as with a 2D and 3D VAFI (FA_{AFI} = 60°, n = 1000 ms / 200 ms = 5, 2D: matrix size = [128x128], FOV = (40x40) mm², 16 slices with slice thickness = 0.75 mm - 3D: matrix size = [128x128x16], FOV = (40x40x12) mm³). T₁ values for each vial of CuSO₄ solution and for water were then statistically analyzed via one-way analysis of variance (ANOVA) with Posthoc Tukey's honestly significant difference procedure (p<0.05) [48].

To further assess the accuracy of the slice profile correction method for VAFI, acquisition were also performed on a water phantom as well as on a fixed ex vivo rabbit head. A bulk Inversion Recovery Spin Echo with analogous spatial parameters and 15 inversion times in the [50,5000] ms interval and TR = 12000 ms was acquired as a gold reference method and fitted against an inversion recovery curve for the water phantom, while a 3D VAFI reference dataset was preferred to IRSE to reduce scan time and was acquired as a reference for the ex vivo brain. In this case, for the evaluation of the slice correction method, a manual segmentation of 4 different brain structures – parietal cerebral cortex, olfactory bulb, thalamus, and hippocampus – was performed with ITK-SNAP [49] based on an atlas reference [50], and T₁ and κ values were computed for a 3D reference as well as for the original VAFI maps and the slice corrected maps.

4.3 Results

4.3.1 2D multislice AFI

The sequence pulse diagram for a 2D AFI acquisition with the necessary input for VAFI mapping is reported in Figure 4.1.



Figure 4.1: Pulse sequence diagram for a 2D AFI acquisition.

Once the parameters defining the different components of the sequence and the timings of the pulses are known, TR_{min} can be computed. This represents the shortest time interval needed for the SPGR unit of AFI to play the RF pulse, the slice gradients (selection, refocusing, and spoiler), readout gradients (prephase, readout, and spoiler), and phase gradients (encoding and rephasing), which are in part overlapping to reduce the shortest achievable echo time. For n = 1, in each TR_1 interval, the highest amount of k-space lines in different slices that can be acquired is given by $N_{TR1} = TR_1/TR_{min}$. For n > 1, the maximum number of slices acquired in a TR_1 -TR₂ interval can be computed as

$$N_{max} = \begin{cases} \left\lfloor \frac{\mathsf{TR}_1 * (n+1)}{2\mathsf{TR}_{\min}} \right\rfloor = \left\lfloor \frac{N_{TR1} * (n+1)}{2} \right\rfloor & \text{for odd } n \\ \left\lfloor \frac{\mathsf{TR}_1 * n}{2\mathsf{TR}_{\min}} \right\rfloor = \left\lfloor \frac{N_{TR1} * n}{2} \right\rfloor & \text{for even } n \end{cases}$$
(4.4)

as TR_{min} is repeated twice for every TR_1-TR_2 time interval for each slice.

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The slices should be acquired first in TR₁ and then in TR₂. If all the slices can not be acquired during a single TR₁ repetition ($N_{TR1} < N_S \leq N_{max}$, where N_S is the total number of slices to be acquired), these are subdivided in groups of N_{max} slices acquired every 2TR₁, as shown in Figure 4.2. Whenever $N_S > N_{max}$, multiple batches will be needed for the acquisition of all the slices.



Figure 4.2: Pulse sequence diagram of AFI reporting the 2D acquisition scheme (top) and an example of optimized multislice approach for $N_{TR1} = 8$ and n = 4, leading to $N_{max} = 16$, where each boxed number represents the slice number acquired (bottom) and the box shade represent S_{AFI1} (light blue) and S_{AFI2} (light gold) for each slice. In this example, two groups of slices can be acquired within a single TR (TR₁-TR₂) in a sequential or interleaved fashion. If $N_S > N_{max}$ (eg: for 17 or more slices) then multiple scans with different batches of slices will be needed.

With respect to an equivalent conventional 3D acquisition, the time-optimized multislice 2D AFI images are acquired N_S times faster, up to a maximum of N_{max} , over which multiple batches of slices will be needed. This is done by using the idle time of TR₂ for signal excitation and acquisition.

The total acquisition time T_{tot} for a 2D AFI and M SPGR images used for VAFI fitting of B₁-corrected T₁ maps then correspond to

$$T_{tot} = T_{AFI,2D} + MT_{SPGR,2D} = = \left\lceil \frac{N_S}{N_{max}} \right\rceil * \operatorname{TR}_1(n+1)n_{pe} + \left\lceil \frac{N_S}{N_{TR1}} \right\rceil * \operatorname{TR}_1 n_{pe} = = \operatorname{TR}_1 n_{pe} \left[(n+1) \left\lceil \frac{N_S}{N_{max}} \right\rceil + \left\lceil \frac{N_S}{N_{TR1}} \right\rceil \right]$$
(4.5)

which includes the acquisition time for a 2D AFI scan $T_{AFI,2D}$ and M 2D SPGR scans T_{SPGR} , and n_{pe} represent the number of gradient steps (hence k-space lines) in the phase encoding direction.

We report an example with TR = 200 ms, n = 5, and a matrix of [128x128x16], where the conventional 3D acquisition took 40 minutes and 58 seconds, while the time-optimized 2D acquisition took 2 minutes and 34 seconds (16x faster), and the images for AFI₁ and AFI₂ are reported in Figure 4.3.



(a)

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Figure 4.3: Multislice 2D AFI images (AFI₁ (a) - AFI₂ (b)) acquired on a fixed ex vivo rabbit brain at 7 T. The acquisition of the 16 slices – with TR₁ = 200 ms, n = 5, FOV = (50x50) mm², slice thickness of 1 mm, and matrix size = [128x128] lasts 2 minutes and 34 seconds. With 8 additional SPGR images for B₁-corrected T₁ mapping, the total acquisition time was 5 minutes and 59 seconds.

4.3.2 Slice profile corrected VAFI

The Bloch equation solution for the computation of the slice profile requires the computation of the RF shape and slice gradients. As the slice profile represents the point-wise description of the signal along the slice thickness, this directly translates into a flip angle profile. An example of the flip angle profile for AFI and SPGR for 3 lobe sinc pulse is reported in Figure 4.4. It can be noticed that the flip angle distribution extends over the nominal thickness of the slice reported as vertical dashed lines, which warrants the use of an interleaved slice scheme instead of a sequential one to reduce slice cross-talk effects. Also, for this RF pulse, the flip angle distribution does not match the nominal flip angle except for the central point of the slice profile.



Figure 4.4: Example of AFI (red) and SPGR (orange) slice profile for a 3 lobe sinc pulse, for $T_1 = 1500 \text{ ms}$, TR = 100 ms, n = 5, FA_{AFI} = 60° FA_{SPGR} = 20.7° (Ernst angle). The vertical dashed lines represent the nominal 1 mm thickness of the slice.

Slice profile effects can impact the computation of B_1 and T_1 in a non-linear way, resulting in a bias that depends on both B_1 and T_1 . Figure 4.5 reports the boxplots for both B_1 and T_1 estimation bias before and after the slice profile correction for a range of repetition times and repetition time ratio n, for FA_{AFI} = 60° and FA_{SPGR} matching the Ernst angle. Median pre-correction estimation biases for B_1 show an increasing trend for increasing n as well as for increasing TR₁, ranging from -1.6% to 4.6% with mean interquartile range of 3.37%. The T₁ pre-correction estimation bias has higher variability, with median values ranging from -14.5% to -8.8% and median interquartile range of 13.95%. The application of the slice profile correction reduces this estimation bias for both B_1 and T₁, with median values for B_1 being less than 0.07% (median inter quartile range 0.26%) and T₁ less than 0.02% (median inter quartile range 0195%) with respect to the nominal values.



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Figure 4.5: Boxplots for the estimation bias for B_1 (a) and T_1 (b), expressed in percentage points, for an array of TR_1 values, before (left) and after (right) the slice profile correction. Four different repetition time ratio n were tested in the range [3,6] color-coded as red, orange, green and blue, respectively.

When looking at the specific application of the correction for $TR_1 = [100,200]$ ms, n = 5, TE = 3 ms, $FA_{AFI} = 60^\circ$, $FA_{SPGR} = [10, 20, 30, 40, 50, 60, 70, 80]^\circ$, the dependency of the bias for B_1 has a lower variability with respect to the T_1 bias pre-correction, with value of the absolute B_1 estimation bias values within 5% for most of the parameter combinations, as reported in Figure 4.6. Higher error values are found in the high range of T_1 values, while a few outliers are found for $T_1 \approx TR$ in the lower range of T_1 of the tables.



Figure 4.6: Absolute estimation bias for B_1 (left) and T_1 (right), as a function of κ and T_1 expressed in percentage points, for $TR_1 = 100$ ms (a) and $TR_1 = 200$ ms (b).

The results of the slice profile correction via correction factor are reported in Figure 4.7, which shows estimation biases within 3% for all the combinations of values for TR = 100 ms, while the range for the correction gets larger for TR = 200 ms, for both B_1 and T_1 , with higher biases for high T_1 values. Nevertheless, the slice profile correction method is able to restore the nominal T_1 and B_1 values while keeping the estimation bias in a much smaller range with respect to the uncorrected estimations.





Figure 4.7: Estimation bias for B_1 (left) and T_1 (right) after the slice profile correction for TR = 100 ms (a) and TR = 200 ms (b), expressed in percent points.

VAFI was run on a revolver phantom with increasing $CuSO_4$ concentrations, and the results for the computed T_1 for the gold standard Inversion Recovery as well as for a 3D VAFI, slice profile corrected and not corrected 2D VAFI can be found in Figure 4.8. While the T_1 values from uncorrected VAFI maps are lower than the other methods for most of the contrast concentrations, the values from slice corrected VAFI approach those of VAFI 3D and IRSE. ANOVA tests show that the four datasets do not come from the same distribution, and the pair-wise p-values for the Tukey tests are reported under the boxplots for each concentration.



Figure 4.8: An AFI₁ image of the revolver phantom reporting CuSO₄ concentrations (top), and T₁ values estimated at 7 T with Inversion Recovery Spin Echo, VAFI 3D, VAFI 2D with slice profile correction (corr) and without (uncorr). Under the boxplot are reported the matrices with p-values from pair-wise comparisons of the T₁ distributions via Tukey multiple comparison test. * = p < 0.05, ** = p < 0.01, *** = p < 0.001.

Experimental results of the slice profile correction on phantoms were compared to the T₁ values reconstructed via bulk Inversion Recovery fitting. While a water phantom provided an IR T₁ value of 2.30 s with 95% confidence interval [2.28, 2.31] s, VAFI fitting without any corrections provided an estimate of (mean \pm standard deviation) 2.16 \pm 0.32 s corresponding to -6.1% with respect to IR value, and the application of the slice profile correction provides a T₁ value of 2.31 \pm 0.33 s, +0.43% with respect to IR value. Similarly, for another tap water phantom and another scanner at a similar magnetic field, T₁ via IR was estimated to be 2.42 [2.33, 2.52] s, which was close to the value from slice profile corrected VAFI of 2.46 \pm 0.32 s (+1.7% with respect to IR value) with respect to the uncorrected T₁ value for VAFI of 2.29 \pm 0.31 s (-5.4%).

The analysis of T₁ values in a fixed rabbit brain provides mean (± standard deviation) values for the original 2D multislice dataset, the corrected dataset, and the 3D reference to be 705 ± 51, 711 ± 47, and 713 ± 27 ms for the parietal cerebral cortex, 668 ± 60, 673 ± 58, and 688 ± 55 ms for the olfactory bulb, 691 ± 32, 700 ± 29, and 718 ± 39 ms for the thalamus, and 728 ± 43, 732 ± 39, 749 ± 37 ms for the hippocampus, showing

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that all of the segmented brain structures better approach the values provided by the 3D reference when the slice profile correction is applied. The normalized κ values for the B₁ field also improve in the same way: 0.85 \pm 0.03, 0.82 \pm 0.03, and 0.79 \pm 0.06 ms for the parietal cerebral cortex, 0.81 \pm 0.03, 0.78 \pm 0.07, and 0.69 \pm 0.05 ms for the olfactory bulb, 0.86 \pm 0.02, 0.83 \pm 0.01, and 0.76 \pm 0.06 ms for the thalamus, and 0.86 \pm 0.01, 0.83 \pm 0.01, and 0.80 \pm 0.06 ms for the hippocampus, as reported in Figure 4.9.



Figure 4.9: T_1 (top row) and κ (bottom row) values estimated at 7 T with VAFI 3D, VAFI 2D with slice profile correction (corr) and without (uncorr) for segmentations of the parietal cerebral cortex, olfactory bulb, thalamus and hippocampus for a fixed rabbit brain.

Examples of an AFI₁ image for the fixed rabbit brain, as well as the reconstructed and slice profile corrected T_1 and B_1 are reported in Figure 4.10. The SNR computed as mean value of the foreground over the standard deviation of the background for AFI₁ provides a value of 203 for the 2D multislice dataset and 205 for the 3D dataset acquired with analogous sequence parameters.



Figure 4.10: Example of AFI_1 image (a), T_1 (b - top) and B_1 (b - bottom) maps after slice profile correction for a fixed rabbit brain scanned at 7 T.

4.4 Discussion

Multislice AFI can be used to acquire high resolution images for accurate B_1 and T_1 mapping while removing the waiting time in conventional 3D AFI. We have presented an approach for multislice AFI, much faster than the corresponding 3D conventional one, where the maximum number of individual k-space lines in different slices that can be acquired in a single TR_1 - TR_2 interval is a function of the sequence parameters such as the repetition times and the minimum achievable repetition time TR_{min} of the SPGR unit of AFI. Specifically, the maximum amount of slices that can be acquired using a single batch (group of slices) is N_{max} , a value corresponding to half the ratio between the total AFI repetition time TR_1 + TR_2 and TR_{min} for an odd number of slices. This approach allows to sample AFI images in a time-efficient manner, speeding up the acquisition up to N_{max} times. However, an important limitation of this approach is the considerable increase in the gradient and RF duty cycles, which translates into a higher specific ab-

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sorption rate. The temperature of the patient (or phantom) in the field of view should be monitored and kept constant during the acquisition of images for T_1 mapping, as T_1 is a temperature-dependent parameter [51]. This becomes critical in AFI and SPGR acquisitions, especially for short TR and TR_{min}, when the duty cycle of the scanner is high and strong spoiler gradients are applied to acquire a spoiled signal close to the ideal steady state. Also, in preclinical imaging, the gradients are placed in higher proximity to the subject than in clinical scanners, and the temperatures of the gradients need to be monitored and kept constant while scanning for accurate T_1 mapping.

The slice profile correction of VAFI can then provide an environment to exploit multislice AFI for multiparametric quantitative mapping. We have shown how the slice profile introduces a non-negligible bias in the T_1 and B_1 values fitted with a VAFI approach on 2D images, and how a slice profile correction based on simulated data can restore unbiased parameters. Simulations on a wide array of T_1 and κ values have shown the robustness of the approach, which was backed by experimental data on phantoms and ex vivo tissues. Using the multislice AFI approach and the slice profile correction method, we reconstructed accurate B_1 -corrected T_1 maps on 16 slices to cover the full volume of interest with a matrix size of [128x128] acquired under 6 minutes of total scan time, with the AFI portion of it lasting less than 3 minutes. It should be recalled that the acquisition of 2D multislice AFI images should not be used as a standalone to compute B_1 maps unless the TR \ll T₁ condition for both AFI repetition times is respected. This is because the long repetition times used in AFI (especially for AFI_2 , which is n times longer TR₁) can directly contradict the AFI assumption for which TR should be much shorter than the maximum expected T_1 in the scanned FOV. Instead, 2D multislice AFI should be integrated into a VAFI approach, which provides both T₁ and B₁ maps and does not rely on the TR \ll T₁ assumption.

Ideally, a T₁- and B₁-specific correction for each voxel of the imaged volume should be performed as the correction factor slightly varies as a function of T₁ and B₁ as seen in Figure 4.7. The correction of the slice profile effects using an approximation of κ and the average index for minimizing the distance between the simulated and the reconstructed T₁ represent a suboptimal solution in terms of estimation accuracy. However, this minimization is an underdetermined analytical issue, and the constraint applied to T₁ to compute the average value represents a reasonable trade-off as it still takes into account the effects of slice profiles and we have proved that the correction for a wide array of T₁ and B₁ values is able to considerably reduce the median estimation bias from [-14.5%,-8.8%] to less than 0.02% for T₁ and from [-1.6%,4.6%] to less than 0.07% for B₁. We reported results on an array of aqueous solutions of cupric sulfate, where T₁ values comparable to IRSE values for all cases and approach VAFI 3D values, confirming how the slice profile correction improves the accuracy of 2D VAFI. Similar conclusions can be drawn for water phantoms and an ex vivo study, which could pave the way to a faster and accurate 2D multislice T_1 mapping. Interestingly, it can be observed that two water phantom scanned with different 7 T systems provide slightly different T_1 values, which could be due to the effect of uncontrolled factors such as temperature and composition of tap water. A study of the robustness of this slice profile correction with respect to the amplitude of background noise should be performed, and the stability of the approach should be expected to improve for longer repetition times, higher n values, and an optimized set of flip angles.

Both the AFI 2D multislice approach and the slice profile effect correction could be employed in other techniques based on multi-TR sequences. For example, this approach can be extended to EPI versions of the VAFI method, EPIFANI [52], which uses long repetition times to fit the EPI k-space acquisition and would then benefit from an interleaved acquisition scheme to further reduce total scan time.

4.5 Conclusion

Multislice 2D AFI is a time-efficient approach for the acquisition of high resolution images for B_1 and T_1 mapping with VAFI. As different slices in multi-TR sequences can not be acquired in a straight-forward sequential interleaved fashion, we proposed a new method for stacking the signal acquisition compactly, with a considerable time advantage with respect to 3D scans. Besides, 2D mapping approaches require to consider the effects of slice profiles and we presented a correction technique for VAFI based on lookup tables computed on the sequence parameters, and we showed how this restores unbiased B_1 and T_1 estimations comparable to reference 3D scans.

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Chapter 5 Simultaneous T₁, B₁, and T₂^{*} mapping with RAMSES, Relaxation Alternate Mapping of Spoiled Echo Signals

Parts of the work in this chapter were presented as an abstract [1] for the 2021 ESMRMB Annual Scientific Meeting.

5.1 Introduction

MR relaxometry has seen increasing interest during the last decades since parameters such as T_1 and T_2^* have been investigated as possible biomarkers in a variety of pathopathological conditions. For example, T₁ is being used to assess cortical myelin for studies on development and aging [2, 3], Parkinson's disease, and brain cancers as well as the radiation-induced toxicities while T₂^{*} can be used as a surrogate measure to identify regions of increased T₂ such as stroke and edematous areas [4], and the correlation between T_2^* and iron overload had been studied in intracranial hemorrhage [5], beta thalassemia major [6], and as a starting point of myelin water fraction mapping [7]. Although providing different information on relaxation properties, both T_1 and T_2^* have been used as versatile biomarkers for the investigation of stroke, multiple sclerosis, as well as for studying the pathogenesis and the evolution of neurodegenerative diseases, tumor identification and characterization, inflammation and demyelination processes [8, 9, 10]. Traditionally, at least two independent scans are acquired for a multiparametric estimation, and the images may then need to be co-registered. A joint multiparametric mapping of T_1 and T_2^* can help avoid this issue, as well as reduce scan time and provide further insights for the investigation of brain composition. Sequences like QRAPTEST [11] and MP2RAGEME [12] have been suggested for fast simultaneous quantification. These are both based on a Look-Locker approach and, unfortunately, are not free from limitations: for example, while QRAPTEST is very sensitive to the flip angle used and can be performed only with very small flip angles, MP2RAGEME shows intrinChapter 5. Simultaneous $T_1, B_1,$ and T_2^{\ast} mapping with RAMSES, Relaxation Alternate Mapping of Spoiled Echo Signals

sic B_1 sensitivity. One of the main issues in T_1 mapping is indeed the requirement to account for the excitation field B_1 , whose inhomogeneities could hinder accuracy in T_1 estimation, especially at high magnetic field [13].

Acquisition time efficiency – as well as accuracy and precision in subsequent parameter quantification – represents the targets of any parameter estimation, hence a fast sequence for B₁-corrected T₁ and T^{*}₂ estimation is required. Among the proposed sequences for multiparametric mapping, Variable Flip angle with Actual Flip angle Imaging (VAFI) [14] uses Actual Flip angle Imaging (AFI) [15], a dual-TR gradient echo sequence with two asymmetrical repetition times, and Spoiled Gradient echo (SPGR) acquisitions. 3D AFI and SPGR scans are acquired and then used to map B₁ and T₁ simultaneously thanks to the different steady-state values reached during TR₁ and TR₂, while a good part of TR₂ remains unused for signal acquisition although still needed to provide image contrast. The asymmetry of the repetition times could allow us to accommodate a multi-gradient echo readout to sample the T^{*}₂ signal decay when TR₂ is sufficiently long.

Here, we propose the Relaxation Alternate Mapping of Spoiled Echo Signals sequence (RAMSES) for simultaneous T_1 , T_2^* , and B_1 mapping by the application of a bipolar multi-gradient echo readout to the AFI sequence and by the acquisition of at least a spoiled gradient echo (SPGR) image. Indeed, as part of TR₂ is generally unused and hosts relaxation-induced signal decay, this could be sampled via multi-gradient echo readout without any time penalty. T_1 and T_2^* can be independently estimated from different subsets of the acquired echoes.

5.2 Materials and Methods

Among the proposed sequences for B₁ mapping, Actual Flip angle Imaging (AFI) [15] stands out to be a low-SAR [16] gradient echo based sequence that implements two repetition times ($TR_2 = n \cdot TR_1$, with n > 1) to sample each k-space line in two different steady states. When at least a spoiled gradient echo (SPGR) acquisition is also performed, the Variable flip angle with Actual Flip angle Imaging (VAFI) [14] approach can be used to map T₁, B₁, and the equilibrium magnetization M^{*}₀ via a multiparametric fitting, where the latter term includes T^{*}₂ effects. The majority of TR₂ is idle time, and since *n* determines the contrast as well as the accuracy of AFI B₁ estimations, TR₂ can span from a few tens to a few hundreds of milliseconds per TR, which represents idle time for the scanner. We developed the RAMSES sequence starting from AFI, including a multi-gradient echo readout following the RF excitation in TR₂ to sample the T^{*}₂ relaxation-induced signal decay.

For the first two signals acquired, the signal acquired with RAMSES can be analytically expressed as

$$S_{R1,2} = S_0 \sin(\kappa \alpha) \cdot \frac{1 - E_{2,1} + (1 - E_{1,2})E_{2,1}\cos(\kappa \alpha)}{1 - E_1 E_2 \cos^2(\kappa \alpha)} \exp(-\mathsf{TE}/\mathsf{T}_2^*)$$
(5.1)

as derived from Bloch equations for AFI, where S_0 represents the net magnetization signal directly proportional to the proton density, $E_{1,2} = \exp(-\text{TR}_{1,2}/\text{T}_1)$ with the subscripts 1 and 2 representing the respective repetition times, and κ represents the flip angle scaling factor, that is the voxel-wise B₁ field value normalized by the nominal flip angle. The application of a multi-gradient echo readout after S_{R2} will then result in a T₂^{*} decay of the signal starting from the steady-state value reached in TR₂, which can expressed as

$$S_{Ri} = S_2 \sin(\kappa \alpha) \exp(-\mathsf{TE}_i/\mathsf{T}_2^*) \quad \text{for} \quad i \ge 3.$$
(5.2)

Unless slice profile effects are taken into account, RAMSES should be employed as a 3D technique, making sure to employ sufficient gradient spoiling at the end of the acquisition in TR_1 and TR_2 .

5.2.1 T₁ and B₁ estimation

The estimation of T_1 is performed via voxel-wise fitting of the signal from the first two echoes of the RAMSES signal and the signal from at least a SPGR signal, according to the method proposed by Hurley used for VAFI [14]. T_1 and B_1 are estimated together with the equilibrium magnetization M_0^* to take into account the inhomogeneities of the excitation field: a L-BFGS-B algorithm [17] for bound constrained minimization was employed in the fitting procedure for both simulations and experimental data ($T_1 \in [1,10]$ s, starting value 2 s; $M_0^* \in [1,1e9]$ a.u., starting value 5e6 a.u.; $\kappa \in [0.7,1.2]$, starting value 1.0) aimed at minimizing the following figure of merit:

$$[\mathbf{T}_{1}, M_{0}^{*}, \kappa] = \underset{\mathbf{T}_{1}, M_{0}^{*}, \kappa}{\arg\min\left(\sum_{i=1}^{2} \left(S_{R_{i}} - \hat{S}_{R_{i}}\right)^{2} + \sum_{i=1}^{M} \left(S_{S, i} - \hat{S}_{S, i}\right)^{2}\right)}, \quad (5.3)$$

where M is the number of the SPGR signals, S_R and S_S represent the observed voxelwise signal intensities for RAMSES and SPGR signals, and \hat{S} represents the respective value of the signal model. We assume that the echo time is negligible with respect to T_2^* (TE $\ll T_2^*$), which allows us to remove the T_2^* dependency for the T_1 estimation. After a first estimation of the parameters is completed, the B₁ map is smoothed via a median filter (3 voxels, isotropic) which makes the map to better represent the excitation field as the B_1 field is slowly changing in space, and the estimation of T_1 and M_0^* is performed again while B_1 is used as an input.

5.2.2 T_2^* estimation

 T_2^* provides a quantitative measure of the transverse magnetization and the dephasing caused by all field inhomogeneities. Multi-gradient echo sequences are employed as references for T_2^* estimation - for both single and multicompartmental applications on a wide range of values.

In a refocused, perfectly spoiled, multi-gradient echo sequence, T_2^* can be computed by fitting an exponential decay to the signal intensity. Assuming that the signal can be described by a single T_2^* component, the acquired signal S_i at echo time TE_i can be expressed as

$$S_i = S_0 \exp(-\mathsf{TE}_i/\mathsf{T}_2^*) + \nu_i$$
 (5.4)

where S_0 is the apparent relative proton density and ν is additive noise from a Gaussian distribution. Fitting was performed via a linear least-square estimation following log-transformation, considering $S_0 = S_{R2}$. To avoid the bias in the estimation of T_2^* values, the signal at the latest echoes was visually checked and truncated from the fitting procedure when it approached low SNR (level of background noise).

Considering the short duration of T_2^* decay, especially at high fields where the inhomogeneity term becomes prevalent, the echo train acquisition is usually designed to sample the MR signal as fast as possible, employing the shortest possible first echo time and inter-echo time as well. Thus, high receiver bandwidth is a common feature in T_2^* multi-gradient echo imaging.

5.2.3 Experiments

RAMSES was developed as an RF-spoiled SPGR-based sequence and tested at 4.7 T and 7 T with an MRI preclinical scanner (MR Solutions, Guildford, UK).

We performed sequence simulations via Extended Phase Graph model [18] in order to define the spoiling increment to be used for TR₁ = [20, 40, 100, 200] ms, n = 5, T₁ \in [0.5, 4.5] s, T₂ \in [0.1, 1] s, $D \in$ [0, 0.002] mm²/s, flip angle $\alpha = 60^{\circ}$. RF phase for the j-th pulse was incremented as $\phi_j = \phi_{j-1} + j\phi_0$ according to a popular RF phase cycling scheme [19].

 T_1 and T_2^* of gelatin phantom and Gd-DOTA water solutions (Dotarem, Guerbet, Villepinte, FR) were investigated at 4.7 T and 7 T. Ground truth values were estimated based on MRI data acquisition using a 22-points Inversion Recovery (TR = 10 s, TI \in

[0.075, 3.5] s) and a multi-gradient echo (MGE) with bipolar readout (TR = 20 ms, α = 60°, TE₁ = 2.19 ms, Δ TE = 1.24 ms, 6 echoes), and literature values for T₁ were reported [20, 21]. RAMSES data were acquired with matrix size = [128×128×64], FOV = (40×40×40) mm³, TR₁ = 20 ms, n = 4, TE = 2.19 ms, Δ TE = 1.24 ms, 5 echoes, read direction only spoiling gradient areas for TR₁ and TR₂ = 327.1/1414.7 mT·ms/m. SPGR images were acquired with the same parameters, with α = [5,14,24]°, for a total of M = 3 volumes.

A fixed rat head phantom was scanned to acquire RAMSES, AFI, MGE and SPGR images both in a 2D multislice and a 3D fashion, maintaining the same parameters for a better comparison: TR₁ = 40 ms, n = 5, TE₁ = 3.13 ms, Δ TE = 2.72 ms, 9 echoes, $\alpha =$ 60° , matrix size = $[128 \times 128 \times 16]$, FOV = $(50 \times 50 \times 12)$ mm³ for 3D acquisition and matrix size = $[128 \times 128]$, FOV = $(50 \times 50)^2$ with 16 slices and slice thickness 0.75 mm for multislice 2D acquisitions. Total acquisition time for RAMSES and AFI acquisitions was 8:12 minutes, while for MGE this was 6:50 minutes and for 8 SPGR scans (FA array = [10, 20, 30, 40, 50, 60, 70, 80]°) it was 10:55 minutes. An analogous 2D single slice and 3D acquisition in vivo was performed on a mouse brain with TR₁ = 200 ms.

Values are reported as mean \pm standard deviation unless otherwise stated.

5.3 Results

Figure 5.1 shows the pulse diagram for RAMSES and its implementation as either a 2D or a 3D sequence. In 3D, rephasing gradients are found in both phase encoding directions, while for 2D sequences, the slice rephasing gradient at the end of the acquisition is substituted by a spoiling gradient. A bipolar multi-gradient echo scheme is found in TR_2 .

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Figure 5.1: RAMSES pulse sequence diagram and representation of the required inputs for parameter estimation. The diagram shows the two SPGR units of RAMSES with asymmetric TR, with a single echo acquisition during TR_1 and a multi-gradient echo acquisition during TR_2 , and an example of the respective magnitude signals intensities. For 3D RAMSES, phase gradient rewinders are placed at the end of the acquisition for both the phase encoding directions, while a spoiler gradient is found in the readout direction.

The total acquisition time T_{tot} for a single RAMSES scan (NEX = 1) will then correspond to

$$T_{tot} = T_{AFI} + MT_{SPGR} = \mathsf{TR}_1(n+1)n_{pe,1}n_{pe,2} + M\mathsf{TR}_1n_{pe,1}n_{pe,2} =$$
$$= \mathsf{TR}_1n_{pe,1}n_{pe,2}(n+M+1)$$
(5.5)

which includes the acquisition time for an AFI scan T_{AFI} and M SPGR scans T_{SPGR} , where $n_{pe,1}$ and $n_{pe,2}$ represent the number of gradient steps (hence k-space lines) in the first and the second phase encoding direction, respectively.

RF spoiling characteristics for RAMSES follow the behavior of AFI sequence, with a period of 180° and symmetry around 90° , so we chose the RF spoiling characteristic

phase increment $\phi_0 = 30^\circ$, which both minimizes the median and the range of the absolute distance between the simulated signal and the ideally spoiled steady-state signal for S_{R1} and S_{R2} as reported in Figure 5.2 and Figure 5.3, respectively. This phase increment represents a compromise for the array of repetition times investigated, which show median values closer to the ideal steady state to vary in the [20,40]° range, with increasing TR resulting in increasing optimal phase increment. This is particularly important for short TR, fast 3D sequences, as spoiling gradients can be limited in both amplitude and duration and they are only applied along the readout direction.



Figure 5.2: Spoiling features for signal S_{R1} of RAMSES (continuous line) compared to AFI₁ (dashed line) represented by the distance between the simulated signal and the ideal steady-state signal represented by the dashed line at zero. The three lines for each sequence represent the 5th percentile, median, and 95th of the distribution for the array of T₁, T₂ and diffusion coefficients. A zoomed-in section of the plot is reported for RF increment in the range [20,40]° for TR₁ = [20, 40, 100, 200] ms.

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Figure 5.3: Spoiling features for signal S_{R2} of RAMSES compared to AFI₂. See caption of Figure 5.2 for details.

Full 3D RAMSES volumes with three additional SPGR volumes were acquired on a gelatin and Gd-DOTA water solutions phantom with a total acquisition time of 22 minutes and no additional time with respect to AFI and SPGR acquisitions in the VAFI method. Mean and standard error for T_1 and T_2^* estimates from RAMSES on phantoms are reported in Figure 5.4 and compared to IR and MGE values, respectively. T_1 literature values for similar Gd concentrations are reported as well. T_1 values show an underestimation with respect to the ground truth values, with relative difference lower than 10% except for the sample concentration 12.5 mM. T_2^* values report relative differences lower than 8%.

	T ₁				T ₂ *		
	mean (SE) [ms]				mean (SE) [ms]		
Sample [B0]	RAMSES	IR	relative difference (%)	literature values	RAMSES	MGE	relative difference (%)
gelatin [4.7T]	2448 (273)	2481(2)	1.3	-	31.6(5)	31.5 (5)	0.3
Gd-DOPA 0.7mM [7T]	364 (35)	367 (<1)	0.8	444-590	207 (53)	224 (51)	7.6
1.5 mM [7T]	207 (23)	213 (<1)	2.8	207-275	157 (47)	163 (37)	3.7
3.1 mM [7T]	114 (18)	125 (<1)	8.8	100-133	68 (14)	67 (11)	1.5
6.3 mM [7T]	83 (13)	91(<1)	8.8	49-66	37 (5)	37 (5)	0.0
12.5 mM [7T]	36(6)	25 (<1)	44.0	25-33	13(2)	14(3)	7.1

Figure 5.4: Estimated T_1 and T_2^* mean and standard error values of the phantoms (gelatin and Gd-DOPA solutions) for RAMSES and their relative ground truth estimated via Inversion Recovery for T_1 and multi-echo gradient echo for T_2^* .

Examples for RAMSES images acquired in vivo on a mouse head are reported in Figure 5.5. It can be noticed how increasing *i* number results in decreasing signal intensity and how the signal close to tissue interfaces (and especially close to the air-body boundaries) decays faster due to susceptibility differences than for other areas of the region of interest such as deep brain structures. In this case, the first two images, together with the SPGR images, were used to fit a T₁ and κ map via Equation, while all the volumes but the first one were used to reconstruct a T₂^{*} maps. All the maps reconstructed with RAMSES and their respective references acquired with VAFI and MGE are reported in Figure 5.6, which show good agreement between the two with overall median differences of 7.08% for T₂^{*}, -2.81% for T₁, and 1.06% for κ computed over the whole mouse brain. Chapter 5. Simultaneous T_1 , B_1 , and T_2^* mapping with RAMSES, Relaxation Alternate Mapping of Spoiled Echo Signals



(a)



(b)

Figure 5.5: Examples of RAMSES images representing 12 central slices of a mouse head (a), and the S_{Ri} signal with $i \in [1, 10]$, for TR₁ = 200 ms, n = 5, 9 echoes (*i* increases from left to right, top to bottom) for a central slice of the 3D volume acquired (b).



Figure 5.6: Example of estimated T_1 , T_2^* and κ maps acquired with RAMSES at 7 T on a mouse head (right) and reference images (left) for the same parameters acquired with VAFI and MGE fitting.

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In 3D ex vivo scans, values for T₁ in the cerebral cortex and thalamus were 1007 \pm 145 ms and 1053 \pm 88 ms for VAFI while RAMSES values for the same tissues were 967 \pm 148 ms (-3.97%) and 990 \pm 77 ms (-5.98%), respectively. From RAMSES multi-gradient echo readout, T^{*}₂ values were 21.48 \pm 5.53 ms and 19.61 \pm 3.33 ms for cerebral cortex and thalamus, respectively, while MGE T^{*}₂ values were 21.99 \pm 5.95 ms and 20.18 \pm 2.79 ms, respectively, leading to underestimations in the order of -2.32% and -2.82% in terms of relative difference. Similar results were found for 2D RAMSES, with T₁ of 860 \pm 76 and 922 \pm 102 ms compared to VAFI values of 954 \pm 88 and 1046 \pm 130 ms, leading to -9.85% and -11.85% for RAMSES with respect to 2D VAFI, and -14.60% and -12.44% with respect to the reference 3D VAFI results. T^{*}₂ values were 18.51 \pm 3.62 ms and 18.37 \pm 1.40 ms for MGE, and 18.38 \pm 3.75 ms and 18.18 \pm 1.47 ms for RAMSES, -0.71% and -1.03% with respect to 2D MGE, and -16.42% and -7.29% with respect to 3D, respectively.

5.4 Discussion

We introduced RAMSES, a new dual-TR multi-gradient echo sequence for quantitative relaxometry mapping which, in combination with at least one SPGR acquisition, is able to provide accurate T_1 , T_2^* , and B_1 maps. This sequence stems from the AFI and VAFI method, adding a multi-echo readout to a part of the sequence that would otherwise only host T_1 recovery and T_2 decay and represent idle time for the scanner.

RAMSES is a steady-state technique, and as such, it requires spoiling characteristics to be carefully taken into account to avoid ghost artifacts and biases from the ideal steady state which may arise when a completely spoiled regime is not reached. We have determined an optimal RF phase increment around 30° with two fixed parameters – namely the flip angle of 60° and n = 5 used to guarantee enough contrast between the first two signals – and over arrays of repetition times, T_1 , T_2 and diffusion coefficients that can be implemented for future quantitative studies with RAMSES. However, should the fixed parameters need to be changed, Bloch simulations and the search for optimal RF features need to be performed anew, especially when strong spoiler gradients can not be employed and short repetition times are needed.

 T_1 and T_2^* values with RAMSES for gelatin and doped water solutions approach the reference values provided by the gold standard methods (inversion recovery and multigradient echo, respectively), and mean and standard errors for both parameters are comparable to ground truth values with relative differences within 10% for most of the samples, and with similar T_1 values with respect to the one found in scientific literature. The only exception is given by the sample doped with the highest Gadolinium concentration, and we assume this to be likely due to the violation of the $T_2^* \gg TE$ assumption of RAMSES which results in a higher estimation bias.

The results obtained ex vivo and in vivo on mouse heads further validate the accuracy of RAMSES: in ex vivo scans, a smaller bias (around 2-3%) for the estimation of T_2^* was found when compared to MGE results, with respect to T_1 results that had a mean bias of 4-6% with respect to VAFI. In vivo data show a similar trend, with a small overestimation of T_2^* and a slight underestimation of T_1 . As absolute differences are well within 10%, we have shown that RAMSES allows accurate and precise estimation of both T_1 and T_2^* for a range of values at high magnetic field where B_1 inhomogeneities can result in variations of the flip angle amplitude exceeding 40% of the nominal value. Although RAMSES is an extension of AFI used as a 3D sequence, a 2D application was also tested and provided comparable results to its 3D counterpart, but with higher biases (between -7% and -15%) with respect to the reference maps for both T_1 and T_2^* . Indeed, when RAMSES is used as a 2D mapping sequence, slice profile effects should be investigated to improve the accuracy of the estimation.

We have introduced RAMSES, studied the spoiling properties, and validated this approach in experiments, but this study is certainly not free from limitations and possible improvements. First, as T_2^* effects are encompassed in the equilibrium magnetization term M_0^* of the T_1 estimation, RAMSES could be used to remove this dependency just by performing a voxel-wise division of M_0^* and T_2^* . Further study and a possible computation of the equilibrium magnetization based on M_0^* and T_2^* maps should be integrated to disentangle the former from the latter. Also, the impact of T_2^* values on the T_1 computation needs to be investigated, as the RAMSES assumption of a negligible TE with respect to the longitudinal relaxation time might not always be respected. Other joint estimations of T_1 and T_2^* might be investigated as well instead of using two separate fitting steps.

RAMSES could also be used to fit T_2^* values with multiexponential models, as a number of samples can be acquired during the T_2^* decay. In case of multicompartmental analysis, the application of multiexponential decay models should be studied to estimate T_2^* for different tissues or species (such as intra- and extra-cellular water).

Also, correlation studies between RAMSES and previously published multiparametric approaches should be performed to compare their performance over a broad array of T_1 , T_2^* and B_1 values, and to investigate the use of RAMSES for low iron content quantification. On top of this, the optimal number of echoes acquired during the multi-gradient echo module of RAMSES should be studied, as noisy echoes can bias the T_2^* estimation when performed via linear least-square post log-transformation, or weighted estimation approaches could be used as an alternative.

Besides T_1 and T_2^* estimation, the multi-gradient echo images acquired in RAMSES can also be used to extract information about susceptibility differences. Susceptibility differences between tissues and air-tissue interfaces generate macroscopic variations in the static field which result in intravoxel field gradients enhancing signal decay [22, 23]. This affect T_2^* quantification, as these gradients cause an additional signal loss as a function of the magnitude of the gradients relative to the voxel dimensions. For this reason, in order to provide an accurate estimation of T_2^* , susceptibility-induced field effects need to be taken into account, either prospectively (relying on shimming and tailored excitation pulses [24]) or retrospectively (via B_0 estimation through two gradient echo phase images acquired at different TEs [25]). In particular, the retrospective correction of susceptibility effects in RAMSES would bridge the gap between this and a Quantitative Susceptibility Mapping approach.

To conclude, future studies should focus on parameter optimization as well as in the investigation and correction of the slice profile effects in RAMSES, and in the investigation of QSM mapping in 2D multislice RAMSES as recently new 2D QSM multislice sequences have been developed [26]. However, for multislice sequences, in-plane contributions of the susceptibility effects due to intravoxel gradients are often neglected as the effect is predominant in the through-plane direction, as slice thickness is typically much larger than the in-plane voxel dimensions. For this reason, a comparison between the susceptibility effects rising in a 2D multislice and 3D version of RAMSES should also be performed.

5.5 Conclusion

We proposed RAMSES, a time-efficient 3D multi-echo gradient echo sequence for accurate B_1 , T_1 , and T_2^* mapping based on the VAFI and MGE approaches. The spoiling characteristics for RAMSES were studied, and the sequence was validated in phantom studies, as well as in ex vivo and in vivo.

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Chapter 6 Introducing EPIFANI: an ultrafast T₁ and B₁ mapping technique

Parts of the work in this chapter were presented as an abstract [1] for the 2022 Annual Meeting and Exhibit, as well as in 'A preparation pulse for fast steady state approach in Actual Flip angle Imaging' [2], and are in preparation for submission as a research paper to Magnetic Resonance in Medicine.

6.1 Introduction

MRI quantitative maps allow a non-invasive tissue characterization, and enable the identification of discriminant pathophysiological features, as well as the quantification and potential early detection of diseases, and the study of multiple parameters simultaneously [3, 4, 5, 6, 7]. However, the variability in acquisition and post-processing techniques and physical and technical constraints in MRI make fast and accurate relaxometry mapping challenging [8, 9]. In particular, T₁ has been investigated as a potential biomarker in neuroradiology for the study of neurodegenerative diseases, as well as tumor characterization and identification, which has promoted the development of T₁ mapping techniques in the last few decades. Nevertheless, T₁ mapping is still not widely used in clinical imaging protocols mainly due to long scanning times, lack of standardization, and calibration sensitivity [10, 11]. For example, knowledge of the excitation field B₁ is of cardinal importance for quantitative imaging at high magnetic field [12], as inhomogeneities in the excitation field are to be expected and cause an unequal tissue excitation, but this is often overlooked [13].

Yet, the development of ultrafast approaches for accurate T_1 mapping represents a hot research topic and this could promote the use of quantitative MRI as a clinical tool. Very few implementations of ultrafast T_1 mapping have been proposed so far, and they mainly rely on the use of parallel imaging, or the development of new sequences including either dictionary-based approaches or fast readout schemes. Examples of ultrafast T_1 approaches include 3D-EPTI [14], RUFIS VFA [15], U-FLARE [16]. While a dictionarybased approach such as 3D-EPTI exploits parallel imaging thus depending on the availability of phased-array RF coils, RUFIS relies on the acquisition of a stand-alone B₁ map through a silent magnetization prepared map acquisition, and U-FLARE is a relatively slow single-slice technique. Other options based on fast 3D Look-Locker (LL) [17], LL-EPI [18], and LL-spiral readout [19] are sensitive to B₁ heterogeneity and to pulse imperfections, in both the inversion and the excitation pulses, thus requiring the acquisition of a B₁ map for correction. Slice profile effects for 2D acquisitions and EPI characteristics and main challenges such as sensitivity to magnetic field inhomogeneities, low SNR, and chemical shift artifacts have limited EPI applicability in developing ultrafast mapping approaches. Other main EPI pitfalls including geometric distortions, signal void/pile-up, and Nyquist ghosting [20] can affect EPI as well, while T^{*}₂ decay provides a non-uniform weighting of the echoes acquired during the zig-zag traversal of k-space.

However, a method that can be adapted to acquire k-space with an EPI readout is the Variable flip angle with Actual Flip angle Imaging (VAFI) [21], a fast and low-SAR joint T₁ and B₁ mapping technique which relies on the acquisition and fitting of Actual Flip angle Imaging (AFI) [22] and spoiled gradient echo signals. Although originally presented as a method for 3D acquisitions, AFI can be adapted to sample the k-space in a 2D fashion by the application of a slice correction technique [23]. The development of a 2D EPI-AFI approach could then provide standalone B₁ maps through an AFI approach when the repetition time can be kept short enough to respect the original assumption of AFI (TR \ll T₁). This could also be applied to perform simultaneous mapping of T₁, B₁, and T₂^{*}-reduced equilibrium magnetization M₀^{*} with a VAFI approach when at least a conventional gradient echo GRE-EPI is acquired.

Here we introduce a 2D EPI implementation of VAFI called Echo Planar Imaging Fast Actual Nutation Imaging (EPIFANI) with both a single-shot and a multi-shot fashion, first presented in a recent abstract [24]. A slice profile correction technique was integrated in the computation of the reconstructed B₁ maps and compared in terms of accuracy and precision to the results obtained without any corrections applied. We also apply EPIFANI for ultrafast simultaneous B₁ and T₁ mapping. The application of EPIFANI allows the acquisition of images for the online reconstruction of quantitative maps, providing high acquisition efficiency to a multiparametric scan. We report simulations to validate the method including T^{*}₂ decay effects, as well as phantom, ex vivo and in vivo results at high magnetic field.

6.2 Materials and Methods

EPIFANI was developed including a 2D EPI readout to acquire data from both an AFI and GRE sequence (Figure 6.1).

As the signal excitation is analogous to the AFI one, the value of steady-state signals $S_{A1,2}$ in EPIFANI is unchanged [22]. These can be derived by solving the Bloch equations for a sequence with asymmetric repetition times:

$$S_{A1,2} = \mathsf{M}_0 \sin \alpha \cdot \frac{1 - E_{2,1} + (1 - E_{1,2})E_{2,1}\cos \alpha}{1 - E_1 E_2 \cos^2 \alpha} \exp(-\mathsf{TE}/\mathsf{T}_2^*) \tag{6.1}$$

where M_0 represents the net magnetization signal, α represents the flip angle, $E_{1,2} = \exp(-TR_{1,2}/T_1)$, *n* represent the ratio between TR₂ and TR₁, and the subscripts 1 and 2 represent the respective repetition times. With respect to a Cartesian readout, the effects of T₂^{*} is expected to impact the EPI acquisition and reconstructed images, and its effects need to be investigated.

The stand-alone computation of B_1 maps in EPIFANI assumes that $TR_{1,2} \ll T_1$ for which $E_{1,2}$ can be approximated by 1, so that the flip angle can be computed with a "direct" approach as

$$\alpha \approx \arccos \frac{S_{A2}/S_{A1} \cdot n - 1}{n - S_{A2}/S_{A1}} \quad . \tag{6.2}$$

When n = 1 and the sequence plays with symmetric repetition times, this becomes a conventional GRE-EPI and the SS signal is the degenerate well-known solution

$$S_B = M_0 \sin \alpha \cdot \frac{1 - E_1}{1 - E_1 \cos \alpha} \exp(-\text{TE}/\text{T}_2^*)$$
 . (6.3)

Hurley described the VAFI method for the joint estimation of B_1 , T_1 and steadystate magnetization M_0^* by a least-square fit of one AFI and an arbitrary number of SPGR acquisitions overcoming the intrinsic T_1 /TR limitation of the original AFI method [21].

This method uses a simultaneous voxel-wise fitting and requires a minimum of 3 values, provided by AFI₁, AFI₂ and GRE-EPI signals. We implement an analogous approach for EPIFANI by minimizing the residual sum of squares:

$$[\mathsf{T}_{1},\mathsf{M}_{0}^{*},\kappa] = \underset{T_{1},M_{0}^{*},\kappa}{\arg\min\left(\sum_{i=1}^{2}\left(S_{Ai}-\hat{S}_{Ai}\right)^{2}+\sum_{i=1}^{M}\left(S_{B,i}-\hat{S}_{B,i}\right)^{2}\right)}$$
(6.4)

where S_A represents EPIFANI scans, S_B represents GRE-EPI scans, M represents the number of the GRE-EPI signals included in the fitting procedure – acquired with the *i*-th flip angle – and \hat{S} represents the signal model value. The RF excitation map B₁ is estimated through the computation of a map of κ values, where κ represents the proportionality constant between the voxel-wise perceived and nominal flip angle, whose linearity has been demonstrated in a wide range of flip angles, with higher uncertainties for low values [25, 26]. As the actual B₁ map is generally spatially slow-varying, a second stage of the algorithm can be used to generate a smoothed version of the B₁ field, and another round of fitting is performed for T₁ and equilibrium magnetization estimation only. This method will be referred to as the "simultaneous" approach for parameter estimation.

Although originally used as a 3D technique, AFI has been used for 2D data acquisition [2, 27] and can be adapted to acquire multislice 2D data. As 2D encoding leads to systematic errors in the computation of the transmit field B_1 values, accurate mapping can be achieved by using RF pulses with adequate spatial excitation profile, and reducing the slice cross-talk, as well as by the implementation of slice profile correction strategies [23]. These help in mitigating measurement errors and produce reliable B_1 maps for arbitrarily chosen slice selective RF pulses, opening the possibility to implement the technique in an interleaved or distributed fashion [28] while improving time efficiency.

With a conventional Cartesian readout, the dependency over the effective transverse relaxation T_2^* is minimized by using short echo times. In VAFI, T_2^* effects and additional factors such as coil sensitivity and receiver gain are encompassed in the magnetization term, being estimated jointly with it. However, when acquiring GRE-EPI volumes in EPIFANI, T_2^* decay effects can emerge and show up in the form of artifacts, potentially impacting parameter mapping. Simulations for the analysis of effects on parameter estimation of T_2^* induced signal decay ($T_2^* \in [0.02, 0.2]$ s, log-spaced) were performed: a series of concentric rings with 4 different combinations of equilibrium magnetization and T_1 were simulated (T_1/M_0 [s]/[a.u.] were respectively 1/1, 2/0.5, 3/2, 4/4 from the outer to the inner circles). An eccentric homogeneous excitation was assumed and no slice profile correction was needed. The simulation was performed with a 2 shot acquisition, with matrix size = [128x128], $\alpha_A = 60^\circ$, $\alpha_B = [15,20,25]^\circ$, n = 5, and a bandwidth of 50 kHz with negligible gradient execution time, for a total acquisition time of 164ms per shot.

In order to test EPIFANI on an array of T_1 values, a 'revolver' 50 mL falcon containing vials (NMR tubes of 5 mm outer diameter) filled with aqueous cupric sulfate (CuSO₄) solutions of increasing concentrations (0.2, 0.4, 0.5, 0.6, 0.8, 1.0 mM and no CuSO₄ in the surrounding water) arranged in a circle was designed and made based on a previous validation study [29]. This was scanned with a Spin Echo Inversion Recovery (IRSE) with

TR = 10000 ms, matrix size = [64x64], FOV = (40x40) mm², slice thickness = 1 mm, TI array = [50, 100, 250, 500, 750, 1000, 1250, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000] ms, as well as with a 2D and 3D VAFI ($\alpha_A = 60^\circ$, n = 1000 ms / 200 ms = 5, matrix size = [128x128x16], FOV = (40x40x12) mm³) and EPIFANI ($\alpha_A = 60^\circ$, n = 1000 ms / 200 ms = 5, matrix size = [128x128], FOV = (40x40) mm², slice thickness = 0.75 mm). T₁ values were then analyzed via one-way analysis of variance (ANOVA) and successively via Tukey's honestly significant difference procedure [30].

An ex vivo mouse brain was imaged (TE/TR = 23/300 ms, $\alpha_A = 60^\circ$, $\Delta \phi = 37^\circ$, n = 5, $T_{rec} = 3666$ ms) to analyze the effects of the application of a preparation pulse on the steady-state signal compared to the application of dummy pulses.

Images of a fixed rat head were also acquired with EPIFANI (TE/TR = 5/500 ms, FA = 60°, n = 5, 4 shots, slice thickness = 0.5 mm, matrix size = [126x140], FOV = (35x35) mm², 1 navigator) and 8 GRE-EPI images (FA = [10, 20, 30, 40, 50, 60, 70, 80]° for the computation of B₁, T₁ and M₀* maps. Results were then compared to a 3D VAFI acquisition (TE/TR = 2.8/40 ms, $\alpha_A = 60^\circ$, $\alpha_B = [10, 20, 30, 40, 50, 60, 70, 80]^\circ$, n = 5, slice thickness = 0.5 mm, matrix size = [128x128], FOV = (35x35) mm²). An in vivo test on a mouse head was performed with similar scan parameters for both EPIFANI and a 2D VAFI. Values are reported as mean \pm standard deviation unless otherwise stated.

Steady state was reached with the application of a preparation pulse [2] and 10 additional dummy pulses and, for each shot, the same k-space lines were sampled in a consecutive TR_1 - TR_2 period. A single EPIFANI acquisition with the phase encoding gradient switched off was integrated into the sequence right before data acquisition of each slice and used as a navigator for Nyquist ghost correction. Even lines of the k-space of the individual shots were first flipped and phase errors were corrected by removing the phase offset provided by the navigator after inverse-Fourier transformation along the readout direction.

For the direct approach, a slice profile correction was implemented for the computation of B₁ values following Malik's method [2, 23]. Numerical integration of Bloch simulations solved for a 3 lobes sinc pulse, for the relevant gradient waveforms parameters and for an array of B₁ values was used to obtain the flip angle distribution and the signal received with 2D spatial encoding, estimated by integration over the slice thickness. T₁ and T₂ values were matched to those computed from experimental values when available, else T₁ = 1000 ms was used and the effects of transverse relaxation were neglected according to the original slice profile correction method. For the simultaneous approach, T₁, B₁, and M₀^{*} were fitted via voxel-wise minimization of the residual sum of squares of the signal intensities and the model signal for EPIFANI and GRE-EPI. A slice profile correction was applied based on the approach in Chapter 4.

6.3 Results

The pulse sequence diagram for EPIFANI is reported in Figure 6.1. Analogously, the sequence can be adapted for multi-shot and multi-slice applications. Fat saturation and saturation blocks should be applied, when needed, before each RF pulse, thus increasing the minimum TR achievable. It can be noticed that EPIFANI shares the same structures of GRE-EPI and can indeed be described as a dual-TR GRE-EPI sequence, an EPI version of AFI.



Figure 6.1: Pulse sequence diagram of the EPIFANI sequence. EPIFANI acquires the k-space for a single slice in two different steady states and with one or more shots.

The acquisition time $T_{EPIFANI}$ for N_S slices with a single EPIFANI scan (NEX = 1)

will then correspond to

$$T_{EPIFANI} = N_S * \mathsf{TR}_1(n+1)n_{shots}$$
(6.5)

where n_{shots} corresponds to the number of shots used. Then, including M GRE-EPI acquisitions for B₁ and T₁ mapping, the total acquisition time T_{tot} becomes

$$T_{tot} = T_{EPIFANI} + MT_{GRE-EPI} = N_S \mathsf{TR}_1(n+1)n_{shots} + N_S M \mathsf{TR}_1 n_{shots} =$$
$$= N_S \mathsf{TR}_1(n+M+1)n_{shots} \quad (6.6)$$

which includes the acquisition time for an EPIFANI scan $T_{EPIFANI}$ and M GRE-EPI scans $T_{GRE-EPI}$. Additional overhead time needs to be allocated for the acquisition of navigator scans for phase correction (corresponding to $T_{EPIFANI}$ and $T_{GRE-EPI}$ for the two types of scan, respectively), as well as a mask for Nyquist ghost corrections.

Simulations on a virtual phantom were performed and Figure 6.2 reports the geometry of the simulated phantom as well as the respective excitation field. The effects of short T_2^* values on the reconstructed images can be seen as blurring of the image, overrepresentation of the high spatial frequencies with respect to the rest of the k-space, as well as altered image contrast and Gibbs effect as shown in Figure 6.3.



Figure 6.2: Simulations for EPIFANI fitting: a virtual phantom with concentric structures with different magnetic properties (left) was generated and simulated in an inhomogeneous B_1 field (right). Values for magnetization and T_1 for each annulus are reported.



Figure 6.3: Simulations for the artifacts generated by T_2^* effects on EPIFANI images (S_{A1}) of the virtual phantom. Simulations were performed with T_2^* log-spaced between 0.02 and 0.2 s.

Maps of computed T_1 and B_1 for the simulation phantom were normalized by their nominal values and show values around 1, thus reliably recovering the original input values but with increasing inaccuracies and instability of the reconstructed values found for lower T_2^* values as well as along the tissue interfaces. Magnetization maps encompass most of the signal intensity variations provided by T_2^* decay in k-space (see Figure 6.4). For T_2^* values smaller than 50 ms with a single-shot acquisition, median inaccuracies in T_1 and κ greater than 10% arise. However, a second iteration of the fitting algorithm decreases estimation variability in T_1 .



Figure 6.4: Simulations for EPIFANI fitting: parameters results for first iteration (top) and second iteration after B_1 smoothing (bottom) of the joint approach for increasing T_2^* values (the shift to higher T_2^* values is represented by the shift from red to black). T_2^* effects are included in the M_0^* results and increasing values of T_2^* provide more precise results for both T_1 and κ .

When analyzing the approach to steady state with EPIFANI with a direct approach on a mouse brain, the first set of AFI images acquired without preparation or discarded acquisitions shows an artifact in the reconstructed image and relative κ map (Figure 6.5).

As reported in in the Bland-Altman plots, the steady-state κ reports a difference of 0.5% with respect to AFI derived κ values, while images acquired without preparation, with a dummy, two dummies and the preparation module show a bias of -5.8%, 0.5%, -0.9%, and -0.1%, respectively. This bias is higher when considering the agar: -9.6% (steady state), -8.3% (no preparation), -8.1% (one dummy), -8.7% (two dummies), and -10.3% (preparation module). The preparation with dummies in this EPIFANI example took 3000 ms for each dummy, while the proposed preparation module required 3666 ms.



(a)



Figure 6.5: Examples of AFI₁ images (a) and corresponding κ maps of data acquired with EPIFANI on an ex vivo mouse brain. Acquisitions at steady-state, without preparation, with one and two dummy pulses, and with the proposed preparation module are reported. A 3x3 median filter was applied on the κ maps to represent better the slowly varying B₁ field. Bland-Altman plots referring to both the mouse brain (b) and the agar (bottom right) are reported.

With a simultaneous approach, a single-slice acquisition on a gelatin phantom for EPIFANI takes around 11 seconds (7.2 seconds for EPIFANI, 3.6 seconds for GRE-EPI) and provides mean T_1 values of 2.056 s (standard error: 0.020 s) with a small overestimation with respect to a reference value computed via inversion recovery of 2.054 s (standard error: 0.001 s).

EPIFANI was run on a revolver phantom with increasing $CuSO_4$ concentrations, and the results for the computed T_1 can be found in Figure 6.6, which shows that slice corrected EPIFANI approaches VAFI 2D and 3D values as well as IRSE median values. ANOVA



tests show that the four datasets do not come from the same distribution, and the pvalues for the Tukey tests are reported under the boxplots for each concentration.

Figure 6.6: An AFI₁ image of the revolver phantom reporting CuSO₄ concentrations (top). T₁ values estimated at 7 T with Inversion Recovery Spin Echo, VAFI 3D, VAFI 2D, and EPIFANI are reported in the boxplots, while the bottom row reports the matrices with p-values from pairwise comparisons of the T₁ distributions via Tukey multiple comparison test. * = p < 0.05, ** = p < 0.01, *** = p < 0.001.

Figure 6.7 reports S_{A1} and S_{A2} images from EPIFANI as well as the T₁ and κ map reconstructed via simultaneous approach on a fixed ex vivo rat head. B₁-corrected T₁ values on the cortical gray matter and on the thalamus were 786 \pm 136 ms and 887 \pm 149 ms, respectively, while values for the same regions computed via simultaneous approach on a reference 3D AFI and SPGR images were 943 \pm 128 ms and 985 \pm 149 ms, respectively. However, when a slice profile correction was implemented – based on the approach shown in Chapter 4 – the estimation bias was reduced: cortical gray matter T₁ estimated with EPIFANI was 852 \pm 145 ms, while thalamus values were 961 \pm 159 ms.



Figure 6.7: S_{A1} image, S_{A2} image (top), T_1 map and κ map (bottom) reconstructed via EPIFANI with a simultaneous approach for an ex vivo fixed rat head scanned at 7 T.

Similarly, VAFI values in vivo on a mouse head are reported in Figure 6.8 and were 1425 \pm 205 and 1311 \pm 233 ms for cortical gray matter and the thalamus, respectively, while slice profile corrected values were 1589 \pm 219 ms and 1457 \pm 249 ms. EPIFANI uncorrected values were 1485 \pm 450 and 1209 \pm 458 ms, while slice profile correction returned values of 1603 \pm 467 and 1324 \pm 481 ms.



Figure 6.8: S_{A1} image, S_{A2} image (top), T₁ map and κ map (bottom) reconstructed via EPIFANI with a simultaneous approach for a mouse head scanned at 7 T.

6.4 Discussion

The implementation of EPIFANI as a dual-TR gradient echo sequence with an EPI readout is straightforward, as it stems from EPI methods readily available in the majority of MR scanners. EPIFANI was developed with the use of asymmetric repetition times, and two quantitative approaches were used: a direct approach allows the computation of B₁ maps exclusively, while the acquisition of EPIFANI and at least a GRE-EPI dataset allows mapping of both B₁ and T₁ simultaneously.

The acquisition of the whole k-space via single-shot EPI takes place during the T_2^* decay of the MR signal. The analysis of the effects of T_2^* decays on the simultaneous approach shows that EPIFANI is able to reconstruct accurate maps for both T_1 and B_1 , while T_2^* effects are encompassed in the equilibrium magnetization term M_0^* . However, for very short T_2^* values, the reconstructed maps can report inaccuracies, as EPIFANI and GRE-EPI images have an over-representation of high frequencies in k-space with respect

to its center, which leads to unreliable image contrast and artifacts.

We have shown that EPIFANI benefits from the use of a preparation pulse [2] to reach steady state. We reported examples of normalized B_1 maps computed via a direct approach on an ex vivo mouse brain acquired with EPIFANI and found that the preparation pulse helps in preserving the accuracy of the B_1 values in the foreground (the mouse brain itself) and in the agar, although lower accuracy is reached in the latter.

Using the simultaneous approach for multiparametric mapping on a rat head phantom, EPIFANI underestimated T_1 of -16.7% and -9.9% on the cortical gray matter and the thalamus respectively with respect to the 3D VAFI reference value. However, when a slice profile correction was implemented, the estimation bias was reduced significantly to -9.7% and -2.4%. When EPIFANI was acquired in vivo and compared to a slice corrected 2D VAFI acquisition, the difference was 0.9% and -9.1%. A validation on a revolver phantom with multiple T_1 values confirms how EPIFANI accurately maps T_1 values with respect to VAFI 2D, VAFI 3D and IRSE for most of the CuSO₄ concentrations, while also coming with a significant time acquisition advantage with respect to both the 3D reference methods.

It should be noted that with respect to AFI, the repetition time in EPIFANI is significantly longer, which can significantly increase SNR while keeping the acquisition of the whole k-space within seconds. At the same time, this can pose an issue to B₁ mapping for short T₁ tissues in the direct approach for which we assume that T₁ \gg TR. This assumption is not made and thus does not pose an issue when mapping is performed with the joint approach.

EPIFANI is affected by EPI restrictions and artifacts. In particular, the maximization of B_0 homogeneity through shimming is a critical preparation step, especially at high magnetic field, where susceptibility differences can severely affect image quality with artifacts. Another intrinsic EPI-related limitation is the acquisition with a long TE while T_2^* decay is taking place, which might require to employ via multi-shot EPI as well as partial Fourier approaches to shorten TE.

Future studies with EPIFANI should focus on the optimization of sequence parameters to improve image quality and T_1 accuracy, as well as on the possible disentanglement of the T_2^* effects on the magnetization maps. A validation of EPIFANI on a larger cohort of samples and tissues should also be investigated.

6.5 Conclusion

Quantitative MRI would benefit from ultrafast acquisitions to promote its use in a preclinical and clinical environment. We presented EPIFANI, a gradient echo EPI sequence that allows 2D ultrafast acquisitions for accurate T_1 and B_1 maps that compare well to other 2D and 3D reference approaches. The use and optimization of EPIFANI should minimize T_2^* effects and guarantee that the steady state is reached before signal sampling, which is fundamental for accurate relaxometry mapping.

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Chapter 7 Conclusions and future work

Quantitative MRI is able to provide additional information for clinical diagnosis and comes with several advantages as it aims at obtaining an objective, user-independent, and quantified measure of tissue physical and functional properties.

In this thesis, we have reported some of the recent advancements in the quantification of relaxometry parameters, specifically of T_1 and T_2^* . They all stem from modifications and advancements of the Actual Flip angle Imaging (AFI) sequence, which is used for B_1 mapping when the repetition time used can be considered to be much shorter than the T_1 values for the tissues scanned. Variable flip angle with AFI (VAFI) has been another important resource for these studies as it can be used for B_1 -corrected T_1 mapping starting from an AFI acquisition and at least a spoiled gradient echo acquisition, a simple and widespread pulse sequence. All of the studies have been supported by a theoretical background as well as MR simulations (either based on Extended Phase Graphs or Bloch equations), tested on phantoms, and then eventually we have reported proofs of concept in a preclinical setting – both ex vivo and in vivo – which serve as an initial validation for clinical applicability.

7.1 Contributions summary

First, we have proposed a new preparation module for AFI and AFI-based sequences which results in a fast approach to steady state conditions for B_1 mapping. The preparation module comprises an adiabatic pulse, spoiler gradients, and a recovery time whose analytical expression is T_1 -independent in biological tissues. The approach is robust to variations of the pulse amplitude, and the use of the preparation module removes discarded acquisitions and artifacts occurring at the beginning of AFI-based EPI acquisitions as well as of scans using center-out k-space trajectories. Besides improving parametric accuracy in reconstructed maps, the use of a preparation module can provide an advantage in terms of acquisition time and this approach could be applied to other dual-TR sequences as well.

The study of a 2D version of AFI sampled with interleaved slices and corrected for slice profile effect has also been reported. This method allows compact slice stacking and can be applied in multi-TR sequences that can not be acquired in a simple sequential interleaved fashion, making 2D multislice acquisitions significantly faster. As one of

the main issues in relaxometry maps achieved with 2D acquisitions lies in the effects that the slice profile has on the signal, we have presented how slice profile effects can be mitigated through a look-up table correction based on Bloch simulations, and how T_1 and B_1 maps accuracy can be improved, restoring values close to the gold standard methods. Together, these developments allow a highly time-efficient approach for high resolution and accurate B_1 -corrected T_1 mapping when 2D VAFI is implemented.

For joint T_1 and T_2^* mapping, we have developed RAMSES, a version of the 3D AFI sequence with a multi-gradient echo readout and we have studied its spoiling characteristics as well as its accuracy in multiparametric estimation. This is achieved without any time penalty, as the added T_2^* mapping portion is added during the idle time in TR₂, which naturally presents a signal decay and otherwise would not contribute to the duty cycle of the sequence. The results in terms of quantitative maps have shown to be comparable to VAFI for T_1 and to a gold-standard multi gradient echo for T_2^* mapping.

Eventually, EPIFANI, a 2D ultrafast EPI version of VAFI for B_1 -corrected T_1 mapping, was developed and tested. This represents a natural but challenging development of AFI and VAFI, as high-field EPI scans tend to present several artifacts mainly due to the need for great field homogeneity (that can result in a burdensome shimming procedure) and T_2^* effects. We have reported the use of the slice profile effect correction on EPI-FANI, which provided more accurate T_1 results, closer to reference methods. EPIFANI provides high acquisition efficiency for a multiparametric approach, incorporating T_2^* effects into a bias of the equilibrium magnetization while leaving the accuracy of T_1 and B_1 unchanged.

The developments that we reported here hope to be a step towards a more quantitative view of MRI, as these advancements were reached with the intent to make the use of quantitative MRI techniques smoother and able to provide accurate and fast results, improving the methods that are currently described in the state of the art.

7.2 Translation potential

For the clinical practice, it can be argued that the acceleration methods and multiparametric sequences herein described can promote the use of quantitative MRI for a broader characterization of tissues and the study of the dynamics of the magnetic properties (relaxometry times) in pathophysiological conditions.

In particular, the preparation module for AFI represents a quick and versatile tool for steady state approach, which removes the uncertainty around the amount of discarded acquisition needed. This could be applied to all AFI scans used for B₁ mapping as well as

for VAFI, reducing the overhead time for these kinds of acquisitions from a few seconds to milliseconds for each slice.

The use of a slice profile corrected 2D multislice AFI/VAFI can find application in all current B_1 and B_1 -corrected T_1 mapping protocols. With respect to the current status of 3D AFI and VAFI, this would allow a significant scan time reduction (up to a factor corresponding to the maximum amount of slices that can be acquired within the same total AFI repetition time TR_1+TR_2) while preserving the accuracy and precision of the techniques. Hence, this can be a significant factor to stimulate AFI/VAFI diffusion and application in a clinical setting. Ultimately, the advantage of B_1 and B_1 -corrected T_1 mapping is to be researched in their use as biomarkers. A fast 2D multislice VAFI could be used for T_1 mapping studies of brain development and aging, as well as for the characterization of multiple sclerosis, brain cancer, and Parkinson's disease for example.

RAMSES is a powerful tool for multiparametric imaging. While a full 3D RAMSES acquisition might still require too much time for a widespread use of the sequence, this can still be used wherever and whenever 3D VAFI is used for T_1 mapping, providing supplementary accurate T_2^* information with no additional scan time required for myelin water fraction mapping studies as well as hemorrhage and iron overload studies.

With its ultrafast EPI readout, EPIFANI could be used for dynamic studies including BOLD imaging for functional MRI, as well as perfusion imaging via Dynamic Susceptibility Contrast (DSC). In a broader context, EPIFANI can be used to acquire B_1 maps via a direct approach and B_1 -corrected T_1 maps via a simultaneous approach within a few seconds for a broad variety of studies, especially for tissue characterization and possible differentiation via T_1 .

7.3 Future developments

Future works for the developed sequences and methods include the application of the preparation pulse for non-cartesian sampling patters for VAFI - including radial and spiral applications - as well as the application of the time-efficient slice stacking for interleaved EPIFANI and other multi-TR sequences.

We also plan to widen the use of the slice profile effect correction for other sequences, especially for RAMSES when this is applied in a 2D fashion. While the application of the correction to T_1 mapping for RAMSES is straightforward, the impact of slice profile effects on T_2^* mapping should also be analyzed and accounted for.

When 3D RAMSES volumes are acquired, susceptibility effects show up in areas characterized by significant differences in magnetic susceptibility, affecting the signal.

Quantitative Susceptibility Mapping (QSM) and Susceptibility Weighted Imaging (SWI) are imaging methods that can potentially be employed for RAMSES and that could untangle susceptibility effects from the estimation of T_2^* . Notably, QSM has been used for the separation of diamagnetic calcium from paramagnetic iron, as well as the iron deposition and blood byproducts quantification for the differentiating intracranial calcifications from hemorrhage, and the white matter myelination quantification for the study of brain development and aging processes. Taking into account these effects could generate an optimized environment for multiparametric estimation, making RAMSES an even more powerful mapping tool.

Lastly, RAMSES and EPIFANI should be optimized and thoroughly tested to provide data in terms of sequence stability, precision, and accuracy. EPIFANI is expected to require more case-specific tuning, as EPI sequences require a good quality pre-acquisition shim, especially at high magnetic fields. Experimental EPIFANI-based T_1 maps can show a slight bias with respect to other mapping methods and further investigations are needed to restore higher parametric accuracy. Once EPIFANI has been validated against gold standards with larger datasets, it could be used as a next-generation B_1 -corrected T_1 sequence, filling the gap between accurate and ultrafast sequences available.

7.4 Conclusive thoughts

Although the results we reported represent a preclinical application of new mapping techniques, we hope that this manuscript was able to provide a theoretical background on quantitative MRI, especially relaxometry, and that the analysis we reported can show how multi-layered and complex (in the philosophical sense of complexity) the acquisition of MRI images can be. What is behind the click of a mouse on the console of the MRI technologies and, more, what's behind the contrast of MRI images comes from years of research and tests. As developers and scientists of the qMRI community, we believe our duty is to work towards accuracy and precision while considering time efficiency, to then train the current and the next generation of technologists and radiologists on the interpretation of new imaging modalities to achieve new objectives in precision medicine.

Yet, the path for standardized, unanimously approved techniques for parameter mapping in quantitative MRI is, unfortunately, far from being reached. Speed limitations, issues with reproducibility and repeatability, and lack of validation for clinical translation are the main barriers interfering with a paradigm shift from qualitative to quantitative MRI.

The implementation of fast mapping techniques such as RAMSES and EPIFANI and

the application of preparation modules and correction methods for higher accuracy in relaxometry mapping can represent an important step towards a new kind of imaging. Although maybe not revolutionary, it could be argued that small and slow progress in noninvasive diagnosis and quantitative techniques like the one reported in the previous pages places the foundation for more informative imaging and healthcare. MRI, as an imaging technique, is less than 50 years old, and research in this field is flourishing with thousands of conference abstracts and papers presented every year. This fast advancement can make previous publications quickly obsolete in theory, but the clinical application of research is notoriously slower and characterized by a distinct inertia toward changes. As scientists, it is our job to seek knowledge and make the world a better place, step by step, leading the way for everyone to follow. This can only happen if one is able to communicate their research, which is easier when you can show MRI images and let your audience understand both how fundamental it is to acquire bioimages nowadays for noninvasive investigations and how beautiful and interesting those pictures can be. I still remember when I saw my first brain MRI and how exciting it was to be able to look at its anatomy. Now our job is to make these images not only beautiful but objectively informative. After all, if a picture is worth a thousand words, a parametric map is music.

Chapter 7. Conclusions and future work

Chapter 8 Academic Overview

8.1 Journal papers

- 1. **Zampini M.A.**, Sijbers J., Verhoye M., Garipov R.: A preparation pulse for fast steady state approach in Actual Flip angle Imaging. *Medical Physics* 51 (2023).
- 2. Paganelli C.*, **Zampini M.A.***, Morelli L., Buizza G., Fontana G., Anemoni L., Imparato S., Riva G., Iannalfi A., Orlandi E., Baroni G.: Optimizing b-values schemes for diffusion MRI of the brain with segmented Intravoxel Incoherent Motion (IVIM) model. *Journal of Applied Clinical Medical Physics* 24 (2023).
- 3. Reiter R., **Zampini M.A.**, Guidetti M., Majumdar S., Royston T.J., Klatt D.: Tabletop MR elastography for investigating effects of the freeze-thaw cycle on the mechanical properties of biological tissues. *Journal of the Mechanical Behavior of Biomedical Materials* 135 (2022).
- 4. **Zampini M.A.**, Guidetti M., Royston T.J., Klatt D.: Measuring viscoelastic parameters in Magnetic Resonance Elastography: A comparison at high and low magnetic field intensity. *Journal of the Mechanical Behavior of Biomedical Materials* 120 (2021).
- Buizza G.*, Zampini M.A.*, Riva G., Molinelli S., Fontana G., Imparato S., Ciocca M., Iannalfi A., Orlandi E., Baroni G., Paganelli C.: Investigating DWI changes in white matter of meningioma patients treated with proton therapy. *Physica Medica* 84 (2021).
- Guidetti M., Zampini M.A., Jiang Y., Gambacorta C., Smejkal J.P., Crutison J., Pan Y., Klatt D., Royston T.J.: Axially- and torsionally-polarized radially converging shear wave MRE in an anisotropic phantom made via Embedded Direct Ink Writing. *Journal of the Mechanical Behavior of Biomedical Materials* 119 (2021).
- Zampini M.A., Buizza G., Paganelli C., Fontana G., D'Ippolito E., Valvo F., Preda L., Baroni G.: Perfusion and diffusion in meningioma tumors: a preliminary multiparametric analysis with Dynamic Susceptibility Contrast and IntraVoxel Incoherent Motion MRI. *Magnetic Resonance Imaging* 67 (2020)

8. Guidetti M., **Zampini M.A.**, Gandini G., Gupta A., Li W., Magin R.L., Wang V.M.: Diffusion Tensor Imaging of Tendons and Ligaments at Ultra-High Magnetic Fields. *Critical Reviews in Biomedical Engineering* 46.4 (2018).

8.2 Books

1. **Zampini M.A.**, Morelli L., Parrella G., Baroni G., Parker, G.J.M., Paganelli C.: Quantitative imaging in particle therapy. In Imaging in Particle Therapy: Current practice and future trends. *Bristol*, *UK: IOP Publishing*, 2024 Jun 1 (pp. 11-1).

8.3 Conference abstracts

- 1. **Zampini M.A.**, Sijbers J., Verhoye M., Garipov R.: EPIFANI: an ultrafast T1, B1 and magnetization mapping technique. Proceedings of the *31st Annual Meeting of the International Society for Magnetic Resonance in Medicine*. London, United Kindgdom; 2022: 1708. Digital poster presentation.
- 2. **Zampini M.A.**, Sijbers J., Verhoye M., Garipov R.: EPIFANI for ultrafast B1-corrected T1 and PD mapping. Proceedings of the *37th Congress of the European Society for Magnetic Resonance in Medicine and Biology*. Virtual; 2021. Oral presentation.
- Buizza G., Zampini M.A., Sablone G., Fontana G., Imparato S., Riva G., Iannalfi A., Orlandi E., Paganelli C., Baroni G.: Optimization of intravoxel incoherent motion diffusion MRI for brain tumours biomarkers estimation. Proceedings of the *European SocieTy for Radiotherapy and Oncology conference*. Madrid, Spain; 2021. Poster presentation.
- 4. Zampini M.A., Sijbers J., Verhoye M., Garipov R.: RAMSES: Relaxation Alternate Mapping of Spoiled Echo Signals sequence for simultaneous accurate T1 and T2* mapping. Proceedings of the 30th Annual Meeting of the International Society for Magnetic Resonance in Medicine. Virtual; 2021: 3051. Digital poster presentation.
- 5. Zampini M.A., Garipov R.: Fast Steady-State Approach for 3D T1 and B1 Mapping with an Updated Optimization Merit Function for an Improved Accuracy and Precision. Proceedings of 36th Congress of the European Society for Magnetic Resonance in Medicine and Biology. Virtual; 2020. Digital poster presentation and lightning talk.

- 6. Zampini M.A., Guidetti M., Royston T.J., Klatt D.: Fractional calculus models of viscoelasticity measured using Magnetic Resonance Elastography at high and low field intensities. Proceedings of the *179th Meeting of the Acoustical Society of America*. Virtual; 2020. Oral presentation.
- 7. **Zampini M.A.**, Garipov R.: A fast steady-state approach for B1 mapping via Actual Flip angle Imaging. Proceedings of the *International Society for Magnetic Resonance in Medicine Italian Chapter*. Virtual; 2020. Digital poster presentation.
- 8. **Zampini M.A.**, Nicastro M.: Super-Resolution in the B-Q MINDED project: developing fast isotropic MRI relaxometry Proceedings of the MCAA General Assembly *and Annual* conference. Virtual; 2020. Digital poster presentation.
- Reiter R., Guidetti M., Zampini M.A., Majumdar S., Palnitkar H., Hamm B., Royston T., Klatt D.: Tabletop MR Elastography (MRE): Preliminary Results Towards an Assessment of Frozen Tissue Bank Samples. Proceedings of the 27th Annual Meeting of the International Society for Magnetic Resonance in Medicine. Montreal, Canada; 2019: 3963. Digital poster presentation.

8.4 Awards

- 1. Educational Stipend Award 2022 for the work "EPIFANI: an ultrafast T1, B1 and magnetization mapping technique" in Proceedings of the *31st Annual Meeting of the International Society for Magnetic Resonance in Medicine*. London, United Kindgdom; 2022: 1708. Digital poster presentation.
- Educational Stipend Award 2021 for the work "RAMSES: Relaxation Alternate Mapping of Spoiled Echo Signals sequence for simultaneous accurate T1 and T2* mapping" in Proceedings of the 30th Annual Meeting of the International Society for Magnetic Resonance in Medicine. Virtual; 2021: 3051. Digital poster presentation.

Chapter 8. Academic Overview

Chapter 9 Acknowledgements

The journey

The past 6 years have been quite a journey. I started this PhD in December 2018, when I was 25, freshly graduated from the University of Illinois Chicago, and while I was preparing to defend my Master's thesis at the Politecnico di Milano. I had heard about this PhD/Marie Curie project from a friend, gave the first interview a shot during lunchtime in a loud college canteen, and finally (got) accepted the position, found a small room to rent, and moved to the cloudy Guildford in the United Kingdom, where I would work in the headquarters of MR Solutions. Through the company and the Universiteit Antwerpen, I had the chance to meet and work with a group of MR enthusiasts, where I felt I fit right in. I lived here and there for this PhD, experiencing a strong and interesting blend of homesickness and travel excitement, until COVID-19 hit and everything slowed down, and we got even more used to meeting people virtually, working remotely, and being chronically online. Almost two years later, I found myself in a new phase of my life. I started drafting this thesis – with not much to write about to be completely honest - and I decided to take another leap of faith and move to the Midwest of the US, backed by this company, that entrusted me and sponsored my visa. Three years have passed since then, I have two dogs, I have applied for permanent residency here, and I've visited and collaborated with a good amount of research groups from all over the world. I have accepted that I was not the fastest at getting my PhD as I first thought I would be (silly me), I have grown (I guess) and resized my expectations, but I've never stopped dreaming and aspiring for something more. I have learned a lot, changed a lot, traveled a lot, and now I am here, working from my favorite coffee shops in Kansas City (MO), in a judgment-free and loving environment. Even after all this time, I feel I can hardly consider myself an expert in what I do, and I've always been skeptical of people who claim to be messiahs of knowledge and I, for sure, don't aspire to be one. However, here's my PhD thesis, so bear with me while we learn about quantitative MRI together.

MRI - a personal note

MRI is fascinating. It takes a bunch of components and parameters, all synchronized and tuned, and that's what makes it such a powerful imaging technique. Looking inside the body in a non-invasive way – and being able to extract so much information from this – is sheer magic, and it always leaves me in awe. Being in an MRI scanner, however, is a whole different experience. It can be claustrophobic, loud, and uncomfortable. That's why developing methods that can make this experience shorter (hence less painful) while not sacrificing information is so important. In a nutshell, this thesis is about making MRI faster and more informative than the current one. If you want an extended version of this (or you want to test how fast you can fall asleep), start from Page 1. Anyway, before diving into the details of this PhD thesis, here's a quick list of my favorite references you (and I) may find useful in the future:

- "MRI from Picture to Proton" by Donald W. McRobbie, Elizabeth A. Moore, Martin J. Graves, and Martin R. Prince for newbies and experts, this book takes you by the hand and makes you understand MRI step-by-step;
- "Handbook of MRI Pulse Sequences" by Kevin F. King, Matt A. Bernstein, and Xiaohong Joe Zhou - a more technical tome, with everything you need to know about pulse sequence design;
- "Quantitative Magnetic Resonance Imaging" by Nicole Seiberlich and Vikas Gulani - a comprehensive book about the birth and growth of quantitative MRI;
- mriquestions.com for whenever you need a quick reference or reminder about k-space, acquisition strategies, sequences, and any MR-related topic.

In this stream of consciousness, here's something completely unrelated. The past few years have set off ChatGPT as a popular tool, so here's a quick AI Q&A for your entertainment:

Q: What is MRI?

A: MRI stands for Magnetic Resonance Imaging, which is a medical imaging technique that uses strong magnets and radio waves to create detailed images of the internal structures of the body. It is a non-invasive diagnostic tool that can be used to visualize soft tissues, organs, and bones in great detail, without the use of ionizing radiation. MRI is commonly used to diagnose a wide range of medical conditions, including neurological disorders, joint injuries, tumors, and cardiovascular disease.

Q: Why is MRI hard to understand?

A: MRI can be hard to understand because it involves complex physics and mathematics. The underlying principles of MRI involve the interaction of magnetic fields and radio waves with the body's tissues, and the resulting signals are processed using sophisticated algorithms to create detailed images. Additionally, MRI technology is constantly evolving, with new techniques and applications being developed all the time. As a result, understanding the intricacies of MRI requires a strong background in physics, mathematics, and computer science, as well as specialized training in medical imaging.

Q: Why is MRI so interesting?

A: MRI is interesting for several reasons. First, it is a non-invasive imaging technique, which means that it does not require the use of ionizing radiation or invasive procedures, making it a safer and less invasive alternative to other diagnostic tools like X-rays or CT scans.

Second, MRI has the ability to produce detailed images of soft tissues, such as the brain and spinal cord, that are not easily visualized by other imaging techniques. This has made it an invaluable tool in the diagnosis and treatment of neurological disorders, such as multiple sclerosis and brain tumors.

Third, MRI is a versatile imaging modality that can be used to study a wide range of biological processes, from blood flow and metabolism to brain activity and neural connectivity. This has opened up new avenues of research and has led to many important discoveries in neuroscience and other fields.

Overall, MRI is a fascinating and important technology that has revolutionized the field of medical imaging and has the potential to advance our understanding of the human body and mind in countless ways.

Q: What is MRI in 20 words?

A: MRI stands for Magnetic Resonance Imaging, a medical imaging technique that uses strong magnets and radio waves to create detailed images.

This is actually 21 works.

Q: What is MRI in 0 words?

A: 🤔

People and pets

I would like to express my gratitude to my supervisors, Ruslan Garipov, Marleen Verhoye, and Jan Sijbers, for their guidance and support throughout my PhD journey. Their insightful feedback has been instrumental in shaping my research and pushing the boundaries of my work, and I am incredibly grateful for the opportunities they provided with the B-Q MINDED project.

Working remotely for more than half of the time I've spent on this career as a PhD student has made me appreciate how a reliable internet connection is fundamental in the era of digital nomads, and also how easy it is to reach out and annoy people. All the results and images that were shown in this thesis were acquired while someone kindly helped me by preparing the MR scanner and the specimen, so if you are reading this: thank you.

My journey would have not been the same without a few people:

- Gina (Martina), you have been by my side from the beginning, giving me a boost of confidence whenever I needed it. I know I can always rely on you to spot the (often overlooked) minuscule details that can make a difference. And thank you for being my technical consultant I wholeheartedly enjoy refining the art of complaining with you. You have been instrumental for my growth in the past few years, with your moral compass and your compassion. Our friendship started in Chicago, and I hope we will reunite there soon, but in the meantime, I can not forget all the moments and the laughter we shared together. Seeing the Grand Canyon with you is one of my core memories for so many reasons.
- Puglia (Annalisa), thank you for always listening to my endless voice messages. I really believe we should make a podcast production of our lives, that would be as entertaining and full of inside jokes as it can get. You know me like nobody does, and I know you will always have an accepting and curious-driven look, and that's one of the features I like the most. I know you've always had big dreams for your future, and I know I will be there to see them all realized, one right after the other. I have always been so proud of every hard decision you have taken, and I know how hard you have been working for years now. I can't wait to see you on this side of the Atlantic Ocean and to live with you the TV show we call 'life'. Never stop dreaming.
- Greta, this is the first time we haven't graduated together since we met, and I have to be honest, it is bittersweet. I know I can count on you for everything, and that

we will always celebrate our Friends/Thanksgiving whenever we get the chance to. Also, I enjoy how random our conversations can get and how our minds are so alike when it comes to science and life. Talking to you is easy because I know you will always be a careful listener, and I feel our bond has not changed a bit since we randomly met. Most of all, I miss finding new places and looking for cheap/discounted/free food with you.

- Laura, I hope I will always be the only one who is allowed to see the drying rack wherever you live. I think we are an example of how two different people can appreciate so much each other, just as long as there is respect and interest. Getting to know you was understanding the whirlpool of emotions and adventures there is behind that introverted facade. I know that people are lucky to get to know you because you are a genuine and smiley person. My hope is that you will always be this person full of life and happiness, because we all need a little bit more of it, and you are my personal source for that.
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- KC friends: all of you have made a difference in my life in the past three years. Getting to know new people when working remotely, being a grown-up, and living outside of your culture can be challenging, and I am so glad we found each other.
 I am learning how to be a grown-up and how to take important decisions with you, and I appreciate your unconditional support

I remember all of you in my fondest memories, and I hope I was able to leave a mark in your lives just as much as you did in mine. As you may know, I tend to overshare my life and create genuine relationships with people. If you are not on this list, it doesn't mean that I don't remember you or what we have experienced together. It probably means that life went by, and we both got distracted by bigger and bigger things, but I sincerely wish you the best.

To my family: sorry I moved so far away. I have to be honest when I say I don't regret letting you know my intentions late because I know how dysfunctional we all are at processing bad news. Sometimes all we need is time and space to appreciate what we have, and I think this pretty much resonates with me. I love every one of you and I can not wait to see your faces soon. My dream is to have a vacation all together, somewhere in the world. Time is passing way too fast, and I know we all deserve some rest far away from the places we know way too well. Mamma and papà: sometimes I don't realize how lucky I was to have such loving parents, I hope you know you have done an amazing job creating a safe environment for us all, fighting through the hard times and our worst enemies. Gabry: I know your plans change so fast, and I know you deserve to find happiness and a place you can call home soon. Tata: thank you for all the support you have given me, I know you will always pick up the phone and listen, and I know you are always ready to fight for me, at any cost. You all deserve so much more than what life is giving you.

To the Dare family: thank you for welcoming me with open arms. I never take anything for granted, so knowing that you are always there to back me up is incredibly special to me. We might not share the same culture or the same ideas, but you have helped me so much, supporting me and becoming my foster family in the States.

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And Ross. You came into my life when I needed you the most. You have grown to be my best friend and confidant, and I am so grateful to wake up every morning next to you. It goes without saying, but I love our dynamics and how safe the world feels with you. I love how you overanalyze everything, and I will always be there to listen to you and offer another perspective because, with you, I love to talk and I like to fight. I have an endless list of moments with you that I cherish, and I don't think picking only a few of them to list here would be fair. Know that you are the first person who has ever made me feel special. You know how complicated, skeptical, and self-reliant I am. You are kind and caring, committed and smart, selfless and diligent, and you made me understand that I can trust people. Or maybe just you, but that's more than enough. Even if I am not the easiest person to deal with, especially when it comes to love, you know when to talk and when to listen, when to give me space, and when to hug me. Thank you for taking a chance on me and for waiting for this moment with me. Let's start the rest of this journey together.