
TECHNIQUES FOR SIGNAL ACQUISITION, RECONSTRUCTION AND ANALYSIS IN SODIUM MAGNETIC RESONANCE IMAGING

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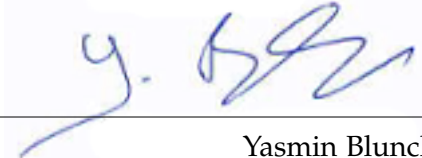
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Doctor of Philosophy

Declaration

This is to certify that

- (i) the thesis comprises only their original work towards the Ph.D except where indicated in the preface;
- (ii) due acknowledgement has been made in the text to all other material used; and
- (iii) the thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.



Yasmin Blunck

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Date

Abstract

Over the last decades, Magnetic Resonance Imaging (MRI) has undergone a high-paced development rendering it an extremely versatile imaging technique with revolutionary impact on medical practice and research. Typically, MRI acquisitions are sensitised to hydrogen-1 nuclei which facilitates high resolution images with unprecedented soft tissue contrast but lacks specificity as it only offers an indirect link to pathologies. The study of other MR-observable nuclei (so called x-Nuclei MRI) offers the potential to extend standard MRI to the detection of pathologies without apparent structural abnormalities and enhance therapy monitoring capabilities. Sodium as the second most abundant MR-observable nucleus and as a direct link to cell integrity and vitality via the Sodium-Potassium-Pump promises means for a quantitative insight into pathological processes.

Despite its potential and its early beginnings in the 1980s, Sodium MRI is still considered a niche of MRI and plays no significant role in clinical routine. Its progression is hampered by its relatively low in vivo signal strength and challenging NMR-signal characteristics. While the former can be mitigated through the use of stronger magnetic fields, the latter dictates the acquisition principle but also provides great analysis potential. This thesis focusses on the second challenge, the Sodium NMR-signal, and exploits its aspects across the three main stages of an MRI experiment: signal acquisition, signal reconstruction, and signal analysis.

Beginning with signal acquisition, this thesis introduces zG_{RF} -RHE, an improved sequence timing concept for a reduction of encoding time. Compared with the conventional ultra-short echo time (UTE) sequence timing approach, the presented technique mitigates T_2^* -induced blurring artefacts and improves image SNR. It illustrates a general sequence timing concept with applicability to any centre-out trajectory design.

With regards to signal reconstruction, this work demonstrates a comprehensive investigation of Compressed Sensing (CS) reconstructions with a focus on parameter optimisation and an evaluation of accurate image intensity reconstructions.

Lastly, concerning both acquisition and signal analysis, this thesis investigates the diverse Sodium NMR-signal characteristics. It presents an optimised multi-echo acquisition scheme together with a Rician-noise corrected parameter estimation approach facilitating a differentiation of underlying motion regimes. It provides a time-efficient measurement protocol from which multiple parameters are obtainable within the course of a standard Sodium-density weighted acquisition.

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List of Publications

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Conference abstracts

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Further Scientific Contributions

Conference Abstracts

- Syeda, W.T., **Blunck, Y.**, Ng, A.C.L., Cleary, J.O. and Johnston, L.A. "A Continuum of Components: Robust Parameter Mapping in Sodium MRI", *Proceedings of the 26th Annual Meeting of ISMRM*, Paris, France, 2018.
- Kolbe, S.C., **Blunck, Y.**, Glarin, R.K., Taqdees, S.W., Moffat, B.A., Ordidge, R.J., Johnston, L.A. and Cleary, J.O. "Interpreting short and long 23 Na relaxation components in human brain: comparisons with tissue microstructure at 7 Tesla.", *Proceedings of the 26th Annual Meeting of ISMRM*, Paris, France, 2018.
- Korte, J.C., Tahayori, B., Farrell, P.M., **Blunck, Y.** and Johnston, L.A. "Efficient imaging of Rabi modulated trajectories using balanced Steady-State Driven Trajectory (bSSDT) imaging", *Proceedings of the 26th Annual Meeting of ISMRM*, Paris, France, 2018.
- Cleary, J. O., Ng, A., Shanahan, C., **Blunck, Y.**, Strik, M., Moffat, B. A., Kilpratck, T. J., Ordidge, R. J. and Kolbe, S. C. "Ultra High Field Regional Quantitative Susceptibility Mapping in Patients with Relapsing-Remitting Multiple Sclerosis: A Pilot Study.", *Proceedings of the 25th Annual Meeting of ISMRM*, Honolulu, USA, 2017.
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- ANZMAGazine. "Publication Highlights: 'Salt in the wound: tackling the challenges of Sodium MRI', 5(2), Dec 2017.

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Nuclear Magnetic Resonance is a physical phenomenon that was independently described by Felix Bloch and Edward Purcell in 1946 (Bloch, 1946; Purcell et al., 1946). It relates to the behaviour of nuclei in a magnetic field and provides means for the investigation of their properties. The fundamental importance of this principle earned the two discoverers the Nobel prize in 1952. Only a few decades later, it was extended to provide spatial encoding during an experiment and henceforth enabled ‘imaging’, i.e. a spatially resolved investigation of nuclei based on magnetic resonance (Lauterbur, 1973; Mansfield, 1977), an innovation that is nowadays referred to as Magnetic Resonance Imaging (MRI). Its revolutionary contributions to Medicine were rewarded with the Nobel prize in Medicine for Paul Lauterbur and Sir Peter Mansfield in 2003. These discoveries were the starting point of high-paced technological and methodological developments with immense contributions to medical diagnosis and treatment planning and ongoing vigorous research up until today.

MRI experiments can be performed on any nucleus with an odd number of protons and/or neutrons. Naturally, due to its high natural abundance and favourable physical properties, hydrogen-1 nuclei (^1H or short ‘proton’) are routinely chosen for human in vivo MRI application. The high concentration of protons within human soft tissues and fluids facilitate high resolution imaging. Additionally, distinct MR signal characteristics between tissue types bestow MRI with unprecedented imaging capacities for non-invasive soft tissue contrast. The complex interaction of nuclei within their environments and the variety of technical components that interact during an MRI experiment equip such image acquisitions with a multitude of parameters. It is these experimental parameters that make MRI so versatile by enabling a fine-tuning of tissue contrasts as well as the detection of functional parameter. Common MRI contrasts are selective to, e.g. the total number of nuclei (spin-density), NMR-signal related properties (T_1 , $T_2^{(*)}$) or local interactions (susceptibility). Typical functional parameters that can be inferred are diffusion, perfusion or functional activity.

Proton-based MRI has a significant impact on clinical routine and a wide application in research. Nevertheless, the information content that can be inferred from hydrogen-1 nuclei is relatively limited due to its non-specific relation to biochemical processes. The detection of other nuclei (so called x-Nuclei) has the potential to close this gap. MR-observable nuclei with physiological meaning in the human body include for example: Sodium (^{23}Na) with its direct link to cell vitality; Phosphorus (^{31}P) as a

correlate for cellular energy levels; or Oxygen (^{17}O) providing insight into the oxygen metabolism.

The potential of x-Nuclei MRI was recognised early. In 1985, only a few years after the first proton-based images were published, Sodium was the second nucleus in the human body that was imaged non-invasively using MRI (Hilal et al., 1985). The choice of Sodium ions for first in vivo x-Nuclei experiments is again grounded on natural abundance since, after hydrogen, it constitutes the second highest concentration of MR-observable nuclei in biological tissues. Despite these early beginnings, x-Nuclei imaging in general and Sodium MRI in particular, did not see the same high-paced progression as proton-based MRI techniques. This downturn was mostly caused by the low quality of Sodium images which were significantly impeded by technical limitations as well as the low in vivo concentration and complicated NMR-signal characteristics of Sodium nuclei. The experimental difficulties were more and more overcome towards the end of the last century through significant technical improvements of both, hardware, i.e. coil and magnet developments, and software, i.e. acquisition strategies. Particularly the movement towards higher magnetic field strengths with the associated linear increase in achievable image signal-to-noise ratio have boosted the application of Sodium MRI in the last years.

Today, Sodium MRI has come a long way with an ever increasing number of clinical studies and investigated pathologies. Nevertheless, Sodium image quality is still comparatively low and current Sodium MRI research is mostly routed along two paths: 1) technological advancements related to image acquisition and reconstruction and 2) the application of new emerging techniques across a range of pathologies. This thesis is concerned with the former path, i.e. Sodium MRI method development, and is particularly focused on the signal acquisition and reconstruction as well as its analysis. The main interests are an improvement of image quality (Chapter 5), a reduction of acquisition time (Chapter 6) and an investigation of signal characteristics in human brain images (Chapter 7).

Thesis Outline

This thesis is structured in two parts. **Part I** provides the motivation and theoretical background of Sodium MRI. It is structured in three chapters and outlines the physiological basis of Sodium ions in biological tissue as well as some relevant NMR physics and the resulting imaging requirements for Sodium nuclei.

Chapter 2 Physiological Role of Sodium describes the biological background of Sodium ions in the human body. It provides an overview of the biochemical meaning of Sodium ions in healthy physiology. In particular, it covers its significance in cell metabolism and integrity governed by the Sodium-potassium-pump as well as its function as a counter-balancing ion for large macromolecules in extracellular spaces. Furthermore, the disturbances of Sodium ion homeostasis in a range of pathological conditions across the human body are discussed briefly.

Chapter 3 Nuclear Magnetic Resonance reviews the fundamentals of Nuclear Mag-

netic Resonance from a quantum mechanical perspective. This framework is required for the understanding of the particular NMR-signal characteristics of Sodium nuclei. The chapter commences with an introduction to NMR quantum mechanics, followed by a description of Sodium $3/2$ -spin dynamics. Particular attention is given to the relaxation mechanism which provides an interesting means for a deeper analysis of the underlying spin environment. At the end, a brief discussion of Sodium-based NMR experiments with regards to its signal-to-noise ratio and quantitative aspects is given.

Chapter 4 x-Nuclei Magnetic Resonance Imaging is the last background chapter and closes the circle from physiology and NMR principles to imaging. It describes both signal detection and reconstruction of Sodium MRI. It commences with a recapitulation of NMR-based imaging principles where particular attention is given to MRI aspects with a special relevance for the remainder of this work. The chapter proceeds with an overview of Sodium MRI specific imaging approaches. With regard to the acquisition side, this chapter looks at common sampling trajectories and discusses advantages and disadvantages of current sequence timing approaches with relevance to Sodium signal detection. The last part of this chapter deals with the reconstruction of Sodium images. Due to the commonly non-Cartesian acquisition approaches, this part requires special attention in Sodium MRI. Two common reconstruction approaches are examined: 1) standard image reconstruction based on regridding or a non-uniform Fourier Transform; 2) iterative reconstruction based on Compressed Sensing techniques. The latter approach is of special interest due to its significant potential for shortened image acquisition.

Part II illustrates the key novel contributions of this work. Within the scope of this thesis, advancements in Sodium MRI were explored from three different angles each of which is represented in a single chapter in this second part. They are followed by a final conclusion chapter.

Chapter 5 Signal Acquisition introduces zero-Gradient Ramped-Hybrid-Encoding (zG_{RF} -RHE), a new sequence timing approach in Sodium MRI that aims at an optimisation of encoding time. This method belongs to the Ramped Hybrid Encoding (RHE) sequence class and is akin to PETRA. The presented method aims to overcome the inherent inefficiency imposed on data acquisition via the dead-time delay while still adhering to the necessary high flip angle excitation resulting from the low Sodium signal. The sequence approach is compared with a standard Ultra-short echo time (UTE) image acquisition in simulations, phantom and human in vivo experiments. An improvement of image SNR and a reduction of T_2^* -related blurring effects are shown.

Chapter 6 Signal Reconstruction explores the reconstruction aspects of Sodium MRI. It investigates common Compressed Sensing (CS) approaches on human brain Sodium data and aims to identify the potential for a reduction of acquisition time while maintaining adequate image quality and preserving quantitative assessment aspects. This chapter provides a comprehensive investigation of CS parameter in radially undersampled Sodium MRI acquisitions of five healthy human subjects. The analysis presents an optimisation study of CS reconstruc-

tion parameter and shows that, with an optimised reconstruction setup, up to four times undersampling yields good image quality and maintains structural details. For the quantitative interpretation, the denoising aspects of CS-based reconstructions have been investigated and suggest the exclusion of background signal for quantification purposes.

Chapter 7 Signal Analysis investigates one of the major potentials of Sodium MRI inherent in its rich signal information content. This chapter presents 3D-MERINA, a sequence for the 3D radial acquisition of gradient-refocused echoes, together with a two-step estimation procedure for signal decay parameter. This chapter illustrates the sequence scheme which is optimised for echo readout durations and is applied to phantom and in vivo human brain acquisitions. The analysis of the acquired echo time series allows for an estimation of bi-exponential signal decay based on a Rician noise corrected maximum likelihood estimator and facilitates a concomitant inference of fluid and tissue signal origins. The acquisition protocol offers a time-efficient signal detection that yields information about several quantitative parameter during a single Sodium-density weighted MRI experiment.

Chapter 8 Conclusion presents the last chapter of this thesis and summarises the main contributions of this work. Furthermore, an outlook for future research is provided.

Theory and Background

Motivation and Principles of Sodium MRI

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Sodium is one of the most abundant cations in the human body and a cornerstone of various biochemical processes and functions. A deeper understanding of its role in physiological processes foreshadows the comprehension of its relation to certain pathologies. The physiological role forms the basis for a discussion about potential implications for early diagnosis and therapy control. Hence, this chapter intends to give an overview of the biological role of Sodium ions in the human body and briefly outlines how its disturbances relate to pathologies.

2.1 Sodium in Health

Sodium's role in the human body can be loosely categorised in two parts: an active, i.e. energy driven, task related to the well-known Sodium-potassium pump (Na^+/K^+ -ATPase) and a passive contribution as a counterbalancing ion to macromolecules (Thulborn, 2016). Both roles yield clinical biomarker potential and are discussed in the following sections.

2.1.1 Membrane Transport – the active role

There exists a strong electrochemical gradient between intra- and extracellular spaces. This gradient is a fundamental cell characteristic and relates to the amount of Sodium and potassium ions in and outside the cell: in healthy cells the concentration of Sodium ions inside the cell (10-15 mM) is roughly 10 times lower than outside (140-150

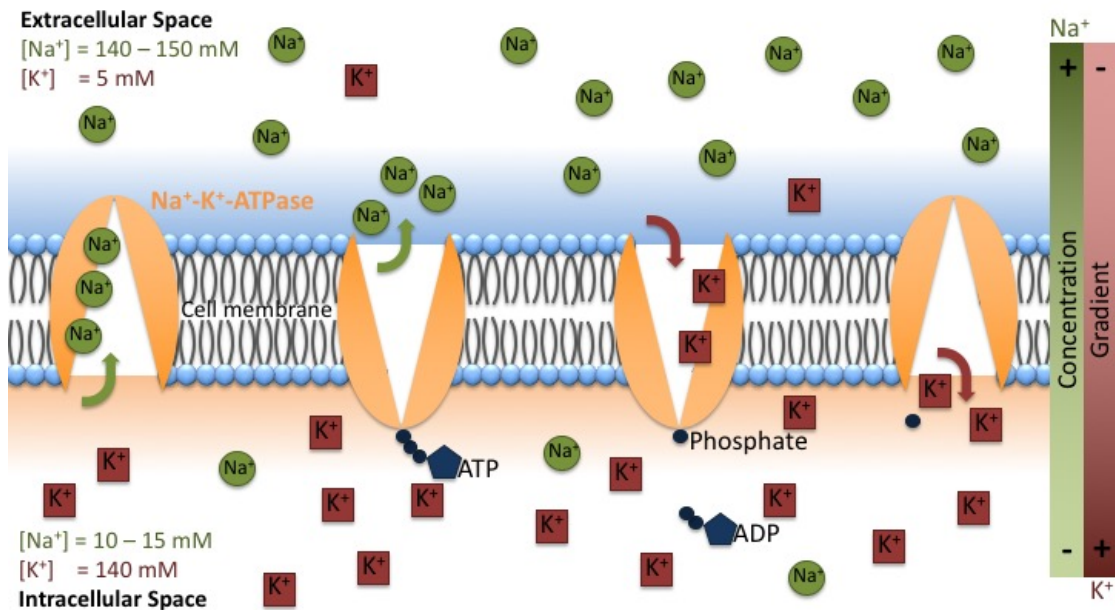


Figure 2.1: Illustration of Na⁺/K⁺-ATPase activity. The protein complex is located on the cell membrane and translocates ions (Removal of three Sodium ions from intracellular space; Insertion of two Potassium ions into the cell). The ion pumping is powered via the hydrolysis of ATP to ADP and results in an ion concentration gradient between intra- and extracellular space.

mM); contrarily, the intra- and extracellular concentrations of potassium are around 140 and 5 mM, respectively.

Several exchange mechanisms provide a route for the influx and outflux of Sodium ions – the first and foremost process is governed via the Na⁺/K⁺-ATPase. This membrane-bound protein complex is found in most eukaryotic¹ cells and can be considered as an enzyme (ATPase) or ion-pump where the latter viewpoint has resulted in the commonly used term Sodium-potassium pump or just Sodium pump.

The energy consuming pumping mechanism is of fundamental importance to various processes and earned the discoverer of this complex, Jens Christian Skou, a share of the Nobel prize in 1997 (Skou, 1957). In the following, the principal functions relating to the Na⁺/K⁺-ATPase are briefly discussed.

Membrane Transport The pump function of the protein complex facilitates a controlled translocation of Sodium and potassium ion across the semi-permeable membrane that encompasses a cell. This transport mechanism works against the existing electrochemical ion concentration gradient and consequently requires energy that is supplied via the hydrolysis of adenosine triphosphate (ATP). The pumping process is depicted in Figure 2.1 and consists of the shifting of three Sodium ions out of the cell and two potassium ions into the cell, i.e. ultimately removes one positive charge from inside the cell. The continuous operation of this process powers several secondary transport proteins that enable the release and uptake of essential substrates and products, like the acquisition of metabolites and nutrients (e.g. glucose), the transport of other ions (e.g. cal-

¹A eukaryote is a cell with an enclosed nucleus.

cium, proton) or the translocation of neurotransmitter (e.g. glutamate). It is remarkable that all these complex membrane transports essentially go down to a mutual power provider, highlighting the vital significance of the Sodium-potassium pump to the cell's metabolism and function.

Homeostasis A secondary active transport mechanism that plays a key role in the maintenance of stable bodily functions is the *Na-K-Cl cotransporter*. Its activity is dependent on the electrochemical gradient of Sodium, i.e. the activity of the Na^+/K^+ -ATPase. The Na-K-Cl cotransporter is a protein that is found in cell membranes of fluid secreting organs, particularly the kidneys, and supports the absorption of Sodium, potassium and chloride. The kidneys are a regulating organ that is in charge of filtering plasma and maintaining homeostatic body fluids and electrolytes via the production of urine and the concomitant excretion of by-products or the reabsorption of water. The urine production is strongly dependent on extracellular Sodium levels in the kidney medulla. A high Sodium concentration gradient yields a reabsorption of water based on the countercurrent principle. Secondary effects are the regulation of blood volume and blood pressure as well as pH levels.

Cell volume Intra- and extracellular compartments are filled with macromolecules and positively and negatively charged ions. The sum of the chemical compounds within a cell define its *osmolarity* or *osmotic concentration*. Depending on the ionic concentration outside the cell water influx aims to establish an equilibrium via a passive process called *osmosis*. The Na^+/K^+ -ATPase activity is an antagonist of this mechanism that regulates the ion gradient of Sodium and potassium in and out the cell and consequently regulates the water influx and resulting cell volume. A disturbance of this regulation leads to cell swelling and eventual rupture.

Signal transmission The removal of a positive charge carrier by the Na^+/K^+ -ATPase yields a negative potential across the cell membrane (negative 60 – 70 mV). It is commonly referred to as *resting potential*. For a group of cells called *excitable cells* this potential provides the basis for the transmission of a signal. Examples for excitable cells are neurons and muscle cells where the former propagate a signal for communication across cells and the latter utilise the signal as an impulse for intracellular processes like contraction. The signal transmission is based on disturbances of the resting state potential beyond a certain threshold which cause *voltage-gated ion channels* on the cell membrane to open and facilitate an influx of Sodium ions. The sudden inflow of Sodium ions leads to a reversal of the membrane polarity with a resulting closure of these ion channels. The re-establishment of the resting state potential is obtained via the Na^+/K^+ -ATPase.

2.1.2 Counter-ion – the passive role

Articular cartilage is the elastic surface coating of long bones at the joints and consequently a component of the musculoskeletal system. Its functionality is of mechanical nature supporting load-bearing via the absorption of compressive stress forces and reducing friction between joints during motion. This tissue type only contains a small

cellular content (< 5% of cartilage volume) which consists exclusively of chondrocytes producing collagen (15 – 20% of cartilage volume) and proteoglycan (3 – 10% of volume) for the extracellular matrix. The latter is a macromolecule with attached glycosaminoglycans (GAG). It is these glycoproteins that yield a negative charge of the extracellular matrix of articular cartilage. This negative net charge attracts positively charged counter-ions, e.g. Sodium, for an establishment of electroneutrality. In healthy cartilage the molar concentration of Sodium ions is as high as 300 mM and therefore provides an insightful correlate for GAG content. The accumulation of Sodium ions attracts water which eventually manifests the biggest component of cartilage with 65 – 80%.

2.2 Sodium in Disease

Sodium ions fulfil versatile tasks within the complex biochemistry of the human metabolism. Abnormalities of these strongly regulated physiological processes are expected to play a central role in the etiology of various diseases. The activity of the Na^+/K^+ -ATPase is essential for the vitality and functioning of any animal cell. A breakage of a cell's energy metabolism (i.e. insufficient ATP supply) or leakage in the membrane integrity yield an increase of intracellular Sodium concentration. The concomitant change in osmolarity leads to an inflow of water and ultimately to cell death. Intracellular Sodium concentrations are, therefore, a valuable marker for tissue viability and cell membrane integrity.

Excellent reviews of the link between a disturbed Sodium balance and certain pathologies have been published (Madelin et al., 2014; Thulborn, 2016). For the scope of this thesis, Sodium within the human brain was of particular interest and the informative potential of Sodium within a few selected neurological applications will be focussed on in the following overview. For completeness, other promising applications for Sodium ion detection across the human body will also be reviewed briefly.

2.2.1 Brain diseases

Metabolic parameters based on Sodium ion distribution have been discussed for a wide range of neurological applications. A malfunctioning of the Na^+/K^+ -ATPase is coupled with cellular integrity and tissue viability rendering Sodium ions as a probe for neurological diseases with effects on brain tissues.

Stroke Stroke is characterised by an impairment of blood supply to the brain with a fast onset of neurological symptoms. It is a major cause of subsequent disability or death worldwide. Depending on the origin of the blood flow interruption, stroke is subclassified into hemorrhagic (i.e. blood vessel rupture) or ischaemic (i.e. blockage of blood supply to the brain) where the latter is the more common manifestation ($\approx 87\%$).

The decrease in blood supply exhausts the provisioning of oxygen to the brain tissue and consequently affects the hydrolysis rate of ATP in the cells. The lack of energy production depletes the ion pumping function dissipating the ion homeostasis via an influx of Sodium ions into the cell and ultimately causing cell death with a concomitant increase of extracellular spaces. Sodium ion distribution across tissue compartments is therefore a sensitive marker of cell health and can aid at identifying viable tissue. The management and treatment of stroke is time-critical and aims at a reperfusion of viable brain tissue. A measurement of Sodium ions can be used to infer tissue viability and the likelihood of recovery for a better informed therapy decision-making and improved outcomes.

Tumours The abnormal growth of tissue called *neoplasm* or *tumour* can be of benign, potentially malignant or malignant nature. The latter case is referred to as cancer and is invasive and destructive towards neighbouring tissues, can spread to other body parts, and, if untreated or unresponsive to treatment, is eventually fatal. The unregulated cell division is associated with a reduced Na^+/K^+ -ATPase activity, i.e. an increase in intracellular Sodium concentration. Furthermore, angiogenesis, i.e. the neovascularisation of tumour tissue, leads to an increased extracellular matrix. Consequently, tumour cells differ significantly from normal cells with regards to Sodium ion concentration manifested in an overall increase of Sodium ions.

The detection of Sodium concentration for an identification of tumour tissue is, however, not the main potential of Sodium ion based investigations. Other than in stroke where Sodium ions are of interest for an appropriate treatment decision, the study of Sodium ions in tumours is of great potential in actual therapy monitoring. A measure of tissue viability facilitates an evaluation of tumour cell death, i.e. the reverse aspect of the discussion in stroke. Relating to the viability of a cell based on Na^+/K^+ -ATPase activity provides a direct probe for tumour cell death and, hence, treatment efficacy.

Multiple Sclerosis Multiple sclerosis is a debilitating disease with a versatile profile and progression. A detailed understanding of the complex cellular and molecular mechanisms causing the neurodegeneration is still subject of ongoing research. The disease is characterised by inflammations (focal and diverse) in white matter resulting in axonal demyelination, leading to neuronal injury and loss.

An overload of intra-axonal calcium is associated with axon degeneration and is suggested to result from high influx of Sodium ions into the axon (Waxman et al., 2004; Waxman, 2008). A partial blockade of Sodium channels prevented axonal degeneration in experimental models (Lo et al., 2003; Bechtold et al., 2006). Sodium channel blockers may be neuroprotective if given in early MS (Raftopoulos et al., 2016). Consequently, an early detection of abnormalities in the neuronal energy metabolism is proposed as a marker for the pathogenesis of neuronal death. Oedema resulting from inflammation as well as an expansion of extracellular spaces due to axonal loss can cause an increased Sodium concentration.

2.2.2 Other organ diseases

Beyond the brain, Sodium ions provide a precious marker in a range of other diseases across the human body, some of which are briefly outlined below.

Kidney (Kidney disease) The kidneys are an essential organ regulating various physiological parameters, e.g. electrolyte concentration, blood volume, toxin filtration and pH. Kidney function is partly driven by the extracellular Sodium concentration in the kidneys. The measurement of this Sodium concentration can therefore provide insight into kidney function and support an assessment of kidney failure or the monitoring of kidney transplantation outcome without the need of exogenous contrast or a radioactive tracer.

Heart (Myocardial infarction) A myocardial infarction, also commonly referred to as heart attack, describes the sudden decrease or total interruption of blood supply to the cardiac muscles. Just like in stroke, the insufficient supply of oxygen due to the decrease in blood flow yields a failure of the Na^+/K^+ -ATPase and eventual cell death. Again this is preceded by an increased influx of Sodium ions into the cell. An extensive occurrence of cell death leads to the formation of scar tissue and oedema which cause an expansion of extracellular spaces. The value of Sodium ion measurement in cardiac disease is therefore again manifested in an evaluation of tissue viability and infarction assessment together with an appropriate treatment planning.

Musculoskeletal (Osteoarthritis) Osteoarthritis is an age-related, degenerative disease of the articular cartilage. Early stages of this disease are characterised by a reduction in GAG and subsequent decrease of negative charges in the extracellular matrix. The lower potential attracts less positive Sodium counterions and, hence, detecting Sodium content in articular cartilage is a potent correlate of GAG content for an assessment of osteoarthritis and cartilage repair therapies.

2.3 Motivation for Sodium Imaging

Apart from the prevention of illness, the main focus of healthcare and research lies on an efficient management of diseases which is grounded in an early and accurate diagnosis as well as the monitoring of treatment. Many disease manifestations commence on a cellular level with perturbations of cell structure and metabolism. Ideally, detection techniques measure the onset of biochemical changes prior to the onset of clinical symptoms and facilitate an accurate assessment of physiological parameter following treatment.

Imaging methodologies are a non-invasive means for a spatially localised depiction of a particular parameter, e.g. Sodium ion density. The attraction of Sodium-based imaging lies in its direct link to biochemical information like cell integrity and tissue

viability bestowing biomarker potential for diagnostic and monitoring applications. The concept of magnetic resonance imaging (MRI) establishes a means for the non-invasive, in vivo detection of Sodium ions and is therefore of great clinical interest. Compared with the commonly acquired hydrogen-1 nuclei (^1H) MRI, Sodium ions provide a specific marker for cell physiology enabling a distinct interpretation. The advancement of Sodium MRI techniques in human brain applications is the purpose of this thesis.

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3.1 Nuclear Spin and Angular Momentum

Fundamentally, any physical matter is made up of atoms which themselves consist of an atomic hull, containing negatively charged electrons, and a nucleus, comprising charge-free neutrons and positively charged protons. Essential physical properties originate from these elementary particles. This work is concerned with one of these properties in particular, spin – more specifically the nuclear spin.

Spin is an intrinsic property of particles. It is a purely quantum mechanical concept and as such very abstract and difficult to grasp. It is often analogised with a rotational motion (like a tiny planet) and implies an angular momentum. Protons in atomic nuclei present a system of spin angular momenta, the nuclear spin I , a property that provides a probe into the atomic structure as well as the molecular composition from several atoms up to macroscopic information of an investigated sample.

Nuclear spin I (henceforth simply denoted spin) is a fundamental characteristic of atomic nuclei – just like its atomic number Z (number of protons) and mass number A (number of nucleons, i.e. protons and neutrons). For a spin to be observable it needs to be different from 0 (i.e. consist of an odd number of protons and/or neutrons). Unfortunately, common nuclei in organic substances, like Carbon-12 and Oxygen-16, possess spin $I=0$. Consequently, Hydrogen-1 (routinely referred as ‘proton’ due to the single proton in the nucleus) has become the nucleus of choice for standard clinical applications. It exhibits a spin-1/2 and provides a high in vivo concentration.

This thesis deals with Sodium-23, the 23rd element of the periodic table and only stable isotope of Sodium, consisting of 11 protons and 12 neutrons in the nucleus. Other than proton, it is a spin-3/2 which results from the 11th unpaired proton on the outermost nuclear shell. As will be discussed in the remainder of this chapter, spins $> 1/2$ entail distinct properties which make such nuclei interesting and challenging at the same time.

3.2 Introduction to Quantum Mechanics

Quantum Mechanics, a physics field which only arose in the early 20th century, is concerned with the description of energy levels in particles and their atomic complexes. Its vast theory is beyond the scope of this thesis. However, some of its aspects are essential to an understanding of spin-3/2 dynamics and shall be briefly introduced here. The fundamental concepts of Quantum Mechanics as well as common mathematical techniques and notations will be reviewed. The description closely follows [Levitt \(2001\)](#) and [Dubbers and Stöckmann \(2013\)](#) to which the interested reader is referred for more comprehensive derivations and details. A complete description of magnetic resonance concepts can be found in [Slichter \(1990\)](#), [Abragam \(1961\)](#) and [Cohen-Tannoudji \(1977\)](#).

3.2.1 Wavefunction

Wavefunctions are mathematical descriptions of a system, providing probabilities for so-called quantum states. In Quantum Mechanics these states are quantised, i.e. they are limited to discrete values. In this work we are concerned with nuclear spin whose wavefunctions Ψ are given by

$$\Psi = \sum_j a_{m_j} |m_j\rangle \quad (3.1)$$

where $|m_j\rangle$ represents the spin-states and a_{m_j} is a complex-valued coefficient that relates to the probability of the respective spin-state.

The Dirac notation is commonly utilised in Quantum Mechanics and is notated through angle brackets $\langle \cdot | \cdot \rangle$. Its individual components are referred to as ‘bra’ $\langle m|$ and ‘ket’ $|m\rangle$, where the ‘ket’-notation implies the adjoint of its ‘bra’-notation. The Dirac notation can be applied to spin-states as well as wavefunctions and operators (which will be discussed in the next section).

Spin-states are orthonormal. Hence,

$$\langle m_j | m_k \rangle = \delta_{jk} \quad (3.2)$$

with δ_{jk} being the Kronecker delta function. The inner product $\langle \Psi_{m_j} | \Psi \rangle = a_{m_j}^* \langle m_j | \Psi \rangle = a_{m_j}^* a_{m_j}$ provides the magnitude of a_{m_j} which indicates the probability of finding a spin in state m_j .

3.2.2 Operator

Operators are a cornerstone in Quantum Mechanics. They are commonly denoted by a hat (^) and act on wavefunctions to describe the probability for an observation in an experiment. A wide range of operators exists, however, for it to provide access to the experimental observation of a system property it needs to be *Hermitian*, i.e. $\hat{Q} = \hat{Q}^\dagger$ with $\hat{Q}^\dagger$ describing the *adjoint*¹ of operator $\hat{Q}$.

For this work, the energy of a particle system is of interest. Operators acting on energy are termed *Hamiltonians* and will be more closely investigated for spin-3/2 in Section 3.3.3.

Special attention needs to be given to some operator relationships:

Commutation The commutation of two operators $\hat{Q}_1$ and $\hat{Q}_2$ is given by

$$[\hat{Q}_1, \hat{Q}_2] = \hat{Q}_1 \hat{Q}_2 - \hat{Q}_2 \hat{Q}_1 \quad (3.3)$$

If Equation 3.3 is zero, operators $\hat{Q}_1$ and $\hat{Q}_2$ are said to *commute*.

Anti-commutation, denoted by $[\cdot, \cdot]_+$, is defined as $[\hat{Q}_1, \hat{Q}_2]_+ = \hat{Q}_1 \hat{Q}_2 + \hat{Q}_2 \hat{Q}_1$.

Cyclic Commutation Three operators $\hat{Q}_1$, $\hat{Q}_2$ and $\hat{Q}_3$ are said to commute cyclically if a cyclic permutation of two operators generates the third, i.e.

$$\begin{aligned} [\hat{Q}_1, \hat{Q}_2] &= i\hat{Q}_3 \\ [\hat{Q}_3, \hat{Q}_1] &= i\hat{Q}_2 \\ [\hat{Q}_2, \hat{Q}_3] &= i\hat{Q}_1. \end{aligned} \quad (3.4)$$

Sandwich formula The cyclic commutation of three operators entails the following relationship

$$\exp\{-i\theta\hat{Q}_1\} \hat{Q}_2 \exp\{+i\theta\hat{Q}_1\} \hat{Q}_2 = \hat{Q}_2 \cos \theta + \hat{Q}_3 \sin \theta \quad (3.5)$$

In a geometric analogy this can be interpreted as a 'rotation' of operator $\hat{Q}_2$ by operator $\hat{Q}_1$ with angle θ .

The sandwich formulation introduced exponential of operators which can be approximated through an expansion into

$$\exp\{i\hat{Q}\} = \mathbb{1} + i\hat{Q} + \frac{i^2}{2!}\hat{Q}^2 + \frac{i^3}{3!}\hat{Q}^3 + \dots \quad (3.6)$$

where $\mathbb{1}$ defines the unity operator.

¹The adjoint of an operator is its conjugate or conjugate transpose for matrix operators.

3.2.2.1 Angular Momentum Operator

The spin angular momentum I is of central interest in this work. For the description of its orientation in 3-dimensional space there exist three operators $\hat{I}_x$, $\hat{I}_y$ and $\hat{I}_z$ describing the angular momentum along Cartesian axes. These operators are both Hermitian and commute cyclically.

Additionally, so-called *ladder* or *shift operators* are useful complements to angular momentum operators. The *raising* $\hat{I}^+$ and *lowering* $\hat{I}^-$ operator relate to the Cartesian angular momentum operators via:

$$\begin{aligned}\hat{I}^+ &= \hat{I}_x + i\hat{I}_y & \hat{I}_x &= \frac{1}{2}(\hat{I}^+ + \hat{I}^-) \\ \hat{I}^- &= \hat{I}_x - i\hat{I}_y & \hat{I}_y &= \frac{1}{2i}(\hat{I}^+ - \hat{I}^-)\end{aligned}\quad (3.7)$$

The squared total angular momentum operator, $\hat{I}^2$, is given by

$$\hat{I}^2 = \hat{I}_x^2 + \hat{I}_y^2 + \hat{I}_z^2. \quad (3.8)$$

and commutes with all angular momentum operator, i.e. $[\hat{I}^2, \hat{I}_x] = [\hat{I}^2, \hat{I}_y] = [\hat{I}^2, \hat{I}_z] = 0$.

3.2.2.2 Rotations

The investigation of nuclear spin angular momenta makes extensive use of rotations; their application ranges from the description of excitation to relaxation behaviour of spin systems. Therefore it is useful to introduce *unitary*² rotation operators in accordance with Equation 3.5

$$\hat{R}_n(\beta) = \exp\{-i\hbar\beta\hat{I}_n\} \quad (3.9)$$

where n denotes a Cartesian angular momentum operator along the n -axis. The factor $\hbar$ stands for the reduced Planck's constant and is often incorporated into the physical units.

Rotation and respective angular momentum operator commute, i.e.

$$\hat{R}_n(\beta)\hat{I}_n\hat{R}_n(-\beta) = \hat{I}_n. \quad (3.10)$$

For a simplified investigation of spin dynamics it is often helpful to apply coordinate system transformation. This is done through three successive rotations. i.e. a three-dimensional rotation operator

$$\hat{R}(\alpha, \beta, \gamma) = \hat{R}_z(\alpha)\hat{R}_y(\beta)\hat{R}_z(\gamma) = \exp\{-i\hbar\alpha\hat{I}_z\}\exp\{-i\hbar\beta\hat{I}_y\}\exp\{-i\hbar\gamma\hat{I}_z\} \quad (3.11)$$

with α , β and γ denoting Euler angles.

²The adjoint of a unitary rotation operator is equal to its inverse, i.e. $\hat{R}^{-1} = \hat{R}^\dagger$

3.2.2.3 Irreducible Tensor Operator

NMR experiments can be decomposed into a series of operators acting on a spin system. As will be shown in the next section, an ensemble of spin-states can be conveniently expressed through tensors. It is possible to find a subset of tensors that provides an *irreducible* group of base operators. The transformation of these tensor operators during an NMR experiment simply results in a linear combination of the relevant tensor operators. Due to spherical symmetry and rotational effects of operators, the tensor description is closely related to spherical harmonics and, hence, also commonly referred to as *spherical irreducible* tensors.

3.2.3 Eigenfunction and Eigenvalues

Quantum mechanical properties of a system, i.e. quantum states, are described through wavefunctions. Operators are required for an observation of these quantum states. In fact, a fundamental concept in Quantum Mechanics is that it is actually only the *probability* of observing a certain state during an experiment that can be evaluated. For an operator to provide access to an eigenstate (i.e. *observable*) the respective wavefunction needs to be its eigenfunction. That means for a wavefunction $\Psi = |m\rangle$ the eigenequation is given by

$$\hat{Q}|m\rangle = q|m\rangle \quad (3.12)$$

where $|m\rangle$ and q are the respective eigenfunction and eigenvalue of the operator $\hat{Q}$. For a description of experiments with physical observables, the eigenvalue q needs to be real which necessitates the operator $\hat{Q}$ to be Hermitian. If an operator has distinct eigenvalues, i.e. no two eigenfunctions share the same eigenvalue, the eigenvalues are called *non-degenerate* (otherwise they are said to be *degenerate*). For Hermitian operators, eigenfunctions with distinct eigenvalues are, furthermore, orthogonal. It is also important to note, that two commuting operators share the same eigenstates.

The probabilistic nature of Quantum Mechanics cannot predict the outcome of an individual experiment. Rather, the average result of many observations is described.

$$\langle \hat{Q} \rangle = \Psi^\dagger \hat{Q} \Psi = \langle m | \hat{Q} | m \rangle \quad (3.13)$$

defines the *expectation value* of the observable operator $\hat{Q}$.

3.2.3.1 Spin angular momentum eigenstates

Of central importance are the eigenstates and eigenvalues of the total angular momentum operator $\hat{I}^2$, the z-component of the spin angular momentum operator $\hat{I}_z$ and the ladder or shift operators $\hat{I}^\pm$. A derivation of their eigenfunctions and eigenstates can be found in the [Appendix](#).

Eigenstates for nuclear spins are commonly denoted $|j, m\rangle$ with properties as summarised below:

- j can take integer or half-integer values and is commonly termed the *total angular momentum*.
- quantum number m is often named the *azimuthal quantum number* and ranges from $-j \leq m \leq j$ with a step size of 1. Hence, there exist $2j + 1$ values for m .
- the following eigenequations result:

Angular momentum operator along the z-axis

$$\hat{I}_z |j, m\rangle = \hbar m |j, m\rangle \quad (3.14)$$

Total square angular momentum operator

$$\hat{I}^2 |j, m\rangle = \hbar^2 j(j+1) |j, m\rangle \quad (3.15)$$

Ladder operators

$$\hat{I}^\pm |j, m\rangle = \sqrt{(j(j+1) - m(m \pm 1))} |j, m \pm 1\rangle \quad (3.16)$$

The eigenstates or ‘ket’s $|j, m\rangle$ are orthonormal basis vectors (cf. Equation 3.2) of a $(2j + 1)$ -dimensional Hilbert space. It is therefore convenient to express them as a $(2j + 1) \times 1$ vector

$$|j, m\rangle = \begin{pmatrix} 0 \\ \vdots \\ 0 \\ 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix} \quad (3.17)$$

where 1 occurs at the m^{th} position.

Based on this notation and the quantified number of possible eigenstates $|j, m\rangle$ it is convenient to write an operator as a square matrix with dimension $(2j+1)$. The rank of the matrix is given by j . The mapping of an operator into a matrix is called ‘representation’ and written as

$$I_{mm'}^{(j)} = \langle j, m | I | j, m' \rangle. \quad (3.18)$$

The matrix entries can be calculated through the operator eigenequations (3.14 – 3.16)

and operator relationships (Equations 3.7). They are given by

$$\langle j, m' | \hat{I}_x | j, m \rangle = (\delta_{m', m+1} + \delta_{m'+1, m}) \frac{1}{2} \sqrt{j(j+1) - m'm} \quad (3.19)$$

$$\langle j, m' | \hat{I}_y | j, m \rangle = (\delta_{m', m+1} - \delta_{m'+1, m}) \frac{1}{2i} \sqrt{j(j+1) - m'm} \quad (3.20)$$

$$\langle j, m' | \hat{I}_z | j, m \rangle = \delta_{m', m} m \quad (3.21)$$

$$\langle j, m' | \hat{I}^+ | j, m \rangle = \delta_{m', m+1} \sqrt{j(j+1) - m'm} \quad (3.22)$$

$$\langle j, m' | \hat{I}^- | j, m \rangle = \delta_{m'+1, m} \sqrt{j(j+1) - m'm} \quad (3.23)$$

$$\langle j, m' | \hat{I}^2 | j, m \rangle = \delta_{m', m} j(j+1) \quad (3.24)$$

The matrix representations of spin-3/2 systems are presented in the [Appendix](#).

3.2.3.2 Rotation and Wigner D-matrix

In the following, the rotation concept introduced in Section [Rotations](#) is re-visited and investigated for the effects on spin eigenstates $|j, m\rangle$. Using Equation 3.11, the application of a rotation operator on spin eigenfunctions can be expressed as the consecutive operations

$$\hat{R}(\alpha, \beta, \gamma) |j, m\rangle = \exp\{-i\alpha \hat{I}_z \hbar\} \exp\{-i\beta \hat{I}_y \hbar\} \exp\{-i\gamma \hat{I}_z \hbar\} |j, m\rangle \quad (3.25)$$

As shown before, the z-component spin operator $\hat{I}_z$ preserves m , whereas the y-component spin operator $\hat{I}_y$ consisting of ladder operators (cf. Equation 3.7) raises or lowers m . The spin quantum number j is unaffected by both operators. Rotations can, hence, be interpreted as a linear combination of operators transforming quantum number m to m' .

$$\hat{R}(\alpha, \beta, \gamma) |j, m\rangle = \sum_{m'} D_{m'm}^{(j)}(\alpha, \beta, \gamma) |j, m'\rangle \quad (3.26)$$

where D introduces the Wigner D-matrix.

Since the eigenfunctions are orthogonal, the rotation matrix can be obtained through

$$D_{m'm}^{(j)}(\alpha, \beta, \gamma) = \langle j, m' | \hat{R}(\alpha, \beta, \gamma) | j, m \rangle \quad (3.27)$$

$$= \langle j, m' | \exp\{-i\alpha \hat{I}_z \hbar\} \exp\{-i\beta \hat{I}_y \hbar\} \exp\{-i\gamma \hat{I}_z \hbar\} | j, m \rangle \quad (3.28)$$

Using the eigenequation of operator $\hat{I}_z$ this expression can be significantly simplified. Since $\hat{I}_z |j, m\rangle = m\hbar |j, m\rangle$

$$\exp\{-i\gamma \hat{I}_z \hbar\} |j, m\rangle = \exp\{-i\gamma m\} |j, m\rangle \quad (3.29)$$

$$\langle j, m' | \exp\{-i\alpha \hat{I}_z \hbar\} = \langle j, m' | \exp\{-i\alpha m'\} \quad (3.30)$$

This yields

$$D_{m'm}^{(j)}(\alpha, \beta, \gamma) = \exp\{-i(\alpha m' + \gamma m)\} d_{m'm}^{(j)}(\beta) \quad (3.31)$$

where

$$d_{m'm}^{(j)}(\beta) = \langle j, m' | \exp\{-i\beta \hat{L}_y / \hbar\} | j, m \rangle \quad (3.32)$$

with $d_{m'm}^{(j)}$ commonly termed the *reduced* Wigner d-matrix. The rotation matrix $d_{m'm}^{(3/2)}$ is shown in the [Appendix](#).

3.2.3.3 Wigner-Eckart Theorem

The effects of a rotation operator on spin eigenstates can be expressed as a simple linear combination of basis tensors. The concept of describing a basis set for the expression of operator and spin-system interactions has been introduced in the previous Section ([Irreducible Tensor Operator](#)) and shall now be discussed in some more detail. Since spin operators are well representable in matrix notation, the concept of irreducibility shall now be extended to tensors. Irreducible tensor operators $T_{n,q}$ with rank $n = 0, 1, 2, \dots$ and order q show the same rotation behaviour

$$\hat{R}(\alpha, \beta, \gamma) T_{n,q} = \sum_{q'} D_{q'q}^{(l)}(\alpha, \beta, \gamma) T_{n,q'} \quad (3.33)$$

They are defined by the Wigner-Eckart Theorem ([Bowden and Hutchison, 1986](#); [Bowden et al., 1986](#))

$$\langle j, m | T_{n,q} | j, m' \rangle = \sqrt{2j+1} \langle jm' nq | jm \rangle \langle j || T_n || j \rangle \quad (3.34)$$

where $\langle jm' nq | jm \rangle$ describes the Clebsch-Gordan coefficients and $\langle j || T_n || j \rangle$, the *reduced matrix element*, which provides a scaling according to

$$\langle j || T_n || j \rangle = \sqrt{\left[\frac{n! n! (2j+n+1)!}{2^n (2n)! (2j-n)!} \right]}. \quad (3.35)$$

The number of irreducible tensor operators is related to its rank n by $2n+1$ (similar to the degeneracy of eigenvalues). Notably, irreducible tensor matrix elements are zero if $m' + q \neq m$. Irreducible tensor operator up to rank $n = 3$ for $j = 3/2$ are shown in the [Appendix](#).

It is possible to decompose the irreducible tensor operators into a linear combination of Cartesian spin operators. While such a decomposition is not necessary for the use of irreducible tensor operators, it assists their interpretation. Table 3.1 lists the tensor operators up to rank 3 for spins $j = 3/2$ together with a Cartesian operator decomposition and interpretation. Tensor operators are defined through their rank n and order q where the order is also commonly referred to as *coherence*.

Irreducible Tensor operators are orthogonal; to form a basis set they need to be scaled to unit length according to ([Bowden and Hutchison, 1986](#))

$$\hat{T}_{n,q} = \sqrt{\left[\frac{(2n+1)(2j-n)! 2^n (2n)!}{(2j+n+1)!} \right]} T_{n,q}. \quad (3.36)$$

Tensor Operator	Decomposition by Rank-0 and Rank-1 ST operators	Interpretation
$T_{0,0}$	$\mathbb{1}$	Identity
$T_{1,0}$	$\hat{I}_z$	proportional to longitudinal magnetisation m_z
$T_{1,\pm 1}$	$\mp \frac{1}{\sqrt{2}} \hat{I}^{\pm}$	symmetric and asymmetric combination (Equation 3.38) proportional to transverse magnetisation m_x and m_y , respectively
$T_{2,0}$	$\frac{1}{\sqrt{6}} (3\hat{I}_z^2 - j(j+1))$	quadrupolar spin polarisation
$T_{2,\pm 1}$	$\mp \frac{1}{2} [\hat{I}_z, \hat{I}^{\pm}]_+$	rank-two single-quantum coherences
$T_{2,\pm 2}$	$\frac{1}{2} \hat{I}^{\pm} \hat{I}^{\pm}$	rank-two double-quantum coherences
$T_{3,0}$	$\frac{1}{\sqrt{10}} (5\hat{I}_z^3 - \frac{3j(j+1)-1}{\hat{I}_z})$	octopolar spin-polarisation
$T_{3,\pm 1}$	$\mp \frac{1}{4} \sqrt{\frac{3}{10}} [5\hat{I}_z^3 - j(j+1) - \frac{1}{2}, \hat{I}_{\pm}]_+$	rank-three single-quantum coherences
$T_{3,\pm 2}$	$\frac{1}{2} \sqrt{\frac{3}{4}} [\hat{I}_z, (\hat{I}^{\pm})^2]_+$	rank-three double-quantum coherences
$T_{3,\pm 3}$	$\mp \frac{1}{2\sqrt{2}} (\hat{I}^{\pm})^3$	rank-three triple-quantum coherences

Table 3.1: Expression of Irreducible Tensor Operators with respect to Cartesian operators. $[\cdot, \cdot]_+$ indicates anti-commutation.

Consequently, for spin $j = 3/2$ systems the scaling factors are given by $\hat{T}_{0,0} = (1/2)T_{0,0}$; $\hat{T}_{1,q} = (1/\sqrt{5})T_{1,q}$; $\hat{T}_{2,q} = (1/\sqrt{6})T_{2,q}$; $\hat{T}_{3,q} = (\sqrt{2}/3)T_{3,q}$. The Hermitian conjugate $\hat{T}_{n,q}^{\dagger}$ is given by $\hat{T}_{n,q}^{\dagger} = (-1)^m \hat{T}_{n,-q}$, where $\hat{T}$ indicates a normalised operator according to Equation 3.36.

The symmetric (s) and antisymmetric (a) combinations of these unit operators are given by

$$\hat{T}_{n,q}(s) = \frac{1}{\sqrt{2}} (\hat{T}_{n,-q} + \hat{T}_{n,q}) \quad (3.37)$$

$$\hat{T}_{n,q}(a) = \frac{1}{\sqrt{2}} (\hat{T}_{n,-q} - \hat{T}_{n,q}). \quad (3.38)$$

3.3 Spin-3/2 Dynamics

The concept of eigenfunctions $|j, m\rangle$, operators $\hat{I}$ and in particular irreducible tensor operator $\hat{T}_{n,q}$ is fundamental to the description of interactions and observations in an

NMR experiment. The following section provides an overview of NMR-experiments on spin-3/2 systems from a quantum mechanical perspective.

3.3.1 Zeeman Eigenstates

Corresponding to the $2j + 1$ quantum numbers m of nuclear spins, there exist 4 eigenstates for Sodium spin $j = 3/2$ nuclei. In the absence of a magnetic field all eigenstates possess the same energy and are called degenerate. This degeneracy is lifted through the application of a magnetic field B_0 , a reaction which is called *Zeeman splitting* and which is schematically shown in Figure 3.1. As will be shown in Section 3.3.3.1 the energy shift between eigenstates depends on the applied magnetic field B_0 and the magnetic moment of the nucleus μ . The eigenstates are defined through the quantum numbers j and m and can be denoted

$$|\alpha_1\rangle = \left| \frac{3}{2}, +\frac{3}{2} \right\rangle; \quad |\alpha_2\rangle = \left| \frac{3}{2}, +\frac{1}{2} \right\rangle; \quad |\alpha_3\rangle = \left| \frac{3}{2}, -\frac{1}{2} \right\rangle; \quad |\alpha_4\rangle = \left| \frac{3}{2}, -\frac{3}{2} \right\rangle. \quad (3.39)$$

It is also common to denote the eigenstates in vector notation.

$$|\alpha_1\rangle = \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad |\alpha_2\rangle = \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \end{pmatrix} \quad |\alpha_3\rangle = \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} \quad |\alpha_4\rangle = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \end{pmatrix} \quad (3.40)$$

The description of the eigenstates as basis vectors is particularly useful for the specification of an arbitrary state which can be written as a linear combination (*superposition*) of these basis states

$$|\Psi\rangle = c_1|\alpha_1\rangle + c_2|\alpha_2\rangle + c_3|\alpha_3\rangle + c_4|\alpha_4\rangle \quad \text{with vector form} \quad |\Psi\rangle = \begin{pmatrix} c_1 \\ c_2 \\ c_3 \\ c_4 \end{pmatrix}. \quad (3.41)$$

It should be noted that the wavefunction $|\Psi\rangle$ is usually defined with regard to a spatial position x and time point t . Within this work, particles will be considered *stationary* and, hence, the dependence on x will be omitted.

3.3.2 Spin Density Operator

Common NMR experiments are performed on a sample containing numerous spins. The sheer number of spins renders it impossible to investigate them as individual components. In addition, the probabilistic nature of quantum mechanical observations makes the description of an individual spin state impossible.

It can well be assumed that all these particles are identical and independent allowing the system to be treated as a *spin ensemble*. It is described through the *Spin Density*

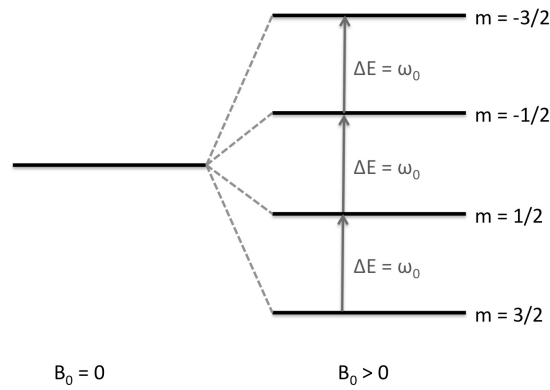


Figure 3.1: Energy Level Diagram with Zeeman Splitting in the presence of an external magnetic field B_0 for spin-3/2.

operator $\hat{\rho}$ (a detailed description can be found in the [Appendix](#)). The expectation value of an observable is obtainable from the *trace*³ Tr

$$\langle \hat{Q} \rangle = Tr\{\hat{\rho}\hat{Q}\}. \quad (3.42)$$

3.3.3 Hamiltonian

Until this point, the description of spin-systems has focused on states and operators for their representation. The following sections are concerned with the dynamics of nuclear spins. These dynamics result from experimental (external) as well as inherent, structural (internal) interactions, hence, providing a probe for experimental observations. As will be discussed in the next chapter the application of a magnetic field results in energy differences between states which cause observable magnetic moments related to the nuclear spin system. The operator that corresponds to the kinetic and potential energy of a system is termed *Hamiltonian* and commonly denoted by a $\hat{H}$. Its eigenvalues represent the *energy states* of a system, the eigenfunctions are referred to as *stationary/energy eigenstates*. The description of spin dynamics in Quantum Mechanics is grounded in two closely-connected fundamental equations:

Schroedinger Equation The Schroedinger Equation describes the time-evolution of *pure quantum states*.

$$i\hbar \frac{\partial}{\partial t} |\Psi(t)\rangle = \hat{H} |\Psi(t)\rangle \quad (3.43)$$

Louville-von Neumann Equation The Liouville-von Neumann Equation describes the time-evolution of the *spin density operator*.

$$\frac{\partial \hat{\rho}}{\partial t} = \frac{i}{\hbar} [\hat{H}, \hat{\rho}] \quad (3.44)$$

It is convenient to incorporate the factor $\hbar^{-1}$ in this Equation in physical units.

³The trace of a square matrix describes the sum of the main diagonal elements.

This work is concerned with spin systems and, hence, the spin density operator. The solution of Equation 3.44 is given by

$$\hat{\rho}(t) = \hat{G}(t)\hat{\rho}(0)\hat{G}^\dagger(t). \quad (3.45)$$

where $\hat{\rho}(0)$ is the initial spin density operator at time $t = 0$ and $\hat{G}$ is the wavefunction propagator.

For *time-independent* Hamiltonians $\hat{G}(t)$ is given by

$$\hat{G}(t) = \exp\{-i\hat{H}t\}. \quad (3.46)$$

3.3.3.1 External Hamiltonian

External spin Hamiltonians describe interactions with external energy sources, i.e. the experimental setup. For NMR experiments there mainly exist two sources for external energy impact on the spin system: the main magnetic field B_0 and the excitation RF-pulse B_1 .

Zeeman Hamiltonian and Energy Level The magnetic moment $\hat{\mu}$ is another important property of nuclei. It is related to the nuclear spin via the gyromagnetic ratio γ .

$$\hat{\mu} = \gamma\hat{I} \quad (3.47)$$

The gyromagnetic ratio is a characteristic constant of nuclei, $\gamma_{^{23}\text{Na}}/2\pi = 11.3 \text{ MHz T}^{-1}$.

During an NMR experiment, spins are exposed to a strong external magnetic field B_0 which causes an interaction with the inherent magnetic moment. It is convenient to define the external magnetic field in alignment with the z-direction of the spin angular momentum, $\mathbf{B} = (0, 0, B_0)$. The resulting Hamiltonian (commonly referred to as Zeeman-Hamiltonian $\hat{H}_z$) is, hence, given by

$$\hat{H}_z = -\hat{\mu} \cdot \mathbf{B} = -\gamma\hat{I}_z \cdot B_0 \quad (3.48)$$

The energy levels E_m are the eigenstates of the Hamiltonian, i.e.

$$\hat{H}_z|j, m\rangle = E_m|j, m\rangle = -\gamma\hat{I}_z \cdot B_0|j, m\rangle. \quad (3.49)$$

The energy levels are, hence, given by

$$E_m = -\gamma\hbar m B_0 \quad (3.50)$$

with energy splitting

$$\Delta E = E_{m+1} - E_m = \gamma\hbar B_0. \quad (3.51)$$

The forking of energy levels is the previously described Zeeman splitting. Most spins will be in a superposition state of energy levels (cf. Equation 3.41), however, due to the energy level differences there exists a small tendency towards lower energy states.

This trend provides the detectable *macroscopic magnetisation*, commonly denoted by M_0 . The probability of finding a particle in state m is calculated according to the *Boltzmann distribution*

$$p_m = \frac{\exp\{-E_m/k_B T\}}{\sum_{m=-j}^m \exp\{-E_m/k_B T\}} \quad (3.52)$$

where k_B is the Boltzmann constant and T denotes temperature. The denominator is known as the *canonical partition function* Z .

For the density matrix $\hat{\rho}$ at equilibrium this leads to

$$\hat{\rho}_{eq} = \frac{\exp\{\hbar\gamma B_0 \hat{I}_z / k_B T\}}{Z} \quad \text{where } Z = \text{Tr}\{\exp\{\hbar\gamma B_0 \hat{I} / k_B T\}\} \quad (3.53)$$

Using the high temperature approximation ($E_m \ll k_B T$) a first order approximation yields $\exp\left\{-\frac{E_m}{k_B T}\right\} \approx 1 - \frac{E_m}{k_B T}$ which simplifies Z to $2j+1$ and hence

$$\hat{\rho}_{eq} = \frac{1}{2j+1} \left(\mathbb{1} + \underbrace{\frac{\hbar\gamma B_0}{k_B T}}_{\text{Boltzmann constant}} \hat{I}_z \right) \quad (3.54)$$

where the Boltzmann constant is commonly denoted $\mathbb{B}$. The constant related to the identity matrix $\mathbb{1}$ does not contribute to an experimental observable and is commonly omitted leading to the typical initialisation of

$$\hat{\rho}_{eq} = \hat{\rho}_0 = \frac{1}{2j+1} \mathbb{B} \hat{I}_z. \quad (3.55)$$

A quantification of macroscopic magnetisation depends on the number of spins (N) in a sample volume (V) and the observable magnetic moment

$$M_0 = \frac{N}{V} \langle \hat{\mu} \rangle \quad (3.56)$$

The magnetic moment is related to the spin operator via the gyromagnetic ratio (cf. Equation 3.47) and the estimation value of an observable is given by the trace with the spin density operator $\hat{\rho}$ (cf. Equation 3.42). Hence,

$$M_0 = \frac{N\gamma}{V} \hat{I} = \frac{N\gamma}{V} \text{Tr}\{\hat{\rho} \hat{I}\}. \quad (3.57)$$

Using the density operator at equilibrium $\hat{\rho}_{eq}$ (Equation 3.55) the maximum observable magnetisation can be approximated by

$$M_0 \approx \frac{N}{V} \frac{\gamma^2 \hbar^2 j(j+1)}{3k_B T} B_0. \quad (3.58)$$

The evolution of the spin density operator under the influence of a Zeeman Hamiltonian H_z can be investigated using a quantum mechanical description. The evolution

of the spin density operator can be obtained through the Liouville-von Neumann Equation 3.44. Using the definition of H_z from Equation 3.48 yields

$$\begin{aligned}\hat{\rho}(t) &= \exp\{-iH_z t\} \hat{\rho}(0) \exp\{iH_z t\} \\ &= \exp\{i\gamma B_0 \hat{I}_z t\} \hat{\rho}(0) \exp\{-i\gamma B_0 \hat{I}_z t\} \\ &= \exp\{i\omega_0 \hat{I}_z t\} \hat{\rho}(0) \exp\{-i\omega_0 \hat{I}_z t\}\end{aligned}\quad (3.59)$$

where $\omega_0 = \gamma B_0$ introduces the *Larmor frequency*. From Equation 3.9 it is evident that this can be expressed in terms of rotation operators $\hat{R}$.

$$\hat{\rho}(t) = \hat{R}_z(\omega_0 t) \hat{\rho}(0) \hat{R}_z(\omega_0 t) \quad (3.60)$$

describes a rotation of the initial density operator $\hat{\rho}(0)$ around $\hat{I}_z$ with the Larmor frequency ω_0 . This is the concept of *free precession*.

RF pulse The net magnetisation M_0 caused by the Zeeman interaction aligns with the external field B_0 and, therefore, cannot be observed directly. To create detectable signal the magnetisation needs to be ‘tipped’ into the *transverse plane*⁴, a process known as *excitation*. For that, an additional magnetic field B_1 is applied perpendicular to the static field B_0 . The B_1 field possesses two important characteristics: 1) it is only switched on over a relatively short period of time (usually a few hundred μs) and is therefore referred to as a *pulse*; 2) it is applied as an oscillating field with a frequency equal to the Larmor frequency, i.e. in the radio-frequency range, and is, consequently, termed an *RF pulse*. It is often assumed to be aligned with the x-axis, i.e. $\mathbf{B}_{RF} = (B_1 \cos(\omega_{RF} t), 0, 0)$ with B_1 denoting the applied field strength and ω_{RF} the oscillation frequency. The Hamiltonian of an RF-pulse $\hat{H}_{RF}$ is therefore given by

$$\hat{H}_{RF} = -\hbar\omega_1 \hat{I}_x \cos(\omega_{RF} t) \text{ where } \omega_1 = \gamma B_1. \quad (3.61)$$

During excitation, the spin system experiences two magnetic influences and, hence, the Hamiltonian during an RF-excitation is given by

$$\hat{H} = \hat{H}_z + \hat{H}_{RF} \quad (3.62)$$

The evolution of the spin density operator under RF-excitation is therefore given by

$$\frac{\partial \hat{\rho}}{\partial t} = i [\hat{H}_z + \hat{H}_{RF}, \hat{\rho}] = i [\hat{H}_z, \hat{\rho}] + i [\hat{H}_{RF}, \hat{\rho}]. \quad (3.63)$$

The constant interaction of the Zeeman Hamiltonian and the time-varying nature of the RF-pulse Hamiltonian complicate this calculation and, hence, it is desirable to find a framework in which the Zeeman Hamiltonian vanishes and the RF-pulse Hamiltonian becomes time-independent. These requirements introduce the concept of the *rotating reference frame*. It is created by a transformation of all operators with the Zeeman Hamiltonian. From Equation 3.60 it is shown that this results in a rotation of an operator $\hat{Q}$ around the z-axis at the Larmor frequency, i.e. $\hat{Q}^* = \hat{R}_z(\omega_0 t) \hat{Q} \hat{R}_z(\omega_0 t)$

⁴The transverse plane describes the plane orthogonal to the external field B_0 . When M_0 is aligned with B_0 it is commonly referred to as *longitudinal* magnetisation.

with $\hat{Q}^*$ denoting an operator in the rotating reference frame. Since $\hat{H}_z$ commutes with itself, $[\hat{\rho}^*, \hat{H}_z] = 0$ and the density operator in the rotating reference frame can be calculated as

$$\frac{\partial \hat{\rho}^*}{\partial t} = [\hat{\rho}^*, \hat{H}_{RF}^*]. \quad (3.64)$$

The transformation of $\hat{H}_{RF}$ is shown in the [Appendix](#). At resonance, i.e. $\omega_{RF} = \omega_0$, it is given by

$$\hat{H}_{RF}^* = -\hbar\omega_1 \hat{I}_x. \quad (3.65)$$

Due to the relatively short-lived detectable Sodium NMR-signal dynamics, its excitation is usually performed with a rectangular hard pulse. Given the short duration of these pulses, other interactions (i.e. relaxation effects) are often neglected in theoretical evaluations of the spin density operator evolution during a hard RF-pulse. Since $\hat{H}_{RF}^*$ is time-independent, the evolution of the spin density operator in the rotating reference frame can be calculated using Equation 3.45

$$\hat{\rho}^* = \exp\{i\omega_1 \hat{I}_x t\} \hat{\rho}^*(0) \exp\{-i\omega_1 \hat{I}_x t\} \quad (3.66)$$

which illustrates that the effects of $\hat{H}_{RF}$ in the rotating frame of reference can be interpreted as a rotation of the current spin density operator about the x-axis. The rotation angle α results from $\omega_1 t = \gamma B_1 t$, i.e. the strength and duration of B_1 and is commonly denoted *flip angle*.

The Hamiltonian $\hat{H}_{RF}^*$ can easily be expressed in terms of tensor operators

$$\hat{H}_{RF}^* = -\hbar\omega_1 \hat{I}_x = \omega_1 T_{1,1}(a) \quad (3.67)$$

Therefore, the time-evolution of the density operator can be calculated from

$$\frac{\partial \hat{\rho}^*}{\partial t} = -i [\hat{H}_{RF}^*, \hat{\rho}^*] = -i\omega_1 [T_{1,1}(a), \hat{\rho}^*] \quad (3.68)$$

Using the conveniently tabulated commutator relationships from [Bowden et al. \(1986\)](#) this results in a set of coupled differential equations

$$\frac{\partial}{\partial t} \begin{pmatrix} \hat{T}_{1,0} \\ \hat{T}_{1,1}(s) \end{pmatrix} = \begin{pmatrix} 0 & -i\omega_1 \\ -i\omega_1 & 0 \end{pmatrix} \begin{pmatrix} \hat{T}_{1,0} \\ \hat{T}_{1,1}(s) \end{pmatrix} \quad (3.69)$$

$$\frac{\partial}{\partial t} \begin{pmatrix} \hat{T}_{2,1}(a) \\ \hat{T}_{2,2}(a) \end{pmatrix} = \begin{pmatrix} 0 & -i\omega_1 \\ -i\omega_1 & 0 \end{pmatrix} \begin{pmatrix} \hat{T}_{2,1}(a) \\ \hat{T}_{2,2}(a) \end{pmatrix} \quad (3.70)$$

$$\frac{\partial}{\partial t} \begin{pmatrix} \hat{T}_{2,0} \\ \hat{T}_{2,1}(s) \\ \hat{T}_{2,2}(s) \end{pmatrix} = \begin{pmatrix} 0 & -i\sqrt{3}\omega_1 & 0 \\ -i\sqrt{3}\omega_1 & 0 & -i\omega_1 \\ 0 & -i\omega_1 & 0 \end{pmatrix} \begin{pmatrix} \hat{T}_{2,0} \\ \hat{T}_{2,1}(s) \\ \hat{T}_{2,2}(s) \end{pmatrix} \quad (3.71)$$

$$\frac{\partial}{\partial t} \begin{pmatrix} \hat{T}_{3,1}(a) \\ \hat{T}_{3,2}(a) \\ \hat{T}_{3,3}(a) \end{pmatrix} = \begin{pmatrix} 0 & -i\sqrt{5/2}\omega_1 & 0 \\ -i\sqrt{5/3}\omega_1 & 0 & -i\sqrt{3/2}\omega_1 \\ 0 & -i\sqrt{3/2}\omega_1 & 0 \end{pmatrix} \begin{pmatrix} \hat{T}_{3,1}(a) \\ \hat{T}_{3,2}(a) \\ \hat{T}_{3,3}(a) \end{pmatrix} \quad (3.72)$$

$$\frac{\partial}{\partial t} \begin{pmatrix} \hat{T}_{3,0} \\ \hat{T}_{3,1}(s) \\ \hat{T}_{3,2}(s) \\ \hat{T}_{3,3}(s) \end{pmatrix} = \begin{pmatrix} 0 & -i\sqrt{6}\omega_1 & 0 & 0 \\ -i\sqrt{6}\omega_1 & 0 & -i\sqrt{5/2}\omega_1 & 0 \\ 0 & -i\sqrt{5/2}\omega_1 & 0 & -i\sqrt{3/2}\omega_1 \\ 0 & 0 & -i\sqrt{3/2}\omega_1 & 0 \end{pmatrix} \begin{pmatrix} \hat{T}_{3,0} \\ \hat{T}_{3,1}(s) \\ \hat{T}_{3,2}(s) \\ \hat{T}_{3,3}(s) \end{pmatrix} \quad (3.73)$$

where (s) and (a) describe the evolution of the symmetric and antisymmetric combinations of the spherical tensor operators, respectively.

This set of equation highlights an important effect of $\hat{H}_{RF}$ on a spin system: tensor operators of different rank n are decoupled, i.e. a hard pulse only affects the order q of a tensor operator (in brief: $\hat{T}_{n,q} \xrightarrow{\hat{H}_{RF}} \hat{T}_{n,q'}$).

The results hold for an RF-pulse along the x-axis. For an arbitrary excitation with a relative phase ψ with respect to the x-axis, the reference frame needs to be adjusted. This can be done via a rotation of the coordinate axes with ψ and $-\psi$ about the z-axis before and after excitation interaction. The rotation of a tensor operator is simply calculated through

$$\hat{T}_{n,q}(s) \rightarrow \hat{T}_{n,q}(s) \cos(q\psi) + i\hat{T}_{n,q}(a) \sin(q\psi) \quad (3.74)$$

$$\hat{T}_{n,q}(a) \rightarrow \hat{T}_{n,q}(a) \cos(q\psi) + i\hat{T}_{n,q}(s) \sin(q\psi) \quad (3.75)$$

A useful tabulation for arbitrary flip angle along the x-axis as well as standard $\beta = \pi/2$ -pulses along the x- or y-axis can be found in [Van der Mareel \(2003\)](#).

3.3.3.2 Internal Hamiltonian

The composition and structure of a sample causes additional magnetic and electric fields that interact with the spin system. Since these interactions are caused from inherent properties of the sample, they are called internal interactions. There are various mechanisms, e.g. chemical shifts, dipole-dipole interactions or J-coupling. For spin systems with $j > 1/2$ there exists an additional interaction process based on the electric quadrupole moment. It is by far the most efficient perturbation process. While for example the dipole interaction strength is on the order of 10^4 - 10^5 s⁻¹, the impact of quadrupole interactions is several magnitudes higher with 10^6 - 10^8 s⁻¹ ([Werbelow, 2007](#)). For spin-3/2 systems, the investigation of internal energy mechanisms is, hence, commonly reduced to this main influence for which the quadrupole Hamiltonian needs to be determined.

Electric Field Gradients A non-zero quadrupole moment results from a non-spherical distribution of electric charges around the nucleus. It is described via a *traceless*⁵ tensor. Its components can be calculated via

$$Q_{kl} = \int \rho(\mathbf{r})(3r_k r_l - \delta_{kl} r^2) d^3r \quad (3.76)$$

where ρ indicates the charge density as a function of position and the indices k, l run over the Cartesian coordinates x, y, z .

The charge distribution of a nucleus is symmetric along the same axis as the nuclear angular momentum. For a nucleus, the quadrupole moment Q is described by a scalar

⁵The diagonal elements of the tensor sum to 0, i.e. $\sum_k Q_{kk} = 0$.

indicating how *prolate*, i.e. ‘stretched’, or *oblate*, i.e. ‘squashed’, the electric charges around the nucleus are distributed. For Sodium, $Q = 0.110^{-24}\text{cm}^2$ and is therefore prolate.

Classically, the interaction energy E , i.e. the potential energy between charges of a nucleus and the electric potential originating from its surrounding, can be described via

$$E = \int \rho(\mathbf{r})V(\mathbf{r})d^3r \quad (3.77)$$

where V illustrates the electric potential at the nucleus caused from the local environment. It is commonly approximated via a Taylor series expansion around the origin of the nucleus

$$V(\mathbf{r}) = V(0) + \sum_k r_k \left. \frac{\partial V(\mathbf{r})}{\partial r_k} \right|_{\mathbf{r}=0} + \frac{1}{2!} \sum_{k,l} r_k r_l \left. \frac{\partial^2 V(\mathbf{r})}{\partial r_k \partial r_l} \right|_{\mathbf{r}=0} + \dots \quad (3.78)$$

Introducing the short-hand notation

$$V_k = \left. \frac{\partial V(\mathbf{r})}{\partial r_k} \right|_{\mathbf{r}=0} \quad \text{and} \quad V_{k,l} = \left. \frac{\partial^2 V(\mathbf{r})}{\partial r_k \partial r_l} \right|_{\mathbf{r}=0} \quad (3.79)$$

and using the Taylor series expansion of Equation 3.78 up to third order in Equation 3.77 yields

$$E = V(0) \int \rho(\mathbf{r})d^3r + \sum_k V_k \int r_k \rho(\mathbf{r})d^3r + \frac{1}{2!} \sum_{k,l} V_{k,l} \int r_k r_l \rho(\mathbf{r})d^3r \quad (3.80)$$

The nucleus is considered a point source and, hence, the first term in Equation 3.80 vanishes. Furthermore, it can be assumed that the centre of mass and charge coincide which causes the second term (the dipole moment) to be negligible. The third term, the quadrupole moment, contributes the dominant interaction energy.

Using the definition of electric quadrupole moments from Equation 3.76, the quadrupole term can be expressed with respect to Q

$$\int r_k r_l \rho(\mathbf{r})d^3r = \frac{1}{3} \left(Q_{k,l} + \int \delta_{kl} r^2 \rho(\mathbf{r})d^3r \right). \quad (3.81)$$

Reducing the interaction energy description to the third term and using the equality from Equation 3.81 condenses the interaction energy term from Equation 3.80 to

$$E = \frac{1}{6} \sum_{k,l} V_{k,l} Q_{k,l} + V_{k,l} \delta_{kl} \int r^2 \rho(\mathbf{r})d^3r. \quad (3.82)$$

The electric potential V needs to satisfy Laplace’s Equation, i.e. $\nabla^2 V = 0$. Hence, $\sum_k V_{k,k} = 0$ annihilates the second term of Equation 3.82. Finally, the interaction energy can be expressed as

$$E = \frac{1}{6} \sum_{k,l} V_{k,l} Q_{k,l}. \quad (3.83)$$

Quadrupole Hamiltonian The underlying Hamiltonian can be obtained via converting the quadrupole term Q in Equation 3.83 into a quantum mechanical operator $\hat{Q}$. It is given by (Slichter, 1990; Abragam, 1961)

$$\hat{Q}_{k,l} = \frac{eQ}{j(2j-1)} \left(\frac{3}{2} (\hat{I}_k \hat{I}_l + \hat{I}_l \hat{I}_k) - \delta_{kl} \hat{I}^2 \right) \quad (3.84)$$

where e is the unit electric charge and Q describes the scalar nuclear quadrupole moment introduced before.

Via rotations the symmetric tensor $V_{k,l}$ can be transformed into a traceless *principal axis system PAS* where $V_{k,l} = 0$ for $k \neq l$. The diagonal non-zero entries define the coordinate axis V_{xx} , V_{yy} and V_{zz} and are chosen such that $|V_{xx}| \geq |V_{yy}| \geq |V_{zz}|$. From Equation 3.83, the quadrupole Hamiltonian $\hat{H}_Q$ in the PAS is given by

$$\begin{aligned} \hat{H}_q &= \frac{1}{6} \sum_k V_{kk} \hat{Q}_{kk} \\ &= \frac{eQ}{4j(2j-1)} \left[V_{zz}(3\hat{I}_z^2 - j(j+1)) + (V_{xx} - V_{yy})(\hat{I}_x^2 - \hat{I}_y^2) \right]. \end{aligned} \quad (3.85)$$

In biological tissue, i.e. non-solid environments, the Electric Field Gradient (EFG) will vary over time and partly average to zero within the time-course of standard NMR experiments. To distinguish between the effects of time-varying and static components of the quadrupole Hamiltonian it is split into two parts: the static quadrupole Hamiltonian $\hat{H}_{QS}$ and the fluctuating quadrupole Hamiltonian $\hat{H}_{QF}$.

Static Quadrupole Hamiltonian The static component describes the non-vanishing, i.e. non-zero time-averaged, contribution of the quadrupole Hamiltonian. Hence, it results from time-averaged components of the EFG $\overline{V_{kk}}$. In biological tissue, i.e. environments with significant motion, they are assumed to obey axial symmetry, i.e. $\overline{V_{zz}} \geq \overline{V_{xx}} = \overline{V_{yy}}$. Defining q as the field gradient, $\overline{V_{zz}}$ is furthermore quantified as eq . Following Equation 3.85, the static quadrupole Hamiltonian is defined by

$$\hat{H}_{QS} = \frac{e^2 q Q}{4j(2j-1)} [3\hat{I}_z^2 - j(j+1)] \quad (3.86)$$

During NMR experiments, a spin system is under the constant influence of a Zeeman Hamiltonian resulting from the main external magnetic field. Although this is not an internal mechanism, it is advisable to combine both static influences into a single Hamiltonian. For that, the z-axes of both interactions need to coincide. The angle between B_0 and the quadrupole interaction direction is denoted θ and is likewise considered as a time-averaged value. Due to the significant magnitude differences between Zeeman and quadrupole interactions the latter can be considered as a first order perturbation with respect to the principal axes of B_0 . They can be combined as two components of $\hat{H}_{static}$

$$\begin{aligned} \hat{H}_{static} &= \hat{H}_z + \hat{H}_{QS} \\ &= \gamma \hbar B_0 \hat{I}_z + \frac{e^2 q Q}{4j(2j-1)} \left[\frac{1}{2} (3 \cos^2 \bar{\theta} - 1) (3\hat{I}_z^2 - j(j+1)) \right] \end{aligned} \quad (3.87)$$

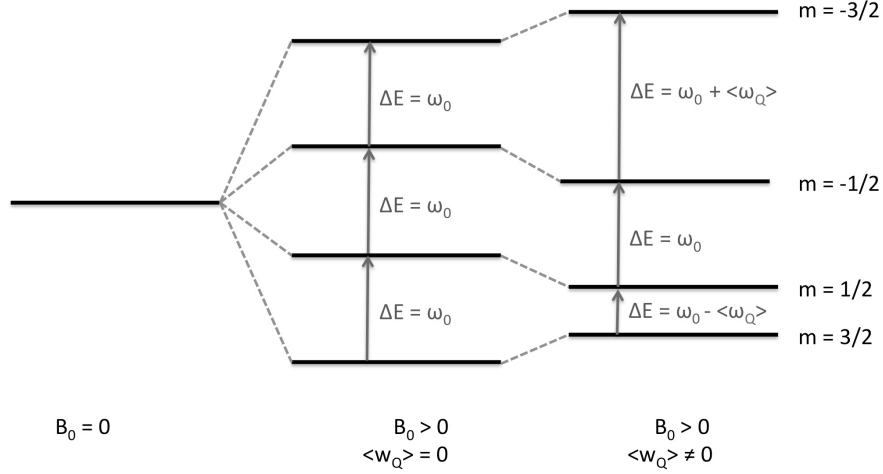


Figure 3.2: Extension to Energy Level Diagram for spin-3/2 from Figure 3.1 with Energy Level shifts due to non-zero time-averaged Quadrupole Interactions, i.e. $\overline{\omega_Q} = \langle \omega_Q \rangle \neq 0$.

This introduces two terms:

Quadrupole Coupling Constant

$$\chi = \frac{e^2 q Q}{\hbar} \quad (3.88)$$

Quadrupole Interaction Frequency

$$\omega_Q = \frac{\chi}{4} (3 \cos^2 \bar{\theta} - 1) \quad (3.89)$$

Combining these expressions the quadrupole Hamiltonian is given as

$$\hat{H}_{QS} = \frac{\hbar \omega_Q}{6} (3 \hat{I}_z^2 - j(j+1)) \quad (3.90)$$

and the corresponding eigenvalues cause an offset to the spin energy states by

$$\Delta E_m = \frac{\hbar \omega_Q}{2} \left(m^2 - \frac{5}{4} \right). \quad (3.91)$$

Under quadrupole interaction, the spin's inner energy states ($m = \pm 1/2$) and outer energy states ($m = \pm 3/2$) experience opposite offsets. While this preserves the absolute energy range and the central energy transitions, it causes a change in the outer satellite transitions as depicted in Figure 3.2.

Fluctuating Quadrupole Hamiltonian For the description of fluctuating components it is convenient to express the quadrupole Hamiltonian in terms of tensor operators. Such a representation can be derived when looking at the quadrupole Hamiltonian (Equation 3.85) in terms of ladder operators

$$\hat{H}_Q = \frac{eQ}{4j(2j-1)} \left[V_0 2(3 \hat{I}_z^2 - j(j+1)) + V_{\pm 1} \sqrt{6} (\hat{I}^{\pm} \hat{I}_z + \hat{I}_z \hat{I}^{\pm}) + V_{\pm 2} \sqrt{6} (\hat{I}^{\pm})^2 \right] \quad (3.92)$$

with

$$\begin{aligned} V_0 &= \frac{1}{2} V_{zz} \\ V_{\pm 1} &= \frac{1}{\sqrt{6}} (V_{zx} \pm i V_{zy}) \\ V_{\pm 2} &= \frac{1}{2\sqrt{6}} (V_{xx} - V_{yy}) \end{aligned} \quad (3.93)$$

It should be noted that some literature chooses to rename the spatial tensor V into F at this point (Madelin et al., 2014). Here the notation as V is continued to highlight the relation to the EFG.

The above set of Equations appears very complicated, however, looking into Table 3.1 reveals that this combination of ladder operators can easily be transformed into irreducible tensor operators. Essentially, each component of the quadrupole moment can be expressed as a rank-2 tensor $T_{2,q}$ leading to

$$\hat{H}_Q = \frac{eQ}{\sqrt{6}} \sum_{q=-2}^2 T_{2,q} V_q(t). \quad (3.94)$$

This expression also necessitates an addendum to the previously described static quadrupole Hamiltonian, which can also be expressed in terms of tensor operators through

$$\hat{H}_{QS} = \frac{\hbar\omega_Q}{6} (3\hat{I}_z - j(j+1)) = \hbar\omega_Q \hat{T}_{2,0}. \quad (3.95)$$

Returning to the expression of the quadrupole Hamiltonian using tensor operators in Equation 3.94 it is re-emphasised that EFG (V_q) are time-dependent due to the varying molecular environment. Subtracting the time-averaged (static) component of the EFG from this description provides an extraction of the fluctuating component of the quadrupole Hamiltonian operator $\hat{H}_{QF}$

$$\hat{H}_{QF} = \frac{eQ}{\sqrt{6}} \sum_{q=-2}^2 T_{2,q} (V_q(t) - \overline{V_q}) \quad (3.96)$$

For an evaluation of the fluctuating quadrupole interactions this operator needs to be transformed into the rotating frame of reference. The rotation of tensor operators is described in Equation 3.33 with the Wigner D-matrix elements defined in Equation 3.32. The transformation into the rotating reference frame amounts to a simple rotation around the spin's z-component with the Larmor frequency ω_0 , i.e. $\exp\{iq\omega_0 t\}$.

$$\hat{H}_{QF} = \frac{eQ}{\sqrt{6}} \sum_{q=-2}^2 (-1)^q T_{2,q} (V_{-q}(t) - \overline{V_{-q}}) \exp\{iq\omega_0 t\} \quad (3.97)$$

It should be noted that the frame rotation in a negative sense requires the additional term $(-1)^q$ and entails sign changes for the EFG indices.

This concludes the general description of quadrupole interactions and the extraction of static and fluctuating components. The quadrupole moment of spin-3/2 is a strong mechanism that 'pushes' the spin system back into a thermal equilibrium after perturbation. The description of this process follows in the next section.

3.4 Thermal Relaxation

A physical system aims to obtain and maintain a steady state, a so-called equilibrium state. Any perturbation of such a system, i.e. the distraction from equilibrium, results in a dynamic process towards the re-establishment of equilibrium. The mechanism leading to the re-creation of the equilibrium state is called *relaxation*. This process is strongly dependent on the system itself. Probing the relaxation mechanism, hence, provides a powerful tool for a detailed investigation of the underlying spin system sample. The following section is concerned with the description of this dynamic for 3/2-nuclei and provides an important basis for the understanding of observable relaxation processes and the related parameter together with their physical meaning.

3.4.1 Relaxation Superoperator

The evolution of the spin density operator is based on the Liouville-von Neumann Equation 3.44 and its solution in Equation 3.45. These formulations assume a time-independent Hamiltonian operator. For the incorporation of a time-dependent relaxation process this Equation needs to be extended

$$\frac{\partial \hat{\rho}(t)}{\partial t} = -i [\hat{H}, \hat{\rho}(t)] - \hat{\Gamma}(\hat{\rho}(t) - \hat{\rho}_0) \quad (3.98)$$

where $\hat{\Gamma}$ introduces the *relaxation superoperator* and $\hat{\rho}_0$ represents the spin density operator at equilibrium. Equation 3.98 is furthermore known as the *Quantum Mechanical Master Equation*. The Redfield theory provides an approach for the description of the relaxation superoperator which fulfils conditions of NMR-experiments on biological tissues. It is based on considering the time-dependent Hamiltonian $\hat{H}_1$ as a second order perturbation of the much stronger Zeeman-Hamiltonian $\hat{H}_z$, which can be incorporated in the Liouville-von Neumann Equation as

$$\frac{\partial \hat{\rho}(t)}{\partial t} = -i [\hat{H}_z + \hat{H}_1(t), \hat{\rho}(t)] \quad (3.99)$$

A transformation into the rotating frame simplifies the expression to

$$\frac{\partial \hat{\rho}^*(t)}{\partial t} = -i [\hat{H}_1^*(t), \hat{\rho}^*(t)] \quad (3.100)$$

where

$$\hat{H}_1^*(t) = \exp\{-i\hat{H}_z t\} \hat{H}_1(t) \exp\{i\hat{H}_z t\} \quad (3.101)$$

$$\hat{\rho}^*(t) = \exp\{-i\hat{H}_z t\} \hat{\rho}_1(t) \exp\{i\hat{H}_z t\} \quad (3.102)$$

This evolution of the density operator in the rotating frame can be approximated. The result up to second order is given by

$$\hat{\rho}^*(t) \approx \hat{\rho}^*(0) - i \int_0^t [\hat{H}_1^*(t'), \hat{\rho}^*(0)] dt' - \int_0^t dt' \int_0^{t'} dt'' [\hat{H}_1^*(t'), [\hat{H}_1^*(t''), \hat{\rho}^*(0)]] \quad (3.103)$$

Differentiating the above with respect to time and defining $\tau = t - t'$ yields

$$\frac{\partial \hat{\rho}^*(t)}{\partial t} \approx -i \overline{[\hat{H}_1^*, \hat{\rho}^*(0)]} - \int_0^t d\tau \overline{[\hat{H}_1^*(t), [\hat{H}_1^*(t-\tau), \hat{\rho}^*(0)]]} \quad (3.104)$$

where $\overline{[\dots]}$ again indicates the ensemble average due to the probabilistic nature of the process.

Based on the following assumptions (all of which are fulfilled in NMR-experiments on biological samples)

1. The relaxation process is random and unbiased. Hence, $\overline{\hat{H}_1} = 0$.
2. The correlation time τ_c is short compared to the relaxation time of interest, i.e. the correlation between $\hat{H}_1^*$ and $\hat{\rho}^*(0)$ is negligible which entails that:

$$\bullet \quad \overline{[\hat{H}_1^*(t), \hat{\rho}^*(0)]} = \overline{[\hat{H}_1^*(t), \hat{\rho}^*(0)]} = 0 \quad (3.105)$$

$$\bullet \quad \overline{[\dots, [\dots, \dots]]} = \overline{[\dots, [\dots, \dots]]} + \overline{[\dots, [\dots, \dots]]} \quad (3.106)$$

3. The system relaxes to equilibrium state, i.e. $\overline{\hat{\rho}^*(0)} = \overline{\hat{\rho}^*(t)} = \hat{\rho}_0$.
4. The process converges to equilibrium, i.e. the upper bound of the integral in Equation 3.104 is ∞ .

Equation 3.104 can be simplified to

$$\frac{\partial \hat{\rho}^*(t)}{\partial t} = - \int_0^\infty d\tau \overline{[\hat{H}_1^*(t), [\hat{H}_1^*(t-\tau), \hat{\rho}^*(t) - \hat{\rho}_0]]} \quad (3.107)$$

Leaving the rotation frame and re-stating the above in the laboratory frame gives

$$\frac{\partial \hat{\rho}(t)}{\partial t} = -i [\hat{H}_z, \hat{\rho}(t)] - \underbrace{\int_0^\infty d\tau [\hat{H}_1(t), [\exp\{-i\hat{H}_z\tau\} \hat{H}_1(t-\tau) \exp\{i\hat{H}_z\tau\}, \hat{\rho}(t) - \hat{\rho}_0]]}_{\text{relaxation superoperator } \hat{\Gamma}} \quad (3.108)$$

The indication of ensemble averaging is henceforth omitted for notational simplicity.

The time evolution of the spin density operator in the laboratory frame is stated for completeness. Practically, it is investigated in the rotating frame which can now be used to incorporate the static and fluctuating quadrupole Hamiltonians

$$\begin{aligned} \frac{\partial \hat{\rho}^*(t)}{\partial t} = & -i [\hat{H}_{QS}^*, \hat{\rho}^*(t)] \\ & - \int_0^\infty d\tau [\hat{H}_{QF}^*(t), [\exp\{-i\hat{H}_{QS}^*\tau\} \hat{H}_{QF}^*(t-\tau) \exp\{i\hat{H}_{QS}^*\tau\}, \hat{\rho}^*(t) - \hat{\rho}_0]] \end{aligned} \quad (3.109)$$

Strictly speaking, the static component in above equation should also contain a term for an RF-Hamiltonian during excitation. As short pulses are typically applied, this component is, however, commonly ignored. In the following relaxation behaviour in the absence of an RF-pulse is described.

3.4.2 Motion Regimes

The actual relaxation characteristics depend on the underlying media:

Isotropic media Isotropic media define samples with no long-range position or orientation order, i.e. over the time frame of an NMR experiments the experienced EFG V average to zero ($\overline{V_{2,q}} = 0$) and the static quadrupolar Hamiltonian $\hat{H}_{QS}$ vanishes. For isotropic media, the evolution of the density operator is therefore given by

$$\frac{\partial \hat{\rho}^*(t)}{\partial t} = - \int_0^\infty d\tau [\hat{H}_{QF}^*(t), [\hat{H}_{QF}^*(t-\tau), \hat{\rho}^*(t) - \hat{\rho}_0]] \quad (3.110)$$

Applying the tensor operator based definition for the fluctuating quadrupole interaction (Equation 3.97) results in

$$\begin{aligned} \frac{\partial \hat{\rho}^*(t)}{\partial t} = & - \sum_{q=-2}^2 \left[T_{2,q}, \left[T_{2,q}^\dagger, \hat{\rho}^*(t) - \hat{\rho}_0 \right] \right] \\ & \int_0^\infty d\tau \left(\frac{eQ}{\hbar\sqrt{6}} \right)^2 [V_{-q}(t) - \overline{V_{-q}}] [\overline{V_{-q}} - V_{-q}(t)] \exp(iq\omega_0\tau) \end{aligned} \quad (3.111)$$

where the Hermitian adjoint is $T_{2,q}^\dagger = (-1)^q T_{2,-q}$ (as defined in Section [Wigner-Eckart Theorem](#)).

The integral in Equation 3.111 represents the power spectral density of the fluctuating interaction (comparable to the Fourier Transform of an auto-correlation function). It is important to note that the lower bound of the integral at zero yields real and imaginary parts with the latter resulting in only very small shift and, hence, is often omitted. The real component of the power spectral density is commonly termed $J_q(\omega)$ denoting frequencies $\omega = q\omega_0$.

Equation 3.111 can therefore be summarised to

$$\frac{\partial \hat{\rho}^*(t)}{\partial t} = - \sum_{q=-2}^2 \left[T_{2,q}, \left[T_{2,q}^\dagger, \hat{\rho}^*(t) - \hat{\rho}_0 \right] \right] J_q(\omega) \quad (3.112)$$

The double commutator in above equation implies some interesting properties:

1. The coherence orders q are decoupled, i.e. relaxation only changes the operator rank n . This is opposite to the excitation behaviour under RF-Hamiltonians where the rank is conserved and the coherence order changes.
2. Even and odd rank tensor operators are decoupled. Since the equilibrium state in the presence of a magnetic field is $T_{1,0}$, i.e. the longitudinal magnetisation, an

Spin Order		Relaxation function	Relaxation Rate
$\hat{T}_{1,0} \xrightarrow{R^{(0)}} \hat{T}_{1,0}f_{1,1}^{(0)}(t) + \hat{T}_{3,0}f_{3,1}^{(0)}(t)$		$f_{1,1}^{(0)} = \frac{1}{5}(e^{-R_1^{(0)}t} + 4e^{-R_2^{(0)}t})$	$R_1^{(0)} = 2J_1$
$\hat{T}_{3,0} \xrightarrow{R^{(0)}} \hat{T}_{3,0}f_{3,3}^{(0)}(t) + \hat{T}_{1,0}f_{1,3}^{(0)}(t)$		$f_{1,3}^{(0)} = \frac{2}{5}(e^{-R_1^{(0)}t} - e^{-R_2^{(0)}t})$	$R_2^{(0)} = 2J_2$
$\hat{T}_{2,0} \xrightarrow{R^{(0)}} \hat{T}_{2,0}f_{2,2}^{(0)}(t)$		$f_{3,1}^{(0)} = f_{1,3}^{(0)}$	$R_3^{(0)} = 2J_1 + 2J_2$
		$f_{3,3}^{(0)} = \frac{1}{5}(4e^{-R_1^{(0)}t} + e^{-R_2^{(0)}t})$	
		$f_{2,2}^{(0)} = e^{-R_3^{(0)}t}$	
Single-Quantum		Relaxation function	Relaxation Rate
$\hat{T}_{1,\pm 1} \xrightarrow{R^{(1)}} \hat{T}_{1,\pm 1}f_{1,1}^{(\pm 1)}(t) + \hat{T}_{3,\pm 1}f_{3,1}^{(\pm 1)}(t)$		$f_{1,1}^{(\pm 1)} = \frac{1}{5}(3e^{-R_1^{(\pm 1)}t} + 2e^{-R_2^{(\pm 1)}t})$	$R_1^{(1)} = J_0 + J_1$
$\hat{T}_{3,\pm 1} \xrightarrow{R^{(1)}} \hat{T}_{3,\pm 1}f_{3,3}^{(\pm 1)}(t) + \hat{T}_{1,\pm 1}f_{1,3}^{(\pm 1)}(t)$		$f_{1,3}^{(\pm 1)} = \frac{\sqrt{6}}{5}(e^{-R_1^{(\pm 1)}t} - e^{-R_2^{(\pm 1)}t})$	$R_2^{(1)} = J_1 + J_2$
$\hat{T}_{2,\pm 1} \xrightarrow{R^{(1)}} \hat{T}_{2,\pm 1}f_{2,2}^{(\pm 1)}(t)$		$f_{3,1}^{(\pm 1)} = f_{1,3}^{(\pm 1)}$	$R_3^{(1)} = J_0 + J_1 + 2J_2$
		$f_{3,3}^{(\pm 1)} = \frac{1}{5}(2e^{-R_1^{(\pm 1)}t} + 3e^{-R_2^{(\pm 1)}t})$	
		$f_{2,2}^{(\pm 1)} = e^{-R_3^{(\pm 1)}t}$	
Double-Quantum		Relaxation function	Relaxation Rate
$\hat{T}_{2,2} \xrightarrow{R^{(2)}} \hat{T}_{2,2}f_{2,2}^{(2)}(t)$		$f_{2,2}^{(2)} = e^{-R_1^{(2)}t}$	$R_1^{(2)} = J_0 + 2J_1 + J_2$
$\hat{T}_{3,2} \xrightarrow{R^{(2)}} \hat{T}_{3,2}f_{3,3}^{(2)}(t)$		$f_{3,3}^{(2)} = e^{-R_2^{(2)}t}$	$R_2^{(2)} = J_0 + J_2$
Triple-Quantum		Relaxation function	Relaxation Rate
$\hat{T}_{3,3} \xrightarrow{R^{(3)}} \hat{T}_{3,3}f_{3,3}^{(3)}(t)$		$f_{3,3}^{(3)} = e^{-R_1^{(3)}t}$	$R_1^{(3)} = J_1 + J_2$

Table 3.2: Relaxation from Quadrupole Interaction in Isotropic Media. Evolution of Tensor operator is given in arrow notation with relaxation functions and corresponding relaxation rates. The superscript indicates quantum coherence of the relaxation. Spectral density $J_n = J(n\omega_0)$.

RF-pulse preserves the rank $q = 1$, this means that rank-2 coherences cannot be created through relaxation.

These have been presented by [Van der Mareel \(2003\)](#) and are summarised in Table 3.2.

In the presence of quadrupole interaction, both longitudinal and transverse relaxation processes are bi-exponential due to the coupling of rank-1 and rank-3 tensors. The longitudinal relaxation occurs with short ($T_{1,short} = \frac{1}{R_2^{(0)}} = \frac{1}{2J_2}$) and a long ($T_{1,long} = \frac{1}{R_1^{(0)}} = \frac{1}{2J_1}$) relaxation times. They contribute to 80% and 20% of the signal decay, respectively (cf. $f_{1,1}^{(0)}$ in Table 3.2). The measurement of transverse relaxation is of particular interest in this thesis. The short ($T_{2,short} = \frac{1}{R_1^{(\pm 1)}} = \frac{1}{J_0 + J_1}$) and long ($T_{2,long} = \frac{1}{R_2^{(\pm 1)}} = \frac{1}{J_1 + J_2}$) relaxation times contribute to 60% and 40% of the signal decay (cf. $f_{1,1}^{(\pm 1)}$ in Table 3.2). Observed relaxation times in biological tissues as tabulated by [Madelin et al. \(2014\)](#) are shown in Table 3.3.

As shown in Figure 3.2 the energy splitting due to quadrupole interactions results

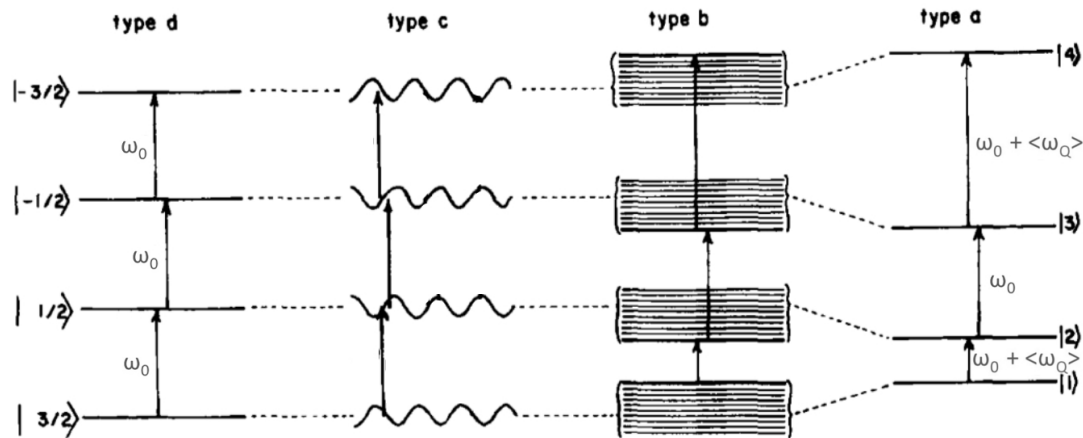


Figure 3.3: Classification of energy level splitting types for spins-3/2. *Type a* energy level splitting is observed in anisotropic media with non-vanishing EFG. *Type b* also referred to as Powder spectrum is found in liquid crystals. *Type b* indicates a slower modulation of frequency and shows the most common energy splitting situation in biological tissues. *Type a* describes the extreme narrowing limit, i.e. strong motional averaging of EFG (e.g. liquid media), where three isochronous peak of equal widths are observed in the spectrum. Adapted from [Rooney and Springer \(1991\)](#).

in a shift of the satellite transitions. The modulation of these energy states leads to the fast decaying signal component. The relative signal contribution from central and satellite transitions can also be derived analytically from the $\hat{I}_z$ operator ([Werbelow and Marshall, 1981](#)).

[Rooney and Springer \(1991\)](#) distinguished 4 types of spectra that can arise from an NMR measurement of spin-3/2 system (Figure 3.3). Differentiation between environments is made with regards to ω_0 and correlation time ($\tau_Q = (\omega_Q)^{-1}$) (cf. Equation 3.89).

1. For $\tau_Q \omega_0 \ll 1$, a *type a* spectrum is created. Such environments show strong motion and EFG, i.e. ω_Q , rapidly average to zero. This leads to $J_0 = J_1 = J_2 = 2\tau_Q$ and mono-exponential NMR signal decay is observed due to equal transitions between energy states.
2. Biological tissues usually show *type b* and *type c* spectra or superpositions thereof. The EFG fluctuate much slower due to the interaction with macromolecules in

Tissue	$T_{2,short}(ms)$	$T_{2,long}(ms)$
Brain		
White Matter	0.8 – 3	15 – 30
Gray Matter	0.8 – 3	15 – 30
CSF	–	55 – 65
Cartilage	0.5 – 2.5	10 – 30
Blood	2 – 3	12 – 20
Muscle	1.5 – 2.5	15 – 30

Table 3.3: Bi-exponential transverse relaxation times in in vivo human tissues. CSF – cerebrospinal fluid. Taken from [Madelin et al. \(2014\)](#).

the environment, i.e. $\tau_Q \omega_0 \gtrsim 1$. With decreasing modulation of ω_Q the spectrum is commonly termed *powder spectrum*.

3. If ω_Q never averages to zero, the case of a constant quadrupole interaction arises. Such environments are anisotropic, i.e. show long range order, and are discussed below.

This thesis utilises agar-based phantoms for the investigation of bi-exponential signal decay. Agarose is a polysaccharide molecule and one of the main components in agar. These molecules cause slowly fluctuating EFG. It should be noted that agar gels do not exhibit any long range order, i.e. they are isotropic.

Anisotropic media The case of anisotropic media, i.e. motion regimes with constant EFG over the time course of an NMR experiment, have been observed in biological tissue (Stobbe and Beaulieu, 2014, 2016). It will however only briefly be discussed in this work. The interested reader is referred to Van der Mareel (2003) for more detail.

In anisotropic media, the static quadrupole Hamiltonian $\hat{H}_{QS}$ does not average to zero and needs to be accounted for in the relaxation process. Equation 3.112 extends to

$$\frac{\partial \hat{\rho}^*(t)}{\partial t} = -\frac{i\omega_Q}{\sqrt{6}} [T_{2,0}, \hat{\rho}^*(t) - \hat{\rho}_0] - \sum_{q=-2}^2 \left[T_{2,q}, \left[T_{2,q}^\dagger, \hat{\rho}^*(t) - \hat{\rho}_0 \right] \right] J_q(\omega) \quad (3.113)$$

While this still preserves the decoupling between rank and orders (relaxation in anisotropic media only changes the coherence order and keeps the tensor rank), the decoupling between even and odd rank tensors is lifted. Triexponential signal decay is observed.

3.5 NMR experiments

The complex signal characteristics of Sodium (spin-3/2) NMR dynamics provide promising means for the investigation of molecular environments. The application of Sodium NMR in human acquisition in vivo is driven by an interest in the detection and interpretation of signal decay properties as well as quantitative investigations. In particular the latter point has been discussed for its non-invasive biomarker capabilities (Thulborn, 2016). The following section provides an introduction to the experimental aspects of Sodium NMR with limitations resulting from the specific NMR-sensitivity and low in vivo concentration. Furthermore, a brief overview of quantitative assessment approaches is presented.

3.5.1 Sensitivity

The detection of an NMR signal is based on the induction of a voltage in a receive coil transverse to the main magnetic field. The induced voltage U_{ind} is proportional to the expectation value of the transverse magnetisation

$$U_{ind} \propto \langle M_{xy} \rangle \quad (3.114)$$

Given that the magnetisation is directly proportional to the spin operators it is found that

$$\langle M_{xy} \rangle = \langle M_x + iM_y \rangle \propto \langle \hat{I}^+ \rangle = \text{tr}\{\hat{\rho}\hat{I}^+\} \quad (3.115)$$

where the proportionality ignores constant factors (cf. Equation 3.57).

All non-zero entries of the raising operator $\hat{I}^+$ are in the first upper off-diagonal (cf. Table 3.A.1). Hence, the trace will only access components of the first lower off-diagonal in the spin density operator. This means that only $\Delta m = -1$ coherences can be observed in NMR experiments.

Under the assumption of a homogeneous static magnetic field B_0 and a perfect $\pi/2$ RF-pulse neglecting relaxation effects, the macroscopic magnetisation is detected, i.e. $M_{xy} = M_0$. This situation provides the strongest signal amplitude and consequently highest signal-to-noise ratio (SNR). Ignoring constant factors from Equation 3.58 the macroscopic magnetisation M_0 of a sample is proportional to

$$|M_0| \propto bj(j+1)\gamma^2 \quad (3.116)$$

introducing an additional factor b describing the *natural abundance* of an isotope. It is 1 for ^{23}Na and approximately 1 for ^1H .

The signal strength in an NMR-experiment is given by (Brown et al., 2014)

$$|S| = \frac{N}{V} \omega_0 M_0 B_1. \quad (3.117)$$

Assuming a homogeneous B_1 excitation and noting that $M_0 \propto B_0$ and $\omega_0 = \gamma B_0$ yields

$$|S| \propto \frac{N}{V} B_0^2 \gamma \quad (3.118)$$

This results in a quadratic increase in signal strength with higher magnetic fields B_0 . It should, however, be noted that also noise increases linearly with higher magnetic fields consequently providing a linear increase in SNR.

For a relative assessment of signal strength with respect to ^1H -based NMR (the most commonly studied nuclei in human in vivo experiments) all nuclei-unspecific parameter can be neglected, yielding

$$S_j = \frac{N_j}{V} \gamma_j M_0 \quad (3.119)$$

for a specific spin j .

Using Equation 3.116 gives

$$S_j = \frac{N_j}{V} \underbrace{\gamma_j^3 aj(j+1)}_{\text{NMR sensitivity}} \quad (3.120)$$

The number of spins N_j over a volume element V essentially describes the concentration, the remainder of the above Equation is referred to as NMR sensitivity. Relatively to ^1H -NMR experiments, the ^{23}Na signal produces $S_{Na} \approx \frac{N_{Na}}{N_H} \cdot 0.09 \cdot S_H$. For this thesis, concentrations within the human brain are of interest. With an approximate Sodium brain-tissue concentration of 35 mM compared to 80 M of proton, the total Sodium signal magnitude is circa 20,000 times smaller than that of proton.

3.5.2 Quantitative Sodium

The physiological role of Sodium ions in metabolic processes creates a direct link to pathology. The strongly regulated concentration of these ions within biological compartments provides direct insight into healthy and diseased states. Associating a quantitative measure with the Sodium-NMR signal is a promising correlate for a range of pathologies and has consequently been the predominant focus of clinical investigations in Sodium MRI.

3.5.2.1 Tissue Sodium Concentration

The estimation of total concentration values from NMR signal strength provides the most elementary quantification measurement. With an appropriate experimental setup, signal intensities can be interpreted as spin-density measurements and, hence, can be used to infer Sodium ion concentration values. Such acquisition schemes are referred to as *density-weighted* measurements and usually have the following characteristics:

- maximum excitation, i.e. $\pi/2$ RF-pulses, for a detection of full M_0 magnetisation
- time interval in between two excitation pulses is sufficiently long for a full recovery of longitudinal magnetisation M_0 (long repetition time, TR)
- fast onset of signal sampling after excitation to limit the influence of relaxation effects (short echo time, TE)
- additional measurements for correction of potentially biasing inhomogeneities in B_0 and B_1

Density-weighted measurements are routinely performed in the presence of calibration phantoms. These are designed to match the investigated sample (e.g. human brain) with regard to coil loading and signal decay characteristics. For that, the phantoms usually contain a concentration of agar to match transverse decay characteristics and a known Sodium concentration. After correction for potential signal bias due to field inhomogeneities the NMR-signal from each phantom can be associated with the underlying Sodium concentration and utilised for quantification. Signal intensities within the sample can be mapped with a simple linear regression

$$C^{Na, \text{sample}} = \frac{I'^{\text{sample}}}{I'^{\text{ref}}} C^{Na, \text{ref}} \quad \text{where} \quad \begin{aligned} I'_{x_1}^{\text{sample}} &= I_{x_1}^{\text{sample}} \cdot \text{Corr}_{x_1}^{B1} \cdot \text{Corr}_{x_1}^{B0} \\ I_{x_2}^{\text{ref}} &= I_{x_2}^{\text{ref}} \cdot \text{Corr}_{x_2}^{B1} \cdot \text{Corr}_{x_2}^{B0} \end{aligned} \quad (3.121)$$

C represents concentration and I represents NMR-signal intensities with I' indicating bias-corrected values with regard to field inhomogeneities using correction factors Corr . Non-uniformities in the magnetic fields are localised with x_1 and x_2 indicating spatial positions.

The interpretation of Sodium concentration values is often based on a two or three compartment model, where Sodium signal is considered to originate from extra-

and intra-cellular or plasma, interstitial and intracellular compartments, respectively. Given the insignificant amount of Sodium in plasma it is commonly ignored. The tissue Sodium concentration (TSC) is hence described by (Thulborn et al., 2016)

$$\text{TSC} = \text{CVF} \cdot C_{in} + (1 - \text{CVF})C_{ex} \quad (3.122)$$

where C_{in} and C_{ex} indicate intra- and extracellular Sodium concentration and CVF represents the cell volume fraction. Intra and extra-cellular Sodium concentration in healthy brain tissue is found to be around 12 and 145 mM, respectively.

3.5.2.2 Intra-cellular Sodium Weighting

The delicate concentration gradient between intra- and extracellular spaces is a vital component of cell physiology. A disruption of this mechanism is indicated by an elevation of intra-cellular Sodium ions and, hence, a valuable marker for pathology. The isolation of the intra-cellular Sodium signal has been a focus in *in vivo* Sodium-NMR development. There mainly exist three different approaches for the selective evaluation of intra-cellular Sodium which shall now be discussed briefly.

Frequency Shift Reagents Shift reagents comprise rare earth metals, like dysprosium and thulium, and can be understood as a substance of negatively charged paramagnetic molecules. As the name suggests, these agents cause a chemical shift of the NMR-frequency. Since they are impermeable to cellular membranes this shift is exclusive to extra-cellular Sodium ions and consequently two resonances are produced for intra- and extracellular Sodium ions. The separation of resonances has been confirmed in suspensions of cells and animal studies (Gupta and Gupta, 1982; Naritomi et al., 1987). However, there exist two major drawbacks to the application of shift reagents: 1) high toxicity; 2) impassable blood-brain-barrier would necessitate a direct infusion into CSF space.

Relaxation-based Approaches These non-invasive approaches derive intra-cellular signal fractions using filtering of the Sodium signal's NMR dynamics. These approaches are based on the assumption that the differing macromolecular environments in intra- and extracellular spaces cause different signal relaxation characteristics. There exist two main approaches for the relaxation-based weighting towards intracellular signal:

Multiple-Quantum Filtering There exist filtering techniques for the detection of higher quantum coherences (most commonly triple-quantum coherences due to higher sensitivity). The selective detection of higher order coherences is grounded in the fact that such coherences only occur in the presence of non-vanishing EFG which are attributed to stronger influences from surrounding macromolecules. It is believed that such situations more commonly occur in intracellular compartments (Pekar and Leigh, 1987). For higher order coherences to be observable, the NMR-measurement needs to encompass at least 3 appropriately spaced RF-pulses. The signal is summed over repeated acquisitions with incrementing receiver phases.

Triple-Quantum-Filtered (TQF) acquisitions have been performed in phantom, animal and human experiments and demonstrated the successful suppression of mono-exponential NMR-signal. Such measurement schemes, however, suffer from very low SNR and comparatively long acquisition times (particularly at higher field strength due to SAR⁶ constraints). Bi-exponential decay is furthermore expected to occur in both intra- and extracellular environments and, hence, TQF-acquisitions can only aim at a weighting towards intracellular signal components (Rooney and Springer, 1991).

Inversion Recovery The selective suppression of signal due to differing T1-relaxation times has been proposed by Stobbe and Beaulieu (2005). The approach is based on the annihilation of certain signal components with the use of an inversion (π or 180°) pulse and appropriately timed $\pi/2$ -pulse. It is grounded in the assumption that intracellular Sodium signal exhibits shorter T1 relaxation than extracellular signal components (Winter and Bansal, 2001). The successful suppression of signal from CSF and ventricular spaces was demonstrated, however the remaining signal suffers from relatively low SNR.

⁶Specific Absorption Rate

Appendix

Derivation of spin angular momentum eigenstates

The eigenfunctions and eigenvalues of spin angular momentum operators can be derived from their commutation relationships:

$$\begin{aligned} [\hat{I}^2, \hat{I}_x] &= 0 & [\hat{I}^2, \hat{I}_y] &= 0 & [\hat{I}^2, \hat{I}_z] &= 0 \\ [\hat{I}_x, \hat{I}_y] &= i\hbar\hat{I}_z & [\hat{I}_y, \hat{I}_z] &= i\hbar\hat{I}_x & [\hat{I}_z, \hat{I}_x] &= i\hbar\hat{I}_y \end{aligned} \quad (3.A.123)$$

Since $\hat{I}^2$ and $\hat{I}_z$ commute, they share a basis of eigenstates $|a, b\rangle$. Furthermore, eigenvalues for $\hat{I}^2$ and $\hat{I}_z$ can be defined as

$$\hat{I}^2|a, b\rangle = \hbar^2 a|a, b\rangle \quad (3.A.124)$$

$$\hat{I}_z|a, b\rangle = \hbar b|a, b\rangle \quad (3.A.125)$$

where $\hbar$ is the reduced Planck's constant with the dimension of angular momentum. Hence, the eigenstates $|a, b\rangle$ are dimensionless. The eigenstates $|a, b\rangle$ are furthermore normalised, i.e. $\langle a, b|a, b\rangle = 1$.

The eigenvalues of $\hat{I}^2$ and $\hat{I}_z$ can be further specified through the application of *ladder operators* $\hat{I}^\pm$ defined in Equation 3.7. While $\hat{I}^\pm$ commutes with $\hat{I}^2$ and, hence, has no effect on the total angular momentum operator, the situation with $\hat{I}_z$ is more interesting. Using Equation 3.7 and the commutation relationships stated in Equation 3.A.123 it can be shown that

$$\begin{aligned} [\hat{I}_z, \hat{I}^\pm] &= [\hat{I}_z, (\hat{I}_x \pm i\hat{I}_y)] \\ &= [\hat{I}_z, \hat{I}_x] \pm i[\hat{I}_z, \hat{I}_y] \\ &= i\hbar\hat{I}_y \pm \hbar\hat{I}_x \\ &= \pm\hbar\hat{I}^\pm. \end{aligned} \quad (3.A.126)$$

The explicit commutation relationship can, therefore, be written as $\hat{I}_z\hat{I}^\pm - \hat{I}^\pm\hat{I}_z = \pm\hbar\hat{I}^\pm$. Applying this relationship to the eigenstates $|a, b\rangle$ gives

$$\begin{aligned} \hat{I}_z\hat{I}^\pm|a, b\rangle - \hat{I}^\pm\hat{I}_z|a, b\rangle &= \pm\hbar\hat{I}^\pm|a, b\rangle \\ \hat{I}_z\hat{I}^\pm|a, b\rangle &= \hat{I}^\pm\hat{I}_z|a, b\rangle \pm \hbar\hat{I}^\pm|a, b\rangle \end{aligned} \quad (3.A.127)$$

Using the eigenvalue definition of $\hat{I}_z$ from Equation 3.A.125 this simplifies to

$$\begin{aligned} \hat{I}_z\hat{I}^\pm|a, b\rangle &= b\hat{I}^\pm|a, b\rangle \pm \hbar\hat{I}^\pm|a, b\rangle \\ &= \hbar(b \pm 1)|a, b\rangle \end{aligned} \quad (3.A.128)$$

This concludes that $\hat{I}^\pm|a, b\rangle$ are eigenvectors of $\hat{I}_z$ with eigenvalues $\hbar(b \pm 1)$. The incrementing and decrementing effect of $\hat{I}^\pm$ on eigenvalues of $\hat{I}_z$ explains the common notation of raising and lowering operator.

The ladder operators $\hat{I}^\pm$ are not Hermitian, i.e. their eigenvalues are complex. However, each operator is the *Hermitian conjugate* of the other, i.e. $(\hat{I}^+)^\dagger = \hat{I}^-$. Since $\hat{I}^\pm|a, b\rangle$ is colinear with $|a, b \pm 1\rangle$,

$$\hat{I}^\pm|a, b\rangle = c_\pm|a, b \pm 1\rangle \quad (3.A.129)$$

where $c_\pm$ are complex numbers.

Given the Hermitian conjugate relationship between $\hat{I}^+$ and $\hat{I}^-$ it can be shown that

$$|c_\pm|^2 = (\langle a, b | \hat{I}^\mp) (\hat{I}^\pm | a, b \rangle) = \langle a, b | \hat{I}^\mp \hat{I}^\pm | a, b \rangle \quad (3.A.130)$$

where $\hat{I}^\mp \hat{I}^\pm$ can be computed as

$$\begin{aligned} \hat{I}^\mp \hat{I}^\pm &= (\hat{I}_x \mp i\hat{I}_y)(\hat{I}_x \pm i\hat{I}_y) \\ &= \hat{I}_x^2 - i(\hat{I}_x \hat{I}_y - \hat{I}_y \hat{I}_x) \mp \hat{I}_y^2. \end{aligned} \quad (3.A.131)$$

Using $[\hat{I}_x, \hat{I}_y] = i\hbar\hat{I}_z$ from Equation 3.A.123 and $\hat{I}_x^2 + \hat{I}_y^2 = \hat{I}^2 - \hat{I}_z^2$ from Equation 3.8 gives

$$\hat{I}^\mp \hat{I}^\pm = \hat{I}^2 - \hat{I}_z^2 \mp \hbar\hat{I}_z. \quad (3.A.132)$$

Using the eigenstates defined in Equation 3.A.125 this results in

$$|c_\pm|^2 = \hbar^2 [a - b(b \pm 1)]. \quad (3.A.133)$$

This result confers some fundamental conditions on the eigenstates $|a, b\rangle$. Since $|c_\pm|^2$ are positive values, a and b need to be limited. In particular, upper and lower limits of b need to fulfil $a = b_{\max}(b_{\max} + 1)$ and $a = b_{\min}(b_{\min} + 1)$. Since $b_{\min} < b_{\max}$ this yields $b_{\max} = -b_{\min} > 0$. All eigenvalues of b from $b_{\min}$ to $b_{\max}$ can be accessed through the ladder operator $\hat{I}^\pm$ and a step size of 1 as shown before. Denoting the number of steps between $b_{\min}$ and $b_{\max}$ as k yields

$$b_{\max} = b_{\min} + k = \frac{k}{2} = -b_{\min} \quad \text{where } k \in \mathbb{N} \quad (3.A.134)$$

Spin Density Operator

Each spin within an ensemble is in a superposition state (cf. Equation 3.41):

$$|\Psi\rangle = \begin{pmatrix} c_1 \\ c_2 \\ c_3 \\ c_4 \end{pmatrix} \quad (3.A.135)$$

The observable in an NMR experiment is given through the expectation value of an operator $\hat{Q}$ (cf. 3.13)

$$\langle \hat{Q} \rangle = \langle \Psi | \hat{Q} | \Psi \rangle \quad (3.A.136)$$

$$= (c_1^*, c_2^*, c_3^*, c_4^*) \begin{pmatrix} \hat{Q}_{c_1, c_1} & \hat{Q}_{c_1, c_2} & \hat{Q}_{c_1, c_3} & \hat{Q}_{c_1, c_4} \\ \hat{Q}_{c_2, c_1} & \hat{Q}_{c_2, c_2} & \hat{Q}_{c_2, c_3} & \hat{Q}_{c_2, c_4} \\ \hat{Q}_{c_3, c_1} & \hat{Q}_{c_3, c_2} & \hat{Q}_{c_3, c_3} & \hat{Q}_{c_3, c_4} \\ \hat{Q}_{c_4, c_1} & \hat{Q}_{c_4, c_2} & \hat{Q}_{c_4, c_3} & \hat{Q}_{c_4, c_4} \end{pmatrix} \begin{pmatrix} c_1 \\ c_2 \\ c_3 \\ c_4 \end{pmatrix} \quad (3.A.137)$$

$$= c_1 c_1^* \hat{Q}_{c_1, c_1} + c_1 c_2^* \hat{Q}_{c_1, c_2} + c_1 c_3^* \hat{Q}_{c_1, c_3} + c_1 c_4^* \hat{Q}_{c_1, c_4} \\ c_2 c_1^* \hat{Q}_{c_2, c_1} + c_2 c_2^* \hat{Q}_{c_2, c_2} + c_2 c_3^* \hat{Q}_{c_2, c_3} + c_2 c_4^* \hat{Q}_{c_2, c_4} \\ c_3 c_1^* \hat{Q}_{c_3, c_1} + c_3 c_2^* \hat{Q}_{c_3, c_2} + c_3 c_3^* \hat{Q}_{c_3, c_3} + c_1 c_4^* \hat{Q}_{c_3, c_4} \\ c_4 c_1^* \hat{Q}_{c_4, c_1} + c_4 c_2^* \hat{Q}_{c_4, c_2} + c_4 c_3^* \hat{Q}_{c_4, c_3} + c_4 c_4^* \hat{Q}_{c_4, c_4} \quad (3.A.138)$$

This summation can be easily expressed as the trace Tr of two matrices,

$$\langle \hat{Q} \rangle = Tr \left\{ \underbrace{\begin{pmatrix} c_1 c_1^* & c_1 c_2^* & c_1 c_3^* & c_1 c_4^* \\ c_2 c_1^* & c_2 c_2^* & c_2 c_3^* & c_2 c_4^* \\ c_3 c_1^* & c_3 c_2^* & c_3 c_3^* & c_3 c_4^* \\ c_4 c_1^* & c_4 c_2^* & c_4 c_3^* & c_4 c_4^* \end{pmatrix}}_{\text{spin density}} \begin{pmatrix} \hat{Q}_{c_1, c_1} & \hat{Q}_{c_1, c_2} & \hat{Q}_{c_1, c_3} & \hat{Q}_{c_1, c_4} \\ \hat{Q}_{c_2, c_1} & \hat{Q}_{c_2, c_2} & \hat{Q}_{c_2, c_3} & \hat{Q}_{c_2, c_4} \\ \hat{Q}_{c_3, c_1} & \hat{Q}_{c_3, c_2} & \hat{Q}_{c_3, c_3} & \hat{Q}_{c_3, c_4} \\ \hat{Q}_{c_4, c_1} & \hat{Q}_{c_4, c_2} & \hat{Q}_{c_4, c_3} & \hat{Q}_{c_4, c_4} \end{pmatrix} \right\} \quad (3.A.139)$$

In fact, it should be highlighted that the spin density operator is observed as the average over all spin particles in the ensemble. For spin-3/2 systems it consists of 16 entries and can be succinctly denoted as

$$\hat{\rho} = \overline{|\Psi\rangle\langle\Psi|}. \quad (3.A.140)$$

Its diagonal denotes the mean probability for state c_a , the off-diagonal elements provide probabilities for superposition state $c_{a,b}$. The coherence order is defined as the difference between quantum number a and b .

From Equation 3.A.139, it follows that the expectation value of an observable can be obtained through

$$\langle \hat{Q} \rangle = Tr\{\hat{\rho}\hat{Q}\}. \quad (3.A.141)$$

3/2-Spin Operator Matrices

[h!]

Cartesian Spin Operators			
$\hat{I}_x = \frac{1}{2} \begin{bmatrix} 0 & \sqrt{3} & 0 & 0 \\ \sqrt{3} & 0 & 2 & 0 \\ 0 & 2 & 0 & \sqrt{3} \\ 0 & 0 & \sqrt{3} & 0 \end{bmatrix}$	$\hat{I}_y = \frac{1}{i2} \begin{bmatrix} 0 & \sqrt{3} & 0 & 0 \\ -\sqrt{3} & 0 & 2 & 0 \\ 0 & -2 & 0 & \sqrt{3} \\ 0 & 0 & -\sqrt{3} & 0 \end{bmatrix}$	$\hat{I}_z = \frac{1}{2} \begin{bmatrix} 3 & 0 & 0 & 0 \\ 0 & 2 & 0 & 0 \\ 0 & 0 & -2 & 0 \\ 0 & 0 & 0 & -3 \end{bmatrix}$	
Ladder Operators		Squared Total Spin Operator	
$\hat{I}^+ = \begin{bmatrix} 0 & \sqrt{3} & 0 & 0 \\ 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & \sqrt{3} \\ 0 & 0 & 0 & 0 \end{bmatrix}$	$\hat{I}^- = \begin{bmatrix} 0 & 0 & 0 & 0 \\ \sqrt{3} & 0 & 0 & 0 \\ 0 & 2 & 0 & 0 \\ 0 & 0 & \sqrt{3} & 0 \end{bmatrix}$	$\hat{I}^2 = \frac{15}{4} \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$	

Table 3.A.1: Matrix notation of spin-3/2 operators.

Irreducible Tensor Operator Matrices

$\hat{T}_{0,0}$ $\begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$									
$\frac{1}{2} \hat{T}_{1,0}$ $\begin{bmatrix} 3 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & -3 \end{bmatrix}$	$\frac{-1}{\sqrt{2}} \hat{T}_{1,1}$ $\begin{bmatrix} 0 & \sqrt{3} & 0 & 0 \\ 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & \sqrt{3} \\ 0 & 0 & 0 & 0 \end{bmatrix}$								
$\sqrt{\frac{3}{2}} \hat{T}_{2,0}$ $\begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & 1 \end{bmatrix}$	$\sqrt{3} \hat{T}_{2,1}$ $\begin{bmatrix} 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \end{bmatrix}$	$\sqrt{3} \hat{T}_{2,2}$ $\begin{bmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$							
$\frac{3}{2\sqrt{10}} \hat{T}_{3,0}$ $\begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & -3 & 0 & 0 \\ 0 & 0 & 3 & 0 \\ 0 & 0 & 0 & -1 \end{bmatrix}$	$\frac{3}{\sqrt{10}} \hat{T}_{3,1}$ $\begin{bmatrix} 0 & -1 & 0 & 0 \\ 0 & 0 & \sqrt{3} & 0 \\ 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 \end{bmatrix}$	$\frac{3}{2} \hat{T}_{3,2}$ $\begin{bmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$	$\frac{-3}{\sqrt{2}} \hat{T}_{3,3}$ $\begin{bmatrix} 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$						

Table 3.A.2: Matrix notation of irreducible tensor operators up to rank $n = 3$ for spin-3/2 systems. The respective $T_{n,-q}$ are given by $T_{n,-q} = (-1)^q T_{n,q}^\dagger$.

Reduced Wigner d-matrix elements

Matrix elements order from $m = m' = j$ in upper left to $m = m' = -j$ in lower right entry.

$$d^{(3/2)}(\beta) = \begin{pmatrix} \cos^3 \frac{1}{2}\beta & -\sqrt{3} \sin \frac{1}{2}\beta \cos^2 \frac{1}{2}\beta & & & \\ \sqrt{3} \sin \frac{1}{2}\beta \cos^2 \frac{1}{2}\beta & \cos \frac{1}{2}\beta (3 \cos^2 \frac{1}{2}\beta - 2) & & & \\ \sqrt{3} \sin^2 \frac{1}{2}\beta \cos \frac{1}{2}\beta & -\sin \frac{1}{2}\beta (3 \sin^2 \frac{1}{2}\beta - 2) & & & \\ \sin^3 \frac{1}{2}\beta & \sqrt{3} \sin^2 \frac{1}{2}\beta \cos \frac{1}{2}\beta & & & \\ & \sqrt{3} \sin^2 \frac{1}{2}\beta \cos \frac{1}{2}\beta & -\sin^3 \frac{1}{2}\beta & & \\ & \sin \frac{1}{2}\beta (3 \sin^2 \frac{1}{2}\beta - 2) & \sqrt{3} \sin^2 \frac{1}{2}\beta \cos \frac{1}{2}\beta & & \\ & \cos \frac{1}{2}\beta (3 \cos^2 \frac{1}{2}\beta - 2) & -\sqrt{3} \sin \frac{1}{2}\beta \cos^2 \frac{1}{2}\beta & & \\ & \sqrt{3} \sin \frac{1}{2}\beta \cos^2 \frac{1}{2}\beta & \cos^3 \frac{1}{2}\beta & & \end{pmatrix}$$

RF-Hamiltonian in the rotating frame of reference

The Zeeman Hamiltonian can be expressed in terms of irreducible tensor operators as follows

$$\hat{H}_z = -\omega_0 \hat{I}_z = -\sqrt{5}\omega_0 T_{1,0} \quad (3.A.142)$$

The transformation of a tensor operator into the rotating frame of reference can be obtained via the Baker-Campbell-Hausdorff equation

$$\exp\{X\}Y\exp\{-X\} = \sum_{k=0}^{\infty} \frac{1}{k!} [X, Y]_k \quad (3.A.143)$$

where

$$[X, Y]_k = [X, [X, Y]_{k-1}] \text{ and } [X, Y]_0 = Y. \quad (3.A.144)$$

A tensor operator in the rotating frame of reference is, therefore, given by

$$\begin{aligned} T_{n,q}^* &= \exp\{\hat{H}_z t\} T_{n,q} \exp\{-\hat{H}_z t\} \\ &= \sum_{k=0}^{\infty} \frac{1}{k!} [\hat{H}_z t, T_{n,q}]_k \end{aligned} \quad (3.A.145)$$

Using Equation 3.A.142

$$T_{n,q}^* = \sum_{k=0}^{\infty} \frac{1}{k!} (-i\sqrt{5}\omega_0 t)^k [T_{1,0}, T_{n,q}]_k \quad (3.A.146)$$

The commutator relationship between $T_{1,0}$ and $T_{n,q}$ is given by

$$[T_{1,0}, T_{n,q}] = \frac{q}{\sqrt{5}} T_{n,q} \quad \text{and} \quad [T_{1,0}, T_{n,q}]_k = \left(\frac{q}{\sqrt{5}}\right)^k T_{n,q} \quad (3.A.147)$$

Hence,

$$\begin{aligned} T_{n,q}^* &= \sum_{k=0}^{\infty} \frac{1}{k!} (-iq\omega_0 t)^k T_{n,q} \\ &= T_{n,q} \exp\{-iq\omega_0 t\} \end{aligned} \quad (3.A.148)$$

By definition $\cos(z) = \frac{1}{2} (\exp\{iz\} + \exp\{-iz\})$ and, hence, the Hamiltonian for a RF-pulse can be written as

$$\hat{H}_{RF} = -\hbar\omega_1 \hat{I}_x \cos(\omega_{RF} t) = -\frac{1}{2} \hbar\omega_1 \hat{I}_x (\exp\{i\omega_{RF} t\} + \exp\{-i\omega_{RF} t\}) \quad (3.A.149)$$

Since

$$\hat{I}_x = \frac{1}{2} (\hat{I}^+ + \hat{I}^-) = \frac{\sqrt{10}}{2} (T_{1,-1} - T_{1,1}) \quad (3.A.150)$$

Equation 3.A.149 can be expanded to

$$\begin{aligned} \hat{H}_{RF} &= -\frac{\sqrt{10}}{4} \hbar\omega_1 (T_{1,-1} \exp\{i\omega_{RF} t\} + T_{1,-1} \exp\{-i\omega_{RF} t\} \\ &\quad - T_{1,1} \exp\{i\omega_{RF} t\} - T_{1,1} \exp\{-i\omega_{RF} t\}) \end{aligned} \quad (3.A.151)$$

Using the transformation of $T_{n,q}$ into the rotating reference frame (Equation 3.A.148) yields

$$\begin{aligned} \hat{H}_{RF}^* &= -\frac{\sqrt{10}}{4} \hbar\omega_1 (T_{1,-1} \exp\{i(\omega_{RF} - \omega_0)t\} + T_{1,-1} \exp\{-i(\omega_{RF} + \omega_0)t\} \\ &\quad - T_{1,1} \exp\{i(\omega_{RF} - \omega_0)t\} - T_{1,1} \exp\{-i(\omega_{RF} + \omega_0)t\}) \end{aligned} \quad (3.A.152)$$

The Larmor frequency is in the range of MHz and for the RF-pulse to be effective ω_{RF} needs to be identical. Furthermore, $T_{1,-1} \exp\{i\Omega t\} - T_{1,1} \exp\{-i\Omega t\} = \sqrt{2} (\hat{I}_x \cos(\Omega t) + \hat{I}_y \sin(\Omega t))$ and hence $T_{1,-1} \exp\{-i(\omega_{RF} + \omega_0)t\} \approx 0$ and $T_{1,1} \exp\{-i(\omega_{RF} + \omega_0)t\} \approx 0$.

Assuming an on-resonance pulse, i.e. $\omega_{RF} = \omega_0$, simplifies Equation 3.A.152 further to

$$\hat{H}_{RF}^* = -\sqrt{\frac{5}{2}} \hbar\omega_1 (T_{1,-1} - T_{1,1}) = -\sqrt{5} \hbar\omega_1 T_{1,1}(a) = -\hbar\omega_1 \hat{I}_x. \quad (3.A.153)$$

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4.1 Principles of Magnetic Resonance Imaging

The field of Magnetic Resonance Imaging (MRI) has grown at an enormous pace over the last decades and this thesis cannot attempt to provide a comprehensive overview over this exciting field. Instead, this chapter aims at the introduction of the fundamental concepts and rules which are of particular interest for Sodium-based MRI and of importance for the second part of this thesis. A comprehensive overview of MRI can be found in [Callaghan \(1993\)](#).

MRI pursues a localised visual representation of detectable NMR signal. The previous chapter elucidated the background of the Sodium NMR signal and its specific characteristics. Up to this point, NMR experiments are constituted by a strong external magnetic field and RF coils for signal excitation and reception. For imaging, the received bulk signal of a spin ensemble needs to be disentangled with respect to the spatial distribution. On that account, the last main components of an MRI machine, the magnetic field gradients, are introduced in this chapter leading to the concepts of spatial encoding in MRI and the notion of *k-space*. Furthermore, this chapter investigates the noise effects in MRI. The explanations follow [Brown et al. \(2014\)](#).

4.1.1 Spatial Encoding – k-space

The signal strength in an NMR experiment has been discussed in section [Sensitivity](#). It is given by Equation 3.117

$$S = \Lambda \omega_0 M_0 B_1 \quad (4.1)$$

where Λ incorporates constant factors, i.e. the spin concentration. The magnetisation exhibits precession and induces a time-dependent signal, i.e.

$$S(t) \propto M_{xy}(t) = M_{xy}(0) \exp\{i(\Omega t + \Phi(t))\} \quad (4.2)$$

where $M_{xy}(0)$ describes the transverse magnetisation at time $t = 0$ and Ω and Φ denote the offset frequency and phase, respectively. $M_{xy}(0)$ is related to the net magnetisation M_0 and is, therefore, directly proportional to the spin density according to Equation 3.58. Constant factors relating the spin density to the transverse magnetisation M_{xy} can be combined into an effective spin density ρ_{eff} .

$$S(t) = \rho_{\text{eff}} \exp\{i(\Omega t + \Phi(t))\} \quad (4.3)$$

Above equation essentially describes a signal integrated over a volume. For imaging purposes, this needs to be considered with regards to the spatial position r , i.e.

$$S(t) = \int dr \rho_{\text{eff}}(r) \exp\{i(\Omega t + \Phi(t, r))\}. \quad (4.4)$$

It should be noted that this description ignores relaxation effects. In an experiment, the relaxation-based signal decay contributes an additional time-dependent factor to the measured signal. For the sake of simplicity, this can be ignored in the description of spatial encoding concepts in MRI.

For a homogeneous magnetic field, the offset frequency is the Larmor frequency ω_0 . Since this precession is directly proportional to the applied magnetic field via $\omega = \gamma B$, spatial modifications to the magnetic field due to an additional gradient G , hence, exhibit spatially dependent variations in the precession frequency.

$$\omega(r) = \omega_0 + \omega_G r \quad (4.5)$$

related to the two magnetic field components via the gyromagnetic ratio γ . This spatially-dependent alteration of ω_G is referred to as *frequency encoding* along r . It should be noted that the applied gradient G can be time-varying leading to ω_G also being time-dependent.

The application of a gradient leads to a time and spatially dependent accumulation of phase Φ .

$$\Phi_G(r, t) = - \int_0^t dt' \omega_G(r, t') = -\gamma r \int_0^t dt' G(t') \quad (4.6)$$

where the negative sign results from the counter-clockwise positive sign convention.

The detected oscillating signal (cf. Equation 4.4) in the presence of additional gradients can be sensitised to the gradient-induced variations via demodulation of the underlying Larmor frequency

$$S(t) = \int dr \rho_{\text{eff}}(r) \exp\{i\Phi_G(t, r)\} \quad (4.7)$$

Recalling the spatial dependence of Φ_G from Equation 4.6 yields

$$S(k) = \int dr \rho_{\text{eff}}(r) \exp\{-i2\pi kr\} \quad \text{with} \quad k(t) = \gamma \int_0^t dt' G(t') \quad (4.8)$$

$$S(k) = \mathcal{F}[\rho_{\text{eff}}(r)] \quad (4.9)$$

Here, k describes *spatial frequencies* and underlines why the signal space in MRI is referred to as k-space. The above Equation essentially describes a Fourier transform ($\mathcal{F}$). This relationship is a cornerstone of MRI establishing the connection between spin density and NMR signal as a well-known linear transform. The spin density is simply related to the acquired signal via the *inverse* Fourier transform ($\mathcal{F}^{-1}$)

$$\rho_{\text{eff}}(r) = \int dk S(k) \exp\{i2\pi kr\} \quad (4.10)$$

$$\rho_{\text{eff}}(r) = \mathcal{F}^{-1}[S(k)] \quad (4.11)$$

For constant gradients, k simplifies to

$$k = \gamma Gt. \quad (4.12)$$

4.1.2 Gradient Echoes and T_2^*

Gradients introduce a spatially dependent phase accumulation across the excited spin ensemble. This phase dispersion grows with longer gradient duration, i.e. increasing k , as described in Equation 4.6. Consequently, the application of gradients leads to a decrease of the net NMR signal through dephasing. This signal loss can be recovered through a counteracting gradient, i.e. a gradient of opposite polarity which refocuses the introduced field inhomogeneity. For such a signal refocusing, two gradients G_1 and G_2 need to fulfil

$$\Phi_{G_1} - \Phi_{G_2} = -\gamma r \int_{t_0}^{t_1} dt'_1 G_1(t'_1) + \gamma r \int_{t_1}^{t_2} dt'_2 G_2(t'_2) = 0 \quad (4.13)$$

i.e. the integral over both gradients needs to cancel ($\int G(t)dt = 0$). At t_2 , the signal is fully refocused and creates a so-called *echo*. The time interval from t_0 to t_2 is termed *echo time* (TE).

It should be noted that only gradient induced inhomogeneities are reverted. Inherent dephasing through other mechanisms, e.g. quadrupole interactions, are not recoverable and, hence, the echo underlies signal loss through T_2 processes. In the presence of additional external inhomogeneities, e.g. B_0 field non-uniformities, the signal decay is also affected by a secondary component, commonly termed T_2' .

The total echo signal is hence governed through two decay processes which are combined to T_2^* via

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'} \quad (4.14)$$

where

$$\frac{1}{T_2'} = \gamma \Delta B \quad (4.15)$$

with ΔB denoting the local field inhomogeneity. For completeness it should be noted that T_2' furthermore depends on the time scale of the FID. Given the low gyromagnetic ratio of Sodium, T_2^* usually presents a close correlate to the actual T_2 .

There exists another signal refocusing mechanism which shall be mentioned here for completeness. The phase dispersion of spins can also be unravelled via a 180° -pulse. The effect is often loosely analogised with a 'pancake-flip', i.e. spins end up experiencing effects from the opposite field inhomogeneity spectrum. This pulse-based re-focusing of the signal is referred to as *spin echo*. Its major advantage lies in the fact that the 'spin-flipping' also cancels dephasing effects that were induced through field inhomogeneities, i.e. it allows a direct measure of T_2 signal decay. The application of a 180° -pulse entails, however, two disadvantages:

1. The additional power disposition accelerates the reaching of SAR limits necessitating longer acquisition times, particularly at high field strengths ($\geq 7T$), and
2. since it is not possible to detect signal during excitation, the additional time spent on the application of the refocusing RF-pulse greatly reduces the information content that can be sampled, which is particularly detrimental for the detection of the fast Sodium signal decay.

4.1.3 Excitation in the Presence of Gradients

The application of gradients is primarily used for a traversal through k-space after signal generation through an RF-pulse. The encoding capacities of spatial gradients are, however, also of interest during the preceding excitation process.

In the presence of gradients, the Fourier pair of spin density and NMR signal (Equations 4.9 and 4.11) is weighted by the spectral profile of the RF pulse $P(\omega)$. This factor is simply obtained by the Fourier transform of the pulse in time domain $p(t)$.

$$S(k) = \mathcal{F} [\rho_{\text{eff}}(r) \cdot P(\omega)] \quad (4.16)$$

with $\omega = \gamma G r$

$$(4.17)$$

$$S(k) = \mathcal{F} [\rho_{\text{eff}}(r) \cdot P(r)] \quad (4.18)$$

It should be noted that P can furthermore be dependent on k in the case of varying gradients during excitation.

The RF pulse acts as a filter over the range of spin precession frequencies invoked from the applied gradient. This relation provides a useful tool for spatial selectivity. In the following, two common RF pulses are investigated showcasing the occurrence of desired and undesired slice selectivity effects:

Sinc Pulse In routine MRI applications, it is desired to acquire an object through the measurement of distinct slices. The selective excitation of a slice essentially denotes a rectangular spectral profile along an axis. Consequently, the required time-course of the pulse is obtained through its Fourier counterpart – a sinc function. The spectral width of the pulse as well as the gradient strength along the slice-selection axes define the slice's width.

Hard Pulse For a quick sampling onset, the acquisition of fast decaying NMR signals are commonly based on a more efficient rectangular hard pulse. The corresponding spectral profile is sinc-shaped which causes a non-uniform excitation profile depending on the gradient strength during the RF-pulse. Excitations with a rectangular hard pulse are only non-selective in the absence of gradients.

4.1.4 Data Acquisition Principles – Nyquist Sampling

The Fourier transform is a continuous linear mapping between time and frequency domains. In practical situations, the acquired signal is neither continuously sampled, nor measured over an infinite time. The discrete sampling as well as truncated data acquisition do not prohibit the use of the Fourier relationship between the acquired signal and the resulting spin ensemble image. However, the data collection process needs to obey certain criteria for an artifact-free reconstruction.

4.1.4.1 Discrete Sampling

The continuously induced signal in the receive coil is digitised via an ADC¹. This corresponds to a discrete sampling of k-space. The finite sampling interval Δt relates to the sample spacing in k-space according to Equation 4.12

$$\Delta k = \gamma G \Delta t. \quad (4.19)$$

Denoting each integer sampling step p , the data acquisition can be described via a comb-function III

$$III(k) = \Delta k \sum_{p=-\infty}^{\infty} \delta(k - p\Delta k) \quad (4.20)$$

where δ describes the Dirac delta function. The discretised signal $S_d(k)$ is simply given by a multiplication of the continuous signal $S(k)$ with the above infinite sum of evenly spaced sampling points

$$S_d(k) = S(k) \cdot III(k) \quad (4.21)$$

The Fourier theorem states that this sampling result can be transformed into the image domain as a convolution

$$\rho_d(r) = \rho(r) * III(r) \quad (4.22)$$

¹Analog-to-digital converter

where $*$ indicates a convolution and the transformation of the comb-function $\text{III}(k)$ into the time-domain is simply given by

$$\text{III}(r) = \sum_{q=-\infty}^{\infty} \delta\left(r - \frac{q}{\Delta k}\right) \quad (4.23)$$

with q denoting integer sampling steps. The convolution of any function with a delta function $\delta(x - x_0)$ is a copy of the original function displaced by x_0 . Hence,

$$\rho_d(r) = \sum_{q=-\infty}^{\infty} \rho\left(r - \frac{q}{\Delta k}\right). \quad (4.24)$$

The above Equation illustrates that discrete sampling in k -space results in an infinite series containing the spin ensemble as a function of space displaced by $q/\Delta k$. This relation poses a fundamental condition on the discrete k -space sampling – the periodicity $1/\Delta k$ needs to encompass the entire imaged object

$$\frac{1}{\Delta k} = \text{FOV} \quad (4.25)$$

where FOV denotes the field of view containing the object. This condition is referred to as the *Nyquist sampling criterion*.

4.1.4.2 Truncated Signal Acquisition

The sampling duration of the NMR signal is time-limited. This results from two simple factors: First, the experimental time and hence, the measurement time is limited, and second, the inherent decay leads to an eventual obliteration of signal. The limited sampling can be expressed as a finite discrete Fourier Transform (cf. Equation 4.10 and 4.20 - 4.21)

$$\rho_d(r) = \Delta k \sum_{p=-n}^{n-1} S(p\Delta k) \exp\{i2\pi p\Delta k r\} \quad (4.26)$$

with p denoting integer-valued sampling steps ranging across the finite sampling region from $-n$ to n . The total number of sampling points $N = 2n$ provides the basis for the *spatial resolution* of the reconstructed image due to

$$\Delta r = \frac{\text{FOV}}{N} = \frac{1}{N\Delta k} = \frac{1}{2n\Delta k} \quad \text{with} \quad n\Delta k = k_{\max} \quad (4.27)$$

$$= \frac{1}{2k_{\max}}. \quad (4.28)$$

This concludes that smaller spatial detail requires outer k -space sampling, i.e. the acquisition of higher spatial frequencies. In general, the peripheral parts of k -space encode edge details whereas the central k -space components contain contrast information.

This finding completes the description of the discrete and finite signal sampling counterpart to Equation 4.26

$$S_d(k) = \Delta r \sum_{q=-n}^{n-1} \rho(q\Delta r) \exp\{-i2\pi q\Delta r k\}. \quad (4.29)$$

4.1.4.3 Point Spread Function

The finite acquisition principle with discrete sampling can be understood as a filter across k -space. The inverse Fourier transform of this filter provides the so-called *point spread function PSF* which defines the associated convolutional effects in image space. The truncated acquisition of k -space, hence, leads to a sinc-shaped point spread profile, i.e. the information in each image location results from a weighted contribution across the entire acquisition space.

The PSF is furthermore dependent on the concomitant signal decay during measurement. The frequency space counterpart of the PSF that combines the influences of k -space sampling and signal decay is called *Modulation Transfer Function MTF*.

The sampling pattern in k -space may contribute to artifacts in the reconstructed image. Originating from the Fourier series representation, functions with step discontinuities, i.e. sharp transitions between signal intensities, can lead to a well-known artifact called *Gibbs' ringing*. It results in a signal overshoot at the object's edges. There exist two approaches for an alleviation of this effect. Firstly, the artifact can be reduced by acquiring more sampling points N or decreasing the FOV. Secondly, if such changes are infeasible for a particular experiment, the ringing can be reduced via a post-processing filter, primarily a *Hann filter*. In k -space this symmetrical filter is defined as

$$H_{Hann}(k) = \frac{1}{2} \left[1 + \cos \left(\frac{\pi k}{n} \right) \right] = \cos^2 \left(\frac{\pi k}{2n} \right) \quad (4.30)$$

In the image domain, it is given by its inverse Fourier transform

$$h_{Hann}(r) = \frac{1}{2} \delta(r) + \frac{1}{4} (\delta(r - \Delta r) + \delta(r + \Delta r)) \quad (4.31)$$

Hence, the impact of the filter is

$$\rho_{d,Hann} = h_{Hann}(r) * \rho_d(r) \quad (4.32)$$

$$= \frac{1}{4} \rho_d(r - \Delta r) + \frac{1}{2} \rho_d(r) + \frac{1}{4} \rho_d(r + \Delta r) \quad (4.33)$$

and can be interpreted as a simple averaging in the image domain.

4.1.5 Noise in MRI

For an interpretation of MRI acquisitions, it is of great importance to understand the involved noise characteristics. Just like any other physical measurement it is corrupted by random and systematic noise. There exist two manifestations of noise, one in the acquired raw data and one in the reconstructed image itself.

From Faraday's law, the spins' magnetic flux creates an electromotive force (emf) in the receive coil. The main noise component in the received signal originates from random voltage fluctuations in the electronics. Their variance is given by

$$\text{var}(\text{emf}_{\text{noise}}) = \sigma_{\text{thermal}}^2 \propto 4kT \cdot R \cdot \text{BW} \quad (4.34)$$

where BW denotes the receiver bandwidth and R describes the coil loading.

The voltage fluctuations result in additive complex Gaussian white noise η on the measured k-space signal $S_m(k)$

$$S_m(k) = S(k) + \eta_m(k) \quad \text{with} \quad \eta_m \sim \mathcal{N}(0, \sigma_{\text{thermal}}) \quad (4.35)$$

Within the image domain this leads to an image noise variation of $\sigma_I^2 = \sigma_{\text{thermal}}^2 / N$.

This relationship implies two significant characteristics between data acquisition and image noise:

1. The variance within an image location is the same across the entire image and is N times smaller than the raw data variance.
2. With altered sampling (sN), e.g. longer sampling, the noise variation in the resultant image scales by a factor of $1/\sqrt{s}$.

Signal Averaging A characteristic for the accuracy of an MRI experiment is the signal-to-noise ratio SNR. It is defined as the ratio between averaged signal and the standard deviation of noise. It is well-known that image SNR can be enhanced through averaging repeated acquisitions. The signal mean is commonly taken in k-space

$$S_{m,avg}(k) = \frac{1}{N_{acq}} \sum_{i=1}^{N_{acq}} S_{m,i}(k) \quad (4.36)$$

It is assumed that the individual measurements are statistically independent. Therefore, while the mean signal remains unaffected

$$\overline{S_{m,avg}(k)} = \frac{1}{N_{acq}} \sum_{i=1}^{N_{acq}} \overline{S_{m,i}(k)} = \frac{1}{N_{acq}} (N_{acq} s(k)) = s(k) \quad (4.37)$$

the signal variance is reduced

$$\sigma_{\text{thermal},avg}^2 = \frac{1}{N_{acq}^2} \sum_{i=1}^{N_{acq}} \sigma_{\text{thermal},i}^2 = \frac{\sigma_{\text{thermal}}^2}{N_{acq}} \quad (4.38)$$

Hence, the noise variance in an averaged signal is reduced by a factor of $1/\sqrt{N_{acq}}$ consequently also yielding an increase in SNR by a factor of $\sqrt{N_{acq}}$.

With these findings it is, however, important to notice that the described noise reducing effects of averaging and prolonged signal sampling are not taking relaxation effects into account.

Signal and Noise in Magnitude Images The image data is complex with zero mean Gaussian noise in real and imaginary components and equal standard deviation σ_0 . In MRI, typically the magnitude image is used. This nonlinear mapping is known to change the noise characteristics (Gudbjartsson and Patz, 1995).

The signal in magnitude images $\tilde{\rho}$ follows a Rician distribution which turns into a Rayleigh distribution in the signal-free background, i.e. $\rho \rightarrow 0$

$$\begin{array}{ll} \text{Rician Distribution} & \text{Rayleigh Distribution} \\ p_{\tilde{\rho}} = \frac{\tilde{\rho}}{\sigma_0^2} \exp \left\{ -\frac{\tilde{\rho}^2 + \rho^2}{2\sigma_0^2} \right\} I_0 \left(\frac{\tilde{\rho} \cdot \rho}{\sigma_0^2} \right) & p_{\tilde{\rho}} = \frac{\tilde{\rho}}{\sigma_0^2} \exp \left\{ -\frac{\tilde{\rho}^2}{2\sigma_0^2} \right\} \end{array} \quad (4.39)$$

where I_0 is the modified Bessel function.

The Rayleigh distribution facilitates an estimation of σ_0 from the magnitude image. The mean and variance in regions without NMR signal are determined analytically via

$$\bar{\tilde{\rho}} = \sigma_0 \sqrt{\frac{\pi}{2}} \quad \sigma_{\tilde{\rho}}^2 = \left(2 - \frac{\pi}{2} \right) \sigma_0^2 \quad (4.40)$$

For large SNR, the Rician distribution of magnitude image intensities approaches a Gaussian distribution. Given the relatively low SNR achievements in x-Nuclei imaging the Rician noise bias is, however, of particular interest in Sodium MRI and will be of special importance in Chapter 7.

The Rician noise needs to be taken into account for an unbiased estimation of SNR. Commonly, this is achieved through a simple correction of magnitude image intensities $\tilde{\rho}$ as suggested by Gudbjartsson and Patz (1995)

$$\rho \approx \sqrt{|\tilde{\rho} - \sigma_0^2|}. \quad (4.41)$$

4.2 Image Acquisition

The preceding sections described the principles of k-space sampling. There exists a multitude of image acquisition approaches, each tailored to the individual objectives of an MRI experiment. In the case of Sodium MRI, the major constraint results from the fast decay of the NMR signal. This condition requires dedicated sequence timing concepts and sampling strategies and will be discussed in this section in more detail.

4.2.1 Non-Cartesian 3D Sampling Trajectories

The rapid bi-exponential Sodium NMR-signal decay with a fast component of down to 0.5 ms (cf. Table 3.3) necessitates a quick onset of sampling. Consequently, Sodium MRI sampling approaches usually commence in the centre of k-space, i.e. right after

signal excitation. Such centre-out sampling schemes often result in non-Cartesian trajectories. Additionally, due to the higher efficiency, non-selective hard pulses are utilised which result in a 3D acquisition of k-space. In the following, the most common of such non-Cartesian 3D sampling patterns are covered.

4.2.1.1 Radial

The shortest, i.e. fastest, trajectory towards high spatial frequencies is a straight line from the centre of k-space, k_0 , to k_{max} . The measurement of k-space is filled through successive trajectories radiating out along distinct polar (ϕ) and azimuthal (θ) angles. This means that the acquisition of k-space is performed in a radial fashion. Such coverage scheme has historical meaning since the first published NMR image by [Lauterbur \(1973\)](#) was obtained from radial reconstructions² and was a significant component of his Nobel prize together with Mansfield in 2003. The recent revival of radial sampling has mostly been a result of specialised applications with strong time constraints, i.e. short T_2 species or real-time imaging (e.g cardiac MRI).

Each radial spoke describes a projection of an associated plane and, hence, such method is also often referred to as *projection imaging*. Given the centre-out sampling each spoke encodes a *half-projection*.

A homogeneous sampling of k-space is essential. The work in this thesis employed an approach published by [Saff and Kuijlaars \(1997\)](#) for a homogeneous distribution of points on a sphere. For a given number of half-projections N_{proj} within a spherically sampled k-space, a uniform distribution of spokes with polar angle ($0 \leq \theta \leq \pi$) and azimuthal angle ($0 \leq \phi \leq 2\pi$) can be obtained from

$$\begin{aligned} \theta_k &= \arccos(h_k) \\ \text{with } h_k &= -1 + \frac{2(k-1)}{(N_{proj}-1)} \text{ and } 1 \leq k \leq N_{proj} \end{aligned} \quad (4.42)$$

$$\begin{aligned} \phi_k &= \left(\phi_{k-1} + \frac{3.6}{\sqrt{N_{proj}}} \frac{1}{\sqrt{1-h_k^2}} \right) \pmod{2\pi} \\ \text{with } 2 \leq k &\leq N_{proj}-1 \text{ and } \phi_1 = \phi_{N_{proj}} = 0 \end{aligned} \quad (4.43)$$

Transforming the spherical coordinates into a Cartesian gradient scheme is straightforward. The respective readout gradient components in each spatial direction are

$$\begin{aligned} G_x &= G \sin \theta \cos \phi \\ G_y &= G \sin \theta \sin \phi \\ G_z &= G \cos \theta \end{aligned} \quad (4.44)$$

²It should be noted that Lauterbur's work did not yet provide a notion of k-space and images were measured from only 4 projections.

The maximum applied gradient strength $G = \sqrt{G_x^2 + G_y^2 + G_z^2}$ depends on the desired readout duration T_{RO} and the chosen spatial resolution that defines k_{max} . It can be obtained from Equation 4.12.

Sampling of k-space is conditioned via the Nyquist-Theorem as described in Section [Data Acquisition Principles – Nyquist Sampling](#) which implies requirements for the minimum sampling density Δk and maximum sampled frequency k_{max} according to Equations 4.25 and 4.28.

Three-dimensional radial projection imaging samples within a sphere in k-space with high oversampling of lower frequencies and sparse sampling towards higher frequencies. Hence, in order to fulfil the Nyquist sampling condition, the sampling density requirement has to be met on the sampled sphere's surface area $S = 4\pi k_{max}^2$. The number of required projections is therefore given by the ratio between the surface area and the cell area that is associated with each projection, $(\Delta k)^2 = (1/FOV)^2$ (Boada et al., 1997a). The number of projections for a given resolution follows from

$$N_{proj} = \frac{S}{(\Delta k)^2} = 4\pi k_{max}^2 FOV^2. \quad (4.45)$$

It should be noted that $k_{max} FOV$ can also be interpreted as the number of sampling steps along each projection (with uniform sampling along the spoke).

4.2.1.2 Density-Adapted Radial

While radial sampling provides the quickest traversal from central to peripheral k-space, the resulting sampling pattern is characterised by strong variations in sampling density with high oversampling of k-space centre and decreasing density towards higher spatial frequencies. Non-uniformity leads to a reduction in image SNR due to an inhomogeneous noise distribution in k-space (Liao et al., 1997; Tsai and Nishimura, 2000).

$$\sigma_I^2 \propto \int dk \frac{\sigma_{thermal}^2}{D(k)} \quad \text{with} \quad D_{rad}(k) \propto \frac{1}{k^2 G(k)} \quad (4.46)$$

where $D(k)$ describes the local sampling density around k .

The effects of a non-uniform sampling density on SNR can be integrated in an additional efficiency factor κ (Gurney et al., 2006)

$$\kappa = \frac{\sum_i 1/D(k_i)}{\sqrt{N_k \sum_i 1/D(k_i)^2}} \quad (4.47)$$

with N_k denoting the number of k-space samples. 3D radial acquisitions with negligible gradient ramp-up yield an efficiency factor of $\kappa = \sqrt{5/9}$.

An improvement in sampling density for radial trajectories in Sodium MRI was proposed by Nagel et al. (2009). The 3D density-adapted radial sampling approach is based on modifications of the gradient shapes such that the outer part of k-space

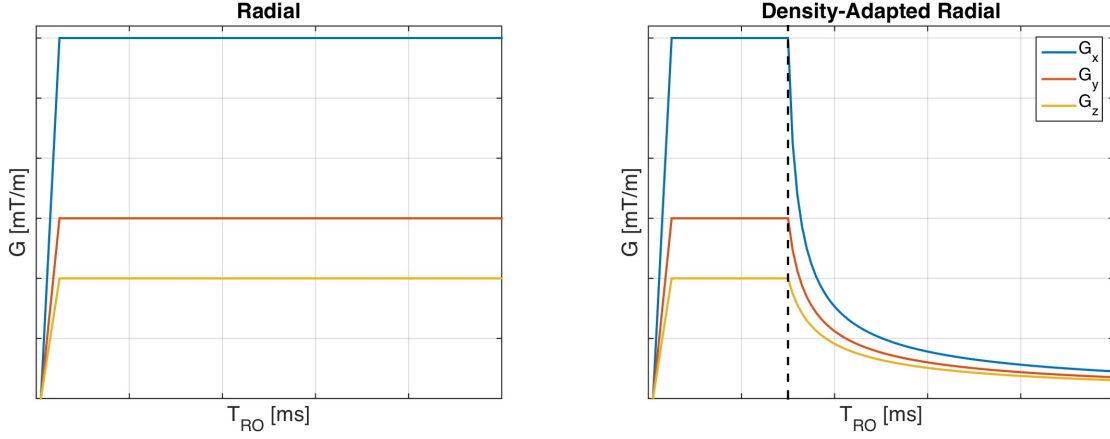


Figure 4.1: Exemplary gradient waveforms for 3D radial and 3D density-adapted radial acquisitions. Gradient ramp-up and initial traversal are identical up until k_0 at t_0 indicated by the black dotted line which marks the onset of density adaptation that is achieved through gradient strength reduction and consequent slow-down in k-space traversal speed. Gradient ramp-down is not displayed.

maintains a constant sampling density. The method follows a standard radial trajectory up to k_0 and density-corrected sampling from k_0 to k_{max} . The value of k_0 is dictated by hardware limitations, that is the gradient slew rate in most practical situations.

Using the radial sampling density from Equation 4.46, the uniform sampling requirement for all $k > k_0$ yields

$$\frac{1}{k^2 G(k)} = \frac{1}{k_0^2 G(k_0)}. \quad (4.48)$$

Recalling Equation 4.19, the gradient can be described with respect to the time-derivative of k as $G(t) = \gamma^{-1} \dot{k}$, which combined with above gives

$$\frac{\partial}{\partial t} k = \gamma G(k_0) \frac{k_0^2}{k(t)^2} \quad (4.49)$$

with solution

$$k(t) = \sqrt[3]{3\gamma k_0^2 G(k_0)[t - t_0] + k_0^3} \quad (4.50)$$

where t_0 indicates the time point of k_0 . The gradient waveform can be extracted from the derivative of above Equation. Figure 4.1 compares standard radial and density-adapted radial waveform designs.

In summary, density-adapted radial imaging provides two main advantages: 1) its implementation is relatively simple and flexible as it is based on a standard radial sequence; 2) for a fixed readout duration T_{RO} , the increased sampling homogeneity improves image SNR compared with a standard radial acquisition.

4.2.1.3 Twisted Projections

Apart from the SNR efficiency loss, the inhomogeneous radial sampling pattern suffers from relatively long acquisition times. Recalling Equation 4.45, the comparison of

required 3D radial projections versus 3D Cartesian phase encoding steps yields

$$\begin{array}{ll} \text{3D Radial:} & \text{3D Cartesian:} \\ N_{proj} = 4\pi \left(\frac{MTX}{2} \right)^2 = \pi MTX^2 & N_{phase} = MTX^2 \end{array} \quad (4.51)$$

where MTX indicates the matrix size of the reconstructed image, i.e. $FOV/\Delta r$. Hence, for any image size and FOV the number of radial acquisitions to fill k-space according to the Nyquist criterion is prolonged by a factor of π compared with a conventional Cartesian sampling scheme.

The objective of Twisted Projection Imaging (TPI) is to reduce acquisition time by sampling spirally along concentric cones in k-space. Although this implies longer trajectories from k-space centre to k_{max} , the twisted trajectory design can be optimised to concomitantly mitigate sampling inefficiency. The concept has been suggested by Jackson et al. (1992) in 2D who showed that through the twisting of spokes a more homogeneous sampling density can be achieved.

Boada et al. (1997b) have extended this idea into 3D. To ensure spherically symmetric sampling in k-space the number of sampling points within a spherical shell needs to be proportional to the shell's volume. This condition is expressed via two differential equations

$$\dot{k} = \frac{a}{k^2} \quad (4.52)$$

and

$$k^2 + k^2(\dot{\theta}^2 + \sin^2 \theta \dot{\phi}^2) = \gamma^2 G^2 \quad (4.53)$$

where a is a constant.

Equation 4.52 is essentially a generalisation of Equation 4.49 and consequently has the same solution as given in Equation 4.50 with an initial condition $k_0 \neq 0$.

Equation 4.53 provides the twisting component and contains two time-dependent unknowns ($\dot{\theta}$ and $\dot{\phi}$). There exist multiple solutions. Considering two special cases with constant ϕ and θ result in spiral- and helix-like trajectories, respectively. The latter case can be interpreted as a generalisation of the projection imaging idea (i.e. uniform sampling of k-space on the surface of cones spanned by projections originating from the centre of k-space). The solution for $\dot{\theta} = 0$ is given by

$$\begin{aligned} \phi(t) &= \frac{1}{2 \sin \theta_0} (\chi(t) + \arctan \left(\frac{1}{\chi(t)} \right)) + \phi_0 \\ \chi(t) &= \sqrt{\frac{k^4}{k_0^4} - 1} \end{aligned} \quad (4.54)$$

In brief Twisted Projection Imaging contains two major steps:

1. The sampled sphere in k-space is divided into N_R latitudinal rings. The spacing between each circle is given as FOV^{-1} (according to the Nyquist criterion 4.25). Together with the centre of k-space each ring defines a cone onto which the sampling points shall be evenly distributed.

2. Due to hardware restrictions and the initial condition of $k_0 \neq 0$, the twisting trajectory starts after a fraction p of the spoke, i.e. sampling starts in a radial way from the centre of k-space and traverses in a twisted form (according to Equations 4.50 and 4.54) after $p k_{max}$.

The choice of p influences the number of projections required to achieve uniform sampling distributions on each cone. A lower fraction of radial sampling trajectory will reduce the number of needed projections by a factor of p and, hence, reduce the total data acquisition time by a factor $1 - p$. However, lower p requires higher slew rates SR of the readout gradient as

$$SR_{max} = \frac{\gamma G^2 FOV}{p}. \quad (4.55)$$

Another consideration for the choice of p lies in the desired readout time T_{RO} . Shorter radial fractions lead to more twisting and consequently longer sampling trajectories. The highest traversing speed through k-space is limited by the achievable gradient strength and, hence, another design parameter in TPI acquisitions. It should be noted that p is kept constant throughout the whole acquisition to ensure an isotropic point spread function.

Lu et al. (2010) presented a modification of TPI (flexTPI) with increased flexibility in the utilised gradient strength G . It encompasses a dynamic increase in gradient strength at higher k-space radii based on the decreased slew rate requirements in such regions. Stobbe and Beaulieu (2008) proposed sampling density weighting during the acquisition for an enhancement of image quality.

TPI and flexTPI offer a significant reduction in acquisition time together with a homogeneous sampling pattern for good SNR characteristics. The complicated trajectory design, however, poses challenges on implementation and hardware. Furthermore, the readout trajectory length is inherently limited through the fast decay of Sodium NMR signal. Nevertheless a comparison of standard sodium acquisition schemes with fixed readout durations and measurement times underlined the increased image quality from twisted projection sampling (Romanzetti et al., 2014).

4.2.1.4 3D Cones

TPI consists of two components with different sampling strategies: 1) $k \leq k_0$ is sampled radially with G_{rad} and 2) $k > k_0$ is acquired along spiral cone trajectories with G_{circ} . The transition between radial and twisted sampling generally marks the point of greatest slew rate constraint. Gurney et al. (2006) presented 3D Cones, a numerical algorithm for radial and twisted trajectories in 3D focusing on slew rate constraints. The application of this trajectory design in Sodium MRI has been demonstrated by Staroswiecki et al. (2010) and Riemer et al. (2014).

In 3D Cones the ratio of twisting is introduced as

$$G_{twist} = \frac{G_{circ}}{G_{rad}} \quad (4.56)$$

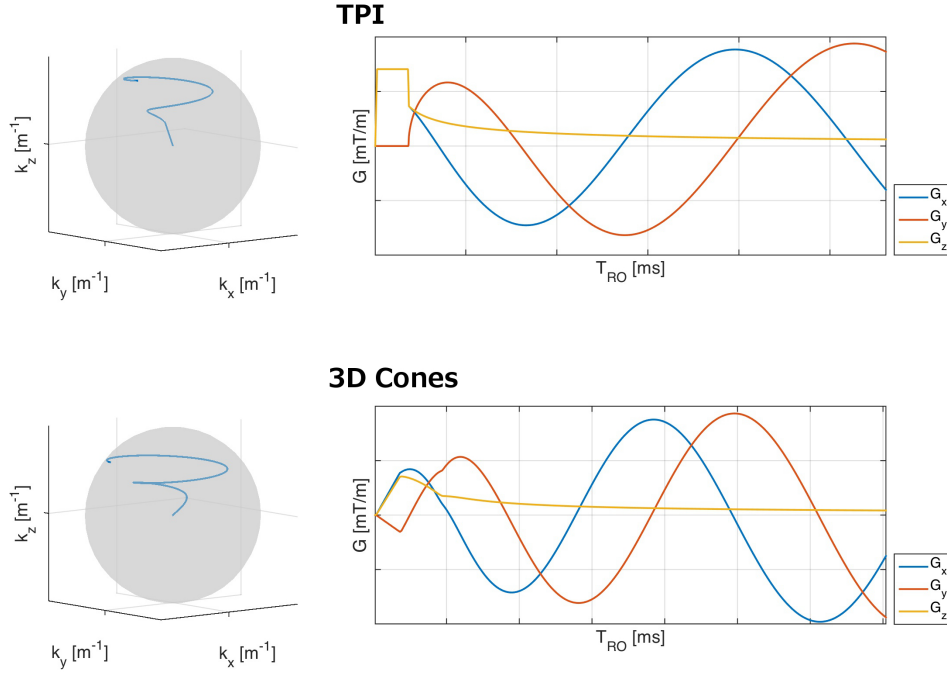


Figure 4.2: Comparison between TPI and 3D Cones trajectories and gradient waveforms. Both concepts pursue a twisted trajectory along cones in k-space. TPI consists of distinct radial and twisted components, whereas 3D Cones trajectories achieve a smoother transition between G_{rad} and G_{twist} .

Based on the circumference of the n^{th} cone ($c = \cos(\theta_n)k$) and the chosen FOV, the gradient waveform is limited by

$$G_{\text{twist}}(k) \geq \sqrt{\max \left(0, \left[\frac{2\pi \cos(\theta_n)k}{N_{\text{int}}(\theta_n)} \frac{\text{FOV}}{1 + \sqrt{\max(0, 1 - 4(k/k_{\text{max}})^2)}} \right] \right)} \quad (4.57)$$

where $N_{\text{int}}(\theta_n)$ defines the number of interleaves for the n^{th} cone.

3D Cones emphasises hardware constraints and provides an elegant description of a gradient waveform. However, the condition of homogeneous sampling density is less stringently pursued and hence, the SNR efficiency is lower compared to TPI and density-adapted radial acquisitions.

4.2.2 Short TE Sequence Timing Concepts

MRI sequences describe the temporal arrangement of RF excitation pulses, gradients and signal sampling. The acquisition of NMR signal from nuclei with rapid signal decay requires dedicated sequences with an emphasis towards quick commencement of sampling, i.e. ADC onset. There exist two sequence families that focus on the acquisition of fast T_2 species: Ultra-short Echo Time (UTE) and zero Echo Time (zTE) sequences. In the following the general concept of these two sequence classes together with the respective advantages and disadvantages are elucidated. Furthermore, Hybrid Imaging techniques, that use a combination of approaches for the selective acquisition of different parts in k-space, will be discussed.

4.2.2.1 Ultra-short Echo Time (UTE) Sequences

UTE sequences describe a straightforward sequence timing concept where, similar to a standard *pulse-acquire* experiment, signal sampling commences directly after RF excitation. The encoding of k-space is performed together with signal detection, i.e. all encoding gradients are switched on with the ADC. As described before, this yields a sampling pattern that commences in the centre of k-space with radial or twisted waveforms as described in the preceding sections. For time reasons, excitation is performed with a more efficient rectangular hard pulse and no slice selection gradients leading to a 3D acquisition of k-space. Table 4.1a depicts a sequence diagram of a radial UTE acquisition.

The application of gradients is limited by their slew rates SR , i.e. the speed at which gradients are ramped up to the desired strength G .

$$T_{RU} = \frac{G}{SR} \quad (4.58)$$

where T_{RU} denotes the ramp-up time.

Finite slew rates limit the initial traversal speed in k-space. Using the definition of k for time-varying gradients as given in Equation 4.8 yields different k-space sampling points for ramp-up and constant gradient (*plateau*) acquisition

$$k(t) = \begin{cases} \frac{1}{2}\gamma SR t^2 & \text{for } t \leq T_{RU} \\ k_R + G (t - T_{RU}) & \text{otherwise} \end{cases} \quad \text{with } k_R = \frac{G^2}{2 SR} \quad (4.59)$$

where k_R describes the point in k-space at which gradients have been fully ramped-up.

Additionally to finite gradient slew rates, hardware constraints also affect the switching time between RF excitation and ADC sampling, commonly denoted *transmit-receive* (TR) switch time or *dead-time* t_d . For common clinical systems, this time ranges between 40 and 100 μs where often the waiting time for sampling onset is chosen conservatively more to the longer end of this time range.

Limited B1 strength results in finite pulse durations t_{RF} (usually on the order of a few hundred μs for $\pi/2$ -pulses in Sodium MRI at 7T). The sampling onset time TE is defined as the time interval originating from the system dead-time and half the length of the excitation pulse

$$TE = \frac{1}{2}t_{RF} + t_d \quad (4.60)$$

where the notation TE is slightly misleading since only a simple FID (free induction decay) signal is sampled and no echo is created. However, this term is conventionally used for the definition of sampling onset in the centre of k-space.

Based on the sampling onset, TE, and the traversing speed through k-space (Equation 4.59) each k can be associated with a required encoding time t_{enc} , i.e. the time interval until k is sampled.

$$t_{enc}(k) = TE + \begin{cases} \sqrt{\frac{2k}{SR}} & \text{for } t \leq T_{RU} \\ T_{RU} + \frac{k-k_R}{G} & \text{otherwise} \end{cases} \quad (4.61)$$

While t_{enc} is strongly dependent on the applied gradient strength, the above equation also emphasises the reduced efficiency during ramp-up imposing a limit on the reliable acquisition of fast T_2 decays.

4.2.2.2 Zero Echo Time (zTE) Sequences

The time-inefficiency during initial k-space sampling in UTE is addressed in zTE sequence timing approaches. Here the limiting factor of finite gradient slew rates is pushed to the beginning of the sequence, i.e. before the excitation pulse. As a result, gradients are ramped to full strength when sampling is commenced and the traversal through k-space is performed at the desired speed with evenly spaced samples along the measured projection. A sequence diagram of a radial zTE acquisition is shown in Table 4.1a.

The zTE concept alleviates initial sampling speed problems of UTE sequences. The inherent hardware constraint resulting from the dead-time delay, however, cannot be overcome. The non-zero gradients during this time-delay lead to a traversal in k-space that is not actively sampled. Hence, zTE sequences end up with a gap in the centre of k-space. The first sampling point k^* depends on the chosen gradient strength and system dead-time

$$k^* = \gamma G (t_{RF} + t_d) = \gamma G TE \quad (4.62)$$

Algebraic methods for the retrospective estimation of central k-space data have been suggested (Kueth et al., 1999). However, such methods are only accurate for relatively small k-space gaps. Other approaches are based on hybrid imaging techniques where the central k-space data is acquired additionally and will be discussed later.

The application of an RF-pulse in the presence of gradients causes additional challenges as described in Section [Excitation in the Presence of Gradients](#). Two sequence parameters can be adjusted to reduce the undesired excitation profile with, however, other adverse side effects: 1) pulse duration can be shortened but limits the attainable flip angle; 2) gradient strength can be reduced but results in lower k-space traversing speed.

Single-Point Sequences A special case of zTE sequences are Single Point (SP) acquisitions, which, as the name suggests, sample k-space in a point-wise manner. SP measurements follow a zTE time scheme, i.e. ramp gradients prior to sampling. However, with each excitation only one distinct point in k-space is sampled. Commonly, single points are acquired on a Cartesian grid, however, any point arrangement is generally possible. The most common examples of SP sequence schemes are ‘Rapid Single Point’ (RASP) (Heid and Deimling, 1995) and ‘Single Point Ramped Imaging with T1 Enhancement’ (SPRITE) (Balcom et al., 1996). A schematic of a Single Point Sequence Diagram is shown in Table 4.1a.

SP acquisitions are also often referred to as *constant imaging* techniques since every sampled point is acquired with the same t_{enc} . The required gradients for each k-space

location can be simply derived from Equation 4.19

$$G = \frac{k}{\gamma t_{\text{enc}}} \quad (4.63)$$

Thanks to the constant t_{enc} across k-space, the resulting image is free from convolutional T_2^* effects. For clinical settings, SP sequence designs are however generally impractical due to the extensive acquisition time.

SP and zTE acquisition schemes are not commonly employed in Sodium MRI due to the significant constraints in excitation. The low Sodium signal requires high flip angles which are not readily achievable in pre-ramped imaging conditions. [Romanzetti et al. \(2006\)](#) compared SPRITE imaging schemes for Sodium MRI acquisitions and used averaging approaches to compensate for lower attainable flip angle. Overall, the measured SNR was, however, lower than in UTE-based acquisitions.

4.2.2.3 Hybrid Imaging

The acquisition of fast decaying signal is challenging and all previously described conventional sequence timing concepts entail compromises since they are either limited by encoding efficiency (UTE), extensive acquisition times (SP) or a biased selection profile and incomplete k-space acquisition (zTE). Hybrid imaging merges sequence approaches to combine individual advantages with the primary focus on optimised t_{enc} in clinically feasible scan times. The most common hybrid encoding concepts are discussed below and illustrated in Table 4.1b.

WASPI Water- and Fat-Suppressed Proton Projection MRI (WASPI) was presented by [Wu et al. \(2007\)](#). It splits k-space acquisition in two parts: the outer hull and the central sphere.

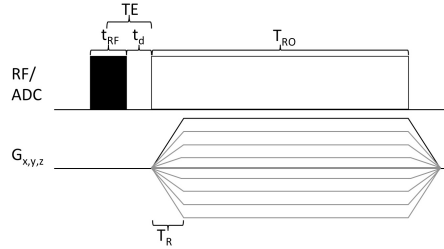
The outer k-space hull is acquired with a conventional radial zTE sequence. Afterwards, the resulting k-space gap is subsequently measured with a reduced gradient strength. For that, the authors use the simple relationship between k^* and G shown in Equation 4.62 which demonstrates that the unmeasurable portion $k < k^*$ shrinks proportionally with reduced G . The second set acquiring the central k-space gap is much smaller than the outer part and, hence, only a very small number of additional projections is required. The central k-space point is acquired in the absence of G .

PETRA [Grodzki et al. \(2012\)](#) proposed Pointwise Encoding Time Reduction With Radial Acquisition (PETRA). Similar to WASPI, the outer k-space and central gap are acquired individually, however, the gap filling is performed using Cartesian SP measurements. Consequently, the central k-space component is consistently sampled at the shortest possible t_{enc} . This overall concept is akin to *keyhole imaging* ([Van Vaals et al., 1993](#)). [Froidevaux et al. \(2018\)](#) recently showed that PETRA, i.e. the combination of radial and Cartesian sampling, offers the most robust performance and provides good image quality for a wide range of fast T_2 species and imaging situations.

RHE WASPI and PETRA are primarily targeting the central k-space gap in zTE imaging. Recently, Jang et al. (2016) suggested a more generalised concept, named ramped hybrid encoding (RHE), which furthermore addresses the inhomogeneous excitation profile in zTE-based acquisitions. Just like PETRA, this approach combines radial and Cartesian acquisitions. However, unlike PETRA, gradients are ramped in two steps: 1) gradients are first ramped to an intermediate strength G_{RF} at which the RF pulse is applied; 2) immediately after excitation, i.e. during dead-time, gradients are further ramped up to their final strength for k-space traversal. This generalised concept offers greater flexibility in the sequence design with more tailoring options for the individual species under investigation. It encompasses two main benefits: 1) The lower gradients during excitation, mitigate undesired selectivity effects from the RF pulse facilitating higher flip angles; 2) The additional ramping of gradients for k-space readout further reduces the required t_{enc} for every point in k-space.

It should be noted that the wider bandwidth of excitation pulses, i.e. shorter pulse duration, in zero TE imaging results in altered SAR values compared with common UTE sequences. This is of particular importance for sequence designs at higher field strength.

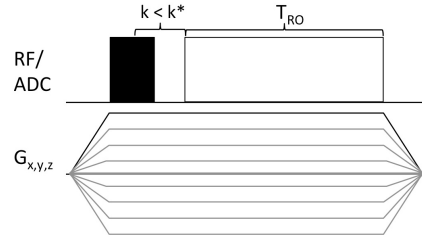
Ultrashort TE



Gradient ramp-up and data acquisition are synchronised and commence after dead-time t_d . ADC readout length is T_{RO} . Echo Time (TE) results from t_d and then pulse length (T_{RF}). Gradient ramp-up time is denoted T_R .

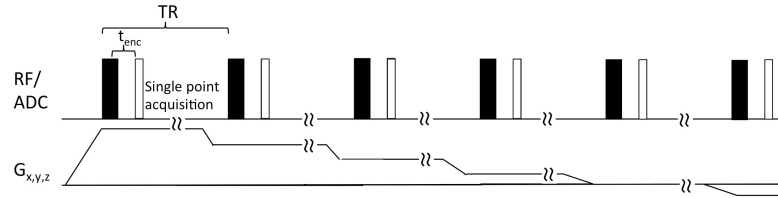
zero TE

radial zTE



Gradient ramping occurs prior to RF-excitation. Central k-space ($k < k^*$) is missed until ADC commences.

Single Point



Gradients are ramped successively to each k-space location and single points at $t = TE = t_{enc}$ are acquired under the ADC. Commonly lower flip angle (i.e. shorter RF-pulses) are applied to shorten the repetition time (TR) between point acquisitions.

Table 4.1a: Sequence Diagrams for measurement of short TE species. Upper rows in diagrams display RF excitation and ADC sampling as black and white rectangles, respectively. Lower rows illustrate Cartesian gradients. For simplicity, all diagrams are shown with radial trajectories. Modifications of the waveforms are however possible.

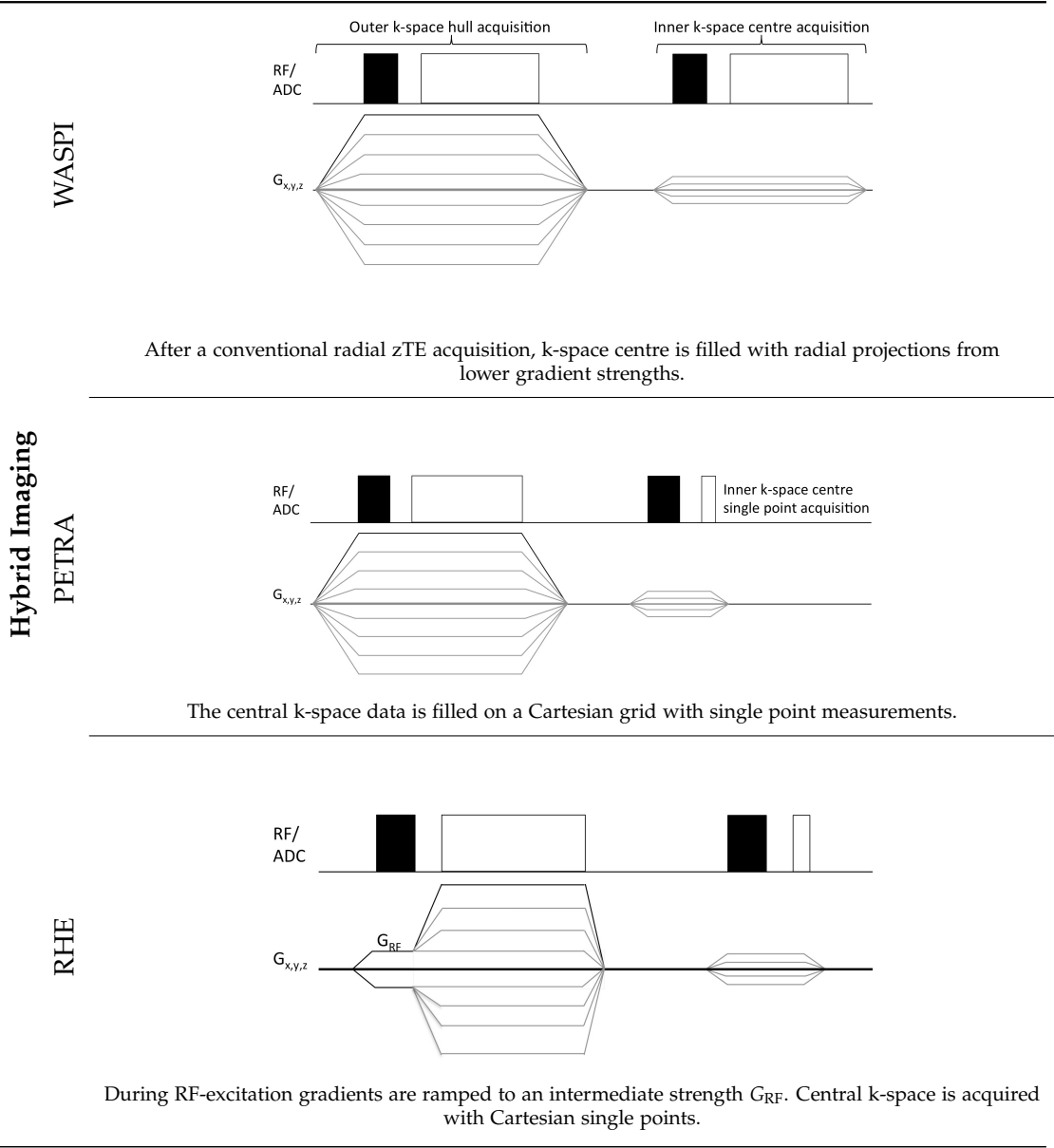


Table 4.1b: Continued Sequence Diagrams with hybrid imaging approaches. The acquisition of outer k-space (left component of diagrams) is followed by a retrospective filling of central k-space (right component of diagrams).

4.3 Image Reconstruction

Thus far, the NMR signal measurement principles as well as particular acquisition specifics for fast decaying Sodium signal have been outlined. The relatively complicated signal sampling strategies in Sodium MRI resulting in 3D non-Cartesian data points (cf. Section [Non-Cartesian 3D Sampling Trajectories](#)) require an elaborate image calculation.

The image reconstruction approaches can be loosely categorised into standard and iterative reconstruction schemes. The former aim to calculate an image from the measured projections alone and the latter describes the image formation via a constrained optimisation. Since standard reconstruction schemes solely rely on the detected data, such methods require a sufficiently sampled k-space (cf. [Data Acquisition Principles – Nyquist Sampling](#)). Iterative approaches enable the incorporation of additional knowledge about the underlying object facilitating the reconstruction of the image from a reduced number of samples. This concept is known as *Compressed Sensing*. For reasons that will be explained later, non-Cartesian sampling is particularly suited for such reconstruction approach.

In the following, an introduction to Sodium MRI reconstruction is provided. After a short explanation of required raw data pre-processing, also known as density compensation, standard (Gridding and NUFFT) as well as iterative reconstruction approaches (Compressed Sensing) will be discussed.

4.3.1 Density Compensation

Independent of the chosen reconstruction scheme, non-uniformly measured data needs to be pre-processed with regard to the sampling inhomogeneity. This requirement results from the uneven weighting of k-space and is referred to as density compensation. In general, all previously described sampling schemes result in an uneven weighting of k-space. Each presented trajectory scheme contains a radial component, which by default leads to a strong oversampling of central k-space components. The unfiltered use of the acquired raw data hence suffers from a relative underrepresentation of edge information and results in a blurry reconstruction of the underlying object.

A good description for general inhomogeneity compensation can be found in [Pipe and Menon \(1999\)](#). For radial k-space projections, the required weighting is simply given by the distance from k-space center. [Niellès-Vallespin et al. \(2007\)](#) define a weighting function w with respect to the area around each sampled point

$$w_n = \frac{\pi}{N_{proj}} \left[\left(\frac{k_{n+1}}{2} \right)^2 + \left(\frac{k_n}{2} \right)^2 \right] \quad (4.64)$$

with k_n indicating a sampling point along each spoke.

The underlying noise characteristics of actual raw data with increasing noise contribution towards the tail end of the projection, however, often necessitate an adjustment

that penalises higher frequency components. [Niellès-Vallespin et al. \(2007\)](#) suggest to plateau the filter after 25% of the projection length. In this work, the filter has been combined with a Hann window (as described in Section [Point Spread Function](#)) which is a common weighting component in Sodium MRI that mitigates Gibbs' ringing and enhances the resulting SNR.

4.3.2 Standard Non-Cartesian Reconstruction

In case of radially acquired data, the underlying image can be calculated using projection reconstruction, a method more widely used in another tomographic imaging approach, x-ray computed tomography (CT). It underlies the Fourier slice theorem, i.e. each measured projection represents the Fourier transform of the orthogonal object profile. Hence, given a sufficient number of measured spokes, an overlay of all Fourier transformed projections along the respective angle renders the imaged object. This approach is quite elegant and particularly useful in 2D acquisitions since the back projection process can be efficiently computed using a *Radon transform*. In 3D and particularly for an arbitrary distribution of sampling points in k-space, this approach becomes more cumbersome and therefore non-Cartesian MRI data is usually reconstructed by other methods which essentially aim to associate the measured data into a Cartesian grid. Using the convenient Fourier relationship between k-space and image (cf. Equation [4.9](#) and [4.11](#)), uniformly spaced n-dimensional Cartesian data can be reconstructed very efficiently via an n-dimensional Fast Fourier Transform (FFT).

4.3.2.1 Regridding

The introduction of the Fast Fourier Transform by [Cooley and Tukey \(1965\)](#) has made the calculation of complex Fourier series computationally efficient. It reduced the complexity of the Fourier Transform of an N -point signal to $O(N \log N)$, as opposed to $O(N^2)$ operations in case of the discrete Fourier Transform. To apply this transform the sampled data points must lay on a Cartesian grid. If the acquisition scheme is not inherently Cartesian, re-gridding methods can be used to approximate the measured samples onto a Cartesian grid. Ideally, the re-gridding would be performed via a (1) convolution of a rectangular function in the spatial domain (i.e. sinc-function in frequency domain) followed by (2) a re-sampling onto Cartesian grid points. It should be noted that the process of a convolution with a sinc-function and a subsequent projection of samples onto a uniform grid is not a strict interpolation scheme and, therefore, more appropriately referred to as gridding ([O'Sullivan, 1985](#)).

The overall concept can be described as follows ([Jackson et al., 1991](#)):

Sampling Data As described in Equation [4.8](#), the 3D NMR-signal acquisition S is related to the imaged spin ensemble ρ via a Fourier Transform

$$S(u, v, l) = \int_{-\infty}^{\infty} \rho(x, y, z) \exp[-2\pi i(ux + vy + lz)] dx dy dz \quad (4.65)$$

with 3D k-space and image dimensions denoted u, v, l and x, y, z , respectively.

Referring to Equation 4.21, the sampled signal is denoted S_d and is measured by some sampling function ι_s

$$S_d(u, v, l) = S(u, v, l) \cdot \iota_s(u, v, l) \\ \text{with } \iota_s(u, v, l) = \sum_{k=1}^N \delta(u - u_k, v - v_k, l - l_k) \quad (4.66)$$

where ι_s describes a general discrete sampling with variable-density. In case of a non-uniform distribution of data samples, the acquired signal S_d needs to be compensated for these density-inhomogeneities. The weighted signal is given as $S(u, v, l)_{dw} = S_d(u, v, l) \cdot w(u, v, l)$ with an example for w in radial acquisitions given in Equation 4.64.

Convolution The finite image support yields a convolution of sampling space with a sinc-function (cf. Section [Point Spread Function](#)). Denoting the sampled and convolved signal S_{dwc} , this effect can be incorporated via a convolution kernel C

$$S_{dwc}(u, v, l) = [S(u, v, l) \cdot \iota_s(u, v, l) \cdot w(u, v, l)] * C(u, v, l) \quad (4.67)$$

Optimally, the acquired signal would be convolved with a sinc-function. The infinite extent of the sinc function indicating contribution from all measurement points to each grid point makes its implementation impractical. Instead several other convolving functions (cosines, Gaussian, etc.) have been investigated ([Jackson et al., 1991](#)).

A truncated zero-order prolate spheroidal wave function (PSWF) of the first kind is well band-limited, i.e. it shows a minimal energy outside the desired bandwidth. However, it is also computationally challenging. The Kaiser-Bessel function is a good approximation to the zero-order PSWF and is easily computed (both in image and frequency domain):

Kaiser-Bessel (frequency domain):

$$C_{KB}(u) = \frac{1}{W} I_0 \left[\beta \sqrt{1 - b(2u/W)^2} \right] \quad (4.68)$$

with I_0 the zero-order modified Bessel function of the first kind, W defining the kernel width and β a free tuning parameter which can be calculated according to [Beatty et al. \(2005\)](#).

Kaiser-Bessel (image domain):

$$c_{KB}(x) = \frac{\sin \sqrt{\pi^2 W^2 x^2 - \beta^2}}{\sqrt{\pi^2 W^2 x^2 - \beta^2}} \quad (4.69)$$

with width W and tuning parameter β as described before.

Gridding After convolving the sampled and density-compensated data with a finite Kaiser-Bessel kernel, the filtered sampling points are gridded onto a Cartesian grid via the comb-function (cf. Equation 4.23)

$$III(u, v, l) = \sum_i \sum_j \sum_k \delta(u - i, v - j, l - k) \quad (4.70)$$

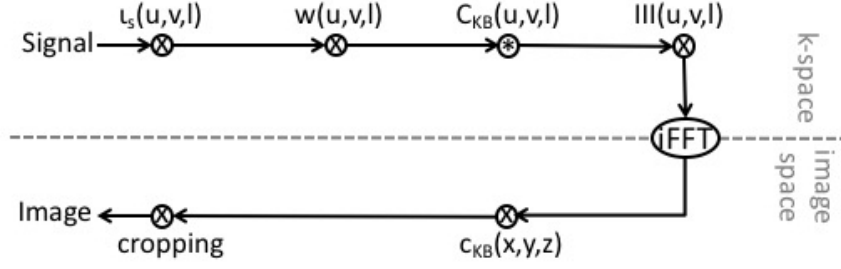


Figure 4.3: Overview of gridding process.

The discretised, weighted, convolved and re-sampled signal is given by

$$S_{dwcs}(u, v, l) = [(S(u, v, l) \cdot \iota_s(u, v, l) \cdot w(u, v, l)) * C(u, v, l)] III(u, v, l) \quad (4.71)$$

Deapodisation Performing the signal convolution with an approximation filter instead of the computationally impractical sinc-kernel implies inaccuracies. The approximated kernels (e.g. Kaiser-Bessel window) do not replicate a perfect rectangular function in the image domain, but contain rolloffs towards the side of the image. This leads to an attenuation at the image borders that can, however, be corrected for by dividing the signal in the image domain with the inverse Fourier Transform of the applied regridding kernel. For the Kaiser-Bessel window, this deapodisation function is given in Equation 4.69.

The image of the detected spin ensemble ρ can, therefore, be calculated by

$$\rho(x, y, z) = \frac{\mathcal{F}^{-1} S_{dwcs}(u, v, l)}{c(x, y, z)} \quad (4.72)$$

with $c(x, y, z) = \mathcal{F}^{-1} C(u, v, l)$

Cropping Recalling the effect of a comb-function as a repeatedly shifted response (cf. Equation 4.25) and the implications of a finite image support (cf. Equation 4.28), it is evident that an accurate representation from a gridding reconstruction requires an oversampling of at least a factor of two in each spatial direction (O’Sullivan, 1985)

$$x_l \leq 1/(2u_l), \quad y_l \leq 1/(2v_l), \quad z_l \leq 1/(2l_l) \quad (4.73)$$

where x_l, y_l, z_l and u_l, v_l, l_l describe the truncated image and signal space, respectively.

An overview of the regridding framework is displayed in Figure 4.3.

4.3.2.2 Non-Uniform Fast Fourier Transform – NUFFT

A more general approach for calculating the Fourier Transform of nonuniformly spaced data is described via the nonuniform fast Fourier Transform. Its theory is reviewed here following Fessler and Sutton (2003).

Again the objective is to find an efficient way of computing the Fourier Transform at inhomogeneously spaced frequency locations (ω_m). As we have discretely sampled signal samples x_n , with $n = 0, \dots, N-1$, the purpose can be formulated by a nonuniform discrete Fourier Transform:

$$X(\omega_m) = \sum_{n=0}^{N-1} x_n e^{-i\omega_m n}. \quad (4.74)$$

With $m = 1, \dots, M$, its computation complexity leads to $O(MN)$ which makes it generally impractical.

The general concept of a nonuniform fast Fourier Transform (NUFFT) is to make the calculation of above Equation as efficient and accurate as possible by following two major steps:

1. Generate an oversampled FFT of the given signal.

$$Y_k = \sum_{n=0}^{N-1} s_n x_n e^{-i\gamma kn} \quad (4.75)$$

with $\gamma = \frac{2\pi}{K}$ and $k = 0, \dots, K-1$

represents a K -point weighted FFT of the sampled signal x_n with $K \geq N$ and $s = (s_1, \dots, s_N)$ as scaling vector for each signal sample.

2. Interpolate oversampled signal Y_k onto nonuniform frequency points.

$$\hat{X}(\omega_m) = \sum_{k=0}^{K-1} v_{mk}^* Y_k \quad (4.76)$$

with v_{mk}^* the complex conjugate interpolation coefficient.

This general idea contains two design parameters - scaling vector s and interpolation coefficients v_{mk} . In an ideal case, the oversampled FFT signal Y_k can retrieve x_n (inverse FFT of Equation 4.75) and can be substituted into Equation 4.74 to calculate the desired $X(\omega_m)$. In the simple case of $s = 1$, this leads to

$$X(\omega) = \sum_{n=0}^{N-1} x_n e^{-i\omega n} = \sum_{n=0}^{N-1} \left[\frac{1}{K} \sum_{k=0}^{K-1} Y_k e^{i\gamma kn} \right] e^{-i\omega n}. \quad (4.77)$$

However, this ideal interpolator uses all interpolation coefficients v_{mk} for the calculation of the desired FT values and ends up with a complexity of $O(MK)$. In order to speed up computation, NUFFT algorithms only consider the J nearest neighbours of ω_m which reduces the computation to $O(MJ)$ operations ($J \ll K$).

Let $u_j(\omega_m)$ define the J non-zero nearest neighbour interpolators of ω_m , then

$$\hat{X}(\omega_m) = \sum_{j=1}^J Y_{\{k_m+j\}_K} u_j^*(\omega_m) \quad (4.78)$$

with

$$k_0(\omega_m) = k_m = \begin{cases} (\arg \min_{k \in \mathbb{Z}} |\omega - \gamma k|) - \frac{L+1}{2} & \text{J odd} \\ (\max\{k \in \mathbb{Z} : \omega \geq \gamma k\}) - \frac{L}{2} & \text{J even.} \end{cases} \quad (4.79)$$

The main challenge lies in the optimal choice for the interpolation vector $\mathbf{u}(\omega_m) = (u_1(\omega_m), \dots, u_J(\omega_m))$ providing, on the one hand, an accurate approximation of $X(\omega_m)$ and a reasonable computational effort, on the other hand.

Within this project an implementation of [Fessler and Sutton \(2003\)](#) has been used. The authors define a min-max criterion for determining a choice of interpolation coefficients which is selected such that the worst case approximation error between X_m and $\hat{X}(\omega_m)$ is minimal. They showed that the minimiser of the interpolation vector $\mathbf{u}$ is given by

$$u(\omega_m) = \Lambda'(\omega_m) [C' S S' C]^{-1} C' S b(\omega_m) \quad (4.80)$$

where $S = \text{diag}\{s_n\}$, A' indicates the Hermetian transpose of A , $\Lambda(\omega)$ is a $J \times J$ diagonal matrix, C is a $N \times J$ matrix, and $b(\omega_m)$ is a N -vector with the following entries

$$\begin{aligned} \Lambda_{jj}(\omega_m) &= e^{i[\omega - \gamma(k_0(\omega) + j)]\eta_0} \\ C_{nj} &= \frac{e^{i\gamma j(n - \eta_0)}}{\sqrt{N}} \\ b_n(\omega_m) &= \frac{e^{i(\omega - \gamma k_0(\omega))(n - \eta_0)}}{\sqrt{N}} \end{aligned} \quad (4.81)$$

Since S and C are independent of the frequency location ω_m these matrices can be pre-computed. Further hints on efficient implementation and computation of NUFFT are given in [Fessler and Sutton \(2003\)](#).

The extension of the suggested method to higher dimensions is very straightforward, i.e. calculating an N -dimensional oversampled FFT and computing the interpolator using the N -dimensional J -neighbourhood.

The described method can be interpreted as a linear operator. The combination of Equations 4.75 and 4.78 can be re-written in matrix-form as $\hat{X} = Gx$ with $G = VWS$ where S is defined as in Equation 4.80, W is a $K \times N$ oversampled FT matrix (entries $w_{kn} = e^{-i\gamma kn}$) and V the $M \times K$ interpolation matrix (entries v_{mk}). This fact supports the calculation of the inverse NUFFT by reversing G , i.e. $G'\tilde{y} = S'W'V'\tilde{y}$. Hence, the inverse NUFFT can be calculate following three steps:

1. Interpolation (adjoint of Equation 4.76), i.e.

$$\tilde{X}_k = \sum_{m=1}^M v_{mk} \tilde{y}_m \quad (4.82)$$

2. Calculate the K -point inverse FT of $\tilde{X}_k$ (adjoint of Equation 4.75)

$$\tilde{x}_n = \sum_{k=0}^{K-1} \tilde{X}_k e^{(i2\pi kn)/K} \text{ with } n = 0, \dots, N-1 \quad (4.83)$$

3. Scale $\tilde{x}_n$ by s_n^* .

4.3.3 Iterative Reconstruction

Non-uniform acquisition of k-space is generally inefficient, since the Nyquist criterion needs to be fulfilled in the least densely sampled region of k-space. Consequently, other areas of k-space are oversampled, a fact that is most commonly associated with an increased measurement time and quantified in Equation 4.51 for radial acquisitions.

Maintaining good reconstruction quality from a reduced number of samples is of central interest in many disciplines and is the foundation of a sampling and reconstruction scheme called Compressed Sensing. It aims at an efficient data sampling with sophisticated reconstruction that tries to iteratively approach to a solution that fulfils both the acquired data and the a priori known information about the imaged object.

In the following, an overview of Compressed Sensing is presented. It commences with the theoretical background that emerged from Information Theory. The explanation closely follows the introductory overview presented by Candès and Wakin (2008). The Compressed Sensing concept was soon identified as a promising tool for MRI and the specific application this theory to imaging will be discussed in the second part of this section. It is based on the work published by Lustig et al. (2007).

4.3.3.1 Compressed Sensing

The steady increase of data and information within the modern technology-driven world has led to an extensive study of data compressibility. It is commonly known that data can be stored very efficiently when transformed into an appropriate representation basis, i.e. the information content of most natural signals only lies within a small number of coefficients of some orthonormal basis. This fact leads to most of the acquired data "being thrown away" to allow efficient data storage and transmission. The high compression rates without any perceptual loss of information raise the question whether all the data needs to be acquired in the first place and whether there is a way to directly measure the essential information of interest. This question has initiated the description of efficient, compressed data acquisition protocols known as Compressed Sensing (CS) techniques.

Compressed or compressive sampling can be understood as a novel measurement paradigm that breaks with common principles of data acquisition (Nyquist theorem) by recovering a signal from far fewer samples than commonly required. The concept of Compressed Sensing has been introduced by Candès et al. (2006) and Donoho (2006) and is based on two principles:

- 1) **Sparsity** Sparsity describes the concept that the information content of a signal can be expressed in a concise way, i.e. the information of a signal is much smaller than

indicated through its bandwidth. The sparsity or compressibility of a signal might be apparent in a different basis Ψ . This idea is commonly referred to as transform sparsity.

2) Incoherence Incoherence refers to the impact between signal sensing and its representation domain. An object with a sparse representation in Ψ shows a wide-spread information content in the sampling domain and vice-versa, e.g. a Dirac delta in time domain has an infinite support in the frequency domain.

Given these two principles the image is recovered from the undersampled signal via iterative reconstruction methods.

4.3.3.2 Theory

Compressed Sensing techniques aim to recover a signal f from its measurements y_k

$$y_k = \langle f, \phi_k \rangle \quad k = 1, \dots, m \quad (4.84)$$

with ϕ_k being the sensing waveforms (e.g Dirac delta functions or Fourier coefficients in MRI). It is an efficient sampling method that reconstructs the signal $f \in \mathbb{R}^n$ from highly undersampled measurements, i.e. $m \ll n$.

As mentioned above, CS relies on two fundamental properties of the acquired signal and the respective sensing basis: Sparsity and Incoherence.

Sparsity describes the concise information content of a natural signal in an appropriate basis. A signal $f \in \mathbb{R}^n$ can be decomposed into a linear expression of coefficients x of an orthonormal basis Ψ

$$f(t) = \sum_{i=1}^n x_i \psi_i(t) \quad (4.85)$$

with $\Psi = [\psi_1 \psi_2 \dots \psi_n]$ and $x_i = \langle f, \psi_i \rangle$

Sparsity Z of a signal is described by the number of non-negligible (nonzero) coefficients. Natural signals like images are known to be sparse in a variety of transform domains, e.g. wavelet transform. Transforming an image into the wavelet basis results in a high number of small coefficients and only a few coefficients containing most of the information. Reconstructing the image only based on the few significant coefficients shows no perceptual information loss.

The Z largest coefficients define the compressibility of an object. It is referred to as Z -sparse. The reconstruction of the compressed signal out of the Z highest coefficients is defined as $f_Z = \Psi x_Z$ with x_Z indicating the coefficient vector with all but the Z largest coefficients of x being set to zero.

Due to the orthonormality of the sparsifying transform Ψ , $\|f - f_Z\|_{l_2} = \|x - x_Z\|_{l_2}$. As x_Z is a good approximation of the original coefficient vector x also the error between the reconstructed and the original object is small.

Sparsity is a fundamental principle in CS as it defines how efficiently a signal can be acquired nonadaptively (Candès and Wakin, 2008).

The second core principle of CS is the *incoherence* between sensing and representation bases of the object, referred to as Φ and Ψ , respectively. The incoherence between these orthobases of $\mathbb{R}^n$ is

$$\mu(\Phi, \Psi) = \sqrt{n} \max_{1 \leq k, j \leq n} |\langle \phi_k, \psi_j \rangle| \quad (4.86)$$

i.e. the correlation between any two basis elements of Ψ and Φ . CS techniques rely on a low coherence, i.e. low correlation between sensing and representation bases.

Random matrices have been found to be highly incoherent with any representation basis Ψ . Random acquisition of an object/signal gives a very high probability of a coherence $\mu(\Phi, \Psi)$ of about $\sqrt{2 \log n}$.

Given a signal $f \in \mathbb{R}^n$ with an S -sparse representation in Ψ , the number of random *measurements* m needed to reconstruct the signal is bounded by

$$m \geq C \mu^2(\Phi, \Psi) Z \log n \quad (4.87)$$

for a positive constant C .

This theorem depicts the direct influence of incoherence to the number of measurements. A coherence close to 1 between Φ and Ψ enables an acquisition of down to the order of $Z \log n$ measurements. Sparsity is a fundamental property of the signal. However, no details about the location and magnitude of the non-zero coefficients are required a priori.

In reality, signals are corrupted by noise and are only nearly sparse (i.e. negligible coefficients are not zero, but very small). The *reconstruction* of the object $x \in \mathbb{R}^n$ from m measurements y can, hence, be described as below

$$y = Ax + z \quad (4.88)$$

where A is an $m \times n$ measurement matrix, and z a stochastic or deterministic noise term. In Compressed Sensing the desired object is known to be sparse, i.e. $f = \Psi x$, and the measured signal is undersampled in a sensing domain, i.e. $y = R\Phi f$, where R is the discrete undersampling matrix. The A from Equation 4.88 can, therefore, be rewritten as $R\Phi\Psi$.

As a result of the undersampling process this gives an undetermined system of equations. The desired signal is recovered using the sparsity constraint, i.e. the solution for which the l_1 -norm $\|x\|_{l_1} = \sum_i |x_i|$ is minimised.

$$\min \|x\|_{l_1} \quad \text{subject to} \quad \|Ax - y\|_{l_2} \leq \epsilon \quad (4.89)$$

$\|Ax - y\|_{l_2} \leq \epsilon$ is commonly referred to as data-consistency term and bounds the amount of noise in the data. Reconstruction of Compressed Sensing acquisitions is a convex problem which can be solved iteratively.

Robustness of Reconstruction Robustness of CS is closely linked to the restricted isometry property (RIP)

$$(1 - \delta_Z)\|x\|_{l_2}^2 \leq \|Ax\|_{l_2}^2 \leq (1 + \delta_Z)\|x\|_{l_2}^2 \quad (4.90)$$

with δ_Z defining the isometry constant such that above inequality holds for all Z -sparse vectors x . Loosely speaking, a matrix A obeys the RIP if δ_Z is not close to 1. It implies that A is distance and information preserving for Z -sparse signals (Baraniuk et al., 2010).

4.3.3.3 Compressed Sensing in MRI

Magnetic Resonance Imaging (MRI) is a powerful biomedical imaging method with insightful soft tissue contrast and is commonly applied in clinical routine. Nevertheless, the reduction of data acquisition time is still of great interest to increase clinical efficiency, but also to enable imaging with high temporal or spatial resolution. Imaging time is inherently limited by technical (gradient technology) and physiological (nerve stimulation) constraints. The acquisition of k -space is conditioned via the Nyquist sampling theorem. Its violation leads to aliasing artifacts.

Attempts to increase imaging speed usually exploit redundancy in the image (spatial and or temporal) or frequency domain or seek to find a compromise between SNR loss and imaging time, i.e. limit visual apparent artifacts.

The mathematical concept of Compressed Sensing, i.e. reconstruct an object from highly incomplete samples, has raised a lot of interest in the signal and information theory community and has been shown to potentially impact a variety of applications, e.g. data acquisition under hardware limitations (Candès and Wakin, 2008). As previously stated, it has been shown to be of great potential benefit in MRI applications (Lustig et al., 2007).

As described above the Compressed Sensing algorithm can be subdivided into three different components:

1. The acquired image must be sparse by itself or in a known transform domain.
2. The sampling scheme must be incoherent to the sparse representation of the image (i.e only induce noise-like incoherent artifacts to the sparse image representation).
3. Non-linear reconstruction ensuring sparsity within a certain transform domain and data consistency.

Sparsity There are a variety of sparsifying transforms mapping image data into a sparser representation.

Some images are inherently sparse, i.e. contain a lot of zero intensity voxels, giving the identity matrix $\mathbf{I}$ as sparsity transform. Piece-wise constant images can be sparsified via finite-differences.

The most general and most frequently applied sparsifying transforms for natural images are the discrete cosine transform (DCT) and the wavelet transform (WT):

Discrete Cosine Transform This transform is related to the Fourier Transform and seeks to express a finite signal as a sequence of cosine functions at different frequencies. For a 1-dimensional discrete signal x of length N the transformed signal X can be calculated by

$$X_k = \sum_{n=0}^{N-1} x_n \cos \left[\frac{\pi}{N} \left(n + \frac{1}{2} \right) k \right] \quad (4.91)$$

Its extension to higher dimensions can be achieved by performing the 1-dimensional DCT into each dimension consecutively (similar to a multidimensional Fourier Transform).

Wavelet Transform This transform is the most commonly used compression for natural images and represents a multi-scale representation of the object – low resolution approximations and different level of details. There are different families of wavelet transforms. In general, each of these transforms is defined via a so-called mother wavelet $h(x)$ and its variations based on translation and dilatation

$$h_{jk}(x) = 2^{j/2} \cdot h(2^j x - k) \quad (4.92)$$

for integer values of j and k .

This set of functions defines an orthonormal basis in $L^2(\mathbb{R})$ and can therefore be used to describe a signal $f(x)$ as a linear combination. The wavelet coefficients for a signal $f(x)$ are given by

$$c_{jk} = \int f(x) h_{jk}(x) dx \quad (4.93)$$

With most classes of wavelet functions another orthonormal set $g_{j0k}(x)$ (often referred to as father wavelet, scaling function) is defined. It spans the same subspace as $h_{jk}(x)$. The consecutive decomposition of a signal by these sets of basis functions g and h leads to a description of the original signal on different level of detail, with the resulting coefficients giving an approximation and information about the lost detail, respectively. In image processing these coefficients are usually displayed as approximation and level of detail into each spatial direction (i.e. horizontal, vertical and diagonal for a 2D image).

Haar wavelets were the first set of wavelet functions that were proposed. The

mother function is defined as

$$h(x) = \begin{cases} 1 & \text{for } 0 \leq x < 1/2 \\ -1 & \text{for } 1/2 \leq x < 1 \end{cases} \quad (4.94)$$

the father function is unity on the interval $[0, 1)$

$$g(x) = 1(0 \leq x < 1) \quad (4.95)$$

Daubechie formulated a generalisation of the Haar wavelet (Daubechies, 1992). These sets of wavelets can decompose a piecewise linear signal into a sparse representation and have, therefore, been shown to be a good sparsifying transform in image processing.

In general, Wavelet Transforms perform slightly better on medical images compared with DCT (Lustig et al., 2007).

It should be noted that sparsity can also be exploited in the temporal domain, however this is beyond the scope of this thesis.

Incoherent Sampling As mentioned above, purely random sampling gives a high probability of incoherence with any sparsifying transform and, furthermore, ensures with high probability the satisfaction of the restricted isometry property (cf. Equation 4.90). However, random undersampling of k-space is generally impractical due to hardware limitations (finite slew rate and strength of gradients). In Cartesian acquisitions, undersampling in the frequency encoding direction is furthermore not advisable as these information are acquired "for free" during the readout gradient, i.e. undersampling the readout gradient acquisition would not reduce the scan time. Hence, for Cartesian sampling, randomisation is usually only applied along the phase-encoding direction.

The point spread function (PSF) is a way to assess the incoherence of a particular sampling pattern. It describes the contribution of a pixel i on other pixel j within the image.

$$\text{PSF}(i, j) = e_j^* \mathcal{F}_u^* \mathcal{F}_u e_i \quad (4.96)$$

where $\mathcal{F}_u$ is the Fourier undersampling operator and e_i the i -th basis vector.

The incoherence of an undersampling pattern can be evaluated via the sidelobe-to-peak ratio, $\max_{i \neq j} \left| \frac{\text{PSF}(i, j)}{\text{PSF}(i, i)} \right|$.

In order to assess the incoherence within a sparsifying transform the more generalised Transform Point Spread Function (TPSF) can be analysed.

$$\text{TPSF}(i, j) = e_j^* \Psi \mathcal{F}_u^* \mathcal{F}_u \Psi^* e_i \quad (4.97)$$

Ideally, the TPSF is as small as possible.

Natural images tend to be dominated by lower spatial frequencies components, i.e. contain most energy within the centre of k-space. This fact suggests that an efficient

undersampling scheme would not acquire k-space in a purely random fashion, but distributes sampling points non-uniformly according to the distance from the k-space centre.

The benefit of variable-density sampling make spiral and radial sampling patterns particularly interesting for Compressed Sensing algorithms due to the inherent sample focus in central k-space. The spherical acquisition scheme furthermore provides a greater level of incoherence with regard to the Cartesian image representation.

Non-linear Reconstruction As described in Chapter [Theory](#) the reconstruction of the original signal is achieved via a convex optimisation. Within MRI applications the reconstruction problem of Equation 4.89 can be specified to

$$\min \|\Psi x\|_{l_1} \text{ such that } \|\mathcal{F}_u x - y\|_{l_2} \leq \epsilon \quad (4.98)$$

where x represents the image to be reconstructed, $\mathcal{F}_u$ is the undersampled Fourier operator and y the measured Fourier samples. Hence, the image estimate $\hat{x}$ is given by

$$\hat{x} = \arg \min_x \|\mathcal{F}_u x - y\|_{l_2} + \lambda_1 \|\Psi x\|_{l_1} \quad (4.99)$$

where λ_1 is a tuning parameter for the transform sparsity Ψ . As mentioned before, sparsity can be imposed in the image, time or a transform domain.

Given the noise corruption during any NMR-experiment (cf. Section [Noise in MRI](#)) it is generally not advisable to base the iterative reconstruction on the data consistency, i.e the first term, alone since this will force the algorithm to render the noise in the image estimate and consequently affects image quality. Furthermore, given the under-sampling of y and hence underdetermined system, the second term, i.e. the sparsity information, is essential for the solution and the convergence of the optimisation. In fact, any additional information can greatly improve the robustness and convergence of the reconstruction process. The addition of such terms R is called regularisation which are commonly scaled with a weighting parameter λ .

$$\hat{x} = \arg \min_x \|\mathcal{F}_u x - y\|_2^2 + \sum_i \lambda_i R_i \quad (4.100)$$

There exist a number regularisation terms. One of the most useful constraints was presented as a noise suppression method by [Rudin et al. \(1992\)](#) and is called Total Variation (TV). It implicitly assumes that the underlying object is piecewise constant and therefore suggests that the best estimate of x is given when the spatial derivatives in the image are also minimised. In 3D the TV-regularisation is given by the sum of finite differences across all image voxels x

$$R_{TV} = \sum_i |D_x(x_i) + D_y(x_i) + D_z(x_i)| \quad (4.101)$$

where

$$\begin{aligned} D_x(m, n, k) &= x(m, n, k) - x(m-1, n, k) \\ D_y(m, n, k) &= x(m, n, k) - x(m, n-1, k) \\ D_z(m, n, k) &= x(m, n, k) - x(m, n, k-1) \end{aligned} \quad (4.102)$$

Standard CS reconstruction schemes in MRI include sparsity and TV

$$\hat{x} = \arg \min_x \|\mathcal{F}_u x - y\|_2^2 + \lambda_1 \|\Psi x\|_{\ell_1} + \lambda_2 \text{TV}(x) \quad (4.103)$$

There exist several methods for solving the above optimisation (Lustig et al., 2008; Kim et al., 2007). Within this project a non-linear conjugate gradient (CG) implementation has been used. CG methods were first described by Hestenes and Stiefel (1952) and have since been extended to nonlinear optimisation problems. The general principle of CG methods consists of the iterative execution of two steps until a convergence criteria is fulfilled:

- 1. Optimisation Direction** Denoting the general cost function from Equation 4.100 by J , its optimisation direction is given by the gradient with respect to the parameter space of x , i.e. ∇J ,

$$\nabla J = \nabla \|\mathcal{F}_u x - y\|_2^2 + \sum_i \lambda_i \nabla R_i \quad (4.104)$$

The gradient of the data consistency term is relatively straightforward to compute as

$$\nabla \|\mathcal{F}_u x - y\|_2^2 = 2\mathcal{F}_u^\dagger (\mathcal{F}_u x - y) \quad (4.105)$$

The above Equation facilitates an interpretation of the iterative reconstruction process: The current image estimate x is mapped into frequency space by $\mathcal{F}_u$ and compared with the original data y . The mapping with $\mathcal{F}_u^\dagger$ transforms the result back into the parameter search space, i.e. the image domain.

The gradient resulting from the additional regularisation terms is more difficult to compute due to the use of the ℓ_1 -norm. Using a smooth function an approximation can be estimated via (Lustig et al., 2007)

$$\lambda \nabla \|Rx\|_1 \approx \lambda R^\dagger W^{-1} Rx \quad (4.106)$$

with W being a diagonal matrix with entries

$$w_i = \sqrt{(Rx)_i^\dagger (Rx)_i + \mu} \quad (4.107)$$

and μ being a positive smoothing parameter.

- 2. Line Search** The gradient defines the optimisation direction along which a line search is performed until a minimum is found and the image estimate x is updated.

Reconstruction Artefacts

Iterative reconstructions are involved methods and as such the potential reconstruction artifacts are complex and strongly problem-dependent, i.e. subject to the imaged object, the degree of undersampling and other effects.

Compressed Sensing techniques are particularly applicable to high-contrast images as these result in a few distinct large sparsity coefficients. Low contrast features may,

however, be indistinguishable from the incoherent noise that is induced by the under-sampling. Therefore, CS generally does not suffer from a reduction in resolution but can cause low-contrast components of the image to be unrecoverable.

The l_1 -minimisation has been found to have a tendency of decreasing the magnitude of the reconstructed sparsity coefficients. Additionally, with wavelet-based sparsity, oscillatory artifacts at high frequencies have been described. This problem can partly be overcome by the inclusion of a TV-constraint into the reconstruction algorithm, as described above ([Lustig et al., 2007](#)).

This chapter concludes the background part of this thesis. In the following part II, the novel contributions are presented. It should be noted that each chapter in part II is outlined as a publication manuscript including individual, brief self-contained introductions.

SODIUM MRI TECHNIQUES AT HIGH FIELD

*An Investigation of Signal Acquisition,
Reconstruction and Analysis*

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Abstract

Purpose Fast biexponential transverse signal decay compounds Sodium image quality. This work aims at enhancing image characteristics using a special case of ramped hybrid encoding (RHE). Zero-gradient-excitation (zG_{RF})-RHE provides 1) gradient-free excitation for high flip angle, artefact-free excitation profiles and 2) gradient ramping during dead-time for the optimisation of encoding time (t_{enc}) to reduce T_2 signal decay influence during acquisition.

Methods Radial zG_{RF} -RHE and radial UTE were investigated over a range of receiver bandwidths in simulations, phantom and in in vivo brain experiments. Central k-space in zG_{RF} -RHE was acquired through single point measurements at the minimum achievable TE. T_2^* blurring artefacts and image SNR and CNR were assessed.

Results zG_{RF} -RHE enabled 90° flip angle artefact-free excitation, while gradient pre-ramping provided greater t_{enc} efficiency for any readout bandwidth. Experiments confirmed simulation results, revealing sharper edge characteristics particularly at short readout durations (T_{RO}). Significant SNR improvements of up to 4.8% were observed for longer T_{RO} .

Conclusion zG_{RF}-RHE allows for artefact-free high flip angle excitation with time-efficient encoding improving on image characteristics. This excitation-independent hybrid encoding concept with gradient pre-ramping is trajectory independent and can be introduced in any centre-out UTE trajectory design.

5.1 Introduction

Sodium (^{23}Na) plays a vital role in various processes and body functions. Cells keep up a delicate balance between intra- and extracellular Sodium concentration – a mechanism that is strongly dependent on the cell's metabolism and its membrane integrity. Disturbances of this delicate balance provide a sensitive, early indicator for cell breakdowns and give an insight into cell integrity and tissue viability. With Sodium nuclei providing the second strongest MR-signal in biological tissue, Sodium MRI offers promising potential as a clinical biomarker with capabilities ranging from early diagnosis to therapy response monitoring as well as the detection of diseases without anatomical abnormalities (Thulborn, 2016). Due to hardware advancements, the number of Sodium MRI studies is steadily increasing (Madelin and Regatte, 2013) ranging across a variety of diseases encompassing stroke (Wetterling et al., 2012; Tsang et al., 2011), tumors (Schepkin, 2016; Ouwerkerk et al., 2003), neurodegenerative diseases (Maarouf et al., 2017; Inglese et al., 2010), and musculoskeletal pathologies (Zbyn et al., 2016; Marik et al., 2016; Madelin et al., 2012a).

Nonetheless, Sodium MRI suffers from comparatively low image quality related to two major challenges: a relatively low NMR sensitivity and a fast biexponential transverse signal decay. The latter requires Sodium MRI data to be acquired with dedicated imaging techniques that allow for the measurement of ultra-short TE-values. This class of sequences is termed UTE imaging and is usually characterised by a short non-selective hard-pulse followed by data acquisition from the centre of k-space towards its periphery. Due to the usually non-selective hard-pulse, Sodium acquisitions are most commonly performed in 3D. There mainly exist two approaches for a quick centre-out traversal through k-space: radial or twisted half-projections (Boada et al., 1997b; Lu et al., 2010; Nielles-Vallespin et al., 2007) and variations thereof (Nagel et al., 2009; Riemer et al., 2014).

Signal decay commences from the centre of the excitation pulse, which consequently requires sampling to start as quickly as possible. However, the limited switching time between transmit and receive channel (dead-time) induces an inherent delay to the ADC onset; commonly ranging from 40 to 100 μs on clinical systems. UTE sequences furthermore synchronise the beginning of data sampling with gradient ramp-up. Due to finite gradient slew rates this acquisition strategy leads to a lower initial traversing speed and reduced sample spacing in k-space centre resulting in generally increased encoding time (t_{enc}) for all k-space locations.

An improvement in t_{enc} can be achieved through zero echo time (zTE) imaging where gradients are ramped up prior to RF excitation (Weiger et al., 2011). Such sequence design enables sampling under full gradient strength directly after ADC onset. However, since k-space encoding is prescribed by gradient activation, zTE imaging schemes

cannot readily collect central k-space data as it is immeasurable during the receiver dead-time. A special case of zTE acquisition are single point imaging (SPI) or constant imaging techniques like RASP (Heid and Deimling, 1995) and SPRITE (Balcom et al., 1996) where k-space is filled up pointwise on a Cartesian grid. Since each measurement can be acquired at a fixed t_{enc} the acquired signal is free from convolutional impact of T_2^* . However, the pointwise signal acquisition leads to clinically infeasible scan times. Pointwise Encoding Time Reduction with Radial Acquisition (PETRA) is a hybrid zTE technique which combines radial zTE with SPI in outer and inner k-space, respectively, and has shown to improve image SNR and reduce T_2^* blurring in short T_2 imaging (Grodzki et al., 2012).

While PETRA and other zTE imaging techniques have shown promising results, they are not commonly applied in Sodium MRI. RF excitation in the presence of gradients requires a broad transmit bandwidth necessitating short excitation pulses. With limited B1 power, this leads to a reduced attainable flip angle. Violation of the bandwidth constraint results in variable and nonuniform excitation profiles. Nevertheless, Romanzetti et al. (2006) demonstrated the application of SPRITE in Sodium MRI and found that the signal loss due to the flip angle constraint can be partly overcome through averaging. However, overall SNR was lower than in standard UTE acquisitions.

Recent work by Jang et al. (2016) suggests ramped hybrid encoding (RHE) – an extension to PETRA – by introducing a two-step gradient ramping: 1) initially gradients are ramped to an intermediate strength (G_{RF}) during which the RF pulse is applied; 2) immediately after excitation, gradients are ramped to their final strength for shortest k-space encoding. The flexible excitation and readout gradient setup mitigates slice selectivity effects and enables higher flip angles while still allowing for low t_{enc} .

In this work we investigate zG_{RF} -RHE – a special case of RHE – with zero G_{RF} and an immediate ramp-up after RF excitation, i.e. during dead-time. The missing k-space centre is filled with single point measurements as in PETRA and RHE. Such imaging approach achieves the most optimal t_{enc} for any receiver bandwidth while still allowing high flip angle excitation without any slice selectivity in the excitation profile. We show that the optimised encoding scheme leads to an increase in image SNR. For short readout duration a reduction in T_2^* blurring was observed.

5.2 Methods

5.2.1 Imaging Sequence

Sodium images were acquired with a custom-built 3D radial sequence based on Saff and Kuijlaars' method (Saff and Kuijlaars, 1997) for a homogeneous projection placement. The standard 3D radial UTE sequence consisted of a non-selective hard pulse followed by simultaneous gradient onset and data sampling after dead-time delay. The 3D radial zG_{RF} -RHE sequence (Figure 5.1) was composed of a non-selective hard pulse immediately followed by gradient ramping; data sampling commenced after

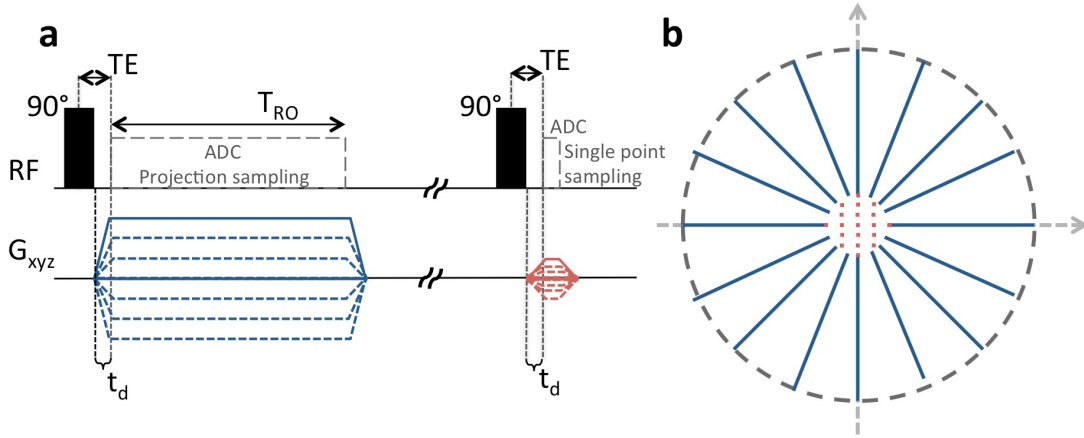


Figure 5.1: Radial zero-Gradient-Excitation Ramped Hybrid Encoding (zG_{RF}-RHE) Sequence Diagram (a) and 2D illustration of hybrid k-space encoding scheme (b). Gradient-free excitation is followed by an immediate gradient ramping, data sampling commences after dead-time. Central k-space is measured separately as single points with the same gradient pre-ramping condition. Echo Time, TE; Readout Duration, T_{RO}; dead-time t_d.

dead-time. The dead-time was set to 100 μ s, a common coil configuration for most clinical systems. The required gradient strength for image resolution and readout duration (T_{RO}) allowed for a full gradient ramp-up within dead-time. The data sampling dwell time was kept at 5 μ s for both imaging sequences. Standard 3D radial UTE and zG_{RF}-RHE were compared with a constant receiver bandwidth. Throughout this paper, T_{RO} is stated with respect to the UTE sequence design. Due to the pre-ramping of gradients, the effective T_{RO} in zG_{RF}-RHE is reduced by the dead-time, i.e.

$$T_{RO,RHE} = T_{RO,UTE} - t_d.$$

In zG_{RF}-RHE, the gap in central k-space was filled with single point acquisitions. It should be noted that all single point measurements were acquired under the same conditions as the projection measurements, i.e. with zero gradients during excitation and ramping during dead-time. Unlike PETRA, single points were therefore not measured with stepwise gradient increase but with gradient ramp up and down between single point measurements. A diagram for zG_{RF}-RHE can be found in Figure 5.1.

5.2.2 Image Reconstruction

Images were reconstructed offline via Kaiser-Bessel re-gridding in MATLAB. The re-gridding oversampling factor was set to 1.5. Radial and single point measurements were combined for zG_{RF}-RHE reconstruction. An iterative density compensation was applied to raw data from UTE and zG_{RF}-RHE measurements prior to re-gridding (Zwart et al., 2012). Radial projection raw data were furthermore weighted with a Hann filter to reduce Gibbs ringing artefacts.

Given the low signal regime of Sodium images, SNR measurements were calculated based on Gudbjartsson and Patz' Rician noise correction scheme (Gudbjartsson and Patz, 1995).

5.2.3 Simulations

The influence of encoding time and biexponential decay on image reconstruction was analysed in a 1D simulation implemented in MATLAB. The profile was composed of tubes with varying Sodium concentrations (0.4, 0.2, 0.3, 0.6 and 1.0) and tube diameters (6.2 mm, 12.4 mm and 24.8 mm). Simulation parameters were set to match the experimental Sodium MR measurements: TE = 0.31 ms, dead-time = 0.1 ms, FOV = 20 cm and 3.1 mm image resolution. Reconstruction characteristics were investigated for T_{RO} of 2 and 8 ms. The profile was simulated for biexponential brain tissue signal decay properties with a fast component of 1.5 ms, a slow component of 20 ms and respective signal fractions of 0.6 and 0.4 (Madelin et al., 2014).

5.2.4 MR Measurements

Imaging was performed on a research 7T MRI scanner (Siemens Healthcare, Erlangen, Germany) with a transmit/receive dual-tuned ^1H - ^{23}Na head coil (QED, Mayfield Village, Ohio USA).

5.2.4.1 Phantom

SNR analysis and T_2^* blurring effects were investigated in phantom experiments. The phantom consisted of Falcon tubes with varying diameter (28, 14 and 6 mm) and saline concentrations (30 and 45 mM). All tubes were submerged in distilled water and filled with 3 % agarose gel to induce biexponential signal decay characteristics. Sodium images were acquired over an isotropic field of view of 20 cm with a nominal isotropic 3.1 mm resolution. Measurements were taken under 90° flip angle and a repetition time (TR) of 160 ms to reduce T1-weighting; 8000 radial projections lead to a total scan time 21 min 20 sec in UTE acquisitions, z_{GRF} -RHE measurements required additional scan time for single point measurements (at the chosen FOV and TR, up to 4.3 sec for $T_{RO} = 2\text{ms}$ acquisition). The RF pulse length was 420 μs . Echo time (TE) was defined as the time interval between the centre of the pulse and the onset of data sampling and was set to 0.3 ms. Images were acquired at different T_{RO} (2, 4, 6 and 8 ms) and measurements were repeated 8 times for a statistical analysis of SNR effects.

Additionally, a proton-based FLASH image was acquired with TR = 11 ms, TE = 3.06 ms, 14° flip angle, 1 mm isotropic resolution, acquisition time 6min 12sec.

B0-field shimming was based on a vendor-provided 3D shimming routine and was performed on the proton channel. Shim optimisation was repeated 5-10 times until shim settings converged.

5.2.4.2 In vivo

All human imaging was conducted with the approval of the University of Melbourne Human Research Ethics Committee and volunteers gave an informed consent prior to the experiment. Human in vivo acquisitions were performed on one healthy female volunteer. Sodium and proton imaging parameters as well as the shimming procedure were identical to the phantom experiments. The volunteer was imaged with 3D radial UTE and 3D radial z_{GRF}-RHE with T_{RO} of 2 ms providing good SNR at a high bandwidth for the chosen image resolution (Blunck et al., 2017).

5.2.4.3 SNR Analysis

Given the low signal regime of Sodium images, SNR measurements from magnitude images were calculated based on Gudbjartsson and Patz' Rician noise correction scheme (Gudbjartsson and Patz, 1995). Magnitude image intensities were corrected according to

$$A = \sqrt{\|M^2 - \sigma^2\|} \quad (5.1)$$

where A and M are the corrected and magnitude image intensities, respectively, and σ the noise standard deviation in the real or imaginary image. SNR measurements were taken from a central ROI within the large (28 mm diameter) phantom vials. The smaller phantom vials were excluded from the statistical SNR analysis due to strong partial volume effects. The analysis of a central region within a larger object is expected to provide higher measurement accuracy (Stobbe and Beaulieu, 2018). A Student's t-test was applied to the ROIs across all eight measurements for a statistical analysis of SNR effects.

5.3 Results

The simulation results are shown in Figure 5.2. The Modulation Transfer Function (MTF) is the frequency space counterpart of the point spread function and describes the contrast of spatial frequencies under t_{enc} and signal decay. Figure 5.2 (a) illustrates the MTF and t_{enc} for 2 and 8 ms T_{RO} under biexponential signal decay as it occurs in brain tissue ($T_{2,short} = 1.5$ ms, $T_{2,long} = 20$ ms; 0.6 and 0.4 signal fractions, respectively). Figure 5.2 (c) depicts the required t_{enc} for each k-space location. At the same readout bandwidth, z_{GRF}-RHE reaches every point in k-space faster than UTE due to gradient pre-ramping. The improved encoding efficiency across all k-space locations for any T_{RO} leads to better MTF characteristics and an overall shortened sampling duration. The t_{enc} gain depends on the chosen T_{RO} and is given by the ratio of dead-time and T_{RO} . Single point measurements in z_{GRF}-RHE result in a constant t_{enc} (fixed at TE) in k-space centre. Given the lower required gradient strength for longer T_{RO} the central k-space gap is smaller compared to faster readouts.

Figure 5.2 (b) and (d) show profile simulation results for UTE and z_{GRF}-RHE based on the MTF and t_{enc} for T_{RO} at 2 and 8 ms. The simulated profile and reconstruction

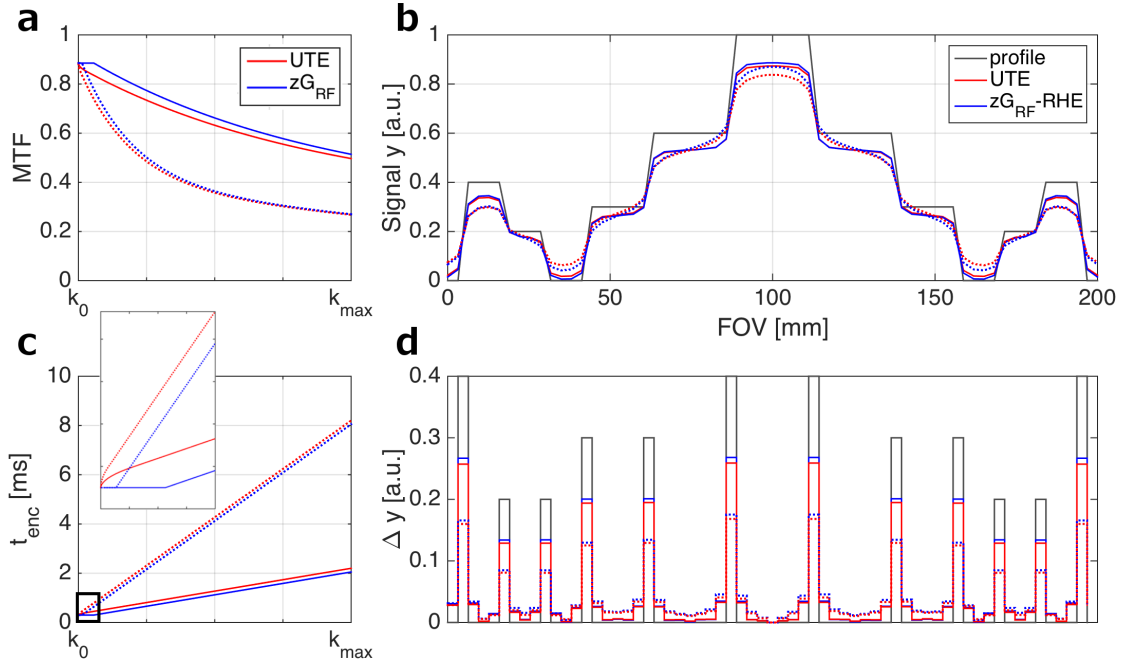


Figure 5.2: UTE and zG_{RF} -RHE sequence characteristics comparison. Left: Modulation Transfer Function (MTF) (a) and encoding time (t_{enc}) (c) over k -space readout. Zoomed-in window highlights reduced encoding efficiency during ramp up in standard UTE (red). Solid line indicates 2 ms T_{RO} , dashed line shows 8 ms T_{RO} . Right: Profile simulation (b) and edge definition analysis (d). (b) Black line illustrates simulated profile, red line shows standard UTE, blue line indicates zG_{RF} -RHE results for $T_{RO} = 2$ ms (solid) and $T_{RO} = 8$ ms (dashed). (d) indicates finite differences of original profile and simulated reconstructions.

results for UTE and zG_{RF} -RHE are illustrated in Figure 5.2 (b). Shorter readout leads to better reconstruction of the profile with less T_2 blurring artefacts. The higher encoding efficiency leads to an improvement in signal strength in zG_{RF} -RHE compared to UTE, particularly at longer T_{RO} . The finite difference illustration in Figure 5.2 (d) further emphasises the better reconstruction of edge details at lower T_{RO} . zG_{RF} -RHE retrieves sharper edges at both investigated T_{RO} .

An analysis of the structural similarity index (sSim) between reconstructions and the original profile further underline the improvements of higher encoding efficiency. At $T_{RO} = 2$ ms, zG_{RF} -RHE simulation results achieved a sSim score of 0.95 compared to 0.94 for a standard UTE reconstruction. At $T_{RO} = 8$ ms, the profile reconstruction scores were 0.82 and 0.79 for zG_{RF} -RHE and UTE, respectively.

The phantom measurement analysis can be seen in Figure 5.3. The setup of phantom vials is depicted in Figure 5.3 (a). A comparison of UTE and zG_{RF} -RHE reconstruction results at the shortest investigated T_{RO} of 2 ms is shown in Figure 5.3 (b). Contour lines from normalised images illustrate sharper edges between tubes in zG_{RF} -RHE measurements at T_{RO} of 2 ms and a better delineation of small details (6 mm 45 mM in upper right corner).

The mean line profile across the central slice of the 14 mm phantom tubes in short (2 ms) and long (8 ms) T_{RO} experiments is plotted in Figure 5.4. Longer readouts lead to a reduction in overall signal strength due to more signal decay during sampling, however, the lower readout bandwidth also results in lower noise levels. At the

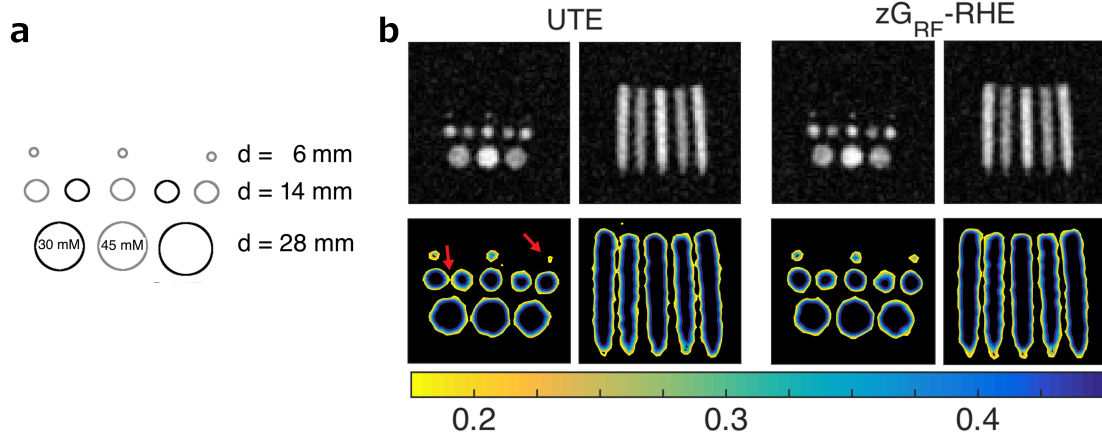


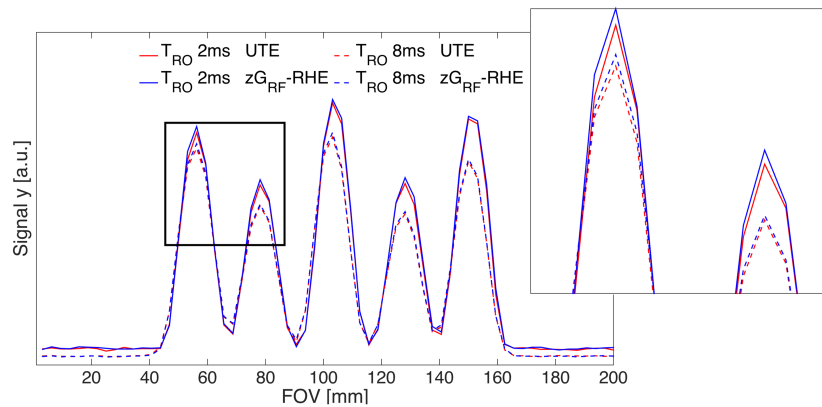
Figure 5.3: Phantom experiment. Illustration of phantom setup (a) and reconstructed images at $T_{RO} = 2$ ms (b) in UTE and zG_{RF}-RHE experiments. Upper rows show raw images at the native FOV, lower rows displays edge characteristics through zoomed in contour lines of normalised images.

same readout bandwidth, zG_{RF}-RHE achieves better signal due to the improved t_{enc} efficiency.

Figure 5.5 depicts the mean edge sharpness in 14 mm tubes across all phantom experiments. To exclude partial volume effects, edges were measured between the central voxel of the tube and 9.3 mm (3 voxel) to either side. The measurements underline the better edge definition at T_{RO} of 2 ms with decreasing sharpness towards longer read-outs. Across all T_{RO} , zG_{RF}-RHE showed small edge enhancements for both Sodium concentrations. SNR analysis results from a central region of the 28 mm tubes are displayed in Table 1. An average SNR increase of up to 4.8% was observed for zG_{RF}-RHE across all T_{RO} with significant gain at longer T_{RO} . Concomitant improvements in contrast-to-noise ratio (CNR) between 30 and 45 mM tubes were found.

Figure 5.6 (a) depicts cross sections through in vivo experiments. zG_{RF}-RHE showed better detail around the brain stem at short T_{RO} . CSF masks were segmented from proton-based FLASH images and registered to UTE and zG_{RF}-RHE Sodium acquisitions using FSL. Figure 5.6 (b) shows three consecutive transverse cross sections of CSF segmentation masks through the ventricles. The overlay of contour masks of both acquisition techniques at $T_{RO} = 2$ ms reveals a better delineation of ventricle in

Figure 5.4: Mean line profiles through 14 mm phantom tubes at shortest (2 ms, solid lines) and longest (8 ms, dashed lines) T_{RO} in UTE (red) and zG_{RF}-RHE (blue) experiments.



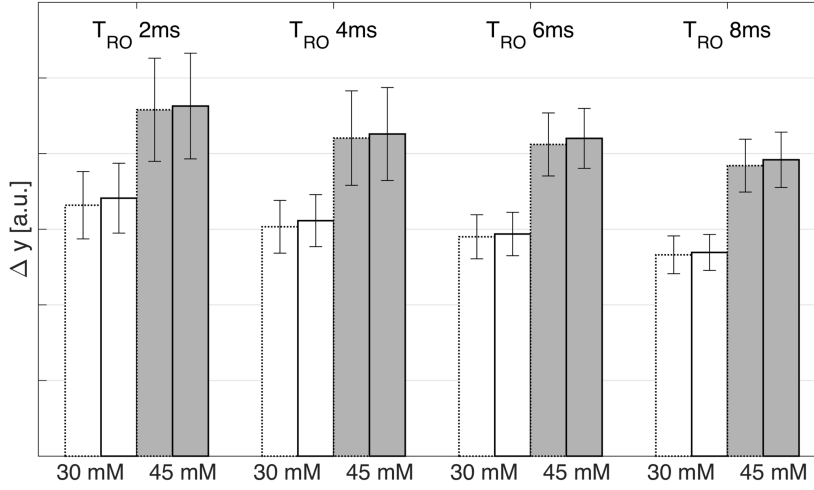


Figure 5.5: Mean edge sharpness, i.e. finite difference between central voxel and neighbouring background voxel, in 14 mm phantom tubes at 45 mM (grey) and 30 mM (white) concentrations across all measured T_{RO} . Dashed line (left bars) indicates standard UTE measurement, solid line (right bars) shows z_{GRF} -RHE edges.

z_{GRF} -RHE measurements.

5.4 Discussion

The fast biexponential decay properties of Sodium need to be addressed with dedicated UTE sequences. Recent advancements in Sodium MRI focused on the improvement of sampling efficiency in k-space (Boada et al., 1997b; Nagel et al., 2009; Riemer et al., 2014) which is an inherent drawback of fast centre-out UTE acquisitions. While these measurement schemes enhance sampling homogeneity for an amelioration of point spread function characteristics and a potential total scan time reduction, the aspect of encoding time efficiency has not yet been explored. A quick signal detection onset is necessary for unbiased Sodium concentration quantification in density-weighted acquisitions (Boada et al., 1994).

The enhanced time encoding scheme of zTE imaging cannot readily be applied in Sodium MRI due to the generally low in vivo Sodium concentration and the very limited attainable flip angle under non-zero gradients and limited B1 power. The concept of hybrid encoding with separated acquisitions of central and peripheral k-space (akin to keyhole imaging) has been introduced in PETRA and generalised in RHE. PETRA and the proposed z_{GRF} -RHE encoding approach with gradient-free excitation and an immediate ramping can be seen as two special cases at opposite ends of the RHE spectrum.

This work utilises the combination of radial and single point acquisition as originally proposed in PETRA (Grodzki et al., 2012). Froidevaux et al. (2018) recently showed that this hybrid encoding strategy for dead-time gap filling generally achieves better image quality than other approaches, e.g. algebraic zTE (Kuethe et al., 1999), WASPI (Wu et al., 2007).

z_{GRF} -RHE preserves a homogeneous excitation profile facilitating high flip angle and improved encoding time for any receiver bandwidth (T_{RO}). Simulation and experimental measurements reflect the benefits of alleviated signal decay during sampling

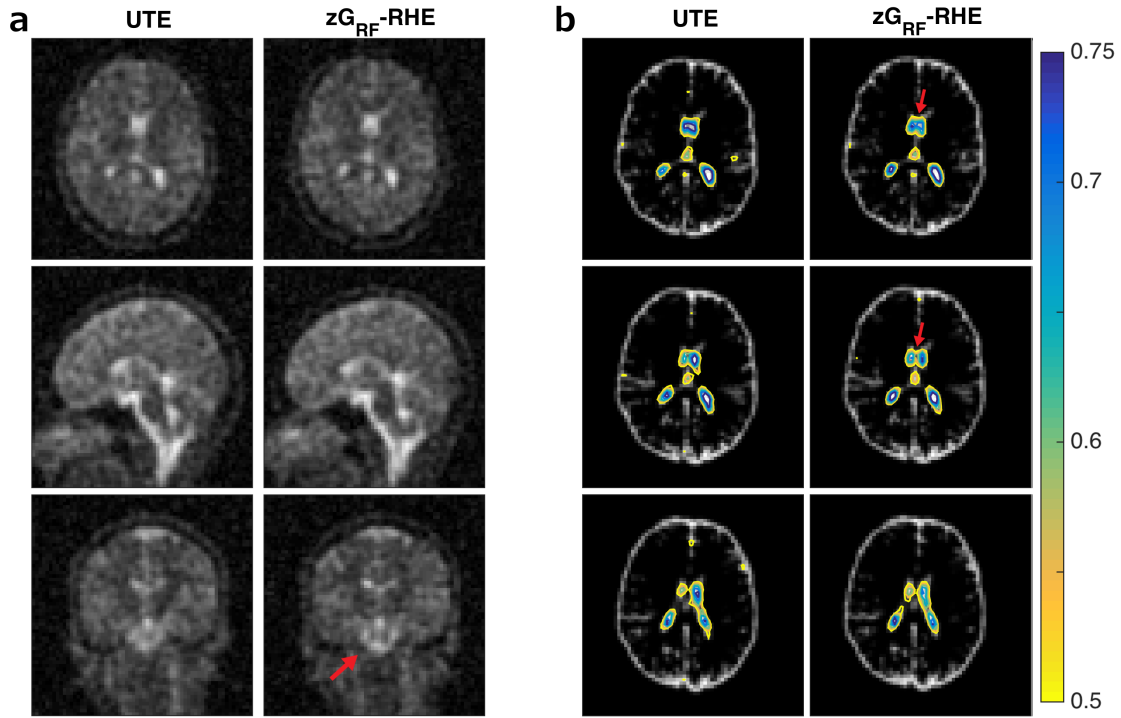


Figure 5.6: (a) Cross sections through matched slices in in vivo experiments at T_{RO} of 2 ms UTE and zG_{RF}-RHE. zG_{RF}-RHE shows sharper details around the brain stem. (b) Three consecutive transverse slices of CSF masks with contour lines of normalised UTE and zG_{RF}-RHE at T_{RO} of 2ms.

in SNR improvements and better encoding efficiency in reduced T_2^* blurring particularly at short T_{RO} .

It should be noted that the observed SNR improvement potentially result from a combination of factors, predominantly the improvement in MTF (cf. Figure 2), and secondly the avoidance of ramp sampling which is known to have lower SNR efficiency (Nagel et al., 2009). This study applied a post-acquisition Hann filter during image reconstruction. Stronger SNR improvements are expected with a Sampling Density Weighted Apodisation (SDWA) trajectory adjustment (Stobbe and Beaulieu, 2008; Konstandin and Nagel, 2013).

Gradient ramping prior to sampling onset leads to an acquisition gap in central k-space that needs to be filled retrospectively through single point measurements. Due to the commonly low resolution and relatively low readout bandwidth in Sodium MRI the filling of central k-space components only requires a comparatively low number of single points. For the measurements presented in this work only up to 27 single points needed to be acquired. Based on the chosen TR of 160 ms this lead to an additional measurement time of 4.3 sec. In zG_{RF}-RHE, central k-space is measured at a fixed t_{enc} equal to the minimum achievable TE.

The single point measurements in zG_{RF}-RHE can be exploited to analyze eddy current related distortions and correct gradient imperfections as suggested by Jang et al. (2016). While this correction has not been applied in this work, it can provide further image quality improvements. Given the the moderate gradient strengths ramped during the dead-time, eddy current effects are, however, expected to be minor in this

study.

This work examined the application of zG_{RF} -RHE in radial trajectories. The zG_{RF} -RHE timing concept is, however, not limited to radial sampling schemes but can in fact be used in combination with any centre-out sampling pattern, e.g. density-adapted radial (Nagel et al., 2009), TPI (Boada et al., 1997b; Lu et al., 2010) or cones (Riemer et al., 2014). Since such sampling patterns commonly utilise higher initial gradients the resulting central k-space gap might, however, be slightly bigger. It should be noted that radial acquisitions provide the most efficient way to get to the edges of k-space at a given readout bandwidth and, hence, offer the greatest potential for T_2^* blurring reduction. Nevertheless, the low SNR regime and particular signal decay characteristics in Sodium MRI render the optimal T_{RO} and trajectory design a challenging choice. Due to the improved sampling homogeneity, twisted or density-adapted trajectories are expected to further improve image characteristics with regard to SNR.

Zero-gradient excitation (zG_{RF}) prevents any additional artifacts during excitation that result from gradient modulation during excitation. This is crucial in Sodium MRI given its inherently low image quality. Recently, RHE has been applied in whole body MR/PET situations where volume-selective SLR pulses were used to mitigate excitation artefacts resulting from outside the field of view (Jang et al., 2018). In the current study we did not observe any unwanted excitation artefacts. Due to the unrealised efficiency, non-selective hard pulses are commonly employed in Sodium MRI acquisitions. Nevertheless it should be noted that the gradient-free excitation approach of zG_{RF} -RHE solely exploits the system's dead-time for encoding efficiency improvements. This excitation-independent efficiency gain brings great flexibility with it and generally facilitates the use of more elaborate excitation schemes beyond rectangular hard pulses.

A benefit of the akin hybrid sampling approach PETRA is the significant acoustic noise reduction due to the low gradient ramp time requirements for radial and single point acquisitions. It should be noted that this condition is not met in this RHE approach as a result of the gradient free excitation requirement – gradients need to be fully ramped up and down between repetitions of both radial and single point measurements. Nevertheless, the readout bandwidth in Sodium MRI is commonly low for better SNR characteristics leading to moderate applied gradient strengths and associated acquisition noise.

The increased encoding efficiency results in slightly shorter total readout times for any readout bandwidth. In multi-echo data acquisitions the time gain allows for faster refocusing and consequently closer echo spacing which is beneficial for the estimation of signal decay parameter, in particular for the short T_2 decay component (Blunck et al., 2017).

The zG_{RF} -RHE acquisition approach shows image quality improvements across investigated T_{RO} , while for shorter T_{RO} an improvement in edge delineation was observed, SNR improvements were found particularly for longer T_{RO} .

Other x-Nuclei of interest in biological tissue like Chlorine-35 and Oxygen-17 with spin $>1/2$ exhibit quadrupolar interactions characterised by short transverse relax-

ation times. It is anticipated that the concept of improved sequence timing with undistorted excitation conditions will provide benefits for such short- T_2 x-Nuclei imaging applications, along with MSK applications for Sodium imaging.

5.5 Conclusion

This work investigates zG_{RF}-RHE for a readout-independent improvement of encoding efficiency in Sodium MRI under preserved non-selective high flip angle excitations. The presented encoding scheme combining pre-ramped radial acquisitions and single-point central k-space data achieves the highest encoding efficiency for any readout bandwidth and improves on image quality with regards to SNR and T_2^* blurring.

While this work investigated radial acquisition schemes, the optimised encoding time concept with hybrid encoding and gradient pre-ramping is applicable to any centre-out trajectory design.

CHAPTER 6

Compressed Sensing in Human Brain Sodium MRI: A comprehensive study of CS parameter and reconstruction performance

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Abstract

Purpose Sodium MRI offers potential as a quantitative biomarker, however, faces challenges in clinical routine due to relatively low image quality and associated long acquisition times. Compressed Sensing (CS) aims at a reduction of measurement time, but has been found to encompass quantitative estimation bias when used in low SNR x-Nuclei imaging. This work presents a comprehensive investigation of CS reconstructions across sparsity domains and over a wide range of undersampling factors with a special interest in image quality as well as intensity reconstruction performance.

Methods CS reconstruction were investigated on brain images of five healthy volunteers over varying CS penalty weights and undersampling factors (USF). Resulting images were compared with highly-sampled and undersampled NUFFT-based images and evaluated for image quality and image intensity bias.

Results Discrete Cosine and Wavelet transforms clearly outperform image-sparsity based and undersampled NUFFT-reconstructions. Wavelet-based reconstructions showed best performance over a wide range of parameters. Optimal CS parameter were well-generalizable across all subjects. Up to an USF of 4, images showed good structural detail with high intensity reconstruction performance in wavelet-based CS-reconstructions.

Conclusion Optimised CS reconstruction setup enhance CS image reconstruction per-

formance, enabling an up to four-fold acquisition speed up while maintaining good structural detail and low intensity bias. The associated acquisition time reduction facilitates a transition of Sodium MRI into clinical routine.

6.1 Introduction

Magnetic Resonance Imaging (MRI) is a powerful tool for the in vivo investigation of soft tissues by means of MR-observable nuclei. Due to its high NMR sensitivity and in vivo concentration, proton (^1H) is often the nucleus of choice for MRI studies in humans. However, there exists a wide range of nuclei (so-called x-Nuclei) with MR-observable spin properties offering a great potential for functional assessments and a strong correlate to pathologies. Thanks to recent advancements in scanner hardware, particularly the emergence of higher magnetic field strengths, and improvements in acquisition techniques the in vivo study of x-Nuclei has seen steadily growing popularity (Konstandin and Schad, 2014).

This work is concerned with Sodium (^{23}Na) the second most abundant MR-observable nucleus in the human body with great significance in cell physiology. Its potential for clinical applications ranges from diagnostic capabilities, extending ‘standard’ MRI to the detection of pathologies without apparent structural abnormalities, to therapy, including treatment monitoring and drug development (Thulborn, 2016). Sodium MRI offers potential as a quantitative clinical biomarker with tissue Sodium concentration (TSC) being the most frequently studied parameter. Healthy cells maintain a well-balanced ion concentration gradient between intra- and extra-cellular space. Pathologies like ischemia, cancer or other tissue damage disrupt this ion-homeostasis leading to raised cytosolic tissue Sodium, detectable as an increase in TSC (Ouwerkerk, 2011).

Sodium MRI is primarily limited by two factors: 1) low NMR sensitivity and in vivo concentration and 2) fast bi-exponential transverse signal decay. The former leads to poor SNR in Sodium images, the latter requires dedicated, usually non-Cartesian acquisition schemes. Consequently, Sodium MRI suffers from long acquisition times and relatively poor image SNR and resolution. So far these challenges have been primarily addressed through acquisition strategy improvements with regards to sampling efficiency and homogeneity (Boada et al., 1997b; Nagel et al., 2009; Lu et al., 2010; Riemer et al., 2014) as well as sequence timing optimisation (Blunck et al., 2018). This work investigates acquisition efficiency improvement potentials from the image reconstruction perspective.

Compressed Sensing (CS) is a technique for iterative image reconstruction from highly undersampled data (Donoho, 2006; Candès et al., 2006; Candès and Wakin, 2008). This method emerged from information theory and has proven to be well-generalizable with great applicability to a variety of fields, particularly MRI (Lustig et al., 2007). The application of CS necessitates two conditions: signal sparsity and incoherent noise-like effects of the chosen sampling pattern in the reconstruction domain. The first condition, sparsity, is commonly exploited in the image, time or a transform domain. The second condition, incoherence, is inherently fulfilled in Sodium MRI due to non-Cartesian sampling patterns producing only noise-like image artifacts (Lustig

et al., 2007). With these conditions in place, CS methods recover a signal through a nonlinear, iterative reconstruction from highly undersampled data. The nonlinear nature of CS reconstructions has, furthermore, been shown to achieve a significant noise suppression in the reconstructed image (Lustig et al., 2007; Block et al., 2007). This denoising property together with fast undersampled data acquisition make CS an enticing method for Sodium MRI.

The potential of CS has been widely studied in ^1H -based MRI, but so far only a few studies explored its applicability in x-Nuclei imaging, e.g. Helium-3 (Ajraoui et al., 2010), Fluorine-19 (Zhong et al., 2013; Liang et al., 2017), Carbon-13 (Hu et al., 2008) and Sodium-23 (Madelin et al., 2012b; Gnahm et al., 2014; Gnahm and Nagel, 2015; Behl et al., 2016). Previous studies of iterative reconstruction in Sodium MRI investigated human knee (Madelin et al., 2012b) and brain imaging (Gnahm et al., 2014; Gnahm and Nagel, 2015; Behl et al., 2016) with a focus on image quality and structural detail. The utilised CS reconstruction focused on image sparsity (Madelin et al., 2012b), ^1H -based anatomical constraints (Gnahm et al., 2014; Gnahm and Nagel, 2015) and sparsity in learned dictionaries (Behl et al., 2016). While promising potential for SNR improvements (Gnahm et al., 2014; Gnahm and Nagel, 2015; Behl et al., 2016) and acquisition time reduction (Madelin et al., 2012b) were found, a bias on quantitative parameter and image contrast from standard CS reconstructions was reported (Madelin et al., 2012b; Gnahm and Nagel, 2015).

With an eye towards image intensity accuracy, a fundamental requirement for bias-free estimation of quantitative parameters in Sodium MRI, this work presents a comprehensive investigation of CS reconstruction approaches in Sodium MRI of the human brain. All common sparsity domains, image domain, discrete cosine and Wavelet transform, were applied over a wide range of undersampling factors in five healthy volunteers and compared with highly-sampled and undersampled standard image reconstructions. The analysis comprised image reconstruction quality and an optimisation of CS reconstruction parameter. The effect of undersampling and iterative reconstruction on image quality, structural detail and image intensity is discussed.

6.2 Methods

6.2.1 MR Measurements

Brain imaging of five healthy human volunteers (three female, two male) was performed on a research 7T MRI scanner (Siemens Healthcare, Erlangen, Germany) with a transmit/receive dual-tuned ^1H - ^{23}Na head coil (QED, Mayfield Village, Ohio USA). The human imaging was conducted with the approval of the University of Melbourne Human Research Ethics Committee and volunteers gave an informed consent prior to the experiment.

Sodium images were acquired with a custom-built 3D radial sequence based on Saff and Kuijlaars' method (Saff and Kuijlaars, 1997) for a homogeneous projection placement. Data acquisition parameter were adjusted for Sodium-density weighted images:

90° flip angle, repetition time (TR) of 160 ms and echo time (TE), defined as the time interval between the centre of the pulse and sampling onset, was set to 0.4 ms. Measurements were taken with $N = 10,000$ projections over a field of view (FOV) of 20 cm with a readout duration (T_{RO}) of 2 ms per projection. The total acquisition time (TA) was 26min 20sec. For brain region investigations, an additional ^1H -based FLASH image was acquired with TR = 11 ms, TE = 3.06 ms, 14° flip angle, 1 mm isotropic resolution and a total acquisition time of 6min 12sec. Brain tissue segmentation was based on a ^1H -MP2RAGE image acquired at inversion times 700 and 2,700 ms; with 5° and 6° flip angle; TR = 4,900 ms; TE = 2.94 ms; GRAPPA factor 4; 0.9mm isotropic resolution; and acquisition time 6min. ^1H -MP2RAGE were imaged using a 32-channel head coil (Nova Medical Inc., Wilmington MA, USA) in a separate imaging session.

B0-field shimming was performed with a ^1H -based vendor-provided 3D shimming routine. Shim optimisation was routinely repeated 10 times prior to image acquisition.

6.2.2 Image Reconstruction

Compressed Sensing (CS) algorithm aim to recover a signal from far fewer samples than theoretically necessary by applying a regularised iterative reconstruction. CS-based reconstructions generally consist of two components: data consistency (① in Eq 6.1) and additional regularisation terms (② in Eq 6.1) which commonly exploits transform sparsity or other a priori information (Gnahn et al., 2014; Gnahn and Nagel, 2015). The applied optimisation problem underlying this work can be formulated as:

$$\hat{x} = \arg \min_x \underbrace{\|\mathcal{F}_u(x) - y\|_2^2}_{\text{① data consistency}} + \underbrace{\lambda_1 \|\Psi x\|_1 + \lambda_2 \text{TV}(x)}_{\text{② regularisation}} \quad (6.1)$$

where $\|\cdot\|_2$ and $\|\cdot\|_1$ denote the l_1 and l_2 -norm, respectively, $\mathcal{F}_u$ is the undersampled NUFFT-operator, x is the reconstructed image, y the undersampled raw data, Ψ the applied sparsity transform and λ_1 and λ_2 the weights on the transform sparsity and total variation (TV), respectively.

This work investigates the performance of CS reconstruction on Sodium brain images across different sparsity domains. The investigated sparsity domains were, identity, i.e. the inherent sparsity in the image domain, Discrete Cosine Transform (DCT) and Wavelet transform (Daubechies 1 with decomposition level 4). A total variation (TV) penalty, i.e. finite difference operator, was added to provoke sparsity in both, the employed sparsity domain and finite differences. Given the piecewise constant character of most natural objects this objective has been shown to be a valuable term for iterative reconstructions (Rudin et al., 1992; Tsaig and Donoho, 2006).

For an analysis of regularisation terms on overall reconstruction results, λ_1 and λ_2 have been tested over a range of weightings: λ_1 (sparsity domain) = [0,1.0] step size 0.1; λ_2 (TV) = [0, 0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05, 0.1, 0.5].

Image reconstruction was performed offline in Matlab (Mathworks, Natick, MA, USA)

with a Nonuniform Fast Fourier Transform (NUFFT) (Fessler and Sutton, 2003) provided in the Michigan Image Reconstruction Toolbox (MIRT). Images were reconstructed onto an isotropic resolution of 3.1 mm. Prior to reconstruction, projection raw data was compensated for density inhomogeneities as described by Nielles-Vallespin et al. (2007). Furthermore, a Hann filter was applied for a reduction of Gibb's ringing artefacts.

The Nyquist criterion dictates k-space sampling requirements: The maximum distance between two adjacent k-space samples is bound to be less than the inverse of the desired FOV. In radial sampling, this requirement furthermore prescribes the number of half-echo projections N_{full} for a specific resolution and FOV (Boada et al., 1997a)

$$N_{full} = 4\pi k_{max}^2 FOV^2 \quad (6.2)$$

where $k_{max} = 2/\Delta x$ with Δx describing the desired image resolution. To compensate the varying number of projections in undersampled reconstructions an additional weighting factor (N/N_{full}) was applied to the raw data to account for the degree of undersampling.

It should be noted that the data consistency term in Equation 6.1 encompasses all raw data weighting. The described optimisation problem was solved with a Matlab-based nonlinear conjugate gradient method (Lustig et al., 2007) over 50 iterations.

The objective of this work was the investigation and evaluation of undersampling effects on image characteristics and quality. For that random projections were omitted from the acquired raw data and the undersampled raw data was reconstructed with 1) standard NUFFT and 2) iterative CS reconstruction with all possible combinations of described regularisation weights and sparsity domains. Undersampling factors (USF) ranged from 2 (50% original data) to 10 (10% of original data) with increments of 1. Undersampled data was compensated for density inhomogeneities, Gibb's ringing, and undersampling as described above. The appropriate weighting on raw data is essential for the data consistency term in Equation 6.1.

6.2.3 Image Analysis

CS-based and standard NUFFT-based image reconstructions of undersampled data were compared to the original, highly sampled (10,000 projections) reconstruction. For an evaluation of reconstruction quality, the ^1H -based FLASH image was registered to the Sodium reconstructions and used for a brain mask extraction. For a specific investigation of brain compartments, CSF, grey matter (GM) and white matter (WM) masks were segmented from the ^1H -based MP2RAGE acquisition and registered to the Sodium reconstructions using a linear registration. All described image processing steps were performed in FSL (Smith et al., 2004).

The NUFFT-based full 10,000 projection reconstruction (I_{ref}) was considered the reference image for reconstruction quality and accuracy analysis.

6.2.3.1 Reconstruction Quality Metrics

For an objective measure of reconstruction results a variety of image similarity measures were investigated. Reconstruction quality parameter were only calculated over the extracted brain regions to avoid the influence of background noise on quality metrics.

Mean Squared Error (MSE) A simple and very common approach for reconstruction error quantification is the Mean Squared Error (MSE), i.e. the average of the squared error between reference I_{ref} and undersampled reconstruction (I_u):

$$MSE = \frac{1}{m} \sum_{i=0}^m [I_{ref}(i) - I_u(i)]^2 \quad (6.3)$$

with m being the number of voxel of the respective brain mask.

While this is a convenient measure of overall signal reproducibility, it essential describes an absolute error which combines a variety of effects including artefacts, image detail and signal intensity preservation. It has been shown to often mismatch perceived image quality and reconstruction degradation (Eskicioglu and Fisher, 1995).

Peak Signal-to-Noise Ratio (pSNR) Another common quality measure is the peak SNR (pSNR) – a measure of peak signal power over corrupting noise power. For a monochrome image it is calculated by

$$pSNR = 10 \log_{10} \left(\frac{\max(I_{ref})}{MSE} \right) \quad (6.4)$$

PSNR is a well established metric for image compression and reconstruction accuracy with higher pSNR indicating better quality. It is however not a reliable measure of perceptual performance.

Structural Similarity (sSim) This perception-based model has been proposed by Wang et al. (2004) and computes an index for structural similarity (sSim) based on human visual perception of structural information. It is a weighted multiplicative combination of image luminance, contrast and structure and has been shown to outperform MSE and pSNR with regards to image degradation and perceived structural changes. It is calculated as

$$sSim(I_{ref}, I_u) = \frac{(2\mu_{I_{ref}}\mu_{I_u} + C_1)(2\sigma_{I_{ref}I_u} + C_2)}{(\mu_{I_{ref}}^2 + \mu_{I_u}^2 + C_1)(\sigma_{I_{ref}}^2 + \sigma_{I_u}^2 + C_2)} \quad (6.5)$$

with μ_I denoting the mean of image I , σ_I its variance and σ_{I_1, I_2} the covariance between images I_1 and I_2 . C_1 and C_2 are constants for computational stability. They are commonly defined as $C_1 = (k_1 L)^2$ and $C_2 = (k_2 L)^2$ where L describes the image's dynamic range and $k_1 = 0.01$ and $k_2 = 0.03$ are typical default values.

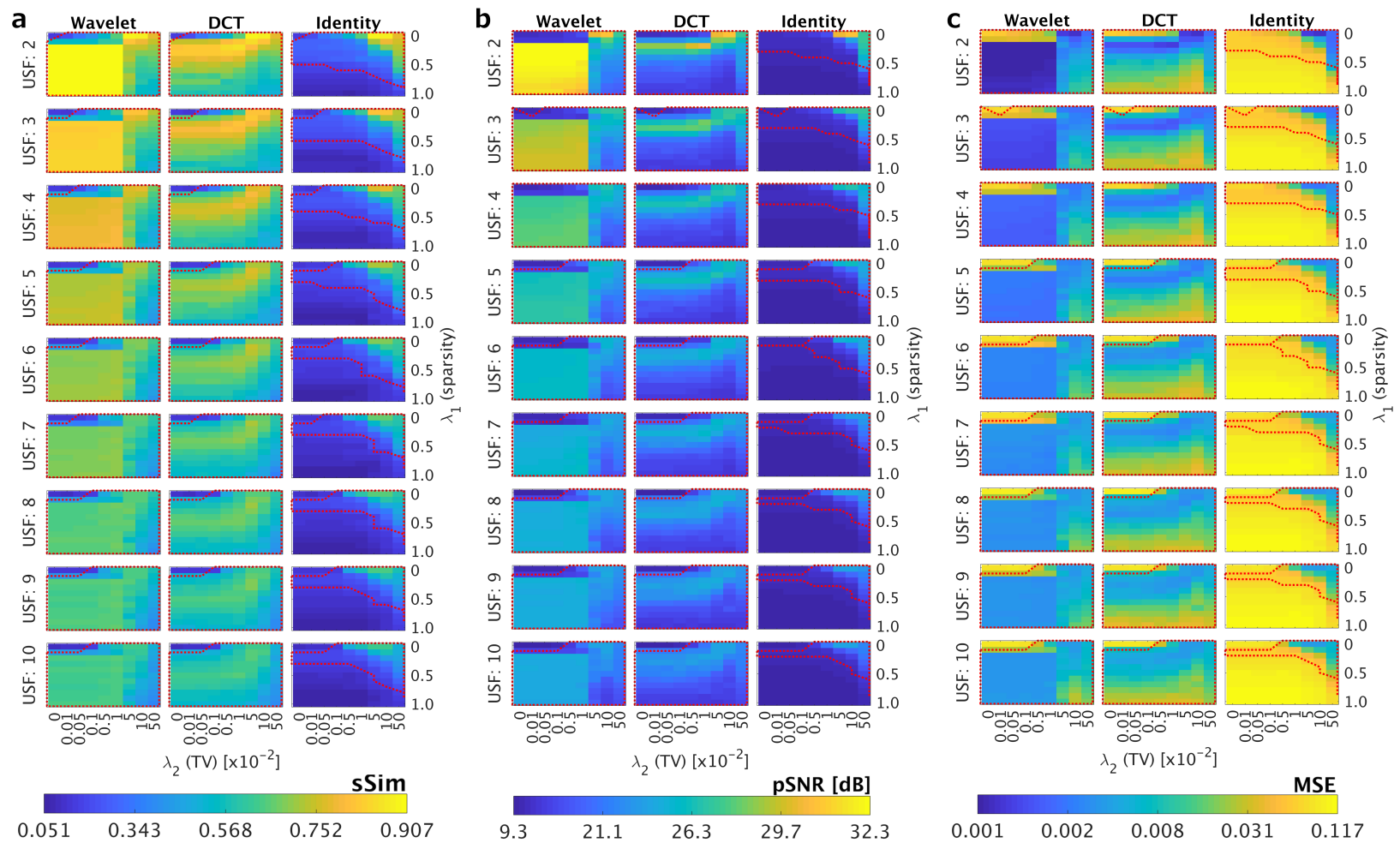


Figure 6.1: CS Reconstruction Analysis. (a) Structural similarity, (b) peak SNR and (c) MSE of in vivo CS reconstruction across undersampling factors, TV and sparsity weighting in investigated sparsity domains. Red dotted line surrounds area with a higher quality score than NUFFT-based reconstructions at the respective undersampling factor. USF, undersampling factor; DCT, Discrete Cosine Transform

6.2.3.2 Image Intensity Reconstruction

The performance of undersampled reconstruction was assessed by comparing local image intensities from I_{ref} with reconstructed image intensities I_{u} . The evaluation was performed on all undersampled reconstructions, i.e. NUFFT and sparsity-based CS reconstructions with highest scores in quality metrics described above. The correlation between I_{ref} and I_{u} was evaluated as a linear function using a least-squares fit in Matlab. The linear fit was interpreted as the potential intensity bias. Its analysis focused on the investigation of the bias slope where 1 was interpreted as overall unbiased intensity distribution; bias slopes greater or smaller than 1 suggest a potential intensity bias compared with I_{ref} . Intensity correlation and bias were analysed on the whole image as well as individual brain regions, brain compartments and background to determine bias and dynamic range changes in structural components, noise and the overall image support.

6.3 Results

6.3.1 Compressed Sensing Parameter Optimisation

CS Reconstruction Performance

Figure 6.1 illustrates the performance of all CS reconstruction results with regards to I_{ref} in all investigated quality parameter, sSim, pSNR and MSE. All quality parameter agree in overall CS reconstruction performance interpretation. Unsurprisingly, reconstruction quality gradually decreases with higher USF.

Wavelet transform reconstructions achieve highest results in sSim and pSNR and lowest MSE. The quality metrics show optimal and robust performance for moderately to high weightings of transform sparsity and low to moderate TV penalty weights.

DCT-based reconstructions achieve similar high scores in sSim and pSNR and comparable MSE to Wavelet transform CS results. The optimal parameter range is, however, much narrower compared to Wavelet-based CS reconstructions.

The **identity** transform, i.e. image sparsity, provides poorest reconstruction quality with best results at high TV weightings and low penalty on sparsity terms.

The dotted red line in Figure 6.1 highlights the region where CS-based reconstruction gives better quality scores than NUFFT-based reconstruction at the same USF. Wavelet and DCT sparsity CS-reconstructions generally outperform NUFFT-based results; the image sparsity domain only provides better quality parameter scores for a small range of CS regularisation weights.

Optimal CS Parameter

Figure 6.2 depicts CS parameter optima across all subjects. The curves show mean and standard errors of quality scores with regards to weights on respective sparsity

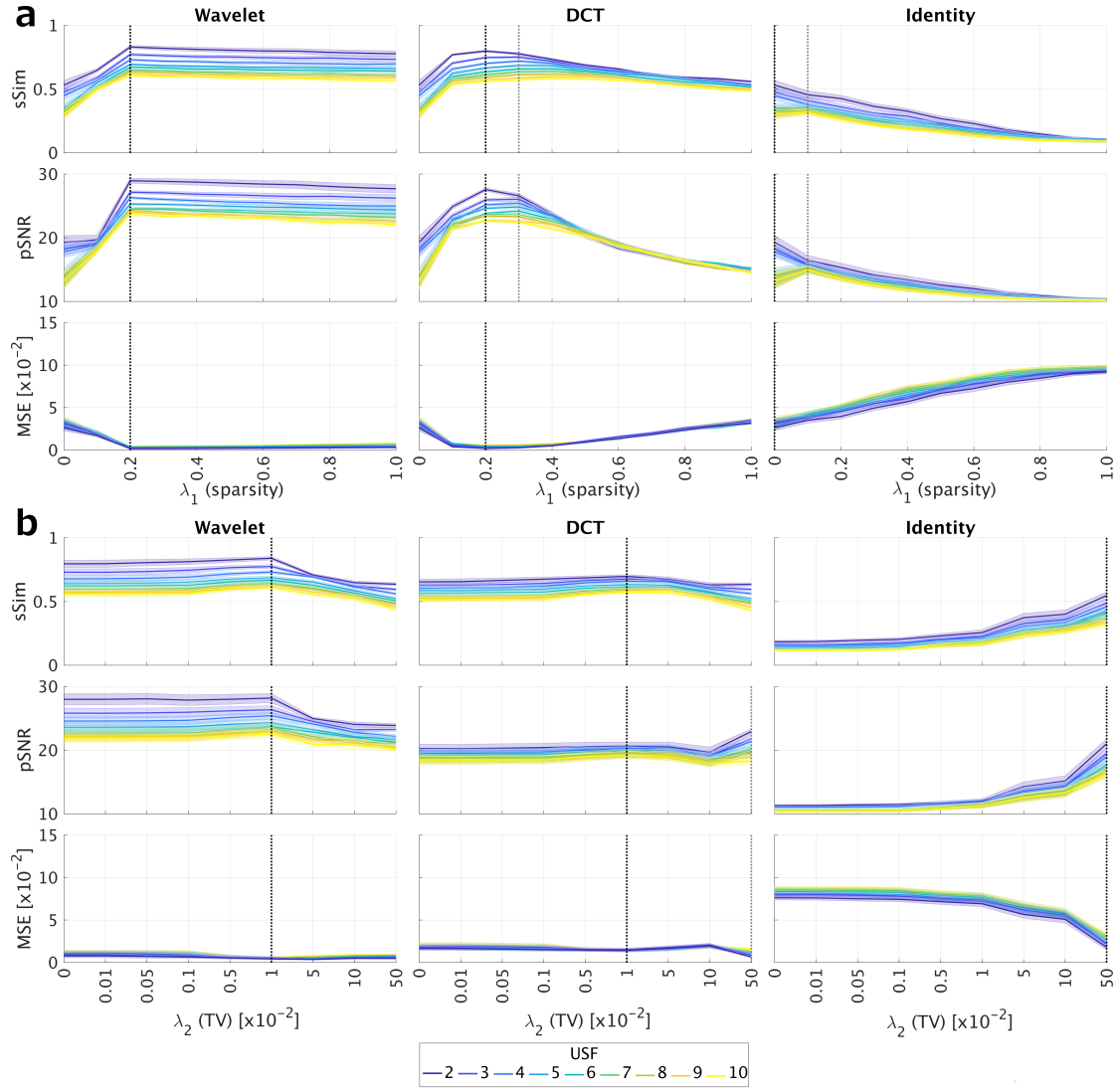


Figure 6.2: Optimal weighting parameter. Mean and standard error of (a) sparsity and (b) TV weighting across subjects and undersampling factors for all investigated quality measures. Dotted black line indicates optimum across all investigated quality parameter, dotted gray line highlights additional optima for a subset of undersampling factors or quality metrics. USF, undersampling factor; TV, total variation; DCT, Discrete Cosine Transform

(Fig 6.2a) and TV (Fig 6.2b) across USF. The curves re-emphasise the overall better performance of Wavelet-based reconstructions. Vertical lines indicate maxima; black lines show maxima across all quality parameter, gray lines indicate additional maxima of individual quality parameter.

For **Wavelet**-based CS reconstructions a clear optimum at $\lambda_1 = 0.2$ (sparsity) and $\lambda_2 = 0.01$ (TV) was found.

DCT-based CS reconstructions showed similar optima. However, curves for higher USF show additional maxima with regard to sSim and pSNR. Very high TV weightings were, furthermore, found to give better scores in pSNR and lower MSE.

Identity-based CS results show best results for $\lambda_1 = 0$, i.e. no sparsity weighting, and very strong TV constraint weights $\lambda_2 = 0.5$. The optimal parameter curves re-accentuate the strongly reduced performance of image sparsity based CS construc-

tions compared with more advanced sparsity transforms.

Figure 6.2 shows a light tendency for pSNR and MSE to favor strong TV weightings, particularly in DCT-weighted CS reconstructions. A high TV weighting was, however, found to result in visually smoothed images with reduced structural detail. SSIM score did not show a bias towards higher TV weights. As a result, the following analysis was based on highest sSim scores in CS reconstruction results.

6.3.2 Reconstruction Accuracy Analysis

Figure 6.3 shows cross sections of the 10,000 spoke standard NUFFT reconstruction (I_{ref}) and the results of NUFFT and CS-based reconstructions across USF. CS reconstructions with highest sSim score are displayed. Higher USF lead to stronger image degradation and an increase of noise which is more contained in iterative CS reconstructions. Wavelet-based transforms provide highest structural detail which decreases for $\text{USF} > 4$.

Figures 6.4 and 6.5 provide an analysis of image intensity reconstruction. Plotted graphs show correlation of image intensities in normalised I_{ref} and I_u across all subjects. Figure 6.4 superimposes reconstruction results across all investigated USF. The black dotted line indicates identity, i.e. a perfect reconstruction.

With higher USF, reconstructed image intensities deviate more strongly, i.e. point clouds show greater spread. While the variation from an ideal reconstruction is slightly more contained in CS-based reconstructions, the point clouds show some non-linear behaviour, particularly for DCT and Identity-based CS reconstructions.

Figure 6.5 provides a detailed matrix overview of image intensity correlation between normalised I_{ref} and I_u . Each row displays the intensity reconstruction performance of NUFFT and CS-based reconstructions at a particular USF. The yellow line indicates the perfect correlation, the red dashed line depicts a linear fit through the point cloud. Again the greater spread with higher USF is easily discernible. The linear point cloud fits (red dashed lines) indicate that the average deviation from the ideal (yellow line) is stronger in NUFFT-based and CS-Identity reconstructions. Up to an USF of 4, linear fits through correlation point clouds of Wavelet-based CS reconstructions show great agreement with the ideal reconstruction which consequently suggests a more unbiased result.

Towards higher USF, all correlation plots show an increasing deviation from the ideal reconstruction with regards to I_{ref} . At high USF (≥ 5), point clouds furthermore demonstrate non-linear behaviour. The divergence from the ideal reconstruction is always manifested as a reduction in the overall dynamic range – that is an overall increase in noise and decrease in high image intensities.

Figure 6.6 illustrates a detailed investigation of the non-linear relation between undersampled I_u intensity reconstruction and I_{ref} intensities. The dynamic range of all reconstructions was normalised to span from 0 to 1 and split into 200 equally spaced

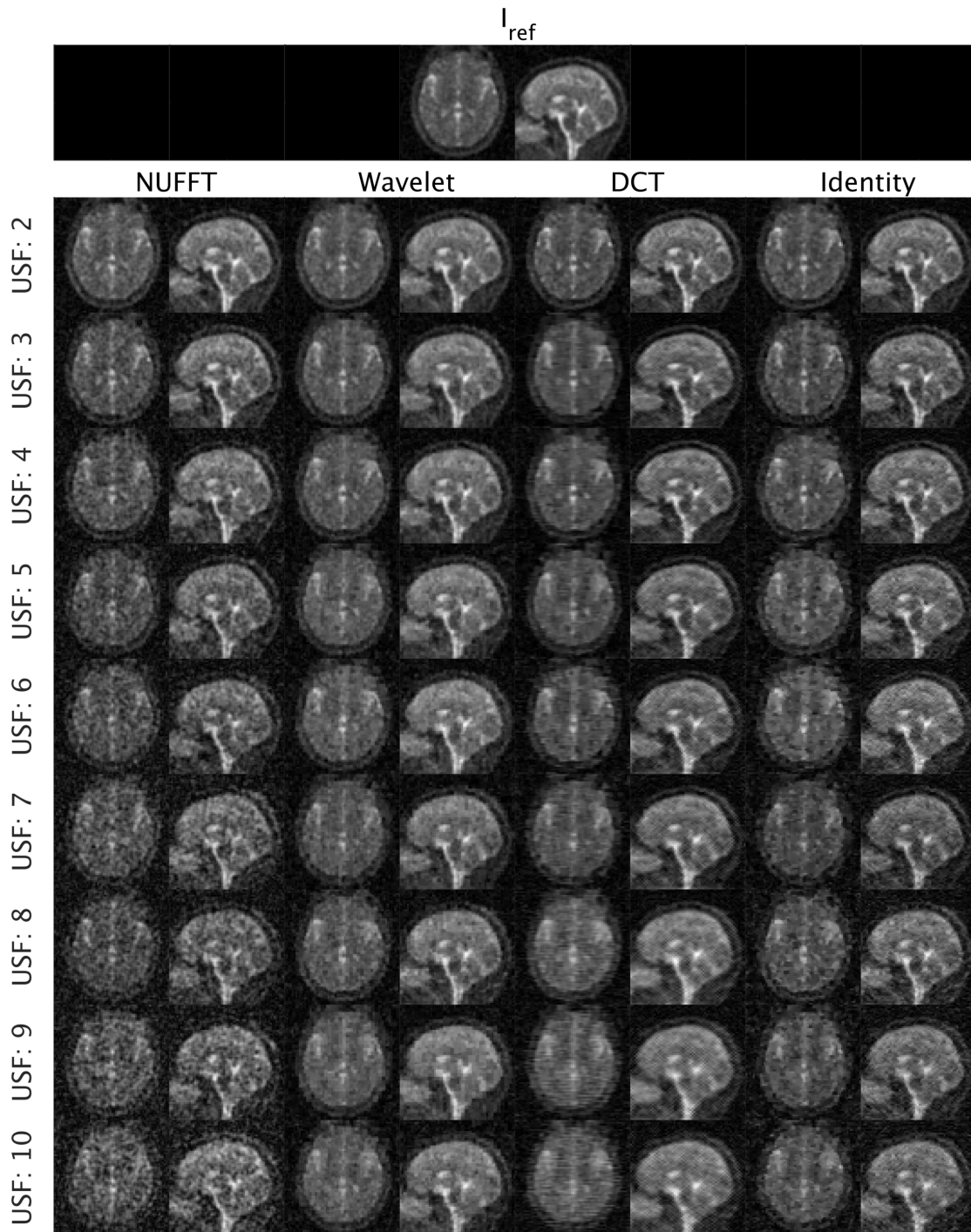


Figure 6.3: In vivo reconstruction. Axial and sagittal cross section of in vivo reconstructions. Top row: Fully sampled (10,000 projections) reconstruction (I_{ref}); lower rows: NUFFT and CS reconstructions across different undersampling factors. CS reconstructions with highest sSim score are displayed. USF, undersampling factor; DCT, Discrete Cosine Transform, I_{ref} , reference image

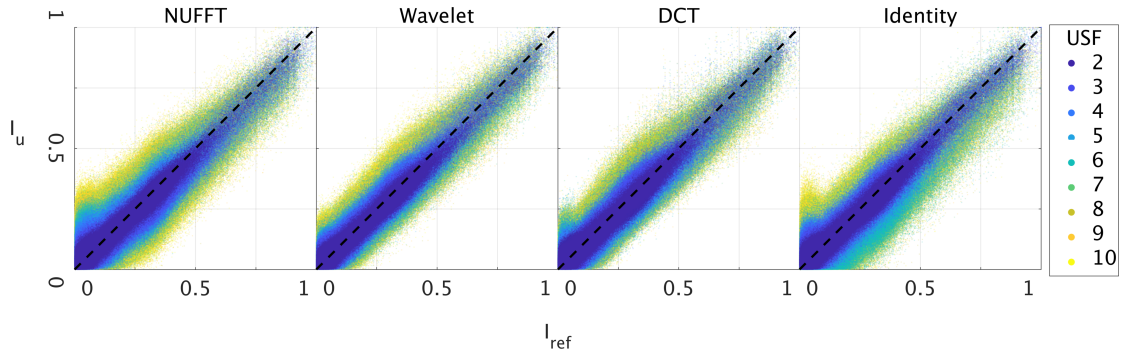


Figure 6.4: CS Intensity Reconstruction Performance. Correlation between reference image intensity I_{ref} and undersampled reconstruction intensities I_u for all undersampled reconstruction schemes. Point cloud overlay of reconstruction accuracy for all USF; black dashed line highlights a perfect correlation. USF, undersampling factor; I_{ref} , reference image; I_u , undersampled image; DCT, Discrete Cosine Transform

intensity ranges. Based on these intensity intervals, I_{ref} voxel were subdivided into intensity groups. For each intensity group, corresponding voxel in the undersampled reconstructions were averaged and plotted over the mean intensity from the respective I_{ref} voxel group. Figure 6.6 depicts the mean intensities across intervals for all undersampled reconstruction schemes. The black dotted line again visualises the perfect correlation.

For all undersampled reconstruction schemes, a mean increase of low image intensities and mean decrease of high image intensities is observed. This effect builds up with higher USF. While NUFFT-based reconstructions show a greater mean noise enhancement, the overall mean intensity curves follow an approximately linear trend. For CS-based reconstructions stronger non-linearities are observable. The red solid box and blue dashed box highlight the upper and lower 15% of image intensities, respectively. The red solid box further evidences the better noise suppression in iterative CS reconstructions. Best noise regulation is seen in Wavelet-based results. Furthermore, Wavelet-based reconstructions follow a more linear trend and lead to smaller drop in high intensity signal.

Figure 6.7 is concerned with the reconstruction of structural intensities. Plotted point clouds show I_u over I_{ref} intensities in a brain region of one subject. Intensity correlations are again plotted for all undersampled reconstruction schemes (columns) with each row representing an USF. Point clouds are coloured by density. The solid black line illustrates $I_{ref,brain} = I_{u,brain}$, i.e. an identical reconstruction of brain structure. The dashed red line displays a linear least-squares fit through data points.

The correlation point clouds across structural components show similar characteristics to the previous whole image analysis (Figures 6.4, 6.5); reconstruction accuracy spread increases with higher intensities. The bias, i.e. deviation of the linear point cloud fit to the ideal identity reconstruction, remains insignificant up until an USF of 4 across all undersampled reconstruction schemes. For high USF, NUFFT and identity-based CS reconstructions divert non-linearly from the ideal reconstruction which is depicted by the slight deformation and offset of the high density cluster. Overall, all undersampled reconstruction schemes demonstrate comparable performance with regards to the deviation of a linear point cloud fit to the ideal reconstruction line. This

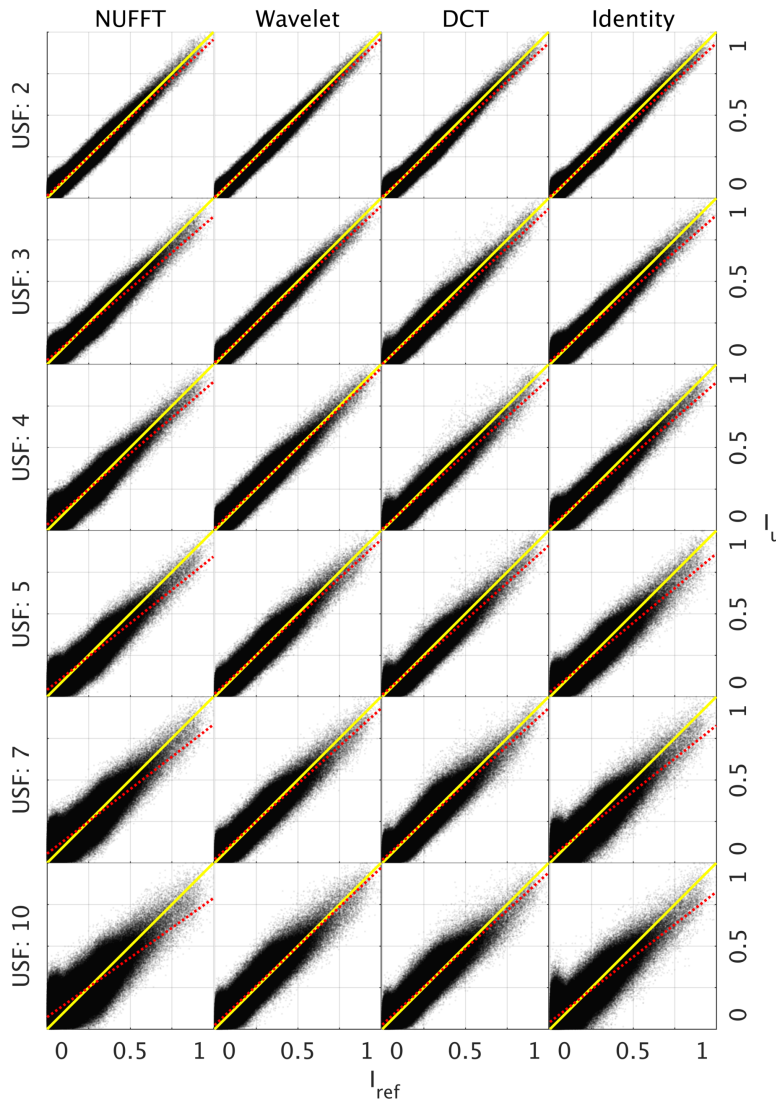


Figure 6.5: CS Intensity Reconstruction Performance. Detailed matrix depicting correlation point cloud between reference image intensity I_{ref} and undersampled reconstruction intensities I_u for individual USF. Yellow solid line indicates identity; red dotted line shows linear least-squares fit through point cloud. USF, undersampling factor; I_{ref} , reference image; I_u , undersampled image; DCT, Discrete Cosine Transform

may imply a reduced bias on structural image intensity values. Again, variations of the point cloud fit to the ideal reconstruction are always manifested as a decreased slope, i.e. a mean reduction in the overall dynamic range of image intensities.

Figure 6.8 provides a more detailed analysis on bias slopes, i.e. the slope of a linear fit through a correlation point cloud. The plotted curves depict mean and standard error of slopes over all investigated subjects across USF. Linear fits through the entire image (cf. Figure 6.5) as well as through the respective brain regions (cf. Figure 6.7) were investigated. For all USF, mean bias slopes are below 1 indicating a decrease in the general dynamic range for undersampled reconstructions. Bias slopes show a decreasing trend with higher USF. NUFFT and CS-based reconstructions perform similarly in the recovery of brain intensity reconstructions for all USF. An investigation across the whole image support exhibits stronger bias slopes reductions for NUFFT and Identity-based CS reconstructions. For DCT and Wavelet, the mean slope across all subjects remains relatively constant.

Figure 6.9 represents the noise equivalent to Figure 6.7 following the same setup, however, displaying image intensities from the background region in a single subject. The

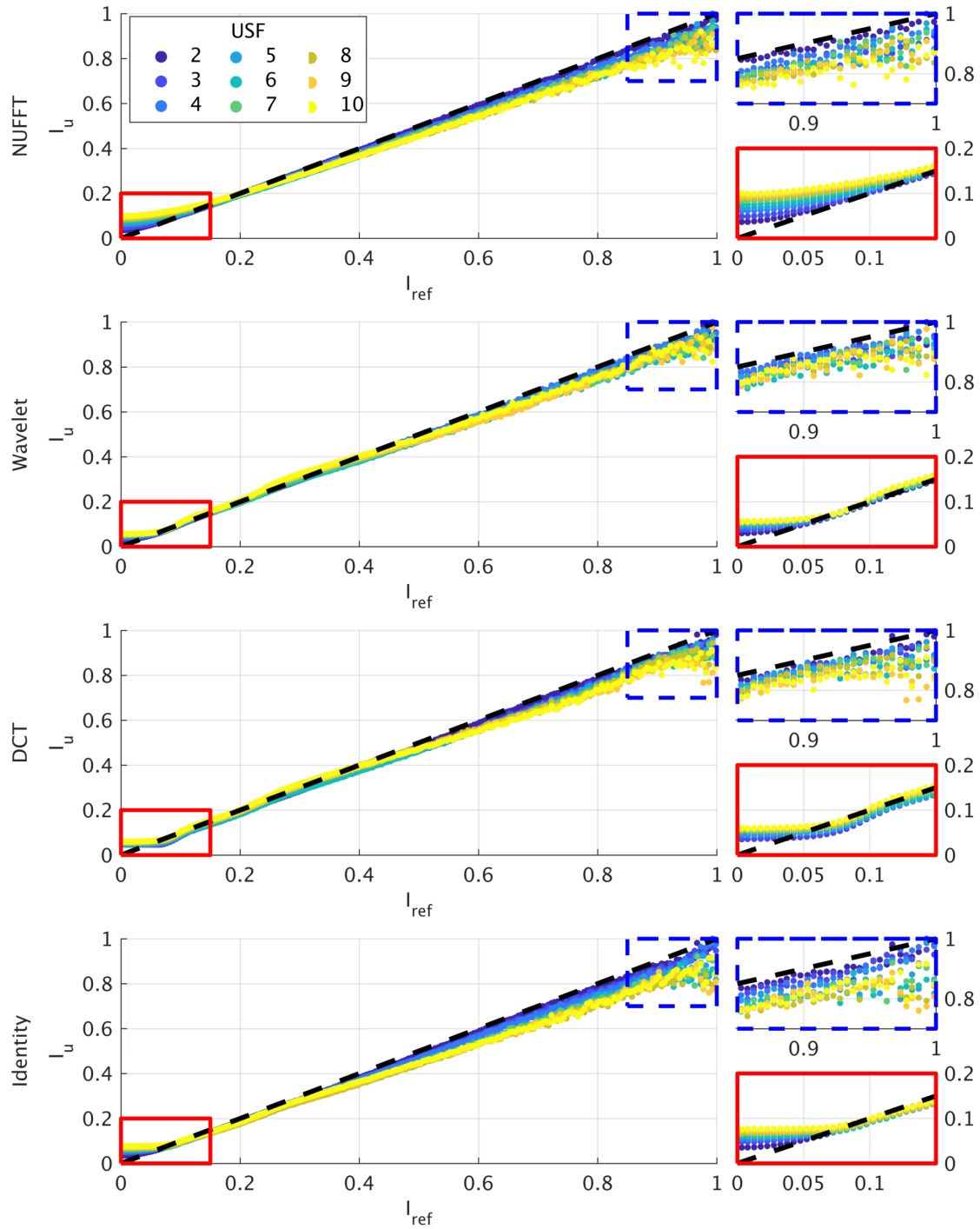


Figure 6.6: Investigation of non-linearity in intensity reconstruction. Mean intensity of voxel groups in resulting from subdivision of I_{ref} into 200 equally-spaced intensity groups. Mean intensity values for all reconstructions of I_u are plotted over mean intensity in I_{ref} across USF. Red solid box and blue dashed box show zoom-in view for lower and upper 15% of intensity groups, respectively. USF, undersampling factor; I_{ref} , reference image; I_u , undersampled image; DCT, Discrete Cosine Transform

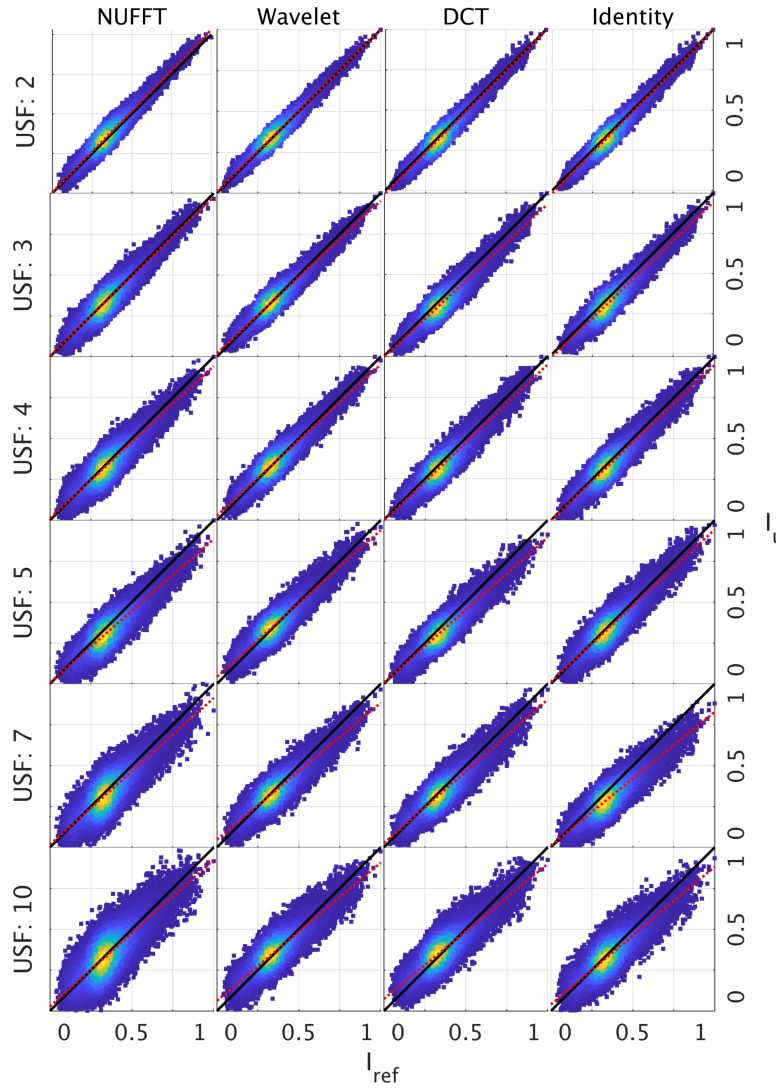
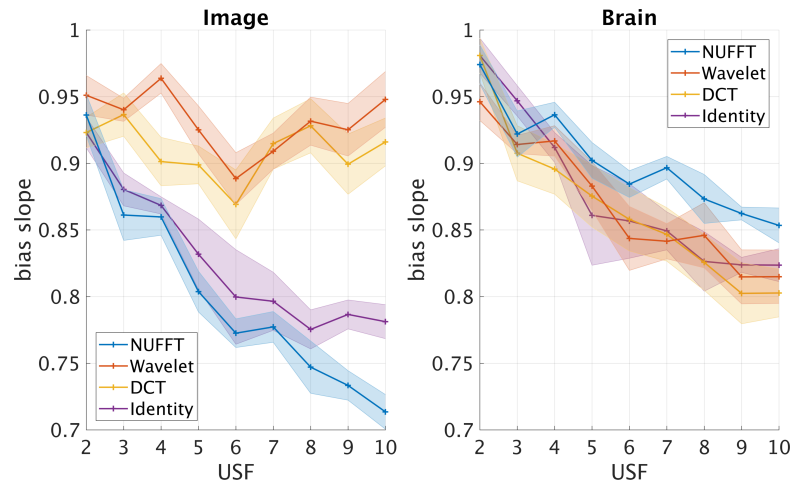


Figure 6.7: Reconstruction of structural intensities. Density-colored scatter plots of I_{ref} and I_u across brain mask in one subject. Matrix displays reconstruction correlation across all undersampled reconstruction schemes (columns) across USF (rows). Black solid line shows identity; red dotted line provides linear least-squares fit through point cloud. USF, undersampling factor; I_{ref} , reference image; I_u , undersampled image; DCT, Discrete Cosine Transform

black solid line refers to $I_{ref} = I_u$ as before. For increasing USF, noise rises, particularly for NUFFT and Identity-based CS. For $USF \leq 3$, Wavelet and DCT-based CS results maintain adequate background level with highest point cloud density across the ideal correlation line. Ultimately, for high USF, the mean noise rise is depicted by an offset and stretch of the point cloud density cluster above the ideal reconstruction (black line) for all undersampled reconstructions.

Figure 6.10 investigates mean intensity effects of undersampled reconstructions in specific image regions. The analysis further evidences the different bias effects in structural components and background regions. In segmented brain tissue compartments, all reconstruction schemes show generally robust mean intensity results in good agreement with mean I_{ref} intensities. Overall signal remains better preserved in Wavelet and DCT-based reconstructions and shows more drop-off in Identity-based and standard NUFFT results. The impact of undersampled reconstructions on noise is more evident with significant mean noise increases at higher USF for all reconstruction schemes. Simple NUFFT-based reconstructions lead to the strongest increase in noise with monotonic growth to higher USF. Iterative reconstruction in CS aids to suppress noise. Identity-based CS produces higher noise level than Wavelet and DCT-based reconstruction methods. For $USF > 5$, all methods exhibit a mean noise increase

Figure 6.8: Investigation of bias slope. Mean and standard error of bias slope from linear fits through reconstruction accuracy point clouds across all investigated subjects. Bias slopes are shown for the entire image reconstruction point cloud fits (left), and fits through intensities across brain masks (right). USF, undersampling factor; DCT, Discrete Cosine Transform



of at least 40%.

6.4 Discussion

Compressed Sensing, a concept originating from information and signal processing theory, has shown great applicability in MRI, a field in which signal acquisition time is a crucial component, not just for time-resolved (e.g. cardiac) imaging but also for clinical use in general. The area of x-nuclei imaging in particular suffers from extensive measurement time and low SNR due to very low in vivo concentration and often reduced NMR sensitivity. Hence, the application of CS in imaging of ‘other nuclei’ does not just entail an enticing potential in acquisition time reduction but also SNR-enhancement capabilities.

This work provides a comprehensive investigation of standard CS reconstruction approaches in Sodium MRI of the human brain. Recent work on the application of CS in Sodium MRI of the human knee could show sufficient sparsity in the image domain (Madelin et al., 2012b). For Sodium MRI of the human brain, as studied in this work, the identity transform was found to be an insufficient sparsity domain. This finding highlights the need for dedicated studies of CS in specific MRI application as CS reconstruction is strongly problem-dependent and not very well generalizable. The Wavelet transform is well known to be a robust method for compression of natural images (Taubman and Marcellin, 2012) and, hence, not surprisingly showed the best performance in this study. DCT-based CS results were able to accomplish similar maximum image reconstruction quality scores. However, reconstruction quality results varied more strongly. Wavelet-based reconstructions showed best image quality scores over a wider range of investigated parameters suggesting a higher stability of Wavelet-based CS reconstructions. The addition of TV regularisation has been shown to be a useful component in iterative reconstructions (Rudin et al., 1992; Block et al., 2007) and was also found to be a beneficial constraint in this study. While a strong TV regularisation stabilises an insufficient sparsity domain (identity), it is generally advisable to apply it in moderation as strong TV-weights lead to visually smoothed images. It was found that a TV regularisation weight of 0.01 supports high image quality scores. Recent studies of CS in Sodium MRI (Madelin et al., 2012b; Gnahn

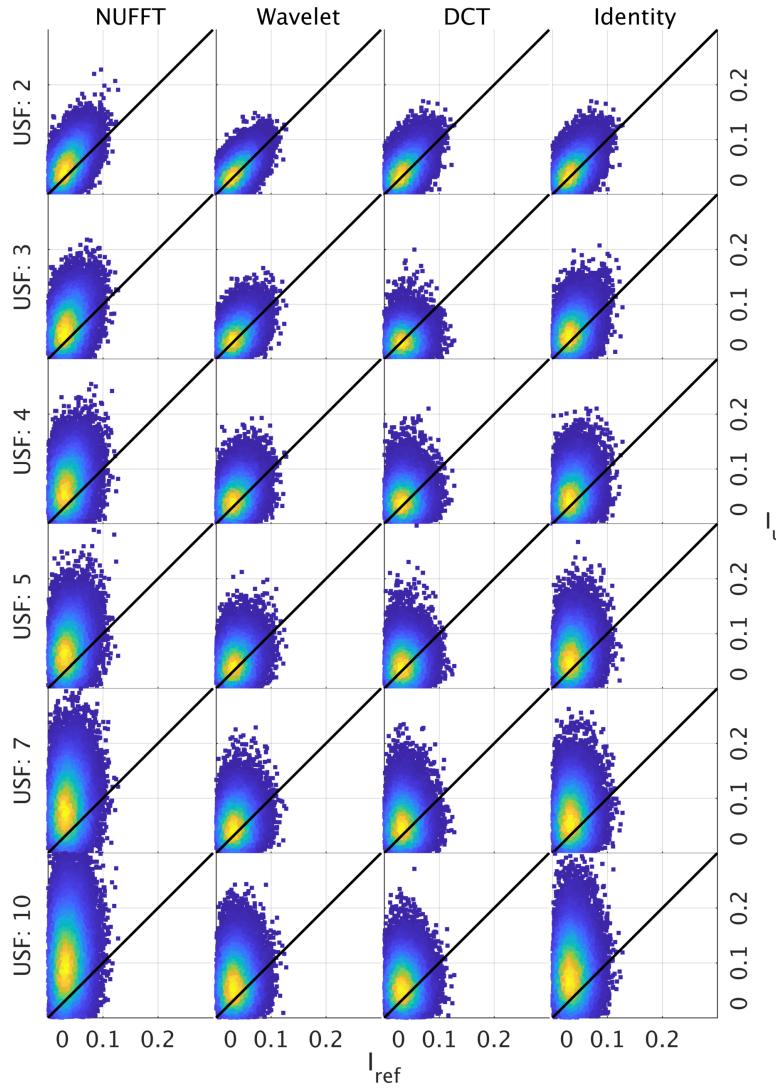


Figure 6.9: Reconstruction performance in noise. Density-coloured scatter plots of I_{ref} and I_u across background region in one subject. Matrix displays reconstruction correlation across all undersampled reconstruction schemes (columns) across USF (rows). Black solid line indicates identity. Black dotted line highlights an identical mean intensity in I_u and I_{ref} . USF, undersampling factor; I_{ref} , reference image; I_u , undersampled image; DCT, Discrete Cosine Transform

et al., 2014) suggest even lower TV weightings. These studies were, however, based on generally lower USF with reconstruction quality assessed by custom quality parameter (Gnahm et al., 2014) and visual inspection (Madelin et al., 2012b). The optimal weighting on reconstruction penalties depends on the SNR of the acquired raw data and the complexity of the imaged object (Block et al., 2007). It should be noted that the investigated quality parameter in this study (sSim and pSNR) assume the reference image to be the perfect ground truth. For in vivo studies such information is not readily available and, hence, a highly sampled standard NUFFT reconstruction was used instead. Reconstruction quality parameter were only evaluated on the brain region to mitigate the influence of noise in reconstruction quality assessment.

Up to an USF of 4, Wavelet-based CS reconstructions were found to provide high image reconstruction quality (sSim = 0.77 ± 0.06 , pSNR = 27.3 ± 1.6 , MSE = $0.0018 \pm 2 \times 10^{-4}$; cf. Figures 6.1, 6.2), good reconstruction of small structural components (Figure 6.3) and low reconstruction bias (Figure 6.5). USFs in this study are expressed with respect to the 10,000 spokes reference image. The theoretical requirement for full sampling in radial-based non-Cartesian acquisitions is described in Equation 6.2. Acquired raw data can, however, be reconstructed onto any desired resolution at the expense of im-

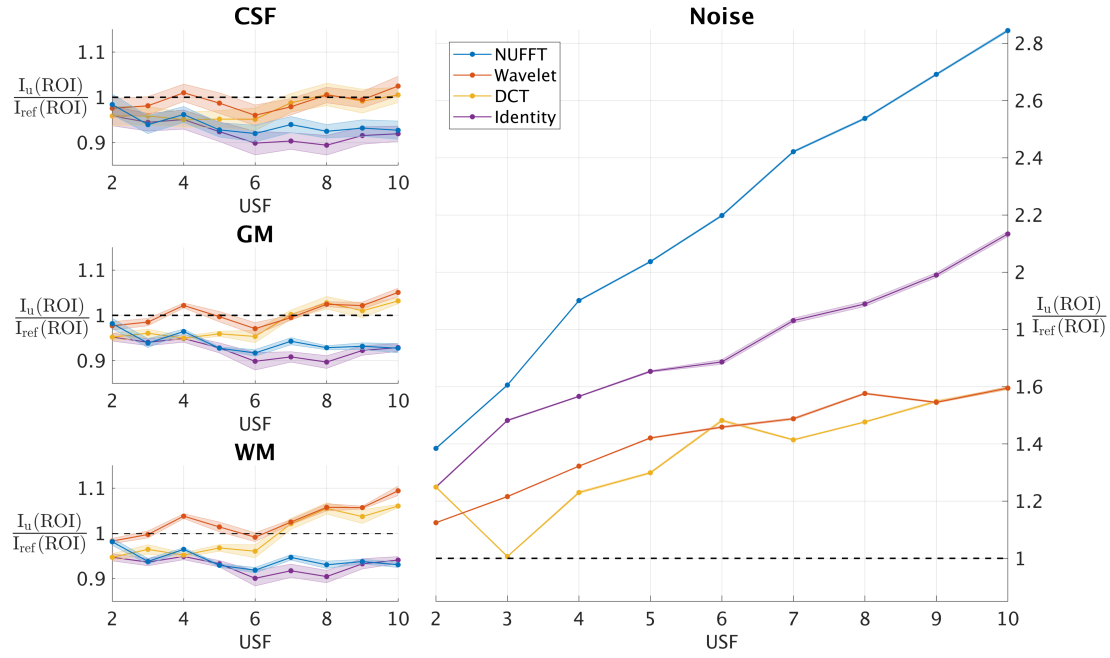


Figure 6.10: Intensity ratio between I_{ref} and I_u in regions of interest (ROI). Mean and standard error of intensity ratios in (left) brain regions and (right) background noise for all investigated reconstruction schemes over USF across all subjects. USF, undersampling factor; I_{ref} , reference image; I_u , undersampled image; DCT, Discrete Cosine Transform; ROI, region of interest; GM, grey matter; WM, white matter; CSF, cerebrospinal fluid

age quality. While the Nyquist theorem states ideal sampling for a nominal resolution, in practice, the acquired number of spokes is a strongly varying factor across studies that is often chosen as a trade-off between total acquisition time and image quality. While the nominal resolution is prescribed in the acquisition and reconstruction, the point spread function of the resulting image underlies different factors including sampling pattern, transverse signal decay and the chosen reconstruction scheme. The results from this study should therefore rather be interpreted as a total number of spokes (USF 4 = 2,500 spokes) and support the conclusion that CS reconstructions with optimised parameter can resemble images with 4-times more densely sampled raw data. It is very complex to assess point spread function effects from CS reconstructions (Wech et al., 2011).

This work addressed the fundamental components of CS algorithms, transform sparsity and TV regularisation. Previous studies on iterative reconstructions in Sodium MRI of the human brain investigated the incorporation of ^1H -based anatomical information (Gnahm et al., 2014; Gnahm and Nagel, 2015) and dictionary-based approaches (Behl et al., 2016). The authors could show that the inclusion of sparsity in learned dictionaries or anatomical constraints improve SNR and maintain good structural detail. Iterative reconstruction are not limited in the number of penalty terms and anatomical information as well as dictionaries could easily be added to the CS cost function that was investigated in this work. The degree of ^1H -based information should, however, be limited to fundamental image support components to reduce the risk of biased reconstruction results (Gnahm and Nagel, 2015). Learned dictionary increase the computational complexity of reconstruction algorithms due to the learning process and introduce several more parameter (sample number, dictionary and block size) that require optimisation.

As mentioned before, the benefits of CS reconstructions can be exploited in two ways: 1) shortened acquisition time (addressed in Madelin et al. (2012b)) with advantages for clinical routine and 2) SNR gain (addressed in Gnahn et al. (2014) and Behl et al. (2016)) with benefits for experimental studies due to increased sensitivity. This work focused on a reduction in acquisition time. It is, however, anticipated that the investigated CS-approach also provides SNR gain potential through signal averaging. Since Sodium MRI suffers from fast bi-exponential transverse signal decay, a fixed measurement time enables repeated acquisition of projections to reduce noise in the raw data and hence increase overall raw data fidelity.

A component that is often investigated in CS reconstructions is SNR/ t , i.e. the SNR achievement over a time interval t . The iterative and non-linear nature of CS reconstructions generally outperforms standard reconstruction methods with regards to SNR if the acquisition window is fixed. The time interval t essentially describes the acquisition time, exclusive of reconstruction. Up to date, reconstruction time is one of the big limiting factors in CS-based reconstructions. In this study, reconstruction times varied from 4 to 2 minutes for Wavelet-based, 3 to 1.4 minutes for DCT-based and 2.5 to 1 minute for Identity-based reconstructions. Gnahn et al. (2014) and Behl et al. (2016) reported 2 to 3.5 hours and 30 minutes for anatomically constrained and dictionary-based iterative reconstructions, respectively. Apart from USF and chosen sparsity transform, the total reconstruction time naturally also depends on the number of iterations. The required number of iterations was not extensively studied in this work. An assessment of quality metrics and visual inspection of results after 100 iterations did not show major improvements suggesting that reconstructions converged well after the chosen 50 iterations. Behl et al. (2016) showed that the number of iterations required for convergence depends on the USF. The authors found that approximately 20 iterations were necessary for convergence with respect to sSim and pSNR.

If acquisition time is not the main point of interest, fast imaging through CS-based reconstruction can also be used for time-resolved acquisitions like cardiac imaging (Bottomley, 2016) and fMRI (Riemer et al., 2015; Bydder et al., 2017). Radial acquisition schemes are particularly well-suited for flexible time-resolved imaging through golden-angle spoke placement with contrast-enhancing potential via view-sharing reconstruction (Winkelmann et al., 2007; Chan et al., 2009).

Iterative CS reconstruction aims to satisfy two main antagonists: data consistency and sparsity terms. The former poses a challenge on the reconstruction of Sodium images due to the considerable noise contribution in the acquired raw data. This effect is observed in the analysis of image reconstruction quality (Figure 6.1) where the lack of image sparsity and TV regularisation ($\lambda_1 = 0$ and $\lambda_2 = 0$) generally lead to lower image quality results than standard undersampled NUFFT reconstructions. As mentioned before, raw data noise can be compensated through averaged spoke acquisitions at the expense of acquisition time.

Other than noisy raw data, noise in the image domain can be successfully mitigated through CS reconstruction. The iterative reconstruction results show a significant reduction in noise level (Figures 6.3, 6.6, 6.9, 6.10) when compared to standard NUFFT reconstructions at the same USF. The denoising effect is a well known benefit of CS in

x-Nuclei MRI (Madelin et al., 2012b; Zhong et al., 2013; Gnahn et al., 2014; Gnahn and Nagel, 2015; Behl et al., 2016; Liang et al., 2017) and originates from the TV-regularised nonlinear reconstruction nature. Unlike standard NUFFT-based noise profiles which follow a well-known Rayleigh distribution, the statistical characteristics of noise from iterative reconstruction is still widely unknown. The effects on statistical and spatial noise distribution impedes SNR calculations and might bias parameter mapping (Blunck et al., 2017).

A main strength of Sodium MRI are its quantitative capabilities. Clinical studies of Sodium MRI commonly focus on the evaluation of tissue Sodium concentration (TSC), a marker known to be well linked to tissue viability (Ouwerkerk, 2011). The quantification of Sodium content is based on signal intensities of Sodium-density weighted acquisitions. Sodium concentration estimates result from a linear regression of mean signal intensity of reference vials with known Sodium content; mean background noise signal is commonly used as a 0 mM marker. Hence, for a reliable estimation of TSC, accurate signal intensities are essential. The question of image intensity reconstruction performance in Sodium MRI CS has not yet been studied in detail. Inaccuracies in the estimation of tissue Sodium concentration from undersampled CS reconstructions have, however, been reported (Madelin et al., 2012b). Aforementioned underestimation effects were also described in quantitative assessment of CS reconstructions in ^{19}F (Zhong et al., 2013). This study provides a comprehensive investigation of Sodium signal in undersampled iterative reconstructions. The denoising effect of TV-regularised CS results was demonstrated and indicates a problematic bias for quantitative assessments. The l_1 -norm for sparsity terms may have signal magnitude shrinking effects (Lustig et al., 2007). Correspondingly, a decrease of high image intensities has been observed in this study. The bias on noise level and high signal intensities was found to increase with higher USF. In this study, we found that USF of up to 4 with Wavelet-based sparsity showed only minor impact on intensity reconstruction accuracy (mean linear bias slope: 0.96 ± 0.02 (image), 0.91 ± 0.02 (brain); cf. Figure 6.8) and good recovery of structural features (Figure 6.3). Recently, Identity-based CS reconstructions of the human knee with $\text{USF} > 2$ were found to result in biased TSC estimates; for ^{19}F -based cell tracking MRI a bias was reported for $\text{USF} \geq 16$. Such findings highlight, the particular vulnerability of Sodium CS MRI to disposed quantification. Moderate undersampling and well-chosen reconstruction constraints (sparsity and weights) can mitigate the bias. Nevertheless, the use of a range of Sodium concentration phantoms across the whole spectrum of brain Sodium concentrations (20 - 150 mM (Madelin et al., 2014)) is advised if quantitative information of Sodium content are to be extracted from CS reconstructed images; the use of background signal as a 0 mM reference should be avoided. The aspect of feature-size in signal intensity bias of CS reconstructions has not been studied in this work, however, an increased bias for small features has been reported for ^{19}F MRI (Zhong et al., 2013).

CS methods contain parameters that require fine-tuning for optimal reconstruction results. This study investigated brain Sodium CS MRI across 5 healthy volunteers and found great robustness in reconstruction results. With regards to the investigated reconstruction quality parameter, global optima for TV and sparsity weights were found. Such generalizable parameter are of key importance if used in clinical routine.

6.5 Conclusion

This work encompasses a wide investigation of sparsity and TV-regularised CS reconstructions in Sodium MRI of the human brain. The investigation was driven by an interest in acquisition time reduction and focused on image quality optimisation with a special concern toward accurate signal intensity reconstruction and the effects of undersampling on parameter estimation bias. A clear advantage towards Wavelet-based CS results was found; a transform domain that, surprisingly, has not been investigated in Sodium MRI CS earlier. This well-known sparsity transform was shown to enable undersampling of up to a factor of 4 with great image quality and structural detail while maintaining good signal intensity reconstruction performance. Together with the observed global optima for CS parameter and overall well-contained reconstruction times, the achievable reduction in scan time greatly supports the transition of Sodium MRI into clinical routine.

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Abstract

Purpose This work demonstrates a 3D radial multi-echo acquisition scheme for time-efficient Sodium (^{23}Na) MR-signal acquisition and analysis. Echo reconstructions were used to produce signal-to-noise ratio (SNR)-enhanced ^{23}Na -images and parameter maps of the biexponential observed transverse relaxation time (T_2^*) decay.

Methods A custom-built sequence for radial multi-echo acquisition was proposed for acquisition of a series of 3D volumetric ^{23}Na -images. Measurements acquired in a phantom and in vivo human brains were analysed for SNR enhancement and multi-component T_2^* estimation.

Results Rapid gradient refocused imaging acquired 38 echoes within a repetition time of 160 ms. Signal averaging of multi-echo time (TE) measurements showed an average brain tissue SNR enhancement of 34% compared to single-TE images across subjects. Phantom and in vivo measurements detected distinguishable signal decay characteristics for fluid and solid media. Mapping results were investigated in phantom and in vivo experiments for sequence timing optimisation and signal decay analysis. The T_2^* mapping results were consistent with previously reported values and facilitated fluid-signal discrimination.

Conclusion The proposed method offers an efficient ^{23}Na -imaging scheme that extends existing ^{23}Na -MRI sequences by acquiring signal decay information with no increase in time or specific absorption rate. The resultant SNR-enhanced ^{23}Na -images and estimated T_2^* signal decay characteristics offer great potential for detailed investigation of tissue compartment characterisation and clinical application.

7.1 Introduction

Sodium (^{23}Na) is the second most abundant MR-observable nucleus in biological tissue and plays a vital role in cell physiology. The electrochemical gradient between intra- and extracellular ^{23}Na concentration is a crucial component of a cell's physiology and is strongly dependent on the cell's metabolism and its membrane integrity. Hence, disturbances of this delicate mechanism are considered as a sensitive, early indicator for cell breakdown and provide an insight into cell integrity and tissue viability (Madelin et al., 2014; Boada et al., 2005; Thulborn, 2016). Based on its involvement in energy as well as structural processes, ^{23}Na is a potential tool for the detection of metabolic parameters; its capabilities as a biomarker aimed at extending clinical MRI to earlier diagnosis and therapy response measurements have been discussed, as well as the application to the detection of diseases without anatomic abnormalities (Thulborn, 2016). Early studies of ^{23}Na -MRI date back to the 1980s (Hilal et al., 1983; Ra et al., 1988) and with advancements in hardware and acquisition strategies (Boada et al., 1997b; Nagel et al., 2009; Riemer et al., 2014; Lu et al., 2010), several more recent studies have investigated the potential of ^{23}Na -MRI across a variety of diseases ranging from neurodegenerative diseases (Inglese et al., 2010; Maarouf et al., 2017), stroke (Wetterling et al., 2012; Tsang et al., 2011) and tumours (Schepkin, 2016; Nagel et al., 2011b; Ouwerkerk et al., 2003) to musculoskeletal pathologies (Zbyn et al., 2016; Marik et al., 2016; Madelin et al., 2012a; Bangerter et al., 2016), and others (Zollner et al., 2016; Madelin and Regatte, 2013).

MR experiments on ^{23}Na nuclei detect signal originating from complex electrical and dynamic spin interactions. Other than ^1H nuclei, electric charges of ^{23}Na nuclei are non-spherically distributed causing an electric quadrupolar moment based on the interaction between the ^{23}Na nucleus and its environment. Consequently, ^{23}Na nuclei are not just affected by local magnetic field interactions but also exhibit impact from local electric fields. ^{23}Na nuclei have a spin of $3/2$ and four corresponding discrete energy states ($3/2$, $1/2$, $-1/2$, $-3/2$). Single-quantum coherence measurements (i.e. acquisitions under single 90° RF-pulses without enhanced filtering techniques) detect transitions between adjacent energy levels. In an isotropic system, e.g. fluid media,

the effects of magnetic and electric fields average out resulting in identical transition rates for all single quantum coherences and, hence, display mono-exponential decay behaviour. In macroscopically structured environments, nuclei experience non-vanishing average electric field gradients leading to a shift in energy levels that produces a frequency splitting on the spectrum (Van der Mareel, 2003; Hubbard, 1970). These interactions cause the satellite transitions (i.e. $-3/2 \rightarrow -1/2$ and $1/2 \rightarrow 3/2$) to occur at faster rates than the central transitions ($-1/2 \rightarrow 1/2$) and result in biexponential T_2 decay. Both ^{23}Na -signal T_2 decay components in anisotropic systems exhibit faster relaxation than the mono-exponential relaxation in isotropic environments (Hubbard, 1970; Andrasko, 1974; Jaccard et al., 1986). The complex interactions that give rise to the ^{23}Na signal suggest the potential for inference of underlying macroscopic structure (Berendsen and Edzes, 1973).

Sensitising ^{23}Na contrast to reveal information about structure has been an active field of research, focusing predominantly on the selective detection of intracellular ^{23}Na contents. Several approaches have been suggested for intracellular ^{23}Na weighted acquisitions: chemical shift reagents for a selective frequency offset of extracellular ^{23}Na signal (Delort and Forano, 2004; Hutchison et al., 1992), triple-quantum-filtered (TQF) imaging facilitating the selective detection of higher quantum coherences (Boada et al., 2005; Fleysher et al., 2010; Griffey et al., 1990; Mirkes et al., 2016; Tsang et al., 2012; Wimperis and Wood, 1991), fluid-suppression based on inversion recovery for an attenuation of fluid ^{23}Na signal (Chang et al., 2012; Feldman et al., 2013; Lee et al., 2016; Madelin et al., 2010; Nagel et al., 2011a; Stobbe and Beaulieu, 2005). Recent work by Qian et al. (2015) suggested the use of ^{23}Na -signal decay for the inference of structural components. The inference of metabolic and macrostructural information in healthy and pathological processes is promising for clinical MRI studies.

Despite recent advancements in hardware, the number of ^{23}Na -MRI based clinical studies is still comparatively small (Madelin and Regatte, 2013). The main challenges for the advancement of ^{23}Na -MRI are low SNR coupled with relatively high SAR exposure (particularly at high fields) and correspondingly prolonged scan times. Recent studies have addressed these challenges by more efficient acquisition methods: SISTINA (Fiege et al., 2013) allows for the detection of single and triple-quantum filtered images in a single TQF-acquisition. Benkhedah et al. (2013) proposed gradient-selected and phase-cycling difference imaging approaches for the acquisition of ^{23}Na -density and single quantum filtered images with the potential for inferring triple-quantum filtered image contrasts.

Our primary contribution is a new acquisition approach based on 3D Multi-Echo Radial Imaging in ^{23}Na (3D-MERINA), from which multiple parameter maps can be inferred from a single scan. The relatively long acquisition times typical of ^{23}Na -MRI originate from SAR limitations and the need for full longitudinal signal recovery in ^{23}Na -density weighted acquisitions. Our method fills vacant imaging time with the acquisition of additional gradient re-focused echoes. We demonstrate that through the use of radial imaging, echoes can be acquired rapidly and subsequently exploited for SNR enhancement and the estimation of T_2^* parameter maps, while still providing ^{23}Na -density weighted images for quantification purposes.

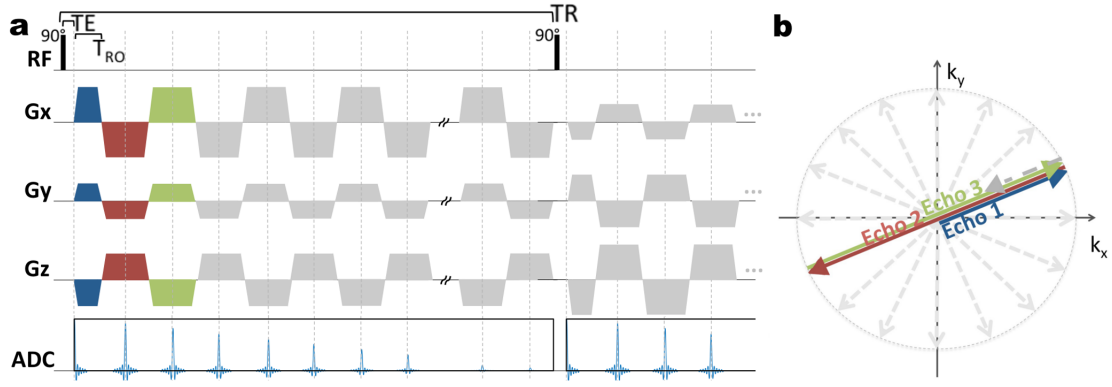


Figure 7.1: (a) Pulse sequence diagram for 3D-MERINA with definition of timing parameters. (b) Simplified 2D illustration of echo sampling. During each excitation, several gradient refocused echoes are acquired. First echo is measured as half-projection; subsequent echoes are sampled as full projections along the same angle. TE, echo time; TR, repetition time; RF, radiofrequency; T_{RO} , readout duration.

7.2 Methods

7.2.1 Sequence Design: 3D Multi-Echo Radial Imaging of ^{23}Na

Imaging was performed on a research 7T MRI scanner (Siemens Healthcare, Erlangen, Germany) with a transmit/receive dual-tuned ^1H - ^{23}Na head coil (QED, Mayfield Village, Ohio USA). The ^{23}Na -based imaging sequence consisted of a nonselective hard pulse (duration 500ms) with a custom-built 3D radial acquisition scheme. The placement of readout spokes was based on Saff and Kuijlaars' algorithm (Saff and Kuijlaars, 1997) for homogeneous projection distribution. For a total number of projections, N , the spherical coordinates of each projection, $\theta \in [0, \pi]$ and $\phi \in [0, 2\pi]$ were determined via:

$$\begin{aligned} \theta_k &= \arccos(h_k), \quad h_k = -1 + \frac{2(k-1)}{N-1}, \quad 1 \leq k \leq N \\ \phi_k &= \left(\phi_k k - 1 + \frac{3.6}{\sqrt{N}} \frac{1}{\sqrt{1-h_k^2}} \right) \bmod 2\pi, \quad \phi_1 = \phi_N = 0, \quad 2 \leq k \leq N-1 \end{aligned} \quad (7.1)$$

The 3D-MERINA sequence acquires multiple gradient echoes via repetitive gradient refocusing along each projection angle. The first echo is based on a center-out half-projection, whereas consecutive echoes are acquired as full projections (Fig. 7.1). The number of acquired echoes depends on the readout duration (T_{RO}) and repetition time (TR).

7.2.2 T_{RO} Optimisation

The choice of sampling durations (T_{RO}) in radial imaging implies a well-known optimisation problem between achievable SNR and T_2^* -induced blurring (Rahmer et al., 2006). For a given resolution and field of view (FOV), shorter T_{RO} requires stronger

gradients and thus gives rise to a higher bandwidth. Given the direct proportionality between BW and thermal noise in the acquired signal, T_{RO} influences the final image quality, that is, longer T_{RO} enhance SNR. However, due to concomitant T_2^* signal decay, the choice of T_{RO} introduces a tradeoff between resultant SNR and PSF (Nagel et al., 2009; Rahmer et al., 2006). The biexponential decay characteristics and broad range of ^{23}Na transverse relaxation times in biological tissue complicate the determination of an optimal T_{RO} . Based on reported relations between short and long decay times of $T_{2\text{long}}^* T_{2\text{short}}^* \approx 10$, it was found that $T_{RO} = 0.14 T_{2\text{long}}^*$ yielded optimal image results in 3D radial projection imaging (Nagel et al., 2009), which consequently suggests a T_{RO} between 2.1 and 4.2 ms for commonly reported brain tissue $T_{2\text{long}}^*$ components of 15 to 30 ms (Madelin et al., 2014).

For the characterisation of fast biexponential signal decay, the 3D-MERINA acquisition scheme expands the constraints of good SNR and narrow PSF to include the extra requirement of multiple fast echo detections. The additional optimisation constraint was investigated experimentally for an isotropic resolution of 3.1 mm and a FOV of 20 cm. Phantom measurements were analyzed with regard to the number of measurable echoes with good signal to noise characteristics. The duration and number of echoes with sufficient signal quality, that is, $y_{TE} \leq 2\mu_{\text{noise}}$, were used to determine an optimal T_{RO} for low ^{23}Na concentrations in fast decaying solid environments.

7.2.3 Reconstruction

Images were reconstructed offline via Kaiser-Bessel re-gridding onto an isotropic, 3.1-mm resolution grid in MATLAB (MathWorks, Natick, MA). The re-gridding oversampling factor was set to 1.5. Prior to re-gridding, raw projection data was weighted to compensate for density inhomogeneities by an approach described by Nielles-Vallespin et al. (2007)

$$w_s = \frac{\pi}{N} \left[\left(\frac{k_{s+1}}{2} \right)^2 + \left(\frac{k_s}{2} \right)^2 \right] \quad s = 0, \dots, S-1 \quad (7.2)$$

where N is the number of half-projections acquired, and S the number of sampling points along each spoke. It should be noted that weighting on refocused echoes is halved compared to the initial echo based on the acquisition of full projections. A Hann filter was applied to raw projection data for the reduction of Gibbs ringing artifacts.

7.2.4 SNR Enhancement

The combination of multiple echoes for SNR enhancement was investigated via averaging of raw k-space data prior to re-gridding. The SNR was determined according to Gudbjartsson and Patz (1995).

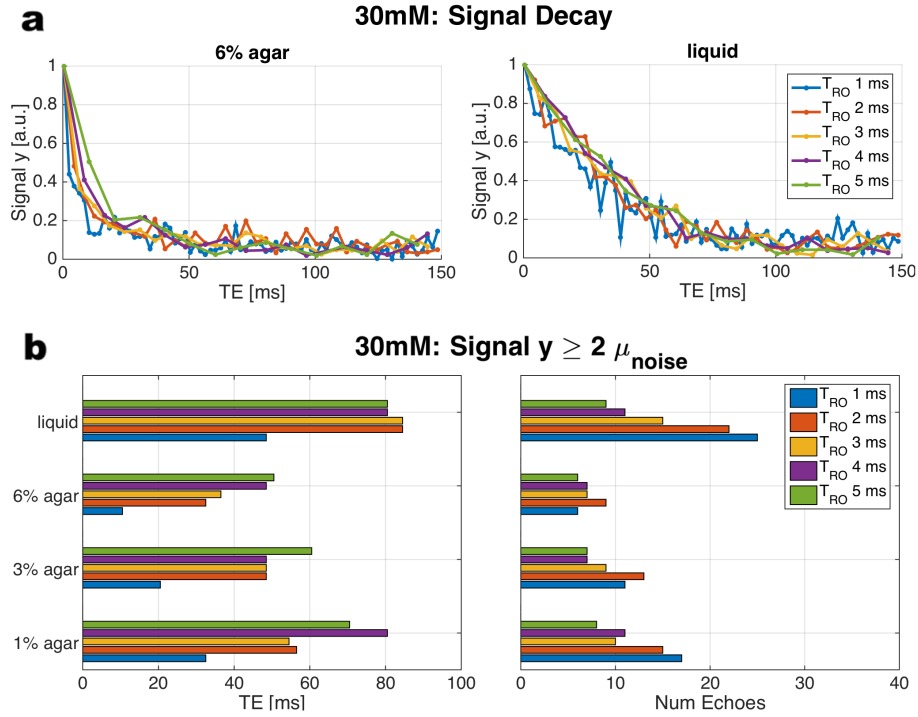


Figure 7.2: (a) Magnitude signal from the central voxel of 30 mM saline phantom vials at high agar concentration (6%) and in liquid media. Curves plot signal decay measured at T_{RO} ranging from 1 to 5 ms. T_{RO} of 1 ms (blue) shows stronger noise contribution. (b) Duration (left) and number of echoes (right) with signal above $2 \mu_{noise}$ in 30 mM NaCl vials across measured T_{RO} . TE, echo time; T_{RO} , readout duration.

7.2.5 Experiments

7.2.5.1 Phantom

Initial experiments were performed on a phantom to investigate optimal timing parameters. Phantom acquisitions were furthermore utilised to assess the sequence's capability of measuring biexponential decay behaviour across different media and ^{23}Na concentrations. The phantom consisted of 16 closely packed vials surrounded by air. Each had a diameter of 3 cm and contained a combination of saline concentration (30, 70, 110, and 150 mM) and agar level (liquid, 1%, 3%, and 6%). ^{23}Na -MRI was performed with 3D-MERINA, as described above. Repetition time was set to 160 ms to allow for a complete signal recovery between 90° RF-excitations. To assess the image quality across a number of readout durations, measurements with T_{RO} ranging from 1 to 6 ms were acquired. The initial TE was kept constant at 400 ms, and was defined as the time interval between the centre of the pulse and the gradient and analogue to digital converter onset. The following TEs, as well as the number of measurable echoes, depended on T_{RO} . The shortest chosen T_{RO} (1 ms) permitted the detection of 75 echoes; for the longest T_{RO} experiment (6 ms), 11 echoes were recorded. The acquired FOV was 20 cm. $N = 10,000$ projections were sampled, leading to an acquisition time of 26 min 40 s. B0-field shimming was based on a vendor-provided 3D shimming routine and was performed on the ^1H channel. Shim optimisation was repeated 10 times prior to each acquisition.

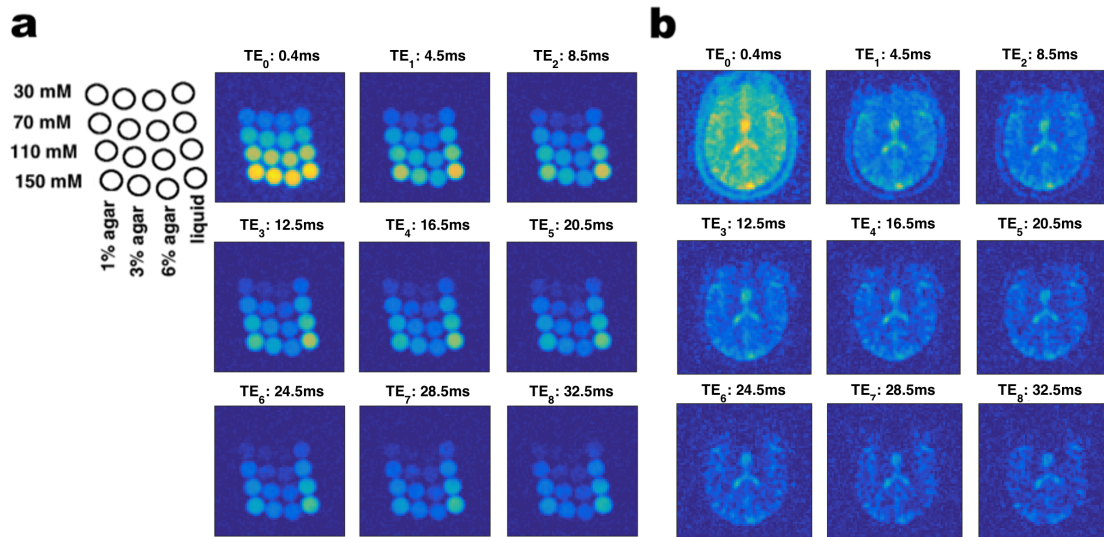


Figure 7.3: Reconstruction of first 9 echoes of phantom (a) and in vivo (b) measurements ($T_{RO} = 2$ ms). Phantom composition is depicted on the left. The curved horizontal alignment resulted from the use of a head-shaped cushion for stabilisation. The initial echo image ($TE_0 = 0.4$ ms) demonstrates the ^{23}Na -density weighted image; the signal-time-series of subsequent TE reconstructions reveal signal decay characteristics specific to the underlying media. TE, echo time; T_{RO} , readout duration.

7.2.5.2 In vivo

All human imaging was conducted with the approval of the University of Melbourne Human Research Ethics Committee, and volunteers gave an informed consent prior to the experiment. Human in vivo acquisitions are performed on four healthy volunteers (2 male, 2 female). ^{23}Na -MRI was based on 3D-MERINA acquisitions, as described in the phantom experiment. T_{RO} was kept at an optimised value of 2 ms, allowing for the detection of 38 echoes while maintaining good SNR properties. The shimming procedure and other imaging parameters were identical to the phantom measurement above. For further analysis of image characteristics, additional ^1H -based images were acquired: A ^1H -FLASH image was measured with $TR = 11$ ms, $TE = 3.06$, 14° flip angle, 1mm isotropic resolution, and acquisition time 6 min 12 s. Brain tissue segmentation was based on a ^1H -MP2RAGE image acquired at inversion times 700 and 2,700 ms; with 5° and 6° flip angle; $TR = 4,900$ ms; $TE = 2.94$ ms; GRAPPA factor 4; 0.9mm isotropic resolution; and acquisition time 6min. ^1H -MP2RAGE were imaged using a 32-channel head coil (Nova Medical Inc., Wilmington MA, USA) in a separate imaging session.

Additional analysis of estimated parameter maps in human in vivo data was performed on tissue segmentations taken from the ^1H -weighted acquisitions. The processing pipeline was done in FMRIB Software Library v.5.x (Oxford, U.K.) (Smith et al., 2004) and involved three main steps: 1) Brain extraction on the FLASH image, 2) registration of brain mask onto MP2RAGE image and tissue segmentation (CSF, grey matter, white matter) of masked MP2RAGE, and 3) registration of segmented brain regions via the FLASH image onto the ^{23}Na -image. The interpolation of segmented brain regions onto the coarser ^{23}Na -image resolution results in masks with strong partial volume effects. A threshold of 2/3 was applied to each mask to limit the contamination of partial volume effects in the analysis.

7.2.6 T₂ Decay Parameter Mapping

7.2.6.1 Signal Model

Spin 3/2 nuclei entail four quantum states that are shaped by dipolar and quadrupolar interactions. The latter is caused by nonspherical electrical environments around the nucleus and results in symmetric perturbations of the satellite Zeeman energy levels. The effects are ²³Na as a biexponential transverse relaxation process. It has been shown that the satellite and central transitions contribute to 60% and 40% of the total ²³Na signal and represent short and long T₂^{*} decay, respectively (Hubbard, 1970).

The applied signal model therefore was defined as a biexponential decay function with fixed component ratios given by

$$A^{bi}(t, \beta_{bi}) = A_0 \left[0.6 \exp\left(-\frac{t}{T_{2,short}^*}\right) + 0.4 \exp\left(-\frac{t}{T_{2,long}^*}\right) \right], \quad (7.3)$$

$$\beta_{bi} = [T_{2,short}^*, T_{2,long}^*, A_0]$$

where A is the signal; $T_{2,short}^*$ and $T_{2,long}^*$ are the short and long decay parameters (ms), respectively; and A_0 the initial maximum signal.

The decay parameters are affected by the correlation time (t_c), that is, the average time it takes a particle to rotate by one radian. If t_c is short, that is, $t_c \leq (\omega_0)^{-1}$, the effects of electric field gradients average to zero. This results in a single resonance line in the spectrum, that is, slow and fast relaxation times coincide. The correlation time, t_c , reflects the interaction with macromolecular charges (Perman et al., 1986) and therefore is short in liquid environments. In human brain ²³Na-imaging, short t_c are expected to occur in CSF areas, and its signal decay therefore is appropriately described by a mono-exponential decay model

$$A^{mono}(t, \beta_{mono}) = A_0 \exp\left(-\frac{t}{T_{2,long}^*}\right), \quad (7.4)$$

$$\beta_{mono} = [T_{2,long}^*, A_0]$$

To account for the complex decay characteristics of both brain tissue and CSF, the parameter estimation process was performed in two steps. Initially, all voxels were fit by a biexponential signal model (Eq. 7.3) using a Rician noise model and a maximum likelihood estimation approach. The $T_{2,short}^*$ estimate was then checked for plausibility: very short (<0.3 ms) and long (>7 ms) $T_{2,short}^*$ were classified as liquid environments and consequently refit by the mono-exponential decay model (Eq. 7.4).

The lower plausibility threshold was determined by the measurement setup because

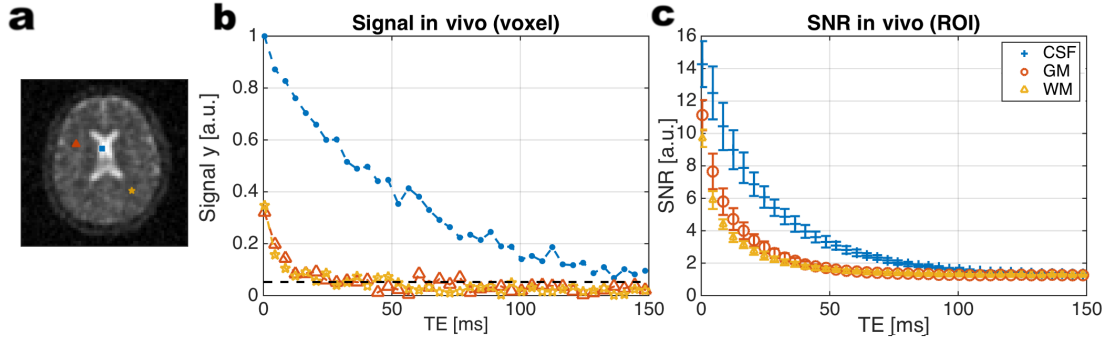


Figure 7.4: Signal evolution over echo reconstructions. TE_0 image of in vivo acquisition (a) indicating location of plotted voxel decay (b). The CSF voxel location has been carefully chosen in the right ventricle to minimise partial volume contamination. Signal decay in voxel in in vivo measurement (b) show slower signal decrease in liquid environments (CSF) compared to tissues. Black dashed line indicates $2\mu_{\text{noise}}$ threshold. (c) Depicts mean and standard deviation of SNR measurements across all subjects in segmented tissue regions (CSF, grey matter, white matter). Longer lasting signal in liquid regions lead to higher SNR in CSF at later echoes compared to grey and white matter. ROI, region-of-interest; SNR, signal-to-noise ratio; TE, echo time.

the initial echo at $TE_0 = 400 \mu\text{s}$ does not practically enable the detection of shorter decay times. The upper threshold was taken from literature commonly reporting biological tissue $T_{2,\text{short}}$ values around 0.5 to 3 ms (Hilal et al., 1983; Shporer and Civan, 1974); however, values up to 6 ms have also been observed (Berendsen and Edzes, 1973).

Compared to biological tissues, relaxation times of ^{23}Na signal in agar media have been found to show longer $T_{2,\text{short}}^*$ components (Andrasko, 1974; Boada et al., 1994) – 4.2 ms and 2.7 ms $T_{2,\text{short}}$ decays have been reported in 8.9% and 10% agar, respectively. Higher concentrations of agar lead to longer t_c and thus cause shorter T_2 decays. Due to the lower agar level in our phantom study, therefore, slightly longer $T_{2,\text{short}}^*$ components are expected. Consequently, the upper plausibility threshold for $T_{2,\text{short}}^*$ was set to 13 ms (3-4 times the reported value) in phantom parameter estimation.

7.2.6.2 Parameter Estimation

The estimation of decay parameters was performed on magnitude images, the noise characteristics of which are well-known to be Rician-distributed (Gudbjartsson and Patz, 1995). It is particularly important to model the Rician noise, given the low SNR regime under which ^{23}Na imaging occurs.

The Rician probability density function is

$$p_{\text{Rician}}(y|A, \sigma) = \frac{y}{\sigma^2} \exp \left[- (y^2 + A^2) / 2\sigma^2 \right] I_0 \left(\frac{Ay}{\sigma^2} \right) \quad (7.5)$$

where I_0 is the 0th-order Bessel function of the first kind; y is the measured data (from a single voxel); and A is the noise-free signal model. The parameter, σ , is the standard deviation of the Gaussian noise in the underlying complex image data.

In zero-signal (noise) regions, that is, $A \rightarrow 0$, the Rician pdf simplifies to a Rayleigh distribution

$$p_{\text{Rayleigh}}(y|\sigma) = \frac{y}{\sigma^2} \exp \left[- (y^2 / 2\sigma^2) \right] \quad (7.6)$$

The Rayleigh mean $\mu = \sigma \sqrt{(\pi/2)}$ is used to estimate σ . It should be noted that half- versus full-projection data collection affects the noise characteristics, leading to a higher noise variance σ^2 in TE_0 compared to the following TE data points. In the estimation process, σ^2 was consequently defined for every TE reconstruction individually.

Let β be the parameter vector of a decay model (bi- or mono-exponential). The maximum likelihood estimator (MLE) approach estimates decay parameters via maximising the likelihood,

$$L(\beta|y, \sigma) = \prod_{i=1}^m p_{\text{Rician}}(y_i | A(TE_i, \beta), \sigma_i^2) \quad (7.7)$$

Here, m is the number of echo measurements and y_i , TE_i , and σ_i the i^{th} measured signal; echo time; and noise variance, respectively. The function $A(\cdot)$ is the biexponential or mono-exponential signal model (Eqs. 7.3 and 7.4), with respective parameter vectors β . It is computationally more efficient to optimise the log-likelihood function,

$$\log L = \sum_{i=1}^m \log \left(\frac{y_i}{\sigma_i^2} \right) - \sum_{i=1}^m \frac{y_i^2 + A(TE_i, \beta)^2}{2\sigma_i^2} + \sum_{i=1}^m \log I_0 \left(\frac{A(TE_i, \beta) y_i}{\sigma_i^2} \right) \quad (7.8)$$

with respect to β

$$\hat{\beta} = \underset{\beta}{\operatorname{argmax}} \log L. \quad (7.9)$$

The maximum-likelihood parameter estimation was implemented in MATLAB (MathWorks) using a constrained nonlinear multivariable solver. Initial conditions for in vivo estimations were based on previously reported values (Madelin et al., 2014) and set to 1.5 ms for $T_{2\text{short}}^*$ and 20 ms for $T_{2\text{long}}^*$. Previous studies of biexponential ^{23}Na decay in 8.9% and 10% agar observed $T_{2\text{short}}$ values of 4.2 ms and 2.7 ms; and $T_{2\text{long}}$ decay of 18 ms and 14.8 ms, respectively (Andrasko, 1974; Boada et al., 1994). Due to lower agar level in this study, slightly longer $T_{2\text{short}}^*$ components are expected, and the estimation process for phantom data thus was initialised at 6 ms and 20 ms for $T_{2\text{short}}^*$ and $T_{2\text{long}}^*$, respectively.

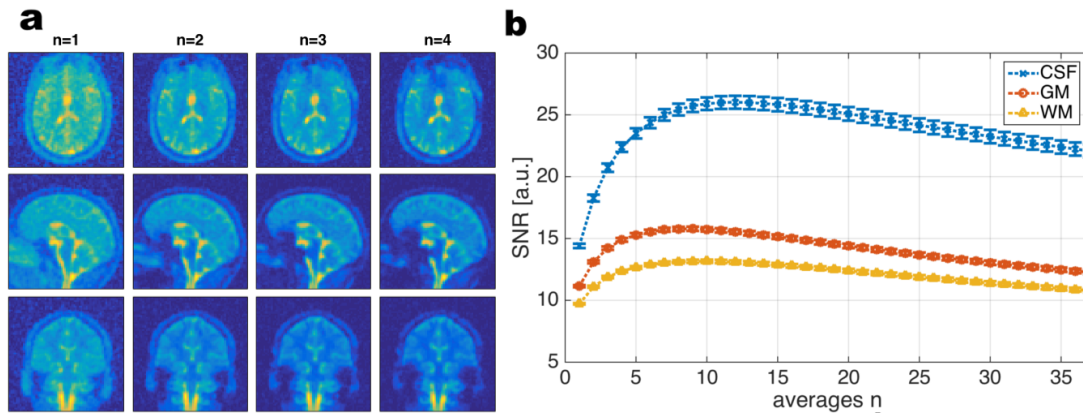


Figure 7.5: (a) Reconstruction of averaged signal over n foremost echoes in vivo. (b) SNR measurements in segmented tissue compartments over n averages. Curves show mean and standard error of SNR across all subjects. Averaging was performed on raw complex k-space data before regridding and image reconstruction. An SNR increase is achieved in all regions of interest for early echo averages, later averaging results decrease in SNR due to low signal in later echoes based on relaxation. Better SNR increase is achieved in fluid regions due to lower relaxation-based signal decrease between echoes. Tissue compartments show most significant gain in SNR for 3 to 4 echo averages. GM, grey matter; SNR, signal-to-noise ratio; WM, white matter.

7.3 Results

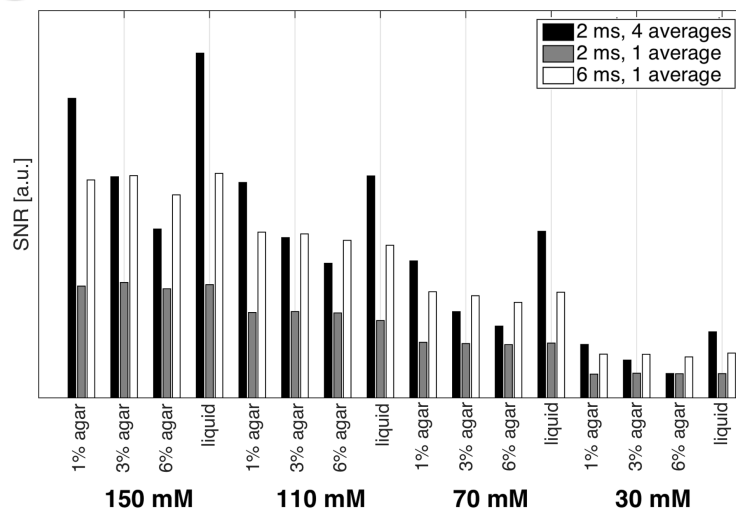
7.3.1 3D-MERINA Readout Duration Optimisation

The effect of T_{RO} on multi-echo acquisition was evaluated experimentally. Phantom experiments for T_{RO} ranging from 1 to 5 ms were performed to identify optimal timing parameters, allowing for rapid multi-echo acquisition while maintaining good SNR characteristics for a subsequent decay analysis.

Figure 7.2 shows normalised signal decays in the central voxel of the 30 mM phantom vials (liquid and 6% agar) for each T_{RO} acquisition. An illustration of signal decays across all saline concentrations and agar level for each T_{RO} can be found in the Appendix (Appendix Fig. 7.A.1). The decay curves show similar results across different T_{RO} . However, the shortest T_{RO} of 1 ms shows an increased noise contribution in the measured signal. Figure 2b illustrates the noise influence in the lowest signal regime (30 mM). The left graph shows the duration of signal with a threshold at double the noise mean ($y_{TE} \leq 2\mu_{noise}$). The right graph displays the corresponding number of echoes that were acquired within that time range. The results show that $T_{RO} \geq 2$ ms detects longer-lasting signal above the noise threshold compared to T_{RO} of 1 ms. Furthermore, a sampling time of 2 ms permits acquisition of a high number of echo samples, particularly in faster decaying environments with higher agar concentrations. Based on these findings, the human in vivo measurements were acquired at an optimised T_{RO} of 2 ms.

Figure 7.3 depicts a series of echo reconstructions from phantom and in vivo measurements acquired at $T_{RO} = 2$ ms. The initial reconstructed image at TE_0 reveals the typically acquired ^{23}Na -density weighted image (Romanzetti et al., 2014; Thulborn et al., 2016). The phantom reconstruction demonstrates that the signal intensities in

Figure 7.6: SNR values within vials of reconstructed images from $T_{RO}=2\text{ms}$ (with and without averaging) and $T_{RO}=6\text{ ms}$. Averaging increases SNR. In fast decaying solutions, longer T_{RO} achieve better SNR than averaging. SNR, signal-to-noise ratio; T_{RO} , readout duration.



the initial echo (TE_0) (Fig. 7.3a, top-left) reflect the ^{23}Na concentration independent of the media, that is, the agar concentration. Subsequent echo images show the expected decrease in signal due to T_2^* relaxation, which reveals a dependency on the underlying structured media. In liquid, the ^{23}Na signal decays slower than ^{23}Na signal in the more solid solutions. Similar characteristics were observed in human in vivo measurements (Fig. 7.3b), with longer-lasting signal in fluid regions (CSF) compared to brain tissue.

7.3.2 Multi-Echo Combination for Image Enhancement

Evidence that the signal decay curves show media- and tissue-specific characteristics is further seen in Figure 7.4b (in vivo) and Appendix Figure 7.A.2 (phantom). Measurements of SNR over tissue regions of interest in the human in vivo data (Fig. 7.4c) underscore this fact; ^{23}Na signal in fluid environments preserves higher SNR for longer, whereas SNR decays quicker in more structured environments. Despite the fast signal decay in tissue, it was found that the measurements in three to four echoes demonstrated signal above noise level in human tissue (dashed line in Fig. 7.4b). This finding was directly translated into an image enhancement technique via averaging (Fig. 7.5a). Figure 7.5b shows measured SNR (mean and standard error) in segmented brain regions over the number of echoes used for averaging, across all subjects. For tissue, it was verified that three to four averages achieved the most significant SNR increase (Appendix Table 7.A.1). As expected, further averaging only provides negligible SNR improvements because the loss of signal at higher echoes penalises averaging results. Due to slower signal decay of fluids, CSF showed a greater and longer-lasting SNR enhancement.

Figure 7.6 compares reconstruction results for single T_{RO} with averaged reconstructions in phantom measurements. Whereas image SNR increases with longer T_{RO} , SNR enhancement can be partly retrieved at lower T_{RO} through averaging. The line profiles show no discernible edge blurring (Appendix Fig. 7.A.3). Due to media-dependent T_2^* decay, intensity values in averaged reconstructions depict a combination of ^{23}Na concentration and T_2^* effects.

7.3.3 Estimation of Parameter Maps

7.3.3.1 Phantom

The result of the MLE in phantom measurements is shown in Figure 7.7a. Mean estimates and corresponding standard deviations within each vial are plotted in Figure 7.7b. In the liquid and 1% agar vial, the estimation results reveal a primarily mono-exponential decay. For more solid environments (3% and 6% agar), $T_{2\text{short}}^*$ components can be differentiated with shorter decay times at higher agar level. The liquid phantom reveals the longest $T_{2\text{long}}^*$ decay; the influence of agar shortens the long component with no obvious dependency on agar concentrations. Although there only is little variance between estimates at higher ^{23}Na concentrations (≤ 70 mM), low ^{23}Na signal-fitting results detect generally lower parameter estimates.

7.3.3.2 In vivo

Figure 7.8a displays the estimated T_2^* decay parameter maps for all subjects. A histogram of estimated values in segmented brain regions is shown in Figure 7.8b, with mean and standard deviations provided in Table 7.1. Both parameter maps allow for a distinction between fluid (CSF) and tissue regions – no $T_{2\text{short}}^*$ decay component was detected in fluid compartments, and $T_{2\text{long}}^*$ decay estimates were higher for fluid than tissue compartments. Although differentiation between CSF and tissue was found, intra-tissue delineation between grey and white matter is indeterminable. Fitting results over a range of initial conditions was found to lead to insignificant variations in decay estimates (± 0.5 ms in $T_{2\text{short}}^*$, ± 2 ms in $T_{2\text{long}}^*$; data not shown).

The two-step estimation procedure described in Methods incorporated the detection of mono-exponential decay through a plausibility check on the $T_{2\text{short}}^*$ estimate. Figure 7.9 shows a binary mask of voxels that were fit as mono-exponential decay (i.e. fluid signal region) compared with the CSF segmentation based on the MP2RAGE ^1H -based acquisition across all subjects. It should be noted that the CSF maps are fractional maps that originate from the interpolation of binary segmentation masks onto the coarser ^{23}Na resolution.

$T_{2\text{short}}^*$ [ms]			$T_{2\text{long}}^*$ [ms]		
CSF	GM	WM	CSF	GM	WM
–	2.02 ± 1.67	1.99 ± 2.09	57.2 ± 6.6	25.9 ± 8.3	22.4 ± 7.8

Table 7.1: In Vivo T_2^* Fitting Results Across Tissue Compartments.

Mean and standard deviation of estimated decay parameters in CSF, grey matter, and white matter across all investigated subjects. GM, grey matter; T_2^* , observed transverse relaxation time; CSF, cerebrospinal fluid; WM, white matter.

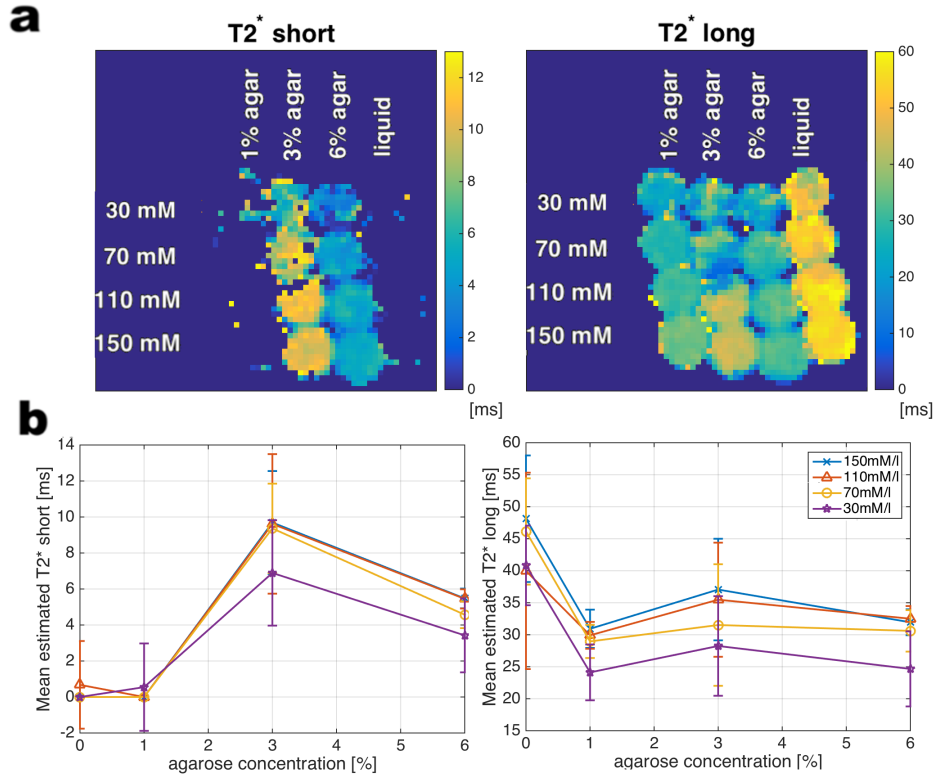


Figure 7.7: (a) T_2^* maps of short and long component in phantom vials. (b) Mean estimates and standard deviation plotted over agar concentration. Colours indicate saline concentrations. $T_{2\text{long}}^*$ maps delineate liquid from agar-doped vials. $T_{2\text{short}}^*$ parameter estimation differentiates higher agar concentrations ($\geq 3\%$). T_2^* , observed transverse relaxation time.

7.4 Discussion

3D-MERINA presents a time-efficient imaging approach that enables the estimation of multiple parameter maps from a single acquisition. The idea of filling vacant ^{23}Na acquisition time with additional imaging has been explored previously; SISTINA (Fiege et al., 2013) as well as phase cycling and gradient selection difference imaging (Benkhedah et al., 2013, 2014) describe methods for the simultaneous acquisition of multiple ^{23}Na images. Their focus lies on the detection of ^{23}Na -density weighted images, together with direct (SISTINA) or indirect (pc/gSDIM) detection of triple quantum coherences, in order to isolate the intracellular ^{23}Na signal. In contrast, our work presents an acquisition scheme that focuses on the signal decay characteristics while also maintaining ^{23}Na -density image contrasts.

^{23}Na -MRI is most applicable to high-field MRI ($\geq 7\text{T}$) given the significant gain in signal strength. However, higher fields are more prone to SAR limitations, often leading to longer TR. In ^{23}Na -density weighted acquisitions, a full relaxation of the longitudinal magnetisation requires a prolonged TR. 3D-MERINA fills this vacant acquisition time through measuring additional signal echoes and reveals more detailed information of macroscopic structures beyond ^{23}Na -density. 3D-MERINA can be used to infer ^{23}Na -density maps (estimated from the initial TE_0 -image), as well as biexponential T_2^* maps (estimated from time series of echoes) in one acquisition protocol. The ad-

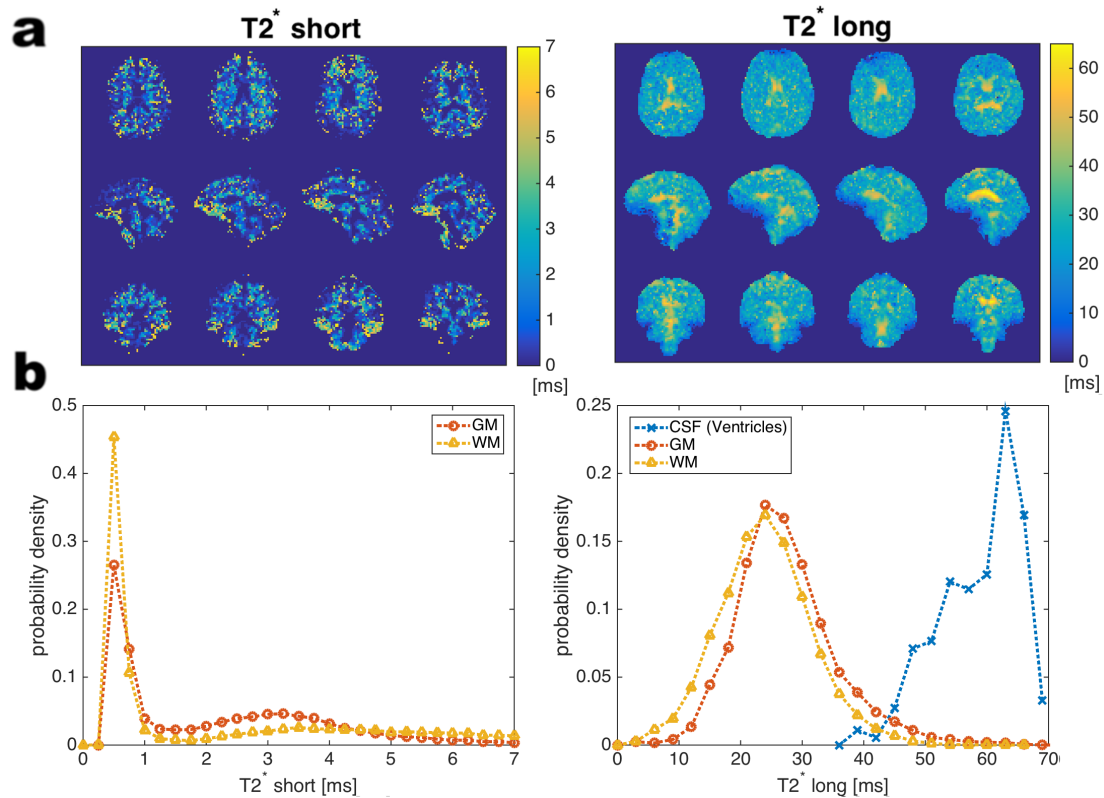


Figure 7.8: (a) T_2^* maps of short and long components across all subjects. (b) Histogram of estimated parameter over segmented brain regions. T_2^* maps show structural information, distinguishing tissue, and fluid ^{23}Na signal areas. $T_{2\text{long}}^*$ estimation results agree with previous studies (Madelin et al., 2014; Bartha and Menon, 2004; Fleysher et al., 2009; Ra et al., 1989). $T_{2\text{short}}^*$ parameter shows spread estimates with increased values in sinus regions. CSF, cerebrospinal fluid; GM, grey matter; T_2^* , observed transverse relaxation time; WM, white matter.

ditional maps come at no cost in scan time and SAR exposure because the imaging protocol times are dictated by ^{23}Na -density weighted conditions, and all imaging is performed with single 90° RF pulses. It should be noted that the total scan time of 26 minutes is based on the choice of TR and the number of measured projections. Although TR is relatively fixed due to the full relaxation constraint, the number of projections remains at the operator's discretion. A low number of projections decreases scan time; however, acquisitions well below the Nyquist sampling condition result in a degradation of image quality. It should be noted that studies with a much lower number of projections showed the possibility of achieving comparable results (Romanzetti et al., 2014).

Given the time range of $T_{2\text{short}}^*$ decay in biological tissue, a fast sampling scheme is crucial for the characterisation of signal decay. Investigations into the effect of T_{RO} on SNR and PSF in 3D radial ^{23}Na -acquisition suggested an optimal sampling time between ≈ 2 to 4 ms in biological tissue (Nagel et al., 2009). The experimental results in this study confirm this finding; although a faster readout of 1 ms facilitates the detection of more echoes, the higher noise disturbances lead to a shortening of high SNR data points (Fig. 7.2).

Our experiment was based on a fixed resolution and FOV and revealed the shortest

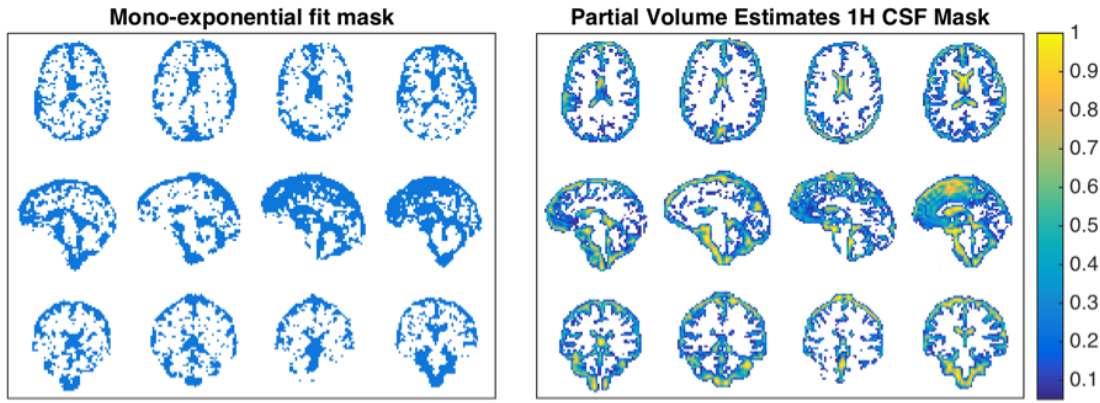


Figure 7.9: Comparison between mono-exponential fit mask of detected fluid ^{23}Na regions and CSF masks obtained from ^1H -MP2RAGE. The estimation of fluid ^{23}Na shows good agreement with fluid CSF regions from ^1H acquisition.

optimal T_{RO} at 2 ms. Although theoretical investigations based on point-source objects suggest an optimised T_{RO} solely based on expected T_2 decay values, common scanning situations with larger objects are expected to show less SNR decrease (Nagel et al., 2009; Rahmer et al., 2006). A reduction in k_{max} , that is, projection length, will aid the detection of faster echoes at the cost of lower image resolution.

Signal averaging for image enhancement showed good SNR improvement in brain tissue when restricting the averaging to early echoes. Under the absence of relaxation-based signal loss, it is well-known that signal averaging provides an increase in image SNR by a factor of $\sqrt{n}$ for n signal averages. Due to the slower relaxation decay, this theoretical SNR improvement is closest achieved in fluid signal regions. However, grey and white matter regions also show a clear improvement in SNR.

Given the relatively low SNR regime of ^{23}Na -MRI, gaining an SNR increase without additional SAR or measurement time is of great value. However, the concomitant increase of SNR in CSF areas may reduce the visual tissue signal gain. Fluid suppression techniques (Stobbe and Beaulieu, 2005) preparing the signal acquisition with a 180° pulse for CSF signal attenuation facilitate a suppression of CSF signal in the measurement process and can help exploit the full potential of tissue SNR enhancement.

It should be noted that alongside hardware components and the imaged object, ^{23}Na -image SNR depends on a variety of factors: sampling efficiency, projection number and image resolution, reconstruction filter, and sampling duration. The final image quality ultimately provides a compromise between resolution and imaging time. Although very short sampling times are required for the detection of biexponential signal decay, short T_{RO} comes at the cost of reduced image SNR. Echo averaging provides a method to regain SNR and achieve comparable image quality, as achieved at longer T_{RO} (Fig. 7.6). Averaging, however, leads to image intensities composed of a combination of ^{23}Na concentration and T_2^* signal decay.

Averaging methods generally may be prone to motion artefacts. However, in a 3D-MERINA acquisition setup, motion effects are minimal because the individual echoes only are separated by T_{RO} (in this study 2 ms), a timeframe in which no discernible motion at the nominal image resolution is expected. Another concern in image aver-

aging lies in the T_2^* blurring that affects later echoes; however, a blurring of edges was not observed in this study (Appendix Fig. 7.A.3) because the optimal SNR improvement was found to be three to four averages. With a T_{RO} of 2 ms, the total acquisition time of 3 to 4 echoes is under 15 ms, and thus below other ^{23}Na acquisition techniques such as twisted projection imaging (TPI) (Boada et al., 1997b; Lu et al., 2010) and 3D Cones (Riemer et al., 2014) commonly using longer sampling trajectories. Imaging in this study was performed with a standard radial sampling scheme. The application of density-adapted trajectories is anticipated to enhance general image SNR and PSF (Nagel et al., 2009; Romanzetti et al., 2014).

A primary strength of 3D-MERINA is that gradient refocused echoes allow for the estimation of T_2^* decays. ^{23}Na -signal in tissue is known to show fast biexponential decay originating from electric field interactions of spins in macromolecular environments. Given the low gyromagnetic ratio of ^{23}Na , T_2^* is expected to be a close correlate for T_2 values. The estimation was performed for short and long T_2^* decay components using a maximum likelihood approach accounting for underlying Rician noise distribution. The resulting parameter maps show good agreement with previously reported values (Berendsen and Edzes, 1973; Perman et al., 1986; Bartha and Menon, 2004; Fleysheer et al., 2009; Ra et al., 1989; Civan and Shporer, 1978). This study captured 38 echoes allowing for a very accurate analysis of underlying noise. The echo spacing was 4 ms. Previous studies on slow T_2^* decay estimation were based on a significantly lower number of recorded echoes: two echoes (Fleysheer et al., 2009) and 10 echoes (Bartha and Menon, 2004) – and mostly higher echo spacing: 25 ms (Fleysheer et al., 2009), and 3.6 ms and 10 ms (Bartha and Menon, 2004). These studies were performed at lower image resolutions, and furthermore required the acquisition of several averages to enhance SNR characteristics.

To our knowledge, this is the first mapping of $T_{2\text{short}}^*$ components in the human brain. Brain tissue short decay components are reported to be of the order of 0.5 to 3 ms. The $T_{2\text{short}}^*$ parameter generally were estimated in this time range. However, close to the sinuses, that is, areas of stronger B_0 inhomogeneities, $T_{2\text{short}}^*$ estimates deviated from the expected range. This is not surprising given that T_2^* in these areas probably is not a close correlate to actual T_2 values.

Although the $T_{2\text{short}}^*$ estimates generally range within expected values (Ra et al., 1989; Madelin et al., 2014), care needs to be taken given the wide distribution of estimates. This is unavoidable, given the low number of measurement points in the very short TE range. More reliable $T_{2\text{short}}^*$ maps require faster T_{RO} to increase the number of data points in the $T_{2\text{short}}^*$ time range. An increase of gradient strength and subsequent reduction of T_{RO} was found to result in poor SNR (Fig. 3). Nevertheless, a decrease in k_{max} would lead to a similar speed up in readout and decrease echo spacing – at the cost of image resolution. A partial readout, as applied in (Bartha and Menon, 2004), can lead to a similar acceleration while maintaining spatial resolution.

In agar-doped solutions, ^{23}Na ions bind to polysaccharide molecules causing slower motion and consequently biexponential signal decay (Andrasko, 1974). The estimated T_2^* short parameter in phantom experiments are in general agreement with previously reported values; $T_{2\text{long}}^*$ estimates are slightly longer than observed previously (Andrasko, 1974; Boada et al., 1994). The variation in parameter estimates even for

$T_{2\text{long}}^*$ results from susceptibility artifacts between vials affecting T_2^* measurements. The estimation process detects fluid and solid environments in the short component mapping, $T_{2\text{long}}^*$ values are higher in fluid environments and decrease in solid media. The effect of lower t_c is less pronounced in the $T_{2\text{long}}^*$ component (Civan and Shporer, 1978), and thus does not show a clear differentiation between agar level.

Despite the agreement of fitting parameter with reported values, it should be noted that biexponential fitting is known to be an ill-posed problem, with lower accuracy and precision at low SNR. Incorporating Rician noise distribution into the estimation process has, however, been shown to give the best performance (Bouhrara et al., 2015).

The initial results in this work have focused on the general mapping of tissue signal decay characteristics. The maximum likelihood estimation process does not account for partial volume effects. Given the relatively coarse resolution in ^{23}Na imaging, a more complete model could include a combination of bi- and mono-exponential decay with fractional volume components. The triexponential model, however, is more difficult to fit robustly.

The two-step estimation process allowed for an inference of fluid signal contributions. The fluid mono-exponential masks showed good agreement with CSF masks obtained from ^1H -acquisitions, demonstrating the potential to infer underlying macroscopic structures. The fitting procedure detected mono-exponential decay even in regions with low (<20%) CSF volume fractions, which suggests a strong sensitivity of the estimation algorithm toward fluid-signal influence.

Difference images for the suppression of fluid ^{23}Na signal were first proposed by Ra et al. (1989). Recent studies of double-echo biexponentially weighted ^{23}Na -MRI (Qian et al., 2015; Benkhedah et al., 2013, 2014) investigated the use of difference imaging approaches to achieve image contrast featuring cellular ^{23}Na component information as achieved through multi-quantum filtered techniques. The use of multi-echo decay data, as demonstrated in this work, enables detailed investigation of such contrast mechanisms.

7.5 Conclusion

This work presents 3D-MERINA, a time-efficient imaging approach for a single acquisition from which multiple parameter maps can be derived. The method will facilitate a detailed investigation of pathologies by enabling a comprehensive investigation of ^{23}Na MR-signal properties, from ^{23}Na -density to signal decay characteristics providing insight into slow (tissue) and fast (fluid) motion regimes.

Appendix

	n=1	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9
CSF	14.4 ± 0.18	18.3 ± 0.28	20.7 ± 0.38	22.4 ± 0.38	23.5 ± 0.41	24.4 ± 0.44	25.0 ± 0.46	25.4 ± 0.48	25.7 ± 0.5
Gain [%]	–	27.1	43.8	55.6	63.2	69.4	73.6	76.4	78.5
GM	11.1 ± 0.09	13.1 ± 0.12	14.2 ± 0.14	14.9 ± 0.15	15.3 ± 0.16	15.5 ± 0.17	15.7 ± 0.17	15.8 ± 0.17	15.8 ± 0.18
Gain [%]	–	18.0	27.9	34.2	37.8	39.6	41.4	42.3	42.3
WM	9.7 ± 0.05	11.1 ± 0.08	11.9 ± 0.09	12.4 ± 0.1	12.7 ± 0.11	12.9 ± 0.12	13.0 ± 0.12	13.1 ± 0.12	13.2 ± 0.13
Gain [%]	–	14.4	22.7	27.3	30.9	32.9	34.0	35.0	36.1
Brain tissue	10.5 ± 0.07	12.2 ± 0.1	13.2 ± 0.12	14.1 ± 0.13	14.3 ± 0.13	14.5 ± 0.14	14.6 ± 0.15	14.6 ± 0.15	14.6 ± 0.15
Gain [%]	–	16.2	25.7	34.3	36.2	38.1	39.0	39.0	39.0

Table 7.A.1: SNR in averaged in vivo reconstructions across tissue compartments. Mean SNR values and standard error in segmented tissue compartments and overall brain tissue for n echo averages and percentage SNR increase compared with single TE_0 reconstruction.

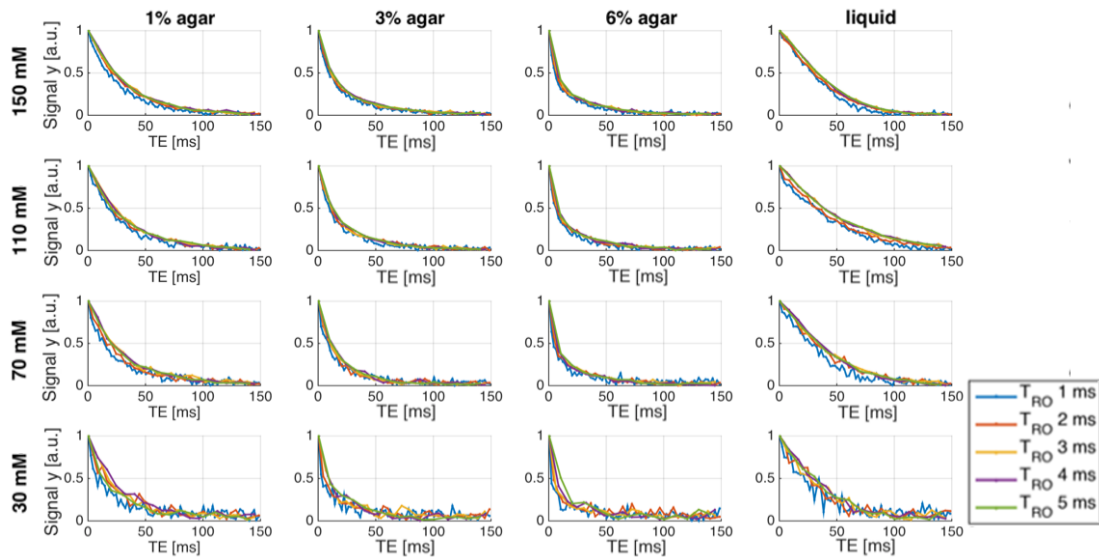


Figure 7.A.1: Magnitude signal from the central voxel of each vial in phantom experiments. Diagram rows showing concentration, columns indicating media. Curves plot signal decay measured at T_{RO} ranging from 1-5 ms. T_{RO} of 1 ms (blue) shows stronger noise contribution.

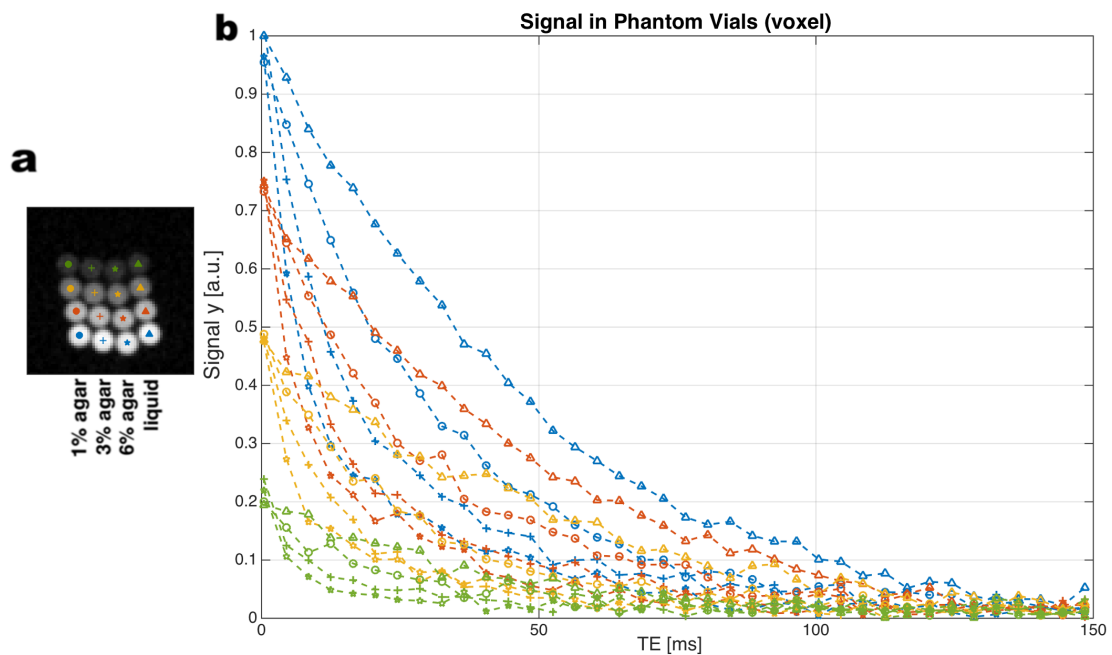


Figure 7.A.2: Signal evolution over echo reconstructions in Phantom. (a) TE_0 image of phantom indicating locations of plotted voxel decays. (b) Decay curves – markers distinguish agar level; colors indicate saline concentration – show distinct decay characteristics, with faster decreasing signal in more solid media (cross, pentagon). Initial signal intensities depend on saline concentrations.

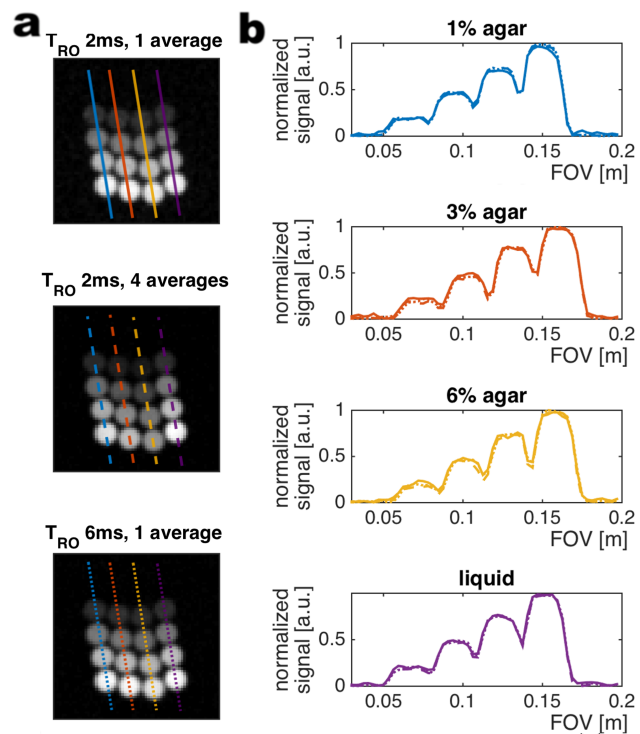


Figure 7.A.3: (a) Reconstructed images from $T_{RO} 2 = ms$ (with and without averaging) and $T_{RO} = 6 ms$. (b) Normalised line profiles along lines indicated in (a). Profiles show strong overlap. No disturbances in edge characteristics are observable.

Over the last four decades, Magnetic Resonance Imaging has developed into a highly versatile non-invasive imaging technique with an ever-increasing range of flexible image contrasts enabling unprecedented high-resolution anatomical images as well as the inference of additional information like diffusion, perfusion and functional activity. It has transformed medical practice, playing an integral role in diagnosis and treatment planning. The significant activity within the research community further emphasises the ongoing potential of this imaging technique.

Hydrogen protons have been the nucleus of choice for standard MRI applications with mostly descriptive interpretation focusing on tissue contrasts and signal appearance. For a better standardisation of image interpretation, a consortium of medical professionals, researchers and industrial partners recently pushed for a paradigm shift away from the ‘imaging device’ and towards a ‘measuring device’ that provides quantitative imaging biomarkers (Kessler et al., 2015). However, the indirect link of hydrogen protons to biochemical processes render it a rather unspecific correlate to various pathologies and make the quantitative assessment of traditional MRI inherently challenging.

X-Nuclei MRI, and in particular Sodium MRI with its significant role in a multitude of biochemical processes, could greatly enhance the medical diagnostic and therapy planning possibilities. Its direct link to cell integrity and tissue viability enables a specific interpretation of Sodium MRI acquisitions. Quantification of its signal entails biochemical dimensions, i.e. metabolic parameter with direct physiological meaning. With an appropriate measurement protocol, Sodium MRI can be interpreted as a clinical biomarker and as such extend and complement current imaging techniques.

Sodium MRI comes with great potential but also similarly significant challenges. On the downside, the clinical use of Sodium MRI is predominantly hampered by its low signal-to-noise ratio and challenging signal characteristics. These two aspects have been the predominant focus of recent developments in Sodium MRI and were also the key focus within this thesis. In the following, the novel contributions of this work will be summarised and will be proceeded by suggestions for future research.

8.1 Thesis Contribution

This work has been concerned with three main aspects of MRI: signal acquisition, signal reconstruction and signal analysis. The main contributions shall be briefly recapitulated in the following:

Chapter 5 – Signal Acquisition The fast decaying Sodium NMR-signal dictates the general acquisition scheme principle constituted by a non-selective rectangular hard-pulse and non-Cartesian sampling schemes. With these constraints in place, recent developments of Sodium MRI acquisition methods predominantly focused on the optimisation of sampling patterns for an amelioration of point spread function characteristics and enhancement of SNR. In this work, the new sequence timing approach zG_{RF} -RHE was introduced. It tackles the rapid signal decay problem by an optimisation of encoding time. The suggested method aims to approach zTE sequence timing conditions while adhering to excitation constraints that result from the low in-vivo concentrations of Sodium which necessitate high flip angle acquisition. The proposed hybrid imaging approach is akin to PETRA but sits on the opposite side of the RHE sequence scheme spectrum and closes the signal sampling inefficiency gap resulting from the dead-time delay. It improves encoding time in k-space irrespective of the chosen readout bandwidth, i.e. gradient strength. This work showed that the reduced encoding time mitigates signal decay effects during acquisition and provides a modest improvement to image SNR. The current investigation was based on a radial sampling scheme. The introduced zG_{RF} -RHE timing concept is, however, not limited to a particular sampling pattern and can be utilised in combination with any centre-out readout trajectory.

Chapter 6 – Signal Reconstruction Iterative reconstruction schemes facilitate the inclusion of additional information during image calculation. This can be utilised to advance image quality, but has also been shown to enable a good image reconstruction from undersampled data and hence provides a great potential for a reduction of data acquisition time. This concept known as Compressed Sensing received much recent attention in many MRI applications. The use of CS in x-Nuclei MRI has however been limited due to its lower SNR regime which affects the applicability of CS-based reconstructions. Furthermore, iterative reconstruction schemes influence noise characteristics in the image and consequently bias the very valuable quantitative aspect of x-Nuclei MRI. The biasing side effect has been reported for Sodium MRI ([Madelin et al., 2012a](#)) but so far has not been investigated in detail. This work delved into a comprehensive analysis of radially acquired and undersampled CS reconstructions in Sodium MRI of the human brain. The investigation encompassed a wide range of undersampling factors and investigated the influence of different regularisation terms and weightings on the reconstruction results. The analysis was driven by an interest in parameter optimisation with an eye towards signal intensity bias which affects quantitative parameter. It was found that, with an appropriate regularisation and weighting, reconstruction results resembled standard NUFFT images from four times higher sampled data with negligible effect on structural intensity values. The denoising effect of iterative reconstructions is, however, prone to bias quantitative assessments and consequently the background signal should

not be incorporated as a zero concentration marker in the estimation of Sodium contents.

Chapter 7 – Signal Analysis The complex NMR-signal properties of spin-3/2 systems like Sodium are challenging and mesmerising at the same time. In comparison with standard proton-based acquisitions, Sodium MRI stands out in terms of signal information content. Its decay characteristics provide potential for a deeper analysis of underlying spin environments. The investigation of these signal properties has been a central interest in recent Sodium MRI research. In Chapter 7, 3D-MERINA, a sequence scheme for the radial acquisition of gradient-refocused echoes, has been presented. The quadrupolar interactions are known to influence the energy splitting and consequently affect the observable signal decay. Within this thesis, a two-step maximum likelihood estimation procedure was implemented which estimated the transverse signal decay times incorporating the Rician noise bias from low SNR data. Based on a plausibility check, a differentiation between bi- and mono-exponential decay was possible and showed great agreement with proton-based CSF masks. These findings suggest that further structural information are obtainable from the characteristic NMR-signal of Sodium spins-3/2. Notably, these parameter maps can be acquired ‘for free’ by filling vacant imaging time during a standard density-weighted acquisition.

In a nutshell, the presented work addresses challenges of Sodium MRI via 1) an optimisation of sequence timing for an enhancement of image quality and 2) the potential for a reduction of acquisition time via a comprehensive study of Compressed Sensing reconstruction methods. Furthermore, this thesis explored the rich information content of Sodium MRI signal via a time-efficient imaging approach that supports the inference of signal decay parameter maps during a standard Sodium-density weighted acquisition. Together these findings push Sodium MRI closer to the translational goal of clinical application.

8.2 Future Research

The ultimate goal of medical-related imaging research lies in its introduction to clinical routine. Sodium MRI with its biomarker potential is of interest for a variety of diseases and body organs. Nevertheless, its challenging acquisition has so far significantly limited its clinical applicability. Technological advancements, in particular the ongoing move towards higher field strengths ($\geq 7\text{T}$) will, however, greatly help to improve image quality issues arising from inherently low concentrations and render x-Nuclei imaging in general and Sodium MRI in particular increasingly feasible.

The clinical applicability of Sodium MRI presents the biggest driver for future research and ongoing development. One major constraint towards clinical routine lies in the extended acquisition times. Compressed Sensing reconstructions as investigated in this thesis provide a relatively straightforward approach for a reduction of measurement time but need to be handled with care and are limited in the achievable undersampling factors. The recent advent of machine-learning algorithms and in

particular Deep Neural Networks has lead to a wide investigation of its use in MRI. Especially its application in image reconstruction (including strongly undersampled acquisitions) has recently shown very promising results and should be investigated for its use in low SNR applications like Sodium MRI (Zhu et al., 2018).

Since its development only a few decades ago, proton-based MRI has turned into a cornerstone of medical diagnosis and therapy. Sodium MRI cannot aim at replacing this highly versatile imaging paradigm and is more to be considered as a complementary information source for a better fine-tuning of diagnosis based on a metabolic correlate. Time-efficiency is a key aspect in clinical routine and has been addressed in 3D-MERINA via the filling of vacant scan time. Aiming at the complementing aspect of Sodium MRI, the time efficiency could also be explored via interleaved acquisitions as it has been suggested by Bruin et al. (2015) and greatly increase measurement time use and efficiency.

The research in this thesis was driven from a methods point of view. In the long run, any novel method, however, needs to prove its ultimate utility and applicability in pathologies. With this in mind, next steps of future research should clearly focus on the application of the suggested methods across diseases with associated Sodium imbalances. In particular, the information arising from altered signal decay characteristics should be investigated. The high information content of Sodium MRI needs to be linked with a biological basis. While the density-weighted acquisition with appropriately set up reference vials is known to yield Sodium concentration values with biochemical dimension, extracting the more interesting parameter of intracellular Sodium concentration is still controversial. It is suggested that cellular environments affect the quadrupolar interaction of Sodium spin and consequently alter its signal decay (Rooney and Springer, 1991). Approaches that try to infer intra-cellular Sodium concentrations from relaxation characteristics (inversion recovery (Stobbe and Beaulieu, 2005) and Triple Quantum Filtering (Fiege et al., 2013)) should be compared to the information obtainable from transverse relaxation estimates.

The estimation of parameter maps particularly at low SNR is challenging. Robustness and specificity of estimates is, however, essential for a reliable and reproducible result in clinical application and research. Current work investigates the further optimisation of echo spacing for a reduced variability in signal parameter estimates (Lommen et al., 2018). Enhanced estimation methods can furthermore greatly improve estimation robustness (Syeda et al., 2018).

Overall, Sodium MRI is an imaging technique with a great potential to complement imaging-based diagnosis and therapy planning as well as monitoring. With the continuous development of measurement techniques as well as technological advancements, it has the capacity to grow from a clinical research tool to a device for healthcare with clinically feasible acquisition protocols and acceptable image quality. Its physiological reference suggests promising insight for currently unmet clinical questions.

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