Accelerating MR Neuroimaging of Stroke Using Sparse Acquisition Coupled with Nonlinear Reconstruction Techniques

Yerly, Jerome

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Accelerating MR Neuroimaging of Stroke Using Sparse Acquisition Coupled with Nonlinear Reconstruction Techniques

by

Jérôme Yerly

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE
DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF ELECTRICAL AND COMPUTER ENGINEERING

CALGARY, ALBERTA

JUNE, 2013

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Abstract

The guiding theme of my research is to accelerate and improve magnetic resonance (MR) imaging such that it becomes the clinical modality of choice in diagnosing, treating, and hopefully preventing stroke. Stroke, be it ischemic or haemorrhagic, is a leading cause of death and permanent disability worldwide: it is a medical emergency that requires rapid diagnosis to initiate early patient treatment and prevent irreversible brain injury. Computed tomography (CT) is currently the preferred imaging modality due to its high spatial and temporal resolution. MR imaging is a slower technique than CT, but it offers a significantly broader and more varied set of image contrasts and functional information than CT. Simply stated, the goal of my research is to accelerate the MR acquisition and/or increase resolution without sacrificing image quality in order to provide high quality diagnostic information.

The most obvious way to scan faster is to acquire fewer data points, although this can often yield undesired reductions in image quality such as blurring, aliasing, or ghosting artefacts. Fortunately, numerous recent developments using multiple channel receiver coils and advanced reconstruction techniques are overcoming these drawbacks. This doctoral thesis investigates many of these advanced signal acquisition and processing techniques as they apply to stroke. In terms of diagnosis, I compare several state-of-the-art paradigms to accelerate key sequences of an acute MR stroke protocol. For treatment, I describe an enhanced passive MR catheter tracking approach that enables continuous monitoring of the catheter during endovascular procedures. And finally, with regards to stroke prevention, I present a novel imaging technique for assessing atherosclerosis in carotid arteries. In all cases, numerical and experimental verifications provided diagnostic images of very high quality (and comparable to conventional MR scans), albeit
acquired 2 to 6 times faster. This work and continued efforts worldwide are inching us closer to making MR imaging the modality of choice in the comprehensive management of acute stroke patients.
Acknowledgements

I would like to take the opportunity to thank all the people that assisted and supported me throughout the last few years of my life to embark on this academic adventure. It would not have been possible to write this doctoral thesis without the help and support of the many kind people around me, to only some of whom it is possible to give particular mention here.

My first debt of gratitude goes to my principal advisor Dr. Richard Frayne. I am thankful to him for giving me the opportunity to work in his lab and for the continuous support throughout my PhD study and research. Richard has given me the tools, means, guidance, and freedom to pursue my research directions. In addition to leading a highly competitive research team, he has also created a very friendly research environment. The many extracurricular activities that he organizes play an important role in the group dynamic. I thank Richard for promoting such a stimulating and welcoming academic and social environment.

I would like to extend my sincere gratitude to my co-supervisor and friend Dr. M. Louis Lauzon. Louis has been my principal mentor and an invaluable source of knowledge and support. His understanding of MR physics, programming languages, and physiology were key to the success of my research. His door was always open and, no matter how busy he was, he always had the patience to answer all of my questions. His ability to explain complex concepts in a way that anyone can understand has always amazed me. I also thank Louis for the hours spent rigorously editing my papers, abstracts, and thesis. His time and effort significantly improved my scientific writing.
I would like to thank all members of my advisory committee for their advice and encouragement throughout my research and for accepting to sit on my examination committee. Particular thanks go to Dr. Robert J. Sevick with whom I have collaborated on several studies presented in this thesis. I also have been fortunate to travel and attend a few conferences with him.

The Seaman Family MR Research Centre (SFMRC) has been a unique and exciting place, mostly because of the people working there. I would like to thank the many former and current members of the SFMRC who contributed to make my time ever more enjoyable and from which I have learned so much. I am particularly grateful to my fellow students Mari E. Boesen and M. Ethan MacDonald for all the time they spent with me discussing various problems and the fruitful collaborations that resulted from it.

I also want to thank Dr. R. Marc Lebel for the many constructive insights he contributed to my research. Marc and I share an enthusiasm for image reconstruction and I have learned so much from our many engaging discussions. I wish he had interacted with our research group earlier, as his knowledge would have been an asset to my research.

I could never have come to Canada without the initial support from the “École d'ingénieurs et d'architectes de Fribourg” and more specifically Dr. Ottar Johnsen. In addition to teaching me the basics of signal processing, Ottar helped me to initiate contacts with the University of Calgary, which ultimately led me to where I am today.

While living in Calgary, I have been very fortunate to meet so many good friends who made this city feel like home. I would like to expressly thank Mireille Tittle-Elmer, Wolfgang Tittel, Mark Taylor, Dave Peabody, Raphael Slawinski and Anthony Pascuzzo for getting me out of the office and sharing many amazing climbing adventures in the spectacular Canadian Rockies with me.
These extra-scholastic activities kept me grounded and sane, and have significantly contributed to the quality of my experience in Canada. I would also like to particularly thank Liana and Henri who have been a family to me. They have tremendously influenced my life and I will forever be thankful for all the wonderful moments we have shared.

My deepest thanks go to my parents, Philippe and Marguerite, my brother, Cédric, and my sister, Corine, for their unconditional love and support. They always encouraged me and provided me with the means to pursue the future I want, even when it meant to let me move far away from them. I could not have done any of this without them. Finally, I want to thank my niece, Léa, and nephews, Thomas and Bastien, who have been a real sunshine in my life.

On a less personal note, I would like to acknowledge financial support for all of the research presented herein. Operational funding was provided by the Canadian Institutes for Health Research, the Natural Sciences and Engineering Research Council of Canada and the Hopewell Professorship in Brain Imaging. During my PhD I was the recipient of salary and research funding from the Alberta Heritage Foundation for Medical Research, iCORE, and the Heart and Stroke Foundation of Canada.
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List of Mathematical Symbols

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<td>$\alpha$</td>
<td>Nutation flip angle</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Tikhonov regularization parameter</td>
</tr>
<tr>
<td>$\Delta$</td>
<td>Voxel size $\Delta = (\Delta x, \Delta y, \Delta z)$</td>
</tr>
<tr>
<td>$\Delta k$</td>
<td>Sample spacing in k-space $\Delta k = (\Delta k_x, \Delta k_y, \Delta k_z)$</td>
</tr>
<tr>
<td>$\nabla$</td>
<td>Gradient operator</td>
</tr>
<tr>
<td>$\nabla \cdot$</td>
<td>Divergence operator</td>
</tr>
<tr>
<td>$\nabla \times$</td>
<td>Curl operator</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Random variable, noise</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Gyromagnetic ratio</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>Lagrange regularization parameter</td>
</tr>
<tr>
<td>$\Lambda$</td>
<td>Noise covariance matrix</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Intrinsic magnetic moment of a spin-$\frac{1}{2}$</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Proton density</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Phase</td>
</tr>
<tr>
<td>$|^\bot$</td>
<td>Comb/sampling function</td>
</tr>
<tr>
<td>$\Psi$</td>
<td>Sparsifying transform operator</td>
</tr>
<tr>
<td>$\omega_0$</td>
<td>Larmor frequency</td>
</tr>
<tr>
<td>$A$</td>
<td>Intensity/amplitude correction matrix</td>
</tr>
<tr>
<td>$B$</td>
<td>Magnetic field vector $B = (B_x, B_y, B_z)$</td>
</tr>
<tr>
<td>$B_0$</td>
<td>Static magnetic field strength pointing in the z-direction</td>
</tr>
<tr>
<td>$C$</td>
<td>Coil sensitivity matrix</td>
</tr>
<tr>
<td>$c_l$</td>
<td>Detection sensitivity of the $l$-th receiver coil</td>
</tr>
<tr>
<td>$D$</td>
<td>Density correction matrix</td>
</tr>
<tr>
<td>$E$</td>
<td>Sensitivity encoding matrix</td>
</tr>
<tr>
<td>ecc</td>
<td>Eccentricity</td>
</tr>
<tr>
<td>$\mathcal{F}$</td>
<td>Fourier transform operator</td>
</tr>
<tr>
<td>$F$</td>
<td>Fourier transform operator expressed in matrix form</td>
</tr>
<tr>
<td>$F_u$</td>
<td>Undersampled Fourier transform operator expressed in matrix form</td>
</tr>
<tr>
<td>$f_{\text{max}}$</td>
<td>Maximum frequency of a bandlimited signal</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>$f_s$</td>
<td>Sampling frequency</td>
</tr>
<tr>
<td>$\mathbf{G}$</td>
<td>Spatial encoding gradient field $\mathbf{G} = (G_x, G_y, G_z)$</td>
</tr>
<tr>
<td>$i$</td>
<td>Imaginary unit $i = \sqrt{-1}$</td>
</tr>
<tr>
<td>$i, j, k$</td>
<td>Unit vectors of the Cartesian coordinate system along the $x$-, $y$-, and $z$-directions</td>
</tr>
<tr>
<td>$\mathbf{J}$</td>
<td>Angular momentum of a spin ($\frac{1}{2}$ for $^1$H proton)</td>
</tr>
<tr>
<td>$\mathbf{k}$</td>
<td>Encoding position in $k$-space (Fourier space)</td>
</tr>
<tr>
<td>$k_{\text{ext}}$</td>
<td>Extent of $k$-space</td>
</tr>
<tr>
<td>$\mathbf{K}_k$</td>
<td>Neighbourhood selection operator for SPIRiT</td>
</tr>
<tr>
<td>$\mathbf{R}_k$</td>
<td>Neighbourhood selection operator for GRAPPA</td>
</tr>
<tr>
<td>$L$</td>
<td>Number of coil elements</td>
</tr>
<tr>
<td>$\mathbf{m}$</td>
<td>Image in vector form</td>
</tr>
<tr>
<td>$\mathbf{M}$</td>
<td>Net magnetization vector $\mathbf{M} = (M_x, M_y, M_z)$</td>
</tr>
<tr>
<td>$M_0$</td>
<td>Thermal equilibrium magnetization</td>
</tr>
<tr>
<td>$M_z^0$</td>
<td>Longitudinal magnetization just after an RF pulse</td>
</tr>
<tr>
<td>$M_{z,ss}$</td>
<td>Steady-state longitudinal magnetization</td>
</tr>
<tr>
<td>$M_{xy}^0$</td>
<td>Transverse magnetization just after an RF pulse</td>
</tr>
<tr>
<td>$\mathbf{M}_{xy}$</td>
<td>Transverse magnetization $\mathbf{M}_{xy} = (M_x, M_y)$</td>
</tr>
<tr>
<td>$\mathbf{r}$</td>
<td>Position vector $\mathbf{r} = (x, y, z)$</td>
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<tr>
<td>$R$</td>
<td>Undersampling or acceleration factor</td>
</tr>
<tr>
<td>$s$</td>
<td>$k$-space coefficients in vector form</td>
</tr>
<tr>
<td>$\mathbf{U}$</td>
<td>Undersampling operator (i.e., extract sampled coordinates)</td>
</tr>
<tr>
<td>$\mathbf{w}$</td>
<td>Transform coefficients or GRAPPA/SPIRiT weights</td>
</tr>
<tr>
<td>$\mathbf{W}$</td>
<td>GRAPPA weights expressed as a series of convolution operators</td>
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<td>Two-dimensional space</td>
</tr>
<tr>
<td>3D</td>
<td>Three-dimensional space</td>
</tr>
<tr>
<td>ACA</td>
<td>Anterior cerebral artery</td>
</tr>
<tr>
<td>A/D</td>
<td>Analog to digital converter</td>
</tr>
<tr>
<td>AP</td>
<td>Anterior-posterior</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>RBW</td>
<td>Receiver bandwidth</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CINE</td>
<td>Retrospective imaging (GE terminology)</td>
</tr>
<tr>
<td>CNR</td>
<td>Contrast-to-noise ratio</td>
</tr>
<tr>
<td>CS</td>
<td>Compressed sensing</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CS-SENSE</td>
<td>Sequential combination of CS and SENSE</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed tomography angiography</td>
</tr>
<tr>
<td>CWBR</td>
<td>Catheter width broadening ratio</td>
</tr>
<tr>
<td>DCT</td>
<td>Discrete cosine transform</td>
</tr>
<tr>
<td>DTPA</td>
<td>Diethylene triamine pentaacetic acid</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion weighted imaging</td>
</tr>
<tr>
<td>EMF</td>
<td>Electromotive force</td>
</tr>
<tr>
<td>EPI</td>
<td>Echo planar imaging</td>
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<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
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<tr>
<td>FFT</td>
<td>Fast Fourier transform</td>
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<tr>
<td>FLAIR</td>
<td>Fluid attenuated inversion recovery</td>
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<tr>
<td>FMC</td>
<td>Foothills Medical Centre</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of view</td>
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<td>FSE</td>
<td>Fast spin echo</td>
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<td>FSPGR</td>
<td>Fast spoiled gradient-recalled echo</td>
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<td>FT</td>
<td>Fourier transform</td>
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<td>Abbreviation</td>
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<tr>
<td>FWHA</td>
<td>Full-width at half amplitude</td>
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<tr>
<td>Gd</td>
<td>Gadolinium</td>
</tr>
<tr>
<td>GE</td>
<td>General Electric</td>
</tr>
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<td>GM</td>
<td>Gray matter</td>
</tr>
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<td>GPE</td>
<td>Global performance error</td>
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<td>GRAPPA</td>
<td>Generalized autocalibrating partially parallel acquisitions</td>
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<td>GRE</td>
<td>Gradient-recalled echo</td>
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<tr>
<td>&quot;1&quot;H</td>
<td>Hydrogen atom</td>
</tr>
<tr>
<td>IA</td>
<td>Intra-arterial</td>
</tr>
<tr>
<td>IA-tPA</td>
<td>Intra-arterial injection of tissue plasminogen activator</td>
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<tr>
<td>ICH</td>
<td>Intracerebral haemorrhage</td>
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<tr>
<td>iFT</td>
<td>Inverse Fourier transform</td>
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<td>INR</td>
<td>International normalized ratio</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<td>IV-tPA</td>
<td>Intravenous injection of tissue plasminogen activator</td>
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<td>L1-SPIRiT</td>
<td>L1 constrained SPIRiT</td>
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<td>LPE</td>
<td>Local performance error</td>
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<td>LR</td>
<td>Left-right</td>
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<td>ODE</td>
<td>Ordinary differential equation</td>
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<td>MCA</td>
<td>Middle cerebral artery</td>
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<tr>
<td>mcPD</td>
<td>Multicycle projection dephaser</td>
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<tr>
<td>MIP</td>
<td>Maximum intensity projection</td>
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<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>MRA</td>
<td>Magnetic resonance angiography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NCCT</td>
<td>Non-contrast computed tomography</td>
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<tr>
<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
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<tr>
<td>NRMSE</td>
<td>Normalized root-mean-square error</td>
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<td>NUFFT</td>
<td>Non-uniform fast Fourier transform</td>
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<td>PCA</td>
<td>Posterior cerebral artery</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>PC-TERA</td>
<td>Phase-constrained TERA</td>
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<tr>
<td>PD</td>
<td>Projection dephaser, or Poisson-disk sampling</td>
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<tr>
<td>PDF</td>
<td>Probability density function</td>
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<tr>
<td>POCS</td>
<td>Projection onto convex sets</td>
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<td>PSF</td>
<td>Point spread function</td>
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<td>PWI</td>
<td>Perfusion weighted imaging</td>
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<td>RF</td>
<td>Radio frequency</td>
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<tr>
<td>RIP</td>
<td>Restricted isometry property</td>
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<tr>
<td>RMSE</td>
<td>Root-mean-square error</td>
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<td>ROI</td>
<td>Region of interest</td>
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<tr>
<td>SENSE</td>
<td>Sensitivity encoding</td>
</tr>
<tr>
<td>SI</td>
<td>Superior-inferior</td>
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<tr>
<td>SMASH</td>
<td>Simultaneous acquisition of spatial harmonics</td>
</tr>
<tr>
<td>SND</td>
<td>Signal-to-noise difference</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal-to-noise ratio</td>
</tr>
<tr>
<td>Sparse SENSE</td>
<td>Merged combination of CS and SENSE</td>
</tr>
<tr>
<td>SPGRE</td>
<td>Spoiled gradient-recalled echo</td>
</tr>
<tr>
<td>SPIRiT</td>
<td>Iterative self-consistent parallel imaging reconstruction from arbitrary k-space</td>
</tr>
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<td>SWI</td>
<td>Susceptibility weighted imaging</td>
</tr>
<tr>
<td>$T_1$</td>
<td>Longitudinal relaxation time constant</td>
</tr>
<tr>
<td>$T_2$</td>
<td>Transverse relaxation time constant</td>
</tr>
<tr>
<td>TE</td>
<td>Echo time</td>
</tr>
<tr>
<td>TERA</td>
<td>Transient error reconstruction algorithm</td>
</tr>
<tr>
<td>TOF</td>
<td>Time-of-flight</td>
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<tr>
<td>tPA</td>
<td>Tissue plasminogen activator</td>
</tr>
<tr>
<td>TPSF</td>
<td>Transform point spread function</td>
</tr>
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<td>TR</td>
<td>Repetition time</td>
</tr>
<tr>
<td>TV</td>
<td>Total variation</td>
</tr>
<tr>
<td>Uni</td>
<td>Uniform sampling</td>
</tr>
<tr>
<td>VD</td>
<td>Stochastic variable density sampling</td>
</tr>
<tr>
<td>WM</td>
<td>White matter</td>
</tr>
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<td>Abbreviation</td>
<td>Definition</td>
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<td>----------------------------------</td>
</tr>
<tr>
<td>WT</td>
<td>Wavelet transform</td>
</tr>
<tr>
<td>ZF</td>
<td>Zero filling reconstruction method</td>
</tr>
<tr>
<td>ZF-DC</td>
<td>Zero filling with density compensation</td>
</tr>
</tbody>
</table>
Epigraph

“The more we study, the more we discover our ignorance.”

— Percy Bysshe Shelley
Chapter One: Introduction

This doctoral thesis investigates advanced signal acquisition and processing techniques and their application to accelerating magnetic resonance (MR) imaging and more specifically neuroimaging methods. MR imaging is based on the physical phenomenon of nuclear magnetic resonance (NMR), which was first observed by Isidor Isaac Rabi (1) in 1938. While at Columbia University, he developed a molecular beam technique for measuring the magnetic characteristics of atomic nuclei and was awarded the 1944 Noble Prize in Physics for his groundbreaking discovery. Whereas Rabi’s work resulted in a molecular beam method for magnetic resonance detection in gas, Felix Bloch (2) at Stanford and Edward Purcell (3) at Harvard were the first to observe the NMR phenomenon in liquids and solids. For their pioneering discoveries they were jointly awarded the 1952 Nobel Prize in Physics. Following these breakthroughs, the NMR phenomenon rapidly became a powerful tool to study the molecular structure of materials.

It was not until 1973 that Paul Lauterbur first demonstrated the application of NMR for the formation of MR images (4). This new imaging technique was originally called zeugmatography (from the Greek: zeugma, to join, and graphein, to record); reflecting the joining of magnetic field gradients and spatially defined radiofrequency fields to generate an image. Along with Lauterbur, Peter Mansfield played a key role in developing the fundamentals of MR imaging (5). They both shared the 2003 Nobel Prize in Physiology and Medicine for their achievements. Lauterbur was recognized for his insight of using magnetic field gradients to perform spatial localization, whereas Mansfield was credited with the foundation of the mathematical formalism and development of efficient gradient utilization for fast imaging. Following these and other breakthroughs, numerous advancements over the last 40 years have dramatically improved the
quality and speed of MR imaging. These developments have revolutionized diagnostic medicine. The first commercial hospital-based (or clinical) MR scanner was introduced in 1980 (6).

Nowadays, MR scanners are used extensively to image anatomical and functional information throughout the whole body. Computed tomography (CT) is another common imaging modality that produces cross-sectional images with higher spatial and temporal resolution than MR. However, MR imaging can potentially provide more diagnostic medical information than CT. It offers numerous types of image contrasts and can measure functional and physiological changes, such as brain oxygen saturation due to neuronal activity (7), diffusion of water molecules (8), blood flow velocity (9), liver iron content (10), temperature (11, 12), and concentration of metabolites (13). In addition, unlike CT, MR imaging produces non-invasive, high-quality diagnostic images without the use of potentially harmful ionizing X-ray radiation (14).

However, the wider application of MR imaging is partially limited by the data acquisition time. MR imaging techniques would greatly benefit from accelerated acquisition and reconstruction techniques. The first body MR image was performed in 1977 and took 4 h and 45 min to acquire (15). Many advances have since significantly reduced the scan time of MR imaging, but further improvement are still necessary. Nowadays, a typical MR scan of a brain varies between five and ten minutes and requires the subject to remain perfectly still to avoid image degradations, known as image artefacts. Such a requirement can be difficult to achieve for certain populations like young children, elderly, and patients experiencing chronic or acute pain. Furthermore, MR imaging protocols typically include multiple scans causing exams to commonly last over 30 min to 45 min in duration.
Some protocols are currently too time consuming to be clinically viable. For example, the diagnosis of patients with acute ischemic stroke (16) is one clinical challenge that would benefit from faster imaging. Acute ischemic stroke already uses advanced neuroimaging protocols that are valuable tools to rule out haemorrhagic stroke and estimate the ischemic penumbra (17), a key concept in ischemic stroke physiology. For these patients, prompt diagnosis is vital to initiate early treatment and minimize irreversible brain damage. Current comprehensive protocols are, however, somewhat lengthy and this precludes their widespread use in the routine evaluation of stroke patients. Accelerating neuroimaging techniques could impact the design of fast diagnosis and treatment protocols for acute ischemic stroke patients.

A number of other medical imaging applications would also benefit from accelerated MR imaging, particularly those that need to image dynamic phenomena in three dimensions, including cardiac imaging, dynamic functional imaging, contrast-enhanced MR imaging, and MR-guided catheter-based therapy. All of these applications require a fast image acquisition in order to observe the evolution of the process under investigation. Faster imaging can also provide high-resolution scans by accelerating otherwise prohibitively long acquisitions.

Another important consideration in favour of accelerating MR imaging is its financial aspect. Although some of the costs are fixed regardless of the length of the scan, the associated cost per hour with MR imaging is expensive, and reducing the examination time could have significant impact on its financial burden to health care.
Finally, the limited access to resources due to the relatively small number of available scanners is another major incentive to accelerate MR imaging. Shorter examination time means that more patients could be scanned, thus reducing the wait time.

Improving acquisition speed has been a major area of research focus ever since the first clinical utilization of MR imaging. Initially, much effort went into improving MR hardware and developing fast pulse sequences that optimize scanning trajectories to collect the raw data. Physical and physiological constraints, however, limit the rate at which we can encode the data using spatially varying magnetic fields, since rapid switching of magnetic fields can induce currents in the subject and cause nerve stimulation (18). These fundamental limits have now led researchers to investigate different approaches to reduce the amount of acquired data without degrading image quality.

Recent efforts have focused on methods based on the fact that MR data are redundant or compressible, and that the underlying image may be extracted from fewer measurements than traditionally considered necessary. In some cases, exact reconstruction is possible from vastly undersampled data.

In fact, multiple sources of redundancy can be (and have been) exploited in MR imaging. Parallel MR imaging uses multiple receivers to measure the signal emitted from the subject and uses this redundancy along with the inherent spatial sensitivity of each receiver element to recover complete images from fewer samples. Many parallel imaging reconstruction techniques have been proposed to resolve the ambiguity arising from undersampling. Some reconstructions explicitly use the spatial sensitivity (19), whereas others have recourse to calibration procedures,
which implicitly rely on the sensitivities (20-22). Parallel imaging has gained tremendous popularity in the MR community and has significantly impacted medical imaging. Several of these techniques are commercially available and routinely used in clinical settings. These methods, however, enable only modest acceleration factors. In theory, the number of coil elements limits the maximum achievable acceleration. Practically, however, accelerations rarely exceed rates of 2× and 4×, beyond which image degradations become clinically unacceptable.

More recently, new methods that exploit other sources of redundancy have emerged. In dynamic imaging, adjacent temporal frames are highly correlated and reconstruction methods can efficiently exploit temporal correlation to reduce the number of acquired data per frame (23, 24). Other methods use data redundancy from the image itself. One particular technique that proved potentially valuable in MR imaging is compressed sensing (CS) (25, 26), also known as compressive sampling. CS was developed based on the premise that all images, including MR images, are compressible with almost no visual compression artefacts, i.e., blocky artefacts such as in JPEG. CS takes advantage of the compressibility or sparsity of the image representation in an appropriate transform domain where the information is concentrated in a few coefficients. While image compression is mostly thought of as a post-processing procedure, CS implicitly compresses the data by acquiring fewer incoherent measurements and enforcing data sparsity in the appropriate transform domain. This sparsity model has enabled modest acceleration factors that depend on the sparsity of the transform coefficients.

Whereas parallel imaging techniques rely on the spatial sensitivity information inherent in an array of multiple receiver surface coils to recover unsampled information, CS reconstructions
rely on *a priori* knowledge (or expectation) of data sparsity in a given domain. These two approaches effectively use complementary information to recover the complete image. Thus, combining them may enable high quality reconstructions from data collected with even greater undersampling factors (22, 27).

My guiding, overarching hypothesis in this research is that combining accelerated acquisition techniques with advanced reconstruction algorithms will significantly reduce the scan time (specifically in neuroimaging) while preserving image quality and spatial resolution. The overall objective of my research is to evaluate the synergy between combinations of modern acquisition and reconstruction strategies in order to accelerate MR imaging, where I use stroke as the underlying motivation. More specifically, I seek to accelerate imaging sequences that can potentially impact prevention, diagnosis and treatment of acute ischemic stroke.

**1.1 Thesis Outline**

This thesis is organized in eight chapters. Chapter 2 provides a brief overview of the clinical background relevant to the work presented in this study. Its main focus is on the physiological and pathophysiological concepts underlying ischemic stroke. After briefly reviewing the normal anatomy and physiology of the brain and arteries, I introduce atherosclerosis (a vascular disease) and stroke, and provide a cursory overview of the current clinical treatments for these diseases. Finally, I illustrate the role of imaging for the diagnosis and treatment of stroke patients by presenting a clinical case.

Chapter 3 presents the technical background underlying the work presented in this thesis. It begins with a basic introduction of MR physics providing sufficient background to understand
the nature of the data acquired in the so-called k-space or Fourier domain. I then introduce a general approach to accelerate MR imaging via undersampling of k-space and present several state-of-the-art reconstruction methods.

Modern treatments of stroke patients can involve minimally invasive endovascular interventions that rely on catheters to deliver thrombolytic drugs directly at the location of the blood clot or to physically remove the blood clot. In Chapter 4, I present a passive MR catheter tracking approach that enables continuous monitoring of the progression of the catheter within the vasculature. The use of CS significantly improves the temporal resolution of MR imaging and enables real-time acquisition of catheter tracking data.

Chapter 5 presents an early attempt of applying CS to visualize small intracranial arteries. For that particular study, acceleration was used to improve image resolution without increasing acquisition time. Despite acquiring and reconstructing high-resolution images, our approach did not reliably depict the small vessels. These inconclusive results led us to investigate different reconstruction techniques.

In Chapter 6, I focus more directly on neuroimaging for stroke assessment. I investigate and compare several state-of-the-art acquisition and reconstruction techniques to accelerate key sequences of the acute MR stroke protocol. I demonstrate that reconstructions combining parallel imaging with CS outperform individual reconstructions.

Next, I deal specifically with time-of-flight (TOF) MR angiography, which is central to stroke assessment. Capitalizing on our work of Chapter 6, Chapter 7 investigates the quality of
prospectively accelerated TOF images using a combination of parallel imaging and CS in a highly time constrained environment to acquire clinically relevant images in about 30 s per slab. I show that the improved resolution available via accelerated TOF approaches provides more details of cerebral vasculature compared to the fully sampled approach collected over the same time interval.

Finally, in Chapter 8, I summarize the contributions of my work to accelerate neuroimaging and stroke imaging more specifically, and provide some insights to possible future research directions. I introduce a spatiotemporal reconstruction that exploits both spatial and temporal correlation to improve image and dynamic resolutions and present a clinical application to characterize the vessel wall over the course of the cardiac cycle. I present some very promising preliminary results, which provides valuable insights and directions for future work. The developed reconstruction has formed a component of another student’s thesis research.

In the appendices, I provide general background information about mathematical optimization techniques relevant to the research presented herein. I also introduce the MR imaging physics of TOF angiography that is used extensively throughout this thesis.

1.2 Contributions

The work presented in this thesis is the result of ongoing efforts and collaborations with a team of research scientists at the Seaman Family MR Research Centre at the Foothills Medical Centre. My principal collaborators (and co-authors on published and presented work) include Dr. Richard Frayne, Dr. M. Louis Lauzon, Dr. Robert J. Sevick, Dr. R. Marc Lebel, Mari E. Boesen, and Chen Henry. Dr. Frayne has provided general guidance and direction to my research. Dr.
Lauzon has provided me with technical and theoretical support, and implemented the greater part of the pulse programming. Dr. Sevick performed the qualitative analysis presented in Chapter 6. Dr. Lebel shared some of his optimized code that significantly sped up my reconstructions presented in Chapter 7. Chen and Boesen acquired the data presented in Chapters 4 and 8, respectively. Otherwise, I was the lead investigator for all contributions presented within this dissertation. My role has been to develop and implement all the reconstructions, acquire and process the data, analyze and interpret the results, and finally present and publish these results.

At the time of writing this thesis, I am the first author on 16 peer-reviewed conference proceedings that have been presented to several international (28-38) and national (39-43) conferences, including 9 oral (28-32, 39-42) and 7 poster (33-38, 43) presentations. Two conference proceedings in 2013 (28, 33) have received the International Society for Magnetic Resonance in Medicine (ISMRM) Magna Cum Laude Merit Award and I have been the recipient of the Award of Excellence for Trainee Presentation at the 2012 Workshop on the Mathematics of Brain Imaging (39). Fruitful collaboration with my colleagues has resulted to date in an additional 9 conference proceedings (44-52) and one journal publication (53) as coauthor.

Chapters four to seven of this thesis have been written with the intent to be published as manuscripts. Because of the adoption of a paper-based thesis format, some chapters may repeat previously presented concepts and issues. Chapter 4 was published in the Journal of Magnetic Resonance in Medicine (54), Chapter 6 was recently submitted for publication in Magnetic Resonance Imaging, and Chapter 7 is in preparation for submission to the Journal of Magnetic Resonance in Medicine.
Chapter Two: **Clinical Background and Literature Review**

This chapter introduces some of the fundamental physiological and pathophysiological concepts underlying the work in this thesis. I first review the normal anatomy and physiology of the brain and arteries, then present atherosclerosis and stroke, and provide a cursory description of the current clinical treatments for these diseases. The next paragraphs will discuss the relevance of this chapter to the work in this thesis.

Briefly stated, the formation of atherosclerosis occurs when fatty material accumulates in the walls of the arteries and forms hard structures called plaques. These plaques can rupture and may cause stroke and/or myocardial infarction. The structure and composition of plaques have been identified as key indicators of plaque vulnerability. Imaging methods able to characterize plaque compositions may improve our understanding of disease etiology and progression as well as provide a tool to better diagnose patients with a high risk of stroke. In the Future Work section of Chapter 8, I present preliminary results of a time-resolved imaging technique for dynamic carotid wall imaging.

One of the most common clinical outcomes of ruptured plaques is ischemic stroke, *i.e.*, occlusion of an artery. This restriction in blood flow can potentially result in irreversible brain injuries if not treated quickly. Among other factors, the extent of the injuries depends on the severity of ischemia as well as its duration. Therefore, prompt diagnosis and appropriate therapeutic response are critical. Imaging stroke patients should ideally provide a full anatomical, vascular, and functional stroke assessment. Current MR imaging stroke protocols can successfully assess stroke patients, but they are lengthy and slower than gold standard CT protocols. To partially
address this drawback, Chapter 6 provides a comparison of state-of-the-art MR reconstruction techniques to accelerate MR imaging.

Treatments of stroke patients often require the use of catheters to deliver thrombolytic drugs directly at the location of the blood clot or to physically remove the blood clot (i.e., thrombectomy). To navigate the catheter through the vascular system, it is necessary to track the catheter progress in real-time. Chapter 4 presents a passive MR catheter tracking approach that enables continuous monitoring of the catheter during endovascular procedures.

This chapter ends with the presentation about a clinical case of an acute ischemic stroke patient that presented at the Foothills Medical Centre in Calgary with severe symptoms. This example illustrates the use of imaging in the care of stroke patients and serves to highlight the requirements on MR imaging to compete with CT for the diagnosis and treatment of stroke patients.

2.1 Human Brain Physiology

Normal brain function requires constant blood supply to deliver oxygen, glucose, and other nutrients, and to remove carbon dioxide, lactic acid, and other metabolic by-products. The four major arteries responsible for supplying blood to the head are, the right and left common carotid arteries, and the right and left vertebral arteries.

The common carotid arteries separate into the external and internal carotid arteries: The external carotid arteries supply blood to the face and scalp, whereas the internal carotid arteries, along with the vertebral arteries, supply blood to the whole brain. These four feeding arteries are
connected through the Circle of Willis, which forms a redundant network. If one of the arteries becomes occluded, the Circle of Willis can redirect the blood flow from the other arteries (i.e., collateral circulation) to preserve sufficient cerebral perfusion and avoid ischemia.

From the Circle of Willis, six main arteries supply blood to the different parts of the brain: The left and right anterior (ACA), the middle (MCA), and the posterior (PCA) cerebral arteries (Figure 2.1). Occlusion of any of the arteries feeding blood to the brain results in a stroke (see section 2.3.2).

Other feeding arteries of interest in this thesis are the lenticulostriate arteries. These small penetrating arteries branch from the MCA and feed blood to the deep brain structures, such as the basal ganglia. Occlusions of lenticulostriates are common in elderly population and are referred to as lacunar strokes (see section 2.3.2.2).

A healthy brain consumes about 20% and 25% of the total oxygen and glucose used by the entire body at rest, respectively. Of the oxygen consumption in the brain, most of it (about 60%) is used to support neuronal electrical activity (55, 56). The brain requires about 50 mL of oxygen and 75 mg of glucose per minute to maintain its metabolism. To sustain such metabolic rate and oxygen demands, the brain requires about 750 mL to 1000 mL of oxygenated blood per min (mL/min), or an average of about 50 mL/min of blood per 100 g of brain tissue (55). Approximately 15% of the resting cardiac output is necessary to deliver this amount of oxygen, glucose, and other nutrients to the brain. The cerebral blood flow (CBF), however, is not homogeneous and varies with tissue type and location. The average CBF in gray matter is 60 mL/100 g/min, while the CBF in white matter is estimated to be 22 mL/100 g/min (57, 58).
Figure 2.1: Vascular anatomy of the human brain. The main arteries of interest in this thesis are the anterior cerebral arteries (ACA), middle cerebral arteries (MCA), posterior cerebral arteries (PCA), and lenticulostriate arteries. From reference (59).
These numbers highlight the complex homeostasis of brain physiology. The key message here is that the high demand of oxygen combined with the inability to store sufficient energy reserves makes the brain highly vulnerable to disruption of cerebral perfusion (60).

2.2 Artery Physiology
Arteries are muscular tubes that expand and contract as they carry oxygenated blood away from the heart. To sustain the high systolic pressure, arteries are composed of three layers (tunica): intima, media, and adventitia (Figure 2.2).

The intima is the innermost layer, which is composed of endothelial cells supported by an elastic membrane called the internal elastic lamina. The endothelium has a smooth surface to reduce blood flow turbulence and acts as a semi-selective barrier. It controls the exchange of materials with the white blood cells and regulates vascular homeostasis to maintain normal vascular tone (contraction), blood fluidity, and to limit vascular inflammation (61). In addition, the endothelium provides a non-thrombogenic surface that prevents blood from clotting (62). The internal elastic lamina is a layer of elastic tissue that forms the barrier between the intima layer and the media layer.

The media is the middle layer and thickest layer in arteries. It is composed of smooth muscle cells, elastin, collagen, and other extracellular components (63). The smooth muscle cells can contract (vasoconstriction) or relax (vasodilatation) to control blood flow in response to physiological stimuli. These muscles control autoregulation of blood supply and maintain the blood flow within a narrow range.
Figure 2.2: Structure of normal muscular artery composed of three layers: Intima, media, and adventitia. From reference (64).

The adventitia is the outermost layer of the blood vessel. It is made up of small nerves, collagen, elastic fibers and connective tissue. It also contains capillaries to supply the blood vessel itself with blood. The connective tissue forms a protective coat over the other layers and helps attach the vessel to surrounding tissue, such as muscles.

2.3 Cardiovascular Disease

Cardiovascular disease refers to any disorder related to the cardiovascular system such as the heart or blood vessels. In 2008, it was responsible for 29% of all deaths in Canada, or about
69500 deaths (65). The two most common forms of the disease include coronary heart disease and cerebrovascular disease (i.e., stroke). Of all cardiovascular deaths in Canada in 2008, 77% were due to ischemic heart disease and 20% to stroke (65). These numbers alone highlight the burden of cardiovascular disease on society.

Atherosclerosis is the most common underlying cause for the disease. It is a clinical condition that occurs when fatty materials accumulate in the walls of the arteries and form hard structures called plaques. The next sections describe atherosclerosis and the two important and related cardiovascular diseases: stroke and lacunar stroke.

### 2.3.1 Atherosclerosis Pathophysiology

Atherosclerosis is a progressive disease characterized by abnormal fatty deposits within the walls of arteries (i.e., atheroma) and abnormal hardening of the arteries (i.e., sclerosis). Figure 2.3 shows the progression of the disease (66). The early atherosclerotic lesions manifest as fatty streaks due to the accumulation of lipid-filled macrophages (foam cells) in the intimal layer of the artery. These fatty streaks are asymptomatic, but they are precursors of more advanced lesions called atheroma or plaques. Plaques have a fibrous cap that encloses the lipid-rich core of the atheroma (66) (Figure 2.4).

It has been observed that atherosclerotic lesions usually form at specific arterial sites (67, 68). The preferred sites of formation appear to depend on hemodynamic factors such as flow velocity and shear stress (68-70). The lesions develop mainly in regions of low or disturbed blood flow, such as at bends and bifurcations in the arterial tree (71). These sites experience low shear stress on the vessel wall, which affects the morphology of the endothelial cells (72). When exposed to
laminar flow, the cell shape is ellipsoid and aligned with flow direction, whereas in regions of perturbed flow, they have polygonal shapes and no preferred alignment. This polygonal arrangement is more permeable to lipid and, therefore, facilitates undesired plaque formation (73).

Figure 2.3: Progression of atherosclerosis lesions. In early stages of the disease, lipid-filled macrophages called foam cells accumulate in the intimal layer of the artery. The fibrous cap enclosing the lipid-rich core characterizes the vulnerability of the lesion. Unstable plaques usually have a thin fibrous cap with a large lipid pool and many inflammatory cells, whereas stable plaques have a thick fibrous cap with a small lipid pool. Adapted from (66).
Figure 2.4: Histology of a section of an advanced human atherosclerotic lesion in the coronary artery. The sample was immunostained for the macrophage-specific antigen EMB-11 (red). The cross-section shows the (A) adventitia, (M) media, (IEL) internal elastic lamina, (I) intima, core, cap, and shoulder of the plaque, which is the most prone location for ruptures. From reference (72).

Plaques can be broadly dichotomized as stable or unstable (70, 74). Unstable plaques are also called vulnerable plaques. The pathophysiology of these lesions is very complex, but stable plaques are generally rich in extracellular matrix and smooth muscle cells, and have an intact and thick fibrous cap. By comparison, unstable plaques are rich in foam cells, have a large lipid core, and generally have a thin fibrous cap (72, 75, 76).

A plaque can grow sufficiently large to block an artery, however, clinical complications are most often the result of thrombosis associated with the rupture of plaques (72). When a plaque ruptures, the lipid-rich core comes in contact with the blood and more specifically the coagulation cells called platelets. The platelets react with the plaque substance and cause the blood to coagulate, i.e., to induce thrombus formation. The thrombus may eventually grow so
much as to occlude the artery. However, it most often detaches and circulates downstream until it occludes a smaller distal branch causing thromboembolism. Common clinical outcomes of such events include stroke and myocardial infarction.

2.3.2 Stroke

Stroke is one of the major causes of permanent disability and death in North America (77, 78). There are over 50,000 strokes annually in Canada and over 11,000 of them are deadly (65, 78). This cerebrovascular accident is characterized by the rapid loss of brain function due to the disturbance of blood supply to the brain. There are many subtypes of stroke (79), but the disturbance usually results either from bleeding (i.e., haemorrhagic stroke) or blockage (i.e., ischemic stroke) of a blood vessel. Of all strokes in Canada, approximately 20% of them are haemorrhagic and 80% are ischemic (78). Haemorrhagic stroke often results from the rupture of an aneurysm at the base of the brain, whereas ischemic stroke can be caused by thrombosis (i.e., blockage by a blood clot forming locally), embolism (i.e., blockage due to an embolus originating from elsewhere), or systemic hypoperfusion. The thrombus or embolus is usually the result of a ruptured atherosclerotic plaque.

2.3.2.1 Ischemic Stroke Pathophysiology

In the event of a stroke, the affected part of the brain may become hypoperfused, i.e., cerebral blood flow (CBF) is less than the average value of 50 mL/100 g/min, which initiates an ischemic cascade that can potentially lead to irreversible injuries (60, 80). The extent of the injuries depends on the severity of ischemia as well as its duration. The lack of oxygen and nutrients associated with ischemia disturbs the brain’s metabolism and electrical function of the cells.
Ischemia inhibits production of high-energy phosphate compounds, like adenosine triphosphate (ATP), which are used for energy transfer in cell metabolism (60). This failure to transport ATP-dependent ion results in swelling of endothelial cells within minutes of hypoxia, i.e., cytotoxic edema (81). If hypoxia persists, the cellular membrane breaks down (i.e., permeability increases). This results in increased extracellular fluid volume, i.e., vasogenic edema (81).

Animal and human studies suggest that there are three important CBF thresholds, namely, the normal, penumbral, and infarction thresholds (82-84). Based on these thresholds, the hypoperfused regions of the brain are identified as oligaemia, penumbra, and ischemic core regions (Figure 2.5)(85, 86). The oligaemia is a slightly hypoperfused region with normal cerebral function. The oligaemic tissue will survive and continue to function in spite of the small reduction in blood flow. The penumbra region corresponds to brain tissue with CBF values below the penumbral threshold of 20 mL/100 g/min in white matter (80, 85). In this significantly hypoperfused region, cytotoxic edema begins to develop within minutes to hours. While the cytotoxic edema is reversible, if not treated quickly by restoring blood flow, vasogenic edema develops over hours to days. Vasogenic edema is considered an irreversible damaging process and causes the penumbra tissue to gradually die (i.e., ischemic necrosis). The ischemic core is the region of tissue with flow rates below the infarction threshold of 6 to 10 mL/100 g/min in white matter (85). The core tissue will suffer irreversible injury and will inevitably die.

The CBF thresholds are dynamic processes that depend on the duration and severity of ischemia (Figure 2.6) (82). When local CBF falls below the penumbral threshold, the disturbances in brain metabolism are potentially reversible if reperfused quickly. Even severe ischemia is reversible
but only for a short period of time. When the CBF falls below the infarction threshold of about 10 mL/100 g/min for at least 2 h, or below the penumbral threshold of about 20 mL/100 g/min permanently, the tissue suffers irreversible infarction (see Figure 2.6). Unlike muscle and other tissues, the human brain does not tolerate extended anaerobic (i.e., cellular respiration without oxygen) condition (60, 80, 87). In the extreme case of complete blood flow disruption, consciousness may be lost in as little as ten seconds and an interruption of just a few minutes may cause irreversible injuries (88).

Figure 2.5: Illustration of the ischemic regions involved in acute stroke. The core region (irreversibly infarcted tissue) is surrounded by the penumbra region (salvageable tissue in early phase of acute ischemic stroke) and the oligaemia region (slightly hypoperfused tissue but functionally intact). The arrows represent the dynamic expansion of the core regions into the penumbra region if recanalization is not performed quickly enough. Modified from The Internet Stroke Centre at www.strokecenter.org.
Figure 2.6: Relationship between cerebral blood flow (CBF), time, functional impairment (i.e., paralysis), and infarction. The area between the penumbral and infarction thresholds is a graphical representation of the penumbra, an area of brain that is functionally inactive but structurally intact and potentially salvageable if reperfused rapidly. From reference (82).

The CBF region between the penumbral threshold and infarction threshold in Figure 2.6 is a graphical representation of the penumbra. The concept of ischemic penumbra is important as it represents the part of brain that is functionally inactive, but structurally intact and potentially salvageable if reperfused rapidly. Imaging the penumbra has been a hot topic of research for several years (85, 89-94).

Reducing the time between the stroke onset and patient treatment is of great importance in order to save the penumbra tissue. Therefore, prompt diagnosis and appropriate therapeutic response are critical. Imaging stroke patients should ideally provide a full anatomical, vascular, and
functional stroke assessment. Current MR imaging stroke protocols, while they may produce more diagnostic information, are often lengthier than clinically accepted CT protocols. To partially address this drawback, Chapter 6 provides a comparison of state-of-the-art MR reconstruction techniques to accelerate MR imaging.

2.3.2.2 Lacunar Stroke

Lacunar strokes account for about 28% of all ischemic strokes (95). It is a condition that results from the occlusion of one of the small penetrating arteries that provides blood to the deep brain structures. These small arteries typically branch off the large arteries arising from the circle of Willis, including the middle cerebral artery, anterior cerebral artery, posterior cerebral artery, posterior communicating artery, and basilar arteries.

Using histopathological techniques, Fisher (96, 97) observed that the most frequent cause of vascular occlusion for arteries with diameters ranging from 400 µm to 900 µm was atherosclerosis. For arteries with diameter less than 200 µm, the main cause of vascular occlusion was lipohyalinosis (a segmental arteriolar wall disorganization characterized by vessel wall thickening). The infarct caused by the occlusion of one of the penetrating artery leaves behind a small lacuna or “empty” space. Most of these occlusions occur in small vessels with diameters less than 600 µm and cause no noticeable symptoms, i.e., silent strokes. But over time, the number of infarcts adds up and can lead to memory loss, confusion, and other signs of dementia.

Studies show that patients with lacunar infarcts are 4 to 12 times more likely to suffer from dementia than the normal population (98). Because dementia is a progressive disease and its
symptoms depend on the location, it is difficult to define and diagnose. In addition, the size of these small vessels makes them difficult to image using MR imaging. Chapter 5 presents an attempt at imaging the lenticulostriate arteries using a 3.0 T MR scanner.

2.4 Clinical Management of Acute Ischemic Stroke Patients

The dynamic evolution of the infarction threshold illustrated in Figure 2.6 guides the current clinical management of patients with acute ischemic stroke. The primary goal of patient treatment is to quickly restore the cerebral blood flow in the penumbra in order to salvage the ischemic brain tissue. The treatment must be initiated within a few hours of the stroke onset to be effective. The three main emergency treatments for stroke are thrombolytic drugs, endovascular procedures, and surgical procedures.

2.4.1 Thrombolytic Drugs

Thrombolysis uses tissue plasminogen activator (tPA) to dissolve blood clots or thrombus. The drug can be administered intravenously (IV) or by local intra-arterial (IA) injection using catheters. Based on the positive outcomes of the NINDS trial (99), the US Food and Drug Administration (FDA) approved IV-tPA for the treatment of acute ischemic stroke patient within 3 h of the onset of symptoms. IV-tPA was also approved by Health Canada for the treatment of acute ischemic stroke. Recent studies, however, have shown that IV-tPA could be effective past its operative time window of 3 h (100, 101). In contrast to IV-tPA, IA-tPA is not currently FDA or Health Canada approved despite evidence of the benefit of the procedure (102, 103).

Thrombolysis via IV-tPA has the advantage of being relatively easy and fast to administer. It does not require technical expertise or highly specialized equipment. However, the drug diffuses
through the whole cardiovascular system and, therefore, requires high doses, which increases the risk of intracerebral haemorrhage (ICH) (103). In contrast, IA-tPA uses microcatheter techniques to administer the thrombolytic drug directly into the thrombus. It requires lower doses and provides faster and more efficient recanalization, while reducing the risk of ICH (103). For these reasons, the treatment window for IA-tPA can be extended beyond the typical 3 h window of IV-tPA (103).

2.4.2 Mechanical Endovascular Procedures
Mechanical intra-arterial endovascular approaches use catheters to access the occlusion site and retrieve the thrombus. The most common techniques include endovascular thrombectomy (thrombus retrieval using snare-like devices) (104-106), endovascular thromboaspiration (suction of the thrombus) (107-109), and thrombus entrapment (angioplasty/stent placement) (110-112). These methods have several advantages over the pharmacological approaches: They generally require less thrombolytic drugs, which reduces the risk of ICH, and they extend the treatment window beyond the limit of 3 h (103). They may also provide faster recanalization and be more efficient at coping with material resistant to drugs. However, the disadvantages of these techniques include the risk of distal embolization due to broken fragments of the thrombus.

Figure 2.7 illustrates a carotid artery angioplasty procedure with stent placement. After confirming the location of the narrowed artery via imaging (Ultrasound, CT, or MRI), the interventional radiologist advances a guide wire with a collapsed balloon to the location of the narrowing usually via a puncture in the femoral artery (Figure 2.7b). A filter called embolic protection device may also be inserted to prevent distal embolization by catching fragments that
may break off during the procedure. Once in place, the balloon is inflated and deflated to crush the plaque and widen the lumen of the artery where the blood flows (Figure 2.7c). A stent may then be placed to ensure that the vessel remains open.

Figure 2.7: Illustration of a carotid artery angioplasty procedure with stent placement. The carotid bifurcation is one of the most common sites of plaque formation (a). The endovascular device is inserted via a puncture in the femoral artery at the level of the groin and guided through the body to the location of the plaque (b). A balloon is inflated to crush the plaque and widen the vessel lumen (c). A stent is placed to keep the vessel open (d). From reference (113).

2.4.3 Catheter Guiding for Endovascular Procedures

Both IA-tPA and mechanical endovascular procedures require navigating a catheter through the vascular system to the site of occlusion. The major disadvantages of catheter navigation include its complexity and level of required technical expertise. If not manipulated carefully, the catheter
can cause important trauma to the vasculature, potentially leading to vessel perforation. Therefore, navigation requires real-time imaging of the position and orientation of the device. Currently, CT is the imaging modality of choice for catheter tracking. However, in Chapter 4, we present a potential solution to guide catheters using MR imaging.

2.4.4 Surgical Procedures

Endarterectomy is a surgical procedure to remove the plaque blocking an artery, such as the femoral artery, abdominal aorta, or carotid artery. Based on the results of three major prospective trials (114-116), it is widely used on the carotid artery as a preventive procedure to reduce the risk of stroke in patients with carotid stenosis greater than 70%. It has been shown that carotid endarterectomy procedure is safer than carotid stenting, while providing similar mid-term stroke prevention (117).

2.5 Exemplar Clinical Case

Clinical management of acute stroke patients is highly time sensitive and follows a well-established protocol. To illustrate this point, here I report a clinical case of a 65-year-old male who had a sudden-onset left-sided weakness at 9h20 and arrived at the Foothills Medical Centre (FMC) at 11h20 (Figure 2.8a). The patient underwent a rapid neurologic examination and was diagnosed with a National Institutes of Health Stroke Scale (NIHSS) (118) of 20, indicating a severe stroke. At 11h40, i.e., just 20 min after arriving at the hospital, the patient received a non-contrast CT (NCCT) of the brain. The images showed an otherwise healthy brain and ruled out any haemorrhage, but revealed a large blood clot in the patient’s right middle cerebral artery (MCA) (arrow in Figure 2.8b). Shortly after, at 11h52, the diagnosis was confirmed with a CT
angiogram that shows a missing right middle cerebral artery (MCA) (Figure 2.8c). The presence of contrast agent past the thrombus attests to the existence of good collateral flow, which helps to maintain viability of brain tissue. The patient was immediately enrolled for intensive medical endovascular therapy to retrieve the blood clot.

At 11h55, the neurointerventionalist punctured the patient’s femoral artery to insert the guide wire and navigated the device to the location of the thrombus. At 12h01, a first run of contrast agent was released, which clearly showed a complete obstruction of the blood vessel (Figure 2.8d). At 12h12, the stent was in place and the surgeon started retrieving the thrombus (Figure 2.8e). Some contrast agent could already be seen past the thrombus indicating early recanalization of blood flow. The blood supply was fully restored at 12h36 as show in Figure 2.8f and the patient completely recovered by 13h00 (NIHSS = 0). Figure 2.8g shows the substantial thrombus retrieved from the patient’s MCA.

This clinical case illustrates an ideal example where rapid management, diagnosis, and treatment yielded the best possible outcome for the patient. Complete recanalization was achieved in less than 1.25 h after the patient was admitted at the FMC. For MR imaging to compete with CT, it needs to offer similar levels of timely performance. Although MR imaging can potentially provide superior anatomical and functional information than CT, the acquisition time is currently the main bottleneck. This thesis focuses on addressing this limitation by accelerating several imaging sequences used for the diagnosis and treatment of stroke patients. More specifically, I investigate modern acquisition and reconstruction techniques to provide full anatomical,
Stroke onset

9h20

11h20

11h40

11h52

11h55

12h01

12h12

12h36

13h00

Arrived at FMC

NCCT

Puncture in femoral artery

Stent in place

Patient moving left side; NIHSS = 0

CT

Angio

First run with contrast

Flow restored in ICA/MCA

Patient moving left side; NIHSS = 0
Figure 2.8: (a) Timeline of the management and treatment of a 65-year-old male who presented at the Foothills Medical Centre (FMC) with a NIHSS of 20; (b) non-contrast CT of the brain showing a hyper-intensity in the right MCA indicating a large blood clot (arrow); (c) CT angiogram showing the missing right middle cerebral artery (MCA); (d) first run with contrast agent showing the lack of blood supply in the right MCA; (e) retrieval of the thrombus with a stent; (f) blood flow restored in the MCA; and (g) thrombus extracted from the patient. (Figure on previous page)

vascular, and functional stroke assessment in a prompt manner and to enable real-time catheter tracking.

Using MR imaging as the standard of care in acute ischemic stroke could potentially improve the diagnosis of patients and better guide therapeutic decision-making. MR imaging can provide full anatomical, vascular, and functional stroke assessment. This is necessary to rule out hemorrhagic stroke, identify occlusion, and estimate the ischemic penumbra region. Of course, this must be done rapidly, robustly, and accurately. Furthermore, MR’s ability to detect the ischemic penumbra and thus identify stroke patients that are more likely to respond to acute therapy, is a major advantage of MR imaging over CT.
Chapter Three: **Technical Background and Literature Review**

This chapter presents the technical background underlying the work in this thesis. I first begin with MR physics and describe the interaction between the bulk material and magnetic fields. The signal resulting from this interaction is received by nearby coils and used to acquire 2D or 3D images that depict the spatial distribution of magnetically susceptible materials, such as biological tissue. An imaging acquisition consists of RF pulses and gradient waveforms to spatially encode the magnetised tissue in Fourier domain, known as k-space. The design of the pulse sequence defines the voxel size and FOV of the reconstructed image. Conventional image reconstruction of Fourier encoded data is presented and several approaches for accelerating MR imaging are explained, including compressed sensing (CS) and parallel MR imaging. Most of these reconstruction methods rely on mathematical optimization techniques to reconstruct the images. Appendix A provides general background information about the optimization techniques relevant to the research presented herein. In addition, Appendix B introduces the MR imaging physics of TOF angiography that is used extensively throughout this thesis.

### 3.1 Magnetic Resonance Imaging

The review of MR imaging in this section is not intended to be exhaustive, but to provide the reader with sufficient background to understand the nature of the data acquired in the so-called k-space or Fourier domain. For a more complete description of MR imaging principles, please refer to (119, 120).
3.1.1 Signal Origin in Magnetic Resonance Imaging

Magnetic resonance imaging is an imaging modality based on the physical phenomenon of nuclear magnetic resonance (NMR). The true nature of NMR is best described with quantum physics, however, MR imaging can be accurately explained at the macroscopic level using classical physics.

The human body is about 60 - 80% water (121, 122) and hence contains many water molecules. The hydrogen (1H) nuclei (i.e., protons) found in water molecules are of great interest in MR imaging. These nuclei absorb and re-emit electromagnetic radiation to form the NMR signal. A fundamental property of nuclei with odd atomic numbers, such as the hydrogen proton, is their angular momentum $\mathbf{J}$, called spin. The hydrogen proton (1H) is a spin-$\frac{1}{2}$ system and it is the only nucleus considered in this thesis. Although the spin is a quantum-mechanical phenomenon, in classical physics, it is conceptualised as a physical spinning of the nuclei similar to the rotation of a top about its axis. The precession frequency, known as the Larmor frequency, is proportional to the external magnetic field $B_0$

$$\omega_0 = \gamma B_0, \quad [3.1]$$

where $\gamma$ is a physical constant known as the gyromagnetic ratio. This ratio is varies with isotope and for the 1H nucleus is $\gamma = 2.67 \cdot 10^8$ rad/s/T, or $\nu = \gamma / 2\pi = 42.58$ MHz/T.

Nuclei have electrical charges and, from a classical point of view, these rotating charges produce a microscopic magnetic field, $\mathbf{\mu} = \gamma \mathbf{J}$, which is the source of the NMR signal. However, MR imaging is a macroscopic imaging modality that looks at the collective behaviour of the spins.
The macroscopic net magnetization of a volume element (i.e., voxel), \( \mathbf{M} \), is the sum of all the spin magnetizations enclosed in the voxel,

\[
\mathbf{M} = \sum_{\text{protons in voxel}} \mathbf{\mu}_i.
\]  

[3.2]

According to the Zeeman splitting phenomenon of quantum theory, in the presence of an external magnetic field, \( \mathbf{\mu}_i \) takes one of two possible orientations: Spin-up state (lower-energy state) or spin-down state (higher-energy state). Because of a very small excess of spins in the lower-energy state, the difference between the two spin states generates a small macroscopic net magnetization, \( \mathbf{M} \). For a more exhaustive description of the quantum theory, please refer to (119). The following sections describe how to form images by manipulating the net magnetization.

3.1.2 Bloch Equations

The phenomenological Bloch equations describe the time-dependent interaction of the magnetization \( \mathbf{M} \) with an external magnetic field \( \mathbf{B} \) (2),

\[
\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B} - \frac{M_x}{T_2} \mathbf{i} - \frac{M_y}{T_2} \mathbf{j} + \frac{M_0 - M_z}{T_1} \mathbf{k},
\]  

[3.3]

where \( \mathbf{M} = (M_x, M_y, M_z) \) is the magnetization spin-density, \( \mathbf{B} = (B_x, B_y, B_z) \) is the magnetic field strength, \( M_0 \) is the thermal equilibrium magnetization spin-density along the z-axis, \( \gamma \) is the gyromagnetic ratio, \( T_1 \) is the spin-lattice relaxation time constant, \( T_2 \) is the spin-spin relaxation time constant, and \( \mathbf{i}, \mathbf{j}, \) and \( \mathbf{k} \) are the unit vectors of the Cartesian coordinate system pointing in
the $x$-, $y$-, and $z$-direction, respectively. The time constants $T_1$ and $T_2$ characterize the relaxation process of the spin system after it has been disturbed from its thermal equilibrium state. More specifically, $T_1$ characterizes the time of regrowth back to equilibrium in the $z$-direction, i.e., longitudinal regrowth, and $T_2$ characterizes the time of dephasing of the magnetization in the transverse plane ($x$-$y$-plane), i.e., transverse decay. Note that both $\mathbf{M}(\mathbf{r}, t)$ and $\mathbf{B}(\mathbf{r}, t)$ are functions of space and time, whereas $M_0(\mathbf{r})$, $T_1(\mathbf{r})$, and $T_2(\mathbf{r})$ are functions of space only.

The magnetization is spatially encoded by modifying the local magnetic field, which changes the local frequency. The next section describes the three main magnetic fields encountered in MR imaging, and their role for spatial encoding and excitation.

### 3.1.3 Magnetic Fields in MR Imaging

#### 3.1.3.1 Static Magnetic Field

The static magnetic field $B_0$ is a strong, static, and relatively homogeneous magnetic field that is oriented along the $z$-direction. The field strength for clinical systems typically ranges from 0.3 T to 7 T. For comparison, the earth’s magnetic field is about $10^5$ times smaller and ranges from 25 to 65 $\mu$T. The strength of $B_0$ determines the Larmor frequency, $\omega_0$, and the net magnetization, $\mathbf{M}$. The field homogeneity is very important for imaging as inhomogeneity results in image distortion artefacts.

#### 3.1.3.2 Spatial Encoding Gradient Field

Spatial encoding requires three orthogonal linear field gradients, $G_x$, $G_y$, and $G_z$. Applying these gradients modifies the local magnetic field strength by adding a linear variation to the main longitudinal $B_0$ field. The magnetic field strength along the $z$-direction varies with position and...
time \( B_z(\mathbf{r},t) = B_0 + \mathbf{G}(t) \cdot \mathbf{r} \), where \( \mathbf{G} = dB_z(\mathbf{r},t)/d\mathbf{r} \). This variation causes the Larmor frequency of the precessing spins to vary linearly in space. It is useful to note that an ideal gradient magnetic field is assumed to only have a \( B_z \) component and no \( B_x \) and \( B_y \) components. Such assumption provides a good approximation (123), however, it is not correct because Maxwell’s equations state that a source free region must have zero divergence \( \nabla \cdot \mathbf{B} = 0 \) and zero rotation \( \nabla \times \mathbf{B} = 0 \). The maximum gradient amplitude for typical clinical scanner is about 500 \( \mu \)T/cm, or a change of 10 mT over a FOV of 20 cm. This variation in magnetic field is used to encode the spatial distribution, as I will show in section 3.1.6.

3.1.3.3 Radio Frequency Field

The radio frequency (RF) field is a transverse field \( B_1(\mathbf{r},t) := B_{xy}(\mathbf{r},t) = B_x(\mathbf{r},t) + i B_y(\mathbf{r},t) \) used to excite the magnetization \( \mathbf{M} \) from its equilibrium. The RF field is tuned to the Larmor frequency, \( i.e., \) resonance frequency, which enables the transfer of energy into the spin system. Some of the spins in the low-energy state absorb energy and move to a high-energy state. This excitation causes the magnetization to tip or nutate away from the longitudinal direction and down to the transverse plane (Figure 3.1). The duration, envelope, and intensity of the RF pulse control the flip angle \( \alpha \) of the magnetization. A typical body RF-coil can produce a field strength of about 16 \( \mu \)T.
3.1.4 Solution to the Bloch Equations

After exciting the equilibrium magnetization, the RF pulse is turned off and the magnetic field strength components are $B_x = 0$, $B_y = 0$, and $B_z = B_0 + G(t) \cdot r$. To investigate the time evolution of the magnetization after an RF excitation, it is convenient to rewrite the set of coupled ordinary differential equations (ODEs) defined in Eq. [3.3] by expressing the system in terms of transverse and longitudinal components,

$$\frac{dM_{xy}}{dt} = -i\gamma M_{xy} B_z - \frac{M_{xy}}{T_2}$$

$$\frac{dM_z}{dt} = \frac{M_0 - M_z}{T_1},$$

Figure 3.1: a) Net magnetization $\mathbf{M}$ aligned to the external field $B_0$ at equilibrium. b) Tipping of net magnetization $\mathbf{M}$ away from the z-axis to produce a transverse magnetization that precesses at the Larmor frequency $\omega_0 = \gamma B_0$. 
where $M_{xy}(r, t) = M_x(r, t) + i M_y(r, t)$ and $i = \sqrt{-1}$. By specifying the initial conditions of the magnetization after the RF pulse as $M_{xy}(r, 0) = M_{xy}^0(r)$ and $M_z(r, 0) = M_z^0(r)$, we find the solution to the ODEs in Eq. [3.4] as,

$$M_{xy}(r, t) = M_{xy}^0(r)e^{-t/T_2(r)}e^{-i\gamma B_0 t}e^{-i\gamma r \cdot \mathbf{g}(r)\, dr}$$

$$M_z(r, t) = M_0(r) + (M_z^0(r) - M_0(r))e^{-t/T_1(r)}.$$ \[3.5\]

The function $M_z(r, t)$ describes the regrowth of the longitudinal magnetization from its initial value $M_z^0(r)$ at time $t = 0$ back to its equilibrium value of $M_0(r)$ as $t \to \infty$ (Figure 3.2a). The $T_1$ relaxation constant in the $e^{-t/T_1(r)}$ term characterizes the rate of regrowth. Note that the longitudinal magnetization experiences no phase modulation.

The function $M_{xy}(r, t)$ describes the time evolution of the transverse magnetization. The term $e^{-t/T_2(r)}$ corresponds to amplitude modulation ($T_2$ decay due to dephasing of the spins) (Figure 3.2b), while all other exponential terms correspond to phase modulation. More specifically, the phase term $e^{-i\gamma B_0 t}$ causes the transverse magnetization to precess about the z-axis at the Larmor frequency $\omega_0 = \gamma B_0$ (Figure 3.2c). Finally, the phase term $e^{-i\gamma r \cdot \mathbf{g}(r)\, dr}$ causes the Larmor frequency of the precessing spins to vary linearly in space by adding a linear gradient field to the main longitudinal magnetic field $B_0$. This spatial encoding gradient in magnetic field is used to encode the spatial distribution, as I will show in a later section.

Figure 3.2d illustrates the 3D trajectory of the magnetization returning to equilibrium after a 90° RF pulse excitation.
Figure 3.2: Illustration of the effect of each term in the Bloch equation on the magnetization: (a) Longitudinal regrowth characterised by the $T_1$ relaxation constant, (b) transverse decay characterised by the $T_2$ relaxation constant, (c) free precession about the $B_0$ field at the Larmor frequency $\omega_0$, and (d) due to dephasing of the spins.

### 3.1.5 Signal Detection

The detection of the MR signal is based on Faraday’s law of electromagnetic induction and the principle of reciprocity (124, 125). The precessing transverse magnetization produces a time-varying magnetic flux through a nearby receiver coil and induces an electromotive force (EMF) in the coil (Figure 3.3). The induced EMF is equal to the rate of change of the magnetic flux, $\Phi_B$, through the coil, i.e., $\text{EMF} = -\frac{d\Phi_B}{dt}$. 
In MR imaging, it is often beneficial to measure the MR signal with multiple receiver coils (multi-receiver coils and parallel imaging will be further discussed in section 3.7). The measured signal with each coil is actually the sum of the transverse magnetization at all positions within the object. After quadrature amplitude demodulation of the acquired signal with the Larmor frequency carrier wave $e^{+iyB_0t}$, the MR signal from the $l$-th coil is given by

$$s_l(t) = \int_{\mathbb{R}} c_l(\mathbf{r}) M_{xy}^0(\mathbf{r}) e^{-t/T_2(\mathbf{r})} e^{-iy\mathbf{r} \cdot \mathbf{B}(\mathbf{r})} d\mathbf{r},$$

where $c_l(\mathbf{r})$ denotes the detection sensitivity at position $\mathbf{r}$ of the $l$-th receiver coil. Using multiple receiver coils to simultaneously measure the MR signal offers many advantages, as I will discuss in a later section. However, for the remainder of this section, I will assume a single-receiver coil with uniform detection sensitivity.
3.1.6 Spatial Encoding and k-Space

Spatial encoding is necessary to resolve the spatial distribution of the magnetization from each image volume element, i.e., a voxel. The encoding occurs in the Fourier space, more commonly known as k-space. By defining

\[ \mathbf{k}(t) := \frac{\gamma}{2\pi} \int_0^t G(\tau) d\tau, \]  

[3.7]

it becomes clear that the signal equation for MR imaging (Eq. [3.6]) is a Fourier transform operation:

\[ s(\mathbf{k}(t)) = \int_\mathbb{R} \rho(\mathbf{r}) e^{-i2\pi \mathbf{r} \cdot \mathbf{k}(t)} d\mathbf{r} \]  

[3.8]

\[ s(\mathbf{k}(t)) = \mathcal{F}\{\rho(\mathbf{r})\}, \]  

[3.9]

where \( \rho(\mathbf{r}) = c(\mathbf{r}) M_z^0(\mathbf{r}) e^{-t/T_2(\mathbf{r})} \). In words, it means that the received signal at time \( t \) is the Fourier transform of \( \rho \) (i.e., the object’s magnetization weighted by the coil sensitivity and \( T_2 \) decay) sampled at the spatial frequency \( \mathbf{k}(t) \). The MR image \( \rho(\mathbf{r}) \) is then calculated from the inverse Fourier transform of \( s(\mathbf{k}) \), namely

\[ \rho(\mathbf{r}) = \int_\mathbf{k} s(\mathbf{k}) e^{+i2\pi \mathbf{r} \cdot \mathbf{k}} d\mathbf{k} \]  

[3.10]

\[ \rho(\mathbf{r}) = \mathcal{F}^{-1}\{s(\mathbf{k})\}. \]  

[3.11]

Such spatial encoding is particular to MR imaging and is fundamentally very different from traditional optical imaging approaches where image voxels are sampled/measured directly.
Figure 3.4: Gradient-recalled echo pulse sequence for a 2D acquisition (a) and its corresponding k-space trajectory (b).

An MR imaging acquisition uses a pulse sequence consisting of RF pulses and gradient waveforms to manipulate/encode the magnetization. The phase, $\phi(r, t) = 2\pi r \cdot k(t)$, of the Fourier kernel, $e^{-i\phi(r,t)}$, is governed by the integral of the gradient waveforms. Therefore, the gradient, $G(t)$, controls the k-space trajectory, $k(t)$. To illustrate these points, consider the pulse sequence diagram of a 2D gradient-recalled-echo (GRE) sequence shown in Figure 3.4a.

A gradient $G_x$ is applied along with an RF pulse to selectively excite a 2D slice within the image volume. After excitation, the gradients $G_x$ and $G_y$ are applied to navigate through k-space (Eq. [3.7]) and spatially encode the MR signal in the $k_x-k_y$ plane. The evolution of the k-space trajectory with respect to the pulse sequence is shown in Figure 3.4b. At time point $t_0$, the magnetization has no phase. Then the gradients $G_x$ and $G_y$ are turned on and the magnetization
accumulates phase via the integral of the gradients until it reaches the top left corner of k-space at time point $t_1$. At that point, the $G_y$ gradient is turned off and the amplitude of the $G_x$ gradient is reversed to navigate across k-space horizontally to time point $t_3$. While traversing k-space, the amplitude and phase of the transvers magnetization (i.e., echo signal) is recorded as a function of time with an analog to digital converter (A/D). Note that time is a parameter of k, i.e., the location in k-space. The experiment is then repeated to acquire all other lines of k-space by changing the amplitude of the $G_y$ gradient.

Most MR acquisitions use a Cartesian sampling approach, i.e., it acquires data on a rectilinear sampling grid as show in Figure 3.4b. Such acquisition schemes have the advantage of providing straightforward image reconstruction by applying the inverse fast Fourier transform (FFT). In addition, Cartesian sampling is robust to many sources of system imperfections. However, the freedom in choosing any sampling trajectory by applying different shape of gradient waveforms plays a major role in MR imaging. Acquisitions using radial trajectories are less susceptible to motion artefacts than Cartesian sampling (126) and can be significantly undersampled (127-129). Spiral trajectories offer another time efficient approach to collect samples and are used in real-time and for rapid imaging applications (130). However, reconstruction from non-Cartesian trajectories are more complex than for Cartesian acquisitions and may require more specialized and/or advanced reconstruction algorithms, e.g., filtered back-projection (119) or gridding algorithms (131).

MR imaging can readily be extended to 3D acquisition by applying a $G_z$ encoding gradient to move along the $k_z$ direction. This may be achieved by changing the amplitude of the rewinding
lobe of the $G_z$ gradient in Figure 3.4a. An illustration of a 3D acquisition is depicted in Figure 3.5.

![Image](308x572 to 320x585)

Figure 3.5: Trajectory of 3D Cartesian acquisitions. The $G_y$ and $G_z$ encoding gradients are changed at each excitation to acquire a different readout line in the volume.

### 3.1.7 k-Space Sampling

Sampling of k-space is a very important concept in this thesis. The position of a k-space sample is determined by the value of $k_x$ and $k_y$ at sampling time $t$ as given by Eq. [3.7]. The separation between two neighbouring lines in k-space (i.e., in the phase encoding direction) is

$$
\Delta k_y = \frac{\gamma}{2\pi} \int_{t}^{t+\tau_y} \Delta G_y(\tau) d\tau,
$$

[3.12]

where $\tau_y$ is the duration of the phase encoding gradient pulse (i.e., time between $t_0$ and $t_1$ in Figure 3.4a), whereas the separation between two pixels in the frequency encoding direction (i.e., in the $k_z$-direction) is
\[ \Delta k_x = \frac{Y}{2\pi} \int_t^{t+\Delta t} G_x(\tau) d\tau. \]  \hfill [3.13]

In words, for Cartesian sampling, the resolution in the phase encoding direction is determined by the change in gradient amplitude and gradient duration, whereas the resolution in the frequency encoding direction depends on the gradient amplitude and the sampling frequency of the signal, \textit{i.e.}, the receiver bandwidth \( RBW := \frac{1}{\Delta t}. \)

3.1.8 Field of View and Spatial Resolution

In designing a standard Cartesian MR imaging acquisition, we need to determine a \( k \)-space sampling trajectory that satisfies the Nyquist–Shannon sampling theorem (132, 133). The trajectory depends on the desired image FOV and spatial resolution \( \text{i.e.} \), voxel size). The FOV must be larger than the imaged object to avoid spatial aliasing artefacts in the image and the resolution should be sufficiently high to resolve the smallest features that we want to observe.

The relationship between the sample spacing, \( \Delta k \), the extent of \( k \)-space, \( k_{\text{ext}} = k_{\text{max}} - k_{\text{min}} \), the voxel size (\( \Delta \)) and the FOV are defined by

\[ \text{FOV} = n \cdot \Delta = \frac{1}{\Delta k} \]  \hfill [3.14]

\[ k_{\text{ext}} = n \cdot \Delta k = \frac{1}{\Delta}. \]  \hfill [3.15]

where \( n \) is the number of acquired samples. These relationships, shown in Figure 3.6, indicate that to increase the image resolution \( \text{i.e.} \), smaller voxel size) while preserving constant FOV, it is necessary to move further away from the centre of \( k \)-space by acquiring more samples, \textit{i.e.},
longer acquisition time. Note that the image resolution is inversely proportional to the voxel size and is given by the extent of k-space, $k_{\text{ext}}$.

It should be noted that the A/D converter highly oversamples the readout signal (i.e., signal along the frequency-encode direction $k_x$) and, therefore, by the application of digital filters can prevent aliasing in the $k_x$-direction.

Figure 3.6: The sample spacing $\Delta k_x$ and $\Delta k_y$ are inversely proportional to the FOV of the reconstructed image in the $x$- and $y$-directions, respectively. Similarly, the voxel size $\Delta x$ and $\Delta y$ are inversely proportional the k-space extent $k_{x,\text{ext}}$ and $k_{y,\text{ext}}$, respectively.

### 3.2 Accelerated MR Imaging

MR acquisition requires sampling the MR signal while traversing k-space. Physical and physiological constraints, however, limit the speed at which we can traverse k-space and make MR imaging inherently slow. Some of the physical constraints include the maximum amplitude and maximum slew-rate of the gradients. The physiological constraints result from high gradient
amplitude and rapid switching of magnetic fields, which can induce an electric field in the patient, and cause peripheral nerve stimulation (18, 134). To protect subjects, safety standards limit exposure to time-varying magnetic fields with $dB/dt$ levels below $20 \, T/s$ (18, 134). These fundamental constraints essentially limit the rate at which we can collect MR data and have led researchers to investigate different approaches to accelerate MR imaging.

Previously, much effort went into developing fast pulse sequences that optimize scanning trajectories to collect the raw data. Echo train imaging acquires multiple echoes (i.e., k-space lines) per excitation, which significantly reduces the acquisition time. Such echo train pulse sequences include echo planar imaging (EPI) (5), GRASE (135), and RARE (136). These pulse sequences utilize a train of gradient and/or spin echoes to acquire a complete slice/volume using only one (i.e., single-shot) or a few (i.e., multi-shot) excitations. However, acquiring multiple echoes per excitation often results in a decreased contrast and/or increased susceptibility to magnetic field inhomogeneity (5, 135-138). The spatial resolution of these techniques is also limited.

An effective approach to accelerate MR imaging is to reduce the number of acquired lines in k-space. For fully sampled k-space acquisitions, this comes at the cost of either lower image resolution for constant FOV, or smaller FOV for constant image resolution (Eq. [3.14]). Another approach consists of maintaining the image resolution and FOV constant, and reducing the number of acquired lines by sub-sampling the k-space phase encodes. However, such undersampling approach violates the Nyquist-Shannon sampling condition and requires knowledge of a priori information to recover the missing data. In the following section, I will
introduce different Cartesian undersampling approaches and their corresponding aliasing artefacts.

### 3.3 Image Aliasing Artefacts

Typically, people think of sampling a time signal and examining the resulting Fourier spectrum. The Nyquist–Shannon sampling theorem (132, 133) states that for a limited bandwidth (band-limited) signal with maximum frequency \( f_{\text{max}} \), the sampling frequency \( f_s \) must be greater than twice the maximum frequency \( f_{\text{max}} \),

\[
f_s > 2 \cdot f_{\text{max}}. \tag{3.16}
\]

Violation of this condition results in fold-over or wraparound artefacts in the Fourier domain, known as aliasing. The appearance of the aliasing artefact depends on the sampling. Uniform (equally spaced) undersampling yields coherent aliasing interference (coherent folding), whereas irregular sampling produces incoherent interference.

In MR imaging, the signal is acquired in k-space. The Fourier encoded time signal \( s(k(t)) \) is sampled at a frequency \( f_s = 1/\Delta k = \text{FOV} \), and the aliasing artefacts occur in image space.

Consider the band-limited 1D temporal signal \( s(k) \) and its spectrum \( \rho(x) \) in Figure 3.7, where \( k \) represents the temporal position and \( x \) denotes the spatial frequency. An ideal A/D converter digitizes the continuous signal \( s(k) \) to get the sampled signal

\[
s_d(k) = s(k) \cdot \frac{1}{\Delta k} \llcorner \left( \frac{k}{\Delta k} \right), \tag{3.17}
\]

where \( \llcorner \) indicates the floor function.
where $\Omega(a)$ is the comb function

$$\Omega(a) := \sum_{n=-\infty}^{\infty} \delta(a - n).$$  \[3.18\]

Taking the Fourier transform of Eq. [3.17] yields

$$\rho_d(x) = \rho(x) \otimes \Omega(x\Delta k)$$

$$\rho_d(x) = \rho(x) \otimes \left[ \frac{1}{\Delta k} \sum_{n=-\infty}^{\infty} \delta\left(x - \frac{n}{\Delta k}\right) \right]$$

$$\rho_d(x) = \frac{1}{\Delta k} \sum_{n=-\infty}^{\infty} \rho\left(x - \frac{n}{\Delta k}\right),$$  \[3.19\]

where $\otimes$ denotes the convolution operator. In words, the spectrum of the sampled signal consists of the original spectrum $\rho(x)$ and its replicated versions with period $1/\Delta k$. When the sampling frequency satisfies the Nyquist-Shannon sampling condition, the harmonic versions of the sampled image do not overlap with the baseband spectrum (Figure 3.7d). However, for sub-Nyquist-Shannon sampling frequencies, fold-over (aliasing) artefacts occur in the image space (Figure 3.8).
Figure 3.7: In MR imaging, the continuous signal is acquired in k-space and sampled at the frequency $f_s = 1/\Delta k = \text{FOV}$. The Fourier transform pairs for a signal example, the sampling function, and the sampled signal are illustrated in (a,b), (c,d), and (e,f), respectively. The product of the signal (a) with the sampling function (c) yields the sampled signal (e). The Fourier transform of the product of the two signals (f) is equivalent to the convolution of the individual inverse transforms (b) and (d). Aliasing is avoided in this figure by selecting a sampling frequency sufficiently large for the FOV to be larger than the object spectrum.
Figure 3.8: Illustration of aliasing occurring when the Shannon-Nyquist sampling condition is not satisfied, i.e., the spectrum of the replicates overlap with the baseband spectrum (f).

The above example illustrates coherent aliasing artefacts arising from uniform undersampling of k-space. However, a wide variety of k-space subsampling patterns have been investigated in the context of accelerated MR imaging. The point spread functions (PSF) of the most encountered subsampling schemes for 3D Cartesian acquisitions are shown in Figure 3.9. Each sampling exhibits different aliasing artefacts. Low-resolution sampling leads to blurring of the image;
Figure 3.9: Common k-space undersampling patterns and their corresponding point spread functions in image space.
equispaced sampling yields coherent interference; and random sampling produces incoherent interference. The degree of coherence can be approximated by the sidelobe-to-peak ratio of the PSF (139).

The appropriate undersampling strategy to accelerate MR imaging depends on the reconstruction technique. For reconstructions that require incoherent aliasing, uniform random undersampling provides the highest degree of incoherence, i.e., the lowest sidelobe-to-peak ratio. However, the energy of images is concentrated near the centre of k-space, which corresponds to the low frequencies (Figure 3.10). Therefore, for better performance, one should acquire more samples near the centre of k-space than in the periphery. A variable probability density function (PDF) random sampling approach is often used for that purpose (Figure 3.9i). Stochastic sampling techniques, in particular Poisson and jittered sampling, are used extensively in computer graphics to enhance the display of virtual scenes (140).

A number of researchers are striving to design algorithms to reconstruct images from these undersampled k-space data without degrading image quality. To resolve the aliasing interference arising from the sub-sampling, algorithms rely on model-based a priori information (25, 26, 139) and/or the spatial sensitivity information inherent in an array of multiple receiver surface coils (19-22, 27, 141, 142).

In the following sections, I will present seven state-of-the-art methods (as of 2013) for rapid imaging based on the two concepts just described. CS (25, 26, 139) is a model-based framework that exploits the inherent compressibility of MR images by promoting sparsity in a given domain. SENSE (19), GRAPPA (21), and SPIRiT (22) are parallel imaging methods that exploit
the data redundancy and spatial sensitivity information of imaging with multiple receiver coils.

The last three methods sparse SENSE (141), CS-SENSE (27), and L1-SPIRiT (22) combine both concepts of parallel imaging and sparsity.

Before presenting each reconstruction algorithm, the next section introduces the general problem of image reconstruction and the basic concepts of mathematical optimization underlying image reconstruction.

Figure 3.10: Illustration of important k-space properties; the centre of k-space corresponds to the low frequencies (i.e., gross information), whereas the periphery of k-space corresponds to the high frequencies (i.e., edge information). For natural images, such as medical images, most of the energy is located near the centre of k-space.
3.4 General Image Reconstruction Problem

The general image reconstruction problem consists of finding an image function $\mathbf{m} \in \mathbb{C}^n$ that is consistent with the measured signal $\mathbf{s} \in \mathbb{C}^m$ according to a known imaging equation

$$\mathbf{s} = \mathcal{L}(\mathbf{m} + \mathbf{\eta}), \quad [3.20]$$

where $\mathcal{L} : \mathbb{C}^n \rightarrow \mathbb{C}^m$ is the measurement/sensing operator and $\mathbf{\eta}$ is the noise. Equation [3.20] is often referred to as the data consistency constraint and any image $\mathbf{m}$ satisfying this constraint is called a feasible reconstruction. Theoretically, if the operator $\mathcal{L}$ is invertible, then a data-consistent estimate $\hat{\mathbf{m}}$ can be obtained from the inverse transform

$$\hat{\mathbf{m}} = \mathcal{L}^{-1}\{\mathbf{s}\}. \quad [3.21]$$

For Fourier spatial encoding, the sensing operator is simply the Fourier transform $\mathcal{F}$. Using matrix notation and omitting noise, the data consistency constraint in Eq. [3.20] can be written as

$$\mathbf{s} = \mathbf{F}\mathbf{m}, \quad [3.22]$$

where $\mathbf{F} \in \mathbb{C}^{m \times n}$, $\mathbf{F}_{r,k} = e^{-i2\pi r k}$ is the matrix representation of the Fourier sensing operator $\mathcal{F}$, and $\mathbf{m} \in \mathbb{C}^n$ and $\mathbf{s} \in \mathbb{C}^m$ are the image and k-space data treated as column vectors, respectively. For well-designed acquisitions, i.e., fully sampled k-space data sampled at the Nyquist rate, the Fourier matrix $\mathbf{F}$ is square ($m = n$) and has full column rank, i.e., $\text{rank}(\mathbf{F}) = m = n$. Therefore, Eq. [3.22] has a unique feasible reconstruction given by the inverse Fourier transform,

$$\mathbf{m} = \mathbf{F}^*\mathbf{s}, \quad [3.23]$$
where * denotes the conjugate transpose, and \( F^* = F^\dagger \) is the adjoint or Hermitian matrix of \( F \), which corresponds to the inverse Fourier transform operator.

For undersampled k-space, the linear system of equations to solve has more unknowns than constraints and is said to be underdetermined, \( i.e., m \in \mathbb{C}^n, s \in \mathbb{C}^m, F_u \in \mathbb{C}^{m \times n}, m < n, \) and \( F_u \) has full row rank, \( \text{rank}(F_u) = m \). Here I use the notation \( F_u = U F \) to represent the undersampled Fourier operator, where \( U \) is the \( m \times n \) matrix extracting the sampled coordinates (\( i.e., \) rows of \( F \)). Underdetermined systems have an infinite number of feasible reconstructions that have \( n - m \) number of free variables (\( i.e., \) degrees of freedom). Some optimality criterion has to be applied to select an image from the many possible ones. See Appendix A.3 for general information about solving linear system of equations.

### 3.5 Model-Based Reconstruction

Model-based methods require \textit{a priori} information about the image to reconstruct. Figure 3.11a conceptually illustrates an example of an underdetermined system where \( m \in \mathbb{C}^2, s \in \mathbb{C}^1, \) and \( F_u \in \mathbb{C}^{1 \times 2} \). The feasible set of reconstructions satisfying this constraint has one degree of freedom and is represented by a line in this example. A particular reconstruction consists of finding the solution with minimum Euclidean norm, \( i.e., \) minimum energy, which is obtained by solving the optimization problem

\[
\begin{align*}
\text{minimize} & \quad \|m\|_2 \\
\text{subject to} & \quad F_u m = s,
\end{align*}
\]  

\[ [3.24] \]
where \( \|\mathbf{m}\|_2 := (\sum |m_i|^2)^{1/2} \) is the Euclidean norm or \( \ell_2 \)-norm. In fact, the above optimization problem has an analytical solution given by the Moore-Penrose right pseudoinverse

\[
m = \mathbf{F}_u^* (\mathbf{F}_u \mathbf{F}_u^*)^{-1} \mathbf{s}.
\]  

[3.25]

This solution corresponds to the point where the line intersects with the \( \ell_2 \)-norm ball of radius \( \|\mathbf{m}\|_2 \) as shown in Figure 3.11f. This closed-form and unique solution makes the use of the \( \ell_2 \)-norm popular in many applications. In MR imaging, it is known as the zero-filled (ZF) reconstruction (143), which is obtained by setting the missing \( k \)-space data to zero prior to applying the inverse Fourier transform.

One can constrain \( \mathbf{m} \) to satisfy other specifications than the least \( \ell_2 \)-norm by generalizing it to the \( \ell_p \) (\( 0 < p < \infty \)) “norms”

\[
\|\mathbf{m}\|_p^p := \sum |m_i|^p.
\]  

[3.26]

Figure 3.11b to Figure 3.11e illustrate the \( \ell_0 \), \( \ell_{0.5} \), \( \ell_1 \), and \( \ell_{1.5} \) measures, respectively. It can be seen that for \( 0 < p \leq 1 \), the \( \ell_p \) function promotes a sparse reconstruction, \textit{i.e.}, a solution with only a few non-zero coefficients. Note that the case \( 0 < p < 1 \) is of interest because it offers highly sparse solutions, but the \( \ell_p \) (\( p < 1 \)) function is non-convex, which implies that the resulting optimization problem will also be non-convex and is considered intractable (see Appendix A.2 for a definition of convex functions). However, the \( \ell_1 \)-norm is convex and can be solved efficiently. Finding a sparse solution is a key concept of compressed sensing, as discussed in the next section.
Figure 3.11: Graphical illustration of the many possible solutions to an underdetermined system of linear equations $F_u m = s$, where $m \in \mathbb{C}^2$, $s \in \mathbb{C}^1$, and $F_u \in \mathbb{C}^{1 \times 2}$ (a), and the particular reconstructions yielding minimum $\ell_0$ (b), $\ell_{0.5}$ (c), $\ell_1$ (d), $\ell_{1.5}$ (e), and $\ell_2$ (f) norms.

### 3.6 Compressed Sensing (CS)

Without *a priori* knowledge, an $n$-element image (*i.e.*, $n$ unknowns) will have maximum signal entropy and so we must acquire $m = n$ data samples (*i.e.*, $m$ equations). The CS framework exploits sparsity as prior information to find solutions to underdetermined linear systems of equations (25, 26, 139, 144, 145). The key result of CS is that it is possible to accurately reconstruct a signal of length $n$ from $m < n$ observations, where $m$ is on the order of $K$, the sparsity of the signal (*i.e.*, number of non-zero coefficients in some domain). This result significantly reduces the number of observations required to reconstruct sparse signals.

The CS framework has three basic components: 1) the sparsifying transform, 2) the sampling pattern, and 3) the nonlinear reconstruction. I first discuss the sparsifying transform.
3.6.1 Sparsifying Transform

Sparsity in MR imaging is most often implicit, i.e., images are not directly sparse in image space, but rather in some other transform domains. The possibility of exploiting transform sparsity is motivated by the widespread success of data compression in imaging. Natural images, such as medical images, are highly compressible with little or no loss of visual information. The JPEG and JPEG-2000 image formats use the cosine (146) and wavelet (147) transforms, respectively, to encode the image content into a vector of sparse coefficients. The most significant coefficients are then stored or transmitted over some media before decoding and reconstruction of the image. Other sparsifying transforms include the finite differences (148) and the contourlet transform (149).

Mathematically speaking, the sparsifying transform $\Psi$ is an orthonormal basis that defines the sparse representation $w = \Psi m$ of an image $m$. The sparsity of the signal is connected to the minimum number of measurements needed to reconstruct the signal (25) (see next section).

Figure 3.12 illustrates the compressibility of a phantom and a brain image. The left column shows the magnitude of the transform coefficients $w$ encoded with the discrete cosine transform (DCT), wavelet transform, and finite differences. The image representations in the transform domains are sparser than the images themselves. Almost all of the image pixels have nonzero values, but most transform coefficients are small, and the relatively few large coefficients capture most of the information. By using only a subset of the largest transform coefficients, a nearly exact reconstruction of the image is achieved. For the phantom image, the finite difference transform performs the best and yields almost perfect reconstruction using only 5% of the largest
Figure 3.12: Transform sparsity of a (a) phantom and (b) brain image. Left column shows the magnitude of the DCT, wavelet, and finite difference transform coefficients. Right columns show the reconstructions using only a subset (2, 5, 10, 20, and 100%) of the largest transform coefficients.
transform coefficients. For natural images, however, the DCT and wavelet transforms outperform the finite difference. They both provide similarly good sparsifying performance with a slight advantage for the wavelet transform, especially for the case involving 5% of the largest coefficients.

3.6.2 Sampling Pattern

To analyse the aliasing incoherence in the transform domain, the notion of point spread function (PSF) is extended to the transform point spread function (TPSF). The TPSF measures how a single transform coefficient of the underlying object leaks into the other transform coefficients as a function of the sampling pattern. The image reconstruction is therefore equivalent to a deconvolution process. Figure 3.13 illustrates the wavelet TPSF of uniform random 2D Fourier undersampling.

![Wavelet coefficients](Image)

![Image coefficients](Image)

![k-Space coefficients](Image)

Figure 3.13: Transform point spread function (TPSF) of uniform random 2D Fourier undersampling.
The image quality with the CS reconstruction from undersampled data highly depends on the measurement/sensing matrix. Precise conditions are given in the literature \((25, 150)\), but the key concept is that the sensing matrix must be properly selected in order to minimise interference coherence in the sparse domain.

To assess the suitability of the sensing matrix for CS, one can theoretically use 1) the restricted isometry property (RIP) \((151)\) and 2) mutual coherence bounds \((150)\) conditions. The RIP condition is useful to study the general robustness of CS. Given a sensing matrix \(F_u\), the RIP defines a constant \(\delta_K\) as the smallest number such that

\[
(1 - \delta_K)\|w\|_2^2 \leq \|F_u \Psi^* w\|_2^2 \leq (1 + \delta_K)\|w\|_2^2
\]  

holds for all \(K\)-sparse vectors \(w\). The condition is satisfied when \(\delta_K\) is not too close to one, meaning that the matrix \(F_u \Psi^*\) preserves the Euclidean length of \(K\)-sparse signals. Since, the matrix \(F_u \Psi^*\) has more columns than rows, it cannot be truly orthogonal. When the condition is satisfied, then all subsets of \(K\) columns taken from \(F_u \Psi^*\) are nearly orthogonal. This mitigates the possibility that the sparse signal lies in the nullspace of the matrix \(\text{Null}(F_u \Psi^*) = \{w \in \mathbb{C}^N : F_u \Psi^* w = 0\}\) \((145)\), otherwise there would be no hope of reconstructing it.

The mutual coherence bounds condition determines the minimum number of measurements \(m\) needed for CS to successfully reconstruct an image. This number is on the order of the sparsity of the signal \(K\) and the mutual coherence \(\mu\) \((150)\) between the measurement \(F_u\) and sparsifying \(\Psi\) matrices.
\[ m = O(\mu^2 (F_u \Psi^*) \cdot K \cdot \log(n)), \]  

where \( n \) is the number of coefficients to reconstruct. The mutual coherence is defined as

\[ \mu(F_u \Psi^*) = \max_{i,j} |\langle f_i, \psi_j \rangle|, \]

where \( f_i \) and \( \psi_i \) denote the rows of \( F_u \) and columns of \( \Psi \), respectively, and \( \langle \cdot, \cdot \rangle \) is the inner product of two vectors. In words, the coherence measures the largest correlation between any two elements of \( F_u \) and \( \Psi \). If \( F_u \) and \( \Psi \) contain correlated elements, the coherence is large and more measurements are required to successfully reconstruct the signal. Ideally, we want to select basis sets that minimize the mutual coherence.

While these theoretical results are useful when the sparsity level is known, natural images are generally not exactly sparse but approximately sparse. Therefore the number of measurements is usually determined empirically.

### 3.6.3 Nonlinear Reconstruction

Compressed sensing describes a mathematical framework for acquiring and reconstructing images that can be represented as vectors \( m \in \mathbb{C}^n \). The image of interest is \textit{a priori} compressible in a known basis \( \Psi \) so that \( \| \Psi m \|_1 \leq K \), where \( K \) is the sparsity of the transform signal. If the observations are exact, \textit{i.e.}, no additive noise, the recovery of the signal \( m \) is achieved by solving the basis pursuit problem.
minimize $\|\Psi \mathbf{m}\|_1$

subject to $\mathbf{F}_u \mathbf{m} = \mathbf{s}$, \hspace{1cm} \text{[3.30]}

where $\mathbf{s}$ is the vector formed from the acquired undersampled k-space data and $\mathbf{F}_u$ represents the undersampled Fourier transform. When the observations are corrupted with noise, as it is in real MR imaging applications, the consistency constraint is relaxed and $\mathbf{m}$ is obtained by solving the basis pursuit-denoising problem instead

$$\minimize \|\Psi \mathbf{m}\|_1$$

subject to $\|\mathbf{F}_u \mathbf{m} - \mathbf{s}\|_2^2 \leq \varepsilon$. \hspace{1cm} \text{[3.31]}

The constrained problem in Eq. [3.31] is usually reformulated into an unconstrained problem using the Lagrange formulation

$$\arg \min_{\mathbf{m}} \|\mathbf{F}_u \mathbf{m} - \mathbf{s}\|_2^2 + \lambda \|\Psi \mathbf{m}\|_1,$$ \hspace{1cm} \text{[3.32]}

where $\lambda$ is the regularization parameter, which weights the reconstruction between ensuring data consistency and enforcing sparsity. A variety of methods have been developed to solve the convex optimization represented by Eq. [3.32], including the conjugate gradient method (GG) (152), interior-point method (153), iterative thresholding (154), and Bregman iterations (155). A description of the steepest descent and CG methods is given in Appendix A.

### 3.7 Parallel MR Imaging

Parallel MR imaging (19-22) uses multiple receiver coils to measure the signal emitted from the object of interest (Eq. [3.6]). It was first introduced to improve the signal-to-noise ratio (SNR) of
images by averaging the signal from multiple coils. Assuming equal noise variances and ignoring correlations across the coils, using $L$ coil elements improves the SNR by a factor of $\sqrt{L}$. In reality, however, the surface coils are coupled because the induced field of one coil affects the others. As a result, the noise in each coil is correlated to some extent and the gain in SNR is less than $\sqrt{L}$ (19). The noise covariance matrix $\Lambda \in \mathbb{C}^{L \times L}$ is estimated from pre-scan data by acquiring noise-only images, i.e., acquisition without applying the excitation radio frequency pulse. The unbiased estimate of the covariance between the $i$–th coil and $j$–th coil is given by

$$
\Lambda_{i,j} = \frac{1}{n-1} \sum_{r} \eta_i(r) \bar{\eta}_j(r),
$$

where $\eta_i(r)$ is the noise image voxel value at position $r$, $\bar{\eta}_j$ the complex conjugate of $\eta_j$, and $n$ is number of voxels or samples in the noise image. The matrix describes the correlation of noise between the receiver channels and can be used to account for noise correlation in parallel imaging.

A surface coil element is essentially a loop of conducting material adjacent to the body part of interest. As a rule of thumb, the penetration depth of the sensitivity profile of a circular surface coil is proportional to the diameter of the loop (156). With parallel imaging, the array of surface coil elements is designed to have highly non-uniform spatial sensitivities (Figure 3.14). This non-uniformity is key for signal separation in accelerated parallel imaging. Currently, the newest scanners are capable of acquiring data from up to 128 independent receiver channels (157, 158).
Several approaches are possible for combining the coil images to produce a single composite image. The sum-of-squares method (156) is the simplest approach that provides nearly optimal combination from an SNR point of view. The voxel of the composite image at position $\mathbf{r}$, $m(\mathbf{r})$, is obtained by calculating the square root of the sum of the squared pixel values from each coil at position $\mathbf{r}$,

$$m(\mathbf{r}) = \sqrt{m^*(\mathbf{r})A^{-1}m(\mathbf{r})}, \quad [3.34]$$

where $m(\mathbf{r})$ is the column vector populated with the voxel values $[m_1(\mathbf{r}), \ldots, m_L(\mathbf{r})]^T$ at position $\mathbf{r}$ from the $L$ coils, $m^*$ is the transpose conjugate of $m$, and $A$ is the noise covariance matrix. If no noise-only pre-scan data is available, the identity matrix is used instead of the noise covariance matrix. This approach reconstructs a magnitude image and discards the phase information.

When the coil sensitivities are known, the noise-normalised SNR-optimal coil combination is given by (156)

$$m(\mathbf{r}) = \frac{c^*(\mathbf{r})A^{-1}m(\mathbf{r})}{\sqrt{c^*(\mathbf{r})A^{-1}c(\mathbf{r})}}, \quad [3.35]$$

where $c(\mathbf{r})$ is the column vector containing the coil sensitivities $[c_1(\mathbf{r}), \ldots, c_L(\mathbf{r})]^T$ at voxel position $\mathbf{r}$. This linear combination yields a uniform noise image. This approach preserves the complex-valued image.
Figure 3.14: Parallel acquisition in MR imaging using a 6 coils array: (a) magnitude coil sensitivity profiles; (b) acquired images without subsampling the k-space; and (c) reconstructed sum-of-squares full FOV image.

3.7.1 Coil Sensitivity Estimation

When exact coil geometry is known, the Biot-Savart law can be used to simulate the spatial sensitivities (156). However, the geometry is usually not available and the Biot-Savart law does not account for the dynamic loading of the coil and mutual coupling between the coils. Therefore, the spatial sensitivities are best determined empirically with the subject in the scanner.

Several approaches have been proposed to measure the sensitivities. Dividing each coil image by the sum-of-squares combined image yields an estimate of the spatial sensitivities. However, this approach assumes that all the phase information belongs to the coils, so the result is not suitable for reconstructing complex-valued images. Another approach consists of acquiring an additional
single-coil image with the body coil, and deriving the sensitivities by dividing the coil images by that single coil image. This approach has the advantage of preserving the phase information. Because coil sensitivities are slowly varying across the FOV, they can be determined from low-resolution acquisitions. In addition, polynomial fitting is commonly used to improve the robustness of the sensitivity estimation to noise.

Sensitivity profiles can also be measured using a more sophisticated approach, called ESPIRiT (159). This approach estimates the sensitivity maps from autocalibration lines in k-space via an eigenvalue decomposition procedure. ESPIRiT yields robust sensitivity maps, but it is also more computationally intensive than polynomial fitting approaches.

3.7.2 Accelerated Parallel Imaging

Over the last 15 years, much research has focused on exploiting the data redundancy and the spatial sensitivity information inherent in an array of receiver coils to accelerate MR imaging. As a result, many different parallel imaging reconstruction techniques have been developed. The most encountered are simultaneous acquisition of spatial harmonics (SMASH) (20), sensitivity encoding (SENSE) (19), generalized autocalibrating partially parallel acquisition (GRAPPA) (21), and iterative self-consistent parallel imaging reconstruction from arbitrary k-space (SPIRiT) (22). SENSE and GRAPPA have become clinical standards, as these techniques are commercially available and used routinely in clinical settings. The next sections introduce the basic concepts of SENSE, GRAPPA, and SPIRiT.
3.7.3 Overview of SENSE

SENSE (19, 160) is a standard reconstruction method for parallel imaging routinely used in clinical settings. It was originally designed to “unfold” coherent aliasing in the image domain arising from Cartesian uniform undersampling of k-space (19). Such subsampling yields deterministic fold-over artefacts, for which the location and distance between periodic repetitions in image domain are well known (Figure 3.15). Each voxel in the reduced FOV coil images contains information from multiple, equidistant voxels in the desired full FOV image. Because of the non-uniformity of the receiver coil, these voxels are weighted with the coil sensitivity at the corresponding location in the full FOV. The number of superimposed voxels depends on the acceleration or undersampling factor $R$. The voxel in the reduced FOV image of the $l$-th coil, $m'_l(\mathbf{r}')$, is given by

$$m'_l(\mathbf{r}') = \sum_{p=1}^{R} c_l(\mathbf{r}_p)m(\mathbf{r}_p),$$  \hspace{1cm} [3.36]

where $m(\mathbf{r}_p)$ is unknown voxel value of the full FOV image at location $\mathbf{r}_p$, and $c_l(\mathbf{r}_p)$ is the $l$-th coil sensitivity corresponding to that location. With one coil, we have one equation and $R$ unknowns. However, by including all $L$ coils, we obtain a set of $L$ linear equations with $R$ unknowns,

$$\mathbf{m}' = \mathbf{Cm},$$  \hspace{1cm} [3.37]

where $\mathbf{m}' = [m'_1(\mathbf{r}') \ldots m'_L(\mathbf{r}')]^T$, $\mathbf{m} = [m(\mathbf{r}_1) \ldots m(\mathbf{r}_R)]^T$, and $\mathbf{C} \in \mathbb{C}^{L \times R}$. The method of least squares is used to calculate the full FOV voxels.
\[ \mathbf{m} = (\mathbf{C}^t \Lambda^{-1} \mathbf{C})^{-1} \mathbf{C}^t \Lambda^{-1} \mathbf{m}'. \]  

[3.38]

Theoretically, the “unfolding” process is possible as long as the matrix inversion in Eq. [3.38] is possible, i.e., the maximum acceleration for a coil of \( L \)-elements is \( R \leq L \). Because of noise, however, \( R \) does usually not exceed 2 or 4 for 16- or 32-channel receiver coil.

![Illustration of the SENSE reconstruction of deterministic aliasing interference arising from uniform undersampling of k-space.](image)

\[ \mathbf{m}' = \mathbf{C} \cdot \mathbf{m} \]

Figure 3.15: Illustration of the SENSE reconstruction of deterministic aliasing interference arising from uniform undersampling of k-space.

A more general implementation allowing reconstruction from arbitrary k-space trajectories was subsequently proposed (160). Neglecting noise correlation between the coils, the general SENSE equation for arbitrary samplings is
\[ \mathbf{E}\mathbf{m} = \mathbf{s}, \]  

where \( \mathbf{m} \) is the unknown vector defining the final composite image to be reconstructed, \( \mathbf{s} \) is the vector formed by concatenating the k-space data from all coils, and \( \mathbf{E} \) is the sensitivity encoding matrix composed of the Fourier kernel and the complex spatial sensitivity. The entries of the sensitivity encoding matrix are

\[ \mathbf{E}_{(l,n),p} = e^{i\mathbf{k}_n\mathbf{r}_p}c_l(\mathbf{r}_p), \]

where \( \mathbf{k}_n \) denotes the position of the \( n \)-th sampling point in k-space, \( \mathbf{r}_p \) the position of the \( p \)-th pixel, and \( c_l(\mathbf{r}_p) \) the complex sensitivity of the \( l \)-th coil at position \( \mathbf{r}_p \). To solve for the least squares solution, Eq. [3.39] is rewritten as

\[ (\mathbf{E}^*\mathbf{E})\mathbf{m} = \mathbf{E}^*\mathbf{s}. \]

Here, \( \mathbf{E}^* \) denotes the conjugate transpose of \( \mathbf{E} \). Pruessmann et al. (160) improved the reconstruction by preconditioning the system of equations in Eq. [3.41] by performing both density and intensity/amplitude corrections,

\[ (\mathbf{A}\mathbf{E}^*\mathbf{D})\mathbf{m} = \mathbf{A}\mathbf{E}^*\mathbf{D}\mathbf{s}, \]

where \( \mathbf{A} \) and \( \mathbf{D} \) are diagonal matrices for intensity/amplitude and density correction, respectively. This equation is often solved using the conjugate gradient method.
3.7.4 Overview of GRAPPA

GRAPPA (21) is another standard reconstruction for parallel imaging, which takes place in k-space. Unlike SENSE, GRAPPA reconstructs every intermediate coil image prior to combining them into a final composite image. To synthesize a non-acquired k-space value, GRAPPA applies a linear combination of the acquired neighbouring k-space data from all coils (Figure 3.16a). Using the formalism introduced by Lustig et al. (22), the recovery of a non-acquired k-space value \( s_I(k) \) at position \( k \) from the \( l \)-th coil is given by

\[
s_I(k) = \sum_j w_{jkl} (\tilde{R}_k s)_j,
\]

where \( \tilde{R}_k \) is a set of operators that select the location of acquired k-space data in the neighbourhood of k-space position \( k \), such that the product \( \tilde{R}_k s \) returns a vector of acquired k-space values in the neighbourhood of position \( k \), and \( w_{jkl} \) is a vector of linear combination weights previously calculated by calibration for the sampling pattern \( \tilde{R}_k \). The calibration procedure uses a fully sampled region at the origin of k-space to calculate the set of weights that is the most consistent with the calibration data in the least-squares sense. In matrix form, the calibration consists of solving

\[
\arg \min_{\mathbf{g}_{kl}} \| \mathbf{S} \mathbf{w}_{kl} - \mathbf{s}_l \|_2^2,
\]

where \( \mathbf{S} \) is a matrix whose entries are all the \( \tilde{R}_k s \) vectors in the calibration region, and \( \mathbf{w}_{kl} \) is a vector formed by concatenating all the \( w_{jkl} \) combination weights. Tikhonov regularization is often used to obtain an explicit solution for the weights:
\[ w_{kl} = (\mathbf{S}^* \mathbf{S} + \beta \mathbf{I})^{-1} \mathbf{S}^* s_l. \]  

[3.45]

Figure 3.16: GRAPPA (a) and SPIRiT (b) reconstructions. GRAPPA synthesizes the missing k-space samples from neighbouring acquired samples only, whereas the iterative SPIRiT reconstruction uses both acquired and non-acquired neighbouring samples. Figure reproduced from (22).

3.7.5 Overview of SPIRiT

SPIRiT (22) can be seen as a generalization of GRAPPA and the techniques share many properties. Whereas GRAPPA uses only acquired neighbouring k-space data to synthesize a non-acquired k-space value, SPIRiT uses both acquired and non-acquired neighbouring k-space data (Figure 3.16b). In other words, the set of operators \( \bar{\mathbf{K}}_k \) in GRAPPA is replaced by the set of
operators $K_k$ in SPIRiT, which selects all points in the immediate neighborhood of $k$, whether they were acquired or not. Therefore, the operator $K_k$ is independent of the actual k-space sampling pattern and remains constant for all k-space positions. The recovery of a k-space value $s_i(k)$ with SPIRiT is given by

$$s_i(k) = \sum_j w_{jl} (K_k s)_j.$$  \[3.46\]

The $w_{jl}$ weights differ from the GRAPPA $w_{kli}$ weights since they are independent of the actual k-space sampling pattern. The calibration procedure in SPIRiT is identical to GRAPPA, but it uses the $K_k$ operator instead of $\tilde{K}_k$. Unlike in Eq. [3.43], the larger set of equations in Eq. [3.46] is coupled because non-acquired data are also used in the calculation. The entire system of coupled equations is conveniently written in matrix form

$$s = Ws,$$  \[3.47\]

where $s$ is the concatenation of the k-space data from all coils, and $W$ is the concatenation of the $w_{jl}$ weights at the appropriate locations. The matrix $W$ is effectively a series of convolution operators and Eq. [3.47] states that the convolution of $s$ and $W$ returns $s$, i.e., $s$ is the eigenvector of $W$ with unit eigenvalue. To avoid trivial solutions such as $s = 0$, it is necessary to constrain the data to be consistent with the acquired undersampled k-space data, namely

$$s_{acq} = Us,$$  \[3.48\]
where \( s_{\text{acq}} \) is the concatenation of the acquired undersampled k-space data, and \( U \) is the operator selecting the acquired undersampled k-space data from the fully sampled data. Finally, the synthesis of non-acquired k-space data is obtained by solving the optimization problem given by

\[
\begin{align*}
\text{minimize} & \quad \| (W - I)s \|_2^2 \\
\text{subject to} & \quad \| Us - s_{\text{acq}} \|_2^2 \leq \varepsilon.
\end{align*}
\]

This constrained problem is usually reformulated into an unconstrained problem using the Lagrange formulation (Eq. [3.49]) and solved with the conjugate gradient algorithm or projection over convex sets (POCS) algorithm:

\[
\arg \min_s \| Us - s_{\text{acq}} \|_2^2 + \lambda \| (W - I)s \|_2^2.
\]

### 3.8 Compressed Sensing Combined with Parallel MR Imaging

To resolve the aliasing interference arising from the sub-Nyquist-Shannon sampling (132, 133), parallel imaging techniques rely on the spatial sensitivity information inherent in an array of multiple receiver surface coils. Compressed sensing (CS), however, depends on the sparsity of the data in a given domain. Since both approaches rely on complementary information to recover the unsampled data, it may be advantageous to combine them for further improvement. Solutions for this include sequential reconstruction of CS and SENSE (CS-SENSE) (27), merged reconstruction of CS and SENSE (sparse SENSE) (161), and \( \ell_1 \)-regularized SPIRiT (L1-SPIRiT) (22).
3.8.1 Overview of CS-SENSE

In CS-SENSE, the CS and SENSE reconstruction steps are implemented sequentially. This approach first applies CS to reconstruct the aliased image from each coil and then SENSE to “unfold” the final composite image. The aliased image with reduced field of view from the $l$-th coil, $m_l^{\text{aliased}}$, is obtained by solving the optimization problem given by

$$\arg\min_{m_l^{\text{aliased}}} \|F_m m_l^{\text{aliased}} - s_l^{\text{aliased}}\|_2^2 + \lambda \|\Psi m_l^{\text{aliased}}\|_1,$$  \hspace{1cm} [3.51]

where $s_l^{\text{aliased}}$ is the aliased and undersampled k-space data acquired with the $l$-th coil. The aliased coil images are then unfolded with SENSE by solving the set of linear equations

$$m^{\text{aliased}} = Cm,$$ \hspace{1cm} [3.52]

where $m^{\text{aliased}}$ is the concatenation of the aliased images from all coils, $m$ is the final composite image, and $C$ is a matrix of sensitivity modulation characterizing the coherent aliasing by mapping the full FOV image $m$ onto the set of aliased images with reduced FOV, $m^{\text{aliased}}$.

3.8.2 Overview of Sparse SENSE

In sparse SENSE, the CS and SENSE reconstructions are merged together. This approach recovers the signal by solving the optimization problem given by

$$\arg\min_{m} \|Em - s\|_2^2 + \lambda \|\Psi m\|_1.$$ \hspace{1cm} [3.53]

This problem is similar to the CS problem in Eq. [3.32], but here $m$ is the unknown final composite image, $s$ is the vector formed by concatenating the k-space data from all coils, and
\[ E = F_u C \] is the sensitivity encoding matrix including both the undersampled Fourier transform and coil sensitivity matrix as defined in Eq. [3.40].

### 3.8.3 Overview of L1-SPIRiT

L1-SPIRiT (22) extends the SPIRiT reconstruction by incorporating a sparsity constraint to the optimization problem. When the image to reconstruct is known to be sparse in a basis \( \Psi \), it is advantageous to include this prior knowledge into the reconstruction by defining the following optimization problem

\[
\arg \min_m \|u s - s_{acq}\|_2^2 + \lambda_1 \|W - 1\|s\|_2^2 + \lambda_2 \|\Psi F^* m\|_1,
\]

where \( F^* \) is the inverse Fourier transform operator (i.e., conjugate transpose of \( F \)), and \( \Psi \) is a sparsifying operator, such as the wavelet or finite-difference operators.

### 3.9 Summary

In MR imaging, the raw data is acquired by astutely applying imaging sequences that combine RF pulses and magnetic field gradients. These data are encoded and mapped into a matrix, known as k-space; it represents the spatial frequencies of the imaged object. In most MR data acquisitions, k-space is evenly sampled on a rectilinear grid, allowing reconstruction of the MR image by applying the inverse Fourier transform. However, measuring each set of k-space samples is very time consuming and severely limits the spatial and/or temporal resolution.

To accelerate MR imaging, one efficient strategy consists of reducing the number of acquired data by sampling only a subset of the k-space coefficients. Undersampled acquisitions, however,
no longer satisfy the Nyquist-Shannon sampling condition and results in aliasing artefacts. Several algorithms have been developed to resolve these aliasing artefacts. The algorithms rely on model-based *a priori* information and/or the spatial sensitivity information inherent in an array of multiple receiver coils. In this chapter, I first presented the CS model-based framework that exploits the inherent compressibility of images by promoting a sparse solution in a given domain. I then introduced parallel imaging methods, *i.e.*, SENSE, GRAPPA, and SPIRiT, that exploit the data redundancy and spatial sensitivity information available with multiple receiver coils. Finally, I discussed the reconstruction methods that combine CS with parallel imaging, *i.e.*, sparse SENSE, CS-SENSE, and L1-SPIRiT.
Passive MR imaging is a promising approach to visualize catheters in guiding and monitoring endovascular intervention (see section 2.4.3), and may offer several clinical advantages over the current “gold standard” of x-ray fluoroscopy. Endovascular MR imaging has limitations, however, such as difficulty to visualize catheters and insufficient temporal resolution. The multicycle projection dephaser (mcPD) method is a background signal suppression technique that improves the conspicuity of passive catheters by generating a sparse (i.e., catheter only) image. One approach to improve the temporal resolution is to undersample the k-space and then apply nonlinear methods, such as compressed sensing (CS), to reconstruct the MR images. This feasibility study investigates the potential synergies between mcPD and CS reconstruction for real-time passive catheter tracking. The mcPD method efficiently suppressed the background signal and CS allowed MR images to be reconstructed with superior catheter conspicuity and spatial resolution when compared to the more conventional zero-filling reconstruction approach. Moreover, CS allowed the shortening of total acquisition time (by up to 32 times) by vastly undersampling the k-space while simultaneously preserving spatial resolution and catheter conspicuity.

4.1 Introduction

Modern treatments for vascular diseases can involve minimally invasive endovascular interventions that rely on catheters to deploy therapeutic devices (e.g., angioplasty balloons, aneurysm coils and stents) or drugs (e.g., thrombolytic agents) (162). This requires continuous monitoring of the progression of the catheter within the vasculature; a refresh rate of 10 frames per second offers relatively good temporal resolution and can be considered effectively near real-time imaging (163). Currently, x-ray fluoroscopy is the “gold standard” for monitoring and guiding catheter-based endovascular procedures because it provides a clinically acceptable catheter conspicuity with high spatial and acceptable temporal resolution (164). However, x-ray imaging suffers from a number of drawbacks: it exposes patients and staff to ionizing radiation, and requires the use of iodinated contrast agents to visualize the vasculature (165, 166). MR-guided endovascular interventions are an alternate and promising approach (164) that offer many advantages over conventional x-ray fluoroscopy, including high soft-tissue contrast and the ability to provide anatomical, physiological and functional information, three-dimensional imaging in arbitrary orientations, and a lack of ionizing radiation or iodinated contrast agents (163, 167, 168).

In comparison to x-ray imaging, catheters, guide-wires and other endovascular devices are not directly visible in MR imaging. Techniques used to make these devices MR visible fall into two categories: active and passive visualizations (169). Active techniques rely on additional hardware, such as miniature local radiofrequency (RF) coils on the catheter tip (170-173), to achieve localization, allowing for spatial and temporal resolutions that rival x-ray imaging. However, active techniques often lack information about device orientation and can have safety
concerns associated with tissue heating due to RF-induced currents in the conductive electrical device (169). Passive catheter visualization, by comparison, relies on the intrinsic signal from the device and thus requires no additional active components, thereby reducing the safety concerns from heating. Passive techniques also yield visualization of the entire length of the catheter, provided that the device stays within the imaged volume. Here, we use the multi-cycle projection dephaser (mcPD) method (174) to visualize catheters, since it efficiently suppresses the background signal and improves catheter conspicuity.

One challenge of passive MR guidance is the difficulty in achieving real-time imaging. For instance, conventional 2D MR imaging techniques acquire a complete and uniformly sampled k-space, and then images are reconstructed by inverse Fourier transform (iFT). The total scan time for 2D imaging is $T_{acq} = N_{av} N_y TR$, where $N_{av}$, $N_y$, and TR are the number of averaged signal acquisitions, the number of phase encodings, and the repetition time, respectively. For $TR = 5$ ms, $N_{av} = 1$, and a $256 \times 256$ acquisition matrix, the total acquisition time per image, $T_{acq}$, is 1.28 s. This corresponds to a frame rate of 0.78 Hz, which is too slow for real-time MR guidance. Reducing $N_y$ represents an effective approach for decreasing the acquisition time, although this results in either a smaller field of view (FOV) or a lower image resolution, neither of which may be acceptable. A more advanced approach consists of reducing $N_y$ while attempting to preserve both FOV and image resolution by acquiring undersampled k-space datasets and using more advanced, nonlinear image reconstruction algorithms. The temporal acceleration factor achieved with such approaches is directly related to the undersampling factor.
The zero filling (ZF) method (143) is the simplest method for reconstructing undersampled k-space datasets. This linear method zeroes the missing data before applying the iFT. Albeit simple and fast, this widely used approach results in image artefacts (119), specifically blurring and ringing. A better and more accurate image reconstruction can be achieved using nonlinear methods, such as projection onto convex sets (POCS) (120, 175, 176), transient error reconstruction algorithm (TERA) (120, 177), or phase-constrained TERA (PC-TERA) (178). Compressed sensing (CS) is a novel nonlinear reconstruction paradigm (25, 26) that was recently shown to successfully reconstruct undersampled k-space datasets (139, 144). CS can reconstruct MR images with high accuracy from significantly fewer k-space samples than required by the Nyquist-Shannon sampling theorem, provided that the images have a sparse representation in one or more domains. When applied to passive catheter tracking, this reduction in sampling allows for shorter acquisition time and thus potentially lays the foundation for achieving real-time MR tracking.

Another approach for reducing $N_r$ is the use of parallel MR imaging, which relies on the spatial sensitivity information inherent in an array of multiple receiver surface coils to perform some of the time-consuming Fourier encoding steps. The most well-known parallel imaging techniques are SENSE (16), SMASH (179), and GRAPPA (21). However, in this study, we only investigate the use of CS for accelerating MR imaging.

Our hypothesis in this feasibility study is that mcPD background suppression produces the appropriate sparse data, which when coupled with an appropriate undersampling scheme and CS image reconstruction, will generate high quality, high temporal resolution images compared to
the conventionally used ZF algorithm. Here, we propose and evaluate a novel combination of acquisition and reconstruction strategies for enhancing temporal resolution of passive catheter tracking using mcPD together with CS. This combination not only preserves the spatial resolution of the catheter but also improves its conspicuity, even for high undersampling factors (up to 32 times).

4.2 Methods

4.2.1 Passive Catheter Tracking

Demonstrated approaches for passive tracking with positive image contrast consist of filling the lumen (180, 181) or coating device (182, 183) with an MR contrast agent, such as gadolinium DTPA. The resulting images generally still have low image contrast relative to background signals making for poor intrinsic conspicuity. The conspicuity can be markedly improved by suppressing the signal from surrounding background tissues, e.g., with the projection dephaser (PD) method (181). This method applies a small magnetic gradient in the slab-select direction, which dephases the tissue signal to near cancellation (Figure 4.1). One can think of the PD method as to encode the image slice in the z-direction by selecting a $G_z$ gradient that yields $k_z = 1$/slice thickness. Smaller devices, such as catheters, are much smaller than the slab and thus are less affected by the dephasing gradient. Although the PD method works well in theory, non-idealities such as tissue inhomogeneities and a non-rectangular slab-selection profile reduce the efficiency of the background signal cancellation. To address these non-idealities, the multi-cycle PD (mcPD) method was implemented (174), which instead of applying one-cycle across the slab, it uses multiple cycles of dephasing.
Here, we capitalize on the additional property that the mcPD method produces images that are, in principle, sparse in the image, as well as in other domains. This is a critical property when contemplating CS reconstruction (139). Ideally, the mcPD method achieves perfect background suppression and produces a catheter-only image (Figure 4.2a). A good theoretical approximation of a straight catheter (with signal intensity $I_0$) is a rectangular function defined by its length, $L$, and its width, $W$, whose k-space representation (Figure 4.2b) is:

\[
S(k_x, k_y) = I_0WL \text{sinc}(k_xW) \text{sinc}(k_yL), \tag{4.1}
\]

where $\text{sinc}(x) := \frac{\sin(\pi x)}{\pi x}$. A comparison of the image and k-space representations confirms that the k-space energy is essentially concentrated along a line perpendicular to the direction of the long axis of the catheter in the image domain and passes through the origin of k-space. This simple model demonstrates that an efficient sampling scheme for catheter images should

Figure 4.1: Schematic illustration of the projection dephaser (PD) method. (a) The catheter lies within the imaging plane and its diameter is much smaller than the slice thickness. (b) The PD method applies a small magnetic gradient in the z-direction, which dephases homogeneous tissue signal to near cancellation, whereas the signal from the catheter is less affected by the dephasing gradient as it is smaller than the slice thickness.
preferably acquire k-space samples along the line perpendicular to the catheter orientation, an observation that has been used in other nonlinear reconstruction approaches (184). Figure 4.2c shows the catheter in the wavelet domain. Like the image domain, the wavelet domain provides a sparse representation of the mcPD catheter image, i.e., it is represented by only a few large coefficients.

![Figure 4.2](image)

Figure 4.2: Illustration of ideal catheter data obtained using the multi-cycle projection dephaser (mcPD) method. Catheter data representation in the image domain (a), k-space domain (b), and wavelet domain (c). The catheter representation in the image domain is approximated by a rectangle of length, $L$, and width, $W$. Both the image (a) and wavelet (c) domains provide a sparse representation of the data.

### 4.2.2 Experiments and Acquisition

*In vivo* catheter visualization experiments were performed in a canine model following a protocol approved by the local Animal Care Committee (see Appendix C for ethics approval). Dogs (20 kg to 25 kg) were used in these studies and their care, sedation, and procedure followed standard techniques as described in Ref (174). Punctures in the femoral artery provided vascular access for 4 F (1 mm diameter) (Polyethylene Catheter; COOK Medical, Bloomington, IN) or 6...
F (2 mm) (Soft-Vu; Angiodynamics, Queensbury, NY) catheters, which were placed into the aorta or common carotid artery under x-ray guidance (OEC 9800; General Electric Healthcare). The catheter was filled with a 20 mM Gd-DTPA (i.e., diluted to 4%, Magnevist, Schering, Wayne, NJ) solution to maximize catheter signal for the mcPD acquisition parameters (185). Then, fully sampled datasets were acquired with the MR scanner. Thereafter, we synthesized real-time acquisition via undersampling of the fully sampled datasets to achieve/demonstrate the feasibility of real-time compressive sampling applied to catheter tracking.

The fully sampled catheter images were acquired with a quadrature head coil on a 3.0 T MR scanner (Signa VH/i; General Electric Healthcare, Waukesha, WI) using a modified fast spoiled gradient-recalled echo (FSPGR) pulse sequence with the following acquisition parameters: TR = 7.1 ms, TE = 3.4 ms, flip angle = 20°, slice thickness = 40 mm, FOV = 16 cm × 16 cm, acquisition matrix = 256 × 256, and total scan time per image = 1.82 s. The modified FSPGR sequence acquired a reference image with no background suppression applied, followed by 40 images with phase cycle lengths varying from 1 mm to 40 mm in 1 mm increments. For the rest of this study, we selected the phase cycle length that resulted in the best compromise between catheter conspicuity and background signal suppression, which was a dephaser cycle length of 3 mm (i.e., slightly larger than the diameter of the catheter being imaged). More in depth discussion about the cycle length selection can be found in (174).

4.2.3 Retrospective Undersampling

Several undersampled k-space datasets were derived from the fully sampled k-data by using circular and elliptical deterministic central zone undersampling schemes. These schemes
simulated acceleration factors of 4, 8, 16, and 32. In order to minimize Gibbs ringing (119) introduced by the truncation of k-space data, the central zone sampling schemes were filtered with a Fermi filter (186) prior to ZF reconstruction. The Fermi filter is defined by \( H(k) = (1 + e^{w_f(|k| - k_f)})^{-1} \), where \( k_f \) determines the full width at half maximum of the filter, and \( w_f \) determines the sharpness of the cutoff frequency. For normalized \(|k| \leq 1\), typical values are \(0.85 \leq k_f \leq 1.0\) and \(10 \leq w_f \leq 30\).

For CS reconstruction, we simulated several undersampled datasets with acceleration factors of 4, 8, 16, and 32 by randomly choosing frequency samples from the fully sampled k-space dataset. The sample selection was based on a probability density function (PDF) to ensure selection of more samples near the centre compared to the periphery of k-space. This PDF varied according to the elliptical distance from the origin, \(d(k_x, k_y) = \sqrt{\frac{k_x^2}{a^2} + \frac{k_y^2}{b^2}}\). The parameters \(a\) and \(b\) are the length of the semi-major and semi-minor axes respectively, and the eccentricity is given by \(ecc = \sqrt{1 - \frac{b^2}{a^2}}\). An eccentricity of zero results in a circular PDF, whereas \(0 < ecc < 1\) results in an elliptical PDF. To ensure better performance, a central zone of k-space of fractional area, \(0.01 \leq f_{ctr} \leq 1.0\), was always acquired. In other words, the PDF is unity at some distance \(d(k_x, k_y) \leq k_0\), such that the distribution function is given by:

\[
PDF(k_x, k_y) = \begin{cases} 
1 & \text{if } d(k_x, k_y) \leq k_0 \\
\left(\frac{k_0}{d(k_x, k_y)}\right)^p & \text{if } d(k_x, k_y) > k_0 
\end{cases}
\]  

[4.2]
where $p \in \mathbb{R}$ (here, $\mathbb{R}$ represents the set of all real numbers) is empirically determined to achieve the desired acceleration factor for a given $k_0$. Figure 4.3 illustrates a PDF for an acceleration factor of 4 with $ecc = 0.95$ and $f_{ctr} = 0.01$. In order to accommodate any catheter orientation, the elliptical PDF can be rotated to any arbitrary angle.

In this feasibility study, we perform random sampling in 2D, which is impractical for MR imaging hardware. In practice, one can only undersample in the phase encode direction. However, true 2D random sampling in the phase encodes is possible when imaging in 3D.

Figure 4.3: Illustration of an elliptical PDF used for k-space undersampling with an acceleration factor of 4, $ecc = 0.95$, and $f_{ctr} = 0.01$. The two cross-section profiles were taken through the centre of the PDF.
4.2.4 Image Reconstruction with Compressed Sensing

To successfully reconstruct an image, CS requires that 1) the image to be reconstructed is sparse (or compressible) in a transform domain (e.g., the wavelet or discrete cosine domains), 2) the aliasing artefacts due to k-space undersampling are incoherent in that transform domain, and 3) an appropriate nonlinear reconstruction algorithm is used. Most medical images, including the mcPD catheter images, meet the first CS requirement. To satisfy the second requirement, the k-space undersampling scheme should ideally be purely random (139), since random sampling prevents constructive aliasing interferences in the transform domain. However, the energy distribution of images is concentrated at the origin of k-space; this suggests that, for better performance, more samples should be acquired at the centre of k-space and less at the periphery of k-space. This prompted Lustig et al. (139) and others (187) to suggest using a PDF sampling scheme. As for the third requirement, the nonlinear reconstruction algorithm must enforce both sparsity of the image representation in the transform domain and consistency with the acquired k-space data (Figure 4.4).

The CS reconstruction paradigm efficiently solves the following nonlinear constrained optimization problem (139)

\[
\begin{align*}
\text{minimize} & \quad \| \Psi \mathbf{m} \|_1 \\
\text{subject to} & \quad \| \mathbf{F}_u \mathbf{m} - \mathbf{s} \|_2^2 \leq \varepsilon,
\end{align*}
\]

where \( \mathbf{m} \) is the reconstructed vector image, \( \mathbf{s} \) is the acquired k-space data, \( \mathbf{F}_u \) represents the undersampled Fourier transform, \( \Psi \) is an orthogonal sparsifying transform (e.g., a wavelet or discrete cosine transform), \( \| \Psi \mathbf{m} \|_1 \) is the sparsity objective or cost function, \( \| \mathbf{F}_u \mathbf{m} - \mathbf{s} \|_2^2 \) is the
data consistency constraint, and \( \| \cdot \|_p^p := \sum |\gamma_i|^p \) is the \( \ell_p \)-norm. The objective function in Eq. [4.3] is the \( \ell_1 \)-norm of the transform coefficients. The \( \ell_1 \)-norm is the key concept introduced by CS and promotes a sparse representation of the image in the transform domain. The \( \ell_2 \)-norm constraint in Eq. [4.3] enforces data consistency. Because of k-space undersampling, there is not a unique solution for \( \mathbf{m} \) that is consistent with the acquired data, \( \mathbf{s} \). However, among all of the possible solutions that satisfy the data consistency constraint, the problem defined in Eq. [4.3] finds a solution that is also sparse in the transform domain. A sparse solution is desired since the image to reconstruct is expected to be sparse in the transform domain. Because mcPD catheter images achieve good suppression and have a sparse representation in both the wavelet and image
domains (see Figure 4.2), in this study we used both the wavelet (188) and the identity transforms as sparse transform domains, such that the Lagrange formulation of Eq. [4.3] becomes:

\[
\arg \min_{\mathbf{m}} \| \mathbf{F}_m \mathbf{m} - \mathbf{s} \|^2_2 + \lambda_1 \| \Psi \mathbf{m} \|_1 + \lambda_2 \| \mathbf{m} \|_1 ,
\]  

[4.4]

where \( \lambda_1 \) and \( \lambda_2 \) are the Lagrange multipliers that characterize the sparsity in the wavelet and image domains, respectively, and \( \Psi \) represents the wavelet transform operator (Daubechies-4). To solve the nonlinear constrained optimization problem defined by Eq. [4.4], we used the conjugate gradient method (152).

Conventional iFT reconstruction was used to reconstruct fully sampled k-space datasets. These reconstructed images serve as the baseline for comparing the performance of CS and ZF reconstruction procedures. For variable density undersampled k-space datasets, the images were reconstructed with the CS algorithm. In this study, we used the Daubechies-4 wavelet for the wavelet transform. The regularization parameters, \( \lambda_1 \) and \( \lambda_2 \), in Eq. [4.4] were varied from 0 to 10. For the Fermi-filtered central zone sampling schemes, the images were reconstructed by ZF. CS and ZF reconstructed images were compared at equivalent acceleration factors. Our iFT, CS and ZF applications were implemented using MATLAB 7.5.0 (Mathworks Inc, Natick, MA).

**4.2.5 Analysis Metrics**

Reconstructed catheter images were assessed qualitatively by visual inspection and quantitatively by measuring the normalized catheter signal-to-noise difference (SND) and the catheter width broadening ratio (CWBR) (184). The SND characterizes the catheter conspicuity and is given as
\[ \text{SND} = 1 - \frac{\sigma_{\text{noise}}}{s_{\text{cath}}} \] (0 \leq \text{SND} \leq 1), where \( s_{\text{cath}} \) and \( \sigma_{\text{noise}} \) are the catheter signal average and background noise standard deviation, respectively, determined from user-defined region of interests. Values close to one or zero imply high or low catheter conspicuity, respectively. The SND was chosen instead of the more common signal-to-noise ratio \( \text{SND} = \frac{s_{\text{cath}}}{\sigma_{\text{noise}}} \) because CS reconstructed images have \( \sigma_{\text{noise}} \) approaching zero. The CWBR is a measure of the image sharpness. The CWBR is explicitly given as \( \text{FWHA}/\text{FWHA}_0 \), where \( \text{FWHA} \) is the value of full-width at half amplitude of the signal intensity profile measured in the undersampled image across the catheter width, and \( \text{FWHA}_0 \) is the FWHA value of the fully sampled image. Values larger or smaller than unity imply reconstruction-induced broadening or thinning of the catheter width, respectively. The CWBR measurements were repeated at 20 different locations along the catheter, and the mean and standard deviation of the measurements are reported.

4.3 Results

Figure 4.5 presents fully sampled k-space and reconstructed image data of a catheter in a canine carotid artery acquired without and with background suppression. As expected, the use of mcPD effectively suppresses the background signal and improves catheter conspicuity (compare Figure 4.5c and Figure 4.5d). Suppressing the background signal also modifies the energy distribution in k-space and aligns it more perpendicular to the catheter orientation (compare Figure 4.5a and Figure 4.5b with Figure 4.2). Figure 4.5d provides experimental support that a well-suppressed mcPD image is sparse – it contains mostly signal from the catheter and little signal from the background tissue.
Figure 4.5: Fully sampled k-space data of a catheter in a canine carotid artery acquired without (a) and with (b) mcPD, and the corresponding inverse FT (iFT) *in vivo* images (c) and (d).
Figure 4.6 presents mcPD catheter images reconstructed using the CS algorithm for a range of different $\lambda_1$ and $\lambda_2$ regularization values. The k-space data were 8-fold undersampled using the elliptical variable density scheme defined in Eq. [4.2] with parameter $ecc = 0.98$. An eccentricity of 0.98 corresponds to a semi-major axis length of about five times that of the semi-minor axis length so as to preferentially skew the sampling PDF along one direction (and oriented perpendicular to the catheter direction). Large values of $\lambda_1$ and $\lambda_2$ force sparsity in the wavelet and image domains, respectively. Visual inspection of Figure 4.6 demonstrates that larger values of $\lambda_1$ and $\lambda_2$ improved catheter conspicuity by further suppressing the background signal. However, excessive values of $\lambda_1$ or $\lambda_2$ resulted in suppression of some of the catheter signal (cf., Figure 4.6o and Figure 4.6p). Figure 4.6n ($\lambda_1 = 0.1$ and $\lambda_2 = 10$) seems to offer a good visual compromise between background signal suppression/catheter conspicuity, and geometric fidelity of the catheter. By appropriately selecting the regularization parameters, variable density sampling with CS preserved high spatial resolution and also removed most of the background noise. The SND measures (Table 4.1) confirm this observation. For large $\lambda_1$ and $\lambda_2$ values, both the SND and the catheter conspicuity increase.
Figure 4.6: CS reconstruction of mcPD catheter images for different $\lambda_1$ and $\lambda_2$ values that enforce sparsity in the wavelet and image domains, respectively. Large values of $\lambda_1$ and $\lambda_2$ efficiently improved catheter conspicuity by further suppressing the background signal. However, excessive increase of $\lambda_1$ or $\lambda_2$ resulted in loss of catheter signal (arrows in Figures o and p).
Table 4.1: Normalized catheter signal-to-noise difference (SND) values derived from catheter images in Figure 4.6.

<table>
<thead>
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<th>$\lambda_1$</th>
<th>0</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
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<tbody>
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<td>0</td>
<td>0.924</td>
<td>0.917</td>
<td>0.912</td>
<td>0.952</td>
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<tr>
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<td>0.894</td>
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<td>0.951</td>
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<td>0.964</td>
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<td>10</td>
<td>0.997</td>
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</tr>
</tbody>
</table>

Figure 4.7 compares images reconstructed from fully sampled and 8-fold undersampled k-space datasets using iFT, ZF and CS and shows a cross-sectional profile through the catheter for each method. The corresponding SND and CWBR measurements are given in Table 4.2. As expected, ZF reconstruction in conjunction with circular central zone sampling of the k-space resulted in a low-resolution image and a broad catheter profile, i.e., larger CWBR value. An improved catheter profile and higher SND were achieved by combining elliptical central zone sampling with ZF, as more high frequency components perpendicular to the catheter orientation were acquired. Circular variable density sampling with CS preserved high spatial resolution and also removed most of the background noise. Elliptical variable density sampling with CS achieved the highest SND yet simultaneously preserved the spatial resolution.
Figure 4.7: Reconstructions of fully sampled and 8-fold undersampled k-space datasets using the iFT, zero filling (ZF) and CS algorithms. The first row depicts the k-space sampling schemes; the middle row shows the reconstructed images; and the bottom row illustrates the cross-section profiles of the catheter shown in red. For the circular and elliptical central zone sampling schemes, the parameters were $ecc = 0.0$ and $ecc = 0.96$, respectively. For the circular variable sampling scheme, the parameters were $ecc = 0.0$, $f_{ctr} = 0.05$, $\lambda_1 = 1.0$, and $\lambda_2 = 7.0$. For the elliptical variable sampling scheme, the parameters were $ecc = 0.96$, $f_{ctr} = 0.05$, $\lambda_1 = 1.0$, and $\lambda_2 = 7.0$. Note the nearly complete removal of background signal in the CS reconstructed images.
Table 4.2: Normalized catheter signal-to-noise difference (SND) and catheter width broadening ratio (CWBR) values derived from catheter images in Figure 4.7. Reported are mean ± standard deviation for zero filing (ZF) and compressed sensing (CS) reconstructions.

<table>
<thead>
<tr>
<th></th>
<th>Fully Sampled</th>
<th>Circular Central Zone Sampled (ZF)</th>
<th>Elliptical Central Zone Sampled (ZF)</th>
<th>Circular Variable Density Sampled (CS)</th>
<th>Elliptical Variable Density Sampled (CS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SND</strong></td>
<td>0.869</td>
<td>0.912</td>
<td>0.932</td>
<td>0.994</td>
<td>0.998</td>
</tr>
<tr>
<td><strong>CWBR</strong></td>
<td>1.00 ± 0.46</td>
<td>1.87 ± 0.67</td>
<td>1.19 ± 0.39</td>
<td>1.10 ± 0.41</td>
<td>0.97 ± 0.36</td>
</tr>
</tbody>
</table>

Figure 4.8 compares reconstructions for 4-, 8-, 16-, and 32-fold undersampled k-space datasets using ZF and CS algorithms. For the elliptical central zone sampling scheme, the higher the undersampling factor, the fewer high frequency components were acquired. Consequently, ZF reconstruction for these largely undersampled datasets provided noisy images with lower spatial resolution (see cross section profiles in Figure 4.8 and CWBR values in Table 4.3 corresponding to ZF reconstruction). By comparison, little image noise and blurring of the catheter was observed in the CS reconstructed images, even for vastly undersampled k-space datasets.
Figure 4.8: Comparison of catheter images reconstructed from 4-, 8-, 16-, and 32-fold undersampled k-space datasets using the ZF (top three rows) and CS (bottom three rows) algorithms. The eccentricity of the various sampling schemes was $ecc = 0.98$. For 4-, 8-, 16-, and 32-fold undersampling factors, the other parameters were $f_{ctr} = \{0.15, 0.08, 0.04, 0.02\}$, $\lambda_1 = \{1.0, 1.0, 1.0, 1.0\}$ and $\lambda_2 = \{9.0, 7.0, 6.0, 5.0\}$, respectively.
Table 4.3: Catheter width broadening ratio (CWBR) values of catheter profiles in Figure 4.8. Reported are mean ± standard deviation for zero filing (ZF) and compressed sensing (CS) reconstructions.

<table>
<thead>
<tr>
<th>Undersampling Factor</th>
<th>4×</th>
<th>8×</th>
<th>16×</th>
<th>32×</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZF CWBR</td>
<td>0.98 ± 0.36</td>
<td>1.11 ± 0.35</td>
<td>1.27 ± 0.38</td>
<td>1.76 ± 0.53</td>
</tr>
<tr>
<td>CS CWBR</td>
<td>0.92 ± 0.38</td>
<td>0.92 ± 0.36</td>
<td>0.93 ± 0.34</td>
<td>1.05 ± 0.33</td>
</tr>
</tbody>
</table>

4.4 Discussion

Compressed sensing is a nonlinear reconstruction algorithm that enforces sparsity of the image representation in the transform domain while simultaneously enforcing consistency with the acquired k-space data. The regularization parameters $\lambda_1$ and $\lambda_2$ determine the sparsity in the corresponding transform domains. Since catheter images acquired with mcPD are expected to have a sparse representation in the wavelet domain as well as in the image domain, the regularization parameters should be selected to favour sparsity over consistency in order to accentuate filtering of the background. As demonstrated in Figure 4.6, an appropriate selection of the regularization parameters allows one to preserve high-spatial resolution while removing most of the background noise. For endovascular MR imaging, a good image of the passive catheter is needed in order to be overlaid (or fused) onto a vascular roadmap. High quality tracking images could potentially be fused without need for further post processing (Figure 4.9).
In addition to $\lambda_1$ and $\lambda_2$, the accuracy of the reconstructed image also depends on the number of iterations in the reconstruction process, which was fixed to 32 in this study as this represented an acceptable convergence threshold with our catheter images (i.e. acceptable based on qualitative assessment). An optimal value for these parameters is image dependent and therefore may need to be determined in advance via some parameter tuning. In this study, we manually adjusted these parameters based on the visual inspection of the reconstructed images, however this procedure could easily be automated using a more quantitative optimization approach.

Since most of the k-space energy is concentrated in the low frequencies, we used a PDF to preferably acquire samples at the centre of k-space over the periphery. One thing to note is that the use of a PDF for the sample selection violates one of the fundamental precepts of the CS theory that requires pure random sampling. However, the gain obtained from acquiring more
preferentially the high-energy samples is more beneficial than the loss caused by violating the pure random sampling criterion.

In the literature, there exist several sparsifying transforms with varying compressibility efficiencies that depend on the characteristic of the image. One of the most common transforms used with CS reconstruction is total variation (TV), which was also tested on our catheter images. Although studies have reported achieving better quality of the reconstructed image by incorporating the TV transform in the reconstruction process, this was not the finding in our case. We achieved best filtering of the background noise while combining the identity transform together with the wavelet transform.

Passive catheter tracking is advantageous compared to most active techniques in that one can visualize the catheter for its entire length and, thus, gather information about the catheter orientation. Still, some active techniques are also capable of visualizing the catheters in their entire length, such as loopless antenna designs (189). In passive catheter tracking, the catheter is visible only if it remains within the imaging slab. The use of mcPD effectively suppresses background signal and, as was described and utilized by Peng (184), effectively concentrates the energy distribution in k-space in the direction perpendicular to the catheter orientation (Figure 4.5). Thus, provided that the orientation of the catheter is known, an efficient sampling scheme should preferably acquire k-space samples along a line perpendicular to the catheter orientation and through the origin of k-space to improve catheter conspicuity and preserve spatial resolution (Figure 4.7). Previously acquired tracking images, or more specifically previously acquired k-space data, can be used to provide an estimate of catheter orientation (184).
In clinical settings, a catheter can loop in-plane and/or through-plane. When the catheter loops in-plane, a potential problem may exist with the sampling strategy, whereas when the catheter loops through-plane, a potential problem may exist with the mcPD method. Here we discuss both scenarios separately.

The promise of using an elliptical sampling scheme to acquire k-space data is to optimize the acquisition for a particular catheter orientation. When the catheter undergoes a bend, its orientation changes and the elliptical sampling scheme is no longer optimal. As a result, the resolution of the catheter in the reconstructed CS image may be significantly deteriorated wherever the catheter orientation is not perpendicular to the elliptical direction. When the direction of the catheter is unknown or if the catheter is looping in-plane, then a circular sampling scheme is preferred.

In the case of the catheter looping through-plane, the catheter risks exiting the imaged slab, in which case, the catheter signal would disappear. Provided that the catheter remains within the imaged slab, another matter to consider is when the catheter takes a direction similar to the slab select direction (z-axis). Under this circumstance, the mcPD method would dephase some of the catheter signal, resulting in the loss of some signal intensity from the catheter.

The ZF reconstruction approach shortens the acquisition time by only acquiring the central zone of k-space, i.e., the low frequency components. For large undersampling factors, however, this approach omits most high-frequency information and, consequently, the reconstructed images suffer from low spatial resolution. CS with an elliptical PDF acquisition overcomes this limitation by acquiring the low and some high frequency components, yet preserves spatial
resolution by synthesizing high frequency information via sparsity and consistency constraints. For identical acceleration factors, CS offers superior catheter conspicuity and geometric fidelity compared to ZF reconstruction. Other nonlinear reconstruction approaches, such as POCS, (176) have been shown to help in recovering some of the high-frequency data, particularly for variable density sampling schemes.

In this chapter, we presented a feasibility study on the use of CS for real-time catheter tracking. Two issues need to be further addressed in order to implement such a system. First in our approach, we have ignored the reality that MR data is best acquired as a series of frequency-encoded samples (i.e., a readout corresponding to a line in k-space). A time-efficient acquisition would likely collect lines of data, though these would not necessarily need to be parallel. In the case of a 2D mcPD approach, this would suggest a stochastic sampling in the phase-encode direction and placement of the readout perpendicular to the device long axis (184). However, our end goal is to perform real-time 3D catheter tracking, which permits true 2D random sampling in the phase encodes ($k_y - k_z$ plane), and the vast undersampling allowed by CS may make 3D catheter tracking feasible.

Second, the real-time system requires development of a minimum latency reconstruction algorithm. Although CS potentially allows us to acquire 32-fold undersampled k-space datasets at a frame rate of 15-20 Hz, the CS reconstruction procedure is currently too slow to keep up with such acquisition rates. Our application was implemented using an interpreted language and therefore inherently slow. On an iMac Intel Core 2 Duo 2.8 GHz (Apple Inc., Cupertino, CA), it takes about 10 s to reconstruct a $256 \times 256$ image using 32 conjugate gradient iterations. Porting
our application using C/C++ and offloading parts of the processing to the already available reconstruction hardware or a graphics processing unit (190) could significantly reduce the reconstruction time and potentially achieve our objective of pseudo real-time catheter tracking.

In summary, this chapter addresses the following two key limitations when using conventional MR imaging in endovascular intervention: difficulty in visualizing catheters and insufficient temporal resolution. To overcome the difficulty in visualizing catheters with MR imaging, we used the mcPD method that efficiently suppresses the background signal and generates sparse and conspicuous catheter images. To improve the temporal resolution, we undersampled the k-space using a variable density function to acquire more data near the origin and then applied CS to reconstruct the MR images. CS allows MR images to be reconstructed with superior catheter conspicuity and spatial resolution when compared to the more conventional ZF reconstruction approach. Moreover, CS preserves spatial resolution even for vastly undersampled k-space.

When a priori information of the catheter orientation is available, an elliptical sampling scheme perpendicular to the catheter orientation is preferred over the circular sampling scheme since it yields superior catheter resolution. In short, we demonstrated that passive MR imaging is a promising approach to visualize catheters in guiding and monitoring endovascular intervention.
Chapter Five: Visualizing Small Intracranial Arteries using Time-of-Flight with Compressed Sensing

Time-of-flight (TOF) magnetic resonance angiography is commonly used to diagnose vascular pathologies in large arteries (see Appendix B for a description of TOF angiography). Detecting pathologies in smaller intracranial arteries, however, is particularly challenging with MR imaging because of the critical trade-off between spatial resolution, acquisition time and signal-to-noise ratio (SNR). Compressed sensing (CS) may prove to be a favourable technique for accurate reconstruction of undersampled k-space datasets, thus enabling acquisition of higher resolution datasets without increasing the total acquisition time. In addition, CS has beneficial denoising properties, which can help improve the SNR. This study investigates potential improvements of the spatial resolution by using CS to reconstruct undersampled high-resolution TOF k-space datasets, while maintaining reasonable acquisition time and SNR. We demonstrate that CS can produce TOF images with moderate-to-high accuracy from significantly fewer k-space samples than suggested by the Nyquist-Shannon sampling theorem. The reconstruction of the undersampled data via CS generally yielded images with higher contrast-to-noise ratio (CNR) and resolution than the more conventionally used zero-filled approaches, although the improvement in image quality was less than expected. Even though the CS paradigm yielded sufficiently high resolution to visualize small intracranial arteries, the number of visible arteries was hindered by the available CNR at 3 T.

5.1 Introduction

Time-of-flight (TOF) (191) is a magnetic resonance (MR) angiography (MRA) technique used to diagnose vascular pathologies, such as stenoses (192-195), occlusions, and aneurysms (196).
However, the visualization of vascular stenosis and occlusion has mainly been limited to large arteries, including the iliac (195), renal (194), carotid (192), and middle cerebral (193) arteries. Visualizing stenoses in smaller arteries, such as the smaller intracranial arteries, has yet to be demonstrated though such a technique could potentially help in the diagnosis and treatment of cerebral small vessel diseases (197). For example, lacunar stroke (more fully described in section 2.3.2.2) is a condition that results from the occlusion of one of the small penetrating arteries that provides blood to the deep brain structures. These small arteries typically branch off the large arteries arising from the circle of Willis, including the middle cerebral artery (MCA), anterior cerebral artery, posterior cerebral artery, posterior communicating artery, and basilar arteries (Figure 2.1). Using pathology techniques, Fisher (96, 97) observed that the most frequent cause of vascular occlusion for arteries with diameters ranging from 400 µm to 900 µm was atheroma. For arteries with diameter less than 200 µm, the main cause of vascular occlusion was lipohyalinosis (or segmental arteriolar wall disorganisation). Other researchers have also attempted to understand the pathophysiology of lacunar infarcts based on correlation of MR imaging, analysis of risk factors for small vessel diseases, and neurological patient outcome (198-201). Here we attempt to directly image these small cerebral vessels using advanced reconstruction methods applied to undersampled TOF data.

Imaging occlusion in these small arteries requires acquiring high-resolution images. This task is particularly challenging in three-dimensional (3D) TOF data acquisition because of the critical and well understood trade-off between 1) spatial resolution, 2) total scan time, and 3) signal-to-noise ratio (SNR). That is, higher spatial resolution is achieved at the detriment of longer scan time and/or lower SNR (202). In clinical settings, there is a critical resolution beyond which the
scan time becomes clinically nonviable and the SNR too low for the detection of low contrast vessels. To successfully visualize small intracranial arteries, it is, therefore, paramount to have high spatial resolution while simultaneously addressing both the scan time and SNR limitations.

Several approaches exist for accelerating MR imaging, such as parallel imaging (19-21, 142) and compressed sensing (CS) (25, 26). All of these approaches can potentially reduce the total scan time by allowing accurate reconstruction of undersampled k-space datasets. To resolve the aliasing interferences arising from the sub-Nyquist-Shannon sampling (132, 133), parallel imaging techniques rely on the spatial sensitivity information inherent in an array of multiple receiver surface coils, whereas CS depends on the sparsity of the data in a given domain. However, the acceleration achieved with parallel MR imaging usually comes at the cost of reduced SNR (19). On the other hand, CS was shown to have beneficial denoising properties (139), which can potentially help to improve the SNR and conspicuity of small arteries. This observation forms the key hypothesis supporting these studies.

Other approaches to imaging small cerebral vessels are possible. Recently, Kang et al. (203) demonstrated visualization of lenticulostriate arteries using 7 T TOF MRA. The inherent improvement in SNR due to higher intrinsic bulk signal with higher magnetic field systems allows for detection of smaller arteries. However, 7 T scanners have greater susceptibility effects, are not widely available, and are currently restricted to research procedures. While intriguing, alternate solutions to visualize small arteries at lower magnetic field strengths are still necessary. In this study, we investigate the potential of improving the spatial resolution by using the CS paradigm to acquire and reconstruct vastly undersampled high-resolution TOF k-space
datasets, while maintaining reasonable scan time and SNR. Our hypothesis is that by judiciously tailoring the undersampled acquisition scheme with CS reconstruction parameters, it is possible to acquire TOF images with resolution and SNR allowing visualizing the largest lenticulostriate arteries. This paradigm can produce TOF images with moderate-to-high accuracy from significantly fewer k-space samples than suggested by the Nyquist-Shannon sampling theorem. It has the potential for improving the resolution of TOF images without increasing the scan time.

5.2 Materials and Methods

5.2.1 MR Protocols and Acquisitions

MRA was performed using a 3 T MR Scanner (Signa VH/i; General Electric Healthcare, Waukesha, WI). We acquired the data with a modified 3D clinical TOF vascular sequence. The modified sequence permitted acquiring undersampled sets of k-space phase encodes in the $k_y$-$k_z$ plane. To satisfy the CS requirement of incoherent aliasing interferences due to k-space undersampling, the phase encode locations were randomly selected based on a probability density function (PDF). The PDF varied according to the elliptical distance from the k-space origin, as described in section 4.2.3. This scheme promoted selection of more samples near the centre compared to the periphery of k-space. In addition, to ensure better performance, we always acquired a central zone of k-space based on the rationale that most of the energy is located near the centre (54).

5.2.1.1 Phantom Data Acquisition

To first validate our acquisition/reconstruction procedure, we acquired a fully sampled and an undersampled k-space dataset from a vendor-supplied quality insurance phantom using the body
coil as the transmitter coil and a four-channel phased array torso coil as the receiver coil. The acquisition parameters were: pulse repetition time (TR) of 30 ms, echo time (TE) of 3.5 ms, flip angle (FA) of 30°, acquisition matrix (N_x × N_y × N_z) of 40 × 64 × 64, and isotropic voxel size of 2.5 mm. For the undersampled dataset, the k_y-k_z phase encode plane was undersampled by a factor of four and the fully sampled central zone represented 2% of k-space. The resulting scan time for the fully sampled and undersampled acquisitions were 2 min 3 sec and 31 sec, respectively.

5.2.1.2 Volunteer Data Acquisition

We conducted experiments on a healthy volunteer using a protocol approved by the Internal Review Board (see Appendix C for ethics approval). The subject provided written informed consent form prior to undergoing MR examination. Before imaging the target vessels, i.e., the lenticulostriate arteries, we conducted lower resolution MRA imaging using a clinical TOF sequence with an isotropic voxel size of 0.9 mm. This preliminary examination provided us with a gross vascular road map image allowing localization of the large vessels originating from the circle of Willis. This vascular road map served as reference to prescribe the following acquisitions by focusing on the main trunk (M1 segment) of the MCA in order to centre the acquisition about the lenticulostriate arteries. The next acquisitions were acquired using our modified 3D clinical TOF vascular sequence, and an 8-channel head coil.

To compare the benefits of the CS approach, we acquired a fully sampled and undersampled k-space dataset. We maintained the FOV and number of acquired phase encodes identical for both acquisitions, changing only the imaging resolution. Figure 5.1 shows a conceptual diagram of the
sampling strategies for the fully sampled (Figure 5.1a) and undersampled (Figure 5.1b) approaches. For the fully sampled data, the acquisition parameters were: TR/TE/FA of 30 ms/3.5 ms/30°, $N_x \times N_y \times N_z$ of 50 $\times$ 238 $\times$ 126, FOV$_x$ $\times$ FOV$_y$ $\times$ FOV$_z$ of 8 cm $\times$ 15 cm $\times$ 8 cm, voxel size of 1600 $\mu$m $\times$ 630 $\mu$m $\times$ 635 $\mu$m, the number of acquired phase encodes of 29,988, and the scan time was 15 min 00 sec. For the undersampled data, the acquisition parameters were identical to the fully sampled acquisition except for: $N_x \times N_y \times N_z$ of 160 $\times$ 750 $\times$ 400, voxel size of 500 $\mu$m $\times$ 200 $\mu$m $\times$ 200 $\mu$m. Only 30,000 of the total phase encodings were sampled, giving an undersampling factor of 10. The fully sampled central zone represented 1.6% of the $k_y$-$k_z$ extent.
Figure 5.1: Conceptual diagram of the sampling strategies used to acquire fully sampled (a) and undersampled (b) k-space data. Each \( k_y-k_z \) slice of the 3D volume was reconstructed individually.

The decrease in voxel size achieved by the undersampled approach comes at the cost of lower

\[
\text{SNR} \propto \Delta_v \sqrt{T_{\text{samp}}} \quad (202),
\]

and more specifically lower SNR efficiency as

\[
\text{SNR}_{\text{eff}} = \frac{\text{SNR}}{\sqrt{T_{\text{samp}}}} \propto \Delta_v.
\]

Here, \( T_{\text{samp}} \) is the sampling time (i.e., the time that the analog-to-digital converter is on) and \( \Delta_v \) is the voxel volume, which is inversely proportional to the image resolution and given in the unit of pixels per cubic millimetre. \( \text{SNR}_{\text{eff}} \) is a direct measure of how much SNR is lost/gained solely by changing the image resolution, without any contribution from the acquisition time. Assuming that the SNR efficiency of the fully sampled approach is 100\%, the SNR efficiency of the undersampled approach is only 3\%.

### 5.2.2 Image Reconstruction

The raw data acquired with our modified 3D TOF sequence were transferred from the scanner to a Macintosh workstation (Apple Inc., Cupertino, CA, Mac Pro, dual 3 GHz Quad-Core Intel Xeon, 8 GB of RAM) and reconstructed offline. We applied a Fourier transform to the 3D data from each coil along the fully sampled direction (i.e., \( k_x \)), and then reconstructed every \( k_y-k_z \) slice individually. Finally, we combined the individual coil images via the sum-of-squares algorithm (204).

#### 5.2.2.1 Central Zone Approach

For the fully sampled approach, we filtered the k-space data with a Fermi filter (186) in order to minimize Gibbs ringing (119) introduced by the truncation of k-space data. The Fermi filter is
defined by $H(k) = \left(1 + e^{w_f(|k| - k_f)}\right)^{-1}$, where $k_f$ determines the full width at half maximum of the filter and $w_f$ determines the sharpness of the cutoff frequency. For normalized $|k| \leq 1$, typical values are $0.85 \leq k_f \leq 1.0$ and $10 \leq w_f \leq 30$. In these studies we used $k_f = 0.85$ and $w_f = 23$. The fully sampled phantom data were reconstructed via Fourier transform of the data. For the fully sampled volunteer data, we artificially increased the resolution by zero-padding the Fermi-filtered k-space data prior to Fourier transform, so as to match the resolution of the undersampled approach (Figure 5.1). In the remainder of this chapter the zero-padded fully sampled approach will be referred to as the central zone approach.

5.2.2.2 Undersampled Approach

For the undersampled approach, we reconstructed each $k_y$-$k_z$ slice of the 3D volume via both zero filled (ZF) (143) and CS reconstructions. The ZF approach sets the missing data to zero prior Fourier transform. We reconstructed the ZF images with (ZF-DC) and without (ZF) sampling density compensation, i.e., multiplying k-space data by the inverse of the PDF. This procedure compensates for the low sampling density near the periphery of k-space, by giving more weight to the high frequency coefficients (205).

For the CS approach, we reconstructed each coil image by solving the nonlinear constrained optimization problem given in Eq. [5.1] and then calculated the final composite image via sum-of-squares combination of the coil images.
\[
\text{minimize } \| \Psi m_l \|_1 + \lambda TV(m_l) \\
\text{subject to } \| F_u m_l - s_l \|_2^2 \leq \varepsilon,
\]

where \( m_l \) is the reconstructed vector image from coil \( l \), \( s_l \) is the undersampled k-space data acquired with coil \( l \), \( F_u \) represents the undersampled Fourier transform, \( \Psi \) represents the wavelet transform operator, \( TV \) represents the total-variation (sum of absolute differences in the image), \( \lambda \) trades wavelet coefficients sparsity with finite differences sparsity, and \( \| \cdot \|_p := \sum | \cdot |^p \) is the \( \ell_p \)-norm. The \( \ell_2 \)-norm term in Eq. [5.1] enforces data consistency with the model error threshold, \( \varepsilon \). The \( \ell_1 \)-norm and \( TV \) operators are the key concepts introduced by CS and can be considered as promoting the image to be sparse in both the wavelet and \( TV \) domains at the same time. Lustig \textit{et al.} (139) demonstrated that combining these two sparsifying transforms potentially allows accurate and high SNR reconstruction of contrast enhanced MR angiography images. To solve the optimization problem defined in [5.1], we formulated the problem in the so-called Lagrangian form,

\[
\arg \min_m \| F_u m_l - s_l \|_2^2 + \lambda_1 \| \Psi m_l \|_1 + \lambda_2 TV(m_l),
\]

and used the conjugate gradient algorithm (152) with backtracking line search to find an optimum solution. The parameters \( \lambda_1 \) and \( \lambda_2 \) in Eq. [5.2] are the Lagrangian multipliers that balance data consistency and sparsity of the wavelet coefficients and finite differences, respectively. We reconstructed the images using different combinations of \( \lambda_1 \) and \( \lambda_2 \), with values ranging from 0.0001 to 0.5. The optimum multipliers were selected through a combination of visual inspection of the reconstructed images and assessment of the analysis metrics described in
the following section. In this study, we used the Daubechies-6 wavelet (147) as it offered good energy compaction.

The conjugate gradient is an iterative algorithm and the number of iterations to converge to the solution depends on several parameters. In order to keep the reconstruction time of high-resolution datasets reasonable, we used a predetermined number of iterations, rather than a stopping criterion based on the absolute differences between objective function values of two successive iterations. The number of iterations was chosen to guarantee sufficient convergence of the algorithm based on our preliminary experiments. To further minimize the reconstruction time, we implemented all algorithms in a Cocoa application using Objective-C and C++ programming languages. The Fourier transform was calculated with the FFTW library (206) and the Wavelet transform was modified from the algorithm provided in (207). Maximum-intensity projection (MIP) (208) images of the 3D TOF data were generated with OsiriX imaging software (version 3.8, http://www.osirix-viewer.com). The MIP procedure is a volume rendering method that projects the 3D data onto a 2D image. The procedure consists of casting parallel rays through the volume and using the maximum intensity along the rays. This technique is routinely used to visualize angiography data. The region of interest (ROI) was placed on the MIP image to focus on the main trunk of the MCA in order to centre the visualization on the lenticulostriate arteries.

5.2.3 Analysis Metrics

5.2.3.1 Phantom Data Analysis

Qualitative assessment was performed through inspection of the signal intensity profile measured along a cross-section parallel to the y-axis (as shown in Figure 5.2). The visual criterion in
assessing the profile was the observational detectability of small phantom details. Close attention was paid to the number of discernable peaks in each profile. Quantitative assessment was performed by measuring the SNR defined as the quotient of the average signal intensity in a region of interest (ROI) within the phantom and the standard deviation of the noise in an ROI outside the phantom, \( \text{SNR} = \frac{\mu_{\text{phantom}}}{\sigma_{\text{noise}}} \).

Figure 5.2: Reconstructions of fully sampled (a) and 4-fold undersampled k-space datasets using the ZF-DC (b), ZF (c), and CS (d) approaches. The bottom row illustrates the corresponding cross-section profiles shown by the dashed line in (a). The fully sampled cross-section profile in (e) exhibits six distinct peaks labeled A-F, respectively. For the CS approach, the reconstruction parameters were \( \lambda_{\text{WT}} = 0.0001 \) and \( \lambda_{\text{TV}} = 0.0001 \). The mean and standard deviation of the SNR values for the phantom images are (a) 110.6±6.5, (b) 7.8±1.4, (c) 20.6±1.9, and (d) 90.3±5.9.

5.2.3.2 Volunteer Data Analysis

We conducted analyses on both the source TOF images and MIP rendered images of the reconstructed volunteer data. The source TOF images were assessed qualitatively and quantitatively. The qualitative assessment focused on the general quality of the reconstructed
images in terms of resolution and noise. The quantitative assessment was performed by measuring the contrast-to-noise ratio (CNR) between the vessels and the different brain regions, including white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF). To measure these ratios ($\text{CNR}_{\text{vessel,WM}}$, $\text{CNR}_{\text{vessel,GM}}$, and $\text{CNR}_{\text{vessel,CSF}}$), we selected multiple ROIs for each brain region and recorded the mean and standard deviation values of the combined ROIs. For the vessel regions, the ROIs were drawn around vessels with relatively low conspicuity. An ROI was also selected in the background to measure the standard deviation of the signal in air, i.e., noise ($\sigma_{\text{noise}}$). From these values, we calculated the CNR as the difference between the vessel and corresponding brain region mean values, divided by the standard deviation of the noise,

$$\text{CNR}_{\text{vessel,region}} = \frac{\mu_{\text{vessel}} - \mu_{\text{region}}}{\sigma_{\text{noise}}}.$$  

For the MIP images, we qualitatively assessed the reconstructions through visual inspection. Close attention was paid to how well the lenticulostriate arteries were depicted in terms of conspicuity and feature detail.

5.3 Results

5.3.1 Phantom Data

Figure 5.2 shows the reconstructions of a source image from the 3D phantom dataset. As expected, visual inspection of the reconstructed images reveals that the ZF-DC resulted in a less blurry but noisier image when compared to the ZF approach without density compensation. The CS approach performed well at suppressing the aliasing interferences arising from the undersampling scheme in k-space, while preserving sharpness and details in the image. The SNR measures (provided in the caption of Figure 5.2) validate the benefit of using CS to improve the conspicuity of regions in the phantom. Qualitative comparison of the cross-section profiles in
Figure 5.2 also confirms that the CS approach better preserved the resolution and details in the image than both ZF approaches. The fully sampled cross-section profile in Figure 5.2e exhibits six distinct peaks labeled A-F, respectively. The two peaks A and F are of special interest in assessing the different reconstruction as they represent single voxel-wide details. Observation of the CS profile in Figure 5.2h shows that both peaks are readily resolvable, in the same way as they are in the fully sampled profile. In contrast, the peaks of the cross-section profiles for both the ZF and ZF-DC images are either blurred out (Figure 5.2) or buried in the interferences (Figure 5.2f).

5.3.2 Volunteer Source Images

Figure 5.3 presents an example of a source image from the 3D volunteer dataset reconstructed using the CS algorithm for a range of relevant $\lambda_1$ and $\lambda_2$ regularization parameters. To better compare the different reconstructed images, Figure 5.4 presents enlarged views corresponding to the ROI shown by the white box in Figure 5.3a. The acquired k-space data were 10-fold undersampled and a central zone of k-space representing 1.6% of the coefficients was fully sampled to ensure better performance. Large values of $\lambda_1$ and $\lambda_2$ forced sparsity in the wavelet and finite difference domains, respectively. Qualitative assessment of Figure 5.3 and Figure 5.4 demonstrates that larger values of $\lambda_1$ and $\lambda_2$ improved vessel conspicuity by further reducing noise in the image. The CNR values shown in Figure 5.5 confirm this observation. In general, increasing $\lambda_1$ and $\lambda_2$ has the tendency to improve the CNR in the image. However, excessive increase of $\lambda_1$ caused the CNR to decrease again ($\lambda_1 > 0.1$ in Figure 5.5) and also introduced some blurring in the reconstructed images (Figure 5.3i and Figure 5.4i). It is important to notice that the combination of $\lambda_1$ and $\lambda_2$ values yielding the highest CNR is not optimum in terms of
Figure 5.3: CS reconstructions of a source image selected from the volunteer 3D dataset for different $\lambda_{WT}$ and $\lambda_{TV}$ values, which enforce sparsity in the wavelet and finite difference domains, respectively. Larger values of $\lambda_{WT}$ and $\lambda_{TV}$ improve the CNR between the vessels and other brain regions. However, excessive increase of $\lambda_{WT}$ introduces image blurring.
resolution as it introduces noticeable blurring artefacts in the reconstructed image. Regularization parameters $0.001 \leq \lambda_1 \leq 0.01$ and $0.001 \leq \lambda_2 \leq 0.01$ offered a good visual compromise between noise suppression/vessel conspicuity, and geometric fidelity of the vessels.

Figure 5.6 compares the same source image reconstructed using the ZF-DC, ZF, and CS approaches. Qualitative assessment of these images shows that, with adequate and judicious selection of the regularization parameters, the CS approach resulted in superior image quality in terms of resolution and CNR when compared to both ZF approaches. The interference level generated by the ZF-DC approach reached amplitudes that significantly compromised the detection of vessels (Figure 5.6a-b). The amplitude of the aliasing interferences was significantly lower in the ZF approach; however, some blurring was noticeable (Figure 5.6c-d). The CS reconstruction, on the other hand, suppressed most of the noise/aliasing interference in the image, thus resulting in higher vessel conspicuity (Figure 5.6e-f). The CS approach yielded the highest CNR values as shown in Table 5.1. In addition, CS better preserved geometric fidelity of the vessels and provided noticeably higher resolution/sharper edges than the ZF approaches. The improvement in resolution, however, was mainly visible at the pixel level.
Figure 5.4: Enlarged views of the CS reconstructed source images shown in Figure 5.3. The enlarged region corresponds to the ROI shown in Figure 5.3a. See caption of Figure 5.3 for details.
Figure 5.5: CNR values for the CS reconstructed TOF source image selected from the volunteer 3D dataset for different $\lambda_{WT}$ and $\lambda_{TV}$ values. Reported are the mean and standard deviation values for $\text{CNR}_{vessel,WM}$ (a), $\text{CNR}_{vessel,GM}$ (b), and $\text{CNR}_{vessel,CSF}$ (c). Larger values of $\lambda_{WT}$ and $\lambda_{TV}$ improve the CNR between the vessels and other brain regions. However, excessive increase of $\lambda_{WT}$ causes the CNR to decrease again.
Figure 5.6: Reconstructions of a TOF source image using the ZF-DC (a,b), ZF (c,d), and CS (e,f) algorithms. The first column depicts the reconstructed source image and the second illustrates a close view of the ROI shown in (a). The parameters for the CS reconstruction were $\lambda_{WT} = 0.005$ and $\lambda_{TV} = 0.005$. Note the removal of noise in the CS-reconstructed images, while persevering the sharpness of edges.
Table 5.1: CNR values for the ZF-DC, ZF and CS reconstructed images shown in Figure 5.6. Reported are the mean and standard deviation values for \( \text{CNR}_{\text{vessel,WM}} \), \( \text{CNR}_{\text{vessel,GM}} \), and \( \text{CNR}_{\text{vessel,CSF}} \). The parameters for the CS reconstruction were \( \lambda_{\text{WT}} = 0.005 \) and \( \lambda_{\text{TV}} = 0.005 \).

<table>
<thead>
<tr>
<th>Figure 5.6</th>
<th>a-b (ZF-DC)</th>
<th>c-d (ZF)</th>
<th>e-f (CS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CNR}_{\text{vessel,WM}} )</td>
<td>2.8±3.2</td>
<td>7.9±4.8</td>
<td>9.7±5.2</td>
</tr>
<tr>
<td>( \text{CNR}_{\text{vessel,GM}} )</td>
<td>3.9±3.1</td>
<td>12.1±4.8</td>
<td>14.5±5.2</td>
</tr>
<tr>
<td>( \text{CNR}_{\text{vessel,CSF}} )</td>
<td>5.0±2.9</td>
<td>17.6±4.7</td>
<td>21.2±5.3</td>
</tr>
</tbody>
</table>

ZF-DC = zero filled density-compensated, ZF = zero filled, and CS = compressed sensing, WM = white matter, GM = grey matter, CSF = cerebrospinal fluid

5.3.3 Volunteer MIP Images

Figure 5.7 shows the MIP rendered images from the coronal view of the CS reconstructed TOF source images for a range of regularization parameters \( \lambda_1 \) and \( \lambda_2 \). The ROI shown by the white box in Figure 5.7a corresponds to a region with a visible lenticulostriate artery branching off the right MCA. For better evaluation of the image quality, a close view of the corresponding ROI for each MIP image is provided in Figure 5.8. Comparing the different MIP rendered images supports our previous observations from Figure 5.3 and Figure 5.4. Large \( \lambda_1 \) and \( \lambda_2 \) resulted in less noisy MIP images, however, excessive increase of \( \lambda_1 \) introduced some blurring (Figure 5.7i).
Figure 5.7: MIP rendered images from the coronal view of the reconstructed dataset using the CS approach for different $\lambda_{WT}$ and $\lambda_{TV}$ values. Larger values of $\lambda_{WT}$ and $\lambda_{TV}$ improve the CNR between the vessels and other brain regions (see Figure 5.5). However, excessive increase of $\lambda_{WT}$ and $\lambda_{TV}$ introduces image blurring (i) and decreases the conspicuity of small arteries (Figure 5.9i).
Figure 5.8: Enlarged views of the CS reconstructed source images shown in Figure 5.7. The enlarged region corresponds to the ROI shown in Figure 5.7a. See caption of Figure 5.7 for details.
Figure 5.9: Comparison of the MIP rendered images for the central zone sampled (a,b) and PDF undersampled (c-h) strategies. The undersampled strategy was reconstructed using ZF-DC (c,d), ZF (e,f), and CS (g,h). The regularization parameters for the CS reconstruction were $\lambda_{\text{WT}} = 0.005$ and $\lambda_{\text{TV}} = 0.005$. Although the differences are subtle, figure (h) has noticeably superior CNR and resolution than figure (f). The CS approach slightly better attenuated the background tissues and sharpened the transition between vessels and background tissues. The window width and level are identical for each visualization.
Figure 5.9 shows the MIP images corresponding to the central zone, ZF-DC, ZF, and CS approaches. The scan time and reconstructed image resolution (5 pixels/mm) was identical for all approaches. However, the inherent acquired resolution of the central zone approach was only 1.6 pixels/mm. Qualitative comparison of the different MIP images reveals that the central zone approach (Figure 5.9a) resulted in higher CNR when compared to the other approaches. As expected, the ZF-DC approach (Figure 5.9c) performed poorly compared to the other approaches due to the significant amplitude of the interference level in the source images. On the other hand, the ZF and CS reconstructions of the undersampled data allowed visualizing smaller vessels and details than the central zone approach (compare Figure 5.9a vs. Figure 5.9e and Figure 5.9g). Generally, the CS approach resulted in noticeably superior quality of the MIP images in term of resolution and CNR when compared to the ZF approach.

5.4 Discussion

The comparison of the source images of the phantom in Figure 5.2 validated that CS can successfully reconstruct undersampled k-space datasets. CS allowed reconstructing images with quality approaching the one of the fully sampled images, while significantly shortening the scan time. In comparison to both ZF reconstructions, the CS approach better suppressed the aliasing interferences resulting from the undersampling scheme in k-space. The CS images had higher resolution and CNR than the ZF images, thus allowing visualizing smaller details.

While less noticeable, we observed similar results with the reconstructed TOF source images from the volunteer dataset. The improvement in resolution and CNR were mainly visible when comparing the source images side-by-side at the voxel level (Figure 5.6). The phantom and
volunteer source images have very different characteristics and, therefore, the CS regularization parameters need to be adjusted accordingly. The phantom images consist of relatively homogeneous piecewise functions and are expected to have sparse representations in the finite difference domain. Reconstruction of such images should emphasize sparsity in the finite difference domain, i.e., larger $\lambda_{TV}$. In contrast, the volunteer images have less of a sparse representation in either the wavelet or finite difference domains. Thus, the complexity of the volunteer images made the selection of the regularization parameters more complex than for the phantom data.

Although we expected the CS approach to outperform the ZF approach in terms of image resolution, our results showed only little improvement. A possible explanation is that forcing sparsity in the wavelet domain, i.e., large $\lambda_{WT}$, introduces some blurring in the reconstructed images (i.e., Figure 5.3i and Figure 5.4i). This blurring arises from the inherent property of the wavelet transform to concentrate most of the energy at the coarsest scale-coefficients, which are closely related to the low frequencies of k-space. Thus, enforcing sparsity in the wavelet domain tends to preserve coarse scale-coefficients (corresponding to low frequencies) and discard detail scale-coefficients (corresponding to high frequencies).

Based on the side-by-side comparison of the source images in Figure 5.6, the CS approach improved upon both ZF approaches in terms of CNR. However, inspection of the MIP images in Figure 5.9 found less of an improvement. This finding was not completely unexpected as the MIP algorithm searches for the maximum intensity along parallel rays cast through the volume.
As a result, the MIP procedure has an intrinsic, non-linear filtering property, which cancels out some of the noise reducing benefit of CS.

To compensate for the low sampling density near the periphery of the undersampled data, the ZF-DC reconstruction divides the k-space coefficients by the sampling PDF prior to Fourier transform. In the case of the volunteer data, the low sampling density near the periphery of k-space causes the corresponding PDF values to approach zero. Thus, dividing the k-space by the PDF results in an amplification of the high frequency components. However, since most of the energy is concentrated near the centre of k-space, the density compensation process mainly amplifies noise. As a consequence, the ZF-DC reconstructed images have low CNR and poor vessel conspicuity.

For identical number of acquired phase encodes (i.e., constant scan time), the variable density undersampling approach covers a greater k-space extent than the central zone sampling approach. Hence, the undersampling approach yields smaller voxel size, i.e., higher image resolution but lower SNR. Despite the loss in SNR, the higher resolution achieved with the undersampled approach enabled visualizing a larger number of small arteries (Figure 5.9), thus potentially allowing for more accurate clinical diagnoses of small vessel diseases.

A major limitation of the CS approach is the reconstruction time, which is significantly longer than for the ZF or ZF-DC approaches. The CS reconstruction is computationally intensive and expensive. One could argue that the improvement in image quality achieved with CS does not justify the considerable increase in computation time. For instance, the CS reconstruction of an image with matrix size of 750 × 400 and 40 iterations takes about 50 sec. In comparison, the ZF
reconstruction for the same image takes only 0.04 sec, i.e., it is 1250 times faster than the CS reconstruction.

Our undersampled approach yielded a voxel size of 500 µm × 200 µm × 200 µm, which is in the order of the smallest lenticulostriate artery diameters (200-900 µm). By comparison, Kang et al. (203) acquired similar TOF images at 7 T with isotropic voxel size of 780 µm, i.e., voxel size in the order of the largest lenticulostriate artery diameters. The TOF parameters were optimized for the given magnetic field strength in both studies and only the voxel size and magnetic field strength differed. Despite achieving a higher resolution, our CS paradigm at 3 T could only visualize a small number of lenticulostriate arteries. In contrast, Kang et al. were able to observe a larger number of lenticulostriate arteries with more conspicuity. This difference suggests that the main limiting factors in visualizing small arteries with TOF MR imaging at 3 T are 1) the available SNR and 2) the less efficient background saturation due to faster longitudinal regrowth.

1) It is expected that larger voxel size results in higher SNR$_{eff}$, but also increases partial volume effect lowering CNR in small vessels. The main gain in SNR arises from the higher intrinsic bulk signal with higher magnetic field systems. 2) The longitudinal relaxation time ($T_1$) of the tissues increases with field strength, thus minimizing the recovery of the longitudinal magnetization.

Since the vascular contrast in TOF image arises from the signal difference between the unsaturated moving spins (blood inflow) and saturated stationary spins (slice being imaged), it is expected that higher field systems will create brighter vascular images (209). Potential solutions to overcome these impediments could be to use contrast agent or increase the number of signal averaging. However, the latter solution defeats the purpose of trying to maintain the scan time clinically viable.
Our modified 3D TOF sequence was designed to acquire undersampled phase encodes in the $k_y$-$k_z$ plane. We then reconstructed each image from the 2D undersampled $k_y$-$k_z$ slice. Lustig et al. (139) showed that such a sampling scheme optimally reduces the aliasing incoherence and best exploits 2D sparsity. To optimize the acquisition time, conventional acquisition schemes would select the readout direction to be the direction with the most coefficients. However, in this study, we preferred minimizing the number of images to be reconstructed via CS and selected the readout direction to be the direction with the least coefficients. We acknowledge that our approach is not optimal in term of acquisition time and could be further optimized.

In summary, we investigated an acquisition/reconstruction paradigm to increase the resolution of TOF images, while maintaining the scan time clinically viable. The paradigm undersamples k-space using a variable-density function that favours acquiring more samples near the origin and then applies CS to reconstruct the TOF source images. We demonstrated that this CS paradigm could produce TOF images with moderate-to-high accuracy from significantly fewer k-space samples than suggested by the Nyquist-Shannon sampling theorem. The reconstruction of the undersampled data via CS generally yielded images with higher CNR and resolution than the more conventional ZF approaches. However, CS offered less of an improvement than expected. In short, the CS paradigm can potentially improve the conspicuity of small vessels.

Unfortunately, the consistency of the described approaches in visualizing lenticulostriate arteries is not sufficiently reliable to help diagnose stenoses in smaller arteries. Further effort investigating methods to improve vessel to background tissue contrast (improved background suppression) and the use of head coils with higher inherent SNR (i.e., 32 channel coils) may increase the clinical viability of this approach.
Chapter Six: Investigating k-Space Undersampling and Advanced Reconstruction Techniques to Accelerate Neuroimaging Protocols†

Neuroimaging is key to diagnosing patients, such as in acute ischemic stroke (section 2.3.2), and prompt diagnosis is often vital to initiate early treatment. Parallel MR imaging techniques (section 3.7) and compressed sensing (section 3.6) enable accelerating neuroimaging protocols via accurate reconstruction of undersampled k-space datasets. This study investigates several combinations of sampling strategies and reconstruction techniques (CS, SENSE, GRAPPA, SPIRiT, L1-SPIRiT, and CS-SENSE) that are used to accelerate several key time-consuming neuroimaging sequences used in stroke imaging ($T_2$ FLAIR, $T_2^*$ GRE, TOF, and SWI) while preserving image quality. The sampling-reconstruction techniques were compared quantitatively using global and local performance metrics, and assessed qualitatively by an experienced neuroradiologist. The qualitative and quantitative results were in good agreement in selecting the optimum combinations of sampling strategy and reconstruction algorithm across subjects. The qualitative results by the clinician showed a clear preference for the $\ell_1$-regularized reconstructions (CS, L1-SPIRiT, and CS-SENSE). All optimum sampling-reconstruction combinations enabled significant acceleration of the acute stroke protocol without effecting the quality and diagnostic content of the images. The best sampling-reconstruction combinations depend on sequence and clinical application.

† This chapter has been submitted to the journal of Magnetic Resonance Imaging.
6.1 Introduction

Neuroimaging plays an essential, and often time-sensitive role in diagnosing and designing treatments for patients. In this study, we use ischemic stroke as an underlying motivation to accelerate several sequences. The disruption of blood supply during ischemia initiates a detrimental cascade in the brain tissue (60). The duration, severity, and location of ischemia determine the extent of damage. Prolonged disruption can cause irreversible damage (210); therefore, prompt diagnosis and appropriate therapeutic response are critical. Neuroimaging of stroke patients should ideally provide a full anatomical, vascular, and functional stroke assessment (i.e., assess the “4 P’s” of stroke, namely parenchyma, pipes, perfusion, and penumbra (211)). Currently, computed tomography (CT) is the most commonly utilized imaging modality because of its availability and rapidity. However, MR imaging has been shown to be equivalent to CT for imaging and diagnosing of acute ischemic stroke (212, 213). A standard stroke MR imaging protocol may include diffusion-weighted imaging (DWI), $T_2$-weighted and fluid attenuation inversion recovery imaging (FLAIR), gradient-recalled echo $T_2^*$-weighted imaging (GRE), time-of-flight MR angiography (TOF MRA), perfusion-weighted imaging (PWI), and susceptibility-weighted imaging (SWI). Because “time is brain” (17), reducing event-to-treatment time is essential.

Several approaches exist for accelerating MR imaging without significantly compromising the spatial resolution or signal-to-noise ratio, such as parallel imaging (19-22) and compressed sensing (CS) (25, 26, 139). Standard parallel imaging reconstructions include sensitivity encoding (SENSE) (19), generalized autocalibrating partially parallel acquisition (GRAPPA) (21), and iterative self-consistent parallel imaging reconstruction from arbitrary k-space
(SPIRiT) (22). To resolve the aliasing interference arising from the sub-Nyquist-Shannon sampling (132, 133), parallel imaging techniques use the spatial sensitivity information of multiple receiver surface coils. CS, however, depends on the sparsity of the data in a given domain. Since both approaches rely on complementary information to recover the unsampled data, it may be advantageous to combine them. Solutions for this include $\ell_1$-regularized SPIRiT (L1-SPIRiT) (22), merged reconstruction of CS and SENSE (sparse SENSE) (161), and sequential reconstruction of CS and SENSE (CS-SENSE) (27).

In this study, we investigate and compare CS, SENSE, GRAPPA, SPIRiT, L1-SPIRiT, and CS-SENSE to accelerate several key sequences used in acute stroke imaging, i.e., $T_2^*$ GRE, SWI, $T_2$ FLAIR, and TOF. We omitted echo-planar imaging-based sequences, such as DWI and PWI, because these sequences are already time-efficient. The investigated reconstruction techniques have different sampling requirements and we expect that the preferred sampling acquisition methodology is a function of the reconstruction technique. It is not yet clear which combination of sampling strategy and reconstruction algorithm will allow for optimal neurological assessment for a given sequence. By tailoring the sampling acquisition strategies to the reconstruction methods, we hypothesize that the best combinations of sampling strategy and reconstruction technique (hereafter sampling-reconstruction combination) will enable significant acceleration of neuroimaging protocols without effecting the quality and diagnostic content of the images. We quantitatively evaluate the diagnostic value of these combinations in comparison to fully sampled imaging via global and local performance measures. An experienced neuroradiologist qualitatively evaluated all reconstructed images for overall quality, diagnostic content, noise, blurring, and contrast.
This chapter first describes the implementation of the sampling strategies and reconstruction techniques, as well as the details of the quantitative and qualitative comparisons. We then present and discuss the results of the different sampling-reconstruction combinations. We show that the tailored optimum sampling-reconstruction combinations allow accelerating the acute stroke protocol while preserving good image quality.

6.2 Methods

6.2.1 MR Protocols and Acquisitions
We conducted all imaging experiments on six healthy volunteers using a protocol approved by the local Internal Review Board (see Appendix C for ethics approval). The subjects provided written informed consent prior to undergoing MR examination. The imaging setup consisted of a 3 T MR scanner (Discovery 750; General Electric Healthcare, Waukesha, WI) equipped with a 12-channel receive only head/neck coil. We used clinically appropriate sequences to acquire fully sampled k-space data. The MR acquisition parameters for each sequence are summarized in Table 6.1. The acquired raw k-space data were then transferred from the scanner to a Macintosh workstation (Apple Inc., Cupertino, CA, iMac, 3.4 GHz Intel Core i7, 16 GB of RAM) and reconstructed offline.

6.2.2 Undersampling Simulations
We simulated four-fold acceleration by undersampling the axial plane of the fully sampled k-space data, regardless of the actual acquisition orientation. This approach allowed us to take advantage of the inherent spatial sensitivity of the phased-array receiver coil to simulate 2D undersampling with parallel imaging. The retrospective undersampling approach does not
completely emulate real MR data acquisition, but the use of dedicated receiver-coil arrays with a greater number of elements and non-uniform spatial sensitivities along the z-direction could potentially enable 2D parallel imaging in any direction.

A target acceleration of four was selected as allowing sufficient reduction in acquisition time but minimizing potential reconstruction artefacts. Because we expect the sparse sampling methodology to be a function of the reconstruction technique, we generated several sampling schemes that satisfy the requirements of the various reconstructions (Figure 6.1). In this study, we only investigated Cartesian sampling schemes.

Table 6.1: Clinical acute stroke protocol MR sequence acquisition parameters. Only the non echo-planar sequences were accelerated.

<table>
<thead>
<tr>
<th>MR parameters</th>
<th>2D $T_2^*$ GRE</th>
<th>3D SWI</th>
<th>3D $T_2$ FLAIR</th>
<th>3D TOF MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetition time (ms)</td>
<td>700</td>
<td>30</td>
<td>7000</td>
<td>22</td>
</tr>
<tr>
<td>Echo time (ms)</td>
<td>14.2</td>
<td>20</td>
<td>73</td>
<td>5.4</td>
</tr>
<tr>
<td>Inversion time (ms)</td>
<td>NA</td>
<td>NA</td>
<td>2156</td>
<td>NA</td>
</tr>
<tr>
<td>Flip angle (°)</td>
<td>18</td>
<td>15</td>
<td>90</td>
<td>15</td>
</tr>
<tr>
<td>Field of view (mm)</td>
<td>$240 \times 180$</td>
<td>$256 \times 256$</td>
<td>$240 \times 216$</td>
<td>$240 \times 180$</td>
</tr>
<tr>
<td>Acquisition matrix</td>
<td>$256 \times 168$</td>
<td>$256 \times 256$</td>
<td>$224 \times 202$</td>
<td>$320 \times 224$</td>
</tr>
<tr>
<td>Number of slices</td>
<td>27</td>
<td>32</td>
<td>84</td>
<td>32</td>
</tr>
<tr>
<td>Slice thickness (mm)</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Receiver bandwidth (+kHz)</td>
<td>20.83</td>
<td>31.25</td>
<td>31.25</td>
<td>31.25</td>
</tr>
<tr>
<td>Echo train length</td>
<td>1</td>
<td>1</td>
<td>140</td>
<td>1</td>
</tr>
<tr>
<td>Acquisition time (min:s)</td>
<td>2:03</td>
<td>4:09</td>
<td>11:15</td>
<td>2:04</td>
</tr>
</tbody>
</table>
Figure 6.1: Undersampling strategies investigated in this study: (a) stochastic variable density sampling, (b) uniform sampling, (c) Poisson-disk sampling, and (d) CS-SENSE sampling.

**Stochastic Variable-Density Sampling:** To satisfy the CS requirement of incoherent aliasing interference, we randomly selected the phase-encode locations based on a probability density function (PDF). The PDF varied according to the distance from the k-space origin, as described in (54). This scheme yields more samples near the centre (high energy) compared to the periphery of k-space (low energy). To optimize performance, we always acquired the central zone of k-space (i.e., 3% of the total number of samples).

**Uniform Sampling:** The SENSE and GRAPPA reconstructions were originally designed to reconstruct images from uniformly undersampled k-space data, which produces coherent and predictable aliasing interference. In this study, we simulated this by uniformly undersampling the $k_y$-$k_z$ plane. In addition, a region of $24 \times 24$ pixels at the origin of k-space was always fully sampled. This fully sampled region was used to calibrate the kernel weights in Eq. [3.45] of the GRAPPA-based reconstructions, and to calculate the sensitivity maps for the SENSE reconstruction.
Poisson-Disk Sampling: To satisfy the requirements of the L1-SPIRiT reconstruction, we sampled the data using a Poisson-disk distribution (214) which provides a high degree of incoherence needed for compressed sensing, while insuring uniform distance between samples for parallel imaging. Analogous to uniform sampling, a region of 24×24 pixels at the origin of k-space was also always fully sampled and used to calibrate the kernel weights and sensitivity maps.

CS-SENSE Sampling: The CS-SENSE sampling approach simulated a 2× undersampled SENSE acquisition by uniformly undersampling the $k_y$ phase encodes, coupled with 2× stochastic variable-density undersampling of the $k_y$-$k_z$ phase encode plane of the reduced field of view k-space (i.e., for a total acceleration factor of 4).

6.2.3 Image Reconstruction

All reconstruction methods were implemented in MATLAB (The MathWorks, Inc., Natick, MA). Because of memory constraints and processing speed, the 3D k-space data were reconstructed slice-by-slice. Please refer to Chapter 3 for a more detailed explanation of the different reconstruction algorithms.

6.2.3.1 CS Reconstruction

We reconstructed each individual coil image by solving the optimization problem given by

$$\arg\min_{\mathbf{m}_l} \| \mathbf{F}_u \mathbf{m}_l - \mathbf{s}_l \|^2_2 + \lambda_{WT} \| \Psi \mathbf{m}_l \|_1 + \lambda_{TV} TV(\mathbf{m}_l),$$

where $\mathbf{m}_l$ is the reconstructed vector image from coil $l$, $\mathbf{s}_l$ is the acquired undersampled k-space data with the $l$-th coil, $\mathbf{F}_u$ represents the undersampled Fourier transform, $\Psi$ represents the
wavelet transform operator, $TV$ represents the Total-Variation (sum of absolute differences in the image), $\lambda_{WT}$ and $\lambda_{TV}$ are the Lagrangian multipliers that balance data consistency and sparsity of the wavelet coefficients and finite differences, respectively. The $\ell_1$-norm and $TV$ operators promote image sparsity in both the wavelet and $TV$ domains simultaneously. We used the conjugate gradient algorithm (152) with backtracking line search to find an optimum solution to Eq. [6.1]. The $\lambda_{WT}$ and $\lambda_{TV}$ multipliers were selected to minimize the global performance error metric described in the following section. In this study, we used the Daubechies-4 wavelet (147) as the sparsifying transform. The CS-reconstructed phase-aligned coil images were then combined via complex summation.

6.2.3.2 SENSE Reconstruction
The quality of sensitivity-based reconstructions depends on the accuracy of the coil sensitivity assessment (19). We used the fully sampled region at the origin of $k$-space to determine the sensitivity maps. These maps were calculated following a similar procedure by Pruessmann et al. (19). Preliminary sensitivity maps were calculated by dividing each coil image by a magnitude reference image obtained via the sum-of-squares of the coil images. This first step yielded coarse sensitivity maps with most of the anatomical information removed. The second step involved a third-order polynomial regression analysis of these coarse sensitivity maps using the bivariate model given by

$$c(x, y) = \sum_{i=0}^{p} \sum_{j=0}^{p-i} a_{ij}x^iy^j, \quad [6.2]$$
where $p$ is the polynomial order, $x$ and $y$ are the spatial position variables, $a_{ij}$ are the complex regression coefficients, and $c(x,y)$ are the complex sensitivity map values. Only non-background values were included in the regression. These ‘valid’ data were obtained by thresholding the magnitude data of the reference image. We then used the regression coefficients to fit the sensitivity maps over all positions in the image. We implemented the SENSE reconstruction using the iterative conjugate gradient method (160). This implementation allows for reconstruction from arbitrary k-space trajectories.

6.2.3.3 GRAPPA Reconstruction
We used the fully sampled region of 24×24 pixels at the origin of k-space to calibrate the GRAPPA kernel weights using Eq. [3.45]. The non-acquired k-space values were then recovered according to Eq. [3.43]. The final composite image was obtained by combing the phase-aligned coil images via complex summation.

6.2.3.4 SPIRiT and L1-SPIRiT Reconstruction
For the SPIRiT and L1-SPIRiT reconstructions, we incorporated the code provided by Lustig et al. (22) in our software. We modified their code to use the fully sampled region at the origin of k-space to calibrate the kernel weights. The phased-aligned coil images were combined via complex summation.

6.2.3.5 CS-SENSE Reconstruction
The CS-SENSE approach reconstructed each individual aliased image using the same approach as described in the CS reconstruction section. The aliased images were obtained by solving the set of optimization problems given by
\[
\arg \min_{m_l} \| F_u m_l^{\text{aliased}} - s_l^{\text{aliased}} \|_2^2 + \lambda_{WT} \| \Psi m_l^{\text{aliased}} \|_1 + \lambda_{TV} TV(m_l^{\text{aliased}}).
\]  

[6.3]

The final composite image was then obtained by unfolding the set of coherently aliased images as described in the SENSE reconstruction overview of Chapter 3.

6.2.4 Assessment of Reconstructed Images

6.2.4.1 Quantitative Assessment

We quantitatively assessed the performance of the various reconstructions by analyzing the complex error between the fully sampled reference image and the accelerated images. The performance analysis was based on the normalized root-mean-square error (NRMSE) given by

\[
\text{NRMSE} = \frac{\text{RMSE}}{m_{\max} - m_{\min}} = \sqrt{\frac{\sum_{p=Voxels \ in \ region} |m_p - m_p^{\text{fully \ sampled}}|^2}{N \max(|m|) - \min(|m|)}},
\]  

[6.4]

where \( m_{\max} \) and \( m_{\min} \) denote the maximum and minimum absolute values in the selected region, \( m_p^{\text{fully \ sampled}} \) is the fully sampled reference voxel at position \( p \), \( m_p \) is the reconstructed voxel from the undersampled k-space, and \( N \) is the number of voxels in the region. From Eq. [6.4], we derived a global performance error (GPE) and two local performance errors (\( LPE_{low} \) and \( LPE_{high} \)). The GPE metric included all non-background values throughout the entire volume of data obtained via thresholding of the fully sampled magnitude image. The \( LPE_{low} \) and \( LPE_{high} \) metrics included only values from user-defined regions of interest containing low frequencies (i.e., homogeneous regions), and high frequencies (i.e., regions with edges), respectively. A lower GPE or LPE value indicates a more accurate reconstruction. Statistical analysis of the
GPE values was performed using SPSS software (IBM, Inc., Armonk, NY). Because of the low number of volunteers involved in this study, we used a nonparametric method to compare the distributions, which does not require the assumption of a normal distribution.

6.2.4.2 Qualitative Assessment
To confirm the results of our quantitative assessment, we correlated the objective metrics with a qualitative assessment. A fellowship-trained neuroradiologist with over 25 years of experience evaluated all reconstructed images. The radiologist was blinded to the reconstruction algorithm, sampling scheme, and volunteer details. The images were presented in a random fashion and were assessed for overall quality by ranking the images based on the presence of noise, blurring, and artefacts. For each volunteer and imaging sequence, the radiologist selected the best four reconstructed datasets and ranked them from 1 (best) to 4. The non-selected datasets were automatically assigned a score of 5 (worst).

6.3 Results
6.3.1 Quantitative Results
First, we determined the optimum sampling strategy for each reconstruction. Figure 6.2 compares the GPE values for the different sampling-reconstruction combinations investigated in this study. CS and L1-SPIRiT reconstructions yielded minimum GPE values when combined with stochastic variable-density sampling regardless of the sequence (i.e., GRE, SWI, FLAIR, and TOF). For the other reconstructions, i.e., SENSE, GRAPPA, and SPIRiT, the uniform sampling approach yielded minimum GPE values and was, therefore, the preferred strategy. These sampling-reconstruction combinations were deemed optimum from a quantitative point of
view. In most cases, the optimum combination yielded significantly lower GPE values than the other combinations, except for the SPIRiT and L1-SPIRiT reconstructions of SWI and FLAIR data. For these sequences, the SPIRiT and L1-SPIRiT reconstructions performed equally well with every sampling strategy (no statistically significant difference). CS and SENSE, however, were the most effected reconstruction techniques with regards to sampling strategy. As expected, CS performed particularly poorly when combined with uniform undersampling, and SENSE failed to reconstruct k-space data that were undersampled using stochastic variable-density sampling. The CS-SENSE reconstruction combines the CS and SENSE techniques sequentially. Therefore, the respective optimum sampling strategy was determined by selecting the optimum sampling strategy for CS (stochastic variable density) and SENSE (uniform sampling).

After determining the best sampling strategy for each reconstruction, we compared these optimum combinations for each sequence. For the $T_2^*$ GRE and TOF sequences, the L1-SPIRiT reconstruction combined with stochastic variable density sampling yielded the lowest median GPE values, whereas SPIRiT and uniform sampling was the preferred combination for the SWI and FLAIR sequences. However these results are inconclusive as no statistically significant difference was observed between the different optimums: every optimum sampling-reconstruction combination performed comparably well for every sequence.
Figure 6.2: Comparison of GPE values for the different sampling-reconstruction combinations investigated in this study, i.e., stochastic variable density (VD), Poisson-disk (PD), uniform (Uni), and CS-SENSE (VD+Uni). The boxplot presents the minimum, lower quartile, median, upper quartile and maximum GPE values for each sampling-reconstruction combination. The circles show outliers defined as GPE values that were greater than 1.5× the interquartile range away from the 25th or 75th percentiles. The asterisks denote distributions with statistically significant difference ($P < 0.05$).
Each combination of sampling strategy and reconstruction technique produces different error characteristics in the final image. Figure 6.3 compares a TOF image reconstructed with the different algorithms tailored to the optimum sampling strategy as determined above. The error maps arising from conventional parallel MR imaging methods, \textit{i.e.}, SENSE, GRAPPA, and SPIRiT, are essentially free of anatomical information and vary across the images according to the $g$-factor \cite{19}. On the other hand, the reconstructions incorporating $\ell_1$-regularization (CS, L1-SPIRiT and CS-SENSE) yield larger errors near edges. The local performance measures (Figure 6.4) confirm this observation. The $\ell_1$-regularized reconstructions yielded smaller $LPE_{\text{low}}$ values and greater $LPE_{\text{high}}$ values than the conventional parallel MR imaging reconstructions. It is interesting to note that CS performed the best in regions containing slowly varying structures \textit{(i.e.,} smallest $LPE_{\text{low}}$ values) and the worst in regions containing rapidly changing structures \textit{(i.e.,} greatest $LPE_{\text{high}}$ values). CS-SENSE did not perform as well as CS and L1-SPIRiT in regions of slowly varying structures, but a similar trend was observed.
Figure 6.3: Comparison of a TOF image reconstructed with each algorithm tailored to its optimum sampling strategy determined from Figure 6.2. For the CS and L1-SPIRiT reconstructions, we used a variable-density sampling scheme, whereas for SENSE, GRAPPA, and SPIRiT, we used a uniform sampling scheme. The CS-SENSE sampling approach was used for the CS-SENSE reconstruction.
Figure 6.4: Comparison of the local performance errors for the optimum sampling-reconstruction combinations determined from Figure 6.2. An ideal sequence would have errors that tend towards the bottom left corner of each plot. Plotted are median errors with error bars indicating the range of measurements.
Figure 6.5: Qualitative ranking of the reconstructed images by the neuroradiologist. The best four reconstructed datasets were selected and ranked from 1 (best) to 4. The non-selected datasets were automatically assigned a score of 5 (worst). Close attention was paid for the presence of noise, blurring, and artefacts. The boxplot presents the minimum, lower quartile, median, upper quartile and maximum rankings for each sampling-reconstruction combination. The circles show outliers defined as $GPE$ values that were greater than $1.5 \times$ the interquartile range away from the $25^{th}$ or $75^{th}$ percentiles.
6.3.2 Qualitative Results

Figure 6.5 shows the overall ranking of the reconstructed images. As expected, the fully sampled image datasets were always ranked first. The ranking of the accelerated images consistently favoured two combinations: L1-SPIRiT and CS reconstruction with stochastic variable density sampling. The combination of L1-SPIRiT with Poisson-disk sampling also ranked highly. CS-SENSE ranked higher than average for the SWI and $T_2^*$ GRE sequences. Although SPIRiT often yielded the lowest $GPE$ (Figure 6.2), it was qualitatively preferred only in the case of the FLAIR sequence.

The qualitative and quantitative results were generally in good agreement. Combinations yielding high $GPE$ values were correlated with a significant degree of image artefacts. These combinations were consistently ranked as poor quality and inadequate for stroke assessment. For example, the noise in the SENSE with stochastic variable density sampling images hindered the diagnostic content, while the combination of CS with uniform sampling produced significant coherent aliasing artefacts. However, the optimum combinations determined quantitatively resulted in good image quality (as determined by the neuroradiologist) that would allow for accurate stroke assessment. Still, minor image artefacts were sometimes noticeable in the optimum combinations.

Figure 6.6 shows a comparison of a $T_2^*$ GRE image reconstructed with the different algorithms tailored to the optimum sampling strategy where artefacts with different degrees of severity are visible. Overall, the reconstruction algorithms using $\ell_1$-regularization (CS, L1-SPIRiT, and CS-SENSE) were less noisy than the conventional parallel MR imaging techniques (SENSE,
GRAPPA, and SPIRiT). Although CS introduced noticeable blurring artefacts, it was still preferred over conventional parallel imaging. SENSE, GRAPPA, SPIRiT, and CS-SENSE exhibited some fold-over artefacts as shown by the arrows in Figure 6.6.

![Figure 6.6: Comparison of a $T_2^*$ GRE image reconstructed with the different algorithms tailored to the optimum sampling strategy. The SENSE, GRAPPA, SPIRiT, and CS-SENSE algorithms exhibit some fold-over artefacts as shown by the arrows. The reconstruction algorithms using an $\ell_1$-regularization process (i.e., CS, L1-SPIRiT, and CS-SENSE) were less noisy than the conventional parallel MR imaging techniques (i.e., SENSE, GRAPPA, and SPIRiT).]

Ranking the SWI reconstructed images qualitatively was found to be the most challenging as several combinations yielded excellent image quality. This observation is consistent with the
quantitative results. The distribution of the $LPE$ values for the SWI sequence in Figure 6.4 is the most compact and closest to the bottom left hand corner (i.e., smallest $LPE$ values). This indicates that all optimum sampling-reconstruction combinations provided equally accurate images. Despite the subtle qualitative differences between the optimum reconstructions, the $\ell_1$-regularized reconstructions (CS, L1-SPIRiT, and CS-SENSE) were clearly preferred over the conventional parallel MR imaging techniques.

6.4 Discussion

We investigated several sampling-reconstruction paradigms to accelerate specific neuroimaging sequences while preserving image quality and diagnostic content. We used ischemic stroke as the underlying motivation for the studied sequences. The images of six healthy volunteers were assessed both quantitatively and qualitatively.

**Quantitative Assessment:** The design of the sampling pattern characterizes the properties of the aliasing interference arising for the sub-Nyquist-Shannon sampling. Figure 6.2 confirms our expectation that the optimum sampling strategy (with respect to GPE and LPE values) depends on the reconstruction technique. The $\ell_1$-regularized reconstructions require a high degree of incoherence, whereas conventional parallel imaging requires uniform distance between samples. These requirements were best satisfied by the stochastic variable-density and uniform undersampling approaches, respectively. CS and SENSE were the most sensitive reconstructions with respect to sampling strategy; CS failed to recover the coherent aliasing arising from uniform undersampling, and SENSE performed poorly in the presence of incoherent aliasing. Despite the large gaps between samples in stochastic variable-density sampling, GRAPPA and SPIRiT
reconstructed images with better accuracy than SENSE. L1-SPIRiT, which synergistically combines CS and parallel imaging, performed well with every sampling strategy, but yielded the best results with stochastic variable-density sampling. GRAPPA, SPIRiT, and L1-SPIRiT were the most flexible and robust reconstructions, and yielded accurate images with every undersampling scheme.

Figure 6.3 and the $LPE$ values in Figure 6.4 show that the $\ell_1$-regularization techniques of CS, L1-SPIRiT, and CS-SENSE performed worse in regions with edges than in homogeneous regions. All these reconstructions enforce sparsity in the wavelet domain, which invariably introduces some blurring in the reconstructed image: the wavelet transform concentrates most of the energy at the coarsest scale-coefficients, which are closely related to the low frequencies of k-space. Note that filtering of the higher frequencies improves background noise suppression, but also increases blurring of important physiological features that could potentially hinder detection of pathologies. The conventional parallel imaging reconstructions, however, did not exhibit any blurring, but were subject to noise amplification due to the $g$-factor (19), which could also preclude an accurate diagnosis.

**Qualitative Assessment:** The qualitative and quantitative results were in good agreement. Combinations of sampling strategy and reconstruction technique with high $GPE$ values received a low ranking, whereas optimum combinations were usually assigned a high score. However, the quantitative optimum did not necessarily correspond to the qualitative optimum as some combinations introduced image artefacts unacceptable to the neuroradiologist.
**Limitations:** Parallel imaging techniques use the spatial sensitivity information inherent in an array of multiple receiver coils to reduce the number of phase encoding steps and the number of receiver coils limits the maximum achievable acceleration factor. Here, we used a 12-channel head/neck coil and selected a fixed acceleration factor of 4. Higher acceleration factors were tested, but the images reconstructed with conventional parallel imaging techniques quickly deteriorated. The reconstructions incorporating $\ell_1$-regularization, however, were not limited by the number of receiver coils and performed better at eliminating the aliasing interference arising from higher acceleration factors than the conventional parallel imaging techniques. In theory, the maximum achievable acceleration factor with CS is limited by the sparsity of the image in a given basis.

Neuroimaging often requires axial acquisitions, such as TOF imaging of the circle of Willis. Therefore, prospectively accelerated acquisitions could undersample the sagittal or coronal $k_y$-$k_z$ phase encode plane. However, the 12-channel head coil used in this study offers little spatial sensitivity variation in the $z$-direction and is sub-optimal for parallel imaging along that direction. For consistency, we chose to simulate axially undersampled acquisitions that allowed us to take advantage of 2D accelerated parallel imaging with every sequence. Although this approach may not be practical with this setting, the use of dedicated receiver-coil arrays with a greater number of elements and highly non-uniform spatial sensitivities could potentially enable 2D parallel imaging in any plane.

Investigating a healthy population instead of actual stroke subjects has some limitation in assessing the diagnostic content of images, but an exhaustive comparison would be difficult to
conduct on stroke patients because of lengthy scan times. We believe that this study still provides valuable insights in determining the appropriate combination of sampling strategy and reconstruction technique to accelerate neuroimaging for stroke assessment. A following study could then focus on using the optimum combinations to prospectively accelerate images from stroke patients and have multiple radiologists to qualitatively assess the diagnostic content.

We implemented the different reconstruction algorithms as originally described in the cited seminal works. Some implementation variations yielding slightly different results may exist, but, to our knowledge, no fundamental difference in the results should ensue. The SENSE reconstruction could be further improved by taking into account the noise correlation in the receiver coils, but this requires extra data acquisitions and computations. The quality of the SENSE reconstruction mainly depends on the accuracy of the sensitivity maps. When the exact sensitivity maps are known, SENSE provides the best reconstruction; however, such maps are often difficult to obtain. In the $\ell_1$-regularized reconstructions, the Lagrangian multiplier that balances data consistency and sparsity plays an important role. This parameter was adjusted through a combination of visual inspection of the reconstructed images and assessment of the analysis metrics (i.e., minimizing the GPE values). We readily recognize that the parameter could be further optimized to tentatively improve the overall reconstruction accuracy.

6.5 Conclusions

We successfully demonstrated that all optimum sampling-reconstruction combinations enabled at least four-fold acceleration of several neuroimaging sequences on a twelve-channel head/neck coil while maintaining image quality within an acceptable clinical tolerance. Although the
quantitative results did not clearly identify a “best” candidate among the optimum combinations, the qualitative results indicated an obvious preference for the $\ell_1$-regularized reconstructions over the conventional parallel imaging techniques.

The judicious application of appropriate sampling and reconstruction methods can significantly accelerate neuroimaging protocols. Applying a four-fold acceleration will reduce the scan time of the sequences in Table 6.1 from ~20 min to ~5 min. With inclusion of DWI and PWI, the total scan time for a comprehensive acute stroke imaging protocol would be about 10 min.
Chapter Seven: Accelerating Time-of-flight with Sparse SENSE

In this chapter, we used a combination of compressed sensing (section 3.6) and parallel imaging (section 3.7) to prospectively accelerate time-of-flight (TOF) imaging (see Appendix B for a detailed description of TOF imaging). This research builds upon the work that was presented in the previous chapter, where we investigated several combinations of sampling strategy and reconstruction technique to retrospectively accelerate some of the key sequences of the acute MR stroke protocol. We observed that reconstructions combining compressed sensing and parallel imaging generally yielded superior image quality both quantitatively and qualitatively. By capitalizing on these results, we used the sparse SENSE approach to implement prospective acceleration of TOF angiography. Our efforts focused on accelerating TOF because it is central to the stroke protocol and used extensively in clinical settings. Accelerating this sequence will, therefore, potentially benefit many patients.

7.1 Introduction

Acute ischemic stroke is a leading cause of permanent disability and death in North America (77). Prompt diagnosis is vital to initiate early patient treatment and minimize irreversible brain damage (60). Currently, computed tomography (CT) is the standard imaging modality for patients presenting with acute ischemic stroke due to its high spatial and temporal resolution, and wide availability (94). Although important progress has significantly reduced the risks associated with CT imaging, the modality still exposes patients and staff to ionizing radiation, which can potentially cause radiation induced cancer (14). In addition, CT also requires iodinated contrast agents to visualize the vasculature, which can induce nephropathy, especially in patients with chronic kidney disease (215). MR imaging, however, does not use radiation nor requires
iodinated contrast agents. More importantly, MR imaging offers a wide variety of image contrasts and functional information that can potentially yield superior diagnostic capabilities than CT. All these reasons motivate the desire to push MR imaging in acute stroke assessment forward and rapid TOF angiography will be central to this transition.

Currently, conventional high-resolution TOF protocols routinely exceed 2-3 min. Shorter protocols would sacrifice spatial resolution and/or volume coverage. Clinical scanners only provide modest acceleration factors (e.g., between $2\times$ and $4\times$ depending on the number of receiver coil elements) via parallel imaging using sensitivity encoding (SENSE) (19) or generalized autocalibrating partially parallel acquisition (GRAPPA) (21). In addition, the accelerated images are generally subject to noise amplification and residual aliasing artefacts that hinder the visualization of small vessels. Other advanced sampling schemes and constrained reconstruction, such as compressed sensing (CS) (139) may provide significant improvements to image quality. In this work, we investigate the quality of accelerated TOF images using a combination of parallel imaging and compressed sensing (sparse SENSE) (27, 141) in a highly time constrained environment by limiting the acquisition to only 30 s per slab. We used the acceleration available with the sparse SENSE approach to increase the acquisition matrix by allowing higher undersampling rates. We hypothesize that the improved resolution available via accelerated TOF approaches will a) provide more details of cerebral vasculature compared to the fully sampled approach collected over the same time interval and b) outweigh the artefacts and additional noise associated with modest to high undersampling factors.
The chapter first describes the variable density Poisson-disk sampling approach used in this study as well as the MR protocol and data acquisition. We then describe the implementation of the investigated sparse SENSE reconstruction technique and the details of the qualitative assessment. We validate our acquisition and reconstruction methodology using both retrospectively and prospectively undersampled data collected on healthy volunteers. We present and discuss the results of this volunteer study and show that the sparse SENSE approach provides more details of cerebral vasculature with higher vessel conspicuity compared to the fully sampled approach collected over the same time interval. After validating our methodology on healthy volunteers, we then evaluate it on two acute stroke patients and compare the images obtained with our approach against those from the standard stroke protocol. This comparison demonstrates that combining parallel imaging with CS is clinically relevant and can potentially enable higher acceleration factors than vendor-supplied parallel imaging.

7.2 Methods

7.2.1 MR Protocols and Acquisitions

We performed 3D TOF imaging experiments on seven healthy volunteers and two acute stroke patients. The local Internal Review Board approved the protocol and the subjects provided written informed consent (see Appendix C for ethics approval). In this section, we first describe the sampling strategy used in this study, present the acquisition parameters for the retrospective and prospective volunteer experiments, and provide the parameters for the prospective patient experiment. Finally, we describe the data acquisition for our in-house coil sensitivity calibration.
7.2.1.1 Variable Density Poisson-Disk Sampling

Poisson-disk sampling distributions (214) have excellent blue noise spectra (*i.e.*, minimal low frequency components and no concentrated spikes in energy or aliasing) and provide the high degree of incoherence needed for CS, while ensuring the uniform sample spacing required for parallel imaging. This sampling distribution is, therefore, suitable for combining CS and SENSE, *i.e.*, sparse SENSE. Because the bulk of the energy is concentrated near the origin of k-space, we modified the Poisson-disk distribution to enable variable density Poisson-disk sampling.

Variable density was achieved by partitioning the $k_y$-$k_z$ plane into a series of $N$ annuli with equispaced densities (Figure 6.1) (216). Each annulus was then assigned a uniform sampling density $\rho_i$ obtained by averaging the density function within the interval of the corresponding annulus (Figure 6.1). The sampling density of each annulus was then used to determine the diameter of the disks defining the exclusion zone in the Poisson-disk sampling to yield the desired undersampling factor (214).

The sampling density function decreased exponentially according to the elliptical distance from the k-space origin $k = \sqrt{k_y^2/a^2 + k_z^2/b^2}$. The parameters $a$ and $b$ represent the length of the semimajor and semiminor axes, respectively, and the eccentricity of the ellipse is defined as $ecc = \sqrt{1 - (b/a)^2}$, where $0 \leq ecc < 1$. For better performance, we enforced a fully sampled central region containing 2% of the total acquired samples, *i.e.*, unity density for $k \leq k_0$. The sampling density function (Figure 6.1a) is given by:

$$ecc = \sqrt{1 - (b/a)^2}, \text{ where } 0 \leq ecc < 1.$$
\[ \rho(k) = \begin{cases} 
\frac{1}{(1 - \rho_{\min})e^{-(|k| - k_0)/\tau} + \rho_{\min}} & \text{if } |k| \leq k_0 \\
\rho_{\min} & \text{if } |k| > k_0 
\end{cases} \]  

[7.1]

where \( \rho_{\min} \) guarantees a minimum sampling density at the periphery of k-space and \( \tau \) represents the exponential decay constant. The minimum sampling density must be chosen to be lower than one over the desired acceleration factor, i.e., \( \rho_{\min} < 1/R \). In this study, we selected \( \rho_{\min} = 1/(R + 1) \), and the decay constant \( \tau \) was empirically determined to achieve the desired acceleration factor for a given \( k_0 \).

Figure 7.1: The sampling density function (a) was designed to fully sample a central region (\( k \leq k_0 \)) and decrease exponentially with the elliptical distance from the k-space origin while guaranteeing a minimum density \( \rho_{\min} \) at the periphery. Variable density Poisson-disk sampling (b) was achieved by partitioning the \( k_y \)-\( k_z \) plane into a series of annuli and assigning each annulus with a uniform sampling density obtained by averaging the density function within the interval of the corresponding annulus.
7.2.1.2 Retrospective Volunteer Study

To validate our sampling strategy and sparse SENSE reconstruction, we used the fully sampled TOF data from our previous study presented in Chapter 6. Please refer to this chapter for the acquisition parameter details. We then simulated 4× accelerated acquisitions by retrospectively undersampling fully sampled data. TOF data are generally acquired axially by aligning the slice encoding direction along the superior-inferior (SI) orientation of the patient (i.e., mostly parallel to the vessels) to maximize the inflow effect of fresh blood. This organization, however, is less optimal from a parallel imaging perspective since coil sensitivities have generally little SI variation. To investigate the effect of the sampling plane orientation, we simulated four-fold acceleration by retrospectively undersampling the fully sampled data in the axial (Figure 7.2a) or coronal (Figure 7.2b) plane. Here we used the convention where undersampling of the axial plane corresponds to a sagittal acquisition, whereas undersampling of the coronal plane corresponds to an axial acquisition. In a sagittal acquisition, the slice, phase, and frequency encoding directions are along the left-right (LR), anterior-posterior (AP), and SI patient axes, respectively. For the axial acquisition, the slice, phase, and frequency encoding directions are along the SI, LR, and AP patient axes, respectively.
Figure 7.2: Illustration of the investigated retrospective undersampling approaches used to validate our acquisition and reconstruction methodology. (a) Undersampling of the axial plane is optimal for 2D acceleration with parallel imaging as it takes advantage of the inherent spatial sensitivity variation of the phased-array receiver coil, however this approach does not completely emulate real TOF data acquisition. (b) TOF images of the circle of Willis are generally acquired axially (i.e., coronal plane undersampling) by aligning the slice encoding direction (z) along the superior-inferior (SI) orientation of the patient to maximize the inflow effect of fresh blood. This acquisition scheme, however, is less optimal from a parallel imaging perspective since coil sensitivities have little SI variation. Coil sensitivity non-uniformity is required to separate the superimposed aliased signal in parallel imaging. Labels: superior (S), inferior (I), anterior (A), posterior (P), right (R), left (L), frequency encoding ($k_x$), phase encoding ($k_y$), and slice encoding ($k_z$).

7.2.1.3 Prospective Volunteer Study

For the prospective volunteer study, we acquired one fully sampled (labeled 1x) and seven prospectively undersampled data sets, ranging from $2\times$ to $8\times$ acceleration, using our modified oblique axial 3D TOF sequence. The data was acquired with a 3 T scanner (Discovery MR750; General Electric Healthcare, Waukesha, WI) and a 12-channel receive-only head coil. We acquired each data set with the same acquisition time of 24 s and used the acceleration available
Table 7.1: MR acquisition parameters for the prospectively accelerated volunteer study. The sampling masks from 1× to 8× accelerations are also shown for reference.

**Constant acquisition parameters**

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<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Sequence</td>
<td>Modified oblique axial 3D TOF</td>
</tr>
<tr>
<td>Repetition time</td>
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</tr>
<tr>
<td>Echo time</td>
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</tr>
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<td>Phase field of view</td>
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<tr>
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<tr>
<td>Options</td>
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<td>Acquisition time</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Accel</th>
<th>N_x×N_y×N_z</th>
<th>Mask</th>
</tr>
</thead>
<tbody>
<tr>
<td>1×</td>
<td>320×68×20</td>
<td></td>
</tr>
<tr>
<td>2×</td>
<td>320×112×24</td>
<td></td>
</tr>
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<td>3×</td>
<td>320×172×24</td>
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</tr>
<tr>
<td>8×</td>
<td>320×320×32</td>
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</table>
with the sparse SENSE approach to increase the acquisition matrix from $320 \times 68 \times 20$ (fully sampled) up to $320 \times 320 \times 32$ ($8\times$ acceleration) by allowing higher undersampling factors. The acquisition parameters for the accelerated scans are summarized in Table 7.1. The sampling masks from $1\times$ to $8\times$ accelerations are shown for reference. Each mask included a fully sampled central region containing 2% of the total acquired samples. To account for the little spatial sensitivity variation in the $z$-direction of the 12-channel head coil used in this study, we selected a sampling density with an eccentricity of $ecc = 0.96$, which reduced the undersampling along the $z$-direction. For smooth transition of sampling densities between the annuli, we partitioned the $k_y-k_z$ plane into a series of 10 annuli. In addition, we also acquired a fully sampled dataset for reference with resolution and parameters equivalent to the $5\times$ undersampled data.

7.2.1.4 Prospective Patient Study

We first introduce the relevant patient clinical information and then present the acquisition parameters. Timeline illustrating the clinical management of both stroke patients is shown in Figure 7.3.

**Patient 1:** A 72-year-old female acute stroke patient was recruited from the emergency department at the Foothills Medical Centre in Calgary, Alberta, Canada, and had a moderately severe stroke ($NIHSS = 18$) with symptom onset within 4 h of admission. The patient had a right middle cerebral artery (MCA) occlusion confirmed by CT angiography (CTA) and showed no signs of intra-cranial haemorrhage on the baseline CT. Although the patient arrived at the hospital within the treatment window for intravenous tissue plasminogen activator (tPA), she did not receive thrombolysis. The patient was already on warfarin (anticoagulation therapy) prior to
her stroke onset and had an international normalized ratio (INR) (217) of 2.2. The INR value is a measure of the clotting tendency of the blood and INR values greater than 1.7 are contraindication for intravenous tPA (IV tPA) therapy because of the increased risk of intracranial haemorrhage (218). The patient was randomized to receive standard of care and continued on warfarin.

**Patient 2:** The second acute stroke patient involved in our study was an 83-year-old female with a moderately severe stroke (NIHSS = 17). The patient showed no sign of haemorrhage on baseline CT, but had a right internal carotid artery (ICA) occlusion with some visible flow in the proximal MCA on CTA. The patient had no contraindications to tPA and was given intravenous tPA without improvement. The patient was then enrolled for endovascular treatment, which only partially debulked the thrombus and resulted in distal embolization into the MCA with no improvement in the flow to the right hemisphere.

**Patient 1**

![Timeline a](Image)

**Patient 2**

![Timeline b](Image)

Figure 7.3: Timeline illustrating the clinical management of both stroke patients involved in this study.
**Acquisition Parameters:** After medical care, the patients were immediately transferred to the 3T MR scanning room and imaged using an in-house stroke protocol of an ongoing research study. The protocol included a clinical 3D TOF sequence with an ASSET (*i.e.*, vendor-supplied SENSE-like approach) acceleration factor of 2 and our modified 3D TOF sequence with an acceleration factor of 4. We used the same acquisition parameters for both sequences, *i.e.*, FOV of $24 \times 24 \times 6 \text{ cm}^3$ and acquisition matrix of $320 \times 224 \times 32$. Table 7.2 summarizes the acquisition parameters for both acquisitions.

7.2.1.5 Coil Sensitivity Calibration Data
To compute the coil sensitivity maps, we acquired low-resolution calibration data in a previous series that was co-registered with the accelerated scan using a similar 3D TOF sequence. The acquisition parameters for the calibration scan were TR of 11 ms, TE of 4 ms, flip angle of 15º, bandwidth of $\pm 31.25 \text{ kHz}$, FOV of $24 \times 24 \times 6.0 \text{ cm}^3$, phase FOV of 0.75, and acquisition matrix of $320 \times 24 \times 24$. We acquired the calibration data without any magnetization transfer preparation, spatial saturation, or fat suppression. We subsequently used the $24 \times 24 \times 24$ central region of the calibration data to compute the spatial sensitivity of each phased-array coil using a polynomial fitting approach similar to the one described in section 6.2.3.2.
Table 7.2: MR acquisition parameters for the prospectively accelerated patient study.

<table>
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<td>Sequence</td>
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<td>Repetition time</td>
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<tr>
<td>Field of view</td>
<td>24 cm × 24 cm × 6 cm</td>
</tr>
<tr>
<td>Phase field of view</td>
<td>0.75</td>
</tr>
<tr>
<td>Acquisition matrix</td>
<td>324 × 224 × 32</td>
</tr>
</tbody>
</table>

| Vendor-supplied 3D TOF                                               |               |
| ASSET acceleration                                                    | 2×            |
| Acquisition time                                                      | 1 min         |
| Echo time                                                            | 2.6 ms (minimum) |
| Receiver bandwidth                                                   | ±31.25 kHz    |
| Options                                                               | Magnetization transfer, spatial saturation, fat suppression |

| Sparse SENSE accelerated 3D TOF                                      |               |
| Sparse SENSE acceleration                                            | 4×            |
| Acquisition time                                                     | 30 s          |
| Echo time                                                            | 4 ms (minimum full) |
| Receiver bandwidth                                                   | ±62.50 kHz    |
| Options                                                               | Magnetization transfer, spatial saturation |


7.2.2 Constrained Reconstruction

The acquired raw k-space data were transferred to an 8-core Macintosh workstation (Apple Inc., Cupertino, CA, iMac, 3.4 GHz Intel Core i7, 16 GB of RAM) and reconstructed offline with MATLAB (The MathWorks, Inc., Natick, MA). Images were reconstructed using a standard 3D sparse SENSE model (27, 216) with multiple spatial constraints. The reconstruction was achieved by solving the optimization problem

$$\arg \min_{m} \|F_u C m - y \|_2^2 + \lambda_1 \| \Psi m \|_1 + \lambda_2 \| T m \|_1,$$  \hspace{1cm} [7.2]

where $F_u$ is the undersampled Fourier operator, $C$ is the sensitivity operator, $m$ is the 3D image to reconstruct, $y$ is the acquired k-space data, $\Psi$ is a 3D wavelet transform, and $T$ is the 3D spatial total variation operator. Sensitivity maps were computed using our in-house calibration data. The regularization parameters, $\lambda_1$ and $\lambda_2$, were selected empirically by visual inspection of the reconstructed images to maintain high data consistency while avoiding geometric and compression artefacts. In this study, we performed 3 levels of wavelet decomposition using the Daubechies 4 wavelet (147).

7.2.3 Image Reconstruction Assessment

Each reconstructed image volume was resampled onto $512 \times 512 \times 256$ matrix size using sinc interpolation. Maximum intensity projections (MIP) of the reconstructed images were qualitatively compared to the fully sampled case based on vessel conspicuity, noise, and reconstruction artefact. Cross section profiles through a region with several small vessels were analyzed and compared based on effective resolution, contrast, and conspicuity.
7.3 Results

7.3.1 Retrospective Volunteer Study

Figure 7.4 compares the fully sampled TOF images with the retrospectively accelerated data where undersampling was simulated in either the axial or coronal plane. All accelerated reconstructions yielded images with good clinical diagnostic quality, but subtle differences in image quality and vessel conspicuity are noticeable in the accelerated images when compared to the fully sampled data. The axial undersampled data successfully depicted most of the small vascular features and resulted in nearly identical image quality as the fully sampled one. The coronal undersampling approach, however, yielded marginally lower image quality and vessel conspicuity than the axial undersampling approach. This observation indicates that sagittal acquisitions of TOF data (i.e., real TOF data acquisition) using our 12 channels receive-only head coil inherently yield sub-optimal reconstruction when compared to axial acquisitions.
Figure 7.4: Comparison of fully sampled TOF images and 4-fold accelerated images obtained by retrospectively undersampling the coronal or axial plane. The coronal undersampling approach yielded marginally lower image quality and vessel conspicuity compared to the axial undersampling approach.
7.3.2 Prospective Volunteer Study

Figure 7.5 shows the axial, and coronal MIP images from the fully sampled (1×) and accelerated (2×–8×) TOF images, each acquired in 24 sec. The improvement in spatial resolution with higher acceleration factors is most noticeable in the coronal MIP images since the image resolution increased with acceleration factors in both y- and z- directions. For better visual assessment and comparison of the accelerated images, Figure 7.6b shows enlarged coronal views of a region around the M2 and M3 segments of the middle cerebral artery indicated by the white box in Figure 7.6a. Vessel–to–tissue contrast was superior in all accelerated cases relative to the fully sampled data. Visually, vessel conspicuity increased with acceleration factor, peaking at 5×. At greater acceleration factors (i.e., 6×, 7× and 8×), residual aliasing and compression artefacts from the constrained reconstruction obstructed small vascular features. In Figure 7.6c, we show the line profiles through the region indicated by the dashed line in Figure 7.6a. Visual assessment of the profiles confirms the above observations. Despite having a higher SNR due to larger voxel size, the fully sampled, low-resolution image failed to resolve the peaks and valleys formed by adjacent small vessels. All accelerated cases provided superior definition of the vessels, but the 5× and 6× accelerations provided the best combination of spatial resolution and contrast. The reconstruction time of our sparse SENSE implementation for the 4× dataset was 102 s.
Figure 7.5: Axial and coronal MIP of the TOF images reconstructed from prospectively undersampled data. The acceleration factor increased from $1 \times$ (fully sampled) to $8 \times$, while maintaining a 24 sec acquisition time. The fully sampled MIP images with resolution equivalent to the 5-fold undersampled dataset are shown for reference.
Figure 7.6: (b) Enlarged views of a region of the M2 and M3 segments of the middle cerebral artery indicated by the white box in (a), and (c) line profiles through the region indicated by the dashed line in (a). Arterial conspicuity increases with acceleration rate up to approximately 5×, above which residual aliasing artefacts and smoothing from the ℓ1 reconstruction penalties begin to excessively obscure small vessels.
7.3.3 Prospective Patient Study

Figure 7.7 shows the MIP images for both stroke subjects. The vendor-supplied SENSE reconstruction is provided on the left, and our sparse SENSE reconstruction, on the right. While the sparse SENSE acquisition took only half the time of the SENSE acquisition (30 s vs. 1 min), both approaches yielded comparable diagnostic quality, and clearly identified the occlusion in the right MCA (arrows in Figure 7.7). Careful visual inspection of the enlarged views of the MIP images from the first patient revealed slightly superior vessel conspicuity and vessel-to-tissue contrast in the images obtained using the vendor-supplied accelerated approach. However, in some regions, our approach yielded better vessel conspicuity and delineation (compare enlarged views of patient 2 in Figure 7.7). Because our proposed approach did not implement any fat suppression, the bright signal from subcutaneous fat hindered the visualization of some of the small vessels, particularly those near the skull and eyes.
Figure 7.7: Comparison of the MIP images from the acute ischemic stroke subjects using the 2x accelerated vendor-supplied SENSE approach (left column) and our 4x accelerated sparse SENSE approach (right column). Both approaches yielded images with comparable diagnostic quality and clearly identified the right MCA occlusion in both patients. The enlarged views of the MIP images show similar vessel conspicuity and delineation between both approaches.
7.4 Discussion

The objective of this study was to investigate the potential of combining parallel imaging with CS to prospectively accelerate TOF imaging by limiting acquisition to only 30 s per slab acquisition. To acquire the data, we developed a variable density sampling scheme based on the Poisson-disk distribution that provided the high degree of incoherence needed for CS, while ensuring the uniform sample spacing required for parallel imaging. For the reconstruction, we used a standard sparse SENSE model with multiple spatial constraints. Our methodology was validated with both retrospectively and prospectively accelerated data. We also demonstrated the clinical relevance of the methodology by applying it to two acute stroke patients.

7.4.1 Retrospective Volunteer Study

We first presented a brief validation of our methodology using retrospectively undersampled data. Because we anticipated that the orientation of the undersampling plane with respect to the spatial sensitivity of the receiver would have a significant impact on the quality of the reconstructed image, we simulated two different sampling approaches. In the first approach, we oriented the sampling $k_y$-$k_z$ plane axially to maximize the sensitivity variation in that plane and take advantage of 2D parallel imaging capabilities. For the second approach, we emulated real TOF data acquisitions by orienting the $k_y$-$k_z$ plane coronally. As expected, our results confirmed that the sampling plane orientation has a perceptible effect on the image quality and conspicuity of small vessels that have relatively low vessel-to-tissue contrast. These observations indicate that the use of dedicated receiver-coil arrays with highly non-uniform spatial sensitivities along the $z$-direction would yield better parallel imaging capabilities and thus further improve the image quality of our sparse SENSE approach. To account/mitigate for the lack of sensitivity
variation along the z-direction, we incorporated an eccentricity in our variable density Poisson-disk sampling that reduces the acceleration along that direction.

### 7.4.2 Prospective Volunteer Study

We also validated our methodology by prospectively acquiring accelerated data on healthy volunteers in a highly time-constrained environment allowing only 24 sec per slab. Acceleration was used to increase spatial resolution, and thus potentially resolve smaller arteries. The constrained reconstruction mitigates the SNR reduction typically associated with higher resolutions, but compression and aliasing artefacts may obscure subtle features and reduce the effective image resolution (based on vascular discrimination). We observed that an acceleration factor of $5 \times$ optimally balanced voxel size and the ability to distinguish small vessels. This result suggests that acceleration rates beyond those available commercially are clinically beneficial and may enable high quality TOF imaging, with potential applications in the acute stroke environment. Although current reconstruction times were $\sim 3.5$ times longer than the acquisition time for the $4 \times$ dataset, optimized reconstruction is anticipated to provide near-instantaneous image reconstruction.

### 7.4.3 Prospective Patient Study

After validating our methodology on healthy volunteers, we then demonstrated its clinical application on two acute stroke subjects and compared the images obtained with our approach against those from the standard stroke protocol. This qualitative study demonstrates that combining parallel imaging with CS is clinically relevant and enables higher acceleration factors than the vendor-supplied parallel imaging approach while preserving comparable diagnostic
quality. We showed $2 \times$ faster acquisitions using our proposed approach with only marginal deterioration in image quality and vessel conspicuity. The lower vessel conspicuity can be explained by the lack of fat suppression with our approach that causes the bright signal from subcutaneous fat to hinder the visualization of some small vessels, particularly those near the skull and eyes.

### 7.4.4 Limitations

The current implementation of our modified 3D TOF sequence only applies a spatial saturation band to suppress the venous flows and a magnetization transfer preparation pulse to improve the vessel-to-tissue contrast. Because fat tissue has a short $T_1$ relaxation time and appears hyperintense in the source TOF images, the bright fat signal hinders the visualization of vessels in MIP angiogram images. Therefore, a fat suppression technique is also highly desirable for TOF imaging. In this study, we experimented with the use of a fat saturation pulse and observed some modulation artefacts in the data that require further investigations.

Another difference between our accelerated 3D TOF approach and the clinical 3D TOF sequence is the echo time. It is generally desirable to minimize the echo time in 3D TOF to mitigate motion-induced phase dispersion due to turbulent or pulsatile flow. To achieve the shortest echo time, the clinical TOF sequence uses fractional echo readout. Because we do not expect significant differences in image quality and were primarily interested in validating the concept of accelerating TOF using the sparse SENSE approach, our sequence did not use fractional echo readout. However, this could easily be implemented and would only require minor modifications in the reconstruction.
Clinical assessment of stroke patients often requires acquiring multiple slabs to cover the vasculature of interest, which generally includes the internal carotid arteries, circle of Willis, and middle cerebral arteries. Although we only presented TOF images from single slab acquisitions, our methodology can also process multi slab acquisitions.

7.5 Conclusions

We have proposed a sampling and reconstruction methodology that enables sub 30 s TOF acquisition per slab using a combination of parallel imaging and CS, i.e., sparse SENSE. We validated our methodology on healthy volunteers and demonstrated its clinical relevance on two acute stroke patients. The proposed method enabled higher acceleration factors than the vendor-supplied parallel imaging approach while preserving comparable diagnostic quality. We believe that the sparse SENSE approach will eventually contribute to a shift towards the use of MR in the standard of care for acute stroke imaging.
Chapter Eight: Conclusions and Future Work

8.1 Conclusions

Since its inception in the 1970’s, MR imaging has become a versatile and powerful tool for clinical imaging and medical research that provides anatomical and functional information of the whole body. Despite all of its benefits, the long acquisition time and higher operational cost remain major limitations. Both of these issues need to be addressed if MR imaging is to become the standard care of acute ischemic stroke patients. Recent developments using multiple channel receiver coils and sparsity models to reconstruct MR images from undersampled data can partially alleviate these hurdles. The work presented in this thesis has focused on applying these modern acquisition and reconstruction techniques to accelerate MR neuroimaging using stroke as the underlying motivation.

In Chapter 2, I reviewed the pathophysiology of ischemic stroke and emphasized the time-sensitive nature of the condition, i.e., prompt recanalization is vital to minimize irreversible brain injuries. Next, I briefly introduced the current treatments of ischemic stroke patients, which often rely on minimally invasive endovascular techniques to deploy therapeutic devices or drugs. I concluded the chapter by describing the important role that imaging plays in the diagnosis and treatment of stroke patients. I presented a clinical case where rapid management, diagnosis, and treatment yielded the best possible outcome for the patient. This example highlighted the requirements that MR imaging must meet to compete with CT in acute ischemic stroke. Although MR scan times may not quite approach those of CT, MR imaging offers numerous types of image contrasts that can measure functional and physiological changes. For example, several groups have suggested that the mismatch between MR diffusion/perfusion imaging can
be used to detect the ischemic penumbra and thus identify stroke patients that are more likely to respond to acute therapy (219, 220). In the following chapters, I investigated techniques to accelerate MR sequences used for the prevention, diagnosis, and treatment of stroke.

Chapter 3 provided technical background on MR imaging and accelerated reconstructions. It started with a brief description of the classical MR physics and the image acquisition process, and introduced a general approach to accelerate MR imaging via undersampling of k-space. Undersampled acquisitions do not meet the Nyquist-Shannon sampling condition and require more complex reconstruction algorithms than the conventional reconstruction of fully sampled data via the Fourier transform. To recover the non-acquired samples, most reconstructions exploit either the redundancy in the data or a priori information about the image to reconstruct, i.e., model-based reconstruction. The redundancy can arise from using multiple receiver coils like in parallel imaging or from spatial and/or temporal correlation in the image. The basic concepts of the different accelerated reconstruction approaches investigated in this thesis were presented at the end of Chapter 3, and include CS, SENSE, GRAPPA, SPIRiT, L1-SPIRiT, sparse SENSE, and CS-SENSE.

In Chapter 4, I presented an accelerated passive MR catheter tracking approach that lays the foundation for endovascular treatment of stroke patients. This work is one of the first peer-reviewed publications applying CS to an MR application. Unlike with the current gold standard imaging approach of x-ray fluoroscopy, catheters are not directly visible in MR imaging because they are made of polymers and do not emit any signal. To overcome this issue, we used a passive visualization approach where the catheter lumen was filled with contrast agent. We further
improved the catheter conspicuity by using a background suppression technique that generated sparse catheter images. To improve the temporal resolution of catheter tracking, we simulated accelerated acquisitions by retrospectively undersampling the fully sampled data and reconstructing the accelerated images using the CS paradigm. Enforcing sparsity in the image domain with CS yielded images with superior catheter conspicuity and spatial resolution when compared to the more conventional zero-filled reconstruction approach. Moreover, CS preserved spatial resolution even for vastly undersampled k-space data. This retrospective undersampled study validated the use of CS to accelerate passive MR catheter tracking.

In Chapter 5, I presented an initial attempt at applying CS to visualize small intracranial arteries with diameter ranging from 100 µm to 900 µm. Detecting such small vascular features with MR imaging is particularly challenging because of the critical trade-off between spatial resolution, acquisition time and signal-to-noise ratio (SNR). For that particular study, the acceleration available with CS was used to improve image resolution without increasing acquisition time or decreasing SNR. We prospectively acquired accelerated higher-resolution data with 10× undersampling factor yielding an in-plane resolution of 200 µm × 200 µm. For this study, we reconstructed each individual coil image with CS followed by a sum-of-squares combination of the coil images to obtain the final composite image. Although we successfully acquired and reconstructed high-resolution images, our approach did not reliably depict the small vessels. These inconclusive results led us to believe that our acquisition and reconstruction approach was sub-optimal both in terms of signal-to-noise ratio and artefact level. Improvements to multi-receive coils or using a reconstruction that combines parallel imaging and CS may significantly
improve the image quality and would, therefore, be the preferred approach if we were to repeat the experiment.

Recognizing this possible limitation of the CS reconstruction (illustrated in Chapter 5) lead us to investigate and compare several state-of-the-art acquisition and reconstruction techniques to accelerate key imaging sequences of the acute MR stroke protocol. Chapter 6 presents the results of this study. We evaluated and compared CS against standard parallel imaging reconstruction techniques (\textit{i.e.}, SENSE, GRAPPA, and SPIRiT) and advanced reconstructions that combine CS with parallel imaging (\textit{i.e.}, CS-SENSE and L1-SPIRiT). We first determined the optimum combination of sampling strategy for each investigated reconstruction technique and then compared the optimum combinations quantitatively and qualitatively. We demonstrated that reconstructions combining parallel imaging with compressed sensing generally outperform reconstruction methods that use a single approach to achieve acceleration.

In Chapter 7, we capitalized on and extended the results of the retrospective accelerated study presented in Chapter 6 and investigated prospective acceleration of time-of-flight (TOF) angiography using a combination of parallel imaging and CS. We acquired the data in a highly time-constrained environment, allowing only 30 s per slab, such that an increase in acceleration allowed increased image resolution. We demonstrated that the accelerated images provide more details of cerebral vasculature compared to the fully sampled approach collected over the same time interval. We also demonstrated that the sparse SENSE reconstruction enables greater acceleration rates than vendor-supplied parallel imaging reconstructions. Accelerating TOF imaging is central to improving the stroke protocol. The high quality diagnostic images obtained
with our accelerated paradigm represent a significant contribution toward a rapid and comprehensive acute stroke exam.

In summary, the unifying theme of my research was to accelerate and improve MR imaging in order to reduce the limitations that prevent MR from becoming the clinical modality of choice in the standard of care of acute stroke patients. In the course of this dissertation, I investigated several modern signal acquisition and processing techniques to advance the use of MR imaging in diagnosing, treating, and hopefully preventing stroke. In terms of diagnosis, I compared several state-of-the-art paradigms to accelerate key sequences of an acute stroke protocol. For treatments, I present a passive MR catheter tracking approach that enables continuous monitoring of the catheter during endovascular interventions. And finally, with regards to stroke prevention, I presented some preliminary evidence in support of a novel imaging technique for assessing atherosclerosis in carotid arteries (see section 8.2.1 in Future Work). Using this research can eventually produce faster diagnosis of stroke and potentially have significant implication in stroke treatment and prevention. Continued efforts can be seen as moving us closer to making MR imaging the modality of choice in the comprehensive management of acute stroke patients.

8.2 Future Work

This section starts by describing an ongoing collaborative research project with a graduate student colleague, which investigates the pulsatile motion of carotid arteries with the cardiac cycle (Section 8.2.1). Thereafter, I provide more general future directions and perspectives for the work presented in this thesis (Section 8.2.2).
8.2.1 Dynamic Carotid Imaging

Identifying patients with unstable atherosclerosis lesion plays an important role in stroke prevention. This initial study investigates a time-resolved imaging technique that allows vessel wall characterization over the course of the cardiac cycle. As with all stroke imaging, rapid acquisition is crucial. I developed and implemented a reconstruction that efficiently exploits temporal correlation to reduce the number of acquired data per frame. In the following paragraphs, I describe the current status of this preliminary research, present initial results, and provide future directions for the project.

8.2.1.1 Introduction

The innermost layer of an artery wall, *i.e.*, the endothelium, plays a key role in regulating vascular homeostasis. It regulates vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation (221). Carotid atherosclerosis is characterized by endothelial dysfunction, such as reduced vasoreactivity, which precedes the development of anatomical changes of the vessel wall (66, 72, 221-223). Early morphological changes include positive arterial remodelling characterized by outward thickening of the vessel wall with relative preservation of the lumen and later luminal narrowing, *i.e.*, stenosis (224). Because early arterial remodelling does not affect the vessel lumen, conventional bright blood angiography techniques that image the flowing blood within the vessel wall, such as X-ray or time-of-flight (TOF) magnetic resonance angiography, may underestimate the degree of atherosclerosis disease.
Although stenosis is important for stroke prevention (114), knowing the structure, composition, dynamics, thickness, and stiffness of atherosclerotic lesions are better indicators of plaque vulnerability (225, 226). Increased vessel wall thickness of the common carotid artery represents atherosclerotic wall changes and is a strong predictor for future cardiovascular events (227). Carotid stiffness can be measured with the distensibility coefficient given by the maximum diameter change over the cardiac cycle divided by blood pressure (228, 229). The combination of vessel wall thickness with distensibility coefficient measurements allows for a comprehensive analysis of the atherosclerosis lesion and improved prediction of plaque vulnerability (230).

High-resolution black blood MR imaging techniques, such as fast spin echo (FSE), provide excellent soft tissue contrast within the vessel wall and can distinguish intact, thick, fibrous caps (i.e., stable plaques) from thin, ruptured caps (i.e., vulnerable plaques) (231). The FSE images can then be used to assess both vessel wall thickness and luminal area, thus enabling the non-invasive detection of subclinical atherosclerosis disease. Currently, full morphological, functional and dynamic assessment of the carotid arteries requires both 2D black blood $T_2$ weighted and 3D $T_1$ CINE imaging (232). The prospectively gated black blood images are used for morphological assessment of the vessel wall, whereas the $T_1$ CINE images are used to assess the dynamics of the vessel wall.

The motion of the vessel wall caused by the change in pressure between systole and diastole can be challenging with MR imaging. To efficiently capture motion, the acquisition is usually prospectively gated to acquire data only at specific time in the cardiac cycle, which is generally during diastole when the motion is minimum (223). Investigating vessel wall motion over the
cardiac cycle using a FSE sequence requires multiple gated acquisitions, each acquired at
different phases in the cycle. Unfortunately, time-resolved FSE acquisitions are often
prohibitively lengthy.

In this preliminary study, we investigated and applied spatiotemporal sparse SENSE (216) to
reconstruct dynamic retrospectively gated FSE data. This novel approach alleviates the need for
acquiring 3D $T_1$ CINE images by providing a dynamic black blood imaging approach. The
reconstruction preserves geometric and temporal fidelity and allows vessel wall characterization
over the course of the cardiac cycle within acceptable clinical acquisition times. This technique
lays the foundation to dynamically study endothelial function, vessel wall thickness, and plaque
composition simultaneously.

8.2.1.2 Methods
We acquired 2D axial FSE images at the carotid bifurcation (Figure 8.1) in six healthy volunteers
using a 3 T MR scanner (Discovery MR 750; General Electric Healthcare, Waukesha, WI) with a
12-channel receive-only head/neck coil. The imaging parameters were: TR/TE of 2500/9.4 ms,
FOV of $14 \times 14$ cm$^2$, acquisition matrix of $256 \times 252$, and slice thickness of 2 mm. We modified
the phase-encode table such that every k$_y$-line was acquired at least once, but those near the
centre of k-space were acquired more frequently, for a total of 1008 phase-encodes. We also
recorded the R-wave of the cardiac cycle with a pulse oximeter and used this to retrospectively
“rebin” the FSE data into 12 uniformly spaced cardiac phases (233). Figure 8.2 illustrates the
retrospectively gated process using the measured R-wave signal. Due to the irregularity of the
cardiac cycle and its incoherence with the acquisition timing, the rebinned data form 3D stacks
(2D spatial + 1D temporal) of undersampled k-space data. The undersampled data was then reconstructed using a sparse SENSE model that combined both spatial and temporal constraints:

$$\arg\min_m \|Em - s\|^2 + \lambda_1 \|\Psi m\|_1 + \lambda_2 \|\bar{m} - m\|_1 + \lambda_3 \|Tm\|_1,$$  \[8.1\]

where $E$ is the sensitivity encoding matrix, $m$ is the stack of 2D time-resolved images to reconstruct, $s$ is the acquired k-space data, $\Psi$ is the 3D spatial wavelet transform, $\bar{m}$ is the temporally-averaged fully-sampled image using all k-lines via averaging, and $T$ is a temporal

Figure 8.1: MR angiogram of a human neck (a) where the dotted line shows the approximate location of the acquired cross-section images at the carotid bifurcation (b).
high-pass filter operator. Starting from the left-most term in Eq. [8.1], the reconstruction includes a data consistency term, a spatial constraint, and two temporal constraints. The data consistency term ensures that the reconstructed images are consistent with the acquired data, the spatial constraint promotes a solution with a sparse representation in the wavelet domain, the first temporal constraint promotes similarity with the fully-sampled temporally-blurred reference image \( \mathbf{m} \), and the second temporal constraint promotes a smooth time course variation. Coil sensitivity maps were computed using the eigenvector decomposition method (159). The regularization parameters, \( \lambda_n \), were selected empirically by visual inspection of the reconstructed images to 1) maintain high data consistency and 2) avoid geometric artefacts and temporal blurring. The vessel wall location was determined at each cardiac phase by finding the maximum intensity gradient. The effective carotid wall motion was then calculated as the difference between the maximum and minimum vessel diameter \( (d_{\text{max}} - d_{\text{min}}) \). In addition, we also manually traced the inner vessel wall boundary of the right common carotid artery for each cardiac phase and reported the measured surface areas. We repeated the tracing five times at different days and measured intra-observer reliability by calculating the correlation between the five independent measurements.
Figure 8.2: Schematic illustration of the binning process of our retrospectively gated FSE approach. The R-wave of the cardiac cycle (a) was recorded along with the k-space data (b). The data was then retrospectively gated into 12 uniformly spaced cardiac phases, forming 3D stacks of undersampled data (c).
8.2.1.3 Preliminary Results

Figure 8.3a shows the location of one cross section of the right internal carotid artery investigated in one of the volunteers. The temporally averaged image, $\bar{m}$, is a static image and its cross section is shown for reference in Figure 8.3b. Figure 8.3c and Figure 8.3d compare the time course of the carotid vessel wall over a cardiac cycle using the zero-filled (ZF) and spatiotemporal sparse SENSE reconstruction approaches, respectively. The incoherent aliasing artefacts in the ZF reconstruction prevented us from accurately determining/locating the vessel wall. In contradistinction, spatiotemporal sparse SENSE reconstruction yielded readily interpretable and quantifiable vessel wall motion; we measured a change of approximately 0.5 mm between $d_{\text{min}}$ and $d_{\text{max}}$ with regularization parameters $\lambda_1 = 0.002$, $\lambda_2 = 0.05$, and $\lambda_3 = 0.05$.

Figure 8.3: Example of a cross section of the right internal carotid artery investigated in one volunteer (a), the temporally averaged image, $\bar{m}$, repeated over 12 cardiac phases (b), and the ZF (c) and spatiotemporal sparse SENSE (d) reconstructions of the time-resolved FSE images over the course of the cardiac cycle. The maximum and minimum vessel diameters ($d_{\text{max}}, d_{\text{min}}$) are shown on the sparse SENSE image.
Figure 8.4 shows one of the five tracings of a cross-sectional area of the common carotid artery with respect to the cardiac cycle. The measurements from all the tracings are summarized in Figure 8.5 and show good reproducibility. The mean correlation coefficient between the repeated

Figure 8.4: Tracings and measurements of the surface area of the right common carotid artery for each cardiac phase.
measurements was 0.921± 0.032, which indicates a good intra-observer reliability. Using the median values of surface area for each cardiac phase, we measured a maximum change in area of 9.7 mm², which correspond to a change in diameter of about 0.98 mm. These measurements are in good agreement with the values reported in other studies (234, 235).

Figure 8.5: Illustration of the intra-observer variability for the five repeated measurements of the surface area of the right common carotid artery for each cardiac phase. The boxplot presents the minimum, lower quartile, median, upper quartile and maximum area for each cardiac phase. The gray solid lines show the time course of the surface area for each set of measurement.
8.2.1.4 Discussion

In this preliminary study, we demonstrated that retrospectively gated FSE combined with spatiotemporal sparse SENSE reconstruction enables temporally efficient, time-resolved characterization of the motion of the carotid vessel wall over a cardiac cycle. Our measurements of the change in diameter and surface area of the common and internal carotid arteries over the cardiac cycle are in good agreement with previously reported values from studies using ultrasound (235, 236) and MR imaging (234). To measure small changes more precisely and reliably, however, an increase in spatial resolution or signal-to-noise ratio, or both, is necessary. Although this could potentially increase scan time, dedicated multi-channel carotid coils coupled with spatiotemporal sparse SENSE reconstruction could mitigate this drawback.

Detecting subtle changes in diameter can be difficult and inaccurate, since the imaging resolution is of the same order of magnitude as the expected variation of the diameter. Measuring changes in surface area of the carotid artery, however, averages over multiple pixels and is therefore more robust and accurate.

Selection of the optimum regularization parameters was difficult because of the trade-off between geometric fidelity and temporal resolution. Large values of the temporal parameters, $\lambda_2$ and $\lambda_3$, yielded significant temporal blurring and hindered the characterization of vessel wall dynamics. As a direct consequence of temporal blurring, the reconstruction tends to introduce a bias that underestimates the actual motion of the vessel wall. Further investigation and validation is warranted to determine the optimum combination of weights and the significance of the introduced bias.
Current examinations of the carotid arteries require prospectively gated FSE black blood imaging to assess vessel wall morphology and $T_1$ CINE imaging for vessel wall dynamics. Our proposed retrospectively-gated FSE black blood imaging approach enables simultaneous assessment of morphological and dynamic properties of the carotid arteries with a single acquisition. Such an imaging tool has the potential to precisely assess the vessel wall for longitudinal studies, e.g., testing the influence of lipid lowering therapy (237), and predict vulnerable carotid plaques in patients with severe stenosis.

**8.2.2 Future Directions and Perspectives**

8.2.2.1 Eliminating Explicit Regularization Parameters

The CS framework exploits transform sparsity as prior information to find solutions to the constrained optimization problem defined in Eq. [3.31]. The constrained problem is usually reformulated into an unconstrained problem using Lagrange’s theorem (Eq. [3.32]) and then solved by minimizing the cost function with a gradient descent algorithm. The Lagrange formulation introduces a regularization parameter, $\lambda$, which balances data consistency and sparsity. In this thesis, the selection of the regularization parameters was determined by exhaustive manual search to find the right balance between data consistency and sparsity. From experience, the weights that tend to work well for a given sampling strategy, object and acquisition parameters will generally provide similar results when used with other similar settings. However, when the acquisition protocol, sampling and/or object experience large changes, the regularization parameter can differ significantly. When using multiple regularization parameters, such as in Eq. [8.1], manual exhaustive searches over $\lambda$’s quickly become overwhelming, laborious, and subjective. I also expect the optimization process to
converge more slowly with multiple constraints. For all these reasons, it is therefore desirable to eliminate the regularization parameters or, at least, minimize the number of parameters. A parameter-free CS reconstruction would alleviate the tuning of the algorithm, improve its overall objectivity, and facilitate its use in clinical applications.

A recent study by Khare et al. (238) proposed a solution to solve the CS constrained optimization problem by using an iterative soft thresholding framework. This parameter-free approach is derived from a wavelet-based adaptive denoising method and the authors state that this method provides a leaner implementation compared with the nonlinear conjugate gradient method. One project proposal is to further explore and evaluate this parameter-free approach to potentially improve CS reconstruction objectivity and flexibility.

Another proposal is to reduce the number of regularization parameters by combining multiple constraints into one. In the case of the dynamic carotid-imaging project, the model-based reconstruction includes three $\ell_1$-constraints (Eq. [8.1]), i.e., one spatial and two temporal constraints. We seek to define a single sparsifying transform that would simultaneously compress the dynamic data spatially and temporally, like in video compression applications. An obvious solution for this is to use a 4D (3D spatial and 1D temporal) wavelet or discrete cosine transforms, $\Psi_{4D}$,

$$\arg\min_{\mathbf{m}} \| \mathbf{E} \mathbf{m} - \mathbf{s} \|_2^2 + \lambda \| \Psi_{4D} \mathbf{m} \|_1. \quad [8.2]$$

This approach equally weights spatial and temporal sparsity. However, temporal correlation between time frames (i.e., cardiac phases) is usually much higher than spatial correlation and,
therefore, requires different weightings. In addition, the dynamic carotid images only have about 12-16 time points depending on the rebinning process. Applying the wavelet transform along that dimension does not efficiently compress the data. A temporal high pass filter, such as the finite difference, is more efficient at sparsifying the data along the time dimension.

To address the above issues, one could construct/design a sparsifying transform that implicitly weights the spatial and temporal sparsity differently. Noting for example in the data of §8.2.1 that the pulsatile motion of the carotid artery over a cardiac cycle roughly approximates a sinusoidal, it is expected that applying the Fourier transform along the temporal dimension will result in a hybrid spatial-frequency space (x-f space) with a relatively compact format. The x-f space could be further compressed by applying a spatial wavelet transform to yield a ψ-f space.

The compression of information is illustrated in Figure 8.6 for a time series of carotid images. The proposed model to reconstruct these dynamic images is given by

$$\arg \min_{m} \|Em - s\|_2^2 + \lambda \|\Psi_s F_t m\|_1 .$$

[8.3]

where $F_t$ indicates the Fourier operator applied along the temporal dimension and $\Psi_s$ is the spatial wavelet operator.
8.2.2.2 Improving the Imaging of Small Intracranial Arteries

Our acquisition and reconstruction strategy used for the small vessel imaging project presented in Chapter 5 failed to reliably depict the lenticulostriate arteries. Part of the problem results from using a non-optimal reconstruction, i.e., we did not take advantage of the parallel imaging capabilities available when using an 8-channel head coil. As mentioned previously, using a combination of parallel imaging and CS can significantly improve the image quality.

8.2.2.3 Dynamic Carotid Imaging Using Non-Cartesian Acquisition

For the dynamic carotid imaging project, we used a Cartesian sampling approach and modified the phase-encode table to acquire the central k-line more frequently since that is where most of the energy is located. This modification significantly improved the image quality obtained with our constrained reconstruction. Using non-Cartesian sampling schemes, such as radial or multi-leaf spiral, have the main advantage that each trajectory goes through the origin of k-space; this approach inherently oversamples the centre of k-space. Moreover, non-Cartesian sampling can
potentially offer further advantages. Acquisitions using radial trajectories are less susceptible to motion artefacts; however, they require \((\pi/2 \text{ times})\) more radial trajectories than Cartesian trajectories to satisfy the Nyquist sampling condition up to the edge of k-space. But artefacts caused by allowing radial undersampling at the periphery of k-space appear less severe than Cartesian undersampling, and therefore fewer trajectories can be acquired while preserving high image quality. Spiral trajectories allow a smaller number of trajectories to fulfill the Nyquist condition, but at the expense of a longer acquisition time per trajectory.

Prospectively gated FSE acquisitions using spiral trajectories have successfully been applied to assess coronary endothelial function (223). Using radial or spiral trajectories to acquire our retrospectively gated FSE data could, therefore, further improve the quality of our dynamic carotid images.

Reconstruction of non-Cartesian data usually involves first resampling the data onto a Cartesian grid and then using a Fourier transform for the reconstruction. The non-uniform fast Fourier transform (NUFFT) (239) algorithm provides an efficient implementation for non-Cartesian reconstruction. This algorithm could be incorporated in our sparse SENSE model to allow reconstruction from spiral data and improve image quality by increasing the sampling density near the origin of k-space.

8.2.2.4 Prospective Acceleration of Stroke Protocol and Diagnostic Comparisons

In Chapter 6, we presented a comparison of different modern acquisition and reconstruction techniques to accelerate the acute MR stroke protocol. In this study, we evaluated the reconstructed images both quantitatively and qualitatively. Only healthy volunteers participated
in the study, therefore the images were free of pathological signs. The qualitative assessment relied solely on image appearance, such as noise, resolution, and image artefact. Such a comprehensive retrospective study is not feasible with stroke patients because of the time sensitive nature of the condition. However, further investigations to assess and compare the diagnostic content of the accelerated images are necessary since the reconstructions can introduce artefacts that hinder the detection of pathologies. Using the optimum combinations determined from our volunteer study, accelerated data could be acquired prospectively and compared for diagnostic contents. Such a comparison is necessary prior to widespread acceptance and use of accelerated reconstructions in the clinical setting. We are currently in the process of recruiting patients for the prospectively accelerated TOF study presented in Chapter 7.

8.2.2.5 Online Reconstruction

Constrained reconstruction, such as sparse SENSE, involves time consuming iterative algorithms. All reconstructions investigated in this thesis were performed offline and images were used for research purposes only. Bringing this technology into clinical settings requires implementing online reconstruction by porting MATLAB code into C/C++ and redesigning the algorithms for efficient parallelization. Moreover, offloading parts of the processing to the already available reconstruction hardware or a graphics processing unit (190) could significantly reduce the reconstruction time.

8.3 Summary

This dissertation investigated several modern signal acquisition and processing techniques to advance the use of MR imaging in diagnosing, treating, and hopefully preventing stroke. Using
the work presented in this research yields faster diagnosis of stroke, while preserving high
diagnostic quality, and can eventually have significant implication in stroke diagnosis, treatment,
and prevention.
APPENDIX A: OPTIMIZATION METHODS

In this appendix, I present some background on the different optimization problems encountered in this thesis and common techniques for solving them. When optimization problems have no closed-form solutions or if closed-form solutions exist, but are computationally impractical, we often turn to iterative methods to find a solution. For an in-depth description of optimization methods, the textbook by Chong (152) proves to be very informative. Most of the material presented here is derived from this source.

Herein I consider the optimization problem:

\[
\begin{align*}
\text{minimize} & \quad f(x) \\
\text{subject to} & \quad x \in \Omega.
\end{align*}
\]  

[A.1]

The function \( f: \mathbb{R}^n \to \mathbb{R} \) is the objective or cost function that we wish to minimize, the vector \( x \in \mathbb{R}^n \) is an \( n \)-vector of independent variables, and the set \( \Omega \) is a subset of \( \mathbb{R}^n \) called the constraint or feasible set. Solving the above optimization problem consists of finding the “best” or optimum vector \( x \) over all possible vectors in \( \Omega \). The optimum vector is the one that minimizes the objective function.

A.1. Optimality Conditions for Functions of Several Variables

In this section, I present the optimality conditions for a point \( x^* \) to be a local minimizer of an unconstrained problem. For problems with inequality constraints, please refer to the Karush-Kuhn-Tucker (KKT) condition (152).
A point $\mathbf{x}^*$ is a strong local minimizer of $f$ if it satisfies the first-order necessary condition and second-order sufficient condition. The first-order necessary condition requires the gradient of the function at $\mathbf{x}^*$ to be zero

$$\nabla f(\mathbf{x}^*) = \frac{\partial f(\mathbf{x}^*)}{\partial x_i} = 0; \quad i = 1 \text{ to } n. \tag{A.2}$$

Any point satisfying this condition is called a stationary point and can be a local minimum, local maximum, or an inflexion point. To find local minimum or maximum stationary points, it is necessary to evaluate the Hessian matrix

$$H(\mathbf{x}^*) = \begin{bmatrix} \frac{\partial^2 f(\mathbf{x}^*)}{\partial x_i \partial x_j} \end{bmatrix}_{n \times n} = 0; \quad i, j = 1 \text{ to } n. \tag{A.3}$$

The second-order sufficient condition states that if the Hessian matrix is positive definite at the stationary point $\mathbf{x}^*$, i.e., $\mathbf{d}^T H(\mathbf{x}^*) \mathbf{d} > 0$ for all $\mathbf{d} \neq \mathbf{0}$, then $\mathbf{x}^*$ is a local minimizer for the function $f(\mathbf{x})$.

**A.2. Convex Functions**

In an optimization problem, convex objectives possess nice theoretical properties and can be efficiently solved numerically to find minima or maxima. A function $f: \mathbb{R}^n \rightarrow \mathbb{R}$ is called convex if and only if for all $\mathbf{x}, \mathbf{y} \in \mathbb{R}^n$ and all $\alpha \in [0,1]$, we have $f(\alpha \mathbf{x} + (1 - \alpha) \mathbf{y}) \leq \alpha f(\mathbf{x}) + (1 - \alpha) f(\mathbf{y})$. In words, it means that, for convex functions, the line segment connecting any two points on the graph of $f$ lies above the graph.
The unconstrained objective function in compressed sensing (Eq. [3.32]) uses a weighted sum of a $\ell_2$-norm for data consistency and a $\ell_1$-norm for data sparsity. It can be shown that such an objective is convex. First, I demonstrate that every norm is a convex function using the above definition of convexity, the triangle inequality property of normed vector spaces, \( i.e., \|x + y\| \leq \|x\| + \|y\| \), and the function homogeneity property, \( i.e., f(\alpha x) = \alpha f(x) \).

\[
\|\alpha x + (1 - \alpha)y\| \leq \|\alpha x\| + \|(1 - \alpha)y\| = \alpha \|x\| + (1 - \alpha)\|y\|. \tag{A.4}
\]

If $f = \|\cdot\|_2$ and $g = \|\cdot\|_1$ are convex functions, then their linear combination $f + \lambda g$ with nonnegative coefficients is also convex. Finally, I show that affine substitutions of the argument preserve function convexity. The superposition $\phi(x) = f(Ax + b)$ of a convex function $f$ on $\mathbb{R}^n$ and affine mapping $x \mapsto Ax + b$ from $\mathbb{R}^m$ to $\mathbb{R}^n$ is convex.

\[
\phi(\alpha x + (1 - \alpha)y) = f(A(\alpha x + (1 - \alpha)y) + b) = f(\alpha(Ax + b) + (1 - \alpha)(Ay + b)) \leq \alpha f(Ax + b) + (1 - \alpha)f(Ay + b) = \alpha \phi(x) + (1 - \alpha)\phi(y). \tag{A.5}
\]

Finding the minimum point of such convex functions can be solved efficiently using various gradient descent algorithms.

**A.3. Solving Linear Equations**

Systems of linear equations can be expressed in matrix form
\[ Ax = b, \quad [A.6] \]

where \( A \in \mathbb{R}^{m \times n} \), \( x \in \mathbb{R}^n \), \( b \in \mathbb{R}^m \), and \( \text{rank } A \leq \min \{ m, n \} \). The relationship between the number of equations, \( m \), the number of unknowns, \( n \), and the rank of the matrix \( A \) determines the behaviour of the linear system. When the system has the same number of equations and unknowns, \( m = n \), and \( \text{rank } A = n \), the system has a unique solution \( x^* = A^{-1} b \), where \( A^{-1} \) is the inverse of \( A \). When \( A \) does not have an inverse (e.g., when \( A \) is not a square matrix), we need to use the pseudoinverse denoted \( A^\dagger \), which plays the role of \( A^{-1} \). For the case of overdetermined systems, \( i.e., A \in \mathbb{R}^{m \times n} \) with \( m \geq n \) and \( \text{rank } A = n \), the pseudoinverse of \( A \) is \( A^\dagger = (A^T A)^{-1} A^T \), and the least squares solution is given by \( x^* = (A^T A)^{-1} A^T b \). For the case of underdetermined systems, \( i.e., A \in \mathbb{R}^{m \times n} \) with \( m \leq n \) and \( \text{rank } A = m \), the pseudoinverse is \( A^\dagger = A^T (A A^T)^{-1} \) and the minimum norm solution is given by \( x^* = A^T (A A^T)^{-1} b \). The least squares solution minimizes the sum of squared differences between the data values \( x \) and their corresponding modeled values \( b \),

\[
 x^* = \min_x \|Ax - b\|^2, \quad [A.7]
\]

whereas the minimum norm solution minimizes the Euclidean norm among all possible solutions

\[
 \minimize \quad \|x\|_2, \quad [A.8]
\]

subject to \( \|Ax - b\|^2 \).
Related to least squares and minimum norm solutions, Tikhonov regularization can be used to solve linear systems. In order to give preference to a particular solution with desirable properties, a regularization term is included in the minimization

\[ \mathbf{x}^* = \min_{\mathbf{x}} \| \mathbf{A} \mathbf{x} - \mathbf{b} \|_2^2 + \| \beta \mathbf{x} \|_2^2, \]  

where \( \beta \) controls the amount of regularization and improves the conditioning of the problem. An explicit solution is given by \( \mathbf{x}^* = (\mathbf{A}^T \mathbf{A} + \beta^2 \mathbf{I})^{-1} \mathbf{A}^T \mathbf{b} \). Note that for \( \beta > 0 \), the matrix \( \mathbf{A}^T \mathbf{A} + \beta^2 \mathbf{I} \) is positive definite regardless of the shape or rank of \( \mathbf{A} \).

Calculating the solution to the least squares problem or minimum norm problem is straightforward. However, when \( \mathbf{A} \) is very large, it is not feasible to compute exact solutions. A wide variety of iterative methods have been developed to approximate solutions to the problems in these situations. Examples of iterative methods include gradient descent, conjugate gradient, and more sophisticated algorithms like LSQR and LSMR. These algorithms provide numerical solution for particular systems of linear equations, namely those whose matrix is symmetric and positive-definite.

**A.4. Descent Methods**

The family of descent methods can be used to solve a linear system of equations by reformulating the system as a quadratic minimization problem \( f(\mathbf{x}) = \| \mathbf{A} \mathbf{x} - \mathbf{b} \|_2^2 \). The goal is to find the vector \( \mathbf{x} \in \mathbb{R}^n \) that minimizes the objective function \( f \),

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\[ \mathbf{x}^* = \minimize_{\mathbf{x}} \| \mathbf{Ax} - \mathbf{b} \|^2_2. \]  

Each iteration of a descent method consists of choosing a suitable descent direction, calculating the optimum step size along that direction to minimize the objective function, and updating the next optimal point \( \mathbf{x} \). In the following sections, I briefly describe the steepest descent and conjugate gradients algorithms, which mainly differ in the choice of descent direction.

### A.4.1. Steepest Descent Algorithm

The steepest descent algorithm, also called gradient descent, uses the current guess of \( \mathbf{x}^{(k)} \) to compute the gradient of the objective function, \( \nabla f(\mathbf{x}^{(k)}) = 2\mathbf{A}^T (\mathbf{Ax}^{(k)} - \mathbf{b}) \), and searches along the negative direction of the gradient to find a new \( \mathbf{x}^{(k+1)} \) that minimizes \( f \). The negative gradient is the direction of steepest descent of the objective function \( f \) at point \( \mathbf{x} \). The line search procedure chooses the step size \( \alpha_k \) to minimize

\[ \alpha_k = \minimize_{\alpha \geq 0} f \left( \mathbf{x}^{(k)} - \alpha \nabla f(\mathbf{x}^{(k)}) \right). \]

In the context of least squares, the line search can be solved analytically, which yields

\[ \alpha_k = \left( \nabla f(\mathbf{x}^{(k)})^T \mathbf{A} \nabla f(\mathbf{x}^{(k)}) \right)^{-1} \left( \nabla f(\mathbf{x}^{(k)})^T \nabla f(\mathbf{x}^{(k)}) \right). \]

The new choice of \( \mathbf{x} \) is \( \mathbf{x}^{(k+1)} = \mathbf{x}^{(k)} - \alpha_k \nabla f(\mathbf{x}^{(k)}) \). These operations are repeated until the algorithm converges to the minimizer.

Unfortunately, the steepest descent method may take many iterations to compute a local minimum for poorly conditioned convex problems and results in exceedingly slow convergence. This is due to the “zigzagging” nature of the gradient vector, which is illustrated in Figure A.1.
The gradient points in the direction of the steepest descent and the minimum of the function may not lie in that direction. Furthermore, the current gradient is not related to the previous gradients, i.e., search directions, and the steepest descent can search along the same direction multiple times. The conjugate gradient provides an alternative that converges in far fewer steps.

**A.4.2. Conjugate Gradient Method**

The conjugate gradient method uses conjugate directions instead of the local gradient to minimize the objective function and reaches the minimum in far fewer steps than the method of steepest descent. In general, the conjugate direction method solves quadratics of $n$ variables in $n$ steps. The method iteratively solves the linear system $\mathbf{A}\mathbf{x} = \mathbf{b}$ for a square, symmetric matrix $\mathbf{A}$ with full rank. For non-square matrix $\mathbf{A}$, the normal equation $\mathbf{A}^T\mathbf{A}\mathbf{x} = \mathbf{A}^T\mathbf{b}$ satisfies these conditions for least-squares problems with $\mathbf{A}$ having full column rank.

Two search direction vectors $\mathbf{d}^{(i)}$ and $\mathbf{d}^{(j)}$ in $\mathbb{R}^n$ are conjugate with respect to this system if $\mathbf{d}^{(i)^T}\mathbf{A}\mathbf{d}^{(j)} = 0$ for all $i \neq j$. We consider a set of $n$ mutually conjugate directions $\{\mathbf{d}^{(1)}, \ldots, \mathbf{d}^{(n)}\}$ that form a basis of $\mathbb{R}^n$, so we can expand the solution $\mathbf{x}^*$ of $\mathbf{A}\mathbf{x} = \mathbf{b}$ in this basis, i.e., $\mathbf{x}^* = \sum_{i=1}^{n} \alpha_i \mathbf{d}^{(i)}$. Pre-multiplying both sides of the linear system by $\mathbf{d}^{(j)}$ yields $\mathbf{d}^{(j)^T}\mathbf{b} = \mathbf{d}^{(j)^T}\mathbf{A}\mathbf{x}^* = \sum_{i=1}^{n} \alpha_i \mathbf{d}^{(j)^T}\mathbf{A}\mathbf{d}^{(i)} = \alpha_j \mathbf{d}^{(j)^T}\mathbf{A}\mathbf{d}^{(j)}$, because $\mathbf{d}^{(i)}$ and $\mathbf{d}^{(j)}$ are mutually conjugate for all $i \neq j$.

Thus, the optimal value of $\alpha_j$ is

$$\alpha_j = \frac{\mathbf{d}^{(j)^T}\mathbf{b}}{\mathbf{d}^{(j)^T}\mathbf{A}\mathbf{d}^{(j)}}. \quad [A.12]$$
To find a suitable set of conjugate directions, we can use an orthonormalization technique such as the Gram-Schmidt process. The problem with the Gram-Schmidt process, however, is that the new search direction \( d^{(k)} \) is constructed from all the old search directions \( d^{(i)}; \ i = 0, \cdots, k - 1 \), which requires to save them in memory. Instead, the conjugate gradient uses the Fletcher–Reeves formula to iteratively compute mutually conjugate directions. The algorithm has the interesting property that the gradient is orthogonal to every previous search direction. The next conjugate direction \( d^{(k+1)} \), is given by

\[
d^{(k+1)} = -\nabla f(x^{(k+1)}) + \frac{\nabla f(x^{(k)})^T \nabla f(x^{(k+1)})}{\nabla f(x^{(k)})^T \nabla f(x^{(k)})} d^{(k)}.
\]  

\[ \text{[A.13]} \]

The conjugate gradient algorithm is summarized below.

1. Set \( k := 0 \); select initial point \( x^{(0)} \).
2. \( g^{(0)} = \nabla f(x^{(0)}) \). If \( g^{(0)} = \mathbf{0} \), stop; else, set \( d^{(0)} = -g^{(0)} \).
3. \( \alpha_k = -\frac{g^{(k)}^T d^{(k)}}{d^{(k)}^T A d^{(k)}} \)
4. \( x^{(k+1)} = x^{(k)} + \alpha_k d^{(k)} \).
5. \( g^{(k+1)} = \nabla f(x^{(k+1)}) \). If \( g^{(k+1)} = \mathbf{0} \), stop.
6. \( \beta_k = -\frac{g^{(k+1)^T} g^{(k+1)}}{g^{(k)^T} g^{(k)}} \).
7. \( d^{(k+1)} = -g^{(k+1)} + \beta_k d^{(k)} \).
8. Set \( k := k + 1 \); go to step 3.

Figure A.1 illustrates an example of slow convergence of the steepest descent method and fast convergence of CG. In this example, the gradient descent method has not converged after 20 iterations \( \|Ax^{(20)} - b\| = 0.0021 \), while the conjugate gradient method has converged in just two iterations.
Figure A.1: Comparison of convergence between the steepest descent (dashed line) and conjugate gradient (solid line) methods for $A = [2, 2; 2, 6]$, $b = [2; -8]$, and $x^{(0)} = [-2; -2]$.

A.4.3. Nonlinear Conjugate Gradient Method

The nonlinear conjugate gradient method generalizes the linear conjugate gradient method for nonlinear optimization problem. The two methods are very similar, but differ in the calculation of the step size along the search direction. The nonlinear method performs a line search along the search direction $d$ to find the local minimum of the nonlinear function $f(x)$. The following steps summarizes the algorithm:

1. Set $k := 0$; select initial point $x^{(0)}$.
2. $g^{(0)} = \nabla f(x^{(0)})$. If $g^{(0)} = 0$, stop; else, set $d^{(0)} = -g^{(0)}$.
3. $\alpha_k = \arg\min_{\alpha} f(x^{(k)} + \alpha d^{(k)})$. 

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4. $x^{(k+1)} = x^{(k)} + \alpha_k d^{(k)}$.
5. $g^{(k+1)} = \nabla f(x^{(k+1)})$. If $g^{(k+1)} = 0$, stop.
6. $\beta_k = -\frac{g^{(k+1)\top} g^{(k+1)}}{g^{(k)\top} g^{(k)}}$.
7. $d^{(k+1)} = -g^{(k+1)} + \beta_k d^{(k)}$.
8. Set $k := k + 1$; go to step 3.
APPENDIX B: TIME-OF-FLIGHT ANGIOGRAPHY

In this appendix, I present the MR imaging physics of time-of-flight (TOF) angiography. I describe the mathematics that governs TOF imaging, some sources of image artefact, and some of the techniques used to reduce the effect of these artefacts. For an in-depth description of TOF, the textbooks by Haacke (119) and Kim (240) prove to be very informative. Most of the material presented here is derived from these books.

B.1. Time-of-Flight Effect

TOF angiography is a widely used technique for producing images of the vasculature without the use of contrast agent. The technique uses a spoiled gradient echo (SPGRE) sequence with relatively short TR to suppress/saturate the stationary background tissue and relies on the inflow effect of unsaturated flowing blood to create bright angiographic images. The TR is adjusted to be short enough to minimize longitudinal relaxation, but long enough to ensure that a sufficient amount of fresh blood can flow into the imaging slab. The contrast between the saturated stationary tissue and the unsaturated moving blood flow creates a bright vascular image.

When the spins in the stationary tissue experience a large number of RF pulses, their longitudinal magnetization approaches a steady-state equilibrium value that is independent of their position in the slab. In contradistinction the flowing spins enter the slab with full longitudinal magnetization and may only experience a few RF pulses before exiting the slab. Depending on the blood flow velocity and the slab thickness, the moving spins may never reach the steady-state equilibrium value. A simplistic example of blood vessel perpendicular to the slab being imaged is illustrated
in Figure B.1. In this example, we assume uniform blood flow velocity, $v$, throughout the radius of the vessel. The number of RF pulses that a flowing spin experiences depends on the flow velocity, $v$, and the time between each RF pulse, $TR$. If the velocity of the blood is exactly at the critical speed $v_c := z/TR$ or greater, the displacement of the moving spins is equal or larger than the slab thickness, $z$, and all the blood within the selected slab is completely replaced with fresh blood that contains unsaturated spins. When the blood flows slower than the critical velocity,
\( v \leq v_c \), the moving spins experiences multiple RF pulses while traversing the slab and partial saturation of the blood occurs. Figure B.1 shows an example where the moving spins experience \( n = 4 \) RF pulses before exiting the slab.

**B.2. MR Physics of Time-of-Flight Imaging**

The TOF effect results in signal difference between the saturated stationary spins and the unsaturated or partially saturated flowing spins. Saturated spins have experienced many RF pulses and their longitudinal magnetization has reached the steady-state or equilibrium magnetization, \( M_{z \text{ss}} \). The steady-state magnetization is governed by the SPGR pulse sequence given by (119):

\[
M_{z \text{ss}} = \frac{M_0 \left(1 - e^{-TR/T_1}\right)}{1 - e^{-TR/T_1} \cos \alpha}, \tag{B.1}
\]

where \( \alpha \) is the flip or nutation angle, \( TR \) is the repetition time of the sequence, \( T_1 \) is the longitudinal relaxation time of the spin, and \( M_0 \) is the equilibrium longitudinal magnetization. In contradistinction, the partially saturated moving spins have only experience a few RF pulses and partial saturation occurs. The evolution of the longitudinal magnetization of the flowing spins depends on the number of RF pulses, \( n \), and the flip angle, \( i.e., \), (119)

\[
M_z(n^-, \alpha) = M_{z \text{ss}} + (M_0 - M_{z \text{ss}})(e^{-TR/T_1 \cos \alpha})^{n-1}, \tag{B.2}
\]

where \( M_z(n^-, \alpha) \) indicates the longitudinal magnetization just before the \( n \) –th pulse. The second term in Eq. [B.2] represents the signal difference between the stationary spins with steady-state magnetization, \( M_{z \text{ss}} \), and the moving spins with partially saturated magnetization, \( M_z \). As the
number of RF pulses, \( n \), increases, the contribution from the right term in Eq. [B.2] gets very small, and thus the signal difference decreases.

Finally, the transverse magnetization at echo time, \( TE \), after the \( n \)–th RF pulse is given by

\[
M_{xy}(n, \alpha) = M_z(n^-, \alpha) \sin \alpha e^{-TE/T_2^*}.
\]  

[B.3]

**B.3. Phase Dispersion and Flow Compensation**

In the previous example, we assumed uniform blood velocity throughout the radius of the blood vessel. However, the frictional forces or shear stress induced by the blood viscosity causes non-uniform velocity profile. The blood at the centre of the vessel generally flows faster than the blood closer to the vessel wall, resulting in a parabolic velocity profile. The spins within a voxel accumulate different phases causing intra-voxel phase dispersion, and thus smaller net magnetization. Pulsatile and turbulent flows can also increase phase dispersion due to multiple directions and accelerations of the blood. Using the Taylor series expansion of \( r(t) = r_0 + v_0 t + 1/2 a_0 t^2 + \cdots \), the time-dependent accumulated phase at position \( r \) is given by

\[
\phi(t) = \int \gamma G(t) r(t) dt
\]

\[
\phi(t) = r_0 \gamma \int G(t) dt + v_0 \gamma \int G(t) t dt + \frac{1}{2} a_0 \gamma \int G(t) t^2 dt + \cdots
\]  

[B.4]

\[
\phi(t) = r_0 \gamma m_0 + v_0 \gamma m_1 + \frac{1}{2} a_0 \gamma m_2 + \cdots,
\]
where $r_0$ is the initial position of the spin, $v_0$ is the initial velocity, $a_0$ is the initial acceleration, and $m_j$ is the $j$–th moment of the gradient. Equation [B.4] indicates that the accumulated phase by a moving spin is a function of its initial position, velocity, acceleration, and gradient strength. Therefore, two moving spins with different velocities accumulate different phases. If not corrected, this intra-voxel phase dispersion results in signal loss.

It is possible to correct for this velocity-induced phase dispersion by using a technique called first-order gradient moment nulling. Gradient moment nulling is accomplished by adding an extra lobe to the gradients used for the slice selection and readout. The amplitude of the lobe is adjusted to ensure that the phase at the echo is zero for both stationary and constant velocity moving spins (Figure B.2). This technique works independently of the velocity of the moving spins as long as the velocity remains constant. Correction of acceleration-dependent phase dispersion can be corrected in a similar way using second-order gradient moment nulling.

**B.4. Additional Sources of Artefact and Compensatory Mechanisms**

To further mitigate motion-induced phase dispersion, it is desirable to minimize the echo time, TE. The shortest possible echo time is usually achieved by using fractional echo readout and a short duration or asymmetric RF excitation pulse.

Ramped RF excitations are often used to compensate for partial saturation of the blood and maintain uniform blood signal across the imaging slab. Ramped RF excitations use spatially varying tip angle, where the angle is chosen relatively small at the slab entrance and increases progressively with distance into the slab.
TOF angiography often uses spatial or slice-selective saturation pulses to eliminate the signal from one flow direction. Since the flow in arteries and veins generally moves in opposite
directions, a spatial saturation RF pulse can be applied superior to the imaging slab to eliminate the signal from the flow entering the slab from the opposite side.

Fat has a short $T_1$ relaxation time and appears hyperintense in the source TOF images. Since TOF angiogram images are obtained by taking the maximum intensity projection (MIP) across the volume, the bright fat can hinder the visualization of the vessels. Therefore, TOF generally uses spectrally-selective RF pulse to suppress the fat signal.

Finally, magnetization transfer preparation pulses can be used to further suppress the signal intensity from background tissue. These spectrally-selective RF pulses use off-resonance excitation to excite large macromolecules that have a broad NMR resonance band. These macromolecules then exchange their magnetization with nearby free water molecules and the net magnetization in the tissue is reduced. Because blood has lower concentration of macromolecules than tissue, the MT pulses minimally affect the water molecules in the blood and the blood magnetization remains unchanged.
APPENDIX C: ANIMAL AND HUMAN ETHICS APPROVALS

Figure C.1: All animal experiments were conducted under ethics approval of the Health Sciences Animal Care Committee, University of Calgary.
Figure C.2: Ethics approval to collect and store MR images with a view to future research from the Conjoint Health Research Ethics Board, University of Calgary.
References


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