

UC San Diego

UC San Diego Electronic Theses and Dissertations

Title

Enhanced Detection Sensitivity of Fluorine-19 Cellular MRI through Systematic Acquisition-Reconstruction Co-Design

Permalink

<https://escholarship.org/uc/item/92v541t5>

Author

Chen, Jiawen

Publication Date

2024

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA SAN DIEGO

Enhanced Detection Sensitivity of Fluorine-19 Cellular MRI through Systematic
Acquisition-Reconstruction Co-Design

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Electrical Engineering (Signal and Image Processing)

by

Jiawen Chen

Committee in charge:

Professor Piya Pal, Chair
Professor Eric T. Ahrens, Co-Chair
Professor Thomas T. Liu
Professor Truong Q. Nguyen
Professor Bhaskar D. Rao

2024

Copyright

Jiawen Chen, 2024

All rights reserved.

The Dissertation of Jiawen Chen is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego

2024

DEDICATION

To my family and friends who have been supportive throughout this journey.

TABLE OF CONTENTS

Dissertation Approval Page	iii
Dedication	iv
Table of Contents	v
List of Figures	vii
List of Tables	ix
Acknowledgements	x
Vita	xii
Abstract of the Dissertation	xiii
Chapter 1 Introduction	1
1.1 Background and Motivation	1
1.2 Outline and Contributions	5
Chapter 2 Towards Sensitive Cellular MRI-A Systematic Measurement-Algorithm Co-Design Approach	7
2.1 Limits of Detection	8
2.2 Pulse Sequence Considerations	10
2.3 Co-design of ^{19}F Pulse Sequence and Reconstruction	15
2.4 Theoretical Modeling of Acquisition-Reconstruction Pipeline	20
2.5 Conclusions	24
2.6 Acknowledgements	24
Chapter 3 Enhanced Detection of Paramagnetic Fluorine-19 MRI via Compressed Sensing Zero Echo Time (CS-ZTE)	25
3.1 Introduction	26
3.2 Methods	27
3.2.1 CS-ZTE k-space and pulse sequence design	27
3.2.2 Reconstruction pipeline	28
3.2.3 Noise simulation studies using synthetic ^{19}F data	31
3.2.4 Simulation of regularization parameters	32
3.2.5 Experimental phantom studies	33
3.2.6 <i>In vivo</i> animal studies	34
3.2.7 CS-ZTE sampling and reconstruction quality quantification	35
3.3 Results	37
3.3.1 CS-ZTE simulation study	37
3.3.2 Simulated PSF analysis	40

3.3.3	Performance in phantom studies	41
3.3.4	Spin quantification accuracy	45
3.3.5	Sensitivity to image sparsity	45
3.3.6	Reconstruction error analysis	46
3.3.7	<i>In vivo</i> CS-ZTE scans in mice	50
3.4	Discussion	51
3.5	Acknowledgements	57
3.6	Appendices	57
3.6.1	Appendix A: CS-ZTE measurement model	57
3.6.2	Appendix B: Error bound derivation	59
Chapter 4	Physics-Informed Deconvolution of Multi-Spectral Fluorine-19 MRI Using Radial Sampling	62
4.1	Introduction	63
4.2	Prior Work	65
4.2.1	Chemical shift multi-spectral signal model	65
4.2.2	Cartesian spectral deconvolution	66
4.3	Learned deconvolution of radial multi-spectral MRI	67
4.3.1	Radial multi-spectral measurement model	68
4.3.2	Physics-driven iterative spectral deconvolution	69
4.3.3	Recovering undersampled noisy radial multi-spectral measurements through learned unrolling	70
4.4	Simulation Results	72
4.5	Discussion and Conclusion	75
4.6	Acknowledgements	76
Chapter 5	Emerging Directions and Conclusions	77
5.1	Exploring Novel Generative Priors with Applications in ^{19}F Cellular MRI	78
5.1.1	Supervised Recovery Technique with Data-Driven Prior	79
5.1.2	Data-Driven Regularizer and Initializer	81
5.1.3	Phantom Simulations	84
5.1.4	Discussion	85
5.2	Combating Adverse ^{19}F Data Scenarios-Towards Learning Based Acquisitions-Reconstructions	87
5.2.1	Model-based deep unrolling and self-supervised reconstruction approaches	87
5.2.2	Chemical shift encoding inspired multi-spectral separation	88
5.2.3	Active information acquisition and multimodal guided imaging	90
5.3	Conclusion	91
5.4	Acknowledgements	93
Bibliography		94

LIST OF FIGURES

Figure 2.1.	SNR_{eff} maps for different pulse sequences.	12
Figure 2.2.	Simulation of fixed scanning time ^{19}F ZTE MRI measurement of paramagnetic PFC nanoemulsion.	15
Figure 2.3.	CS undersampling patterns ($u = 16$) used for CS-RARE Cartesian 3D imaging.	16
Figure 3.1.	Spherical sampling of radial trajectory generated by Poisson disk point selection.	29
Figure 3.2.	CS reconstruction results from synthetic ^{19}F CS-ZTE 3D data with varying u and noise level σ	39
Figure 3.3.	Simulated PSFs of 3D radial undersampling trajectories used in CS-ZTE. .	41
Figure 3.4.	Results reconstructed by the sparsity-driven algorithm of experimental ^{19}F Phantom 1 (TFA) data acquired by the CS-ZTE pulse sequence with a fixed scan time of 13 s.	42
Figure 3.5.	LOD evaluation using the CS-ZTE method at 11.7 T with a fixed scanning time of 3 min 30 s.	44
Figure 3.6.	Calculated PSNR from sparsity-driven reconstructions of Phantom 1 CS-ZTE data with changes in regularization parameters.	47
Figure 3.7.	Pareto optimality and reconstruction error analysis from the joint TV- ℓ_1 -norm regularized least square algorithm ($\sigma = 0.4$).	48
Figure 3.8.	Pareto optimality and reconstruction error analysis from the joint TV- ℓ_1 -norm regularized least square algorithm ($\sigma = 0.1$).	49
Figure 3.9.	<i>In vivo</i> 3D ^{19}F MRI mouse data showing ^{19}F labeled FSDCs injected into the hind footpads.	51
Figure 3.10.	Lasso error under fixed sparsity and different noise levels.	53
Figure 3.11.	Modeling illustration of artifact suppression using CS reconstruction in inhomogeneous imaging scenario.	55
Figure 4.1.	Demonstration of Cartesian and radial chemical shift artifacts in multi-spectral ^{19}F MRI.	64

Figure 4.2.	Reconstruction of simulated multispectral ^{19}F Cartesian phantom data and quantification results.	67
Figure 4.3.	Illustration of projection slice theorem.	68
Figure 4.4.	Radial k-space via Radon Transform domain adaptation.	69
Figure 4.5.	Primal-dual hybrid gradient (PDHG) algorithm used to solve Eq. 4.8 with TV regularization $\ \nabla \mathbf{x}\ _1$	70
Figure 4.6.	Learned unrolling of primal-dual (UPD) for radial multi-spectral deconvolution.	71
Figure 4.7.	Framework of data-driven unrolling algorithm on the simultaneous unmixing of multi-spectral accelerated radial ^{19}F cellular MRI.	72
Figure 4.8.	Deconvolution of two ^{19}F component images using PDHG and UPD.	73
Figure 4.9.	Reconstructed chemical shift ^{19}F phantom images using PDHG and UPD under input SNR = 5 dB.	74
Figure 4.10.	Reconstructed chemical shift ^{19}F phantom images using PDHG and UPD under input SNR = 20 dB.	75
Figure 5.1.	Reconstructed cellular MRI images using three different methods: CSGM, Alg.1, and Alg. 2. Here $M = 300$, SNR=10, -10 dB.	81
Figure 5.2.	Reconstructed cellular MRI images using three different methods: CSGM, Alg.1, and Alg. 2. Here $M = 100$, SNR=10, -10 dB.	85

LIST OF TABLES

Table 3.1.	Characteristics of PSFs measured by SPR and FWHM.	40
Table 4.1.	Impact of reconstruction quality over change of $\mathcal{A}$	75
Table 5.1.	Data-Dependent Regularizer	83
Table 5.2.	Regularizer-Free Solver	83
Table 5.3.	RMSE standard deviations over 10 random trials ($\mathbf{A}$ is fixed for each M). ..	86

ACKNOWLEDGEMENTS

I would like to acknowledge Professor Piya Pal and Professor Eric Ahrens for their support as my PhD advisors through the years. I would also like to thank Professor Thomas T. Liu, Professor Truong Q. Nguyen, and Professor Bhaskar D. Rao for serving on my committee and providing their valuable time and feedback.

Chapter 2, in part, is a reprint of material in submission as:

- J. Chen, P. Pal, E. T. Ahrens, “Systems engineering approach towards sensitive cellular fluorine-19 MRI” (Journal paper under preparation).

The dissertation author was the primary investigator and author of the paper. We thank Dr. Amy Schwartz for critical reading of the manuscript.

Chapter 3, in part, is a reprint of the material as it appears in the following papers:

- J. Chen, P. Pal, and E. T. Ahrens, “Enhanced detection of paramagnetic fluorine-19 magnetic resonance imaging agents using zero echo time sequence and compressed sensing,” *NMR in Biomedicine*, vol. 35, no. 8, p. e4725, 2022.
- J. Chen, P. Pal, E. T. Ahrens, “Enhanced detection of paramagnetic fluorine-19 MRI agents using compressed sensing zero echo time sequence,” in *31st Annual Scientific Meeting of the ISMRM*, London, 2022.

The dissertation author was the primary investigator and author of these papers.

Chapter 4, in part, is a reprint of the material as it appears in the following papers:

- J. Chen, E. T. Ahrens, and P. Pal, “Physics-driven learned deconvolution of multi-spectral cellular mri with radial sampling,” in *2023 57th Asilomar Conference on Signals, Systems, and Computers*, pp. 1453–1457, IEEE, 2023.
- J. Chen, P. Pal, E. T. Ahrens, “Physics-driven learned deconvolution of multi-spectral fluorine-19 MRI with multiple agents using radial sampling” in *33rd Annual Scientific Meeting of the ISMRM*, Singapore, 2024.

The dissertation author was the primary investigator and author of these papers.

Chapter 5, in part, is a reprint of the material as it appears in the following paper:

- S. Shahsavari, J. Chen, and P. Pal, “Exploring the geometry of generative priors with applications in cellular MRI,” in 2022 56th Asilomar Conference on Signals, Systems, and Computers, pp. 1010–1015, IEEE, 2022.

S. Shahsavari was the primary author of the paper, proposed the latent space clustering idea, and developed the algorithms. The dissertation author contributed towards paper writing, phantom data processing, and helped the integration of CS-MRI into the algorithm framework. Chapter 5 is also, in part, a reprint of material in submission as:

- J. Chen, P. Pal, E. T. Ahrens, “Systems engineering approach towards sensitive cellular fluorine-19 MRI” (Journal paper under preparation).

The dissertation author was the primary investigator and author of the paper.

VITA

2017	B.Eng in Electronics and Information Engineering, Sichuan University
2020	M.S. in Electrical Engineering, University of California San Diego
2022	AI in Communications Summer Intern, Nokia Bell Labs, Murray Hill, NJ
2023	Sensing Algorithm Systems Engineer Intern, Apple, Cupertino, CA
2024	Ph.D. in Electrical Engineering, University of California San Diego

PUBLICATIONS

J. Chen, P. Pal, and E. T. Ahrens, “Enhanced detection of paramagnetic fluorine-19 magnetic resonance imaging agents using zero echo time sequence and compressed sensing,” *NMR in Biomedicine*, vol. 35, no. 8, p. e4725, 2022.

J. Chen, P. Pal, E. T. Ahrens, “Enhanced detection of paramagnetic fluorine-19 MRI agents using compressed sensing zero echo time sequence,” in *31st Annual Scientific Meeting of the ISMRM*, London, 2022.

S. Shahsavari, J. Chen, and P. Pal, “Exploring the geometry of generative priors with applications in cellular MRI,” in *2022 56th Asilomar Conference on Signals, Systems, and Computers*, pp. 1010–1015, IEEE, 2022.

J. Chen, E. T. Ahrens, and P. Pal, “Physics-driven learned deconvolution of multi-spectral cellular mri with radial sampling,” in *2023 57th Asilomar Conference on Signals, Systems, and Computers*, pp. 1453–1457, IEEE, 2023.

E. T. Ahrens, B. M. Helfer, C. F. O’Hanlon, D. R. Lister, J. L. Bykowski, K. Messer, B. I. Leach, J. Chen, H. Xu, G. A. Daniels, et al., “Method for estimation of apoptotic cell fraction of cytotherapy using in vivo fluorine-19 magnetic resonance: pilot study in a patient with head and neck carcinoma receiving tumor-infiltrating lymphocytes labeled with perfluorocarbon nanoemulsion,” *Journal for immunotherapy of cancer*, vol. 11, no. 6, 2023.

J. Chen, P. Pal, E. T. Ahrens, “Physics-driven learned deconvolution of multi-spectral fluorine-19 MRI with multiple agents using radial sampling” in *33rd Annual Scientific Meeting of the ISMRM*, Singapore, 2024.

J. Chen, P. Pal, E. T. Ahrens, “Systems engineering approach towards sensitive cellular fluorine-19 MRI” (Journal paper under preparation).

ABSTRACT OF THE DISSERTATION

Enhanced Detection Sensitivity of Fluorine-19 Cellular MRI through Systematic
Acquisition-Reconstruction Co-Design

by

Jiawen Chen

Doctor of Philosophy in Electrical Engineering (Signal and Image Processing)

University of California San Diego, 2024

Professor Piya Pal, Chair
Professor Eric T. Ahrens, Co-Chair

Fluorine-19 MRI is an emerging technique offering specific detection of labeled cells *in vivo*. Lengthy acquisition times and modest signal-to-noise ratio (SNR) makes 3D spin-density weighted ^{19}F imaging challenging. Importantly, recent innovations in molecular ^{19}F tracer design and image acquisition-reconstruction methods have achieved significant leaps in ^{19}F MRI sensitivity, and integration of these new materials and methods into studies can result in > 10 -fold improvement in detection sensitivity. These developments may help unlock the full potential of clinical ^{19}F MRI for cellular imaging applications, particularly when considering the systematic measurement-algorithmic signal processing frameworks.

The overarching goal of this dissertation is to investigate joint acquisition-reconstruction imaging techniques for enhanced detection through the lens of ^{19}F cellular MRI. This includes a theoretical signal processing development perspective, pulse sequence programming, and reconstruction software workflow implementation on the MRI scanner. The dissertation starts with the introduction of sensitivity analysis dependent on the LOD and theoretical MR signal modeling. Given that ^{19}F -MRI generally involves the detection and localization of low concentrations of ^{19}F -containing compounds, many signal averages are required to achieve acceptable SNR. Since sensitivity is governed by SNR/time, the study also focuses on integrating spin physics and chemical domain knowledge into the systematic co-design of pulse sequences and reconstruction algorithms to accelerate ^{19}F MRI. To further enhance the sensitivity of paramagnetic metallo-PFC (MPFC), a compressed sensing scheme is described and implemented using a novel ultrafast 3D radial pulse sequence, with data reconstructed via a hand-crafted sparsity-promoting algorithm. Combined with recent innovations in physics-driven deep learning, we employ deep unrolling of radial chemical shift deconvolution arising from ^{19}F multiple cell target detection tasks. Unlike typical ^1H water-fat separation, the large chemical frequency shifts in ^{19}F cellular MRI provide a new avenue to model the chemical offsets and enable artifact-free separation under adverse data scenarios. Finally, we explore generative priors for a preliminary study in cellular MRI detection under high compression and low SNR regimes, shedding light on future research directions involving active sensing and self-supervised reconstruction for cellular MRI applications. One can readily generalize the techniques studied in this dissertation to similar X-nuclei applications, such as ^{23}Na , without any particular restrictions.

Chapter 1

Introduction

1.1 Background and Motivation

^{19}F MRI is an emerging technology enabling *in vivo* cell detection of ^{19}F -labeled inflammatory infiltrates and cytotherapy [1, 2]. The ^{19}F nucleus has a similar gyromagnetic ratio to proton (^1H), differing by about 6%, resulting in a relative NMR sensitivity of 0.83 [3]. There is negligible endogenous ^{19}F in biological tissues thus enabling background-free, ‘hot-spots’ imaging [4]. Use of ^{19}F MRI for ‘*in vivo* cytometry’ has been described [1, 5, 6] to non-invasively image and quantify selected cell populations in the body. In this approach, cell populations of interest are labeled *ex vivo* with perfluorocarbon (PFC) nanoemulsion; following transfer to the subject, cell population ^{19}F ‘hot-spots’ are spin density-weighted imaged and placed into the anatomical context using high resolution, co-registered ^1H MRI [7]. Specifically, *in vivo* ^{19}F datasets exhibit true sparsity, with of the order of 0.5%–5% voxels containing significant signal in a background of pure noise [8]. The total ^{19}F signal can be readily calculated from the *in vivo* data, providing tracking information for both the localization and absolute, intravoxel spin numbers.

A limitation of ^{19}F MRI is its low signal-to-noise ratio (SNR), thereby necessitating significant signal averaging and potentially lengthy scan times to achieve desirable limits of detection (LOD). This challenge is particularly pronounced for three-dimensional (3D) acquisitions with isotropic voxels. Recent advancement in paramagnetic (Fe^{3+}) PFC nanoemulsions (NEs)

has achieved > 10 -fold reduction in T_1 longitudinal relaxivity [9], yielding 4-fold sensitivity enhancement through rudimentary SNR modeling of conventional gradient echo (GRE) pulse sequence. However, at high metal doping into nanoemulsion the ^{19}F transverse relaxation time (T_2) can become very short (e.g., $T_2 < 5$ ms), which causes signal loss due to T_2 linewidth broadening and constrains the achievable SNR performance. Thus, the choice of ^{19}F MRI pulse sequence is crucial for acquiring paramagnetic relaxation enhancement (PRE) NE tracer data. It plays a key role in achieving the highest potential SNR gains and sensitivity enhancement.

PFCs with the most promising biocompatibility characteristics [10] usually have complex MR spectra with multiple resonances. These resonance peaks typically occupy over a broad frequency range, *i.e.*, 10000 Hz for clinical scanners [11] and cause chemical shift artifact patterns (depending on the k-space sampling trajectory) that spread the signal across neighboring voxels. This effect becomes even more pronounced when operating at high-field preclinical scanners [12] and thus degrades the SNR further. There are mainly two types of techniques to address these challenges. One technique is based on the selective suppression and excitation of a subset of targeted spectral peaks [13, 14]. This approach comes at the expense of increased scan time and the discarding of non-excited ^{19}F resonance signals. The other technique, using chemical shift spectroscopic imaging [10] or multi-echo encoding [11, 15], separates ^{19}F resonances based on their phase evolution but suffers from prolonged acquisition times. To enable simultaneous multi-spectral or “multicolor” acquisitions, multiple cell populations are labeled with different PFC tracers with distinct ^{19}F nuclear MR frequencies [16]. This necessitates the need for developing SNR-efficient acquisition-reconstruction scheme to separate the ^{19}F compounds free from artifacts.

Pioneering work such as SparseMRI [17] has successfully reduced scan time for ^1H anatomical MRI by enabling reliable recovery from compressed sensing (CS) measurements with multifold undersampling factors. This is essentially an ill-posed inverse problem since the number of measurements is less than the dimension of the image signal. The corresponding optimization problem is solved by integrating structural or geometrical priors (*e.g.*, sparsity) as

the regularization term. CS theory demonstrates that efficient reconstruction of sparse vectors is guaranteed by the restricted isometry property (RIP) [18] of the sensing matrix. However, these proofs are typically built upon the Gaussian random matrix assumptions, which does not take the physical constraints of the imaging system into account. Unlike ^1H anatomical scans, the aim is to boost the SNR efficiency of ^{19}F imaging rather than simply reduce the acquisition time. Previous work in a macrophage inflammation study [19] has adapted incoherent Cartesian pseudorandom sampling patterns into 3D spin echo ^{19}F scans and observed a ~ 8.5 -fold SNR boost. To further enhance the detection sensitivity, novel non-Cartesian sensing schemes need to be carefully designed in combination with the ^{19}F relaxivity property of PRE NE tracer in a synergistic manner.

The performance of classical CS reconstruction relies on hand-crafted priors and is heavily dependent on deliberate parameter tuning with high bias. Recent advances in data-driven and deep learning techniques have demonstrated the representation power of neural networks. These networks are essentially low-bias models. In particular, generative models such as Generative Adversarial Networks (GAN) [20] and Variational Autoencoder (VAE) [21] are known for capturing latent low-dimensional geometry of the signal. CS recovery is performed by integrating the pre-trained generator network as prior information while solving the optimization problem [22], without any sparsity assumptions on the interest signal. It is demonstrated that generative priors show performance advantages over hand-crafted structural priors under extreme data compression scenarios [22]. More recently, researchers have employed a score-based generative model to obtain robust out-of-distribution reconstruction from undersampled ^1H MRI k-space measurements [23]. Training such large scale generative models requires thousands of clean ground truth MRI images typically from public available datasets [24]. This makes the deployment of generative priors for cellular MRI somewhat challenging due to lack of high quality abundant ^{19}F datasets.

Alternatively, algorithm unrolling has attracted enormous attention in biological imaging field [25], since they are capable of achieving on-par accuracy compared to end-to-end deep

learning methods while only requiring hundreds of training samples [26]. By unfolding a conventional iterative algorithm for a fixed number of iterations, the unrolled networks naturally inherit prior structures as well as domain knowledge [26]. The overall unrolling for CS MRI frameworks explicitly incorporates known physics-based forward sensing operators into deep learning networks and training [27]. This approach ensures data consistency of the reconstruction with k-space measurements. The feature gives rise to high-efficiency lightweight architectures with tremendous reduction in network parameters.

The overarching goal of this dissertation is to investigate joint acquisition-reconstruction imaging techniques with enhanced detection through the lens of ^{19}F cellular MRI applications. This includes both the theoretical signal processing development perspective and pulse sequence programming and reconstruction software workflow implementation on the MRI scanner. We will start with introduction of the sensitivity analysis dependent on the LOD and theoretical modeling of MR signal. Since sensitivity is governed by SNR/time, we focus on integrating spin physics and/or chemical domain knowledge into the systematic pulse sequence and reconstruction algorithm co-design for accelerated ^{19}F MRI. To further enhance the sensitivity of paramagnetic metallo-PFC (MPFC), we describe a CS scheme, implemented using a novel ultrafast 3D radial pulse sequence, with data reconstructed via a hand-crafted sparsity-promoting algorithm. Combined with recent advancements in physics-driven deep learning, we exploit the deep unrolling of radial chemical shift deconvolution arisen from ^{19}F multiple cell targets detection applications. Unlike typical ^1H water-fat separation, large chemical frequency shifts in ^{19}F cellular MRI provides new avenue to model the chemical shift artifacts and enable SNR-robust separation under adverse data scenarios. Finally, we will explore generative priors for a preliminary study in cellular MRI detection under high compression and low SNR regime and indicate future research directions. All the techniques studied in this dissertation can be readily generalized to similar X-nuclei applications such as ^{23}Na without any particular constraints.

1.2 Outline and Contributions

Chapter 2 analyzes the key factors that limit cell LOD including chemical, algorithmic and hardware considerations. Specifically, our focus is to introduce the ^{19}F pulse sequence acquisition and reconstruction co-design paradigm, guided by the theoretical modeling of measurement-algorithm pipeline inspired from the accelerated sensing techniques in signal processing field. The discussion will be mostly based on using ^{19}F MRI and PFC nanoemulsion tracers for *in vivo* cell detection, however many of the study design principles apply to other classes of ^{19}F agents and fluorinated drugs.

In Chapter 3, we describe a compressed sampling (CS) scheme, implemented using a ‘zero’ echo time (ZTE) sequence, with data reconstructed via a sparsity-promoting algorithm. Our CS-ZTE scheme acquires k-space data using an undersampled spherical radial pattern and signal averaging. Image reconstruction employs off-the-shelf sparse solvers to solve a joint total variation (TV) and ℓ_1 -norm regularized least square problem. To evaluate CS-ZTE, we performed simulations and acquired ^{19}F MRI data at 11.7 T in phantoms and mice receiving MPFC-labeled dendritic cells.

Detection of multiple ^{19}F labeled cell targets requires the ability to unmix images corresponding to different tracer molecules with different chemical shifts. Chapter 4 addresses these perspectives through the lens of radial spectral deconvolution. The goal is to develop suitable modeling of the radial chemical shift artifacts using Radon transform, which will guide our design of sensing operators that favor specific multi-spectral imaging tasks. To effectively unmix the component images under low SNR regime, we will further exploit physics-informed learning-based unrolling strategies that enable simultaneous artifact removal and weak signal detection, both of particular interest in ^{19}F MRI.

The CS-ZTE acquisition-reconstruction co-design framework described in Chapter 3 is under the classical unsupervised regime that rely on structural/geometric hand-crafted prior information of the signal. Importantly, data-driven prior can help to augment conventional

regularizers and therefore lead to further detection sensitivity enhancement. In Chapter 5, we will first investigate how geometrical aspects of generative priors can lead to robust design of data-driven regularizers through the lens of a typical ^{19}F cellular MRI detection task. Next, we will discuss the state-of-the-art acquisition-reconstruction techniques to combat some frequently encountered adverse data scenarios in ^{19}F MRI. An alternative chemical shift encoding formulation of multi-spectral ^{19}F components separation is subsequently introduced with the purpose to mitigate the severe radial smearing artifacts occurred in low SNR scenarios. We will also connect with active information acquisition to enable adaptive MRI k-space sensing. Finally, this dissertation concludes by summarizing the explored techniques and their achievements in enhancing the sensitivity of ^{19}F cellular MRI.

Chapter 2

Towards Sensitive Cellular MRI-A Systematic Measurement-Algorithm Co-Design Approach

Fluorine-19 MRI signal intensity is restricted by the total amount and tissue distribution of the F-tracer post-administration. However, for a given experiment, the achievable sensitivity is also strongly dependent on the specific composition of the formulated tracer, cell type of interest, cell activity, data acquisition, reconstruction methods, magnetic field strength, and MRI radio frequency (RF) coil design. Importantly, recent innovations in molecular ^{19}F tracer design and image acquisition-reconstruction methods have achieved significant leaps in ^{19}F MRI sensitivity, and integration of these new materials and methods into studies can result in > 10 -fold improvement in LOD [9]. These developments may help unlock the full potential of clinical ^{19}F MRI [28] for cellular imaging applications. In this chapter, we will analyze the key factors that limit cell LOD including chemical, algorithmic and hardware considerations. Specifically, our focus is to introduce the ^{19}F pulse sequence acquisition and reconstruction co-design paradigm, guided by the theoretical modeling of measurement-algorithm pipeline inspired from the accelerated sensing techniques in signal processing field. The discussion will be mostly based on using ^{19}F MRI and PFC nanoemulsion tracers for *in vivo* cell detection; however, many of the study design principles apply to other classes of ^{19}F agents, such as bio-responsive probes [29], and fluorinated drugs [30].

2.1 Limits of Detection

The LOD parameter reflects the sensitivity of ^{19}F cellular MRI and can be used to guide the rationale behind the design of successful imaging studies. In general, LOD is defined as the lowest threshold value which allows signals to be accurately and reliably distinguished from background noise. In 1948, Rose [31] first proposed a simple model of signal detectability using a human observers' perspective and the performance of an imaging device with a given absolute quantum efficiency, for example an X-ray based imaging system. The model assumes a signal region in area A spanning multiple voxels. We define contrast from background as $C = \mathbb{E}(\Delta n_s)/\mathbb{E}(n_B)$, where $\mathbb{E}(\Delta n_s)$ is the expected extra photons per unit area for the signal and $\mathbb{E}(n_B)$ is the expected number of photons per unit area in the background region [32]. Rose suggested using a threshold SNR, denoted as SNR_T , to characterize the signal detectability using

$$SNR_T = C\sqrt{A\mathbb{E}(n_B)} \quad (2.1)$$

where $SNR_T = 4$ is determined experimentally to be the most likely value [32]. The threshold method is widely used by the radiology community for X-ray techniques and (^1H) MRI [33, 34].

The Rose model precedes the formal development of signal detection theory (SDT) [35, 36] built on Bayesian ideal observer probabilistic analysis. In prior work [32], SDT is used to derive a so-called 'detectability index' γ based on a binary hypothesis that aims to distinguish two Gaussians with population means $\mathbb{E}(\Lambda_S)$ and $\mathbb{E}(\Lambda_N)$, together with corresponding variances $\sigma_{\Lambda_S}^2$ and $\sigma_{\Lambda_N}^2$, using likelihood ratios under two equally probable state S (signal presence) and N (signal absence)

$$\gamma^2 = \frac{(\mathbb{E}(\Lambda_S) - \mathbb{E}(\Lambda_N))^2}{(\sigma_{\Lambda_S}^2 + \sigma_{\Lambda_N}^2)/2} \quad (2.2)$$

Here, γ is a normalized Euclidean distance measure that describes the separation of the two population means (signal present and absent) relative to the average of population standard

deviation. It has been demonstrated [32] that under suitable assumptions, γ^2 (2.2) is equivalent to SNR_T^2 (2.1) defined by Rose [31]. First, the approximation of noise equal variance is only valid in the low-contrast signal regime. Second, unlike the Gaussian noise assumption in the SDT approach, noise is modeled as a Poisson distribution. Overall, the Rose criterion focuses on both statistical properties and human observation [31, 32, 37]. However, for ^{19}F MRI, a computational analysis of signal and noise determines voxels with probable ^{19}F signal, and the human eye is only relevant in terms of determining anatomical context for the ^{19}F signal, aided by ^1H MRI data. Importantly, in ^{19}F cell tracking there is essentially no ^{19}F background, and in contrast to ^1H anatomical imaging, where one requires a high SNR to visualize fine anatomical features, ^{19}F images most often only display a sparse number of voxels at low SNR (e.g., < 5), where co-localized ^1H MRI provides anatomical information [38]. Therefore, it is likely that the Rose Model criteria as overly conservative for ^{19}F MRI LOD analysis [39].

To describe LOD parameterization of ^{19}F MRI data, our view is that a voxel-based measurement has advantages over regional (area) contrast measurements, as used in Rose model. We describe LOD in terms of ^{19}F spins/voxel. By parameterization of sensitivity on a per voxel basis, one renders the metric insensitive to the spatial extent of the localized pool of ^{19}F signal, and LOD reporting does not rely on voxel dimensions. The voxel size (and image resolution) is set by the MRI practitioner, and should be adequately sized to capture sufficient numbers of ^{19}F signal generators within a given tissue/organ of interest to achieve signals above LOD; voxels sizes can range from submillimeter to whole-organ voxel dimensions [40]. To set ^{19}F spins/voxel LOD levels, we suggest a threshold $SNR \sim 2.5$; this cutoff value was previously used in clinical ^{19}F MRI cell tracking studies yielding $> 99\%$ confidence that the voxel is signal-positive and above noise [1]. For a given experiment, one can measure the absolute ^{19}F /voxel in each pixel via quantification of the image voxel intensity along with the intensity of an external reference voxel; often this reference is a concentration-calibrated F-phantom positioned alongside the subject in the image field of view [1]. As the signal is linearly proportional to the number of ^{19}F spins, one can extrapolate downward the voxel intensity to $SNR \sim 2.5$ to determine LOD for a

particular study and experimental configuration.

Moreover, for *ex vivo*-type cell labeling experiments, one can measure the mean ^{19}F /cell value, post-labeling, via quantitative NMR of a pellet of known cell count [1]. This cell labeling parameter can be used to convert LOD to (F-labeled) cells/voxel. In the example in [1], the DCs were labeled with a mean of 3.7×10^{12} ^{19}F /cell, and the cell-based LOD parameter was benchmarked at $\sim 10^5$ DCs/voxel. Also, note that the noise-dependent bias from the magnitude images are non-negligible under low SNR (< 5) scenarios, and Rician-distributed voxel intensities [41] should be corrected for this systematic noise bias before thresholding [1, 42].

Overall, there is no standardized format for calculating and reporting cellular detection sensitivity. In this thesis, we express LOD in terms of ^{19}F spins/voxel yielding a SNR ~ 2.5 . This is the cut-off value previously used in clinical ^{19}F MRI cell tracking studies yielding 99% confidence in the signals detected [1].

2.2 Pulse Sequence Considerations

The choice of ^{19}F MRI pulse sequence is crucial to achieve satisfactory SNR and cell detection sensitivity. Ideally, ^{19}F acquisitions should provide three-dimensional (3D) data with isotropic voxels and whole-body images of tracer distribution, analogous to positron emission tomography methods. The SNR efficiency for a conventionally-acquired 3D ^{19}F image can be represented as [43]

$$SNR_{eff} \propto \frac{S_{avg}}{\sigma_n} \Delta x \Delta y \Delta z \sqrt{N_{acq} N_x N_y N_z \Delta t / TR} \quad (2.3)$$

where S_{avg} is the average signal intensity, σ_n is the standard deviation of apparent noise, $\Delta x \Delta y \Delta z$ denotes the voxel volume, N_{acq} is the number of acquisitions/averages/excitations, $N_x N_y N_z$ is the total number of encoding samples, TR is the repetition time, and $\Delta t = 1/BW_{read}$ corresponding to the readout bandwidth BW_{read} . General approaches to enhance ^{19}F sensitivity include optimization of imaging parameters in (2.3). Since S_{avg} exhibits complex interdependencies with many

parameters and does not have a closed-form expression, we consider utilizing the maximum signal intensity S_{max} as a surrogate to facilitate comparisons across different sequences. The PFC properties (spin-density, T_1 , T_2 , T_2^*) and the relevant acquisition parameters (TR, TE, flip angle α) determine the achievable S_{max} . Using rudimentary simulations, we demonstrate below that the actual SNR_{eff} is only determined by a subset of these parameters, depending on the choice of pulse sequence. In practice, optimal parameters can be determined via simulation with the Bloch equations [44].

Pulse sequences with inherently high SNR per image acquisition time are preferred for ^{19}F imaging. Spin echo based pulse sequences, such as Turbo Spin Echo (TSE) or Fast Spin Echo (FSE), are commercial implementations of RARE (rapid acquisition with relaxation enhancement) [45, 46]. RARE has a 90° RF pulse followed by a train of 180° refocusing pulses specified by the RARE factor (or echo train length). For most PFC tracers, combinations of RARE factors ranging from 8 to 20, and TRs set between 0.5 and 1.2 times T_1 , provide the highest SNR_{eff} [47]. As displayed in the SNR_{eff} map for RARE (Figure 2.1), the long TRs result in lengthy scan times and thus limits RARE's sensitivity performance across a wide range of (T_1, T_2) . In sum, SNR_{eff} of RARE can be represented as a function of $(T_1, T_2, BW, \text{RARE factor, TR})$ [47].

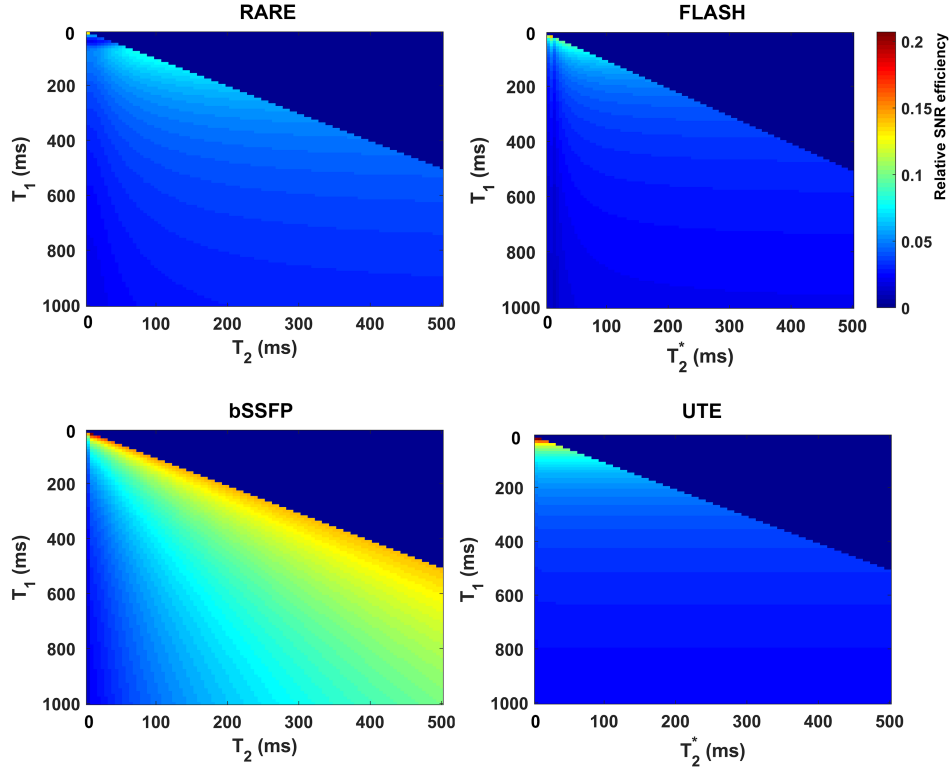


Figure 2.1. SNR efficiency (*i.e.*, SNR_{eff} in (2.3)) maps for (A) RARE, (B) FLASH, (C) bSSFP, and (D) UTE. All the displayed ^{19}F signal intensities are normalized by square root of constant scan time to reflect relative SNR efficiency. The impractical area ($T_1 < T_2$) is labeled as deep blue color corresponding to intensity value of 0. Note that the signal intensities are calculated based on the optimal combinations of parametric pairs. Specifically, RARE is optimized across all possible (TR, RARE factor) pairs. For FLASH and bSSFP, optimum BW is pre-selected between 5 and 200 kHz for each (T_1, T_2) pair based on the maximum signal intensity generated. The flip angle of FLASH is set to Ernst angle; for bSSFP, the optimal flip angle is calculated using a function of (T_1, T_2) . The optimization of UTE parameters is dependent on the BW and optimum α achievable (60° in our case), which is aligned with the requirements of high field scanners.

Gradient echo (GRE)-based pulse sequences, such as fast low angle shot (FLASH) [48], serve as faster alternatives to spin-echo methods as their TRs are typically on the order of 5-100 ms. Transverse magnetization is generated by a small flip angle RF pulse (typically set at Ernst angle), followed by a gradient-induced dephasing and a rephasing process creating an echo at TE [49]. After readout, residual transverse magnetization is dephased via spoiler gradient. The FLASH method results in low steady-state magnetization and low signal per RF shot.

Balanced steady-state free precession (bSSFP) was introduced to increase the signal amplitude by a balanced refocusing gradient and recycle of the residual transverse magnetization [49]. The steady-state of bSSFP also causes unwanted sensitivity towards B_0 inhomogeneities, which may be problematic for application in high field scanners or in non-homogeneous tissues. The SNR_{eff} for the FLASH/bSSFP sequence is dependent on $(T_1, T_2^*/T_2, BW)$ since the minimum TR is set by BW [47]. The SNR_{eff} maps of FLASH and bSSFP are displayed in Figure 2.1 as a function of T_1 (y-axis) and T_2^*/T_2 (x-axis). Overall, bSSFP displays greater sensitivity compared to FLASH across all investigated (T_1, T_2) combinations investigated. Notably, both sequences consistently show greater sensitivity at shorter T_1 values (Figure 2.1).

For 3D imaging with isotropic voxels, conventional spin-echo and gradient-echo methods have prohibitively long acquisition times, especially when used with signal averaging, which limits clinical use. More time-efficient methods, such as echo-planar imaging (EPI) [50] can have severe artifacts for body imaging, particularly when working at high magnetic field strengths. Consequently, ^{19}F image quantification with EPI can be challenging in vivo.

Radial projection-type pulse sequences, such as ultrafast echo-time (UTE) [51, 52] and ‘zero’ echo-time (ZTE) [53] methods serve as excellent candidates for detection of fast- T_1 materials, for example using paramagnetic tracers [9]. As suggested by the calculated SNR_{eff} for the free induction decay (FID)-based UTE method (Figure 2.1), the sequence reaches its optimal sensitivity when T_2^* is in the millisecond range, outperforming the bSSFP method. UTE exploits T_1 -weighting, and T_2^* -effects are minimized due to microsecond-level TE values [54]. The radial center-out acquisition scheme of both UTE and ZTE requires a minimal receiver deadtime after RF pulse (a few microseconds) to enable immediate FID sampling; this results in higher SNR efficiency, especially for short T_1 (< 10 ms) materials [54, 55]. Notably, the gradient ramping module of ZTE precedes the hard RF pulse, with no slice selection, making ZTE an intrinsically-fast 3D acquisition method [53].

Detection of the paramagnetic PRE nanoemulsions is well suited to the ZTE/UTE methods due to the materials’ short (T_1, T_2) relaxation times. For example, Figure 2.2 displays

simulations for ZTE MRI to investigate optimal imaging parameters. Following Eq. 1 [54], the signal equation can be written as

$$SI_{ZTE} = S_0 \cdot \sin(\alpha) \cdot \frac{1 - E_Z}{1 - E_Z \cos(\alpha)} \exp\left(-\frac{TE}{T_2^*}\right) \quad (2.4)$$

where $E_Z = \exp\left(-\frac{TR}{T_1}\right)$, S_0 denotes the maximum available signal, and α represents flip angle. Several assumptions should be considered when simulating the ZTE ^{19}F signal intensity using (2.4). We assume $\exp(-TE/T_2^*) \approx 1$ since ZTE signal encoding starts immediately after the gradient. Ideally, the flip angle should be set to Ernst angle to optimize the signal. However, for ultra-short pulse sequence such as ZTE, the achievable α is constrained by RF power limitations. An increase in α requires an increase in dead time Δ (i.e., the duration between the pulse and signal collection) and further results in additional missing data towards the k-space center [56] as well as a decrease in bandwidth (BW). In practice, $\Delta < 1/BW$ should be required in order to ensure the output image quality [57]. According to the phantom experiments on 11.7 T, we set $\alpha_{max} = 10^\circ$ to be the maximum achievable flip angle. Because of the short T_1 of MPFC, we only explore TR values within the range between 1.6 ms (minimum achievable for $BW = 60$ kHz) and 10 ms. As we are interested in comparing results within a fixed scan time, the total imaging time was set to 10 min (the same as the *in vivo* imaging performed) and NA was accounted for during the simulation of Eq. 2.4. The simulated signal values are rendered in colormap and displayed in Figure 2.2. The highest signal intensity resides in the bottom left corner, which corresponds to TR = 1.6 ms (minimum) and $\alpha = 10^\circ$. Thus, we will utilize these optimized parameters for the CS-ZTE experiments using MPFC described in Chapter 3.

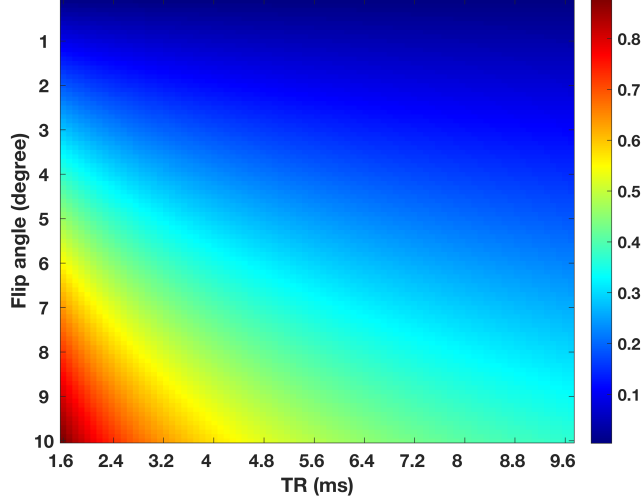


Figure 2.2. Simulation of fixed scanning time ^{19}F ZTE MRI measurement of paramagnetic PFC nanoemulsion ($T_1 = 7$ ms, $T_2^* = 1.5$ ms at 11.7 T) with dependence on flip angle α and TR. Simulations are based on Eq. 2.4. The values of TR (x-axis) and α (y-axis) are selected based on the constraints of hardware and the ZTE sequence. Specifically, we explore TR values within the range between 1.6 ms and 10 ms. The highest SNR_{eff} resides at the bottom left corner, which corresponds to TR = 1.6 ms (minimum) and $\alpha = 10^\circ$ within the possible ranges.

2.3 Co-design of ^{19}F Pulse Sequence and Reconstruction

To further improve ^{19}F MRI detection, pulse sequences and reconstruction methods can be tailored to yield greater SNR/time performance by exploiting the ^{19}F signal characteristics of sparsity and no background. The baseline approach is to apply MRI signal reconstruction algorithms for noise suppression. The goal is to denoise or smooth the background while preserving features in the output image. Rather than performing a conventional inverse Fourier transform, one can employ algorithms that apply spatial filtering, such as non-local means [58], use inferences from a probabilistic model [59, 60], or exploit structural characteristics of the imaging object [61]. For ^{19}F MRI in particular, processing paradigm ℓ_1 -norm regularization [42], low-rank structure from neighboring pixels [62], and iterative sparse deconvolution [12] have been studied in the denoising context yielding the expected SNR improvement. Importantly, this increased SNR is simply a consequence of noise reduction, without an actual gain (or recovery) of the total available signal.

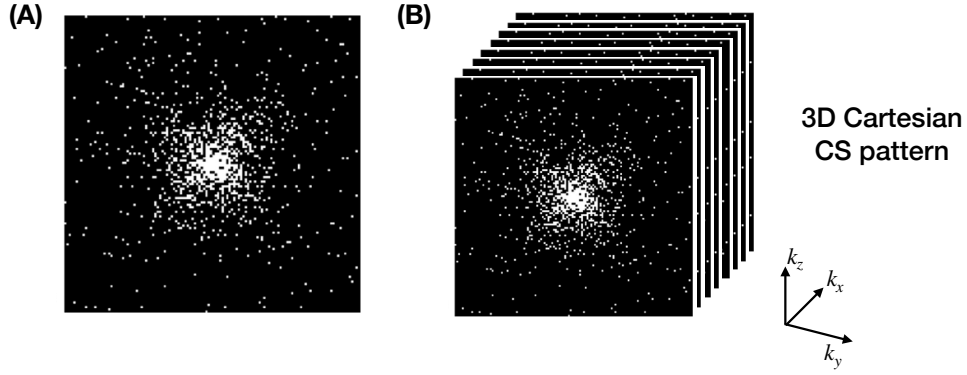


Figure 2.3. CS undersampling patterns ($u = 16$) used for CS-RARE Cartesian 3D imaging. (A) shows the pseudorandom phase encoding pattern along k_y and k_z with density weighted towards the center. (B) is the corresponding Cartesian 3D sampling trajectory fully sampled along k_x .

From the acquisition perspective, the most obvious option to improve SNR_{eff} is judicious selection of a subset of k-space samples for acquisition. Early efforts using this approach were in the constrained MRI regime [63], where sub-Nyquist samples are chosen based on spatial-support constraints [64] or multiband theory [65]. The evolution of compressed sensing (CS) theory [66, 67] enables the feasibility of accurate recovery of sparse signals from undersampled data. CS was first introduced to the MRI community via the ‘SparseMRI’ framework by Lustig *et al* [17]. The elements of CS-MRI encompass pseudorandom sampling patterns, sparsifying transform $\mathbf{W}$, and an algorithm with sparsity-promoting regularizers. By exploiting the wavelet domain sparsity, SparseMRI reconstructs ^1H anatomical images from undersampled k-space measurements, acquired with a commensurate time reduction. Since most critical information of an imaged object is encoded in the low-frequency Fourier domain, a density-weighted pseudorandom Cartesian undersampling pattern for phase encoded k-space lines can yield an accelerated scan speed of up to 8-fold in ^1H anatomical MRI [17]. The sparse MRI method has been extended to multi-coil parallel MRI [68], dynamic MRI [69, 70], and non-Cartesian k-space acquisitions [71, 72, 73].

It should be noted that sparsity is commonplace in the canonical spatial domain (meaning $\mathbf{W} = \mathbf{I}$) for some X-nuclei imaging modalities such as ^{23}Na [73] and ^{19}F [39, 19]. The sparsity

nature of the ^{19}F data therefore lends itself to the application of CS theory, which provides a framework for accurate recovery of sparse signals using undersampled k-space data. Specifically, for ^{19}F Cartesian MRI, CS has been combined with increased signal averaging to achieve image sensitivity improvements for inflammation imaging and cell tracking [8, 19], chemical-shift imaging [74, 75], as well as to enable motion artifact reduction [76]. In Zhong *et al.* [19], 3D ^{19}F CS-MRI was used to quantify *in vivo* macrophage burden in a wounding-inflammation rodent model following *in situ* labeling with PFC nanoemulsion. The study demonstrated 8-fold acceleration in image acquisition time using undersampled Cartesian k-space lines and CS reconstruction, all while maintaining accurate ^{19}F signal distribution with no loss in image SNR. A key use of ^{19}F CS-MRI is to improve the SNR_{eff} (or LOD) given a limited scan-time budget. Specifically, we consider the i^{th} copy of single-coil k-space (spatial frequency) ^{19}F measurements $\mathbf{y}_i \in \mathbb{C}^M$ as

$$\mathbf{y}_i = \mathbf{F}_u \mathbf{x}^* + \boldsymbol{\varepsilon}_i, \quad \mathbf{F}_u \in \mathbb{C}^{M \times N} \quad (2.5)$$

where $\mathbf{x}^*$ is approximately s -sparse in the transform domain $\mathbf{W}$ with $s \ll N$, possibly block-sparse. $\boldsymbol{\varepsilon}_i \in \mathbb{C}^M$ denotes the thermal noise term modeled as complex-valued white Gaussian noise (WGN) $\sim \mathcal{CN}(\mathbf{0}, \sigma^2 \mathbf{I})$ [77]. $\mathbf{F}_u$ is the forward measurement model encoding the sampling trajectory, which corresponds to an undersampled DFT operator in Cartesian CS-MRI. The operator $\mathbf{F}_u$ is a constrained sensing matrix with a unique structure stemming from MRI hardware limitations. It can be further decomposed into two elements, $\mathbf{F}_u = \mathbf{S}\mathbf{W}$, where $\mathbf{W}$ denotes the spatial Fourier transform operator and $\mathbf{S} = \{0, 1\}^{M \times N}$ is the row selection matrix that identifies the sample locations and is governed by pre-determined binary undersampling masks. For CS acquisitions

of factor $u = N/M$, we average the following u copies of measurements together

$$\begin{aligned} \mathbf{y}_1 &= \mathbf{F}_u \mathbf{x}^* + \boldsymbol{\varepsilon}_1 \\ \mathbf{y}_2 &= \mathbf{F}_u \mathbf{x}^* + \boldsymbol{\varepsilon}_2 \\ &\vdots \\ \mathbf{y}_u &= \mathbf{F}_u \mathbf{x}^* + \boldsymbol{\varepsilon}_u \end{aligned} \tag{2.6}$$

Undersampling of k-space allows one to accumulate u copies of signals, which are summed (“averaged”), in the same total scan time [76], *i.e.*,

$$\mathbf{y} := \frac{1}{u} \sum_{i=1}^u \mathbf{y}_i = \mathbf{F}_u \mathbf{x}^* + \frac{1}{u} \sum_{i=1}^u \boldsymbol{\varepsilon}_i \tag{2.7}$$

Clearly, this leads to an expected $\sim \sqrt{u}$ -fold SNR improvement due to suppression of the noise term, which is reminiscent of repetition coding in wireless communications [78]. It is also reported by Starke and colleagues [79] that CS enables a favorable trade-off between undersampling losses and SNR gain by averaging to detect weak ^{19}F signals close to the LOD.

In terms of CS 3D radial acquisitions, golden-means [80], and spiral phyllotaxis [81] schemes have been explored for undersampled radial data collection. These trajectories are integrated into UTE pulse sequences [82] in order to achieve higher acceleration capability while suppressing motion artifacts. On the implementation side, pulse sequences are programmed with pre-defined gradient amplitudes (G_x, G_y, G_z) , corresponding to radial angle views (θ, ψ) . We note that a power-efficient design should consider minimizing the gradient increments, since magnetic field gradient direction switching is more hardware intensive compared to sampling along each radial spoke. In particular, it has been shown that 3D radial Poisson disk sampling can outperform both golden-means and phyllotaxis due to its ability to push aliasing noise towards high frequencies [83]. On the other hand, the initial dead time of ZTE causes missing k-space points close to origin, which can be compensated by oversampling and an algebraic reconstruction

process [53], as detailed in section 3.2.2. By leveraging this trade-off between limited gradient (k-space) directions and oversampling along each spoke, we will show the CS-ZTE detection strategy [39] introduced in Chapter 3 can accelerate ^{19}F acquisitions by up to ~ 16 -fold, with commensurate undersampling, without producing noticeable artifacts.

Recovering the 2D/3D imaging object $\mathbf{x}$ from undersampled noise-corrupted measurement $\mathbf{y}$ is an ill-posed inverse problem. By regularizing the objective function with hand-crafted structural priors, the optimization problem is formulated as

$$\min_{\mathbf{x}} \|\mathbf{y} - \mathbf{F}_u \mathbf{x}\|_2^2 + \lambda \mathcal{R}(\mathbf{x}) \quad (2.8)$$

Here for non-Cartesian acquisitions, $\mathbf{F}_u$ is often approximated as a regridding operator that can interpolate non-Cartesian samples as a linear combination of its neighboring Cartesian points [84]. Alternatively, due to the Fourier slice theorem [85] in radial projection sampling, $\mathbf{F}_u$ can be modeled directly as Radon transform with a 1D FFT operator [86], which potentially leads to a more accurate forward operator modeling.

Regularizer $\mathcal{R}(\mathbf{x})$ is one or a combination of penalty terms enforcing the structural priors from $\mathbf{x}$. CS theory [66, 67] provides a theoretical foundation for accurate recovery of sparse signals using undersampled data. The sparsity can exist in the transform domain $\mathbf{W}$; for example, SparseMRI [17] utilizes wavelet-domain sparsity and finite difference sparsity in $\nabla \mathbf{x}$ (*i.e.*, total-variation, or TV), as ^1H anatomical MRI is not sparse in the spatial domain. The Lasso [87] framework, or ℓ_1 -norm, is known to promote sparsity (*e.g.*, through soft-thresholding for fully sampled data). As evident in section 3.2.2, a joint regularization of ℓ_1 and TV-norm [88], *i.e.*, $\mathcal{R}(\mathbf{x}) = \lambda_1 \|\mathbf{W}\mathbf{x}\|_1 + \lambda_2 \|\nabla \mathbf{x}\|_1$, is often a favorable choice for ^{19}F CS imaging due to its simultaneous denoising and edge-preservation features. Alternatively, the CS recovery problem can be converted into a matrix completion formulation with nuclear norm $\|\mathbf{x}\|_*$ [89, 90] to enforce the low-rank structure in the k-space data. Off-the-shelf solvers, for example, non-linear conjugate gradient [17], alternating directional method of multiplier (ADMM) [91], and primal-

dual [92] algorithms are common approaches for solving (2.8). The problem automatically reduces to denoising when $\mathbf{F}_u = \mathbf{I}$.

The regularization parameters λ_1 and λ_2 control the amount of penalization applied, and thus (λ_1, λ_2) should be chosen with consideration of the sparsity of the image signal pattern of the subject, the practical resolution achievable, and the noise level. In practice, a data-driven Pareto frontier curve is deployed to search for the optimal trade-off, as detailed in section 3.3.6. Another option is to automatically control the regularization strength by following Morozov’s discrepancy principle [79]. More recently, post-processing resampling methods have been incorporated to reduce the spike artifacts in CS ^{19}F CSI data [75]. This approach is inspired from bootstrapping in statistics, and it does not require additional data acquisitions for visible SNR improvement.

2.4 Theoretical Modeling of Acquisition-Reconstruction Pipeline

In silico modeling provides insights into the performance characteristics of acquisition-reconstruction pipelines involving accelerated pulse sequences and CS reconstruction. The objectives of such simulations encompass validating the co-design pipeline, as well as error quantification. The modeling results can provide a quality assurance measure for envisioned *in vivo* experiments. A sufficient condition for the success of CS sparse signal recovery is the incoherence of the undersampling patterns, which is related to the mathematical condition called the restricted isometry property (RIP) [18]. Due to the highly structured Fourier encodings in the forward sensing operator $\mathbf{F}_u$, it is difficult to satisfy RIP in MRI applications [93]. Alternatively, the point spread functions (PSF) represents a tool to characterize the incoherence of an imaging system empirically [94], enabling both qualitative and quantitative measures of k-space sampling

patterns. PSF is defined as

$$PSF(i, j) = \mathbf{e}_j^H \mathbf{F}_u^H \mathbf{F}_u \mathbf{e}_i \quad (2.9)$$

where $\mathbf{e}_i$ denotes the i^{th} vector of the canonical basis. The PSF of an ideal imaging system is a delta impulse function. The effects of undersampling manifest as convolution between the neighboring pixels, which broadens the delta peak and produces non-zero values off-center, called side-lobes. Specifically, the maximum side-lobe-to-peak ratio (SPR) serves as a simple measure for incoherence

$$SPR = \max_{i \neq j} |PSF(i, j) / PSF(i, i)| \quad (2.10)$$

where a larger SPR indicates more incoherence and less aliasing artifacts [17]. The full width at half maximum (FWHM), defined as the width of the peak measured at 50% of its maximum height, is a metric of resolution change across different undersampling levels [76]. A narrow FWHM implies greater ability to resolve detailed structures with minimal blurring artifacts. Simulations of PSFs have been investigated to analyze CS sampling patterns for both ^{19}F Cartesian [76] and radial trajectories [39], and they are especially useful for guiding the choice of undersampling factor u . For example, as we will see in Section 3.3.2, streaking artifacts caused by aliasing become more pronounced as undersampling level increases and finally spread across the center. This suggests an intermediate u -factor (4 or 8) is preferable to maintain a balance between reliable reconstruction and SNR efficiency.

Prior to testing on real prospective CS data, the reconstruction algorithm (Eq. 2.8) can also be validated via synthetic ^{19}F data. A convenient way to simulate CS k-space data is to perform retrospective undersampling of a prior (real) fully-sampled data by selective editing of the k-space lines for the desired sampling pattern prior to reconstruction [74, 75, 79, 95]. However, this approach is limited to Cartesian k-space data; for non-Cartesian radial acquisitions,

the newly designed undersampling pattern may not necessarily belong to a subset of the fully sampled trajectory as the spherical endpoints are drawn randomly by an algorithm [39]. Moreover, the fully-sampled dataset determines the noise level in the retrospective CS data and therefore may not be suitable to perform quantitative error analysis systematically.

Another approach is to simulate ground truth (noise-free) synthetic signal images $\mathbf{x}$ from contrived intensity distributions resembling ^{19}F signals [96, 75, 97] or by using previously acquired high SNR phantom data as a template [39]. Next, noise-free k-space data is generated through multiplying $\mathbf{x}$ with CS forward operator $\mathbf{F}_u$, without any constraints on the undersampling patterns. Depending on the noise levels investigated, complex Gaussian noise with different variances is added to mimic ^{19}F imaging experiments. This type of modeling provides a launch point for gaining insights into how noise affects the image appearance and ^{19}F quantification error. Due to the non-linearity induced by the iterative algorithms, noise residuals in the CS reconstructed images obtained by solving Eq. 2.8 do not follow a closed-form distribution such as Rayleigh distribution [41]. However, the Pareto frontier curve method can be employed to search for regularization parameters. As we will show in section 3.2.4, the ℓ_2 -reconstruction error of the joint ℓ_1 -TV-norm can be upper-bounded by the well characterized Lasso error [98] with the certain restraint imposed on λ_1 . Simulation of template images in Chapter 3 suggests that joint CS pulse sequence and reconstruction algorithm design lessens constraints on choice of (λ_1, λ_2) to reach the minimal ℓ_2 -error and therefore is preferred compared to simply denoising with fully sampled dataset [39].

When testing newly designed pulse sequences, phantom MRI experiments can play a steppingstone in transitioning from synthetic data simulations to in vivo imaging experiments. ^{19}F phantoms are typically constructed with a series of calibrated F-reference materials packaged in vessels [39, 19, 76, 99]. Well-defined regions of interest with known signal intensity ratios can be readily identified from the output image and can be used for validating F-spin quantifications [39, 19] and assessing LOD [39, 99]. Furthermore, phantom data can be used with conventional image quality metrics, such as peak signal-to-noise ratio (PSNR), root-mean-square error (RMSE), root-

mean-square deviation (RMSD), structural similarity index (SSIM) [100] and Dice similarity coefficient (DSC) [101]; all of these calculations require a ‘ground truth’ reference image, which is knowable for phantoms, but is generally inaccessible for *in vivo* scenarios. For high SNR ^{19}F phantom fully-sampled data acquired at high SNR, the ground truth reference image can be approximated by a simple masking segmentation technique [76].

Calculating reference image-based metrics for CS-acquired images enable comprehensive evaluations on the joint sensing reconstruction design. From CS phantom results in Section 3.3.1, the SNR was observed to be sensitive to changes in regularization parameters (3.1). The SNR alone may not reflect CS’s true ability to preserve the image features and resolution [76], since acquisitions at high u -factors ($u > 8$) tend to produce over-smoothing effects. However, use of PSNR provides a complementary performance measure of the maximum achievable level of undersampling due to its ability to capture the reconstruction accuracy. In another example, PSNR analysis (Section 3.3.5) also reveals that tuning λ_1 and λ_2 using Pareto frontier curves does not naively favor increasing λ_2 at low SNR and provides insight into the choice of sparsity level (*e.g.*, image field of view at fixed matrix size).

Additionally, statistical measures such as signal-level-specific true positive rates (TPRs) and false discovery rates (FDRs) can be utilized to measure detection sensitivity and fidelity performance [79]. Importantly, it has been shown that TPRs for CS reconstructions were consistently superior to other reconstructions at low signal levels [79]. Qualitatively, rendering intensity data as histograms to display raw signal and noise provide an intuitive visualization of their separability and overall performance of the reconstruction pipeline [39], as also manifested in Section 3.3. Moreover, task-specific metrics, such as DSC, are helpful for evaluating the motion artifact reduction in ^{19}F CS frameworks [76].

2.5 Conclusions

Overall, ^{19}F MRI cell tracking using PFC tracer agents is a rapidly emerging alternative to ^1H -based approaches using metal-ion-based contrast agents. Future improvements in sensitivity and functionality of ^{19}F -based cell tracking will require an integrated and interdisciplinary approach that rigorously applies principles of chemistry, biology, spin physics, and signal image processing. Our view is that these technical undertakings are worthwhile, as work in this field to date has shown that this sub-field of MRI cell tracking can produce unique information about cellular processes *in vivo* in a diverse range of applications. Importantly, the materials and methods for sensitivity enhancement described above and the use of co-designed pulse sequences and reconstruction methods can be simultaneously integrated into future clinical studies to enable multi-pronged enhancement of cell detection. In the next chapter, we will see that $> 30\times$ improvement in the LOD over ‘first-generation’ tracers is readily achievable and will enable unprecedented precision in cell tracking and other ^{19}F MRI applications under this measurement-reconstruction co-design paradigm.

2.6 Acknowledgements

Chapter 2, in part, is a reprint of material in submission as:

- J. Chen, P. Pal, E. T. Ahrens, “Systems engineering approach towards sensitive cellular fluorine-19 MRI” (Journal paper under preparation).

The dissertation author was the primary investigator and author of the paper. We thank Dr. Amy Schwartz for critical reading of the manuscript.

Chapter 3

Enhanced Detection of Paramagnetic Fluorine-19 MRI via Compressed Sensing Zero Echo Time (CS-ZTE)

In this chapter, we describe a compressed sampling (CS) scheme, implemented using a ‘zero’ echo time (ZTE) sequence, with data reconstructed via a sparsity-promoting algorithm. Our CS-ZTE scheme acquires k-space data using an undersampled spherical radial pattern and signal averaging. Image reconstruction employs off-the-shelf sparse solvers to solve a joint total variation (TV) and ℓ_1 -norm regularized least square problem. To evaluate CS-ZTE, we performed simulations and acquired ^{19}F MRI data at 11.7 T in phantoms and mice receiving MPFC-labeled dendritic cells. For MPFC-labeled cells in vivo, we show SNR gains of 6.3 $\times$ with 8-fold undersampling. We show that this enhancement is due to three mechanisms including undersampling and commensurate increase in signal averaging in a fixed scan time, denoising attributes from the CS algorithm and paramagnetic reduction of T_1 . Importantly, ^{19}F image intensity analyses yield accurate estimates of absolute quantification of ^{19}F spins. Overall, the CS-ZTE method using MPFC probes achieves ultrafast imaging, a substantial boost in detection sensitivity, accurate ^{19}F spin quantification and minimal image artifacts.

3.1 Introduction

Fluorine-19 MRI is an emerging technique offering specific detection of labeled cells *in vivo*. Lengthy acquisition times and modest signal-to-noise ratio (SNR) makes 3D spin-density weighted ^{19}F imaging challenging. Recent advances in tracer paramagnetic metallo-perfluorocarbon (MPFC) nanoemulsion probes have shown multifold SNR improvements due to an accelerated ^{19}F T_1 relaxation rate and a commensurate gain in imaging speed and averages. However, ^{19}F T_2 -reduction and increased linewidth limit the amount of metal additive in MPFC probes, thus constraining the ultimate SNR, as described in Chapter 2.

The ‘zero’ echo time (ZTE) pulse sequence is based on a non-selective excitation, constant gradients and 3D center-out radial acquisitions [102]. Similar to ultrashort echo-time (UTE), ZTE is also a variant of a pulse-acquire free induction decay (FID) pulse sequence, where the readouts cover half of the k-space diameter. ZTE has desirable properties such as sensitivity to ultra-short T_2 materials, robustness against off-resonances, and silent and fast operation [53, 56, 103]. With the goal of improving ^{19}F MRI detection, we combine the ZTE sequence with CS. CS-ZTE acquires k-space data using a spherical radial CS pattern with ultrashort acquisition periods, which is repeated multiple times. The repeated copies of independent compressed measurements are averaged to boost image quality. Reconstructing the denoised image from these time-averaged compressive measurements is an ill-posed inverse problem. Hence, we exploit the natured sparsity of ^{19}F images as an effective prior to regularize the inverse problem and recover the ground truth. Our reconstruction algorithm involves modifying off-the-shelf sparse solvers for time-averaged CS-ZTE measurements to solve a joint total variation (TV)- ℓ_1 -norm regularized least square problem, with regularization parameters chosen using a Pareto frontier curve in a data-driven fashion. The performance with respect to both SNR and peak-signal-to-noise ratio (PSNR) were evaluated using data simulation. Data were also acquired using ^{19}F MRI in phantoms and live mice that received MPFC-labeled dendritic cell injections. We also explored the impact of varying intravoxel ^{19}F spin density and spatial sparsity, as well

as the ^{19}F spin limits of detection (LOD) on a high-field scanner (11.7 T).

Overall, the combination of three mechanisms, including signal averaging of multiple copies of compressive measurements, denoising effects from the compatibility of the algorithm with ^{19}F image’s natural sparsity, and PRE effects in MPFC, collectively yield striking image detectability enhancements. The CS-ZTE ^{19}F method may be suitable for a range of multi-nuclear MRI applications.

3.2 Methods

3.2.1 CS-ZTE k-space and pulse sequence design

ZTE utilizes a 3D radial center-out trajectory k-space pattern defined by a sphere (k, θ, ψ) , where k denotes length of radius and (θ, ψ) represent angular directions; the spokes resemble a “koosh-ball” [104]. One must satisfy the Nyquist sampling criterion to avoid aliasing, thus a minimum number of $\pi \cdot N^2$ readouts with regularly spaced directions are required for a 3D radial trajectory [85], where N is the image matrix size along each dimension. To accelerate ZTE acquisitions, we undersample in angular directions. Magnetic field gradient switching to obtain a large (θ, ψ) increment is potentially hardware intensive, compared to sampling along each spoke. Thus, judicious selection of the (θ, ψ) steps is necessary to minimize gradient increment and eddy currents [105]. The 3D radial sampling pattern is constructed by projections with endpoints on a sphere surface. Poisson disk sampling displays spectral properties that push aliasing noise towards high frequencies [106]. For arbitrary dimension Cartesian grids, Poisson disk sampling points can be generated by randomly choosing an initial sample point and selecting points from its neighbors, guaranteeing a minimum distance limit between samples [107]. The Poisson disk scheme can be applied to non-Cartesian space, for example to draw random points on a 3D spherical surface [83]. This yields a greater incoherent aliasing pattern than other spherical point picking methods, such as 3D golden means [80] and spiral phyllotaxis [108], for 3D radial trajectory reconstructions.

CS-ZTE was implemented on an 11.7 T MRI scanner (BioSpec, Bruker BioSpin, Billerica, MA), equipped with ParaVision 6.0.1 software, a 40 mm dual-tuned $^1\text{H}/^{19}\text{F}$ bird cage resonator and 750 mT/m gradients. Offline, we first generated (θ, ψ) angular sampling patterns on sphere surface, distributed in a Poisson disk fashion (Figure 3.1 A,C). In this manner, the sequence acquired k-space radial data with an undersampling factor, denoted u , varying from 1 (fully sampled), 2, 4, 8, 16, and 32. The radial trajectory is naturally density weighted with respect to the inverse of radius, which is similar to the incoherent pseudorandom sampling patterns widely applied in CS Cartesian MRI [17, 19]. Examples of sampling patterns are displayed in Figure 3.1 B, D. The surface endpoints were then transformed into a gradient table that controls the gradients (G_x, G_y, G_z) used for MRI acquisitions using the manufacture’s ZTE pulse sequence. For a fixed scan time with $u > 1$, acquisitions with the set of undersampling points were implicitly averaged u times.

3.2.2 Reconstruction pipeline

Our CS-ZTE reconstruction pipeline is divided into two steps, including preprocessing in the k-space domain and sparsity-promoting regularized reconstruction. For imaging experiments with fixed scan time, preprocessing begins with averaging of the u repeated acquisitions along the same radial line, followed by an algebraic encoding process [109, 53, 56]. Due to the receiver dead time following the radio frequency (RF) transmitter pulse, there are initial data gaps close to $k = 0$ in raw k-space data [57] where low frequency image information is encoded. Oversampling along each radial projection enables recovery of the missing points in the data gap. Specifically, we compute the pseudoinverse $\mathbf{F}$ of the corresponding harmonic encoding matrix $\mathbf{E}_{m,j}^{(\pm)} = \exp(\pm i\gamma t_m G r_j)$, whose exponential entries are defined by the gyromagnetic ratio γ , sampling time t_m , gradient strength G , and the image grid r_j within the 1D FOV. We denote the averaged u copies k-space raw data as $\mathbf{s}$. By multiplying $\mathbf{F}$ with raw k-space data, a projection image corresponding to each radial spoke is obtained. The 1D image space data is then transformed back to k-space by multiplying with a discrete Fourier Transform (DFT)

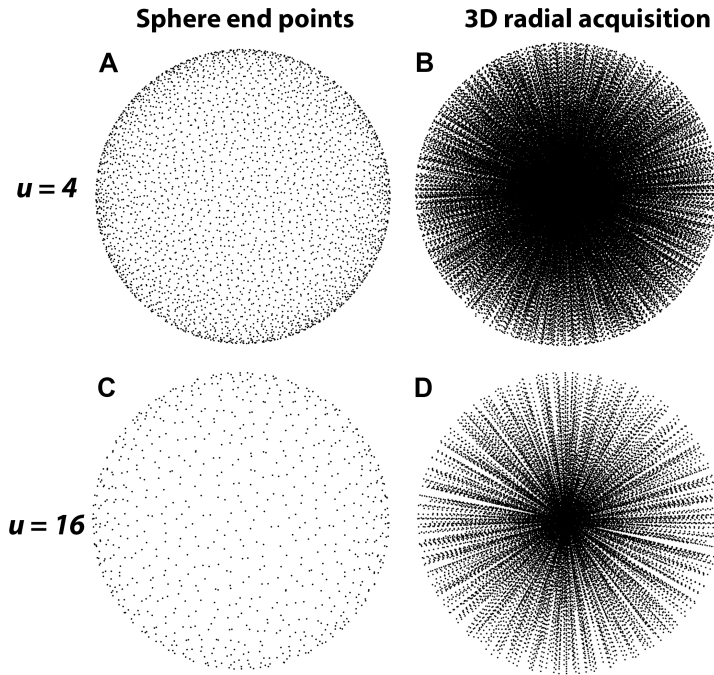


Figure 3.1. Spherical sampling of radial trajectory generated by Poisson disk point selection. The patterns are based on acquisition of a 3D image with size 64^3 . Panel (A) displays 1628 end points with $u = 4$, and (B) displays the corresponding 3D radial acquisition. Panels (C) and (D) show the same perspectives for 407 end points with $u = 16$. Here, undersampling is in angular directions, with full sampling along radial directions.

matrix $\mathbf{W}$. The overall algebraic reconstruction matrix $\mathbf{A}_r$ is a block diagonal matrix with $\mathbf{W} \cdot \mathbf{F}$ on the main diagonal. Thus, we denote the algebraic reconstructed k-space data as $\mathbf{y} = \mathbf{A}_r \mathbf{s}$. Preprocessed k-space data $\mathbf{y}$ are normalized by the maximum absolute intensity to maintain consistency across different u . Details regarding CS-ZTE measurement model are presented in Appendix A (section 3.6.1). The code for the algebraic reconstruction was written in MATLAB software (R2019a, MathWorks, Natick, MA).

Since the 3D radial sampling points are non-Cartesian, the nonuniform fast Fourier transform (NUFFT) [84] package is used to generate the forward operator $\mathbf{F}_u$, whose row index is determined by u . The NUFFT operation is based on a min-max interpolator that can approximate non-Cartesian samples as a linear combination of its neighboring Cartesian points. To enforce sparsity, while enabling denoising without sacrificing important details in the reconstructed ^{19}F image, both ℓ_1 -norm and first-order discrete gradient (i.e., ℓ_1 -norm of ∇ , where ∇ is the finite difference operator, also known as TV-norm) terms are added as regularizers, yielding the following optimization problem [39]

$$\min_{\mathbf{f} \in \mathbb{C}^{N^3}} \|\mathbf{y} - \mathbf{F}_u \mathbf{f}\|_2^2 + \lambda_1 \|\mathbf{f}\|_1 + \lambda_2 \|\nabla \mathbf{f}\|_1 \quad (3.1)$$

Here $\mathbf{y} = \frac{1}{C_u} \sum_{i=1}^u \mathbf{y}_i$ is the preprocessed k-space data, where C_u is a normalization constant that is linearly proportional to the u -factor, $\mathbf{y}_i$, where $i = 1, \dots, u$ denote the repeated copies of algebraic reconstructed k-space data, and $\mathbf{f}$ is the vectorized 3D ^{19}F image. The regularization parameters λ_1 and λ_2 control the amount of penalization applied, and $\|\nabla \mathbf{f}\|_1$ represents a 3D anisotropic total variation semi-norm. In practice, we tune λ_1 and λ_2 by means of a Pareto frontier curve [110, 111] as follows. We first set $\lambda_2 = 0$ (ignoring the TV regularization) and let λ_1 assume values from the following list: $(10^{-5}, 4 \times 10^{-4}, 5 \times 10^{-3}, 0.01, 0.02, 0.04, 0.06, 0.08, 0.1, 0.2, 0.4, 0.6, 0.8, 1)$. We then select the value of λ_1 that corresponds to the knee point of the Pareto curve. After tuning the value of λ_1 , the same procedure is repeated for λ_2 by retaining the value of λ_1 obtained from the first step. The optimization problem defined in (3.1) is solved by modifying

the SparseMRI software package [17], where a nonlinear conjugate gradient descent algorithm, with backtracking line search, is introduced. The NUFFT operator $\mathbf{F}_u$ is changed with the image size and input radial sampling trajectories. For the corresponding min-max NUFFT operator, we fix the number of neighboring voxels [84] to be 6 and the oversampling ratio to be 2 isotopically for the interpolator specifications. It should be noted that ^{19}F signal is naturally sparse in the image domain. As a result, the sparsifying transform is simply an identity matrix.

3.2.3 Noise simulation studies using synthetic ^{19}F data

To verify the feasibility of 3D radial undersampling and the reconstruction pipeline, we computationally simulated ^{19}F CS-ZTE datasets with different u and noise levels. An arbitrary *in vivo* ^{19}F 3D image derived from an inflammation model [19] was heavily thresholded and segmented to obtain a noise-free 3D image $\mathbf{f}^*$, which serves as a sparse image template. The NUFFT forward operators $\mathbf{F}_u$ were generated based on our spherical Poisson disk trajectories, with u ranging from 1 to 32, and these were used to transform the image to k-space data. To observe the effect of algebraic encoding, k-space data were oversampled and the initial data gap was included. Complex white Gaussian noise, with standard deviations (denoted as σ) 0.5 and 2 was added to the normalized k-space data, yielding image SNRs of 20 and 5, respectively. Here, $\sigma = 0.5$ represents moderate noise, whereas $\sigma = 2$ would be more typical of the low SNR ^{19}F images encountered. To mimic signal averaging, this process was repeated u times. The simulated CS-ZTE data was first algebraically reconstructed, and then (3.1) was solved by the reconstruction pipeline using the modified SparseMRI package, as described above. To account for the randomness of the noise, twenty datasets were generated for each u and reconstructed with (λ_1, λ_2) tuned by the Pareto curve. Additionally, we examined the Bruker-supplied ZTE gridding reconstruction as a baseline.

3.2.4 Simulation of regularization parameters

To tune the regularization parameters λ_1 and λ_2 for our joint reconstruction algorithm in (3.1), we focused on the so-called minimal points of the optimization problem where the corresponding regularization parameters give the optimal trade-offs among the objectives [112]. This is referred to as Pareto optimal analysis, which has been exploited for the selection of the regularization parameter λ in the standard Lasso problem with only ℓ_1 -norm regularizers [111]. In these studies, the Pareto optimum λ is identified from the knee of the Pareto frontier curve. For ease of notation, we replace $\mathbf{F}_u$ with operator Φ . Note that (3.1) can be decoupled as $L(\hat{\mathbf{f}}) + \lambda_2 \|\nabla \hat{\mathbf{f}}\|$, where $L(\hat{\mathbf{f}}) = \|\mathbf{y} - \Phi \hat{\mathbf{f}}\|_2^2 + \lambda_1 \|\hat{\mathbf{f}}\|_1$ is the classic Lasso problem. We evaluate the expected reconstruction error with choice of (λ_1, λ_2) . Results using the classic Lasso method provide reconstruction guarantees for the associated model $\mathbf{y} = \Phi \mathbf{f}^* + \mathbf{w}$, where $\mathbf{w}$ is the additive noise and $\mathbf{f}^*$ is the unknown signal to be reconstructed. Standard analysis of the Lasso problem assumes that $\mathbf{f}^*$ is s -sparse (*i.e.*, number of non-zeros in $\mathbf{f}^*$), with indices of non-zero elements of $\mathbf{f}$ being given by the set $S \subset [1, p]$, $\|S\|_0 = s$. Following equation 11.10 in Hastie *et al.* [98], we define κ as

$$\kappa = \arg \min_{\Delta} \frac{\|\Phi \Delta\|_2^2}{\|\Delta\|_2^2}, \quad \text{s.t. } \Delta \in \mathcal{C}(S; 3) := \{\Delta \in \mathbb{R}^p, \Delta \neq \mathbf{0} \mid \|\Delta_{S^c}\|_1 \leq 3\|\Delta_S\|_1\} \quad (3.2)$$

The quantity κ is known as the restricted eigenvalue (RE) of Φ , which is an adapted version of the RIP constant [18] in classical CS theory that measures incoherence. According to Theorem 11.1 in Hastie *et al.* [98], if $\kappa > 0$ and λ_1 is chosen such that $\lambda_1 \geq 2\|\Phi^H \mathbf{w}\|_\infty$, then the minimizer $\hat{\mathbf{f}}'$ of the classic unconstrained Lasso problem satisfies

$$\|\hat{\mathbf{f}}' - \mathbf{f}^*\|_2 \leq \frac{3}{\kappa} \sqrt{s} \lambda_1 \quad (3.3)$$

This guarantee also provides guidance on the choice of λ_1 . If we set the regularization parameter to be larger than the above threshold (which depends on noise $\mathbf{w}$), then the ℓ_2 -error of the Lasso

problem can be deterministically upper-bounded by the RE κ , sparsity s , and λ_1 (Eq. 3.3).

Having determined the choice of λ_1 , we then obtained the Pareto curve by plotting $L(\hat{\mathbf{f}})$ (for a fixed λ_1) versus $\|\nabla \hat{\mathbf{f}}\|$ and chose the value of λ_2 corresponding to the knee point of this curve. To illustrate this, a noise-free 3D synthetic ^{19}F phantom image with size 64^3 was generated with sparsity levels $s = 1030, 4121$ and transformed to CS-ZTE acquisitions with u ranging from 1 to 16. Complex-valued white noise was added to the k-space data with $\sigma = 0.1, 0.4$ after data normalization. Simulations were performed with $\lambda_1^* = 2\|\Phi^H \mathbf{w}\|_\infty$ and by setting λ_2 from 0 to 10; the optimum λ_2^* was picked from the regularization parameter pair located at the knee of $L(\mathbf{f})$ versus $\|\nabla \hat{\mathbf{f}}\|$. To verify that $\|\hat{\mathbf{f}} - \mathbf{f}^*\|_2$ is indeed minimal with the λ_2^* choice, we plotted $\|\hat{\mathbf{f}} - \mathbf{f}^*\|_2$ with respect to the λ_2 values tested.

3.2.5 Experimental phantom studies

Three different phantoms were prepared and corresponding ^{19}F phantom images were acquired using CS-ZTE with the calculated trajectories. Phantom 1 was a 50 mL conical tube containing five agarose-embedded 5 mm NMR tubes, each with 1 mL sodium trifluoroacetate (TFA) in $\text{H}_2\text{O}/\text{D}_2\text{O} = 9/1$, with percent concentrations of 5%, 10%, 15%, 20% and 30% (corresponding to ^{19}F concentrations of 1.1, 2.2, 3.3, 4.4 and 6.6 Molar). We performed two sets of CS-ZTE scans for Phantom 1. For the first set, images were acquired using matrix size $64 \times 64 \times 64$ only with u ranging from 1 to 16 (*i.e.*, the number of averages (NA) scaled with u , and ranged from $NA = 1$ to 16) with a fixed scan time of 13 s, field of view (FOV, cm units) = $50 \times 50 \times 50$, bandwidth (BW) = 100 kHz, repetition time (TR) 1 ms, and flip angle $\alpha = 1^\circ$. For the second set, to further investigate the sensitivity of CS-ZTE (particularly with $u \geq 2$), we varied FOV from $3.6 \times 3.6 \times 3.6$ cm, $4.8 \times 4.8 \times 4.8$ cm, and $6 \times 6 \times 6$ cm to alter image sparsity; to maintain the same resolution across FOVs, matrix sizes were varied from $48 \times 48 \times 48$, $64 \times 64 \times 64$ to $80 \times 80 \times 80$, respectively, with a fixed scan time of 2 min. We note that Phantom 1 serves as a baseline experiment to test the efficiency of CS-ZTE alone, thus the imaging parameters were not optimized as the signal was concentrated in this phantom.

Phantom 2 was prepared with three 2 mm NMR tubes containing serial dilutions of 100%, 50%, 25% (i.e., ^{19}F concentrations of 2.7, 1.35 and 0.68 Molar) of PFC nanoemulsion (perfluoro-15-crown-5-ether, $T_1 = 685$ ms at 11.7 T, ~ 160 nm mean diameter droplet size, 20% v/v). The PFC images were acquired using 3D FLASH (fast low angle shot) with minimum echo time (TE) 2 ms, TR=50 ms, FOV = $3 \times 3 \times 3$ cm, matrix size $64 \times 64 \times 64$, $BW = 50$ kHz, $NA = 1$, and $\alpha = 22^\circ$ (Ernst angle). The choice of TR is to constrain scanning time, and the minimum TE and Ernst angle were set to optimize the GRE sequence acquisition.

Phantom 3 was comprised of three embedded tubes containing dilutions of 100%, 50%, 25% (same ^{19}F concentrations as Phantom 2) of MPFC nanoemulsion. The chemical synthesis and characterization of the MPFC nanoemulsion harboring metal chelate (“SALTAME”) is described in elaborate detail in Jahromi *et al.* [113]; and the PFC nanoemulsion formulation used in Phantom 2 used similar formulation methods, but without metal additive. The MPFC had T_1 and T_2^* values of 7 ms and 1.5 ms, respectively, at 11.7 T. Datasets were acquired using both Bruker ZTE and CS-ZTE with parameters: FOV = $3 \times 3 \times 3$ cm, matrix size $64 \times 64 \times 64$, TR=1.6 ms, $BW = 60$ kHz, pulse duration = $10 \mu\text{s}$, dead time = $16 \mu\text{s}$, readout duration = 0.53 ms, $NA = 10$, and $\alpha = 10^\circ$; except with CS-ZTE $u = 8$ ($NA = 80$). All the datasets for both Phantoms 2 and 3 were acquired with the same scan time of 3 min 30 s.

3.2.6 *In vivo* animal studies

For ^{19}F cell labeling, a fetal skin-derived dendritic cell (FSDC) line [7] was cultured in Roswell Park Memorial Institute (RPMI) medium supplemented with 10% (v/v) fetal bovine serum overnight in an incubator at 37°C , 5% CO_2 . PFC or MPFC nanoemulsion [113] at 2.5 mg/mL was added to the culture and co-incubated for four hours. Excess nanoemulsion not taken up by FSDCs was removed by a ($3\times$) wash with phosphate-buffered saline, and cells were detached by trypsinization and counted using Countess II FL Cell Counter (Life Technologies, Carlsbad, CA). To estimate ^{19}F uptake, cells were pelleted and resuspended in $100 \mu\text{L}$ of lysis buffer (0.5% Triton X-100 mM NaCl, 20 mM Tris). The solution was transferred to a 5 mm

NMR tube and mixed with 100 μL of 0.1 wt% TFA/D₂O reference compound. The intracellular ¹⁹F uptake was estimated from ¹⁹F NMR peak integration measurements at -91.8 ppm and -76 ppm for the nanoemulsion and TFA, respectively, using a 9.4 T spectrometer (Bruker Ascend 400).

All animal experiments followed protocols that were approved by University of California San Diego’s Institutional Animal Care and Use Committee (IACUC). FSDCs, labeled with either PFC or MPFC, were injected into the left and right footpad (5×10^6 cells per side), respectively, of female, 6-8 week, C57BL/6 mice ($N = 3$, Jackson Laboratory, Bar Harbor, ME). Mice were anesthetized with Isoflurane anesthesia in air, placed on a heated pad, and scanned at 11.7 T approximately one hour after injection. Three-dimensional ¹⁹F images were acquired using a fixed scan time of 10 min for both CS-ZTE ($u = 1$ and $u = 8$) and FLASH sequences with FOV = $6 \times 6 \times 6$ cm and matrix size = $64 \times 64 \times 64$. For CS-ZTE, the $u = 8$ acquisition used $NA = 240$, and the remaining parameters were the same as for Phantom 3. The FLASH data were acquired using $NA = 3$ and the same optimized parameters used in Phantom 2. Additionally, for anatomical reference, ¹H images were acquired using a two-dimensional RARE (rapid acquisition with relaxation enhancement) sequence with TE/TR = 23/2500 ms, FOV = 6×6 cm, 384×384 matrix, $NA = 4$, RARE factor of 8, and 0.47 mm thick slices. In order to perform ¹⁹F/¹H image slice overlays, the ¹⁹F image data was interpolated to yield the same slice thickness as the ¹H. For display purposes, the ¹⁹F image data were rendered in hot-iron pseudo-color using VivoQuant software (2020, Invicro, Boston, MA) and overlaid onto the greyscale ¹H image.

3.2.7 CS-ZTE sampling and reconstruction quality quantification

To evaluate the impact of radial undersampling, simulations of point spread functions (PSFs) were conducted. For the generated 3D radial undersampling trajectories with $u = 1, 2, 4, 8, 16, 32$, PSFs were calculated using a conventional gridding method (without CS algorithm). At each u , the side-lobe-to-peak ratio (SPR) and full width at half maximum (FWHM) were investigated for the output PSF. Maximum SPR is a simple measure to assess the incoher-

ence [17], whereas FWHM is a measure of resolution changes across different undersampling levels. The obtained PSFs are 3D, and the central 2D slice was extracted for display purposes.

Reconstructed images were evaluated using both SNR and PSNR metrics. Prior to further analysis, all the imaging data presented were reconstructed with Eq. 3.1 using (λ_1, λ_2) tuned by the Pareto frontier curve method. Normalization was performed on the reconstructed image $\mathbf{f}_{rec}$ according to the highest signal intensity. The image SNR was estimated using the average ^{19}F signal intensity in a region of interest (ROI) free of partial voluming divided by the standard deviation of background noise intensity in a second ROI. We note that the total scan time was kept constant for datasets acquired in the same study, thus, $SNR/\sqrt{t}$ is equivalent to the measured SNR.

The definition of PSNR (in dB) is as follows

$$PSNR = 20\log_{10} \left(\frac{MAX_{\mathbf{f}^*}}{NRMSE(\mathbf{f}^*, \mathbf{f}_{rec})} \right) \quad (3.4)$$

where $\mathbf{f}^*$ is the ground truth image, $MAX_{\mathbf{f}^*}$ is the maximum signal intensity value of the voxel ($MAX_{\mathbf{f}^*} = 1$ due to the above normalization), and normalized RMSE is defined as

$$NRMSE = \sqrt{\frac{1}{mnp} \sum_{i=1}^m \sum_{j=1}^n \sum_{k=1}^p [\mathbf{f}^*(i, j, k) - \mathbf{f}_{rec}(i, j, k)]^2} \quad (3.5)$$

where $\mathbf{f}^*(i, j, k)$ is the corresponding (i, j, k) voxel of either the entire image or within a 3D ROI containing ^{19}F signals. To investigate CS-ZTE's sensitivity to regularization parameters, for Phantom 1, reconstructions for CS-ZTE were performed via different combinations of λ_1 and λ_2 within the range of $[0, 1]$. We normalized the intensity of each tube by the intensity value of the tube with the highest concentration. To evaluate the PSNR, additional Phantom 1 reference image data were acquired using a conventional ZTE sequence with a high number of averages ($NA = 32$), and the output image served as the ground truth. Calculated PSNRs were rendered in colormap and graphed with respect to (λ_1, λ_2) . For the chosen Pareto-optimal pair, a linear

regression (OriginLab, Northampton, MA, USA) was performed by fitting averaged intensities of each concentration across five u values, and the slope was compared to the theoretical linear change with ^{19}F concentration.

In Phantoms 2 and 3 we assessed the limit of detection (LOD), which is defined as the ^{19}F atom count per voxel to an (extrapolated) $\text{SNR}=2.5$ threshold [1]. To assess the LOD, the results were plotted as SNR versus ^{19}F content measured for each sample tube and a linear fit was performed, and the coefficient of determination (R^2) was also calculated. For the 3D *in vivo* image, quantification was performed using VivoQuant software. We defined a 3D signal ROI with 109 voxels encompassing each footpad (*i.e.*, the injection site), and ROI ^{19}F signal data were exported and rendered in histograms using MATLAB. Similarly, noise ROI were defined in regions containing 152 voxels distant from ^{19}F signal. Here, we omitted the PSNR quantification for *in vivo* ^{19}F imaging, as the ground truth image is unknowable due to the intrinsically low signal intensity and arbitrary spatial distribution.

3.3 Results

3.3.1 CS-ZTE simulation study

Simulations on synthetic ^{19}F data show that significant signal sensitivity enhancement is possible by using CS-ZTE when off-the-shelf solvers such as SparseMRI are employed. An arbitrary, noise-free sparse image is depicted in Figure 3.2A. As displayed on Figure 3.2B, F, the vendor-supplied ZTE gridding method fails to preserve the signal features, where signals are hidden in the background noise. Reconstruction of conventional ZTE ($u = 1$) data using the algorithm of (3.1) shows noticeable noise reduction (Figures 3.2C, G), and the measured SNR can be significantly improved by increasing u (Figures 3.2D, H, $u = 8$). A further increase in u does not achieve substantial visual improvement, and the hot-spots appear to be overly smooth and spurious false-positive signals are generated close to the objects' boundaries ($u = 32$, Figures. 3.2E, I).

At higher u -factors, the PSNR metric is sensitive to the degradation of image quality and can potentially be used to find the optimal undersampling level. From Figure 3.2J, the increase in measured SNR slows down around $u = 16$ and diminishes at $u = 32$, a trend that is more pronounced by the PSNR metric (Figure 3.2K). As confirmed by the simulated PSFs (below), the aliasing artifacts induced by radial undersampling become unavoidable when $u \geq 16$ (Figures. 3.2E, F). In order to reconstruct the denoised image, the aliasing degradation in radial undersampling requires relatively heavier regularization using (3.1), at the price of sacrificing the reconstruction error measured by PSNR. For the noisier case $\sigma = 2$ (Figure. 3.2K), the averaged standard deviation of PSNR calculated from the 20 random iterations is about 50% higher than the $\sigma = 0.5$ case for each u .

This simulation suggests CS-ZTE can effectively boost the detection sensitivity of low SNR datasets, which are commonly encountered in ^{19}F MRI. For $u \leq 8$, the PSNR values are maintained at a constant level after increasing initially from $u = 1$ to 2. This shows that over this range of u , SNR boosting can be achieved without degrading the PSNR. Additionally, artifacts introduced by CS-ZTE are minimal, at least over the range of u investigated (*i.e.*, $u < 16$).

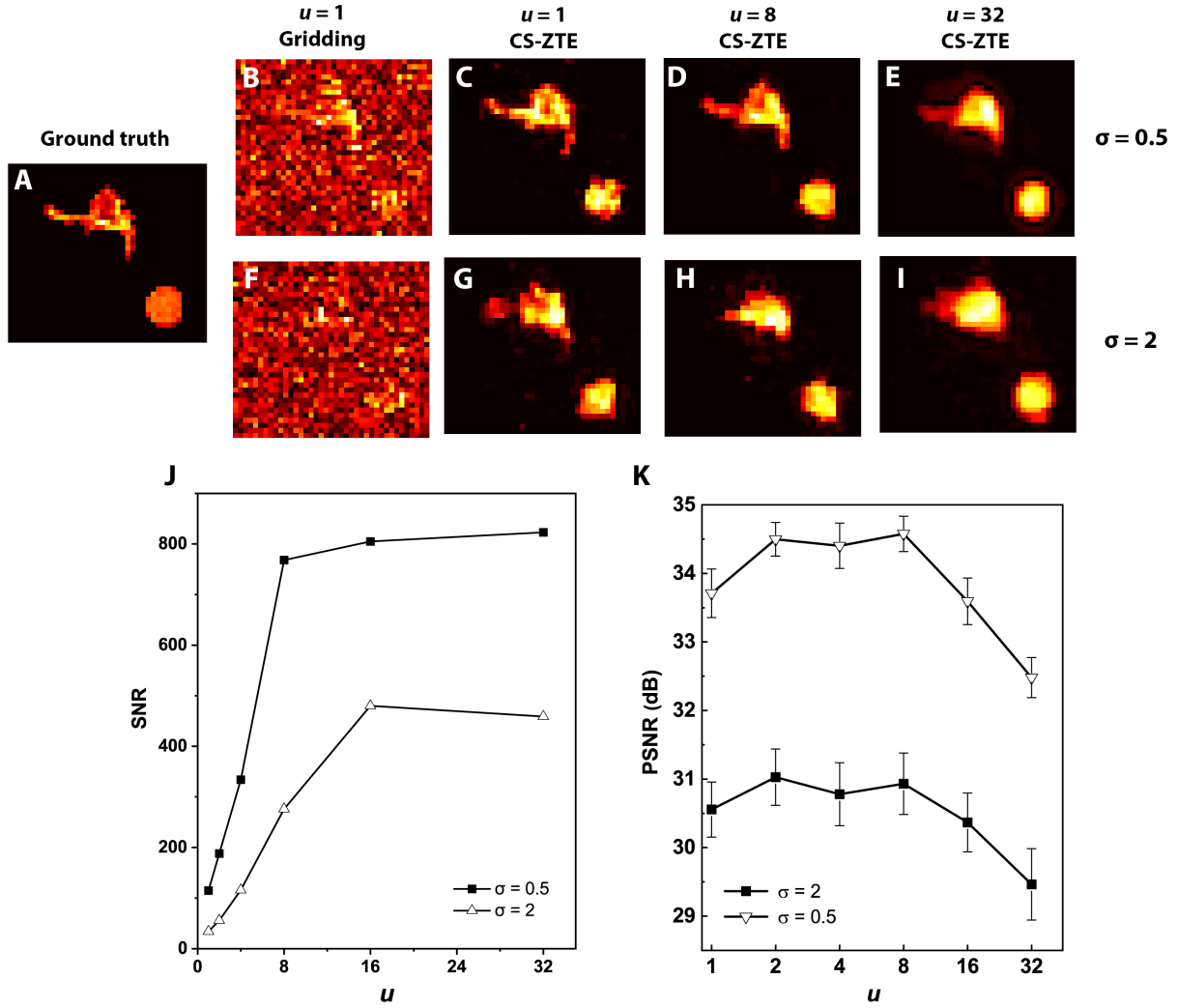


Figure 3.2. CS reconstruction results from synthetic ^{19}F CS-ZTE 3D data with varying u and noise level σ . Panel (A) shows the initial noise-free image slice. Images (B) and (F) are fully sampled data ($u = 1$) reconstructed using the Bruker ZTE sequence gridding method, whereas, (C) and (G) display $u = 1$ ZTE data reconstructed using the algorithm given by (3.1) with regularization parameters tuned by the Pareto frontier curve. The reduced background noise can be attributed to the algorithm's denoising feature with $u = 1$. Panels (D) and (H) correspond to CS-ZTE reconstruction from a moderate level of undersampling $u = 8$. Panels (E) and (I) correspond to CS-ZTE reconstruction from a high level of undersampling $u = 32$ where blurry edges are observed. The reconstruction quality of CS-ZTE data, measured by PSNR, are displayed in (K). The calculated SNRs versus u are plotted in (J) for noise values $\sigma = 0.5$ and 2.

3.3.2 Simulated PSF analysis

An additional simulation performed to evaluate the PSF can provide further guidance on choosing the undersampling level of CS-ZTE to ensure image fidelity. Figures 3.3A-F (lower panels) display 2D slice PSF modeling results. Overall, the appearance of streaking artifacts become more pronounced as u increases. When the undersampling level is low ($u = 2$), the aliasing artifacts are mostly present in the periphery of the PSF (Figure. 3.3B). When undersampling reaches intermediate levels ($u = 4, 8$), the streaking artifacts appear closer towards the center (Figures. 3.3C-D). At higher undersampling values ($u = 16, 32$), artifacts are present over the entire PSF (Figures. 3.3E-F). These observations are in alignment with the trends observed in the SPR (Table 3.1). It should be noted that the measured FWHM is minimally affected by u . Specifically, FWHM only accounts for a small change (0.22 pixel) when $u = 8$ compared to the fully sampled case, which implies that radial trajectory has the capability of preserving the resolution during undersampling. In fact, this feature of radial sampling has been previously investigated both in MRI numerical simulations [114] and in imaging experiments [115].

Table 3.1. Characteristics of PSFs measured by SPR and FWHM.

	$u = 1$	$u = 2$	$u = 4$	$u = 8$	$u = 16$	$u = 32$
SPR	0.2969	0.3051	0.3335	0.3919	0.4408	0.4952
FWHM [pixel]	1.406	1.438	1.5	1.625	1.75	2.0

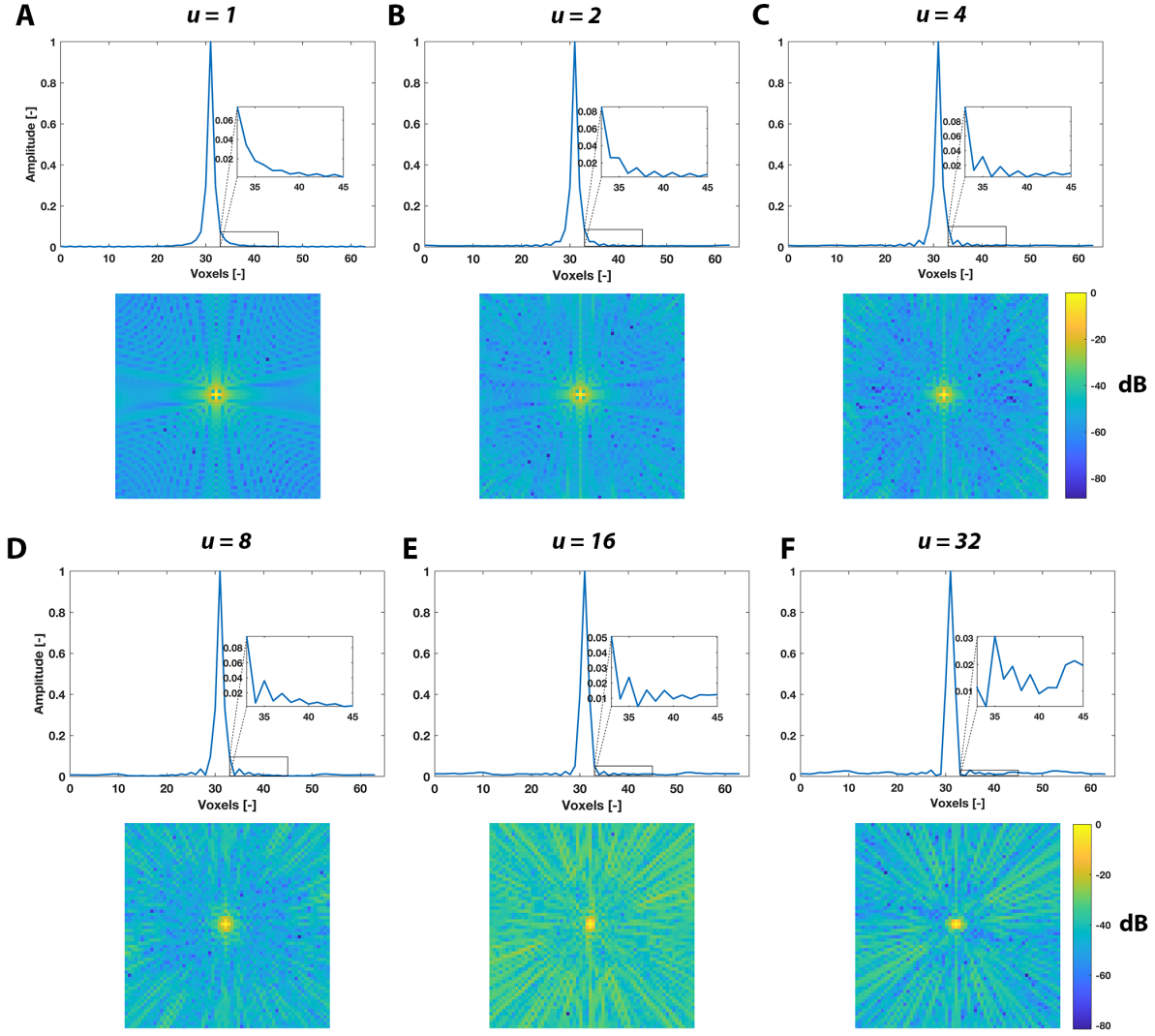


Figure 3.3. Simulated PSFs of 3D radial undersampling trajectories used in CS-ZTE. PSFs are calculated using conventional gridding method with u ranging from 1 (fully sampled) to 32. For display purposes, the central slice of the 3D PSF is extracted, normalized, and rendered in dB ($20\log_{10}$) scale. To further observe the peak side-lobe ratio change, 1D view PSF (extracted from the central line of the central slice) is also displayed on top of the 2D PSF slice.

3.3.3 Performance in phantom studies

Significant sensitivity gains are observed in phantom experiments using our sparsity-driven regularized algorithm. The LOD metric of signal detectability, assumed to be $SNR = 2.5$, increases with increasing u at constant scan time; for example, an 8.5-fold improvement is observed for $u = 8$ (Phantom 1, Figure 3.4B). At fixed u , the SNR changes proportionally with

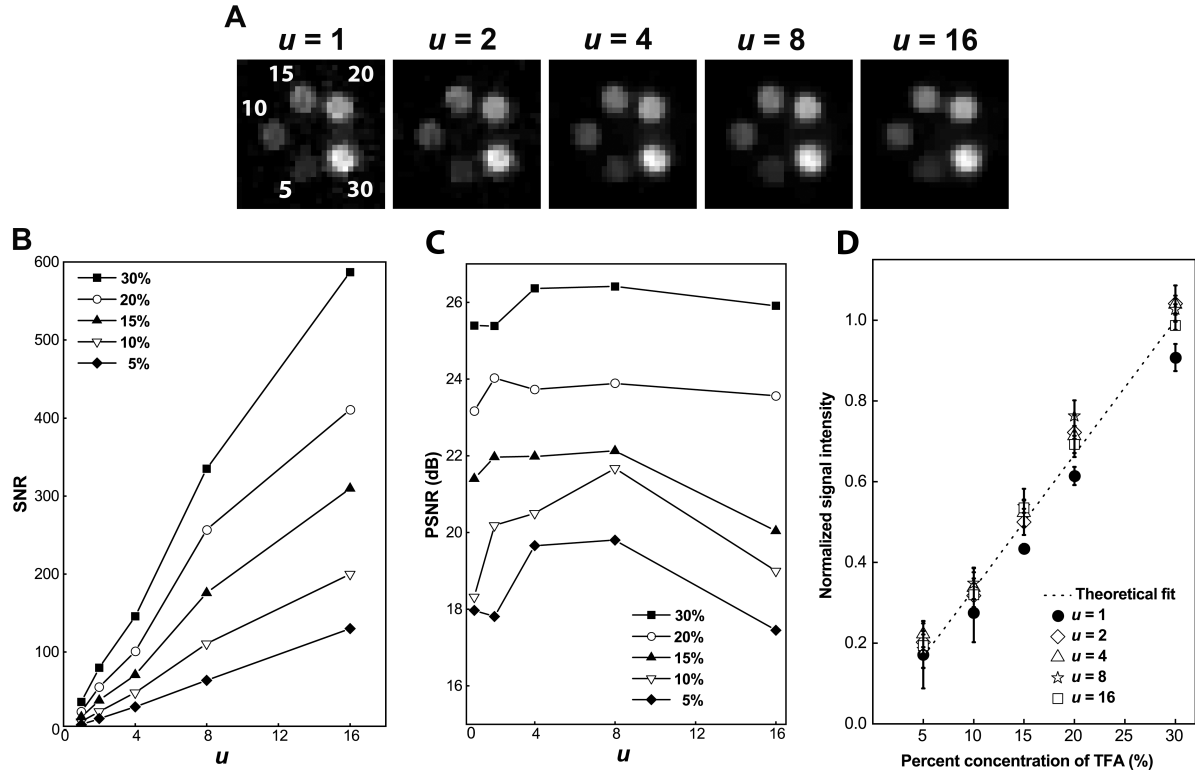


Figure 3.4. Results reconstructed by the sparsity-driven algorithm of experimental ^{19}F Phantom 1 (TFA) data acquired by the CS-ZTE pulse sequence with a fixed scan time of 13 s. Panel (A) shows the central slice. Panel (B) displays the measured SNR as a function of u and percent [TFA], and panel (C) shows the calculated PSNR. Panel (D) displays the spin quantification results with different u and percent [TFA]. The ‘Theoretical fit’ dotted line denotes the normalized ^{19}F spin density (arbitrary units) calculated from the actual [TFA]. All calculations are based on the average of the central four voxels within each tube from three contiguous slices.

the ^{19}F concentration ($R^2 > 0.98$ for all tested u) as expected. At constant spin density, SNR increases linearly proportional to u ($R^2 \geq 0.98$, Figure 3.4B). It is observed that the amount of SNR improvement with respect to u surpasses $\sqrt{u}$ (when $u \leq 16$), as would be expected for conventional signal averaging with multiple excitations [116]; this is the case for both the synthetic (Figure 3.2J) and experimental data (Figures 3.4B). This boost in apparent SNR is a consequence of both signal averaging of undersampled CS data and denoising due to the sparsity feature pronounced by the off-the-shelf joint TV- ℓ_1 -norm regularization algorithm. For Phantom 1, the PSNR for each tube with different ^{19}F concentrations were evaluated (Figure 3.4C). The measured PSNRs of ROIs with higher concentrations are consistently larger than those with

lower concentrations. This is expected, as a larger ^{19}F signal intensity enables reconstruction with higher accuracy, thus resulting in improved image quality. When concentration is fixed, PSNR increases as u varies from 1 to 8 (Figure 3.4C), where these variances are more significant (2-3 dB) at low ^{19}F concentrations (10%, 5%). At higher concentrations ($\geq 15\%$), PSNR variance is ~ 1 dB (Figure 3.4C). This observation highlights CS-ZTE's enhanced sensitivity for detecting low intensity signals, which is essential in ^{19}F cell tracking applications. Increasing u beyond 16 does not yield improved PSNR.

Based on our results in Phantom 1, we selected $u = 8$ for the follow-up MPFC and *in vivo* imaging experiments. Notably, this choice of optimal u is also aligned with the conclusion of the PSF simulations presented in Figure 3.3.

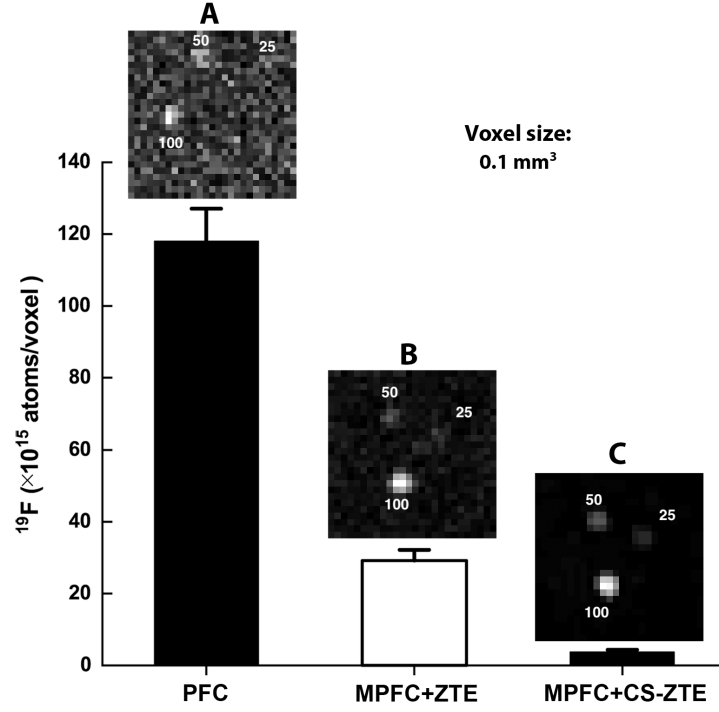


Figure 3.5. LOD evaluation using the CS-ZTE method at 11.7 T with a fixed scanning time of 3 min 30 s. Here, LOD represents the ^{19}F spin concentration at an extrapolation to $\text{SNR} = 2.5$, expressed as ^{19}F atom count per voxel (with voxel volume 0.1 mm^3). Column (A) corresponds to PFC control (Phantom 2) acquired with optimized 3D GRE sequence. Columns (B) and (C) corresponds to MPFC (Phantom 3) acquired with optimized ZTE ($u = 1$) and CS-ZTE ($u = 8$), respectively. The values 100, 50, 25 on slices represent percent nanoemulsion dilution, where 100 is undiluted. The PFC control yields an LOD $\sim 1.1 \times 10^{17}$ ^{19}F atoms/voxel (A). Overall, detection sensitivity improves ~ 30 -fold in MPFC due to PRE (B) and CS-ZTE pipeline (C).

For the MPFC data acquired with $u = 8$ (Phantom 3, Figure 3.5C), the LOD displays 8.1-fold improvement (from $\sim 3 \times 10^{16}$ to $\sim 3.7 \times 10^{15}$ ^{19}F atoms per voxel) compared to $u = 1$ acquisition (Figure 3.5B) reconstructed by Eq. 3.1. When we compare the MPFC sample (Figure 3.5B) with the metal-free PFC sample (Figure 3.5A), there is an additional ~ 3.7 -fold LOD gain attributed to PRE effect; this effect, together with the use of $u = 8$ CS-ZTE, yields a total of ~ 30 -fold LOD improvement (Figure 3.5C) in Phantom 3. Notably, CS-ZTE approach is an ultrafast, isotropic 3D imaging method for MPFC, with a total imaging time of ~ 3 min for $u = 1$ and ~ 25 s for $u = 8$ using $NA = 1$ in both cases and optimal imaging parameters.

3.3.4 Spin quantification accuracy

The ^{19}F spin concentration values of CS-ZTE data in TFA (Phantom 1) are shown in Figure 3.4D. The CS-ZTE method enables greater measurement accuracy of the slope of SNR versus [TFA], where for example, using $u = 16$ one obtains a slope of 0.32 ($R^2 = 0.995$), which is in near agreement with the theoretical value (0.33). Measurement at $u = 1$ across concentrations systematically underestimates the spin density change due to the low SNR, resulting a measured slope of 0.302 ($R^2 = 0.995$). At fixed u , the measured signal intensities display 3-5% variance on average among the five spin concentrations.

The relative percent variance of estimated signal intensities decreases as spin concentration increases (Figure 3.4D), with the averaged value ranging from 2.5-5%. However, CS-ZTE can improve the consistency of the estimation (i.e., less variance) under low spin concentration scenarios. For example, at 5% [TFA], $u = 1$ displays $\sim 8\%$ variance, and with $u \geq 2$ only $< 5\%$ is observed.

Overall, our results suggest that the CS-ZTE method does not adversely impact spin quantification accuracy compared to the conventional ZTE acquisition for the same scan time.

3.3.5 Sensitivity to image sparsity

The parameter pair (λ_1, λ_2) should be chosen with consideration of the sparsity of the image signal pattern of the subject and the practical resolution achievable. Figure 3.6 indicate future research directions displays the PSNR results calculated from Phantom 1 experiments and rendered in colormaps as a function of λ_1 and λ_2 ; the horizontal rows show that low PSNR regions (blue colored) in the colormap shrink as u increases. This suggests that the reconstruction quality of CS-ZTE with higher u is more robust with respect to tuning of regularization parameters, as greater averages are performed for high u for a fixed scan time. We also note that low u scans require larger λ_2 values to reach a higher PSNR. Nonetheless, increasing the weight of TV-norm regularizer does not always guarantee accurate structural textures of the imaged object and often

leads to image artifacts, as described elsewhere [117]. Our method for tuning λ_1 and λ_2 using Pareto frontier curves does not naively favor increasing λ_2 at low SNR and therefore is able to avoid such artifacts. From the column view of Figure 3.6, as FOV increases, the image has less spatial support and thus becomes sparser. For a fixed u , PSNR performance improves as FOV increases. Since all the experiments were performed with the same 0.75 mm isotropic resolution, this enhancement in PSNR can be attributed to the increased sparsity level induced by the FOV. As well established in the CS literature [118], a sparse image object (more signal-free background pixels) enables fewer measurements and thus a higher undersampling factor can be used for reliable feature recovery.

3.3.6 Reconstruction error analysis

The Pareto frontier curves displayed in Figures 3.7A-B and 3.8A-B show the dependence of regularization parameter choice on the number of measurements (u). When $u = 8, 16$, Pareto-optimal λ_2^* , i.e., the knee point on each curve marked in blue on Figures 3.7A-B and 3.8A-B, is close to the ℓ_2 -error-optimal $\hat{\lambda}_2$ (marked in red), defined as the value of λ_2 that produces $\hat{f}$ corresponding to the minimum of $\|\mathbf{f} - \mathbf{f}^*\|_2$ over the tested regularization parameters. Discrepancy between Pareto-optimal and ℓ_2 -error-optimal points increase as $u \leq 4$. Thus, a larger TV regularization is preferred for ℓ_2 -error-optimality in low undersampling scenarios. The results in Figures 3.7C-D and 3.8C-D validate that the ℓ_2 -error of λ_2^* values chosen from the Pareto curve are close to the smallest value of $\|\mathbf{f} - \mathbf{f}^*\|_2$. When sparsity s and noise level σ are fixed, the value of $\hat{\lambda}_2$ decreases as u increases (Figure 3.7C-D). Nonetheless, a similar minimum ℓ_2 -error can be reached over a wider range of values of u . The dynamic range of $\|\mathbf{f} - \mathbf{f}^*\|_2$ across λ_2 also decreases as u increases. This indicates that choosing higher u puts less restraint on the choice of λ_2 , which implies that one is more likely to obtain a reasonable reconstruction error over a larger range of choices for λ_2 . Thus, these results suggest that increasing the FOV (or decreasing s) and setting higher u for the CS-ZTE experiments leads to improved reconstruction.

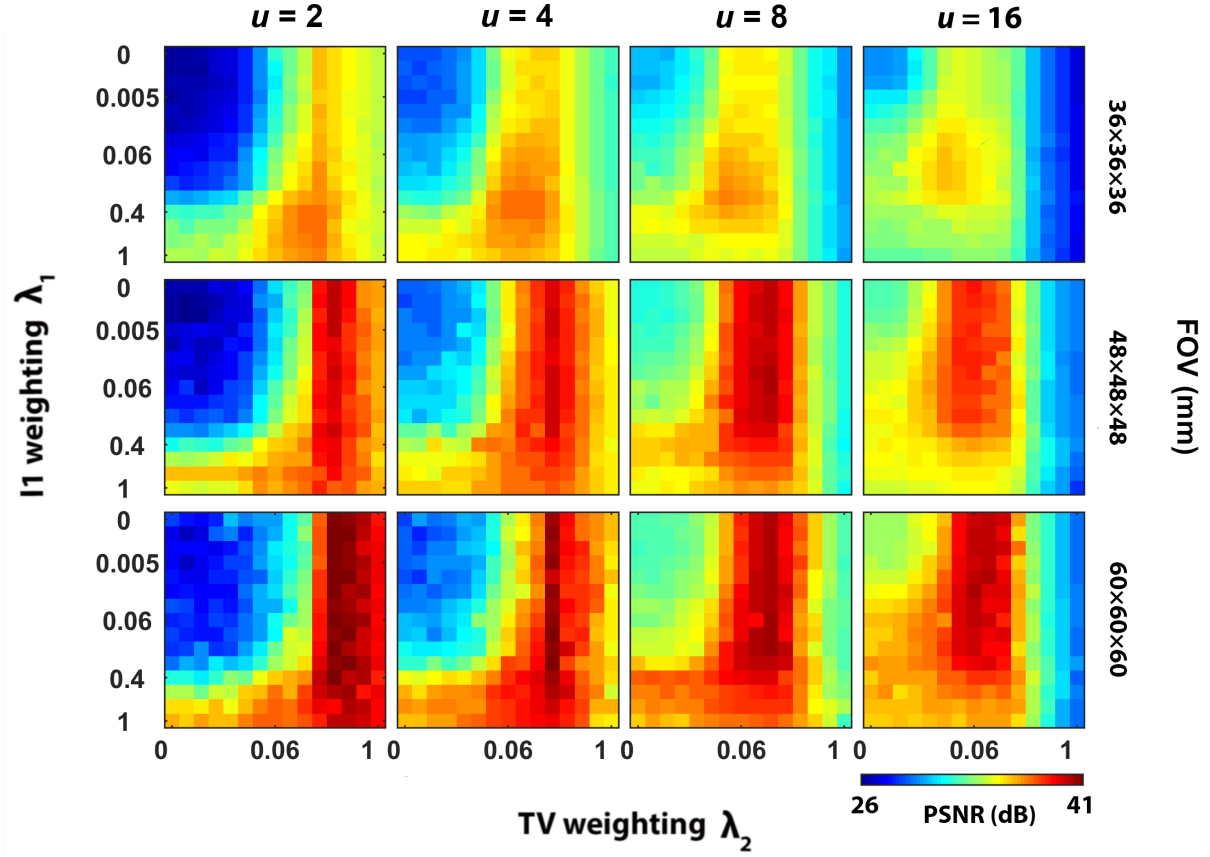


Figure 3.6. Calculated PSNR from sparsity-driven reconstructions of Phantom 1 CS-ZTE data with respect to changes in TV (λ_2) and ℓ_1 -regularization (λ_1) weighting parameters, both ranging from 0 to 1. From left to right, each column represents data acquired with u -factors 2, 4, 8, and 16, respectively. From top to bottom, each row represents different FOVs with increasing spatial sparsity, at constant isotropic resolution (0.75 mm). The color bar shows relative voxel PSNR in dB.

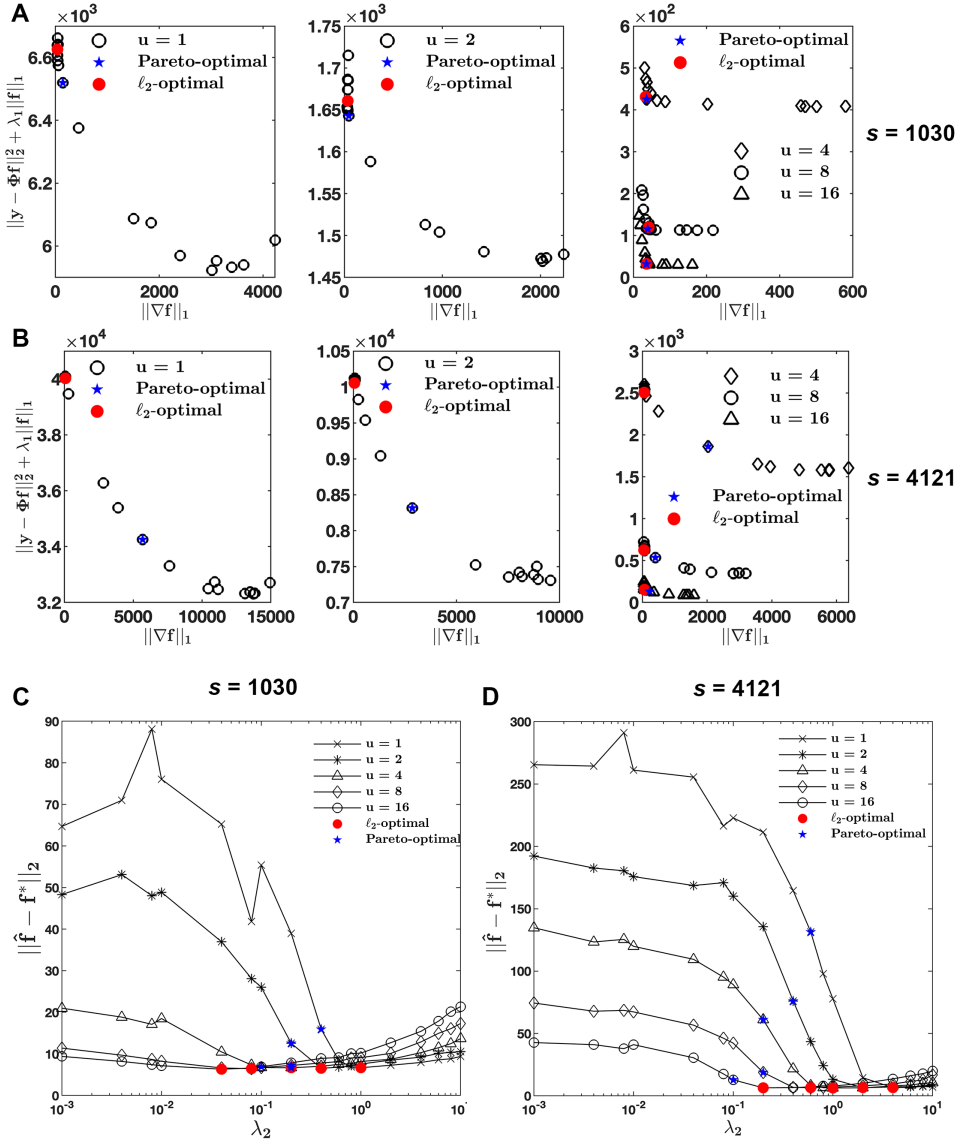


Figure 3.7. Pareto optimality and reconstruction error analysis from the joint TV- ℓ_1 -norm regularized least square algorithm. Synthetic datasets are generated with sparsity $s = [4121, 1030]$ and contaminated with complex-valued white noise with standard deviation $\sigma = 0.4$. Image data are generated using $u = 1, 2, 4, 8, 16$ and reconstructed using different combinations of λ_1 and λ_2 . The λ_1 values are chosen such that $\lambda_1^* = 2\|\Phi^H \mathbf{w}\|_\infty$. Panels (A) and (B) show Pareto frontier curves of a bi-objective function comprised of $L(\mathbf{f}) = \|\mathbf{y} - \Phi \mathbf{f}\|_2^2 + \lambda_1^* \|\mathbf{f}\|_1$ (y-axis) and $\|\nabla \hat{\mathbf{f}}\|_1$ (x-axis) for different sparsity levels ($s = 1030$ and $s = 4121$, respectively) and u . Candidates of Pareto optimum $\hat{\lambda}_2$ are chosen from knee points on the Pareto curves (marked in blue), which are neighboring the λ_2^* values (marked in red) producing the minimum values of $\|\hat{\mathbf{f}} - \mathbf{f}^*\|$. Panels (C-D) displays the ℓ_2 -error in the joint reconstruction of data along with λ_1^* and a range of λ_2 values from 0 to 10 (x-axis in log scale); points corresponding to the standard Lasso problem ($\lambda_2 = 0$) are located on the leftmost ordinate. These analyses indicate that the estimation error of standard Lasso is larger than fused Lasso when λ_2 is chosen according to Pareto optimal curves.

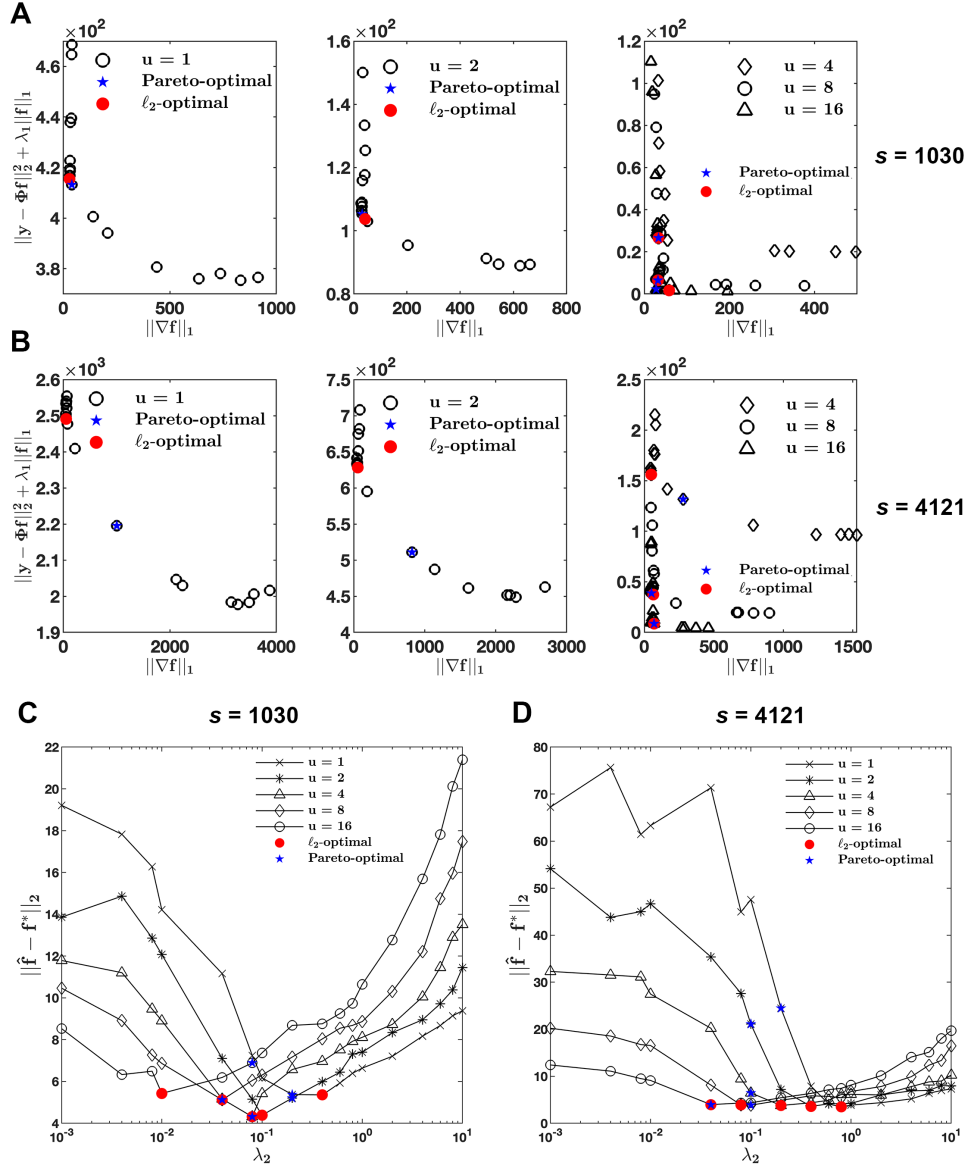


Figure 3.8. Pareto optimality and reconstruction error analysis from the joint TV- ℓ_1 -norm regularized least square algorithm. Synthetic datasets are generated with sparsity $s = [4121, 1030]$ and contaminated with complex-valued white noise with standard deviation $\sigma = 0.1$. Image data are generated using $u = 1, 2, 4, 8, 16$ and reconstructed using different combinations of λ_1 and λ_2 . The λ_1 values are chosen such that $\lambda_1^* = 2\|\Phi^H \mathbf{w}\|_\infty$. Panels (A) and (B) show Pareto frontier curves of a bi-objective function comprised of $L(\mathbf{f}) = \|\mathbf{y} - \Phi \mathbf{f}\|_2^2 + \lambda_1^* \|\mathbf{f}\|_1$ (y-axis) and $\|\nabla \hat{\mathbf{f}}\|_1$ (x-axis) for different sparsity levels ($s = 1030$ and $s = 4121$, respectively) and u . Candidates of Pareto optimum $\hat{\lambda}_2$ are chosen from knee points on the Pareto curves (marked in blue), which are neighboring the λ_2^* values (marked in red) producing the minimum values of $\|\hat{\mathbf{f}} - \mathbf{f}^*\|$. Panels (C-D) displays the ℓ_2 -error in the joint reconstruction of data along with λ_1^* and a range of λ_2 values from 0 to 10 (x-axis in log scale); points corresponding to the standard Lasso problem ($\lambda_2 = 0$) are located on the leftmost ordinate.

3.3.7 *In vivo* CS-ZTE scans in mice

We show that the CS-ZTE method is effective for *in vivo* scans and yields substantial sensitivity improvements. The FSDCs were labeled *ex vivo* by co-incubation with MPFC or PFC nanoemulsion, which yielded a mean uptake of $\sim 6.4 \times 10^{12}$ fluorine atoms per cell via ^{19}F NMR measurements in cell pellets prior to injection. For all 3D acquisitions, the scan time was fixed at 10 min with 0.94 mm isotropic voxels. The corresponding image voxel histogram distributions of unthresholded signals and noise are displayed in Figures 3.9A-B. Importantly, the wider intensity range and larger number of signal-positive voxels observed with the CS-ZTE method highlights its ability to detect smaller numbers of cells per voxel, which is a key motivation for a systematic co-design. Figures 3.9C-D show representative *in vivo* ^1H (grayscale) / ^{19}F (pseudo-color) MRI results in mice ($N = 3$) that were injected with PFC- and MPFC-labeled FSDCs (5×10^6 cells) in the left and right hind footpad, respectively. The CS-ZTE sequence with $u = 1$ readily detects the MPFC labeled cells, which appears as a hot-spot in the right footpad (Figure 3.9C) with a mean $SNR = 12$ calculated from the histogram (Figure 3.9A) derived from the 3D ROI. With $u = 8$, a significantly improvement in the mean $SNR (= 75)$ is observed (Figure 3.9D). Cells labeled with metal-free PFC (left footpad) fall below the detection limits at the same resolution and cannot be observed using Bruker ZTE, CS-ZTE, or by using the FLASH sequence.

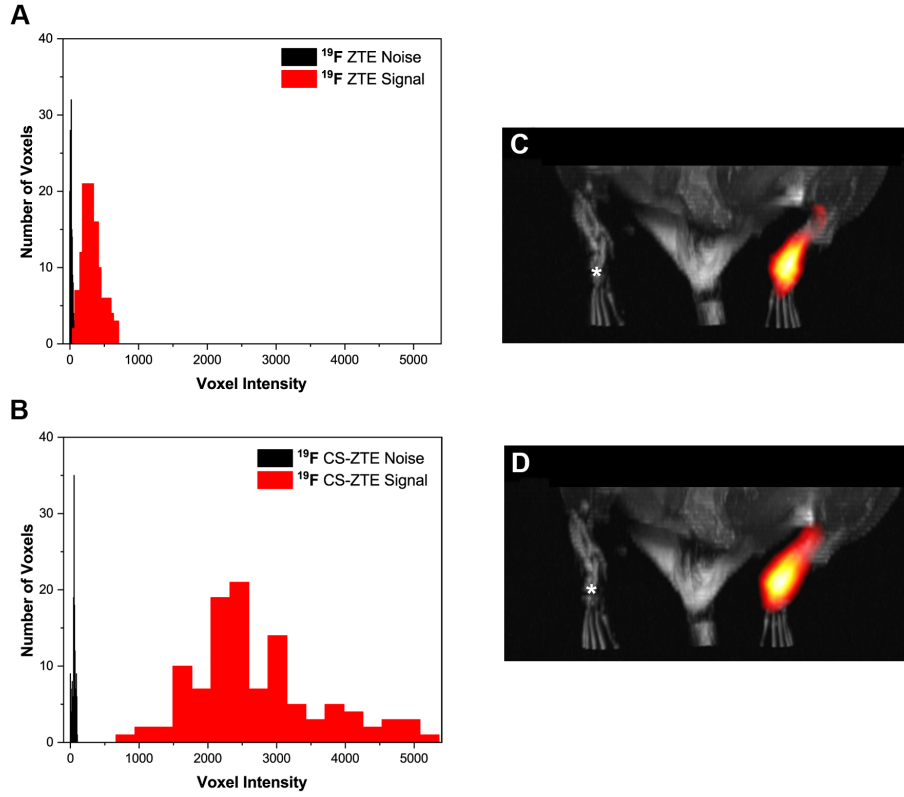


Figure 3.9. *In vivo* 3D ^{19}F MRI mouse data showing ^{19}F labeled FSDCs injected into the hind footpads. FSDCs, labeled with either PFC or MPFC, were injected into the left and right footpad (5×10^6 cells per side), respectively. The Bruker ZTE ($u = 1$) and $u = 8$ CS-ZTE ^{19}F data, both acquired in 10 min, are rendered in pseudo-color and co-registered with a coronal ^1H anatomical image. Panels (A) and (B) display the histogram of unthresholded ^{19}F image data of Bruker ZTE and CS-ZTE methods, respectively. The 3D ROI are defined for both signal and noise regions, and are kept constant across datasets. The CS-ZTE acquired signals (red bars) show a prominent intensity increase compared to ZTE and have a more expansive distribution, indicating enhanced detection to sparse cell densities. Panels (C) and (D) display cell deposit hot-spots in right footpad corresponding to the MPFC-labeled FSDCs acquired by ZTE and CS-ZTE, respectively. Cells labeled with iron-free PFC nanoemulsion (left footpad, asterisk) are below the LOD using the sequences tested in the same scan time (10 min).

3.4 Discussion

In summary, three combined components contribute to potential sensitivity improvements using the CS-ZTE method. First, the undersampled CS-ZTE pulse sequence shortens the 3D acquisition time and enables increased signal averages within the same total scan time. Second, sparsity-driven image reconstruction leads to denoising by exploiting the natural sparsity of

^{19}F images. Finally, PRE in MPFC shortens the T_1 enabling more rapid acquisitions and increased signal averaging in the same scan time. We have shown the combination of these three enhancement contributions can yield significant improvement in sensitivity *in vivo*, without a scan time penalty or significant image artifacts. Reliable reconstructions can be obtained from the CS-ZTE method, as tested both theoretically and experimentally. Quantitative analysis of absolute ^{19}F spin counts from images reveal the robustness of the CS-ZTE method with respect to changes in u and spin density differences.

It is established that ℓ_1 -norm promotes sparsity [98], and without the TV regularizer, (3.1) can be identified as the classic Lasso problem [87]. In practice, the TV-norm is computed as the ℓ_1 -norm of discrete gradients in the image domain. The denoising property of TV-norm has been widely recognized because of its ability to impose sparsity on the spatial derivatives [119] while at the same time, retaining important features such as edges and boundaries. In fact, a similar paradigm with (3.1) has been applied for non-CS (i.e., $u = 1$) scans [117] and achieved successful denoised reconstructions. However, with a fixed scan time, CS scans with $u > 1$ can enhance the raw k-space data and improve the detection sensitivity due to averaging. We also show that the choice of regularization parameter pairs (λ_1, λ_2) can affect the quantification accuracy of the ^{19}F signal intensity values in output images. Thus, we employ Pareto frontier curves to search for the optimal trade-off between λ_1 and λ_2 in a purely data-driven fashion.

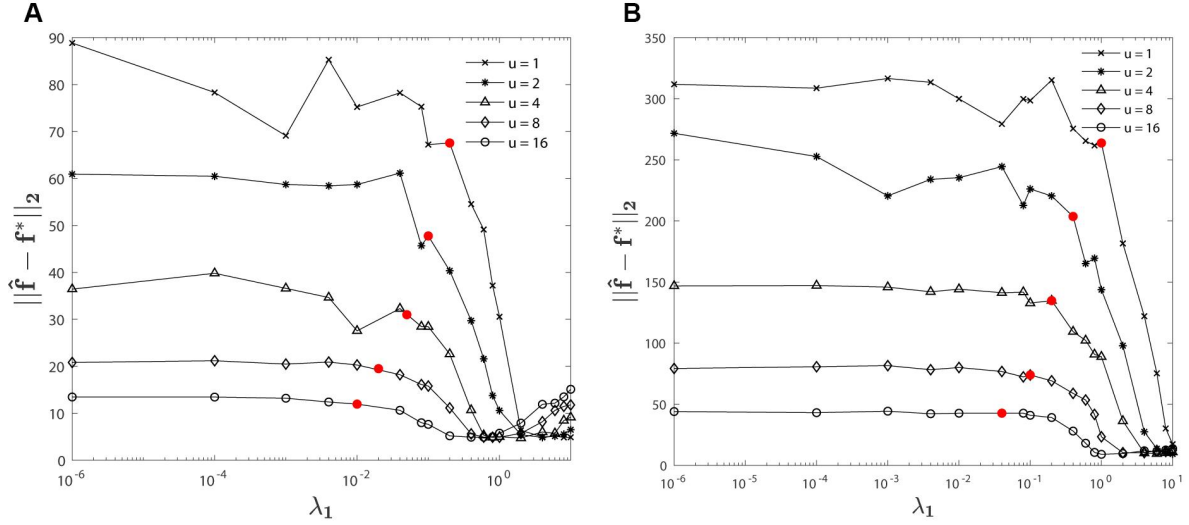


Figure 3.10. Lasso error under fixed sparsity and different noise levels. CS-ZTE datasets ($u = 1, 2, 4, 8, 16$) are generated with a fixed sparsity $s = 4121$ and contaminated with noise levels $\sigma = 0.1$ and $\sigma = 0.4$ for (A) and (B), respectively. To evaluate ℓ_2 -error, reconstruction is performed using a standard Lasso algorithm ($\lambda_2 = 0$) with λ_1 ranging from 0 to 10. Then $\|\hat{\mathbf{f}} - \mathbf{f}^*\|_2$ (y-axis) is calculated and plotted with respect to λ_1 (x-axis, in log scale). Specifically, the $\|\hat{\mathbf{f}} - \mathbf{f}^*\|_2$ values corresponding to $\lambda_1^* = 2\|\Phi^H \mathbf{w}\|_\infty$ for each u are marked in red on each Lasso error curve to show ‘turning point’.

As pointed out in Chapter 2, LOD is calculated with a threshold of $SNR = 2.5$ that has been applied in clinical ^{19}F cell studies with $> 99\%$ confidence against false positive signals [1]. Alternative choices of LOD threshold include the Rose Model [34] with $SNR = 4$, which accounts for both statistical properties and human perception. However, definitive interpretation of acquired ^{19}F MRI data is most often performed computationally, for example by per-voxel spin quantification and statistics, and human image perception is of lesser importance, except for identifying the (^1H -based) anatomical context of the ^{19}F signals. Thus, our view is that Rose Model criteria of $SNR = 4$ is overly conservative.

The NUFFT-based measurement operator $\mathbf{F}_u$ used in our reconstruction from (3.1) is a highly structured matrix. Its lack of sufficient randomness prevents us from exploiting restricted isometry property, which is commonly used in CS literature for random measurement matrices to evaluate the reconstruction error. However, it may be possible to estimate the RE given in

(3.2) by comparing the standard Lasso error from reconstruction. Specifically, we considered CS-ZTE acquisitions with fixed sparsity but different levels of additive noise. We reconstructed the data using the standard Lasso algorithm $\lambda_2 = 0$ with λ_1 from 0 to 10 and plotted the results with the corresponding $\|\hat{\mathbf{f}}' - \mathbf{f}^*\|_2$. We observe that $\lambda_1^* = 2\|\Phi^H \mathbf{w}\|_\infty$ serves as a ‘turning point’ on the plot (Figure 3.10). In other words, once $\lambda_1 > 2\|\Phi^H \mathbf{w}\|_\infty$, the error $\|\hat{\mathbf{f}}' - \mathbf{f}^*\|_2$ decreases drastically. This trend is aligned with the theorem presented in Eq. 3.3. Thus, it would be an interesting future direction to design MRI sampling patterns that can lead to larger values of κ , which could imply smaller reconstruction error via (3.3) [120].

The classic SNR is a commonly accepted metric for ^{19}F MRI to characterize the image quality. However, use of SNR has limitations for evaluating the images reconstructed from CS algorithms (*e.g.*, (3.1)), as it does not reflect the deviation of the reconstructed image from the ground truth. Thus, the PSNR metric is also calculated to characterize the reconstruction quality. At high u values, the CS reconstructed images lose detail and tend to blur. Such degradation in textures cannot be effectively detected from SNR which relies on average intensity measurements over ROI. For example, in Figures 3.2, 3.3, as the PSNR displays noticeable decrease (> 1 dB) for $u > 8$, the measured SNR does not appear to degrade. However, a practical disadvantage of using the PSNR metric, as well as alternative metrics such as SSIM [121] or DSC [101], is that they all require a ground truth image for calculation. For phantom experiments, the ground truth can be approximated by acquiring the dataset with a high number of averages. For *in vivo* experiments, it is not practical to obtain the ground truth image, thus limiting the application of these metrics. Consequently, *in vivo* data is rendered in histograms (Figure 3.9) to display CS-ZTE performance.

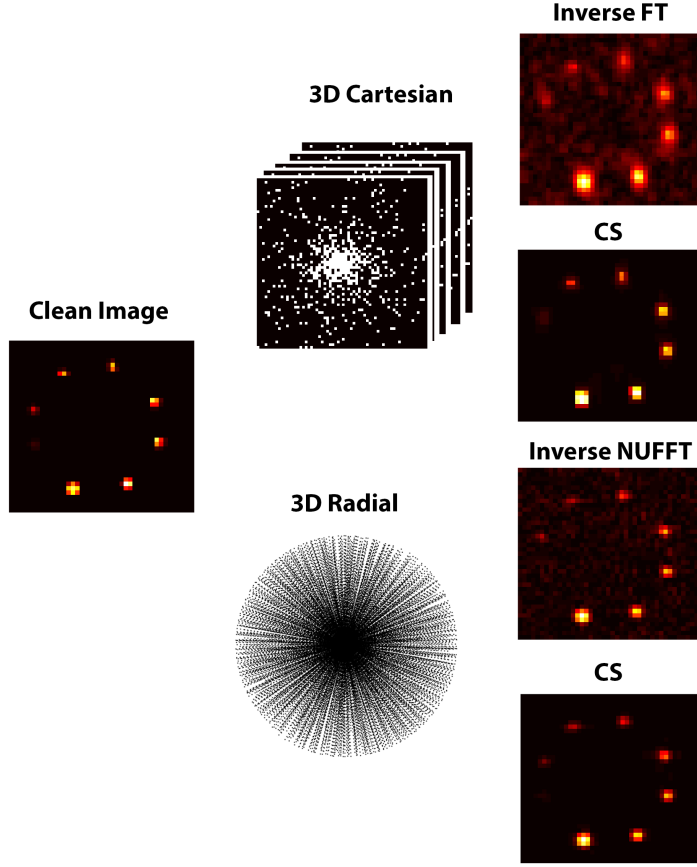


Figure 3.11. Modeling illustration of artifact suppression using CS reconstruction in inhomogeneous imaging scenario. A clean 3D ^{19}F phantom image1 (only central slice displayed) with multiple hot spots is first transformed to k-space data and then undersampled with both the Cartesian density-weighted k-space trajectory and 3D spherical Poisson disk radial trajectory using the same undersampling factor of 8. The simulated Cartesian dataset is reconstructed using both the conventional inverse Fourier transform (FT) and the CS reconstruction algorithm. Similarly, the simulated radial dataset is reconstructed with both the gridding-based inverse NUFFT and the CS reconstruction algorithm. The output image generated by the CS algorithm displays clear advantages over the alternative approaches, as it does not generate background image artifacts and preserves subject features and resolution.

CS-ZTE imaging is applicable to scenarios where hot-spots are distributed inhomogeneously. For conventional reconstruction approaches, such as inverse Fourier transform, the reconstruction works as a naïve linear interpolation and oftentimes results in overestimation of the true signal. However, for CS reconstruction algorithm, if the underlying image is sparse enough, then by tuning regularization parameter pair (λ_1, λ_2) , our sparsity-promoting algorithm

(Eq. 3.1) will favor inhomogeneous outputs rather than homogeneously smooth outputs. This is illustrated by the simulations in Figure 3.11. In addition to the benefit of CS algorithm, the radial sampling has the capability of preserving high frequency features and FWHM in the output image, as shown in the PSF analysis presented in Figure 3.3 and Table 3.1.

Besides MPFC, other fluorine MRI probes are under development that have short T_1 and/or T_2 and could benefit from CS-ZTE methods. Inorganic nanocrystals [122] comprised of water-soluble calcium fluoride (CaF_2) nanoparticles show promise in preclinical inflammation studies. Synthesizing CaF_2 with phosphate-based capping ligand results in dramatically shortened relaxation times [123], and thus signal enhancements using the CS-ZTE method would be an attractive approach. In another example, inert fluorinated gaseous, such as sulfur hexafluoride (SF_6), are increasing being used for pulmonary airway ^{19}F MRI as a lower cost [124], but less sensitive, alternative to hyperpolarized ^{129}Xe or ^3He gas [125]. The low T_1 and T_2 values of SF_6 ($T_1 = 1.7$ ms, $T_2^* < 2$ ms at 1.5 T) [126] make it amenable to CS-ZTE detection with potential sensitivity improvements over prior ultrashort echo-time (UTE) based approaches [127, 128].

We note that the need for large-bandwidth excitation pulses with ZTE may lead to high specific absorption rate (SAR), which can hamper clinical use [129]. The same CS-framework described herein can also be applied to other less SAR-intensive sequences, such as UTE imaging, which is an alternative ultrafast pulse sequence with radial acquisitions and has previously been adopted for CS [130, 131] and used clinically [82].

In conclusion, we show that the CS-ZTE acquisition combined with signal averaging and sparsity-driven reconstruction framework is effective at significantly improving image detectability for ultrafast 3D ^{19}F MRI without impairing data fidelity. Overall, the CS-ZTE method displays tremendous potential for future preclinical cellular-molecular and other X-nuclei imaging applications.

3.5 Acknowledgements

Chapter 3, in part, is a reprint of the material as it appears in the following papers:

- J. Chen, P. Pal, and E. T. Ahrens, “Enhanced detection of paramagnetic fluorine-19 magnetic resonance imaging agents using zero echo time sequence and compressed sensing,” *NMR in Biomedicine*, vol. 35, no. 8, p. e4725, 2022.
- J. Chen, P. Pal, E. T. Ahrens, “Enhanced detection of paramagnetic fluorine-19 MRI agents using compressed sensing zero echo time sequence,” in 31st Annual Scientific Meeting of the ISMRM, London, 2022.

The dissertation author was the primary investigator and author of these papers. We thank Hongyan Xu for phantom and cell preparations, Chao Wang for MPFC formulation and Benjamin Leach for critical reading of the manuscript.

3.6 Appendices

3.6.1 Appendix A: CS-ZTE measurement model

The input of our CS-ZTE reconstruction algorithm (3.1) has already been algebraic reconstructed. Recall in the general scenario (2.5), we introduced noise $\boldsymbol{\epsilon}_i \sim \mathcal{CN}(\mathbf{0}, \sigma^2 \mathbf{I})$ as part of the raw k-space data. Thus, the resulting noise after algebraic reconstruction should be modeled as colored Gaussian instead of white Gaussian in (2.5). We denote the (oversampled) stacked raw data obtained from scanner during i^{th} acquisition as $\mathbf{s}_i$. Because every radial projection needs to be preprocessed by the same $\mathbf{A}_r = \mathbf{W}\mathbf{F}$, the whole operator is a repeated

block diagonal (RBD) matrix, which is referred as $RBD(\mathbf{A}_r)$. We have

$$\mathbf{y}_i = RBD(\mathbf{A}_r)\mathbf{s}_i = \begin{bmatrix} \mathbf{W}\mathbf{F} & & & \\ & \mathbf{W}\mathbf{F} & & \\ & & \ddots & \\ & & & \mathbf{W}\mathbf{F} \end{bmatrix} \mathbf{s}_i \quad (3.6)$$

Since $RBD(\mathbf{A}_r)$ is a linear transformation, the transformed noise (denoted as $\mathbf{w}_i$) is still Gaussian, which satisfies $\mathcal{CN}(0, \sigma^2 RBD(\mathbf{A}_r \mathbf{A}_r^H))$.

For CS acquisitions with factor of u , we add the u copies of acquisitions together and divide by normalization factor $C_u := Cu$ (where C is some normalization value that remains unchanged among u -factors, depending on the optimization solver, *i.e.*, (2.8) or (3.1)), and obtain

$$\frac{1}{C_u} \sum_{i=1}^u \mathbf{y}_i = \frac{1}{C} \mathbf{F}_u \mathbf{f}^* + \frac{1}{C_u} \sum_{i=1}^u \mathbf{w}_i \quad (3.7)$$

Let averaged transformed noise $\mathbf{w} := \frac{1}{C_u} \sum_{i=1}^u \mathbf{w}_i$. Since noise in the raw data $\boldsymbol{\varepsilon} := \frac{1}{C_u} \sum_{i=1}^u \boldsymbol{\varepsilon}_i$ is complex-valued WGN, we have $\boldsymbol{\varepsilon} = \boldsymbol{\varepsilon}_R + \boldsymbol{\varepsilon}_I j$, where $\boldsymbol{\varepsilon}_R, \boldsymbol{\varepsilon}_I \sim \mathcal{N}(0, \frac{\sigma^2}{C^2 u} \mathbf{I})$. Let $\Gamma = RBD(\mathbf{A}_r)$, we have

$$\begin{aligned} \mathbf{w} &= \Gamma \boldsymbol{\varepsilon} \\ &= (\Gamma_R + \Gamma_I j)(\boldsymbol{\varepsilon}_R + \boldsymbol{\varepsilon}_I j) \\ &\vdots \\ &= (\Gamma_R \boldsymbol{\varepsilon}_R - \Gamma_I \boldsymbol{\varepsilon}_I) + (\Gamma_I \boldsymbol{\varepsilon}_R + \Gamma_R \boldsymbol{\varepsilon}_I)j \\ &= \mathbf{w}_R + \mathbf{w}_I j \end{aligned} \quad (3.8)$$

where $\mathbf{w}_R, \mathbf{w}_I \sim \mathcal{N}(0, \Sigma)$, with $\Sigma = \frac{\sigma^2}{C^2 u} (\Gamma_R \Gamma_R^H + \Gamma_I \Gamma_I^H) = \frac{\sigma^2}{C^2 u} \Gamma \Gamma^H$, which is equivalent to $\mathbf{w} \sim \mathcal{CN}(0, \frac{\sigma^2}{C^2 u} RBD(\mathbf{A}_r \mathbf{A}_r^H))$. Now denote the algebraic reconstructed signal as $\mathbf{y} := \sum_{i=1}^u \mathbf{y}_i$, the

corresponding signal model is

$$\mathbf{y} = \frac{1}{C} \mathbf{F}_u \mathbf{f}^* + \mathbf{w} \quad (3.9)$$

For simplicity, we let $\Phi = \mathbf{F}_u$. The optimization we are going to solve can be represented as

$$\min_{\mathbf{f} \in \mathbb{C}^{N_3}} \|\mathbf{y} - \frac{1}{C} \Phi \mathbf{f}\|_2^2 + \lambda_1 \|\mathbf{f}\|_1 + \lambda_2 \|\nabla \mathbf{f}\|_1 \quad (3.10)$$

3.6.2 Appendix B: Error bound derivation

To connect with the Lasso ℓ_2 -error given in Theorem 11.1 in [98], we want to derive the tail bound $P(\|\mathbf{w}\|_2 \geq t)$. Because $\mathbf{w}$ is a complex valued and its real and imaginary components are independently and identically distributed, we first find the tail bound of $\mathbf{w}_R$ (or $\mathbf{w}_I$).

Lemma 1. $\mathbf{w}_R \in \mathbb{R}^N$ is a sub-Gaussian (SG) random vector with parameter Σ_{op} if $\mathbf{w}_R \sim \mathcal{N}(0, \Sigma)$, where $\|\cdot\|_{op}$ represents the “Operator Norm” (or spectral norm) and $\|\Sigma\|_{op} = \max_i \sigma_i$, i.e., the largest of singular value of Σ [132].

We have shown $\Sigma = \frac{\sigma_u^2}{C^2} \Psi \Psi^H$ and singular values of $\Psi \Psi^H$ are easy to compute. Let the largest singular value of $\Psi \Psi^H$ be η_{max} . Then $\|\Sigma\|_{op} = \frac{\sigma_u^2}{C^2} \eta_{max}$.

Lemma 2. If $\mathbf{w}_R$ is a N -dimensional SG random vector with parameter $\|\Sigma_{op}\|$, $\|\mathbf{w}_R\|$ is the euclidean norm, then for $t > 0$ [133]:

$$P\left(\frac{\|\mathbf{w}_R\|}{\sqrt{N}} \geq t\right) \leq 4^N \exp\left\{-\frac{Nt^2}{8\|\Sigma\|_{op}}\right\} \quad (3.11)$$

Remark 1. i). First, suppose $t^2 \leq 8\|\Sigma\|_{op} \ln 4$. Plug back into (3.11) we obtain:

$$P\left(\frac{\|\mathbf{w}_R\|}{\sqrt{N}} \geq t\right) \leq 1 \leq 2e^{-\frac{t^2}{16\|\Sigma\|_{op}}} \quad (3.12)$$

ii). When $t^2 > 8\|\Sigma\|_{op} \ln 4$, let $t^2 = 8\|\Sigma\|_{op} \ln 4 + s$ (where $s > 0$) and therefore:

$$P\left(\frac{\|\mathbf{w}_R\|}{\sqrt{N}} \geq t\right) \leq 4^N \exp\left\{-\frac{Nt^2}{8\|\Sigma\|_{op}}\right\} = e^{-\frac{Ns}{8\|\Sigma\|_{op}}} \leq e^{-\frac{s}{16\|\Sigma\|_{op}}} = 2e^{-\frac{t^2}{16\|\Sigma\|_{op}}} \quad (3.13)$$

We note that case ii). will be potentially helpful for deriving our error bound. Because $\mathbf{w}_R$ and $\mathbf{w}_I$ are identically and independently distributed, we can obtain the tail bound for complex-valued $\|\mathbf{w}\|_2$ via the following lemma.

Lemma 3. *If $\mathbf{w}$ is a complex-valued SG random vector with real and imaginary parts satisfying $P(\frac{\mathbf{w}_{R,I}}{\sqrt{N}} \geq t) \leq e^{-\frac{Ns}{8\|\Sigma\|_{op}}}$, where $t^2 = 8\|\Sigma\|_{op} \ln 4 + s$ and $s > 0$ then $P(\frac{\|\mathbf{w}\|_2}{\sqrt{N}} \geq t) \leq 2e^{-\frac{Ns}{32\|\Sigma\|_{op}}}$ [134]*

In (3.10), we defined Φ as our forward sensing matrix. Let Φ_j be the j^{th} column. Since $\frac{|\Phi_j^H \mathbf{w}|}{C} \leq \frac{\|\mathbf{w}\|_2 \|\Phi_j\|_2}{C} \leq \|\mathbf{w}\|_2$, we obtain $P(\frac{|\Phi_j^H \mathbf{w}|}{C\sqrt{N}} \geq t) \leq P(\frac{\|\mathbf{w}\|_2}{\sqrt{N}} \geq t) \leq 2e^{-\frac{Ns}{32\|\Sigma\|_{op}}}$ based on Lemma 3. Given $j = 1, 2, \dots, p$, if we combine with union bound,

$$P\left(\frac{\|\Phi^H \mathbf{w}\|_\infty}{C\sqrt{N}} \geq t\right) \leq \sum_{j=1}^p P\left(\frac{\|\mathbf{w}\|_2}{\sqrt{N}} \geq t\right) \leq 2e^{-\frac{Ns}{32\|\Sigma\|_{op}} + \log p} \quad (3.14)$$

On the other hand, this indicates $P(\frac{\|\Phi^H \mathbf{w}\|_\infty}{C\sqrt{N}} \leq t) \geq 1 - 2e^{-\frac{Ns}{32\|\Sigma\|_{op}} + \log p}$. Since $s > 0$, let $s = \|\Sigma\|_{op} \ln 4$ such that $t = \sqrt{9\|\Sigma\|_{op} \ln 4} = 3\sqrt{\ln 4 \|\Sigma\|_{op}}$. Plug back into the probability and we obtain:

$$\begin{aligned} P\left(\frac{\|\Phi^H \mathbf{w}\|_\infty}{C\sqrt{N}} \leq t\right) &\geq 1 - 2e^{-\frac{Ns}{32\|\Sigma\|_{op}} + \log p} \\ P\left(\frac{\|\Phi^H \mathbf{w}\|_\infty}{C\sqrt{N}} \leq 3\sqrt{\ln 4 \|\Sigma\|_{op}}\right) &\geq 1 - 2e^{-\frac{N \ln 2}{16} + \log p} \end{aligned}$$

since $\lambda_1 \geq \frac{2\|\Phi^H \mathbf{w}\|_\infty}{C}$,

$$P\left(\frac{2\|\Phi^H \mathbf{w}\|_\infty}{C} \leq 6\sqrt{N \ln 4 \|\Sigma\|_{op}} \leq \lambda_1\right) \geq 1 - 2e^{-\frac{N \ln 2}{16} + \log p} \quad (3.15)$$

Recall that $\|\Sigma\|_{op} = \frac{\sigma_u^2}{c_u^2} \eta_{max}$. Thus, we have $\lambda_1 \geq 6\sqrt{M \eta_{max} \ln 4} \frac{\sigma}{c_u}$.

Since we already know the estimation error of Lagrangian Lasso [98], then with probability at least $1 - 2e^{-\frac{N\ln 2}{16} + \log p}$, the Lasso estimation error satisfies

$$\|\widehat{\boldsymbol{f}}' - \boldsymbol{f}^*\|_2 \leq \frac{3}{\kappa} \sqrt{s} \lambda_1 \quad (3.16)$$

Chapter 4

Physics-Informed Deconvolution of Multi-Spectral Fluorine-19 MRI Using Radial Sampling

In ^{19}F cellular MRI, detection of multiple cell targets requires the ability to unmix images corresponding to different tracer molecules with different chemical shifts. The resulting chemical shift artifacts of conventional Cartesian sampling are well-defined, appearing as ‘ghost images’ along the readout direction. Use of radial/projection-based FID acquisition of ^{19}F spectra date back to 1980s, along with rudimentary deconvolution techniques for removing the effects of chemical shift [135]. However, a key challenge with radial sampling is that frequency offsets lead to non-linear smearing artifacts throughout the image. Plain deconvolution such as direct inversion in the presence of noise often suffers from noise amplification and affects the output ^{19}F image quality. Thus, proper modeling of forward sensing operators is crucial, as the successful deconvolution of artifacts relies on the joint design of acquisition scheme and sampling pattern. In this chapter, we aim to address these perspectives through the lens of radial spectral deconvolution. Our goal is to develop suitable modeling of the radial chemical shift artifacts using Radon transform, which will guide our design of sensing operators that favor specific multi-spectral imaging tasks. To effectively unmix the component images under low SNR regime, we will further exploit physics-informed learning-based unrolling strategies that enable simultaneous artifact removal and weak signal detection, both of particular interest in ^{19}F

MRI.

4.1 Introduction

Fluorine-19 (^{19}F) MRI is an emerging method that uses perfluorocarbon (PFC) nanoemulsion tracers to enable background-free, “hot-spot” *in vivo* targeted cell tracking [1]. ^{19}F datasets exhibit true sparsity, with of the order of 0.5%–5% voxels containing significant signal in a background of pure noise. However, SNR of cellular MRI is limited by the amount of ^{19}F that can be taken up by cells of interest, and thus often a long scan time is needed for averaging in order to improve detectability. Recent advances in ^{19}F tracers have achieved a multifold boost in sensitivity using radial pulse sequences [9]. The addition of compressed sampling has further enhanced the cell detection sensitivity [39] under single cell target experiments. Detection of multiple cell targets requires the ability to separate/unmix images acquired using different PFC molecules with different chemical shifts [12]. Blind inversion of Fourier-based sensing operator results in chemical shift artifacts caused by model mismatch. The resulting artifacts using conventional Cartesian k-space sampling appear as displacements (Figure 4.1a-b) along the readout direction, whereas radial chemical shifts lead to smearing artifacts throughout the image (Figure 4.1c-d). This is reminiscent of the fat/water separation in ^1H MRI, where to reduce off-resonance blurring, radial chemical shifts are modeled in k-space and integrated into the nonuniform fast Fourier transform (NUFFT) operator [136]. This approach is not directly transferable to ^{19}F MRI for two reasons. First, different PFC molecules have larger frequency offsets compared to fat/water, which lead to highly non-trivial artifacts. Second, NUFFT [84] is essentially a regridding operator, and the approximation is not as accurate especially when accounting for the large chemical shift offsets. Alternatively, chemical shift effects can be modeled directly in the spatial domain and separating multiple component images becomes a deconvolution problem. This has been demonstrated in [12] for fully sampled ^{19}F Cartesian acquisitions. However, radial chemical shifts are much less characterized, and the performance of iterative deconvolution is

constrained by the input SNR and undersampling level.

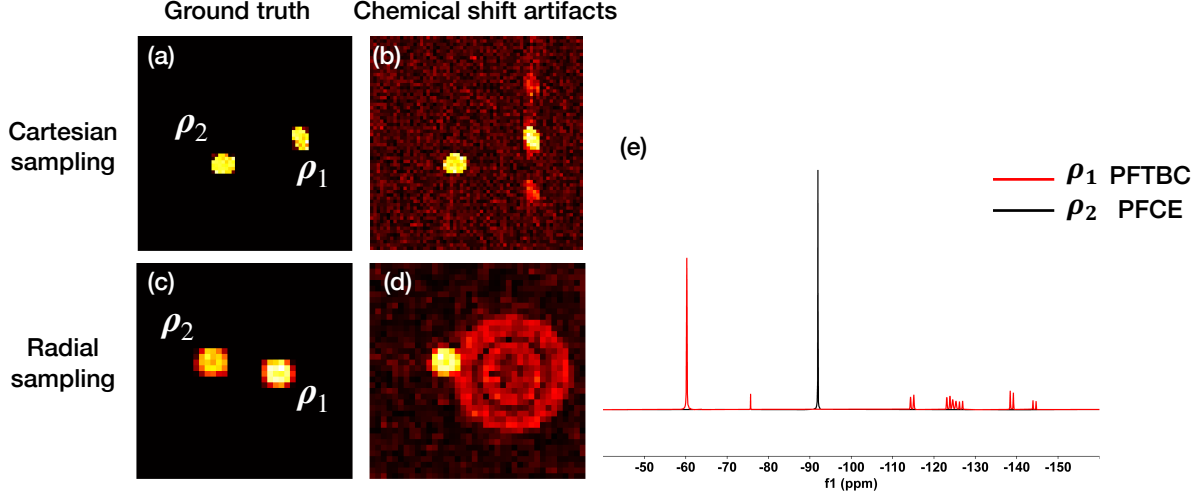


Figure 4.1. Demonstration of Cartesian and radial chemical shift artifacts in multi-spectral ^{19}F MRI. (a). Cartesian sampling ground truth (GT) and its chemical shift artifacts (b) appearing as ‘ghost images’ along the readout (vertical) direction. (c). Radial sampling GT and its chemical shift artifacts (d) lead to non-linear smearing. (e). ^{19}F NMR spectra of ρ_1 and ρ_2 .

Data-driven learning methods have been explored in compressed sensing MRI reconstruction tasks [22, 137, 138]. Although generative priors have shown promising results in recovering undersampled highly noisy cellular MRI data [97], training such models requires thousands of fully sampled ground truth (GT) images, which is not practical in most medical imaging applications. Meanwhile, learned unrolling networks for sparse-view computed tomography (CT) [139] have shown significant improvement over conventional model-based reconstruction because of its ability to accommodate the non-linear artifacts. Notably, training of deep unrolling network typically requires < 500 images, because a forward sensing operator is injected as part of the architecture, but these methods do not focus on the chemical shift spectra unmixing in low SNR imaging scenarios.

Our contribution: In this paper, we aim to address these perspectives through the lens of radial spectral deconvolution, which is currently missing in the literature. We develop a novel Radon transform modeling of forward operator for radial chemical shift MRI and employ a physics-informed deconvolution scheme to unmix the multi-spectral components. Furthermore,

we exploit physics-informed deep learning-based priors through unrolling that demonstrate effectiveness in simultaneous artifact removal as well as detection of ^{19}F MRI signals in the low SNR regime.

4.2 Prior Work

4.2.1 Chemical shift multi-spectral signal model

We consider two PFC imaging components with the former in the presence of multiple chemical frequency shifts $\{\Delta f_m\}_{m=1}^M$ with relative amplitudes α_m (Figure 4.1e), representing perfluorotert-butyl cyclohexane (PFTBC as ρ_1) and perfluoro-15-crown-5-ether (PFCE as ρ_2). The reference frequency is set as the main peak of PFCE (-92.5 ppm at 9.4 T). Supposing resonance frequency is set as ρ_2 's single peak for 2D sampling, the acquired k-space measurements over time are given by

$$\bar{s}(k_x, k_y, t) = \int \int_{x,y} [\rho_1(x, y) \cdot \sum_{m=1}^M \alpha_m e^{i2\pi t \Delta f_m} + \rho_2(x, y)] \cdot e^{i2\pi y k_y} \cdot e^{i2\pi x k_x(t)} dx dy. \quad (4.1)$$

We note that the above model can be generalized to accommodate > 2 PFC species with non-overlapping resonances. The phase evolution during frequency readout (in time) becomes a function of $\{\Delta f_m\}_{m=1}^M$, and this causes mixing between the images corresponding to multiple species, which ultimately has the effect of spectral convolution (denoted as $\mathbf{H}$) on top of the spatial 2D Fourier transform $\mathbf{F}$. Discretization of (4.1) leads to the matrix representation of the measurement model as follows [140, 12]

$$\mathbf{s} = \mathbf{F}\mathbf{H} \begin{bmatrix} \rho_1 \\ \rho_2 \end{bmatrix} + \mathbf{w}, \quad \mathbf{w} \sim \mathcal{CN}(\mathbf{0}, \sigma^2 \mathbf{I}). \quad (4.2)$$

We note that $\mathbf{F}$ is dependent on the sampling trajectory employed, which may involve under-sampling methods. Importantly, alternating the acquisition schemes will affect the modeling of

the artifact patterns in $\mathbf{H}$. Thus, joint design of two components in sensing operator $\mathcal{A} := \mathbf{F}\mathbf{H}$ is required in order to guarantee the recovery of $\boldsymbol{\rho}_1$ and $\boldsymbol{\rho}_2$. These issues become especially pronounced when considering ^{19}F measurements $\mathbf{s}$ with a low SNR, which is commonplace.

4.2.2 Cartesian spectral deconvolution

For Cartesian sampling, if we consider the imaging object as a unit impulse at (x_0, y_0) with the frequency encoding readout direction along k_x , the point spread function (PSF) in the presence of frequency offsets at position (x, y) associated with $\mathbf{H}$ is given by [43]

$$h(x, y) = \sum_{m=1}^M \alpha_m \delta(x - x_0 - d_m) \delta(y - y_0). \quad (4.3)$$

where d_m denotes the amount of spatial shift governed by Δf_m . Thus, to enable acquisitions, one can cycle the readout along orthogonal directions, and $\mathbf{s}_h$ and $\mathbf{s}_v$ are acquired to unmix the species and mitigate the artifacts. The following model is employed in [12]

$$\begin{bmatrix} \mathbf{s}_h \\ \mathbf{s}_v \end{bmatrix} = \begin{bmatrix} \mathbf{F}_2 & \mathbf{0} \\ \mathbf{0} & \mathbf{F}_2 \end{bmatrix} \begin{bmatrix} \mathbf{H}_h & \mathbf{I} \\ \mathbf{H}_v & \mathbf{I} \end{bmatrix} \begin{bmatrix} \boldsymbol{\rho}_1 \\ \boldsymbol{\rho}_2 \end{bmatrix} + \mathbf{w} \quad (4.4)$$

The resulting artifacts from Cartesian sampling are predictable and well-defined, appearing as ‘ghost images’ along the readout direction (Figure 4.1b). This makes it somewhat easier to develop effective acquisition strategies (such as cycling the readout direction along horizontal and vertical) to mitigate their effects. This is illustrated in Figure 4.2, where similar to [12], we demonstrate how changing the readout directions can be an effective way to unmix the species.

However, this scheme is not adaptable to radial trajectories due to the nature of acquisition and corresponding artifacts, as frequency shift artifacts produced by other species from radial sampling will not appear as simple displacements. Furthermore, $\mathbf{F}_2$ only serves as a fully-sampled Fourier matrix [12] and is incompatible with compressed sensing regime [39].

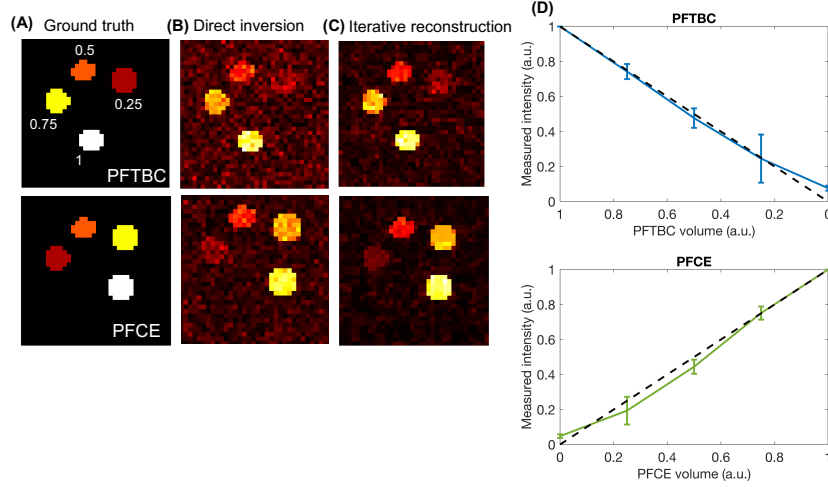


Figure 4.2. Reconstruction of simulated multispectral ^{19}F Cartesian phantom data and quantification results. Panel (A) displays the ground truth PFTBC and PFCE distribution generated by linearly varying the ratios in the signal intensity as: (0/1; 0.25/0.75; 0.5/0.5; 0.75/0.25; 1/0 [PFTBC]/[PFCE], respectively). Ground truth images are first converted into Cartesian k-space data by multiplying the sampling convolution operator, (with chemical shift spectrum information encoded). To mimic noisy acquisitions, complex Gaussian noise is then added to obtain 10 dB measurements. In (B) and (C), we display reconstructed/unmixed PFTBC and PFCE images from direct inversion (baseline, panel B) and iterative ℓ_1 -minimization algorithm (panel C). Measured SNR in (C) shows improvement compared to (B) due to the denoising effects stemmed from the sparsity-promoting feature of ℓ_1 -minimization. Panel (D) displays normalized mean signal intensities and standard deviation in the phantoms as function of PFTBC and PFCE volume ratio contributions. The dashed black line indicates a linear change between 0 and 1.

4.3 Learned deconvolution of radial multi-spectral MRI

Unlike Cartesian sampling, the $\mathbf{H}$ associated with radial smearing cannot be easily identified in the Cartesian coordinate system due to its rotational feature. Instead, the PSF of $\mathbf{H}$ is characterized via Radon transform $\mathcal{R}(\cdot)$ with respect to polar/spherical coordinates (r, ϕ) [141]

$$\check{h}(r, \phi) = 2\pi \sum_{m=1}^M \int_0^\infty k \alpha_m e^{i2\pi d_m k} J_0(2\pi k r) dk \quad (4.5)$$

Our analytical computations identify this mathematically using Radon transforms and Bessel functions, where k represents radial k-space variable, d_m denotes the amount of spatial shift governed by Δf_m , and J_0 is the zeroth order Bessel function.

4.3.1 Radial multi-spectral measurement model

From Fourier slice theorem, radial k-space data $s(k, \phi)$ can be obtained by taking 1D Fourier transform $\mathcal{F}_k$ along the t direction of the projection data $\mathcal{R}_\phi(t)$ [43]

$$\begin{aligned} s(k, \phi) &= \int dt e^{-i2\pi kt} \int \int dx dy \rho(x, y) \cdot \delta(t - x \cos \phi - y \sin \phi) \\ &= \int dt \mathcal{R}_\phi(t) e^{-i2\pi kt} = \mathcal{F}_k\{\mathcal{R}_\phi(t)\} \end{aligned} \quad (4.6)$$

As illustrated in Figure 4.3, the theorem can convert radial k-space data into sinogram data, analogous to parallel beam X-ray CT. The undersampling radial trajectory is encoded via Radon transform $\mathcal{R}_\Phi$. Unlike NUFFT operators, re-gridding of the radial data to Cartesian space is not required, which makes the reconstruction more accurate [86].

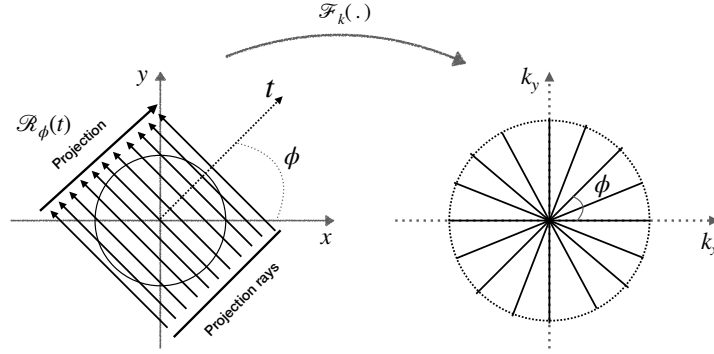


Figure 4.3. Illustration of projection slice theorem. Radial k-space data (right) can be converted into sinogram projection data (left) analogous to parallel beam X-ray CT.

By acquiring $P = 2$ sets of undersampled measurements $\mathbf{s} = \{\mathbf{s}_j\}_{j=1}^P$ with varying readout bandwidths and hence varying effective sampling time [142], distinct harmonic structure in the temporal/spectral domain can be produced. Specifically, for j^{th} acquisition, spatial shifts $d_m^{(j)}$ are dependent on the readout bandwidth. Since radial k-space measurements $\mathbf{s}$ are obtained by

“rotating” the angle of projection spokes, we can utilize 1D radial Fourier transform $\mathbf{F}_k$, which converts each integral line from Radon domain into 2D Fourier radial samples [43]. We propose the following radial multi-spectral measurement model

$$\mathbf{s} = \mathbf{F}_k \mathcal{R}(\check{\mathbf{H}} \begin{bmatrix} \boldsymbol{\rho}_1 \\ \boldsymbol{\rho}_2 \end{bmatrix}) + \mathbf{w} = \mathbf{F}_k \mathcal{R}(\begin{bmatrix} \check{\mathbf{H}}_1 & \mathbf{I} \\ \check{\mathbf{H}}_2 & \mathbf{I} \end{bmatrix} \begin{bmatrix} \boldsymbol{\rho}_1 \\ \boldsymbol{\rho}_2 \end{bmatrix}) + \mathbf{w} \quad (4.7)$$

We denote $\{\check{\mathbf{h}}_j\}_{j=1,2}$ as the PSF of $\{\check{\mathbf{H}}_j\}_{j=1,2}$, where $\check{\mathbf{h}}_j = \mathbf{h}_j(r) * \mathbf{h}_w(r)$. Specifically, $\mathbf{h}_j(r) = 2\pi \sum_{m=1}^M \int_0^\infty k \alpha_m \cdot e^{i2\pi d_m^{(j)} k} J_0(2\pi k r) dk$ describes the smearing artifacts induced by the radial chemical shifts $\{\Delta f_m\}_{m=1}^M$. $\mathbf{h}_w(r) = 2\pi \int_0^{k_{max}} k J_0(2\pi k r) dk$ denotes Hankel transform of rect(.) function used for truncation of k-space [143]. Unlike the real-valued sinograms from CT acquisitions, here $\mathcal{R}$ generates complex-valued sinograms due to the physics of real MRI acquisitions.

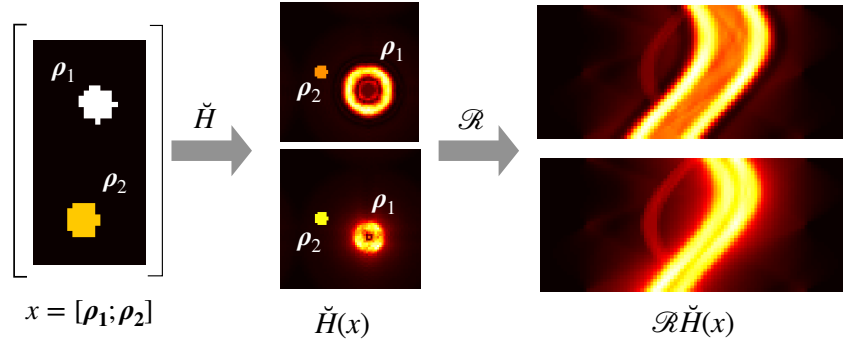


Figure 4.4. Radial k-space via Radon Transform domain adaptation. Assume the resonance frequency is set at the spectra peak of ρ_2 , the frequency offsets from ρ_1 generates a radial smearing pattern (middle), which can be described using the convolutional matrix $\check{\mathbf{H}}_1$ and $\check{\mathbf{H}}_2$. Projection sinogram data (right) is obtained by applying radon transform $\mathcal{R}$.

4.3.2 Physics-driven iterative spectral deconvolution

We propose to solve the following model-based radial multi-spectral deconvolution problem

$$\min_{\mathbf{x}=[\boldsymbol{\rho}_1;\boldsymbol{\rho}_2]} \|\mathbf{s} - \mathcal{A}(\mathbf{x})\|_2 + \lambda \mathcal{D}(\mathbf{x}) \quad (4.8)$$

where $\mathcal{A} := \mathbf{F}_k \mathcal{R} \check{\mathbf{H}}$ is the overall forward operator from (4.7) derived from the chemical shift multi-spectral information (Figure 4.1E). Conventional iterative reconstruction involves hand-crafted regularizers $\mathcal{D}(\cdot)$ that enforce low-dimensional structural prior on $\mathbf{x}$, such as ℓ_1 -norm, total-variation (TV) norm $\|\nabla \cdot\|_1$, or nuclear norm, to recover from limited k-space measurements. Inspired by the sparse view CT reconstruction, we solve (4.8) with TV regularization using Primal Dual Hybrid Gradient (PDHG), which serves as a reasonable baseline to compare with our data-driven method. Solving (4.8) is equivalent to solving the following objective [92]

$$\min_{\mathbf{x}} (\mathcal{F}(\mathcal{L}(\mathbf{x})) + \mathcal{G}(\mathbf{x})). \quad (4.9)$$

The implementation details of PDHG algorithm are displayed in **Algorithm. 1**. Here the proximal operator $\text{prox}(\cdot)$ is defined explicitly as $\text{prox}_{\eta} \mathcal{G}(\mathbf{x}) = \arg \min_{\mathbf{x}' \in X} \{ \frac{1}{2\eta} \|\mathbf{x}' - \mathbf{x}\|_X^2 + \mathcal{G}(\mathbf{x}') \}$. As suggested, PDHG requires manual tuning of parameters σ, η, τ to obtain optimal performance. The performance of PDHG may be also hampered by the low SNR ^{19}F cellular MRI data.

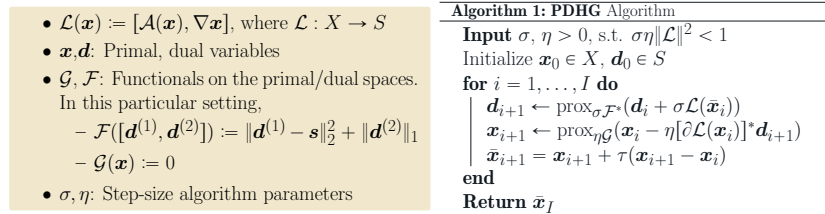


Figure 4.5. Primal-dual hybrid gradient (PDHG) algorithm used to solve Eq. 4.8 with TV regularization $\|\nabla \mathbf{x}\|_1$.

4.3.3 Recovering undersampled noisy radial multi-spectral measurements through learned unrolling

Inspired by the work in [139], we replace the explicit $\text{prox}(\cdot)$ in PDHG with learned proximal operators through unrolling of the primal-dual algorithm (UPD). The overall framework is trained in a supervised end-to-end fashion and displayed on Figure 4.7. Given a set of training sample pairs $(\mathbf{s}^{(1)}, \mathbf{x}^{(1)}), \dots, (\mathbf{s}^{(N)}, \mathbf{x}^{(N)})$, the goal is to learn a non-linear mapping $\mathcal{A}_{\theta}^{\dagger} : S \rightarrow X$ such that $\mathcal{A}_{\theta}^{\dagger}(\mathbf{s}) \approx \mathbf{x}$. We minimize the following empirical loss function:

$$\hat{L}(\theta) = \frac{1}{N} \sum_{n=1}^N \|\mathcal{A}_{\theta}^{\dagger}(\mathbf{s}^{(n)}) - \mathbf{x}^{(n)}\|^2 \quad (4.10)$$

Specifically, at each iteration $i = 1, 2, \dots, I_M$, we replace the $\text{prox}(\cdot)$ operators with convolutional neural networks (CNNs), denoted as $\Gamma_{\theta_i^d}, \Lambda_{\theta_i^p}$ for learned dual/primal proximals correspondingly (**Algorithm. 2**). The intuition is that the residual structures of Γ_{θ^d} and Λ_{θ^p} are able to capture the non-linear chemical shift artifacts from the undersampled noisy data $\mathbf{s}$ without prior assumptions about the structure of $\mathbf{x}$. Information about forward operator $\mathcal{A}$ and its adjoint $\mathcal{A}^{\dagger}$ is integrated into the architecture as PyTorch transform layers [144]. Number of channels N_p, N_d from primal/dual variables $\mathbf{x}$ and $\mathbf{d}$ are both set to 4 to account for the real and imaginary channels of the MRI data. This approach is different from [139] as the sparse nature of the cellular MRI does not require an extension of the primal space to achieve desirable outputs. UPD benefits from the power of domain adaptation and enables learning the distinct artifact patterns in a data-driven manner, which is essential for separating multi-spectral component images under low SNR and extreme compression regime. It also alleviates the restraints on manual parameter tuning for solving Eq. 4.8 using classical methods such as PDHG.

• N_p, N_d: Number of memory channels of primal and dual variables. Here $N_p = N_d = 4$ • I_M: Number of unrolling iterates. $I_M = 8$ • $\mathcal{L}(\mathbf{x}) := \mathcal{A}(\mathbf{x})$ to incorporate forward model • $\Gamma_{\theta_i^d}, \Lambda_{\theta_i^p}$: CNNs with different learned parameters θ_i^d and θ_i^p	Algorithm 2: Unrolling of Primal-Dual (UPD) Input Initialize $\mathbf{x}_0 \in X^{N_p}, \mathbf{d}_0 \in S^{N_d}$ for $i = 1, \dots, I_M$ do $\mathbf{d}_i = \mathbf{d}_{i-1} + \Gamma_{\theta_i^d}(\mathbf{d}_{i-1}, \mathcal{L}(\mathbf{x}_{i-1}), \mathbf{s})$ $\mathbf{x}_i = \mathbf{x}_{i-1} + \Lambda_{\theta_i^p}(\mathbf{x}_{i-1}, [\partial \mathcal{L}(\mathbf{x}_{i-1})]^* \mathbf{d}_i)$ end Return $\bar{\mathbf{x}}_{I_M}$
--	--

Figure 4.6. Learned unrolling of primal-dual (UPD) for radial multi-spectral deconvolution. Zero-initialization is deployed for $\mathbf{x}_0$ and $\mathbf{d}_0$ and different parameters are learned at each unfolded iteration.

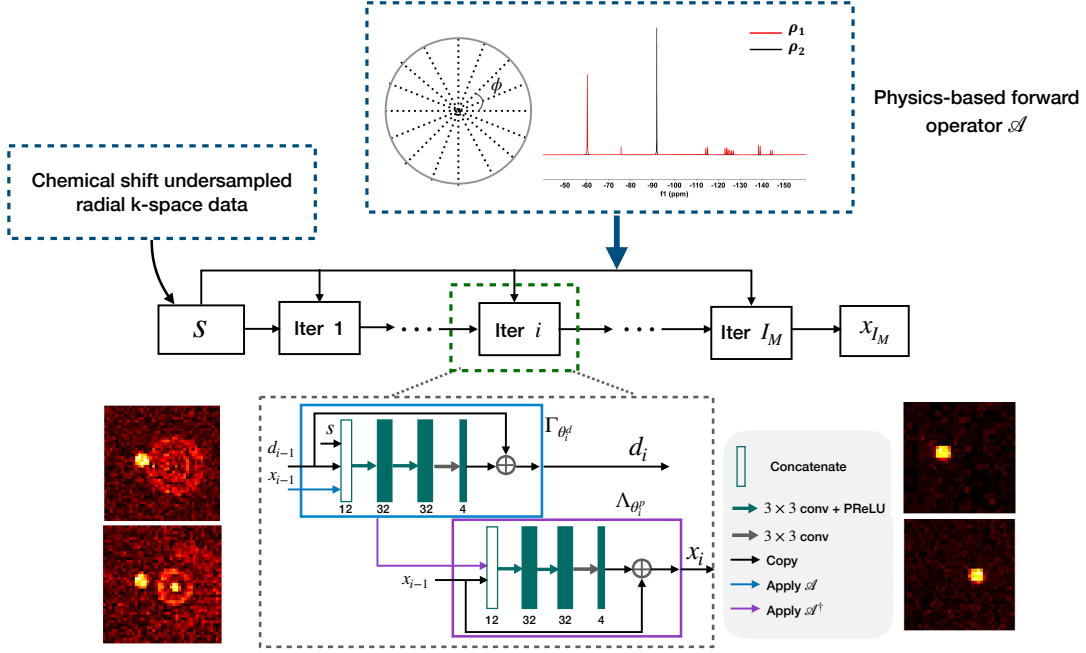


Figure 4.7. Framework of data-driven unrolling algorithm on the simultaneous unmixing of multi-spectral accelerated radial ^{19}F cellular MRI.

4.4 Simulation Results

We trained UPD with $N = 250$ synthetic PFC image pairs (each consisting of two component images of 64^2 size to simulate ^{19}F phantoms) as GT $\{\mathbf{x}^{(n)}\}_{n=1}^N$ in Eq. 4.10. This is aligned with practical cellular MRI scenarios when fully sampled phantom data with a high number of averages are served as GT for initial evaluations [39]. Synthetic uniformly undersampled 2D noisy radial k-space data were generated using Eq. 4.7 yielding input SNR = 20, 5 dB (defined as $20 \log_{10}(\|\mathcal{A}(\mathbf{x})\|_2 / \|\mathbf{w}\|_2)$), which corresponds to moderate and high noise, respectively. The number of radial projections were chosen to be 10 and 20 (*i.e.*, 10, 5-fold undersampling according to radial Nyquist criterion). $\tilde{\mathbf{H}}$ was derived from the chemical shift spectra displayed on Figure 4.1e with readout BW = 100 kHz – 200 kHz. Test data were generated using a separate set of phantom images with the same $\mathcal{A}$ and input SNRs. We examined the PDHG reconstruction with optimally tuned parameters with $I = 500$ iterations as a baseline. The network was trained for 4000 iterations by minimizing Eq. 4.10 using Adam optimizer with

customized cosine annealing [145]. All implementations are based on Python using Operator Discretization Library (ODL) [144] and PyTorch.

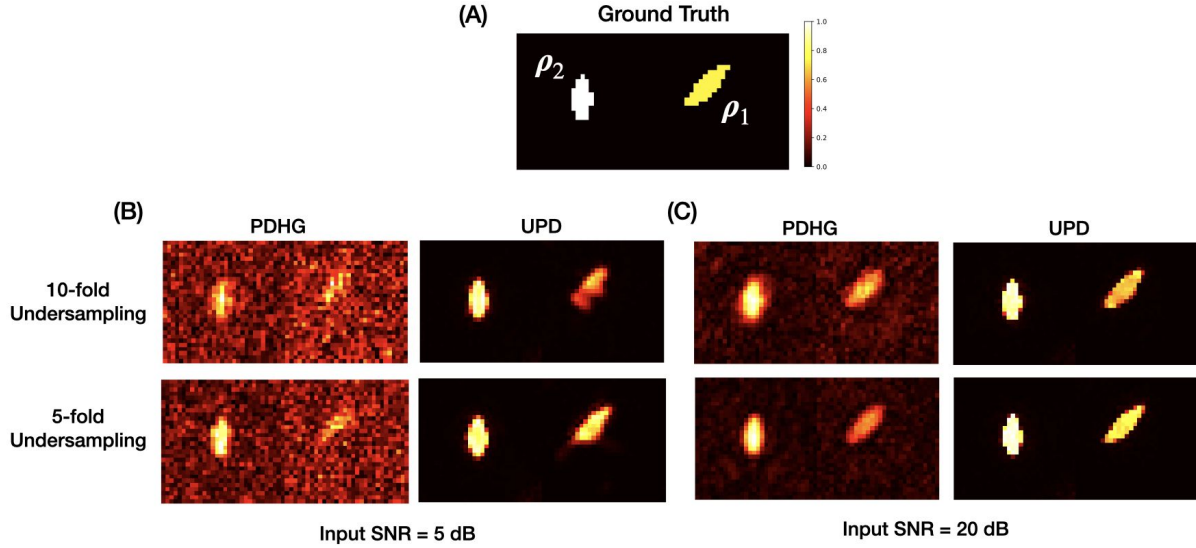


Figure 4.8. Deconvolution of two ^{19}F component images using PDHG and UPD. (A). Ground truths $\mathbf{x}$ representing PFCE (ρ_2 , at resonance frequency) and PFTBC (ρ_1 , multi-spectral frequency offsets). Noisy undersampled radial k-space measurements are generated using derived model in (4.7). (B). Results from input-SNR = 5dB. PDHG is not able to recover the weaker signals in ρ_1 , however, UPD has the capability to unmix the two with suppressed noise. (C). Results from input-SNR = 20 dB. Notice that PDHB suffers from overblurring artifacts due to the TV-norm. The output images from UPD preserves the resolution.

The proper modeling of $\mathcal{A}$ enables successful chemical shift deconvolution across all the test cases (Figures 4.8, 4.9, 4.10). Indeed, two component images are separable using both algorithms, whereas noise suppression is limited under low SNR scenarios for PDHG (Figure 4.8, 4.9b-c, Figure 4.10b-c). For input SNR = 5 dB, some of the weak ^{19}F signals are not detectable with PDHG (Figure 4.9b-c) due to the limitations of structural TV prior under highly noisy scenarios. When increasing input SNR to 20 dB, PDHG reconstruction produces false-positive signals along the blurring edges (Figure 4.10b-c), especially for $10\times$ case. In contrast, learned UPD is capable of enhancing the signal detection with much more pronounced noise removal effects, which yields > 10 dB improvement in peak signal-to-noise ratio (PSNR, $20\log_{10}(M/\|\mathcal{A}_{\theta}^{\dagger}(\mathbf{s}) - \mathbf{x}\|_2)$), where M denotes the maximum possible pixel value) compared

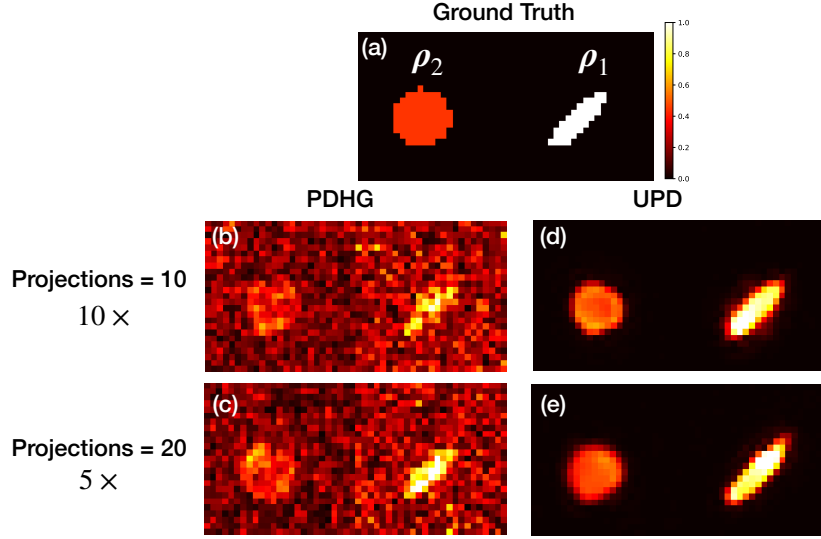


Figure 4.9. Reconstructed chemical shift ^{19}F phantom images using PDHG and UPD under input SNR = 5 dB. Here two undersampling levels (10-fold and 5-fold) are considered for 2D radial k-space measurements.

to PDHG (Table 4.1). Approximately ≈ 1 dB improvement is achieved using $\check{\mathbf{H}}$ with BW = 200, 100 kHz (Table 4.1, left) against BW = 150, 100 kHz, respectively (Table 4.1, right). This implies that joint design of $\mathcal{R}$ and $\check{\mathbf{H}}$ in the overall sensing operator $\mathcal{A}$ is necessary to guarantee recovery. Unlike prior work on compressed sensing ^{19}F imaging, we did not employ multiple acquisitions (*i.e.*, averaging) here, which is considered as an effective approach to improve SNR [39]. Alternatively, the significant PSNR gap (Table 4.1) between PDHG and UPD is expected to be narrowed if radial chemical shift deconvolution is performed using data with multiple signal averages, with the price of prolonged scanning time compared to undersampled pulse sequence. Our view is that learned unrolling is capable of boosting SNR even though the collected measurements are highly undersampled, without being compensated for a fixed scan time.

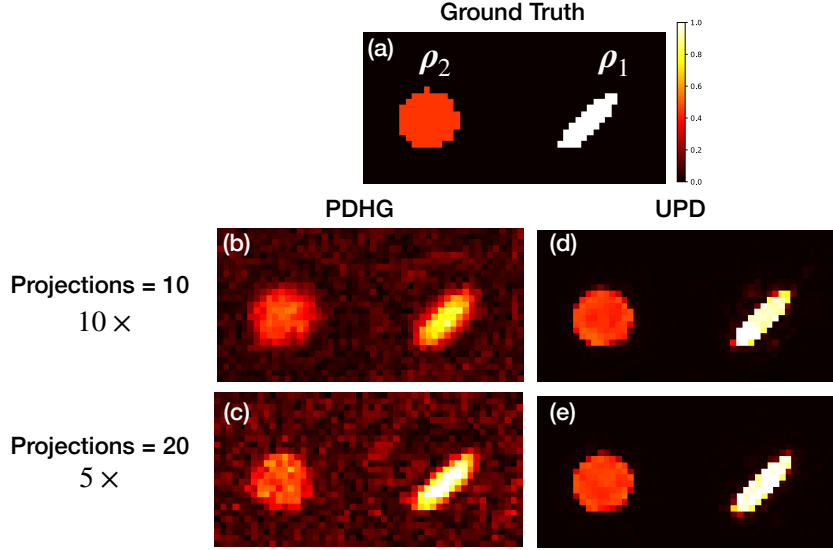


Figure 4.10. Reconstructed chemical shift ^{19}F phantom images using PDHG and UPD under input SNR = 20 dB. Here two undersampling levels (10-fold and 5-fold) are considered for 2D radial k-space measurements.

Table 4.1. Impact of reconstruction quality over change of $\mathcal{A}$. Table shows average PSNR calculated over 20 randomized noise trails, which corresponds to (left) BW = 100 kHz and 200 kHz and (right) BW = 100 kHz and 150 kHz.

PSNR (dB)	BW = 100 kHz, 200 kHz				BW = 100 kHz, 150 kHz			
Undersampling Factor	10×		5×		10×		5×	
Input SNR (dB)	5 dB	20 dB	5 dB	20 dB	5 dB	20 dB	5 dB	20 dB
Algorithm-1: PDHG	9.06	16.88	11.54	20.17	9.21	17.31	11.99	20.29
Algorithm-2: UPD	30.46	36.02	31.55	36.99	29.59	35.22	30.46	36.98

4.5 Discussion and Conclusion

Modeling of multi-spectral MRI chemical shifts as convolutional effects provides a new avenue to unmix the component images. Leveraging the connection between radial sampling and Radon transform enables more accurate reconstruction. Learned primal-dual through unrolling significantly improved the performance of radial multi-spectral deconvolution for highly noisy data in the extreme compression regime.

Furthermore, we recognize that recovering ^{19}F signals with low SNR is essentially a detection task. The detectability of weak signals can be potentially enhanced by incorporating novel model observer regularization into the training loss [146]. Additionally, we note that the intimate relationship between the Radon transform, which naturally arises from MRI radial projections, and function space analysis [147, 148] will also guide the design of new regularization techniques that are favorable for promoting the desirable sparsity in the imaging object. Going forward, another future goal is to separate/unmix images corresponding to different PFC molecules with different chemical shifts and quantify the ^{19}F atoms of each species intravoxel, as well as to accurately estimate the ratios of the different molecular species.

4.6 Acknowledgements

Chapter 4, in part, is a reprint of the material as it appears in the following papers:

- J. Chen, E. T. Ahrens, and P. Pal, “Physics-driven learned deconvolution of multi-spectral cellular mri with radial sampling,” in 2023 57th Asilomar Conference on Signals, Systems, and Computers, pp. 1453–1457, IEEE, 2023.
- J. Chen, P. Pal, E. T. Ahrens, “Physics-driven learned deconvolution of multi-spectral fluorine-19 MRI with multiple agents using radial sampling” in 33rd Annual Scientific Meeting of the ISMRM, Singapore, 2024.

The dissertation author was the primary investigator and author of these papers.

Chapter 5

Emerging Directions and Conclusions

In recent years, data-driven reconstruction frameworks have demonstrated promise for ^1H CS-MRI resulting in improved image quality. Most of these frameworks are based on deep neural networks. However, data-driven methods have remained largely unexplored in ^{19}F cellular MRI, possibly due to (i) challenges in acquiring high-quality imaging data, and (ii) lack of large-scale public datasets. The CS-ZTE acquisition-reconstruction co-design framework described in Chapter 3 is under the classical unsupervised regime that relies on structural/geometric hand-crafted prior information of the signal. This conventional formulation suffers from several drawbacks. Firstly, tuning the regularization parameter λ in (2.8) is non-trivial and imposes non-negligible effects, especially in the low SNR regime commonly encountered in ^{19}F cellular MRI. Secondly, the structural assumption on $\mathbf{x}$ may not be adequate to capture model mismatches. As a result, hand-crafted $\mathcal{R}(\mathbf{x})$ may be unable to capture hidden signal structure. Importantly, data-driven prior can help to augment conventional regularizers and therefore lead to further detection sensitivity enhancement. In this chapter, we will first investigate how geometrical aspects of generative priors can lead to robust design of data-driven regularizers through the lens of a preliminary ^{19}F cellular MRI detection task. Next, we will discuss the state-of-the-art acquisition-reconstruction techniques to combat some frequently encountered adverse data scenarios in ^{19}F MRI. Specifically, model-based deep unrolling and self-supervised/unsupervised reconstruction approaches are able to overcome the data scarcity hurdle, a major concern in

medical imaging data-driven techniques. An alternative chemical shift encoding formulation of multi-spectral ^{19}F components separation is subsequently introduced with the purpose to mitigate the severe radial smearing artifacts occurred in low SNR scenarios. We will also connect with active information acquisition to enable adaptive MRI k-space sensing. Aided by multi-modal imaging such as PET providing complementary knowledge, this scheme will potentially to improve the overall sensitivity and SNR/time further. Finally, we will conclude the dissertation summarizing all the explored sensitivity enhancement techniques for ^{19}F cellular MRI.

5.1 Exploring Novel Generative Priors with Applications in ^{19}F Cellular MRI

Reconstruction of cellular MRI images from so-called k-space measurements [149] is performed by solving an inverse problem, where the optimization problem includes a data-consistency term and regularization terms induced by structural priors on the unknown imaging object. These priors are chosen based on the structural/geometric information of the signal, such as those introduced in Section 2.4 solving (2.8). However, these hand-crafted priors may not always adequately capture additional structures in the signal/image. Generative models are known for capturing hidden low-dimensional geometry of the signal of interest through a non-linear mapping. Recent lines of work have used variations of Generative Adversarial Networks (GAN) to train end-to-end models in CS-MRI, leading to improved texture details of anatomical structures [150, 151]. Recently, generative priors have also gathered attention for solving CS inverse problems (CSGM) [22]. This is different from end-to-end methods [150, 151] since generative models are trained only using unlabeled images, and the forward measurement model is only used at the testing phase. Data-driven priors have been investigated in the CS anatomical MRI setting, where they have exhibited promising performance [23, 152] in high and moderate SNR scenarios. In [23], posterior sampling via Langevin dynamics has been employed to achieve high quality reconstructions on out-of-distribution samples.

Our Contribution: In this work, we use the geometry of the latent space of generative networks to propose a regularizer-free optimization framework, aided with data-dependent initialization. The goal is to improve noise robustness and reduce the overall reconstruction complexity for reconstructing cellular “hot-spot” MRI images from compressed Fourier measurements. We note that the performance of algorithms such as CSGM [22] may be degraded at low SNR and high compression regimes typically encountered in cellular MRI measurements. Our work also distinguishes from other works [153, 23] in the context of generative prior CS-MRI, since the focus here is to achieve better localization of “hot-spots”, rather than to improve the texture details of anatomical structures.

5.1.1 Supervised Recovery Technique with Data-Driven Prior

Data-driven priors have been recently employed as a means of regularization and achieved promising results in several biomedical imaging applications including MRI [153, 23]. Generative models are known to capture low-dimensional latent structure of signals of interest through a highly non-linear mapping as well as representing natural signals with high fidelity [154, 155]. Therefore, a generative network trained on a set of training images $\mathcal{X} = \{\mathbf{x}_i\}_{i=1}^T$ (representative of those encountered in MRI) can serve as a data-driven regularizer to make the estimation problem well-posed. Despite the promising results, there are several outstanding issues with algorithms that employ data-driven generative priors. Firstly, their convergence (and nature of the solution upon convergence) is sensitive to the choice of initialization. Secondly, they typically require elaborate hyper-parameter tuning, which can be very challenging in low SNR regimes. It is to be noted that cellular MRI image reconstruction techniques typically need to operate in low SNR regimes, and it is important to enhance their robustness beyond what is achieved by existing methods.

Consider a generative model represented by a mapping $\mathbf{D} : \mathbb{R}^S \rightarrow \mathbb{R}^N (S < N)$. This mapping is often parameterized by a Deep Neural Network (DNN). The trained model $\mathbf{D}$ is able to map low dimensional vectors $\mathbf{z} \in \mathbb{R}^S$ to high dimensional images $\mathbf{x} = \mathbf{D}(\mathbf{z})$ resembling

training samples $\mathcal{X}$. Given the trained model $\mathbf{D}$, one can recast the objective function in (2.8) as the problem of finding a vector $\mathbf{z} \in \mathbb{R}^S$ such that $\mathbf{AD}(\mathbf{z})$ matches the observed compressed measurements $\mathbf{y}$,

$$\hat{\mathbf{z}} = \arg \min_{\mathbf{z}} \|\mathbf{AD}(\mathbf{z}) - \mathbf{y}\|_2. \quad (5.1)$$

Considering the fact that off-the-shelf generative networks such as GAN or VAE often impose a Gaussian prior distribution on the input space, authors in [22] regularize the optimization problem (5.1) as follows,

$$\hat{\mathbf{z}} = \arg \min_{\mathbf{z}} \|\mathbf{AD}(\mathbf{z}) - \mathbf{y}\|_2^2 + \lambda \|\mathbf{z}\|_2^2, \quad (5.2)$$

where the role of ℓ_2 -regulaizer $\|\mathbf{z}\|_2^2$ is to encourage the exploration of the latent space in the regions favored by the network. However, $\|\mathbf{z}\|_2^2$ might undesirably force latent codes towards the origin, while for a high-dimensional Gaussian, the majority of the mass is located near the surface of a sphere with radius $\sqrt{S}$ [156]. Moreover, in some applications such as “hot-spot” MRI, experiments show that the low-dimensional latent codes corresponding to training samples are distributed in separate clusters which are not necessarily located around the origin. Thus, the ℓ_2 -regulaizer might induce an implicit bias toward a set of clusters located close to the origin. This issue motivates the need for novel regularizers or a set of regularized optimization problems that can benefit from exploring around the latent code clusters. In the next section, we propose a set of data-driven regularizers which can offer faster convergence as well as higher noise robustness.

Since problem (5.2) is non-convex, clever design of non-convex techniques are required to recover the signal of interest $\mathbf{x}$. Since generative models are typically differentiable, iterative gradient based techniques can be applied to yield a solution [22]. However, iterative recovery methods are typically *sensitive to the choice of the initial point*, and require a proper initialization

in order to converge close to the ground truth. In CSGM [22], the authors have suggested repeating the procedure with multiple random initializations to increase the chance of convergence. In this work, we show how unlabeled training samples can guide the design of more systemic initialization schemes for any iterative techniques.

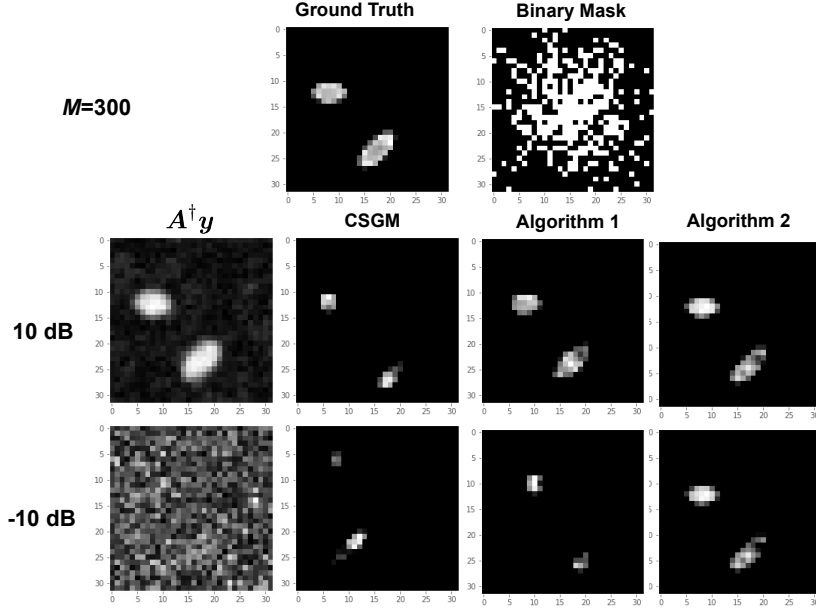


Figure 5.1. Reconstructed cellular MRI images using three different methods: CSGM, Alg. 1, and Alg. 2. Here $M = 300$, SNR=10, -10 dB.

5.1.2 Data-Driven Regularizer and Initializer

In [157], the authors exploited the special geometry induced in the latent space by generative models to develop sensing strategies for solving linear inverse problems. Inspired by the ideas proposed in that work, we develop two novel reconstruction methods that leverage the clustering of latent codes associated with data points and the distinctive geometry of the generative prior’s latent space.

Consider a Variational Autoencoder (VAE) comprising of an encoder-decoder pair, which is trained on a set of “hot-spot” MRI images $\mathcal{X}$ of size $T = |\mathcal{X}|$. Let $\mathbf{D} : \mathbb{R}^S \rightarrow \mathbb{R}^N$, $\mathbf{E} : \mathbb{R}^N \rightarrow \mathbb{R}^S$, respectively denote the decoder and encoder of the trained VAE. Details of Latent Space Clustering (LSC) procedure are summarized in Table 1 from [97]. The inputs to LSC

consist of the trained encoder $\mathbf{E}$, training data samples $\mathcal{X}$, a given integer L , and a given point $\hat{\mathbf{z}} \in \mathbb{R}^S$. First, we extract a set $\mathcal{Z} = \{\mathbf{z}_i\}_{i=1}^T$ of latent codes corresponding to the training samples in $\mathcal{X}$, *i.e.*, $\mathbf{z}_i = \mathbf{E}(\mathbf{x}_i), \forall i \in [T]$. Next, we cluster the elements in the set $\mathcal{Z}$ in an unsupervised fashion, using an off-the-shelf clustering technique (such as K-means). The centroids of these clusters are stored in the set $\mathcal{C}_{\mathcal{Z}}$. Finally, given a vector $\hat{\mathbf{z}} \in \mathbb{R}^S$, we return a set $\mathcal{P}_{L,\hat{\mathbf{z}}}$ containing the L closest elements of $\hat{\mathbf{z}}$ from the set $\mathcal{C}_{\mathcal{Z}}$ in a ℓ_2 sense.

The first method proposed by us (Algorithm 1) employs a Data-dependent regularization strategy and it is summarized in Table 5.1. We first map the measurements $\mathbf{y}$ to the space of the unknown signal $\mathbf{x}$ as $\mathbf{A}^\dagger \mathbf{y}$, and then pass it through the trained encoder in order to obtain a coarse estimate of the true latent code $\mathbf{z}^* = \mathbf{E}(\mathbf{x})$:

$$\mathbf{z}_{ps} = \mathbf{E}(\mathbf{A}^\dagger \mathbf{y}). \quad (5.3)$$

We employ the LSC procedure to obtain the set $\mathcal{P}_{L,\mathbf{z}_{ps}} = \text{LSC}(\mathbf{E}, \mathcal{X}, \mathbf{z}_{ps}, L)$ which returns the centroids of L most probable clusters that might contain the unknown ground truth latent code, $\mathbf{z}^*$. Here, L is determined based on the measurement noise level and the intra-cluster distances. Replacing the regularizer term in (5.2) by a shifted regularizer $\|\mathbf{z} - \tilde{\mathbf{z}}\|_2^2$ will enforce the solver to explore around $\tilde{\mathbf{z}}$ instead of the origin. Inspired from this intuition, we solve L parallel problems, each equipped with a different shifted regularizer corresponding to the elements in the set $\mathcal{P}_{L,\mathbf{z}_{ps}}$. Algorithm 1 then computes $\mathbf{D}(\hat{\mathbf{z}}^*)$, where $\hat{\mathbf{z}}^*$ is a latent code with minimum measurement error over the set $\{\hat{\mathbf{z}}_1, \dots, \hat{\mathbf{z}}_L\}$ (Table 5.1).

This training data-driven regularization strategy demonstrates a higher noise robustness in practice compared to solving problem (5.2) as considered in [22]. However, it still requires tuning the regularizer parameter λ , which can be a challenging task especially in the low SNR regime. Furthermore for non-convex optimization problems, proper initialization ($\mathbf{z}_0$) is often critical for recovering the desired ground truth. To address these issues, we propose a regularizer-free reconstruction technique, which is equipped with a data-driven initializer.

Table 5.1. Data-Dependent Regularizer

Algorithm 1:
Input $\mathbf{y}, \mathbf{A}, \lambda, L, \mathcal{X}$, Trained VAE: $\mathbf{D}, \mathbf{E}$ $\mathbf{z}_{ps} = \mathbf{E}(\mathbf{A}^\dagger \mathbf{y})$ $\mathcal{P}_{L, \mathbf{z}_{ps}} = \text{LSC}(\mathbf{E}, \mathcal{X}, \mathbf{z}_{ps}, L)$ for $\mathbf{c}_i \in \mathcal{P}_{L, \mathbf{z}_{ps}}$ do $\hat{\mathbf{z}}_i = \arg \min_{\mathbf{z}} \ \mathbf{AD}(\mathbf{z}) - \mathbf{y}\ _2^2 + \lambda \ \mathbf{z} - \mathbf{c}_i\ _2^2$ end $\hat{\mathbf{z}}^* = \min_{i \in [L]} \ \mathbf{y} - \mathbf{AD}(\hat{\mathbf{z}}_i)\ _2$ Return $\mathbf{D}(\hat{\mathbf{z}}^*)$

Table 5.2. Regularizer-Free Solver

Algorithm 2:
Input $\mathbf{y}, \mathbf{A}, L, \mathcal{X}$, Trained VAE: $\mathbf{D}, \mathbf{E}$ $\mathbf{z}_{ps} = \mathbf{E}(\mathbf{A}^\dagger \mathbf{y})$ $\mathcal{P}_{L, \mathbf{z}_{ps}} = \text{LSC}(\mathbf{E}, \mathcal{X}, \mathbf{z}_{ps}, L)$ for $\mathbf{c}_i \in \mathcal{P}_{L, \mathbf{z}_{ps}}$ do initialize $\mathbf{z}$ with $\mathbf{c}_i$ and solve $\hat{\mathbf{z}}_i = \arg \min_{\mathbf{z}} \ \mathbf{AD}(\mathbf{z}) - \mathbf{y}\ _2^2$ end $\hat{\mathbf{z}}^* = \min_{i \in [L]} \ \mathbf{y} - \mathbf{AD}(\hat{\mathbf{z}}_i)\ _2$ Return $\mathbf{D}(\hat{\mathbf{z}}^*)$

The method (Algorithm 2) is summarized in Table 5.2. The key novelty here is to utilize the trained encoder and training data to obtain a set of possible initializers for any standard solver. Specifically, we employ gradient descent to solve the following unregularized problem, while initializing the iterations with entries from the set $\mathcal{P}_{L, \mathbf{z}_{ps}}$. In particular, we solve the following problem L times, and each time we initialize the solver with a new element of set $\mathcal{P}_{L, \mathbf{z}_{ps}}$. Similar to Algorithm 1, we finally return $\mathbf{D}(\hat{\mathbf{z}}^*)$, where $\hat{\mathbf{z}}^*$ is a latent code that minimizes measurement error over the set $\{\hat{\mathbf{z}}_1, \dots, \hat{\mathbf{z}}_L\}$. Exploiting the interplay between the training dataset and the geometry of the input space of generative networks not only allows us to avoid parameter tuning, but also improves the convergence of off-the-shelf non-convex solvers via data-driven initialization.

5.1.3 Phantom Simulations

In order to evaluate the performance of proposed methods we consider a scenario arisen in cellular MRI application. A VAE (3-layer encoder-decoder) is trained on the 60000 MNIST training samples and the trained decoder serves as a generative prior. The simulation experiments are based on the compressed cellular MRI data in the low-SNR regime. Clean “hot-spot” 32×32 ($N = 1024$) images are generated with varied shapes, orientations, and locations, with a total of 60000 2D slices, where 55000 slices are reserved for the training of the VAE and the test images are randomly selected from the remaining 5000 images. two SNR levels, which correspond to moderate and noisy acquisition scenarios. Here, following [152], SNR is defined as $10\log_{10}(\|\mathbf{Ax}\|_2^2/\|\mathbf{w}\|_2^2)$. During the testing phase, three methods—CSGM and the proposed Algorithms 1 and 2—are evaluated, where basic recovery using the pseudoinverse solution $(\mathbf{A}^\dagger \mathbf{y})$ serves as the the baseline. For CSGM, in order to account for the randomness due to initialization of $\mathbf{z}$, we solve (5.1) ten times (each with a different random initialization) and record the reconstructed image with the minimum RMSE defined by $\|\mathbf{x} - \hat{\mathbf{x}}\|/\sqrt{N}$ [152]. The test images are first converted to k-space measurements through Fourier transform (by applying the Fourier matrix $\mathbf{F} \in \mathbb{C}^{N \times N}$) and then undersampled by a factor of 3 and 10 ($M = 100$ and 300, compression rate 10% and 30%) using pseudorandom binary masks.

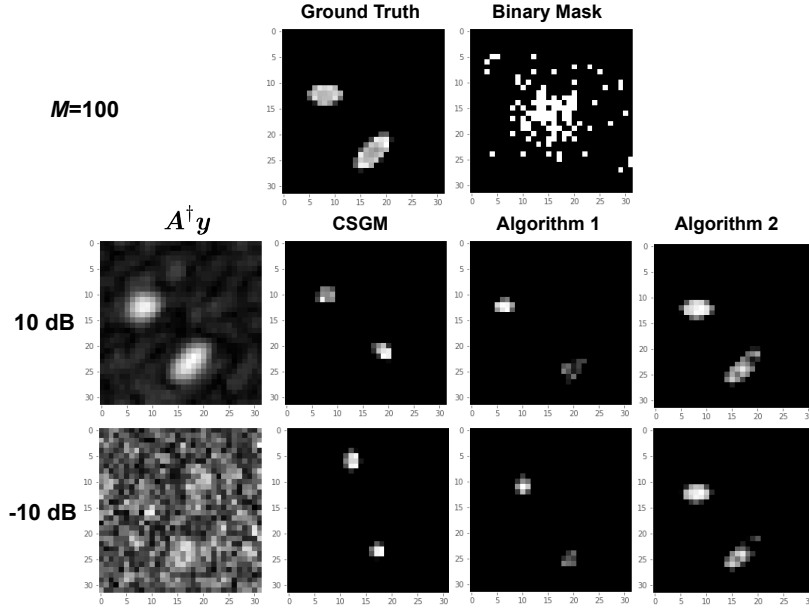


Figure 5.2. Reconstructed cellular MRI images using three different methods: CSGM, Alg.1, and Alg. 2. Here $M = 100$, SNR=10, -10 dB.

Figure 5.1 and 5.2 illustrate a test case under the aforementioned scenarios. Figure 5.1 demonstrates that both the proposed algorithms are able to produce artifact-free images with the refined structures of the “hot-spots” at 10 dB, while the baseline and CSGM struggles with either overestimating or underestimating the region of interest. As the compression rate increases (Figure 5.2), Algorithm 2 with data-dependent initializer demonstrates its superior ability to recover the “hot-spots” from extremely compressed measurements whereas all the other methods failed to preserve these features. As for quantitative evaluations, RMSEs computed over 10 randomized noise trails are shown in Table. 1. The results are aligned with Figures 5.1 and 5.2, as both of the proposed algorithms outperform the two baselines for 10 dB SNR. The performance of Algorithm 1 degrades as the SNR decreases to -10 dB. However, Algorithm 2 is able to maintain its robustness against compression and noise.

5.1.4 Discussion

We studied certain geometrical aspects of generative priors through the lens of cellular MRI image reconstruction, and showed how the interplay between training data and the geometry

Table 5.3. RMSE standard deviations over 10 random trials ($\mathbf{A}$ is fixed for each M). The lowest RMSE for each case is marked in red.

		$\mathbf{A}^\dagger \mathbf{y}$	CSGM	Algorithm 1	Algorithm 2
10 dB	$M = 100$	0.1454 (0.0023)	0.1767 (0.0156)	0.1381 (0.0080)	0.0698 (0.0012)
	$M = 300$	0.1260 (0.0035)	0.1736 (0.0221)	0.0668 (0.0014)	0.0614 (0.0012)
-10 dB	$M = 100$	0.3272 (0.0307)	0.1894 (0.0173)	0.1751 (0.0117)	0.0777 (0.0233)
	$M = 300$	0.3284 (0.0330)	0.1755 (0.0221)	0.1694 (0.0087)	0.0635 (0.0134)

of the latent space of generative networks can be used to improve performance. We designed data-driven initialization and Latent Regularizer-Free techniques for inverse imaging problems. The proposed method exhibits robustness at low SNR and extreme compression regimes, without the need for hyper-parameter tuning or test & trial initialization. In the future, we plan to use cryo-fluorescence tomography (CFT) [158] as ground truth images in the training phase in order to compensate for the lack of clean training data in cellular MRI.

The proposed algorithms require the knowledge of set $\mathcal{C}_{\mathcal{X}}$ at test time. Due to limited storage capacity and/or privacy concerns, it may not always be practical to access the set $\mathcal{C}_{\mathcal{X}}$ during testing. To address this issue, the spatial geometry of the latent space induced by ReLU generative networks can be further used to indirectly obtain an estimate of the set $\mathcal{C}_{\mathcal{X}}$. It has been shown that neural networks with ReLU nonlinearities induce a partition on their input space, and then maps the inputs belonging to each partition to the output space via a different affine mapping [159]. This special geometry of ReLU neural networks has been widely studied in the context of training [160, 161]. Using these partitions induced in the latent space of a ReLU generative network, one can replace the cluster centroids $\mathcal{C}_{\mathcal{X}}$ (which is function of training data), with a network-dependent estimate $\hat{\mathcal{C}}_{\mathbf{E}}$ in the future. This replacement not only reduces computational and storage complexity of the proposed method but can also provide higher robustness against noise.

5.2 Combating Adverse ^{19}F Data Scenarios-Towards Learning Based Acquisitions-Reconstructions

5.2.1 Model-based deep unrolling and self-supervised reconstruction approaches

Most existing work on deep learning reconstruction for ^1H CS-MRI rely on a large volume ($> 10\text{k}$) of public-shared datasets, such as fastMRI [24]. The training data is used to solve an inverse problem, aided by, for example, a learned convolutional neural network (CNN)-based pre-trained plug-and-play type of denoiser [138], a deep generative model [150], or a generative prior [23, 97]. In addition, model-based deep unrolling networks [162, 137] have emerged as good candidates for solving CS-MRI reconstruction tasks as they typically only require < 500 training images. For example, in Chapter 4, we described a synthetic phantom study to separate two different PFC materials with different ^{19}F chemical shifts for ‘multicolor’ imaging using undersampled radial k-space acquisitions and unrolled primal-dual deconvolution; the results showed a > 5 dB improvement in PSNR compared to the classical iterative algorithm (4.9). Overall, it is challenging to acquire training datasets for ^{19}F MRI. One possible direction is to utilize self-supervised or unsupervised learning techniques [163] that can directly learn from undersampled noisy measurements. Self-supervised data-driven algorithms, such as Noise2Noise [164] and Regularization by Denoising (RED) [165], have been explored for undersampled MRI reconstruction [166, 167] as they do not require clean, ground-truth datasets.

More recently, an untrained learning method dubbed “Deep Image Prior” (DIP) [168] has been proposed and has witnessed strong performance for solving inverse problems in computational imaging domain, such as denoising and super-resolution. Unlike previous generative prior approach (5.1) when network weights θ is obtained from training, DIP learns θ directly from test data by leveraging CNN as an implicit prior. This is because the structure of a decoder generator network D is sufficient to capture a great deal of low-level image statistics prior to any learning, without explicit probabilistic priors on either z or θ . Extension of DIP for CS-MRI

reconstruction can be formulated as

$$\boldsymbol{\theta}^* = \min_{\boldsymbol{\theta}} \|\mathbf{y} - \mathbf{A}\mathbf{D}_{\boldsymbol{\theta}}(\mathbf{z})\|_2, \quad \hat{\mathbf{x}} = \mathbf{D}_{\boldsymbol{\theta}}(\mathbf{z}) \quad (5.4)$$

Existing works [169] to solve (5.4) mainly focus on ^1H anatomical CS-MRI data acquired with relatively high quality. However, it is prone to overfitting [170] and a careful selection of stopping criterion via significant hyperparameter tuning is required in order to achieve on-par performance with supervised learning architectures, *e.g.*, U-Net [169]. Importantly, for ^{19}F CS-MRI reconstruction, selecting this stopping condition from noisy low SNR measurements may introduce unwanted bias that can deteriorate its noise taming ability. The image generative model proposed in [171] demonstrated a set of inverse problems can be solved simultaneously without the use of a spatial image prior by instead inferring a shared image generator with a low-dimensional latent space. This could potentially lead to robust performance for ^{19}F CS-MRI detection tasks as the framework does not assume any explicit example ground truth images to construct an image prior.

5.2.2 Chemical shift encoding inspired multi-spectral separation

The complexity of the ^{19}F -tracer spectrum is also another critical factor for improving detection sensitivity. Ideally, most of the fluorine sites should be spectrally equivalent to form a single resonance, thereby avoiding chemical shift artifacts and simplifying MRI data acquisition methods. Imaging species with multiple peaks can be achieved using selective, narrow-bandwidth acquisitions, over a portion of the spectrum that is chemically shifted from other molecular sites; this approach comes at the cost of reduced sensitivity, as all ^{19}F spins do not contribute to signal. Methods for broad bandwidth spectral capture, with post-processing signal reconstruction, for use with tracers displaying multiple spectral peaks, are also described [11, 15], but at a cost of prolonged scan time due to multi-echo imaging. These methods all focus on conventional Cartesian pulse sequences and generalization to CS non-Cartesian acquisitions is non-trivial.

In Section 4, we described a novel modeling for radial chemical shift deconvolution through the lens of simultaneous detection of ^{19}F -labeled multiple cell targets. The proposed analytical form (4.7) is derived in the spatial domain as large ^{19}F frequency offsets translate into significant spatial smearing.

Alternatively, separation of multi-spectral ^{19}F components can be potentially implemented via chemical shift encoding methods, similar to off-resonant blurring correction in the context of ^1H fat-water imaging [172, 136]. To account for the off-resonant blurring of fat spectral peaks due to radial readout, an extra non-linear modulation term $D(t) = \sum_{m=1}^M \alpha_m \cdot \exp(i2\pi\Delta f_m \cdot t)$ is taken into the consideration on top of the NUFFT operator $\mathbf{F}_u$, modeling chemical shift in k-space at readout point t . The corresponding j^{th} set of k-space measurements therefore becomes [136]

$$\mathbf{s}_j(t) = D_j(t)\mathbf{F}_u\boldsymbol{\rho}_1 + \mathbf{F}_u\boldsymbol{\rho}_2 \quad (5.5)$$

At n^{th} iteration, the non-linearity can be linearized in the Jacobian form at estimate $\mathbf{x}^{(n)} = [\boldsymbol{\rho}_1^{(n)}, \boldsymbol{\rho}_2^{(n)}]$ as [172]

$$\mathbf{s}(\mathbf{x}_n + d\mathbf{x}) \approx \mathbf{s}(\mathbf{x}_n) + d\mathbf{s}(\mathbf{x}_n)d\mathbf{x} \quad (5.6)$$

This formulation is also extended to learned unrolling in the context of water-fat separation following multi-echo Cartesian chemical shift encoding [173]. Direct translation into radial acquisitions is not straightforward due to the additional handling of NUFFT operator. Recent work featuring in off-resonance correction has shown promise in separating fat tissues from blurring artifacts caused by spiral sampling [174]. However, its performance may be constrained by the wide chemical shift frequency range imposed by ^{19}F components magnified by intrinsic large spacing from radial samples.

5.2.3 Active information acquisition and multimodal guided imaging

In Chapter 3, we presented the CS-ZTE [39] pipeline where we perform repeated acquisitions followed by signal averaging with the aim to boost SNR. It is a non-adaptive scheme, reminiscent of ‘repetition coding’ [78] for multiple independent and identical acquisitions. While this scheme provides robustness, it is not the most optimal way, in terms of striking a balance between robustness and sample complexity. It is known that adaptive strategies can lead to better performance over non-adaptive techniques, especially at low SNR with the same sample complexity [175]. Hence, adaptive sensing seems to be a promising direction for ^{19}F MRI since SNR/time is of the essence.

On the one hand, by combining sensing design with CS reconstruction into a joint adaptive learning framework, one can potentially outperform the classical co-design pipeline. One such unexplored area is attempting to train a joint network to learn a sampling trajectory and reconstruction parameters simultaneously [176] or deploy reinforcement learning to actively learn the pattern [177]. However, these frameworks all rely on a large MRI training database which does not currently exist for ^{19}F MRI applications as, to date, studies are conducted at small sample size. Suitably designed active information acquisition schemes, on the other hand, are known to be asymptotically optimal [178] in achieving capacity, and significant improvements in performance at lower SNRs. The overall idea is to apply sequentially designed sensing matrix using previous collected measurements as guidance to optimize the information gain, especially consider the desire signal is sparsely represented [179, 180]. This line of work has found its roots in wireless communications, for example, estimating the dominant paths of mmWave channels [181] and sequentially optimizing the beamforming vectors based on a low-complexity hierarchical beamforming codebook [182].

Since adaptive strategies are developed within a Bayesian framework, the use of effective “priors” plays an important role in the context of active MRI acquisition. One option is to apply statistical sparsity characteristics of images, *e.g.*, product of super-Gaussian (Laplace) potentials

[183], incorporated by way of a prior distribution when optimizing the MAP (maximum a posteriori) objective. This approach is intended for real-time adaptive sampling design, in which each subsequent k-space sampling location is chosen greedily on-the-fly using real-time feedback, calculated from posterior uncertainty criterion [183]. However, this approach suffers from high computational complexity, which makes real-time implementation unrealistic. Another option is to utilize imaging information from Positron emission tomography (PET) scans acquired on the same subject as a prior, inspired from previous study on multimodal PET and ^{19}F MRI for inflammatory macrophage detection [184]. While PET and MRI both aim to capture the same ground truth, their measurement models are sufficiently diverse. The “side information” information provided by PET can work synergistically with the ^{19}F MRI data to yield a more accurate representation of tracer distribution in tissue, by either providing an additional set of complementary measurements, or by helping to guiding the MRI sampling trajectories in an adaptive signal acquisition framework. This acquisition scheme can be potentially combined with the implicit Neural Representation reconstruction [185] framework in order to further improve the overall sensitivity and SNR/time, when large-scale training data is unavailable.

5.3 Conclusion

^{19}F MRI cell tracking using PFC tracer agents is a rapidly emerging alternative to ^1H -based approaches using metal-ion-based contrast agents. Future improvements in sensitivity and functionality of ^{19}F -based cell tracking will require an integrated and interdisciplinary approach that rigorously applies principles of chemistry, biology, spin physics, and signal image processing. In the first part of the dissertation, the materials and methods for sensitivity enhancement described above and the use of co-designed pulse sequences and reconstruction methods can be simultaneously integrated into future clinical studies to enable multi-fold sensitivity enhancement of cell detection.

An example of such systematic acquisition-reconstruction co-design pipeline is described

in Chapter 3, where pulse sequence data reconstruction algorithms were optimized to image PRE ^{19}F tracers incorporating paramagnetic metal ions. A limiting factor in sensitivity enhancement is T_2 line broadening, which constrains the maximum useful concentration of Fe^{3+} in the nanoemulsion. Because this sensitivity barrier falls as $\text{TE} \rightarrow 0$, we explored the use of the CS-ZTE pulse sequence with undersampled radial k-space spokes followed by CS reconstruction using Eq. 3.1 tuned with Pareto optimality. CS-ZTE can acquire 3D images in ~ 25 s with 64^3 image points using an 8-fold k-space undersampling factor [39]. This short acquisition time enables a commensurate increase in signal averages per scan to boost sensitivity. A $> 30\times$ improvement in the LOD is readily achievable for the same scan time when using a combined PRE nanoemulsion tracer ($T_1 = 7$ ms, $T_2^* = 1.5$ ms, at 11.7 T) and CS-ZTE, as compared to nanoemulsion without metal and a standard GRE sequence. This dramatic leap in sensitivity suggests a cell population labeled with Fe-nanoemulsion at a mean $\sim 10^{12}$ ^{19}F /cell, $\sim 1,000$ cells/voxel should be detectable. Overall, coupling CS-ZTE with PRE nanoemulsion leads to sensitivity enhancement by three distinct mechanisms, namely (i) undersampling, and the commensurate increase in signal averaging for a fixed scan period, (ii) paramagnetic reduction of T_1 , which accelerates data acquisition and enables further signal averaging in scan period, and (iii) the intrinsic ‘denoising’ properties of the CS algorithm [39].

The second part of the dissertation focuses on leveraging robust learning-based techniques under adverse ^{19}F data scenarios. Moving towards multicolor ^{19}F with multiple labeled cell targets, the modeling of radial MRI chemical shifts as convolutional effects provides effective alternatives to unmix the component images. By leveraging the connection between radial sampling and the Radon transform, learned primal-dual through unrolling significantly improves the performance (> 5 dB reconstruction PSNR) of radial multi-spectral deconvolution [96]. The proposed work in Chapter 4 will not only enable detection of multiple ^{19}F tracer probes *in vivo*, but provide new avenues to separate multicolor radial chemical shifts for other X-nuclei imaging applications, *e.g.*, ^{23}Na [186]. Notably, the method requires minimal sequence adaptation and therefore can be easily implemented across different MRI systems. We studied certain

geometrical aspects of generative priors through the lens of cellular MRI image reconstruction, and showed how the interplay between training data and the geometry of the latent space of generative networks can be used to improve performance. We designed data-driven initialization and Latent Regularizer-Free techniques for inverse imaging problems. The proposed method exhibits robustness at low SNR and extreme compression regimes, without the need for hyperparameter tuning or test and trial initialization, as opposed to classical iterative algorithms with hand-crafted priors. In addition, cryo-fluorescence tomography (CFT) [158] can be utilized as ground truth templates during the training phase in order to compensate for the lack of clean data. In the future, to optimize information gain, previously collected measurements can be utilized as guidance for the sequential design of k-space acquisition/sensing. This scheme will potentially improve SNR/time further, aided by multi-modal imaging such as PET providing complementary prior knowledge. Overall, systematic acquisition-reconstruction co-design will empower unprecedented precision in cell tracking and other ^{19}F MRI applications.

5.4 Acknowledgements

Chapter 5, in part, is a reprint of the material as it appears in the following paper:

- S. Shahsavari, J. Chen, and P. Pal, “Exploring the geometry of generative priors with applications in cellular MRI,” in 2022 56th Asilomar Conference on Signals, Systems, and Computers, pp. 1010–1015, IEEE, 2022.

S. Shahsavari was the primary author of the paper, proposed the latent space clustering idea, and developed the algorithms. The dissertation author contributed towards paper writing, phantom data processing, and helped the integration of CS-MRI into the algorithm framework. Chapter 5 is also, in part, a reprint of material in submission as:

- J. Chen, P. Pal, E. T. Ahrens, “Systems engineering approach towards sensitive cellular fluorine-19 MRI” (Journal paper under preparation).

The dissertation author was the primary investigator and author of the paper.

Bibliography

- [1] E. T. Ahrens, B. M. Helfer, C. F. O’Hanlon, and C. Schirda, “Clinical cell therapy imaging using a perfluorocarbon tracer and fluorine-19 mri,” *Magnetic resonance in medicine*, vol. 72, no. 6, pp. 1696–1701, 2014.
- [2] J. W. Bulte and H. E. Daldrup-Link, “Clinical tracking of cell transfer and cell transplantation: trials and tribulations,” *Radiology*, vol. 289, no. 3, pp. 604–615, 2018.
- [3] U. Flögel and E. T. Ahrens, *Fluorine magnetic resonance imaging*. Jenny Stanford Publishing, 2016.
- [4] J. Ruiz-Cabello, B. P. Barnett, P. A. Bottomley, and J. W. Bulte, “Fluorine (19f) mrs and mri in biomedicine,” *NMR in Biomedicine*, vol. 24, no. 2, pp. 114–129, 2011.
- [5] J. Zhong, K. Narsinh, P. A. Morel, H. Xu, and E. T. Ahrens, “In vivo quantification of inflammation in experimental autoimmune encephalomyelitis rats using fluorine-19 magnetic resonance imaging reveals immune cell recruitment outside the nervous system,” *PLoS one*, vol. 10, no. 10, p. e0140238, 2015.
- [6] M. Srinivas, M. S. Turner, P. A. Janjic, Jelena M. M., D. H. Laidlaw, and E. T. Ahrens, “In vivo cytometry of antigen-specific t cells using 19f mri,” *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 62, no. 3, pp. 747–753, 2009.
- [7] E. T. Ahrens, R. Flores, H. Xu, and P. A. Morel, “In vivo imaging platform for tracking immunotherapeutic cells,” *Nature biotechnology*, vol. 23, no. 8, pp. 983–987, 2005.
- [8] E. T. Ahrens and J. Zhong, “In vivo mri cell tracking using perfluorocarbon probes and fluorine-19 detection,” *NMR in biomedicine*, vol. 26, no. 7, pp. 860–871, 2013.
- [9] A. A. Kislukhin, H. Xu, S. R. Adams, K. H. Narsinh, R. Y. Tsien, and E. T. Ahrens, “Paramagnetic fluorinated nanoemulsions for sensitive cellular fluorine-19 magnetic resonance imaging,” *Nature materials*, vol. 15, no. 6, pp. 662–668, 2016.
- [10] C. Jacoby, S. Temme, F. Mayenfels, N. Benoit, M. P. Krafft, R. Schubert, J. Schrader, and U. Flögel, “Probing different perfluorocarbons for in vivo inflammation imaging by 19f mri: image reconstruction, biological half-lives and sensitivity,” *NMR in Biomedicine*, vol. 27, no. 3, pp. 261–271, 2014.

- [11] R. B. van Heeswijk, R. Colotti, E. Darçot, J. Delacoste, M. Pellegrin, D. Piccini, and D. Hernando, “Chemical shift encoding (cse) for sensitive fluorine-19 mri of perfluorocarbons with complex spectra,” *Magnetic resonance in medicine*, vol. 79, no. 5, pp. 2724–2730, 2018.
- [12] J. Schoormans, C. Calcagno, M. R. Daal, R. C. Wüst, C. Faries, A. Maier, A. J. Teunissen, S. Naidu, B. L. Sanchez-Gaytan, A. J. Nederveen, and Z. Fayad, “An iterative sparse deconvolution method for simultaneous multicolor 19f-mri of multiple contrast agents,” *Magnetic resonance in medicine*, vol. 83, no. 1, pp. 228–239, 2020.
- [13] D. Freeman, H. Muller, R. Hurd, and S. Young, “Rapid 19f magnetic resonance imaging of perfluorooctyl bromide in vivo,” *Magnetic resonance imaging*, vol. 6, no. 1, pp. 61–64, 1988.
- [14] M. J. Goette, J. Keupp, J. Rahmer, G. M. Lanza, S. A. Wickline, and S. D. Caruthers, “Balanced ute-ssfp for 19f mr imaging of complex spectra,” *Magnetic resonance in medicine*, vol. 74, no. 2, pp. 537–543, 2015.
- [15] K. D. Ludwig, D. Hernando, N. T. Roberts, R. B. van Heeswijk, and S. B. Fain, “A chemical shift encoding (cse) approach for spectral selection in fluorine-19 mri,” *Magnetic resonance in medicine*, vol. 79, no. 4, pp. 2183–2189, 2018.
- [16] J. W. Bulte, “Detecting different cell populations using multispectral 19f mri,” 2019.
- [17] M. Lustig, D. Donoho, and J. M. Pauly, “Sparse mri: The application of compressed sensing for rapid mr imaging,” *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 58, no. 6, pp. 1182–1195, 2007.
- [18] E. J. Candes, J. K. Romberg, and T. Tao, “Stable signal recovery from incomplete and inaccurate measurements,” *Communications on Pure and Applied Mathematics: A Journal Issued by the Courant Institute of Mathematical Sciences*, vol. 59, no. 8, pp. 1207–1223, 2006.
- [19] J. Zhong, P. H. Mills, T. K. Hitchens, and E. T. Ahrens, “Accelerated fluorine-19 mri cell tracking using compressed sensing,” *Magnetic resonance in medicine*, vol. 69, no. 6, pp. 1683–1690, 2013.
- [20] I. Goodfellow, J. Pouget-Abadie, M. Mirza, B. Xu, D. Warde-Farley, S. Ozair, A. Courville, and Y. Bengio, “Generative adversarial nets,” *Advances in neural information processing systems*, vol. 27, 2014.
- [21] D. P. Kingma and M. Welling, “Auto-encoding variational bayes,” *arXiv preprint arXiv:1312.6114*, 2013.
- [22] A. Bora, A. Jalal, E. Price, and A. G. Dimakis, “Compressed sensing using generative models,” *International Conference on Machine Learning*, 2017.

- [23] A. Jalal, M. Arvinte, G. Daras, E. Price, A. G. Dimakis, and J. Tamir, “Robust compressed sensing mri with deep generative priors,” *Advances in Neural Information Processing Systems*, vol. 34, pp. 14938–14954, 2021.
- [24] F. Knoll, J. Zbontar, A. Sriram, M. J. Muckley, M. Bruno, A. Defazio, M. Parente, K. J. Geras, J. Katsnelson, H. Chandarana, *et al.*, “fastmri: A publicly available raw k-space and dicom dataset of knee images for accelerated mr image reconstruction using machine learning,” *Radiology: Artificial Intelligence*, vol. 2, no. 1, p. e190007, 2020.
- [25] Y. B. Sahel, J. P. Bryan, B. Cleary, S. L. Farhi, and Y. C. Eldar, “Deep unrolled recovery in sparse biological imaging: Achieving fast, accurate results,” *IEEE Signal Processing Magazine*, vol. 39, no. 2, pp. 45–57, 2022.
- [26] V. Monga, Y. Li, and Y. C. Eldar, “Algorithm unrolling: Interpretable, efficient deep learning for signal and image processing,” *IEEE Signal Processing Magazine*, vol. 38, no. 2, pp. 18–44, 2021.
- [27] K. Hammernik, T. Küstner, B. Yaman, Z. Huang, D. Rueckert, F. Knoll, and M. Akçakaya, “Physics-driven deep learning for computational magnetic resonance imaging: Combining physics and machine learning for improved medical imaging,” *IEEE signal processing magazine*, vol. 40, no. 1, pp. 98–114, 2023.
- [28] E. T. Ahrens, B. M. Helfer, C. F. O’Hanlon, D. R. Lister, J. L. Bykowski, K. Messer, B. I. Leach, J. Chen, H. Xu, G. A. Daniels, *et al.*, “Method for estimation of apoptotic cell fraction of cytotherapy using in vivo fluorine-19 magnetic resonance: pilot study in a patient with head and neck carcinoma receiving tumor-infiltrating lymphocytes labeled with perfluorocarbon nanoemulsion,” *Journal for immunotherapy of cancer*, vol. 11, no. 6, 2023.
- [29] T. Nakamura, H. Matsushita, F. Sugihara, Y. Yoshioka, S. Mizukami, and K. Kikuchi, “Activatable 19f mri nanoparticle probes for the detection of reducing environments,” *Angewandte Chemie International Edition*, vol. 54, no. 3, pp. 1007–1010, 2015.
- [30] G. Brix, M. E. Bellemann, U. Haberkorn, L. Gerlach, P. Bachert, and W. J. Lorenz, “Mapping the biodistribution and catabolism of 5-fluorouracil in tumor-bearing rats by chemical-shift selective 19f mr imaging,” *Magnetic resonance in medicine*, vol. 34, no. 3, pp. 302–307, 1995.
- [31] A. Rose, “The sensitivity performance of the human eye on an absolute scale,” *JOSA*, vol. 38, no. 2, pp. 196–208, 1948.
- [32] A. E. Burgess, “The rose model, revisited,” *JOSA A*, vol. 16, no. 3, pp. 633–646, 1999.
- [33] R. F. Wagner, “Toward a unified view of radiological imaging systems. part ii: Noisy images,” *Medical physics*, vol. 4, no. 4, pp. 279–296, 1977.

- [34] R. Watts and Y. Wang, “k-space interpretation of the rose model: noise limitation on the detectable resolution in mri,” *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 48, no. 3, pp. 550–554, 2002.
- [35] W. Peterson, T. Birdsall, and W. Fox, “The theory of signal detectability,” *Transactions of the IRE professional group on information theory*, vol. 4, no. 4, pp. 171–212, 1954.
- [36] D. Van Meter and D. Middleton, “Modern statistical approaches to reception in communication theory,” *Transactions of the IRE Professional Group on Information Theory*, vol. 4, no. 4, pp. 119–145, 1954.
- [37] A. Rose, “Vision: human and electronic,” in *Applied Solid State Physics*, pp. 79–160, Springer, 1973.
- [38] T. K. Hitchens, Q. Ye, D. F. Eytan, J. M. Janjic, E. T. Ahrens, and C. Ho, “19f mri detection of acute allograft rejection with in vivo perfluorocarbon labeling of immune cells,” *Magnetic resonance in medicine*, vol. 65, no. 4, pp. 1144–1153, 2011.
- [39] J. Chen, P. Pal, and E. T. Ahrens, “Enhanced detection of paramagnetic fluorine-19 magnetic resonance imaging agents using zero echo time sequence and compressed sensing,” *NMR in Biomedicine*, vol. 35, no. 8, p. e4725, 2022.
- [40] L. Starke, J. M. Millward, C. Prinz, F. Sherazi, H. Waiczies, C. Lippert, M. Nazaré, F. Paul, T. Niendorf, and S. Waiczies, “First in vivo fluorine-19 magnetic resonance imaging of the multiple sclerosis drug siponimod,” *Theranostics*, vol. 13, no. 4, p. 1217, 2023.
- [41] H. Gudbjartsson and S. Patz, “The rician distribution of noisy mri data,” *Magnetic resonance in medicine*, vol. 34, no. 6, pp. 910–914, 1995.
- [42] M. Meissner, M. Reiser, T. Hugger, J. Hennig, D. von Elverfeldt, and J. Leupold, “Revealing signal from noisy 19f mr images by chemical shift artifact correction,” *Magnetic resonance in medicine*, vol. 73, no. 6, pp. 2225–2233, 2015.
- [43] R. W. Brown, Y.-C. N. Cheng, E. M. Haacke, M. R. Thompson, and R. Venkatesan, *Magnetic resonance imaging: physical principles and sequence design*. John Wiley & Sons, 2014.
- [44] M. Packard, W. W. Hansen, and F. Bloch, “Nuclear induction,” in *Physical Review*, vol. 69, pp. 680–680, AMERICAN PHYSICAL SOC ONE PHYSICS ELLIPSE, COLLEGE PK, MD 20740-3844 USA, 1946.
- [45] B. Ebner, P. Behm, C. Jacoby, S. Burghoff, B. A. French, J. Schrader, and U. Flögel, “Early assessment of pulmonary inflammation by 19f mri in vivo,” *Circulation: Cardiovascular Imaging*, vol. 3, no. 2, pp. 202–210, 2010.

- [46] M. Srinivas, P. Morel, L. A. Ernst, D. Laidlaw, and E. T. Ahrens, "Fluorine-19 mri for visualization and quantification of cell migration in a diabetes model," *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 58, no. 4, pp. 725–734, 2007.
- [47] C. Faber and F. Schmid, "Pulse sequence considerations and schemes," *Fluorine Magnetic Resonance Imaging. Singapore: Pan Stanford Publishing*, pp. 1–28, 2016.
- [48] A. Haase, J. Frahm, D. Matthaei, W. Hanicke, and K.-D. Merboldt, "Flash imaging. rapid nmr imaging using low flip-angle pulses," *Journal of Magnetic Resonance (1969)*, vol. 67, no. 2, pp. 258–266, 1986.
- [49] B. Hargreaves, "Rapid gradient-echo imaging," *Journal of Magnetic Resonance Imaging*, vol. 36, no. 6, pp. 1300–1313, 2012.
- [50] M. K. Stehling, R. Turner, and P. Mansfield, "Echo-planar imaging: magnetic resonance imaging in a fraction of a second," *Science*, vol. 254, no. 5028, pp. 43–50, 1991.
- [51] C. J. Bergin, J. M. Pauly, and A. Macovski, "Lung parenchyma: projection reconstruction mr imaging.," *Radiology*, vol. 179, no. 3, pp. 777–781, 1991.
- [52] J. Rahmer, P. Börnert, J. Groen, and C. Bos, "Three-dimensional radial ultrashort echo-time imaging with t2 adapted sampling," *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 55, no. 5, pp. 1075–1082, 2006.
- [53] M. Weiger, K. P. Pruessmann, and F. Hennel, "Mri with zero echo time: hard versus sweep pulse excitation," *Magnetic resonance in medicine*, vol. 66, no. 2, pp. 379–389, 2011.
- [54] K. Strobel, V. Hoerr, F. Schmid, L. Wachsmuth, B. Löffler, and C. Faber, "Early detection of lung inflammation: exploiting t1-effects of iron oxide particles using ute mri," *Magnetic Resonance in Medicine*, vol. 68, no. 6, pp. 1924–1931, 2012.
- [55] F. Schmid, C. Hölte, D. Parker, and C. Faber, "Boosting 19f mri—snr efficient detection of paramagnetic contrast agents using ultrafast sequences," *Magnetic resonance in medicine*, vol. 69, no. 4, pp. 1056–1062, 2013.
- [56] M. Weiger, D. O. Brunner, M. Tabbert, M. Pavan, T. Schmid, and K. P. Pruessmann, "Exploring the bandwidth limits of zte imaging: Spatial response, out-of-band signals, and noise propagation," *Magnetic resonance in medicine*, vol. 74, no. 5, pp. 1236–1247, 2015.
- [57] R. Froidevaux, M. Weiger, D. O. Brunner, B. E. Dietrich, B. J. Wilm, and K. P. Pruessmann, "Filling the dead-time gap in zero echo time mri: principles compared," *Magnetic resonance in medicine*, vol. 79, no. 4, pp. 2036–2045, 2018.
- [58] Y. Gal, A. J. Mehnert, A. P. Bradley, K. McMahon, D. Kennedy, and S. Crozier, "De-noising of dynamic contrast-enhanced mr images using dynamic nonlocal means," *IEEE transactions on medical imaging*, vol. 29, no. 2, pp. 302–310, 2009.

- [59] S. P. Awate and R. T. Whitaker, “Feature-preserving mri denoising: a nonparametric empirical bayes approach,” *IEEE Transactions on Medical Imaging*, vol. 26, no. 9, pp. 1242–1255, 2007.
- [60] F. Baselice, G. Ferraioli, V. Pascasio, and A. Sorriso, “Bayesian mri denoising in complex domain,” *Magnetic resonance imaging*, vol. 38, pp. 112–122, 2017.
- [61] R. W. Liu, L. Shi, W. Huang, J. Xu, S. C. H. Yu, and D. Wang, “Generalized total variation-based mri rician denoising model with spatially adaptive regularization parameters,” *Magnetic resonance imaging*, vol. 32, no. 6, pp. 702–720, 2014.
- [62] S. H. Chung, K. M. Huynh, J. L. Goraliski, Y. Chen, P. Yap, A. S. Ceppe, M. Z. Powell, S. H. Donaldson, and Y. Z. Lee, “Feasibility of free-breathing 19f mri image acquisition to characterize ventilation defects in cf and healthy volunteers at wash-in,” *Magnetic Resonance in Medicine*, vol. 90, no. 1, pp. 79–89, 2023.
- [63] J. P. Haldar and Z.-P. Liang, ““early” constrained reconstruction methods,” in *Advances in Magnetic Resonance Technology and Applications*, vol. 7, pp. 105–125, Elsevier, 2022.
- [64] S. K. Nagle and D. N. Levin, “Multiple region mri,” *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 41, no. 4, pp. 774–786, 1999.
- [65] N. Aggarwal and Y. Bresler, “Region-of-interest mri: k-space sampling conditions,” in *3rd IEEE International Symposium on Biomedical Imaging: Nano to Macro, 2006.*, pp. 41–44, IEEE, 2006.
- [66] E. J. Candès, J. Romberg, and T. Tao, “Robust uncertainty principles: Exact signal reconstruction from highly incomplete frequency information,” *IEEE Transactions on information theory*, vol. 52, no. 2, pp. 489–509, 2006.
- [67] D. L. Donoho, “Compressed sensing,” *IEEE Transactions on information theory*, vol. 52, no. 4, pp. 1289–1306, 2006.
- [68] M. Uecker, P. Lai, M. J. Murphy, P. Virtue, M. Elad, J. M. Pauly, S. S. Vasanawala, and M. Lustig, “Espirit—an eigenvalue approach to autocalibrating parallel mri: where sense meets grappa,” *Magnetic resonance in medicine*, vol. 71, no. 3, pp. 990–1001, 2014.
- [69] R. Otazo, E. Candes, and D. K. Sodickson, “Low-rank plus sparse matrix decomposition for accelerated dynamic mri with separation of background and dynamic components,” *Magnetic resonance in medicine*, vol. 73, no. 3, pp. 1125–1136, 2015.
- [70] S. G. Lingala and M. Jacob, “Blind compressive sensing dynamic mri,” *IEEE transactions on medical imaging*, vol. 32, no. 6, pp. 1132–1145, 2013.
- [71] C. A. Baron, N. Dwork, J. M. Pauly, and D. G. Nishimura, “Rapid compressed sensing reconstruction of 3d non-cartesian mri,” *Magnetic resonance in medicine*, vol. 79, no. 5, pp. 2685–2692, 2018.

- [72] L. Feng, L. Axel, H. Chandarana, K. T. Block, D. K. Sodickson, and R. Otazo, “X-d-grasp: golden-angle radial mri with reconstruction of extra motion-state dimensions using compressed sensing,” *Magnetic resonance in medicine*, vol. 75, no. 2, pp. 775–788, 2016.
- [73] Y. Blunck, S. C. Kolbe, B. A. Moffat, R. J. Ordidge, J. O. Cleary, and L. A. Johnston, “Compressed sensing effects on quantitative analysis of undersampled human brain sodium mri,” *Magnetic resonance in medicine*, vol. 83, no. 3, pp. 1025–1033, 2020.
- [74] T. Kampf, A. Fischer, T. Basse-Lüsebrink, G. Ladewig, F. Breuer, G. Stoll, P. Jakob, and W. Bauer, “Application of compressed sensing to in vivo 3d 19f csi,” *Journal of Magnetic Resonance*, vol. 207, no. 2, pp. 262–273, 2010.
- [75] T. Kampf, V. J. Sturm, T. C. Basse-Lüsebrink, A. Fischer, L. R. Buschle, F. T. Kurz, H.-P. Schlemmer, C. H. Ziener, S. Heiland, M. Bendszus, *et al.*, “Improved compressed sensing reconstruction for 19 f magnetic resonance imaging,” *Magnetic Resonance Materials in Physics, Biology and Medicine*, vol. 32, pp. 63–77, 2019.
- [76] E. Darçot, J. Yerly, T. Hilbert, R. Colotti, E. Najdenovska, T. Kober, M. Stuber, and R. B. van Heeswijk, “Compressed sensing with signal averaging for improved sensitivity and motion artifact reduction in fluorine-19 mri,” *NMR in Biomedicine*, vol. 34, no. 1, p. e4418, 2021.
- [77] D. G. Nishimura, *Principles of magnetic resonance imaging*. Stanford Univ., 2010.
- [78] M. Bossert, *Channel coding for telecommunications*. John Wiley & Sons, Inc., 1999.
- [79] L. Starke, A. Pohlmann, C. Prinz, T. Niendorf, and S. Waiczies, “Performance of compressed sensing for fluorine-19 magnetic resonance imaging at low signal-to-noise ratio conditions,” *Magnetic resonance in medicine*, vol. 84, no. 2, pp. 592–608, 2020.
- [80] R. W. Chan, E. A. Ramsay, C. H. Cunningham, and D. B. Plewes, “Temporal stability of adaptive 3d radial mri using multidimensional golden means,” *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 61, no. 2, pp. 354–363, 2009.
- [81] W. Y. R. Fok, Y. C. I. Chan, J. Romanowicz, J. Jang, A. J. Powell, and M. H. Moghari, “Accelerated free-breathing 3d whole-heart magnetic resonance angiography with a radial phyllotaxis trajectory, compressed sensing, and curvelet transform,” *Magnetic resonance imaging*, vol. 83, pp. 57–67, 2021.
- [82] X. Zhu, M. Chan, M. Lustig, K. M. Johnson, and P. E. Larson, “Iterative motion-compensation reconstruction ultra-short te (imoco ute) for high-resolution free-breathing pulmonary mri,” *Magnetic resonance in medicine*, vol. 83, no. 4, pp. 1208–1221, 2020.
- [83] E. Johnson, K. Pauly, and J. Pauly, “Spherical-surface poisson disc point selection for radial-trajectory mri,” in *Proc ISMRM*, 2017.

- [84] J. A. Fessler and B. P. Sutton, "Nonuniform fast fourier transforms using min-max interpolation," *IEEE transactions on signal processing*, vol. 51, no. 2, pp. 560–574, 2003.
- [85] F. Natterer, *The mathematics of computerized tomography*. SIAM, 2001.
- [86] Y. Han, J. Yoo, H. H. Kim, H. J. Shin, K. Sung, and J. C. Ye, "Deep learning with domain adaptation for accelerated projection-reconstruction mr," *Magnetic resonance in medicine*, vol. 80, no. 3, pp. 1189–1205, 2018.
- [87] R. Tibshirani, "Regression shrinkage and selection via the lasso," *Journal of the Royal Statistical Society Series B: Statistical Methodology*, vol. 58, no. 1, pp. 267–288, 1996.
- [88] J. C. Ye, "Compressed sensing mri: a review from signal processing perspective," *BMC Biomedical Engineering*, vol. 1, no. 1, p. 8, 2019.
- [89] K. H. Jin, D. Lee, and J. C. Ye, "A general framework for compressed sensing and parallel mri using annihilating filter based low-rank hankel matrix," *IEEE Transactions on Computational Imaging*, vol. 2, no. 4, pp. 480–495, 2016.
- [90] G. Ongie and M. Jacob, "A fast algorithm for convolutional structured low-rank matrix recovery," *IEEE transactions on computational imaging*, vol. 3, no. 4, pp. 535–550, 2017.
- [91] Y. Wang, J. Yang, W. Yin, and Y. Zhang, "A new alternating minimization algorithm for total variation image reconstruction," *SIAM Journal on Imaging Sciences*, vol. 1, no. 3, pp. 248–272, 2008.
- [92] A. Chambolle and T. Pock, "A first-order primal-dual algorithm for convex problems with applications to imaging," *Journal of mathematical imaging and vision*, vol. 40, pp. 120–145, 2011.
- [93] Y. Yang, F. Liu, Z. Jin, and S. Crozier, "Aliasing artefact suppression in compressed sensing mri for random phase-encode undersampling," *IEEE Transactions on Biomedical Engineering*, vol. 62, no. 9, pp. 2215–2223, 2015.
- [94] T. Wech, D. Stäb, J. C. Budich, A. Fischer, J. Tran-Gia, D. Hahn, and H. Köstler, "Resolution evaluation of mr images reconstructed by iterative thresholding algorithms for compressed sensing," *Medical Physics*, vol. 39, no. 7Part1, pp. 4328–4338, 2012.
- [95] M. A. Neal, B. J. Pippard, K. G. Hollingsworth, A. Maunder, P. Dutta, A. J. Simpson, A. M. Blamire, J. M. Wild, and P. E. Thelwall, "Optimized and accelerated 19f-mri of inhaled perfluoropropane to assess regional pulmonary ventilation," *Magnetic Resonance in Medicine*, vol. 82, no. 4, pp. 1301–1311, 2019.
- [96] J. Chen, E. T. Ahrens, and P. Pal, "Physics-driven learned deconvolution of multi-spectral cellular mri with radial sampling," in *2023 57th Asilomar Conference on Signals, Systems, and Computers*, pp. 1453–1457, IEEE, 2023.

- [97] S. Shahsavari, J. Chen, and P. Pal, “Exploring the geometry of generative priors with applications in cellular mri,” in *2022 56th Asilomar Conference on Signals, Systems, and Computers*, pp. 1010–1015, IEEE, 2022.
- [98] T. Hastie, R. Tibshirani, and M. Wainwright, “Statistical learning with sparsity,” *Monographs on statistics and applied probability*, vol. 143, no. 143, p. 8, 2015.
- [99] S. Waiczies, J. M. Millward, L. Starke, P. R. Delgado, T. Huelnhagen, C. Prinz, D. Marek, D. Wecker, R. Wissmann, S. P. Koch, *et al.*, “Enhanced fluorine-19 mri sensitivity using a cryogenic radiofrequency probe: technical developments and ex vivo demonstration in a mouse model of neuroinflammation,” *Scientific reports*, vol. 7, no. 1, p. 9808, 2017.
- [100] G. P. Renieblas, A. T. Nogués, A. M. González, N. Gómez-Leon, and E. G. Del Castillo, “Structural similarity index family for image quality assessment in radiological images,” *Journal of medical imaging*, vol. 4, no. 3, pp. 035501–035501, 2017.
- [101] L. R. Dice, “Measures of the amount of ecologic association between species,” *Ecology*, vol. 26, no. 3, pp. 297–302, 1945.
- [102] M. Weiger and K. Pruessmann, “Mri with zero echo time. emagres,” 2012.
- [103] M. Weiger, K. P. Pruessmann, A.-K. Bracher, S. Köhler, V. Lehmann, U. Wolfram, F. Henkel, and V. Rasche, “High-resolution zte imaging of human teeth,” *NMR in Biomedicine*, vol. 25, no. 10, pp. 1144–1151, 2012.
- [104] S. Nam, M. Akçakaya, T. Basha, C. Stehning, W. J. Manning, V. Tarokh, and R. Nezafat, “Compressed sensing reconstruction for whole-heart imaging with 3d radial trajectories: a graphics processing unit implementation,” *Magnetic resonance in medicine*, vol. 69, no. 1, pp. 91–102, 2013.
- [105] F. Wiesinger, L. I. Sacolick, A. Menini, S. S. Kaushik, S. Ahn, P. Veit-Haibach, G. Delso, and D. D. Shanbhag, “Zero te mr bone imaging in the head,” *Magnetic resonance in medicine*, vol. 75, no. 1, pp. 107–114, 2016.
- [106] D. P. Mitchell, “Spectrally optimal sampling for distribution ray tracing,” in *Proceedings of the 18th annual conference on Computer graphics and interactive techniques*, pp. 157–164, 1991.
- [107] R. Bridson, “Fast poisson disk sampling in arbitrary dimensions,” *SIGGRAPH sketches*, vol. 10, no. 1, p. 1, 2007.
- [108] D. Piccini, A. Littmann, S. Nielles-Vallespin, and M. O. Zenge, “Spiral phyllotaxis: the natural way to construct a 3d radial trajectory in mri,” *Magnetic resonance in medicine*, vol. 66, no. 4, pp. 1049–1056, 2011.
- [109] M. Weiger and K. Pruessmann, “Mri with zero echo time,” *eMagRes*, 2007.

- [110] J. N. Tehrani, A. McEwan, C. Jin, and A. Van Schaik, "L1 regularization method in electrical impedance tomography by using the l1-curve (pareto frontier curve)," *Applied Mathematical Modelling*, vol. 36, no. 3, pp. 1095–1105, 2012.
- [111] E. Van Den Berg and M. P. Friedlander, "Probing the pareto frontier for basis pursuit solutions," *Siam journal on scientific computing*, vol. 31, no. 2, pp. 890–912, 2009.
- [112] S. P. Boyd and L. Vandenberghe, *Convex optimization*. Cambridge university press, 2004.
- [113] A. H. Jahromi, C. Wang, S. R. Adams, W. Zhu, K. Narsinh, H. Xu, D. L. Gray, R. Y. Tsien, and E. T. Ahrens, "Fluorous-soluble metal chelate for sensitive fluorine-19 magnetic resonance imaging nanoemulsion probes," *ACS nano*, vol. 13, no. 1, pp. 143–151, 2018.
- [114] K. T. Block, "Advanced methods for radial data sampling in magnetic resonance imaging," 2008.
- [115] D. C. Peters, R. J. Lederman, A. J. Dick, V. K. Raman, M. A. Guttman, J. A. Derbyshire, and E. R. McVeigh, "Undersampled projection reconstruction for active catheter imaging with adaptable temporal resolution and catheter-only views," *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 49, no. 2, pp. 216–222, 2003.
- [116] R. H. Hashemi, W. G. Bradley, and C. J. Lisanti, *MRI: the basics: The Basics*. Lippincott Williams & Wilkins, 2012.
- [117] F. Knoll, K. Bredies, T. Pock, and R. Stollberger, "Second order total generalized variation (tgv) for mri," *Magnetic resonance in medicine*, vol. 65, no. 2, pp. 480–491, 2011.
- [118] E. J. Candès and M. B. Wakin, "An introduction to compressive sampling," *IEEE signal processing magazine*, vol. 25, no. 2, pp. 21–30, 2008.
- [119] L. I. Rudin, S. Osher, and E. Fatemi, "Nonlinear total variation based noise removal algorithms," *Physica D: nonlinear phenomena*, vol. 60, no. 1-4, pp. 259–268, 1992.
- [120] G. Raskutti, M. J. Wainwright, and B. Yu, "Restricted eigenvalue properties for correlated gaussian designs," *The Journal of Machine Learning Research*, vol. 11, pp. 2241–2259, 2010.
- [121] Z. Wang, A. C. Bovik, H. R. Sheikh, and E. P. Simoncelli, "Image quality assessment: from error visibility to structural similarity," *IEEE transactions on image processing*, vol. 13, no. 4, pp. 600–612, 2004.
- [122] I. Ashur, H. Allouche-Arnon, and A. Bar-Shir, "Calcium fluoride nanocrystals: Tracers for in vivo ¹⁹f magnetic resonance imaging," *Angewandte Chemie International Edition*, vol. 57, no. 25, pp. 7478–7482, 2018.

- [123] R. Mashiach, D. Cohen, L. Avram, T. Harris, I. Pinkas, L. Houben, H. Allouche-Arnon, and A. Bar-Shir, "Inducing defects in 19f-nanocrystals provides paramagnetic-free relaxation enhancement for improved in vivo hotspot mri," *Nano Letters*, vol. 20, no. 10, pp. 7207–7212, 2020.
- [124] J. Ruiz-Cabello, J. Pérez-Sánchez, R. P. de Alejo, I. Rodríguez, N. González-Mangado, G. Peces-Barba, and M. Cortijo, "Diffusion-weighted 19f-mri of lung periphery: Influence of pressure and air-sf6 composition on apparent diffusion coefficients," *Respiratory physiology & neurobiology*, vol. 148, no. 1-2, pp. 43–56, 2005.
- [125] M. J. Couch, I. K. Ball, T. Li, M. S. Fox, B. Biman, and M. S. Albert, "19f mri of the lungs using inert fluorinated gases: Challenges and new developments," *Journal of Magnetic Resonance Imaging*, vol. 49, no. 2, pp. 343–354, 2019.
- [126] A. Scholz, U. Wolf, M. Fabel, N. Weiler, C. P. Heussel, B. Eberle, M. David, and W. G. Schreiber, "Comparison of magnetic resonance imaging of inhaled sf6 with respiratory gas analysis," *Magnetic resonance imaging*, vol. 27, no. 4, pp. 549–556, 2009.
- [127] M. Tibiletti, M. Tschechne, A. Bianchi, D. Stiller, and V. Rasche, "Ventilation imaging with sulfur hexafluoride in free-breathing mice: initial experience," in *Proceedings of International Society for Magnetic Resonance in Medicine*, vol. 2912, 2016.
- [128] M. J. Couch, I. K. Ball, T. Li, M. S. Fox, S. L. Littlefield, B. Biman, and M. S. Albert, "Pulmonary ultrashort echo time 19f mr imaging with inhaled fluorinated gas mixtures in healthy volunteers: feasibility," *Radiology*, vol. 269, no. 3, pp. 903–909, 2013.
- [129] M. Weiger, D. O. Brunner, B. E. Dietrich, C. F. Müller, and K. P. Pruessmann, "Zte imaging in humans," *Magnetic resonance in medicine*, vol. 70, no. 2, pp. 328–332, 2013.
- [130] H. T. Fabich, M. Benning, A. J. Sederman, and D. J. Holland, "Ultrashort echo time (ute) imaging using gradient pre-equalization and compressed sensing," *Journal of Magnetic Resonance*, vol. 245, pp. 116–124, 2014.
- [131] X. Yang, Y. R. Zheng, M. Yang, and L. Ma, "Compressed sensing with non-uniform fast fourier transform for radial ultra-short echo time (ute) mri," in *2015 IEEE 12th International Symposium on Biomedical Imaging (ISBI)*, pp. 918–921, IEEE, 2015.
- [132] V. Koltchinskii and K. Lounici, "Concentration inequalities and moment bounds for sample covariance operators," *Bernoulli*, pp. 110–133, 2017.
- [133] C. Jin, P. Netrapalli, R. Ge, S. M. Kakade, and M. I. Jordan, "A short note on concentration inequalities for random vectors with subgaussian norm," *arXiv preprint arXiv:1902.03736*, 2019.
- [134] H. Biermé and C. Lacaux, "Modulus of continuity of some conditionally sub-gaussian fields, application to stable random fields," 2015.

- [135] L. Busse, S. Thomas, R. Pratt, L. Clark Jr, J. Ackerman, R. Samaratunga, and R. Hoffmann, “Deconvolution techniques for removing the effects of chemical shift in ^{19}F nuclear magnetic resonance imaging of perfluorocarbon compounds,” *Medical physics*, vol. 13, no. 4, pp. 518–524, 1986.
- [136] T. Benkert, L. Feng, D. K. Sodickson, H. Chandarana, and K. T. Block, “Free-breathing volumetric fat/water separation by combining radial sampling, compressed sensing, and parallel imaging,” *Magnetic resonance in medicine*, vol. 78, no. 2, pp. 565–576, 2017.
- [137] H. K. Aggarwal, M. P. Mani, and M. Jacob, “Modl: Model-based deep learning architecture for inverse problems,” *IEEE transactions on medical imaging*, vol. 38, no. 2, pp. 394–405, 2018.
- [138] R. Ahmad, C. A. Bouman, G. T. Buzzard, S. Chan, S. Liu, E. T. Reehorst, and P. Schniter, “Plug-and-play methods for magnetic resonance imaging: Using denoisers for image recovery,” *IEEE signal processing magazine*, vol. 37, no. 1, pp. 105–116, 2020.
- [139] J. Adler and O. Öktem, “Learned primal-dual reconstruction,” *IEEE transactions on medical imaging*, vol. 37, no. 6, pp. 1322–1332, 2018.
- [140] E. K. Brodsky, J. H. Holmes, H. Yu, and S. B. Reeder, “Generalized k-space decomposition with chemical shift correction for non-cartesian water-fat imaging,” *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 59, no. 5, pp. 1151–1164, 2008.
- [141] K. Scheffler and J. Hennig, “Reduced circular field-of-view imaging,” *Magnetic resonance in medicine*, vol. 40, no. 3, pp. 474–480, 1998.
- [142] M. Engström, G. McKinnon, C. Cozzini, and F. Wiesinger, “In-phase zero te musculoskeletal imaging,” *Magnetic resonance in medicine*, vol. 83, no. 1, pp. 195–202, 2020.
- [143] O. Doganay, T. Wade, E. Hegarty, C. McKenzie, R. F. Schulte, and G. E. Santyr, “Hyperpolarized ^{129}Xe imaging of the rat lung using spiral ideal,” *Magnetic Resonance in Medicine*, vol. 76, no. 2, pp. 566–576, 2016.
- [144] J. Adler, H. Kohr, and O. Öktem, “Operator discretization library (odl),” *Zenodo*, 2017.
- [145] I. Loshchilov and F. Hutter, “Sgdr: Stochastic gradient descent with warm restarts,” *arXiv preprint arXiv:1608.03983*, 2016.
- [146] G. Ongie, E. Y. Sidky, I. S. Reiser, and X. Pan, “Optimizing model observer performance in learning-based ct reconstruction,” in *Medical Imaging 2022: Image Perception, Observer Performance, and Technology Assessment*, vol. 12035, pp. 55–59, SPIE, 2022.
- [147] G. Ongie, R. Willett, D. Soudry, and N. Srebro, “A function space view of bounded norm infinite width relu nets: The multivariate case,” in *International Conference on Learning Representations*, 2020.

- [148] R. Parhi and R. D. Nowak, “Banach space representer theorems for neural networks and ridge splines,” *The Journal of Machine Learning Research*, vol. 22, no. 1, pp. 1960–1999, 2021.
- [149] D. G. Nishimura, *Principles of magnetic resonance imaging*. Stanford University, 1996.
- [150] M. Mardani, E. Gong, J. Y. Cheng, S. S. Vasanawala, G. Zaharchuk, L. Xing, and J. M. Pauly, “Deep generative adversarial neural networks for compressive sensing mri,” *IEEE transactions on medical imaging*, vol. 38, no. 1, pp. 167–179, 2018.
- [151] G. Yang, S. Yu, H. Dong, G. Slabaugh, P. L. Dragotti, X. Ye, F. Liu, S. Arridge, J. Keegan, Y. Guo, *et al.*, “Dagan: deep de-aliasing generative adversarial networks for fast compressed sensing mri reconstruction,” *IEEE transactions on medical imaging*, vol. 37, no. 6, pp. 1310–1321, 2017.
- [152] V. A. Kelkar, S. Bhadra, and M. A. Anastasio, “Compressible latent-space invertible networks for generative model-constrained image reconstruction,” *IEEE Transactions on Computational Imaging*, vol. 7, pp. 209–223, 2021.
- [153] V. A. Kelkar and M. Anastasio, “Prior image-constrained reconstruction using style-based generative models,” in *International Conference on Machine Learning*, pp. 5367–5377, PMLR, 2021.
- [154] A. Lucas, M. Iliadis, R. Molina, and A. K. Katsaggelos, “Using deep neural networks for inverse problems in imaging: beyond analytical methods,” *IEEE Signal Processing Magazine*, vol. 35, no. 1, pp. 20–36, 2018.
- [155] A. Bora, E. Price, and A. G. Dimakis, “Ambientgan: Generative models from lossy measurements,” in *International conference on learning representations*, 2018.
- [156] S. Menon, A. Damian, S. Hu, N. Ravi, and C. Rudin, “Pulse: Self-supervised photo upsampling via latent space exploration of generative models,” in *Proceedings of the IEEE/CVF conference on computer vision and pattern recognition*, pp. 2437–2445, 2020.
- [157] S. Shahsavari and P. Pal, “Exact solution of inverse problems with relu generative priors and the role of sensing in taming computational complexity,” *Under Preparation*.
- [158] C. Wang, S. R. Adams, and E. T. Ahrens, “Emergent fluorine molecules and their uses in molecular imaging,” *Accounts of Chemical Research*, vol. 54, no. 15, pp. 3060–3070, 2021.
- [159] R. Balestrieri, S. Paris, and R. Baraniuk, “Max-affine spline insights into deep generative networks,” *arXiv preprint arXiv:2002.11912*, 2020.
- [160] T. Ergen and M. Pilanci, “Convex geometry of two-layer relu networks: Implicit autoencoding and interpretable models,” in *International Conference on Artificial Intelligence and Statistics*, pp. 4024–4033, PMLR, 2020.

- [161] T. Ergen and M. Pilanci, “Global optimality beyond two layers: Training deep relu networks via convex programs,” in *International Conference on Machine Learning*, pp. 2993–3003, PMLR, 2021.
- [162] K. Hammernik, T. Klatzer, E. Kobler, M. P. Recht, D. K. Sodickson, T. Pock, and F. Knoll, “Learning a variational network for reconstruction of accelerated mri data,” *Magnetic resonance in medicine*, vol. 79, no. 6, pp. 3055–3071, 2018.
- [163] B. Yaman, S. A. H. Hosseini, S. Moeller, J. Ellermann, K. Uğurbil, and M. Akçakaya, “Self-supervised learning of physics-guided reconstruction neural networks without fully sampled reference data,” *Magnetic resonance in medicine*, vol. 84, no. 6, pp. 3172–3191, 2020.
- [164] J. Lehtinen, J. Munkberg, J. Hasselgren, S. Laine, T. Karras, M. Aittala, and T. Aila, “Noise2noise: Learning image restoration without clean data,” *arXiv preprint arXiv:1803.04189*, 2018.
- [165] Y. Romano, M. Elad, and P. Milanfar, “The little engine that could: Regularization by denoising (red),” *SIAM Journal on Imaging Sciences*, vol. 10, no. 4, pp. 1804–1844, 2017.
- [166] P. Huang, C. Zhang, X. Zhang, X. Li, L. Dong, and L. Ying, “Self-supervised deep unrolled reconstruction using regularization by denoising,” *IEEE Transactions on Medical Imaging*, 2023.
- [167] J. Liu, Y. Sun, C. Eldeniz, W. Gan, H. An, and U. S. Kamilov, “Rare: Image reconstruction using deep priors learned without groundtruth,” *IEEE Journal of Selected Topics in Signal Processing*, vol. 14, no. 6, pp. 1088–1099, 2020.
- [168] D. Ulyanov, A. Vedaldi, and V. Lempitsky, “Deep image prior,” in *Proceedings of the IEEE conference on computer vision and pattern recognition*, pp. 9446–9454, 2018.
- [169] M. Z. Darestani and R. Heckel, “Accelerated mri with un-trained neural networks,” *IEEE Transactions on Computational Imaging*, vol. 7, pp. 724–733, 2021.
- [170] R. Heckel and P. Hand, “Deep decoder: Concise image representations from untrained non-convolutional networks,” *arXiv preprint arXiv:1810.03982*, 2018.
- [171] O. Leong, A. F. Gao, H. Sun, and K. L. Bouman, “Discovering structure from corruption for unsupervised image reconstruction,” *IEEE Transactions on Computational Imaging*, vol. 9, pp. 992–1005, 2023.
- [172] M. Doneva, P. Börnert, H. Eggers, A. Mertins, J. Pauly, and M. Lustig, “Compressed sensing for chemical shift-based water–fat separation,” *Magnetic resonance in medicine*, vol. 64, no. 6, pp. 1749–1759, 2010.
- [173] S. Li, C. Shen, Z. Ding, H. She, and Y. P. Du, “Accelerating multi-echo chemical shift encoded water–fat mri using model-guided deep learning,” *Magnetic Resonance in Medicine*, vol. 88, no. 4, pp. 1851–1866, 2022.

- [174] A. De Goyeneche, S. Ramachandran, K. Wang, E. Karasan, J. Cheng, S. X. Yu, and M. Lustig, “Resonet: Noise-trained physics-informed mri off-resonance correction,” in *Thirty-seventh Conference on Neural Information Processing Systems*, 2023.
- [175] S.-E. Chiu, N. Ronquillo, and T. Javidi, “Active learning and csi acquisition for mmwave initial alignment,” *IEEE Journal on Selected Areas in Communications*, vol. 37, no. 11, pp. 2474–2489, 2019.
- [176] C. D. Bahadir, A. Q. Wang, A. V. Dalca, and M. R. Sabuncu, “Deep-learning-based optimization of the under-sampling pattern in mri,” *IEEE Transactions on Computational Imaging*, vol. 6, pp. 1139–1152, 2020.
- [177] T. Bakker, H. van Hoof, and M. Welling, “Experimental design for mri by greedy policy search,” *Advances in Neural Information Processing Systems*, vol. 33, pp. 18954–18966, 2020.
- [178] O. Shayevitz and M. Feder, “Optimal feedback communication via posterior matching,” *IEEE Transactions on Information Theory*, vol. 57, no. 3, pp. 1186–1222, 2011.
- [179] E. Arias-Castro, E. J. Candes, and M. A. Davenport, “On the fundamental limits of adaptive sensing,” *IEEE Transactions on Information Theory*, vol. 59, no. 1, pp. 472–481, 2012.
- [180] M. L. Malloy and R. D. Nowak, “Near-optimal adaptive compressed sensing,” *IEEE Transactions on Information Theory*, vol. 60, no. 7, pp. 4001–4012, 2014.
- [181] A. Alkhateeb, O. El Ayach, G. Leus, and R. W. Heath, “Channel estimation and hybrid precoding for millimeter wave cellular systems,” *IEEE journal of selected topics in signal processing*, vol. 8, no. 5, pp. 831–846, 2014.
- [182] S.-E. Chiu, N. Ronquillo, and T. Javidi, “Active learning and csi acquisition for mmwave initial alignment,” *IEEE Journal on Selected Areas in Communications*, vol. 37, no. 11, pp. 2474–2489, 2019.
- [183] M. Seeger, H. Nickisch, R. Pohmann, and B. Schölkopf, “Optimization of k-space trajectories for compressed sensing by bayesian experimental design,” *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 63, no. 1, pp. 116–126, 2010.
- [184] C. Wang, B. I. Leach, D. Lister, S. R. Adams, H. Xu, C. Hoh, P. McConville, J. Zhang, K. Messer, and E. T. Ahrens, “Metallofluorocarbon nanoemulsion for inflammatory macrophage detection via pet and mri,” *Journal of Nuclear Medicine*, vol. 62, no. 8, pp. 1146–1153, 2021.
- [185] L. Shen, J. Pauly, and L. Xing, “Nerp: implicit neural representation learning with prior embedding for sparsely sampled image reconstruction,” *IEEE Transactions on Neural Networks and Learning Systems*, 2022.

- [186] F. Riemer, B. S. Solanky, C. Stehning, M. Clemence, C. A. Wheeler-Kingshott, and X. Golay, “Sodium (^{23}Na) ultra-short echo time imaging in the human brain using a 3d-cones trajectory,” *Magnetic Resonance Materials in Physics, Biology and Medicine*, vol. 27, pp. 35–46, 2014.