K-space undersampling strategies for functional and cardiac MRI: Achieving rapid acquisition while maintaining image quality

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Onur Afacan

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The dissertation of Onur Afacan was read and approved* by the following:

Dana H. Brooks  
Professor of Electrical and Computer Engineering, Northeastern University  
Dissertation Adviser  
Chair of Committee

Craig Ferris  
Professor of Psychology, Northeastern University  
Dissertation Reader

W. Scott Hoge  
Brigham and Women’s Hospital and Harvard Medical School  
Dissertation Reader

Lee Makowski  
Professor of Electrical and Computer Engineering, Northeastern University  
Dissertation Reader

Istvan A Morocz  
Brigham and Women’s Hospital and Harvard Medical School  
Dissertation Reader

Ali Abur  
Professor of Electrical and Computer Engineering, Northeastern University  
Department Head

* Signatures are on file in the Graduate School.
Abstract

Northeastern University

Department of Electrical and Computer Engineering

Doctor of Philosophy in Electrical Engineering

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Scan time is the limiting factor in many magnetic resonance imaging applications. One approach to reduce the scan time is undersampling k-space below the Nyquist sampling rate. In this work, for three different MRI applications, we investigate the effects of existing and novel undersampling schemes on both the acquisition time and the resulting image quality. In the first application, a new accelerated multi-shot 3D EPI sequence is proposed to increase the temporal resolution of complex cognitive fMRI studies. A careful combination of two modern acceleration techniques, UNFOLD and GRAPPA, is proposed for use in the secondary phase encoding direction to reduce the scan time effectively with minimal loss in image quality. The sequence was tested using two different fMRI paradigms. The accelerated sequence was able to provide more information on timing of the complex sequence of interrelated brain functions. In the second application, fast spin echo sequences for fMRI in functional brain mapping studies of small animals were investigated. Partial Fourier acquisition was implemented to reduce the number of phase encoding lines in order to reduce the blurring resulting from $T_2$ decay. The sequence was tested on a 7T animal scanner using CO$_2$ challenge and forepaw stimulation experiments. With the proposed sequence it was possible to generate images with good functional sensitivity as well as high quality anatomical information. In the third application, different undersampling strategies and reconstruction methods for variable density spiral k-space trajectories were compared. Comparison metrics included signal to noise ratio, root mean square error and resolution. We also present the use of a new analysis tool, the singular value spectrum of the Fourier basis cross-correlation matrix, to analyze the information content and SNR efficiency of undersampled spiral trajectories.
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Abbreviations

MRI  Magnetic Resonance Imaging
fMRI  functional Magnetic Resonance Imaging
GRAPPA  Generalized Autocalibrating Partially Parallel Acquisition
UNFOLD  UNalising by Fourier encoding the OverLaps using the temporal Dimension
EPI  Echo Planar Imaging
EVI  Echo Volumar Imaging
TE  Echo Time
TR  Repetition Time
SNR  Signal to Noise Ratio
tSNR  time series Signal to Noise Ratio
CNR  Contrast to Noise Ratio
HRF  Hemodynamic Response Function
FOV  Field of View
VD  Variable Density
TV  Total Variation
PSF  Point Spread Function
NUFFT  Non-Uniform Fast Fourier Transform
RMSE  Root Mean Square Error
RF  Radio Frequency
FSE  Fast Spin Echo
BOLD  Blood-Oxygenation-Level-Dependent
Chapter 1

Introduction

Magnetic Resonance Imaging (MRI) is an important non-invasive diagnostic tool for viewing organs and early detection of diseases. It offers excellent soft-tissue characterization and has no ionizing radiation. More importantly, MRI offers various image contrast mechanisms making it one of the most used diagnostic tools for many applications. However, a major limitation of MRI is the imaging speed. The speed at which the MRI image can be acquired is limited by the physical constraints of the MRI scanner.

There has been considerable amount of work for searching methods to reduce scan time. Standard MRI scans sample the k-space (frequency domain) with the Nyquist criteria to guarantee aliasing free images. Most of the methods that try to reduce the scan time rely on undersampling the k-space with respect to the Nyquist sampling rate. In order to remove the aliasing introduced by undersampling the k-space they either use priori assumptions about the image (or sets of images) or use extra information provided by additional hardware such as multiple coils. For example in Partial Fourier reconstruction, the image is assumed to be real (or the phase information is assumed to be recoverable from a low resolution image), in compressed sensing the image is assumed to be sparse in some domain and in k-t space undersampling methods dynamic redundancies are used. On the other hand, parallel imaging uses extra coil sensitivity information and trades off signal to noise ratio (SNR) with removing aliasing artifacts. In this thesis we have explored the effect of certain k-space undersampling methods applied to functional MRI and spiral MRI.
Functional MRI in an excellent tool that measures the tiny metabolic changes that take place in an active part of the brain. It has excellent spatial coverage and spatial resolution compared to other functional imaging tools such as Electroencephalography (EEG) and Magnetoencephalography (MEG). However, temporal resolution is too low to perform meaningful complex cognitive studies. Instead of the standard fMRI imaging sequence, 2D EPI (Echo Planar Imaging), we investigated the feasibility of multi-shot 3D EPI that excites the whole brain at each repetition time (TR) and acquires a $k_z$ slice using 2D EPI readouts. Also two k-space undersampling techniques, [UNFOLD–Unalising by Fourier encoding the OverLaps using the temporal Dimension [1]] and spatial encoding [GRAPPA–GeneRalized Autocalibrating Partially Parallel Acquisition [2]] were used to reduce the total scan time.

Although EPI [3] based methods had been the backbone of functional MRI studies, in fMRI studies where precise localization is required, artifacts related to fast readout gradients prevent the use of EPI. A possible alternative is Fast Spin Echo sequence in which the magnetization is refocused using 180 degree pulses between each phase encoding acquisition. We investigated fast spin echo sequences for fMRI in functional brain mapping studies of small animals in high field. We have used Partial Fourier acquisition to reduce the number of phase encoding lines. Also the sequence was modified with an extra 180 degree RF pulse in order to achieve an echo time that optimizes functional information. The sequence was tested in two separate fMRI experiments on 8 rats and it was shown that the proposed sequence can be used in functional brain mapping studies effectively due to its high spatial resolution, reduced image artifacts and good functional sensitivity.

Spiral MRI offers an alternative to standard cartesian sampling by effectively using the gradients and reducing the scan time needed to traverse the k-space. Spirals also offer superior flow and motion characteristics. However, one disadvantage of spiral MRI is the need for non-trivial image reconstruction since taking the inverse Fourier Transform does not produce correct results. Either the Fourier samples should be weighted using a density compensation function (DCF) or a system of linear equations should be solved. A method to further improve the scan time is undersampling the spirals beyond the Nyquist rate using a variable density function. We have investigated the effect of different variable density functions and reconstruction methods on the image quality metrics. These different reconstruction methods make it difficult to analyze and design different spiral trajectories. To help with this problem we suggested the use of the singular value spectrum of the cross-correlation matrix.
The rest of the proposal is organized as follows. In chapter 2, we describe how we use two modern acceleration techniques UNFOLD and GRAPPA to increase temporal resolution in fMRI studies using multi-shot 3D EPI. We also show results from real fMRI experiments where we compare accelerated fMRI acquisitions with standard fMRI acquisition techniques. In Chapter 3, we show results from fast spin echo experiments on a high field animal scanner for functional brain mapping studies. Partial Fourier acquisition was implemented to reduce the number of phase encoding lines in order to reduce the blurring resulting from T2 decay. The sequence is tested using CO2 challenge and forepaw stimulation experiments. In chapter 4, we investigate the effects of various undersampling schemes and different reconstruction methods used in spiral MRI in terms of imaging metrics such as SNR, RMSE and spatial resolution. In chapter 5, we investigate the use of the singular value spectrum of the cross-correlation Fourier basis matrix as an analysis tool in spiral MR imaging in terms of the information content and SNR efficiency of undersampled spiral k-space trajectories. The main results of the thesis is summarized and also future work is discussed in Chapter 6.
Chapter 2

Rapid Full-Brain fMRI with an Accelerated Multi-Shot 3D EPI Sequence Using Both UNFOLD AND GRAPPA

2.1 Summary

The desire to understand complex mental processes using functional MRI drives development of imaging techniques that scan the whole human brain at a high spatial and temporal resolution. In this work an accelerated multi-shot 3D EPI sequence is proposed to increase the temporal resolution of these studies. A combination of two modern acceleration techniques, UNFOLD and GRAPPA is used in the secondary phase encoding direction to reduce the scan time effectively. The sequence (TR=1.02s) was compared with standard 2D EPI (3s) and multi-shot 3D EPI (3s) sequences with both block design and event-related fMRI paradigms. With the same experimental setup and imaging time, the temporal resolution improvement with our sequence yields similar activation regions in the block design fMRI paradigm with slightly increased t-scores. Moreover, additional information on the timing of rapid dynamic changes was extracted from accelerated images for the case of the event related complex mental paradigm.
2.2 Introduction

When complex cognitive processes are studied with functional MRI (fMRI), a goal of increasing interest in the neuroscience community, a cascade of brain signal changes is typically observed [4] [5]. Involvement of numerous brain areas makes whole brain coverage a high priority for cognitive brain mapping. At the same time, a voxel size no larger than the cortical thickness is preferred to improve localization and specificity. However, this combination of whole brain coverage with high spatial resolution currently reduces achievable temporal resolution to a level where complex analysis or time retrieval becomes difficult. Thus, improving the temporal resolution of fMRI acquisitions becomes a critical need for these studies.

In this work we propose an fMRI acquisition sequence which improves the temporal resolution of an fMRI exam without losing spatial coverage. The most common approach for fast fMRI employs 2D Echo Planar Imaging (EPI). However, the imperfect slice profile of 2D EPI increasingly becomes an issue at higher resolution. Here instead of 2D EPI we employ a multi-shot 3D EPI sequence in which each excitation pulse excites the whole brain at each repetition time (TR). This eliminates slice profile issues since the encoding is achieved by a secondary phase encoding direction rather than 2D slice excitation. Multi-shot 3D EPI, as is also true for stack-of-spirals imaging [6], has an SNR advantage over methods employing 2D EPI [7], since in both methods the whole brain is excited at once at each TR. The SNR advantage of both methods depends on the T1 of tissue of interest, the TR of the 3D and comparative 2D acquisitions, and flip angles. The benefit of 3D EPI increases as the number of \( k_z \) encodings increase [6]. The disadvantages of 3D EPI include higher sensitivity to motion and flow artifacts than its 2D counterpart. In addition we note that T1 contrast will change with respect to that obtained with 2D EPI.

With this sequence the third dimension of the excited slab (the slice encoding direction in 2D EPI) is spatially encoded by phase encoding gradients. This turns out to offer additional opportunities for accelerated imaging, thus allowing an improved tradeoff between spatial and temporal resolution. We exploit this extra phase encoding dimension by undersampling k-space in that dimension. We employ a novel combination of temporal encoding [UNFOLD–Unalising by Fourier encoding the OveLaps using the temporal Dimension [1]] and spatial encoding [GRAPPA–GeneRalized Autocalibrating Partially Parallel Acquisition [2]] to reduce image acquisition time.
In related work, Poser et al [8] have implemented and demonstrated the use of 3D EPI with GRAPPA parallel imaging and partial Fourier capability along both ky and kz phase encoding directions and were able to demonstrate BOLD contrast to noise advantages of highly accelerated 3D EPI over 2D EPI at 7T. Temporal resolution of this method can further be increased by the method suggested in this thesis. Other accelerated whole brain sequences are 3D Echo Volumar Imaging (EVI) [9] and 2D multi-slice, multi-band imaging [10, 11, 12]. EVI requires very high acceleration factors due to rapid $t_2^*$ decay. Feinberg et al [12] has recently published a method that uses multiplexed EPI (M-EPI) that combines 2D multiband excitation, GRAPPA parallel imaging and SIR multi-slice excitation, where they acquired full volume coverage in less than 0.5s. Our acceleration method can be implemented in these scenarios but this is beyond the scope of this report. Lee et al [13] have presented a novel 3D radial technique with GRAPPA for multi-echo fMRI; where the radial trajectory interleaves were chosen such that reconstruction could be performed flexibly at either high temporal or high spatial resolution.

We briefly explain both UNFOLD and GRAPPA and then explain how we use them jointly. UNFOLD belongs to the class of techniques [14][15][16][17] that exploits the significant k-space signal redundancy from frame to frame that occurs in temporally dynamic applications. Temporal encoding strategies introduce a time-varying signal phase modulation between consecutive frames. This phase shift then tags the aliased components that contribute to the dynamic variability of pixels in images formed from sub-sampled k-space. In particular, UNFOLD decreases the number of samples needed to reconstruct the k-t space data by leveraging the assumption that the temporal encoding of the aliased dynamic pixels makes the aliased components separable from the unaliased signals of interest in the temporal frequency spectrum. GRAPPA is a parallel coil imaging reconstruction technique that supports self-referencing. A sufficient number of lines in the center of k-space are acquired at the spatial-domain Nyquist sampling rate, to model reconstruction coefficients for the unacquired lines. Those coefficients are estimated from those fully sampled lines and then in turn used to estimate the unaliased lines, thus allowing speedup through reduced sampling of k-space.

In the approach reported here, GRAPPA is applied with UNFOLD along the secondary phase encoding direction. We use an acceleration factor of 4 in the high-spatial-frequency coordinates of $k_z$ space through this combined approach. Since a $k_z$ plane in the 3D Fourier domain is acquired at each TR, undersampling in this direction directly reduces
the total scan time for each volume [8]. The scan time, in principle, can be further shortened by undersampling in the phase encoding direction, $k_y$, to reduce the readout time. However, this does not improve the time resolution substantially since a minimum echo time (TE) is required for the mean blood-oxygenation-level-dependent (BOLD) signal to form, which imposes a minimum time between the RF excitation pulse and the readout gradients. But, the in-plane susceptibility artifacts can be reduced by the shortened readout time due to a reduction in off-resonance effects, whereas the through-plane artifacts will be unaffected [18].

We compare our accelerated 3D Multi-shot EPI sequence with both standard 2D EPI and non-accelerated multi-shot 3D EPI sequences. We tested our sequence with both block design and event-related fMRI paradigms. For the block design study, we used aperiodic visuo-spatial stimuli. For the event-related design, we used a self-paced complex mental task involving multiplication and comparison of numbers. We show that under the same experimental setup and imaging time, the temporal resolution improvement with our sequence yields (a) similar activation regions for both the block design and event design fMRI paradigms but with slightly increased t-scores using a standard HRF analysis method, and (b) more information on the temporal behaviour of the complex cognitive processes from the accelerated images for the case of event related complex mental paradigms. We also show that this information can be used to help identify the timing of cognitive processes when we employ an alternative analysis method (Finite Impulse Response) that is more sensitive to temporal information data.

2.3 Methods

2.3.1 Data Acquisition

Figure 2.1 shows the pulse sequence diagram for each TR. An RF pulse that excites the whole FOV was applied at each TR. Since the whole brain is excited at each TR, a small flip angle calculated from the Ernst equation was used to optimize the signal intensity. The phase encoding ($y$) and frequency encoding gradients ($x$) were exactly the same as standard 2D EPI. Unlike 2D EPI, an additional phase encoding gradient (highlighted in red) was applied in $z$. At each TR, the area of the $z$-phase encoding gradient was adjusted to traverse a corresponding specified $k_z$ plane in the 3D frequency domain. This process
was repeated for each $k_z$ plane required. In non-accelerated multi-shot 3D EPI, therefore, the number of TRs was determined directly by the desired FOV coverage and resolution along $z$.

We first divide k-space into inner (low-frequency) and outer (high frequency) regions. The $k_z$ planes in the inner region are acquired at full density as in standard 3D imaging. In the outer region we acquire only one out of every four planes, which we can conceptualize as every other odd-indexed plane. The fully-sampled planes are used to estimate the GRAPPA coefficients. In the standard UNFOLD acquisition, k-space is shifted by $\Delta_k$ between consecutive time frames. As we will see, because of our joint use of GRAPPA with UNFOLD, we shift by two $k_z$ planes ($2\Delta_k$) at even time frames. Thus half of the odd indexed $k_z$ planes are acquired at the odd time frames and the other half are acquired at the even time frames. The even indexed $k_z$ planes were never acquired but rather were reconstructed as described below. An illustration with 50 $k_z$ planes is shown in Figure 2.2, where at each volume only 17 $k_z$ planes (7 $k_z$ planes at the center of k-space and 10 $k_z$ planes at the outside) are acquired using the scanner.
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2.3.2 Image Reconstruction

For fully acquired k-space data, the images were reconstructed in a standard fashion, using a 3D inverse Fourier transform and a Nyquist ghost correction method [19], where the latter is required because of sampling errors inherent to all EPI acquisitions. For the UNFOLD+GRAPPA acquisitions, Figure 2.3 depicts the flow chart for the reconstruction process. We first start by correcting for any instabilities or drifts by phase aligning the frames along time. Then the missing odd indexed $k_z$ planes are reconstructed using UNFOLD. In this step a low-pass filter with a cut-off frequency, selected as described in the next paragraph, is applied on a voxel-by-voxel basis along the temporal dimension of the 4D k-t data to filter out the dominant near Nyquist rate component (i.e the aliased near DC component of the undesired aliasing voxel).

An important parameter in the UNFOLD reconstruction, as mentioned in the previous paragraph, is the cut-off frequency for the temporal filter used to remove aliasing. A well-chosen bandwidth is required to remove the aliased near-DC component of the undesired

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**Figure 2.2:** Subsampling pattern in $k_z$ for $FOV_z$ of 150mm with a resolution of 3mm. Red-colored $k_z$ planes are acquired using the sequence. Those planes are used to reconstruct the green-colored planes using the UNFOLD algorithm. Then the black $k_z$ planes are reconstructed from the red and green planes using the GRAPPA algorithm. The red $k_z$ planes at the center of the k-space are acquired for all time frames to use as reference planes for GRAPPA reconstruction.
aliasing voxel. On the other hand this temporal filtering induces temporal coherence which lowers the temporal resolution. The cut-off frequency was chosen after analyzing a data set acquired using the unaccelerated 3D EPI sequence. A heuristic method of determining this parameter was adopted; we performed a visual inspection of the temporal spectrum in the unaliased dataset of all voxels which would alias in the accelerated datasets, and determined that the majority of their frequency content was consistently below $\pm 8\%$ of the Nyquist frequency. Since with the UNFOLD scheme this frequency range will alias to be centered at $\pi$, we designed our filter to cutoff at $0.92\pi$ using a filter design method described below.

Since filtering is only done along the temporal direction, the time series of each voxel can be filtered independently to reduce computer memory requirements and it is straightforward to distribute this aspect of the whole volume reconstruction across multiple parallel computing nodes.

The output of the UNFOLD reconstruction produces a k-space dataset that has data in odd numbered $k_z$ planes in the outer regions of $k_z$ space as described earlier. This dataset, along with the 4 reference planes acquired as described above is then processed at each time point using the GRAPPA reconstruction algorithm. Specifically, first a Fourier Transform was applied along the $k_x$ dimension to transform the data to the $x$-$k_y$-$k_z$ domain. Then for each $k_z$-$k_y$ plane (i.e for each $x$), a 2D GRAPPA matrix calculated from the reference data was applied to estimate the remaining missing $k_z$ planes, using a 2x3 GRAPPA kernel.

### 2.3.3 Experiments

#### 2.3.3.1 MRI Measurements

Experiments were performed with an 8-channel head coil on a 3T GE EXCITE scanner with a maximum gradient of 40mT/m and maximum slew rate of 140T/ms. The field of view (FOV) was $192 \times 192 \times 150\, mm^3$, with a matrix size of $64 \times 64 \times 50$, resulting in an isotropic 3 mm resolution. For 3D EPI sequences, a 2D RF pulse [20] was used with a flip angle of $15^0$, and the readout bandwidth was 100kHz. The flip angle for the 2D EPI sequence was set at $90^0$ to have a fair comparison. The echo time (TE) was chosen as 30ms for all experiments. A sagittal orientation was selected to optimize the
Figure 2.3: Flow chart for the reconstruction process for the 3D EPI UNFOLD GRAPPA sequence. The numbers shown on the right above each red box show the number of voxels in the dataset at each stage of the process. Note that the number of $k_z$ planes increases as unacquired data is restored through the process. Specifically, 17 $k_z$ planes were acquired for each time point. After phase correction, the UNFOLD reconstruction was used to reconstruct 11 even numbered $k_z$ planes. Using these $k_z$ planes and the reference $k_z$ planes the GRAPPA matrix was constructed in the mixed $x-k_y-k_z$ domain for each time point to estimate the remaining 22 planes, thus fully reconstruct the data.

coil sensitivity distribution for GRAPPA. The acquisition orientation was; 3D encoding direction: left-right, EPI-readout direction: anterior-posterior, phase encoding (EPI-blip) direction: superior-inferior.

Three different sequences were applied to each subject, chosen so that we could compare our proposed accelerated 3D method to both 2D EPI to 3D EPI:

1. A standard 2D EPI sequence with full $kt$-space coverage, where we acquired exactly $64 \times 64$ k-space points for each of the 50 planes, resulting in a TR for the whole volume of 3 seconds.

2. A multi-shot 3D EPI sequence with full $kt$-space coverage, where we acquired exactly $64 \times 64 \times 50$ k-space points for each time frame. For each RF excitation we acquired 64 EPI readout lines. This led to a repetition time of 60ms between RF pulses. Since we acquire 50 $k_z$ planes, again 3 seconds were required to acquire all of k-space.
3. Accelerated 3D EPI with spatial and temporal encoding along the $z$ direction. $64 \times 64$ k-space points for 17 k-space planes were acquired at each time frame, reducing the acquisition time to 1.02 seconds per volume. Repetition time was also 60ms for this sequence.

The sequences were also used in phantom studies for SNR measurements.

### 2.3.3.2 fMRI Paradigms

We tested each sequence using two different fMRI paradigms. Institutional review board (IRB) approval was obtained for both studies, and informed consent was obtained for all subjects.

- **Aperiodic Block Design Paradigm**: Visuospatial-motor task: subjects were exposed to visual quadrants with high-contrast random noise patterns and asked to focus on a center dot. A finger motion scheme was exerted in the left or right hand when the visual wedge was active in the upper left or upper right quadrants, respectively. Block lengths of the stimulating quadrants varied between 5s and 15s. Noise patterns changed at a frequency of 5Hz. In a total imaging time of 3 minutes, 60 volumes were acquired at full kt-space coverage using both 2D EPI and 3D EPI and 171 volumes were acquired using the accelerated 3D EPI method. This visuospatial-motor task was tested on six healthy volunteers.

- **Event Related Paradigm**: The second paradigm was an event-related, selfpaced, audio-visual fMRI study solving arithmetic problems. They were presented, by randomly chosen auditory or visual stimuli, simple multiplication problems followed by an incorrect result (example: $4 \times 5 = 23$). They indicated by a button press if the incorrect product presented was (a) close to the correct solution, (b) too big or (c) too small. Stimulus events lasted between 4 to 8 seconds depending on subject response time, while the inter-stimulus interval was kept at 2 seconds. In a total imaging time of 10 minutes, 200 volumes were acquired at full kt-space coverage with both 2D EPI and 3D EPI and 588 volumes were acquired with accelerated 3D EPI. The event-related multiplication paradigm was tested on 4 healthy volunteers.

For all experiments, the first 5 volumes were discarded due to significant intensity fluctuation before a steady state was reached. In order to make a fair comparison between the
sequences, scan time was taken as a constant for all the experiments. For the block design paradigm the scan time was set to 180 seconds whereas for event-related paradigm it was set to 600 seconds.

![Images from a healthy volunteer acquired using a) standard 2D EPI (TR=3s), b) multi-shot 3D EPI (TR=3s) and c) accelerated multi-shot 3D EPI (TR=1.02s). Top row: axial images, middle row: coronal images, bottom row: sagittal images.](image)

Data processing and statistical analysis were computed with the SPM8 software. Spatial preprocessing consisted of realignment (rigid transformation) and 3D smoothing with a FWHM kernel size of 8mm. Conventional analysis was performed for the block design paradigm, using a stimulus onset vector convolved with the Hemodynamic Response
Function (HRF). With the event related design experiments, a Finite Impulse Response (FIR) method [21] presented with a window length of 12s was chosen with a train length (order) of 12 bins for the accelerated 3D EPI acquisition (1.02s) and 4 bins for full 3D EPI acquisition (3s). Parametric regressors were applied for the corresponding values of the number size effect (logarithm of effective correct product size). T-score thresholds were kept at $p < 0.001$ for the HRF analysis, and at $p < 0.05$ corrected for the FIR data. Activation maps were overlayed on the corresponding mean BOLD image.

As noted, for the UNFOLD part of the reconstructions filtering was done directly on the temporal Fourier Transform coefficients. The entire time series was used for this part of the filtering to ensure maximum possible temporal resolution. As noted in the discussion below, more sophisticated filtering schemes could be employed to enable more rapid reconstructions.

## 2.4 Results

Figure 2.4 illustrates sample images acquired with each of the different sequences. The 3D EPI images had fewer in-slice artifacts but they are more T1-weighted compared to 2D EPI. They also show more coverage in fronto-orbital and temporal lobes due to reduced through-plane signal loss in 3D EPI. As expected due to the undersampling, the accelerated 3D EPI images have slightly more artifacts (shown by the red arrow) in the 3D slice encoding direction compared to non-accelerated 3D EPI.

Table 1 summarizes the difference in time series Signal to Noise Ratio (tSNR) of all sequences in both phantom and in-vivo studies. The tSNR for each voxel was calculated by dividing the mean of the time series of that voxel by its standard deviation. Drifts in the signal magnitude were corrected and images were realigned before the tSNR calculations. For each volunteer, tSNR was calculated using several $3 \times 3$ spatial regions that showed no activation. These regions were manually selected using a T1 map to separate gray and white matter. The mean and the variance of tSNR in gray and white matter are reported separately. The tSNR per unit time was calculated since TR was not held constant for all sequences.
Chapter 2. Rapid Full-Brain fMRI with an Accelerated Multi-Shot 3D EPI Sequence Using Both UNFOLD AND GRAPPA

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TSNR Phantom (per unit t)</th>
<th>TSNR GM (per unit t)</th>
<th>TSNR WM (per unit t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2DEPI</td>
<td>102.1 (58.94)</td>
<td>65.2 (37.64) ± 4.1</td>
<td>74.4 (42.95) ± 3.1</td>
</tr>
<tr>
<td>3DEPI full</td>
<td>111.8 (64.54)</td>
<td>54.7 (31.58) ± 3.1</td>
<td>61.8 (35.68) ± 2.9</td>
</tr>
<tr>
<td>3DEPI acc.</td>
<td>68.2 (66.86)</td>
<td>43.8 (43.2) ± 4.1</td>
<td>48.9 (48.3) ± 4.6</td>
</tr>
</tbody>
</table>

**TABLE 2.1:** SNR and Time Series SNR comparison between the three sequences. For the phantom studies tSNR values are given as the median tSNR over voxels. For the in-vivo studies, tSNR values in grey (GM) and white matter (WM) are given separately as the mean of the median tSNR (over voxels) ± variance over 6 different volunteers. Also tSNR per unit time calculated as tSNR divided by the squareroot of the acquisition time is reported in paranthesis.

For the phantom studies, 3D EPI had a slight tSNR advantage compared to 2D EPI. The tSNR drop of 3D EPI UNFOLD GRAPPA compared to 3D EPI is a result of the undersampling in k-space and is consistent with the SNR equation \( \text{SNR} \propto \text{Voxel Size} \times \sqrt{\text{Number of measurements}/\text{BW}} \). The SNR advantage of multi-shot 3D EPI did not translate to the in vivo studies due to increased susceptibility of 3D EPI to motion and flow artifacts, and we observed that 2D EPI had slightly better tSNR values for both gray and white matter. The difference between the tSNR drop calculated using the above SNR equation and the experimental values may be explained by physiological noise.

Figure 2.5 shows SPM analysis results for the Block Design experiment for three different sequences. The activated regions correspond to the case where upper right quadrant is active with a noise pattern which requires a right hand finger tapping from the volunteer. In all cases similar activation regions were observed. Table 2 gives a comparison between all sequences in terms of number of activated voxels, t-scores in motor and visual cortex, and the percentage signal change of BOLD activation. 3D EPI UNFOLD GRAPPA, although it has a lower tSNR and percentage signal change, resulted in better t-scores when compared with fully acquired 2D EPI and 3D EPI sequences. The statistical power gained by acquiring three times as many time samples with the accelerated 3D sequence more than compensated for the lowered tSNR, in agreement with previous studies [8],[12]. The number of activated voxels was similar for the three sequences.

HRF activation regions corresponding to the auditory regressor (product size effect) for the event-related multiplication paradigm are shown in Figure 2.6. The regions for non-accelerated 3D EPI (top) and 3D EPI UNFOLD GRAPPA (top) acquisition are projected on to the mean images of each sequence. Both maps show strong activation in the auditory
cortex as expected. However, the activation map for non-accelerated 3D EPI does not feature numerous areas typically recruited during mental arithmetic whereas the accelerated 3D EPI sequence shows strong activation in such regions.

Figure 2.7 illustrates the results of FIR analysis of 2D EPI, non-accelerated 3D EPI and 3D EPI UNFOLD GRAPPA sequences. This graph shows the results from one representative subject. Similar results were obtained with all participants. In this graph, FIR bins corresponding to voxels from brain areas related to audio input (auditory cortex), number recognition (intra-parietal sulcus (IPS)) and button press (motor cortex) were averaged and plotted against time. For both sequences in all three regions, an HRF curve can be observed. The peak of the HRF curve for the non-accelerated 3D EPI occurs accumulatively at the third FIR bin (6 seconds after the start of an event) for all three regions. On the other hand, with an accelerated 3D EPI sequence (TR=1.02s) it is possible to distinguish the peaks corresponding to these three events. The effect of long auditory stimuli can be seen consistently in both sequences as the auditory response is stronger than the shorter button press and IPS activation. Also it should be noted that the right hand side of the graph corresponding to the second event is hard to interpret since the order of audio and visual stimuli is randomized, which distorts the temporal consistency.

The increased temporal resolution in the 3D EPI GRAPPA+UNFOLD data results in an overall much more informative picture, in contrast to the temporal resolution of the full data set that is insufficient to capture rapid dynamic changes intrinsic to the complex mental task.
Chapter 2. Rapid Full-Brain fMRI with an Accelerated Multi-Shot 3D EPI Sequence Using Both UNFOLD AND GRAPPA

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Activated Voxels</th>
<th>% dSignal (VC)</th>
<th>% dSignal (MC)</th>
<th>Max T-score (VC)</th>
<th>Max T-score (MC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2DEPI</td>
<td>261 ± 8.2</td>
<td>5.76 ± 0.38</td>
<td>6.01 ± 0.41</td>
<td>10.86 ± 1.28</td>
<td>10.13 ± 1.98</td>
</tr>
<tr>
<td>3DEPI full</td>
<td>268 ± 8.4</td>
<td>5.62 ± 0.44</td>
<td>6.23 ± 0.45</td>
<td>9.13 ± 1.32</td>
<td>8.51 ± 2.13</td>
</tr>
<tr>
<td>3D EPI acc.</td>
<td>272 ± 9.2</td>
<td>4.79 ± 0.24</td>
<td>6.03 ± 0.39</td>
<td>12.76 ± 1.94</td>
<td>15.33 ± 2.61</td>
</tr>
</tbody>
</table>

Table 2.2: fMRI activation analysis comparing the three different sequences for the visuospatial-motor task (Block Design). Number of active voxels, relative amplitude of the BOLD signal to the mean signal (dSignal) and maximum t-scores in visual cortex (VC) and motor cortex (MC) are given. We did not observe a statistically important difference between the quadrants, so only the right upper quadrant is reported here.

2.5 Discussion

Although we observed improved t-scores with block design paradigms acquired with our accelerated multi-shot 3D EPI sequence, the real benefit is more evident when a complex mental task is studied in an event related design. With an accelerated sequence, not only were we able to observe a better activation map using a standard HRF analysis but we were also able to gain more information about the timing of events with a more complex analysis (FIR). Techniques to take advantage of this information to achieve time retrieval of complex mental processes \[22\] will be investigated in future work. With the emergence of fMRI analysis using machine learning tools \[23\] \[24\] and state space analysis \[25\], increased temporal resolution will also be helpful in providing more highly temporally resolved data.

A major problem in fMRI studies is that the small signal changes from neural activity are vulnerable to physiological noise, such as respiration and heartbeat. Therefore in this respect, another potential advantage of increased temporal resolution is the ability to more correctly estimate and remove physiological noise from the data. For whole brain imaging with high spatial resolution, breathing artifacts can be estimated and removed but with a TR=1.02s we are not yet able to compensate for artifacts associated with cardiac activity. A highly accelerated single shot 3D Echo Volumar Imaging (EVI) \[26\] may be better suited for this goal by reducing TR to the 100ms range. However, EVI will be limited in how many kz planes can be acquired due to the rapid $t_2^*$ decay. This decay causes excessive signal blurring along the slow secondary phase encoding direction, and hence is difficult to apply for fMRI without high acceleration factors. In contrast, a sequence that employs temporal sub-sampling (UNFOLD) combined with multiband excitation and
simultaneous refocusing [12] might enable an increase in temporal resolution to a level where physiological artifacts can be removed.

One problem that arises with subsampled phase encoding in accelerated EPI sequences is increased Nyquist ghosting. Especially for long fMRI scans, methods that rely on a reference scan can be unreliable in the presence of system instabilities. Here we used a self-referenced Nyquist ghost correction [19] in order to solve this problem, without requiring an extended EPI echo train. Unreliability of reference scans in long fMRI experiments was also the main reason that we preferred a self-referenced parallel imaging method. GRAPPA was used instead of SENSE [27], since less auto-calibration data is needed in this low resolution scenario.

The sequence might be further accelerated by subsampling the reference planes and using UNFOLD to reconstruct the missing reference planes. However, we observed severe reconstruction artifacts along $z$ after the GRAPPA reconstruction was applied with this approach. Also it is possible to acquire [8] the reference data at the start of the scan and use it throughout. This will reduce the acquisition time (calculated to be a reduction from 1.02 seconds to 780ms in this specific case) and would also allow acquisition of more reference planes at the start. However, in our setup, during a total scan time of 10 minutes for each exam, we experienced a significant change in the auto-calibration data between the start and end of the acquisition. Possible reasons for this are scanner bore heating [28] and magnetic field disruption from external electromagnetic sources [29]. Another approach to potentially increase temporal resolution is to use PRESTO [30]. However, unless higher acceleration along the phase encoding direction can be achieved, the empty space between the RF pulse and the readout gradient is currently not long enough to make use of PRESTO with our setup. PRESTO might be a viable option for a longer echo time or a smaller magnetic field.

The temporal resolution can also be increased by reducing the spatial coverage using an oblique trajectory. A standard 8-channel head coil was used in this work, and therefore a sagittal orientation was selected to optimally use coil sensitivities to accelerate along the slice encoding direction. Using a head coil with distributed coil sensitivities along all three dimensions should enable an oblique FOV orientation. In this case, the number of acquired $k_z$ planes could be reduced while still covering the entire brain.

Partial Fourier methods [31] could also be used in either the phase encoding, $k_y$, or slice encoding, $k_z$, direction to reduce the scan time. In a previous work [32], we applied...
Partial Fourier in conjunction with UNFOLD for a multi-shot 3D EPI sequence. However, our experiments showed that when a small number of reference lines was used, significant image artifacts were observed due to phase inconsistencies and susceptibility artifacts.

It should be noted that although the whole volume is acquired in 1.02 seconds for the accelerated sequence, some part of the temporal frequency spectrum is lost in the UNFOLD filtering process. This filtering will introduce correlations in the time domain that will reduce the effective temporal resolution which will depend on the width of the filter. In our case 8 percent of the spectrum was removed which reduces the temporal resolution to 1.1 seconds.

Our current accelerated 3D EPI approach will require some modification to enable its use in real time fMRI, as the typical reconstruction times are in the range of ten minutes for a long fMRI study. In particular, the UNFOLD filtering should be done using a more sophisticated filter design implemented via a difference equation in the time domain, and both the GRAPPA and UNFOLD reconstructions should be parallelized, to achieve reasonable reconstruction time. This has been implemented in more recent versions of the Fast Imaging Library [33] used in this work, and is a subject of future work.

A sample slice from a tSNR map for resting state studies is shown in Figure 2.8 for a) Full k-space coverage, b) GRAPPA applied along the z direction with an acceleration factor of 2 and 6 reference slices, c) UNFOLD applied along the 3D encoding direction with an acceleration factor of 2, d) Both UNFOLD and GRAPPA applied along the z direction, with a combined acceleration factor of 4 with 6 reference slices. GRAPPA based methods appear to suffer from tSNR losses near the center of the images, consistent with g-factor SNR losses, whereas UNFOLD based methods performed worse in regions with flow and motion.

### 2.6 Conclusion

A multi-shot 3D EPI sequence accelerated along the secondary phase encoding direction using UNFOLD and GRAPPA was implemented to improve the temporal resolution of complex fMRI studies. Compared to traditional 2D EPI and 3D EPI methods, our experiments with a block design fMRI paradigm showed that the increased temporal resolution achieved by our 3D EPI UNFOLD GRAPPA sequence improved the sensitivity of the
reconstructed images to BOLD activation. Moreover, our results from event-related studies imply that this increased temporal resolution gives richer information about complex neural processes in cognition and in particular furthers our knowledge about the temporal schedule of such processes.
FIGURE 2.6: SPM results showing the HRF analysis (Auditory Regressor) for the event-related multiplication task using: (top) 2D EPI (TR=3s), (middle) multi-shot 3D EPI (TR=3s) and (bottom) accelerated 3D EPI (TR=1.02s). Activation regions are projected on to the mean images in sagittal (left column) and coronal (right column) views. All three sequences show strong activation in the auditory cortex (blue arrows) and motor cortex (green arrows); however primarily the accelerated sequence reveals activation in the cortical regions responsible for number recognition and processing (red arrows).
Figure 2.7: SPM results showing the FIR analysis (Auditory Regressor) for the event-related multiplication task using: (top) 2D EPI (TR=3s), (middle) multi-shot 3D EPI (TR=3s) and (bottom) accelerated 3D EPI (TR=1.02s). For each sequence, FIR bins corresponding to areas related to auditory input, number recognition and button press are plotted along time.
Figure 2.8: Sample tSNR maps for (from left to right), Full acquisition, 2x GRAPPA, 2x UNFOLD and 2x GRAPPA+2x UNFOLD
Chapter 3

Investigation of Fast Spin Echo Sequences in Small Animal fMRI for Brain Mapping Studies

3.1 Introduction

2D Gradient echo EPI [3] is the most common fMRI sequence. It provides high contrast to noise ratio, has low Specific Absorbtion Ratio (SAR), and has short acquisition times compared to other sequences. Recently, Spin Echo EPI has been shown to work well as an alternative [34, 35, 36, 37] especially with high field strength. Extravascular effects from large vessels can be eliminated with spin echo methods because the 180° RF pulse refocuses the static dephasing induced by field inhomogeneities around large vessels. This results in spin echo signal being weighted more towards the microvasculature networks which correlate more closely with neuronal activities. Therefore, functional specificity can be increased at the cost of a functional CNR. [38]

With Spin Echo EPI, through plane susceptibility artifacts are reduced compared to gradient echo EPI but there is still geometric distortion and in-plane susceptibility artifacts due to long EPI readouts. Fast Spin Echo (FSE) sequences produce artifact free images in cost of temporal resolution. Figure 3.1 shows the same image slice acquired using Spin Echo EPI (left) and Fast Spin Echo (right). Severe artifacts near the sinuses can be seen in the EPI
images. This is especially critical in small animal studies where sinuses are much larger compared to the brain volume.

In an fMRI study where precise localization of brain activity is important, EPI based methods may fail to provide a high fidelity anatomical information. For example in functional brain atlas studies, geometric distortion due to EPI readouts might create registration errors and also the susceptibility artifacts will make the information near the sinuses less reliable. A typical segmented atlas of the rat based on cytoarchitecture and immunohistochemistry of cell markers and neurotransmitters displays several hundred brain areas. Understanding the cellular and molecular activity of these brain areas and their interconnections forms the foundation of years of neurobiological research on the brain. If the study of brain activity with fMRI is going to make a meaningful contribution to this knowledge base, then localizing signal changes to discrete brain areas within a subject and across subjects is important. To do so requires high image resolution and neuroanatomical fidelity. Many brain areas in a segmented rat atlas have in-plane boundaries of less than 400 microns and may extend for over 1000 microns in the rostral/caudal plane. With the advent of segmented, annotated 3D MRI atlases for rodents it is now possible to localize functional imaging data to precise 3D volumes of interest in clearly delineate brain areas. Therefore, it is critical that the images are a very accurate reconstruction of the original brain. While there are many things that contribute to image fidelity one of the most important is the choice of pulse sequence.

Fast spin echo sequences have already been shown to work well in 3T human studies in Poser et.al [39]. They showed that with high acceleration rates provided by parallel imaging it is possible to use FSE sequences for functional studies. Ye et al. [40] used a modified GRAPPA algorithm to further decrease the scan time and also analyzed the trade-offs with respect to certain scan parameters such as flip angle and echo time.

In this work we investigated fast spin echo sequences for fMRI in functional brain mapping studies of small animals in high field. In particular we implemented a modified HASTE (Half-Fourier Acquisition Single shot Turbo spin Echo) sequence in a 7T Bruker system. We tested our sequence with CO$_2$ challenge and forepaw stimulation in rats.
Chapter 2. Investigation of Fast Spin Echo Sequences in Small Animal fMRI for Brain Mapping Studies

3.2 Methods

3.2.1 MRI Pulse Sequence

A multi-slice single-shot Fast Spin Echo sequence was used for functional images. Due to the $T_2$ decay it is critical to reduce the number of phase encoding lines in order to reduce the blurring. To this end, we used partial Fourier acquisition with a 9/16 ratio. (This sequence is called half-Fourier acquisition single shot turbo spin echo by Siemens). As shown in Figure 1, a three-lobed $180^\circ$ sinc pulse was used to refocus to first echo. With this inclusion [39] the echo time can be moved to a desired value by shifting the distance between the first $90^\circ$ pulse and the $180^\circ$ sinc pulse. In our experiments we have used an echo time of 50ms which was determined using Carbon Dioxide ($CO_2$) challenge. After the echo is refocused, a train of single-lobed sinc pulses is applied giving an inter-echo TE of 4ms.
3.2.2 Image Acquisition

MRI experiments were performed on a 7T Bruker BioSpec 70/20 (Oxford Instrument, Oxford, UK) system equipped with maximum gradient strength of 300 mT/m and a slew rate of 1100 T/m/s. A single-channel quadrature transmit/receive, volume coil (Insight NeuroImaging Systems, Leominster, Massachusetts) where remote tuning and matching were achieved via long tuning rods was optimized for imaging the entire mouse brain. A small animal restrainer (Insight Neuroimaging Systems, LLC, Worcester, MA) was used to minimize motion artifacts.

20 interleaved slices were acquired with a FOV of 3cm x 3cm. Slice thickness was set at 1mm which was enough to cover the whole brain including the olfactory bulb. 54 phase encoding lines were acquired for each slice and then a matrix size of 96x96 was reconstructed using Partial Fourier reconstruction, resulting in a resolution of 312 microns in the x-y direction. Echo time of 48ms was used and repetition time (TR) was 5.4 seconds.

3.2.3 fMRI Experiments

8 adult male long-evans rats were imaged with two different stimuli:
Chapter 2. Investigation of Fast Spin Echo Sequences in Small Animal fMRI for Brain Mapping Studies

1. CO$_2$ challenge: For each trial, BOLD images were acquired for 30 repetitions during baseline (air) and 30 repetitions during CO$_2$ challenge and 30 repetitions during second baseline. Ten percent CO$_2$ was used for these experiments.

2. Forepaw stimulation: Two needle electrodes were placed under the skin of the forepaw. Electrical currents with a pulse duration of 0.5 ms at 9 Hz and a magnitude of 9 mA were used for stimulation. For each trial, images were acquired for 30 repetitions during baseline 30 repetitions during stimulation and 30 repetitions during second baseline.

Data processing and statistical analysis were computed with the SPM8 software. Spatial preprocessing consisted of realignment (rigid transformation) and 3D smoothing with a FWHM kernel size of 600 microns. Stimulus onset vector was convoluted for the conventional HRF-based (hemodynamic response function) analysis. T-score thresholds were kept at $p < 0.01$ uncorrected for CO$_2$ challenge, and at $p < 0.05$ uncorrected for the forepaw stimulation. Activation maps were overlayed on a sample FSE image.

SNR was calculated by dividing the standard deviation of a signal region in brain to a standard deviation from a region in background. The tSNR for each voxel was calculated by dividing the mean of the time series of that voxel by its standard deviation. Drifts in the signal magnitude were corrected and images were realigned before the tSNR calculations.

### 3.3 Results

Figure 3.3 shows sample images from different slices in the rat brain from inferior (a) to superior (f). In Figure 3.4, activation maps corresponding to CO$_2$ challenge are overlayed on FSE images for different slices, whereas Figure 3.5 shows the activations maps for forepaw stimulation.

In Table 3.1, mean and standard deviation of SNR over 8 experiments is reported. For each experiment median of tSNR was calculated and the mean and variance of that median tSNR is reported in Table 3.1. Percent signal change was calculated as the maximum signal change compared to the mean of the baseline signal for a sample active voxel.
Chapter 2. Investigation of Fast Spin Echo Sequences in Small Animal fMRI for Brain Mapping Studies

Figure 3.3: Sample slices from 6 different slices. In b, c regions with large sinuses can be seen without any susceptibility artifacts.

Figure 3.4: Activation maps for 4 different slices for the CO2 challenge. Whole brain is found to be active with high t-scores.

3.4 Discussion

As can be seen in Figure 3.3, no geometric distortion and susceptibility artifacts were observed in functional images. High resolution functional images with good anatomical information acquired using this sequence will make the registration process easier since high resolution multi-shot Fast Spin Echo sequences are usually used to acquire the reference images. Both sequences produce the same contrast and artifacts. It is even possible
FIGURE 3.5: Activation maps for 3 different slices for the forepaw stimulation. Activation in the motor cortex was found as well as other brain areas.

<table>
<thead>
<tr>
<th>Metric</th>
<th>RAREst</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNR (dB)</td>
<td>52.1 ± 4.2</td>
</tr>
<tr>
<td>tSNR (dB)</td>
<td>40.3 ± 2.3</td>
</tr>
<tr>
<td>Percent signal change</td>
<td>5.62 ± 2.11</td>
</tr>
<tr>
<td>Max T-score (CO$_2$)</td>
<td>17.12 ± 3.21</td>
</tr>
<tr>
<td>Max T-score (forepaw)</td>
<td>4.79 ± 1.11</td>
</tr>
</tbody>
</table>

TABLE 3.1: Summary of image and functional information metrics for all experiments. For all quality metrics, standard deviation was reported over 8 experiments.

to skip the anatomical reference scan and use the acquired images as reference.

With CO$_2$ challenge, as expected, voxels from all over the brain was found to be activated with very high t-scores (8-16). Forepaw stimulation resulted in activation in the motor cortex, but with lower t-scores.

With this sequence, it was possible to cover the whole brain including olfactory bulb under 5 seconds. An alternative to this sequence is using a multi-shot FSE sequence. Although multi-shot FSE will provide better anatomical accuracy (less T$_2$ blurring), in our setup 8.2 seconds are needed to cover the whole rat brain with a matrix size of 64x64.

Same volume can be acquired in under 2 seconds using Spin Echo EPI (or Gradient Echo EPI). Spin Echo EPI also produces higher percent signal change resulting in higher t-scores. So with this sequence we trade-off higher temporal resolution and functional CNR with better functional localization.

It is possible to reduce the image time or increase spatial resolution using reduced field of view methods. Saturation pulses or selective RF pulses can be used to remove the
unwanted signal outside the brain, resulting in an increase in x-y resolution. Multiple channel coils can be used to decrease the time required to acquire each volume but with a cost of SNR. Also reducing the number of phase encoding lines will help to reduce the blurring associated with $T_2$ decay.

Although the restrainers limit the head motion, we have experienced artifacts due to jaw motion when the k-space is subsampled in $k_y$, direction. On the other hand it is possible to subsample in $k_x$ when a slightly higher FOV is selected, which will make certain k-t space undersampling techniques [1, 14, 15] feasible.

Matrix size of 64 (467 micron resolution) can be acquired in 3s per volume. Due to $T_2$ blurring and scan time constraints $128 \times 128$ matrix size (70 phase encoding lines with PF) did not produce usable results. Main reason is $T_2$ decay resulting in very low SNR in higher frequencies.

Due to Specific Absorption Rate (SAR) limits, the sequence might need modifications in order to be used in human studies.
Chapter 4

Variable Density $k$-Space Trajectories: An Analysis of Tradoffs

4.1 Summary

A number of recently developed techniques have employed so-called variable density $k$-space trajectories (most often spirals) in order to increase acquisition speed and thus achieve enhanced MRI applications ranging from angiography to multi-dimensional RF excitation. In such variable density trajectory schemes, the sampling density is reduced below the Nyquist limit for some axis, typically as a function of distance from the center of $k$-space. These undersampled trajectories achieve reduced aliasing and/or increased resolution when compared to a trajectory of equivalent duration but that is fully sampled at the Nyquist rate. Unfortunately, to date there has been no systematic comparison of the various undersampling schemes that have been proposed and used, nor has there been a systematic characterization of the tradeoffs versus benefits. Such an analysis, using simulations and experiments based on well-known metrics such as signal-to-noise, root-mean-square error and resolution, is provided in this work for some of the more commonly used undersampling schemes.
4.2 Introduction

Scan time is the limiting factor in many Magnetic Resonance Imaging (MRI) applications. Trajectories which sample $k$-space non-uniformly, such as spirals [41], reduce scan time by making more efficient use of gradient hardware capabilities. Variable density (VD) trajectories have been proposed to achieve further scan time gains, as they allow increased flexibility in the tradeoff between resolution, field of view (FOV), and acquisition duration. In VD schemes, $k$-space sampling density is reduced below the Nyquist rate, typically decreasing in density, as a function of distance from the origin. However, as a consequence of the below Nyquist rate sampling, the collected data does not in general provide sufficient information to completely resolve the imaged object.

Standard non-uniform image reconstruction methods such as density compensation and gridding reconstruction [42] can be applied to samples collected using VD trajectories, relying on the trajectory to minimize artifacts [43, 44]. Inverse solution formulations of the imaging problem have also been devised relying on various regularization schemes to limit artifacts for a given trajectory. Inspired by the paper written on compressed sensing by Lustig et al. [45], using sparsity in a transformation domain to regularize the solution of the inverse problem has become widely popular. In all VD MR imaging, resolution, artifacts, and signal-to-noise ratio (SNR) properties are affected not only by the choice of trajectory and undersampling parameters, but also by the parameters of the particular reconstruction method.

Many of these properties have typically been selected using heuristic arguments. For example, resolution and aliasing are quantified by visual examination of the point-spread function (PSF). Indeed, a fact that has been rarely noted in the literature is that the PSF concept is inherently ambiguous with the use of regularized linear solvers, as they are not spatially invariant. Similarly, SNR efficiency is typically quantified simply based on the trajectory duration, neglecting the impact of the choice of image reconstruction algorithm. The latter effect is intrinsic to the SNR of non-uniform $k$-space sampling in MRI, since the linear MR imaging problem is ill-conditioned for typical non-uniform sampling schemes [46].

To more fully illuminate the importance of these algorithm and parameter choices, in this thesis we present a systematic comparison of commonly used VD trajectories and reconstruction methods in order to quantify the relevant trade-offs. Specifically, we compared
VD schemes with linearly decreasing, quadratically decreasing and piecewise constant $k$-space densities, over wide ranges of undersampling factors. In order to have a ground truth for comparison, the analytically defined Fourier transform of a resolution phantom was computationally sampled for each trajectory, and, after adding Gaussian noise to the samples, four different reconstruction methods were used to generate an image: the Pipe and Menon density compensation function (DCF) [47] followed by a non-uniform FFT (NUFFT) [48], and commonly used regularized solvers based on 2-norm ($L_2$) [49], 1-norm ($L_1$) [45], Total Variation (TV) [45] and a combination of $L_1$ and TV regularization. Comparison was performed using carefully defined quantitative metrics: root mean square error (RMSE), SNR, detectability of image features and FWHM of the PSF at a specific image location.

4.3 Theory

In this work we focus on 2D k-space trajectories $k(t) = kx(t) + iky(t)$, modeled after Archimedian spirals in the complex plane of the form:

$$k(t) = ar(t)e^{i2\pi nr(t)}$$

(4.1)

where $a$ denotes the maximum k-space radius reached by the trajectory, $n$ the number of complete turns, $0 < r(t) < 1$ the azimuthal function, $i$ is the imaginary number ($\sqrt{-1}$), and $0 < t < 1$ denotes time normalized by the trajectory duration $T$.

In order to satisfy the Nyquist sampling rate for a desired radial field-of-view (FOV) dimension, the azimuthal function should be chosen so as to sufficiently separate each turn of the spiral by a fixed k-space distance $k_r$ [41, 50]. For this choice, $a = nk_r$, and the first aliasing sidelobe of the PSF will occur at a radius of approximately $1/k_r$ in the spatial domain [50].

Ideally, $k_r$ is chosen such that the disk-shaped FOV fully encompasses the imaged object. Unfortunately, because the image resolution achieved is proportional to the magnitude of the parameter $a$, as the required FOV is increased, resolution is decreased for a fixed number of spiral turns. When scan time is the limiting factor and it is not possible to reach the desired $a$ with a given FOV, either a smaller $a$ should be selected, thereby reducing the
spatial resolution, or, a larger $k_r$ must be used, which will potentially move the aliasing sidelobe into the imaged object and increase reconstruction error due to aliasing.

As first suggested by Spielman et al. [51] and Tsai et al. [44], variable density spirals can be used to trade off resolution and reconstruction error in these cases. Specifically, using the fact that most of the energy of relevant objects is concentrated around the low frequency region, the sampling rate can be selected in a way such that it is approximately equal to the Nyquist rate near the central low frequency region (DC), and decreases towards the “edges” of k-space. Given that the PSF emanates from a superposition of all the frequency components [50], the aliasing side-lobe will then become more distributed (i.e., spread out), so that the visual effects of aliasing will be reduced compared to the case where an insufficient fixed density causes the aliasing side-lobe to occur within the imaged sample.

Such variable density trajectories can be formulated as:

$$k(t) = a f(t)r(t)e^{2\pi nr(t)}$$

(4.2)

where $f(t)$ is the sampling density function along the radial direction. A common concept defined in variable density imaging for sampling density function is “effective FOV” (eFOV). Effective FOV is defined as the inverse of the sampling interval in $k_r$. Whereas with fixed sampling density the eFOV is constant and equal to the actual FOV, with variable density the eFOV decreases as the k-space radius increases. Each spatial frequency in an image possesses a different effective PSF, and will thus exhibit different aliasing structure. Selection of the sampling density function $f(t)$ (and thus, eFOV) in Eq. 4.2, which controls this aspect of the imaging process will effect the tradeoffs among the spatial resolution, reconstruction error and signal-to-noise ratio.

A main disadvantage of non-uniform trajectories such as spirals in MR imaging is the increased complexity of the reconstruction process. In order to reconstruct the image from the non-uniformly acquired samples, either a density compensation function [42], [52], [47] should be applied, followed by either gridding the compensated data onto a Cartesian grid [42] or employing a non-uniform FFT [48], or, based on the imaging equation an iterative approach such as conjugate gradients [27], [49] must be used.
Chapter 4. Variable Density k-Space Trajectories: An Analysis of Tradeoffs

4.4 Methods

As stated above, the goal of this work is to characterize and quantitate imaging quality tradeoffs based on the choice of both the sampling density function $f(t)$ in Eq. [2] and of the reconstruction method. To this end, simulations and experiments were performed for various different choices of the sampling density, described below. In order to produce comparable results, the number of sampling points was kept constant across all trajectories used. That is, each trajectory was of equal duration in time while the maximum k-space radius reached depended on the undersampling function and the parameters determining that function. All trajectories were designed for an eFOV of 22 cm near DC. That is, the center of k-space was sampled at a sufficient density to support that eFOV. Four different sampling density functions were explored, linearly and quadratically decreasing [44], and 2 different piecewise constant [51] (details vide infra). The least undersampled trajectory for each of the above 4 schemes was sampled at the Nyquist rate throughout the extent of $k$-space. The most undersampled trajectory for all schemes reached a common fixed maximum $k$-space radius. 100 instantiations of each scheme smoothly transitioned between these two extremes. In terms of image resolution, the least undersampled version of the schemes was chosen to produce an 85x85 image matrix size to cover the 22 cm FOV (2.59 mm resolution), while the most undersampled versions reached a $k$-space radius equivalent to a resolution of 1.72 mm (128x128 image matrix).

All trajectories were segmented to 8 interleaves (i.e., arms), with 1024 sampling points per interleave.

**Trajectories** Specified variable density trajectories were generated for four choices of the form of the sampling density function $f(t)$ (c.f., Eq. [2]. These were:

- linearly decreasing density, i.e.,

  $$f(t) = \alpha r(t)$$  \hspace{1cm} (4.3)

  with 100 different choices of $\alpha$, equispaced between $\frac{5}{22}$ and 1,

- quadratically decreasing density, i.e.,

  $$f(t) = \alpha r(t)^2$$  \hspace{1cm} (4.4)
also with 100 different choices of $\alpha$, equispaced between $\frac{2}{22}$ and 1,

- piecewise constant in two contiguous domains, i.e.,

$$f(t) = \begin{cases} 
1 & \text{if } 0 \leq t \leq \delta, \\
\frac{1}{2} & \text{if } \delta < t \leq 1.
\end{cases}$$

(4.5)

with 100 different choices of $\delta$, equispaced between $\frac{1}{5}$ and 1,

- piecewise constant in each half of the domain,

$$f(t) = \begin{cases} 
1 & \text{if } 0 \leq t \leq \frac{1}{4}, \\
\beta & \text{if } \frac{1}{4} < t \leq 1.
\end{cases}$$

(4.6)

i.e. with 100 different choices of $\beta$, equispaced between 1 and $\frac{1}{4}$.

Examples of the ranges of sampling density function for selected values of their respective undersampling parameter are plotted in Fig. 4.1 for all schemes. The plot presents the eFOV of each selected trajectory as a function of k-space location. Sample k-space trajectories are shown in Fig. 4.2.

### 4.4.1 Simulations

The trajectories described above were used to simulate MR data acquisition for the resolution phantom shown in Figure 4.3. This phantom consists of two regions. In the upper region there are small objects (with magnitude 1) which each has a size of 1 FWHM of the PSF for the fully sampled scheme (one voxel) in both directions. The distance between the objects was selected as integer multiples of FWHM to avoid any discretization errors. In the lower region, the same distances are used but the magnitudes of the objects and the background are reversed (which we will see below matters for l1-based regularization). The phantom consists of only rectangular objects, making it is easy to calculate the analytical Fourier Transform of the phantom and to reduce simulation errors, from discretization.

For each trajectory signal acquisition was simulated by calculating the Fourier coefficients of the phantom at the $k$-space locations (spatial frequencies) composing each trajectory.
Figure 4.1: Plots of the eFOV as a function of k-space radius for each sampling density function used - a) linearly decreasing, b) quadratically decreasing c) piecewise1, d) piecewise2, each shown over a selected range of the parameters used with the corresponding function. The base eFOV at the center of each trajectory is 22 cm. Red curves show the least undersampled trajectory (fixed density) and blue the most undersampled trajectory.

Gaussian noise with fixed standard deviation chosen to yield an approximate SNR of 15 (high noise scenario) or 25 (low noise scenario) was added to the simulated samples. Four different image reconstruction methods were used: a) the Pipe and Menon DCF method \cite{47} (maximum error bound 0.01 or convergence in 5000 iterations)\(^1\) in conjunction with NUFFT, b) minimum \(L_2\) error linear system solution, c) linear system solution with \(L_1\) regularization, d) linear system solution with TV regularization, and e) linear system solution with joint \(L_1\) and TV regularization. The formulation for the joint \(L_1\) and TV norm is given below in Eq. 4.7, where \(\hat{x}\) and \(y\) are vectors that correspond to the reconstruction and k-space data respectively, and \(F\) denotes the Fourier transform on the given k-space.

\(^1\)We also tested the Voronoi tessellation method but results were nearly identical and are thus omitted for space reasons.
Figure 4.2: K-space plots of the fixed density spiral (red) compared to the most undersampled spiral (blue) for a) linearly decreasing, b) quadratically decreasing c) piecewisea, d) piecewiseb trajectory. TV norm is calculated as the integral of the Euclidean norm of the gradient. Note that pure L1 and pure TV regularization can be obtained by setting the other $\lambda$ as zero. For the non-linear constrained solvers we employed a non-linear CG optimization algorithm using the Fletcher-Reeves criterion [53]. For the $L_2$ regularized problem, we used a linear CG algorithm. To avoid the non-differentiability of the $L_1$ and TV constraints at zero, a small positive constant was used to regularize the solution. The gradient of the TV term was calculated using [54]. Each image reconstruction method was tested for a wide range of regularization parameters.

$$\hat{x} = \arg\max_x \{ \|y - Fx\|^2_2 + \lambda_1 \|x\|_1 + \lambda_2 TV(x) \}$$ (4.7)
4.4.2 Experiments

We also performed experimental measurements using an imaging phantom. All experiments were performed on a GE Excite MR scanner (GE Medical Systems, Milwaukee, WI), equipped with 4 G/cm gradients capable of 15 G/cm/ms slew rate. The maximum slew rate was derated by 5 percent for all trajectories generated. A quadrature head coil was used for RF transmission and reception. The gradient hardware period was 4 µs. The manufacturer-supplied spiral gradient recalled echo (GRE) sequence was modified in order to read the gradient waveforms from external files, and then used for all experiments. The ADNI (Alzheimer’s Disease Neuroimaging Initiative) Magphan phantom was imaged with each selected trajectory. Pertinent imaging parameters were 30° flip angle, 200 ms
TR, 2.2 ms TE, 5 mm slice thickness, and 125 kHz bandwidth. A single image was acquired at magnet iso-center in order to minimize concomitant field effects [55].

### 4.4.3 Image Quality Metrics

Image quality assessment was based on SNR, RMSE, resolution, and aliasing power measurements. To calculate SNR, each simulation and experiment was repeated 1000 times (in the case of simulation with different pseudo-random noise) in order to obtain the variance of the reconstructed value of individual pixels in the images. This variance provides an accurate measure of achieved SNR. The normalized RMSE (NRMSE) was computed for all simulations as:

\[
NRMSE = \frac{||m_r - m_t||}{||m_t||}
\]  

(4.8)

where \(m_r\) denotes the reconstructed image, \(m_t\) denotes the ground truth image, and ||\(\cdot\)|| denotes the \(L_2\) norm. NRMSEs are reported as percentages. For the phantom experiments a high resolution, high SNR gradient echo image (Figure 4.14) was used as the true image.

Although PSF is a good indicator to determine resolution and aliasing in DCF based reconstructions, when a regularized linear system solution method is used it fails to give an accurate estimation of resolution. In these cases the PSF is not only space-variant but it may also depend on the object itself (as will be illustrated in the results sections). In order to quantify resolution for these methods, detectability of relevant image features was used. Since the simulated phantom image consists of objects that are multiple FWHM distance apart from each other, an indicator of resolution is whether the two objects that are FWHM apart from each other can be separated for a particular selection of trajectory and reconstruction method. The difference in magnitude between the two objects and the background region between them was calculated to quantify this resolution indicator.
4.5 Results

4.5.1 Simulation Results

Figure 4.4 (low noise) and 4.5 (high noise) show the RMSE achieved by each trajectory for different reconstruction techniques versus the maximum k-space radius of that trajectory. Each color corresponds to a family of generated trajectories and each marker corresponds to a reconstruction method.

![Graph showing RMSE vs k-space radius for different trajectories](image)

**Figure 4.4:** High SNR scenario: RMSE plotted against maximum k-space radius for all trajectories and reconstruction methods. Colors represent the undersampling method (linearly decreasing-red, quadratically decreasing-blue, piecewisea-green, piecewiseb-black) and the markers represent the reconstruction method.

For each trajectory and reconstruction method, SNR maps calculated using the standard deviation of 1000 reconstructions were generated. Sample standard deviation maps are...
Figure 4.5: Low SNR scenario: RMSE plotted against maximum k-space radius for all trajectories and reconstruction methods. Layout same as previous figure.

shown in Figure 4.6 (for the fixed density spiral) and 4.7 (for the most undersampled linearly decreasing trajectory). Figure 4.8 shows the mean of the standard deviation over all voxels and Figure 4.9 shows the standard deviation corresponding to the voxel with maximum variation over 1000 reconstructions.

Sample images are shown in Figure 4.10 for the fixed density spiral and in Figure 4.11 for the most undersampled linearly decreasing spiral (as shown by the blue trajectory in Figure 4.2).

Figure 4.12 and 4.13 quantify the separability of two objects that are one FWHM apart from each other. In Figure 4.12 the magnitude difference between the two objects (high magnitude) and the background (low magnitude) is plotted against the maximum k-space
Figure 4.6: For a fixed density spiral, standard deviation for each voxel over reconstructions with 1000 different noise instantiations for a) DCF, b) L2 norm, c) L1 norm, d) TV norm. Note that colormaps differ for each panel.

radius whereas for Figure 4.13 objects have low magnitude and background has high magnitude.

4.5.2 Experimental Results

A high resolution image of the phantom is shown in Figure 4.14. Figure 4.15 compares the RMSE for different trajectories and reconstruction methods for the phantom experiments. Sample reconstructions are shown in Figure 4.16. Figure 4.17 shows the mean of the standard deviation over all voxels and Figure 4.18 shows the standard deviation corresponding to the voxel with maximum variation over 1000 different phantom experiments.
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**Figure 4.7:** For the most undersampled (linearly decreasing) spiral, Standard deviation for each voxel over reconstructions with 1000 different noise instantiations for a) DCF, b) L2 norm, c) L1 norm, d) TV norm.

### 4.6 Discussion

The results will be discussed in terms of various image quality metrics including RMSE, SNR and resolution below. For each metric, first the results that make a comparison between different trajectories will be discussed followed by an analysis of different reconstruction methods. For each metric results from simulated experiments as well as phantom experiments will be considered. Discussion section will conclude with overall comments on the effects of trajectory and reconstruction mode selection.
Chapter 4. Variable Density k-Space Trajectories: An Analysis of Tradoffs

4.6.1 RMSE

Comparison of trajectories: For all the reconstruction methods, trajectories with a smooth undersampling function (Figure 4.1) produced lower RMSE errors compared to the piece-wise constant trajectories. As reported in Lee et al. [43], smoother sampling functions should produce less coherent aliasing artifacts. This was especially critical when DCF or L2 norm reconstructions were used. The smoother undersampling functions are expected to result in a PSF with more distributed sidelobes, consistent with the lower level of artifacts seen here. At least for the examples tested, RMSE was insensitive to choice of undersampling functions when TV norm reconstructions were used.

Although in terms of RMSE we did not observe a statistically significant difference between the undersampling functions, linearly and quadratically decreasing functions produced less visible artifacts especially for the highly undersampled trajectories.

![Figure 4.8: Average value of the standard deviation over all voxels in a reconstructed image plotted against the maximum k-space radius for all 5 reconstruction methods.](image-url)
Comparison of reconstruction methods: Overall, DCF reconstructions produced the highest RMSE and L1+TV norm produced the lowest RMSE (see Figure 4.4 and 4.5) with TV norm producing slightly higher RMSE at less undersampled trajectories. As the trajectory got more undersampled, DCF and L2 norm reconstructions had higher RMSE due to the aliasing introduced by sub-Nyquist sampling. Interestingly this was not true for the L1, L1+TV and TV reconstructions. L1+TV norm produced similar RMSE errors for the trajectories with different maximum k-space radius. For L1 norm reconstructions, the RMSE even decrease marginally when the trajectory was more undersampled.

For the phantom experiments, consistent with the simulation results, TV norm reconstructions resulted in lower RMSE for all trajectories. Also RMSE versus maximum k-space radius curve was steeper for the DCF and L2 norm based reconstructions compared to L1 and TV reconstructions. L1 norm reconstructions produced the sharpest images but
without removing the artifacts. TV norm reconstruction produced smooth images with low RMSE, however, some edge information was lost.

### 4.6.2 SNR

*Comparison of trajectories:* As would be expected, there was a trade-off between SNR and maximum k-space radius for each type of trajectory (see Figure 4.8 and 4.9). Besides the theoretical loss in SNR efficiency due to the variable density scheme as noted in Tsai et al.[44], there is additional loss of SNR due to acquisition of higher frequencies in the k-space. Unlike [44], where each trajectory had similar resolution and similar maximum k-space point, in this paper, each trajectory had different maximum k-space points. Assuming that the noise power is constant over the k-space and that the image
energy is concentrated at the center, points that are further away from the k-space center are expected to have decreased SNR and provide better resolution in the reconstruction.

Comparison of reconstruction methods: Another important point to note is that the DCF method had a much sharper increase in variability as a function of maximum k-space sample (Fig 4.8 and Fig 4.9) compared to the regularized solutions. Two likely contributing factors to this phenomena are: 1) Regularization acted as a filter that denoises the image, 2) In more undersampled trajectories, the distance between points in the outer regions of k-space increased. DCF weighed these points with a higher magnitude to compensate, even though these outer k-space points have lower SNR compared to the inner k-space points. It would be potentially possible to select a DCF that does not weigh outer k-space more than inner k-space points, but in this case resolution will be sacrificed.
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![Graph showing mean of normalized magnitude for voxel 1 versus max k-space radius. The graph includes lines for DCF, L1 Norm, TV Norm, L1+TV norm, and L2 norm methods.]

Figure 4.12: Magnitude difference (averaged over 1000 reconstructions) between the two objects that are 1FWHM distance apart and the background voxel between them. Here the background has a magnitude zero and the objects a magnitude 1.

L1 and TV norm solutions had more structured noise patterns compared to the L2 norm and DCF solutions, whose standard deviation maps were similar. TV norm solutions produced more stable reconstructions (wrt noise), especially in the smooth regions. Overall TV norm reconstructions produced the lowest average standard deviation (highest SNR) for all trajectories as seen in Figure 4.8. The points where the variation is highest are the regions with a high gradient. L1 and TV norm reconstructions had higher maximum variation compared to L2 norm and DCF reconstructions. It is interesting to note that as the trajectory got more undersampled, maximum standard deviation in L1 and TV norm solutions decreased.

SNR behaviour with respect to k-space radius was consistent with the simulation results for all the reconstruction methods.
Figure 4.13: Magnitude difference (averaged over 1000 reconstructions) between the two objects that are 1FWHM distance apart and the background voxel between them. Here the background has magnitude 1 and the objects has a magnitude zero.

4.6.3 Resolution

Comparison of trajectories: As expected, variable density trajectories produced sharper (higher resolution) images but with more artifacts. Fixed density spirals did not have enough k-space coverage to separate the objects that are 1 voxel (FWHM of the highest undersampled trajectory) apart. An interesting exception was the L1 norm reconstruction where these objects were separable when the background had low magnitude and the object had high magnitude.

For all reconstruction methods the separability increased as the trajectory got further in the k-space. L1 norm produced much sharper looking images in both simulations and experiments but when the magnitude of the object and the background were reversed it
failed to distinguish the object and the background. This also shows that the resolution varies over the image for the regularized linear solutions, one of the reasons why the PSF does not offer a viable analysis tool.

### 4.6.4 Overall Analysis

L1 and TV norm reconstructions removed the aliasing artifacts more effectively compared to DCF and L2 norm reconstructions. They produced lower RMSE for both the simulated data and in the experimental setup. TV norm also resulted in the lowest overall standard deviation in reconstructions while L1 norm produced the highest. Although DCF
reconstructions performed much worse in terms of RMSE and SNR when highly undersampled trajectories were used, they outperformed TV norm reconstructions in terms of resolution.

4.6.5 Additional Comments

For all the examples in this paper the center of the k-space was sampled close to the Nyquist sampling rate as the results were found to be significantly worse if the center of the k-space was undersampled.

As suggested by Lustig et al. [45], randomized spirals might be used for compressed sensing applications. Unfortunately since one of the biggest advantages of spirals is the
Figure 4.16: Left column shows reconstructions from the fixed density spiral and the right column reconstructions from the most undersampled quadratically decreasing trajectory. Row 1) DCF reconstruction, 2) L2 Norm, 3) L1 Norm, 4) TV Norm.
Figure 4.17: Average value of the standard deviation over all voxels for the experimental phantom plotted against the maximum k-space radius.

effective use of gradients, even small perturbations results in a spiral trajectory that does not reach the same maximum k-space as the non-randomized spiral. Randomizing the angle between the spirals might be an alternative and will be explored in future work.

It should also be considered that DCF and L2 norm reconstructions (less than a second) are much faster compared to L1 and TV reconstructions which take 30-60 seconds per image. So for real-time applications a faster reconstruction method should be used for L1 and TV norms.
Figure 4.18: Maximum value of the standard deviation over all voxels for the experimental phantom plotted against the maximum k-space radius.
Chapter 5

Comparing MR Imaging Properties of Spiral Trajectories using the Singular Spectrum of the Analytic Fourier Basis Cross-correlation Matrix

5.1 Summary

We compare fixed and variable density and randomized spiral trajectories for MR imaging in terms of PSF resolution and stopband ripple and noise amplification, with the singular value spectrum of the cross-correlation Fourier basis matrix as an analysis tool. We explain the rationale behind using that matrix and why its singular spectrum is meaningful. We show that the relative number of singular values above an easily determined threshold is an indicator of resolution, and the shape of the rest of the spectrum an indicator of noise vs. reconstruction accuracy tradeoffs.

5.2 Introduction

In many Magnetic Resonance Imaging (MRI) applications, scan time is the limiting factor. Trajectories which sample k-space non-uniformly, such as spirals, reduce the scan time
by sampling the image more efficiently, using the fact that most of the image information (energy) is concentrated around the origin of the k-space. More efficient sampling may not only result in rapid imaging [51] but may also reduce artifacts, such as motion and flow. [44]

Undersampling the k-space pattern designed for a given desired Field-Of-View (FOV) can also further reduce scan time, although this naturally results in image aliasing. Because the image aliasing pattern is controlled by the k-space undersampling pattern, there is nonetheless some opportunity to choose an undersampled trajectory with acceptable image aliasing. The selection of good undersampling schemes, for example for spiral trajectories, is at present an interesting problem particularly given the complex interactions with other factors, such as SNR efficiency.

In an attempt to address some of these issues, in Ref. [13], several different undersampled spiral trajectories were analyzed in terms of their resolution and the amount of ripple in the stop-bands of the corresponding point spread functions (PSF). The authors concluded that under a constant scan time constraint with comparable resolution, variable density spirals are more effective than fixed sampling density spirals since the aliasing signals are smoothed.

Our group recently presented a new algorithm [46] that has potential application for several aspects of imaging with spiral trajectories. This algorithm, presented in the context of density compensation, projects, or cross-correlates the spiral samples onto the underlying Fourier basis vectors. For standard fields of view these projections can be computed analytically, and in any case they can be computed numerically via numerical integration with arbitrarily high precision. The result is a matrix of cross-correlation values which determines a linear system whose solution gives the desired density compensation. As we describe in more detail below, this matrix gives the normal equations for the overdetermined linear system presented in [56], modulo the difference between direct sampling of the Fourier functions as in [56] compared to analytically computing the matrix elements as in [46]. More importantly, unlike the direct linear system in [56] where the final image must be known (as is the case for the problem of radio-frequency (RF) excitation design), the normal equations can also be solved for the problem of image reconstruction from acquired samples. Further, in [46] the singular value spectrum of the cross-correlation matrix was used to illustrate differences between trajectories in terms of the degree of independence of their components and their noise sensitivity. The RF excitation design (in
the low flip angle regime), and density compensation and image reconstruction problems are closely related (indeed the work in [56] was concerned with pulse design but followed on early work from that group [57] on image reconstruction). In this work, we extend the use of the singular spectrum of this cross-correlation matrix to examine the design of spiral trajectories, similarly to the effort in [13]. We show that we can use this singular spectrum to analyze simultaneously the resolution of the point spread function (PSF) and the concordant noise amplification properties of a given trajectory. We also study the relationship of spectrum with the degree of sidelobe ripple of the PSF. We carefully simulate the PSF given the trajectory, compare its properties to those found using the singular spectrum, and draw some conclusions about some specific tradeoffs among trajectories.

5.3 Theory

The problem of image reconstruction from acquired k-space samples can be written as a linear system

\[ Fx = b, \quad (5.1) \]

where \( x \) represents the unknown image, \( b \) is the k-space data acquired (Fourier coefficients), and \( F \) is the matrix of discretized Fourier basis functions. Each column of \( F \) contains samples of \( f^{(j)}(x, y) \), a 2D Fourier basis function corresponding to the trajectory, discretized and reshaped into a vector. Similarly, for the problem of low flip angle RF excitation design, where \( b \) is the unknown k-space weighting that must be applied during excitation and \( x \) is the known image (desired excitation profile), we can write

\[ F'b = x, \quad (5.2) \]

where \( F' \) denotes Hermitian conjugate.

These systems of equations can be solved by iterative methods [56, 57] that combine the conjugate gradient (CG) algorithm with nonuniform FFT (NUFFT) operations as appropriate. In the limit, if we discretize the matrix \( F \) with infinite precision and then form the normal equations for either system of Eqns. (5.1),(5.2), we arrive at a system of equations with a system matrix composed of cross-correlations of Fourier basis functions. Specifically, we have a system of the form

\[ Ac = z, \quad (5.3) \]
where the elements of $A$, $\alpha^{(j,j')}$, are simply

$$\alpha^{(j,j')} = \int_{R} f^{(j)}(x,y) (f^{(j')}(x,y))^* \, dx \, dy,$$

computed over some desired region $R$. For example, for the specific case of a disk-shaped FOV ($R$ the disk of radius $r = 1$), appropriate for a spiral trajectory,

$$\alpha^{(j,j')} = \begin{cases} \pi/4 & \text{when } j = j' \\ \frac{1}{2\Delta q^{(j,j')}} J_1 (\pi \Delta q^{(j,j')}) & \text{when } j \neq j' \end{cases}$$

where $\Delta q^{(j,j')} = \sqrt{(k_{x}^{(j)} - k_{x}^{(j')})^2 + (k_{y}^{(j)} - k_{y}^{(j')})^2}$, and $J_1(\cdot)$ is the Bessel function of the first kind.

We note that, if we ignore the differences induced by the different ways in which the problem may be discretized, the singular values of $A$, which we use here, are the squares of the singular values of the ideal $F$. Our goal here is to use the singular spectrum of $A$ to characterize k-space trajectories as defined by the particular set of functions $f^{(j)}(x,y)$ corresponding to the k-space locations that are visited by them. The rationale behind this analysis is that however the solution of Eqns. 5.1, 5.2 is achieved, the singular value spectrum of the analytically constructed matrix $A$ must be the determining factor of both the dimensionality of $x$, as well as of the noise amplification (when we extend the known vector in the problems to include a vector $\eta$ representing white noise, such as for example Eq. 5.1 becomes $F x = b + \eta$). For the former issue, this relationship is clearly depicted in MRI by the fact that however arbitrarily we discretize $F$ the reconstructed image or excited profile has a pre-determined resolution that is entirely dependent on the choice of trajectory. Noise amplification properties of inverting a linear system for MR imaging are also well-understood [27, 58].

### 5.4 Methods

In order to exemplify the relationship between the singular value spectra of the cross-correlations matrix and imaging system properties, a number of trajectories were designed
with the number of points on each trajectory held constant, since scan time is directly proportional to the number of sample points. In the usual terminology of MRI, all trajectories were designed for a 26 cm FOV and a desired resolution of 5 mm.

The design variable in this case becomes the sampling density, i.e., the distribution of the sample points along the spiral. We adopt here the terminology of Lee et al. [13], where the sampling density of a spiral can be assumed to be equivalent to the FOV in the uniform-density sampling case, which can be called effective FOV.

Considering the sampling structure of a spiral, modification of the sampling density between consecutive spiral loops yields an “effective” FOV that is a function of k-space radius \( k_r = \sqrt{k_x^2 + k_y^2} \). For example, if the density is reduced with increasing loop number (i.e., with increasing radial distance from the center of k-space), the effective FOV when the low spatial frequencies are acquired is larger than that when the higher spatial frequencies are acquired. Accordingly, different spatial frequencies in the image will exhibit different aliasing properties.

The trajectories we considered were similar to those considered in [13]. These are (a) a fixed density trajectory designed for a 20 cm FOV (i.e., undersampled by a constant factor of 1.3 compared to the desired 26 cm imaging FOV we are interested in), (b) a variable density trajectory with eFOV linearly decreasing from 26 cm at the center of k-space to 16 cm at the edge, and (c) a variable density trajectory with eFOV decreasing quadratically from 26 cm to 14 cm.

In addition we considered randomly perturbed spirals, as suggested by Lustig et al. [45]. Up to this point all the trajectories designed were single-shot spirals. However, since the random perturbation suggested by [45] also requires a random perturbation of the angle between interleaves for a spiral trajectory, we also implemented interleaved spirals with 16 arms for each case in Fig. (5.1). Although the singular value spectra of the cross-correlations matrix for single-shot and interleaved spirals that are designed with the same parameters are similar, to keep comparisons fair in the sense of trajectories having the same number of samples, we only compared 16 armed spiral to the randomly perturbed spiral with 16 arms.

To compare the PSF’s corresponding to each spiral trajectory, we calculated the resulting PSF using an independent gridding reconstruction algorithm ([42]). The idea was to use
an independent approach to get the PSF so as not to bias the comparisons using our singular spectrum approach. A Kaiser-Bessel function was used as the convolution kernel in the gridding reconstruction. From each PSF we extracted resolution and a measure of the aliasing magnitude. Specifically, resolution was defined as the Full Width Half Maximum (FWHM) of the main lobe of the PSF. While to quantify the amount of aliasing we calculated both the infinity norm (for the maximum ripple) and the two norm of the PSF between the second side lobe and the end of the desired 26cm FOV.

![PSF functions for different spiral trajectories](image)

**Figure 5.1:** PSF function for: a) Fixed density spiral, b) Linearly undersampled spiral, c) Quadratically undersampled spiral, d) Randomly perturbed spiral (single shot) for fixed density

Finally, these resolution and ripple measures were compared with the singular value spectra of the cross-correlations matrix, calculated for the desired imaging region of 26cm FOV.
5.5 Results

The resolution, sidelobe ripple performance and singular value properties for the single shot trajectories are presented in Table 1. The sidelobe ripple values are consistent with previous work [13] such that the fixed density spiral trajectory has a significant aliasing sidelobe since first aliasing sidelobe (at 20 cm) occurs within the 26 cm desired FOV. On the other hand the trajectories with linear and quadratically decreasing sampling density have progressively less aliasing. However, our simulations show that although all the trajectories were designed to achieve same resolution, the fixed density spiral achieves a better resolution than the variable density spirals (More than eight percent).

<table>
<thead>
<tr>
<th>FOV (cm)</th>
<th>FWHM (mm)</th>
<th>Maximum Ripple(%)</th>
<th>Ripple 2-Norm</th>
<th>Singular Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.7246</td>
<td>0.0541</td>
<td>79.28</td>
<td>1426</td>
</tr>
<tr>
<td>26-10</td>
<td>(</td>
<td>k</td>
<td>/k_m)</td>
<td></td>
</tr>
<tr>
<td>26-14</td>
<td>(</td>
<td>k</td>
<td>^2/k_m)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 5.1: Resolution and ripple performance of the three undersampled spiral trajectories. Maximum ripple is normalized with respect to the maximum point of the main lobe.

To examine the relationship of the quantitative measures with the singular value spectra, the number of singular values above a certain threshold as noted in the last column of Table 1. The threshold value was selected manually after analyzing the singular value spectra graphs. As can be seen from the table the relationship between these two parameters is nearly linear. A trajectory with a greater number of significant singular values has more basis functions that contribute nearly equivalent information to the PSF, which apparently results in a better resolution.

The singular value spectra is also a useful tool in understanding the noise amplification of the system. In the reconstruction process, the singular values below a certain threshold will result in an amplification of the noise, causing a degradation in SNR efficiency of the system. With this assumption, by using the cross-correlation algorithm we can control the trade-off between the noise amplification and resolution of the constructed image since we can truncate the singular values below a certain level or determine the regularization level of a Tikhonov or other regularization scheme.

To illustrate this concept, a graph comparing the singular value spectra of a variable density spiral and a randomly perturbed version of the same spiral is shown in Figure 3. The
Figure 5.2: Singular Value Spectra of the three different undersampled spiral trajectories.

Figure 5.3: Singular Value Spectra for a variable density spiral and randomly perturbed version of the same spiral. Both trajectories have 16 arms.

The non-randomized spiral contains more singular values above 1 compared to the randomized spiral. However, there is a crossing point beyond which the singular values of the randomized spiral are larger than those of the non-randomized spiral, until the same floor is reached for both spectra. So according to these results, in order to gain additional independent information from the random spiral, we need to truncate less singular values which will result in a decrease in SNR efficiency of the system. Which means depending on the characteristics of a particular image we may be able to extract more image detail from the random spiral samples, using higher indexed singular vectors, without as much noise amplification, with the randomized spiral.
5.6 Conclusion and Future Work

We described the use of the singular value spectra of the cross-correlation matrix of the Fourier basis functions underlying a k-space trajectory as a way to analyze the information content and SNR efficiency of undersampled spiral k-space trajectories. Further work may provide insight into whether variable density trajectories are indeed more efficient than fixed trajectories designed e.g., for the same duration but with a lower design resolution. SNR analysis based on monte carlo simulation may also help reveal the optimal tradeoff of CG linear system reconstructions in terms of how much additional resolution can be obtained by sacrificing an acceptable amount of reconstructed image SNR. Finally, trajectory design algorithms can incorporate the singular value spectra as each element of the trajectory is designed, in order to optimize information content vs. SNR tradeoffs.
Chapter 6

Conclusions and Future Work

In this dissertation we addressed different k-space undersampling strategies that increase the data acquisition speed while maintaining image quality. We applied these approaches to three different MRI applications. In the first application, we carefully combined one k-t space undersampling strategy (UNFOLD) with a parallel imaging method (GRAPPA) in order to increase the temporal resolution of complex cognitive functional MRI studies. We first showed that when the main assumption (dynamic separability of two aliasing voxels) required by UNFOLD holds it was possible to increase temporal resolution of block design fMRI studies. We also showed that with the help of sampling the center of the 3D k-space at Nyquist rate, it was also possible to increase the temporal resolution even when the expected response is not periodic. Even with the SNR decrease due to undersampling, temporal resolution loss due to UNFOLD filtering and artifacts introduced from the high frequencies in k-f space, temporal resolution gain can help in identifying temporal characteristics of neuronal events in the brain.

An important future work for this part of the thesis is implementing a Partial Fourier algorithm in two dimensions \((y, z)\) that can massively reduce the time needed to scan the k-space. As stated in the Chapter 3, homodyne detection method can be used to reconstruct k-space that is subsampled with a ratio of 9/16 when a fast spin echo sequence was used. When the same algorithm is applied even with a 12/16 ratio in either dimension for the 3D EPI sequence severe signal voids were observed. We conjecture that the main reason is the susceptibility artifacts caused by rapid EPI readouts.
In the second application we addressed the problem of creating functional images that also provide high resolution anatomical information and correct localization. We showed that with the increased field strengths and improvements in gradients, Fast Spin Echo sequences can be used for these problems in small animal studies. In order to increase temporal resolution and reduce artifacts related to the large number of refocussing pulses, we applied a Partial Fourier method. Also to increase functional CNR we used an additional sinc pulse that moved the time that the center of the k-space was sampled to match $T_2$. We showed in two different fMRI experiments that it was possible to have accurate functional information with high spatial resolution and reduced artifacts using the developed sequence.

As future work, k-space subsampling methods can be implemented to further increase the temporal resolution or increase spatial resolution. One major roadblock for this approach is the jaw motion. Another way of increasing spatial resolution is using reduced field of view methods. Unfortunately with the current setup, the functional CNR is too low.

In the final application, we have investigated the effects of different undersampling strategies and reconstruction methods for spiral imaging. It was shown that undersampling functions with a smooth eFOV vs k-space radius curve can be used effectively in combination with regularized solvers to increase the spatial resolution with slightly increased image artifacts. In case of sparse images, total variation based methods can remove the artifacts effectively and create images similar to fixed density spirals. But our results also highlight some concerning issues about regularized linear solvers. With TV norm regularization, a careful selection of the regularization parameter is needed, as the achieved resolution is highly dependent on this parameter. Also it should be carefully noted that PSF does not offer a viable analysis tool as the resolution varies over the image for the regularized linear solutions.

As future work, results of the phantom experiments needs to be verified in a real human imaging setup. Related with Chapter 2, these spirals can also be used as stack of spirals similar to the 3D EPI setup. The only difference between the two sequences will be replacing the EPI readouts with variable density spiral readouts found to be suitable in Chapter 5. Of course in a setup like this the effects of undersampling in kx-ky plane and kz plane should expected to be quite different than the 3D EPI scenario. Another future work is exploring randomized spirals. One practical method to introduce randomness is changing the angle between spiral interleaves. It is also possible to perturb the trajectory of
each spiral arm. However, we found out that perturbing the trajectory too much decreases the effective use of gradients.

In the last chapter we showed that the singular value spectra of the cross-correlation matrix of the Fourier basis functions underlying a k-space trajectory can be used to analyze the information content of undersampled spiral k-space trajectories.

Spiral trajectory design optimizing the singular value spectra of the cross-correlation matrix can be achieved by starting from the center of the k-space and adding point along a spiral trajectory. This will be investigated in future.


List of Publications

The following list includes all the papers published or submitted for publication by the author during her graduate studies.


Dimitris Mitsouras, Robert V. Mulkern, Onur Afacan, Dana H. Brooks, Frank J. Rybicki. “Basis function cross-correlations for Robust k-space sample density compensation, with application to the design of radiofrequency excitations”, Magnetic Resonance in Medicine, 2007, 57-2, 338-352


