

Accelerated Radial Imaging with Compressed Sensing Reconstruction for Breast DCE-MRI

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University of Wisconsin-Madison

Abstract

Breast cancer is one of the most common diseases for the female population across all ages and is one of the most common causes of cancer death in females. MRI of the breast has been shown to provide very high sensitivity for breast cancer, primarily due to the use of intravenous contrast agents that enable not only morphologic evaluation but also the ability to visualize neoangiogenesis associated with tumor progression. Therefore, DCE-MRI is a powerful tool for diagnostic screening, evaluation for extent of disease, and treatment planning and monitoring. However, conventional Cartesian acquisition requires a tradeoff between spatial and temporal resolution. The lesion curves measured from conventional DCE-MRI, with high spatial resolution but low temporal resolution imaging protocols, are not sufficient to characterize the contrast dynamics. This results in only moderate specificity for characterizing different lesion types.

With recent advances in MRI, many studies have proposed advanced acquisition and reconstruction approaches to achieve high temporal resolution while still maintaining clinically relevant spatial resolution. In this work, we propose the use of a stack-of-stars radial acquisition with a compressed sensing reconstruction for high spatial-temporal resolution breast DCE-MRI.

The goal of this thesis is to evaluate the spatial and temporal performance of the proposed approach under a broader range of imaging conditions (including the presence of cardiac and respiratory motion, varying tissue contrast kinetics, and different noise levels) to characterize the performance limits. Further, there is a need to validate the accuracy and robustness of quantitative pharmacokinetic parameter estimation using the proposed technique if this approach is to be used for quantitative DCE in clinical practice.

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List of Abbreviations

Abbreviation	Meaning
1D	1 Dimension
2D	2 Dimension
3D	3 Dimension
3T	3 Tesla
5T	5 Tesla
ACR	American College of Radiology
AIF	Arterial Input Function
CA	Contrast Agent
CNN	Convolutional Neural Network
CNR	Contrast-to-noise ratio
CTC	Concentration Time Curves
DCE	Dynamic Contrast Enhanced
DISCO	Differential Subsampling with Cartesian Ordering
DL	Deep learning
DRO	Digital reference object
DWI	Diffusion-weighted imaging
EES	Extravascular Extracellular Space
ETM	Extended Tofts Model
EUSOMA	European Society of Breast Cancer Specialists
FA	Flip Angle
FFT	Fast Fourier Transform
FOV	Field of View
FSE	Fast Spin Echo
GRAPPA	GeneRalized Autocalibrating Partial Parallel Acquisition
GRE	Gradient Echo
HR	High Spatial Resolution
i.i.d.	independent identically distributed
ICA	Independent Component Analysis
LR	Low Spatial Resolution
MOCCO	data-driven low-rank based CS reconstruction
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
NLS	Nonlinear Least Squares
nRMSE	Normalized Root-Mean-Square-Error
NUFFT	Non-Uniform Fast Fourier Transform
PCB	Principal Component Basis
PK	Pharmacokinetic
ROI	Region of Interest
SD	Standard Deviation

SENSE	sensitivity encoding
SNR	Signal-to-Noise Ratio

Chapter 1

Introduction

1.1 Specific Aims

MRI is widely accepted as the most effective imaging modality for breast cancer detection due to its ability to provide high soft tissue contrast, even in patients with high breast density^{1,2}. Compared to mammography, MRI provides the opportunity for increased anatomic coverage through bilateral imaging. This allows simultaneous imaging of the entire breast tissue in addition to the axillary tail, lymph nodes and pectoralis major muscle. Furthermore, dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) provides both tumor morphology and contrast kinetics information, which makes it known as the most sensitive imaging modality for breast cancer detection³. However, higher sensitivity compared to lower specificity of DCE-MRI can result in indeterminate findings requiring biopsy and/or imaging follow-up. Quantitative pharmacokinetic (PK) modeling of DCE-MRI has been used to improve the disproportionately lower and varying specificity due to its potential to provide additional functional information from the measured PK parameters. Many studies have suggested using the PK parameters for differentiating benign and malignant lesions⁴, as well for treatment planning⁵, screening⁶ and treatment response assessment⁷. However, high temporal resolution is required for accurate estimation of the PK parameters while high spatial resolution is needed to detect and characterize lesions^{8,9}. Current high spatial resolution DCE-MRI protocols typically only leave time to acquire

four low temporal resolution time-frames, which can only support semi-quantitative analysis (i.e. lesion washout). Patient motion is another issue that can reduce the accuracy of lesion detection and characterization, especially in the dynamic imaging.

Our long-term goal is to improve the utility of breast DCE-MRI. The goal of this thesis is to develop a three-dimensional (3D) stack-of-stars (SOS) radial acquisition combine with different reconstruction strategies to provide motion robust high spatial and temporal resolution breast DCE-MRI to enable quantitative pharmacokinetic analysis. In this work, we will address the challenges and opportunities with the following aims:

Aim 1. Technical development of breast DCE-MRI

The SOS radial acquisition sampling strategy has the ability to provide arbitrary temporal resolution image series. However, this relies on the application of different reconstruction strategies. Therefore, multi-scale temporal resolution reconstructions will be developed for different clinical applications. A data-driven low-rank compressed sensing reconstruction will be developed for time-resolved DCE-MRI to provide both high spatial and temporal resolution images. Quantitative pharmacokinetic analysis will be performed to test the temporal fidelity of the imaging approach and demonstrate the potential of the proposed imaging methods to provide additional physiological information. Further, a respiratory self-gating technique combined with the proposed CS reconstruction will be developed for supine breast DCE-MRI. For multi-phased reconstructions, a conventional radial reconstruction combined with deep-learning reconstruction will be used to provide high quality multi-phased DCE-MR images.

Aim 2. Validate imaging techniques developed in Aim 1 using a digital reference object (DRO) breast phantom

This aim will develop DROs to validate imaging performance including image quality in the presence of motion including cardiac, respiratory, and/or bulk motion. Further, we will extend the validation to assess the ability to recover specific contrast kinetics from an established PK model.

Aim 3. Translate to clinical patient volunteers

This aim will focus on evaluating the presence and degree of motion artifacts including those caused by cardiac motion in both the proposed radial acquisition and the conventional clinical Cartesian acquisition. Here, we will enroll patient volunteers to compare the 3D SOS radial acquisition and the current standard clinical Cartesian acquisition used at UW Health.

1.2 Background and Significance

Breast cancer is one of the most common diseases for female populations across all ages. Recent reports from the American Cancer Society have shown that 1 out of 8 women are diagnosed with breast cancer in United States¹⁰. But higher survival rates are observed if the cancers can be detected in the early stages, prior to the progression of malignant tumors. The process of progression of malignant tumors usually involves the growth of new blood vessels surrounding the tumor, which is called angiogenesis. Usually, a rim of microvessels is formed around the ducts at the early development of high-grade carcinoma. As the tumor continuous to progress, increasing microvascular density and blood flow are observed¹¹. Therefore, many imaging techniques have been proposed to identify the progression of tumor angiogenesis. The three most widely used imaging modalities are digital mammography, ultrasound, and magnetic resonance imaging (MRI). Each modality has advantages and limitations: mammography is routinely used for annual screening due to its short scan time and low cost. Recent studies have shown breast cancer mortality decreased due to early detection of cancer through mammographic screening^{2,12,13}.

Previous studies have revealed that mammographic screening can effectively detect early-stage cancer in the population age range of 50 and 70 years of age. However, the sensitivity was decreased for detecting tumors in the young population, who typically have denser breasts than the older population^{14,15}. Ultrasound is frequently used in biopsy due to the capabilities for real-time image guided needle placement. However, ultrasound suffers from relatively limited FOV as well as poor visualization of some lesion types^{16,17} that can restrict its application for diagnostic purposes. MRI is widely accepted as the most effective imaging modality for breast cancer detection due to its ability to provide high soft tissue contrast, even in patients with high breast density. Further, there is flexibility to readily allow clinicians to choose between unilateral and bilateral acquisitions based on specific clinical considerations. For bilateral acquisitions, MRI provides a much larger FOV and allows evaluation of both breasts as well as axilla region simultaneously, which is difficult to achieve when using other image modalities. MRI of the breast has also demonstrated very high sensitivity for breast cancer detection due to the injection of the contrast agent since it can provide not only the morphologic evaluation but also the ability to visualize neoangiogenesis associated with tumor progression. This has led to a rapid increase in the use of breast MRI for many other clinical applications, such as diagnostic screening, evaluation for extent of disease, and treatment planning and monitoring.

1.2.1 Current breast MRI protocols

Typical clinical diagnostic breast screening protocols include several MRI acquisitions and are acquired in the prone position using a dedicated multichannel-RF coil. First, pre-contrast images are collected including a T2-weighted sequence, a T1-weighted sequence without fat saturation, and a diffusion-weighted sequence. These pre-contrast images are used to identify

anatomical structures within the breast, including features such as fibroglandular tissue, fat, cysts, and lymph nodes. Next, dynamic imaging is performed consisting of pre- and post-contrast dynamic contrast-enhanced (DCE) T1-weighted acquisitions with fat suppression to detect enhancing lesions. Gadolinium (Gd)-based contrast agent (CA) is administered during the DCE-MRI acquisition to provide increased contrast between different tissues in the breast. Gd-based CAs are paramagnetic resulting in an increase in the T1 and T2 relaxation rates (decrease in the T1 and T2 times), as given by equation [1]:

$$\frac{1}{T_1} = \frac{1}{T_{1_0}} + r_1[Gd] \quad [1]$$

where r_1 is the relaxivity of the contrast agent and $[Gd]$ is the concentration of the Gd- based CA. T1-weighted acquisitions are designed to provide sensitivity to regional variations in T1 (longitudinal relaxation time). The T1 recovery is an exponential re-growth of the longitudinal relaxation, M_z component describing the recovery back to its initial magnetization M_0 at a rate characterized by T1, which is described by equation [2] and Figure 1.2.1.

$$M_z = M_0(1 - e^{TR/T_1}) \quad [2]$$

Typically, T1-weighted acquisitions include relatively short repetition times (TRs) to increase sensitivity to the recovery of the magnetization. In the setting of DCE-MRI, imaging speed is an important consideration when aiming to capture rapidly occurring contrast changes. For this reason, gradient echo-based (GRE) acquisition strategies are typically used for high temporal resolution DCE-MRI. Since short TRs were often used in basic GRE acquisitions to reduce the acquisition time, the transverse magnetization (M_{xy}) does not fully decay and therefore the final steady state signal intensity is determined by both the longitudinal and the transverse magnetization resulting in a more complex contrast behavior. Therefore, the spoiled-GRE sequence is specifically

designed to dephase the transverse magnetization to produce the T1-weighted images. The signal change measured over time for a spoiled-GRE sequence can be modeled by using equation [3]:

$$S_1 = k[H] \frac{\sin(\alpha) \cdot (1 - e^{-TR/T_1})}{1 - e^{-TR/T_1} \cdot \cos(\alpha)} e^{-TE/T_2^*} \quad [3]$$

where the flip angle (α), repetition time (TR), and echo time (TE) are user selected acquisition parameters. The measured tissue signal S_1 is correlated to multiple components and the signal equation can be dissected to four components: (1) the signal S_1 is always proportional to proton density of the targeted tissue $[H]$ by a factor of k . (2) TE relates to T_2^* signal decay. When TE is small, the term of e^{-TE/T_2^*} approaches unity and the T_2^* is minimized. (3) Flip angle scales the T1-weighting. When α is small, $\cos(\alpha) \approx 1$ so the $1 - e^{-TR/T_1}$ term is canceled, resulting in signal proportional to the proton density and T_2^* -weighting. Increasing the flip angle

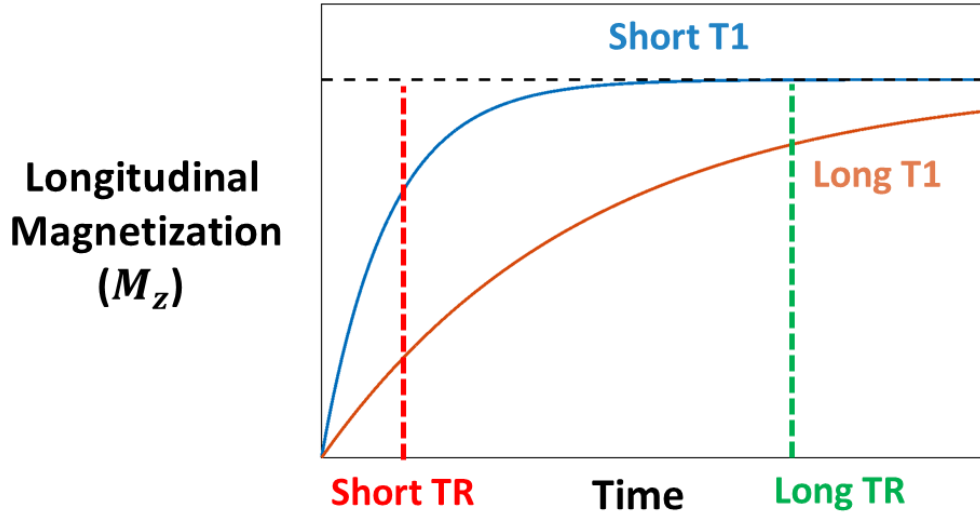


Figure 1.2.1: The graph of the recovery of longitudinal magnetization with the growth rate of T1 relaxation time after a RF pulse with 90° flip angle. The blue and orange line demonstrated two different tissues with short and long T1, respectively. For this example, increased T1 contrast can be generated by applying shorter TR (red dash line) compared to longer TR (green dash line). progressively increases the T1-weighting. (4) The selection of the TR, which relates to T1 signal

recovery, will determine the T1-weighting. When a shorter TR is used, the term $1 - e^{-TR/T1}$ becomes large and T1-weighting increases.

To ensure consistent and high performance standards for breast MRI, the Breast Imaging Reporting and Data System by the American College of Radiology (ACR)¹⁸ and the European Society of Breast Cancer Specialists (EUSOMA)¹⁹ have outlined specific requirements and guidelines for breast MRI screening. Minimal requirements include: dedicated multi-channel bilateral breast coils to allow full coverage over the entire breast region, field strength of at least 1.5T to achieve sufficient spatial resolution, in-plane spatial resolution of 1 mm² or less, and slice thickness of 3 mm or less, and the first post-contrast time frame to be completed within 120 s after the end of the contrast injection²⁰. The total acquisition time of a conventional fully encoded Cartesian acquisition (**Figure 1.2.2**) is given by $scan\ time = TR \cdot N_y \cdot N_z$, where N_y is the number of phase-encoding steps in the y direction, and N_z is the number of phase-encoding steps

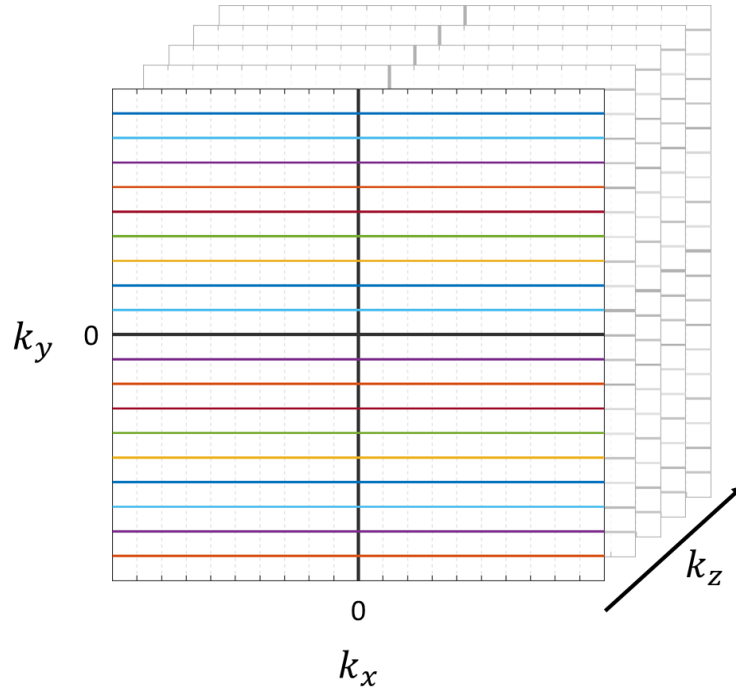


Figure 1.2.2: The graph of 3D Cartesian k-space sampling schemes.

in the z direction. The N_y and N_z are usually large to ensure the requirements for full FOV,

required spatial resolution, and slice coverage at z direction as a result of increased acquisition time. For example, the multi-phase Cartesian encoding used in our clinical protocol is usually performed with $TR = 4.7$ ms and required matrix sizes of $\sim 448 \times 448 \times 142$. The total acquisition time is 299s per frame. This only allows the acquisition of four time-points to describe the full lesion contrast kinetics (~ 4 frame at 120 s/frame) with the use of parallel imaging²¹ (**Figure 1.2.3**). These relatively low temporal resolution time points only allowed limited assessment of the contrast enhancement patterns in the breast. The ACR standard Breast Imaging Reporting and Data

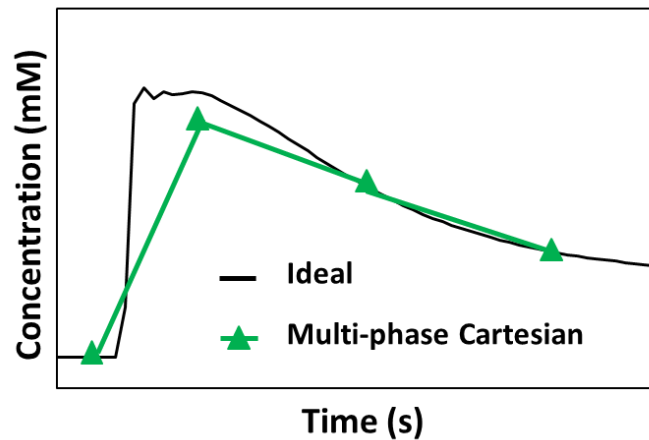


Figure 1.2.3: A temporal enhancement curve from an idealized lesion (black line), and the resulting enhancement curve generated from a multi-phase Cartesian acquisition resulting in only four measured time-points (green triangles).

System (BI-RADS) lexicon²² provides guidelines for assessment of semi-quantitative kinetic curves from DCE-MRI examinations using 2 measures with 3 categories each as shown in **Figure 1.2.4**. These semi-quantitative analysis methods are commonly used in routine clinical practice however, this analysis only provides rough depiction of lesion kinetics, which is insufficient to capture rapid signal changes from specific types of lesions as a result of moderate to low diagnostic specificity. Although different wash-in characteristics were included in the guidance, there is still

a lack of qualitative way to distinguish the level of the wash-in slope unless further comparison with the surrounding tissue was delivered and reported a difference related to these.

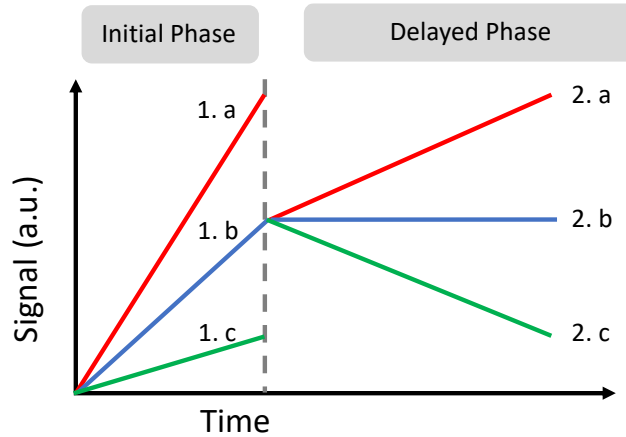


Figure 1.2.4: BI-RADS lexicon guidelines for assessment of semi-quantitative kinetic curves from DCE-MRI examinations. Kinetic curves are condensed into two temporal phases: initial and delayed phase. The initial phase of the temporal curves is divided into three categories based on the shape of the wash-in slopes, which are identified as fast (red, 1.a), medium (blue, 1.b), and slow (green, 1.c). The delayed phase is divided to three categories based on the shape of the wash-out slope, including persistent (red, 2.a), plateau (blue, 2.b), and washout (green, 2.c) curves.

1.2.2 Quantitative analysis of breast DCE-MRI

Recently, there has been increasing interest in looking at kinetic features from DCE-MRI to improve the disproportionately lower and varying specificity, ranging from 37% to 97%²³. Many studies have shown that better depiction of the wash-in slope is correlated to tumor physiological properties providing improved differentiation of lesion types. In addition, time-resolved DCE-MRI offers the promise of deriving pharmacokinetic (PK) parameters that could provide quantitative data to evaluate tumoral neoangiogenesis and biological aggressiveness²⁴. Most methods of analyzing DCE-MRI have used the model developed by Tofts et al²⁵, which is based on a two-

compartment model with three principle parameters: the transfer constant (K^{trans}), the extravascular extracellular space (EES) fractional volume (v_e), and the rate constant (κ_{ep}). The rate constant is the ratio of K^{trans} and v_e . However, the Tofts model is based on the assumption that there is negligible intravascular tracer, which may lead to an overestimation of K^{trans} . Therefore, a modified two component model with an additional parameter, volume fraction of the plasma space (v_p), was developed and is commonly referred to as the extended Tofts model (ETM)²⁶. The diagram of the ETM is shown in **Figure 1.2.5**, and is given in equation [4]:

$$C_t(t) = K^{trans} \int_0^t C_p(t) \exp\left(-\left(\frac{K^{trans}}{v_e}\right)(T-t)\right) dt + v_p C_p(t) \quad [4]$$

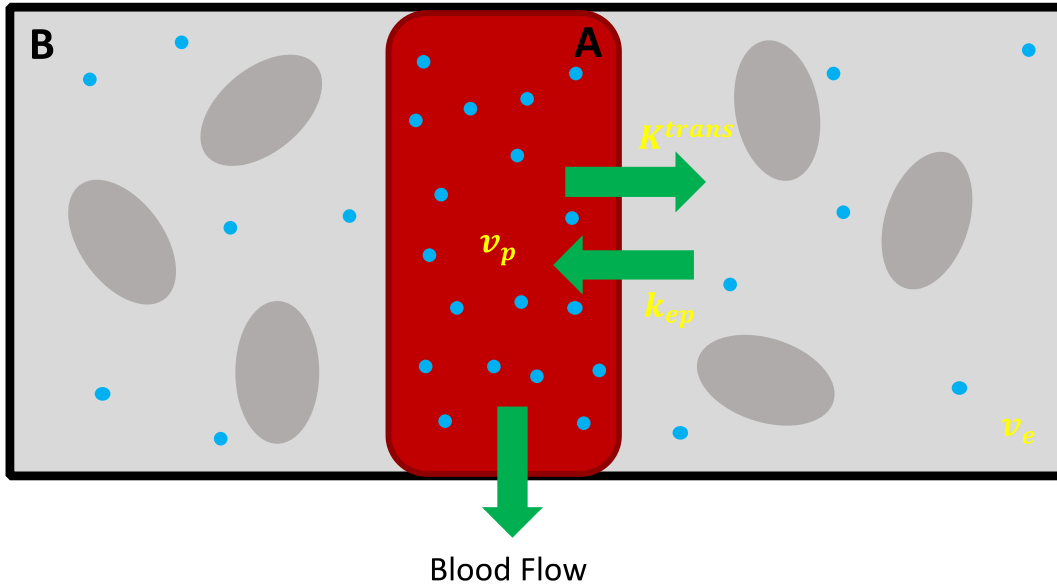


Figure 1.2.5: Diagram of the two-compartment extended Tofts model. It consists of a plasma compartment (A) with volume v_p and an extravascular extracellular compartment (B) with volume v_e . The concentration time curves of $C_p(t)$ and $C_t(t)$ are also measured by placing ROIs in the plasma and EES compartments, respectively. K^{trans} is the fraction of the CA from plasma enters to the EES and the k_{ep} is the fraction of the CA that flows back from the EES to plasma.

where $C_t(t)$ is the Gd concentration-time curve in the tissue of interest. $C_p(t)$ is the plasma concentration of contrast agent, also known as the arterial input function (AIF).

Simulation of the tissue concentration time curves replicated the results from Tofts et al gives us a better understanding about the relationship between the lesion contrast kinetics and the PK parameters (**Figure 1.2.6**). Key observations include: :

- (1) K^{trans} correlates with the initial wash-in slope of the concentration time curve. Sharper wash-in slopes result in larger K^{trans} values.
- (2) v_e correlates with the peak height and with time-to-peak of the concentration time curves.
- (3) v_p reflects the AIF curves. When v_p is small, there is little effect on the tissue curves, whereas larger v_p results in sharper wash-in and wash-out tissue concentration slopes as well as higher peak height.

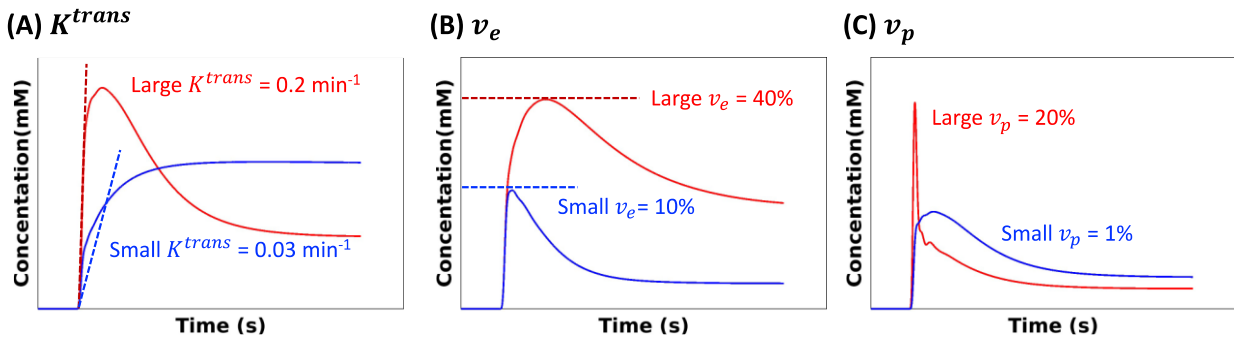


Figure 1.2.6: Simulation of tissue concentration time curves for a range of K^{trans} , v_e , and v_p values. (A) Changing K^{trans} , with fixed $v_e = 20\%$, and $v_p = 0.1\%$. (B) Changing v_e , with fixed $K^{trans} = 0.2 \text{ min}^{-1}$, and $v_p = 0.1\%$. (C) Changing v_p , with fixed $K^{trans} = 0.2 \text{ min}^{-1}$ and $v_e = 20\%$.

The ACR BI-RADS breast MRI Lexicon provides an outline of PK parameter ranges for different lesion types, shown as Table 1.2.1. However, quantitative parameters derived from DCE-MRI are sensitive to temporal resolution in that, high temporal resolution data is needed to accurately

represent rapid physiological processes²⁷. El Khouli et. al. showed that use of 15 s temporal resolution could better capture wash-in and wash-out slopes, and further discriminate between benign versus malignant categories of breast lesions²⁸. Therefore, temporal resolutions of 10 s or higher are typically accepted as the minimum needed to achieve quantitative results for breast DCE-MRI.

Table 1.2.1: ACR BI-RADS assessment of DCE-MRI for PK parameters

Lesion types	$K^{trans}(min^{-1})$	$k_{ep} = K^{trans}/v_e(min^{-1})$
Benign	< 0.25	< 1.0
Intermediate	$>0.25^*$	< 1.0
Malignant	> 0.25	> 1.0

* Some tissue types such as fibroadenomas can have higher K^{trans} values

1.2.3 Limitations of conventional acquisition approaches

1.2.3.1 Cardiac motion artifacts

There is increasing interest in the radiological assessment of axillary lymph nodes in patients with breast cancer, especially in the preoperative and post-neoadjuvant chemotherapy settings²⁹. Traditionally, assessment of the axilla has been performed using a second imaging modality such as ultrasound. However, as high-risk screening has progressively moved toward greater reliance on MRI it becomes more important to provide comprehensive evaluation of the breasts as well as the axillae³⁰. Yet, DCE using conventional Cartesian sampling is known to be susceptible to ghosting artifacts, and for routine bilateral breast imaging, this includes ghosting due to cardiac motion³¹ (**Figure 1.2.7**). To avoid artifacts across the breast, the phase encoding direction can be oriented medial-lateral (for axial imaging) or superior-inferior (for sagittal imaging). However,

this leads to ghosting across the axillae in the commonly used axial scan plane, which may obscure the axilla and reduce the ability to accurately characterize temporal enhancement.

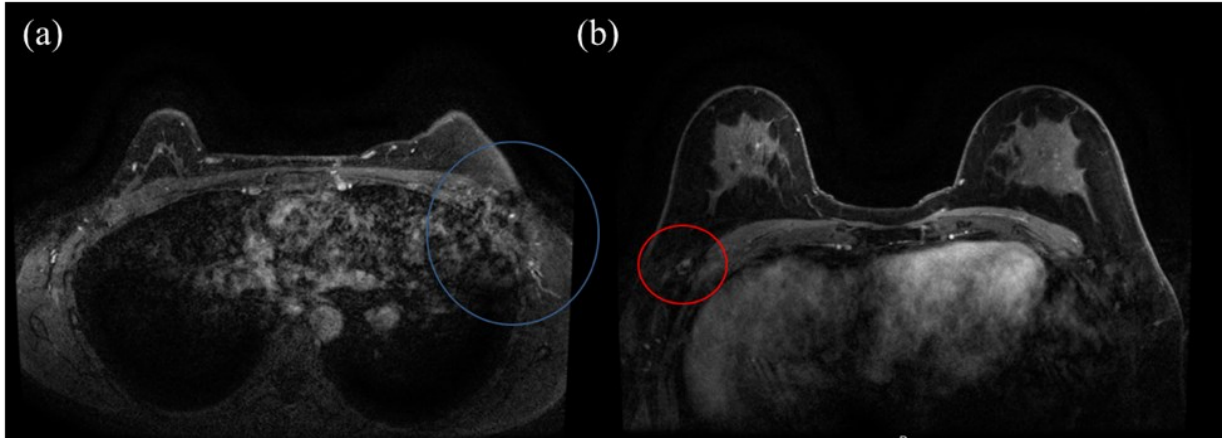


Figure 1.2.7: Two clinical cases demonstrating severe ghosting artifacts in the routine DCE Cartesian acquisition. (a) In one case, artifact obscures the entire left axilla region (blue circle). (b) In the other case a known cancer was obscured due to ghosting (red circle).

1.2.4 Image acceleration techniques

There are several strategies that can be applied to improve the temporal resolution for breast DCE-MRI. The most common approaches highly use time-efficient data acquisition strategies, undersampled data acquisition strategies, advanced reconstruction algorithms, or a combination of these three.

1.2.4.1 Time-efficient / undersampled data acquisition

Within breast DCE-MRI, the term Ultrafast Imaging has come to refer to protocols with temporal frame update times on the order of 7-9 s with lower spatial resolution³²⁻³⁴. Hybrid approaches combining the use of Ultrafast imaging for the first minute after contrast injection followed by four 60-80 s temporal resolution time frames have been suggested to provide

improved detection of early contrast enhancement associated with malignancy.^{34,35} However, these approaches show the tradeoff between spatial and temporal resolution and further restrict the analysis to either full quantitative analysis but lack of the spatial resolution for morphological evaluation or semi-quantitative analysis to capture the early wash-in kinetics but sacrifice the late wash-out information to acquire high spatial resolution images at later time frames. Another approach is to use an interleaved acquisition to improve both temporal and spatial resolution by alternating between frames of high temporal resolution imaging and high spatial resolution imaging during the contrast passage.³⁶ However, the sequence is sensitive to timing mismatch between contrast administration and image acquisition due to the relatively short pre-contrast interval.

Several acceleration schemes employing undersampled Cartesian acquisition have been proposed, such as keyhole³⁷, TRICKS³⁸ as well as several other view sharing strategies^{39,40}. These techniques divide the k-space into separate regions. Generally, these approaches frequently and fully sample a central region of k-space that contains the low spatial frequency contrast information, interleaved with less frequent sampling of the peripheral k-space regions. To overcome the potential loss of spatial resolution caused by undersampling, the high spatial frequencies can be synthesized from data acquired before and after the desired image time point. However, these approaches have been shown to suffer from temporal blurring as discussed in the literature⁴¹.

Non-Cartesian acquisition strategies diverge from the conventional data sampling based on a regular Cartesian grid, allowing for variable sampling densities (i.e. radial) as well as more time efficient data collection (i.e. spiral). The radial acquisition fills in the k-space data with radial spokes that each spoke goes through the k-space center, which was first proposed by Lauterbur in 1973⁴². The process of continuously acquiring the radial spokes allows capturing the contrast

change over time, which is suitable for time-resolved DCE-MRI. There are multiple radial sampling schemes that have been investigated including uniform-angle, golden-angle, bit-reversed, and random sampling. Further, more works have extended the sampling pattern from 2D to 3D acquisition including the stack-of-stars radial acquisition⁴³ and isotropic-voxel radial projection imaging (VIPR)⁴⁴. These had been applied to breast MRI to achieve higher spatial-temporal resolution^{45–47}.

1.2.4.2 Advanced reconstruction algorithms

Parallel imaging is a well-developed imaging technique typically implemented by regular undersampling in k-space followed by image reconstruction that leverages the unique spatial sensitivity pattern of multi-channel RF receive coils. Several different reconstruction strategies have been proposed, including the image-based parallel imaging reconstruction known as sensitivity encoding (SENSE)⁴⁸. This method begins with a Fourier transform to the image domain resulting in aliased individual coil images. The image from each RF coil channel is then reweighted using the spatial information from the respective coil sensitivity map. Another class of techniques known as auto-calibrating data driven parallel imaging approaches, rely on data fitting to estimate linear weights needed to generate missing k-space data from regions of fully sampled data. The most well-known of these approaches is GeneRalized Autocalibrating Partial Parallel Acquisition (GRAPPA)⁴⁹ which aims to fill in the missing k-space lines, prior to the Fourier transform, by estimating the coil-weighting matrix from a set of fully-sampled center lines in k-space. Typically, parallel imaging approaches have been demonstrated to perform well for acceleration factors of 1.5-3 in either 2D or 3D images. Disadvantages of parallel imaging include: 1) the image quality of the reconstructed images is highly dependent on the accuracy of the measured coil sensitivity maps, which may cause residual aliasing, 2) the direction that you can accelerated is restricted by

the design of the coil, 3) the drop in the signal-to-noise ratio, and 4) cost and design complexity increases significantly at higher RF coil channel counts. To evaluate the image noise propagating through the parallel imaging reconstructions, the g-factor is often used to characterize the noise amplification of the reconstructed images which has been applied to both image-based and k-space-based parallel imaging reconstructions⁵⁰. The g-factor can be formulated by equation [5]:

$$g = \frac{SNR_{unaccelerated}}{SNR_{accelerated} \cdot \sqrt{R}} = \frac{SD_{accelerated}}{SD_{unaccelerated} \cdot \sqrt{R}} \quad [5]$$

where R is the acceleration factor, SD is the image noise standard deviation. Despite of these disadvantages, parallel imaging is widely leveraged in clinical breast MRI^{18,21}.

The compressed sensing theory was first proposed by David L. Donoho^{51,52}, which described that the signal and/or the image can be recovered from fewer incoherent measurements than would be needed to fully sample the data. This theory is based on two basic assumptions about the sparsity and incoherence of the acquired data. Specifically, the first assumption is that the signal/images are sparse and compressible, which assumes that the signals/images can be expressed as a linear representation in some transform domain. The representation contains many coefficients that are close to or equal to zero in the transform domains. Further, the images can be recovered by only including a small number of important components with larger weighting. The second assumption is that the sensing matrix (acquired data) should be sufficiently incoherent in the sampling domain. This can be explained by the duality between time/spatial and frequency domain. The incoherent sampling pattern in frequency domain usually results in noise-like artifacts in the time/spatial domain, which is also shown as one of the representations with small coefficients in the selected transform domain. Lustig et al first proposed the concept of using the CS to reconstruct MR images⁵³. CS has been shown to provide an accurate reconstruction of MR

images if they possess a sparse representation in some basis and if the k-space data has been acquired with a randomized sampling pattern producing incoherent artifacts. CS was first

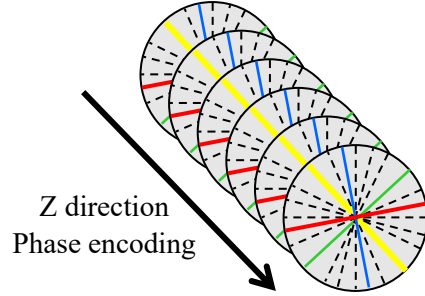


Figure 1.2.8: 3D stack-of-stars radial acquisition

performed on data with sparse representations in the spatial domain⁵⁴ however time-resolved image data often has a sparse representation in the temporal dimension⁵⁵. CS has been proposed as an alternative reconstruction for undersampled dynamic MRI^{56,57}. Hybrid techniques have been shown for exploiting correlations in both k-space and time using randomly sampled Cartesian acquisitions combined with CS^{57,58}. Several applications of the CS reconstruction in the setting of breast DCE-MRI have been demonstrated to provide 6-10x scan time reduction^{59,60}.

1.2.5 Overview of 3D stack-of-stars radial acquisition trajectory

1.2.5.1 3D stack-of-stars radial sampling scheme

The 3D stack-of-stars (SOS) radial approach performs radial acquisition in the k_x - k_y plane with Cartesian encoding performed in the k_z -plane (**Figure 1.2.8**). The SOS approach has been demonstrated for insensitivity to motion due to signal averaging of the low spatial frequencies from oversampling of the central k-space data^{43,61}.

Studies have shown that this approach can sufficiently reduce artifacts from respiratory and cardiac motion during free breathing in multiple imaging applications^{62–66}. The golden-angle sampling strategies increments the radial sampling pattern by a fixed angular increment of with $\vartheta = 180^\circ \frac{1+\sqrt{5}}{2} \approx 111.246^\circ$. A diagram of the golden angle sampling is shown is **Figure 1.2.9**. This has the advantage of limiting the azimuthal gaps and provides relatively uniform angular distribution from any arbitrary number of projection numbers. This also allows retrospectively reconstructing images with any arbitrary temporal window.

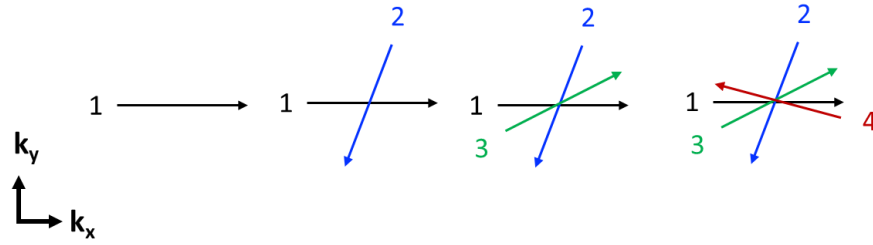


Figure 1.2.9: The radial golden-angle increment with $\vartheta = 180^\circ / \frac{1+\sqrt{5}}{2} \approx 111.246^\circ$.

1.2.5.2 Image reconstruction

Unlike rectilinear Cartesian acquisition, which can be reconstructed by using the fast Fourier transform (FFT), radial acquisition requires either resampling of the data to place it on a rectilinear grid to enable the use filtered back-projection or standard Fourier algorithms. Gridding is currently the most commonly used reconstruction approach for radial acquisition. The 2-D gridding procedure is illustrated in **Figure 1.2.10** and is described in the following steps:

1. Determine the k-space location on the Cartesian grid (k_x - k_y) **Figure 1.2.10** (B) and the corresponding density compensation for each radial point **Figure 1.2.10** (C).
2. Interpolate the radial point to the Cartesian grid by convoluting the projection data with a kernel function of finite width (w) **Figure 1.2.10** (D).
3. Apply inverse FFT to generate the image **Figure 1.2.10** (E).
4. Check if oversampling was used to limit the aliasing artifacts on Cartesian grid. If yes, crop the image to the desired matrix size **Figure 1.2.10** (F).

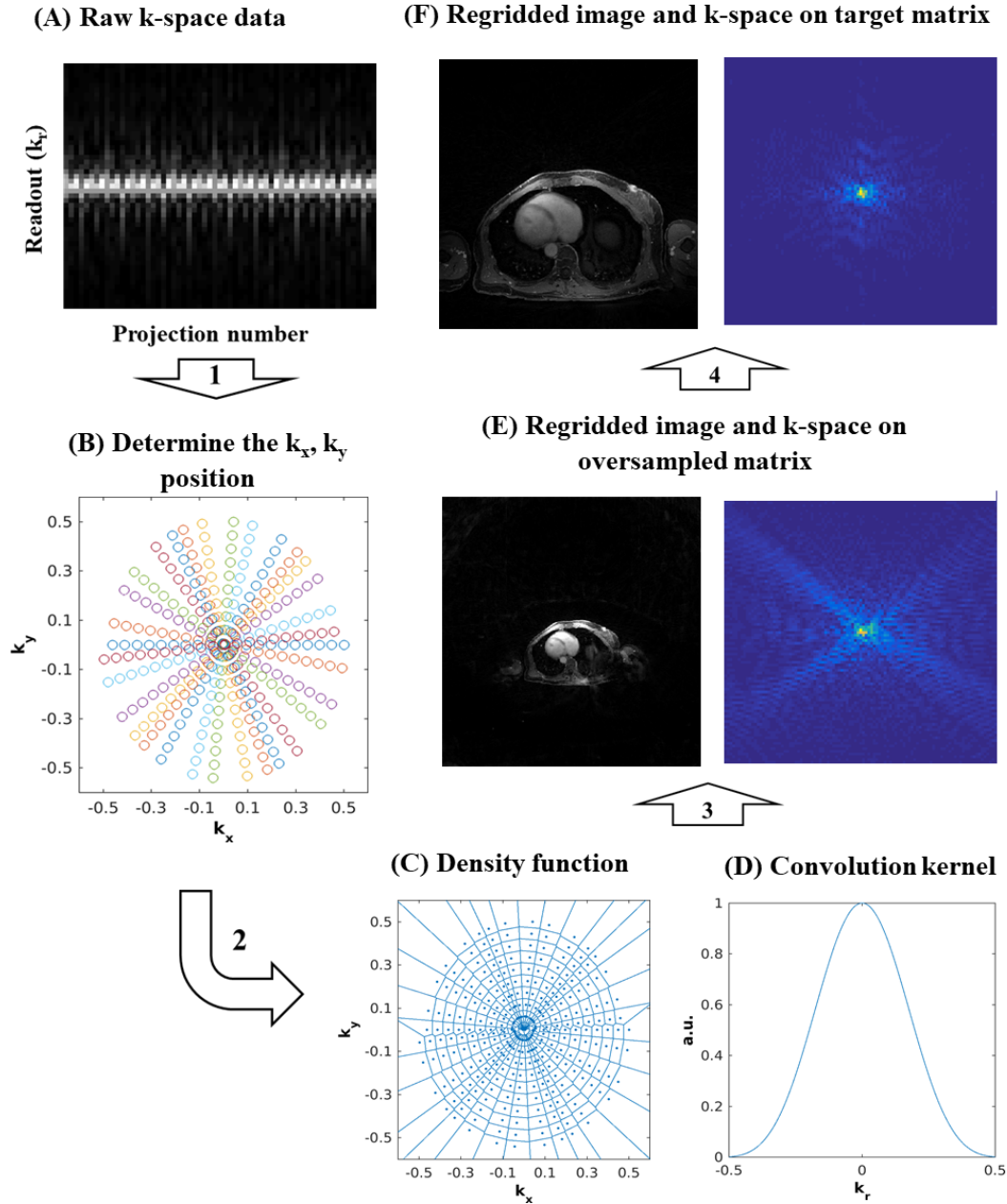


Figure 1.2.10: Diagram of 2-D gridding reconstruction. (A) An example of the raw radial k-space data where x-axis demonstrates the number of the projection and y-axis is the radial readout direction. The k-space raw data are first (C) density compensated by using the selected density compensation function (e.g. Voronoi) and convolved with the (D) convolution kernel (e.g. Kaiser-Bessel function) onto (B) the oversampled Cartesian grid (k_x, k_y). (E) The gridded image on oversampled matrix after the inverse FFT (iFFT) and the corresponding k-space image. (F) The gridded image on target matrix after the iFFT and the corresponding k-space image.

Further, the non-uniform fast Fourier transform (NUFFT)⁶⁷ was proposed to improve reconstruction error compared with the conventional shift-invariance KB approach but still maintain the computational efficiency. However, this method is often not suitable for highly undersampled time-resolved DCE-MRI where severe streak artifacts persist.

To provide high spatial resolution and high temporal resolution images, several techniques have combined non-Cartesian acquisition with advanced reconstruction algorithms, which including projection-reconstruction for time-resolved contrast-enhanced imaging (PR-TRICKS)⁶⁸ and k-space weighted image contrast (KWIC)⁶⁹ using radial acquisition, , which have been explored for breast MRI^{70,71}. Recently, the combination of radial acquisition and compressed sensing reconstruction has been widely applied in time-resolved breast DCE-MRI. As known that the essential factor of CS is the incoherent sampling. The golden-angle radial sampling can be seen as one of the incoherent sampling schemes, which caused the noise-like streak artifacts in image domain. This makes the golden-angle radial acquisition as a promising method for CS reconstruction⁵⁴, and studies have demonstrated that golden-angle ordering outperformed other radial sampling pattern on the CS reconstruction^{72,73}.

1.3 Innovation

This work will develop and optimize a motion robust imaging technique combined with advanced reconstruction for time-resolved DCE breast MRI to achieve higher spatial-temporal resolution and perform characterization and validation of recently proposed techniques. The innovation of this work is summarized below:

Evaluation of motion-robust DCE breast MRI using radial acquisition. Previous studies have shown that radial acquisition is less sensitive to motion allowing the acquisition of body images

during free breathing⁶³. However, an evaluation of performance during motion and overall image quality of SOS radial acquisition in multi-phase breast DCE-MRI has not been demonstrated. Therefore, this proposal will evaluate the image quality in the presence of cardiac motion for breast DCE-MRI using radial acquisition.

Combining radial acquisition with MOCCO reconstruction for breast DCE-MRI.

Compressed sensing reconstructions, such as iGRASP, have been proposed for undersampled radial acquisition in the abdomen⁷⁴ and breast⁷⁵ for DCE-MRI. However, applying iGRASP in different imaging settings and applications may result in unique temporal sparsity transformations that necessitate use of corresponding unique reconstruction parameters, on a case-by-case basis. Kim et al. has demonstrated that additional optimization process is required for different acquisition setting to provide sufficient image quality, especially the selection of the regularization weighted. Although many acceleration techniques have shown promising results for providing high spatial and temporal resolution^{74,75}, additional evaluations are needed to characterize the performance of these approaches under a broader range of imaging conditions such as noise level, lesion size, and contrast kinetics. However, there is a lack of rigorous validation for advanced acceleration techniques in breast DCE-MRI due to difficulty in obtaining a known ground truth of patient physiology. In this proposal, we have applied MOCCO reconstruction to breast DCE-MRI motivated by studies showing it to be less sensitive to reconstruction parameter selection and therefore more robust across a broad range of imaging settings. MOCCO uses pre-estimated temporal models, generated from the original imaging data, as a temporal constrain to reduce the sensitivity to modeling error. Further, the temporal accuracy of our proposed method will be validated by using a DRO breast phantom.

Development of DRO breast phantoms for validation. In practice, comparison and validation of new techniques such as motion-robust acquisition and advanced reconstruction in DCE-MRI are difficult to perform in patients due to the lack of ground truth when interpreting the results. The goal of this proposal is to develop DRO breast phantoms for DCE-MRI that include several motion models to evaluate the performance of new imaging techniques. Further, the DROs will be designed to pair with pharmacokinetic (PK) analysis software packages to allow validation of the temporal accuracy from new reconstruction methods as well as assessment of how these may reflect in changes to standard PK parameters.

1.4 Thesis Outline

In accordance with the aforementioned aims of this work, the thesis is organized as follows:

- **Chapter 2:** Preliminary studies for multi-phase breast images using radial acquisition
 - This chapter contains multiple preliminary studies to evaluate the feasibility of using radial acquisition in multi-phase breast DCE-MRI
- **Chapter 3:** Time-resolved radial acquisition with compressed sensing reconstruction
- **Chapter 4:** Quantitative DCE-MRI using pharmacokinetic modeling
- **Chapter 5:** Respiratory self-gated free breathing supine breast DCE-MRI
- **Chapter 6:** A final summary of this work and discusses on potential future works are described.

Chapter 2

Preliminary studies for breast imaging using radial acquisition

2.1 Introduction

Breast MRI is becoming increasingly common for management of screening for women at increased risk based on BRCA mutations or a family history of breast cancer^{1,2}. Comparing to mammography, the wider coverage of anatomical structure could be achieved by applying bilateral imaging, which includes not only breast tissue but also axillary tail, lymph nodes and pectoralis major muscle. Furthermore, T1w 3D dynamic contrast-enhanced (DCE) MRI is currently widely accepted as the most sensitive modality for detection of breast cancer³. DCE-MRI relies on the use of intravenous contrast agents and differences in contrast kinetics in tumors relative to normal tissues allowing for tumor visualization as well as providing the promise for tumor characterization. It's known that morphological and dynamic information from the difference between pre- and postcontrast images could provide excellent sensitivity to distinguish malignant from benign lesions³.

Historically, clinical bilateral breast MRI exams typically used multi-phase fully sampled Cartesian encoding to achieve high spatial resolution (at or below 1 x 1 mm in-plane pixel size) over the large field of view (FOV) however this allowed only limit temporal resolution (60-120

s)⁷⁶. This clinical breast DCE-MRI protocol has been proof to allow detection of small lesions and assessment of lesion morphology⁷⁷. However, the Cartesian acquisition is well known sensitive to the presence of patient motion. The main sources of motion related artifacts in breast MRI are from normal physiologic process such as cardiac and respiratory or due to bulk patient motion such as movement due to discomfort. Artifacts due to regular cardiac and respiratory motion are well known to result in ghosting artifacts in the phase-encoding direction of Cartesian image acquisitions. For this reason, it is common for clinical breast MRI to perform the phase-encoding in the right-left direction during axial acquisitions to focus the motion related ghosting artifacts of the heart in the right-left direction and away from the majority of the breast tissue. However, in many individuals this results in motion related ghosting that obscures clear visualization of the axilla region. Applying motion-management techniques such as cardiac triggering or gating may help reducing ghosting artifacts but come with the penalty of increasing scan time which in turn reduces temporal resolution making these impractical for breast MRI.

A 3D stack-of-stars acquisition with a golden-angle radial sampling scheme performs radial acquisition in the x-y plane with Cartesian encoding performed in the z-plane, which has been proven to provide arbitrary temporal resolution with reasonable spatial quality⁷². The radial acquisition is also known to be less sensitive to the patient motion. In this chapter, we present three preliminary studies to demonstrate the feasibility of using a 3D stack-of-stars radial acquisition for multi-phase DCE-MR images. The first study is to evaluate the performance of radial acquisition during cardiac motion using a digital reference object. The second study characterizes the overall image quality of the SOS radial acquisition using a gridding reconstruction for in-vivo data. The third study assesses the performance of deep-learning based post-processing algorithm to designed to denoise the data, improve image sharpness, and remove streaking due to undersampling.

2.2 Validation of motion-robust DCE breast MRI using radial acquisition

Radial sampling has an intrinsic advantage for diminishing motion artifacts by averaging low spatial frequency signals through oversampling of central k-space data. Studies have shown that the radial acquisition has the ability to accelerate via angular undersampling as well as reduce sensitivity to respiratory and cardiac motion during free breathing in multiple imaging applications^{78–80}. Block et al⁸¹ has demonstrated the robustness of reducing the respiratory motion artifacts in liver multi-phase scan. They also showed that the radial acquisition is less sensitive to the off-resonant fat signal in the breast exam, which could lead to the chemical-shift artifact along the readout direction for Cartesian acquisition. However, there is limited work exploring the use of radial MRI to address motion artifacts in breast imaging. The purpose of this preliminary study is to demonstrate the feasibility of using a 3D stack-of-stars radial acquisition to provide cardiac and respiratory artifact free visualization of the entire breasts, including the axillae through the bilateral breast images.

2.2.1 Methods

Digital reference object

A flow chart of the numerical simulations is shown in **Figure 2.2.1**. A numerical breast phantom was designed to simulate an anatomically correct T1-weighted DCE acquisition with fat suppression⁸². Within the phantom, lesions were placed in the fibroglandular tissue of the right breast and in the axillary tail region bilaterally with unique contrast agent kinetics simulated individually for each lesion. The signal characteristics of the phantom were derived based on MR system parameters including: repetition time (TR) = 5.87 ms; echo time (TE) = 2.79 ms; FOV = 38 cm; flip angle = 10; receiver bandwidth = 63.3 kHz; acquisition matrix = 448 x 448, 0.8 x 0.8

mm in-plane resolution, and 8 channel coil sensitivity maps. The cardiac motion was represented using 10 cardiac phases per beat at a rate of 72 beats/min for total scan time of 12 min 26 s. Both anatomical breast images and cardiac phases were multiplied by the sensitivity maps to generate individual coil images, which were then used to generate simulated k-space data collected from either a Cartesian or golden angle stack-of-stars radial acquisition trajectory consisting of 1024 projections $\times$ 8 coils by using the same NUFFT methods. The k-space data of anatomical breast images and cardiac phases were then recombined to simulate motion images to generate the four time-frame breast DCE MR images. For radial acquisition, images were reconstructed by using

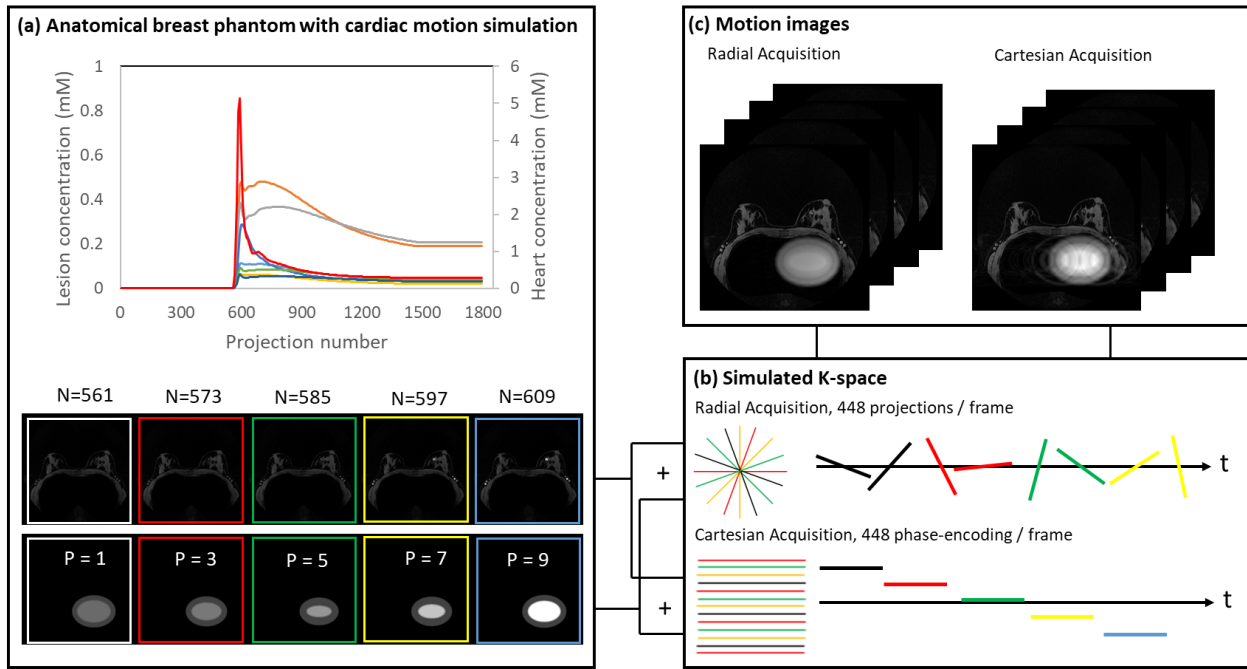


Figure 2.2.1: Workflow of the DRO with cardiac motion and simulated lesions generated with seven different contrast enhancement patterns. (A) The DRO was designed to include static features of the anatomical breast tissue, simulated enhancing lesions, as well as different cardiac phases. (B) Each image series were transformed to k-space and resampled simulating a radial or Cartesian acquisition. (C) The final motion images were then reconstructed by combining the subsets of k-space data from each cardiac phase.

256 projections per time frame (equal to angular sampling factor of 0.36) to match the same acquisition time for Cartesian acquisition using in clinical protocol. For comparison purposes, motion-free reference images were created by assuming an idealized instantaneous time that could capture the specific cardiac phase along the contrast curve.

2.2.2 Results

Digital object phantom

A four time-frame breast DCE MR images reconstructed by using the Cartesian and radial sampling and the corresponding motion-free reference images are shown in **Figure 2.2.2.1**. The radial acquisition with angular sampling factor of 0.36 showed overall similar image quality in breast region compared with the Cartesian acquisition. Further, the axilla region was well presented in radial images. The cardiac motion only resulted in localized blurring of the cardiac wall, which are more visually consistent with motion-free reference images. However, slightly loss of the sharpness was observed at the lesion edge. On the contrary, severe ghosting artifacts were shown in the Cartesian acquisition across the entire axillary region along all four-time frames due to the cardiac motion. The ghosting artifacts resulted in blurring of both the chest wall and lesion edge.

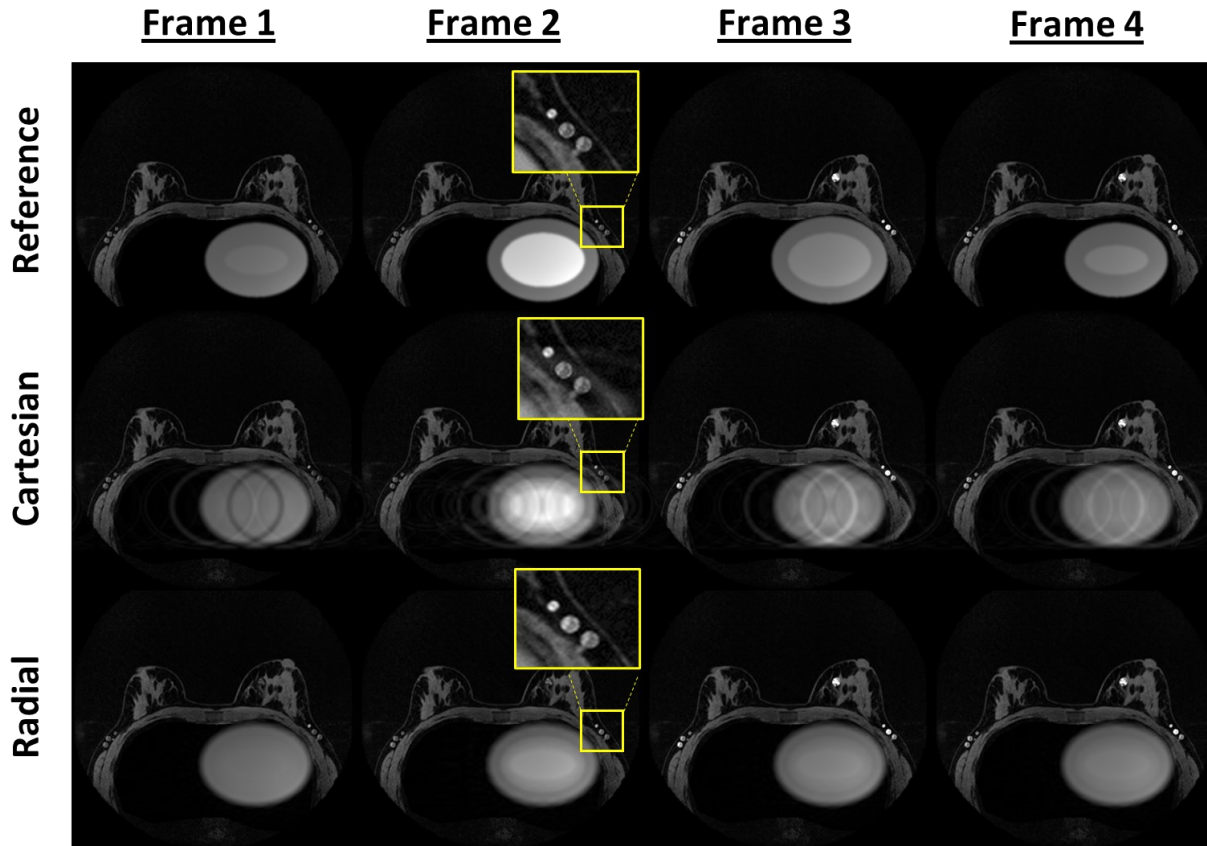


Figure 2.2.2.1: Simulation images: The first row is the motion-free reference images. Shown in other two row are images reconstructed with different acquisition (Cartesian, and SOS radial acquisition). Each column was the different contrast time frame. The zoomed-in images are demonstrated in frame 2 located at left axillary region.

2.2.3 Discussion

In this work, we present a framework to compared radial and Cartesian acquisition schemes in bilateral breast imaging for the reduction of phase ghosting across the axillae. Numerical simulations are employed to evaluate the characteristic with the presence of cardiac motion between radial and Cartesian acquisition. Cardiac motion is known to cause ghosting artifacts in the phase-encoding direction during Cartesian MRI acquisition, while cardiac motion causes

localized blurring and/or streak artifacts using radial MRI acquisition. Further, the results demonstrated that the radial acquisition allows better visualization of chest wall and axilla region due to the reduction of ghosting artifacts. The simulation results demonstrated that the ghosting artifacts were visible in all frames using Cartesian acquisition and greatest when high signal occurred in the heart due to the presence of contrast agent (**Figure 2.2.2.1**). The degree to which the ghosting impacted evaluation of the chest wall and axilla depended on both the heart rate as well as the location of the heart relative to the chest. For example, individuals with heart walls located more closely to the chest wall resulted in greater impact of ghosting to the nearby axilla region. Our results suggest, this technique could benefit patient with lymph nodes or fibroglandular tissue located in axilla region, especially patients with chest geometries resulting in more of the axillary tissue curving around the heart.

2.3 Evaluation of overall image quality for breast images using radial acquisition

The previous study is to demonstrate the feasibility of using a 3D stack-of-stars radial acquisition to provide cardiac-motion free images of the entire breast region including the axilla in bilateral breast images. However, our results lack an overall image quality assessment for radial acquisition in the in-vivo setting. Therefore, the purpose of this preliminary study is to provide a qualitative analysis to evaluate the image properties of SOS radial acquisition for the use of clinical multi-phase breast DCE-MRI. Specifically, a reader study was conducted in in-vivo data and the results were compared against the conventional Cartesian acquisition.

2.3.1 Methods

2.3.1.1 Human subjects

Thirty-five volunteers were enrolled in this institutional review board-approved and HIPPA compliant study. Imaging was performed using an 8-channel breast coil (GE Healthcare, Waukesha, WI). Ten normal volunteers underwent non-contrast radial and Cartesian imaging on a 3 T scanner (MR750w, GE Healthcare, Waukesha, WI) and were monitored to ensure no bulk motion. The remaining twenty-five volunteers were scanned) on a 3 T scanner (Signa PET/MR, GE Healthcare, Waukesha, WI) with contrast injection (gadobenate dimeglumine, Multihance; Bracco Inc, Milan, Italy). Four contrast enhanced normal volunteers were scanned with multi-phase images acquired with radial and Cartesian trajectory in randomized order. The other twenty-one subjects were the clinical patients and were imaged using the routine clinical breast MR protocol at our institution including a multi-phase Cartesian acquisition during contrast injection followed by a radial acquisition as a last scan.

2.3.1.2 MR acquisition

Radial imaging was performed using a 3D stack-of-stars golden-angle 3D spoiled gradient echo (SPGR) sequence imaging sequence. The radial field of view (FOV) was oversampled by doubling the sampling bandwidth to limit aliasing from signal outside the FOV. Cartesian images were using a DCE T1-weighted SPGR sequence with intermittent chemical fat saturation and a parallel imaging factor of 2 in the slice phase-encoding direction using the coil sensitivity-based ASSET option. Acquisition parameters included: repetition time (TR) = 5.87 ms; echo time (TE) = 2.79 ms; FOV = 38 cm; flip angle = 10; receiver bandwidth = +/-63.3 kHz; acquisition matrix = 448 x 448 x 142, acquired spatial resolution = 0.8 x 0.8 mm in-plane resolution and 1.4 mm out of plane. Acquisition times were 2:43 (min:sec) for the Cartesian and 2:52 (min:sec) for the radial

acquisitions with 256 projections per time/frame (equal to angular sampling factor of 0.36). A weight-based dose (0.1 mmol/kg) of a gadolinium-based contrast agent (gadobenate dimeglumine, Multihance; Bracco Inc, Milan, Italy) was administered followed by a 20-mL saline flush, both injected at a rate of 2 mL/s using a power injector. Conventional Gridding was used to reconstruct radial images.

2.3.1.3 Reader study

For the radial acquisition using the conventional reconstruction, the image quality was evaluated by two fellowship-trained radiologist and one radiologist specializing in breast imaging with four, four, and six years of experience. Cartesian and radial images were displayed side-by-side with random order (left or right). Readers scored the images for overall image quality, sharpness, presence of artifacts in both the breast and axilla, signal-to-noise ratio (SNR), and quality and degree of fat saturation. The radiologists also indicated if they felt the image was of sufficient quality to use in a clinical evaluation. Scoring was performed using a five-point Likert-scale (1: Very poor and non-diagnostic; 2: Poor and affecting clinical assessment; 3: Fair but not affecting clinical assessment; 4: Good; 5: Excellent). Specific details for each image features were presented in **Table 2.3.1.1**. Scores for all three readers were compared between sequences using Mann–Whitney U test. P values of 0.05 or less were considered statistically significant.

Table 2.3.1.1: Criteria for image quality comparison between radial and Cartesian acquisitions

Score	Criteria
A: Artifacts in breast region ^a & B: Artifacts in the axilla region ^b	
1	Severe artifacts, non-diagnostic
2	From moderate to severe image artifact, impact on diagnostic capability
3	Moderate image artifact, no impact on diagnostic capability
4	Minimal image artifact, no impact on diagnostic capability
5	No artifacts
C: Quality of normal anatomic structures ^{a,b}	
1	Very poor: loss of anatomical detail in all anatomical structures
2	Poor: loss of anatomical detail in multiple structures
3	Fair: loss of anatomical detail in one structure
4	Good : no deficiencies in all anatomical structures
5	Excellent: no deficiencies in all anatomical structures
D: Perceived sharpness in breast tissue ^a & E: Perceive sharpness in the axilla region	
1	Very poor: non-diagnostic with significant overall blurring
2	Poor: significant localized blurring or moderate overall blurring that is diagnostically significant
3	Fair: moderate localized blurring but not diagnostically relevant
4	Good : Slightly localized blurring but not diagnostically relevant
5	Excellent: all structures with sharp edges
F: Signal-to-noise ratio (SNR)	
1	Non-diagnostic
2	Poor: difficult to resolve structures
3	Fair: sufficient to resolve most structures
4	Good: sufficient to resolve relevant structures
5	Excellent: high quality visualization of all structures
G: Fat suppression	
1	Very poor: inhomogeneity and non-diagnostic
2	Poor: inhomogeneity that affects clinical assessment
3	Fair: inhomogeneity but not affecting clinical assessment
4	Good: Slight inhomogeneity
5	Excellent suppression
H: Overall image quality	
1	Very poor: non-diagnostic with significant artifact, failure of fat suppression, and loss of anatomical detail
2	Poor: deficient in two of the following: artifact, fat suppression, visualization of anatomic detail
3	Fair: deficient in one of the following: artifact, fat suppression, visualization of anatomic detail
4	Good: no deficiencies in the image
5	Excellent: very high quality image with no deficiencies

^a Breast region^b Axilla region, which includes lymph nodes, blood vessels, chest wall, pectoral muscle and any relevant pathology in the axillary region

2.3.2 Results

Table 2.3.2.2 presents image quality scoring results from three radiologist readers. Compared to the Cartesian acquisition, the radial approach yielded significantly higher scores for the absence of artifacts in the axilla ($p=0.003$). However, the Cartesian acquisition was scored to have significantly greater sharpness in the breast tissue ($p=0.003$). There was no significant difference in the other image quality parameters. Overall average image quality scores for both sequences were 3.6 (Good-to-Excellent). Readers found 89% of the radial acquisitions were sufficient for clinical evaluation, 5% less than for Cartesian.

Table 2.3.2.2: Image quality scores for cardiac motion evaluation

Image Quality	Cartesian sampling	Radial sampling	P-value
Artifacts (Breast)	3.83±0.75	3.72±0.85	0.200
Artifacts (Axilla)	3.07±0.82	3.41±1.00	0.002*
Sharpness/Resolution (Breast)	3.99±0.64	3.73±0.79	0.0004*
Sharpness/Resolution (Axilla)	3.22±0.80	3.08±0.83	0.202
SNR	3.61±0.76	3.75±0.73	0.100
Quality of fat saturation	3.71±0.98	3.80±0.93	0.071
Overall Image Quality	3.50±0.70	3.52±0.78	0.794
Sufficient for clinical evaluation	79/84 (94%)	75/84 (89%)	

*Indicates statistically significant difference

Typical results from a volunteer demonstrate overall high image quality for both techniques, as showed in **Figure 2.3.2.1**.

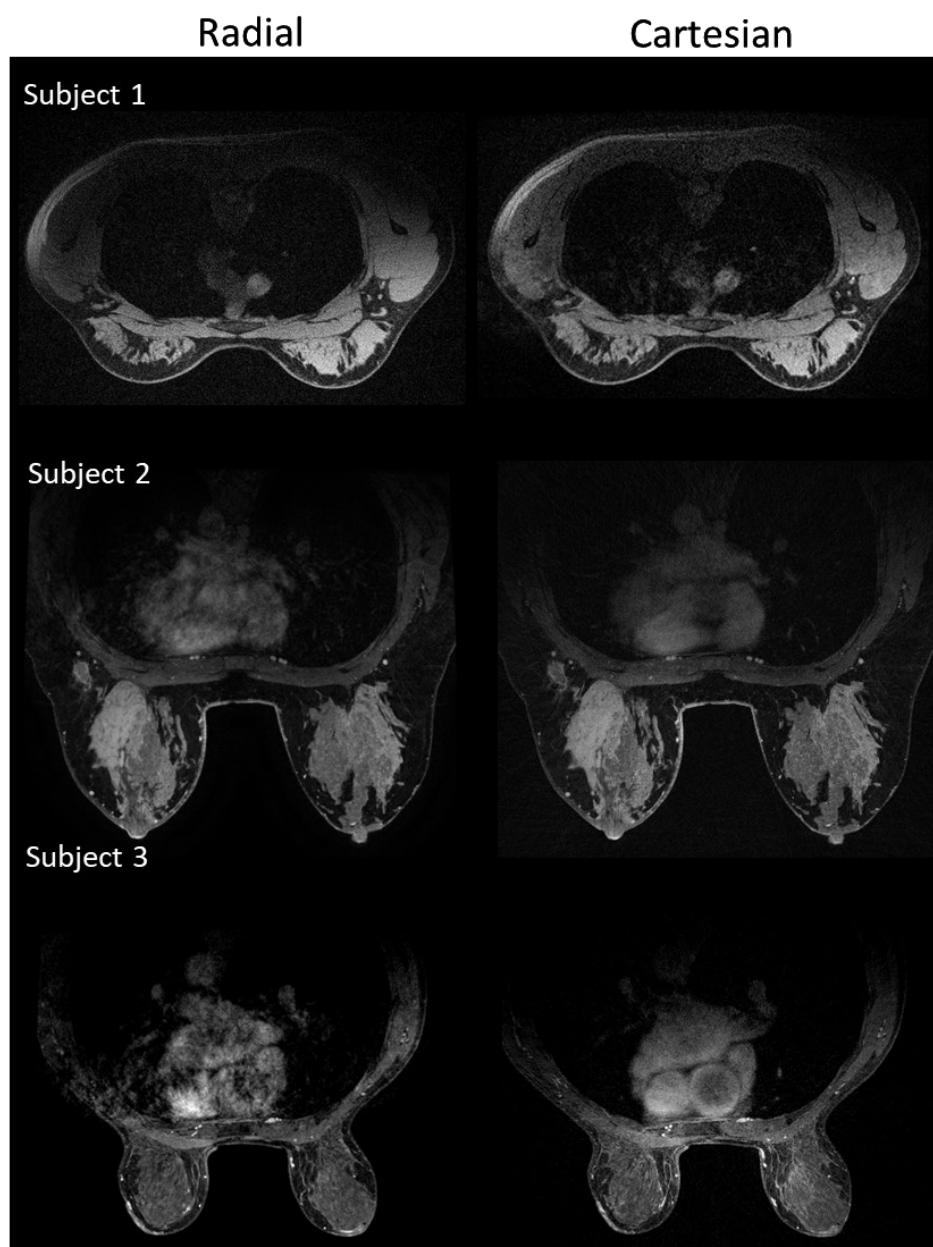


Figure 2.3.2.1: Examples of three volunteers showing no significant image quality difference between two acquisition. The fibroglandular tissues are well present in both acquisitions. The axilla region has slightly improved in radial acquisition due to not much ghosting artifacts in the Cartesian acquisition. However, the radial acquisition performed high-quality breast MRI compared with Cartesian acquisition.

However, in one volunteer the ghosting artifacts in the Cartesian acquisition was seen to obscure the axilla and lymph nodes as well as the axillary tail breast tissue (**Figure 2.3.2.2**). Better visualization of axilla region was found using the radial acquisition due to the reduced ghosting artifacts. This is highlighted in both axial (**Figure 2.3.2.2 c,d**) and sagittal (**Figure 2.3.2.2 e,f**) views. Other example also demonstrated that the axillary lymph nodes, vessels and musculature of the chest wall were hard to distinguish with the Cartesian acquisition due to the severe ghosting artifacts (**Figure 2.3.2.3 d,f**). The contour of those structure could be better captured in radial acquisition **Figure 2.3.2.3 c,e**). We have observed that six out of eighteen of in-vivo datasets showed significantly more streak artifacts than others. **Figure 2.3.2.4** showed one example that the lymph nodes were found less sharp in radial acquisition than in Cartesian acquisition due to the failure of fat saturation.

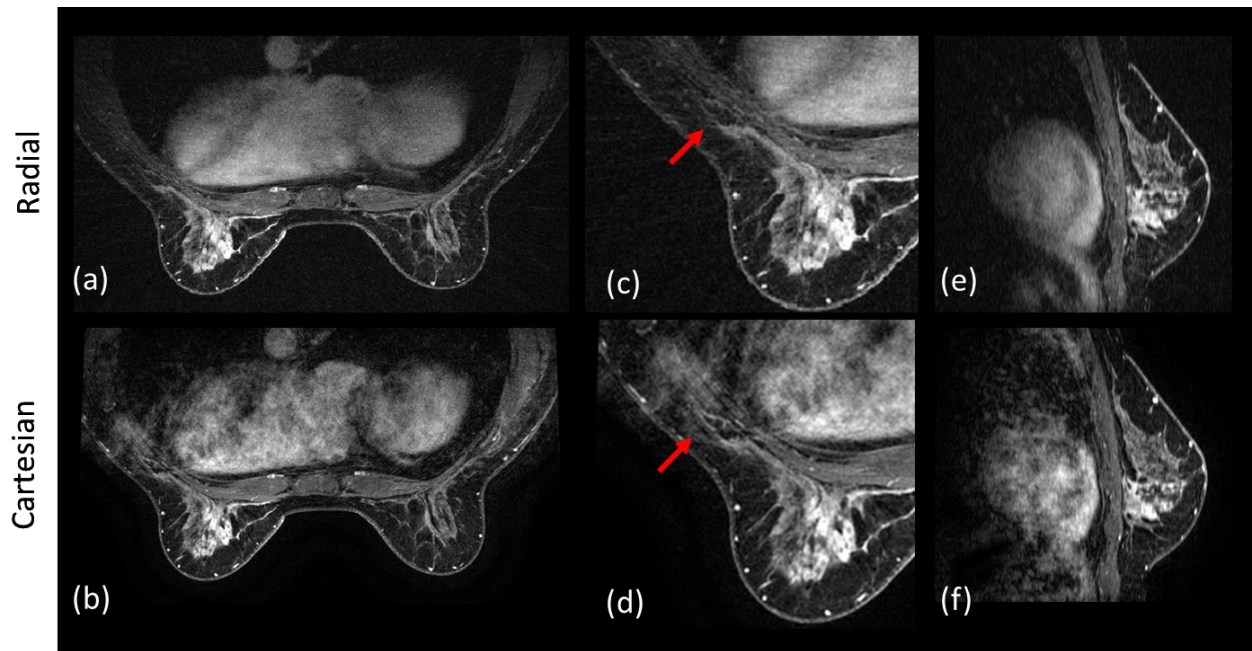


Figure 2.3.2.2: Both Radial and Cartesian acquisitions have the ability to provide good tissue contrast in multi-plane reformats. Although the axillary tail was not clearly visualized with Cartesian sampling due to the ghosting artifacts (red arrows), radial acquisition provided improved visualization.

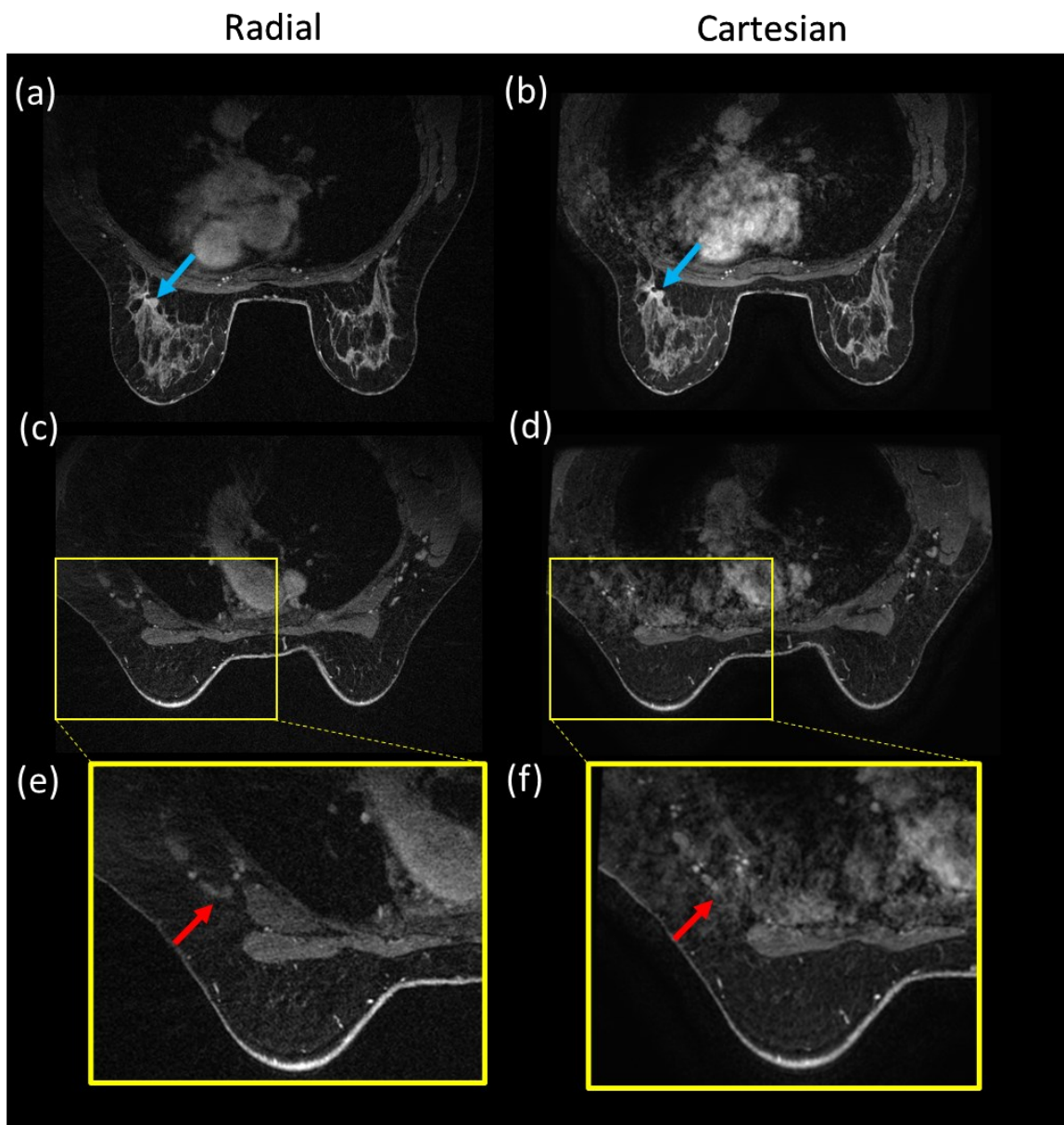


Figure 2.3.2.3: Different slices from a subject with post-contrast, T1-weighted radial and Cartesian axial breast MR images. A known breast cancer (invasive lobular carcinoma, blue arrows) is present in both acquisitions (a, b). However, significant ghosting artifacts are present in the axilla with the Cartesian acquisition obscuring the lymph nodes (e and f, red arrows). In contrast, the radial acquisition provides artifact clear visualization of the axilla.

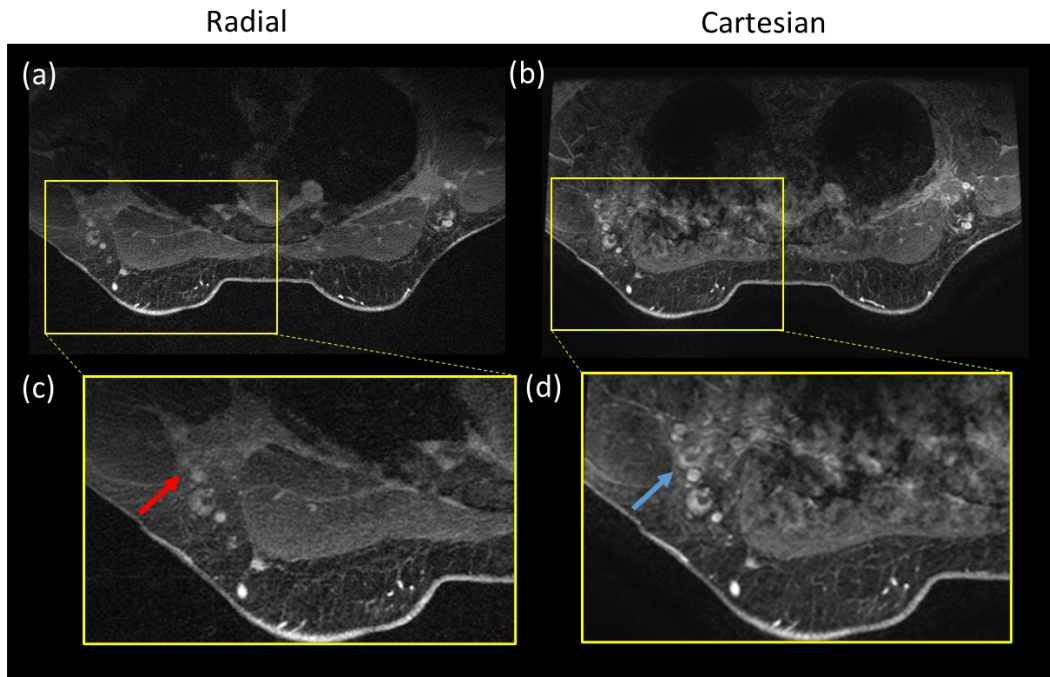


Figure 2.3.2.4: Example images from a very challenging case where the radial approach provided much greater overall reduction of cardiac artifacts as evident in the heart and chest wall (a) however there is residual blurring evident in the axilla (c, red arrow). Comparatively, the Cartesian data shows significant ghosting that obscures the heart, lungs, and chest wall (b) but was found to provide better visualization of the axilla and associated lymph nodes (d, blue arrow).

2.3.3 Discussion

In this preliminary study, we reported results from a reader study to assess image quality of a 3D SOS radial acquisition using the clinical required spatial resolution. Since the radial scheme provides great flexibility in the optimization of acquisition time and angular undersampling, this work has optimized for higher spatial resolution at the expense of a small increase in undersampling artifact. The undersampled radial images were further compared against the conventional Cartesian acquisition.

Our previous study has demonstrated the motion robustness with the presence of the cardiac motion using the radial acquisition in the numerical simulation. Similar results were observed in in-vivo data where radial images allow better visualization of chest wall and axilla region due to the reduction of ghosting artifacts. Most of our subjects showed significant improvement in radial acquisition due to severe ghosting artifact in Cartesian acquisition, but others showed consistent results between two acquisitions. However, the radial images were also found to have overall less sharpness in both the breast and axilla regions. There are multiple factors can lead to the reduction of sharpness in breast tissue and the increased of streak artifacts: 1) the failure of the fat saturation, which was most commonly observed on the inferior portion of the breast due to shimming challenges, 2) some levels of angular undersampling 3) gradient timing delays, which could lead to mis-centering of the k-space trajectories. These trajectory errors are known to introduce artifacts including impacts to the low spatial frequencies during radial acquisition⁸³. To address this limitation, a separate calibration scan can be performed to measure the gradient delay. However, the source of the streak artifacts in our dataset is still under investigation but is suspected to be due to a technical failure of the MRI hardware during acquisition of some individual radial spokes. To identify the corrupted spokes, we transferred all k-space data to sinogram space where the erroneous spokes could be identified due to their lower intensity relative compared to the adjacent spokes as a function of projection angle. Another method to improve the sharpness and/or reduce the streak artifact in radial image with gridding reconstruction is to increase the number of projects to avoid uneven spacing between the k-space spokes but at the expense of increasing the temporal resolution. In conclusion, we demonstrate the promise of a 3D stack-of-stars radial acquisition to reduce phase ghosting artifacts in breast MRI, particularly across the bilateral axillae. This has important clinical applications, as evaluation of the axillary lymph nodes is important in the setting

of known breast cancer, a suspicious breast lesion, and post-neoadjuvant therapy. However, reduction of the sharpness in the breast tissue and axilla region was observed.

2.4 Evaluation of a deep-learning based approach to remove residual undersampling artifacts

Radial DCE-MRI is a promising approach having shown similar diagnostic accuracy when compared to conventional Cartesian sampling for breast imaging in the sagittal view⁴⁶. However, radial sampling is known to produce streak artifacts in many settings including angular undersampling and motion. Our previous studies also showed some levels of streak artifacts caused signal blurring of the anatomical structures due to the motion and/or the undersampled effect as a result of reduction of the overall image quality in the radial acquisition. One possible solution to this problem is to apply coil selection to remove the coil with severe streak artifacts. This method is especially helpful if the streak source is located toward the outer edges in larger FOV images⁸⁴, whereas this method is not able to improve the overall sharpness in the breast. Recent developments in deep convolutional neural networks have provided substantial improvements in SNR and perceived spatial resolution.^{85–89} It may be possible to apply a deep learning (DL) algorithm to improve the overall image quality by reducing the noise and artifacts in the setting of breast imaging. Therefore, the purpose of this preliminary study is to evaluate the image quality when using a DL algorithm as a post-processing step for radial images. Phantom imaging was performed to demonstrate the impact on the CNR and image sharpness. Patient subjects undergoing a clinical MR exam were scanned with the additional radial acquisition followed by a gridding reconstruction.

2.4.1 Methods

2.4.1.1 Resolution phantom

The non-Cartesian patient imaging protocol was used to scan a resolution phantom at slice thicknesses of 0.4, 0.6, 1.0, and 1.4 mm and angular sampling factors of 2, 1, 0.5, 0.333, 0.25, and 0.125 relative to the Nyquist criterion ($\pi/2$ views to readout points). Line profiles were generated across the edge of the phantom, and CNR was calculated by: (signal in phantom – signal in background)/noise in background.

2.4.1.2 Human subjects

Fourteen subjects were enrolled in this IRB-approved and HIPPA-compliant study. Imaging was performed using a 16-channel breast coil (GE Healthcare, Waukesha, WI) on a 3T scanner (Premier, GE Healthcare, Waukesha, WI) and was monitored to ensure no significant bulk motion. All subjects were imaged using the routine clinical breast MR protocol at our institution including a multi-phase Cartesian acquisition during contrast injection (gadobenate dimeglumine, Multihance; Bracco Inc, Milan, Italy) followed by a radial acquisition as a last scan.

2.4.1.3 MR acquisition

Radial imaging was performed using a 3D stack-of-stars golden-angle 3D spoiled gradient echo (SPGR) sequence imaging sequence. The radial field of view (FOV) was oversampled by doubling the sampling bandwidth to limit aliasing from signal outside the FOV. Cartesian images were collected using a DCE T1-weighted SPGR sequence with intermittent chemical fat saturation and a parallel imaging factor of 2 in the slice phase-encoding direction using the coil sensitivity-based ASSET option. Acquisition parameters included: repetition time (TR) = 5.87 ms; echo time (TE) = 2.79 ms; FOV = 38 cm; flip angle = 10; receiver bandwidth = +/-63.3 kHz; acquisition matrix = 448 x 448 x 142, acquired spatial resolution = 0.8 x 0.8 mm in-plane resolution and 1.4 mm out of

plane. Acquisition times were 2:43 (min:sec) for the Cartesian and 2:52 (min:sec) for the radial acquisitions. A weight-based dose (0.1 mmol/kg) of a gadolinium-based contrast agent (gadobenate dimeglumine, Multihance; Bracco Inc, Milan, Italy) was administered followed by a 20-mL saline flush, both injected at a rate of 2 mL/s using a power injector.

2.4.1.4 Reconstruction

Non-Cartesian image reconstruction utilized the standard pipeline including gridding followed by a derivative of a DL technique (AIR Recon DL, GE Healthcare, Waukesha, USA) as a post-processing step, which in this case was designed to reduce noise, improve sharpness, and reduce streak artifact. A convolutional neural network was constructed with ~4.4 million parameters in ~10,000 kernels. A model was trained via supervised learning which compared over 10,000 ground truth radial images to corresponding images degraded by noise, blurring, and angular undersampling artifact. An ADAM optimizer was used to minimize the loss between the image pairs. Note that the radial images used for the cardiac motion evaluation do not include the DL post-processing step.

2.4.1.5 Reader study

For the evaluation of radial acquisition with the deep learning-based reconstruction, two radiologists specializing in breast imaging with 11, and 20 years of experience were included to evaluate the image quality. Cartesian, radial, and radial with DL reconstruction (Radial+DL) images were displayed side-by-side with random order (left, center, or right). Readers scored the images for overall image quality, sharpness, presence of artifacts in both the breast and axilla, signal-to-noise ratio (SNR), and quality and degree of fat saturation. The radiologists also indicated if they felt the image was of sufficient quality to use in a clinical evaluation. Scoring was performed using a five-point Likert-scale (1: Very poor and non-diagnostic; 2: Poor and affecting clinical

assessment; 3: Fair but not affecting clinical assessment; 4: Good; 5: Excellent). Specific details for each image features were presented in **Table 2.3.1.1**. Scores for all three readers were compared between sequences using Mann–Whitney U test. P values of 0.05 or less were considered statistically significant.

2.4.2 Results

2.4.2.1 Resolution phantom

Images from phantom scanning are shown in **Figure 2.4.2.1** comparing standard gridding and DL reconstructions as a function of varying slice thickness and undersampling factor. Images reconstructed with gridding (**Figure 2.4.2.1, a**) display increased noise with thinner slices and greater streak with reduced radial sampling. However, the apparent noise and streak are both much lower in the Radial+DL images (**Figure 2.4.2.1, b**). Note that the high frequency noise is disproportionately more suppressed in the Radial+DL images compared to the streak artifact which was not as greatly reduced at the thinnest slices and most undersampled reconstructions.

Both techniques were unable to recover image quality for the lowest Nyquist sampling factor of 0.125. From each of the images shown in **Figure 2.4.2.1**, a corresponding line profile is plotted in **Figure 2.4.2.2**. Note increased edge sharpness with the Radial+DL. Corresponding CNR measurements are shown in **Figure 2.4.2.3** demonstrating increased CNR with the Radial+DL for all but the lowest sampling factor of 0.125.

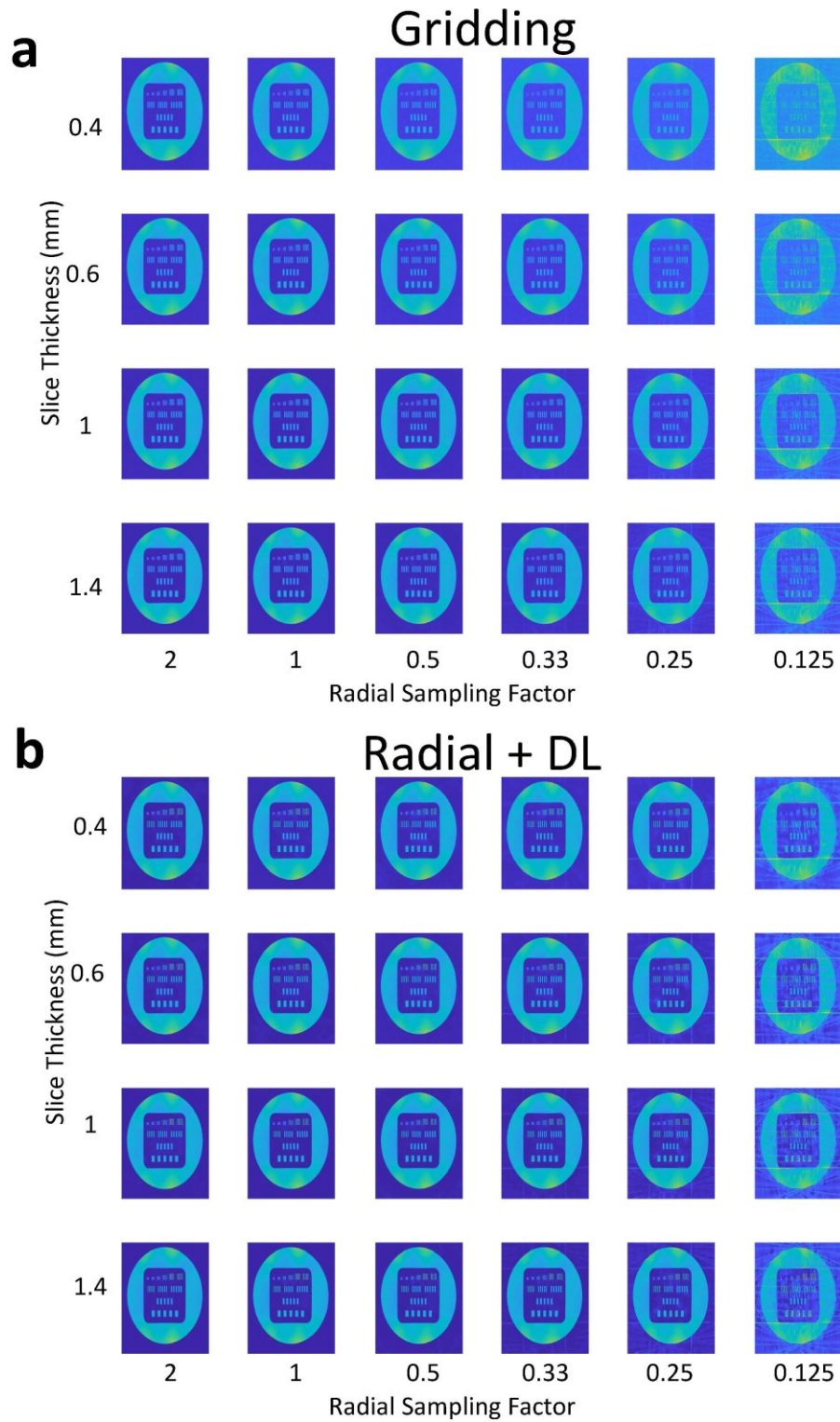


Figure 2.4.2.1: Phantom images are shown for varying slice thickness (rows) and Nyquist radial sampling factor (columns). Images reconstructed with Gridding a) and Radial+DL images b) are displayed.

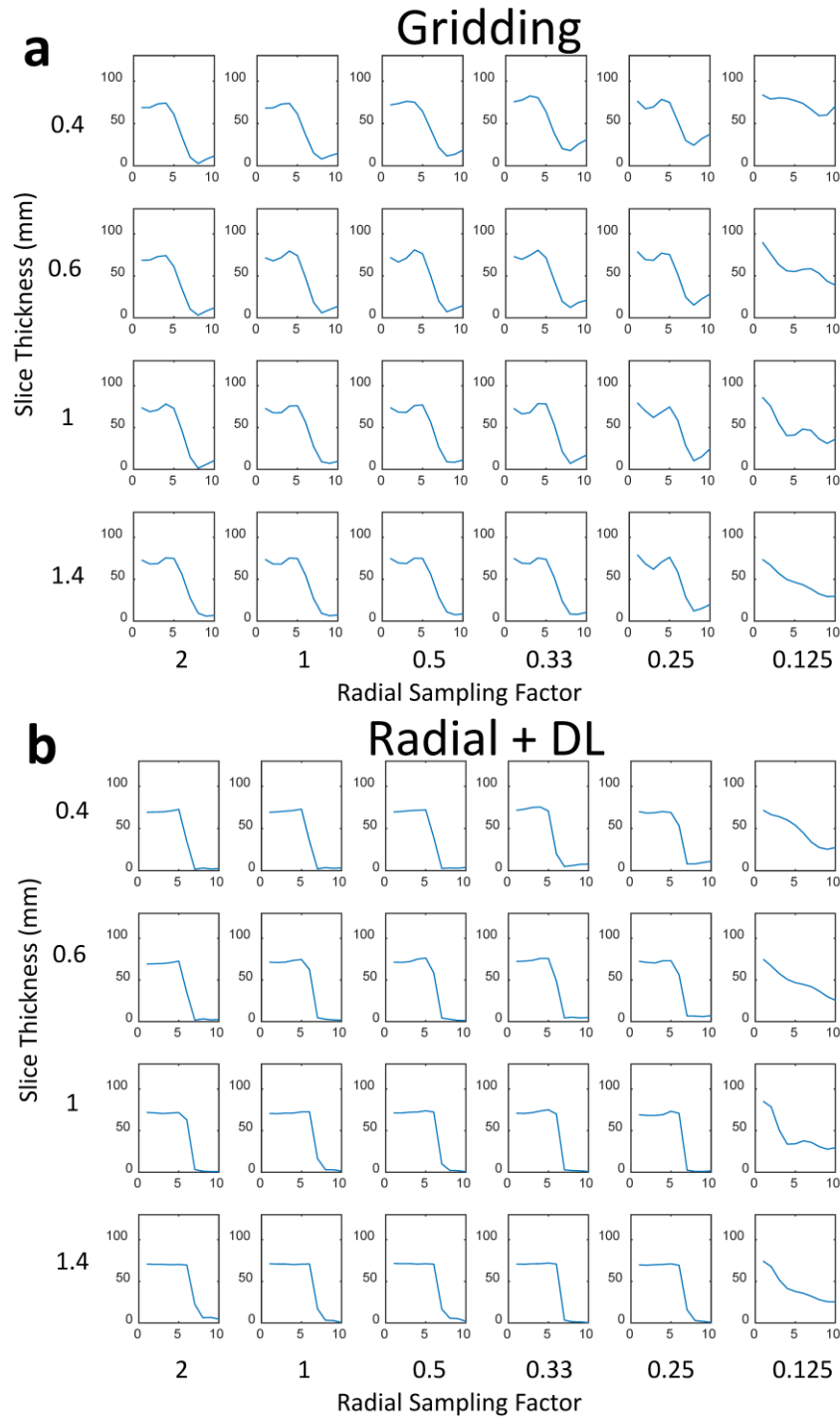


Figure 2.4.2.2: Line profiles depicting the edge response in Gridding a) and Radial+DL reconstructions b). Much sharper edge representation as well as reduced signal oscillations adjacent to the edge are found using the Radial+DL reconstruction for Nyquist sampling factors down to 0.25.

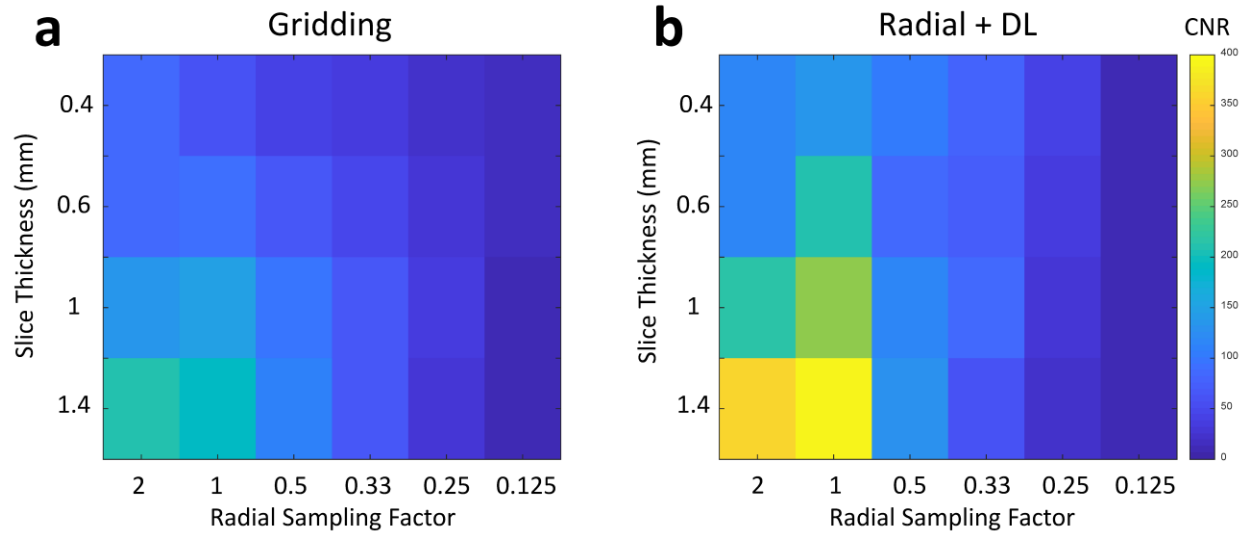


Figure 2.4.2.3: CNR was found to be lower with Gridding a) compared to Radial+DL b). In general, both reconstructions showed reduced CNR with thinner slices and a reduced Nyquist sampling factor.

2.4.2.2 Human subjects

Mean pooled reader scores are shown in **Table 2.4.2.1**. The mean pooled reader scores for Cartesian and Radial+DL were 4 or higher on the five-point scale for all eight categories,

Table 2.4.2.1: Mean pooled reader scores

	Radial	Cartesian	Radial+DL
Artifacts (Breast)	3.61	4.64	4.21
Artifacts (Axilla)	3.82	4.50	4.29
Quality of normal anatomic structures	4.29	4.50	4.11
Sharpness (Breast)	3.93	4.21	4.43
Sharpness (axilla)	3.79	4.00	4.39
SNR	3.75	4.39	4.79
Quality of fat saturation	4.5	4.61	4.43
Overall image quality	4.04	4.43	4.32

1 = Very poor, 2 = Poor, 3 = Fair, 4 = Good, 5 = Excellent

indicating that the images were scored as good in reader scores. On the contrary, the Radial showed image quality between fair and good for SNR, artifacts, and sharpness in both breast and axilla region. The Radial+DL showed higher scored in SNR, and sharpness in both breast and axilla regions compared to clinical Cartesian acquisition. However, Radial+DL has the lowest value in the category of quality of normal anatomic structures between three image techniques.

Figure 2.4.2.4 shows the boxplot of the radiologist scores for eight image quality categories that illustrate the scoring distribution of three image techniques (radial, Cartesian, and Radial+DL). With the exception of one subject whose Radial+DL images had scores below 3 in the categories depiction of artifacts in breast, and quality of normal anatomic structures. The boxplot results indicated that radial images in general have more artifacts, reduction of sharpness in both breast and axilla region and overall lower SNR. With the exception of one subject whose Radial+DL

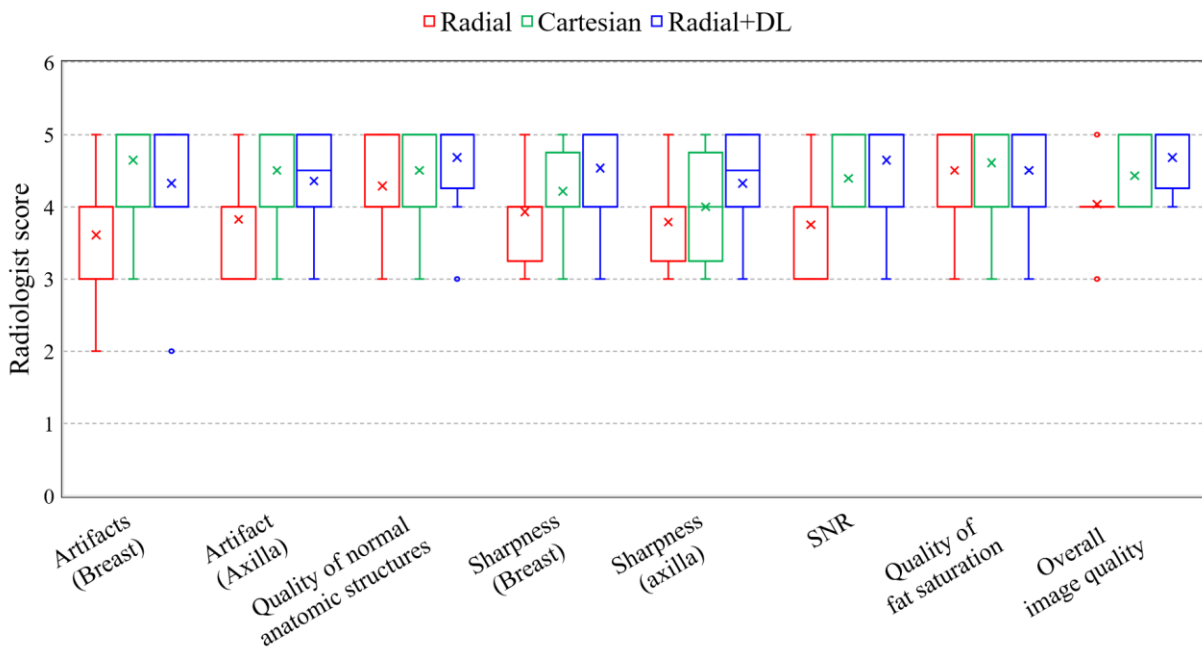


Figure 2.4.2.4: Boxplot of reader scores for three different image series (Radial (red), Cartesian (green), and Radial+DL (blue)). Mean (x), medium (the line fall inside the box), and outliers (circles) are shown. The whiskers represent 1.5 times the interquartile range.

images had scores below 3 in the categories depiction of artifacts in breast, and quality of normal anatomic structures. 75% of the Radial+DL images were considered to have good image quality (score equal or above 4) in all eight image quality categories and received mean reader scores higher than 4 on the five-point scale.

The preference results were shown in **Table 2.4.2.2**. We noticed an opposed preference between two readers. One preferred Radial+DL due to the overall improvement of the SNR and sharpness in reader 1, whereas reader 2 showed more concern of the over-smoothing effect in radial+DL, which reduced some heterogeneity between normal tissues, and loss of some textural information.

Table 2.4.2.2: Image preference by reader

	Cartesian	Radial	Radial+DL
Reader 1	1 (7.1%)	2 (14.3%)	11 (78.6%)
Reader 2	10 (71.4%)	2 (14.3%)	2 (14.3%)
Pooled	11 (39.3%)	4 (14.3%)	13 (46.4%)

Figure 2.4.2.5 and **Figure 2.4.2.6** show two representative cases from patient scanning with visibly perceived increased SNR, reduced streak artifact, and improved overall sharpness using Radial+DL.

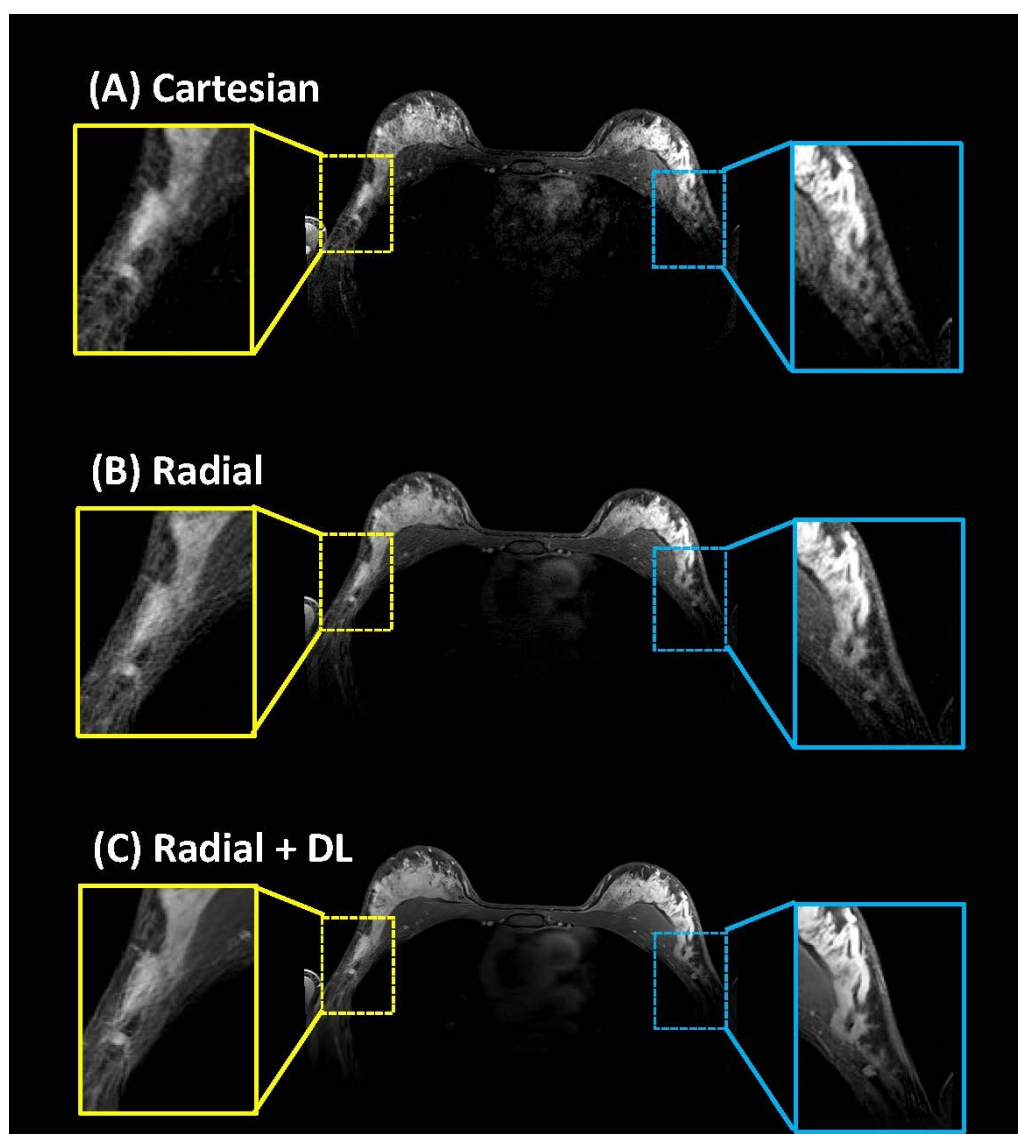


Figure 2.4.2.5: Bilateral contrast-enhanced breast exam in a clinical volunteer comparing Cartesian A), Radial B), and Radial+DL C). Enlargements of the left and right axilla show greatly improved visual SNR with sharper edges using Radial+DL. Streak artifacts visible in Radial (yellow box, B) are greatly reduced in the Radial+DL (yellow box, C). Note the reduced ghosting artifact due to cardiac motion with the radial acquisitions. Also note improved SNR in the chest wall where coil sensitivity is falling off.

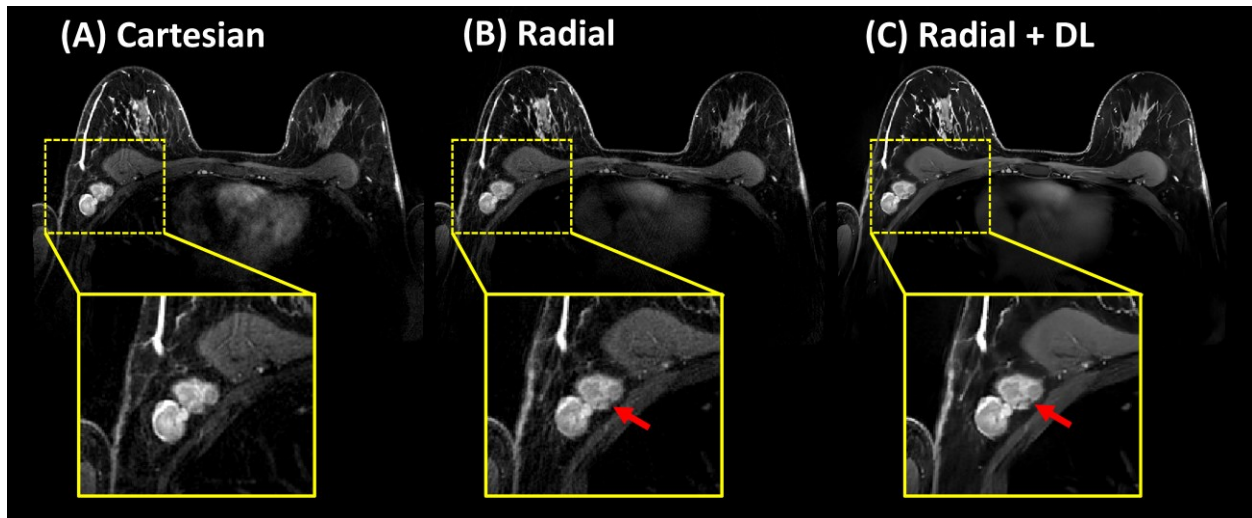


Figure 2.4.2.6: Bilateral contrast-enhanced breast exam in a clinical volunteer comparing Cartesian A), Radial B), and Radial+DL C). Enlargements of the left and right axilla show greatly improved visual SNR with sharper edges using Radial+DL. Streak artifacts visible in Radial (yellow box, B) are greatly reduced in the Radial+DL (yellow box, C). Note the reduced ghosting artifact due to cardiac motion with the radial acquisitions. Also note improved SNR in the chest wall where coil sensitivity is falling off.

2.4.3 Discussion

In this study, we investigated the image quality of using radial acquisition with DL algorithm for multi-phase breast DCE-MRI compared with original gridding images. We hypothesized that both breast and axilla region can be visualized with higher image quality using DL algorithm. Our results demonstrated that radial+DL images outperformed original radial images for categories in SNR, image sharpness, and artifacts in phantom and in-vivo exam.

Radial acquisition is known to be less sensitive to motion and was used to minimize left-right ghosting artifacts caused by cardiac motion, which was validated in our previous study. However, we observed the reduction of the overall image quality due to the loss of image sharpness and the presence of streak artifacts in the radial images. Radial+DL was extended to account for noise,

ringing artifacts, streak artifacts, and the loss of image sharpness. The results from the phantom studies suggest that the image sharpness and SNR can be improved by using DL algorithm for images with radial angular sampling factor above 0.33 and slice thickness above 1mm. Our in-vivo exam also matched this limit. Additionally, radial+DL achieved improved visual SNR and image sharpness on normal tissue near the axilla region, chest wall, as well as sharper lesion edge. However, three radial+DL images showed over-smoothing in the normal tissue resulted in nondiagnostic images according to the subjective evaluation from one of the readers in our study. This may be related to the fact that the pattern of the tissue heterogeneity is similar to the noise distribution. Therefore, additional validation work is needed to optimize denoising weighted from DL algorithm to match the clinical preference.

A limitation of this preliminary study was the relatively small number of patients demonstrating severe ghosting artifacts in the Cartesian acquisition and most of the Cartesian images provide great image visualization in axilla region without severe ghosting artifacts, whereas radial+DL showed slightly lower scores in category of artifacts in breast and axilla.

In conclusion, this study demonstrates the feasibility to improve the overall image quality by using radial acquisition with DL algorithm for multi-phase breast DCE-MRI. It showed greater improvement in both breast and axilla region compared with gridding images. Although this study was focused on evaluating image quality for a multi-phase strategy, there is great potential for radial methods to improve the performance of dynamic imaging compared with Cartesian MRI. This is due to the greater flexibility in the optimization between acquisition time and angular undersampling using radial MRI, which could provide higher temporal resolution without sacrificing the spatial resolution.

Chapter 3

Time-resolved radial acquisition with compressed sensing reconstruction

This is a non-final version of an article published in final form in Wang, P. N., Velikina, J. V., Strigel, R. M., Henze Bancroft, Holmes, J. H, et al (2021). Comparison of data-driven and general temporal constraints on compressed sensing for breast DCE MRI. *Magnetic Resonance in Medicine*, 85(6), 3071-3084.

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3.1 Abstract

Purpose:

Current breast DCE-MRI strategies provide high sensitivity for cancer detection but are known to be insufficient to fully capture rapidly changing contrast kinetics at high spatial resolution across both breasts. Advanced acquisition and reconstruction strategies aim to improve spatial and temporal resolution and increase specificity for disease characterization. In this work, we evaluate the spatial and temporal fidelity of a modified data-driven low-rank based (MOCCO) compressed sensing reconstruction compared to compressed sensing with temporal total variation (CS-TV) with radial acquisition for high spatial-temporal breast DCE-MRI.

Methods:

Reconstruction performance was characterized using numerical simulations of a golden-angle stack-of-stars breast DCE-MRI acquisition at 5 second temporal resolution. Specifically, MOCCO was compared to CS-TV and conventional SENSE reconstructions. The temporal model for MOCCO was pre-learned over the source data whereas CS-TV was performed using a first-order temporal gradient sparsity transform.

Results:

MOCCO was able to capture rapid lesion kinetics while providing high image quality across a range of optimal regularization values. MOCCO also recovered kinetics in small lesions (1.5 mm) in line-profile analysis and error images, while g-factor maps showed relatively low and constant values with no significant artifacts. CS-TV demonstrated either recovery of high spatial resolution with reduced temporal accuracy using large regularization values, or recovery of rapid lesion kinetics with reduced image quality using low regularization values.

Conclusion:

Simulations demonstrated that MOCCO with radial acquisition provides a robust imaging technique for improving temporal fidelity while maintaining high spatial resolution and image quality in the setting of bilateral breast DCE-MRI.

3.2 Introduction

Dynamic contrast-enhanced (DCE) MRI plays an essential role in the diagnosis and staging of breast cancer³. High spatial resolution is routinely prioritized in clinical diagnostic DCE-MRI protocols to allow detection of small lesions and assessment of lesion morphology⁷⁷. Historically, clinical bilateral breast MRI exams typically used multi-phase fully sampled Cartesian encoding to achieve high spatial resolution (at or below 1 x 1 mm in-plane pixel size) over the large field of

view (FOV) however this allowed only limit temporal resolution (60-120 s)⁷⁶. Studies have showed that a temporal resolution of 90 s or faster was sufficient to allow lesion detection and assessment prior to the occurrence of lesion washout and maximal background parenchymal enhancement that might otherwise obscure these findings in the diagnostic setting^{3,90}. The authors also found washout-like lesion kinetics to be present in approximately 85% of cancers. However, much higher temporal resolution may enable more advanced quantitative kinetic analysis including quantitative pharmacokinetic (PK) modeling of DCE-MRI. PK modeling has shown promise in providing additional non-invasive information for differentiating benign and malignant lesions^{91,92} and assessing response to therapy^{93,94}. It relies on fitting the PK model to DCE-MRI data to extract physiologic parameters, but requires very high temporal resolution (< 10 s) for the entire acquisition series to accurately do so^{95,96}. To achieve such high levels of temporal and spatial resolution, more advanced acquisition and reconstruction approaches are needed.

Within breast DCE-MRI, the term Ultrafast Imaging has come to refer to protocols with temporal frame update times on the order of 7-9 s. Hybrid approaches combining the use of Ultrafast imaging for the first minute after contrast injection followed by four 60-80 s temporal resolution time frames have been suggested to provide improved detection of early contrast enhancement associated with malignancy.^{34,35} However, these approaches reduce the achievable spatial resolution, imaging FOV, or both. Further, these acquisition strategies only allow for semi-quantitative analysis due to the lack of the wash-out information. Another approach is to use an interleaved acquisition to improve both temporal and spatial resolution by alternating between frames of high temporal resolution imaging and high spatial resolution imaging during the contrast passage.³⁶ This approach prevents the sharing of temporal data between individual images to improve temporal fidelity. However, the sequence is sensitive to timing mismatch between

contrast administration and image acquisition due to the relatively short pre-contrast interval. Moreover, it may not allow for a detailed morphologic evaluation in the early enhancement phase due to the interleaved and non-continuous nature of the temporal and spatial resolution.

Undersampled Cartesian acquisitions combined with view-sharing reconstructions have been proposed more recently as another approach to achieve high spatial and temporal resolution^{6,97–100}. In these methods, the undersampled high spatial frequencies are filled in using data from other time points in order to mitigate the loss of spatial resolution. However, these approaches have been shown to suffer from temporal blurring⁴¹ that may compromise evaluation of lesion features and temporal kinetics. Compressed sensing (CS) has been proposed as an alternative reconstruction strategy that exploits the availability of a sparse representation of MR images and relies on randomized k-space sampling with incoherent artifacts to produce images via nonlinear constrained reconstruction⁵⁴. A sparse representation can be considered in the spatial⁵⁴, temporal¹⁰¹, or other parametric domains, with the level of sparsity directly affecting achievable acceleration factors. Several CS-based techniques, such as k-t BLAST/k-t SENSE¹⁰², or k-t FOCUSS⁵⁷, have exploited correlations in both k-space and time to reduce the scan time by factors of 6 - 10^{60,103}. However, it is a challenge for Cartesian acquisitions to achieve higher acceleration factors. Non-Cartesian sampling schemes, such as radial or spiral, present alternative acquisition approaches that are readily amenable to use with CS techniques and can provide higher acceleration factors⁴³.

A 3D stack-of-stars acquisition with a golden-angle radial sampling scheme can provide nearly uniform k-space coverage for any arbitrary number of projections⁷². However, undersampled radial acquisition results in streak artifacts, making it a proxy for random sampling that is required by the CS theory^{54,73,104,105}. A CS reconstruction using a temporal total variation

(TV) sparsifying transform with undersampled golden-angle radial acquisition, referred to as iGRASP¹⁰⁶, has been demonstrated for abdomen²¹ and breast DCE-MRI¹⁰⁷. Kim et. al. demonstrated that high spatial resolution can be achieved at 5 s temporal resolution. However, the demonstrated image quality may not be achievable for different breast imaging protocols because a general transform may not result in the necessary level of sparsity for situations with complex spatial and/or kinetic features. An alternative data-driven low-rank-based method, known as MModel Consistency COndition (MOCCO), uses temporal models estimated from the acquired data itself and thereby has the ability to adapt to varying imaging protocols and to reduce modeling error¹⁰¹. Preliminary results have been presented demonstrating the feasibility of MOCCO with radial acquisition for high spatial resolution breast DCE-MRI with 10 s temporal resolution¹⁰⁸.

Although advanced acquisition and reconstruction techniques, such as view sharing and CS-based algorithms, show promise for providing high spatial and temporal resolution, additional studies are needed to characterize the performance of these approaches under a broader range of imaging conditions such as noise level, lesion size, and contrast kinetics. In practice, comparison and validation studies of new techniques for advanced acquisition and reconstruction in breast DCE-MRI are difficult to perform in patients due to the lack of a known ground truth in patient physiology and low reproducibility due to physiologic variability between patients and exams. To minimize patient dependent variation, retrospective simulations, which generate undersampled data from fully-sampled series, have been used to validate time-resolved CS reconstructions^{109–112}. However, such approaches still lack a known ground truth to evaluate temporal fidelity. To overcome these limitations, breast digital reference objects (DROs) present an alternative strategy since they can be readily programmed to reproducibly simulate tissue features, such as lesion

morphology, physiology, and MR tissue characteristics, without suffering from confounders due to MRI hardware biases or patient related factors such as positioning and motion.

In this work, we evaluate the performance of undersampled stack-of-stars radial acquisition and CS reconstruction using a DRO. Two different reconstruction algorithms, temporal TV and MOCCO, are compared for time-resolved bilateral breast DCE-MR with a goal to achieve high temporal resolution (~ 5 s) while maintaining required spatial resolution. To test the reconstruction performance, we carry out simulations to mimic clinical scenarios and evaluate the reconstruction performance in the spatial and temporal domains as compared with the simulated ground truth.

3.3 Theory

The MRI measurements m of an image series s acquired using an encoding matrix E can be modeled in the matrix form as

$$m = Es \quad [6]$$

In many applications, MR images or image series possess a representation in some basis that has only a relatively small number of non-zero coefficients, i.e., a sparse representation. The sparse representation can be learned and extracted from prior knowledge or assumptions about signal behavior. The CS theory guarantees that under certain conditions on the encoding matrix and sparsity level, the signal s can be recovered from the undersampled data m by solving the following minimization problem

$$\hat{s} = \underset{s}{\operatorname{argmin}} \|Es - m\|_2^2 + \lambda \|\Phi s\|_1 \quad [7]$$

where E is the encoding matrix comprising coil sensitivity values and Fourier encoding terms, Φ is an operator mapping the signal s to the selected representation space (sparsifying transform), and λ is a regularization parameter providing a balance between the data consistency and the sparsity terms. Minimizing the ℓ_1 norm promotes sparsity of the image representation, while simultaneously allowing for outlying values.

For dynamic imaging, different image pixels often have similar temporal enhancement curves. Therefore, an image series can have a sparse representation in a properly chosen basis of temporal waveforms. The compressed sensing with temporal total variation (CS-TV) regularization can be defined as

$$\hat{s} = \underset{s}{\operatorname{argmin}} \|Es - m\|_2^2 + \lambda \|\nabla_t s\|_1 \quad [8]$$

where ∇_t is the first order temporal gradient.

When a low-resolution estimate of an image series is available (e.g. obtained from the fully sampled k -space center in radial imaging), it can be utilized to construct a tailored basis for representation of temporal behavior of different pixels in the image series. MOCCO uses such basis to construct a temporal model of the image series, which provides a sparsifying transform. The image series is then reconstructed as

$$\hat{s} = \underset{s}{\operatorname{argmin}} \|Es - m\|_2^2 + \lambda \|(U_K U_K^* - I_t)s\|_1 \quad [9]$$

where U_K is the matrix constructed from K elements of this basis. In this work, U_K was learned through complex independent component analysis (ICA).¹¹³ The ICA technique assumes that each component is statistically independent from the source signals, which has been shown to be a robust method to identify key components of the perfusion series and remove unwanted image-to-image fluctuations.¹¹⁴

3.4 Methods

3.4.1 Simulation

All simulations were performed using a modified breast DRO based on work by Bancroft et. al.⁸² and generated using MATLAB (Math-Works, Inc., Natick, Massachusetts, USA). The DRO was designed to include both static features derived from a standard T_1 weighted breast MRI with fat saturation as well as simulated enhancing features as shown in **Figure 3.4.1**. Imaging simulation parameters were chosen to replicate a conventional clinical bilateral breast protocol: FOV = 340 mm x 340 mm, in-plane spatial resolution = 0.75 mm x 0.75 mm, slice thickness = 1.4 mm, flip angle (FA) = 30°, TE/TR = 2.4 ms / 4.7 ms, and matrix size = 448 x 448 x 142. Circles with diameters of 1.5 mm, 5 mm, 8 mm, and 10 mm were used to simulate lesions with circumscribed margins. The extended Tofts model^{115,116} was used to simulate lesion signal changes as a function of time similar to what is observed in vivo. An arterial input function curve based on the publicly available dispersion model described by Barboriak et. al. was used to generate the DCE-MRI data.¹¹⁷ To cover a range of different lesion types, seven lesions were simulated based on PK parameters outlined in the ACR BI-RADS Breast Magnetic Resonance Imaging²² including two malignant lesions ($K^{trans} > 0.25 \text{ min}^{-1}$ and $k_{ep} > 1.0 \text{ min}^{-1}$), three benign lesions ($K^{trans} < 0.25 \text{ min}^{-1}$ and $k_{ep} < 1.0 \text{ min}^{-1}$) and two intermediate lesions ($K^{trans} > 0.25 \text{ min}^{-1}$ and $k_{ep} < 1.0 \text{ min}^{-1}$). Simulation parameters for all lesions are listed in **Table 3.4.1**: Simulated pharmacokinetic (PK) parameters for each lesion in the DROs. The spoiled gradient recalled echo (SPGR) signal model was then used to generate signal time curves assuming a field strength of 3 T, T_1 value of breast tissue ($T_{10} = 1444 \text{ ms}$ ¹¹⁸), and contrast agent relaxivity of $r_1 = 4.9 \text{ mM}^{-1}\text{s}^{-1}$ to simulate Gd-BOPTA (gadobenate dimeglumine, Multihance, Bracco, Milan, Italy)¹¹⁹, and imaging flip angle (FA =

30°). Images containing both static and dynamic features were then sampled using the non-uniform fast Fourier transform (NUFFT) to simulate k-space data generated from an undersampled golden-angle radial acquisition consisting of 1024 projections $\times$ 16 coils.

Table 3.4.1: Simulated pharmacokinetic (PK) parameters for each lesion in the DROs

	K^{trans}	V_e	V_p	Simulated Lesion Type
Lesion 1	0.430	0.620	0.06	Intermediate
Lesion 2	0.280	0.633	0.06	Intermediate
Lesion 3	0.321	0.137	0.0153	Malignant
Lesion 4	0.122	0.137	0.0153	Benign
Lesion 5	0.515	0.137	0.0153	Malignant
Lesion 6	0.082	0.137	0.0153	Benign
Lesion 7	0.062	0.137	0.0153	Benign

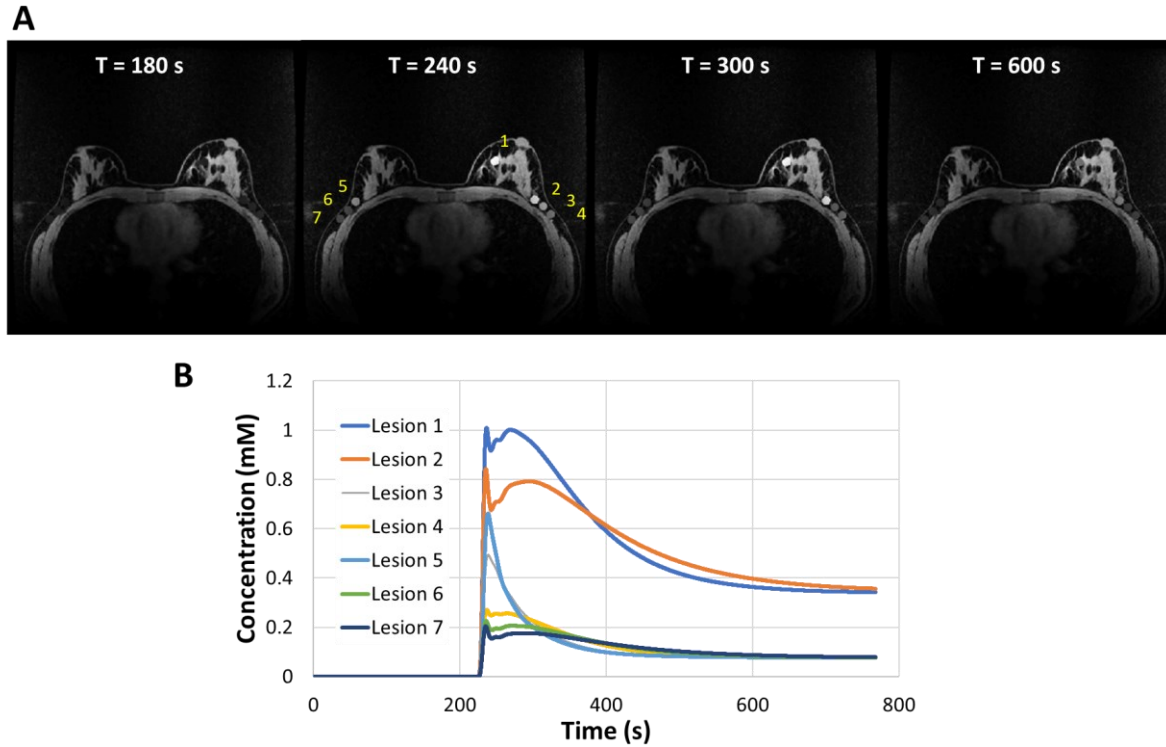


Figure 3.4.1: Simulations using the DRO. (A) Fully-sampled reference images at 180, 240, 300, and 600 s post contrast injection. Simulated lesions were placed in the left central/medial breast (lesion 1) as well as the left (lesions 2, 3, 4) and right axilla and axillary tail breast tissue (lesions 5, 6, 7). (B) Concentration time curves for each lesion generated from the pharmacokinetic models.

3.4.2 Reconstruction

The undersampled radial data were reconstructed at 5 s temporal resolution corresponding to 8 projections per time frame (undersampling factor, $R = 88$) using MOCCO, CS-TV, and iterative SENSE. For the purposes of providing reference images for comparison, fully-sampled radial data consisting of 704 individual projections per time frame were generated by matching the temporal resolution of the undersampled radial images. Next, reference images were reconstructed using iterative SENSE reconstruction from fully sampled k-space data. Both MOCCO and CS-TV

were implemented using iteratively re-weighted least squares minimization¹²⁰. To reconstruct source data without noise added, iterations were performed until the relative norm of the k-space residual was less than a specified tolerance (10^{-9}) or until a maximal number of iterations ($n=250$) was reached. The regularization parameter (λ) for both CS-TV and MOCCO was selected from a wide range of values (from 0.05 to 100) to minimize the normalized root-mean-square-error (nRMSE) between the reconstructed and reference image series. The optimized λ values for MOCCO and CS-TV were then used for all subsequent analysis.

3.4.3 Analysis

Temporal curves from regions-of-interest (ROIs) placed in each lesion were measured across all image series in the time-series to evaluate the temporal fidelity of the reconstruction algorithm. The curves from the reconstructed data were compared to the original signal model. The nRMSE(%) between the reconstructed image x_{recon} and reference image x_{ref} was evaluated either within lesion ROIs or the whole image for all time points to demonstrate the reconstruction accuracy. nRMSE(%) values were reported as the percentage of the mean value of the reference images given in equation [10]

$$nRMSE(\%) = 100 \times \sqrt{\frac{\sum_{t=1}^m \sum_{i=1}^n |x_{recon}(i,t) - x_{ref}(i,t)|^2}{\sum_{t=1}^m \sum_{i=1}^n |x_{ref}(i,t)|^2}} \quad [10]$$

where n is equal to the number of pixels in the region of interest and m is the number of time points. PK modeling was also performed to evaluate the temporal fidelity by assessing the ability to recover the original kinetic parameters from the temporal curves. PK modeling was performed using the ROCKETSHIP toolbox¹²¹ by fitting the extended Tofts model to the time-signal curves

using the Levenberg-Marquardt algorithm. The obtained PK parameters were then compared to the PK parameters used to generate the input time curves for the simulation to determine how well the acquisition and reconstruction could recover the time curves. The input PK parameters are listed in **Table 3.4.1**.

To evaluate the spatial fidelity for varying lesion sizes, signal intensity line profiles were measured across each lesion for both reference and MOCCO images. To evaluate the performance of the MOCCO reconstruction in the presence of noise, Monte-Carlo simulations were performed to measure the noise amplification factor (g-factor, g_R).¹²² One hundred realizations of independent and identically distributed (i.i.d.) complex Gaussian noise with zero mean and standard deviation of 10% and 30% of the mean k-space magnitude were added to the k-space data resulting in 200 unique datasets (100 for each noise level). Each dataset was then reconstructed with MOCCO and SENSE. Iterations were carried out until the residual error fell below 10^{-9} or a maximum number of iterations (set to 100) was reached. Additionally, 100 reconstructions were performed using fully-sampled data with additive i.i.d. Gaussian noise with the standard deviation matched to the undersampled data. The propagation of noise was estimated by calculating g_R :

$$g_R = \frac{\sigma_R}{\sigma_F \sqrt{R}} \quad [11]$$

where σ_R and σ_F are noise variances for the undersampled and fully-sampled reconstructions, respectively, calculated across Monte-Carlo samples. The mean g_R values from ROIs including breast tissue, axilla region, and chest wall were measured across all time frames for all reconstructions. The reconstruction bias was assessed by taking a pixel-wise mean across all Monte-Carlo samples and calculating the normalized image difference between the undersampled and the fully sampled images.

3.5 Results

Example signal intensity time curves are shown for several simulated lesions with varying enhancement patterns following iterative SENSE, CS-TV, and MOCCO reconstructions in **Figure 3.5.1**. Note that the displayed time interval ranges from 150 s to 400 s to allow better visualization over the points of greatest change. The complete time-curves are shown in **Figure 3.5.2**. Both the CS-TV and MOCCO approaches generated temporal signal curves that were free of signal oscillations compared to iterative SENSE. The MOCCO technique was found to better represent the lesion temporal enhancement kinetics, such as rapid wash-in and wash-out in lesion 5 (**Figure 3.5.1**, H) as well as minor deviations within all simulated lesions in the difference image (**Figure 3.5.3**, I). The choice of regularization parameter in the CS-TV approach allows the user to optimize between image quality and temporal characteristics. A smaller regularization parameter ($\lambda = 0.1$) provides a relatively accurate depiction of the lesion signal intensity (**Figure 3.5.1**, A-D) but leads to larger residual error in the background breast tissue which is easily visible in the difference image (**Figure 3.5.3**, G). However the larger regularization parameter ($\lambda = 2$) displays overall similar image quality to the reference image (**Figure 3.5.3**, D) but induces temporal blurring in the measured signal time curves from the simulated lesions (**Figure 3.5.1**, A-D).

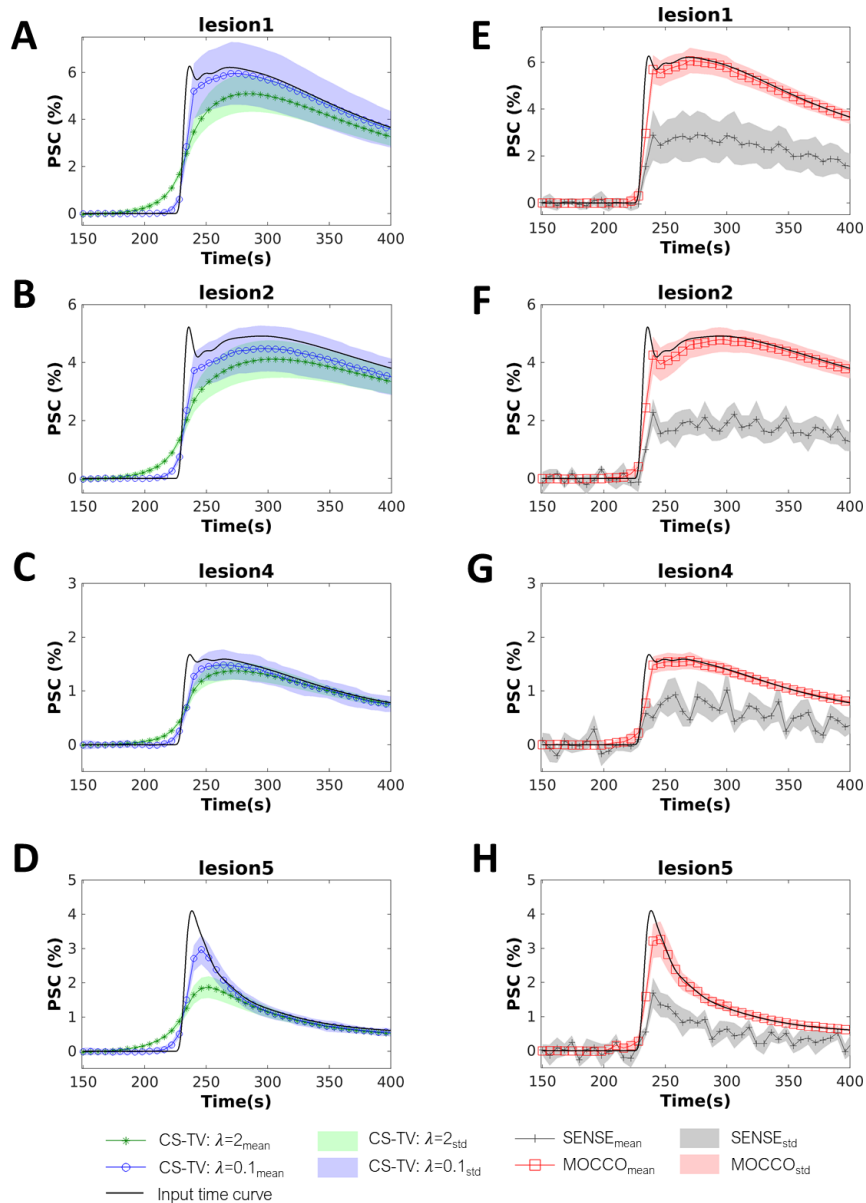


Figure 3.5.1: Simulated contrast agent uptake curves (displayed for a subset of time from 150 to 400 s). Mean percent signal change measured for four 8 mm lesions with varying pharmacokinetics (lesions 1, 2, 4 and 5 as defined in **Figure 3.4.1**) reconstructed using CS-TV with $\lambda = 0.1$ (A-D, blue circles), CS-TV with $\lambda = 2$ (A-D, green stars), MOCCO (E-F, red squares) and iterative SENSE (E-F, gray pluses). Standard deviations are shown with banded areas. The input time curves (“true”) used to generate the source data are plotted with dark black lines in all frames.

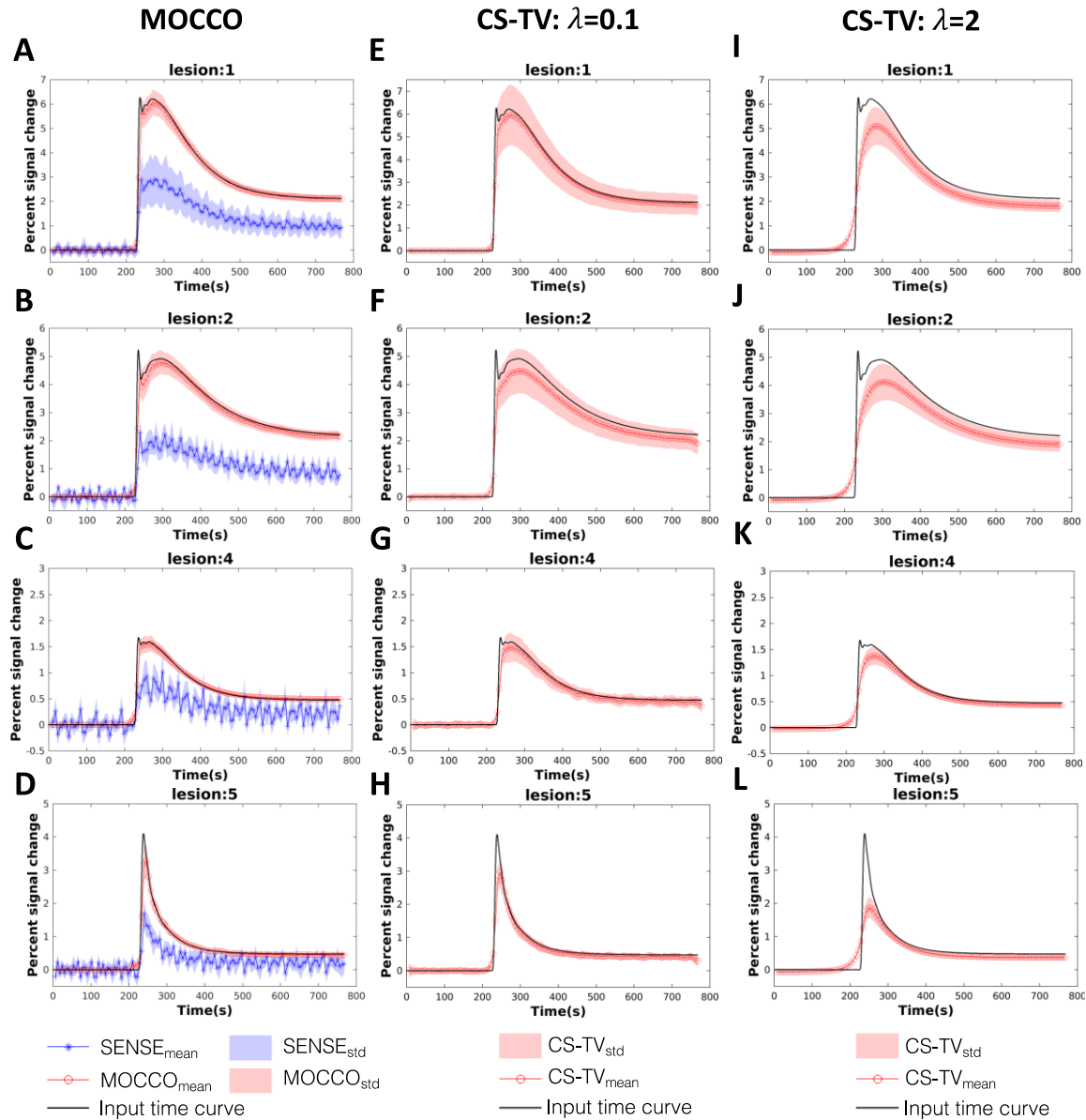


Figure 3.5.2: Simulated contrast agent uptake curves plotted for the time interval from 0 s to 720 s, including pre-contrast and post-contrast wash-out phases. Mean percent signal change measured in four uniquely enhancing 8 mm lesions (lesions 1, 2, 4 and 5 as defined in **Figure 3.4.1**) reconstructed using MOCCO (A-D, red circles), CS-TV with $\lambda = 0.1$ (E-H, red circles), CS-TV with $\lambda = 2$ (I-L, red circles) and iterative SENSE (A-D, blue stars). Standard deviations are shown with banded areas. The input time curves used to generate the source data are plotted with black lines in all frames.

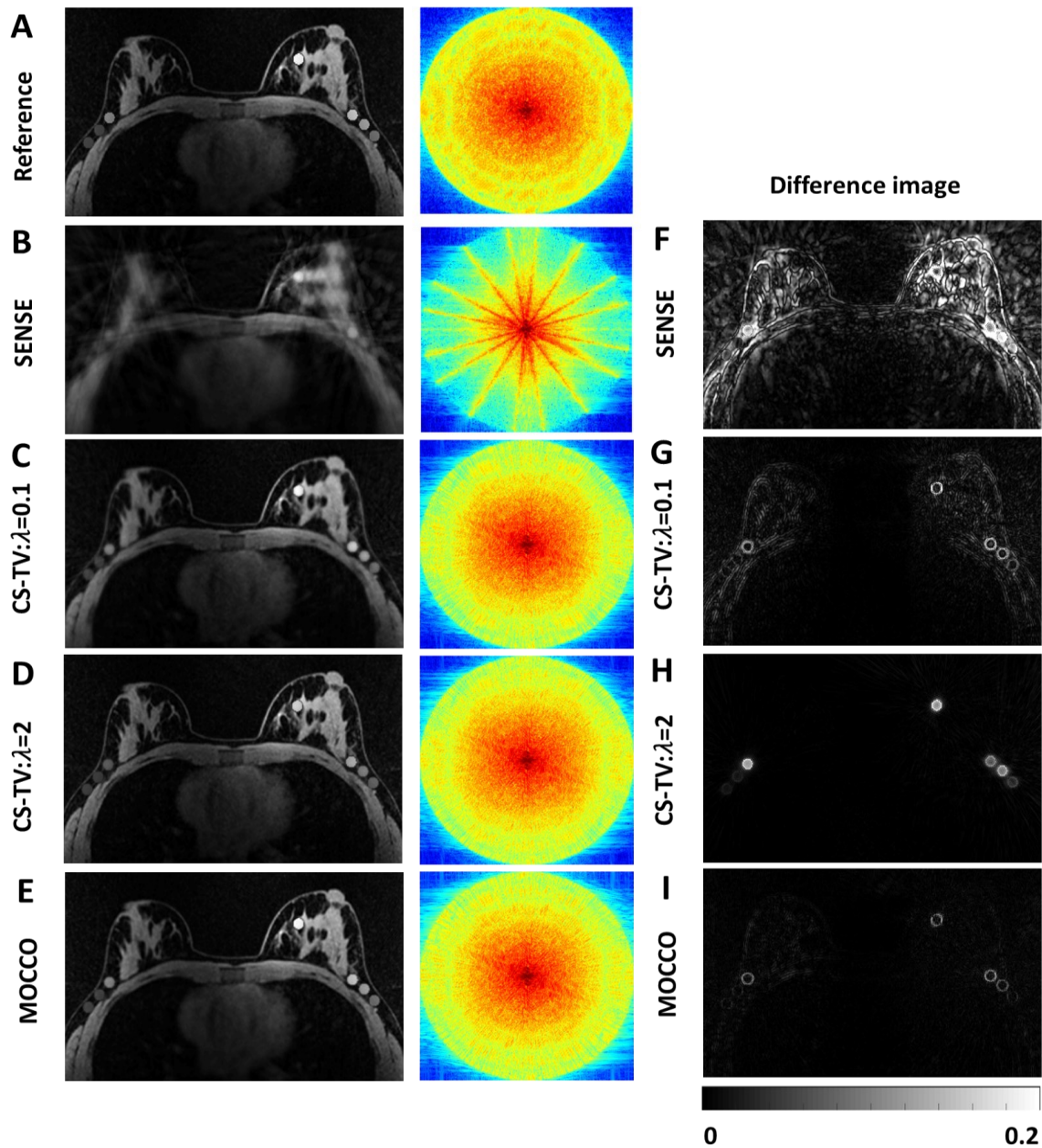


Figure 3.5.3: Reference image (A), reconstructed images (B-E), and corresponding difference images (F-I) all shown for 5 s temporal resolution at time = 240 s. Difference images were measured by subtracting the reconstructed images from the reference image and normalized to the maximum value of the reference image. Log scale k-space plots show how well high and low spatial frequency data were recovered.

Plots of nRMSE(%) over the entire FOV for MOCCO and CS-TV with different values for λ are shown in **Figure 3.5.4**. The corresponding reconstructed images are shown in **Figure 3.5.5**. Although the nRMSE(%) measured over the full FOV is too general to provide a precise metric for both spatial and temporal quality assessment, the plots provide a quantitative measure for the

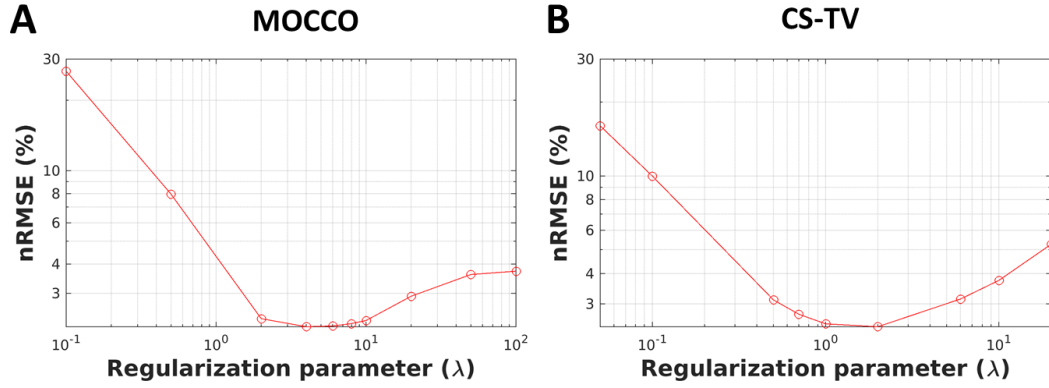


Figure 3.5.4: Plot of nRMSE(%) from the reconstructed images using MOCCO (A) and CS-TV (B) as a function of the regularization parameter (λ) to indicate the reconstruction accuracy.

overall errors. Both methods decreased the nRMSE(%) when increasing λ from 0-10 for MOCCO and λ from 0-2 for CS-TV. The curves of the nRMSE(%) for MOCCO show a relatively stable region between $\lambda = 5$ -10, whereas CS-TV shows a narrow range of λ over which nRMSE(%) has been minimized. For larger regularization parameters ($\lambda > 20$ for MOCCO and $\lambda > 6$ for CS-TV), the reconstruction was strongly dominated by the minimization of the temporal constraint, so the reconstructed images were observed to be overly smoothed and resulted in increased nRMSE(%). The images can be found in **Figure 3.5.5**, B, for $\lambda = 100$, and **Figure 3.5.5**, C, for $\lambda = 20$.

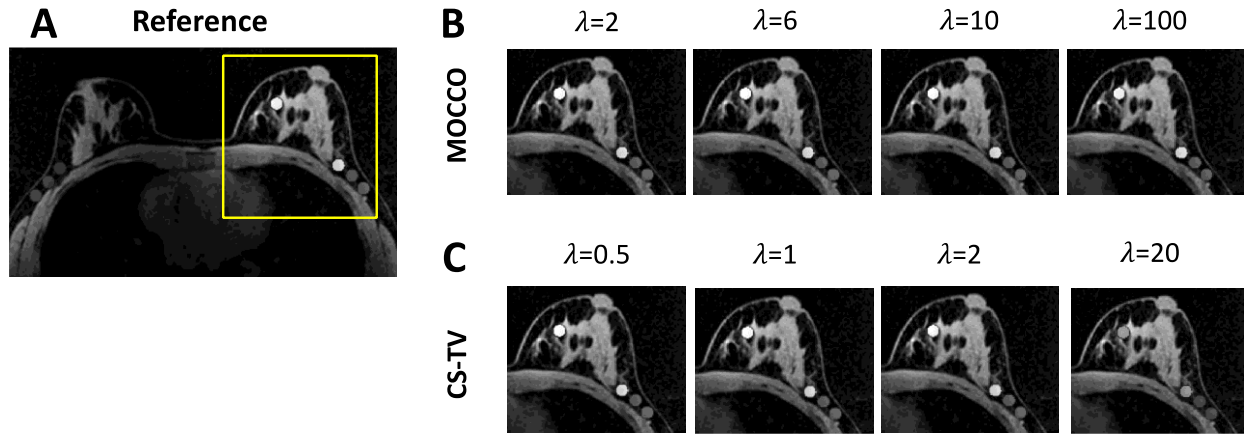


Figure 3.5.5: Images reconstructed from the fully sampled reference data (A), MOCCO (B), and CS-TV (C) with different values for the regularization parameter (λ). Both methods showed improved image quality when increasing λ from 0-10 for MOCCO and λ from 0-2 for CS-TV. For larger λ ($\lambda > 20$ for MOCCO and $\lambda > 6$ for CS-TV), the reconstructed images were observed to be overly smoothed and resulted in lower intensity due to over constrained reconstruction.

Results for PK parameters obtained from MOCCO ($\lambda = 10$), CS-TV ($\lambda = 0.1$ and $\lambda = 2$), and fully-sampled reference images for 8 mm lesion size are shown in **Table 3.5.1**. Percent error (%) of PK parameters fit from the signal-time curves generated from 8 mm lesions in MOCCO, CS-TV: $\lambda = 0.1$, CS-TV: $\lambda = 2$, and the fully-sampled reference images shown in **Figure 3.5.1**. Fully-sampled reference images with 5 s temporal resolution showed overall accurate measurements in K^{trans} and V_e ($< 2\%$) in most lesions. Lesion 3 and 5 with the most rapid temporal enhancement showed underestimation in K^{trans} , which demonstrated that this kind of sharp peak is difficult to recover by 5 s temporal resolution. Larger overall errors were also found for V_p , which matched the results in Litjens et al¹²³ that suggested 5 s temporal resolution may not be sufficient to provide reliable V_p measurements. Both MOCCO and CS-TV: $\lambda = 0.1$ showed promising results in K^{trans} and V_e (within 10% error range). However, underestimation was observed for both methods in lesions with the most rapid temporal enhancement (lesion 3 and 5). CS-TV: $\lambda = 2$

showed overall higher error in K^{trans} that was likely due to temporal over-smoothing of the wash-in slope. Larger overall errors were found for V_p in all reconstructions.

Table 3.5.1: Percent error (%) of PK parameters from different reconstructions

Lesion #		1	2	3	4	5	6	7
Reference	K^{trans} (%)	0.18	0.24	-3.31	1.88	-7.46	1.90	1.95
	V_e (%)	-1.23	-1.55	-0.06	-0.03	0.70	-0.44	-0.18
	V_p (%)	-27.34	-23.59	-34.58	-29.00	-34.50	-24.70	-23.31
MOCCO	K^{trans} (%)	4.31	4.44	-17.54	-3.33	-30.96	-1.25	1.78
	V_e (%)	3.96	2.16	1.41	4.42	-0.38	3.65	1.01
	V_p (%)	-65.59	-60.88	-34.64	-34.64	-34.64	-34.64	-34.57
CS-TV $\lambda = 0.1$	K^{trans} (%)	-1.21	-2.11	-31.99	-11.88	-49.21	-8.59	-4.50
	V_e (%)	2.11	-1.20	-1.61	0.07	-5.95	-1.92	-0.73
	V_p (%)	-70.80	-65.65	-34.64	-34.64	-34.64	-34.64	-34.58
CS-TV $\lambda = 2$	K^{trans} (%)	-16.84	-11.93	-44.60	-19.91	-65.24	-16.98	-11.18
	V_e (%)	-4.82	-5.72	-5.51	-1.60	-13.63	-3.22	-1.57
	V_p (%)	-70.21	-69.92	-34.64	-34.64	-28.65	-34.64	-34.62

In order to evaluate the reconstruction accuracy of the MOCCO approach for different lesion sizes, temporal curves and the corresponding line profiles were created and are plotted with lesion sizes of 1.5, 5, 8 and 10 mm in **Figure 3.5.6** and **Figure 3.5.7**. No significant error was

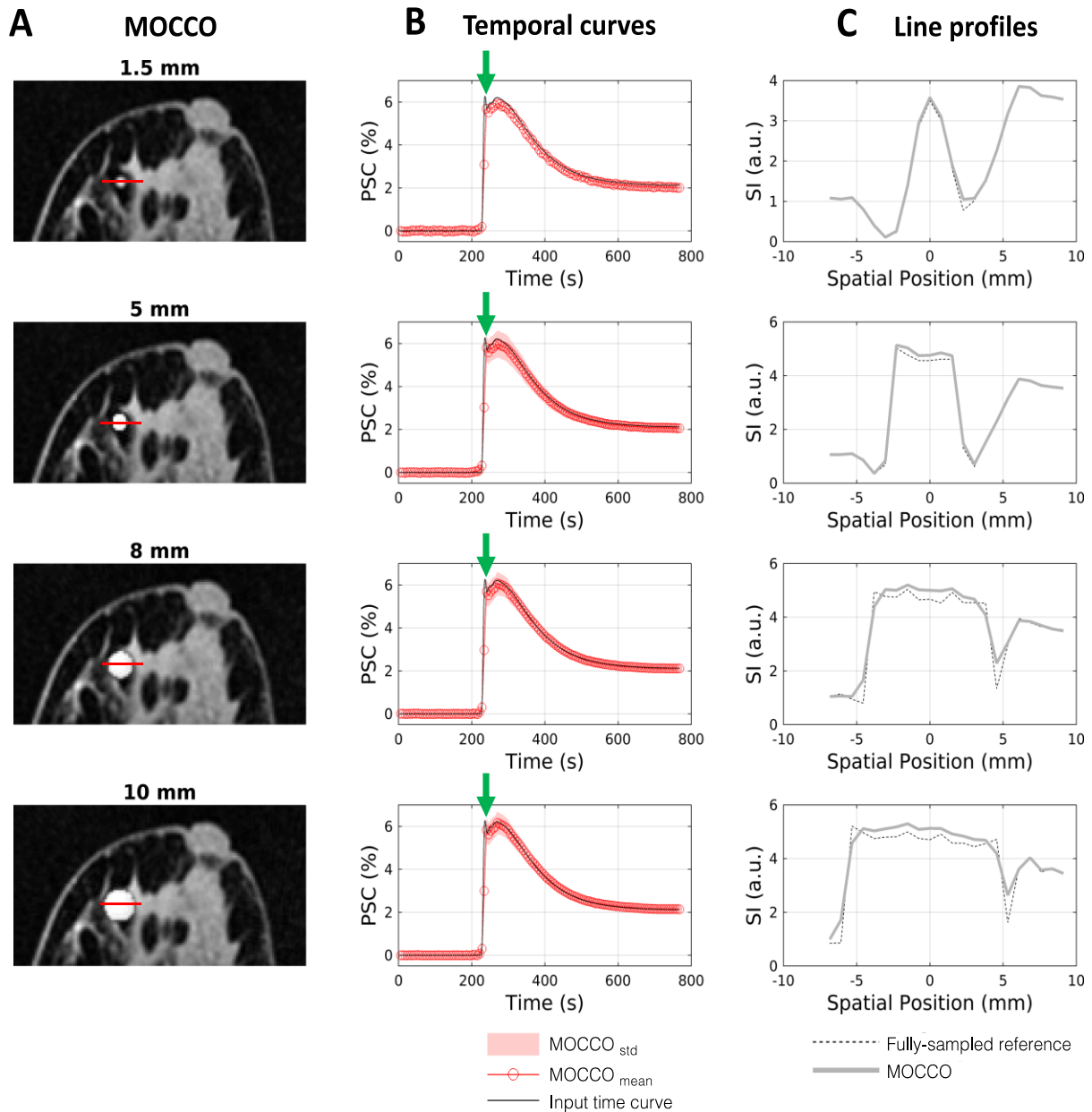


Figure 3.5.6: Performance of spatial and temporal fidelity for lesion 1, which has general curve shape but highest percent signal change (PSC) compared with other lesions. Example images with lesion sizes of 1.5 mm to 10 mm for matched representative time frames (A). Corresponding percent signal time curves compared to the input time curves (B). The line profiles (C) through the center of the lesion (red line in (A)) plotted for MOCCO-reconstructed (solid line) and fully-sampled reference images (dashed line) corresponding to $T = 240$ s (green arrows in B).

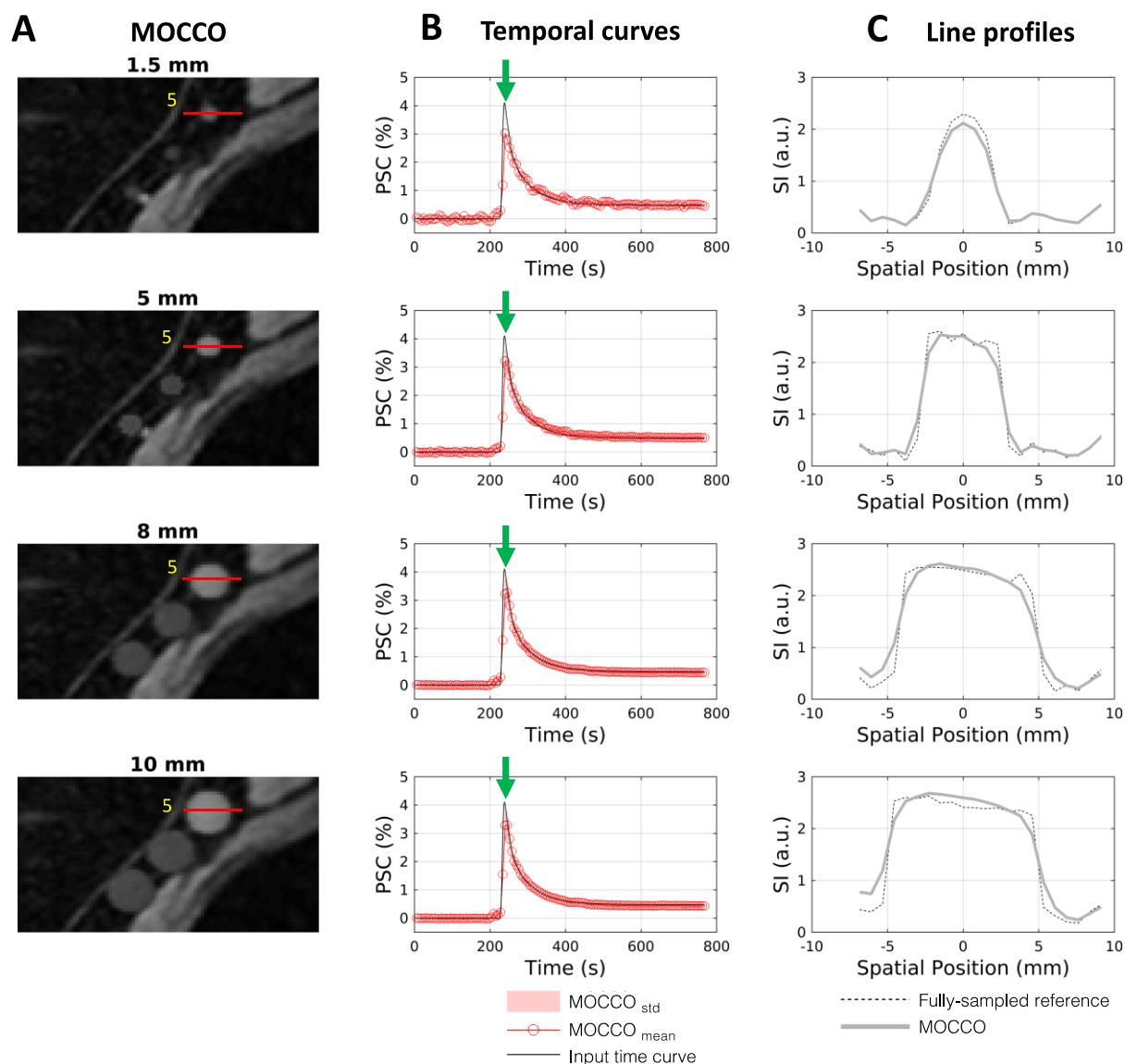


Figure 3.5.7: Evaluation of spatial and temporal fidelity for a lesion with sharper wash-in and wash-out contrast kinetics. Zoomed-in region at the right side of the axilla with lesions 5 - 7 is shown for MOCCO (A) at $T = 240$ s. Percent signal time curves evaluated for lesion 5 show modest temporal blurring at small lesion sizes (1.5 mm) (B). Line profiles shown in (C) were measured horizontally through lesion 5 as indicated by red lines in (A). The dash line profile is from the fully-sampled reference images. The solid gray profile is from the MOCCO image. Note underestimation of the signal intensity at the center of the lesion although the edges are well preserved.

observed in the temporal curves as a function of the decreasing lesion size. The corresponding line profiles are well matched to those measured in the fully-sampled reference images. The nRMSE(%) of all lesion time curves are summarized in **Table 3.5.2** showing that the temporal error is increased for small lesion sizes (1.5 and 5 mm) with nRMSE(%) around 13-20%. For lesions larger than 8 mm, the nRMSE(%) was found to be $\leq 13\%$ for most lesion types with the exception of lesions 3 and 5 that simulated very rapid wash-in and wash-out characteristics.

Table 3.5.2: nRMSE(%) for CS-TV: $\lambda=0.1$, CS-TV: $\lambda=2$ and MOCCO with varying lesion sizes ranging between 1.5 - 10 mm with no additional noise added.

	CS-TV		MOCCO			
	Regularization parameter (λ)		Lesion size (mm)			
Lesion #	0.1	2	10	8	5	1.5
1	22.97	22.79	11.11	11.24	12.77	8.40
2	20.03	22.20	11.69	11.95	13.08	11.84
3	22.81	28.72	16.94	17.00	19.67	17.47
4	22.15	19.21	12.78	12.77	14.31	11.64
5	27.27	40.58	21.28	21.46	25.00	24.01
6	26.52	19.29	11.95	12.16	14.04	13.77
7	28.17	17.60	11.42	12.04	14.38	14.43

Results for PK parameters obtained from fully-sampled reference images and MOCCO for varying lesion sizes are shown in **Table 3.5.3** and **Table 3.5.4**, respectively. In **Table 3.5.3**, The fully-sampled reference images allowed recovery of K^{trans} and V_e across lesion sizes larger than 5 mm (within 5% error range). However, underestimation of K^{trans} and V_e was observed in the 1.5 mm lesion (within 10% error range). Although, larger overall error were found for V_p , the error

range was consistent with the fully-sampled reference results in **Table 3.5.1** across different lesion sizes. Only lesions with 1.5 mm showed increased error ($\sim 5\%$ increased).

Table 3.5.3: Percent error (%) of the PK parameters fit from the signal-time curves generated from fully-sampled reference images.

Lesion size	Lesion #	1	2	3	4	5	6	7
1.5 mm	K^{trans} (%)	-3.10	-5.58	-8.42	-4.87	-13.77	-4.35	-3.55
	V_e (%)	-4.45	-7.30	-5.23	-6.36	-5.49	-5.93	-5.76
	V_p (%)	-29.62	-27.87	-34.57	-32.64	-34.63	-29.07	-27.68
5 mm	K^{trans} (%)	1.34	0.87	-1.85	1.14	-6.27	0.99	2.85
	V_e (%)	-0.10	-0.95	1.07	0.24	1.80	-0.33	0.75
	V_p (%)	-26.48	-23.03	-34.59	-27.13	-34.52	-25.21	-22.55
8 mm	K^{trans} (%)	0.18	0.24	-3.31	1.88	-7.46	1.90	1.95
	V_e (%)	-1.23	-1.55	-0.06	-0.03	0.70	-0.44	-0.18
	V_p (%)	-27.34	-23.59	-34.58	-29.00	-34.50	-24.70	-23.31
10 mm	K^{trans} (%)	0.83	0.39	-2.41	1.63	-7.16	1.91	1.76
	V_e (%)	-0.67	-1.41	-0.12	0.23	0.96	0.00	-0.51
	V_p (%)	-27.34	-23.57	-34.59	-28.63	-34.64	-24.74	-21.08

In **Table 3.5.4**, Lesion size simulations showed consistent results across all three PK parameters for MOCCO reconstruction. MOCCO reconstruction resulted in errors of less than 6% in K^{trans} and V_e across the lesion sizes greater than 5mm, which was 1% higher than the corresponding results from fully-sampled reference images. Both K^{trans} and V_e from the 1.5 mm lesion showed similar errors to those from the fully-sampled reference (within 10% error range). Lesions with the fastest wash-in and wash-out (Lesions 3 and 5) showed underestimation of K^{trans} , consistent with incomplete recovery of the wash-in slope. The error in K^{trans} was also found to increase with decreasing lesion size. Larger overall errors were found for V_p in all lesion sizes.

Table 3.5.4: Percent error (%) of PK parameters fit from the signal-time curves generated from MOCCO: $\lambda = 10$.

Lesion size	Lesion #	1	2	3	4	5	6	7
1.5 mm	K^{trans} (%)	3.70	0.07	-27.80	-9.61	-43.66	-0.50	3.86
	V_e (%)	1.09	-8.31	-2.58	-0.46	0.48	-9.75	-12.40
	V_p (%)	-63.34	-40.06	-34.64	-34.64	-34.64	-34.64	-34.62
5 mm	K^{trans} (%)	4.58	4.33	-25.08	-7.00	-38.55	5.25	11.01
	V_e (%)	2.38	-4.77	2.33	5.01	4.85	-2.32	-8.32
	V_p (%)	-63.12	-43.03	-34.64	-34.64	-34.64	-33.61	-34.58
8 mm	K^{trans} (%)	4.31	4.44	-17.54	-3.33	-30.96	-1.25	1.78
	V_e (%)	3.96	2.16	1.41	4.42	-0.38	3.65	1.01
	V_p (%)	-65.59	-60.88	-34.64	-34.64	-34.64	-34.64	-34.57
10 mm	K^{trans} (%)	5.78	4.84	-16.91	-2.42	-29.94	0.47	2.60
	V_e (%)	5.44	1.99	1.62	4.81	-0.31	4.64	0.85
	V_p (%)	-64.69	-60.50	-34.64	-34.64	-34.64	-34.64	-34.64

Figure 3.5.8 shows the reconstructed images when different levels of noise were added to the projection source data for the iterative SENSE (**Figure 3.5.8, A**) and MOCCO reconstructions (**Figure 3.5.8, B**). For better visualization of the reconstruction error, corresponding error images are also shown in **Figure 3.5.9** on the same scale. MOCCO reconstructed images were visually well matched to the reference image with only small normalized image difference (< 0.22) located at the lesion edges (**Figure 3.5.9, C and D**). In contrast, iterative SENSE was not able to preserve the high spatial frequency information due to the noise in the source data (**Figure 3.5.9, A and B**) (with maximum normalized image difference < 0.65). The temporal curves obtained from MOCCO with noise levels of 10% and

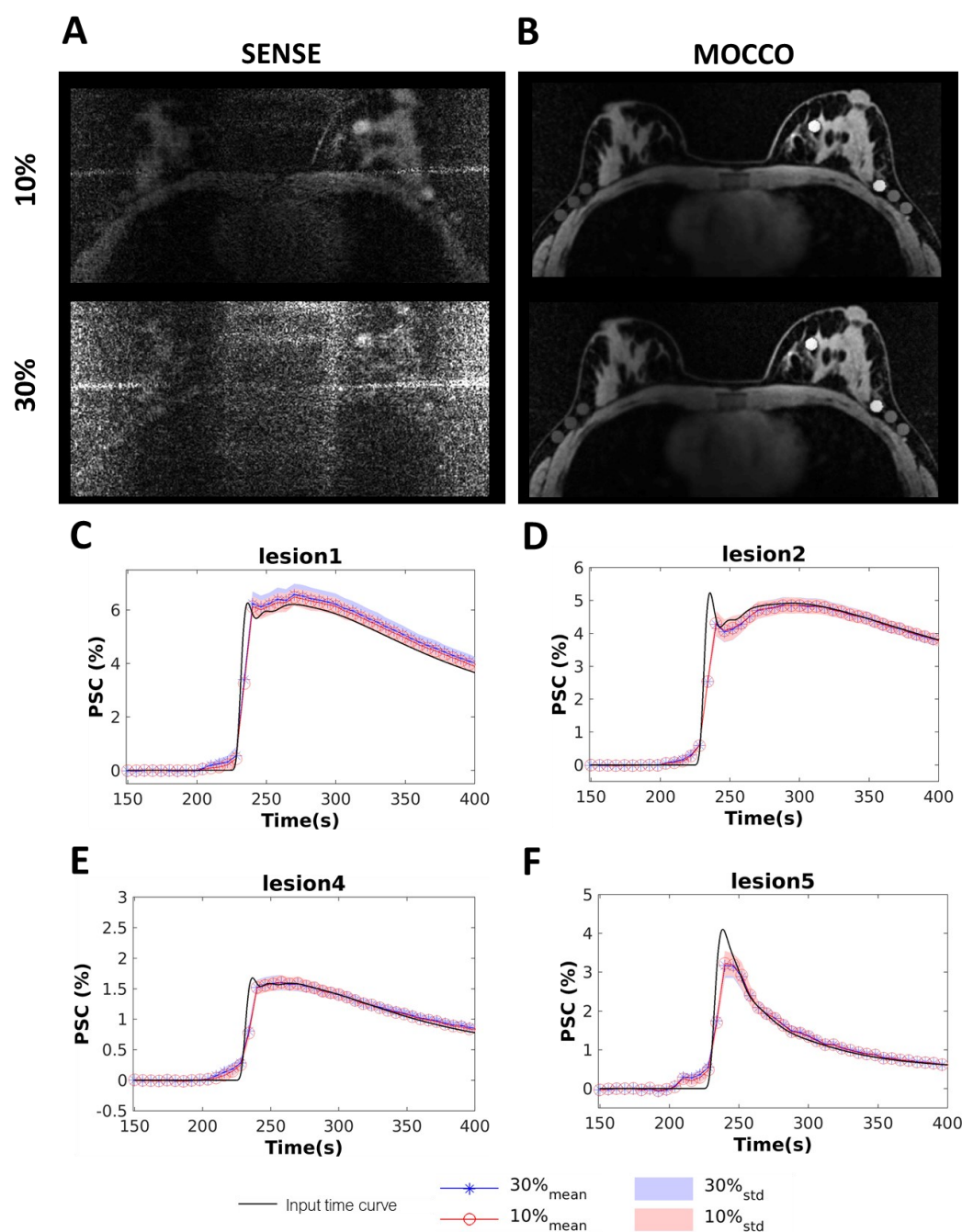


Figure 3.5.8: SENSE (A) and MOCCO (B) images with additive Gaussian noise equal to 10% and 30% of the mean k-space magnitude at time = 300 s. The corresponding mean percent signal change time curves of lesion 1, 2, 4 and 5 for MOCCO (C-F) with 10% (red circles) and 30% (blue stars) additive noise. Standard deviations are represented by the banded areas. The input time curve is plotted with dark black lines.

30% of the mean signal values (**Figure 3.5.8**, C-F) were found to both closely match the curves from the ground truth.

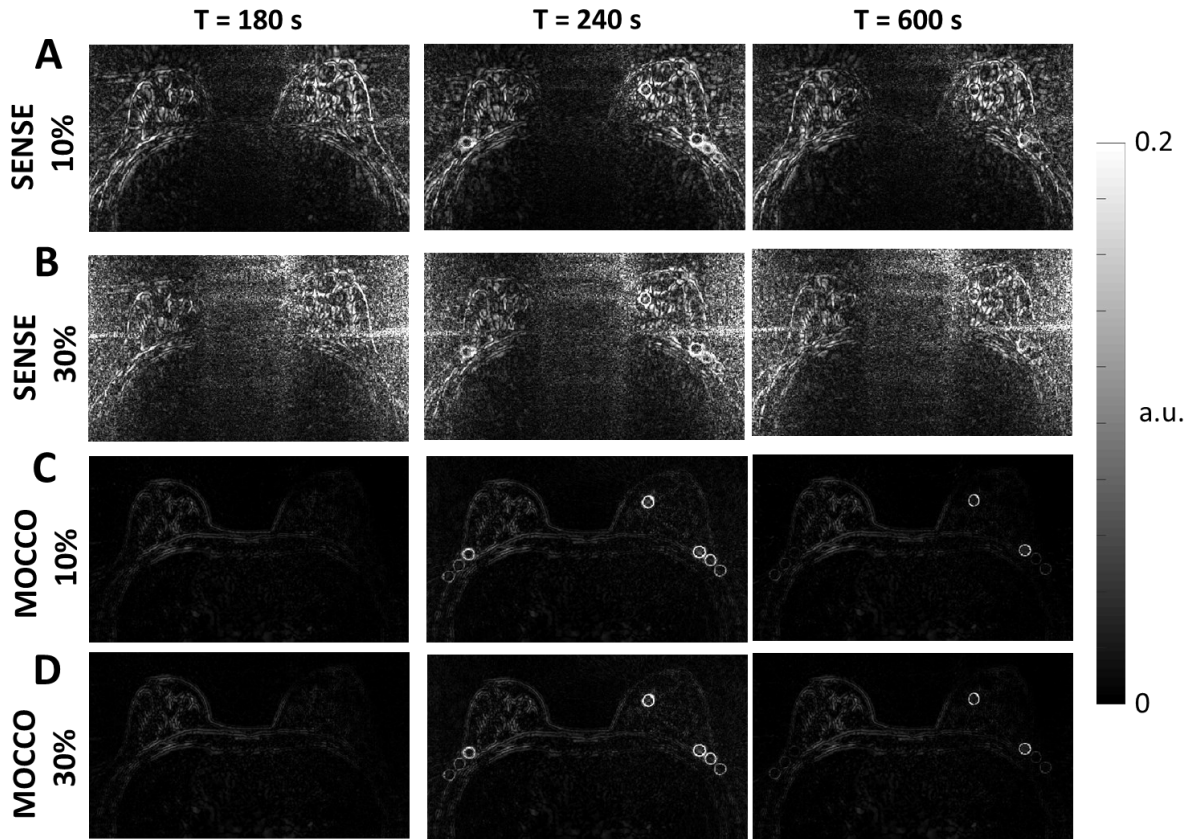


Figure 3.5.9: Error images measured by subtracting the reference mean images from reconstructed mean images. The mean images were averaged over the 100 Monte-Carlo iterations at $t = 180$, 240, and 600 s. Error images for SENSE with 10% (A) and 30% (B) noise level showed increased error with increasing noise level. Error images for MOCCO with 10% (C) and 30% noise level (D) demonstrated reduced overall error compared to SENSE.

Quantitative g -factor maps for iterative SENSE and MOCCO reconstructions with 5 s temporal resolution are shown in **Figure 3.5.10**. The mean g_R values of the g -factor maps for iterative SENSE (**Figure 3.5.10**, A and B) are 1.93 and 6.28 for the 10% and 30% noise levels, respectively. MOCCO was found to greatly reduce the mean g_R value to 0.06 and 0.08 for the 10%

and 30% noise levels and provide less reconstruction error. The overall performance of MOCCO was found to be consistent with increasing the noise levels from 10% to 30% (Figure 3.5.10, C and D).

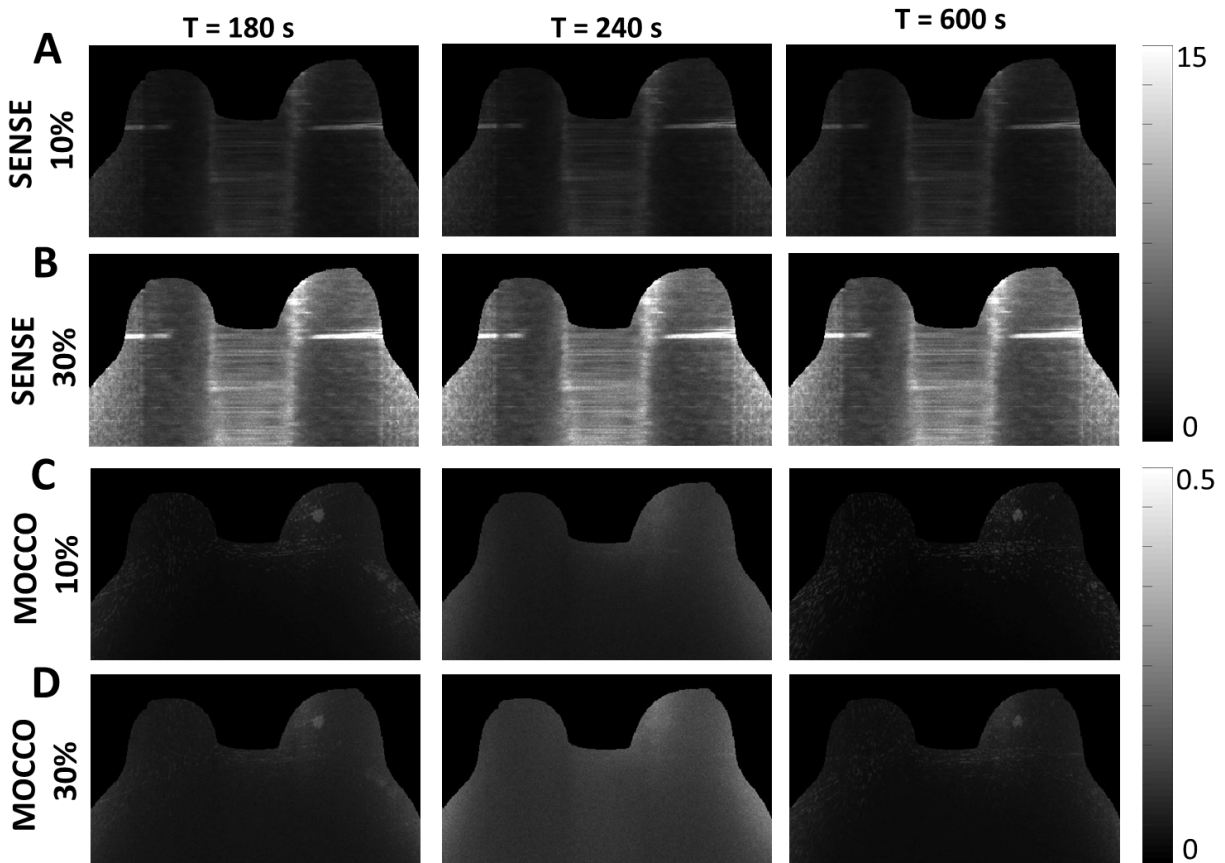


Figure 3.5.10: Performance in the presence of noise with an undersampling factor $R = 88$ (5 s temporal resolution). SENSE reconstruction g-factor maps with 10% (A) 30% (B) noise level at $t = 180, 240$, and 600 s . MOCCO reconstruction g-factor maps with 10% (C) and 30% (D) noise level.

3.6 Discussion

In this work, we present a framework to achieve high spatial and temporal resolution breast DCE-MRI through a combination of golden-angle stack-of-stars radial acquisition with a data-driven low-rank based CS reconstruction (MOCCO). Numerical simulations are employed to evaluate the reconstruction accuracy under representative imaging conditions to mimic those found in vivo. The MOCCO approach is compared to another CS-based reconstruction algorithm that uses temporal total variation as a sparsity transform (CS-TV) as well as the more conventional iterative SENSE technique.

We have demonstrated that by applying basis functions generated using ICA to construct a signal-specific temporal model, reconstruction performance was improved as compared to the use of a generic sparsity transform in the form of the temporal TV approach. The TV algorithm can attain high frequency detail and ensure the same visually perceived image sharpness at larger λ , but at the expense of over smoothing the wash-in and wash-out time-signal slope when rapid temporal changes occurred. On the contrary, MOCCO provided a relatively robust balance between image quality and temporal fidelity across a wide range of λ indicating that MOCCO is less sensitive to the selection of a specific value for λ . This can be explained by the fact that the temporal TV approach efficiently sparsifies those time curves that have small first derivatives. Therefore, if the actual time course does not meet this assumption by satisfying this model, the reconstruction result may exhibit a bias that manifests in the form of smoothing of the temporal behavior. In contrast, learning the reconstruction basis functions from the source data using ICA analysis during the MOCCO reconstruction allows for the accommodation of more complex temporal behavior patterns including rapid signal changes.

Prior work has demonstrated the potential for time-resolved breast DCE to improve diagnostic specificity by evaluating correlations of morphologic features and contrast enhancement patterns for lesions ~ 1 cm^{124,125}. However, conventional DCE-MRI protocols are challenged in the need to encode large FOVs at both high spatial and temporal resolutions. In this study, MOCCO achieved 5 s temporal resolution with highly undersampled data while still providing high image quality for bilateral axial imaging with less than 1 mm in-plane voxel size, which meets the minimum requirement for spatial resolution by the American College of Radiology for breast DCE-MRI²².

Although iterative SENSE reconstruction for radial acquisition is becoming more common, a critical challenge for this algorithm is the tradeoff between signal-to-noise ratio (SNR) and the level of artifacts in the reconstructed images¹²⁶. Literature has shown that radial sampling combined with iterative SENSE can achieve high image quality with acceleration factors between 4-12^{127,128} but noise amplification has been observed at higher undersampling factors where greater numbers of iterations are typically needed⁴⁸. In our simulation results, iterative SENSE showed significantly higher divergence from the fully-sampled reference images at higher noise levels with $R = 88$ (**Figure 3.5.9, B**). This is in agreement with prior studies looking at the convergence behavior of iterative SENSE in the presence of low SNR and undersampled data¹²⁶. The MOCCO technique was found to be less impacted by noise in the source data and provided better reconstruction accuracy as demonstrated in the Monte-Carlo simulations. Further, the MOCCO approach showed decreased g-factors ($g_R < 0.1$) compared with iterative SENSE ($g_R = 6.28$) for the larger noise level indicating limited impact of causing spatially varying noise amplitudes^{48,122}.

The breast DRO used for this study was generated using in vivo T₁ breast MRI images followed by introducing artificial tumor mimicking objects with lesion specific contrast kinetics

based on a user defined pharmacokinetic model⁸². MR parameters for the simulation were chosen to match those from the in vivo exam to ensure that the simulated k-space data were reflective of typical in vivo data. Such a strategy has several advantages over other simulation techniques. The digital phantom provides the advantage of readily allowing simulations to model a variety of different lesion specific spatial and temporal behaviors that would be challenging to replicate using physical phantoms¹²⁹. Using this numerical phantom approach, the performance of various reconstruction algorithms can be evaluated by measuring the errors in morphologic and dynamic features in reconstructed images including through directly comparing them with the ground truth used to generate the simulation. Further, PK modeling can be performed to determine how well the input PK parameters can be recovered following the simulated data acquisition and reconstruction. Examples are presented in **Table 3.5.1.**, **Table 3.5.3** and **Table 3.5.4**. It should be noted that breast DCE-MRI presents a challenge in terms of validating novel imaging techniques due to the long clearance time of contrast agent precluding comparisons with multiple injections. Reproducibility is a further confounder due to time dependent physiological variability as well as subject motion. Digital simulations provide a critical step in the overall validation process by eliminating non-reproducible subject dependent physiological confounders for the purposes of comparisons between imaging techniques.

While the use of a realistic DRO has several advantages as a platform for initial development and validation work, the current simulation is still relatively simplistic in comparison to the complexity of the in vivo environment. Future work is needed to assess performance of the reconstruction algorithms in these more complex imaging environments such as heterogeneous lesion morphologies and enhancement patterns, non-mass enhancement, and the degree and distribution of background breast parenchymal enhancement. In this work we have assumed the

data are free of motion artifacts; however, further validation is needed to characterize these algorithms in the presence of subject motion. Further, this work has aimed to better characterize the temporal fidelity of two promising CS-based approaches for breast imaging and further evaluation is needed to test the robustness and limitations of PK modeling approaches in vivo using this understanding.

3.7 Conclusion

In this paper, we compared both spatial and temporal performance of iterative SENSE, CS-TV, and MOCCO for breast DCE-MRI. We demonstrated the use of these advanced reconstructions with stack-of-stars radial acquisition for breast DCE-MRI to allow for an effective temporal resolution of 5 s. Achieving such a temporal resolution using modern MRI scanners across the large imaging volumes and slice coverage typically used in MR breast imaging allows for the acquisition of only 8 unique radial projections angles per time frame. With such high angular undersampling factors, significant streaking artifacts were observed in the iterative SENSE reconstruction. CS-TV provided the best suppression of background artifacts but showed compromised performance in terms of recovering the original temporal kinetics of the lesions. The MOCCO technique demonstrated improved temporal fidelity when matching spatial resolution and coverage from routine clinical protocols as compared with CS-TV. The results from this study demonstrate that MOCCO is less sensitive to the selection of the regularization parameter for very high undersampling factors ($=88$).

Chapter 4

Quantitative DCE-MRI using pharmacokinetic modeling

A portion of this chapter is submitted as a full paper in journal of Medical Physics in Wang, P. N., Velikina, J. V., Strigel, R. M., Henze Bancroft, Holmes, J. H, et al. The influence of radial acquisition and data-driven compressed sensing reconstruction on quantitative pharmacokinetic parameter measurements in breast DCE MRI

4.1 Abstract

Purpose:

Radial acquisition with MOCCO reconstruction has been proposed for high spatial and temporal resolution breast DCE imaging. In this work, we characterize MOCCO across a wide range of temporal contrast enhancement in a digital reference object (DRO).

Methods:

Time-resolved radial data was simulated using a DRO to model a bi-lateral axial acquisition using a 16-channel breast coil. Homogeneously enhancing round lesions were simulated with different pharmacokinetic (PK) parameters to generate slow, intermediate, and fast changing lesion kinetics. The undersampled data were reconstructed at 5 s temporal resolution, corresponding to 8 projections/frame (undersampling factor $R=88$) using the data-driven low-rank temporal model for MOCCO and more conventional low-rank reconstruction (PCB). The impact of the selected temporal model for MOCCO and PCB on PK measurements was also performed and compared

with the ground truth values. Monte-Carlo simulations were used to evaluate the performance of the MOCCO reconstruction in the presence of noise and the results were compared against the fully sampled images.

Results:

The MOCCO was able to recover curves with K^{trans} values ranging from 0.01 to 0.8 min^{-1} and fixed $V_e = 0.3$, where the fitted results are within a 10% bias error range. Slightly higher error was observed on curves with K^{trans} values larger than 0.8 min^{-1} . MOCCO reconstruction showed less impact on the selection of different temporal model than conventional low-rank reconstruction and the greater error was observed with the PCB. The spatial error maps demonstrate similar results where slow and intermediate lesion kinetics showed relatively low and constant error values across the entire lesion, whereas the rapid lesion kinetics showed increased error on the edges of the lesion. For the Monte-Carlo simulations, MOCCO was found to provide the most accurate reconstruction results for curves with intermediate lesion kinetics in the presence of noise. Underestimation of V_e was observed in slow lesion kinetics, whereas overestimation of K^{trans} was observed in rapid lesion curves.

Conclusion:

This study was designed to evaluate the temporal fidelity of MOCCO and to gain insight into the impact of the estimation errors in K^{trans} and V_e for DCE-MRI. We have evaluated the MOCCO reconstruction under varying conditions, including a wide range of PK parameters and different temporal models in the presence of noise to better match typical in-vivo settings. MOCCO was able to provide reconstructed time-series data that resulted in a more accurate measurement of PK parameters than the general low-rank technique (PCB).

4.2 Introduction

Dynamic contrast enhanced (DCE) MRI is widely accepted as the most sensitive imaging method for detection of breast cancer^{3,77}. Further, DCE-MRI has shown potential for assessing response to therapy due to its ability to reveal functional perfusion changes^{130–132}. Conventional DCE-MRI protocols using high spatial resolution (at or below $1\text{ mm} \times 1\text{ mm}$ in-plane pixel size) but low temporal resolution (60-120 s/time-frame)⁷⁶ enable evaluation of lesion morphology as well as the kinetic features of lesions based on the MRI BI-RADS lexicon²². Kinetic features, including assessment of early wash-in and late wash-out phase images, are used to differentiate between benign and malignant lesions to improve sensitivity and specificity¹³³. However, studies have shown that there is the overlap between the kinetic features between benign and malignant lesions^{134–138}. Kinetic evaluation is also limited by standard low temporal resolution clinical protocols.

To overcome limitations in the specificity of DCE-MRI, previous work has proposed including quantitative pharmacokinetic (PK) analysis to extract more detailed physiological information from the lesion contrast kinetics and has shown potential for improving diagnostic accuracy and specificity^{139–142}. In breast studies, the extended Tofts model (ETM) is commonly used¹²³ to inform insight into correlations between tumor angiogenesis and contrast agent (CA) kinetics from the derived PK parameters. For example, the K^{trans} (min^{-1}) value is correlated to the wash-in slope, which demonstrates the transfer rate of CA from plasma to extravascular extracellular space (EES). V_e (%) is the volume fraction of EES, which correlates with the peak height of the signal time-intensity curves. V_p (%) is the volume fraction of blood plasma, which shows the resemblance of the signal time-intensity curves to the arterial input function. These

parameters have shown potential in the evaluation of treatment planning⁵, screening⁶ and treatment response assessment^{7,143}, yet their clinical usage has been severely hampered due to the uncertainty of measurement accuracy. This challenge can lead to non-reproducibility of PK parameters that impacts the ability to differentiate malignant from benign lesions using standard breast MRI protocols.

To accurately measure PK parameters, multiple factors should be considered such as the measurement of the native T_1 value of the tissue¹⁴⁴, the choice of the arterial input function, and the T_1 -weighted imaging sequence including the temporal resolution of the time-resolved images^{8,9}. Lopata et al¹⁴⁵ demonstrated that the accuracy of the K^{trans} estimation is highly dependent on the temporal resolution, which becomes increasingly more important for K^{trans} values greater than 0.5 min^{-1} . Another simulation study conducted by Giovanni et al⁸ evaluate the fitting error base on different temporal resolution. The results showed that the error can be less than 10% for $K^{\text{trans}} > 0.5 \text{ min}^{-1}$ if a temporal resolution of less than 20 s could be achieved in the setting of breast DCE-MRI. To achieve such high temporal resolution while maintaining the required spatial resolution and full breast bilateral coverage, advanced acquisition and reconstruction approaches are needed.

Several accelerated data acquisition approaches have been proposed for dynamic image reconstruction, such as parallel imaging, view-sharing techniques^{6,97-100}, low-rank matrix recovery approaches¹⁴⁶ and compressed sensing reconstruction^{54,73,104,105}. The use of parallel imaging alone can only provide moderate acceleration factors. View-sharing techniques can provide higher nominal temporal resolution but have been shown to suffer from temporal blurring due to the sharing of k-space data between different time points⁴¹. The low-rank matrix recovery approaches

assume that the dynamic image series can be modeled by a low-dimension subspace, that is only a few temporal basis functions are needed to estimate the kinetic features of each voxel¹⁴⁶. Studies have exploited the use of rank reduction^{147,148} and have shown that a low-rank matrix of the image series can be recovered from undersampled k-space data. However, low-rank techniques are known to suppress temporal dynamics in the cases of complex tissue kinetics, that cannot be accurately represented by a small number of temporal basis functions, especially when high undersampling factors are required. More recently, the data-driven low-rank method known as the model consistency condition (MOCCO)¹⁰¹ was optimized for breast DCE-MRI and demonstrated the ability to provide 5 s temporal resolution while still matching the in-plane spatial resolution and full volume coverage typically used in routine clinical protocols¹⁴⁹.

In most studies, the temporal curves generated by using the proposed accelerated techniques were compared with the state-of-the-art technique, such as non-uniform fast Fourier transform (NUFFT)^{73,150,151}, and demonstrated the improvement of the temporal fidelity. However, the temporal accuracy of PK parameters derived from these advanced reconstruction methods has not been studied in a wide range of PK values and scan parameters for bi-lateral breast DCE-MRI due to the lack of the ground truth in the in-vivo setting. Digital reference objects (DROs) and simulations can provide an important tool for validation purpose due to the ability to provide ground truth for quantitative analysis. Current community initiatives such as the Radiological Society of North American Quantitative Imaging Alliance (QIBA) proposes using DROs to validate the quantitative accuracy of the proposed techniques if these approaches are to be used in clinical practice.

The aim of this study is to evaluate accuracy of PK parameter estimation of the data-driven low-rank compressed sensing (MOCCO) reconstruction with 5 s temporal resolution for breast

MRI using a range of relevant tissue contrast kinetics and matched the clinical required spatial resolution. Specifically, we will determine how well the MOCCO reconstruction is able to recover relevant slow to rapid contrast kinetics using a breast DCE digital reference object (DRO) with signal characteristics generated using the ETM.

4.3 Methods

To validate the temporal accuracy of our proposed imaging techniques for estimating quantitative PK parameters, a DRO was used to generate k-space data that included a wide range of tissue contrast kinetics. It was shown that the error of MOCCO reconstruction depends both on the rank of the temporal model and on the ability to learn temporal basis functions from the available data¹⁰¹. To evaluate the impact of each source of error on quantitative accuracy, we compared MOCCO reconstructions using temporal models derived from both high and low spatial resolution images. Additionally, Monte-Carlo simulations were performed to evaluate the accuracy and precision of quantitative PK parameters from MOCCO reconstruction in slow and rapid tissue contrast kinetics in the presence of noise.

Digital reference object (DRO)

The DRO used in this study allowed for generation of various tissue structures including uniquely assigned contrast kinetics for user defined tissue structures (**Figure 4.3.1**)¹⁵². Imaging simulation parameters were chosen to replicate a conventional clinical bilateral breast protocol: FOV = 340 mm × 340 mm, in-plane spatial resolution = 0.75 mm × 0.75 mm, slice thickness = 1.4 mm, flip

angle = 30° , TE/TR = 2.4 ms / 4.7 ms, and acquired matrix size = $448 \times 448 \times 142$. Homogeneous round lesions with a diameter of 8 mm were added to simulate enhancing lesions.

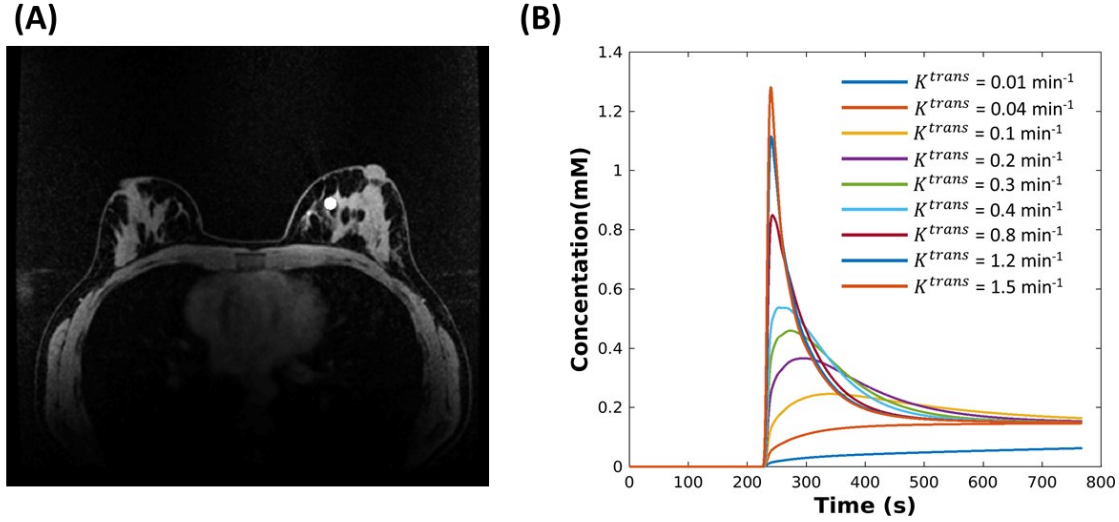


Figure 4.3.1: A breast digital reference object (DRO) (matrix size $448 \times 448 \times 142$) phantom is shown with one lesion located in the fibroglandular tissue (A). Nine configurations of the DRO phantom were evaluated, each with an 8 mm diameter lesion at the same location and having contrast kinetics generated by assigning the fixed $V_e = 0.3$, fixed $V_p = 0.001$, and K^{trans} ranging from 0.01 to 1.5 using the extended Tofts model (b), respectively.

Note that the flip angle = 30° is not typical for standard breast protocol but is better for PK modeling. The concentration time curves (CTC) for the lesions were modeled using the extended Tofts model (ETM)^{116,153}. Parameters for the ETM were chosen to span relatively wide ranges of $K^{trans} = 0.01 - 1.5 \text{ min}^{-1}$ and fixed value of $V_e = 0.3$, and $V_p = 0.001$ values. These ranges were selected to extend slightly beyond the typical range of slow, intermediate, and rapid changing lesion kinetics to allow performance assessment extending to the limits of the expected parameter ranges. An arterial input function (AIF) curve was simulated by using the publicly available dispersion model described by Barboriak et al¹¹⁷. A hematocrit of 0.45 was assumed. The spoiled gradient recalled echo (SPGR) signal model was then used to generate signal time curves assuming

a field strength of 3T, T_1 value of breast tissue ($T_{10}=1444 \text{ ms}^{118}$), and contrast agent relaxivity of $r_1 = 4.9 \text{ mM}^{-1}\text{s}^{-1}$ to simulate Gd-BOPTA (gadobenate dimeglumine, Multihance, Bracco, Milan, Italy)¹¹⁹, and imaging flip angle ($\text{FA} = 30^\circ$). Images containing both static and dynamic features were then sampled using the NUFFT⁶⁷ to simulate k-space data generated from an undersampled golden-angle radial acquisition consisting of 1024 radial projections with a 16-channel coil array. The coil sensitivity maps were derived from the acquired MRI images from the breast shaped water phantom followed by a local fitting method to remove the Gibbs ringing artifacts and noise⁴⁸.

Reconstruction

The undersampled radial data were reconstructed at 5 s temporal resolution corresponding to 8 projections per time frame (undersampling factor, $R = 88$) using MOCCO:

$$\hat{s} = \arg \min_s (\|Es - m\|_2^2 + \lambda \|(\tilde{T}_K \tilde{T}_K^* - I_t)s\|_1) \quad [12]$$

Here m denotes the measured MRI signal of the underlying image series, which was acquired using an encoding matrix E comprising the coil sensitivity values and Fourier encoding terms. λ is a regularization parameter providing a balance between the data consistency and the regularization terms. $\tilde{T}_K$ is a matrix of rank K defining the temporal model, whose columns are temporal basis functions learned from the data, and $\tilde{T}_K^*$ is its adjoint matrix. To evaluate the impact of $\tilde{T}_K$ on reconstruction accuracy, we evaluated two approaches to generate the temporal basis functions for MOCCO:

- 1) Behavior with temporal models derived from high resolution images (HR): the $\tilde{T}_K$ for this approach included two elements of the pre-estimated temporal matrix, which included the reference CTCs and temporal curve with constant value to simulate dynamic and static tissue signal changes.

- 2) Performance with temporal models derived from low resolution images (LR): in this approach, $\tilde{T}_K$ was learned through the low frequency region from fully-sampled central k-space data using progressive learning with cubic spline approximation^{154,155} followed by complex independent component analysis (ICA)¹⁵⁶. The ICA technique assumes that each component is statistically independent from the source signals, which has been shown to be a robust method to identify key components of the perfusion series and remove unwanted image-to-image fluctuations.¹¹⁴

MOCCO with $\tilde{T}_K$ using the HR approach (MOCCO-HR) can provide a theoretical baseline when ideal temporal model is available. However, MOCCO using LR approach (MOCCO-LR) presents a more realistic scenario where the temporal model is learned from the data itself. Both MOCCO-HR and MOCCO-LR were implemented using iteratively re-weighted least squares minimization¹²⁰. For comparison, we also applied a more conventional low-rank reconstruction^{146,148} approach using a principal component basis (PCB), which assumes that the image series $\hat{s}$ is restricted to a low dimensional subspace, i.e. is of the form

$$\hat{s}(x, t) = \tilde{T}_K(t) \tilde{C}_K(x) \quad [13]$$

where $\tilde{T}_K(t)$ is temporal model of rank K and the spatial coefficients $\tilde{C}_K(x)$ can be determined by solving a quadratic minimization problem:

$$\tilde{C}_K = \arg \min_C \left(\|E \tilde{T}_K C - m\|_2 \right). \quad [14]$$

As with MOCCO, two different temporal models were also used for PCB, denoted as PCB-HR and PCB-LR, and quadratic minimization was implemented using conjugate gradient method. A regularization (λ) value of 10 was used for both MOCCO based on previous studies using the same

DRO configuration¹⁵⁷. Iterations of the reconstruction were performed until the relative norm of the k-space residual was less than a specified tolerance (10^{-9}) or until a maximal number of iterations $n = 400$ was reached for MOCCO and PCB, respectively.

Analysis

PK fitting was performed to determine how well the original curve shapes were recovered using the radial acquisition and advanced reconstruction methods. Specifically, the fitting was used to measure how well the original kinetic parameters could be recovered from the reconstructed temporal curves. Signal intensity time curves from regions-of-interest (ROI) placed in the lesion locations were measured across all image time-series and subsequently converted to CTCs. PK modeling was performed using the ROCKETSHIP toolbox¹²¹ by fitting the ETM to the CTCs using the Levenberg-Marquardt algorithm with a step tolerance of 1×10^{-6} and a function tolerance of 1×10^{-8} . Fitting bounds were set between 0 and 1 with randomly selected initial estimates for K^{trans} , V_e , and V_p . The fitted voxel-wise PK parameters were then compared to the original PK parameters to generate % error maps. Bland-Altman plots were used to evaluate the agreement between the PK parameters measured from two different reconstructions and the corresponding ground truth.

Monte-Carlo simulations were performed to evaluate the performance of the MOCCO reconstruction in the presence of noise. Thirty realizations of independent identically distributed (i.i.d.) complex Gaussian noise with zero mean and standard deviation of 20% of the mean k-space magnitude were added to each coil channel for three k-space data sets that included lesions with $K^{\text{trans}} = 0.01, 0.3, \text{ and } 1.5 \text{ min}^{-1}$ resulting in 90 unique datasets (30 for each tissue contrast kinetics). Additionally, 90 realizations (30 for each tissue contrast kinetics) were performed using fully-

sampled data with additive i.i.d. Gaussian noise with the standard deviation matched to the undersampled data. The reconstruction accuracy was assessed by taking a pixel-wise mean and standard deviation across all Monte-Carlo realizations and calculating the percent error between the ground truth and the Monte-Carlo mean from undersampled and fully sampled images, respectively.

4.4 Results

Figure 4.4.1 illustrates the temporal performance of MOCCO-HR, MOCCO-LR, PCB-HR and PCB-LR for recovering the simulated lesion CTCs with varying enhancement patterns. Note that the displayed time interval ranges from 150 s to 400 s to allow for a better visualization over

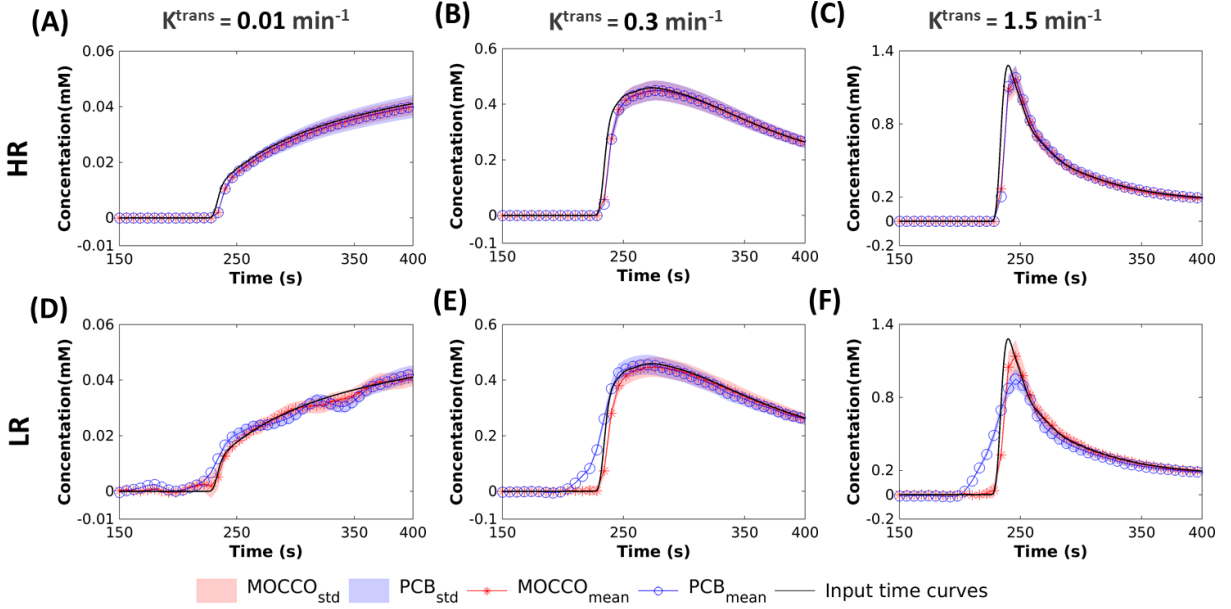


Figure 4.4.1: Simulated CTCs with slow (A,D), intermediate (B,E), and rapid (C,F) contrast kinetics in noise-free data (displayed for a subset of time from 150 to 400 s). Mean CTCs measured for three lesions with varying K^{trans} values reconstructed using MOCCO (red star) and PCB (blue circle) with the temporal model derived from high spatial resolution (HR) (A-C) and low spatial resolution (LR) images (D-F). The corresponding standard deviations within the lesions are shown with banded area. The input time curves (“true”) used to generate the source data are plotted with dark black lines in all frames.

the period of greatest signal change. The HR approach with $K=2$ represents the best approximation of lesion kinetics for the reconstructions when using the reference CTCs as the temporal basis. Therefore, as illustrated in **Figure 4.4.1** A-C, the mean concentration value of the temporal curves generated by both PCB-HR and MOCCO-HR are closely matched to the original reference time

curves in the noise-free dataset. For the LR approach with $K=3$ in **Figure 4.4.1 D-F**, MOCCO-LR showed similar results to the MOCCO-HR with only slightly increased of standard deviation whereas PCB-LR has shown severe temporal blurring on wash-in slopes in both intermediate (**Figure 4.4.1, E**) and rapid (**Figure 4.4.1, F**) contrast kinetics. Bland-Altman plots of the fitted K^{trans} and V_e within the lesion ROI in noise-free data and in data with 20% noise added are shown in **Figure 4.4.2** and **Figure 4.4.3**, respectively. In noise-free data, the fitted K^{trans} and V_e were within a 10% bias error range of the corresponding ground truth K^{trans} and V_e for MOCCO-HR (**Figure 4.4.2, A**) and PCB-HR (**Figure 4.4.2, C**). The results from MOCCO-LR (**Figure 4.4.2, B**) were aligned with MOCCO-HR (**Figure 4.4.2, A**) for CTC with $K^{\text{trans}} < 0.8 \text{ min}^{-1}$. For the cases with $K^{\text{trans}} \geq 0.8 \text{ min}^{-1}$, the error range was close to or slightly larger than the limits of the 10% error range. On the contrary, the PCB-LR (**Figure 4.4.2, D**) showed much greater underestimation of the fitted K^{trans} and V_e (errors exceeding the 10% range) when $K^{\text{trans}} \geq 0.3 \text{ min}^{-1}$. In data with 20% noise added, the CTCs with $K^{\text{trans}} = 0.01$ and 0.04 in MOCCO-HR (**Figure 4.4.3, A**) and PCB-HR (**Figure 4.4.3, C**) showed greater increased standard deviation within the lesions, whereas similar results of the mean % error reconstructed by MOCCO-LR (**Figure 4.4.3, B**) and PCB-LR (**Figure 4.4.3, D**) were observed compared with the results in noise-free data (**Figure 4.4.2, B and D**). Note that the same reconstruction parameters were used to reconstruct noise-free and the corresponding noisy-data.

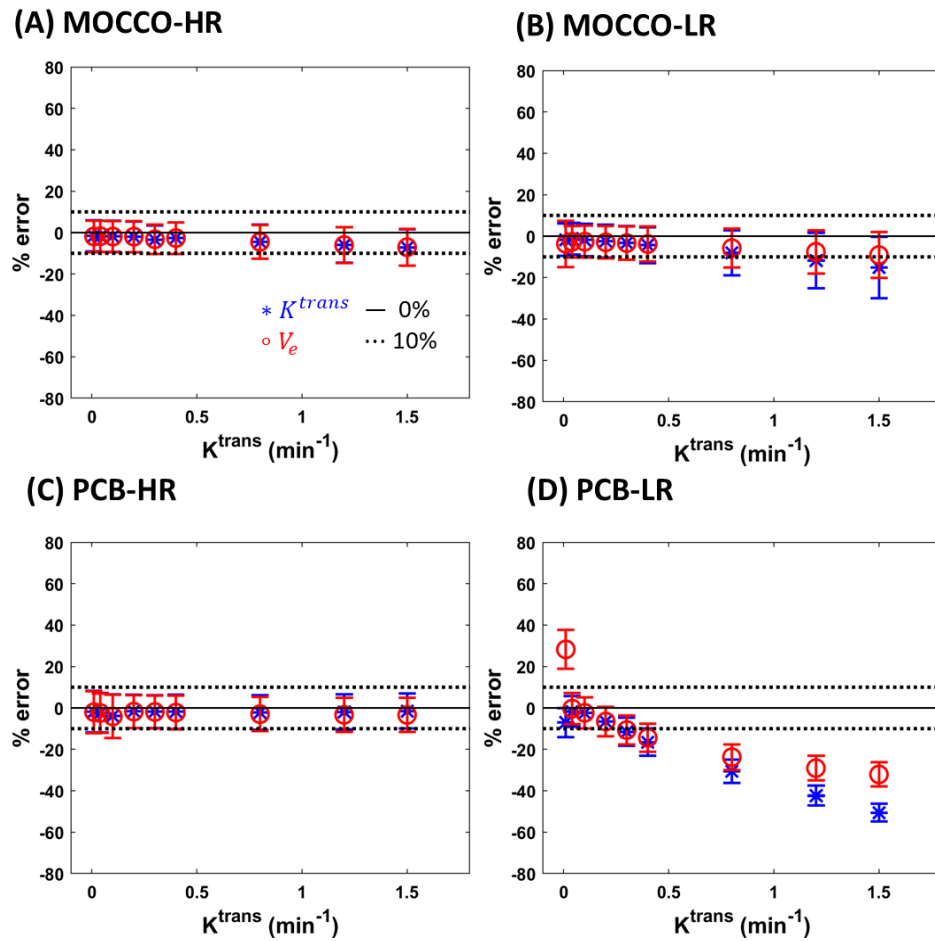


Figure 4.4.2: The influence of temporal model in noise-free data using MOCCO (A-C) and PCB (D-F) reconstruction on parameter estimation of K^{trans} and V_e . Bland-Altman plots show the mean ($\pm$ standard deviation) of K^{trans} (blue stars) and V_e (red circles). The $\pm 10\%$ error range is shown as black dash lines.

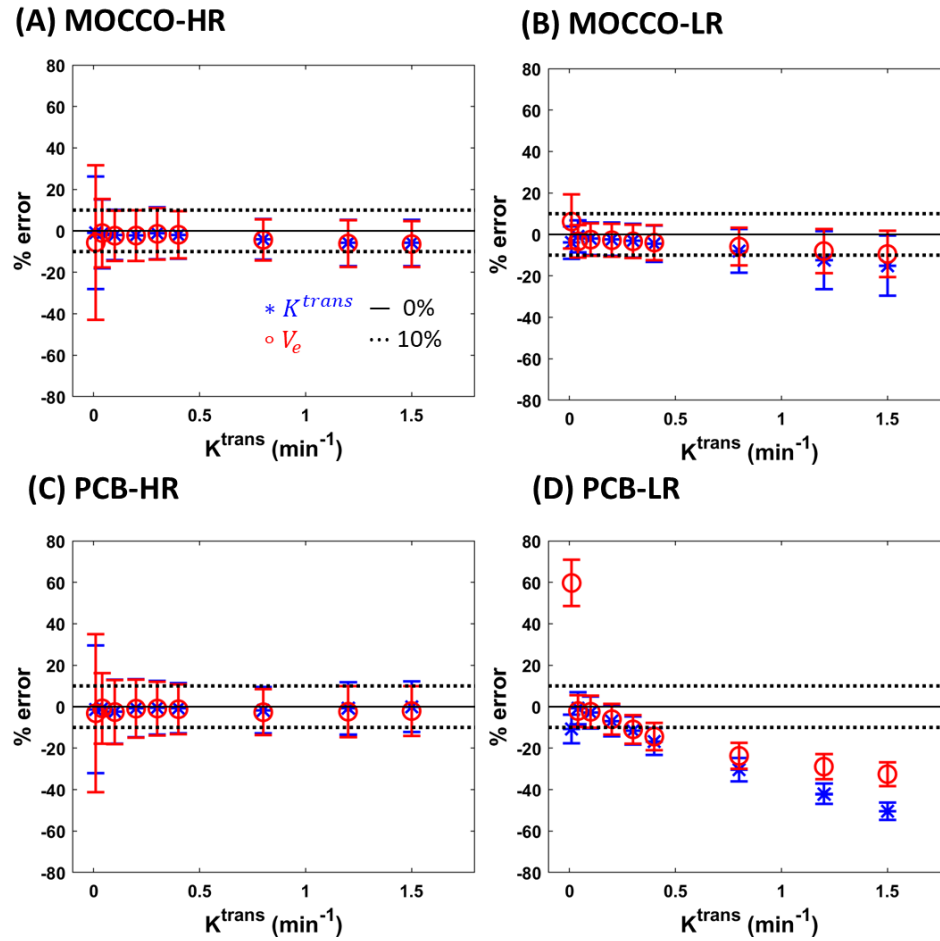


Figure 4.4.3: The influence of temporal model and noise using MOCCO (A-C) and PCB (D-F) reconstruction on parameter estimation of K^{trans} and V_e . Bland-Altman plots show the mean ($\pm$ standard deviation) of K^{trans} (blue stars) and V_e (red circles). The $\pm 10\%$ error range is shown as black dash lines.

In order to better assess the source of the signal differences within the lesion including the increased standard deviation observed with some of the reconstructions, spatial mapping of the PK fitting results was performed. **Figure 4.4.4** and **Figure 4.4.5** demonstrate the percent difference zoomed-in error maps of the derived K^{trans} and V_e from MOCCO and PCB, respectively. Color maps of the lesion with $K^{\text{trans}} = 0.01, 0.3$ and 1.5 were selected to show the difference between the slow, intermediate, and rapid contrast kinetics with and without noise added. In results of noise-free data, the zoomed-in error map from MOCCO-HR (**Figure 4.4.4, A**) showed relatively homogenous under-estimation of K^{trans} and V_e in the error distribution for the intermediate and rapid contrast kinetics. Only results from the lesion with slow contrast kinetics ($K^{\text{trans}} = 0.01 \text{ min}^{-1}$) displayed a mixed response with over- and under-estimation of both K^{trans} and V_e with an error range within $\pm 10\%$. MOCCO-LR (**Figure 4.4.4, B**) demonstrated similar error distribution compared with MOCCO-HR, with only slightly increased error observed at the lesion edge for

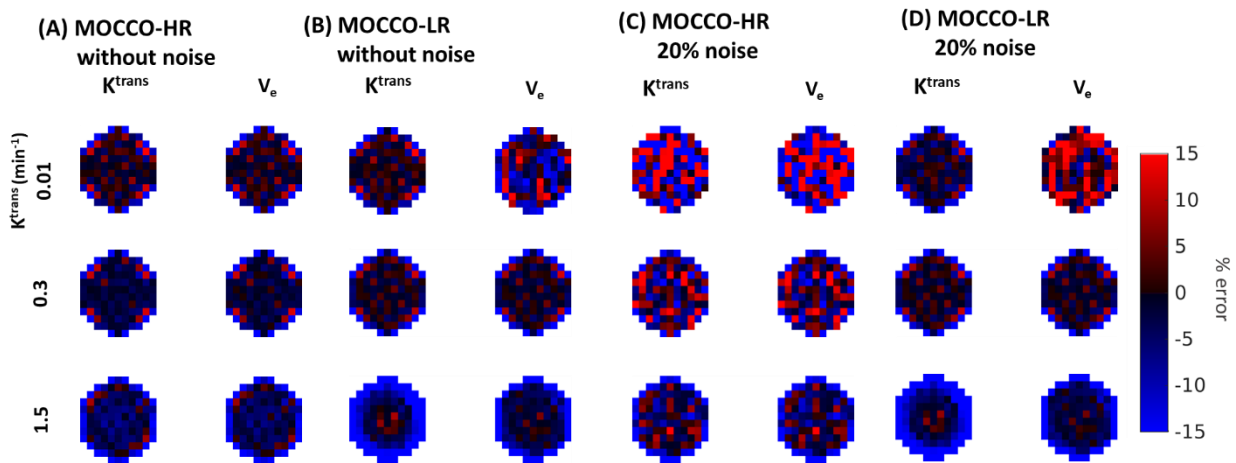


Figure 4.4.4: Visualization of zoomed-in error maps for K^{trans} and V_e from (A) MOCCO-HR, (B) MOCCO-LR without noise, and (C) MOCCO-HR, and (D) MOCCO-LR with 20% noise added to the simulated lesions with $K^{\text{trans}} = 0.01, 0.3, 1.5 \text{ min}^{-1}$, obtained by measuring the % differences between the fitted parameters and the true values for the lesion.

rapid contrast kinetics ($K^{\text{trans}} = 1.5 \text{ min}^{-1}$) in error map of K^{trans} and V_e . In data with 20% noise

added, an increased deviation in the percent error of both K^{trans} and V_e was observed in MOCCO-HR (**Figure 4.4.4, C**) but no major difference was observed in MOCCO-LR (**Figure 4.4.4, D**). Only increased error was observed in error map of V_e with $K^{\text{trans}} = 0.01 \text{ min}^{-1}$.

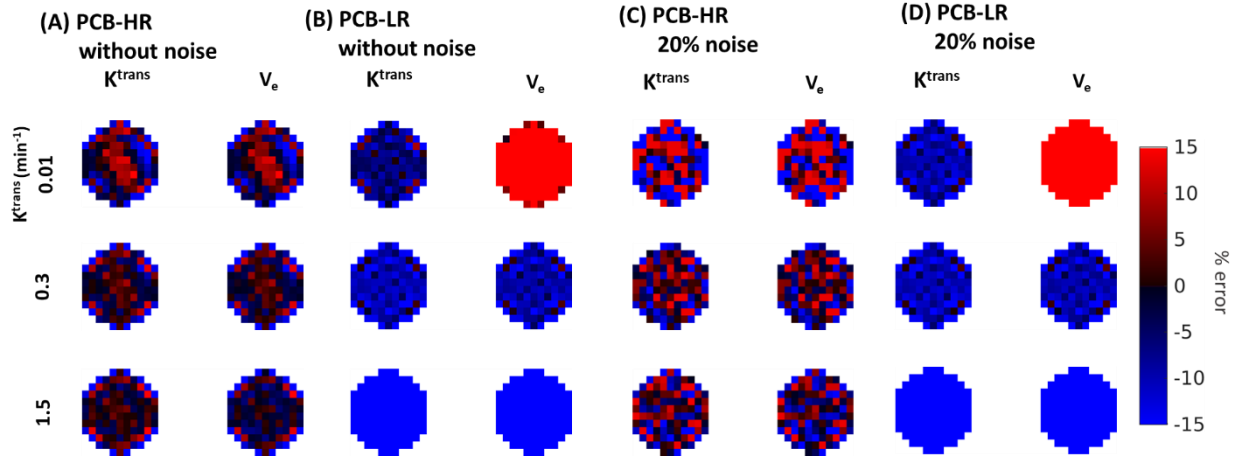


Figure 4.4.5: Visualization of zoomed-in error maps for K^{trans} and V_e from (A) PCB-HR, (B) PCB-LR without noise, and (C) PCB-HR, and (D) PCB-LR with 20% noise added to the simulated lesions with $K^{\text{trans}} = 0.01, 0.3, 1.5 \text{ min}^{-1}$, obtained by measuring the % differences between the fitted parameters and the true values for the lesion.

In contrast, there is a discrepancy in the error distributions between PCB-HR (**Figure 4.4.5, A and C**) and PCB-LR (**Figure 4.4.5, B and D**). The error maps derived from PCB-HR (**Figure 4.4.5, A and C**) displayed more heterogeneous over- and under-estimation over the entire lesion but resulted in lower % error across all three lesions for both K^{trans} and V_e , which results in lower mean error but higher standard deviation (Note that the % mean and standard deviation were showed in **Table 4.4.1**). The PCB-LR (**Figure 4.4.5, B and D**) demonstrated a relatively homogeneous error distribution within the lesion but showed an overall increased under-estimation of both K^{trans} and V_e . Only error map of V_e with $K^{\text{trans}} = 0.01 \text{ min}^{-1}$ showed overestimation of the entire lesion.

Table 4.4.1: Summary of results and % errors for K^{trans} and V_e from PK model fitting to the reconstruction results.

		Reference	MOCCO-HR		PCB-HR		MOCCO-LR		PCB-LR	
	K^{trans}	0%	0%	20%	0%	20%	0%	20%	0%	20%
% error for K^{trans}	0.01	-4.7	-1.65 $\pm$ 7.52	-0.99 $\pm$ 27.14	-1.79 $\pm$ 10.11	-1.32 $\pm$ 30.77	-1.74 $\pm$ 7.81	-3.91 $\pm$ 7.87	-7.04 $\pm$ 7.02	-10.77 $\pm$ 6.84
	0.04	0.06	-1.72 $\pm$ 7.49	-1.46 $\pm$ 16.54	-2.36 $\pm$ 9.50	-0.80 $\pm$ 17.04	-1.21 $\pm$ 7.67	-0.92 $\pm$ 7.75	-1.69 $\pm$ 7.5	-0.68 $\pm$ 7.71
	0.1	0.09	-1.72 $\pm$ 7.51	-2.03 $\pm$ 12.07	-3.96 $\pm$ 10.49	-2.40 $\pm$ 15.48	-1.83 $\pm$ 7.78	-2.07 $\pm$ 7.85	-2.3 $\pm$ 7.52	-2.79 $\pm$ 7.74
	0.2	-0.13	-2.04 $\pm$ 7.47	-2.22 $\pm$ 12.2	-1.64 $\pm$ 8.03	-0.70 $\pm$ 13.96	-2.38 $\pm$ 8.02	-2.33 $\pm$ 8.1	-6.54 $\pm$ 7.13	-6.94 $\pm$ 7.3
	0.3	-1.50	-3.53 $\pm$ 6.9	-1.15 $\pm$ 12.49	-1.72 $\pm$ 7.97	-0.59 $\pm$ 12.98	-3.22 $\pm$ 8.19	-3.09 $\pm$ 8.17	-11.51 $\pm$ 6.86	-11.5 $\pm$ 6.84
	0.4	-1.91	-2.7 $\pm$ 7.55	-1.97 $\pm$ 11.43	-1.87 $\pm$ 8.17	-0.72 $\pm$ 12.05	-4.35 $\pm$ 8.64	-4.45 $\pm$ 8.74	-16.58 $\pm$ 6.59	-16.79 $\pm$ 6.46
	0.8	-2.71	-4.39 $\pm$ 8.16	-4.04 $\pm$ 9.86	-2.13 $\pm$ 8.36	-1.67 $\pm$ 11.21	-8.07 $\pm$ 10.85	-7.94 $\pm$ 10.65	-30.54 $\pm$ 5.6	-30.43 $\pm$ 5.67
	1.2	-3.64	-6.03 $\pm$ 8.55	-5.83 $\pm$ 11.23	-1.90 $\pm$ 8.44	-0.80 $\pm$ 12.58	-11.76 $\pm$ 13.32	-12.49 $\pm$ 13.97	-42.34 $\pm$ 4.86	-42.04 $\pm$ 4.88
	1.5	-4.86	-7.17 $\pm$ 8.76	-5.81 $\pm$ 11.19	-1.48 $\pm$ 8.42	-0.05 $\pm$ 12.23	-15.1 $\pm$ 14.86	-15.04 $\pm$ 14.54	-50.6 $\pm$ 4.28	-50.44 $\pm$ 4.27
% error for V_e	K^{trans}	0%	0%	20%	0%	20%	0%	20%	0%	20%
	0.01	-8.38	-1.86 $\pm$ 7.55	-5.65 $\pm$ 37.29	-2.03 $\pm$ 10.10	-3.18 $\pm$ 38.12	-3.71 $\pm$ 11.14	6.22 $\pm$ 13	28.27 $\pm$ 9.47	59.68 $\pm$ 11.16
	0.04	-0.36	-1.74 $\pm$ 7.49	-1.07 $\pm$ 16.49	-2.44 $\pm$ 9.49	-0.80 $\pm$ 17.04	-2.72 $\pm$ 7.68	-3.37 $\pm$ 7.77	-0.35 $\pm$ 7.59	-2.09 $\pm$ 7.59
	0.1	-0.08	-1.9 $\pm$ 7.51	-2.35 $\pm$ 12.11	-4.12 $\pm$ 10.46	-2.60 $\pm$ 15.44	-2.65 $\pm$ 7.68	-2.51 $\pm$ 7.82	-2.36 $\pm$ 7.51	-2.46 $\pm$ 7.76
	0.2	-0.13	-1.95 $\pm$ 7.5	-2.28 $\pm$ 12.25	-1.79 $\pm$ 8.02	-0.96 $\pm$ 13.92	-2.98 $\pm$ 7.86	-2.81 $\pm$ 7.88	-6.56 $\pm$ 7.12	-6.05 $\pm$ 7.37
	0.3	-0.73	-3.24 $\pm$ 7.02	-1.44 $\pm$ 12.38	-1.93 $\pm$ 7.95	-0.90 $\pm$ 12.94	-3.34 $\pm$ 8.03	-3.36 $\pm$ 8.04	-10.67 $\pm$ 6.93	-10.96 $\pm$ 6.88
	0.4	-0.95	-2.66 $\pm$ 7.59	-1.88 $\pm$ 11.39	-2.23 $\pm$ 8.14	-1.22 $\pm$ 12.00	-3.79 $\pm$ 8.39	-3.91 $\pm$ 8.49	-14.4 $\pm$ 6.77	-14.43 $\pm$ 6.64
	0.8	-1.42	-4.48 $\pm$ 8.15	-4.34 $\pm$ 9.93	-3.00 $\pm$ 8.28	-2.68 $\pm$ 11.09	-5.78 $\pm$ 9.37	-5.86 $\pm$ 9.14	-23.77 $\pm$ 6.15	-23.73 $\pm$ 6.22
	1.2	-1.67	-6.04 $\pm$ 8.59	-6.13 $\pm$ 11.23	-3.34 $\pm$ 8.31	-2.41 $\pm$ 12.36	-7.57 $\pm$ 10.45	-8.02 $\pm$ 10.58	-29.09 $\pm$ 5.98	-28.93 $\pm$ 5.99
	1.5	-1.87	-7.06 $\pm$ 8.86	-6.39 $\pm$ 11.06	-3.37 $\pm$ 8.25	-2.10 $\pm$ 12.00	-9.13 $\pm$ 11.03	-9.45 $\pm$ 11.13	-32.13 $\pm$ 5.89	-32.57 $\pm$ 5.82

Figure 4.4.6 shows the temporal curves with $K^{\text{trans}} = 0.01, 0.3, \text{ and } 1.5 \text{ min}^{-1}$ obtained from MOCCO-LR and the corresponding fully-sampled images by measuring the mean across the Monte-Carlo realizations with noise levels of 20%. The results demonstrated that the mean signal values were found to closely match the curves from the ground truth with very small standard deviation.

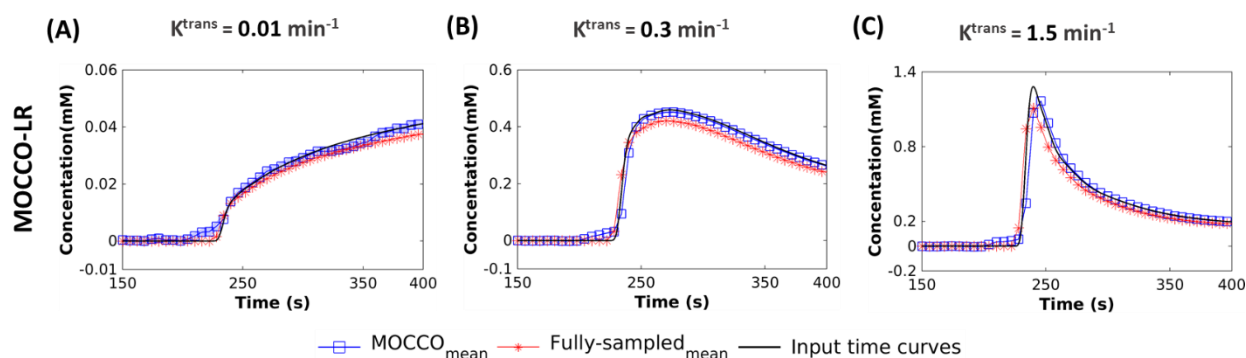


Figure 4.4.6: Simulated CTCs with 20% noise added (displayed for a subset of time from 150 s to 400 s). Mean CTCs measured for three lesions with varying K^{trans} values reconstructed using MOCCO-LR. The input time curves (“truth”) used to generate the source data are plotted with dark black lines in all frames.

Figure 4.4.7 depicts the results of the Monte-Carlo simulation in estimating the mean (**Figure 4.4.7, A**), standard deviation (**Figure 4.4.7, B**), and percent error between the Monte-Carlo mean and the true values for lesions (**Figure 4.4.7, C**) from MOCCO-LR images. Corresponding results are shown for the fully sampled data in **Figure 4.4.8**. MOCCO-LR was found to provide the most accurate reconstruction results for curves with the middle value of $K^{\text{trans}} = 0.3 \text{ min}^{-1}$, where the overall performance was consistent with fully-sampled dataset. Only slightly higher standard deviation ($\sim 5\%$) was found in MOCCO-LR for the Monte-Carlo simulation including noise. For curves with slow contrast kinetics ($K^{\text{trans}} = 0.01 \text{ min}^{-1}$), there was no obvious difference between MOCCO-LR and the fully sampled data in the mean and standard deviation of K^{trans} on visual inspection. However, increased variations in estimates of V_e were observed. For curves with fast contrast kinetics ($K^{\text{trans}} = 1.5 \text{ min}^{-1}$), the V_e value was recovered with low reconstruction error. Although MOCCO-LR showed relatively accurate measurements of the mean K^{trans} values, increased standard deviation was observed in the Monte-Carlo simulation.

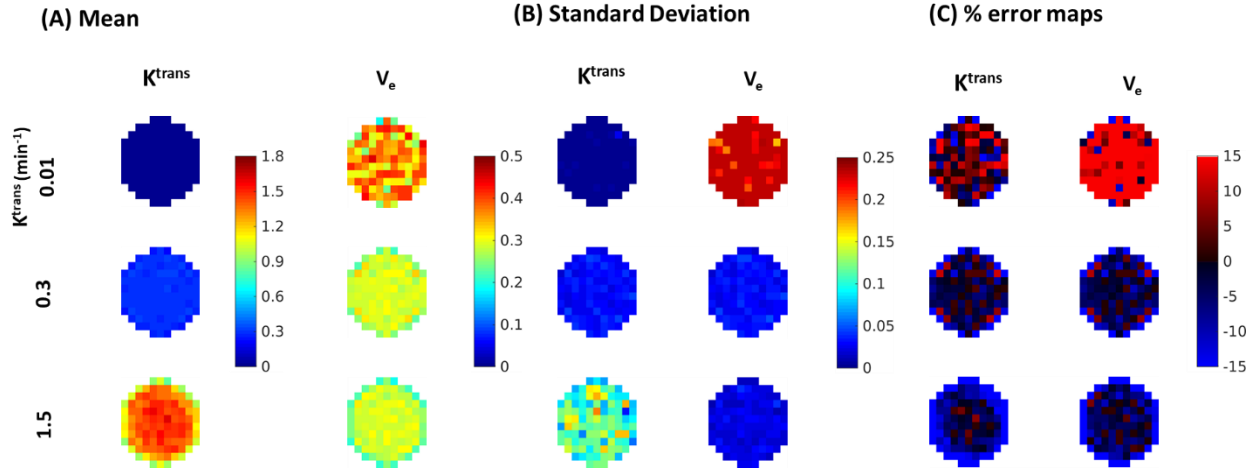


Figure 4.4.7: Visualization of zoomed-in color maps for K^{trans} and V_e from MOCCO-LR with 20% noise added to $K^{\text{trans}} = 0.01, 0.3, 1.5 \text{ min}^{-1}$ obtained by measuring the (A) mean, (B) standard deviation, (C) percent differences between the fitted parameters from all Monte-Carlo noise realizations and the true values for the lesions.

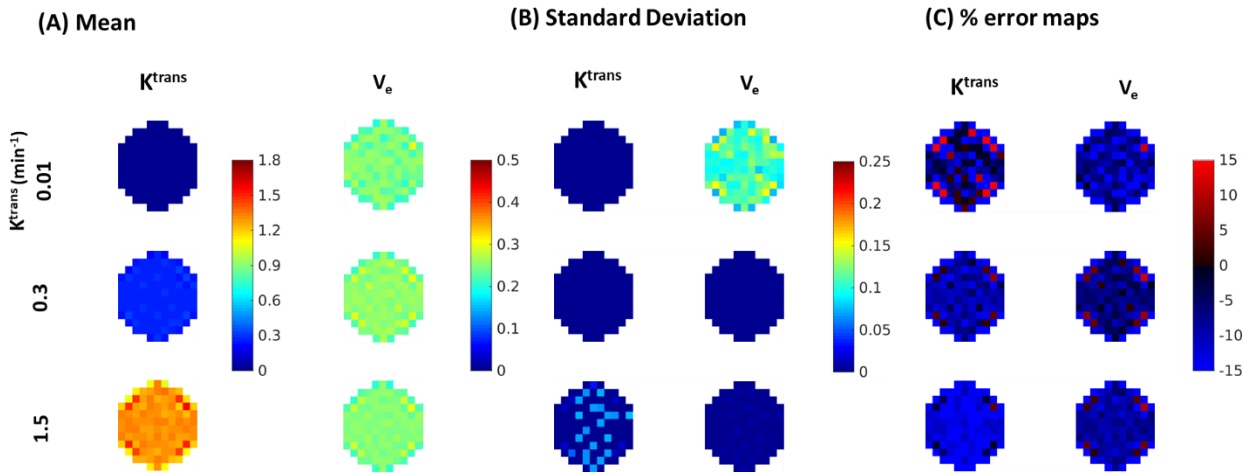


Figure 4.4.8: Visualization of zoomed-in color maps for K^{trans} and V_e from fully-sampled data with 20% noise added to $K^{\text{trans}} = 0.01, 0.3, 1.5 \text{ min}^{-1}$ obtained by measuring the (A) mean, (B) standard deviation, (C) percent differences between the fitted parameters from all Monte-Carlo noise realizations and the true values for the lesions.

4.5 Discussion

In this work, we present a framework to evaluate the temporal fidelity of our proposed technique, the combination of golden-angle stack-of-stars radial acquisition with a data-driven low-rank based CS reconstruction (MOCCO), using quantitative PK analysis for breast DCE-MRI. The DRO used in this study can be employed to simulate a wide spectrum of tissue contrast kinetics with a user-defined PK model and different levels of noise in the data. This simulation approach provides the opportunity to validate the accuracy of our proposed technique for quantitative analysis, which can be difficult to achieve in patient studies. MOCCO reconstruction was also compared to another low-rank method (PCB) to assess the performance with respect to the selection of temporal model and in the setting of noisy data.

We have demonstrated two different approaches to generate temporal basis functions using either the ICA on high spatial resolution images (HR) or ICA on low spatial resolution images (LR) to construct a signal-specific temporal model. The results from HR provide a lower bound on the reconstruction accuracy of MOCCO in the theoretical setting where the exact temporal can be learned. This scenario resulted only a small error when compared with reference CTC with 5 s temporal resolution. The LR approach learned the temporal model from the undersampled data, which has been demonstrated to be an effective approach in many other applications^{101,148}. In our simulation results, MOCCO-LR produced time-resolved images with high temporal fidelity that enabled robust and consistent estimation of K^{trans} and V_e compared with MOCCO-HR. On the other hand, we observed increased error using PCB-LR, especially in lesions with the highest K^{trans} value (1.5 min^{-1}). This can be explained by the fact that MOCCO was shown to produce high-rank solutions even using low-rank temporal model¹⁰¹, whereas PCB approach limits the reconstruction result to a low-dimensional subspace, which may be inadequate for describing complex contrast

dynamics. In our simulations, MOCCO was found to be less sensitive to the selection of the temporal model and led to a more stable solution, which is consistent with the conclusion from prior works^{101,157}.

The PK parameters obtained from tissue CTCs with very low $K^{\text{trans}} < 0.04$ were found to be vulnerable to noise for both MOCCO-HR and MOCCO-LR. This is attributed to the low intensity of signal enhancement that can be easily corrupted by the background noise. Otherwise, both techniques were found to be less affected by noise in the source data with $K^{\text{trans}} > 0.04$ and provided similar measurements of PK parameters to the results in the noise-free simulations. The Monte-Carlo simulations also demonstrated that MOCCO-LR was less impacted by noise in the source data and provided better reconstruction accuracy with K^{trans} above 0.3 min^{-1} that are typically of greater interest for characterizing suspicious lesions.

In our simulations we found that the increased reconstruction error in the low contrast kinetics ($K^{\text{trans}} = 0.01 \text{ min}^{-1}$) was mostly due to the overall lower maximum lesion CTC peak amplitude. This effect was demonstrated by increased standard deviation in estimations of V_e including for lesions measured from the fully sampled data, however slower contrast kinetics are usually of less clinical interest.

Although multiple studies have proposed new imaging methods to improve the spatial and temporal resolution for breast DCE-MRI, few studies have investigated absolute quantification of the derived PK parameters. One of the challenges is the lack of known ground truth measurements of the contrast signal kinetics due to the need for high temporal and 3D spatial resolution as well as confounding effects such as physiological variability, motion, B_0 and B_1 inhomogeneities, and accurate tissue T_1 values. The DRO used in this study allowed for simulating a wide spectrum of known ground truth contrast kinetics to compare reconstruction techniques and characterize

performance. In this study, we focus on the impact of temporal accuracy under 5 s temporal resolution, which shows the potential to provide robust quantitative PK parameters and can be applied to different clinical settings, such as differentiating lesion types, and evaluating response to neoadjuvant chemotherapy^{7,143}

There are some limitations to the current study. We have shown that accuracy of the PK parameters estimated with both PCB and, to a lesser degree, MOCCO depend on the availability of an adequate temporal model. However it may be more challenging to obtain such temporal models in situations with highly undersampled data and/or in the presence of motion, based on our current strategy. Therefore, further work is needed to investigate obtaining temporal models using other techniques (e.g. dictionary learning¹⁵⁸). In this study, emphasis was placed on the evaluation of temporal fidelity of MOCCO reconstruction, and therefore populated AIF curves were used. Although population-based AIFs are still routinely used due to the inability to achieve sufficiently high temporal and spatial resolution to resolve the extremely rapid kinetics, these do represent a limitation to the ability to accurately model a given individual perfusion setting. Future work will aim to validate these results through in-vivo studies in the setting of breast cancer.

4.6 Conclusion

This study was designed to evaluate the temporal fidelity of our proposed data-driven low-rank compressed sensing reconstruction (MOCCO) and to gain insight into the impact of the estimation errors in K^{trans} and V_e for DCE-MRI. We have evaluated the MOCCO reconstruction under varying conditions, including a wide range of PK parameters and different temporal models in the presence of noise to better match typical in-vivo settings. We have demonstrated that using MOCCO reconstruction for an image series at a temporal resolution of 5 sec and spatial resolution

of 0.8 mm x 0.8 mm x 1.2 mm would lead to an error with 10% or less for V_e across all K^{trans} values and an error of -0.9% to -10% for K^{trans} values of less than 0.8 min^{-1} in this DRO simulation matching the clinical setting for DCE-MRI. Only contrast kinetics with very high K^{trans} values beyond the typical in-vivo range showed larger errors. Overall, MOCCO was able to provide a reconstructed time-series that resulted in a more accurate measurement of PK parameters than the general low-rank technique (PCB).

Chapter 5

Respiratory self-gated free breathing supine breast DCE-MRI

5.1 Introduction

Breast dynamic contrast enhanced (DCE) MRI is known to be the most sensitive image modality for breast cancer detections. Due to its ability to provide accurate assessment of the lesion morphological information and distinguish different tissue types, breast DCE-MRI has been applied to multiple clinical applications, such as screening, diagnostic evaluation, and surgical planning. For most exams, breast DCE-MRI is conventionally performed in the prone position using dedicated multi-channel breast RF coils. This approach has the advantage of minimizing respiratory motion during longer time-resolved imaging studies typically needed to acquire sufficient contrast kinetics and spatial resolution with full organ coverage. However, other clinical breast applications, such as biopsy^{159,160}, radiotherapy, presurgical planning and breast surgery¹⁶¹, are performed in the supine position. This positioning mismatch results in significant spatial deformation¹⁶² leading to challenges with localizing the tumor location during these interventional procedures.

Prior studies have suggested performing breast deformation using finite element models to predict the prone to supine reorientation to provide more accurate registration results between different positions and imaging modalities^{163,164}. Others have proposed collecting additional supine breast MR images following the standard prone breast MRI, which showed the potential to provide better alignment of tumor deformation and positioning for subsequent clinical procedures^{160,165}. However, respiratory and/or cardiac motion are the main challenges as these can obscure the anatomic structures in the breast due to motion artifacts thereby reduce the overall image quality.

To overcome motion artifacts in supine breast MRI, previous work has investigated using the respiratory triggering to avoid the ghosting artifacts caused by respiration¹⁶⁶. This approach showed significant improvement in image sharpness compared to supine imaging without respiratory triggering. Further, it also demonstrated increased SNR and CNR compared with conventional prone imaging. However, this approach required longer acquisition times that compromised the achievable temporal resolution and restricted the assessment of lesion contrast kinetics. As an alternative, study has proposed using a 3D stack-of-stars golden-angle radial acquisition to generate self-gating signal followed by k-space sorting to generate motion-free images¹⁶⁷ in abdominal MR images. This technique offers robustness to patient specific breathing pattern by retrospective data sorting in the same k-space data. Additionally, a recent proposed technique, XD-GRASP, has successfully combined this motion sorting algorithm with the compressed sensing reconstruction using temporal total variation (CS-TV) to generate high spatial and temporal resolution images for free-breathing liver DCE-MRI^{168–170}. However, further study has observed trade-off between spatial quality and temporal resolution by using CS-TV in the liver exam¹⁷¹. The results indicated that while a higher number of motion states and higher number of

spokes improves overall image quality, the resulting lower temporal resolution can introduce high error in quantitative parameters for rapid tissue contrast kinetics.

Recently, a data-driven low-rank compressed sensing method with temporal regularization known as the model consistency condition (MOCCO)¹⁰¹ was optimized for breast DCE-MRI and shown to have the ability to provide 5 s temporal resolution while still matching the in-plane spatial resolution and full volume coverage typically used in routine clinical protocols¹⁴⁹. However, to the best of our knowledge, this technique has not been validated yet in supine breast DCE-MRI. With liver DCE routinely performed in the supine position, we hypothesize that these self-gating techniques can be extended to supine breast DCE MR imaging.

The aim of this study is to evaluate the feasibility of providing motion-free high spatial-temporal resolution supine breast DCE-MRI using radial acquisition combined with self-gating and MOCCO reconstruction. In this work, we propose a radial acquisition combined with self-gating and MOCCO reconstruction and compare this approach against a more general compressed sensing reconstruction that uses temporal total variation (CS-TV). We assess performance of these methods using a simulated breast phantom with respiratory motion and contrast kinetics allowing evaluation of reconstruction accuracy against the ground truth kinetics. Evaluation of both spatial and temporal quality was also performed in a first in-vivo patient volunteer.

5.2 Methods

5.2.1 Numerical simulation

A supine breast digital reference object (DRO) that included respiratory motion was developed for simulating a 3D stack-of-stars radial acquisition (**Figure 5.2.1**). Imaging simulation parameters were chosen to replicate a conventional clinical bilateral breast protocol with prone position in terms of coverage and spatial resolution: FOV = 340 mm x 340 mm, in-plane spatial resolution = 0.75 mm x 0.75 mm, and matrix size = 448 x 448 x 142. Circles with diameters of 10 mm, 13 mm, 17 mm, and 20 mm were used to simulate lesions with circumscribed margins. The extended Tofts model^{115,116} was used to simulate lesion signal changes as a function of time similar to what is observed in-vivo. An arterial input function based on the publicly available dispersion model described by Barboriak et. al. was used to generate the DCE-MRI data.¹¹⁷ To cover a range of different lesion types, seven lesions were simulated based on PK parameters outlined in the ACR BI-RADS Breast Magnetic Resonance Imaging²² including two malignant-like lesions ($K^{trans} > 0.25 \text{ min}^{-1}$ and $k_{ep} > 1.0 \text{ min}^{-1}$), three benign-like lesions ($K^{trans} < 0.25 \text{ min}^{-1}$ and $k_{ep} < 1.0 \text{ min}^{-1}$) and two intermediate-like lesions ($K^{trans} > 0.25 \text{ min}^{-1}$ and $k_{ep} < 1.0 \text{ min}^{-1}$). A total of 1024 respiratory phases based on respiratory self-gating signal with frequency of 20 cycles per minute were simulated and the corresponding k-space radial lines were sampled from the motion images. Data from the end-expiration phase (phase 4) were selected using the self-navigation algorithm (Fig 1A) for the contrast enhanced reconstruction. The spoiled gradient recalled echo (SPGR) signal model was then used to generate signal time curves assuming a field strength of 3 T, T_1 value of breast tissue ($T_{10} = 1444 \text{ ms}$ ¹¹⁸), and contrast agent relaxivity of $r_1 = 4.9 \text{ mM}^{-1}\text{s}^{-1}$ to simulate Gd-BOPTA (gadobenate dimeglumine, Multihance, Bracco, Milan,

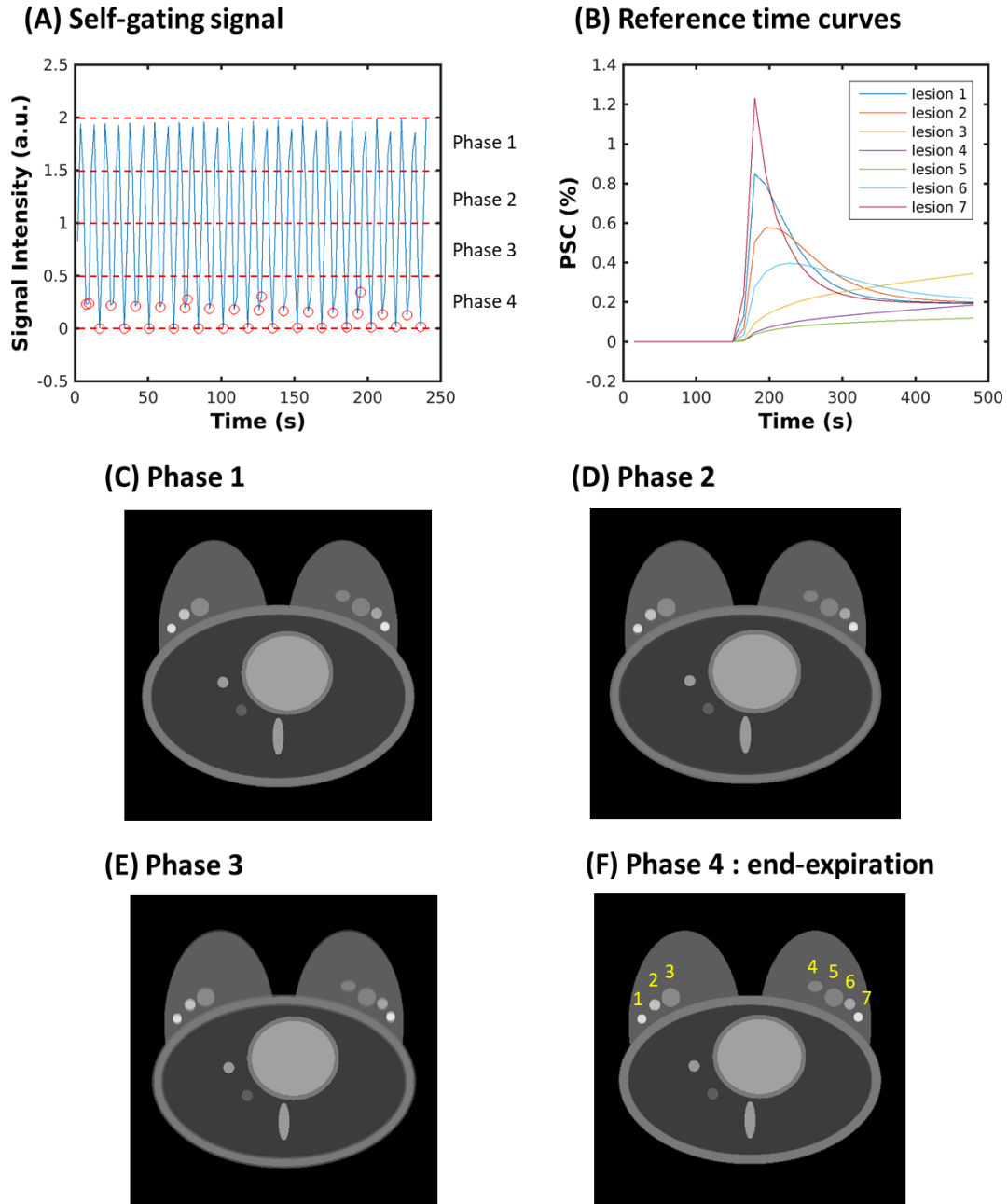


Figure 5.2.1: A breast DRO with respiratory motion and simulated lesions generated with seven different contrast enhancement patterns. Example of four different respiratory phases (C-F) generated by averaging the motion images from the corresponding time points sorted by the respiratory self-gating signal (A). The accepted radial spokes from end-expiration phase (F) are shown as red circles, and the corresponding curves of the true percent signal change (PSC) for seven lesions are shown in (B).

Italy)¹¹⁹ , and imaging flip angle (FA = 30°). Images containing both static and dynamic features were then sampled using the non-uniform fast Fourier transform (NUFFT) to simulate k-space data generated from an undersampled golden-angle radial acquisition consisting of 1024 projections $\times$ 16 individual RF coil elements.

5.2.2 Reconstruction

Self-gating was performed on the simulated k-space data to group similar respiratory positions and minimize intra-time-frame motion. The self-gating signal was extracted from the DC components of projections at $k_z=0$ and a low pass filter with frequency of 0.6 Hz was applied to the DC series to select respiratory-only signal. A 1D Fourier transform was performed to generate projection intensity profiles from each coil, followed by principle component analysis. The principle component with the highest peak was selected to represent the self-gating respiratory signal. Following this, the respiratory signal was divided into four distinct respiratory states and time-resolved images with 15 s temporal resolution were reconstructed using a MOCCO algorithm¹⁰¹ with quadratic (l_2) regularization. MOCCO relies on a temporal model of order K (number of temporal basis functions) which is typically estimated from low resolution images reconstructed from fully sampled k-space center via independent component analysis (ICA)¹¹³. Since the number of projections per individual respiratory phase image may be low due to rejection of data due to motion, a regularized SENSE reconstruction¹⁷² was used to estimate low-resolution images to improve SNR. Model orders K=5 and K=3 were selected for MOCCO reconstruction of both numerical simulation and in-vivo data, respectively. A regularization parameter of 10 was used for both MOCCO and CS-TV. Iterative SENSE, and compressed sensing with temporal total variation (CS-TV) were also performed for comparison.

5.2.3 Human Subjects

Three subjects were enrolled in this IRB-approved and HIPPA-compliant study including one patient volunteer. Imaging was performed using a clinical 3T MR scanner (Premier, GE Healthcare, Waukesha, WI) with a very lightweight and flexible peripheral receive array (AIR Coil, GE Healthcare) placed over the top of the volunteer as well as the in-table receive array below. A radial stack-of-stars acquisition with golden angle view ordering was performed during a free-breathing contrast injection (gadobenate dimeglumine, Multihance; Bracco Inc, Milan, Italy) followed by a Cartesian acquisition using navigator-gating. Scan parameters included: TR/TE = 4.57/2.08 ms; FOV = 40 cm; flip angle = 15; receiver bandwidth = 83.3 kHz; acquisition matrix = 448 x 448 x 100; acquisition resolution = 0.9 x 0.9 mm in-plane and 1.4 mm out of plane resolution. The total scan time for radial acquisition was 8 mins; for single time frame Cartesian acquisition with navigator-gated is 8:43 (min:s).

5.3 Results

Signal intensity time curves are shown for all simulated lesions with varying enhancement patterns following SENSE, CS-TV, and MOCCO reconstructions in **Figure 5.3.1**. Both the CS-TV and MOCCO approaches generated temporal signal curves that were free of signal oscillations including those due to respiratory motion, as compared to iterative SENSE. MOCCO reconstruction with higher model order $K=5$ was found to better recover the original lesion temporal enhancement kinetics, including rapid wash-in and wash-out in lesion 1 (**Figure 5.3.1, B**) and lesion 7 (**Figure 5.3.1, H**).

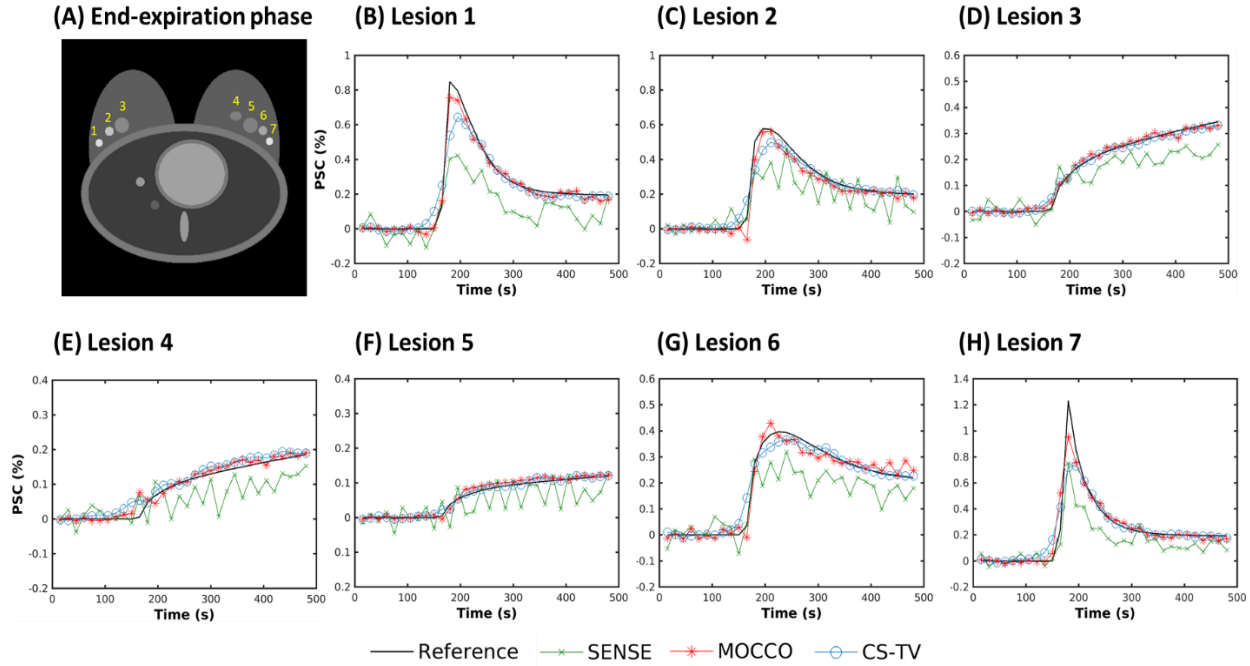


Figure 5.3.1: Percent signal change (PSC) measured in ROIs placed at seven lesions with different contrast kinetics (A). Curves from SENSE (green, X) showed large oscillations due to the presence of undersampling artifacts. Both MOCCO (red, stars) and CS-TV (blue, circles) displayed accurate recovery of most lesion kinetics (C-G). Note some underestimation of the sharp wash-in and wash-out slopes in lesion 1 (B) and lesion 7 (H) was observed.

Results from SENSE, CS-TV, and MOCCO reconstruction at end-expiration phase are shown in **Figure 5.3.2**. Both CS-TV and MOCCO showed significant improvement in recovering spatial resolution compared with SENSE. Some residual low intensity streak artifact is visible at the edge of the axillae region due to remaining data inconsistency from the chest wall motion compared to the motion-free reference image. Despite showing slightly more streak artifacts, MOCCO provided better overall temporal fidelity and sharper lesion edges compared with CS-TV.

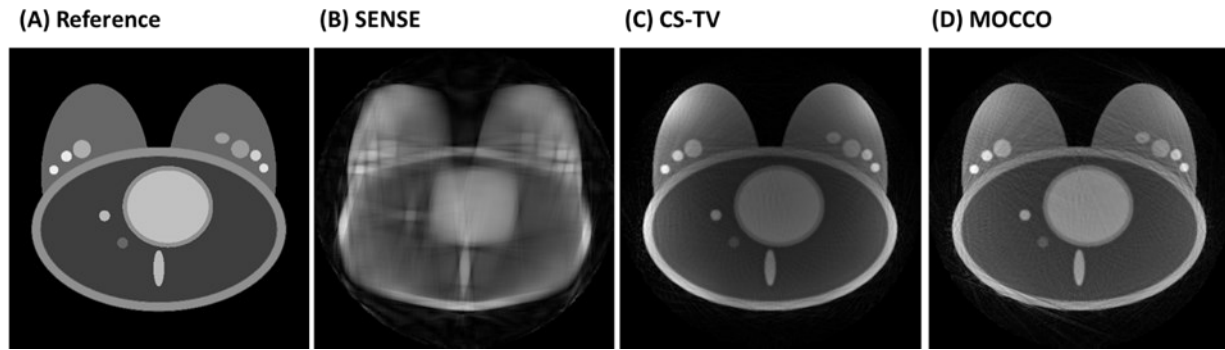


Figure 5.3.2: A representative time-frame at the peak intensity (time = 200s) comparing reference image (A) with undersampled reconstructions using SENSE (B), CS-TV (C), and MOCCO (D) at end-expiration phase.

Figure 5.3.3 shows example images reconstructed by using SENSE, CS-TV, MOCCO reconstruction compared against the conventional Cartesian acquisition with navigator-gating at the end-expiration respiratory phase in the patient volunteer. Free-breathing radial acquisition using CS-TV and MOCCO with model order $K=3$ allows visualization of enhancing lesions in the fibroglandular tissue without evidence of motion and/or significant undersampling artifacts. Both reconstruction methods demonstrated similar image quality to the conventional Cartesian acquisition with navigator-gating. However, the Cartesian acquisition with navigator-gating requires much more time to acquire only a single motion-resolved time frame, which is not suitable for time-resolved imaging.

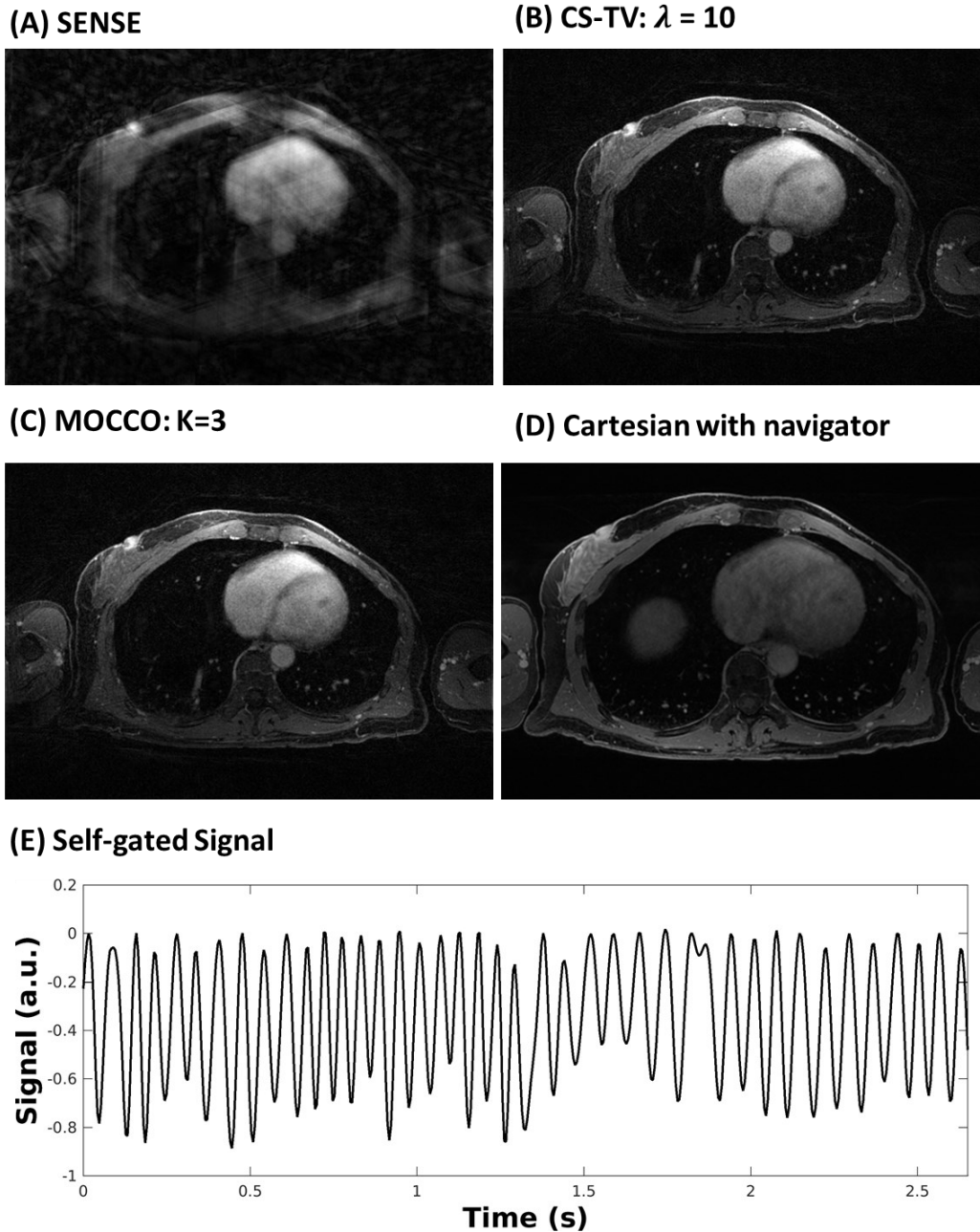


Figure 5.3.3: Time frames with peak intensity (time = 240 s) reconstructed using SENSE (A), CS-TV (B), MOCCO with model order K=3 (C) with temporal resolution of 15 s. High image quality is observed for both regularized reconstructions (B, C). Note the late-phase post-contrast enhanced image (D) was acquired with Cartesian acquisition using navigator-gating, which resulted in a longer acquisition time (8:43 min:s). (E) demonstrated the self-gated signal extracted from the acquisition k-space data.

Signal intensity time curves are shown for aorta, lesion, and fibroglandular tissue following SENSE, CS-TV, and MOCCO reconstruction in **Figure 5.3.4**. Temporal curves measured from MOCCO with $K=3$ showed better recovery of the temporal fidelity in all three tissue types. On the contrary, to fully recover the spatial resolution, a high regularization parameter was used for CS-TV resulting in over-smoothing of the tissue intensity.

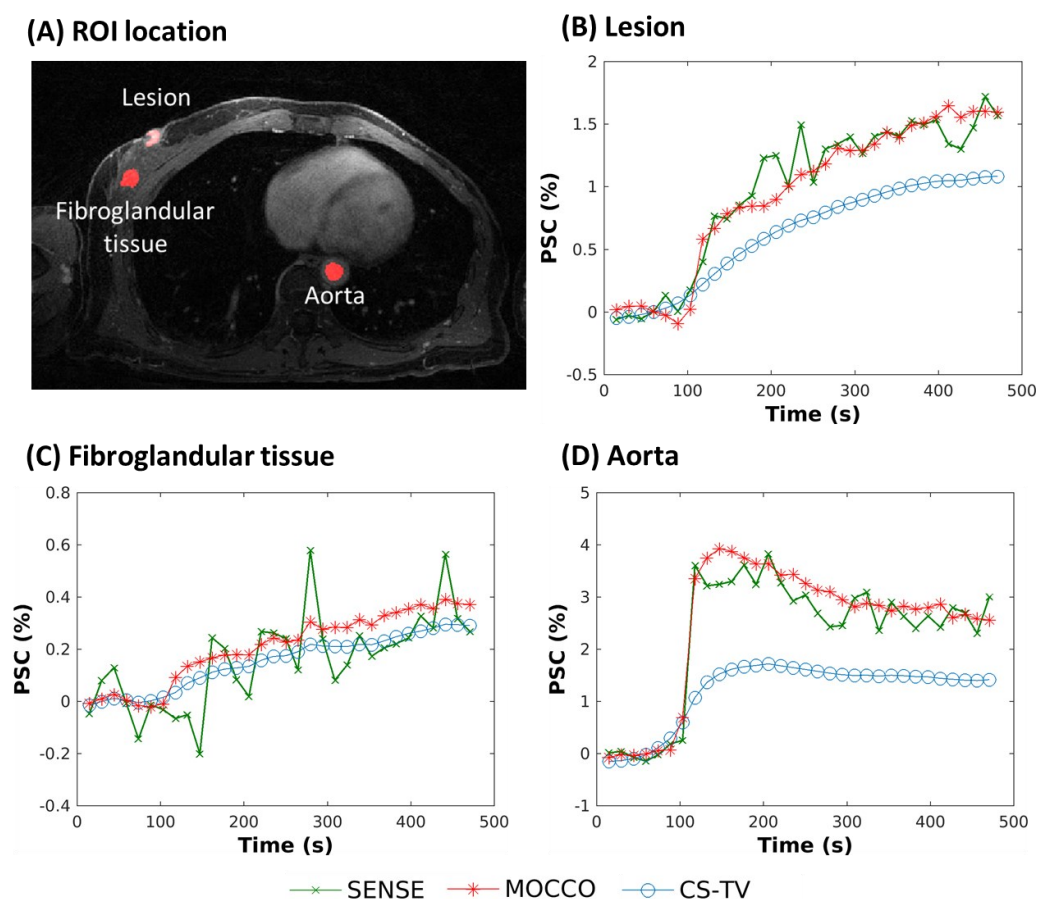


Figure 5.3.4: Supine images from a patient volunteer reconstructed using SENSE (green, X), CS-TV (blue, circles), and MOCCO with model order $K=3$ (red, stars) with 15 s temporal resolution. PSC (%) are plotted from ROIs placed in the lesion, fibroglandular tissue, and aorta (A). Rapid wash-in and wash-out contrast kinetics are observed in the aorta. The lesion showed relatively rapid contrast update, while the fibroglandular tissue showed slower contrast uptake.

5.4 Discussion

In this study, we demonstrate the feasibility of providing motion-free high spatial and temporal resolution supine breast DCE-MRI using radial acquisition with MOCCO reconstruction. Numerical simulations are employed to evaluate the reconstruction accuracy on both spatial and temporal quality with the presence of the respiratory motion. Further, the proposed technique is applied to in-vivo data with the acquisition parameters matched the current clinical protocol for prone position. The MOCCO approach is compared to another CS-based reconstruction algorithm that uses temporal total variation as a sparsity transform (CS-TV) as well as the more conventional SENSE technique.

We have demonstrated that by extracting the DC term of each radial spoke at z-direction to conduct patient specific respiratory self-gating signal can provide sufficient information for the motion sorting process. To show that the self-gating signal has the ability to represent patient breathing motion over time, we have compared the respiratory self-gating signal to the respiratory signal recorded from the MRI vendor provided built-in respiration belt. A high correlation was observed between the two respiratory signals in our normal volunteer scans (shown in **Figure 5.4.1**). Many studies have proposed using this technique for free-breathing liver DCE-MR liver images. To the best of our knowledge, no studies have demonstrated proposed self-gating technique for bilateral supine breast DCE-MRI. The challenge of bilateral supine breast DCE-MRI comes in the tradeoff between spatial and temporal resolution, which further accentuated in supine imaging due to the need to accommodate motion robustness. Our patient volunteer results indicate that the proposed technique could provide motion robust supine breast images with 15s temporal resolution, and spatial resolution of 0.9×0.9 mm, which meets the minimum requirement for spatial resolution by the American College of Radiology for breast DCE-MRI²².

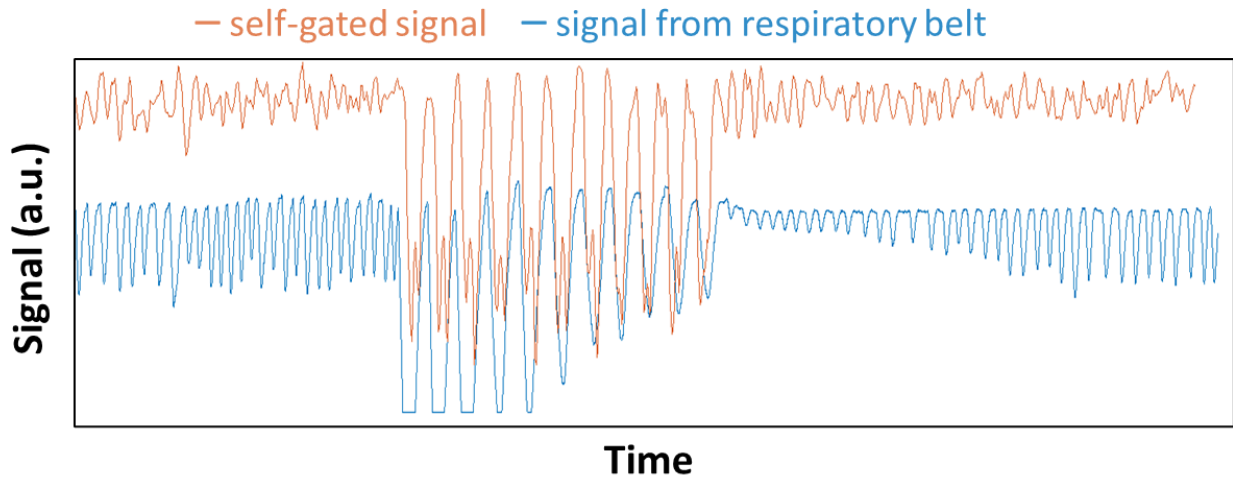


Figure 5.4.1: Example of respiratory signals from one of our normal volunteers. The subject was asked to take normally breaths at the beginning of the acquisition. During the scan, the volunteer was instructed to take several deep breaths followed by normal breathing until the end of the acquisition. High agreement was observed between the self-gated signal extracted from radial acquisition (orange) and respiratory signal recorded from the respiratory belt.

Previous studies have demonstrated that MOCCO was less sensitive to the selection of the regularization parameters in the setting of prone position for breast DCE-MRI¹⁵⁷. The results showed that MOCCO has the ability to provide similar balance between image quality and temporal fidelity across a wide range of regularization parameters. The optimized λ value ($\lambda=10$) used in previous study showed great recovery of both spatial and temporal fidelity in prone position with 5s temporal resolution. In the proposed setting of supine imaging, both simulation and in-vivo results showed that an effective temporal resolution of 15 s with matched spatial resolution was achievable for supine breast DCE-MRI using the same regularization parameter ($\lambda=10$). On the contrary, our study showed that additional tuning of the regularization parameter is required for CS-TV and that it was necessary to choose between image quality and temporal fidelity when

changing the imaging protocol. Further, our proposed technique has the ability to generate both time-resolved images for one respiratory phase and/or multiple respiratory motion-phase images, which may enable evaluation of the lesion contrast kinetics for treatment monitoring or the evaluate of the lesion movements for treatment planning and surgical planning.

Our study has several limitations. The current work demonstrates initial feasibility with only limited in-vivo results. A future study in a larger patient cohort is needed to better assess image quality and the potential clinical value, such as in the setting of pre-surgical or treatment planning, and treatment monitoring. Some residual streak artifacts can still be observed using MOCCO reconstruction due to the high undersampling factors and future work is needed to improve the spatial quality. Third, the results also indicated that it may be especially challenging to obtained sufficient temporal basis ($K=3$) in situations with highly undersampled images due to the increased number of motion states. Therefore, further work is needed to investigate obtaining the temporal basis from other techniques (e.g. dictionary learning¹⁵⁸). This work presented the ability to characterize different tissue types by plotting the tissue signal curves from the reconstructed images; however, further evaluation is needed to test the robustness of quantitative PK modeling approaches.

5.5 Conclusion

In conclusion, we have introduced a technique for free-breathing supine breast DCE-MR. We compared both spatial and temporal performance of SENSE, CS-TV, and MOCCO reconstruction in numerical simulations and in-vivo data. Both simulation and in-vivo results demonstrated that an effective temporal resolution of 15 s with spatial resolution of 0.9×0.9 mm was achievable for free-breathing supine breast DCE-MRI. The MOCCO technique demonstrated improved temporal

fidelity when matching spatial resolution and coverage from routine clinical protocols at prone position as compared with CS-TV.

Chapter 6

Summary and Future Work

6.1 Summary

DCE-MRI using conventional Cartesian acquisition is currently applied in routine clinical practice due to its high sensitivity for detecting breast cancer, however, temporal resolution is usually sacrificed to achieve sufficient spatial resolution. A new technique, 3D stack-of-stars golden angle radial acquisition combined with compressed sensing reconstruction, has been proposed to achieve high spatial and temporal resolution breast DCE-MRI to provide not only high-quality spatial images but also robust quantitative measurements. However, to translate this radial approach into clinical practice it is necessary to address several remaining questions. The goal of this work was to evaluate the spatial and temporal characteristics of using the proposed technique when applied to breast DCE-MRI with high temporal resolution while maintaining clinically acceptable spatial resolution.

6.1.1 Preliminary studies for breast images using radial acquisition

The continuously acquired radial acquisition using Golden Angle view ordering has the flexibility to allow image reconstruction using relatively arbitrary selection of the temporal resolution. In this chapter, we delivered three preliminary studies to evaluate the performance of radial acquisition using gridding reconstruction for multi-phase breast DCE-MRI compared against the conventional Cartesian acquisition. Our preliminary studies showed that radial acquisition mitigates the left-right ghosting artifact typically seen on breast DCE images caused by cardiac motion that may

obscure important visualization of the chest wall, lymph nodes, and axillary structures. However, data inconsistencies due to motion or overly aggressive angular undersampling was found to lead to a reduction of image sharpness or streak artifacts in radial acquisition. The degradation of the image sharpness resulted in a negative impact on the preference of radiologist readers toward this technique. Additionally, based on previous success with a deep-learning (DL) reconstruction using CNN to reduce noise, blurring, and ringing in Cartesian acquisition, this work investigated repurposing this DL algorithm to also mitigate streak in radial acquisition. The results demonstrate that a DL algorithm can be used to improve the overall SNR, sharpness, and remove streak artifacts. However, one disadvantage of the DL reconstruction is that it may cause over-smoothing in normal tissue and result in loss of some textural information. Therefore, further optimization of the DL reconstruction is needed.

6.1.2 Time-resolved radial acquisition with compressed sensing reconstruction

Multi-phase breast DCE-MRI with high spatial resolution provide high sensitivity for breast cancer detection but are known to have insufficient temporal resolution to fully capture rapidly changing contrast kinetics across both breasts. Advanced acquisition and reconstruction strategies aim to improve spatial and temporal resolution and increase specificity for disease characterization. In this chapter, we proposed using radial acquisition combined with a modified data-driven low-rank based (MOCCO) compressed sensing reconstruction to achieve high spatial and temporal resolution images. The spatial and temporal fidelity were validated by using a digital reference object as the ground truth. The results were compared to compressed sensing with temporal total variation (CS-TV).

The results demonstrated that the use of MOCCO reconstruction with stack-of-stars radial acquisition for breast DCE-MRI allows for an effective temporal resolution of 5 s at a clinically relevant spatial resolution. The numerical simulation showed that radial acquisition with MOCCO was able to capture rapid lesion kinetics while providing high image quality across a range of optimal regularization values, whereas the CS-TV demonstrated either recovery of high spatial resolution with reduced temporal accuracy using large regularization values, or recovery of rapid lesion kinetics with reduced image quality using low regularization values.

6.1.3 Quantitative DCE-MRI using pharmacokinetic modeling

Radial acquisition with MOCCO reconstruction has been proposed for generating high spatial and temporal resolution breast DCE-MRI. In our previous chapter, we demonstrated improved temporal fidelity while matching spatial resolution and coverage from routine clinical protocols as compared with CS with total variation. However, there is a need to validate the accuracy and robustness of pharmacokinetic (PK) parameter estimation using our proposed technique if it is to be used in clinical practice. In this work, we use a breast digital reference object with the ability to provide a wide range of lesion contrast kinetics using the extended Tofts model for PK simulation. A voxel-by-voxel quantitative analysis was applied and compared with the ground truth.

The results indicated that MOCCO was able to recover curves with K^{trans} values ranging from 0.01 to 0.8 min^{-1} and fixed $V_e = 0.3$, where the fitted results are within a 10% bias error range. Underestimation of K^{trans} was found in the fastest lesion kinetic curves but MOCCO still showed the ability to capture rapidly enhancing lesion characteristics.

6.1.4 Respiratory self-gated free breathing supine breast DCE-MRI

Advanced acquisition and reconstruction methods have been proposed to improve spatial and temporal resolution for prone breast DCE. However, limited work has been performed in the supine setting, which is used in most downstream clinical services including surgery and biopsy. The major challenge of the supine position is the presence of the respiratory motion. To minimize the effect of the respiratory motion in the time-resolved images, we proposed using radial acquisition combined with self-gating and MOCCO reconstruction to provide motion-free high spatial-temporal resolution breast DCE-MRI. We assess performance of these methods using a simulated breast phantom with respiratory motion and contrast kinetics allowing for the evaluation of reconstruction accuracy relative to the assigned ground truth. Evaluation of both spatial and temporal quality was also performed in in-vivo patient volunteers. The results were all compared to CS-TV.

In these results, both simulation and in-vivo data demonstrated that the effective temporal resolution of 15 s with spatial resolution of 0.9x0.9 mm was achievable for supine breast DCE-MRI using radial acquisition combined with self-gating and MOCCO reconstruction. Further, our results also indicated that MOCCO outperformed CS-TV with respect to recovering varying lesion contrast kinetic while still maintaining similar image quality.

6.2 Future Work

Pharmacokinetic (PK) modeling offers a quantitative approach to analyze the tissue response of gadolinium-based contrast agent and provide perfusion properties in the microenvironment of the targeted tissue. However, dynamic image intensity in DCE-MRI images

cannot be used directly for kinetic model fitting because it does not proportionally reflect the contrast agent concentration in tissues. Our previous study demonstrated that radial acquisition with MOCCO reconstruction can provide high temporal fidelity and robustness to recover temporal enhancement curves for quantitative analysis in the setting of breast DCE-MRI. However, a measurement of the native T_1 value of the tissue is also needed to accurately measure PK parameters¹⁴⁴.

The standard method for T_1 mapping uses 2D-inversion recovery (IR) fast spin echo (FSE)⁸ due to its high SNR and accurate measurement of T_1 . However, long acquisition times and limited spatial coverage makes this approach unsuitable for routine clinical usage. Using another approach, 3D variable flip angle (VFA) acquisitions, we acquire multiple SPGR images at multiple flip angles⁹. The gradient echo acquisition helps to reduce the scan time and allow for higher spatial resolution. However, even the 3D VFA approach is still typically considered too long to include in routine clinical protocols.

Multiple T_1 mapping approaches have combined Cartesian acquisition with parallel imaging to reduce the total scan time and yield single-slice T_1 maps within 10-20s with modest spatial resolution (~2mm in-plane), which is used for cardiac and abdominal imaging applications¹⁷³. Non-Cartesian approaches, such as radial acquisition, are an alternative sampling pattern. The golden-angle radial acquisition has an intrinsic tolerance of certain level of undersampling. Therefore, studies have proposed using radial acquisition with golden-angle ordering for T_1 mapping in brain, chest and abdominal lesions^{72,174} to reduce the total acquisition time. To the best of our knowledge, the VFA combined with radial acquisition has not been validated yet in breast DCE-MRI. The purpose of this proposal is to demonstrate the feasibility of measuring T_1 map using VFA method with radial acquisition for breast DCE-MRI.

6.2.1.1 Experiments and Preliminary Results

A T1 phantom was constructed consisting of four vials filled with CuSo₄ at concentrations of 0.5, 1, 2, and 4mM to generate different T1 values along with 2% agarose gel (**Figure 6.2.1**: Photograph of vials containing CuSo₄ at concentration of 0.5, 1, 2, and 4 mM.

). The phantom was maintained at room temperature at all times. Imaging was performed on a clinical PET/MRI (Signa PET/MR, GE Healthcare, Waukesha, WI) with an 8-channel head coil (GE Healthcare, Waukesha, WI).



Figure 6.2.1: Photograph of vials containing CuSo₄ at concentration of 0.5, 1, 2, and 4 mM.

Images were acquired in the axial plane using 2D inversion recovery (IR) fast spin echo (FSE) (2D-IR-FSE) with several inversion times. The acquisition parameters of the 2D-IR-FSE scans were as follows: TR/TE = 3000/7.124 msec; slice thickness = 4 mm; slice number = 3; acquisition matrix size = 128× 128; FOV= 140×140 mm; FA = 90; echo train length = 8; inversion time (TI) = 50, 100, 150, 200, 250, 500, 750, 1000, 1250, 1500, 1750, 2000, 2250, 2500 msec, and the scan time for each TI is 1 min 4 sec, for a total scan time of 14 min 55 sec.

The measured T1 values from the 2D-IR-FSE data were considered as the reference method to validate the 3D radial VFA approach. To estimate T1 values, a non-linear least squares (NLS)

regression was performed with a three-parameter signal model using the built-in functions in MATLAB (version 2015b; The Mathworks, Natick, MA, USA).

$$S \propto M_0 \left(1 - 2e^{-\frac{TI}{T_1}}\right) \quad [15]$$

$$S = a + be^{-TI/T_1} \quad [16]$$

A 3D T1 mapping with VFA were acquired with 3D stack-of-stars golden-angle spoiled gradient echo (SPGR) imaging sequence. The acquisition parameters of 3D radial VFA for T1 mapping were as follows: TR/TE = 6.28/1.44 msec; slice thickness = 4 mm; slice number = 18; acquisition matrix size = 128×128; FOV= 140×140 mm; FA = 2, 5, 10, 15, 20, 30. Each flip angle included 128 projections with scan time of 22 sec. The total scan time for 6 flip angle is 2 min 12 sec. To convert the SPGR signal intensity to the T1 value, the SPGR signal equation was described as:

$$S_{SPGR} = \frac{M_0(1-E_1)\sin\alpha}{1-E_1\cos\alpha} \quad [17]$$

where $E_1 = \exp\left(-\frac{TR}{T_1}\right)$, α is the flip angle, M_0 is the equilibrium longitudinal magnetization,

Further, the measured T1 values can be extracted by applying a two-compartment model with a NLS regression, $Y = mX + b$ showed as:

$$\frac{S_i}{\sin\alpha_i} = E_1 \frac{S_i}{\tan\alpha_i} + M_0(1 - E_1) \quad [18]$$

From the fitting result, the slope m is the estimated E_1 , and the T1 could be extracted:

$$T_1 = -TR/\ln(m) \quad [19]$$

To evaluate the spatial accuracy of the T1 measurements reconstructed by applying different undersampling factors, the FA images were reconstruction with projection number (N_{proj}) of 128, 50, 34, 25, 20, 17, with the corresponding undersampled factor of 1.5, 4, 6, 10, and 12. **Figure 6.2.2** shows the example of the radial profiles with projection number of 128, 50, and 17.

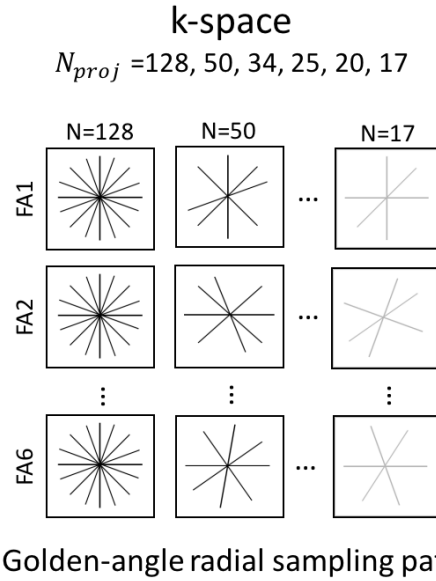


Figure 6.2.2: Placements of the radial profiles with the golden-angle radial increments. Six undersampling factors were assigned to reconstruct the image series with different flip angle.

T1 measurements made in phantoms with both the IR-FSE and VFA with undersampled radial acquisition techniques at 3T are summarized in **Table 6.2.1**. The T1 values were decreased as the CuSO4 concentration increased. The same result could be seen in all T1 measurements.

Table 6.2.1: T1 measurements among different parameters

CuSO4	0.5mM	1mM	2mM	4mM
IR-FSE	1003.43±97.9	730.45±38.5	436.43±12.2	258.50±4.5
VFA: $N_{proj}=128$	1053.96±37.3	803.89±20.6	479.46±14.8	278.67±14.9
VFA: $N_{proj}=50$	1061.20±72.2	824.66±41.3	483.89±17.0	283.14±22.0
VFA: $N_{proj}=34$	1073.64±55.1	837.15±30.6	499.48±22.3	294.60±17.3
VFA: $N_{proj}=25$	1083.53±120.4	856.15±41.3	512.42±22.3	303.87±17.1
VFA: $N_{proj}=20$	1103.44±116.5	887.59±69.6	534.99±26.2	315.41±18.5
VFA: $N_{proj}=17$	1098.63±83.1	902.89±39.2	544.52±21.6	309.49±20.0

The reconstructed FA images with different total radial projections are shown in **Figure 6.2.3**. The vials were well represented with $N_{\text{proj}} = 128$ and 50, with the corresponding undersampling factor of 1.5 and 4. However, the streak artifacts were observed when N_{proj} less than 34.

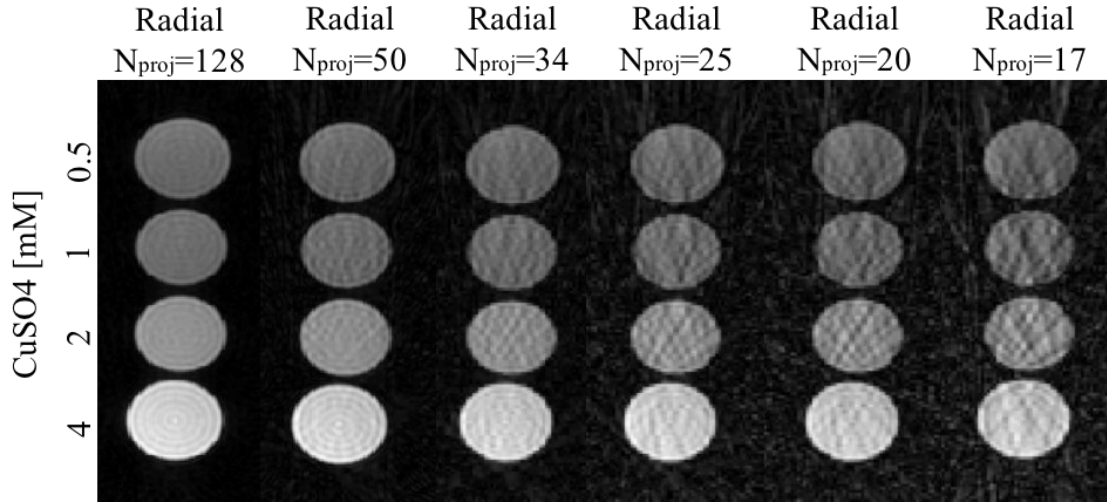


Figure 6.2.3: One example of the reconstructed radial images with FA = 10. The incoherent streak artifacts could be observed with $N_{\text{proj}} < 50$. The streak artifacts may obscure the entire vial with $N_{\text{proj}} = 17$.

In **Figure 6.2.4**, the reference images using IR-FSE showed homogeneous T1 measurements across the entire vials for all four CuSO₄ concentrations. VFA images with $N_{\text{proj}} = 128$ demonstrated similar image quality with IR-FSE, but the total scan time is 6 times shorter. With $N_{\text{proj}} < 128$, the acquisition time could be reduced by the additional factor of 4, 6, 8, 10 and 12 associated with the $N_{\text{proj}} = 50, 34, 25, 20$ and 17. However, the T1 maps showed increased heterogeneity as the degree of undersampling factor increased.

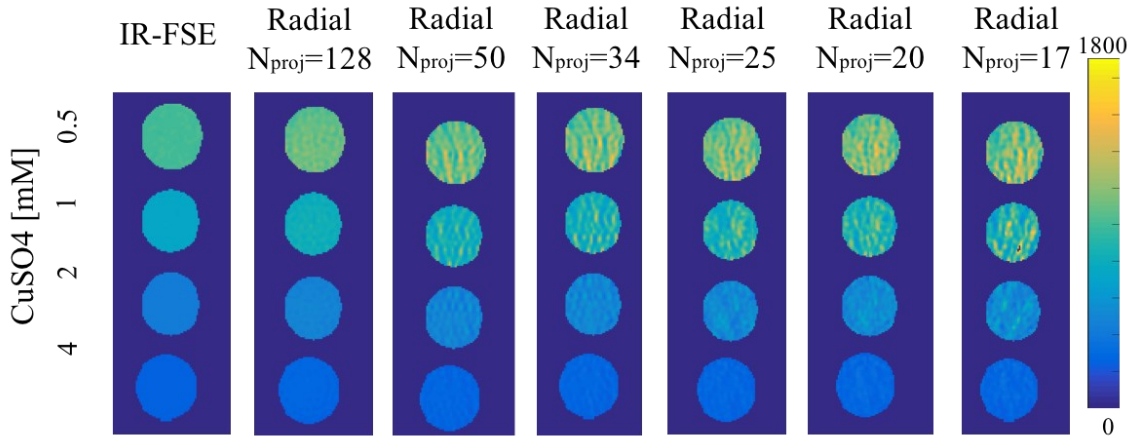


Figure 6.2.4: T1 maps with IR-FSE and VFA with fully and undersampled radial acquisition. The degree of heterogeneity in T1 vials could be observed as the function of the decreasing projection numbers as well as the decreasing CuSO_4 concentration (T1 value).

6.2.1.2 Research plan

The preliminary results show the feasibility of generating T1 maps by using VFA with radial acquisition. One limitation of this preliminary study is that the acquisition protocol is not optimized for our clinical application. To achieve the same spatial resolution and spatial coverage, a higher undersampling factor is required for radial acquisition to match the same acquisition time. However, we noted in the phantom study that increasing the acceleration factor can introduce additional streak artifact that is assumed to be one of the factors to cause the inaccurate measurements of the T1 values. One potential solution is to combined radial acquisition with more advanced compressed sensing reconstruction to mitigate the streak artifacts and several studies have shown that using the proposed technique can provide robust T1 map for cardiac imaging^{175,176}. Therefore, we hypothesize that this technique can be extended to breast imaging, where the combined radial acquisition and compressed sensing reconstruction strategy can maintain spatial resolution and but provide more robust T1 measurements.

6.2.2 Improvement of the current DL algorithm for breast MRI

According to our reader study results in the evaluation of image quality of radial+DL, we found that radial+DL showed slightly lower score in the category of artifacts in breast and axilla. One of our readers indicated that the radial+DL tend to over-smoothing the anatomical structure as a result in loss of the texture and heterogeneity in normal tissue. We have learned that there are several parameters could be tuned to adjust the image quality in the deep learning algorithm and de-noise weighted is one of the possible factors that could cause the over-smoothing problem. **Figure 6.2.5** showed the radial+DL images with denoise weighted from 0.05 to 1 and compared against the original radial images without using deep learning algorithm. According to the results, the original radial images showed some heterogeneity within the fibroglandular tissue, whereas the loss of the texture were observed with the increased of the denoise weighted. These results indicated that the choice of the reconstruction parameters in the DL reconstruction allows the user to optimize the image quality.

In addition, the images reconstructed by using the compressed sensing reconstruction can also be incorporated into the training process due to its ability to improve SNR and spatial resolution in undersampled radial data. This technique may pave the way for more challenging imaging scenarios such as supine breast imaging for the purpose of surgical/radiation treatment planning or patient comfort where respiratory motion then becomes another source of artifact. This technique may pave the way for more challenging imaging scenarios such as supine breast imaging for the purpose of surgical/radiation treatment planning or patient comfort where respiratory motion then becomes another source of artifact.

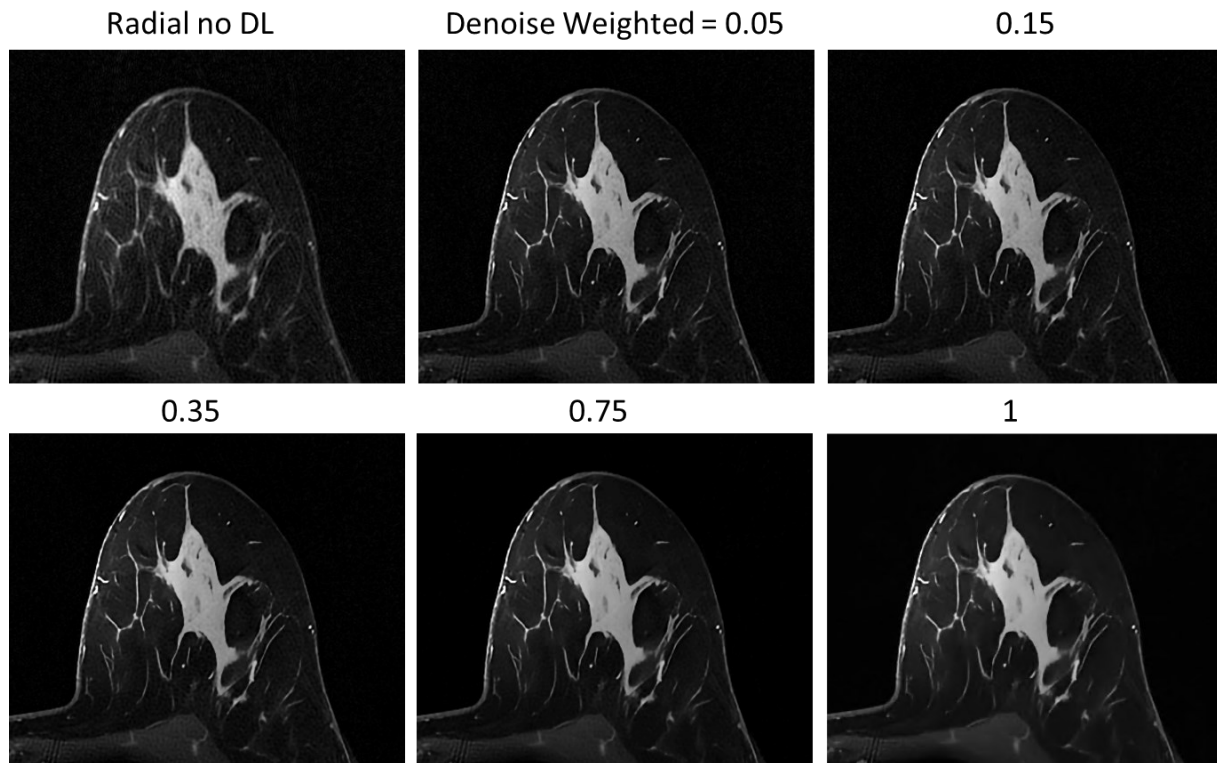


Figure 6.2.5: A patient example comparing the image performance with different denoise weighted. Note that the radial+DL images included in the reader study were reconstructed using denoise weighted at 0.75.

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