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Advances in Brief
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COVER ILLUSTRATION
Diagnosis of early stage acute kidney injury would benefit from timely assessment of local-regional tissue hypoxia. In the paper by Pohlmann et al., the feasibility of intravascular contrast-enhanced MRI is examined for monitoring renal blood volume fraction. Findings provide a foundation towards advancing multiparametric MRI for renal blood volume mapping to ultimately yield an image-based renal MR oximetry measure for assessment of acute kidney injury.
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Ultra-Low-Dose Sparse-View Quantitative CT Liver Perfusion Imaging

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Key Words: sparse-view image reconstruction, compressed sensing, radiation dose reduction, quantitative liver perfusion imaging, hepatic arterial blood flow

Abbreviations: Hepatic arterial blood flow (HABF), hepatocellular carcinoma (HCC), dynamic contrast-enhanced (DCE), filtered backprojection (FBP), compressed sensing (CS), computed tomography perfusion (CTP)

Radiation dose of computed tomography liver perfusion imaging can be reduced by collecting fewer x-ray projections in each gantry rotation, but the resulting aliasing artifacts could affect the hepatic perfusion measurement. We investigated the effect of projection undersampling on the assessment of hepatic arterial blood flow (HABF) in hepatocellular carcinoma (HCC) when dynamic contrast-enhanced (DCE) liver images were reconstructed with filtered backprojection (FBP) and compressed sensing (CS). DCE liver images of a patient with HCC acquired with a 64-row CT scanner were reconstructed from all the measured projections (984-view) with the standard FBP and from one-third (328-view) and one-fourth (246-view) of all available projections with FBP and CS. Each of the 5 sets of DCE liver images was analyzed with a model-based deconvolution algorithm from which HABF maps were generated and compared. Mean HABF in the tumor and normal tissue measured by the 328-view CS and FBP protocols was within 5% differences from that assessed by the reference full-view FBP protocol. In addition, the tumor size measured by using the 328-view CS and FBP average images was identical to that determined by using the full-view FBP average image. By contrast, both the 246-view CS and FBP protocols exhibited larger differences (>20%) in anatomical and functional assessments compared with the full-view FBP protocol. The preliminary results suggested that computed tomography perfusion imaging in HCC could be performed with 3 times less projection measurement than the current full-view protocol (67% reduction in radiation dose) when either FBP or CS was used for image reconstruction.

INTRODUCTION

There has been considerable improvement in the therapeutic treatments for hepatocellular carcinoma (HCC) and other metastatic diseases in recent years. These advanced therapies require diagnostic and surveillance tools beyond morphology to prevail (1). Quantitative computed tomography perfusion (CTP) can go beyond morphological classification and provide a more accurate tissue characterization via quantitative assessment of hepatic arterial blood flow (HABF), which is a useful marker of primary and metastatic hepatic malignancies (1). However, one limitation of the CTP assessment of HABF is the higher radiation dose arising from repeatedly scanning the liver after contrast administration (1-3).

Radiation dose reduction for a hepatic CTP study can be achieved by scanning the liver with low x-ray tube current (measured in milliampere) (4, 5). Although the x-ray photon noise in projections can be modeled and corrected for using statistical iterative reconstruction algorithms (6), the dominant electronic noise in very low milliampere conditions cannot be properly modeled with Poisson statistics alone (7), which may lead to poor tumor visualization and inaccurate assessment of hepatic perfusion. Alternatively, dose reduction can be achieved by reducing the number of projections collected in each gantry rotation. However, the aliasing artifact arising from projection undersampling could substantially affect the dynamic contrast-enhanced (DCE) liver images, which could lead to inaccurate hepatic perfusion measurement.

Compressed sensing (CS) was first introduced for signal recovery from underdetermined linear measurements (8) and later exploited for magnetic resonance imaging and computed tomography (CT) reconstruction in sparse sampling conditions (9-12). In this study, we investigated the effectiveness of CS and the conventional filtered backprojection (FBP) for reconstructing DCE-CT images of the liver from a subset of measured projections in an HCC perfusion study, to determine if sparse-view dynamic acquisition and image reconstruction are feasible for ultra-low-dose CT liver perfusion imaging.
MATERIALS AND METHODS

CS-Based CT Image Reconstruction

CT images are typically smooth except at the boundaries, that is, differences in image values (expressed in Hounsfield units) between adjacent pixels are insignificant, and hence, the first derivative of the images tends to be zero except at the edges where different neighboring materials constitute abrupt changes in image values. This spatial sparsity can be exploited by compressed sensing (CS), where CT image reconstruction is formulated as a constrained optimization problem (12):

$$\min_x \sum_i \|D_i x\|_1, \text{ s.t. } Ax = p$$

where $x$ is the reconstructed attenuation coefficient, $D_i x$ is the discreet gradient of $x$, $A$ is the design matrix, $p$ is the measured projection, and $\|\cdot\|$ is the 2-norm. We used the total variation minimization in our CS algorithm to more effectively preserve the edges compared with other available algorithms (12), thus prohibiting the spillover of the high-density regions to adjacent low-density regions. The total variation minimization in the above equation was solved using the augmented Lagrangian multiplier method as described in Li et al.’s study (12).

RESULTS

Figure 1A–C shows the average liver images that correspond to the full-view (984-view) FBP (Figure 1A), sparse-view (328-view) FBP (Figure 1B), and sparse-view CS (Figure 1C) protocols. The 328-view FBP and CS average images were comparable with the reference full-view FBP average image in terms of anatomical details, as the diameter of the liver tumor measured by using each average image was 1.39 cm.

Figure 2, A–C shows the $H_{ABF}$ maps acquired by the same protocols as in Figure 1. The mean $H_{ABF}$ value in the tumor region measured by using the full-view FBP $H_{ABF}$ map was 59.8 ± 14.1 mL/min/100g (Figure 2A), which was within 2.6% and 0.7% of the mean $H_{ABF}$ value measured by using the 328-view FBP $H_{ABF}$ map (61.4 ± 15.0 mL/min/100g; Figure 2B) and the 328-view CS $H_{ABF}$ map (59.4 ± 14.8 mL/min/100g; Figure 2C), respectively. A similar agreement in $H_{ABF}$ measurement was observed in the adjacent normal tissue region: 26.0 ± 8.2 mL/min/100g from full-view FBP (Figure 2A) compared with 24.8 ± 5.1 mL/min/100g from the 328-view FBP (Figure 2B) and 25.6 ± 12.1 mL/min/100g from the 328-view CS (Figure 2C).

When the number of projection views further reduced to 246 (extremely sparse-view condition), both FBP and CS reconstruction manifested larger anatomical and functional discrepancies with respect to the full-view FBP scheme. The tumor diameter measured by using the 246-view FBP and CS average images was 1.06 cm (Figure 1D) and 1.13 cm (Figure 1E), respectively, which were 26.9% and 20.6% smaller than that measured by using the 984-view FBP average image (1.39 cm; Figure 1A). With regard to $H_{ABF}$ measurement, the 246-view FBP and CS protocols overestimated $H_{ABF}$ in the normal liver region by 26% (32.7 ± 22.8 mL/min/100g) and 35% (35.1 ± 25.4 mL/min/100g), respectively, relative to the full-view FBP protocol (26.0 ± 8.2 mL/min/100g). By contrast, differences in $H_{ABF}$ in the tumor region were <5% among the 3 protocols, as follows: 57.7 ± 33.4 mL/min/100g from 246-view FBP versus 56.9 ± 16.2 from 246-view CS versus 59.8 ± 14.1 mL/min/100g from 984-view FBP. Although the mean $H_{ABF}$ measured from the two 246-view protocols was comparable, the 246-view FBP protocol exhibited a larger standard deviation of the mean compared with the 246-view CS protocol (33.4 vs 16.2 mL/min/100g).

The liver in each map is outlined by an orange solid line. All $H_{ABF}$ maps are displayed with a color scale ranging from 0 to 250 mL/min/100g.
DISCUSSION

CT perfusion is a useful tool for quantitative measurement of \( H_2BF \), which is a useful marker of primary and metastatic hepatic malignancies. In this study, we simulated the sparse-view dynamic acquisition for low-dose CT liver perfusion imaging by reconstructing the DCE liver images from an evenly spaced subset of the measured projections. The results from this simulated sparse-view HCC patient study suggested that the \( H_2BF \) measured from 328-view dynamic acquisition with either FBP or CS image reconstruction was comparable with that measured from the conventional full-view dynamic acquisition with FBP reconstruction.

Furthermore, the DCE liver images acquired with the 328-view FBP and CS protocols had a slightly smoother appearance compared with those acquired with the full-view FBP; this was because of the regularization applied in the CS algorithm to reduce the streak artifacts arising from sparse projection sampling. Owing to the ill-conditioning of the CT reconstruction, a regularization is necessary to minimize error propagation in the presence of noise during image reconstruction.

Although the edges in the 328-view CS DCE image (Figure 1C) were slightly smoother compared with the reference 984-view FBP DCE image (Figure 1A), the spatial resolution was sufficient to assess the location and extent of the HCC lesion. In our study, the diameter of the tumor lesion measured by using the 328-view CS and 984-view FBP DCE images was identical (1.39 cm). Further, the high resolution of DCE liver images is not necessary for measuring liver perfusion because liver perfusion maps are generated at one-half of the spatial resolution of the source images. This is evident by the example shown in Figure 2, in which the hepatic arterial blood flow maps in Figure 2A–C had comparable perfusion values in the tumor and normal tissue regions. However, further reduction in the number of projections to <328 has led to substantial degradation in the DCE liver images and to inaccurate \( H_2BF \) measurement, regardless of whether FBP or CS was used for image reconstruction.

These results have 2 implications—first, the radiation dose of a liver CT perfusion study could be reduced by 67% from the full-view dynamic acquisition protocol without affecting the accuracy of hepatic perfusion measurement. The effective radiation doses of the full-view and the sparse-view protocols for 80-mm coverage of the liver were 11.3 and 3.8 mSv, respectively. Our finding also suggests that the DCE liver images could not be reconstructed with fewer than 328 projections without affecting the image resolution (tumor visualization) and accuracy of the hepatic perfusion measurement. Although additional

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**Figure 1.** Average dynamic contrast-enhanced (DCE) liver images acquired with different image reconstruction protocols: 984-view FBP (A), 328-view FBP (B), 328-view CS (C), 246-view FBP (D), and 246-view CS (E). All images are displayed with 50 Hounsfield Units (HU) window width and 70HU window level.
dose reduction could be achieved by reducing the x-ray tube current in conjunction with the sparse-view dynamic acquisition, the increased projection noise may pose challenges to both analytical (FBP) and iterative (CS) image reconstructions, particularly in the sparse sampling condition. Second, the conventional and fast FBP algorithm may be sufficient for the reconstruction of DCE liver images from sparsely sampled projections without the need of CS, which is computationally intensive. The shorter image reconstruction time with FBP may facilitate the clinical implementation of the sparse-view CT liver perfusion imaging.

The computation time required to reconstruct one DCE liver image with CS is about 10 times longer than that required to reconstruct the same with FBP. For the 984-view reconstruction using a desktop computer (the computer specifications have been provided in the main text above), the average time required for FBP and CS to reconstruct one DCE image was 20.4 and 207.6 seconds, respectively; for the 328-view reconstruction, the corresponding time required for FBP and CS to reconstruct one DCE image was 7.1 and 69.2 seconds, respectively. The process time was roughly linearly proportional to the number of projections used for image reconstruction. It should be noted that all clinical CT systems are equipped with a much more powerful processing unit than our desktop computer. Hence, the computation time required for the 328-view CS reconstruction should be much shorter.

Apart from the sparse-view approach, x-ray exposure in quantitative CT-liver perfusion imaging can be decreased by reducing the x-ray photon flux (controlled by the x-ray tube current measured in milliampere) used for scanning. Reducing x-ray tube current in conjunction with sparse projection sampling may further decrease the radiation dose of a CT-liver perfusion imaging study. However, decreasing the tube current may limit the visualization of low-contrast components (5), which can be problematic for quantitative assessment of CT perfusion. Further investigation is needed to determine the effect of low milliampere on sparse-view image reconstruction with CS.

In conclusion, our findings obtained on the basis of the study conducted in a single patient with HCC showed that the diagnostic quality of the liver anatomical images and $H_A BF$ maps acquired with a sparse-view (328-view) dynamic acquisition and reconstruction protocol was not inferior to that acquired with a conventional full-view (984-view) dynamic acquisition and FBP reconstruction protocol. Although the preliminary findings suggested that the proposed sparse-view approach could lead to a substantial dose reduction (up to 67%
lower) compared with the conventional protocol, more HCC studies are needed to confirm the usefulness of the proposed sparse-view approach for low-dose quantitative CT perfusion imaging of the liver.

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REFERENCES
High-Frequency 4-Dimensional Ultrasound (4DUS): A Reliable Method for Assessing Murine Cardiac Function

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Key Words: ultrasound, cine MRI, cardiac disease, mouse, hypertrophy

INTRODUCTION

Murine cardiac disease models have become the foundation for systematically studying mechanisms and factors that influence negative outcomes such as heart failure (1-3). Although ex vivo techniques (eg, histology, proteomics) provide substantial information regarding gross and molecular composition, their information is limited to the state of tissue at sacrifice. In vivo imaging, on the other hand, can provide longitudinal information and result in a more comprehensive understanding of disease progression, particularly when studying changes in cardiac function. Although many noninvasive imaging modalities exist, high-frequency ultrasound and cine magnetic resonance imaging (MRI) are most widely used to assess murine cardiac function (4-6).

High-frequency ultrasound uses megahertz-frequency ultrasonic waves to acquire images of the heart, with contrast corresponding to differences in acoustic impedance between tissue types. This modality is particularly useful for imaging mice, as even with their rapid heart rates (approaching 600 bpm), near-real-time temporal resolution can be achieved. Nevertheless, standard ultrasound imaging techniques for calculating cardiac function (eg, short-axis motion-mode or M-Mode [SAX MM]) require the use of geometric models to estimate the ventricular volumes as spheres, ellipsoids, or other shapes (7, 8). Although these geometric assumptions are commonly used to study heart function in vivo (9, 10), the left ventricle (LV) in a mouse has a complicated 3-dimensional shape, which can increase in complexity with varying disease states.

Cardiac cine MRI exploits the contrasting magnetic properties of myocardial tissue and flowing blood to collect volumetric information across a heartbeat. These 4-dimensional (3-dimensional + time) data are spatiotemporally compiled from spatially adjacent slices of cine data across the heart. Compared with ultrasound, cine MRI takes longer to process images because the region of interest must be sampled several times before each slice of cine data can be properly reconstructed. However, cine MRI is often considered a gold standard method for acquiring LV information, as the chamber’s entire boundary can be directly imaged (11-13). Unfortunately, acquiring cine MRI data is often costlier owing to system availability, maintenance, and required infrastructure for operating a superconducting magnet.

Building upon the idea of spatiotemporally compiling loops of MRI data, we present here an automated 4D ultrasound (4DUS) technique that provides comparable information to cine MRI through spatiotemporally synced imaging of cardiac motion. Cardiac function metrics derived from SAX MM, cine MRI, and 4DUS data show close agreement between cine MRI and 4DUS but overestimations by SAX MM. The inclusion of a mouse model of cardiac hypertrophy further highlights the precision of 4DUS compared with that of SAX MM, with narrower groupings of cardiac metrics based on health status. Our findings suggest that murine 4DUS can be used as a reliable, accurate, and cost-effective technique for longitudinal studies of cardiac function and disease progression.
technique that can provide comparable information free of heuristics. We compared this technique against conventional SAX MM and cine MRI by using cardiac function metrics to assess their relative performance. The results of this murine study suggest that cardiac 4DUS has advantages over standard 2D techniques and can be used as an alternative to cine MRI.

**METHODOLOGY**

**Murine Models**

In total, 10 female mice were used in this study. All mice were bred at Purdue University and derived from Cpt2-/- mice crossed with Cre-expressing mice, in which Cre was driven by the muscle creatine kinase promoter [Stock No: 006475; Jackson Laboratories, Bar Harbor, ME, USA; (14, 15)]. Mice deficient in cardiac Cpt2 (Cpt2M-/-; n = 5; age = 11.2 weeks; body mass = 20.1 [0.71] g), hereafter referred to as the Cpt2M cohort, have impaired cardiomyocyte fatty acid oxidative metabolism owing to compromised transport of long-chain fatty acids into the mitochondria through acyl-carnitine-mediated transport (14). Our previous work showed that the loss of cardiac Cpt2 results in left ventricular hypertrophy (15). Control mice, hereafter referred to as the wild-type cohort, were littermates lacking the Cre gene (Cpt2fl/fl; n = 5; age = 11.2 weeks; body mass = 19.5 [0.57] g). All animal experiments were approved by the Purdue Animal Care and Use Committee.

**Magnetic Resonance Imaging**

Cardiac MRI data were compiled for each mouse from adjacent short-axis cine loops across the LV by using a small-bore 7 T MRI system (BioSpec 70/30 USR, Bruker Corporation, Billerica, MA). A circularly polarized transmit/receive 1H volume coil was used in combination with a retrospectively gated Fast Low-Angle SHot (IntraGateFLASH) sequence with in-slice navigator used in combination with a retrospectively gated Fast Low-Resolution -/H11005/ H11002/ H11003 (16, 17) with repetition time/echo time of 300 fps cardiac- and respiratory-gated cine loops and spatiotemporally compiled them into 4D data. A volumetric field of view was prescribed to ensure that the end-diastolic epicardium would fit in all frames, spanning from the apex to the aortic valve. The axial and lateral pixel sizes were set at 12.0 × 55.2 µm (axial resolution = 40 µm; lateral resolution = 90 µm), with a step-size of 76.2 µm. Figure 1B shows a representative example of 4DUS data at end-diastole, with axial, sagittal, and coronal slices through the center of the LV, similar to the magnetic resonance data display.

Following 4D data collection, the probe was positioned midpapillary with a short-axis orientation. A line and cursor defining the SAX MM data were prescribed down the center of the ventricle, and ~5 seconds of data were acquired. Figure 1A shows a representation of the prescribed cursor and corresponding SAX MM data.

**Anesthesia and Physiological Monitoring**

Mice were anesthetized during each imaging procedure using a low-flow vaporizer (SomnoSuite, Kent Scientific, Torrington, CT) with ~2.5% isoflurane at 250 mL/min (18). The exact anesthetic level was modulated as needed to maintain a heart rate near 500 beats/min and respiration rate near 60 breaths/min. During MRI, heart rate and respiration were monitored by means of 3 subcutaneous needle electrodes and a pneumatic pillow pressure sensor, respectively (SA Instruments, Stony Brook, NY). Furthermore, each animal was maintained at 37°C by using a feedback-modulated fan that blew heated air into the bore of the magnet. During ultrasound imaging, a heated stage with integrated gold-plated electrodes (Vevo Imaging Station, FUJIFILM VisualSonics Inc.) warmed the animal to a temperature of approximately 37°C while also obtaining heart rate and respiratory signals. Respiratory signals were simultaneously extracted from gold-plated electrodes by filtering low-frequency signal fluctuations, caused by changes in impedance across the lungs during inhalation. Rectal temperature probes were used to monitor core body temperature with both imaging systems.

**Cardiac Function Assessment**

Using a custom MATLAB GUI and Vevo 3100 compatible VevoLAB analysis software (v3.0) for the MRI and 4DUS data, respectively, the endocardial and epicardial borders of the LV were manually outlined across short-axis views of the heart. The endocardial border was used to define the LV chamber, and the endocardial and epicardial borders were used in conjunction to define the LV myocardium. Maintaining conventions set by the American Society of Echocardiography (9, 10), the proximal extent of the LV cavity was defined as the mitral and aortic valves, and the papillary muscles were considered part of the LV cavity. These guidelines were followed across all animals, regardless of gross differences in heart size or shape. Figure 2, A and B illustrates an example of the aforementioned border definitions.

Expanding mask creation in the 4DUS data, we manually outlined slices that were ~0.3–0.5 mm (ie, 4–6 slices) apart and we then used cubic spline interpolation to fill in the boundaries over skipped regions (Figure 2C; middle). To ensure that using such interpolation will not produce large deviations from the expected ground truth, a sensitivity analysis was performed; LV mask volumes were compared over a series of gap sizes and
position paradigms. Figure 2C shows an example cross-sectional area profile for a mask without any gaps (ie, complete masking) and for 2 subsequent gap paradigms. Quantifying the percent difference in the volume of every gap paradigm from the complete masking, Figure 2D shows the results of sensitivity analysis for an example wild-type, early-stage disease, and late-stage disease mouse. We observed that gap sizes approximately /H11349 0.5 mm did not produce percent differences in mask volumes /H11022 1%, thus providing us confidence in the reliability of our masking protocol.

To extract measurements from the SAX MM data, the VevoLAB software was used to draw lines corresponding to the endocardial and epicardial borders through at least 3 cardiac cycles. Estimates of left ventricular geometry were thus calculated using the mean of corresponding measurements at end-diastole and peak-systole (ie, maximum and minimum distances between endocardial borders). A single reviewer performed all measurements to prevent interoperator variability.

Ventricular chamber volumes defined by the endocardial border from MRI and 4DUS data measured at end-diastole volume (EDV) and peak-systole volume (PSV) were used to calculate the LV stroke volume (SV) and ejection fraction (EF). To estimate the mass of the LV myocardium (ie, left ventricle mass [LVM]), EDV was subtracted from the total volume defined by the epicardial border at EDV (EpiEDV), and the resultant volume

Figure 1. Representative displays of the imaging modalities used on an example mouse: short-axis M-Mode (SAX MM) (A), 4D ultrasound (4DUS) (B), and bright-blood gradient echo magnetic resonance imaging (MRI) (C). The SAX MM row shows the prescribed cursor for sampling (dashed yellow line) along with corresponding data time-synced to ECG signals. Both 4DUS and MRI rows show long-axis (left), short-axis (center), and 4-chamber (right) views at corresponding slice locations (scale bar = 2.0 mm).
multiplied by a cardiac tissue density of 1.05 mg/μL (19, 20). The equations used to calculate cardiac function include:

\[
EF = \frac{(EDV - PSV)}{EDV} \times 100
\]

\[
SV = EDV - PSV
\]

\[
LVM = 1.05 \times (EpiEDV - EDV)
\]

In contrast to direct measurements from the volumetric data, the M-Mode analysis used the Teichholz equation to quantify the LV volume (LVV), as follows:

\[
LVV = \frac{7.0}{(2.4 + LVID)} \times LVID^3
\]

Where left ventricular inner diameter (LVID) is used to estimate the geometry of the ventricle at any corresponding point in the cardiac cycle (21). These estimated EDV and PSV values were incorporated into the same equations as above to calculate EF and SV. Calculations of LVM on the basis of M-Mode data incorporated the measured thickness of the LV anterior wall (LVAW) and LV posterior wall (LVPW), as shown in the following equation:

\[
LVM = 1.05 \times (EpiEDV - EDV)
\]
LVM = \(1.05 \times [\text{LVID} + \text{LVAW} + \text{LVPW}]^3 - \text{LVID}^3\) \times 0.8

**Histology**
Following imaging, mice were euthanized with CO\(_2\) overdose and cervical dislocation. Hearts were excised and then placed directly in 4.0% paraformaldehyde and stored at 4°C. After 6 days, hearts were transferred to 0.1% paraformaldehyde and again stored at 4°C until histology was performed. Each heart was embedded in paraffin and sectioned along the midpapillary short axis of the LV. Tissue sections were stained with H&E and Masson’s Trichrome following standard protocols.

**Statistical Analysis**
Differences between imaging methods were assessed in scatter dot plots. A 1-way ANOVA with multiple comparisons was performed to identify significant differences between each pairing of methods. To compare cardiac function metrics between the 3 methods and 2 groups of mice (ie, wild-type and Cpt2\(_{M}\)/–/–), 2-way ANOVA with Tukey corrections for multiple comparisons was performed.

**RESULTS AND DISCUSSION**
The present study introduces an automated 4DUS technique and compares its performance in assessing cardiac function with that of conventionally used SAX MM and MRI methods. Quantified metrics of cardiac function (ie, EDV, PSV, EF, SV, and LVM) from each of the 3 aforementioned techniques, acquired on each subject, were the basis for comparison. The 4DUS and MRI methods did not produce significant differences in any of the used metrics, whereas the SAX MM overestimated these values on average (Figure 3). The 1-way ANOVA indicated a significantly larger EF obtained from SAX MM than from 4DUS (\(P = .020\)), larger SV from SAX MM than from both 4DUS (\(P = .001\)) and MRI methods (\(P = .005\)), and larger EDV from SAX MM than from 4DUS (\(P = .021\)). Because cine MRI data are widely accepted as a gold standard in measuring chamber volumes, our findings suggest that 4DUS could be a reliable alternative to cine MRI. Furthermore, as 4DUS and MRI do not rely on simplified models of LV geometries, these results provide further evidence that the geometric models used in SAX MM could be a source of inaccuracy in assessing cardiac function (8-10).

Subsequent analysis compared method performance taking into account cohort classifications (ie, wild-type or Cpt2\(_{M}\)/–/–). Table 1 shows metric averages separated by cohort and identifies significant differences following a 2-way ANOVA, which incorporated both imaging modality and cohort as factors. Neither wild-type nor diseased mice showed any significant difference between the 4DUS and MRI techniques, similar to the results of our initial 1-way ANOVA analysis. However, significantly larger values were observed for SAX MM versus MRI methods in (1) the wild-type group for EDV (\(P = .014\)) and SV (\(P = .002\)) and in (2) the diseased group for EF (\(P = .02\)) and LVM (\(P = .002\)). Furthermore, the SAX MM had significantly larger values than the 4DUS methods in (1) the wild-type group.
for EDV ($P = .013$) and SV ($P = .001$) and in (2) the diseased group for SV ($P = .014$) and LVM ($P = .002$). The only insignificant interaction between imaging method and cohort was for LVM ($P = .116$); however, this is most likely because of the large overestimation by SAX MM in the $Cpt2^{M/-}$ cohort. Interestingly, SAX MM overestimated EDV in our wild-type mice, but the differences in LVM measurements were not significant; an opposite trend was observed in the $Cpt2^{M/-}$ group. We originally hypothesized that if either SAX MM metric (ie, EDV or LVM) would be inaccurate, it would be when cardiac morphology deviated from the wild-type state. Instead, the observed overestimation of LVM in the wild-type cohort suggests that the wild-type murine myocardium may be smaller than assumed in the used geometric models. Conversely, future use of SAX MM in murine models may consider refinement of the equations used to calculate the presented metrics, to better match the morphology of the murine heart.

Although we have so far focused on the agreement between each imaging modality, the use of $Cpt2^{M/-}$ mice also shows the benefit of acquiring reliable function metrics toward characterizing cardiac remodeling and the ultimate progression to heart failure. As observed in recent literature, this mouse model develops early concentric hypertrophy of the LV followed by chamber dilation (15). Representative histology (Figure 4) confirms the

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Representative Masson’s Trichrome histology of the various disease stages imaged, with magnifications at $4\times$ (scale bar = 1.0 mm) (A), $10\times$ (scale bar = 200 $\mu$m) (B), and $40\times$ (scale bar = 100 $\mu$m) (C). The first row shows a representative nonmutated mouse ($n = 5$), in which wild-type cardiomyocyte size and density are observed. The second row shows an early stage of hypertrophy ($n = 3$), in which enlarged cardiomyocytes are observed without any noticeable necrosis. The third row shows a late stage of hypertrophy ($n = 2$), in which enlarged cardiomyocytes and cell necrosis with less stain uptake are both observed.
presence of both late (n = 2) and early (n = 3) stages of the disease within the Cpt2\textsuperscript{M\textsuperscript{-/-}} cohort, characterized by gross cardiomyocyte hypertrophy with or without notable cardiomyocyte necrosis (ie, hypereosinophilia and loss of cross striations), respectively. Plots of EF versus SV and EDV versus LVM (Figure 5) illustrate how both the wild-type and diseased cohorts can be characterized by physiologic- or morphologic-oriented metrics, respectively. In plots of EF versus SV, we note that while the stroke volume is relatively conserved for all mice, only early-stage-disease mice preserve an EF comparable to wild-type mice. In plots of EDV versus SV, both metrics seem to gradually increase with the relative stage of disease, illustrating somewhat distinct groupings based on the wild-type, Cpt2\textsuperscript{M\textsuperscript{-/-}} phenotype with early-stage disease, and Cpt2\textsuperscript{M\textsuperscript{-/-}} phenotype with late-stage disease. To demonstrate these groupings, data were displayed as both individual points and average distributions for the wild-type and Cpt2\textsuperscript{M\textsuperscript{-/-}} cohorts. These plots qualitatively exhibit the method agreement between MRI and 4DUS methods that have been quantitatively studied above.

Despite the advantages of 4DUS including rapid acquisition (eg, 5–10 min for 4DUS, <1 min for SAX MM, and 45–60 min for cine MRI), relatively low cost, and high spatiotemporal resolution, this approach does have several limitations compared with cine MRI. First, sternum, rib, and lung artifacts limit the imaging window and can obscure portions of the heart. This can be particularly difficult if interested in right ventricular pathologies, as the sternum artifact can blur a large portion of its endocardial borders. Second, similar to cine MRI, accurate ECG and respiration signals are required to spatiotemporally compile the 4DUS images. To this end, pathologies that include cardiac arrhythmias will need to be tested to ensure proper spatiotemporal compilation. Third, the higher spatial and temporal resolution of 4DUS information comparably increases the digital size of the data. Although most commonly available computational resources can handle such data sizes for analysis, down-sampling in the spatial and/or temporal domain can serve to reduce computational costs if desired.

In conclusion, we show in this study that 4DUS can provide data that are comparable to cine MRI for quantifying cardiac function metrics, with improved precision and accuracy over SAX MM ultrasound. Nevertheless, SAX MM is used widely as a relatively rapid and economical option for longitudinal studies of cardiac disease in murine studies (4, 5). Fortunately, the benefits of ultrasound and volumetric acquisition can be combined with only a slightly longer scan time compared with SAX MM. Using 4DUS imaging, rapid assessments with high-frequency ultrasound can be conducted with the crucial advantage of producing reliable measurements similar to the gold standard of cardiac MRI without assuming an idealized geometric model. Furthermore, the added benefit of higher through-plane resolution compared with MRI may help provide clearer data for studying cardiac disease models in which the myocardium evolves into more complex
High-Frequency 4-Dimensional Ultrasound

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REFERENCES


Experimental MRI Monitoring of Renal Blood Volume Fraction Variations En Route to Renal Magnetic Resonance Oximetry

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INTRODUCTION
Kidney diseases are a global health burden with steadily increasing incidence (1-4), leading to an estimated worldwide death toll of 2 million per year from AKI (5-7). The currently available methods of assessing risk and therapeutic options for AKI are limited (5, 6, 8-10). Although a number of biochemical markers are being evaluated for use in diagnosis, risk assessment, and prognosis of AKI, there are currently no specific biomarkers that permit point-of-care diagnosis for early-stage AKI (4, 11, 12). Translational approaches for the assessment of early-stage AKI and for the study of renoprotective strategies are urgently required (13-16). Strategies under consideration include novel imaging techniques being evaluated for use in diagnosis, risk assessment, and prognosis limited (5, 6, 8-10). Although a number of biochemical markers are being assessed for use in diagnosis, risk assessment, and prognosis of AKI, there are currently no specific biomarkers that permit point-of-care diagnosis for early-stage AKI (4, 11, 12). Translational approaches for the assessment of early-stage AKI and for the study of renoprotective strategies are urgently required (13-16). Strategies under consideration include novel imaging techniques being evaluated for use in diagnosis, risk assessment, and prognosis limited (5, 6, 8-10).

Early features in the pathophysiology of AKI that could lend themselves to detection by noninvasive magnetic resonance imaging (MRI) include renal tissue hypoperfusion and hypoxia—factors that are also important during the progression from AKI to chronic kidney diseases (16, 19-25). An imbalance between renal oxygen supply and demand appears to also play a prominent role in the pathophysiology of diabetic nephropathy (26). Renal oxygenation can be indirectly assessed through the blood oxygenation level-dependent (BOLD) magnetic resonance imaging (MRI) contrast (27), which can be observed through measurements of effective transversal relaxation time T2*. Indeed, mapping of renal T2* (or its reciprocal, R2*) is an established MRI method that is increasingly being used to study kidney disorders (28-30).

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Abbreviations: Acute kidney injury (AKI), blood volume fraction (BVf), free induction decay (FID), magnetic resonance imaging (MRI), oxygen saturation of hemoglobin (SO2), ultrasmall superparamagnetic iron oxide (USPIO), near-infrared spectroscopy (NIRS), signal-to-noise ratio (SNR), time-of-flight (TOF), venous occlusion (VO), radiofrequency (RF), repetition time (TR), echo time (TE), regions of interest (ROIs), multiecho gradient-echo (MGE), multi-spin echo (MSME)

ABSTRACT
Diagnosis of early-stage acute kidney injury (AKI) will benefit from a timely identification of local tissue hypoxia. Renal tissue hypoxia is an early feature in AKI pathophysiology, and renal oxygenation is increasingly being assessed through T2*-weighted magnetic resonance imaging (MRI). However, changes in renal blood volume fraction (BVf) confound renal T2*. The aim of this study was to assess the feasibility of intravascular contrast-enhanced MRI for monitoring renal BVf during physiological interventions that are concomitant with variations in BVf and to explore the possibility of correcting renal T2* for BVf variations. A dose-dependent study of the contrast agent ferumoxytal was performed in rats. BVf was monitored throughout short-term occlusion of the renal vein, which is known to markedly change renal blood partial pressure of O2 and BVf. BVf calculated from MRI measurements was used to estimate oxygen saturation of hemoglobin (SO2). BVf and SO2 were benchmarked against cortical data derived from near-infrared spectroscopy. As estimated from magnetic resonance parametric maps of T2 and T2*, BVf was shown to increase, whereas SO2 was shown to decline during venous occlusion (VO). This observation could be quantitatively reproduced in test–retest scenarios. Changes in BVf and SO2 were in good agreement with data obtained from near-infrared spectroscopy. Our findings provide motivation to advance multiparametric MRI for studying AKIs, with the ultimate goal of translating MRI-based renal BVf mapping into clinical practice en route noninvasive renal magnetic resonance oximetry as a method of assessing AKI and progression to chronic damage.
Renal BOLD MRI is based upon the $T_2^*$ dependence on $O_2$ saturation of hemoglobin (SO$_2$) and motivated by the link between SO$_2$, blood partial pressure of O$_2$ (pO$_2$), and tissue pO$_2$. However, questions have been raised regarding the interpretation of BOLD MRI data in the kidney as a surrogate of tissue oxygenation (30). These concerns were triggered by the following recent findings from renal $T_2^*$ mapping: simultaneous renal pO$_2$ and $T_2^*$ measurements showed considerable discrepancies in the quantitative relationship between changes in renal $T_2^*$ and those in renal tissue pO$_2$ for different functional regions of the kidney and for various (patho)physiological scenarios (31). The renal $T_2^*$ to tissue pO$_2$ relationship is not governed exclusively by renal blood oxygenation, but it is also heavily influenced by a number of confounders (30, 31). Of particular importance are renal blood oxygenation, but it is also heavily influenced by renal BVf (38). The USPIO nanoparticle preparation ferumoxytol (36, 37). Analyzing the dynamic susceptibility contrast changes during bolus passage necessitates fast imaging with a temporal resolution of about 1 s, as well as measurement of the arterial concentration–time curve and its deconvolution from the tissue time curves. Renal dynamic susceptibility contrast was successfully implemented in dogs (36) and rats (37), but the methodological requirements limit the achievable spatial resolution and make this approach particularly challenging in small animals.

More recently, steady-state renal BVf measurements were performed by taking advantage of blood pool markers such as ultrasmall superparamagnetic iron oxide (USPIO) agents (38, 39); the change in transverse relaxation rate $R_2$ was examined in the kidney of mice (40) and rats (38). The steady-state approach comprises the simple subtraction of pre- and postcontrast maps of $R_2^*$ (41) (or $R_2$ if only small vessels are of interest), and it has the further benefit of facilitating the continuous monitoring of renal BVf (38). The USPIO nanoparticle preparation ferumoxytol has proven very useful for this (38, 42–45), as it can be administered intravenously without the risk of impaired renal oxygenation or perfusion (46), and it exhibits a long intravascular half-life of >14 h in humans and ~2 h in small rodents (43, 44, 47). The goal of the current study was to determine whether intravascular contrast-enhanced MRI can be used as a means of monitoring BVf in physiological settings, in which significant variations in both renal BVf and renal oxygenation are expected, and, furthermore, to explore the possibility of correcting renal BOLD measurements for BVf variations. A previous study by Storey et al. (38) used steady-state BVf monitoring during the administration of vasoactive drugs, but the induced $R_2$ variations (in the absence of USPIO) were attributed to changes in tubular volume fraction rather than BVf or oxygenation. Here, we investigate the feasibility of renal BVf monitoring in rat kidneys at 9.4 T as a means of achieving a comprehensive renal MR oximetry protocol. For this purpose, ferumoxytol-enhanced renal $T_2^*$ and $T_2^*$ mappings were performed under baseline conditions and after a short-term reversible intervention of renal vein occlusion. This intervention is known to cause marked changes in renal blood pO$_2$ and renal BVf. Local BVf was calculated on the basis of changes in $T_2^*$, which is equally sensitive to vessels of all sizes, unlike previous works that used $T_2$ (38, 40), which is more sensitive to small vessels (48). Local SO$_2$ of the kidney was estimated using a model-based multiparametric MR technique (49), and variations in BVf and SO$_2$ were benchmarked against reference data obtained from near-infrared spectroscopy (NIRS). Given the lack of information in the literature on a suitable ferumoxytol dose for renal BVf measurements at 9.4 T, we performed dosage experiments to establish a useful level of sensitivity to changes in BVf and SO$_2$.

**METHODOLOGY**

**Animal Preparation and Control of Vital Functions**

All experiments were approved by the Animal Welfare Department of the Berlin State Office of Health and Social Affairs and were performed in accordance with the German Animal Protection Law. The procurement of animals, husbandry, and experiments conformed to the *European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes* (Council of Europe No 123, Strasbourg 1985). Male Wistar rats (age, 12–13 weeks; body weight [BW], 288–330 g; n = 4; Harlan-Winkelmann, Borchen, Germany) underwent surgical preparation and MRI under urethane anesthesia (20% in H$_2$O; 6 mL/kg BW intraperitoneal; Sigma-Aldrich, Steinheim, Germany). In this approach, anesthesia is provided for several hours, leaving cardiovascular reflexes largely undisturbed.

To monitor arterial blood pressure, a catheter was placed into the femoral artery with its tip pointing towards the aorta. The catheter was connected to a pressure transducer (DT-XX, Viggo-Spectramed, Swindon, UK) and an amplifier (TAM-A Plugsys Transducer; Hugo Sachs Elektronik—Harvard Apparatus GmbH, March-Hugstetten, Germany). A second catheter was inserted into the right jugular vein, which permitted the administration of isotonic saline and USPIO. Core body temperature was monitored within the abdominal cavity by means of a fiber-optic temperature probe (OTP-M, AccuSens, Opons, Québec City, Canada). Body temperature was maintained at 37°C with a pad supplied with steady warm water circulation.

**Renal VO as Test Intervention**

To induce renal VO during the MR study, a remotely operated inflatable cuff (occluder) was positioned around the left renal vein. Time-of-flight (TOF)-based MR angiography was performed immediately after cuff inflation and deflation to confirm the suc-
ccessful occlusion and reperfusion of the kidney. In the rare case of a failed occlusion, we could detect the problem quickly and could perform a second attempt of the stimulus without a substantial delay.

The occlusion of the renal vein is known to induce both deoxygenation of the intrarenal blood and a substantial increase in intrarenal blood volume (32). Cessation of the venous outflow of blood increases blood pressure in intrarenal veins, thus resulting in their circular distension. The increased amount of deoxygenated blood in the renal tissue amplifies the BOLD effect, which induces a reduction in the $T_2^*$-weighted MR signal in response to VO. A further reduction in the MR signal due to $T_2^*$-shortening induced by the USPIO might lower the signal-to-noise ratio (SNR) to a critical level at which the MR image/data quality might become insufficient. Therefore, VO in combination with USPIO represents an extreme scenario with respect to the expected $T_2^*$ shortening.

**BVf Measurement**

BVf was measured using the USPIO ferumoxytol (Feraheme®, AMAG Pharmaceuticals, Inc., Lexington, MA). Ferumoxytol is approved in the USA and the EU as an intravascular Fe supplement therapy for patients with iron deficiency anemia related to chronic kidney disease. The intravenous injection of ferumoxytol does not have any measurable effects on renal physiology at doses up to 41 mg Fe/kg BW in rats; the presence of ferumoxytol also does not significantly alter the control of renal hemodynamics and oxygenation as studied by aortic occlusion and hypoxia (46).

Renal BVf was calculated by comparing pre-ferumoxytol data ($R_2^*$-maps) with post-ferumoxytol data ($R_2^*$USPIO-maps) (41):

$$BVf = \frac{3}{4\pi} \cdot \frac{(R_{2,USPIO}^* - R_2^*)}{\Delta\chi_{USPIO} \cdot B_0 \cdot \gamma} = \frac{3}{4\pi} \cdot \frac{\Delta R_{2,USPIO}^*}{\Delta\chi_{USPIO} \cdot B_0 \cdot \gamma}$$

where $\gamma$ is the gyromagnetic ratio, which is $2.675 \times 10^8$ rad/s/T; $B_0 = 9.4$ T; and $\Delta\chi_{USPIO}$ is the susceptibility difference between blood with and without added USPIO: $\Delta\chi_{USPIO} = 0.024$ ppm (cgs units) × [USPIO dose in milligram Fe per kilogram BW] (50).

**Ferumoxytol Dose-Finding Study**

Considering the lack of information on a suitable ferumoxytol dose for renal BVf measurements at 9.4 T, we performed a dose-finding study. To accomplish this, the following 3 competing effects had to be balanced:
(1) sensitivity of the BVf measurements increases with the USPIO dose;
(2) the SNR of MR images decreases with the USPIO dose; and
(3) sensitivity to changes in BVf also decreases at high USPIO doses because $T_2^*$ tends to zero.

For these reasons, a ferumoxytol dose ranging from 2 to 8 mg Fe/kg BW was used.

**Experimental Protocol**

The experimental protocol comprised 5 phases with increasing cumulative doses of ferumoxytol as illustrated in Figure 1:

1. **Phase 1**: Baseline–stimulus–recovery without USPIO
   a. Baseline $T_2^*$ and $T_2$ mapping and TOF MR angiographic confirmation of renal blood flow.
   b. VO performed by remote inflation of the cuff.
   c. The absence of renal blood flow was checked immediately using TOF MR angiography.
   d. $T_2^*$ and $T_2$ mapping during VO.
   e. Release of the venous cuff. Effective duration of VO was $\sim$3 min (depended on acquisition time of respiration-gated MRI scans performed in steps c and d).
   f. Restoration of renal blood flow was checked by TOF angiography.
   g. Recovery phase, during which $T_2^*$ and $T_2$ mapping was continued: 5 repetitions, approximately every 3 mins covering a 12- to 14-min period (dependent of respiratory rate because scans were respiration-triggered).

2. **Phase 2**: Baseline–stimulus–recovery with first USPIO dose
   h. The intravascular contrast agent (USPIO; 2 mg of Fe/kg body mass) was administered using a power injector at a rate of 0.25 mL/min via the jugular vein catheter.
   i–o. Following the conclusion of the injection and an additional 3-min mixing time, the steps of phase 1 were repeated to obtain matching post-USPIO data for phase 1.

3. **Phase 3**: Baseline–stimulus–recovery with second USPIO dose
   Same as phase 2 but with a different USPIO dose: the additional injection of 2 mg of Fe/kg USPIO yielded the approximate cumulative dose of 4 mg of Fe/kg USPIO.

4. **Phase 4**: Baseline–stimulus–recovery with third USPIO dose
   Same as phase 2 but with a different USPIO dose; the additional injection of 2 mg of Fe/kg USPIO yielded an approximate cumulative dose of 6 mg of Fe/kg USPIO.

5. **Phase 5**: Baseline–stimulus–recovery with fourth USPIO dose
   Same as phase 2 but with a different USPIO dose; the additional injection of 2 mg of Fe/kg USPIO yielded the approximate cumulative dose of 8 mg of Fe/kg USPIO.

The duration of the experimental phase was $\sim$20 min, which is short in comparison to the duration of the plasma half-life of ferumoxytol in rats (up to 3 h) (38).

**MR Imaging Experiments**

MRI experiments were performed on a 9.4 T animal MR system ( Biospec 94/20, Bruker Biospin, Ettlingen, Germany) using a radiofrequency (RF) coil setup established for renal imaging (linear polarized birdcage RF resonator for transmission in conjunction with a curved 4-channel receive RF coil array; Bruker Biospin, Ettlingen, Germany).

$T_2$-weighted pilot scans for geometrical planning and section positioning were acquired. We conducted a local volume-selective shimming of the magnetic field homogeneity on a voxel enclosing only the kidney, using an automatic optimization algorithm based on the FID length.

Interleaved $T_2^*$ and $T_2$ mapping was performed with respiratory-gated (Model 1025, SA Instruments, Stony Brook, NY) imaging protocols. For $T_2^*$ mapping, a multiecho gradient-echo sequence was applied with $	au$ values ranging from 20 to 40 ms.
(MGE) sequence (repetition time [TR] = 50 milliseconds; number of echoes = 10; first echo time [TE] = 1.43 milliseconds; ΔTE = 2.14 milliseconds; averages = 4) with a total acquisition time of ~1 min 20 s was used. For T₂ mapping, a multi-spin echo (MSME) sequence (TR = 550 milliseconds; number of echoes = 7; first TE = 10 milliseconds; ΔTE = 10 milliseconds; averages = 1) with a total acquisition time of around 1 min 40 s was applied. For MGE measurements, the respiratory trigger window included the entire expiratory plateau, which allowed for the acquisition of several k-space lines within this window. For MSME measurements, the respiratory trigger window was set to 10 milliseconds at the beginning of the expiratory plateau, resulting in the acquisition of 1 k-space line per breath, with the effective TR being equal to the respiratory interval.

A coronal oblique section was placed such that it covered the kidney centrally at its maximum extension. An in-plane spatial resolution of (226 × 445) μm², field of view = (38.2 × 50.3) mm², matrix size = 169 × 113 zero–filled to 169 × 215, and a section thickness of 1.4–1.5 mm was used.

For TOF angiography, we used a spoiled gradient echo technique (2D FLASH; TR = 11 milliseconds; TE = 3 milliseconds; flip angle = 80°) with a spatial in-plane resolution of (200 × 268) μm² and 15 sections (section thickness = 1.0 mm).

**Region of Interest Analysis**

We extended the semiautomated kidney segmentation approach used in our previous studies (31, 51) to provide 5 regions of interest (ROIs) in the renal cortex and 5 ROIs in the renal outer medulla (Figure 2). In brief, a rectangle was manually placed around the kidney borders, followed by drawing lines at the crossing of the kidney border and 2 automatically placed diagonals. Further, 10 ROIs were placed automatically at locations in the cortex and outer medulla that had been predefined with respect to the reference rectangle.

**Effects of Magnetic Field Inhomogeneity on Renal T₂**

Three-dimensional mapping of B₀ was performed to correct the B₀ inhomogeneity effects on T₂* (49). This B₀ correction involves (i) acquiring a 3D B₀ map of the kidney; (ii) estimating intra-voxel field dispersion across the kidney by fitting a 3D polynomial to the B₀ map; (iii) calculating intravoxel dephasing; and (iv) using this for correcting the measured T₂* map of the kidney.

To assess the need for B₀ correction in renal T₂* mapping, we performed B₀ correction on a kidney for different shim settings and compared the corrected renal T₂*-maps with the measured, uncorrected T₂*-maps. All shims were first set to zero to allow for significant B₀ inhomogeneities, and then first-order local shimming was performed on a voxel tightly enclosing the kidney to make B₀ uniform across the kidney. The latter was performed 3 times to account for any variability. A 3D polynomial function of the third order was fitted to the measured 3D B₀ map (in-house developed program; MATLAB, MathWorks, Natick, WA). This polynomial function was used to estimate the spin dephasing on a subvoxel grid of 2 × 2 × 4 voxels per image voxel (voxel size = 0.22 × 0.23 × 1.40 mm³). Subvoxel grids finer than 2 × 2 × 4 did not yield significantly different results.

**Model-Based MRI Data Analysis**

Multiecho MR data were converted into parametric maps of absolute T₂ and T₂ by pixelwise monoexponential fitting to the signal intensities of denoised (SANLM filter, VBM8 toolbox, SPM8; www.fil.ion.ucl.ac.uk/spm) series of T₂* and T₂-weighted images acquired as a function of the TE (in-house developed program; MATLAB, MathWorks, Natick, WA). The relaxation rates were calculated as R₂* = 1/T₂* and R₂ = 1/T₂. The subtraction of precontrast maps from corresponding postcontrast maps yielded ΔR₂*-maps, which were used for the calculation of BVf-maps using equation (1).
Renal blood SO₂ was estimated by applying a multiparametric MR technique (49) to the R₂*, R₂ and BVf data from the kidney. This approach was originally proposed for human brain MRI (52) and is based on a theoretical model of the BOLD contrast (53). This approach was refined by replacing a complex model fit with a simpler single parameter fit combined with actual MR measurements of R₂, BVf, and B₀ (49). Assuming that the magnetic field inhomogeneity is negligible and constant throughout the duration of the experiment, we solved the model equation

\[ SO₂ ≈ 1 - \left( \frac{3}{4\pi} \cdot \frac{(R₂* - R₂)}{γ \cdot Δχ₀ \cdot BVf \cdot Hct \cdot B₀} \right) \]

Here \( Δχ₀ = 0.264 \text{ ppm} \) (54), which represents the susceptibility difference between deoxygenated and oxygenated red blood cells, \( B₀ = 9.4 \text{ T} \), and SO₂ is given in arbitrary units (because \( B₀ \) is uncorrected). A hematocrit of 0.40 was used for the cortex and the outer medulla (85%-95% of systemic hematocrit, which was assumed to be 0.45) (55). In this feasibility study, the data analysis was performed using equations (1) and (2), as these permit access to both parameters of interest, that is, SO₂ and BVf.

To evaluate intrasubject reproducibility, we compared results from the baseline with those obtained after 10 min of recovery and also repeated the baseline–occlusion–recovery experiment (~25 min later). Moreover, before repeating the experiment, we increased the USPIO dose by 2 mg Fe/kg BW to assess the dependency of the results on the USPIO dose.

**Figure 4.** T₂*-weighted images (echo time [TE] = 3.6 milliseconds, spatial resolution = 226 × 422 μm) of a rat kidney at baseline, during venous occlusion (VO), and at the beginning of the recovery phase. Without USPIO (top row), the short-term VO induces a very strong signal decrease in the renal cortex and the outer medulla. The impact of USPIO administration on T₂*-weighted image contrast (left column) lends itself to an estimation of blood volume fraction (BVf). A hypointense area stretching from the papilla via the inner medulla to the central outer medulla becomes prominent with increasing USPIO dose. This hypointensity might represent the influence of large Fe-rich vessels located close to the image section rather than medullary tissue properties (see Discussion).

**NIRS**
Quantitative information on the relative changes of total cortical hemoglobin per tissue volume (as a surrogate for BVf) and cortical SO₂ during VO were obtained using multidistance continuous wave NIRS in a separate cohort of 10 male Wistar rats. The NIRS measurements are based on recording spatially resolved diffuse reflectance with a linear fiber probe. This probe permitted sampling of the renal tissue up to a maximum depth of ~2 mm and provided information about the renal cortex. The results presented here were obtained by a refined model analysis of data reported in Grosenick et al. (32), with improved separation of tissue absorption changes from changes in tissue scattering. To reference our results against these data, the high-temporal-resolution NIRS data were averaged over the duration of each MGE MRI scan.
RESULTS

Ferumoxytol Dose-Finding Study

The dose-finding study was performed to ensure that BOLD effects were detectable after USPIO administration taking into account that SNR may be further reduced by changes in $T2^*$ owing to the deoxygenation of blood. By performing Monte Carlo simulations for a wide range of $T2^*$ and SNR, we estimated the SNR-dependence of the $T2^*$ mapping error (Figure 3).

$$\Delta T2_{error}^* = T2_{calc}^* - T2_{true}^*$$  

(3)

with “true” indicating the true $T2^*$ value used as an input and “calc” indicating the $T2^*$ value calculated by curve fitting to the noisy signal intensity data versus TE. For cortical and outer medullary $T2^*$ the absolute error in $T2^*$ was <1.0 milliseconds.

$T2^*$-Weighted MR Imaging

We observed a significant change in contrast and image quality following short-term VO and after increasing USPIO concentrations (Figure 4). VO caused a very strong signal decrease in the renal cortex and in the outer medulla. Even after a USPIO administration of 4 or 6 mg of Fe/kg BW, the strength of this decrease of the signal during VO remained similar and was easily detectable. Although the signal loss suggested renal hypoxia, that is, a decrease in oxygen saturation of hemoglobin, this remained speculative because, at this point, possible changes in BVf had not been considered. Comparing the $T2^*$-weighted images at baselines for different USPIO doses shows the impact of USPIO administration on image contrast, which lends itself to an estimation of BVf.

Important for estimating the BVf is the sensitivity for detecting the change in $T2^*$ caused by labeling the blood with USPIO. As expected, a larger USPIO dose provided more sensitivity for the measurement of:

$$\Delta T2_{USPIO}^* = T2_{USPIO}^* - T2^*$$  

(4)

because the larger the cumulative USPIO dose, the larger the change in $T2^*$ compared with the baseline (Figure 5A). This $T2^*$ change was more pronounced in the outer medulla than in the renal cortex. In contrast to the sensitivity to USPIO effects, the sensitivity in $T2^*$ induced by VO decreased rapidly with the Fe dose (Figure 5B):

$$\Delta T2_{VO}^* = T2_{VO}^* - T2_{baseline}^*$$  

(5)

The sensitivity to changes in $T2^*$ induced by VO fell below $\Delta T2^*$ = 2.0 milliseconds in the outer medulla for USPIO doses of 6 mg of Fe/kg and more. The relative $\Delta T2^*$, as percentage of baseline $T2^*$, did not change much and stayed between ~60% and 80%.

Considering the sensitivity of $T2^*$ to USPIO injection (relevant for BVf estimation) and the $T2^*$ sensitivity to VO (physiological stimulus) at different cumulative USPIO doses. Plots of changes in cortical and outer medullary $T2^*$ induced by the injections of USPIO (A). Absolute $\Delta T2^*$ in milliseconds (left panel) and relative $\Delta T2^*$ as percentage of $T2^*$ without USPIO (right panel) increased rapidly with USPIO dose. Plots of changes in cortical and outer medullary $T2^*$ induced by VO ($T2^*$ values during a given VO versus $T2^*$ before the respective VO) (A). Although absolute $\Delta T2^*$ in milliseconds (left panel) decreased with USPIO dose, the percentage $\Delta T2^*$ (right panel) remained between ~60% and 80%. Group means and SEMs (n = 4) of cortical and outer medullary $\Delta T2^*$ obtained from the ROIs are determined as shown in Figure 2.

Figure 5. Comparison of the $T2^*$ sensitivity to USPIO injection (relevant for BVf estimation) and the $T2^*$ sensitivity to VO (physiological stimulus) at different cumulative USPIO doses. Plots of changes in cortical and outer medullary $T2^*$ induced by the injections of USPIO (A). Absolute $\Delta T2^*$ in milliseconds (left panel) and relative $\Delta T2^*$ as percentage of $T2^*$ without USPIO (right panel) increased rapidly with USPIO dose. Plots of changes in cortical and outer medullary $T2^*$ induced by VO ($T2^*$ values during a given VO versus $T2^*$ before the respective VO) (A). Although absolute $\Delta T2^*$ in milliseconds (left panel) decreased with USPIO dose, the percentage $\Delta T2^*$ (right panel) remained between ~60% and 80%. Group means and SEMs (n = 4) of cortical and outer medullary $\Delta T2^*$ obtained from the ROIs are determined as shown in Figure 2.

Effects of Magnetic Field Inhomogeneity on Renal $T2^*$

Macroscopic gradients in the magnetic field $B0$—for instance, owing to imperfect $B0$ shimming—may cause undesirable spin dephasing and could artificially shorten $T2^*$. Before mapping renal $R2^*$, BVf, and $SO2^*$, we tested whether the susceptibility weighting and $T2^*$ were dominated by microscopic $B0$ susceptibility gradients. We investigated whether $B0$ correction could reverse unwanted magnetic field inhomogeneity effects on $T2^*$ by comparing measured and corrected renal $T2^*$-maps acquired in vivo for different magnetic field shim settings as shown in Figure 6.

The 3D polynomial fits to the measured $B0$-maps described the magnetic field inhomogeneity with high fidelity. A notable...
Macroscopic magnetic field inhomogeneity was present with the shim settings adjusted to zero. For this shim setting, $B_0$ correction markedly increased $T_2^*$, particularly in the inner medulla, where $T_2^*$ is typically large. $B_0$ inhomogeneity across the kidney was very small after local shimming on the kidney. After $B_0$ correction, the renal $T_2^*$-maps obtained for all 3 $B_0$ shim settings displayed high agreement. For local shimming, which we perform routinely in renal MR studies, the effect of $B_0$ correction on $T_2^*$ was negligible. This confirms that macroscopic intravoxel dephasing causes only minor $T_2^*$ effects for the TE range and the voxel size used and ensures that $T_2^*$ is governed by microscopic $B_0$ susceptibility gradients.

**Renal $R_2$, $R_2^*$, BVf, and $SO_2$ Mapping**

Parametric maps were calculated for renal $T_2$ and $T_2^*$, which were then converted to $R_2^*$- and $R_2$-maps, respectively. Such quantitative maps permit comparisons between animals and over time, as they are not biased by external factors such as RF coil sensitivity ($B_1$) or the position of the subject under investigation with respect to the receive RF coil. The difference between $R_2^*$- and $R_2$-maps ($\Delta R_2$ and $\Delta R_2^*$, respectively), acquired before and after USPIO administration is closely related to the local BVf. The blood volume measurement procedure is illustrated in Figure 7, which shows parametric maps of renal $R_2$ and $R_2^*$ relaxation rates under baseline conditions, without and with USPIO (4 mg of Fe/kg), along with their difference. Dissimilarities between $\Delta R_2$ and $\Delta R_2^*$ are expected owing to their different sensitivities to large vessels (see Discussion).

Analysis of BVf-maps obtained at baseline and during renal VO (Figure 8) revealed an increase in cortical and medullary BVf upon VO. Renal BVf returned to baseline after 10 min of recovery. Next, maps of renal $SO_2$ were calculated using the multiparametric BOLD model outlined in equation (2), which requires $T_2^*$ and BVf as input data to analyze $SO_2$ at baseline, upon VO and on recovery (Figure 8). The reduction in renal $T_2^*$ during VO was associated with a decrease in $SO_2$ in the cortex and outer medulla combined with a substantial increase in blood volume.

To show the necessity of monitoring BVf (rather than using a fixed literature value), we also calculated $SO_2$-maps that assume renal BVf to remain constant and identical to the baseline condition during the entire experiment (Figure 8, lower panel). Almost everywhere in the cortex and outer medulla, $SO_2$ values were considerably lower in the experiments neglecting BVf changes compared with experiments taking BVf changes into account.

Reproducibility of results was very high: the results obtained for the cortical and outer medullary BVf and $SO_2$ at baseline conditions and after 10 min of recovery were almost
Deduced T2 maps acquired before and after USPIO is closely related to the local BVf. For a discussion of the apparent high-BVf area, please refer to the Discussion section.

DISCUSSION
This work makes an important contribution to the literature on renal functional MRI by assessing changes in the renal BVf and in the renal SO2 in response to VO. To achieve this goal, BVf measurements were implemented for rat kidneys at 9.4 T, including a dose-finding study for the intravascular contrast agent ferumoxytol. Multiparametric analysis was performed to estimate renal SO2. Occlusion-induced changes in BVf and SO2 derived from MRI were benchmarked against BVf and SO2 references obtained from NIRS. Our main findings are that (1) a 4 mg of Fe/kg dose of ferumoxytol is suitable for BVf measurements at 9.4 T using baseline, VO and recovery; (2) the proposed approach provides high reproducibility for BVf and SO2 assessment as demonstrated by the test–retest experiments; (3) relative changes in cortical BVf and cortical SO2 derived from MRI were in accordance with relative changes in BVf and SO2 derived from NIRS; and (4) without the monitoring of BVf, MRI overestimates the SO2 decrease during renal VO. The results of this work permitted a noninvasive detection of BVf increase upon VO and a removal of its effects on blood oxygenation-sensitized renal MR.

We found BVf to be higher in both outer and inner medulla than in the cortex, as shown by both ΔR2* and ΔR2*-maps. Although these observations do not agree with recent results obtained by 3D microcomputed tomography (where cortical BVf was reported to be larger than medullary BVf) (56), they are in alignment with previous reports on ΔR2*-based BVf estimates in rats and mice (38, 40), as well as with a series of earlier reports that measured renal BVf by means of (51) Cr-labelled red cells and 125I-γM-immunoglobulin: Rasmussen (55) reported medullary BVf in rats to be approximately twice the cortical BVf. There is no gold standard method, and the results provided by different techniques differ significantly. A hypointensity in T2*-weighted images had already suggested that BVf was higher in the medulla, but the ΔR2*-maps depicted this even more clearly. The area with apparently very high BVf stretches from the papilla via the inner medulla to the central outer medulla. We hypothesize that these phenomena represent the influence of large Fe-rich vessels (57) located close to the image section, rather than the actual medullary tissue properties. The dissimilarity between ΔR2* and ΔR2*-maps in revealing this area of unexpectedly high BVf further support our hypothesis: unlike ΔR2*, ΔR2 is predominantly sensitive to small vessels and capillaries, because it relies on water diffusion within the near environment of the vessel walls, and the surface-to-volume ratio is highest for small vessel diameters. Hence, ΔR2 would be much less susceptible to the long-distance effects of a high amount of USPIO within extremely large blood vessels. Indeed, the locations of apparently high BVf in the papilla and inner medulla colocalize with the renal artery and vein, and the interlobar arteries and veins (56).

In the outer medulla, BVf displayed a rather high spatial heterogeneity and large spatial gradients along the longitudinal
(rostral–caudal) axis. Here, large blood vessels (interlobar arteries and veins) surrounding the image section, as well as arcuate arteries and veins that run along the border between cortex and medulla (56), may play a role. Owing to the relatively large section thickness, the $T_2^*$-weighted images are considerably susceptible to magnetic field and frequency dispersions perpendicular to the image plane, created by large USPIO-loaded vessels. This hinders the assessment of the renal medulla. The choice of an axial section orientation or much thinner section thickness (if permitted by the SNR) could help resolve this issue. Despite these limitations, the variations in cortical BVf during renal VO were in good agreement with the results obtained from NIRS.

Our approach of parametric mapping of renal $T_2^*$ and $T_2$ made use of MGE and MSME techniques including respiratory triggering for respiratory motion compensation. The duration of each scan was 60–90 s, permitting a TR of ~3 min for interleaved $T_2^*$ and $T_2$ mapping. These protocols are available on clinical MR scanners, and hence it will be easily translatable to clinical use. The translation of our approach into the clinic is fueled by an increasing number of reports that eloquently speak of the off-label use of ferumoxytol for a broad spectrum of preclinical and diagnostic imaging applications (32, 43, 44, 58, 59). In the clinical setting, renal $T_2^*$ and $T_2$ mapping will most likely be used at time points that are at least hours, if not days or months, apart. In such a context, a 90-s delay between $T_2^*$ and $T_2$ scans appears to be short enough. Protocols affording breathhold acquisitions could make respiratory triggering unnecessary, and parallel imaging capabilities are readily available on human MR scanners, both permitting acceleration of data acquisition.

In a laboratory setting, a higher temporal resolution might be needed to study some acute stimuli applied to animals. Fast physiological changes demand shorter scan durations and higher repetition rates. Imaging techniques that provide $T_2^*$- and $T_2$-weighted data (52, 60) provide an alternative to these preclinical applications. Fast spin-echo variants for $T_2$ and $T_2^*$ mapping permit choosing any desired $T_2^*$-weighting (including ultrashort times down to zero) and provide the extra benefit of being almost immune to image distortion (61, 62). Simultaneous dual-contrast 2-in-1 rapid acquisition with relaxation enhancement

![Figure 8. Maps of renal cortical and outer medullary $T_2^*$, together with estimated maps of BVf and oxygen saturation of hemoglobin ($SO_2$) at baseline, during VO and the recovery phase. The maps at baseline and after 10 min of recovery are almost indistinguishable, confirming that the effects of VO are reversible. Within-subject repeatability is demonstrated for renal BVf and $SO_2$ by comparing the maps derived from 2 different experimental phases, namely, phase 3 (4 mg of Fe/kg USPIO) and phase 4 (6 mg of Fe/kg USPIO). Test–retest reliability (repeatability) was high—the differences between both iterations are nearly negligible, even though more USPIO had been injected in between them. In addition, $SO_2$ maps were calculated assuming that renal BVf remains constant and identical to the baseline condition (bottom row); the missing compensation for BVf changes during VO results in $SO_2$ values being considerably lower than when BVf was monitored.](image-url)
Figure 9. Relative changes in cortical BVf and SO₂ derived from the MR model analysis for the cortical ROIs (top panel; n = 4), referenced against related quantitative parameters obtained with near-infrared spectroscopy (NIRS; bottom panel; n = 6). HbT = total Hb concentration (per tissue volume). A large increase of BVf measured with MR during VO was mirrored by a similarly large increase in hemoglobin concentration measured by NIRS, which is considered a BVf surrogate. Cortical SO₂ derived from both methods decreased markedly during the short-term venous occlusion (VO).

presents a valuable alternative to sequential T₂* and T₂-weighted fast-spin echo acquisitions and promises to eliminate section-misregistration artifacts induced by bulk or physiological motions (63). Further enhancements of the SNR and spatial resolution could be gained by using cryogenically cooled RF coils in a preclinical setting (64, 65).

The multiparametric BOLD approach based on combining the monitoring of T₂* and T₂ with BVf has not previously been attempted for renal MR blood oximetry. This study demonstrates the feasibility of this approach in rats. A high reproducibility of T₂* and T₂ mapping and BVf measurements translated into SO₂ estimates with similarly high reproducibility.

The impact of the assumptions embedded in the model has previously been studied and it indicates that the model is sufficiently realistic (66) for the brain. The assumptions about the microvascular architecture should also hold for the kidney, except that the BVf used in the numerical study (4%) should be higher in renal tissue (literature values are contradictory but typically exceed 10%). However, because the model does not take into account the effects of renal tubuli, the presented study results may serve as only an approximate indicator for the usefulness of such a model-based approach and further investigation will be needed to advance the model for the kidney.

The current implementation of the model-based analysis has some methodological constraints that can be improved in future work. For the current study, intrarenal hematocrit was assumed to be 0.40, but, in fact, this value is known to vary throughout the kidney. Strategies to account for this may be necessary. To account for the susceptibility difference between blood with and without added ferumoxytol, a literature value of Δχ for a different USPIO of the same size and at the same magnetic field strength was used (50). It would be an added refinement to measure the Δχ for ferumoxytol and include it in the BVf calculations in the future. Because of our focus on fast, short-term changes in renal oxygenation, we assumed a constant magnetic field homogeneity, which might change modestly with respect to the kidney owing to respiratory motions and changes in renal size (renal tissue moves within B₀). SO₂ results were reported in arbitrary units because B₀ effects were not accounted for in this study. Our initial experiments (Figure 6) had shown that the effects of magnetic field inhomogeneity on renal T₂* were negligible after local shimming on the kidney, which we performed routinely. Generally, acquiring B₀-maps for each subject are recommended to permit a B₀ correction, if needed, and exclude a possible bias. Alternatively, acquiring high-resolution T₂* data makes a separate B₀ correction unnecessary owing to the reduced intravoxel dephasing (49, 67, 68), and it could represent an attractive way forward, presuming that the scan time penalty for increasing the spatial resolution is either of no relevance for the application or can be counteracted by strategies to accelerate acquisition. This can be accomplished, for example, by using combined acquisition techniques that integrate a minimum of 2 imaging strategies for T₂* and T₂ (69).

Benchmarking BVf and SO₂ results against a quantitative reference is an obvious means of validating experimental results obtained from a novel MR technique. Currently, a perfect quantitative counterpart for MR-derived BVf and SO₂ is not available, as is the case for most MR techniques. Invasive tissue pO₂ probes can sample only very small regions, and they measure tissue pO₂ rather than blood oxygenation. NIRS allows measurements of the oxygen saturation of hemoglobin and tissue concentration of hemoglobin—a surrogate for BVf—but is currently limited to probing the cortex due to its low penetration depth. Comparisons between the occlusion-induced changes in cortical BVf and SO₂ obtained by MRI with the NIRS results for the cortex yield very good agreement, which should motivate the
further development of the MR approach proposed here into a comprehensive renal MR oximetry protocol.

In conclusion, this work established ferumoxytol-based steady-state MR measurements of renal BFVs for rats at a magnetic field strength of 9.4 T. Combining the BFV measurements with the monitoring of T2* and T2 allowed us to implement multiparametric quantitative BOLD MRI for the kidney as a promising approach to route renal blood oximetry. The findings are encouraging and should stimulate efforts to further improve this multiparametric technique, with the ultimate aim of translating it into clinical practice for the evaluation of AKIs and the development of chronic damage. Accomplishing this goal will require calibrations through simultaneous quantitative measurements with invasive physiological probes and NIRS in the same kidney. Once available to the clinicians, multiparametric renal MR oximetry will represent the first noninvasive method to reliably measure renal blood oxygenation. It could be combined with MR techniques for perfusion and diffusion (to probe tubular volume fraction) to route a comprehensive characterization of renal hemodynamics and tissue oxygenation, which may be an important biomarker for the early stages of a range of kidney diseases.

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REFERENCES


Performing chemical exchange saturation transfer (CEST) magnetic resonance imaging (MRI) in lung tissue is difficult because of motion artifacts. We, therefore, developed a CEST MRI acquisition and analysis method that performs retrospective respiration gating. Our method used an acquisition scheme with a short 200-millisecond saturation pulse that can accommodate the timing of the breathing cycle, and with saturation applied at frequencies in 0.03-ppm intervals. The Fourier transform of each image was used to calculate the difference in phase angle between adjacent pixels in the longitudinal direction of the respiratory motion. Additional digital filtering techniques were used to evaluate the breathing cycle, which was used to construct CEST spectra from images during quiescent periods. Results from CEST MRI with and without respiration gating analysis were used to evaluate the asymmetry of the magnetization transfer ratio (MTRasym), a measure of CEST, for an egg white phantom that underwent cyclic motion, in the liver of healthy patients, as well as liver and tumor tissues of patients diagnosed with lung cancer. Retrospective respiration gating analysis produced more precise measurements in all cases with significant motion compared with nongated analysis methods. Finally, a preliminary clinical study with the same respiration-gated CEST MRI method showed a large increase in MTRasym after radiation therapy, a small increase or decrease in MTRasym after chemotherapy, and mixed results with combined chemoradiation therapy. Therefore, our retrospective respiration-gated method can improve CEST MRI evaluations of tumors and organs that are affected by respiratory motion.
sented by calculating an $MTR_{asym}$ parameter that evaluates the asymmetry in the CEST spectrum (7). More specifically, $MTR_{asym}$ is the ratio of CEST contrast produced by mobile proteins with longer T2 relaxation time constants, relative to a relayed nuclear Overhauser effect (rNOE) produced by less mobile proteins with shorter T2 relaxation times. Therefore, $MTR_{asym}$ is sensitive to the concentration of the protons being saturated (for both CEST and rNOE effects). $MTR_{asym}$ is also sensitive to the exchange rate of the labile protons on endogenous molecules, which increases with increasing pH (owing to the base-catalyzed processes of chemical exchange with most endogenous molecules), and therefore, $MTR_{asym}$ may be sensitive to changes in tumor metabolism that affect tissue pH.

Amide proton transfer (APT) MRI is a specific type of CEST MRI that involves the exchange between endogenous amide protons from mobile proteins and bulk water. Past studies have shown higher APT contrast in tumor tissue than in normal tissue (8), as well as correlations between APT signal intensity and tumor grade as assessed by means of histopathology (9, 10). Thus, measuring the APT contrast in the tumor tissue could eventually become a noninvasive tumor grading technique for evaluating tumors, which may be beneficial for guiding treatment plans.

Most APT studies have been performed to study cerebral stroke and glioma in the brain. Unlike the brain tissue, the lung is difficult to image with MRI owing to motion that blurs the image of the lung and also causes artifacts in the phase dimension of the image. Some studies in the lung have shown that APT MRI can differentiate malignant from benign tumors (11, 12). Unfortunately, one study was completed in the absence of respiratory gating, which decreased the image quality. The other study was completed with murine models where the breathing rate was controlled via a ventilator so that the acquisition portion of the CEST sequence was in sync with the quiescent period of the respiratory cycle. The use of a ventilator during MRI with humans is impractical. A respiration-gated technique is desired to generate high-quality results in the lung in free breathing patients.

Recent studies have extracted the breathing signal from features within the image (13–16). These methods eliminate the need for invasive procedures or devices that monitor breathing rates. Extracting the breathing signal from the image features relies on the translational property of Fourier transform (FT) imaging theory, which states that a geometric shift in the space domain results in a phase shift in the Fourier space (17). We used this property to develop an innovative CEST MRI protocol with retrospective respiratory gating. The goal of our study was to examine the strengths and limitations of respiratory-gated CEST MRI when imaging the lungs of healthy volunteers and patients diagnosed with lung cancer.

**METHODOLOGY**

**MRI Acquisition Protocol**

Our previous clinical CEST MRI protocol used a saturation period that was at least 3 seconds in length, followed by an MRI acquisition sequence (18). This saturation period is considerably long to sample multiple stages of a typical breathing cycle, which can be 3 seconds at 20 breaths per minute for patients with compromised respiratory function due to chronic obstructive pulmonary disease (19). Thus, we shortened the saturation pulse to 200 milliseconds to accommodate our CEST MRI method. This shorter duration allowed us to adequately sample stages of a normal respiratory cycle. However, a 200-millisecond saturation pulse is insufficient to generate a steady-state saturation with a series of saturation frequencies that have an interval $>0.3$ ppm. We also aimed to ensure that a sufficient number of data points in the CEST spectrum were acquired to distinguish the APT and rNOE in the CEST spectrum after retrospectively removing CEST points not acquired during the quiescent stage of breathing. Thus, we shortened the saturation frequency interval for our CEST MRI method to 0.03–ppm units for the entire CEST spectrum so that frequencies next to the saturation frequency being irradiated would also be partially saturated. In doing so, we hypothesized that the CEST spectrum from our CEST MRI method would be similar to a standard CEST spectrum acquired with steady-state saturation, except for the first few CEST magnetic resonance (MR) images of the series that do not experience steady-state saturation.

**Simulations**

To address the potential pitfalls of insufficiently achieving a steady-state saturation with our saturation scheme, we simulated CEST spectra with a labile pool at 3.5 ppm and 500 mM by using the Bloch equations modified for chemical exchange (20). CEST spectra were simulated using a continuous-wave, rectangular saturation pulse of 200 milliseconds, followed by a delay of 196 milliseconds to account for CEST decay during Fast Imaging with Steady-state Precession (FISP) acquisition, applied to each saturation frequency one time before incrementing to the next saturation frequency in 0.03-ppm increments. We termed this simulation as the “stationary pulsed” saturation scheme. CEST spectra were also simulated with a saturation pulse of 200 milliseconds followed by a delay of 196 milliseconds to account for FISP acquisition, and these parameters were applied to the same saturation frequency 1000 times before iterating the saturation frequency. We refer to this simulation as the “iteratively pulsed” saturation scheme (21). CEST spectra were also simulated by using a saturation pulse of 3.0 seconds followed by a 196-millisecond delay, applied to each saturation frequency 1 time, termed “standard CEST saturation”. The $B_S$ saturation power was set to 1.0 $\mu$T for each saturation pulse. In addition, we repeated simulations with a T1 relaxation time constant of 0.8, 1.4, 2.0, and 3.0 seconds, which are characteristic T1 relaxation times of human tissue at 3 T magnetic field strength (22).

**Phantom Studies**

A solution of egg whites was prepared in a 200-mL plastic container and placed in a larger 500-mL plastic container that was filled with agar (23). The large plastic container was attached to a customized motion device that oscillated in the direction of the longitudinal axis of the magnet. The motion device was placed with the plastic container inside a 3 T MRI scanner (Magnetom Skyra, Siemens). A standard CEST-FISP MRI protocol with steady-state saturation was acquired with a saturation period of 3 seconds and data points from $-7$ ppm to $+7$ ppm in 0.2-ppm units (24). Then an iteratively pulsed CEST
MRI protocol was acquired with a saturation period of 200 milliseconds and saturation frequencies from −7 ppm to +7 ppm in 0.03-ppm units. For both CEST-FISP MRI protocols, a continuous wave, rectangular pulse shape at 1.0 μT saturation power was used. Both protocols were performed with the phantom container held stationary and with the phantom container moving. The FISP MR images were acquired in a coronal orientation by means of the following parameters: repetition time (TR), 196 milliseconds; echo time (TE), 0.97 milliseconds; excitation angle, 15°; section thickness, 20 mm; in-plane resolution, 4.7 × 4.7 mm²; field of view (FOV), 300 mm²; centric encoding; 25% phase oversampling; average, 1; and scan time, 3 minutes. For the scans acquired with the phantom in motion, the phantom container was set to move 3 cm toward the front of the magnet over a 1-second time frame, move 3 cm back to its original position over a 1-second time frame, pause for 3 seconds, and then repeat the process to simulate breathing motion.

Clinical Studies
Three healthy volunteers and 3 patients diagnosed with lung cancer underwent scanning to compare standard CEST MRI vs. our iteratively pulsed CEST MRI method with and without retrospective respiratory gating. Then 4 patients with lung carcinoma or mesothelioma treated with radiation therapy and/or chemotherapy underwent scanning using our iteratively pulsed CEST MRI method with retrospective respiratory gating. These studies were performed with the approval of the Institutional Review Board of the University of Arizona. Images were acquired with the same clinical MRI instrument used for imaging phantoms. A 3-dimensional (3D) T1-weighted gradient-echo acquisition was used to localize the liver and lung. Images were acquired in a coronal orientation using the following parameters: TR, 2.93 milliseconds; TE, 1.23 milliseconds; excitation angle, 9°; section thickness, 3 mm; number of sections, 96; section oversampling factor, 33%; in-plane resolution, 1.5 × 1.5 mm²; FOV, 420 mm²; partial k-space of 6/8, with a 3D caipirinha acceleration factor, a factor of 3 in the phase direction, and a factor of 2 in the section direction; linear encoding; average, 1; and scan time, 12 seconds. For patients with cancer, a 2D multisection T2-weighted HASTE acquisition was also used to further localize the tumor. Images were acquired in a coronal orientation by means of the following parameters: TR, 1500 milliseconds; TE, 75 milliseconds; excitation angle, 80°; refocusing angle, 160°; section thickness, 6 mm; number of sections, 35; in-plane resolution, 1.0 × 1.0 mm²; FOV, 400 mm²; 2D GRAPPA with a factor of 3; k-space sampling, 5/8; linear encoding; average, 1; and scan time, 54 seconds. This sequence was performed with fat suppression by using spectral attenuated inversion recovery. CEST-FISP MR images were acquired using the same method as the phantom experiment.

Image Processing and Analysis
We segmented the temporal series of CEST spectra on the basis of the quiescent period during expiration of the breathing cycle because the quiescent period would have the most consistent positioning of the liver and tumor (25). To segment the breathing cycles, we selected a region of interest (ROI) around the liver dome because the intersection between the liver dome and the lung has great contrast and the movement of the liver dome is a direct result of inhalation and exhalation. This ROI was selected using the first FISP image and then applied for all FISP images acquired with our iteratively pulsed CEST MRI method.

We obtained the respiration cycle from the CEST MR images. An FT was applied to the ROI in all FISP images to convert the spatial image to k-space (Figure 1, A and B). The pixel at the center of k-space and the adjacent pixel along the longitudinal axis of displacement were selected for analyses. A ratio of the MR signal amplitudes of these 2 pixels was used to determine the difference in the phase angle between the 2 pixels (Figure 1C).

We used these 2 pixels because the phase angle differences between these pixels are the most sensitive to respiratory motion (14). Plotting the phase angle difference for each FISP image acquired with respect to time represented the overall motion including the respiratory cycle.

We applied a series of digital filtering techniques to refine the monitored respiratory cycle (Figure 1, D–F). First, we applied an FT to the phase angle difference spectrum and then applied a bandpass filter to retain the frequencies between 0.11 Hz (7 bpm) and 0.48 Hz (29 bpm) because these breath rates between these values correspond to typical respiratory rates (19). Next, we applied an inverse FT to the digitally filtered data to generate a refined respiratory cycle plot. Because we sought to obtain the quiescent period of the breathing cycle, we adjusted the respiratory cycle plot so that the quiescent period was centered at 0 radians.

We identified the quiescent period of the plot by assuming that the respiratory cycle was sinusoidal [equations (1) and (2)].

\[
S(\theta) = A \cdot \sin(B + \theta) + S
\]

where \( A \) = amplitude, \( B \) = phase angle shift, \( \theta \) = respiratory phase, and \( S \) = nonsinusoidal signal

\[
S(\theta) = C \cdot \sin(\theta) + D \cdot \cos(\theta) + S
\]

where \( C \) and \( D \) are the amplitudes of the sine and cosine components, respectively. The values of \( C, D, \) and \( S \) were determined from the inner product between \( \sin(\theta) \) and the respiratory signal, \( \cos(\theta) \) and the respiratory signal, and the respiration signal. Once \( C \) and \( D \) were determined, the phase shift of the respiratory cycle was found using equation (3).

\[
B = \tan(C/D)
\]

All CEST data points that had an FISP image with a phase angle difference of <1 radian from B were retained in the final CEST spectrum (Figure 1, G and H). This threshold of 1 radian retained ~30% of the images that were used to obtain the final CEST spectrum.

MTRsym Analysis
To adjust for \( B_0 \) inhomogeneity, the minimum signal of each CEST spectrum was set to 0 ppm. Then, the CEST spectrum was fit with a single Lorentzian line shape conducive to the spectral shape for direct water saturation (26). The fitted offset value for
This line shape was used to further adjust the 0-ppm value of the CEST spectrum. To generate an MTR\text{asym} value, a straight line was drawn through all points from 2.5 to 4.5 ppm, and the center point of the line was taken as the contrast value for the APT effect (S\text{APT}) (27). The same procedure was used for points between 2.5 and 4.5 ppm to generate the contrast value for the rNOE (S\text{rNOE}). MTR\text{asym} was determined from S\text{APT}, S\text{rNOE}, and the signal amplitude of the last CEST spectrum data point (S\text{0}; equation (4)) (7).

\[
\text{MTR}_{\text{asym}} = (S_{\text{rNOE}} - S_{\text{APT}}) / S_{\text{0}} \tag{4}
\]

In healthy subjects, an ROI was selected around the entire liver, and each pixel within the ROI was analyzed using MTR\text{asym} analysis as described above. The same approach was performed for patients diagnosed with lung cancer, except that the ROI for the tumor was selected by a board-certified radiologist with access to standard-of-care diagnostic CT and/or PET/CT imaging. The standard deviation was calculated from the MTR\text{asym} values from all pixels within the ROI.

**RESULTS**

**Simulations of CEST MRI**

The simulated CEST spectrum constructed with the iteratively pulsed saturation scheme was identical to the simulated CEST spectrum constructed with stationary pulsed saturation at all T1 times tested (Figure 2). Therefore, iterating the saturation frequency in small 0.03-ppm increments had no effect on the image contrast when using a small 200-millisecond saturation pulse. Both simulations with a 200-millisecond saturation pulse produced less APT contrast at 3.5 ppm than the standard CEST spectrum.
MRI pulse sequence with saturation applied for 3.0 seconds. This lower contrast was expected, because interleaving a 196-millisecond delay with the saturation pulses to account for the FISP acquisition sequence lowered the duty cycle of the saturation during the entire CEST MRI protocol.

**Phantom Studies**

Our studies with phantoms undergoing motion showed that the iteratively pulsed CEST MRI acquisition with retrospective respiration gating analysis generated more precise MTR$_{sym}$ values compared with the standard CEST MRI acquisition method and the standard CEST saturation (solid black line), stationary pulsed saturation (dashed black line), and iteratively pulsed saturation (dashed gray line) at T1 relaxation times of 0.8 seconds (A), 1.4 seconds (B), 2.0 seconds (C), and 3.0 seconds (D).

**Figure 3.** Respiration-gated CEST magnetic resonance imaging (MRI) studies of an egg white phantom. The standard CEST MRI protocol without respiration-gating analysis detected 10% MTR$_{sym}$ in a stationary phantom, whereas the iteratively pulsed CEST MRI protocol with or without respiration gating analysis detected 5% MTR$_{sym}$. When the phantom was moving in an oscillatory fashion, only the iteratively pulsed CEST MRI protocol with retrospective respiration gating analysis produced a similar MTR$_{sym}$ contrast map relative to results with the stationary phantom.
the iteratively pulsed CEST MRI method without retrospective respiration gating (Figure 3; Table 1). The iteratively pulsed CEST MRI acquisition and respiration-gated analysis estimated similar MTR_{asym} values and standard deviations of the pixelwise maps when the phantom box was stationary and when the phantom box was moving. CEST MRI acquisitions without retrospective respiratory gating analysis estimated considerably different MTR_{asym} values and standard deviations when the phantom was held stationary compared with a moving phantom. In addition, the mean MTR_{asym} value with the standard CEST MR acquisition was significantly higher than the mean MTR_{asym} value with the iteratively pulsed CEST acquisition for the stationary

<table>
<thead>
<tr>
<th>Phantom or Patient</th>
<th>Phantom Status or Tissue Type</th>
<th>Standard CEST MRI</th>
<th>Iteratively Pulsed CEST MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phantom</td>
<td>Stationary</td>
<td>9.5 ± 2.0</td>
<td>4.1 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>Moving</td>
<td>−5.7 ± 21.7</td>
<td>−5.6 ± 15.5</td>
</tr>
<tr>
<td>Patient 1</td>
<td>Tumor in mediastinum</td>
<td>2.5 ± 1.9</td>
<td>0.1 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>0.8 ± 32.8</td>
<td>−4.3 ± 19.8</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Tumor in mediastinum</td>
<td>21 ± 9.2</td>
<td>17.7 ± 8.1</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>21 ± 9.2</td>
<td>17.7 ± 8.1</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Tumor in mediastinum</td>
<td>−1.2 ± 10.5</td>
<td>1.3 ± 20.8</td>
</tr>
<tr>
<td></td>
<td>Tumor near collapsed lung</td>
<td>−9.7 ± 23.1</td>
<td>3.0 ± 11.2</td>
</tr>
<tr>
<td></td>
<td>Collapsed lung</td>
<td>−0.7 ± 6.7</td>
<td>0.8 ± 22.1</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>−0.7 ± 6.7</td>
<td>0.8 ± 22.1</td>
</tr>
</tbody>
</table>

Table 1. %MTR_{asym} of Phantoms and Patients Diagnosed With Lung Cancer

Figure 4. CEST MRI imaging of healthy volunteers. A reference image showed the location of the liver dome (A). When analyzed without retrospective respiration gating, the MTR_{asym} was heterogeneous throughout the liver (B, C). When using the iteratively pulsed CEST MRI protocol with retrospective respiration gating, the results throughout the liver were relatively homogenous (D). CEST spectra of the liver dome are shown with the standard acquisition method (E) and with iteratively pulsed saturation without (F) and with (G) retrospective respiration gating analysis. The average MTR_{asym} values of the liver were similar for the 3 volunteers only when the iteratively pulsed CEST MRI protocol with respiration gating analysis was used (H). Error bars represent the standard deviation of the distributions of pixelwise MTR_{asym} values.
phantom. This difference in mean $MTR_{asym}$ values was attributed to the difference in the duty cycle during saturation. This finding agreed with results observed in simulations.

**Clinical Studies**

Our clinical studies showed that iteratively pulsed CEST MRI acquisition method with retrospective respiratory gating analysis produced more precise $MTR_{asym}$ values compared with CEST MRI acquisition methods without retrospective respiration gating. This improvement in $MTR_{asym}$ measurements was observed for the liver of healthy subjects (Figure 4), as well as the tumor, collapsed lung tissue, and liver of patients diagnosed with lung cancer (Figure 5; Table 1). In the 3 healthy subjects, the standard deviation of the $MTR_{asym}$ values of the pixels of the liver was 3.8%, 3.6%, and 3.9% with our respiration gated analysis method; 72%, 11%, and 32% with the standard CEST MRI acquisition method; and 21%, 22%, and 17% with the iteratively pulsed CEST MRI acquisition without respiration gating. In addition, in the 3 patients diagnosed with lung cancer, the standard deviation of the $MTR_{asym}$ values of the pixels of the liver was less with our respiration gated method than with methods without respiration gating, further showing the superiority of CEST MRI with retrospective respiration gating in the liver.

The locations in the lung varied for the tumors in the 3 patients diagnosed with lung cancer. Tumors that moved significantly with breathing were measured with more precision by using CEST MRI with respiratory gating compared with methods without respiratory gating. Tumors that experienced only minor lung motion showed comparable results with or without respiration gating (patients 1 and 3).

To perform an exploratory clinical study, 4 patients with lung carcinoma or mesothelioma were imaged with iteratively pulsed, retrospective respiratory-gated CEST MRI before and after treatment with radiation therapy and/or chemotherapy (Figure 6; Table 2). Two patients were scanned before and after radiation therapy alone, and 1 patient was scanned before and after chemotherapy alone. One patient was scanned before and after chemoradiation therapy and then again before and after chemotherapy alone. From these 4 patients, 8 tumor sites were analyzed before and after therapy. The initial $MTR_{asym}$ value varied from −0.27% to 8.18% among the tumors, suggesting a range in mobile protein content and/or pH among the tumors. All 3 tumors that were treated with radiation therapy showed a large increase in the $MTR_{asym}$ value after treatment, indicating an increase in mobile protein content or an increase in tumor pH. All 3 tumors when treated with chemotherapy alone showed a small increase or decrease in $MTR_{asym}$. One of the 2 tumors treated with chemoradiation showed a large increase in $MTR_{asym}$, whereas the other tumor treated with chemoradiation showed a small decrease in $MTR_{asym}$. These results may indicate that CEST MRI is more sensitive to radiation therapy than to chemotherapy. Finally, the increase in $MTR_{asym}$ was related to the initial $MTR_{asym}$ value in 7 of the 8 tumors and treatments studied (Figure 6B), suggesting that the initial $MTR_{asym}$ value may predict the mag-

---

**Figure 5.** CEST MRI of a patient with lung cancer. A reference image showed the location of 2 tumors (labeled as a and b), as well as liver and a region of collapsed lung (A). When analyzed without respiration gating analysis, the $MTR_{asym}$ value was heterogeneous throughout all regions (B, C). When using the iteratively pulsed CEST MRI protocol with retrospective respiration gating, the results throughout the liver and collapsed lung tissue were relatively homogeneous (D). CEST spectra of tumor a are shown with the standard acquisition method (E) and with iteratively pulsed saturation without (F) and with (G) retrospective respiration gating analysis. The average $MTR_{asym}$ values of the 4 tissue regions are shown (H). Error bars represent the standard deviation of the distributions of pixelwise $MTR_{asym}$ values.
nitude of the treatment-induced change in CEST MRI. Statistical significance of these results was not evaluated, because this exploratory study was intended to show feasibility for evaluating patients with lung cancer who were undergoing treatment, regardless of the type of tumor or treatment. Therefore, these results provide a foundation for future clinical studies that can more robustly evaluate these initial observations.

**DISCUSSION**

We have established a protocol for performing retrospective respiratory gating for CEST MRI of the lung in a clinically relevant time frame of 3 minutes. Our protocol tracked respiration during the acquisition of CEST MR images, and removed the images that were acquired while the patient was not in the quiescent phase of respiration. We demonstrated that slowly incrementing the saturation frequency is a viable solution to generate CEST image contrast when a short 200-millisecond saturation pulse is required to accommodate respiration. Our retrospective respiratory-gated analysis method clearly improved the precision of MTR\textsubscript{asym} measurements.

The MTR\textsubscript{asym} values of liver with our respiration gated CEST MRI protocol were in good agreement with previously reported values of liver MTR\textsubscript{asym} (28), whereas the results of the standard method were different from those previously reported. We also showed in phantoms and in vivo that the localization of MTR contrast improved by the iteratively pulsed CEST MRI technique with respiration gating, particularly near the interface between tissues and between air and tissue. This type of air/tissue localization is particularly relevant in the lung and liver. Our results also showed that measurement precision is not improved with our respiration-gated technique in tissues that are generally stationary during respiration. This finding indicates that retrospective respiratory gating is only needed when the tissue of interest is moving significantly during respiration.

**Table 2. %MTR\textsubscript{asym} of Patients With Cancer Undergoing Treatment**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Type</th>
<th>Treatment</th>
<th>Tumor Label</th>
<th>Mean %MTR\textsubscript{asym}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stage IIIB lung adenocarcinoma</td>
<td>60 Gy, 30 fractions</td>
<td>a</td>
<td>Before Treatment: 1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Stage IIIA Non-small cell lung carcinoma</td>
<td>60 Gy, 30 fractions</td>
<td>a</td>
<td>Before Treatment: 8.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Stage IV sarcomatoid pleural mesothelioma</td>
<td>40 Gy, 10 fractions and 6 cycles of Alimta/carboplatin</td>
<td>a</td>
<td>Before Treatment: 4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>c</td>
<td>Before Treatment: 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b</td>
<td>Before Treatment: 4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>d</td>
<td>Before Treatment: 0.5</td>
</tr>
<tr>
<td>4</td>
<td>Stage IV mesothelioma</td>
<td>6 cycles of Alimta/carboplatin</td>
<td>a</td>
<td>Before Treatment: -0.3</td>
</tr>
</tbody>
</table>
To implement our iteratively pulsed CEST MRI technique with respiration gating for clinical imaging, we initially selected a 20-mm-thick imaging section to ensure that the tissue of interest remained in the section plane during imaging. This spatial resolution is insufficient to measure small lesions <8 mm in diameter, which comprise the majority of lung lesions that are not immediately biopsied (29). To evaluate these smaller lesions, 3D imaging can be implemented through extremely rapid imaging via CAIPIRINHA (30), segmentation of the 3D acquisition, partial k-space acquisition methods (31), or parallel imaging techniques (32, 33).

Our decision to select images with a phase shift within 1 radian aided the retention of ~30% of the images, resulting in about 140 points in each CEST spectrum. This level of spectral digitization was adequate for MT$\text{r}^\text{asy}$m analyses. Although many other clinical CEST MRI research studies have shown that the MT$r^\text{asy}$m parameter provides some diagnostic value, MT$r^\text{asy}$m is sensitive to changes in both rNOE and APT, which can confound the interpretation of changes in MT$r^\text{asy}$m (6). Because we acquire a full Z-spectrum, future studies could use a more rigorous and quantitative fitting technique, such as fitting CEST spectra with Lorentzian line shapes (26) or the Bloch–McConnell equations (20), or using machine learning techniques that analyze CEST spectra (34). These advanced analysis techniques can potentially evaluate CEST spectra with fewer points. This would allow for a narrower tolerance for the phase shift to be used, which would further reduce the effects of respiratory motion on CEST spectra and reduce the total scan time. Therefore, acquiring CEST spectra with the iteratively pulsed CEST MRI acquisition method with retrospective respiration gating may lead to multiple advantages in future studies.

**REFERENCES**


The Empirical Effect of Gaussian Noise in Undersampled MRI Reconstruction

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Key Words: image reconstruction, noise analysis, MRI, undersampling, compressed sensing

INTRODUCTION

Undersampling in Fourier-based medical imaging provides a variety of clinical benefits including shorter exam times, reduced motion artifacts, and the ability to capture fast-moving dynamics, such as cardiac motion. Undersampling reduces acquisition time by collecting fewer measurements in the frequency domain than required by the Nyquist rate. However, undersampling causes two specific challenges for the reconstruction system, namely, an underdetermined system of linear equations and lower SNR (signal-to-noise ratio) because of reduced measurement time. When reconstruction algorithms are able to overcome these challenges, undersampling can benefit a variety of Fourier-based imaging modalities, including magnetic resonance imaging (MRI) with parallel imaging or compressed sensing (1, 2), computed tomography (CT), positron emission tomography (PET), maximum a posteriori (MAP), weighted least squares (WLS), mean squared error (MSE), repetition time (TR), flip angle (FA), echo time (TE), field of view (FOV), 1-dimensional (1D), 2-dimensional (2D), 3-dimensional (3D)

In Fourier-based medical imaging, sampling below the Nyquist rate results in an underdetermined system, in which a linear reconstruction will exhibit artifacts. Another consequence is lower signal-to-noise ratio (SNR) because of fewer acquired measurements. Even if one could obtain information to perfectly disambiguate the underdetermined system, the reconstructed image could still have lower image quality than a corresponding fully sampled acquisition because of reduced measurement time. The coupled effects of low SNR and underdetermined system during reconstruction makes it difficult to isolate the impact of low SNR on image quality. To this end, we present an image quality prediction process that reconstructs fully sampled, fully determined data with noise added to simulate the SNR loss induced by a given undersampling pattern. The resulting prediction image empirically shows the effects of noise in undersampled image reconstruction without any effect from an underdetermined system. We discuss how our image quality prediction process simulates the distribution of noise for a given undersampling pattern, including variable density sampling that produces colored noise in the measurement data. An interesting consequence of our prediction model is that recovery from an underdetermined nonuniform sampling is equivalent to a weighted least squares optimization that accounts for heterogeneous noise levels across measurements. Through experiments with synthetic and in vivo datasets, we demonstrate the efficacy of the image quality prediction process and show that it provides a better estimation of reconstruction image quality than the corresponding fully sampled reference image.

ABSTRACT

In Fourier-based medical imaging, sampling below the Nyquist rate results in an underdetermined system, in which a linear reconstruction will exhibit artifacts. Another consequence is lower signal-to-noise ratio (SNR) because of fewer acquired measurements. Even if one could obtain information to perfectly disambiguate the underdetermined system, the reconstructed image could still have lower image quality than a corresponding fully sampled acquisition because of reduced measurement time. The coupled effects of low SNR and underdetermined system during reconstruction makes it difficult to isolate the impact of low SNR on image quality. To this end, we present an image quality prediction process that reconstructs fully sampled, fully determined data with noise added to simulate the SNR loss induced by a given undersampling pattern. The resulting prediction image empirically shows the effects of noise in undersampled image reconstruction without any effect from an underdetermined system. We discuss how our image quality prediction process simulates the distribution of noise for a given undersampling pattern, including variable density sampling that produces colored noise in the measurement data. An interesting consequence of our prediction model is that recovery from an underdetermined nonuniform sampling is equivalent to a weighted least squares optimization that accounts for heterogeneous noise levels across measurements. Through experiments with synthetic and in vivo datasets, we demonstrate the efficacy of the image quality prediction process and show that it provides a better estimation of reconstruction image quality than the corresponding fully sampled reference image.

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When designing an undersampled reconstruction system, the primary concern is often focused on compensating for the underdetermined system caused by sub-Nyquist sampling, for example choosing a sparse representation for compressed sensing. However, we should not overlook the fact that collecting fewer measurements in practice leads to overall lower SNR in the acquired data. If the measurements are too noisy, the low SNR will lead to poor reconstructed image quality even if the reconstruction system were fully determined. On the other hand, with high SNR measurements, the resulting image quality will be

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limited by how well the reconstruction can constrain the underdetermined system. The effects of the underdetermined system and the lower SNR are coupled during the reconstruction process, making it difficult to analyze one without the other. It is important, however, to analyze how both issues impact the reconstruction system to determine the empirical limits of undersampling and gain insight on how to improve undersampled acquisition and reconstruction when targeting specific applications.

Compressed sensing theory has provided us with extensive analysis on the bounds for the successful signal recovery from undersampled data. Candès (7) describes a bound on the squared error of the recovered signal limited by the undersampling rate and the sparsity of the data. He also shows that this bound scales linearly with the variance of the noise in the measured data. Candès and Plan (8) provide a more general compressed sensing theory that addresses a combination of practical concerns. For instance, they derive the bounds on squared error of the recovered signal for systems with Fourier encoding matrices, noise measurements, and approximately sparse signals. Unfortunately, while squared error is an important tool in measuring similarity between signals, it often fails to provide a good measure of perceptual image quality. Wainwright (9) improves upon the squared error definition of success by studying the undersampling rates and sparsity levels for which there is a high probability of successfully recovering the support of the sparse signal.

Although it is important to have a theory showing that reconstruction techniques are mathematically founded, when testing a reconstruction algorithm on a new undersampled clinical dataset shows unacceptable image results, it is difficult to leverage the theoretical bounds to understand the cause of the failure. Conversely, when an undersampled reconstruction is successful at a certain undersampling rate, it is natural to then ask, how much further can we push undersampling? In this case, it is difficult to translate theoretic analyses, such as time constants for polylogarithmic bounds (8), into practice. Our goal in this paper is to provide the tools to empirically analyze the effects of lower SNR from reduced measurement time using a reconstruction system that is fully determined, rather than underdetermined. To this end, we present the image quality prediction process (Figure 1). The image quality prediction process takes a Nyquist-sampled (fully determined) reference dataset and adds the proper amount of noise to mimic the lower SNR produced by a given undersampling pattern. By reconstructing this noisy, but still Nyquist-sampled dataset, we have a prediction image that has been affected by lower SNR because of reduced acquisition time but not by artifacts from an underdetermined reconstruction. The image quality prediction process gives us the following three benefits:

- Comparing the prediction image to the reference reconstruction allows us to see the impact of lower SNR from reduced measurement time on the reconstruction system.
- Comparing the prediction image to the underdetermined reconstruction, we are able to assess the added effect of the underdetermined system on the reconstructed image.
- The prediction image provides a better estimate of undersampled image quality than overoptimistically comparing an underdetermined reconstruction to a fully sampled reference reconstruction.

As exemplified in Figure 2, for a given clinical application and undersampling pattern, pulse sequence and reconstruction developers can use the image quality prediction process to determine if low SNR, rather than the underdetermined system, is the limiting factor for a successful reconstruction. Specifi-
cally, an unsatisfactory prediction image indicates that the undersampled acquisition contains more noise than the reconstruction can handle. On the other hand, a high quality prediction image and poor results from the underdetermined reconstruction indicate that the constraints on the underdetermined system are not adequate for the limited number of samples acquired. Once developers understand the limiting factor in a given undersampling application, they can then recommend changes to the acquisition protocol to adjust the measurement SNR or the undersampling rate. Developers can also appropriately focus their efforts on improving the reconstruction algorithm to better account for the noise distribution or to improve the reconstruction constraints, such as the sparsity model.

Before describing the details of the image quality prediction process, we first specify how measurement time affects SNR, specifically when undersampling. We complete this section by introducing a weighted least squares optimization that generalizes the reconstruction process for both undersampled data and the fully determined prediction data.

**Measurement Time and SNR**

For MRI reconstruction, we can model the signal \( s \) as the discrete Fourier transform of the unknown target image object \( m \):

\[
s_k = (Fm)_k
\]

where \( F \) is the multidimensional discrete Fourier transform operator and \( k \) is the \( k \)-th location in \( k \)-space. However, each measurement \( s_k \) comes with an associated noise. We can model the noisy measurement \( Y_k \) as:

\[
Y_k \sim N(Re(s_k), \sigma_{acq}^2/\tau_k) + iN(Im(s_k), \sigma_{acq}^2/\tau_k)
\]

where \( Y_k \) is a random variable drawn from a complex-valued Gaussian distribution with mean \( s_k \) and variance defined by the system noise variance, \( \sigma_{acq}^2 \), scaled by one over the measurement time, \( \tau_k \), as described in (10). With this definition, we assume that the signal is deterministic based on our model, the signal is independent of the noise, and that the noise is independent and identically distributed. In cases where these assumptions do not hold, additional care may be taken to adjust the data to this model, for example, prewhitening coil channels in parallel imaging or accounting for echo time variation in fast spin echo acquisitions.

Again following (10), we define SNR as the signal intensity divided by the standard deviation of the noise and note that from equation (2) we see that the SNR for measured data at the \( k \)-th location in \( k \)-space scales with \( 1/\sqrt{\tau_k} \) is:

\[
\text{SNR} = \frac{\text{signal}}{\sqrt{\text{noise var.}}} = \frac{s_k}{\sqrt{\sigma_{acq}^2/\tau_k}}
\]

As an example, if we double measurement time at each \( k \)-space location (e.g., acquire two samples rather than one), the modeled signal remains the same, the noise variance is reduced by a factor of 2, and the SNR increases by a factor of \( \sqrt{2} \).

We model the measurement time at the \( k \)-th location in \( k \)-space, \( \tau_k \), as the acquisition time per sample times the number of samples:

\[
\tau_k = \tau_{acq} n_k
\]

Without loss of generality, we assume a fixed acquisition time for every sample, \( \tau_{acq} \), defined by the acquisition parameters and the number of samples, \( n_k \), that may vary across \( k \)-space locations.

The measurement time \( \tau_k \) is not necessarily equal for all \( k \)-space locations. Variable density sampling across \( k \)-space can be a natural effect of certain acquisition techniques, such as radial sampling. Variable density sampling may also be used to take advantage of the higher energy in the low frequency regions to improve SNR (similar to Weiner filtering) or to account for asymptotic incoherence (11). A variable density distribution of measurement time generates a corresponding distribution of expected noise variance across \( k \)-space. Lower sampling density at the high frequency \( k \)-space locations results in higher vari-

**Figure 2.** Using the image quality prediction process to adjust scan parameters. This 2D fast spin echo acquisition with 1 mm slice thickness and 4x undersampling produces poor reconstruction image quality (top right). The corresponding prediction image (top left) also has poor image quality, indicating that noise is the limiting factor. Increasing to 2 mm slice thickness (center row) reduces the noise and produces higher image quality in both the prediction and the underdetermined reconstruction. Further accelerating the scan with 6x undersampling (bottom row), the prediction image quality is significantly higher than the reconstruction image quality, indicating that the underdetermined system is the limiting factor for those scan parameters.
Undersampling and Expected Measurement Time

Fast and/or short acquisitions require a limit on the total measurement time. Unfortunately, some systems and applications have constraints on the minimum measurement time at a single $k$-space location. In this case, it is not feasible to sample $k$-space such that the reconstruction system is fully determined (Figure 3, second column). Undersampling is required to meet the measurement time constraints without sacrificing other scan requirements, such as spatial resolution, that are defined by the desired measurement time distribution (Figure 3, dashed green curve). Without loss of generality, we will define the system’s minimum measurement time to be one sample of duration $\tau_{acq}$ and any shorter acquisition times, $\tau_k < \tau_{acq}$, are infeasible.

Undersampling (Figure 3, third column) avoids acquiring fractional samples by measuring either one or zero samples at each $k$-space location. A binary undersampling pattern can be constructed to fit the desired sampling density, whether it be uniform or variable density. This technique of constructing a continuous output with discrete inputs is analogous to pulse-width modulation in digital signal generation and to digital halftoning in computer graphics.

At first, it may appear that the SNR using these binary undersampling patterns is the same as a fully sampled acquisition because at the $k$-space locations where we collect a measurement, it has the same variance, $\sigma^2_{acq}$ as any fully sampled measurement. Also, at locations where we don’t measure any signal, we also don’t collect any noise. However, the Fourier transform effectively averages the measured $k$-space locations with the zeros from the missing measurements, scaling the SNR by the square root of the sampling density equation (3). To model this averaging effect based on the density of binary sampling patterns, we consider the expected measurement time at each $k$-space location, $\tau_k$.

We model the expected measurement time for random undersampling patterns by considering the generation of a random sampling pattern. The binary value for each location in the pattern may be determined by drawing a random sample from a Bernoulli distribution. To generate a pattern with a particular sampling density, the mean parameter of each Bernoulli distribution is set to the desired fractional measurement time, $\rho_k$, for that location. Specifically, let us model $T_k$ as a Bernoulli random variable representing the measurement time at a single location in $k$-space. The expected value of $T_k$ is $\tau_{pred,k}$:

$$\text{Sample}_k \sim \text{Bern}(\rho_k)$$  \hspace{1cm} (5)

$$T_k = \tau_{acq} n_k \text{Sample}_k$$  \hspace{1cm} (6)

$$\tau_{pred,k} = E[T_k] = \tau_{acq} \rho_k$$  \hspace{1cm} (7)

$\tau_{pred,k}$ gives us the expected measurement time per $k$-space location, which in turn leads us to the expected noise variance per $k$-space location, $\sigma^2_{pred,k} = \sigma^2_{acq} / \tau_{pred,k}$.

Image Quality Prediction

Using the expected measurement time described in the previous section, the image quality prediction process generates an image that shows the empirical effects of reduced measurement time without any effects of an underdetermined system caused by undersampling. This process, as depicted in Figure 1, creates the prediction image by adding noise (based on the expected measurement time of a specific undersampling pattern) to a fully sampled reference $k$-space dataset and then passing that adjusted $k$-space through the regularized weighted least squares reconstruction algorithm described in the following section.

Figure 3. With limited measurement time, the sampling density distribution $\tau$ (dashed green line) may fall below one unit of measurement time. For systems with a minimum measurement time, fractional samples (second column) are not possible/do not contribute to reduction in scan time, and we are forced to sample below the Nyquist rate (third column) to meet the required measurement time limit. To simulate the infeasible Nyquist-sampled, fully determined acquisition (second column), the image quality prediction process adds noise to a fully determined reference acquisition (fourth column). Note that all three of these datasets have the same distribution of expected noise variance across $k$-space (bottom row).
The first step in the prediction process is to determine the expected measurement time at each \(k\)-space location, \(\tau_{\text{pred,}k}\), for the given undersampling pattern. For random sampling patterns, this sampling density distribution is readily available, as it is the same distribution that generated the sampling pattern. When the sampling density is not explicitly or analytically available, the measurement time distribution may be approximated from the sampling pattern with local averaging, Voronoi diagrams, or other techniques used in sampling density compensation.

From the measurement time distribution, we calculated how much noise needs to be added to the fully sampled (fully determined) reference \(k\)-space dataset to match the equivalent statistical noise produced by the given undersampling pattern. To simulate an undersampled acquisition with Gaussian noise variance \(\sigma_{\text{add,}k}^2 = \sigma_{\text{add}}^2/\tau_{\text{pred,}k}\), we simply added complex-valued Gaussian noise to the reference \(k\)-space based on the expected measurement time distribution, \(\tau_{\text{pred,}k}\) from equation (7), (Figure 3, right). Given that \(\sigma_{\text{ref}}^2 = \sigma_{\text{acq}}^2/\tau_{\text{ref}}\) is the Gaussian noise variance measured from the reference data, we can calculate the variance of the complex Gaussian noise, \(\sigma_{\text{add,}k}^2\), to add to location \(k\) in the reference \(k\)-space:

\[
\sigma_{\text{add,}k}^2 = \sigma_{\text{ref}}^2 + \sigma_{\text{add}}^2
\]

(8)

\[
\sigma_{\text{add,}k}^2 = \sigma_{\text{pred,}k}^2 - \sigma_{\text{ref}}^2
\]

(9)

\[
\sigma_{\text{add,}k}^2 = \left(\frac{\tau_{\text{ref}}}{\tau_{\text{pred,}k}} - 1\right)\sigma_{\text{ref}}^2
\]

(10)

where \(\tau_{\text{ref}} = \tau_{\text{acq}}n_{\text{ref}}\) in equation (4) and \(n_{\text{ref}}\) is the number of samples acquired in the reference data. The detailed derivation between equations (9) and (10) may be found in the online supplementary Appendix. Often \(n_{\text{ref}} = 1\); however, the reference data may be acquired using many samples, for example the number of averages might equal two or, in the case of our first two experiments, \(n_{\text{ref}} = 144\) (Figure 4).

Note that with variable density sampling patterns, \(\tau_{\text{pred,}k}\) is not constant across \(k\)-space, and thus, the variance of the added noise, \(\sigma_{\text{add,}k}^2\), will also vary across \(k\)-space.

The noise to add at each point in \(k\)-space is drawn from a complex-valued, zero-mean Gaussian distribution with variance equal to \(\sigma_{\text{add,}k}^2\) for that \(k\)-space location. This noise is simply added to the reference \(k\)-space to produce fully determined \(k\)-space with the noise distribution matching that of the undersampled data (Figure 3, right).

The final step in the image quality prediction process is to pass the reference \(k\)-space with added noise through the regularized weighted least squares reconstruction algorithm described in the following section, producing a prediction image that gives an estimate of the reconstruction image quality assuming no effect from an underdetermined reconstruction system.

**Weighted Least Squares Reconstruction**

We require a consistent reconstruction formulation that supports standard fully sampled and undersampled data as well as the prediction data. To this end, we use a maximum a posteriori (MAP) formulation of MRI reconstruction that leads, in general, to a regularized weighted least squares optimization. Equations (1) and (2) combine to give us a Gaussian likelihood probability of measuring a signal \(y_k\) given an image object \(m\):

\[
P(y_k|m) = \frac{1}{\sqrt{2\pi\sigma_{\text{acq}}^2/\tau_k}} \exp\left(-\frac{|y_k - (Fm)_k|^2}{2\sigma_{\text{acq}}^2/\tau_k}\right)
\]

(11)

With this Gaussian likelihood and assuming a general prior probability on our image data \(P(m)\), the resulting MAP formulation leads to a weighted-least squares optimization:

\[
m^* = \arg\max_m P(m|y)
\]

(12)

\[
m^* = \arg\max_m P(y|m)P(m)
\]

(13)

\[
m^* = \arg\min_m \sum_{k=1}^{N_p} \tau_k|y_k - (Fm)_k|^2 - \log P(m)
\]

(14)

\[
m^* = \arg\min_m \frac{1}{2} \|Wy - WFM\|^2 - \log P(m)
\]

(15)

where \(m\) is the vectorized image with \(N_p\) number of pixels; \(y\) is the vectorized acquired \(k\)-space locations with \(N_p\) number of elements; \(F\) is the \(N_p \times N_p\) multidimensional discrete Fourier transform operator; and \(W\) is an \(N_p \times N_p\) diagonal matrix with
$W_{k,k} = \sqrt{\tau_k}$ values along the diagonal. The detailed derivation between equations (13) and (14) may be found in the online supplementary Appendix.

In this paper, we will use a Laplacian-based prior to promote sparsity, $(-\log P(m) = \lambda \|\Psi(m)\|_1)$, where $\Psi$ is a sparsity transform function and $\lambda$ is the Laplace prior parameter. This $\ell_1$ regularized weighted least squares (WLS) optimization does not have an analytic solution, and finding the solution requires a nonlinear reconstruction algorithm. In general, we can solve this optimization using an iterative algorithm, such as fast iterative shrinkage-thresholding algorithm (FISTA) (12) or alternating direction method of multipliers (ADMM) (13).

This optimization framework, given the proper weight values described below, generalizes the reconstruction of a) fully sampled, b) undersampled, and c) image quality prediction datasets.

a) Fully sampled weights: The least squares weights for a fully sampled dataset (both uniform and variable density sampling) are simply equal to the square root of the measurement time, $W_{k,k} = \sqrt{\tau_k} = \sqrt{\tau_{acq} n_k}$ for the $k$-th sample. Assuming, again, that the acquisition time per sample is constant across k-space, $\tau_{acq}$ may be pulled out of the $\ell_2$ norm term, simplifying the weights to be equal to the square root of the number of samples, $W_{k,k} = \sqrt{n_k}$.

Note that with $n_k$ constant across k-space and a uniform prior $P(m)$, the MAP optimization becomes the standard least squares optimization:

$$m' = \arg\min_m \frac{1}{2} \|y - Fm\|^2_2$$

(16)

b) Undersampled weights: When undersampling, the weights, $W_{k,k}$, are simply set to one or zero depending on whether or not that k-space location has been sampled (assuming the same measurement time at each sampled location). With these binary weights, the operator $W$ in equation (15) becomes the undersampling operator defined by the binary sampling pattern. With a Laplacian-based prior, the MAP reconstruction becomes the standard Lasso optimization (14) commonly used in compressed sensing. In addition to strictly binary undersampling patterns, the WLS optimization also allows for undersampling patterns that have zero measurement time at certain locations and a range of measurement times across the remaining locations, for example, an acquisition with undersampled high frequencies and oversampled low frequencies.

c) Prediction weights: The prediction data are designed to simulate the noise variance from the expected measurement time for a given sampling density $\rho_s$, leading us to WLS weights $W_{k,k} = \sqrt{\tau_{pred,k}} = \sqrt{\tau_{acq} n_k \rho_s}$, which may be simplified to $W_{k,k} = \sqrt{n_k}$ assuming constant sampling time and constant number of samples per location in the fully sampled reference data.

**METHODOLOGY**

In this institutional review board-approved study, we acquired MRI data by scanning two healthy, adult volunteers.

**Effect of Measurement Time Distribution**

To better understand effects of reduced measurement time and undersampling and to test our image quality prediction process, we created an experiment that enables us to compare the reconstructions of 1) a fully determined dataset, 2) an underdetermined dataset, and 3) the corresponding prediction data, all using the same total measurement time and sampling density distribution.

The foundation of this experiment is a “stack” of 144 fully sampled k-space images (Figure 4). Each entry in the k-space stack is a different noisy acquisition of the same object slice. With 144 samples available at each of the $N$ k-space locations, we are able to select a subset of these samples to simulate acquiring a specific number of samples at each k-space location based on a desired measurement time distribution.

We used two different datasets for this experiment. The first dataset was the classic Shepp-Logan digital phantom (15) with a slight modification to add a set of parallel dark bars that will help analyze spatial resolution. This phantom was chosen because it has an explicitly sparse representation (many true zero values) in the finite differences domain (often seen in total variation reconstructions), implying that we can use compressed sensing to find a proper solution to the underdetermined system of equations caused by undersampling. As seen in Candès, Romberg, and Tao (16), the Shepp-Logan phantom, without noise, may be perfectly recovered after severe undersampling. To analyze how noise propagates through the reconstruction system, we generated a different instance of complex-valued, zero-mean, Gaussian noise to add to 144 copies of the k-space for the Shepp-Logan phantom. The second dataset is 144 actual MRI acquisitions of a tomato at a single slice location. These data were acquired on a 3T scanner (Siemens Healthineers, Erlangen, Germany) using a T1-weighted gradient echo sequence with 10 ms echo time (TE), 35 ms repetition time (TR), 12° flip angle (FA), 90 mm field of view (FOV), 2 mm slice thickness, and 192 × 192 acquisition matrix. Only the body coil was used during acquisition to both simplify the reconstruction model and ensure that each of the 144 acquisitions had relatively low SNR.

For both datasets, we selected a subset of the full stack of k-space samples based on three different sampling distributions, as depicted in the top row of Figure 5: reference, using all 144 $N$ samples (where $N$ is the number of k-space locations); fully determined, selecting only $18N$ samples according to either a uniform or variable density sampling distribution across k-space locations; and underdetermined, selecting $18N$ samples and following the same density distribution but collecting all 144 samples at $N/8$ randomly chosen k-space locations and collecting zero samples for the remaining locations. We also reconstructed both datasets using the image quality prediction process to add noise to the 144$N$ reference dataset to simulate the noise level from the $18N$ fully determined dataset.

For all reconstructions, the selected k-space samples were averaged at each k-space location to create a single k-space image to be reconstructed ($y$, from equations (12) and (15)).

We reconstructed all data using our implementation of ADMM, formulated for the regularized weighted least squares optimization, with the weights equal to the number of measurements acquired at each k-space location, as specified in the weighted least squares reconstruction section of the introduction. For the digital phantom dataset, we used isotropic total variation as the sparsity model. For the single-channel MRI...
acquired data, we used Daubechies-4 wavelets with translation invariant cycle spinning (17) as the sparsity model.

Effects of Measurement Noise and Undersampling Rate

Given enough acquisition time, we can satisfy a given sampling density distribution by either Nyquist sampling $k$-space or by undersampling. Both of these sampling patterns produce similar distributions of expected noise variance in our data, but undersampling incurs an additional cost from having an underdetermined system of equations. In this experiment, we will extend the oversampled stack experiment above to take a closer look at the effect of measurement noise and undersampling rate on reconstruction image quality. We accomplish this by varying both the measurement noise level and the undersampling rate and then comparing the mean squared error (MSE) images reconstructed from variable density fully determined data and from variable density underdetermined data.

As in the measurement time experiment above, we have a stack of $k$-space data, and we generate an output image by reconstructing a subset of $k$-space samples, selected according to either a fully determined variable density sampling pattern or an underdetermined pattern following the same measurement time distribution.

In this experiment, the $k$-space stack is generated from copies of a single relatively high SNR (31.3 dB) in vivo head acquisition. Similar to the Shepp–Logan $k$-space stack, we added to $k$-space a sample of complex-valued, Gaussian noise with zero mean and a given standard deviation. We executed the experiment using three different values for the added noise standard deviation (1, 5, 8) and four undersampling rates ($2\times$, $4\times$, $8\times$, and $12\times$ undersampled).

The head dataset for this experiment is an axial slice of a three-dimensional (3D) fully sampled, spoiled gradient echo dataset acquired on a 1.5T scanner (GE Healthcare, Waukesha, WI) with 8 receive channels, 5 ms TE, 12 ms TR, 20° FA, 184 $\times$ 230 mm FOV, 1 mm slice thickness, and $256 \times 256$ acquisition matrix. This multichannel dataset was preprocessed, using ES-
PIRiT coil sensitivity maps (18), to combine the data into a single channel, allowing us to use a simpler reconstruction model for this experiment. This head dataset has relatively high SNR, so we were able to experiment with very low noise and subsequently experiment with higher noise levels by adding Gaussian noise to the k-space stack for this dataset. This head dataset also provides a real example of an image that is only approximately sparse in the wavelet transform domain.

We repeated these 12 experiments (three noise levels by four undersampling rates) 100 times, each time reconstructing the fully determined data and the underdetermined data, as well as the corresponding prediction data. We then plotted the resulting MSE values (relative to the original head image) (Figure 6).

**Image Quality Prediction**

We demonstrate the image quality prediction process by comparing the output of the actual undersampled reconstruction to both the generated prediction image and the fully determined reference image. We executed this experiment for two in vivo fully sampled MRI datasets using increasingly aggressive retrospective undersampling rates.

**In vivo Knee**

The in vivo knee dataset is an axial slice of a 3D fully-sampled, fast spin echo dataset acquired on a 3T scanner (GE Healthcare, Waukesha, WI) with 8 receive channels, 25 ms TE, 1550 ms TR, echo train length of 40, 160 mm FOV, 0.6 mm slice thickness, and 320 × 320 acquisition matrix. This dataset was collected by Epperson et al. (19) and is available at (20).

The two retrospective undersampling patterns used were 4 × and 12 × undersampled, variable density Poisson disc. Both patterns fully sampled the center of k-space to allow for ESPIRiT auto-calibration (18). Neither the reference data nor the undersampling patterns included the corners of k-space, a common acquisition acceleration.

The optimization equation for this parallel imaging, compressed sensing reconstruction is an extension of equation (15), modified to include parallel imaging and a Laplacian prior:

\[
\min_{m} \frac{1}{2} \| Wy - WFSm \|^2_2 + \lambda \| \Psi m \|_1
\]

where \( m \) is the vectorized image with \( N_P \) number of pixels; \( y \) is the vectorized acquired multichannel k-space data with \( N_C N_P \) number of elements (\( N_P \) is the number of pixels, \( N_C \) is the number of coils); \( F \) is the \( N_C N_P \times N_C N_P \) two-dimensional (2D) Fourier transform operator for each coil independently; \( S \) is the \( N_C N_P \times N_C N_P \) block diagonal sensitivity maps generated with ESPIRiT calibration; \( \Psi \) is the sparsity transform; \( \lambda \) is the regularization parameter; and \( W \) is the \( N_C N_P \times N_C N_P \) diagonal weight matrix.

Note that the reconstruction process now includes the parallel imaging coil combination operator \( S^H \). With the addition of parallel imaging, the undersampled reconstruction system is now both ill-conditioned and underdetermined. Previous works have provided tools to empirically analyze the noise propagation through the ill-conditioned parallel imaging system, for example by computing the geometry-factor (21) or with Monte Carlo simulations with added noise (22). The image quality prediction process will empirically show the effect of lower SNR because of reduced measurement time on the compressed sensing and parallel imaging reconstruction without any effect from an underdetermined or ill-conditioned system. The actual underdetermined reconstruction will then produce an image affected by similar lower SNR as well as the effects from the ill-conditioned and underdetermined parallel imaging and compressed sensing system.

The sparsity filter (associated with \( \Psi \)) used within the reconstruction was wavelet soft-thresholding using Daubechies-4 with translation invariant cycle spinning (17).

The regularized weighted least squares optimization for both prediction and underdetermined reconstruction used our implementation of the ADMM algorithm. The only difference between the two reconstructions was the appropriate change to the weights as specified in the weighted least squares section of the introduction. Specifically, the weights for the prediction reconstruction were the square root of the sampling density, \( \rho_k \), at each k-space location, and the actual underdetermined reconstruction weights were binary with ones for acquired locations and zeros elsewhere.
The image quality prediction process requires an understanding of the existing noise level in the fully sampled reference data \( (\sigma_{\text{full}}^2) \). Ideally, this noise level could be obtained from an explicit measurement of the received signal using the coils on the same scanner, prior to the actual exam. In our experiments, we measured the noise level from the reference data directly by Fourier transforming the (multichannel) \( k \)-space data and measuring the variance of the values from a 11 × 11 background patch in each coil image. The noise level was measured and applied independently for each coil channel.

A direct inverse 2D Fourier transform followed by coil combination \( (\mathbf{m}_{\text{ref}} = S^H F^{-1} \mathbf{y}_{\text{ref}}) \) was used on the reference \( k \)-space to generate the fully sampled reference image for comparison (Figure 7, top).

**In vivo Head**

The in vivo head dataset is an axial 2D fast spin echo dataset acquired on a 3T scanner (Siemens Healthineers, Erlangen, Germany) with 12 receive channels, 91 ms TE, 6000 ms TR, echo train length of 11, 195 × 220 mm FOV, and 286 × 320 acquisition matrix. The 12 coil channels were reduced to 4 channels with Siemens coil compression. Multiple slices were acquired at slice thicknesses of 1 mm and 2 mm. The phase encode lines were retrospectively undersampled at \( 4 \times \) and \( 6 \times \) acceleration using a one-dimensional (1D) variable density Poisson disc sampling with the central 24 lines fully sampled. This dataset was processed in the same manner as the in vivo knee dataset above.

**RESULTS**

The following three results are shared across all of our experiments:

1. the prediction image has equivalent or worse image quality than the reference image,
2. the undersampled reconstruction image has equivalent or worse image quality than the prediction image,
3. the prediction image for a given sampling density has equivalent image quality to the fully determined image with the same sampling density.

**Effect of Measurement Time Distribution**

Figure 5 shows the results of our experiment to test the effect of various measurement time distributions on reconstruction image quality. For both the Shepp-Logan digital phantom and the MRI acquisition of the tomato, the fully determined images with reduced measurement time show lower image quality than the images reconstructed from the reference acquisition data. As seen specifically in the blurred spatial vertical bars, the fully determined images did not fully recover from the limited acquisition time despite not having any corruption from an underdetermined system of equations.

The variable density underdetermined Shepp-Logan reconstruction (Figure 5, third row, right) was successful and has nearly identically image quality to the fully determined reconstruction but still lower image quality than the reference reconstruction. This indicates that the underdetermined reconstruction recovered well from the underdetermined system, but still could not completely recover from the lower SNR because of reduced measurement time. For the acquired tomato dataset, however, the underdetermined image quality (Figure 5, bottom, right) is lower than the prediction and fully determined image quality, indicating that the reconstruction could not completely recover from the underdetermined system. This is not a surprising result because the tomato image is not sufficiently sparse in the wavelet transform domain, especially when compared to the explicit sparsity of the Shepp-Logan phantom in the finite differences domain.

Figure 5 also shows the results of the image quality prediction process for the same two datasets and sampling distributions. The second and third columns in this figure show that the fully determined reconstructions have essentially identical image quality to the fully determined reconstructions but still lower image quality than the reference reconstruction. This verifies that the image quality prediction process closely simulates the noise level and reconstructed image quality of the associated fully determined acquisitions.
Similar results from the same experiment with uniform density sampling have been included in the online supplementary Appendix.

**Effects of Measurement Noise and Undersampling Rate**

By varying the input noise level and the undersampling rate, we see the differences in the resulting MSE for the reconstructions of the fully determined data and underdetermined data, both with the same measurement time distribution. Figure 6 shows that for a fixed noise level and increasing undersampling rate, the MSE of the fully determined images increases, showing that the reduced measurement time affects image quality despite no undersampling. Also, as we increase the undersampling rate, the MSE of the underdetermined images increases significantly faster than the fully determined images. This gap in image quality shows the degrading effect of the underdetermined reconstruction increasing as the undersampling rate increases and the sparsity transform can no longer adequately model the image in a sufficiently sparse representation.

As seen in Figure 6, the MSE of the prediction images matches the MSE of the fully determined reconstructions for all noise levels and undersampling rates, indicating that the image quality prediction process is consistently simulating the expected noise level for the given sampling density.

The results from this experiment help us to see that when the image quality of the prediction image is unacceptable, the actual undersampled reconstruction will also be unacceptable (i.e., higher MSE). In this situation, the low SNR of the acquisition is the limiting factor in the reconstruction, not the artifacts because of the underdetermined system. To improve the reconstruction in this case, steps should be taken to adjust the acquisition parameters to increase the SNR or better handle the expected noise levels (e.g., reducing spatial resolution, decreasing undersampling rate, or improving the image prior $P(m)$).

**Image Quality Prediction**

Figure 2 shows the prediction and underdetermined reconstruction images for the in vivo head experiment. This figure illustrates how the prediction image may be used to gain insight into the causes of poor undersampled image quality and adjust scan parameters, such as slice thickness, as needed.

Figure 7 shows the reference, prediction, and underdetermined reconstruction images for the in vivo experiment using the knee dataset and various undersampling rates. Figure 7 shows the following three qualitative results: 1) the reference image has better image quality than the prediction images; 2) the prediction images have better image quality than the corresponding underdetermined images; and 3) the underdetermined images are more similar in image quality to the prediction images than the reference image. That the reference images look better than the prediction images is expected because the prediction process adds more noise to the fully sampled reference data. That the prediction images look better than the underdetermined image is expected because the underdetermined reconstruction had to find a proper solution to an underdetermined system of equations in addition to recovering from the lower SNR from reduced measurement time. Finally, the prediction image provides a better estimate of reconstruction image quality than the reference image.

With a reasonable amount of undersampling, the $4 \times$ underdetermined images only have slightly lower image quality than the prediction images. As undersampling increases to $12 \times$, the image quality gap between the underdetermined and prediction images increases. These results are consistent with our effect of measurement noise and undersampling rate experiment when increasing sampling rate.

**DISCUSSION**

The presented image quality prediction process provides an empirical upper bound on undersampled image quality, which serves as a better metric for evaluating the effectiveness of a reconstruction algorithm than direct comparison to a fully sampled reference reconstruction. The prediction process enables an analysis of a reconstruction algorithm's ability to handle lower SNR because of reduced measurement time without any effect from an underdetermined system. By simulating the effect of lower SNR without any underdetermined effects, the prediction process allows us to determine whether a reconstruction is actually limited by our sparse recovery or simply limited by low acquisition SNR. Comparison of the prediction image to the reference reconstruction provides a means to assess the effects of lower SNR on reconstruction image quality. Comparison of the prediction image to the underdetermined reconstruction enables us to analyze what artifacts are introduced when undersampling is used rather than fully determined following the same measurement time distribution. The image quality prediction results and analysis are consistent with our experiments using our highly oversampled datasets to explicitly compare reconstruction results from variable density fully determined and underdetermined data.

An additional benefit of the prediction process is that it may be used to compare and tune different reconstruction algorithms or parameters, assessing how different reconstruction systems handle the lower SNR because of reduced measurement time in addition to comparing the actual undersampled reconstructions.

A limitation of the image quality prediction process is that it requires a fully sampled reference dataset. Access to a fully sampled acquisition is not always possible, especially in cases with 3D or four-dimensional (4D) dynamic imaging, where long, fully sampled acquisition times are not practical. Also, the image quality prediction process can isolate the effects of low SNR from the effects of an underdetermined system, but it cannot do the contrary, that is, it cannot isolate the effects from an underdetermined system from the effects of low SNR. Future work could investigate the effects of underdetermined systems using in vivo data by reconstructing fully sampled reference datasets that are highly oversampled to have minimal input noise, $\sigma_{\text{ref}}$. Of course, the effects of the underdetermined system would still be dependent on the image content, which varies significantly across clinical applications.

While developing the image quality prediction process, we use a maximum a posteriori formulation to derive a general weighted least squares optimization framework that accounts for both uniform and variable density sampling patterns, with
undersampling as a special case using binary weights. This WLS formulation adjusts the standard least squares term to account for the colored noise arising from the distribution of expected measurement time across k-space locations. Future work could develop methods to similarly incorporate the effects of measurement time distribution into the sparsity regularization term, allowing the sparsity filters to better recover from colored noise in addition to incoherent aliasing.

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References


Supplemental Materials

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