An x-space magnetic particle imaging scanner

Patrick W. Goodwill, Kuan Lu, Bo Zheng, and Steven M. Conolly

Department of Bioengineering, University of California, Berkeley, California 94720-1762, USA

(Received 30 July 2011; accepted 28 February 2012; published online 22 March 2012)

Magnetic particle imaging (MPI) is an imaging modality with great promise for high-contrast, high-sensitivity imaging of iron oxide tracers in animals and humans. In this paper, we present the first x-space MPI hardware and reconstruction software; show experimentally measured signals; detail our reconstruction technique; and present images of resolution and “angiography” phantoms. © 2012 American Institute of Physics. [<http://dx.doi.org/10.1063/1.3694534>]

I. INTRODUCTION

Magnetic particle imaging (MPI) is an imaging modality that directly detects magnetic nanoparticles¹ and shows extraordinary promise as a safe substitute for iodinated or gadolinium contrast angiograms, especially for patients with poor kidney function who have difficulty in excreting these standard contrast agents. The technique uses the clever observation that the nonlinear magnetic characteristics of a magnetic nanoparticle can be used to generate an image whose resolution is defined by the magnetic properties of an iron oxide nanoparticle tracer and by the strength of an applied magnetic field gradient. This means that the native imaging resolution is not defined by the wavelength of the radiation used to interrogate the magnetic nanoparticles. For perspective, MPI excitation frequencies are typically below 25 kHz, which corresponds to a wavelength in the body of about 1 km. MPI resolution, on the other hand, can be more than 6 orders of magnitude finer than the wavelength and is measured in millimeters. Imaging is performed using time-varying magnetic fields, and so the technique does not use ionizing radiation. The human body is diamagnetic and so tissue induces no MPI signal. Moreover, tissue is completely transparent to the low-frequency magnetic fields used in MPI. Hence, MPI is ideal for detecting nanoparticle contrast agents with no background and zero depth attenuation.

We believe MPI is ideally suited for imaging blood vessels. An ideal angiography method would see only tracer and not tissue. Tissue is visible in x-ray and magnetic resonance imaging (MRI), and results in a background signal that can obscure clinically important vessel details, especially in a projection imaging technique like x-ray angiography. Hence, physicians typically rely on catheterized arterial injections, with approximately 30-fold higher contrast concentration than venous injections, to achieve adequate contrast. Since MPI only detects tracer, MPI angiography would have exceptional contrast with no background. Further, the iodine used in x-ray fluoroscopy and Gd used in MRI can pose a risk for patients with chronic kidney disease (CKD). Iodine, used in x-ray fluoroscopy and CT Angiography, is the dominant tracer for clinical angiography and places millions of patients at risk for contrast-induced nephropathy (CIN).² Although rare (<1%), severe CIN can require dialysis and is associated with high in-hospital mortality (36%) and high two year mortality (81%).^{3,4} Importantly, the iron oxide tracers

used in MPI are processed in the liver and do not affect the kidneys.^{5,6}

Three MPI reconstruction techniques have been shown experimentally. The most published technique is harmonic-space MPI, which uses a *system matrix* that is comprised of the Fourier components of the temporal signal for every possible location of a point source.^{1,7-12} Reconstruction is achieved through regularization and matrix inversion techniques such as singular value decomposition or algebraic reconstruction. This inversion can be complex since the size of the *system matrix* is large and contains millions of elements. The second technique is a narrowband technique, which reconstructs harmonic images into a composite image using a modified Wiener deconvolution.^{13,14} The third technique, which we use in this paper, is x-space reconstruction.^{15,16} X-space offers several advantages over harmonic-space MPI matrix reconstructions.¹¹ Specifically, x-space MPI is experimentally proven to generate Linear Shift-Invariant (LSI) images, as well as real-time image reconstruction speed as it involves only division by a scalar to reconstruct each point in the image. Importantly, x-space MPI makes no attempt to deconvolve the MPI signal to improve resolution over the resolution determined by the physics of the nanoparticles and field gradient, and thus avoids the significant noise gain of deconvolution (see the noise gain in Ref. 17).

The x-space MPI technique is distinct from the harmonic-space technique with significant differences in the pulse sequences, signal processing, and image reconstruction. This paper details the construction of a small scale MPI scanner, pulse sequence, signal processing, and image reconstruction necessary to form a native x-space MPI image. We also demonstrate the LSI properties of x-space MPI by imaging a resolution phantom and an angiography phantom.

II. X-SPACE THEORY OF MPI

We recently introduced a comprehensive systems theory for MPI, x-space MPI.^{15,16} X-space MPI finds that the imaging equations that govern MPI are similar to those seen in the *k*-space theory of MRI, with the dominant difference that the x-space signal is in the spatial domain and the *k*-space signal is in the spatial frequency domain.^{18,19}

X-space MPI theory requires three assumptions:¹⁴⁻¹⁶ First, we can generate a strong magnetic field gradient

FIG. 1. Two strong opposing magnets produce a field gradient with a millimeter-scale field free point (FFP) at the isocenter where SPIO nanoparticles are not magnetically saturated. Magnetic particles are fully saturated elsewhere. The FFP can be moved across the sample using additional magnetic fields or mechanically in a scanning trajectory to produce an image.

(>2.5 T/m) with a unique null point (see Fig. 1). Second, super-paramagnetic iron oxide nanoparticles (SPIOs) can be adiabatically aligned and saturated with an applied magnetic field greater than about 5 mT. Last, low-frequency nanoparticle signals filtered out during signal detection are recoverable. The problem of lost low-frequency signals is not unique to x-space MPI; system matrix reconstruction must contend with the lost information as well.

It is possible to construct a magnetic gradient that forms a null point, of field free point (FFP – see Fig. 1). The FFP is a millimeter-scale spheroid where the field is below a critical threshold field required to magnetically saturate the SPIO tracer. At all positions in the magnet except at the FFP, SPIOs are magnetically saturated, and produce no time-varying magnetic field. At the FFP, SPIOs are unsaturated and can produce a time-varying magnetic field.

The position of the FFP in the scanner can be moved in what is known as a “pulse sequence.” The combination of mechanical translation, time-varying uniform fields, and a gradient effectively shifts the FFP. Imaging occurs when the FFP is rapidly shifted across the sample using a uniform field, causing the magnetization of SPIOs passing through the FFP to unsaturate as well as flip, inducing a voltage in a receive coil. The receive chain detects the magnetic response of the nanoparticles (while rejecting the excitation signal). Further processing is necessary to recover the particle signal at the excitation frequency in order to result in LSI images.¹⁶

Mathematically, x-space theory^{15,16} describes the MPI process in 1D as

$$s(t) = B_1 m \rho(x) * h(x) \Big|_{x=x_s(t)} \frac{G}{H_{sat}} \dot{x}_s(t),$$

where $\rho(x)$ [particles/m³] is the nanoparticle distribution and $x_s(t)$ is the instantaneous position of the FFP. A number of constants govern the magnitude of the received signal, including the sensitivity of the receive coil B_1 [T/A], the magnetic moment of the nanoparticles m [Am²], the gradient strength G [A/m/m], and the field sufficient for saturation of the magnetic nanoparticle tracer, H_{sat} [A/m]. The point spread function (PSF) in 1D is the derivative of the Langevin function and has the simple form

$$h(x) = \mathcal{L}'\left(\frac{Gx}{H_{sat}}\right).$$

The 1D PSF is similar to a Lorentzian function,¹⁵ and has a full-width at half-maximum (FWHM) that becomes finer with increasing gradient G and decreasing H_{sat} . Neglecting relaxation effects, $H_{sat} \propto d^{-3}$, where d is the magnetic nanoparticle diameter,^{11,15} and so FWHM improves *cubically* with increasing nanoparticle diameter.

Once we have the MPI signal, we form the x-space MPI image in a simple two-step process of velocity compensation followed by gridding of the received signal to the instantaneous position of the FFP. Following reconstruction, the resulting image equation is

$$\hat{\rho}(x(t)) = \frac{H_{sat}}{m B_1 G} \frac{s(t)}{\dot{x}_s(t)} = \rho(x) * h(x).$$

Thus, x-space theory describes how to obtain a native x-space MPI image, $\hat{\rho}(x)$ that is a convolution of the nanoparticle density, $\rho(x)$ with a PSF, $h(x)$. The MPI signal and image equations tell us that the MPI signal is simply a sampling of the native MPI image at the instantaneous position of the FFP. Then, by knowing the position of the FFP, we can reconstruct a native MPI image by velocity compensating and gridding the received signal. Because the resulting image can be described using a convolution with a well-behaved PSF, the resulting x-space MPI technique is LSI. The x-space MPI process in 1D can be seen visually in Fig. 2.

We can extend the x-space formulation to three-dimensions, which we have described in our second x-space paper,¹⁶ where we find that the 3D PSF shape is anisotropic, and rotates with the FFP velocity vector (see Fig. 3). The goal of the scanner described in this paper is to validate the 1D and 3D theoretical results.

III. IMAGING HARDWARE

A. Main field gradient

MPI requires a main field gradient, also known as a selection field,^{1,11} to form the FFP. We can linearly improve resolution (and shrink the size of the FFP) by increasing the magnetic field gradient strength. Due to the properties of the nanoparticles, resolution improves cubically with increasing nanoparticle core diameter.^{11,15,16,26}

FIG. 2. Overview of the x-space MPI imaging process. (a) Let us consider a one-dimensional phantom and rapid movement of the FFP across the sample. (b) As the FFP passes over iron oxide nanoparticles in the sample, the total magnetic moment, $M(t)$, changes in a non-linear manner. (c) An inductive receive coil detects the time-varying magnetic moment as a voltage, $s(t)$. The received signal is then converted into a native x-space MPI image using a two-step process of velocity compensation and gridding to the instantaneous position of the FFP.

We have designed our imager to work with a commercially available nanoparticle tracer, Resovist (Bayer-Schering), which produces a signal similar to a nanoparticle with 17 ± 3.4 nm core diameter.^{16,20} We have found that a 6.0 T/m (3.0 T/m transverse to the bore) gradient is reasonable to build with permanent magnets using the Maxwell-like permanent magnet configuration shown in Fig. 4. Our gradient is built using two opposed, high-grade (N45), NdFeB ring magnets (ID = 8.89 cm, OD = 14.6 cm, THK = 3.2 cm) mounted on G10 fiberglass composite structural plates. The magnets generate a 6.0 T/m gradient down the bore, and 3.0 T/m transverse to the bore. The reduced gradient strength in the transverse axis is fundamental to Maxwell's equations.¹⁶ With Resovist, this system has a measured resolution of ≈ 1.6 mm down the bore. Because of the reduced transverse field gradient strength and since we do not excite in a transverse axis, x-space theory predicts that the transverse resolution is 7.4 mm, or 460% worse than the collinear PSF.¹⁶ The addition of transverse transmit and receive coils (in the x and y axes) would improve the transverse resolution to ≈ 3.2 mm.

Native MPI Image Formation in 2D

FIG. 3. The MPI process can be generalized into two- and three-dimensions, but with a point spread function, $h(\mathbf{x})$, that changes orientation depending on the FFP velocity vector, $\dot{\mathbf{x}}_s(t)$.

An important practical note is the tolerances required for MPI imaging. The gradient linearity need not be better than 5%, as gradient non-linearity results in image distortion similar to rubber sheet distortion from MRI gradients. Because of the small field of view (FOV) of this magnet, we currently neglect this distortion. Further, several Kelvin temperature variation in the gradient magnets are well tolerated. This is in contrast to the milliKelvin temperature stability required for NMR/MRI applications with NdFeB magnets since the field coefficient of rare Earth magnets is typically 1 ppt/K.

B. Analog signal chain

The analog signal chain is broken down into two parts that interact extensively, the transmit and receive sub-systems. The excitation field, also known as a drive field,^{1,11} rapidly moves the FFP across the sample to produce a nanoparticle signal. Simultaneously, the receive sub-system inductively detects and isolates the nanoparticle signal while rejecting the large excitation field. Both subsystems are shown in Fig. 5.

The goal of the transmit chain is to excite the sample with a pure sinusoid with no energy content above the excitation frequency. To this end, we have designed the transmit-receive filters shown in Fig. 2. The transmit filter is composed of a third order low-pass filter that is power matched to a resonant transmit coil. The transmit filter achieves 60 dB isolation at $\times 2$ the fundamental frequency and 65 dB isolation at $\times 3$ the fundamental frequency.

The resonant transmit coil ($f_0 = 19$ kHz) is wound with 10 gauge square magnet wire and is driven by a high power linear amplifier (LVC5050, AE Techtron) filtered by a third-order low-pass filter. The transmit coil generates 30 mTpp with a peak power output of 5 kW, most of which is dissipated as heat in the water-cooled eddy current shield. We employ a 2.5 mm thick copper cylinder to shield the RF transmit and receiver coils from the permanent magnet (PM) gradient. This crucial passive shield greatly diminishes harmonics produced by non-linearities within the PM gradient, and also diminishes any produced harmonics from being picked up in the receiver coil. The RF-gradient shield is also strong enough to serve as a structural component. The shield requires active water cooling because most of the transmit energy is deposited in the shield due to eddy current heating. The peak current and voltage in the transmit coil are approximately 100 A and 180 V. The transmit coil can heat up from resistive heating during extended scanning sessions, and so we have filled the space between the water cooled shield and the transmit coil with a thermally conductive epoxy.

The goal of the receive chain is to receive a wide bandwidth particle signal while suppressing the fundamental frequency. The fundamental frequency must be suppressed from the received spectrum because it is over 140 dB, or 10×10^6 times, larger than the nanoparticle signal. The system described in this paper achieves better than 110 dB of suppression, leaving considerable room for improvement.

The receive coil is wound in a gradiometer-like configuration inside the transmit coil to minimize total shared flux. The signal from the receive coil is notch filtered by a

FIG. 4. Hardware overview. (a) 3D MPI scanner with $2\text{ cm} \times 2\text{ cm} \times 4\text{ cm}$ FOV. The excitation coil generates a 30 mT peak-to-peak oscillating magnetic field at 19 kHz. The NdFeB magnets generate a gradient of $G_z = 6.0\text{ T/m}$ down the imaging bore. (b) Photograph of the small-scale x-space MPI scanner. The free bore before addition of the transmit and receive coils is 8.4 cm. The scanner is potted in epoxy to eliminate vibration.

fourth-order resonant notch, and amplified by a battery-powered low noise pre-amplifier (Stanford Research Systems SRS560). The signal is further conditioned by a noise matched 8th order analog Butterworth high-pass filter (HPF) ($F_{3\text{ dB}} = 25\text{ kHz}$, Stanford Research Systems SIM965), followed by a second stage of amplification (Stanford Research System SIM911). The signal is digitized at 1.25 MSPS (National Instrument, NI-6259), digitally phase corrected, low pass filtered at 200 kHz, and gridded to the instantaneous position of the FFP.

The tolerance of the transmit and receive systems to magnetic field inhomogeneity is quite reasonable. We calculate that the system achieves no better than 5% transmit and receive magnetic field homogeneity within the imaging region, and yet the resulting image artifacts are benign.

IV. PULSE SEQUENCE

The path of the FFP through x-space is considered the MPI pulse sequence. In this scanner, we have implemented a raster pulse sequence (see Fig. 6) for ease of implementation. Any pulse sequence that covers the entire FOV is adequate but optimal sequences are possible to cover the design space

of superior SNR, speed, avoidance of dB/dt stimulation, and prevention of undue stress to the transmit hardware.

In the raster pulse sequence implemented here, we apply a 30 mTpp excitation waveform at 19 kHz that rapidly moves the FFP $\pm 2.5\text{ mm}$ in the z axis while simultaneously translating the sample mechanically in the x axis by up to 2 cm. This covers a region of $5\text{ mm} \times 2\text{ cm}$, which we term a partial FOV (pFOV).

The pFOV is crucial to meet safety limits as it allows us to scan sub-regions of the image within instrumentation limits, SAR limits, and magneto-stimulation limits, and then stitch the resulting sub-regions into a full image. For example, translation of $\pm 2.5\text{ mm}$ does not cover the entire sample. To image a larger FOV, we acquire multiple overlapping partial FOVs by stepping in the z axis. We later stitch the partial FOVs together to form a full image across the desired FOV (see Sec. V C), which is up to 10 cm in the z axis. Magneto-stimulation limits place an upper bound on the size of a partial FOV, and the 30 mTpp field used in this scanner already exceeds the limits for magneto-stimulation for a theoretical human-sized MPI chest scanner.¹⁵ While we use mechanical translation of the sample in this small system, it is straightforward to slowly move the FFP electronically to cover the full FOV using high power, current-controlled

FIG. 5. Analog signal chain.

FIG. 6. Two-dimensional pulse sequence used in the Berkeley x-space scanner. (a) Rapid movement in z of ± 2.5 mm occurs at 19 kHz through the use of a resonant transmit coil, moving the FFP at approximately 200 m/s in the z axis. The FFP displacement is proportional to the current in the transmit coil. This is a schematic representation as the actual movement as over 12×10^3 cycles occur during the scanning period. (b) The sample is mechanically translated down the bore in the z axis in steps of 2.5 mm per scan for a 50% partial FOV overlap. (c) The sample is mechanically rastered during the scan across the FOV in the x axis. (d) The full 2D pulse sequence in real space. For a 3D scan, we mechanically step the sample in the y axis in a similar manner to the stepping in the z axis.

electro-magnets, which we have implemented in the past in a narrowband mouse imaging system.^{13,14}

V. POST-PROCESSING

A. Phase recovery filter

The received signal has corrupted phase because it is conditioned in the analog domain with a HPF before digitization (Fig. 2). This filter removes what can be significant interfering signals from the fundamental excitation sinusoid, mains noise, and $1/f$ noise. Removing these prevents saturation of later stages of amplification. Unfortunately, this complicates reconstruction because x-space MPI requires linear phase throughout the receive system as non-linear receive phase causes an image artifact in the spatial domain.

In the analog domain, our filter is an eighth-order Butterworth HPF, whose transfer function we can write as H_{hpf}

FIG. 7. (Top) Magnitude and phase of signal following 8th order Butterworth analog filtering in the receive chain. (Bottom) Recovered phase following inverse filtering. The stop-band also benefits with improved rejection.

($e^{j\omega}$). We can then write the filtered analog signal as

$$\tilde{S}(e^{j\omega}) = H_{hpf}(e^{j\omega}) S(e^{j\omega}),$$

where $S(e^{j\omega})$ is the signal from the receive coil, and $\tilde{S}(e^{j\omega})$ is the filtered analog signal. Butterworth filters are simple to design in the digital domain,²¹ and we can readily calculate the analog filter's digital counterpart, which has the same transfer function as the analog filter, $H_{hpf}(e^{j\omega})$. We reverse the non-linear phase accrued from the analog HPF by re-filtering with its digital counterpart, but in reverse-time. This is equivalent to filtering with the non-causal filter $H_{hpf}(e^{-j\omega})$. Then, the cascaded analog and digital filters have the straightforward transfer function

$$\begin{aligned} \hat{S}(e^{j\omega}) &= H_{hpf}(e^{-j\omega}) \tilde{S}(e^{j\omega}) \\ &= |H_{hpf}(e^{j\omega})|^2 S(e^{j\omega}). \end{aligned}$$

This is shown graphically in Fig. 7, which shows that the total system has zero-phase accrual and a deeper stop-band. This concept can be considered a modification of zero-phase filtering (see problem 5.68 in Ref. 21) in which a digital filter is applied twice, once in forward direction, and once in the backwards direction. However, in the case presented here, one direction is in the analog domain and the reverse direction occurs digitally.

B. Gridding and velocity compensation

Gridding is the process of sampling the time domain signal into the spatial image domain, introduced to MPI in our first x-space paper.¹⁵ Because the pulse sequence controls the location of the instantaneous position of the FFP, we can assign the received signal to a specific location in space. This straightforward and simple technique does not require regularization, optimization techniques, or prior knowledge of the magnetic response of the tracer such as what is required in harmonic-space MPI.¹¹

The received signal must also be velocity compensated because the induced signal is proportional to the instant-

neous FFP velocity. Then, the gridded, velocity compensated signal is

$$\hat{\rho}(\mathbf{x}(t)) = \frac{\hat{s}(t)}{\|\hat{\mathbf{x}}_s\|}.$$

In practice, we interpolate and average $\hat{\rho}(\mathbf{x})$ using a nearest neighbor or linear interpolation.

During reconstruction in this scanner, we have assumed that the FFP velocity unit vector is constant. This assumption is reasonable because of the speed at which the resonant transmit coil moves the FFP when compared to the speed we mechanically move the sample. In this system, we calculate that the FFP moves at approximately 200 m/s. Mechanical movement of the FFP occurs three orders of magnitude slower, and so it is reasonable to assume the FFP velocity unit vector $\hat{\mathbf{x}}_s$ is a constant.

The x-space process of gridding and velocity compensation can be compared directly to k -space sampling in MRI. In MRI, the received signal corresponds to the instantaneous position in k -space;¹⁸ in MPI the received signal corresponds to the instantaneous position in x-space. To form a k -space image in MRI, the gridded signal must be density compensated.²² Similarly, in MPI the gridded signal must be velocity compensated. Interestingly, because MRI and MPI signal acquisition occur in different domains, MRI k -space artifacts lead to coherent artifacts over the entire image while artifacts in x-space MPI translate to local defects.

C. Image assembly

The analog and digital high-pass filters remove all low-frequency information in the received signal and break the LSI properties of the system. We approach the problem of the loss of low frequencies by considering the HPF of the time domain signal as a loss of low spatial frequency information. For temporal frequencies near the fundamental frequency, our experimental data show that the lost signal corresponds to a dc offset across the FOV. Surprisingly, this means that if we acquire overlapping partial FOVs, we can calculate the dc offset between partial FOV images that maximizes continuity and ensures zero signal outside of the FOV. To form a composite image, we simply add together the overlapped partial FOVs weighted by the SNR of each point. This technique is shown in Fig. 9.

D. Image deconvolution

Image deconvolution is not necessary in x-space MPI to form a native MPI image. However, the native x-space MPI PSF is similar to a Lorentzian distribution, and so a point source will have long tails that add a grey background to the image. For the low resolution imager described in this paper, Wiener deconvolution can provide a way to remove the background and visually improve the image. In practice, we perform Wiener deconvolution in k -space where each k -space point is calculated²³

$$\tilde{\rho}(k) = \frac{1}{H(k)} \frac{|H(k)|^2}{|H(k)|^2 + 1/SNR} \hat{\rho}(k)$$

using an estimate of the image SNR. We used moderate Wiener deconvolution with a SNR cutoff of 50 in k -space so as to minimize image artifacts that become significant when over-deconvolving. The point spread function input into Wiener deconvolution can be measured experimentally or calculated theoretically (see Appendix). In the deconvolution shown here, we have used the theoretically calculated PSF, which we can consider a form of *model based deconvolution*.^{9,10} In the future as we build higher resolution MPI imagers, we hope that deconvolution will not be necessary.

VI. EXPERIMENTAL RESULTS

In Fig. 8, we show the phase corrected signal for a point source sample translated through the origin. We see the amplitude of the signal envelope changes slowly as we scan the position of the FFP along the y axis. This envelope corresponds to the Normal signal envelope in the multidimensional x-space MPI theory.¹⁶

In Fig. 9, we show how it is possible to assemble multiple partial FOVs into a full FOV of arbitrary size. Fig. 9 (top) first shows that the phase corrected, velocity corrected, gridded signal is missing the dc component. Using a simple continuity algorithm, we obtain the dc corrected signal in Fig. 9 (middle). Assembling the dc corrected partial FOVs results in a high quality, native MPI image seen in Fig. 9 (bottom).

In Fig. 10, we see the correspondence between the theoretical and measured collinear component of the PSF. The measured FWHM is 1.6 mm down the bore of the imager, and 7.4 mm transverse to the bore.

In Fig. 11, we show the line scan of a resolution phantom containing point sources separated by 1 mm, 2 mm, and 3 mm. As can be seen, the 1 mm spaced samples are not resolvable as the spacing between them is less than the native resolution of the system (FWHM $\approx$ 1.6 mm).

In Fig. 12, we demonstrate the potential of x-space MPI for imaging complex phantoms by imaging an “angiography” phantom. The phantom is composed of 300 μ m ID tubes filled with undiluted Resovist tracer, and covers an area of

FIG. 8. Measured signal showing phase corrected signal from a single scan across a point source in z and y . (Top) The amplitude changes slowly as we scan 1.5 cm in y . (Bottom) Time-slice near $y = 0$ showing the raw signal as we rapidly scan ± 2.5 mm in z . Total scan time of 650 ms.

FIG. 9. (Top) Experimental data showing 40 overlapped partial FOV scans of a $400\ \mu\text{m}$ wide Resovist point source phantom without baseline correction. (Middle) Experimental data with baseline correction. (Bottom) The assembled image recovers the linearity across the full FOV.

approximately $1.5\ \text{cm} \times 2\ \text{cm}$. The phantom aims to mimic the branching of coronary arteries in the heart, and is a test of the ability of the imaging system to image a continuous nanoparticle density as opposed to point sources that can be easier to deconvolve.

VII. DISCUSSION

A. Linear and shift invariance

The recovery of the dc shifts in individual partial FOVs is crucial to producing a native x-space MPI image that is LSI. The importance of LSI properties in an imaging system cannot be overstated. For the native images produced by x-space MPI, linearity ensures image brightness is linear with concentration, and shift invariance ensures image brightness does not change with position of the object. With LSI, we then know that the images produced accurately reflect the concentration

FIG. 10. Comparison between theoretical and measured collinear component of the PSF. The measured FWHM is $1.6\ \text{mm}$ along the imager bore and $7.4\ \text{mm}$ transverse to the imager bore. Total imaging time of 28 s not including robot movement. The resolution of the PSF can be improved by increasing the main gradient field strength.

FIG. 11. Line scan of a linear resolution phantom with point sources separated by 1 mm, 2 mm, and 3 mm. As can be seen, the 1 mm spaced samples are not resolvable as the spacing between them is less than the native resolution of the system (FWHM $\approx 1.6\ \text{mm}$).

and distribution of the nanoparticles in the sample being imaged.

B. Sensitivity

The signal received by the x-space scanner has high SNR and repeatability. Our early (non-optimized) prototype scanner presented here can detect 200 ng of tracer in a single voxel, but we believe the electronics could be improved in

FIG. 12. X-space MPI generates a native MPI image. Further processing of the native image can be done with standard image processing techniques.²³ (a) Acrylic phantom with $300\ \mu\text{m}$ ID tubing containing undiluted Resovist tracer. (b) Native x-space MPI image. (c) Native MPI image deconvolved using Wiener deconvolution. Total imaging time of 28 s, not including robot movement.

future hardware revisions to reach physical sensitivity limits. With our current voxel size of $1.6 \text{ mm} \times 7.4 \text{ mm} \times 7.4 \text{ mm}$, this corresponds to a sensitivity limit of approximately $2 \mu\text{mol/L Fe}$. In theory, the sensitivity of the MPI technique pushed to its theoretical limit would approach 20 nmol/L Fe sensitivity in a single pixel.^{1,15} Certainly, significant work on both the tracer as well as the hardware must occur before any group approaches this limit.

The primary technical difficulty in the system has been to build a high power transmit system with low total harmonic distortion (THD), high rejection of noise, and high rejection of interference above the excitation frequency. For the phantoms shown here, the detected second and third harmonics of the excitation frequency are approximately half of the magnitude of the MPI signal from our phantoms. To counteract this distortion, we first take a baseline with no sample in the bore and subtract this from the received signal. However, the feedthrough drifts and so still remains our dominant noise source.

The source of the interfering harmonics of the excitation signal has a complex origin. The transmit chain is driven by a linear amplifier with better than 80 dB THD. The transmit filter achieves better than 60 dB isolation at frequencies greater than double the transmitted frequency. However, the distortion detected in the receive coil is significantly higher than what would be predicted by these two measures. We believe that the interfering signal instead arises from distortion in the capacitors in the resonant transmit coil and in the transmit filter, as well as mechanical vibrations. We are actively working to reduce this distortion in future scanners. We note that the mechanical vibrations can be significant. During development of the system, at times we tuned the transmit scanner to frequencies in the audible range, which can be painfully loud because of the transmit coil Lorentz-force interaction with the main field gradient. However, at the current 19 kHz excitation frequency, the system is inaudible because it is beyond the range of human hearing. As MPI is scaled to humans, however, the optimal excitation frequency for imaging in the chest nears the audible range and may require an audible system to reach the optimal SNR while remaining within SAR limits.¹⁵

C. Resolution

The native resolution of the system is of vital importance to building a clinically relevant imaging system. We estimate the resolution of this small-scale MPI scanner to be 1.6 mm down the bore (see Fig. 10) using the Houston criteria for resolution, which states that the resolution is approximately the FWHM of a point source.²⁴ This is exactly what we would expect from the formula from Rahmer *et al.*¹¹ and from Goodwill *et al.*^{15,16,20} if we assume the particles in Resovist are approximately 17 nm in diameter. In Fig. 11, we see a resolution phantom that shows an image of point sources spaced below the resolution limit, slightly above the resolution limit, and firmly above the resolution limit. The scan of the resolution phantom shows that the Houston criteria for resolution is an appropriate measure for resolution.

MPI resolution is a fundamental property of the gradient strength and nanoparticle properties, and is independent of the bore size. The low resolution of the system transverse to the bore of 7.4 mm is a limitation of this specific scanner and not the MPI technique. The low resolution arises from the weaker transverse gradient (3 T/m) and the single excitation coil and receive coil pair oriented down the bore. The clearest method to improving the resolution without a new magnet design would be to build excitation and receive coils in the transverse axes, which would improve the transverse resolution to 3.2 mm.

Current MPI systems re-purpose a magnetic nanoparticle tracer used in MRI for the detection of liver cancer.²⁵ There are differing views on the effective diameter of Resovist when fit to a Langevin model for magnetic nanoparticles. In Refs. 1 and 17, the authors indicate Resovist acts like a 30+ nm magnetic nanoparticle. In a second work by the same group,²⁶ experimental results indicate that the effective diameter is approximately 17 nm. Our recent results^{15,16,20} as well as the imaging results in this paper lend support for the smaller 17 nm diameter. Since Resovist is not optimized for MPI, there remains significant room for improvement²⁷ as the resolution looks to improve with the cube of the nanoparticle diameter.^{11,16}

D. Scaling

As we scale MPI imagers to human sizes, our sensitivity will be limited by dB/dt and SAR limits.¹⁵ X-space MPI theory works well as we scale to larger sizes since we can choose the partial FOV to be the maximum size allowed by dB/dt or SAR safety limits and then assemble the full FOV from the partial FOV scans. While similar in goal to the “focus field” approach of Philips,²⁸ we use a very different methodology, including our pulse sequence, image reconstruction through gridding, as well as our image assembly algorithm.

We also do not see any hardware limits that would prevent scaling MPI to human sizes beyond our ability to generate magnetic field gradients sufficient for high resolution imaging across a large volume. Reasonable human-sized MPI magnet gradients constructed using electromagnets with iron returns or permanent magnets are limited to gradient field strength of approximately $<2.5 \text{ T/m}$. Unfortunately, such a scanner would suffer from low native resolution with existing nanoparticle tracers.^{15,16,20} For the gradient field strength of the scanner shown in this paper (6 T/m), a human magnet would require a superconducting magnet gradient, and would put system costs and complexity similar to that of a modern superconducting MRI system.

VIII. CONCLUSION

We believe that MPI will find its place in rapid angiography, cell tracking, and cancer detection through dynamic contrast enhancement. To do these tasks, the overall technique must give a signal that linearly changes with tracer quantity and gives the same signal no matter where in the animal the tracer resides. In short, the technique must be LSI.

In this paper, we have reviewed the generalized x-space theory, described the construction of a small scale MPI scanner, and demonstrated the necessary signal processing to result in a native x-space MPI image. We believe that the x-space theory enables LSI imaging, which we have demonstrated experimentally but are still working to prove theoretically. As such, we believe that the x-space theory is an important step in the development of MPI theory and hardware. Here we focused on critical hardware components which have never been published.

Significant work remains before x-space MPI can become pre-clinically and clinically relevant. Critically, we believe that at present x-space MPI resolution is not competitive with small animal MRI and CT imaging, where resolution is routinely finer than 250 μm . However, this deficit can be improved through the development of new tracers designed for MPI^{27,29} and the construction of stronger magnetic field gradients.

ACKNOWLEDGMENTS

This work was supported in part by CIRM Tools and Technology Grant RT1-01055-1, and a UC Discovery grant. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of CIRM or any other agency of the State of California. This work was supported in part by Grant Number 1R01EB013689 from the National Institute of Biomedical Imaging and Bioengineering. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Biomedical Imaging and Bioengineering or the National Institutes of Health.

APPENDIX: CALCULATION AND MEASUREMENT OF THE PSF WITH LOGNORMAL DIAMETER DISTRIBUTION

Here, we describe how x-space predicts the shape of the point spread function (PSF). To calculate the theoretical PSF, we must consider the nanoparticle distribution. Specifically, if we assume the receive coil is collinear with the transmit coil, we can calculate the collinear component of the point spread function as

$$h_{\text{dist}}(\mathbf{x}) = \int_d m(d) H_{\text{sat}}^{-1}(u_d) f_X(u_d; \mu, \sigma) \hat{\mathbf{x}}_s \cdot \mathbf{h}(u_d, \mathbf{x}) \hat{\mathbf{x}}_s du_d,$$

where we integrate across the distribution of diameters d , f_X is a lognormal distribution function with mean μ and standard deviation σ ,²⁶ $m(d) = \frac{\pi}{6} M_{\text{sat}} d^3$ [Am^2] is the magnetic moment of a single nanoparticle, and $H_{\text{sat}}^{-1}(d) = \mu_0 m(d) / k_B T$ [m/A] is the inverse of the saturation field of the magnetic nanoparticle. We weight the signal by $m(d)$ because the signal induced in the receive coil from a single nanoparticle increases with the nanoparticle's magnetic moment. We also weight the signal by $H_{\text{sat}}^{-1}(d)$ because the induced signal increases as the Langevin curve becomes sharper.¹⁵ Thus, neglecting relaxation, doubling the diameter of a nanoparticle increases the induced signal by a factor of 2^6 .

By imaging a phantom smaller than the native resolution of the system, we can experimentally measure the point

spread function of the system. As shown in Fig. 10, the theoretical PSF visually matches the experimentally measured PSF. The shape of the PSF is not surprising given the governing principle behind MPI. From the adiabatic assumption, we can assume that the magnetic nanoparticle remains aligned with the locally experienced magnetic field vector. Introducing a single nanoparticle, we see that the magnetic moment de-saturates, flips, and re-saturates to follow the FFP as it passes over the nanoparticle. Since we inductively detect a signal, the change in magnetic moment as well as flipping of the moment induces a signal “blip” in the receiver coil. If we move off axis so that the FFP does not pass directly over the nanoparticle, we see that the nanoparticle flips slower, and so the signal “blip” is smaller and more spread out. Thus, the PSF has the best signal and resolution when the FFP passes directly over the nanoparticle, and is wider when we no longer pass directly over the nanoparticle.

¹B. Gleich and J. Weizenecker, *Nature(London)* **435**, 1214 (2005).

²R. W. Katzberg and C. Haller, *Kidney Int., Suppl.* S3 (2006).

³P. A. McCullough, R. Wolyn, L. L. Rocher, R. N. Levin, and W. W. O'Neill, *Am. J. Med.* **103**, 368 (1997).

⁴P. McCullough, *J. Am. Coll. Cardiol.* **51**, 1419 (2008).

⁵E. A. Neuwelt, B. E. Hamilton, C. G. Varallyay, W. R. Rooney, R. D. Edelman, P. M. Jacobs, and S. G. Watnick, *Kidney Int.* **75**, 465 (2009).

⁶M. Lu, M. H. Cohen, D. Rieves, and R. Pazdur, *Am. J. Hematol.* **85**, 315 (2010).

⁷B. Gleich, J. Weizenecker, and J. Borgert, *Phys. Med. Biol.* **53**, N81 (2008).

⁸T. Knopp, S. Biederer, T. Sattel, J. Weizenecker, B. Gleich, J. Borgert, and T. M. Buzug, *Phys. Med. Biol.* **54**, 385 (2008).

⁹T. Knopp, T. F. Sattel, S. Biederer, J. Rahmer, J. Weizenecker, B. Gleich, J. Borgert, and T. M. Buzug, *IEEE Trans. Med. Imaging* **29**, 12 (2010).

¹⁰T. Knopp, S. Biederer, T. Sattel, J. Rahmer, J. Weizenecker, B. Gleich, J. Borgert, and T. Buzug, *Med. Phys.* **37**, 485 (2010).

¹¹J. Rahmer, J. Weizenecker, B. Gleich, and J. Borgert, *BMC Med. Imaging*, **9**, 4 (2009).

¹²J. Weizenecker, J. Borgert, and B. Gleich, *Phys. Med. Biol.* **52**, 6363 (2007).

¹³P. Goodwill and S. Conolly, in *Proceedings of the First International Workshop on Magnetic Particle Imaging, Lubeck, Germany, 2010*, edited by T. M. Buzug (World Scientific Publishers, 2010).

¹⁴P. Goodwill, G. Scott, P. Stang, and S. Conolly, *IEEE Trans. Med. Imaging* **28**, 1231 (2009).

¹⁵P. W. Goodwill and S. M. Conolly, *IEEE Trans. Med. Imaging* **29**, 1851 (2010).

¹⁶P. Goodwill and S. Conolly, *IEEE Trans. Med. Imaging* **30**, 1581 (2011).

¹⁷T. Knopp, S. Biederer, T. F. Sattel, M. Erbe, and T. M. Buzug, *IEEE Trans. Med. Imaging* **30**, 1284 (2011).

¹⁸D. B. Twieg, *Med. Phys.* **10**, 610 (1983).

¹⁹S. Ljunggren, *J. Magn. Reson.* **54**, 338 (1983).

²⁰P. Goodwill, A. Tamrazian, L. Croft, C. Lu, E. Johnson, R. Pidaparathi, R. Ferguson, A. Khandhar, K. Krishnan, and S. Conolly, *Appl. Phys. Lett.* **98** (2011).

²¹A. Oppenheim and R. Schaffer, *Discrete-Time Signal Processing*, 2nd ed. (Prentice Hall, 1999).

²²J. I. Jackson, C. H. Meyer, D. G. Nishimura, and A. Macovski, *IEEE Trans. Med. Imaging* **10**, 473 (1991).

²³R. C. González and R. E. Woods, *Digital Image Processing* (Prentice Hall, 2008).

²⁴W. Houston, *Phys. Rev.* **29**, 478 (1927).

²⁵J. Ferrucci and D. Stark, *Am. J. Roentgenol.* **155**, 943 (1990).

²⁶S. Biederer, T. Knopp, T. Sattel, K. Lüdtke-Buzug, B. Gleich, J. Weizenecker, J. Borgert, and T. Buzug, *J. Phys. D: Appl. Phys.* **42**, 205007 (2009).

²⁷R. M. Ferguson, K. R. Minard, and K. M. Krishnan, *J. Magn. Magn. Mater.* **321**, 1548 (2009).

²⁸J. Weizenecker, B. Gleich, J. Rahmer, H. Dahnke, and J. Borgert, *Phys. Med. Biol.* **54**, L1 (2009).

²⁹R. M. Ferguson, K. R. Minard, A. P. Kandhar, and K. M. Krishnan, *Med. Phys.* **38**, 1619 (2011).