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High resolution magnetic nanoparticle tracers for early disease diagnosis in Magnetic Particle Imaging

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Abstract

Magnetic Particle Imaging (MPI) is a breakthrough in medical imaging technology. MPI already showed great promise towards cancer, gastrointestinal bleeds, pulmonary embolisms, stroke and WBC imaging, and it could soon provide a rapid, high-resolution and zero-radiation alternative to Nuclear Medicine studies like PET and SPECT. MPI could soon give unequivocal CAR-T cell immunotherapy treatment efficacy feedback in just 3 days instead of 3 months, allowing nimble treatment optimization for each patient. Currently, the biggest obstacle in MPI is the poor spatial resolution of MPI tracers. In this work, we report a recently discovered commercially available tracer — Synomag®-D — that shows a 3.5-fold resolution boost when imaged with a weaker drive field. This resolution boost could reduce the gradient cost and hardware constraints and bring MPI a step closer to clinical translation.

I. Introduction

Our immune system plays a key role in cancer, autoimmune diseases, and inflammation. Scintigraphy and SPECT are used clinically to image autologous white blood cells (WBCs) to allow MDs to track a patient's immune response. However, the radioactive tags (Tc99m or In111) are toxic to WBCs, leading to poor specificity [1, 2]. Magnetic Particle Imaging (MPI) is a potential breakthrough in medical imaging [3–8]. MPI could soon be ideal for cell tracking in cancer immunotherapy, providing a rapid, high-quality, and zero-radiation complement to clinical Nuclear Medicine studies, with no WBC toxicity [7].

The only remaining technical challenge for MPI is its poor resolution (~1.5 mm in a mouse) [9]. Hence, it is crucial to design high-resolution, MPI-tailored superparamagnetic iron oxide (SPIO) tracers to scale up MPI scanners to safe and affordable whole-human MPI. Here we show a serendipitous finding that one commercially available tracer Synomag®-D demonstrates significantly better spatial resolution (3.5-fold sharper) than VivoTrax when imaged with a weaker drive field [9, 10].

II. Methods

We characterized the MPI performance of Synomag®-D-70nm-plain (micromod Partikeltechnologie GmbH, Germany) and VivoTrax (Magnetic Insight, USA) using our in-house arbitrary waveform relaxometer (AWR) at both high and low drive fields [11]. We measured their point spread functions (PSFs) at both 2 mT and 20 mT am-

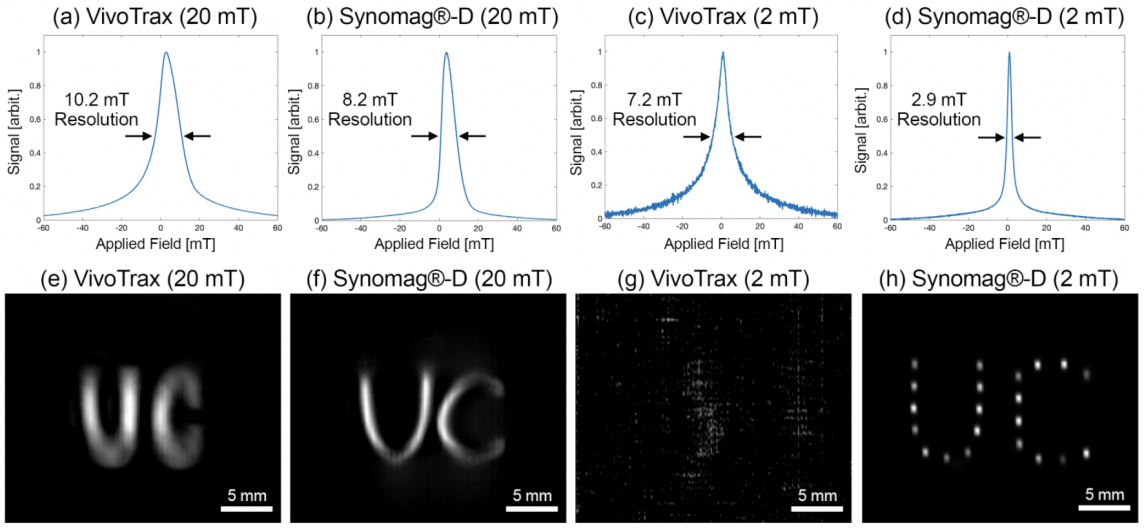

Figure 1: Equalization filter robustly removes the haze of an MPI image without amplifying noise (a,b) UC phantoms for MPI scans in (c) for Synomag®-D at 2 mT and (d) 20 mT amplitudes. The 1D equalization filter in k-space effectively removes the long tails of an MPI PSF, so the images in (e) and (f) have improved contrast and conspicuity with no significant SNR loss.

plitudes. We prepared point source phantoms for both Synomag®-D and VivoTrax using 0.3 mm I.D. capillary tubes with 1.5 mm center-to-center spacing between the tubes. The phantoms were imaged in a 6.3 T/m field-free line MPI scanner. 2D projection images were acquired with a field of view of 4 cm x 6.2 cm and a 20 kHz drive field at 2 mT and 20 mT amplitudes. The MPI images were reconstructed using x-space reconstruction algorithms and filtered by k-space equalization filters [12–15].

III. Results and Discussion

Multi-amplitude evaluation of Synomag®-D and VivoTrax showed that at 20 mT amplitude, both Synomag®-D and VivoTrax have comparable resolutions at roughly 1.5 mm (Fig. 2a,b,e,f). When the drive field amplitude is reduced from 20 mT to 2 mT [16, 17], Synomag®-D has a resolution of 2.9 mT / 6.3 T/m = 460 µm. This low-excitation amplitude [11] provides a 3.5-fold boost in resolution compared to VivoTrax with roughly 1.2 mm in resolution (Fig. 2c,d,g,h). Figure 2 g&h demonstrates this significant boost in resolution. The Synomag®-D point sources are distinct and easily resolved, compared to VivoTrax where the signal-to-noise ratio (SNR) is low at 2 mT amplitude to visualize the phantom. This unexpected 3.5-fold boost in magnetic resolution could enable a dramatic cost reduction for future clinical MPI scanners. Because the cost of MPI scanner hardware scales quadratically with gradient strength, a 3.5-fold reduction in gradient strength could reduce the MPI scanner cost by 11-fold [16]. The SNR tradeoffs and nanoscale physics mechanism underlying this resolution boost merit deeper study.

Point Spread Function Equalization Deconvolution methods can improve the resolution of images, but they typically come with significant SNR loss or require significant constraints. Hence, deconvolution is often not medically advisable. In MPI, the PSF has long tails that produce haze and reduce image contrast and conspicuity. We previously found that the haze is mathematically well-behaved, and the PSF can be reshaped with equalization filters without significant SNR penalty [15]. In Figure 1, we show that 1D equalization filters can dehaze MPI images and improve image contrast and conspicuity. The equalization filters effectively remove low frequency haze and noise and have no effect on the desired signal and high frequency noise, so there is no significant SNR loss.

IV. Conclusion

Recently, we demonstrated that superferromagnetic iron oxide nanoparticles (SFMIOs) can provide a 10-fold improvement in resolution and SNR per gram of tracer [18]. However, biocompatible formulations of SFMIOs remain an open challenge, whereas the Synomag-D tracers are already biocompatible and available commercially. So this high-resolution MPI technique shows immediate promise for reducing the cost of clinical MPI scanners and accelerating the adoption of MPI for imaging CAR-T response to immunotherapies.

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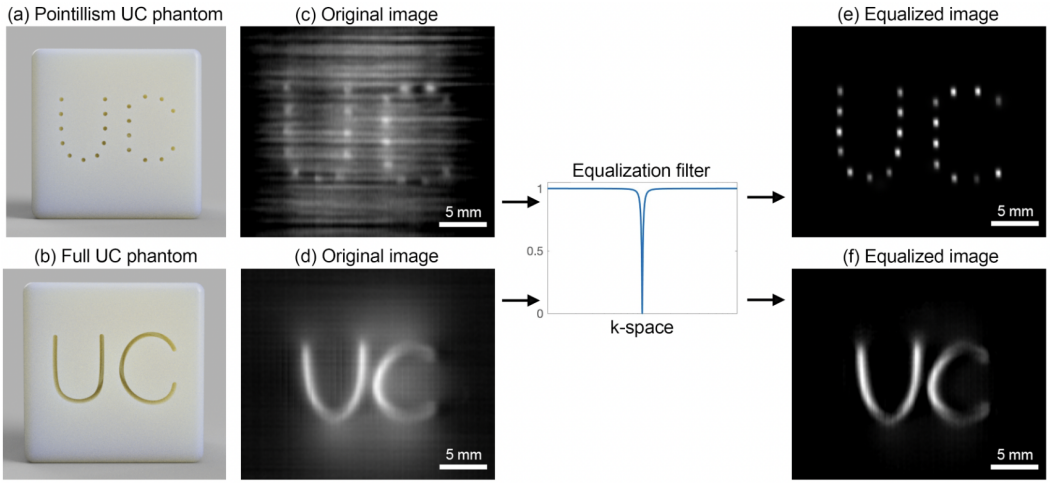

Figure 2: MPI Tracers (a-d) Point spread functions and (e-h) signal peak-normalized 2D MPI images of VivoTrax and Synomag®-D at 2 mT and 20 mT amplitudes. At 20 mT, VivoTrax and Synomag®-D have comparable resolution. At 2 mT, the SNR tradeoff for a resolution boost renders the VivoTrax scan with low sensitivity. While there is also an SNR tradeoff for Synomag®-D at a lower amplitude, Synomag®-D shows a 3.5-fold boost in resolution compared to e and f, resolving the point sources of the phantom.

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Author's statement

Conflict of interest: Dr. Conolly is a co-founder of a startup company that manufactures and sells preclinical MPI scanners. Part of this work was presented at the world molecular imaging congress.

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