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Elucidating super-resolution Magnetic Particle Imaging: superferromagnetic remanence decay through MPI signal evolution informs super-resolution MPI scan strategies

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Abstract

Magnetic particle imaging (MPI) is a tracer imaging modality that detects superparamagnetic iron oxide nanoparticles (SPIOs), enabling sensitive, radiation-free imaging of cells and disease pathologies. Preclinical MPI resolution is limited to 1-2 mm (with ferucarbotran) due to scanner and particle constraints. Recent SPIOs have shown 10-fold resolution and signal improvements at high concentrations, with unusually sharp magnetic responses. Dubbed superferromagnetic iron oxide particles (SFMIOs), these particles appear to interact with neighbours, effectively amplifying applied fields. SFMIO signal is highly dependent on the remanence of magnetically-generated SFMIO superstructures. This work explores SFMIO remanence evolution after magnetic polarization, showing zero-field decay around 120 ms, and various strategies for maintaining SFMIO behaviour that set the minimum scan speed for *in vivo* usage. The resolution improvements provided by generating and maintaining SFMIO superstructures will allow for 10-fold reduction in scanner field strength and thus a 100-fold reduction in cost.

I. Introduction

Magnetic particle imaging (MPI) is an emerging tracer imaging modality that detects superparamagnetic iron oxide nanoparticles (SPIOs), enabling sensitive, ionizing-radiation-free imaging of cells, cancer, and gut bleed with no background signal [1–3]. MPI resolution is limited to 1-2 mm (with ferucarbotran) due to practical scanner and particle constraints [4]. Recent SPIOs have shown 10-fold resolution and signal improvements at high concentrations [5], with unusually sharp magnetic responses (Fig. 1A). Dubbed superferromagnetic iron oxide particles (SFMIOs), these particles appear to interact with neighbours, effectively amplifying applied fields. This resolution improvement is *crucial* for MPI, as scaling current preclinical scanners to human scale would require scanner magnets with field strengths equivalent to 7 T MRIs, precluding access for many healthcare settings. With the resolution improvements offered by SFMIOs, scanner field strengths could be reduced 10-fold while maintaining 1-2 mm resolution in humans, allowing for a 100-fold reduction in manufacturing cost.

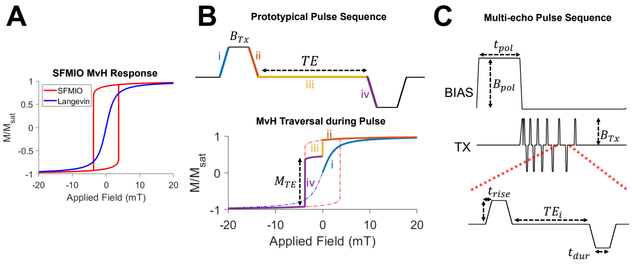

Figure 1: Characterizing SFMIO remanence decay: Magnetic waveforms can be used to characterize the SFMIO magnetic response (A). The prototypical pulse sequence (B, top) polarizes the SFMIOs (i), allows the SFMIOs to sit at 0 field for some echo time (TE) (ii, iii), and then reads out the resulting remanence M_{TE} (iv), as shown in the traversal in the MvH response (B, bottom). The complete multi-echo sequence (C) concatenates multiple primitives to measure remanence as a function of TE.

While SFMIOs offer incredible benefits, its properties are highly dependent on the remanence of magnetically-generated SFMIO superstructures [4]. It is thus critical to investigate the evolution of SFMIO remanence during the course of a standard MPI scan to preserve the observed superresolution behaviour. This work characterizes SFMIO remanence evolution after magnetic polarization, using magnetic and mechanical forces, to inform future MPI scan strategies, and demonstrates strategies for managing SFMIO remanence.

II. Methods and materials

30-nm magnetite nanoparticles (SFMIOs) were synthesized via thermal decomposition [6] and suspended in hexane. 40 µL of SFMIOs, at estimated concentration of 12.1 mg Fe/ml, were measured in an arbitrary-waveform relaxometer [7]. The point spread function (PSF) was measured using 20 kHz fields of 1-8 mT, and SFMIO remanence decay was measured using custom pulse sequences (Fig 1). The prototypical sequence used to measure remanence (Fig 1B, top) traverses the SFMIO hysteresis curve(Fig 1B, bottom), first polarizing the sample (Fig 1B, i) , then allowing the sample to sit at 0 mT for some echo time TE (Fig 1B, ii-iii), then measuring the resultant remanence M_{TE} (Fig 1B, iv). The complete, multi-echo sequence (Fig. 1C) concatenates said prototypical pulses with increasing TE at 0 mT. Specifically, SFMIOs were polarized using strong fields ($B_{\mathrm{pol}} = 30\,\mathrm{mT}$, $t_{\mathrm{pol}} = 30\,\mathrm{s}$), and then measured with alternating trapezoidal pulses ($t_{\mathrm{rise}} = 10\,\mu\mathrm{s}$, $t_{\mathrm{dur}} = 2\,\mathrm{ms}$, $B_{\mathrm{Tx}} = \pm 32\,\mathrm{mT}$) with increasing inter-pulse duration ($\mathrm{TE}_i = [100\,\mu\mathrm{s}, 80\,\mathrm{ms}]$). The resultant signal represents remanence as a function of increasing echo time TE_i, providing a surrogate measurement of SFMIO remanence and its evolution of the course of an MPI scan.

This pulse sequence was then modified to further interrogate SFMIO remanence evolution. To assess decay in scan environments, the remanence decay was measured at various steady-state fields ($B_{\mathrm{ss}} = [-4\,\mathrm{mT}, 1\,\mathrm{mT}]$) (Fig. 3A). To assess the importance of geometric and structural integrity, the SFMIOs were also measured after manual mechanical agitation of the sample.

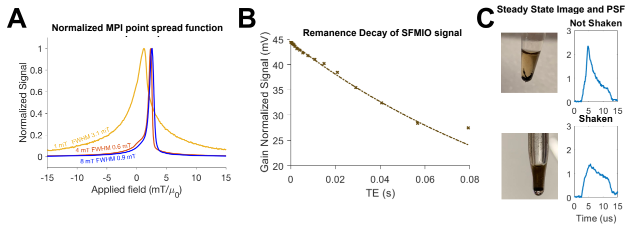

Figure 2: Characterization, zero-field remanence decay and steady state behavior: The SFMIOs showed super-resolution behaviour above 4 mT amplitude (A). When subjected to the multi-echo pulse sequence (B), SFMIO remanence decayed with $\tau \approx 120\,\mathrm{ms}$. (C) Steady-state remanence was magnetically and visually observed at $t = 12\,\mathrm{s}$, and was eliminated through mechanical agitation

III. Experiments

The SFMIOs demonstrated super-resolution PSFs for $B_{\mathrm{Tx}} \geq 4\,\mathrm{mT}$ (Fig. 2A). The MPI signal of SFMIOs exponentially decayed with increasing TE at 0 mT field ($\tau_{\mathrm{decay}} \approx 120\,\mathrm{ms}$) (Fig. 2B), but did not fully lose super-resolution behaviour (Fig 2B,C). At 12s ($\gg 5\tau_{\mathrm{decay}}$), SFMO signal remained, only losing super-resolution behaviour after mechanical agitation (Fig 2C).

Fig. 3 shows the remanence evolution as a function of steady-state field for SFMIOs polarized in the negative direction. When fields parallel to the structure were applied, the SFMIO signal showed minimal decay. In comparison, applying zero field and minimal anti-parallel fields showed greatly accelerated decay with ($\tau_{\mathrm{decay}} \approx 13\,\mathrm{ms}$) in the fastest case.

IV. Discussion

As seen in the initial experiment in Fig. 2, these SFMIO superstructures show remanence decay as a function of time at 0 mT. While not so fast as to disrupt super-resolution behaviour in standard MPI scans acquired at a 20 mT amplitude and 20 kHz excitation frequency, the variability of signal would be worrying for MPI properties such as linearity, if not for the behaviour in response to steady-state applied fields.

From Fig. 3, it is observed that fields parallel to SFMIO structures reinforce the structures, and minimize decay overall, allowing for consistent signal strength. In comparison, anti-parallel fields tended to severely accelerate

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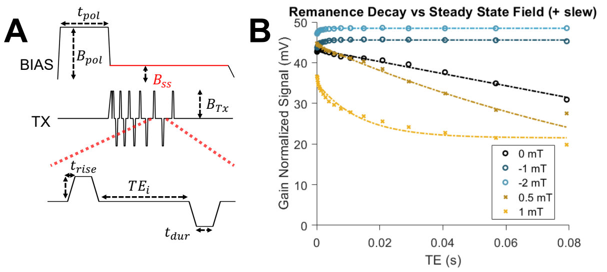

Figure 3: **Remanence decay under steady-state bias fields:** The multi-echo sequence was modified to have a steady-state bias field (A). The resultant remanence (B) showed minimal decay with fields parallel to the chains (negative fields in blue), and accelerated decay with fields anti-parallel to the chains (positive fields in yellow)

decay. As the magnetic potential energy generated by fields antiparallel to a magnetic structure is at an unstable minimum, the decay may be due to the torque generated on the SFMIO structures given any imperfect alignment to the field, and may cause accelerated misalignment from the measurement axis. However, during the course of a standard MPI scan, SFMIO structures tend to experience reinforcing fields, with zero or antiparallel fields only occurring between 0 mT and the coercivity of the SFMIOs (seen in Fig. 1(A)). This suggests that a minimum scan speed for SFMIOs, with effective frequency $f_{\min} \approx \frac{B_{\text{coercivity}}}{B_{\text{Tx}}\tau} \approx 2$ Hz for a 20 mT amplitude field and these 4 mT coercivity SFMIOs is needed to maintain super-resolution behaviour.

These results have notable ramifications for both encapsulation and MPI scan strategies. The asymptotic and long-term remanence of SFMIOs appear to be due to the geometric alignment of SFMIO structures, and could be dependent on the applied field and encapsulation structure. However, the time-varying decay of SFMIO signal is reassuringly mitigated by applied fields. These results suggest that super-resolution behaviour will be well maintained above a certain scanning slew rate, consistent with previous investigations of SFMIO behaviour as a function of drive frequency [5]. Future work should further characterize delay patterns at fields, to generate a map of $\tau(B)$, to yield a better estimate of this minimum scanning frequency for standard scans. Moreover, the SFMIO reformation behaviour post magnetic transition should be investigated, to estimate maximum scan speeds for SFMIOs.

V. Conclusion

This work investigated the signal evolution of SFMIO particles post structure formation, and found signal decay dependent on mechanical and mechanical agitation. Based on our results, SFMIOs should be reinforced rather than decay during the course of a standard MPI scan, ensuring that minimal magnetics barriers are present for translating the 10-fold resolution improvements to *in vivo* usage. As more is understood about SFMIO signal behaviour over the course of a scan, SFMIOs will be more easily translated into *in vivo* usage. These developments are crucial for the future of clinical MPI, through efficient cost reductions and improved safety parameters.

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Author's statement

Conflict of interest: S. M. C. is a co-founder of an MPI company, Magnetic Insight, and holds stock in this company. The authors declare no other conflict of interest.

References

[1] B. Gleich and J. Weizenecker. Tomographic imaging using the nonlinear response of magnetic particles. *Nature*, 435(7046):1214–1217, 2005, doi:10.1038/nature03808.

[2] P. W. Goodwill, E. U. Saritas, L. R. Croft, T. N. Kim, K. M. Krishnan, D. V. Schaffer, and S. M. Conolly. X-Space MPI: Magnetic Nanoparticles for Safe Medical Imaging. *Advanced Materials*, 24(28):3870–3877, 2012, doi:10.1002/adma.201200221.

[3] E. Y. Yu, P. Chandrasekharan, R. Berzon, Z. W. Tay, X. Y. Zhou, A. P. Khandhar, R. M. Ferguson, S. J. Kemp, B. Zheng, P. W. Goodwill, M. F. Wendland, K. M. Krishnan, S. Behr, J. Carter, and S. M. Conolly. Magnetic Particle Imaging for Highly Sensitive, Quantitative, and Safe in Vivo Gut Bleed Detection in a Murine Model. *ACS Nano*, 11(12):12067–12076, 2017, doi:10.1021/acsnano.7b04844.

[4] Z. W. Tay, D. Hensley, J. Ma, P. Chandrasekharan, B. Zheng, P. Goodwill, and S. Conolly. Pulsed Excitation in Magnetic Particle Imaging. *IEEE Transactions on Medical Imaging*, 38(10):2389–2399, 2019, doi:10.1109/TMI.2019.2898202.

[5] Z. W. Tay, S. Savliwala, D. W. Hensley, K. L. B. Fung, C. Colson, B. D. Fellows, X. Y. Zhou, Q. Huynh, Y. Lu, B. Zheng, P. Chandrasekharan, S. Rivera-Jimenez, and S. M. Conolly. Superferromagnetic nanoparticles enable order-of-magnitude resolution and sensitivity gain in magnetic particle imaging. *Small Materials*, 2021.

[6] E. C. Vreeland, J. Watt, G. B. Schober, B. G. Hance, M. J. Austin, A. D. Price, B. D. Fellows, T. C. Monson, N. S. Hudak, L. Maldonado-Camargo, A. C. Bohorquez, C. Rinaldi, and D. L. Huber. Enhanced Nanoparticle Size Control by Extending LaMer's Mechanism. *Chemistry of Materials*, 27(17):6059–6066, 2015, doi:10.1021/acs.chemmater.5b02510.

10.18416/ijmpi.2022.2203051

[7] Z. W. Tay, P. W. Goodwill, D. W. Hensley, L. A. Taylor, B. Zheng, and S. M. Conolly. A High-Throughput, Arbitrary-Waveform, MPI Spectrometer and Relaxometer for Comprehensive Magnetic Particle Optimization and Characterization. *Scientific Reports*, 6(1):34180, 2016, doi:10.1038/srep34180.

10.18416/ijmpi.2022.2203051