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MPI tracer interactions and their effect on signal stability

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Abstract

Nanoparticles tend to agglomerate following their in vivo or in vitro application. This leads to particle interaction and, for magnetic particle imaging (MPI) tracers, to magnetic coupling phenomena. Here, we investigate these effects and their influence on magnetic particle spectroscopy (MPS) and MPI signal stability. Highly magnetic flame-made Zn-ferrites with controlled interparticle distance are suggested as a stable MPI tracer system. Due to their pre-aggregated morphology, additional agglomeration does not substantially alter their magnetic response. This is in strong contrast to frequently investigated polymer-coated iron oxide nanoparticles, which show a massive MPS signal loss in a biologically relevant dispersion medium compared to water. This effect is also shown during MPI and renders these tracers inapplicable to further applications. Our flame-made Zn-ferrites, on the other hand, show sufficient signal stability, which allows their detailed quantification via MPI.

I. Introduction

The MPI performance with respect to resolution and reproducibility depends on the exact characteristics of the used tracer particles; a topic that is still in its infancy. Theoretical predictions have to consider complex magnetic relaxation mechanisms, which depend on particle composition and morphology, thermal fluctuations, and, the topic of this work, particle interactions. The latter is of crucial importance but also frequently neglected. Nanoparticles tend to agglomerate after their in vitro exposure or in vivo injection due to the harsh conditions faced.[1] This changes the system morphology from an initial well-characterized monodisperse state to complex fractal-like networks of varying compactness. For MPI-tracers, this agglomeration results in interactions between the magnetic nanoparticles which again affects their magnetic response[2] and thus their overall signal.

This magnetic coupling phenomenon has been investigated for magnetic resonance imaging[3] and MPS[4] sensing applications but mostly neglected with respect to MPI signal stability. Khandhar et al. reported a signal decrease of 53 % of polymer-coated iron oxide particles in cell-culture medium compared to water.[5] A similar effect has been observed during encapsulation of standard MPI tracers in red blood cells.[6] Recently, we have shown the importance of magnetic interactions for MRI contrast agents.[7] Due to decoupling of ultra-small iron oxide core by an extensive SiO_2 matrix we could boost their T_1 contrast enhancement.

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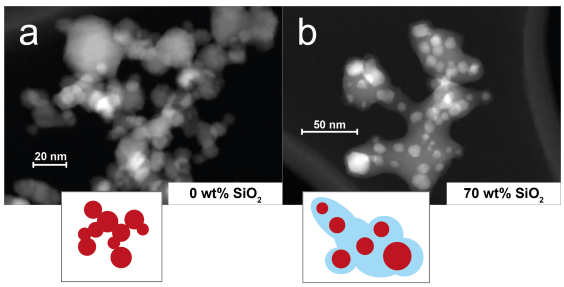

Figure 1: STEM images of (a) bare and (b) SiO_2 $Zn_{0.4}Fe_{2.6}O_4$ nanoparticles.

II. Methods and materials

Highly magnetic $Zn_{0.4}Fe_{2.6}O_4$ nanoparticles with a core diameter of approximately 14 nm were produced by flame spray pyrolysis, as previously described.[8] Different thicknesses of SiO_2 coating (0, 70 wt%) were applied in situ. PVP-coated Fe_3O_4 nanoparticles were obtained from Nanocomposix. Scanning transmission electron microscopy (STEM) were obtained on a Talos F200x microscope. Magnetic particle spectrometry was performed on a custom-made calibrated device at 20 mT and 26.042 kHz. MPI experiments were conducted on a preclinical scanner (Bruker). 8 µL cubic particle samples (17 g/L in water) were measured (gradient = 2 T/m, drive field strength = 12 mT, field of view = 24 x 24 mm, 13 x 13 voxels of size 1.85 x 1.85 mm, signal-to-noise threshold = 5, minimum frequency = 80 kHz, Image reconstruction via iterative regularized Kaczmarz algorithm: relaxation parameter = 0.001, iterations = 100).

III. Results and discussion

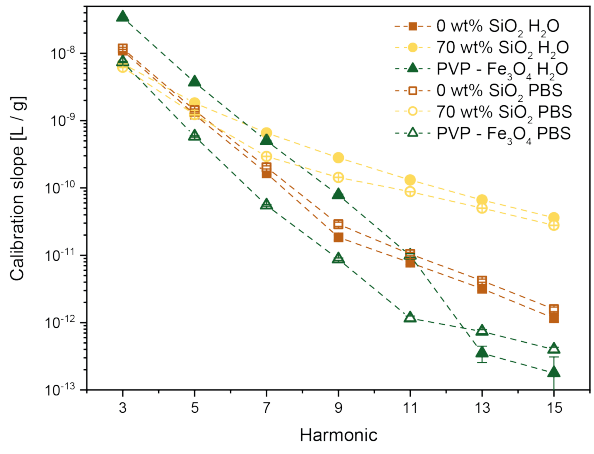

Figure 2: Slopes of MPS calibration lines as a function of harmonic frequencies for all systems.

STEM images of the prepared bare and SiO_2 coated $Zn_{0.4}Fe_{2.6}O_4$ nanoparticles (Figure 1) show the aggregate morphology characteristic for flame-made nanomaterials. While the bare particles (a) are in close contact, the homogeneous SiO_2 coating leads to a clear separation of the magnetic cores. The latter is of the intended non-stochiometric ferrite crystal structure, as confirmed by x-ray diffraction (data not shown). The magnetic measurements (hysteresis and field-cooling curves, not shown) indicate a stronger magnetic interaction between the bare particles, as expected.

This was further analyzed via MPS measurements (Figure 2). Spectra were obtained for the different tracers dispersed in water and phosphate-buffered saline (PBS) at 11 different particle concentrations from 17 to 0.0166 mg/mL. Calibrations were conducted by linearly fitting the spectrum amplitudes for each harmonic frequency to the particle concentration. The corresponding slopes are shown in Figure 2 as a function of the used harmonic. SiO_2-coated Zn-ferrites show an excellent signal strength (high slope values) up to the 15th harmonic. Bare $Zn_{0.4}Fe_{2.6}O_4$ and the commercial PVP-coated Fe_3O_4 nanoparticles perform worse at higher harmonics. Most importantly, both flame-made Zn-ferrites have similar calibration slopes in water compared to PBS. Minor differences can be explained by measurement inaccuracies or particle instabilities. The commercial PVP-coated tracers, on the other hand, attain differences of up to one order of magnitude. This can be explained by their strong agglomeration in PBS, while being in a monodisperse state in water. Additional coagulation of the already aggregated flame-made particles, however, does not substantially influence their MPS signal. This is confirmed by dynamic light scattering and the corresponding hydrodynamic diameters of the samples measured in water and PBS (data not shown). While the flame-made particles attain a size of approximately 100 nm in H_2O, the commercial PVP-coated Fe_3O_4 has a size of approximately 30 nm. Interestingly, upon exposure to PBS bare Zn-ferrite and the commercial PVP-coated Fe_3O_4 show a strong size increase to about 1000 nm. This increase can be explained by the high ionic strength of PBS and the thus weakened repulsive forces leading to stronger agglomeration. The hydrodynamic diameter of SiO_2-coated $Zn_{0.4}Fe_{2.6}O_4$ nanoparticles, on the other hand, decreases.

This is also reflected in the MPIs shown in Figure 3. SiO_2-coated $Zn_{0.4}Fe_{2.6}O_4$ can be perfectly located in both water and PBS. The commercial PVP-coated Fe_3O_4 nanoparticles, on the other hand, cannot be imaged in PBS at all and only in H_2O. This renders these particles inapplicable to realistic MPI applications. Flame-made Zn-ferrite tracers could be utilized and quantified in both dispersion media.

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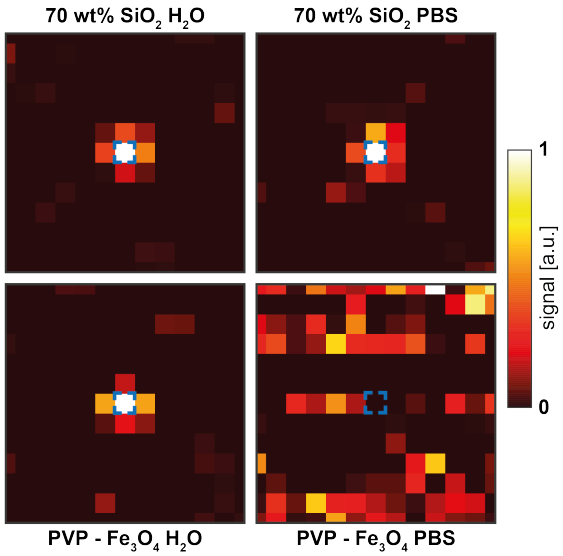

Figure 3: MPIs of samples dispersed in water and PBS. Blue square indicates actual sample location. Intensities are normalized to respective maxima.

IV. Conclusions

MPI signal stability over different dispersion states is a crucial requirement for an accurate diagnosis. We have shown that commercial PVP-coated Fe_3O_4 nanoparticles lose the majority of their MPS and MPI signal, if dispersed in PBS compared to water, due to strong agglomeration and magnetic interactions. Our flame-made Zn-ferrites, on the other hand, do not suffer from this issue. We explain this by their aggregated state attained already during their synthesis. This allows their precise quantification and localization via MPI irrespectively of the dispersion medium and renders them highly promising for further applied investigations.

Author's statement

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