Low threshold detection of USPIO concentrations in different environments simulating tissue diversity

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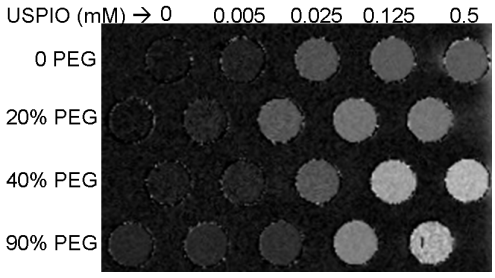
Introduction: Ultra-small Super-Paramagnetic Iron Oxide (USPIO) is commonly used as an MRI labeling agent to track cell migration. Different methods exist for USPIO detection, including gradient-based methods (1), and RF-based methods (2,3). Among the latter, IRON relies on suppression of on-resonant spins using a conventional water saturation pre-pulse, and results in positive contrast in a bloom pattern surrounding dense USPIO clusters (2). On the other hand, Off-Resonance Saturation (ORS) uses a pre-pulse to saturate off-resonant spins, resulting in negative contrast within the locus of the particles, and was found to be sensitive to low concentrations of USPIO in water solution (3). Zurkiya et al. examined USPIO detection with varying diffusion properties to simulate the diverse environments in living organisms, but only at higher USPIO concentrations (3), while in physiological applications, much lower detection levels may be necessary. The aim of the present study was to examine the detection threshold of USPIO concentrations in different environments simulating tissue diversity. Therefore, we extended the investigation of Zurkiya et al. to a range of low USPIO concentrations in solutions with varying polyethylene glycol 400 (PEG 400) fractions, which modulates the diffusion coefficient of the solution. Firstly, we examined the detection effectiveness of a variety of ORS pre-pulses. Secondly, having chosen an appropriate pre-pulse, we noted the USPIO detection threshold of the ORS method.

Methods: *System:* Imaging was performed on a Siemens Espree 1.5 T clinical scanner with TIM coil system (Siemens Medical Solutions, Erlangen, Germany). *USPIO-PEG Phantom:* Different volume fractions of PEG 400 (Sigma-Aldrich, St. Louis, MO, USA) were dissolved in water - 0%, 20%, 40%, and 90% PEG respectively - doped with USPIO concentrations of 0, 0.005, 0.025, 0.125, and 0.5 mM, respectively. *Pulse Sequences:* We used 2D FLASH with TR = 27 ms, TE = 4.59 ms, FA = 10°, 32 averages, $(0.6\ mm)^2$ in-plane resolution and slice thickness of 5 mm, repeated with different ORS pre-pulses, each pulse having two bands - 250 Hz wide - centered at $f_0 \pm f_{offset}$, with f_{offset} = 375, 675 and 975 Hz respectively. Pulse duration was 16 ms. RF power was below clinical SAR. The same sequence was used with pre-pulses having 1000Hz bands, centered at $f_0 \pm f_{offset}$, with f_{offset} = 750, 1000, 1250, and 1500 Hz respectively. In the latter cases, pulse duration was 4 ms, allowing a TR of 17 ms. Corresponding images were obtained without a pre-pulse to calculate the ORS Ratio (OSR). For comparison, an IRON acquisition was obtained with a FSE sequence having parameters as described in (2), with the water saturation pulse set internally by our system. *OSR:* A pixel-by-pixel OSR was taken as $1\text{-}S_{pre\text{-}pulse}/S_{no\text{-}pulse}$, where S represents the MR signal from the FLASH acquisitions.

Results and Conclusion: The pulse having two 250 Hz bands, centered at $f_0 \pm 375$ Hz respectively, provided the greatest detection (highest OSR) at all USPIO concentrations and all PEG fractions. Figure 1 and table 1 depict the OSR calculated using this pulse.



Offset = ±375 Hz; BW = 250 Hz					
USPIO -->	0 mM	0.005 mM	0.025 mM	0.125 mM	0.5 mM
PEG0 (0%)	7.3±3.0	11.1	27.4	30.2	30.3
PEG1 (20%)	6.8±4.0	11.8	29.1	38.4	38.9
PEG2 (40%)	9.3±3.9	12	28	53.7	60
PEG3 (90%)	12.7±2.0	13.8	16.1	43.2	56.7

Figure 1 (left): OSR grayscale map. **Table 1 (right):** OSR values (%) at different USPIO concentrations and PEG volume fractions. The first column includes standard deviations representing variability due to noise. The arrangement of the table corresponds to the figure for easy comparison.

We consider the OSR detection threshold in a single voxel to be two standard deviations above the 0 mM OSR, which falls between 0.005 mM and 0.025 mM - closer to 0.005 mM for most PEG levels. The IRON method showed positive contrast blooms only around 0.5 mM USPIO, and therefore, low concentrations were undetectable using IRON. Within the test tubes, the IRON signal was difficult to interpret – signal enhancement occurred in some PEG samples but not others, even with 0 mM USPIO – further analysis would be necessary to determine the effect of PEG on IRON acquisitions. In future work, we will measure the diffusion levels in USPIO-labeled cells and will compare the computed OSR with that from PEG solutions having similar diffusion properties. The goal is to determine whether, at low USPIO concentrations, knowledge of the diffusion environment and OSR is sufficient to quantify USPIO concentration accurately, as would be desirable in biological labeling applications.

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