Sensitivity of Off-Resonance Susceptibility Separation with Superparamagnetic Iron Oxide

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Introduction: Superparamagnetic iron oxide (SPIO) particles are commonly used as contrast agents for MRI, particularly for liver and lymph node imaging. SPIO particles are also attractive contrast agents for cell tracking, due their ease of incorporation into cells, and they have been used successfully for MRI labeling and targeting of cells *in vivo* and *in vitro*. Recently, Cunningham et al. described a positive contrast method for imaging SPIO-labeled cells with spectrally selective excitation pulses designed for off-resonance excitation of spins in the vicinity of focal B_o perturbations. In this work, we apply a new method for positive contrast that separates off-resonance from on-resonance spins with varying concentrations of SPIOs to quantify the sensitivity of this method.

Theory: The off-resonance perturbation surrounding a superparamagnetic sphere has two symmetrical polar regions of positive frequency shift, and two symmetrical equatorial regions with negative shifts that are half the magnitude of the polar frequency perturbations. With this off-resonant distribution, and assuming If the density of spins surrounding the sphere is uniform, the signal from the voxel containing the sphere measured at time t_n (n=1,…,N) can be modeled as,

$$s(t_n) = \rho_o + \rho_m \left(e^{i2\pi \Delta f\, t_n} + e^{-i\pi \Delta f\, t_n} \right) \quad (1)$$

where ρ_o is the signal from on-resonance spins, ρ_m is the signal from off-resonance spins located near the SPIO, and Δf is the off-resonance frequency of these spins. Eq. 1 can be written in matrix format,

$\mathbf{S} = \mathbf{A}\boldsymbol{\rho}$ (2) where $\mathbf{S} = [s(t_1) \quad s(t_2) \quad \ldots \quad s(t_N)]^T$, $\boldsymbol{\rho} = [\rho_o \quad \rho_m]$ and $\mathbf{A} = \begin{bmatrix} 1 & c_1 \\ 1 & c_2 \\ \ldots & \ldots \\ 1 & c_N \end{bmatrix}$ with $c_n = \left(e^{i2\pi \Delta f\, t_n} + e^{-i\pi \Delta f\, t_n} \right)$. Estimates of the on- and off-resonant components are obtained from the pseudoinverse of Eq. (2), ie:

$$\hat{\boldsymbol{\rho}} = \left(\mathbf{A}^H \mathbf{A} \right)^{-1} \mathbf{A}^H \mathbf{S} \quad (3)$$

where "H" denotes the Hermitian transpose, thereby separating on- and off-resonant components of the signal within the voxel.

Methods: A phantom containing twelve vials containing 14ml of 3 wt% agar, 43.6 mM $NiCl_2$ and 0.5% NaCl, and increasing concentrations of superparamagnetic ferumoxide (Feridex, Berlex Imaging, Wayne, NJ, USA) ranging from 0 μg/mL, 14 μg/mL, and then from 18 μg/mL to 179 μg/mL in 18 μg/mL intervals. $NiCl_2$ was used to shorten T_1 slightly for improved SNR. Vials were suspended in surrounding media composed of 3 wt% agar, 43.6 mM $NiCl_2$ and 0.5% NaCl.

All imaging was performed on a 1.5T GE Signa Excite HD scanner (TwinSpeed, Waukesha, WI, USA) using a modified spoiled gradient (SPGR) pulse sequence that allows shifts in echo time (TE). Imaging parameters included: 256 x 256 matrix, FOV=28.0 cm, slice=10 mm, flip=15˚, and BW= ± 31 kHz using a single channel product head coil. Repetition time (TR) was fixed at 100 ms and echo times were 1.98, 2.37, 2.75, 3.14ms. Vials were aligned parallel to the B_o field, in order to minimize field perturbations in the surrounding agar bath.

Separation of on- and off-resonance signal was performed using Matlab (Mathworks, Natick, MA). Because the SPIOs affect both T_1 and T_2^*, a proportion image of signal intensities was calculated [off/(off+on)] to obtain the proportion of separated on- and off resonance signals. An off-resonance frequency of 1100Hz was used in Eq. 1, empirically providing the best off-resonance separation, as well as suppression of background signal in the on-resonance image.

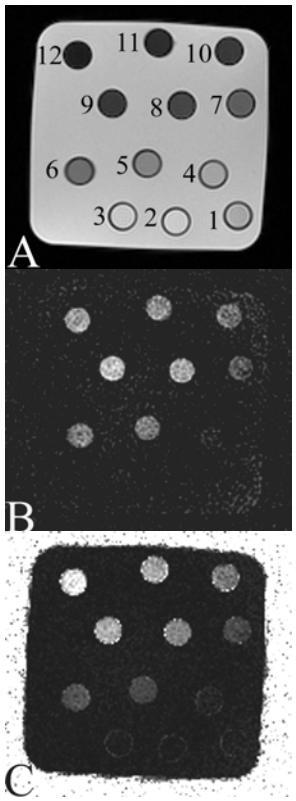

Figure 1: Feridex-labeled Phantom A) On-resonance image, B) Off-resonance image, C) Off-resonance proportion image. Concentrations (μg/mL) for vials 1-12 are 0, 14, 18, 36, 54, 71, 8 9, 107, 125, 143, 161, 179, respectively.

Results: Fig. 1 A and B show the on- and off- resonance images, respectively, and the off-resonance proportion image is shown in Fig. 1 C. Measurements of the signal response were made from ROIs containing 55 pixels, from the 12 tubes in the off-resonance proportion image. These measurements (±error) are plotted in Fig. 2. The data were linearly regressed and found to have a slope and intercept of 0.815 (units = (% separated signal/SPIO concentration (μg/mL)), intercept of –1.018%, and an R-value of 0.95.

Discussion: Based on these results, the off-resonance separation method shows a linear increase in separation of signal with increasing SPIO concentration. In addition, separation was detectable for SPIO concentrations of 54μg/mL and above.

In this study, the SPIO particles were not compartmentalized, which may influence the sensitivity of this approach. For example, Bowen et al. describes an increase in sensitivity of R_2^* with SPIO concentration when SPIO particles are compartmentalized within cells. The results from Bowen's work are consistent with the "static dephasing regime" (SD) [5], which appears to hold for compartmentalized SPIOs but not necessarily for non-compartmentalized SPIOs as in our study. The SD regime appears to increase the sensitivity of iron load on R_2^*. This suggests that the off-resonance separation method presented in this work may be more sensitive to cells labeled with SPIOs rather than free SPIOs. Further work with SPIO labeled cells will be necessary to understand the effect of compartmentalization within cells on the sensitivity of our method.

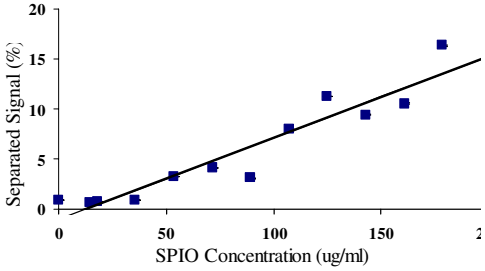

Figure 2: Separated Signal (%) plotted against SPIO concentration, demonstrates a linear relationship (R^2=0.95). Slope and intercept were 0.815 and -1.018.

Conclusion: Positive contrast susceptibility separation methods demonstrate a linear increase of in off-resonance signal separation with increasing concentrations of SPIOs.

References:

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