Novel detection of super-paramagnetic tracers using an off-resonance preparation pulse with short-echo-time gradient echo imaging

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Introduction:
Contrast agents incorporating superparamagnetic iron oxide nano-particles have become increasingly popular in MR imaging for labeling cells, such as macrophages, in order to track their migration in biological systems. These nano-particles create strong field inhomogeneities around the labeled cells, resulting in strong off-resonance effects and T2* effects. T2*-weighted imaging allows easy identification of the labeled cells due to the strong signal loss caused by dephasing [1]. The conspicuity of the region of labeled cells can be improved by increasing the echo time (TE); however longer TE's are also associated with greater 'blooming' artifacts due to differences in magnetic susceptibility. Longer TE's also increase the potential for artifacts caused by the MRI system, such as B_0 inhomogeneities, or others caused by differences in tissue susceptibility, for example and especially, at bone or air interfaces. We propose an alternate technique that utilizes an off-resonance preparation pulse (centered at 1.2 kHz) to dephase the spins subject to the inhomogeneity caused by the nano-particles. The potential advantage of this technique is that we aim to selectively saturate spins in the vicinity of the nano-particles exclusively, while still maintaining very short echo times. This is done by playing the preparation pulse far enough off-resonance so as to saturate only spins with strong shifts in their Larmor frequencies, namely those in the near vicinity of the nano-particles. Additionally, because of the short echo times, T2*-related artifacts, such as blooming, are reduced. Thus the signal loss would be more specific to the labeled cells, because the technique aims to circumvent T2*-related artifacts that may result from field inhomogeneities (besides those due to labeling) that are not strong enough to cause a frequency shift as high as 1.2 kHz. Alternatively, a frequency-selective positive contrast technique could be used to selectively excite the same high-frequency band that we are targeting [1]. However, the disadvantage of such approaches is that all background signal is suppressed, thus eliminating anatomical information. For this reason, we propose spectrally-selective saturation rather than excitation.

Methods:
Human monocyte-derived macrophages (THP-1, ATCC) were labeled by incubation with 50µg Fe/mL USPIO (SH U 555C, Bayer Schering Pharma, AG) for 24hrs. USPIO internalization was verified by Prussian Blue staining, and intracellular iron content was evaluated by ICP-AES. Cells were washed, fixed and pelleted in 750µL test tubes (radius of cell pellet ~3mm). Labeled macrophages were imaged using the technique proposed. The setup included a control sample containing unlabeled macrophages, a second sample containing a mix of labeled and unlabeled macrophages (with one third of the cells labeled), and a third sample containing a mix with one twelfth of the macrophages labeled. The pulse sequence used in all acquisitions was a proton density-weighted 3D Gradient Echo with TR = 24 ms, TE = 3.57 ms and flip angle of 25°. Twenty averages were obtained to boost the signal-to-noise ratio. The preparation pulse was played at the beginning of every TR. The pulse used was a high-power, narrow-band, Gaussian pulse that is typically used to generate magnetization transfer contrast. Here, it is used to dephase off-resonance components in the vicinity of the nano-particles, prior to spatially-selective excitation. The resolution was set to 0.5 mm x 0.5 mm x 1 mm. A corresponding volume was obtained with identical sequence parameters less the preparation pulse, in order to calculate the percentage of signal loss due to the preparation pulse. The two volumes were co-registered, and identical ROI's in the two volumes were selected, one in each test tube. The percentage signal loss was calculated as $100\% \cdot (1 - \frac{S_1}{S_0})$, where S_1 is the signal with the dephasing preparation pulse, and S_0 is the signal without the pulse.

Results:
The percentage signal loss in each test tube is summarized in figure 1. Perliminarily, with a few data points, a trend seems to emerge. It is important to note that the intercept is not at zero signal loss, because of the magnetization transfer effect that occurs due to the interaction between bound protons in cell macromolecules with free water protons.

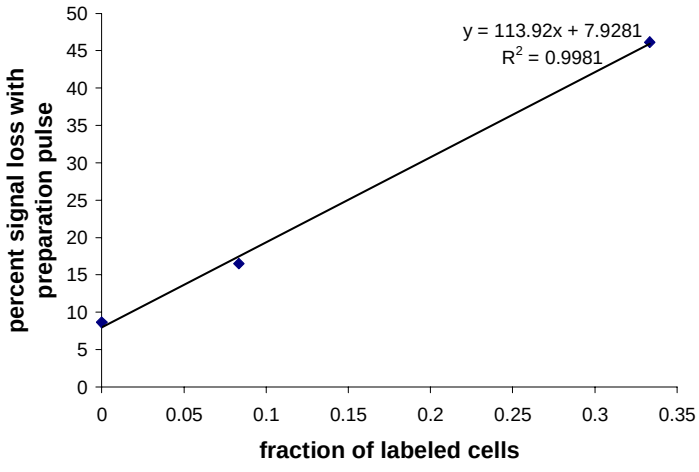

Figure 1 – percentage signal loss plotted against the fraction of labeled cells.

Conclusion:
The present technique is likely a feasible way to detect iron-oxide labeled cells, as contrast seems to increase in some predictable fashion with increasing concentrations of labeled cells. The technique avoids the artifacts of T2*-weighted methods, while maintaining background information that is lost with frequency-selective positive contrast methods. We expect that the effect due to the preparation pulse would be more prominent with a preparation pulse having broader bandwidth, as it would more effectively saturate a wider range of frequencies within the gradients in the vicinity of the superparamagnetic nano-particles. This improvement in pulse design may be especially useful in the case of diffuse labeling.

References:
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