Positive Contrast MRI of Cells Labeled with Magnetic Nanoparticles

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INTRODUCTION Contrast agents incorporating super-paramagnetic iron-oxide (SPIO) nanoparticles [1] have shown promise as a means to visualize labeled cells using MRI. With conventional methods, labeled cells appear as a void in the image. This negative contrast depends critically on image resolution, as partial volume effects will obscure the signal void in larger voxels. Also, differentiating the negative contrast from other voids in the image is challenging, as is quantification of the void volume. In this abstract, a new method is demonstrated for imaging labeled cells with positive contrast. The source of signal is similar to that imaged with an alternative positive contrast method [2], but the mechanism is different.

THEORY A collection of labeled cells will cast a field pattern in the water molecules immediately surrounding the cells. The field pattern can be approximated by a dipole field from a magnetized sphere [3]. Instead of using the field surrounding the labeled cells to de-phase the NMR signal from nearby water molecules, here this gradient is used to selectively excite and refocus a spin echo from a narrow band of water molecules. Fig. 1 illustrates the concept.

METHODS Spectrally-selective RF pulses were designed using the Shinnar-Le Roux (SLR) algorithm [4] implemented in MATLAB (The Mathworks Inc., Natick, MA). By matching the profiles of a 90-degree excitation and a 180-degree refocusing pulse, a spin-echo sequence with million-fold (120 dB) suppression of on-resonance water was designed (see Fig. 2). The properties of the sequence were explored using a 3-dimensional Bloch equation simulation in MATLAB.

The off-resonance (OR) pulse sequence was implemented on GE Signa 1.5T and 3T whole-body MRI systems (GE Healthcare Technologies, Waukesha, WI). Mouse embryonic stem cells (MESCs) labeled with ferumoxides (Feridex I.V(r), Advanced Magnetics, Cambridge, MA) were injected into a section of excised porcine myocardium as well as the hind limb of a live mouse. Scans were performed with conventional gradient-echo (GRE) imaging and the OR method (offset of -800Hz).

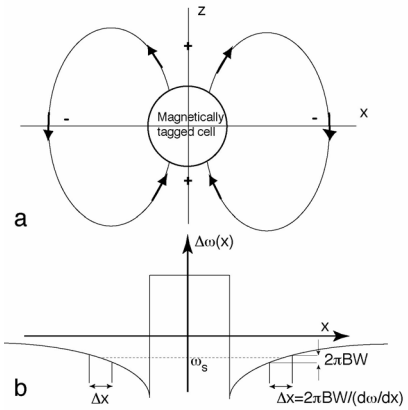

Figure 1: Schematic representation of the new method. (a) The magnetic-field lines induced outside a magnetized sphere. (b) By applying an RF pulse with carrier frequency ω_s and bandwidth BW, the regions with thickness Δx are excited. Similar to conventional slice selection, a spatial shell of water is excited using the intense microgradient. Since only this shell is excited, the image demonstrates positive contrast.

RESULTS and DISCUSSION The simulation results in Fig. 2 show the regions that give signal with the OR method. With a negative shift, the region is narrower because the the field shift drops off more quickly in this direction. Interestingly, the simulations showed that despite the differently shaped regions giving signal with positive and negative shifts (Fig. 2 (c) and (d)), the integrated signal is identical. The results shown in Fig. 3 demonstrate the feasibility of the new method. In all cases, the new method gave positive contrast at the sites where the labeled cells were injected.

The spins that give signal with the OR method are a subset of the those that are dephased with conventional gradient-echo methods, so the net signal should be similar in both cases. However, the advantage of positive contrast is that partial volume effects are much less problematic. With signal only from the labeled cells, fast projections such as those in Fig. (d) are feasible, and could be useful for rapidly locating injected cells. With positive contrast and a suppressed background, physiologic motion will cause only a blurring, whereas negative-contrast signal can be completely lost in the background. Lastly, the signal from the OR method is linearly proportional to the volume of labeled cells, and thus quantitative study of cellular proliferation is a promising application [5].

CONCLUSIONS Imaging of SPIO contrast agents with positive contrast is feasible using the off-resonance method. This could enable faster scans without partial voluming artifacts, allow detection of labeled cells in regions obscured by physiologic motion, and simplify cell quantification in vivo.

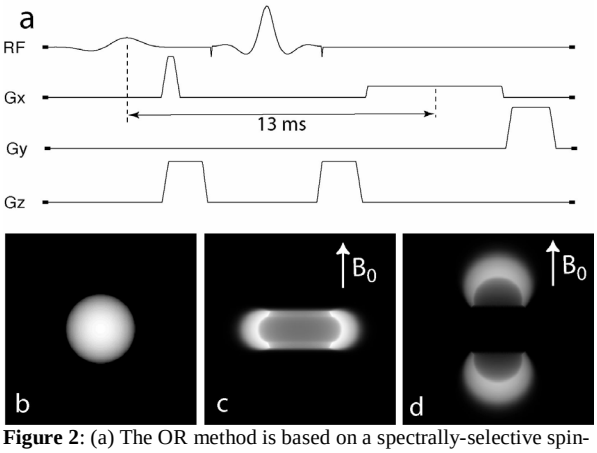

Figure 2: (a) The OR method is based on a spectrally-selective spin-echo pulse sequence. The result of the Bloch simulations using the RF pulses in (a) demonstrates the spatial distribution of the excited/refocused spins, as seen in a projection through a uniform volume. (b) For the simulation, the dipole field was induced by a 5 mm magnetized sphere with 100 ppm susceptibility shift. (c) With a -800 Hz center-frequency shift, the spins in a shell around the equator of the magnetized sphere contribute signal. (d) With a +800 Hz shift, spins at the poles of the sphere are excited/refocused.

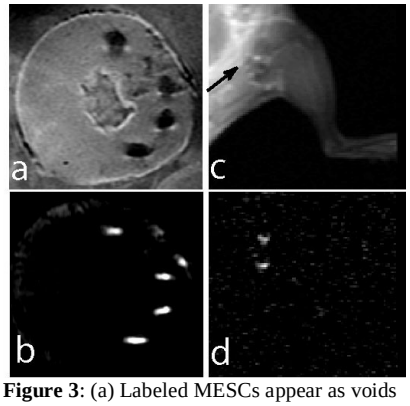

Figure 3: (a) Labeled MESCs appear as voids in the GRE scan of the myocardium, but appear as bright signal with the new method (b). (c) A slight artifact is seen in a projection image at the site where MESCs were injected into the mouse limb. (d) Bright signal at the corresponding site with the OR sequence.

REFERENCES

[1] Dias and Lauterbur. MRM 3:328-330 (1986)
[2] Coristine et al. Proceedings of the ISMRM, 163 (2004)
[3] Hardy and Henkelman. MRI 7:265-275 (1989)
[4] Pauly et al. IEEE TMI 10:53-65 (1991)
[5] Arai et al. Proceedings of the Society for Molecular Imaging, 350, (2004)