Active Contrast Modulation of Iron Oxide Nanoparticles using Rotary Saturation

B. Zhu[1,2], T. Witzel[1,2], S. Jiang[3], D. G. Anderson[3], R. S. Langer[3], B. R. Rosen[1,2], and L. L. Wald[1,2]

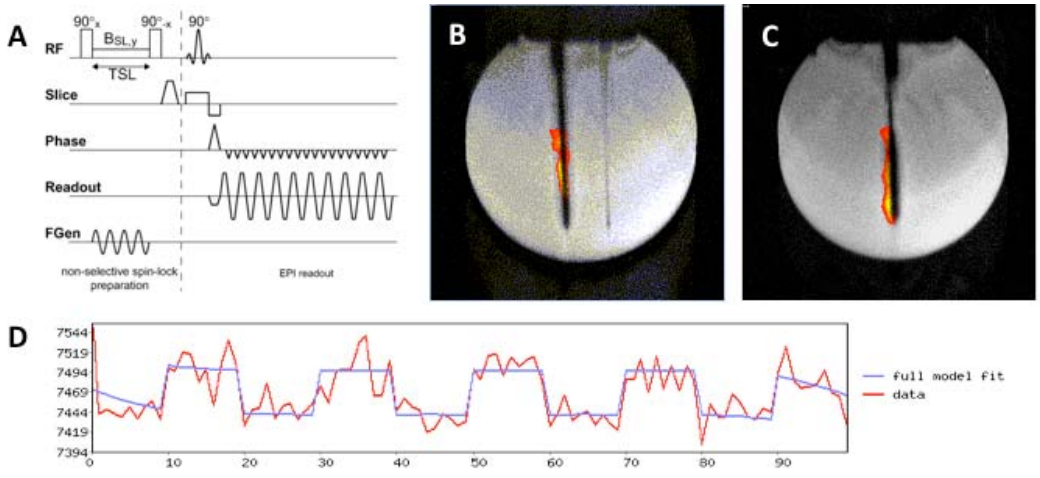
[1]Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA, United States, [2]Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, United States, [3]Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA, United States

Introduction: Resonant rotations of magnetization in the rotating frame around audio frequency oscillating magnetic fields during Spin-Lock (the Rotary Saturation effect) [3] has been under investigation as the basis for a novel contrast mechanism [1,2]. The resonance frequency of the effect (γB_{1spin_lock}) enables the signal changes to be tuned by controlling the spin-lock field and/or the frequency of oscillating magnetic fields (in the 10Hz – 10kHz range). Previous work demonstrated this method with wire current dipoles as the source of the oscillating magnetic field and assessed the method for detecting oscillatory neuronal currents in the brain [1]. In this Abstract, we assess the spin-locked Rotary Saturation technique for actively modulating the image contrast from iron-oxide contrast agents vibrated by an external audio-frequency source such as sound waves applied to the body. In this scheme, the nanoparticle's contrast is activated only when the externally applied vibration frequency is resonant with the spin-lock condition and is therefore "switchable" via choice of the externally applied vibration frequency. We demonstrate the principle of the method in phantom studies.

Methods: A glass capillary tube filled with 1 mg/ml aqueous suspension of 25 nm Fe_3O_4 nanoparticles and a control tube filled with distilled water are lowered vertically into a liquid water phantom (4 in. dia. cylinder) through an opening near the top. The tops of the glass tubes (extending out from the phantom opening) were glued to a piezoelectric bender actuator driven by a piezoelectric amplifier (T220-A4-203X model actuator and EPA-104-115 amplifier, Piezo Systems Inc, Woburn MA). Driven with an audio frequency function generator, the piezo induces vertical displacements of the nanoparticle-filled and control tubes. For the 80V waveforms applied, we estimate the tube displacements are 10μm based on optical measurements. A spin-lock prepared EPI pulse sequence (Figure 1A, described in [1]) is used with γB_{1spin_lock} = 40Hz to capture $T_{1\rho}$ –weighted images with 256x256 matrix, 12-cm FOV, 5mm slice thickness, TE of 67 ms, and TR of 2.7 s. A block design experiment was carried out by switching the vibration frequency on and off resonance (40Hz and 60Hz respectively) with 10 time-points per condition, 100 time-points total. Analysis of the signal changes between on and off resonance vibration was carried out using standard fMRI methods; FEAT (FMRI Expert Analysis Tool) Ver. 5.98, in FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Time-series statistical analysis was performed using FILM (FMRIB's Improved Linear Model) and contrasts were cluster corrected at threshold of $Z > 2.3$ ($p < 0.05$).

Results: The signal difference between vibrations on-resonance vs. 20Hz off-resonance can be observed in the activation analysis (Fig. 1B). Statistically significant signal appears only surrounding the tube of iron oxide nanoparticles but not near the control (water) tube. Figure 1C shows the results of the same experiment done without the control tube. Removing the control tube decreased the mechanical load on the piezoelectric actuator and allowed for larger vibration amplitudes > 10μm. Figure 1D shows the time-series of the voxels with significant activation (red plot) and the GLM model fit (blue plot).

Discussion: These preliminary results demonstrate the ability to perform frequency-selective, tunable imaging of vibrating iron oxide nanoparticles, showing the potential for generating this modulation of the contrast through acoustic vibration. Our results encourage us to perform experiments directed towards ultimately *in-vivo* applications; thus we are currently evaluating this technique in agarose gel phantoms with nanoparticle inclusions (representing tumors after iron oxide uptake) being vibrated acoustically. The ability to actively modulate the agent's contrast *in-vivo* would enable more accurate localization and quantification of the contrast agent by allowing rapidly interleaved comparisons between the activated and non-activated states (vibrations on and off resonance) as well as probing the mechanical environment of bound contrast.



References: 1. Witzel T et al. (2008) *Stimulus-induced Rotary Saturation (SIRS): A potential method for the detection of neuronal currents with MRI.* Neuroimage, 42:1357–1365. **2.** Halpern-Manners NW, et al. (2010) *Magnetic resonance imaging of oscillating electrical currents.* Proc Natl Acad Sci 107:8519-8524. **3.** Redfield, A.G., 1955. *Nuclear magnetic resonance saturation and rotary saturation in solids*. Phys. Rev. 98, 1787.

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Figure 1: (A) Pulse sequence diagram for spin-lock prepped EPI (from [1]). FGen signal indicates function generator oscillation signal delivered to the piezoelectric actuator to vibrate the iron oxide nanoparticle tube. (B) Image intensity changes of the on-resonance vs. off-resonance $T_{1\rho}$ imaging of nanoparticle tube (left) and control water tube (right, faintly visible) displayed with an fMRI-like analysis of the block-design experiment. (C) Activation analysis with larger amplitude nanoparticle vibrations, with no control tube in phantom. (D) Time course analysis demonstrating signal changes of nanoparticle ROI (red) matches with GLM model fit (blue).