Self-refocused spatial-spectral pulse pair for positive contrast imaging of cells labeled with superparamagnetic iron-oxide (SPIO) nanoparticles

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Introduction: We have developed a self-refocused spatial-spectral (SPSP) pulse pair to achieve slice-selective, short-echo-time, spin-echo imaging of off-resonant spins. Using separate, phase-matched, SPSP 90° and 180° pulses to create a spin echo would lengthen the minimum echo time considerably and result in increased signal dephasing. A self-refocused SPSP pulse pair is essentially a phase-matched 90° SPSP pulse and 180° SPSP pulse combined into one pulse through a series of approximations, resulting in a considerably shorter echo time than possible with two separate pulses [1]. Thus, the self-refocused SPSP pulse pair is suitable for any application requiring spatial and spectral selectivity at short echo times. Slice-selective positive-contrast imaging of superparamagnetic iron-oxide (SPIO) nanoparticle-labeled cells is one such application. When used with standard imaging sequences, the SPIO nanoparticles lead to signal dephasing and act as a negative contrast agent. However, negative contrast agents cannot be distinguished from voids in the image and can suffer from partial volume effects. To avoid these errors, several techniques have been proposed for positive contrast imaging of SPIO-labeled cells [2-5]. One of these techniques uses spectrally selective pulses to image off-resonant water near the labeled cells [5]. Although these spectrally selective pulses enable flexible selection of the excited frequency range, they are not slice-selective, resulting in interfering background signal. The SPSP self-refocused pulse pair we have developed enables slice-selective imaging of off-resonant frequencies, hence eliminating background signal from sources of off-resonance outside the slice of interest.

Method: A minimum-phase 180° pulse with a bandwidth (BW) of 164 Hz was designed using the Shinnar Le-Roux (SLR) algorithm [6]. Using this algorithm, each RF pulse can be described by a pair of complex polynomials ($\beta(k_z,k_\omega)$, $\alpha(k_z,k_\omega)$). If $\beta_{180}(z,\omega)$ and $\alpha_{180}(z,\omega)$ are the transforms of the polynomials for the minimum phase 180° pulse, then $\beta_{final}(z,\omega)$ and $\alpha_{final}(z,\omega)$ for the self-refocused pulse pair are given by Equations 1 and 2.

$$\beta_{final}(z,\omega) = \frac{1}{\sqrt{2}}\beta_{180}(z,\omega) \quad (1) \qquad \text{and} \qquad \alpha_{final}(z,\omega) = \alpha_{180}(z,\omega)\varepsilon^{-1} - \frac{1}{\sqrt{2}}\beta_{180}(z,\omega)e^{i\phi} \quad (2)$$

where φ is echo phase, $\varepsilon = e^{i\gamma G_x(\Delta T)}$ is the echo delay and ΔT is the time between the end of the pulse and the occurrence of the spin echo. For this design, a ΔT of 5.8 ms was used. The general form of the expression for the final spectral profile of the self-refocused pulse pair is: $S(z,\omega) = 2\alpha_{final}(z,\omega)^* \beta_{final}(z,\omega)$ **(3)**

Because the self-refocused approximation incorporates a pair of phase-matched pulses into a single pulse, there is no room left for crushers. Consequently, acquisitions from two different self-refocused pulse pairs are required: pulse 1, with the echo phase $\varphi = 0°$ and pulse 2 with $\varphi = 180°$. If the profile of pulse 2 is subtracted from the profile of pulse 1, the component that is not refocused is eliminated. The final self-refocused SPSP pulse pairs were comprised of 53 conventional small tip-angle subpulses scaled by the sampled values of the self-refocused pulse pair envelopes. The final pulse duration was 38 ms, and the resultant spatial bandwidth was 4937 Hz. The main passband and sidebands of the spectral profile were separated by 1.39 kHz. Although the pulse duration is long, most of the energy is concentrated towards the end of the pulse, resulting in an echo time of 10 ms. Figure 1 shows (A) the magnitude of each self-refocused SPSP RF pulse pair, (B) the final spectral profile obtained after subtracting the profiles of pulse pairs 1 and 2, (C) the 2D spatial-spectral profile and (D) the RF and gradient waveforms for the sequence utilizing the self-refocused SPSP pulse pair to create a spin echo. The transmit frequency of the pulses is shifted off-center by 450 Hz to image off-resonant spins.

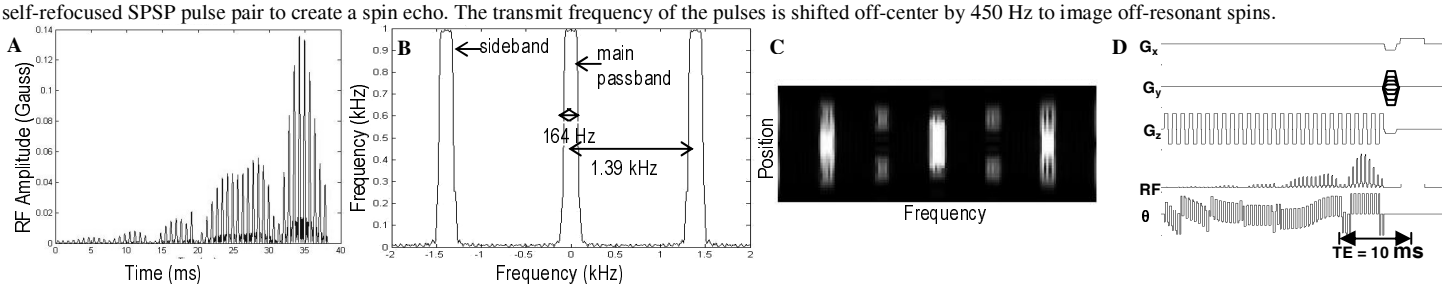

Figure 1: (A) Magnitude, (B) spectral profile, and (C) 2D spatial-spectral profile of self-refocused pulse pair. (D) RF, phase and gradient waveforms for pulse sequence using a self-refocused SPSP pulse-pair.

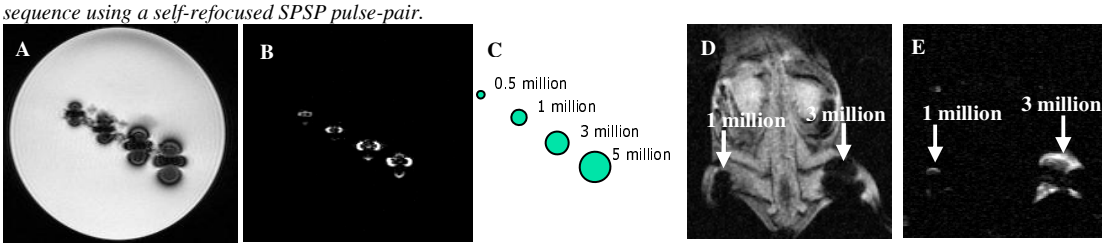

Figure 2: (A) GRE image of phantom with SPIO-labeled cells, (B) Positive contrast image of phantom using self-refocused pulse pair and (C) labeled cell concentrations. (D) GRE image of mouse with SPIO-labeled cells injected into hind legs and (E) Positive contrast image using self-refocused pulse.

Results: Data were obtained from an agar phantom with varying concentrations of SPIO-labeled human stromal cells. Scans were performed with a standard birdcage head coil at 1.5T (Echospeed whole-body magnet; GE Healthcare, Waukesha, WI, USA). Acquisition parameters were: Slice thickness = 6mm, TE/TR = 10/800 ms and matrix size = 256x128, transmit frequency = +450Hz. Figure 2 A shows the image obtained using a standard GRE sequence and Fig. 2 B shows the positive-contrast image of the same slice obtained using the self-refocused SPSP spin-echo sequence. SPIO-labeled cell concentrations are given in Fig. 2 C. In vivo data were obtained from a mouse, with 1 million and 3 million SPIO-labeled cells injected into the hind legs. Scans were performed at 1.5T one day after injection with a standard 3-inch surface coil. Acquisition parameters were: slice thickness = 9.2 mm, TE/TR = 10/800 ms and matrix size = 256x128, transmit frequency= -450Hz. Figure 2 D shows the image obtained using a standard GRE sequence and Fig. 2 E shows the positive-contrast image obtained using the self-refocused SPSP spin-echo sequence. Cell concentrations are labeled on the images.

Discussion: Phantom and in vivo data demonstrate that the self-refocused SPSP pulse is successful in creating positive-contrast images of SPIO-labeled cells for a selected slice. Similar positive-contrast images may be created using a pair of spectrally selective 90° and 180° pulse [5]; however, the lack of spatial selectivity results in background artifacts. Changing the 90° and 180° pulses into spatial-spectral pulses provides slice selectivity but only at the expense of significantly lengthening the minimum TE. The self-refocused spin-echo SPSP pulse pair developed in this work provides slice selectivity with much shorter echo times.

References: [1] Lim KO, et al. *Magn Reson Med* 1994 Jul; 32(1):98-10. [2] Seppenwoolde JH, et al. *Magn Reson Med* 2003; 50(4):784-790. [3] Heyn C, et al. *Magn Reson Med* 2005; 53(2):312-320. [4] Mani V, et al. *Magn Reson Med* 2006;55(1):126-135. [5] Cunningham CH, et al. *Magn Reson Med* 2005; 53(5):999-1005. [6] Pauly J, et al. *IEEE Trans Med Imaging* 1991; 10: 53-65.

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