Sub-Millimolar PARACEST Detection Using EPI-CEST

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Introduction

Chemical exchange saturation transfer (CEST) [1] has been shown to be an effective technique to detect both endogenous (e.g., amide protons) and exogenous (e.g., Europium) exchangeable protons. The CEST technique uses a long RF pulse applied at a frequency $\delta\omega$ from water and the water signal is measured. The standard method of quantifying the change in signal intensity is to compare the signal when a saturation pulse is applied at a frequency $\delta\omega$ from water (where the exchangeable protons resonate) to the signal when a saturation pulse is applied at a frequency $-\delta\omega$ (control case: no exchangeable protons). The change in signal is normalized by the signal intensity when no saturation pulse is applied or normalized by the control signal intensity. Our new method of the detection of exchangeable protons used a train of saturation pulses $[(-\delta\omega)_4\ (\delta\omega)_4]_N$ to create a signal intensity modulation. The signal intensity modulation was detrended, Fourier transformed, band passed filtered, and inverse Fourier transformed to create a detrended, noiseless time-course. This time-course was cross-correlated with the applied saturation pulse modulation.

Methods

Samples of 0.1 mM and 0.6 mM Eu-DOTAM-Gly-Phe were placed in 5 mm NMR tubes and scanned using a 40 mm transmit/receive millipede coil on a 9.4T Varian INOVA. A 40 μT or 60 μT CEST saturation pulse was applied for 3 seconds prior to image acquisition using a 4 shot EPI sequence. Saturation frequency offsets $\delta\omega=(-48)_4$, $[(-48)_4, (48)_4]_{10}$ ppm were applied. Each series took 4.6 minutes. Data points 21 through 84 were linearly detrended (Fig 1), the earlier points were not used as they were not in a steady state. An unpaired student's t-test was used to compare the image signal intensities at 48 ppm and -48 ppm using the detrended data to determine if there is a significant difference. The detrended data was further bandpassed filtered at the frequency of the saturation pulse modulation to remove extraneous signal modulations. The correlation coefficient and p-value were calculated from the filtered time course using the 48 ppm ('on') and -48 ppm ('off') as a regressor. The p-value from the t-test was compared to the p-value from the cross correlation method.

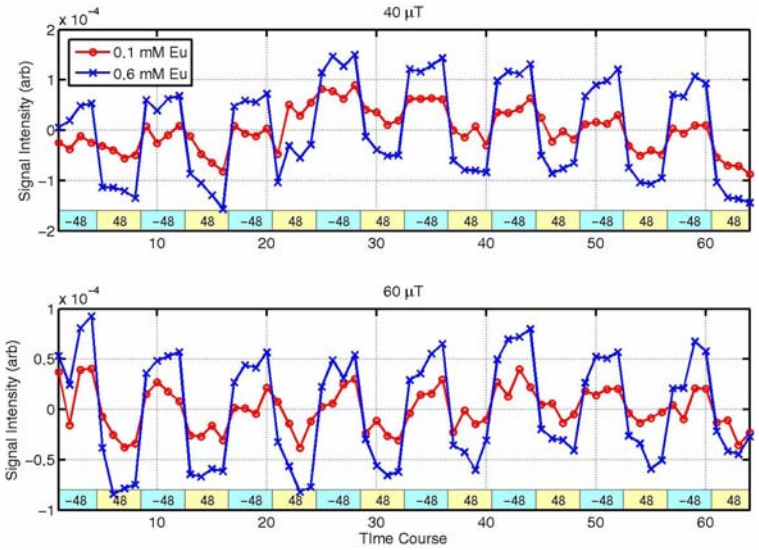

Figure 1: Linearly detrended data of the 0.1 mM (red, circle) and 0.6 mM (blue, 'x') Eu-DOTAM phantoms using 40 μT and 60 μT saturation pulse.

Results and Discussion

Fig 1 shows the detrended -48/48 ppm on/off style signal modulation as a function of concentration and saturation pulse power and is similar to a BOLD time course in fMRI. Fig 2 shows maps of p-values calculated voxel-by-voxel from the correlation method (left) and t-test method (right). For both concentrations and saturation powers the correlation method had lower p-values than the p-values from the t-test. The median correlation coefficient was -0.7534 for the correlation method (negative as the signal intensity decreases in the 'on' state). Even for a low concentration of 0.1 mM and 40 μT saturation pulse, 88% of the voxels in the region had a p-value < 0.01.

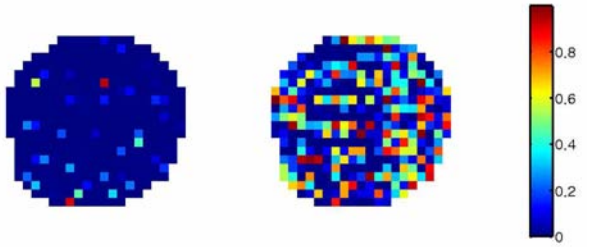

Figure 2: Maps of p-values of the 0.1 mM Eu phantom using a 40 μT saturation pulse. Correlation method (left) and signal difference method (right).

Conclusions

The correlation method of detecting signal differences as a function of offset frequency was shown to be efficient even for sub-millimolar concentrations with reasonable saturation power. This method will enable simple and fast detection of low concentrations of PARACEST agents using low amplitude saturation pulses.

References: 1) Ward KM, et al., JMR 2000;143:79-87.