

## Exchange-Relayed Nuclear Overhauser Effect MRI

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**Introduction:** Recently, chemical exchange saturation transfer (CEST) MRI has been used to detect the signals of mobile proteins and peptides *in vivo* through the exchange between amide protons and water protons (1). This so-called amide proton transfer (APT) effect has subsequently been used to detect changed protein content in brain tumors in animals (2) and humans (3,4). One issue is that the NH-based signal change reflects both pH and protein content, and it would be useful to separate these effects. It is well known that mid to large size mobile macromolecules should experience cross-relaxation effects called Nuclear Overhauser Enhancements (NOEs), the build-up of which should be slower than exchange effects. Actually, Ling et al. (5) when studying glycosamines, reported some signals at lower frequency from water that were attributed to NOEs. We hypothesized that exchange-relayed NOEs of mobile proteins should be visible in CEST images *in vivo*, but at a slower time scale than exchange effects (6,7), and only if the B1 irradiation field is sufficiently small to avoid competing effects from exchange and semi-solid magnetization transfer (MT) effects. In an attempt to detect NOEs, we used a low-power steady-state 3D CEST sequence to this condition.

**Methods:** A pulsedCEST sequence was used to acquire data at 68 frequency offsets between -10 and 10 ppm around the water resonance (shown as small red points in Fig 1 top). Data was acquired on a 7T Philips scanner with a 32 channel SENSE receive coil. Each saturated volume was acquired with a 3D-FFE with EPI-factor of 7, TR=65 ms, TE=6 ms and 2 mm isotropic voxels and an inter-volume delay of 7s. The saturation pulse was a 25 ms, 1  $\mu$ T single lobe sinc-gauss. To remove signal from direct water saturation, the normalized signal intensity (Z-spectrum) was fit using a Lorentzian function based on signal around the water frequency ( $|f| < 0.7$  ppm) and points far downfield ( $f > 8$  ppm) (fit points shown as dark green points and fit shown as green curve in Fig 1 top). The acquired data points and Lorentzians were shifted to correct for B0 inhomogeneity differences between voxels. A difference spectrum was calculated per voxel (e.g., Fig 1, bottom). Maps of the APT signal (mean difference between 3.2 and 3.8 ppm, per voxel) and NOE signal (mean difference between -1 and -5 ppm) were calculated.

**Results and Discussion:** The difference (Fig 1, bottom) between the direct water saturation Lorentzian (Fig 1, top, green curve) fit and the acquired data (Fig 1, top, blue points) shows large signal differences on both sides of the water. There is a peak around 3.5 ppm (annotated as 'APT') along with other peaks between 0 and 3.5 ppm. There is also a large peak at lower frequency from water that we attribute to exchange-relayed nuclear overhauser effects, in line with spectroscopy studies showing such effects *in vivo* in this region (5,6). The NOE map (Fig 2) clearly distinguishes between white matter ( $5.1\% \pm 0.8\%$ ) and gray matter ( $3.4\% \pm 1.6\%$ ). Notice that for the pulse sequence parameters used, one must be careful in doing a traditional asymmetry map, which would give contaminated APT and CEST results.

**Conclusions:** A pulsedCEST technique was used to minimize MT and fast exchange effects and to maximize NOEs, which led to a large signal at low frequency from water, attributed to exchange-relayed NOEs. The NOE signal was found to differentiate white matter and gray matter. Such signal should be useful in the study of protein content of tissue and demonstrates the occurrence of exchange-based signals the APT and NOE effects independent of any assumptions about z-spectrum symmetry. The data also show that care has to be taken when using asymmetry analysis as the results of these may vary with pulse sequence parameters such as B1 level and timing.

**References:** (1) Zhou et al, *Nat Med* v9(8), 2003; (2) Zhou et al, *MRM* v50(6), 2003; (3) Jones et al, *MRM* v56(3), 2006; (4) Zhou et al, *NMR in Biomed* 21(5), 2008; (5) Ling et al. *PNAS* 105, 2008; (6) Mori et al, *MRM* 40(1), 1998; (7) van Zijl et al, *MRM* 49(3), 2003.

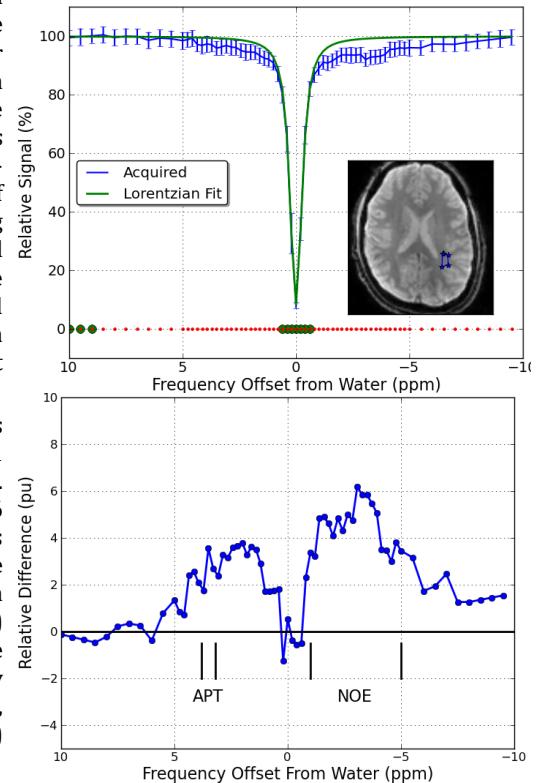


Fig 1: (top) Acquired z-spectrum (blue) and Lorentzian fit (green). The difference spectrum (bottom). The APT and NOE regions are annotated.

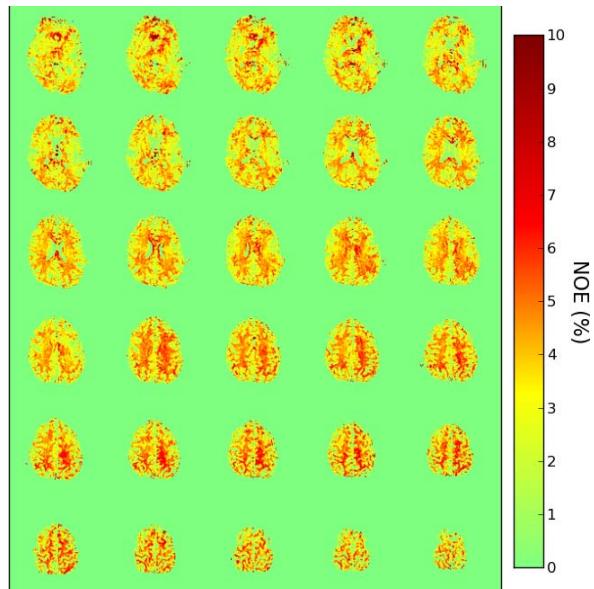


Fig 2: Map of the integrated area under the NOE region from Fig 1, bottom.