Combining CEST with CESL to differentiate slow exchanging pool from fast exchanging pool: mapping the concentration of Glutamate and Amides separately

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Purpose: CEST is widely used to detect diverse exchanging proton pools from endogeneous or exogeneous molecules. However a major problem is that of separating overlapping peaks from species resonating at the same frequencies. For example Glutamate resonates at 3ppm, in between amides resonating at 3.5ppm and other amines resonating closer to the water frequency. The challenge is to disentangle these species based on their intrinsic properties such as their chemical exchanging rate. It has been shown recently that CESL can produce spectra similar to the CEST spectra, with the advantage of being insensitive to near on-resonance saturation for short saturation power[1]. In this work it will be assumed that the two different approaches (CEST and CESL) have different linear sensitivities to the fast and slow exchanging species so that the concentration of the fast and slow exchanging species can be determined from the saturation signals obtained in both sequences. **Aim:** to develop a system of linear equations to use combined signals from CESL and CEST spectra to differentiate slow from fast exchanging species, specifically amides from Glutamate.

Methods: Numerical (Runge-Kutta) simulations were carried out using a Bloch McConnell model with four different pools. CEST and CESL acquisition was performed with pulsed continuous waves[2], either with a 1ms gap between adjacent pulses (CEST) or a hard pulse flipping the magnetization in and out of the effective field of the spin lock (CESL). The saturation was varied both in amplitude (B_1 from 0.5 to 10μT) and in duration (CW between 0 to 1000ms). Pools simulated were defined as follow: free water (T_1=1.2s, T_2=45ms), macromolecular pool with superlorentzian lineshape (T_1=1s, T_2=10us, k_{ex}=50Hz, M_{ob}=8%), amide proton pool (T_1=1s, T_2=20ms, k_{ex}=20Hz, M_{od} from 0 to 2%) and amine proton pool from Glutamate (T_1=1s, T_2=20ms,k_{ex}=1kHz, M_{on} from 0 to 2%).

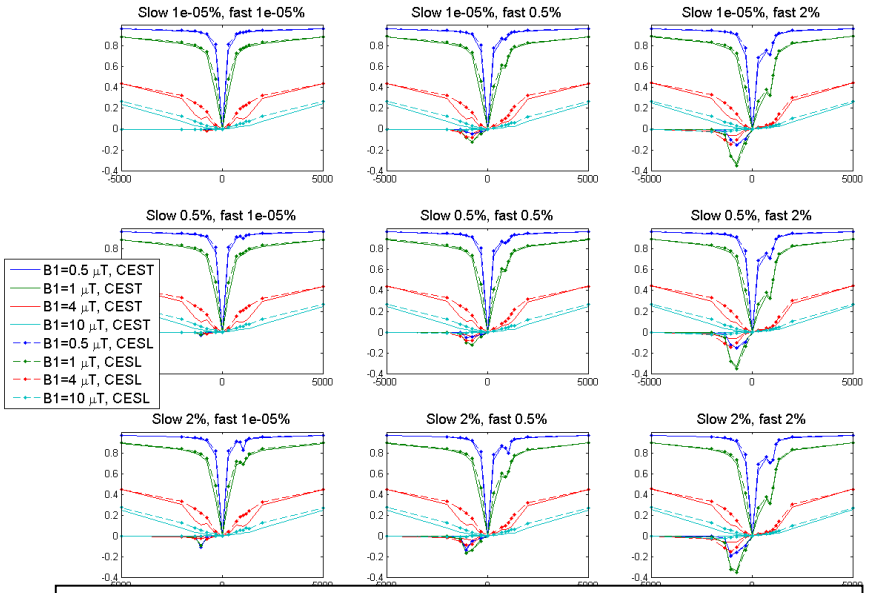

Figure 1: Simulated z-spectra acquired via CEST (plain line) and CESL (dotted line), with varying slow and fast exchanging pool size, and varying $B1_{sat}$ for a saturation duration of 400ms.

Results: Simulated asymmetry (fig 1) was measured for all proton pools for all saturation schemes: 2 different B1 saturation powers and 2 different saturation durations (pulse number) for both the CEST (S_T) and the CESL (S_L) methods. The increase in asymmetry was reasonably linear with concentration over the ranges considered.

A system of linear equations was established describing the relationship between the asymmetry signals for each sequence and the concentration of amides (C_d) and amines (C_n): $\begin{pmatrix} S_T \\ S_L \end{pmatrix} = A.\begin{pmatrix} C_d \\ C_n \end{pmatrix}$. This was inverted $\begin{pmatrix} C_d \\ C_n \end{pmatrix} = A^{-1}.\begin{pmatrix} S_T \\ S_L \end{pmatrix}$. to yield the A^{-1} matrix for each saturation scheme available (total of 6 different saturation amplitudes (B_1) for 7 different saturation durations). The difference between the concentration estimated from the resulting linear system and the initial simulated concentration was minimized over all concentrations to find the best combination of saturation schemes. The resulting sequences used CEST and CESL both with saturation powers were 0.5μT and 1μT, for a duration of 200ms and 400ms, well within SAR limit for in-vivo application.

Discussion: Differentiation between glutamate and amide protons is theoretically possible via a simple linear combination of asymmetry signals obtained from both CEST and CESL sequences at optimum saturation duration and amplitude. Further optimization can be done, for instance taking into account variability in field homogeneities. The sequence described here is directly applicable on clinical scanner, and should prove useful in quantification of fast exchanging proton pools.

References: 1 Jin, Kim, NMR in Biomed 2014. 2 Roeloffs et al, NMR in Biomed 2014. **Acknowledgements:** Medical Research Council.