**High-Sensitivity Glutamate Quantification with CEST, Water-Resonant Spin-Locking, and MR Fingerprinting**

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**INTRODUCTION:** Chemical exchange saturation transfer (**CEST**) is useful for characterizing diseases and monitoring treatment, such as for brain cancers. Currently, most clinical CEST involves amide proton contrast, which is sensitive to changes in protein content and/or pH within cells. There is a great need to expand CEST to detect and quantify fast-exchanging amine protons to monitor changes in small molecules such as glutamate (**Glu**), which enhances glioma cell motility and growth[1]. While CEST magnetic resonance fingerprinting (**CEST-MRF**) can generate quantitative maps of amide proton exchange rate and concentration in animals and humans[2–4], the faster proton exchange of Glu poses challenges for generating sufficient contrast. In theory, water-resonant chemical exchange spin-locking (**CESL**) generates more contrast from intermediate-exchange protons than by direct saturating via CEST[5,6]. Therefore, we hypothesized that introducing CESL elements into an MRF schedule would improve the accuracy of exchange parameter maps.

**METHODS:** Solutions of glutamate were prepared at 10-80 mM concentrations and titrated to pH 6.0 or 7.0 at room temperature. Samples were placed in tubes, arranged within a four-tube imaging phantom, and imaged on a horizontal-bore 4.7 T preclinical scanner at room temperature. Imaging scans included $T_1$ and $T_2$ mapping sequences and the MRF imaging schedules ($n$ = 30 iterations), each using an echo-planar imaging (**EPI**) readout. Water-resonant CESL used a locking field of 2 μT and a locking duration varying randomly from 0-5 s. To determine the proton exchange rate, QUantification of Exchange rate using varying Saturation Power (**QUESP**)[7,8] imaging was performed on the same phantom setup at 9.4 T. MRF dictionary generation and dot-product matching were performed with custom Python scripts, and image ROI data were processed in MATLAB. Error maps were generated between MRF-derived parameter maps and the nominal Glu concentration or the average exchange rate across all four tubes, as determined using QUESP at 9.4 T.

**RESULTS:** The signal ratio between different Glu concentrations was higher using CESL rather than CEST with similar parameters, increasing between 10 and 80 mM by a factor of ~5.5 (**Fig. 1A-B**). $T_{1\rho}$ values ranged from roughly 200 ms (80 mM tube) to 1000 ms (10 mM tube). By substituting half of the MRF schedule iterations with water-resonant CESL, accurate concentrations within ±7 mM were obtained for all tubes except the 80 mM tube, and the exchange rates were within ±200 $s^{-1}$ of the QUESP-measured values (**Fig. 1C**). In contrast, a CEST-only schedule had very large inaccuracies (**Fig. 1D**).

**DISCUSSION:** Glutamate CEST (**GluCEST**) requires a 7 T or higher field strength to keep Glu amine proton exchange in the slow-exchange regime for sufficient contrast. By enhancing the detectability of intermediate-exchange solute protons, CESL may enable GluCEST for widely available MRI scanners at 3 T, since the water-proton chemical shift dispersion nearly matches the reported *in vivo* Glu amine exchange rate at 3 T[9]. Combining CEST and CESL in a single MRF schedule leverages the specificity of CEST to particular proton shifts and the sensitivity of CESL to rapidly exchanging protons. The concentration error we obtain with the combined CEST-CESL schedule will likely improve by sampling shorter spin-lock times to better capture the signal decay during locking.

**CONCLUSION:** MRF imaging schedules incorporating water-resonant CESL substantially improve proton exchange quantification at lower magnetic fields, where the exchange rate approaches the chemical shift dispersion from water. In the near future, we will develop an MRF schedule to resolve amide and amine proton signals and then perform initial *in vivo* imaging experiments.

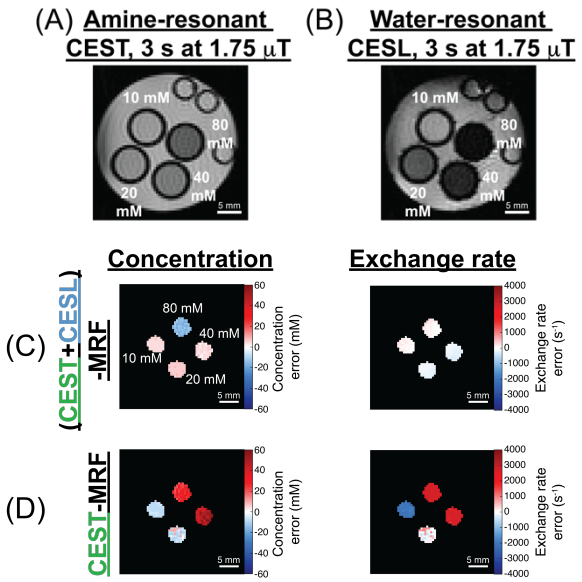


**Figure 1.** CESL on water improves exchange contrast for quantifying rapidly exchanging protons at 4.7 T. (A-B) Comparison of CEST vs. CESL contrast, pH 6. The mean color intensities of the 10 mM tubes are equal. (C-D) Error maps of MRF-quantified Glu concentration and exchange rate, pH 7, showing lower error with CESL elements in the MRF schedule.

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