Isolating chemical exchange contrast from amide and amine protons in the presence of asymmetric macromolecular magnetization transfer with off-resonance spin locking at 3T in the human brain

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Purpose: Chemical exchange saturation transfer (CEST) from endogenous amide and amine protons has shown promise as an indicator of tissue pH[1,2]. Quantifying pH in-vivo, however, remains difficult due to concurrent signal contributions from multiple exchangeable protons and broad macromolecular magnetization transfer (MT) asymmetry. It has been shown at high field that spin-lock methods can generate chemical exchange contrast tuned to protons with specific exchange rates by matching the spin lock amplitude to the exchange rate[3]. In this abstract, we demonstrate how spin-lock amplitude and duration can be optimized for human imaging on clinical scanners at 3T to isolate contrast from either amide or amine protons while minimizing MT asymmetry.

Methods: Spin-lock (SL) signal was simulated for Bloch equation solutions with chemical exchange[4] and super Lorentzian MT[5] with exchange rates k_{amide}=30Hz, k_{amine}=5000Hz, k_{MT}=50Hz, concentrations f_{amide}=1/1000, f_{amine}=1/400, f_{MT}=1/20, resonance frequencies ω_{amide}=3.5ppm, ω_{amine}=2.8ppm, ω_{MT}=-2.3ppm, and water relaxation times T_{1w}=1.5s, T_{2w}=70ms. Spin-lock duration ranged from TSL=0 to 20sec and amplitude from B_1=0 to 10μT. Six healthy volunteers (age, 31-52 years) were scanned on a 3T GE MRI scanner. Single-slice saturation transfer images were acquired using CW RF saturation followed by a single shot EPI readout [TR/TE=2000/16ms, FOV=24cm, matrix=96x96, slice=8mm]. Spin-locking was achieved by adiabatically ramping the RF power to the CW amplitude B_1. Z-spectra were acquired with B_1=0.5, 1.5, 3, and 6μT and TSL=100ms and 200ms at 64 frequency offsets up to ±40ppm (scan time=35min). All images were motion corrected and z-spectra were B_0 corrected using the WASSR[6] method. Amide and aliphatic proton peaks were identified by fitting the 0.5μT z-spectrum[7,8]. Saturation transfer was quantified by asymmetry analysis: $MTR_{asym}=[S_{sat}(-\omega)-S_{sat}(+\omega)]/S_0$.

Results and Discussion: The simulated spin-lock CEST signal from slowly exchanging amide protons (Fig 1a) with no other sources of saturation transfer was maximized with low B_1=0.45μT and long TSL≥9s while fast exchanging amine signal (Fig 1b) was maximized at high B_1=4.75μT and short TSL=490ms. When TSL and B_1 were optimized for amide proton exchange, the amide peak was the dominant signal contribution (3.7%) with little concurrent amine saturation transfer (0.3%) but the MT asymmetry (Fig 1c) was large (-1.6%) adding significant errors to the total MTRasym(3.5ppm) (Fig 1d). When TSL and B_1 were optimized for amine proton exchange, the amine peak was the dominant signal contribution (2.5%) with little contamination from amide protons (0.3%) or MT asymmetry (-0.3%) Therefore, amine CEST images can be obtained with less errors due to MT asymmetry (Fig 1d) compared to amide CEST. We also note that the optimum amine peak was shifted to 4.1ppm due to line broadening at high power. Therefore, significant amine contamination to MTR_{asym}(3.5ppm) is present at high powers.

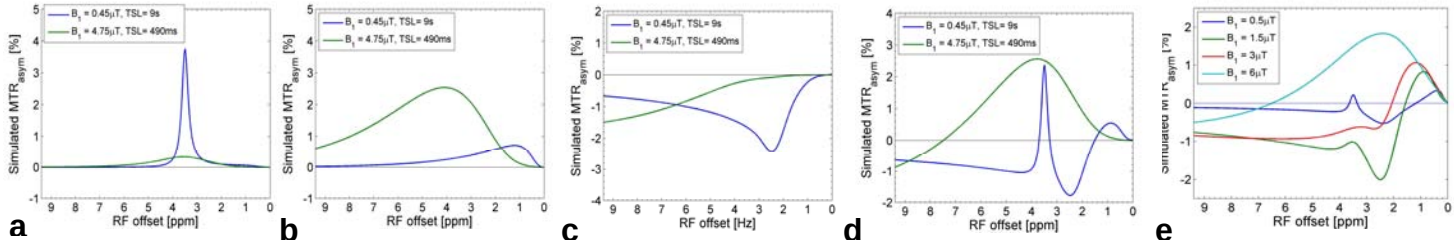

Fig 1: Simulated MTR_{asym} for a) amide protons alone, b) amine protons alone, c) macromolecular protons alone, d) amide, amine and macromolecular protons with optimal B1 and TSL. e) Simulated MTR_{asym} for amide, amine and macromolecular protons with in-vivo acquisition parameters.

The maximum achievable TSL on our clinical scanner was 200ms. Simulations show that the amide peak, in the absence of other saturation transfer effects, was still maximized at B_1=0.45μT but with smaller amplitude than with TSL=9s (Fig 1e) (0.5% vs. 3.7%). For amine protons, however, reducing TSL to 100ms increased the power needed to maximize the peak. As a result, the simulated amine peak at B_1=6μT was only 20% smaller than with optimal B_1 and TSL (Fig 1e) (1.9% vs. 2.5%). In-vivo, MTR_{asym} (3.5ppm, B_1=0.5μT) showed little evidence of the amide peak (Fig 2e). The images were negative (Fig 2a) indicating a primary contribution from MT asymmetry and aliphatic protons at -3.5ppm. The amide peak at 3.5ppm, however, could be isolated by fitting the z-spectrum and its amplitude was in good agreement with simulations (Fig 2c-d). At B_1=1.5μT, the amide peak was no longer identifiable due to increasing MT and direct water saturation. At higher B_1 = 3 and 6μT, the amine peak became significant while the MT asymmetry was strongly reduced (Fig 2e). Therefore, amine MTR_{asym} images could be obtained with decreased errors from MT asymmetry and other sources of saturation transfer than amide MTR_{asym} images (Fig 2b).

Conclusion: Amide proton transfer requires long spin-lock durations at low RF power to achieve maximum signal at 3T. With the limited spin-lock duration achievable on clinical scanners, APT was a weak signal suffering from significant concurrent signal contributions from MT asymmetry and aliphatic protons. With short saturation and high RF power, near optimal amine proton exchange could be achieved on clinical scanners with negligible MT asymmetry . Therefore, amine spin-lock CEST images may be more suitable for exchange rate measurement and pH quantification than amide weighted images at 3T.

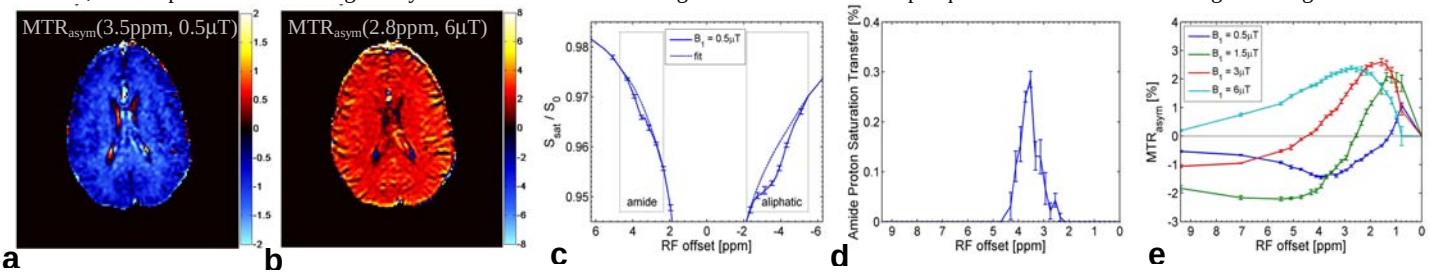

Fig 2: Amide (a) and amine (b) weighted CEST images in the healthy brain. c) Low power z-spectrum can detect the amide and aliphatic peaks. d) Amide peak obtained from fitting the low power z-spectrum. e) MTRasym as a function of spin-locking amplitude and duration.

References: [1]Zhou et al. Nat Med 2003:50. [2]Jin et al. Neuroimage 2012:59. [3]Jin et al. MRM 2011:65. [4]Trott & Palmer JMR 2002 :154. [5]Quesson JMR 1998 :130. [6]Kim et al. MRM 2009:61. [7]Jin et al. MRM 2012. [8]Jones et al MRM 2012:67.