Quantitative CEST imaging with Reduced MT Interference using Dual-frequency Irradiation

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Introduction Chemical Exchange Saturation Transfer (CEST) MRI has been shown to be promising in detection of high-grade gliomas without exogenous contrast agent[1]. However, there are limitations with the sensitivity and efficiency of the CEST images due to the signal losses from conventional magnetization transfer (MT) and direct saturation (DS) effects on water. Recent work suggests that the dual-frequency(DF) irradiation for saturation transfer may be promising for improving CEST imaging[2-4]. For example, Lee et. al. suggested that a uniform saturation of the strongly coupled spin system might be feasible[2]. A direct use in CEST imaging for detecting amide protons, named SAFARI[4], works by subtracting two times of an image using the DF irradiation of +/- 3.5ppm from the sum of images using the CW saturation separately at 3.5ppm and -3.5ppm. We have chosen to investigate how CEST maps can be manipulated through varying the modulation frequency (ω_s) of DF pulses on a series of DIACEST agents with different exchangeable protons (*in vitro)* and on 9L gliomas in live mice.

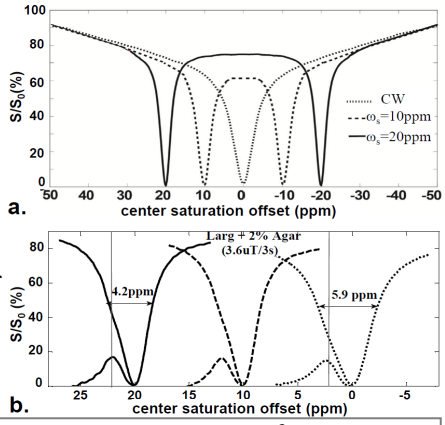

Fig.1 Zspectra changes with ω_s of Dual-Freq. pulse

Theory Saturation pulses with cosine-modulated amplitude of $B_1(t) = \sqrt{2}B_1\cos(\omega_s t)$, will produce signal loss over two bands centered at $+\omega_s$ and $-\omega_s$ simultaneously[2-3]. When the center freq. of the pulse is incremented to produce a Zspectrum, the Zspectrum displays two dips at $+\omega_s$ and $-\omega_s$ (Fig.1a), with the signal relatively uniform in between them (representing MT contrast at ω_s) and the area outside following the envelope of MT line(Fig.1a, 4% agar). The MTR_{asym} spectrum (Fig. 1b) using the DF pulse for an agent of exchangeable frequency(Δ) can be calculated in a similar fashion to CW saturaton, where the peak CEST contrast is achieved with a DF pulse centered at ($\omega_s + \Delta$).

Materials and Methods *Phantom:* Three CEST agents with protons at different chemical shift: Myo-inostol ('M',1ppm), L-arginine ('R', 2ppm) and Barbuturic Acid ('BA', 5ppm) were mixed with 2% Agar to mimic the *in vivo* situation with signal losses from CEST, MT and DS. Two control tubes are 2% Agar and BA in PBS ('BA' in blue). *Animal preparation :* 9L rat glioma cells were transplanted into the brains of adult NOD-SCID male mice resulting in a bilateral tumors and imaged at Day 8 post injection. *Image Acquisition and Analysis:* Phantoms were imaged using a Bruker 500MHz 11.7T vertical scanner and *in vivo* using a 9.4T scanner. The 12 CW (ω_s=0) or DF pulses of 250ms and 3.6uT were added before a RARE sequence (RARE Factor 8) for a single slice of 1mm, with the center frequency sweeping from ω_s-7ppm to ω_s+7ppm for phantom and from ω_s-5ppm to ω_s+5ppm for *in vivo* with 0.25ppm increment. For both CW and DF pulse, B0 inhomogeneity was corrected using WASSR[5] with saturation pulse 0.5uT/500ms, freq. from -1ppm to 1ppm (0.1ppm increment).Other parameters are: matrix size 64X32, FOV 1.15cmx0.25cm and TR/TE= 6000ms/11.52ms for phantom and matrix size 96*64, FOV 1.7cmx1.5cm and TR/TE=5000ms/17.58ms for *in vivo*. The saturation images are normalized by an image without saturation(S_0), and CEST contrast maps are generated by spline fitting of Zspectra with WASSR correction.

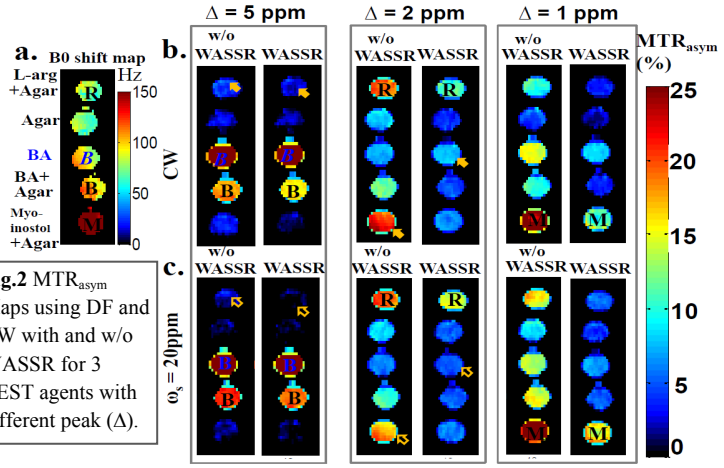

Fig.2 MTR_{asym} Maps using DF and CW with and w/o WASSR for 3 CEST agents with different peak (Δ).

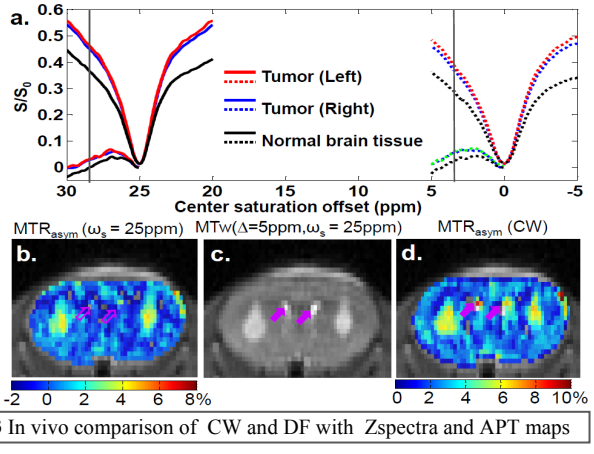

Fig.3 In vivo comparison of CW and DF with Zspectra and APT maps

Results and Discussion We varied ω_s of the DF pulse from 5ppm to 40ppm, to attempt to optimize ω_s for minimizing MT while keeping the same CEST contrast, so that the CNR between CEST agent and background should be increased. In Fig. 1b the Zspectra and corrected MTR_{asym} spectra are displayed for L-arginine with two different ω_s. Using ω_s = 20 ppm produced the sharpest linewidth (1.7ppm < CW) while retaining the CEST contrast and increased the water signal by 10-15%. We also collected CEST contrast maps using DF saturation (ω_s=20ppm) and CW saturation corrected by WASSR (Fig. 2). The DIACEST agents possess exchangeable protons resonating at 5ppm, 2ppm and 1ppm from water to highlight the effects of DS. For 5ppm and 2ppm the WASSR-corrected DF saturation images display contrast only in the desired tubes but not others (empty arrow). CW images highlight undesired tubes more (solid arrow). Even for the maps w/o WASSR, DF saturation shows less contaminations in the undesired tubes (empty arrow) than CW(solid arrow).This also occurs *in vivo*, for example in the preliminary two tumor 9L glioma DF MTR_{asym} map shows similar contrast for both tumors and little else. For the CW image, contrast was observed in the ventricles (purple arrows, Fig.3c).

Conclusion By using a cosine-modulated DF pulse and WASSR correction, we reduced the MT contribution in the saturation images by 10%-15% for both phantom and *in vivo* brain experiments, leading to the improved CEST contrast maps with suppressed background artifacts.

Reference:1. Wen,et al.Neuroimage(2010)51:616-62. 2. Lee et al. J Chem Phys (2008)128:114504. 3. Narvainen et al. JMR(2010)207:242-250. 4. Scheidegger et al ISMRM 2769:2011 5. Kim et al. MRM (2009)61:1441. 6.Song ISMRM 1701:2011.This work is supported by NIH R01 EB012590, R01 EB015031and R01 EB015032.