Quantitative Description of Magnetization Transfer (MT) Asymmetry in Experimental Brain Tumors

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Introduction: Magnetization transfer (MT), an MR imaging technique was first demonstrated by Wolff and Balaban (1), allows indirect detection of solid-like macromolecules via the water signal through the exchange coupling of magnetization between the spins associated with bulk water and macromolecules. A normalized plot of saturated water signal intensity as a function of irradiation frequency offsets is commonly called the MT spectrum or z-spectrum, in which the amount of water signal drop from 1 is defined as MT ratio (MTR). Among several quantitative models of MT, Henkelman's two-pool model is one of the most widely used (2). Several researchers have reported that the z-spectrum is slightly asymmetric about the water proton resonance frequency, with a center frequency in the upfield range of the proton spectrum (3-5). Before this discovery, it was generally assumed that the resonant frequencies of the bulk water and solid-like macromolecule pools are identical, which leads to symmetric z-spectra. However, the z-spectrum asymmetry suggested that this assumption might not be correct. In this study, we investigated the conventional MT asymmetry in 9L glioma implanted rat brains and quantified it with a model extended from Henkelman's classical MT theory (6).

Materials & Methods: Fischer 344 rats (n = 6) received 9L gliosarcoma cells (25,000 cells/2 μl) by stereotactic injection to right caudate/putamen. On post-implantation day (PID) 11 to 13, isoflurane anesthetized rats were imaged using a horizontal bore 4.7T Biospec animal imager. Single-shot spin-echo EPI was used for data acquisition (matrix 64×64, FOV 28×28 mm^2, slice thickness 2 mm). Four MRI scripts are: (i) MT (continuous wave pre-saturation, saturation time 4 s, TR 10 s, TE 30 ms, saturation power 0.9, 1.7, and 2.7 μT, frequency offset -30ppm to 30ppm with a step of 2.5ppm); (ii) T_2 map (spin echo, TR 3 s, TE 30-90 ms); (iii) T_1 map (inversion recovery, delay 3 s, TE 30 ms, TI 0.05-3.5 s); and (iv) ADC map (single-shot trace diffusion weighting, TR 3 s, TE 80 ms, b-value 0-1000 s/mm^2). The classical two-pool MT model (2) was extended with a chemical shift difference between bulk water and the solid-like macromolecule pool (Δ_{mw}). Using a global fitting procedure (2), all of the six model parameters ($RM_0^m/R_{1w}, 1/R_{1w}T_{2w}, \Delta_{mw}, R, T_{2m}, R_{1m}$) were fitted from the z-spectra (3 power levels with 20 offsets each, 60 measurements in total for one fitting). The fitting was carried out using a least squares optimization algorithm (7).

Results & Discussion: Figs. 1a and 1c show z-spectra of the contralateral normal brain and 9L glioma regions, respectively, acquired at three saturation power levels. The z-spectra are asymmetric about the water resonant frequency, with a lower negative offset side ($P < 0.001$). Figs. 1b and 1d show the corresponding MT asymmetry spectra, which are defined as the difference between the z-spectra intensities at negative and corresponding positive offsets with respect to water. For contralateral normal brain, the MT asymmetry is around -2% for the offset region far from water (>20ppm) and between 1% and -5% for the region close to water (0-10ppm) , while it is approximately -1% and between 3% and -3%, for these two regions respectively, in the 9L glioma. Fig. 2 shows two of the six fitted MT parameter maps and compares them with T_1, T_2 and ADC maps and histology. From the ROIs selected with reference to the histology image, the fitted Δ_{mw} values were 2.4±0.3ppm for the contralateral normal brain region, consistent with a previous report in the cat brain (3), and 1.5±0.2ppm for the 9L glioma region. One possible interpretation is that in brain tumors, because of the drastic changes in physiological and pathological conditions, the distribution of the solid-like macromolecule population altered and thus did the location of the chemical shift center. The relative size of the solid-like macromolecule pool (M_0^m, the macromolecule proton to water proton ratio) map was computed from the six parameters and the measured T_1 values (2). From the same ROIs, the M_0^m values were 9.8±1.8% for normal brain and 2.9±0.5% for glioma, which implies an increase of water protons and/or a decrease of macromolecule protons in brain tumors. In the region of plausible edema shown in T_1, T_2 and ADC maps, the fitted Δ_{mw} and M_0^m values were 2.0±0.2ppm and 5.1±0.6% respectively, which suggests that in edema macromolecule distribution does not change much but water protons increase comparing to normal brain tissue. These maps are consistent with the conventional MR images and manifested a fairly good match to the histology image. Note that these results are from a six-parameter numerical fitting procedure, further study is needed to validate the values.

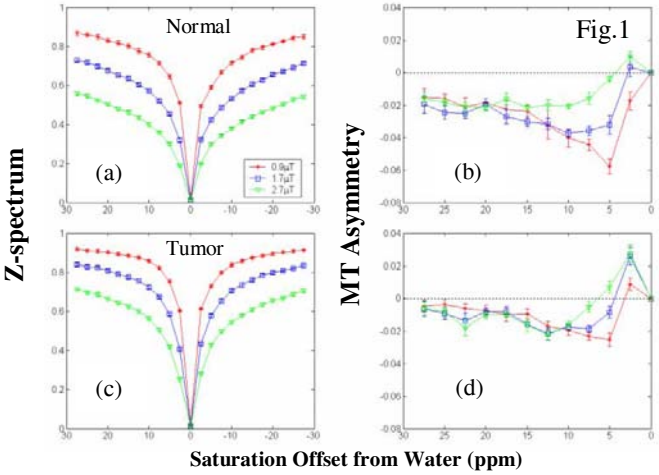
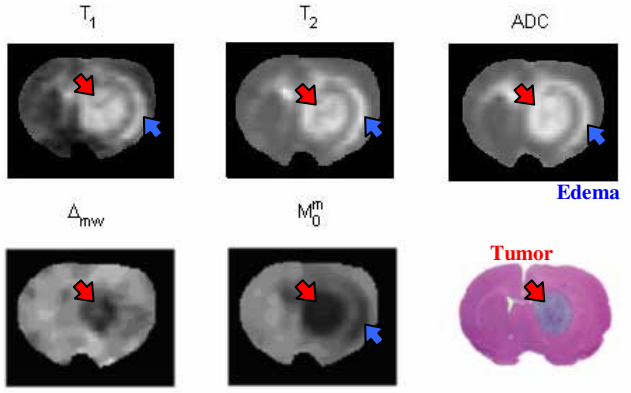


Fig.1

Fig.2: Comparing MR images with histology image.



Conclusion: The asymmetry of conventional MT and the fitted model parameters to z-spectra, including Δ_{mw} and M_0^m, could be exploited as a potential method to assess brain tumors *in vivo*.

(1) Wolff SD, Balaban RS. MRM 1989;10:135. (2) Henkelman RM, et al. MRM 1993;29:759. (3) Pekar J, et al. MRM 1996;35:70. (4) Swanson SD & Pang Y. ISMRM 2003;11:660. (5) Zhou J, et al. Nat. Med. 2003;9:1085. (6) Hua J, et al. ISMRM 2005;13:416. (7) HAN S. J OPTIMIZ THEORY APP 1977;22(3):297. Thank Dr. John Laterra and Dr. Amandeep Salhotra provided the brain tumor model used in this study.