Z Spectral analysis for the quantification of multiple slow-exchanging metabolites

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Introduction:
MRI on the basis of the CEST effect from amine, amide and hydroxyl protons has been shown to provide imaging maps of metabolites in tissue, including amide protons (APT)[1], liver glycogen [2], cartilage glycosaminoglycans [3] and brain myo-inositol [4]. Recently, using relatively high-magnitude radiofrequency (RF) saturation pulses (e.g. 250Hz) we have demonstrated CEST MRI of relatively fast exchanging protons of brain glutamate at 7T[5]. CEST contrast is usually calculated from magnetic transfer ratio (MTR) asymmetry. This conventional quantification method may be confounded by the intrinsic MTR asymmetry as well as the Nuclear Overhauser Effect (NOE) effect[6], especially when using low RF saturating amplitude, such as 50Hz. To decouple these confounding effects, Lorentzian functions have been proposed for fitting the major contributions to the Z spectrum[7]: direct saturation, MT and a CEST pool. A recent study reveals a total of five contributors to the Z spectra acquired with low saturation RF magnitude, including direct saturation, MT, APT, NOE and a off-resonance 2ppm peak [6]. In this study, we demonstrate a comprehensive Lorentzian fitting of Z spectra in brain tumor.

Methods:
Intra-cranial 9L gliosarcomas were developed in Fisher rats (n=5) using previously reported protocols[5]. All animal experiments were performed according to a protocol approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania. Four weeks post tumor cell inoculation, Z spectra up to 100ppm of the tumor central slice was acquired using 50Hz continuous-wave saturation RF pulse lasting for 3s and single shot Fast Low-Angle SHot imaging (FLASH) readout[5] (shot TR=11.4s and TE=3ms). Total imaging time for 2 averages was about 24 min. Following Z spectra acquisition, images for B_0 and B_1 mapping were acquired[5]. Nonlinear constrained fitting routine "lsqcurvefit" was performed in MATLAB to fit pixel by pixel Z spectral data within ~±10ppm range, normalized by 100ppm and center-corrected using B_0 map. The flipped Z spectra ($1-M_z/M_0$) were fitted using five Lorentzian functions for NOE, MT, water, a 2ppm peak and APT, located at -3.2, -1.5, 0 and 2.0 and 3.6 ppm respectively. Fitting was loosely constrained as amplitude within 0.01 to 10 times of initials, line-width 0.5 to 2 times of initials and chemical shifts vary within 10% of corresponding line-widths. After the first round of fitting, water and MT peaks were subtracted from the entire Z spectra and a 2nd round of fine-tuning fitting of the remaining peaks was performed. Fitting R^2 was calculated pixel by pixel.

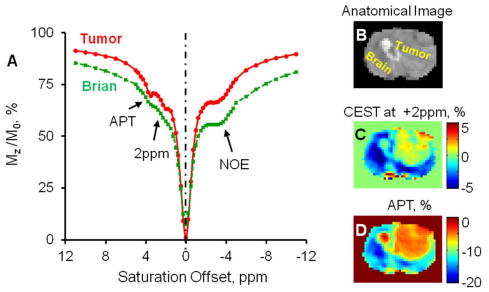


Figure 1. Z spectra (A) from tumor (Red) and normal brain (Green) tissue acquired using low saturating RF amplitude show clearly multiple peaks. Conventional MTR asymmetry based quantification method provides mostly negative contrast at 2ppm and 3.6ppm (APT, D).

Results and Discussion:
Conventional CEST MTR asymmetry quantification method shows mostly negative CEST contrast (Figure 1) from the 2ppm peak and APT in the brain due to the intrinsic MT asymmetry and NOE effect on the high-field side of Z spectra. Comprehensive fitting of Z spectra with the five-component fit is demonstrated in Figure 2 and 3. Results show an increased APT integral (or peak area) in tumor compared to normal brain tissue due to increases in APT amplitude and line-width. This probably indicates elevated amide proton concentration and chemical-shift variation in tumor. The peak amplitude of the 2ppm peak doesn't appear to change in tumor (10.1±0.7%) comparing to normal brain tissue (11.6±0.8%). Its integral reduces in tumor by 58.6±4.2% due to narrower peak line-width which probably because of the changes in T_2 and pH. The pixel by pixel fitting provides us the integral, chemical shift, line-width and amplitude maps of these five components contributing to Z spectra (Figure 3). Most pixels are fitted with R^2 >0.95 except the hydrocephalus, which arises due to enlarged ventricle. The novel Z spectral analysis method used for quantifying multiple metabolites contributing to Z spectra may be used for differentiating tumor metabolic profile from normal tissue.

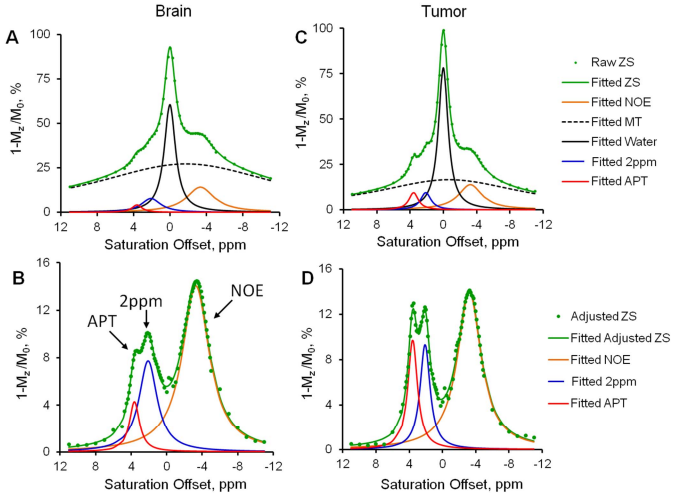


Figure 2. Z spectra (ZS) from normal brain (Left column) and tumor (Right column) were fitted as five Lorentzian functions (A and C). The second fine-tuned fitting of adjusted Z spectrum for NOE, a 2ppm peak and APT (B and D).

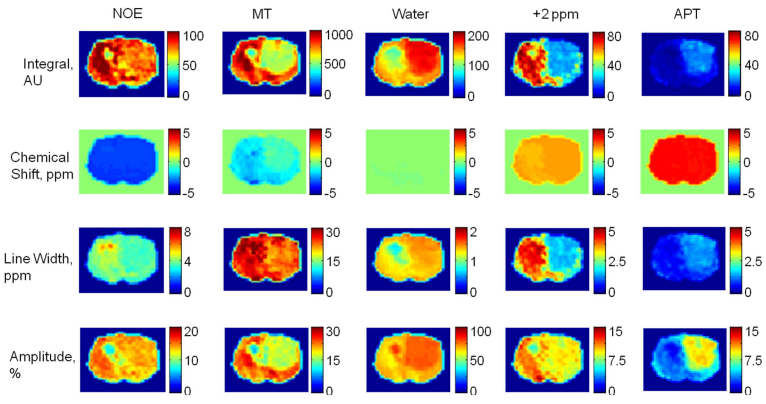
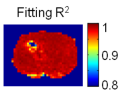


Figure 3. Pixel-by-pixel fitting of a 4-week 9L tumor provides integral, chemical shift, line width and amplitude maps of multiple slow exchanging metabolites contributing to the Z spectra. Fitting R^2 map is shown at bottom right.



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