The Influences on Amide Proton Transfer (APT) Signal Metrics at 3T: Simulation and In-Vitro Study

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INTRODUCTION: Amide Proton Transfer (APT) shows great promise and clinical relevance for detecting progression in brain tumours such as gliomas[1,2]. Clinical glioma APTw imaging uses the standard MTR_{asym} metric, however, there are additional APTw metrics, which may have different sensitivities to biological changes such as protein concentration, a potential marker for tumour cell proliferation. Previous studies show that T_1 may influence APTw signal, especially at 7T. Since T_1 may change with fluid or blood content, T_1-sensitive APT metrics may be clinically misleading. While the impact of T_1 on the APTw signal at 3T is expected to be minimal, supporting literature is sparse[3,4,5]. This work investigated the sensitivity of four APTw metrics to changes in protein concentration and T_1 in simulated and *in-vitro* acquired Z-spectra.

METHODS: Simulations used a 4 pool Lorentzian fit (water, broad magnetization transfer, APT, and Nuclear Overhauser Enhancement) with a block pulse (B1=2μT, T_{sat}=2sec, and field strength=3T)[7]. Input parameters for pools were based on reported literature values in tumour tissue at 3T[6]. The APT pool relative concentration varied over 0.001-0.008, in 0.001 increments. T_1-varied simulations took T_1 values of 2200ms-800ms, in 200ms increments. Egg white phantoms were prepared by volumetric dilution with deionized water to concentrations of 100%, 50%, 25%, 10%, 5%, 2.5%, 1.25%, and 1%. A second egg white concentration dilution series was made using Dotarem-doped deionized water, so all dilutions would have the same T_1. A series of varied T_1 with constant 50% egg white concentration was also prepared. MRI was acquired on a 3T Philips Elition X Scanner, with a B_1-corrected T_1 map calculated using variable flip angle imaging data (TE=0.87ms, TR=10.6ms, spiral readout, Flip angles=2°,6°,10°,12°,15°) and 32 offset CEST acquisition (TE=8.30ms, TR=5925ms, Flip angle=90°, Readout=3D TSE_1 , Offsets=(-1560(S_0), ±10, ±5, ±4.75, ±4.5, ±4.25, ±4.0, ±3.75, ±3.5(x3), ±3.25, ±3.0, ±2.5, ±2, ±1,0ppm), B_1=2μT, T_{sat}=2sec, Voxel Size=0.89x0.89x6.0mm^3, Number of slices=10, Acquisition time=12min50sec). Artifact-free regions of interest (ROI) were drawn for each tube on the T_1 map and the APT S_0 image. The mean and standard deviation of each metric was calculated over these ROIs. Metrics used to quantify the simulated Z-spectra were MTR_{asym}, MTR_{rex}, APT* and AREX. Evaluation of each metric was done by linear fitting of metric signal as a function of concentration or T_1 change for all data series (simulated, T_1-varied, doped concentration-varied, undoped concentration-varied).

RESULTS AND DISCUSSION: An example slice of the computed MTR_{asym}, MTR_{rex}, APT* and AREX maps of the phantoms are shown in Figure 1. Linear fitting showed MTR_{rex} was the most T_1-sensitive for both simulated and *in-vitro* data. Simulations showed minimal T_1-sensitivity for all other metrics. In contrast, linear fits for *in-vitro* data show MTR_{asym} as the least T_1-sensitive metric, and overcorrection for T_1-variation in the AREX metric. Simulation and *in-vitro* data showed better agreement in concentration change sensitivity of the metrics MTR_{rex}, MTR_{asym} and AREX. MTR_{rex} was the most concentration-sensitive, followed by MTR_{asym} and then AREX. *In-vitro,* concentration sensitivity of AREX and MTR_{asym} were not statistically different and the APT* metric lacked the sensitivity to provide meaningful values *In-vitro*. AREX was the most consistent between the doped and undoped series, with no significant difference in the gradients, but appears to overcorrect for T_1. Over the measured range of protein concentrations, the MTR_{rex} was most sensitive to concentration change but also most impacted by T_1-variation. Though not the most sensitive metric, MTR_{asym} showed concentration sensitivity, while being robust to T_1-variation.

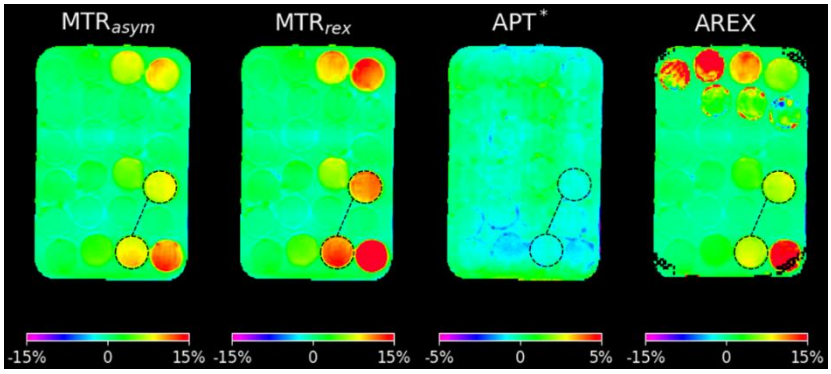

Figure 1. *From left to right: Representative slice of the MTRasym, MTRrex, APT* and AREX metric maps of sample tubes with various egg white concentration dilutions and Dotarem doping. The two tubes connected by the dashed line demonstrates the 50% undoped (bottom) and 50% Dotarem-doped*

CONCLUSION: This study demonstrates that at 3T the impact of T_1-variation on APTw metrics is minimal, with larger impact from concentration variation. Simulation and *in-vitro* results suggest MTR_{asym} is the most clinically useful metric due to least variability to T_1 change while remaining sensitive to concentration.

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