Accurate fitting of a Multi-Pool Proton Exchange System with *a Priori* Fitted Two-Pool MTC Information

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Introduction

CEST imaging is an important molecular MRI technique that can generate contrast based on the saturation transfer between bulk water protons and low-concentration solute labile protons[1]. Because RF radiation to saturate the solute labile protons induces large direct water saturation and conventional MT from semi-solid macromolecules, the quantitative CEST measurement and theoretical simulation are complicated[2-5]. In this study, we investigated the mixed MT, APT, and NOE effects in a multi-pool proton exchange model with the *a priori* fitted two-pool MTC information.

Methods

Six human glioblastoma-bearing adult Fisher 344 rats were scanned on a horizontal bore Bruker 4.7 T. CEST image data were obtained using a fat-suppressed spin-echo pulse sequence with a single-shot EPI readout (TR = 10 s; TE = 30 ms; matrix size = 64 x 64 mm^2; FOV = 32 x 32 mm^2; slice thickness = 1.5 mm; and RF saturation time = 4 s). Two sets of z-spectra with 26 frequency offsets were acquired to quantify conventional MT, NOE, and APT effects, using three RF saturation powers (0.5, 1.3, and 2.1 µT): (1) $Z_{21\sim-21ppm}$: 21 to -21 ppm at intervals of 1.75 ppm for MT modeling with the super-Lorentzian lineshape; (2) $Z_{6\sim-6ppm}$: 6 to -6 ppm at intervals of 0.5 ppm for the quantification of NOE and APT effects. The wide-offset data were fitted to two-pool MT model with the super-Lorentzian lineshape[2]. Data points of small frequency offsets between 7 and -7 ppm in B_0-corrected $Z_{21\sim-21ppm}$ were excluded ($Z'_{21\sim-21ppm}$) to avoid APT and most NOE contributions prior to conventional MT modeling. Next, a four-pool exchange model was analytically solved with the fitted two-pool MT information, and the parameter fitting was performed using the minimum norm estimate. The post-hoc test was performed for $p < 0.05$: <: significantly smaller; >: significantly larger; not indicated: no significant difference.

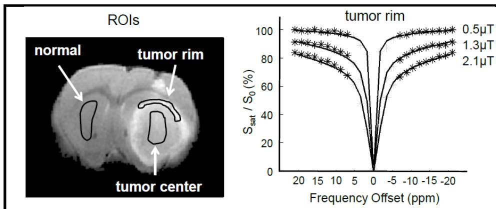

Fig. 1. ROIs and average two-pool MT fitted results (solid) and experimental data (black asterisk) obtained from the tumor rim

Table 1. Fitted two-pool MT model parameters. (*N=normal, TC=tumor center, TR=tumor rim*)

n=6	R (s^{-1})	T_{2m} (µs)	$RM_0^mT_{1w}$	T_{1w}/T_{2w}	T_{2w} (ms)	T_{1w} (s)	T_{1w}^{obs} (s)	M_0^m (%)
Normal	17.7 ± 0.8	18.7 ± 1.6	2.17 ± 0.15	44.6 ± 0.5	31.5 ± 0.4	1.40 ± 0.02	1.36 ± 0.02	8.7 ± 0.7
Tumor center	20.3 ± 1.3	19.8 ± 0.4	1.39 ± 0.14	39.4 ± 0.9	50.0 ± 0.9	1.97 ± 0.05	1.91 ± 0.05	3.6 ± 0.3
Tumor rim	21.5 ± 1.1	18.5 ± 1.2	1.34 ± 0.04	29.9 ± 0.5	64.7 ± 0.8	1.93 ± 0.04	1.88 ± 0.05	3.1 ± 0.2
Post-hoc	*N<TC,TR*		*N>TC,TR*	*N>TC>TR*	*N<TC<TR*	*N<TC,TR*	*N<TC,TR*	*N>TC>TR*

***w**: free bulk water, **m**: semi-solid macromolecule, **R**: exchange rate between two pools, **M_0**: proton pool size*

Results and Discussion

The two-pool MT model accurately fitted the behavior of the semi-solid MT system for wide frequency offsets as shown in **Fig. 1**. The MT parameters (except T_{2m}) were significantly different between the normal tissue and the tissue in the tumor center or rim as shown in **Table 1**. Four-pool APT and NOE exchange model fitted the $Z_{6\sim-6ppm}$ behavior very well as shown in **Fig. 2**. As expected (**Table 2**), the APT-related pool sizes of the tumor center and the tumor rim were significantly larger than that of the normal tissue, while the NOE-related pool sizes of the tumor center and the tumor rim were significantly smaller than that of the normal tissue.

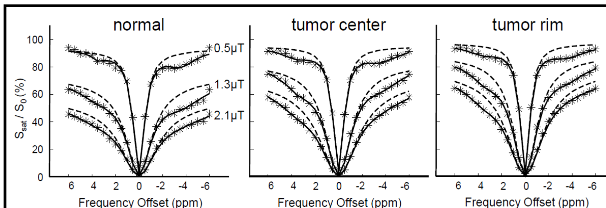

Fig. 2. Average four-pool fitted results (solid), experimental data (asterisk), and two-pool MT curves (Z_{EMR}, dashed)

Table 2. Fitted four-pool proton exchange model parameters

	Amide proton pool (S_1)			*NOE-related proton pool (S_2)*		
n = 6	M_0^{S1} (%)	k_{S1w} (Hz)	T_{2s1} (ms)	M_0^{S2} (%)	k_{S2w} (Hz)	T_{2s2} (ms)
Normal	0.31 ± 0.03	23.9 ± 6.8	11.5 ± 1.1	0.66 ± 0.22	16.3 ± 8.3	0.40 ± 0.1
Tumor center	0.39 ± 0.03	21.5 ± 2.5	10.1 ± 3.4	0.39 ± 0.07	17.6 ± 4.1	0.38 ± 0.2
Tumor rim	0.40 ± 0.05	28.3 ± 9.6	11.2 ± 2.5	0.36 ± 0.13	15.4 ± 5.8	0.39 ± 0.4
Post-hoc	*N<TC,TR*			*N>TC,TR*		

Further, by subtracting experimental data ($Z_{6\sim-6ppm}$) or simulated four-pool data from Z_{EMR}, $APT^{\#}$ and $NOE^{\#}$ signals could be obtained (Fig. 3). The $APT^{\#}$ signals in all ROIs were lowest at the RF saturation power of 0.5 µT and seemingly peaked at 1.3 µT, while the $NOE^{\#}$ signals were lowest at 2.1 µT. The $APT^{\#}$ signals of the tumor center and the tumor rim were both significantly higher than those of the normal tissue across all power levels ($p < 0.05$). The $NOE^{\#}$ signals were generally lower in the tumor center and rim than in the normal tissue, which reached statistical significance ($p < 0.05$) in the tumor center at 1.3 µT.

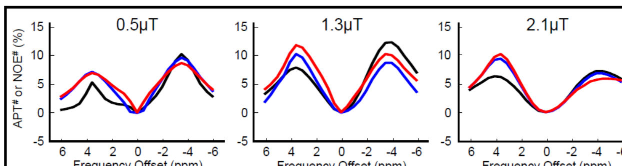

Fig. 3. Simulated downfield $APT^{\#}$ and upfield $NOE^{\#}$ signals

Conclusions

Four-pool fitting using extrapolated semi-solid MTC parameters as prior known information could reduce the over-fitting errors. The quantitative results would provide some insight into the mechanisms of APT and NOE effects in tissue.

References

1. Ward et al. JMR 143:79 (2000). 2. Li et al. MRM 60:1197 (2008). 3. Zaiss M, et al. JMR 211:149 (2011). 4. Liu et al. MRM 70:1070 (2013). 5. Desmond KL, et al. MRM 71:1841 (2014). 6. Henkelman et al. MRM 29:759 (1993).