Quantitative Model-Based Analysis of Amide Proton Transfer MRI

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Introduction: Amide Proton Transfer (APT) imaging is a Chemical Exchange Saturation Transfer (CEST) variant that exploits the exchange of endogenous amide and water protons to generate pH weighted contrast [1]. Clinically, characterization of pH changes in acute stroke may be useful for assessing ischemic tissue at risk for infarction [2], and APT is believed to be useful for tumor grading as well [3,4]. The APT effect is dependent upon both the concentration of amide protons and rate of exchange of these protons with those in water, the latter being proportional to pH [1]; in principle it is possible to obtain quantitative values for these contributions from APT data. However, this is difficult *in vivo* due to magnetization transfer (MT) effects, frequency shift of the water resonant frequency due to B_0 field inhomogeneity, and B_1 saturation field inhomogeneity. It is theoretically possible to account for these effects by sampling an APT spectrum over a range of saturation frequencies and using model fitting. However, whilst this has been performed in other CEST modalities, it is particularly difficult for APT due to the large number of free parameters and poor signal-to-noise ratio. In this work we investigated whether model-based quantitative analysis of APT data *in vivo* was feasible when employing a probabilistic non-linear model-fitting algorithm that permitted the incorporation of prior information about the parameters to regularise the analysis.

Methods: *Experimental*. Seven healthy volunteers provided informed consent and were scanned using a pulsed APT sequence at 3T (Siemens Verio). Single-slice transverse imaging was performed mid brain with TR/TE=4000/26 ms, matrix 80 x 80, slice thickness = 5 mm. Saturation was achieved using a series of Gaussian pulses of duration 20 ms with 20 ms spacing to achieve an equivalent continuous saturation B_1 value of 0.3 μT. Data were acquired for saturation frequency offsets from -4.5 to 4.5 ppm with 0.3 ppm increment plus a reference image with no saturation, resulting in 32 volumes acquired in 2 min 55 s. In all subjects WASSR data [5] were also acquired using the same sequence, but with a single 50 ms Gaussian pulse with effective of B1 = 0.15 μT, offset range -0.5 to 0.5 ppm, 0.0333 ppm increment. A T1 structural image (1x1x5 mm) was also acquired from which grey and white matter masks were derived via segmentation and transformed into the CEST image space using a rigid body transformation.

Modeling: APT spectra were analysed by voxelwise fitting of the data to a 3-pool model: water, APT and MT. The model was based on the Bloch-McConnell equations [6] and thus included proton concentration ratios (PCR) relative to water protons and proton exchange rate (PER) constants for APT and MT along with T_1 and T_2 values for each pool. The model also incorporated, as parameters to be inferred from the data, a shift in the resonant frequency of water and variability in the applied B_1 saturation power. Model fitting was performed using a probabilistic algorithm [7] and parameters were subject to normally distributed priors with means and standard deviations as given in Table 1. For the majority of parameters the priors represented knowledge about their values from the literature with an associated degree of variability or uncertainty. The PCR values ($M0_{APT}/M0_w$ and $M0_{MT}/M0_w$) for the APT and MT pools were deliberately set to be effectively non-informative. The model was implemented using a matrix exponential form [6] and the natural logarithm of the PER values were inferred. The mean PCR and log(PER) were calculated within the GM and WM masks for each subject and the group mean and standard deviation was determined. For reference, images of asymmetric magnetization transfer ratio (MTR_{asym}) [1] were also calculated from the measurements at ±3.5 ppm and the offset in the water centre frequency was estimated using the WASSR data and the procedure given in [5].

Table 1: Model parameters with prior values – expressed as the mean and standard deviation (SD) of a normal distribution, $i \in \{w,APT,MT\}$.

	Water Pool		APT Pool		MT Pool	
Parameter	Mean	SD	Mean	SD	Mean	SD
$M0_i$	0	10^6	-	-	-	-
PCR_i	-	-	0	1.0	0	1.0
PER_i (s^{-1})	-	-	20 [1]	-	40 [8]	-
$\log(PER_i)$	-	-	3.0	1.0	3.7	1.0
T_1 (s)	1.3	0.15	0.77	0.15	1.0	0.15
T_2 (ms)	50	10	10	2	0.2	0.04
ω_i (ppm)	0	0.1	3.5 [1]	0.1	-2.41 [9]	0.1

Table 2: Group mean and standard deviation within grey and white matter for APT PCR and PER, and MT PCR estimates.

Parameter	Grey matter		White matter	
	Mean	SD	Mean	SD
$rM0_{APT} \times 10^{-3}$	0.0030	0.0003	0.0033	0.0001
$\log(k_{APT,w})$	2.66	0.14	2.87	0.08
$rM0_{MT} \times 10^{-3}$	0.085	0.005	0.123	0.007

Results: Fig. 1 shows MTR_{asym} in three subjects along with the estimated PCR for the MT pool from the model-based analysis. The MT PCR was higher in WM than GM as expected and the MTR_{asym} images were seen to be contaminated by MT effects. Fig. 2 shows estimated amide PCR and log(PER) in three subjects. The amide PCR was observed to be relatively homogenous in all subjects consistent with the healthy brain. Table 2 shows the group mean and standard deviation of the APT and MT parameters within the GM and WM masks. PER values correspond to pH of 6.8 and 6.9 for GM and WM respectively using the relationship in [1], the MT PCR values appear consistent with those in the literature [8,9]. Fig. 3 shows water centre frequency offset in three subjects from the model-based analysis and WASSR method, good correspondence was generally found between these two images.

Discussion: The results indicate that is it feasible to apply model-based analysis to *in vivo* APT imaging. However, validation using phantoms is still required to test the accuracy with which amide PCR and PER can be determined and changes in these measured. The challenge of independently measuring PCR and PER is well established and the use of samples at multiple saturation field strengths or durations has been proposed [10,11]. The model-based approach to analysis could naturally be extended to utilize information at a range of saturation frequencies, field strengths and durations. The model-based approach is also well suited to the use of more optimized acquisition strategies, such as that employed by [4], where more relevant parts of the spectrum are more frequently sampled. A three-pool model was employed to account for MT effects, which are a significant source of asymmetry in the APT spectrum *in vivo*. The three-pool model treats MT effects as having a Lorentzian lineshape, studies have indicated that a super-Lorentzian lineshape is more appropriate [8,9]. This may lead to some inaccuracies in the analysis as implemented here, although within an APT spectrum a Lorentzian lineshape may be a sufficiently good approximation given the results in [8].

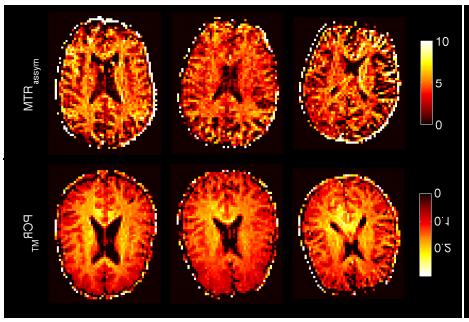

Fig. 1 MTR asymmetry (top) in 3 subjects. PCR of MT pool from model-based analysis (bottom)

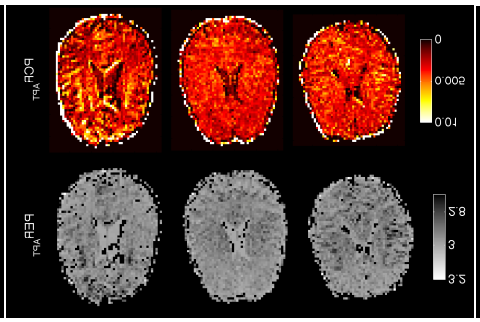

Fig. 2 Estimated PCR and PER of amide pool from model-based analysis.

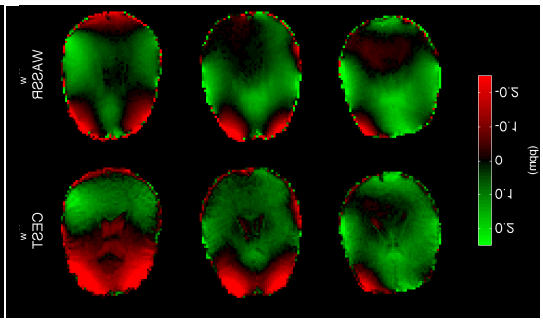

Fig. 3 Estimated offset in the centre frequency of water using model-based and WASSR analyses.

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