Sensitivity of CEST MRI for absolute pH measurement in brain metastases

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Target audience: Researchers interested in the quantification of labile proton exchange rate (pH) from CEST MRI, and its applications in oncology.

Purpose: Metastasis is the leading cause of cancer morbidity and mortality. A major limitation to the treatment of brain metastases is the impact of microenvironmental factors on treatment efficacy, particularly tumour pH. Thus, measurement of tumour pH may be critical in stratifying patients into likely responders and non-responders for particular therapies. CEST MRI has emerged as a potential candidate for performing measurements of pH *in vivo* [1]. However, pH measurement by CEST is confounded by several factors such as the concentration of exchangeable protons and the MRI relaxation parameters, T_1 and T_2. Before CEST MRI can be used to map absolute pH *in vivo*, the contributions of these factors to the CEST signal must be elucidated and quantified. The aim of this study was to determine the sensitivity of CEST signal to changes in pH, labile proton concentration, T_1 and T_2 in realistic phantom models.

Methods: Perchloric acid extracts were made from naive mouse brain ('*Ex vivo* NB'), *in vitro* cultured 4T1-GFP mouse metastatic breast carcinoma cells ('*In vitro* 4T1'), and *in vivo* subcutaneously grown 4T1-GFP cells ('*Ex vivo* 4T1'). Bovine Serum Albumin (BSA) was added to the extracts and these were used as models representing the intracellular environment of each cell type, with serially varied pH, BSA content, T_1 time and T_2 time. CEST MRI experiments were performed at 9.4T. Z-spectra were acquired using saturation by 300 Gaussian pulses with 26ms duration each (50% duty cycle), total saturation duration 7.8s with average B_1 power of 0.8μT, followed by 8-shot spin-echo echo planar readout at 85 saturation frequency offsets (between ±10ppm). Asymmetry analysis (MTR_{asym} [1]), an inverse Z-spectrum multiple-offset analysis (MTR_{Rex}^{Rev} [2]), and model based analysis (PTR* [3]) were used to analyse Z-spectra for the CEST effect evident at 2.8ppm. B_0 inhomogeneity was corrected prior to MTR_{asym} and MTR_{Rex}^{Rev} analysis by shifting the minimum point of the Z-spectrum to 0ppm; no correction was necessary for PTR* [3]. Linear regression determined the relationship between the calculated CEST effect and the varied parameters, and the gradient of the linear regression termed the CEST Sensitivity (in % M_0 / parameter unit change).

Results: Fig 1 shows that PTR* is the most sensitive measure of CEST effect since it exhibits the highest sensitivity to changes in pH and BSA content. Comparing PTR* for each phantom model, no significant difference in CEST sensitivity to changes in pH or BSA content is evident.

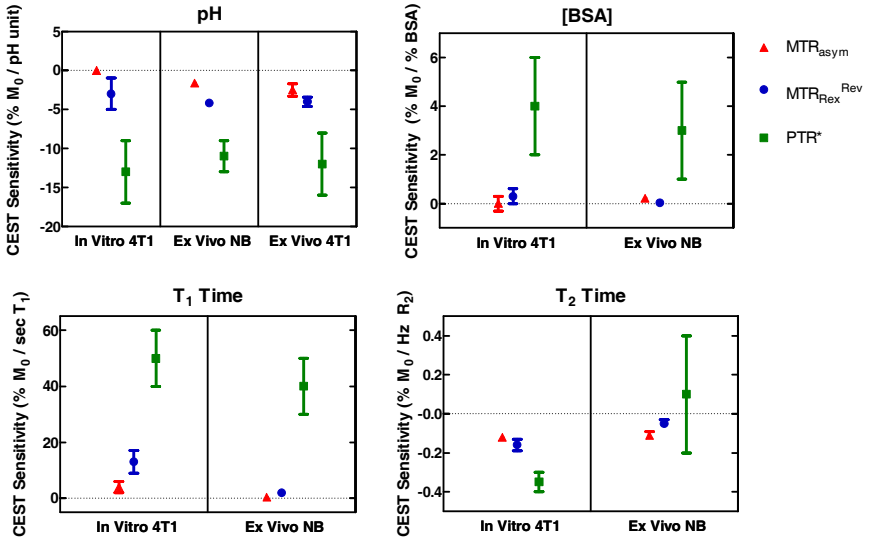

Fig 1: CEST Sensitivity for three analyses in all phantom models. Data points represent the gradient of the linear regression for each analysis method across all phantom models. Error bars are 95% confidence intervals for the gradient value.

Discussion: The novel phantom models used in this study are more relevant to the intracellular environment of naive brain and metastatic breast carcinoma cells than phantoms used in previous studies [4,5], enabling more immediate translation of these results to *in vivo* preclinical work. The qualitatively expected response of CEST effect to changes in pH, protein content, T_1 and T_2 is seen in all phantom models compared to simulation [4]. *In vitro* and *in vivo* grown 4T1-GFP cells exhibited similar CEST sensitivities as measured by each metric, indicating that cultured cells provide a representative and relevant model for evaluating CEST signals. The similarity in CEST response to parameter changes for naive mouse brain and tumour tissue suggests that segmentation of tumour boundaries will not be necessary when measuring absolute pH *in vivo*. Although magnetisation transfer effects have not been included in these phantoms, the contribution of this process *in vivo* may be accounted for by including it as an extra pool in the PTR* analysis [3].

Conclusion: An average CEST response of -12±6 %M_0/pH unit was measured by PTR*. Since these phantom models are more representative of an *in vivo* environment than phantom models used previously, the results presented here can be translated to absolute *in vivo* pH mapping more quickly, and we hypothesise that pH changes on the order of 0.1 pH units can be measured accurately and sensitively using CEST MRI.

References: [1] – Zhou *et. al.*, Nat. Med. 9:1085-90, 2003. [2] – Xu *et. al.*, NMR Biomed. 27:406-16, 2014. [3] – Chappell *et. al.*, MRM. 70:556-67, 2013. [4] – Zong *et. al.*, MRM. 71:118-32, 2014. [5] – Sun *et. al.*, CMMI. 9:268-275, 2014.