Differentiation and quantification of exchanging protons in different pool resonating at the same frequency in CEST

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Purpose: CEST is increasingly used to study a wide range of endogenous and exogenous species [1]. However different species overlap in the z-spectra due to line broadening caused by exchange, therefore it is essential to develop methods to differentiate them. Varying the irradiation flip angle (FA) can help address this problem [2] but is difficult to implement, since the pulse amplitude constraints lead to wide variations in pulse bandwidth (BW) on whole body scanners. Here we propose a new combination of acquisition and analysis approaches to separate fast and slow exchanging species. *Acquisition:* the FA was altered while keeping the pulse BW constant, overcoming the problem of varying direct saturation. Furthermore the whole z spectrum was acquired at a range of pulse amplitudes, thus including information about line width, which depends on exchange rate. *Analysis*: spectra from pure samples of species of interest were used as basis sets for fitting spectra from mixed species, fitting different amplitudes simultaneously. **Aim:** (1) To find, via simulations, a combination of CEST spectra acquired with varying FA which can be used to distinguish two pools at similar offset frequency, but different exchanging rates. (2) To verify this method for separating species experimentally.

Method: Five phantoms were prepared: Phantom 1: Creatine (Cr) only (12mM), Phantom 2: Glucose (Glc) only (12mM), Phantom 3: Cr and Glc mix (6mM + 6mM), Phantom 4: Cr and Glc mix (3mM + 3mM), Phantom 5: Water only. Scanning was performed on a 7T Philips scanner with a 32 channel receiver coil. Data were acquired using a MT-TFE sequence [3]. Saturation consisted of 50 sinc shaped RF pulses (BW=120Hz; T_{pulse}=50ms) applied at 100 ms intervals, at 13 FA varying from 60°- 780° (B_{1max}=0.45-5.85μT); the acquisition consisted of a Turbo-Field Echo readout of 600 FFE, with low-high k-space ordering. z-spectra were sampled at 48 off-resonance frequencies (-4ppm to +4ppm) for each FA. The central frequency of the spectra was corrected via a B_0 map. This experiment was also simulated using numerical solutions of the Bloch equations for a three pool model [2], assuming 2 exchanging pools at the same frequency (one fast exchanging pool with a rate of 1000Hz, one slow exchanging pool with a rate of 50Hz) and a free water pool. Analysis: The z-spectra from phantoms 1, 2 and 5 were considered to form a basis set of spectra at different FAs, which could be used in combination to fit the other spectra for their Glc and Cr contents. Different FA give different sensitivities to the fast and slow exchanging species [1] but it would not be practical to acquire data at a wide range of FA and offsets. Therefore simulations were used to select 2 pairs of flip angles that would give good sensitivity to [Glc] and [Cr]. Initial simulations suggested that 240° and 720° (B_{1max} of 1.8 and 5.4 μT) were a good combination. Pairs of z-spectra acquired at these FA were then used to fit the data for concentrations of each pool in the mix.

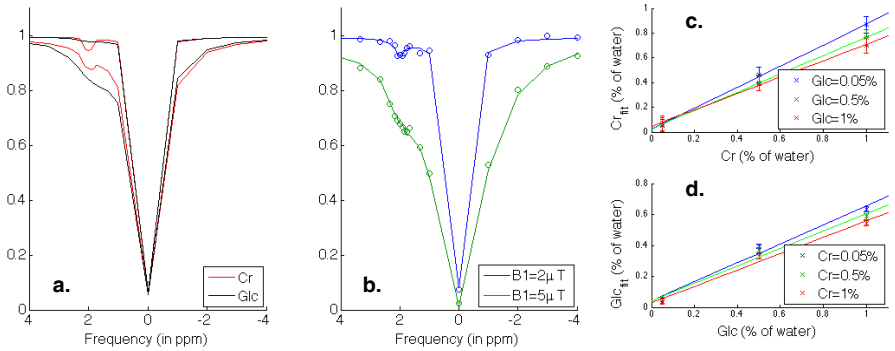

Fig 1: CEST spectra simulated for a 3 pool model with water, a slow exchanging pool (50Hz) and a fast exchanging pool (1000Hz) at different concentrations. Basis spectra (a) were used to fit mixed spectra (b) acquired at different FA. Fit results for the simulation with 1% of noise are presented in (c,d), with a good agreement between the input of the simulation (x-axis) and the fit (y-axis).

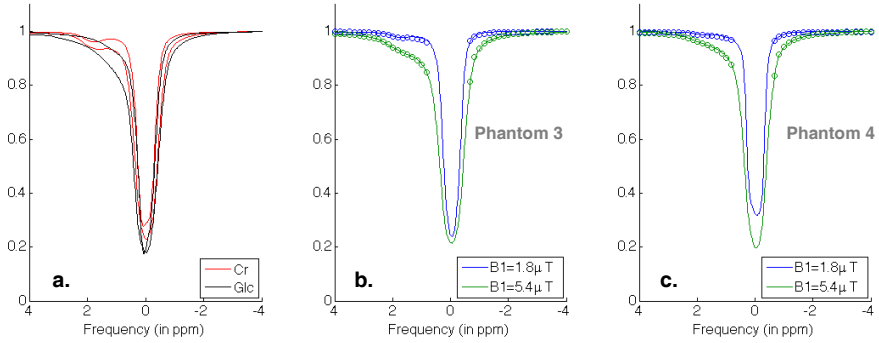

Fig 2: Z-spectra acquired on (a) phantoms 1 (red) and 2 (black) or a mixed phantoms 3 and 4 (circles in b and c), together with fitting results (continuous green and blue lines in b and c).

Results: Simulation: Simulated spectra of the mixed phantoms at different pairs of flip angle combinations were simultaneously fitted to linear combinations of the simulated basis set spectra (fig 1a) with the relative amplitudes of each components scaled for pool size ps=0.005, 0.05, 0.1 and 1% of water. Good fits were obtained for both flip angle combinations (fig.1b). The results gave a reasonable correlation (R=0.98 for noise level of 1% of unsaturated signal) between the simulated ps and the fitting results, even for ps an order of magnitude lower or higher than the mix (fig1c and d). For larger ps (0.5%), a different basis set was simulated and produced the same linear relationship between simulation and results. Robustness of the fit was investigated by adding different levels of noise on the z-spectra, with only small effect on the results (error bar on c and d for noise level of 0.1% of non-saturated signal). Experimental: Similar fitting was performed using the data from 'pure' phantoms 1, 2 and 5 (Cr, Glc and water phantoms) as basis z-spectra to fit the data from mixed phantoms 3 and 4. Good agreement was found between the fitted results and the initial concentration in the phantoms: Phantom3: Cr=6.36 ±0.01 mM and Glc=6.36 ±0.01 mM compared to an expected 6 mM for both; Phantom 4: Cr=2.52±0.01 mM and Glc=4.08±0.01 mM compared to an expected 3mM. Errors come from repeated measurements.

Discussion: We have succeeded in separating overlapping slow and fast components in the z-spectrum by fitting spectra acquired at different FAs. The basis functions could be extended to include further exchanging species and the macromolecular pool. Z-spectra were acquired at 2 FAs at 48 off resonances have been acquired. Future work will involve a more formal optimization of the acquisition scheme. Since the z-spectrum amplitude is not linear in pool size, the basis sets are only accurate over a limited range of amplitudes, but this is unlikely to be a problem in vivo.

References: [1] van Zijl 2011, MRM 65 (4). [2] Zu 2012, MRM 68 (3). [3] Woessner 2005, MRM 53 (4). [4] Mougin 2010, Neuroimage 49 (1).