High Throughput Screening of Contrast Agents by Ultrafast CEST Imaging

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Target audience: Those interested in chemical exchange saturation transfer (CEST) and screening CEST agents.

Purpose: Traditionally, CEST and MT effects are studied by plotting the normalized signal intensity of water protons as a function of saturation frequency offset, i.e. a Z-spectrum. Methods have been developed to shorten experiment time by screening multiple samples simultaneously[1] but frequency sweeping is still required. Although a one-shot method was proposed by Swanson for MT,[2] until recently, this approach has never been used for CEST. Recently, an ultrafast technique was developed to acquire the whole Z-spectrum in just two scans by utilizing a gradient concurrently with the saturation pulse.[3] This approach has great potential for characterizing CEST contrast agents and monitoring temporal changes such as temperature in a system in a fast manner.[3,4] In this study, we extend the ultrafast CEST method to imaging, allowing the screening of multiple samples at the same time; furthermore, by interleaving a number of saturation and readout periods within the TR, a series of CEST images with different saturation times can be acquired allowing quantification of the exchange rates using variable saturation time (QUEST)[5] approach.

Method: The pulse sequence used in the study is shown in Fig 1. When the gradient and the saturation pulse are simultaneously applied, the saturation offsets become a function of spatial position along the gradient direction in the sample. An EPI sequence was implemented for image acquisition. Using a low flip angle for excitation allows multiple readout blocks to be repeated during the total saturation period so that the each CEST image corresponds to a different saturation time.

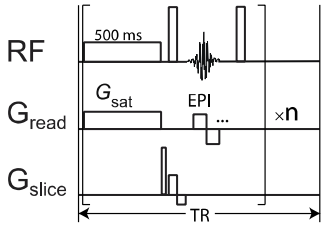

Fig. 1. Pulse sequence for ultrafast CEST imaging.

MRI experiments were performed on a Bruker 17.6 T NMR spectrometer equipped with a Micro 2.5 gradient system. A 20 mm diameter volume coil was used for RF transmission and reception. An assembly of phantoms consisting of multiple NMR tubes filled with several typical tissue metabolites such as creatine (10 mM, pH = 7.4), glutamate (10 mM, pH= 7.4) and myo-inositol (7.5 mM, pH = 7.3) were imaged using a segmented EPI readout with TR/TE = 5 s/8.86 ms. 4 segments were used. As shown in Fig. 2a, a 4 mm slice covering 3 phantoms was selected with a FOV of 2×2 cm^2. The frequency encoding direction of the Z-spectra (image readout direction) was chosen to be along the long axis of the tubes. 128 points were acquired along this direction, which corresponds to a frequency resolution of 100 Hz for the Z-spectra. 16 phase encoding steps were applied. A reference scan without the saturation pulse is needed to normalize the proton density and eliminate imperfections of the gradient and spatial irregularities of the sample. For the scan with saturation, a 2 μT pulse with a duration of 0.5 s was applied simultaneously with a 15 μT/mm gradient field and the EPI readout was repeated 4 times corresponding to saturation times of 0.5, 1.0,1.5 and 2 s for each image, respectively. All the parameters are identical for the reference scan except that the saturation pulse is turned off. The total time for both scans was 40 s.

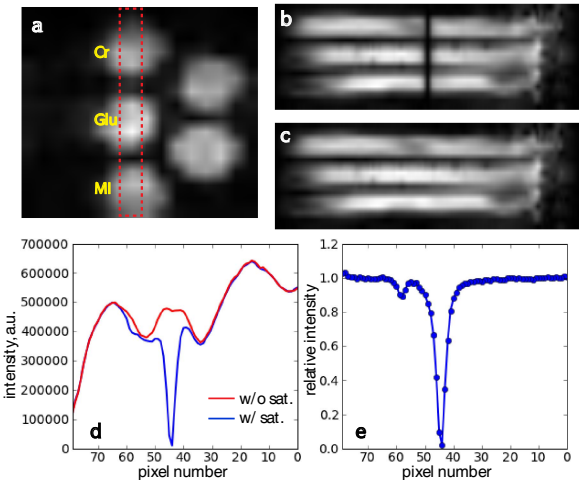

Fig. 2. a, Phantom arrangement and slice selection; b, c, image acquired with and without saturation; d, 1d projection of one phantom; e, a sample Z-spectrum obtained after normalization.

Results and Discussion: Figs. 2b and 2c show the ultrafast CEST images for a saturation time of 0.5 s and the corresponding reference image. When normalizing 2b to the reference 2c, the image artifacts due to susceptibility changes at the glass-water interface and the imperfections of the gradient field do not affect quality of the Z- spectra as illustrated in Figs. 2d and 2e which show a 1D profile taken from the creatine phantom. Fig. 3 shows Z-spectra from all three phantoms with increasing saturation times. For protons with a relatively slow exchange rate, such as those in creatine, a distinguishable peak around 1.9 ppm can be clearly seen; for faster exchangeable protons in myo-inositol, a shoulder appears around 1.5 ppm downfield of water resonance; for very fast exchanging protons, such as the amine protons in glutamate at high pH, only a weak broadening around 2 ppm can be seen for the current saturation time and power. Similar to the QUEST approach, exchange rates can be extracted by fitting the Z-spectra with different saturation times using the coupled Bloch equations. Notice that there is a slight signal loss during each readout period, which is a trade off of the ultrafast method compared to the conventional QUEST approach. Nevertheless, the exchange rate can still be obtained with reasonable accuracy. For example, an exchange rate of 2000 Hz was obtained for myo-inositol by fitting the Z-spectra, which is similar to the value obtained by an independent conventional QUEST measurement (1700 Hz). In addition to extracting the exchange rate, the series of Z-spectra acquired can be used to determine the optimal saturation time, and also be summed to increase the signal to noise ratio of the Z-spectra.

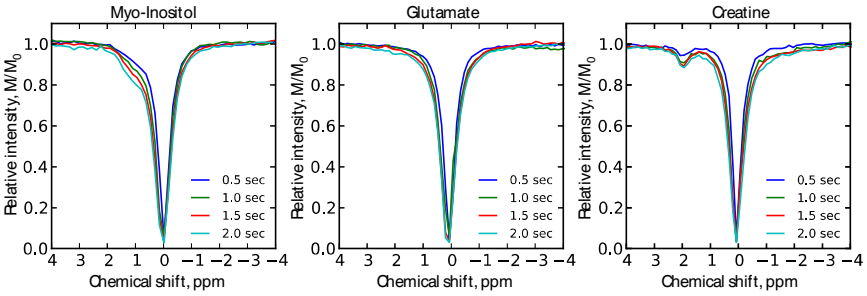

Fig. 3. Z-spectra of phantoms at different saturation times.

Conclusion: We demonstrated that a QUEST type series of Z-spectra can be acquired rapidly for multiple samples by using the ultrafast Z-spectra approach together with EPI. This method offers great potential for high throughput screening of CEST agents.

Reference: [1]. G. Liu, *et al*, *Contrast Media Mol. Imaging*, 2010, 5, 162; [2]. S. D. Swanson, *J. Magn. Reson*, 1991, 95, 615; [3]. X. Xu, *et al*, *Angew. Chem. Int. Ed*, 2013, 52, 8281; [4]. J. Dopfert, *et al*, *J. Magn. Reson*, 2013, 237, 34; [5]. M. T. McMahon, *et al, Magn. Reson. Med*, 2006, 55, 836. **Funding Support:** RO1 EB015032.