Analyzing the Minimum Discretization of Pulses Required to Speed Up Model-based Analysis for Pulsed CEST

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Introduction: Currently, pulsed chemical exchange saturation transfer (CEST) imaging, which uses multiple short saturation pulses, is the only irradiation scheme possible for clinical application of CEST methods due to specific absorption rate and hardware limitations. However, solving the time-varying Bloch-McConnell equations to describe the signal is time consuming because there is no simple analytical solution, unlike for continuous CEST. This is particularly critical for model-based quantification of CEST data, where multiple iterations are required within an optimization algorithm. The saturated magnetization arising from pulsed CEST has previously been calculated by discretizing each pulse into 64 [1] or 512 [2] intervals using the closed form analytical solution of continuous CEST [3] to propagate the magnetization though each interval, where the final values of one interval serve as the initial conditions for the following one. Since the number of intervals, *N*, correlates linearly to the processing time required, it is important to discretize the pulses into the minimal *N* to speed up the model-based analysis of CEST spectra. In this study, simulations were used to find the minimal *N* required across a range of pulsed parameters, the optimal value was then used to perform model-based analysis on both *in vitro* and *in vivo* data to assess the goodness of fit.

Methods: *Simulation.* Bloch-McConnell equations [3] for a two-pool model (water & amide protons) were used to generate simulated data. Pulse parameters were: Gaussian pulse shape, flip angle (FA) from 60 ° to 300 ° with intervals of 60 °, pulse duration (irradiation pulse + inter-pulse delay, T_{pd}) = 20, 40, 80, 100 and 200 ms, and duty cycle (DC) from 0.3 to 0.8 with 0.1 increments. Saturation was applied from -4.5 to 4.5 ppm with 0.1 ppm increments for a total of 2 s. Crusher gradients were modelled by setting the transverse magnetization to zero at the end of each inter-pulse delay. Each pulse was discretized into 2^n intervals to find the optimal number of intervals required at 3, 4.7 and 7 T, where n = 1 to 10. The computational time required to calculate the spectrum of each discretization using an Intel Xeon CPU E5520 @ 2.27 GHz with 8G of RAM was recorded. The minimal *N* was determined by finding the difference in calculated magnetization between spectra and the reference case of n = 10. The smallest *n* which had normalized root mean square error smaller than 0.1% was selected as the best *N* for that set of pulse parameters. The other parameters used were amide proton exchange rate, C_b = 50 s^{-1}, and proton concentration ratio = 0.0033. The relaxation times were magnetic field dependent, these parameters at 3 T being set to $T_{1a,b}$ = 1.3 [4], 1.5 [5] s, $T_{2a,b}$ = 75 [6], 50 [7] ms, 4.7 T as $T_{1a,b}$ = 1.5 [8], 1.6 s, $T_{2a,b}$ = 60 [8], 40 ms and 7 T as $T_{1a,b}$ = 1.7, 1.7 s, $T_{2a,b}$ = 48, 33 ms [7].

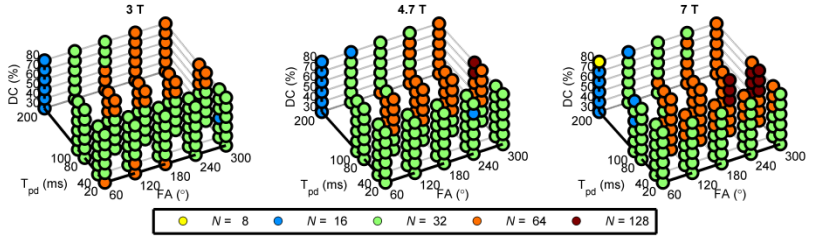

Fig. 1: Minimal *N* found for different combinations of pulsed parameters for 3, 4.7 and 7 T.

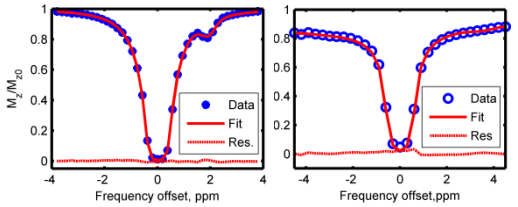

Fig. 2: Fitted spectra of 125mM phantom at pH 6 (left) and white matter of subject 1 (right). The line (Res) below the spectrum is the residual.

In vitro: Tissue-like creatine phantoms with different combinations of concentrations (100 and 125 mM) and pH values (5.5, 6 and 6.5) were prepared. The CEST experiment was performed using a 4.7 T Varian DirectDrive™ spectrometer (Varian Inc.), with matrix size of 64 x 64, slice thickness of 1 mm and TR/TE = 15000/20 ms. The phantoms were saturated by Gaussian pulses, which had FA = 180 °, T_{pd} = 40 ms and 50 % DC each, for a total of 2s. Saturation was applied from -3.8 to 3.8 ppm with increments of 0.19 ppm. CEST data were acquired in 5 min 37 s. MATLAB (Mathworks, Natick, MA,USA) was used for the voxel-wise model fitting using a 3-pool model (water, amide and MT) and the pulses were discretized using the *N* found from simulation.

Table 1: Coefficient of Determination, R^2 (%) mean ± standard deviation

Phantom	pH 5.5	pH 6.0	pH 6.5
100 mM	99.82 ± 0.2	99.93 ± 0.05	99.87 ± 0.07
125 mM	99.94 ± 0.05	99.92 ± 0.06	99.9 ±0.06
Human	Subject 1	Subject 2	Subject 3
WM*	99.13 ± 2.1	99.66 ± 0.53	99.77 ± 0.55
GM*	97.93 ± 3.76	99.24 ± 1.71	99.55 ± 1.54
* WM / GM refers to the white / grey matter			

In vivo: Three healthy subjects were scanned at 3 T (Siemens Verio®) under a development protocol approved by the local ethics committee. Single-slice transverse imaging was performed mid brain with matrix size of 80 x 80, slice thickness of 5 mm and TR/TE = 4000/26 ms. Saturation was achieved using Gaussian pulses with the properties same as the *in vitro* study from -4.5 to 4.5 ppm with 0.3 ppm increments, resulting in 32 volumes (plus a no saturation scan) in 2 min 55 s. The acquired CEST spectra were fitted voxelwise to a 3-pool model using a probabilistic algorithm [9]. Each Gaussian pulse was discretized into the optimal *N* found using the stimulation.

Results: Fig. 1 shows the minimal *N* required for different pulse parameters under different field strengths. The largest discretization required was 64 for 3 T and 128 for 4.7 and 7 T. For the set of pulsed parameters used in the phantom and human study, 32 intervals per pulse were the optimal. Fig. 2 is the fitted spectra for the *in vitro* and *in vivo* data, respectively, excellent fits were found using the optimal *N*. The coefficients of determination, R^2, for the fitted spectra are given in table 1, all the data were fitted very well (mean R^2 > 97.9 %) using the optimal *N* found.

Discussion: From the results shown, 32 intervals per pulse were sufficient to generate accurate simulated spectra for fairly typical CEST experimental protocols. This result is especially important when quantifying the important parameters such as amide proton exchange rate using model-based analysis, as it will result in a substantial reduction in computational cost. The computation time required to calculate a spectrum using 512 intervals per pulse was roughly 16 times (9.8 min/0.629 min) longer than 32 intervals per pulse and 8 (9.8 min/1.25 min) and 4 (9.8 min/2.483 min) times longer than the largest discretization needed for 3 T and the higher (4.7 and 7 T) field strengths, respectively. When model fitting, which requires iterative calculation of the magnetization, is applied, the amount of processing time saved using the smaller number of intervals will thus be significant. Furthermore, irradiation time should typically be greater than five times the longitudinal relaxation time to achieve steady state in a CEST experiment [3], resulting in a larger number of pulses needed; thus, it is essential to discretize the pulses into the smallest possible *N* for efficient processing.

References: 1. Sun *et al.*, MRM 66: 1042-48, 2011. 2. Desmond *et al.*, MRM in press. 3. Woessner *et al.*, MRM 53:790-799, 2005. 4. Wright *et al.* MRM PHY 21: 121-130, 2008. 5. Ethofer *et al.* MRM 50: 1296-1301, 2003. 6. Barker *et al.* MRM 45: 765-769, 2001. 7. Jones *et al.* MRM in press. 8. Zhou *et al.*, Nat. Med. 9:1085-1090, 2003. 9. Chappell *et al.*, 19th ISMRM, p. 4490, 2010.