CEST Sensitivity Functions Based Sampling Schedule

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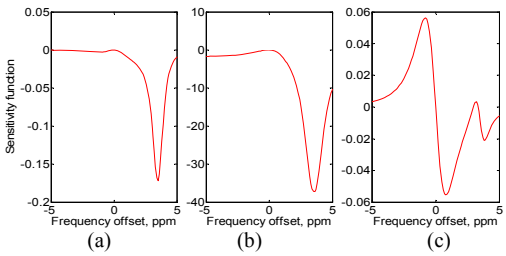
Introduction: Chemical exchange saturation transfer (CEST) provides an indirect way of measuring the presence of mobile proteins and peptides with only millimolar concentration *in vivo* through a change in the water signal intensity. The exchange rate of the amide protons, C_{ba}, has been found to be correlated to the intracellular pH [1] the measurement of which may provide a means of assessing tissue at risk of infarction in ischemic stroke [2]. Quantitative measures of C_{ba} can be obtained by sampling the z-spectrum over a range of saturation frequencies and then using model fitting [3]. However, the evenly distributed sampling schedule (EDS) normally acquired consists of samples that are minimally informative for the parameters of interest. For example, C_{ba} changes mainly affect saturation frequencies near the chemical shift for amide protons at 3.5 ppm [4]. In order to obtain more accurate C_{ba} estimates and sufficient signal-to-noise ratio, an unevenly distributed sampling schedule (UDS) [5] has been designed to place more acquisitions at and around ± 3.5ppm. In this work, we design an optimal sampling strategy (OSS) using an approach previously applied to magnetization transfer imaging [6] and arterial spin labelling [7]. The OSS saturation frequencies are chosen based on the sensitivity functions for the parameters of interest to maximize the useful information in the spectrum. The proposed OSS is compared with EDS and UDS on simulated data to assess the theoretical improvement that can be gained.

Theory: The analysis of CEST spectrum involves the minimization of a cost function on the error between model prediction and the data. The principle behind optimal design is to minimize the variance associated with the parameter estimates. Typically, a cost function comprising the sum-of-squared errors is used. Under this cost function, the variance of the parameters is given by the Hessian matrix, $\boldsymbol{H}$ containing terms [7]:

$$H_{jk} = \sum_{i=1}^{N} \left[\frac{\partial \boldsymbol{M}(f_i;\boldsymbol{p})}{\partial p_j} \frac{\partial \boldsymbol{M}(f_i;\boldsymbol{p})}{\partial p_k} \right],$$

where $\boldsymbol{M}(f_i;\boldsymbol{p})$ is the chosen model as a function of the sampling parameters, $\boldsymbol{p}$; and f_i is the i sampling point: saturation frequency in this case. The differential terms (with respect to each parameter) represent sensitivity functions. The aim of OSS is to choose $\boldsymbol{f}$ (a vector of saturation frequencies) such that this variance is minimized. The D-optimality criterion is used whereby the OSS maximises the determinant of $\boldsymbol{H}$.



(a) (b) (c)
Fig.1: Sensitivity functions of (a) C_{ba}, (b) M_{b0} and (c) W_a.

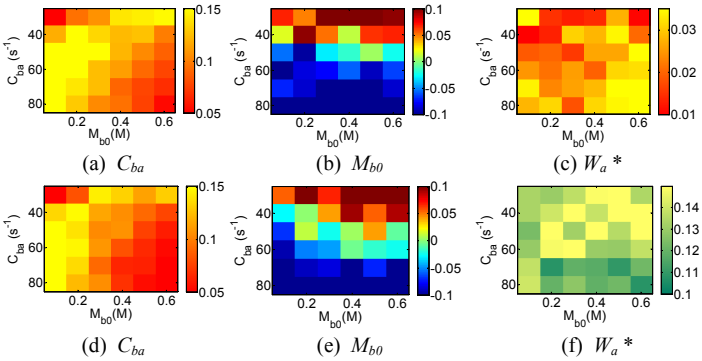
Table 1: Proposed OSS. NA - number of acquisitions.

Offset(ppm)	NA	Offset(ppm)	NA
-1	2	3.6	8
-0.9	8	3.7	2
-0.8	13	4	6
-0.7	8	4.1	11
-0.6	2	4.2	10
3.3	2	4.3	5
3.4	9	4.4	2
3.5	13	**Total**	**101**

Methods: The CEST spectrum was modelled using the Bloch-McConnell equations [4] and three parameters were chosen for which the variances were to be minimized. Alongside C_{ba}, the concentration of amide protons, M_{b0} was included because these both affect the magnitude of the CEST effect, but only C_{ba} is related to pH. Optimization was also performed for the water centre frequency offset, W_0, since it is necessary to account for shifts in this due to B_0 field inhomogeneity [8]. An OSS was generated starting from an EDS with saturation frequency offsets from -5 to 5 ppm (0.1 ppm increments; 101 points in total) using the iterative searching algorithm of [7]. This was performed for multiple combinations of 'true' values for the parameters sampled from plausible distributions of their values which were taken to be Gaussian with the following means and standard deviations (STD): C_{ba} (50 ± 20 s^{-1}), M_{b0} (0.3 ± 0.2 M) and W_0 (0 ± 0.5 ppm). The remaining terms used in the simulation were defined according to [4], assuming a 3T scanner was used: T_{1a} = 1.3 s, T_{2a} = 0.07 s, T_{1b} = 0.77 s, T_{2b} = 0.01 s, T_{sat} = 15 s, B_1 = 42.6 Hz, M_{a0} = 100 M.

Simulated Data: In order to validate the approach theoretically, simulated spectra were generated for a range of C_{ba} and M_{b0} values (C_{ba} varies from 30 to 80 s^{-1} and M_{b0} changes from 0.1 to 0.6 M, which is equivalent to 0.001 to 0.006 for the proton concentration ratio, M_{b0}/M_{a0}). 1000 datasets were created for each simulated spectrum by adding white noise with STD equal to 5% of the unsaturated signal. The noisy simulated data were then fitted to a 2-pool model (water and amide protons) sampled by OSS, UDS or EDS using a non-linear least squares method with lower and upper bound for C_{ba}, M_{b0} and W_0 equal to [5 100] s^{-1}, [0.05 1] M and [-0.2 0.2] ppm, respectively. The coefficients of variance (CV) of the fitted parameters for each sampling scheme were calculated and the performance of each sampling scheme was compared by finding the difference in CV. Since there were only 59 sampling points for UDS within the investigated frequency range [5], the number of sampling points for OSS was reduced to match it when the performance of them was compared.

Results: Figure 1 shows the sensitivity functions of the investigated parameters. The sensitivity functions of C_{ba} and M_{b0} have the highest magnitude at 3.5 ppm (chemical shift of amide protons). W_a was found to be most sensitive around ± 0.8 ppm. The CEST OSS found is listed in Table 1. Figure 2 is the performance comparison of the different sampling schemes with W_a = 0.1 ppm. OSS performed better than EDS and UDS in finding the C_{ba} and W_a. OSS had better estimations for M_{b0} only at lower values of C_{ba}. Improvements by OSS over EDS were generally larger than over UDS, reflecting the greater accuracy of UDS except for W_0, reflecting the lack of samples in UDS near 0 ppm (no sampling point at 0.1 ppm).



(a) C_{ba} (b) M_{b0} (c) W_a *
(d) C_{ba} (e) M_{b0} (f) W_a *
Fig. 2: Difference in simulated CV between OSS vs EDS (top row, (a) – (c)) and OSS vs UDS (bottom row, (d) – (f)). $CV_{EDS\ or\ UDS}$ minus CV_{OSS}, where positive values indicate OSS performs better than its counterpart. (*The scale is different.)

Discussion: An OSS has been designed that offers more accurate quantification of amide proton exchange rate than either EDS or UDS. Validation using phantoms is required to assess the performance of the different sampling scheme in practice. It is well established that accurate independent quantification of C_{ba} and M_{b0} is difficult from CEST data because they have similar effects upon the spectrum [9]. It has been proposed that samples at multiple B_1 saturation field strengths could be employed to improve the estimation [9]. A further extension of this work will, therefore, be to extend the OSS to two-dimensional problem in both saturation frequencies and field strengths.

References: 1. Zhou *et al.*, Nat. Med. 9:1085-1090, 2003. 2. Sun *et al.*, JCBFM 27:1129-1136, 2007. 3. Sun *et al.*, JMR 175:193-200, 2005. 4. Woessner *et al.*, MRM 53:790-799, 2005. 5. Wen *et al.*, NeuroImage 51:616-622, 2010. 6. Cercignani *et al.*, MRM 56:803-810, 2006. 7. Xie *et al.*, MRM 59:826-834, 2008. 8. Sun *et al.*, MRM 58:1207-1215, 2007. 9. Sun *et al.*, JMR 202: 155-161, 2010.