Optimal Design of Pulsed ASL Sampling Schedules

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Introduction: Quantitative measurement of CBF typically requires multiple inversion times to be sampled to yield precision, requiring a sampling scheme to be devised. Optimal Sampling Schedule (OSS) theory [1] has been used in model-based physiological and pharmacological experimental design of nuclear medicine tracer kinetic studies and to clinical trial studies, as it can improve the precision of parameter estimation from experimental data, and provides a formal framework for optimally selecting a limited number of samples. Here we apply the OSS strategy to Pulsed ASL experiment design. We then assess the advantages of using OSS to determine an optimal sampling schedule over a more standard evenly distributed sampling schedule (EDS). These sampling schedules are assessed with simulated and experimental data, in the latter case by using a test and re-test study design.

Theory: The principle behind optimal design is to minimize the variance associated with particular parameter estimates. The D-optimality criterion [2] was adopted in our PASL OSS design to optimize the distribution of TI sampling points. This is accomplished by maximizing the determinant of the Fisher information matrix, which in this context is equivalent to the Hessian matrix. The Hessian matrix is defined as:

$$H_{jk} = \sum_{i=1}^{N} \frac{1}{\sigma_i^2} \left[\frac{\partial y(t_i;\bar{P})}{\partial p_j} \cdot \frac{\partial y(t_i;\bar{P})}{\partial p_k} \right]$$

where $y(t_i;\bar{P})$ denotes the PASL standard kinetic model [3], which is a function of inversion time t_i and the parameter vector $\bar{P}$=[Δt, *f*] (*f*=CBF, Δt=tag transit time); and σ_i^2 is the variance of the measurement noise at t_i. From previous experiments, the within-TI variance of noise was observed to increase linearly with increasing TI. This effect has been included in our calculation. We also assume that the tag width (τ) is experimentally determined using a technique such as QUIPSS II [4]. An iterative search algorithm was developed to maximize the determinant of the Hessian matrix, against all possible sampling schedules, assuming a particular pair of 'true' *f* and Δt values. Under these assumptions, OSS suggests an optimal sampling strategy of only two locations (TI=Δt and TI=Δt+τ) in the proportion 48:52. By then assuming a physiologically plausible Gaussian distribution of *f* (0.012±0.004s^{-1}, i.e. 72±24 ml/100g/min) and Δt (0.7±0.3s) values for the population as a whole, we obtained a probability distribution of sampling points (bins in Fig. 1). We then divided the probability distribution into *N* equal parts to obtain an OSS with *N* TI sampling points. This is compared with an EDS also with *N* points.

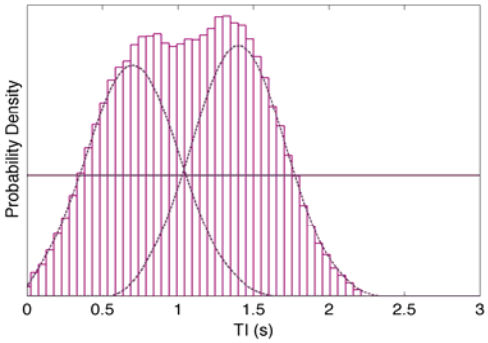

Figure 1: Probability Distribution of OSS *(bins)* and EDS *(horizontal line)*

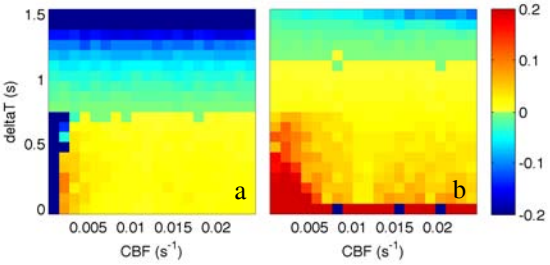

Figure 2: Difference in simulated Coefficient of Variance between OSS and EDS for CBF (a) and Δt (b) estimates. CV_{EDS} minus CV_{OSS} (positive values indicate where OSS performs better than EDS).

Simulated Data: To validate the approach theoretically we selected 400 pairs of *f* and Δt in a 2D parameter space as 'true' values (see Fig. 2 for range). Experimentally plausible Gaussian-distributed noise was added to the theoretical data for 1000 repeats to produce 1000 sets of simulated measurement data for each pair of true values. The simulated data were then fitted to the standard ASL kinetic model, sampled using either the OSS or EDS sampling schemes. The coefficients of variance (CV) of the fitted parameters for OSS and EDS were calculated for each *f*-Δt pair. Fig. 2 shows the CV difference images for *f* and Δt (EDS−OSS).

Experimental Data: 6 healthy volunteers (4 female, 2 male, age 20-28) were scanned using a Siemens 3T TIM Trio system fitted with a single-channel T/R head coil. 5 axial slices (4×4×6mm voxels) were acquired, positioned such that the middle slice intersected the thalamus. A GRE-EPI QUIPSS II [4] PASL sequence was used, with TR/TE = 3200/23ms and a variable TI according to either the OSS or EDS schemes. Test and re-test runs were performed for both OSS and EDS in all subjects, with the run order counterbalanced across subjects. Each run lasted ~11 minutes. OSS had 100 sampling points calculated theoretically using the method presented above. EDS contained 100 sampling points evenly distributed between 150ms and 3s. The order of the 100 TIs for EDS and OSS were randomized to reduce sensitivity to small CBF drift. Each slice took 53ms to acquire. The timings were adjusted to ensure that the middle slice was acquired at the specified TIs.

Using Matlab, data were fitted to the ASL kinetic curve voxel-by-voxel within a grey matter mask. Pearson Correlation Coefficients (PCC) between the parameter estimates for test and re-test runs were calculated for each subject. A non-parametric Kruskal-Wallis test was used to compare the PCC values between OSS and EDS.

Results and Discussion: CBF reproducibility is not predicted to be significantly altered by use of OSS or EDS (Fig. 2a), a result borne out by the experimental PCC estimates (indeed Fig. 3a shows marginally improved reproducibility for EDS for the middle slice, KW p=0.117, and similar performance between EDS and OSS in the other slices, KW p=0.347). The reproducibility for Δt estimation is predicted to be improved by use of OSS over a wide range of *f* and Δt values (Fig. 2b). This is observed in the experimental PCC values (Fig. 3b, KW p=0.028 for middle slice, KW p=0.9168 for the first slice, KW p=0.1172 for the second slice, and KW p=0.009 across the most superior two slices). Experimental results showed good agreement with theoretical simulation, indicating an improvement particularly in Δt estimation. OSS was observed to improve the reliability of parameter estimates, especially in the superior slices. Since the maximum TI is about 2.3s in OSS, versus 3s in EDS, the information per unit time could potentially be improved by using a TR that varies with the TI (subject to tag replenishment requirements). The OSS approach can also be applied for optimization of more than two parameters, e.g. when the bolus width τ is not fixed. In this work, we optimized for both CBF and Δt estimates. In a study where CBF is the primary parameter of interest, OSS could be designed for CBF optimization alone (at the expense of precision in Δt).

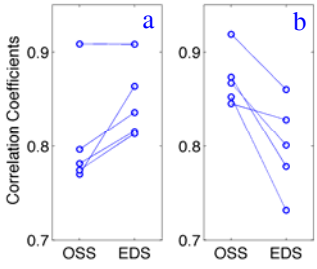

Figure 3: PCC values of CBF (a) and Δt (b) estimated from test and re-test matrices for the middle slice. One subject's data was discarded due to significant artefacts.

Conclusion: In conclusion, we have demonstrated that OSS provides a logical strategy for choosing an otherwise arbitrary TI sampling scheme.

References: [1] DiStefano, Am. J. Physiol. 1982 24:531-534; [2] Li *et al*, CMPB 2001 65:45-59; [3] Buxton *et al*, MRM 1998 40:383-396; [4] Wong *et al*, MRM 1998 39(5) 702-8;