Estimation Efficiency and Bias in ASL-based functional MRI: Frequency Response of Differencing Strategies

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Introduction

Recent improvements in Arterial Spin Labeling techniques have made perfusion based fMRI a practical tool in the study of brain function. Subtraction of tag/control pairs yields ASL noise which is whiter than standard BOLD noise, but which is sensitive to the specific subtraction technique used for obtaining the perfusion weighted images from the raw ASL images [TEN1](1,3,6). ASL data analysis has been examined in terms of a general linear approach by Liu et al (2), who pose a general linear models (GLM) for control and label data. We also pursue a GLM approach, but just consider a single model $\mathbf{Y=X\beta+\varepsilon}$ which embeds the tag/control modulation in the design matrix X, allowing for a generic differencing with $\mathbf{DY=DX\beta+D\varepsilon}$. The differencing approach is specified by the contents of the matrix **D** (2). This approach permits the consideration of no differencing at all. Building the differencing into the model, instead of a filter, preserves more data. Our focus is on the efficiency of parameter estimation, as efficiency is monotonically related to statistical power. In order to understand our results, we examined the frequency response of the differencing strategies to ASL signals, white and auto-correlated noise.

Methods

TurboCASL perfusion fMRI time series (N=258 samples, 500 realizations, TR=1.4 sec) were simulated consisting of random ISI events (uniform distribution, 5<ISI<12sec.), fixed ISI events (ISI=20sec). AR(1) noise was added to the simulated data. These perfusion series were "sampled" according to TurboCASL schemes (TR=1.4s) and differenced. A general linear model was generated as illustrated in figure 1 (first 50 points only). The model's Parametes estimates from were calculated from the un-subtracted data (Method 1) as well as the "pairwise subtraction" (Method 2) and "running subtraction" (Method 3) schemes. The efficiency of those estimates was calculated as the inverse of the standard deviation of the estimates over the simulations. The bias was calculated as the absolute % difference between truth and estimated value. The frequency response of the pairwise subtraction and the running subtraction were derived using digital signal processing theory and applied to white, 1/f noise and AR(1) noise and confirmed through numerical simulations. The differencing schemes were also applied to experimental time courses containing active and non-active voxels. We used two coil turboCASL (4) time series data collected from a finger tapping event related experiment (ISI=18 sec, 360 sec. duration, TR=1.4 sec.). Active voxels were identified by correlation analysis, and time courses (length = 258 points) were extracted from 87 active voxels, and from 87 non-active voxels in the frontal lobe.

Results: Table 1 shows the calculated estimated efficiencies in each of the three methods expressed relative to pairwise subtraction. It should be noted that the running subtraction differencing approach produces more efficient estimation of the model parameters and the least bias. This is consistent with the predicted effects of the differencing schemes on the frequency spectrum of data (see figure 2). Note that the effect of alternating the control and tagged images is akin to modulation by the nyquist frequency, effectively pushing the paradigm's energy to the higher frequency range in the spectrum. The theory and simulations show that the un-differenced and running subtraction methods preserve the high frequency content of the data without aliasing. Running subtraction has the added benefit of removing the majority of the autocorrelated noise. Sinc subtraction was also considered and found to yield similar results to pairwise subtraction with variations depending on the interpolation kernel's characteristics (not shown).

Table 1.
Relative Estimation Efficiency and Bias of the three differencing methods.

	Efficiency (rel. units)	Mean Bias
I. No Differencing	1.31	45%
II. Pairwise subtraction	1.0	57%
III.Running subtraction	1.33	42%

Figure 1.
Design Matrix

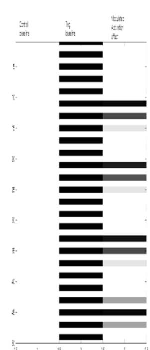
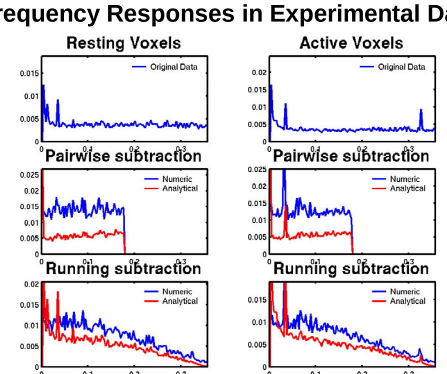


Figure 2.
Frequency Responses in Experimental Data



Discussion: In contrast to the white noise found with pairwise differencing, our work requires autocorrelation estimation for accurate intrasubject inference. However, it should be noted that group inferences do not require intrasubject variance estimates, as a combined between and within subject variance estimate is made implicitly at the second level (5). Hence intrasubject parameter efficiency, and not intrasubject variance estimation, should be the primary concern in group inference based on ASL data.

References: (1) Aguirre et al, Neuroimage 15, 448-500, 2002, (2) Liu et al: Neuroimage 16, 269-282, 2002 (3) Wang et al: Neuroimage 19, 1449-1462, 2003 (4) Hernandez et al, MRM 51(3), 577-585, 2004 (5) Holmes & Friston, NI 7(4(2/3)), S754, 1999 (6) Liu: Neuroimage, in press, 2004.

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