Robust, unbiased general linear model estimation of phMRI data in the presence of variance in the temporal response profile

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Introduction: Pharmacological MRI (phMRI) allows the detection of direct effects of an administered drug on brain function [1,2]. This approach can help elucidate brain circuits underlying pharmacological action and provide a translatable, pharmacodynamic biomarker of CNS activity for novel compounds in the early phases of drug development. As applications increasingly shift to compounds whose direct effects on brain activity may be more subtle – including new chemical entities and novel target profiles – there is increasing demand on accurate and robust estimation of the phMRI signal [3,4]. Here we address the question of modeling phMRI data in the presence of variations in the temporal response within the general linear model (GLM) framework. If not properly accounted for, variability in signal time courses results in a large bias and uncontrolled increase in variance for the contrast of interest. We present a simple method to generate parsimonious design matrices and ensure low values of an objective function capturing the bias-variance decomposition over expected yet uninteresting variation in temporal profile.

Method: For a given signal model, the steps in computing the design matrix are as follows (see Fig. 1): (a) Construct a matrix whose columns contain (i) the signal model regressor, (ii) additional regressors such as drift terms, and (iii) vectors, based on (i), encompassing a range of expected variation in the model. (b) Orthogonalize each of (1.iii) to the model function 1.i (2.iii). (c) Calculate the singular value decomposition (SVD) of (2.iii). The final design matrix is given by (1.i, 1.ii) with additional columns given by the first *n* SVD components (rank-*n* approximation to (2.iii)).

We illustrate the method with a real example in which the opioid analgesic buprenorphine (0.2mg/70kg i.v., healthy male volunteers, N=10) or its vehicle saline was infused over 12min during a 25min BOLD phMRI scan in a two-way crossover design. The signal model derived from the infusion paradigm comprised a 12min ramp from baseline to a post-injection plateau. In addition to possible linear drift, temporal delays in the onset of the phMRI response were anticipated. The latter were modeled by including successive temporally shifted versions of the regressor in the input design matrix (Fig. 1(a)). The resulting design matrix (Fig. 1(a-i,ii and c) was evaluated using simulated signals (SNR=2,5,10,15) where the true underlying signal amplitude was known and also applied to the *in vivo* buprenorphine phMRI data.

Results: The first two components of the SVD of anticipated variance are shown for our worked example in Fig. 1(c). The first component can be thought of as a generalization of the temporal derivative (shown as dashed line for reference). Indeed, for this and other model function profiles, the first SVD component approaches the temporal derivative as a limiting case as the modeled delay decreases.

Simulations confirmed that the GLM estimation, for signals with onset delay up to that modeled, is robust and accurate in the presence of both drift and onset variation using design matrices generated with this method. Furthermore, we confirmed that a function capturing simultaneously the bias and variance of the estimated signal amplitude is reduced substantially over the range of modeled potential delays (Fig. 2(A)). Application to the *in vivo* data showed an increased sensitivity to drug effects in key pain modulation regions including the insula (Fig. 2(B)).

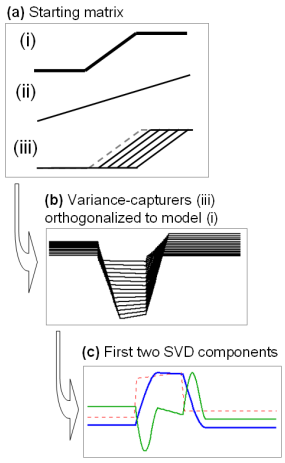

Fig. 1: Construction of design matrix, illustrated for anticipated variation in signal onset.

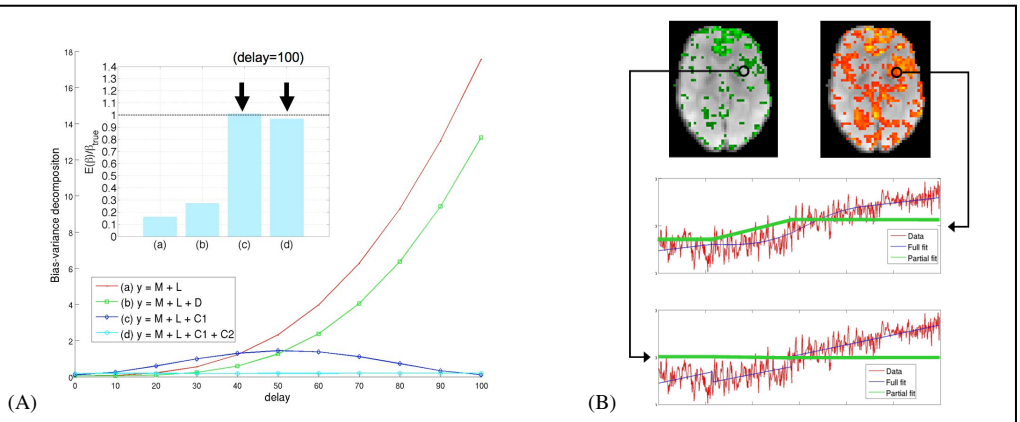

Fig. 2: (A) Estimated bias-variance tradeoff (ideally zero) for delays up to the 100 time points modeled, for design matrices without (a,b) and with (c,d) components generated using the proposed method (SNR=5). [Abbreviations: *M*=model, *L*=linear drift term, *D*=temporal derivative, *C1*,*2*=SVD components.] *Inset*: improved accuracy in signal amplitude estimates in the presence of drift using proposed method. **(B)** Use of optimized design matrix yields robust estimate of response amplitude and improves detection of drug effect in the insula. Green overlay (bottom time course) = M + L + D model; Red overlay (top time course) = M + L + C1 + C2 model.

Discussion: We have described a straightforward method based on an SVD across expected signal variations to generate phMRI design matrices that are "optimal" in the sense of (a) estimating the contrast of interest with a small bias and (b) maintaining the estimate of variance to be approximately unbiased. Presented here for a specific worked example, the framework is quite general and can be applied to different contrasts, model functions and expected variation (e.g., variation in response shape of peaked bolus responses). This approach should prove useful in robust and accurate mapping of drug-induced signal changes in phMRI data.

References: [1] Chen YI *et al.* (1997) *Magn. Reson. Med.* **38**(3) 389; [2] Becerra L *et al.* (2006) *Pain Med.* **103**(1) 208; [3] Schwarz AJ *et al.* (2007) *J Neurosci Meth* **159**(2) 346; [4] Liu C *et al.* (2008) *NeuroImage* **34**(3) 1042.