Testing whether the brain flow-metabolism coupling ratio is the same for two different stimulus responses without a calibration experiment

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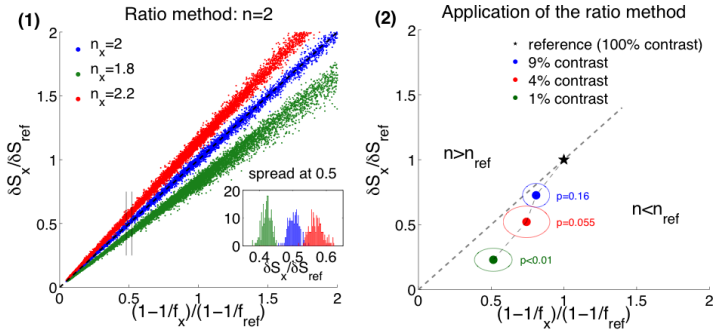
Audience: Those studying coupling of cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen ($CMRO_2$).

Purpose: Brain activity is a highly energetic process necessitating the metabolism of oxygen for the production of ATP, with CBF supplying the necessary metabolites including oxygen. Yet the coupling ratio *n* of CBF and $CMRO_2$ responses is neither constant nor simple and instead varies depending on factors that include stimulus type [1-2] and subject state [3-4]. Current calibrated BOLD studies to test the variability of *n* rely on the Davis model [5] to analyze combined BOLD and CBF signals, yet we recently found that the complexity of the mathematical form of the Davis model tends to obscure an underlying simplicity [6]. This led us to propose a simpler heuristic model of the BOLD response [7] that has comparable accuracy to the Davis model when tested with a much more detailed BOLD signal model. Importantly, within this model the BOLD signal is a pure nonlinear function of CBF scaled by a lumped factor that includes the CBF/$CMRO_2$ coupling ratio *n*. Inspired by the mathematical form of this model, we propose here a simple and straightforward "*ratio method*" to test whether the CBF-$CMRO_2$ coupling ratio *n* is the same for two different stimulus responses using only combined CBF and BOLD measurements, independent of model parameters, and without a calibration measurement. The ratio method was tested using a full detailed BOLD model (DBM) [6] and then applied to data from a recent study of visual stimulus contrast [1].

Methods: We previously presented the simple heuristic model for analyzing combined BOLD (δS) and CBF (*f*) data: $\delta S = M\left(1-1/f\right)\left(1-\alpha_v-1/n\right)$ (Eqn. 1) [7]. Because the flow response term is separate from the term containing the coupling ratio *n*, we can use Eqn. 1 to directly compare whether two stimulus responses have the same flow-metabolism coupling. To do so, we first create a null hypothesis that *n* is the same for two stimulus types. Setting one of the responses as a reference ("ref") and taking the ratio of Eqn. 1 for the two stimulus responses produces a simple ratio of BOLD and the flow terms: $\delta S_x \big/ \delta S_{ref} = \left(1-1/f_x\right) \big/ \left(1-1/f_{ref}\right)$ (Eqn. 2). This method assumes that α_v remains constant between the two stimulus responses and that the responses are being compared across the same region of interest and from the same baseline state so that *M* remains constant. However the exact values of *M* and α_v are not needed (i.e., the ratio in Eqn. 2 is independent of the model parameter values when *n* is the same). Differences in *n* can easily be detected using a sign rank test or similar statistical analysis. To test the accuracy of this new method, we employed the DBM to simulate BOLD and CBF responses for a reasonable range of physiological and imaging parameters at 3T: baseline blood volume (CBV) fraction=0.03-0.07 with the arterial fraction=0.15-0.25 and venous fraction=0.3-0.5, constants relating total CBV to CBF=0.25-0.55 and venous CBV to CBF=0.1-0.38, hematocrit=0.37-0.5, resting oxygen extraction fraction=0.3-0.5, fraction of O_2 desaturation occurring prior to capillaries=0-0.2, resting extravascular signal decay rate=20-28 s^{-1}, intravascular to extravascular spin density ratio=1.15, and echo time=32ms. A reference data set with n_{ref}=2 was produced and test cases considered were n_x=1.8, n_x=2 and n_x=2.2. These are all typical values for fMRI activation experiments [1-6, 8-9]. We also used this method to re-examine published combined BOLD and CBF data associated with changes in visual stimulus contrast [3].

Results: Simulations by the detailed BOLD model testing the ratio method (Eqn. 2) show that when the coupling parameter differs between the sets of data, a plot of the BOLD response ratio versus the nonlinear CBF response ratio deviates from the identity line with the deviation growing as the difference in *n* grows (Fig. 1). The inset histograms show that even at smaller BOLD and flow ratios there is good separation between the data, which was taken from between the black lines around a non-linear flow ratio of 0.5. Applying this model to experimental data examining the effect of diminishing contrast of a visual stimulus, we find that lower levels of contrast produce smaller coupling ratios. Specifically using a sign rank test to compare the BOLD and CBF ratios, 1% contrast was found to be significantly different than 100% contrast ($p<0.01$) implying that the CBF response is smaller relative to the $CMRO_2$ response for 1% contrast versus 100% contrast. These results are consistent with those in the published paper with the difference at 4% contrast trending toward significance [1].



Discussion: Separation of blood flow and coupling parameter terms in the heuristic model make it uniquely suited to comparing *n* between stimulus responses. Here using the detailed model of the BOLD response, we show that the heuristic model and ratio method (Eqn. 2) predict a definite relationship between the BOLD response ratio and a nonlinear combination of the CBF responses when two stimulus responses produce the same *n* (blue dots, Fig. 1). A significant departure from the predicted ratio indicates variation in *n*.

Conclusions: The ratio method (Eqn. 2) is a straightforward and effective approach for comparing stimulus responses using only measured BOLD and CBF signals in order to explore the variability of CBF-$CMRO_2$ coupling without the added complexity of a calibration experiment, although such an experiment is required to determine absolute values of *n*.

References: [1] Liang et al., NIMG 64:104, 2013. [2] Lin et al., MRM 60:380, 2008. [3] Griffeth et al., NIMG 57:809, 2011. [4] Moradi et al., NIMG 59:601, 2012. [5] Davis et al., PNAS 95:1834, 1998. [6] Griffeth and Buxton, NIMG 58:198, 2011. [7] Griffeth et al., ISMRM 2012, #2910. [8] Hoge et al., MRM 42:849, 1999. [9] Stefanovic et al., NIMG 22:771, 2004.