Modeling the Effect of Changes in Hematocrit, O_2 Extraction Fraction, and Blood Volume Distribution on the BOLD Signal and Estimates of $CMRO_2$ Change with a Calibrated BOLD Method

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Purpose: We developed a detailed model of the BOLD response including effects of intravascular and extravascular signal changes, hematocrit (*Hct*), oxygen extraction fraction (*E*), and blood volume distribution to test accuracy of simpler models [1,2] used for the estimation of the cerebral metabolic rate of O_2 ($CMRO_2$) with a calibrated-BOLD methodology.

Background: Calibrated BOLD depends on an accurate model of how the BOLD effect depends on the mismatch between cerebral blood flow (CBF) and cerebral metabolic rate of O_2 ($CMRO_2$). However other factors such as hematocrit, oxygen extraction fraction, and cerebral blood volume (CBV) distribution at rest and with activation also affect the BOLD signal. The original Davis model [1] is widely used, but it assumes CBV changes are uniformly distributed across vascular compartments, and neglects intravascular signal changes and exchange effects as CBV changes. More recent studies suggest that venous CBV changes are smaller than arterial changes [3,4], and that intravascular signal changes and CBV exchange effects can bias estimated $CMRO_2$ [5,6]. Recently, an alternative simple model including these effects was proposed [2]. In both this simple model and the Davis model, a scaling factor (A or M respectively) that is variable between subjects and experiments is measured typically with hypercapnia. This scaling factor absorbs many of the variable factors that affect the BOLD response, and the essential question for the calibrated BOLD experiment is whether these factors also affect the basic mathematical form of the model. We tested this by developing a much more complete BOLD model similar to [7] to simulate hypercapnia and activation data for a specified $CMRO_2$ change. We then tested the accuracy of $DCMRO_2$ estimates by analyzing the synthetic data with the two models where *f* is normalized flow and *r* is normalized $CMRO_2$.

Davis Model:

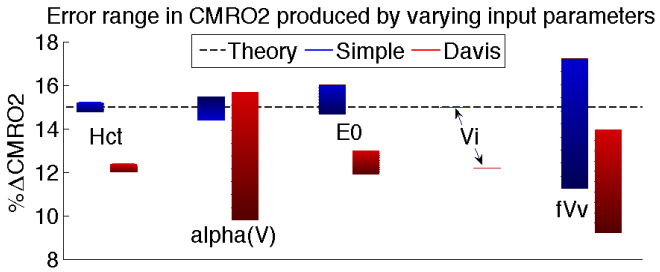
$$\delta S = M\left[1 - f^{\alpha}\left(\frac{r}{f}\right)^{\beta}\right]$$

Simple Model:

$$\delta S = A\left[\left(1 - f^{\alpha v}\frac{r}{f}\right) - \kappa\left(1 - f^{\alpha}\right)\right]$$

Methods: We modeled the intravascular and extravascular components of the BOLD signal and included effects of *Hct*, *E*, arterial O_2 saturation (Y_a), baseline blood volume fraction (V_i), baseline fractional blood volume distribution between arteries (fV_a), capillaries (fV_c) and veins (fV_v), and the venous flow-volume power law relationship described by α_v. With reasonable estimates for the input parameters (*Hct*=0.44, E_0=0.4 [8], Y_a=0.99, V_i=0.047 [9], α_v=0.23 [3], fV_a=0.2, fV_c=0.4, fV_v=0.4 [10]), the variation of the BOLD signal with changes in CBF and CMRO2 was captured by the simple model with parameters α=0.38 [11], κ=0.376 and α_v=0.23. We then compared theoretical data generated as we varied the input parameters *Hct*, E_0, α_v, V_i and fV_v for a CBF increase of 30% and $CMRO_2$ increase of 15% to assess expected errors in $CMRO_2$ estimates produced by the Davis model and simple model.

Results: For the specified base parameters, the Davis model shows a systematic underestimation of $CMRO_2$ from the true value of 15% to 12.18% (18.8% smaller). This is due to the Davis model's reliance on the Grubb parameter α, which assumes that blood volume changes with activation distribute evenly to all compartments. Conversely, the simple model incorporates both an overall a used to account for the change in total deoxyhemoglobin as well as an α_v that models venous CBV changes, assumed to be less than a to describe CBV changes dominated by arterial changes. We examined the effect of varying the following parameters on estimates of $CMRO_2$ by the two models and plotted the results (figure 1): *Hct* (0.38-0.50), α_v (0-0.45), E_0 (0.35-0.60), V_i (0.4-0.55) and fV_v (0.2-0.6, assuming constant fV_a of 0.2 with capillaries comprising the rest of the vascular volume). The parameter most affecting estimates of $CMRO_2$ by both models is fV_v which is associated with increasing the resting venous blood volume distribution. The error ranges are 11.2-17.2% for the simple model and 9.2-13.9% for the Davis model. Increasing α_v similarly has a large effect on the Davis model estimation (9.8-15.7%) and a smaller and inversely related effect on the simple model (15.5-14.4%). Increasing E_0 also has a sizeable but smaller effect on both models (Simple: 14.6-16% and Davis: 11.9-13.0%). *Hct* and V_i have the smallest effects over the ranges studied. Variations due to V_i are quite small as they are likely accounted for in the scaling parameters of the models.



Conclusions: Based on these results, the Davis model systematically underestimates $CMRO_2$ while a simple model incorporating intravascular signal changes and blood volume exchange effects more accurately estimates $CMRO_2$. We suggest focusing experimental effort on determining both resting blood volume distribution and blood volume distribution with activation to provide the most critical data needed for defining the model.

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