Measurement of oxygen extraction fraction (OEF): an optimised BOLD signal model for use with hypercapnic and hyperoxic calibration

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Target audience - Researchers and clinicians interested in brain physiology, cerebral oxygen metabolism and calibrated functional MRI, MR physicists developing models of BOLD fMRI signal.

Purpose - Relative changes in the cerebral metabolic rate of oxygen consumption ($CMRO_2$) can be estimated by exploiting a mathematical model that relates BOLD-fMRI signals to cerebral blood flow (CBF)[1]. Recently, methods[2,3,4] based on hypercapnia and hyperoxia have been developed to estimate absolute $CMRO_2$. Here we empirically optimize a BOLD signal '*calibration model*'[4], through a simulation study, to produce a '*simplified calibration model*' that aims to improve our ability to estimate oxygen extraction fraction (OEF) and therefore absolute $CMRO_2$ from experiments using manipulation of CO_2 and O_2 levels.

Methods - A set of synthetic BOLD signals was created using a detailed BOLD model[5] to simulate a variety of experiments (respiratory task designs) at 3T, in which CBF was elevated by hypercapnia and arterial oxygen content was elevated by hyperoxia. We have previously performed similar experiments for the measurement of $CMRO_2$[4]. A wide range of underlying physiological conditions was simulated varying the parameters input to the detailed model: baseline cerebral blood volume ([0.5 10.5] ml/100g), baseline cerebral blood flow ([23 83] ml/100g/min), baseline oxygen extraction fraction (OEF_0, [0.29 0.56]) and haematocrit ([0.31 0.53]). For each respiratory task design 1000 BOLD signals were generated with different combinations of these underlying physiological parameters. The analysis focused on the optimization of two parameters from the calibration model (Eq. 1), α and β, that produced the best agreement when this model was fit to the simulated data. Two metrics were used to evaluate the agreement: (1) the sum of squared residuals (RSS) calculated between the generated BOLD signal and that fitted with the calibration model (the only metrics available in a real case scenario) and (2) the absolute discrepancy between the fixed and estimated values of OEF_0 (dOEF), only available in the simulation environment. These indices were evaluated over the (α,β)-space among all the simulated datasets permitting the assessment of optimal values of (α,β) and the definition of a new empirical calibration model, dubbed the 'simplified calibration model' (Eq. 2), with the optimal parameter θ lumping together the information of α and β. Finally, the synthetic signals were fit using the RSS index (real case scenario) using the simplified model with its optimised θ.

$$\frac{\Delta S}{S_0} = M\left\{1-\left(\frac{CBF}{CBF_0}\right)^{\alpha}\left(\frac{[dHb]}{[dHb]_0}\right)^{\beta}\right\} \quad \textbf{Eq. 1}$$

$$\frac{\Delta S}{S_0} = M\left\{1-\left(\frac{CBF}{CBF_0}\right)^{\theta}\left(\frac{[dHb]}{[dHb]_0}\right)\right\} \quad \textbf{Eq. 2}$$

Results - The analysis of the respiratory task designs shows that the maximum information content in the data is given by respiratory challenges with either simultaneous delivery of O_2 and CO_2 or an interleaved pattern including modulation of CO_2 levels over time. It was shown that α and β are largely collinear when considering only the RSS index (Fig. 1), pointing out the redundancy of the calibration model. Considering also the dOEF index, we were able to cancel out one parameter and to define the simplified calibration model finding an overall optimal $\theta = 0.06$. The real case scenario fitting of the data with the calibration model and literature values of α and β led to inaccurate estimates of OEF_0 and therefore absolute $CMRO_2$, with mean percentage error distributions above 10% (Fig. 2 - A, B). Instead the application of the simplified calibration model with the calculated optimal θ allowed us to accurately assess OEF_0, with error distributions well within the ±5% range (Fig. 2 - C) and to exploit effectively a range of respiratory challenge designs tested.

Conclusions – We propose the simplified model (Eq. 2) as a tool for absolute $CMRO_2$ evaluation in hyperoxic-hypercapnic studies. The simulation framework presented can also be applied to evaluate the most suitable value of θ for new respiratory task designs under the assumption that the detailed BOLD model is sufficiently realistic in simulating BOLD data for the respiratory challenges considered.

References – 1. Davis TL et al., *Proc. Natl. Acad. Sci. USA* (1998), 1834-39 - 2. Gauthier CJ et. al., *Neuroimage* (2012), 1212–25 - 3. Bulte DP et. al., *Neuroimage* (2012), 582–91 - 4. Wise RG et. al., *Neuroimage* (2013) ,135–147 - 5. Griffeth VEM et. al., *Neuroimage* (2011), 198–212

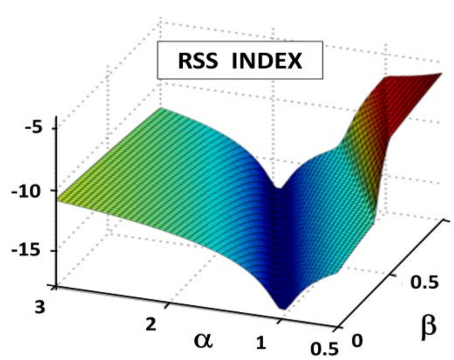

***Figure 1**: Logarithmic values of RSS index show near collinearity between α and β (simultaneous gas design)*

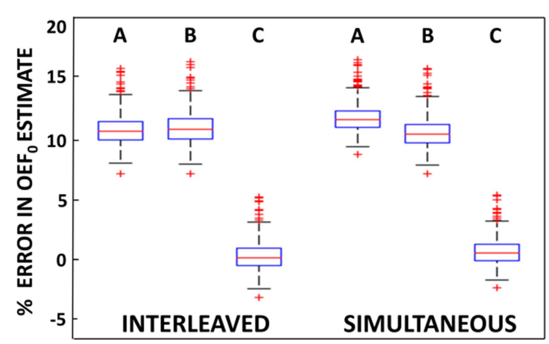

***Figure 2**: Distribution of errors in OEF_0 estimate over all physiological conditions, considering interleaved and simultaneous respiratory gas designs. Data fitted with the calibration model (Eq. 1) and literature values of (α,β) [A = (0.2,1.3), B = (0.14,0.91)] and with the simplified model (Eq. 2) and optimum $\theta = 0.06$ (C).*