A simple heuristic model for the BOLD response (that works remarkably well)

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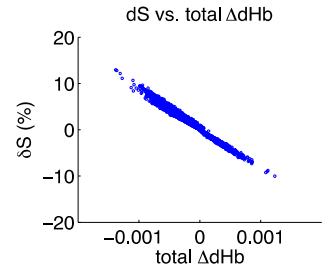
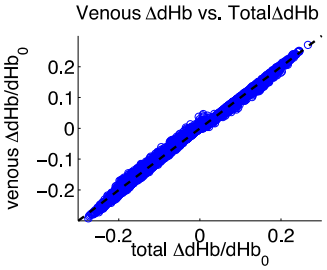
Purpose: To develop a heuristic model of the BOLD signal that is accurate, straightforward, and provides insight into the dependence of the BOLD signal change on blood flow and metabolic coupling.

Background: The calibrated BOLD approach and examinations of the coupling relationship between cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen ($CMRO_2$) have relied on the Davis model of the BOLD signal change ($\delta S=\Delta S/S_0$) [1]. This model was derived from the assumption that the BOLD effect behaves as a change in the transverse relaxation rate, ΔR_2^*, which is itself related to the magnetic susceptibility difference between blood and tissue ($\Delta\chi$) raised to the power β. $\Delta\chi$ is in turn dependent on amount of deoxyhemoglobin (dHb) in the blood. However, this model leaves out many of the complexities of the BOLD response, including intravascular signal changes and volume exchange effects. Recently we developed a detailed model of the BOLD signal that includes all of these effects, and found that the mathematical form of the Davis model still works reasonably well, particularly if the original parameters are optimized [2]. However, in doing that these parameters lose their physical meaning. Our goal here was to develop a simpler model, with a more transparent dependence on the underlying physiology, as an alternative to the Davis model, and test it for accuracy against the detailed BOLD model. The new model depends explicitly on the three physiological terms that drive the change in deoxyhemoglobin: the normalized change in CBF (f), the coupling of CBF and $CMRO_2$, $n=(f-1)/(r-1)$ where r is the normalized change in $CMRO_2$, and the exponent α_v describing the venous blood volume change as a power law function of f.

Methods and Results: The previously developed detailed BOLD signal model for 3T includes effects of intravascular and extravascular signal changes, hematocrit (*Hct*), oxygen extraction fraction (*OEF*), and blood volume distribution [2]. We used this model to address two questions:

1. Is δS simply proportional to the absolute change in dHb tissue concentration in a voxel, $\delta S \propto -\Delta\{dHb\}$ (Fig. 1)?
2. Is the fractional change of total dHb ($\Delta\{dHb\}/\{dHb\}_0$) equal to the fractional venous change ($\Delta\{dHb\}_v/\{dHb\}_{v,0}$) (Fig. 2)?





Note that these are tissue concentrations of dHb as denoted by "{}" and not intravascular concentrations. The parameters that describe the underlying physiology were randomly varied within plausible ranges (*Hct*=0.37-0.5, OEF_0=0.3-0.55, α_v=0.1-0.38, and baseline CBV fraction=0-0.1 and distribution to arteries=0.2, capillaries=0.4 and veins=0.4) and the model repeatedly used to generate the values to be compared. Figures 1 and 2 show that these simple approximations are reasonably accurate despite the underlying complexity of the BOLD response, which is described by the detailed model. Following the argument in [3] and employing the first assumption, we can define the scaling parameter M as $-\delta S/M=\Delta\{dHb\}/\{dHb\}_0$. We then combined this with our second assumption and the physiological relationship $\Delta\{dHb\}_v/\{dHb\}_{v,0}=\frac{vr}{f}-1$ where v is the normalized change in cerebral venous blood volume (CBV). This led to the equation $\delta S=M\left(1-\frac{vr}{f}\right)$, which we partially linearized to develop a heuristic model:

$$\delta S = M\left(1-\frac{1}{f}\right)\left(1-\alpha_v-\frac{1}{n}\right)$$

We then tested the accuracy of this new model and the optimized Davis model in predicting $\Delta CMRO_2$ from the simulated calibrated BOLD experiment using the detailed model. The heuristic model works well for $CBF/CMRO_2$ coupling ratios (n) from 1.3-5. In particular for n=2.5, the heuristic model produces nearly identical errors to the optimized Davis model (see [2] for values) as input parameters to the detailed model are varied. As with the optimized Davis model, the largest errors are associated with unknown variation in α_v. However, the heuristic model is much less accurate when a CBF decrease is accompanied by a $CMRO_2$ increase. Specifically for $\Delta CMRO_2$=30% and ΔCBF=-25%, the model underestimates these changes in $CMRO_2$ and is about -20% in error (calculated $\Delta CMRO_2$=23%).

Discussion: Here we presented a simple model for the BOLD signal with transparent dependence on underlying physiology as an alternative to the Davis model. The model exhibits the nonlinear dependence on f that leads to the BOLD ceiling effect, and directly defines the null line of the BOLD response to be $n=1/(1-\alpha_v)$, the coupling ratio that would produce no BOLD response. The term β does not enter because the curve in Fig. 1 is reasonably straight. Comparing with the detailed BOLD model, we found that this simple model is remarkably accurate for coupling ratios, n, from 1.3-5. It is much less accurate when a CBF decrease is accompanied by a $CMRO_2$ increase as is typical of caffeine ingestion. The importance of accurately determining α_v is again emphasized as this parameter has the largest effect on errors in calculated $\Delta CMRO_2$. Furthermore, the model predicts that the ratio of two BOLD signals in the same region depends only on the two CBF changes if n is constant, and thereby provides a simple mechanism by which to compare $CBF/CMRO_2$ coupling for two stimuli without calibrating to measure M.

[1] Davis, PNAS 95:1834, 1998; [2] Griffeth and Buxton, NIMG 58:198, 2011. [3] Gauthier and Hoge, HBM, 2011 (in press).