Dynamic estimation of cerebral metabolic rate of oxygen from BOLD and flow signals

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Purpose: To develop a detailed physiologic model for dynamic Blood Oxygen Level Dependent (BOLD) modulations.

Background: The relation between BOLD signal and underlying neural activity is complicated by nonlinear changes in vascular volumes and saturations linked to blood flow dynamics. The effect of physiological variables on steady-state BOLD response is well understood[1] and a calibrated BOLD methodology could be relatively robust to such variables[2]. A comparable detailed theoretical framework for BOLD dynamics is lacking.

Methods: Variations of oxygen saturation and deoxyhemoglobin content from arterioles to veins were approximated by dividing the vascular bed into numerous discrete sequential compartments. A viscoelastic balloon model[3] was used for the relation between compartment volumes and inflow. Changes in blood oxygen content were estimated from permeability area product and oxygen partial pressure gradient between tissue and each compartment. We applied the model to experimentally measured flow and BOLD signals estimating relative cerebral metabolism rate of oxygen ($CMRO_2$) as a function of time. An approximate solution that minimizes the difference between observed and predicted BOLD signal was found by linearizing the effect of changing oxygen metabolism at each time point by a fixed amount on predicted BOLD signal shortly afterwards.

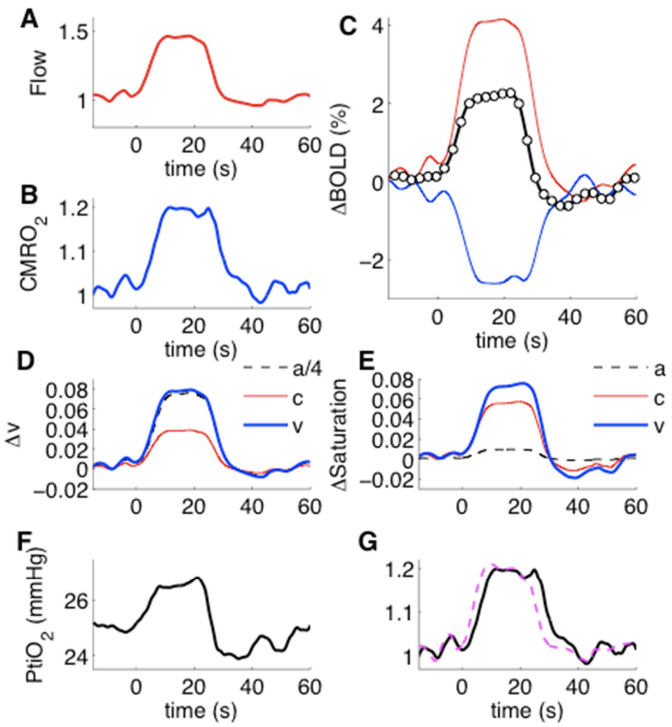

***Figure 1**. Simulation of dynamic BOLD response to visual stimulus (0–20s) from a prior experiment [4]. A) Observed normalized flow. B) Normalized oxygen metabolism (estimated). C) Simulated vs. observed BOLD responses. The effect of flow, oxygen metabolism, and combination of them. D-E) Changes in volume and saturation of arteriolar, capillary, and venous compartments. F) Dynamics of tissue P_{O2}. G) Comparison to $CMRO_2$ estimation using steady state equations (dashed).*

Results: The multi-compartment dynamic model is able to fit experimental data well (*Figure* 1) and link the observed BOLD signal to underlying physiology. Results do not critically depend on number of compartments, and converge well when the number of compartments is sufficiently large (≥100). Even a basic dynamic model with three compartments (arteriole, capillary, venule) captures dynamic features of BOLD with relatively small transient differences from the full model at onset and offset of the response. The estimated $CMRO_2$ response using the dynamic model is delayed compared to a naïve estimate based on steady-state models of the BOLD signal (*Figure* 1G). This delay is likely related to transit time of blood through the vascular three: changes in oxygen metabolism would affect the BOLD signal sooner than inflow of oxygenated blood.

The effect of various physiologic parameters on $CMRO_2$ estimations is depicted in Figure 2. When total cerebral blood volume change is dominated by arterioles, the rate of venous volume change has only minimal effect on $CMRO_2$ estimates. If venules dominate total CBV change, however, dynamics of estimated metabolic response would depend on venous viscoelastic time constant.

Discussion: We propose a theoretical framework for estimation of dynamic modulations of $CMRO_2$ by expanding a previous steady state model[1] and combining it with the balloon model. A multi-compartment formalism is flexible, allowing integration of future experimental results with the model to improve its accuracy. Examples demonstrate how the model can be applied to analyze experimental data and make empirically verifiable predictions. Taking into account transient changes in blood volume distribution increases temporal accuracy of $CMRO_2$ estimates compared to applying steady-state analysis to dynamic data.

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References:

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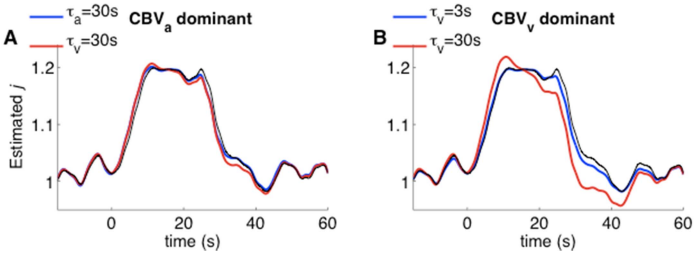

***Figure 2.** The effect of arteriolar and venous viscoelastic time constant on $CMRO_2$ estimation (using balloon model $\tau\ dv/dt = f - v^{1/\alpha}$).*