HST.583 Functional Magnetic Resonance Imaging: Data Acquisition and Analysis
Fall 2008

Problem Set 3: Imaging Physiology Block
Due: October 31, 2008

1. The figure below shows the BOLD effect's "ceiling" (i.e. **M**), a theoretical region where a change in blood flow will not yield a change in the BOLD signal.   From a physiological standpoint, why do you think this could happen?
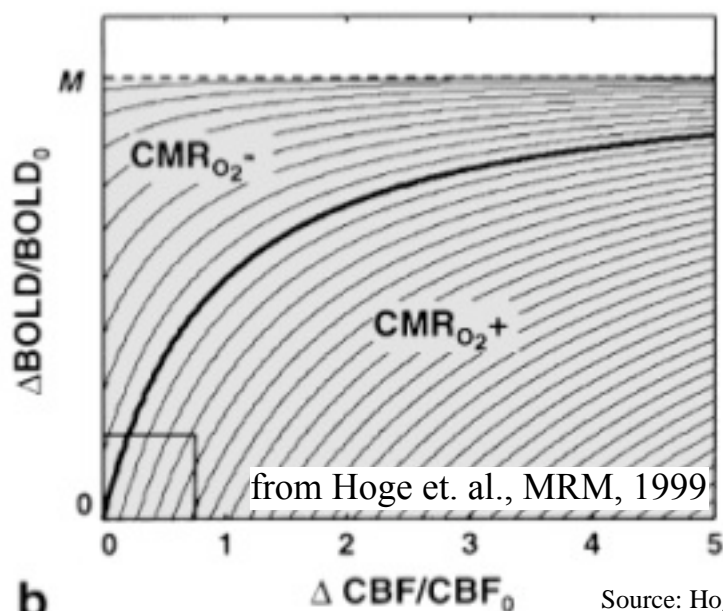
Source: Hoge, R., et al. *MRM* 42 (1999): 849-63.
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As flow increases become large, more and more deoxyhemoglobin is washed out of the venous system, resulting in the concentration of dHb to decrease substantially. As the limit is approached, very large flow increases are necessary for only incremental decreases in dHb concentration. At the theoretical limit of extremely high flow rates, dHb is completely washed out and venous blood becomes fully oxygenated. At this limit, additional flow will not cause a change in the BOLD signal, since there is no dHb left to wash out!

2. SE-BOLD theoretically can eliminate extravascular BOLD signal around larger veins, thereby more specifically targeting late capillaries and early venules. Why would this be advantageous?   Given conventional scanners available at most imaging centers, why do you think this is not routinely done?

Neuronal activation is hypothesized to be spatially localized to capillary beds, rather than draining veins. Imaging approaches that are exclusively sensitized to these areas are thus likely to be highly specific to neuronal activation. SE-BOLD, however, is probably not commonly used on conventional scanners for at least two reasons: 1) SE-BOLD loses considerable CNR (and thus sensitivity), versus GRE-BOLD, and 2) at conventional field strengths (i.e. 1.5T and 3.0T) there is significant large vessel **intravascular** *contribution to the BOLD signal. Therefore, the BOLD signal will still contain both large and small vessel contributions, and it will be impossible to separate the two. As such, small vessel sensitivity is lost.*

3. List two benefits and three drawbacks of going to higher fields for BOLD imaging? Explain.

   Advantages: higher SNR, shorter T_2/T_2^* of blood, leading to less intravascular effect; both these factors will make SE-BOLD more feasible. Drawbacks: greater susceptibility effects, increased distortion, more energy deposition in subject (SAR) requiring long TRs, less homogeneous transmit and receive, shorter tissue T_2/T_2^*. Other answers accepted.

4. Right now there are pulse sequences that can acquire data at incredibly fast rates; with TRs on the order of a few milliseconds. Explain why this may **not** be incredibly useful for doing BOLD fMRI?

   With BOLD imaging, we are essentially limited by the speed of the hemodynamic response, which is on the order of seconds. Even if we wanted to accurately evaluate the shape of this response, few millisecond resolution is overkill.

Three photos removed due to copyright restrictions.
Figure 1a, b, and c in Schwartz, W. J., et al. "Metabolic Mapping of Functional Activity in the Hypothalamo-Neurohypophysial System of the Rat." *Science* New Series 205, no. 4407 (August 17, 1979): 723-725.

5. The figure on the left from Schwartz and colleagues summarizes one of the first experiments to use autoradiographic techniques to map glucose metabolism (1977). They subjected rats to an osmotic load which stimulated cell bodies in the PVN and SON (a). Interestingly, they saw a large increase in metabolism in the posterior pituitary - the terminal end of PVN/SON axons (c), but did *not* see an increase in metabolism near the SON/PVC nuclei (c). Comment on this finding in light of Logothetis' observation that fMRI signals are more highly correlated to LFPs than APs.

These data essentially support Logothetis' observations. If we assume that metabolism roughly co-localizes with flow increase, then we would see a BOLD response in the posterior pituitary, where the axon potentials are synpasing (i.e. modulating LFP), and not at the site of PVC/SON nuclei, where the action potentials are originating.

6. In lecture 3, we asserted that the BOLD response is roughly ***linear***. In reality, there are definitely some non-linear components to the signal. Speculate on where non-linearities could arise, considering the problem from a neuronal, metabolic, and vascular point of view (i.e. one example for each; i.e. three total).

Neuronal: adaptation would certainly affect linearity.

Metabolic: Some have suggested that CMRO$_2$ and CBF are initially uncoupled, due to immediate energy demands being met by anaerobic respiration. Under this model, responses to short stimuli (which favor anaerobic respiration) may not scale with stimuli duration -- as stimulus times increase, metabolism will shift to aerobic respiration.

Vascular: As seen in question 1, there clearly is a non-linear relationship between BOLD and CBF.

7.   CBF increases in response to neural activation. Most evidence suggests that this occurs by increasing capillary blood velocity, *not* by capillary recruitment. Imagine for a second, that this is actually wrong; i.e. there *is* significant capillary recruitment during neuronal activation. Does this alter our view of the oxygen limitation model as an explanation of why CBF increases significantly more than CMRO$_2$ during activation?

This would cast doubts on the model, which assumes that oxygen extraction decreases since capillary transit time decreases upon increased CBF. If CBF increased by recruitment, instead of by velocity increase, capillary transit time should remain the same, and extraction should not decrease.

8.   *(Extra Credit)* As we saw in Lecture 4, water diffusing around small vessels experience a range of fields, such that phase offsets acquired in the first half of the experiment are different from those acquired in the second half. This leads to an *inability* to completely refocus the signal during a spin echo experiment, resulting in a small but measurable phase change between activated and baseline states (*circled*). This Δphase alters the T$_2$/R$_2$ and produces a modest change in the SE-BOLD signal (*thick red double arrow*).

We also discussed why this effect is reduced around large vessels (*thin red double arrow*): the field size is large compared to the diffusion size; water molecules feel a *constant* field, leading to a *linear* phase accrual, which can be reversed with a spin echo.

We did not discuss, however, the fact that the effect peaks around vessels with radius of ~7 um, and **decreases** with smaller vessels. At a vessel radius of 1 um (for example), the spin echo sequence does *not* cause much of T$_2$/R$_2$ change (*thick blue arrows*). Explain why this is the case.
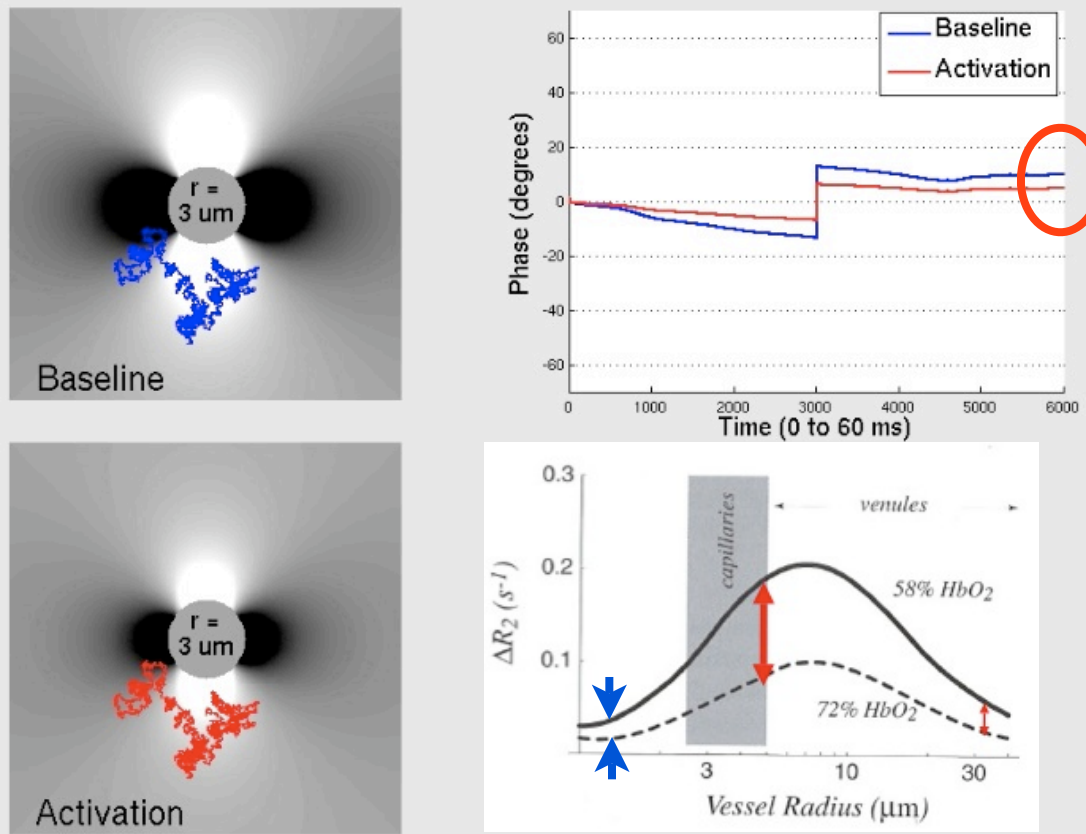
*If diffusion is considerably larger than the local field perturbation caused by the vessel, each water molecule will diffuse past **many** vessels and thus sample the **full range** of field distortions. If the diffusing spins feel all the variations, the net phase acquired by each is roughly the same and there is very little phase dispersion. Thus, at the echo time, there will be essentially zero phase accrual in both the activated and baseline states, and Δphase is zero! Note that this means there will be little signal change in BOTH the GRE an SE BOLD experiment around these very small vessels!*