The Balloon Model

Bernd Müller-Bierl

August 1, 2007

1 The balloon model

We assume no capillary recruitment, so that blood volume changes occur primarily in the venous compartment. The vascular bed within a small volume of tissue is modeled as an expandable venous compartment that is fed by the output of the capillary bed. The volume flow rate (ml/s) into the tissue, $F_{\text{in}}(t)$, is an assumed function of time that drives the system. The volume flow rate out of the system, $F_{\text{out}}(t)$, is assumed to depend primarily on the pressure in the venous compartment.

We assume that $F_{\text{out}}(t)$ is a function of the venous volume, V. The rate of change of the volume of the balloon is the difference between $F_{\text{in}}(t)$ and $F_{\text{out}}(t)$:

$$\frac{dV}{dt} = F_{\text{in}}(t) - F_{\text{out}}(V)$$

We then consider the total deoxyhemoglobin, $Q(t)$, in the tissue element. We neglect the capillary contribution and assume that all of the deoxyhemoglobin is in the venous compartment. The rate of entry of deoxyhemoglobin into the venous compartment is $F_{\text{in}}EC_a$ where E is the net oxygen extraction from the blood as it passes through the capillary bed, and C_a is the arterial O_2 concentration (assumed to be due to a fully oxygenated hemoglobin concentration). On the other side, the clearence rate of deoxyhemoglobin from tissue is $F_{\text{out}}\times$ the average venous concentration, $Q(t)/V(t)$ so that

$$\frac{dQ(t)}{dt} = F_{\text{in}}EC_a - F_{\text{out}}(V)\frac{Q(t)}{V(t)}$$

By scaling each of these variables with their value at rest ($t = 0$) these equations can be written in terms of the dimensionless variables $q(t) = Q(t)/Q_0$, $v(t) = V(t)/V_0$, $f_{\text{in}}(t) = F_{\text{in}}(t)/F_0$, and $f_{\text{out}}(v) = F_{\text{out}}(V)/F_0$:

$$\begin{aligned}\frac{dq}{dt} &= \frac{1}{\tau_0}\left[\frac{E(t)}{E_0}f_{\text{in}}(t) - \frac{q(t)}{v(t)}f_{\text{out}}(v)\right]\\ \frac{dv}{dt} &= \frac{1}{\tau_0}\left[f_{\text{in}}(t) - f_{\text{out}}(v)\right]\end{aligned}$$

where Q_0 is the resting deoxyhemoglobin content, V_0 is the resting volume, F_0 is the resting flow, $\tau_0 = V_0/F_0$ is the mean transit time through the venous compartment at rest, E_0 is the resting net extraction of O_2 by the capillary bed, and $q(0) = v(0) = f_{\text{in}(0)} = f_{\text{out}}(v(0)) = 1$.

Note that τ_0 simply sets the time scale for the changes and that the only other parameter that appears explicitely is E_0. However, two functions remain to be specified: $E(t)$ and $f_{\text{out}}(v)$. We argued elsewhere that a nonlinear expression for $E(f)$ is a reasonable approximation for a wide range of transport conditions: [2]

$$E(f) = 1 - (1 - E_0)^{1/f}$$

The formulae of $E(f_{\text{in}}(t))$ is substituted for $E(t)$ in the balloon model in the 2 Eqs. above. Different functional forms of $f_{\text{out}}(v)$ correspond to different pressure/volume curves for the venous balloon. For the calculations, Buxton et al. modeled $f_{\text{out}}(v)$ as a sum of a linear component and a power law.

2 Computations with the balloon model

As "input" driving function, we used a trapezoidal function with raise time of 4...6 s and variable duration. The resting net extraction of O_2 by the capillary bed was set to $E_0 = 0.4$. The timescale was given by $\tau_0 = 2s$. As extraction of O_2 we used $E(t) = 1 - (1 - E_0)^{1/f_{\text{in}}(t)}$. The response flow out of the capillary bed was assumed as a linear, respectively non-linear function of time (cf. Fig. 1 and Fig. 2. in the Buxton article).

The requested values are: [3]

[**Deoxy-Hb**] The total seoxyhemoglobin content is given by the variable $q(t) = Q(t)/Q_0$.

[**Volumen**] The total volumen is given by the variable $v(t) = V(t)/V_0$

[**Flow**] f_{in} is passed to the model; $f_{\text{out}}(t) = f_{\text{out}}(v(t))$ is also passed to the model.

[**BOLD**] The BOLD signal is given by

$$\frac{\Delta S}{S} = V_0 \left[k_1(1-q) + k_2(1-\frac{q}{v}) + k_3(1-v) \right]$$

where $k_1 \approx 2.8$, $k_2 = 2$ and $k_3 \approx 0.6$ for $B_0 = 1.5$T, TE $= 40ms$

[**CMRO$_2$**] $\text{CMRO}_2 = E\ \text{CBF}\ (O_2)_{\text{art}}$

The Balloon Model

Bernd Müller-Bierl

September 11, 2007

1 Abstract

Focus of the work is the haemodynamic response consisting of CBF and blood oxygenation. Different models are examined as there are

1. BOLD as a function of changes in cerebral oxygen fraction (E) and cerebral blood volume (CBV)
2. The balloon model proposed to describe the transient dynamics of CBV and deoxyhaemoglobin (HB) and how they affect the BOLD signal
3. Neurovascular coupling, relating the responses in CBF and cerebral metabolic rate of oxygen (CMRO2) to the neural activity response
4. A simple model for the temporal nonlinearity of the neural response itself

These models are integrated into a mathematical framework describing the steps linking the stimulus to the measured BOLD and CBF responses.

Experimental results examining transient features of the BOLD response (post-stimulus undershoot and initial dip), nonlinearities of the haemodynamic response, and the role of the physiologic baseline state in altering the BOLD signal are discussed in the contect of the proposed models. Quantitative modeling of the haemodynamic response, when combined with experimental data measuring the BOLD and CBF responses, makes possible a more specific and quantitative assessment of brain physiology than is possible with standard BOLD imaging alone.

2 Introduction

Changes in the metabolic state of the brain affect the local MR signal and provide an intrinsic mechanism for detecting brain activation (Kwong et al. 1992, Ogawa et al. 1990). The origin of the effect is the change of magnetic susceptibility in the presence of deoxyhaemoglobin which leads to a slight alteration of the local MR signal. Following increased neural activity of the brain, the local cerebral blood flow (CBF) increases much more than the cerebral metabolic

rate of oxygen (CMRO2), and as a result, E decreases with activation. Because the local blood is more oxygenated, there is less deoxyhaemoglobin present, the magnetic field distortions are reduced, and the local MR signal increases slihtly. This is the BOLD signal change, which is used in most fMRI applications.

In such fMRI experiments, the BOLD signal does not directly measure the neuronal activity itself. Instead, the BOLD effect is sensitive to changes in CBF, CMRO2, and cerebral blood volume (CBV), the set of physiological responses that are referred to as the haemodynamic response to activation. A critical goal for interpreting fMRI data is to understand the underlying link between neuronal activity and the naemodynamic response.

Our goal is to develop a mathematical description of the translation from an applied stimulus pattern to the measured BOLD signal.

When the BOLD change is combined with other MRI methods for measuring CBF directly, it becomes possible to untangle some of the factors that influence the BOLD effect, enabeling a much more detailed modeling of the physiological processes. Arterial spin labeling (ASL) techniques provide a means of measuring both the BOLD signal and CBF simultaneously. The image difference, control minus tag, ias direct reflection how much blood was delivered to each voxel and so provides a map of CBF (see Buxton 2002 for a review).

When all factor are taken into account. ASL offers a powerful probe of brain physiology. With a dual echo acquisition, with subsequent acquisitions alternating betwee tag and control, the data can be processed to yield essentially independent measurements of the local CBF and BOLD time series. In addition, newer MRI techinques promise to provide measurements of CBV over time as well (Lu et al. 2003). In the following discussion of models of the haemodynamic response, we will assume that the measurable quantities are time series of CBF and BOLD, and that under some circumstances CBV can be measured as well.

Four models are considered, which when combined provide a model of the full path from the temporal stimulus pattern to a measured CBF response and a measured BOLD response. The models treat (1) the BOLD signal as a function of changes in E and CBV; (2) the ballon model, proposed to describe the transient dynamics of CBV and deoxyhaemoglobin and how they affect the BOLD signal; (3) neurovascular coupling, relating the responses in CBF and CMRO2 to the neural activity response; and (4) a simple model for the temporal nonlinearity of the neural response itself. Recent experimental findings on the linearity of the BOLD response and the effect of the baseline physiological state on the BOLD response are considered in the light of these models.

3 Experimental characterization of the haemodynamic response

Based on numerous experimental studies of the BOLD and CBF responses to brain activation, the following are the key findings that motivate the modeling:

1. CBF increases much more than CMRO2

2. The CBF and BOLD responses to even a brief stimulus are delayed
3. A post-stimulus undershoot of the BOLD signal is common
4. Initial dip of the BOLD signal
5. The BOLD response typically exhibits a temporal nonlinearity
6. Nonlinearity has been reported as a "refractory period"
7. Baseline CBF can have a strong effect on the magnitude of the BOLD response

4 Definition of dynamic variables

The stimulus pattern (1) $s(t)$ drives the neural response $N(t)$; (2) $N(t)$ drives the CBF response $f(t)$ and the CMRO2 response $m(t)$; (3) $f(t)$ and $m(t$ drive the balloon model to produce the CBV response $v(t)$ and the total deoxy-haemoglobin response $q(t)$; and (4) $q(t)$ and $v(t)$ combine to produce the BOLD signal. Upper case variables refer to absolute quantities, whereas lower case variables are the same quantity normalized to its baseline value. At baseline, $f = m = q = v = 1$, and $E = E_0$. The neural response is defined such that $N(t) = 1$ on the plateau of a sustained stimulus when no adaption effects are operating.

For the calculations shown here, we are particularly interested in transient features and nonlinearities of the BOLD response. To emphasize these effects, we assume simple forms for scaling the stimulus and the neural response. The stimulus is considered to be a brief event (e.g. one reversal of a visually presented checkerboard) and these events can be presented in any pattern, including direct concatenation to produce a sustained stimulus (e.g. a flickering checkerboard). The stimulus pattern $s(t)$ is then a time series of oenes and zeros defining when events occured. The neural response is defined such that $N(t) = 1$ on the plateau of a sustained stimulus when no adaption effects are operating.

5 physiological relationship

The CBF increase associated with neural activity is triggered by a relaxation of the smooth muscle in the wall of the arterioles. By relaxing they quickly decrease vascular resistence and thereby the pressure drop across these vessels also decreases, thereby raising the pressure in the capillaries and veins. These vessels may also expand due to the increased pressure, further increasing the CBV. Experimental studies have indicated that the steady-state relationship between CBF and CBV can be described by a power-law

$$v = f^{\alpha}$$

where the exponent is approximately $\alpha = 0.4$. This empirical relationship applies to the entire blood volume and is often used in modeling the BOLD effect.

At steady state, CBF and CMRO2 are related to each other by the arterial oxygen concentration and the net oxygen extraction fraction E:

$$\text{CMRO2} = E \cdot C_a \cdot \text{CBF}$$

$$m = \frac{E}{E_0} f$$

The local oxygenation of the venous blood depends directly on E.

For modest changes around an awake baseline state, experiments suggest that the relationshi between CBF and CMRO2 changes can be characterized as linear with a slope n defined as the fractional change in CMRO2

$$n = \frac{\Delta\text{CBF}/\text{CBF}_0}{\Delta\text{CMRO2}/\text{CMRO2}_0}$$

$$n = \frac{f - 1}{m - 1}$$

The fact that $n > 1$, so that E decreases with activation, is the physiological source of the BOLD effect, and this was originally described as an uncoupling of CBF and CMRO2 in the seminal work of Fox and Raichle (1986). However, a promising alternative explanation developed over the last few years is the oxygen limitation model (Buxton 2002). By this model, the drop in E with activation plays a functional role rather than serving as a marker of an uncoupling. The key idea of this model is to think of the O_2 flux down a diffusion gradient from the mean capillary value to the mean value in mitochondria. To increase the net flux (i.e. increase CMRO2), the gradient must be increased. If ther is no capillary recruitment, so the O_2 source cannot be brought closer to the mitochondria, and the mean mitochondrial pO_2 is very low, the only way to increase the O_2 flux is to raise the average capillary pO_2. The average capillary pO_2 lies somewhere between the venous and the arterial pO_2 values, and because the arterial pO_2 is fixed, the only local control available is to raise the venous pO_2. And raising venous pO_2 requires a reduction of the oxygen extraction fraction E. In this way, the decrease in E is necessary to increase the O_2 diffusin gradient from capillaries to mitochondria. For the calculation in this paper, we will simply use the empirical relationships presented above.

6 Modeling the BOLD effect

Generally, two sources of signal changes must be modeled: The intravascular and the extravascular signal changes. Although the intrinsic intravascular signal is much less than the extravascular signal, the sensitivity of the intravascular signal to the oxygenation of blood is much greater. The result is that the intravascular contribution likely accounts for half or more of the signal change

observed at 1.5 T. The total deoxyhaemoglobin content could change either by changing the volume of the venous blood, so the role of volume changes must be included. Finally, for the smallest vessels, diffusion effects can be important.

Thus modeling the BOLD effect depends not only on the biophysical models, for how intravascular susceptibility differences alter the signal, but also physiological models for how CBF, CBV, and CMRO2 change with activation. The relative changes in CBF and CMRO2 determine the level of oxygenation of the blood, and the CBV determines the total amount of blood (and thus the total deoxyhaemoglobin present in the voxel).

7 Magnetic Susceptibility Effects and the MR Signal

Ogawa et al. (1993) introduced a biophysical model of the BOLD effect and Davies et al. (1998) extended this model based on reasonable approximations and the results of numerical simulations. Because of its simplicity, the model has proven to be a useful tool for understanding the BOLD effect in a quantitative way and has provided a method for calibrating the BOLD signal and measuring CMRO2 changes.

The MR signal decay for GRE is given by

$$S = S_{\max} \cdot \exp(-TE \cdot R_2^*)$$

where $R_2^* = R_2^*(0) + R$. R is the quantity that changes, otherwise stated as $R = \Delta R_2^* = R_{\text{act}} - R_0$.

With

$$\begin{aligned} S_0 &= \exp(-R_2^*(0)TE) \\ S_{\text{act}} &= \exp((-R_2^*(0) + R)TE) \end{aligned}$$

we get

$$\begin{aligned} \frac{S_{\text{act}} - S_0}{S_0} &= \frac{\exp((-R_2^*(0) + R)TE) - \exp(-R_2^*(0)TE)}{S_0} \\ &= \exp(-RTE) - 1 \approx \Delta R_2^* TE \end{aligned}$$

The key question is: how does ΔR_2^* depend on blood oxygenation and volume? The magnetic susceptibility difference can be accurately modeled as having a linear dependence on the local deoxyhaemoglobin concentration in blood and this quantity in turn can be expressed in terms of the change in the oxygen extraction fraction E. To model the spread of phases, Davis et al. assumed a power law $R \propto \Delta B^\beta$. Numerical simulations (Boxerman et al., Ogawa et al.) suggest that when diffusion is not important, $\beta \approx 1$, but that $\beta \approx 2$ gives a better description around the smallest vessels when diffusion effects are important. Numerical simulations for a mixture of vessels suggest that $\beta = 1.5$ is a good approximation for 1.5 - 3 T, but that at higher fields, β should approach 1.

In addition to the change in E with activation, a change in blood volume also affects R. For example, even if the oxygenation of the blood did not change but the venous blood increased, the total deoxyhemoglobin would be increased, and we would expect this to in crease R and decrease the MR signal. Numerical simulations suggest that a resonable approximation is to assume that $R \propto V$, the venous blood volume. Combining these dependencies, the contribution of deoxyhemoglobin to the relaxation rate is modeled as

$$R \propto VE^{\beta}$$

8 The BOLD signal change

Following Davies et al. these ideas can be combined to model the MR signal in terms of blood voulme (V) and oxygen extraction fraction (E):

$$\frac{\Delta S}{S_0} \approx A \cdot \left[1 - \frac{V_{\text{act}}}{V_0}\left(\frac{E_{\text{act}}}{E_0}\right)^{\beta}\right]$$

A decrease of either of the physiological quantitites (V or E) will decrease the local deoxyhemoglobin concnetration and so increase the MR signal. A is the maximum BOLD signal change that could occur, corresponding to complete removal of deoxyhemoglobin from the voxel. The parameter β should be primarily be field dependent, it is not a function of brain region. A however, is a local parameter and may vary across different voxels in the brain.

Note that β is proportional to the value of R at rest, the relaxation rate produced by deoxyhemoglobin in the baseline state. The more deoxyhemoglobin is present at rest, the larger the BOLD signal change will be for the same fractional change in V and E with activation.

In our notation, with dynamic variables normalized to their baseline values and assuming Eqn. 1 is accurate, the basic BOLD signal equation is

$$\frac{\Delta S}{S_0} = A \cdot \left(1 - f^{\alpha-\beta}m^{\beta}\right)$$

Although, Eqn. 8 is a very useful model, the reader should bear in mind that it does not necessarily describe all of the effects that may contribute to the measured signal change in an activation experiment. Specifically, small direct effects of CBF and CBV changes on the MR signal that are independent of the BOLD effect are likely present in real data. In most applications, these effects are thought to be small compared to the BOLD effect, especially at higher magnetic fields, but they may not be negligible.

9 Calibrated BOLD approach for measuring CMRO2 changes

Measuring both the BOLD signal change with activation and the CBF change with activation, and analyzing these data in terms of the BOLD signal model, it is possible to estimate the change in the CMRO2. The essential problem in applying Eq. 8 to measured data is the uncertainty about the local value of A. If A is known, then m can be determined from Eqn. 8 when f and ΔS are measured with an ASL experiment. To measure A, Davies et al. and others have exploited a well-established – but poorly understood – physiological phenomenon: breathing CO2 significantly raises CBF but has little or no effect on CMRO2. This provides a way to calibrate the BOLD experiment with a hypercapnia experiment. By measuring f and ΔS in response to breathing CO2 combined with the assumption that CMRO2 remains constant ($m = 1$) the value of A is calculated from Eqn. 8. The same equation is applied again to the measured activation signal in that region, and with a known value of A, the value of m with activation can be calculated. Because of the assumptions involved (Eqn. 1) this is essentially a steady-state measurement of CMRO2 change from baseline. However, if both CBF and CBV time courses are measured independently, a dynamic curve for CMRO2 can be calculated (Mandeville et al. 1999a).

10 Alternative Forms for the BOLD signal model

An alternate form of the BOLD signal equation was proposed to model the dynamics of the BOLD effect in context of the balloon model. The derivation of this model is based on separate estimates of the intravascular and extravascular signal changes. In this way, the model can be used to analyzeexperiments in which flow-nulling bipolar gradients are applied to destroy the signal of moving blood, and thus eliminate the intravascular signal changes from the BOLD effect. The key physiological variables are the total deoxyhemoglobin (q) and the blood volume (v), both normalized to their values at rest. In this model, the BOLD signal change is written as:

$$\frac{\Delta S}{S} \approx V_0 \left[a_1(1-q)a_2(1-v)\right]$$

where V_0 is the resting venous blood volume fraction (e.g. 0.03) and the dimensionless parameters a_1 and a_2 depend on several experimental and physiological parameters. The values estimated by Obata et al. (2004) for a magnetic field of 1.5 T with TE = 40 ms, and $E_0 = 0.4$ are $a_1 = 3.4$ and $a_2 = 1.0$.

Eqs. 8 and 9 are framed in terms o different variables, but they are approximately equivalent expressions for the BOLD signal change. Fig. 2 shows curves of the BOLD response as a function of the CBF change calculated with the two models with $A = 0.075$ in Eqn. 8 and $V_0 = 0.03$ in Eqn. 9 (other parameters were standard values listed in Table 1). These curves were calculated for steady state changes using the relation $q/v = E/E_0$ to relate the variables of the two

equations. In their calibrated BOLD experience in human visual cortex, Davis et al. found an average value of $A = 0.097$, and 3% is a resonable estimate fo the venous blood volume fraction. This suggests that the theoretical assumptions that led to the estimates of a_1 and a_2 in Eqn. 9 are in resonable agreement with experimental data, and the similarity of the two curves illustrates the consistency of the two models.

Eqn. 8 is useful for calibrated BOLD studies, because it explicitely includes CBF, a measurable quantity. On the other hand, Eqn. 9 deals explicitely with the variables of the balloon model, and so is more convenient for most of the modeling calculations described in this paper.

Based on Eqn. 9 we can look at the BOLD signal as a contour plot in the q/v plane, because the dynamic variables q and v determine the signal. Fig. 2B shows such a plot, along with a curve of constant oxyhemoglobin (a line of constant deoxyheomoglobin is vertical). Note that the BOLD signal does not purely follow total deoxyhemoglobin or oxyhemoglobin. Because of this, it is possible for the BOLD signal to increase despite an increase of deoxyhemoglobin. As an example, consider a scenario in which the increase in CBV and the decrease in E happen to combine to produce no change in total deoxyhemoglobin, so that $q = 1$ and $v > 1$. In this case, the field distortions outside the vessel will be similar, but the concentration of deoxyhemoglobin in the blood must have decreased. The intravascular signal depends strongly on the deoxyhemoglobin concentration, and so this component of the signal will increase, The result is a BOLD signal increase with no change in deoxyhemoglobin. This subtlety of the BOLD signal may become important n comparing fMRI data with optical or near-infrared results that are sensitive to oxyhemoglobin and deoxyhemoglobin: there is no one-to-one correspondence between the BOLD signal and the total deoxyhemoglobin (Hess et al. 2000).

Analyzing the bold signal in the q/v plane is also useful for visualizing the physiological dynamics accompanying brain activation. Fig. 2B shows a simle trajectory that would result for a gradual CBF increase of 50% with $n = 3$, if the physiological quantities all followed their steady state relationships (Eqs. 1-3) at all times. The interesting dynamics develops when the physiological variables transiently depart from these relationships in the transition to a new steady-state, and then the trajectories become rather more complicated. The following model attempts to describe these dynamics.

11 The balloon model

The balloon model was motivated by the observation in an animal study (Mandeville et al. 1998) that CBV returned to baseline more slowly than CBF after the end of the stimulus, and the idea that this effect may explain the post-stimulus undershoot of the BOLD signal that often is observed. A similar windkessel model was proposed by Mandelville et al. (1999b) to embody the same concept and provide a biomechanical mechanism for a delayed CBV return to baseline. The balloon model has been refined and compared with experimental

data (...), and some errors in the original parameter estimates were recently corrected (Obata et al 2004). The model is capable of producing post-stimulus undershoots that match well with experimental data.

However, the central promise of the model , that the undershoot occurs when CBV returns slowly to baseline, ahs not been definitively established and focussed experimental tests of theis quastion are needed (e.g. Mandeville et al. 1999a, Toronov et al. 2003).

The central idea of the model is that the venous compartement is treated as a distensible balloon. Thze inflow to the ballonn f_{in} is the central blood flow (f in our current notation), while the outflow from the balloon f_{out} is an increasing function of the balloon volume. The two dynamical variables are the total deoxyhemoglobin $q(t)$ and the volume of the balloon $v(t)$. The equations of the balloon model represent mass conservation for blood and deoxyhemoglobin as they pass throught the venous balloon:

$$\frac{dq}{dt} = \frac{1}{\tau_{\text{MTT}}}\left[f(t)\frac{E(t)}{E_0} - \frac{q(t)}{v(t)}f_{\text{out}}(v,t)\right]$$

$$\frac{dv}{dt} = \frac{1}{\tau_{\text{MTT}}}\left[f(t) - f_{\text{out}}(v,t)\right]$$

The net extraction fraction of oxygen is $E(t)$, and the resting value is typically $E_0 = 0.4$. The time dimension of the equations is scaled by the time constant τ_{MTT}, the mean transit time through the balloon at rest. For a cerebral blood flow of 60 ml min^{-1} 100 ml^{-1} of tissue (equivalent to a rate constant of 0.01 s^{-1}) and a resting venous blood volume fraction of $V_0 = 0.03$, the mean transit time is $\tau_{\text{MTT}} = 3s$.

The driving function of the system is the quantity $f(t)E(t)$. In the original formulation of the balloon model, the extraction fraction was modeled as a fixed function of the inflow f, a tight coupling of flow and oxygen metabolism. The equations were generalized by Obata et al. (2004), treating $E(t)$ as an independent quantity to be able to explore the dynamics that result from uncoupling of blood flow and oxygen metabolism. Note that the quantity fE/E_0 is simply the CMRO2 value normalized to its value at rest (m).

in the original formulation of the balloon model, the outflow was modeled as a pure function of blood volume v. Steady State experiments, altering CBF with inhaled CO2, found that the steady state relationship between CBF and total blood volume was well described by an empirical power law (Eq. 1). However, interesting dynamics occur, when the blood volume transiently lags behind the steady state relationship, for example, due to viscoelastic effects. In the original discussion of the balloon model, the description of these transients was an arbitrary mathematical form, chosen just to illustrate the type of effects that could occur. However, that approach is not well-suited to data modeling. In particular, it would be useful to have a simple model that could be tested again multiple data sets, such as experiments varying the duration of the stimulus.

To that end, we proposed a simple model for these viscoelastic effects in

which f_{out} is treated as a function of the balloon volume and the rate of change of that volume

$$f_{\text{out}}(v) = v^{\frac{1}{\alpha}} + \tau \frac{dv}{dt}$$

With this form, the balloon initially resists a change in volume, but eventually settles into a new steady state that conforms with the power-law model in Eqn. 1. THe time constant τ controls how long this transient adjustment requires. A nonzero value for τ produces hysteresis in the curve $f_{\text{out}}(v)$, so that the system follows a different curve on inflation (τ_+) and deflation (τ_-).

For a specific driving function $f(t)E(t)$, and values for the parameters τ_{MTT}, E_0, α, τ_+ and τ_- Eqs. 10 and 11 can be integrated numerically to yield dynamic time courses for $q(t)$ and $v(t)$. These dynamic physiological quantities can then be combined with the BOLD signal model (Eqn. 9) to generate MR signal curves. Fig. 3 shows balloon model curves for a simple, smooth trapezoidal form for $f(t)$ and a fixed CBF/CMRO2 coupling parameter $n = 3$. A nonzero value for τ_+ creates an initial overshoot of the BOLD signal, and a nonzero value for τ_- creates a poststimulus undershoot. These curves show that quiet different BOLD responses can result from the same underlying CBF and CMRO2 response.

12 Neurovascular coupling

We do not currently have a quantitative understanding of the mechanisms that couple neural activity to CBF and CMRO2 changes. In fact, ther is no consensus on exactly which aspect of neural activity drives the hemodynamic response. Experimental studies comparing electrophysiological measurements with BOLD and CBF changes have found that the hemodynamic response correlate better with local mean-field potential, rather than local spiking rates, suggesting that the hemodynamic response is dominantly driven by input synaptic activity rather than output spiking activity. Theoretical analysis of the energy budget for neuronal signaling provide some support for that picture as well. The primary expenditure of energy is required to restore the ion gradients degraded during neural activation. The intracellular-extracellular sodium gradient is far from equilibrium, so pumping sodium against this gradient is a strong uphill reaction in a thermodynamic sense. For this reason, the most costly effect for neural activity is likely to be excitatory synaptic activity in which glutamate opens sodium channels.

Indeed, the action of the sodium-potassium pump is thought to consume a large fraction of the ATP energy budget in the brain. In a recent animal experiment, blocking voltage-dependent sodium channels substantially reduced the CBF response, supportin the idea that the dominant energy consuming process in the brain is recovery from excitatory activity. Finally, there is some evidence that inhibitory activity does not elicit a measurable BOLD response.

Friston et al. introduced a simple neurovascular coupling model in which the rate of change of CBF is proportional to the concentration of a vasoactive agent

released by neural activity. Using this model, they showed that an observed set of nonlinearities modeled with Volterra Kernels could be well described with this more physiological model. This model was also used to explore the effects of nonlinearity in different experimental designs.

One of the goals of modeling the hemodynamic response is to un derstand the origins of the nonlinearities of the response, and for that purpose, it is useful to have a model that includes a nonlinear transformation from the stimulus pattern $s(t)$ to the CBF response $f(t)$. Such a nonlinearity could arise in the stepp from $s(t)$ to the neural response $N(t)$, as, for example, in adaption. In addition, the step from the neural activity to CBF response could be nonlinear, for example, through a ceiling effect on CBF change. Given our poor understanding of the mechanisms of neurovascular coupling, we take here a simplke approach and assume that the nonlinear step is entirely in the transformation from $s(t)$ to $N(t)$ and in the next section we introduce a simple model for this process that includes adaption. We then assume that both CBF and CMRO2 are linear convolutionsof an impulse response function $h(t)$ with the appropriate measure of neural activity $N(t)$.

A plausible shape for $h(t)$ is a gamma-variate function with a full-width at half maximum (FWHM) of about 4 s. For the calculations, here we used the form

$$h(t) = \frac{1}{k\tau_h(k-1)!}\left(\frac{t}{\tau_h}\right)^k \exp(-t/\tau_h)$$

with k = 3. For the calculation in this paper we also add a delay of this response (typically about 1 s) to model the observed lag of the hemodynamic response.

The shape $h(t)$ is then scaled to provide the desired amplitude and duration of the impulse response. For this shape and a desired FWHM of τ_f, the time constant in Eqn. 12 is given by the empirical expression $\tau_h = 0.242\tau_f$. The CBF and CMRO2 responses to activation are then

$$\begin{aligned} f(t) &= 1 + (f_1 - 1)h(t - \delta t_f) * N(t) \\ m(t) &= 1 + (m_1 - 1)g(t - \delta t_f) * N(t) \end{aligned}$$

The symbol $*$ denotes convolution. The parameter f_1 scales the response shape to the appropriate amplitude and represents the normalized flow increase on the plateau of the CBF response to a sustained neural activity with unit amplitude. For example, if $N(t)$ is a 30 s block with amplitude 1, and the model parameters are $f_1 = 1.5$ and $\tau_f = 4s$, the CBF response is a smoothed version of the block due to the 4-s wide smothing kernel, and on the plateau CBF is increased by 50%. The parameter δt_f is the delay after the start of the stimulus before the CBF response begins.

We model the CMRO2 response in Eqn. 13 as an independent convolution with potentially independent amplitude, width, and delay defined by $g(t)$. In the calculation here, we assume a coupled response such that the amplitude of the CMRO2 impulse response is given by $(m_1 - 1) = (f_1 - 1)/n$, and the width is the same. In this way, the steady state response is constrained to follow the empirical relationship in Eqn. 3. However, by introducing a delay

$\delta t = \delta t_f - \delta t_m$ of the CBF response relative to the CMRO2 repsonse, we can introduce interesting dynamics such as an initial dip of the BOLD response. This approach is analogous to the balloon model, where the model is constrainted to follow the physiological relationship in Eqn. 1 at steady state, but allows substantial range for transient responses.

Fig. 4 illustrates the type of transient features that can result from combining the balloon model with the independent convolution model. The figure show different dynamic responses of CBF, CMRO2, and CBV to the same 20-s uniform block of neural ectivity. In these calculations, the responses $f(t)$ and $m(t)$ calculated from the independent convolutions were used as input to the balloon model to calculate $v(t)$ and $q(t)$. The first pannel shows the response when the viscoelastic time constants of the balloon model are zero, there is no delay between $f(t)$ and $m(t)$. In the second panel, τ_- was increased to 20 s, and in the third panel, the impulse response for CBF was delayed by $\delta t = 1s$relative to the CMRO2 response. The BOLD response for the last combination shows both an initial dip and a poststimulus undershoot. The physiological dynamics is also shown as a trajectory in the q/v plane on the right side of Fig. 4, and the BOLD signal is a one-dimensional projection of this two-dimensional trajectory.

13 Modeling the neural response

As discussed in the previous section, the approach we have adopted is to model the CBF and CMRO2 responses as linear convolutions with the neural activity $N(t)$, and uses a model for the step from the stimulus $s(t)$ to $N(t)$ that includes the possibility for adaption. We chose a simple inhibitory feedback system, in which the neural response $N(t)$ is treated as the difference between an excitatory input $s(t)$ and an inhibitory input $I(t)$. The inhibitory input $I(t)$ is driven by the neural response $N(t)$ with a gain factor κ and a time constant τ_{I}. The set of equations is

$$\begin{aligned} N(t) &= s(t) - I(t) \\ \frac{dI}{dt} &= \frac{\kappa N(t) - I(t)}{\tau_{\mathrm{I}}} \end{aligned}$$

From these equations, the neural response to a sustained stimulus is an initial peak followed by decay to a lower plateau level, with the difference between the peak and plateau valued determined by κ. As written, these equations are linear, and the initial peak of the response would be balanced by a dip after the end of the stimulus, and such a post-undershoot of the neural response has been observed. We introduce a nonlinear component as well as the possibility of a post-stimulus neural undershoot, by introducing a baseline nerual activity N_0, and the requirement that the neural repsonse is a positive quantity (i.e. if the calculated quantity $N_0 + N(t) < 0$, it is replaced by zero). Then if the resting stimulus level is $N_0 = 0$, there is no dip following the end of the stimulus. This is the adaption pattern originally proposed by Boynton et al. to describe the observed nonlinearities of the BOLD response in the visual cortex. On the

other hand, if $N_0 > 0$, there will be a post-stimulus undershoot of the neural response. In addition to diminishing the response to a sustained stimulus, this model aslo introduces a "refractory" effect. If two events are presented close together (within τ_I) of each other, then the net responseof both events will have less than twice the area of the response to a single event.

This model provides a simple form for introducing a nonlinearitythat can be applied to any stimulus pattern: the amplitude of this nonlinear effect is governed by κ and the duration of the "refractory" period is determined by τ_I. Fig. 5 shows an example that includes both a two pulse inhibition experiment and a sustained stimulus.