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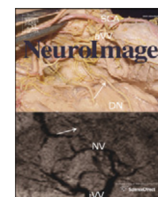

Improving estimates of the cerebral metabolic rate of oxygen from optical imaging data

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ABSTRACT

The cerebral metabolic rate of oxygen ($CMRO_2$) is an important measure of brain function. Since it is challenging to measure directly, especially dynamically, a number of neuroimaging techniques aim to infer activation-induced changes in $CMRO_2$ from indirect data. Here, we employed a mathematical modelling approach, based on fundamental biophysical principles, to investigate the validity of the widely-used method to calculate $CMRO_2$ from optical measurements of cerebral blood flow and haemoglobin saturation. In model-only simulations and simulations of *in vivo* data changes in $CMRO_2$ calculated in this way differed substantially from the changes in $CMRO_2$ directly imposed on the model, under both steady state and dynamic conditions. These results suggest that the assumptions underlying the calculation method are not appropriate, and that it is important to take into account, under steady state conditions: 1) the presence of deoxyhaemoglobin in arteriolar vessels; and 2) blood volume changes, especially in veins. Under dynamic conditions, the model predicted that calculated changes in $CMRO_2$ are moderately correlated with the rate of oxygen extraction – not consumption – during the initial phase of stimulation. However, during later phases of stimulation the calculation is dominated by the change in blood flow. Therefore, we propose that a more sophisticated approach is required to estimate $CMRO_2$ changes from these types of data.

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Introduction

The cerebral metabolic rate of oxygen ($CMRO_2$), which represents the rate at which oxygen is consumed to meet the energy demands of the working brain, is an important measure of neural activity in health and disease. However, there are many aspects of the metabolic changes that are caused by variations in neuronal activity which are not fully understood; for example, the nature of the cellular energy pathways which sustain the increased demand, the relative magnitude of the metabolic changes compared with changes in blood flow, and the evolutionary advantage conferred by this process remain unclear (Attwell et al., 2010; Buxton, 2010; Fox, 2012; Pellerin and Magistretti, 2012). Better knowledge of this fundamental process is vital to improve our understanding of basic neuronal function. In addition, it may also enable more accurate, and perhaps even quantitative interpretation of non-invasive neuroimaging modalities such as functional Magnetic Resonance Imaging (fMRI) using the Blood Oxygenation Level Dependent (BOLD) signal.

Part of the uncertainty that surrounds neural metabolism is likely caused by the difficulty in measuring $CMRO_2$ directly. For example, steady-state measurements of $CMRO_2$ with PET require three separate scans, each with different oxygen-15 labelled tracers (Mintun et al., 1984). However, the measurements still rely on the assumption that there is no back flux of oxygen from tissue to the vasculature, and require a model to interpret the effects of CBF, $CMRO_2$ and CBV (cerebral blood volume) on the observed tracer kinetics (Buxton, 2010; Mintun et al., 1984).

Steady-state $CMRO_2$ can also be measured using several magnetic resonance spectroscopy techniques following inhalation of oxygen-17 labelled O_2 gas (*e.g.* Mellon et al., 2009; Zhu et al., 2013). These approaches have a number of advantages, particularly the ability to distinguish between oxygen that has not been metabolised (*i.e.* O_2) and that has (*i.e.* H_2O). However, measurements using these techniques are not yet widespread due to the high cost of oxygen-17 and difficulties in extending the approach to larger animals (Buxton, 2010; Zhu and Chen, 2011).

Dynamic measurements of $CMRO_2$ during neuronal activation are even more complicated, since the increase in $CMRO_2$ (*i.e.* O_2 demand) is confounded by a larger, concomitant increase in cerebral blood flow (CBF, *i.e.* O_2 supply). This phenomenon is often referred to as 'uncoupling' of CBF and $CMRO_2$ (Fox and Raichle, 1986). It is also possible to

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qualitatively estimate changes in $CMRO_2$ independently of CBF using flavoprotein autofluorescence imaging (FAI, Vazquez et al., 2012; Weber et al., 2004), although it is not clear how to relate the measured change in fluorescence to quantitative changes in $CMRO_2$.

Therefore, because of the technical challenges and relatively poor temporal resolution of the direct approaches, many studies aim to infer dynamic changes in $CMRO_2$ indirectly using an imaging modality sensitive to oxygenation, such as optical imaging (Dunn et al., 2005; Jones et al., 2001; Mayhew et al., 2000) or BOLD-fMRI (Davis et al., 1998; Hoge et al., 1999; Hyder et al., 2010; Mandeville et al., 1999). These techniques require a framework to convert a signal that represents oxygen *concentration* into a metric that represents the *rate* of oxygen *consumption*. The approaches considered here rely on Fick's principle, which states that the amount of oxygen extracted from the blood is proportional to CBF and the arterio-venous oxygenation difference. We contend that these methods are limited by two assumptions.

First, the approaches explicitly or implicitly assume that $CMRO_2$ is proportional to O_2 extraction, which may be normalised and referred to as the oxygen extraction fraction or OEF (Davis et al., 1998; Dunn et al., 2005; Hoge et al., 1999; Jones et al., 2001; Mandeville et al., 1999; Mayhew et al., 2000). Under steady state conditions, $CMRO_2$ and O_2 extraction are matched, as tissue oxygen partial pressure (PO_2) does not vary significantly through time (Russell et al., 2012). This steady-state coupling may be an important regulator of metabolism or vascular development, since capillary density is strongly correlated with the activity of the metabolic enzyme cytochrome oxidase (Weber et al., 2008), in addition to CBF and cerebral glucose consumption (Klein et al., 1986).

However, O_2 extraction and $CMRO_2$ are not necessarily matched under dynamic conditions. A number of studies have reported a robust increase in tissue PO_2 following neural activation (Masamoto et al., 2008; Thompson et al., 2003; Vazquez et al., 2010), suggesting that the O_2 extracted from the blood may not be consumed immediately; *i.e.* transient changes in O_2 extraction exceed changes in $CMRO_2$. Therefore, we propose that it is inappropriate to use O_2 extraction as a proxy for $CMRO_2$ outside of steady state conditions.

Secondly, many of the approaches assume complete saturation of haemoglobin in arteries (Davis et al., 1998; Dunn et al., 2005; Hoge et al., 1999; Jones et al., 2001; Mandeville et al., 1999; Mayhew et al., 2000). However, more recent evidence suggests that the small arteries which supply individual cortical regions contain non-negligible levels of deoxyhaemoglobin (Kasischke et al., 2011; Yaseen et al., 2011), and this is likely to be even more significant under free breathing conditions without supplied oxygen (Vovenko, 1999). In addition, vascular PO_2 measurements imply that the saturation of cerebral arteries may change during neural activation, albeit by a relatively small amount (Vazquez et al., 2010).

In this study, we investigate the validity of these approaches using a predictive mathematical model. Rather than assuming $CMRO_2$ and O_2 extraction are equivalent, the model treats $CMRO_2$ as a tissue 'oxygen sink', in which oxygen is irreversibly consumed by the mitochondria during aerobic respiration. Then, we model oxygen extraction independently, using a mass balance approach, where net O_2 flux from blood to tissue is driven by the PO_2 gradient (*i.e.* Fick's first law). In addition, we do not assume complete saturation of arterial haemoglobin, and instead calculate the baseline oxygen saturation from *in vivo* measurements.

While the basic principles behind our approach extend to any oxygenation based signal, in this study we focus on the widely-used calculation of dynamic $CMRO_2$ changes from optical measurements of haemoglobin (Dunn et al., 2005; Jones et al., 2001; Mayhew et al., 2000). Initially, we compare the existing calculation method to our proposed approach using model only simulations, and then we apply both methods to a published set of *in vivo* data (Jones et al., 2002).

Table 1
List of dynamic variables.

Symbol	Description
$c_i(t)$	Vascular compliance
$c_{O_2,i,j}(t)$	O_2 concentration of $f_{i,j}(t)$
$\Delta c^{\star}_{HbO}(t)$; $\Delta c^{\star}_{dHb}(t)$	Adjusted haemoglobin concentration changes
$cmr_{O_2}t$	Cerebral metabolic rate of O_2
$f_{i,j}(t)$; $\overline{f}(t)$	Blood flow from i to j; average flow
$j_{O_2,i}(t)$; $j_{O_2,s}(t)$	O_2 flux to tissue; flux through shunt
$n_{X,i}(t)$	Amount of X, where $X \in \{O_2, HbO, \ldots\}$
$p_i(t)$; $\Delta p_i(t)$	Entrance fluid pressure; fluid pressure drop
$p_{O_2,i,j}(t)$; $\overline{p}_{O_2,i}(t)$	O_2 partial pressure of $f_{i,j}(t)$; average PO_2
$r_i(t)$	Viscous resistance
$s_{O_2,i}(t)$	O_2 saturation
$v_i(t)$	Blood volume

Materials and methods

The blood flow and oxygen transport models used here have been described in detail previously (Barrett and Suresh, 2013; Barrett et al., 2012), but a summary of the theory and principal equations is given below. Table 1 contains a list of dynamic variables used in the model, and Supplementary Table 1 contains a list of the parameters. Similar to other models (Huppert et al., 2007; Zheng et al., 2005) we represent the complex cerebrovascular network as four lumped compartments: arteries, capillaries, veins, and tissue. These are referred to by the subscripts 1, 2, 3, and t respectively. The subscripts 0 and 4 refer to unmodelled larger arterial and venous compartments. Continuing a previous convention, variables in upper case are absolute quantities, while those in lower-case are dimensionless. The superscript * (*e.g.* $cmr^*_{O_2}$) represents a steady state value, typically at baseline.

Blood flow model

The model of fluid dynamics predicts changes in CBF and CBV in response to functional activation. Since the signalling pathways responsible for neurovascular coupling remain unclear (Attwell et al., 2010), in the model these changes are driven by an empirical vasodilatory stimulus which reduces arterial compliance and induces arterial dilation. The model generates predictions consistent with *in vivo* experimental measurements of CBF, CBV, blood vessel diameter and red blood cell velocity (Barrett et al., 2012).

The derivation and additional mathematical detail can be found in the original publication (Barrett et al., 2012), but briefly, the volume of blood within a vascular compartment i, $v_i(t)$, is conserved according to the equation

$$\frac{dv_i}{dt} = f_{i-1,i}(t) - f_{i,i+1}(t), \quad (1)$$

where $f_{i,j}(t)$ is the blood flow from compartment i to j. To conserve energy, the pressure at the entrance to each compartment, $p_i(t)$, can be written as

$$p_i(t) = \frac{1}{2} r_i(t) f_{i-1,i}(t) + \frac{v_i(t)}{c_i(t)}. \quad (2)$$

Here, the viscous resistance $r_i(t)$ is based on Poiseuille's law and depends on $v_i(t)$. The vascular compliance $c_i(t)$ incorporates the effects of volume stiffening, viscoelasticity and smooth muscle activation. Finally, the pressure drops across each compartment, $\Delta p_i(t)$, must sum to the total (reference) pressure drop, Δp_r, such that

$$\Delta p_r - \sum_{i=1}^{3} \Delta p_i(t) = 0. \quad (3)$$

With three vascular compartments, Eqs. (1)–(3) define a system of seven differential-algebraic equations in four flows and three volumes.

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