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Modelling confounding effects from extracerebral contamination and systemic factors on functional near-infrared spectroscopy

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ABSTRACT

Haemodynamics-based neuroimaging is widely used to study brain function. Regional blood flow changes characteristic of neurovascular coupling provide an important marker of neuronal activation. However, changes in systemic physiological parameters such as blood pressure and concentration of CO_2 can also affect regional blood flow and may confound haemodynamics-based neuroimaging. Measurements with functional near-infrared spectroscopy (fNIRS) may additionally be confounded by blood flow and oxygenation changes in extracerebral tissue layers. Here we investigate these confounds using an extended version of an existing computational model of cerebral physiology, 'BrainSignals'. Our results show that confounding from systemic physiological factors is able to produce misleading haemodynamic responses in both positive and negative directions. By applying the model to data from previous fNIRS studies, we demonstrate that such potentially deceptive responses can indeed occur in at least some experimental scenarios. It is therefore important to record the major potential confounders in the course of fNIRS experiments. Our model may then allow the observed behaviour to be attributed among the potential causes and hence reduce identification errors.

1. Introduction

Neuroimaging techniques relying on changes in tissue haemodynamics and oxygenation, such as functional near-infrared spectroscopy (fNIRS) and blood oxygen level dependent (BOLD) based functional magnetic resonance imaging (fMRI), have been widely and productively used to investigate cerebral function. Regional haemodynamic changes provide a marker of neuronal activation due to tight neurovascular coupling (Logothetis et al., 2001; Gagnon et al., 2015; Weber, 2015).

It is well known that a variety of systemic physiological factors also significantly affect cerebral blood flow (Rostrup et al., 2002; Ainslie and Duffin, 2009; Battisti-Charbonney et al., 2011; Sobczyk et al., 2016). Changes to these factors can occur in the course of functional experiments. Such changes may, of course, be unrelated to the experimental procedure, but may also arise more systematically (Tachtsidis and Scholkmann, 2016). For example, task-evoked changes in mean blood pressure have been demonstrated in protocols including anagram solving (Tachtsidis et al., 2009), visual stimulation (Minati et al., 2009) and video gaming (Tachtsidis and Papaioannou, 2013). Similarly, changes to blood CO_2 concentration have been observed in tasks involving speaking (Scholkmann et al., 2013a) and mental arithmetic (Scholkmann et al., 2013b). In the case of fNIRS, there is further scope for confounds arising from haemodynamic/oxygenation changes in the extracerebral compartment of the head. Near-infrared light passes through the overlying scalp and skull tissue layers in order to interrogate the cerebral tissues underneath, and significant optical absorption and scattering can occur in these layers (Franceschini et al., 1998; Kirilina et al., 2012; Erdoğan et al., 2014).

It is important to understand and account for such potential confounds in order to reach reliable conclusions (Minati et al., 2011; Scholkmann et al., 2014b; Tachtsidis and Scholkmann, 2016). Numerous approaches have been proposed, ranging from purely statistical signal processing to biophysical modelling at various levels of detail.

Statistical models rest on the identification of shared variational relationships between different contributory elements in the measured signals. Importantly, systemic factors such as blood pressure and heart rate, along with contaminant estimators such

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as fNIRS recordings with short channel separations, may be included as additional regressors (Saager et al., 2011; Gagnon et al., 2012; Goodwin et al., 2014; Brigadoi and Cooper, 2015; Yücel et al., 2015).

In contrast, biophysical modelling approaches constrain system behaviour based on knowledge of the underlying physiology. Cerebral haemodynamics are affected by both active regulation and the passive biomechanics of the blood vessels and surrounding tissue, in turn constrained by the rigid enclosure of the skull (Zhang, 2002; Hu et al., 2006; Tzeng and Ainslie, 2013; Ainslie, 2014). Interactions between these elements and the response to neuronal activation are complex (e.g. (Maggio et al., 2014)) and have been modelled in numerous ways.

The system is usually considered as one or more conductive compartments that offer some resistance to flow and have some capacity to distend. A convenient analogy is to an electrical circuit, with blood flow corresponding to electrical current through resistors and volume to charge stored on capacitors. The Balloon (Buxton et al., 1998; Friston et al., 2000; Buxton et al., 2004) and Windkessel (Mandeville et al., 1999; Olufsen et al., 2002; Boas et al., 2003) models are archetypes of this form. Resistances and capacitances are not fixed and may have functional dependencies on flow, volume and other stimuli. An important foundation for treatments of the latter is the Ursino-Lodi family of models (Ursino and Lodi, 1997, 1998; Ursino et al., 2000), which are based on similar principles to the Balloon and Windkessel models but include influences from systemic factors such as blood pressure and blood CO_2 concentration, as well as the production and reabsorption of cerebrospinal fluid. These models originate in the study of autoregulation and intracranial pressure rather than neuroimaging.

Modelled haemodynamics relate to fNIRS data via the quantities of marker species, particularly oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (HHb), present in the imaged volume. The amounts of each change with blood flow in and out of the tissue and also with oxygen diffusion and consumption. Typically fNIRS-oriented models treat the imaged tissue as effectively homogenous, simply estimating the NIRS measurements from relative blood volume, but there have been a number of attempts to give a more detailed characterisation of the relationships between blood flow, tissue oxygenation and the optical signals (Fantini, 2002, 2013, 2014; Diamond et al., 2006, 2009).

In this paper we use a modified version of the BrainSignals biophysical model (Banaji et al., 2008; Caldwell et al., 2015) to investigate confounding by systemic and extracerebral factors, with particular reference to the issue of misleading 'false positive' results, which have the appearance of activation when in fact none occurred, and 'false negative' results, which do not show evidence of activation even though it was actually present (Tachtsidis and Scholkmann, 2016). The existing model, a simplified descendant of the earlier BrainCirc (Banaji et al., 2005), addresses the cerebral compartment only. It incorporates both a haemodynamic component that models autoregulation and CO_2 reactivity (drawing on (Ursino and Lodi, 1998)) and a model of a portion of the mitochondrial metabolism (drawing on (Korzeniewski and Zoladz, 2001)) to model oxygen consumption. Here we extend this with an additional compartment to model scalp haemodynamics.

The purpose of the joint model is to provide a tool by which the potential contributions to measured fNIRS signals can be understood and to assist the interpretation of experimental data that may be subject to confounding. This is in contrast to more 'model-free' denoising approaches, in which the systemic factors are directly regressed out of the measurements. While these approaches can be very successful (Saager and Berger, 2005; Tachtsidis et al., 2010b; Gagnon et al., 2014b), the implicit assumption that confounds map linearly to fNIRS artefacts may fail to capture more complex or interacting effects. Moreover, if the systemic changes are correlated to the cerebral activation there is a risk that some of the functional brain activity may be regressed out along with systemic contributions. A more explicit modelling approach allows the inclusion and exploration of key interactions governing system behaviour from known physiology. As the relationship between fNIRS measurements and systemic physiological parameters is often non-linear and non-stationary, this approach allows a better description of this complexity. In addition to providing a tool of data integration and denoising, this approach provides a test base platform for computational simulation investigations of various physiological scenarios such as the ones presented in this paper.

2. Methods

2.1. Modelling

The model used here, termed BSX (from BrainSignals eXtended), derives from earlier models described in Caldwell et al. (2015) and Banaji et al. (2008). The overall structure shared by all these models is depicted in Fig. 1. There are two main interacting functional compartments: a haemodynamic compartment representing blood flow and oxygen delivery to the brain tissue, and a metabolic compartment, representing oxygen consumption in the neuronal mitochondria. There are important feedback relationships between the two compartments, since metabolism depends on the supply of O_2, while O_2 concentration and metabolic demand are among the modulators of blood flow. The state variables in the two compartments are used to predict NIRS measurements of haemoglobin and cytochrome *c* oxidase (CCO).

In the haemodynamic compartment, blood flow is driven by, and regulated in response to three systemic inputs—mean arterial pressure (P_a), arterial partial pressure of carbon dioxide (P_aCO_2) and arterial oxygen saturation (S_aO_2)—together with an explicit

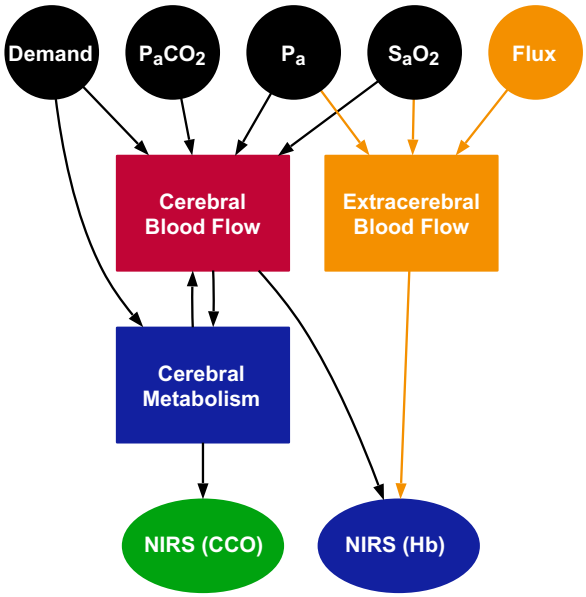

Fig. 1. Main structure of the BSX model. Model inputs are represented as circles, the main dynamic compartments as rectangles and outputs as ellipses. Two distinct NIRS outputs are simulated: haemoglobin-based measurements (labelled Hb), estimated from the blood flow compartments, and measurements of the cytochrome *c* oxidase redox state (labelled CCO), estimated from the metabolic model. Elements shown in orange are new to BSX, while those in blue are modified from the previously published model B1M2 in Caldwell et al. (2015). The remaining elements are adopted unchanged. (A more detailed diagram showing the relationships between all variables and parameters in the model can be found in Supplementary Fig. 1.).