Practical Steps for Applying a New Dynamic Model to Near-Infrared Spectroscopy Measurements of Hemodynamic Oscillations and Transient Changes:

Implications for Cerebrovascular and Functional Brain Studies

Jana M. Kainerstorfer, PhD, Angelo Sassaroli, PhD, Bertan Hallacoglu, PhD, Michele L. Pierro, MSc, Sergio Fantini, PhD

Rationale and Objectives: Perturbations in cerebral blood volume (CBV), blood flow (CBF), and metabolic rate of oxygen ($CMRO_2$) lead to associated changes in tissue concentrations of oxy- and deoxy-hemoglobin (ΔO and ΔD), which can be measured by near-infrared spectroscopy (NIRS). A novel hemodynamic model has been introduced to relate physiological perturbations and measured quantities. We seek to use this model to determine functional traces of $cbv(t)$ and $cbf(t) - cmro_2(t)$ from time-varying NIRS data, and cerebrovascular physiological parameters from oscillatory NIRS data (lowercase letters denote the relative changes in CBV, CBF, and $CMRO_2$ with respect to baseline). Such a practical implementation of a quantitative hemodynamic model is an important step toward the clinical translation of NIRS.

Materials and Methods: In the time domain, we have simulated $O(t)$ and $D(t)$ traces induced by cerebral activation. In the frequency domain, we have performed a new analysis of frequency-resolved measurements of cerebral hemodynamic oscillations during a paced breathing paradigm.

Results: We have demonstrated that $cbv(t)$ and $cbf(t) - cmro_2(t)$ can be reliably obtained from $O(t)$ and $D(t)$ using the model, and that the functional NIRS signals are delayed with respect to $cbf(t) - cmro_2(t)$ as a result of the blood transit time in the microvasculature. In the frequency domain, we have identified physiological parameters (e.g., blood transit time, cutoff frequency of autoregulation) that can be measured by frequency-resolved measurements of hemodynamic oscillations.

Conclusions: The ability to perform noninvasive measurements of cerebrovascular parameters has far-reaching clinical implications. Functional brain studies rely on measurements of CBV, CBF, and $CMRO_2$, whereas the diagnosis and assessment of neurovascular disorders, traumatic brain injury, and stroke would benefit from measurements of local cerebral hemodynamics and autoregulation.

Key Words: Hemodynamic model; near-infrared spectroscopy; cerebral autoregulation; cerebral blood flow; metabolic rate of oxygen.

Near-infrared spectroscopy (NIRS) can assess noninvasively cerebral hemodynamics and brain function by being sensitive to cerebral concentrations of deoxyhemoglobin (D) and oxy-hemoglobin (O). Noninvasive measurements of task-related functional activity with NIRS, or fNIRS, have been reported (1–3). These hemodynamic changes result from changes in the cerebral blood volume (CBV), cerebral blood flow (CBF), and metabolic rate of oxygen ($CMRO_2$) as a result of brain activation and neurovascular coupling. Understanding the interplay between these physiological/functional/metabolic processes and the measured signals with functional neuroimaging techniques such as fNIRS and functional magnetic resonance imaging is the major objective of hemodynamic models (for a review, see Buxton, 2012 (4)).

A novel hemodynamic model has been recently introduced to provide an analytical tool for the study of oscillatory (frequency domain) and time varying (time domain) hemodynamics that are measurable with NIRS (5). The model relates

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From the Department of Biomedical Engineering, Tufts University, 4 Colby St, Medford, MA 02155 (J.M.K., A.S., B.H., M.L.P., S.F.); and Cephalogics, LLC, Boston, MA (B.H., present address). Received August 9, 2013; accepted October 26, 2013. This article is dedicated to the Commemoration of Dr. Britton Chance's 100th birthday, a small tribute to his immense legacy. This research is supported by the National Science Foundation (Award No. IIS-1065154) and National Institutes of Health (Grant no. R01-CA154774). Drs. Kainstorfer and Sassaroli contributed equally to the work. **Address correspondence to:** J.M.K. e-mail: jana.kainerstorfer@tufts.edu

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normalized perturbations in CBV, CBF, and $CMRO_2$ to the dynamics of O and D concentrations in tissue. In particular, this model treats the cerebral microvasculature in terms of three compartments (arterial, capillary, venous) and describes the effects of changes in blood volume in all three compartments (even though the capillary contribution to blood volume changes may be negligible), and the effects of changes in blood flow and metabolic rate of oxygen in the capillary compartment (direct effects) and the venous compartment (indirect effects). This novel model can be applied to measurements in the time domain ($O(t)$, $D(t)$), where hemodynamic changes are induced over time, and in the frequency domain (via the phasors $\mathbf{O}(\omega)$, $\mathbf{D}(\omega)$), where induced hemodynamic oscillations are measured as a function of the frequency of oscillation. Hemodynamic oscillations at a specific frequency can be induced by a number of protocols including paced breathing (6), head-up-tilting (7), squat-stand maneuvers (8), and pneumatic thigh-cuff inflation (9), leading to a technique that we have recently proposed, coherent hemodynamics spectroscopy (CHS) (5,10).

In this article, we use a new formulation of this hemodynamic model by Fantini (11) to develop its practical implementation for NIRS and fNIRS measurements. In the time domain, we show how the model can be used to translate time traces of $O(t)$ and $D(t)$ into time-varying measures of $\mathrm{cbv}(t)$ and the difference $\mathrm{cbf}(t) - \mathrm{cmro}_2(t)$*. In the frequency domain, we demonstrate how the model can be used to measure a number of physiologically relevant parameters such as the blood transit time in the microvasculature and the cutoff frequency for cerebral autoregulation. The work presented here demonstrates, in practical terms, that the new hemodynamic model is a workable model for translation of NIRS measurements into functional and physiological parameters. The feasibility of a practical implementation of this mathematical model, in combination with noninvasive NIRS and fNIRS measurements, is a critical element for its translation toward functional and clinical studies.

HEMODYNAMIC MODEL

In the time domain, all of the time-dependent quantities are represented by time varying real functions. In the frequency domain, all of the oscillatory quantities are represented by phasors (5). In the following sections, we discuss how the model equations can be implemented in practice to measure (1) the time dependence of the CBV, and a combination of CBF and $CMRO_2$ associated with brain activation (functional neuroimaging) or (2) a set of physiological parameters on the basis of frequency-resolved measurements of the amplitude and phase of hemodynamic oscillations (CHS).

Time domain equations

We denote with lowercase letters the relative changes in CBV, CBF, and $CMRO_2$ with respect to baseline ($\mathrm{cbv}(t) = \Delta\mathrm{CBV}(t)/\mathrm{CBV}_0$, $\mathrm{cbf}(t) = \Delta\mathrm{CBF}(t)/\mathrm{CBF}_0$, $\mathrm{cmro}_2(t) = \Delta\mathrm{CMRO}_2(t)/\mathrm{CMRO}_2|_0$), where $\Delta\mathrm{CBV}(t) = \mathrm{CBV}(t) - \mathrm{CBV}_0$, $\Delta\mathrm{CBF} = \mathrm{CBF}(t) - \mathrm{CBF}_0$, and $\Delta\mathrm{CMRO}_2 = \mathrm{CMRO}_2(t) - \mathrm{CMRO}_{2|0}$. The time-dependent expressions for the absolute tissue concentrations of $O(t)$, $D(t)$, and total hemoglobin ($T(t)$) are given by (11):

$$O(t) = \mathrm{ctHb}\Big[S^{(a)}\mathrm{CBV}_0^{(a)}\big(1+\mathrm{cbv}^{(a)}(t)\big) + \langle S^{(c)}\rangle \mathrm{F}^{(c)}\mathrm{CBV}_0^{(c)} + S^{(v)}\mathrm{CBV}_0^{(v)}\big(1+\mathrm{cbv}^{(v)}(t)\big)\Big] +$$
$$+\mathrm{ctHb}\left[\frac{\langle S^{(c)}\rangle}{S^{(v)}}\big(\langle S^{(c)}\rangle - S^{(v)}\big)\mathrm{F}^{(c)}\mathrm{CBV}_0^{(c)}h_{RC-LP}^{(c)}(t) + \big(S^{(a)} - S^{(v)}\big)\mathrm{CBV}_0^{(v)}h_{G-LP}^{(v)}(t)\right] * [\mathrm{cbf}(t) - \mathrm{cmro}_2(t)], \quad (1)$$

$$D(t) = \mathrm{ctHb}\Big[\big(1-S^{(a)}\big)\mathrm{CBV}_0^{(a)}\big(1+\mathrm{cbv}^{(a)}(t)\big) + \big(1-\langle S^{(c)}\rangle\big)\mathrm{F}^{(c)}\mathrm{CBV}_0^{(c)} + \big(1-S^{(v)}\big)\mathrm{CBV}_0^{(v)}\big(1+\mathrm{cbv}^{(v)}(t)\big)\Big] +$$
$$-\mathrm{ctHb}\left[\frac{\langle S^{(c)}\rangle}{S^{(v)}}\big(\langle S^{(c)}\rangle - S^{(v)}\big)\mathrm{F}^{(c)}\mathrm{CBV}_0^{(c)}h_{RC-LP}^{(c)}(t) + \big(S^{(a)} - S^{(v)}\big)\mathrm{CBV}_0^{(v)}h_{G-LP}^{(v)}(t)\right] * [\mathrm{cbf}(t) - \mathrm{cmro}_2(t)], \quad (2)$$

$$T(t) = \mathrm{ctHb}\ \mathrm{CBV}_0[1+\mathrm{cbv}(t)]. \quad (3)$$

Note that the right sides of Equations (1)-(3) are given by the sum of time-independent terms (which correspond to the baseline values O_0 in Eq. (1), D_0 in Eq. (2), and T_0 in Eq. (3)) and time-dependent terms associated with $\mathrm{cbv}^{(a)}(t)$, $\mathrm{cbv}^{(v)}(t)$, $\mathrm{cbv}(t)$, $\mathrm{cbf}(t)$, and $\mathrm{cmro}_2(t)$. Explicitly, the time-independent, baseline concentrations of O, D, and T are given by:

$$O_0 = \mathrm{ctHb}\Big[S^{(a)}\mathrm{CBV}_0^{(a)} + \langle S^{(c)}\rangle \mathrm{F}^{(c)}\mathrm{CBV}_0^{(c)} + S^{(v)}\mathrm{CBV}_0^{(v)}\Big], \quad (4)$$

$$D_0 = \mathrm{ctHb}\Big[\big(1-S^{(a)}\big)\mathrm{CBV}_0^{(a)} + \big(1-\langle S^{(c)}\rangle\big)\mathrm{F}^{(c)}\mathrm{CBV}_0^{(c)} +$$
$$\big(1-S^{(v)}\big)\mathrm{CBV}_0^{(v)}\Big], \quad (5)$$

*Lowercase letters denote the relative changes in CBV, CBF, and $CMRO_2$ with respect to baseline.