Nonlinear extension of a hemodynamic linear model for coherent hemodynamics spectroscopy

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HIGHLIGHTS

- Coherent hemodynamics spectroscopy (CHS) quantifies hemodynamic oscillations.
- Near-infrared spectroscopy can measure CHS spectra in a variety of tissues.
- A linear hemodynamic model yields biological meaning of CHS spectra.
- A nonlinear model is presented here to treat cases beyond the linear approximation.
- Cerebral autoregulation and blood flow are among the processes assessed by CHS.

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ABSTRACT

In this work, we are proposing an extension of a recent hemodynamic model (Fantini, 2014a), which was developed within the framework of a novel approach to the study of tissue hemodynamics, named coherent hemodynamics spectroscopy (CHS). The previous hemodynamic model, from a signal processing viewpoint, treats the tissue microvasculature as a linear time-invariant system, and considers changes of blood volume, capillary blood flow velocity and the rate of oxygen diffusion as inputs, and the changes of oxy-, deoxy-, and total hemoglobin concentrations (measured in near infrared spectroscopy) as outputs. The model has been used also as a forward solver in an inversion procedure to retrieve quantitative parameters that assess physiological and biological processes such as microcirculation, cerebral autoregulation, tissue metabolic rate of oxygen, and oxygen extraction fraction. Within the assumption of "small" capillary blood flow velocity oscillations the model showed that the capillary and venous compartments "respond" to this input as low pass filters, characterized by two distinct impulse response functions. In this work, we do not make the assumption of "small" perturbations of capillary blood flow velocity by solving without approximations the partial differential equation that governs the spatio-temporal behavior of hemoglobin saturation in capillary and venous blood. Preliminary comparison between the linear time-invariant model and the extended model (here identified as nonlinear model) are shown for the relevant parameters measured in CHS as a function of the oscillation frequency (CHS spectra). We have found that for capillary blood flow velocity oscillations with amplitudes up to 10% of the baseline value (which reflect typical scenarios in CHS), the discrepancies between CHS spectra obtained with the linear and nonlinear models are negligible. For larger oscillations (~50%) the linear and nonlinear models yield CHS spectra with differences within typical experimental errors, but further investigation is needed to assess the effect of these differences. Flow oscillations larger than 10–20% are not typically induced in CHS; therefore, the results presented in this work indicate that a linear hemodynamic model, combined with a method to elicit controlled hemodynamic oscillations (as done for CHS), is appropriate for the quantitative assessment of cerebral microcirculation.

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1. Introduction

Hemodynamic models are needed in order to interpret the signals measured in neuroimaging techniques, in terms of the underlying physiological dynamics of blood flow, blood volume and metabolic rate of oxygen. This interpretation is usually

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facilitated by hemodynamic models that include both of the following two categories: a) models focusing on the intrinsic dynamic relationship between physiological parameters in several conditions; b) models that are dedicated to understand how the dynamics of physiological parameters are linked to the dynamics of measured signals. For example, a model that explains the coupling or uncoupling between blood flow and oxygen metabolism belongs to the first category. A model dedicated to finding the relationship between the blood oxygen level dependent (BOLD) signal measured in functional magnetic resonance imaging (fMRI), or the optical signal measured in near infrared spectroscopy (NIRS), and the dynamics of blood flow and oxygen metabolism, belongs to the second category. While the models in the first category are general (and therefore usable by different neuroimaging techniques), those in the second category are specific to each neuroimaging modality. Historically, several hemodynamic models have been proposed for interpreting the signal measured in BOLD fMRI or in Positron Emission Tomography (PET). We remind briefly two of the major models that were originally proposed for fMRI, and that had a large impact also for other neuroimaging modalities. Buxton and Frank (1997) proposed an oxygen diffusion limitation model in order to explain the large imbalance (often observed in PET experiments) between changes in blood flow and oxygen consumption during brain activation. They showed that such an imbalance could be consistent with tight coupling between flow and metabolism in the presence of a limitation in oxygen availability. Their model provided a static relationship between the oxygen extraction fraction (a metabolic parameter) and blood flow (a hemodynamic parameter) that could be used to interpret the BOLD signal. Originally, they considered only the extravascular component of the BOLD signal and concluded that if flow and metabolism were coupled, BOLD signal could be used as a robust estimator of flow changes. Later, Buxton (Buxton et al., 1998) in order to explain the BOLD signal when both the intra- and extravascular components were considered, proposed the "balloon model" for the relationship between deoxyhemoglobin concentration and blood volume in the venous compartment. The balloon model used typical mass conservation properties in order to obtain a system of coupled differential equation linking blood volume and deoxyhemoglobin concentration. The temporal trend of blood flow entering the venous compartment was assumed as the typical boxcar function used for brain activation. The blood flow exiting the venous compartment was modeled as a power law of the venous blood volume, extending improperly a static property, Grubb's law (Grubb et al., 1974) to a dynamic situation. Mandeville (Mandeville et al., 1999), based on experimental observations of different temporal dynamics of blood flow (measured with laser Doppler flowmetry) and blood volume (measured with MRI) during forepaw stimulation in rats, proposed a windkessel model for the relationship between flow and volume which was mathematically given by coupled partial differential equations having the dynamic trends of flow and volume as unknown. The authors derived this system of partial differential equation by using more basic physiological principles, such as the fact that blood flow in the capillary and venous compartments is modulated by changes in blood pressure due to changes in arteriolar resistance, and that veins (due to the presence of muscle cells) respond to an increase in pressure with a delayed compliance, as observed *in vivo* (Porciuncula et al., 1964). In the original windkessel model (Mandeville et al., 1999), the capillary and venous compartments were lumped in a single compartment (windkessel compartment), but the authors also proposed a serial windkessel model where the volume contributions from these two compartments could be separated. The windkessel model also had a large impact in NIRS. A first example is found in the work of Boas (Boas et al; 2003), where the authors

used the windkessel model in order to assess the ratio between the changes in cerebral metabolic rate of oxygen ($CMRO_2$) and the changes in blood flow during a finger tapping task. Their model used 13 parameters to fit the changes of oxy-, deoxy-, and total hemoglobin concentrations measured on the subjects during a finger tapping task. Six of these parameters where held fixed, whereas the remaining seven were varied in an optimization scheme. Among the parameters retrieved by the fit, four parameters characterized the dynamics of the arteriolar resistance and the windkessel transit time (comprising the transit time in the capillary and venous compartments). Expanded (three compartments) windkessel models have also been proposed (Zheng et al., 2005; Huppert et al., 2007, 2009). Huppert (Huppert et al., 2007) extended the three compartments windkessel model proposed by Zheng (Zheng et al., 2005), by introducing the concept of capillary compliance and allowing oxygen extraction to occur also in the arterioles and small veins. The authors used multimodal optical imaging, combining the information of laser speckle imaging and NIRS in order to measure the changes in blood flow and hemoglobin concentration in tissue during a rat whisker stimulation protocol. The coupled partial differential equations for blood volume and flow, and also for oxygen extraction, were solved based on the optimization of 14 state variables that were retrieved by the inversion procedure. Seven of these parameters were used to model the dynamic arteriolar expansion and the dynamic change of $CMRO_2$ in tissue. Other parameters retrieved by the model were the vascular transit time, the pial vessel transit time and the baseline hemoglobin saturations in the three compartments (showing an interesting possibility of the model, to retrieve absolute baseline values from relative optical intensity measurements). One of the results of this work was that a three compartment windkessel model could fit the experimental data better than a single compartment windkessel model. The windkessel model, together with a model of oxygen dynamics and exchange with tissue, has also been used for more complicated vascular networks, comprising 32 arterioles, 32 venules and 64 capillaries (Boas et al., 2008). This study was an important step toward the modeling of more realistic vascular networks. However, the model proposed was used only as a "forward" solver in order to predict the distribution of blood flow velocity, pressure, and hemoglobin saturation along the network for a steady state response to localized arterial dilation, and also during transient arterial dilation and oxygen consumption. The changes in the concentration of oxy-, deoxy-, and total hemoglobin were also calculated and averaged in the arterioles, capillaries and venules. Finally, we mention the work of Diamond (Diamond et al., 2009), where the authors developed a complex multi-compartment model (comprising 13 different compartments) in order to model the baseline fluctuations of intensity measured in NIRS. In summary, most of the hemodynamic models found in the literature, and described briefly above, are based on the solution of a system of partial differential equations in order to retrieve physiological information during different conditions.

Recently, our group proposed a novel technique to study tissue hemodynamics, named coherent hemodynamic spectroscopy (CHS) (Fantini, 2014a, 2014b). The technique is based on inducing controlled and stable hemodynamic oscillations by a forcing mechanism (e.g. paced breathing, cyclic thigh cuff inflation/deflation etc.) at different frequencies. The oscillations are induced during hemodynamic and metabolic "equilibrium" states of a tissue under investigation in order to measure some underlying physiological parameters (like the capillary and venous transit times and the autoregulation cutoff frequency). For this purpose, a hemodynamic model was also proposed in order to interpret the induced oscillations in optical intensity measured by NIRS in terms of blood flow, blood volume, and metabolic dynamics. From a