Development of a Model to Aid NIRS Data Interpretation: Results from a Hypercapnia Study in Healthy Adults

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Abstract The use of a mathematical model of cerebral physiology and metabolism may aid the interpretation of experimentally measured data. In this study, model outputs of tissue oxygen saturation (TOS) and velocity of blood in the middle cerebral artery (Vmca) were compared with experimentally measured signals (TOS using near infrared spectroscopy and Vmca using transcranial Doppler) acquired during hypercapnia in healthy volunteers. Initially, some systematic discrepancies between predicted and measured values of these variables were identified. The model was optimised to best fit the measured data by adjusting model parameters. To improve the fit, three additional model mechanisms were considered. These were: an extracerebral contribution to TOS, a change in venous volume with CO_2 levels, and a change in oxygen consumption with CO_2 levels. Each mechanism, when used alone, improved the fit of the model to the data, although significant parameter changes were necessary. It is likely that a combination of these mechanisms will improve the success of modelling of TOS and Vmca changes during hypercapnia.

1 Introduction

Changes in carbon dioxide levels are known to alter cerebral blood flow [1]. Hypercapnia studies have been carried out in healthy volunteers to characterise brain tissue oxygenation and blood flow changes, measured with near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD) [2].

Here we apply the BrainSignals model [3], a physiological model of brain circulation and metabolism, to data from a hypercapnia study in healthy adults [4]. The model predicts several physiological variables, including those which can be measured with NIRS and TCD. It has previously been used successfully to de-

scribe the effects of hypoxia, also in healthy adults. We aimed to reproduce the experimental results as closely as possible with the model, and in doing so, enhance our understanding of the measurements, and the effects of hypercapnia.

2 The BrainSignals model

The structure of the model is illustrated in Figure 1. The circulatory part of the model comprises three compartments: arteries and aterioles, capillaries and veins. The venous and capillary volumes are fixed, but the arterial/arteriolar compartment has variable resistance which is sensitive to four input variables: the arterial pressure of carbon dioxide ($PaCO_2$), the arterial oxygen saturation, the mean arterial blood pressure (MBP), and a parameter representing neuronal activation. $PaCO_2$ affects the resistance via the following equations.

$$\frac{\mathrm{d}\nu}{\mathrm{d}t} = \frac{1}{\tau}(\mathrm{PaCO}_2 - \nu) \tag{1}$$

$$\eta = R_C\left(\frac{\nu}{\nu_n} - 1\right) + \ldots \tag{2}$$

Here, τ is a time constant, and ν represents a low-pass filtered version of $PaCO_2$ with normal value ν_n. R_C is a parameter controlling the magnitude of the response to $PaCO_2$ changes and has a default value of 2.2. The muscular tension in the arterial wall depends on η, which is the sum of the $PaCO_2$ term shown and three similar terms for the other input variables listed above. An average vessel radius is calculated from the balance of pressures and tensions in the vessel wall. This in turn determines the resistance of the arterial/arteriolar tree via Poiseuille's law. An increase in vessel radius leads to an increase in blood volume and blood flow. The model output of velocity of blood in the middle cerebral artery (Vmca) is proportional to cerebral blood flow.

All blood compartments have a fixed haemoglobin concentration [Hb] whose default value in the model is 2.275mM. In each compartment, a fraction of this haemoglobin is oxygenated. These fractions are determined from the arterial oxygen saturation (a model input), and from the rate of oxygen transport to the mitochondria for respiration. The tissue oxygen saturation (TOS) is the overall percentage of oxygenated haemoglobin in the arteries and veins. The steady state changes of Vmca and TOS with default model parameters and varying $PaCO_2$ are shown in Figure 2.

3 Methods

Data were analysed from a hypercapnia study of fourteen healthy adult volunteers [4]. This involved a 1.5 kPa increase in end tidal CO_2 ($EtCO_2$) for 10 min, with 5 min at baseline before and after. Throughout the study, the subjects' heart rate, mean blood pressure (MBP) and arterial oxygen saturation (SaO_2) were monitored. The blood velocity in the middle cerebral artery (Vmca) was also monitored, using transcranial Doppler. The tissue oxygen saturation (TOS), a measure of the percentage of oxygenated haemoglobin, was obtained using the NIRO 300 (Hamamatsu Photonics KK). All signals were smoothed and filtered, and any periods with obvious instrumentation noise were identified by inspection and replaced by a linear interpolation. SaO_2, $EtCO_2$ and MBP were input to the model, and its outputs compared with the measured Vmca and TOS.

Parameter optimisation was carried out using a version of Powell's method implemented in SciPy [5]. The rms difference between a measured and simulated signal was calculated by a numerical integration of the squared difference between the two signals, over all time points. The aim of optimisation was to minimise this rms difference for each subject, using TOS, Vmca, or a weighted combination of the two. For Vmca, the simulated data from each parameter set was rescaled so that its average value matched that of the measured data, prior to error calculation. Initially, two model parameters were optimised: blood haemoglobin concentration [Hb] (or haematocrit), chosen for its influence on the absolute TOS value, and R_C, which represents the sensitivity of the flow response to $PaCO_2$ changes.

The success of a simulated dataset was judged by its rms difference, and also by comparing its response with that of the measured data. To calculate the response, a period of hypercapnia and a subsequent baseline period were identified by inspection of the $EtCO_2$ trace for each subject. The response was then calculated from the means during these periods, after resampling to 1 Hz, as follows

$$\text{TOS response} = \text{TOS(hypercapnia)} - \text{TOS (baseline)} \tag{1}$$

$$\text{Vmca response} = \frac{\text{Vmca(hypercapnia)} - \text{Vmca(baseline)}}{\text{Vmca(baseline)}} \times 100\% \tag{2}$$

After analysing the results, three new mechanisms were added to the model in turn. Firstly, to simulate an extracerebral contribution to TOS, TOS(corrected) was calculated as the weighted sum of intra and extracerebral compartments

$$\text{TOS(corrected)} = (1- t)\ \text{TOS(i)} + t\ .\ \text{TOS(e)} \tag{3}$$

where t is the fractional contribution of the extracerebral compartment, and TOS(e) its fixed TOS value. TOS(i), the intracerebral TOS, was calculated as before. TOS(e) and t were optimised together with R_C. Secondly, venous volume

was varied with CO_2 levels. Previously, it was fixed at 0.75 of the normal total blood volume ($V_{blood,n}$). This was changed to

$$\text{venous volume} = (0.75 + v\,(PaCO_2 - PaCO_{2,n}))\, V_{blood,n} \quad (4)$$

where $PaCO_{2,n}$ is the model's normal value of $PaCO_2$. The constant v was included as an optimisation parameter. Finally, a change linking metabolic rate to CO_2 levels was introduced, via a parameter representing the demand. This was varied in a similar way to venous volume

$$\text{demand} = 1.0 + d\,(PaCO_2 - PaCO_{2,n}) \quad (5)$$

and d was optimised. Changes in demand also have a direct effect on the blood flow; but this was removed here by setting the relevant parameter R_u to zero.

4 Results

The measured data are summarised in Table 1. The mean (± SD) TOS and Vmca responses were 1.1 ± 0.8% and 26 ± 11%, respectively.

Table 1 Summary of the measured data, mean (SD) across the 14 subjects.

	Normocapnia	Hypercapnia
Duration (s)	240 (20)	500 (50)
$EtCO_2$ (kPa)	5.2 (0.3)	6.9 (0.3)
TOS (%)	69 (6)	70 (6)
Vmca (cms^{-1})	42 (11)	52 (13)

The six differently optimised datasets are summarised in Table 2. Parameter values not given in the table were set at their defaults, except for [Hb]. In optimisations 2 and 4–6 [Hb] was fixed at its value from optimisation 1. The errors in TOS and Vmca response for each subject in each of these optimisation sets, and for no optimisation, are shown in Figure 3. With no optimisation, mean simulated TOS response was 7.1 ± 1.1%. Vmca was better predicted, with a mean response of 32 ± 6%. The response of each signal could be matched well when optimising to that signal alone. The parameter [Hb] was not included in the Vmca optimisation since it only had a small effect on the response. The mean value of R_C resulting from optimisation 2 was significantly larger than that from optimisation 1; i.e. a greater sensitivity of blood flow to CO_2 was required to explain the changes measured in Vmca, than that required to explain the changes measured in TOS. Consequently, optimisation 3, which attempted to match both signals, was less successful: in every subject, simulated TOS response was too large, whilst simulated Vmca response was too small.

Table 2 Details of the optimisation methods and results. The first row contains the mean (SD) across the 14 subjects of the optimised parameter values. No value given indicates that a parameter was fixed.

Optimisation		1	2	3	4	5	6
Parameters optimised	R_C	0.3 (0.2)	1.5 (0.6)	1.1 (0.4)	1.6 (0.6)	1.4 (0.6)	1.2 (0.4)
	[Hb] (mM)	2.1 (0.7)	-	2.0 (0.7)	-	-	-
	t	-	-	-	0.79 (.13)	-	-
	TOS(e) (%)	-	-	-	69 (6)	-	-
	v (mmHg)$^{-1}$	-	-	-	-	0.06 (0.05)	-
	d (mmHg)$^{-1}$	-	-	-	-	-	0.16 (0.05)
Signals optimised to	TOS	x	-	x	x	x	x
	Vmca	-	x	x	x	x	x

All three new model mechanisms reduced this discrepancy. The additional compartment for TOS was the most successful, leading to simulated TOS and Vmca responses of 1.1 ± 0.6% and 22 ± 6%. The mean optimum weight of the extracerebral compartment was 0.8 (range 0.45-0.95). With a varying venous volume, simulated response was reduced to 1.6 ± 0.9% for TOS and 20 ± 7%, for Vmca, and therefore matched better the measured signals. However, this corresponded to a mean venous volume change of 100%, (range 20-230%). When optimising the change in oxygen metabolism, the mean resulting cerebral metabolic rate of oxygen consumption ($CMRO_2$) increase was 18 ± 8.5%. Simulated TOS and Vmca responses were 1.5 ± 0.9% and 21 ± 8% which matched well with the measured signals. An example of the $CMRO_2$ change in one subject, along with the measured and modelled TOS and Vmca, is shown in Figure 4.

5 Discussion

As expected, Vmca and TOS increased during hypercapnia. The model behaviour was qualitatively correct, but consistently overestimated the ratio of TOS response to Vmca response. All three additional mechanisms reduced this discrepancy; however, the magnitude of the changes required for optimum fitting suggested that no single mechanism is likely to be successful in its own right.

TOS has been shown to have a high sensitivity and specificity to intracerebral changes [6]. It is surprising therefore, that an 80:20 extracerebral to intracerebral weighting was required to optimise the fitting of the TOS data.

The method of changing venous volume was very simplistic. A more realistic method could be incorporated, as in other models [7]. However, a large change in venous volume would still be required to fit TOS response accurately. Evidence from PET studies indicates that the cerebral blood volume changes seen during hypercapnia are caused primarily by arterial volume changes [8]. Our optimisation

suggests a doubling of the venous volume during the hypercapnia challenge, which seems unlikely.

Finally, linking of $CMRO_2$ to CO_2 levels allowed improved simulations of Vmca and TOS. But as before, the 18% increase was unexpectedly large. Changes in brain blood flow and oxygenation during CO_2 challenges are well documented; however, there are still open questions regarding the changes in metabolism [9]. CO_2 is usually assumed to be metabolically neutral. For example, in fMRI studies, hypercapnia is often used with this assumption to estimate oxygen metabolism changes from the BOLD signal [10]. However, recently Tachtsidis and colleagues have analysed the NIRS measured change in concentration of cytochrome c oxidase (CCO), and reported an increase in the CCO redox state in healthy volunteers during hypercapnia, that cannot be exclusively attributed to the increase in oxygen delivery [4]. We are currently exploring whether CCO measurements can provide additional data to help discriminate between the different hypotheses presented above.

In conclusion, there is an anomalous (small) change of TOS in response to hypercapnia that cannot be explained by optimisation of a single parameter in our model. We are currently attempting to optimise to a combination of factors simultaneously. If this does not prove possible it will suggest that TOS as measured optically does not report on the cerebral oxygen saturation as defined in our model,

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References

1. Reivich M (1964) Arterial PCO_2 and cerebral hemodynamics. Am J Physiol 206:25-35
2. Tisdall M, Taylor C, Tachtsidis I et al. (2009) The Effect on Cerebral Tissue Oxygenation Index of Changes in the Concentrations of Inspired Oxygen and End-Tidal Carbon Dioxide in Healthy Adult Volunteers. Anesth Analg 109(3):906-913
3. Banaji M, Mallet A, Elwell C et al (2008) A model of brain circulation and metabolism: NIRS signal changes during physiological challenges. PloS Comput Biol 4:e1000212
4. Tachtsidis M, Tisdall M, Leung T et al (2009) Relationship between brain tissue haemodynamics, oxygenation and metabolism in the healthy human adult brain during hyperoxia and hypercapnea. Adv Exp Med Biol 645:315-320
5. Jones E, Oliphant T, Peterson P et al (2001) SciPy Open source scientific tools for Python. http://www.scipy.org
6. Al-Rawi P, Smielewski P, Kirkpatrick P (2001) Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. Stroke 32:2492-2500

7. Ursino M, Lodi C (1998) Interaction among autoregulation, CO2 reactivity, and intracranial pressure: a mathematical model. Am J Physiol 274:H1 715-H1 728
8. Ito H, Ibaraki M, Kanno I et al (2005) Changes in the arterial fraction of human cerebral blood volume during hypercapnia and hypocapnia measured by positron emission tomography. J Cereb Blood Flow Metab 25:852-857
9. Siesjo B (1980) Cerebral metabolic rate in hypercarbia–a controversy. Anesthesiology 52:461-465
10. Davis T, Kwong K, Weisskoff R et al (1998) Calibrated functional MRI: mapping the dynamics of oxidative metabolism. Proc Natl Acad Sci USA 95:1834-1839

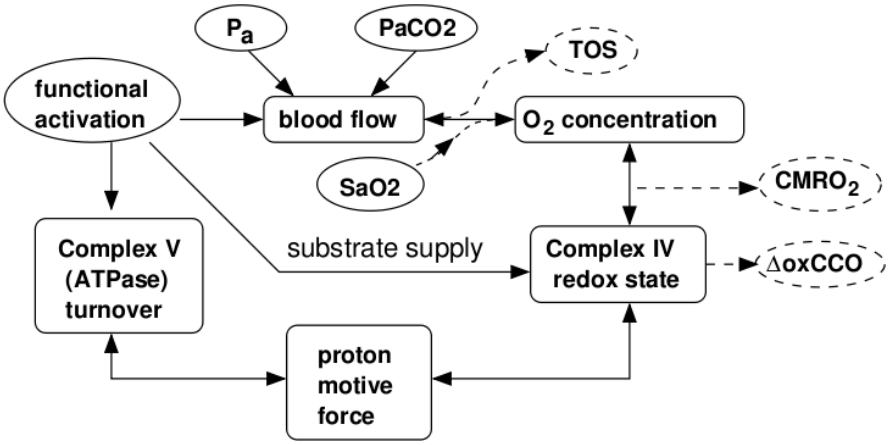

Fig. 1. A diagram of the BrainSignals model. Inputs are shown in solid ovals and outputs in dashed ovals. Model processes are shown in rectangles. Figure reproduced from Banaji *et al.* [3].

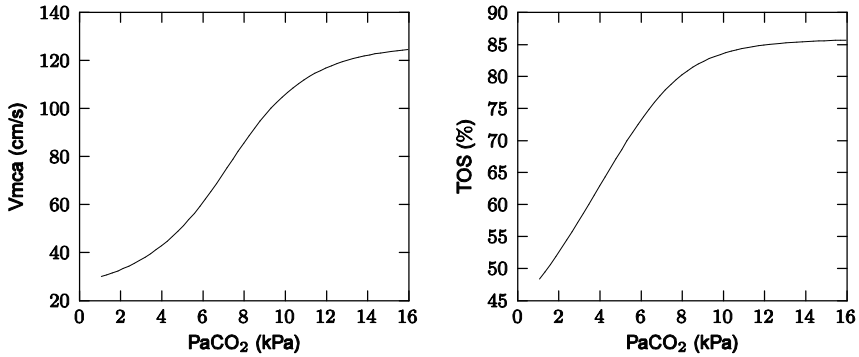

Fig. 2. Prediction o f Vmca and TOS by the model at different $PaCO_2$ values.

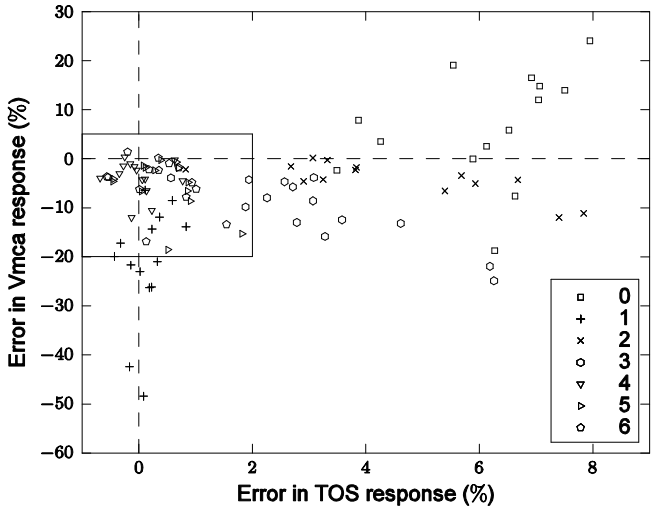

Fig. 3 Modelled response minus measured response for TOS vs Vmca. The response is the difference (TOS) or percentage change (Vmca) of the mean at hypercapnia from the mean at baseline. The legend refers to the six optimisation methods described in Table 2. Series 0 represents no optimisation. Each point within a series represents a subject. The box at the origin surrounds all the points from optimisations 4-6, where new mechanisms were introduced.

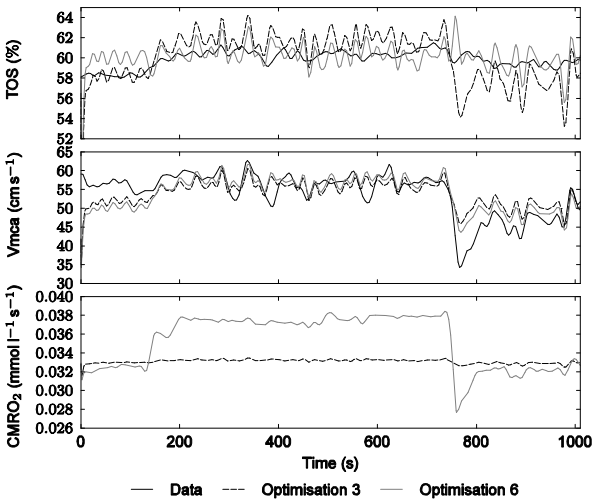

Fig. 4. Examples of TOS, Vmca and $CMRO_2$ from one volunteer. The graphs show the measured signal (solid black), the modelled signal after optimisation 3 (dashed) and the modelled signal after optimisation 6 (solid grey).