

DR. STEPHEN JOHN PAYNE (Orcid ID : 0000-0003-1156-2810)

Article type : Original Research

Oxygen delivery from the cerebral microvasculature to tissue is governed by a single time constant of approximately 6 seconds

SJ Payne^{1,*} and C Lucas²

¹Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford

Parks Road, Oxford OX1 3PJ, UK

²School of Engineering, University of Warwick, Coventry CV4 7AL

* Corresponding author

stephen.payne@eng.ox.ac.uk; c.lucas@warwick.ac.uk

Short running title: Oxygen delivery from cerebral microvasculature

Abstract

The cerebral microvasculature plays a key role in the coupling between cerebral blood flow and metabolism. Although experimental imaging techniques now allow for finely detailed measurements

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/micc.12428

This article is protected by copyright. All rights reserved.

of flow and oxygenation, within humans measurements remain confined to a voxel level scale, of order 1 mm. Mathematical models are thus key in interpreting such data. However, these can be highly complicated, due to the large number of vessels and the non-linearities in the governing equations. We thus propose here a new model of the cerebral microvasculature and show how its behaviour can be simplified based on order of magnitude arguments. The resulting model shows a dependence upon just two time constants, termed 'slow' and 'metabolic' time constants; the tissue oxygenation response can be characterised by convolution of the difference between the fractional flow and metabolic responses with a single exponential, with time constant equal to half the ratio of tissue volume to blood flow multiplied by the ratio of effective oxygen solubility in tissue and blood. The overall response time for the whole network is approximately 6 seconds; this value indicates that the flow response to increases in metabolic activity cannot be driven solely by changes in tissue oxygenation.

Keywords: Cerebral blood flow; oxygen transport

1 Introduction

The cerebral microvasculature plays a crucial role in the delivery of oxygen from the bloodstream to the surrounding tissue. This vasculature comprises many vessels over a range of length scales, with vessel diameters in the range from a few μm to hundreds of μm . The transport of oxygen between the bloodstream and the surrounding tissue takes place over a number of different vessel generations, Lipowsky (2005): under baseline conditions, oxygen saturation drops from around 95 % to approximately 75 % prior to entering the capillary vessels and thereafter to close to 55 % on entry to the venules, with only a small drop after this. The coupling between cerebral blood flow and

oxygen delivery is thus dependent upon the properties of these generations, most importantly the last few generations of the arteriolar vasculature and the capillary bed.

However, at this length scale, individual vessels can only be imaged in animal models, with human imaging data restricted to a resolution of order 1 mm. Given the importance of the coupling between flow and metabolism, particularly in terms of the neurovascular coupling, there have been a number of models that examine this response. Models that simulate the flow through casts of animal microvascular networks have been developed by a number of authors, for example Fang et al. (2008), Weber et al. (2008), Reichold et al. (2009), Tsai et al. (2009), Guibert et al. (2010), Blinder et al. (2010), Safaeian et al. (2011), Kasischke et al. (2011), Linninger et al. (2013), Gagnon et al. (2015), Gould et al. (2017) and Schmid et al. (2017). Models based on human data, extracted from post-mortem tissue, have also been developed, for example Lorthois et al. (2011).

The difficulties involved with this approach, which are the strong dependence of any results on the choice of boundary conditions and the high computational expense of simulating the flow in volumes of any significant size, have motivated a parallel approach to modelling these networks. Based on the generation of artificial networks that match the available experimental data, Su et al. (2012), homogenization techniques have been proposed that allow for the scaling up of networks to a voxel length scale, El-Bouri and Payne (2015), El-Bouri and Payne (2016). Such approaches can then be linked to voxel-based imaging data through the use of metrics such as perfusion and transit time distributions, Park and Payne (2013).

However, the equations that govern the transport of oxygen and its delivery to tissue also need to be considered. These are more challenging as they are non-linear and oxygen transport occurs over a number of vessel generations, making a network model necessary. Such models are, however, required in order to scale up models of oxygen transport computationally efficiently. They are also important to help to interpret the response to changes in metabolic activity, in particular quantifying the speed of different components of this response; this is difficult since there are many factors

acting to balance the supply to and consumption of oxygen in cerebral tissue, although recent models have shown promise in performing these simulations computationally efficiently, see for example Gould et al. (2017). The classical view that it is hypoxia that drives changes in flow has now largely superseded by the idea that it is a parallel process with two separate responses, Buxton (2012). The model proposed here thus considers the passive response of the tissue to changes in flow and metabolism that will provide a rigorous basis for more detailed models of the feedback mechanisms involved in the regulation of flow in response to changes in metabolism as part of the neurovascular coupling.

2 Materials and Methods

2.1 Governing Equations

We use the same modelling framework as proposed by Boas et al. (2008). This approach considers a vessel in terms of its average oxygen concentration, \bar{c} :

$$\frac{\partial(V_b \bar{c})}{\partial t} = F_{in}c_{in} - F_{out}c_{out} - 2\pi jRL \quad (1)$$

where the vessel has inlet flow, F_{in} , and concentration, c_{in} , and outlet flow, F_{out} , and concentration, c_{out} . The volume of the blood vessel is $V_b = \pi R^2 L$, where the vessel has radius R and length L . The flux of oxygen between vessel and tissue per unit area is given by j . Since the rate of change of volume can be directly related to flow:

$$\frac{\partial V_b}{\partial t} = F_{in} - F_{out} \quad (2)$$

and we assume that average oxygen concentration is the mean of the inlet and outlet values, we find:

$$V_b \frac{1}{2} \left(\frac{\partial c_{in}}{\partial t} + \frac{\partial c_{out}}{\partial t} \right) + \frac{1}{2} (F_{in} + F_{out})(c_{out} - c_{in}) = -2\pi jRL \quad (3)$$

which we use as the basis for the model. It is worth noting that there are a number of assumptions inherent to this model, as described by Boas et al. (2008), and that it is based on the area-averaged concentration for simplicity. It should be noted that these governing equations are based on conservation of blood volume and oxygen and are not intended as the basis for a numerical scheme, which we do not make use of here.

The corresponding equation for the surrounding tissue is:

$$V_t \frac{\partial c_t}{\partial t} = 2\pi jRL - MV_t \quad (4)$$

where we assume that the tissue compartment is well-mixed with volume, V_t , and concentration, c_t , set by the metabolic rate, M . For simplicity, we assume that there is a linear relationship for oxygen flux proportional to the pressure difference between vessel and tissue; in the vessel this is again taken to be the average value, hence:

$$j = \frac{K}{h} \left(\frac{1}{2}(p_{in} + p_{out}) - p_t \right) \quad (5)$$

where the oxygen permeability of the wall is given by K and the wall has thickness h . Note that we do assume that each vessel generation supplies an independent tissue volume and that we thus neglect diffusion within the tissue; we do this as we do not consider the spatial behaviour of the network. This limitation of the model is considered again in the Discussion.

One of the main difficulties in solving the coupled model is the strongly non-linear relationship between concentration and partial pressure of oxygen in the bloodstream. We assume here a linear relationship for oxygen concentration and saturation of the form:

$$c_b = c_{Hb}HS \quad (6)$$

where c_{Hb} is the oxygen-carrying capacity per unit volume of red blood cells, H is the blood haematocrit and S is the oxygen saturation of haemoglobin. Note that we neglect the solubility of

oxygen in blood for simplicity, since this is only a few per cent of the total. The non-linearity then occurs in the relationship between oxygen saturation and partial pressure. In the tissue, we can, however, assume a linear relationship with partial pressure:

$$c_t = \alpha_t p_t \quad (7)$$

where α_t is the solubility of oxygen in brain tissue.

Making the necessary substitutions, these reduce the equations to:

$$V_b \frac{1}{2} \left(\frac{\partial S_{in}}{\partial t} + \frac{\partial S_{out}}{\partial t} \right) + \frac{1}{2} (F_{in} + F_{out}) (S_{out} - S_{in}) = - \frac{2\pi KRL}{h c_{Hb} H} \left(\frac{1}{2} (p_{in} + p_{out}) - p_t \right) \quad (8)$$

$$\alpha_t V_t \frac{\partial p_t}{\partial t} = \frac{2\pi KRL}{h} \left(\frac{1}{2} (p_{in} + p_{out}) - p_t \right) - MV_t \quad (9)$$

The non-linearity between partial pressure and saturation in the bloodstream prevents exact solutions of these equations except under very particular conditions. However, we can gain considerable insight into the model behaviour by considering the relative magnitudes of the different terms. To do this, we reduce the governing equations to non-dimensional form, except that we retain the time dimension for reasons that will become apparent later. Relating partial pressures of oxygen in the bloodstream and tissue to baseline values \bar{p}_b and \bar{p}_t respectively and using the star to denote a value as a fraction of its baseline value, we obtain:

$$\varepsilon T_t \frac{1}{2} \left(\frac{\partial S_{in}^*}{\partial t} + \frac{\partial S_{out}^*}{\partial t} \right) + \frac{1}{2} (f_{in}^* + f_{out}^*) (S_{out}^* - S_{in}^*) = -\kappa \left(\frac{1}{2} (p_{in}^* + p_{out}^*) - \gamma_p p_t^* \right) \quad (10)$$

$$\gamma_c T_t \frac{\partial p_t^*}{\partial t} = \kappa \left(\frac{1}{2} (p_{in}^* + p_{out}^*) - \gamma_p p_t^* \right) - \gamma_c \frac{T_t}{T_m} m^* \quad (11)$$

where:

$$\gamma_p = \frac{\bar{p}_t}{\bar{p}_b} \quad (12)$$

$$\gamma_c = \frac{\bar{c}_t}{c_{Hb}H} \quad (13)$$

$$\kappa = \frac{2\pi KRL\bar{p}_b}{hFc_{Hb}H} \quad (14)$$

the first two of these being the ratios of partial pressures and concentrations respectively and the third being a non-dimensional mass transfer coefficient. We also define two time constants:

$$T_t = \frac{V_t}{F} \quad (15)$$

$$T_m = \frac{\bar{c}_t}{M} \quad (16)$$

where F and M are baseline values of flow and metabolism, and the ratio of blood to tissue volume:

$$\varepsilon = \frac{V_b}{V_t} \quad (17)$$

Note that this parameter is small, since blood occupies only a few percent of total brain volume.

Since saturation is already non-dimensional, we retain it in its original form.

Having presented the governing equations (apart from the precise form of the saturation-partial pressure relationship, which we will examine in more detail later) and non-dimensional groups, we next consider their values in a cerebral vascular network. This will then provide the basis for investigating solutions to the governing equations.

2.2 Network model

Boas et al. (2008) describe the generation of a vascular network that covers all of the generations of vessels that have any significant role in the transport of oxygen to tissue (the last few generations of the arteriolar tree and the capillary bed). We use this model as a starting point, although we adapt it since we are particularly interested in the magnitudes of the time constants and we therefore do not wish to assume a constant vessel length in all of the arterioles and venules, as was done in this

earlier study. It should also be noted that a 20 % reduction in arteriolar diameter at each branch and a 20 % increase in venule diameter at each branch was assumed, with a set capillary diameter of 8 μm . Through direct matching of the model to experimental data, we are able to propose a network generation procedure that requires fewer assumptions than used by Boas et al. (2008); this procedure can thus also be generalised in future to any similar network.

As with Boas et al. (2008), we assume a bifurcating network with 13 generations (6 arteriolar, 1 capillary and 6 venule) and assume that the capillary diameter is 8 μm . Conservation of flow yields:

$$D_i^2 U_i = 2D_{i+1}^2 U_{i+1} \quad (18)$$

for consecutive arteriolar generations i and $i + 1$, where D and U denote vessel diameter and flow velocity respectively (an equivalent equation is used on the venous side). We then use the data presented by Zweifach and Lipowsky (1977) that give a relationship between diameter and velocity: using Equation 18, values of vessel diameter and flow velocity can be interpolated across all the vessel generations, as detailed in Lucas (2012).

The next parameter to be calculated is the vessel length, which is calculated based on the drop in blood pressure along each individual vessel. The Poiseuille equation is then used in the form:

$$L = \frac{\Delta p D^2}{32\mu U} \quad (19)$$

where the viscosity is calculated from the relationships proposed by Pries et al. (1992), with haematocrit assumed to be constant at a value of 0.42. The choice of constant haematocrit is based on application of the recently proposed model of Gould and Linninger (2015), which, given the assumptions of bifurcating vessels with constant vessel cross-sectional area in each generation, reduces to constant haematocrit throughout the network; we then select the baseline value quoted by these authors. We note that this approach is different from that taken by Boas et al. (2008) and

that this is a significant assumption; the potential influences of this assumption will be examined in more detail in the Discussion.

The pressure drops across each vessel are also interpolated from the data of Zweifach and Lipowsky (1977). For both completeness and reproducibility, we include the data that were extracted and used in this interpolation algorithm in Appendix A. We also give a schematic of the method of calculation of the vascular parameters in Figure 1, showing how once the initial capillary diameter (denoted in this figure by D_1) is specified, the velocity and pressure can be found by interpolation and the remaining vascular parameters can be calculated iteratively across first generations A6-A1 and then V1-V6 using a combination of experimental correlations and Equations 18 and 19.

Figure 1 Schematic of method of calculation of vascular parameters: (18) = Equation 18; (19) = Equation 19; (P) = correlations of Pries et al. (1992); (Z) = data of Zweifach and Lipowsky (1977)

The resulting values of vessel diameter and length, and flow haematocrit, viscosity and velocity are given in Table 1. The values of oxygen saturation in the different vessels are reproduced from Boas et al. (2008), since these are found to be in good agreement with the data of Lipowsky (2005), although we make slight adjustments (all less than 1 %) to these values in order to smooth the trend in order to perform linear interpolation, as described below.

The final parameter that needs to be calculated is the wall thickness. Note that this is not calculated in Boas et al. (2008), since they lump together all of the parameters in the wall oxygen transfer into an 'oxygen extraction coefficient', which is assumed to be constant across all vessel generations. Since we assume instead that the oxygen permeability of the vessel wall is constant, we need to calculate the vessel wall thickness directly.

We do this based on the experimental data of Harper and Bohlen (1984), which shows that the cross-sectional area of the wall varies with vessel internal diameter. We fit a quadratic expression

using a least-squares error approach to these data, quoted in Table 1 of Harper and Bohlen (1984), to give the following relationship:

$$\frac{A}{\pi} = 0.16D^2 + 1.4D + 14 \quad (20)$$

with all dimensions being in mm and A denoting cross-sectional area of the vessel wall. The wall thickness can then be calculated from:

$$h = \frac{-D + \sqrt{D^2 + 4(A/\pi)}}{2} \quad (21)$$

For completeness, to calculate the tissue volume, we balance the transfer of oxygen from each vessel with the metabolic demands of the surrounding tissue, assuming essentially that each vessel supplies an independent volume of tissue for simplicity. As a result:

$$V_t = \frac{C_{Hb}H\Delta S}{M} \quad (22)$$

for each vessel. Since we take the experimental values of oxygen saturation to denote the vessel average, we interpolate linearly across the network to calculate the drop in oxygen saturation for each vessel. This is the reason for the slight adjustments to oxygen saturation mentioned above, since otherwise the interpolation can result in negative gradients and hence negative tissue volumes; since the alterations are all less than 1 %, this has only a very small impact on the overall behaviour of the model. The resulting complete set of vascular parameters is given in Table 1.

The resulting variations in blood pressure and oxygen saturation are shown in Figure 2 alongside a picture of the vascular model: since we develop the model based directly on the experimental data, we do not plot the experimental data as they have been fitted exactly. Note that, although the vessels are shown in Figure 2 with the correct lengths, the relative positions of vessels are arbitrary, being shown in this layout purely for visual convenience. It is worth noting, as also shown in Boas et al. (2008), that the largest drops in oxygen saturation occur in the last three generations of the

arteriolar and the capillary branches; these are thus the generations that largely control oxygen transport to tissue. We use a conversion factor from moles of oxygen to ml of oxygen equal to $4.46 \times 10^{-5} \text{ mol_O}_2/\text{ml}$ throughout.

Figure 2 Model network: network geometry (top); and variations (bottom) in (left) blood pressure and (right) oxygen saturation

In order to calculate the non-dimensional groups and time constants listed in Equations 12-17, additional parameters are required and these are given in Table 2, together with their sources. The resulting non-dimensional groups are then plotted in Figure 3 across the different generations of vessels. We immediately note that the non-dimensional wall transfer coefficient is much larger than one, and that the ratios of concentrations and partial pressures are both much less than one, as would be expected. The ratio of blood to tissue volume varies over quite a wide range of values, although it is consistently much less than one in the arterioles and capillary vessels, only rising in the venules. This is due to the small predicted values of tissue volume, based on the small drops in oxygen saturation in the post-capillary vessels, Equation 22, and thus has only a small effect on the overall behaviour of the model.

Figure 3 Variations in non-dimensional groups in the vascular branches of the network model

3 Results

Based on the values of the parameter groups and time constants calculated in the previous section, we now return to the model equations (Equations 10 and 11) to consider how they can be simplified based on the relative magnitudes of the parameter groups as shown in Figure 3. Since the governing equations are non-linear, we first perform a linearization about baseline conditions. Although an approximation, this is a valuable starting point, particularly in this context, where the changes across each individual vessel are relatively small (noting that the baseline conditions are then of course different in each vessel generation).

We begin by considering a locally linear approximation between saturation and partial pressure of the form:

$$S - \bar{S} = G(p^* - \bar{p}^*) \quad (23)$$

where this is referenced to a local baseline condition, \bar{S} and \bar{p}^* . This is essentially a Taylor series approximation for the partial-pressure/saturation curve that will be different for each vessel, since the local sensitivity of saturation to partial pressure, G , varies strongly with partial pressure. We can justify this approximation in individual vessels since there is a relatively small drop in partial pressure in each vessel, making a linear approximation a reasonable assumption over each vessel.

We then also assume that the changes in flow are relatively small, which reduces the governing equations to the following:

$$\varepsilon G T_t \frac{1}{2} \left(\frac{\partial p_{in}^*}{\partial t} + \frac{\partial p_{out}^*}{\partial t} \right) + G(p_{out}^* - p_{in}^*) + G \Delta f^* (\bar{p}_{out}^* - \bar{p}_{in}^*) = -\kappa \left(\frac{1}{2} (p_{in}^* + p_{out}^*) - \gamma_p p_t^* \right) \quad (24)$$

$$\gamma_c T_t \frac{\partial p_t^*}{\partial t} = \kappa \left(\frac{1}{2} (p_{in}^* + p_{out}^*) - \gamma_p p_t^* \right) - \gamma_c \frac{T_t}{T_m} m^* \quad (25)$$

where we introduce a new parameter Δf^* , which is the change in flow as a fraction of its baseline value, as also used in Equations 14 and 15. The overbar is used to denote the baseline conditions for partial pressure in each individual vessel and can be calculated as the solution to the steady state form of Equations 24 and 25, giving:

$$\bar{p}_{in}^* - \bar{p}_{out}^* = \frac{\gamma_c T_t}{G T_m} \quad (26)$$

Equations 24 and 25 can easily be solved, most simply using the Laplace transform. The resulting transfer function between partial pressures of oxygen in tissue and outlet flow and changes in flow and metabolism can then be written in the form:

$$p_{out}^* = H_{out} p_{in}^* + J_{out} \Delta f^* + K_{out} m^* \quad (27)$$

$$p_t^* = H_t p_{in}^* + J_t \Delta f^* + K_t m^* \quad (28)$$

where s is the Laplace variable and where the transfer functions are given by:

$$H_{out} = T_t^2 \frac{\left(-s^2 \frac{\varepsilon \gamma_c}{\gamma_p \kappa} T_t^2 - s \left(\varepsilon + \frac{\gamma_c}{2\gamma_p}\right) T_t + 1\right)}{(sT_s + 1)(sT_f + 1)} \quad (29)$$

$$H_t = \frac{1}{\gamma_p} \frac{1}{(sT_s + 1)(sT_f + 1)} \quad (30)$$

$$J_{out} = \frac{\gamma_c T_t}{GT_m} \frac{\left(\frac{s\gamma_c T_t}{\gamma_p \kappa} + 1\right)}{(sT_s + 1)(sT_f + 1)} \quad (31)$$

$$J_t = \frac{\gamma_c T_t}{2\gamma_p GT_m} \frac{1}{(sT_s + 1)(sT_f + 1)} \quad (32)$$

$$K_{out} = -\frac{\gamma_c T_t}{GT_m} \frac{1}{(sT_s + 1)(sT_f + 1)} \quad (33)$$

$$K_t = -\frac{\gamma_c T_t}{2\gamma_p GT_m} \frac{\left(\frac{2s\varepsilon GT_t}{\kappa} + 1\right)}{(sT_s + 1)(sT_f + 1)} \quad (34)$$

Note that the denominator of all of these equations is second order and can thus be written in the form of two time constants: these are found from the factorisation of the characteristic equation:

$$s^2 T_t^2 \frac{\varepsilon \gamma_c}{\gamma_p \kappa} + s T_t \left(\varepsilon + \frac{\gamma_c}{2\gamma_p G} + \frac{\gamma_c}{\gamma_p \kappa}\right) + 1 = 0 \quad (35)$$

The values of these time constants, denoted 'fast' and 'slow', are shown in Figure 3 in comparison with the metabolic time constant, Equation 16. It can immediately be seen that the fast and slow time constants are very different in magnitude: one is of order 1 whilst the other is of order 10^{-5} – 10^{-4} seconds. The response is thus governed by a very fast component and a much slower component. These can be closely approximated, based on Equation 35, by:

$$T_s = \frac{\gamma_c}{2\gamma_p G} T_t \quad (36)$$

$$T_f = \frac{2\varepsilon G}{\kappa} T_t \quad (37)$$

and these are shown in Figure 4 in comparison with the exact values, illustrating that the approximations are very close to the exact values (noting that this is particularly the case in the arterial and capillary vessels, with a larger discrepancy being found in the venous vessels, where the response is less important given the small changes in saturation found in these vessels). The metabolic time constant is also included for comparison: this is typically about one order of magnitude less than the 'slow' time constant on the arteriolar and capillary side, but still much larger than the 'fast' time constant.

Figure 4 Time constants governing model, both exact and approximate solutions shown

It is worth considering these two time constants in more detail, since they play a key role in the vascular response to changes in flow and metabolism. Returning them to dimensional form yields:

$$T_s = \frac{1}{2} \frac{V_t}{F} \frac{\alpha_t}{\alpha_b} \quad (38)$$

$$T_f = \frac{\alpha_b h R}{\kappa} \quad (39)$$

where we have defined an 'equivalent local' solubility of oxygen in the bloodstream:

$$\alpha_b = \frac{\partial c_b}{\partial p_b} \quad (40)$$

to simplify the expressions above. This parameter is, of course, not constant, rather varying with the absolute value of partial pressure of oxygen in the bloodstream, as discussed earlier. It is in fact, however, a key parameter, being the only one that controls both time constants. The fact that it

increases as the partial pressure reduces explains why the fast time constant tends to increase and why the slow time constant tends to decrease as the flow passes towards the capillary bed.

These two time constants govern the response of each individual vessel to changes in flow and metabolism; they are thus crucial in the response to these changes. The fact that they are so different in magnitude, however, means that the response can be significantly further simplified. We do this by considering the system in terms of its impulse response to changes in both flow and metabolism: although this is not the only way of characterising the response, it provides a compact representation of the linear component of the response of the system to these changes.

The tissue response to small changes in flow can be expressed in terms of its impulse response:

$$j_t = \frac{1}{T_m} \left(e^{-\frac{t}{T_s}} - e^{-\frac{t}{T_f}} \right) \quad (41)$$

and similarly in response to changes in metabolism:

$$k_t = -\frac{1}{T_m} \left(e^{-\frac{t}{T_s}} - \frac{2G}{\kappa} e^{-\frac{t}{T_f}} \right) \quad (42)$$

taken from the inverse Laplace transforms of Equation 32 and 34 respectively. For simplicity, in Equation 42 we have neglected second order terms. Note that we use lower case for the impulse responses to emphasise the fact that these are expressed in the time domain. These two responses can then be approximated, since the fast time constant is so rapid, by:

$$j_t = \frac{1}{T_m} e^{-\frac{t}{T_s}} \quad (43)$$

$$k_t = -\frac{1}{T_m} e^{-\frac{t}{T_s}} \quad (44)$$

The responses are thus at this level of approximation equal in magnitude and opposite in direction to each other. This means that the responses of tissue oxygenation to small fractional changes in flow and metabolism are equal and opposite both in magnitude and speed.

The tissue response to small changes in flow and metabolism can thus be written as a simple convolution with a decaying exponential with time constant equal to the 'slow' time constant and scaling equal to one over the metabolic time constant:

$$p_t^* = \frac{1}{T_m} \left\{ (\Delta f^* - m^*) \otimes e^{-\frac{t}{T_s}} \right\} \quad (45)$$

The fractional tissue response is governed by just two parameters: the metabolic time constant and the slow time constant, the values of which are shown in Figure 4. It is worth noting that within the arteriolar and capillary beds, these values are close to constant and thus the response of the tissue to changes in flow and metabolism is largely invariant over the different generations (since the venous side of the microvasculature contributes little to oxygen delivery, these values are of lesser importance).

Hence it is the slow time constant that governs the speed of the metabolic response (noting again that this is not simply the ratio of volume to flow): the fast time constant essentially has no effect on the tissue oxygenation response, since it is so much more rapid than the slow time constant, which dominates the response. This does mean that a number of parameters in the original model have essentially only minimal impact on the model behaviour. For example the permeability of the vessel wall has only a very small effect on the response (since it is sufficiently large to enable oxygen to transport freely across the vessel wall): variations in this parameter will have only a minimal effect on the overall model response. The key parameters are those that set the slow time constant, i.e. those in Equation 38.

We now consider the response of the whole network. The model considers each generation of blood vessels to be surrounded by a separate block of tissue. If we can assume that the tissue is well mixed

at this length scale, then we can consider the whole tissue response to be the weighted sum of the responses of each vessel generation:

$$p_t^* = \frac{1}{\sum_{i=1}^I N_i V_{t,i}} \sum_{i=1}^I \frac{N_i V_{t,i}}{T_{m,i}} (\Delta f^* - m^*) \otimes e^{-\frac{t}{T_{s,i}}} \quad (46)$$

where the summation is over all of the vessel generations, where each generation, denoted by subscript i , has N_i vessels. Substitution of the expressions for tissue volume and noting that conservation of flow gives:

$$N_i F_i = F \quad (47)$$

yields:

$$p_t^* = \frac{1}{T_m} (\Delta f^* - m^*) \otimes \frac{1}{\Delta c_b} \sum_{i=1}^I \Delta c_{b,i} e^{-\frac{t}{T_{s,i}}} \quad (48)$$

where:

$$\Delta c_{b,i} = c_{Hb} H_i \Delta S_i \quad (49)$$

$$\Delta c_b = \sum_{i=1}^I \Delta c_{b,i} \quad (50)$$

Hence the different impulse responses are weighted by the drop in oxygen concentration in the relevant blood vessel generation. For the network proposed here, this gives the overall network impulse response shown in Figure 5, where the individual responses of each type of vessel are also shown. Note that the metabolism responses are the same but multiplied by minus one. There are very substantial variations across the different generations of vessels, as would be expected, with the venous vessels responding very rapidly and the arteriolar and capillary vessels response times lying in the approximate range 4-12 seconds.

Figure 5 Impulse response of whole network (solid line), in comparison to individual vessels:
arterioles (dashed lines); capillaries (dotted line); venules (dash-dot lines)

The overall time constant of this network is equal to 6.37 seconds, being as expected within the range shown by the arteriolar and capillary vessels. It should be noted that this approach is only an approximate estimate of the time constant, since the full network model should strictly be solved and the complete response simulated; however, the method described here does provide a very simple means of obtaining a first order estimate of the tissue response. The advantage of this approach is also that it provides a proper physiological basis for calculating the relevant time constants, based on a physical model of oxygen transport. The result is also scale invariant, since the time constants calculated on this microvascular network can be applied to larger volumes without adjustment, as long as the physiological properties of these small networks retain spatial invariance. Any changes in vascular properties can also easily be accounted for within this framework.

4 Discussion

In this paper we have investigated the response of the oxygenation of brain tissue to changes in flow and metabolism. We have proposed a new model of the cerebral microvasculature, one that matches explicitly the experimental data with fewer assumptions than were made in the similar model by Boas et al. (2008). With further experimental data, it would be possible to adapt the model. The total tissue volume considered in this model is approximately 0.006 mm^3 , which is a very small volume, much smaller than an imaging voxel: however, the approach here is scale invariant and can thus be applied to any larger volume of tissue that matches the same properties.

We have shown that the response of the partial pressure of oxygen in the tissue can be accurately described by two time constants, of which the most important is the 'slow' time constant, since the 'fast' time constant is essentially so small that this component of the response is in quasi-equilibrium at all times. This slow time constant is given by Equation 38, showing that the key parameters are

the ratio of tissue volume to blood flow and the ratio of the values of effective solubility of oxygen in tissue and blood. The overall network response is a weighted sum of the individual responses to each generation of vessels, yielding an overall time constant of approximately 6 seconds.

It is worth noting that the flow changes through the network, as controlled by local and global autoregulatory processes, equilibrate very rapidly in comparison with the resulting changes in oxygenation, so the flow can be assumed to be in quasi-steady-state in comparison with changes in tissue oxygenation. Changes in baseline flow will of course alter both the baseline levels of oxygen saturation in the bloodstream and the tissue; we also note here that the slow time constant is inversely proportional to baseline flow, so that any changes in this will affect the speed of response (higher flow rates yielding a faster response and vice versa), although these are unlikely to make a very substantive difference to the approximate magnitude of this time constant. Changes in baseline metabolism will not affect the slow time constant: rather they will simply affect the magnitude of the fractional response (if not the magnitude of the absolute response).

It is important to note that we have considered a purely passive network here. As a result, the fact that the tissue responds equally to both fractional changes in flow and metabolism is not surprising: this means that if flow changes in the same proportion to metabolism, the partial pressure of oxygen in the tissue will remain unchanged. This is, however, not what is found experimentally, where the ratio of changes in flow to changes in metabolism is known to be significantly higher than 1, see for example Buxton (2012). Hence, it is important to consider the overall response as the sum of the passive and the active responses.

One important aspect of this is that we have assumed that each vessel generation supplies a local tissue volume. This essentially assumes that tissue is supplied predominantly by the nearest vessel and neglects the diffusion of oxygen through the tissue. This is obviously a significant limitation to the model and one that was utilised for simplicity. Additionally, we have neglected the three-dimensional nature of the vasculature, considering a purely hierarchical network, as shown in Figure

2. A more detailed model that considered the full three-dimensional nature of the cerebral vasculature, such as those described in the Introduction, embedded within a spatially-varying tissue model would be a valuable next step and this is currently under development, following the work of El-Bouri and Payne (2016). The aim of the model presented here was to provide a simple means of gaining an insight into the dynamic model behaviour without the complexity of a three-dimensional model. It will be very interesting to compare these results with those obtained from more accurate three-dimensional models in order to assess the validity of the approach that we have presented here.

We also note that we have assumed a constant haematocrit throughout the network; although this is a direct mathematical consequence of our other assumptions, it should be noted that the haematocrit in fact varies widely throughout the cerebral microvasculature. The results of Gould and Linninger (2015) have shown that the choice of model can significantly influence the patterns of haematocrit predicted in the microvasculature and that there are significant spatial variations in the distribution of red blood cells, as has also been examined by Schmid et al. (2017) using a model that tracks individual red blood cells. Our assumption is thus a significant approximation and one that should be re-examined in future; in particular to examine the likely statistical impact of these variations in haemodynamic states on the overall model response. This planned future work will link with our three-dimensional model as mentioned above.

Cerebral blood flow is tightly regulated in response to global changes in blood pressure (the phenomenon termed cerebral autoregulation) and adjusted in response to local increases in metabolic activity (the phenomenon termed the neurovascular coupling). The traditional view has been that it is changes in arteriolar tone that is the dominant mechanism, with alterations in smooth muscle stiffness controlling vessel diameter. However, the role of pericytes has received much recent attention, since these have been shown actively to relax to induce vasodilation, with capillary dilation occurring faster than arteriolar dilation in a rat model, Hall et al. (2014). It is now thought

that this highly localised control mechanism plays a key role, particularly within the context of the neurovascular coupling. This will be particularly important at small length scales, such as those considered here.

Since the time constant for changes in tissue oxygenation in response to changes in local metabolism is approximately 6 seconds, the tissue responds relatively slowly to such changes. This provides support for the view that changes in the flow occur in parallel with those in metabolism, since the response would be very slow otherwise. Hall et al. (2014) show that the response time of both capillary and arteriole diameter is of order 5 seconds (from visual inspection of Figure 3 in their paper), meaning that this must be controlled by a mechanism other than a response to hypoxia, since the 6 second time constant means that this pathway would be too slow to be the dominant response.

This slow response could also help to explain the magnitude of the active response, since to avoid hypoxia there must be an active response that is sufficiently large to counterbalance the slow tissue response to changes in flow: the tissue is responding to both with the same response time, so transient hypoxia can only be avoided if the flow response is exactly in parallel with the change in metabolism or if the flow response is much bigger than the metabolic response (to compensate for any initial drop). Studies have shown that the partial pressure of oxygen is indeed maintained through an increase in CBF, Devor et al. (2011) and Buxton (2012), indicating clearly, in conjunction with the results presented here, that the active flow response must be very rapid, much more so than would be possible in response to the slow hypoxic alterations.

It will thus be necessary to consider the integrated response that includes the effects of regulation of blood flow within both the microvasculature described in the model here (which controls oxygen transport) and the upstream vasculature (which controls blood supply through setting inlet blood pressure). The model presented here provides the first component of this model that can now be incorporated within a larger framework, since its behaviour has been characterised in a simple form

that makes it easy to implement within larger models. This will allow for more detailed validation against experimental data. This model will thus be able to help to interpret the varying responses to different stimuli, ranging from autoregulation to the neurovascular coupling and in assessing the tissue response to changes in metabolic activity.

Perspectives

The cerebral microvasculature response to changes in flow and metabolism is governed by two time constants: the 'slow' time constant and the metabolic time constant.

The 'slow' time constant is equal to half the ratio of tissue volume to blood flow multiplied by the ratio of effective oxygen solubility in tissue and blood: these are thus the key parameters in the response of the microvasculature to changes in flow and metabolism.

The dominant time constant is approximately 6 seconds, which means that the response of tissue to changes in flow and metabolism is relatively slow: hence the flow response must respond to factors other than just hypoxia.

References

- Blinder P, Shih AY, Rafie C, Kleinfeld D. Topological basis for the robust distribution of blood to rodent neocortex. *Proc Natl Acad Sci USA*. 2010;107:12670–12675.
- Boas DA, Jones SR, Devor A, Huppert TJ, Dale AM. A vascular anatomical network model of the spatio-temporal response to brain activation. *Neuroimage*. 2008 Apr 15;40(3):1116-29
- Buxton RB. Dynamic models of BOLD contrast. *Neuroimage*. 2012 Aug 15;62(2):953-61. doi: 10.1016/j.neuroimage.2012.01.012. Review.

Clark DK, Erdmann W, Halsey JH, Strong E. Oxygen diffusion, conductivity and solubility coefficients in the microarea of the brain. (Measurements with noble metal microelectrodes). Adv Exp Med Biol. 1977 Jul 4-7;94:697-704.

Devor A, Sakadzic S, Saisan PA, Yaseen MA, Roussakis E, Srinivasan VJ, Vinogradov SA, Rosen BR, Buxton RB, Dale AM, Boas DA. "Overshoot" of O₂ is required to maintain baseline tissue oxygenation at locations distal to blood vessels. J Neurosci. 2011 Sep 21;31(38):13676-81. doi: 10.1523/JNEUROSCI.1968-11.2011.

El-Bouri WK, Payne SJ. Multi-scale homogenization of blood flow in 3-dimensional human cerebral microvascular networks. J Theor Biol. 2015 Sep 7;380:40-7.

El-Bouri WK, Payne SJ. A statistical model of the penetrating arterioles and venules in the human cerebral cortex. Microcirculation. 2016 Oct;23(7):580-590. doi: 10.1111/micc.12318.

Fang Q, Sakadzic S, Ruvinskaya L, Devor A, Dale AM, Boas DA. Oxygen advection and diffusion in a three- dimensional vascular anatomical network. Optics Express. 2008;16:17530–17541.

Gagnon L, Sakadžić S, Lesage F, Musacchia JJ, Lefebvre J, Fang Q, Yücel MA, Evans KC, Mandeville ET, Cohen-Adad J, Polimeni JR, Yaseen MA, Lo EH, Greve DN, Buxton RB, Dale AM, Devor A, Boas DA. Quantifying the microvascular origin of BOLD-fMRI from first principles with two-photon microscopy and an oxygen-sensitive nanoprobe. J Neurosci. 2015 Feb 25;35(8):3663-75. doi: 10.1523/JNEUROSCI.3555-14.2015.

Gould IG, Linninger AA. Hematocrit distribution and tissue oxygenation in large microcirculatory networks. Microcirculation. 2015 Jan;22(1):1-18. doi: 10.1111/micc.12156.

Gould IG, Tsai P, Kleinfeld D, Linninger A. The capillary bed offers the largest hemodynamic resistance to the cortical blood supply. J Cereb Blood Flow Metab. 2017 Jan;37(1):52-68. Epub 2016 Oct 10.

Guibert R, Fonta C, Plouraboué F. Cerebral blood flow modeling in primate cortex. *J Cereb Blood Flow Metab.* 2010 Nov;30(11):1860-73. doi: 10.1038/jcbfm.2010.105.

Hall CN, Reynell C, Gesslein B, Hamilton NB, Mishra A, Sutherland BA, O'Farrell FM, Buchan AM, Lauritzen M, Attwell D. Capillary pericytes regulate cerebral blood flow in health and disease. *Nature.* 2014 Apr 3;508(7494):55-60. doi: 10.1038/nature13165.

Harper SL, Bohlen HG. Microvascular adaptation in the cerebral cortex of adult spontaneously hypertensive rats. *Hypertension.* 1984 May-Jun;6(3):408-19.

Huppert TJ, Allen MS, Benav H, Jones PB, Boas DA. A multicompartiment vascular model for inferring baseline and functional changes in cerebral oxygen metabolism and arterial dilation. *Journal of Cerebral Blood Flow and Metabolism.* 2007;27:1262–1279.

Kasischke KA, Lambert EM, Panepento B, Sun A, Gelbard HA, Burgess RW, Foster TH, Nedergaard M. Two-photon NADH imaging exposes boundaries of oxygen diffusion in cortical vascular supply regions. *Journal of Cerebral Blood Flow and Metabolism.* 2011;31:68–81.

Linninger AA, Gould IG, Marinnan T, Hsu CY, Chojecki M, Alaraj A. Cerebral microcirculation and oxygen tension in the human secondary cortex. *Ann Biomed Eng.* 2013 Nov;41(11):2264-84. doi: 10.1007/s10439-013-0828-0. Epub 2013 Jul 11.

Lipowsky HH. Microvascular rheology and hemodynamics. *Microcirculation.* 2005;12:5–15.

Lorthois S, Cassot F, Lauwers F. Simulation study of brain blood flow regulation by intra-cortical arterioles in an anatomically accurate large human vascular network: Part I: methodology and baseline flow. *Neuroimage.* 2011 Jan 15;54(2):1031-42.

Lucas C. An anatomical model of the cerebral vasculature and blood flow. DPhil thesis, University of Oxford. 2012.

- Mintun MA, Lundstrom BN, Snyder AZ, Vlassenko AG, Shulman GL, Raichle ME. Blood flow and oxygen delivery to human brain during functional activity: theoretical modeling and experimental data. *Proc Natl Acad Sci U S A*. 2001 Jun 5;98(12):6859-64. Epub 2001 May 29.
- Park CS, Payne SJ. A generalized mathematical framework for estimating the residue function for arbitrary vascular networks. *Interface Focus*. 2013 Apr 6;3(2):20120078. doi: 10.1098/rsfs.2012.0078.
- Popel AS, Pittman RN, Ellsworth ML. Rate of oxygen loss from arterioles is an order of magnitude higher than expected. *Am J Physiol*. 1989 Mar;256(3 Pt 2):H921-4.
- Pries AR, Neuhaus D, Gaehtgens P. Blood viscosity in tube flow: dependence on diameter and hematocrit. *Am J Physiol*. 1992 Dec;263(6 Pt 2):H1770-8. Review.
- Reichold J, Stampanoni M, Lena Keller A, Buck A, Jenny P, Weber B. Vascular graph model to simulate the cerebral blood flow in realistic vascular networks. *J Cereb Blood Flow Metab*. 2009 Aug;29(8):1429-43.
- Safaeian N, Sellier M, David T. A computational model of hemodynamic parameters in cortical capillary networks. *J Theor Biol*. 2011;271(1):145-156.
- Schmid F, Tsai PS, Kleinfeld D, Jenny P, Weber B. Depth-dependent flow and pressure characteristics in cortical microvascular networks. *PLoS Comput Biol*. 2017 Feb 14;13(2):e1005392. doi: 10.1371/journal.pcbi.1005392. eCollection 2017 Feb.
- Secomb TW, Hsu R, Beamer NB, Coull BM. Theoretical simulation of oxygen transport to brain by networks of microvessels: effects of oxygen supply and demand on tissue hypoxia. *Microcirculation*. 2000; 7(4): 237–247.
- Su SW, Catherall M, Payne S. The influence of network structure on the transport of blood in the human cerebral microvasculature. *Microcirculation*. 2012;19:175–187.

Tsai PS, Kaufhold JP, Blinder P, Friedman B, Drew PJ, Karten HJ, Lyden PD, Kleinfeld D. Correlations of neuronal and microvascular densities in murine cortex revealed by direct counting and colocalization of nuclei and vessels. *Journal of Neuroscience*. 2009;29:14553–14570.

Vovenko E. Distribution of oxygen tension on the surface of arterioles, capillaries and venules of brain cortex and in tissue in normoxia: an experimental study on rats. *Pflügers Arch*. 1999;437:617–623.

Weber B, Keller AL, Reichold J, Logothetis NK. The microvascular system of the striate and extrastriate visual cortex of the macaque. *Cerebral Cortex*. 2008;18:2318–2330.

Zweifach BW, Lipowsky HH. Quantitative studies of microcirculatory structure and function. III. Microvascular hemodynamics of cat mesentery and rabbit omentum. *Circ Res*. 1977 Sep;41(3):380-90.

Branch	Number of vessels	Diameter	Length	Wall thickness	Velocity	Viscosity	Pressure drop	Saturation
		μm	μm	μm	mm/s	mPa.s	mmHg	%
A1	1	23.97	1267.6	4.84	8.2	1.59	6.93	94
A2	2	19.17	930.3	4.25	6.41	1.50	5.87	93
A3	4	15.28	543.6	3.81	5.05	1.42	4.02	92
A4	8	12.08	302.3	3.49	4.03	1.34	2.70	89
A5	16	9.46	161.2	3.27	3.29	1.28	1.82	84
A6	32	7.32	154.7	3.14	2.75	1.23	2.35	76.5
C	64	8	243.9	0.309	2.30	1.24	2.62	66.5
V6	32	11.51	473.9	1.15	1.11	1.33	1.27	61
V5	16	14.53	272.3	1.45	1.40	1.40	0.61	59.75
V4	8	17.79	426.6	1.78	1.86	1.48	0.89	58.75
V3	4	21.45	632.5	2.15	2.56	1.55	1.31	58.25
V2	2	25.70	844.2	2.57	3.57	1.62	1.78	57.75
V1	1	30.77	936.3	3.08	4.97	1.70	2.01	57.25

Table 1 Vascular parameters used in network model

Parameter	Definition	Value	Source
P_A	Arteriolar blood pressure	60 mmHg	Lipowsky (2005)*
\bar{p}_t	Partial pressure of oxygen in brain tissue	15 mmHg	Vovenko (1999)*
α_t	Solubility coefficient of oxygen in brain tissue	2.6×10^{-5} ml_O ₂ /ml.mmHg	Clark et al. (1977), Mintun et al. (2001)
c_{Hb}	Oxygen-carrying capacity per unit volume of red blood cells	0.2 ml_O ₂ /ml	Secomb et al. (2000), Huppert et al. (2007)
M	Oxygen metabolism of brain tissue	30×10^{-9} mol_O ₂ /ml.s	Mintun et al. (2001)
K	Oxygen permeability of vascular wall	5×10^{-8} ml/m.s.mmHg	Popel et al. (1989)*

Table 2 Parameter values used in vascular network (* = as quoted by Boas et al. (2008))

Appendix A

For completeness, we list the data that we extracted from the results of Zweifach and Lipowsky (1977): full details of the extraction procedure are given in Lucas (2012). The parameters of the model proposed here are calculated from interpolation of these data points, as described above.

Vessel type	Diameter (μm)	Velocity (mm/s)	Pressure (mmHg)
Arteriole	54.6	15.0	87.2
	50.7	14.7	84.5
	47.3	14.4	82.0
	43.4	13.8	78.5
	40.3	13.3	75.3
	36.1	12.7	70.8
	30.5	11.0	63.3
	26.2	9.4	58.3
	24.4	8.7	55.8
	22.9	8.0	53.7
	19.5	6.7	49.2
	15.6	5.0	43.3
	12.5	3.2	38.3
	11.6	3.4	37.9
	10.0	2.8	35.8
Capillary	8	2.3	34.2
Venule	12.0	1.7	31.7
	15.0	1.8	30.0
	16.8	1.8	29.7

	18.7	1.9	27.6
	21.1	2.3	28.1
	23.4	3.0	26.9
	26.0	3.4	26.3
	29.3	4.5	24.6
	31.6	5.0	25.7
	36.6	6.3	23.3
	41.0	8.5	23.3
	46.1	9.3	22.9
	51.7	10.2	22.2









