A Multi-scale Model of Oxygen Transport in the Entire Human Brain: Towards In-Silico Clinical Trials

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Abstract

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1. Introduction

Diseases of the brain, or injuries to the brain, are among the leading causes of death and disability in the world. Stroke, in particular, is the second leading cause of death and third leading cause of disability in adults worldwide (Johnson et al. 2016). Ischemic stroke – where a thrombus blocks an artery supplying oxygenated blood to the brain – occurs in 90% of strokes (Andersen et al. 2009). This sudden loss of oxygenated blood to a region of the brain results in deprivation of nutrients and oxygen to the brain tissue, leading to rapid brain cell death and loss of neurological function. Due to the lack of energy stores in the brain, time is crucial; every hour delay reducing the efficacy of treatment (Fransen et al. 2016; Kim et al. 2015).

Up until recently, the main treatment for ischemic stroke has been to lyse the clot with Alteplase to break down the clot and allow blood flow to resume. Since then, thrombectomy – the physical removal of a clot with a stent – has been shown to be an effective and clinically safe treatment (Berkhemer et al. 2014). Despite these advances in treatment, around half of patients have unfavourable outcomes post-treatment, with the no reperfusion phenomenon – where flow is not restored despite the removal of the clot – leading to most patients becoming functionally dependant or worse. In addition, treatments rarely pass clinical trials, with less than 10% of compounds currently estimated to go from clinical trial to market (Hay et al. 2014). The introduction of thrombectomy is the exception, as opposed to the rule.

Increasingly, the role of computational modelling in healthcare and in the development of drugs and devices has become more important. In-silico clinical trials have the opportunity to explain why treatments fail and to improve the ratio of compounds and treatments that make it to market. As a part of this, the INSIST consortium (in-silico clinical trials for the treatment of ischemic stroke) is attempting to develop in-silico clinical trials for ischemic stroke treatment. This paper forms a part of this joint European wide effort. Of course, in order to have in-silico clinical trials of ischemic stroke,

we require computational models of oxygen transport in the entire human brain. This is no trivial feat, in part due to the sheer number of blood vessels in the human brain (approximately 8000 /mm3 in the grey matter) (Cassot et al. 2006).

Previous attempts at modelling oxygen transport in the brain on a whole-organ scale have thus revolved around compartmentalisation. Some of the earliest models treated vascular compartments as equivalent circuits, although these were primarily for blood flow models as opposed to oxygen transport models (Piechnik et al. 2001; Sorek, Bear, and Karni 1989; Ursino and Giannessi 2010). Multi-compartment models of oxygen transport in brains include those of Sharan et al. (Sharan et al. 1989; SHARAN and POPEL 2002)and Ye et al. 1993 (Ye, Moore, and Jaron 1993) – although these models were developed in steady-state with no measured morphological parameters from the microcirculation informing the global model. More recently, a two-compartment model of the human brain vasculature has been proposed for tracer-kinetic modelling, although it is again uncertain how the microvasculature effects the parameters used in the compartmental model (Hodneland et al. 2019). Multi-scale models of other whole organs such as the heart (Hyde et al. 2013; Michler et al. 2013) and the liver (Rohan, Lukeš, and Jonášová 2018) have previously been developed.

Clearly, there is a need for in-silico clinical trials for ischemic stroke in the human brain – to help us understand why there are unfavourable outcomes in the majority of patients despite treatment; and to help improve the delivery of drugs and devices to market by providing an opportunity to model treatments prior to physical clinical trials. We therefore propose here a novel multi-scale model of oxygen transport in the entire human brain by introducing a 4-compartment model for the vasculature and tissue. Each compartment is coupled through either bulk flow of oxygen representing blood moving oxygenated blood from one vascular generation to another, and/or through diffusive flux into tissue. The coupled oxygen transport equations are implicitly linked to microvascular models of capillary networks and penetrating vessels based on ex-vivo human data through pre-computed parameters (El-Bouri and Payne 2015, 2016, 2018). As such, changes in the microvasculature will inform whole-brain oxygen transport through updates in the parameters derived from the microvascular models. This multi-scale oxygen model is thus applied to a finite-element mesh of a healthy human adult (Garcia-Gonzalez et al. 2017) and oxygen transport is simulated in healthy and pathological states.

2. Methods and Materials

2.1 Model Framework

The framework developed for modelling oxygen transport in the microvasculature of the human brain over multiple compartments is shown in Figure 1. The brain is split into 4 compartments: a penetrating arteriole compartment, a capillary compartment, a venule compartment, and a tissue compartment. Each of these compartments represent the respective vasculature or tissue as a homogenous porous medium with – crucially – the parameters used for modelling the oxygen transport derived from statistical models of the microvasculature (El-Bouri and Payne 2015, 2016, 2018) which are themselves in turn derived from morphological data of the human brain microvasculature (Cassot et al. 2006, 2010; Lauwers et al. 2008). The compartmentalisation of the brain into 4 spatial scales allows us to investigate, in more detail that previously possible, the effects that changes to the microvasculature – through micro-occlusions or otherwise – have on whole-brain blood flow and oxygen transport.

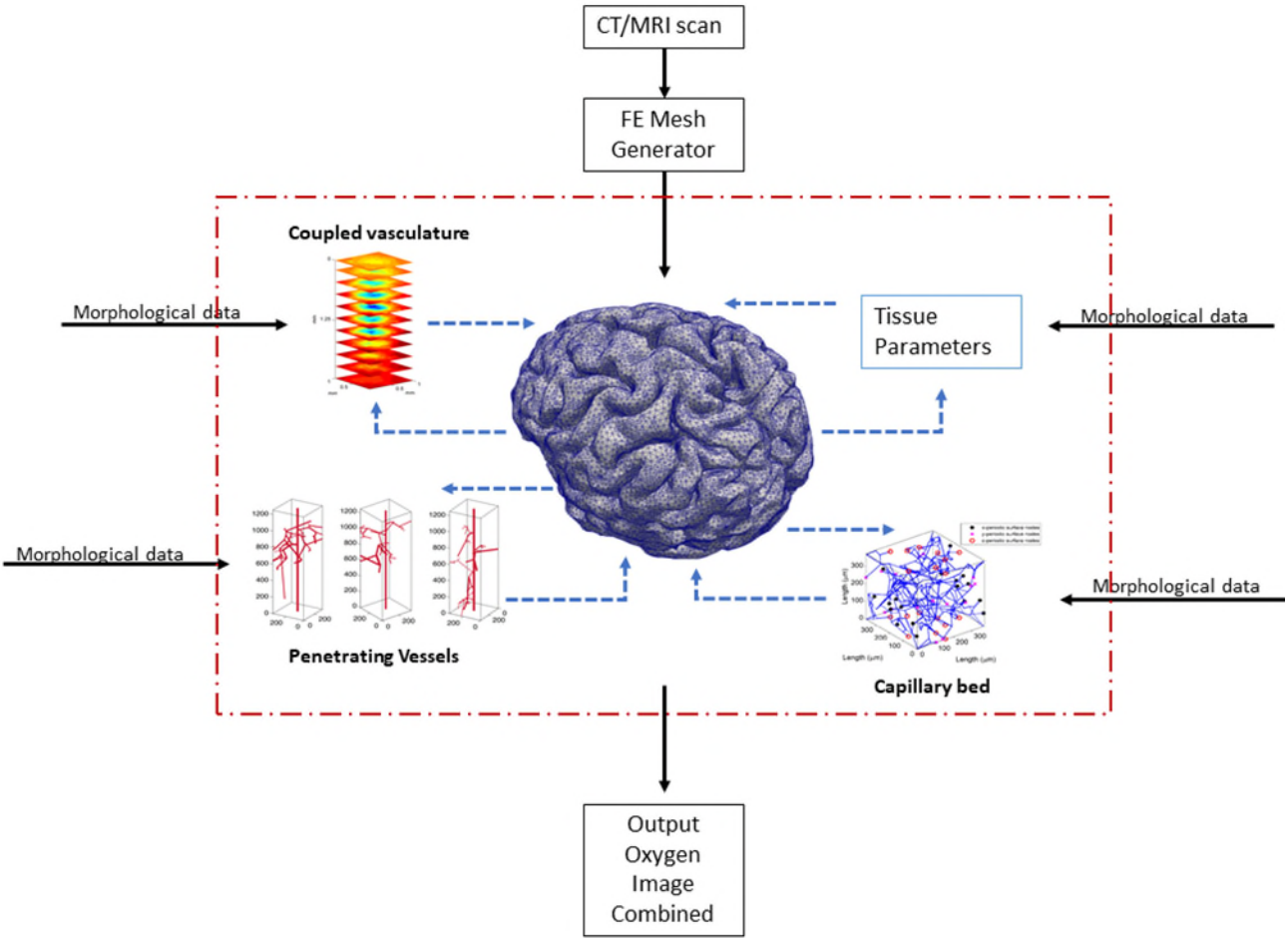


Figure 1 *The schematic framework of the model pipeline developed for modelling oxygen transport in the microvasculature of the human brain. From a given CT/MRI scan, a finite element (FE) mesh can be generated of a personalised human brain. The continuum model of oxygen transport on the FE mesh depends on parameters derived from the micro-scale models – indicated by the dashed blue arrows between the models and the brain. These micro-scale models have previously been developed (refs) and are based on morphological data (refs). The red dot-dash box indicates the current scope of this paper – developing the coupled micro-macro oxygen transport representation. The capillary bed figure, the penetrating trees figure, and the coupling figure are reproduced with permission from…*

It is worth noting here that the framework developed here is easily extended into an automated pipeline (Fig. 1). Currently, the framework is applied to one brain mesh. However, it should be possible to automate mesh generation from CT/MRI scans and apply the model (discussed below) to each brain. The scope of this paper, however, is to develop this multi-compartment model and demonstrate its applicability on one brain mesh.

2.2 Compartmental model of Oxygen Transport

The model for oxygen transport in the full human brain is derived through an ‘upscaling’ or averaging approach. Starting with the advection-diffusion equation to model oxygen transport in each microvascular compartment (with the knowledge that oxygen diffuses from both the arterioles and capillaries into tissue (ref)) we can write the following transport equations for each compartment:

$$\phi_a \frac{\partial c_a}{\partial t} + \overline{\boldsymbol{u_a}}.\nabla \mathrm{c_a} = -\beta_{ac}(p_a - p_c)c_a - \phi_a \gamma_{at} \frac{S_a}{V_a}(c_a - c_t) \quad (1)$$

$$\phi_v \frac{\partial c_v}{\partial t} + \overline{\boldsymbol{u_v}}.\nabla \mathrm{c_v} = \beta_{cv}(p_c - p_v)c_c \quad (2)$$

$$\phi_c \frac{\partial c_c}{\partial t} + \overline{\boldsymbol{u_c}}.\nabla \mathrm{c_c} = D_c \nabla^2 c_a + \beta_{ac}(p_a - p_c)c_a - \beta_{cv}(p_c - p_v)c_c - \phi_c \gamma_{ct} \frac{S_c}{V_c}(c_c - c_t) \quad (3)$$

$$\phi_t \frac{\partial c_t}{\partial t} = D_t \nabla^2 c_t + \phi_a \gamma_{at} \frac{S_a}{V_a}(c_a - c_t) + \phi_c \gamma_{ct} \frac{S_c}{V_c}(c_c - c_t) - \phi_t \frac{G c_t}{C_{50} + c_t} \quad (4)$$

Where subscript *a* refers to the arteriole compartment, subscript *c* refers to the capillary compartment, subscript *v* refers to the venule compartment, and subscript *t* refers to the tissue compartment. c is the concentration of oxygen, t is the time, and $\overline{\boldsymbol{u_i}}$ is the Darcy velocity in compartment i which is calculated from the solution of the porous blood flow problem in the brain – which can be found in a companion paper (ref Tamas). ϕ is the volume fraction of the given compartment, β_{ij} is the blood flow coupling coefficient between compartment i and compartment j, and p is the blood pressure in the compartment (calculated from the porous blood flow problem). γ_{ij} is the diffusive mass transport coefficient across the vessel wall from compartment i to compartment j, $\frac{S_i}{V_i}$ is the surface area to volume ratio of the vessels in compartment i, and D is the diffusion coefficient of oxygen. Finally, the non-linear metabolic term in the tissue compartment contains the constants G and C_{50} which are the maximum metabolic consumption rate of oxygen and the oxygen concentration at which the reaction rate is half the maximum respectively (assuming Michaelis-Menten kinetics).

As can be seen from the above equations, the arteriole and venule compartments are modelled as advection equations without diffusion. This is due to the fact that the Péclet number is of the order 1000 in these compartments, and hence advection dominates the transport of oxygen. In the capillary bed, the Péclet number is of the order 1 hence both advection and diffusion are maintained, and in the tissue compartment the Péclet number is $\ll 1$ and hence diffusion dominates.

It should be noted here that there are a number of parameters required for this coupled model of oxygen transport through the microvasculature. Some of these parameters can be obtained from experiments, whilst others depend on the microvascular models. In particular, the surface area to volume ratios and coupling coefficients (as well as the Darcy velocity) must be precomputed prior to solving the above equations.

2.3 Parameter estimation from the microvasculature

Statistical models of the capillary bed, penetrating vessels, and coupling between the two have previously been developed for the human brain microvasculature (El-Bouri and Payne 2015, 2016, 2018). In brief, these models rely on morphological data obtained from ex-vivo human brains (Cassot

et al. 2006, 2010; Lauwers et al. 2008). Based on the data, statistical models are generated of the capillary beds and penetrating trees separately, from which the parameters required for blood flow transport e.g. permeability, and oxygen transport e.g. surface-area-to-volume, can be calculated.

Here we calculate the surface-area-to-volume ratio for the capillary bed and penetrating arterioles. In order to ensure that this is the converged value for the statistical models, the cube size of the capillary bed and penetrating trees is increased until the parameter of interest converges to the value that represents the network. This is then taken to be the effective surface-area-to-volume ratio of the network. This is also done for the volume fractions. The coupling coefficients are obtained from the optimisation of the porous blood flow problem in a companion paper (ref Tamas).

2.4 Finite Element Model

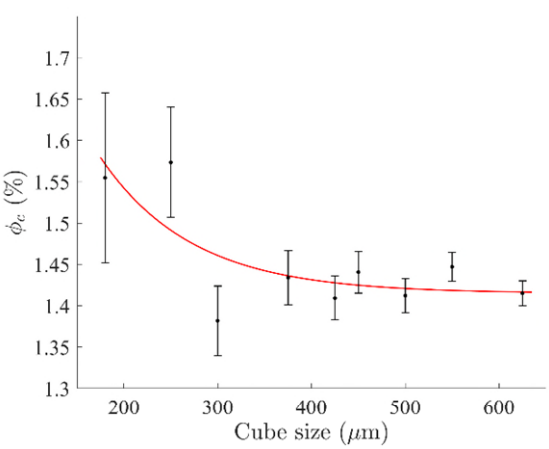
3. Results

We will present the results of our parameter estimation from our micro-models first, before going on to present the use of these parameters in a finite element representation of oxygen transport in the human brain.

3.1 Parameterisation

The capillary bed was varied in size and the converged values of surface-area-to-volume ratio and volume fraction were calculated (Fig. 2). The volume fraction converged to a value of 1.4 % and the surface-area-to-volume-ratio converged to a value of 613 mm^2/mm^3. Similarly, the values of surface-area-to-volume ratio and volume fraction were calculated for the penetrating arterioles (Fig. 3). The volume fraction converged to a value of 1.8 % and the surface-area-to-volume-ratio converged to a value of 188 mm^2/mm^3.

Table 1 shows a comparison between our calculated values and values found in morphological data, indicating good agreement between our statistical models and observed values. As such, these parameters can now be used (along with the blood flow parameters) to calculate oxygen transport in the entire human brain.



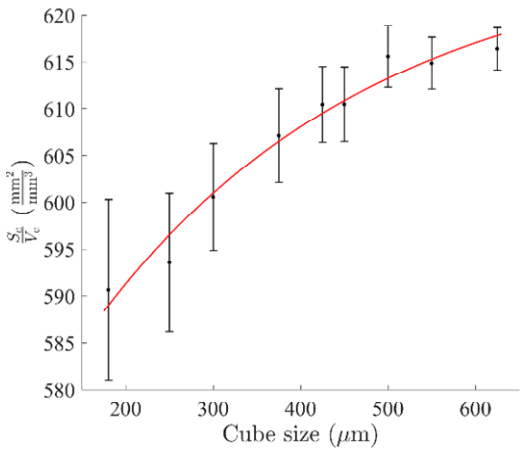


Figure 2 *a) The volume fraction of the capillaries as cube size increases. Converged value 1.4 %. b) The surface-area-to-volume ratio of the capillary network as cube size increases. Converged value 613 mm^2/mm^3*

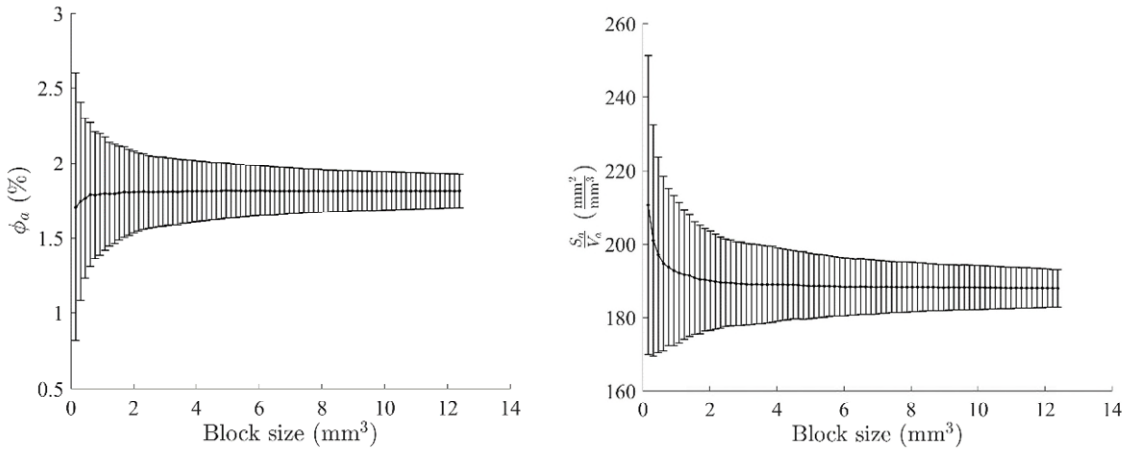


Figure 3 *a) The volume fraction of the arterioles as cube size increases. Converged value 1.8 %. b) The surface-area-to-volume ratio of the arteriole network as cube size increases. Converged value 188 mm^2/mm^3*

	ϕ_i (%)	$\frac{S_i}{V_i}\left(\frac{\text{mm}^2}{\text{mm}^3}\right)$	$\frac{V_i}{S_i}$ (μm)	$\frac{S_i}{V_{Total}}\left(\frac{\text{mm}^2}{\text{mm}^3}\right)$
(Cassot et al. 2006)	2.44/1-4	-	4.55	5.37
(Lauwers et al. 2008)	2.685/2-4	-	2.3	11.74
(Risser et al. 2009)	2.74	-	3.51	7.87
Capillary Parameters	1.415	613	1.624	8.702
Arteriole Parameters	1.814	188	5.320	3.406
Capillary + Arterioles	3.229	801	3.250*	6.372*

* calculated with arteriole accounting 44% of the volume and capillary accounting 56% of the volume (Lauwers et al. 2008; Risser et al. 2009)

Table 1 *A comparison of the parameters calculated from our statistical models, and morphological parameters found in the literature. ϕ_i is the volume fraction of compartment i, $\frac{S_i}{V_i}$ is the surface-area-to-volume ratio and $\frac{S_i}{V_{Total}}$ is the surface area to total volume (of the vessels and tissue) ratio. All calculated parameters are in good agreement with morphological values.*

3.2 Steady State Oxygen Transport

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