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Investigating the effects of a penetrating vessel occlusion with a multi-scale microvasculature model of the human cerebral cortex

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ABSTRACT

The effect of the microvasculature on observed clinical parameters, such as cerebral blood flow, is poorly understood. This is partly due to the gap between the vessels that can be individually imaged in humans and the microvasculature, meaning that mathematical models are required to understand the role of the microvasculature. As a result, a multi-scale model based on morphological data was developed here that is able to model large regions of the human microvasculature. From this model, a clear layering of flow (and 1-dimensional depth profiles) was observed within a voxel, with the flow in the microvasculature being driven predominantly by the geometry of the penetrating vessels. It also appears that the pressure and flow are decoupled, both in healthy vasculatures and in those where occlusions have occurred, again due to the topology of the penetrating vessels shunting flow between them. Occlusion of a penetrating arteriole resulted in a very high degree of overlap of blood pressure drop with experimentally observed cell death. However, drops in blood flow were far more widespread, providing additional support for the theory that pericyte controlled regulation on the capillary scale likely plays a large part in the perfusion of tissue post-occlusion.

Introduction

The microvasculature is recognized as playing a key role in both perfusion and oxygen transport in the brain. Any reduction of blood flow to the brain can lead to tissue death at a time scale of the order of tens of seconds to minutes. Increasingly, the microvasculature, and changes to its topology, has been linked to diseases such as Alzheimer's disease, vascular dementia, and brain tumours (Bullitt et al., 2005; Jain, 2005; Jellinger, 2008; Meyer et al., 2008). For example, although Alzheimer's disease, the leading cause of dementia, has traditionally been thought to be due to the formation of amyloid plaques and neurofibrillary tangles, it is now appreciated that there is also a strong vascular component to this pathology (Toledo et al., 2013).

Despite the importance of the microvasculature in maintaining a healthy supply of blood and oxygen to the brain, little is known about the specific effects that the topology of these vessels has on blood and oxygen transport. This is predominantly due to the relatively low resolution of modern clinical imaging techniques that can only discern vessels larger than approximately 0.8–0.9 mm in diameter (Mut et al., 2014). There is thus an imaging gap relating to the microvasculature of the human brain, which can only currently be filled using mathematical models. These models must be based on accurate physiological data, either obtained post-mortem or from animal models. To quantify this link between the microvasculature and clinical imaging techniques, models of the scale of a standard clinical MRI voxel i.e. with a length scale in the order of mm are required. Such models allow us to explore the links between the geometry of the microvasculature and perfusion and blood pressure measurements, as well as the relationship between flow and metabolism in more detail.

There are various smaller scale models (length scale order 100 μm or less), both cast-based and statistical, modelling both human and rat cerebral capillary networks (Fang et al., 2008; Safaeian and David, 2013; Secomb et al., 2000; Su et al., 2012). Although useful, these models are too small to provide a direct one-to-one comparison to clinical imaging voxel data. Most of the large-scale models (order mm length scale) that are available in the literature are based on animal models – and most of these are cast-based models – due to the relative ease of imaging the microvasculature in animal models to a higher resolution than in the human microvasculature (Gagnon et al., 2015; Schmid et al., 2017a; Gould et al., 2017; Guibert et al., 2010); although more recently much progress has been made in acquiring these networks accurately (Gould et al., 2017), it can still be a labour intensive and expensive process. However, the link between these animal microvasculatures and the human microvasculature has not yet been quantified. For example, rat

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brains have more penetrating venules than penetrating arterioles in the cortex, which is opposite to the situation in human brains (Blinder et al., 2010; Schmid et al., 2017b). As well as this, these animal models are based on casts which, although valuable in modelling flow and oxygen transport for that particular network, are specific to that given region. The simulation results are thus restricted to the experimental conditions that they were derived from and strongly dependent upon the choice of boundary conditions. Reichold et al. (2009). previously attempted to overcome this by using an 'upscaling' approach for averaged quantities of an artificial 2-dimensional capillary network. This averaged network was then coupled to penetrating vessels in a 2-dimensional grid, demonstrating good agreement between the upscaled model and the non-upscaled model. However, since this was only performed for an artificially generated non-morphological network in 2-dimensions, the simulations did not fully represent the rat cerebrovasculature.

In comparison, large-scale models of the human microvasculature are few, mainly due to the relative scarcity (and difficulty) of obtaining physiological data compared to animal models. Lorthois et al. (2011). developed a blood flow model based on available human cerebral data (Cassot et al., 2006); this discrete cast model was found to rely heavily on the prescribed boundary conditions, with heterogeneities in blood flow within the network controlled by the vascular architecture. The same cerebral data was also used by Linninger et al. (2013). to generate a large-scale model that also modelled the individual vessels of the microvasculature discretely, with the capillary network statistically generated matching physiological data, and the penetrating vessels generated using constrained constructive optimization (CCO). Thus, these penetrating vessels are not directly based on physiological data. Additionally, developing larger models of the vasculature becomes very computationally expensive using discrete models such as these.

To the best of our knowledge, there are currently no models of the human microvasculature that investigate the effects of penetrating vessel occlusions on the perfusion and blood pressure of the human microvascular network. The effects of penetrating vessel occlusions (micro-infarcts) have, however, been investigated in mice (Blinder et al., 2013; Nishimura et al., 2007) and rats (Shih et al., 2013) experimentally. The studies found clear conical regions of cerebral tissue supplied by the penetrating vessels, with robustness to blood flow drops/tissue death deeper in the cortex. This led to penetrating arterioles being labelled as a "bottleneck" in cerebral perfusion (Nishimura et al., 2007). Studies in patients with dementia identified a large number of cortical micro-infarcts with diameters in the order 0.1–1 mm (Arvanitakis et al., 2011; Jouvent et al., 2011; Kovari et al., 2007; Vinters et al., 2000). However, whether these are predictive of or a cause of dementia is as yet unknown due to the inability of conventional clinical imaging to resolve at the length scale of penetrating vessel diameters. As a result, computational models are required to investigate flow at this scale.

The aim of this paper is thus to generate a multi-scale model of the human microvasculature that is able to predict the effect of a penetrating vessel occlusion on local and global flow and perfusion whilst mitigating the effects of the prescribed boundary conditions. This model is based on physiological data, combining a homogenized capillary bed (El-Bouri and Payne, 2015) with statistically generated penetrating vessels (El-Bouri and Payne, 2016), is computationally scalable, and generalizable to any available data set. The mean CBF is calculated through these voxel sized models and validated against experimental data. Pressure and volume averaged velocity are investigated, as well as layered flow within the voxels. This is done for both the healthy vasculature and for the occluded vasculature, with the effects of such occlusions compared to the experimental literature.

Materials and methods

The data used in this paper come from the collateral sulcus in the temporal lobe of the human brain. Thick sections of India-ink injected human brain were scanned using confocal laser microscopy and the network reconstructed (Cassot et al., 2006). Statistical data were extracted from these networks, delineated into capillary and penetrating vessel data. Full details of the data used can be found in the literature (Cassot et al., 2006, 2010; Lauwers et al., 2008; Lorthois et al., 2014).

Morphometry of the microvasculature

The data detailed above have previously been used to generate statistically accurate models of both the cerebral capillary network (Su et al., 2012) and the cerebral penetrating vessels (El-Bouri and Payne, 2016) which were morphometrically validated against experimental data. The capillary network was then mathematically homogenized (El-Bouri and Payne, 2015) to extract the macro-scale properties of the capillary network and to allow these networks to be scaled up to large volumes computationally efficiently. This allows the capillary network to be characterised as a porous medium where the permeability encapsulates the morphological characteristics of the network. This permeability is calculated from the morphologically accurate networks described above, as detailed previously (El-Bouri and Payne, 2015).

A large-scale model ($1 \times 1 \times 2.5$ mm) of a clinically sized MRI voxel is generated here by combining the models mentioned above. The depth of the model (2.5 mm) runs from the pial surface down to the grey matter/white matter interface (Lauwers et al., 2008). The porous capillary bed is assumed to cover the entire volume with a constant, isotropic permeability tensor as previously calculated (El-Bouri and Payne, 2015).

The penetrating vessels start at the pial surface and penetrate into the cortex. Their terminal nodes terminate in the porous capillary bed and act as sources and sinks delivering and removing blood to and from the capillary bed. It is assumed that there are 12 penetrating vessels/mm^2 in the ratio 2:1 arterioles-to-venules, as found morphologically (Cassot et al., 2010; Risser et al., 2009). As the precise spacing of these vessels is uncertain, and this model is statistical, the 1 mm^2 area is split into 4 quadrants, each containing 2 arterioles and 1 venule randomly placed on the pial surface (Fig. 1a).

Two voxel cases are chosen: case 1 with mean arteriole diameters of 20 μm and mean venule diameters of 50 μm; and case 2 with mean arteriole diameters of 40 μm and mean venule diameters of 110 μm. The latter case is chosen to provide a direct comparison to a previous model of the human microvasculature which used mean arteriole diameters of 40 μm and mean venule diameters of 115 μm (Linninger et al., 2013). As we wish to investigate the effect of penetrating vessel diameter on flow and pressure pre- and post-occlusion in the network, case 1 is then chosen to have arteriolar diameter half that of the latter case to provide a comparison. The depths of the penetrating vessels were assumed to be linearly related to their diameters with larger diameters penetrating deeper (as observed experimentally) (Duvernoy et al., 1981). The arteriole depths were centred on a mean 1.25 mm depth for the mean diameter vessel, and the venules similarly on a 1.75 mm depth. A full list of the parameters used in this voxel model is shown in Table 1. 100 simulations were run for each voxel case, and the density of the penetrating vessel network validated against experimental data. It should be noted that all other attributes of the capillary network and penetrating vessels, such as connectivity, length distributions, area ratios, and bifurcation angles, have previously been validated (Su et al., 2012; El-Bouri and Payne, 2015, 2016).

Simulating blood flow through the voxel

Coupled ODE/PDE model of the blood flow

Using homogenization theory it was previously shown that the capillary bed can be modelled as a porous medium using a volume averaged form of Darcy's law (El-Bouri and Payne, 2015):

$$\mathbf{u}_c = -\mathbf{K}\nabla p_c \tag{1}$$

where $\mathbf{u}_c$ is the volume averaged capillary velocity, $\mathbf{K}$ is the permeability