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Modelling dynamic changes in blood flow and volume in the cerebral vasculature

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ABSTRACT

The cerebral microvasculature plays a key role in the transport of blood and the delivery of nutrients to the cells that perform brain function. Although recent advances in experimental imaging techniques mean that its structure and function can be interrogated to very small length scales, allowing individual vessels to be mapped to a fraction of 1 μm, these techniques currently remain confined to animal models. In-vivo human data can only be obtained at a much coarser length scale, of order 1 mm, meaning that mathematical models of the microvasculature play a key role in interpreting flow and metabolism data. However, there are close to 10,000 vessels even within a single voxel of size 1 mm^3. Given the number of vessels present within a typical voxel and the complexity of the governing equations for flow and volume changes, it is computationally challenging to solve these in full, particularly when considering dynamic changes, such as those found in response to neural activation.

We thus consider here the governing equations and some of the simplifications that have been proposed in order more rigorously to justify in what generations of blood vessels these approximations are valid. We show that two approximations (neglecting the advection term and assuming a quasi-steady state solution for blood volume) can be applied throughout the cerebral vasculature and that two further approximations (a simple first order differential relationship between inlet and outlet flows and inlet and outlet pressures, and matching of static pressure at nodes) can be applied in vessels smaller than approximately 1 mm in diameter. We then show how these results can be applied in solving flow fields within cerebral vascular networks providing a simplified yet rigorous approach to solving dynamic flow fields and compare the results to those obtained with alternative approaches. We thus provide a framework to model cerebral blood flow and volume within the cerebral vasculature that can be used, particularly at sub human imaging length scales, to provide greater insight into the behaviour of blood flow and volume in the cerebral vasculature.

Introduction

Since 2006 there has been a great deal of interest in models of the cerebral microcirculation. This has been driven by the recent ability to obtain experimental data about microvascular networks, both in humans and in animal models. The former has mainly been based on the collection of post-mortem casts obtained by Duvernoy et al. (1981), and these experimental data have been presented in detail by Cassot et al. (2006), Lauwers et al. (2008) and Lorthois et al. (2011). Casts of animal microvascular networks have also been extracted and the flow in them modelled, see 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). Many of the models listed above have also examined the transport of oxygen and the coupling between this and cerebral blood flow.

Although there has been a great deal of progress on robustly extracting vascular networks from imaging data and converting them into accurately segmented three-dimensional networks, see for example Gould et al. (2017), acquiring large volumes of such data remains a time-consuming and expensive task that can only be undertaken with considerable expertise. The strong dependence of vessel resistance on vessel radius means that accurate values of the vessel diameter are critical if the flow field is to be calculated accurately. The strong dependence of the chosen boundary conditions on the flow simulations has also been noted by many authors, for example Lorthois et al. (2011).

These factors, together with the high vessel density that means that solving the flow field in volumes of tissue that are of the length scale of a

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human imaging voxel (of order 1 mm) is highly computationally challenging, has driven the development of homogenisation techniques based on the creation of artificial networks that match experimentally measured properties, Su et al. (2012), El-Bouri and Payne (2015) and El-Bouri and Payne (2016), and coupling these with models over multiple length scales, El-Bouri and Payne (2018). These techniques enable a scaling up of networks to a voxel scale and hence the flow fields can be related to imaging data, most easily through the use of transit time distributions, see for example Park and Payne (2013). Other authors have developed vascular networks through the use of bifurcating vessels, for example Boas et al. (2008) and Payne and Lucas (2018), although in these models no spatial information is considered.

At a voxel level, the vasculature comprises vessels over a relatively wide range of length scales, with diameters ranging from a few micrometres to hundreds of micrometres. Consideration does thus need to be given to the assumptions and choice of equations that govern blood flow over these length scales, in particular when attempting to bridge the 'imaging gap', when the assumptions valid in the large vessels and those in the microvasculature may be significantly different. At the smallest length scales, nearly all authors use the Poiseuille equation in some form, with viscosity either taken to be constant, based on vessel diameter or based on vessel diameter and haematocrit, as shown in Table 1. In the latter two cases, empirical relationships are normally used, with a variety of different relationships having been applied. Once the resistance to flow is known, then the network reduces to a conductance matrix, which can be solved numerically, either by simple inversion for networks with constant haematocrit or by iteration for networks with non-constant haematocrit. It is usually assumed that at small length scales static pressure is conserved at nodes, as has been done in all the studies listed thus far.

Most of the models listed in Table 1 assume steady state flow conditions, with only a few considering the dynamic response, although this plays an important part in interpreting the response to changes in neural activity. Only the models by Boas et al. (2008), Reichold et al. (2009), Gagnon et al. (2015) and Payne and Lucas (2018) consider the dynamic response of the small vessels in the cerebral vasculature. These mostly assume a non-linear compliance of the vessels, enabling changes in flow to drive changes in volume. Such changes in blood volume are of particular importance in the context of imaging techniques such as the BOLD response, where short-term changes in blood volume can strongly influence the response.

Other approaches have taken a more 'top-down' methodology, where lumped parameter models (e.g. windkessel models) are used, with the lumped parameters aiming to capture the overall behaviour of flow through large numbers of vessels in a very small number of parameters, see for example those used by Ress et al. (2009), Kim et al. (2013) in the context of models of oxygen delivery, and Buxton et al. (1998) and many subsequent studies (for example Aquino et al. (2014)) in the context of models of the BOLD response. Such models have a valuable role to play in understanding the behaviour at large scales, but are inevitably limited by both their simplicity and the difficulties involved in linking the model parameters to the underlying network physiology.

The assumptions made are often very different in models of flow in the larger vessels, for example when the dynamic behaviour of the flow field plays an important part in both flow and volume, and when total pressure is often conserved at nodes, see for example Alastruey et al. (2007). In order to link models across the 'imaging gap', care has to be taken and the limits of assumptions fully understood. For a comprehensive review of models of cerebral blood flow, the reader is referred to Payne (2017).

In this paper we thus consider the modelling of cerebral blood flow and volume in networks of blood vessels in detail, justify suitable approximations that can be made, and propose a framework that can be used that is mathematically rigorous and computationally simple. We will also consider the limits of the approximations and hence illustrate how models can be developed that will cover multiple scales. In order to do this, we consider the governing equations and use these to develop a model relating blood flow and volume to pressure in a single vessel; finally we link vessels together within a network and then show how the equations can be solved dynamically within a network. In the last section we will consider each of these in turn before illustrating our proposed approach in the context of the cerebral vasculature, comparing simulation results with those obtained using previous approaches.

Theory

We assume blood to be a Newtonian fluid of viscosity μ and density ρ in a flow field that is governed by the incompressible form of the Navier-Stokes equations. These fundamental fluid flow equations are based on the concepts of conservation of mass and balance of forces; a full explanation and derivation can be found in many sources, see for example Acheson (1990). Hence:

$$\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u}.\nabla)\mathbf{u} = -\frac{1}{\rho}\nabla p + \frac{\mu}{\rho}\nabla^2\mathbf{u} \tag{1}$$

with velocity field $\mathbf{u}$ driven by a pressure field p. In an axisymmetric vessel this reduces to:

$$\frac{\partial u}{\partial t} + u\frac{\partial u}{\partial x} = -\frac{1}{\rho}\frac{\partial p}{\partial x} + \frac{\mu}{\rho}\nabla^2 u \tag{2}$$

where the flow velocity has only an axial component, u, which is a function of radius, r, axial position, x, and time, t. In this latter case, the pressure gradient can be shown to be only a function of axial position and time, i.e. the pressure is uniform over the cross-sectional area, based on order of magnitude arguments, Canic and Kim (2003). A similar order of magnitude argument can be used to neglect the radial component of the velocity field when the variations in the vessel cross-section are not too fast, Canic and Kim (2003). We note that the assumption of a Newtonian fluid is a limitation to this analysis, but one that we will consider more fully in the Discussion. For ease of reference, schematics of the different components of the model are shown in Fig. 1, to which we refer throughout.

Result 1: The advection term can be neglected when $\frac{E}{\rho U^2}\frac{h}{R} \gg \frac{3}{2}$ (E is Young's modulus, ρ is fluid density, U is flow velocity, h is wall thickness and R is vessel inner radius)

The first result that we show is that the advection term can be neglected in models of cerebral blood flow when the vessel wall stiffness scaled by wall thickness to radius ratio is greater than a multiple of the dynamic head. This result is required first to enable us to write down the governing equations in a simplified form so that we can derive a model for the inlet and outlet flows in the next section.

We will demonstrate this in two parts. We first consider the flow in individual vessels, Fig. 1a, since a simple result can be obtained, before considering the flow field across multiple scales, Fig. 1b. This latter approach allows us to consider the flow field as a whole; this is valuable since it links to previous work that has shown how the flow field in the capillary vessels can be modelled using homogenisation, El-Bouri and Payne (2015). For simplicity we only consider the steady state solution, but this does not affect the result.

Single vessels

We firstly reduce the steady state form of Equation (2) to non-dimensional form, where we reference velocity and pressure to characteristic values, U and P respectively:

$$u^*\frac{\partial u^*}{\partial x^*} = -\left(\frac{P}{\rho U^2}\right)\frac{\partial p^*}{\partial x^*} + \frac{1}{Re_L}\nabla^2 u^* \tag{3}$$