Locating a blockage in the cerebral vascular network

Problem presented by

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Executive Summary

Ischemic strokes make up 70-80% of strokes, and are characterised by blockages of arteries carrying blood to the brain. This problem involves the identification of blockages using a species distribution derived from an MRI scan of the brain. Blood flow in the brain may be described using a network of branching vessels which are the sources for porous media-type flow in the capillary bed. The topologically intricate nature of the branching blood vessels hinder most attempts at simplifying the problem, and the report concludes that a longer-term modelling process would be required in order to provide therapeutically useful conclusions. Some recommendations for the direction such future work could take are also included.

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Contents

1 Background

Measurement of brain perfusion using arterial spin labelling (ASL) based MRI has many potential important clinical applications [7]. Due to its noninvasive nature, ASL MRI has gained considerable interest for studies of various brain disorders, including neurodegenerative diseases such as Alzheimer's disease [12, 1], other dementias [6, 5], and chronic and acute cerebrovascular diseases [15, 14] as well as for functional studies of the brain [14]. A particular interesting application of the technique is the measurement of cerebral blood flow (CBF) [4] and blood oxygenation [8]. A relevant question of clinical importance, asked by GE at the KAUST Study Group, is whether an MRI technique (such as the ASL MRI) can be used to detect and locate a blockage or blockages in the cerebral vasculature. In particular, the problem presented by GE involes the identification of such blockages based on a model of the distribution of a species which is being convected by the flow of blood. The species could be magnetized water molecules or oxygenated hemoglobin, both of which decay (due to relaxation or dissociation and consumption) while they are convected by the blood stream.

It is important to point out that the problem proposed by GE is both relevant and complex. First of all, ischemic strokes make up 70-80% of strokes, and are characterised by blockages of arteries carrying blood to the brain causing oxygen depletion (hypoxia) in supplied tissue, as shown in fig. 1. Secondly, when oxygen transport to cerebral tissue is disrupted, the resulting tissue damage leads to various serious neurological effects. For example, due to neurovascular coupling, damage in cerebral tissues could cause the spreading of cortical depression, a slow wave of depolarization of cell membrane potential, as well as mass redistribution due to hemostasis, the restoration of which requires additional energy and oxygen supplies [2]. Furthermore, vascular supply to the brain proceeds through a hierarchy of vessels of decreasing diameter to the capillaries, from which oxygen is supplied to brain tissue, cf. Fig. 2. It covers a wide range of scales in vessel size and the use of a detailed model of the vasculature would require intense computational power. Finally, the existing MRI methodology has several technical limitations. These include a relatively poor spatial resolution, limited volume coverage, and low signal-to-noise ratio (SNR). It is difficult to improve any of these aspects because ASL method requires rapid image acquisition [7]. Therefore, the modelling approach ideally should be able to predict the effects to the species distribution on the spatial scale that is comparable to the resolution of MRI measurement, e.g., on the order of a few hundred microns.

In this report, we outline the work that has been carried out during the KAUST Study Group. Due to the complexity of the problem and the time constraint, the modelling carried out by the participants is of an exploratory nature and only simplified cases were considered.

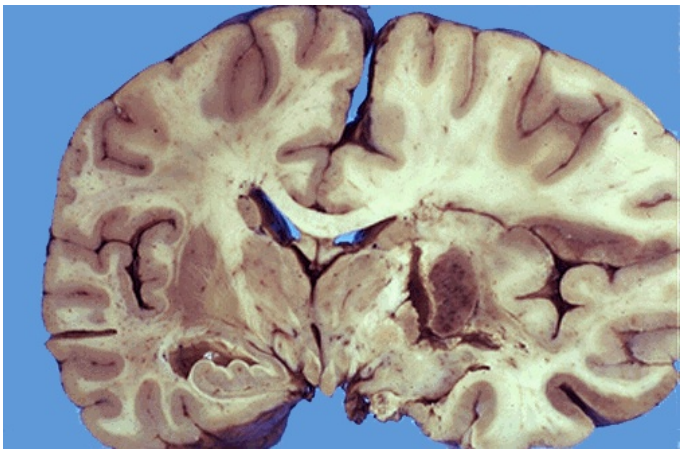

Figure 1: Damage from a cerebral infarct—a blockage of blood flow to a deep region of the brain (right of centre).

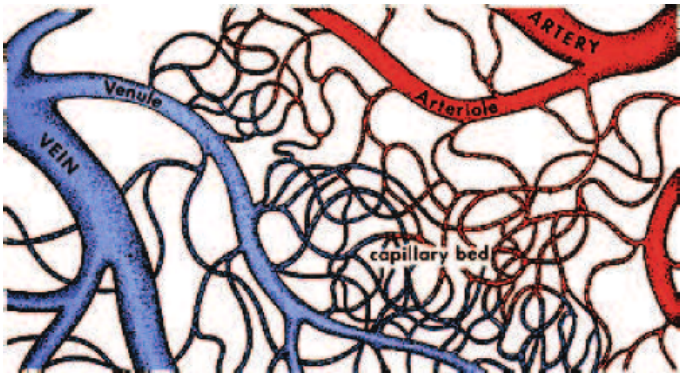

Figure 2: Schematic of the branching of vessels leading to the capillary bed.

2 Porous flow model

Motivated by the nature of the cerebral vasculature as shown in Fig. 6, the first idea pursued during the KAUST Study Group was to treat the blood flow in the capillary beds as a flow through a porous medium. Capillaries are the smallest vessels in the circulatory system, and have a typical size of 5-10 microns. The average separation of capillaries and the diffusion distance for oxygen in the interstitial fluid ensures that every cell receives an adequate supply. The small scale (relative to the resolution and size of the MRI scan) of individual capillaries suggests that treating the capillary bed as a porous medium is a valid modelling approach. The species (oxygen) distribution is modelled by the convective transport by the blood as well as diffusion into and uptake from the surrounding tissue.

The transport of oxygen by the blood is given by a convection-diffusion equation incorporating a sink term which models the uptake of oxygen by the surrounding tissue.

$$\nabla \cdot (\boldsymbol{v}c - D^* \nabla c) = -F(c) \tag{1}$$

The *effective diffusion coefficient*, D^*, is the result of the macroscopic scale of the

porous flow equations. It is given by

$$D^* = \frac{\phi D}{\tau^2}$$

where ϕ is the *porosity* and τ the *tortuosity* of the capillaries in the tissue, and D is the molecular diffusion coefficient of oxygen in plasma. The uptake term, $F(c)$, represents the consumption of oxygen by the surrounding tissue, and is modelled empirically by either of

$$F(c) = \frac{F_0 c}{\phi(c_0 + c)} \quad \text{or} \quad F(c) = F_0 c.$$

The blood flow term, $\boldsymbol{v}$, in (1) is modelled using the Darcy-Brinkman equation for porous flow [3]. The additional term (compared with the "standard" Darcy equation) accounts for boundary effects in the flow, and is used in biological porous flows, including blood flow [10].

$$\frac{K}{\mu}\nabla p = -\boldsymbol{v} + \frac{\bar{\mu}}{\mu} K \nabla^2 \boldsymbol{v} \tag{2}$$

The permeability, K, may be tensorial to model anisotropic effects, and $\bar{\mu}$ is the effective dynamic viscosity.

Numerical simulations were carried out on a simple 2d domain, with an obstacle (blockage) modelled by a region of the domain with zero permeability. It was quite apparent that decreases in oxygen concentration would remain close to the blockage, and was of a similar size to the blockage.

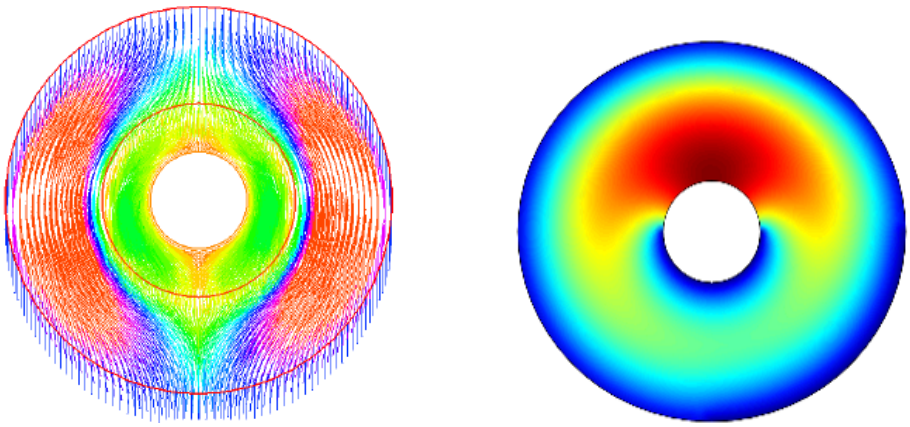

Figure 3: Flow field (left) and species concentration (right) in a porous medium with a blockage. Red colours denote higher values, the flow is from top to bottom.

One possible extension of the porous flow model is to consider a dual- or multiple-porosity formulation of the porous flow equations, see fig.4. These methods are widely used in oil reservoir simulations and other fields in which a network of channels (fissures in the oil case, larger arterioles here) carries fluid to and around a smaller-scale porous material. The different levels of structure in the problem result in porous media equations which incorporate the effects caused by the different scales. However, for reasons discussed in the following section, the geometry of the vascular network would appear to be more important in the mechanism of blockage.

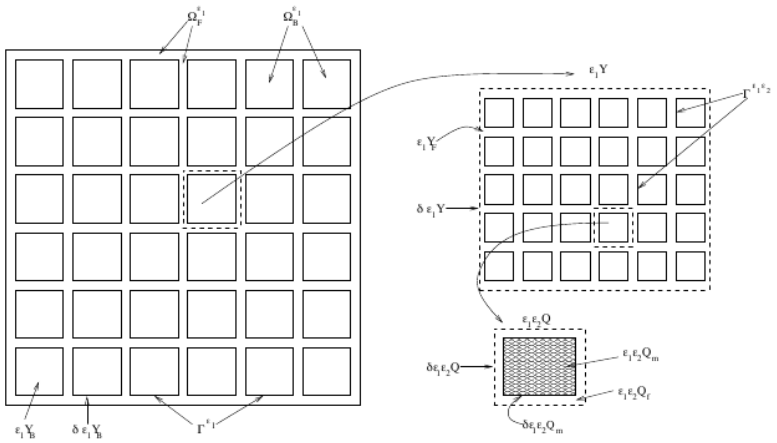

Figure 4: Levels of structure in a multiple porosity model.

3 Modelling concerns

There are several important omissions in the porous medium-convection-diffusion-reaction model presented in the previous section. Firstly, the convective term in (1) does not take into account a number of factors. Oxygen in the blood exists as free oxygen dissolved in the plasma, and oxyhaemoglobin — 4 molecules of oxygen loosely bound to one of haemoglobin — in equilibrium. Oxygen in the plasma can diffuse into the interstitial fluid and be absorbed by cells. This means that the release of oxygen should take into account the oxygen saturation curve shown in Fug. 5, e.g., by the Hill's equation [9]

$$s(c) = \frac{c^n}{c^n + c_{50}^n} \tag{3}$$

where n is an empirical constant and c_{50} is the concentration at 50% saturation. The oxygen transport equation in (1) can be replaced by the following equation

$$\nabla \cdot (\boldsymbol{v}(c + Ns) - D^* \nabla c) = -F(c) \tag{4}$$

where N is the concentration of haemoglobin.

A more serious difficulty with the simple porous medium approach was identified when examining the structure of the vasculature in brain tissue, fig. 6. A stroke-causing blockage is most likely to occur at branching points, where a vessel of similar or smaller radius than the blockage bifurcates from a parent vessel. The region of the capillary bed (and tissue) supplied by such a vessel may be separated from the branching point, and so the hypoxic area (which shows up on the MRI scan) may not contain the blockage. The geometry and topology of the vascular network appears to be an important consideration. To address these topological concerns, two other models were discussed and below we will provide the main ideas of these models.

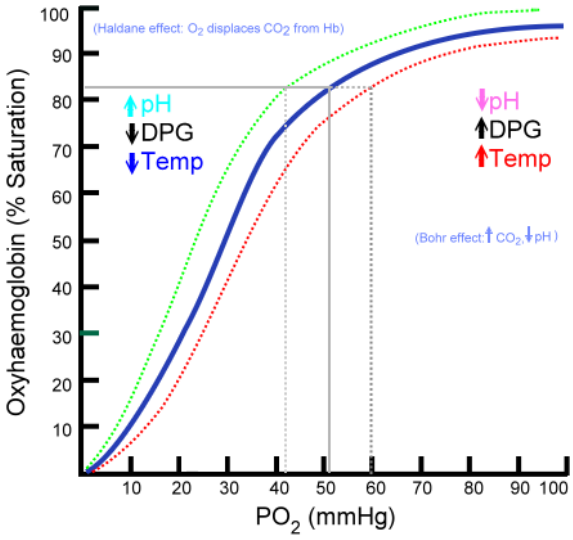

Figure 5: Dissociation curve for oxyhaemoglobin.

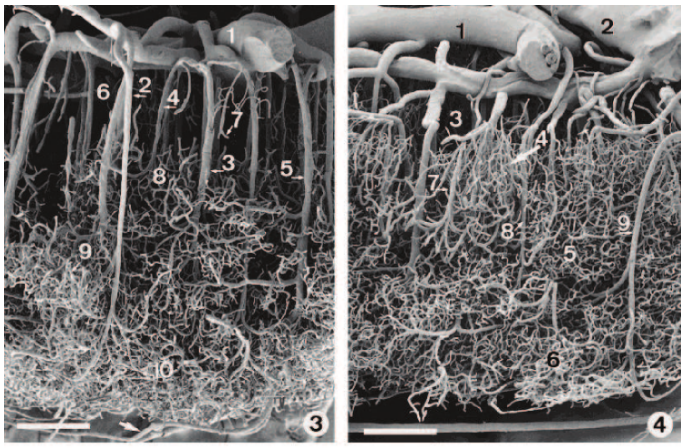

Figure 6: Images of the vasculature of human brain tissue. A blockage at a branch point, such as the beginning of the vessel marked 2 in the left image, would disrupt oxygen supply to a region of the capillary bed in the region marked 10.

4 Hybrid Network-porous media and dual porosity models

To study the effect of blockage at the levels of arterioles and small arteries, it is necessary to build a model that combines

- the (anisotropic and inhomogeneous) network characteristics of the cerebral vasculature; and
- the capillary bed previous modelled as a porous medium, which may or may not be isotropic and inhomogeneous.

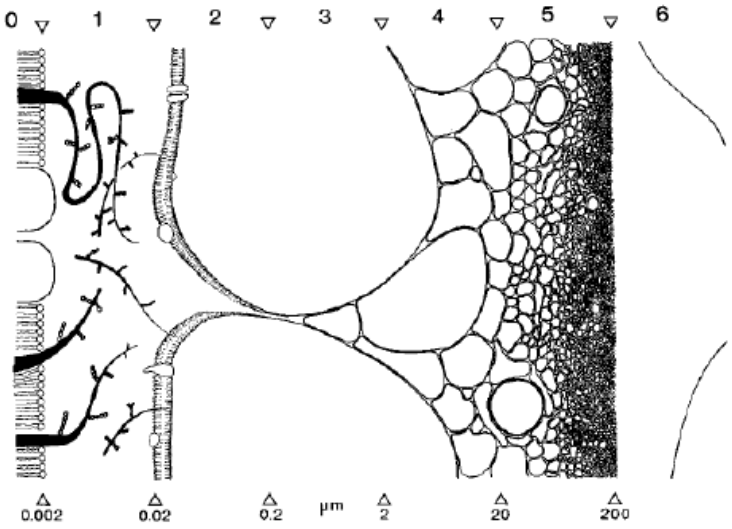

Figure 7: Schematic of blood-vessel scales, logarithmic.

In order to build such a model, we need to know the quantitative (statistical) characteristics of the cerebral vascular tree such as *connectivity* and *redundancy*. This can be done using anatomic data or using a computational approach. In a recent study [11], a computational model was proposed to study the effect of geometrical effects on flow patterns inside a capillary bed. A possible approach is to build a porous medium flow model that captures the main statistical properties of such a network model. This may provide a path towards a computationally robust yet realistic porous medium model for the cerebral capillary beds.

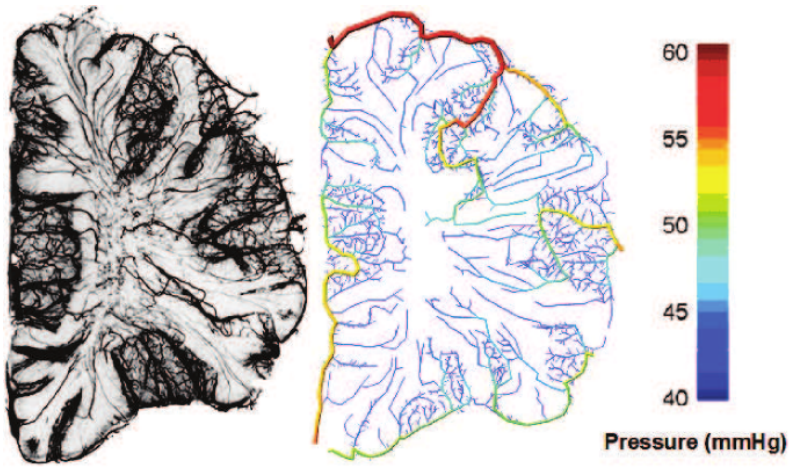

Figure 8: Illustration of the vascular network in the brain, alongside a computer model.

There are existing codes for modelling flows in vascular networks, eg. [13], these could be used for the arterial flow and coupled with a porous model for the capillary

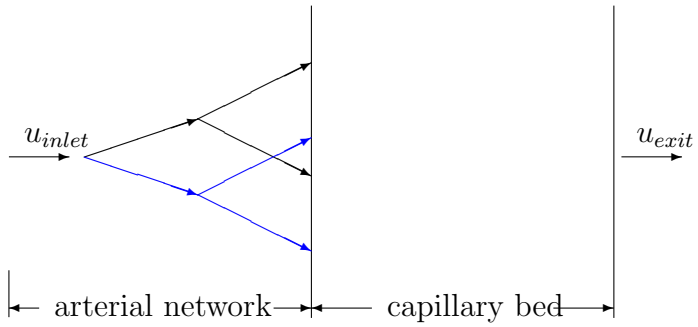

Figure 9: *Schematic of hybrid network and porous medium model.*

bed — this would be a substantial project and beyond the scope of this meeting.

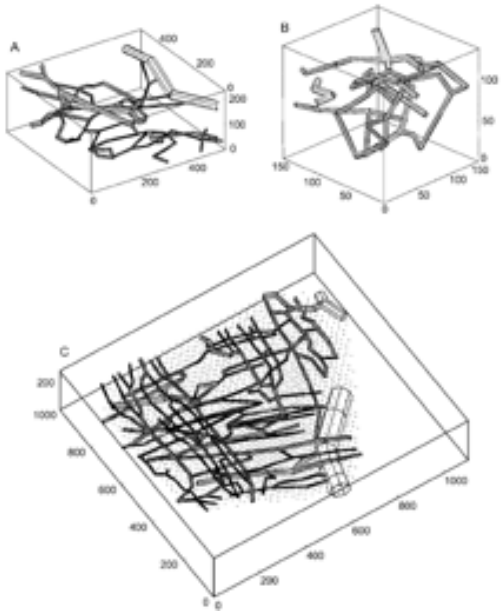

Figure 10: Computer model of a portion of the vascular network in the brain, from [13].

The hybrid network-porous medium approach could be computationally intensive. As an alternative, a multiple porosity approach was suggested to incorporate effects due to the vessels which are slightly larger than the capillaries. The basic idea is to use two or more overlapping compartments to represent the cerebral vasculature at different levels with inter-compartmental fluxes. This approach has been used in the petroleum industry and Fig. 4 illustrates this idea.

5 Inverse problem

So far, our discussions have been focused on building models for species distribution (oxygen) by the cerebral vasculature. The problem proposed by GE is to identify blockages in the vasculature by measuring species concentration using the MRI technique. This falls in the framework of inverse problems. During the Study Group, discussions on how to set up a suitable inverse problem eventually led to the conclusion that statistical and optimization-based inverse problem approaches could both be considered. However, these would require a significantly more comprehensive forward model and a reasonable *prior*.

6 Findings and recommendations

The discussions among the participants at the KAUST Study Group provide several directions for more detailed followup investigations. The major findings and recommendations are listed as follows.

- Blockages on the capillary scale (10-50 microns) will not significantly disrupt oxygen supply to large regions of the brain. Any blockage on this scale will likely only affect nearby tissue.
- A hybrid network-porous media model for the whole brain could be constructed, this would be a longer term project requiring dedicated effort. This makes it difficult to apply inverse problem techniques, which require a comprehensive and sufficiently precise forward model.
- The arteriole scale, the final levels before the capillary bed, could be incorporated into such a model using multiple-porosity techniques.
- Recommendation: apply statistical techniques to correlate locations of blockages with hypoxic regions. The learning from the local forward modelling could be used to enhance the statistics-based decision.

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