Mathematical Modelling of Blood Perfusion and Oxygen Transport in the Cerebral Microvasculature of Ischemic Stroke

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Abstract— **Most frequently (80%) strokes result from the occlusion of one or several brain vessels and are called ischemic strokes (in the other cases, strokes are hemorrhagic strokes). Measurements of haemodynamics and oxygen delivery on microscopic scales are technically difficult or impossible in many cases, especially during brain activity. One way to study the disease is to establish mathematical models to better understand the dynamic process of blood perfusion and oxygen transport in an ischemic stroke. In this paper, we propose a mathematical modelling system to investigate the haemodynamics and oxygen transport through a 2D cerebral microvascular network during ischemic stroke. The microvessel network is based on the anatomical brain microcirculation structure. The haemodynamic calculation is carried out on the microvessel network by fully coupling the intravascular blood perfusion, the transvascular flow and the interstitial fluid flow. In addition, the compliance of microvessels and blood rheology with hematocritic distribution are also considered. The coupling procedure is based on the iteratively numerical simulation techniques in our previous study for tumour microvessels. The oxygen delivery is described by the time-varying oxygen advection diffusion equation which includes oxygen diffusion and advection in individual microvessel segments, oxygen flux across the vascular wall, and then oxygen diffusion and consumption within the brain tissue. The haemodynamic information and oxygen distribution are investigated under physiological and pathological conditions.**

Keywords— **Ischemic stroke; Blood perfusion; Oxygen transport; Cerebral microvasculature; Mathematical modelling**

I. Introduction

Stroke is a transient or permanent loss of brain function resulting from a disturbance in the blood supply to the brain, and is the third cause of death and the first cause of disabilities in adults in developed countries. When a brain vessel is occluded, the surrounding tissues receive less oxygen and glucose, which is responsible for the evolution of brain cells towards necrosis. Ischemic stroke might lead to irreversible brain damage and even death if the blood supply is not restored within a short timeframe.Understanding of blood flow and oxygen transport in the brain microcirculation is of the most importance to study the pathophysiological mechanisms and develop new therapeutic strategies of ischemic stroke since no treatments are currently available for most stroke patients.

The complexity of pathophysiological knowledge of microenvironment in brain tissue has generated an increasing interest in mathematical modelling and numerical simulation of blood perfusion, haemodynamics and mass transport in cerebral microvasculature. S. Lorthois *et al*. [1] established an anatomically accurate large human intra-cortex vascular network which can be considered as the union of a random homogeneous capillary mesh and of quasi-fractal trees with a lower cut-off corresponding to the characteristic capillary length. Reichold*et al*. [2] proposed a vascular graph modeling framework that can simulate blood pressure, flow and scalar transport in realistic vascular networks. However, the interstitial fluid flow and transvascular flow, which have important influences on the cerebral microvascular blood perfusion after the damage of the blood brain barrier (BBB) in an ischemic stroke, are excluded in above models. Mathematical modeling of oxygen transport have been developed to simulate the spatial distribution of oxygen levels in cerebral microvessel network. Magnus W Roos [3] proposed a theoretical model of cerebral microischemia, including the acute change in glucose and oxygen transport. Qianqian Fang *et al*. [4] established a discrete model based on the advection-diffusion equation, using a hybrid numerical algorithm and a general work-flow to model the 3D time-varying oxygen transport. This model can be used to simulate a complex anatomical micro vascular network and provides a quantitative and computationally feasible approach for dynamic modeling.

In this paper, we propose a mathematical modelling system to investigate the haemodynamics and oxygen transport through a 2D cerebral microvascular network during ischemic stroke. The haemodynamic calculation is carried out on the microvessel network by fully coupling the intravascular blood perfusion, the transvascular flow and the interstitial fluid flow. The oxygen delivery is described by the time-varying oxygen advection diffusion equation which includes oxygen diffusion and advection in individual microvessel segments, oxygen flux across the vascular wall,

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and then oxygen diffusion and consumption within the brain tissue. The haemodynamic information and oxygen distribution are investigated under physiological condition and ischemic stroke. Futhermore, the influences of different levels of vessel occlusion on the oxygen transport in tissues are discussed.

II. METHOD

A. 2D cerebral microvascular network

The image data for 2D cerebral microvascular network is obtained from the anatomical thick sections (300μm) of a 60 year old female's brain by confocal laser microscopy in the published paper [5]. Then image processing is carried out to delete unnecessary vessel segments and generate the basic model. Five main vessels are set to be three arteriole with inlet pressure Pin=75mmHg at y=0 and two venules with outlet pressure Pout=15mmHg at y=0. Another venule vessels are also set to be outlet with the same pressure. We classify vessel branches according to the Strahler system, a well-established method for describing stream order. In Strahler's system, leaf segments are assigned Strahler order one. The Strahler order will increase when two vessels with the same Strahler orders join into one vessel. However, two vessels with different Strahler order meeting will not create a vessel with higher order. In our model, there are five Strahler orders to show a brief tree architecture of an arteriolar branching pattern. Strahler orders (N=0, 1, 2, 3, 4), corresponding to the radius of 16,10,7,5, 3.5μm, respectively. The relationship between Strahler order and the vessel radius is based on the experimental equation [6].

B. Haemodynamic analysis

The haemodynamic calculation is carried out on the microvascular network by coupling the intravascular blood flow with the interstitial fluid flow. Briefly, the basic equation for the intravascular blood flow is the flux concentration and incompressible flow at each node. Flow resistance is assumed to follow Poiseuille's law in each vessel segment. The interstitial fluid flow is controlled by Darcy's law. The intravascular and interstitial flow is coupled by the transvascular flow, which is described by Starling's law.

a) Main principles and equations

The main equations for blood flow calculation are as follows:

$$Q_v = \frac{\pi R^4 \Delta P_v}{8\mu\Delta l} \quad (1)$$

$$Q_t = 2\pi R \cdot \Delta l \cdot L_p\left(P_v - P_i - \sigma_T(\pi_v - \pi_i)\right) \quad (2)$$

$$Q = Q_v - Q_t \quad (3)$$

Where Q is the flow rate of each vessel segment, which has a value zero at each node of the vessel network due to the assumption of flux conservation and incompressible flow. Q_v is the vascular flow rate without fluid leakage; Q_t is the transvascular flow rate. Δl and R are the mean length and radius of vessel segment. Pv and Pi are the intravascular pressure and the interstitial pressure, respectively. Lp is the hydraulic permeability of the vessel wall. $\sigma_T$is the average osmotic reflection coefficient for plasma proteins; π_v and π_i are the colloid osmotic pressure of plasma and interstitial fluid, respectively.

The velocity of intravascular Uv and interstitial flow Ui satisfies

$$U_v = Q/\pi R^2 \quad (4)$$

$$U_i = -K\nabla P_i \quad (5)$$

$$\nabla \cdot U_i = \frac{L_p S}{V}(P_v - P_i - \sigma_T(\pi_v - \pi_i) \quad (6)$$

Where K is the hydraulic conductivity coefficient of the interstitium; S/V is the surface area per unit volume for transport in the interstitium.

The distribution of red blood cells (RBCs) at a microvascular bifurcation is calculated based on the approach proposed by Pries [7]. The details of blood rheology simulation were described in Wu *et al*. [8].

b) Iterative steps for microcirculation simulation:

1. Set P_{in} and P_{out} of every vascular in the region and initial solutions P_V^o, P_i^o.

2. Solving Pv and relative errors $errP_V = \sum\left|P_{V,(j,k)} - P_{V,(j,k)}^o\right| / \sum P_{V,(j,k)}$ by the iteration computations described above.

3. If there is in the health condition, skip this step. On the contrary, solving Pi and relative errors $errP_i = \sum\left|P_{i,(j,k)} - P_{i,(j,k)}^o\right| / \sum P_{i,(j,k)}$ by the iteration computations described above.

4. According to the given initial R, calculating intravascular hematocrit H and blood viscosity μ, viscosity is obtained according to Pries empirical equation.

5. Compute Uv using Eq. (4).

6.Calculate the maximum error $err = \max(errP_V, errP_i)$. The new set of solutions is fed back into step 2 with $P_V \Rightarrow P_V^o, P_i \Rightarrow P_i^o$. Repeat 2-5 until $err \le 1e^{-6}$, indicating the microcirculation reaches the steady state.

C. Oxygen transport:

We used advection-diffusion equation to describe oxygen transport [4]:

$$\frac{\partial C_O}{\partial t} = \vec{v} \cdot \nabla C_O + \nabla \cdot (D_{O2} \nabla C_O) - OC \quad (7)$$

Where C_O is oxygen concentration, $\vec{v}$ denotes the intravascular blood flow velocity which is obtained from the haemodynamic simulation, D_{O2} is the diffusion coefficient of oxygen, and OC is the oxygen consumption rate by tissues.

The computational space is separated into three domains to characterize three distinct physiological processes, which are (a) the oxygen convection equation inside the vessel, (b) the oxygen flux across the vessel wall and (c) the free oxygen diffusion in the tissue. Specifically, the Eq. (7) is applied on the different simulation domains as follows:

Vessel network: $$\frac{\partial C_O}{\partial t} = -\vec{v} \cdot \nabla C_O \quad (8)$$

Tissue: $$\frac{\partial C_O}{\partial t} = \nabla \cdot (D_{O2} \nabla C_O) - OC \quad (9)$$

Oxygen flux across the vessel wall is simplified, we consider the oxygen in the vessel as diffusion source with a coefficient relating to the vessel wall permeability and the concentration difference inside and outside the wall.

The initial condition of oxygen concentration is set to be a relatively high value at the arteriole inlets, and a much lower homogeneous value in the vessels to get a driving force for advection, as for the background, the concentration value is set to be an approximate value of zero. No-flux boundary conditions are used in the simulation field. The central difference scheme is utilized to investigate the oxygen delivery through the cerebral microvessels and the brain tissue.

III. Result

A. Result of heamodynamic

The spatial distribution of intravascular blood pressure and flow velocity in the network are shown in Fig1 A&B. High pressure regions evidence the functional territories of the three arterioles whereas low pressure regions evidence the functional territories of venules. Regarding flow maps, high flow segments correspond to the main trunks of arteriolar trees, with significantly decreasing flow in secondary vessels and capillaries. It is noteworthy that zero flow are highly distributed in the capillary segments with highest Strahler order, *i.e.*, smallest vessel diameter.

B. Oxygen transport in physiological condition

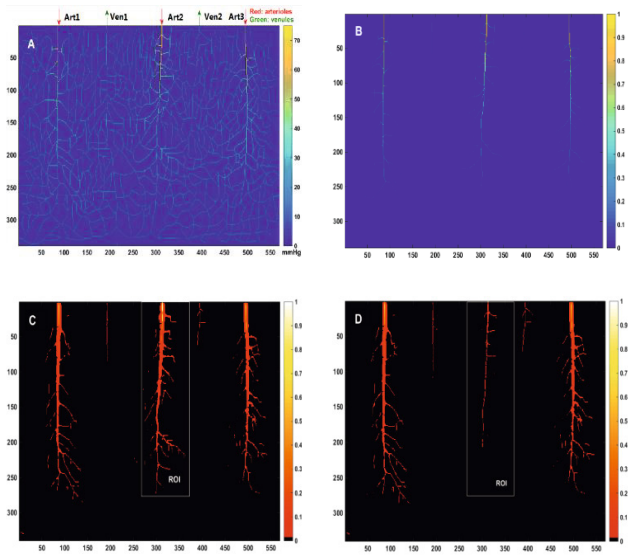

Fig.1 A. Inravascular pressure (Pv) distribution in the anatomical network; B. Inravascular velocity (Uv) distribution; C. oxygen concentration distribution in physiological condition; D. oxygen concentration distribution when the arteriole2 occluded by 75%. The surrounding area of the occluded arteriole is defined to be the region of interest (ROI), shown a white solid line box in C and D.

Oxygen concentration distribution is normalized to be 0 to 1, and shown in Fig.1 C. The arterioles clearly has the highest oxygen concentration compared to the venules and capillaries. The high oxygen around the arterioles drops off rapidly with distance, while the lower oxygen around the capillaries is much more spatially uniform. The mean oxygen concentration versus vessel radius of different vessel orders is shown in Fig.2 A

C. Oxygen transport during ischemic stroke

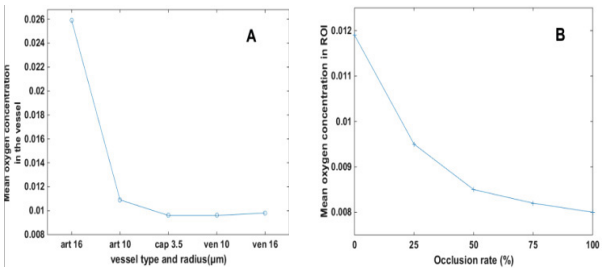

Fig.2 A. The mean oxygen concentration of different vessel type and radius in physiological condition; B. The mean oxygen concentration in different occlusion rate conditions.

Four occlusion rate (25%, 50%, 75%, 100%) of arteriole 2 are applied to investigate the influence of different occlusion levels in ischemic stroke on the whole oxygen delivery. Fig.1 D demonstrated the oxygen concentration distribution when the occlusion rate is 75%. We define the surrounding area of the occluded arteriole as region of interest (ROI), shown as white line box in Fig. 1C & D. The mean oxygen concentration in ROI in different occlusion conditions is shown in Fig.2 B. The tissue oxygen decreases up to 21% when 25% occlusion occurs in ROI. However, 100% occlusion contributes to a 33% decreasing of oxygen. This suggests that the compensatory action caused by collateral circulation is significant especially in the severe occlusion during ischemic stroke.

IV. Conclusions

In this work, we have proposed a mathematical modelling system of haemodynamics and oxygen delivery through the cerebral microvessels. Based on a 2D microvascular network from a published anatomical image, haemodynamic calculation is carried out by fully coupling the intravascular blood flow, the interstitial fluid flow and the transvascular flow. In addition, the compliance of vessel wall and the rheology of blood are included in the coupled model. The haemodynamic information such as intravascular blood velocity is used in the oxygen transport model. The computational space is separated into three domains to characterize three distinct physiological processes, which are (a) the oxygen convection equation inside the vessel, (b) the oxygen flux across the vessel wall and (c) the free oxygen diffusion in the tissue.

The results of haemodynamics and oxygen concentration distribution during ischemic stroke are shown and compared with the normal condition. Furthermore, the influences of different levels of vessel occlusion on the oxygen transport in tissues have been discussed. The sensitivity of certain parameters in the model, such as microvessel density, vessel wall permeability, and the difference of pressure in initial conditions, can be analyzed in the future.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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