Computation of baseline flow across the mouse cortex using two-photon microscopy and vascular anatomical network modeling

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Abstract: We demonstrate the feasibility of computing baseline flow in the mouse cortex using vascular anatomical network constructed from two-photon microscopy measurements. The values obtained are in good agreement with values reported in the literature.

OCIS codes: (180.6900) Three-dimensional microscopy; (170.5380) Physiology

1. Introduction

The hemodynamic response to brain activation involves a complex cascade of neuronal processes leading to increased oxidative metabolism. Over the last decade, optical microscopy has become a powerful method to study this processes at the microscopic level [1, 2]. The partial pressure of oxygen (pO2) and cerebral blood flow (CBF) are two important physiological parameters for the delivery of oxygen to the tissue. pO2 can be measured noninvasively and with high spatial resolution and depth penetration using phosphorescence lifetime measurements of a two-photon-enhanced phosphorescent nanoprobe PtP-C343 [3]. High spatio-temporal resolution three-dimensional maps of CBF can be measured using Doppler Optical Coherence Tomography (Doppler OCT) [4].

The integration of these measurements through detailed vascular anatomical network (VAN) modeling [5] provides a unique opportunity to understand hemodynamic processes at the microvascular level. This approach allows the computation of some important physiological parameters such as the oxygen extraction from the vasculature. Moreover, VAN modeling provides a microscopic description of the biophysics of the functional MRI (fMRI) signals. This provides useful information for the development of new MR pulse sequences for quantitative measurement of physiological parameters, such as the cerebral metabolic rate of oxygen ($CMRO_2$) [6, 7], and open the door for a physiological interpretation of the fMRI signals, which requires a detailed understanding of the competing effects of increased CBF and $CMRO_2$ [8].

We applied VAN modeling to a three-dimensional microvascular network acquired with two-photon microscopy combined with the injection of fluorescein isothiocyanate (FITC). Our approach allows the computation of baseline CBF and red blood cell velocity across the vascular three.

2. Experimental measurements

The experimental procedure is similar to one presented in our previous report [3]. We anesthetized C57BL/6 mice (male, 25-30 g) with isoflurane (1–2% in a mixture of O_2 and air) under constant temperature (37 °C). We then opened a cranial window with dura removed and sealed it with a 150-μm-thick microscope coverslip. Blood plasma was labeled with FITC at 500 nM concentration. We acquired a 600 μm x 600 μm x 662 μm stack of the vasculature with a two-photon microscope (1.17 μm x 1.17 μm x 2.0 μm voxel size).

3. Computation of velocity and flow

Our approach has been described previously in Fang et al [9]. Each segment of the VAN was first vectorized (i.e. graphed) using a custom-designed software in Matlab (MathWorks, Inc.). The diameter of each vascular segment was estimated using the following method: the image intensity was first thresholded at 2% of the maximum image intensity. This procedure allowed us to define the X-Y boundary of each segment due to the high contrast-to-noise ratio of the FITC two-photon measurement. Each segment was then discretized into several similar portions along its axis. For each of these points, we considered lines crossing this point and oriented uniformly every 3 degrees in the local X-Y plane perpendicular to the segment axis. The diameter for each portion of the segment was estimated by

finding the minimum distance from vessel edge to vessel edge using these perpendicular lines. The diameter of the segment was computed as the mean of the individual diameter of each portion forming the segment. The resistance of the segment was then computed using Poiseuille's law

$$R = \frac{128\eta l}{\pi d^4} \qquad (1)$$

where η is the viscosity of blood (η = 15x10^{-6} mmHg s), l is the length of the segment, and d is the diameter of the segment.

The flow in each segment was computed using a flow-pressure relation analogous to Ohm's law for electrical circuits

$$\Delta P = F \cdot R \qquad (2)$$

where ΔP is the pressure difference between the two ends of the segment, F is the flow and R is the resistance of the segment. The pressure at the end nodes of the VAN was set using values taken from the literature for pressure as a function of vessel diameter [10]. Given the boundary conditions on blood pressure and the resistor network, the set of equations for blood pressure and flow at each node can be solved simultaneously as described in Fang et al [9]. Once the flow is estimated for every segment, the velocity v is computed by dividing the flow by the cross-section area of the corresponding segment

$$\upsilon = \frac{F}{\pi d^2} \qquad (3)$$

4. Results

The VAN constructed from our data resulted in 1441 nodes joined by 1887 segments. Pressure boundary conditions were assigned for the 294 end nodes based on literature values [10]. One example of the velocity and flow computed from our model are show in Fig. 1. The velocity values are in good agreement with values previously reported in the literature [10]: around 10 mm/s in the arteries, decreasing to ~1 mm/s in the capillaries and coming back to 5-6 mm/s in the veins. Our flow values in arteries (~8 um^3/s) are also in good agreement with literature OCT values [4].

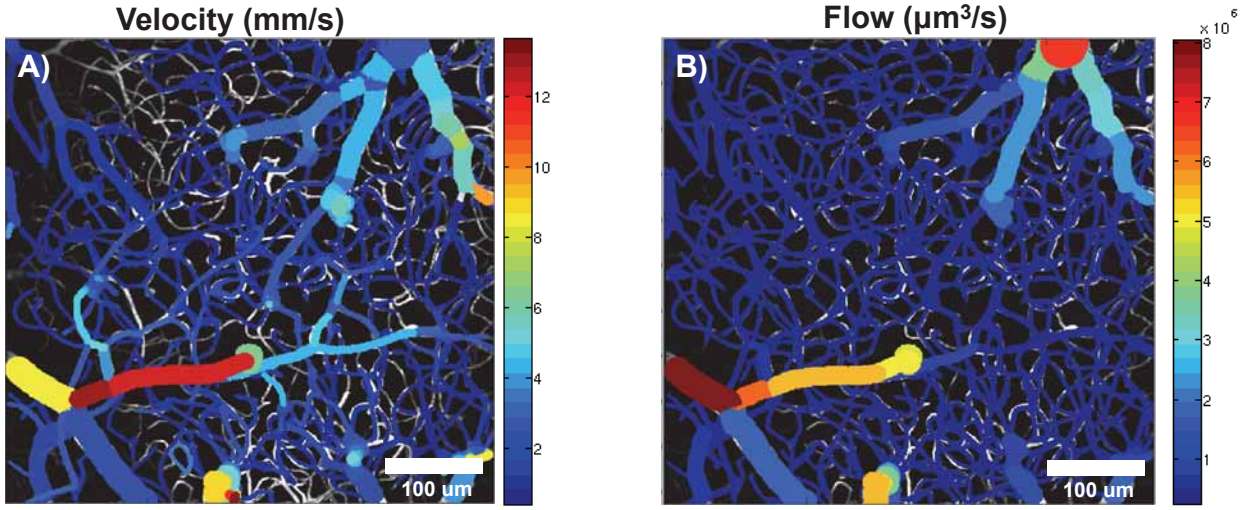

Fig 1. Baseline flow parameters computed with the VAN. (A) Velocity (B) Flow

5. Conclusion and future work

Our preliminary work demonstrates the potential of VAN modeling to compute baseline flow across the mouse cortex using large-scale tri-dimensional network acquired with two-photon microscopy.

In future work, our flow computation will be compared directly against CBF measurements obtained with Doppler OCT [4]. We will also investigate how the information obtained from OCT data could constrain the flow computation and provide a more robust estimation of CBF across the VAN.

6. References

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