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Three Dimensional Vascular Anatomical Network Model of Dynamic Oxygen Delivery

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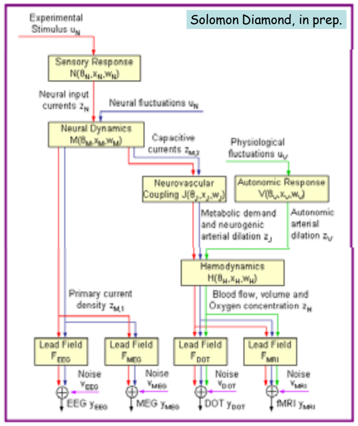
1. Motivation

We have recently developed a vascular model with a distributed network of branching vessels to explore the spatial point spread function of the hemodynamic response to brain activation. With this distributed network model, we found that blood flow in the surrounding vessels could passively decrease in response to a center arteriole dilation driving greater blood flow increase in the center. The model suggests, however, that this passive response is not sufficient to explain the surround negativity observed in our recent experiments in the rat whisker barrel cortex, that active surround vaso-constrictive mechanisms are additionally required.

We are now extending this vascular network model to three dimensional space to more accurately model oxygen advection and diffusion given the connectivity of experimentally measured networks from rodents. This model will guide interpretation of recent experiments measuring the partial pressure of tissue oxygen changes during brain activation, help validate Windkessel model estimates of oxygen consumption, help us understand tissue zones most at risk to reduced oxygen delivery, and help understand oxygen efflux.

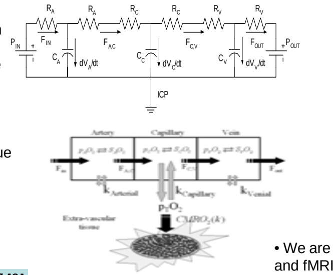
We present our present progress on obtaining 3D vascular anatomical networks from rat brains obtained with 2 photon microscopy, the graphing of these networks for the computer model, and implementation of oxygen advection-diffusion on these graphed networks.



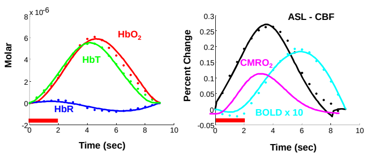
2. Windkessel Model Estimates of Oxygen Metabolism

Analogous to a circuit model with oxygen diffusion

- Flow/Volume changes are driven by changes in arteriole resistance
- Oxygen diffusion between each compartment and extra-vascular tissue
- Mitochondrial metabolism drains tissue pO_2



Huppert JCBFM 2007 [3]



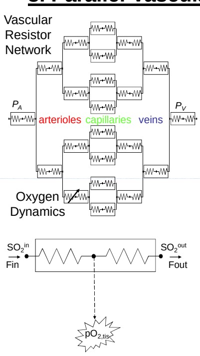
	NIRS, BOLD and ASL	BOLD and ASL
Baseline $CMRO_2$ [ml O_2/100g/min]	5.2 ± 0.2	5.4 ± 0.1
$\Delta CMRO_2$ [max] [%]	16.8 ± 0.6	13.6 ± 0.6
ΔFlow(%) : ΔConsumption(%) Ratio	1.5 ± 0.1	1.8 ± 0.1
ΔFlow(%) : ΔVolume(%) Ratio	3.33 ± 0.03	3.06 ± 0.03

Table 1: Estimate of $CMRO_2$ response using different data combinations. Errors given as standard deviation. Note that oxygen extraction fraction is assumed in the fMRI only case, which can introduce an additional 15% uncertainty as extraction fraction can vary from 0.30 to 0.35.

- We are able to precisely estimate relative $CMRO_2$ change from NIRS/fMRI data and fMRI data alone with unprecedented temporal resolution.
- Is it accurate?

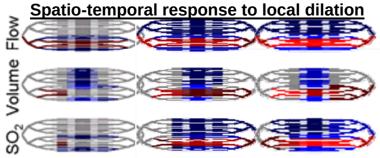
Huppert submitted

3. Parallel Vascular Network



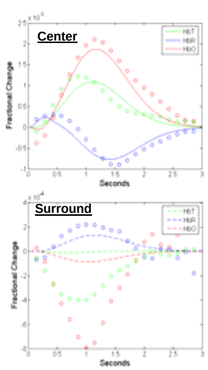
- To explore accuracy of our Windkessel model estimates of oxygen consumption and arteriole dilation, we are developing a microscopic model of the vascular network based on physically measurable parameters.
- The model produces spatio-temporal responses comparable to experimental data. It suggests that passive blood steal does occur, but that active mechanisms are required to observe our observed surround negativity.
- We still need to properly handle 3D diffusion of oxygen.

Spatio-temporal response to local dilation



- Flow and volume respond rapidly
- Delayed oxygenation change
- Surround negativity

Boas submitted



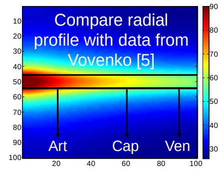
4. 3D Advection Diffusion of Oxygen

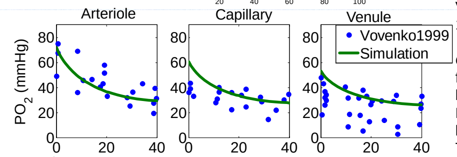
$$\frac{\partial C_T}{\partial t} = -\vec{v}\cdot\nabla C_T + D\nabla^2 C - G(C)$$

$$C_T = C + 4C_{Hb}HS_{Hb}(C)$$

C_T – Total oxygen concentration (free plus bound)
C – the free oxygen concentration
v – blood velocity
D – oxygen diffusion coefficient
G – cerebral metabolic rate of oxygen
C_{Hb} – hemoglobin concentration
H – hematocrit
S_{Hb} – hemoglobin oxygen saturation

Solve using finite difference iteratively time stepping over advection terms (multiple small time steps) and diffusion /consumption terms (larger time step) [1].





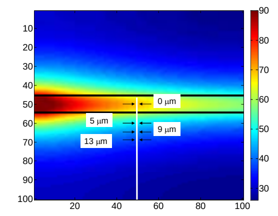
$CMRO_2$ = HGB CBF (SaO_2 – SvO_2) / MW_{HG}
Confirmed expected variation with CBF, HGB, and $CMRO_2$

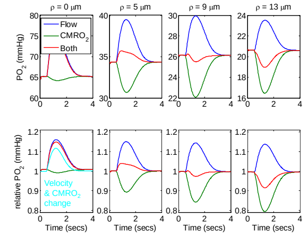
Simulation Parameters

v = 1.0 mm/s
D = 2.4 10^{-3} mm²/s [1]
$G*10$ = 2.5 μmol / g / min
= 5.6 ml O_2 / 100 g / min [2]
C_{Hb} = 5.3 mM [1]
H = 0.40 [1]

Volume is 100 x 100 x 100 μm³
10 μm diameter vessel

G of 2.5 μmol / g / min is value for rat brain [2]. But we reduced by a factor of 10 as otherwise PO_2 dropped too fast and too low radially from the vessel. This could be compensated by a faster velocity and/or neighboring vessels.

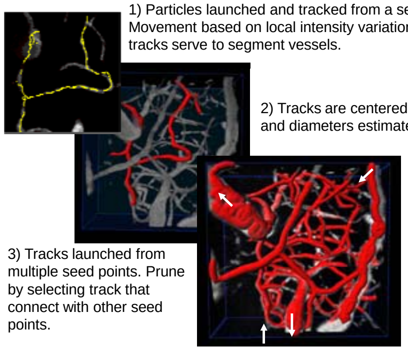




PO_2 Temporal Variation induced by Flow and $CMRO_2$ Changes

We induced a transient increase in velocity and/or oxygen consumption. The temporal trace of the function is shown by the cyan trace in the lower left plot. Velocity was increased by 100% and $CMRO_2$ by 50%. Traces of the PO_2 changes taken from inside the vessel, and 5, 9, and 13 μm outside of the vessel are shown for just a flow change, $CMRO_2$ change, and both changing. Observe that the tissue response is purely positive (negative) near (far from) the vessel and biphasic in between. Details depend on relative onset timing of flow and $CMRO_2$.

5. Building the 3D VAN Model

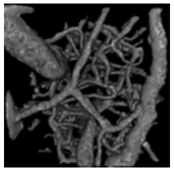


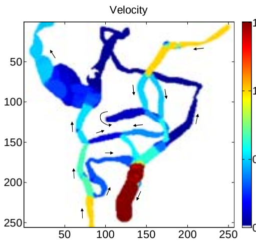
1) Particles launched and tracked from a seed point. Movement based on local intensity variation. Summed tracks serve to segment vessels.

2) Tracks are centered in Imaris and diameters estimated.

3) Tracks launched from multiple seed points. Prune by selecting track that connect with other seed points.

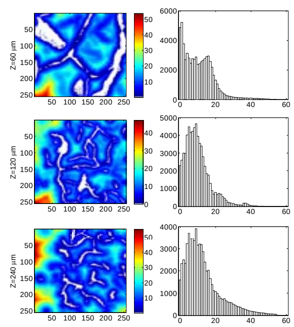
4) Algorithms automatically remove small loops. Then we manually correct a small number of vessel connections.



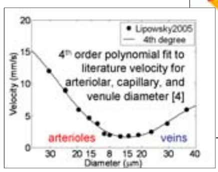


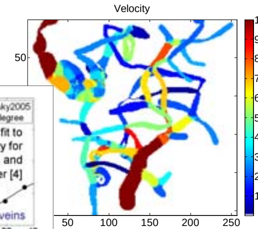
Here we specified the input velocity at two capillaries at 1 mm/s. We set the pressure of the two draining venules to 30 mmHg. All other ending vessel segments given zero velocity boundary condition.

Distance to Nearest Vessel



From the segmented vessel stack we can calculate the distance to the nearest vessel in 3D space. The histograms show the distribution of distances in micrometers (mean 11±1 μm)





Here, we specify an input velocity for every input vessel segment given by the diameter of the input segment and set the pressure of the two draining venules to 30 mmHg. Draining venule velocity exceeds expected result. Likely due to some input vessels actually draining blood.

6. Summary

Advection–Diffusion of oxygen applied to a 3D single vessel and 3D vascular network. We observe a biphasic PO_2 response 10 μm from vessel when $CMRO_2$ and flow increase simultaneously. If $CMRO_2$ precedes flow then biphasic response seen in vessel. We have a semi-automatic method to graph vascular network and can solve velocities within network. Our preliminary analysis of tissue distance to vessel suggests that oxygen needs to diffuse no more than 25 μm from a vessel. More to come on characteristics of oxygen delivery and validation of Windkessel estimates by using microscopic network to simulate OIS and fMRI signals thus giving ground truth for Windkessel analysis.

[1] Beard, Bassingthwaighte (2001) *Ann Biomed Eng* 29:298-310
[2] Herman et al (2006) *J Cereb Blood Flow Metab* 26:79-91
[3] Huppert et al (2007) *J Cereb Blood Flow Metab 27:1262-1279*
[4] Lipowsky (2005) *Microcirculation* 12:5-15
[5] Vovenko E. (1999) *Pflugers Arch* 437:617-623