

# Spatially distributed balloon model of the cerebral vascular response to brain activation

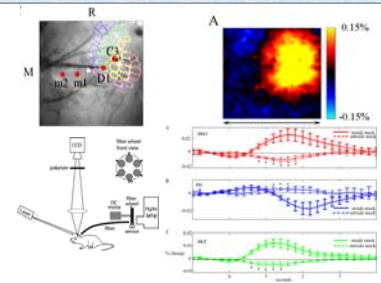


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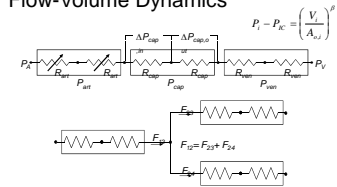
## Motivation

Our recent experimental data from rodent whisker barrel cortex suggests a center-surround negativity in the hemodynamic response to brain activation that does not arise from neuronal inhibition but rather from a passive redistribution of blood flow [Devor2003, Devor2005, Jones (poster 454.9)] Representative data is shown on the right revealing the surround decrease in total-hemoglobin and oxy-hemoglobin and increase in deoxy-hemoglobin.



Here, our goal is to extend the Balloon (Buxton1998) and Windkessel (Mandeville1999) models to a vascular network to determine if a localized arterial dilation giving rise to center increase in blood flow and volume and decrease in doxy-hemoglobin, could result in a surround negativity in these responses. In addition, by modeling a vascular network, we are able to use literature biophysical parameters for the model rather than effective lumped parameters, and thus potentially more quantitatively test hypotheses about neuro-vascular coupling.

## Flow-Volume Dynamics



## Oxygen Dynamics

$$\gamma_a F_a SO_{2in} - \gamma_v F_v SO_{2in} - 0.25 \cdot OE = \frac{\partial [HbO]}{\partial t}$$

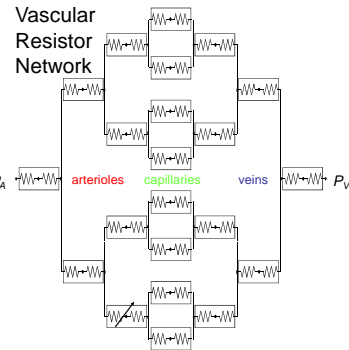
$$V \left( \frac{\partial SO_{2in}}{\partial t} + \frac{\partial SO_{2out}}{\partial t} \right) = (F_{in} + F_{out})(SO_{2in} - SO_{2out}) - 2 \cdot OE (4 \cdot 2.3 \cdot 10^{-3})^{\dagger}$$

$$SO_{2in} = \frac{P_{O2in} - P_{O2out}}{R_{in} + R_{out}}$$

$$J_{O_2} = -K_a \frac{P_{O2in} - P_{O2out}}{W} \quad OE = \alpha [J_{O_2}] \left( \frac{P_{O2in} - P_{O2out}}{R_{in} + R_{out}} \right)$$

$$OE = \alpha [J_{O_2}] \left( \frac{P_{O2in} - P_{O2out}}{R_{in} + R_{out}} \right) = k_{O_2} (P_{O2in} - P_{O2out})$$

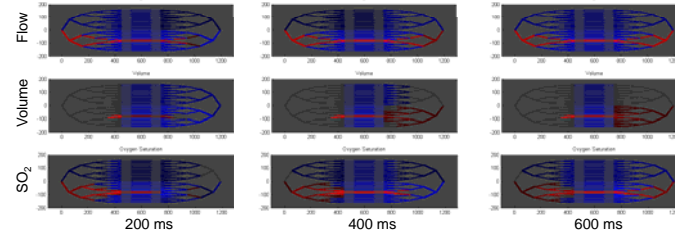
$$\frac{\partial PO_2}{\partial t} = -j_{O_2} (OE - CMRO_2) \left( \frac{1}{\alpha V_{cap}} \right) \left( \frac{1}{\alpha V_{cap}} \right) PO_2$$



The vascular network is represented as a resistor network with a voltage drop (i.e. pressure drop) of  $P_A$  from the arterioles to  $P_V$  in the veins. Flow is determined from the pressure and resistance. Decreasing the resistance of a single pre-capillary arteriole locally increases volume and flow and results in a washout of deoxygenated hemoglobin. Downstream capillaries and venules compliantly increase diameter in response to increased pressure with a non-linearity indicated by  $\beta$ .

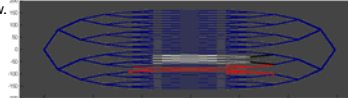
Arterial hemoglobin is saturated with oxygen. This oxygen extracted from the vessel by diffusing down a concentration gradient and is consumed by the mitochondria in the tissue. Thus, hemoglobin saturation leaving a vessel segment is reduced from that entering the segment.

## Steady State Response



## Flow-Volume Relationship

The fractional change in flow has been related to the fractional change in volume by a power-law relationship  $f = v^{\alpha/\beta}$ , where  $\alpha=2$  for laminar flow and  $\beta$  accounts for non-linearity in vascular compliance. In a simple two compartment Windkessel model, the steady-state response log ratio would be 3 and 4 given  $\beta=1$  and 2 respectively. We see that the network produces an effectively smaller (larger)  $\beta$  when including (not including) the arteriole volume change. The flow and volume were averaged over the red ROI indicated below.



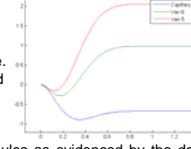
Pre-capillary arteriolar diameter is locally increased as

$$d = d_o + \Delta d (1 - \exp(-t/0.3s))$$

This results in a rapid local increase in flow and volume and a slower local increase (RED) in oxygen saturation. The surround flow is seen to decrease (BLUE) as flow prefers to follow the path of least resistance through the dilated arterioles. Surround volume initially decreases in the compliant capillaries and venules, but then increases downstream due to back-pressure. Oxygen saturation is decreased in the surround as reduced flow results in increased oxygen extraction.

## Back Pressure

Arterial dilation results in increased pressure downstream as evidence of the increased venule volume. As downstream venule blood volume increases, the increased downstream pressure backs up on surrounding converging venules as evidenced by the delayed increased surrounding venule volume. This figure shows the fractional change in blood volume in the surround capillary, post-capillary venule (ven6), and the next venule (ven5), indicated by the white, gray, and black ROI's below-left. Note that further downstream in the surround increases first followed by more upstream segments.



## Surround Decrease

The surround decrease in blood flow averaged over the surround white-to-black ROI is illustrated above compared to the center red ROI. Blood volume does not exhibit a noteworthy increase or decrease related to the backpressure effect. Deoxy-hemoglobin, however, exhibits a noticeable increase in the surround.

## Transient Response

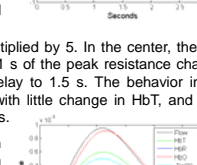
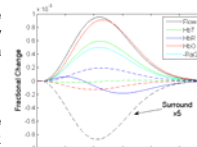
To model our experimental data we dilated the pre-capillary arterioles by decreasing their resistance with a gamma function of the form

$$R_t = R_o \left( 1 - 0.01 \frac{H(t - 0.1)^{\gamma} \exp(-(H(t - 0.1)/1.0)^{\beta})}{\max} \right)$$

This is shown by the cyan line. The corresponding flow, HbT, HbO, and HbR response in the center (solid line) and surround (dashed line) is indicated.

Note that the surround response is multiplied by 5. In the center, the flow and HbT peak just after 1.0 s within 0.1 s of the peak resistance change. HbO is slightly delayed and HbR is delay to 1.5 s. The behavior in the surround is characteristically different with little change in HbT, and flow, HbO, and HbR all peaking just after 1.0 s.

Note that above an early increase in HbR is observed with an increase in HbT and HbO. This arises from the initial HbT increase before any HbR washout. An HbR increase (i.e. "Dip") before an HbT increase can only occur if CMRO2 increases before an arteriole dilation. This is illustrated to the right. Note that consumption increase is coincident with arteriole dilation.



## Fit to Experimental Data

This spatially distributed balloon model produces a hemodynamic center and surround response that is in qualitative agreement with our experimental data as illustrated by the two figures to the right. The simulation was modified to dilate more arterioles, but with the same dilation and consumption response.

**Agreement** - The model gets right the relative time-to-peaks of HbT, HbO, and HbR in center and surround. Correct relative amplitudes in center and surround HbR.

**Issues** - (1) Data has bigger relative decrease in HbT and HbO in surround. (2) Data transit time reduced by 25%. We need to increase model transit by increasing length of vessel segments or add more segments.

## Summary

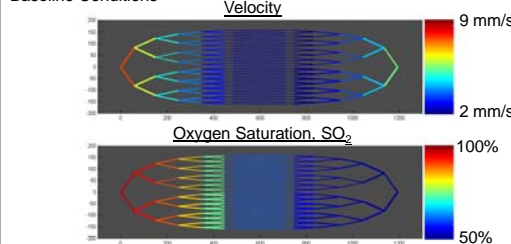
We've modeled the vascular network with a balloon/windkessel model and shown that a surround decrease in blood flow, HbO, and increase in HbR can arise passively as a result of blood flow redistribution to the center path of less resistance. This indicates that active vasoconstriction resulting from perhaps neuronal inhibition is not required for this surround "steal" phenomenon.

In addition, the model has strong qualitative agreement with the experimental data.

## Model Parameter List

|             |   |                                      |
|-------------|---|--------------------------------------|
| $PO_{2in}$  | Partial pressure of oxygen in tissue arterial $i^{\text{th}}$ segment | mmHg                                 |
| $PO_{2i}$   | Partial pressure of oxygen in $i^{\text{th}}$ segment                 | mmHg                                 |
| $OE$        | Oxygen extraction from $i^{\text{th}}$ segment                        | mol $^{-1}$                          |
| $CMRO_2$    | Cerebral metabolic rate of oxygen                                     | mol $^{-1}$                          |
| $K_a$       | Ideal gas constant  | mmHg mol $^{-1}$ K $^{-1}$           |
| $T$         | Temperature   | K                                    |
| $R_{cap}$   | radius around vessel consuming oxygen                                 | mm                                   |
| $d$         | Diameter of $i^{\text{th}}$ segment                                   | mm                                   |
| $l$         | Length of $i^{\text{th}}$ segment                                     | mm                                   |
| $F_{in}$    | Flux of oxygen from $i^{\text{th}}$ segment                           | ml cm $^{-2}$ s $^{-1}$              |
| $K_a$       | Oxygen permeability of segment wall                                   | ml cm $^{-1}$ s $^{-1}$ mmHg $^{-1}$ |
| $\alpha$    | Bunsen solubility coefficient   | ml $\mu$ L $^{-1}$ mmHg $^{-1}$      |
| $w$         | Thickness of segment wall   | mm                                   |
| $V_i$       | Volume of blood in $i^{\text{th}}$ segment                            | mm $^3$                              |
| $\beta$     | Vascular compliance non-linearity                                     | $\mu$                                |
| $SO_{2in}$  | Oxygen saturation of blood arriving in network                        | %                                    |
| $SO_{2i}$   | Oxygen saturation in $i^{\text{th}}$ segment                          | %                                    |
| $SO_{2out}$ | Oxygen saturation of blood delivered to $i^{\text{th}}$ segment       | %                                    |
| $SO_{2in}$  | Oxygen saturation of blood leaving $i^{\text{th}}$ segment            | %                                    |
| $F_{in}$    | Blood flow into $i^{\text{th}}$ segment                               | $\mu$ L s $^{-1}$                    |
| $F_{out}$   | Blood flow out of $i^{\text{th}}$ segment                             | $\mu$ L s $^{-1}$                    |
| $[HbO]$     | Quantity of oxygenated hemoglobin                                     | mol                                  |
| $[HbT]$     | Total quantity of hemoglobin  | mol                                  |
| $[HbR]$     | Quantity of deoxygenated hemoglobin                                   | mol                                  |
| $\gamma_a$  | Conversion of blood to moles of hemoglobin                            | mol $\mu$ L $^{-1}$                  |
| $\gamma_v$  | Conversion of blood to moles of hemoglobin                            | mol $\mu$ L $^{-1}$                  |
| $\alpha$    | Viscosity of plasma   | 1 cP = 2.5 10 $^{-3}$ mmHg s         |
| $R$         | Resistance of $i^{\text{th}}$ segment                                 | mmHg mm $^{-3}$ s                    |
| $P$         | Pressure at $i^{\text{th}}$ segment                                   | mmHg                                 |
| $P_a, P_v$  | Pressure of feeding arteriole, draining venule                        | mmHg                                 |

## Baseline Conditions



|                 |  |
|-----------------|--|
| $\alpha$        | $1.275 \cdot 10^{-3}$ mol $\mu$ L $^{-1}$ mmHg $^{-1}$ |
| $d_{arteriole}$ | 50 $\mu$ m   |
| $d_{capillary}$ | 15 mmHg  |
| $R_a$           | $5 \cdot 10^{-3}$ ml mm $^{-3}$ s $^{-1}$ mmHg $^{-1}$ |
| $SO_{2in}$      | 98%  |
| $\gamma_a$      | 60 mmHg  |
| $\gamma_v$      | 1 cP = 2.5 10 $^{-3}$ mmHg s                           |
| $R$             | mmHg mm $^{-3}$ s                                      |
| $P$             | mmHg   |
| $P_a, P_v$      | mmHg   |

| Branch # segs | Length (mm) | Diameter (mm) | Volume ( $\mu$ L) | Hct (%) | Viscosity (cP) | Resistance (mmHg mm $^{-3}$ s $^{-1}$ ) | Velocity (mm/s) | Transit Time (ms) | SO $_2$ (%) |
|---------------|-------------|---------------|-------------------|---------|----------------|---|-----------------|-------------------|-------------|
| A1-1          | 100         | 30.5          | 73                | 14.1    | 0.56           | 197                                     | 9.8             | 10                | 98          |
| A2-2          | 100         | 24.4          | 94                | 11.5    | 0.43           | 184                                     | 7.6             | 13                | 96          |
| A3-4          | 100         | 19.5          | 120               | 9.8     | 0.34           | 179                                     | 6.0             | 17                | 94          |
| A4-8          | 100         | 15.6          | 153               | 9.4     | 0.31           | 198                                     | 4.7             | 21                | 90          |
| A5-16         | 100         | 12.5          | 196               | 9.1     | 0.28           | 221                                     | 3.6             | 28                | 83          |
| A6-32         | 100         | 10.0          | 251               | 8.8     | 0.26           | 249                                     | 2.8             | 35                | 74          |
| Cap-64        | 150         | 8.0           | 304               | 8.5     | 0.24           | 297                                     | 2.2             | 112               | 60          |
| V5-32         | 100         | 12.0          | 362               | 8.8     | 0.27           | 125                                     | 2.0             | 51                | 55          |
| V6-32         | 100         | 15.0          | 263               | 8.8     | 0.29           | 108                                     | 2.5             | 39                | 53          |
| V7-8          | 100         | 18.7          | 221               | 8.8     | 0.30           | 93                                      | 3.2             | 31                | 52          |
| V3-4          | 100         | 23.4          | 173               | 11.1    | 0.41           | 103                                     | 4.1             | 24                | 51          |
| V2-2          | 100         | 29.3          | 135               | 15.1    | 0.59           | 122                                     | 5.3             | 19                | 51          |
| V1-1          | 100         | 36.6          | 105               | 18.0    | 0.75           | 127                                     | 6.8             | 15                | 51          |