Mathematical Model for Metabolic Blood Flow Regulation in Microvascular Networks

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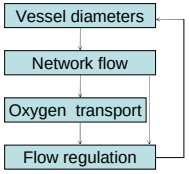
INTRODUCTION

- Oxygen exchange between blood and tissue occurs primarily in the microcirculation
- Blood flow is regulated according to local metabolic demands of the tissue
- The microcirculation has a heterogeneous structure with wide variation in vessel geometry and flow rates

Objectives

- To use a theoretical model to simulate oxygen transport and flow regulation in a heterogeneous network structure
- To test the ability of a mechanism based on a red blood cell derived signal to provide metabolic regulation of blood flow, in response to an increase in oxygen demand

METHODS



Flow calculation

- Flow q_j in segment j of the network is assumed to be governed by Poiseuille's Law
- By conservation of mass, the sum of the flows at each interior node is zero; this gives a set of equations that can be solved for the flows in each vessel
- At vessel bifurcations, there is a phase separation of red blood cells (RBCs), such that the daughter vessel with the higher flow rate has a larger hematocrit [Pries et al., *Circ Res* 67: 826, 1990]; H_D in each vessel is calculated using an iterative procedure

Oxygen calculation

- Represent blood vessels as a set of discrete oxygen sources, and represent PO_2 field in the tissue as a superposition of fields resulting from these sources [Secomb et al., *Ann Biomed Eng* 32: 1519, 2004]
- Steady-state tissue PO_2:

$$D\alpha\nabla^2 P = M(P)$$
$$= \text{complex distribution of sinks and sources}$$

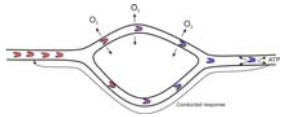
- Formulate in terms of Green's functions $G(\boldsymbol{x},\boldsymbol{x}_i)$:

$$D\alpha\nabla^2 G(\boldsymbol{x},\boldsymbol{x}_i) = -\delta(\boldsymbol{x}-\boldsymbol{x}_i)$$
$$P = \sum_i G(\boldsymbol{x},\boldsymbol{x}_i) q_i$$

- Iterative procedure used to solve system, giving PO_2 and saturation level in each vessel

Metabolic flow regulation by RBC-derived signal

- Red blood cells respond to reduced oxygen saturation in vessels by releasing ATP, which generates a signal that is conducted upstream, causing active vasodilation in the feeding arterioles [Ellsworth et al., *AJP* 269: H2155, 1995]



- Increased wall tension causes vasoconstriction (myogenic response)
- Increased wall shear stress causes vasodilation (shear-dependent response)
- Circumferential wall tension is given by T = PD/2
- Flow regulation is modeled based on length-tension characteristics of vascular smooth muscle (VSM) [Carlson et al., *AJP* 295: H1572, 2008]
- Total tension in the vessel wall is represented as the sum of a passive component, T_{pass}, and an active component generated by the VSM [Carlson et al.]:

$$T_{total} = T_{pass} + AT_{act}^{\max}$$

- Activation (A) represents the level of VSM tone, and varies between 0 and 1:

$$A_{total} = \frac{1}{1+\exp(-S_{tone})}$$

where S_{tone} is the stimulus that influences VSM tone, and depends on wall tension (T), wall shear stress (τ), and conducted response signal (S_{CR}):

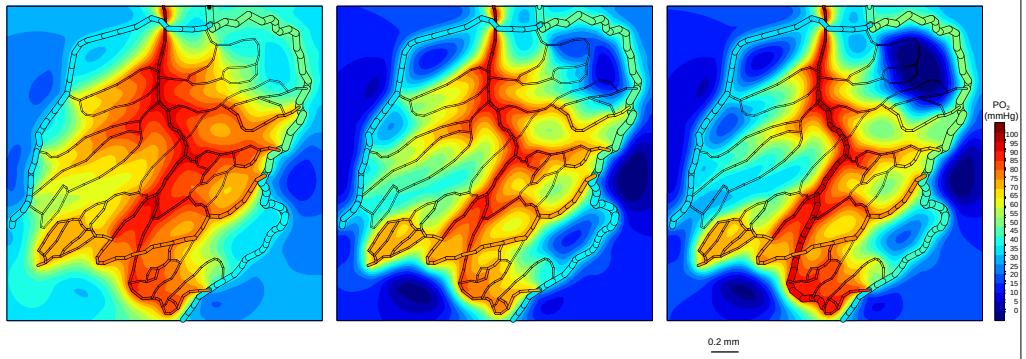
$$S_{tone} = C_{myo}T - C_{shear}\tau - C_{meta}S_{CR} + C_{tone}^{''}$$

- Behavior of arteriolar diameters in response to pressure changes can be represented as follows [Arciero et al., *AJP* 295: H1562, 2008]:

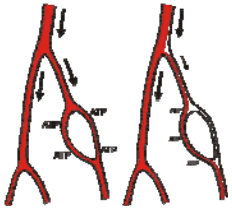
$$\frac{dD}{dt} = \frac{1}{\tau_d}\frac{D_c}{T_c}(T - T_{total})$$
$$\frac{dA}{dt} = \frac{1}{\tau_a}(A_{total} - A)$$

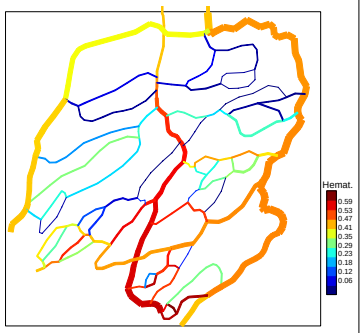
- With updated diameters, program steps forward and re-calculates flows and tissue oxygen levels to simulate time-dependent flow regulation after an increase in oxygen demand
- A control state is established at a low oxygen consumption rate with measured diameters, such that S_{tone} = 0 in every vessel

RESULTS AND DISCUSSION



- Figure above shows initial tissue PO_2 distribution with maximum oxygen consumption rates (M_0) of 0.5 and 1.0 cm^3 O_2/(100 cm^3 · min), and tissue PO_2 distribution after 20 seconds with M_0 = 1.0 cm^3 O_2/(100 cm^3 · min)
- After 20 seconds, the metabolic flow regulation is able to redistribute blood flow such that the hypoxic tissue regions at the bottom and on the right side of the network increase PO_2 levels
- However, tissue regions with low PO_2 at the top left and top right of the network *do not* become better oxygenated after ATP-driven metabolic flow regulation, and in fact become less oxygenated
- Figure on the right shows that in these regions, hematocrit is at or near 0
- This is due to the hematocrit partition at vessel bifurcations, which results in a red blood cell flux decline in smaller vessels, leading to a reduced metabolic signal





- The poor oxygenation of these regions results from an instability of flow regulation by this mechanism:
  - Reduced flow causes reduced hematocrit in some vessels as a result of phase separation at bifurcation
  - Reduced hematocrit causes reduced ATP release and reduced metabolic signal
  - Upstream arteriole constricts, further reducing flow

CONCLUSIONS

- Metabolic flow regulation by a RBC-derived signal leads to improved oxygenation in some regions but worse oxygenation in others, due to instability generated by phase separation at bifurcations
- This suggests that some other mechanism – not dependent on RBCs – must contribute to metabolic flow regulation, as implied by recent experimental results [Ngo et al., *Eur J Physiol* 460: 41, 2010]