Modeling BOLD-fMRI on real vascular stacks measured with two-photon microscopy during functional activation

Louis Gagnon1,2,3, Sava Sakadaki1, Frederic Lesage1, Joseph J. Musacchia1, Joel Lefebvre1, Gianqian Fang1, Meryem A. Yuce1, Karleyton C. Evans1, Emini T. Mandeville1, Julien Cohen-Adad1, Jonathan R. Polimeni1, Mohammad A. Yaseen1, Eng H. Lo1, Douglas N Greve1, Richard B. Buxton4, Anders M. Dale4, Anna Devor1,4 and David A. Boas1,2

1-Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA. 2-2-Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA, USA. 3-3-Department of Electrical Engineering, Ecole Polytechnique de Montreal, Montreal, QC, Canada. 4-4-Department of Radiology and Neuroscience, University of California San Diego, La Jolla, CA, USA.

Background
Detailed modeling of T2 and T2* signals has been limited to uniformly oxygenated vessel networks under static conditions [1]. New quantitative microscopy techniques (2.3) allow dynamic, 3-dimensional measurements of blood flow and the distribution of oxygen in the microscopic vasculature at rest and during functional activation, providing new opportunities to study cerebral microvascular physiology.

Experimental setup
Hybrid OCT/2-photon system
- 860-nm OCT System
- PIP-C343 excitation/emission=498/680nm
- 2-photon Ti-Saph laser: 840nm
- Electro-optic modulator: 110 fs, 80 MHz
- PO2 obtained from fluorescence lifetime

Animal preparation
- C57BL/6 mice: 25-30 g
- Anaesthetized with isoflurane (1-2 % mixed w/ O2 and air)
- Surgical procedure: Cranial window with dura removed
- α-chloralose infused throughout experiment

Vascular Anatomical Network (VAN) modeling
- 2.5 VAN models were created in this work.
- From each animal, a graph of the vasculature and a 3D mesh (B) were constructed.
- Assuming global perfusion (100 ml/100g/min), the flow was computed in all vascular segments.
- Oxygen extraction fraction (OEF) was computed from two-photon PO2 measurements.
- Given flow and OEF, CMRO2 was computed for each animal.
- Given flow and CMRO2, oxygen advection was computed in all vascular segments.
- The resulting simulated PO2 distributions were validated against the experimental PO2 distribution (E).
- Good agreements were obtained for all animals between simulated and experimental PO2 distributions (F).

Arterial dilation during forepaw stimulation
- The dynamics of arteries and arterioles were measured during forepaw stimulation using two-photon microscopy (9) on a separate set of animals.
- Arteries were computed across all animals for different branching orders and vessel segments of the vascular tree.

Dynamic VAN model of O2 advection
- The experimental averaged dilation traces were passed as input to the six VAN models to compute the flow and the volume responses for each vessel.
- Given the flow and volume, the temporal evolution of the SO2 distribution during the forepaw stimulation was computed in each of the six VAN models.

Validation of Dynamic VAN model
- The dynamic VAN model was validated by experimental measurements of SO2 changes during forepaw stimulations. Measurements were performed on a separate set of animals with confocal microscopy with an oxygen sensitive dye.

BOLD model
- From the SO2 volumes (A), the magnetic susceptibility induced by the vasculature was computed at each time point, for each of the six animals.
- From the susceptibility shift, a ΔB volume was computed (B).
- Assuming hematocrit values for arteries, capillaries and veins, the transverse relaxation time of blood (T2) was computed given SO2.
- Given ΔB and T2, the fMRI signals were computed by simulating the diffusion of 1x10^10 protons in the volume, keeping track of the phase accrual for each proton.
- Spatial gradients were applied during the simulation (C) to simulate gradient-echo and spin-echo fMRI signals (E).

Validation of BOLD model
- Good agreement were obtained between our simulated BOLD signals and experimental BOLD data measured during forepaw stimulation and under the same physiological conditions (F).

Acknowledgements
The work was funded by the National Institute of Neurological Disorders and Stroke (R01NS089431). The Mouse Imaging Center was supported by the National Institute of Neurological Disorders and Stroke (R01NS089431). The authors thank Dr. Richard A. Iorio and colleagues at the Martinos Center for Biomedical Imaging for their support.

References
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Conclusion
Our simulations predicted that the amplitude of the BOLD response depends on the orientation of the folded cortical surface relative to the main magnetic field of the scanner.
- To test this prediction, BOLD were recorded on humans (n=5) during a hypercapnic challenge (pCO2 = 8 mmHg).
- A surface analysis was performed with FreeSurfer and the angle between the folded cortical surface and B0 was computed for all cortical voxels.
- BOLD was plotted as a function of cortical angle.
- Experimental measurements confirmed our theoretical predictions.

BOLD vs Orientation of Folded Cortical Surface
- Our VAN model combined with our 2-photon measurements allow us to quantify microvascular physiology at rest and during cerebral activation.
- The temporal evolution of O2 distribution combined with Monte Carlo simulations allow us to model spin echo and gradient echo fMRI signals at the microscopic level.
- Our methodology allows to compute the contributions of individual vascular segments to the BOLD response.
- We found that the amplitude of the BOLD response can vary by up to 40% depending on the orientation of the folded cortical surface relative to the main magnetic field of the MRI scanner.