MGH/HST Athinoula A. Martinos Center for Biomedical Imaging

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

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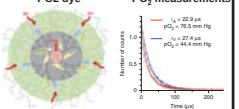
Background

Detailed modeling of T_2 and T_2* signals has been limited to uniformly oxygenated vessel networks under static conditions [1]. New quantitative microscopy techniques [2,3] allow dynamic tridimensional measurements of blood flow and the distribution of oxygen in the microvasculature of the cerebral cortex of the rodent. These high-resolution measurements (1 um cubic) constitute a unique opportunity for modeling the fMRI signals at the microscopic level in space and time. These detailed models will provide a goal-standard to validate (and refine if necessary) more simplified models [4,5] that can be used to infer physiological parameters such as cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen ($CMRO_2$) from fMRI measurements, as well as new quantitative fMRI sequences [6,7]. It also provides a powerful way of simulating the effect of pathological conditions on the BOLD signal.

Experimental setup

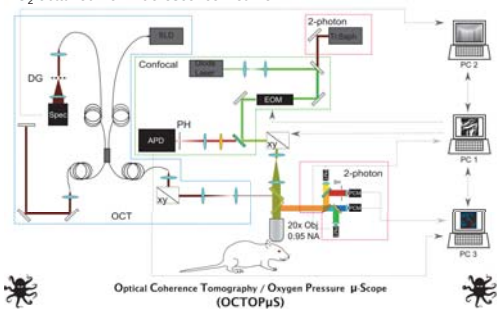
PtP-C343 PO2 dye

2-photon liftetime PO_2 measurements



Hybrid OCT/2-photon system

- 850nm OCT system
- PtP-C343 exitation/emission= 498/680nm
- 2-photon Ti-Saph laser: 840nm
- Electro-optic modulator: 110 fs, 80 MHz
- PO_2 obtained from fluorescence lifetime



Optical Coherence Tomography / Oxygen Pressure µ-Scope (OCTOPµS)

Animal preparation

- C57BL/6 mice (male, 25-30 g)
- Animal ventilated at all times
- Anesthesized with isoflurane (1-2 % mixed w/ O_2 and air)
- Surgical procedure: Cranial window with dura removed
- α-chloralose infused throughout experiment

Experimental protocol

Microvascular hemodynamics at rest

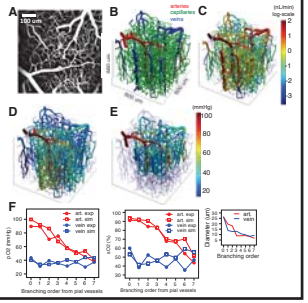
- PO_2 distribution at rest (2-photon + PtP-C343, [2])
- Cerebral Blood Flow at rest (Doppler OCT, [3])
- Angiogram (2-photon + FITC)

Functional activation

- 2-sec forepaw electrical stimulation
- Arterial dilation during stimulation (2-photon, [9])

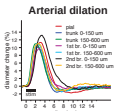
Vascular Anatomical Network (VAN) modeling

- 6 VAN models were created in this work.
- From each angiogram (A), 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 (C).
- Oxygen extraction fraction (OEF) was computed from two-photon PO_2 measurements.
- Given Flow and OEF, $CMRO_2$ was computed for each animal.
- Given Flow and $CMRO_2$, oxygen advection was computed in all vascular segments (D).
- The resulting simulated PO_2 distribution was validated against the experimental PO_2 distribution (E) collected for each animal.
- Good agreements were obtained for all animals between simulated and experimental PO_2 distribution (F).



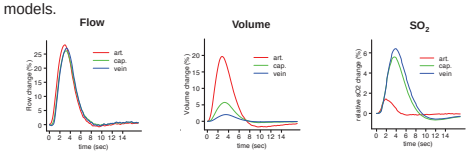
Arterial dilation during forepaw stimulation

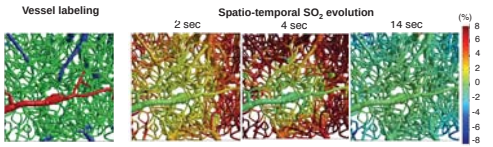
- The diameter of arteries and arterioles were measured during forepaw stimulation using two-photon microscopy [9] on a separate set of animals.
- Averaged traces were computed across all animals for different branching orders and vessel segments of the vascular tree.



Dynamic VAN model of O_2 advection

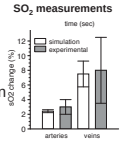
- The experimental averaged dilation traces were passed as input to the six VAN models to compute the flow and the volume responses for each vessel.
- Given the flow and volume, the temporal evolution of the SO_2 distribution during the forepaw stimulation was computed in each of the six VAN models.





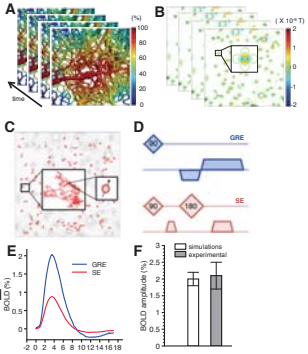
Validation of Dynamic VAN model

- The dynamic VAN model was validated by experimental measurements of SO_2 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 SO_2 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 (T_2) was computed given SO_2.
- Given ΔB and T_2, the fMRI signals were computed by simulating the diffusion of $1x10^6$ protons in the volume, keeping track of the phase accrual for each proton (C).
- Spatial gradients were applied during the simulation (D) to simulate gradient-echo and spin-echo fMRI signals (E).

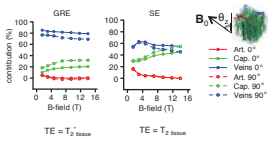


Validation of BOLD model

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

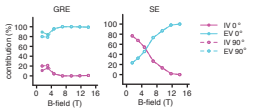
Artery, Capillary and Venous contributions to BOLD

- Our approach allowed to compute the contribution of specific vascular compartments to the BOLD response.
- Venous contributions is about 80% BOLD for GRE but is reduced to 60% for SE



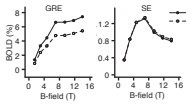
Intravascular and Extravascular contributions to BOLD

- Extravascular BOLD dominates the GRE signal for B_0>7T.
- Extravascular BOLD increases with B_0 for SE.



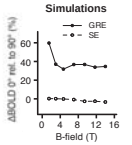
BOLD amplitude vs Magnet strength

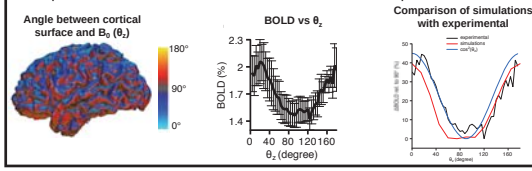
- For GRE, BOLD amplitude shows a fast increase with magnet strength up to 7T and slower increase for B_0>7T.
- For SE, the short T_2 of tissue at high fields results in weaker BOLD response.



BOLD vs Orientation of Folded Cortical Surface

- Our simulations predicted that the amplitude of the BOLD response depends on the orientation of the folded cortical surface relative to the magnetic field of the scanner.
- To test this prediction, BOLD were recorded on humans (n=5) during a hypercapnic challenge (pCO_2 = +8 mmHg).
- A surface analysis was performed with FreeSurfer and the angle between the folded cortical surface and B_0 was computed for all cortical voxels.
- BOLD was plotted as a function of cortical angle.
- Experimental measurements confirmed our theoretical prediction.





Conclusion

- 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 O_2 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.

Acknowledgements

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