

TARGET AUDIENCE MR physicists developing models of fMRI signals and MR engineers working towards the development of new fMRI sequences.

PURPOSE Detail modeling of T2 and T2* signals has been limited to uniformly oxygenated vessel network under static condition [1]. New quantitative microscopy techniques [2,3] allow dynamic tridimensional measurements of the distribution of oxygen in the microvasculature of the cerebral cortex of the mouse. These high-resolution measurements (1 μm^3) constitute a unique opportunity for modeling the fMRI signals at the microscopic level in space and time. These detailed models will provide goal standards 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 (CMRO₂) 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.

METHODS Mice were anesthetized with isoflurane and a cranial window was opened. The baseline distribution of partial pressure of oxygen (pO₂) was measured in layers 1-3 of the mouse cortex (FOV=600x600x660 μm) using two-photon microscopy with an oxygen-sensitive contrast agent (PtP-C343) [2]. A detailed angiogram was also obtained with two-photon microscopy using an intravascular FITC contrast agent. Quantitative measurements of absolute cerebral blood flow were performed using Doppler Optical Coherence Tomography [3]. The vasculature extracted from the angiogram was graphed to construct a vascular anatomical network model (VAN) [8]. Both OCT and two-photon measurements were interpolated through the VAN which allowed to model pO₂ in both the vasculature and the cortical tissue. The temporal evolution of oxygen concentration in the vessels was then computed using the VAN model together with arterial dilation profile inputs obtained from two-photon microscopy measurements during forepaw stimulation [9]. The fMRI signals were then modeled from the 3D distribution of oxygen. The temporal evolution of oxygen saturation was converted to a shift in magnetic susceptibility that was used to compute a magnetic perturbation (ΔB) volume [1] at each time-point following the forepaw stimulation. The resulting fMRI signals were computed by simulating the diffusion of 10⁷ protons in the ΔB volume at each time point. Spatial gradients were applied during the simulation to produce gradient echo (GE) and spin echo (SE) signals.

RESULTS The 3D reconstruction of the baseline physiological parameters is shown in Fig. 1. The arterial dilation traces measured during forepaw stimulation are shown in Fig. 2A. Traces were averaged for surface pial arteries as well as for shallow and deep descending arteries. The fMRI signals predicted from the MC simulation using the temporal dilation profiles are shown in Fig. 2B. The gradient echo signal increased by 1% following the forepaw stimulation while the spin echo signal increased by 0.5%.

DISCUSSION The shape of the fMRI traces computed from our model agrees well with *in vivo* fMRI traces measured under the same physiological conditions during forepaw stimulations [9]. In future work, we will perturb the physiological parameters of our model (e.g. vessel compliance, hypoxic tissue, etc) to simulate pathological conditions and see how they affect the GE and SE signals. We will also investigate the accuracy of simplified BOLD models [4,5] and quantitative fMRI sequences [6,7] to recover CMRO₂ by generating synthetic fMRI signals with our detailed model for different sets of physiological parameters.

CONCLUSION Our work provides a method to model the biophysics of fMRI signals at the microscopic level from quantitative measurements of microvascular physiology. This detailed model will serve as a gold standard to test the accuracy of more simplified models and new quantitative fMRI sequences to recover clinically relevant physiological parameters from fMRI measurements.

REFERENCES [1] Christen et al. MRM 67:1458 (2011). [2] Sakadzic et al. Nature Meth. 7:755 (2010). [3] Srinivasan et al. JCBFM 31:1339 (2011). [4] Davis et al. PNAS 95:1834 (1998). [5] Gauthier et al. NeuroImage 60:1212 (2012). [6] He et al. MRM 57:115 (2007). [7] Bolar et al. MRM 66:1550 (2011). [8] Fang et al. Opt. Express 16:17530 (2008). [9] Tian et al. PNAS 107:15246 (2010).

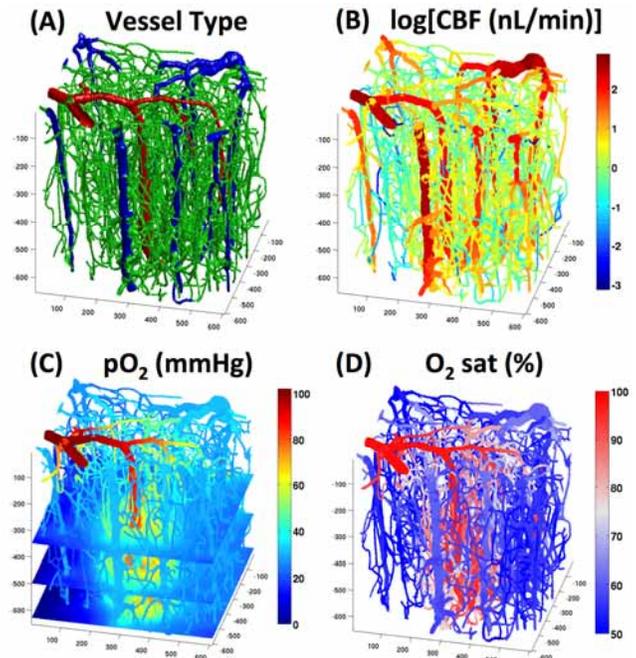


Figure 1 3D reconstruction of baseline physiological parameters from 2-photon and OCT measurements. A) Vessel type (red: arteries, green: capillaries, blue: veins) B) Cerebral blood flow (in log-scale) C) pO₂ D) O₂ saturation

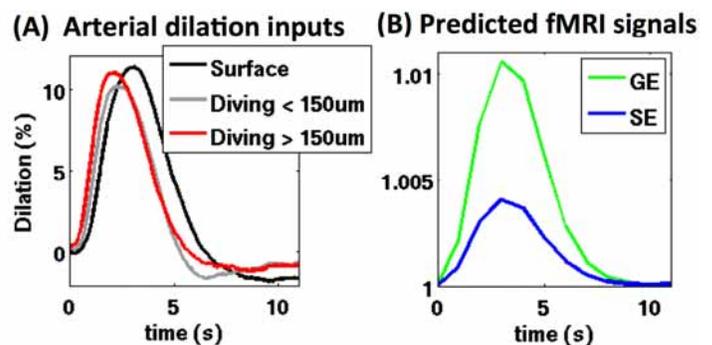


Figure 2 Computation of the fMRI signals (GE: gradient echo, SE: spin-echo) from the VAN model using arterial dilation inputs measured during forepaw stimulation. A) Arterial dilation traces measured with 2-photon microscopy B) Computed fMRI traces (TE=30 ms).