Insights from numerical simulations of brain blood flow regulation in large anatomical networks

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Blood micro-circulation plays a central role in the local adaptation of cerebral blood flow to neural activity (neuro-vascular coupling). A growing body of evidence indicates that neurons, glia, and cerebral blood vessels, acting as an integrated unit, have a crucial role in mediating the activation-induced changes in blood flow. In particular, the smooth muscle cells surrounding the arterioles, and possibly pericytes, at capillary level, convert the bio-chemical signals that originate from this integrated unit into changes in vascular diameter, thus regulating blood flow by modulating vascular resistance [1]. However, the relative role of arterioles and capillaries in the control of cerebral blood flow is still controversial [1]. In particular, it is at present not clear whether the capillary dilatation experimentally observed in vivo by several groups is a passive consequence of upstream arteriolar dilatation via an alteration in perfusion pressure or the result of an active regulation of the capillary diameter via contraction/relaxation of pericytes [1]. Answering this question is of importance in the context of functional neuroimaging. The spatial resolution and specificity of hemodynamically based functional imaging techniques (including fMRI and PET) are indeed bound to the density and localization of the blood flow regulating structures [2].However, using experimental means for that purpose is extremely challenging. For example, the penetration depth of the most recent intravital two-photon microscopy techniques(typically ~500 µm) does neither allow to investigate the cortical layers of highest capillary density, which are located approximately in the middle third of the cortex [3] nor those where the fastest capillary dilation occurs [4].By contrast, several authors [1,5] have pointed out that modelling using anatomically accurate representations of the intra-cortical vascular network allows a better and more quantitative understanding of cerebral blood flow control. In particular, such an approach can be valuable for generating predictions as to the likely impact of pericyte-mediated capillary diameter regulation [1].Our group has recently performed the first numerical simulations of blood flow in an anatomically accurate large human intra-cortical vascular network (~ 10000 segments), using a1D non-linear model taking into account the complex rheological properties of blood flow in microcirculation (i.e. Fahraeus, Fahraeus-Lindquist and phase separation effects) [6].This model predicts blood pressure, blood flow and hematocrit distributions, volumes of functional vascular territories, regional flow at local, voxel and network scales, etc. Using this approach, we have studied the flow re-organizations induced by arteriolar vasodilations, highlighting the hemodynamic component of various functional neuroimaging techniques [7]. In the present paper, the variations in cerebral blood flow induced by global or localized capillary vasodilations are studied and compared to these previous results, demonstrating that pericyte-mediated regulation of blood flow at capillary level would be efficient for neuro-vascular coupling. By contrast to a regulation situated at the level of arterioles [7], the changes in blood volume can be highly localized in space, with the potential to be as close as possible of areas of neuronal activation. However, the changes in blood flow are much more diffuse. This imposes limits on the ultimate spatial resolution of hemodynamically based brain functional imaging techniques, whatever the localization of the blood flow regulating structures.

Hamilton NB et al., Pericyte-mediated regulation of capillary diameter: a component of neurovascular coupling in health and disease. Front. Neuroenergetics, 2, 1-14 (2010).

Harel N et al., Frontiers of brain mapping using MRI. J. Magn. Reson. Imaging, 23, 945–57 (2006).

Lauwers F et al., Morphometry of the human cerebral cortex micro-circulation: general characteristics and space-related profiles. Neuroimage, 39, 936-48 (2008).

Tian P, et al., Cortical depth-specific microvascular dilation underlies laminar differences in blood oxygenation level-dependent functional MRI signal. PNAS, 107, 15246-51 (2010).

Weber B et al., The microvascular system of the striate and extrastriate visual cortex of the macaque. Cereb. Cortex 18, 2318–30 (2008).

Lorthois S et al., Simulation study of brain blood flow regulation by intra-cortical arterioles in an anatomically accurate large human vascular network: Part I: Methodology and baseline flow, Neuroimage,54, 1031-42 (2011).

Lorthois S et al., Simulation study of brain blood flow regulation by intra-cortical arterioles in an anatomically accurate large human vascular network: Part II: Flow variations induced by global or localized modifications of arteriolar diameters, Neuroimage, 54, 2840-53 (2011).

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.