

# Quantitative BOLD analysis using a Numerical Model. Blood volume, Oxygenation and Vessel Size measurement in the rat brain.

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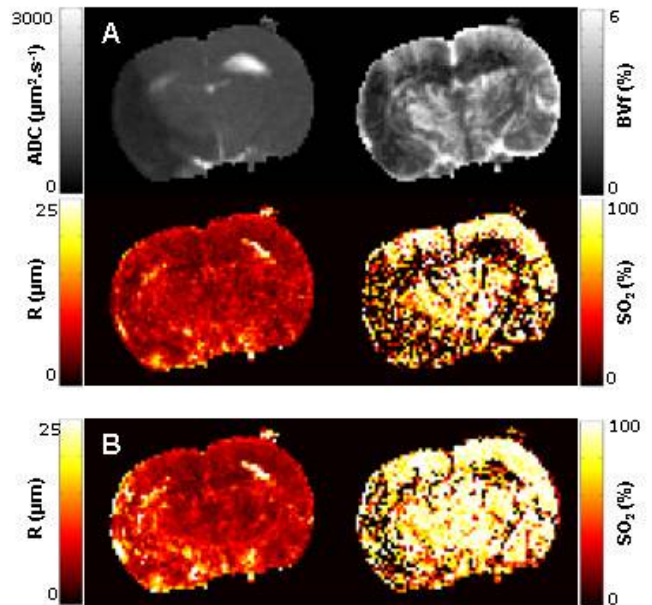
**Introduction:** The analytical description of the susceptibility-related MR dephasing is used to assess the microvasculature [1-5]. Various techniques have been applied to study different pathologies [6-7]. These approaches vary depending on whether a contrast agent (CA) is used. Quantitative BOLD aims at measuring the local blood oxygenation saturation (SO<sub>2</sub>) and the blood volume (Bvf) by modeling the MR signal during the spin echo (SE) [8]. Steady-state approaches use the variation of the transverse relaxation rates (T<sub>2</sub> and/or T<sub>2</sub>') provided by a CA injection and assess BVf, vessel size index (VSI) or vessel density [5]. A recent approach proposes to combine these two techniques [9]. However, analytical solutions are discordant with Monte Carlo simulations and this discrepancy lead to bias vascular estimates [10]. Moreover recent results demonstrate that BVf and SO<sub>2</sub> cannot be assessed at once in qBOLD [11-12]. In this work, we proposed a new integrative approach to simultaneously assess BVf, SO<sub>2</sub> and the radius of the vessel (R). We built up a densely sampled lookup table (LT) by simulating the MR signal provided by a Gradient Echo Sampling of the FID and SE sequence (GESFIDE) prior and post injection of a CA. We acquired the corresponding GESFIDE sequence on two rats with focal brain ischemia and we estimated BVf, R and SO<sub>2</sub> from the LT. We compared our approach to analytical methods.

**Methods: Model:** The MR signal within a voxel was simulated by taking into account the diffusion of the water molecules and the magnetic field perturbations. The voxel contained vessels of radius R that occupied BVf. The magnetic susceptibility difference between the vessels and the tissue was Δχ. The diffusion was modeled with a Gaussian kernel with diffusivity ADC. To speed up the computation, the algorithm was designed in 2D but the magnetic field perturbations were computed in a way that mimics 3D [13]. The lattice was 256x256 points, 96 vessels were randomly spread out and the voxel size was adapted to maintain the BVf constraint. The LT was built up with the range of parameter values: R=[0.5,1.0,...25]μm, Vf=[0.5,1.0,...10]%, Δχ=[0.05,0.1,...1.35]ppm (SI unit, corresponding to SO<sub>2</sub>=[0-100]% using (1-Δχ)/(4πi\*Δχ0\*Hct) with Hct=0.85\*0.42 and Δχ0=0.264) and ADC=[400,450,...1000]μm<sup>2</sup>.s<sup>-1</sup>. To simulate the effect of the CA, another LT with the same range of parameter but translated by Δχ=3.5ppm was built up (768000 individual simulations in total, ~48x25h in CPU thread time). **Animal:** Transient focal ischemia was induced within 2 rats by intraluminal occlusion of the right MCA [14]. **MRI:** Imaging was performed on a 4.7T Bruker system just after occlusion. Water diffusion was assessed by diffusion weighted EPI sequence. The GESFIDE (T<sub>E</sub>=75ms, 10 GE during FID + 26 GE during the spin-echo, 12 slices, 4Ave, 0.254x0.254x0.4μm<sup>3</sup>) was acquired prior (GPr) and post (GPo) the intravenous injection of USPIO (P904, Guerbet, France, 200μmol Fe/kg). The increase in the magnetic susceptibility was set to 3.5ppm SI [5]. Three slices were averaged and a Gaussian kernel (3x3) was applied. **Analysis:** The ratio of GPo/GPr was calculated voxel wise and the closest curve in term of normalized root mean square distance (nRMSD) was extracted from the ratio of the LTs (Fig3A). R, BVf and SO<sub>2</sub> were subsequently evaluated. Voxels with nRMSD<0.75 were rejected in the ROI measurement (about 15% of the overall voxels of the brain). For comparison, the same approach with a fixed ADC set to 800μm<sup>2</sup>.s<sup>-1</sup> and the analytical model that estimates VSI and BVf was also evaluated [5].

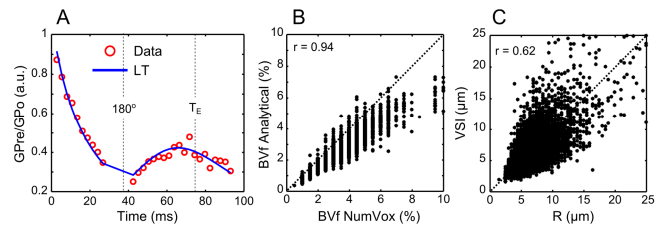
**Results:** Figure 1A illustrates the maps obtained. Mean±Std values in occluded and contralateral hemispheres were respectively: BVf=2.8±0.2% and 3.5±0.2%, R=6.9±0.4μm and 6.5±0.2μm and SO<sub>2</sub>=43±4% and 57±4%. BVf and R are in good agreement with previous reported values, SO<sub>2</sub>, however, is lower. Figure 1B shows the results obtained when ADC is set to 800 μm<sup>2</sup>.s<sup>-1</sup>. This induces an increase in both R and SO<sub>2</sub> (R=8.9±0.4μm and 7.0±0.3μm and SO<sub>2</sub>=68±1% and 77±3% respectively in the left and right hemispheres). The largest deviation appears in the ischemic region where the ADC is lower, highlighting the role of the diffusion in the model. Figures 3BC present the correlation plots between the proposed approach and the analytical model for BVf and R vs VSI. Correlation is high for BVf with higher value in the NumVox approach. The dispersion in radius is larger and correlation weaker. It is worth notice that R and VSI are not equivalent in theory [5].

**Conclusion:** We propose here an integrated approach to assess the microvasculature. It benefits from the larger number of MR signal samples provided by the GESFIDE sequence and from the lesser assumptions required in the numerical model. Using the ratio also avoids the issues about B<sub>0</sub> inhomogeneity and T<sub>2</sub> decay (assuming T<sub>2</sub> remains the same after injection). Although promising, the method needs to be further evaluated.

**Reference:** [1] Yablonskiy et al., MRM, 1994, 6:749-763 [2] Kiselev et al., MRM, 1999, 41:499-509 [3] Sukstanskii et al., JMR, 2004, 167:56-67 [4] Jensen et al., MRM, 2000, 44:224-230 [5] Tropes et al., MRM, 2001, 45:397-408. [6] An et al., Stroke, 2009, 40:2165-2172. [7] Lemasson et al., NMR in Biomed, 2011, 24:473-482. [8] Yablonskiy et al., NMR in Biomed, 2012, early view [9] Christen et al., NMR in Biomed, 2011, 24:393-403. [10] Dickson et al., JMR, 2011, 212:17-25 [11] Sohlh et al., JMIR, 2011, 33:417-425. [12] Sedlacik et al., MRM, 2010, 63:910-921, 1991 [13] Pannetier et al., Plos One, In revision. [14] Longa et al., Stroke, 1989, 20:84-91.



**Fig. 1** – A. Illustration of the ADC, BVf, R and SO<sub>2</sub> maps obtained in one of the ischemic rat. B. Maps of R and SO<sub>2</sub> when the ADC value is set to 800 μm<sup>2</sup>.s<sup>-1</sup>



**Fig. 2** – A. Illustration of the fit obtained in a voxel of the healthy cortex. Note that the signal during the spin-echo is not maximal at T<sub>E</sub> due to the diffusion. B. Correlation plot between BVf evaluated either with our approach or the analytical model. C. Correlation plot for the radius and VSI evaluated either with the proposed approach or the analytical model.