Direct Experimental Evidence of the Two Extravascular Compartments Contribution to The BOLD Signal

Xiaoqi Wang[1], Alexander L Sukstanskii[2], and Dmitriy A Yablonskiy[1,2]

[1]*Department of Physics, Washington University in St. Louis, St. Louis, Missouri, United States,* [2]*Department of Radiology, Washington University in St. Louis, St. Louis, Missouri, United States*

Introduction: Recently introduced qBOLD technique [1] allows quantitative estimate of brain tissue hemodynamic parameters such as deoxygenated blood volume and oxygen extraction fraction. The technique is based on a two extravascular compartment model of MR signal (intra- and extra-cellular) in the presence of blood vessel network and a gradient echo sampling of spin echo (GESSE) sequence [2] for data acquisition. At the same time numerous publications treat BOLD signal in the framework of a single compartment model which can introduce bias if quantitative results are needed. In this work we present direct experimental evidence supporting two extravascular compartments contribution to the BOLD signal.

Theory: MR signal around spin echo time *TE* in GESSE experiment can be presented as [1]:

$$S = S_0 \cdot \left((1-\lambda(TE))e^{-R_2 t} + \lambda(TE)e^{-(R_2-\delta R_2)t - i\omega t}\right) \cdot e^{-\zeta \cdot f(t,TE_c)} \cdot F(t) \qquad (1)$$

where time *t* is counted from *TE*, *ω* is the frequency shift between two compartments, R_2 is transverse relaxation rate constant for intracellular compartment and δR_2 is difference between extra and intracellular R_2. The second factor in (1) describes signal relaxation due to the mesoscopic field inhomogeneities induced by the blood vessel network (*ζ* is the volume fraction of the network); in the static dephasing regime [3] function *f*(t) is an even function of *t*, whereas beyond this approximation (e.g., when diffusion is taken into consideration [4] *f* may contain an odd part as well. The third factor *F*(*t*) (even function of *t*) describes signal attenuation due to the presence of macroscopic field inhomogeneities. The presence of magnetic field inhomogeneities (both meso- and macroscopic) substantially complicates the structure of MR signal and can "obscure" the problem of selecting between one and two compartment models. To simplify the problem, we use the fact that the second and third factors in Eq. (1) are even functions of *t*, and their contribution can be eliminated by considering the following combination:

$$g(t) = \frac{1}{2}\ln\left|\frac{S(t)}{S(-t)}\right| \qquad (2)$$

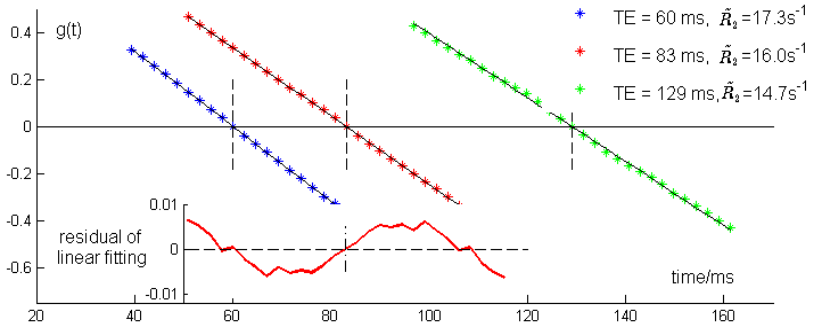
Obviously, the even part of the signal (1) does not contribute to *g*(*t*). In the case of one-compartment model ($\lambda = 0$), the function *g*(*t*) reduces to $g(t) = R_2 t$. However, for more complicated models, *g*(*t*) is (i) a non-linear function *t* and (ii) depends on spin echo time *TE* (through the TE dependence of the compartment fraction *λ*). We use these two properties of *g*(*t*) as a prove of the existence of the second compartment.

For sufficiently small time *t*, the function (2) can be expanded into series with respect to *t*:

$$g(t) = -\tilde{R}_2 t + \beta t^3; \quad \tilde{R}_2 = (R_2 - \lambda \cdot \delta R_2), \quad \beta = \frac{1}{6}\lambda \cdot \delta R_2 \cdot (1-\lambda)(1-2\lambda)(\delta R_2^{\,2} - 3\omega^2) \qquad (3)$$

Methods: All studies were approved by institutional IRB. Data were acquired from healthy volunteer's brain on a Siemens 3T Trio whole body scanner with a 12 channel receive-only head coil. Three 3D Gradient Echo Sampling of Spin Echo (GESSE) sequences were applied consequently, each with spin echo at 10th, 15th and 25th gradient echo position (corresponding to TE = 60, 83, and 130ms) with gradient echo spacing of 2.3 ms, spatial resolution of 4x4x4 mm^3, TR of 250 ms.

Results: The time dependence of the experimentally measured function *g*(*t*) for different *TE* is shown in figure (asterisks) as well as its linear regression (solid lines). The fitting results demonstrate that $\tilde{R}_2$ decreases as *TE* increases (that means $\delta R_2 > 0$). Furthermore, the residual of the linear fit exhibits a systematic deviation from a straight line (shown in inset for *TE* = 83 ms), whereas the fitting with a cubic polynomial in Eq. (3) provides practically ideal fit. It should also be noted that the coefficient *β* is found to be positive for half pixels while negative for the other half pixels. According to Eq. (3), this effect can be explained by different values of $(1-2\lambda)$ and $(\delta R_2^{\,2} - 3\omega^2)$. Since δR_2 is smaller than R_2 , the critical value of frequency shift, at which the coefficient *β* changes its sign, is about 2Hz, which is very small.



Conclusion: Our results demonstrate that, indeed, the "effective" relaxation rate constant $\tilde{R}_2$ depends on the spin echo time *TE* while function g(t) in Eq. (3) exhibits non-linear time dependence. Both these effects are absent in the one-compartment model and, therefore, can serve as a proof of the presence of the second extravascular compartment in the qBOLD MR signal in Eq. (1). This result is also in agreement with previous reports of T2 [5] and T2* [6] measurements.

References: **1**. He, X. and D.A. Yablonskiy, Magn Reson Med, 2007. 57(1): p. 115-26. **2**. Yablonskiy, D.A., Magnetic Resonance in Medicine, 1998. 39(3): p. 417-428. **3**. Yablonskiy, D.A. and E.M. Haacke, Magn Reson Med, 1994. 32(6): p. 749-63. **4**. Sukstanskii, A.L. and D.A. Yablonskiy, J Magn Reson, 2003. 163(2): p. 236-47. **5**. Whittall, K.P., et al., Magn Reson Med, 1997. 37(1): p. 34-43. **6**. Fujita, N., et al., Neuroimage, 2003. 20(4): p. 2071-83.