Biophysical Modeling of Cortical Cell Swelling Effects in functional Diffusion MRI Signal

N. F. Lori[1], D. Le Bihan[2]

[1]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, MO, United States, [2]Service Hospitalier Frederic Joliot, CEA, Orsay, France

Introduction: Recently, a new approach for functional neuroimaging has been proposed based on MRI of water molecular diffusion [1]. This approach potentially represents a dramatic departure from classical PET and fMRI paradigms, as it has been suggested that the observed diffusion change could result from the swelling of the cortical cells produced by activation. Those functional changes in cerebral tissue water diffusion properties are to some extent compatible with the photon scattering changes observed with optical recording techniques [2]. Hence, brain activation could be detected directly from changes in cell structure rather than indirectly from perfusion and thus better defined in space and time. Measured changes in water diffusion occurring during activation have been statistically significant, however very small (around 2%). An important issue is, thus, to estimate whether the observed diffusion decrease is quantitatively compatible with the actual amount of cell swelling, which is also very low [3]. Such a quantitative link between cell size and water diffusion changes would be also very useful to estimate the degree of activation and to optimize acquisition parameters. In this abstract, we develop a realistic model of the cortex to test if agreement with both the neurophysiology and the diffusion MRI results is possible.

Cortical tissue model: Almost all cortical space is made of neurons and glia cells, with both of them occupying about the same portion of the total volume [4][5]. Most of the neuronal volume is made of axons and dendrites [4][5], and almost all of the glia volume is made of astrocytes [4][5]. The astroglia are approximated as a sphere of radius $R_S=7\ \mu m$ [4][5], combined with arbitrary length cylinders of $R_C=1.25\ \mu m$ radius [4][5] coming out of the sphere. The axons are also approximated as a sphere of radius $R_S=7\ \mu m$ [4][5], with axons and dendrites also simulated as arbitrary length cylinders of radius $R_C=1.25\ \mu m$ [4][5]. Considering that only about 20%(=p_{ext}) of the cortex is extra cellular tissue [3], that the fraction volume of glia is ≈50 %, and that the fraction of the glia and neuronal volume occupied by their cell bodies is ≈20 %; it is reasonable to divide the cortex as being *20%(=p_S)* associated to 7 µm radius spheres, and *80%(=p_C)* being associated to 1.25 µm radius cylinders (note that in each of these two divisions, 20% is made of extra cellular tissue). The intra-extra exchange time is about *600 ms(=τ)* [6], the intra-cellular diffusion coefficient in the absence of restriction and exchange effects is *1.3 $\mu m^2/ms$(=D_{in})* (in agreement with ref. [7] after restriction effects are taken into account), and the extra-cellular diffusion coefficient in the absence of exchange effects is *1.7 $\mu m^2/ms$(=Dex)*. In our model we consider that the cylinders are randomly oriented, which is a reasonable assumption in the cortex (the randomization process uses one million different random directions). We also consider that the diffusion encoding time is δ=19 ms [8], that the elapsed-time between diffusion encoding gradients in the simulated spin-echo signal is Δ=31 ms [8], and the direction encoding gradient has intensities (g) ranging from 0 to $40\sqrt{3}$ mT/m [8]. Because τ is so much higher than Δ, we can be considered to be near the slow exchange regime. Therefore if $\Psi_{C;IMP}$ is the normalized MR signal intensity inside an impermeable restricted cylinder (Eq. 8 in [9], based on Eq. 20 in [10]), and $\Psi_{S;IMP}$ is the normalized MR signal intensity inside an impermeable restricted sphere (based on Eq. 19 in [10], and using Eq. 8 in [9]). Then considering that the time-evolution of the cylinder signal intensity in the corresponding Kärger equations [11] is defined in Eq. 1 (left), and the time evolution for the sphere is defined in Eq. 1 (right), with $T_{IC}=\tau$ and $T_{EC}=\tau^*(p_{ex}/(1-p_{ex}))$, then Eq. [1] introduced on the corresponding Kärger equations defines the time dependent MR signal intensities inside the cylinder, Ψ_C, inside the sphere, Ψ_S, and in the extra-cellular medium, Ψ_{EC}. Then using Eq. 3 and 4 of ref. [9], we obtain the MR signal intensity for our cortical model.

$$\frac{\partial \Psi_C}{\partial t_D} = \frac{\partial \Psi_{C;IMP}}{\partial t_D} - \frac{\Psi_C}{T_{IC}} + \frac{\Psi_{EC}}{T_{EC}} \qquad \frac{\partial \Psi_S}{\partial t_D} = \frac{\partial \Psi_{S;IMP}}{\partial t_D} - \frac{\Psi_S}{T_{IC}} + \frac{\Psi_{EC}}{T_{EC}} \qquad [1]$$

In the case of infinitesimal δ, we have that $t_D=\Delta$, but in the case of finite δ, the expression for t_D becomes less obvious [12]. Ref. [12] gives a strong indication that $t_D=\Delta+\delta$ is a more accurate definition. Therefore, in Eq. [1] we used $\partial/\partial t_D \equiv \partial/\partial\Delta + \partial/\partial\delta$.

Defining ADC change in a 2-points diffusion experiment: In diffusion experiments, the ADC is obtained by comparing the MR signal intensity at two different b-values. In our model the low b-value is b_0=0.2 ms/µm^2 [1] and the high b-values are obtained by increasing g. The " % ADC change" corresponds to the percent difference between the active (patient looking at rotating checkerboard in ref. [1]) and the passive states (patient looking at blank screen in ref. [1]). In ref. [1], a 2.0% reduction was obtained. **Simulation results:** In Fig. 1, the cyan circles are the b-decay data for gray matter [7], obtained with diffusion times identical to the ones in the model. The continuous red line is the ADC values predicted by our model, the match is reasonably good, but since the cortex is not made of spheres and cylinders, the match cannot be expected to be perfect. In Fig. 2, we plotted the dependence of the "% ADC change" as a function of g^2, with $b_0=0.2\ ms/\mu m^2$ [1]. The "% ADC change" dependence on g^2 is obtained for several different volume percent changes, 2% for solid red line, 3% for dotted green line, 4% for dot-dashed blue line, and 5% for dashed black line. Analysis of Fig. 2 leads us to conclude that we can reproduce the results in ref. [1] by considering that the cells increase their volume by 2.5 %. If only glia cells increase their volume, they would need to swell by about 5%.

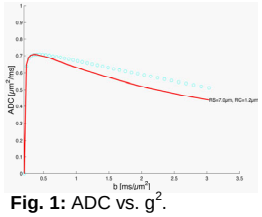

Fig. 1: ADC vs. g^2.

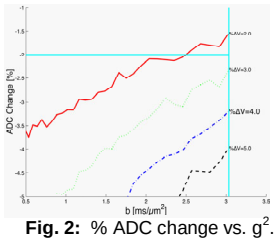

Fig. 2: % ADC change vs. g^2.

Discussion and Conclusion: Ability of this model to predict accurate ADC changes depends on knowledge of neurophysiological data, that is at present incomplete. To test what is the source of the "%ADC change" obtained in ref. [1], it will be necessary to do further studies. But the results presented here indicate that with such knowledge it is maybe possible to interpret ADC change results.

References: [1] A Darquie et al; *PNAS*, USA, 98(16), pp. 9391-9395, 2001; [2] K Sato et al, *Neuroreport*; 8(16):35559-63, 1997; [3] C. Nicholson, E. Sykova, *Trends Neu.*, 21:207-215, 1998; [4] Kandel ER, Schwartz JH, Jessell TM (2000). Principles of neural science. McGraw-Hill; [5]. A Peters, EG Jones, Cerebral Cortex, Plenum Pub Corp, 1984; [6] C Meier, W Dreher, D Leibfritz, *Magn Reson Med*; Vol. 50, pp. 510-14, 2003; [7] JV Sehy, JJH Ackerman, JJ Neil, *Magn. Reson. Med.*; 48(5):765-70, 2002; [8] CA Clark, D Le Bihan, *Magn Reson Med*; Vol. 44, pp. 852-859, 2000; [9] C Meier, W Dreher, D Leibfritz, *Magn Reson Med*; Vol. 50, pp. 500-9, 2003; [10] CH Neuman, J Chem Phys 1974;60:4508-11; [11] J Karger, H Pfeifer, W Heink, Adv Magn Res, 1988;12:1-89; [12] NF Lori, TE Conturo, D Le Bihan, J Mag Reson, 165, (2003), pp. 185-95;