How Reliable are Diffusion Tensor Spectroscopy Measures of Metabolite Diffusion?

J. Ellegood[1], C. C. Hanstock[1], and C. Beaulieu[1]

[1]Department of Biomedical Engineering, University of Alberta, Edmonton, Alberta, Canada

Introduction - The optimal conditions for two point measurements of the Apparent Diffusion Coefficient (ADC) may require a signal intensity drop of at least 40% for ADC values on the order of ~ 0.15 x 10^{-3} mm^2/s (study of 1-octanol) (1). A recent Diffusion Tensor Spectroscopy (DTS) study (2) on the human brain has used b-values of 654 s/mm^2 and 1890 s/mm^2 for a two point measurement of ADC, which leads to a peak signal intensity drop of only ~15%. The Fractional Anisotropy (FA) values reported in that DTS study in two different gray matter regions ranged from 0.50 to 0.80 for the metabolites N-acetyl aspartate (NAA), creatine/phosphocreatine (tCr), and choline (Cho), which is high given the expected isotropy. It was suspected that these elevated FA values could be erroneous because of too much variability in the individual direction ADC measurements. The purpose of this study was to: 1) Test the effect of low ADC values on the FA using isotropic alcohols, with ADCs ranging from ~ 0.50 to ~ 0.12 x 10^{-3} mm^2/s and 2) Examine one of the gray matter regions used in that previous DTS study with both low (b_{max} 1815 s/mm^2) and high (b_{max} 5018 s/mm^2) b-values, and compare the resultant FA and Trace/3 ADC. The results could guide future DTS measurements of human brain.

Methods - All experiments were performed on a SMIS 3T MRI equipped with a maximum gradient strength of 20 mT/m. An in-house single voxel, diffusion weighted PRESS sequence, with a TE of 196 ms (TR = 3 s, acquisition time per metabolite spectra per direction ~3.5 min), was used to measure the diffusion of NAA, tCr, and Cho. ADCs were calculated in six different directions, [(1,1,0), (1,0,1), (0,1,1), (-1,1,0), (-1,0,1), and (0,1,-1)]. Two experiments were performed, one which used b-values of 502 and 1815 s/mm^2 (δ = 22 ms and Δ = 80 ms, low b-value study), and another with b-values of 347 and 5018 s/mm^2 (δ = 36 ms and Δ = 87 ms, high b-value study) per direction. Thirty-two averages were acquired from a 5 mm x 5 mm x 5 mm voxel in the 6 different isotropic alcohols, which was repeated 5 times for each alcohol for both the high and low b-value study. Sixty-four averages were acquired for the in-vivo study from a 2.7 cm x 2.7 cm x 2.7 cm voxel located in the occipital gray matter (OGM) of five healthy volunteers (same five people were used for both the high and low b-value study). The acquisition time for the 12 metabolite spectra was ~42 min in the human subjects.

Results and Discussion – Isotropic Alcohols: The study of six isotropic alcohols was informative and two trends can be seen in Figure 1: (i) as the Trace/3 ADC decreases, the FA increases up to a point in which an isotropic medium registers as anisotropic, and (ii) the low b-value study shows an increase in its FA when compared to the high b-value study. In fact significant differences of FA between the low and high b-value studies are seen at ADCs as high as ~0.40 x 10^{-3} mm^2/s (butanol). Recall that all these phantoms are pure liquids and should yield isotropic diffusion (i.e. low FA values near zero). Figure 1 clearly indicates that greater reductions in signal intensity, facilitated by higher b-values, are needed to minimize variability of the six single direction ADC values and reduce FA.
In-Vivo DTS: Figure 2 shows example spectra taken from the OGM for b-values of 347 s/mm^2 and 5018 s/mm^2, note the ~50% drop in signal intensity between the spectra. Table 1 lists the Trace/3 ADC and FA in the OGM in the human brain, for both the low and high b-value studies. The FA of all the metabolites is significantly increased when DTS uses the low maximum b-value (1815 s/mm^2) rather than the high maximum b-value (5018 s/mm^2). This seems to indicate that the FA values reported in the low b-value work tend to be inflated due to an inaccurate assessment of the single direction ADCs, which in turn leads to a greater spread in the eigenvalues (0.10 to 0.35 x 10^{-3} mm^2/s in the low b-value study compared to 0.14 to 0.23 x 10^{-3} mm^2/s in the high b-value study) thus increasing the FA. The FAs reported from the low b-value study are consistent with the previous DTS FA values in the occipital and frontal gray matter regions (0.51, 0.69, 0.79 for NAA, tCr, and Cho in the OGM region respectively, and 0.53, 0.73, 0.59 for NAA, tCr, and Cho in the frontal gray matter region respectively) (2), which indicates that those values were artefactually inflated. The Trace/3 ADC was significantly increased for NAA and Cho in the low b-value study, although the Trace/3 ADC is generally more robust than FA.

Conclusions - A phantom with an ADC similar to metabolites in tissue (1-octanol, ADC = 0.142 x 10^{-3} mm^2/s) should be used to verify diffusion spectroscopy sequences rather than metabolites in water which have much higher ADC values - this could lead to a false sense of security with low FAs. Furthermore, anisotropic diffusion, given by higher FA values, can be incorrectly inferred in an isotropic environment when the underlying ADC is too low (as it is for metabolites in human brain). DTS acquisition with low b values leads to insufficient signal attenuation and should be viewed with caution. FA measurements where real directional ADC differences may outweigh the variability of the DTS sequence (i.e. say in white matter) may be immune to this effect; however, it needs to be examined.

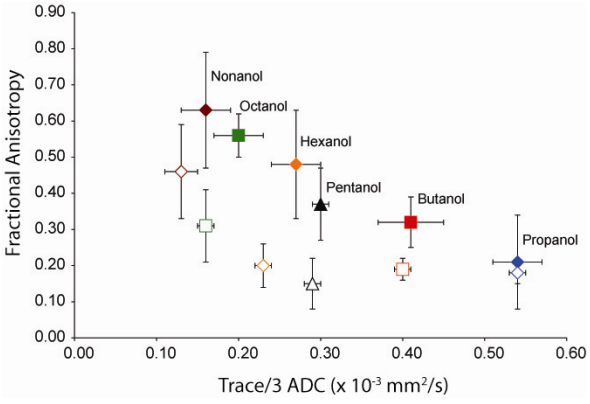

Figure 1 – Fractional Anisotropy vs. Trace/3 ADC for six different isotropic alcohols. Consistently higher FA values were found for the low b value study (1815 s/mm^2, filled) compared to the high b value study (5018 s/mm2, unfilled).

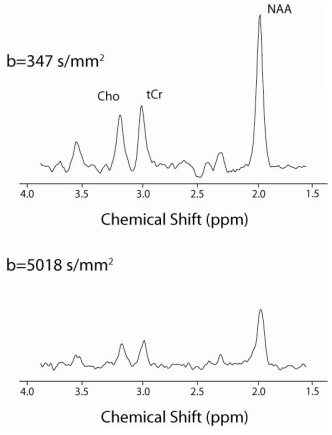

Figure 2 – Example spectra from the high b-value study in the occipital gray matter of human brain.

References – (1) Bedet et al. *Chemical Physics Letters,* **2005**, *408*, 237-240. (2) Ellegood et al. *Magn Reson Med,* **2006**, *55*, 1-8.

Table 1 – Trace/3 ADC and Fractional Anisotropy measurements from the OGM of human brain. * indicates significant differences ($p<0.05$) when compared to the high b-value study.

Metab	Trace/3 ADC (x 10^{-3} mm^2/s)	Fractional Anisotropy
Low b-value (1815 s/mm^2) study (N=5)		
NAA	0.22 ± 0.05*	0.53 ± 0.14*
tCr	0.22 ± 0.05	0.60 ± 0.10*
Cho	0.22 ± 0.05*	0.54 ± 0.13*
High b-value study (5018 s/mm^2) (N=5)		
NAA	0.18 ± 0.02	0.25 ± 0.10
tCr	0.19 ± 0.02	0.30 ± 0.07
Cho	0.17 ± 0.03	0.28 ± 0.06