High Order Diffusion Tensor Imaging for Breast Cancer Differentiation

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Target audience: Scientists and clinicians interested in breast cancer assessment by MRI with a focus in Diffusion Weighted Imaging (DWI).

Purpose: Diffusion Tensor Imaging (DTI) for breast cancer assessment has previously been explored reporting high sensitivity and specificity by means of diffusivity parameters[2]. However, limited potential and lack of agreement have been shown by anisotropy parameters derived from DTI models[2-4]. From brain studies, it is known that 2nd order DTI fails to depict anisotropy when more than one preferred direction of diffusion coexist in the same voxel. Low voxel resolutions and short diffusion times required to obtain enough SNR could limit the anisotropy effect of breast structures, such as ducts. Recently, approaches to overcome these problems by using longer diffusion times with a stimulated echo sequence[5] and increasing the voxel resolution[6] were explored. In both cases, healthy tissue and malignant lesions presented higher FA values. We hypothesized that, a higher order tensor, where more than one preferred direction of diffusion can coexist without being averaged out by the model, would be more appropriate for depicting the ground anisotropy. In this study, potential and added benefits of using a high order tensor model (4th order) in comparison of standard 2nd order DTI for differentiation of malignant and benign lesions, and healthy fibroglandular tissue (FGT) in breast are evaluated.

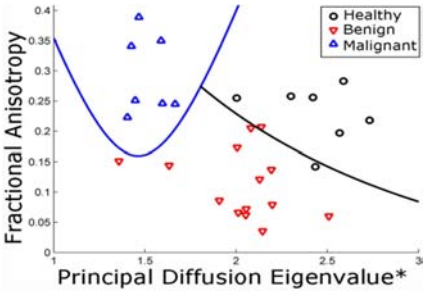

Figure 1.Group classification. *(x10^{-3} mm^2/s)

Methods: Eighteen patients recruited for an ongoing study with biopsy proven breast cancer lesions were studied. From this group 6 patients presented 7 malignant turmors (invasive ductal carcinomas) and 12 patients presented 14 solid benign tumors (12 fibroadenomas, one fibroadenosis, and one phyllodes tumor). Breast MRI was performed using a Siemens 3T Skyra scanner and a 16-channel breast coil. The imaging protocol collected fat-suppressed unilateral sagittal images using a twice-refocused spin echo sequence with an EPI readout (TR/TE: 9300/85 ms, matrix: 90x90, in-plane resolution: 2x2 mm, s.thick: 2.5 mm) and 30 directions for two different b-values (0 and 700 s/mm^2). The total time of this acquisition was 5.35 min. ROIs were placed manually directly on the b_0 diffusion image covering the full extent of each lesion assisted by DCE-MRI subtracted images for more accurate delineation. ROIs of healthy tissue were obtained covering all FGT in one lesion-free slice for 5 of the subjects presenting high density breasts and 2 healthy volunteers. DTI model fitting by means of 2nd and 4th order tensors were calculated employing the implementation provided in[1], that was adapted to our in-house developed software using Matlab (The MathWorks, Natick, NJ). Parametric maps of mean diffusivity (MD), fractional anisotropy (FA), and highest diffusion eigenvalue (λ_1) were obtained for both models.

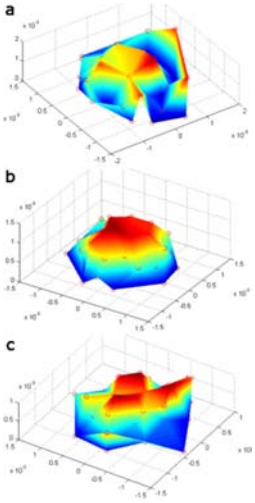

Figure 2. Diffusion profiles at 30 directions within a voxel. **a**.Healthy tissue. **b**.Benign lesion. **c**.Malignant lesion.

Results: For each ROI, median values from all the parameters described were obtained and presented in Table 1. No variation in MD was observed between the models. Increased λ_1 for all three groups was observed when the higher order model was applied, the differences being statistically significant ($p<0.05$) for all of them. Significant increased ($p<0.05$) values of FA for malignant lesions and healthy tissue were observed, while for benign lesions, FA did not show significant change between the two models. All parameters exhibit high statistical significance ($p<0.001$) when comparing the three groups but none of them achieved perfect classification of malignancy (AUC<1.0 for all parameters). When combining FA and λ_1 perfect classification of malignancy was achieved using a quadratic discriminant classifier (Figure 1) only when using the results obtained from the 4th order tensor model.

Table1. Parameters derived using two tensor models for the three groups

Parameter	2nd-order Tensor			4th-order Tensor		
	Healthy	Benign	Malignant	Healthy	Benign	Malignant
MD†	1.92 ± 0.18	1.72 ± 0.24	1.15 ± 0.07	1.92 ± 0.18	1.72 ± 0.24	1.15 ± 0.07
λ_1†	2.18 ± 0.18*	1.89 ± 0.25*	1.37 ± 0.10*	2.43 ± 0.22*	2.03 ± 0.26*	1.51 ± 0.09*
FA	0.13 ± 0.02*	0.11 ± 0.02	0.17 ± 0.02*	0.23 ± 0.04*	0.11 ± 0.05	0.29 ± 0.06*

*Statistically significant values when comparing the two tensor models (paired Student's t test). † (x 10^{-3} mm^2/s)

Discussion: Our results present significant elevated values of FA for malignant lesions and healthy tissue, while for benign lesions values of FA remain at the same level or even diminish when applying a higher order tensor model. Figure 2 can help to understand why FA increases within healthy and malignant lesions but not in benign. While a 2nd order tensor would average out induced anisotropy by the ductal tree in more than one direction within the same voxel, a 4th order tensor would fit more accurately this surface (Fig. 2a). In the case of malignant lesions, anisotropy is not added by ductal tree structures, but it can be seen how the surface is tortuous (Fig. 2c). This tortuosity would be directly averaged out by a 2nd order tensor fitting. In the case of benign lesions (Fig. 2b), it can be seen that there is no structure induced anisotropy, nor tortuosity. Low diffusivity by means of the principal eigenvalue is the main marker for malignant lesion detection using DTI alone[2], however, automated detection is not feasible as benign lesions and healthy tissue may exhibit suspicious regions with low diffusivity. In our study high order tensor FA is presented as a tool that could allow for improved automated detection of malignant tumors due to its capacity for excluding suspicious non-malignant lesions showing low diffusivity as it is shown in Figure 3.

Conclusion: The results of our ongoing study suggest that for proper depiction of anisotropy in breast higher order DTI models have to be applied. Our results present the potential of high order tensor derived FA to play a role in the improvement of automated detection of malignant lesions when combined with a diffusivity measure.

References: 1.Barmpoutis A, Proc IEEE ISBI, 2010. 2.Eyal E, Invest Radiol, 2012. 3.Partridge S, JMRI, 2010. 4.Baltzer PA, Eur Radiol, 2011. 5.Cho GY, Proc ISMRM 2013. 6.Wilmes LJ, Proc ISMRM 2013.

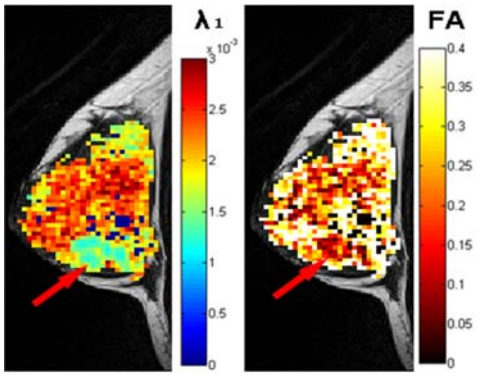

Figure 3. Parametric maps derived from 4th-order tensor model in a slice containing a biopsy-proven fibroadenoma (red arrow) presenting low diffusivity. Only the combination of both parameters (λ_1 and FA) yields accurate classification.