In Vivo Higher-Order Contrast Measured with Generalized Diffusion Tensor Imaging Using Higher-Order Tensors

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INTRODUCTION: The recent realization of non-Gaussian diffusion within tissues and the striving for more accurate description of the diffusion processes have prompted a number of methodological developments (1-6). The higher order tensor (HOT) model by Liu et al (4) proposes to quantitatively characterize general diffusion processes using a series of diffusion tensors with increasing orders. Each order of these tensors offers a well defined physical interpretation, with the second order tensor meaning the second order cumulant (covariance matrix), the third order tensor meaning the third order cumulant (skewness tensor), and the fourth order tensor meaning the fourth order cumulant (kurtosis tensor) and so on so forth. Simulation studies have demonstrated high accuracy of diffusion imaging by using HOT. The improved accuracy has helped to resolve a number of simple crossing fiber structures. In this paper, we present a very first in vivo implementation of generalized diffusion tensor imaging (GDTI) with HOT. Higher order diffusion tensors up to order four are measured. We further propose a set of techniques to generate higher order diffusion contrast. These higher order contrasts provide a vast amount of extra quantitative information, new visualization tools and potential biomarkers.

METHOD: Brain imaging of a healthy volunteer was performed at a 1.5T GE scanner (GE Signa, GE Healthcare, Waukesha, WI). The study was approved by the Institution Review Board of Stanford University, and written consent was obtained from the volunteer prior to the scan. The scanner is equipped with a maximum gradient of 50mT/m and a slew rate of 150 mT/m/s. A custom-built small head coil with improved sensitivity was used for receiving MR signals. Diffusion weighted images were acquired with the self-navigated interleaved spiral (SNAILS) technique (7). The scan parameters were: FOV = 192mm, slice thickness = 3mm, number of slice = 26, TR = 2.5s, TE = 76ms, bandwidth (BW) = 125 kHz, and matrix size =64x64 resulting in an isotropic resolution. Diffusion-weighted images were acquired on a set of 21 diffusion encoding directions. The 21 diffusion directions were repeated for five b-values (500, 1000, 2000, 3000 and 4000 s/mm^2) (8). A set of non-diffusion-weighted image were also acquired for each b-value.

Images were reconstructed using a conjugate-gradient (CG) algorithm (7). The CG algorithm removes the motion induced phase errors that are present in all diffusion-weighted images. HOT up to order four were estimated using all b-values and all encoding directions using a least-squares estimator (5).

Once the higher order diffusion tensors are computed, higher order measures of the underlying diffusion processes can be defined. These higher order measures range from the probability density function (PDF) to scalar and vector measures derived from higher order tensors. Here, we propose two examples of higher order contrasts: the likelihood contrast (LC) and a fourth order fractional anisotropy (FA$_4$). The likelihood contrast is defined as the Kullback-Leibler divergence:

$$LC = \mathbf{K}(p(\mathbf{r}) \,|\, n(\mathbf{r})). \qquad [1]$$

Here, $p(\mathbf{r})$ is the PDF and $n(\mathbf{r})$ is the corresponding normal distribution. The fourth order fractional anisotropy is defined similar to the second order fractional anisotropy (FA$_2$):

$$FA_4 = \left(\sum_{i \neq j} (\lambda_i - \lambda_j)^2\right) / \left(5 \sum_{i=1}^{6} \lambda_i^2\right). \qquad [2]$$

Here, λ is the eigenvalues of the fourth order tensor.

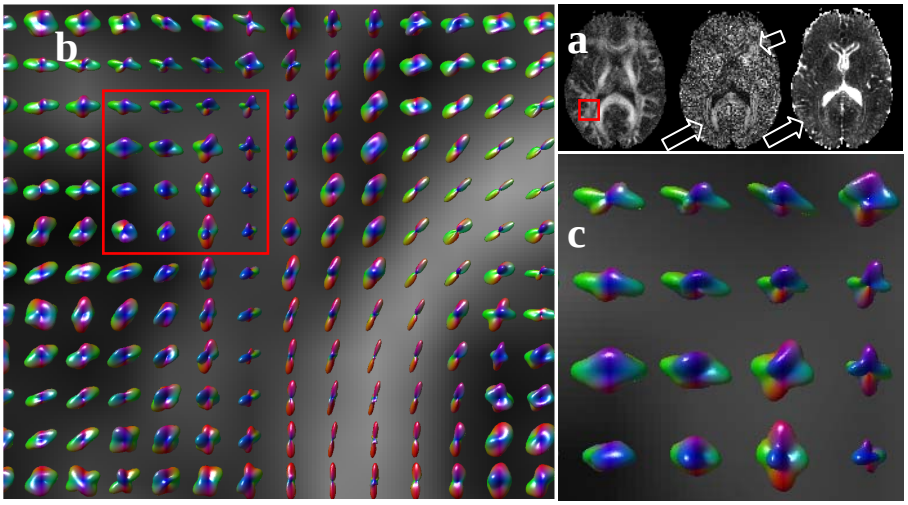

Figure 1 – *in vivo* GDTI-HOT: (a) images from left to right are FA2, FA4 and LC; (b) PDF glyphs in an ROI over sagittal stratum and forceps minor; (c) an enlarged view in the region shown in the red box.

RESULTS: Figure 1a shows the higher order contrasts for a representative slice. Images from left to right are FA2, LC and FA4. All three anisotropy measures indicate the white matter region where diffusion is more ordered. In comparison to FA2, higher order contrasts LC and FA4 appear to highlight the region of more complex structures where fiber crossings may exist or diffusion deviates from Gaussian (see arrows). CSF suppression should further help to improve the LC measurement. Figure 1b shows an example of voxel-wise spherical PDF in a region-of-interest (ROI) over sagittal stratum and forceps minor. Because of the space limitation, only a small ROI was displayed. An enlarged view of a region drawn in red box is shown in Figure 1c. In regions where different fiber groups merge, the reconstructed spherical PDF glyphs exhibit a clear non-Gaussian shape, indicating a multi-modal diffusion pattern.

DISCUSSION: We have demonstrated an *in vivo* implementation of GDTI-HOT. We have shown a successful measurement of higher order tensors up to order four. Those higher order tensors provide extra quantitative information of underlying tissue architecture that is not present in the second order model. We have further proposed and demonstrated a series of high-order contrast functions to provide quantitative measure for complex diffusion patterns.

The vast amount data acquired by GDTI-HOT presents some challenges but also greater opportunities for data visualization. For simplicity, scalar measures derived from HOT can be potentially designed to highlight a certain feature of the diffusion process that is of greater importance. Although we only have illustrated two examples of higher order contrast, namely LC an FA4, many more contrasts measures can be defined accordingly. Although the exact physical and biological nature of these indexes is yet to be understood, it is clear that both LC and FA4 provide information that is independent of second order measures, for example FA2. This higher order information also improves fiber tractography in regions where multi-modal diffusion exists and the second order model may fail.

More importantly, these higher order contrasts provide additional quantification of tissue integrity. In a deceased state, such as stroke and trauma, cellular damages in tissue could alter the diffusion property and possibly change the higher order contrast as a consequence of reduced non-Gaussian diffusion. Further exploration may show the relevance of higher order contrasts as novel biomarkers.

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