A Study of Information Gain in High Angular Resolution Diffusion Imaging (HARDI)

A.D. Leow[1,3], S. Zhu[2], L. Zhan[3], K. McMahon[4], G.I. de Zubicaray[4], M. Meredith[4], M. Wright[4], P.M. Thompson[3]

[1] Neuropsychiatric institute, UCLA
[2] Department of Mathematics, UCLA
[3] Laboratory of Neuroimaging (LONI), UCLA
[4] Functional MRI Laboratory, University of Queensland and Queensland Institute of Medical Research, Brisbane, Australia

Abstract. Diffusion weighted magnetic resonance (MR) imaging is a powerful tool to investigate white matter microstructure, by mapping local 3D displacement profiles of water molecules in brain tissue. High-angular resolution diffusion imaging (HARDI) schemes have been employed to resolve fiber crossing and more complex diffusion geometries. Most recently, the tensor distribution function (TDF) has been proposed as a novel technique for multi-tensor reconstruction by representing the diffusion profile as a probabilistic mixture of tensors. Here, we propose a TDF-based framework for studying the amount of information in HARDI. To illustrate the proposed method, we compared a 94-direction HARDI scheme to its optimally sub-sampled schemes with 20, 40, 60 and 80 directions. We quantified the information gain when more gradient directions are used, as measured by the Shannon entropy of the recovered TDF. Our results showed an absence of significant gain beyond 60 directions, while anisotropy estimates of the recovered fibers stabilized with around 40 directions, suggesting asymptotic but clear advantages of HARDI over conventional DTI.

1 Introduction

In the past decade, diffusion magnetic resonance imaging (MRI) has become a powerful tool for studying the structure of fibrous materials. By applying diffusion-sensitized magnetic field gradients, diffusion MRI characterizes the water diffusivity profile in various tissues. When the duration of the applied diffusion sensitization δ is much smaller than the time between the two pulses, the MR signal attenuation is related to the displacement probability function using a Fourier integral relationship with respect to a wave vector q [1].

In brain imaging, diffusion MRI is particularly advantageous over conventional non diffusion-weighted MRI as it can reveal the configuration and orientation of fiber tracts in white matter. Diffusion Tensor MRI (DT-MRI), proposed in [2], models the water displacement probability function using a zero-mean 3D Gaussian distribution whose covariance matrix, a second-order positive-definite

symmetric tensor, represents the principal directions of diffusion and orientation of local fiber tracts. Although extremely powerful and easy to compute, DT-MRI has some disadvantages. For example, any Gaussian probability distribution function has at most one orientational mode (principal direction), and thus cannot resolve fiber crossing, or more complex diffusion geometries.

More recently, several different approaches have been developed to address this issue, involving sets of diffusion gradients with high angular resolution, and by sampling the q-space on one or more shells with fixed radii. Methods such as the Persistent Angular Structure (PAS) technique [3], spherical deconvolution techniques [4], and the q-ball imaging technique [5] have been proposed to recover partial information on the displacement probability function, while still allowing underlying fiber orientations to be inferred.

If more angular detail is available, fiber orientation distribution functions (ODFs) can be reconstructed from the raw HARDI signal using deconvolution methods, yielding mathematically rich models of fiber geometries using fields of von Mises-Fisher mixtures [6], or higher-order tensors (e.g., 3x3x3 tensors) [7]). Recent fluid registration and stochastic tractography methods have also exploited HARDIs increased angular detail, aligning ODFs using specialized metrics on densities (e.g., Fisher-Rao) from information theory [8].

The tensor distribution function (TDF), which we first proposed in [9], offers a new way to resolve intra-voxel fiber crossing by solving for a probability distribution, defined on the tensor manifold, that optimally reconstructs the observed diffusion-weighted images (also see [10] where a continuous mixture using Wishart distributions was first introduced to model HARDI data). Moreover, the TDF approach also provides a novel way to compute the eigenvalues of each individual crossing fiber (for more details, please refer to the Theory section).

In this paper, we use the TDF concept and compare the information content of HARDI acquisition schemes with 20, 40, 60, 80, and 94 directions. The 94-direction scheme is currently used as a standard protocol in our lab, while the rest of the acquisition schemes are generated by optimally sub-sampling this 94-direction scheme as described in [11].

2 Theory

2.1 The tensor distribution function

In standard diffusion-weighted MRI, images are acquired using the Stejskal-Tanner pulsed gradient spin-echo method. With some simplifications (rectangular pulse profiles), measured image intensities S are linked to p, the displacement probability function of water molecules, via a Fourier transform relationship: $S(q) = S(0) \int p(x) \exp(iq \cdot x) dx$ (here, the wavenumber $q = r\delta G$; r, δ, and G are the gyromagnetic ratio, the duration of the diffusion sensitization, and the applied magnetic gradient vector). Without loss of generality, we assume the constant S(0) is 1.

Assuming a simple one-tensor Gaussian diffusion model, the displacement probability function evaluated at position x (given diffusion tensor D, and diffusion time t) is

$$p(x) = ((4\pi t)^3 \det(D))^{-\frac{1}{2}} \exp\Big(- \frac{x^t D^{-1} x}{4t}\Big) \tag{1}$$

Thus, the measured diffusion MR image intensities in this one-tensor case are simply $S(q) = \exp(-tq^t Dq)$. In the TDF approach, a probability density function P defined on $\mathbb{D}$, the space of symmetric positive definite 3-by-3 matrices, is computed to explain the observed data:

$$S(q) = \int_{D\in\mathbb{D}} P(D) \exp\Big(- tq^t Dq\Big) dD \tag{2}$$

To solve for an optimal TDF P^*, the least-squares principle is used

$$P^* = \text{argmin}_P \sum_i \Big(S_{obs}(q_i) - S_{calculated}(q_i)\Big)^2 \tag{3}$$

Here, different gradient directions are indexed by i. The numerical solution as proposed in [9] is obtained from the following gradient descent equation:

$$\frac{dR}{d\tau}(D) = \sum_i E(q_i) \exp(R(D)) F(D, q_i) + L \exp(R(D)) \tag{4}$$

where the Lagrange multiplier L is

$$L = -\frac{\int_{D\in\mathbb{D}} \exp(R(D)) \sum_i E(q_i) \exp(R(D)) F(D, q_i) dD}{\int_{D\in\mathbb{D}} \exp(R(D))^2 dD}$$

Here, $P(D) = \exp(R(D))$, $E(q_i) = S_{obs}(q_i) - S_{calculated}(q_i)$, τ is an artificial time, and $F(D, q_i) = \exp\big(- tq_i^t Dq_i\big)$. To reduce the dimensionality of the TDF model, every tensor D is assumed to be cylindrical, and thus may be expressed using $D(\lambda, \theta)$, where the eigenvalues $\lambda = (\lambda_1, \lambda_2)$ (with λ_2 the repeated eigenvalue), and $\theta = (\theta_1, \theta_2)$ the azimuthal and polar angles associated with λ_1. The dominant fiber directions can then be determined by examining the local maxima (that exceed a certain threshold, set to 0.2 in this paper) of the Tensor Orientation Distribution Function (TOD). In the case of one dominant fiber direction, we have:

$$\theta^* = argmax_\theta \text{TOD}(\theta) = argmax_\theta \int_\lambda P(D(\lambda, \theta)) d\lambda \tag{5}$$

Once the dominant direction is determined, one can estimate the eigenvalues of dominant fibers (λ^*) by computing the expected values of λ along this direction.

$$\lambda^* = \frac{\int P(D(\lambda, \theta^*))\lambda d\lambda}{\int P(D(\lambda, \theta^*)) d\lambda} \tag{6}$$

Notice that Eq. (6) offers advantages over deconvolution methods, in which eigenvalues for a single fiber tract are usually pre-determined and fixed. Lastly, we can also compute the orientation distribution function (ODF) from the TDF by analytically evaluating the following radial integral:

$$ODF(\tilde{x}) = C \int_{r=0}^{\infty} p(r\tilde{x}) dr$$

$$= C \int_{D \in \mathbb{D}} P(D) \Big(\det(D) \tilde{x}^t D^{-1} \tilde{x} \Big)^{-\frac{1}{2}} dD \tag{7}$$

Here C is a normalizing constant.

2.2 Shannon entropy as a measure of information and the exponential isotropy

Given any TDF P, we observe that its Shannon entropy (H) measures the randomness of this probabilistic ensemble, and thus inversely measures how certainly we can estimate dominant fibers.

$$\mathrm{H}(P(D)) = -\int_{D \in \mathbb{D}} P(D) log P(D) dD \tag{8}$$

Thus, we propose that the amount of information can be measured by the negative of H. Moreover, by taking the exponential of H, we may define the exponential isotropy (EI), which quantifies the overall isotropy of any given voxel.

$$\mathrm{EI}(P(D)) = e^{-\int_{D \in \mathbb{D}} P(D) log P(D) dD} \tag{9}$$

To motivate the concept of EI, we observe that in an ideal one-fiber system (i.e., P(D)=0 everywhere except for one point in the tensor space $\mathbb{D}$), the Shannon entropy is 0 and the EI is 1. For an ideal two-fiber system with equal weights (P(D)=0 everywhere except for two points in the tensor space $\mathbb{D}$, each of which takes a value of 0.5), the Shannon entropy is $ln2$ and the EI is 2. Thus, in general, we expect EI to take a value that is proportional to the number of dominant fibers. As indicated by its name (and opposite to the fractional anisotropy (FA) or the generalized FA (GFA)), the EI is a measure of isotropy instead of anisotropy, and thus takes greater values in gray matter tissue than white matter. As will be shown in the results section, EI is the equivalent of FA or GFA in the TDF framework.

3 Results

In this section, we present experimental results to illustrate the proposed framework for measuring information gain in HARDI. An individual subject was scanned using a diffusion-sensitized gradient protocol on a Bruker Medspec 4

Tesla MRI scanner, with a transverse electromagnetic (TEM) headcoil. The timing of the diffusion sequence was optimized for SNR according to the scheme proposed in [12].

The protocol used 94 diffusion-sensitized gradient directions, and 11 baseline scans with no diffusion sensitization (b-value: 1159 s/mm^2; TE/TR: 92.3/8250 msec; FOV=230x230; in-plane resolution: 1.8mmx1.8mm; 55 x 2mm contiguous slices; acquisition time 14.5 minutes). The area shown in the left panel of Fig. 1, which mainly consists of white matter, was chosen for comparison (the GFA and EI plots of this windowed region are shown in the middle and right panels of Fig. 1). Visually, we notice that the EI plot nicely separates gray matter from white matter, and thus may be useful for tissue segmentation or tractography purposes. The full 94 gradient directions were optimally sub-sampled, as in [11], to determine subsets of 20, 40, 60, and 80 gradient directions. The TDF was computed voxel-wise by using the full 94-direction HARDI and the four sub-sampled schemes. For each voxel, we then computed the TOD, ODF, GFA, and EI of its TDF. To correctly identify dominant fibers and estimate their eigenvalues using Eq. 6, both voxel-wise GFA and TOD peaks are thresholded at a value of 0.2.

Fig. 2 shows, for each scheme, the voxel-wise TOD, ODF, GFA, and EI plots. Here, GFA plots are scaled relative to their contrast. Visually, 60, 80, and 94 directions yield very similar results. Statistics of the estimated eigenvalues and the Shannon entropy are summarized in Table 1. We found that there is an overall increase in λ_1, and a decrease of entropy (i.e., information gain) as the number of gradient directions increases. This is consistent with prior reports [13] that diffusion anisotropy may be underestimated when angular sampling is low, and eigenvalue estimates may be biased. The trend for λ_2 is less clear, although both estimated λ_1 and λ_2 values are consistent with those reported in the literature.

To formally test if these trends are statistically significant, paired t-tests, with respect to the full 94-direction HARDI, were conducted on the estimated eigenvalues λ_1, λ_2, and the Shannon entropy of the recovered TDF (Table 2). Notice that estimations of both eigenvalues do not change significantly beyond 40 directions, while entropy continues to decrease until around 80 directions. Even so, the effect size for entropy decrease or information gain from 60 directions to 94 directions, using Cohen's d, is 0.17, indicating that this statistically significant information gain is of less practical value (the usual cut-off point for a significant effect size using Cohen's d is 0.2).

4 Conclusion

In this paper, we introduced a tensor distribution function-based framework and its mathematical formulations for assessing the amount of information in high angular resolution diffusion imaging. We also proposed the exponential isotropy as a natural measure of isotropy (i.e, inverse measure of anisotropy). In the TDF framework, the exponential isotropy replaces GFA or FA. Borrowing ideas from

Table 1. Means and standard deviations for estimated eigenvalues of dominant fibers (λ_1, λ_2) and for the mean Shannon entropy of the TDF, for the white matter voxels highlighted in Fig. 1, from the four subsampled and full 94-direction HARDI. The FA values computed using these mean eigenvalues are also given.

	20	40	60	80	94
λ_1	1.061 (0.324)	1.049 (0.431)	1.142 (0.435)	1.154 (0.438)	1.169 (0.449)
λ_2	0.308 (0.145)	0.269 (0.155)	0.243 (0.118)	0.255 (0.156)	0.246 (0.122)
FA	0.6565	0.6990	0.7538	0.7436	0.7568
Entropy	6.884 (0.624)	6.070 (1.005)	5.794 (1.056)	5.734 (1.036)	5.743 (1.011)

Table 2. Paired t-tests, with respect to the full 94-direction HARDI, for estimated eigenvalues of dominant fibers (λ_1, λ_2), and the Shannon entropy of the TDF (with n degrees of freedom). The numbers shown in the table are Student's T statistics. Those with a significant p value less than 0.05 are in bold. Notice that eigenvalues do not change significantly beyond 40 directions, while entropy continues to decrease until around 80 directions (however, the effect size for entropy improvement or information gain from 60 directions to 94 directions, using Cohen's d, is 0.17, indicating that this statistically significant information gain may have less practical value.

	20	40	60	80	n
λ_1	**-3.32**	**-3.95**	-0.92	-0.62	255
λ_2	**5.31**	**2.18**	-0.30	1.04	255
Entropy	**26.13**	**14.76**	**2.61**	-0.52	244

probability and information theory, we argued that the ability to accurately estimate dominant fiber eigenvalues and their orientations, as well as to resolve fiber crossing, can be measured by computing and comparing the randomness or Shannon entropy in the corresponding tensor distribution function. In other words, one would expect that, ideally, randomness in the TDF should decrease as the number of gradient directions increases in HARDI acquisition schemes. However, due to the presence of noise and other problems in acquiring HARDI (e.g., motion artifacts), it is likely that the amount of additional information would become negligible once a certain number of gradient directions is reached. This hypothesis is supported by our results, where we demonstrated that the information contained in HARDI is not linearly correlated with the number of gradient directions, and plateaus around 60 to 80 gradient directions in our simulation studies using the 94-direction protocol currently employed in our lab. This finding is also supported by comparing the expected values of eigenvalues along dominant fiber directions. Even so, the issue of whether greater numbers of gradients may still be beneficial for tractography applications (which rely heavily on the orientational information in the ODFs) remains unsolved. In future studies, we plan to apply this framework to systemically investigate the effect of scanner field strength, spatial resolution, and other acquisition parameters in HARDI, as well as how these may affect tractography and its related applications.

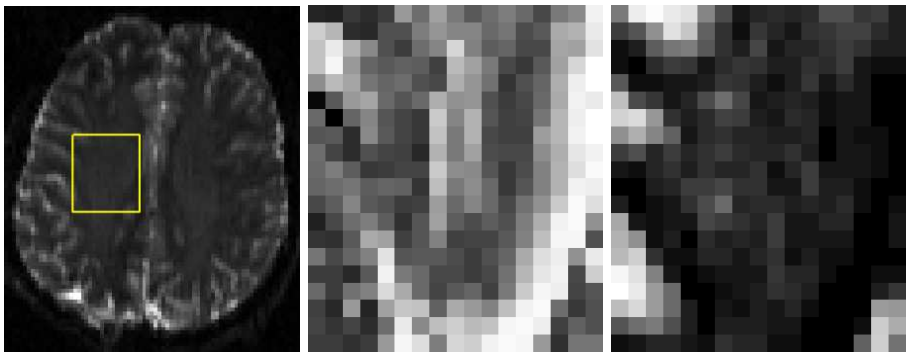

Fig. 1. This figure shows the T2 weighted MRI of a normal human subject derived from the non-difsion sensitized HARDI gradient images. The region over which the patient data was extracted is marked in yellow, with its GFA and EI plots shown in the middle and right panels respectively. Visually, we notice that the EI plot nicely separates gray matter from white matter. Unlike GFA, gray matter has greater EI values than white matter.

References

1. Stejskal, E. O. and Tanner, J. E. "Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient." *J. Chem. Phys.* 42, 288-292, 1965
2. Basser, P. J. "Inferring microstructural features and the physiological state of tissues from diffusion-weighted images." *NMR Biomed* 8, p. 333-344, 1995.
3. Kalvis M Jansons and Daniel C Alexander. "Persistent Angular Structure: New Insights from Diffusion Magnetic Resonance Imaging Data." *Inverse Problems* 19, p. 1031-1046, 2003.
4. J.-D. Tournier, F. Calamante, D. Gadian, and A. Connelly. "Direct estimation of the ber orientation density function from diffusion-weighted MRI data using spherical deconvolution." NeuroImage, 23:1176-1185, (2004)
5. David S. Tuch. "Q-Ball Imaging." *Magnetic Resonance in Medicine* 52, p. 1358-1372, 2004.
6. McGraw, T.; Vemuri, B. C.; Yezierski, B.; Mareci, T. "Von Mises-Fisher mixture model of the diffusion ODF." Biomedical Imaging: Nano to Macro, 3rd IEEE International Symposium on Biomedical Imaging: 65-68. (2006)
7. A. Barmpoutis, and B. C. Vemuri. "Exponential Tensors: A framework for efficient higher-order DT-MRI computations." In Proceedings of ISBI07: IEEE International Symposium on Biomedical Imaging: Page(s): 792-795. (2007)
8. Chiang MC, Barysheva M, Lee AD, Madsen SK, Klunder AD, Toga AW, McMahon KL, de Zubicaray GI, Meredith M, Wright MJ, Srivastava A, Balov N, Thompson PM. "Mapping Genetic Influences on Brain Fiber Architecture with High Angular Resolution Diffusion Imaging (HARDI)." ISBI 2008.
9. Alex D. Leow, Siwei Zhu, Liang Zhan, Katie McMahon, Greig I. de Zubicaray, Matthew Meredith, Margaret Wright, Paul M. Thompson "Tensor distribution function" To appear in Magnetic Resonance in Medicine

10. Bing Jian, Baba C. Vemuri, Evren Ozarslan, Paul R. Carney, and Thomas H. Mareci. "A novel tensor distribution model for diffusion-weighted MR signal." NeuroImage 37: 164-176. (2007)
11. Zhan L, Chiang MC, Barysheva M, Toga AW, McMahon KL, de Zubicaray GI, Meredith M, Wright MJ, Thompson PM "How Many Gradients are Sufficient in High-Angular Resolution Diffusion Imaging (HARDI)?" 13th Annual Meeting of the Organization for Human Brain Mapping (OHBM), Melbourne, Australia, June 15-19, 2008.
12. Jones, D.K., Horsfield, M.A., Simmons, A. "Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging." *Magn. Reson Med.* 42(3), p. 515-525, 1999.
13. B. A. Landman, J. A., S. A. Smith, S. Mori, and J. L. Prince. "Tradeoffs between tensor orientation and anisotropy in DTI: Impact of Diffusion Weighting Scheme." 15th ISMRM Meeting, Berlin. (2007)

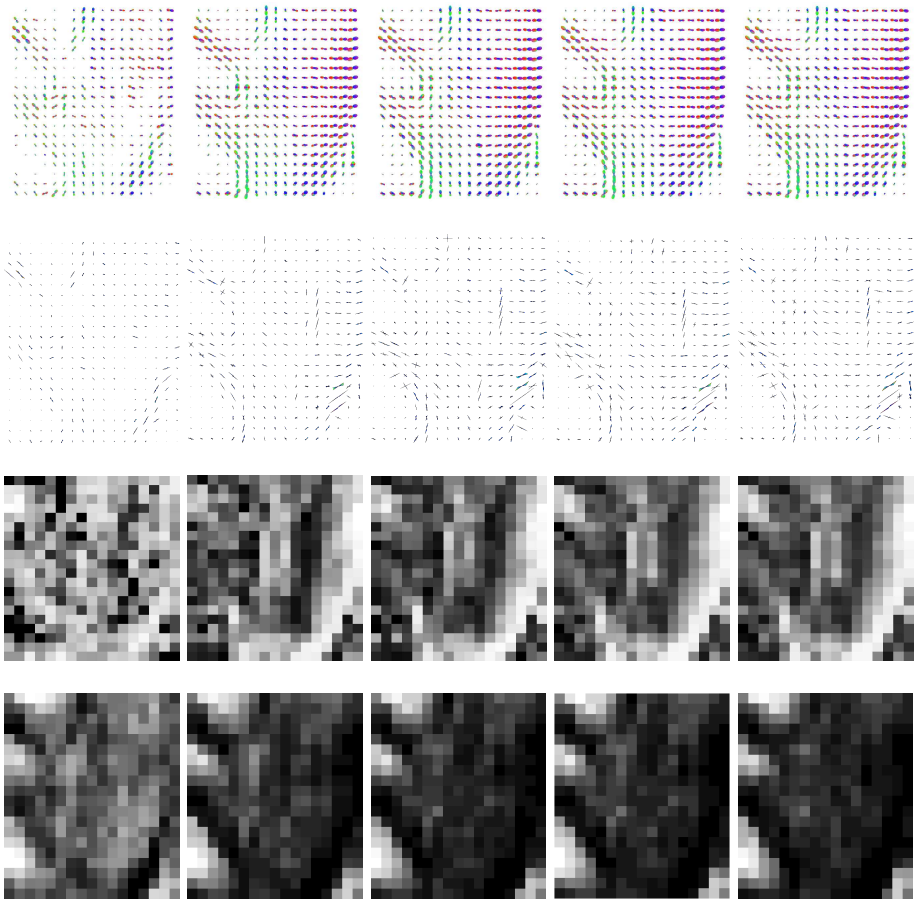

Fig. 2. Top: ODF plots for HARDI sequences with 20, 40, 60, 80, and 94 directions. Second row: respective TOD plots. Third Row: respective GFA maps. Bottom: respective EI plots. Visually, 60, 80 and 94 directions yield very similar results for all four plots.