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Simulated Dataset for Verification & Validation of DT-MRI Analyzing Tools

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Abstract - **In diffusion tensor MRI (DT-MRI), each voxel is assigned a tensor that describes local water diffusion. In this study, a simulated DT dataset for analyzing the diffusion characteristics is developed to verify and validate DT images postprocessed with various DT analyzing codes. This module is intended as a resource for DT-MRI analyzing tools to verify and validate the analysis results. The b factor in our study is the B matrix of size 1x7. In our sample, 6 diffusion weighted images and a null image namely the T2 image creating a set of intensity images of size 256x256x7 is generated for the analysis. The idea is to fullfil the routine DT analysis from the apparent diffusion coefficient ADC image instead of the DT images. This inverse analysis methodology is preparing the basis of the image information to be investigated as known values. According to the Stejskal Tanner equation, D = [Dxx, Dyy, Dzz, Dxy, Dxz, Dyz] is calculated in the algoritm. After the validation of the algorithm with the simulated diffusion tensor dataset, real MR data of human brain and myocardium are used. The eigensystem D is calculated in every pixel, ADC is represented with respect to D. The other characteristic values of diffusivity namely fractional (FA) and relative (RA) anisotropy values are calculated. Developing a reliable and rapid tractography algorithm for the clinical use regarding to these verified results is the future study of the work in progress.**

Index Terms–Diffusion Tensor MRI, tensor, anisotropy, tractography.

I. INTRODUCTION

Diffusion tensor imaging (DTI) is becoming a routine MR technique to study white matter properties, connectivity and alterations of fiber integrity due to pathology. The advanced MRI technique needs post processing by adequate image analysis and visualization tools. Whereas such tools have been developed at various research centers to drive methodological and clinical research, they have not become widely available as software freely distributed to the community.

A. DT-MRI Pulse Sequences: Encoding for Diffusion

Diffusion weighted images are the raw data source used to calculate the diffusion tensor. Diffusion weighted images are measured using the Stejskal-Tanner imaging sequence. A Stejskal-Tanner imaging sequence may be implemented by adding diffusion gradient pulses to standard anatomical MRI pulse sequences. In the most simple example, a Stejskal-Tanner pulse sequence may be implemented using a spin-echo MRI imaging sequence with the addition of two diffusion-encoding gradients [1].

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By systematically applying diffusion gradients in multiple directions, a mathematical construct known as the *diffusion tensor*, $\boldsymbol{D}$, could be estimated at each point in the tissue. The utility of the diffusion tensor is that it provides the direction in three dimensional space in which the rate of diffusion is greatest [2], [3].

B. Diffusion Weighted Imaging and the Diffusion Tensor

Diffusion Tensor Magnetic Resonance Imaging (*DT-MRI*), also known as (DTI), has shown promise as a non-invasive tool for estimating the orientation and quantity of white matter (WM) tracts in vivo. The process of using DTI data to estimate white matter structures is commonly known as *tractography*. DTI tractography is a *unique* imaging modality in that it offers the only clinically applicable means of non-invasively imaging the myelinated axonal structure of the human brain [4]-[9]. The accuracy of WM anatomical maps obtained by DTI is more unclear due to the general in-ability of the DT model to describe multiple orientational maxima within a single voxel.

II. MATERIAL & METHODS

A. Estimation of the Diffusion Tensor

Basser (Basser, Mattiello et al. 1994), building on the work of Skejskal and Tanner (Skejskal 1965), has shown that the diffusion tensor can be calculated from knowledge of signal attenuation and magnetic gradient strengths applied during a diffusion-weighted spin-echo experiment using the following equations;

$$\ln\left(\frac{A(b)}{A(0)}\right) = -bD = -bADC \tag{1}$$

$$\ln\left(\frac{A(b)}{A(b=0)}\right) = -\sum_{i=1}^{3}\sum_{j=1}^{3} b_{ij}D_{ij}$$

$$= -\left(b_{xx}D_{xx} + 2b_{xy}D_{xy} + 2b_{xz}D_{xz} + b_{yy}D_{yy} + 2b_{yz}D_{yz} + b_{zz}D_{zz}\right) \tag{2}$$

$$\ln\left(\frac{A(b)}{A(0)}\right) = -\left(b_{xx} + b_{yy} + b_{zz}\right)D \tag{3}$$

$$b = b_{xx} + b_{yy} + b_{zz} \tag{4}$$

$$Trace(\boldsymbol{D}) = D_{xx} + D_{yy} + D_{zz} = 3\langle D\rangle = \lambda_{xx'} + \lambda_{yy'} + \lambda_{zz'} \tag{5}$$

where $A(b)$ is the voxel attenuated signal (echo) intensity recorded in the presence of gradients (1), $A(0)$ is the gradient-free, unattenuated echo intensity, D_{ij} is the (symmetric, positive definite, 3 by 3) diffusion tensor (2), and b_{ij} is a matrix (2) specified by the magnetic field gradients applied during the spin-echo.

$\sum_{i=1}^{3}\sum_{j=1}^{3} b_{ij}D_{ij} \equiv b:D$ is the standard scalar product of two tensors (2). This so called b-matrix (4) has the form: $A = A_0 e^{(-b:D)}$.

To derive structural information, a measured displacement profile has to be related by means of a model to the physical and geometrical properties of the tissue, such as diffusion coefficients and shapes of semi-permeable membranes of compartments in the system. The behavior of the NMR signal and the measured *anisotropic diffusion coefficient* (ADC) are greatly affected by the cellular architecture of a tissue, mainly because cellular membranes are relatively impermeable to water.

The relationship between loss of phase coherence in the transverse spin RF signal and the gradient pulse g is given by the Stejskal-Tanner equation [1]

$$S_i = S_0 e^{-b\vec{g}_i^T D\vec{g}_i} \quad . \tag{6}$$

where b is the diffusion weighting factor [1] given by:

$$b = \gamma^2\delta^2\left[\Delta - (\frac{\delta}{3})\right]|g|^2 \tag{7}$$

In Equation (7), γ is the Larmor constant, δ is the gradient pulse width, Δ is the time between gradient pulses, |g| is the strength of the diffusion gradient pulses, S_0 is the RF signal received for a measurement without diffusion gradient pulses, and S_i is the signal received with diffusion gradient pulses.

Using the three-dimensional Gaussian Stejskal-Tanner model, the six unique elements of the diffusion tensor **D** may be solved by acquiring at least six diffusion weighted measurements in non-collinear measurement directions *g* along with a non-diffusion-weighted measurement S_0 (8). Taking more than six diffusion weighted measurements creates an over constrained system of equations which may be solved using least square methods [2], [5], [6], [10]. The advantage of over-constraining the solution for **D** is a reduction in the amount of noise propagating from diffusion weighted measurements S_i into the calculated diffusion tensor. The linear system of $n \geq 6$ diffusion weighted measurements constraining the diffusion tensor D may be represented in matrix form [10].

$$\begin{bmatrix} x_1^2 & y_1^2 & z_1^2 & 2x_1y_1 & 2y_1z_1 & 2x_1z_1 \\ x_2^2 & y_2^2 & z_2^2 & 2x_1y_1 & 2y_2z_2 & 2x_2z_2 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ x_n^2 & y_n^2 & z_n^2 & 2x_ny_n & 2y_nz_n & 2x_nz_n \end{bmatrix} \begin{bmatrix} D_{xx} \\ D_{yy} \\ D_{zz} \\ D_{xy} \\ D_{xz} \\ D_{yz} \end{bmatrix} = \begin{bmatrix} -\frac{1}{b}\ln\frac{S_1}{S_0} \\ -\frac{1}{b}\ln\frac{S_2}{S_0} \\ \vdots \\ -\frac{1}{b}\ln\frac{S_n}{S_0} \end{bmatrix} \tag{8}$$

In the linear system of equations $Ad = s$ (8), A is the encoding matrix containing the $n \geq 6$ unit normalized gradient measurement directions, d is a vector specifying the 6 unique elements of the diffusion tensor D, and s is a vector containing natural logarithmic scaled RF signal loss resulting from the Brownian motion of spins.

B. Tensor Analysis and The Diffusion Tensor

The Diffusion Tensor D is a real, symmetric second order tensor, represented in matrix form as a real, symmetric 3x3 matrix (9).

$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \tag{9}$$

Diagonalization of the diffusion tensor ($\mathbf{D}e_i=\lambda_i e_i$) results in a set of three eigenvalues $\lambda_1, \lambda_2, \lambda_3$ listed in decreasing order. The eigensystem of the diffusion tensor may be interpreted graphically as an ellipsoidal surface with semi-major axis oriented in the e_1 direction and semi-minor axis oriented in the e_2 and e_3 directions [2], [5].

The lengths of the axis in this ellipsoidal interpretation are given by the corresponding eigenvalues of each eigenvector, with semi-major axis length λ_1 and semi-minor axis lengths λ_2 and λ_3. In order for the analogy between the symmetric real tensor and the ellipsoid to be physically realizable, the eigenvalues of D must be non-negative [5], [10]. Based on the analogy between the diffusion tensor and an ellipsoidal surface, principal component analysis (PCA) is applied. In cases of purely isotropic diffusion, the diffusion ellipsoid takes on a spherical shape, as $\lambda_1 = \lambda_2 = \lambda_3$. There are two extreme cases of physically realizable anisotropic diffusion [10]. For purely linear anisotropic diffusion, $\lambda_1 = c$, and $\lambda_2 = \lambda_3 = 0$, the diffusion ellipsoid degenerates into a line pointing in the e_1 direction. In the case of purely planar anisotropic diffusion, the diffusion ellipsoid becomes oblate, meaning that $\lambda_1 = \lambda_2$, $\lambda_3 = 0$, and by means of the principal diffusivities, the diffusion is restricted to a plane spanned by the two eigenvectors corresponding to the two largest eigenvalues.

The degree of anisotropy in the diffusion tensor is commonly represented by the Fractional Anisotropy (FA) scalar metric.

$$FA = \frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_1-\lambda_3)^2}}{\sqrt{2(\lambda_1^2+\lambda_2^2+\lambda_3^2)}} \tag{10}$$

For physically realizable diffusion tensors with non-negative eigenvalues, the FA of a diffusion tensor (10) is normalized between zero and one. In an extreme case, a FA value of one denotes linear diffusivity ($\lambda_1 = c$, $\lambda_2 = \lambda_3 = 0$). The fractional anisotropy metric evaluates to zero in the opposite extreme of a completely isotropic diffusion tensor. Although not commonly mentioned in DTI literature, the existence of non-physically realizable diffusion tensors must sometimes be accounted for as a special case in tractography algorithms [4]-[6], [8]-[10].

The b factor in our study, which gives information about the direction and amplitude of the diffusion gradient, is a 1x7 matrix in form B = [B0, Bxx, Byy, Bzz, Bxy, Bxz, Byz]. In our sample, 10 diffusion weighted images and a null image namely the T2 image creating a set of intensity

images of size 256x256x11 is used for the analysis of myocardium data. In the self created synthetic data the matrix size is 256x256x7, and in the real human brain dataset the matrix is 256x256x31, and an additional phantom data located on the diffusion group website for common use had the matrix size 200x200x31. The relation can be expressed in general as B(n,:) has the information of the intensity image S(:,:,n). Regarding to that and the Stejskal Tanner equation D = [Dxx, Dyy, Dzz, Dxy, Dxz, Dyz] is calculated in the algoritm, as an inverse problem. The real data sets of human cardiac and brain diffusion MR images are used after the validation of the algorithm and the toolbox.

III. RESULTS

After post processing the circular shaped synthetic data, the original values and the calculated results are found with %100 accuracy for maximum SNR (Fig. 1), so the algorithm determines the diffusion process and so the tracking path successfully (Fig. 1). Also the synthetic data is examined for different SNR values, the results for SNR=10 are shown Fig. 2.

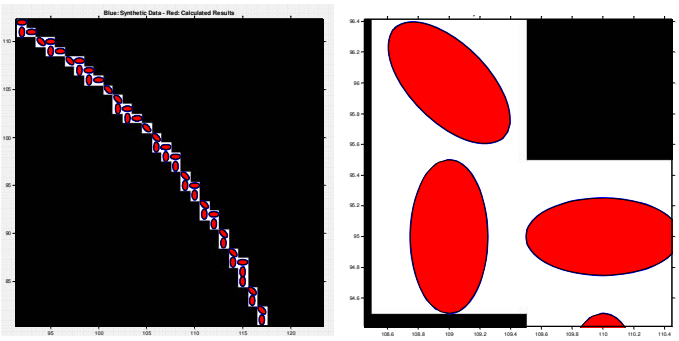

Fig. 1. The donut shaped synthetic data: Sample of its 1.quadrant. The results are totally overlapping. In order to discriminate them, border of the ellipses are represented from the original values (blue), and the inside are from the calculated results (red).

The developed toolbox analyzing different type of geometries with different SNR values is validated as shown in the results (Fig. 2 and Fig. 3). Here are only results of circular and kissing trajectories represented (see Table 3.1 for all). The tractography algorithm may be followed after that verification, and a validated fiber tractography may be visualized.

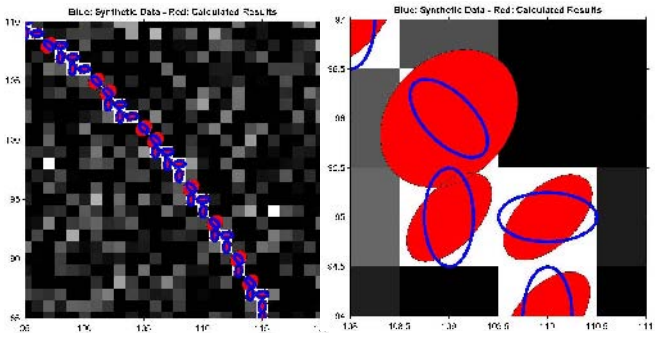

Fig. 2. The donut shaped synthetic data (SNR=10).

Related to the analysis done on the simulated data, the noise effects, and variation on the results because of the change on the SNR value are discriminated how and on which percentage of the correct and reliable tractography they effect (see Table 3.1).

After validating the algorithm for various synthetic data, real human brain and myocardium DT-MR images are processed (Fig. 4 and Fig. 5). The results will provide the base to reliable and proven tracking results.

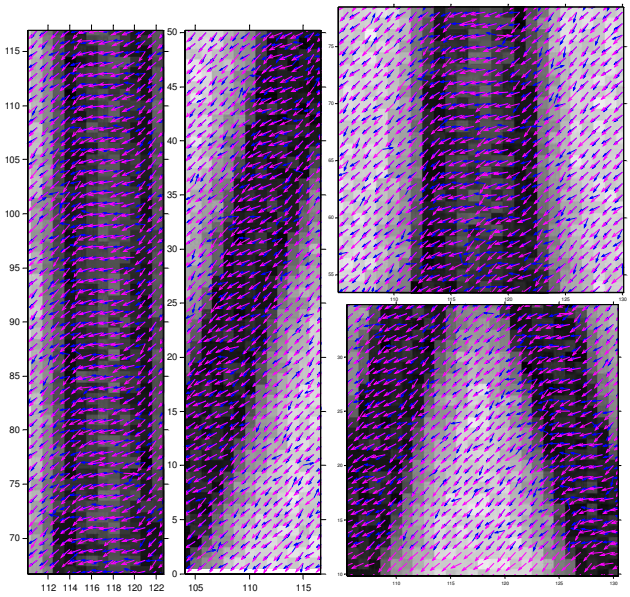

Fig. 3. Synthetic data result in the kissing trajectory. Blue: Original, known values; Magenta:Calculated Results.

TABLE 3.1
PCA RESULTS FOR DIFFERENT TRAJECTORIES

Trajectory Type		min	max		min	max		min	max
Circular	SNR = 30	0	10	SNR = 15	0	30	SNR = 7	0	45
Linear A		0	30		0	30		0	30
Linear B		0	30		0	30		0	30
Orthogonal Crossing		0	45		0	45		0	60
Kissing (branching)		0	30		0	45		0	45

The error is given as the maximum angle variation of the calculated principal eigenvector from the known value for that pixel. (angle units in degree)

IV. DISCUSSION & CONCLUSION

There are still many drawbacks in the literature on the analysis of DTI [3],[9]. In the proposed study, the algorithm is verified on phantom DT images. Developing a reliable and rapid tractography tool for the clinical use is the future study of the work in progress. Diffusion tensor imaging is limited in its ability to accurately describe local tract orientation in cases of branching or crossing structure.

In our study, firstly the diffusion tensor MR data is simulated, and this is followed by the diffusion tensor analysis. The diffusion tensor analyzing toolbox is written in Matlab, where it solves the equations explained in detail in methodology (1), (2), (5), (6).

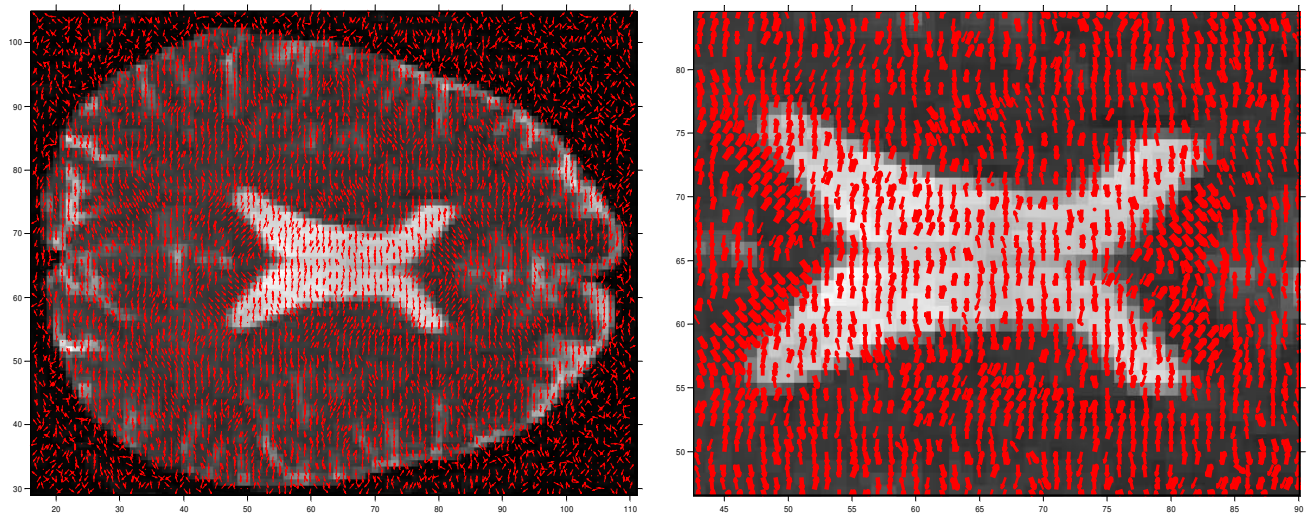

Fig. 4. Real data: Human Brain : left: Outside the brain a chaotic distribution of the tensor data is determined, whereas in the brain region the diffusion tensor is properly distributed. Right:Zoomed in CSF; the distribution of the eigensystem is clearly seen.

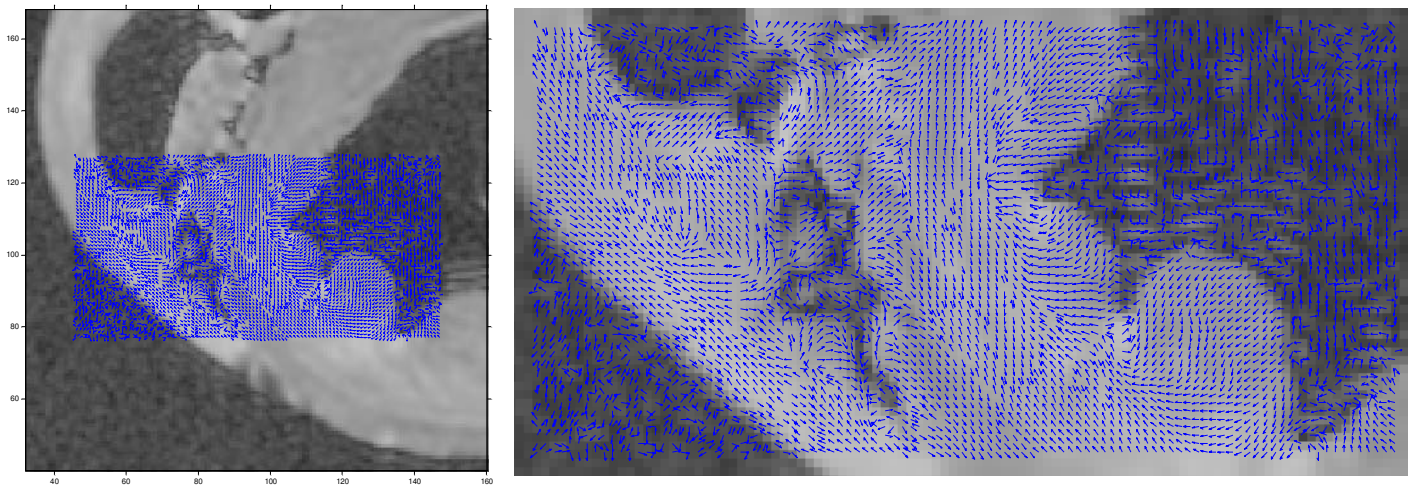

Fig. 5. Real data: Human Myocardium. Region of interest is zoomed on the right, proper distribution of the diffusion tensor is determined.

The PCA helps to get the eigenvectors and eigenvalues of the system, and so the diffusion tensor. In our experimental data, circular, linear, crossing, curved as kissing, and branching trajectories with different SNR values are analyzed (Fig. 1, Fig. 2 and Fig. 3), where blue represents the original, known values and red the calculated results. The results of the synthetic data and the known values are determined with zero error (see Table 3.1). Regarding to this validation and verification, the tool is applied to real human data (Fig. 4 and 5). So to conclude, the simulated data experiment on diffusion tensor analysis is succeeded. As a further conclusion, according to these validated results a verified and reliable tractography may be done on real data.

In the future work, the fiber tractography will be accomplished via a bootstrap method for the estimation of the dispersion associated with pathological tissue, where the bootstrap approach is based on a novel statistic which can be expressed as the smallest eigenvalue of a certain positive definite matrix. As the data are drawn with replacement, many more feasible realizations of a DT-MRI volume can be extracted than with a one acquisition - one data set approach. The algorithm will also be used as a probabilistic tractography method to determine connection likelihoods between two or more DT regions of interest. Tract likelihood maps including uncertainty areas as crossing, branching etc. from the pathological region of interest of pre- and postoperative brains will also be created.

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