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A Basic Introduction to Diffusion Tensor Imaging Mathematics and Image Processing Steps

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Abstract

Diffusion tensor imaging (DTI) is one of the most powerful magnetic resonance imaging (MRI) techniques developed in the twentieth century. In spite of the fact that DTI has been in use for more than two decades, it is still hard to find publications that simplify mathematics behind DTI for DTI users without extensive mathematical background. We believe that this may prevent some researchers from using DTI technique to its fullest extent. To the best of our knowledge, there are no published reviews which have tried to clarify the methods of DTI measurement and analysis. In this article, we attempted to explain the mathematics of DTI in simple terms with the goal of providing DTI users, with a better understanding of this technique and its usage. In addition, we have also described the DTI processing steps and explained the reasons behind each step.

Keywords: Diffusion tensor imaging; Mathematics; Diffusion weighted imaging; Eigen values; Eigen vectors

Background and Purpose

Neurological disorders of the brain which affect the white matter (WM) may bring microscopic changes that eventually affect the water diffusion in and around affected regions. From the perspective of diagnosis and treatment of any disease it is imperative to detect these changes as early as possible. The main advantage of diffusion tensor imaging (DTI) is its ability to capture the information regarding diffusion of water molecules at the microscopic level, which is otherwise not feasible with other conventional magnetic resonance (MR) contrasts. The efficacy and power of DTI in providing this microscopic information non-invasively has enabled clinicians and researchers to study numerous neurological disorders of the brain.

Since its initial development in the early 1990s [1] the field of DTI has advanced rapidly with hundreds of publications describing pathophysiological changes in the brain white matter (WM) brought on by the disease process, as well as properties of the intact brain WM in healthy humans. Many articles and books have been written to describe the theory [2-6] and mathematics behind DTI [7-9] as well as softwares for DTI data processing and analysis [10,11]. Nevertheless, DTI users without extensive mathematical background may lack a good understanding of mathematical concepts of DTI. The DTI literature has a tendency to utilize rigorous mathematical descriptions of the DTI technique [7,8], which may limit the comprehension of the technique for those DTI users without extensive mathematical background. Literature which has tried to explain the underlying concepts of DTI without rigorous mathematics [12] has failed to show a connection between the DTI concepts and the mathematics on which DTI is based. Despite several publications attempting to make this connection, clear descriptions of DTI, DTI image processing and the reasons behind each processing step are needed. The aim of the present article is to provide DTI users with simple, easy-to-understand explanations of the geometrical and physical interpretation of the mathematics behind DTI.

Understanding DTI Mathematics

Brief explanation of the term DTI

Diffusion is a net movement of molecules due to the concentration gradient[1] (in general gradient means a gradual increase or a decrease in magnitude of any physical quantity for e.g. temperature or pressure in space or over time, here it refers to the difference in concentration), called mass transport, arising as a result of mixing particles without requiring any bulk motion (i.e. any non-individual molecule movement) of the particles [13]. In the case of DTI, the particles are water molecules. Applied to the nervous system WM, diffusion is used indirectly as a probe to study the underlying neuronal fiber tracts. The diffusion mobility of water, denoted by a diffusion coefficient in the brain varies spatially due to the orientation and organizational nature of neuronal fiber tracts and it changes with the health of the neuronal fiber tracts. Diffusion phenomenon is explained using Fick's law and Brownian motion. Albert Einstein related Fick's law and Brownian motion to explain diffusion. To remain with the scope of this article we briefly explain Fick's law, Brownian motion and Einstein's relation that unifies them. Imagine a small glass tank which contains a mixture of two different solutions in different concentrations, due to the difference in concentration in the solute particles in different regions there will be net flow of the solute particles from the region of higher concentration to the lower concentration (for e.g. like heat flowing from a higher to a lower temperature region). The net flow of the molecules depends on the concentration gradient and the intrinsic diffusion constant of the molecule. This is explained using Fick's law

[1]Diffusion happens through Brownian motion, even in the absence of any concentration gradients, though in the presence of a concentration gradient there may be net transport of a substance

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(Equation 1 below) which states that the net flow of molecules called the diffusive flux (J) (Latin word for flow) is equal to the concentration gradient (∇C where ∇ denotes gradient and C is the concentration of the particles) multiplied by the diffusion constant D of the molecule [4]. However, even under equilibrium conditions (i.e. without any concentration or temperature or pressure differences) there is still microscopic motion of molecules with no net flow of molecules this is called as Brownian motion (the basis for this comes from Robert Brown's observation of pollen grains which when suspended in water under equilibrium conditions displaced). This microscopic motion of the molecules under equilibrium conditions is measured as the average displacement of the molecules in a given time (say a time interval over which we observe the molecules). Albert Einstein gave a probabilistic model to describe the displacement of an ensemble of molecules (group of molecules) by relating the Fick's law and Brownian motion as given in equation 2 below. The $\boldsymbol{x}^2$ denotes mean square displacement (mean square is used because there is an equal probability that a molecule can move in +x or -x direction thereby giving a zero average value), D is the diffusion constant of the particle and t is the time interval over which the displacement was observed more details can be found in [13].

$$J=D\nabla C \quad (1)$$

$$\boldsymbol{x}^2=2Dt \quad (2)$$

Tensor can be crudely defined as the characterization of the physical system properties. A tensor is a mathematical way to express a physical phenomenon. Briefly, for example a zeroth order tensor is one that is used mathematically to express a physical phenomenon/quantity that has only magnitude (but no direction) for example temperature, pressure (commonly known as scalars), more details are given in section 2.4 below. In DTI, the diffusion process (of water) is described using a second order tensor model.

Image is a visual representation of any physical phenomenon. It is generally a spatial representation i.e. a map of a physical or a non-physical quantity in either 2- or 3- dimensions. In DTI, imaging refers to the spatial distribution of the density of diffused water protons in the underlying tissue.

Why use DTI?

The DW data set can be obtained by applying DW gradients (i.e. in addition to the other gradients used in conventional MR imaging (for more details refer to Supplementary Material 1) in any number of directions to measure water diffusion in the underlying tissue. DW images obtained before the advent of DTI merely applied DW gradients along three orthogonal directions, generally denoted by X, Y and Z. This three-directional diffusion weighted imaging was called "diffusion imaging", and will be referred to as diffusion imaging in the rest of this article. Using this three directional DW dataset diffusion coefficient is estimated which is less than the normal diffusion coefficient of water (1.0×10^{-3} mm^2/s). This reduction in diffusion coefficient occurs due to inhomogeneous (i.e. varying with position) and anisotropic (i.e. varying with direction) nature of the WM fiber tracts. Thus, the coefficient of diffusion is termed as apparent diffusion coefficient (ADC).

Prior to DTI, diffusion imaging failed to fully account for the fact that diffusion in tissues such as WM of the brain carries different values in different directions (i.e. diffusion phenomenon is more than a vector quantity, more on this in upcoming sections). This property of the WM diffusion is referred to as anisotropy (i.e. varying with direction). The anisotropic diffusion in brain WM is due to its highly coherent organization as well as its tissue composition (i.e. axonal membrane, microtubules, microfilaments and myelin). On the other hand, if the value of the physical quantity does not change with direction it is called "isotropic". For instance, when the diffusion of water is entirely unconstrained (e.g. in a cup of water), the diffusion of water molecules is called 'isotropic', meaning that the path a given molecule follows through space is governed by Brownian motion, and it is equally likely to move in any direction. The diffusion imaging approach (before DTI) did not fully capture the anisotropic water diffusion.

For example, Figure 1 (left) shows the isotropic and anisotropic diffusion process; in the case of isotropic diffusion, water molecule displacement is equal in all three directions (i.e. X, Y, and Z) taking a spherical shape as shown in Figure 1 left. On the other hand, when diffusion is anisotropic, water molecular displacement differs when measured in different directions taking an ellipsoidal shape (Figure 1 right)[1]. DW imaging does not capture this ellipsoidal shape hence, insufficient for describing water diffusion in neuronal tracts which are highly convoluted and where water diffusion is anisotropic; however, this limitation has been overcome by DTI

Understanding DTI using the matrix notation of the diffusion constant

The following sections will provide the equivalent mathematical description of the difference between diffusion imaging and DTI. Matrix[2], notations I and II below expresses D matrix for DTI (I) and diffusion imaging (II), indicating the primary difference between DTI and diffusion imaging. If a diffusion sensitizing gradient is applied to only 3 directions (i.e. X, Y and Z) as in the case of diffusion imaging, then diffusion coefficients can be estimated only along these 3 directions which are D_{xx}, D_{yy} and D_{zz}. Due to the fact that the diffusion in the brain WM tracts is anisotropic, measuring diffusion along X, Y and Z directions (i.e. vector model) is not sufficient to describe the diffusion process in this tissue. In essence the diffusion imaging does not fully capture the anisotropic diffusion, (this is denoted by zero off diagonal elements in notation II) whereas DTI does. To capture the anisotropic diffusion in addition to the 3 main directions i.e. X, Y, Z, diffusion is measured along the off diagonal elements XY, XZ and YZ directions with the corresponding diffusion coefficients D_{xy}, D_{xz}, D_{yz}, as presented in notation I. Even though the diffusion matrix for anisotropic diffusion has 9 elements only 6 independent elementsthe Dyx or Dxy tensor element represents more of a correlation between diffusion in the X and Y directions in the chosen reference frame similarly for yz and zx directions, so $D_{yz=}D_{zy}$, $D_{zx}=D_{xz,}$, $D_{xy}=D_{yx}$, $D_{yz}=D_{zy}$, $D_{zx}=D_{xz}$ hence we need to measure only along 6 independent directions D_{xy}, D_{xz}, $D_{yz,}$ $D_{xy,}$ D_{xz} and D_{yz} more information about the tensor and

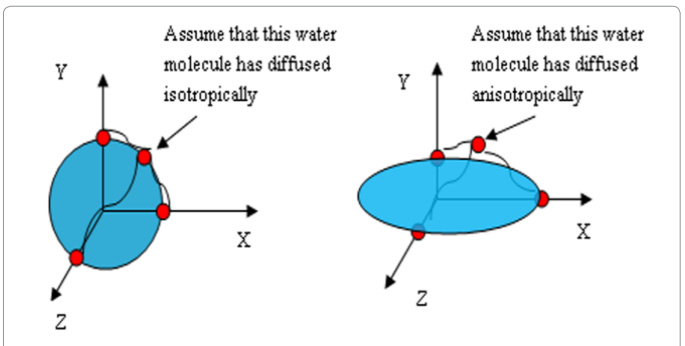

Figure1: Pictorial diagram of isotropic and anisotropic diffusion.

[1]This ellipsoidal shape can be prolate (meaning that if the parallel eigenvalue is very much greater than the perpendicular eigen values $\lambda 1 >> \lambda_2 \approx \lambda_3$) or oblate (where $\lambda_1 \approx \lambda_2 >> \lambda_3$) to capture the range of shapes we see in diffusion tensors.

[2]A matrix is a mathematical notation used to arrange numbers or symbols in terms of the row and column elements.

its symmetric property is given in section 2.4 below) are required to capture anisotropic diffusion i.e. Dxx, Dyy, Dzz, Dxy, Dxz, Dyz.

$$\begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{ZZ} \end{bmatrix} \quad \text{I}$$

$$\begin{bmatrix} D_{xx} & 0 & 0 \\ 0 & D_{yy} & 0 \\ 0 & 0 & D_{ZZ} \end{bmatrix} \quad \text{II}$$

In essence, in the case of anisotropic diffusion, diffusion constants need to be measured in at least 6 different orientations: D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{yz}, D_{zx} (as $D_{xy}=D_{yx}$, $D_{yz}=D_{ry}$, $D_{zx}=D_{xz}$). This is due to the fact that in tissues such as the brain WM, diffusion assumes the shape of an ellipsoid and a *tensor* can best describe the anisotropic diffusion, i.e. the ellipsoid.

Understanding the physical and mathematical description of the tensor

In the matrix notation used to denote D, i.e. D_{xx}, D_{yy}, D_{xy} (using subscripts to D), the notation D with two subscripts is a second order tensor notation. The geometrical description of the ellipsoid in the previous sections is in fact a physical description of the tensor. Mathematically, a tensor denoted by $T_{ij,}$ is called a second order tensor, where the subscript i represents a 3-dimensional coordinate system, such as X, Y and Z, while subscript j represents another set of 3-dimensional coordinates such as X1, Y1 and Z1. The diffusion tensor matrix is a covariate matrix (covariate means variation with respect to two variables) of the stochastic (a stochastic process is one whose statistical properties such as mean, variance etc. vary with time) paths of molecules. For these reasons a tensor has two subscripts and it is symmetric i.e. for example $D_{xy}=D_{yx}$). Because of this symmetric property, the tensor matrix is real valued (numerical values can be real or complex). The eigen values of this tensor matrix are then obtained by a mathematical procedure called matrix diagonalization (matrix diagonalization or eigenvalue estimation is a mathematical procedure where a transformation matrix is found in such a way that it will transform (rotate) the given input matrix to its principal orientation, after diagonalization except the diagonal elements all the off diagonal elements will become zero). The diagonal elements obtained after matrix diagonalization are invariant (do not vary with the direction of measurement) and are called as eigenvalues. Moreover, the eigenvalues are positive since the tensor is positive definite. As shown in Figure 2, in the case of diffusion tensor ellipsoid we need 3 parameters to describe its shape: denoted by L1, L2 and L3, as well as the three coordinates to describe its orientation in space (δ, θ and Φ).

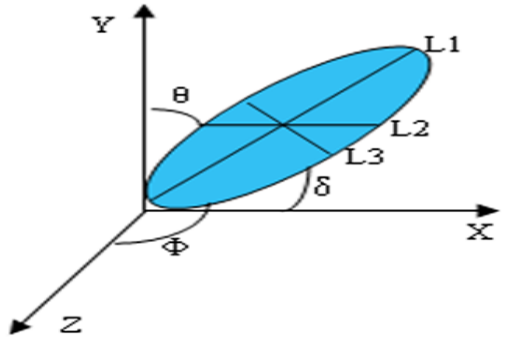

Figure 2: The number of parameters required in order to describe the ellipsoid in space: 1 major axis, L1; two minor axes L2 and L3; and 3 coordinates: δ, θ and Φ.

Imaging

Now that we understand what a tensor is, we can acquire data so that we can estimate this tensor element in every voxel in the brain tissue. As mentioned earlier, the diffusion tensor matrix has only 6 elements (the matrix in total has 9 elements) that are independent i.e. Dxx, Dyy, Dzz, Dxy, Dyz and Dzx. In order to determine these 6 elements DW images have to be acquired in 6 non-collinear (points do not lie along the single straight line) directions. Therefore, the minimum number of directions in which we need to acquire data in order to reconstruct diffusion tensor in each voxel is 6 plus a non-diffusion weighted image which is commonly known as b=0 image (using b=0 image only we can estimate how much diffusion has occurred in the diffusion weighted image).

DTI Image Processing

In this section, we describe DTI image processing step-by-step and also describe briefly the reasons behind each step. The image processing steps are as follows: 1) Oblique angle correction, 2) Susceptibility artifact correction, 3) Eddy current distortion correction and motion correction, 4) Rotating the gradient table, 5) Fitting DTI data and estimating the DTI metrics such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD), 6) Artifacts, noise in DTI and 7) Normalization to template images.

Oblique angle correction

For oblique angle correction, what matters is the oblique angle between the scanner and image coordinates. Scanner coordinates refer to the coordinates of the MRI scanner and image coordinates refers to the coordinates of the DTI images. Both scanner and image coordinates are based on the 3-way coordinate system, denoted by x, y, and z direction. Unlike other conventional MR images, DTI has vectorial information, and thus this vector information has to be preserved correctly during data preprocessing, so that the diffusion tensor matrix can be correctly estimated. The first essential step is to correct for the oblique angle between the scanner and image coordinates. The oblique angle information is stored in the MR image. Open ware MRI convert (http://lcni.uoregon.edu/~jolinda/MRIConvert/) extracts the oblique angle information from the MR image and performs the correction for it and outputs the corrected gradient vector file (in diffusion weighted imaging a gradient file is the one which contains information about the directions in which the diffusion weighting gradients were applied) which will be used in the subsequent processing steps (described below). Statistical parametric mapping (SPM) an open software (software has toolboxes (http://www.fil.ion.ucl.ac.uk/spm/toolbox/) to correct for oblique angle. Explore DTI (http://www.exploredti.com/) can also be used to correct for oblique angle.

Susceptibility artifact correction

DTI data is acquired using echo planar imaging sequence (EPI). EPI is a fast imaging sequence which suffers from susceptibility artifacts, due to the inhomogeneities in the magnetic field. Susceptibility artifacts occur due to differences in magnetic properties (i.e. susceptibility) of different tissues. The susceptibility effects are more pronounced at the air/tissue interfaces in the brain tissue. The phase of the MR signal is mainly determined by the local gradient field (phase and frequency encoding gradients, see Supplementary Material 1) and the magnetic field inhomogeneity (caused by the susceptibility differences between air/tissue interfaces). The phase information in turn determines the position of the voxel in an MR image [14]. The evolution in phase (phase change over time) between two adjacent sample points in

k-space (for details on what is k-space please refer to Supplementary Material 1) is sensitive to the magnetic field inhomogeneities [14]. In the EPI sequence the magnetic field inhomogeneities significantly affect the pixel position along the phase encoding direction when compared to the frequency encoding direction [14]. Therefore, magnetic field inhomogeneity due to the susceptibility differences (air/tissue interfaces) affects the phase of the MR signal causing mislocalization of voxels in the image. These, mislocalized voxels can be repositioned (restored to their original location) using the phase information (MR images are reconstructed using Fourier Transform which is a complex variable i.e. it has both magnitude and phase information). One of the commonly used approaches to correct for susceptibility artifacts is to use field maps. Field maps capture phase evolution over time; this is achieved by acquiring magnitude and phase images over two echo time points (for what is an echo time see Supplementary Material 1). Other approaches that are used to correct for susceptibility artifacts include non-linear registration of the diffusion weighted images to T1-weighted images. The amount of deformation (in voxel positions after non-linear registration) gives the amount of distortion due to susceptibility artifacts. Therefore, the deformation information is used to restore the voxels to their actual positions, more information on this can be found elsewhere [15]. Another approach to correct susceptibility artifact is to acquire two EPI images one traversing the k-space from top to bottom and another from bottom to top. These two images have distortions in opposite direction but with identical magnitudes (these are called as distorted images). A model of the image formation process of spin echo-EPI together with these distorted images is then used to correct for the susceptibility artifacts more details can be found in Andersson et al. [16]. Parallel imaging is now commonly employed in DW imaging. This technique not only reduces the susceptibility artifacts but also the scan time (depending on the parallel imaging factor). Briefly, in parallel imaging the field of view (FOV) (the area to be scanned) is divided among multiple arrays of receiver coils (each receiver coil has the sensitivity profile corresponding to some part of the divided FOV in k-space) and the signal from each receiver coil is then combined to produce a final image. For example, let us assume that we have two receiver coils, the FOV (k-space) is then divided into two halves say top and bottom, array coil one will capture the top of the FOV and the array coil 2 covers the bottom FOV. The signal from these two coils (top of FOV and bottom of FOV) are then combined to get the final image. Since each array coil covers a certain portion of the k-space the number of phase encoding steps is reduced eventually reducing the susceptibility artifact and the scan time (since the signal is captured simultaneously in the two array coils). Different parallel imaging techniques such as SMASH, SENSE, GRAPPA are available depending on whether the image reconstruction is done in the k-space or in image space, more details can be found in [17].

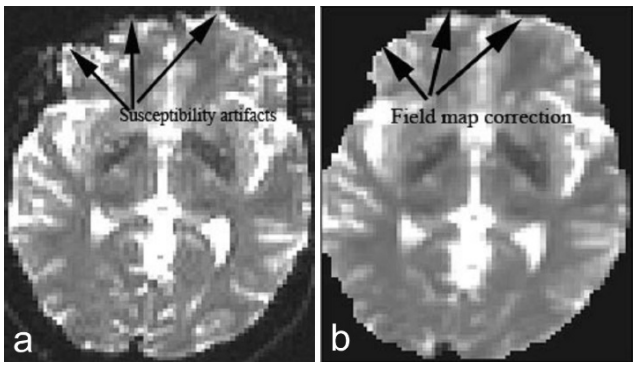

Figure 3: a) Shows susceptibility artifact in DTI data collected from one of our amyotrophic lateral sclerosis (ALS) patients, b) arrows indicate mislocalized voxels that were restored using field map correction procedure.

Briefly the toolboxes that are available to correct susceptibility artifact include FUGUE from FMRIB (Functional Magnetic Resonance Imaging of Brain) software library (FSL) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FUGUE) using field maps, TOPUP toolbox in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TOPUP) performs correction for susceptibility artifact using Andersson et al. [16] approach i.e. using images with opposite the phase encoding blips. Similarly, SPM offers FieldMap toolbox to correct for susceptibility artifacts using field maps (http://www.fil.ion.ucl.ac.uk/spm/toolbox/fieldmap/). Figure 3a and 3b shows typical example of a diffusion weighted image with susceptibility artifact and after its correction.

Eddy current distortion correction and motion correction

Eddy currents are currents (formed due to diffusion gradients) that flow in the direction opposite to the main current. Eddy current artifacts occur because of the on/off switching of the diffusion gradients while acquiring the DW images and cause shearing (i.e. skewing the geometry of an object) and scaling (i.e. changing the size of an object). Most DTI image processing softwares correct for the eddy currents along with motion correction (i.e. patient's head motion in between the DW image acquisitions) by using a 12 parameter transformation (also known as affine transformation) to modify an object so that it matches the target object, non-diffusion weighted b=0 images are used as a target as they do not have the artifact. The rotational and translational parameters of the affine matrix account for the head motion correction and the remaining 6 parameters (i.e. 3 shear and 3 skew values) account for the eddy current distortion correction. MR hardware based eddy current distortion correction methods are also available these include: a) self-shielded gradient coils with additional wiring reduce the gradients outside the gradient coils, b) eddy current arising from RF coils can be minimized by using coils with reduced conductive surfaces and c) the shape of the currents to the gradient hardware can also be adjusted to correct for eddy current distortion, for example in the commonly used trapezoidal shape the current can be increased on the upward and downward slopes of the pulse to the coil [18].

In FSL the diffusion toolbox (FDT) (http://fsl.fmrib.ox.ac.uk/fsl/fsl-4.1.9/fdt/fdt_eddy.html) has both graphical user interface (GUI) and command line option to correct for eddy current distortion. In GUI 'Eddy Current Correction' in FDT toolbox can be used and in command line version option is "eddy_correct" command can be used. Other softwares that offer eddy current correction include SPM toolboxes, DTI Studio (https://www.mristudio.org/wiki/DtiStudioV2) and explore DTI.

Rotating the gradient table (B vector)

Once eddy current correction is performed, the gradient table needs to be re-oriented (to account for the eddy current and motion distortion correction steps), so the gradient table is multiplied with the affine 12 parameter matrix obtained in the above eddy current correction step. The gradient table after oblique angle correction should be used for this correction. This step ensures that the gradient table is in the same orientation as the DW images. In FSL software the command line program "rotate_bvecs" is used to rotate the gradient table after correcting for artifacts. Explore DTI software can also be used to perform this pre-processing step. SPM toolboxes can also be used.

Fitting the data

Finally, the pre-processed DW images are fitted to the DTI model, which refers to the model used to characterize the diffusion of water molecules in tissues, followed by the estimation of the DTI metrics such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) etc. The process of fitting the data is explained below.

There are only six unknowns (D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{yz}, D_{zx}) in the diffusion tensor matrix notation I thus if we have a 6-directional DW data set then the unknown diffusion constants can be obtained by solving the equation. On the other hand, if DW data is acquired in more than 6 directions[3] then the number of equations is more than the number of unknowns and the problem is said to be overdetermined. For an overdetermined system, the solution can be obtained by fitting to the equation 2 below.

$$\frac{S_D}{S_o} = e^{-1000D} \tag{3}$$

In equation 2 S_D is the diffusion weighted data (obtained with b=1000) and S_0 is the b=0 image. More details on the equation 2 and its derivation for readers interested in mathematical details are provided in Supplementary Material 2. Additionally, a simple algebraic analogy is given in Supplementary Material 3 illustrating the difference between solving and fitting procedures.

After fitting the DWI images a diffusion tensor matrix is obtained in each voxel as given in notation II. This tensor matrix, as mentioned above, has 6-dimensional information, we normally reduce the 6-dimensional tensor information to 3 dimensions by a mathematical process, called matrix diagonalization or rotation to principle direction (explained in section 2.4). This step will result in eigenvalues and eigenvectors for each and every voxel in the image. Eigenvalues are useful in characterizing the anisotropy in white matter tissue.

Figure 4 provides an analogy/depiction using a vector for the diagonalization procedure. From Figure 4, we can see that when vector R is not in its principal orientation (inclined at an angle θ with respect to X-axis) R is resolved into the components along X and Y as (X cos θ, Y sin θ). On the other hand, when vector R is rotated to either X or Y (i.e. its principal orientation for present purposes is rotated to the X axis, which can be similarly applied for the Y axis) then the components of the vector R (i.e. X cos θ) become X (as θ=0, cos0=1 and the Y sin θ=0 as sin 0=0). Diagonalization of the diffusion tensor matrix to obtain eigenvalues and vectors is similar to this analogy, and the diffusion tensor matrix after diagonalization gives eigenvalues as shown in matrix notation IV.

$$[x\cos\theta \; y\sin\theta \; 0] \xrightarrow{rotation\,to\,x\,axis} [x\;0\;0] \tag{III}$$

$$\begin{pmatrix} D_{xx} & D_{yy} & D_{zz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} \xrightarrow{Diagonalization} \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} \tag{IV}$$

where λ_1, λ_2, and λ_3 are the eigenvalues. Softwares FSL, SPM, DTI studio, Explore DTI and Track v is (http://trackvis.org/) can be used for tensor fit.

[3]Commonly, DW data are acquired in at least 25 or more directions to improve signal to noise ratio and for the robust estimation of eigenvalues; in other words, there are more than 6 directions

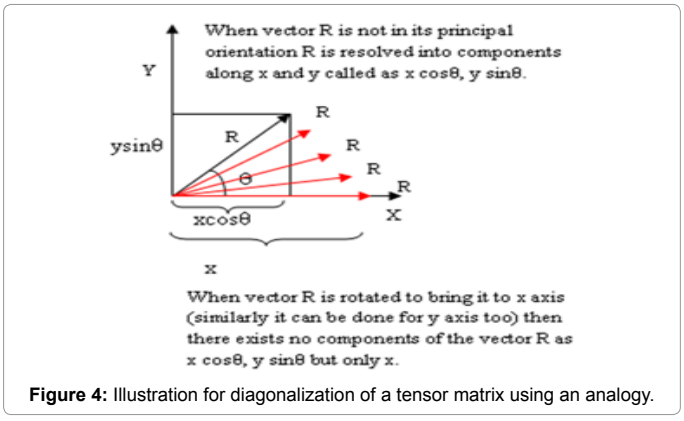

Figure 4: Illustration for diagonalization of a tensor matrix using an analogy.

DTI metrics (derived from the eigenvalues) and their interpretation in pathological tissue

MD, FA, AD and RD (commonly used DTI metrics) and other DTI metrics such as Trace (D)[19], relative anisotropy (RA) and measures that describe the geometry (shape of the diffusion tensor) proposed by Westin such as linear, planar and spherical indices [20,21] can also be calculated from the eigenvalues. The formula for MD, FA, AD, RD, Trace (D), RA, Westin's indices CL, CP and CS using eigenvalues is given in equations 3-11.

$$MD = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3} \tag{4}$$

$$FA = \sqrt{\frac{3}{2}}\sqrt{\frac{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \tag{5}$$

$$AD = \lambda_1 \tag{6}$$

$$RD = \frac{(\lambda_2 + \lambda_3)}{2} \tag{7}$$

$$Trace(D) = \lambda_1 + \lambda_2 + \lambda_3 \tag{8}$$

$$RA = \frac{\sqrt{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}}{MD} \tag{9}$$

$$CL = \frac{(\lambda_1 - \lambda_2)}{Trace(D)} \tag{10}$$

$$CP = \frac{2(\lambda_2 - \lambda_3)}{Trace(D)} \tag{11}$$

$$CS = \frac{3\lambda_3}{Trace(D)} \tag{12}$$

The eigenvectors are obtained from eigenvalues and they provide information about the orientation of the tensor as shown in Figure 5a, where the lines indicate the orientation of the ellipsoid in each voxel. Combining FA values in each voxel with this orientation information from the eigenvector virtual neuronal tracts are reconstructed (Figure 5b), which is termed fiber tractography.

These DTI measures have been interpreted as reflecting different types of pathophysiology related to neuronal degeneration. MD is the average of eigenvalues and provides information regarding the

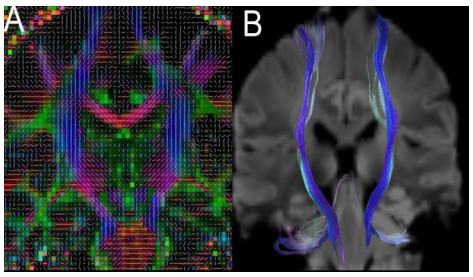

Figure 5: a) Short white lines indicate the eigenvectors in each voxel in a brain coronal slice. b) An example of the typical fiber tractography showing reconstructed virtual neuronal tracts (blue color) based on FA values and eigenvectors.

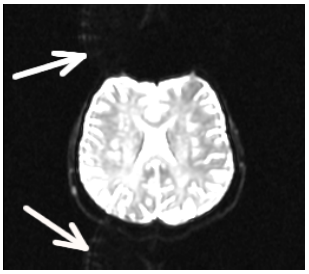

Figure 6: A typical example of an N/2 ghosting artifact commonly seen in DTI data (in one of our amyotrophic lateral sclerosis (ALS) patient data).

amount of obstruction to water molecule diffusion. In general, increase in MD values reflects loss of the integrity of axonal fiber tracts and myelin damage. The FA value is the variance of eigenvalues in a given voxel and a decrease in FA reflects axonal and myelin degeneration. FA values range from 0 to 1 with zero corresponding to isotropic diffusion suggesting loss of neuronal fiber tracts and 1 to anisotropic diffusion suggesting coherent and intact fiber tracts. Madler [22] et al. evaluated whether the anisotropy is due to myelin or axonal integrity by comparing DTI metrics FA and MD with myelin water fraction (MWF) (a measure based on the myelin water content obtained using a quantitative technique called as T2 relaxometry). They observed that FA and AD correlated significantly with MWF, however in regions of highly organized fiber tracts such as corpus callosum (CC) the diffusion anisotropy measures did not correspond to high MWF suggesting that anisotropy is due to both the myelin and axonal integrity. Beaulieu [23] showed that changes in FA values can result from either differences in axial diffusivity, radial diffusivity or both. There is accumulating evidence that the integrity/degeneration of axons is reflected by AD [2] and of myelin by RD [1,24].

Hofling et al. [25] found an increase in RD and a decrease in AD in Globoid cell leukodystrophy patients in whom both axonal and myelin damage were observed. They also found that DTI metric changes correlated significantly with histopathological results of myelin and axonal damage. Aging studies [26] found changes in FA in CC, internal capsules, frontal, parietal and occipital white matter tissues which appeared normal in other conventional images such as T1-Weighted images. Hugenschmidt et al. [27] found widespread reduction in FA values in aging population in white matter tissue when compared to white matter volume changes suggesting that DTI measures are more sensitive to WM damage.

Changes in MD and FA values have been reported in neurological conditions such as stroke (during transition from acute to subacute to chronic stroke, MD decreases and FA increases in acute phase, then renormalizes and then increase in MD with a decrease in FA was found during the chronic stroke) [28], increase in MD with a decrease in FA has been observed in the sclerotic hippocampi of chronic epilepsy patients [29]. In the case of brain tumor patients an increase in MD values with a decrease in FA was observed in cystic or necrotic areas [30]. These changes are interpreted as being reflective of organizational changes (loss of structural organization and expansion of extra-cellular space) when cytoarchitecture is disrupted. We found that AD and RD values were significantly elevated in Amyotrophic Lateral sclerosis patients indicative of myelin and axonal damage [31,32].

Artifacts, noise in Diffusion MRI

Partial volume effects occur due to the heterogeneous nature of different tissue types in the brain (compartments of white matter-white matter, white matter-grey matter etc.). Partial volume effects causes higher uncertainty (since there is always noise along with the signal we measure in the diffusion data, the diffusion tensor estimation always has some uncertainty associated with its estimation) in the estimates of anisotropic measures FA and trace [33]. Similarly, background noise can also cause DW image intensity to reach baseline noise floor leading to biased estimates of eigenvalues. The presence of noise can cause isotropic media to appear as anisotropic and anisotropic media to appear more anisotropic. Pierpaoli and Basser [34] proposed using intervoxel coherence of eigenvectors in the neighboring voxels to improve the estimate of eigenvalues [35].

In addition, the noise in diffusion weighted images affect fiber tracking. The noise characteristics (i.e. improving the effective or measured signal to noise ratio (SNR)) can be changed by using a filter. This is known as regularization. One of the post-processing methods used to filter noise is spatial smoothing. There are three ways to perform the smoothing a) smoothing the diffusion weighted images before fitting the tensor; b) smoothing the eigenvectors and eigenvalues or c) smoothing the tensor itself [36]. The information conveyed by the tensors is lost if we use approach a) i.e. smoothing the DWI dataset or approach b) i.e. smoothing the eigenvalues and eigenvectors. However, tensor regularization methods preserve the information in tensor and are preferred, several tensor regularization methods are available for more details refer to [36,37].

N/2 ghosting (also called a Nyquist ghosting) is another type of artifact commonly seen in DWI dataset. N/2 ghosting [18] occurs because the k-space is sampled in a zig-zag manner with odd lines of k-space displaced from the even k-space lines. Figure 6 shows a typical example of an N/2 ghosting artifact. It can be seen from the Figure 6 that N/2 ghosting occurs in phase encode direction (vertical direction). N/2 ghosting can be mitigated by reducing the number of phase encoding steps; parallel imaging can be used. Another approach is to use navigator echoes (navigator echoes capture the zig-zag information which allows correction using post-processing methods [18].

Normalization to template/Atlas images

Exploratory analysis techniques such as voxel based morphometry (VBM), tensor based spatial statistics (TBSS) require registration of subject's DW (or the maps of FA, MD etc.) images to atlas (or template) space. This is done in order to ensure that homologous regions are being compared across the groups (for example between control and patient groups). Since DTI data has both tensor and scalar (derived from the tensor) information ,normalization can be performed using either maps of scalar measures such as FA (for example in TBSS approach) or using the tensor information itself [38,39]. It is demonstrated that using tensor information for image registration provides better normalization of tract morphology and orientation when compared to using scalar measures such as FA or trace [40,41].

Conclusion

In this overview, we tried to provide a simple explanation of the terms frequently used in DTI studies, as well as the geometrical meaning of the underlying DTI mathematics. We also tried to explain the details related to the DTI image processing steps. In order to stay within the scope of the article, some important details, such as different tractography approaches for reconstructing virtual neuronal fiber tracts, were not covered. The diffusion process can not only be described using a tensor model but it can also be model-free as is the case with diffusion spectrum imaging, not described here. Future reviews will address these components of diffusion weighted imaging.

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