

# Diffusion Tensor Imaging: Concepts Quantification and Quality Issues

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The purpose of this talk is to introduce the basic concepts of diffusion tensor magnetic resonance imaging (DT-MRI), explain how quantitative parameters can be derived and to discuss quality issues.

## CONCEPTS

### Diffusion Tensor Imaging – The Basics

The random molecular / thermal motion of water molecules, known as diffusion, provides a powerful method for probing tissue microstructure. In fluid filled spaces, such as CSF-filled spaces in the brain, water molecules are free to diffuse equally in all directions. In this case, the diffusion process is said to be *isotropic* (i.e., the same in all directions). In tissue in which there is no dominant orientation on the scale of the sample volume (e.g., gray matter within a voxel measuring 2.5 x 2.5 x 2.5 mm), diffusion will also appear isotropic. However, the presence of cell membranes, macromolecules and so forth will hinder the motion of water molecules. This will lead to a reduction in the displacement per unit time along a particular axis, which will *appear* as a reduced diffusion coefficient. Hence, we say that the ‘apparent diffusion coefficient’ or ADC (Le Bihan *et al.* 1985) is lower in gray matter than in CSF. By introducing two large pulsed magnetic field gradients (‘diffusion encoding gradients’) into a standard MR imaging sequence (most typically a spin-echo EPI sequence), one can increase the sensitivity of the signal to diffusion, thus creating a diffusion-weighted image. By acquiring at least two images with differing amounts of diffusion weighting, one can estimate the apparent diffusivity in each voxel to generate a quantitative ADC map.

In tissue which has a dominant orientation on the scale of the sample volume, the *apparent* diffusion coefficient will be higher along the long axis of the structure than in a perpendicular direction. In this case, we say that diffusion is *anisotropic*. Moseley *et al.* (1990) showed that diffusion in cerebral white matter is anisotropic, with higher ADCs along the long axis of the white matter fibers than in a perpendicular orientation. Clearly, a single ADC will be insufficient to fully characterize diffusion in such tissue and a more sophisticated description is needed. Standard diffusion textbooks (Crank 1956) show how diffusion in anisotropic systems can be characterised using a tensor. This is a 3 x 3 symmetric matrix, (i.e. contains only 6 unique elements):

$$\mathbf{D} = \begin{bmatrix} D_{11} & D_{12} & D_{13} \\ D_{12} & D_{22} & D_{23} \\ D_{13} & D_{23} & D_{33} \end{bmatrix} \quad [1]$$

The diagonal elements characterize the displacements along three orthogonal axes, while the off-diagonal elements characterize the *correlation* of displacements along orthogonal axes. For example,  $D_{12}$  is the correlation between displacements along axis 1 and

axis 2. When the off-diagonal elements are equal to zero, this means that displacements in orthogonal directions are uncorrelated. This happens when the tensor is aligned with the fiber frame of reference. In such instances, the *diagonal* elements correspond to the *eigenvalues* ( $\lambda_1, \lambda_2, \lambda_3$ ), of the tensor, i.e. the diffusivities along the principal axes. The orientations of the principal axes are given by the *eigenvectors* ( $\varepsilon_1, \varepsilon_2, \varepsilon_3$ ).

Basser and colleagues (1994) showed how the diffusion tensor can be estimated from a series of diffusion-weighted intensities in which the direction of the applied diffusion encoding gradients is varied. The reader will be familiar with the concept that to find the solution to an equation with  $x$  unknowns, one needs at least  $x$  simultaneous equations. It will be seen from Eq. [1] that there are 6 unique elements of the diffusion tensor (since  $D_{ij} = D_{ji}$ ), hence one needs at least 6 simultaneous equations that relate the elements of the diffusion tensor to find the 6 unknown elements. Basser *et al.* showed how it is therefore possible, by applying gradients in at least six non-collinear directions, to set up a series of equations which could be solved, allowing the diffusion tensor to be estimated in each voxel of the image. This technique is known as diffusion tensor magnetic resonance imaging (DT-MRI).

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## QUANTIFICATION

### Parameters Derived From DT-MRI

There are three main parameters derived from DT-MRI: (a) Trace or Mean diffusivity; (b) Anisotropy; (c) Fibre Orientation.

**Trace:** Without doubt, the most clinically useful measure obtained from diffusion tensor imaging is the Trace. This is the sum of the three diagonal elements of the diffusion tensor (i.e.  $D_{xx} + D_{yy} + D_{zz}$ ). The Trace/3 can be thought of as being equal to the *orientationally averaged* mean diffusivity. Note that, particularly in the earlier diffusion MRI literature, many alternative phrases have been used to describe this measure, including trace ADC and mean trace ADC. These terms are nonsensical since the trace is a property of tensors, while an ADC is a scalar quantity; the use of such terms should therefore be avoided. A remarkable property of the trace is that, in the range of diffusion weightings typically used in clinical studies ( $b < 1000 \text{ s mm}^{-2}$ ), the mean diffusivity is fairly uniform throughout parenchyma ( $0.7 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ). Although homogeneity makes it difficult to distinguish anatomical structures, it does offer the advantage that the effects of anisotropy do not confound detection of diffusion abnormalities, such as acute ischemic lesions (Lythgoe *et al.* 1997).

**Anisotropy:** Prior to the introduction of the tensor model into MRI by Basser *et al.* (1994), several indices for diffusivity were proposed, such as the ratio of ADCs obtained in two orthogonal directions. The limitation of such indices can be understood by imagining a set of fibers oriented at  $45^\circ$  to the  $x$ - and  $y$ -axes, the ratio  $ADC_y/ADC_x$  is equal to unity, for the fibers oriented along the  $y$ -axis, the ratio  $ADC_y/ADC_x$  takes its maximal value, and for the fibers oriented along the  $x$ -axis, the ratio takes its minimal value. As this measure depends on the orientation of the tissue with respect to the laboratory frame of reference, it is said to be *rotationally variant*.

Anisotropy indices formed from the eigenvalues of the tensor will, by definition, be rotationally invariant. The simplest anisotropy index, analogous to the ratio  $ADC_y/ADC_x$  would be the ratio of the largest to the smallest eigenvalue (i.e.,  $\lambda_1/\lambda_3$ ). However, as discussed later, it has been shown that sorting the eigenvalues according to their magnitude

introduces a bias in the measurements at low signal-to-noise ratios (Pierpaoli *et al.* 1996). To circumvent this problem, indices that do not require sorting (Basser and Pierpaoli 1996; Pierpaoli and Basser 1996) have been proposed and have been shown to be less sensitive to the signal-to-noise ratio. The two most popular are the fractional anisotropy ( $FA$ ) and relative anisotropy ( $RA$ ), given by

$$FA = \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1 - \langle \lambda \rangle)^2 + (\lambda_2 - \langle \lambda \rangle)^2 + (\lambda_3 - \langle \lambda \rangle)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad [2]$$

and

$$RA = \sqrt{\frac{1}{3}} \frac{\sqrt{(\lambda_1 - \langle \lambda \rangle)^2 + (\lambda_2 - \langle \lambda \rangle)^2 + (\lambda_3 - \langle \lambda \rangle)^2}}{\langle \lambda \rangle}, \quad [3]$$

where

$$\langle \lambda \rangle = \frac{1}{3}(\lambda_1 + \lambda_2 + \lambda_3). \quad [4]$$

The numerator for both terms is the same and is related to the variance of the three eigenvalues about their mean. The fractional anisotropy index normalizes this measure by the magnitude of the tensor as a whole. Just as the magnitude of a vector can be found from the sum of the squares of its individual components, the magnitude of the tensor is found from the sum of the squares of its eigenvalues. Thus, fractional anisotropy measures the fraction of the tensor that can be assigned to anisotropic diffusion. The fractional anisotropy index is appropriately normalized so that it takes values from zero (when diffusion is isotropic) to one (when diffusion is constrained along one axis only). The denominator of the relative anisotropy index is simply the mean diffusivity. This index is mathematically identical to a coefficient of variation, i.e. standard deviation divided by the mean. To ensure that this index scales from zero to one, Shimony *et al.* (1999) divided the relative anisotropy index by  $\sqrt{2}$ , and renamed the index  $A_\sigma$ , i.e.

$$A_\sigma = \frac{RA}{\sqrt{2}}, \quad [5]$$

The relative merits of the various anisotropy indices have been discussed by Papadakis *et al.* (1999)

**Tensor Orientation:** By finding the direction in which the motion of diffusing molecules is least hindered within each voxel, (given by the eigenvector associated with the largest eigenvalue), one can infer the dominant fiber orientation. Jones *et al.* (1997) and Pierpaoli (1997), showed how robust and readily interpreted fiber orientation maps could be derived by using the information contained within the diffusion tensor (more specifically, the eigenvector associated with the largest eigenvalue). The key idea is that components of the orientation of the fiber are represented using different primary colors. The most commonly used scheme to date is the ‘absolute direction scheme’ – with left-right fibers colored red, anterior-posterior fibers colored green and superior-inferior fibers colored blue (Pajevic and Pierpaoli (1999)).

By viewing fiber orientation in one voxel and following, by eye, a path of smooth transition in color from one voxel to the next, one can gain an impression of the trajectory of the major white matter pathways. In fiber tracking or tractography, algorithms are used to perform a

similar task- i.e. following smooth pathways in the fiber orientation field to reconstruct white matter pathways-in an automated way. Tractography will be discussed in detail in the lecture by Dr Aaron Field

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## QUALITY ISSUES

We will now focus on factors that may disrupt the quality of estimates of quantitative parameters obtained from DT-MRI, and focus on how these factors might limit the comparison of DT-MRI results between different centres. We will also consider factors within the constraints of a clinical setting

**Gradient Calibration:** The most obvious requirement for obtaining high quality DT-MRI data is to ensure that the system is well calibrated. This is particularly true for the diffusion-encoding gradients. If miscalibrated, the effect will be more or less diffusion-related attenuation of the signal than expected – which will result in a bias in anisotropy and a general ‘hue’ in fiber orientation maps. Gradient linearity is also important if the gradient amplitude is to be stepped

**Patient Motion:** The majority of DT-MRI acquisitions utilise EPI-based sequences with the aim of ‘freezing’ motion. However, two forms of motion can still be problematic for quantitative DT-MRI: voluntary and involuntary. The former is the standard head motion seen with even the most compliant subjects, which (if uncorrected) means that the set of signal intensities used to estimate the diffusion tensor do not come from the same tissue, resulting in non-sensical tensor estimates. The latter includes cardiac pulsation which has two detrimental effects on DT-MRI measurements.....

**Cardiac Pulsation:** The effect of cardiac pulsation on uni-directional diffusion-weighted MR measurements has been documented since the 1990s Chien *et al.* 1990; Turner *et al.* 1990; Conturo *et al.* 1995; Skare *et al.* 2001). However, the effects on tensor-derived properties have only recently been investigated (Pierpaoli *et al.* 2003; Jones and Pierpaoli, 2005). The first effect of cardiac pulsation is local displacement of structures (and therefore local mis-registration of diffusion-weighted images), in particular in peri-ventricular regions, which again leads to estimation of the tensor from a set of signal intensities that do not correspond to the same physical location in the brain - again resulting in non-sensical tensor estimates. The second effect of cardiac pulsation is more subtle. The signal attenuation in diffusion-weighted imaging arises due to *incoherent* motion of spins within a voxel. Any distension of the tissue (stretching, shearing) will cause incoherent motion of spins within the voxel, and therefore signal attenuation. The result is therefore additional signal attenuation that will be perceived as extra diffusion parallel to the direction of the applied encoding gradient. This, in turn, will lead to over-estimation of the mean diffusivity, under- or over-estimation of diffusion anisotropy, and biased estimates of fiber orientation (Pierpaoli *et al.* 2003; Jones and Pierpaoli 2005). Nunes and colleagues (1999) have shown that regions superior to the corpus callosum are relatively free of such artefacts, but it is clear that for the remainder of the brain, it is essential to avoid the systolic phase of the cardiac cycle.

Such problems can, and should, be ameliorated by gating the acquisition to the cardiac cycle (either using chest-leads or a peripheral pulse oximeter), ensuring that each diffusion-weighted image for a particular slice location is acquired at the same point in the cardiac cycle (to avoid problems of local-misregistration) and also during the diastolic phase of the cardiac

cycle (Chien *et al.* 1990; Turner *et al.* 1990; Conturo *et al.* 1995; Skare *et al.* 2001; Pierpaoli *et al.* 2003; Jones and Pierpaoli 2005; Nunes *et al.* 2005).

The most common approach is to gate the acquisition of the data to the cardiac cycle using a peripheral pulse oximeter (placed on the finger). Pierpaoli and colleagues have shown that the delay between the onset of the R wave from ECG and the onset of the plethysmographic wave is around 250 ms. The optimal delay from the plethysmographic wave to avoid systole is > 220 ms, (Pierpaoli *et al.* 2003).

**Partial Volume Artefacts:** As with all MR techniques, the information extracted in DT-MRI is quantized on a voxel-by-voxel basis. Hence, the parameters obtained in each voxel represent a *bulk average* of the diffusion properties in the voxel. The larger the voxel – the more media is being averaged. How does this manifest itself in quantification of the three main parameters derived from DT-MRI?

Trace. As stated earlier, the trace is incredibly homogenous throughout parenchyma and hence partial volume contamination of a voxel by two different tissue types, at least in healthy brain, should not represent a problem. However, the trace of the diffusion tensor in CSF is approximately 4 times higher than that in tissue. Thus, at CSF interfaces (which are predominantly gray-matter / CSF interfaces), partial volume contamination by CSF can lead to gross over-estimation of the trace of tissue. Take home message: CSF contamination can lead to over-estimation of the trace. The bigger the voxels – the greater the potential for over-estimation. In comparisons of your data with those from other groups, you should be wary of differences in image resolution.

Anisotropy: The anisotropy of the voxel-averaged diffusion tensor is an indication of the degree to which diffusion is hindered along one particular axis. It should be clear therefore that the more fiber orientations the voxel contains, the lower the anisotropy of the voxel-averaged tensor. The implications for increasing the voxel dimension on anisotropy therefore depend on the underlying microstructural organization. In regions where there is only one dominant fiber orientation, increasing the voxel dimension will only recruit more similarly-oriented fibers, therefore having little effect on anisotropy. However, in regions where there are multiple fiber populations, or a single fiber population that bends, twists, splays etc., increasing the voxel dimension will have the effect of recruiting *different* orientations – with a net result of lowering the anisotropy. This effect will occur if the voxel dimensions are changed in any of the three dimensions. It is therefore desirable that the amount of averaging is the same in all three dimensions – i.e., that the voxels are isometric. This form of anisotropy due to partial voluming occurs predominantly in white matter. A second mechanism for the reduction of anisotropy due to partial volume is inclusion of tissue with lower anisotropy within the voxel. Papadakis *et al.* (2002) and Ma *et al.* (2004) have shown that the anisotropy of the white matter and gray matter, respectively, is reduced by CSF partial volume contamination (the CSF having anisotropy close to zero). Take home message: CSF contamination can lead to under-estimation of the anisotropy. The bigger the voxels – the greater the potential for under-estimation. Second, in regions with non-coherent fiber orientations, bigger voxels lead to ‘powder averaging’ of fiber orientations. In comparisons of your data with those from other groups, you should be wary of differences in image resolution.

Fiber Orientation: Much of the same arguments for anisotropy apply to fiber orientation. For example, powder averaging of fiber orientation. The main problem is that the tensor model only allows for one dominant fiber orientation to be assigned.

**Solutions to the Partial Volume Problem:** An immediately obvious solution to the problem of CSF contamination is to apply an inversion pulse to suppress the signal from the CSF (i.e., FLAIR). Papadakis *et al.* (2002) and Ma *et al.* (2004) have shown elevation of the anisotropy in white and gray matter, respectively, through the use of FLAIR CSF-suppression, and Concha *et al.* (2005) have shown how this can improve tractography results in regions such as the fornix, which pass close to the ventricles. However, the use of cardiac gating (which, as discussed above, is imperative for the majority of the brain) precludes the use of FLAIR (as the effective TR becomes variable, and dependent on the subject's heart rate). An alternative solution is to model the CSF-component (i.e., one 'tissue' tensor compartment and one CSF compartment) (Pierpaoli and Jones 2004; Assaf *et al.* 2005).

Increasing the image resolution and aiming for isotropic voxels will help to ameliorate many of the problems associated with averaging of fiber orientation described above.

**RF Noise:** The effect of RF noise on parameters derived from the eigenvalues of the diffusion tensor have been well-documented by Pierpaoli and Basser (1996). Essentially, the effect of RF noise in the measurement of the tensor is to introduce a bias in the eigenvalues. In isotropic media (e.g., gray matter and CSF), this is rather intuitive – one does not expect to measure three identical eigenvalues due to the effects of noise. The effect of noise in such regions is much more severe than in a region of 'genuine' anisotropy (where there is a genuine difference in the eigenvalues). The main effect is therefore a positive bias in anisotropy – with the effect being most marked in regions of low anisotropy. There is also the issue of the 'sorting bias' – i.e., simplistic anisotropy indices, such as  $\lambda_1/\lambda_3$ , that take the 'largest' eigenvalue and divide it by the 'smallest' eigenvalue (which requires *sorting* the eigenvalues by magnitude) will amplify the effect of the noise-induced eigenvalue repulsion. This led to the development of indices which do not require sorting of the eigenvalues, such as the fractional and relative anisotropies given above. The trace, being the sum of the three eigenvalues, is much less sensitive to noise than indices of anisotropy. The effect of noise on estimates of fiber orientation is obviously to introduce variance in these estimates – which is particularly problematic for fiber-tracking approaches.

**Eddy Currents:** The rapid switching of the large magnetic field gradients used for diffusion encoding will induce eddy currents in the conductive parts of the MR system, resulting in more-or-less gradient strength being used for read-out than expected. Due to the low bandwidth (in the phase-encode direction), EPI-based acquisitions are particularly prone to eddy current artefacts. Residual eddy currents in the x, y and z axes cause, respectively, shear, stretch and displacement of the image along the phase-encode direction. As for patient motion, this results in signals from different regions of tissue being used to estimate the tensor, resulting in non-sensical results. A typical tell-tale sign is a 'rim' of high anisotropy along the phase-encode direction. A number of schemes have been proposed for reduction of eddy current problems including correction at acquisition, and post-processing correction schemes.

Alexander *et al.* (1997), suggested the use of bipolar diffusion-encoding gradients and Papadakis *et al.* (2000) have also suggested applying pre-emphasis to diffusion-encoding gradients as means of ameliorating the problem at the acquisition stage. Post-processing strategies generally aim to warp each DWI to a common template (Haselgrove and Moore, 1996; Bastin 1999). An interesting approach is to use a mutual information criterion to determine a warp that maximizes the overlap within a series of diffusion-weighted images (Poupon *et al.* 1998; Jones *et al.* 1999). Other post-processing methods that have been proposed include correcting the phase map using a model of the effects of the eddy current on

it (Jezzard *et al.* 1998; Bammer *et al.* 2001), and mapping the eddy current induced fields directly (Horsfield 1999; Bastin and Armitage 2000).

**Number of Sampling Orientations:** Although only six DW-images (with gradients applied in non-collinear directions) are required to estimate the diffusion tensor, several studies (e.g., Skare *et al.* 2000; Batchelor *et al.* 2003; Jones 2004) have shown that, if more measurements are obtained, the tensor estimates are improved if more *unique* sampling orientations are used. Results seem to indicate at least 20 unique sampling orientations are needed for the estimate of the tensor to be *statistically rotationally invariant*. However, it is important to realize that there will be clinical applications in which, perhaps, a follow-up scan is required to monitor disease progression or treatment effect. In practice, this means that the structure of interest will be similarly oriented for the two scans. In such cases, it is therefore not essential to acquire 20 images – which, in any case, may require a scan time in excess of the patient’s tolerance.

**Analysis Methods:** There are two main approaches that have been used for quantitative analysis of DT-MRI data. ROI-based approaches (with subsequent statistical testing of mean values from within the ROI), and voxel-based approaches. The former is prone to operator-induced bias and partial volume artefacts. Voxel-based approaches purport to reduce operator induced biases by searching *all* voxels in a data set for significant differences. It is important to realize that a lot of these approaches (e.g. SPM) were developed for PET/ fMRI analysis where either the resolution is typically lower than DT-MRI data, or the heterogeneity of tissue over a localised area is lower than in DT-MRI data. Direct application, therefore, of these techniques introduces a number of problems. In particular, it has been shown that the statistical assumptions underpinning parametric approaches are simply not valid in large regions of the brain (Jones *et al.* 2005). Further, it can be shown that the results obtained are heavily influenced by choice of parameters in the analysis – which can produce a whole spectrum of results from the same data set. Examples will be given in the presentation.

## CONCLUSION

DT-MRI yields quantitative parameters regarding tissue microstructure – but the quality of the data can be affected by a wide range of factors. Therefore, extreme caution is needed when comparing result from different studies/ different centres –

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