Histological and Physiological Features Obtained from Diffusion-Tensor MRI Data

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1. Introduction

It is now well established that the MR measurement of an effective diffusion tensor of water using other imaging modalities. This information includes parameters that help characterize tissue composition, the physical properties of tissue constituents, tissue microstructure and its architectural organization. Moreover, this assessment is obtained non-invasively, without requiring exogenous contrast agents.

Here we examine several well-known useful MR parameters derived from the effective diffusion tensor, such as the Trace as well as familiar measures of diffusion anisotropy and several new parameters and strategies for extracting additional structural and physiological information from diffusion weighted imaging data.

2. Characterizing Diffusion in Biological Systems

In tissues such as brain gray matter, where the measured apparent diffusivity is largely independent of the orientation of the tissue (i.e. isotropic), it is usually sufficient to characterize water diffusion with a single (scalar) apparent diffusion coefficient (ADC). However, in anisotropic media, such as skeletal and cardiac muscle (1) (2), (3) and in white matter (4) (5) (6) no single ADC can characterize the orientation-dependent water mobility in these tissues. The next most complex model that can describe anisotropic (i.e., dependent on the orientation of the tissue) diffusion is one that replaces the scalar ADC with a symmetric effective or apparent diffusion *tensor,* $\underline{D}$ (e.g., see (7)).

While the physical underpinnings of diffusion tensor NMR and MRI have been reviewed elsewhere (most recently in (8)), several new approaches to describing characteristics of anisotropic diffusion in tissues are described below, as well as interesting open research problems and questions relating to characterizing diffusion anisotropy:

3. Quantitative Parameters Obtained by DT-MRI

Quantitative parameters provided by diffusion tensor MRI can be obtained and explained using a geometric approach. Intrinsic quantities that characterize different unique features, for example, that describe the size, shape, orientation or pattern of diffusion ellipsoids within an imaging volume, can be found (9). Scalar parameters, functionally related to the diagonal *and*

off-diagonal elements of the diffusion tensor field, **D(x,y,z),** can also be displayed as an image. These quantities are rotationally invariant, i.e., independent of the orientation of the tissue structures, the patient's body within the MR magnet, the applied diffusion sensitizing gradients, and the choice of the laboratory coordinate system in which the components of the diffusion tensor and magnet field gradients are measured (10; 11). Some examples are given below.

3.1 First Moment of the Diffusion Tensor Field

The first moment of the diffusion tensor field, or the orientationally-averaged value of the diffusion tensor field can be calculated at each point within an imaging volume:

$$<D> = \text{Trace}(\underline{\mathbf{D}}) / 3 = (D_{xx} + D_{yy} + D_{zz}) / 3 = (\lambda_1 + \lambda_2 + \lambda_3) / 3 = <\lambda> \qquad [1]$$

Above, λ_i corresponds to eigenvalue i. Physically, an estimate of <D> can be obtained by taking the arithmetic mean of ADCs acquired uniformly in all directions (12). Integrating overall direction uniformly yields an intrinsic property of the tissue, which is independent of fiber orientation, gradient directions, etc. Recently, terms like "Trace-ADC", "Mean Trace", "Trace Mean", etc. have been used to signify <D>, however these terms are not meaningful. We suggest, as an alternative, the term 'bulk mean diffusivity'.

Several interesting issues about the distribution of Trace(**D**) within tissues remain unresolved. For example, why is Trace(**D**) so uniform within the parenchyma of the normal adult brain. In particular, why is its value so similar in normal white and gray matter (13), even though these tissues are so different histologically? This spatial uniformity has contributed to the clinical utility of Trace(**D**) in disease assessment and monitoring since it often makes diseased regions more conspicuous when juxtaposed against the homogeneous background of normal brain parenchyma. A second reason that makes Trace(**D**) useful is that it appears so similar between and among normal adults. In fact, it appears to be quite similar across a range of normal mammalian brains including mice, rats, cats (14) (15), monkeys (16) and humans (13), (17). An open issue worth considering is whether the extracellular matrix of the mammalian brain is "designed" in a way to ensure Trace(**D**) lies within a narrow range of values, and if so, what is the underlying physiological purpose of this design requirement?

3.2 Measures of Diffusion Anisotropy Using Higher Moments of the Diffusion Tensor Field

The second and higher moments of **D** have been proposed for use as diffusion anisotropy measures because they characterize different ways in which the diffusion tensor field deviates from being isotropic (9). This approach has resulted in a number of diffusion anisotropy measures based upon the second moment of the distribution of the eigenvalues of **D**: $(\lambda_1 - <\lambda>)^2 + (\lambda_2 - <\lambda>)^2 + (\lambda_3 - <\lambda>)^2$, such as the Relative Anisotropy (RA), and the Fractional Anisotropy (FA) (9), which characterize the ratio of the anisotropic and isotropic parts of the diffusion tensor, and the fraction of the diffusion tensor that is anisotropic, respectively. The RA is just the coefficient of variation of the eigenvalues, which has been previously used in crystallography as an "aspherism coefficient" (18). Anisotropy measures based upon the higher moments of the diffusion tensor or the distribution of eigenvalues of **D,** such as the Skewness(λ) or Kurtosis(λ), could potentially be used to characterize diffusion anisotropy more completely, but MR noise make such measures unreliable.

3.3 Other Statistical Measures of Deviation from Isotropy of the Diffusion Tensor Field

Another potential measure of diffusion anisotropy arises from considering isotropic diffusion or specifically measured deviations from it. For isotropic diffusion, $\mathbf{D} = D\,\underline{\mathbf{I}}$ where $\underline{\mathbf{I}}$ is the identity tensor and D is the mean ADC. Then the standard anisotropic diffusion model reduces to (9):

$$A = A_0\, e^{-\underline{b}:D\mathrm{I}} = A_0\, e^{-\mathrm{Trace}(\underline{b})D} \qquad [2]$$

where A_0 is the non-diffusion weighted signal and $\underline{\mathbf{b}}$ is the b-matrix (19; 20) and ":" is the tensor dot product. For N DWI acquisitions, the normalized χ^2 of the isotropic model is

$$\chi^2_{iso} = \sum_{i=1}^{N} \left(\frac{A_i - A_0\, e^{-Trace(b_i)D}}{\sigma_i} \right)^2 \qquad [3]$$

where A_i is the i^{th} measured signal and σ_i^2 is the associated error variance.

The minimum χ^2 for the isotropic diffusion model, χ_{iso}^2, (or features of it, such as its p.d.f. or cumulative probability distribution) could provide a natural set of statistical measures of the degree of anisotropy having the following desirable properties: 1) χ_{iso}^2 is orientationally invariant when the set of gradient directions are sampled isotropically. 2) χ_{iso}^2 is a dimensionless quantity. 3) χ_{iso}^2 explicitly incorporates information about the SNR of the acquisition via a/ making χ_{iso}^2 less sensitive to the acquisition scheme and experimental design. 4) χ_{iso}^2 increases monotonically with the degree of anisotropy. 5) χ_{iso}^2 is a normalized quantity whose value (or whose probability distribution) in each voxel can be meaningfully compared across platforms. 6) The parametric distribution of χ^2 is known *a priori*, so parametric tests can be used to characterize its distribution within a voxel, ROI, or image. 7) Non-parametric tests, such as the bootstrap can also be used to assess the integrity of the DWI acquisitions using an empirically determined χ^2 distribution obtained from the DWI data.

Frank recently proposed the variance of ADCs measured along different isotropically sampled directions as a diffusion anisotropy measure (21). When the diffusion tensor is measured using the single tensor model at low-b values, this represents only a powder average of the underlying component tensors. This always causes the measured diffusion anisotropy to be underestimated. By calculating this variance using high b-value DWIs it appears possible to resolve two or more distinct fiber populations that may occupy a voxel. However, the variance of the ADC about its mean depends explicitly on many more details of the experiment (particularly, the noise level of the DWIs), and its design (e.g., the number of DWIs used, and the choice of gradient strength and directions) than χ_{iso}^2. Also, since Frank's measure is the variance of a diffusion coefficient, it is not dimensionless. The statistics of the variance of the ADC are also not presently known. Finally, this measure was proposed specifically for a DWI acquisition scheme in which the gradient strengths are all uniform. No such constraint on the experimental design applies for the χ_{iso}^2 measure above.

However, it is important to note that any systematic errors in the acquisition of DWIs will increase the minimum χ_{iso}^2 (or Frank's variance measure) making the material appear more anisotropic than it is. For example, distortion of DWIs by eddy currents, misregistration of DWIs by patient motion, or redistribution of signal intensity due to ghosting artifacts all make the set of DWIs more inconsistent, increasing χ_{iso}^2. In each case, the same tissue element no longer corresponds to the same voxel in each DWI, or the signal intensity of a particular element of. tissue

is altered. Moreover, when there are different compartments occupying the same voxel, even two isotropic compartments, such as gray matter and CSF, then the isotropic model may also fail to describe the DWI data, particularly when many different gradient strengths are used. In this case, χ_{iso}^2 will also be larger than if a single compartment were found in the voxel. Thus, a challenge in using a statistical measure of diffusion anisotropy, such as χ_{iso}^2, is to be able distinguish the cause(s) of the departure from isotropy.

3.4 Other Diffusion Anisotropy Measures

Novel anisotropy measures have been proposed that are based on a "barycentric" representation of the diffusion tensor, in which it is decomposed into line-like, plane-like, and sphere-like tensors corresponding to diffusion ellipsoids that are prolate, oblate, and spherical, respectively (22) (23). The information provided by this approach should be compared systematically with the information contained in the first three moments of **D**—the mean, variance, and skewness. One issue that should be examined is the sensitivity of the barycentric representation to the order in which the eigenvalues of **D** are sorted. Whereas the statistical moments of **D** given above are insensitive to the order of the eigenvalues, dependence on their order renders quantities susceptible to a statistical bias caused when these eigenvalues are sorted (16).

4. Characterizing Orientational Properties of the Diffusion Tensor Field

Another important development in DT-MRI is the introduction of quantities that reveal *architectural* features of anisotropic structures, such as nerve fiber tracts in the human brain. Useful information can be gleaned from the *directional pattern* of diffusion ellipsoids within an imaging volume. Early on, it was proposed that in ordered fibrous tissues, the eigenvector associated with the largest eigenvalue within a voxel is parallel to the local fiber orientation (11). Imaging methods that apply this idea include direction field mapping, in which the local fiber direction is displayed as a vector in each voxel, and fiber-tract color mapping, in which a color, assigned to a voxel containing anisotropic tissue, is used to signify the local fiber tract direction (24) (25) (26) (27).

5. Differential Geometry and Algebraic Features of the Diffusion Tensor Field

A less intuitive, but powerful method of motivating and developing quantitative imaging parameters from DT-MRI data is by considering the differential geometry and algebraic properties of the diffusion tensor field itself, whose local features are sampled discretely in a DTMRI experiment. Until recently, this approach was only of academic interest since there was no practical method to obtain a continuous representation of a diffusion tensor field from the noisy, voxel-averaged, discrete diffusion tensor data. However, this situation has changed with the advent of methods to construct such tensor field representations (28) (29) (30). For instance, this approach has led to new applications such as DT-MRI tractography, hyperstreamline and hyperstreamsurface imaging (31), connectivity analysis (32), and should lead to other innovations that were not previously feasible.

For example, in structurally complex anisotropic media, such as the heart, which has a laminar architecture, one can also attempt to describe the deformation (curving, twisting, and bending) of the normal, rectifying, and osculating "sheets" formed by muscle and connective tissue. To do this, we can construct surfaces from the diffusion tensor field, which can be parametrized by two variables. Concepts of the differential geometry of surfaces (33) can then be

used to determine additional geometric features of sheet shape that can be calculated and displayed as intrinsic MRI parameters. These include the First and Second Fundamental Forms, I and II, and the normal, Gaussian, and mean curvatures (33). These parameters are intrinsic because they characterize different features of the local shape of the lamina, independent of the coordinate frame of reference, and constitute new parameters.

6. Complexities in Describing Diffusion in Complex Media Like Tissue

For many of the reasons discussed above, the underlying cause of diffusion anisotropy has not been fully elucidated in brain parenchyma, although most investigators ascribe it to ordered, heterogeneous structures, such as large, oriented, extracellular and intracellular macromolecules, supermacromolecular structures, organelles, and membranes. In the central nervous system (CNS), diffusion anisotropy is not simply caused by myelin in white matter, since several studies have shown that even before myelin is deposited, diffusion anisotropy can be measured using MRI (34) (35-37). Thus, despite the fact that increases in myelin are temporally correlated with increases in diffusion anisotropy, structures other than the myelin sheath must be contributing to diffusion anisotropy (38). This is an important point, because there is a common misconception that the degree of diffusion anisotropy can be used as a quantitative measure or "stain" of myelin content, when, in reality, no such simple relationship exists.

7. Concluding Remarks

DT-MRI provides new means to probe tissue structure at different levels of architectural organization. While experimental diffusion times are associated with water molecule displacements on the order of microns, these molecular motions are ensemble-averaged within a voxel, and then subsequently assembled into multi-slice or 3-D images of tissues and organs. Thus, this imaging modality permits us to study and elucidate complex structural features spanning length scales ranging from the macromolecular to the macroscopic-without the use of exogenous contrast agents. New structural and functional parameters provided by DT-MRI, such as maps of the eigenvalues of the diffusion tensor, its Trace, measures of the degree of diffusion anisotropy and organization and estimates of fiber direction will all help advance our understanding of nerve pathways, fiber continuity, and, potentially, functional connectivity in the CNS.

8. Bibliography

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