Diffusion MRI Theory Methods and Applications

- **Topic**: Anisotropic Diffusion: From the Apparent Diffusion Coefficient to the Apparent Diffusion Tensor
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Contents

Diffusion Anisotropy

- **Anisotropy** means that a property of a material takes on different values when it is measured along different directions.
- Characterizing **diffusion anisotropy** quantitatively can provide information about not only the direction along which these fibers are aligned but also often the organization and properties of its ordered elements.

Diffusion NMR vs. Diffusion Tensor NMR

- **Diffusion NMR** is based on a one-dimensional model of molecular displacements.
- Tanner (1977) proposed the following formula to relate the ADC to the measured NMR signal:

$$\ln\left(\frac{A(b)}{A(b=0)}\right) = -b\mathrm{ADC}$$

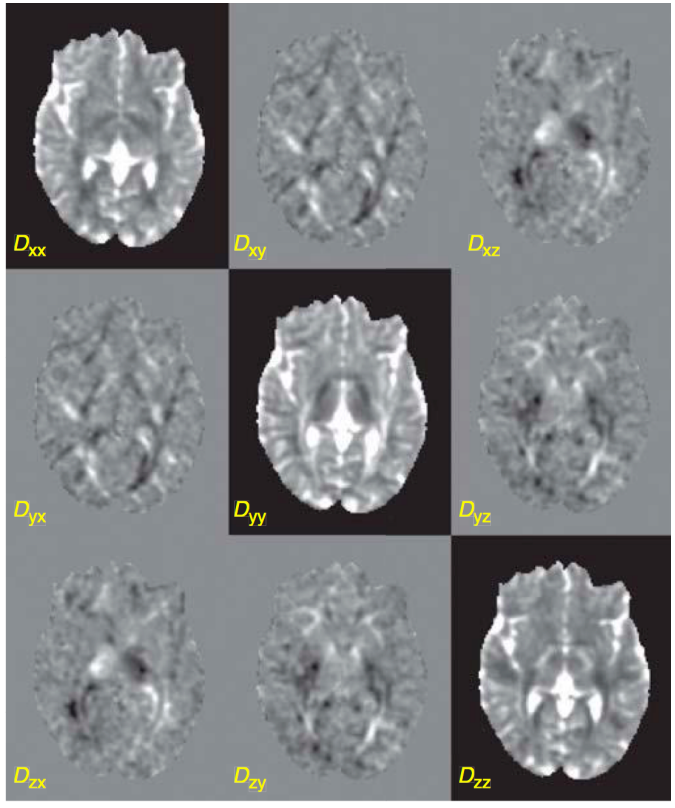
- One-dimensional (1D) Gaussian model is inadequate to characterize the orientation-dependent water mobility.
- In the case of isotropic diffusion, the 3D Gaussian model assumed in diffusion tensor NMR reduces to the 1D Gaussian model assumed in diffusion NMR. Then, $b_{xx} = b_{yy} = b_{zz} = \mathrm{ADC}$, and $b_{xy} = b_{xz} = b_{yz} = 0$.

- **Diffusion tensor NMR** consists of the measurement of D (and functions of it) from a series of diffusion-weighted NMR signals:

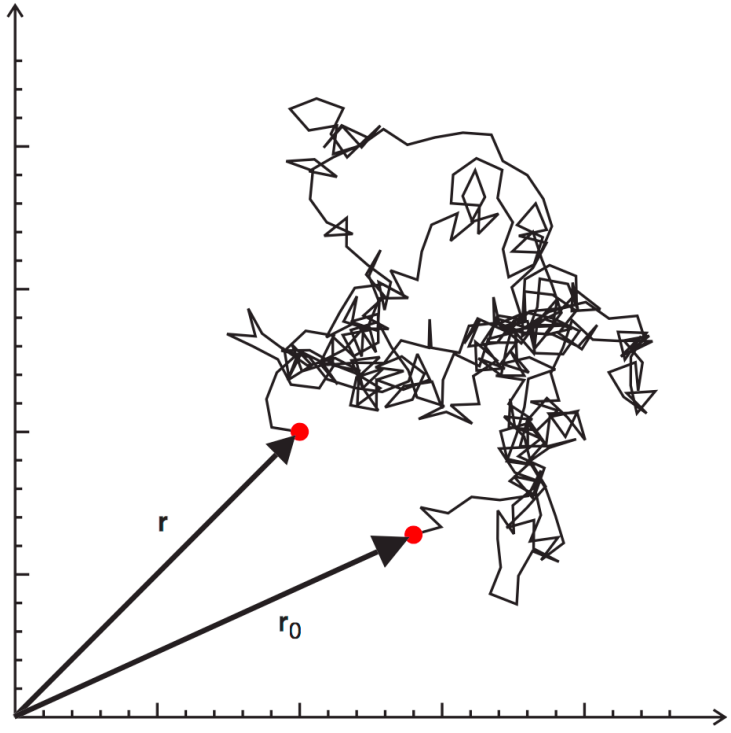
$$\ln\left(\frac{A(b)}{A(b=0)}\right) = -(b_{xx}D_{xx} + 2b_{xy}D_{xy} + 2b_{xz}D_{xz} + b_{yy}D_{yy} + 2b_{yz}D_{yz} + b_{zz}D_{zz})$$

- In diffusion tensor NMR, a symmetric b-matrix is calculated for each DW signal.
- In diffusion tensor NMR, one uses a collection of DW signals and their corresponding b-matrices to estimate D using weighted multivariate linear regression.
- Diffusion gradients along at least six non-collinear, non-coplanar directions must be applied to be able to estimate all six diagonal and off-diagonal elements of D.

- **Figure 6.1** A diffusion tensor image of the human brain.



- **Figure 6.2** The Brownian picture of diffusion.



Geometric Representation of the Translational Apparent Diffusion Tensor in 3D

- In homogeneous (i.e., spatially uniform) anisotropic media, the voxel-averaged displacement distribution is given by:

$$P(R, \Delta|0, 0) = \frac{1}{\sqrt{|D|(4\pi\Delta)^3}} \exp \frac{-R^T D^{-1} R}{4\Delta}$$

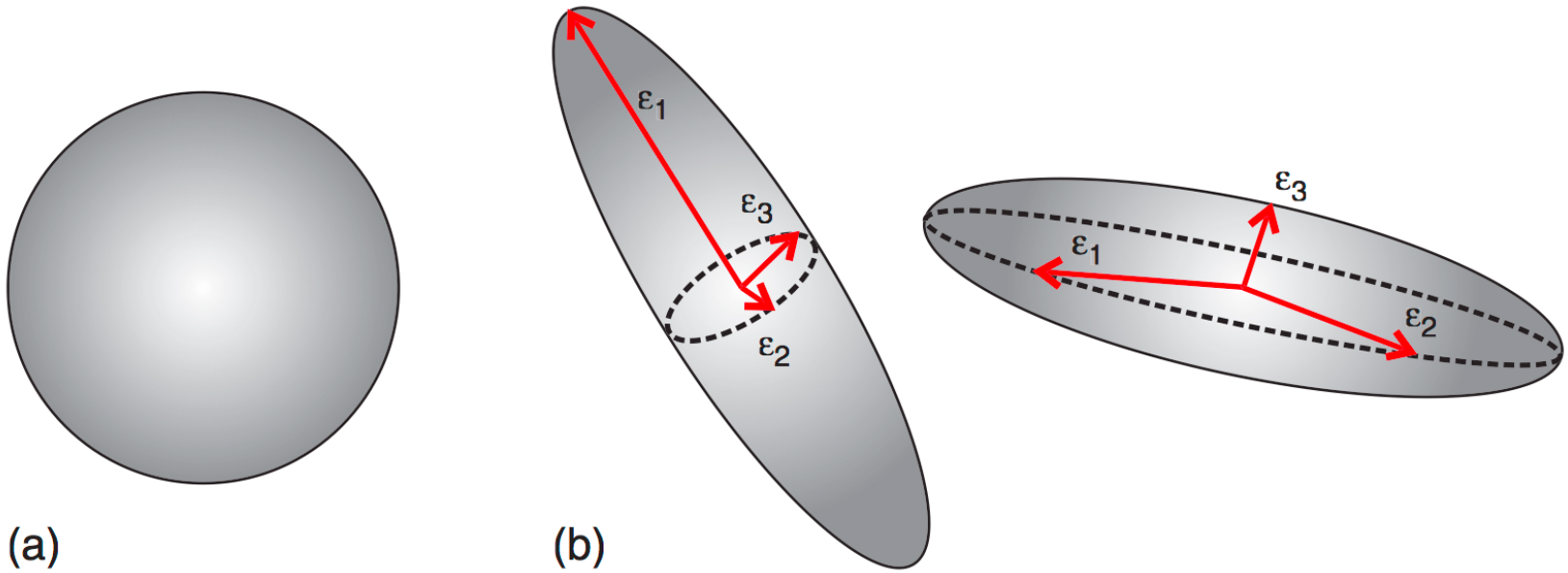
- Surfaces of constant probability or particle concentration can be obtained by setting the exponent in the equation to a constant.
- In order for the above expression to tend to zero for large displacements, all quadratic forms of the diffusion tensor have to be positive, i.e., D has to be a positive definite tensor.

- One can always rotate the laboratory (x-y-z) coordinate axes so that they are aligned with the local principal (x'-y'-z') axes of the **diffusion ellipsoid** in each voxel.
- The diagonal elements of the diffusion tensor are proportional to the second moment of displacements along the three coordinate axes.
- The off-diagonal elements yield the correlation between displacements along orthogonal directions.
- Then the exponent of the displacement distribution takes on a simpler form:

$$\left(\frac{x'}{\sqrt{2\lambda_{x'}\Delta}}\right)^2 + \left(\frac{y'}{\sqrt{2\lambda_{y'}\Delta}}\right)^2 + \left(\frac{z'}{\sqrt{2\lambda_{z'}\Delta}}\right)^2$$

, where λ are the three principal diffusivities (or eigenvalues) corresponding to the three respective principal directions.

- $\epsilon = \sqrt{2\lambda\Delta}$ are the root mean-squared (rms) displacements along these three principal directions at diffusion time, Δ.
- **Figure 6.3** The root mean squared (rms) displacement or diffusion ellipsoid.



Quantitative Parameters Provided by Diffusion Tensor NMR

- Descriptors of the size and shape of the diffusion ellipsoid, should be rotationally invariant.
- Size of the Diffusion Ellipsoid
- Shape of the Diffusion Ellipsoid

Size of the Diffusion Ellipsoid

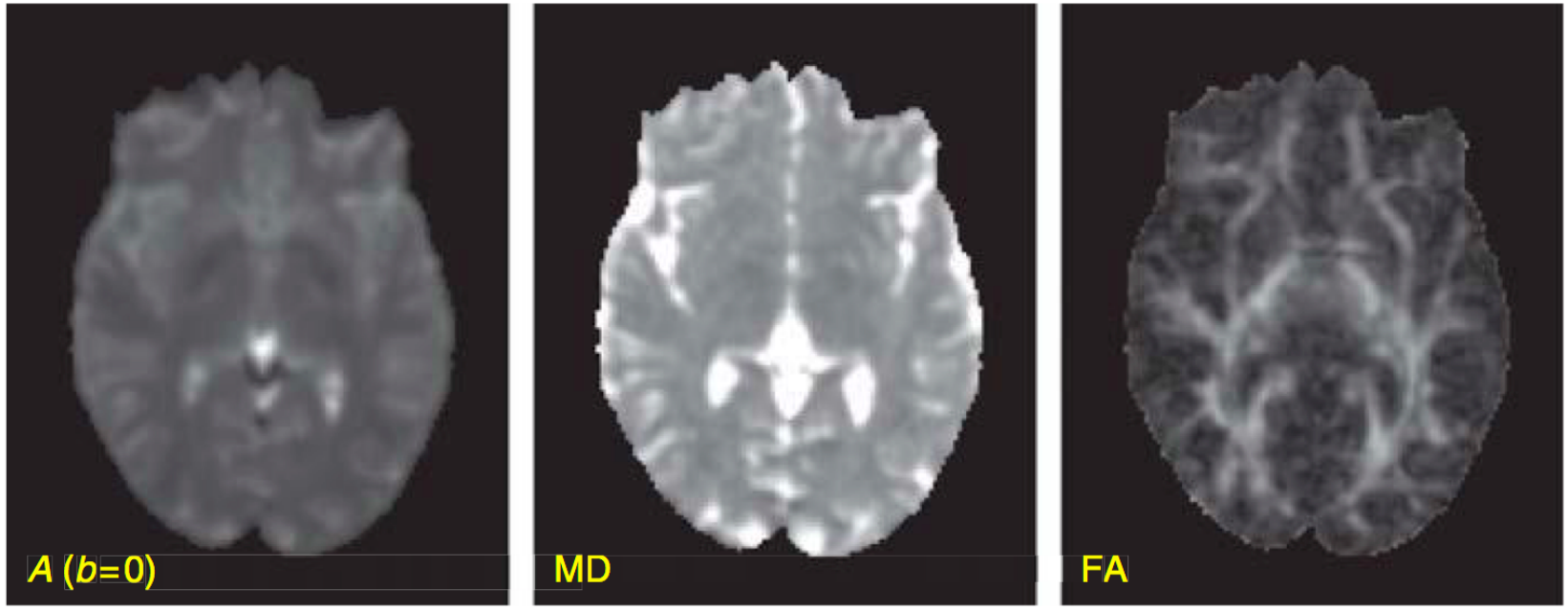
- In an image with no diffusion weighting, the diffusion tensor NMR-derived quantity turns out to be a simple term:

$$\mathbf{Trace}(D) = D_{\mathbf{xx}} + D_{\mathbf{yy}} + D_{\mathbf{zz}} = 3\langle D \rangle = \lambda_1 + \lambda_2 + \lambda_3 = 3\langle \lambda \rangle$$

- $\mathbf{Trace}(D)$ is three times the orientationally averaged diffusivity, $\langle D \rangle$, which can be also be obtained by arithmetically averaging the ADC distribution uniformly over all possible directions.
- $\mathbf{Trace}(D)$ is intrinsic to the tissue; it is independent of fiber orientation, gradient directions, etc.

- Diffusion anisotropy in white matter was considered a confounding factor producing directionally dependent DWI signal intensities, thus complicating their clinical interpretation.
- Displaying $\mathbf{Trace}(D)$ or D instead of an ADC measured along a particular direction eliminates all orientational dependence.
- The success of the Trace or "mean ADC" in stroke assessment may be attributable to:
  - $\mathbf{Trace}(D)$ is fairly uniform in normal brain parenchyma
  - $\mathbf{Trace}(D)$ has virtually the same value in both white and gray matter

- **Figure 6.4** Some orientationally invariant maps obtained from DTI of the human brain.



Shape of the Diffusion Ellipsoid

- The **anisotropic** part of D, or the "**diffusion deviation tensor**," in each voxel, $\mathbb{D}$, is defined as:

$$\mathbb{D} = D - \langle D \rangle \mathbf{I}$$

- $\mathbf{Trace}(\mathbb{D}^2)$, can be shown to be proportional to the sample variance of the eigenvalues or principal diffusivities.
- Several popular diffusion anisotropy measures the degree of "out-of-roundness" of the diffusion ellipsoid:
  - **Fractional anisotropy (FA)**:

$$\mathbf{FA} = \frac{3}{\sqrt{2}} \frac{\sqrt{\mathbf{Var}(\lambda)}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

  - **Relative anisotropy (RA)**:

$$\mathbf{RA} = \frac{\sqrt{\mathbf{Var}(\lambda)}}{\langle D \rangle}$$

- Another useful “shape” parameter is the **third moment** or **skewness** of the eigenvalues $\mathbf{Trace}(\mathbb{D}^3)$.
  - When it is positive, the diffusion ellipsoid is prolate (i.e., cigar shaped).
  - When it is negative, the diffusion ellipsoid is oblate (i.e., pancake-shaped).
- Typically noise in the NMR signal introduces enough bias in the estimates of the eigenvalues to make these higher-order statistics inaccurate.
- Background noise even causes the variance of the eigenvalues to be underestimated and it causes other measures of diffusion anisotropy to be overestimated, owing to a phenomenon called "**eigenvalue repulsion**".

Orientation of Diffusion Ellipsoids and Their Spatial Distribution

- The **b-matrix** summarizes the attenuating effect of all gradient waveforms (i.e., all imaging and diffusion gradient sequences) applied in all three directions, x, y, and z.
- Interactions between imaging and diffusion gradients applied in orthogonal directions, and even between imaging gradients alone applied in orthogonal directions, can introduce additional diffusion weighting.

Exploring Diffusion Tensor Fields and Their Properties

- Some spatial smoothing, for example, using a continuous approximation to the diffusion tensor field (Pajevic et al., 2002) or a regularization scheme (Poupon et al., 1998), must be performed beforehand.

DTI Fiber Tractography

- Several different schemes have been proposed to follow fiber tracts.
- **Deterministic (streamline method)**:
  - Starting from a "**seed point**," fibers are launched in both directions until some stopping or "termination" criteria are satisfied
  - Errors can accumulate during the tract-following process.
- **Probabilistic**:
  - A seed point is assumed to be connected to all points within the imaging volume, but the most probable connections are those that minimize some cost function.
  - We do not know what physical constraints nature uses to construct nerve pathways.

- **Hybrid method:**
  - Uses the streamline method in conjunction with an empirical statistical scheme, bootstrapping (see Pajevic and Basser, 2003), to generate many plausible fiber tract realizations.
  - It generally requires acquiring more DWIs than is necessary for a typical DTI study.
- There are usually a number of thresholds and free parameters that can be set in existing tractography codes whose adjustment can alter one's findings.

Issues in Inferring Tissue Microstructure from the NMR Signal

- The homogeneity of tissue within each voxel cannot be assumed.
- Differences in relaxation parameters can lead to different rates of echo attenuation in each compartment, making it more difficult to explain the cause of signal loss within a voxel.
- Another unknown is whether there is water exchange between compartments.
- Owing to differences in blood flow and thermal conductivity, temperature cannot even be assumed to be uniform throughout a tissue sample.

- At low b-values typical of DTI, most investigators ascribe the underlying cause of diffusion anisotropy to ordered, heterogeneous structures.
- Increases in myelin are temporally correlated with increases in diffusion anisotropy, structures other than the myelin sheath must also be contributing to diffusion anisotropy.
- There is a common misconception that the degree of diffusion anisotropy can be used as a quantitative measure or "stain" of myelin content.
- Putting aside the complexities of obtaining stable estimates of discrete exponentials (i.e., diffusion relaxography), numerous microstructural and architectural configurations could produce the same multiexponential relaxation data.

Limitations of DTI

- In tissue regions where the fiber architecture is complex.
- As q- or b-values are increased, there is evidence that some of the measured diffusion signal arises from water that is trapped within compartments, such as in intra-axonal spaces.
- The Gaussian displacement model does not adequately describe the displacement distribution of spins trapped within pores or closed domains ("restricted diffusion").

Beyond DTI

- Many new methods have been developed to characterize features of the non-Gaussian displacement profile, for example, diffusion spectrum imaging (DSI), high angular resolution diffusion imaging (HARDI), persistent angular structure MRI (PAS-MRI), generalized diffusion tensor MRI (GDTI), q-ball MRI, etc.
- All of these methods must either subsume DTI or reduce to it in the limit of low b (or low q), where the Gaussian diffusion model applies.
- The NMR signal attenuation caused by random displacements projected along the Z direction clearly shows a quadratic dependence on q_z in the small-q limit.

- In the regime in which q is sufficiently small, we can always treat the quadratic decay of $|E(q)|$ vs. q as arising from a Gaussian displacement distribution.
- The likelihood of tissues being misregistered increases as the number of DWIs increases and/or as the b-values increase.
- At high b-values, however, bulk and small-scale motion are difficult to correct, since there are so few landmarks to identify in heavily diffusion-weighted MRIs.
- In this high-b regime, noise becomes increasingly prominent in DWIs.