Outline

Why?
Physics of diffusion
Diffusion weighted imaging
Diffusion tensors
Imaging methodology
Examples
Advanced techniques, breaking the shackles of tensors
Anatomic Imaging

- T2
- T1
- FLAIR

Activation Studies

- Activation gives temporally correlated regions of grey matter
- Connectivity of white-matter

We do not put tracers in humans.
Tracking the Roots of Reading Ability: White Matter Volume and Integrity Correlate with Phonological Awareness in Prereading and Early-Reading Kindergarten Children

Involvement of the right hemisphere in reading comprehension: A DTI study

Fig. 5: TR10 results of significant positive correlated hemispheric-see all in Ref. 10

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Amygdala Functional and Structural Connectivity Predicts Individual Risk Tolerance

Mind-Reading Ability and Structural Connectivity Changes in Aging
graphy to other anisotropic or fibrous soft tissues such as peripheral nerves, the myocardium, ligaments, tendons, and skeletal muscles [12].

The objective of this paper is to provide an introduction to the basics and current advances of MR tractography and to address potential limitations and common pitfalls. Despite the fact that tractography is a relatively novel technique, there have been a few publications that have focused on potential clinical applications and these will also be addressed in this review.

2. Diffusion tensor imaging

In media with anisotropic Gaussian diffusion properties, it has been shown that the displacement front of a diffusing substance can be modeled as an ellipsoid [13]. Hence, each diffusion-weighted measurement reveals, for every voxel during a defined observation interval, the displacement from the origin to a point on the ellipsoid surface along the direction of the diffusion-sensitizing gradient [4]. Acquiring MR data by using various gradient orientations, a set of points has been sampled on the ellipsoid surface to define its size, shape, and orientation to within the limits of sampling error.

The mathematical construct used to characterize anisotropic Gaussian diffusion is a second-order diffusion tensor ($D$). DT-MRI measures the diffusion properties of water along specific directions, which allows one to identify the unknown elements of the tensor for each pixel [3,4]. Since the tensor is symmetric, only six unique elements are required to fully characterize the tensor. A second-rank tensor ($3 	imes 3$ matrix) can be diagonalized, such that only three non-zero elements ($l_1$, $l_2$, and $l_3$) remain along the diagonal. These elements are known as the eigenvalues and are shown in the following matrix factorization:

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

$$
= \begin{bmatrix}
l_1 & 0 & 0 \\
0 & l_2 & 0 \\
0 & 0 & l_3
\end{bmatrix}
$$

The eigenvalues define the diffusion coefficients along the major and minor axes of the diffusion ellipsoid. Here, each eigenvalue is associated with an eigenvector ($v_1$, $v_2$, and $v_3$) [14], where conventionally the largest eigenvalue $l_1$ corresponds to $v_1$. The orientation of these three orthogonal eigenvectors can be expressed in terms of a 3D rotation with respect to the laboratory frame of reference (Fig. 2).

Although diffusion anisotropy exists in unmyelinated nerves (as shown in studies of garfish olfactory nerves [15] and neonates [16]), it is widely assumed that the myelin sheath surrounding nerve fibers acts as the main barrier to water diffusion. Therefore, in DT-MRI tractography it is assumed that the eigenvector associated with the largest eigenvalue is aligned with the direction of the fiber bundle. While this might lead to the assumption that the contrast of diffusion-weighted images is the result of tissue microstructure, it is
Which means 8,000,000 – 1,000,000,000x smaller volume signal.

Physics of Diffusion (Brownian Motion)

Particles (dust, molecules, atom) in liquid/gaseous state randomly move about.

Described by Brown and Einstein


What determines the properties of this random motion?

- Mass
- Size (a.k.a. radius)
- Energy (temperature → velocity)

Stokes-Einstein Equation gives diffusion coefficient $D$

$$D = \frac{kT}{6\pi \eta r}$$

(water versus honey)

Facts about diffusion:
- No net displacement of particles
- But do have mean squared displacement

$$R^2 = 2D\Delta$$

Evolution time $\Delta$
Diffusion Weighted Imaging (DWI)

We need to be able to detect random motion and to image this random motion. However, this random motion is on a microscopic scale compared to imaging resolution.

Concept of Phase
Coherent Phase  
\[ \sum \uparrow = \mathbf{1} \]

Incoherent Phase  
\[ \sum \uparrow = 0 \]

**Equations sidebar**

\[ \omega = \gamma B_0 \]
\[ B(x) = B_0 + Gx \]
\[ \omega(x) = \gamma (B_0 + Gx) \]
\[ \phi(x) = \omega(x) \delta, \ \delta = \text{time} \]
Phase coherence sidebar

\[ S(b) = S_0 e^{-bD} \]

\[ b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3) \]

\[ D = -b \ln(S(b)/S_0) \]

- \(b\) = diffusion weighting
- \(D\) = diffusion coefficient
Phase accrual due to magnetic field gradient, with **no diffusion**.

Phase accrual due to magnetic field gradient, with **diffusion**.
No diffusion and no changing phase

No diffusion, BUT changing phase
Diffusion but NO changing phase

Diffusion AND changing phase
Diffusion (3x, 4x mixing) AND changing phase

Final phase of spins
Diffusion Tensor

\[ S(b) = S_0 e^{-bD} \]

\[ b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3) \]

\[ D = -b \ln(S(b)/S_0) \]

\[ b = "b-value" \]

\[ D = \text{diffusion coefficient} \]

Simple Diffusion Weighted Imaging

\[ S_0 \quad S(b) \quad \text{ADC} \]

\[ b \sim 800 \text{ s/mm}^2 \]

\[ S(b) = S_0 e^{-bD} \]
...but what if there is something that impedes free diffusion?...or even impedes in one direction but not another.

FIGURE 4-6

Magnification of the myelin sheath of another animal. The repeat distance measured at the cytoplasmic surfaces of myelin is 20 Å. The perimeter of a myelin sheath is about 1000 Å. The cell cytoplasm covered by basal lamina (BL) makes up about 20% of the myelin sheath.

FIGURE 4-7

A large portion of the myelin sheath is occupied by the Schwann cell cytoplasm (SC). Two adjacent segments of myelin on one axon are separated by a node of Ranvier. In this region the myelin bilayer is separated from the axon cytoplasm by the Schwann cell cytoplasm (SC). The myelin bilayer is made up of approximately 80% lipid and 20% protein.

FIGURE 4-8

Nodes of Ranvier. The major dense lines (MDLs) are the extensions of the extracellular space. The MDLs are 40 Å in width (measured at the cytoplasmic surfaces); this is one-half of the periodicity of the myelin sheath.

FIGURE 4-9

The loops form membrane complexes with the axolemma called paranodal regions. The loops are situated between the MDLs and the myelin sheath and are called paranodal loops. The loops facilitate ion exchange at the cytoplasmic surfaces. The drawing is not necessarily to scale.

TABLE 4-1

<table>
<thead>
<tr>
<th>Myelin Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelin Basic Protein (MBP)</td>
<td>Concentrated on the cytoplasmic side of the myelin bilayer, making up about 50% of the myelin proteins.</td>
</tr>
<tr>
<td>Proteolipid Protein (PLP)</td>
<td>Making up approximately 30% of the myelin proteins.</td>
</tr>
<tr>
<td>Cyclic Nucleotide Phosphodiesterase (CNP)</td>
<td>Making up approximately 4% of the myelin proteins.</td>
</tr>
</tbody>
</table>

Myelin contains approximately 40% of the weight of myelin (FIG. 1). Myelin appears to have a relatively high-water content (WC). The number of internodes is regulated by axons. When an axon forms a node of Ranvier it is referred to as an internode. Each oligodendrocyte can form multiple myelin internodes with multiple axons, whereas oligodendrocytes appear to have the ability to predict those axons that will attain a large diameter. Each myelin sheath in the central nervous system is separated from the axon cytoplasm by the Schwann cell cytoplasm.
Extracellular space, geometric constraints

→ tortuosity
We must be able to then describe diffusion according to directions.

Simplest is allowing three directions to be independent of each other.

Thus the **diffusion tensor**

(matrix)

\[
D \rightarrow \hat{D} = \begin{pmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{pmatrix}
\]

\[
S(b) = S_0 e^{-bD} \rightarrow S(\hat{b}) = S_0 e^{-\hat{b}\hat{D}}
\]
Imaging

- Must now take diffusion weighted images with magnetic gradients along different directions.
- 7 Unknowns...must make at least 7 measurements.
- Operationally like a time series, but each volume has "diffusion weighting". Very, very sensitive to movement.

Diffusion Tensor - first step away from isotropy
Application of linear algebra

\[
\hat{\lambda} = \begin{pmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{xy} & D_{yy} & D_{yz} \\
D_{xz} & D_{yz} & D_{zz}
\end{pmatrix}
\]

Eigenvalues: \(\lambda_1, \lambda_2, \lambda_3\)

Eigenvectors: \(\epsilon_1, \epsilon_2, \epsilon_3\)

What do these mean?

Eigenvalues give an indication of how freely or bounded the diffusion is.

Eigenvectors inform you of the principal directions.
How can we summarize these highly complex data?

Fractional Anisotropy

\[ FA = \sqrt{\frac{\lambda_1 - \lambda_2}{\lambda_1 + \lambda_2 + \lambda_3}} \]

FA=0, isotropic
FA=1, fully anisotropic

Try:

\[ \lambda_1 = 1, \lambda_2 = 0, \lambda_3 = 0; \lambda = (\lambda_1 + \lambda_2 + \lambda_3)/3 \]

short break
Welcome back questions...?
Diffusion MRI
(we no longer call it diffusion tensor)

Calculate FA

Normalize to MNI

t Tests

as an example
Additionally, the b-matrix was corrected for the rotational information between images using FSL-FLIRT software. ear affine registration by maximizing normalized mutual were also motion and eddy current corrected using a lin-

ormalizing the nonlinear transformation determined on the T1-

College London). Spatial normalization of these maps to

were coregistered to the anatomical T1-weighted images (FMRIB Software Library, The University of Oxford) and 

MD maps were generated using FSL-dtifit software 

can be referred [Sage et al., 2007]. In short, after motion 

-For the new VBA and TBSS analysis, the DW images 

For an extensive description of the preprocessing steps 

An overview of the different steps of the data process-

All patients and controls underwent MR examination on 

Data Acquisition 

Twenty-six healthy age- and sex-matched controls (11 

and were included if there was no history of any other 

in accordance with the Declaration of Helsinki and the study 

neurological and/or vascular disease.

age was 53.7 male, 15 female) were concurrently examined. Their mean 

was approved by the local ethical committee.

A pair of diffusion gradients was applied along 16 non-

covering the entire brain and the brainstem, was acquired. 

182 contiguous coronal slices covering the whole brain 

used resulting in a scan time of 8:58 min. A T1-weighted 

¼ 

112, field of view (FOV) 

256; voxel size 

1.2 mm; matrix size 

0.98 

1.2 mm3; scan 

0.98 

1.2 mm3) was acquired. Three signal averages were 

0 s/mm2) was acquired. Three signal averages were 

4.6 ms; repe-

9.7 ms; slice thickness 

2.2 mm; voxel size 

2.2 mm; matrix size 

112, field of view (FOV) 

256; voxel size 

1.2 mm; matrix size 

0.98 

1.2 mm3; scan 

0.98 

1.2 mm3)

AD

FA

R

L

RD

Chapman MC, Jelsone-Swain L, Johnson TD, Gruis KL, Welsh RC. Diffusion tensor MRI of the 


2013. www.robertcWelsh.com

robert.c.welsh@utah.edu

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ANTS

Schwarz 2014 Neuroimage

FSL Standard Skeleton, FSL

Sage et al 2009

Normalization technique: FSL/TBSS
We can also encode the 1st eigenvector (associated w/ largest eigenvalue) with

- red = L/R
- green = anterior/posterior
- blue = inferior/superior
Tractography

- Tractography
- Non-tensor imaging (q-space, Q-ball, diffusion spectrum, high angular resolution)
- Outstanding issues

Tractography (assuming $r_0$ is on a putative fiber), calculating the direction of the maximum diffusivity ($v_1$), and following that direction for a short distance just as described in the previous paragraph. This is known as Euler's method and is easy to implement but can suffer from large accumulated errors. It is therefore preferable to use other well-known numerical integration methods, such as the fourth-order Runge-Kutta or Adams' method [14, 22] (Fig. 5). These techniques are superior to Euler's method particularly when large step sizes are chosen.

3.1.1. Continuous representation of the vector/tensor field

Due to the MR acquisition process, the diffusion tensor information is only available at discrete points. However, for the aforementioned methods and for the methods which will be discussed below, a continuous representation of the eigenvector/tensor field is required. In other words, $v_1(r)$ and $D(r)$ need to be known everywhere in a continuous 3D domain $\mathbb{R}^3$. This can be accomplished by (linear) interpolation of the vector field or by Lagrange polynomials [20] or by interpolating the tensor field by using B-spline functions [19, 23, 24]. Pajevic et al. [23] also proposed to use a continuous tensor field expressed in terms of B-spline functions that approximates the measured tensor field in a least-squares sense. They termed the former as B-spline interpolation and the latter as B-spline approximation [23, 24]. While interpolation is more sensitive to noise, B-spline approximation is more robust but suffers from slightly diminished spatial resolution (Pajevic, Fig. 3).

From a seed point, the vector field is used as data support for fiber tracking (red trajectory). (b) Space curve representation of a white matter fiber: the local tangent vector, $t(s)$, on the space curve, $r(s)$, is assumed to be equivalent with the eigenvector, $v_1(r(s))$, of the largest eigenvalue of the diffusion tensor $D(r(s))$ at this particular location.

Fig. 4. Principles of tractography: (a) schematics for tracking on a discrete grid. The trajectory follows the indicated direction to the next closest voxel (shaded). The trajectory is limited to branching only to the adjacent eight neighbors and due to the limited angular continuity a strong deviation from the true trajectory is very likely; (b) continuous tracking using the fiber assignment by continuous tracking (FACT) algorithm. The continuous approach follows the fiber tract much more accurately (modified from Mori et al. [17]); (c) flow chart of the fiber tracking algorithm.

Tracula

DTIStudio

DSIStudio  ExploreDTI

BrainSuite
Crossing fibers
Equation [3] can be written in a simpler form by recalling the Hankel transform
\[ f(r, z) \] and the X-ray transform (also known as the planar Radon transform)
\[ \mathcal{X}[f(r, z)] = \int f(r, z) \, dz. \]
We then have
\[ u \propto \mathcal{H}[\mathcal{X}[f(r, z)]] \]
The above relation states that the FRT of the diffusion signal is proportional to the Hankel transform of the X-ray transform of the diffusion function. Note that the X-ray transform evaluated at the origin is equivalent to the radial projection described by Eq. [1]. (It is important to note that the \( \frac{1}{q^2} \) term in Eq. [3] arises from the circle integral and so is equal to unity if the great circle sampling density is independent of the sampling wavevector \( q \).)

To understand Eq. [4] it is helpful to consider the integral in parts. The X-ray transform projects the diffusion function onto \( r \)-plane, which is the tangent plane to the direction of interest \( z \). Evaluating the X-ray transform at the origin \( r = 0 \) would give the radial projection exactly. Instead, the X-ray projection is multiplied by \( J_0 \) through the Hankel transform. The integral over the plane \( dr \) and

FIG. 1. Schematic illustration of the relationship between the Funk–Radon transform and the Bessel beam projection. The \( q \)-space sampling scheme is indicated by the blue spherical lattice. The white arrow gives the direction of interest. The light blue circle indicates the equator around the direction of interest. Integration of the \( q \)-space signal along the equator defines a projection beam, which is shown by the dot pattern. The projection beam (i.e., Bessel beam) falls off in intensity according to the zeroth-order Bessel function. The intensity of the Bessel beam is indicated by the density of the green and yellow dots. The green dots indicate the positive signal contribution and the yellow dots the negative contribution.

FIG. 2. Reconstruction of the diffusion ODF from the diffusion signal using the FRT. The diffusion data are taken from a single voxel from the data set described under Methods. The sampling and reconstruction schemes are also described under Methods. (a) Diffusion signals sampled on fivefold tessellated icosahedron (\( m/252 \)). The signal intensity is indicated by the size and color (white/yellow/red) of the dots on the sphere. (b) Regrid diffusion signals onto equators surrounding fivefold tessellated dodecahedron (\( k/48 \), \( n/36240 \) points). (c) Diffusion ODF calculated using FRT. (d) Color-code spherically polar renderer of ODF. (e) Min–max normalized ODF.

Q-Ball Imaging
1361
68
**Do’s and Don’ts**

Don’t assume that the principal eigenvector of a diffusion tensor is a good indication of the actual fiber orientations in all voxels. Although in fibers, sets of planes parallel to the bundle’s axis do not deviate and all fibers are highly oriented in the voxel, the principal eigenvector may do a good job, it is unsafe to use this simple model throughout the whole brain.

Don’t assume that tractography using a single diffusion tensor will be adequate for all fiber trajectories in the brain. Most fibers cross with others, diverge/converge, twist or kink at some point — and so single tensor-based tracking will result in fiber pathways that are always in error somewhere along their length.

Except in the case of clinically-diagnosed conditions explicitly impacting on white matter, including demyelinating disease, chronic ischemia or tumor infiltration, don’t use the term “white matter integrity.” Use of the term “white matter integrity” is especially discouraged when talking about individual differences in white matter integrity.

Don’t confuse fractional anisotropy with white matter integrity. FA is naturally low in normal white matter areas where fibers cross.

Don’t use the phrase “fiber count” when referring to data derived from diffusion MRI. There are multiple reasons why the number of fibers reconstructed between two regions may differ — some related to real anatomy, others related to performance of the tracking algorithm. “Streamline count” is a preferable term.

Don’t use tractography to provide a quantitative estimate of connection strength. Tractography algorithms largely depend on the coherence information encoded in the DW-MRI signal. To date, no index derived from tractography has been shown to quantify connection strength in an anatomical or physiological context.

Our final quote, in keeping with the title of this manuscript, is “Do continue to use diffusion MRI — it is a fantastic technique for understanding the brain — but don’t over-interprete, mis-interpret and mis-use the terminology!”


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**Microstructure of Temporoparietal White Matter as a Basis for Reading Ability: Distance from Diffusion Tensor Magnetic Resonance Imaging**

**Summary**

Diffusion tensor magnetic resonance imaging (DTI) was used to study the microstructural integrity of white matter in adults with poor or normal reading ability. Subjects with reading difficulty exhibited decreased diffusion anisotropy bilaterally in temporoparietal white matter. ATRM in these regions were

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**Tracking the Roots of Reading Ability: White Matter Volume and Integrity Correlate with Phonological Awareness in Prereading and Early-Reading Kindergarten Children**

Sapir L. Solomon, Elizabeth M. Norton, Beth D. Gerber, Samuel A. Shank, Megan M. Eys, Rebecca Askew, Amanda Scilla, Peter Feith, Matthew Church, and John R. Sabes.

Tracking the roots of reading ability: White matter volume and integrity are related to phonological awareness in prereading and early-reading kindergarten children.


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Artifacts

- Unlike high resolution imaging, very susceptible to shot-to-shot (excitation) error
- VERY susceptible to bulk motion, cardiac pulsatility
- SPIRAL or EPI, but then low-resolution
- Parallel imaging (SENSE), or multi-shot with phase correction

Echo Planar Distortions

Mitigate with multi-shot imaging
  - Difficult to implement and susceptible to motion and requires more time.

Spiral Imaging
  - Speciality

Field map correction
  - Speciality

Field map estimation
  - Speciality (different type)
Two EPI distortion correction implementations

FSL/topup and FSL/applytopup
http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TOPUP

Anima
https://github.com/Inria-Visages/Anima-Public/wiki

FSL/topup and FSL/applytopup
ANIMA

https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/topup
https://github.com/Inria-Visages/Anima-Public/wiki/Registration-tools
Echo Planar Imaging and positive going $k_y$

Echo Planar Imaging and negative going $k_y$
DWI Corrected via distortion correction schemes

Phase Encode Polarity

Up  Down  Corrected

Corrected  Uncorrected
Possible effects of artifacts
Ambiguity of $b$-values

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

- $\Delta = 25 \text{ ms}, \delta = 17 \text{ ms}, g = 50 \text{ mT/m}$
- $\Delta = 65 \text{ ms}, \delta = 9.5 \text{ ms}, g = 50 \text{ mT/m}$
- $\Delta = 65 \text{ ms}, \delta = 1.6 \text{ ms}, g = 300 \text{ mT/m}$

\[ b = 1000 \text{ s/mm}^2 \]
\[ \Delta = 55.0 \text{ ms}, \delta = 13.13 \text{ ms}, g = 40 \text{ mT/m} \]

\[ \Delta = 10.0 \text{ ms}, \delta = 9.54 \text{ ms}, g = 150 \text{ mT/m} \]

\[ b = (y \delta g)^2 (\Delta - \delta/3) \]
Various useful references.


Various diffusion packages

- [Diffusion Imaging tools](https://github.com/Doria-Visages/Anima-Public/wiki/Diffusion-imaging-tools)
- [http://www.mrtrix.org](http://www.mrtrix.org)
- [http://www.brainsuite.org](http://www.brainsuite.org)
- [http://cmrm.med.jhmi.edu](http://cmrm.med.jhmi.edu)
- [http://www.exploredti.com](http://www.exploredti.com)
- [https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide](https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide)
- [https://surfer.nmr.mgh.harvard.edu/fswiki/Tracula](https://surfer.nmr.mgh.harvard.edu/fswiki/Tracula)
- [http://camino.cs.ucl.ac.uk](http://camino.cs.ucl.ac.uk)
Conclusion

- Exploitation of water diffusion leads to mapping of white matter
- DMRI along with variety of mathematical techniques becoming very accessible
- Leads to a better understanding of underlying neuroanatomy
- Application to fundamental neuroscience as well as clinical science/practice.