Speciality area: Diffusion-weighted MRI (Imaging Microstructure)

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Highlights:

- Diffusion MRI (DW-MRI) uses information derived from the dispersion of water molecules over the course of a few miliseconds, to obtain indirect insights into tissue macro- and microstructure. This is possible because diffusion measures change according to the direction in which they are measured.

- Scientists employ many different biophysical models to relate the diffusion signal to tissue microstructure. The most simple formulations are the **apparent diffusion coefficient (ADC)**, which measures the rate of diffusion in tissue, and the **diffusion tensor** (used in **DTI**), which characterises the 3D diffusion process by describing the average amount *and* direction of diffusion in each image voxel.

- Simple DW-MRI acquisition sequences and models such as DTI are insufficient for characterising diffusion in complex microarchitecture leading to unreliable quantitative measures.

- New techniques have been developed which aim to overcome some of these limitations. These methods are predominantly used in the context of preclinical research, and the most useful integrate information from other modalities.

Diffusion basics

Target Audience: Clinicians and scientists who are familiar with the basic princples of MRI and who may be new to the field of diffusion MRI.

Outcomes: Following this presentation, the audience will understand:

- how MRI measurements can be sensitised to diffusion using a basic pulsed gradient spin echo (PGSE) sequence and what physical processes underlie this.
- why diffusion MRI is a useful (but indirect) probe of tissue microstructure in vivo, including the basic relationships between diffusion measurement scales and microanatomy, as well as technical challenges.
- why such challenges and limitations can sometimes make it difficult to ascribe biological meaning to changes in the measured and modelled diffusion signal.
- that new techniques are available which aim to address some of the limitations of more simple acquisition schemes and models.

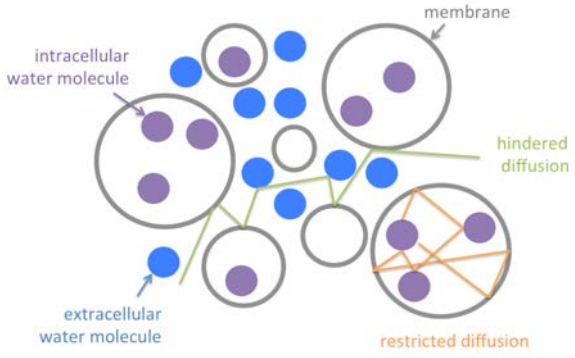
Purpose: To provide a basic overview of diffusion MRI to people seeking a non-technical introduction, and to help them apply the method appropriately in their clinical and/or scientific practice.

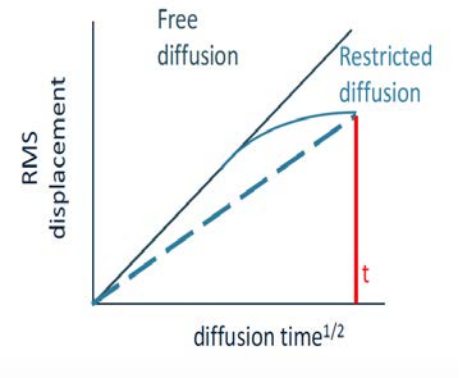
Theoretical Background

What is diffusion?

Diffusion MRI is primarily concerned with the inherent mobility of water molecules (**Brownian motion**) in tissue. In a liquid, each individual water molecule moves away from its starting position in a random fashion due to collisions with neighbouring molecules. Einstein's equation tells us this **"random walk"** will take each molecule further and further away from its starting position over time, i.e. its root mean squared molecular displacement will increase with time (eg . $r.m.s = \sqrt{6Dt}$, where D is the diffusion coefficient).

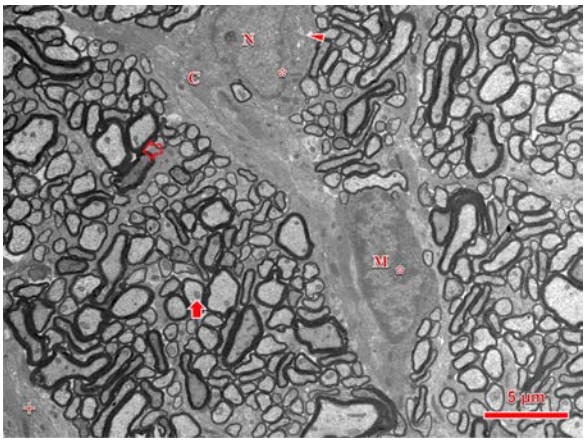
This scenario assumes that the water molecules are free to move in any direction i.e **free diffusion**. Whilst this may be the case in a glass of water, it is never the case in biological tissue because microarchitectural features such as cell membranes and organelles **hinder** and **restrict** the mobility of water molecules. Einstein's equation is thus based on an invalid assumption, and the diffusion coefficient estimated from the MRI signal changes according to how long the molecules are allowed to diffuse. For this reason, the diffusion coefficient derived from the MRI measurement is underestimated. To account for this, it is termed the **"Apparent Diffusion Coefficient (ADC)".**





Diffusion and microstructure

The relationship between MRI based diffusion measurements and microstructure is complex. During the time frame of the diffusion weighting (**ms**), molecules will be influenced by microscopic structures in a limited **µm** range. However, diffusion will be influenced by many factors, including local **temperature**, **viscosity**, **membrane permeability** and **microgeometry**. Most significantly, the contributions of all these properties are **averaged** over a (typical) voxel size of 1-2mm^3. This makes basic DW-MRI **non-specific** with respect to individual microstructural features.

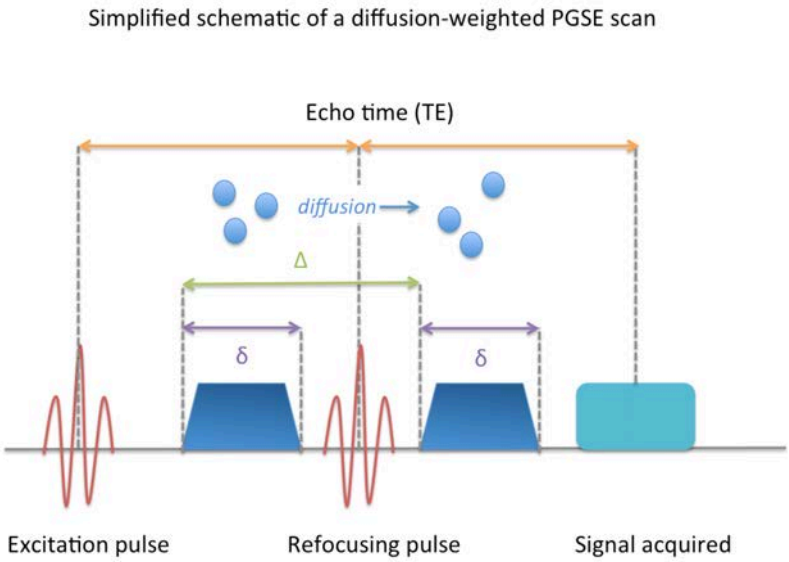


Electron micrograph of a cross-section of excised rat optic nerve illustrating some microstructural elements that influence diffusion measurements (Rowe et al, 2015)

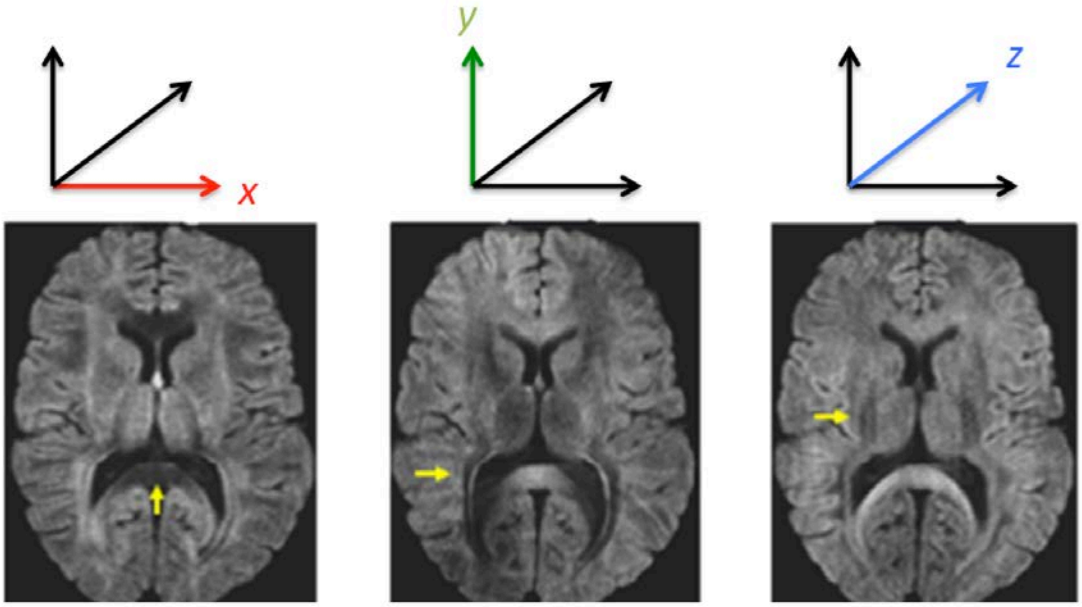
Measuring diffusion with MRI

It is possible to sensitise MRI sequences to these diffusion processes. Perhaps counterintuitively, what we actually measure is the amount of **signal loss** ($Signal = S_0 e^{-bD}$). In this equation, b is a function of the applied gradient strength (G), duration (δ) and separation (Δ) according to the **Stejskal-Tanner** formulation in the context of a basic **pulsed-gradient spin echo sequence:** $b = (\gamma G \delta)^2 (\Delta - \frac{\delta}{3})$.

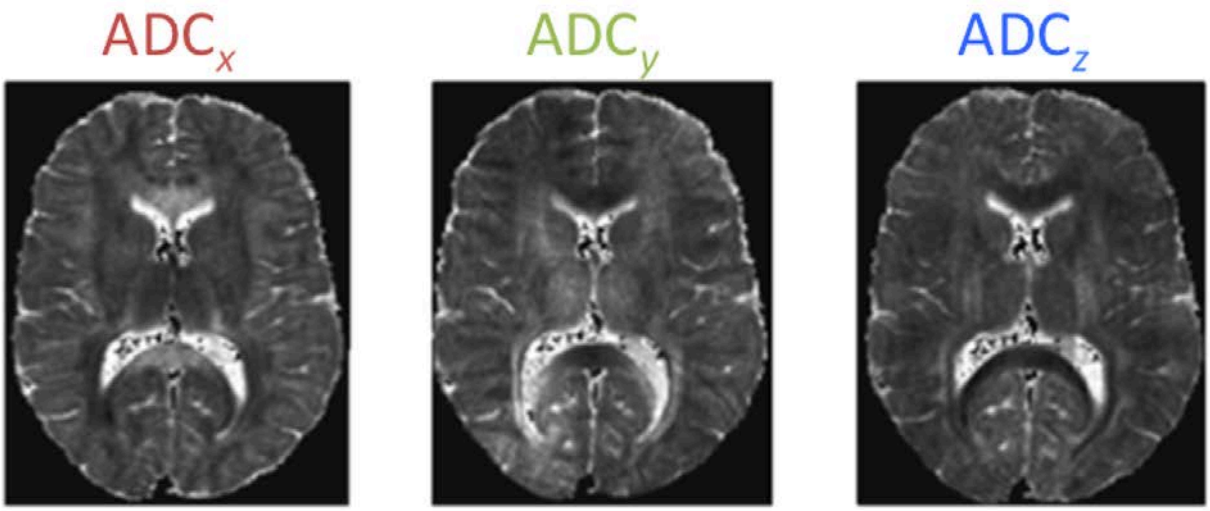
In a PGSE sequence, equal diffusion weighting gradients are applied either side of a 180 degree pulse. However, because water molecules move in the time between the gradients, then refocusing will be incomplete and this will manifest as a loss of signal.



For example, in regions where the **rate of diffusion is high**, then there will be **less signal** and the image will **appear dark**. Conversely, where the rate of diffusion is lower, the image will appear brighter.



We know that ADC depends on the ability of water molecules to diffuse in a given direction. If they encounter an obstacle e.g. cell membrane, this interaction will give rise to a different amount of signal loss than in the case where the molecules diffuse more freely. This produces image contrast that is **directionally dependent**, i.e. the contrast changes depending on the orientation of the tissue relative to the applied diffusion-weighting gradient.



Diffusion tensor imaging (DTI)

The ADC is a first step towards the quantification of diffusion, however, it is limited to two dimensions. In order to characterise diffusion in 3D, a more advanced model is required. The **diffusion tensor** model is the simplest way to do this. The tensor can be diagonalised so that the **eigenvalues** (λ_1, λ_2, λ_3) give the **amount** of diffusion and the **eigenvectors** (ε_1, ε_2, ε_3) give the **direction** of diffusion (relative to the magnet coordinates).

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

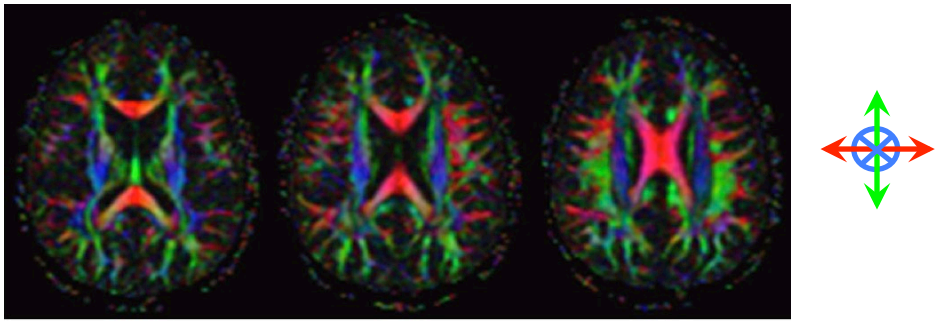
$$\mathbf{D} = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \end{pmatrix}$$

highest

lowest

Many different quantitative parameters can be derived from the diffusion tensor. The most common are the **trace, the total ADC and Mean Diffusivity (MD)**, which quantify the amount of diffusion in a voxel. The **fractional anisotropy (FA)** describes the amount of non-isotropic diffusion and reflects the preferred direction of diffusion averaged across a voxel. In the brain, this could be due to the orientation of axons, where diffusion occurs fastest parallel to axons.

The combination of quantative and directional information can be visualised using directionally-encoded colour maps. Convention dictates that in such images, red represents diffusion occuring left-right, blue, superior-inferior and green, anterior-posterior. For example, in the figure below, the interhemispheric fibres of the corpus callosum are coloured red.



Challenges and limitations

In practice there are a multitude of technical and practical challenges that make DW-MRI particularly difficult to implement and which confound biologically based interpretations. Some examples are summarized below:

- Diffusion-weighted images are typically very noisy and prone to artifacts which lead to inaccurate estimation of quantitative measures in affected regions

- DW-MRI measurements are performed at a different length-scale (mm) than the tissue features they aim to probe (μm), which means the contributions of many microstructural elements are averaged over the voxel.

- Simple models like the diffusion tensor are insufficient for characterizing complex architecture. For example, where there is more than one dominant diffusion direction in a voxel (which is very common in brain tissue).

It is therefore important to understand that although microstructure indisputably influences diffusion MRI measures, quantitative parameters derived from DW-MRI models remain indirect and are only as reliable as the data and models used to calculate them. This is particularly important when using DW-MRI to draw conclusions about tissue ‘integrity’ or when performing analysis techniques derived from diffusion data, such as tractography or connectivity profiling.

Conclusion

When used appropriately, DW-MRI is one of the most useful techniques for investigating tissue microstructure in vivo. Basic DW-MRI is used widely in clinical practice in the evaluation of stroke, and in some centres, DTI has been incorporated into surgical planning routines. DTI and its more recently developed counterparts have been applied widely in neuroscience and preclinical brain research, and are now successfully extending into other non-brain domains. Continued optimization of acquisition and modeling should lead to wider application of DW-MRI in the future.

Additional recommended reading:

Diffusion theory:

E. O. Stejskal, J. E. Tanner, Spin diffusion measurements: spin echoes in the presence of time-dependent field gradient. J. Chem. Phys. 42, 288 (1965).

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