Diffusion Imaging

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Diffusion refers to the random thermally-driven random-walk motion of molecules (in this case water). Over a timescale of ~50ms, water molecules in living tissue will typically travel distances of ~1-10µm, which is comparable to the scale of cellular structures. The distances travelled by diffusing water molecules are strongly influenced by their local environment, in particular by obstacles such as cell membranes. Diffusion can therefore be used to probe tissue microstructure on a scale comparable with cellular structures. This is of particular interest for brain white matter, which consists primarily of densely packed neuronal axons. In this environment, the strongly oriented arrangements of membranes and myelin sheaths causes water molecules to diffuse preferentially along the orientation of the fibres, rather than across them (see [1] for a review). This orientational bias in the diffusion of water molecules can be used to infer the orientation of white matter fibres locally. These orientations can then in turn be used to delineate white matter tracts in the brain by following the estimated white matter orientation from a given seed point using so-called fibre-tracking or tractography methods (see review in [2]). Diffusion imaging therefore provides a means to study brain white matter and its connectivity, and is unique in allowing such investigations to be carried out non-invasively in-vivo.

TOPICS COVERED:

- **Diffusion-weighted MRI**

  MRI can be made sensitive to the microscopic displacements of water molecules using suitably arranged diffusion-weighting (DW) gradient pulses, the simplest of which consists of a pair of gradient pulses of opposite polarity. The first gradient pulse imparts a position-dependent phase shift to the spins; these are then left to diffuse for a fixed diffusion time; the second gradient pulse imparts the opposite phase shift to the spins. Spins that have moved between the two gradient pulses will have a net residual phase shift. Over the scale of an imaging voxel, these phase shifts will be randomly distributed, leading to signal loss [3].

- **The apparent diffusion coefficient (ADC)**

  The simplest model of diffusion is the Einstein equation: $\langle x^2 \rangle = 6D\tau$. However, the Einstein equation is only strictly valid for free, isotropic diffusion. In tissue, barriers to diffusion make the measured diffusion coefficient dependent on the diffusion time τ. For this reason, the term *apparent* diffusion coefficient (ADC) is used.

- **The diffusion tensor model**

  The diffusion tensor model [4] was proposed to model the anisotropic (direction-dependent) diffusion of water in white matter. This model assumes that the probability density function (PDF) of spin displacements is a 3-dimensional Gaussian distribution, characterised by a 3×3 symmetric tensor, and often represented as an ellipsoid (see figure 1). In coherently oriented white matter, the fibre orientation will coincide with the major axis of this diffusion ellipsoid (the major eigenvector of the diffusion tensor).

- **Diffusion anisotropy**

  Anisotropy refers to the deviation of the diffusion tensor from the isotropic spherical case. Several indices have been proposed to quantify anisotropy, of which the most common is fractional anisotropy (FA) [5]. White matter typically has high anisotropy due to the high degree of structural coherence associated with the regular arrangement of axonal fibres. On the other hand, grey matter has low anisotropy due to the 'random' arrangement of its microstructure on the voxel scale. Anisotropy has been shown to be affected by factors such as demyelination and axonal membrane degradation [1], and is for this reason often interpreted as a marker of white matter 'integrity'. However, tensor-based measures of anisotropy are also extremely sensitive to a number of other factors that make robust interpretation of anisotropy observations difficult.

- **Tractography / fibre-tracking**

  Tractography algorithms attempt to delineate the path of white matter pathways based on voxel-wise estimates of fibre orientations. Starting from a user-specified 'seed point', these typically work by stepping along the estimated direction of the white matter fibres by a small fixed distance until some termination criterion is reached (e.g. low anisotropy). Tractography can hence be used to study the large-scale connectivity of the brain.

- **The crossing fibre problem**

  The diffusion tensor model implicitly assumes each voxel contains a single coherent bundle of fibres. It is now becoming clear that this assumption is frequently violated (crossing fibres can be detected in up to 90% of white matter [6]). In such voxels, the estimated diffusion tensor will be 'averaged' over the different fibre populations, leading to a reduction in anisotropy and a bias in the estimated fibre orientations (which no longer correspond to any of the fibre orientations present) [7]. The effect on tractography is profound, since an incorrect orientation estimate at any one point along a track may cause the algorithm to deviate into an adjacent pathway and establish connections to completely unrelated regions of the brain.

- **Higher order models**

  A number of approaches have been proposed to estimate fibre orientations in crossing fibre voxels [e.g. 8-14], and to perform tractography in a much more robust way based on the fibre orientations provided by them [e.g. 15-19]. Yet other higher-order models have been proposed to extract microstructural information, such as axonal radii [e.g. 20,21] or the presence of non-Gaussian diffusion [e.g. 22]. While these models typically require longer acquisition times (i.e. more DW directions and/or more *b*-values), they can potentially provide much more specific and robust information than the diffusion tensor model alone.

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