Imaging microstructure: Diffusion Modelling

Speaker

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Highlights

- Diffusion MRI has the capacity to provide non-invasive quantification of metrics that relate directly to brain function, but it requires models more specific than diffusion tensor imaging.
- Biophysical models of diffusion MRI describe the diffusion in tissue components, such as the intra-axonal or extracellular space, in term of volume fractions, compartment sizes, bulk diffusivities and orientation dispersion.
- An index of the average axon diameter can be estimated from diffusion MRI data, but only above the so-called resolution limit, which is dependent on the acquisition protocol.
- Orientation dispersion is an essential to include in white matter diffusion models.

Target audience

Scientists interested in modelling of diffusion in tissue and its impact on the MR signal

Outcomes/objectives

This lecture aims to outline the models used in diffusion MRI and to providing an overview of

- the diffusion tensor as a versatile model building block
- the components required to successfully model diffusion in white matter
- how axonal diameter estimated from diffusion MRI can be interpreted
- the role of axonal orientation dispersion in white matter diffusion models
- how to compare diffusion MRI models

Purpose

The diffusion tensor imaging (DTI) model is widely used in neuroimaging to provide parameters on brain microstructure that can, for example, be correlated with variations in brain function (Kennedy and Raz, 2009). DTI has also been used extensively to study the impact of neurodegenerative and mental disorders on brain microstructure (Assaf, 2008; Kubicki et al., 2007). Such studies typically find that elevated fractional anisotropy (FA) is "good" in terms of better performance, and reduced FA is "bad" and associated to neurodegeneration. However, findings in disagreement with this notion are common and include, for example, elevated FA in Alzheimer's disease (Douaud et al., 2011), or low FA in fast-reacting subjects (Tuch et al., 2005). Diffusion MRI may be capable of providing non-invasive quantification of metrics that relate directly to brain function, but it requires models more specific than DTI.

Approach [methods and results]

In this context, we refer to a model as a set of equations relating a set of model parameters to diffusion-weighted MR signal intensity for a number of experiments (dMRI data in short), given parameters on how the diffusion sensitisations were performed, for example, b-values, amplitudes and directions of the magnetic field gradients, and diffusion times (Nilsson, 2011). Example of model parameters are the axon density, axon diameter, mean and variance of the axon diameter distribution, or the extracellular diffusion tensor. Given a model, we can infer from the dMRI data what values of the model parameters that best describe the data, i.e., fit the model to the data (assuming some distribution for the noise).

The basic building block of most models employed for modelling dMRI data is the diffusion tensor (Basser et al., 1994), but instead of modelling a whole voxel with a single diffusion tensor, individual diffusion tensors are assigned to each relevant ensemble of water molecules within the voxel. Examples of such ensembles are water molecules in the extracellular space, intra-axonal space, or the cerebrospinal fluid (CSF). Assuming negligible exchange between the components, the model is simply the superposition (i.e. summation) of the dMRI signals from each component. The CSF component is modelled by a spherical tensor. Extra-cellular diffusion is often modelled by a cylinder-symmetric tensor assuming Gaussian diffusion (Assaf et al., 2004), however, the influence of the diffusion time on the effective extracellular diffusion tensor can also be considered (Novikov et al., 2014; Xu et al., 2014). Intra-axonal diffusion is commonly modelled by a cylinder-symmetric diffusion tensor where the radial diffusivity depends on the timing of the diffusion-encoding gradients (Alexander et al., 2010; Assaf et al., 2004). In the axial direction, along the fibres, where the diffusion is not restricted, the diffusivity can be represented by a single value, which is often assumed to be equal in the intra-axonal and extracellular environments.

The simplest models of diffusion in white matter are composed of two tensors, representing extracellular and intra-axonal diffusion, respectively. The radial diffusivity of the intra-axonal space is described by a radius, and a bulk diffusion coefficient that may or may be a free model parameter. Examples of such models are the CHARMED model (Assaf et al., 2004), although similar but slightly more complex models has been used in other studies (Alexander et al., 2010). The AxCaliber model extends the CHARMED model by modelling intra-voxel variation in axon diameters by the Gamma distribution, parameterised by two parameters related to the mean and variance of axon diameters (Assaf et al., 2008). When interpreting axon diameter estimates from such models, three aspects should be kept in mind. (i) In case the model incorporates a single axon diameter only, the parameter represents the volume-weighted axon diameter rather than the number average (Alexander et al., 2010). (ii) Estimating small axon diameters are intrinsically difficult due to low values of the radial diffusivity of the intra-axonal component for small diameters. At a certain diameter, which we refer to as the resolution limit, the radial diffusivity of the intra-axonal component becomes inseparable from zero (Nilsson and Alexander, 2012; Nilsson et al., 2013). The experimental protocol can be optimized to minimize the resolution limit (Alexander, 2008), but ultimately it is limited by the MRI hardware, specifically the maximal gradient amplitude and slew rate. At present, the resolution limit of conventional MRI scanners is higher than the average axon diameters in most structures of the brain (Aboitiz et al., 1992; Dyrby et al., 2012; Liewald et al., 2014). Improved models and the use of oscillating gradients may help reduce the resolution limit (Xu et al., 2014). (iii) We infer the diameter from the variance of the diffusional displacements of water molecules, and thus the diameter will refer to the maximal distance between the restricting barriers, to a first approximation (Nilsson et al., 2012). For cylinders, this distance agrees with the cylinder diameter, but axons do not run in straight paths (Nilsson et al., 2012; Ronen et al., 2013). A positive bias in the axon diameter may thus be expected when comparing results from dMRI with, for example, 2D-histology.

Models for diffusion MRI can also be constructed to capture the within-voxel variation of diffusion tensors rather than the time dependence of the intra-axonal component. Consider a voxel subdivided into regions wherein the diffusion is Gaussian and thus properly described by a diffusion tensor. In this case, DTI simply yields the average diffusion tensor. Higher-order tensors extends DTI, and is employed, for example, in diffusional kurtosis imaging (DKI) (Jensen et al., 2005). The DKI model is related to diffusion tensor variance, however, in order to fully capture the diffusion-tensor covariance, b-tensors of rank 2 or higher must be employed using, for example, q-space trajectory imaging (QTI) to acquire the data (Westin et al., 2014). Models such as DTI, DKI and QTI make no assumptions regarding the shape of the underlying diffusion tensor distribution or how it is affected by the timing of the experiment, but only characterize its moments. Alternatively, the diffusion tensor distribution

can be modelled in terms of known components. This adds prior information that tend to increase the explanatory power of a model.

Orientation distribution of intra-axonal components has a large impact on the diffusion tensor distribution. White matter is, in fact, not composed of parallel cylinders. Instead, there is a large within-voxel orientation dispersion, not only in regions of crossing fibres (Jeurissen et al., 2012), but also in the corpus callosum (Choe et al., 2012; Ronen et al., 2013). Orientation dispersion of axons (or "neurites") is in the NODDI captured by the Watson distribution (Zhang et al., 2012). In order to avoid overparametrisation, the effective axonal diameter is set to zero under the assumption that the true axon diameter is below the resolution limit. The NODDI model also incorporates a spherical diffusion tensor with high diffusivity that represent cerebrospinal fluid (CSF), to account for partial volume effects and "free water" that exists in many parts of the brain (Pasternak et al., 2009). Since the diffusivity of CSF is very similar to that of free water and thus known a priori, it is sufficient to extend the models with the signal fraction of CSF, i.e., a single parameter. By performing powder averaging of the signal across diffusion encoding directions, the NODDI model can be simplified even further (Lampinen et al., ISMRM 2015).

Discussion

Models of the dMRI signal can be varied indefinitely. Some try to describe the data with few parameters, e.g. the CHARMED model. Others require more parameters, but may fit better to the data, e.g. the AxCaliber model. Still others include parameters which cannot be estimated reliably, e.g., where the axon diameter estimate is not reliably higher than zero. In order to assess the value of a model, it has to be compared to other models in terms of how much of the variation in the data that it capture per model parameter. Adding another model parameter without obtaining a significantly better fit to the data leads to over fitting and reduce the trustworthiness of the fitted model parameters. Several tools have been employed for model comparisons in the context of diffusion MRI modelling, for example, the F-test or Bayesian Information Criterion (Nilsson and Alexander, 2012; Panagiotaki et al., 2012). Studies comparing a multitude of models have concluded that at least three components are typically required to describe white matter diffusion (Ferizi et al., 2013; Panagiotaki et al., 2012).

Conclusions

Biophysical models of the diffusion MRI signal hold the promise to allow estimation of specific parameters from dMRI, while retaining the sensitivity of DTI. Metrics related to axon density and axonal orientation dispersion can be reliably estimated from dMRI data, while the axon diameter and its distribution are more challenging to estimate, although recent advancements in modelling and hardware design are promising (Huang et al., 2015; Xu et al., 2014). Apart from applications in white matter, these models also have applications in, for example, oncology (Panagiotaki et al, 2014). The diffusion MRI community is on the verge of enabling non-invasive quantification of metrics that relate to specific aspects of brain microstructure, but the work to understand how such measures relates to brain function and performance has only begun (Pajevic et al., 2014; Zatorre et al., 2012).

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