NeuroImage 111 (2015) 85–99

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Full Length Articles

Exploring the 3D geometry of the diffusion kurtosis tensor—Impact on the development of robust tractography procedures and novel biomarkers

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ARTICLE INFO

Article history:
Accepted 2 February 2015
Available online 9 February 2015

Keywords:
Diffusion kurtosis imaging
DKI
Tractography
Crossing fibres
Multi-compartmental models

ABSTRACT

Diffusion kurtosis imaging (DKI) is a diffusion-weighted technique which overcomes limitations of the commonly used diffusion tensor imaging approach. This technique models non-Gaussian behaviour of water diffusion by the diffusion kurtosis tensor (KT), which can be used to provide indices of tissue heterogeneity and a better characterisation of the spatial architecture of tissue microstructure. In this study, the geometry of the KT is elucidated using synthetic data generated from multi-compartmental models, where diffusion heterogeneity between intra- and extra-cellular media is taken into account, as well as the sensitivity of the results to each model parameter and to synthetic noise. Furthermore, based on the assumption that the maxima of the KT are distributed perpendicularly to the direction of well-aligned fibres, a novel algorithm for estimating fibre direction directly from the KT is proposed and compared to the fibre directions extracted from DKI-based orientation distribution function (ODF) estimates previously proposed in the literature. Synthetic data results showed that, for fibres crossing at high intersection angles, direction estimates extracted directly from the KT have smaller errors than the DKI-based ODF estimation approaches (DKI-ODF). Nevertheless, the proposed method showed smaller angular resolution and lower stability to changes of the simulation parameters. On real data, tractography performed on these KT fibre estimates suggests a higher sensitivity than the DKI-based ODF in resolving lateral corpus callosum fibres reaching the pre-central cortex when diffusion acquisition is performed with five *b*-values. Using faster acquisition schemes, KT-based tractography did not show improved performance over the DKI-ODF procedures. Nevertheless, it is shown that direct KT fibre estimates are more adequate for computing a generalised version of radial kurtosis maps.

Introduction

Diffusion-weighted imaging (DWI) is a magnetic resonance imaging (MRI) modality which can measure the diffusion of water molecules in the brain *in vivo*. DWI measures diffusion over micrometre length scales, and thus it is sensitive to microstructural information that is not resolved by conventional MRI structural images.

Diffusion tensor imaging (DTI), one of the most widely used DWI techniques, models diffusion using a second-order tensor known as diffusion tensor (DT), which is geometrically represented by an ellipsoid (Basser et al., 1994). The DT can be used to extract some rotation invariant parameters, such as mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD) and fractional anisotropy (FA), which can be used as biological markers for microstructural changes in the brain (Pierpaoli and Basser, 1996). Moreover, assuming the simple model that diffusion is larger along directions less limited by barriers (e.g., myelin sheath), the main direction of white matter fibres can be approximated by the principal axis of the diffusion ellipsoid (Basser, 1995). Based on this assumption, DTI can be used to tract white matter pathways (tractography) allowing for a non-invasive visualisation of white matter connections (Fillard et al., 2011).

Although DTI has been shown to be useful in detecting changes related to maturation or degeneration processes of brain microstructure (e.g., Sundgren et al., 2004), this technique has two major limitations. First, it assumes that water diffusion is Gaussian, while experimental

Abbreviations: 3D, three-dimensional; AD, axial diffusivity; AK, axial kurtosis; $D^{(m)}$, diffusion tensor for an individual simulated compartment; DKI, diffusion kurtosis imaging; DKI-ODF, DKI-based estimation of the orientation distribution function; DT, diffusion tensor; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; FA, fractional anisotropy; $f^{(m)}$, compartment volume fraction; f_{ia}, intra-cellular volume fraction; f_p, fibre population volume fraction; MK, mean kurtosis; MD, mean diffusivity; ODF, orientation distribution function; RD, radial diffusivity; RK, radial kurtosis; ROI, region of interest; KT, diffusion kurtosis tensor.

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http://dx.doi.org/10.1016/j.neuroimage.2015.02.004

results have shown that such model is not enough to fully characterise diffusion in biological tissues (Assaf and Cohen, 1998; Niendorf et al., 1996). Second, the DT can only provide accurate directional information for single fibre populations, and thus it fails to characterise the orientation of fibres in regions of crossing or fanning (Weigell et al., 2000).

Several approaches have been proposed to overcome the limitations of DTI. For example, non-Gaussian diffusion can be taken into account by directly applying biological models to the diffusion-weighted signals (e.g., Assaf et al., 2004, 2008; Zhang et al., 2012). Nevertheless, they have a limited scope for clinical applications due to significantly longer scanning times and their dependence on specific biological models. More robust estimation of fibre directions can be obtained using diffusion spectrum imaging (DSI) at the expense, however, of requiring even longer scanning times (Wedeen et al., 2008). Accurate fibre direction estimates from much less diffusion-weighted data are possible using q-ball imaging techniques (Tuch, 2004), yet these were developed specifically for single shell acquisitions which are not compatible with the acquisitions required for non-Gaussian diffusion techniques.

Diffusion kurtosis imaging (DKI) is a simple extension of the DTI model which allows the estimation of the diffusion kurtosis tensor (KT) in addition to the DT using relatively fast acquisition schemes (Jensen et al., 2005; Lu et al., 2006). The KT quantifies the non-Gaussian behaviour of water diffusion and can be interpreted as a measure of tissue microstructural heterogeneity (Jensen and Helpern, 2010). Similarly to the DT, rotation invariant metrics can be extracted from the KT, such as mean kurtosis (MK), axial kurtosis (AK) and radial kurtosis (RK) (Hui et al., 2008). Moreover, by combining the information from both the DT and KT, DKI has recently been shown to be useful in providing estimates of biophysical parameters, such as fibre density and intra- and extra-cellular diffusivities (Fieremans et al., 2011). All these metrics have shown promising results in many human brain studies, revealing additional clinical information relative to the standard DT-based measures (e.g., Falangola et al., 2008; Fieremans et al., 2013; Gonga et al., 2013; Helpern et al., 2011; Hui et al., 2012; Wang et al., 2011; Yoshida et al., 2013). Nevertheless, these metrics are still limited for not taking into account the complex white matter architecture of crossing or fanning fibres.

Being a fourth-order tensor, the KT offers a better characterisation of the spatial arrangement of tissue microstructure. Particularly, in a preliminary DKI study, Lu et al. (2006) showed that KT geometry shows maxima perpendicular to the direction of well-aligned fibres, and it has been shown to be sensitive to orthogonal crossing fibres. Although lacking a direct relationship between the KT's geometry and the direction of crossing fibres, Lazar et al. (2008) proposed a mathematical estimation of the orientation distribution function (ODF) from DKI which was able to predict the direction of two or three fibres crossing at different intersection angles. Recently, this approach was extended by Jensen et al. (2014) showing improvements on the estimation of fibre directions for DKI-based tractography procedures.

In this study, KT geometry is elucidated on synthetic data produced from multi-compartmental models able to simulate fibres crossing at different intersection angles. In particular, the relationship of KT maxima and the ground truth direction of fibres crossing at different intersection angles is established. A novel algorithm to estimate fibre directions mainly based on KT geometry is also proposed. KT geometry and the performance of the newly proposed procedure are compared to the geometry and fibre estimates from DTI and the DKI-based ODF (DKI-ODF) introduced by Jensen et al. (2014), so that the relevance of the findings in improving the current DKI state-of-the-art can be fully assessed. For a realistic biological representation, simulations take into account the diffusion heterogeneity between intra- and extra-cellular media. Moreover, the sensitivity of the results to each model parameter and to synthetic MRI noise is assessed. Finally, the impact of the findings in the development of tractography algorithms and robust biological markers is addressed on real MRI data. Particularly, the fibre direction estimates from the KT and DKI-ODF are used to resolve crossing fibres on brain tractography approaches and to compute generalised versions of RK maps for regions of interest with crossing fibres.

Methods and materials

In this section, the DKI model is reviewed, introducing equations and parameters relevant to our study. Then, strategies to estimate fibre direction are described: directly from the KT and from the DKI-ODF approximation as proposed by Jensen et al. (2014). Finally, details of the multi-compartmental simulations and specifications of *in vivo* imaging parameters and tractography processing protocols are presented.

Diffusion kurtosis imaging model

The DKI model relates the diffusion-weighted signal, S, to the applied diffusion weighting, b, the signal in the absence of diffusion gradient sensitisation, S_0, and the values of diffusion, D, and diffusion kurtosis, K, along the spatial direction n:

$$S(n,b) = S_0 \exp\left[-bD(n) + \frac{1}{6}b^2 D(n)^2 K(n)\right] \quad (1)$$

$D(n)$ and $K(n)$ can be computed from the KT and DT using the following equations:

$$D(n) = \sum_{i=1}^{3}\sum_{j=1}^{3} n_i n_j D_{ij} \quad (2)$$

and

$$K(n) = \frac{MD^2}{D(n)}\sum_{i=1}^{3}\sum_{j=1}^{3}\sum_{k=1}^{3}\sum_{l=1}^{3} n_i n_j n_k n_l W_{ijkl}, \quad (3)$$

where D_{ij} and W_{ijkl} are the elements of the second-order DT and the fourth-order KT tensors, respectively, and MD is the mean diffusivity.

Estimating fibre direction from the KT

Fibre direction can be directly obtained from the KT by first defining the average perpendicular kurtosis along the spatial direction n, which we designate as pK:

$$pK(n) = \frac{1}{2\pi}\int d\Omega_u K(n)\delta(n\cdot u), \quad (4)$$

where δ is the Dirac delta function and K is the directional kurtosis described by Eq. (3). Assuming that the maxima of the KT are distributed around directions perpendicular to the fibres (Lu et al., 2006; Wu and Cheung, 2010), fibre direction estimates can be directly obtained by finding the maxima values of pK using a two-step procedure. First, an initial estimation of the local maxima is obtained from values of pK sampled from a finite number of spatial directions n (125 uniformly distributed directions over a sphere with radius one are computed using a charge repulsion algorithm, Jones et al., 1999). Second, the locations of the pK maxima are refined using a quasi-Newton convergence algorithm (Lagarias et al., 1998). In this study, the latter step is performed until an angular precision lower than 0.1° is reached.