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Kurtosis analysis of neural diffusion organization

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ABSTRACT

A computational framework is presented for relating the kurtosis tensor for water diffusion in brain to tissue models of brain microstructure. The tissue models are assumed to be comprised of non-exchanging compartments that may be associated with various microstructural spaces separated by cell membranes. Within each compartment the water diffusion is regarded as Gaussian, although the diffusion for the full system would typically be non-Gaussian. The model parameters are determined so as to minimize the Frobenius norm of the difference between the measured kurtosis tensor and the model kurtosis tensor. This framework, referred to as kurtosis analysis of neural diffusion organization (KANDO), may be used to help provide a biophysical interpretation to the information provided by the kurtosis tensor. In addition, KANDO combined with diffusional kurtosis imaging can furnish a practical approach for developing candidate biomarkers for neuropathologies that involve alterations in tissue microstructure. KANDO is illustrated for simple tissue models of white and gray matter using data obtained from healthy human subjects.

Introduction

Non-Gaussianity of water diffusion within the brain can be quantified by the diffusional kurtosis tensor, which may be measured with MRI using diffusional kurtosis imaging (DKI) (Hori et al., 2012; Jensen and Helpern, 2010; Jensen et al., 2005; Lu et al., 2006; Poot et al., 2010; Steven et al., 2014; Wu and Cheung, 2010). This kurtosis tensor allows a number of rotationally invariant diffusion metrics to be calculated, including the mean kurtosis (MK), the axial kurtosis, and the radial kurtosis. These metrics are believed to reflect the heterogeneity of the intra-voxel diffusion environment and are thus indicators of microstructural complexity. A number of studies have shown that kurtosis-based diffusion metrics are altered for a variety of neuropathologies, such as stroke (Cheung et al., 2012; Hui et al., 2012; Jensen et al., 2011), cancer (Raab et al., 2010; Van Cauter et al., 2012), Alzheimer's disease (Benitez et al., 2014; Falangola et al., 2013; Fieremans et al., 2013; Gong et al., 2013), epilepsy (Gao et al., 2012; Lee et al., 2013, 2014; Zhang et al., 2013), Parkinson's disease (Kamagata et al., 2013, 2014), attention deficit hyperactivity disorder (Adisetiyo et al., 2014; Helpern et al., 2011), trauma (Grossman et al., 2012, 2013; Zhuo et al., 2012), and autism (Lazar et al., 2014).

Since the kurtosis tensor is a pure diffusion measure, without any explicit connections to specific properties of brain tissue microstructure, a clear-cut biophysical interpretation of the information it provides for a particular circumstance (e.g., brain region or disease) is often challenging (Rudrapatna et al., 2014). It may therefore be useful to combine the kurtosis tensor with tissue models that relate the diffusion information of the kurtosis tensor to particular microstructural features of cellular compartments. With the help of such models, the biological significance of observed changes in kurtosis can be better understood. In addition, the model parameters may serve as candidate biomarkers for microstructural alterations associated with disease.

One such tissue model for the kurtosis tensor has been previously proposed, although its applicability is limited to white matter for which the axons are largely unidirectional (Fieremans et al., 2011). An example of the relationships implied by this model is the formula

$$f_{axon} = \frac{K_{\max}}{K_{\max} + 3}, \tag{1}$$

where f_{axon} is the fraction of MRI-visible water contained within axons and $K_{\max}$ is the maximum value of the diffusional kurtosis as a function of the diffusion direction. This model has already been applied to Alzheimer's disease (Benitez et al., 2014; Fieremans et al., 2013), stroke (Hui et al., 2012), and autism (Lazar et al., 2014).

The purpose of this study is to develop a more general computational framework for relating the kurtosis tensor to tissue models of brain microstructure. This method, which we call kurtosis analysis of neural

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diffusion organization (KANDO), accommodates a variety of models that are suitable for both white matter and gray matter. The models are assumed to consist of ensembles of non-exchanging, Gaussian compartments. This is a plausible class of models that has been widely used to describe non-Gaussian diffusion in brain (Alexander et al., 2002; Assaf et al., 2004; Fieremans et al., 2011; Jespersen et al., 2007; Panagiotaki et al., 2009, 2012; Wang et al., 2011; White et al., 2013; Zhang et al., 2012). While the effects of water exchange between compartments are not incorporated explicitly, their consideration is important for a proper interpretation of these models.

The essence of KANDO is that the model parameters are determined by minimizing a cost function that corresponds to the square of the Frobenius norm (Signoretto et al., 2011) of the difference between the measured kurtosis tensor and the model kurtosis tensor. This contrasts with the algebraic approach utilized by Fieremans and coworkers (Fieremans et al., 2011) in that KANDO requires nonlinear optimization. However, KANDO provides substantially more flexibility than is possible with purely algebraic methods, allowing for a much broader range of model types. Moreover, one can easily construct specific models for KANDO that yield results closely matching those of Fieremans and coworkers for white matter with unidirectional axons. In this sense, KANDO may be regarded as an extension of this prior work.

KANDO is quite analogous to the conventional method of fitting tissue models to the diffusion MRI (dMRI) signal (Assaf et al., 2004; Ferizi et al., 2013; Jespersen et al., 2007; Panagiotaki et al., 2009, 2012; Wang et al., 2011; White et al., 2013; Zhang et al., 2012) with a key difference being that KANDO utilizes only the kurtosis and diffusion tensors as inputs, rather than the full dMRI signal, in order to facilitate a clearer biophysical interpretation of the kurtosis tensor information. KANDO is particularly suitable as an adjunct for DKI, which is specifically designed for estimating the kurtosis and diffusion tensors. One distinction between KANDO and tissue modeling based on fits to the dMRI signal is that KANDO does not require the specification of imaging parameters, such as diffusion gradient directions and b-values, which may help to reduce the dependence on experimental details of results obtained with KANDO. Nonetheless, KANDO estimates for model parameters may be indirectly affected by imaging parameters, as these can influence the accuracy of the measured diffusion and kurtosis tensors (Jensen and Helpern, 2010). As KANDO only includes information encompassed by the kurtosis and diffusion tensors, it may be insensitive to certain microstructural features that affect the full signal.

The main goal of this article is to describe the general theory underlying KANDO, and we illustrate KANDO for three simple models intended to represent white matter and gray matter. For these models, exemplary results are given based on DKI data obtained for healthy human volunteers. In addition, numerical simulations are described that examine potential sources of errors in parameter estimates obtained with KANDO.

Theory

General framework

A fundamental assumption of KANDO is that the tissue model consists of $N+1$ non-exchanging water compartments. Each individual compartment is also assumed to have Gaussian diffusion with its dynamics being completely determined by its diffusion tensor. Let the diffusion tensor for the nth compartment be indicated by $\mathbf{D}^{(n)}$ and the corresponding water fraction by f_n. Here the water fractions are relative only to water that is visible with dMRI. Thus some water pools with short T2, such as water within myelin (Stanisz et al., 1999), might be excluded from the model, depending on the echo time of the dMRI experiment. It should be noted that the total diffusion dynamics of a model with two or more Gaussian compartments will generally be non-Gaussian, as the sum of two or more Gaussian distributions is a non-Gaussian distribution except for the special case that all the distributions are identical.

It is physically appealing to associate the model compartments with cellular compartments of the tissue microstructure, and this is generally justified for cells with low permeability plasma membranes. For example, water within myelinated axons has an exchange time with the surrounding extracellular space that is long compared to typical diffusion times used for dMRI (Nilsson et al., 2013), and thus this compartment can plausibly be approximated as non-exchanging. However, other cell types, such as astrocytes, may have substantially shorter exchange times (Badaut et al., 2011; Solenov et al., 2004). When the exchange time is small compared to the diffusion time, a cellular compartment can be regarded as being in fast exchange with the extracellular space, and it is then effectively part of a larger composite compartment that includes the extracellular space and possibly other cellular compartments also in fast exchange. As there is currently limited knowledge of the exchange times for glial cells and unmyelinated neurites, the precise correspondence between model and cellular compartments may not always be self-evident. When the exchange and diffusion times are comparable, the model compartments can take on a more ambiguous “apparent” status.

The total diffusion tensor for the model is

$$\mathbf{D} = \sum_{n=0}^{N} f_n \mathbf{D}^{(n)}, \tag{2}$$

where the $N+1$ compartments are numbered from $n=0$ to $n=N$ and with the water fractions being normalized so that

$$1 = \sum_{n=0}^{N} f_n. \tag{3}$$

$\mathbf{D}$ is regarded as a measured quantity that is a fixed input from a modeling perspective. It is convenient to introduce the “reduced” diffusion tensors defined by

$$\boldsymbol{\Delta} \equiv \frac{\mathbf{D}}{\overline{D}} \quad \text{and} \quad \boldsymbol{\Delta}^{(n)} \equiv \frac{\mathbf{D}^{(n)}}{\overline{D}}, \tag{4}$$

where $\overline{D} = Tr(\mathbf{D})/3$ is the mean diffusivity for the total system. These reduced tensors are dimensionless and serve to simplify the mathematical expressions that follow. In terms of the reduced tensors, Eq. (2) takes the form

$$\boldsymbol{\Delta} = \sum_{n=0}^{N} f_n \boldsymbol{\Delta}^{(n)}. \tag{5}$$

Since $\boldsymbol{\Delta}$ depends only on $\mathbf{D}$, it is also a given input for KANDO.

Let us now assume that the reduced diffusion tensors for compartments $n = 1, 2, \ldots, N$, as well as their corresponding water fractions, are specified functions of a set of M model parameters $(a_1, a_2, \ldots, a_M)$ so that we have $\boldsymbol{\Delta}^{(n)}(a_m)$ and $f_n(a_m)$, for $n = 1, 2, \ldots, N$. These functions would be based on the biophysical assumptions for the water diffusion dynamics in brain tissue that one wishes to employ. By applying Eqs. (3) and (5), we also have

$$f_0(a_m) = 1 - \sum_{n=1}^{N} f_n(a_m), \tag{6}$$

and

$$\boldsymbol{\Delta}^{(0)}(a_m) = \frac{\boldsymbol{\Delta} - \sum_{n=1}^{N} f_n(a_m)\boldsymbol{\Delta}^{(n)}(a_m)}{1 - \sum_{n=1}^{N} f_n(a_m)}, \tag{7}$$

which determines f_0 and $\boldsymbol{\Delta}^{(0)}$ in terms of the model parameters.