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Review articles

# Non-Gaussian diffusion imaging: a brief practical review

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**Abstract**

The departure from purely mono-exponential decay of the signal, as observed from brain tissue following a diffusion-sensitized sequence, has prompted the search for alternative models to characterize these unconventional water diffusion dynamics. Several approaches have been proposed in the last few years. While multi-exponential models have been applied to characterize brain tissue, several unresolved controversies about the interpretations of the results have motivated the search for alternative models that do not rely on the Gaussian diffusion hypothesis. In this brief review, diffusional kurtosis imaging (DKI) and anomalous diffusion imaging (ADI) techniques are addressed and compared with diffusion tensor imaging. Theoretical and experimental issues are briefly described to allow readers to understand similarities, differences and limitations of these two non-Gaussian models. However, since the ultimate goal is to improve specificity, sensitivity and spatial localization of diffusion MRI for the detection of brain diseases, special attention will be paid on the clinical feasibility of the proposed techniques as well as on the context of brain pathology investigations.


*Keywords:* Water diffusion; Anomalous diffusion; Non-Gaussian diffusion; Stretched-exponential model; DTI; DKI

## 1. Introduction

Diffusion tensor imaging (DTI) [1–4] enables the diffusional motion of water molecules to be measured, providing a unique source of contrast among tissues. Thanks to its ability to image noninvasively soft tissues in vivo, DTI has shown high sensitivity in detecting macroscopic abnormalities occurring in several neurological conditions [5–9], thus providing a substantial contribution in both diagnosis and therapeutic approach.

DTI is based on the diffusion tensor reconstruction, which is obtained by combining diffusion measurements along at least six noncollinear spatial directions. In order to characterize the orientation-dependent water mobility in each voxel and to correlate it with the tissue architecture, parametric maps are usually displayed. DTI indices, such as the mean diffusivity (MD) and the degree of anisotropy (often quantified as fractional anisotropy, FA) of the media, provide information about the underlying microstructural characteristics of biological tissues.

MD and FA indices are currently used in many studies and in clinical routine due to the great advantage of being rotationally invariant indices [1], i.e., they are independent of the reference frame. As a consequence, changes in FA and MD maps are intimately related to intrinsic microstructural changes. The hypothesis at the basis of DTI theoretical framework is that the probability of finding a particle in position $r$ at time $t$, which is proportional to the motion propagator (MP), has a Gaussian shape with its width (i.e., the standard deviation) proportional to the diffusion coefficient.

In DTI acquisitions, the signal is typically recorded by diffusion-sensitized sequences as a function of chosen diffusion weightings or $b$ values (which depend on both

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gradient strength and diffusion time $\Delta$), and it can be described as a monoexponential decay using the Stejskal–Tanner equation [10]. Nonetheless, in the last few years, several experiments have demonstrated that single exponential decay function models poorly predict observed results (see Fig. 1). This evidence comes from a number of studies performed on both animal models [11] and humans [12–15].

Several approaches have been suggested to give a deeper insight into the diffusive phenomenon, in order to identify a better agreement between the data and the proposed fitting curves. These methods generally introduce non-Gaussian MP and are thus referred as non-Gaussian methods. The bi-exponential model [12,16–18] was the first attempt to overcome DTI approximations and can be casted as a non-Gaussian model, even though it considers the signal decay as the superimposition of the signals arising from two water diffusion pools, in each of which the diffusion is Gaussian. Introducing a fast and a slow diffusion coefficient provided a better agreement with the experimental curves and yielded interesting results [13,16,17]. However, the true attribution of the two compartments is still elusive [19–22]. A comprehensive review about this topic has been recently published [18]; hence this article will be focused on more recent and different approaches.

One of the most popular non-Gaussian models is the diffusional kurtosis imaging (DKI) [23,24]. In this model, the deviation from Gaussian behavior is quantified using a convenient dimensionless metric called the excess kurtosis, which is obtained from the first three terms of the expansion of the logarithm of the NMR signal intensity in powers of $b$. This avoids any hypothesis about the shape of the MP governing the molecular displacements. At the moment, DKI proposes parametric maps to be used in combination with DTI conventional

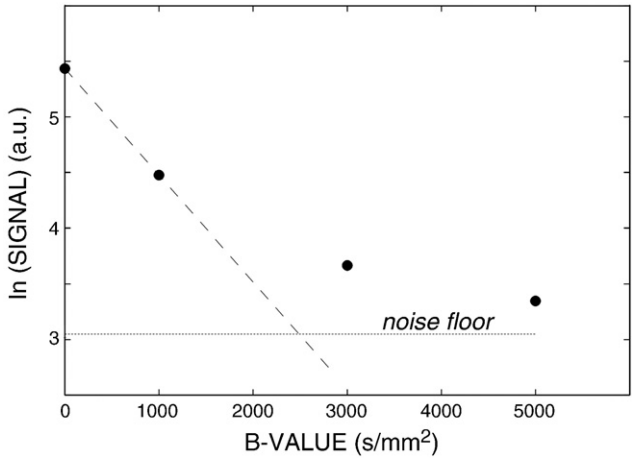


Fig. 1. Plot of the logarithm of signal decay vs. $b$ value in a selected WM ROI belonging to the corpus callosum, averaged over all pixels. The dashed line represents the predicted mono-exponential decay at $b$=1000 s mm$^{-2}$, while the dotted line represents the noise floor, calculated as the average of the pixel intensities in a ROI outside the brain.

outputs and has produced interesting results [25]. The link between microstructural tissue features and the measured kurtosis indices has been clarified in a recent review article [26].

Bennett et al. [27] introduced another innovative strategy a few years ago. The signal decay as a function of $b$ value was modeled as a stretched-exponential function, where the stretching exponent $\gamma$ was linked to the heterogeneity of the media in which the spins diffuse. The method was applied to healthy human brain [27–29] showing the ability to discriminate between different tissues on the basis of their structural complexity. Interestingly, the stretched exponential showed a high sensitivity to pathological alterations like human gliomas, which are known to be histologically more heterogeneous than normal brain tissue [30,31]. A method [28] to quantify not only the magnitude of the stretching exponent but also its anisotropy has since been developed. This approach was based on the measurement of the anomalous exponent, $\gamma$, across several gradient directions, thus obtaining the mean anomalous exponent and its spread along different directions, i.e., the anisotropy. However, none of these methods [27,28] takes into consideration the tensorial nature of diffusion and thus they suffer from the dependence on the chosen measurement directions.

A more rigorous and useful approach to derive the anisotropy from the stretching exponent (i.e., anomalous exponent) was recently introduced [29]. Inspired by the DTI formalism, these authors proposed a tensorial nature for the anomalous diffusion framework in order to quantify both mean anomalous diffusion and its anisotropy independently of the experimental reference. The signal was expressed as a simple stretched-exponential function only along the principal axes of diffusion, while in a generic direction, it was modeled as a combination of three different stretched-exponential functions [29].

Even though the stretched-exponential model was successfully applied to highlight several features of brain tissue, which are not detectable with DTI, none of these authors gave a formal a priori justification to link the non-Gaussian shape of the MP to the stretched decay curve. Rather, the stretched exponent was introduced as a phenomenological model to fit the experimental data. Others have since attempted instead to introduce more rigorous frameworks to derive the stretched-exponential model [32,33]. In particular, Magin et al. [32] successfully motivated the choice of the stretched-exponential function via fractional order calculations.

In this review, DKI and anomalous diffusion imaging (ADI) methodologies will be addressed and discussed, with a particular attention to clinical applications. Indeed, despite their early stage of development, DKI and ADI already showed a great potentiality to detect specific brain structures and alterations. Other non-Gaussian models, while interesting (i.e., Refs. [34] and [35]), have not been included because no practical applications concerning the human brain have been obtained to date.