# Limitations of ADC-Based Models in Characterizing Non-Gaussian Diffusion

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**INTRODUCTION:** Several new methods have been introduced to address the issue of non-gaussian diffusion in neural fiber systems. Some of them are based on apparent diffusion coefficient (ADC) analysis; and some are based on **q**-space analysis. Using ADC-based techniques such as spherical harmonic decomposition (1) and one generalized diffusion tensor imaging (GDTI) method (2), tremendous progresses have been made towards better angular resolution of fiber systems. However, in the situation of non-Gaussian diffusion, there still needs a physical justification for ADC-based techniques. Here we evaluate the possible physical and mathematical foundation of those diffusion models that rely on apparent diffusion coefficient (ADC) measurements. We demonstrate that although ADC-based approaches can qualitatively detect the existence of non-Gaussian diffusion, their ability to characterize non-Gaussian diffusion is fundamentally limited. In addition to the mathematical proof, Monte Carlo (MC) simulation for restricted diffusion is also applied to illustrate the poor data fitting of these ADC models in the presence of non-Gaussian diffusion. Specific comparisons are performed between two GDTI methods: one introduced by Liu et al (which will be referred to here as GDTI-1) (3,4) and one introduced by Özarslan et al (referred to as GDTI-2 here) (2). Finally, we investigate the possibility of imaging asymmetrical fiber structures with GDTI-1.

**THEORY:** Methods based on ADC measurements, such as HARD and GDTI-2, assume that MR signal decays monoexponentially as a function of the b-value. These methods tend to analyze the distribution of measured ADC profiles and use the distribution to characterize the underlying non-gaussian diffusion process. For example, in GDTI-2, an ADC profile is described by the elements of a higher order tensor. Although higher order terms extracted from ADC distributions are thought to be able to characterize the non-gaussian diffusion pattern in multi-fiber systems, the mere existence of these parameters contradicts the assumption of the model.

First, the assumption of a monoexponential signal behavior implies that the underlying diffusion is gaussian. Specifically, write the diffusion gradient $\mathbf{G} = (G,\theta,\varphi)$ in the spherical coordinate, and the random displacement $\mathbf{r} = (x,y,z)$ in the Cartesian coordinate. Let $r_g$ be the projection of **r** along the direction of the diffusion gradient **G**. Assuming that the signal measured along the direction of **G** is an exponential function of the b-value, it can be shown that $r_g$ is a one-dimensional gaussian random variable. To show **r** is a three-dimensional gaussian random variable, we observe the relationship shown in Eq.[1]. Here, $\sigma_x^2$ is the variance of x; $\sigma_{xy}^2$ is the covariance of x and y; and so on. Since $\sigma_{r_g}^2 > 0$, and Eq. [1] is true for any direction defined by $(\theta, \varphi)$, the matrix $\Sigma$ shown in Eq.[2] is positive definite and it forms the covariance matrix of the random vector **r**. Furthermore, since all higher-order cumulants of $r_g$ are zero, higher-order cumulants of **r** are also zero due to the linear relationship between $r_g$ and **r** (5). Therefore, **r** is a gaussian random vector with covariance matrix $\Sigma$.

Second, since a gaussian distribution has only six degrees of freedom, it is not necessary to include higher-order terms in spherical harmonic decomposition which requires more than six free variables, or in the signal equation of GDTI-2.

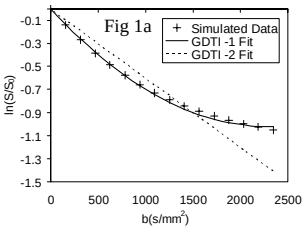
$$\sigma_x^2 \cos^2\varphi \sin^2\theta + \sigma_y^2 \sin^2\varphi \sin^2\theta + \sigma_z^2 \cos^2\theta + 2\sigma_{xy} \cos\varphi \sin\varphi \sin^2\theta + 2\sigma_{xz} \cos\varphi \sin\theta \cos\theta + 2\sigma_{yz} \sin\varphi \sin\theta \cos\theta = \sigma_{r_g}^2 . \quad [1]$$

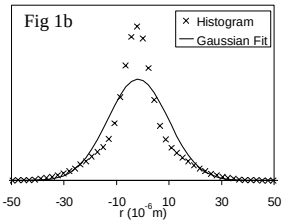
$$\Sigma = \begin{bmatrix} \sigma_x^2 & \sigma_{xy}^2 & \sigma_{xz}^2 \\ \sigma_{yx}^2 & \sigma_y^2 & \sigma_{yz}^2 \\ \sigma_{zx}^2 & \sigma_{zy}^2 & \sigma_z^2 \end{bmatrix} \quad [2]$$

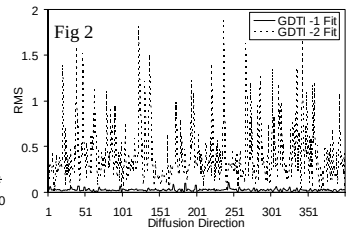
The fundamental difference between GDTI-1 and GDTI-2 is that GDTI-1 does not assume an exponential signal behavior. Instead, GDTI-1 expands the signal equation in a series of higher order b-tensors, which enables an accurate description of complex diffusion signal behaviors including non-Gaussian types.

**METHODS and RESULTS:** To demonstrate the limitations of ADC-based models, MC simulations were performed on two phantoms: 1) a perpendicularly crossing tube (Phantom-1); and 2) a Y-shaped tube (Phantom-2). A total of $6.5 \times 10^6$ spin trajectories with uniformly distributed starting positions were simulated. For an unrestricted diffusion, the diffusion coefficient D was set to be $2 \times 10^{-3}$ mm$^2$/s. The following MR parameters were used: $\delta$ = 30 ms, $\Delta$ = 40 ms, and TE = 80 ms. MR diffusion experiments were simulated on 400 uniformly distributed diffusion-encoding directions. For each direction, 15 different b-values were used with a maximum of 2344 s/mm$^2$. The data were analyzed with both GDTI methods.

Figure 1a plots a representative set of simulated data and curves fitted by both GDTI methods. The diffusion-weighted signal is not an exponential function of the b-value. The fitted curve by GDTI-2 (dotted line) clearly does not agree with the data; on the other hand, GDTI-1 (solid line) produces an overall good fitting. Figure 1b shows the corresponding distribution of the displacement is non-Gaussian. Figure 2 compares the root mean square error (RMS) of both GDTI fittings over all 400 diffusion directions for Phantom-1. The mean RMS over all the directions is 0.029 and 0.41 for GDTI-1 and GDTI-2, respectively. Figure 3 shows the structure of Phantom-2, the diffusivity profile generated using GDTI-2 (2) and skewness maps generated using GDTI-1 with and without considering the phase of the signal (3,4).



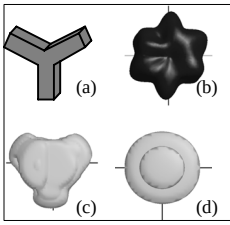




Fig 3 - Comparison of GDTI-1 and GDTI-2.
(a) Phantom-2 structure;
(b) GDTI-2 diffusivity profile;
(c) GDTI-1 skewness map considering signal phase;
(d) GDTI-1 skewness map without signal phase.

**DISCUSSION:** The issue of resolving multiple fiber orientations in regions where fibers cross or merge has become increasingly important in fiber tractography (6). In principle, GDTI-1 is a physically correct formalism and has the capability to resolve the orientations of an asymmetric structure (Fig 3c). In real experiments, however, the accuracy of GDTI-1 is limited by signal to noise ratio (SNR) and the ability of MRI systems to accurately measure the phase of the signal. Our study shows that the phase of the signal is crucial in the reconstruction of an asymmetric PDF (Fig 3c and d).

Because of its ability to characterize non-Gaussian diffusion processs, GDTI-1 provides a mathematical framework for studying complex diffusion processes in neural fiber systems. Based on GDTI-1, we understand that the limitation of an ADC-based model stems from the assumption of an exponentially decaying signal. For a given non-Gaussian diffusion, the signal generally decays non-exponentially and can not be sufficiently described by ADC (Fig 1a). Though along some specific diffusion directions, the signal may decay exponentially as a function of the b-value, this happens only when the projection of random displacements is Gaussian distributed along those specific directions. Consequently, the non-gaussian diffusion process existing in complex biologic tissues can not be fully characterized by ADC-based models. Furthermore, simulations based on GDTI-1 have demonstrated that higher-order b-tensors and higher-order diffusion tensors are required to characterize a non-gaussian signal behavior (Figure 1).

Even though current MR technology does not permit an accurate measurement of the phase, GDTI-1 based on only the magnitude of MR signal already provides an accurate characterization of symmetric fiber structures. Furthermore, the insight gained from GDTI-1 is outstanding and is crucial for our basic understanding of diffusion processes in complex biologic tissues.

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