Complex patterns of non-Gaussian diffusion in artificial anisotropic tissue models

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ABSTRACT

Motional barriers due to geometrical restrictions are ubiquitous in heterogeneous media such as porous rocks or biological tissues. As a consequence, molecular propagation deviates from the patterns of Gaussian diffusion. In this paper, we report on the results of the application of several non-Gaussian and anomalous diffusion models used to describe experimental data in the artificial anisotropic system with well-defined properties. In particular, we focus on the influence of fibre packing density on the quantitative metrics of these models and compare their sensitivity to this parameter. The results are discussed in the context of the importance for better understanding the governing diffusion mechanisms in complex tissue microstructures.

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1. Introduction

Diffusion measurements, combined with pulsed field gradient NMR [1,2], allow one to probe the local geometrical environment in porous materials [2,3], self-assembled systems [4,5], and biological tissues [6]. Diffusion tensor imaging (DTI) [7,8] plays an important role in brain research where it has been used for investigating *in vivo* axonal fibre architecture [9] and its relationship to neurodegenerative disorders. Conventional DTI is limited in that it is based on the Gaussian model of diffusion valid only for low diffusion weightings (*b*-values). For increasing *b*-values, the diffusion-weighted signal of water in the brain tissue deviates significantly [10] from the mono-exponential function expected when employing the Gaussian propagator. This deviation is caused by properties of the cellular microstructure, such as its compartmentalization, restrictions to diffusion, heterogeneity and anisotropy on multiple length scales [11].

In the brain tissue, important parameters such as cellular ("pore") size distribution or axonal volume fraction (fibre packing density) [12] can be elucidated from diffusion studies. In particular, some approaches relevant for diffusion in porous media have been successfully translated to the investigation framework of the white matter [13,14]. The common main factor that influences diffusion in a wide variety of porous systems (natural rocks, zeolites, mesoporous glass, cements, polymeric composites) and biological tissues (brain tissue, cartilage, lungs) is an ubiquitous presence of motional barriers. Geometrical restrictions hinder molecular propagation leading to a reduction of the experimentally measured ("apparent") diffusion coefficient with respect to its intrinsic (bulk)

value, D_0. As a result, the mean squared displacement $\langle r^2 \rangle$ is related to the observation time, t, as [3].

$$\langle r^2 \rangle = 2dD(t)t, \tag{1}$$

where d is the dimensionality, and $D(t)$ is referred to as the "time-dependent diffusion coefficient". For unrestricted diffusion in isotropic liquid, $D(t)$ coincides with D_0.

In porous media studies, $D(t)$ is used as an informative probe of local geometry [3,6]. In the short time limit, it allows one to determine the surface-to-volume ratio, based on the assumption that only a small fraction of molecules in the surface layer with a thickness of approximately $\sqrt{D_0 t}$ would be restricted by the boundaries [15,16]. The asymptotic behaviour in the long time limit was considered in Refs. [17,18]. In well-connected porous media, $D(t \to \infty)$ is reduced with respect to D_0 by a tortuosity factor, κ, which depends on the pore volume fraction and geometry [3]. The time range between the short and long asymptotic limits is often interpolated with the help of the Padé approximation [19]. However, there is no general analytical approach describing diffusion in the full time range.

Complex systems often give rise to anomalous transport properties [20,21] characterized by a power law dependence of the mean squared displacement on time

$$\langle r^2 \rangle = 2dDt^\beta, \tag{2}$$

where D is the proportionality coefficient, and β is the exponent which allows one to distinguish various motional regimes, such as $\beta = 0$, "localized"; $0 < \beta < 1$, "subdiffusive"; $\beta = 1$, "normal"; $\beta > 1$, "superdiffusive"; and some others. In the case of anomalous diffusion expressed by Eq. (2), $D(t)$ in Eq. (1) will scale as Dt^γ, where $\gamma = \beta - 1$. The deviations of the scaling exponents β (or γ) from 1

(or 0) of the Gaussian model can be considered as a measure of the complexity of the environment [22].

In vivo brain diffusion studies performed with the medical scanners are subject to strong restrictions with respect to maximal gradient strengths, pulse durations, etc. In particular, short or/and long time diffusion limits, as well as the conditions of narrow pulse approximations, are hardly achievable. Time-dependent studies using the stimulated echo pulse sequence [23] are also difficult due to signal-to-noise limitations. The majority of studies are usually carried out with conventional spin echoes [1] at low diffusion weightings. They operate with the scalar metrics of the reconstructed diffusion tensor, such as the (apparent) mean diffusivity, tensor eigenvalues, and fractional anisotropy, that are successfully exploited as biomarkers of various pathological brain conditions.

In recent years, increasing efforts have been devoted to the development of new approaches to analyze non-Gaussian diffusion patterns in brain tissue in the extended range of *b*-values [24–29]. The underlying biophysical mechanisms of deviations from the Gaussian model are not yet well understood. One of the reasons is that numerous potential effects of complex microstructural and physiological tissue properties on the average NMR signal cannot be easily decomposed. Some well-established models, such as CHARMED [30], propose the concept of compartmentalization of water molecules within the extracellular (ECS) and intracellular (ICS) spaces. The ECS is characteristic of hindered diffusion (however, not restricted to any localized volumes) and gives rise to the faster diffusion component. More restricted motion in the ICS determines the slow diffusion component. In the frame of such models, the slope of the attenuation curve at low *b*-values is dominated by the faster diffusion in the ECS. One should mention, however, that the model relative ICS and ECS volume fractions tend to contradict those known from histology. For a more detailed survey of the existing approaches the reader is referred to the reviews published in the literature, such as [11] and [28].

In order to better understand the fundamental effects of microstructure on diffusion measurements it is helpful to study less complex model systems of known structure. This can be achieved in two complementary ways: using the Monte Carlo simulations [31,32] or *in vitro* model systems ("phantoms") [32,33]. Recently, we developed a novel multi-section fibre phantom [33] in which there is one section that contains a region of oriented fibres with the gradient of the fibre packing density. Fibres are not hollow (i.e., contain no water inside) and, therefore, model motional barriers in the ECS. Fibre packing density, *f*, (not to be confused with the physical density of the fibre), is an important characteristic of various tissue types, such as fibrous plants or human brain. In particular, the tortuosity of the ECS strongly depends on this parameter. Fibre density may change, for example, as a consequence of an axonal loss caused by neurodegenerative processes, traumatic brain injuries or tumours [34].

The primary purpose of this study is to investigate the influence of fibre density on the quantitative metrics in three non-Gaussian empirical models of diffusion recently introduced in brain research: the diffusion kurtosis model, DKM, [25,29]; the lognormal-distribution model, LNDM, [29]; and the stretched-exponential model, SEM, [26,27]. We also analyse the dependence of axial (parallel to fibres), and radial (perpendicular to fibres) diffusivities on the diffusion times in the broad range.

2. Materials and methods

The construction of an *in vitro* model system with a fibre-density gradient, as well as the diffusion experiments performed on it, are described in Ref. [33]. Data analysis was done using in-house Matlab scripts (Matlab, The MathWorks, Natick, MA, USA). We used a double-refocused spin-echo pulse sequence for studies of non-Gaussian diffusion and the stimulated echo pulse sequence [23] for time-dependent studies. Axial diffusivity, λ_{axial}, (the major tensor eigenvalue), and radial diffusivity, λ_{radial}, (the average of two minor eigenvalues), were derived by a tensor reconstruction for typical *b*-values $\leqslant 1\ \mu m^{-2}$ ms. The dependence of λ_{radial} on the diffusion time, t_d, in the stimulated echo pulse sequence was analysed using the power law function, $\lambda_{radial} \propto t_d^{\gamma}$.

Diffusion attenuation curves in the direction perpendicular to the fibre axis (maximum hindrance) were analyzed in the range of $b \leqslant 7\ \mu m^{-2}$ ms after averaging the signal over the two orthogonal directions in the perpendicular plane. We used the following 3 models for the fits: DKM (Eq. 1 in Ref. [33]), LNDM (Eqs. (3)–(5) in Ref. [29]) and SEM (Eq. (3) in Ref. [27]). The fitting parameters of diffusivities in DKM, LNDM, and SEM will be denoted as D_k (the mean diffusivity), D_{ld} (the peak diffusivity), and D_{se} (the distributed diffusion coefficient), respectively. Further fitting parameters will be denoted as K (the mean excess kurtosis in DKM), σ (the width of the distribution function in LNDM), and α (the stretching exponent in SEM). These parameters (K, σ and α) characterize the deviation from the Gaussian model. DKM, LNDM and SEM reduce to the standard Gaussian model when $K = 0$, $\sigma = 0$, and $\alpha = 1$. Two models, LNDM and SEM, were fitted in the full range of $b \leqslant 7\ \mu m^{-2}$ ms. DKM fits were applied in the reduced range, $b \leqslant 2.5\ \mu m^{-2}$ ms, since the applicability of this model for higher *b*-values [25] is limited due to a truncation of higher orders in the cumulant expansion of the signal.

3. Results

We observed that the attenuation curves of the diffusion-weighted signal, $S(b)$, of water in our model system were, in general, strongly deviating from the mono-exponential function, and that the degree of deviations significantly depended on fibre density. All three applied models, DKM, LNDM, and SEM, provided satisfactory fits for signal amplitudes in the dynamical range of at least one order of the magnitude, $S(b) \gtrsim 0.1$. This is demonstrated, as an example, for two different fibre densities in Fig. 1 showing the experimental data together with their fits (solid curves), and the mono-exponential attenuation of the bulk water signal for comparison. The corresponding fit parameters are indicated in Table 1.

Fibre densities accessed by our phantom design varied in the range from 0.46 to 0.71. For the same *f*, the absolute values of the fitted diffusivities, D_k, D_{ld}, and D_{se}, were slightly different, with the largest one for D_k and the smallest one for D_{se}. These
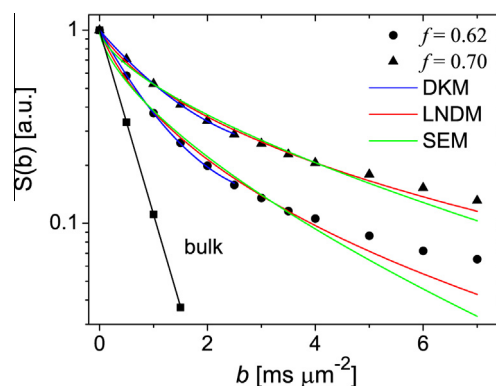

Fig. 1. Typical attenuation curves of the diffusion-weighted signal for two different fibre densities together with their fits (solid curves) using DKM, LNDM, and SEM. The fit parameters are indicated in Table 1. Exponential attenuation of the bulk water signal with $D_0 = 2.3\ \mu m^2\ ms^{-1}$ is shown for comparison.