Published in final edited form as:

NMR Biomed. 2010 August ; 23(7): 711–724. doi:10.1002/nbm.1577.

Monte Carlo study of a two-compartment exchange model of diffusion†

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Abstract

Multisite exchange models have been applied frequently to quantify measurements of transverse relaxation and diffusion in living tissues. Although the simplicity of such models is attractive, the precise relationship of the model parameters to tissue properties may be difficult to ascertain. Here, we investigate numerically a two-compartment exchange (Kärger) model as applied to diffusion in a system of randomly packed identical parallel cylinders with permeable walls, representing cells with permeable membranes, that may serve particularly as a model for axons in the white matter of the brain. By performing Monte Carlo simulations of restricted diffusion, we show that the Kärger model may provide a reasonable coarse-grained description of the diffusion-weighted signal in the long time limit, as long as the cell membranes are sufficiently impermeable, i.e. whenever the residence time in a cell is much longer than the time it takes to diffuse across it. For larger permeabilities, the exchange time obtained from fitting to the Kärger model overestimates the actual exchange time, leading to an underestimated value of cell membrane permeability.

Keywords

diffusion; exchange; permeability; Monte Carlo; kurtosis; diffusion-weighted imaging; Kärger model; axon

INTRODUCTION

Diffusion-weighted imaging (DWI) is a prime imaging modality for probing the structure of soft tissues. The diffusion of water molecules is highly sensitive to the tissue microarchitecture on the scale of individual cells, being strongly affected by the cell packing

†This article is published in *NMR in Biomedicine* as a special issue on Progress in Diffusion-Weighted Imaging: Concepts, Techniques, and Applications to the Central Nervous System, edited by Jens H. Jensen and Joseph A. Helpert, Center for Biomedical Imaging, Department of Radiology, NYU School of Medicine, New York, NY, USA.

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geometry, membrane permeability and the presence of intracellular organelles. As the tissue microarchitecture is closely related to function, this makes the DWI signal an ideal marker of alterations in tissue pathophysiology.

An important challenge for DWI is the quantification of the properties of cells and tissues from the measured signal, which is difficult because of the massive averaging that occurs within the imaging voxel. The averaging is over the Brownian paths of individual water molecules, and over the multiple microscopic structures within a voxel. Although the diffusion length of a typical DWI experiment is about 1–10 μm , making diffusion sensitive to the tissue microstructure, the voxel size in clinical MRI is on the scale of millimeters. This large separation of scales means that most of the structural information will be lost when acquiring a voxel's MR signal. Hence, the quantification of the properties of cells and tissues necessarily relies on the modeling of the DWI signal, and on the subsequent interpretation of the model parameters in terms of the intrinsic tissue properties.

Generally speaking, there exist two types of models for the MR signal from tissues and other complex media. The first type of model explicitly accounts for the structural properties. Such models have well-defined assumptions about the particular tissue geometry, which makes their application and interpretation straightforward. Their applicability is naturally limited to specific geometries. For DWI, a detailed overview is given in refs. (1-3). As an early example, Latour *et al.* (4) assumed that packed erythrocytes were spherical, and applied the theory developed for diffusion in porous media (5) to estimate the surface-to-volume ratio and permeability of biological cells. Szafer *et al.* (6) modeled the diffusion in biological tissue by rectangular cells placed in a square matrix surrounded by permeable membranes. Stanisz *et al.* (7) presented a comprehensive analytical model for diffusion in bovine optic nerve, in which axonal and glial cells were modeled by prolate ellipsoids and spheres. More recent examples include modeling the signal from alveolar ducts and myelinated axons by diffusion in randomly oriented (8,9) and aligned (10-13) impermeable tubes, modeling the effects of permeable membranes by assuming random positions and orientations (14), and representing the spatially varying diffusion coefficient in terms of its correlation functions and associated length scales (15).

The second type of model is not concerned directly with the precise tissue geometry. An important class of these models is formed by the 'multisite exchange models' which are used to describe diffusion and relaxation at the molecular (chemical) level. The defining feature of such models is the presence of a number (two or more) of certain abstract molecular 'pools' or 'sites' with simple properties, e.g. monoexponential relaxation (16,17) and Gaussian diffusion (18-20). Multisite exchange models have gained popularity because their relative simplicity facilitates calculations. Instead of considering the Bloch-Torrey equation in a particular geometry, which includes solving a complicated partial differential equation that is often hard to specify, multisite exchange models are based on ordinary differential (rate) equations that describe simple population dynamics in the pools and the exchange between them. The solutions of such models are, naturally, linear combinations of exponentials whose parameters are 'rotated' with respect to the original compartment parameters as a result of nonzero exchange rates.

Applied to tissues with complex microarchitecture, multisite exchange models appear to be ill-defined and require careful justification. In particular, they should be supplemented by explicitly specifying the pools and their properties. The obvious choice has often been the intra- and extracellular compartments with their respective diffusion coefficients or relaxation rates. The properties of the pools may depend, in general, on the measurement time scale; for instance, for short times, the diffusion coefficients of the molecular pools could correspond to the diffusivities of intra- and extracellular water, whereas, for very long

times, the effective compartment diffusivities may be significantly different. Furthermore, in some cases, the most obvious suggestion of associating the molecular pools with distinct parts of a complex medium may be misleading. As shown recently, both for transverse relaxation in the presence of spatially varying Larmor frequency (21), and for diffusion with spatially varying diffusivity (15) (without membranes), the MR signal appears to be biexponential, even though the ‘compartment parameters’ have little to do with those encountered within the medium.

Despite these limitations, multisite exchange models have nonetheless found numerous applications to predict exchange rate constants in tissue and cell suspensions. The two-site exchange model was first applied by McConnell (17) to analyze Carr–Purcell–Meiboom–Gill (CPMG) experimental data to obtain information about relaxation rates inside and outside cells and to determine cell membrane permeabilities (22–26). Kärger (18,19) and Andrasko (20) applied it to the pulsed gradient spin echo (PGSE) technique and developed a two-compartment model with exchange to analyze DWI, referred to as the Kärger model (KM). KM has been modified to describe non-Gaussian diffusion by taking into account the effect of restricted diffusion and the effect of cell size (7,27,28), and has been adapted to incorporate the effect of different T_2 relaxation rates between the compartments (24). KM has been applied to quantify the exchange rate constants of water in cell suspensions, such as erythrocytes (20,24,29), human breast cancer cells (30) and yeast cells (31,32). KM and other multicompartment models have also been utilized to interpret diffusion data in brain (7,31,33–36). The central question of the validity of KM for tissues, however, has remained relatively unexplored.

In the present work, we consider KM, as it is the simplest and most well-known compartment exchange model for DWI. Our goal is to investigate the accuracy of KM using Monte Carlo (MC) numerical simulations as applied to a model tissue consisting of identical parallel randomly packed cylinders with permeable walls (see Fig. 1). This geometry has been used to describe diffusion in axonal fibers (10,11,13,37,38), and the intuition gleaned from it may be extended to more complex three-dimensional (3D) structures. Our approach allows for arbitrary permeabilities and different diffusion coefficients for the ‘intracellular’ and ‘extracellular’ compartments. Similar MC methods have been applied previously to model diffusion in tissues (6,37).

In this work, we also discuss the justification of KM for tissues in the limit of low cell membrane permeability, starting from the original microscopic description of a single-component magnetization. We describe how the two pools, representing intra- and extracellular water, naturally arise after coarse-graining the tissue on a scale greater than the cell size, thereby elucidating the meaning of the KM parameters.

The outline of the article is as follows. First, we summarize the assumptions behind KM and argue that it can be applicable to tissues on a coarse-grained scale. Then, we describe our tissue model. Next, we focus on KM in relation to our tissue model. In order to utilize KM, we supplement it with effective parameters for the molecular pools. We emphasize that these parameters depend, in general, on both the time scale and orientation with respect to the cylinders. Next, we present the results of the simulations for specific parameter choices. Finally, based on the comparison with MC simulations, we discuss the validity of KM.

THE KÄRGER MODEL

The essence of KM is the following assumption. There exist two molecular spin-carrying pools, labeled 1 and 2, both occupying all the available voxel volume V . In other words, at each point $\mathbf{r}$, there exists a two-component magnetization density:

$$\mathbf{m}(t, \mathbf{r}) = \begin{pmatrix} m_1(t, \mathbf{r}) \\ m_2(t, \mathbf{r}) \end{pmatrix}. \quad [1]$$

The measurable quantity is the total magnetization in a voxel:

$$M(t) = M_1(t) + M_2(t) \equiv \int_V d\mathbf{r} (m_1(t, \mathbf{r}) + m_2(t, \mathbf{r})). \quad [2]$$

The pools ('compartments' or 'sites') contain fractions P_1 and P_2 of the spin-carrying molecules, with $P_1 + P_2 = 1$. This fixes the initial magnetization ratio:

$$\left. \frac{M_1}{M_2} \right|_{t=0} = \frac{P_1}{P_2}. \quad [3]$$

The second KM assumption is that the diffusion of the spin-carrying molecules of types 1 and 2 is Gaussian, with the diffusion coefficients D_1 and D_2 , correspondingly. Any effects of differing longitudinal and transverse NMR relaxation for the two pools are neglected.

The evolution of magnetization, eqn [1], is described by the coupled Bloch–Torrey equations (18,19):

$$\frac{\partial \mathbf{m}}{\partial t} = (\mathcal{D} \nabla^2 - i \mathbf{g}(t) \cdot \mathbf{r}) \mathbf{m} - \mathcal{R} \mathbf{m}. \quad [4]$$

Here, Δ^2 is the Laplacian, $D = \text{diag}(D_1 D_2)$ is the diagonal matrix of compartment diffusivities and $\mathbf{g}(t)$ is the externally applied time-dependent gradient of the Larmor frequency (the same for both magnetization components). The exchange between pools is assumed to occur independent of the position $\mathbf{r}$, at any time and at any place, i.e. completely uncorrelated from diffusion. It is a Poisson process (18,29) governed by the constant rate matrix:

$$\mathcal{R} = \begin{pmatrix} \tau_1^{-1} & -\tau_2^{-1} \\ -\tau_1^{-1} & \tau_2^{-1} \end{pmatrix}. \quad [5]$$

The mean lifetimes (residence times) τ_1 and τ_2 for molecules in the first and second compartments satisfy the detailed balance:

$$\frac{P_1}{\tau_1} = \frac{P_2}{\tau_2}. \quad [6]$$

The diffusion-weighted signal $M_q(t)$, acquired using the balanced gradient pulse $\mathbf{g}(t)$ (39), corresponds to the Fourier transform of the voxel-averaged spin-packet magnetization density, given by eqn [1], with the initial condition:

$$\left. \begin{pmatrix} m_1(t, \mathbf{r}) \\ m_2(t, \mathbf{r}) \end{pmatrix} \right|_{t=0} \propto \begin{pmatrix} P_1 \\ P_2 \end{pmatrix} \delta(\mathbf{r}), \quad [7]$$

according to the population ratio [eqn [3]]. In other words, the DWI signal is the sum of the components of the voxel-averaged diffusion propagator $\mathbf{m}(t, \mathbf{q}) = \int d\mathbf{r} e^{-i\mathbf{q}\cdot\mathbf{r}} \mathbf{m}(t, \mathbf{r})$, where $\mathbf{q} = \int_0^t \mathbf{g}(t') dt'$. The Gaussian diffusion assumption allows one to represent the matrix $D\Delta^2 - i\mathbf{g}(t) \cdot \mathbf{r} \rightarrow -Dq^2$. At this point, the voxel-averaged eqn [4] becomes a system of two ordinary rate equations for compartment magnetizations M_1 and M_2 :

$$\frac{\partial}{\partial t} \begin{pmatrix} M_1 \\ M_2 \end{pmatrix} = - [\mathcal{D}q^2 + \mathcal{R}] \begin{pmatrix} M_1 \\ M_2 \end{pmatrix}, \quad [8]$$

which can be solved in a manner analogous to the treatment of magnetic relaxation in two-phase systems, as introduced by Zimmerman and Brittin (16).

In the absence of exchange between the molecular pools, $R=0$, the DWI signal is a biexponential function with weights P_1, P_2 and compartment diffusivities D_1, D_2 . A nonzero exchange rate results in effective ‘rotation’ in the parameter space. The solution is given by the sum of rapidly and slowly decaying exponentials:

$$\frac{M_q}{M_0} = P'_1 e^{-D'_1 q^2 t} + P'_2 e^{-D'_2 q^2 t}, \quad [9]$$

where M_q represents the diffusion-weighted transverse magnetization with M_0 its value without diffusion weighting, $M_0 = M|_{q=0}$. The rotated parameters are (18-20,31):

$$D'_{1,2} = \frac{1}{2} \left[D_1 + D_2 + \frac{1}{q^2} \left(\frac{1}{\tau_1} + \frac{1}{\tau_2} \right) \pm \sqrt{\left(D_2 - D_1 + \frac{1}{q^2} \left(\frac{1}{\tau_2} - \frac{1}{\tau_1} \right) \right)^2 + \frac{4}{q^2 \tau_1 \tau_2}} \right],$$

$$P'_1 = 1 - P'_2, \quad P'_2 = \frac{P_1 D_1 + P_2 D_2 - D'_1}{D'_2 - D'_1}. \quad [10]$$

We emphasize that the parameters D'_1 and D'_2 are not the diffusion coefficients of molecules in certain compartments with weights P'_1 and P'_2 , as they explicitly depend on the diffusion wavenumber q . The physical diffusivity $D \equiv \langle x^2(t) \rangle / 2t$ is, by definition, independent of q , as the mean square molecular displacement $\langle x^2 \rangle$ cannot depend on the diffusion weighting. It is determined by the lowest (second) order in the cumulant expansion of the DWI signal, as shown below.

Cumulant expansion representation of KM

In principle, to fully validate KM, one has to evaluate the diffusion propagator in a model medium (in our case, parallel permeable cylinders), and compare it with eqn [9]. Instead of calculating the propagator directly, in the following we restrict ourselves to the second and fourth cumulants of KM, which are easier to compute accurately, as well as being of primary physical interest.

The cumulant expansion of the diffusion propagator corresponds to the Taylor expansion in the powers of q of the magnetization logarithm, $\ln M_q$ (40,41). In equilibrium, symmetry implies that only even orders in q contribute. Practically, the expansion is often made in the diffusion-weighting b value which, in the narrow pulse limit, is:

$$b = q^2 t. \quad [11]$$

The second- and fourth-order coefficients in the Taylor series of $\ln M_q$ in q yield the apparent diffusion coefficient D and kurtosis K (42):

$$\ln \frac{M_q}{M_0} = -bD + \frac{1}{6}K(bD)^2 + O(b^3). \quad [12]$$

The second and fourth cumulants of KM (eqn [9]) have been obtained by Jensen *et al.* (42):

$$D_{\text{KM}} = P_1 D_1 + P_2 D_2, \quad [13]$$

$$\text{var}(D_{\text{KM}}) = P_1 P_2 (D_1 - D_2)^2, \quad [14]$$

$$K_{\text{KM},0} = 3 \frac{\text{var}(D_{\text{KM}})}{D_{\text{KM}}^2}, \quad [15]$$

$$K_{\text{KM}} = K_{\text{KM},0} \frac{2}{t} \left[1 - \frac{1}{t} \left(1 - e^{-t} \right) \right], \quad \bar{t} \equiv \frac{t}{\tau_{\text{ex}}}. \quad [16]$$

The time scale

$$\tau_{\text{ex}} = P_1 \tau_2 = P_2 \tau_1 \quad [17]$$

is commonly referred to as the ‘exchange’ or ‘mixing’ time.

One feature of KM that stands out immediately is that its diffusion coefficient, given by eqn [13], is time-independent. In general, the diffusion coefficient in the presence of restrictions depends on time (5,14,15). As we argue below, KM may become asymptotically valid in the long time limit, when the time dependence of the diffusion coefficient becomes negligible. The KM diffusion coefficient, eqn [13], is also independent of the exchange time.

The kurtosis of KM decreases with time, starting at $K_{\text{KM},0}$, described by eqn [15], and approaches zero as $1/t$ for $t \gg \tau_{\text{ex}}$. In the limit $t \rightarrow \infty$, the diffusion becomes Gaussian with the constant diffusion coefficient given by eqn [13].

Applicability of KM: coarse-grained description

The ideal example of a physical system governed by KM is a uniform fluid mixture, where the molecular species under consideration may perform Brownian motion either alone (compartment 1) or attached to some other carrier molecule with a different diffusion coefficient (compartment 2). Hence, it is natural that KM belongs to the multisite exchange type of models.

The microarchitecture of biological tissues is extremely complex and the microscopic proton magnetization $\psi(t, \mathbf{r})$ is governed by a complicated Bloch–Torrey equation which embodies all restrictions to molecular diffusion. The claim that such a simple model as KM applies to

tissues may seem, at first, quite puzzling. In particular, how do the two components of the KM magnetization [eqn (1)] at each spatial point $\mathbf{r}$ correspond to the original single-component magnetization $\psi(t, \mathbf{r})$?

Intuitively, one is tempted to compartmentalize water molecules between the intracellular space (ICS) and extracellular space (ECS). However, simply referring to ICS and ECS as pools 1 and 2 does not cure the above discrepancy of not having two species at each spatial point. Moreover, it creates another: the Laplacian in the coupled Bloch–Torrey equations [eqn [4]] is defined everywhere in the voxel; its definition becomes problematic for the sharply divided ICS and ECS of complex geometry (and especially singular for non-simply connected ICS). The Laplacian also implies unrestricted (Gaussian) diffusion everywhere in the voxel, which is empirically not the case. Foregoing the Bloch–Torrey equation and starting from eqn [8] merely sweeps the above problems under the carpet.

The compartmentalization puzzle can be resolved by satisfying the key KM assumption, eqn [1], after coarse graining (as illustrated in Fig. 1). Let us consider averaging the tissue properties over a length scale exceeding the cell dimensions: we split the voxel into domains larger than the cell size (but still much smaller than a voxel), and map the microscopic magnetization $\psi(t, \mathbf{r})$ within a given domain to the coarse-grained, two-component magnetization, eqn [1], corresponding to the coordinate of the center of this domain. The components of this coarse-grained magnetization correspond to the average magnetization of ICS and ECS within a given domain. Then, the Laplacian in eqn [4], meaningless on the cell scale, becomes well defined on the coarse-grained scale. Moreover, it requires no further correction, as both compartment diffusivities become Gaussian after coarse graining in the long time limit.

The coarse-grained view ceases to resolve individual cells, losing much of the information about their shape and packing; such a loss is an expected outcome of the massive averaging discussed in the Introduction. The remaining structural information is lumped into the coarse-grained magnetization. The relevant tissue characteristics that survive the averaging are the mean residence times and the long-time diffusivities of ECS and ICS. For ECS, the diffusivity is reduced by the tortuosity factor. The effective ICS diffusivity is sensitive to the cell topology. It is zero for compact (finite-volume) cells, which makes the intrinsic ICS diffusivity invisible in this case. (Zero diffusivity causes no diffusion weighting and thereby looks Gaussian in eqn [8].) For effectively infinite-volume cells (e.g. fibers), the ICS diffusivity remains finite along the noncompact cell dimension, although, in general, it can also be reduced compared with the intrinsic ICS value. The Gaussian ICS diffusivity must be additionally verified for the noncompact ICS, otherwise KM does not apply even after coarse graining. The information loss means that the DWI signal on the KM level cannot distinguish between tissues with different microscopic cell geometry for which the coarse-grained parameters (effective diffusivities and residence times) happen to be similar.

The present argument justifies KM as an effective theory on the scale exceeding the correlation length l_c of cell packing; the diffusion length corresponding to l_c defines the time scale t_c for which the tortuosity asymptote is approached, the ICS diffusivity is essentially zero (or a constant for noncompact cells) and the overall diffusion coefficient becomes asymptotically time independent, in agreement with KM. Hence, l_c and t_c determine the coarse-grained length and time scales above which KM applies: $r \gg l_c$ and $t \gg t_c$. The coarse graining also limits the available wavenumbers to $q \ll l_c^{-1}$. It should be noted that, depending on the packing geometry, the length scale l_c can parametrically exceed the cell dimension; in this respect, it is different from the length scales introduced in ref. (43). The corrections to KM are nonuniversal: they depend on the specific tissue geometry on the

scale below l_c , i.e. on the information beyond the residence times and long-time diffusivities.

Let us now focus on the exchange between the KM pools. As the KM parameters are defined only on the coarse-grained spatial and temporal scales, the meaningful residence times must be sufficiently long: $\tau_1, \tau_2 \gg t_c$. From this requirement, it follows that the exchange should be ‘barrier limited’, as empirically suggested by Kärger (18), which physically means poorly permeable cell membranes. In this limit, the exchange process is Poissonian. In the opposite limit of the diffusion-limited exchange (leaky membranes), the magnetization homogenizes within each domain of size l_c on the time scale below t_c , and the two-component magnetization (eqn [1]) becomes obsolete. This can be seen on the level of

eqn [8], when the R term dominates. The ‘slow’ component $\propto \begin{pmatrix} P_1 \\ P_2 \end{pmatrix} M_{\text{slow}}(t, q)$, corresponding to the zero eigenvalue of R and describing the mean magnetization in a domain, survives ($D'_2 \rightarrow D_{\text{KM}}, P'_2 \rightarrow 1$), whereas the weight of the ‘fast’ component, corresponding to the ICS/ECS magnetization imbalance, vanishes: $P'_1 \rightarrow 0$. In this way, we are left with a single-component magnetization, $M_{\text{slow}}(t, q)$, that decays exponentially in agreement with Gaussian diffusion. It is thus not surprising that, in the limit of negligible membrane permeability, KM fails, as has been shown explicitly (15).

From these physical considerations, it becomes evident that multisite exchange models must be independently justified when applied to complex media such as tissues and, in the process of justification, supplemented by the effective coarse-grained parameters which may depend on the orientation, time scale and other factors.

In this study, we supplement KM for a realistic tissue model with effective parameters (compartment diffusivities) to check its validity in the long time limit of restricted diffusion.

TISSUE MODEL

Let us consider a set of parallel randomly packed nonoverlapping identical cylinders with radius R . The space inside the cylinders is regarded as ICS and the space outside the cylinders as ECS. This 3D geometry can serve as a model for axons in white matter (WM). Moreover, the diffusion dynamics in a plane perpendicular to the cylinders can serve as a genuine two-dimensional (2D) model for the diffusion in cell suspensions and *in vivo* tissue. Both ICS and ECS are filled with water, having free diffusion coefficients of D_i and D_e , respectively. The volume fraction of ECS is α .

In the case of impermeable membranes, the diffusion is restricted in ICS and its long-time effective diffusivity in a given direction is:

$$D_{i,\infty}(\theta) = D_i \cos^2 \theta, \quad [18]$$

where θ is the angle with respect to the cylinder axis. We assume here that the transverse diffusion in the cylinders is zero. This approximation seems reasonable when the diffusion length, which is on the order of 5 μm in a typical DWI experiment, is large compared with the cylinder diameter. For the study of diffusion in WM, this assumption may be justified as the axon diameter is typically about 1 μm (44,45). This assumption is also supported by the fact that no time dependence of the diffusion metrics has been observed in WM at clinically available diffusion times (46).

Similarly, for ECS, the diffusion becomes hindered at long times, i.e. with a Gaussian profile but a lower diffusivity. More specifically, we obtain:

$$D_{e,\infty}(\theta) = D_e \left(\cos^2 \theta + \frac{1}{\lambda} \sin^2 \theta \right), \quad [19]$$

where

$$\lambda \equiv \frac{D_e}{D_{e,\infty}(\pi/2)} \quad [20]$$

is the ECS tortuosity for the perpendicular direction. λ is a property of the medium, i.e. the geometry and connectivity of ECS (47). KM can be applied in this long-time limit, where the diffusivities in both ECS and ICS become constant. Although the diffusion is restricted and non-Gaussian in ICS, KM works trivially as the transverse diffusivity in ICS is zero in this limit.

To study the effect of nonzero permeability, we define the water lifetime or residence time for ICS by:

$$\tau_i = \frac{V}{A\kappa} = \frac{R}{2\kappa}, \quad [21]$$

where κ is the permeability of the ICS–ECS boundary (the cell membrane), and V and A are the volume and surface area of the cylinders. The water lifetime for ECS is then:

$$\tau_e = \tau_i \frac{\alpha}{1 - \alpha}, \quad [22]$$

and the exchange time is:

$$\tau_{ex} = \alpha \tau_i = (1 - \alpha) \tau_e. \quad [23]$$

Kärger description applied to the tissue model

The KM description of the diffusion in a given direction θ corresponds to the substitution of D_1 , D_2 , P_1 and P_2 by $D_{e,\infty}(\theta)$, $D_{i,\infty}(\theta)$, α and $(1 - \alpha)$, respectively, in eqns [13],[14],[15] and [16], with the exchange time defined by eqn [23].

In the direction along the cylinders, in particular, we find:

$$D_{KM,\parallel} = (1 - \alpha) D_i + \alpha D_e, \quad [24]$$

$$K_{0,KM,\parallel} = 3 \frac{\alpha (1 - \alpha) (D_i - D_e)^2}{[(1 - \alpha) D_i + \alpha D_e]^2}. \quad [25]$$

Similarly, in the perpendicular direction:

$$D_{\text{KM},\perp} = \alpha \frac{D_e}{\lambda}, \quad [26]$$

$$K_{0,\text{KM},\perp} = 3 \frac{1-\alpha}{\alpha}. \quad [27]$$

The initial KM kurtosis value, given by eqn [27], should be understood on a coarse-grained scale, rather than at $t=0$. It is possible to extract the four model parameters (α , D_i , D_e and λ) by combining eqns [24],[25],[26] and [27].

We note that the KM diffusion in any direction does not depend on the exchange time, and, as a result, is insensitive to the permeability. The KM diffusivity D_{KM} behaves as if the membranes are impermeable, whereas the effect of a nonzero permeability becomes manifest in the KM kurtosis K_{KM} and higher order cumulants.

Applicability of the Kärger description

As our tissue model is anisotropic, so is the coarse-grained description. Hence, we consider the two principal directions (parallel and perpendicular to the cylinders) separately.

We start with the perpendicular case, for which the in-plane diffusion is isotropic, and the ‘2D’ circular cells have finite volume. In accord with the coarse-grained argument developed above, all the time scales must exceed the correlation time t_c on which the effective time-independent ICS and ECS diffusivities emerge:

$$\perp \text{ direction: } t \gg t_c \text{ and } \tau_e, \tau_i \gg t_c. \quad [28]$$

The first condition above is for the diffusion to be in the long-time limit, and the second is for the barrier-limited exchange. As a measure of the correlation time, we choose:

$$t_c = \max \{ t_{D,i}, t_{D,e} \} \quad [29]$$

where the ICS and ECS diffusion times are defined as:

$$t_{D,i} \equiv \frac{R^2}{2D_i}, \quad [30]$$

$$t_{D,e} \equiv \frac{\lambda R^2}{2D_e} \frac{\pi}{1-\alpha}. \quad [31]$$

Here R and $R\sqrt{\frac{\pi}{1-\alpha}}$ are taken as measures of the compartment spatial dimensions of ICS and ECS, i.e. the typical distance traveled by a particle in between encountering the walls.

In the parallel case, the diffusion in both compartments is Gaussian from the outset. Hence, the coarse-graining scale l_c in this direction is zero, and the applicability condition reads:

$$\parallel \text{ direction: } t > 0 \text{ and } \tau_e, \tau_i \gg t_e. \quad [32]$$

The coarse-graining scale for the exchange here is still set by the transverse value, eqn [29], as exchange occurs in the perpendicular direction.

METHODS

MC simulations

The tissue structure is modeled with a geometry consisting of infinitely long, parallel-aligned permeable cylinders having a random in-plane packing geometry (see Fig. 1). The diameter and density of the cylinders have been chosen to be similar to those observed in the human corpus callosum (44,45): a fixed diameter of 1.25 μm and a packing density $\alpha=0.5$, corresponding to an axonal fiber density of 40 fibers per 100 μm^2 .

Values for the bulk diffusivities in ICS and ECS have been chosen to be 0.5 and 1 $\mu\text{m}^2/\text{ms}$ for D_i and 1 and 2 $\mu\text{m}^2/\text{ms}$ for D_e . Three different combinations for the intracellular and extracellular diffusivities are simulated to evaluate the effect of their ratios: $D_e/D_i=1, 2$ and 4. Table 1 summarizes the combinations of D_e and D_i , and the corresponding characteristic diffusion times and correlation times according to eqns [29],[30] and [31].

We emphasize that these particular choices for the physical parameters are made for the sake of physical definiteness. By rescaling, our quantitative results are actually applicable to a broader range of models. In addition, our qualitative results should be generally valid.

The diffusion process is modeled by 3D MC dynamics of random walkers, which are initially dispersed randomly within the volume. The trajectory of each random walker is generated by moving the particle during each time step dt over a distance $dr = \sqrt{6D dt}$ in a randomly chosen radial direction (48). The second- and fourth-order moments of the total traveled distance of the random walkers in a given direction are used to calculate the time-dependent apparent diffusion coefficient $D(t)$ and diffusional kurtosis $K(t)$ according to the definitions:

$$D(t) = \frac{1}{2t} \langle (\mathbf{n} \cdot \mathbf{r})^2 \rangle, \quad [33]$$

$$K(t) = \frac{\langle (\mathbf{n} \cdot \mathbf{r})^4 \rangle}{\langle (\mathbf{n} \cdot \mathbf{r})^2 \rangle^2} - 3, \quad [34]$$

where $\mathbf{r}$ is the net displacement of a random walker during a diffusion time t in a given direction $\mathbf{n}$, with $\mathbf{n}$ being the unit vector.

The exchange of random walkers between the inside and outside of cylinders is represented in terms of the transmission probabilities $P_{T,i \rightarrow e}$ and $P_{T,e \rightarrow i}$ for a random walker to pass through a membrane from the intracellular to the extracellular side, and vice versa (see Appendix 1 for derivation):

$$P_{T,i \rightarrow e} = 2ds \frac{\kappa}{D_i}, \quad [35]$$

$$P_{T,e \rightarrow i} = 2ds \frac{\kappa}{D_e}. \quad [36]$$

Here, ds is the distance between the random walker and the membrane surface, and the equations are only applied if $ds \leq dr$ and the random walker were to cross the membrane. It should be noted that eqns [35] and [36] are similar to the formula derived by Szafer *et al.* (6).

Simulations were performed for varying permeabilities κ between 0.0016 and 4 $\mu\text{m}/\text{ms}$, such that the corresponding exchange times (22 in total) varied between 0.075 and 100 ms. (Table 2 summarizes the permeabilities and exchange times for the examples plotted in Figs. 2, 4 and 5.) For each set of κ , D_i and D_e , the dynamics of 2×10^6 random walkers in total were simulated for a diffusion time t up to $50\tau_{\text{ex}}$. The time step dt of the simulation was chosen so that the maximum possible transmission probabilities (i.e. $ds=dr$) were less than 0.01 and the ratio dr/R was less than 0.1.

The random walk simulator was developed in C++. The simulations were performed on the NYU General Cluster, which is a multipurpose high-performance cluster offering 140 compute nodes, each containing two Intel Xeon Quad-Core 64-bit processors, running at 2.33 GHz. With an average of 200 CPU cores used simultaneously, all simulations took about 120 h.

Evaluation of the accuracy of KM

The simulated diffusivity $D(t)$ becomes constant in the long-time limit, as shown in Fig. 2. We compare this long-time diffusivity D_∞ with the diffusivity predicted by KM, given by eqn [13] for the general case and eqns [24] and [26] for diffusivity in the parallel and perpendicular directions, respectively (as explained in the section on Kärger description applied to the tissue model). To evaluate the accuracy of KM for the diffusivity, we consider the relative error, defined by:

$$\text{error } D_{\infty, \text{KM}} = \frac{D_{\text{KM}} - D_\infty}{D_\infty}. \quad [37]$$

The simulated kurtosis $K(t)$ decreases towards zero at long times, as shown in Fig. 4. The formula for the time-dependent KM kurtosis (eqn [16]) was fitted to each simulated $K(t)$ curve using a Levenberg–Marquardt algorithm (only the long-time intervals of the simulated curves were used, as described below). The fitted values $\tau_{\text{ex,fit}}$ and $K_{0, \text{KM,fit}}$ were compared with the true values for τ_{ex} , defined by eqn [23], and KM for the initial kurtosis $K_{0, \text{KM}}$, as described by eqn [15] in the general case and eqns [25] and [27] for kurtosis in the parallel and perpendicular directions, respectively. To evaluate the accuracy of KM for kurtosis, we consider the relative errors, defined by:

$$\text{error } K_{0, \text{KM,fit}} = \frac{K_{0, \text{KM,fit}} - K_{0, \text{KM}}}{K_{0, \text{KM}}}, \quad [38]$$

$$\text{error } \tau_{\text{ex,fit}} = \frac{\tau_{\text{ex,fit}} - \tau_{\text{ex}}}{\tau_{\text{ex}}}. \quad [39]$$

Each simulated dataset for a combination of k , D_i and D_e of 2×10^6 random walkers was generated in five subgroups, such that each subgroup of 4×10^5 could be evaluated individually. We consider the mean values and standard deviation over these five subgroups.

RESULTS

Diffusivity

Figure 2 shows the simulated $D(t)$ curves for varying permeability in the parallel ($\theta = 0$) and perpendicular ($\theta = \pi/2$) directions, as well as in an intermediate direction ($\theta = \pi/4$).

The diffusion in the parallel direction, as shown in Fig. 2c, f, i, is independent of the permeability and is accurately described by KM (eqn [24]). The diffusivity in all other directions (examples shown in Fig. 2a, b, d, e, g, h) becomes constant only in the long-time limit, and the value of this terminal diffusivity depends on the permeability. For low permeability, i.e. long τ_{ex} , there is agreement between the simulated terminal diffusivity and D_{KM} predicted by KM, given by eqn [13], where the tortuosity λ is chosen to be 1.74 [this value is taken from ref. (48) from simulations in a random packing density with $\alpha = 0.5$].

Figure 3 shows the relative errors in diffusivity made by KM, as described by eqn [37]. In connection with the coarse-graining argument, the errors are plotted as a function of τ_c/t_c , where the correlation time is defined in eqn [29] (cf. Table 1). In this way, the errors for the perpendicular direction scale similarly for the three combinations of D_i and D_e , which is expected from the condition given by eqn [28]. As an example, the error of D_∞ is about 25% when $\tau_c/t_c = 1$. Numerically we observe that errors become negligible when $\tau_c/t_c \sim 10$. This can be understood by applying a more refined analysis based on the density correlation function for the packing geometry (21), which leads to a correlation length of about $2.6R$ and a correlation time about 7 times larger than that defined by Eq. [29]. It should be noted that the errors in diffusivity are always negative, as D_{KM} is permeability independent and behaves as if the membranes are impermeable. Hence, for finite permeability, D_{KM} is lower than the observed diffusivity.

Diffusional kurtosis

Figure 4 shows the simulated $K(t)$ curves for varying permeability in the parallel ($\theta = 0$), perpendicular ($\theta = \pi/2$) and intermediate ($\theta = \pi/4$) directions.

The initial kurtosis value $K_0 \equiv K(t)/t=0$ reflects the diffusion heterogeneity and is correctly described by eqn [25] in all directions. In the parallel direction, $K(t)$ decreases monotonically towards zero with time, as shown in Fig. 4c, f, i. There is agreement with KM (eqn [16]) for long τ_{ex} , although this agreement becomes less for decreasing τ_{ex} . In the other directions, $K(t)$ first increases with time, reaches a maximum value and subsequently decreases at long times (see Fig. 4a, b, d, e, g, h). That time-dependent decrease in K coincides with KM (eqn [16]) in the limit of long τ_{ex} . The value for the maximum kurtosis in that limit is approximately given by the initial KM kurtosis value $K_{0,\text{KM}}$ in that direction according to eqn [15]. In the case of perpendicular diffusion, $K_{0,\text{KM},\perp}$, given by eqn [27], depends only on αa , the ECS fraction.

The KM kurtosis time dependence, eqn [16], which decreases with time, can be used to describe the kurtosis decrease after the moment it reaches its peak. For these times, all data

curves fit well to the KM approximation (correlation coefficients of 0.999 and higher), as illustrated in Fig. 5. The time interval considered for the fitting was always taken in the range starting from the time at which kurtosis reaches its maximum to where it becomes smaller than a noise threshold of 0.05. Changing the interval for fitting within this range did not affect the fitting results significantly.

Although KM fits the time dependence in the long-time limit accurately, the fitted values for the initial kurtosis $K_{0,KM,fit}$ and exchange time $\tau_{ex,fit}$ differ significantly from the KM initial kurtosis value $K_{0,KM}$ (eqns [25] and [27]) and the real exchange time τ_{ex} for larger permeabilities. The relative errors of K_0 and τ_{ex} as defined by eqns [38] and [39] are shown in Fig. 6 for the different combinations of D_i and D_e and for different directions.

The errors of $K_{0,KM}$ are given in Fig. 6a, c, e. The value $K_{0,KM}$ is underestimated; the error in this parameter increases with decreasing τ_{ex} and increasing θ (from the parallel to the perpendicular direction). The errors in τ_{ex} are given in Fig. 6b, d, f, showing that the KM exchange time overestimates the true value. This effect increases with decreasing true exchange value τ_{ex} and increasing θ .

For the perpendicular direction, the absolute values of the relative errors of $K_{0,KM}$ and τ_{ex} are similar. In the parallel direction, the errors in τ_{ex} are about one-half of those for the perpendicular case, whereas the errors of $K_{0,KM}$ become negligible.

The errors in Fig. 6 are plotted as a function of τ_e/t_c . In this way, the errors for the perpendicular direction scale similarly for the three combinations of D_i and D_e . As an example, the error of $\tau_{ex,\perp}$ is about 20% when $\tau_e/t_c \approx 2$.

DISCUSSION

Validity of KM

This study has been devoted to the validity of KM for the quantification of diffusion in complex tissue microarchitecture. We have provided the physical reasoning that justifies KM as a coarse-grained description of tissues, summarized its general applicability conditions and confirmed them using MC simulations of diffusion in an idealized tissue geometry of randomly packed parallel cylinders. In particular, we have established the following.

- i. KM provides an effective description on the coarse-grained scale exceeding the cell packing correlation length l_c . The coarse-grained magnetization naturally breaks into two components [eqn (1)] with the compartments interpreted as ICS and ECS. The description of exchange between the compartments is consistent as long as the membranes separating ICS and ECS are sufficiently impermeable.
- ii. MC simulations confirm that KM can be applied in the long-time limit, when the time exceeds the correlation time t_c determined by the correlation length l_c (cf. eqns [28] and [32]). KM has, inherently, a time-independent overall diffusivity and, in practice, applies in the regime in which the diffusivity time dependence becomes negligible (the tortuosity limit). The KM compartment diffusivities appear to be reduced when compared with their intrinsic ICS and ECS values. The KM diffusivity coincides with the diffusivity in the zero exchange limit, i.e. for impermeable membranes. Hence, for permeable membranes, the KM diffusivity is lower than the observed value. In the opposite case of fast exchange, KM fails and the diffusion becomes Gaussian, as discussed above in the section on Applicability of KM: coarse-grained description.

- iii. The diffusional kurtosis of KM decreases with time, and is shown to describe the simulated kurtosis reasonably well after it reaches its peak. When the membrane permeability is sufficiently low, the time dependence of the observed kurtosis can be used to quantify the exchange time and, hence, given the geometry, the membrane permeability as well. For higher permeabilities, however, a fit to KM may significantly overestimate the exchange time, i.e. underestimate the permeability k .
- iv. The anisotropy of our tissue model results in different KM applicability conditions for different directions (cf. eqns [28] and [32]). We discuss these separately below.

Water molecules diffusing in the direction parallel to the cylinders do not encounter barriers in that direction; hence, the diffusion is Gaussian in both compartments at all times. The simulated diffusivities (Fig. 2c, f, i) agree precisely with the KM value. The simulated kurtosis values (Fig. 4c, f, i) confirm that KM applies for the time-dependent kurtosis in this direction for sufficiently long exchange times. For short exchange times, the exchange becomes correlated with the diffusion because of the existence of two physical compartments, and the condition of eqn [32] does not apply, as demonstrated by the simulation results.

For diffusion in the perpendicular direction, the molecules encounter barriers, resulting in restricted diffusion and time-dependent diffusivities. In this case, both the condition for the long-time limit and for barrier-limited exchange apply (cf. eqn [28]). KM is a valid approximation for the total diffusivity at long times in the limit of impermeable walls (long τ_{ex}), as shown in Fig. 2a, d, g. As the fitting results did not depend on the considered time interval, we conclude that, once the kurtosis reaches a maximum, the system is in the long-time regime, and KM describes the time dependence of kurtosis well for long exchange times, as shown in Fig. 4a, d, g. The fitted exchange time $\tau_{\text{ex,fit}}$ is overestimated for higher permeabilities.

Applications

The simulation results for a geometry of parallel cylinders may be applied to diffusion in anisotropic tissues with a strongly aligned fibrous microstructure, such as found in brain WM (49) and skeletal muscle (50). In addition, the results in this study for diffusion in the perpendicular direction can be extended to isotropic tissues and cell suspensions, e.g. of erythrocytes.

For the simulations, permeability values were chosen to cover the entire range of cell permeability values listed in the literature (34). For most cells, the water membrane permeability is lower than that of erythrocytes, but larger than $0.001 \mu\text{m/ms}$ (51). The residence time or lifetime of the cell relates to its membrane permeability and surface to volume ratio according to eqn [21]. As a consequence, the water lifetime inside cells is proportional to the cell size, as illustrated by Stanisiz *et al.* [see Table 2 in ref. (51)]. Hence, by rescaling the lifetime as well as the exchange time, defined by eqn [23], and the correlation times, defined by eqns [30] and [31], the simulation results in this study can be applied to estimate the validity of KM for other cell types as well.

The KM conditions, given by eqns [28] and [32], are in favor for small cells with low permeability values, as the diffusion in these systems has reached the long-time limit at clinically available diffusion times and the ICS residence time τ_i is sufficiently long. As an example, Stanisiz *et al.* (7) used a three-compartment exchange model to estimate the exchange times for axons and glial cells in bovine optic nerve to be 72 and 45 ms, respectively, corresponding to membrane permeabilities of 0.009 and $0.017 \mu\text{m/ms}$, respectively, and cell dimensions of 2.6 and $3.1 \mu\text{m}$. They checked the validity of these

estimates by comparison of the analytical model with MC simulations in the specific geometry of glial and axonal cells, finding good agreement for sufficiently long times ($t \geq 15$ ms). Using their numbers, our study indicates that the application of KM should indeed be valid.

This study, however, also indicates that, for large cells, such as neuronal cell bodies, the correlation time can be relatively long compared with τ_i , making KM less likely to be valid for clinically available diffusion times. Moreover, the diffusion in large cells can also be impeded inside the cell cytoplasm by internal membranes from organelles, resulting in multiple compartments and barriers with different permeabilities, which makes KM less straightforward to apply.

Red blood cells have a diameter of 6–8 μm and a thickness of 2 μm , making them potential candidates for the application of KM to estimate the exchange times and related ICS residence time. There exists extensive literature on the permeability and related τ_i values of erythrocytes [for an overview, see ref. (52)], estimated using either measurement of the transverse relaxation in the presence of extracellular contrast agent (22,24), or DWI combined with KM or other multicompartment models (20,24,53,54). The measured lifetime ranged between 6 and 17 ms. Conlon and Outhred (22) determined τ_i of erythrocytes to be 8.2 ms at 37°C using T_2 relaxation experiments where ECS is doped with paramagnetic contrast agent and thus does not contribute to the measured NMR signal. Andrasko (20) reported τ_i of 17 ms at 25°C using DWI, a twofold larger value. The simulation results presented here might explain the discrepancy between the measured τ_i values between the two experiments: it is likely that the applicability of the two-compartment model for relaxation (16) may be broader, as ECS is effectively not contributing, placing less of a demand on the value of the ECS residence time. In this case, the T_2 method may be more accurate, whereas the KM method of ref. (20) may have overestimated the exchange time, in accord with our findings.

In this study, we have presented a specific model for diffusion in anisotropic tissue. Hence, the simulation results may be directly relevant to the study of diffusion in axonal and muscle fibers. In the context of the brain, Quirk *et al.* (34) measured τ_i in rat brain tissue using the longitudinal relaxation in the presence of extra-cellular contrast agent, and reported a mean τ_i of 552 ms, corresponding to a permeability of 0.001 $\mu\text{m}/\text{ms}$. Meier *et al.* (35) measured τ_i in rat brain tissue using DWI, and reported a mean τ_i of 622 ms. Regarding muscle tissue, Landis *et al.* (25) measured an average water lifetime in the thigh muscle sarcoplasm of 1.1 s, corresponding to a permeability of 0.013 $\mu\text{m}/\text{ms}$. For both muscle and brain tissue, the related exchange times are relatively long, which is favorable to the applicability of KM, especially in WM, because the diffusion is already in the long-time limit at clinically available diffusion times (46).

This study shows that, for tissue anisotropy, the KM kurtosis along and across the fibers contains complementary information. The initial kurtosis in the direction along the fibers, $K_{0,\text{KM},\parallel}$, reflects the diffusional heterogeneity between ICS and ECS, whereas kurtosis in the direction perpendicular to the fibers, $K_{0,\text{KM},\perp}$, is determined by the fiber volume fraction. The latter parameter could potentially provide information for the assessment of WM pathologies, such as Alzheimer's disease (55) and multiple sclerosis (56,57). However, further studies are required to evaluate the benefit of using anisotropic KM parameters in clinical applications.

CONCLUSIONS

The present MC study shows that KM, although highly idealized, can accurately model diffusion for a realistic tissue geometry at long times, provided that the compartment diffusivities are time independent and the permeability is sufficiently low such that exchange between the compartments is barrier limited. The time dependence of kurtosis allows one to determine the exchange time. The simulations show, however, that, for more permeable membranes, i.e. when the exchange becomes correlated with diffusion, the KM-derived exchange times are overestimated.

Acknowledgments

We would like to thank the New York University (NYU) High Performance Computing (HPC) group for their support in running the simulations on the NYU General Cluster (DellCluster).

Support for this work was provided by the Litwin Foundation for Alzheimer's Research, National Institutes of Health (grant R01AG027852) and the Henri Benedictus Fund, King Baudouin Foundation.

APPENDIX 1

To derive the relationships described by eqns [35] and [36] between the transmission probability of a membrane and its permeability, an approach has been applied, similar to that used in Powles *et al.* (58). In that work, the transmission probability is derived for random walk simulations in the one-dimensional (1D) case, where the random walkers and the membranes are positioned on a discrete lattice of equidistant points. We derive here the transmission probability for the case in which the positions of both the random walkers and the membranes can take any values.

First, let us consider the 1D case with the diffusion coefficient D being the same on both sides of the membrane, positioned at $x=x_M$. The population of particles at position $x=x_p$, on the right side of the membrane, with $x_p - x_M \leq dx$ at time $T+dt$, is given in terms of the populations at time T by (see Fig. 7):

$$\mathcal{P}(x_p, T+dt) = \frac{1}{2} \mathcal{P}(x_p+dx, T) + \frac{P_T}{2} \mathcal{P}(x_p - dx, T) + \frac{1-P_T}{2} \mathcal{P}(2x_M - x_p+dx, T), \quad [40]$$

where P is the particle population at a given position and time, dx is the step over which a particle moves during dt , P_T is the probability of a particle to be transmitted and $(1 - P_T)$ is the probability for a particle to be reflected at the membrane surface. As illustrated in Fig. 7, $dx_- = x_M - x_p$ and $dx_+ = x_p + dx - x_M$ are the distances between the membrane and the random walker at time T and time $T+dt$, respectively, where the subscripts ‘-’ and ‘+’ denote infinitesimally to the left and right of the membrane at $x=x_M$.

Each term in eqn [40] can be expanded around $x=x_M$ using a Taylor series. In the further derivation, we consider the terms up to the first-order derivative in time $\partial P / \partial t$ and the second-order spatial derivative $\partial^2 P / \partial x^2$ and neglect higher order terms.

The distribution P obeys the diffusion equation away from the membrane:

$$\frac{\partial \mathcal{P}}{\partial t} = D \frac{\partial^2 \mathcal{P}}{\partial x^2}. \quad [41]$$

All second-order terms in $\partial^2 P / \partial x^2$ of the Taylor expansion vanish by substitution of eqn [41] and taking into account that $\partial^2 P / \partial x^2$ is continuous across the membrane (58) and $dx^2 = 2D dt$ in the 1D case.

The boundary condition at the permeable membrane with permeability κ is (58):

$$\kappa(\mathcal{P}_- - \mathcal{P}_+) = -D \frac{\partial \mathcal{P}}{\partial x} \Big|_- \quad [42]$$

Using eqn [42] and the boundary condition that $\partial P / \partial x$ is continuous across the membrane, we derive:

$$P_T = \frac{2dx_- \kappa / D}{1 + 2dx_- \kappa / D}. \quad [43]$$

This equation can be simplified to:

$$P_T = \frac{2dx_- \kappa}{D} \quad [44]$$

when $2dx_- \kappa / D \ll 1$.

In the following case, when D is different on each side of the membrane, the first boundary condition becomes:

$$D_- \frac{\partial \mathcal{P}}{\partial x} \Big|_- = D_+ \frac{\partial \mathcal{P}}{\partial x} \Big|_+ \quad [45]$$

where D_- and D_+ are the diffusion coefficients in the compartments left and right of the membrane. The transmission probability $P_{T,- \rightarrow +}$ to pass the membrane from the left side becomes:

$$P_{T,- \rightarrow +} = \frac{2dx_- \kappa}{D_-}. \quad [46]$$

Extension onto higher dimensions can be derived from the 1D case by assuming that the displacement during the time step dt is very small, such that the membrane surface can be considered to be flat. Equations [35] and [36] are derived from eqn [46] by replacing dx_- by the corresponding normal distance ds to the membrane, and D_- by the free diffusion coefficient in ICS and ECS, respectively.

Abbreviations used

1D	one-dimensional
2D	two-dimensional
3D	three-dimensional
CPMG	Carr–Purcell–Meiboom–Gill

DWI	diffusion-weighted imaging
ECS	extracellular space
ICS	intracellular space
KM	Kärger model
MC	Monte Carlo
PGSE	pulsed gradient spin echo
WM	white matter

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Figure 1.

A cross-section of $125\ \mu\text{m} \times 125\ \mu\text{m}$ through the structure of parallel cylinders generated to simulate the diffusion, showing the random packing and the fixed diameter of the cylinders. Coarse graining involves dividing the sample into domains with size corresponding to the correlation length of the packing geometry (dashed lines).

Figure 3. Relative errors of the long-term diffusivity D_{∞} in comparison with the Kärger model (KM), as defined by eqn (37), for the different combinations of D_i and D_e in the order listed in Table 1. The errors increase for decreasing τ_{ex} and increasing angle θ .

Figure 4.

Comparison between the Kärger model (KM) (black lines) and the simulated time-dependent kurtosis K in three directions for the different combinations of D_i and D_e in the order listed in Table 1. The arrows indicate how the curves in the figure change with increasing permeability (τ_{ex} decreases from 20 to 0.075 ms; the corresponding permeabilities are given in Table 2). K at time zero depends on the ratio D_i/D_e and is the same in all directions. K decreases monotonically with time in the parallel direction, whereas, in the other direction, K first peaks before decreasing towards zero. KM agrees with the simulated K for long τ_{ex} in the time interval during which K decreases with time.

Figure 5. Simulations of the time-dependent perpendicular kurtosis $K_{\perp}$ (a) and parallel kurtosis $K_{\parallel}$ (b) for varying exchange times with $D_i = 0.5 \mu\text{m}^2/\text{ms}$ and $D_e = 2 \mu\text{m}^2/\text{ms}$. The Kärger model (KM) approximation given by eqn (16) is fitted through each series of data points. Although the KM approximation (represented by the full lines) fits the simulated data points accurately, the fitted exchange times $\tau_{\text{ex,fit}}$ start to deviate from the real τ_{ex} as τ_{ex} decreases. The error in τ_{ex} is roughly twice as high in the perpendicular direction than in the parallel direction.

Figure 6.

Relative errors in $K_{0,KM}$ and τ_{ex} made when fitting the simulated $K(t)$ to the Kärger model (KM), as defined by eqns [38] and [39]. The mean values of the errors for the five subgroups of 4×10^5 walkers are plotted; the error bars represent the standard deviations. $K_{0,KM}$ is underestimated, whereas τ_{ex} is overestimated. Both errors increase for decreasing τ_{ex} and increasing angle θ . The errors in the perpendicular direction, when plotted as a function of τ_e/t_c , are quantitatively the same for the three different combinations of D_i and D_e (plotted here in the same order as listed in Table 1).

Figure 7.

Illustration in one dimension of the evaluation of a population of particles at position $x=x_p$ time $T+dt$ near a permeable membrane at position $x=x_M$. A random walker at this position may originate from three possible positions at time T , marked on the axis by open circles. The probability for a random walker to move is indicated for each of the three positions on top of the round arrows. P_T is the probability of transmission at the membrane, whereas $1 - P_T$ is the probability of reflection.

Table 1

Combinations of D_i and D_e used for the simulations and the corresponding characteristic diffusion times and correlation time according to eqns [31], [30] and [29]

D_e ($\mu\text{m}^2/\text{ms}$)	D_i ($\mu\text{m}^2/\text{ms}$)	$t_{D,e}$ (ms)	$t_{D,i}$ (ms)	t_c (ms)
1	1	2.1	0.2	2.1
2	1	1.0	0.2	1.0
2	0.5	1.0	0.4	1.0

Table 2

Overview of the permeabilities κ and corresponding exchange times τ_{ex} used in Figs. 2, 4 and 5

κ ($\mu\text{m/ms}$)	τ_{ex} (ms)
0.008	20
0.056	2.8
0.16	1.0
0.4	0.4
2	0.08