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Numerical study of a cylinder model of the diffusion MRI signal for neuronal dendrite trees

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Abstract

We study numerically how the neuronal dendrite tree structure can affect the diffusion magnetic resonance imaging (dMRI) signal in brain tissue. For a large set of randomly generated dendrite trees, synthetic dMRI signals are computed and fitted to a cylinder model to estimate the effective longitudinal diffusivity $D_L$ in the direction of neurites. When the dendrite branches are short compared to the diffusion length, $D_L$ depends significantly on the ratio between the average branch length and the diffusion length. In turn, $D_L$ has very weak dependence on the distribution of branch lengths and orientations of a dendrite tree, and the number of branches per node. We conclude that the cylinder model which ignores the connectivity of the dendrite tree, can still be adapted to describe the apparent diffusion coefficient in brain tissue.

Keywords: Diffusion MRI; cylinder model; neurites; dendrite trees;

1. Introduction

The relation between the complex geometrical structure of brain tissue and the diffusion magnetic resonance imaging (dMRI) signal has yet to be clarified [1, 2, 3, 4]. A starting point for many previous works on modeling the dMRI signal in the brain is a relatively simple geometrical model of the tissue. In white matter, bundles of parallel
axons (myelinated or not) are usually modeled by cylinders, yielding anisotropic water diffusion. In turn, gray matter contains neuron bodies with axons and randomly oriented dendrites resulting in nearly isotropic diffusion under typical imaging conditions. These constituents and other cells (e.g., astrocytes) are often represented as spheres (or ellipsoids) and cylinders, all embedded in the extra-cellular space. For example, the geometrical model in [5] is a regular lattice of parallel cylinders in which approximate expressions for the apparent diffusion coefficients (ADCs) at long times were derived. In [6], the geometrical model contains prolate ellipsoids (axons) and spheres (glial cells) and water exchange was effectively accounted for by macroscopic terms. In [7] parallel cylinders were used to model axons while water exchange with the extra-cellular space was neglected. In [8], non-monoexponential dMRI signal decay was explained by restricted diffusion in an ensemble of differently oriented cylinders. The model of thick-walled (myelinated) cylindrical tubes (axons) arranged periodically in a regular lattice and immersed in the surrounding medium was used in [9]. In [10, 11], another tissue model distinguishing three types of microstructural environment – intra-cellular, extra-cellular, and cerebrospinal fluid compartments – was proposed to account for the neurite orientation dispersion. In this so-called “neurite orientation dispersion and density imaging” (NODDI) model, the intra-cellular signal contribution was obtained for cylinders whose random orientations followed the Watson distribution. The role of water exchange between several “layers” and towards the outer space was studied in [12, 13]. Cylinders with spherical bumps were introduced to model neurite beading and to explain experimental findings after ischemic stroke [14]. A general relation between the long-time asymptotic behavior of ADC and the structural disorder of the medium was investigated in [15, 16]. Some other theoretical models and concepts of brain dMRI were reviewed in [17]. The original Callaghan’s model [18] of infinitely long and uniformly distributed cylinders and its extensions were employed to interpret the dMRI signal in biological tissues [8, 19, 20, 21, 22, 23]. For instance, the dMRI signal $S$ in brain tissue was often modeled as the sum of two non-exchanging components: the signal $S_e$ from the extra-cellular compartment (dendrites and axons) and the signal $S_i$ from the intra-cellular compartment (modeled as a Gaussian hindered diffusion) [8, 20]:

$$S = (1 - v)S_e + vS_i,$$  

(1)

where $v$ is the volume fraction of water associated with the intra-cellular compartment. Furthermore, axons and dendrite branches were modeled by straight cylinders that are long enough so that the signal from each cylinder is

$$S_{cyl} \propto \exp\left(-b \left(D_L \cos^2 \beta(e,u_g) + D_T \sin^2 \beta(e,u_g)\right)\right),$$  

(2)

2
where $\beta(e, u_g)$ is the angle between the cylinder (oriented along the unit vector $e$) and the unit vector $u_g$ parallel to the diffusion-encoding gradient $g$, and $D_L$ and $D_T$ are the effective longitudinal and transverse diffusivities. The $b$-value is

$$b \equiv \gamma^2 |g|^2 \int_0^{TE} du \left( \int_0^u f(s) ds \right)^2,$$

where $f(s)$ is the effective temporal profile of diffusion-encoding gradient, and $TE$ is the echo time. For a standard Stejskal-Tanner pulsed-gradient spin-echo (PGSE) profile with two rectangular pulses of duration $\delta$ separated by diffusion time $\Delta$, $b = \gamma^2 |g|^2 \delta^2 (\Delta - \delta/3)$ [24]. Integration over the orientation distribution $Q(\theta, \phi)$ of the cylinders yields

$$S_i = \int \exp \left( -b \left( D_L \cos^2 \beta(e_{\theta, \phi}, u_g) + D_T \sin^2 \beta(e_{\theta, \phi}, u_g) \right) \right) Q(\theta, \phi) \, d\theta \, d\phi,$$

where the cylinder orientation $e_{\theta, \phi}$ is described by spherical coordinates $(\theta, \phi)$. The cylinder model was used to fit neurites density $v$ in Eq. (1) and orientation distribution $Q(\theta, \phi)$ in Eq. (3), see [21, 22]. Such characterization of neuronal morphology was validated on the digitally reconstructed neurons from the NeuroMorpho.org database [23, 25].

In this paper, we perform a numerical study of the quality of the cylinder model of Eqs. (2, 3) in describing the dMRI signal from dendrite trees. The motivation is that, even neglecting the bending of dendrite branches, the cylinder model does not account for the fact that the dendrite branches are linked to each other in a tree structure and water molecules may be moving to adjacent branches during the diffusion time. We aim to quantify this effect that may become important when the diffusion length,

$$L_{\text{diff}} = \sqrt{2D_0(\Delta + \delta)},$$

which typically varies between $5\mu$m and $25\mu$m, is comparable to or longer than dendrite branch lengths (here $D_0$ is the intrinsic diffusion coefficient of water). Note that the importance of diffusive exchange between branches of acinar trees on the dMRI signal in lungs was outlined in [26, 27].

We make two simplifications in treating the above problem. The first is that we neglect transverse diffusion in the dendrite branches because their diameter is usually less than a micron, i.e., much smaller than their lengths and typical $L_{\text{diff}}$. The second simplification consists in fitting only the apparent diffusion coefficient instead of the full dMRI signal. Expanding Eq. (3) to the first order in $b$, one gets

$$ADC_0 = D_L \int \cos^2 \beta(e_{\theta, \phi}, u_g) Q(\theta, \phi) \, d\theta \, d\phi,$$
where $D_T$ was neglected, and the subscript 0 in $ADC_0$ emphasizes that ADC is computed in the limit $b \to 0$. For an idealized model of infinitely long randomly oriented cylinders, one gets $D_L = D_0$ due to unrestricted diffusion along these cylinders. Since the branches of a dendrite tree are connected and of finite lengths, Eq. (5) is not necessarily valid. We aim therefore at verifying the usefulness of a cylinder model for the analysis of dMRI signals from dendrite trees. For each generated tree, we compute both the integral over angles $\theta$ and $\phi$ from the chosen branch orientation distribution, and $ADC_0$ from the dMRI signal obtained by solving numerically the Bloch-Torrey equation on the dendrite tree. Repeating this computation for many random realizations of dendrite trees, we define the effective longitudinal diffusivity $D_L$ from a least squares fit. We examine how the value of $D_L$ and the quality of the fit by Eq. (5) are affected by the tree-like structure of neuronal dendrites. In particular, we show the weak dependence of $D_L$ on the branch orientation and length distributions, and the strong dependence on the diffusion time and the average branch length. Both the finiteness of branch lengths and the connectivity of the dendrite tree influence the longitudinal diffusivity.

2. Method

In order to mimic the diversity in shapes and sizes of neuronal dendrite trees, we generate a large sample of randomly constructed trees, choosing the lengths and orientations of the branches from physiologically reasonable ranges for their distributions [28, 29, 30]. We emphasize however that our simplified numerical model is not meant to reproduce precisely the complicated architecture of physiological dendrite trees. Our primary goal here is not to capture as accurately as possible various features of the experimental dMRI signal in cortex tissue, but to understand the effect of tree connectivity onto dMRI measurements that was ignored so far. For each generated tree, we fix the principal orientation along the z-axis and distribute branches with a chosen branch orientation distribution $Q_b(\theta, \phi)$ (see below). The $ADC_0$ of each dendrite tree is extrapolated from the dMRI signal computed numerically by solving the Bloch-Torrey equation on a tree. We study the effect of branch orientations onto the dMRI signal for a single dendrite tree. While a reliable interpretation of the overall dMRI signal in a macroscopic voxel would require the average over many dendrite trees with their own orientation distribution, the analysis is kept at the scale of a single dendrite tree (its extension to multiple trees being straightforward). We detail the procedure in the following subsections.
2.1. Generation of a large sample of dendrite trees

We model a dendrite tree as the union of linked one-dimensional segments that represent the branches of the tree. We denote a one-dimensional dendrite tree embedded in the three-dimensional space by \( \mathcal{N} = \bigcup_{k=1}^{K} T_k \subset \mathbb{R}^3 \), where \( K \) is the number of branches, and \( T_k \) is a branch (a 1D line segment) of length \( \ell_k \). We consider two types of trees, with regular and random structures. For trees with regular structure, the number of branches per node is fixed. In turn, we use the algorithm in Appendix A to generate dendrite trees with random structure for which the number of branches per node is random but does not exceed the prescribed maximal number \( J_{\text{max}} \). In both cases, dendrite trees are forced to grow up along the z-axis by imposing the directionality constraint \( 0 \leq \phi \leq \phi_{\text{max}} \) on branch angles \( \phi \) with the z-axis, where \( \phi_{\text{max}} \leq \pi/2 \) is the prescribed directionality parameter that characterizes the dispersion of dendrite branches around the principal direction (z-axis): smaller \( \phi_{\text{max}} \) mean stronger alignment of branches with the z-axis. In other words, we choose the branch orientation distribution \( Q_b(\theta, \phi) \) to be uniform in the spherical cap of angle \( \phi_{\text{max}} \) around the z-axis. Note that \( \phi_{\text{max}} \) plays the similar role as the “concentration parameter” \( \kappa \) of the Watson distribution in the NODDI model [10, 11].

The sample is characterized by the following parameters:

- the sample size (i.e., the number of trees in a sample), \( W \);
- the maximum number of branches at each tree node, \( J_{\text{max}} \);
- the directionality parameter \( \phi_{\text{max}} \);
- the number \( K_i \) of branches for \( i \)-th tree;
- the distribution of branch lengths.

Figure 1 illustrates a random dendrite tree generated by the algorithm in Appendix A for the following parameters: \( J_{\text{max}} = 4 \), \( \phi_{\text{max}} = \pi/2 \), \( K = 51 \), and the branch lengths are chosen randomly with a uniform distribution in the interval \([10 \mu m, 100 \mu m]\). Since all branch lengths are independent, the empirical mean length is close to \( \frac{1}{2}(\ell_{\text{max}} + \ell_{\text{min}}) = 55 \mu m \), while the standard deviation is simply \( \sigma_u / \sqrt{\langle K \rangle} \approx 4.7 \mu m \), where \( \sigma_u = (\ell_{\text{max}} - \ell_{\text{min}}) / \sqrt{12} \) is the standard deviation for the uniform distribution over \([\ell_{\text{min}}, \ell_{\text{max}}]\), and \( \langle K \rangle = 30 \) is the mean number of branches for this example.
2.2. Synthetic dMRI signal of dendrite trees

Throughout this paper, we focus on the dMRI signal from isolated dendrite trees by ignoring water diffusion in the extra-cellular space. To compute synthetic dMRI signals of the generated dendrite trees, we solve the Bloch-Torrey equation on one-dimensional tree structures. The transverse magnetization $M_k(r, t)$ of water protons satisfies the Bloch-Torrey equation on each branch $T_k$ of a dendrite tree

$$\frac{\partial}{\partial t} M_k(s, t) = -i \gamma f(t) \mathbf{g} \cdot (\mathbf{p}_k + s \mathbf{e}_k) M_k(s, t) + D_0 \frac{\partial^2}{\partial s^2} M_k(s, t),$$

(6)

where we neglected the water exchange with the extra-cellular space, following Refs. [21, 22]. Here $i$ is the imaginary unit, $\gamma = 2.67513 \times 10^8$ rad s$^{-1}$ T$^{-1}$ is the gyromagnetic ratio of water proton, and the branch $T_k$ has the natural parametrization $T_k = \mathbf{p}_k + s \mathbf{e}_k$, $s \in [0, \ell_k]$, $\mathbf{p}_k$ being the starting point of the segment, and $\mathbf{e}_k$ its orientation. Since we aim to understand the influence of a dendrite tree structure on dephasing of water protons due to their diffusion under gradient pulses, other relaxation mechanisms such as $T_1/T_2$ relaxation or susceptibility-induced internal gradients are omitted. Although various aspects of diffusion on trees have been thoroughly investigated (see [31, 32, 33] and references therein), the effect of gradient pulses and the consequent dMRI signals remain poorly understood.

Two conditions have to be imposed at the tree junctions. The first condition is the
continuity of the magnetization:

\[ M_k(\ell_k, t) = M_{k'}(0, t), \quad (7) \]

for all \( k, k' \in \{1, \ldots, K\} \) such that \( p_{k'} = p_k + \ell_k e_k = r \) (i.e., at the junction \( r \) of branches \( k \) and \( k' \)). The second condition is the Kirchhoff law ensuring the conservation of flux:

\[ \sum_{k: p_k = r} \left( \frac{\partial}{\partial s} M_k(s, t) \right)_{s=0} - \sum_{k: p_k + \ell_k e_k = r} \left( \frac{\partial}{\partial s} M_k(s, t) \right)_{s=\ell_k} = 0, \quad (8) \]

where the first sum represents outfluxes through branches started at \( r \) (with \( p_k = r \)) while the second sum includes influxes from branches ended at \( r \) (with \( p_k + \ell_k e_k = r \)). We impose the uniform magnetization as the initial condition:

\[ M_k(s, 0) = 1, \quad k = 1, \ldots, K. \quad (9) \]

At the terminal nodes, homogeneous Neumann boundary condition is imposed:

\[ D_0 \left( \frac{\partial}{\partial s} M_k(s, t) \right)_{s=\ell_k} = 0, \quad (10) \]

where \( p_k + \ell_k e_k \) is the end node of a terminal branch \( k \).

The dMRI signal from the whole dendrite tree is then

\[ S(b) \equiv \frac{1}{L} \sum_{k=1}^{K} \int_{r \in T_k} M_k(r, TE) \, dr, \quad (11) \]

where the total branch length \( L \) is

\[ L \equiv \sum_{k=1}^{K} \ell_k = K \ell_{\text{ave}}. \]

The division by \( L \) ensures the conventional normalization of the dMRI signal: \( S(0) = 1 \).

The extrapolated apparent diffusion coefficient

\[ ADC_0 \equiv -\frac{\partial}{\partial b} \log \left( \frac{S(b)}{S(0)} \right)_{b=0}, \quad (12) \]

is calculated numerically by using a cubic polynomial fit of \( \log(S(b)) \) and taking the coefficient in front of the linear term in \( b \). Defined in this way, \( ADC_0 \) exists for arbitrary, not necessarily mono-exponential, dependence of the dMRI signal on \( b \)-value. In what follows, we focus on \( ADC_0 \) (instead of the dMRI signal) as a source of information about the medium.
2.3. Fitting the cylinder model

For a given dendrite tree, there is only one free fitting parameter in Eq. (5), namely, the longitudinal diffusivity $D_L$. In other words, since we know exactly the orientations and the lengths of its $K$ branches, we can rewrite Eq. (5) more explicitly as

$$ADC_0 = a D_L$$

(13)

with

$$a = \sum_{k=1}^{K} \frac{\ell_k}{\sum_{j=1}^{K} \ell_j} \cos^2(\beta_k),$$

(14)

where $\beta_k \equiv e_k \cdot u_g$ is the angle between the $k$-th branch and the diffusion-encoding gradient direction $u_g$. Here $a$ is the sample dendrite-weighted mean of $\cos^2(\beta)$ which combines purely geometrical characteristics of a tree and its branch orientations with respect to the gradient direction. Formally, Eq. (13) determines the effective longitudinal diffusivity $D_L$ which a priori depends on the whole structure of the dendrite tree. In practice, one aims to infer some geometrical characteristics of dendrites (e.g., the average branch length) from experimentally estimated $D_L$. Such an inference procedure would be possible if $D_L$ is only sensitive to these averaged characteristics but (almost) independent of the orientation distribution of branches (which is already included in $a$).

When all branches have the same length, Eq. (14) is reduced to an empirical mean of $\cos^2(\beta)$ over $K$ independent random realizations of branch orientations. This is a random variable whose mean and standard deviation can be computed analytically for uniform distribution of branch orientations with the directionality constraint $0 \leq \phi \leq \phi_{\text{max}}$:

$$\langle a \rangle = \frac{1}{2\pi(1 - \cos \phi_{\text{max}})} \int_0^{\phi_{\text{max}}} \int_0^{2\pi} d\theta \sin \phi \cos^2 \beta$$

\[= \frac{2 - \cos \phi_{\text{max}} - \cos^2 \phi_{\text{max}} + 3 u_z^2 \cos \phi_{\text{max}} (1 + \cos \phi_{\text{max}})}{6},\]

(15)

where $u_z$ is the projection of the gradient direction $u_g$ onto the $z$-axis, and $\langle \cdots \rangle$ denotes the expectation with respect to the probability distribution of branch orientations. In particular, one retrieves $\langle a \rangle = 1/3$ for both $\phi_{\text{max}} = \pi$ (uniform distribution over the whole sphere) and $\phi_{\text{max}} = \pi/2$ (uniform distribution over the upper hemi-sphere) as expected. In these isotropic cases, the geometrical factor $\langle a \rangle$ does not depend on the gradient direction $u_g$. In turn, $\langle a \rangle$ does depend on the gradient
direction for \( \phi_{\text{max}} < \pi/2 \). In the extreme case \( \phi_{\text{max}} = 0 \) when all branches are parallel to the z-axis, one gets \( \langle a \rangle = u_z^2 \), as expected. One can also compute the standard deviation of \( a \) for a tree with \( K \) branches:

\[
\text{std}\{a\} = \frac{1}{\sqrt{K}} \left[ \frac{(1 - \cos \phi_{\text{max}})^2(17 \cos^2 \phi_{\text{max}} + 41 \cos \phi_{\text{max}} + 32)}{360} \right.
\]

\[
+ \cos \phi_{\text{max}}(1 - \cos^2 \phi_{\text{max}})u_z^2 \left( \frac{7 \cos \phi_{\text{max}}}{12} - u_z^2 \frac{5 \cos \phi_{\text{max}} + 3}{8} \right) \right]^{1/2}.
\]

For \( \phi_{\text{max}} = \pi \) and \( \phi_{\text{max}} = \pi/2 \), the standard deviation is equal to \( 2/\sqrt{45K} \), while in the limit \( \phi_{\text{max}} \to 0 \), the standard deviation vanishes, as expected.

2.4. Computational procedure

To investigate the applicability of the cylinder model for inferring geometrical information on dendrite trees from dMRI, we apply the following procedure:

1. Choose the desired form of dendrite trees: regular or random structure, distribution of branch lengths, directionality constraint, distribution of the number of branches, the maximal number of branches per node;
2. Generate a sample of \( W \) dendrite trees: \( \{N^1, \ldots, N^W\} \). The \( i \)th tree \( N^i \) has \( K^i \) branches of lengths \( \{\ell^i_k\} \) and orientations \( \{e^i_k\} \), \( k = 1, \ldots, K^i \);
3. Determine the factors \( \{a_1, \ldots, a_W\} \) for all trees according to Eq. (14);
4. Compute synthetic dMRI signals at eleven \( b \)-values spaced between 0 and 500 s/mm\(^2\) for each of the \( W \) trees by solving Eqs. (6-10) using an adapted version of a finite element method developed in [34];
5. Calculate the associated \( ADC_0 \), \( \{ADC_0^1, \ldots, ADC_0^W\} \), using a cubic polynomial fit of the logarithm of the signal in \( b \)-values;
6. Fit Eq. (13) by solving the least squares problem: finding \( D_L \) that minimizes

\[
\sum_{i=1}^{W} (a_i D_L - ADC_0^i)^2 , \text{i.e.,}
\]

\[
D_L = \frac{\sum_{i=1}^{W} a_i ADC_0^i}{\sum_{i=1}^{W} a_i^2}.
\]

For the chosen form of dendrite trees, this procedure produces the longitudinal diffusivity \( D_L \) for a prescribed gradient direction \( u_g \) and sequence timing (\( \delta \) and \( \Delta \)).
use the standard PGSE sequence with two rectangular gradient pulses of the fixed pulse duration $\delta = 2.5\text{ms}$ and the diffusion time $\Delta$ ranging from $2.5\text{ms}$ to $100\text{ms}$. The intrinsic diffusion coefficient is set to $D_0 = 3 \cdot 10^{-3}\text{mm}^2/\text{s}$ that corresponds to free diffusion of water at $37^\circ\text{C}$. While higher viscosity and molecular overcrowding in cells can reduce threefold the water diffusion coefficient $[35, 36, 37, 38, 39]$, choosing the appropriate value for $D_0$ in brain tissue is a difficult or even controversial issue. For our purposes, this choice is not critical. In fact, we will show that the $ADC_0$ mainly depends on the ratio between the average branch length and the diffusion length $L_{\text{diff}}$ so that a change in $D_0$ would simply rescale the diffusion length according to Eq. (4). We will investigate the dependence of the computed $D_L$ on the diffusion time $\Delta$ and gradient direction $u_g$, on one hand, and on various structural features of the dendrite trees, on the other hand.

Beside the best fit $D_L$, useful quantities associated with the least squares problem are:

(i) the root mean squared fitting error,

$$
RMSE \equiv \sqrt{\frac{1}{W} \sum_{i=1}^{W} (a_i D_L - ADC_0^i)^2},
$$

(ii) the normalized fitting error,

$$
\epsilon_{\text{fit}} \equiv \frac{RMSE}{\sqrt{\frac{1}{W} \sum_{i=1}^{W} (ADC_0^i)^2}},
$$

and (iii) the scatter $\epsilon_{D_L}$ of the best fit $D_L$,

$$
\epsilon_{D_L} \equiv \sqrt{\frac{1}{W} \sum_{i=1}^{W} \left( \frac{ADC_0^i}{a_i} - D_L \right)^2}.
$$

Note that $\epsilon_{D_L}$ characterizes $D_L$ whereas $\epsilon_{\text{fit}}$ characterizes the $ADC_0$.

Each simulation was performed for $W = 1000$ random realizations of dendrite trees. We also checked on larger samples with 10000 trees that both the normalized fitting error $\epsilon_{\text{fit}}$ and the scatter $\epsilon_{D_L}$ reach their limiting values for $W \gtrsim 1000$ (not shown). This verification justifies our choice of the sample size $W = 1000$ which produces statistically representative results.
3. Numerical results

In this section, we investigate how the longitudinal diffusivity \( D_L \) depends on various structural features of dendrite trees: branch length (Sec. 3.1), branch length distribution (Sec. 3.2), maximal number of branches per node (Sec. 3.3), directionality constraint (Sec. 3.4), and gradient direction (Sec. 3.5). Throughout this section (except for the last subsection), the gradient direction is set to \( \mathbf{u}_g = (1, 1, 1)/\sqrt{3} \). At this gradient direction, the geometrical factor \( \langle a \rangle \) from Eq. (15) takes the value \( 1/3 \) independently of the directionality constraint \( \phi_{\text{max}} \) which by default is set to \( \phi_{\text{max}} = \pi/2 \) (isotropic case).

3.1. Dependence on diffusion time and branch length

First, we generated \( W = 1000 \) regular trees with 39 branches (\( K = 39 \)), spread on three levels: 3 branches at the root, connected to 9 branches on the second level and 27 branches on the third level. The branch lengths, \( \ell_1, \ldots, \ell_{39} \) were chosen randomly from an array containing two lengths: 27\( \mu m \) (30 times) and 90\( \mu m \) (9 times). Figure 2 shows the distribution of the simulated \( ADC_0^i \) versus the geometrical factors \( a_i \) defined in Eq. (14) at \( \Delta = 2.5\text{ ms} \) (Fig. 2(a)), \( \Delta = 40\text{ ms} \) (Fig. 2(b)), and \( \Delta = 80\text{ ms} \) (Fig. 2(c)). The closer the data lie on a straight line, the more accurate the relation Eq. (13) is. Alternatively, one can look on histograms of the slopes \( ADC_0^i/a_i \) plotted in Fig. 2(d) – 2(f) for the three diffusion times. We see clearly that the cylinder model is better at lower diffusion times (the narrowest histogram, with the standard deviation of \( ADC_0^i/a_i \) being 0.03 \( \times 10^{-3} \text{ mm}^2/\text{s} \)) and worse at higher diffusion times (the broadest histogram, with the standard deviation of \( ADC_0^i/a_i \) being 0.13 \( \times 10^{-3} \text{ mm}^2/\text{s} \)). At \( \Delta = 2.5\text{ ms} \), the diffusion length \( L_{\text{diff}} \approx 5.5\mu m \) is much smaller than the branch lengths. At \( \Delta = 80\text{ ms} \), the diffusion length \( L_{\text{diff}} \approx 22\mu m \) is on the same order as the length of the shorter set of branches, \( \ell = 27\mu m \). The normalized fitting errors \( \epsilon_{\text{fit}} \) are 1%, 4%, and 5%, respectively. This level of model error may be considered acceptably low for some applications. The mean values of the \( ADC_0^i \) for the three diffusion times are: 0.94 \( \times 10^{-3} \text{ mm}^2/\text{s} \), 0.79 \( \times 10^{-3} \text{ mm}^2/\text{s} \), and 0.72 \( \times 10^{-3} \text{ mm}^2/\text{s} \), respectively, while \( D_L \) from Eq. (17) are 2.81 \( \times 10^{-3} \text{ mm}^2/\text{s} \), 2.38 \( \times 10^{-3} \text{ mm}^2/\text{s} \), and 2.16 \( \times 10^{-3} \text{ mm}^2/\text{s} \), showing the dependence of \( D_L \) on the diffusion time. Note that the ratios between the mean \( ADC_0^i \) and \( D_L \) are close to 1/3, as expected for the isotropic case with \( \phi_{\text{max}} = \pi/2 \). We emphasize that the above values of the best fit \( D_L \) are very close to the sample means of the slope \( ADC_0^i/a_i \): 2.80 \( \times 10^{-3} \text{ mm}^2/\text{s} \), 2.36 \( \times 10^{-3} \text{ mm}^2/\text{s} \), and 2.14 \( \times 10^{-3} \text{ mm}^2/\text{s} \), respectively. In other words, one could introduce the longitudinal diffusivity for each tree as the
ratio between \( ADC^i_0 \) and \( a_i \), and then define \( D_L \) as the sample mean of these ratios:

\[
D_L' = \sum_{i=1}^{W} \frac{ADC^i_0}{a_i}.
\]  

(21)

Both approaches yield very similar results, and we keep using the best fit \( D_L \) from Eq. (17).

Figure 2: Distribution of the simulated \( ADC^i_0 \) versus \( a_i \) (defined in Eq. (14)), \( i = 1, \cdots, 1000 \), at \( \Delta = 2.5\text{ms} \) (2(a)), \( \Delta = 40\text{ms} \) (2(b)), \( \Delta = 80\text{ms} \) (2(c)). The related histograms of the slopes \( ADC^i_0/a_i \) at \( \Delta = 2.5\text{ms} \) (2(d)), \( \Delta = 40\text{ms} \) (2(e)), \( \Delta = 80\text{ms} \) (2(f)), with means and standard deviations: \( (2.80 \pm 0.03) \cdot 10^{-3}\text{mm}^2/\text{s}, (2.36 \pm 0.10) \cdot 10^{-3}\text{mm}^2/\text{s}, \) and \( (2.14 \pm 0.13) \cdot 10^{-3}\text{mm}^2/\text{s}, \) respectively. Simulations were performed on 1000 regular trees, each with \( K = 3 + 9 + 27 = 39 \) branches over three levels (\( J_{\text{max}} = 4 \)): 30 branches of length \( 27\mu\text{m} \) and 9 branches of length \( 90\mu\text{m} \). We set \( \sigma_{\text{max}} = \pi/2 \) and \( \mathbf{u}_g = (1, 1, 1)/\sqrt{3} \).

The longitudinal diffusivity \( D_L \) also depends on the branch length \( \ell \). When \( \ell \) is long as compared to the diffusion length \( L_{\text{diff}} \), most of the water protons remain within one branch and thus dephase at a single gradient strength \( |\mathbf{g}| \cos \beta \) (where \( \beta \) is the angle between the gradient direction and that branch orientation). In the limit of infinitely long branches, the nuclei experience the classical dephasing of free one-dimensional diffusion, with \( D_L \) being equal to the intrinsic diffusion coefficient.
$D_0$. In the opposite short $\ell$ limit, nuclei are likely to visit several branches during the diffusion time and thus to experience dephasing at various gradient strengths $|g| \cos \beta_k$. The resulting dMRI signal accounts for switching between branches that yields smaller $D_L$.

In order to assess the effect of branch length, we generated $W = 1000$ regular trees for which all the branches have the same length $\ell$. We simulated 11 values of $\ell$: $\ell = 10, 15, 20, 30, 35, 40, 45, 55, 70, 100\mu m$. As previously, each tree has $K = 3 + 9 + 27 = 39$ branches on three levels. The results are shown in Fig. 3. One can see that $D_L$ depends on both the branch length $\ell$ (Fig. 3(a)) and the diffusion time $\Delta$ (Fig. 3(c)). For example, at $\Delta = 10$ms, the diffusion length is $L_{\text{diff}} \simeq 8.7\mu m$, and $D_L = 1.8 \cdot 10^{-3}\text{mm}^2/\text{s}$ is much lower than the intrinsic diffusion coefficient $D_0 = 3 \cdot 10^{-3}\text{mm}^2/\text{s}$ at $\ell = 10\mu m$ ($\sim L_{\text{diff}}$), while $D_L = 2.75 \cdot 10^{-3}\text{mm}^2/\text{s}$ is close to $D_0$ at $\ell = 40\mu m$ ($\gg L_{\text{diff}}$). In summary, the longitudinal diffusivity $D_L$ deviates significantly from $D_0$ unless the branch lengths are much longer than the diffusion length. We also see in Fig. 3(b,d) that the scatter of $D_L$, measured by $\epsilon_{D_L}$ from Eq. (20), is smaller when the branch lengths are much longer than the diffusion length, as expected.

The above analysis suggests that the signal and thus the $ADC_0$ depend on the ratio between the branch length $\ell$ and the diffusion length $L_{\text{diff}}$. When plotted versus the dimensionless ratio $\ell/L_{\text{diff}}$, all $D_L$ fall onto one master curve as illustrated in Fig. 3(e). For comparison, we also plotted $D_L$ for a model of randomly oriented disconnected (isolated) branches of length $\ell$ (see Appendix B). One can see that the connectivity of the dendrite tree plays an important role, i.e., the dependence of $D_L$ on the diffusion time cannot be reduced only to the finiteness of branch lengths. Figure 3(f) shows that rescaling by the diffusion length is applicable to $\epsilon_{D_L}$.
Figure 3: $D_L$ and $\epsilon_{D_L}$ versus branch length $\ell$ (a, b) and diffusion time $\Delta$ (c, d) for dendrite trees for which all the branches have the same length $\ell$. When plotted versus the dimensionless ratio $\ell/L_{\text{diff}}$, $D_L$ and $\epsilon_{D_L}$ fall onto one master curve (e, f). Solid line in Fig. 3(e) shows $D_L/D_0$ from Eq. (B.2) for a model of disconnected branches. Solid line in Fig. 3(f) indicates the slope $-1$ in the log-log plot: $0.1(\ell/L_{\text{diff}})^{-1}$. Simulations were performed on 1000 regular trees with $K = 3 + 9 + 27 = 39$ branches over three levels ($J_{\text{max}} = 4$), with $\phi_{\text{max}} = \pi/2$ and $u_g = (1, 1, 1)/\sqrt{3}$. 
3.2. Little influence of branch length distribution

We compare four samples of $W = 1000$ random trees:

1. For each tree, all the branches have the same length $\ell_{\text{ave}}$;
2. For each tree, the branch lengths are chosen randomly from a uniform distribution on the continuous interval $[\ell_{\text{min}}, \ell_{\text{max}}]$ such that $\ell_{\text{ave}} = (\ell_{\text{min}} + \ell_{\text{max}})/2$;
3. For each tree, the branch lengths are chosen randomly from a Gaussian distribution conditioned to have a prescribed support $[\ell_{\text{min}} - \varepsilon, \ell_{\text{max}} + \varepsilon]$ (with $\varepsilon > 0$) to avoid negative (or too small) lengths:
   \[
p_g(\ell) = \frac{1}{\text{erf}(L/\sigma_g \sqrt{2})} \cdot \frac{1}{\sqrt{2\pi}\sigma_g} \exp\left(-\frac{(\ell - \ell_{\text{ave}})^2}{2\sigma_g^2}\right),
   \]
   where the first prefactor is the normalization of this conditioned distribution, erf($z$) is the error function, the auxiliary parameter $\varepsilon$ is fixed to be $\ell_{\text{min}}/2$, $L = \varepsilon + \frac{1}{2}(\ell_{\text{max}} - \ell_{\text{min}}) = \ell_{\text{max}}/2$, and $\sigma_g$ is the standard deviation which is matched to the standard deviation of the above uniform distribution, $\sigma_u = (\ell_{\text{max}} - \ell_{\text{min}})/\sqrt{12}$, according to
   \[
   \sigma_u^2 = \sigma_g^2 - 2L\sigma_g \frac{\exp\left(-\frac{L^2}{\sigma_g \sqrt{2}}\right)}{\sqrt{2\pi} \text{erf}\left(L/\sigma_g \sqrt{2}\right)}.
   \]
4. For each tree, the branch lengths are chosen randomly from a lognormal distribution
   \[
p_{\ln}(\ell) = \frac{1}{\ell \sqrt{2\pi} \sigma_{\ln}} \exp\left(-\frac{(\ln(\ell/\ell_{\text{ave}}) + \sigma_{\ln}^2/2)^2}{2\sigma_{\ln}^2}\right),
   \]
   where $\sigma_{\ln}^2 = \ln(1 + \sigma_u^2/\ell_{\text{ave}}^2)$.

By construction, all three considered distributions which are fixed by setting $\ell_{\text{min}}$ and $\ell_{\text{max}}$ have the same mean $\ell_{\text{ave}}$ and variance $\sigma_u^2$. In all four samples, the number of branches, $K$, is chosen randomly from a uniform distribution in the set of integers $\{10, 11, \ldots, 50\}$, while the maximal number of branches per node is set to $J_{\text{max}} = 4$.

The best fit $D_L$ and the scatter $\epsilon_{D_L}$ for the four samples are reported in Table 1 for two choices: $\{\ell_{\text{min}} = 10\mu m, \ell_{\text{max}} = 100\mu m\}$ and $\{\ell_{\text{min}} = 10\mu m, \ell_{\text{max}} = 60\mu m\}$. We can see very little difference between $D_L$ and $\epsilon_{D_L}$ for all the diffusion times between 2.5ms and 100ms. We conclude that $D_L$ mainly depends on the average branch length of the dendrite tree, and it is not significantly affected by the specific distribution of branch lengths.
Table 1: Comparison between $D_L$ and $\epsilon_{D_L}$ as functions of the diffusion time $\Delta$ from the set \{2.5ms, 10ms, 40ms, 80ms, 100ms\} on four samples of dendrites trees with different branch length distributions: fixed, uniform, conditioned Gaussian, and lognormal, as described in Sec. 3.2. We set $\ell_{\text{min}} = 10\mu m$ and consider two choices for $\ell_{\text{max}}$: 60$\mu m$ (yielding $\ell_{\text{ave}} = 35\mu m$) and 100$\mu m$ (yielding $\ell_{\text{ave}} = 55\mu m$). For each sample, simulations were performed on 1000 random trees generated by the algorithm in Appendix A. For each tree, the number of branches $K$ is randomly chosen between 10 and 50, $J_{\text{max}} = 4$, and we set $\phi_{\text{max}} = \pi/2$ and $u_g = (1, 1, 1)/\sqrt{3}$.

<table>
<thead>
<tr>
<th>$\ell_{\text{ave}}$</th>
<th>Distrib.</th>
<th>$D_L$, $\times 10^{-3}\text{mm}^2/\text{s}$</th>
<th>Scatter $\epsilon_{D_L}$, $%$</th>
</tr>
</thead>
<tbody>
<tr>
<td>35$\mu m$</td>
<td>Fixed</td>
<td>2.78, 2.63, 2.30, 2.03, 1.93</td>
<td>1.3, 2.4, 5.2, 7.9, 9.0</td>
</tr>
<tr>
<td></td>
<td>Uniform</td>
<td>2.78, 2.64, 2.32, 2.08, 1.99</td>
<td>1.7, 3.0, 5.9, 8.3, 9.2</td>
</tr>
<tr>
<td></td>
<td>Gaussian</td>
<td>2.79, 2.64, 2.33, 2.09, 2.00</td>
<td>1.6, 2.8, 5.7, 8.1, 9.0</td>
</tr>
<tr>
<td></td>
<td>Lognormal</td>
<td>2.78, 2.63, 2.31, 2.06, 1.97</td>
<td>1.6, 2.9, 6.1, 8.8, 9.8</td>
</tr>
<tr>
<td>55$\mu m$</td>
<td>Fixed</td>
<td>2.86, 2.77, 2.56, 2.38, 2.31</td>
<td>0.8, 1.4, 3.0, 4.5, 5.2</td>
</tr>
<tr>
<td></td>
<td>Uniform</td>
<td>2.86, 2.77, 2.57, 2.40, 2.34</td>
<td>1.0, 1.8, 3.6, 5.1, 5.7</td>
</tr>
<tr>
<td></td>
<td>Gaussian</td>
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<td>1.0, 1.8, 3.6, 5.0, 5.5</td>
</tr>
<tr>
<td></td>
<td>Lognormal</td>
<td>2.86, 2.77, 2.56, 2.39, 2.32</td>
<td>1.0, 1.9, 3.9, 5.6, 6.3</td>
</tr>
</tbody>
</table>

3.3. Little effect of the maximal number of branches per node

We also study the effect of the maximal number of branches per node. We fixed the branch length to be $\ell = 10\mu m$, and generated two samples of $W = 1000$ regular trees: in the first sample, each tree has $K = 3 + 9 + 27 = 39$ branches over three levels ($J_{\text{max}} = 4$), while in the second sample, each tree has $K = 4 + 16 + 64 = 84$ branches over three levels ($J_{\text{max}} = 5$). Table 2 summarizes the values of $D_L$ and $\epsilon_{D_L}$ for broad range of diffusion times. One can see that there is no significant difference in the longitudinal diffusivity $D_L$ between the two samples, though the values of $D_L$ for $J_{\text{max}} = 4$ are systematically greater than that for $J_{\text{max}} = 5$. Note also that the scatter $\epsilon_{D_L}$ grows with the diffusion times. A similar comparison has also been performed for random trees when the total number of branches and the number of branches per node are random (the latter being limited by $J_{\text{max}}$). In this case, the $D_L$ are even closer for the two cases $J_{\text{max}} = 4$ and $J_{\text{max}} = 5$ (data not shown). In fact, most of nodes do not attain the maximal number of branches per node so that two samples are closer in this case. We also checked that the effect of $J_{\text{max}}$ is diminished even further for longer branches as the nuclei would move less frequently between branches (checked for $\ell = 55\mu m$, data not shown).
Table 2: Comparison between $D_L$ and $\epsilon_{D_L}$ as functions of the diffusion time $\Delta$ from the set {2.5ms, 10ms, 40ms, 80ms, 100ms} on two samples of 1000 regular trees. In the first sample, each tree has $K = 3 + 9 + 27 = 39$ branches over three levels ($J_{\text{max}} = 4$), while in the second sample, each tree has $K = 4 + 16 + 64 = 84$ branches over three levels ($J_{\text{max}} = 5$). We set $\ell = 10\mu m$ or $\ell = 55\mu m$, $\phi_{\text{max}} = \pi/2$ and $u_g = (1, 1, 1)/\sqrt{3}$.

<table>
<thead>
<tr>
<th>$\ell$</th>
<th>$J_{\text{max}}$</th>
<th>$D_L \times 10^{-3}\text{mm}^2/\text{s}$</th>
<th>Scatter $\epsilon_{D_L}$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>10µm</td>
<td>4</td>
<td>2.20 1.70 0.99 0.68 0.60</td>
<td>2.5 7.7 13 18 20</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2.17 1.65 0.92 0.62 0.55</td>
<td>2.8 5.2 9.1 13 14</td>
</tr>
<tr>
<td>55µm</td>
<td>4</td>
<td>2.85 2.75 2.53 2.34 2.26</td>
<td>0.6 1.0 2.1 3.2 3.6</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2.85 2.74 2.51 2.32 2.24</td>
<td>0.4 0.7 1.5 2.2 2.6</td>
</tr>
</tbody>
</table>

3.4. Directionality constraint (branch orientation distribution)

We now look at the effect of the branch orientation distribution. We recall that the angles $\phi$ the branches make with the z-axis is limited to $\phi_{\text{max}}$: $0 \leq \phi \leq \phi_{\text{max}}$. We generate three samples of $W = 1000$ trees for three values of $\phi_{\text{max}}$: $\phi_{\text{max}} = \pi/2$, $\phi_{\text{max}} = \pi/6$, $\phi_{\text{max}} = \pi/12$. In other words, we limited the branch orientations to an increasingly smaller area around the North pole of the unit sphere. The branch lengths were fixed to be $\ell = 55\mu m$, $J_{\text{max}} = 4$, and $K$ is randomly chosen between 10 and 50 for each tree. Figure 4 shows that the empirical distributions of the geometrical factor $a$ defined in Eq. (14) for the three cases are different. In turn, the empirical means of $a$ (0.337, 0.337, 0.335) are close to the theoretical value $\langle a \rangle = 1/3$ at the chosen gradient direction $u_g = (1, 1, 1)/\sqrt{3}$. This observation confirms that the number of branches in simulated trees is sufficiently large to make a discrete sampling representative. We emphasize that the value 1/3 here is not universal as $\langle a \rangle$ would depend on the gradient direction for $\phi_{\text{max}} < \pi/2$ (see below). Note that the same value $\langle a \rangle = 1/3$ for the isotropic case (with $\phi_{\text{max}} = \pi/2$) is independent of the gradient gradient, in which case the classical relation $ADC_0 = D_L/3$ is retrieved. The standard deviations of $a_i$ are 0.06, 0.04, 0.02, respectively, in agreement with Eq. (16), if the mean $\langle K \rangle = 30$ is substituted for the number of branches.
We also computed $D_L$ and $\epsilon_{D_L}$ for each of the above three values of $\phi_{\text{max}}$. Figure 5 shows that the relative difference between $D_L$ for these three cases is small (in fact below 5%). The scatter is larger when $\phi_{\text{max}}$ is larger, but $\epsilon_{D_L}$ is no more than 5% even at the longest diffusion time $\Delta = 100\text{ms}$. One can conclude that the effect of directionality constraint on the longitudinal diffusivity is minor.

3.5. Effect of gradient direction

To observe the effect of diffusion-encoding gradient direction on $D_L$ and $\epsilon_{D_L}$, we consider one previous sample of 1000 random trees with $\phi_{\text{max}} = \pi/6$ and set three
gradient directions: $\mathbf{u}_g = (1, 0, \sqrt{3})/2$, $\mathbf{u}_g = (1, 0, 1)/\sqrt{2}$, $\mathbf{u}_g = (\sqrt{3}, 0, 1)/2$. Figure 6 illustrates a small difference between $D_L$ for the three gradient directions and for all diffusion times between 2.5ms and 100ms.

Figure 6: $D_L$ (a) and $\epsilon_{D_L}$ (b) for three gradient directions $\mathbf{u}_g = (1, 0, \sqrt{3})/2$, $\mathbf{u}_g = (1, 0, 1)/\sqrt{2}$, $\mathbf{u}_g = (\sqrt{3}, 0, 1)/2$. Simulations were performed on 1000 random trees with branches of the same length $\ell = 55\mu m$, $\phi_{\text{max}} = \pi/6$, $J_{\text{max}} = 4$, and $K$ is randomly chosen between 10 and 50 for each tree.

Numerical results for some other directionality constraints $\phi_{\text{max}}$ and several gradients directions $\mathbf{u}_g$ are summarized in Table 3. The empirical means and standard deviations of $a_i$ and $ADC_0^i$ were computed by averaging over 1000 random trees with $\ell = 55\mu m$, $J_{\text{max}} = 4$, and $K$ is randomly chosen between 10 and 50 for each tree. One can easily check that, for all $\phi_{\text{max}}$ and $\mathbf{u}_g$, the empirical means and standard deviations of $a_i$ are close to their theoretical values $\langle a \rangle$ and $\text{std} \{a\}$ given by Eqs. (15) and (16), respectively. As expected, $a_i$ and $ADC_0^i$ are independent of the gradient direction for the isotropic case with $\phi_{\text{max}} = \pi/2$. In general, $ADC_0^i$ are slightly smaller at the longer diffusion time $\Delta = 80\text{ms}$. Note also that the ratio between the empirical means of $ADC_0^i$ and $a_i$ may be different from the best fit $D_L$ from Eq. (17) due to correlations between $ADC_0^i$ and $a_i$.

4. Discussion

In the idealized limit of infinitely short gradient pulses (i.e., the double limit $\delta \rightarrow 0$ and $g \rightarrow \infty$ with $b$-value being fixed), $ADC_0$ from Eq. (12) becomes

$$ADC_0 = \frac{1}{2\Delta} \langle [(\mathbf{r}_\Delta - \mathbf{r}_0) \cdot \mathbf{u}_g]^2 \rangle,$$

(22)
Table 3: Empirical means and standard deviations of $a_i$ and $ADC_i$ for $\Delta = 40\text{ms}$ and $\Delta = 80\text{ms}$ at three directionality constraints $\phi_{\text{max}}$ and five gradient directions: $u_g^{(1)} = (1, 0, \sqrt{3})/2$, $u_g^{(2)} = (1, 0, 0)$, $u_g^{(3)} = (1, 0, 1)/\sqrt{2}$, $u_g^{(4)} = (\sqrt{3}, 0, 1)/2$, $u_g^{(5)} = (1, 1, 1)/\sqrt{3}$. Simulations were performed on 1000 random trees with branches of the same length $\ell = 55\mu m$, $J_{\text{max}} = 4$ and $K$ is randomly chosen between 10 and 50 for each tree. The empirical mean and standard deviation of $a_i$ are in excellent agreement with the theoretical formulas (15), (16), when $K = 30$ is used as the mean value of $K$. 

<table>
<thead>
<tr>
<th>$\phi_{\text{max}}$</th>
<th>$a_i$</th>
<th>$ADC_i \times 10^{-3}\text{mm}^2/\text{s}$</th>
<th>$ADC_i \times 10^{-3}\text{mm}^2/\text{s}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\pi/6$</td>
<td>$u_g^{(1)}$</td>
<td>1.8 ± 0.11</td>
<td>1.7 ± 0.11</td>
</tr>
<tr>
<td>$\pi/3$</td>
<td>$u_g^{(2)}$</td>
<td>0.16 ± 0.03</td>
<td>0.15 ± 0.03</td>
</tr>
<tr>
<td>$\pi/2$</td>
<td>$u_g^{(3)}$</td>
<td>1.2 ± 0.12</td>
<td>1.2 ± 0.12</td>
</tr>
<tr>
<td>$\pi/3$</td>
<td>$u_g^{(4)}$</td>
<td>0.69 ± 0.11</td>
<td>0.65 ± 0.10</td>
</tr>
<tr>
<td>$\pi/2$</td>
<td>$u_g^{(5)}$</td>
<td>0.87 ± 0.12</td>
<td>0.82 ± 0.11</td>
</tr>
<tr>
<td>$\pi/6$</td>
<td>$u_g^{(1)}$</td>
<td>0.67 ± 0.04</td>
<td>0.67 ± 0.04</td>
</tr>
<tr>
<td>$\pi/3$</td>
<td>$u_g^{(2)}$</td>
<td>0.06 ± 0.01</td>
<td>0.06 ± 0.01</td>
</tr>
<tr>
<td>$\pi/2$</td>
<td>$u_g^{(3)}$</td>
<td>0.47 ± 0.05</td>
<td>0.47 ± 0.05</td>
</tr>
<tr>
<td>$\pi/3$</td>
<td>$u_g^{(4)}$</td>
<td>0.27 ± 0.04</td>
<td>0.27 ± 0.04</td>
</tr>
<tr>
<td>$\pi/2$</td>
<td>$u_g^{(5)}$</td>
<td>0.33 ± 0.04</td>
<td>0.33 ± 0.04</td>
</tr>
</tbody>
</table>

$\Delta = 40\text{ms}$
where the average is taken over all starting points \( r_0 \) and arrival points \( r_\Delta \) in a confining domain [18]. This is the mean square displacement along the gradient direction \( u_g \), i.e., a purely diffusive characteristics of the medium. When the gradient pulses are not instantaneous, \( ADC_0 \) is in general affected by dMRI measurement features such as, e.g., the gradient temporal profile [3]. Throughout this paper, the gradient pulse duration \( \delta \) was fixed to be 2.5ms which is representative for brain dMRI. During each gradient pulse, water molecules move on average 3-4 microns so that such \( \delta \) is not considered to be instantaneous.

The linear relation (13) between \( ADC_0 \) and \( D_L \) constitutes a simple way to translate a dMRI measurement (ADC) depending on the experimental setup (e.g., the PGSE sequence timing) into a purely diffusive characteristics (\( D_L \)) of a confining medium. This quantity characterizes an effective slowing down of diffusion by confinement during the diffusion time \( \Delta \). For a valid “translation”, the longitudinal diffusivity \( D_L \) should be disentangled from dMRI, i.e., be independent of measurement features. In turn, the proportionality coefficient \( a \) in Eq. (13) captures the gradient direction.

The Callaghan’s model of uniformly distributed cylinders and its extensions were often employed to describe the dMRI signal in biological tissues [8, 18, 19, 20, 21, 22, 23]. If the width of cylinders is negligible as compared to the diffusion length, the \( ADC_0 \) is simply one third of the longitudinal diffusivity \( D_L \). In this isotropic case, the estimated \( ADC_0 \) is evidently independent of the gradient direction and is close to \( D_0/3 \) for long enough cylinders. In this paper, we investigated the effect of tree connectivity onto the dMRI signal which was ignored so far. A simple model of random dendrite trees grown up along one preferred direction was introduced in order to get statistically representative results. For this purpose, the branch orientations were chosen uniformly over a spherical cap around the North pole (the z-axis) with the directionality constraint \( 0 \leq \phi \leq \phi_{\text{max}} \leq \pi/2 \). The maximal angle \( \phi_{\text{max}} \) can be varied from \( \pi/2 \) (upper hemi-sphere) to 0 (all branches are parallel to the z-axis).

We aimed to verify the usefulness of the \( ADC_0 \) as a source of information about dendrite trees.

We showed that the coefficients \( a_i \) for randomly generated trees exhibit a relatively narrow distribution around the mean value \( \langle a \rangle \) for which an explicit formula is obtained. In fact, if branch orientations in a tree are independent, the standard deviation of \( a \) decreases as \( 1/\sqrt{K} \) with the number of branches \( K \). As a consequence, for large dendrite trees, the random coefficient \( a_i \) is not spread much and is close to the mean value. In principle, one can measure the dMRI signal along multiple gradient directions in order to get even better estimate of \( a_i \).

Our numerical results show that, unless the branch lengths are much longer than the
diffusion length $L_{\text{diff}}$, the longitudinal diffusivity $D_L$ depends significantly on the ratio between the average branch length of a dendrite tree and the diffusion length (the latter being controlled in experiments through the diffusion time $\Delta$). In contrast to an idealized model of infinitely long cylinders (for which $D_L = D_0$), the dependence of $D_L$ on the diffusion time is caused by the finiteness of branch lengths and by the connectivity of the dendrite tree. Both effects are significant because a simplified model of disconnected branches of finite lengths which ignores the connectivity (see Appendix B), underestimates $D_L$ as illustrated on Fig. 3(e). On one hand, it is a warning that ignoring the connectivity can be misleading. On the other hand, this observation suggests a possibility to characterize a tree-like structure from ADC measurements. Importantly, we found that the distribution of branch lengths has almost no effect on $D_L$, thus supporting the hypothesis that $D_L$ describes an average branch length of the dendrite trees rather than a specific distribution of the branch lengths. We found also that $D_L$ is not affected by the branch orientation distribution, the gradient direction, and the maximal number of branches per node.

The present study relies on several assumptions and simplifications.

- Random trees were constructed in order to provide a flexibility in changing various characteristics of dendrites such as the average branch length and branch length distribution, dispersion of branch orientations, and the maximal number of branches per node. The use of synthetically constructed trees allowed us to get a reliable statistical sampling and to reveal the relative roles of these neuronal characteristics. An interesting perspective consists in applying the efficient numerical technique developed in this paper for solving the Bloch-Torrey equation on a tree, to real digitally reconstructed neurons from the NeuroMorpho.org database (see [23, 25]).

- The transverse diffusivity $D_T$ was neglected because the radius $R$ of dendrites (below a micron) is much smaller than the diffusion length $L_{\text{diff}}$ which ranges between 5 and 25 microns in typical dMRI experiments. In order to validate this approximation, one can estimate the signal attenuation due to restricted diffusion of water in the transverse cross-section of a cylinder in the motional narrowing regime [3, 40]:

$$S_{\text{cross}} \simeq \exp \left( -bD_0 \frac{2\zeta_{-1} R^4}{D_0^2 \delta(\Delta - \delta/3)} \right),$$

(23)

where $\zeta_{-1} = 7/96$ is a numerical factor. Setting $R = 1\mu$m and $\Delta = \delta = 2.5$ms yields a negligible signal attenuation in the transverse plane: $S_{\text{cross}} \simeq \exp(-0.002bD_0) \simeq 1$.

- Throughout this paper, we focused on the apparent diffusion coefficient as a source of information about the dendrite tree, and thus discarded additional information that could potentially be inferred from the whole dependence of the dMRI signal on $b$-
value. This simplification is applicable to arbitrary confining domain and it does not require any \textit{a priori} fitting model for the dMRI signal. The analysis of dMRI signals from dendrite trees instead of their ADCs presents another perspective of this study. These signals, which are easily computable for an arbitrary tree structure, and their non-Gaussian features can provide further information on neuronal microstructure [1, 2, 3, 4, 41, 42, 43].

* Yet another important point is that we focused on the dMRI signal uniquely from \textit{isolated} dendrite trees. The first extension of the model can consist in including the signal from the extra-cellular space. Since the extra-cellular space cannot be decomposed into simple structural elements (as we did for the dendrite tree which was decomposed into one-dimensional segments), one would need to solve the Bloch-Torrey equation over the whole (sub)-voxel in order to compute the related signal. Other constituents of the brain tissue (such as glial cells) can also be included. Although such a computation is feasible on a small sub-voxel domain (e.g., by using a finite element method developed in [34]), this problem is much more computationally demanding. In a first approximation, one could treat the extra-cellular space as a Gaussian pool with a reduced effective diffusion coefficient (see [20]). In the next step, one can attempt to account for the diffusive exchange between the dendrite tree and the extra-cellular space. In this case, one would need to solve the coupled Bloch-Torrey equations for the interior and exterior compartments in three dimensions. This is a challenging numerical problem for a realistic tissue microstructure. In turn, our simplified model allows for rapid numerical solution of essentially one-dimensional Bloch-Torrey equation on large samples of real or randomly generated synthetic dendrite trees.

5. Conclusion

We numerically studied a cylinder model of the dMRI signal in brain tissue, which relies on a longitudinal diffusivity $D_L$ in the neurites. Using a least squares fit of the cylinder model to the $ADC_0$ from synthetically generated dMRI signals, we analyzed how the dendrite tree structure affects the value and the quality of the fit for the longitudinal diffusivity. We found that $D_L$ depends on the ratio between the average branch length and the diffusion length. When the dendrite branches are short compared to the diffusion length, $D_L$ varies significantly with the diffusion time. On the other hand, $D_L$ has very weak dependence on branch orientation and branch length distributions and on the number of branches per node. We conclude that the cylinder model which ignores the dendrite tree connectivity, can still be a useful description of the $ADC_0$ in brain tissue.
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Appendix A. Algorithm for generating random dendrite trees

For $i = 1, 2, \cdots, W$

1. Choose the number of branches, $K$ (fixed at a prescribed value or chosen randomly, to be specified).
2. Choose randomly the $K$ branch orientations: $\{e_1, \cdots, e_K\}$ (unit vectors in $\mathbb{R}^3$), from a uniform distribution in the spherical cap of the unit sphere that satisfies $0 \leq \phi \leq \phi_{\text{max}}$, where $\phi$ is the angle with respect to the z-axis. We restrict $\phi_{\text{max}} \leq \pi/2$ to ensure that the dendrite tree always grows up. By default, we set $\phi_{\text{max}} = \pi/2$ (unless another choice is explicitly specified).
3. Choose the branch lengths, $\ell_1, \cdots, \ell_K$ (fixed at a prescribed value or chosen randomly, to be specified).
4. The first node of the tree is always at the origin: $v_0 = (0, 0, 0)$. For the current set of nodes $\{v_0, \cdots, v_{k-1}\}$, we add a new branch by choosing a node $v$ randomly from $\{v_0, \cdots, v_{k-1}\}$. Then $T_k \equiv \{v + s e_k, s \in [0, \ell_k]\}$ is a new branch of the tree and $v_k \equiv v + \ell_k e_k$ is a new node (added to the list). The maximum number of branches at each node is limited to be $J_{\text{max}}$ (i.e., if the chosen node $v$ has $J_{\text{max}}$ branches, it is ignored, and the selection is repeated until the chosen node has less than $J_{\text{max}}$ branches). This iterative construction is repeated $K$ times to produce $K$ branches $T_1, \cdots, T_K$ and $K + 1$ nodes $v_0, \cdots, v_K$.
5. Define the tree $N^i \equiv \bigcup_{k=1}^K T_k$.

End For.

Appendix B. Randomly oriented isolated branches of finite length

For a single isolated infinitely thin branch of length $\ell$, the Gaussian phase approximation yields the dMRI signal for a standard PGSE sequence with two rectangular gradient pulses as [3]

$$S = \exp \left( -\frac{b \cos^2(\beta)}{2} D_L \left( \frac{D_0 \Delta}{\ell^2}, \frac{D_0 \delta}{\ell^2} \right) \right), \quad (B.1)$$
where $\beta$ is the angle between the gradient and the branch directions, and the longitudinal diffusivity is

$$D_L(\tau_\Delta, \tau_\delta) = D_0 \frac{2}{\tau_\delta(\tau_\Delta - \tau_\delta/3)} \left[ \frac{1}{120} - \frac{4}{\tau_\delta} \sum_{m=1}^\infty \frac{2 + e^{-(\tau_\Delta + \tau_\delta)\lambda_m} + e^{-(\tau_\Delta - \tau_\delta)\lambda_m} - 2e^{-\tau_\Delta\lambda_m} - 2e^{-\tau_\delta\lambda_m}}{\lambda_m^4} \right] \quad (B.2)$$

with $\lambda_m = \pi^2(2m - 1)^2$. While the signal representation (B.1) is an approximation (valid for small $b$-values), Eq. (B.2) for $D_L$ is exact. In the long length limit $\ell \to \infty$, $D_L(\tau_\Delta, \tau_\delta)$ approaches $D_0$, as expected. In the opposite short length limit $\ell \to 0$, the sum can be neglected (as compared to $1/120$) yielding $D_L \simeq \frac{\ell^2}{60D_0\delta(\Delta - \delta/3)}$ in the motional narrowing regime [3]. As expected, the longitudinal diffusivity vanishes in this limit.

For a large sample of randomly oriented branches of random lengths, the total dMRI signal is obtained by summing weighted contributions from all branches. If the probability density $Q_b(\theta, \phi)$ for branch orientations is independent from the probability density $p(\ell)$ for branch lengths, one retrieves Eq. (5) for $ADC_0$ with the longitudinal diffusivity $D_L$ averaged over the distribution of branch lengths:

$$D_L = \int d\ell \ p(\ell) \ D_L(D_0\Delta/\ell^2, D_0\delta/\ell^2). \quad (B.3)$$

This diffusivity depends on the diffusion time $\Delta$ and on the gradient pulse duration $\delta$ (the latter dependence being weak if the branch length $\ell$ is greater than $\sqrt{D_0\delta}$).

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Graphical Abstract

branch length/diffusion length

longitudinal diffusivity

diffusion time:
\( \Delta = 2.5 \text{ ms} \)
\( \Delta = 10 \text{ ms} \)
\( \Delta = 40 \text{ ms} \)
\( \Delta = 80 \text{ ms} \)
\( \Delta = 100 \text{ ms} \)

connected

disconnected
* How the neuronal dendrite tree structure can affect the dMRI signal in brain tissue?
* Numerical study of ADC in synthetic randomly generated dendrite trees
* Longitudinal diffusivity DL depends on averaged branch length over diffusion length
* Weak sensitivity of DL to dendrite tree branch length and orientation distributions
* Cylinder model, though ignoring the connectivity, can be adapted to describe ADC