Diffusion modeling in brain cell geometries parameterized according to morphometric statistics

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TARGET AUDIENCE: Researchers in diffusion-weighted MRI/MRS interested in diffusion modeling to assess brain cell architecture.

PURPOSE: Brain cell architecture has a critical influence on molecular diffusion as measured by diffusion-weighted (DW) imaging and spectroscopy (MRS). To date, two main modeling approaches were developed to quantify the impact of cellular geometry on diffusion. The 1st approach consists in simplifying cellular architecture to basic geometries, such as spheres or cylinders, for which analytical solutions generally exist. Beyond the computing speed, the advantage is that geometry is described by a small set of parameters, making it efficient to fit data and extract parameters such as axon diameter and density (e.g. [1,2]). However, it clearly misses the complexity of cell architectures in the brain. In contrast, the 2nd approach relies on Monte Carlo simulations of many particles diffusing in "realistic" cells, generally requiring large computing resources. Furthermore, realistic cell geometries are generally directly built manually or from microscopy data, rather than being generated by a set of parameters, limiting that approach to a few individual cells and failing to capture cell heterogeneity. Here we propose a 3rd approach to capture some features of brain cells complexity and heterogeneity, while parameterizing the model with a small set of parameters based on cell morphometric statistics as derived from microscopy. We exemplify how this approach allows evaluating the effect of long-range cell morphology on the apparent diffusion coefficient (ADC) of intracellular molecules, as may be measured by DW-MRS at long diffusion times T_d.

THEORY & METHODS:

Context and relevant morphometric statistics: Here we will consider that molecules are purely intracellular, and we will focus on long-range geometrical characteristics which affect the molecular displacement over long distances. Hence we assume that signal attenuation due to displacement in the transverse plane of fibers is negligible. This corresponds to $d^2 << 2D_{free}T_d$ (where d is the fiber diameter and D_{free} the free diffusion coefficient in cells), which is valid for T_d longer than a few dozen ms. Hence d will not be considered, but the number of processes N_{proc}, the number of successive segments between branching points along processes N_{seg}, and the length of each segment L will be (**Fig. 1A**), yielding a representation of astrocytes and some neurons.

Diffusion in synthetic cells: The ramifying processes radiating from the cell body are built iteratively, by adding successive segments that follow morphometric statistics. N particles (typically a few thousands) are then randomly positioned in the cell. A particle's position in a given segment is described by a 1D coordinate x. Then for each particle and each time step (duration τ), a displacement of magnitude $\sqrt{2D_{free}\tau}$ is randomly drawn towards smaller or greater x values. If the particle goes through a node connected to other segments, it is randomly assigned a new segment connecting this node. At the extremity of a process, it undergoes a simple reflection. The phase evolution in the presence of gradients is computed for each particle, before summing to calculate overall signal.

Influence of morphometry: For a given set of distributions, a significant amount of cells (typically a few dozens) can be generated to account for cellular heterogeneity (e.g. **Fig. 1B** and **1C**), and particles diffusion can then be simulated in these cells to compute overall signal.

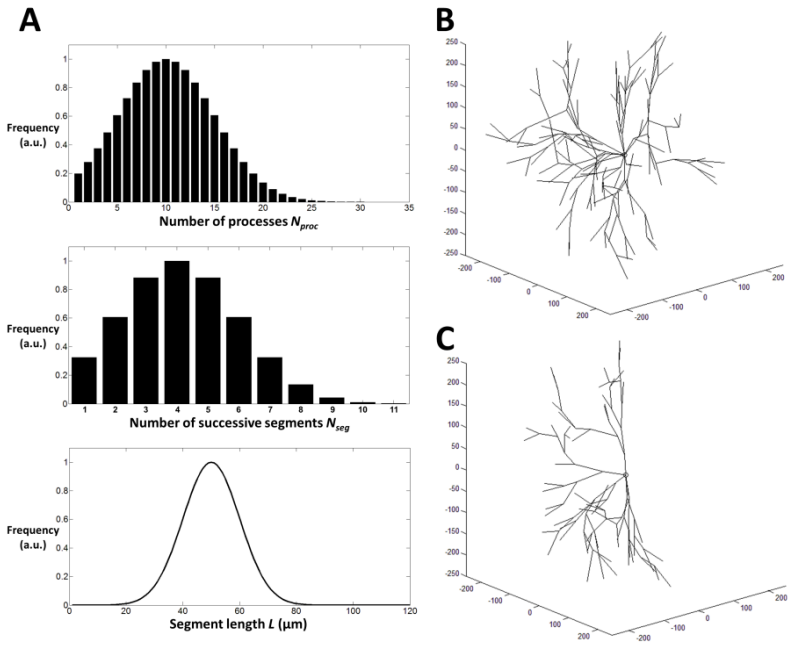

Figure 1: *A) Morphometric statistics for parameters used in the present work; Examples of two cells generated from these distributions are given in B) and C).*

Matlab implementation: Implementation was done in Matlab (The Mathworks, Natick, MA, USA), using the Parallel Computing Toolbox. Using a personal computer (8-Go RAM, 6-core 2.66-GHz CPU) and running 6 workers, it takes ~190 seconds to simulate diffusion during T_d=1 second in 20 cells satisfying Fig. 1A statistics, with 3000 particles in each cell and a 0.5-ms time step resolution, i.e. with simulation complexity [3] (number of particles×number of iterations) of 1.2×10^8.

RESULTS & DISCUSSION: The approach proposed here allows exploring various effects. For example, it is possible to test how mean and s.d. of segment length L affect intracellular ADC as a function of T_d. While mean L has a strong effect (shorter L leading to stronger ADC drop), the s.d. only has a moderate impact (see **Fig. 2A** for details), suggesting that a strong cellular heterogeneity, as may occur in large MRS voxels, should not strongly affect diffusion measurements. The same effect is observed for N_{seg} (not shown). To go further, one may wonder if long T_d DW-MRS is only sensitive to restriction at the extremity of processes, i.e. only depends on the total process length $L\times N_{seg}$, or if it can allow untangling the effect of L and N_{seg}. To test that, we simulated diffusion in different sets of cells all satisfying $L\times N_{seg}$=100 µm but varying mean L or N_{seg}. It appears that ADC time dependency does not only depend on total process length, but specifically depends on L and N_{seg}: large N_{seg}/small L lead to strong ADC drop before stabilization at longer T_d, while small N_{seg}/large L lead to steadier ADC decrease as T_d is increased (**Fig. 2B**).

CONCLUSION: The modeling approach proposed here can be generalized and refined by adding other morphometric parameters, depending on the context (e.g. fiber diameter might be considered for short T_d or high b experiments, or apical dendrites properties to simulate pyramidal neurons). Although it is based on numerical simulation, our approach remains computationally manageable due to its compact and flexible description of cell morphology. We therefore think it is a valuable alternative to existing modeling strategies. In particular, it might be used to analyze experimental diffusion data and quantify long-range geometrical features such as process length, which have not received much attention so far.

1. Assaf et al., MRM 2008;59:1347; 2. Alexander et al., NeuroImage 2010;52:1374; 3. Hall et al., IEEE Trans Med Imag 2009;28:1354.

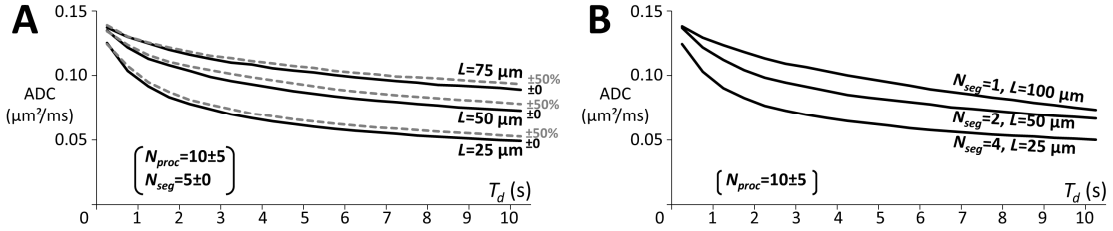

Figure 2: *A) Effect of L distribution on intracellular ADC, as a function of T_d. From top to bottom: mean L=75, 50 and 25 µm. Solid line stands for s.d.(L)=0, gray dotted line for s.d.(L)=50% of mean L; B) Differential effect of N_{seg} and L for constant process length $L\times N_{seg}$. Gaussian distributions were used. D_{free} was set to 0.5 µm²/ms. ADC was computed by taking the log of signal attenuation between b=0 and 2 ms/µm² obtained with a pair of short gradient pulses.*