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Extracellular Diffusion in Oriented Bundles of Brain Fibers with Variable Volume Fraction

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1. Introduction

A major source of diffusion anisotropy in the central nervous system is the presence of oriented fibers; a prime example is the corpus callosum (CC), which is composed of aligned neuronal axons [1]. The extracellular diffusion properties of the CC have been explored experimentally using a point-source release paradigm based on tetramethylammonium (TMA; [1, 2]). To better understand such results, a series of Monte Carlo simulations using the program MCell (www.mcell.psc.edu; [3]) was developed to model diffusion from a point source in bundles of rectangular fibers with extracellular volume fractions (α) ranging from 0.02 - 0.8.

2. Methods

The simulation employed 64 rectangular rods each of 0.6 × 0.6 μm in cross-section with surfaces that reflected the particles. Rods were spaced appropriately to obtain the required α and the length of each rod was chosen to make the rods into a cubic ensemble. A population of 250,000 point particles was released into the center of the ensemble with free diffusion coefficient (D), equal to that for TMA, and the simulations run with a time-step of 10 ns for 1 ms. These parameters ensured that the particles remained within the ensemble. The effective diffusion coefficient D^* and tortuosity λ (a measure of hindrance to diffusion) were calculated from:

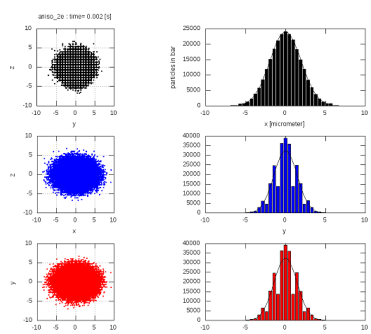

Fig.1. Left panels: projection of particles on planes. Right panel corresponding histograms showing Gaussian distribution.

$$D^*_x = \langle x^2\rangle/2t,\ D^*_y = \langle y^2\rangle/2t,\ D^*_z = \langle z^2\rangle/2t,$$

$$\lambda_x = (D/D^*_x)^{0.5},\ \lambda_y = (D/D^*_y)^{0.5},\ \lambda_z = (D/D^*_z)^{0.5}.$$

where $\langle x^2\rangle$ represents the mean square value of all the x-coordinates of the particle measured at time t and similar relations apply to the y and z coordinates. The medium is anisotropic, so both D^* and λ will be tensors. Because the rods were oriented in the x-axis, $D^*_y = D^*_z$ and $\lambda_y = \lambda_z$.

3. Conclusion and Results

The distribution of particles was approximately circular when projected on the *y*-*z* plane but showed a characteristic ellipsoidal pattern when projected on the orthogonal planes (Fig. 1, Left panels). The distribution of particle coordinates was accurately fitted by Gaussian curves (Fig. 1, Right panels) although the histograms showed the effect of forbidden regions (rods) in the *y* and *z* axes. It was found that the component of the effective diffusion tensor, D^*_x, aligned with the direction of the bundles was equal to D so the tortuosity was unity in this axis. For the two symmetrical components of D^* in the orthogonal axes, λ was a function of α that could be accurately described by an expression derived by Bell & Crank [4]. These results are shown together with those already obtained for an assembly of cubes [5] (Fig. 2).

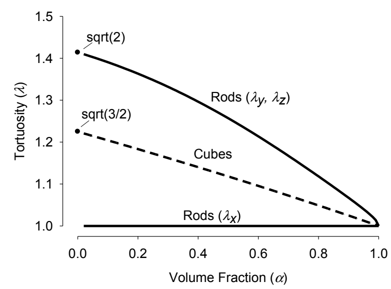

Fig. 2. Tortuosity v extracellular volume fraction for rods and cubes.

Table 1 compares the results obtained with MCell to those obtained experimentally in adult rat CC [1].

	λ_x	λ_y	λ_z
Measured [1]	1.4	1.7	1.7
MCell	1.0	1.4	1.4
MCell × 1.4	1.4	1.9	1.9

Table 1. Tortuosity values for $\alpha = 0.26$.

It is evident that these measured values indicate significant hindrance in the *x*-axis, compared to none in the model and also show higher tortuosity values in the *y* and *z* axes. If the *x*-axis hindrance (λ_x) is attributed to interstitial viscosity and applied also to the model values in the *y* and *z* axes (i.e. multiply MCell values by 1.4, c.f. [6]), then there is a rough agreement between theoretical and experimental values.

References

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