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Monte Carlo simulation study of geometrical factors causing anomalous diffusion in brain extracellular space

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1. Introduction

Brain cells are surrounded by the extracellular space (ECS) where signaling molecules, nutrients and therapeutic agents are transported to their targets by diffusion. The biophysical parameters of the ECS and the extracellular diffusion have to be determined if we aim for quantitative understanding of any of these processes. Recently, we have reported that the extracellular diffusion is *anomalous* in the granular layer (GL) of rat cerebellum (anomalous diffusion model quantified an average anomalous exponent $d_w = 5.0$; [1]). In this respect, the GL significantly differs from most brain regions where the extracellular diffusion is *normal* (i.e., $d_w \approx 2.0$). It is known that anomalous diffusion can be induced by traps that transiently hold diffusing particles [2]. In the GL, abundant large synaptic glomeruli are formed by concave processes of astrocytes that ensheathe complex synapses [3]. We propose that these glomeruli act as traps and cause anomalous extracellular diffusion in the GL. To test this hypothesis, we studied diffusion in several simplified geometrical models (Fig. 1); models C and D were designed to mimic the trap-like structure of glomerulus.

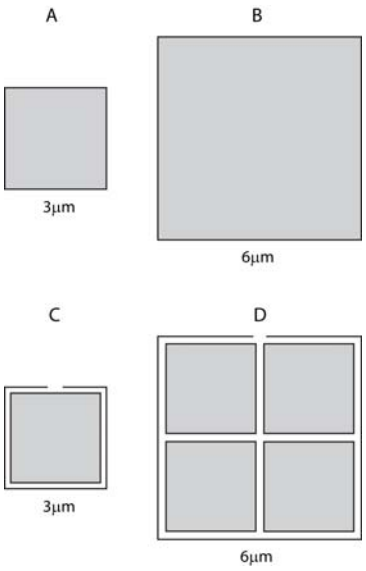

Fig. 1: Geometrical models used in numerical simulation. Two-dimensional cross sections of a single unit from each model are shown.

2. Methods and Simulation Results

The Monte Carlo diffusion was simulated using the Monte Carlo Simulation of Cellular Microphysiology (*MCell*) program [4]. A 600*600*600 μm^3 array of units was constructed for each model (Fig. 1). The total ECS volume fraction was 22%. For the models C and D, volume fraction inside the concave wrapping was 12%. Typically, 2000 molecules were released from a point source and a free diffusion coefficient of these molecules was set at 2.2e-6 cm^2s^{-1}. Results from MCell simulations were analyzed with a Matlab-based program developed in-house.

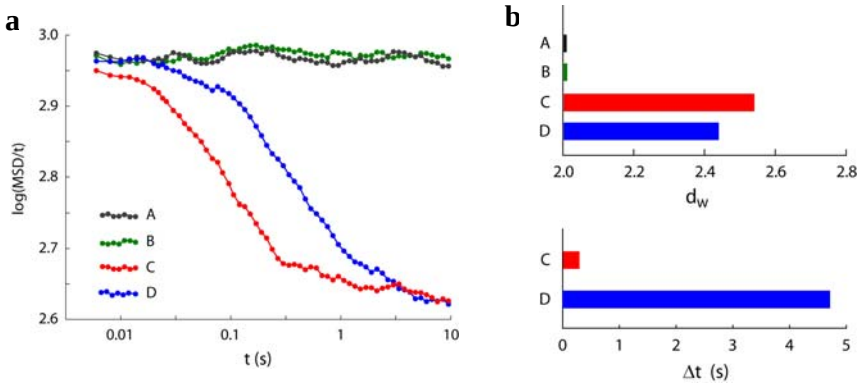

Fig. 2: **a**, Log-log plot MSD/t as a function of time. Models C and D show transient anomalous diffusion. **b**, Summary of quantitative results from MCell simulations.

Extracellular diffusion is normal ($d_w \approx 2.0$) in the models A and B containing only convex cubes (Fig 2). In contrast, extracellular diffusion is transiently anomalous in the models C and D containing convex cubes with concave wrapping. The anomalous exponents were 2.54 and 2.44 for model C and model D, respectively.

In the models C and D, we quantified the time duration of transient anomalous diffusion and found that it depended on a size of single unit (Fig. 1). The anomalous diffusion lasted about 0.28 s for model C, but it was about 16 times longer for model D. All quantification results are plotted in Fig. 2b.

3. Conclusion

Using numerical simulations, we found that concave wrappings of convex elements can cause anomalous diffusion ($d_w \approx 2.5$). Our simulations also showed that the duration of anomalous diffusion is related to the size of a single unit. We note that the anomalous exponents obtained in our simulations are smaller than $d_w \approx 5.0$ measured in the GL. This is likely due to the simplicity of our models. Our simulations suggest that the glomeruli cause, at least in part, anomalous diffusion observed in the GL. In future, more realistic geometrical models and other factors will be investigated.

Our findings have implications for modeling the diffusion of neurotransmitters and neuromodulators and for drug delivery in the GL.

References

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