A model of anomalous extracellular diffusion: source location matters

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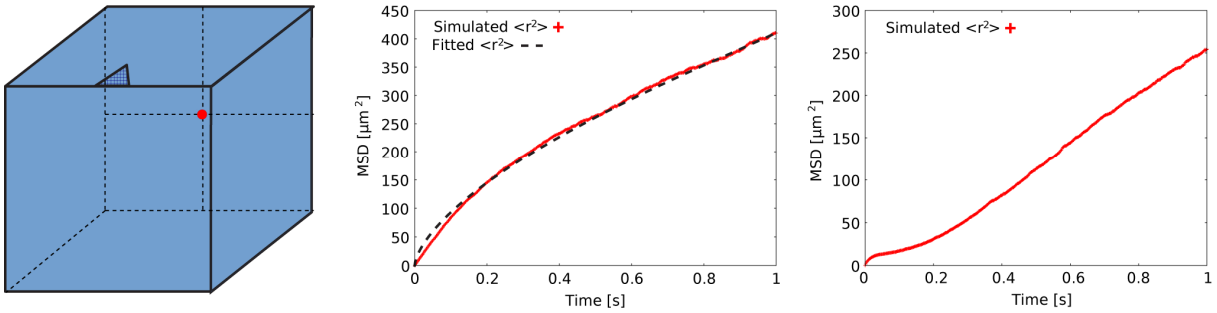
Brain extracellular space (ECS) serves as a transportation channel for biologically significant molecules but the diffusion-mediated transport through the ECS is hindered by its geometrically complex structure. We proposed that the hindrance originated in large part from the presence of dead space microdomains which can transiently retain diffusing molecules [1]. Such pocket-like structures, e.g., those formed by astrocytic wrappings, result in three consecutive diffusion regimes [2]. Following a brief and rapid free diffusion after release, an anomalous diffusion phase gradually reduces the diffusion rate until the bulk hindered normal diffusion is reached. The anomalous diffusion thus facilitates a smooth transition between two normal diffusion regimes. We have shown that when the diffusion source is placed in the well-connected compartment outside of any pockets, the anomalous phase can be described as subdiffusion characterized by its anomalous exponent $d_w > 2$ [2]. Here, we examine the effect of the instantaneous point source placement, inside or outside of the dead-end pockets, on the transiently anomalous diffusion phase.

ECS diffusion was simulated with the MCell program [3]. Cubes representing the cells were wrapped in shell-shaped elements with small triangular openings into the well-connected ECS (left figure shows the shell with its opening and one possible point source location). This motif was replicated in all three directions every 6 μm and randomly rotated, providing an environment volume of 204^3 μm³. The total ECS volume fraction was 0.2, two-thirds of which belonged to the dead-space compartment found in the pockets between the cells and their shells. Molecules (N = 2000) were released from a point source placed close to one of the face centers of the central element, either outside or inside the shell, which led to a total of 12 different configurations. The free diffusion coefficient was set to 220 μm²/s and the diffusing molecules were elastically reflected upon reaching the surfaces of the cells or shells. All simulations were carried over a total diffusion period of 1 s.

When the source was placed in the well-connected compartment, the mean square displacement $\langle r^2 \rangle$ behaved for about 0.8 s as subdiffusion with d_w of about 3.0, regardless of the exact source placement (middle figure). However, when the source was inside the pocket, the anomalous diffusion morphed from subdiffusion to superdiffusion before ultimately leveling off (right figure). Both types of the anomaly became more pronounced when the release site was placed further from the pocket entrance. We conclude that in the real estate of molecular release sites, location matters.



References

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[3] http://mcell.org/publications.html

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