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The Open-Access Journal for the Basic Principles of Diffusion Theory, Experiment and Application

The Effect of Dead-Space Microdomain Entrance Size and Volume on Brain Extracellular Space Diffusion

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(Received: 2025/10/01, Published online: 2025/11/03)

Brain extracellular space (ECS) is the space surrounding brain cells. It is quantified by the ECS volume fraction (ECS volume / total brain tissue volume) which typically reaches 20% in a healthy brain. ECS serves as a major transport system for molecules involved in drug delivery and signal communication between cells [1]. Diffusion governs molecule movement in the ECS. It is quantified by diffusion permeability ($\theta = D^* / D$, where D^* is the effective diffusion coefficient in the brain tissue and D is the free diffusion coefficient) [2]. Experimental studies of small molecules in healthy brain tissue identified θ at ~ 0.40 [3]. Yet, simulations and theoretical studies of geometrical models with convex elements [2,4] can only yield values above 0.66. Concave invaginations within brain's ECS, termed dead-space microdomains (DMs), were proposed as a possible explanation for slower effective diffusion. They can temporarily trap molecules and consequently decrease θ to a value that matches the experimental results [2]. However, most DM models were built on the assumption of narrow DM entrance sizes [2], which is likely violated given the non-uniform nature of the brain ECS [5]. Few simulation studies have systematically explored how a wider range of DM entrance sizes would affect diffusion permeability [6].

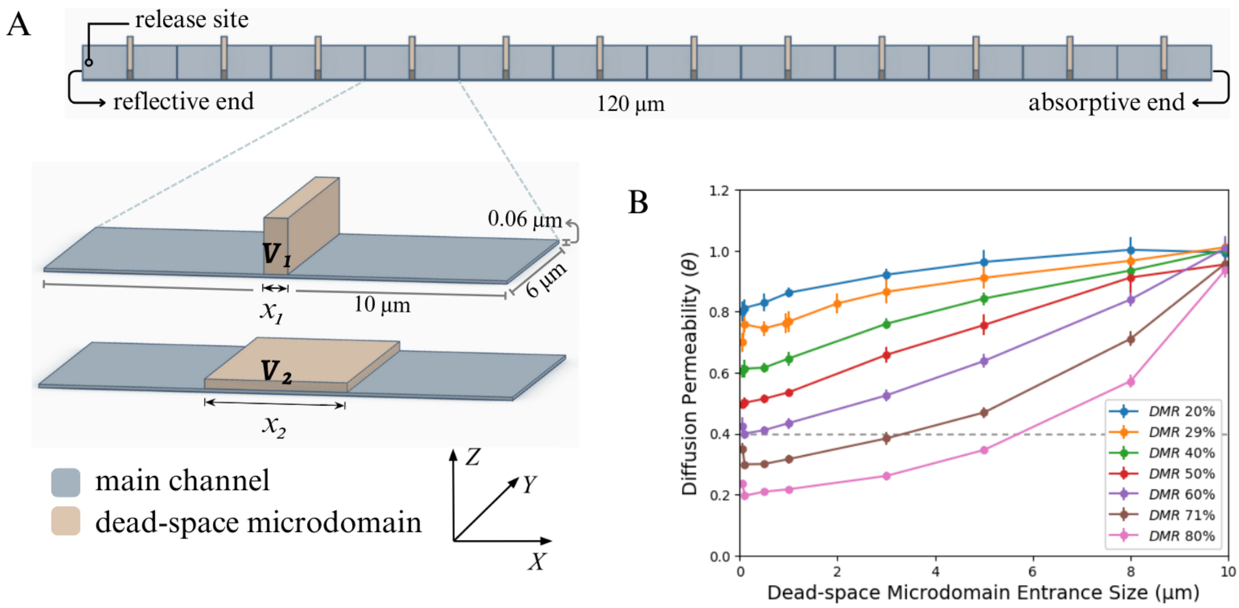

Fig. 1. Monte Carlo simulations of diffusion. A) Model geometry. Molecules were released next to the reflective surface on the left side and absorbed by the surface on the extreme right side. The volume of the vertical DMs varies based on the *DMR*. However, for any given *DMR*, the DM volume remains constant ($V_1 = V_2$) while entrance size varies ($x_1 < x_2$). **B)** Simulation results show the dependence of θ on DM entrance size and *DMR*. The dashed horizontal line ($\theta = 0.4$) demonstrates that many different combinations of the *DMR* and DM entrance size yield the same effective diffusion.

Here we systematically investigated the impact of DM entrance size on diffusion in a simple one-dimensional model. We started with a *DMR* of 40% (*DMR* = DM volume / total ECS volume) to reflect the proportion of dead space previously estimated in healthy brain tissue [3]. The model geometry is shown in Fig. 1A. A long main channel with a total length (x-direction) of 120 µm, width (y-direction) of 6 µm, and height (z-direction) of 0.06 µm is complemented by 12 DMs (z-direction). We tested eight different DM entrance sizes (x-direction) ranging from 0.06 µm to 9.94 µm while maintaining a constant width of 6 µm. The DM height decreased proportionally for larger entrance sizes to maintain a constant DM volume. The surfaces of the ECS were all modeled as reflective except for one extreme end of the main channel, which was made absorptive. Molecules were released at a negligible distance of 0.001 µm from the opposite end at $x = 0$. Due to symmetry, this reflective boundary effectively doubled the simulation world length without additional simulation runtime. Under this setup, Monte Carlo simulations of 2,000 diffusing molecules were performed using the MCell program [7]. The free diffusion coefficient was set to 220 $\mu m^2/s$. We ran 10 repeated trials of this simulation for each DM entrance size, using a different random seed for each trial. For each simulation, a linear fit of the mean squared displacement (MSD) along the x-direction vs. time identified the D^* needed to estimate θ.

The results are summarized in Fig. 1B. As expected, we found θ of 0.6 (a 40% decrease from diffusion without DMs) for the smallest entrance size, which is equivalent to the θ of 0.4 in 3D (a 40% decrease from 0.66) reported previously [2]. Conversely, θ approached 1.0 as DM entrance size increased to its maximum (~10 µm). Therefore, we concluded that the delay effect of the same DM volume gradually diminished with larger DM entrance sizes. Given the wide range of DM entrance sizes in the brain, this suggests that 40% *DMR* cannot reduce overall θ to 0.40. We therefore tested a series of *DMRs* to understand the combined effect of DM entrance size and *DMR* on θ. We found that larger DMs with wider entrances can mimic θ values obtained with smaller DMs with narrower entrances. For example, a *DMR* of 50% and entrance size of 9.94 µm would result in the same θ of 0.96 as a 20% *DMR* and entrance size of 5 µm. For all entrance sizes tested, a larger *DMR* produced a lower θ, as would be expected.

In conclusion, we explored the influence of DM entrance size and *DMR* on θ in macroscopically 1D diffusion. The results suggest a higher proportion of DM in the ECS than previously estimated. Our results may guide the development of more complex 3D models.

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