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Monte Carlo simulation of dead-space microdomains with a 1D diffusion model

Brain extracellular space (ECS), dominating over 20% of the total brain tissue volume, serves as a major transport system for molecules involved in drug delivery and signal communication between cells. Diffusion governs molecule movement in the ECS. It is quantified by diffusion permeability $\theta = D^* / D$, where D^* is the effective diffusion coefficient in brain tissue and D is the free diffusion coefficient. Although experimental studies of small molecules in healthy brain tissue identified θ at ~ 0.40, simulations and theoretical studies of geometrical models with convex elements can only yield values above 0.66. Concave invaginations within the ECS, termed dead-space microdomains (DMs), were proposed as a possible explanation for lower experimental θ, by temporarily trapping molecules. However, most DM models were built on the assumption of narrow DM entrance sizes, which is likely violated given the non-uniform nature of the brain ECS. Here we systematically investigated how a wider range of DM entrance sizes impacts θ in a 1D model. We started with a 40% DM ratio (DMR = DM volume / total ECS volume) to reflect the proportion of dead space previously estimated in healthy brain tissue. Molecules were released at the center of the geometry and let to diffuse in Monte Carlo simulations using the MCell program. We found that the delay effect diminished with larger DM entrance sizes. Given the wide range of DM entrance sizes in the brain, this implies that 40% DMR is not enough to reduce overall θ to 0.40. Thus, we tested a series of DMRs to understand the combined effect of DM entrance size and DMR on θ. We found that, for the same entrance size, a larger DMR produced a lower θ. In conclusion, our findings suggest the DMR is likely greater than 40% in healthy brain tissue which contains a range of DM entrance sizes. We explored patterns of the influence of DM entrance size and DMR on θ that may advance our quantitative understanding of the ECS structure.