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Modeling Ca^{2+} diffusion in brain extracellular space

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Molecular diffusion in brain extracellular space (ECS) is primarily controlled by interactions with the geometry and the interstitial matrix. Both factors increase λ, the tortuosity, a measure of hindrance to diffusion where $\lambda^2 = D/D^*$ with D the free diffusion coefficient and D^* the effective diffusion coefficient in brain [1]. Geometry lengthens diffusion paths or creates holdup in local voids of dead-spaces in the ECS [2] and matrix interacts via specific binding reactions, some illustrated in Fig. 1a.

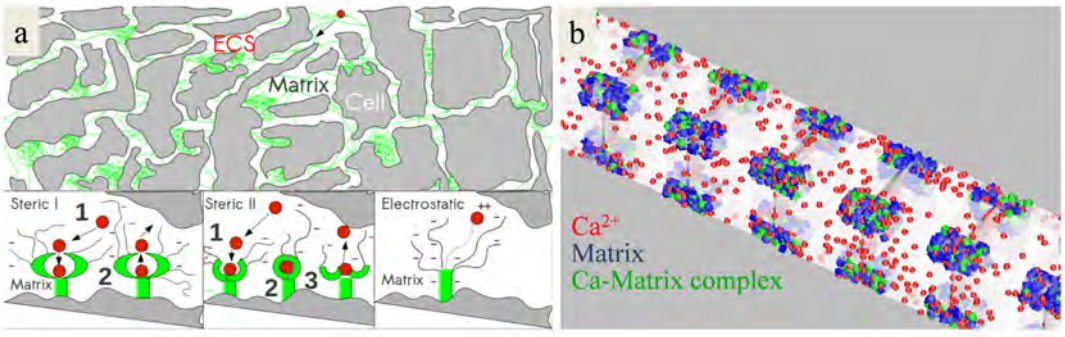

Figure 1: ECS geometry and matrix interactions, a) Schematic b) *MCell* model

Previous experiments showed a reduction in Ca^{2+} diffusion via interactions with chondroitin sulfate, a component of the matrix [3]. Here, we 1) modeled the combination of matrix and ECS geometry to determine how both factors interact to affect diffusion, and 2) studied the effect of matrix distribution.

ECS geometry was constructed from 512 impermeable cubic 'cells' aligned in a long tube and separated by a uniform ECS. To obtain a λ-value equal to that measured experimentally for ions with no matrix interactions ($\lambda \sim 1.6$), the corners of the cubes were cut off, creating a medium with voids [2]. Ca^{2+} ions were released from an instantaneous point-source and diffusion simulated with the Monte Carlo program, *MCell* (www.mcell.org) (Fig. 1b). D^* was calculated as $\langle r^2 \rangle / 6t$ where r was the distance of an ion from the source at time t. The matrix had a reduced effective concentration to take account of background cations, and interaction with Ca^{2+} was represented by a fast equilibrium binding reaction [4]. Matrix was either distributed uniformly in the ECS or localized to the voids.

Our simulations result in a $\lambda \sim 2$ (i.e. $D^* = D/4$) when geometrical hindrance and matrix interactions combine. This agrees with experimental measurements in brain slices [3], and shows that molecules that undergo interaction with matrix are more hindered than those which do not. Our model also shows that matrix localized to the voids can be as effective as when uniformly distributed, if the local concentration is elevated to maintain the average ECS concentration.

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References

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