

Monte Carlo Modeling of Molecular Diffusion in Brain Extracellular Space

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1. Introduction

Diffusion of molecules in brain extracellular space (ECS) is controlled by two major factors: Geometry and extracellular matrix (ECM) interactions [1]. ECS geometry hinders free diffusion of molecules and ECM interacts through electrostatic, steric or viscous mechanisms with the diffusing molecules (Fig. 1). Geometrical hindrance causes a general reduction in free diffusion coefficient of all small molecules and exerts no specificity in interaction [2, 3]. In contrast, most ECM interactions relate to specific molecules and their characteristics. Here our objective was to identify the least number of parameters that can replicate ECM, in order to first explore a functional role for the matrix and second to study the way in which ECM and ECS geometry combine to affect molecular diffusion. We based our analysis on available data for two different molecules: Ca^{2+} [4] and FGF-2 [5].

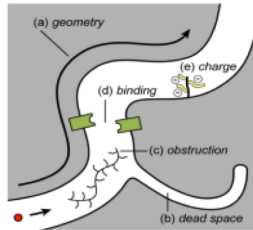


Fig. 1: Schematic of ECM interactions [1].

We used Monte Carlo simulations [6] to model diffusion of molecules within ECS. The simplest element used to construct ECS geometry was a population of $2 \times 2 \times 2$ cube-shaped cells separated by a uniform ECS with volume fraction of 0.2 [1]. By removing one of the eight cubes, a void was generated that could be filled with matrix (Fig. 2). More complex geometries were then generated by replicating and translating the basic elements. Molecules were released from a point source to mimic experiments [1, 4] and the interaction between molecules and ECM was modeled using a fast equilibrium reaction scheme. Ca^{2+} was selected as an example molecule

2. Methods & Results

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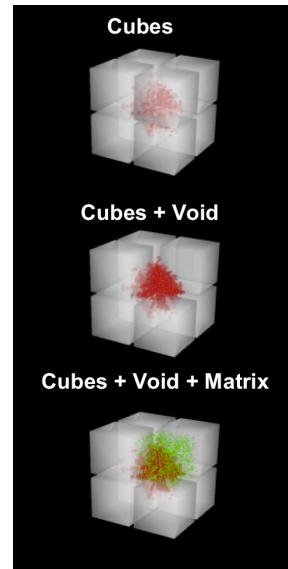


Fig. 2: Basic elements of the geometry and matrix used in the model. **Red**: molecules released from center, **Green**: matrix molecules.

because of available experimental data [2] which provided a test of the consistency of modeling parameters. The growth factor FGF-2 was selected as another example because of available rate constants for specific reactions with the matrix [5].

For a population of molecules released from the origin at $t = 0$ in a 3-D medium, diffusion coefficient, D , was calculated from $D = \langle r^2 \rangle / 6t$. The distributions of molecules in the x , y , and z axes were confirmed to be Gaussian (Fig. 3). In hindered medium, D is reduced to an effective diffusion coefficient D^* and the hindrance to diffusion was calculated as a tortuosity factor, $\lambda = (D/D^*)^{0.5}$.

Our results show that λ increases as molecules explore their microenvironment. As shown previously [2, 3], the presence of a hindered geometry leads to an increased tortuosity value, λ_g that ranges from a free-medium value of 1 to 1.18 - 1.6, depending on the geometry and volume fraction. The value of λ_g generated by an ensemble of cubes [2] is further increased by the dead-spaces arising from the addition of voids [7].

The presence of the matrix provided an additional tortuosity value λ_m that was a function of the forward and backward rate constants, concentration of binding sites (or negatively charged components of the matrix), as well as volume fraction of the matrix. Our simulations showed that the combined effects of ECS geometry and matrix on diffusion were represented by the product of λ_g and λ_m .

3. Conclusion

The geometry of ECS and ECM together can increase the tortuosity of extracellular space to experimentally observed values. Our modelling data is consistent with theoretically predicted values for ECS tortuosity under the assumption that the matrix interaction can be represented by a fast equilibrium reaction. Under these conditions the diffusion equation is obeyed and the distribution of molecules is Gaussian in the three orthogonal axes (Fig. 3) with a new effective diffusion coefficient $D^* = D/(\lambda_g \lambda_m)^2$.

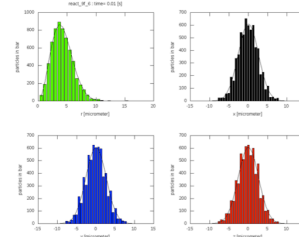


Fig.3: Histograms of 10000 molecules in a medium of cubes with voids containing matrix.

References

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Acknowledgement

Supported by NIH/NINDS Grant R01-NS-28642.