Modelling Microscale Diffusion in Geometrically Resolved Brain Extracellular Space in Live Tissue

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Project at a glance

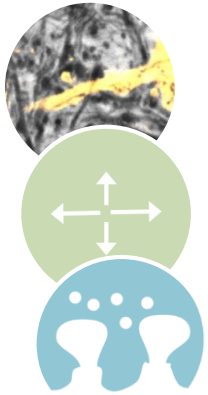


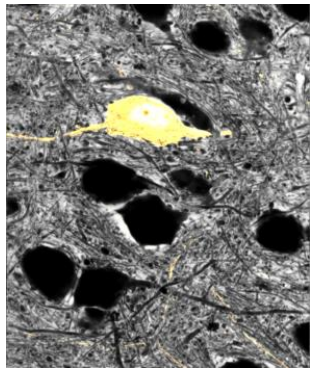
Image the nanoscale geometry of the ECS in live brain tissue.

Model how ECS structure shapes diffusion paths of transmitters.

Understand how the ECS modulates extra-cellular synaptic crosstalk, excitability, and plasticity

Introduction

The extracellular space (ECS) is emerging as an important regulator of brain functions such as metabolite clearance and volume transmission. Yet, how diffusion is shaped around individual cellular sub-structures remains unknown, due to the lack of knowledge about ECS nanoscale geometry in live tissue. Recent Super Resolution Shadow Imaging (SUSHI) reveals the nanoscale organization of the ECS in brain slices [1].
Here, we propose a computational microscale diffusion model based on live tissue SUSHI images.



SUSHI Image from [1]. Live YFP-labelled CA1 neuron in the context of the ECS.

Methods

Mathematical model

Diffusion equation for mass transport

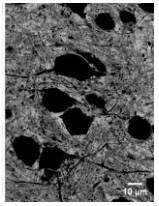
$$\frac{\partial C}{\partial t} = \nabla \cdot \boldsymbol{D}(\nabla C) + S - \kappa C$$

C : concentration
D : diffusion coefficient
S : source magnitude
κ : non-specific clearance

Geometrical description

The effective diffusion coefficient () is defined at each point by the SUSHI mask.

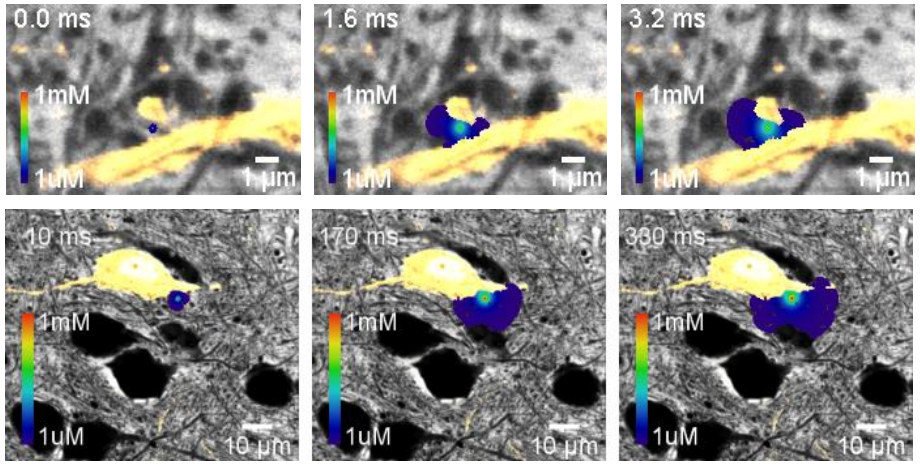
$$\boldsymbol{D_{eff}} = p \cdot D_{free}$$



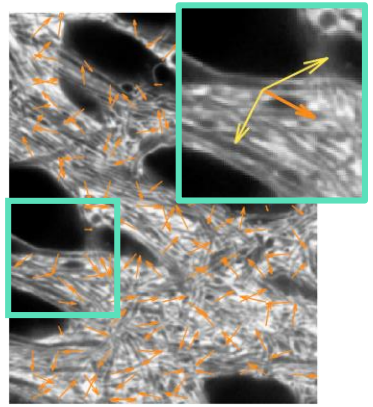
The diffusion probability ($\boldsymbol{p}$) is effectively the relative pixel intensity corrected for background

min	max	intermediate
$p = 0$	$0 < p < 1$	$p = 1$

Simulations



Diffusion on different scales. Diffusion simulations at different spatiotemporal scales. The model allow us to study the effect of ECS geometry on the diffusion of transmitters around a dendritic spine, or at a larger scale.

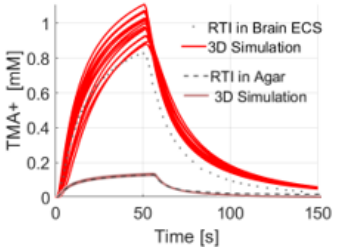


Direction maps. The model allows simulations for multiple source points, from which the predominant diffusion direction can be obtained and compared to the underlying ECS geometry.

We can estimate the ECS volume fraction ($\boldsymbol{\alpha}$) and the tortuosity ($\boldsymbol{\lambda}$) from the image.

$$\alpha = \frac{Mean\ pv - Min\ pv}{Max\ pv - Min\ pv} \qquad \lambda = \sqrt{D_{free}/D_{av}}$$

	Brain	Agar
α	RTI : 0.26 Image: 0.31	RTI: 1 Image: 1
λ	RTI: 1.60 Image: 1.59	RTI: 1 Image: 1



Comparison to RTI measurements. Simulations were compared to corresponding classical Real Time Iontophoresis (RTI) measurements from [2].

Model simulations where carried out in SUSHI images of live brain tissue, as well as in homogeneous images to mimic agarose.

Conclusions

- The proposed model allows predictions about diffusion of molecules released in super-resolved images of live brain tissue.
- Diffusion of any number of any size molecules can be modeled from any point in the image.
- We plan to expand the model to accept 4D dynamic images through future work.

References

[1] Tønnesen *et al.* Super-Resolution Imaging of the Extracellular Space in Living Brain Tissue. Cell, 2018

[2] Hrabětová & Nicholson. Biophysical Properties of Brain Extracellular Space Explored with Ion-Selective Microelectrodes, Integrative Optical Imaging and Related Techniques. In: *Electrochemical Methods for Neuroscience*. 2007.