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Model of extracellular diffusion in layered structure of hippocampus

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1. Introduction

The extracellular space (ECS) surrounding neurons and glia facilitates diffusion of nutrients, neurotransmitters, metabolites, and pharmaceuticals in the brain. Measurements of extracellular diffusion with methods such as real-time iontophoresis (RTI) [1] reveal that the ECS typically comprises about 20% of tissue volume (i.e. the ECS volume fraction $\alpha = V_{ECS}/V_{tissue}$ is typically ≈ 0.2) and diffusion permeability D_{ECS} is typically about 40% of that in an obstacle-free medium ($\theta = D_{ECS}/D_{free}$ is typically ≈ 0.4) [2].

In the CA1 region of the hippocampus, a thin layer (≈ 50 μm) of tightly packed pyramidal cell bodies (stratum pyramidale or SP) separates the stratum oriens (SO) and stratum radiatum (SR) layers (see Fig. 1). This thin SP layer impedes extracellular diffusion [3].

We developed a model of extracellular diffusion in layered structures in order to estimate α and θ in the SP layer of rat hippocampus from RTI data reported in [3]. In these experiments, tetramethylammonium (TMA^+) ions were released into CA1 by iontophoresis from a source electrode and detected with an ion-selective probe electrode about 100 μm away. The usual assumption of homogeneous diffusion environment is not valid for the SP layer because it is thinner than the electrode spacing.

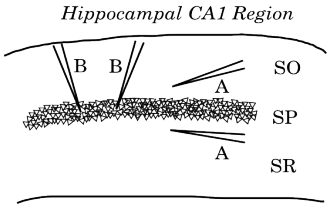

Fig. 1: CA1 region of the rat hippocampus with stratum oriens (SO), stratum pyramidale (SP), and stratum radiatum (SR) layers. Measurements both across the SP layer (A-A) and along the SP layer (B-B) were reported [3].

2. Theory

Here we derive the diffusion equation for the ECS concentration $c(\mathbf{r}, t)$ of a substance at position $\mathbf{r}$ and time t in a region with inhomogeneous $\alpha(\mathbf{r})$ and $\theta(\mathbf{r})$. The tissue concentration is $\alpha(\mathbf{r})\, c(\mathbf{r}, t)$. From conservation of mass, the rate of change of substance in a volume of tissue V is

$$\frac{\partial}{\partial t}\int_V \alpha(\mathbf{r})c(\mathbf{r},t)\,dV \; + \oint_S \mathbf{j}(\mathbf{r},t)\,dS = \int_V \sigma(\mathbf{r},t)\,dV \;,$$

where $\mathbf{j}(\mathbf{r}, t)$ is tissue flux through the surface S enclosing V and $\sigma(\mathbf{r}, t)$ are the sources.

The ECS flux is D_{ECS} grad $c(\mathbf{r}, t)$, assuming Fick's law is valid for the ECS compartment. We can relate it to the tissue flux through the surface S by Delesse's Principle, which states that the fraction of tissue surface area that crosses the ECS is

equal to the volume fraction α. Therefore we can replace the tissue flux in the surface integral with $\alpha(\mathbf{r})\, D_{\mathrm{ECS}}$ grad $c(\mathbf{r}, t)$. Applying Gauss's theorem, we obtain a generalized diffusion equation with both $\alpha(\mathbf{r})$ and $\theta(\mathbf{r})$ spatially variable:

$$\frac{\partial}{\partial t} c(\mathbf{r},t) = \frac{1}{\alpha(\mathbf{r})}\left[\nabla\left(\alpha(\mathbf{r})\theta(\mathbf{r}) D_{\mathrm{free}} \nabla c(\mathbf{r},t)\right) + \sigma(\mathbf{r},t)\right] .$$

In a multilayer model, α and θ are constant in each layer. The boundary conditions are

$$\alpha(\mathbf{r}^-)\theta(\mathbf{r}^-)\, \mathbf{n}\cdot\nabla c(\mathbf{r}^-,t) = \alpha(\mathbf{r}^+)\theta(\mathbf{r}^+)\, \mathbf{n}\cdot\nabla c(\mathbf{r}^+,t) \ , \quad c(\mathbf{r}^-,t) = c(\mathbf{r}^+,t) \ ,$$

where superscripts – and + denote positions below and above the boundary, respectively, and **n** is a unit vector perpendicular to the boundary.

For the forward problem, we used the Forward Time Centered Space differencing scheme in cylindrical coordinates. For the inverse problem, we used the downhill simplex method to find α and θ of the SP layer.

3. Results

It was reported that α and θ in SO were not significantly different than in SR (22% and 45%, respectively) [3]. Measurements in the SP layer were affected by the presence of the SO and SR layers. We determined α and θ of the SP layer by fitting the multilayer model to data from measurements made across the SP layer (electrode placement A-A in Fig. 1), using the known parameters from the SO and SR layers. These fitted SP parameters were used to generate the model curve for the measurements made along the SP layer (electrode placement B-B in Fig. 1), validating the model (Fig. 2).

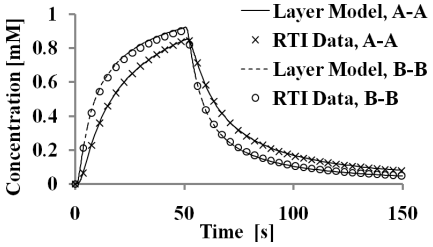

Fig. 2: Concentration of TMA^+ in the ECS, layered model (solid and dashed lines) vs. data (x and o). The source was on for 50 s. A-A and B-B refer to orientation of the electrodes as shown in Fig. 1. Electrode spacing was 120 µm for A-A and 90 µm for B-B.

4. Conclusion

Surprisingly, traditional analysis of RTI data from measurements across the SP layer led to a physically unrealistic α of 28%. The analysis presented here, which took into account the multilayered structure of CA1, gave a value of 12% for α in the SP layer.

This work was supported by NIH/NINDS grants R56NS047557 and R01NS047557.

References

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