Finite Element Analysis of Induced Electroosmotic Flow in Brain Tissue and Application to *ex vivo* Determination of Enzyme Activity

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INTRODUCTION

Ectopeptidases, outward-facing membrane-bound peptidases, are commonly accepted to be a means of clearing active peptides. However, studies have shown that they can also regulate peptide activity.[1-3] We have developed a technique of electrokinetic push-pull perfusion (Ek-PPP, Figure 1) to examine this largely unexplored mechanism of modulation of peptide function. We push the neuropeptide galanin through p7 organotypic hippocampal slice cultures (OHSCs), an *ex vivo* model of neonatal ischemia, and perform quantitative and qualitative analyses on the sampled solution. However, there are variables we cannot experimentally measure in our studies. These include the power dissipation in the tissue, the concentration profile, the residence time distribution of galanin in the tissue, and the spatial resolution of the sampling method. Using COMSOL's multiphysics capabilities, we can determine these variables and, in future work, even calculate a basal enzyme rate for ectopeptidase(s) responsible for galanin hydrolysis.

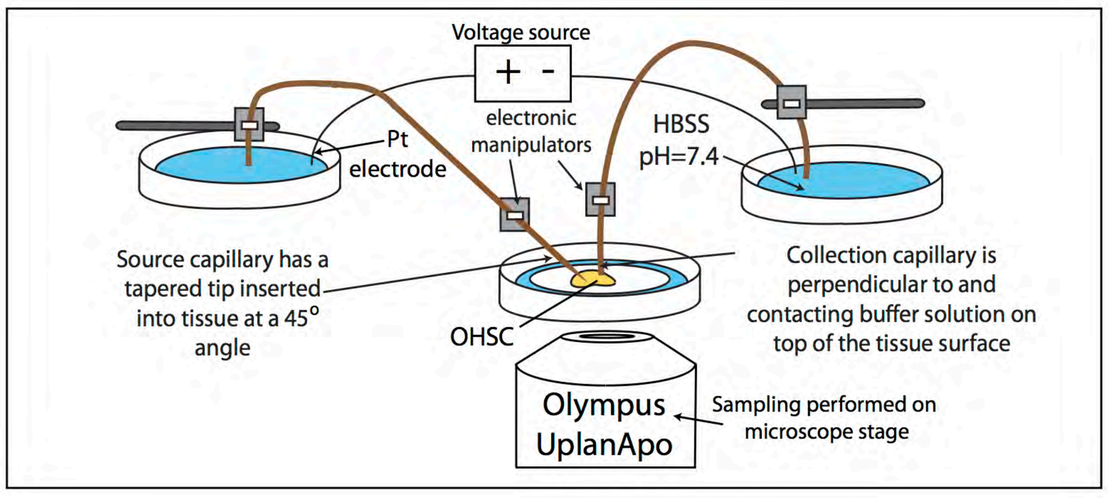


Figure 1. Electrokinetic push-pull perfusion setup.

COMPUTATIONAL METHODS

The setup consists of two electrolyte-filled capillaries in electrical contact with an OHSC (Figure 1) and is recreated in COMSOL (Figure 2). Applied voltage and the resulting current are the primary driving forces for bulk fluid movement through the tissue (! -potential = -0.023 V) and capillaries (! -potential = -0.050 V) in a process called electroosmosis. The combination of this process, electrophoresis, and diffusion determines the resulting species velocity and, consequently, concentration profile. The three physics modules utilized are Electric Currents, Free and Porous Media Flow, and the Transport of Diluted Species. The first and third modules were solved without any modifications to the equations in COMSOL. However, the Free and Porous Media Flow module uses equations that apply most straightforwardly to a homogeneous porous medium. Because we direct fluid through the brain tissue from open capillary tubes, the coefficients in these equations must be adjusted to account for changes in porosity (") as well as tortuosity (#$). We do this by providing COMSOL with volume-averaged parameters derived from known microscopic parameters and adding an effective charge density term in the medium.[4]

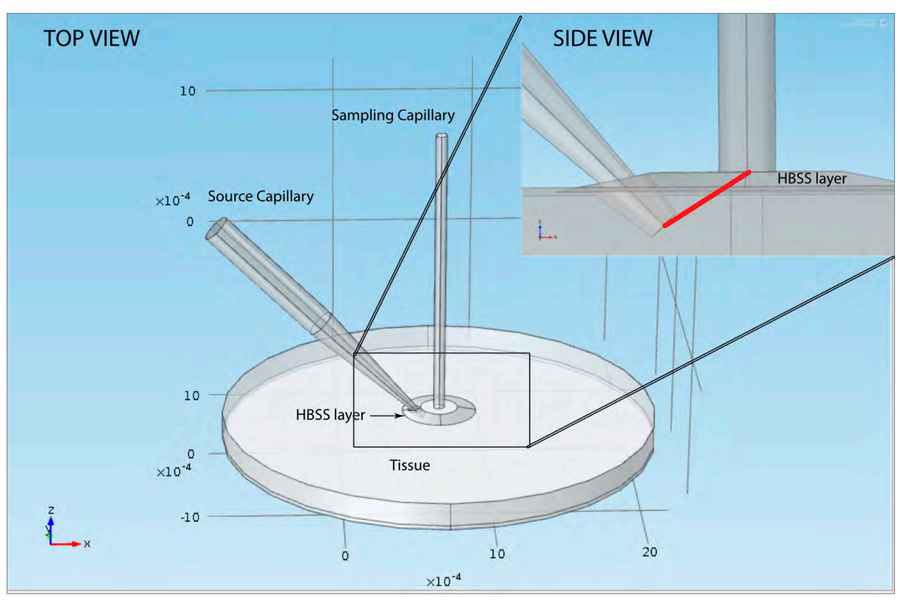
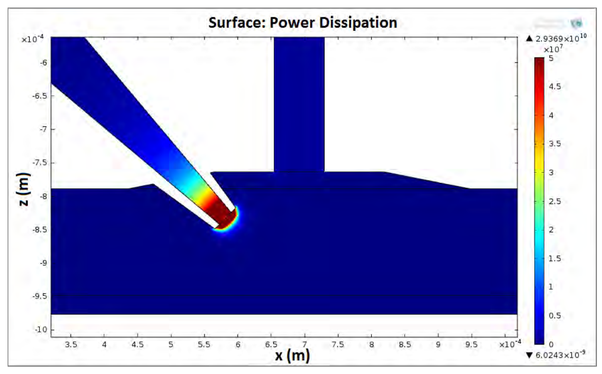


Figure 2. Electrokinetic push-pull perfusion setup recreated in COMSOL.

RESULTS

Figure 3. Power dissipation in the source capillary, the tissue, and the sampling capillary. Most of the power dissipation occurs at the tip of the source within the capillary itself. In fact, the electric field decreases to 10% of its magnitude within 20 µm of the source capillary tip inside the tissue. This means only one or two 30-µm pyramidal cells would be exposed to this high field.



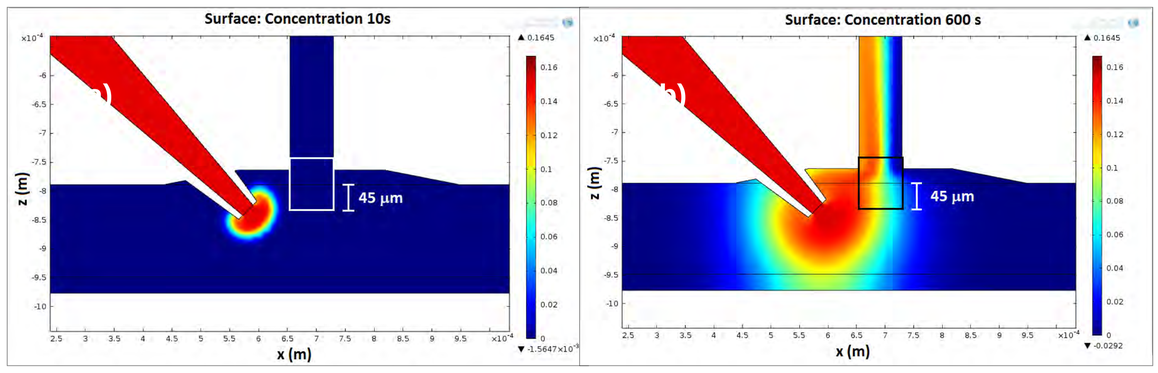


Figure 4. Snapshots of the concentration of galanin at two simulation times: a) 10 seconds and b) 600 seconds. The concentration in the source capillary is a constant 150 µM during the sampling runs. Species flow from the source capillary, through the tissue, and into the sampling capillary.

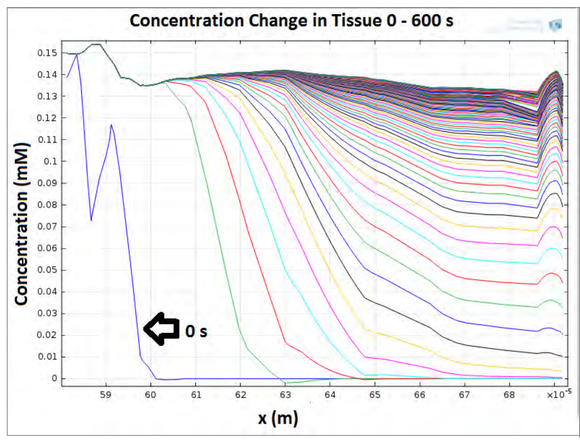


Figure 5. Concentration in the tissue from the tip of the source capillary to the tip of the sampling capillary (see red line in Figure 2) across a 10-min simulation time. The concentration reaches steady state.

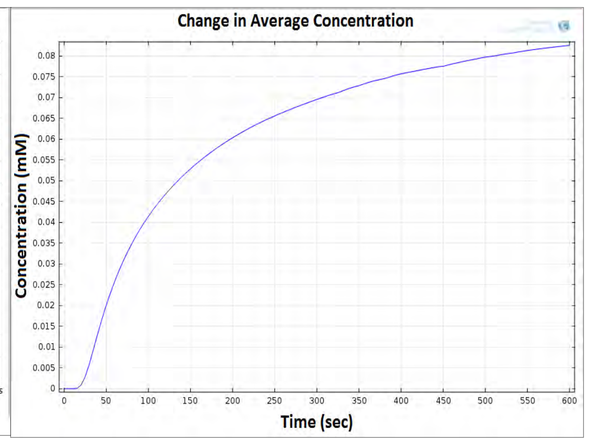


Figure 6. Predicted fluorescence intensity from the 3-D concentration distribution as a function of time convoluted with the point spread function of the microscope. This agrees with experimental data.

CONCLUSION

From the simulation calculations, we were able to determine various parameters unattainable through experiments. The results showed that the method of Ek-PPP is minimally damaging, despite the application of a relatively high voltage. The concentration profile shows some of the advantages of Ek-PPP over traditional pressure-driven flow: that it can be directionally controlled and provides better spatial resolution. The finite element calculations, however, also present room for potential improvement in our setup. Specifically, the sampling capillary is not filled to its entirety after the experiment, thus diluting the samples. This can be prevented by positioning the source capillary closer to its sampling counterpart. Future work will involve using the simulations to calculate the basal enzyme reaction rate.

REFERENCES

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