# Numerical Simulation of Electrokinetic Convection-Enhanced Delivery of Macromolecules

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## INTRODUCTION

The brain is a heterogeneous, anisotropic porous medium. Measurements of tortuosity showed that diffusion in grey matter is isotropic, whereas it is anisotropic in white matter[1]. For example, Voříšek and Syková found that for the corpus callosum (CC), which is a long line of axonal bundles, the tortuosity differs depending on whether a molecule is traveling along the projections in a parallel manner($\lambda_{||}$ = 1.46) or perpendicularly through the tract ($\lambda_{\perp}$ = 1.70) [2].

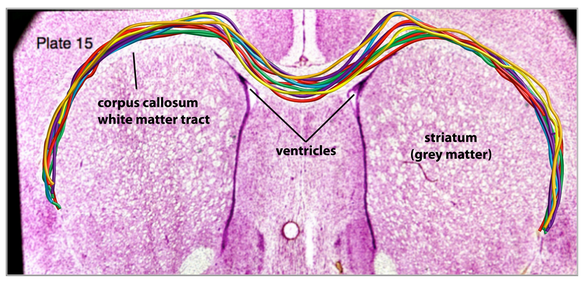


**Figure 1.** Coronal section of rat hippocampus with the corpus callosum white matter tract artificially drawn over the micrograph to illustrate its anisotropic nature. Figure adapted from the Rat Atlas by Paxinos and Watson, 4th ed.[3]

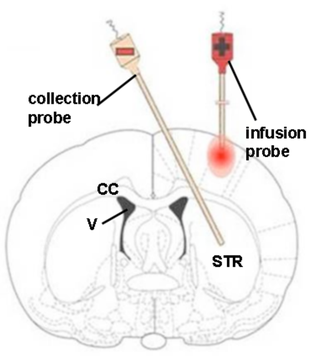


**Figure 2.** Schematic showing electrokinetic convection-enhanced delivery (ECED) technique. CC = corpus callosum; V = ventricle; STR = striatum.

Pressure-driven convection-enhanced delivery (CED) of macromolecules was first described in the mid-90s to introduce high concentration of macromolecules into the cat brain[4]. It was successful in delivering higher volume of molecules into the brain than by diffusion alone. However, it was limited by the backflow of infusate into the implanted tracts, edema, and lack of directional control[5-6].

We developed an electrokinetic convection enhanced delivery (ECED) method in order to address some of these limitations (Fig. 2). It uses electric field as the driving force instead of pressure.

## COMPUTATIONAL METHODS

The brain was created in the COMSOL Multiphysics v5.2 geometry interface using a parametric curve (based on coordinates from the Rat Atlas) and was modeled as a non-elastic porous medium. The infusion and collection capillaries were modeled as hollow cylinders. The model uses the Electric Currents, Free and Porous Media Flow, and Transport of Diluted Species in Porous Media modules to calculate the infusion of a cationic fluorophore $Ru(bpy)_3^{2+}$ into the rat striatum. To simulate the anisotropic nature of the CC, the model uses the Diffusion Method in the Curvilinear Coordinates module to define a new coordinate system in which the Cartesian coordinate follows the shape of the CC tracts (Fig. 3b). We simulated 300 min (or 5 hours) of infusion.

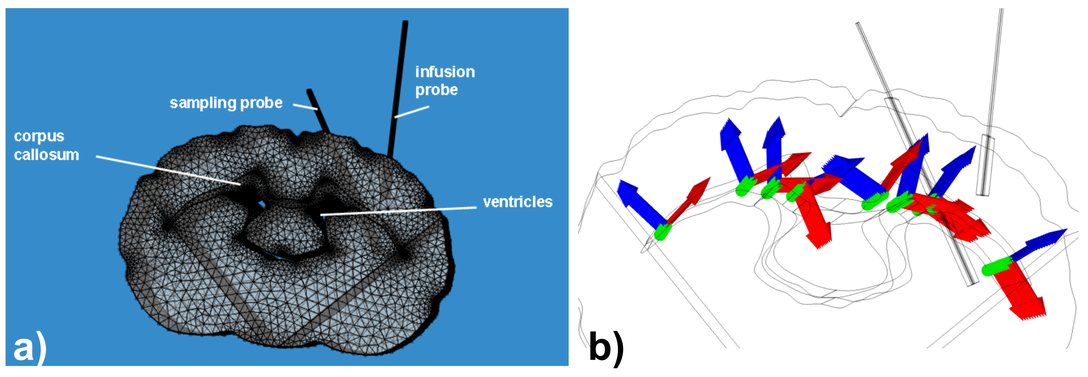


**Figure 3.** a) Meshing of the geometry with the various components labeled. b) Same geometry showing the curvilinear coordinate system (x = red, y = green, z = blue).

A form of the Brinkmann equation was used for flow in porous media:

$$\frac{\eta}{\kappa}u + \nabla P + \frac{\varepsilon_w \zeta \varepsilon}{\lambda^2 \kappa}\nabla\phi = 0$$

The following equation was used to calculate the time-dependent concentration of $Ru(bpy)_3^{2+}$, taking into account diffusion, migration, and convection by electrokinetic driving force (in this case, both electroosmosis and electrophoresis).

$$\varepsilon\frac{\partial c_i}{\partial t} = u\cdot\nabla c_i + \nabla(-D_{e,i}\nabla c_i) + \varepsilon\nabla(-\mu_{ep,i}c_i\nabla\phi)$$

## RESULTS

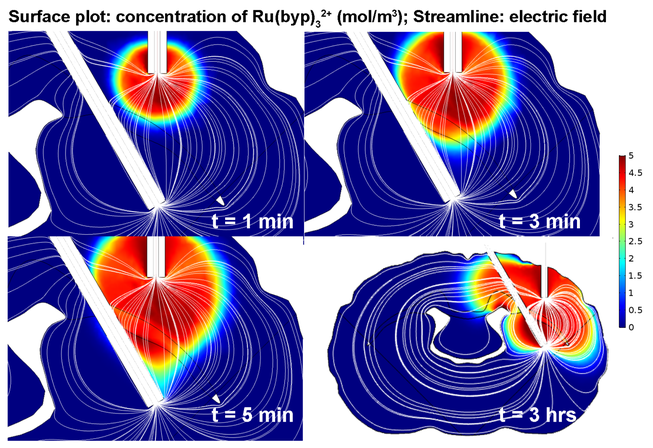


**Figure 4.** Surface plot of a cross section of the 3D model showing that the tip of the collection probe reaches a concentration of 5 mol/m$^3$ (or 10% of initial infusion concentration, $c_0$) 10 min into infusion. Clearly there is directionality in the flow, as evident at t = 5 min. Electric field lines are shown in white.

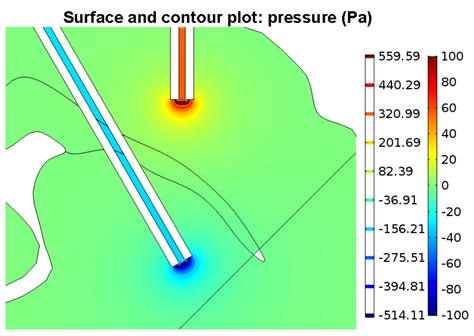


**Figure 5.** Surface and contour plots of pressure in Pa. Even though there is no external pressure applied, an internal pressure gradient is generated due to the mismatch in ζ-potential between the tissue and capillaries. The result is a positive pressure near the infusion probe and a negative pressure near the collection probe. This pressure should increase with the amount of current applied and aides in the infusion of molecules into the brain.

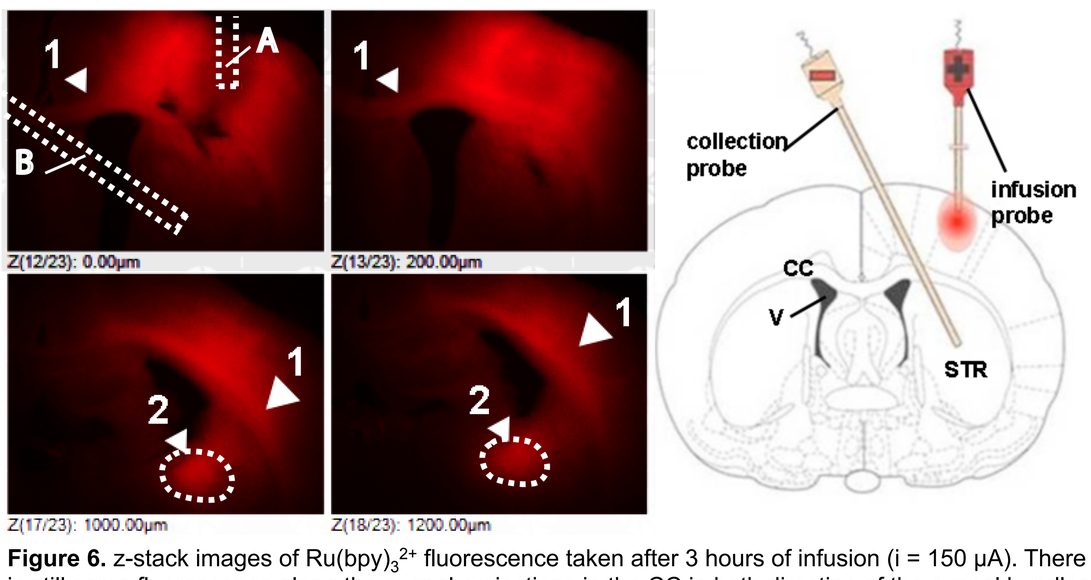


**Figure 6.** z-stack images of $Ru(bpy)_3^{2+}$ fluorescence taken after 3 hours of infusion (i = 150 µA). There is still some fluorescence along the axonal projections in the CC in both direction of the axonal bundles (toward the other hemisphere as well as down toward the striatum), see arrow 1. However, the fluorophore was successfully delivered across the axonal bundles in the CC to the striatum (arrow 2, also circled). The dark area in the cortex is the location of the infusion probe (A). It and the collection probe (B) are outlined. On the right, the schematic was reproduced to clarify the experimental setup.

Calculations (Fig. 4) show that approximately 8 µL of the brain is infused at 10 min and 100 µL of the brain is infused after 3 hours. This translates to approximately 2 and 20% of the total rat brain volume (~500 µL)[7], respectively. The concentration profile follows the path of the current, as shown by the electric field lines in the xz plane. Interestingly, the concentration profile at t = 5 min shows that the solutes are pulled into the collection capillary once it is in close proximity. This is expected for electroosmosis in systems with different ζ-potentials. Despite the lack of an external pressure force, an internal pressure gradient results from the mismatch in ζ-potential between the probes[8] and tissue[9] (Fig. 5). This pressure gradient facilitates the general infusion of molecules into the brain. Guided by simulations, we performed 3-hr infusion of $Ru(bpy)_3^{2+}$ at 150 µA current. Even though there was some fluorescence *along* the CC tract, as shown in Fig. 6, $Ru(bpy)_3^{2+}$ was successfully delivered *through* the white matter tract of the CC to the striatum using ECED.

## CONCLUSION

We showed using simulation that ECED can be used to infuse molecules via a current-directed manner that is not restricted by the anisotropic nature of brain tissue. We verified these results with successful experimental infusion of $Ru(bpy)_3^{2+}$ into the rat striatum.

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