Numerical Simulation of Electrokinetic Convection-Enhanced Delivery of Macromolecules

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Abstract

The brain is a heterogeneous porous medium with regions of anisotropy. Measurements of tortuosity (λ) showed that diffusion in gray matter (e.g. striatum) is isotropic (λ = 1.65), whereas it is anisotropic in white matter (e.g. corpus callosum) (λparallel = 1.38, λperpendicular = 1.80)[1-2]. Pressure-driven convection-enhanced delivery (CED) of macromolecules (e.g. drugs) was first described in the mid-90s to introduce high concentration of macromolecules into cat brain[3]. It was successful in delivering significantly higher volume of molecules to the brain than by diffusion alone. However, it was limited by several factors, including backflow of infusate of implanted tracts, edema, and lack of directional control[4-5]. Fluid and infused molecules have a tendency to travel to regions of higher permeability, e.g. along the axonal projections of corpus callosum rather than perpendicular through them. This makes any pressure infusions into low permeability regions, e.g. dorsal-ventral delivery across the corpus callosum, a difficult task.

We developed an electrokinetic convection-enhanced delivery (Ek-CED) method in order to address some of these limitations. The main difference between the two methods is the driving force: Ek-CED uses an external electric field to drive fluid flow rather than pressure. As there are various complex processes taking place during this infusion process, a mathematical model is required for experimentalists to understand and implement the technique without performing costly experiments. Thus, we developed a brain model that includes that anisotropic nature of the corpus callosum by using a curvilinear coordinate system. The model uses the Electric Currents, Free and Porous Media Flow, and Transport of Diluted Species in Porous Media interfaces in the COMSOL Multiphysics® software. Infusion of anionic fluorophore over 5 hours was simulated from a source capillary located in the cortex to a collection capillary in the striatum, passing perpendicular through the corpus callosum. We used calculations as a guide to determine optimal currents for infusion, the minimum time required for samples to reach the collection capillary, and whether or not directionality can be controlled. Calculations, along with experiments, show that while there is still some delivery along the axonal tract, there is a significant improvement in direction-controlled delivery to the striatum.

Reference

1. L. Vargová, E. Syková, "Heterogeneous and anisotropic diffusion in the developing rat spinal cord." Neuroreport 1997, 8. 3527-3532.
2. A. A. Linninger, et al., "Computational methods for predicting drug transport in anisotropic and heterogeneous brain tissue." Journal of biomechanics 2008, 41. 2176-2187.
3. R. H. Bobo, et al., "Convection-enhanced delivery of macromolecules in the brain." Proceedings of the National Academy of Sciences 1994, 91. 2076-2080.
4. M. Y. Chen, et al., "Variables affecting convection-enhanced delivery to the striatum: a systematic examination of rate of infusion, cannula size, infusate concentration, and tissue-cannula sealing time." Journal of neurosurgery 1999, 90. 315-320.
5. D. Ding, et al., "Convection-enhanced drug delivery to the brain." Drug Delivery to the Central Nervous System 2010. 291-318.

Figures used in the abstract

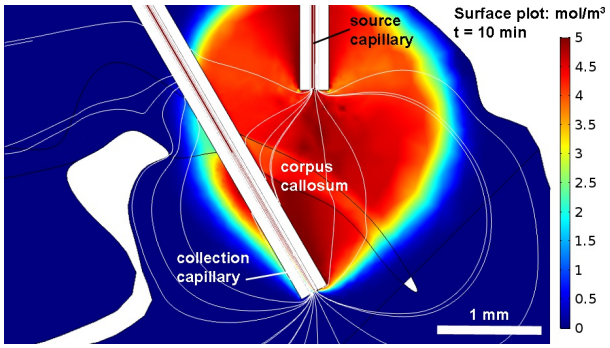

Figure 1: 2D surface plot of a cross section in the 3D brain model showing concentration profile after 10 min of infusion. White streamlines are also shown to indicate the relative trajectories of the fluid/molecular path.