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A 3D Finite Element Model to Evaluate Drug Infusion in the Cerebral Cortex

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***Abstract*— Drug delivery to the cerebral cortex by infusion was modeled using finite element analysis. The results support that this method of drug delivery could be effective in treating a relevant volume of brain tissue over short time scales.**

***Clinical Relevance*— Studies often investigate Convection-Enhanced Delivery in terms of hours-long infusion regimens [1], [2], [3]. The results of this study support the feasibility of medicating a target structure on-demand, within a small timeframe.**

I. INTRODUCTION

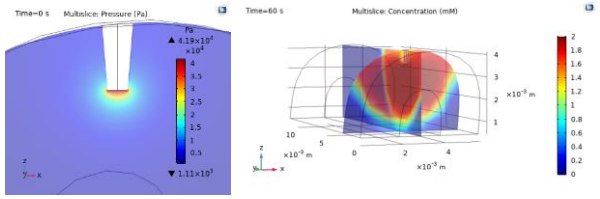
Significant challenges to treating neurological disorders include the selective permeability of the blood-brain barrier and the inability to direct therapeutic compounds into the CNS [1], [2]. Convection-enhanced delivery (CED) is a method to administer drugs in which a drug is directly injected into the brain to chemically modulate neurons [3]. CED offers great potential for precise spatiotemporal control of the drug release and maximizing therapeutic effects. The purpose of this study is to model and evaluate the rapid delivery of medication to the cerebral cortex.

II. METHODS

A model of a gyrus (6x12x4mm^3) was designed in COMSOL Multiphysics, a finite element analysis software package, and is based on MRI images of the human cerebral cortex. COMSOL's *Transport of Diluted Species in Porous Media* and *Darcy's Law* interfaces were used. The former module applies Fick's Second Law, which is affected by the velocity field calculated through Darcy's Law. The drug was injected through a modeled catheter with a diameter of 0.2 mm. The compound diffuses mostly through gray matter (porosity of 0.20; tortuosity of 1.6 for molecules of interest [1]). The drug used in this simulation was 2.0 mM valproate (an anti-epileptic drug), which has a diffusion coefficient of 6.11E-10 m^2/s at 37°C, density of 1 g/cm^3, and dynamic viscosity of 7.8E-4 Pa*s [2]. The Darcy permeability of the brain tissue is 5.0E-15 m^2 [2]. The pressure of the tissues and tissue boundaries is 1110 Pa [2]. The initial pressure of injection was 1110 Pa, with a mass flow rate of 0.01 g/min of liquid medication. This is based on a tested injection rate of 10 µL/min, which was found to be low enough to prevent drug reflux and tissue damage [3].

III. RESULTS

In the model, 10 µL of valproic acid (2.9 µg valproate) was injected into the cerebral cortex over 60 s, creating a pressure gradient of 40,800 Pa (0.40 atm) at the catheter tip (Fig. 1a). The pressure distribution was found to be constant throughout the infusion. Due to the nature of fluid flow, the concentration of valproate in the affected brain tissue (shown in red) is fairly homogeneous (2 mM), with a steep gradient approaching 0.0 mM at the perimeter of the affected volume (Fig. 1b). Valproate is known to exert effects on neurons in concentrations between 0.2-2.0 mM [4], which applies to a relevant volume of brain tissue (Fig. 1b); the volume of the cerebral cortex affected by the medication is approximately 25 mm^3 within 30 s and 50 mm^3 within 60 s.



a b

Figure 1. a) Close-up of pressure distribution at t=60s, which is uniform throughout the infusion. The needle has a lower diameter of 0.2mm. b) Concentration distribution of valproate at t=60s.

IV. DISCUSSION & CONCLUSION

The results support the hypothesis that CED can be applied to medicate small target structures in the cerebral cortex within a short timeframe. This broadens the potential uses of CED, as many previous studies focused on infusions lasting multiple hours or days [2], [3]. On-demand medication could be an effective intervention for certain diseases; for example, immediate treatment is necessary during seizure activity in an epileptic patient. Furthermore, this model can be applied to specific patients' target geometries to determine how CED therapy can be optimized for them.

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