Introduction

Motivation

- Direct application for improved medical treatments of neurological disorders
  - Alzheimer’s, Parkinson’s, Autism, Cerebrovascular disease
- Improved treatment for
  - Abnormal vascular structures (tumors)
  - Stroke conditions

Objective

- Many therapeutic drugs for treatment of neurological conditions are blocked from the brain by the blood brain barrier. Convection-enhanced drug delivery offers treatment options that can bypass the blood brain barrier. Testing is needed to determine a standard protocol for infusion with minimal reflux. Computer simulated reflux can eliminate preliminary animal testing.

Blood Brain Barrier

- Serves as a protective barrier to the brain.
- Tight-junctions between the endothelial cells of blood vessels prevent large molecules (more than 800 amu) from entering the brain.
- Many medications for neurological conditions are large molecules, and are blocked from entering the brain through the blood stream.

Convection-Enhanced Delivery Experiments

Experimental Design

- New Era Pump System syringe pump
- Polyethylene tubing (various gauges)
- Stainless steel catheters (various gauges)
- 1.0 ml medical syringes
- 1 mm stainless steel rat brain matrix
- Thermal plastic catheter clamp
- 6.0% Agarose gel
- 0.25% Bromophenol blue dye
- Glass cell block
- 30 watt light table
- Stainless steel razor blades
- Canon EOS Rebel Xti camera

6% Agarose Gel Infusion

- 0.25% bromophenol blue dye infused at 0.5 µm/min
- 0.25% bromophenol blue dye infused at 1.0 µm/min
- 0.25% bromophenol blue dye infused at 2.5 µm/min
- 0.25% bromophenol blue dye infused at 5.0 µm/min

Rat Brain Infusion

- Rat brain infused with 0.25% bromophenol blue dye using a 25 gauge catheter and a 0.5 µl/min infusion rate.
- Rat brain infused with 0.25% bromophenol blue dye using a 25 gauge catheter and a 0.5 µl/min infusion rate.
- Rat brain infused with 0.25% bromophenol blue dye using a 25 gauge catheter and a 0.5 µl/min infusion rate.
- Rat brain infused with 0.25% bromophenol blue dye using a 25 gauge catheter and a 0.5 µl/min infusion rate.

Coronal slices of rat brain showing distribution profile of bromophenol blue dye.

Computer Simulation

- Using Image J computer program, marking physical structures and point of infusion
- Computational grid mapping the structures of the infused rat brain
- Fluent computer simulation of infusion into fixed rat brain

Results

- Extensive reflux occurred in agarose gel at infusion rates greater than 1.0 µl/min.
- Computer simulation of infusion in fixed rat brain produces comparable results to experimental data.

Conclusion

- Lower infusion rates and smaller diameter catheters produced minimal reflux in agarose gel brain phantoms.
- Computer simulation of convection–enhanced delivery produced comparable results to experimental data.

Future Studies

- Improved Accuracy in Slicing Brain Tissue
  - Studying various techniques to improve the precision and ability to capture distribution profile in unfixed brain tissue. Methods include cyrosectioning, and use of a microtome.

Acknowledgements

- NSF CBET EEC-0743068 Grant, Chicago Science Teacher Research (CSTR) Program Director, A. Linninger
- Members of LPPD, Andreas Linninger, Madhu Iyer, Sukhi Basati, Komal Prem
- RET Fellows at UIC
- Dr. James Kerns