DRUG DELIVERY INTO THE HUMAN BRAIN

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Motivation

Motivation for Targeted Drug Delivery

- More than 80 million people are affected with Central Nervous System (CNS) disorders. (Ref: www.nih.gov)
- CNS diseases range from epilepsy to Parkinson's, Alzheimer's disease and brain tumors.
- Blood Brain Barrier (BBB) prevents large therapeutic drug molecules to reach the CNS.
- Direct injection methods using infusion catheters are deployed to circumvent BBB.

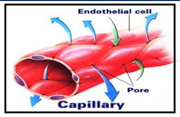
Types of Drug Administration Techniques

- Non-Invasive drug delivery techniques include
  1. Carrier-Mediated Transport 2. Protein Cationization Methods 3. Peptide Technology
- Invasive techniques using catheters by direct injection include
  1. Intracerebral Implants 2. Intracerebroventricular infusion by infusion catheters

Need for Improved Drug Delivery

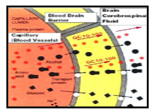
- Determine the optimal infusion policy for CNS diseases treatment for a specific drug.
- Decision support to doctors parallel to animal testing by quantifying Penetration Depths and Treatment Volumes.

Blood Brain Barrier



Endothelial Cell

Nutritional Medicine Research, UK, 1991



Blood Brain Barrier

Nutritional Medicine Research, UK, 1991

BBB is formed by a network of endothelial cells and is impermeable to large molecular weight chemotherapeutic agents (large proteins).

CNS Disorders Requiring LARGE Molecules Drug Therapy

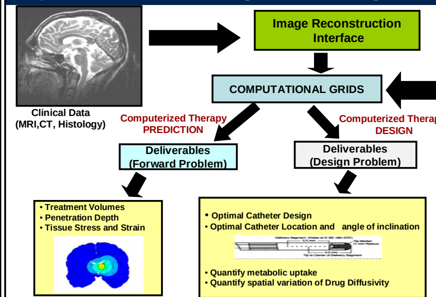
- Alzheimer's Disease
- Parkinson's Disease
- Huntington's Disease
- Autism
- Multiple Sclerosis
- Brain Cancer
- Stroke
- Brain Trauma
- Lysosomal Storage Disorders
- Inherited Ataxias

CNS Disorders Treatable With small Drug Molecules

- Depression
- Schizophrenia
- Chronic Pain
- Epilepsy

Ref: William M. Pardridge, 2005

Systematic Design of Drug Delivery Therapies



MATHEMATICAL MODELS (applied to porous brain tissues)

Forward/Simulation Problem using CFD

- Conservation of Mass
- Conservation of Momentum
- Conservation of Species

Design Problem using Optimization Techniques

- Levenberg-Marquardt method
- Newton Method
- Powell Dogleg Method

Mathematical Model

Pure Diffusive Transport of a Drug Molecule

$$\frac{\partial}{\partial x}\left(\rho D_x \frac{\partial C_i}{\partial x}\right) + \frac{\partial}{\partial y}\left(\rho D_y \frac{\partial C_i}{\partial y}\right) + R_i = 0$$

Prediction of Bulk Diffusivity of a Drug: $D_{Bulk} = \dfrac{9.40 * 10^{-15} T}{\mu\,(M)^{1/3}}$

Effective Diffusivity in Porous Tissues: $D_{eff} = \dfrac{\varepsilon}{\tau} D_{Bulk}$

Convection – Enhanced Drug Transport in Porous Brain Tissues

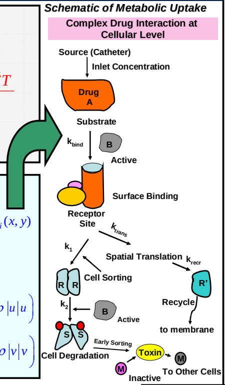
$$\frac{\partial}{\partial x}(\rho u(x,y)C_i) + \frac{\partial}{\partial y}(\rho v(x,y)C_i) = -\frac{\partial}{\partial x}\left(\rho D_x \frac{\partial C_i}{\partial x}\right) - \frac{\partial}{\partial y}\left(\rho D_y \frac{\partial C_i}{\partial y}\right) + R_i(x,y)$$

Continuity $$\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} = 0$$

x-momentum $$\rho u\frac{\partial u}{\partial x} + \rho v \frac{\partial u}{\partial y} = -\frac{\partial p}{\partial x} + \mu\left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2}\right) - \left(\frac{\mu}{\alpha}u + C_2 \frac{1}{2}\rho |u| u\right)$$

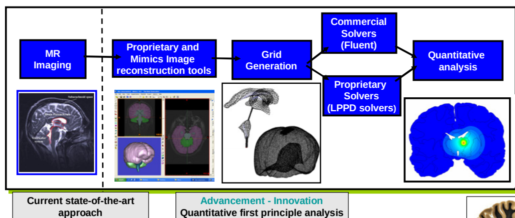
y-momentum $$\rho u\frac{\partial v}{\partial x} + \rho v \frac{\partial v}{\partial y} = -\frac{\partial p}{\partial y} + \mu\left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2}\right) - \left(\frac{\mu}{\alpha}v + C_2 \frac{1}{2}\rho |v| v\right)$$

Schematic of Metabolic Uptake



MRI-Image Reconstruction Interface

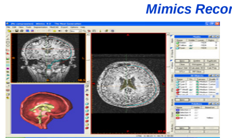
Schematic of the workflow in the computer assisted diagnosis approach

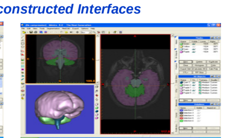


Deliverables

- ICP variation due to injection
- Prediction of the flow field
- Drug concentration
- Quantification of the metabolic uptake
- Prediction of cell deformation, tissue-strain& stress

Mimics Reconstructed Interfaces





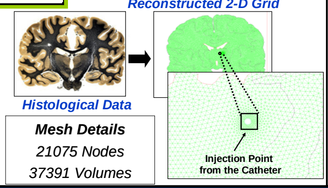
Histological Data

Mesh Details

21075 Nodes

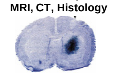
37391 Volumes

Reconstructed 2-D Grid

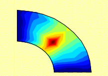


Kinetic & Transport Inversion Problem

Clinical Data Input from MRI, CT, Histology



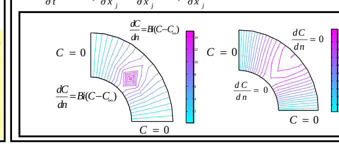
Simplified representation of Clinical data



Inversion Problem with Diffusion only

$$\min_{\Omega} \psi(\Omega) = \sum \left(\Phi(x,t,\Omega) - \Theta(x,t)\right)^2$$

$$\rho\frac{\partial\Phi}{\partial t} + \rho u_j \frac{\partial\Phi}{\partial x_j} = \frac{\partial}{\partial x_j}\left(D_{xy}\frac{\partial\Phi}{\partial x_j}\right) + S$$



Postulate Mechanism

$$A \xrightarrow{k_1} B$$
$$\gamma_A = -k_1 C_A$$
$$\gamma_B = k_1 C_A$$

Recover Transport and Kinetic Parameters

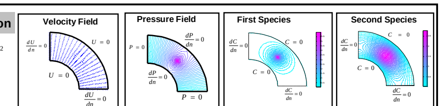
D1 = 11.45

K1= 1.01

Inversion Problem with Convection

$$\min_{\Omega} \psi(\Omega) = \sum \left(\Phi(x,t,\Omega) - \Theta(x,t)\right)^2$$

$$\rho\frac{\partial\Phi}{\partial t} + \rho u_j \frac{\partial\Phi}{\partial x_j} = \frac{\partial}{\partial x_j}\left(D_{xy}\frac{\partial\Phi}{\partial x_j}\right) + S$$

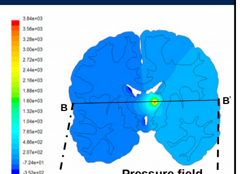


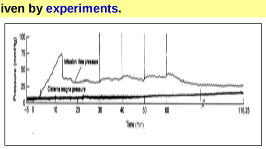
Fsolve in Matlab	55 min
Sparse solver in Matlab	6 min

Recover unknown transport and Kinetic properties that caused a flow field

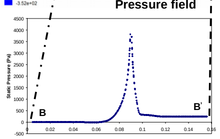
Validation of Pressure Field

- The limitation of the CED protocol is described the threshold (~ 35 to 60 mm Hg) pressure drop (ΔP).
- Values of ΔP > Threshold will lead to large scale tissue displacement
- Our simulation results were in good agreement with the allowable value of ΔP given by experiments.



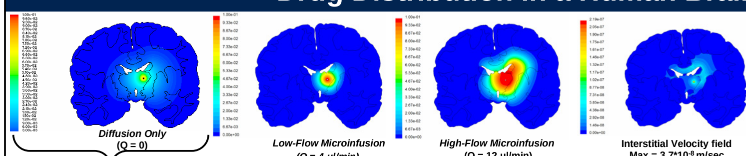


Mean pressure near the injection point (experimental - animal data) = 4000 Pa



Mean pressure near the injection point (simulated): ~35 mmHg = 4700 Pa

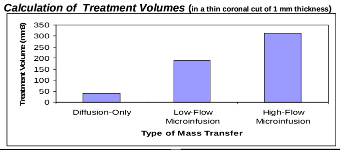
Drug Distribution in a Human Brain



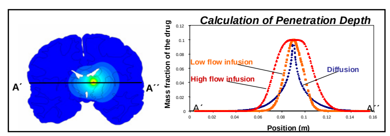
PURE DIFFUSION *leads to insufficient Treatment Volumes*

CONVECTION *Enhanced Drug Delivery (CED) leads to greater treatment volumes in the order of a few cm³*

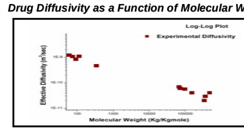
Calculation of Treatment Volumes (in a thin coronal cut of 1 mm thickness)



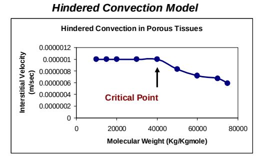
Calculation of Penetration Depth



Drug Diffusivity as a Function of Molecular Weight

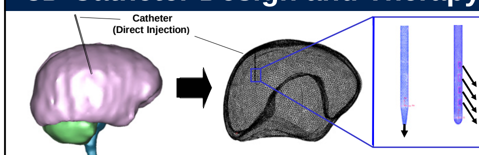


Hindered Convection Model

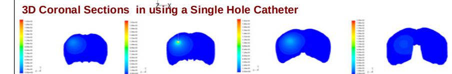


- *Molecular Weight Cut - Off begins at the Critical Point in Convective Flow.*
- *This cut-off is normally given by the molecular weight of many Neurotrophic compounds.*

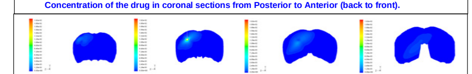
3D Catheter Design and Therapy



3D Coronal Sections in using a Single Hole Catheter



Concentration of the drug in coronal sections from Posterior to Anterior (back to front).



Velocity field in coronal sections from Posterior to Anterior (back to front).

Conclusions

- Seamless integration of image reconstruction with first principles.
- CED protocol significantly increased the Treatment Volumes and Penetration Depth.
- The simulated value of pressure gradient was validated with animal experiments.
- *Future Work*: Tissue displacement, Hindered Convection model, 3D Catheter Design and Therapy, Reabsorption of the bulk into the blood.

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- NSF-REU, University of Illinois at Chicago, Chicago, IL, 60607.
- Materialise, Inc., (Mimics), http://www.materialise.be/mimics/main_ENG.html.
- The Fluent Inc., (Gambit/Fluent/Fiidap), www.fluent.com .