Computational Design of Drug Delivery Policies

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Conference: AICHE Annual Meeting, Sanfrancisco, CA, USA
Date: Nov 12-17, 2006

Area: Systems and Process Design (10A)
Session: Design of Biological, Pharmaceutical and Alternative Energy Systems (10A06)

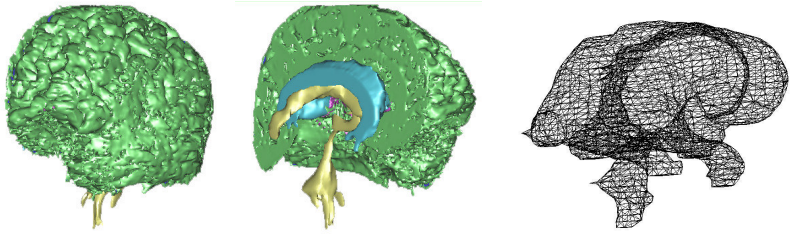
Abstract

Motivation: The development of systematic drug delivery for diseases of the central nervous system (CNS) is a formidable challenge and there is hardly any successful treatment protocol for many CNS diseases. Data published by National Institutes of Health suggest that CNS diseases such as Parkinson's, Alzheimer's and Huntington's affect millions of people worldwide. Targeted delivery of large macromolecules to specific locations in the brain is a challenging task in CNS drug delivery owing to the presence of blood-brain barrier (BBB) [1]. In addition, the restriction offered by the white matter tracts hampers the transport and metabolism of drugs in target areas and pose difficulty to catheter design and placement [2].

Methodology: In this presentation, we propose three innovations embedded into a hierarchical design procedure. The systematic approach to designing drug targeting faces three challenges and we aim to address them in this presentation:

1. Accurate three-dimensional reconstruction of the *patient-specific* brain geometry
2. Quantification of achievable treatment volume subject to anisotropy
3. Optimal catheter design and placement

The first challenge is to reconstruct the physiologically consistent three-dimensional *patient-specific* brain geometry and specific substructures of the midbrain considered as infusion sites. Fig.1a depicts an accurate geometric rendering of a normal human brain. Reconstruction step is imperative for quantification of transport processes. State of the art geometric image reconstruction tools are used to render and construct computational grids from novel imaging techniques such MRI and histological data [3], [4]. Fig.1b depicts the computational grid of lateral ventricles of a normal subject required for quantitative analysis.



(a) Patient-Specific reconstruction of the cortex of a normal subject

(b) Computational grid of the lateral ventricles

Fig.1: Computer Assisted Brain Analysis

The second task is to calculate the *achievable treatment volume* in anisotropic regions of the brain using transport and kinetic inversion problem (TKIP). The TKIP approach extracts the unknown *diffusion tensor* of the drug in anisotropic regions of the brain. Specifically, the white matter tracts are aligned

parallel to each other and confine drug transport along its length. This restriction may defeat the purpose of drug targeting and may lead to toxicity in peripheral regions of the brain. By interpreting the concentration profiles obtained from advanced imaging techniques in-vivo, we propose to adjust the unknown transport and kinetic properties so that the measured concentration field observed in the image and the model predictions match [3]. We solve with mathematical programming a large-scale transport and kinetic inversion problem for the unknown parameter set that will provide specifications for optimal catheter design [5].

The third challenge concerns optimal *catheter design.* Specifically, the optimal placement and orientation of the infusion catheter, its dimensions, shape, and number of drug release ports specific to the target area and the bimolecular properties of the drug are subject to optimization.

Broader Impact: Novel analytical imaging techniques like MRI, functional MRI, Diffusion Tensor Imaging (DTI), Computer Tomography (CT), Positron Emission Tomography (PET), etc, have improved medical diagnosis. However, the existing technologies do not produce information such as effective drug diffusivity, soft-tissue properties, metabolic reaction constant and binding coefficients required for quantitative analysis. There appears to be a gap between high quality of imaging techniques and their use in quantitative analysis in the clinical practice. The sketchy understanding of the intracranial dynamics and drug transport mechanisms prevents the implementation of effective invasive drug delivery into the brain. The proposed approach integrates state-of-the-art imaging techniques and first principles models for transport phenomena in order to provide the medical community with a computer-aided tool to reduce the number of *in- vivo* tests by better capitalizing on the results of fewer experiments with the help of advances in computational methods.

References

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