Targeted Drug Delivery into the Human Brain

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EXTENDED ABSTRACT

Summary

More than 80 million people are being affected neurological diseases in the United States as per the NIH statistics. These diseases range from brain tumors to Parkinson's disease, Alzheimer's disease. Most of these disorders of the central nervous system (CNS) require large molecules drug therapy (using large molecular weight proteins such as trophic factors) as against a very few that are cured by just small molecules. The problem in delivering large molecules to the affected regions in the brain parenchyma is due to the presence of a network of tightly knit endothelial cells called as the Blood Brain Barrier (BBB). Due to the selective permeability of the BBB, large chemotherapeutic agents cannot pass through and thus cannot overcome the barrier. Diseases of the CNS such as Alzheimer's, Parkinson's, Autism, Multiple Sclerosis, Brain Cancer, Huntington's disease etc need large molecules such as proteins that may include trophic factors such as glial derived neurotrophic factor (GDNF), Nerve Growth Factor (NGF), brain derived neurotrophic factor (BDNF). In addition, the type of drug chosen is specific to a particular kind of brain disorder and the therapeutic efficacy of a given drug may not be generic to all kinds of cerebral disorders. For example, for treating Parkinson's disease hydrophilic drugs are generally used but are trapped in the BBB with the exception of Levodopa.

Methodology

This work deploys methods of computational fluid dynamics (CFD) to study the drug release in a two-dimensional model of the human brain. Clinical data from healthy subjects have been collected from a high power three Tesla MRI machine. We are able to resolve very accurately the brain geometry and render physiologically consistent the distribution of the complex brain inner organization. We distinguish between gray and white matter and assign transport properties of relevance according to the data obtained by MR images or histological data. In this presentation, we have demonstrated our systematic design approach by choosing caudate nucleus as the target. We assume that the targeted drug distribution is a function of properties of the drug, catheter location, its size, and the type of infusion policies required. For effective drug distribution to caudate nucleus, four injection locations 1. Near Reticular Thalamic Nucleus 2. Internal capsule 3. Putamen 4. Lateral Ventricle with three different catheter outer diameters 1.2 mm, 1.4 mm, 1.6 mm have been examined on a thin coronal slice of thickness 1 mm. We quantify with numerical simulations the diffusive and convective transport of the drug in the porous brain tissues and the effectiveness of the drug release to targeted regions. This approach will help to evaluate precisely the achievable treatment volumes over a certain

period for a given infusion policy specific to a target. The computational model is detailed in that it captures the microstructures to study the constraints offered by the dimensions and regional heterogeneity to estimate the achievable treatment volumes in a desired region of interest (ROI) for a given injection area. The anisotropy of the white matter and the resistance offered by the directionality of the axonal fibers to the bulk flow field and its influence on the penetration depth and volume of drug distribution (V_d) that was realized in the computer simulations. In order to effectively distribute the drug into the caudate nucleus, injection with a 1.2 mm outer diameter catheter near the internal capsule was found out be the optimal location with a constant infusion of 12µl/min based on a four-week study. We adopted a scaling procedure by incorporating transport and kinetic inversion problem (TKIP) to obtain the structural properties of the tissues in brain parenchyma. However, the scope of TKIP is beyond the scope of the present presentation. We also inferred the existence of multiple time scales that quantifies the time required for different ROI to attain the steady state drug distribution and gives an insight for the proper choice of injection location.

Significance

Our methodology of systematic drug delivery therapies integrates interdisciplinary expertise from medical imaging and diagnosis, systems biology and engineering optimization. The approach will allow physicians and scientists to design and optimize invasive drug delivery therapies in a systematic fashion complimenting clinical trials on primate studies. Understanding the parameters that could potentially influence drug targeting in convective delivery of drugs in the CNS is very important because, it will improve the current medical approaches. The proposed methodology will provide a systematic approach to optimally choose catheter dimensions, infusion rates, drug concentrations etc. The information obtained from these accurate simulations could be used to model inverse kinetic problems capable of predicting the mass diffusivity of the drug and the kind of metabolism that actually takes place.

References

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