Systematic design of drug delivery therapies

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Abstract

This paper presents an engineering approach for optimal drug delivery to the human brain. The hierarchical design procedure addresses three major challenges: (i) physiologically consistent geometric models of the brain anatomy, (ii) discovery of unknown transport and metabolic reaction rates of therapeutic drugs by problem inversion, and (iii) a rigorous method for determining optimal parameters for delivering therapeutic agents to desired target anatomy in the brain. The proposed interdisciplinary approach integrates medical imaging and diagnosis with systems biology and engineering optimization in order to better quantify transport and reaction phenomena in the brain in vivo. It will enhance the knowledge gained from clinical data by combining advanced imaging techniques with large scale optimization of distributed systems. The new procedure will allow physicians and scientists to design and optimize invasive drug delivery techniques systematically based on in vivo drug distribution data and rigorous first principles models.

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1. Introduction

An increasing number of people are affected by neurodegenerative diseases of the central nervous system (CNS) such as Parkinson’s, Alzheimer’s and Huntington’s disease (NIH, 2007). Development of more efficient therapies for diseases of the CNS is hampered by difficulties related to administering therapeutic agents to the affected areas deep inside the brain. Many of the larger proteins with promising pharmacological potency in vitro cannot pass the blood brain barrier (BBB), thus never reaching the cells they are targeted to remedy. Direct injection of the drugs via catheters into the region of interest in the brain can effectively by-pass the BBB, and the penetration depths can be enhanced by convection (Morrison, Laske, Bobo, Oldfield, & Dedrick, 1994). This technique imposes a convective bulk flow field in the extracellular space of the porous brain tissues, thus carrying the drug deep into the brain.

Molecular transport properties of new drugs are usually studied by animal experiments. The interpretation of three-dimensional drug distribution data inside the tissues of rats, rabbits or sheep is not amenable to simplistic lumped or one-dimensional mathematical models. Moreover, the enormous size differences between the human and animal brains make the scaling of drug delivery modalities a non-trivial task. Therefore, there exists a need to create a systematic data-driven approach for the effective design of invasive drug delivery therapies that takes into account the geometric, physiological and biochemical complexity of brain–drug interactions.

Novel analytical imaging techniques such as MRI, functional MRI (fMRI), diffusion tensor imaging (DTI), computer tomography (CT) and positron emission tomography (PET) have improved medical diagnosis. However, the existing imaging technologies are serving physicians only in a qualitative sense. Quantitative information such as transport or metabolic reaction properties are typically not derived from images directly. There appears to exist a gap between high quality of imaging data and their use in quantitative analysis. In order to address the open challenges in accurately predicting drug distribution, its metabolic reaction rates and drug clearance through the blood, a new computational approach integrating clinical imag-
ing data with first principles transport equations is presented. The proposed computer aided design methodology depicted in Fig. 1 aims at overcoming three major challenges. The first issue addresses the accurate reconstruction of the three-dimensional brain geometry. A process to seamlessly integrate imaging data with state-of-the-art geometric image reconstruction tools is presented. The second issue concerns the lack of physical and chemical properties such as diffusivity and metabolic uptake for novel drugs. A computational method for the accurate determination of transport and reaction properties from in vivo medical images with novel mathematical programming techniques called transport and kinetic inversion problem (TKIP) will be introduced. The TKIP will be illustrated via a simplified case study for dopamine kinetics. Finally, drug transport and metabolic rate coefficients will be used to determine optimal parameters for drug administration. These design parameters include: optimal placement and orientation of the injection catheter, catheter dimensions, and the number of drug release openings.

1.1. Outline

Section 2 describes the approach for the accurate reconstruction of the brain anatomy from images. Section 3 introduces the TKIP approach for the estimation of unknown parameters like diffusivity and kinetic reaction rates. Section 4 describes the finite volume method using generalized curvilinear coordinates for unstructured computational grids. Section 5 quantifies the distribution of a trophic factor and the intravenous injection of L-dopa in different regions of the human brain.

2. Capturing the complex brain geometry

Quantification of transport processes requires accurate reconstruction of the complex brain anatomy. Brain dimensions and physiological differences from subject to subject justify a patient-specific approach. Fig. 2a shows the brain’s inner structure as seen in a histological image (Warner, 2001). Fig. 2b displays the reconstructed two-dimensional computational mesh.

This two-dimensional brain model is composed of volumes and boundary surfaces reconstructed from digital images using image reconstruction algorithms like noise filtering, contrast enhancement and edge detection (Materialise, 2007). The subsequent grid generation step segregates the geometric objects into a computational mesh with well-defined mathematical properties (Bohm, Galuppo, & Vesnaver, 2000). The computational grid delineates the geometric domain for predicting the drug transport and pharmacokinetics using first principles models (Linninger, Somayaji, Xenos, & Kondapalli, 2005; Linninger et al., 2007). Before predicting the drug distribution, key transport and reaction properties of the drug have to be known. A methodology for estimating these unknown transport and metabolic reaction parameters is introduced in the following section.

3. Discovery of unknown transport properties and metabolic rates

The stages of the computer assisted brain analysis methodology are depicted in Fig. 1. The brain geometry reconstruction was discussed above. The solution of the inversion problem using the finite volume method with the sensitivity equations is described next. We propose a computational method to accurately quantify unknown transport drug properties by inter-