Computational methods for predicting drug transport in anisotropic and heterogeneous brain tissue

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Abstract

Effective drug delivery for many neurodegenerative diseases or tumors of the central nervous system is challenging. Targeted invasive delivery of large macromolecules such as trophic factors to desired locations inside the brain is difficult due to anisotropy and heterogeneity of the brain tissue. Despite much experimental research, prediction of bio-transport phenomena inside the brain remains unreliable. This article proposes a rigorous computational approach for accurately predicting the fate of infused therapeutic agents inside the brain. Geometric and physiological properties of anisotropic and heterogeneous brain tissue affecting drug transport are accounted for by in-vivo diffusion tensor magnetic resonance imaging data. The three-dimensional brain anatomy is reconstructed accurately from subject-specific medical images. Tissue anisotropy and heterogeneity are quantified with the help of diffusion tensor imaging (DTI). Rigorous first principles physical transport phenomena are applied to predict the fate of a high molecular weight trophic factor infused into the midbrain. Computer prediction of drug distribution in humans accounting for heterogeneous and anisotropic brain tissue properties have not been adequately researched in open literature before.

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1. Introduction

Targeting specific brain regions for drug therapy by direct infusion is difficult. The area covered by direct intraparenchymal drug delivery is limited by diffusion and is typically only a few millimeters. Considerable research has been done to enlarge the region of the brain that might be reached by employing high rates fluid flow which carry medication by convection, known as "convection-enhanced delivery" (CED). Unfortunately, computational methods for predicting drug distribution by diffusion with convection enhancement are still in their infancy. Species transport in the porous brain is subject to tissue anisotropy and heterogeneity. Especially, white matter such as the corpus callosum, internal capsule and corona radiata contain axonal bundles, in which the species transport is greatest in the direction of fiber alignment. In addition, the density and fiber orientation vary spatially, so that transport in the brain exhibits heterogeneity and strong directional anisotropy.

Numerous groups have studied molecular diffusion in the brain’s extracellular space (Krewson et al., 1995, 1996; Mota et al., 2004; Nicholson, 1985, 2001; Saltzman and Radomsky, 1991; Saltzman et al., 1994; Stroh et al., 2003). Recent research helped determining extracellular space parameters of brain tissue as well as tissue phantoms (Vorisek and Sykova, 1997; Vorisek et al., 2002). Age-related changes in diffusion parameters were studied by Sykova’s group (Sykova et al., 1998, 2002). Volumes of distribution of selected macromolecules with convection

Abbreviations: AWD, apparent water diffusion tensor; CFD, computational fluid dynamics; CSF, cerebrospinal fluid; DTI, diffusion tensor imaging; f, Face.

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enhancement have been determined in animal models (Ai et al., 2003; Bobo et al., 1994; Chen et al., 1999; Morrison et al., 1993, 1999). Finite element modeling has been applied for predicting the intracranial distribution of interleukin-2 in rabbits (Kalyanasundaram et al., 1997). Previous research has characterized diffusion anisotropy with a tortuosity tensor (Mazel et al., 1998; Nicholson and al., 1994, 1999). Finite element modeling has been applied primarily to qualitatively trace the white matter tracts in the brain (Basser et al., 1994; Lazar et al., 2003; Lebihan et al., 2001; Mori and van Zijl, 2002; Zhang et al., 2003). Recently, electric conductivity properties of porous media were found to correspond to diffusion tensor imaging (DTI) data (Tuch et al., 2001). So far, DTI has been used primarily to qualitatively trace the white matter tracts in the brain (Basser et al., 1994; Lazar et al., 2003; Lebihan et al., 2001; Mori and van Zijl, 2002; Zhang et al., 2003). Other investigators deployed quantitative DTI to model interstitial transport in spinal cords of rats (Sarninorandon et al., 2003, 2006). Our study presents magnetic resonance and DTI to accurately delineate patient-specific brain geometry and to construct physiologically consistent transport tensors for bulk fluid permeation and species transport through the brain tissue. Moreover, we propose finite volume methods to predict distribution of infused therapeutic agents using rigorous transport principles.

1.1. Outline

Section 2 describes the experiments to acquire quantitative patient-specific brain geometry and diffusion tensor data. Section 3 presents three-dimensional computational results predicting the distribution of a trophic factor. The simulation results also allow us to assess the effect of different catheter designs on achievable volumes of distribution. Computational methods to predict drug distribution as a function of different catheter configura-
tions is a first to the best of our knowledge. The discussion in Section 4 will emphasize the need to account for physiologically consistent tissue properties and catheter design considerations for systematic design of convection-enhanced drug delivery. The paper closes with conclusions.

2. Methods

2.1. In-vivo measurement of water diffusion using diffusion tensor imaging

Axial and coronal images were acquired from six healthy volunteers on a 3 T GE Signa system (GE Medical Systems, Milwaukee, WI, USA). The protocol and patient consent were approved by the Institutional Review Boards of the University of Illinois and the University of Chicago. The scanner is equipped with a standard quadrature birdcage head coil; a turboprop-DTI pulse sequence is used for DTI with parameters: field of view = 24 cm × 24 cm, repetition time, TR = 5000 ms, 8 spin-echoes per TR, 5k space lines per spin-echo, 16k space blades per image, 192 samples per line reconstructed to matrix of 256 × 256 (Basser and Jones, 2002; Pipe et al., 2002). Typically, 36 slices with slice thickness 3 mm and slice gap of 0 mm are collected. Two images with a b-factor of \( b = 0 \) s/mm\(^2\) are collected and images with a diffusion weighting of \( b = 900 \) s/mm\(^2\) are acquired for 12 non-collinear gradient directions (Stejskal and Tanner, 1965). Individual apparent free water diffusion (AWD) tensors are estimated for each voxel of size 0.9375 \( \times \) 0.9375 \( \times \) 3.0 mm\(^3\). Concurrently, \( T_1\) and \( T_2\)-weighted images (\( b = 0 \) s/mm\(^2\)) were recorded to define the reference coordinates.

2.2. Patient-specific image reconstruction

We used computer-assisted image reconstruction to accurately delineate the main dimensions of the brain. Fig. 1 provides an overview of the processing steps, more details can be found elsewhere (Linninger et al., 2005, 2007, 2008; Somayaji et al., 2008). First, patient-specific images and diffusion tensor data are acquired to obtain an anatomically consistent representation of size and shape of brain target areas. Image data such as pixel matrices representing planar brain slices are converted into geometric surfaces and interconnected regions (Mimics, Materialise Inc., Amira, Visage Imaging Inc.). Domain regularization methods partition the domain enclosed by reconstructed surfaces into a finite number of tetrahedrons. Each small finite volume is logically linked to its neighbors thus forming a connected computational mesh (Bohm et al., 2000; Watson, 1981). In the grid generation steps, optimization algorithms divide the domain to preserve suitable aspect ratios of the finite volumes of the computational domain (Gambit, Ansys Inc.). These computational meshes constitute the physical domain for which the transport equations will be solved. Three-dimensional computational meshes typically entailed 400,000–500,000 volumes for the entire brain.

Fig. 1. Overview of patient specific computer-assisted approach for the systematic design of drug delivery therapies based on DTI derived data. The first step entails the collection of medical images from magnetic resonance diffusion tensor imaging. Image reconstruction detects sharp boundaries and functional regions inside the brain. Grid generation partitions surfaces and volumes into small tetrahedrons for finite-volume discretization of the transport equations. Computational analysis solves the discretized transport equations to predict the drug distribution.

Fig. 2. Axial and coronal DTI measurements for a 38-year-old normal subject showing anisotropy and brain tissue heterogeneity. The local diffusion tensor in each voxel of axial and coronal brain sections is represented by an ellipsoid. Four sample locations—(A) corpus callosum, (B) corona radiata, (C) internal capsule, and (D) gray matter regions show the orientation of apparent water diffusion tensor ellipsoids in more detail.