Turboprop Diffusion Tensor Imaging for Computational Design of Drug Transport in Brain

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Introduction: Targeted delivery of large drug macromolecules to specific locations by direct infusion in the brain is a challenging task in the treatment of neurodegenerative diseases of the Central Nervous System (CNS) due to anisotropy and heterogeneity of the brain parenchyma. The area covered by infusion into the parenchyma from a catheter 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 of fluid flow which carry medication by convection, so-called "convection enhanced delivery" (CED). Unfortunately, computational methods for predicting drug distribution by diffusion and convection in the brain are still in their infancy. Integrating Turboprop diffusion tensor imaging[1] with first principles models for transport phenomena, we have developed a rigorous computational approach for reliably predicting the fate of infused chemotherapeutic agents by accounting for the effects of anisotropic and heterogeneous brain tissue in drug transport.

Methods: Axial images covering most of the whole brain were acquired using Turboprop DTI on a 3T GE Signa system(GE Medical Systems, Milwaukee, WI, USA). The scanner was equipped with a standard quadrature birdcage head coil and Turboprop-DTI pulse sequence was used for DTI. The parameters for DTI were field of view (FOV) = 24cmx24cm, TR=5000ms, 8 spin-echoes per TR, 5 k-space lines per spin-echo, 16 k-space blades per image, 192 samples per line reconstructed to matrix of 256x256. A total 36 slices were collected with slice thickness 3 mm and slice gap 0 mm. Two b = 0 s/mm^2 reference images were collected and images with a diffusion-weighting of b=900 s/mm^2 were acquired for 12 non-collinear gradient-directions. Diffusion tensors were estimated in each voxel of size 0.9375x0.9375x3.0 mm^3. A set of 30 slices of high resolution fast spin echo (FSE) T2 weighted images were also collected. The FSE images were acquired using FOV = 24.0cm x 24.0cm, TR = 5000 ms, TE = 126 ms, slice thickness = 5 mm, slice gap = 0 mm, matrix size = 512x256, interpolate to 512x512, phase FOV = 0.75.

The b = 0 reference image was converted by image reconstruction into surfaces and interconnected regions (Mimics, v. 9.0, Ann Arbor, MI, Amira v. 4.1, Carlsbad,CA). Domain regularization methods partition the reconstructed surfaces and spatially connected regions into a finite number of tetrahedrons enclosed by triangular faces. Each small finite volume is logically linked to its neighbors thus forming a connected computational mesh. Grid generation algorithms optimally divide the domain to preserve suitable aspect ratios of the finite volumes of the computational domain (Gambit, Fluent, Lebanon, NH). These computational meshes constitute the physical domain for which the transport equations will be satisfied.

We assume DTI information accurately represents the local anisotropy of the drug transport in the brain and that the direction of maximum interstitial transport corresponds to the direction of the major eigenvector of the apparent water diffusion tensor. The effective drug diffusion tensor D_e was estimated by scaling the normalized eigenvalues of the water diffusion tensor with molecular diffusivities of a specific drug. The hydraulic tissue permeability K_e was estimated in a similar way to drug diffusivity. Drug distribution is predicted using the fundamental conservation laws of mass, momentum and species transport[2].

Results and discussion: There is no observable distortion in FA map. The layout of fiber groups correspond very well with the anatomic structure as shown in the T2 weighted image(Fig.1). Using multiple-linear fitting method, negative eigenvalues occurred frequently at pixels of large FA and low SNR value[3], these pixels could crash the computational program. Non-linear tensor estimate algorithm[4] corrected these negative eigenvalues to positive values and enforced the diffusion tensor to be positive definite(Fig.2). The non-linear algorithm also regularized the diffusion tensors and made the fiber estimation more coherent. Fig.3 shows a simulated asymmetric distribution of a neurotrophic factor in the brain tissue during four weeks infusion time. The neurotropic factor, with inlet concentration $X_0 = 3.7 \cdot 10^{-3}$ mol/l, is injected into the midbrain near the putamen from a single hole catheter, with outer diameter d =1.0 mm, at a constant infusion rate of Q = 4 µl/min. Preferential transport is seen in the periventricular region. The drug distribution is asymmetric because of the anisotropic and heterogeneous tissue properties.

The novel approach accounts for anisotropy and heterogeneity in drug transport inside the human brain. DTI of specific patients indicated strong directional dependence along the fibrous white matter tracts. When incorporating these tensor properties into first principle transport models, the predicted drug distribution patterns were asymmetric and followed directional influences. The methodology was validated against rat experiments as well as gel phantom infusion with satisfactory agreement.

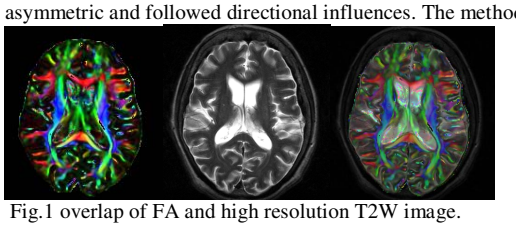

Fig.1 overlap of FA and high resolution T2W image.

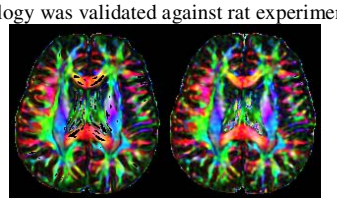

Fig.2 Non-linear correction of negative eigenvalues.

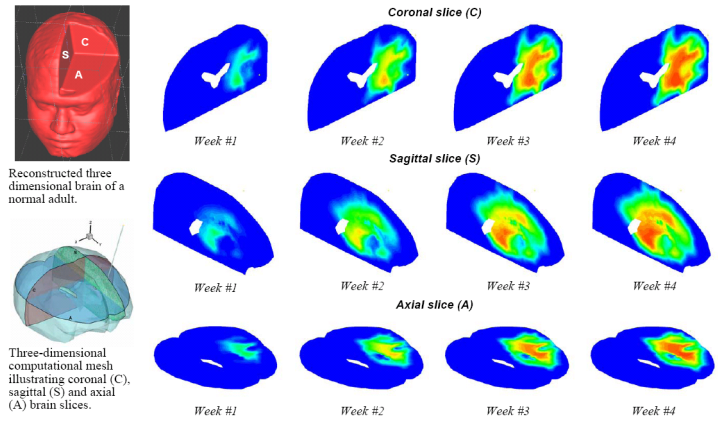

Fig.3 Distribution of the high molecular weight trophic factor over four weeks infusion time. The infusion was made near internal capsule–putamen boundary at a constant infusion rate of, Q = 4 µl/min. The white matter anisotropy distributes the drug asymmetrically in accordance with the local tissue anisotropy and heterogeneity.

Dependence of interstitial fluid flow on the hydraulic conductivity tensor field and target anatomy significantly affects drug distribution. Consequently, the achievable penetration depths and treatment volumes without using anatomical tissue properties would lead to poor predictions.

The diffusion tensor of the drug and the permeability tensor of the tissue are assumed to share the same eigenvectors with free water diffusion in human brain. Therefore, accurate estimation of effective water diffusion tensor in human brain is a key step to calibrate the drug transport properties. Turboprop DTI provides distortion-free DTI data while dramatically reduces the acquisition time. In this study, it took about 19 minutes to collect 36 slices axial images which covering most of the whole brain. Although EPI is much fast, and takes a few minutes to acquire the same number of 36 slices images, EPI is very sensitive to motion and suffers susceptibility and eddy current distortion. On the contrary, the inherent data of Turboprop DTI can be used to correct for patient head motion.

References:

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