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A Finite Element Model of Molecular Diffusion in Brain Incorporating *in vivo* Diffusion Tensor MRI Data

P.G. McQueen*, A.J. Jin*, C. Pierpaoli°, and P.J. Basser^
*PSL, DCRT; °NB, NINDS; ^BEIP, NCRR; National Institutes of Health, Bethesda, MD 20892

INTRODUCTION

The development of realistic models of water and macromolecular transport in living tissues is of immense benefit (1). Till now, the primary obstacle to modeling transport processes *in vivo* has been the inability to measure transport coefficients, particularly in anisotropic and heterogeneous tissues (e.g., white matter and skeletal muscle). Diffusion Tensor MRI furnishes a "map" of the effective diffusion tensor of water, **D**, in tissues (2). Using physiologically reasonable assumptions, we show how to use this data to develop a heterogeneous, anisotropic finite element model (FEM) of *in vivo* macromolecular transport. Here we model the delivery of sucrose with an ALZET® osmotic pump.

METHODS

DW-MRIs of live cat brain were acquired with a GE 2-T Omega system equipped with self-shielded Acustar 290 gradients, and a home-made 13cm quadrature RF coil. We acquired 21 axial multi-slice 2D PGSE in under 3 hours. Acquisition parameters were: four axial slices, 2mm st, TR/TE = 2000/70, two nx, 90mm FOV, 128x256 in-plane resolution. Peak b-matrix values were on the order of 850 s/mm^2. **D** was estimated in each voxel using methods described previously (3, 4) yielding a diffusion tensor "map", $\mathbf{D_W(x)}$, where **x** is the position vector.

To simulate a sucrose delivery regimen, we assume it diffuses in each principal direction in the same way as water; i.e., that their tortuosity is the same. Thus, the diffusion tensor of sucrose, $\mathbf{D_S(x)}$, in the extracellular space is related to the diffusion tensor of water, $\mathbf{D_W(x)}$, by

$$\mathbf{D_S(x)} = (D_S / D_W)\, \mathbf{D_W(x)} \sim 0.2\, \mathbf{D_W(x)}, \quad (1)$$

where D_S is the isotropic diffusion coefficient of sucrose in water, and D_W is the self-diffusion coefficient of pure water. Second, we ignore sucrose clearance over the time scale of a few hours. Finally, we assume that the pump produces no distortion of interstitial space and convective flow. Therefore, we model the transport of small macromolecules within the brain interstitium as a purely diffusive process (5):

$$\frac{\partial C(\mathbf{x},t)}{\partial t} = \nabla \bullet (\mathbf{D_S(x)}\, \nabla C(\mathbf{x}, t)) \quad (2)$$

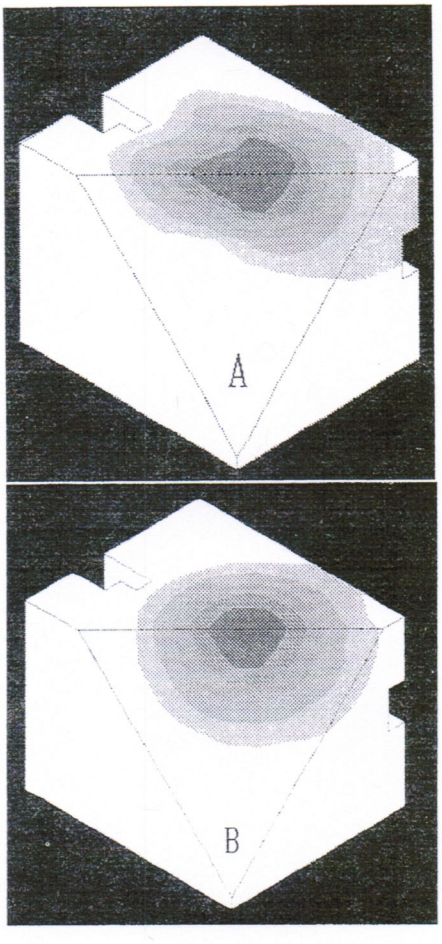
$C(\mathbf{x},t)$ is the 3-D sucrose concentration profile; $\mathbf{D_S(x)}$ is heterogeneous and anisotropic. ANSYS (6) was used to build and solve the FEM of Eq [2]. Each voxel of the DT-MRI becomes a 3D rectilinear element with a diffusion tensor, $\mathbf{D_S(x)}$. As the small sucrose macromolecules are assumed to be restricted to the white and gray matter, brain tissue was segmented into grey, white matter and CSF using Trace($\mathbf{D_W(x)}$) and the degree of diffusion anisotropy as features. Elements containing CSF were then removed and non-flux conditions were imposed in their place.

RESULTS

The FEM was used to predict infusion of sucrose from an osmotic pump into a 5.63 × 6.03 × 7.13 mm^3 (0.24 ml) slab of living cat brain, containing a white matter bundle in the ventral internal capsule. Pump flow rate was 0.2µl/hr. To assess the contribution of tissue anisotropy while controlling for heterogeneity, we constructed an isotropic, but spatially heterogeneous tensor field, $\mathbf{D_{Si}(x)}$:

$$\mathbf{D_{Si}(x)} = \langle \mathbf{D_S(x)} \rangle \mathbf{I}, \quad [3]$$

where $\langle \mathbf{D_S(x)} \rangle$ = Trace($\mathbf{D_S(x)}$)/3 is the average diffusivity of sucrose at position **x**, and **I** is the identity tensor. Fig 1 shows iso-concentration profiles of sucrose 9375 sec after pumping begins a) in the heterogeneous, *anisotropic* model, and b) in the heterogeneous, *isotropic* model (i.e., using Eq [3]). The displayed contours are 1.25, 2.5, 5, 10, 20, and 40 µg/mm^3. The source lies in the darkest region; the same flow rate is used in both simulations.



DISCUSSION AND CONCLUDING REMARKS

We found that white matter anisotropy profoundly biases the distribution of the delivered solute along the fiber tract direction, as seen above. Both heterogeneity and anisotropy of brain tissue must be accounted for in modeling water (or macromolecular) diffusion in living brain. A Finite Element Model (FEM) incorporating diffusion tensor data from *in vivo* DT-MRI is flexible enough to describe transient and steady state macromolecular clearance in regions of irregular shape, with complicated boundary and initial conditions.

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