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Development of a Finite Element Model of Molecular Diffusion in Living Brain from *in vivo* Magnetic Resonance

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Abstract: Magnetic resonance imaging techniques measure *in vivo* the diffusion tensor of water in tissues. With some physiologically reasonable assumptions, this data can be incorporated into a finite element model of diffusive transport of macromolecules within living tissue. Here we present the results of applying this approach to model the transport of sucrose in living cat brain. We show that white matter fibers strongly bias the transport due to their anisotropic diffusive properties.

I. INTRODUCTION

The development of a model of macromolecular diffusive transport would be of immense benefit in designing drug delivery systems to treat various disorders [1, 2]. A major obstacle to modeling transport processes has been the inability to measure *in vivo* transport coefficients in anisotropic and heterogeneous tissues such as white matter and skeletal muscle. However, using a recently developed magnetic resonance imaging technique called diffusion tensor imaging (MR-DTI), such data can now be obtained from living brain with high resolution [3]. Here we show that these data can be used to construct a heterogeneous, anisotropic finite element model (FEM) of a living brain which can be used to study realistic macromolecular transport problems.

We applied the ANSYS [4] commercial finite element package to build the FEM and to predict the spread of sucrose from an osmotic pump source. Some pharmacologically active macromolecules cannot cross the "blood-brain" barrier, so to mimic their delivery via an osmotic pump source (such as an ALZET® pump), we chose to model the diffusion of sucrose into brain tissue. Sucrose is a small molecule with a lifetime of about one day in brain tissue, so it is a good example of an agent that does not readily exchange between blood and brain. Its transport via an osmotic pump should be diffusion dominated on time scales of a few hours.

In this paper, we shall review the DT-MRI measurements (Sec. II), discuss assumptions necessary to construct a realistic transport FEM from the MR-DTI data (Sec. III), and demonstrate that the white matter bundles (with there high degree of diffusion anisotropy [5]) strongly bias the concentration profiles predicted by the FEM (Sec. IV). Finally, future directions for research are discussed (Sec. V).

II. THE MRI MEASUREMENTS

MR data were obtained with a General Electric 2.0 T Omega MR system (GE NMR Instruments, Fremont, CA) equipped with self-shielded gradient coils (Acustar 290) capable of producing pulses up to 4.0 Gauss/cm. A home-built quadrature coil (13 cm diameter) was used as a RF transmitter and receiver. We acquired 21 axial multi-slice diffusion-weighted 2D spin-echo images of living cat brain in under 3 hours. Imaging acquisition parameters were as follows: four axial slices, 2 mm slice thickness, TR/TE of 2000/70, two repetitions per image, 90 mm field of view, 40 kHz bandwidth, 128x256 in-plane resolution. Different levels of diffusion weighing were obtained by varying the strength between 0 and 3 Gauss/cm of two trapezoidal gradient pulses placed on both sides of the 180° RF pulse [6-8]. The diffusion sensitizing gradients had a duration of 19 ms and were separated by a time interval of 20ms. The largest b-matrix values were on the order of 850 s/mm^2. Diffusion gradients were applied in 7 non-collinear directions [9]. From the measured T_2 signal, A(TE), and the b-matrix calculated from each sequence [10], we estimated $\mathbf{D_W}$, the effective self-diffusion tensor of water, in each voxel, using weighted multivariate linear regression described in [9] :

$$\ln\left(\frac{A(TE)}{A(0)}\right) = -\sum_{i=1}^{3}\sum_{j=1}^{3} b_{ij} D_{w_{ij}}. \qquad (1)$$

The MR-DTI technique makes it possible to obtain the tensor components of $\mathbf{D_W}$ in brain tissue as a function of position $\mathbf{x}$. The spatial resolution (about 0.5 mm) is small enough to allow white matter bundles to be distinguished from gray matter regions, and from the cerebrospinal-fluid-filled ventricles.

The MR-DTI signal is believed to be dominated by water in the extracellular space between cells. In addition, the characteristic time needed for water to cross the cell membrane is an order of magnitude greater than the characteristic time of the MR-DTI measurement, so $\mathbf{D_W}$ should be a good indicator of the motion of extracellular water. Consequently, the measured $\mathbf{D_W}$ reflects the physical properties and tortuosity of the extracellular or interstitial space.

Two measures of the diffusive characteristics are useful in distinguishing between different tissue types. These are the

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average diffusivity in a voxel centered at position (vector) x

$$\langle D(x) \rangle = \frac{Tr(\mathbf{D_W}(x))}{3}, \qquad (2)$$

and the anisotropy index at x:

$$AI(x) = \frac{3}{2} \frac{(\mathbf{D_W}(x) - \langle D(x) \rangle \mathbf{I}) : (\mathbf{D_W}(x) - \langle D(x) \rangle \mathbf{I})}{\mathbf{D_W}(x) : \mathbf{D_W}(x)} \qquad (3)$$

Here **I** is the 3x3 identity matrix, and ":" signifies the tensor dot product where

$$\mathbf{A:B} = \sum_{i=1}^{3} \sum_{j=1}^{3} A_{ij} B_{ij} \qquad (4)$$

Experimentally, cerebrospinal fluid (CSF) has a high <D> but is isotropic (small AI). White and gray matter both have a much smaller <D>, but gray matter is almost isotropic (small AI), while white matter bundles are extremely anisotropic (large AI). Typically, <D> ranges from 600 to 850 μm^2/sec in neuronal matter, and from 1200 to 4000 μm^2/sec in CSF. AI is less than 0.1 for gray matter and CSF, but ranges from 0.15 to 1 in white matter.

III. CONSTRUCTING THE FEM

To model biomedical drug delivery systems, we make the following approximations. First, we assume that the small macromolecule (like sucrose) will diffuse in each principal direction in the same way as water; i.e., that the paths of molecular diffusion have the same tortuosity as those of water. Thus, we take a simple scaling law for the diffusion tensor, $\mathbf{D_S}(x)$, of a given small macromolecule in the extracellular region as

$$\mathbf{D_S}(x) = (D_S/D_W)\, \mathbf{D_W}(x), \qquad (5)$$

where D_S is the isotropic diffusion coefficient of the small macromolecule in water, and D_W is the self-diffusion coefficient of pure water. For example, $D_W = 2500\ \mu m^2$/sec at 25 C [11] and $D_S = 500\ \mu m^2$/sec for sucrose [12], so that their ratio is 0.2. We can readily assume such ratios remain valid in (5) at body temperature. Next, in this calculation, we ignore absorption and emzymatic degradation. We also assume that trafficking mediated by blood flow is inhibited by membrane layers between blood and brain (the blood/brain barrier). Likewise, because a similar membrane barrier impedes the transport of sucrose between the CSF-filled ventricle spaces and the gray and white matter, we assume that the small macromolecule delivered into the neuronal matter will not cross into the CSF-filled ventricles. For sucrose, these assumptions should be valid on a time scale of a few hours due to its long lifetime in brain tissues of about one day. Accordingly, we make the assumption that the source occupies a small volume, and that infusion rate is lower than a few µl/hr, so that the distortion of interstitial space and convective flow due to pressure gradients can be ignored.

Thus, we model the transport of small macromolecules within the neuronal matter as a purely diffusive process [13]:

$$\frac{\partial C(x,t)}{\partial t} = \nabla \bullet (\mathbf{D_S}(x)\, \nabla C(x,t)) \qquad (6)$$

Here C(x,t) is the three dimensional sucrose concentration profile. Note that $\mathbf{D_S}(x)$ is a function of position and is very anisotropic in white matter.

The ANSYS commercial finite element package was used to build the FEM and solve it (6). Each voxel in the MR-DTI was transformed into a three-dimensional rectilinear element whose material properties were assigned to be the measured diffusion tensor. As argued above, the infused small macromolecules were restricted only to the white and gray matter where (6) applies. Thus, while the model was being built, elements corresponding to CSF were removed and non-flux conditions were imposed at their boundaries. The ANSYS package has the capability to solve (6) for a region of irregular shape with such boundary conditions and a small volume source. We stress that the problem is explicitly anisotropic and transient.

IV. TRANSPORT OF SUCROSE IN A TISSUE BLOCK

Here we report the results of the FEM prediction of infusion of sucrose from an osmotic pump into a 5.625 mm X 6.016 mm X 7.109 mm (0.24 ml) slab of living cat brain. An MR-DTI scan was done of the brain of a live cat, and the data scaled according to (5) above for a small volume of that brain which contained a prominent white matter bundle. For the model, we assumed a source that had a volume of 0.187 mm^3 and pumped 93.5 µg/hr into the block, and that the initial sucrose concentration was zero. (Assuming that the solution is water near saturation with sucrose, this corresponds to a pump flow rate of 0.2µl/hr.) To assess the effects of anisotropy directly, we performed an additional FEM simulation by constructing an isotropic but spatially heterogeneous tensor field $\mathbf{D_{si}}(x)$:

$$\mathbf{D_{si}}(x) = (D_S/D_W) \langle D(x) \rangle \mathbf{I}, \qquad (7)$$

where <D(x)> is the average diffusivity of water at position x calculated from $\mathbf{D_S}(x)$. Both FEM simulations are of the same tissue block, but one model is constructed using the spatially heterogeneous and anisotropic tensor $\mathbf{D_S}$ given by (5) above, and the other is constructed using the spatially heterogeneous but isotropic tensor $\mathbf{D_{si}}$ given by (7). The same source and flow rate is used in both models.

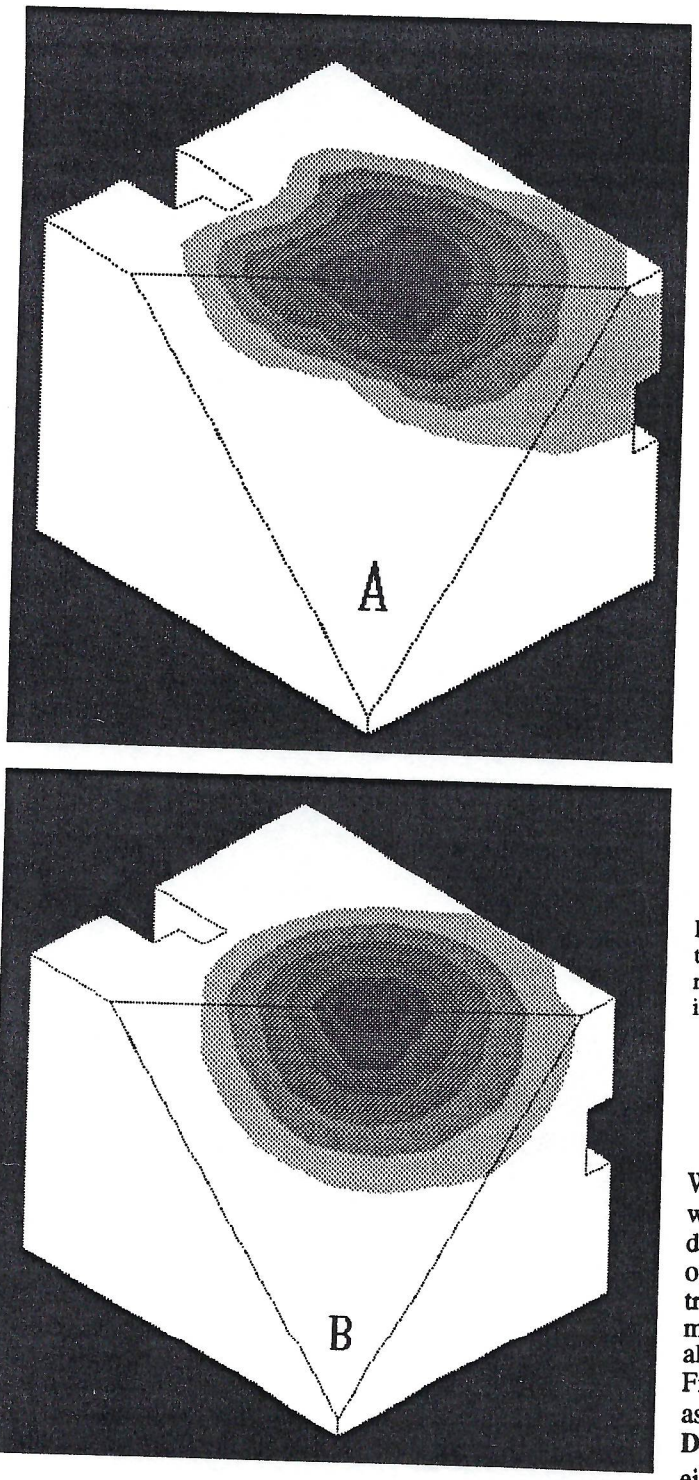

Fig. 1. A three dimensional iso-concentration profile of sucrose in a region of living cat brain calculated using the FEM constructed data obtained *in vivo* by DT-MRI. a) results of heterogeneous, anisotropic model, and b) results of the heterogeneous, isotropic model. In both figures, the contours are 1.25, 2.5, 5, 10, 20, and 40 $\mu g/mm^3$. The pump is in the darkest region.

We found that white matter anisotropy profoundly biases the distribution of the delivered solute along the fiber tract direction, as can be seen in Fig. 1a-b. This figure is a plot of the constant concentration contours in the tissue block (sliced open) that have formed 9375 sec after the pump has been activated. Note that the location of contour for 1.25 $\mu g/mm^3$ differs by millimeters between the two FEM's. Even near the pump, the effects of anisotropy cannot be ignored, as can be seen in Fig. 2. On a time scale of just a few hours, the predictions of the concentration near the pump given by the two models differ by 20%.

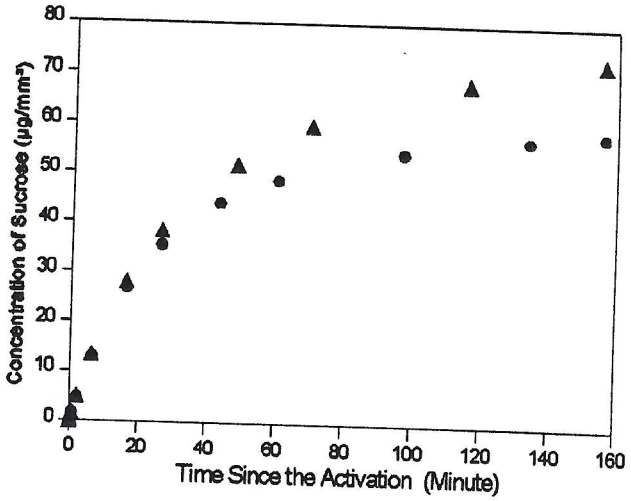

Fig. 2. Concentration of sucrose at the infusion site vs infusion time. Triangles indicate results of heterogeneous, anisotropic model, and circles indicate the corresponding heterogeneous, isotropic model.

V. Discussion and Concluding Remarks

We have found that the heterogeneity and anisotropy of the white matter bundles must be considered in modeling diffusive processes in brain, even for predicting the behavior on a time scale of a few hours. In order to model the transport of macromolecular chemotherapeutic agents, some modification of the basic assumptions may be required, although we still expect to see the same qualitative behavior. First, the effective diffusion tensor may not scale as simply as in (5) above. We still expect that the principal axes of $\mathbf{D_s(x)}$ would remain the same, but the ratios of the eigenvalues are not necessarily the same as those of water. Moreover, absorption by CSF or blood, or enzymatic degradation would have to be considered even on the time scale of a few hours. This can be represented as a sink term in (6) and is solvable. Furthermore, for pump flow rates above a few μl/hr, convection in the extracellular space may have to be included in the FEM, but there is no reason in principle why this could not be included.

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