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Voxelized Model of Interstitial Transport in the Rat Spinal Cord Following Direct Infusion Into White Matter

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Abstract

Direct tissue infusion, e.g., convection-enhanced delivery (CED), is a promising local delivery technique for treating diseases of the central nervous system. Predictive models of spatial drug distribution during and following direct tissue infusion are necessary for treatment optimization and planning of surgery. In this study, a 3D interstitial transport modeling approach in which tissue properties and anatomical boundaries are assigned on a voxel-by-voxel basis using tissue alignment data from diffusion tensor imaging (DTI) is presented. The modeling approach is semi-automatic and utilizes porous media transport theory to estimate interstitial transport in isotropic and anisotropic tissue regions. Rat spinal cord studies compared predicted distributions of albumin tracer (for varying DTI resolution) following infusion into the dorsal horn with tracer distributions measured by Wood et al. in a previous study. Tissue distribution volumes compared favorably for small infusion volumes ($<4 \mu\text{l}$). The presented DTI-based methodology provides a rapid means of estimating interstitial flows and tracer distributions following CED into the spinal cord. Quantification of these transport fields provides an important step toward development of drug-specific transport models of infusion.

Keywords

convection-enhanced delivery (CED); diffusion tensor imaging (DTI); drug delivery; computational fluid dynamics (CFD); mathematical modeling; permeability; hydraulic conductivity; intraparenchymal infusion

1 Introduction

In central nervous tissues, direct intraparenchymal infusion, i.e., convection-enhanced delivery (CED), of therapeutic agents is a promising administration technique that bypasses the blood-brain barrier, overcomes transport problems associated with slow diffusion, and increases the tissue distribution volume of macromolecular agents [1–3]. Predictive models of tissue distribution during CED are required for treatment optimization and planning. To account for large infusion volumes, such models should incorporate interstitial fluid flow patterns which are affected by anatomical boundaries and anisotropic tissue transport properties of aligned white matter tissue regions.

Previous central nervous system (CNS) models of drug release and CED have been developed assuming that nervous tissues can be characterized as porous media. By using rigid porous media assumptions, Morrison et al. [4] successfully modeled high-flow microinfusion of 180 kDa macromolecules into a homogeneous brain tissue, e.g., gray matter, and Kalyanasundaram et al. [5] simulated the controlled release of drug from an implant in a rabbit brain. Previous infusion studies have also used biphasic, poroelastic, and poroviscoelastic models to account for local tissue deformation and interstitial fluid flow for idealized, spherical infusion sources [6–12]. These studies applied isotropic and homogeneous tissue transport conditions. However within white matter regions, interstitial transport has been shown to be anisotropic [1,13–15]. Studies show transport to be dependent on the orientation of white matter tracts such that preferential transport occurs within the interstitial space parallel to myelinated axonal fibers. Our group has developed computational transport models that account for underlying convection and diffusion anisotropy within white matter regions [16] for direct infusion of macromolecular compounds into the spinal cord.

Tissue transport anisotropy can be visualized with diffusion-weighted magnetic resonance (MR) imaging. With these diffusion weighted MR images, the self-diffusion of water molecules in tissue can be modeled, on a voxel-by-voxel basis, as a rank-2 tensor that provides a complete description of the averaged three-dimensional translational self-diffusion (in units of cm^2 / s). Anisotropy in this diffusivity measurement results from restricted water movement in the underlying structure and combines information from both the extracellular and intracellular spaces. By using this diffusion tensor imaging (DTI) approach, preferential directions of water diffusion can be determined, which have been found to correspond to aligned fiber directions [17]. Thus by using DTI data, fiber-tract trajectories can be calculated within fibrous tissues [18–22]. Computational transport models developed by our group incorporate tissue alignment data from DTI to assign preferential transport directions for CED in the spinal cord [23].

In previous spinal cord transport models, a 3D reconstruction of anatomically-realistic boundaries and tissue volumes was based on high-resolution MRI data [16,23,24]. Associated image segmentation and volume reconstruction methods are time consuming and labor intensive, especially when working with complex geometries. In this study, a new voxelized modeling methodology for developing models of interstitial transport in the central nerve system is presented. This semi-automatic approach assigns tissue properties and volumes on a voxel-by-voxel basis from DTI data allowing for expedited building of computational porous media models and rapid estimation of tracer transport. This modeling approach was used to develop models of CED of albumin tracer (molecular weight ~66 kDa) into the spinal cord. Predicted CED distributions in the dorsal white matter column of the rat spinal cord were compared with experimental distributions of radiolabeled albumin measured by Wood et al. [3]. Computational predictions using high-resolution DTI from

excised tissues were also compared with lower resolution in vivo DTI data to determine the effect of imaging resolution on transport predictions.

2 Methods

2.1 Diffusion Tensor Imaging

2.1.1 In Vivo Imaging—All animal studies were conducted in accordance to a protocol approved by the Animal Care and Use Committee of the University of Florida. Adult female Sprague-Dawley rats (~250 g) were anesthetized and MR imaging procedures were conducted using a Bruker Avance 11.1 Tesla magnet system (Bruker NMR Instruments, Billerica, MA). For DTI, a diffusion-weighted spin-echo sequence was used with a total acquisition time of 72 min, recovery time (TR) of 2000 ms, and echo time (TE) of 30 ms and one average. Low-diffusion-weighted data (100 s/mm²) were acquired in six directions, defined by the tessellation of an icosahedron on a unit hemisphere, and high-diffusion-weighted data (800 s/mm²) were acquired in 21 directions. A field of view (FOV) of 2.4×2.4 cm² in 1 mm slices with a matrix of 80×80 in 15 slices covering vertebral levels T13 to L2.

2.1.2 Excised, Fixed Tissue Imaging—To obtain high-resolution microstructural information, excised and fixed rat spinal cord tissue was used in long scan-time diffusion tensor measurements. The fixed (4% paraformaldehyde) rat spinal cord was imaged in phosphate buffered saline (PBS) after removal of the fixative, and DTI data sets were obtained using a 14.1 Tesla magnet (Bruker NMR Instruments, Billerica, MA). The spinal cord images were centered at vertebral levels L1-T13.

Multiple-slice images, weighted by water translational diffusion, were measured (~11 h) using a spin-echo pulse sequence. Measurements were performed with TR=1400 ms, TE=25 ms. The diffusion-weighted images had a FOV of 4.3×4.3 ×12 mm³ (60×60×300 μm³ voxel resolution). Images with low diffusion-weighting (100 s/mm²) and a higher diffusion-weighting (1250 s/mm²) were measured in six gradient-directions and 46 gradient-directions, respectively.

2.1.3 Image Processing—The diffusion-weighted images were interpolated (bilinear interpolation, with nearest neighbor sampling) by a factor of two in each dimension (data matrix of 144 ×144×80 for excised data and 40×40×30 for in vivo data). After initial image processing, the multiple-slice DTI data were fitted to the water translational diffusion tensor, $\mathbf{D}_e$, using multiple-linear regression [19]. In the simplest case, a series of diffusion-weighted images may be used to calculate D_{eij} (a single-rate apparent diffusion tensor component) and S_0 , by the relationship below [25].

$$\ln(S/S_0) = - \sum b_{ij} D_{eij} \quad (1)$$

where b_{ij} is the diffusion weight factor and S is the b -dependent signal intensity. S_0 value is T2-weighted, proton-density (i.e., free-water-density) dependent signal intensity in the absence of diffusion. A scalar measure of anisotropy is introduced by fractional anisotropy

$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \bar{D})^2 + (\lambda_2 - \bar{D})^2 + (\lambda_3 - \bar{D})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad (2)$$

where $\bar{D} = \text{Tr}(\mathbf{D}_e)/3$ is the average diffusivity and λ_i are the eigenvalues. FA takes on values between 0 (isotropic) and 1 (anisotropic).

2.2 Semi-Automatic Image Segmentation

Tissue transport properties were assigned to each DTI voxel corresponding to S_0 and FA threshold ranges for white matter, gray matter, bone, or surrounding tissues (Table 1). Since white matter is composed of bundles of myelinated axonal fibers running in parallel, water more freely undergoes translational diffusion in the direction of these fibers. However, gray matter consists of cell bodies and dendrites of neurons and glial cells, which do not restrict water translational diffusion to a particular direction. The calculated S_0 image does not include any diffusion information but reflects the proton-density and T2 relaxation time of the tissue and has been shown to be lower in white matter than in gray matter [26] due to differences in tissue structure, e.g., mainly lower proton-density (water density) in white matter. However, contrast in the FA image reflects the underlying tissue structure, where anisotropy of the water diffusion tensor varies with the extent of tissue alignment within the image voxel. Therefore, oriented bundles of white matter result in higher FA values than gray matter tissue, which is more isotropic. Segmented tissue regions were highlighted in visualization software (AMIRA v.4.1, TGS, San Diego, CA) by adjusting threshold values (S_0 or FA) and these threshold values were confirmed by eye by matching qualitatively with anatomical boundaries defined in a rat spinal cord atlas [16]. Segmented regions were used to assign tissue properties in the computational transport model (see Sec. 2.3.2).

It was not possible to segment gray and white matter regions using the in vivo DTI-derived S_0 images because the signal-to-noise ratio and resolution were too low (Fig. 1(b)). However, segmentation was possible in the FA image, which has higher contrast between gray and white matter (Fig. 1(a)). Since the excised tissue image had both a high signal-to-noise ratio and resolution, gray and white matter could be segmented using either S_0 or FA (Figs. 1(d) and 1(e)).

2.2.1 In Vivo DTI Data—FA values were used to differentiate voxels in each tissue region. White and gray matter regions were well defined, Fig. 1, and FA ranges for each tissue are listed in Table 1. Dorsal regions of the gray matter column were assigned as white matter due to underlying neurons in this region that interdigitate with fibers of the dorsolateral tract, and some of the dorsal nerve root afferents resulting in greater fiber alignment [27]. For these low-resolution imaging data sets, the cerebrospinal fluid (CSF)-filled space surrounding the spinal cord was not distinguishable. For the in vivo data set, a layer of fluid-filled voxels was introduced surrounding the spinal cord tissue voxels to account for surrounding CSF, Fig. 1.

2.2.2 Excised, Fixed Tissue DTI Data— S_0 values were used to differentiate voxels of each tissue region and S_0 ranges for each tissue region are listed Table 1. It should be noted that baseline S_0 values gradually changed over the length of the spinal cord, possibly due to variation in the spin density and/or T2 relaxation times. To account for this, two different ranges of S_0 were applied over the craniocaudal (z) length of the spinal cord. The PBS fluid regions surrounding the imaged spinal cord were assigned as CSF regions of the intrathecal space in the transport model. As a result, the CSF volume surrounding the spinal cord was larger than for in vivo conditions.

2.3 Tissue Transport Model

This study assumes nervous tissue to be a rigid porous medium, which is valid for low rates of interstitial infusion where elastic expansion effects are not large. The continuity equation is

$$\nabla \cdot \mathbf{v} = 0 \quad (3)$$

where $\mathbf{v}$ is the tissue-averaged interstitial fluid velocity. Local sources and sinks of interstitial fluid were neglected in the infusion models because tissues of the CNS lack an active lymphatic system [23], are characterized by low rates of fluid transfer across the capillary walls at the pressures encountered during interstitial infusion at a moderate flow rate [4], and have negligibly low rates of water formation by metabolism [5]. Porous media fluid flow is governed by Darcy's law for fluid flow in a rigid porous medium [28].

$$\mathbf{v} = -\mathbf{K} \cdot \nabla p \quad (4)$$

where p is the pore fluid pressure, and $\mathbf{K}$ is the hydraulic conductivity tensor which is dependent on the pore geometry and fluid viscosity. Instead of the Navier–Stokes equation, the momentum equation for the CSF fluid region along the exterior of the spinal cord was simplified to Darcy's law. In this case, a porosity (fluid volume fraction) of $\phi = 1$ was used and the hydraulic conductivity was chosen to be higher than within white matter tissue since flow resistance within CSF should be lower than within tissues. Implications of this assumption are discussed in Sec. 4. For fluid velocity solutions, zero fluid flux boundary conditions were applied along axial faces, and zero pressure boundary conditions were assigned along transverse faces.

Albumin is a nonbinding and nonreacting macromolecule that is commonly used as an interstitial tracer in distribution studies. Assuming no sources or sinks for this molecule, tracer transport through tissue following infusion is governed by convection and diffusion,

$$\phi \frac{\partial c}{\partial t} + \nabla \cdot (\mathbf{v}c) = \nabla \cdot (\phi \mathbf{D}_t \cdot \nabla c) \quad (5)$$

where t and ϕ are time and tissue porosity, respectively. $\mathbf{D}_t$ is the diffusivity tensor of the macromolecule in the porous medium (a volume averaged term) and c is the tracer concentration averaged with respect to tissue volume. Albumin concentration was solved in terms of the normalized variable,

$$\tilde{c} = \frac{c}{c_i \phi} \quad (6)$$

where c_i is the infusate concentration. A normalized concentration of $\tilde{c} = 1$ was assigned at the infusion site boundaries, and $\tilde{c} = 0$ was assigned at outer boundaries. Initial conditions for albumin transport assumed no tracer in the tissue ($\tilde{c} = 0$).

2.3.1 Interstitial Transport Tensors— $\mathbf{K}$ and $\mathbf{D}_t$ of gray matter and CSF regions were considered to be isotropic. In white matter regions, each spatial node point in the computational model was assigned a spatially-varying, anisotropic transport tensor which took into account preferential transport directions for which DTI data provide underlying directional information for bundles of fibers averaged within the image-voxel volume. $\mathbf{D}_e$ tensors from DTI data were assumed to share the same maximum eigenvectors (directions of maximum transport) as $\mathbf{K}$ and $\mathbf{D}_t$ [29]. $\mathbf{K}$ and $\mathbf{D}_t$ tensors were assigned using the methodology described in Sarntinoranont et al. [23] on a voxel-by-voxel basis. $\mathbf{K}$ and $\mathbf{D}_t$ eigenvectors were assigned from $\mathbf{D}_e$ and eigenvalues (magnitude values) were determined

from published literature (Table 2). The baseline value for CSF hydraulic conductivity was taken to be approximately three orders of magnitude higher than that of gray matter. Also to test the assumption of Darcy's law for CSF, a parameter sensitivity analysis of the hydraulic conductivity of CSF was performed with four different K values, $1000 < K_{\text{csf}} / K_{\text{gm}} < 15,000$.

2.3.2 Computational Model—To reduce computation times associated with a large mesh size, only the dorsal side of the spinal cord and surrounding CSF was modeled using a computational fluid dynamics (CFD) software package, FLUENT (v.6.3.26, Fluent, Lebanon, NH), which solved for porous media transport. Isolating this tissue region is valid given the localized transport associated with the small infusion volumes simulated. For the 3D computational tissue model, a rectangular volume ($6 \times 6 \times 15 \text{ mm}^3$ for in vivo data and $2.12 \times 4.27 \times 11.85 \text{ mm}^3$ for excised data) covering the dorsal side was created (GAMBIT v.2.4.6, Fluent, Lebanon, NH), see Fig. 1. The FOV of the image data sets (i.e., the axial length of the tissue models) limited the transient tracer analysis to small infusion volumes, $< 4 \mu\text{l}$. Eight-node brick elements were used, and the mesh consisted of 48,000 and 829,440 nodal points for models created from in vivo and excised image data, respectively. Each brick element corresponded to an interpolated image voxel ($30 \times 30 \times 150 \mu\text{m}^3$ for excised and $150 \times 150 \times 500 \mu\text{m}^3$ for in vivo tissue data) from the DTI data set. (Only a portion of the DTI image data set for excised, fixed tissue was rendered for the model). Within FLUENT, a user-defined function was used to assign K and D_t for nodes in each element using the segmentation and property assignment methodologies of Secs. 2.2 and 2.3.1. Additionally, a cube infusion site corresponding to the outer diameter of a 31 gauge needle ($150 \times 150 \times 150 \mu\text{m}^3$) was placed in the white matter dorsal column at depths of 0.84 (T13) and 0.68 mm (L1) from the dorsal surface in the in vivo and excised tissue models, respectively. The infusion site was modeled as a region with constant pressure, which corresponded to a constant infusion rate of $0.1 \mu\text{l} / \text{min}$ similar to the study of Wood et al. [3].

Equations (3)–(5) for interstitial fluid flow, pressure, and albumin tracer transport were solved within FLUENT using a control-volume-based technique as described previously [23]. Darcy's law was substituted for the conservation of momentum equation. For Darcy's law to apply, convective acceleration was neglected due to low fluid velocities. For tracer transport simulations, a user-defined flux macro was used to account for tracer diffusion anisotropy (Eq. (5)). Also a weakly-coupled solution was employed which assumes that albumin transport was not significantly affected by osmotic effects or changes in viscosity with changes in concentration. Therefore, tracer concentration predictions were predicted using a steady-state velocity field.

Axial distribution lengths and tissue distribution volumes for predicted tracer distributions were calculated using a threshold of $\sim 15\%$ of the maximum concentration. Tracer distribution volumes were calculated as the spread (or integrated tissue volume) in white and gray matter regions only. To calculate average velocity profiles from the point of infusion, nine virtual lines through the cube infusion site (with separate nodal points) were averaged together for each orthogonal direction.

To determine the effect of voxel size (and element size) on predicted tracer transport, the high-resolution DTI data set obtained for the excised spinal cord tissue was resampled at lower resolutions, and computational transport models with coarser grids were created from these lower resolution data. Predicted tracer distributions from these varying resolution data were compared (high-resolution voxel size = $30 \times 30 \times 150 \mu\text{m}^3$, mid-resolution = $60 \times 60 \times 300 \mu\text{m}^3$, and low-resolution = $120 \times 120 \times 600 \mu\text{m}^3$). Threshold values used for tissue segmentation were adjusted with each data set to obtain comparable tissue volumes in each tissue region ($\sim 1\%$ variation).

3 Results

3.1.1 DTI and Segmentation

In vivo FA and excised tissue S_0 scans of the rat spinal cord show well-defined regions of white and gray matter tissue, Fig. 1. Our semi-automatic segmentation scheme results in a small number of isolated white matter-labeled voxels in gray matter and some isolated gray matter-labeled voxels in white matter. They result from locally high or low values of FA or S_0 values, which may be due to local tissue structure variation. Since these small isolated tissue regions do not appear in the rat spinal cord atlas, we labeled these voxel regions as “artifacts,” Fig. 1. Total artifact voxel volume was estimated less than ~2% of the total spinal cord and CSF volume. Also, gray matter regions in the model generated from in vivo data were underestimated in dorsal horn regions and had an ~2% smaller tissue volume than the spinal cord model generated from excised tissue data. Overall, white matter tissues volumes in this model were also ~1.5% smaller than in the excised tissue model.

3.1.2 Albumin Transport

Steady-state interstitial fluid flow was predicted for 0.1 $\mu\text{l/min}$ infusion into the spinal cord white matter. The predicted interstitial fluid velocity dropped rapidly with penetration distance, and was preferentially channeled along the axis of the spinal cord with larger velocity components in the z -direction. Albumin distribution contours generated from in vivo and excised tissue data sets are overlaid on corresponding FA and S_0 spinal cord images in Figs. 2 and 3, respectively. Tracer spread conformed to anatomical white matter boundaries and was along the direction of the structured white matter tracts with preferential transport along the axis of the cord. Greater transverse spread of tracer was seen in the in vivo model with time due to connected dorsal and lateral white matter regions. Average concentration contours through the infusion site are graphed in Fig. 4. Due to the lower hydraulic conductivity values assigned to gray matter [3,13], there was more limited tracer penetration into these regions over the time scales simulated (<0.5 mm). While distributions were relatively uniform within the white matter dorsal horn some dips in the concentration were noted in the vicinity of artifact voxels (assigned as gray matter). Conversely, local increases in concentration were predicted near artifact voxels (assigned as white matter) in the gray matter columns of the spinal cord.

Convection-dominated regions estimated by Peclet number contours are presented in Fig. 5. ($Pe = vL/D$ where L is a length scale parameter, $L = 1$ mm, and $Pe \gg 1$ in convection-dominated regions.) These zones corresponded to white matter regions in the vicinity of the infusion site and extended significant distances from the point of infusion in the craniocaudal direction. The calculated Peclet number was as high as ~4900 (excised tissue model) and ~1800 (in vivo data model) next to the infusion site and decreased proportionally with the velocity magnitude. Differences in the Peclet contours are due to local velocity differences that are confined to the immediate vicinity of the infusion site and are likely due to differences between embedded infusion sites. Overall, interstitial fluid flow in the excised spinal cord model is more confined by (1) gray matter horns that extend to the dorsal surface and (2) a more deeply embedded infusion site. Both of these effects result in greater channeling of flow and higher interstitial fluid velocities along the axis of the spinal cord.

3.1.3 Validation and Parameter Analysis

Predicted tissue distribution volumes for the albumin tracer were found to be consistent between the two computational spinal cord models generated from excised tissue and in vivo imaging data sets, as well as the experimental distribution studies by Wood et al. [3] that measured spread of ^{14}C -labeled albumin following CED into approximately the same region of the rat spinal cord, Fig. 6. Distribution volumes from models using the in vivo imaging

(low-resolution) data predicted larger distributions than those using excised (high-resolution) data for the range of small infusion volume studied, $<4 \mu\text{l}$. For simulations using baseline tissue transport parameters, normalized root mean square deviation values of 0.28 and 0.19 were achieved comparing predicted and experimental tracer distribution volumes for the models using in vivo and excised data, respectively.

For the parameter sensitivity analysis varying the hydraulic conductivity of CSF, the relation between the tracer infusion volume and tissue distributions at the end of infusion ($4 \mu\text{l}$) are presented in Fig. 7(a). This graph shows that tracer tissue distributions were within $\pm 3\%$ of the average distribution. The effect of varying the resolution or size of the imaging voxels used to create the computational model was also considered, Fig. 7(b). The voxel size range corresponded to high-resolution scans for the excised tissue to lower resolution data comparable to in vivo scans. Final tracer tissue distributions versus the volume infused were compared and showed albumin tissue spread within $\pm 10\%$ of the average distribution. This variation is likely due to changes in tissue boundaries with grid coarsening. This low variation shows consistency of predicted results within a range of likely imaging resolutions

4 Discussion

This study presents a rapid, semi-automatic segmentation approach for modeling interstitial transport in the spinal cord that avoids labor intensive and time consuming processes such as slice-by-slice contouring and polynomial surface reconstruction used in previous tissue transport modeling approaches [16,23,24,30,31]. DTI-derived FA and S_0 values for both in vivo and excised tissue data sets were used to assign tissue transport properties for each voxel, and these properties were input into a voxelized computational model that predicted interstitial transport using porous media equations. The computational model also accounts for interstitial transport anisotropy in white matter tissues.

Computational transport models using in vivo (low-resolution) and excised tissue (high-resolution) DTI data sets predicted tracer distribution trends observed experimentally including preferential transport along the axis of the cord and limited distribution in gray matter. Also, albumin concentration was dramatically decreased at boundaries between white matter and gray matter and CSF regions due to changes in $\mathbf{K}$ and $\mathbf{D}$ properties between these regions. Simulated tracer distributions showed an approximately linear relationship between distribution and infusion volumes [3,13]. Nonlinear trends may increase with infusion volume as more tracer and fluid is channeled to adjacent CSF regions that offer less flow resistance.

In addition, predicted tracer distributions were found to be comparable with experimental measures by Wood et al. [3] in the rat spinal cord. Predicted and measured tracer distribution volumes were comparable for small infusion volumes. Volume differences may be due to differences in spinal cord tissue volumes between animals, differences in infusion site location, and/or uncertainties in CNS transport properties such as porosity or hydraulic conductivity. It should be noted that few experimental data points are available for comparison at this time, e.g., three data points from Wood et al [3]. Compared with experimental concentration profiles, the voxelized models also predicted greater variation in the concentration profiles (less uniform) due to the inclusion of artifact voxels within tissue regions, i.e., small, isolated tissue regions. This tissue variation is a result of our semi-automatic segmentation scheme based on certain threshold values. However, the total volume for these artifact voxels was calculated to be small. Methods to account for the effects of fiber crossings in our DTI data set may further reduce the incidence of these voxels in the model.

Tissue segmentation thresholds for FA or S_0 were based on one DTI image data set each. Thus, the threshold values are specific to the particular image data set. In general, threshold values will vary between image data sets due to variation in signal-to-noise ratio, MR coil tuning, and other instrument factors, as well as differences between subjects. However, most of this variability will occur in the S_0 value since the FA value is more insensitive to these factors [32] and mainly depends on tissue structure. Some differences in tissue boundaries were noted between models generated using FA or S_0 . In particular, substantia gelatinosa regions of the gray matter in the dorsal horn have larger FA values than adjacent gray matter due to fibers entering the spinal cord, so these regions were assigned as white matter in the in vivo data set model. These tissue transition regions will likely exhibit some combination of white and gray matter transport behavior. However, additional experimental studies are required to determine how transport properties vary in these transition zones. In this study, assignment of these dorsal regions as white matter resulted in greater transverse spread of the albumin tracer due to connected white matter regions when compared with models that assign the same regions as gray matter using S_0 thresholds.

To allow for rapid modeling, CSF regions were treated as a porous media with $\phi = 1$. This assumption appears to be valid for our spinal cord transport model since fluid flow boundary layers that develop in the CSF likely have a small influence on transport within the spinal cord. Parameter sensitivity studies showed that even after increasing CSF hydraulic conductivity, the relation between the tracer infusion volume and the final tissue distribution volumes were only slightly influenced. This showed insensitivity to this transport parameter for small infusion volumes. The current model also does not account for local sources and sinks for interstitial fluid. This assumes an inactive lymphatic system, negligible water formation due to metabolism, and low rates of capillary uptake. However, this assumption may underestimate fluid transfer across the capillary walls and lead to some overestimation of interstitial tracer concentration, especially at higher infusion pressures or over longer infusion times than our current study.

Parameter sensitivity studies looking at the effect of imagevoxel resolution showed greater tracer transport variation. After resampling the same DTI data set at varying resolutions, the predicted tracer distribution volumes decreased with resolution due to the effect of discrete, stepwise boundary changes. Specifically, segmentation maps for the low-resolution voxel model changed significantly with small changes in S_0 threshold values resulting in changes in the predicted tracer distribution volumes. However, after matching gray and white matter tissue volumes between models, the sensitivity of albumin tracer spread to changes in voxel resolution was reduced.

In this study, MR scans of excised, fixed tissues were used to attain a high-resolution DTI data set. The sample was surrounded by PBS fluid which was assigned CSF properties in our infusion transport model. As a result, greater CSF dilution of tracer is predicted than in vivo since the CSF volume is larger than the actual intrathecal space, see Fig. 3. However, this effect appears to be minimal for small infusion volumes. For models generated using in vivo tissue data, a voxel layer of CSF was introduced surrounding the spinal cord to provide a low resistance pathway adjacent to the spinal cord. Increasing in vivo DTI resolution scans may allow for direct segmentation of the intrathecal space in future studies. Other limitations of using excised, fixed tissue scans are associated with changes due to possible tissue shrinkage with fixation. For example, nonuniform shrinkage may lead to changes in fiber orientation, i.e., the eigenvectors of $\mathbf{D}_e$. We assume such changes to be small and fiber orientation will likely not change with uniform shrinkage. Also, expansion of the interstitial space due to infusion and backflow along the cannula tract were not accounted for in these CED models. Future work may consider viscoelastic behavior of tissue and fluid flow between the cannula and surrounding tissue.

In this study, a new voxelized modeling approach was developed to provide estimates of interstitial tracer transport during CED. The developed methodology accounts for the next step in modeling tissue transport in nervous tissues by providing a rapid process for incorporating realistic, complex anatomical boundaries. The spinal cord is an ideal location for validation studies because of its well-characterized bulk alignment of white matter axonal fibers along its axis. However, additional experimental comparisons using larger infusion volumes, and varying infusion sites are required for further testing of this modeling approach. In future studies, the developed methodology will also be used to account for anatomical boundaries within the brain to predict more complex distributions [33].

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Fig. 1.

DTI-based segmentation: (a) FA image from a transverse DTI scan of the in vivo spinal cord at level T13 (voxel resolution= $150 \times 150 \times 500 \mu\text{m}^3$) Gray matter tissue is hypo-intense and white matter tissue is hyperintense. (b) Corresponding S_0 image with uniform intensity in gray and white matter, and (c) tissue segmentation image used in the voxelized computational model (dark blue=white matter, light blue=gray matter, yellow=CSF, red = bone, and surrounding tissues). (d) FA image from a transverse DTI scan of excised tissue at L1 (voxel resolution= $30 \times 30 \times 150 \mu\text{m}^3$) and (e) corresponding S_0 image, where gray matter tissue is hyperintense and white matter tissues is hypo-intense. (f) Corresponding high-resolution tissue segmentation image (blue=white matter, green=gray matter, and red = CSF). The yellow box outlines the dorsal tissue region used in the voxelized model. Artifact voxels resulting from the semi-automatic segmentation method are also identified. Please refer to the digital version of this article for full color images.

Fig. 2. Predicted albumin distributions in the spinal cord using voxelized transport models generated from in vivo DTI (low-resolution) data. Distribution contours in transverse and sagittal planes intersecting the infusion site are overlaid on FA images at varying times after the start of infusion (infusion rate = $0.1 \mu\text{l}/\text{min}$). Tracer concentration contours are for normalized tissue concentrations.

Fig. 3.

Predicted albumin distributions in the spinal cord using voxelized transport models generated from DTI of excised, fixed tissues (high-resolution). Distribution contours from excised in transverse and sagittal planes intersecting the infusion site are overlaid over S_0 images at varying times after the start of infusion (infusion rate=0.1 $\mu\text{l}/\text{min}$). Tracer concentration contours are for normalized tissue concentrations.

Fig. 4. Predicted concentration profiles for albumin tracer during direct tissue infusion at $0.1 \mu\text{l} / \text{min}$. Concentration profiles are for three orthogonal lines passing through the infusion site: (a) vertical line in the transverse plane, (b) horizontal line in the transverse plane, and (c) axial line. Normalized tissue concentrations are given and concentration is the averaged value for nine lines passing through the infusion site. All simulations were using the high-resolution voxel transport model generated from excised DTI data.

Fig. 5. Peclet number contour maps in the transverse plane of the spinal cord generated using voxel transport models from (a) in vivo and (b) excised tissue image data. Peclet contours are overlaid on S_0 images in (a) transverse and sagittal planes and (b) transverse and coronal planes intersecting the infusion site. As an approximation, convection-dominated regions correspond to Peclet number > 300.

Fig. 6.

Comparison of predicted and measured distributions of albumin tracer in the rat spinal cord following direct infusion into the dorsal horn. Tracer tissue volumes calculated from the voxel transport models using in vivo and excised tissue data sets are plotted. Wood et al. [3] measured distribution of ^{14}C -labeled albumin following CED into a similar region. Bars correspond to ± 1 SD. The threshold value used for volume distribution analysis was 15% of the infusate concentration.

Fig. 7.

Parameter sensitivity analysis comparing the final distribution volume (Vd) and the total infusion volume (Vi) on a log-log scale for (a) the hydraulic conductivity of CSF and (b) the image-voxel resolution (high-resolution voxel size=30×30×150 μm³, mid-resolution=60×60×300 μm³, and low-resolution=120×120×600 μm³). Vd and Vi were calculated using the excised tissue data set. Vd was calculated for regions within the gray and white matter tissue regions only. Solid lines correspond to the average Vd value ±3% and ±10% for the set of K ratios and voxel resolutions simulated, respectively.

Table 1

FA and S_0 ranges used to segment the spinal cord DTI data. FA ranges were used to segment in vivo imaging data sets. S_0 was used for excised, fixed tissue data and two different ranges were used over the axial length of the spinal cord. The values of S_0 were normalized by the surrounding PBS value.

Spinal cord region (in vivo)		FA range
White matter		0.466–1
Gray matter		0.05–0.466
Bone and surrounding tissues		0–0.05
Spinal cord region (excised)	S_0 range ($1 \leq z \leq 59$)	S_0 range ($60 \leq z \leq 80$)
White matter	0–0.412	0–0.455
Gray matter	0.412–0.558	0.455–0.600
PBS fluid regions	0.558–1	0.600–1

(z : Transverse plane slice number, slice thickness: 0.15 mm).

Table 2

Tissue transport properties used in the interstitial transport simulations. D and K values correspond to tensor components of D_t and K .

Parameter	Value	Reference
ϕ	0.26	[3,16]
D_{tgm}	$1.60 \times 10^{-7} \text{ cm}^2 / \text{s}$	[34]
$D_{twm\parallel}$	$2.29 \times 10^{-7} \text{ cm}^2 / \text{s}$	[14,34]
$D_{twm\perp}$	$1.34 \times 10^{-7} \text{ cm}^2 / \text{s}$	[14,34]
D_{CSF}	$1.34 \times 10^{-7} \text{ cm}^2 / \text{s}$	[14,34]
$K_{wm\parallel}$	$6.75 \times 10^{-9} \text{ cm}^4 / \text{dyn s}$	[23]
$K_{wm\perp}$	$4.22 \times 10^{-10} \text{ cm}^4 / \text{dyn s}$	[23]
K_{gm}	$4.22 \times 10^{-12} \text{ cm}^4 / \text{dyn s}$	[23]

wm: white matter; gm: gray matter.