Rigorous Mathematical Modeling Techniques for Optimal Delivery of Macromolecules to the Brain

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Abstract—Several treatment modalities for neurodegenerative diseases or tumors of the central nervous system involve invasive delivery of large molecular weight drugs to the brain. Despite the ample record of experimental studies, accurate drug targeting for the human brain remains a challenge. This paper proposes a systematic design method of administering drugs to specific locations in the human brain based on first principles transport in porous media. The proposed mathematical framework predicts achievable treatment volumes in target regions as a function of brain anatomy and infusion catheter position. A systematic procedure to determine the optimal infusion and catheter design parameters that maximize the penetration depth and volumes of distribution will be discussed. The computer simulations are validated with agarose gel phantom experiments and rat data. The rigorous computational approach will allow physicians and scientists to better plan the administration of therapeutic drugs to the central nervous system.

Index Terms—Catheter placement, convection-enhanced delivery, drug targeting, invasive.

NOMENCLATURE

\( B \) Tissue averaged drug concentration due to binding or internalization in cells [mol/L].
\( C \) Drug tissue averaged concentration [mol/L].
\( C_\infty \) Drug concentration in the cerebrospinal fluid space, \( C_\infty = 0.0 \text{ mol/L}. \)
\( d \) Catheter outer diameter (mm).
\( d_p \) Port diameter in multiple port configuration (mm).
\( D_e \) Effective diffusion tensor (m²/s).
\( k \) Mass transfer coefficient (m/s).
\( k_{\text{app}} \) Lumped first-order rate constant (s⁻¹).
\( \mathbf{r} \) Hydraulic conductivity tensor (m⁻¹ N⁻¹ s⁻¹).
\( M \) Molecular weight of the species such as drug or dye (kg/kmol).
\( N \) Number of trials for the experiment (infusion experiment).
\( p \) Interstitial pressure (Pa).
\( p_{\text{CSF}} \) Intracranial pressure in the cerebrospinal fluid space (Pa).
\( Q \) Infusate flow rate (µL/min).
\( R \) Metabolic reaction term (mol/Ls).
\( S \) Loss term (Kg/m³ s).
\( S_B \) Source terms (Kg/m³ s).
\( t \) Time (s).
\( T \) Temperature (K).
\( \vec{v} \) Superficial fluid velocity in porous medium or clear fluid velocity inside catheter (m/s).
\( x_0 \) Inlet concentration of the drug in the infusate (mol/L).
\( x_a \) Absolute concentration threshold (mol/L).
\( x_r \) Relative concentration threshold (mol/L).

Greek Symbols

\( \varepsilon \) Porosity: ratio of fluid volume to the total volume.
\( \mu \) Fluid viscosity, \( \mu = 0.89 \times 10^{-3} \text{ (Pa-s)} \).
\( \rho \) Fluid density, \( \rho = 998.0 \text{ (kg/m³)} \).
\( \phi \) General transport quantity (mass, momentum, and species).
\( \Gamma_b \) External pial boundary.
\( \Gamma_v \) Lateral ventricle boundary.
\( \Gamma_{\text{tip}} \) Catheter tip located in the injection sites (e.g., thalamus, putamen, and ventricle).
\( \Gamma_{\text{catheter}} \) Catheter inlet.
\( \Omega_{\text{GM}} \) Gray matter regions (e.g., thalamus, caudate nucleus, and globus pallidus).
\( \Omega_{\text{WM}} \) White matter regions (e.g., corpus callosum, internal capsule, and corona radiata).
\( \Omega_p \) Putamen.
\( \Omega_T \) Thalamus.
\( \Omega_V \) Lateral ventricle.

I. INTRODUCTION

Increasing numbers of people affected by neurodegenerative diseases such as Parkinson’s, Alzheimer’s, and Huntington’s create a growing need for effective treatment protocols [1]. In addition, malignant gliomas remain rapid and almost uniformly fatal despite existing therapeutic modalities. However, the blood–brain barrier prevents large molecules from entering the brain often rendering common oral or intravenous drug administration inefficient [2], [3]. Therefore, successful treatment methods for the central nervous system require novel
therapeutic drugs, and also depend critically on their effective delivery to target regions of the brain.

A promising approach to drug delivery without the need for chemical drug transformations includes invasive drug administration.

Invasive techniques insert a dilute drug solution into the cerebral extracellular space via an infusion catheter, thus bypassing the blood–brain barrier. Convection-enhanced delivery (CED) has received attention because larger distribution volumes can be achieved than by molecular diffusion alone. The effectiveness of convection-enhanced drug delivery has been demonstrated in vivo in animal models [4]–[7]. In CED, volumes of drug distribution depend on: 1) infusion parameters like infusion pressure, flow rate, and drug concentration; 2) molecular properties such as effective diffusivity and hydraulic conductivity as well as 3) catheter design and position. How to select these parameters for achieving desired drug distribution in a systematic fashion is the objective of this study.

Outline: The paper is organized as follows. Section II will introduce a new methodology for better predicting achievable drug distribution in the human brain based on state-of-the-art medical imaging. Section III will present experimental and computational results for achievable drug distributions as a function of different injection protocols in agarose gel phantoms and in the human brain. The discussion in Section IV will emphasize outcomes and design consideration of convection-enhanced drug delivery. Section V offers validation data of the computer predictions in rat brain tissue. The paper closes with conclusions and outlook for future research.

II. METHODOLOGY

Accurate prediction of drug distribution requires anatomically consistent representation of size and shape of target areas inside the brain. The main brain dimensions and the specific location of target areas in the midbrain differ from subject to subject, thus patient-specific metrics are significant. We, therefore, propose to improve the prediction and calculation of achievable drug distribution volumes based on detailed patient-specific brain models, anatomically consistent tissue properties, and first principles mathematical transport equations. A more detailed discussion of this novel computer-assisted brain analysis outlined in Fig. 1 follows.

A. Brain Geometry Reconstruction

1) Patient-Specific Brain Imaging Data (Step 1): Axial and coronal images were acquired from healthy volunteers on a 3T GE Signa system (GE Medical Systems, Milwaukee, WI). The protocol and patient consent were approved by the Institutional Review Boards of the University of Illinois and University of Chicago. The scanner is equipped with a standard quadrature birdcage head coil; a turboprop—diffusion tensor imaging (DTI) pulse sequence is used for DTI with the following parameters: field of view = 24 cm × 24 cm, repetition time (TR) = 5000 ms, eight spin-echoes per TR, five k-space lines per spin-echo, 16 k-space blades per image, and 192 samples per line reconstructed to matrix of 256 × 256 [8], [9]. Typically, 36 slices are collected with slice thickness 3 mm and slice gap of 0 mm. Individual apparent free water diffusion (AWD) tensors are estimated for each voxel of size 0.9375 mm × 0.9375 mm × 3.0 mm. Concurrently, T1 and T2-weighted images (b = 0 s/mm²) were recorded to provide reference coordinates for the physical brain mesh.

2) Reconstruction of the Brain Geometry (Step 2): Image reconstruction is the process of accurately delineating the main dimensions of the brain, the substructures of interest, and the boundaries between regions with different chemical or physical properties. A fine resolution of the midbrain is desirable as most target areas for treating neurodegenerative diseases are located in the midbrain [10]–[12]. Image reconstruction converts image data of step 1—typically pixel matrices representing planar brain slices—into geometric surfaces and regions. It also involves smoothing, contrast enhancement, and edge detection to convert the MR voxel data into geometrical surfaces and volumes [13]. More details can be found elsewhere [14]–[16].

3) Grid Generation (Step 3): Domain regularization methods partition the reconstructed surfaces and regions into a finite number of tetrahedrons enclosed by triangular faces [17]. 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 volume mesh of the computational domain. These computational meshes constitute the physical domain for which the transport equations will be satisfied as discussed later.
NGF mean diffusivity as from DTI, as given in Table I. Prior experiments determined the mus was estimated using the apparent water diffusion tensor data and heterogeneity of drug distribution patterns. We have quantified methods do not account for the directional dependence of brain anisotropy and heterogeneity. The tissue anisotropy and heterogeneity vary in space according to local fiber density and alignment. The tissue anisotropy and heterogeneity of the brain can be detected with DTI. Current computational models, whose components were determined by introducing diffusion and hydraulic conductivity tensor imaging [18]–[23]. For example, the nerve growth factor (NGF) diffusion tensor $\mathcal{D}_e$ near the thalamus was estimated using the apparent water diffusion tensor data from DTI, as given in Table I. Prior experiments determined the NGF mean diffusivity as $D_e = 28 \pm 12 \times 10^{-12} \text{m}^2/\text{s}$, which was equated to the first invariant of the measured diffusion tensor [24]–[26].

**B. Calibration of Physical Properties**

Step 4: Porous brain tissue possesses strong directional dependence of its material properties especially along the fibrous white matter tracts, as depicted in Fig. 2. Moreover, transport properties in the brain are heterogeneous so that the degree and orientation of anisotropy vary in space according to local fiber density and alignment. The tissue anisotropy and heterogeneity of the brain can be detected with DTI. Current computational methods do not account for the directional dependence of brain properties often resulting in unrealistic predictions of symmetric drug distribution patterns. We have quantified brain anisotropy and heterogeneity by introducing diffusion and hydraulic conductivity tensor models, whose components were determined by advanced diffusion tensor imaging [18]–[23]. For example, the nerve growth factor (NGF) diffusion tensor $\mathcal{D}_e$ near the thalamus was estimated using the apparent water diffusion tensor data from DTI, as given in Table I. Prior experiments determined the NGF mean diffusivity as $D_e = 28 \pm 12 \times 10^{-12} \text{m}^2/\text{s}$, which was equated to the first invariant of the measured diffusion tensor [24]–[26].

**C. Transport Phenomena in Porous Brain Tissues**

Step 5: Drug distribution is predicted using first principle conservation laws. The infusate obeys the laws of fluid motion in a porous medium [27]–[29]. The interstitial infusate flow satisfies continuity in terms of the superficial fluid velocity vector $\vec{v}$, which is correlated to the average velocity through the tissue porosity $\varepsilon$, as in (1). The net transport of bulk fluid into an interstitial volume element is determined by the term $S_B$, which accounts for the loss of the bulk fluid into the cerebral vasculature as a function of capillary hydraulic conductivity, the interstitial pressure $p$, and the effective Starling pressure $\delta$ [30]. The bulk momentum balances in (2) relating the superficial velocity $\vec{v}$ with interstitial fluid pressure $p$ resemble the Navier–Stokes equations with an additional term to account for fluid friction in the porous cell matrix, where $\mu$ and $\rho$ are the fluid viscosity and density and $\mathcal{R}(\vec{x})$ is the hydraulic conductivity tensor.

Bulk mass balance

$$\nabla \cdot (\rho \vec{v}) = S_B. \quad (1)$$

Bulk momentum balances

$$\rho \left( \frac{\partial \vec{v}}{\partial t} + \vec{v} \cdot \nabla \vec{v} \right) = -\nabla p + \mu \nabla^2 \vec{v} - \mathcal{R}(\vec{x}) \vec{v}. \quad (2)$$

1. **Drug Transport in Porous Tissues:** In addition, molecules travel due to concentration gradients. The convective–diffusive drug dispersion can be calculated according to the species transport equation given in (3). The term $\mathcal{D}_e \nabla C$ is the diffusion flux with the tissue averaged species concentration $C(\vec{x}, t)$, and $\mathcal{D}_e(\vec{x})$, is the effective diffusion tensor. The effective diffusion tensor depends on the molecular properties of the drug as well as the tissue porosity and its tortuosity [31], [32]. To account for the anisotropic and heterogeneous porous brain tissue, we model the effective diffusivity $\mathcal{D}_e$ as second-order tensor field. The reaction term $R(C, \vec{x})$ represents enzymatic drug decomposition, possible metabolic drug interactions, or other pharmacokinetic effects. The term $B$ accounts for drug-receptor binding or drug internalization. In fast binding mechanisms, the drug binding is often described by first-order binding equilibrium constants [33]. In addition, interaction with the brain microvasculature may introduce additional sink terms $S(C, \vec{x})$, such as capillary exchange or blood clearance. Bulk fluid and molecular drug transport equations are fully coupled via the flow field $\vec{v}$. The solution of the fundamental conservation laws of mass, momentum, and species transport lead to the desired predictions of drug distribution $C(\vec{x}, t)$, the superficial velocity $\vec{v}(\vec{x}, t)$, as well as the pressure fields $p(\vec{x}, t)$ as functions of space $\vec{x}$ and time $t$. However, the irregular brain geometry makes analytical solutions prohibitive. Instead, the conservation laws are solved numerically after finite volume discretization over unstructured computational meshes.

Drug transport

$$\varepsilon \frac{\partial C}{\partial t} + \vec{v} \cdot \nabla C = \nabla \cdot \left( \mathcal{D}_e(\vec{x}) \nabla C \right)$$

$$+ R(C, \vec{x}) - \frac{\partial B}{\partial t} + S(C, \vec{x}). \quad (3)$$

2. **Finite Volume Discretization of the Transport Equations:** We propose the finite volume discretization for the numerical solution of the transport problem in (1)–(3) [34], [35]. The finite volume discretization converts partial differential equations...