ABSTRACT
Diffusion MRI (DMRI) signal is characterized by the self-diffusion propagation profile within the brain white matters. Despite previous efforts on quantification of this physical phenomenon in the literature, most existing methods suffer from a number of constraints which severely limit the extent of their practical applicability. In this work, we relax these limitations to a large degree by addressing the solution of the self-diffusion process in its most general partial differential equation (PDE) form. Specifically, we develop an approach based on the finite element method (FEM) to obtain numerical self-diffusion solution in multi-compartments models of the white matters. Besides, due to sensitivity of the DMRI signal to the average self-diffusion process, we provide a formulation for this process of a voxel in terms of microstructure parameters of white matters. Several simulation results based on the proposed FEM method are given to demonstrate its flexibility and accuracy.

Index Terms—Diffusion MRI, DTI, self-diffusion, white matters, axons, FEM

1. INTRODUCTION
During the past two decades, Diffusion Magnetic Resonance Imaging (DMRI) has found applications in diagnoses and studies of diseases and abnormalities associated with the central nervous system such as Ischemia [1] and Alzheimer’s disease [2]. It is the only tool available for in vivo assessments of white matter tracts anatomy. The DMRI signal is characterized by the Brownian motion of water molecules within biological tissues, a process known as self-diffusion [3]. The brain white matter tracts consist of parallel and well-organized multi-compartment material which causes the self-diffusion process to have propagation tendency along the orientation of axonal fibers. Therefore, they are good candidates to study with DMRI.

One fundamental problem in the study of white matters with DMRI is to assess tissues structures from the measured self-diffusion profile. It is well known that inferring the structure of white matters from measured DMRI signals is an ill-posed problem. To address this issue, accurate quantification of the self-diffusion process in the white matter environment is important, since it can help identify salient constraints so as to facilitate the assessment of the tissue structure from the incomplete data. There are several analytical and numerical attempts in the literature for self-diffusion quantification. Due to complexity of biological tissues, analytical solutions [4] are confined to oversimplified models of tissues. The Monte Carlo (MC) simulation [5, 6] is the most prevalent numerical approach nowadays. However, it demands a large amount of computational complexity. How to select a proper number of simulation particles to balance the complexity and performance accuracy is still an open problem.

In this work, we tackle this problem from another angle by providing a solution to the self-diffusion-governing PDE with the finite element method (FEM). This approach leads to great reduction in computational complexity as compared with the MC simulation. Besides, it allows more flexibility in handling the complex geometry of white tracts and their constituting material. Note that the limited resolution DMRI signal observed at a voxel is characterized by the average behavior of the self-diffusion process in the voxel. We show how to derive the voxel average values analytically and compute them numerically based on the proposed approach.

2. SELF-DIFFUSION IN WHITE MATTER TRACTS

Fig. 1. (Left) A single axon model, where the self-diffusion coefficients of the cytoplasm and myelin regions are denoted by $D_c$ and $D_m$, respectively. (Right) The hexagonal array of cylinders model for a bundle of axons in white matter tracts.

The white matter tracts of human brains consist of bundles of axons, and the space among axons is filled with extracellular fluid. Three major compartments of an axon are...
illustrated in Fig. 1, which are the cytoplasm, the membrane wall, and the myelin sheath. Here, by following [4], we lump the membrane layer partial permeability into the myelin layer. The self-diffusion propagator, denoted by \( P_{\tau} (\vec{r}, t) \), is one of the major parameters involved in the DMRI signal formation process. It is defined as the probability density function of motion of a water molecule from start position at \( \vec{r} \) to destination position at \( \vec{r}' \) after \( t \) seconds. The DMRI principal signal formation equations are in form of Fourier transform pair [3] as

\[
S(k, \varphi) \propto \int \rho(\vec{r}) e^{2\pi ik \cdot \vec{r}} \int P_{\tau} (\vec{r}, t) e^{2\pi i \varphi (\vec{r}' - \vec{r})} d\vec{r} d\vec{r}'
\]

where \( S(k, \varphi) \) and \( E_\Delta (\vec{r}, \varphi) \) are the k-space signal and the reconstructed magnetic resonance image, respectively, \( k \) is the k-space sample, \( \varphi \) is proportional to the scanner diffusion gradient and \( \rho(\vec{r}) \) is the effective local water molecules density. The spatial and temporal evolutions of the self-diffusion propagator in the 3D space are governed by the following PDE [3]:

\[
\frac{\partial P_{\tau} (\vec{r}, t)}{\partial t} = \nabla D(\vec{r}) \nabla P_{\tau} (\vec{r}, t), \quad (3)
\]

where \( D(\vec{r}) \) is the local self-diffusion coefficient. Typical initial and boundary conditions can be written as

\[
P_{\tau} (\vec{r}, 0) = \delta (\vec{r} - \vec{r}'), \quad (4)
\]

\[
P_{\tau} (\vec{r}, t) = 0, \quad (5)
\]

\[
J_{\pm} (\vec{r}, t) = D_{\pm} (\vec{r}) \nabla P_{\tau}_{\pm} (\vec{r}, t), \quad (6)
\]

\[
J_{+} (\vec{r}, t) = J_{-} (\vec{r}, t), \quad (7)
\]

where \( J \) is defined as the propagator flow, and subscripts + and - are used to discriminate between the quantities on two opposite sides of a surface and \( \vec{n} \) is the surface normal. To solve the above PDE by FEM, we express the solution in form of

\[
P_{\tau} (\vec{r}, t) = \sum_{i=1}^{n} \alpha_{\tau,i}(t) \varphi_{i}(\vec{r}). \quad (8)
\]

where \( \varphi_{i}(\vec{r}) \)'s are FEM polynomial basis functions and \( \alpha_{\tau,i}(t) \)'s are unknown parameters to be solved numerically. Linear triangle elements are a popular choice for \( \varphi_{i}(\vec{r}) \) in FEM. It is however possible to consider basis functions of a higher degree in higher-order FEM.

3. PROPOSED NUMERICAL SIMULATION METHOD

The characteristics of the proposed solution approach and our main contributions are highlighted in Sec. 3.1. They can be examined from two aspects. First, the self-diffusion process is studied in the microscopic scale of axons dimensions and a method is proposed to make the standard FEM applicable to solution of self-diffusion PDE. This will be detailed in Sec. 3.2. The measured DMRI signal can be conveniently linked to the average self-diffusion in a voxel, which is discussed in Sec. 3.3.

3.1. Contributions of Proposed Solution

The contributions of our research lies in two main characteristics of this proposed numerical solution. They are detailed below. First, it is worthwhile to point out the standard FEM is not directly applicable to solution of the self-diffusion PDE of interest because it cannot guarantee the layer boundary conditions in equation(7). Thus, we devise conditions to allow a feasible FEM solution. The developed FEM solver is able to accommodate complicated geometry of white matters and provide a large degree of flexibility for parameters of the white tracts material. It can quantitatively evaluate the effects of microscopic parameters of white matters such as myelin thickness, axons diameter and spacing, and self diffusion coefficients of different material, on the self-diffusion propagator profile. These characteristics are not offered by other solvers such as the finite difference (FD) method [7], which cannot handle irregular geometries easily. In addition, since the PDE deals with the self-diffusion propagator which is a probability density function, we are concerned with the statistical behavior of water molecules motions, as opposed to the MC method which deals with individual particles. As a result, our solution has a significant advantage over the MC method in terms of computational complexity. This is especially true for complex white matters geometries. For the MC method, the more irregular the geometry of axons becomes, the more particles are needed for valid MC simulation. In contrast, such an increase in computational complexity is negligible for the proposed FEM solver.

Second, the observed signal from a DMRI voxel is attributed by the average of the self-diffusion propagation over the entire voxel. In this work, we express the average value of the self-diffusion propagator at each voxel in terms of microscopic parameters of the material confined to the voxel. In other words, our approach is able to quantify the microscopic self-diffusion process which is in the axon dimension but not observable by the DMRI measurement as well as the macroscopic aggregate effect of all positions of a voxel, which can be measured by actual DMRI measurements. This is of special interest for researchers to establish salient prior models from the self-diffusion profiles.

3.2. FEM Solution of Self-Diffusion PDE

As a standard step in the FEM-based PDE solution, the original PDE is transformed into the variational domain by multiplying both sides of the equation by arbitrary function \( u(\vec{r}) \) and integrating over the whole spatial domain [8]. For the multi-compartment environment, it is shown in [9] that the variational formulation of self-diffusion PDE can be simplified as

\[
\int_{C_i} \frac{\partial P_{\tau} (\vec{r}, t)}{\partial t} u(\vec{r}) \, d\vec{r} = \sum_{i} \left[ - \int_{C_i} D(\vec{r}) \nabla u(\vec{r}) \cdot \nabla P_{\tau} (\vec{r}, t) \, d\vec{r} + \int_{S_i} u(\vec{r}) D(\vec{r}) \nabla P_{\tau} (\vec{r}, t) \cdot d\vec{s} \right], \quad (9)
\]

where \( C_i \) is the entire region of compartment \( i \). Note that the right-hand-side of Eq. (9) consists of two terms contributed by compartment \( i \); namely, the volume integral and the surface integral.
Since the surface integral is over the surfaces of compartments boundaries it is not appealing to the FEM implementation. We need to replace it with something easier to compute. The true solution of the original PDE of Eq. (3) always fulfills the layer boundary conditions given by Eq. (7), which eliminates the surface integral. However, for the standard approximate FEM solution of Eq. (8), the layer boundary conditions may not be satisfied due to the smoothness criteria imposed on the solution [10]. Thus, it could be difficult to proceed with a valid FEM solution. Fortunately, the FEM technique comes with a host of properties which define the characteristics of the solution. By exploring these properties, we derive constraints on the FEM mesh generation procedure as well as the order of polynomial basis functions to satisfy the layer boundary conditions. For more details about the theoretical derivation, we refer to [9].

3.3. Aggregate Self-Diffusion Propagator of MRI Voxels

In this subsection, we first argue that the DMRI has limited resolution in reality and the reconstruction is voxel-wise. Then, we link the average value of the self-diffusion propagator at each voxel to the microstructure parameters of the material in the voxel level.

The process of image formation in real MRI scanners is prone to a number of artifacts and distortions. The limited k-space sampling [11] is one of the practical constraints, which induces blurring in the image. The blurring occurs in form of spatial convolution of the ideal (non-blurred) image with the point spread function of the sampling window of the k-space. Since a convolution represents a measure of the local average of the original signal, we conclude that the signal observed from an MRI voxel is an average (up to scaling) over the voxel volume.

For DMRI, it was proved in [9] that the observed signal from a voxel is sensitive to the average value of the self-diffusion propagator over that voxel, rather than the values of the propagator at local points of the voxel. For this reason, it is also called the aggregate self-diffusion propagator. After some mathematical derivation, the aggregate propagator of a voxel, denoted by $V_j$, can be expressed in form of

$$P_{V_j}(\bar{R}, \Delta) = \frac{1}{N_j} \sum_k \rho_k \int_{C_k} P_r(r^2 + \bar{R}, \Delta) \, dr^2$$

$$= \sum_k f_k \bar{P}_k(\bar{R}, \Delta),$$

where $C_k$ and $\rho_k$ are the spatial domain and the effective density of water molecules of compartment $k$, respectively, $\frac{1}{N_j} \sum_k$ is the total number of effective molecules in voxel $V_j$, $f_k = \frac{\rho_k V_k}{\sum_i \rho_i V_i}$ ($V_k$ is the volume of compartment $k$ within the voxel $V_j$) and $\bar{P}_k(\bar{R}, \Delta)$ is the average propagator of compartment $k$ in the voxel.

In the derivation of the aggregate propagator, it is assumed that the densities of water molecules within compartments are uniform and time invariant. Eq. (10) explicitly shows the dependence of the aggregate self-diffusion propagator of a voxel, which is observable at the macroscopic scale, on the parameters of microstructure of white matters, which are not observables since they are quantities at the microscopic scale.

4. SIMULATION RESULTS

The proposed solution is capable of handling general geometry packs of white matter tracts. For preliminary experimental results presented in this section, we consider the hexagonal array of cylinders model as shown in Fig.1, which has been previously examined [4, 7]. The parameter setup in the simulation is given below. The diffusion time is set to 15 ms ($\Delta = 15 ms$). The dimension of the sample of the white matter model is set to 15x15x15 $\mu m$. We have found in our simulation that, for the above-mentioned simulation time, the values of the propagator solutions are equal to zero if the dimension goes beyond these ranges. The radius of the inner cylinders associated with the cytoplasm regions is set to $R_{in} = 3 \mu m$, and the axons total radius is set to $R_{out} = 4 \mu m$. The spatial distance between two adjacent axons centers is set to $L = 10 \mu m$. The self-diffusion coefficients for the cytoplasm, myelin, and extracellular regions are chosen to $D_c = 1.0 \mu m^2/ms$, $D_m = 0.05 \mu m^2/ms$, and $D_e = 1.9 \mu m^2/ms$, respectively. Also, the effective water molecules densities in these regions are $\rho_c = 0.85$, $\rho_m = 0.5$, and $\rho_e = 0.9$, respectively. The program was executed on a mobile Intel Core 2 Duo CPU with 2 MB RAM. For the above parameter setups, it took about one hour to run the simulation. The result of

Fig. 2. The simulated propagator results along the y-axis at five positions specified in Fig.1 after 15 ms.

the propagator, $P_r(r, \Delta = 15 ms)$, along the y-axis with five start points ($r'$) as shown in Fig. 1 after 15 ms, are illustrated in Fig. 2 as a function of the space. We see that the small value of the myelin self-diffusion coefficient plays a dominant role in the formation of the propagator profile across different compartments. The local computation of the self-diffusion propagator with the FEM solver along with the application of Eq. (10) provides the voxel aggregate self-diffusion profile. The results of such simulations for a single white matter tract are illustrated in Fig. 3. Panel c shows the low level of anisotropy in the myelin region which suggests the minimal contribution of this compartment in anisotropy of the aggre-
gate voxel propagator. Also, panel d illustrates the large degree of propagation in the direction perpendicular to the orientation of the tract. This is mostly due to the spacing among axons. The effect of the large value of the transverse propagator of the extracellular region is evident in reducing the level of anisotropy of the cytoplasm region in the voxel aggregate propagator.

The FEM solver can also quantify the propagator profiles under axons degenerative conditions such as demyelination as depicted in Figure 4. As shown in the figure, the profile becomes severely lateral toward the damaged region.

5. CONCLUSION AND FUTURE WORK

In this work, we presented a numerical simulation method based on the FEM technique for the solution of self-diffusion PDE within general microstructure of white matters. The quantification of the aggregate self-diffusion propagator at an MRI voxel was done analytically. As a future extension to this work, we would like to consider more general models of white matter tracts, by including more microscopic parameters, especially the effect of membrane partial permeability.

6. REFERENCES