Published in final edited form as:

Magn Reson Imaging. 2008 June ; 26(5): 694–702. doi:10.1016/j.mri.2008.01.025.

Mapping Spatio-Temporal Diffusion inside the Human Brain Using a Numerical Solution of the Diffusion Equation

Wang Zhan^{1,2}, Li Jiang³, Murray Loew³, and Yihong Yang^{1,*}

¹ Neuroimaging Research Branch, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD 21224, USA

² Department of Radiology, University of California San Francisco, VA Medical Center 114M, 4150 Clement Street, San Francisco, CA 94121, USA

³ Department of Electrical and Computer Engineering, George Washington University, 801 22nd St., N.W., Washington, DC 20052, USA

Abstract

Diffusion is an important mechanism for molecular transport in living biological tissues. Diffusion magnetic resonance imaging (dMRI) provides a unique probe to examine microscopic structures of the tissues *in vivo*, but current dMRI techniques usually ignore the spatio-temporal evolution process of the diffusive medium. In the present study, we demonstrate the feasibility to reveal the spatio-temporal diffusion process inside the human brain based on a numerical solution of the diffusion equation. Normal human subjects were scanned with a diffusion tensor imaging (DTI) technique on a 3-Tesla MRI scanner, and the diffusion tensor in each voxel was calculated from the DTI data. The diffusion equation, a partial-derivative description of Fick's Law for the diffusion process, was discretized into equivalent algebraic equations. A finite-difference method was employed to obtain the numerical solution of the diffusion equation with a Crank-Nicholson iteration scheme to enhance the numerical stability. By specifying boundary and initial conditions, the spatio-temporal evolution of the diffusion process inside the brain can be virtually reconstructed. Our results exhibit similar medium profiles and diffusion coefficients as those of light fluorescence dextrans measured in integrative optical imaging experiments. The proposed method highlights the feasibility to non-invasively estimate the macroscopic diffusive transport time for a molecule in a given region of the brain.

Keywords

diffusion equation; diffusion tensor imaging (DTI); numerical solution; spatio-temporal process

1. INTRODUCTION

Diffusion plays an essential role in delivering water, glucose, and oxygen from the vascular system to brain tissue as well as transporting informational substances between cells [1].

* Correspondence should be addressed to: Yihong Yang, Ph.D., Neuroimaging Research Branch, National Institute on Drug Abuse, NIH, 5500 Nathan Shock Dr. Room 383, Baltimore, MD 21224, Tel: 410-550-1440x334, Fax: 410-550-1441, Email: yihongyang@intr.nida.nih.gov.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Traditionally, the extracellular diffusion process at small scales (hundreds of micrometers) can be *invasively* measured by using radiotracers [2], real-time iontophoresis (RTI) [3], and integrative optical imaging (IOI) [4] techniques; there are great obstacles to obtaining diffusion images in a large-scale 3-D space. Alternatively, diffusion magnetic resonance imaging (dMRI) techniques have been established as promising noninvasive tools to investigate the brain tissues *in vivo* based on the fact that the measured water diffusion is sensitive to the tissue microscopic structures and can be mapped easily in the whole-brain [5–6]. Diffusion tensor imaging (DTI) has been used widely to assess white matter (WM) integrity and to delineate the neuronal pathways by inferring the anisotropy or major orientation of the diffusion tensor [7–9]. Beyond-tensor techniques, including high angular resolution diffusion imaging (HARDi) [10–11], diffusion spectrum imaging (DSI) [12], and Q-ball imaging (QBI) [13], have also been proposed to provide more reliable characterizations of complex white matter structures such as fiber crossings. A successful application of the dMRI methods in clinical field has been shown in [14].

Current dMRI techniques can, however, characterize only the tissue structures rather than the spatio-temporal evolution of the diffusion process, although the latter is tightly associated with the transport of molecules after penetrating the blood-brain barrier (BBB) [15]. Parker et al. [16] proposed a DTI-based fast marching tractography (FMT) technique using an artificial “front marching” process to recover the WM tracks. The FMT propagation is not a realistic diffusion process, however, because the propagation speed is an arbitrarily presumed parameter irrelevant to the actual diffusive transport. In general, existing dMRI approaches are unable to estimate the spatio-temporal course of a diffusion process in a given region, even though the structural connectivity in the region can be determined, leaving the dynamic information of the diffusion largely unknown on a macroscopic scale.

Based on the fact that the concentration (or density) fluctuation of an *ideal* diffusive medium is governed entirely by the diffusion equation (a partial-derivative description of Fick’s law [17]), a natural strategy to reveal the spatio-temporal diffusion process is to obtain the numerical solution of the diffusion equation [18]. Previous attempts to employ this strategy, however, have not been successful due to their limitations in practical implementations, such as the 2-D or partial-brain calculation domain requirements as stated in [18–20]. Xu et al. [21] recently employed an improved numerical method to diffusion-weighted Bloch-Torrey equation in simulating diffusion MRI measurements on biological tissues, yet not presented the macroscopic evolution of the diffusive concentration. In this paper, we present a method to map the 3-D spatio-temporal diffusion process in the entire brain based on the numerical solution of the diffusion equation, and then compare with an IOI study. There are two major procedures in the method: 1) DTI data are acquired on an entire brain and the diffusion tensor is calculated in each voxel; and 2) the 3-D diffusion equation is discretized in the calculation domain according to the MRI voxel array, and a finite-difference method (FDM) is implemented with improved stability to obtain the dynamic 3-D solution of the diffusion equation.

2. METHODS

2.1. Diffusion Tensor Imaging

Diffusion-weighted MRI experiments were performed on three healthy human subjects (2 male, 1 female, all right handed, aged 28–42) on a 3T Allegra scanner (Siemens Medical Solutions, Malvern, PA) equipped with 4.0 G/cm imaging gradients. Informed consent was obtained in accordance with the guidelines of the Institutional Review Board at the National Institute on Drug Abuse. Ear plugs were used to reduce noise exposure, and foam pads were applied to restrict head motion.

The diffusion-weighted images were acquired using a modified spin-echo, echo-planar imaging (EPI) pulse sequence with b value of 1000 s/mm^2 [22]. Thirty axial imaging slices of 4 mm thickness with 1 mm gap were prescribed to cover the entire brain with an orientation approximately parallel to the anterior-posterior commissure (AC-PC) line (see Fig. 1). The slices were consecutively numbered (Nos. 1–30) from inferior to superior. The in-plane matrix size was 128×128 with a FOV of $24 \times 24 \text{ cm}^2$. The sampling bandwidth was 1497 (Hz/Pixel), repetition time (TR) = 3.0 s and echo time (TE) = 98 ms. The diffusion-weighting gradients were sequentially applied in 12 independent directions described by vectors $\mathbf{E}_n = (g_x^n, g_y^n, g_z^n)$, ($n=1, 2, \dots, 12$), where g_x^n, g_y^n and g_z^n ($n=1, 2, \dots, 12$) are the normalized components proportional to the diffusion-sensitive gradients in the X-, Y- and Z- directions on the scanner coordinate system, respectively. An additional reference EPI image set without diffusion-weighting was also acquired as the reference images for DTI calculation. Each image acquisition was repeated four times to obtain an enhanced signal-to-noise ratio (SNR) of 45 and 120 for the diffusion-weighted and the reference images, respectively. A fast spin-echo sequence with TR = 0.7 s and TE = 25 ms was also used to acquire T1-weighted anatomical images with an in-plane matrix size of 256×256 , and these slices were acquired at the identical locations as those used in the EPI sequence.

The diffusion tensor was calculated in each voxel for the entire brain, according to the procedure described in [5] and [7]. Let S_n ($n=1, 2, \dots, 12$) be the diffusion-weighted image signal intensity corresponding to the diffusion encoding vector $\mathbf{E}_n$ ($n=1, 2, \dots, 12$), and S_0 be the associated reference signal intensity. The diffusion tensor $\mathbf{D}$ of this voxel can be estimated from the exponential relationship between the diffusion-weighted signal attenuation S_n/S_0 and the diffusion coefficient, such that

$$S_n/S_0 = \exp \left(- \sum_{i=x,y,z} \sum_{j=x,y,z} b_{ij}^n D_{ij} \right) \quad n=1, 2, \dots, 12 \quad (1)$$

where D_{ij} ($i, j = x, y, z$) represent the 9 elements of the tensor $\mathbf{D}$, whereas b_{ij} are the associated b factors given by $b_{ij}^n = g_i^n \cdot g_j^n \cdot b$ ($i, j = x, y, z$). Due to the symmetry of $\mathbf{D}$, the 12 equations in Eq. (1) can be combined to estimate the 6 independent elements of $\mathbf{D}$ using a minimum-mean-square-error (MMSE) method. The mean diffusivity $\langle \mathbf{D} \rangle$ and the fractional anisotropy (FA) indices were calculated on a voxel-by-voxel basis. If the data were noisy, more sophisticated diffusion tensor estimation methods other than MMSE could be applied to achieve a better performance based on the priori knowledge of diffusion tensor regulation [23] and/or the non-Gaussian distribution of the noise [24].

2.2. Diffusion Equation

The spatio-temporal behavior of a quasi steady-state diffusion process in an inhomogeneous environment is governed by the diffusion equation [25], i.e.,

$$\frac{\partial C}{\partial t} = \nabla \cdot \mathbf{D} \nabla C \quad (2)$$

where C is the concentration distribution of the diffusive medium in the 3-D space, and $\mathbf{D}$ is the local diffusion tensor. The vector of the concentration gradient is ∇C , whereas $\nabla \cdot$ denotes the divergence operation applied to the diffusion flux density $\mathbf{D} \nabla C$. Here, the first derivative of the concentration with respect to time can be approximated by a first-order backward difference, such that

$$\frac{\partial C}{\partial t} = \frac{C_{i,j,k}^{n+1} - C_{i,j,k}^n}{\delta t} + O(\delta t), \quad i,j,k=1,2,\dots,Nx(Ny,Nz) \quad (3)$$

where $C_{i,j,k}^n$ is the concentration at the node of discrete spatial coordinates (i, j, k) and temporal coordinate (n) . The δt denotes the discrete step length in time.

Similarly, the second-order derivatives of the concentration with respect to the spatial coordinates can be approximated by the second-order central difference estimations, such that

$$\begin{aligned} \frac{\partial^2 C}{\partial x^2} &= \frac{C_{i-1,j,k}^n - 2C_{i,j,k}^n + C_{i+1,j,k}^n}{(\delta x)^2} + O(\delta x^2) \\ \frac{\partial^2 C}{\partial y^2} &= \frac{C_{i,j-1,k}^n - 2C_{i,j,k}^n + C_{i,j+1,k}^n}{(\delta y)^2} + O(\delta y^2) \\ \frac{\partial^2 C}{\partial z^2} &= \frac{C_{i,j,k-1}^n - 2C_{i,j,k}^n + C_{i,j,k+1}^n}{(\delta z)^2} + O(\delta z^2) \end{aligned} \quad (4)$$

where δx , δy , and δz represent the discrete steps in x-, y-, and z- directions, respectively.

Incorporating the discrete approximations Eq. (3) and Eq. (4), the derivative form of the diffusion equation Eq. (2) can be equivalently expressed [26] in an algebraic form

$$\mathbf{C}^{n+1} - \mathbf{C}^n = \mathbf{A} \cdot \mathbf{C}^n \quad (5)$$

where $\mathbf{C}^n$ is a column vector of length $N_{xyz} = Nx \cdot Ny \cdot Nz$ that comprises all nodal concentrations $C_{i,j,k}^n$, $i,j,k=1,2,\dots,Nx(Ny,Nz)$ in the entire calculation domain at the time point (n) , while $\mathbf{A}$ is an N_{xyz} by N_{xyz} sparse matrix that incorporates the discretization parameters and all local diffusion tensor $\mathbf{D}$ data in the calculation domain. To obtain matrix $\mathbf{A}$, the boundary conditions on the surface of the brain and the calculation domain (see Figure 1) were specified in accordance with the following two rules, where the term “brain” includes regions of cerebrum, cerebellum and brain stem:

1. The concentration inside the calculation domain but outside the brain was set to zero, i.e.,

$$C_{i,j,k}^n \equiv 0, \quad 1 \leq i,j,k \leq Nx(Ny,Nz) \text{ and } (i,j,k) \notin \text{Brain}$$

1. The concentration Laplacian was set to zero at the boundaries of the calculation domain, i.e.,

$$\nabla^2 C_{i,j,k}^n \equiv 0, \quad i,j,k=1 \text{ or } i,j,k=Nx(Ny,Nz)$$

Note that the discrete mesh is identical to the EPI imaging matrix, i.e., each node in the calculation domain corresponds to the center of an image voxel. The above-defined boundary conditions are equivalent to these assumptions: 1) the brain is immersed in a solution of zero concentration, and 2) the diffusion at the boundaries of the calculation domain is balanced, i.e., no abrupt concentration fluctuation occurs at the domain boundaries. A mask of the brain was obtained by applying a skull-stripping program in Analysis of Functional NeuroImages (AFNI) (<http://afni.nimh.nih.gov/afni/>) onto the T1-weighted MRI images.

2.3. Crank-Nicholson Scheme

Given an initial condition $\mathbf{C}^0$, a time series of the numerical solution of the diffusion equation described above can be obtained from an iteration procedure suggested in Eq. (5), i.e.,

$$\mathbf{C}^{n+1} = (\mathbf{I} + \mathbf{A}) \cdot \mathbf{C}^n, n=0,1,2,3,\dots,Nt-1 \quad (6)$$

The numerical stability of this iteration, however, is generally poor according to the von-Neumann stability analysis [27]. For example, the numerical solutions of an ideal 1-D diffusion equation (e.g., in the x-direction) can be stable only if the temporal step length δt is impractically small, such that

$$\delta t < \frac{(\delta x)^2}{D_x} \quad (7)$$

where D_x is the diffusion coefficient in the corresponding direction. Violation of the stability condition would result in increasingly strong oscillatory artifacts in the numerical solution iterations.

We implemented a Crank-Nicholson scheme [27] to significantly enhance the stability of the numerical solution based on a 2-point averaging approximation in time, i.e.,

$$\mathbf{C}^n \approx \frac{1}{2} (\mathbf{C}^{n+1} + \mathbf{C}^n), \quad n=1,2,3,\dots,Nt \quad (8)$$

Incorporating Eq. (8) into Eq. (7), we have an improved iteration scheme, such that

$$\mathbf{C}^{n+1} = (\mathbf{I} - \mathbf{A})^{-1} \cdot (\mathbf{I} + \mathbf{A}) \cdot \mathbf{C}^n, \quad n=0,1,2,3,\dots,Nt-1 \quad (9)$$

It has been shown that this method is unconditionally stable in the diffusion equation solution for arbitrary parameters of $\delta x, \delta y, \delta z$ and δt [27].

The initial concentration $\mathbf{C}^0$ for the Crank-Nicholson iteration was specified by seed regions at the body of the corpus callosum (CC) or the corticospinal tract (CST), as shown in Fig. 1. The initial concentration was set to 1 inside the seed region, and 0 for all voxels outside. As illustrated in Fig. 2, the FA maps of the corresponding imaging axial slices No. 20 and No. 9 were used to locate the initial regions at the CC and CST white matter tracts, respectively. The initial seeds in CST were 4 clusters, each with a size of 2–4 voxels. The initial seeds in CC constituted a stick-like cluster of 8 voxels aligned along an A-P line.

3. RESULTS

Results from one subject (male, age=39) was chosen to present as follows due to high consistency of the results across the subjects. The spatio-temporal diffusion process reconstructed with the CC seed region is shown in Fig. 3 (a), (b), and (c) for the axial, sagittal and coronal view, respectively. The calculated concentration fluctuations are plotted at six successive diffusion time points of 0, 3, 6, 9, 12, and 15 minutes. Their instantaneous concentration distributions are illustrated by yellow contour curves overlaid on the corresponding T2-weighted brain images at the imaging slices crossing the seed region. The five closed contours denote the relative concentrations of 0.833, 0.667, 0.500, 0.333 and 0.167 with respect to the concurrent peak concentration at the center of the contours. The time courses of the absolute concentration values are given in Fig. 4.

It is shown in Fig. 3 that the diffusive concentration spreads to the entire brain volume as a function of the diffusion time, while the peak concentration stays at approximately the same place of the initial seed region. In the initial period of the diffusion process, the contour curves spread at a higher rate, while the spreading gradually slows down along with the diffusion time. The contour curves have an approximately isotropic shape, especially in the axial view. This effect can be explained by the Fick's law that diffusive flux is proportional to the local concentration gradient, and the fact that a stronger gradient occurs at the direction perpendicular

to the stick. Thus, the “stick-like cluster” will quickly evolve into a circular shaped profile in the early period of diffusion process. In sagittal and coronal views, the boundaries of the brain exhibit observable restrictive effects on the concentration distribution when the contour curves approximate the brain boundaries. The average radius ($\pm$ standard deviation) of the innermost contour (corresponding to the 0.833 relative concentration) is estimated as 4.69 ± 0.57 , 7.32 ± 0.41 , 9.37 ± 0.32 , 11.06 ± 0.30 , and 12.38 ± 0.29 mm at the diffusion time points of 3, 6, 9, 12, and 15 minutes, respectively. For the outermost contour (corresponding to the 0.167 relative concentration), the average radius ($\pm$ standard deviation) is measured as 23.44 ± 1.21 , 30.02 ± 1.14 , 35.62 ± 1.07 , 41.25 ± 1.23 , and 44.96 ± 1.46 (mm) at the same diffusion time points. The minor contour “bumps” in the coronal view are produced by small “holes” in the brain mask due to the regional lower intensities of ventricular CSF in T1-weighted images. We leave these mask holes unfilled because the ventricular CSF is anatomically connected to the outside CSF, which is presumed to be a zero- concentration solution in our calculations.

In Fig. 4, the time course of the absolute peak concentration at the seed region is shown as a black solid curve in the semi-logarithm plot with respect to the diffusion time. The peak concentration shows a decrease from one during the first 2 minutes of the diffusion process until reaching approximately 10^{-2} when the decay rate becomes moderately stable. A multiple exponential pattern of the peak concentration decay is clearly demonstrated. The dashed curves of color blue, magenta, red, and green represent the absolute concentration time courses measured at nearby off-seed voxels at distances of 5, 10, 15 and 20 mm from the seed region, respectively. The off-seed concentrations start from 0 and quickly increase and approach their maxima at 1~2 minutes. After that, the off-seed concentrations begin to decay at a similar rate as that of the corresponding seed region. Given a sufficiently large diffusion time, the concentrations of both on-seed and off-seed regions converge. It is also evident that the off-seed points closer to the seed region reach a relatively higher maximum concentration value at an earlier diffusion time.

The diffusion process calculated with the corticospinal tract (CST) seed region is shown in Fig. 5, using the same illustration conventions as in Fig. 3 (identical diffusion time points and the relative concentrations contours). In general, the contour curves in Fig. 5 demonstrate a spreading pattern similar to that in Fig. 2. One difference is that the CST seed region is composed of four separate initial seeds. These separate contour peaks completely merged into one bigger contour cluster during the first 3 minutes of diffusion. Compared to Fig. 3, the concentration contours move slightly faster in the superior direction. The measured average radius ($\pm$ standard deviation) of the innermost contours is 4.83 ± 1.21 , 7.49 ± 1.38 , 9.61 ± 1.53 , 11.32 ± 2.04 , and 12.24 ± 2.25 mm at the diffusion times of 3, 6, 9, 12, and 15 minutes, respectively. In comparison, the measured average radius ($\pm$ standard deviation) of the outmost contours is 21.57 ± 2.29 , 29.21 ± 2.31 , 34.59 ± 2.75 , 40.21 ± 3.20 , and 43.82 ± 3.71 mm for the diffusion times of 3, 6, 9, 12, and 15 minutes, respectively.

4. DISCUSSION

We have demonstrated that the spatio-temporal evolution of the diffusion process in the human brain can be revealed by a numerical solution of the diffusion equation, with a diffusion tensor field estimated from DTI. We note that the virtually reconstructed diffusion process shows an agreement with the diffusion process physically measured in a recent study of integrative optical imaging (IOI) on ejection of fluorescence agents into dilute agarose and in vivo rat neocortex [28]. Both techniques illustrate the quasi-isotropic Gaussian-shaped pattern of the diffusive media, spreading at comparable rates as characterized by the diffusion coefficients. Due to the limitation of EPI resolutions, the proposed method aims to map the dynamic process at the scale of several centimeters rather than the hundred microns as accessed in IOI. For a small dextran molecule (TR-dex3), the IOI-measured diffusion coefficient (D) is $(2.3 \pm 0.16) \times$

10^{-4} (mm²/s) [28], in comparison with the DTI-measured water mean diffusivity values of $(4.5 \pm 0.21) \times 10^{-4}$ (mm²/s) in gray matter. For larger molecules (dextran TR-dex70 and quantum dots QD655), the IOI-measured D values are $(0.47 \pm 0.06) \times 10^{-4}$ and $(0.18 \pm 0.05) \times 10^{-4}$ (mm²/s), respectively, substantially smaller than the DTI-measured diffusion coefficients of water in brain tissues. Consequently, the peak concentration in Fig. 4 decays mildly faster than the TR-dex3 but much faster than TR-dex70 or QD655 as depicted by the time course of fluorescence intensity profiles shown in [28]. The relatively slow diffusion estimation in IOI study can be explained by 1) TR-dex70 and QD655 have larger molecular weights (70,000 Mr and higher) resulting in slower random motions than free water, whereas TR-dex3 is much lighter (3,000 Mr), and 2) IOI measurements examine only diffusion in the extracellular space (ECS), in which the tortuosity of the ECS leads to an decrease of effective diffusion coefficient especially for larger size particles [15]. Given the previously estimated ECS width ranging from 10 to 60 nm in cortex, as well as the hydrodynamic diameters of TR-dex3, TR-dex70 and QD655 probes as 2.95, 14.1 and 35.4 nm, respectively, enhanced tortuosity ($\lambda=1.5-10.5$) is expected for ECS [28]. In comparison, the proposed DTI-based method provides the measurements for both intra- and extracellular spaces by using the water molecule as an endogenous probe. Our approach extends the capability of dMRI from the assessment of microstructures of biological tissues to the investigation of macroscopic spatio-temporal process of the diffusive medium, while preserving the noninvasive advantages over fluorescence methods.

The tight coupling between water diffusion processes and molecular transportation suggests that the proposed method may provide useful transportation information on molecules other than water. In an ideal diffusion in liquid water, for example, the molecular diffusion coefficients of soluble organic compounds in water can be established as a function of temperature, molecular weights, water viscosity, and the molecular solubility in water [29]. A recent diffusion tensor spectroscopy (DTS) study [30] has made it possible to directly map the diffusion tensor of metabolites in the brain, such as N-acetyl aspartate (NAA), creatine and phosphocreatine (tCr), and choline. In theory, the method proposed here can be implemented to solve the spatio-temporal diffusion process noninvasively for these molecules once the diffusion tensor field and the boundary conditions can be determined. Insufficient spatial resolution, however, remains a major challenge to the current DTS. For small water-resolvable molecules that possess water-like diffusion behaviors, e.g., glucose, the calculated process based on water diffusion tensor data can be a good approximation to their actual diffusive transport [18]. Based on the fact that in anisotropic diffusion media the diffusion process moves faster in the direction parallel to the fibers, a potential application of the proposed method is to provide fiber connectivity information by determining the direction of fastest diffusive propagation [19]. Furthermore, biological heat transfer processes follow a similar relationship as described by the diffusion equation [31], thus the present technique may also be used to virtually reconstruct internal heat transfer and temperature fluctuations in a noninvasive manner.

Effects of imperfect behaviors of real-world diffusion in living biological tissues, such as restricted diffusion, volume fraction, tortuosity, extracellular uptake process, and bulk flow, are not characterized in the original form of Fick's Law, but can be sufficiently modeled by including additional terms in the generalized diffusion equations as described in [15] and [23]. Thus, more comprehensive solutions for the realistic diffusion process can be obtained by applying our technique based on the extended diffusion equations without changing the framework of the proposed method, given that the associated parameters are estimated appropriately. In addition to the finite-difference method (FDM), the finite-element method (FEM) could be an alternative technique for numerical solution of the diffusion equation [31]. The FDM is typically more computationally efficient, whereas the FEM is good at handling complex geometry or arbitrary meshing structures [32]. Therefore, the FDM was a

reasonable choice in the present study, because a simple Cartesian meshing in accordance with the MRI imaging array was used.

As implied by Eq. (9), the solution of the diffusion equation is linearly related to the initial conditions if the diffusion parameters and the boundary conditions are specified. This fact indicates that the solution for an arbitrary initial condition can be equivalently obtained by summing up all the solutions corresponding to each of the initial voxels. This property resembles the superposition relationship of a typical time-invariant linear system. Thus, the solution corresponding to an individual seed voxel can be regarded as the point-spread function (PSF) of a linear system. The calculation for the diffusion process with arbitrary initial conditions (that could be space- and time-variant) can be implemented alternatively by a convolution process if all the involved point-spread functions are known.

For arbitrary seed voxel inside the human brain, the estimated PSF looks generally similar to the dynamic diffusion processes shown in Figs. 3–5. This is because the initial regions used for the calculation are composed of only a few seed points close to each other, and their point-spread functions emerge quickly once diffusion begins. The nearly circular shape of the concentration contours indicates that the diffusion propagation occurs in an approximately isotropic pattern, if the near boundary does not exert influence in a significantly anisotropic manner. The orientations of the white matter have a minor impact on the concentration contours especially when the diffusion time is relatively large. This can be partially explained by the blurring effects induced by the convolution of the PSFs.

5. CONCLUSIONS

The feasibility for mapping the 3-D spatio-temporal diffusion process inside the human brain has been demonstrated based on a numerical solution of the diffusion equation. The DTI technique was implemented to estimate the diffusion tensor field, and a finite-difference method using a Crank-Nicholson scheme was employed to model spatio-temporal evolution in the diffusive medium with enhanced numerical stability. This approach is likely to be useful to provide information on molecular transport mechanisms in biological tissues.

Acknowledgements

This research was supported by the Intramural Research Program of the NIH, the National Institute on Drug Abuse. The authors thank Drs. Elliot A. Stein and Clara Scholl at the National Institute on Drug Abuse for their helpful discussions.

References

1. Johnston, D.; Wu, MW. *Foundations of Cellular Neurophysiology*. Cambridge, MA: MIT Press; 1995.
2. Rall DP, Oppelt WW. Extracellular space of brain as determined by diffusion inulin from the ventricular system. *Life Sci* 1962;2:43–48.
3. Nicholson C, Phillips JM. Ion diffusion modified by tortuosity and volume fraction in the extracellular microenvironment of the rat cerebellum. *J Physiol (Lond)* 1981;321:225–257. [PubMed: 7338810]
4. Nicholson C, Tao L. Hindered diffusion of high molecular weight compounds in brain extracellular microenvironment measured with integrative optical imaging. *Biophys J* 1993;65:2277–2290. [PubMed: 7508761]
5. Basser PJ, Mattiello J, Le Bihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson* 1994;103:247–254.
6. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson Series B* 1996;111:209–219.
7. Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H. Diffusion tensor imaging: concepts and applications. *J Magn Reson Imaging* 2001;13:534–546. [PubMed: 11276097]

8. Xue R, Van Zijl PCM, Crain BJ, Solaiyappan M, Mori S. In vivo tree-dimensional reconstruction of rat brain axonal projections by diffusion tensor imaging. *Magn Reson Med* 1999;42:1123–1127. [PubMed: 10571934]
9. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. *Magn Reson Med* 2000;44:625–632. [PubMed: 11025519]
10. Frank LR. Characterization of anisotropy in high angular resolution diffusion weighted MRI. *Magn Reson Med* 2002;47:1083–1099. [PubMed: 12111955]
11. Zhan W, Gu H, Xu S, Silbersweig DA, Stern E, Yang Y. Circular spectrum mapping for intravoxel fiber structures based on high angular resolution apparent diffusion coefficients. *Magn Reson Med* 2003;49:1077–1088. [PubMed: 12768586]
12. Wedeen VJ, Hagmann P, Tseng WYI, Reese TG, Weisskoff RM. Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magn Reson Med* 2005;54:1377–1386. [PubMed: 16247738]
13. Tuch DS, Reese TG, Wiegell MR, Wedeen VJ. Diffusion MRI of complex neural architecture. *Neuron* 2003;40:885–895. [PubMed: 14659088]
14. Ross BD, Moffat BA, Lawrence TS, et al. Evaluation of Cancer Therapy Using Diffusion Magnetic Resonance Imaging. *Molecular Cancer Therapeutics* 2003;2:581–587. [PubMed: 12813138]
15. Nicholson C. Diffusion and related transport mechanisms in brain tissue. *Reports on Progress in Physics* 2001;64:815–884.
16. Parker GJM, Claudia AM, Kingshott W, Barker GJ. Estimating distributed anatomical connectivity using fast marching methods and diffusion tensor imaging. *IEEE Trans Med Imag* 2002;21:505–512.
17. Smith, WF. *Foundations of Materials Science and Engineering*. 3. McGraw-Hill; 2004.
18. McQueen, PG.; Jin, AJ.; Pierpaoli, C.; Basser, PJ. A finite element model of molecular diffusion in brain incorporation in vivo diffusion tensor MRI data. *Proc. The 4th Annual Meeting of the ISMRM*; New York. 1996. p. 193
19. Shimony, J.; Snyder, AZ.; Conturo, TE. Mapping Diffusive Spread in Nerve Fibers. *Proc. The 7th Annual meeting of the OHBM*; Brighton. 2001. p. 965
20. Gembris, D.; Schumacher, H.; Suter, D.; Zilles, K. A first-principles approach for diffusion tensor based fiber tracking. *Proc. The 7th Annual meeting of the OHBM*; Brighton. 2001. p. 123
21. Xu J, Does MD, Gore JC. Numerical study of water diffusion in biological tissues using an improved finite difference method. *Phys Med Biol* 2007;52:N111–N126. [PubMed: 17374905]
22. Mattiello J, Basser PJ, Le Bihan D. The b matrix in diffusion tensor echo-planar imaging. *Magn Reson Med* 2000;37:292–300. [PubMed: 9001155]
23. Fletcher PT, Joshi S. Riemannian geometry for the statistical analysis of diffusion tensor data. *Signal Processing* 2007;87:250–262.
24. Sijbers J, den Dekker AJ. Maximum likelihood estimation of signal amplitude and noise variance from MR data. *Magn Reson Med* 2004;51:586–594. [PubMed: 15004801]
25. Thomas DL, Lythgoe MF, Pell GS, Calamante F, Ordidge RJ. The measurement of diffusion and perfusion in biological systems using magnetic resonance imaging. *Phys Med Biol* 2000;45:R79–R138.
26. Leonard BP. Note on the von-Neumann stability of the explicit FTCS convective diffusion equation. *Appl Math Model* 1980;4:401–402.
27. Teukolsky SA. Stability of the iterated Crank-Nicholson method in numerical relativity. *Physical Review D* 2000;61:Art. No. 087501.
28. Thorne RG, Nicholson C. In vivo diffusion analysis with quantum dots and detrains predicts the width of brain extracellular space. *Proc National Academy of Sciences* 2006;103:5567–5572.
29. Delgado JMPQ. Molecular diffusion coefficients of organic compounds in water at different temperatures. *J Phase Equilib Diff* 2007;28:427–432.
30. Ellegood J, Hanstock GC, Beaulieu C. Diffusion tensor spectroscopy (DTS) of human brain. *Magn Reson Med* 2006;55:1–8. [PubMed: 16342152]
31. Chatter I, Adams RE. Finite-element thermal modeling of the human body under hyperthermia treatment for cancer. *Int J Comput Appl T* 1994;7:151–159.

32. Hundsdorfer, W.; Verwer, JG. Numerical Solutions of Time-Dependent Advection-Diffusion-Reaction Equations. Springer; 2003.

Fig. 1.

In DTI acquisitions, 30 axial slices (numbered ascending towards superior) were positioned upon the solid yellow box to cover the entire brain. Two boundary conditions were applied in the solution of the diffusion equation: (1) For the dashed yellow boundaries of the brain (including the cerebrum, cerebellum and brain stem), the concentration value was constant zero; and (2) For the solid yellow box (the boundaries of the calculation domain), the Laplacian of the concentration distribution was constant zero. Two initial seed regions in corpus callosum (CC) and corticospinal tract (CST) were placed in the slice No. 20 and No. 9, respectively.

Fig. 2.

The initial conditions for the diffusion equation calculation were specified by two seed regions, i.e., the body of corpus callosum (CC) and corticospinal tract (CST), as plotted in red on the background of the FA maps of the corresponding imaging slices No. 20 and No. 9, respectively. The initial region in CST was comprised of 4 separate small seeds, whereas the initial region in CC was intra-connected.

Fig. 3.

The calculated diffusion process with the initial region at the corpus callosum (CC). The concentration contours are plotted on the background of the corresponding T2-weighted images. Successive six diffusion time points at 0, 3, 6, 9, 12 and 15 minutes are used to illustrate the instant concentration distribution. The 5 outwards enclosed contour curves denote the

relative concentrations of 0.833, 0.667, 0.500, 0.333 and 0.167, respectively, with respect to the current peak concentration at the center of the contours.

- (a) Axial view of the diffusion process with the initial region at the CC.
- (b) Sagittal view of the diffusion process with the initial region at the CC.
- (c) Coronal view of the diffusion process with the initial region at the CC.

Fig. 4.

The time courses of the absolute diffusion concentrations. The black solid curve represents the absolute concentration changes measured at the seed region of the contour center shown in Fig. 3. Dashed curves in the color of blue, magenta, red and green represent the concentration changes measured at off-seed voxels with the distances of 5, 10, 15 and 20 (mm) to the seed region, respectively.

Fig. 5.

The calculated diffusion process with the initial region at the corticospinal tract (CST). The concentration contours are plotted on the background of the corresponding T2-weighted images. Successive six diffusion time points at 0, 3, 6, 9, 12 and 15 minutes are used to illustrate the instant concentration distribution. The outwards 5 enclosed contour curves denote the relative concentrations of 0.833, 0.667, 0.500, 0.333 and 0.167, respectively, with respect to the current peak concentration at the center of the contours.

(d) Axial view of the diffusion process with the initial region at the CST.

(e) Sagittal view of the diffusion process with the initial region at the CST.

(f) Coronal view of the diffusion process with the initial region at the CST.