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Optimization of a free water elimination two-compartment model for diffusion tensor imaging

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ABSTRACT

Diffusion tensor imaging is used to measure the diffusion of water in tissue. The diffusion properties carry information about the relative organization and structure of the underlying tissue. In the case of a single voxel containing both tissue and a fast diffusing component such as free water, a single diffusion tensor is no longer appropriate. A two-tensor free water elimination model has previously been proposed to correct for the case of volume mixing. Here, this model was implemented in a straightforward but novel manner without the use of spatial constraints. The optimal acquisition parameters were investigated through Monte Carlo simulations and human brain imaging studies. At a signal-to-noise ratio of 40 with 64 diffusion-weighted encoding images, the most accurate estimates of fast diffusion signal were obtained with two diffusion-weighted shells (*b*-value in s/mm^2 × number of directions) of 500 × 32 and 1500 × 32. The potential bias in fractional anisotropy induced by this two-compartment model was more than an order of magnitude less than the error of using the single diffusion tensor model in the presence of partial volume effects with free water. This strategy may be useful for characterizing the diffusion of tissues adjacent to cerebral spinal fluid (CSF), tissues affected by edema, and removing artifacts from blurring and ghosting of the CSF signal.

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Introduction

Diffusion weighted imaging (DWI) is a non-invasive magnetic resonance imaging (MRI) technique capable of measuring properties that describe the molecular displacements of water in biological tissues. Diffusion tensor imaging (DTI), an application of DWI, is used to quantify the three-dimensional movement of water with the assumption that simple Gaussian diffusion is a good descriptor of the water diffusion within a voxel (Basser et al., 1994). The most common application of DTI is brain imaging. In this application, the diffusion information is used to draw conclusions about brain architecture and microstructure. DTI has shown a great deal of utility in routine clinical use, as well as in brain research (Alexander et al., 2007).

The relative ease or resistance to diffusion along any single direction yields information about tissue structure and organization. Free water, which is characterized by uninhibited movement, displays isotropic diffusion and an apparent diffusion coefficient (ADC) of roughly 3×10^{-3} mm^2/s (Alexander et al., 2001). Meanwhile, more structured tissue such as white matter (WM) displays distinctly anisotropic diffusion. In the brain, free water exists as cerebral spinal fluid (CSF) in the ventricles and bordering the parenchyma of the brain. Gray matter (GM) is characterized by a lower degree of anisotropy than white matter, as well as more hindered diffusion than CSF. GM and WM both have an ADC of approximately 0.8×10^{-3} mm^2/s (Sener, 2001).

The free water elimination (FWE) model seeks to remove the deleterious effect of CSF partial volume effects on diffusion measurements. While the initial description of this two-compartment diffusion model was described using multiple *b*-values (Pierpaoli and Jones, 2004), more recent implementations estimated the fast diffusing component using only a single *b*-value acquisition with local spatial constraints on the model (Pasternak et al., 2009). This approach is ill-posed without these constraints and assumptions. The FWE model is solvable using multiple *b*-value measurements, yet few studies have applied these schemes for DTI (Pasternak et al., 2012a). None of these implementations have undertaken a rigorous assessment of the accuracy of the FWE fitting. Likewise, a determination of the best acquisition parameters has not been investigated. This work sets out to determine the accuracy and reliability of the fitting as well as what acquisition is best suited to fitting the FWE model.

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Recent work with more advanced diffusion models such as diffusion basis spectrum imaging (DBSI) (Wang et al., 2011), neurite orientation distribution diffusion imaging (NODDI) (Zhang et al., 2012), multiple fascicle models (Scherrer and Warfield, 2012), and combined hindered and restricted diffusion (CHARMED) imaging (Assaf et al., 2004) have included an isotropic free water component in their models. While there is growing interest in these complex models of diffusion for characterizing brain tissue microstructure, the acquisition times are long and computational demands for these models are high relative to clinical DTI protocols. However, the simple DTI model with an additional fast diffusion compartment may provide a rapid and simple model for estimating and removing fast diffusion effects in many DWI studies.

This work sets out to develop a relatively simple, yet novel, method for estimating the fast diffusing component and the underlying tissue parameters. The DWI protocol for the FWE DTI model was optimized through successive simulations that took into account different experimentally realistic factors in the optimization. All the while, clinical feasibility, as defined by a maximum of 70 DWI measurements, was maintained. Thus, the number of gradient directions was fixed at 64 and 6 $b = 0$ images, which corresponded to a minimum whole-brain imaging time of 6 min and 30 s at 2.5 mm isotropic resolution on our MRI system.

Materials and methods

In this section we introduce our two-compartment FWE DTI model and describe two independent, but complimentary methods to solve the FWE DTI model. The first method is a weighted linear least squares method using a brute force region contraction approach to solve for the free water component. Although not as robust or accurate as our second approach, this method has the advantage of being computationally efficient and serves well as either a stand-alone estimate or the initial guess for non-linear search methods. The second model is a modified Newton's method approach (Koay et al., 2006) with a dynamically adjusted dampening parameter to control step size and direction.

Free water elimination model

Errors arise in DTI when the tissue within a single voxel is a mixture of multiple tissue types resulting in partial volume effects (Alexander et al., 2001). A two-compartment model has been used previously to estimate the diffusion characteristics of brain tissue in the presence of the partial volume effect with a fast diffusing component such as free water (Pierpaoli and Jones, 2004). The tissue compartment, which could be white or gray matter, is modeled as a tensor just as in DTI. The fast diffusing compartment is modeled as having isotropic diffusion with a fixed diffusivity equal to the theoretical expected diffusivity of unhindered water at body temperature. The relative signal contribution of the fast diffusing component is described by f, a scalar volume fraction. The free water elimination DTI signal model is described by

$$S_i = S_0\left[(1-f)\ \exp\left(-b_i g_i^T D_{tissue} g_i\right) + f\ \exp\left(-bD_{iso}\right)\right] \quad (1)$$

where, S_i and S_0 are the signal from the i-th diffusion and non-diffusion weighted measurements, respectively, $D_{iso} = 3 \times 10^{-3}$ mm^2/s is the free water diffusivity, D_{tissue} is the tissue diffusion tensor, b_i and g_i are the diffusion-weighting amplitude (in mm^2/s) and unit gradient encoding vector, respectively. This two-compartment model is attractive because of its similarity to DTI. The tissue signal compartment results in the same scalar metrics of DTI. The addition of the isotropic compartment is intended to compensate for confounding partial volume effects from CSF and also edema. This will improve the ability to characterize tissue parenchyma microstructure in voxels with partial volume averaging and multiple diffusion components.

Fitting procedures

Initially the tissue compartment tensor was fit using a weighted linear least squares (WLLS) region contraction approach. This was accomplished by recasting Eq. (1) as

$$\frac{S_i - S_0 f\ \exp\left(-b_i D_{iso}\right)}{(1-f)} = S_0\ \exp\left(-b_i g_i^T D_{tissue} g_i\right) \quad (2)$$

and solving for D_{tissue} using fixed f values. A weighted linear least squares (WLLS) estimation was carried out to estimate the diffusion tensor, D_{tissue} (Koay et al., 2006), for each fixed value of f and $D_{iso} = 3 \times 10^{-3}$ mm^2/s was set as a constant. The WLLS result was a diffusion tensor that best fit the measured data for a corresponding volume fraction. This procedure was carried out for a range of f between 0 and 1.

Once a (f, D_{tissue}) pair was calculated, the WLLS objective function

$$F_{\mathrm{WLLS}}(\gamma) = \frac{1}{2}\sum_{i=1}^{m} \omega_i^2 \left(y_i - \sum_{j=1}^{7} W_{ij}\gamma_j\right)^2 \quad (3)$$

was used to judge which (f, D_{tissue}) best fit the measured data. Here $i = 1,\ldots, m$, where $m =$ the number of images obtained, $s_i =$ the measured signal including noise, $\omega_i =$ the weights for each s_i, and y_i and γ_i are defined differently for DTI and FWE as described below. The weights were set equal to the signal magnitude ($\omega_i = s_i$). This technique emphasizes acquisitions with higher signal that result from lower b-value shells and gradient directions aligned with lower diffusion distances. The diffusion encoding matrix is

$$W = \begin{pmatrix} 1 & -b_1 g_{1x}^2 & -b_1 g_{1y}^2 & -b_1 g_{1z}^2 & -b_1 g_{1x} g_{1y} & -b_1 g_{1y} g_{1z} & -b_1 g_{1x} g_{1z} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & -b_m g_{mx}^2 & -b_m g_{my}^2 & -b_m g_{my}^2 & -b_m g_{mx} g_{my} & -b_m g_{my} g_{mz} & -b_m g_{mx} g_{mz} \end{pmatrix}.$$

Smaller objective function values indicate a better fit. Thus, by systematically fitting diffusion tensors to many volume fractions and then evaluating which (f, D_{tissue}) minimizes the objective function, it is possible to determine which isotropic volume fraction and tissue compartment tensor best represents the measured data.

To identify the optimum f would require many small steps in presumed f from zero to one, which would be cumbersome and time consuming. Howõever, the WLLS routine was further modified so that multiple volume fractions could be fit simultaneously. Furthermore, it was seen that the total number of fittings was greatly reduced by systematically refining the size of the Δf step.

This was implemented by simultaneously solving for the diffusion tensor with multiple f-values. Initially, a coarse Δf step size of 0.1 was used over the range from zero to one. The objective function for each of these initial eleven (f, D_{tissue}) pairs was evaluated with the lowest value being passed on as the best estimate. The next iteration used steps of 0.01 over the range of the previous best estimate $\pm .05$. A third step reduced the step size by another order of magnitude.

The method did not display any drop off in estimation accuracy compared to the use of an initial step size of 0.001. However, the series of refined steps reduced the number of WLLS estimations from 1001 to 31 per voxel.

We investigated the search space of f by comparing the value of the objective function across the entire range of f values from $f = 0$ to $f = 1$ using an increment of 0.001. This was performed independently for 50 voxels from an in vivo data set with an SNR of 36. The voxels were chosen to represent a wide range of different f values, as determined by the WLLS procedure described above, as well as widespread anatomical locations within the brain. The objective function was manually inspected for the position of the global minimum compared to local minima.

The WLLS routines for DTI and FWE-DTI are similar, as both share the same objective function with some modification. There are two