Acquisition Parameters for Diffusion Tensor Imaging to Emphasize Fractional Anisotropy: Phantom Study

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Diffusion tensor imaging (DTI) is a magnetic resonance (MR) imaging technique that has attracted attention in recent years for applications such as nerve fiber tracking, neurography, and tumor detection. In DTI measurements, 2 motion-probing gradient (MPG) pulses are applied to evaluate water diffusion. In DTI for nerve fiber tracking, acquisition parameters, such as strength, duration, and separation of MPGs, influence the MR signal.

In this study, we set acquisition parameters in DTI to emphasize fractional anisotropy to clarify the direction of nerve fibers. We performed Monte Carlo simulations of restricted diffusion in a cylinder model and phantom measurements with capillary plates to examine the relationship between the acquisition parameters in DTI and the size of restricted structures, particularly their diameter and length, which we will refer to as “compartment size.”

We confirmed that normalized signal intensities in DTI measurements depend on diffusion time, which, in turn, depends on the separation and duration of the MPG, and they decrease with increase in compartment size. Furthermore, our simulation and phantom results suggest that use of a longer diffusion time effectively emphasizes fractional anisotropy to clarify the direction of nerve fibers.

Keywords: acquisition parameters, diffusion tensor imaging, diffusion-weighted imaging, fractional anisotropy, Monte Carlo simulation

Introduction

Diffusion-weighted imaging (DWI) is a magnetic resonance (MR) imaging technique used in such applications as diagnosis of acute stroke,1,2 tumor detection,3 and functional neuroimaging.4 Considerable progress in DWI in recent years has included the development of diffusion tensor (DTI) and q-space imaging (QSI).5–9

In general, DWI measurements use Stejskal-Tanner’s pulsed gradient spin-echo sequence (Fig. 1), which employs 2 motion-probing gradient (MPG) pulses to assess water diffusion.10 In DWI measurements, the diffusion-related MR signal, $S$, can be expressed as a monoexponential function as:

$$S = S_0 \exp (-bD),$$

where $S_0$ is the MR signal when the MPG is not applied, $b$ is a measure of diffusion weighting strength, and $D$ is the diffusion coefficient of water. Eq. (1) assumes that nothing restricts water diffusion. Therefore, when the molecular motion of water is unrestricted and the molecules diffuse freely in biological objects, such as cerebrospinal fluid, the diffusion coefficient of water can be determined using 2 b-values, such as $b = 0$ and $b = 1000$ s/mm$^2$.

However, microscopic flows, such as cerebral

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blood flow, cannot be distinguished from water diffusion, so the diffusion coefficient measured by DWI differs from the actual coefficient and is termed the apparent diffusion coefficient (ADC).

In practice, various microstructures, such as cell membranes and nuclei, also restrict water diffusion and counteract diffusion-related MR signal decay. Therefore, restricted diffusion imaging is used to detect diseased brain tissue, such as ischemia, and has been used to measure the direction of nerve fibers in DTI. The contribution of restricted diffusion depends on the strength ($g^2$) and duration ($d^3$) of the MPG and the separation of MPGs ($\delta$) (Fig. 1). In other words, the signal intensity, $S$, of DWI depends, in a complicated way, on the acquisition parameters mentioned above. However, the influence of those parameters on signal intensity has often been discussed in terms of $b$-value, defined as:

$$b = \gamma^2 g^2 \delta^2 \left( \Delta - \frac{\delta}{3} \right),$$

where $\gamma$ is the gyromagnetic ratio of protons. Note that the acquisition parameters are not always identical, even if $b$-values are. In addition, diffusion time and q-value are important in the choosing the parameters when discussing restricted diffusion. Diffusion time, $t_d$, is expressed as:

$$t_d = \Delta - \frac{\delta}{3},$$

and q-value is defined in QSI as:

$$q = \frac{\gamma g \delta}{2\pi}.$$  

Equations (2), (3), and (4) show that the q-value is in inverse proportion to the square root of the diffusion time when the b-value is fixed. Tanner proposed diffusion-weighted imaging with a stimulated-echo (STE) sequence (Fig. 2), in which a long separation can be selected with smaller penalty of the signal-to-noise ratio (SNR) than in a standard spin-echo sequence. Use of this sequence allows selection of a wide range of settings as acquisition parameters in DTI measurements.

In DTI, the diffusion tensor is frequently estimated by fitting ADCs to a 3-dimensional (3D) ellipsoid. The length of the longest, middle, and shortest axes, called eigenvalues $\lambda_1$, $\lambda_2$, and $\lambda_3$, their orientations, called eigenvectors $v_1$, $v_2$, and $v_3$, and fractional anisotropy (FA), expressed as

$$FA = \sqrt{\frac{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}},$$

are frequently used as the properties of the 3D ellipsoid model in the diffusion tensor.

We performed simulations and phantom studies of restricted diffusion to elucidate the relationship between signal and acquisition parameters in DWI, and we discuss parameters that can be used to emphasize FA and clarify the direction of nerve fibers in DTI measurements.

**Materials and Methods**

In the human brain, myelinated axons are cylindrical and much longer than they are across. On the other hand, it has been reported recently that a biexponential model can be used to describe diffusion-related MR signal decay in the brain, and that 80% of changes in the ADC are due to changes in the intracellular space fraction and 20%, to the extracellular space fraction. Therefore, in our phantom studies, we used glass plates with capillaries to model the intra- or extracellular space fraction in the myelinated axon of a neuron and water exchanges across cell membranes as a cylindrical model. In our simulation experiments, we used the cylindrical restricted diffusion compartment model to simulate the capillary plates shown in Fig. 3. We used the cylindrical model to confirm restricted diffusion with the acquisition parameters used in clinical scanners, although previous simulations of restricted diffusion have used theoretical calculations with a short gradient condition and simulations with a model of white matter based on a composite hindered and restricted model of diffusion (CHARMED).

A. Simulation studies

Our cylindrical model was assumed to be bounded by walls that could not transmit water. The diameter, $d$, and length, $l$, of the cylinder (Fig. 3) are referred to as “compartment size.” Here, the cylinder is assumed to be much longer than it is across,
that is, \( l \gg d \). When the compartment size is not constant, MR signal intensity is expressed as the sum of the signal intensities for each compartment size. In the simulation, we applied 6 MPGs along the directions \((1, 1, 0)\), \((-1, 1, 0)\), \((1, 0, 1)\), \((1, 0, -1)\), \((0, 1, 1)\), and \((0, -1, 1)\) as a minimum number of directions to calculate the diffusion tensor. The directions could not always be optimized to the measurement object but were conveniently selected in the simulation model and phantom. In addition, we applied 3 more MPGs in the X, Y, and Z directions to confirm the relationship between signal intensity and acquisition parameters but not to calculate the diffusion tensor. The motion and magnetic moments of the protons were simulated using the Monte Carlo method. The simulation procedure was:

1. \( N \) protons with their magnetic moments were assumed to be present in the compartment.
2. The initial position of each proton in the compartment was generated by uniform random numbers.
3. The position of each proton was updated by normal random numbers at a time interval \( t \), where the mean of the 3D normal random numbers was zero and the covariance matrix, \( C \), was Eq. (6) and followed the Einstein-Smoluchowski formula.

\[
C = \begin{pmatrix}
2D\tau & 0 & 0 \\
0 & 2D\tau & 0 \\
0 & 0 & 2D\tau
\end{pmatrix}
\]

4. When an MPG was applied, the phase shift of each magnetization was updated according to Bloch’s equations.
5. Steps 3 and 4 were iterated until the MR signals were sampled.
6. We calculated the sampled MR signal intensity by adding all the magnetic moments.

In this simulation, the MR signal intensities were normalized as:

\[
E = S/S_0
\]

Additionally, because the Einstein-Smoluchowski formula expresses the existence probability of the particles taking into consideration the thermal motion, intermolecular force, and collision of particles, it is unnecessary to consider the collision and overlap of the particles in Step 3.

To examine the influence of acquisition parameters and compartment size on the FA of the diffusion tensor in DTI measurements, we performed simulations using varying q-values, i.e., diffusion times, keeping the b-value at 1000 s/mm\(^2\). In this simulation, we assumed that \( d = 6, 10, 20, 50, \) and \( 100 \) \( \mu \text{m} \) and \( l = 2 \) mm, according to the properties of the capillaries in the phantom studies described below. In addition, we set the amplitude of the MPG as a maximum gradient of about 42.73 mT/m in each direction and calculated the duration and separation of MPGs using Eqs. (2) and (4). Based on these simulations, we calculated the diffusion tensor and its FA to determine the relationship between FA and acquisition parameters or compartment size. In these simulations, we used a diffusion coefficient of \( D = 2.27 \times 10^{-3} \) mm\(^2\)/s because that is the diffusion coefficient of water at a temperature of 25°C.\(^\text{20}\) We used a time interval of \( \tau = 100 \mu\text{s} \) and set the number of protons at \( N = 1.0 \times 10^6 \) to provide a high degree of accuracy for the simulation, so that the error between the simulation result and corresponding theoretical value obtained from Eqs. (1) and (7) would remain less than 0.1%. We generated the simulation codes with Visual C++ 2005 (Microsoft Corporation, Redmond, WA, USA) and used the Intel Math Kernel Library (Intel Corporation, Santa Clara, CA, USA) as the random number generator.

B. Phantom studies

We used 5 glass plates with capillaries of 6, 10, 20, 50, and 100 \( \mu \text{m} \) in diameter (Hamamatsu Photonics K.K., Hamamatsu, Japan) (Fig. 4) in the phantom studies to investigate the relationship between FA and compartment size or acquisition parameters in DTI. We arranged the centers of the capillaries in a hexagonal lattice, and each capillary plate had an aperture ratio of about 60%. We filled each capillary with purified water by cleaning the capillary plates with an ultrasonic washing machine, saturating them with purified water and vibrating them to remove air from the capillaries. We then built the phantom without removing the plates from the water (Fig. 4).

We performed DTI measurements with an EXCELART Vantage 1.5-tesla MR imaging scanner.
Fig. 4. Glass plates with capillaries 6, 10, 20, 50, and 100 μm in diameter, which were filled with purified water. These capillaries are captured by optical microscope with 50-times power.

(Toshiba Medical Systems Corporation, Otawara, Japan) and used a pulsed gradient stimulated-echo (PGSTE) sequence (Fig. 2) because it allows a long diffusion time with good SNR. In this study, we compared SNRs in imaging for each diffusion time, although the SNR in imaging is less than that in the spectrum. We performed the DTI measurements in this sequence using repetition time (TR), 2000 ms; field of view (FOV), 64×64 mm; 2-mm slice thickness; and image size, 64×64 pixels. For the phantom studies, we applied 6 MPGs along the same directions as in the simulation experiments. We set the amplitude of the MPG to the maximum gradient, about 42.73 mT/m in each direction, b-value to 1000 s/mm², and q-value to 10, 15, 20, 25, and 30/mm. We calculated the duration and separation of MPGs from the parameters mentioned and from Eqs. (2), (3), and (4). In addition, we set the diffusion time in each q-value setting to 253.31 ms (for 10/mm), 112.93 ms (for 15/mm), 63.33 ms (for 20/mm), 40.54 ms (for 25/mm), and 28.15 ms (for 30/mm). Table shows the acquisition parameter settings, where echo time (TE) and mixing time (TM) were minimized for each q-value.

Results

A. Simulation studies

Figure 5A and B shows the normalized signal intensities that resulted from the simulations as a function of q-value with a fixed b-value of 1000 s/mm². Figure 5C shows the FA calculated from the result of each simulation. The normalized signal intensities with an MPG in the X direction (Fig. 5A) are larger than those in the Z direction (Fig. 5B) for all diameters of capillaries and all q-values, and the normalized intensities in the Z direction are close to 0.10 (Fig. 5B), which is the value in free diffusion. On the other hand, Fig. 5A shows that the normalized signal intensity changes significantly as the diameter of the capillary varies. Although the normalized signal intensity changes little for q-values in the capillary plates with diameters of 6, 10, and 100 μm, it changes significantly for q-values in those with 20 and 50 μm. These changes in the normalized signal intensity appear as changes in FAs in Fig. 5C. Furthermore, for all the capillary diameters, the FAs increased when the acquisition parameters were set to a long diffusion time (i.e., small q-value).

B. Phantom studies

Figure 6 shows the FA maps calculated from the results of DTI measurements, and Fig. 7 shows the means and standard deviations of the FAs in a capillary region of 10×10 pixels indicated by a square region at the top left row in Fig. 6. The lines in Fig. 7 show the simulation results of FAs for various q-values with compartment sizes of d=6, 10, 20, 50, and 100 μm and l=2 mm.

Figures 6 and 7 demonstrate good agreement between phantom measurements and simulation results. In particular, phantom study and simulation results were almost identical for capillaries 6,
Fig. 5. Simulation results as a function of q-value (i.e., diffusion time) with b-value set at 1000 s/mm². Resulting normalized signal intensities simulated with motion-probing gradients (MPGs) along the X direction (A) and Z direction (B). Calculated fractional anisotropy (FA) for each q-value (i.e., diffusion time) (C).

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10, and 20 μm in diameter. However, the results were inconsistent for capillary plates with diameters of 50 and 100 μm. Furthermore, the increase of FAs by prolonging diffusion time, i.e., decreasing q-value, for all conditions was identical to the results in simulation studies.

As Fig. 7 shows, errors in the FAs between the phantom and simulation results were greater for \( d = 50 \) and 100 μm than for 6, 10, and 20 μm. In practice, the normalized signal intensities for MPGs in every direction included errors caused by various effects, such as eddy current, in every diameter considered. On the other hand, although the normalized signal intensities for MPGs applied along the directions (1, 1, 0) and (−1, 1, 0) rarely decayed in the case of small diameters, they decayed similarly to the MPGs applied in the other directions for large diameters. Thus, the SNRs of the normalized signal intensities were impaired more for large diameters than small. Therefore, more errors occurred for large diameters than small when the diffusion tensors and FAs were calculated. Additionally, because noise increased the difference between the directions for the normalized signal intensities, the FAs were estimated to be larger than those in the simulations for large diameters. This may result in relatively larger errors in the FAs between the phantom and the simulation results for \( d = 50 \) and 100 μm. On the other hand, signals from outside the capillary plates may be mixed depending on slice profile. However, because we carefully adjusted slice positions and errors in the FAs between the phantom and the simulation results were less than 2% for \( d = 6 \) and 10 μm, it was reasonable to consider that there were few signals from outside the capillary plates in all images.

Discussion

In restricted diffusion, the walls reflect a greater fraction of protons when duration and separation of the MPG are prolonged or compartment size is reduced. Therefore, even if identical b-values are selected, prolonged duration and separation may influence DTI signal intensity. However, few protons seem to reflect on the walls when duration and separation are shortened and compartment size increased. In the case of DTI measurements with a fixed b-value, because a reduction of q-value implies prolonged separation, i.e., diffusion time, the discussion about compartment size is consistent with the results shown in Fig. 5. Our results and the discussion above agree with the those of Tanner’s and Norris’s groups. In the cylindrical model with \( l \gg d \), normalized signal intensities along \( v_i \) are close...
Fig. 6. Fractional anisotropy (FA) maps calculated from the results of diffusion tensor imaging (DTI) measurements for each q-value (i.e., diffusion time) with a fixed b-value of 1000 s/mm².

Fig. 7. The mean and standard deviation (SD) of calculated fractional anisotropy (FA) for each q-value (i.e., diffusion time) with a fixed b-value of 1000 s/mm². The lines indicate the simulation results.

to those of free diffusion (Fig. 5B). However, normalized signal intensities along \( v_2 \) or \( v_3 \) are changed by the diameter \( d \) of the cylinder or the q-value settings in DTI measurements (Fig. 5A). FA reflects the difference between the ADC along \( v_1 \) and those along \( v_2 \) or \( v_3 \) according to Eq. (5), because ADCs along \( v_1, v_2, \) and \( v_3 \) correspond to \( l_1, l_2, \) and \( l_3 \). In addition, ADCs along \( v_1, v_2 \) and \( v_3 \) are proportional to the natural logarithmic functions of the normalized signal intensities along \( v_1, v_2, \) and \( v_3 \) according to Eqs. (1) and (7). On the other hand, selecting a small q-value and fixed b-value reduces the signal decay caused by diffusion and improves the SNR of normalized signal intensities, including those along \( v_2 \) or \( v_3 \). Therefore, selecting a small q-value setting and fixed b-value improves the accuracy for diffusion tensor, \( \lambda_1, \lambda_2, \lambda_3 \), and FA obtained from the normalized signal intensities.

Recently, axon diameters ranging from 0 to 20 μm have been reported in formalin-fixed tissue samples of porcine sciatic and optic nerves and porcine spinal cord. Assuming similar diameters of nerve fibers from human brain tissue and porcine nerves, fiber distribution is expected to range from...
0.9 to 1.0 with a diffusion time of 253.31 ms, i.e., a q-value of 10/mm, although the FAs of nerve fibers are expected to range from 0.7 to 1.0 with a diffusion time of 28.15 ms, i.e., a q-value of 30/mm. Therefore, long diffusion times, or small q-values, lead to DTI measurements with emphasized FA for the human brain when the b-value is fixed. In addition, although use of long diffusion time facilitates discrimination of FAs when cylinder diameter is less than 20 μm, such discrimination is difficult when the diameter exceeds 50 μm (Fig. 7). Similarly, use of a short diffusion time aids FA discrimination when cylinder diameter exceeds 50 μm, but it is difficult to discriminate when cylinder diameter is less than 20 μm. Long diffusion time settings are also expected to improve the SNR for FA in DTI measurements when a stimulated-echo sequence is used.

In this study, we employed a restricted diffusion phantom with fixed anisotropy and direction. However, in some areas of the human brain, such as a border region between white and gray matter, the tissue fraction with anisotropic diffusion is less than that in white matter. In these regions, we expect that selection of a longer diffusion time, as mentioned, will be effective in emphasizing FA and clarifying the direction of nerve fibers. Longitudinal relaxation in the stimulated-echo sequence causes the signal decay in mixing time, and the signal intensity obtained with diffusion time of 253.31 ms is estimated at about 6% less than that for 28.15 ms, considering a longitudinal relaxation time (T1) of 510 ms and transverse relaxation time (T2) of 67 ms in the white matter of human brain.28 Therefore, we can measure the human brain by stimulated-echo sequence with long diffusion time, which suggests that DTI measurements with long diffusion time can be applied in clinical settings using stimulated-echo sequence. In addition, in regions of the human brain where fibers cross and FA decreases, measurement of the different directions of emphasized FAs does not improve despite their identification using long diffusion time settings for each fiber. Therefore, setting long diffusion times does not seem to clarify the direction of nerve fibers. However, improved short pulse condition using Q-ball imaging29 and diffusion spectrum imaging30 with long diffusion time is believed to emphasize the FA in each fiber and clarify the directions in crossing fiber bundles.

In this study, we did not address b-value settings and different MPG directions, but other studies have reported results on the b-value in DTI or DWI measurements and selecting MPG directions.31–33 Because emphasis of FA can improve angular resolution and SNR, combining the diffusion time settings described above with these strategies for b-value and MPG directions will enable highly accurate measurement of the FA-emphasized diffusion tensor. Furthermore, measuring using a sequence with eddy current reduction, such as the bipolar longitudinal eddy current delay pulse sequence proposed by Bar-Shir, seems an effective way to improve SNR.34 This sequence is expected to reduce signal decay caused by long diffusion time and distortion caused by eddy currents.

Conclusion

In this study, we conducted simulations and phantom studies to reveal the relationship between normalized signal intensities of DTI or FA and acquisition parameters or compartment size. Based on our results, we propose acquisition parameter settings that will emphasize FA and clarify the direction of nerve fibers. In particular, we recommend longer diffusion time, which may be applicable as well in neurography and cancer detection.

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