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Rapid measurement of three-dimensional diffusion tensor

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In this article, the authors demonstrate a rapid NMR method to measure a full three-dimensional diffusion tensor. This method is based on a multiple modulation multiple echo sequence and utilizes static and pulsed magnetic field gradients to measure diffusion along multiple directions simultaneously. The pulse sequence was optimized using a well-known linear inversion metric (condition number) and successfully tested on both isotropic (water) and anisotropic (asparagus) diffusion systems. © *2007 American Institute of Physics*. [DOI: 10.1063/1.2717188]

I. INTRODUCTION

Diffusion is a three-dimensional process. In bulk fluids at a given temperature, diffusion can be fully characterized by a single scalar, the diffusion coefficient D. In the presence of anisotropic motion due to restricting or hindering boundaries in a medium such as liquid crystals, biological tissues, or geological sediments, a symmetric 3×3 diffusion tensor is required in general to describe molecular mobility along different directions and its correlation between them.[1–3]

The principle of NMR detection of the diffusion process lies in the fact that the signal decay due to translational motion of spins in the presence of magnetic field gradient can be measured along the gradient direction. Standard methods of diffusion tensor measurement generally require at least six independent scans with noncollinear field gradient directions and often variable field gradient strength to determine the full diffusion tensor.[4] For time-sensitive processes, it may be useful to obtain the full diffusion tensor in a minimal scan time.

Here, we demonstrate a rapid method based on the multiple modulation multiple echo (MMME) sequence,[5] which generates a train of spin echoes with different diffusion weighting in both direction and magnitude. This provides sufficient measurements to determine six diffusion tensor components simultaneously. This work is inspired by the successful measurement of two-dimensional (2D) diffusion tensor[6,7] and three-dimensional (3D) flow vector[8] in very few scans. All of these varieties employ a static gradient along one direction and pulsed magnetic field gradients along other directions.

The attenuation of the spin magnetization due to anisotropic diffusion depends on the diffusion tensor (D_{ij}) and corresponding diffusion weighting matrix (b_{ij}) according to the following matrix equation:[7]

$$A = BD, \tag{1}$$

where $A=-\ln(M/M_0)$ is the measured signal attenuation, B is the diffusion weighting matrix for one echo given by $B=(b_{xx}, b_{yy}, b_{zz}, 2b_{xy}, 2b_{yz}, 2b_{xz})$, and $D=(D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{yz}, D_{xz})$ is the diffusion tensor in a vector form. The diffusion weighting factors b_{ij} are calculated from the gradient wave forms $g(t)$[4]. M and M_0 refer to the spin magnetization with and without diffusion weighting, respectively.

The advantage of the MMME sequence is that a train of well-separated spin echoes can be generated with different diffusion weighting using a few rf pulses [$n=(3^{N-1}-1)/2$, where n and N are the number of echoes and rf pulses, respectively]. Detailed descriptions and various applications of the MMME sequence can be found elsewhere.[5–10] With optimized gradient pulses, one can obtain $A(1\times n)$ and $B(6\times n)$ sufficient (when $n\geqslant 6$) to determine a full diffusion tensor (D) in only two scans: a fully encoded scan and an equally timed reference scan.

II. OPTIMIZATION

Figure 1 and Table I describe a MMME sequence with corresponding gradient values which is capable of determining six diffusion components. Thirteen echoes are generated with four rf pulses under a constant gradient field along one direction (z), and pulsed gradients are applied for efficient sensitization of the diffusion tensor along the other directions (x and y). The main difference of the above sequence from previous 2D diffusion measurements[6,7] is the insertion of a gradient pulse in period "1" in Fig. 1. The insertion of this gradient pulse increases the orthogonality of diffusion weighting of each echo at the cost of more refocusing gradient pulses before every echo.

To optimize the MMME sequence, we need to determine a suitable diffusion weighting (B) matrix so that we can extract all components of D_{ij} with the least error from the measured attenuation of spin magnetization as input data. The gradient values of the sequence were optimized based on the

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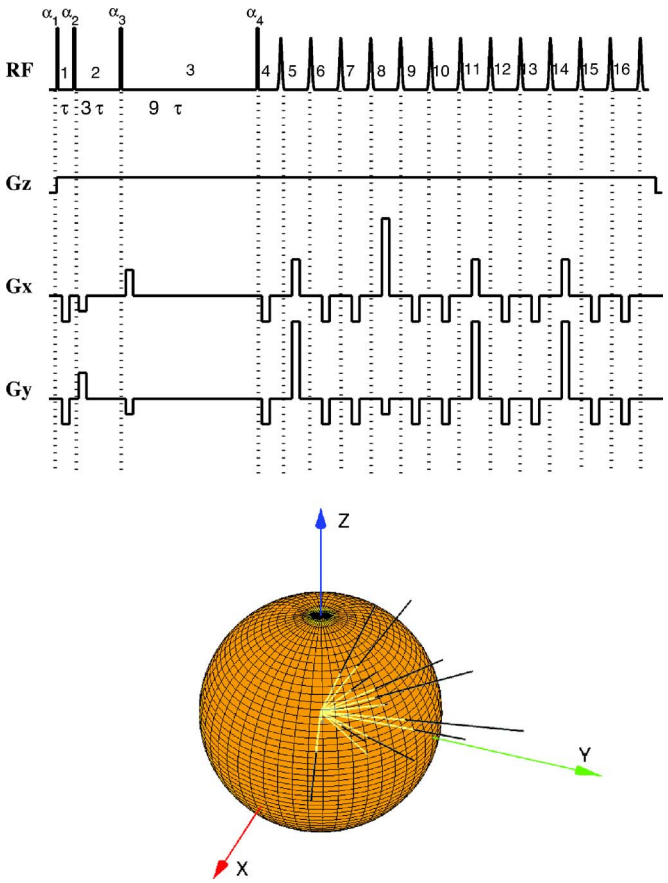

FIG. 1. MMME pulse sequence for a rapid diffusion tensor measurement. τ was set to 4 ms and the duration of each gradient pulse along the x and y directions is set to 2 ms. Gradient values were listed in Table I. α_1, α_2, α_3, and α_4 are rf pulses with a flip angle combination of [54°, 71°, 71°, 110°]. The bottom figure shows effective diffusion sensitizing directions calculated from the diffusion weighting matrix used to generate 3D diffusion tensor data. See text for more details.

condition number, which is a well known quantitative measure for inversion problems.[11,12] The condition number of the diffusion weighting matrix (B) relates the relative error in the input data (attenuations) to that in the output parameters (diffusion tensor elements) and is also equal to the ratio of the maximum and minimum singular values of B. Clearly, a lower condition number is favorable. A six-dimensional search is required to find the best configuration of gradient pulses along the two axes during periods "1," "2," and "3" which has the lowest condition number. The remaining refocusing gradient pulses ("4"–"16") are constrained to their values by the need for a balanced gradient wave form for each echo's coherence pathway. In this study, we fixed τ =4 ms, δ=2 ms (the duration of pulsed gradient), and G_z =1.5 G/cm. The pulsed gradient values in periods 1–3 were searched from −5 to 5 G/cm at an increment of 2 G/cm. This parameter range was chosen for a reasonable search time and moderate gradient strengths. The condition number of each B matrix was calculated using standard numerical methods and software (MATLAB) for each combination of gradient pulses. The minimum condition number was found to be 4.9, including the effect of a reference scan (G_z =1 G/cm, G_x=G_y=0 G/cm). The lower panel of Fig. 1 shows a visualization of the 13 effective diffusion sensitizing directions for this sequence. These vectors are calculated from the net diagonal diffusion weighting elements according to $v=(\sqrt{(b_{xx})}, \sqrt{(b_{yy})}, \sqrt{(b_{zz})})$. While not formally equivalent to the direction sets involved in standard diffusion tensor imaging (DTI), they give useful intuition on the angular sensitivity of the MMME sequence in this work. Table I lists the value of gradient pulses for the optimal configuration. The minimum condition number of a similar MMME sequence without the gradient pulse during period 1 was 318.

III. EXPERIMENTS

The samples used in the experiment were tap water and an asparagus sample cored into a 5 mm NMR tube. Asparagus is a soft material with numerous properties such as diffusivity and relaxation times in common with tissues, which makes it a good test sample to demonstrate the relevance of the MMME diffusion tensor technique for potential biophysical and biomedical applications. The stem of asparagus is composed of bundles of elongated cells along the stalk axis (z), and this structure leads to an axial diffusion anisotropy due to the reduced water permeation across the cell membrane. This anisotropy, with a smaller diffusivity transverse to the stalk axis, has been noted in previous studies.[6,13]

Experiments were performed in a 2 T horizontal bore magnet (Nalorac Cryogenics) operating at a proton frequency of 85.1 MHz. A Bruker Biospec spectrometer and a home-built 1 cm diameter saddle coil rf probe were used. The MMME diffusion tensor experiment consisted of two scans: (1) the fully encoded MMME sequence in Fig. 1 and Table I and (2) a reference scan with Gz=1 G/cm and Gx =Gy=0. The ratio of the two scans was used for data processing. The net diffusion weighting matrix b_{ij} was that calculated from scan (1) with b_{zz} elements reduced by the b_{zz} weighting factors of the reference scan. Each echo from the MMME sequence is normalized with an equal timing reference experiment, so that the effects of rf pulse flip angle and relaxation are canceled. The amplitude ratios of the corresponding echoes between the two scans directly probe diffusion. Because the gradient strengths along the z direction for each sequence are different (as they must be to maintain net

TABLE I. Gradient values used for the MMME sequence. The top row refers to the gradient pulse number, as indicated in Fig. 1. A reference experiment is performed with G_z=1 G/cm and G_x=G_y=0 G/cm. The condition number of the combined analysis was 4.9.

Gradient Pulse No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
G_z (G/cm)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
G_x (G/cm)	−5	−3	5	−5	7	−5	−5	21	−5	−5	7	−5	−5	7	−5	−5
G_y (G/cm)	−5	5	−3	−5	15	−5	−5	−3	−5	−5	15	−5	−5	15	−5	−5

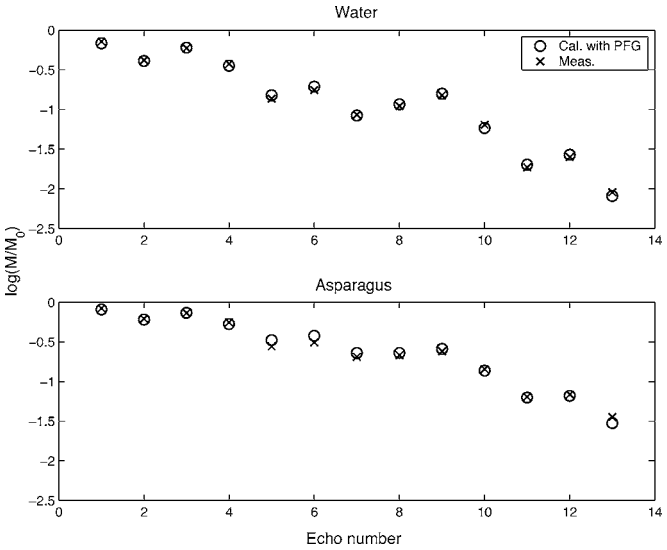

FIG. 2. Comparison of measured echo intensities from the MMME sequence with the calculated values using the diffusivity obtained from PFG measurements. Each echo is normalized with the corresponding echo from the reference experiment.

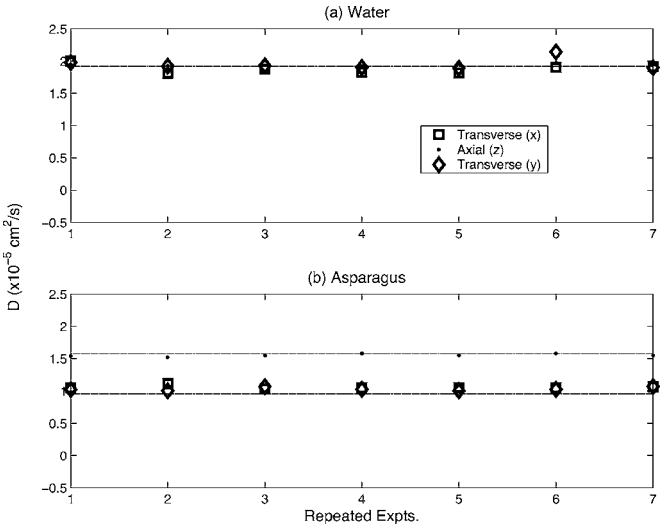

FIG. 3. Eigenvalues of diffusion tensor for both water and asparagus samples obtained with the MMME sequence. Solid lines represent the corresponding values for PFG measurements.

diffusion weighting along the z direction), the maximum amplitude of each echo in the time domain was measured to avoid effects of echo shape differences. Note that this approach is potentially problematic for an imaging implementation, particularly if the static gradient is used for frequency encoding, as was done previously.[6,7] This difficulty could be avoided by varying the acquisition bandwidth or the reference scan timing, with due care to the consequent variation in noise figure or relaxation weighting. For gradient calibration and validation of the diffusion tensor results from the MMME sequence, conventional diffusion-weighted stimulated echo sequences[1,4] were performed for both water and asparagus samples at a diffusion time of 70 ms.

Figure 2 shows the experimentally measured attenuation of each echo with the MMME sequence and compares it with the expected value calculated using diffusion tensor values from the conventional pulsed field gradient (PFG) stimulated echo sequence for both water and asparagus samples, shown in Fig. 3.

Figure 3 shows the eigenvalues of the estimated diffusion tensors from repeated MMME experiments along with the eigenvalues from the PFG measurements (solid line) for both water and asparagus samples. Diffusion tensor values for water with the PFG measurement are also used to calibrate gradient strengths. The anisotropy of diffusion in asparagus sample and the expected isotropic diffusion in water sample are correctly reproduced with the MMME sequence, showing its qualitative and quantitative accuracies. The data analysis did not assume an isotropy or an axial symmetry of the diffusion tensor for either system.

On the other hand, the MMME sequence is seen to produce slightly larger (~7%) transverse (x and y) diffusion components than those values from the PFG measurement, as shown in Fig. 3(b). It was pointed out previously that a time-dependent diffusion coefficient $D(t)$ (Refs. 14 and 15) might limit the accurate estimation of apparent diffusion constant (ADC) from the MMME sequence because of the change of ADC during the time scale of the echo train.[7] The echo train ranges from 50 to 100 ms for the MMME sequence in this work, and the change in ADC during this time may be a source for the ~7% error in transverse diffusion components with the MMME sequence. Figure 4 shows $D(t)$ measurements using a standard stimulated echo PFG method on an asparagus sample to confirm this speculation. There is no significant change of ADC for the axial direction (z). On the other hand, there exists an ~10% drop in transverse ADC in the course of 50–100 ms, which may be the source of mismatch of the ADC values between the MMME and PFG sequences. Note that the asparagus sample used for $D(t)$ measurement was different from that for the MMME sequence; thus, a slight variation of the absolute diffusion coefficient is possible.

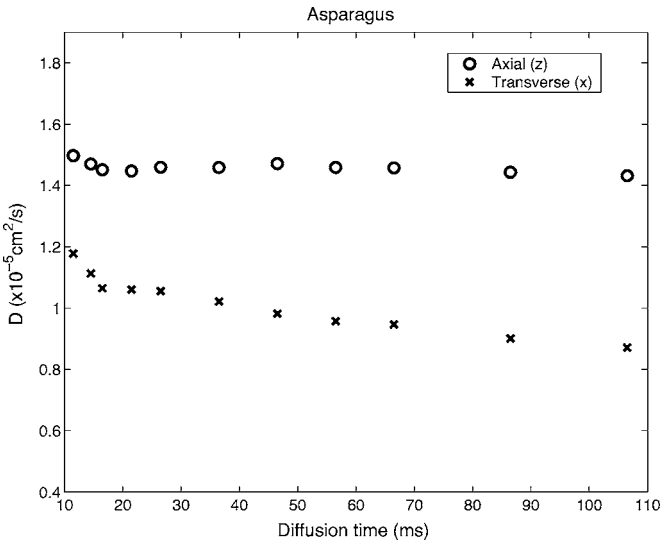

FIG. 4. $D(t)$ measurement using the stimulated echo PFG sequence on the asparagus samples.

IV. CONCLUSION

In summary, we have demonstrated successful measurements of a three-dimensional diffusion tensor for both an isotropic water sample and an anisotropic asparagus sample. Anisotropy of asparagus sample was properly reproduced with the MMME sequence. This was accomplished with 13 spin echoes with optimized diffusion weighting factors with four rf pulses, which were sufficient to determine six diffusion tensor components. The extension of this work to include an imaging modality will significantly increase the efficiency of the MEDITATE (multiple echo diffusion tensor acquisition technique) sequence[7] as an alternative diffusion tensor imaging (DTI) acquisition method[2,3] and may find application in studying time-sensitive processes in medical and chemical applications.

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