Novel diffusion-diffraction patterns in double-PFG NMR afford accurate microstructural information in size distribution phantoms

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Introduction. The most important methodology to date in diffusion NMR and MRI is the single-pulsed-field-gradient (s-PFG) which enables accurate measurement of the apparent diffusion coefficient (ADC) in restricting compartments. When s-PFG experiments are conducted with sufficiently long diffusion periods in monodisperse restricted compartments, the diffusion-diffraction minima can be observed in the E(q) plots, from which the accurate compartment size can be extracted[1,2]. The compartment size can be extremely important in a variety of applications including in neuronal tissues; however, when the specimen is characterized by size distributions, the diffusion-diffraction minima are not observed in s-PFG, and a non-mono-exponential decay is usually observed[3]. Therefore, the microstructural information that the diffusion-diffraction minima convey is lost in s-PFG.

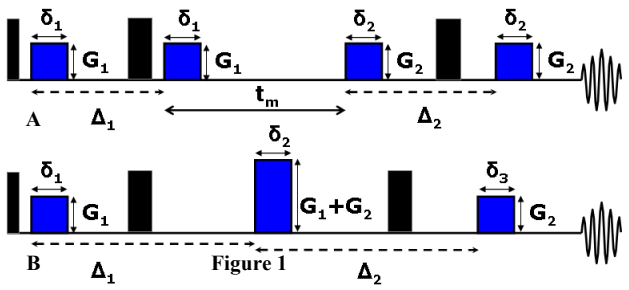

Figure 1

The double-PFG (d-PFG) is emerging as a new powerful tool for studying restricted diffusion, especially where s-PFG is inherently limited[4-6]. The d-PFG is an extension of s-PFG, and employs two gradient pairs $\mathbf{G_1}$ and $\mathbf{G_2}$ which are separated by a mixing time (t_m) (Fig. 1A). Another variant of d-PFG was recently introduced, in which the middle gradients are superimposed, yielding t_m=0ms, a desirable property for some applications (Fig 1B). The diffusion periods, and gradient durations are also introduced in Figure 1. Recent theoretical studies predicted that when the d-PFG is employed in monodisperse specimens in the restricted direction, zero-crossings would be observed[7]. The zero-crossings are analogous to the diffusion-diffraction minima in s-PFG. Recent experimental studies have verified the existence of these zero-crossings, and the effect of numerous experimental parameters on these zero-crossings has been studied[8]. The theory in [7] predicted that the zero-crossings should persist even in specimens characterized by broad size distributions, whereas the diffusion-diffraction minima were predicted to vanish. We therefore studied the signal decay in both s- and d-PFG in size distribution phantoms, where the ground-truth is known *a-priori*.

Materials and Methods. All experiments were performed on an 8.4 T Bruker NMR spectrometer with a micro5 probe capable of producing up to 195 G/cm along the x- y- and z-directions. Water-filled microcapillaries with well characterized nominal inner diameters (ID) were counted to comprise accurate volumetric ratios for three different size distribution phantoms, namely SD001, SD002 and SD003. The microcapillaries were packed in a glass sleeve and were placed in a 5 mm NMR tube with their principal axis in the z-direction, parallel to the main magnetic field. All experiments were performed in the x-direction, i.e. perpendicular to the main axis of the microcapillaries. Single-PFG measurements were conducted with Δ/δ=150/3 ms and with G_{max}=160 G/cm, resulting in a q-value of 2043cm^{-1}. The number of scans was set to 32. The corresponding d-PFG experiments were conducted with the sequence shown in Fig 1B with the following parameters: $\Delta_1=\Delta_2$=150ms, $\delta_1=\delta_2=\delta_3$=3 ms, with $G_1^{max}=G_2^{max}$=80G/cm resulting in q_{max}=1021.5cm^{-1} and with NS=32. The results of d-PFG are plotted as function of 2q to be comparable with the s-PFG results.

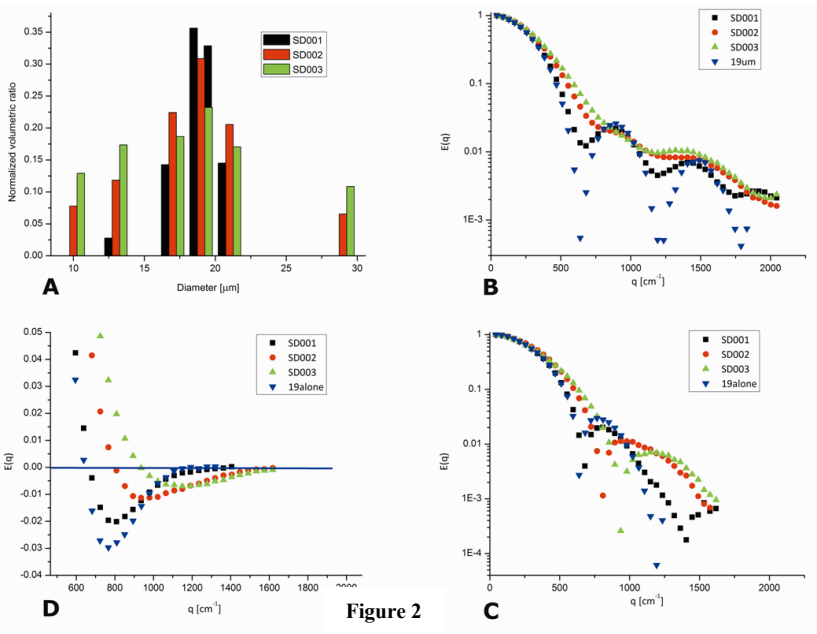

Figure 2

Results. The volumetric ratios of microcapillaries for each size distribution phantom can be seen in Figure 2A. The average diameters and standard deviations for SD001, SD002, and SD003 are 18.8±1.9, 16.0±4.3, and 14.9±4.6 μm respectively. We computed the σ/r_{av} ratio for the discrete size distribution phantoms, which are σ/r_{av}=0.10, 0.27, and 0.31 for SD001, SD002, and SD003 respectively (where σ and r_{av} are the standard deviation and the average radius of the compartments respectively). The results for the size distribution phantoms and for monodisperse microcapillaries with ID=19±1 μm are shown in Figure 2B-D.The s-PFG experiments on monodisperse microcapillaries yielded well resolved, deep diffusion-diffraction troughs, with the first minimum observed at q=638 cm^{-1}, corresponding to a compartment size of 19.1 μm (Fig 2B). However the E(q) profile changed dramatically when the measurements were performed on the SD001 phantom. Although SD001 was designed to have only a slight variation of diameters (σ/r_{av}=0.10) , the diffusion-diffraction troughs in s-PFG becomes profoundly shallower, yielding wider minima which are nevertheless still observable at q~680 cm^{-1}. When SD002 and SD003 are used (σ/r_{av}=0.27 and 0.31 respectively), the sharp diffusion-diffraction minima are almost completely lost, and it is impossible to use the E(q) data to obtain microstructural information characterizing the phantoms. A "bump" in the signal decay can be observed at q~1150 cm^{-1} for SD003, which may reflect a very shallow diffusion-diffraction dip, but from which accurate structural information cannot be obtained. Examining the E(q) plots for the d-PFG experiments performed on these phantoms (Fig. 2C, data are magnitude calculated and plotted as a function of 2q to be comparable to the s-PFG data) reveals a completely different picture. Here, the diffusion-diffraction minima are sharp and present for all of the size distribution phantoms used. The location of the first minima for 19±1 μm (monodisperse), SD001, SD002, and SD003 correspond to diameters of 19.1, 17.9, 15.1, and 13.0 μm respectively, in good agreement with the average diameters of the size distribution phantoms, with a slight deviation towards smaller sizes, most likely due to a slight violation of the SGP approximation. Figure 2D shows the real signal decay, for d-PFG experiments, which show the actual zero-crossings. Note that the q-value in which a minimum point of the plot is achieved becomes higher with increasing width of distribution, and that the rate of return of the signal to noise level in the negative part also depends strongly on the width of the distribution, affording at least a qualitative measure on the width of the distribution.

Conclusions. d-PFG yielded well resolved zero-crossings even when size distributions were present in the specimen, while the diffusion-diffraction minima in s-PFG vanished. This enables better characterization of the specimen, and may be of importance in obtaining microstructural information from specimens characterized by size distributions.

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