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Artefacts and pitfalls in diffusion measurements by NMR

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When applying pulsed field gradient (PFG) NMR experiments to determine the molecular mobility characterized by the diffusion coefficient, it is crucial to have control over all experimental parameters that may affect the performance of the diffusion experiment. This could be diffusion measurement in the presence of magnetic field transients, internal magnetic field gradients, either constant or spatially varying, convection, mechanical vibrations, or in the presence of physical restrictions affecting the diffusion propagator. The effect of these parameters on the diffusion experiment is discussed and visualized. It is also outlined how to minimize their influence on the measured diffusivity that is extracted from the PFG-NMR experiment. For an expanded and more general treatment we refer to the excellent reviews by Dr William S. Price (*Concepts Magn. Reson.* 1997; 9: 299; 1998; 10: 197) and the references therein. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: NMR; pulsed field gradient; diffusion

INTRODUCTION

The pulsed field gradient (PFG) NMR method is a well-established technique for studying molecular motion without disturbing the system under investigation. A large variety of sequences or techniques have been proposed that are optimized for different tasks, such as diffusion measurements in the presence of internal magnetic field gradients,[1–9] convection[10–14] or large eddy current field transients.[15,16] This variety of PFG sequences not only reflects the increasing interest in using the NMR technique in diffusion studies, but also shows that it is not necessarily a trivial task to extract the true diffusion coefficient from a PFG-NMR experiment.

The basic PFG stimulated echo sequence shown in Fig. 1 consists of three intervals, a preparation, a store and a read interval. In the preparation interval, the molecules are labelled with a phase proportional to the integral of the effective gradient $g(t)$. This magnetic field gradient, g, imposes a position-dependent frequency on the system, and with which the nuclear magnetic moment of the nucleus is oscillating in a plane transverse to the external magnetic field, B_0:

$$\omega = \gamma B_0 + \gamma g z \tag{1}$$

where γ is the gyromagnetic ratio and z is the position of the molecule along the direction of the magnetic field gradient, which again is collinear with B_0 or the longitudinal direction.

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After the application of the second pulse, the net magnetic moment is stored in the longitudinal direction, and is thus unaffected by the presence of any longitudinal gradients. In the read interval, the nuclear spins are unlabelled and, if the molecules have travelled a distance during the PFG sequence, there is a dephasing of the net magnetic moment given by

$$\Delta\varphi = \gamma g \delta (z_2 - z_1) \tag{2}$$

where $(z_2 - z_1)$ is the distance travelled by the spins, when assuming infinitely short gradient pulses. The induced current in the r.f. coil, the NMR signal, will be attenuated because of the dephasing. This will be apparent in the natural logarithm of the pulsed field gradient stimulated echo attenuation $[\ln(I/I_0)]$ expressed as a function of the diffusion time and the gradient strength.

When assuming a Gaussian distribution of diffusivities and a mono-exponential attenuation of the NMR signal due to relaxation processes, the signal amplitude can be written as[4]

$$I = I_0 \mathrm{e}^{-\frac{t_1}{T_2}} \mathrm{e}^{-\frac{t_2}{T_1}} \mathrm{e}^{-\gamma^2 g^2 D \int_0^t \left(\int_0^{t'} g(t'')\mathrm{d}t'' \right)^2 \mathrm{d}t'} \tag{3}$$

where

t_1 = duration when the NMR signal is influenced by transverse relaxation processes;
t_2 = duration when the NMR signal is influenced by longitudinal relaxation processes;
$g(t'')$ = total magnetic field gradient, external and internal;
D = diffusion coefficient;
T_1 = characteristic longitudinal relaxation time;

Figure 1. The ordinary PFGSTE sequence where the preparation interval labels the nuclear spin with a position-dependent phase, the store interval allows the spin to diffuse, and the read interval unlabels the spin.

T_2 = characteristic transverse relaxation time;
I_0 = initial intensity of the NMR signal.

The usual way to conduct the diffusion experiment is to fix the diffusion time and vary the applied magnetic field gradients, so that the reduction of the NMR echo due to transverse and longitudinal relaxation processes will be constant during the experiment. A general expression for the amplitude of echo signal can then be written as

$$I = I_0' e^{-\gamma^2 g^2 D \int_0^t \left(\int_0^{t'} g(t'')dt'' \right)^2 dt'} \quad (4)$$

In the following, we will focus on PFG-NMR sequences where the diffusion coefficient is measured from an attenuated NMR signal that is generated by incrementing the applied gradient strength. The relaxation terms can then be incorporated into the initial intensity of the NMR signal, I_0. When incrementing the gradient strength and keeping the diffusion time fixed, the diffusing molecules will probe the heterogeneity of the sample to the same degree during the NMR experiment. The measured diffusion coefficient will then represent a stable system with the respect to the fraction of molecules experiencing the heterogeneity of the sample. This is important when measuring physical parameters such as tortuosity, surface to volume ratio or surface relaxation.[17,18]

The experimental data presented here were recorded on several spectrometers with different magnetic field strengths: Bruker DMX200 (4.7 T), Bruker DRX600 (14.1 T) and Resonance Instruments Maran 23 (0.55 T).

CALIBRATION OF THE STRENGTH OF THE MAGNETIC FIELD GRADIENT

Before measuring the diffusion coefficient by NMR, it is important to calibrate the applied magnetic field gradient strength properly. The most common approaches are to determine the strength of the gradient from a profile experiment[19] or to calibrate the gradient strength from a PFG-NMR experiment performed on a substance with a known diffusion coefficient.[20,21] Even though the use of a profile experiment seems to be a more direct and accurate method for determining the actual gradient strength, it does not necessarily return the effective magnetic field gradient as experienced by the diffusing molecules during a PFG-NMR experiment. When using the profile experiment, one finds the magnitude of the applied gradient strength in a steady state. However, this approach for determining the gradient strength does not account completely for gradients induced by magnetic field transients. Figure 2 shows two gradient pulses and the response from two different diffusion probes, one with low impedance (left) and the other with high impedance (right). The gradient coil impedance limits the fidelity with which the desired pulse shape can be produced. This is the origin of the overshoot shown by the Hall probe trace for the high-impedance probe. The lack of active or passive shielding of the gradient coil, on the other hand, is responsible for greatly increased eddy currents, hence the long decay shown by the Hall probe trace for the high-impedance probe. Equation (4) indicates that the effective gradient strength is found by integrating over the duration of the PFG-NMR sequence and, as seen in the response, there is a significant contribution from the eddy currents that generate a magnetic field transient in the response. As the duration of the transient magnetic field is longer than the rise time of the gradient pulse, the area over the response from the Hall probe is larger than the area of a rectangular pulse with the same amplitude and gradient pulse duration. The calibrated gradient strength that is found from a profile experiment is therefore less than the calibrated gradient strength determined when using an actual PFG-NMR experiment on a sample with

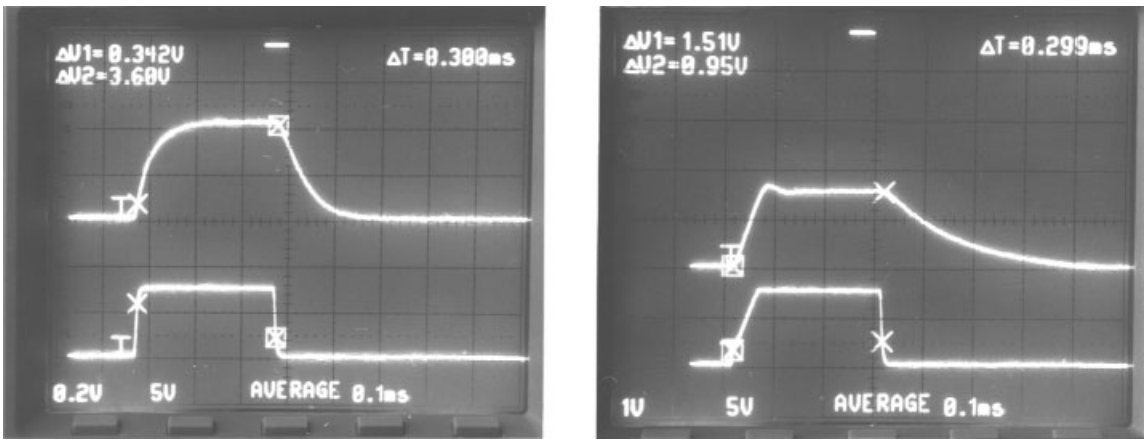

Figure 2. The recording of the responses from two different gradient probes on a current pulse running through the gradient coils. The left picture shows the current pulse (lower) and the response from the low impedance diffusion probe (upper) is recording using a Hall probe. To the right the response from the high impedance diffusion probe is shown.

known diffusion coefficient. The response from the different diffusion probes, one actively shielded low impedance and one unshielded high impedance, shows that the potential error is larger for the unshielded diffusion probe. The eddy current dead time is longer and, in addition, the PFG amplifier is not able to generate rectangular gradient pulses in the high impedance probe. Using the unshielded diffusion probe the profile experiment returns a calibrated gradient strength of 11 G cm^{-1} A^{-1}, while the calibrated gradient strength was found to be 18 G cm^{-1} A^{-1} when performing a diffusion experiment on a substance of known mobility. As expected from Fig. 2, the error was significantly smaller when using the actively shielded diffusion probe ($g_{\text{profile}} = 4.5$ G cm^{-1} A^{-1} while $g_{\text{diffusion}} = 4.7$ G cm^{-1} A^{-1}).

The use of a profile experiment to find the magnetic field gradient strength may therefore lead to a measured diffusion coefficient that is higher than the actual value. To ensure that the most correct calibration value for the gradient strength is used, one should compare the profile experiment with a diffusion experiment performed on a sample of known mobility. If the profile experiment returns smaller gradient strength than the diffusion experiment, it is most likely that the correct gradient strength is found from the diffusion experiment.

Most field gradient calibration methods in current use ignore gradient non-uniformity, which may be a significant source of error when working with a set of gradient coils that is not optimized for gradient linearity. An effective remedy is then to map the calibrated gradient distribution using a substance with known diffusion coefficient. The diffusion coefficient of an unknown sample may then be determined by using this map.[22]

TRANSIENT MAGNETIC FIELDS FOLLOWING MAGNETIC FLUX CHANGES

When switching the magnetic field gradients on or off in a PFG experiment, magnetic flux changes induce eddy current field transients in the vicinity of the gradient coils. This eddy current generates magnetic field transients that affect the phase of the nuclear spin,[23] and may cause baseline and lineshape distortions in high-resolution experiments. As the applied magnetic field is increased in the PFG experiment, the eddy current transient also increases. This increase does not necessarily appear as a linear function of the applied magnetic field. If the eddy current dead time, the time between switching off the gradient pulse and the start of acquisition of the r.f. signal, is too short, the NMR echo signal will suffer a reduction due to loss of phase coherence. The loss is caused by a mismatch of the effective gradients in the preparation and read intervals, and the mismatch is more likely to occur when the spin-echo is recorded in the presence of large magnetic field transients. A typical PFG spin-echo attenuation that is affected by eddy current field transient is shown in Fig. 3. Initially, the $\ln(I/I_0)$ attenuation is linear, as the magnetic field transient is not large enough to generate a significant mismatch of the effective gradients in the preparation and read intervals. As the applied gradient is increased, it is evident that there is no linear response between $\ln(I/I_0)$ and the square of applied gradient strength. The magnetic field transients (eddy current magnetic field transients) cause this behaviour.

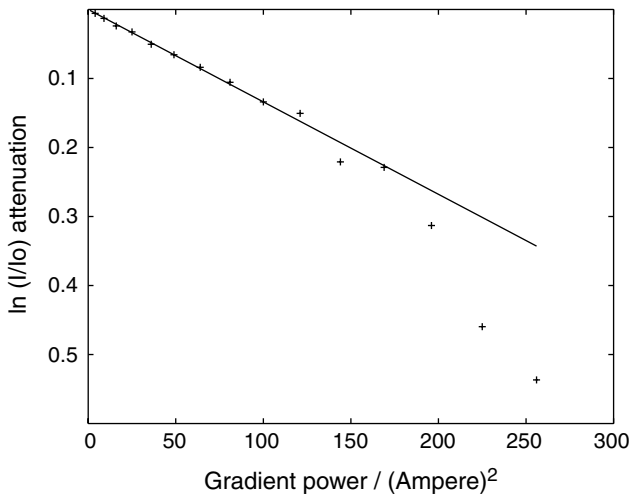

Figure 3. The effect of the eddy current magnetic field transient on the PFGSE experiment performed on a one-component homogeneous system. The experiment was recorded using an 18 mm bench-top Maran 23 (0.5 T) instrument from Resonance Instruments.

Several approaches can be used to avoid the influence of eddy current fields caused by gradient switching. One obvious approach is to increase the eddy current dead time, such that the spin-echo is recorded at an insignificant eddy current field even at the highest applied gradient strength. With the current technology, one can actually reduce the eddy current dead time by allowing for a pre-emphasis adjustment.[16,24] Then, a decaying multi-exponential current is run through the gradient coils during the gradient switching. The amplitudes and time constants are adjusted in order to minimize the effect from the magnetic field transients, which also may be represented by a decaying multi-exponential eddy current field.

One may also use preparatory gradient pulses that, depending on the polarity, either reduce the eddy current field or saturate the eddy current field. As is seen when using bipolar pulsed field gradient pairs in the PFG experiment,[25] preparatory gradient pulses of opposite polarity to the applied gradient pulses will partially cancel out the magnetic field transients.[12,26] As shown in Fig. 4, this is an effective tool for improving the stability of the deuterium lock signal, which leads to better high-resolution NMR spectra.[12] Figure 5 shows two high-resolution FFT spectra that were recorded with and without the use of preparatory gradients. With the preparatory gradients in use, it is evident that baseline and lineshape distortions are reduced due to a significant reduction of the eddy current transients.

If the preparatory gradient pulses are of the same polarity as in the PFG experiment, the effect of the pulses is to saturate the eddy current transient.[15] Then, the spin-echo is recorded in the presence of a large but stable eddy current field, such that the mismatch between the effective gradients in the preparation and read intervals is reduced to an insignificant value. With this method it is possible to perform reliable diffusion measurements on low-field bench-top systems with

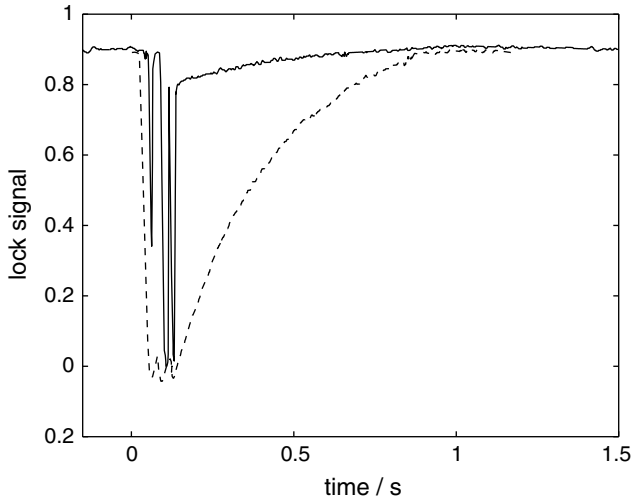

Figure 4. A recording of the lock signal during an ordinary double PFGSTE sequence (dashed line) and a double PFGSTE sequence with preparatory gradient pulses (solid line). The lock signal was recorded on a Bruker Avance DRX600 spectrometer.

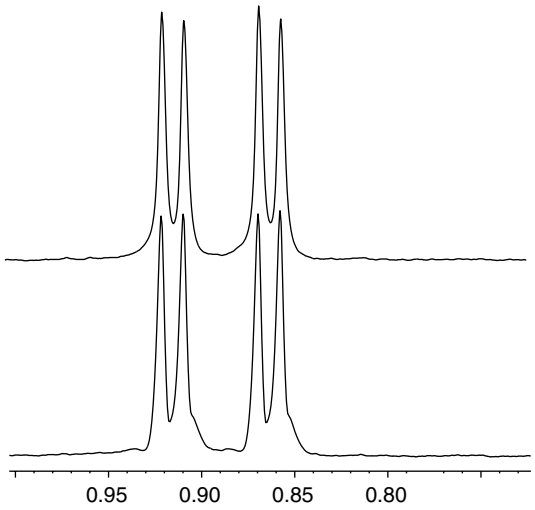

Figure 5. Four peaks arising from two CH_3 groups in the amino acid valine. The lower FFT spectrum was recorded with the ordinary double PGFSTE sequence and the upper spectrum using the double PFGSTE with preparatory gradient pulses. The experiment was recorded on a Bruker Avance DRX600 spectrometer and the spectra are displayed in units of ppm.

permanent magnets generating the external field B_0. On such systems there is usually no need for pre-emphasis adjustment and actively shielded gradient coils.

CONSTANT BACKGROUND AND INTERNAL MAGNETIC FIELD GRADIENTS

When measuring diffusion by NMR, a constant background gradient throughout the whole sample can increase or decrease the apparent diffusion coefficient in a mono-polar experiment, depending on whether they interfere constructively or destructively with the applied gradient pulses. Although constant background gradients can be minimized by the use of electrical shims or even a small electrical current running through the gradient coils, this approach does not minimize the effect from internal magnetic field gradients that are induced due to magnetic susceptibility changes over the sample.[27] In heterogeneous system, such as a porous rock or a biological tissue, where susceptibility differences are present, the internal gradients will be roughly symmetrically distributed with a mean value of zero. Thus, some molecules experience positive internal gradients while others experience negative internal gradients within the same sample. The effect of such a distribution of internal gradients is always a measured apparent diffusion coefficient that is smaller than the actual one.[28]

The magnitude of the internal gradient in a system of macroscopic particles surrounded by the probe substance is approximately given by[27]

$$g_{\text{internal}} \approx \frac{\Delta B_0}{d_{\text{particle}}} \tag{5}$$

where ΔB_0 is the width of the magnetic field distribution, which is related to the magnetic susceptibility differences over the sample, and d_{particle} is the typical diameter of the particles. Thus, the strength of the internal gradient will vary with the physical properties of the different components within the sample and also with the heterogeneity within the sample. If the diffusing molecules within a heterogeneous system are experiencing internal magnetic field gradients during the PFG experiment, the attenuation of the echo signal will be non-linear, and the extracted diffusion coefficient will be lower than the actual one.[28]

As for the difficulties with eddy current transients, several approaches have been developed for avoiding the impact of constant background or internal magnetic field gradients on the measured diffusivity. As the magnitude of the internal gradient is essentially proportional the external magnetic field, an obvious approach is to work with spectrometers employing low magnetic fields, say 0.55 T or less. However, as found by Hürlimann,[29] some heterogeneous systems may have significant internal gradients even at 0.047 T, and below this magnetic field strength the signal usually becomes too poor for observation.

Another approach is to reduce the influence from internal gradients either by rotating the applied magnetic field gradient[8] or physically rotating the sample.[9] A rotation of the applied magnetic field gradient implies the use of r.f. gradients, which puts a restriction on the available strength of the applied gradient. On the other hand, a physical rotation of the sample at the magic angle puts a restriction on the dimension of the sample, and the rapid rotation may change the properties of a heterogeneous sample as compared with a stationary sample.

The most common solution to the problem is to apply bipolar pairs of magnetic field gradients separated by 180 r.f. pulses in the so-called bipolar PFGS(T)E experiments.[3–7] Provided that the internal magnetic field experienced by the diffusing molecules does not vary during the sequence, the impact of an internal magnetic field gradient may be reduced to an insignificant level.

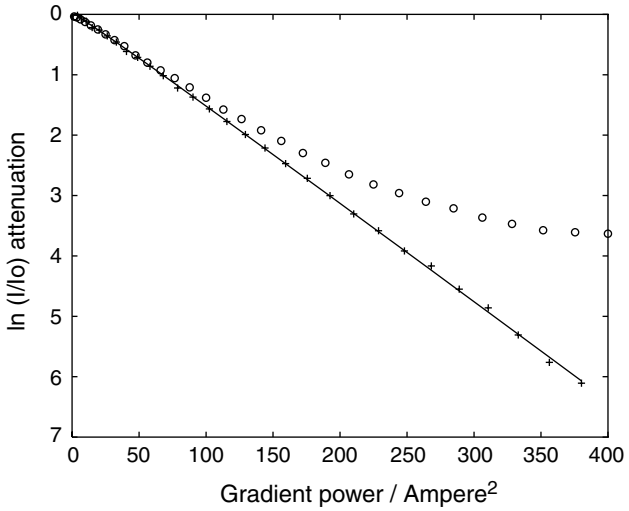

Figure 6. The $\ln(I/I_0)$ attenuation from distilled water using the 13-interval PFGSTE sequence either with equal bipolar gradients (○) or unequal bipolar gradients (×). The experiment was performed with a Bruker DMX200 spectrometer.

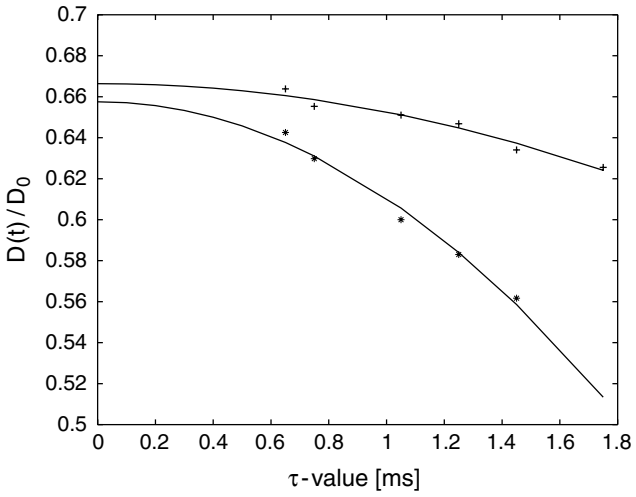

Figure 7. Measurements of $D(t)/D_0$ of water immersed in compact mono-sized glass spheres using the 13-interval bipolar PFGSTE sequence with different τ values but keeping the observation time constant ($\Delta = 800$ ms). The τ dependence of $D(t)/D_0$ was recorded using two spectrometers at different field strengths, a 4.7 T BrukerDMX200 (+) and a 14.1 T Bruker DRX600 (*). At an observation time of 800 ms, the measured $D(t)$ will correspond to $D_\infty(\tau)$ as shown in Eqn (7).

However, there are two major pitfalls when applying bipolar PFG experiments. By introducing more r.f. pulses into the PFG experiment, the number of unwanted coherence transfer pathways is increased. The bipolar PFGS(T)E sequences therefore require sophisticated phase cycles[25] or the use of unequal bipolar gradients.[6] Figure 6 shows the effect of signals from unwanted coherence transfer pathways and demonstrates how it is reduced either by a phase cycling or by using unequal bipolar gradients. The use of unequal bipolar gradients is a faster experiment, as the minimum number of accumulating scans is only two, while the minimum number of scans using a proper phase cycle is eight.[25]

The successful use of bipolar magnetic field gradients assumes no spatial variation of the internal gradients during the experiment. If the diffusing molecule experiences an internal gradient in the preparation interval that is significantly different from the one experienced in the read interval, the attenuation from the bipolar PFGS(T)E experiment will again be affected by the internal gradients.[30] The consequence is that when a diffusing molecule experiences the heterogeneity of the sample during the experiment, the measured diffusion coefficient will be a function of the spatially varying internal magnetic field gradients. As the observation time in the diffusion experiment increases, the diffusion coefficient is reduced due to physical restrictions in the heterogeneous system. At observation times where the root mean squared displacement exceeds the typical dimension of the heterogeneity of the sample, the diffusion coefficient approaches asymptotically a limiting value D_∞ which defines the tortuosity T:[17]

$$\frac{1}{T} = \frac{D_\infty}{D_0} \tag{6}$$

where D_0 is the unrestricted diffusion coefficient. The tortuosity can be determined by measuring the diffusivity at very short and long diffusion times. However, this approach fails if the effect from spatially varying internal gradients is not corrected for in the PFGSTE experiment. Seland *et al.*[30] found that the functionality between the diffusion coefficient and the internal gradient depends on the duration of the preparation and read intervals ($=2\tau$). One can therefore correct for the effect caused by internal gradients by measuring the diffusion coefficient at a constant observation time and varying the τ value. In Eqn (7), the τ-dependent diffusion coefficient is presented as a series expansion:

$$\frac{D_\infty(\tau)}{D_0} = \frac{D_\infty(\tau)}{D_0}_{(\tau=0)} + C_1\tau + C_2\tau^2 + \varphi(\tau^3) \tag{7}$$

where $\varphi(\tau^3)$ indicates that higher order terms are neglected. Figure 7 shows how the true diffusion coefficient may be found using the series expansion up to τ^2. In this case, the influence of spatially varying gradients has been corrected for, and the fitted diffusion coefficient will reflect the true tortuosity of the system.

The use of bipolar magnetic field gradients is currently the most common way to suppress the effect from internal magnetic field gradients. However, at short observation times care must be taken with respect to signals arising from unwanted coherence transfer pathways, while at longer observation times one must correct for the existence of spatially varying internal magnetic field gradients.

UNWANTED FLOW WITHIN THE SAMPLE

When measuring true self-diffusion coefficient of liquids, the molecules are travelling distances of the order of micrometres during the experiment. Any unwanted flow within the sample will increase the distance travelled significantly, and the attenuation of the PFG experiment will appear non-linear. The true self-diffusion coefficient is then not extractable from the initial slope of the attenuation.[11]

The flow within the system may originate from temperature gradients, as for example when measuring at ambient temperature by heating the sample with gas from below. Using a smaller sample dimension can significantly reduce this type of convection, in that the conditions for the onset of flow (i.e. changing the critical Rayleigh number Ra_c[31]) would require higher temperature gradients than are available.[32]

Mechanical vibration can also induce an unwanted movement within the sample, as in connection with gradient switching that may cause knocking of the gradient coils. This can result in transmission of vibrations from the gradient coil to the sample, and to minimize this potential source of error, one should isolate the sample from any contact with the gradient coils and other items that may set the sample into movement.[33]

Imperfect 180° r.f. pulses are corrected for in every even echo in the Carr–Purcell–Meiboom–Gill (CPMG) sequence and likewise is the effect from laminar flow corrected for in every even echo in a multi PFGSE sequence.[10] Figure 8 shows the spin-echoes in a multi-PFGSE experiment from a sample that is subjected to vibration effects, and it is apparent that the odd echoes do not fit into the same decay as the even ones. To reduce the possibility of errors arising from convection or vibration, it is recommended to make use of double PFGS(T)E methods.[10–14] Figure 9 shows single and double PFGSE experiments performed on acetonitrile at 15 °C. It is evident that the use of the double PFGSE sequence yields a mono-exponential decay that is unaffected by the laminar flow within the sample, whereas the single PFGSE yields an attenuation that is non-exponential and may even return a negative NMR signal.

It is shown that by combining the use of the second PFG spin-echo with preparatory gradient pulses, the performance of a high-resolution PFG experiment is improved, with respect to both convection and eddy current field transients.[12]

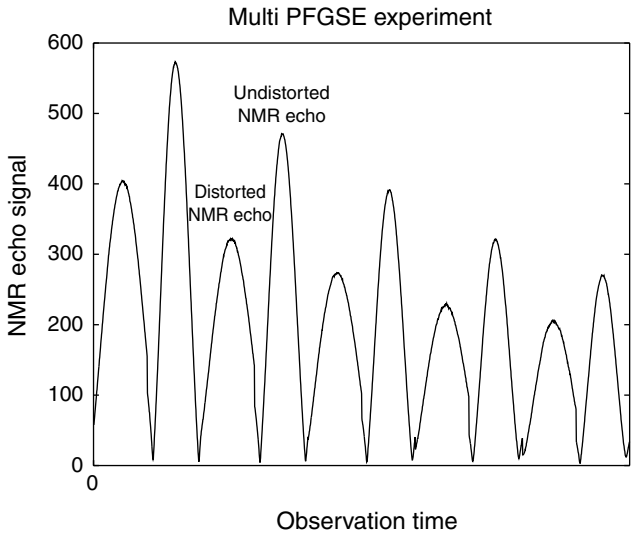

Figure 8. A multi-PGFSE experiment performed under the influence of mechanical vibration. The experiment was recorded using a Maran 23 spectrometer from Resonance Instruments. Along the *x*-axis only the acquisition of the spin-echoes is shown. Each echo was acquired over 0.4 ms and the duration between each spin-echo was 4 ms.

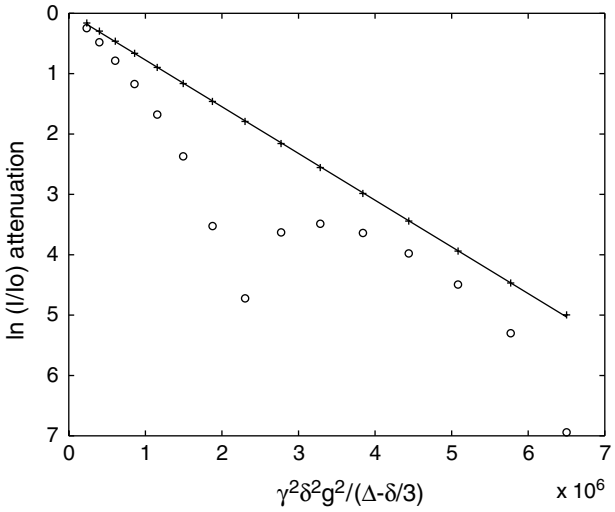

Figure 9. An ordinary single PFGSE experiment (○) and a convection-compensating double PFGSE experiment (+) performed on acetonitrile at 15 °C. The experiment was recorded using a Bruker DMX200 spectrometer.

Then, the number of r.f. pulses can be minimized and a less a sophisticated phase cycle is required compared with the bipolar double PFGS(T)E sequences.[11,13] When studying diffusion in liquids, where there is no need for bipolar sequences to suppress the effect from internal gradients, a double PFGSE experiment with preparatory gradients is then a simpler but just as effective experiment to employ.

CORRECTED EFFECTIVE DIFFUSION TIMES

When one is interested in fitting models to a measured diffusion coefficient, it may be necessary to define the observation time properly. In heterogeneous media it is of great interest to measure the diffusion coefficient as a function of observation time, at both shorter and longer times.[17,18] However, when working with heterogeneous media, it is not obvious that the diffusion propagator is Gaussian,[34] as would be the case in a homogeneous system. If the molecules experience the heterogeneity of the sample during the preparation or the read intervals, this will be apparent as non-linear decay of the logarithm of the PFG attenuation.

Assuming a finite gradient pulse length, the phase from the preparation and read intervals must be written as a time integral:

$$\Phi = \gamma \int_0^{\delta} g z(t) \mathrm{d}t \tag{8}$$

where g is the applied gradient strength and $z(t)$ is the position of the diffusing molecule at time t. The assumption that the diffusing molecule is experiencing a constant gradient during the experiment can be interpreted as if the molecule is labelled at rest during the gradient pulse at a mean position

$$\langle z \rangle = \frac{1}{\delta} \int_0^{\delta} z(t) \mathrm{d}t \tag{9}$$

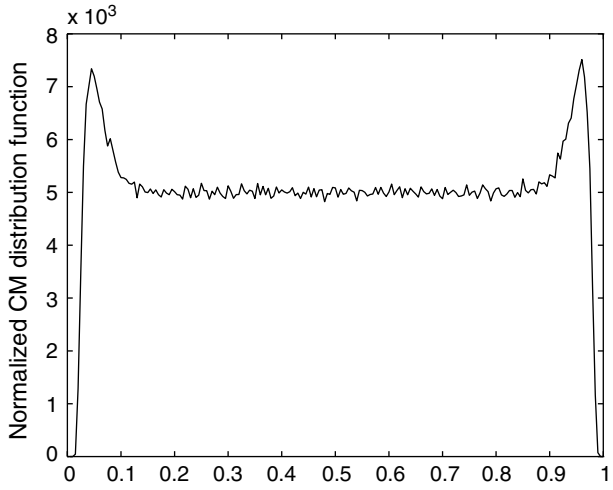

Figure 10. Normalized centre of mass distribution function for random walkers with a root-mean-square displacement of 0.1 in a box of unit length.

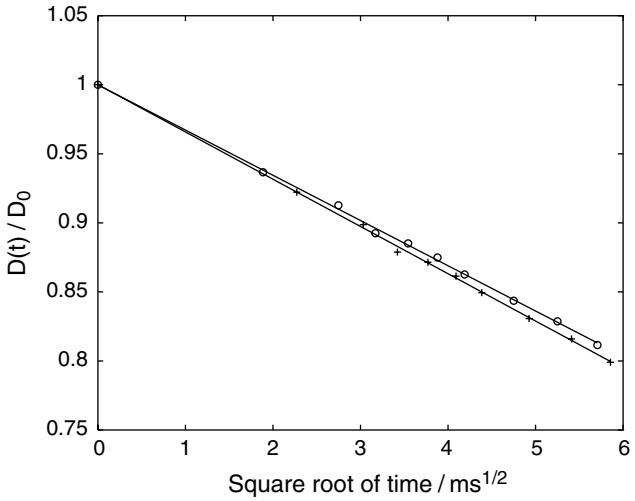

Figure 11. Normalized observation time-dependent diffusion coefficient of water immersed in compact mono-sized spheres. The ○ symbols represents the data set using standard effective diffusion times, and the + symbols represent the data set using corrected effective diffusion times. The experiment was recorded using a Bruker DMX200 spectrometer.

where $\langle z \rangle$ defines the centre of mass of the distribution of phases that is generated by the applied magnetic field gradient during the preparation or the read intervals.[34] If the diffusing molecules sense restrictions during the gradient pulses, this will affect the centre of mass and thus the functionality of the diffusion propagator. Figure 10 shows how the centre of mass senses restrictions in a one-dimensional model system. Because molecules close to the surface can only move away from it, and not into it, their average phases look like those of molecules further away from the surface, and the phase centre of mass distribution shows two peaks some way in from the walls. To correct for the restricted diffusion during the preparation or read intervals, Fordham *et al*. introduced corrected effective diffusion times.[35] In order to extract the true diffusion coefficient from a non-linear attenuation, one makes use of the second cumulant approximation.[36] Then, the non-linear attenuation is assumed to consist of a sum of terms with expanding power of the applied gradient. At small gradient strengths the square of the gradient is the most dominant, and one may extract the true diffusion coefficient by analysing the initial decay as a function of the square of the applied gradient strength.

By combining the corrected effective diffusion times with the second cumulant approximation, one may study diffusion coefficients as a function of observation times, for example by applying the short observation time diffusion model developed by Mitra *et al*.[37] In Figure 11 the normalized diffusion coefficient of water amongst compact mono-sized spheres of mean diameter 98.7 μm it plotted against the square root of the diffusion time.[38] Here it is demonstrated that the best fit between experiment and theory is achieved by using corrected effective diffusion times.

CONCLUSION

The use of PFG-NMR to measure the mobility of a nucleus is a powerful tool that may return information that is not accessible by other experimental techniques. However, it is very important to make sure that the experimental settings truly return a data set unaffected by artefacts and potential pitfalls.

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