

# Strategies for Diagnosing and Alleviating Artifactual Attenuation Associated with Large Gradient Pulses in PGSE NMR Diffusion Measurements

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**The generation of phase-based artifacts resulting from mismatch in the effective areas (i.e., the time integrals) of sequential gradient pulses is discussed in the context of large gradient pulsed-gradient spin-echo (PGSE) NMR diffusion measurements. Such effects result in artifactual attenuation and distortion in the spectra which, in the first instance, are similar to (and commonly mistaken for) the effects of eddy currents. Small degrees of mismatch cause “unphysical” concave downward curvature in PGSE attenuation plots of freely diffusing species. However, larger mismatches can result in artifactual diffraction peaks in the plots which could easily be confused for true restricted diffusion effects. Although “rectangular” gradient pulses are preferable from a theoretical viewpoint, we found that shaped gradient (e.g., half-sine) pulses, which due to their slower rise and fall times were more tractable for the current amplifier, were more sequentially reproducible. As well as generating fewer phase-based artifacts such shaped pulses also decrease the likelihood of vibration problems.** © 1999 Academic Press

**Key Words:** artifact; diffraction; diffusion; gradient; mismatch; pulsed-gradient spin echo.

## INTRODUCTION

Pulsed-gradient spin-echo (PGSE) NMR diffusion measurements (also sometimes referred to as DOSY) of species that have any of the following characteristics, a small diffusion coefficient ( $D$ ), small gyromagnetic ratio ( $\gamma$ ), or short spin-spin relaxation time, necessitate the use of large magnetic field gradients ( $I$ – $6$ ). Large gradients are also advantageous in probing restricted diffusion (i.e.,  $\mathbf{q}$ -space imaging). A major and widely recognized problem with gradient pulses in PGSE measurements is that the gradient pulses can generate eddy currents although their effects have been greatly reduced by the advent of shielded gradient coils; this and other techniques for minimizing their effects have recently been reviewed ( $6$ ). The time required for the dissipation of eddy currents defines the minimum delay that must be left after a gradient pulse prior to

signal acquisition or the application of a refocussing RF pulse. For example, a spectrum acquired in the presence of eddy currents will have a combination of phase and amplitude distortions (see, for example Fig. 6 in Ref. ( $6$ )).

Two other serious problems, although less widely discussed in the literature, are that of mismatch between sequential gradient pulses and vibration/sample movement with respect to the gradient coils. The effects of both of these problems can be confused with eddy currents. In the PGSE experiment the effective area (i.e., the time integral) of the first (i.e., dephasing) gradient pulse must exactly match that of the second (i.e., rephasing) gradient pulse. An extremely small mismatch of the gradient pulses, while too small to measure using conventional techniques (e.g., by oscilloscope), will result in a residual phase-twist which causes a severe loss in echo signal intensity ( $7$ ). On the other hand vibration/sample movement results in a net phase-shift through the spectrum similar to the case of flow (see Ref. ( $4$ )). In fact Callaghan ( $7$ ) has noted that current instability of the order of 1 ppm and/or sample movement on the order of 10 nm restricts self-diffusion measurements to  $D \geq 10^{-15} \text{ m}^2\text{s}^{-1}$ .

Recently, while characterizing our newly installed high-amplitude gradient systems, we encountered artifactual diffraction peaks in samples that contained only freely diffusing species. In the present work we describe our investigation of these effects. We first show that these are not due to eddy currents and then investigate the effects of residual phase-twists due to gradient pulse mismatch ( $I$ ,  $7$ – $9$ ) and residual phase-shifts due to vibration/sample movement ( $I$ ,  $7$ ,  $10$ ) using large (freely diffusing) monodisperse polymer samples. Although some of the problems and their solutions have been previously mentioned in the literature (N.B., appropriate references are given throughout this paper), in the present work we are particularly concerned with problems in the context of very-high-amplitude gradient pulses.

The major findings are that residual phase effects not only cause “unphysical” downward curvature in PGSE attenuation plots but also in extreme cases can even produce artifactual

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“diffraction” peaks. It was found that rectangular gradient pulses are particularly difficult to sequentially reproduce reliably. The reproducibility was also sensitive to the interval between successive gradient pulses which is probably related to the pulses causing gradient coil heating which will produce a corresponding time-dependence in the coil resistance during the pulse sequence in addition to changes in amplifier performance. Thus, the degree of mismatch is also likely to increase as either the magnitude or the duration of the gradient pulses is increased. It was found that by using shaped gradient pulses (half-sine in the present instance) such that the pulse rise and fall times are decreased, the current amplifier was more able to generate reproducible gradient pulses. Slowing the rise and fall times also appears to reduce vibration problems. Although phase-based artifacts can also be reduced by prefixing gradient pulses before the PGSE sequence (e.g., (11)), this solution may only have limited applicability at high-gradient duty cycles. These results have extreme significance for high-gradient PGSE NMR diffusion measurements.

## MATERIALS AND METHODS

Two reasonably monodisperse polystyrene samples were prepared in 5-mm (od) NMR tubes: (1) a solution of an extremely high-molecular-weight polystyrene was prepared containing 8 mg polystyrene MW 20,000,000, MW/Mn = 1.3 (Cat. No. 16244, Polysciences, Inc., PA) in 0.1 ml CCl<sub>4</sub> and (2) a solution containing 10 mg of a lower molecular weight polystyrene MW 28,500, MW/Mn = 1.03 (Batch No. 20132-3, Polymer Laboratories, MA) in 0.1 ml CCl<sub>4</sub>. In both cases, the NMR sample heights were limited to about 5 mm so that the entire sample was well inside the constant region of the magnetic field gradient. These polystyrene samples, although having high molecular weights and low diffusion coefficients, have reasonably narrow linewidths favorable for use in PGSE NMR experiments.

Two NMR spectrometers were used: (1) a Bruker (Karlsruhe, Germany) DRX 300 (standard bore) spectrometer operating at a <sup>1</sup>H frequency of 300 MHz using a probe equipped with a Diff30 (actively shielded) gradient set powered by a BAFPA-40 current amplifier (max. output current = 40 A) with preemphasis capability. The spectrometer also had B<sub>0</sub> compensation powered by an additional BAFPA-40 amplifier. This system can provide gradient strengths, *g*, up to about 11.5 T m<sup>-1</sup>; (2) a modified JEOL (Tokyo) GSH 200 (wide bore) spectrometer controlled by a TecMag (Houston) GAL-AXY system operating at a <sup>1</sup>H frequency of 200 MHz. The JEOL spectrometer was equipped with an actively shielded gradient probe and a current amplifier supplied by JEOL providing gradient strengths up to 9.5 T m<sup>-1</sup>. Both spectrometers were able to produce rectangular or sine-shaped gradient pulses. All PGSE measurements were performed using a modified Hahn spin-echo sequence (i.e., the Stejskal and Tanner sequence) containing two identical rectangular or half-sine-

shaped gradient pulses (i.e., one pulse in each  $\tau$  period). The second half of the echo was acquired using quadrature detection and used as the FID (i.e., sampling was started from  $t = 2\tau$ ). The FID was Fourier transformed and displayed in either phase-sensitive or absolute value mode. All measurements were conducted at ambient temperature.

## RESULTS AND DISCUSSION

### *Initial System Characterization Using a Rectangular Gradient Pulse*

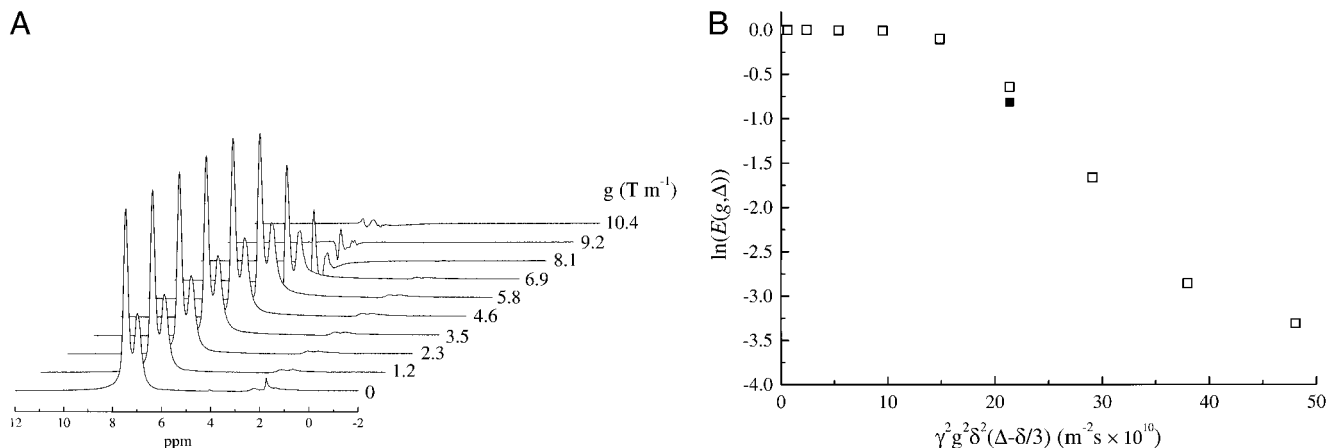
The eddy current settling time on the Bruker system after a gradient pulse was characterized using the high-molecular-weight polystyrene (MW 20,000,000) in the standard way (6, 9). The eddy current effects were found to have decayed to a negligible level by 3 ms after a rectangular gradient pulse of duration  $\delta = 2$  ms and strength  $g = 10.4$  T m<sup>-1</sup>. Similar performance was obtained for the JEOL spectrometer.

For the Stejskal and Tanner sequence using rectangular gradient pulses the echo signal attenuation due to free diffusion is given by (4, 12)

$$E_{\text{rectangular}}(g, \Delta) = \exp(-\gamma^2 g^2 D \delta^2 (\Delta - \delta/3)), \quad [1]$$

where  $\Delta$  is the separation between the start of the gradient pulses. Thus for the same polymer sample using the experimental parameters of  $\Delta = 20$  ms and  $\delta = 2$  ms and  $g$  values up to 10.4 T m<sup>-1</sup>, it can be realized that only very small signal attenuation should be achieved due to this polymer's very small diffusion coefficient ( $D \sim 1 \times 10^{-13}$  to  $1 \times 10^{-14}$  m<sup>2</sup>s<sup>-1</sup>; e.g., see Ref. (13)). However, even though delays considerably longer than 3 ms were allowed after the gradient pulses for the eddy currents to dissipate, significant attenuation and phase distortion were observed in the PGSE measurement, and these effects were observed to increase dramatically with  $g$  (see Fig. 1A). Thus, the observed attenuation is neither true diffusion-based attenuation nor artifactual attenuation due to eddy currents. This distortion results in an unphysical downward concave curvature in the corresponding attenuation plot shown in Fig. 1B (N.B., free diffusion should result in a straight line when the PGSE data are plotted on these axes). Further, the attenuation plot is different depending upon whether the integrals of the polymer resonances were taken from the phase-sensitive or absolute value spectra (not shown).

It is well-known that any gradient mismatch, that is, the integral over all gradients (i.e., applied including residual spikes and ringing or residual) present in the first  $\tau$  period does not equal that in the second  $\tau$  period, will result in the echo not refocussing at  $t = 2\tau$  (e.g., see Ref. (8)). Unfortunately this behavior is generally not obvious on modern spectrometers because of how the acquired signal is displayed and if it is assumed (as is normally the case) that  $t = 2\tau$  defines the top of the echo and sampling is begun at this point (i.e., the second



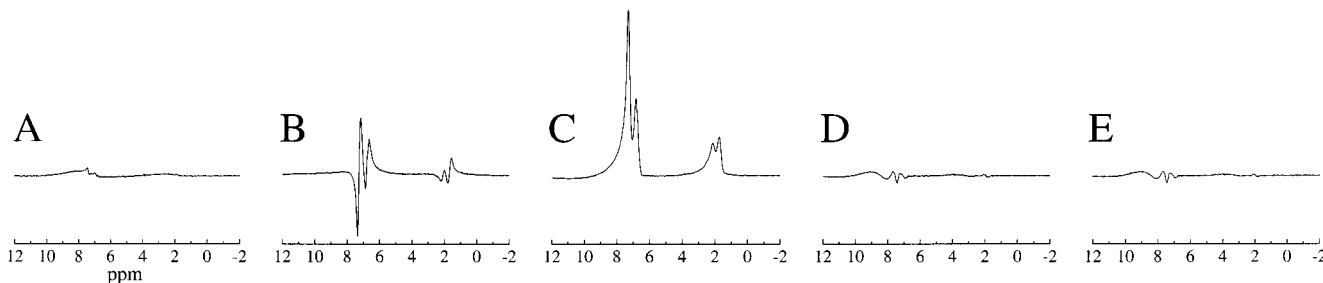
**FIG. 1.** (A)  $^1\text{H}$  PGSE NMR spectra of the extremely slowly diffusing MW 20,000,000 polystyrene sample using rectangular gradient pulses. The experimental parameters were  $\Delta = 20$  ms,  $\delta = 2$  ms, and  $g$  ranging in equal increments from 0 to  $10.4 \text{ T m}^{-1}$ . The spectra are plotted on the same scale and are presented in phase-sensitive mode. No attempt was made to accurately reference the chemical shift values. Each of the spectra is the average of four scans; however, similar results were found using only one scan. Within experimental error, the signal shows little attenuation or phase distortion up to  $g = 4 \text{ T m}^{-1}$ . Above  $g = 5 \text{ T m}^{-1}$  there was severe phase-shifts/distortion and it was not possible to phase the spectra into purely absorption lineshapes. Above  $7 \text{ T m}^{-1}$  severe artifactual attenuation (i.e., not diffusion related) of the signal was observed. The corresponding echo signal attenuation calculated using integrals of the phase-sensitive spectra (■) and integrals of the corresponding absolute value spectra (□) are plotted in (B). For smaller values of  $g$  the phase-sensitive and absolute value spectra give the same result (the data points are overlapped on the graph). However at larger values the phase-sensitive data attenuate more rapidly and in fact become negative after the seventh point (N.B., this negative excursion of the data is hidden if absolute value spectra are used). Of particular interest is the unphysical concave downward nature of the attenuation data.

half of the echo is used as the FID) the spectrum will be phase and amplitude distorted. Von Meerwall and Kamat (11) have shown that residual gradients such as eddy currents can cause the two  $\tau$  periods to be imbalanced and, if the residual gradients are a function of the amplitude of the gradient pulses, a downward curvature in the PGSE attenuation plot will result. They noted that this effect is generally only operative for small  $\Delta$  values where the residual gradients generated by the first gradient pulse have not totally decayed by the time of application of the (refocussing)  $\pi$  pulse and “feed through” into the second  $\tau$  period creating the imbalance. However, in the present experiments the delay after the gradient pulses was

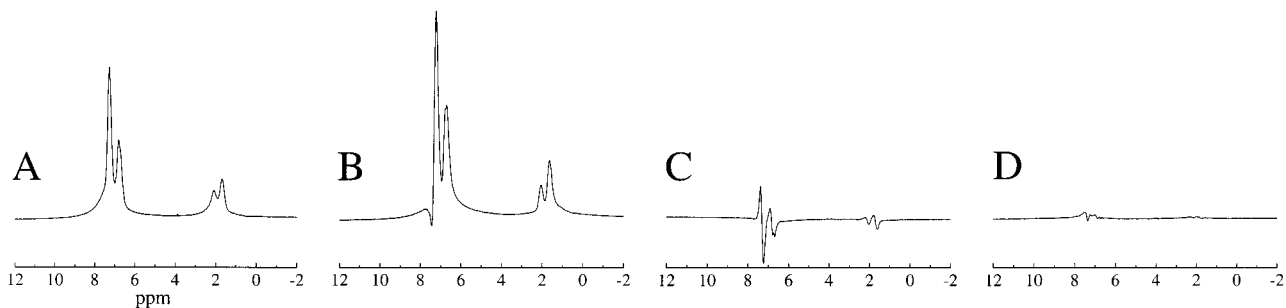
more than sufficient to allow all of the eddy currents to decay. We then attempted to find the source of the artifactual attenuation/phase-based artifacts starting with the knowledge that it was not due to eddy currents.

#### Intentional Residual Phase-Shift

We modified the Hahn spin-echo sequence so that the width of the two gradient pulses could be independently varied. Some examples of spectra obtained with very slightly duration mismatched high-amplitude ( $9.2 \text{ T m}^{-1}$ ) rectangular gradient pulses are shown in Fig. 2. It has been previously shown that



**FIG. 2.**  $^1\text{H}$  PGSE NMR spectra of the slowly diffusing MW 28,500 polystyrene sample obtained using varying degrees of intentional duration mismatched rectangular gradient pulses. The duration of the first gradient pulse (i.e.,  $\delta_1$ ) was fixed and the duration of the second gradient pulse (i.e.,  $\delta_2$ ) was varied. The spectra were acquired with  $g = 9.2 \text{ T m}^{-1}$ ,  $\Delta = 12$  ms,  $\tau = 20$  ms,  $\delta_1 = 1.0000$  ms, and  $\delta_2 =$  (A) 0.9990 ms, (B) 1.0000, (C) 1.0004, (D) 1.0010, (E) 1.0020 ms. All of the spectra are plotted on the same scale and are presented in phase-sensitive mode. These spectra show that the signal intensity is extremely sensitive to the degree of matching of the two sequential gradient pulses. Clearly the apparently matched pulses (i.e., spectrum B) are in reality not well matched and by increasing the duration of the second pulse by only  $0.4 \mu\text{s}$  (0.04%) a better match is obtained and much of the signal intensity is recovered and the phase distortion largely removed.



**FIG. 3.**  $^1\text{H}$  PGSE NMR spectra of the slowly diffusing MW 28,500 polymer using matched and intentionally duration mismatched sine-shaped gradient pulses with various gradient strengths. The sine-shaped gradient pulses were approximated by changing the gradient through 64 increments. The spectra were acquired with  $\Delta = 12$  ms and  $\tau = 20$  ms, using apparently matched (i.e.,  $\delta_1 = \delta_2 = 1.000$  ms) gradient pulses with  $g = 10.4$  T m $^{-1}$  (A) and mismatched (i.e.,  $\delta_1 = 1.000$  ms,  $\delta_2 = 0.999$  ms) gradient pulses with  $g =$  (B) 1.2, (C) 5.8, and (D) 10.4 T m $^{-1}$ . All of the spectra are plotted on the same scale and are presented in phase-sensitive mode. Spectrum (A) shows the maximum attenuation due to diffusion. From spectra B, C, and D, it can be seen that the effect of the mismatched gradient pulses becomes much more severe as the gradient strength increases (conversely the required precision of the match of the two gradient pulses increases with  $g$ ).

a small duration mismatch of the gradient pulses has an almost negligible effect on the attenuation of the signal due to diffusion (8, 14). For example, if the first and second gradient pulses have durations  $\delta_1 = \delta$  and  $\delta_2 = \delta + \varepsilon$ , respectively, then the attenuation function for free diffusion now becomes (14)

$$E_{\text{rectangular}}(g, \Delta) = \exp(-\gamma^2 g^2 D \delta^2 (\Delta - \delta/3) + \varepsilon^2 (2\tau - t_1 - \Delta - \delta - 2\varepsilon/3)), \quad [2]$$

where  $t_1$  is the time between the  $\pi/2$  pulse and the start of the first gradient pulse. We found that a small increase in the duration of the second gradient pulse considerably improved the phase and intensity of the observed spectrum (see Fig. 2C). The results in Fig. 2 show that with gradient strengths of the order of 9 T m $^{-1}$ , extreme accuracy in the matching of the gradient pulses is required (i.e., to considerably better than 99.996%) if the spectra are not to be distorted. Clearly these intentionally duration mismatched spectra are very similar to those observed using (apparently) equal gradient pulses (i.e., see Fig. 1A). This shows that the true cause of the attenuation and spectral disturbances is not eddy currents but in reality very small gradient pulse mismatch. To further illustrate this effect we acquired more PGSE spectra with intentionally duration mismatched sine-shaped gradient pulses and increased the gradient magnitude, the results are shown in Fig. 3. The reason for using the sine-shaped gradient pulses, as shown below, is that they are easier to reproducibly generate. It is clear that the degree of spectral disturbance increases drastically with gradient strength. Put another way, to obtain undistorted spectra the precision required of the gradient pulse match expressed as a fraction of the integral of the gradient pulses must increase with  $g$ .

### Theoretical Analysis of Residual Phase-Twist and Residual Phase-Shift Effects

It is interesting to theoretically consider the effects of the gradient pulse mismatch and vibration/sample movement. We define

$$\mathbf{q} = \frac{1}{2\pi} \mathbf{g} \gamma \delta (\text{m}^{-1}) \quad [3]$$

and perform an analysis similar to that of Callaghan (7). Starting from the average propagator representation (15) of the short gradient pulse approximation, but including the effects of a phase-shift,  $\phi$ , due to the effects of a gradient mismatch,  $\Delta\mathbf{q}$ , and sample movement,  $\Delta\mathbf{r}$ , between the first and second gradient pulses in the PGSE sequence (N.B., in  $\Delta\mathbf{q}$  and  $\Delta\mathbf{r}$  “ $\Delta$ ” denotes differential and is not to be confused with the interval  $\Delta$  between the gradient pulses). Thus we have (7)

$$E(\mathbf{q}, \Delta) = \int \rho(\mathbf{r}_0) \int P(\mathbf{R}, \Delta) e^{i[2\pi\mathbf{q}\cdot\mathbf{R} + \phi]} d\mathbf{R} d\mathbf{r}_0, \quad [4]$$

where  $\rho(\mathbf{r}_0)$  is the spin density,  $\mathbf{R}$  is the dynamic displacement defined by  $\mathbf{r}_1 - \mathbf{r}_0$  (the starting and finishing positions of a spin with respect to the first and second gradient pulses),  $P(\mathbf{R}, \Delta)$  is the average propagator (i.e., the probability that a spin will move by a displacement  $\mathbf{R}$  during the time interval  $\Delta$ ), and the phase term can be expressed as

$$2\pi\mathbf{q} \cdot \mathbf{R} + \phi = 2\pi[(\mathbf{q} + \Delta\mathbf{q}) \cdot (\mathbf{r}_0 + \mathbf{R} + \Delta\mathbf{r}) - \mathbf{q} \cdot \mathbf{r}_0]. \quad [5]$$

For simplicity the gradient (and therefore  $\mathbf{q}$ ) is taken to be oriented along the  $z$ -direction and it is assumed that  $\Delta\mathbf{q}$  is parallel to  $\mathbf{q}$  (i.e., a magnitude mismatch). Thus we are only

concerned with the  $z$ -components of  $\mathbf{r}_0$ ,  $\mathbf{R}$ , and  $\Delta\mathbf{r}$  (i.e.,  $z_0$ ,  $Z$ , and  $\Delta z$ , respectively) and so Eq. [5] becomes

$$2\pi\mathbf{q} \cdot \mathbf{R} + \phi = 2\pi[qZ + (q + \Delta q)\Delta z + \Delta qz_1], \quad [6]$$

and thus, Eq. [4] can be rewritten as

$$E(q, \Delta) = \underbrace{\int P(Z, \Delta) e^{i2\pi qZ} dZ}_{E_{\text{diff}}(q, \Delta)} \underbrace{\{ e^{i2\pi(q + \Delta q)\Delta z} \}}_{\phi(\Delta z)} \underbrace{\int \rho(z_1) e^{i2\pi\Delta qz_1} dz_1}_{E_{\text{phase}}(\Delta q)}. \quad [7]$$

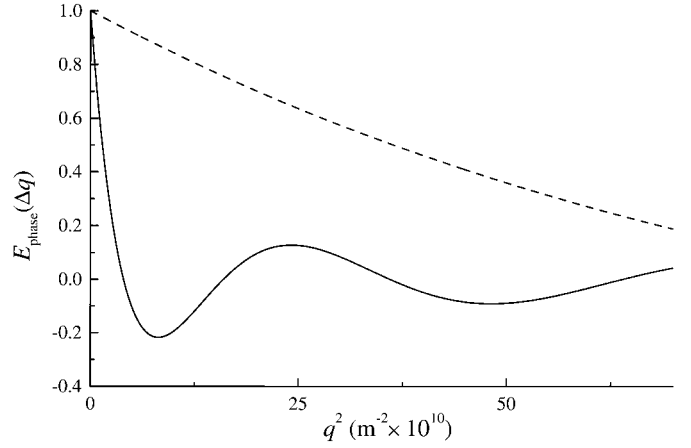
The first term (i.e.,  $E_{\text{diff}}(q, \Delta)$ ) is the attenuation due to diffusion and it is what is really sought in a PGSE measurement.  $E_{\text{diff}}(q, \Delta)$  is a real valued function. In the case of free diffusion it is given by Eq. [1] (N.B., strictly the  $-\delta/3$  correction term should be removed in the short gradient pulse approximation).

The second term (i.e.,  $\phi(\Delta z)$ ) is the residual phase-shift due to vibration/sample movement (or flow). This term is a complex valued function and produces net-phase-shifts and is likely to produce complicated phase behavior through the series of spectra in a PGSE measurement since  $\Delta z$  is likely to be a function of  $q$ . Note that this term depends on  $\Delta z$  and not on  $z$  (i.e., it is position-independent). As noted by Callaghan (7), the effects of  $\phi(\Delta z)$  can be removed by individually phase correcting each spectrum or by computing the absolute value (or magnitude) spectrum (recall,  $|\exp(i2\pi(q + \Delta q)\Delta z)| = 1$ ), although this entails a loss of signal resolution and makes all of the noise in the spectrum positive. If the degree of sample movement is not constant for a given  $q$  and if a number of scans are averaged, this term has the potential to produce some signal attenuation. Nevertheless, this problem can still be removed by individual phasing or computing the absolute value spectrum after each scan and then adding the spectra.

The third term (i.e.,  $E_{\text{phase}}(\Delta q)$ ) is the residual phase-twist resulting from the gradient pulse mismatch. It is the integral of the position (i.e.,  $z$ )-dependent phase-shifts (this has clear similarity to  $\mathbf{k}$ -space encoding in imaging, e.g., Refs. (2, 16)), and is independent of  $D$  and the interval  $\Delta$ . This term can result in severe artifactual signal attenuation.  $E_{\text{phase}}(\Delta q)$  contributes a sample shape (relative to the gradient orientation) -dependent signature to  $E(q, \Delta)$  and thus  $E_{\text{phase}}(\Delta q)$  is different for different sample/gradient geometries. For a cylindrical sample of length  $l$  centered in the gradient we obtain

$$E_{\text{phase}}(\Delta q) = \frac{\int_{-l/2}^{l/2} e^{i2\pi\Delta qz_0} dz_0}{l} \quad [8]$$

$$= \text{sinc}(\pi\Delta ql).$$

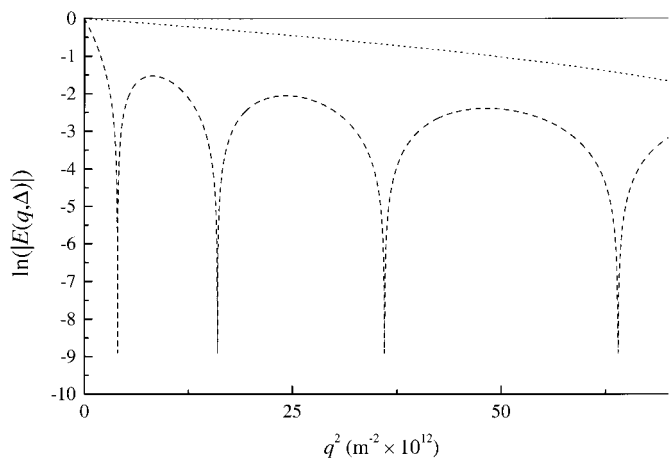


**FIG. 4.** Plots of  $E_{\text{phase}}(\Delta q)$  calculated using Eq. [8] with  $l = 5$  mm and  $\Delta q = q \times 2 \times 10^{-4}$  (---) which corresponds to, for example, a  $0.4\text{-}\mu\text{s}$  error mismatch between a pair of  $2\text{-ms}$  gradient pulses and  $\Delta q = q \times 10^{-3}$  (—) which corresponds, for example, to a  $2\text{-}\mu\text{s}$  mismatch between a pair of  $2\text{-ms}$  gradient pulses. The plots show that increasing pulse mismatch causes an enormous loss of signal intensity.

Some example plots of  $E_{\text{phase}}(\Delta q)$  are shown in Fig. 4, where it has been simplistically assumed that  $\Delta q$  is a fixed proportion of  $q$ .  $E_{\text{phase}}(\Delta q)$  is a damped oscillation with the degree of damping and the periodicity being exquisitely sensitive to the degree of mismatch. Note that the  $E_{\text{phase}}(\Delta q)$  term cannot be removed by phase correction or by computing absolute value spectra. However, computing absolute value spectra will make negative attenuations positive. Further, if the sample is not centered in the gradient,  $E_{\text{phase}}(\Delta q)$  will be a complex valued function.

#### Diagnosing the Presence of Phase-Based Artifacts in PGSE NMR Data

We now consider the case of signal attenuation including the effects of attenuation due to diffusion and phase-twist artifacts for the case of a gradient oriented along the long axis of a cylindrical sample. In addition to the aforementioned reasons, phase-sensitive Fourier transformed spectra are preferred over absolute value spectra when analyzing PGSE spectra because they are more informative about the presence of phase-based artifacts. Further, as pointed out by Stilbs (1), the individual bandshapes of absolute value Fourier transformed spectra are not additive in overlapping regions. Some example plots of  $\ln(|E(q, \Delta)|)$  are presented in Fig. 5. It can be clearly seen that as the mismatch increases, the measured (i.e., apparent) diffusion coefficient increases; this is in agreement with ‘‘Callaghan’s law’’ (5) that any error in the PGSE sequence results in a larger apparent diffusion coefficient. At larger values of  $q$ , artifactual diffractive minima occur and these move to lower values of  $q$  as the degree of mismatch (i.e.,  $\Delta q$ ) increases. Generally such artifactual diffraction peaks would not be visible in measurements of a small freely diffusing species since



**FIG. 5.** Plots of  $\ln(|E(q, \Delta)|)$  calculated using Eqs. [7] and [8] with  $D = 1 \times 10^{-14} \text{ m}^2 \text{ s}^{-1}$ ,  $\Delta = 20 \text{ ms}$ ,  $l = 5 \text{ mm}$ ,  $\Delta z = 0 \text{ mm}$ , and  $\Delta q = 0$  (—) (i.e., no mismatch, this corresponds to  $E_{\text{diff}}(q, \Delta)$ ),  $\Delta q = q \times 2 \times 10^{-4}$  (⋯) and  $\Delta q = q \times 10^{-3}$  (---). With such a low value of  $D$  the diffusive attenuation should be negligible as shown for the case of  $\Delta q = 0$ , however, the residual phase-shift resulting from gradient pulse mismatch causes enormous artifactual attenuation resulting in a huge increase in the apparent diffusion coefficient (i.e., if the attenuation data are interpreted assuming that all of the observed attenuation resulted from  $E_{\text{diff}}(q, \Delta)$ ). At larger  $q$  values (and therefore  $\Delta q$ ) artifactual diffraction peaks are evident. The degree of mismatch strongly influences the position of the diffraction peaks with the diffractive peaks appearing at smaller values of  $q$  as the degree of mismatch increases.

the signal would already have decayed by diffusive attenuation ( $E(q, \Delta)$  is dominated by  $E_{\text{diff}}(\Delta q)$ ). However, this is not the case for very slowly diffusing species (e.g., large polymers; see, for example, Fig. 6) or species undergoing restricted diffusion. The origin of the diffraction effects would be particularly confusing in systems where restricted diffusion is expected. A significant difference between artifactual and real diffraction peaks is that the real diffraction peaks generally do not appear until the signal has more significantly attenuated.

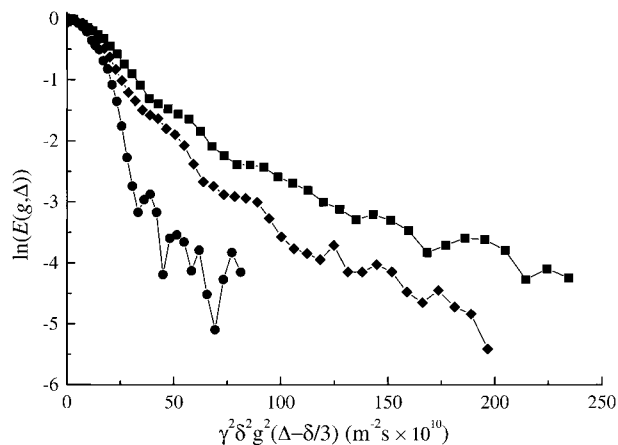
The presence of phase-based artifacts can be detected by performing measurements on a freely diffusing sample with a very small diffusion coefficient (e.g., large polymer) using the same experimental parameters (i.e.,  $q$  and  $\Delta$ ) to be used in the intended experiment. Thus there should be little attenuation and true diffraction peaks cannot occur. If there is significant attenuation, especially unphysical concave downward curvature in the attenuation plots and phase distortion, the presence of gradient pulse mismatch can be assumed and possibly also sample movement/vibration. If a phase-shift is observed but there is little attenuation after taking absolute value spectra it is likely to result from sample movement/vibration. If there is no sample vibration/movement or gradient pulse mismatch there would be no  $q$ -dependent phase change and the signal attenuation determined from either phase-sensitive data or absolute value data would be the same. We note that if the sample were repositioned slightly away from the center of the gradient, but still within the constant region of the gradient, then  $E_{\text{phase}}(\Delta q)$  would become a complex valued function, whereas such repositioning would leave  $\phi(\Delta z)$  unchanged. This procedure may provide further information on the source of phase-based artifacts.

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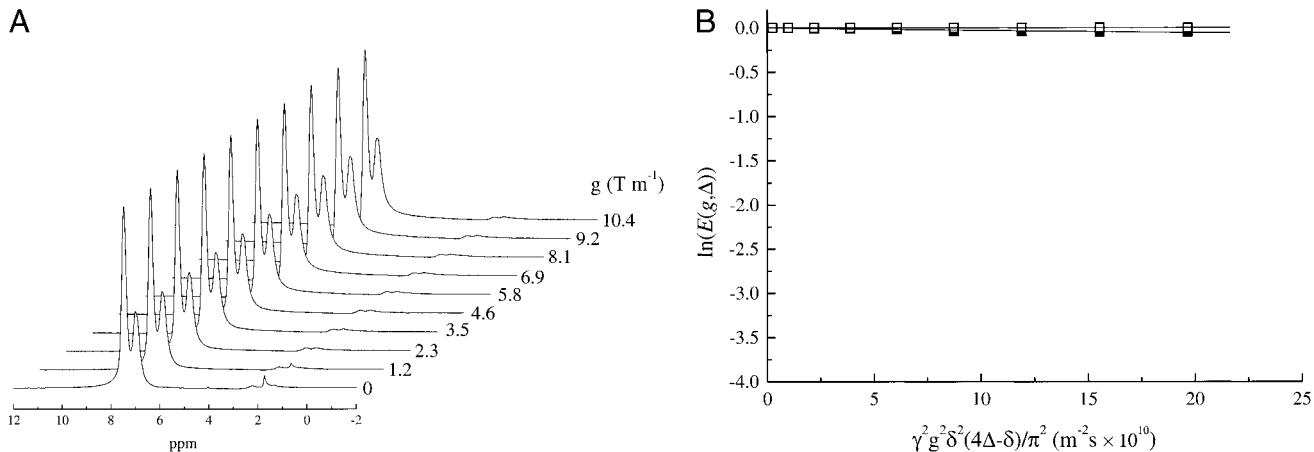
### Means for Reducing Phase-Based Artifacts

It is well-known that residual phase-shifts due to vibration/sample movement can be reduced by making the probe, gradient coil, sample, and means of holding the sample more rigid (5, 10). In any case, as mentioned above, this problem can always be removed by individual phasing of the PGSE spectra or by computing absolute value spectra.

The means for removing the residual phase-twist resulting from gradient pulse mismatch are more troublesome. Modern current amplifier designs have considerably improved the reproducibility of the current pulses, for example, Boerner and Woodward (17) have developed a current amplifier capable of providing rectangular pulses of up to 15 A, which can generate gradient pulses with amplitudes of up to  $3.1 \text{ T m}^{-1}$  which are matched apparently to within 10 ppm. Nevertheless most users are limited to nonhardware solutions to the gradient mismatch problem such as empirically matching the gradient pulse pairs by finely adjusting the duration of one of the pulses so that the maximum echo signal is obtained. However, this approach is tedious and difficult due to the very high precision needed, especially with very large gradients. Further, the correction



**FIG. 6.**  $^1\text{H}$  PGSE attenuation data of the extremely slowly diffusing MW 20,000,000 polystyrene sample acquired on the JEOL spectrometer. The data were acquired using rectangular gradient pulses with three different values of  $\Delta$  (●, 20 ms; ◆, 30 ms, and ■, 40 ms) with  $g$  set to  $6.5 \text{ T m}^{-1}$  and varying  $\delta$ . The phase-sensitive spectra (not shown) had noticeable phase disturbances. The integrals were taken from absolute value spectra. Particularly interesting are the large changes in the attenuation curves with  $\Delta$ . Due to the relatively small range of  $\Delta$  used, it is unlikely that the large difference in attenuation between the three plots results from different time-dependencies of the polymer reptational motion and entanglement. At the smallest value of  $\Delta$  used (i.e., 20 ms) artifactual diffraction peaks are clearly apparent. A measurement was subsequently performed using sine-shaped gradient pulses (the sine-profile was approximated by dividing  $\delta$  into 90 increments of  $g$ ) and only very small attenuation was observed.



**FIG. 7.** (A) A  $^1\text{H}$  PGSE NMR diffusion measurement similar to that shown in Fig. 1 using the extremely slowly diffusing MW 20,000,000 polystyrene sample except that now sine-shaped gradient pulses are used. The sine-shaped gradient pulses were approximated by changing the gradient amplitude through 64 increments. The spectra are plotted on the same scale and are presented in phase-sensitive mode. There is much less artifactual attenuation than observed for the rectangular gradient pulse; nevertheless even using the sine-shaped gradient pulses there is evidence of slight phase distortion at higher  $g$  values. Note that for the same duration and gradient amplitude a sine gradient pulse has an integral of only  $\sim 0.64$  of its rectangular counterpart and an alternative comparison can be made via the corresponding attenuation plots given in (B) where the same ordinate scale has been used as in Fig. 1B together with the same units for the abscissa. The integrals of the phase-sensitive spectra are denoted by (■) and integrals of the corresponding absolute value spectra are denoted by (□). At small values of  $g$  the phase-sensitive and absolute value data points are overlapped. Although the small degree of attenuation precludes an accurate estimation of the diffusion coefficient, linear regression of Eq. [9] on the data (denoted by the solid lines) gives the diffusion coefficient of the polymer to be  $2.9 \pm 0.3 \times 10^{-13} \text{ m}^2\text{s}^{-1}$  using the phase-sensitive data and  $1.5 \pm 0.6 \times 10^{-14} \text{ m}^2\text{s}^{-1}$  using the absolute value data.

time depends on  $g$ ,  $\delta$ , and  $\Delta$  and above all, for a given set of experimental conditions, the degree of mismatch may not be a constant.

Another approach is the MASSEY sequence (7) which uses an imaging approach to remove the phase-twist. A limitation with this approach is that it is not suitable for spectra containing more than one resonance since the free induction decay is acquired in the presence of a read gradient. Similarly the imposition of a background gradient in the PGSE experiment increases the likelihood of attaining the refocusing condition so that the echo maximum occurs close to the ideal case of  $t = 2\tau$  (8, 11, 12), but again at the expense of spectral resolution.

Two simpler solutions for reducing the phase-twist problem but which retain spectral information are: (i) to use a number of dummy gradient pulses (“prepulses”) prior to the PGSE sequence (5, 11) to increase the reproducibility of the pulses or (ii) to use shaped gradient pulses with slower rise times (e.g., ramped or sine-shaped (14)) that are easier to generate reproducibly by the amplifier electronics (i.e., slew rate and feedback circuits). We tried a series of prepulses spaced by  $\Delta$  and kept the interval between the last of the dummy gradient pulses and the  $\pi/2$  pulse and the first gradient pulse in the PGSE sequence and the  $\pi$  pulse the same. The rationale behind keeping the gradient pulses equally spaced by  $\Delta$  is that the amplifier response and gradient coil temperature might more closely attain a steady state, whereas by keeping the separation of the gradient pulses with respect to the  $\pi/2$  and  $\pi$  pulses the same, (any) eddy current contributions should be the same in both  $\tau$  periods (11). We found that while one gradient prepulse

was a significant improvement over no prepulses and two prepulses were much better than one, there was little further improvement by using three prepulses. We note, however, that such prepulses add significantly to the duty cycle of the gradients and thus for very high gradients their implementation may be dangerous to the gradient coil. Comparable, if not better, results were obtained using shaped gradient pulses (see Fig. 7). The attenuation due to free diffusion in the Stejskal and Tanner sequence using half-sine-shaped gradient pulses is given by (14)

$$E_{\text{sine}}(g, \Delta) = \exp(-\gamma^2 g^2 D \delta^2 (4\Delta - \delta) / \pi^2). \quad [9]$$

Rectangular gradient pulses are the ideal shape since they maximize the degree of dephasing in a given time, thereby giving the closest correspondence with the short gradient pulse approximation which allows considerable mathematical simplification in modeling the echo attenuation in complicated systems (e.g., (18)). Further, on older spectrometers it was generally easier to design gradient generation systems that, at least theoretically, produced rectangular pulses. By using sine-shaped gradient pulses the sequential reproducibility of the gradient pulses is greatly increased even if the gradient strength is very large. Of course for the same duration, the rectangular gradient pulses produce greater attenuation but by comparing Eqs. [1] and [9], we can see that at a gradient strength of  $10.4 \text{ T m}^{-1}$ ,  $\delta = 2 \text{ ms}$ ,  $\Delta = 20 \text{ ms}$ , and  $D = 1 \times 10^{-13} \text{ m}^2\text{s}^{-1}$ , the attenuation of the echo signal produced by the rectangular

gradient pulses should only be a little more than double that produced by the sine-shaped gradient pulses (i.e.,  $E_{\text{rectangular}} = 0.94$  and  $E_{\text{sine}} = 0.98$ ). However, by comparing Figs. 1 and 7 we can see that the attenuation produced by the rectangular pulses is much more than physically possible due to diffusion and clearly results from the effects of gradient pulse mismatch. Slightly better results were obtained by using sine-shaped gradient pulses and prepulses.

With modern spectrometers and sophisticated software control, almost any conceivable gradient pulse shape is possible; however, starting from the Bloch–Torrey equations only some gradient pulse shapes lead to compact solutions akin to Eqs. [1] or [9]; other possibilities are given elsewhere (e.g., (6, 14)). The slower rise times associated with not-quite-rectangular gradient pulses also have the advantage of decreasing eddy current generation (e.g., (6, 12)). Also, we found that application of large-magnitude rectangular pulses caused a “clicking” sound from the probe indicative of some form of physical movement; however, such clicking was not audible with sine-shaped gradient pulses. Thus the sine-shaped pulses are less likely to cause vibrations. Further, “ringing” was observed on the top of the rectangular gradient pulses when observed using an oscilloscope. Such ringing was not observed with sine-shaped gradient pulses.

### CONCLUSIONS

This work has shown that while eddy currents are undoubtedly a major problem in very-high-gradient PGSE, phase artifacts, especially the residual phase-twist due to mismatched gradient pulses, are very troublesome. Even extremely small gradient pulse mismatch results in an increase in the measured diffusion coefficient. Importantly mismatch can even generate artifactual diffraction peaks which can be confused with genuine diffractive phenomena. When using rectangular gradient pulses, mismatch effects increase drastically with gradient strength. Although gradient prepulses can be used to reduce the mismatch their use may be restricted by the allowable duty cycle of the gradient system. A more generally practicable solution is to use gradient pulses with slower rise and fall times (e.g., half-sine-shaped gradient pulses). Ideally both of these approaches would be used in the PGSE sequence. Phase-sensitive spectra are preferable to absolute value spectra for determining the presence of phase-based artifacts.

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