Diffusion Measurements at Long Observation Times in the Presence of Spatially Variable Internal Magnetic Field Gradients

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Diffusion measurements in heterogeneous media may contain a significant source of error, the influence of the coupling between the applied and internal magnetic field gradients on the attenuation of the NMR signal. The application of bipolar magnetic field gradients has been introduced to suppress this error. The basic assumption for the successful removal of the coupling is that the diffusing molecules are experiencing a constant internal gradient during the experiment. We will provide theoretical and experimental evidence that the application of bipolar magnetic field gradients may fail to suppress the effect from all the cross terms between internal and applied gradients effectively at long observation times. It will be shown experimentally that a successful suppression of the cross terms is strongly dependent on the observation time, and on the τ value in the bipolar pulsed field gradient stimulated echo experiment. © 2000 Academic Press

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INTRODUCTION

When a heterogeneous sample is placed in a constant magnetic field, internal magnetic field gradients are induced. The strength of these gradients depends on the magnetic susceptibility difference when going from one phase to another in the heterogeneous sample, on the operating magnetic field, and on the different geometries of phases within the sample (*1*). Due to the heterogeneity of the sample, the internal gradients may consist of a large distribution of values with both polarities (*2, 3*). As diffusion measurements by NMR are performed by introducing applied magnetic field gradients into the pulse sequence, a coupling between the applied and internal gradients will occur in the echo attenuation of the NMR signal (*4*). The measured diffusivity may therefore not correspond to the actual diffusion coefficient of the probing molecules within the heterogeneous sample (*2*).

Over the past decade several pulse sequences applying bipolar magnetic field gradients for diffusion measurements in heterogeneous media have been proposed in order to suppress the cross terms between the applied and the internal magnetic field gradients (*5–7*). The basic assumption for the successful

removal of these cross terms is that each diffusing molecule is experiencing a constant internal magnetic field gradient throughout the pulsed field gradient stimulated echo (PFGSTE) sequence (*6*). If this assumption fails, it is no longer generally valid that a significant cross term is absent in the echo attenuation. Latour *et al.* (*5*) has unambiguously shown the effect caused by a nonuniform internal gradient during the preparation and read intervals in the PFGSTE experiment. However, one must also consider the effect of a change in the strength and/or the polarity of the internal gradient experienced by a diffusing molecule when going from the preparation to the read interval in the bipolar PFGSTE experiment (Fig. 2). The purpose of this article is to provide evidence that even if the attenuation results from a bipolar magnetic field gradient experiment with a τ value so short that the constant internal gradient approximation holds for the preparation and read intervals, there may still be cross terms which affect the measured diffusivity significantly.

BIPOLAR PFGSTE IN THE PRESENCE OF INTERNAL GRADIENTS

Tanner (*4*) showed the existence of the cross terms in an ordinary monopolar PFGSTE experiment, for which (Fig. 1) the attenuation is written (*4*)

$$
\ln\left(\frac{I}{I_0}\right) = -\gamma^2 D\bigg[\delta^2(\Delta + \tau - \delta/3)\, g^2
$$
$$
+ \delta\bigg(2\tau\Delta + 2\tau^2 - \frac{2\delta^2}{3}
$$
$$
- \delta(\delta_1 + \delta_2) - (\delta_1^2 + \delta_2^2)\bigg) g G_0
$$
$$
+ \tau^2\bigg(\Delta + \frac{2\tau}{3}\bigg) G_0^2 \bigg]. \quad [1]
$$

γ is the gyromagnetic ratio, D is the diffusion coefficient, g is the applied magnetic field gradient, and G_0 is the internal
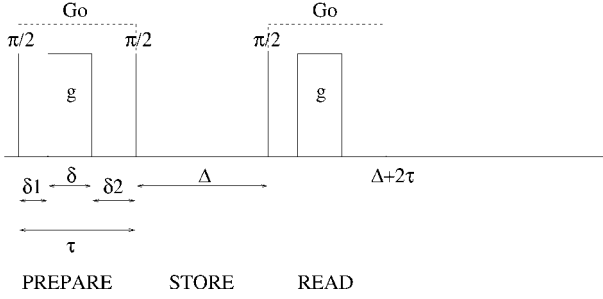
FIG. 1. The ordinary PFGSTE sequence with monopolar gradients.

FIG. 3. The 13-interval PFGSTE sequence with unequal bipolar gradients. The real polarity of G_0 is changed from the preparation interval to the read interval.

magnetic field gradient. The time constants δ_1, δ_2, δ, τ, and Δ are defined according to Fig. 1, and the procedure for deriving the echo attenuation from a pulsed field gradient sequence is given in Refs. (6, 7, 9). From Eq. [1] one finds cross terms between the applied and internal magnetic field gradient.

Due to these cross terms, an erroneous interpretation of the measured diffusivity is likely to occur. The measured diffusivity using this sequence in the presence of internal magnetic field gradients will be lower than the actual diffusion coefficient, as found by Zhong *et al.* (2), who based their argument on the presence of internal gradients of both polarities.

The impact of the cross terms in Eq. [1] may be greatly reduced when applying a bipolar 13-interval pulsed field gradient stimulated echo sequence as shown in Fig. 2. The echo attenuation is written (6, 7)

$$\ln\left(\frac{I}{I_0}\right) = -\gamma^2 D\Big[\delta^2(\Delta + 3\tau - \delta/3)g^2$$
$$+ \delta^2(\Delta + \tau - \delta/3)f^2 + 2\delta^2(\Delta + \tau)gf$$
$$+ \delta\tau(\delta_1 - \delta_2)(f + g)G_0 + \frac{4\tau^3}{3}G_0^2\Big]. \quad [2]$$

When letting δ_1 equal δ_2, the cross terms are suppressed completely. However, the assumption of constant internal gradients is valid only at observation times during which the molecules are not probing the heterogeneity of the medium (6, 9). This range of observation times is also denoted short observation times, and it has been shown that the bipolar gradient pulses effectively suppress the cross terms in this range (10). When the observation time is of such length that the
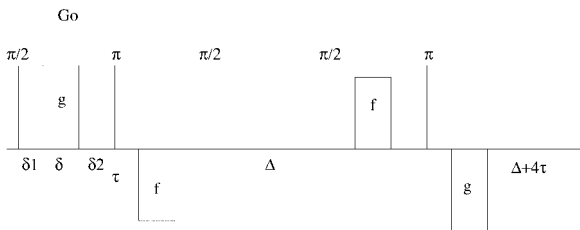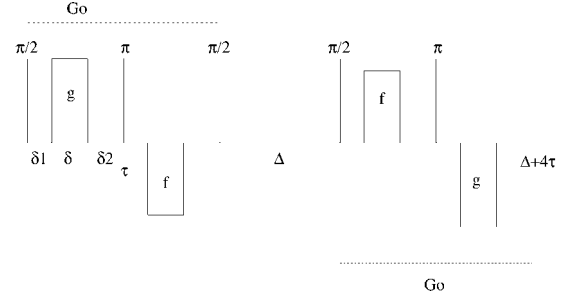
molecules probe the heterogeneity of the medium, the correlation is practically lost between the strength and the polarity of the internal gradients in the preparation and the read interval.

In Fig. 3 the situation with an internal gradient of opposite polarity but the same strength in the read interval is displayed. At long observation times this situation is just as probable as the situation shown in Fig. 2. The echo attenuation for this sequence is written

$$\ln\left(\frac{I}{I_0}\right) = -\gamma^2 D\Big[\delta^2(\Delta + 3\tau - \delta/3)g^2$$
$$+ \delta^2(\Delta + \tau - \delta/3)f^2 + 2\delta^2(\Delta + \tau)gf$$
$$+ \delta/3((2\delta_1^2 + 2(\delta_1 + \delta)^2$$
$$+ \delta_1(2\delta_2 - 3\tau) - 3\delta2\tau)(f - g)$$
$$+ 3\tau^2(f + 3g))G_0 + \frac{4\tau^3}{3}G_0^2\Big]. \quad [3]$$

Comparing the cross terms in Eq. [1] and Eq. [3], it is evident that the Δ-dependent cross term still is suppressed. However, the τ-dependent cross term is now not suppressed, and when $f \simeq g$ the surviving cross term is written

$$\ln\left(\frac{I}{I_0}\right)_{\text{cross}} = -4\gamma^2 D\delta\tau^2 gG_0. \quad [4]$$

Such a τ-dependent term is also present if one makes use of the more sophisticated 17-interval bipolar PFGSTE sequences (6). In order to have the echo attenuation within the domain where the second cumulant approximation is valid (11), the strength of the applied gradient pulses must be reduced when Δ is increased. The unwanted cross terms in Eq. [3] may then become significant compared to the other terms. So the question is then to what extent this affects the echo attenuation and thus the measured diffusivity.

FIG. 2. The 13-interval PFGSTE sequence with unequal bipolar gradients (7).

EXPERIMENTAL

All the experiments were performed on a Bruker Avance DMX200 instrument, using a commercial diffusion probe from Bruker (PH MIC DIF 200 WB ^{1}H SAT 5/10 probe). An applied gradient strength in the range 0–960 G/cm was used. Unless stated otherwise, the experiments were performed at a temperature of $25.0 \pm 0.5°C$.

Mono-sized spheres immersed in distilled water were studied. Two types of polystyrene and soda lime glass spheres were used, one set with a mean diameter of 30 μm, and one set with a mean diameter of 100 μm. The samples were prepared by immersing the particles in distilled water, followed by treatment in an ultrasonic bath, in order to achieve a good and similar packing of the different samples. All samples were delivered from Duke Scientific (U.S.A.).

The 13-interval stimulated echo pulse sequence with unequal bipolar gradients (Fig. 2) was used in all of the diffusion experiments. In each diffusion experiment the different time intervals were kept constant, while the strength of the gradients was varied. The length of the gradient (δ) was 0.5 ms in most of the experiments. In the experiments where it was necessary to have as low a τ value as possible we used $\delta = 0.25$ ms.

Gradient preemphasis was applied, and the dead time (δ_2) achieved was 0.3 ms for the gradient strengths used in our experiments. In order to minimize the cross terms between applied and internal gradients all the diffusion experiments were performed with $\delta_1 = \delta_2$.

The applied gradient strength was calibrated by performing diffusion experiments in distilled water slightly doped with $CuSO_4$.

The diffusion coefficients were determined from the initial slope of the attenuations, according to the second cumulant approximation (11), which predicts a Gaussian behavior at low values of the gradient strength.

RESULTS AND DISCUSSION

Because of the dephasing of magnetization originating from molecules diffusing in internal magnetic field gradients, the bandwidth of a spectrum gives an indication of the size of the internal gradients in a system. For water in the system of polystyrene spheres (both 30 and 100 μm) the bandwidth at half-height was around 30 Hz, indicating that the size of the internal gradients is low in these systems. For water in the system of 100-μm glass spheres the bandwidth at half-height was 1500 Hz, while for the system of 30-μm glass spheres it was around 2000 Hz. According to Drain (1) the size of the internal gradients in a system of grains surrounded by a liquid is approximately given by

$$g_i \approx \frac{\Delta B_0}{d_{grain}}. \qquad [5]$$

Here ΔB_0 is the broadening of the magnetic field (induction) caused by susceptibility changes in the sample, and d_{grain} is the mean diameter of the particles (grains). ΔB_0 is related to the total transverse dephasing time, T_2^*, and the transverse nuclear magnetic relaxation time, T_2, according to the relation (12)

$$\gamma \frac{\Delta B_0}{2} = \left(\frac{1}{T_2^*} - \frac{1}{T_2} \right). \qquad [6]$$

The inhomogeneity contribution caused by the superconducting magnet is then neglected. If the internal gradients are large, $T_2 \gg T_2^*$, and the second term on the right-hand side of Eq. [6] can be neglected. Since $\Delta \nu = 1/\pi T_2^*$, where $\Delta \nu$ is the linewidth at half-height of the Fourier-transformed signal from the water between the spheres, the size of the internal gradient is approximately given by

$$g_i \approx \frac{2\pi}{\gamma} \frac{\Delta \nu}{d_{grain}}. \qquad [7]$$

Using this relationship, the internal gradients in the polystyrene samples are estimated to be less than 1 G/cm, while the values for the 30- and 100-μm glass spheres were 160 and 40 G/cm, respectively. These estimates indicate that there are large internal gradients in the systems of glass spheres, while in the polystyrene systems the internal gradients are insignificant.

In the standard diffusion experiment (Fig. 1) one should therefore expect to see effects from the cross term between internal and applied gradients when studying the glass sphere systems. No effects should be observed studying the polystyrene sphere systems, regardless of pulse sequence used.

In Fig. 4 the results from the time-dependent diffusion measurements in the 30- and 100-μm systems, using the bipolar 13-interval PFGSTE pulse sequence, are presented. The measured normalized diffusion coefficients are plotted as a function of the effective observation time. It clearly shows that the time dependency of the diffusion coefficients of the polystyrene and glass systems is different. The systems show an equal behavior at short observation times, but as the observation time increases, the diffusion coefficient for the glass sphere system drops to a lower level than what is seen in the corresponding polystyrene system. In the 30-μm system the separation of the curves starts very early, and at a diffusion time of around 10 ms, the deviation is clear. In the 100-μm system, the separation of the curves starts at an effective diffusion time of around 150 ms. This corresponds to a diffusion distance, $\sqrt{6D(t)t}$, of about 10 and 45 μm, respectively.

The idea behind studying a system of glass spheres and a polystyrene system with similar sphere diameters immersed in water is that the polystyrene system does not generate significant internal magnetic gradients, while the glass sphere system does generate such internal gradients. These internal gradients are found to be of the same order of magnitude as the applied magnetic field gradients. However, before assigning the results shown in Fig. 4 to an effect of a spatially variable internal
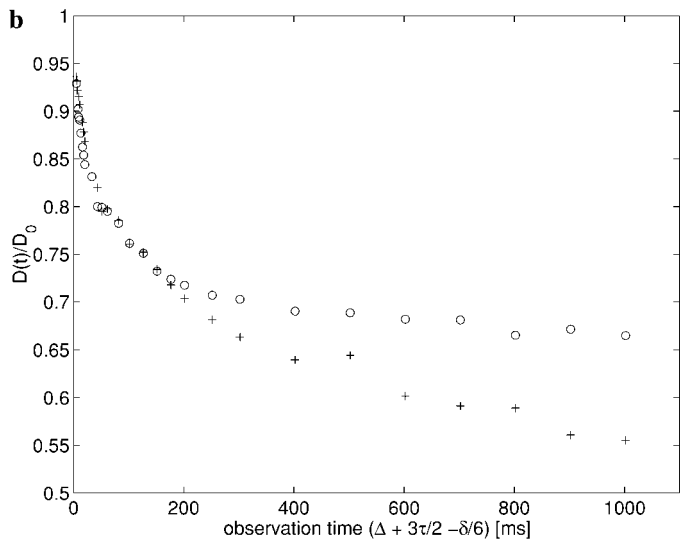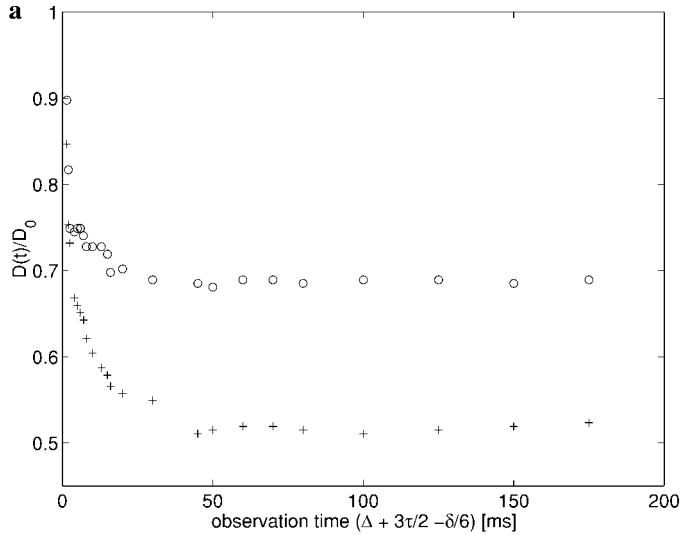
FIG. 4. The measured normalized diffusion coefficients $D(t)/D_0$ in the 30-μm (a) and 100-μm (b) systems as a function of observation time. ($\bigcirc$) Polystyrene; (+) glass.

gradient, it is important to discuss other effects that may cause the time-dependent diffusion coefficient to be different in the polystyrene and glass systems.

Porosity

The diffusion behavior in the limit of long observation time is described by the tortuosity, $\mathcal{T}$,

$$\frac{D_\infty}{D_0} = \frac{1}{\mathcal{T}}, \qquad [8]$$

where D_0 is the value of the diffusion coefficient at $t = 0$, i.e., the value of bulk diffusion for water, and D_∞ is the diffusion time at $t = \infty$. The tortuosity, and porosity, ϕ, of a system consisting of mono-sized spheres depends on how the spheres

are packed. It is important that the packing be as equal as possible in the samples which are compared to each other. At short observation times the approximation given by Mitra *et al.* (*13*) is valid

$$\frac{D(t)}{D_0} = 1 - \frac{4}{9\sqrt{\pi}} \frac{S}{V} \sqrt{D_0 t}, \qquad [9]$$

where $\frac{S}{V}$ is the surface-to-volume ratio of the particles, and $D(t)$ is the time-dependent diffusion coefficient. $\frac{S}{V}$ is related to the mean diameter of the spheres and the porosity of the sample, according to

$$\phi = \frac{1}{\frac{d}{6}\frac{S}{V} + 1}, \qquad [10]$$

where d is the mean diameter of the spheres.

In order to determine the porosity, we performed short time diffusion experiments. The measurements presented in Fig. 5 show that the porosities of the two 100-μm systems are very similar, and that different packing of the spheres is not the reason for the different behavior of $D(t)/D_0$ in the two systems at longer observation times.

Surface Relaxivity

The different behavior of $D(t)/D_0$ for the two mono-sized systems might also be explained by a different surface relaxivity. When the diffusing molecules move from one cavity to another, they may move through narrow channels or throats where it is more likely that they will be subjected to surface relaxation
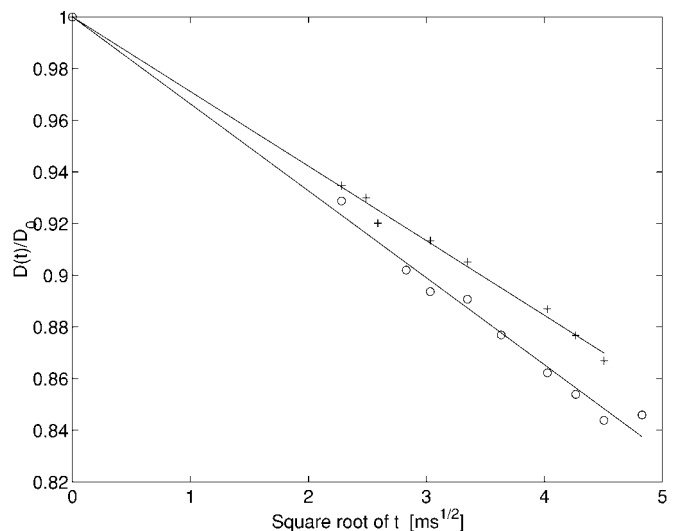

FIG. 5. $\sqrt{t}$ dependency of the measured diffusion coefficients in the 100-μm systems of polystyrene ($\bigcirc$) and glass (+) spheres at short observation times. Solid lines are linear fits of Eq. [9] to the experimental points. The determined porosities were 0.44 ± 0.01 for the glass spheres and 0.41 ± 0.01 for the polystyrene spheres.
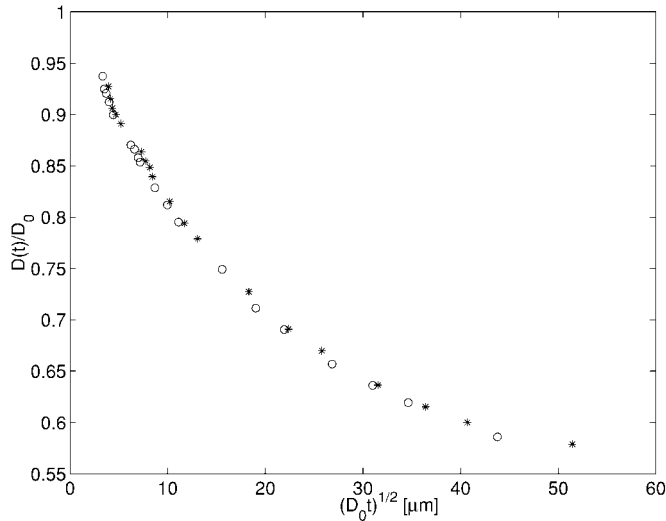
FIG. 6. Measured normalized diffusion coefficients $D(t)/D_0$ as a function of diffusion length $(D_0t)^{1/2}$ at 25°C (○) and 40°C (∗) in the system of 100-μm glass spheres.

processes. Sen *et al.* (*14*) have performed numerical simulations for ordered and disordered systems of spherical particles with different values of surface relaxivity, and Fig. 4 has a close resemblance to simulation results from $D(t)/D_0$ in a disordered dense packed system with porosity 0.376. The numerical simulation with no surface relaxation can be compared to our diffusion measurements among polystyrene particles, and the numerical simulation with a nonzero surface relaxation can be compared to our diffusion measurements among the glass spheres. The surface relaxation strength has been measured in our systems of glass spheres, and it is found to be of the same order as the one used by Sen *et al.* (*14*). However, there are several observations which show that surface relaxivity is not a significant effect on the behavior of $D(t)/D_0$.

First, the porosity of the different samples is found to be approximately 0.43 using the short time approximation by Mitra *et al.* (*13*). With this value of porosity, the spheres are more loosely packed than a random packing of spheres (*15*). A large number of narrow channels at which the diffusing molecules experience strong surface relaxation and lose their coherence does then not exist.

Second, like Hürlimann *et al.* (*8*) we do expect to see the same dependency of $D(t)/D_0$ against $\sqrt{D_0t}$ at different temperatures if $D(t)/D_0$ is independent of the surface relaxivity. If the surface relaxation has a significant effect on the measured diffusion coefficient, this will cause the diffusion coefficient to scale to first order as t, and not as the diffusion length, $\sqrt{D_0t}$. Figure 6 shows that this indeed is the case. Here we compare $D(t)/D_0$ as a function of $\sqrt{D_0t}$ for the 100-μm glass spheres at 25 and 40°C. The value of D_0 at 40°C was measured to be 3.3×10^{-5} cm^2 s^{-1}, compared to 2.3×10^{-5} cm^2 s^{-1} at 25°C. Within the limit of uncertainty there is no significant difference between the results at 25 and 40°C, and similar results are obtained for the 30-μm glass spheres.

However, we do not expect to see a different behavior of $D(t)/D_0$ at different temperatures due to the failure of the assumption of a constant internal gradient. In Fig. 6, $D(t)/D_0$ is plotted against $\sqrt{D_0t}$, and thus the same number of molecules is experiencing the same amount of internal gradient inhomogeneities. A difference in temperature should therefore not affect $D(t)/D_0$ in Fig. 6, as the figure is scaled according to the different mobility at different temperatures.

Spatially Variable Gradients

At the time when the curves in Fig. 4 start to deviate from each other, the water molecules are able to diffuse from one end of the cavity to the other. In the glass sphere system, where the internal gradients are strong, there is then an increased possibility that the size and/or the polarity of the internal gradient is uncorrelated between the prepare and read interval of the pulse sequence used. It was shown in Eq. [1] and Eq. [3] that if the internal gradient changes polarity between the prepare and read interval, the Δ-dependent cross term is suppressed, but the τ-dependent one is not. The effect of the nonconstant internal gradient is therefore not directly related to the value of Δ, but to the τ value. The surviving cross term is given by Eq. [4]. As the applied magnetic field gradient couples to a distribution of internal gradients with a mean value of zero, the echo attenuation will be weighted toward those molecules experiencing an effective internal gradient with sign opposite to that of the effective applied gradient (*2*). The measured apparent diffusivity will be lower than the actual one.

In order to study the effect of the cross term given by Eq. [4], we performed experiments with different τ values at long observation times. The values of the diffusion coefficients obtained performing such experiments in the 30- and 100-μm systems are given in Fig. 7. The variation in the diffusion coefficients for the polystyrene systems is within the experimental uncertainties, so here no significant τ dependency of $D(t)/D_0$ is observed. In the glass systems the τ dependency of the diffusion coefficients is clear. As the τ value increases, the value of the diffusion coefficient decreases. The deviation is higher in the 30-μm system, indicating that the effect of the cross term, and thus the internal gradients, is more significant in this system than in the corresponding 100-μm system. This is expected from the estimations of the size of the internal gradients in these systems.

The τ dependence of the measured diffusion coefficient originates from the coupling of internal gradients with the applied gradients as shown in Eq. [4]. As the τ value increases the influence of the coupling increases. Deriving Eq. [4] for a distribution of internal gradients is beyond the scope of this paper. However, in order to correct for the τ dependency on the tortuosity, one may perform a series expansion of $D(t)/D_0$ as a function of τ. To the first-order correction one would then have

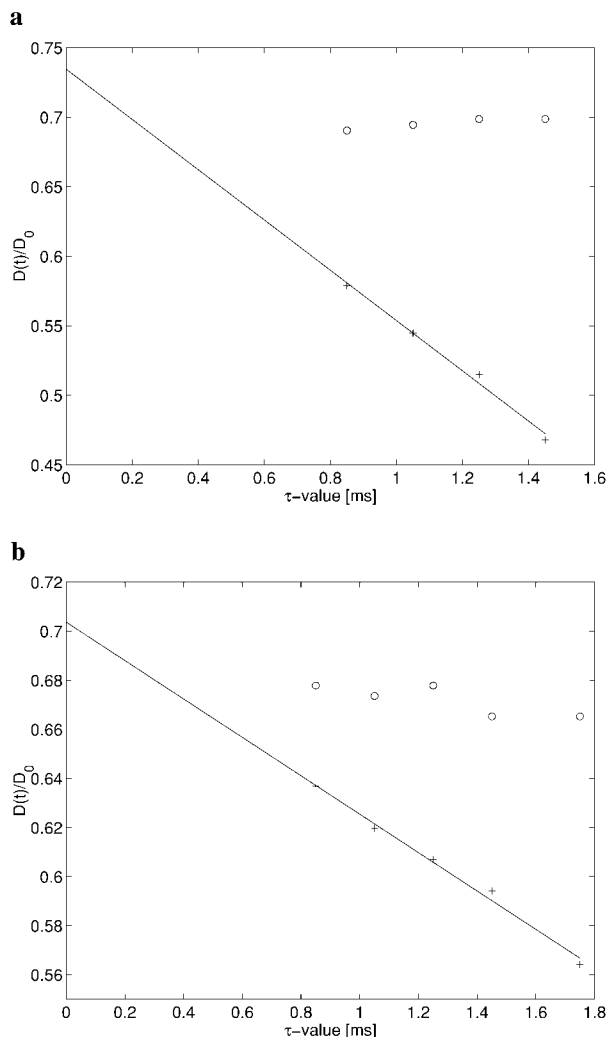$$\frac{D(t)}{D_0} = \frac{D(t)}{D_0}(\tau = 0) + C\tau + \mathbb{O}(\tau^2), \qquad [11]$$

a

b

FIG. 7. The diffusion coefficients $D(t)/D_0$ obtained at different τ values in the 30-μm (a) and 100-μm (b) systems of polystyrene ($\bigcirc$) and glass ($+$) spheres. The length of the gradient pulse (δ) was 0.25 ms. The length of Δ was 125 ms in the 30-μm systems and 800 ms in the 100-μm systems. The solid lines are linear fits of Eq. [11] to the experimental values of $D(t)/D_0$ from the glass sphere systems. The value of C obtained was 0.18 for the 30-μm system and 0.08 for 100-μm system. The corresponding values of $D(t)/D_0$ at $\tau = 0$ are 0.73 and 0.70, respectively.

where C is an undetermined constant. Using this equation, one can extrapolate the value of $D(t)/D_0$ to $\tau = 0$. This is done in Fig. 7, where Eq. [11] has been fitted to the experimental values of $D(t)/D_0$ for the glass sphere systems. When the values of $D(t)/D_0$ from the glass systems are extrapolated back to $\tau = 0$, we get values that are close to the values obtained for the corresponding polystyrene systems, though the values from the extrapolations seem to systematically be slightly higher. The discrepancy can be explained by the fact that we are measuring a higher porosity in the glass sphere system as compared to the polystyrene sphere system (Fig. 5). This should result in a higher value for D_∞/D_0, which we find when using Eq. [11].

Thus, the extrapolation can be used in order to estimate the

real value for $D(t)$, and thus the tortuosity, $\mathcal{T}$, in systems where a long observation time makes it difficult to suppress the cross term between the internal and applied gradients.

In our opinion it is evident that the τ-dependent measurements of diffusion at long observation times and in the presence of internal magnetic field gradients significantly affect the measured tortuosity.

CONCLUSIONS

We have shown that the existence of internal magnetic field gradients in the glass sphere systems has a significant influence on the diffusion measurements at long observation times. These gradients are caused by differences in magnetic susceptibility between the water and the solid material, and are insignificant in the systems of polystyrene spheres, where the difference in magnetic susceptibility is much lower. Like Zhong *et al.* (*2*) we believe that these gradients have a distribution of both polarities, with a mean value of 0 G/cm.

We have given theoretical and experimental evidence that a successful suppression of the cross terms in PFGSTE diffusion measurements depends on the observation time, and on the τ value in the bipolar pulsed field gradient stimulated echo experiment. Thus, at long observation times, such a suppression is difficult to obtain in a system of spatially variable internal magnetic field gradients, even if a bipolar pulse sequence is used.

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