Multiple wave-vector extensions of the NMR pulsed-field-gradient spin-echo diffusion measurement

Partha P. Mitra
Room 1D-329, AT&T Bell Laboratories, 600 Mountain Avenue, Murray Hill, New Jersey 07974
(Received 7 November 1994)

Multiple wave-vector extensions of NMR pulsed-field-gradient diffusion measurements are discussed in the context of diffractionlike effects of restricted diffusion. In the case of two independent wave vectors, it is shown that the dependence of the amplitude on the relative angle between the wave vectors carries information that is absent in the usual single-wave-vector amplitude. It is shown that a two-wave-vector measurement is sensitive to restricted diffusion even at small wave vectors, in contrast with the single-wave-vector case. It is proposed that the angular dependence noted above may be used to distinguish effects of restricted diffusion from those arising from a distribution of diffusion constants.

I. INTRODUCTION

The NMR pulsed-field-gradient spin-echo (PFGSE) measurement[1,2] has been a powerful probe of the diffusive motion of fluid molecules. In the limit of narrow pulses, the measurement corresponds to a Fourier transform of the diffusion propagator of the molecules, at a wave vector given by the area under the relevant gradient pulse.[3] When the diffusion is hindered or restricted, the PFGSE amplitude deviates from Gaussian dependence on the wave vector. The deviation carries information about the restricting geometry.[4–6] In this paper, I analyze some extensions of the PFGSE sequence, where more than one wave vector is introduced. In general, such measurements carry more information than can be obtained in the usual PFGSE experiment. These measurements can therefore be used to resolve ambiguities in interpreting the PFGSE amplitude. A similar observation was made in an earlier proposal by Cory, Garroway, and Miller,[7] but these authors did not investigate the implications of multiple-wave-vector measurements in detail. Callaghan and Manz[8] have also introduced a two-wave-vector sequence which probes fluid flow in more detail than is available from the simple PFGSE measurement. In the present work, the information content of multiple-wave-vector measurements is analyzed in the case of restricted diffusion. It is shown how a two-wave-vector measurement unambiguously distinguishes between multicompartment diffusion and diffractionlike behavior arising from restricted diffusion. Both of these might cause smooth deviations from Gaussian wave-vector dependence of the PFGSE amplitude.

II. MULTIPLE-WAVE-VECTOR SEQUENCES

The analogy between the PFGSE measurement and scattering experiments (e.g., neutron scattering) has been emphasized in recent works.[4] However, there is one important difference between these techniques, namely, that measurements such as neutron scattering are usually confined to single-scattering events due to experimental limitations. In the case of PFG measurements, however, the measurements corresponding to multiple scattering are not much more difficult than the single-scattering case. In general, the idea is to have more than two gradient pulses, with the gradient vectors pointing in general in different directions. Since we do not want inhomogeneous broadening to affect the diffusion measurement, there is one constraint, namely, that the vectorial sum of all the wave vectors associated with the gradient pulses (with correct signs to account for any π pulses) be zero. Thus, if there are n gradient pulses, there are in general $n-1$ independent wave vectors and $n-1$ independently variable diffusion times. This could be implemented in a variety of ways; for the purpose of concreteness, one possible pulse sequence is illustrated in Fig. 1(a), where gradient pulses of strength $\mathbf{g}_i$ have been interleaved with a Carr-Purcell-Meiboom-Gill sequence.[9] Note that the increased number of π pulses is not in general necessary,

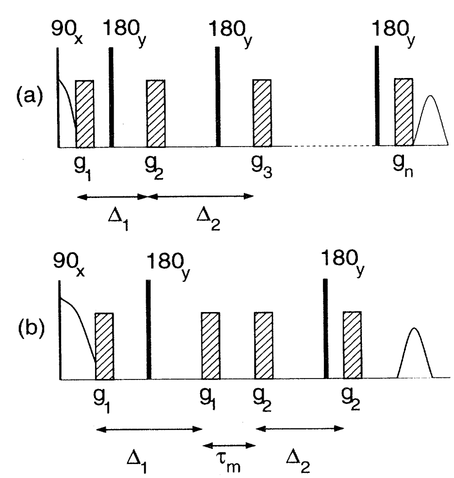

FIG. 1. (a) Schematic illustration of a generalized multiple-wave-vector PFG sequence. The sequence consists of a Carr-Purcell-Meiboom-Gill sequence interspersed with gradient pulses. The successive gradient pulses in general have different gradient directions and are assumed to be of equal duration δ. (b) A specific two-wave-vector sequence chosen for detailed analysis. The sequence follows those proposed earlier in similar contexts (Refs. 7 and 8). The gradient pulses are chosen to have equal duration δ.

0163-1829/95/51(21)/15074(5)/$06.00 51 15 074

and multiple gradient pulses could be implemented with any desired number of π pulses. In the particular example of Fig. 1(a), the constraint is satisfied if $\mathbf{g}_1-\mathbf{g}_2+\mathbf{g}_3-\cdots+(-1)^{n-1}\mathbf{g}_{n-1}=0$. Note that all the pulses have been taken to be of equal duration δ, which in our analysis we will assume to be small. The wave vectors associated with the gradient pulses are $\mathbf{k}_i=\gamma\delta\mathbf{g}_i$, where γ is the gyromagnetic ratio. Recall that in the usual case, where there are two gradient pulses with associated wave vectors both equal to $\mathbf{k}$, the echo amplitude is given by[3]

$$M(\mathbf{k},\Delta)=\langle e^{i\mathbf{k}\cdot[\mathbf{r}(\Delta)-\mathbf{r}(0)]}\rangle \ . \tag{1}$$

The phase of the exponential reflects the phases acquired by the diffusing spin during the two gradient pulses separated by a time Δ, with a minus sign to account for the π pulse separating the gradients. Arguing along similar lines, the echo amplitude in the multiple-wave-vector case is given by

$$M(\mathbf{k}_1,\mathbf{k}_2,\ldots,\Delta_1,\Delta_2,\ldots)=\left\langle \exp\left[(-1)^{n-1}i\mathbf{k}_1\cdot\mathbf{r}(0)+(-1)^{n-2}i\mathbf{k}_2\cdot\mathbf{r}(\Delta_1)-\cdots+i\mathbf{k}_n\cdot\mathbf{r}\left[\sum_{j=1}^{n-1}\Delta_j\right]\right]\right\rangle \ . \tag{2}$$

The expression above is clearly analogous to a multiple-scattering experiment and for $n>2$ involves more than one independent wave vector. We denote the real-space diffusion propagator by $G(\mathbf{r},\mathbf{r}',\Delta)$. G gives the probability density that a diffusing particle originally at $\mathbf{r}'$ will be found at $\mathbf{r}$ after a time Δ elapses. Using the Markovian nature of G, the amplitude may also be expressed as

$$M(\{\mathbf{k}_j\},\{\Delta_j\})=\int d\mathbf{r}_1\rho(\mathbf{r}_1)e^{i(-1)^{n-1}\mathbf{k}_1\cdot\mathbf{r}_1}\prod_{j=2}^{j=n}d\mathbf{r}_j e^{i(-1)^{n-j}\mathbf{k}_j\cdot\mathbf{r}_j}G(\mathbf{r}_j,\mathbf{r}_{j-1},\Delta_{j-1}) \ . \tag{3}$$

For free diffusion, the amplitude computed from this formula is a product of Gaussians corresponding to successive diffusion intervals and can be shown to be

$$M_{\text{free}}(\{\mathbf{k}_j\},\{\Delta_j\})=\exp\left[-D\sum_{j=1}^{j=n-1}q_j^2\Delta_j\right] , \tag{4}$$

where $\mathbf{q}_1=\mathbf{k}_1$, $\mathbf{q}_2=\mathbf{k}_1-\mathbf{k}_2$, and in general $\mathbf{q}_l=\sum_{j=1}^{j=l}(-1)^{j-1}\mathbf{k}_j$. However, this factorization of the multiple-wave-vector amplitude into a product of single-wave-vector amplitudes occurs only in the case of free diffusion; for restricted diffusion, such a factorization does not hold, and the multiple-wave-vector amplitude carries information that is not present in the single-wave-vector amplitude.

III. TWO INDEPENDENT WAVE VECTORS

The simplest case of multiple wave vectors is to have two independent wave vectors. This is the case in the sequences proposed by Cory, Garroway, and Miller[7] and by Callaghan and Manz.[8] The sequences proposed by these authors utilize two wave vectors, which are either orthogonal or collinear. Here we consider the more general case where the angle between the wave vectors is arbitrary, the emphasis being on the dependence of the measured echo amplitude on the relative angle between the wave vectors.

The sequence considered below is illustrated in Fig. 1(b). In principle, two independent wave vectors could be implemented with three gradient pulses; the middle pulse has been decomposed into two pieces in keeping with the sequences proposed earlier. There are two pairs of gradient pulses, of strength $\mathbf{g}_1$ and $\mathbf{g}_2$, where the vectors $\mathbf{g}_1$ and $\mathbf{g}_2$ are in general noncollinear. All four pulses have equal duration δ, the first pair being separated by a time Δ_1 (measured from the centers of the pulses) and the second pair by Δ_2. A time τ_m elapses between the leading edges of the third and fourth gradient pulses. The two independent wave vectors associated with the sequence are $\mathbf{k}_1=\gamma\delta\mathbf{g}_1$ and $\mathbf{k}_2=\gamma\delta\mathbf{g}_2$. For free diffusion, the phase acquired by a diffusing spin is a linear combination of displacements which themselves have Gaussian distributions. From such considerations, the echo attenuation for free diffusion may be shown to be given by

$$M_2(\mathbf{k}_1,\mathbf{k}_2,\Delta_1,\Delta_2,\delta,\tau_m)=e^{-D[k_1^2(\Delta_1-\delta/3)+k_2^2(\Delta_2-\delta/3)]} \ . \tag{5}$$

In the above, we have retained the effects of a finite pulse width δ, which causes the above expression to be somewhat different from Eq. (4). For finite pulse widths, the expression given in Eq. (3) for the attenuation in terms of the diffusion propagator no longer applies, but considerations leading to the replacement of Δ by $\Delta-\delta/3$ to account for a finite pulse width are standard and can be found in the original treatment of the PFGSE experiment.[1,2]

Note that the amplitude for free diffusion depends only on the magnitudes k_1 and k_2, and not on the angle between the vectors $\mathbf{k}_1$ and $\mathbf{k}_2$. In general, for restricted diffusion, the amplitude will depend on this angle. This angular dependence contains the crucial extra information present in the two-wave-vector amplitude.

Let us first consider the case of diffusion in isolated pores of arbitrary shape. Most of the considerations in this paper will be restricted to the limiting case of δ-function sharp gradient pulses. The effects of finite pulse widths on the amplitude are quite subtle and have been discussed in a separate paper[10] for the case of the single-wave-vector PFGSE amplitude. The effects of finite pulse width on the multiple-wave-vector amplitude will be of a similar nature.

For simplicity, the discussion in this section is confined to $\Delta_1=\Delta_2=\Delta$. Let us suppose that the isolated pores are of a typical size a. The time scale for diffusion across the pore will be denoted by $\tau_D=a^2/(6D)$. I consider below two limiting cases: (i) $\Delta \gg \tau_D$ and $\tau_m \gg \tau_D$ and (ii) $\Delta \gg \tau_D$ and $\tau_m=0$. In both cases, it is assumed that $\delta \ll \tau_D$, although the effects discussed below can be expected to persist as long as δ is not significantly larger than τ_D.

The two-wave-vector amplitude is given by

$$M_2(\mathbf{k}_1,\mathbf{k}_2,\Delta,\tau_m)=\langle e^{i\mathbf{k}_1\cdot[\mathbf{r}(0)-\mathbf{r}(\Delta)]+i\mathbf{k}_2\cdot[\mathbf{r}(2\Delta+\tau_m)-\mathbf{r}(\Delta+\tau_m)]}\rangle \ . \tag{6}$$

Under the limiting conditions assumed in (i), namely, that $\Delta,\tau_m \gg \tau_D$, the position vectors $\mathbf{r}(0)$, $\mathbf{r}(\Delta)$, $\mathbf{r}(\Delta+\tau_m)$, and $\mathbf{r}(2\Delta+\tau_m)$ are independently distributed, each position vector being distributed uniformly in the pore. Therefore, in case (i), we obtain, for the two-wave-vector amplitude,

$$M_2(\mathbf{k}_1,\mathbf{k}_2,\Delta\to\infty,\tau_m\to\infty)=\sum_{i=1}^{N}|\tilde{\rho}_i(\mathbf{k}_1)|^2|\tilde{\rho}_i(\mathbf{k}_2)|^2 \ . \tag{7}$$

Here $\tilde{\rho}_i(\mathbf{k})$ is the Fourier transform of the density of spins in the ith pore $\rho_i(\mathbf{r})$, namely,

$$\tilde{\rho}_i(\mathbf{k})=\int e^{i\mathbf{k}\cdot\mathbf{r}}\rho_i(\mathbf{r})d\mathbf{r} \ . \tag{8}$$

The summation in Eq. (6) runs over all pores in the system. Assuming the pores are randomly oriented, the amplitude will not depend on the absolute orientation of $\mathbf{k}_i$, but it may depend on the relative angle between $\mathbf{k}_1$ and $\mathbf{k}_2$. Consider the following ensembles of pores: (a) spherical pores and (b) randomly oriented ellipsoidal pores. In case (a), $\tilde{\rho}_i(\mathbf{k})$ depends only on the magnitude of the wave vector $\mathbf{k}$. Thus, for spherical pores, M_2 will not depend on the relative angle between the two wave vectors. In contrast, in case (b), $\tilde{\rho}_i(\mathbf{k})$ depends on the relative orientation of $\mathbf{k}$ to the axes of the ellipsoid. After an average over isotropically oriented ellipsoids, M_2 will still depend on the relative angle between the two wave vectors, since the product of $\tilde{\rho}_i(\mathbf{k}_1)$ and $\tilde{\rho}_i(\mathbf{k}_2)$ is taken before the orientational average is taken. Thus the dependence of the two-wave-vector amplitude on the relative angle straightforwardly distinguishes spherical pores from ellipsoidal pores in case (i). However, this angular dependence manifests itself only at large wave vectors, as can be seen by expanding Eq. (6) for small wave vectors. The expansion shows that the quadratic term in the amplitude is proportional to $k_1^2+k_2^2$, which is explicitly independent of the angle between the wave vectors. The angular dependence appears only in the quartic term in the wave-vector magnitude, which is of the order of $(ka)^4$ where k is a representative wave-vector magnitude and a is a representative pore size.

In case (ii), namely, when $\tau_m=0$, corresponding to simultaneous application of the second and third gradient pulses, the results are more interesting than in case (i). In this case, as demonstrated below, the dependence of the amplitude on the relative angle between the two independent wave vectors appears even at small wave vectors. This is remarkable, because in studying the wave-vector dependence of the usual PFGSE amplitude, the signature of restricted diffusion appears only at large wave vectors. In the present case, the two-wave-vector amplitude is given by

$$M_2(\mathbf{k}_1,\mathbf{k}_2,\Delta,\tau_m=0)=\langle e^{i\mathbf{k}_1\cdot[\mathbf{r}(0)-\mathbf{r}(\Delta)]+i\mathbf{k}_2\cdot[\mathbf{r}(2\Delta)-\mathbf{r}(\Delta)]}\rangle \ . \tag{9}$$

In contrast with case (i), for $\Delta \gg \tau_D$ there are three independent position vectors in the phase governing the amplitude. Assuming that $\mathbf{r}(0)$, $\mathbf{r}(\Delta)$, and $\mathbf{r}(2\Delta)$ are independently and uniformly distributed in the pore space, which should be the case for Δ large, it follows that

$$M_2(\mathbf{k}_1,\mathbf{k}_2,\Delta\to\infty,\tau_m=0)=\sum_{i=1}^{N}\tilde{\rho}_i(\mathbf{k}_1)\tilde{\rho}_i(\mathbf{k}_2)\tilde{\rho}_i(-\mathbf{k}_1-\mathbf{k}_2) \ . \tag{10}$$

We concentrate again on the angular dependence of the amplitude, by setting $\mathbf{k}_1=k\hat{\mathbf{n}}_1$ and $\mathbf{k}_2=k\hat{\mathbf{n}}_2$, where $\hat{\mathbf{n}}_1$ and $\hat{\mathbf{n}}_2$ are unit vectors. Let the relative angle between the wave vectors be θ, so that $\hat{\mathbf{n}}_1\cdot\hat{\mathbf{n}}_2=\cos(\theta)$. Expanding Eq. (10) for small k, we obtain

$$M_2(k\hat{\mathbf{n}}_1,k\hat{\mathbf{n}}_2,\Delta\to\infty,\tau_m=0)=1-\tfrac{1}{3}k^2\langle r^2\rangle[1+2\cos^2(\theta/2)]+O(k^4) \ , \tag{11}$$

where $\langle r^2\rangle$ is the mean-squared radius of gyration of the pores. It is interesting to note that the angular factor in the above expression is independent of the details of the pore shapes. Thus, in the limit $\Delta \gg \tau_D, \tau_m=0$, a strong angular dependence is obtained even in the lowest-order dependence of M_2 on the wave vectors. This is to be contrasted with case (i) where the angular dependence first appears only in the term quartic in the wave vector. To put the discussion in context, note that in the relevant experimental context, the usual object to measure would be the slope of $\ln(M_2)$ with respect to k^2. In summary of the above discussion, we note that this initial slope is independent of the relative angle between wave vectors in case (i), but that there exists a strong angular dependence for the slope in case (ii). In that case, as θ varies from 0 to π, the initial slope of $\ln(M_2)$ with respect to k^2 changes by a factor of 3. Recall that the derivation is for isolated pores; however, we can expect an angular dependence to exist even for a connected pore space at small wave vectors for some range of values for Δ.

IV. DISTINGUISHING MULTICOMPARTMENT DIFFUSION FROM RESTRICTED DIFFUSION

In interpreting the usual PFGSE amplitude where smooth deviations from Gaussian wave-vector dependence is observed, there exists the inherent difficulty of distinguishing the effects of restricted diffusion from the effects of a distribution of diffusion coefficients. As an example, consider the diffusion of fluid molecules confined to narrow, randomly oriented tubes. We will neglect the radial thickness of the tubes, considering them to be one-dimensional objects. A theoretical expression for the corresponding PFGSE amplitude is given by[11]

$$M(k,\Delta,\delta)=\int_0^1 \exp[-Dk^2(\Delta-\delta/3)x^2]dx \; . \tag{12}$$

The restrictions cause the PFGSE amplitude $M(k,\Delta,\delta)$ to deviate from a Gaussian, as shown in Fig. 2 by the solid line. However, this deviation might *a priori* have been produced by the existence of different diffusion constants in different parts of the system. The symbols in Fig. 2 correspond to two-component diffusion. The corresponding PFGSE amplitude is given by

$$M(k,\Delta,\delta)=p\,\exp[-D_1k^2(\Delta-\delta/3)] + (1-p)\exp[-D_2k^2(\Delta-\delta/3)] \; . \tag{13}$$

Here the two components are assumed to have relative populations p and $1-p$ and diffusion constants D_1 and D_2. In Fig. 2 the diffusion constants and relative fractions have been adjusted to minimize the least-squares difference from the randomly oriented tubes case. As can be seen from the figure, these two very different microscopic mechanisms produce virtually identical wave-vector dependences for the PFGSE amplitude, thus emphasizing the ambiguity in interpretation.

The considerations in this paper lead straightforwardly to a proposal to distinguish the case of restricted diffusion from a distribution in diffusion constants (assuming that the diffusion is locally isotropic). In the latter case, the two-wave-vector amplitude would be *independent* of the angle between the two wave vectors. This can be seen by considering two-wave-vector amplitude for free diffusion. From Eq. (4), it follows that for a distribution of diffusion constants given by the probability density function $f(D)$, the two-wave-vector amplitude is given by

$$M_2=\int f(D)dD\, e^{-D[k_1^2(\Delta-\delta/3)+k_2^2(\Delta-\delta/3)]} \; . \tag{14}$$

In the above, we have retained the effects of a finite pulse width, which has been taken to be the same for all pulses,

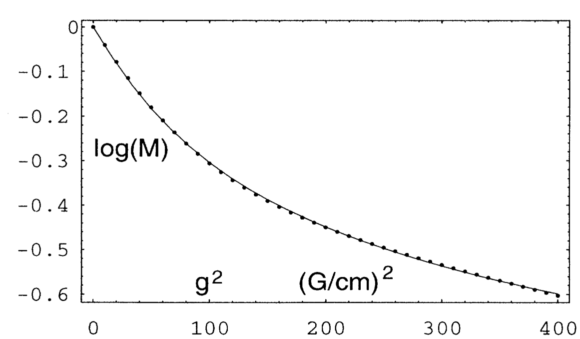

FIG. 2. Comparison of the PFG amplitude obtained for a randomly oriented array of narrow tubes (solid line) with that obtained for a particular case of two-component diffusion (symbols). In each case, $\Delta=25$ ms and $\delta=10$ ms. For the randomly oriented tubes case, the free-diffusion has been taken to be 2×10^{-5} cm^{2}s^{-1}. For two-component diffusion, the components were chosen to have diffusion constants of $D_1=1.056\times10^{-5}$ cm^{2}s^{-1} and $D_2=0.954\times10^{-6}$ cm^{2}s^{-1}, with relative populations of 0.551 and 0.449, respectively.

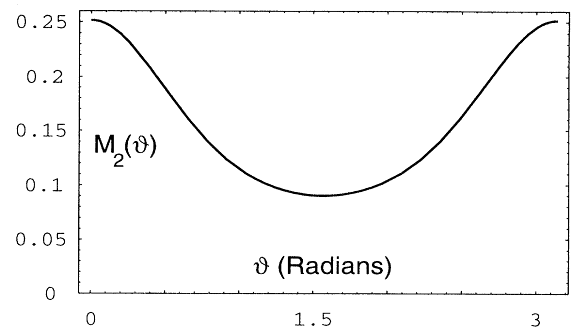

FIG. 3. Dependence of the two-wave-vector amplitude for the randomly oriented tubes model on the relative angle θ between the wave vectors. The parameters chosen were $\Delta_1=\Delta_2=25$ ms, $\delta=10$ ms, $D=2\times10^{-5}$ cm^{2}s^{-1}, and the gradient strength for all pulses $g=14$ G cm^{-1}. In this case, the amplitude does not depend on τ_m as long as τ_m satisfies the limits given in the text.

and assumed that $\Delta_1=\Delta_2=\Delta$ as well as $\tau_m>\delta$. It is clear from the above equation that the two-wave-vector amplitude does not depend on the angle between the wave vectors when there is a distribution of diffusion constants. Note that it has been assumed that even though there is a distribution of diffusion constants, the diffusion is locally isotropic.

In contrast, for restricted diffusion there will in general be a significant angular dependence. As shown in the previous section, for isolated pores in the limit of $\Delta\rightarrow\infty$ and $\tau_m=0$, the two-wave-vector amplitude plotted against k^2 has a slope proportional to $[1+2\cos^2(\theta/2)]$, θ being the angle between the wave vectors. Consider the randomly oriented tubes model used above, where diffusion is not fully restricted. The situation here is quite different from that discussed before for isolated pores, since the diffusing species is free to escape to infinity along the axis of the tube. However, it is easy to work out an analytical expression for the two-wave-vector amplitude $M_2(k\hat{\mathbf{n}}_1,k\hat{\mathbf{n}}_2,\Delta,\tau_m)$ by direct generalization of the arguments leading to the single-wave-vector PFGSE amplitude.[11] The resulting expressions are tedious and will not be reproduced here, but the angular dependence of $M_2(k\hat{\mathbf{n}}_1,k\hat{\mathbf{n}}_2,\Delta,\tau_m)$ is plotted in Fig. 3 for some realistic parameter values. The tubes have been assumed to be infinitely narrow and infinitely long; however, as long as Δ,δ,τ_m are long compared to diffusion across the tube diameter and short compared to tube length, the result should be quantitatively valid. In addition, we assume that $\tau_m>\delta$. Under these conditions, the amplitude does not depend on τ_m. It is evident that the amplitude shows a very strong angular dependence, varying by a factor of approximately 2.8 between the extremes.

V. CONCLUSION

In conclusion, multiple-wave-vector extensions of the PFGSE measurement have been discussed in the context of restricted diffusion. By treating a particular two-wave-vector sequence in detail, it has been shown that the dependence of the spin-echo amplitude on the angle between the two wave vectors contains information that is absent in the conventional PFGSE measurement. Under appropriate conditions, restricted diffusion effects are visible even in the small wave-vector dependence of the amplitude, in contrast with the case of the PFGSE measurement. It has been proposed that the angular dependence of the two-wave-vector amplitude may be used to remove ambiguities in the single-wave-vector amplitude. This angular dependence distinguishes between pores of different eccentricity. It can also be used to distinguish between restricted diffusion effects and the effects of a distribution of diffusion constants. This is possible because the two-wave-vector amplitude has no dependence on the relative angle between the wave vectors when there is a distribution of diffusion constants, assuming that the diffusion is locally isotropic. In contrast, a significant angular dependence is in general expected in the case of restricted diffusion.

ACKNOWLEDGMENTS

The author would like to thank P. B. Littlewood and R. Kleinberg for critical readings of the manuscript.

[1]E. O. Stejskal, J. Chem. Phys. **43**, 3597 (1965).

[2]J. E. Tanner and E. O. Stejskal, J. Chem. Phys. **49**, 1768 (1968).

[3]See the article by J. Karger, H. Pfeifer, and W. Heink, in *Advances in Magnetic Resonance,* edited by J. S. Waugh (Academic, San Diego, 1981), Vol. 12, p. 1.

[4]P. T. Callaghan, D. MacGowan, K. J. Packer, and F. O. Zelaya, Nature **351**, 467 (1991); J. Magn. Reson. **90**, 177 (1990).

[5]D. G. Cory and A. N. Garroway, Magn. Reson. Med. **14**, 435 (1990).

[6]P. P. Mitra, P. N. Sen, L. M. Schwartz, and P. Le Doussal, Phys. Rev. Lett. **68**, 3555 (1992).

[7]D. G. Cory, A. N. Garroway, and J. B. Miller, Polym. Prep. Am. Chem. Soc. Div. Polym. Chem. **31**, 149 (1990).

[8]P. T. Callaghan and B. Manz, J. Magn. Reson. A **90**, 106 (1994).

[9]H. Y. Carr and E. M. Purcell, Phys. Rev. **94**, 630 (1954); S. Meiboom and D. Gill, Rev. Sci. Instrum. **29**, 688 (1959).

[10]P. P. Mitra and B. I. Halperin, J. Magn. Reson. A (to be published).

[11]P. P. Mitra and P. N. Sen, Phys. Rev. B **45**, 143 (1992).