

# Weak-Diffusion Theory of NMR Signal in Magnetically Heterogeneous Media

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**A general theory is developed for the effect of molecular diffusion on the NMR signal obtained from magnetically heterogeneous media in the limit of weak diffusion. The theory is based on a rigorous expansion in the diffusion constant  $D$ , with the correction to first order in  $D$  being given explicitly for unrestricted, isotropic diffusion. The expansion allows for an arbitrary sequence of field gradients and  $180^\circ$  spin-flip pulses, making it applicable to a wide variety of NMR protocols. The theory may be useful for estimating the magnitude of diffusion effects and in determining some of a medium's microscopic magnetic properties.** © 1997 Academic Press

for the effects of diffusion to first order in  $D$ . A general formulation is utilized that allows an arbitrary sequence of gradients and  $180^\circ$  spin-flip pulses to be considered, permitting a direct application to many of the complex sequences now employed for MR imaging.

The  $O(D)$  correction is shown to depend on two functions,  $F_0$  and  $F_1$ , that are determined by the details of the random magnetic field. As examples, explicit expressions are obtained for  $F_0$  and  $F_1$  for a Gaussian random field and a field due to randomly distributed impurities. We also discuss in detail the effect of diffusion for the standard cases of free-induction decay and spin echo. Finally, we demonstrate how a modified Carr–Purcell sequence can, in principle, be used to measure  $F_0$  and  $F_1$ .

## INTRODUCTION

The behavior of the NMR signal obtained from a magnetically heterogeneous medium is currently of interest because of its importance to MR imaging of the human body (1). In particular, quasi-random magnetic fields are generated by variations in the magnetic susceptibility within, for example, the brain (2, 3) and bones (4–7). In the brain, susceptibility differences due to changes in blood flow and blood oxygenation are the basis of the recently developed technique of functional imaging (8–11).

A magnetically heterogeneous medium may be modeled as consisting of a static random magnetic field and a randomly distributed set of mobile spins that are subject to diffusion. The mobile spins would typically correspond, in a physical system, to the hydrogen nuclei of water, and the appropriate diffusion constant is that of a water molecule. The NMR signal produced by such a system is affected by both the random magnetic field and molecular diffusion. Previous work has investigated NMR diffusion effects using both mean field theory (12, 13) and numerical Monte Carlo methods (14).

In this paper, we describe a theory of the NMR signal which is based on a rigorous expansion in the diffusion constant  $D$  and hence valid in the weak-diffusion limit. This limit is relevant to many physical situations, as diffusion effects are often small. The theory is a natural extension of the established theory of the static (i.e., without diffusion) NMR signal (15). Our main result is an exact expression

## DEFINITION OF PROBLEM

This paper deals only with the transverse or secular relaxation effects due to the combination of a random static magnetic field and diffusion. In practice, the effect of other relaxation mechanisms can often be approximated by including additional factors derivable, for example, from the phenomenological Bloch equations (16).

The free-induction-decay signal at a time  $T$  after an initial  $90^\circ$  spin-flip pulse can be written (17)

$$S(T) = S_0 e^{-i\gamma B_0 T} \langle e^{-i\gamma \int_0^T dt B(\mathbf{r}(t))} \rangle_{\text{diff.} + \text{ran. fld.}} \quad [1]$$

where  $S_0$  is the initial signal strength,  $\gamma$  is the gyromagnetic ratio,  $B_0$  is the magnitude of the uniform static field,  $B(\mathbf{r})$  is the magnitude of the random perturbation of the magnetic field, and  $\mathbf{r}(t)$  is a diffusion path. The angle brackets indicate an average over both diffusion paths and the random field. The derivation of Eq. [1] relies upon the random component of the field being much smaller than the uniform component, as is typically the case.

A more general expression may be obtained by introducing a time-dependent external field gradient  $\mathbf{f}(t)$  and a  $180^\circ$  spin-flip function  $\sigma(t)$ . The field gradient may be an arbitrary function of time. The spin-flip function can only take

on the values  $\pm 1$  and hence is piecewise constant with each sign change representing an ideal  $180^\circ$  spin-flip pulse. The signal for an arbitrary sequence of gradients and spin flips can then be written

$$S(T) = S_0 e^{i\theta} e^{-i\gamma B_0 a(T)} \langle e^{-i\gamma \int_0^T dt \sigma(t) \{B[\mathbf{r}(t)] + \mathbf{f}(t) \cdot \mathbf{r}(t)\}} \rangle_{\text{diff.} + \text{ran.fld.}}, \quad [2]$$

where

$$a(T) = \int_0^T dt \sigma(t) \quad [3]$$

and  $\theta$  is a real phase that depends upon the axes about which the  $180^\circ$  spin flips are performed. The phase  $\theta$  changes only during a spin flip and is usually of little significance. Assuming the probability distribution that governs the random field is translationally invariant, it is easy to show (in the infinite volume limit) that  $S(T)$  vanishes unless the condition

$$\int_0^T dt \sigma(t) \mathbf{f}(t) = 0, \quad [4]$$

is satisfied.

Now define a correction function  $\Phi(T)$  so that

$$S(T) = S_0 e^{i\theta} e^{-i\gamma B_0 a(T)} e^{-i\Phi(T)}. \quad [5]$$

$\Phi(T)$  is in general a complex function with its real and imaginary parts giving the phase shift and amplitude decay of the signal relative to the ideal case where both diffusion and the random field are absent.

For a well-behaved random field,  $\Phi$  can be expanded in powers of the diffusion constant  $D$  as

$$\Phi(T) = \sum_{n=0}^{\infty} D^n \Phi_n(T). \quad [6]$$

The  $n = 0$  term simply corresponds to the static result discussed in (15). In the following, we assume isotropic, unrestricted diffusion and derive an explicit expression for the  $n = 1$  term, which gives the leading effect of diffusion for small  $D$ .

### GENERAL EXPRESSION FOR WEAK DIFFUSION CORRECTION

If  $D = 0$ , Eq. [2] reduces to

$$S(T) = S_0 e^{i\theta} e^{-i\gamma B_0 a(T)} \left[ \frac{1}{V} \int d^3 r_0 e^{-i\gamma \int_0^T dt \sigma(t) \mathbf{f}(t) \cdot \mathbf{r}_0} \right] \times \langle e^{-i\gamma B a(T)} \rangle_{\text{ran.fld.}}, \quad [7]$$

where  $V$  is the volume of the system and the random field  $B$  may be evaluated at an arbitrary position due to the assumption of translational invariance. Applying condition [4], Eq. [7] can be rewritten as

$$S(T) = S_0 e^{i\theta} e^{-i\gamma B_0 a(T)} \langle e^{-i\gamma B a(T)} \rangle_{\text{ran.fld.}}. \quad [8]$$

Comparing Eq. [8] with Eqs. [5] and [6], we find the static limit of the correction function to be

$$\Phi_0(T) = i \log \{ F_0[a(T)] \}, \quad [9]$$

where

$$F_0(\tau) = \langle e^{-i\tau\gamma B} \rangle_{\text{ran.fld.}}. \quad [10]$$

The dimensionless function  $F_0(\tau)$  is related to the probability  $P(B)$  that at any given position the random field has a value  $B$  by

$$P(B) = \frac{\gamma}{2\pi} \int_{-\infty}^{\infty} d\tau F_0(\tau) e^{i\tau\gamma B}, \quad [11]$$

and so  $F_0(\tau)$  is essentially the Fourier transform of  $P(B)$ .

In the weak-diffusion limit, the important diffusion paths  $\mathbf{r}(t)$  deviate only slightly from the initial position  $\mathbf{r}_0 \equiv \mathbf{r}(0)$ . It is then valid to expand Eq. [2] in powers of  $[\mathbf{r}(t) - \mathbf{r}_0]$ . The linear term vanishes by symmetry, assuming the diffusion is invariant with respect to reflections, and so the leading correction comes from the quadratic term. The details of this expansion are given in the Appendix.

For unrestricted, isotropic diffusion, the diffusion average of the quadratic term can be carried out explicitly with the help of the theorem

$$\begin{aligned} \langle [r_j(t) - r_{0j}][r_k(t') - r_{0k}] \rangle_{\text{diff.}} \\ = D \delta_{jk} (t + t' - |t - t'|), \end{aligned} \quad [12]$$

where  $\delta_{jk}$  is the Kronecker delta. For cases with restricted diffusion, the correlation function is more complex, but can in practice often be approximated by the form [12] if the diffusion constant is replaced by an apparent diffusion constant (18). (If the diffusion is anisotropic, [12] is generalized by replacing  $D\delta_{jk}$  with a diffusion tensor  $\mathbf{D}_{jk}$ , and the central results of this paper may be readily extended.)

Using [12], the  $n = 1$  term of expansion [6] is found to be  $D$  times

$$\begin{aligned} \Phi_1(T) = \frac{i\gamma^2}{2} \int_0^T \int_0^T dt dt' |t - t'| \sigma(t) \sigma(t') \\ \times \{ F_1[a(T)] + \mathbf{f}(t) \cdot \mathbf{f}(t') \}, \end{aligned} \quad [13]$$

with

$$F_1(\tau) = [F_0(\tau)]^{-1} \langle |\nabla B(\mathbf{r}_0)|^2 e^{-i\tau\gamma B(\mathbf{r}_0)} \rangle_{\text{ran.fld.}}. \quad [14]$$

By translational invariance,  $F_1(\tau)$  is independent of the choice of  $\mathbf{r}_0$ . For  $\tau = 0$ , Eq. [14] reduces to

$$F_1(0) = \langle |\nabla B(\mathbf{r}_0)|^2 \rangle_{\text{ran.fld.}}, \quad [15]$$

and so  $F_1(0)$  is simply the mean square of the gradient of the random field.

As shown by Eq. [13],  $\Phi_1$  has two parts: one depending on the random field through the function  $F_1$  and one depending on the external gradients. Note that  $\Phi_1$  does not vanish in the absence of a random magnetic field. In fact, in this case it can be shown that  $\Phi(T) = D\Phi_1(T)$ , as all the terms of the expansion [6] are zero for  $n \neq 1$ ; Eq. [5] then reduces to the well-known result for diffusion in the presence of an external gradient (16, 17, 19).

The decoupling of the external gradients and the random field is special to the  $n = 1$  term of expansion (6) and greatly simplifies the analysis of the  $O(D)$  effect of gradient sequences. In higher-order terms, the coupling between the external gradient and the random field must be considered (19, 20).

### GAUSSIAN AND IMPURITY RANDOM FIELDS

As examples, we determine the functions  $F_0$  and  $F_1$  for two types of random magnetic fields.

The simplest model to treat is that of a Gaussian random field, for which the probability of a particular field configuration  $B(\mathbf{r})$  is proportional to

$$e^{-\iint d^3r d^3r' B(\mathbf{r})C(\mathbf{r}-\mathbf{r}')B(\mathbf{r}')}, \quad [16]$$

where  $C(\mathbf{r})$  is an assigned function. Using standard methods,  $F_0$  and  $F_1$  may, in this case, be deduced as

$$F_0(\tau) = e^{-(1/2)K\gamma^2\tau^2}, \quad [17]$$

where

$$K = \langle [B(\mathbf{r}_0)]^2 \rangle_{\text{ran.fld.}}, \quad [18]$$

and

$$F_1(\tau) = F_1(0) = \langle |\nabla B(\mathbf{r}_0)|^2 \rangle_{\text{ran.fld.}}. \quad [19]$$

Thus, the correction function  $\Phi$  is completely determined to order  $D$  by just the mean squares of the random field and its gradient.

Another model which has often been used to approximate physical systems is that of a random distribution of identical

magnetic impurities. If each impurity generates a magnetic field perturbation with a magnitude of the form  $\lambda(\mathbf{r})$ , then

$$F_0(\tau) = \exp \left\{ \rho \int d^3r [e^{-i\tau\gamma\lambda(\mathbf{r})} - 1] \right\}, \quad [20]$$

and

$$F_1(\tau) = \rho \int d^3r |\nabla\lambda(\mathbf{r})|^2 e^{-i\tau\gamma\lambda(\mathbf{r})}, \quad [21]$$

with  $\rho$  being the impurity density. In deriving [20] and [21], it is assumed that the impurity centers can be arbitrarily close. Results for the static NMR signal similar to Eq. [20] are given in (15).

### FREE-INDUCTION DECAY AND SPIN ECHO

Let us now consider the evaluation of the general expression [13] for particular pulse sequences. Since  $\sigma(t)$  is piecewise constant with  $|\sigma(t)| = 1$ , it can be written as

$$\sigma(t) = \sum_{j=1}^{N_s} (-1)^{N_s+j} \alpha(t; t_{j-1}, t_j), \quad [22]$$

where  $N_s$  is the number of spin-flip pulses, including the initial  $90^\circ$  pulse,  $t_j > t_{j-1}$ ,  $t_0 = 0$ ,  $t_{N_s} = T$ , and

$$\alpha(t; t_{j-1}, t_j) = \begin{cases} 1, & \text{if } t_{j-1} < t \leq t_j; \\ 0, & \text{otherwise.} \end{cases} \quad [23]$$

The function  $a(T)$  defined by Eq. [3] then takes the form

$$a(T) = \sum_{j=1}^{N_s} (-1)^{N_s+j} (t_j - t_{j-1}), \quad [24]$$

and the integral in Eq. [13] that multiplies  $F_1$  can be written as

$$\begin{aligned} I_1(T) &\equiv \int_0^T \int_0^T dt dt' |t - t'| \sigma(t) \sigma(t') \\ &= \frac{1}{3} \sum_{j=1}^{N_s} (t_j - t_{j-1})^3 + \frac{1}{2} \sum_{j=1}^{N_s} \sum_{k=1}^{N_s} (-1)^{j+k} \\ &\quad \times (t_j - t_{j-1})(t_k - t_{k-1}) |t_j + t_{j-1} - t_k - t_{k-1}|. \end{aligned} \quad [25]$$

The simplest pulse sequence is that which generates a free-induction decay, for which  $N_s = 1$ . In this case,

$$\begin{aligned} a(T) &= T, \\ I_1(T) &= \frac{1}{3} T^3, \end{aligned} \quad [26]$$

which implies that

$$\Phi_1(T) = \frac{i\gamma^2}{6} F_1(T) T^3. \quad [27]$$

Note that since  $F_1(0)$  is, as indicated by Eq. [15], real and positive, the effect of diffusion, at least for small  $T$ , is to *increase* the strength of the NMR signal. This reflects an effective smoothing out of the random field by diffusion and is closely related to the so-called motional narrowing phenomenon (16, 17).

Now consider a simple spin-echo sequence having  $N_s = 2$ . Equations [24] and [25] then give

$$\begin{aligned} a(T) &= T - 2t_1, \\ I_1(T) &= \frac{1}{3} T^3 - 2t_1 T^2 + 2t_1^2 T. \end{aligned} \quad [28]$$

At the spin echo time  $T = 2t_1$ , Eq. [28] reduces to

$$\begin{aligned} a(T) &= 0, \\ I_1(T) &= -\frac{1}{6} T^3, \end{aligned} \quad [29]$$

and we find

$$\Phi_1(T) = -\frac{i\gamma^2}{12} F_1(0) T^3. \quad [30]$$

Thus, diffusion *decreases* the signal intensity in this case. Equation [30] is equivalent to the mean field result given by (12). As  $a(T) = 0$ ,  $\Phi_0$  vanishes, and  $\Phi_1$  gives the dominant effect of the random field. It is also interesting to note that for  $T = (3 \pm \sqrt{3})t_1$ ,  $I_1(T)$  and hence  $\Phi_1(T)$  are zero, implying that the  $O(D)$  diffusion correction is absent. This fact may be of use if it is desired that diffusion effects be suppressed.

### ACCURACY OF WEAK-DIFFUSION CORRECTION

The accuracy of the NMR signal predicted using the weak-diffusion correction [13] depends on the details of the random magnetic field and on the sequence of pulses and gradients. Therefore, a rigorous criterion for its validity must be determined on a case-by-case basis. However, the nature of the approximation provided by [13] can be illustrated by considering a simple model that allows for an exact solution.

Assume that the random field  $B(\mathbf{r})$  consists of perfect gradients of the form  $\mathbf{G} \cdot (\mathbf{r} - \mathbf{r}_0)$  with  $\mathbf{r}_0$  being uniformly distributed and  $\mathbf{G}$  obeying a Gaussian distribution. One then has

$$\begin{aligned} e^{-i\Phi(T)} &= \frac{1}{V} \left(\frac{b}{\pi}\right)^{3/2} \int d^3 G e^{-b|\mathbf{G}|^2} \int d^3 r_0 e^{-i\gamma a(T) \mathbf{G} \cdot \mathbf{r}_0} \\ &\times \langle e^{-i\gamma \int_0^T dt \sigma(t) \{[\mathbf{G} + \mathbf{f}(t)] \cdot \mathbf{r}(t)\}} \rangle_{\text{diff.}}, \end{aligned} \quad [31]$$

where  $3/2b$  is the mean-square gradient. Carrying out the integral over  $\mathbf{r}_0$  shows that the NMR signal vanishes, in the limit  $V \rightarrow \infty$ , unless  $a(T) = 0$ . For  $a(T) = 0$ , evaluating the diffusion average and the integral over  $G$  leads to

$$\begin{aligned} -i\Phi(T) &= -\frac{3}{2} \ln \left[ 1 - D \frac{\gamma^2}{2b} I_1(T) \right] \\ &+ D \frac{\gamma^2}{2} \int_0^T \int_0^T dt dt' |t - t'| \sigma(t) \sigma(t') \\ &\mathbf{f}(t) \cdot \mathbf{f}(t') + D^2 \frac{\gamma^4}{4b} \left[ 1 - D \frac{\gamma^2}{2b} I_1(T) \right]^{-1} \\ &\times \left| \int_0^T \int_0^T dt dt' |t - t'| \sigma(t) \sigma(t') \mathbf{f}(t) \right|^2. \end{aligned} \quad [32]$$

Expanding [32] in powers of  $D$  shows that a necessary condition for the validity of a weak-diffusion approximation is

$$D \frac{\gamma^2}{2b} |I_1(T)| \ll 1. \quad [33]$$

Since for this model  $F_1(0) = 3/(2b)$ , [33] can be rewritten as

$$D \frac{\gamma^2}{3} F_1(0) |I_1(T)| \ll 1. \quad [34]$$

If it is further assumed that the external gradient  $\mathbf{f}(t)$  is independent of time, then it can be shown that [34] is also a sufficient condition.

For more realistic models, it is reasonable to apply [34], as long as it is regarded as a rule of thumb. Less precisely, one can say that the weak-diffusion approximation should be valid for sufficiently short times. In particular, one would expect that the weak-diffusion approximation to break down when the typical diffusion length  $\sqrt{6DT}$  exceeds some characteristic length of the random field, such as the correlation length or impurity size. Therefore, the weak-diffusion theory is most likely to be accurate for systems with slowly varying random fields and for measurements with short echo times.

MEASURING  $F_0$  AND  $F_1$ 

Assuming both that diffusion effects are observable and that the weak-diffusion approximation is accurate, the functions  $F_0$  and  $F_1$ , which depend on the details of the random field, can be, in principle, measured with a Carr–Purcell sequence (16, 17) modified so that the external gradient is not switched on until a time  $t = t_c$  after the initial  $90^\circ$  spin-flip pulse. This technique then gives an experimental method for determining microscopic characteristics of the magnetic field.

First consider a conventional Carr–Purcell sequence of  $N_s$  spin-flip pulses,  $N_s \geq 2$ , occurring at the times  $t_0 = 0$  and  $t_j = (2j - 1)\Delta t$  for  $1 \leq j \leq N_s - 1$ . (Recall that  $N_s$  is the number of spin-flip pulses including the initial  $90^\circ$  pulse.) With a constant external gradient, an echo forms when  $T = 2\Delta t(N_s - 1)$ , i.e., when condition [4] is satisfied. At this time, Eqs. [24] and [25] give

$$\begin{aligned} a(T) &= 0, \\ I_1(T) &= -\frac{4}{3}(\Delta t)^3(N_s - 1). \end{aligned} \quad [35]$$

Observe that  $I_1(T)$  depends linearly on  $N_s$ . Equations [5], [6], [13], and [25] then imply that after the factor involving the external gradient is divided out, the signal amplitude  $A$  behaves as

$$A(T) \sim e^{-\eta T}, \quad [36]$$

where

$$\eta = \frac{\gamma^2}{3} DF_1(0)(\Delta t)^2. \quad [37]$$

A measurement of the decay constant of the exponential then yields the value of  $F_1(0)$ .

Now assume that the external gradient is not switched on until a time  $t_c$ ,  $0 < t_c < \Delta t$ , and afterward is maintained at a constant value. An echo then forms when  $T = 2\Delta t(N_s - 1) - (-1)^{N_s}t_c$ , and one finds that

$$\begin{aligned} a(T) &= (-1)^{N_s+1}t_c, \\ I_1(T) &= -\frac{4}{3}(\Delta t)^3(N_s - 1) - \frac{1}{3}(-1)^{N_s}t_c^3 \\ &\quad + [1 + (-1)^{N_s}]t_c(\Delta t)^2. \end{aligned} \quad [38]$$

This shows that the NMR signal depends on the random magnetic field only through  $F_0(\pm t_c)$  and  $F_1(\pm t_c)$ , with the sign depending on whether  $N_s$  is even or odd. Therefore,  $F_0$  and  $F_1$  for a selected time can be inferred from measurements

of the NMR signal for various values of  $N_s$ . Note that the amplitude of an echo still decays exponentially with  $T$ , but the decay constant  $\eta$  is generalized to

$$\eta = \frac{\gamma^2}{3} D[\text{Re } F_1(t_c)](\Delta t)^2. \quad [39]$$

An important physical system to which the above considerations could be applied is deoxygenated blood. Measurements of  $\eta$  for  $\Delta t = 2$  ms and  $t_c = 0$  have been performed by Brooks *et al.* (21), using field strengths ranging from 0.02 to 1.5 T. They find that  $\eta$  depends quadratically on  $B_0$  with a proportionality constant

$$\eta/B_0^2 = 7.2 \text{ s}^{-1}/\text{T}^2. \quad [40]$$

Assuming that Eq. [37] holds, we then have

$$F_1(0) = \frac{3\eta}{DB_0^2\gamma^2(\Delta t)^2} B_0^2 = 0.030 \text{ m}^{-2} B_0^2, \quad [41]$$

where we have used the values  $D = 2.5 \times 10^{-9} \text{ m}^2/\text{s}$  and  $\gamma = 2.675 \times 10^8 \text{ s}^{-1}/\text{T}$  (15).

As the magnitude of the field perturbation caused by a deoxygenated blood cell is on the order of  $\chi B_0$ , where  $\chi \approx 8 \times 10^{-8}$  (15), Eq. [19] suggests that

$$F_1(0) \sim \frac{\chi^2 B_0^2}{l^2}, \quad [42]$$

with  $l$  being a length scale characterizing the spatial variation of the field. For Eqs. [41] and [42] to be consistent requires that

$$l \sim \frac{\chi}{\sqrt{0.03}} \text{ m} \approx 0.5 \text{ } \mu\text{m}, \quad [43]$$

which is comparable to the distance over which the field produced by a red blood cell changes significantly (22).

This agreement points to the possible validity of the weak-diffusion approximation in this case. While for the field strengths used in (21), it would most likely be difficult to observe any change in  $F_1$  with  $t_c$ , field strengths of 4 T or higher may well show an effect. Indeed Eq. [21], which should hold approximately for blood cells, indicates that a necessary criterion for a significant  $t_c$  dependence is  $\chi B_0 \gamma \Delta t \sim 1$ . For  $B_0 = 4$  T and  $\Delta t = 2$  ms,  $\chi B_0 \gamma \Delta t \approx 0.17$ .

## CONCLUDING REMARKS

The central result of this paper is Eq. [13], which gives the leading correction to the NMR signal due to molecular diffusion. This correction depends on the random magnetic

field only through the functions  $F_0$  and  $F_1$ . In addition, Eq. [13] shows that to  $O(D)$  the effects of the random field and the external gradients decouple, facilitating the analysis of complicated gradient sequences.

Possible applications of Eq. [13] are to check the validity of calculations based on static spins, to test numerical models, and under appropriate conditions, to predict experimental measurements. Furthermore, when a weak-diffusion approximation based on Eq. [13] is sufficiently accurate,  $F_0(\tau)$  and  $F_1(\tau)$ , for given values of  $\tau$ , may be determined with a modified Carr–Purcell sequence, allowing microscopic properties of the random magnetic field to be inferred.

## APPENDIX

In order to derive Eq. [13], the exponential appearing inside the average in Eq. [2] is expanded about the initial position  $\mathbf{r}_0$  as

$$\begin{aligned} e^{-i\gamma\int_0^T dt \sigma(t)\{B[\mathbf{r}(t)] + \mathbf{f}(t) \cdot \mathbf{r}(t)\}} &= e^{-i\gamma a(T)B(\mathbf{r}_0)} \\ &\times \left\{ 1 - i\gamma \int_0^T dt \sigma(t) [\nabla_j B(\mathbf{r}_0) + f_j(t)] [r_j(t) - r_{0j}] \right. \\ &\quad - \frac{i\gamma}{2} \int_0^T dt \sigma(t) \nabla_j \nabla_k B(\mathbf{r}_0) [r_j(t) - r_{0j}] \\ &\quad \times [r_k(t) - r_{0k}] - \frac{\gamma^2}{2} \int_0^T \int_0^T dt dt' \sigma(t) \sigma(t') \\ &\quad \times [\nabla_j B(\mathbf{r}_0) + f_j(t)] [\nabla_k B(\mathbf{r}_0) + f_k(t')] \\ &\quad \left. \times [r_j(t) - r_{0j}] [r_k(t') - r_{0k}] + \dots \right\}, \quad [A1] \end{aligned}$$

where definition [3] and condition [4] have been used. In [A1], the repeated indices  $j$  and  $k$  are summed from 1 to 3. The diffusion average of the right side of [A1] can then be performed explicitly using Eq. [12] and

$$\langle [r_j(t) - r_{0j}] \rangle_{\text{diff.}} = 0, \quad [A2]$$

which follows from reflection symmetry. One finds

$$\begin{aligned} \langle e^{-i\gamma\int_0^T dt \sigma(t)\{B[\mathbf{r}(t)] + \mathbf{f}(t) \cdot \mathbf{r}(t)\}} \rangle_{\text{diff.}} &= e^{-i\gamma a(T)B(\mathbf{r}_0)} \\ &\times \left\{ 1 - iD\gamma \nabla^2 B(\mathbf{r}_0) \int_0^T dt \sigma(t) t - D \frac{\gamma^2}{2} \int_0^T \int_0^T \right. \\ &\quad \times dt dt' \sigma(t) \sigma(t') [\nabla B(\mathbf{r}_0) + \mathbf{f}(t)] \\ &\quad \left. \times [\nabla B(\mathbf{r}_0) + \mathbf{f}(t')] (t + t' - |t - t'|) + \dots \right\}. \quad [A3] \end{aligned}$$

The terms not shown in the expansion [A3] are of order  $D^2$  or smaller.

To do the average over the random magnetic field, the following identities are useful:

$$\begin{aligned} \langle e^{-i\gamma\tau B(\mathbf{r}_0)} \nabla B(\mathbf{r}_0) \rangle_{\text{ran.fld.}} &= \frac{i}{\gamma\tau} \langle \nabla e^{-i\gamma\tau B(\mathbf{r}_0)} \rangle_{\text{ran.fld.}} \\ &= \frac{i}{\gamma\tau} \nabla F_0(\tau) = 0, \quad [A4] \end{aligned}$$

and

$$\begin{aligned} \langle e^{-i\gamma\tau B(\mathbf{r}_0)} \nabla^2 B(\mathbf{r}_0) \rangle_{\text{ran.fld.}} &= \left\langle \frac{i}{\gamma\tau} \nabla^2 e^{-i\gamma\tau B(\mathbf{r}_0)} + i\gamma\tau e^{-i\gamma\tau B(\mathbf{r}_0)} |\nabla B(\mathbf{r}_0)|^2 \right\rangle_{\text{ran.fld.}} \\ &= \frac{i}{\gamma\tau} \nabla^2 F_0(\tau) + i\gamma\tau F_0(\tau) F_1(\tau) = i\gamma\tau F_0(\tau) F_1(\tau). \quad [A5] \end{aligned}$$

In deriving [A4] and [A5], we have used the fact that  $F_0$  is independent of  $\mathbf{r}_0$ . Averaging [A3] over the random field and applying [A4] and [A5] gives

$$\begin{aligned} \langle e^{-i\gamma\int_0^T dt \sigma(t)\{B[\mathbf{r}(t)] + \mathbf{f}(t) \cdot \mathbf{r}(t)\}} \rangle_{\text{diff. + ran.fld.}} &= F_0[a(T)] \left\{ 1 + D\gamma^2 a(T) F_1[a(T)] \int_0^T dt \sigma(t) t \right. \\ &\quad - D \frac{\gamma^2}{2} \int_0^T \int_0^T dt dt' \sigma(t) \sigma(t') \{ F_1[a(T)] \\ &\quad \left. + \mathbf{f}(t) \cdot \mathbf{f}(t') \} (t + t' - |t - t'|) + O(D^2) \right\}. \quad [A6] \end{aligned}$$

Simplifying, with the help of Eqs. [3] and [4], [A6] reduces to

$$\begin{aligned} \langle e^{-i\gamma\int_0^T dt \sigma(t)\{B[\mathbf{r}(t)] + \mathbf{f}(t) \cdot \mathbf{r}(t)\}} \rangle_{\text{diff. + ran.fld.}} &= F_0[a(T)] \left\{ 1 + D \frac{\gamma^2}{2} \int_0^T \int_0^T dt dt' |t - t'| \sigma(t) \right. \\ &\quad \left. \times \sigma(t') \{ F_1[a(T)] + \mathbf{f}(t) \cdot \mathbf{f}(t') \} + O(D^2) \right\}. \quad [A7] \end{aligned}$$

From [6], one has the expansion for the correction factor

$$e^{-i\Phi(T)} = e^{-i\Phi_0(T)} [1 - iD\Phi_1(T) + O(D^2)]. \quad [A8]$$

Finally, comparing Eqs. [2], [5], [9], [A7], and [A8] leads directly to Eq. [13].

## REFERENCES

1. J. F. Schenck, *Med. Phys.* **23**, 815 (1996).
2. B. Drayer, P. Burger, R. Darwin, S. Riederer, R. Herfkens, and G. A. Johnson, *Am. J. Neuroradiol.* **7**, 373 (1986).
3. B. P. Drayer, W. Olanow, P. Burger, G. A. Johnson, R. Herfkens, and S. Riederer, *Radiology* **159**, 493 (1986).
4. F. W. Wehrli, J. C. Ford, M. Attie, H. Y. Kressel, and F. S. Kaplan, *Radiology* **179**, 615 (1991).
5. J. C. Ford and F. W. Wehrli, *Magn. Reson. Med.* **17**, 543 (1991).
6. J. C. Ford, F. W. Wehrli, and H.-W. Chung, *Magn. Reson. Med.* **30**, 373 (1993).
7. H. Chung, F. W. Wehrli, J. L. Williams, and S. D. Kugelmass, *Proc. Natl. Acad. Sci. USA* **90**, 10250 (1993).
8. S. Ogawa, T.-M. Lee, A. S. Nayak, and P. Glynn, *Magn. Reson. Med.* **14**, 68 (1990).
9. J. W. Belliveau, B. R. Rosen, H. L. Kantor, R. R. Rzedzian, D. N. Kennedy, R. C. McKinstry, J. M. Vevea, M. S. Cohen, I. L. Pykett, and T. J. Brady, *Magn. Reson. Med.* **14**, 538 (1990).
10. R. Turner, D. Le Bihan, C. T. W. Moonen, D. Despres, and J. Frank, *Magn. Reson. Med.* **22**, 159 (1991).
11. B. R. Rosen, J. W. Belliveau, H. J. Aronen, D. Kennedy, B. R. Buchbinder, A. Fischman, M. Gruber, J. Glas, R. M. Weisskoff, M. S. Cohen, F. H. Hochberg, and T. J. Brady, *Magn. Reson. Med.* **22**, 293 (1991).
12. S. Majumdar and J. C. Gore, *J. Magn. Reson.* **78**, 41 (1988).
13. R. P. Kennan, J. Zhong, and J. C. Gore, *Magn. Reson. Med.* **31**, 9 (1994).
14. C. R. Fisel, J. L. Ackerman, R. B. Buxton, L. Garrido, J. W. Belliveau, B. R. Rosen, and T. J. Brady, *Magn. Reson. Med.* **17**, 336 (1991).
15. D. A. Yablonsky and E. M. Haacke, *Magn. Reson. Med.* **32**, 749 (1994).
16. C. P. Slichter, "Principles of Magnetic Resonance," 3rd ed., Springer-Verlag, Berlin, 1990.
17. A. Abragam, "Principles of Nuclear Magnetism," Oxford Univ. Press, Oxford, 1983.
18. J. Kärgler, H. Pfeifer, and W. Heink, in "Advances in Magnetic Resonance" (J. S. Waugh, Ed.), Vol. 12, Academic Press, San Diego, 1988.
19. X. Hong and W. T. Dixon, *J. Magn. Reson.* **99**, 561 (1992).
20. J. Lian, D. S. Williams, and I. J. Lowe, *J. Magn. Reson. A* **106**, 65 (1994).
21. R. A. Brooks, J. Vymazal, J. W. M. Bulte, C. D. Baumgarner, and V. Tran, *J. Magn. Reson. Imaging* **4**, 446 (1995).
22. P. Gillis, S. Petö, F. Moiny, J. Mispelter, and C.-A. Cuenod, *Magn. Reson. Med.* **33**, 93 (1995).