IDE▲L®

Corrected Equations for Susceptibility-Induced T_2-Shortening

Pierre Gillis,*,[1] Alain Roch,† and Rodney A. Brooks‡

*Biological Physics Department and †NMR Laboratory, Department of Organic Chemistry, Université de Mons-Hainaut, B-7000 Mons, Belgium;
and ‡Neuroimaging Branch, NINDS, National Institutes of Health, Bethesda, Maryland 20892

Local field gradients created by paramagnetic entities shorten water proton relaxation times, particularly T_2. This "novel" relaxation mechanism, now known as susceptibility-induced relaxation, was described twenty years ago by Gueron, and later extended by others to superparamagnetic particles which have a much larger magnetization. Unfortunately, because of subtle but significant errors, those results are valid only in the strict zero-field limit. These errors are corrected in the present article, and new versions of the relaxation equations are presented. The correction is shown to be significant, not only for transverse and longitudinal relaxation in aqueous superparamagnetic colloids, where the "Gueron" effect is known to be important, but even in some cases for transverse paramagnetic relaxation. © 1999 Academic Press

Key Words: susceptibility-induced relaxation; Curie relaxation; superparamagnetic particles; relaxometry; nuclear magnetic relaxation dispersion (NMRD).

INTRODUCTION

In 1975, Maurice Gueron (*1*) introduced "a novel mechanism" into the theory of nuclear magnetic relaxation by electronic spins, viz., the effect of the *time-averaged* electronic moment μ as it aligns with the applied field B_0. This induced magnetization creates local field inhomogeneities that dephase nearby protons, and hence cause T_2-shortening. Since the field gradients are a microscopic manifestation of macroscopic susceptibility, the effect is often referred to as susceptibility-induced relaxation. Gueron called the aligned component the "Curie spin" because the alignment of paramagnetic (PM) ions increases with field strength according to Curie's law. He then showed that its effect on nuclear magnetic relaxation differs from that of the fluctuating spin because "relaxation by the constant Curie spin . . . is modulated only by the molecular motion . . . [while] relaxation by the field of the fluctuating part of the spin [is] modulated both by spin relaxation and molecular motion."

Gueron's theory has become more important with the emergence of a new type of MRI contrast agent known as magnetic

[1] To whom correspondence should be addressed, at: Physique biologique, Faculté de médecine, Université de Mons-Hainaut, Avenue du Champ de Mars, 24, B-7000 Mons, Belgium. Fax: +32-65-373537; E-mail: pierre.gillis@umh.ac.be.

"nanoparticles"; these are small coated ferrimagnetic crystals with superparamagnetic (SPM) moments that are much larger than PM moments. The theory was accordingly extended to describe such particles (*2, 3*), using the Brillouin function, rather than Curie's law, to describe the larger induced magnetization.

Unfortunately, all of these treatments contain subtle but significant errors. The purpose of this note is to correct those errors and to present, for the first time, what we hope is a correct theory for this important type of nuclear magnetic relaxation. For ease of comparison, we have used the same notation as the original references wherever possible, while maintaining internal consistency. All equations are in centimeter-gram-second (cgs) units.

INNER-SPHERE RELAXATION

Gueron (*1*) was concerned with PM ions, and therefore used "inner-sphere" relaxation theory, which is the dominant mechanism for most PM ions. Inner-sphere relaxation occurs when protons bind temporarily to ions or ion complexes; the resulting rapid relaxation is then transferred to the free proton pool by proton or water exchange.

Decomposition of Spin

Gueron separated the component of electronic spin along the applied field, S_z, into two subcomponents: a time-averaged (or, as he called it, "Curie") spin, $\langle S_z \rangle = S_C$, and a fluctuating spin, s_z:

$$S_z = S_C + s_z. \qquad [1]$$

Since, by definition, $\langle s_z \rangle = 0$, it follows that

$$\langle S_z^2 \rangle = S_C^2 + \langle s_z^2 \rangle. \qquad [2]$$

Gueron then showed that the effect of each component on proton relaxation can be obtained by modifying the standard relaxation equations. Now these equations contain coefficients that are based on the zero-field relation

AP

$$\langle S_z^2 \rangle = S(S + 1)/3. \qquad [3]$$

The modifications, therefore, involve replacing the coefficient $S(S + 1)/3$ by the correct expression for $\langle S_z^2 \rangle$ in the presence of alignment.

Time-Averaged Component

Gueron used Curie's law to describe the time-averaged aligned spin, as is appropriate for PM ions. For the sake of greater generality, we shall use the Brillouin function B_S (which, of course, reduces to Curie's law for small spins). Thus we write

$$S_C = \langle S_z \rangle = SB_S(x), \qquad [4]$$

where

$$B_S(x) = \frac{S + \frac{1}{2}}{S} \coth \frac{(S + \frac{1}{2})x}{S} - \frac{1}{2S} \coth \frac{x}{2S},$$

$$x = S\hbar\gamma_S B_0/(kT),$$

and the constants have their usual meanings.

The relaxation effect of S_C is obtained by replacing $S(S + 1)/3$ with S_C^2 in the standard relaxation equations, and also setting the electronic relaxation time[2] $\tau_S \rightarrow \infty$ (1). The latter change is necessary because S_C, being a time average, is not affected by electronic spin fluctuations. This part of Gueron's treatment remains unaltered.

Fluctuating Component

As the aligned component grows, the mean-squared fluctuating component $\langle s_z^2 \rangle$ is clearly reduced from its zero-field value of $S(S + 1)/3$. This consideration led Gueron to write

$$\langle s_z^2 \rangle = S(S + 1)/3 - S_C^2, \qquad [5]$$

under the assumption that $\langle S_z^2 \rangle$—i.e., the sum of the squared amplitudes of average and fluctuating spins (Eq. [2])—remains constant. But $\langle S_z^2 \rangle$ is *not* constant; it increases steadily from $S(S + 1)/3$ at zero field to S^2 in the high-field limit.

A correct expression for $\langle s_z^2 \rangle$ may be obtained from the following general expression for the total mean-squared spin in the z-direction:

$$\langle S_z^2 \rangle = (1/Z) \sum_{m=-S}^{S} m^2 e^{mx/S}, \qquad [6]$$

[2] There are actually two electronic relaxation times—longitudinal (τ_{S1}) and transverse (τ_{S2}); it is the former which is referred to here. The subscript 1 is omitted for simplicity of notation.

where

$$Z = \sum_{m=-S}^{S} e^{mx/S}.$$

Using the definition of average magnetization,

$$\langle S_z \rangle = (1/Z) \sum_{m=-S}^{S} m\, e^{mx/S},$$

which may be written as

$$\langle S_z \rangle = (S/Z) \frac{\partial Z}{\partial x}, \qquad [7]$$

we obtain

$$\langle S_z^2 \rangle = (S^2/Z) \frac{\partial^2 Z}{\partial x^2}$$

$$= (S/Z) \frac{\partial(Z \cdot S_C)}{\partial x}$$

$$= S \frac{\partial S_C}{\partial x} + S_C^2.$$

Differentiating and squaring the expression for S_C (Eq. [4]), and using the identity $\cosh^2(x) - \sinh^2(x) = 1$, we finally obtain

$$\langle S_z^2 \rangle = S(S + 1) - S_C \coth \frac{x}{2S}. \qquad [8]$$

Thus the mean-squared fluctuating component is, from Eq. [2],

$$\langle s_z^2 \rangle = \langle S_z^2 \rangle - S_C^2 = S(S + 1) - S_C \coth \frac{x}{2S} - S_C^2. \qquad [9]$$

Equations [5] and [9] are compared in Fig. 1, for $S = 25$. While they agree at zero field, the difference increases, initially as x^2, and becomes quite large at high fields. (The value $S = 25$ was chosen to illustrate the correction more clearly, and also because SPM particles, discussed below, have much larger spins. However, even for PM spins such as $S = \frac{7}{2}$, the effect of the correction is noticeable at 7 T, the field used by Gueron as an illustration.)

Relaxation Equations

The equations for T_1 and T_2 may now be obtained using the modification procedure described by Gueron, but using Eq. [9] instead of Eq. [5] for the fluctuating spin. The final result is
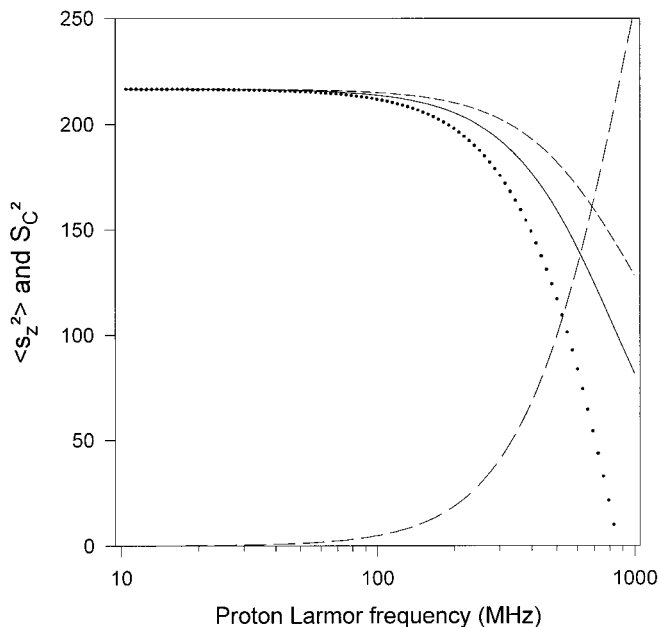
FIG. 1. Three different expressions for $\langle s_z^2 \rangle$, the mean-squared fluctuating component of spin along the applied field. The solid line shows the correct expression, Eq. [9], and the dotted and dashed lines show earlier incorrect versions, Eqs. [5] and [13], respectively. The mean-squared aligned spin, S_C^2, is also shown for comparison (long dashed line). The plots are drawn for $S = 25$, a value that is intermediate between PM and SPM spins.

$$1/T_1 = (6/5)\Delta^2 \left\{ S_C^2 \tau_D j_i(\omega, \tau_D) + \left[S(S+1) \right.\right.$$

$$\left.\left. - S_C \coth \frac{x}{2S} - S_C^2 \right] \tau j_i(\omega, \tau) \right\} \qquad [10]$$

$$1/T_2 = (1/5)\Delta^2 \left\{ S_C^2 \tau_D [3j_i(\omega, \tau_D) + 4] + \left[S(S+1) \right.\right.$$

$$\left.\left. - S_C \coth \frac{x}{2S} - S_C^2 \right] \tau [3j_i(\omega, \tau) + 4] \right\}, \qquad [11]$$

where $\Delta = \hbar \gamma_I \gamma_S / r^3$. Following Gueron, a term in the standard equations that involves the electron Larmor frequency was omitted as being negligible at high fields. In these equations, γ_I and γ_S are, respectively, the proton and electron gyromagnetic ratios, r is the binding distance, and τ is the correlation time of the fluctuating magnetic field seen by the proton, given by

$$\tau^{-1} = \tau_D^{-1} + \tau_S^{-1},$$

where τ_D is the motional time constant (a combination of rotational correlation time and residence time), and τ_S is the electronic relaxation time.[2] (Note that this definition of τ_D, introduced by Gueron, is not the same as the usual definition of τ_D as diffusion time.)

The dependence on magnetic field B_0 (or, equivalently, on

proton Larmor frequency ω) is incorporated in the inner-sphere spectral density function

$$j_i(\omega, \tau) = 1/(1 + \omega^2 \tau^2). \qquad [12]$$

This function is unity at zero frequency and falls to zero at high frequencies, with a breakpoint at $\omega = \tau^{-1}$ (see Fig. 2).

Equations [10] and [11] should replace Eqs. [14] and [15] of Ref. (1) (although the succeeding Eqs. [14'] and [15'] remain valid because of the stated restrictions). The meaning of the equations is, as Gueron said, "transparent." The first line of each equation represents relaxation by the "Curie spin," and is proportional to S_C^2; the second line corresponds to relaxation by the residual fluctuating spin, and falls off as S_C increases. These equations are plotted in Fig. 3 for $S = 25$ (again, an intermediate value between PM and SPM spins), $\tau = 0.5$ ns, and $\tau_D = 3\tau$ (i.e., $\tau_S = \tau_D/2$), and they are compared with the standard relaxation equations (dotted lines), where $\langle S_z^2 \rangle$ is supposed to be field independent and equal to $S(S + 1)/3$. The susceptibility effect increases strongly as τ becomes smaller than τ_D, and the difference from the standard relaxation rates is already important for $\tau_D = 3\tau$. This alters Gueron's assertion (1) that the new equations "differ significantly from [the standard ones] only if $\tau_D \gg \tau$." His statement followed from the (incorrect) assumption that $\langle S_z^2 \rangle$ is constant, since the reduction in the fluctuating term (proportional to S_C^2) then tends to balance the relaxation effect of the Curie term (also proportional to S_C^2) as τ approaches τ_D. However, a proper accounting of the field dependence of $\langle S_z^2 \rangle$, as in Eq. [8], intro-
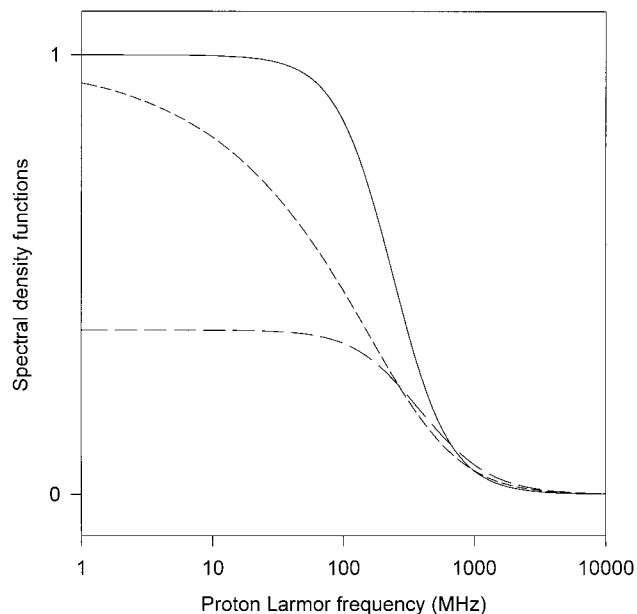

FIG. 2. Spectral density functions used in the relaxation equations. The solid line shows the inner-sphere function, j_i, for $\tau_D = 2$ ns. The long and short dashed lines show the outer-sphere function, j_o, for $\tau_D = 2$ ns with $\tau_S = 1$ and 1000 ns, respectively.
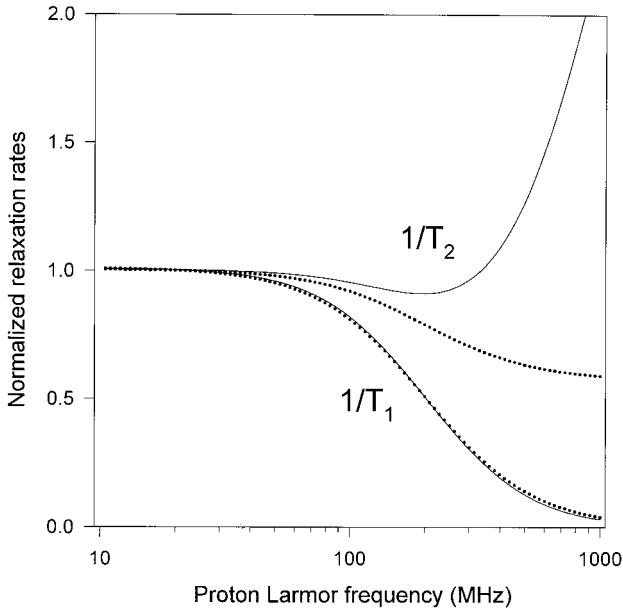
FIG. 3. Inner-sphere relaxation rates, $1/T_1$ and $1/T_2$ (Eqs. [10] and [11]), for $S = 25$, $\tau = 0.5$ ns, and $\tau_D = 3\tau$ (solid lines). For comparison, the rates without the susceptibility effect (standard relaxation equations) are shown by dotted lines. Note that the magnitude of the susceptibility effect depends on the motional correlation time τ_D, as well as on the total correlation time τ. A term that is important at low fields has been omitted from these plots.

duces a second difference from the standard equations that remains even for $\tau \cong \tau_D$, even if referring to a susceptibility effect becomes not appropriate.

As shown in Fig. 3, the effect of susceptibility on T_2 is particularly strong because of the so-called "secular" terms in Eq. [11]. That is, the additive constants "4" permit the first term of $1/T_2$ to continue to increase (with increasing S_C or τ_D) despite the spectral density function j_i. For T_1, the situation is different; both components of $1/T_1$ fall off because of the j_i factors, with the Curie term falling first because it has the lower breakpoint. Thus T_1 exhibits a noticeable susceptibility effect only if the aligned component S_C becomes significant before the first breakpoint is reached (at $1/\tau_D$). Even then the increase in $1/T_1$ will fall off with j_i, and there may even be a net reduction before the second breakpoint is reached (at $1/\tau$). This explains why the susceptibility effect can either increase or decrease $1/T_1$. In many situations the susceptibility effect on T_1, positive or negative, is too small to be of interest, but for larger spins, typical of SPM particles, these deviations can be significant.

OUTER-SPHERE RELAXATION

The first attempt to address the question of relaxation caused by magnetic "nanoparticles" was made by Gillis and Koenig (4), using outer-sphere theory. This theory applies to water protons that diffuse past or near magnetic ions or particles, but do not bind. However, that paper failed to take into account the "Curie" effect (aligned magnetization), and therefore the secular term was underestimated by a factor of 3. The alignment was later taken into

account by Roch and Muller (2), followed by Koenig and Kellar (3), using a variation of Gueron's approach.

Time-Averaged Component

The approach taken, as before, is to separate the z-component of spin into two parts: static and fluctuating (Eq. [1]). In this case, use of the Brillouin function to describe S_C, the time-averaged z-magnetization, is mandatory because of the much larger magnetic moment. As before, the relaxation effect of S_C is obtained by replacing $S(S + 1)/3$ with S_C^2, using Eq. [4], in the standard relaxation equations and setting the electronic relaxation time[2] $\tau_S \rightarrow \infty$.

Fluctuating Component

For the fluctuating component of spin, Roch and Muller (2), followed by Koenig and Kellar (3, Eq. [11]), wrote

$$\langle s_z^2 \rangle = [1 - B_S(x)^2]S(S + 1)/3, \qquad [13]$$

based on the fact that $\langle s_z^2 \rangle$ must approach zero as the alignment becomes complete. As shown in Fig. 1, Eq. [13] is an improvement over Eq. [5], but it still leaves a significant error, which becomes worse at higher spins. The correct expression, as we have shown, is Eq. [9].

Relaxation Equations

The equations for T_1 and T_2 are obtained by modifying the standard outer-sphere equations as before, using Eq. [9] for the fluctuating spin instead of Eq. [13]. The final result is

$$1/T_1 = 6c\tau_d\left\{ S_C^2 j_o(\omega_I, \tau_d, \tau_S \rightarrow \infty) + \left[S(S + 1) \right. \right.$$
$$\left. \left. - S_C\coth\frac{x}{2S} - S_C^2 \right] j_o(\omega_I, \tau_d, \tau_S) \right\} \qquad [14]$$

$$1/T_2 = c\ \tau_d\left\{ S_C^2[3j_o(\omega_I, \tau_d, \tau_S \rightarrow \infty) + 4j_o(0, \tau_d, \tau_S \rightarrow \infty)] \right.$$
$$+ \left[S(S + 1) - S_C\coth\frac{x}{2S} - S_C^2 \right]$$
$$\left. \times [3j_o(\omega_I, \tau_d, \tau_S) + 4j_o(0, \tau_d, \tau_S)] \right\}, \qquad [15]$$

where $c = (16\pi/135000)\ \hbar^2\gamma_s^2\gamma_I^2 N_A[M]/r^3$. In these equations, τ_d is the motional (diffusion) time constant ($=r^2/D$), τ_s is the longitudinal electronic relaxation time, N_A is Avogadro's number, [M] is the molar concentration of magnetized particles (in moles per liter), r is the distance of closest approach, and D is the water diffusion coefficient.

The spectral density function for outer-sphere relaxation, j_o, is more complex than j_i, and depends separately on τ_d and τ_s (5),

$$j_o(\omega,\ \tau_d,\ \tau_s) = \text{Re}\left[\frac{1 + \Omega^{1/2}/4}{1 + \Omega^{1/2} + 4\Omega/9 + \Omega^{3/2}/9} \right],$$

where $\Omega = (i\omega + 1/\tau_s)\tau_d$. However, its behavior is similar to that of j_i (see Fig. 2). In fact, if $\tau_s \ll \tau_d$, it is essentially proportional to j_i, but with a low-field value less than unity (but never less than $9\tau_s/4\tau_d$), and with a breakpoint around $\omega = \tau_s^{-1}$. As the ratio τ_s/τ_d increases, the low-field value of j_o approaches unity, and the decrease becomes more gradual, while in the limit $\tau_d \ll \tau_s$, the breakpoint approaches τ_d^{-1}. (This observation corrects an additional error in Ref. (3), in which $j_o(0, \tau_d, \tau_s)$ was incorrectly set to unity for all values of τ_s.)

The similarity between Eqs. [14] and [15] and Eqs. [10] and [11] is obvious, and the interpretation is equally "transparent."

Low-Field Terms

The principal difference between Refs. (2) and (3) is the inclusion of an electronic precession term in the latter. This term, which is present in the standard relaxation equations for PM ions, is usually negligible at high fields (i.e., when the susceptibility effect becomes important), and was therefore omitted by Gueron. While it is important at low fields, its applicability to SPM particles is complicated by the crystalline anisotropy; this question is discussed in a separate publication (6).

Because this term was included in Ref. (3), we will temporarily ignore the anisotropy effect and reevaluate the term in light of the above theory. The term contains contributions arising from the correlation functions of the electronic transverse spin components. Their amplitudes are not given by Eq. [9], but they can easily be estimated as

$$\langle S_+ S_- \rangle = \langle S_x^2 \rangle + \langle S_y^2 \rangle + \langle S_z \rangle$$
$$= S(S+1) - \langle S_z^2 \rangle + \langle S_z \rangle$$
$$= \left(\coth \frac{x}{2S} + 1 \right) S_C \qquad [16]$$

and similarly

$$\langle S_- S_+ \rangle = \left(\coth \frac{x}{2S} - 1 \right) S_C, \qquad [17]$$

where $S_+ = S_x + iS_y$, and $S_- = S_x - iS_y$. These equations demonstrate that the spin fluctuations are *not* equally distributed along the three spatial coordinates, as was implicitly assumed in the derivation of Eq. [13] (2).

Introducing Eqs. [16] and [17] into the expressions for the low-field contributions (3) leads to the corrected terms

$$[1/T_1]_{lf} = 7cS_C\tau_d\coth\left(\frac{x}{2S}\right)j_o(\omega_s, \tau_d, \tau_{S2}) \qquad [18a]$$

$$[1/T_2]_{lf} = 6.5cS_C\tau_d\coth\left(\frac{x}{2S}\right)j_o(\omega_S, \tau_d, \tau_{S2}). \qquad [18b]$$

(Note that the spectral density function used here involves the transverse electron relaxation time τ_{s2}, not the longitudinal time used earlier, τ_s.) These equations may be added to Eqs. [14] and [15] to obtain the corrected versions of Eqs. [13a] and [13b] in Ref. (3).

High-Spin Limit

If $S \gg 1$, the Brillouin function reduces to the Langevin function,

$$L(x) = \coth(x) - 1/x.$$

Since SPM particles, by definition, have high spins, it is useful to restate the relaxation equations in terms of the Langevin function. This entails changing parameters from spin S to magnetic moment μ, defined by

$$\mu = \hbar\gamma_S S,$$

so that $x = \mu B_0/kT$. With this change, Eq. [4] becomes

$$\mu_C = \mu L(x), \qquad [19]$$

and Eq. [8] becomes

$$\langle \mu_z^2 \rangle = \mu^2[1 - 2L(x)/x], \qquad [20]$$

where we have used the property $\lim_{y\to 0}[y\coth(y)] = 1$, for $y = \frac{x}{2S}$. Finally, the mean-squared fluctuating component of μ_z (Eq. [9]) is given by

$$\langle \mu_z^2 \rangle - \mu_C^2 = \mu^2[1 - 2L(x)/x - L^2(x)], \qquad [21]$$

and the transverse fluctuating component is

$$\langle \mu_x^2 \rangle + \langle \mu_y^2 \rangle = \mu^2 2L(x)/x. \qquad [22]$$

Making these substitutions in Eqs. [14] and [15], we obtain for the relaxation rates at high field

$$1/T_1 = c'\mu^2\tau_d\{3L^2(x)j_o(\omega_I, \tau_d, \tau_S \to \infty)$$
$$+ 3[1 - 2(L(x)/x) - L^2(x)]j_o(\omega_I, \tau_d, \tau_S)\} \qquad [23a]$$

$$1/T_2 = c'\mu^2\tau_d\{L^2(x)[3j_o(\omega_I, \tau_d, \tau_S \to \infty)$$
$$+ 4j_o(0, \tau_d, \tau_S \to \infty)] + [1 - 2L(x)/x - L^2(x)]$$
$$\times [3j_o(\omega_I, \tau_d, \tau_S) + 4j_o(0, \tau_d, \tau_S)]\}, \qquad [23b]$$

where $c' = (16\pi/135000)\gamma_I^2 N_A[M]/r^3$.

Applying the same results to the low-field terms, as given by Eqs. [18a] and [18b], we obtain

$$[1/T_1]_{lf} = 7c'\mu^2\tau_d[L(x)/x]j_o(\omega_S, \tau_d, \tau_{S2}) \quad [24a]$$

$$[1/T_2]_{lf} = 13c'\mu^2\tau_d[L(x)/x]j_o(\omega_S, \tau_d, \tau_{S2}). \quad [24b]$$

Again, these quantities may be added to Eqs. [23a] and [23b] to obtain the complete correct expressions that correspond to Eqs. [13a] and [13b] of Ref. (*3*).

REFERENCES

1. M. Gueron, Nuclear relaxation in macromolecules by paramagnetic ions: A novel mechanism, *J. Magn. Reson.* **19,** 58–66 (1975).

2. A. Roch and R. N. Muller, Longitudinal relaxation of water protons in colloidal suspensions of superparamagnetic crystals, *in* "Proceedings, 11th Annual Meeting of the Society of Magnetic Resonance in Medicine," Works in Progress, 1447 (1992).

3. S. H. Koenig and K. E. Kellar, Theory of $1/T_1$ and $1/T_2$ NMRD profiles of solutions of magnetic nanoparticles, *Magn. Reson. Med.* **34,** 227–233 (1995).

4. P. Gillis and S. H. Koenig, Transverse relaxation of solvent protons induced by magnetized spheres: application to ferritin, erythrocytes, and magnetite, *Magn. Reson. Med.* **5,** 323–345 (1987).

5. J. H. Freed, Dynamic effects of pair correlation functions on spin relaxation by translational diffusion in liquids. II. Finite jumps and independent T_1 processes, *J. Chem. Phys.* **68,** No. 9, 4034–4037 (1978).

6. A. Roch, R. N. Muller, and P. Gillis, Theory of proton relaxation induced by superparamagnetic particles. J. Chem. Phys., (in press).