Nuclear magnetic resonance signal dynamics of liquids in the presence of distant dipolar fields, revisited

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The description of the nuclear magnetic resonance magnetization dynamics in the presence of long-range dipolar interactions, which is based upon approximate solutions of Bloch–Torrey equations including the effect of a distant dipolar field, has been revisited. New experiments show that approximate analytic solutions have a broader regime of validity as well as dependencies on pulse-sequence parameters that seem to have been overlooked. In order to explain these experimental results, we developed a new method consisting of calculating the magnetization via an iterative formalism where both diffusion and distant dipolar field contributions are treated as integral operators incorporated into the Bloch–Torrey equations. The solution can be organized as a perturbative series, whereby access to higher order terms allows one to set better boundaries on validity regimes for analytic first-order approximations. Finally, the method legitimizes the use of simple analytic first-order approximations under less demanding experimental conditions, it predicts new pulse-sequence parameter dependencies for the range of validity, and clarifies weak points in previous calculations. © 2009 American Institute of Physics. [DOI: [10.1063/1.3116107](https://doi.org/10.1063/1.3116107)]

I. INTRODUCTION

During a correlated spectroscopy revamped by asymmetric *z*-gradient echo detection (CRAZED) pulse sequence,¹ properly applied gradients are able to break spatial isotropy of a homogeneous liquid preserving dipolar field interactions that at long distances are not averaged out by molecular diffusion. These long-range dipolar interactions are responsible for the observation of multiple echoes on time-domain nuclear magnetic resonance (NMR) as well as intermolecular multiple-quantum coherence (iMQC) peaks in the two-dimensional (2D) frequency domain.^{1,2} These effects attracted interest in diverse areas such as chaotic dynamics,³ high-resolution spectroscopy,⁴ and medical imaging.^{5,6} In particular, a new form of imaging contrast has been suggested,⁵ where subvoxel information can be obtained by tuning the dipolar field interaction range to some characteristic length of the sample under investigation. However, despite the considerable amount of research on controlled simple phantoms,^{7–11} evaluating this dipolar-tuned contrast sensitivity in biological systems has been elusive.^{12–15} The role of diffusion in processes occurring in the presence of dipolar field interactions has also been a topic of active research.^{16–18} Primarily, diffusion affects the signal-to-noise efficiency making a more general use of dipolar field based methods difficult. In addition, recent results have shown that diffusion plays an important role when trying to quantify dipolar-field contrast.¹⁵

Addressing diffusion effects proved to be straightforward both theoretically and numerically via a classical

formalism.¹⁹ This approach, which will be adopted hereafter, consists of averaging the long-range dipolar interactions over space utilizing a mean-field approximation where the resulting term, also referred to as the distant dipolar field (DDF), is incorporated into the Bloch–Torrey equations. Unfortunately, DDF interactions generate spatially variable magnetic field gradients, which preclude a general analytic solution including diffusion.²⁰ Therefore most treatments rely either on numerical calculations or on approximations. The validity of the approximate calculations used to quantify most experiments presented in the literature^{21–26} and the methods by which these approximations are performed is what we plan to revisit in this article.

We start the article presenting experimental results showing that the range of validity for approximations describing diffusion effects in the NMR signal refocused by DDF is too restrictive. In addition, the agreement between these approximations and the experiments appears to depend on pulse-sequence parameters. In order to explain these observations, we implemented an iterative approach for solving the modified Bloch–Torrey equations, where the solution is obtained as a power series with the dipolar field and diffusion contributions described in terms of integral operators. The new method provides a powerful algorithm for accessing higher order terms in the series expansion representing the solution. This enables one to study the convergence rates in the series and evaluate a more realistic range of validity for the first-order solution, which is then compared with the experiments and also with the complete solution obtained via numerical methods.

II. EXPERIMENTAL RESULTS AND MOTIVATION

The CRAZED sequence¹ and its variants, diagrammed in Fig. 1, were used for most of our studies. Following excita-

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FIG. 1. (Color) Gradient (red blocks) and rf (black blocks) pulses in the CRAZED sequence. (a) standard CRAZED sequence. (b) The inclusion of a π pulse permits the signal build up independent of t_1 . (c) A train of π pulses included to speed up acquisition as well as decrease diffusion attenuation by local field inhomogeneities. p is the number of echoes acquired per scan.

tion, the sequence can be divided into two intervals: (i) an interval t_1 where the signal evolves under the action of diffusion and relaxation in a way dependent upon the ratio n of the area under the applied gradient pulses,²⁷ and (ii) an acquisition interval t_2 , where the magnetization is detected in the presence of the DDF. Our main focus will be on the magnetization dynamics during the acquisition t_2 interval.

Figure 2 shows experimental DDF signal (open circles) as a function of t_2 for the case $n=2$ for a sample containing doped water using the pulse sequence depicted in Fig. 1(b) (see Sec. VI for more details) at a field of 9.4 T. The two panels show data where the only variable parameter was the magnetic field gradient amplitude. Figure 2(a) shows results acquired with the gradients oriented parallel to the polarizing B_0 field, whereas Fig. 2(b) depicts the case where the gradient is applied perpendicular to B_0 . The solid-line curves are plots utilizing the following formula:

$$\overline{M^+(t_2)}^{(1)} = -\frac{M_0 \Delta_s \sin \beta}{2\tau_d} e^{-2[Dk_m^2(t_1 - \delta/3) + t_1/T_2]} \sin^2 \frac{\beta}{2} e^{-t_2/T_2} \times \left[\frac{1 - e^{-(2Dk_m^2 + 1/T_1)t_2}}{2Dk_m^2 + 1/T_1} \right]. \quad (1)$$

The overline means an average over the whole sample and the top indices indicate a first-order approximation of the modified Bloch–Torrey equations that will be explained in detail in the following sections. The parameter $\tau_d \equiv 1/\mu_0\gamma M_0$ denotes a characteristic time for the dipolar field to build up an appreciable amount of signal.¹ $\Delta_s = (3\cos^2\theta - 1)/2$, where θ is the angle between the polarizing field B_0 and the modulating gradient G . The parameter $k_m = \gamma G \delta$ rep-

resents the wave vector of spatial modulation of the magnetization caused by the magnetic field gradient with amplitude G and duration δ . D denotes the self-diffusion coefficient of the nuclei under investigation and β is a radio frequency (rf) pulse angle depicted in Fig. 1. It should be mentioned that, according to the prevailing methods of solution,²³ Eq. (1) is a valid approximation for the magnetization dynamics if $(\tau_d D k_m^2)^{-1} \ll 1$. However, the experiments presented in this section agree with the theory under a much less restrictive condition (compare values in figure captions).

The solid lines on each panel of Figs. 2–4 are plots of Eq. (1) with no attempt of fitting the data. The parameters utilized for the plots are actually obtained independently by employing standard NMR methods (see Sec. VI). τ_d was the only parameter not obtained experimentally. Instead, it was estimated from theoretical predictions²⁸ of M_0 considering the value of pure water magnetization at the given polarizing field B_0 , with γ as the gyromagnetic ratio for ^1H and μ_0 denoting the magnetic permeability in vacuum. The agreement between data and the plots given by Eq. (1) is very good except for the first curve (black line) in each panel.

Figure 3 shows experiments obtained at 7 T, where the DDF signal (open circles) is recorded as a function of t_2 for a pure-water sample using the sequence of Fig. 1(c) for the cases (a) $n=2$ and (b) $n=0$. For $n=0$, as depicted by the solid lines in Fig. 3(b), the term $\sin^2(\beta/2)$ in Eq. (1) is replaced by $\cos \beta$. Here, effects of relaxation were reduced by choosing a sample with long relaxation times. However, due to the longer detection interval t_2 needed, background gradient might cause undesirable attenuation. The sequence of Fig. 1(c) remedies that by utilizing a Carr–Purcell–Meiboom–Gill (CPMG) train where background gradient effects are reduced leaving intact the modulations created previously by the encoding gradients.¹⁸ Again, the solid lines in Fig. 3 represent plots of Eq. (1) with no adjustable parameters.

Figure 4 shows experimental DDF signal (open circles) versus gradient amplitude obtained using the sequence in Fig. 1(b) for a sample containing doped water at 9.4 T. The data were recorded for several values of the modulating gradient amplitude while keeping t_2 fixed. The curves on Fig. 4(a) are for the case $G \parallel B_0$ and those on Fig. 4(b) show the case $G \perp B_0$. The solid lines represent plots given by Eq. (1) and the dashed lines show the standard pulsed-gradient spin-echo (PGSE) decay $e^{-Dk_m^2(\Delta - \delta/3)}$ expected when diffusion is unrestricted.²⁹ The agreement between experiment and Eq. (1) is improved when the gradient is applied perpendicular to the polarizing field B_0 .

Finally, the results presented so far appear to indicate limitations in the prevailing theory regarding approximate analytic solutions for accounting for the joint effect of diffusion and DDF in the NMR signal dynamics. Due to the simplicity and predictive power of Eq. (1), here we aim at extending the theory behind it by answering the main following questions raised by the experiments shown above. Is there a more accurate indicator to assess the validity of Eq. (1)? Are there additional parameters that influence this validity range? Are there more general analytical expressions accounting for the role of diffusion in DDF-based sequences?

FIG. 2. (Color) Experimental DDF-signal amplitude (open circles) vs t_2 for a sample containing doped water recorded at 9.4 T with the pulse sequence depicted in Fig. 1(b) with parameters $n=2$, $\beta=\pi/2$, $\delta=2$ ms, and $t_1=5$ ms. From top to bottom on each panel $(\tau_d D k_m^2)^{-1}=6.58, 1.64, 0.73$, and 0.41 . (a) $G \parallel B_0$ and (b) $G \perp B_0$. The solid lines represent plots of Eq. (1) utilizing the following parameters: $T_2=250$ ms, $T_1=288$ ms, $D=2.15 \times 10^{-9}$ m² s⁻¹, and $\tau_d=98$ ms.

III. THEORY: SIGNAL DYNAMICS IN THE CLASSICAL FORMALISM

Assuming negligible space fluctuations of the dipolar field—a realistic assumption in the case of liquids—a mean-field treatment can be utilized whereby the DDF contribution is obtained through an integration over the whole sample.¹⁹ In the rotating frame, the Zeeman-averaged dipolar field is

$$\mathbf{B}_d(r, t) = \frac{\mu_0}{4\pi} \int \frac{1 - 3 \cos^2 \theta'_r}{2|r - r'|^3} [3M_z(r', t)\hat{z} - \mathbf{M}(r', t)] d^3 r', \quad (2)$$

where $\hat{z}$ denotes the unit vector parallel to B_0 , θ'_r denotes the angle between the interspin vector $\mathbf{r} - \mathbf{r}'$ and $\hat{z}$, and μ_0 is the vacuum permeability. Analytical expressions can be obtained in special cases,¹⁹ e.g., when the magnetization is sinusoidally modulated along a single direction $\hat{s}$ with $k_m L \gg 1$,

where L is the sample smallest dimension and $k_m = \gamma G \delta$. Under these conditions the z component of the DDF can be written in what is defined as a local form $B_{dz}(s) = -\mu_0 \Delta_s M_z(s)$, where $\Delta_s = (3 \cos^2 \theta - 1)/2$, i.e., the field is proportional to the local magnetization. Now θ is the angle between the polarizing field $B_0 \hat{z}$ and the modulating gradient $G \hat{s}$.

The magnetization evolution in the transverse plane, $M^+ \equiv M_x + iM_y$, is dictated by the Bloch–Torrey equations modified to include the DDF.¹⁹ In a frame rotating at the Larmor frequency of a single species of spin, with gyromagnetic ratio γ , after the application of the first $(\pi/2)_x$ pulse and the gradient pulse of area $G\delta$ along a direction $\hat{z}$, the magnetization density becomes $M^+(r, \delta) = iM_0 \exp(-ik_m z)$ and $M_z = 0$, where M_0 denotes the uniform thermal equilibrium magnetization density. (Here we assume that the gradients modulate the magnetization instantaneously and relax-

FIG. 3. (Color) Experimental DDF-signal amplitude (open circles) vs t_2 for a sample containing pure water recorded at 7 T using the pulse sequence depicted in Fig. 1(c) with $G \parallel B_0$ and $\tau = 5$ ms: (a) $n=2$, $\beta = \pi/2$ and (b) $n=0$, $\beta = \pi/4$. From top to bottom on each panel $(\tau_d D k_m^2)^{-1} = 1.33$, 0.59, and 0.33. The solid lines are based on Eq. (1) using the following parameters: $T_2 = 1.66$ s, $T_1 = 2.53$ s, $D = 1.97 \times 10^{-9}$ m² s⁻¹, and $\tau_d = 132$ ms.

ation can be ignored during the gradient interval duration.) In the rotating frame, assuming that rf inhomogeneities and background gradients can be neglected,

$$\frac{\partial M^+}{\partial t} = -i\gamma[\mathbf{G} \cdot \mathbf{r} + B_{dz}(r, t)]M^+ + D\nabla^2 M^+ - \frac{M^+}{T_2}, \quad (3)$$

$$\frac{\partial M_z}{\partial t} = D\nabla^2 M_z - \frac{M_z - M_0}{T_1}, \quad (4)$$

where B_{dz} is the DDF component in the z direction, D is the self-diffusion coefficient, T_2 and T_1 are, respectively, the spin-spin and spin-lattice relaxation times. The longitudinal magnetization is not affected by the DDF and is described by the Bloch–Torrey equations with no additional terms (transverse components of the dipolar field that could rotate the longitudinal magnetization cancel out via cross product). For $t > t_1$ the solution of Eq. (4) for modulated M_z is $M_z(r, t_2) = M_z(r, t_1^+) e^{-[Dk_m^2 + 1/T_1]t_2}$ with $M_z(r, t_1^+) = -M_0 \sin \beta e^{-Dk_m^2[t_1 - 2\delta/3]} e^{-t_1/T_2} \cos k_m z$. (The superscripts + in t_1 above represent the instant immediately after the second

gradient pulse.) Terms that are not modulated by the gradients produce, at most, shifts in frequency for nonspherical samples and thereby will be neglected. For repetition times $T_R \gg T_1$ the stimulated-echo contribution can be neglected in advance. Inserting B_{dz} into Eq. (3) for $t > t_1 + n\delta$ and using t_2 as the origin of time,

$$\frac{\partial M^+}{\partial t_2} = +D\nabla^2 M^+ - \frac{M^+}{T_2} - i\gamma e^{-[Dk_m^2 + 1/T_1]t_2} B_{dz}(r, 0) M^+. \quad (5)$$

$B_{dz}(r, t) = e^{-[Dk_m^2 + 1/T_1]t_2} B_{dz}(r, 0)$ was separated in spatial and temporal variables assuming D and T_1 are space independent. The explicit value for B_{dz} is obtained from the longitudinal magnetization $M_z(r, t_2)$ calculated in the text above.

Ignoring DDF effects for a moment, the solution of Eq. (5) with $B_{dz} = 0$, for $t > t_1 + n\delta$, yields

FIG. 4. Experimental DDF-signal amplitude (open circles) vs gradient amplitude for a sample containing doped water acquired at 9.4 T utilizing the pulse sequence of Fig. 1(b) with $n=2$, $t_1=5$ ms, $\delta=2$ ms, and $t_2=600$ ms. (a) $G \parallel B_0$ and (b) $G \perp B_0$. The solid lines are based on Eq. (1) and the dashed lines are the expected Stejskal-Tanner diffusion attenuation decays assuming $\Delta=t_2$.

$$M_0^+(r, t_2) = iM_0 e^{-Dk_m^2[t_1 - (2-n)\delta/3]} e^{-[t_1+t_2]/T_2} \times \left[\cos^2 \frac{\beta}{2} e^{-i(n+1)k_m z} e^{-D(n+1)^2 k_m^2 (t_2 - n\delta)} - \sin^2 \frac{\beta}{2} e^{-i(n-1)k_m z} e^{-D(n-1)^2 k_m^2 (t_2 - n\delta)} \right]. \quad (6)$$

When averaged over the whole sample this magnetization gives observable signal only for $n=1$. Therefore, in the absence of additional magnetic field gradients, signal with $n \neq 1$ can only be observed if the DDF term is present. Equation (6) will be used in the iterative procedure described in the next section.

IV. THE ITERATIVE PROCEDURE

All investigations regarding diffusion in the presence of DDF have been limited to linear or first-order approximations regarding the DDF contribution in the modified Bloch-Torrey equations. In order to attempt the goal of obtaining higher order terms, the solution of Eq. (5) will be cast in the following form:

$$m^+(r, t_2) = m^+(r, 0) + [\mathbf{S} + \mathbf{T}]m^+(r, t_2), \quad (7)$$

where T_2 relaxation is embedded in $M^+(r, t_2) = iM_0 e^{-t_2/T_2} m^+(r, t_2)$. The terms $\mathbf{S}$ and $\mathbf{T}$ are defined as

$$\mathbf{S}m^+(r, t_2) \equiv D \int_0^{t_2} \nabla^2 m^+(r, t) dt, \quad (8)$$

$$\mathbf{T}m^+(r, t_2) \equiv -i\gamma \int_0^{t_2} e^{-[Dk_m^2 + 1/T_1]t} B_{dz}(r, 0) m^+(r, t) dt. \quad (9)$$

The iterative method requires an attempt solution, a “seed,” that replaces m^+ on the right-hand side of Eq. (7). The solution obtained is then reinserted into Eq. (7) and a new solution, hopefully improved, is obtained. This process generates a power series of $[\mathbf{S} + \mathbf{T}]$ operators. It will prove advanta-

geous to rearrange these terms as a power series of the dipolar operator $\mathbf{T}$ noting that ordering is important. The first four iterations are given below as

$$m_1^+(r, t_2) = m_0^+(r, 0) + \{\mathbf{S} + \mathbf{T}\}m_0^+(r, t_2) = \{\mathbf{1} + \mathbf{T}\}m_0^+(r, t_2),$$

$$m_2^+(r, t_2) = m_1^+(r, 0) + \{\mathbf{S} + \mathbf{T}\}m_1^+(r, t_2) = \{\mathbf{1} + [\mathbf{S}\mathbf{T} + \mathbf{T}] + \mathbf{T}^2\}m_0^+(r, t_2),$$

$$m_3^+(r, t_2) = m_2^+(r, 0) + \{\mathbf{S} + \mathbf{T}\}m_2^+(r, t_2) = \{\mathbf{1} + [\mathbf{S}^2\mathbf{T} + \mathbf{S}\mathbf{T} + \mathbf{T}] + [\mathbf{S}\mathbf{T}^2 + \mathbf{T}\mathbf{S}\mathbf{T} + \mathbf{T}^3]\}m_0^+(r, t_2),$$

$$m_4^+(r, t_2) = m_3^+(r, 0) + \{\mathbf{S} + \mathbf{T}\}m_3^+(r, t_2) = \{\mathbf{1} + [\mathbf{S}^3\mathbf{T} + \mathbf{S}^2\mathbf{T} + \mathbf{S}\mathbf{T} + \mathbf{T}] + [\mathbf{S}^2\mathbf{T}^2 + \mathbf{S}\mathbf{T}\mathbf{S}\mathbf{T} + \mathbf{T}\mathbf{S}^2\mathbf{T} + \mathbf{S}\mathbf{T}^2 + \mathbf{T}\mathbf{S}\mathbf{T} + \mathbf{T}^2] + [\mathbf{S}\mathbf{T}^3 + \mathbf{T}\mathbf{S}\mathbf{T}^2 + \mathbf{T}^2\mathbf{S}\mathbf{T} + \mathbf{T}^3] + \mathbf{T}^4\}m_0^+(r, t_2). \quad (10)$$

$\mathbf{1}$ is the identity operator, the lower indices in m^+ indicate the iteration number, $m^+(r, 0)$ has no temporal dependence, and $m_0^+(r, 0) = m_1^+(r, 0) = m_2^+(r, 0) \cdots$. Note that the terms inside the square brackets are grouped in powers of the operator $\mathbf{T}$. Extending the expansion until the fifth iteration yields

$$m_5^+(r, t_2) = m_4^+(r, 0) + \{\mathbf{S} + \mathbf{T}\}m_4^+(r, t_2) = \{\mathbf{1} + [\mathbf{S}^4\mathbf{T} + \mathbf{S}^3\mathbf{T} + \mathbf{S}^2\mathbf{T} + \mathbf{S}\mathbf{T} + \mathbf{T}] + [(\mathbf{S}\mathbf{T}\mathbf{S}^2\mathbf{T} + \mathbf{S}^2\mathbf{T}\mathbf{S}\mathbf{T} + \mathbf{S}^3\mathbf{T}^2 + \mathbf{T}\mathbf{S}^3\mathbf{T}) + (\mathbf{S}^2\mathbf{T}^2 + \mathbf{S}\mathbf{T}\mathbf{S}\mathbf{T} + \mathbf{T}\mathbf{S}^2\mathbf{T}) + (\mathbf{S}\mathbf{T}^2 + \mathbf{T}\mathbf{S}\mathbf{T}) + \mathbf{T}^2] + [(\mathbf{T}\mathbf{S}\mathbf{T}\mathbf{S}\mathbf{T} + \mathbf{T}\mathbf{S}^2\mathbf{T}^2 + \mathbf{S}^2\mathbf{T}^3 + \mathbf{S}\mathbf{T}\mathbf{S}\mathbf{T}^2 + \mathbf{S}\mathbf{T}^2\mathbf{S}\mathbf{T} + \mathbf{T}^2\mathbf{S}^2\mathbf{T}) + (\mathbf{S}\mathbf{T}^3 + \mathbf{T}\mathbf{S}\mathbf{T}^2 + \mathbf{T}^2\mathbf{S}\mathbf{T}) + \mathbf{T}^3] + [(\mathbf{S}\mathbf{T}^4 + \mathbf{T}\mathbf{S}\mathbf{T}^3 + \mathbf{T}^2\mathbf{S}\mathbf{T}^2 + \mathbf{T}^3\mathbf{S}\mathbf{T}) + \mathbf{T}^4]\}$$

$$+ \mathbf{T}^5\} m_0^+(r, t_2), \quad (11)$$

where within the square brackets, the round brackets group different orders of the $\mathbf{S}$ operators. This recurrence scheme, assuming the series as being convergent, should yield the exact solution when the number of iterations goes to infinity.

A. Signal without diffusion effects

Neglecting the effect of diffusion, making $D=0$ in Eq. (8) and using Eq. (7), after an infinite number of iterations,

$$m^+(r, t_2) = \{1 + \mathbf{T} + \mathbf{T}^2 + \mathbf{T}^3 + \cdots\} m_0^+(r, 0) \\ = \left\{ \sum_{N=0}^{\infty} \mathbf{T}^N \right\} m_0^+(r, 0). \quad (12)$$

In this case m_0^+ has no time dependence and can be cast outside the time integrals. When the $\mathbf{T}$ operator is made explicit in Eq. (12) the sum exhibits an exponential closed form. More conveniently, it can be written as a series of Bessel-function harmonics via the Jacobi–Anger relation $e^{i\zeta \cos \theta} = \sum_{n=-\infty}^{+\infty} i^n J_n(\zeta) e^{in\theta}$. Applying this relation in Eq. (12) yields

$$\overline{M^+(t_2)} = -iM_0 i^{n+1} e^{-[t_1+t_2]/T_2} \left[\cos^2 \frac{\beta}{2} J_{n+1}(\zeta(t_2)) \right. \\ \left. + \sin^2 \frac{\beta}{2} J_{n-1}(\zeta(t_2)) \right], \quad (13)$$

where the overline means an average over the whole sample and $\zeta(t_2) = e^{-t_1/T_2} (\Delta_s \sin \beta / \tau_d) [1 - e^{-t_2/T_1}] T_1$. This result is an exact solution known from the literature.²⁶ However, its connection with intermolecular multiple-quantum coherences is sometimes misinterpreted. iMQC evolutions occur during the interval t_1 and their effect can be observed as extra peaks in a 2D experiment. There is an additional T_2 attenuation during the interval t_1 , which is associated with the number of spins contributing to a given quantum coherence. One could be tempted³⁰ to introduce a $T_{2n} = T_2/n$ into Eq. (13), where n represents the number of quanta involved in the relaxation process. However, this is not correct. Only when considering the small argument approximation for the Bessel functions $\zeta \ll 1$, $J_n(\zeta) \approx (\zeta/2)^n / n!$, can the relaxation terms during t_1 be regrouped resulting naturally in the relation given above. This is because at this regime, and only at this regime, the number of quanta, $n=2$, coincides with the number of spins involved in the process. If the small argument condition is lifted, peaks associated with any number of interacting spins producing a given n coherence with its corresponding relaxation decays can be observed.³¹

B. Including the effect of diffusion

For the case $D \neq 0$, as the iteration number grows, there is an exponential increase in the number of terms in Eq. (11) for any order in the series making the calculation rather tedious after a few iterations. Although from this perspective a

complete solution seems not practical, the convergence of the series can still be studied and, under certain conditions, higher order contributions become negligible. Another important point is that standard NMR signal is only detectable if the magnetization has no spatial dependence at the moment of acquisition. Simple inspection of Eq. (11) reveals that any term containing the diffusion operator $\mathbf{S}$ placed as the first one in the left is spatially modulated. Therefore, without any approximation, the first-order contribution of the $\mathbf{T}$ expansion contains only one observable term, which becomes available after the first iteration.

The tentative solution necessary to start the iteration process, referred to as the zeroth iteration solution, is conveniently chosen to be Eq. (6) recasted as $M_0^+(r, t_2) = iM_0 e^{-t_2/T_2} m_0^+$. Inserting it on the right side of Eq. (7) and using Eq. (9), the first iteration term follows:

$$m_1^+(r, t_2) = m_0^+(r, t_2) - i\gamma e^{-Dk_m^2[t_1-(2-n)\delta/3]} e^{-t_1/T_2} B_{dz}(r, 0) \\ \times \left[\cos^2 \frac{\beta}{2} \lambda_1^{n+1} e^{-i(n+1)k_m z} \right. \\ \left. - \sin^2 \frac{\beta}{2} \lambda_1^{n-1} e^{-i(n-1)k_m z} \right], \quad (14)$$

where

$$\lambda_1^{(n\pm 1)} = \int_0^{t_2} e^{-[D((n\pm 1)^2+1)k_m^2+1/T_1]t'} dt' \\ = \left(\frac{1}{Dk_m^2} \right) \frac{1 - e^{-[D((n\pm 1)^2+1)k_m^2+1/T_1]t_2}}{[(n\pm 1)^2+1+1/Dk_m^2 T_1]}.$$

λ includes all temporal dependences of the DDF contribution. This is the complete first-order contribution before the spatial averaging. In particular, for $n=2$, explicitly stating $B_{dz}(r, 0)$ in its local form and performing the spatial average, we obtain Eq. (1) with the advantage of no additional assumption required.²⁵ Simple inspection shows that for $n > 2$, after spatial averaging, there are no contributions coming from this first-order term.

In order to establish the conditions where the first-order solution is a good approximation for the complete solution based on the perturbation scheme, it is necessary to calculate the next nonzero order in the series expansion. For the cases of interest, $n=0$ and $n=2$, inspection shows that all second order terms spatially average to zero, which leads us to third-order terms. A third-order contribution based on five iterations, as given by Eq. (11), will be investigated in the following sections. This contribution is obviously incomplete and since proceeding with additional iterations will generate more observable terms. The complication relies from the joint operator $(\mathbf{T} + \mathbf{S})^s$, with s as an integer exponent, which requires, since it does not commute, special attention with ordering.

V. RESULTS AND DISCUSSION

A perturbation theory comprises the concept of a perturbation parameter, e.g., α , where a given solution with $\alpha=0$ is known and a complete solution can be obtained as a series of

terms ordered as powers of this perturbation parameter.³² If α is small, the first few terms in the series might suffice to represent the solution. Performing an explicit evaluation of the terms in the series expansion representing the solution of the modified Bloch–Torrey equations (see Appendix B) and rearranging the constants in the expansion, we identified a parameter $\alpha \equiv [(Dk_m^2 + 1/T_1)\tau_d']^{-1}$ whose exponent increases according to the perturbation order. We also defined $\tau_d' \equiv \tau_d e^{Dk_m^2(t_1 - 2\delta/3)} e^{t_1/T_2} / (\Delta_s \sin \beta)$ as an effective dipolar time that better represents the amount of longitudinal magnetization available for generating the DDF during t_2 . For instance, in the extreme case of $\beta=0$, there is no DDF available albeit a finite τ_d still prevails. As expected, this parameter depends on the diffusion coefficient D and on the modulating gradient amplitude k_m . Perhaps less obvious is the α dependence on relaxation times and on external parameters associated with the pulse sequence. This opens additional possibilities for controlling the magnitude of the dipolar and diffusion contributions and consequently the convergence of the series solution.

A rigorous estimate of an approximate-solution range of validity depends on the ratio of that solution with the next order contribution. Unfortunately, for the specific case dealt here, the number of new terms for a given perturbation order increases as the iteration proceeds, which precludes the calculation of the total contribution. Nevertheless, α can be used as an effective criterion in assessing the validity of the first-order approximation, using the agreement with the experimental data and with numerical calculations as a benchmark.

A. The first-order approximation

According to the discussion above, the data in Figs. 2–4 can be analyzed in terms of the new parameter α . As will be verified in the next section, the convergence of the series is faster for smaller values of the parameter α , which reduces higher order contributions and improves the agreement of the first-order solution with the experiments.

From top to bottom plots, in Fig. 2(a), $\alpha=2.2, 1.12, 0.60$, and 0.36 with $\tau_d'=91, 92, 95$, and 99 ms, respectively. For Fig. 2(b) α depicts half of these values. This is due to the angle between the encoding gradient G and the polarizing field B_0 , embedded in Δ_s .

For Fig. 3(a), from top to bottom plots, $\alpha=1.22, 0.55$, and 0.30 with $\tau_d'=135, 139$, and 144 ms, respectively. For Fig. 3(b), from top to bottom plots, $\alpha=0.86, 0.38$, and 0.21 with $\tau_d'=191, 196$, and 203 ms, respectively. In Fig. 3(b) the effect of the pulse angle β can be observed. In this case, with $n=0$, $\beta=\pi/4$ and with a smaller resulting α , there is a better agreement between data and theory.

Overall, examining the curves for $\alpha < 1/2$, the first-order solution is enough to describe all the experimental results. This condition is clearly less restrictive than $(Dk_m^2\tau_d)^{-1} \ll 1$. The results in Fig. 3 depict similar behavior for the cases $n=0$ and $n=2$. However, comparing the values of $(\tau_d Dk_m^2)^{-1}$ and the respective agreement with the first-order solution for Figs. 2 and 3, there is poor agreement for the measurements with a pure water sample. This discrepancy is again corrected by the more realistic α parameter that incorporates the effect of T_1 relaxation.

Figure 4, apart from the gradient orientation effect that renders a better agreement with theory for $G \perp B_0$, also deserves some discussion regarding the sensitivity of the DDF signal to diffusion attenuation. It was claimed previously that the signal generated by DDF would be more sensitive to diffusion than the conventional PGSE method.²² Indeed, if one considers the diffusion attenuation during the evolution interval t_1 , where iMQCs evolve, there is enhanced diffusion attenuation.²⁷ However, by means of an additional pair of gradients,²⁷ this enhanced diffusion effect can actually be separated from the diffusion attenuation caused during t_2 by the DDF. Here we reduced the iMQC diffusion-attenuation contribution simply by decreasing the t_1 interval. Considering only the interval of interest, the refocusing period t_2 , the DDF diffusion attenuation (solid lines), as seen in Fig. 4, is actually weaker than the PGSE case (dashed lines).

Figure 5 depicts DDF-signal based on a complete numerical solution (dashed lines) of the modified Bloch–Torrey equations²⁰ (see Sec. VII). The numerical solution provides additional test for the theoretical results by eliminating potential experimental imperfections. The solid lines depict the first-order solution given by Eq. (1). One can note that, as also shown in the experiments, $\alpha < 1/2$ ensures the agreement of the first-order approximation with the complete numerical solution. Furthermore, as α is increased via, for instance, decreasing the gradient amplitude, although the first order solution still holds at short t_2 , it deviates from the complete solution at longer t_2 . Figure 5(b) shows the case $G \perp B_0$, where the fitting to the first-order solution is clearly improved.

B. Assessing contributions from higher order terms

In order to formally address, based on our perturbation scheme, the conditions where the first-order solution is a good approximation for the complete solution, it is necessary to calculate the next nonzero order in the series expansion. As already mentioned, the second-order contribution is zero for the cases $n=0$ and $n=2$. Let us reproduce Eq. (11) considering only terms of third-order in $\mathbf{T}$,

$$M_3^+(t_1, t_2)^{(3)} = iM_0 e^{-t_2/T_2} [(\mathbf{TSTST} + \mathbf{TS}^2\mathbf{T}^2 + \mathbf{T}^2\mathbf{S}^2\mathbf{T}) + (\mathbf{TST}^2 + \mathbf{T}^2\mathbf{ST}) + \mathbf{T}^3] m_0^+(r, t_2). \quad (15)$$

FIG. 5. Numerical results for DDF-signal amplitude (dashed lines) vs t_2 : (a) $n=2$, $\beta=\pi/2$ with $\tau_d'=98$ ms and $G \parallel B_0$. From top to bottom $\alpha=5.2$, 1.29, 0.55, and 0.3. (b) Same as (a) but with $G \perp B_0$. α is halved accordingly. The solid lines represent the first-order solution given by Eq. (1) with $T_1=T_2 \rightarrow \infty$.

Because of the average performed over the sample volume, as indicated by the overline, only the observable (not spatially dependent) terms from Eq. (11) remain.

Figure 6 shows each one of the six terms of Eq. (15) (see Appendix B for details), normalized by the first-order contribution given by Eq. (1), plotted as a function of t_2 for several values of the parameter α . The values of α on each one of the panels of Fig. 6 correspond to the simulated DDF-signal plots depicted in Fig. 5(a). Although the third-order contribution is far from complete after five iterations, observing the behavior of a limited number of terms proves useful. Note first that the sign of each individual term alternates as a function of the number of times the operator **S** appears. These terms tend to cancel out which somewhat suggests why the first-order solution prevails for a longer period even when these terms, individually, have magnitude comparable to the first-order contribution. Based on Fig. 6, we divided the discussion of third-order terms contribution into three different regimes according to the parameter α : (i) $\alpha > 1$, (ii) $1/2 < \alpha < 1$, and (iii) $\alpha < 1/2$.

- (i) The first-order solution shows poor agreement with the experiments in this domain. There is some agreement only at short t_2 as indicated by Figs. 2, 3, and 5. This is mostly because, as Fig. 6 portrays, all terms depicted are small at short t_2 , especially those associated with the **S** operator. The first term to show a relevant contribution is $\mathbf{T}^3$. Actually, if one extrapolates α to infinity, e.g., by choosing $D \approx 0$, only this term will survive and Eq. (12) is recovered until the third order.
- (ii) In this regime, each term is relevant for the result. However, by adding them together, there is a partial cancellation, which maintains the first-order solution as a fair approximation. Furthermore, for the experiments [Figs. 2(b) and 4(b)] where the gradient orientation with respect to B_0 is orthogonal and the regime $\alpha > 1$ is reduced by half, the agreement with the first-order approximation is improved. This behavior is also shown for the same regime with the numerical simulations shown in Fig. 5.

FIG. 6. (Color) Magnetization terms of the third-order contribution, Eq. (16), normalized by the first-order term, given by Eq. (1), plotted as a function of t_2 . From top to bottom in each panel: T^3 , $TSTST$, TS^2T^2 , T^2S^2T , TST^2 , and T^2ST . Each figure displays results for a specific value of α : (a) 5.24, (b) 1.29, (c) 0.55, and (d) 0.30.

- (iii) The first-order solution works really well as depicted again in Figs. 2, 3, and 5. The agreement is expected since any term of the third-order contribution depicted in Fig. 6 gives a negligible contribution at this regime. The analysis consists of a finite number of terms, whereas in reality there is an infinite number of terms to be added. However, for the terms depicted here there is an almost perfect symmetry, which essentially averages out the third-order contribution. We expect that this symmetry is preserved for an infinite number of terms.

Finally, it is tempting to add the terms in Eq. (15) together with the first-order approximation in order to improve the solution. However, as already mentioned, a real higher-order contribution involves an infinite number of terms. We

tested the incomplete third-order approximation given by the terms above (data not shown) and noticed, as expected, that the agreement of the solution with the experiments depends on which terms on the series are added. This behavior is related to the alternating sign of the individual terms, which improves the sum cancellation depending on which terms are considered.

C. General solutions

General solutions considering the role of diffusion in the presence of DDF interactions have been a topic of debate.^{33,34} The general solution, proposed in Ref. 22 using the concept of an effective dipolar field and reproduced in Ref. 23 by other methods, is

$$\overline{M^+}(t_2) = -iM_0 t^{n+1} e^{-[t_1+t_2]/T_2} \left[\cos^2 \frac{\beta}{2} J_{n+1}(\zeta(t_2)) + \sin^2 \frac{\beta}{2} J_{n-1}(\zeta(t_2)) \right]. \quad (16)$$

The overline means an average over the whole sample and $\zeta(t_2) = e^{-t_1/T_2} (\Delta_s \sin \beta) / (\tau_d) [1 - e^{-(2Dk_m^2 + 1/T_1)t_2}] / (2Dk_m^2 + 1/T_1)$.

Although Eq. (16) has been used extensively in the literature, reproducing this closed-form expression via the iterative method presented here requires neglecting all terms associated with the operator **S**. Although maybe useful as a fitting function, Eq. (16) appears deprived of physical meaning.³³ Terms coming from the **S** operator, which are discarded in order to reproduce Eq. (16), must be included in a general scenario. Moreover, when compared with numerical simulations for $n > 2$, Eq. (16) shows enormous discrepancies.^{20,33} Nevertheless, there are regimes where similar approximations as those leading to Eq. (16) are acceptable leading to analytic compact solutions.³⁵

Remarkably, when considering the regime of small argument for the Bessel functions in Eq. (16) while neglecting the higher-order Bessel argument contribution on the grounds of its higher diffusion-attenuation,²⁶ which is valid when $(Dk_m^2 \tau_d)^{-1} \ll 1$, an expression that coincides with the first-order approximation, Eq. (1), is obtained. Therefore the explanation for the good agreement of the general expression above with the data is that, in fact, only the small argument contribution has been relevant for the experimental regimes investigated.

VI. EXPERIMENTAL METHODS

The experiments were conducted at room temperature utilizing horizontal MR scanners operating at polarizing fields of 7 and 9.4 T corresponding to ^1H resonance frequencies of 300 and 400 MHz. Each system was equipped with transmission-detection birdcage coils of 25 mm (i.d.) and 38 mm (i.d.), respectively. The samples were placed inside glass spheres of 8 mm (i.d.) and centered inside the rf coil in order to, respectively, prevent anisotropic DDF effects and ensure rf homogeneity. Self-shielded orthogonal gradient coils able to generate magnetic field gradients up to 0.25 T/m were also available.

The NMR parameters of interest were measured using standard CPMG, inversion-recovery, and PGSE pulse sequences.³⁶ At 7 T for pure water: $T_2 = 1.66$ s, $T_1 = 2.53$ s, and $D = 1.97 \times 10^{-9}$ m² s⁻¹. For water doped with CuSO₄ at 9.4 T: $T_2 = 250$ ms, $T_1 = 288$ ms, and $D = 2.15 \times 10^{-9}$ m² s⁻¹.

Measurements of the DDF-signal evolution during the interval t_2 , Figs. 2 and 3, were obtained by collecting the echo peaks refocused after t_2 intervals varying from 18 to 612 ms for doped water and from 18 ms to 4 s for pure water. A four-part phase cycling scheme was implemented for $n = 2$, whereas for $n = 0$, a pulse cycling¹⁸ where the data were recorded from a subtraction of two acquisitions with pulse angle $\beta = 45^\circ$ and $\beta = 135^\circ$. The gradient amplitudes used for the data in Fig. 2 were $G = 0.05, 0.1, 0.15$, and 0.2 T/m with

$\delta = 2$ ms. For Fig. 3, $G = 0.05$ T/m was omitted. This range of gradient amplitudes ensured the validity of the local form approximation for the DDF.¹⁹ The length scale of diffusion for the water spins during the longest period of measurements, $\sqrt{2Dt_2}$, was well within the unrestricted regime. Repetition times $T_R = 3$ s and $T_R = 10$ s (for doped and pure water, respectively) mitigated possible stimulated-echo contamination.¹⁴ All experiments were recorded with four averages.

Regarding the pulse sequence depicted in Fig. 1(c), in order to improve performance, the first pulse was replaced by an adiabatic 90° pulse. Furthermore, the train of 180° pulses had each component designed as a composite 90° - 180° - 90° hard pulse.

VII. NUMERICAL METHODS

The numerical solution of the Bloch–Torrey equations including diffusion and DDF term were obtained utilizing a MATLAB routine (ode23tb) for solving differential equations. The DDF was considered in its local form and diffusion was considered unrestricted. The set of coupled equations was handled utilizing the approach described in Ref. 20. Radiation damping and the structural dependence of the DDF contribution, although feasible, were out of the scope of this article.^{23,37}

VIII. SUMMARY AND CONCLUSIONS

The joint effect of molecular self-diffusion and DDF interactions in the NMR magnetization dynamics was re-examined. New analytic expressions for the magnetization evolution were obtained by solving the modified Bloch–Torrey equations by means of an iterative procedure where, in a clear and systematic way, the solution was represented as a power series of the DDF contribution. A new parameter α , associated with the series convergence rate, was extracted from the theory and successfully used to set a more realistic boundary, $\alpha < 1/2$, for the validity regime of the first-order contribution. Moreover, the dependence of the validity domain on several pulse-sequence parameters became evident. Worth mentioning is the unexpected dependence on gradient orientation, which is particularly important for methods where probing DDF anisotropy effects is a key element.³⁸ Additional care was also drawn to the finite gradient-pulse duration whose contribution was shown to depend on n (see Appendix A).

Although the agreement of the theory with the experimental data was very good, numerical calculations of the Bloch–Torrey equations were performed in order to rule out experimental imperfections or contributions from radiation damping that could portray similar effects as those acknowledged as from DDF origin. Although the numerical and analytic approximations agree very well with the experiments, some discrepancies were apparent on the data obtained for $\alpha > 1/2$, where CPMG-type sequences were used. This discrepancy is likely due to imperfect 180° pulse refocusing.³⁹ The extension of the first-order approximation for heteronuclear systems or chemical-shift distinct nuclei (mixture of

single-line solvents) is straightforward.^{24,25} Regimes of restricted diffusion and nonlocal form of the DDF will deserve more attention in the future.

In conclusion, the data presented here reinforce the importance of including diffusion effects, as well as relaxation contributions, in any realistic interpretation of DDF-signal contrast dependence or signal gain optimization. Although the classical theory behind DDF effects in the presence of diffusion seems to be well understood by means of numerical solutions of the modified Bloch–Torrey equations, it lacks predictive power. By setting new boundaries and ways to control the range of validity of the first-order solution, our method legitimizes its use in standard DDF-imaging conditions and in methods for simultaneous measurement of D and T_2 .^{17,18} Although not providing new improved solutions, the investigation was useful to determine $(Dk_m^2\tau_d)^{-1} \ll 1$ as a sufficient but not necessary condition for the validity of the first-order approximation. Moreover it also established α as a more realistic control parameter for the first-order contribution regime of validity. Finally, the calculations presented here do not support the use of the closed-form solution Eq. (16) for generally describing the role of diffusion in the presence of DDFs.

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APPENDIX A: FINITE GRADIENT INTERVAL DURING t_1

The magnetization attenuation in the presence of diffusion occurs, according to Torrey approach,⁴⁰ as $e^{-D\gamma^2 F^2(t)}$, where $F(t)$ is the total accumulated squared-phase variation generated by diffusion in the presence of the gradients

$$F^2(t) = \int_0^t \left[\int_0^{t'} g(t'') dt'' \right]^2 dt', \quad (\text{A1})$$

where $g(t'')$ is the amplitude of the gradient applied at the instant t'' . For the magnetization evolution in a CRAZED sequence [see Fig. 1(a)] the transverse contribution of the attenuation term is given by

$$\begin{aligned} F_{\pm}^2(t) &= \int_0^{\delta} (Gt')^2 dt' + \int_{\delta}^{t_1} G^2 \delta^2 dt' + \int_{t_1}^{t_1+n\delta} \\ &\quad \times [\pm G\delta + G(t-t_1)]^2 dt' + \int_{t_1+n\delta}^t [\pm G\delta + Gn\delta]^2 dt' \\ &= G^2 \delta^2 (t_1 - 2\delta/3) + G^2 \delta^3 (n \pm n^2 + n^3/3) \\ &\quad + (n \pm 1)^2 G^2 \delta^2 (t - t_1 - n\delta), \end{aligned} \quad (\text{A2})$$

where the $\pm$ represents the two possible components, $(n+1)$ and $(n-1)$ in Eq. (6), for the transverse magnetization. For the longitudinal contribution responsible for the dipolar field, since there is no effect of the second gradient, only the two first terms in the expression above are considered. This yields

$$\begin{aligned} F_z^2(t) &= \int_0^{\delta} (Gt')^2 dt' + \int_{\delta}^{t_1} G^2 \delta^2 dt' + \int_{t_1}^t G^2 \delta^2 dt' \\ &= G^2 \delta^2 (t_1 - 2\delta/3) + G^2 \delta^2 (t - t_1). \end{aligned} \quad (\text{A3})$$

These two contributions, transverse and longitudinal, when mixed by the iteration procedure, result in the gradient-length dependence shown in Eq. (1).

APPENDIX B: THIRD ORDER CONTRIBUTION

Let us define $a = D(n+1)^2 k^2$ and $b = D(n-1)^2 k^2$ as the diffusion attenuation contributions of the transverse magnetization components and $c = Dk^2 + 1/T_1$ as the attenuation from the longitudinal magnetization term. We also define $A = M_0 \cos^2(\beta/2) e^{-\gamma D F_+(t_1)}$ and $B = M_0 \sin^2(\beta/2) e^{-\gamma D F_-(t_1)}$ for the transverse magnetization component during the t_1 interval. The first iteration of Eq. (7) using Eq. (6) as a seed gives

$$\begin{aligned} \mathbf{T}m_0^+(r, t) &= \left\{ A \left[\frac{1 - e^{-(a+c)t}}{a+c} \right] e^{-i(n+1)kz} \right. \\ &\quad \left. - B \left[\frac{1 - e^{-(b+c)t}}{b+c} \right] e^{-i(n-1)kz} \right\} \frac{i \cos kz}{\tau_d'}, \end{aligned} \quad (\text{B1})$$

where $\mathbf{S}m_0(r, t) = m_0(r, t)$. When averaged over the sample volume, the space-dependent terms disappear and the first-order approximation given by Eq. (14) is recovered. Using the local form of the DDF $B_d(r, t)$, Eq. (1) is obtained instead. Performing a second iteration in the expression above yields

$$\begin{aligned} \mathbf{T}\mathbf{T}m_0^+(r, t) &= \left\{ \frac{A}{a+c} \left[\frac{1}{c} (1 - e^{-ct}) - \frac{1}{a+2c} (1 - e^{-(a+2c)t}) \right] \right. \\ &\quad \times e^{-i(n+1)kz} - \frac{B}{b+c} \left[\frac{1}{c} (1 - e^{-ct}) \right. \\ &\quad \left. \left. - \frac{1}{b+2c} (1 - e^{-(b+2c)t}) \right] e^{-i(n-1)kz} \right\} \left(\frac{i \cos kz}{\tau_d'} \right)^2, \end{aligned} \quad (\text{B2})$$

$$\begin{aligned} \mathbf{S}\mathbf{T}m_0^+(r, t) &= - \left\{ \frac{A}{a+c} \left[t - \frac{1}{a+c} (1 - e^{-(a+c)t}) \right] \right. \\ &\quad \times ((n+2)^2 e^{-i(n+2)kz} + n^2 e^{-inkz}) \\ &\quad \left. - \frac{B}{b+c} \left[t - \frac{1}{b+c} (1 - e^{-(b+c)t}) \right] \right. \\ &\quad \left. \times ((n-2)^2 e^{-i(n-2)kz} + n^2 e^{-inkz}) \right\} \left(\frac{i D k^2}{2 \tau_d'} \right). \end{aligned} \quad (\text{B3})$$

Note that if the expansion stopped here, this last term could

not be detected because all its elements are spatially modulated during the acquisition interval. Moreover, for the same reason, the second order iteration as any even power of the operator $\mathbf{T}$ does not give any observable term for the cases

$n=0$ and $n=2$ and will not be considered from now on in this appendix.

The third iteration for $\mathbf{T}$ including also terms where the diffusion operator appears once yields

$$\mathbf{T}\mathbf{T}\mathbf{T}m_0^+(r,t) = \left\{ \frac{A}{a+c} \left[-\frac{1}{c(a+2c)}(1-e^{-ct}) + \frac{1}{2c^2}(1-e^{-ct})^2 + \frac{1}{(a+2c)(a+3c)}(1-e^{-(a+3c)t}) \right] e^{-i(n+1)kz} \right. \\ \left. - \frac{B}{b+c} \left[-\frac{1}{c(b+2c)}(1-e^{-ct}) + \frac{1}{2c^2}(1-e^{-ct})^2 + \frac{1}{(b+2c)(b+3c)}(1-e^{-(b+3c)t}) \right] e^{-i(n-1)kz} \right\} \left(i \frac{\cos kz}{\tau_d'} \right)^3, \quad (\text{B4})$$

$$\mathbf{T}^2\mathbf{S}\mathbf{T}m_0^+(r,t) = - \left\{ \frac{A}{a+c} \left\{ \frac{te^{-2ct}}{c^2} - \frac{3}{4c^3}(1-e^{-2ct}) + \frac{1}{c^3}(1-e^{-ct}) - \frac{1}{a+c} \left(\frac{1}{c} \left(\frac{1-e^{-ct}}{c} - \frac{1-e^{-2ct}}{2c} \right) - \frac{1}{c(a+2c)}(1-e^{-ct}) \right. \right. \right. \\ \left. \left. + \frac{1}{(a+2c)(a+3c)}(1-e^{-(a+3c)t}) \right) \right\} \left[(n+2)^2 e^{-i(n+2)kz} + n^2 e^{-inkz} \right] - \frac{B}{b+c} \left\{ \frac{te^{-2ct}}{c^2} - \frac{3}{4c^3}(1-e^{-2ct}) \right. \\ \left. + \frac{1}{c^3}(1-e^{-ct}) - \frac{1}{b+c} \left(\frac{1}{c} \left(\frac{1-e^{-ct}}{c} - \frac{1-e^{-2ct}}{2c} \right) - \frac{1}{c(b+2c)}(1-e^{-ct}) + \frac{1}{(b+2c)(b+3c)}(1-e^{-(b+3c)t}) \right) \right\} \\ \left. \times [-(n-2)^2 e^{-i(n-2)kz} + n^2 e^{-inkz}] \right\} Dk^2 \left(\frac{i}{2\tau_d'} \right)^3 (\cos kz)^2, \quad (\text{B5})$$

$$\mathbf{T}\mathbf{S}\mathbf{T}^2m_0^+(r,t) = \left\{ \frac{A}{a+c} \left\{ \frac{1}{c^2} \left(-te^{-ct} + \frac{1}{2c}(1-e^{-2ct}) \right) - \frac{1}{a+2c} \left(-\frac{1}{c}te^{-ct} + \frac{a+c}{c^2(a+2c)}(1-e^{-ct}) + \frac{1}{(a+2c)(a+3c)}(1-e^{-(a+3c)t}) \right) \right\} \right. \\ \left. \times [-(n-1)^2 e^{-i(n-1)kz} - 2(n+1)^2 e^{-i(n+1)kz} - (n+3)^2 e^{-i(n+3)kz}] - \frac{B}{b+c} \left\{ \frac{1}{c^2} \left(-te^{-ct} + \frac{1}{2c}(1-e^{-2ct}) \right) \right. \right. \\ \left. \left. - \frac{1}{b+2c} \left(-\frac{1}{c}te^{-ct} + \frac{b+c}{c^2(b+2c)}(1-e^{-ct}) + \frac{1}{(b+2c)(b+3c)}(1-e^{-(b+3c)t}) \right) \right\} \right. \\ \left. \times [-(n-3)^2 e^{-i(n-3)kz} - 2(n-1)^2 e^{-i(n-1)kz} - (n+1)^2 e^{-i(n+1)kz}] \right\} 2Dk^2 \left(\frac{i}{2\tau_d'} \right)^3 \cos kz. \quad (\text{B6})$$

When averaged over space, these terms lead to the respective contributions plotted in Fig. 6. Other contributions can be obtained in a similar fashion.

¹W. S. Warren, W. Richter, A. H. Andreotti, and B. T. Farmer II, *Science* **262**, 2005 (1993).

²R. Bowtell, R. M. Bowley, and P. Glover, *J. Magn. Reson.* **88**, 643 (1990).

³Y.-Y. Lin, N. Lisitz, S. Ahn, and W. S. Warren, *Science* **118**, 118 (2000).

⁴S. Vathyam, S. Lee, and W. S. Warren, *Science* **272**, 92 (1996).

⁵W. S. Warren, S. Ahn, M. Mescher, M. Garwood, K. Ugurbil, W. Richter, R. R. Rizi, J. Hopkins, and J. S. Leigh, *Science* **281**, 247 (1998).

⁶W. Richter, M. Richter, W. S. Warren, H. Merkle, P. Andersen, G. Adriany, and K. Ugurbil, *Magn. Reson. Imaging* **18**, 489 (2000).

⁷R. Bowtell and P. R. Robyr, *Phys. Rev. Lett.* **76**, 4971 (1996).

⁸S. M. Brown, P. N. Sen, and D. G. Cory, *J. Magn. Reson.* **154**, 154 (2002).

⁹C. Ramanathan and R. W. Bowtell, *Phys. Rev. E* **66**, 041201 (2002).

¹⁰L.-S. Bouchard, R. R. Rizi, and W. S. Warren, *Magn. Reson. Med.* **48**, 973 (2002).

¹¹L.-S. Bouchard and W. S. Warren, *J. Magn. Reson.* **170**, 299 (2004).

¹²F. Fasano, S. Capuani, G. E. Hagberg, T. Branca, I. Indovina, A. Castriota-Scanderbeg, and B. Maraviglia, *Magn. Reson. Imaging* **21**, 1151 (2003).

¹³P. L. de Sousa, D. Gounot, and D. Grucker, *C. R. Chim.* **7**, 311 (2004).

¹⁴G. D. Charles-Edwards, G. S. Payne, M. O. Leach, and A. Bifone, *J. Magn. Reson.* **166**, 215 (2004).

¹⁵A. Schäfer and H. E. Möller, *Magn. Reson. Med.* **58**, 696 (2007).

¹⁶S. D. Kennedy and J. Zhong, *Magn. Reson. Med.* **52**, 1 (2004).

¹⁷W. Barros, Jr., J. C. Gore, and D. F. Gochberg, *J. Magn. Reson.* **178**, 164 (2006).

¹⁸W. Barros, Jr., and D. F. Gochberg, *Chem. Phys. Lett.* **431**, 174 (2006).

¹⁹G. Deville, M. Bernier, and J. M. Delrieux, *Phys. Rev. B* **119**, 5666 (1979).

²⁰J. Jeener, *Concepts Magn. Reson.* **14**, 79 (2002).

²¹P. Robyr and R. Bowtell, *J. Magn. Reson., Ser. A* **121**, 206 (1996).

²²I. Ardelean and R. Kimmich, *J. Chem. Phys.* **112**, 5275 (2000).

²³C. Ramanathan and R. Bowtell, *J. Chem. Phys.* **114**, 10854 (2001).

²⁴I. Ardelean, E. Kossel, and R. Kimmich, *J. Chem. Phys.* **114**, 8520 (2001).

²⁵M. Engelsberg and W. Barros, Jr., *J. Chem. Phys.* **122**, 034501 (2005).

²⁶J. P. Marques, S. Grant, S. Blackband, and R. W. Bowtell, *J. Chem. Phys.* **123**, 164311 (2005).

²⁷J. Zhong, Z. Chen, E. Kwok, and S. Kennedy, *Magn. Reson. Imaging* **19**,

- 33 (2001).
- ²⁸W. Richter and W. S. Warren, *Concepts Magn. Reson.* **12**, 396 (2000).
- ²⁹E. O. Stejskal and J. E. Tanner, *J. Chem. Phys.* **42**, 288 (1965).
- ³⁰B. Ozus, G. D. Clarke, S. J. Dodd, and G. D. Fullerton, *Magn. Reson. Med.* **53**, 1183 (2005).
- ³¹S. Ahn, N. Lisitza, and W. S. Warren, *J. Magn. Reson.* **133**, 266 (1998).
- ³²F. W. Byron, Jr. and R. W. Fuller, *Mathematics of Classical and Quantum Physics* (Dover, New York, 1992).
- ³³J. Jeener, *J. Chem. Phys.* **116**, 1204 (2002).
- ³⁴I. Ardelean and R. Kimmich, *J. Chem. Phys.* **116**, 1206 (2002).
- ³⁵W. Barros, Jr., D. F. Gochberg, and J. C. Gore, *J. Magn. Reson.* **189**, 32 (2007).
- ³⁶C. P. Slichter, *Principles of Magnetic Resonance, 3rd Enlarged and Updated Edition* (Springer, New York, 1990).
- ³⁷T. Enss, S. Ahn, and W. S. Warren, *Chem. Phys. Lett.* **305**, 101 (1999).
- ³⁸L.-S. Bouchard and W. S. Warren, *J. Magn. Reson.* **177**, 1 (2005).
- ³⁹J. T. Schneider and C. Faber, *Magn. Reson. Med.* **60**, 850 (2008).
- ⁴⁰H. C. Torrey, *Phys. Rev.* **104**, 563 (1956).