A single-shot measurement of time-dependent diffusion over sub-millisecond timescales using static field gradient NMR

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Time-dependent diffusion behavior is probed over sub-millisecond timescales in a single shot using an NMR static gradient, time-incremented echo train acquisition (SG-TIETA) framework. The method extends the Carr-Purcell-Meiboom-Gill (CPMG) cycle under a static field gradient by discretely incrementing the pulse spacings to simultaneously avoid off-resonance effects and probe a range of timescales (50–500 µs). Pulse spacings are optimized based on a derived ruleset. The remaining effects of pulse inaccuracy are examined and found to be consistent across pure liquids of different diffusivities: water, decane, and octanol-1. A pulse accuracy correction is developed. Instantaneous diffusivity, \( D_{\text{inst}}(t) \), curves (i.e., half of the time derivative of the mean-squared displacement in the gradient direction), are recovered from pulse accuracy-corrected SG-TIETA decays using a model-free, log-linear least squares inversion method validated by Monte Carlo simulations. A signal-averaged, 1-minute experiment is described. A flat \( D_{\text{inst}}(t) \) is measured on pure dodecamethylcyclohexasiloxane whereas decreasing \( D_{\text{inst}}(t) \) are measured on yeast suspensions, consistent with the expected short-time \( D_{\text{inst}}(t) \) behavior for confining microstructural barriers on the order of microns.

I. INTRODUCTION

As molecules diffuse, they interact with their surroundings and "feel" the boundary, causing their ensemble displacement behavior to be influenced by the morphology of the microenvironment. More specifically, long-range correlations such as confining barriers impart a nonlinear time-dependence to the ensemble-averaged net mean-squared displacement, \( \langle r^2(t) \rangle \) (in \( \mathbb{R}^3 \)). This leads to a time-dependent diffusion coefficient:

\[
D(t) = \frac{\langle r^2(t) \rangle}{6t} = \frac{1}{3t} \int_0^t (t - t') \text{tr}(\mathbf{D}(t')) dt',
\]

where \( \mathbf{D}(t') = H(t')\langle \mathbf{v}(t')\mathbf{v}(0) \rangle \equiv \partial_r^2 H(t)\langle \mathbf{r}(t)\mathbf{r}(0) \rangle \) is the causal velocity autocorrelation tensor, \( H(t) \) is the unit step function, and “tr” is the trace operation.

Microstructural features can be inferred from the behavior of \( D(t) \) at limiting short and long timescales (see Sen12 and Reynaud13 for review). At the short-time limit, \( D(t) \) exhibits universal behavior which depends on the barrier surface-to-volume ratio, \( S/V \),

\[
D(t) \simeq D_0 \left[ 1 - \frac{S}{V} \left( \frac{4D_0}{3\sqrt{\pi}} \right)^2 \right], \quad t \to 0,
\]

where \( \ell_D = \sqrt{D_0/6} \) is the diffusion length scale and \( D_0 \equiv D(t)|_{t=0} \) is the free diffusivity. As \( \ell_D \) increases, the barrier permeability, \( \kappa \), may begin to affect \( D(t) \). While \( \ell_D \) remains short, barriers appear flat to the small fraction of nearby walkers that encounter them14,15, introducing a linear \( \kappa t \) term in Eq. (2):

\[
D(t) \simeq D_0 \left[ 1 - \frac{S}{V} \left( \frac{4D_0}{3\sqrt{\pi}} - \kappa t \right) \right], \quad t \ll \tau_D,
\]

where \( \tau_D = \bar{a}^2/(2D_0) \) is the time to diffuse across the mean pore of size \( \bar{a} = 6V/S \). Curvature16 and surface-relaxivity17 may also affect \( D(t) \). Tortuosity principally affects the long-time \( D(t) \) and can be categorized into disorder classes with structural exponent, \( \eta \).18,19 The long-time \( D(t) \) follows a \( p \)-dependent power law:

\[
D(t) \simeq D_\infty + \text{const.} \cdot t^{-\vartheta}, \quad t \to \infty,
\]

where \( D_\infty = \lim_{t \to \infty} D(t) \) and \( \vartheta = (p + 3)/2 \).

Diffusion-weighted (DW) nuclear magnetic resonance (NMR) methods are highly sensitive to \( \langle r^2(t) \rangle \),14,20 and provide a powerful means to probe rich \( D(t) \) behaviors and infer distinct microstructural features. DW-NMR experiments have been used to study the short- and long-time \( D(t) \) in porous media ranging from sedimentary rock to skeletal muscle5,12,13,21–25.

The NMR spin echo dephasing, however, is not simply written in terms of \( D(t) \) itself. Instead, the echo dephasing is often expressed in terms of the real part, \( \Re \), of the Fourier transform of \( \mathbf{D}(t) \).

\[
\frac{\text{tr}(\mathbb{R}[\mathbf{D}(\omega)])}{3} = D_0 + \int_0^{\infty} \partial_r^2 \left[ tD(t) \right] e^{i\omega t} dt.
\]
High and low frequency tr(|D(\omega)|) behaviors reveal the short- and long-time $D(t)$, respectively. The relationship between $\Re\{D(\omega)\}$ and the ensemble echo dephasing follows from a cumulant expansion of the phase expectation value and a Gaussian phase distribution approximation\textsuperscript{29}, yielding the normalized echo intensity\textsuperscript{30,31},

$$\frac{I(T)}{I_0} = \exp\left(-\frac{1}{\pi} \int_{0}^{\infty} F^T(\omega) \Re\{D(\omega)\} F(\omega) \, d\omega\right), \quad (6)$$

where $F(\omega)$ is the truncated Fourier transform of $F(t)$ at the echo time (i.e., $F(T) = 0$),

$$F(t) = \gamma \int_{0}^{t} G(t') dt', \quad G(t) \text{ is the gradient waveform, and } \gamma \text{ is the gyromagnetic ratio. The assumed Gaussian phase approximation is valid for most relevant experimental cases.}$

Eqs. (6) and (7) show that spectral tuning of $|F(\omega)|^2$ results in narrow sampling of $\Re\{D(\omega)\}$ in the gradient direction, $\hat{g}$. $G(t)$ can be periodically time-modulated\textsuperscript{22} (e.g., by using a sinusoidal $G(t)\textsuperscript{22}$ so that the spectral density of $|F(\omega)|^2$ concentrates near some frequency, $\omega_F$. In this case, $I(T)/I_0$ becomes well-approximated by

$$b(T) = \int_{0}^{T} \frac{|F(t)|^2}{2} \, dt \approx \frac{1}{\pi} \int_{0}^{\infty} |F(\omega)|^2 \, d\omega. \quad (8)$$

Individual experiments become a point-wise sampling of $\hat{g}^T \Re\{D(\omega_F)\} \hat{g}$. This “temporal diffusion spectroscopy”\textsuperscript{26} approach is robust, but has limited time resolution because it individually probes $\omega_F$. Furthermore, the shortest probeable timescale (i.e., largest $\omega_F$) is limited to about 10 ms by the pulsed gradient hardware\textsuperscript{38}. An alternative approach is needed for the real-time study of $D(t)$ across timescales and to reach the information-rich, short-time regime ($\lesssim 1$ ms) in biological systems.

II. THEORY

A. Time-dependent signal representation

To begin, an alternative signal representation is used. The echo attenuation is related to the stationary position autocorrelation tensor, $\mathcal{R}(t, t') = \langle r(t) r^T(t') \rangle \equiv \mathcal{R}(\{t - t'\})$ – again assuming a Gaussian phase distribution\textsuperscript{30,31},\textsuperscript{33} by

$$\frac{I(T)}{I_0} = \exp\left(-\frac{\gamma^2}{2} \int_{0}^{T} \int_{0}^{T} G^T(t) \mathcal{R}(t, t') G(t') \, dt \, dt'\right), \quad (9)$$

Eq. (9) can be rewritten according to Ning et al.\textsuperscript{32} by integrating along the level set of $t-t'$. For unidirectional encoding, i.e., $G(t) = ||G(t)||$ and $F(t) = \gamma \int_{0}^{t} G(t') dt'$,

$$\frac{I(T)}{I_0} = \exp\left(-\int_{0}^{T} C(t) D_{\text{inst}}(t) \, dt\right), \quad (10)$$

where $D_{\text{inst}}(t)$ is the instantaneous diffusivity along the gradient direction $\hat{g}$,

$$D_{\text{inst}}(t) := \partial_t \left[ \frac{\hat{g}^T \mathcal{R}(t) \hat{g}}{2} \right] \equiv \partial_t \left[ \frac{||r(t) \cdot \hat{g}||^2}{2} \right], \quad t > 0, \quad (11)$$

(dropping $\hat{g}$ as implied) and $C(t)$ is the cumulative integral of the $\gamma G(t)$ autocorrelation function,

$$C(t) = \int_{0}^{t} \mathcal{G}(t') dt', \quad (12)$$

schematized in Fig. 1. The attenuation becomes a sampling of $D_{\text{inst}}(t)$ weighted by $C(t)$, similar to how Eq. (6) describes a sampling of $\Re\{D(\omega)\}$ by $|F(\omega)|^2$.

B. Recasting the problem

Eq. (10) is advantageous compared to Eq. (6) because $C(t)$ is simple for general, non-periodic $G(t)$. The ill-posed inverse problem of finding $D_{\text{inst}}(t)$ from many trivial $G(t)$ is tractable. For a train of $N$ echoes refocusing at times $T_n$, $C_n(t)$ can be evaluated for each inter-echo attenuation, i.e., $I(T_n)/I(T_{n-1})$ ($T_0 = 0$). By discretizing the time domain into $K$ bins of variable width, $\Delta(t)$, the problem can be cast into a weighted and regularized log-linear least squares (LLS) form:

$$\arg\min_{X} ||W^{1/2} (AX - B)||_2^2 + \lambda ||TX||_2^2, \quad (13)$$

with coefficients

$$A = \begin{bmatrix} \int_{0}^{\Delta(t)} C_1(t) \, dt & \cdots & \int_{0}^{\Delta(t)} C_K(t) \, dt \\ \vdots & \ddots & \vdots \\ \int_{0}^{\Delta(t)} C_N(t) \, dt & \cdots & \int_{0}^{\Delta(t)} C_{N-K}(t) \, dt \end{bmatrix},$$

$$X = \begin{bmatrix} 1/\Delta(t) \int_{0}^{\Delta(t)} D_{\text{inst}}(t) \, dt \\ \vdots \\ 1/\Delta(t-\Delta(t-1)) \int_{0}^{\Delta(t-\Delta(t-1))} D_{\text{inst}}(t) \, dt \end{bmatrix},$$

where $X$ consists of time-interval $D_{\text{inst}}(t)$ averages,
and \( \mathbf{B}^T = -\ln \left[ I(T_1)/I_0 \ldots I(T_N)/I(T_{N-1}) \right] \). The regularization matrix, \( \mathbf{\Gamma} \), is chosen to consist of first and second-order finite difference matrices, reflecting an \textit{a priori} assumption of the smoothness and concavity of \( D_{\text{inst}}(t) \). The norm is weighted by a proportionality of the signal-to-noise ratio (SNR); since \( \mathbf{B} \) consists of log ratios, the appropriate weights matrix, \( \mathbf{W} \), is an \( N \times N \) matrix of signal differences, i.e., \( I(T_{n-1}) - I(T_n) \). In this way, \( D_{\text{inst}}(t) \) can be estimated from a single echo train with varied \( C_n(t) \).

We arrive at the motivating question of this Communication: Can a DW-NMR method probe the time-varying diffusivity in real-time? With Eq. \([13]\) in mind, the question can be separated into two parts: (1) How can \( C_n(t) \) of various time sensitivities be produced in one echo train? (2) How can every echo be made accurate? The answer to the first part follows from a well-known DW-NMR protocol. A Carr-Purcell-Meiboom-Gill (CPMG) pulse train under an SG in the radiofrequency (RF) field produces a triangle wave \( F(t) \) with \( \omega_F = (\pi/2\tau) \text{ rad/s} \), where \( 2\tau \) is the spacing between \( \pi \)-pulses. This SG-CPMG is uniquely capable of probing the short-time diffusion regime in small \((\tilde{a} \lesssim \mu \text{m})\) structures.\([35,39,40,43]\)

Varying the \( \pi \)-pulse spacing in an SG-CPMG-type acquisition is therefore the best method to produce many varied \( C_n(t) \) in one shot. Spacings might be incremented to retain signal. We choose the spacing between \( \pi \)-pulses to take the form: \( 2\tau + m_j\delta \), where \( j \) indexes the \( \pi \)-pulseto-pulse spacing, \( m_j \in \mathbb{N} \), and \( \delta \) is a unit time increment. We term this discrete spacing method the SG, time-incremented echo train acquisition (SG-TIETA), e.g., Fig. 2 for SG-TIETA,

\[
C_n(t) = \gamma^2 g^2 \left\{ \begin{array}{ll}
0 \leq t < h_n \\
(\frac{\pi}{2\tau} - h_n) + 2h_n^2 & h_n \leq t \leq 2h_n
\end{array} \right.,
\]

where \( h_n \) is the \( n \)th peak of \( |F(t)|/\gamma g \).

**C. Avoiding off-resonance signal contributions**

Ignoring magnetic susceptibility, spin-spin \((T_2)\) relaxation, and surface-relaxivity effects, the predominant source of extraneous signal decay is off-resonance coherence transfer pathways (CTPs). When the bandwidth of Larmor precession frequencies spanned by an SG exceeds the bandwidth of \( \pi \)-pulses, every pulse is slice-selective and excites all CTPs.\([39]\) For SG-CPMG measurements, the number of refocused off-resonance CTPs grows exponentially with \( N \approx 3^N \), resulting in significant deviations from the expected echo attenuation.\([34,47]\) Phase cycling remediation schemes require \( \sim 2^N \) steps and are thus infeasible. Unconventional approaches such as time-based avoidance of CTPs become necessary. An SG aids these time-based approaches by acting as an always-on crusher gradient. The minimum time separation to avoid undesired signal, \( \tau_{\text{sep}} \), is shortened. Specifically, \( \tau_{\text{sep}} \) is constrained by \( \tau_{\text{sep}} \geq \tau_p \), where \( \tau_p = 2\pi/(\gamma g \Delta \xi) \)

![FIG. 2. Example SG-TIET A sequence. (a) Timings: \( m_j = \{1, 3, 1, 2, 1\} \), \( \tau = 4\delta \), and \( \delta = 14 \mu \text{s} = 1 \text{ dash} \). \( \pi \)-pulses occur at \( t_n \) and echoes form at \( T_n \). Magenta line indicates timing behavior: \( T_n = t_n + h_n \), where \( h_n \) is the normalized \( |F(t)|/\gamma g \) “height” at \( t_n \), given by \( h_1 = \tau \) and \( h_n = 2\tau + m_j\delta - h_{n-1} \) for \( n > 1 \). (b) Direct echo \( F(t) \) and other coherence pathways that refocus (red, dash-dot) or do not refocus (gray, dotted).](image1.png)
start with $\sum \Delta F(t)$ containing an odd multiple of $\tau$ (i.e., $\tau = 2j\tau$). Choosing $\tau$ and $\delta$ such that $(\tau \bmod \delta) = \delta/2$ thus ensures that $\sum \Delta F(t) \geq \delta/2$. Incorporating $\tau_p$:

(vi) $\delta$ and $\tau$ satisfy $(\tau \bmod \delta) = \delta/2$ and $\delta > 2\tau_p$.

Note that $(\tau \bmod \delta) = 0$ results in the refocused CTPs in Fig. 2). This limited ruleset (i–vi) may be sufficient to ostensibly avoid off-resonance effects considering that singly stimulated echoes are known to be the most significant contributor to SG-CPMG off-resonance effects14–17.

The generation of $m_j$ that satisfies rules (i–v) is discussed in the Supplementary Material (SM) Section I. Python code is provided. A solution for $\tau$, $\delta$, and $m_j$ that probes $t$ from $\sim 50$ to $500 \mu$s is

$$
\tau = 49 \mu s, \quad \delta = 14 \mu s,
$$

$$
m_j = \left\{ 1, 3, 6, 7, 10, 12, 11, 15, 20, 21 \right\} \cup \left\{ 24, 26, 20, 21, 33, 35, 33, 34, 33, 33, \ldots \right\}.
$$

(15)

This timing sequence is used throughout.

## III. EXPERIMENTAL SETUP

NMR measurements were performed at $B_0 = 0.3239$ T (proton $\omega_0 = 13.79$ MHz) using a PM-10 NMR MOUSE single-sided permanent magnet52 (Magritek, Aachen Germany) and a Kea 2 spectrometer (Magritek, Wellington, New Zealand). The decay of the magnetic field with distance from the magnet produces a strong $g = 15.3$ T/m (650 kHz/mm) static gradient. Measurements used a home-built test chamber and a $13 \times 2$ mm solenoid RF coil and RF circuit. Additional information concerning the experimental setup can be found in Williamson et al.55. The SG-TIETA pulse program was written in Prospa V3.22, modified from the standard CPMG sequence. See SM Section IV for further details.

For measurements on twice-distilled water, decane (Sigma-Aldrich, St. Louis, MO, USA.), 1-octanol (Sigma-Aldrich), and dodecamethylcyclohexasiloxane (D6) kinematic Viscosity $= 6.6$ cSt @ 25°C (Gelest, inc. Morrisville, PA, USA.), the liquids were transferred to 2 cm glass capillary sections (1.1 mm OD, Kwik-Fil®. World Precision Instruments, Inc., Sarasota, FL, USA) and the capillaries were sealed with a hot glue gun.

For measurements on yeast ($S. cerevisiae$), 1.72 g of dry yeast was mixed in 10 ml of tap water and stored in a 50 ml tube with the lid screwed on loosely to allow gas to escape. After three days (72 h), the yeast was re-suspended and samples were taken for NMR experiments and for cell density measurement. The cell density of the first sample (yeast #1) was measured to be $2.84 \times 10^9$ cells/ml using a hemocytometer. The remaining yeast was centrifuged, the pellet was re-diluted to 2X the initial concentration, and a second sample (yeast #2) was taken for NMR experiments. Immediately prior to experiments, yeast was transferred to 2 cm KrosFlow® Implant Membrane sections (500,000 Dalton molecular weight cut off, 1 mm OD, SpectrumLabs, Waltham, MA, USA) and the membranes were sealed by pinching the membrane with heated forceps. Yeast was kept from drying out by performing measurements immediately upon filling and sealing the capillary and by lining the inside with wet tissue paper to increase humidity.

Experiments were performed at ambient temperature. Sample temperature was monitored with a fiber optic sensor (PicoM Opsens Solutions Inc., Québec, Canada). The average temperatures of the samples during the course of the experiments were 25°C, 22°C, 22°C, 23°C, and 24°C for the water, decane, octanol-1, D6, and yeast.

## IV. RESULTS AND DISCUSSION

As an initial proof-of-principle, the LLS inversion described in Eq. (13) is demonstrated in Fig. 3 on noisy SG-TIETA decays generated using the timings in Eq. (14) and $\langle |r(t) \cdot \hat{g}|^2 \rangle$ curves from Monte Carlo simulations54. Further details and MATLAB code are provided in SM Section II. Inverted $X$ values are accurate and robust to noise. No systematic errors other than potential over-regularization (e.g., blue curve, Fig. 3) are observed.

Echo-to-echo accuracy remains experimentally difficult to achieve, however. Consider the signal decay due to
$T_2$ relaxation and pulse inaccuracy effects. Relaxation may be ignored if $(2\tau + m_j\delta) \ll T_2 \forall j$. Diffusion-weighted $T_2$ values for each sample, as shown in Table 1, indicate that this condition holds for all pure liquids studied here. However, the yeast is described by a distribution of $T_2$ with a 5% water population with $T_2$ similar to max [$2\tau + m_j\delta$] = 539 $\mu$s. The instantaneous diffusion measurements of yeast may be slightly weighted by $T_2$ relaxation. See SM Section IV for relaxation measurement methods and yeast #2 $T_2$ distribution analysis. Unlike $T_2$, pulse inaccuracy cannot be ignored. Inaccuracy effects may be described using an $n$-dependent pulse accuracy factor, $A_p(n)$. The signal is then corrected as $I(T_n)/I_0 \times [1/\prod_{l=1}^n A_p(l)]$, assuming total avoidance of off-resonance CTPs via rules (i–vi).

TABLE I. Relaxation times.

| Sample          | $T_1$ [ms] | $T_2$ [ms] |
|-----------------|------------|------------|
| water           | 3250       | 133        |
| decane          | 1340       | 166        |
| octanol-1       | 440        | 217        |
| D6              | 788        | 292        |
| yeast #1 (2.84B cells/mL) | 625 | 59 |
| yeast #2 (5.68B cells/mL) | 319 | 41 |

Calibration $A_p(n)$ values were approximated from decays of pure liquids, shown in Fig. 3. A 16 $\mu$s echo window was used. All decays were normalized to the first echo and each repetition consisted of 32 summed (i.e., signal-averaged) scans. To better understand the expected $A_p(n)$ behavior, we consider the spatial, i.e., slice effects. The bandwidth or slice excited by refocusing $\pi$-pulses has inconsistent frequency content$^{55,56}$ such that $A_p(n) < 1$. With each pulse, spins which rotate by angles other than $\pi$ do not refocus until only a stable, central slice remains. In the time domain, this slice-thinning and loss of frequency content is expected to broaden the echo width, which we experimentally verify in Fig. 4. Based on the evolution of the echo shape, $A_p(n)$ should sharply increase then taper. This behavior is observed in Fig. 4 and is consistent across liquids of vastly different $D_0$. Similar $A_p(n)$ values were also obtained for $\tau = 77$ $\mu$s (see SM Section III, Fig. S5), further supporting that $A_p(n)$ is independent of the diffusion weighting.

Another preprocessing step is designed to mitigate the effects of early $A_p(n)$ variability and to ensure the non-negativity of $B$ and $W$ entries. A piece-wise linear fit of adjacent $\ln (I(T_n)/I_0)$ points vs. $b$ is performed, specifying (1) an intercept with $[b, \ln (I(T_n)/I_0)] = [0, 0]$; (2) no slope exceeds $D_0$, and (3) the piece-wise slopes decrease monotonically (i.e., $D_{\text{inst}}(t)$ has no negative concavity). Altogether, SG-TIETA decays are analyzed in five steps: (1) summing $32 \times$, (2) normalization to the first echo, (3) $I(T_n)/I_0 \times [1/\prod_{l=1}^n A_p(l)]$ correction, (4) a constrained log-$b$ domain fit to the repetition(s), and, finally, (5) the LLS inversion. This pipeline was applied to SG-TIETA decays of D6 and yeast using the 1-octanol and water $A_p(n)$ values obtained in Fig. 2, respectively.

Results are summarized in Fig. 4. The $D_{\text{inst}}(t)$ for D6 -- with $D_0 = 0.114 \pm 0.008$ $\mu$m$^2$/ms -- is expected flat, thus validating the $A_p(n)$ correction. The $D_{\text{inst}}(t)$ for yeast are the key results of this Communication. For comparison, the short-time $D_{\text{inst}}(t)$ predicted by Eq. 3 (i.e., $d[tD(t)]/dt$) is plotted for several $S/V$ and $\kappa$ values. Fig. 3 indicates that $\bar{a} \approx 2$ $\mu$m and that a doubling of the cell density approximately halves $\bar{a}$. For yeast’s $\approx 4$ $\mu$m spherical diameter, $\bar{a}$ is calculated as 42 and 21 $\mu$m at these cell densities, suggesting contributions from sub-cellular length scales. This ensemble $\bar{a}$ estimate of $\approx 2$ $\mu$m ($\equiv V/S \approx 3$ $\mu$m) is within the range of estimates ($\bar{a} \approx 1 - 5$ $\mu$m) reported in previous PFG and SG DW-NMR studies of similar yeast densities$^{57,61}$. These yeast results are considered non-quantitative, however, due to $T_2$ contributions, the Gaussian phase approximation, and the stationary $\vec{g} \cdot \vec{R}(t, t')$ assumption. Heterogeneous microenvironments result in progressive signal weighting towards less mobile spins and thus violate inter-echo stationarity. Indeed, heterogeneity may explain the convergence of the yeast $D_{\text{inst}}(t)$. Nonetheless, the sensitivity of SG-TIETA to apparent microstructural features is clear.

V. CONCLUSIONS

We have developed a real-time protocol to measure time-varying diffusion. Inversion for $D_{\text{inst}}(t)$ from experimental SG-TIETA decays is demonstrated. A $\approx 1$-minute ($32 \times$ repetition time of 2 s) experiment is described. In contrast to conventional temporal diffusion spectroscopy methods, the single-shot nature of SG-TIETA permits true signal averaging in order to improve SNR. A post hoc $A_p(n)$ correction is proposed to improve the quantitative accuracy of the method. To support the validity of this correction, we present preliminary evi-
FIG. 5. Comparison of SG-TIET A (blue) and CPMG (orange) attenuation and echo shape for 1-octanol with $2\tau = TE = 98$ ms. Echo shapes show real (solid lines) imaginary (dotted lines) signal normalized by the area under the real signal curve. The echo width of the CPMG decreases with $n$ and stabilizes around $n = 3$, consistent with the approach to asymptotic behavior described in Hürlimann & Griffin. In contrast, the SG-TIET A echo width increases and stabilizes around $n = 3$, consistent with the direct echo CTP being preferential to the on-resonance signal.

dence in the observed echo shape behavior and in the consistency of $A_p(n)$ values across different diffusion weightings. Regarding potential applications, SG-TIET A at this $g$ can probe porous media microstructure on micron length scales, i.e., over sub-millisecond timescales. SG-TIET A can also be used to study phenomena associated with other long-range correlations, e.g., polymer dynamics, the glass transition, and high Péclet fluxes driven by flagella, which likewise exhibit time-dependence in this sub-millisecond range. The methods contained in this Communication may open new avenues of research within DW-NMR.

SUPPLEMENTARY MATERIAL

In the supplementary material, we include sections containing (I) Python code to generate $m_j$, (II) MATLAB code for the Monte Carlo simulations, fitting procedures, and LLS inversion, (III) a replication of the analysis in Figs. 4 and 6 using SG-TIET A decays for $\tau = 77 \mu$s, and (IV) additional NMR experimental methodology.

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ments; NHW and TXC analyzed data; TXC prepared the manuscript; PJB supervised the project. All authors edited the manuscript.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding authors upon request. The SG-TIETA pulse program and macro can be downloaded from the GitHub repository: https://github.com/nathanwilliamson/SG-TIETA

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