A single-shot measurement of sub-millisecond, time-dependent diffusion using optimized, unequal pulse spacings in a static field gradient

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INTRODUCTION

• Time-varying diffusion – i.e., non-linear time-dependence in the net mean-squared displacement (MSD) – is ubiquitous in biological systems.

• Oscillating gradient waveforms can be used to directly probe the time-varying diffusivity [1].

• Usually, the echo intensity is related to the spectrum of the time integral of the gradient waveform, \( F(\omega) \), and of the velocity autocorrelation function, \( 2D(\omega) \):

\[
\frac{I(T)}{I_0} = \exp\left(\frac{1}{\pi} \int_0^\infty F^T(\omega) D(\omega) F(\omega) d\omega\right)
\]

• On conventional scanners, however, oscillating gradient methods are limited to \( \omega \sim 100 \) Hz and probe just one timescale per scan.

Here, we ask:

1) Can an NMR method probe short times (< 1 ms)?
2) Can the method be performed quickly (~ 1 min)?

PULSE SEQUENCE DESIGN

• Permanent magnet setups (i.e., single-sided NMR) can produce strong, static field gradients (SG) [2].

• A \( \pi \)-pulse train (CPMG) under a strong SG can produce a triangle wave \( F(t) = \gamma \int_0^T G(t) dt \) that is sensitive to times < 1 ms [3], as desired. But ...

• Many off-resonance coherence transfer pathways (CTPs) are excited [4].

\[
F(t) \quad \text{RF} \quad \tau \quad \omega \quad \pi \quad \tau \quad \omega \quad \pi \quad \tau \quad \omega \quad \pi \quad \tau \quad \omega \quad \pi \quad \tau \quad \omega \quad \pi \quad \tau \quad \omega \quad \pi \quad \tau \quad \omega \quad \pi \quad \tau \quad \omega \quad \pi \quad \tau \quad \omega
\]

Fig. 1: Triangle wave \( F(t) \) produced by the SG-CPMG sequence. The associated \( F(\omega) \) focuses near \( \omega = 2\pi/\tau \) over many cycles.

• We can kill two birds with one stone: Unequal \( \pi \)-pulse spacings may be used to avoid off-resonance CTPs and to probe a range of diffusion times.

• We choose the discrete spacing: \( 2\tau + m_\delta \delta \), with unit increment \( \delta \) to produce a (roughly) chirped \( F(\omega) \).

• We term this the SG, time-incremented echo train acquisition (SG-TIETA). Using SG-TIETA, each pair of adjacent echoes is spaced differently.

\[\text{RF} \quad \tau \quad 2\tau + m_\delta \quad \ldots \quad m_\delta \quad \ldots \quad m_\delta \quad \delta \quad \ldots \quad m_\delta \quad \delta \quad \ldots \quad m_\delta \quad \delta \]

Fig. 2: Example SG-TIETA sequence with \( \tau = 45 \) and \( m_\delta = \{1,3,1,2,1\} \). Various off-resonance CTPs which refocus (red, dashed) and do not refocus (gray, dotted) are shown.

• Based on a derived ruleset, we propose a sequence that is optimized to avoid off-resonance CTPs:

\[
\tau = 49 \mu s, \quad \delta = 14 \mu s
\]

\[
m_\delta = \{1,3,6,7,10,12,11,15,20,21,24,26,20,21,33,35,33,34,33,\ldots\}
\]

To analyze these SG-TIETA decays, we developed a pulse accuracy correction, \( 1/\Pi_1 A_p(\tau) \), where the function \( A_p(\tau) \) describes signal loss at each \( \pi \)-pulse.

• We also used a signal representation [5] in the (1-D) instantaneous diffusivity, \( D_{\text{inst}}(t) \), which is half of the time derivative of the MSD in the gradient direction.

\[
D_{\text{inst}}(t) = \frac{1}{2} \frac{d}{dt} D_{\text{ MSD}}(t)
\]

\[
\text{In sum, a method to rapidly probe diffusion times from 50} - 500 \mu s \text{ is validated on yeast and simple fluids.}
\]

EXPERIMENTAL RESULTS

• Experiments were performed using a PM-10 NMR-MOUSE [2] with a SG amplitude of 15.3 T/m.

• Calibration \( A_p(\tau) \) values were obtained on simple fluids – 1-octanol, decane, and water – and were consistent across varying diffusivities.

• SG-TIETA decays for yeast and another simple fluid, D6, were signal averaged 32 \( \times \) and analyzed.

\[\begin{array}{ccc}
\text{a [\mu m], } & \text{b [mm/s]} \\
\hline
\text{a = 2.5, } & \text{b = 0} \\
\text{a = 2.8, } & \text{b = 0.3} \\
\text{a = 2.8, } & \text{b = 0.8} \\
\text{a = 1.4, } & \text{b = 0} \\
\text{a = 1.4, } & \text{b = 0.3} \\
\text{a = 1.4, } & \text{b = 0.8} \\
\end{array}\]

Fig. 3: Summary of results. (a) SG-TIETA decays plotted vs. the cumulative b-value for different experimental samples. (b) Inverted \( D_{\text{inst}}(t) \) curves. The yeast curves are compared to the theoretical short-time behavior [6] for mean pore size \( a \) and permeability \( \kappa \).

References