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, $\mathbf{F}(\omega)$, and of the velocity autocorrelation function, $2\mathbf{D}(\omega)$:

$$\frac{I(T)}{I_0} = \exp\left(\frac{1}{\pi}\int_0^\infty \mathbf{F}^{\mathrm{T}}(\omega)\,\mathbf{D}(\omega)\mathbf{F}(\omega)\,d\omega\right)$$

- 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 π-pulse train (CPMG) under a strong SG can produce a triangle wave $\mathbf{F}(t) = \gamma\int_0^T \mathbf{G}(t)\,dt$ that is sensitive to times < 1 ms [3], as desired. But …
- Many off-resonance coherence transfer pathways (CTPs) are excited [4].

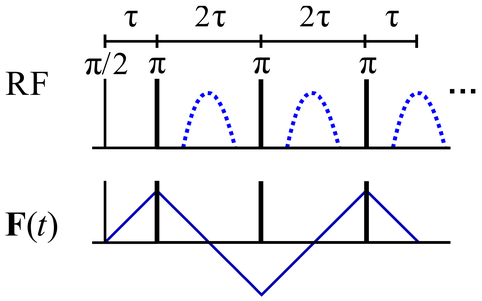


Fig. 1: Triangle wave $\mathbf{F}(t)$ produced by the SG-CPMG sequence. The associated $\mathbf{F}(\omega)$ focuses near $\omega = 2\tau/\pi$ over many cycles.

- We can kill two birds with one stone: Unequal π-pulse spacings may be used to avoid off-resonance CTPs *and* to *p*robe a range of diffusion times.
- We choose the discrete spacing: $2\tau + m_n\delta$, with unit increment δ to produce a (roughly) chirped $\mathbf{F}(\omega)$.
- We term this the SG, time-incremented echo train acquisition (SG-TIETA). Using SG-TIETA, each pair of adjacent echoes is spaced differently.

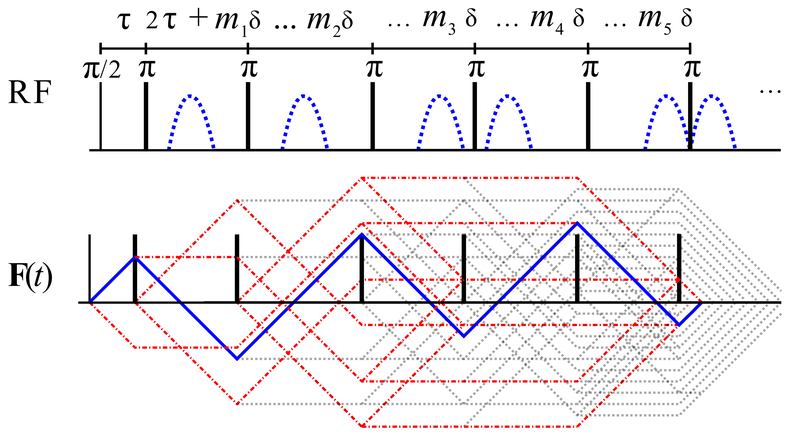


Fig. 2: Example SG-TIETA sequence with $\tau = 4\delta$ and $m_n = \{1, 3, 1, 2, 1\}$. Various off-resonance CTPs which refocus (red, dashed) and do not refocus (gray, dotted) are shown.

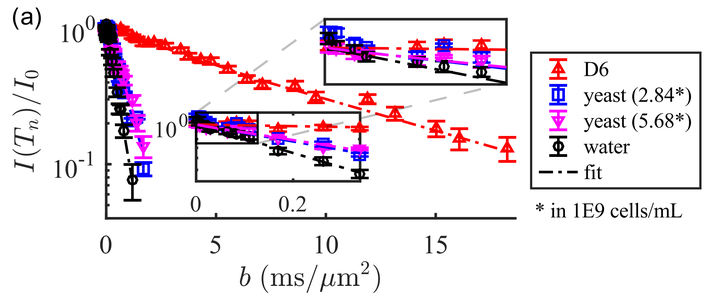
- Based on a derived ruleset, we propose a sequence that is optimized to avoid off-resonance CTPs:

$$\tau = 49\ \mu s, \quad \delta = 14\ \mu s$$
$$m_n = \{1, 3, 6, 7, 10, 12, 11, 15, 20, 21, 24, 26, 20, 21, 33, 35, 33, 34, 33, \ldots\}$$

- To analyze these SG-TIETA decays, we developed a pulse accuracy correction, $1/\prod_l^n A_p(n)$, where the function $A_p(n)$ describes signal loss at each π-pulse.
- We also used a signal representation [5] in the (1-D) *instantaneous* diffusivity, $D_{\mathrm{inst}}(t)$, which is half of the time derivative of the MSD in the gradient direction.

EXPERIMENTAL RESULTS

- Experiments were performed using a PM-10 NMR-MOUSE [2] with a SG amplitude of 15.3 T/m.
- Calibration $A_p(n)$ 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 × and analyzed.



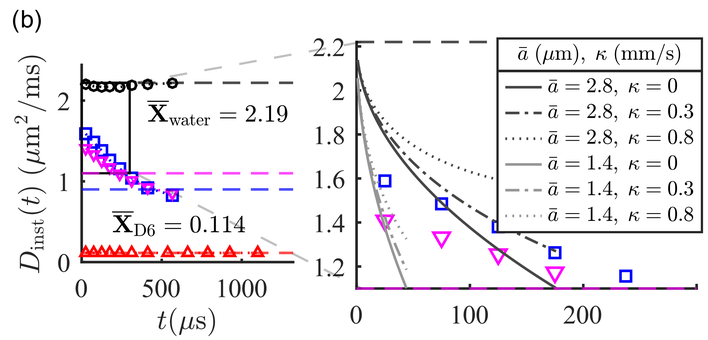


Fig. 3: Summary of results. (a) SG-TIETA decays plotted vs. the cumulative *b*-value for different experimental samples. (b) Inverted $D_{\mathrm{inst}}(t)$ curves. The yeast curves are compared to the theoretical short-time behavior [6] for mean pore size $\bar{a}$ and permeability κ.

In sum, a method to rapidly probe diffusion times from $50 - 500\ \mu s$ *is validated on yeast and simple fluids.*

References

1. P. T. Callaghan, J. Stepišnik, *J. Magn. Reson. A* **117**, 118-122 (1995)
2. G. Eidmann, R. Savelsberg, P. Blümler, B.Blümich, *J. Magn. Reson. A* **122**, 104-109 (1996)
3. L. J. Zielinski and M. D. Hürlimann, *J. Magn. Reson*. **107**, 161-167 (2005).
4. Y.-Q. Song, M. D. Hürlimann, and C. Flaum, *J. Magn. Reson*. **161**, 222 (2003)
5. L. Ning., K. Setsompop, C. F. Westin, Y. Rathi. *Magn Reson Med*. **78,** 763-774. (2017)
6. D. S. Novikov, E. Fieremans, J. H. Jensen, J. A. Helpern. *Nat. Phys.* **7**, 508-514 (2011)