Optimizing Phases of CPMG Pulse Sequence and Applying Exact Solution to Measure Relaxation Time

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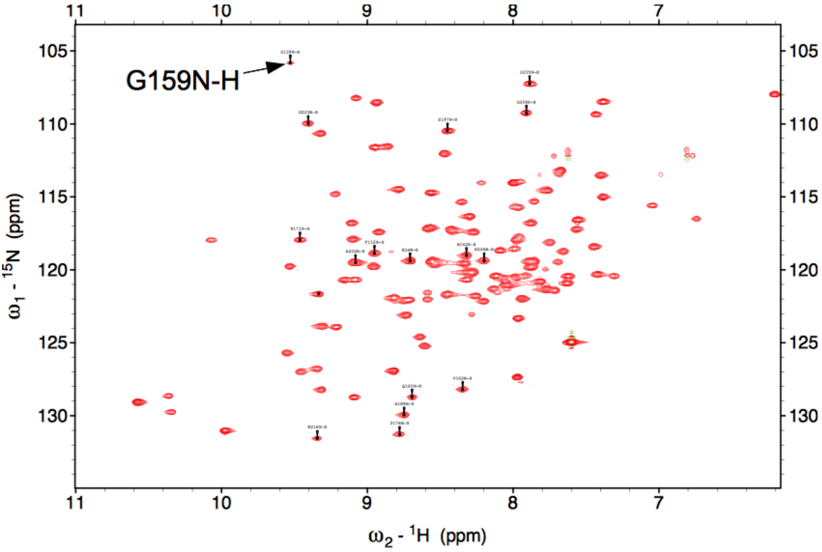
CORS

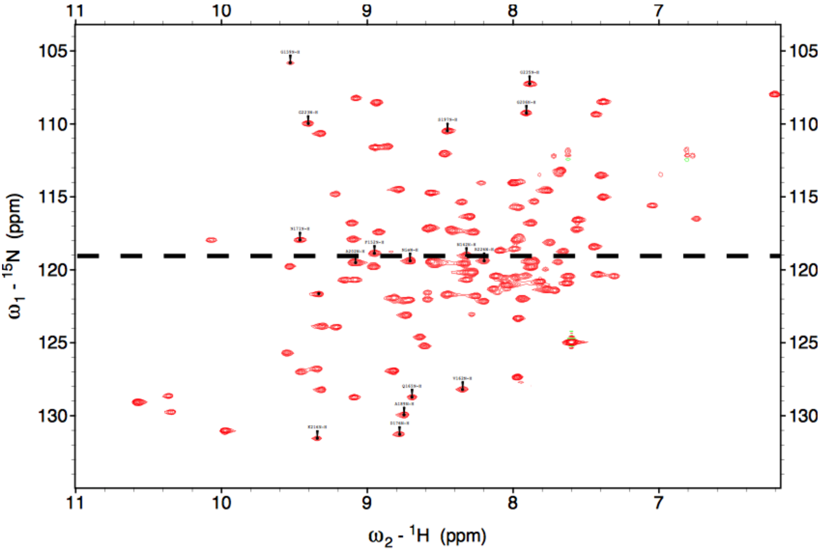
Outline

Measuring Relaxation Time



2D spectroscopy of the Iα of Protein Kinase A (PKA). (Provided by Dr. Melacini's Lab)

Measuring Relaxation Time



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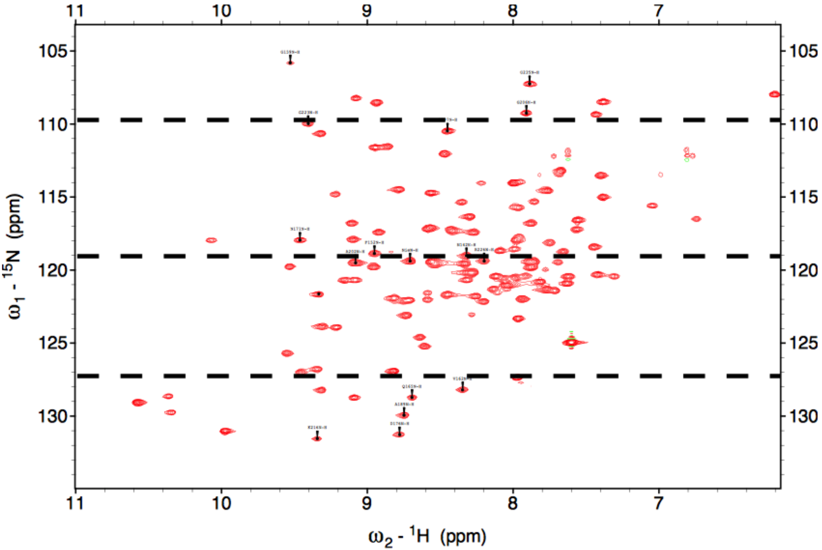

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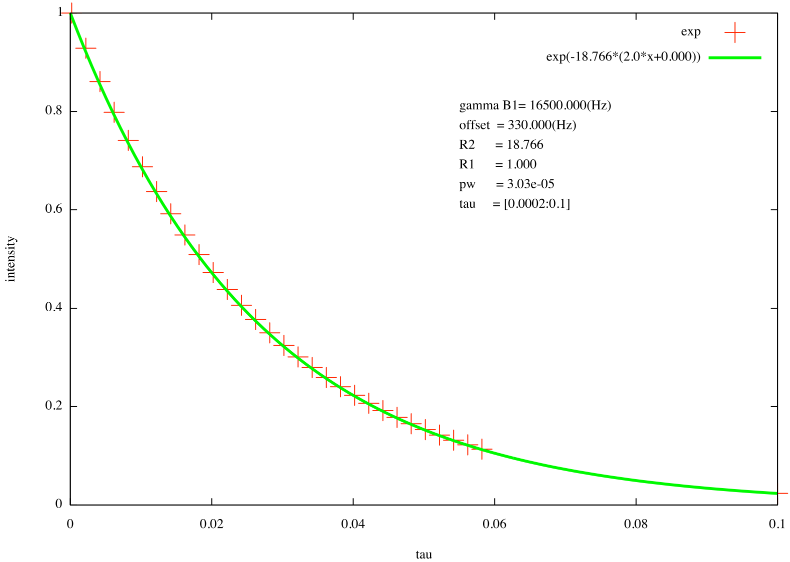
Effect of Offset

The power cannot be infinity.

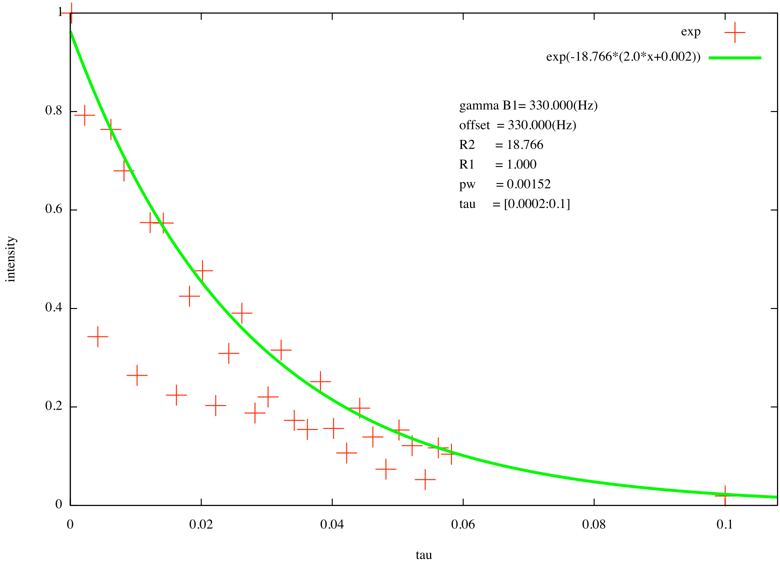
- Some probes require low power;
- Maximum power output by the amplifier is limited;
- Sample may boil if the power is too high;

If sample is a large molecule, the range of offset frequencies may be wide. For example, $\Delta\omega = \gamma B_1$. Offset will significantly affect the measurements.

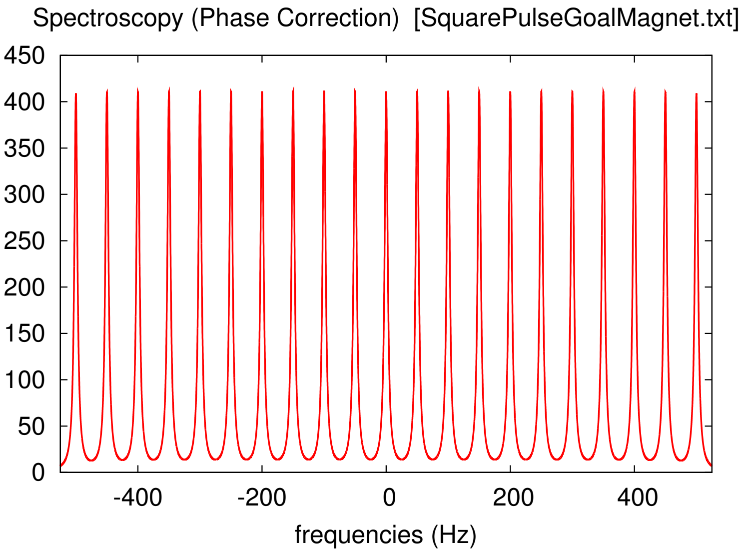
Ideal Experiments



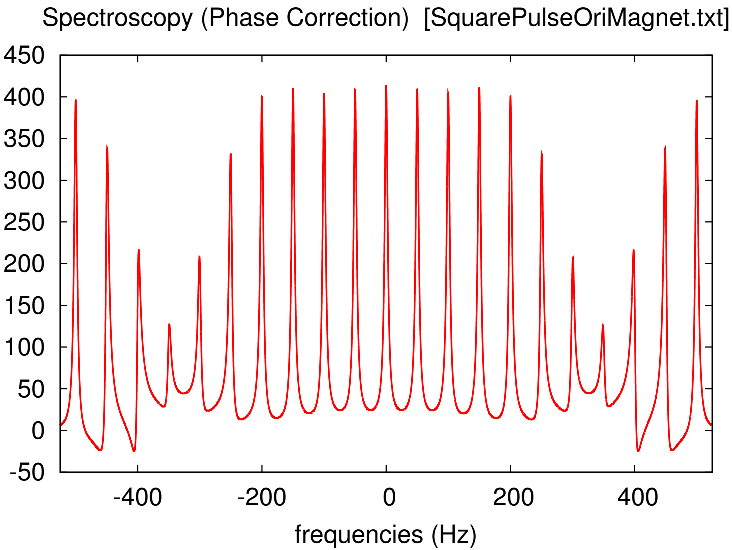
Real Experiments



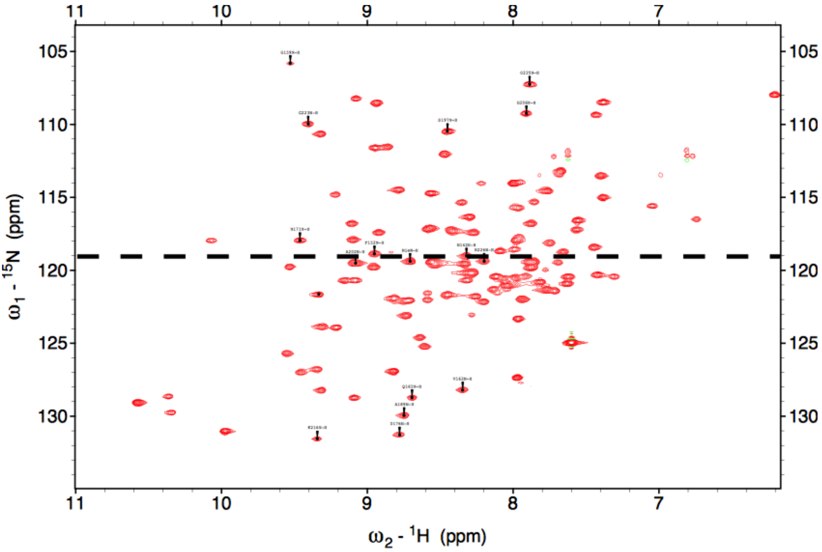
Ideal Experiments



Real Experiments

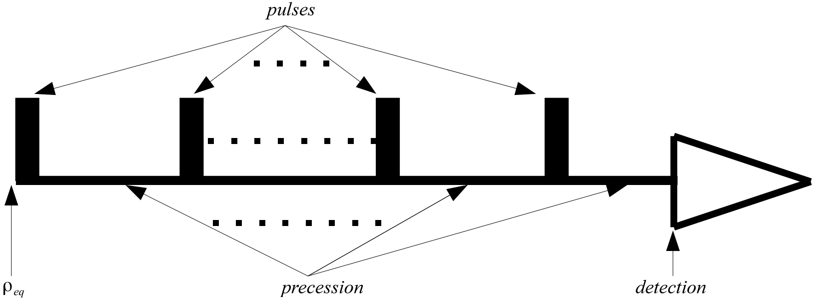


Measuring Relaxation Time



Objective: Can we measure the relaxation time of all nuclei at one carrier frequency?

Calculation of NMR Using Liouville-von Neumann Equation



- Vector of observables (ρ) in Liouville space method
- Evolution of the spin system in Liouville space method

$$\frac{d\,\rho}{d\,t} = -i(\mathcal{L}+\mathcal{B})\rho - \mathcal{R}(\rho-\rho_{eq}) \quad \text{(Inhomogeneous)}$$

$$\frac{d\,\rho}{d\,t} = (-i(\mathcal{L}+\mathcal{B}) - \mathcal{R})\rho \quad \text{(Homogeneous)}$$

Solution of the Liouville Space Method

Precession:

$$\frac{d\rho}{dt} = (-i(\mathcal{L} + \mathcal{B}) - \mathcal{R})\rho$$

Solution of a rectangular pulse:

$$\rho(t) = e^{(-i(\mathcal{L}+\mathcal{B})-\mathcal{R})t}\rho(0)$$

Solution of a shaped pulse or pulse sequence:

$$\rho(t_p) = \hat{L}_N \cdots \hat{L}_1 \rho(0)$$

with

$$\hat{L}_j = e^{(-i(\mathcal{L}+\mathcal{B}_j)-\mathcal{R})\Delta t_j}$$

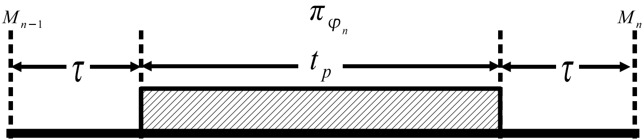
Bloch Equations and Its Solution

$$\frac{d}{dt}\begin{pmatrix} M_x \\ M_y \\ M_z \\ M_e \end{pmatrix} = \begin{pmatrix} -R_2 & -\omega & \gamma B_1 \sin\phi & 0 \\ \omega & -R_2 & -\gamma B_1 \cos\phi & 0 \\ -\gamma B_1 \sin\phi & \gamma B_1 \cos\phi & -R_1 & R_1 \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} M_x \\ M_y \\ M_z \\ M_e \end{pmatrix} \tag{1}$$

$\mathbf{A}$ is used to represent the coefficient matrix. When $\mathbf{A}$ is constant, the solution is

$$\mathbf{M}(t) = e^{\mathbf{A}t}\mathbf{M}(0).$$

CPMG and Its Solution

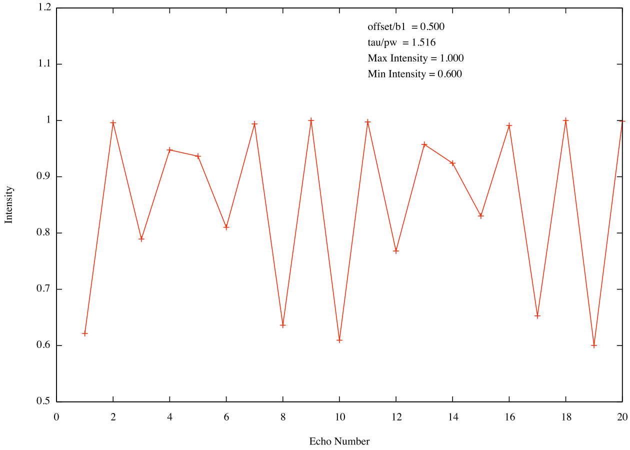


$$\mathbf{M}_n = \mathbf{E}_n \mathbf{M}_{n-1}$$

$$\mathbf{E}_n = \mathbf{E}_{fid} \mathbf{E}_{\pi}(\varphi_n) \mathbf{E}_{fid}$$

$$\mathbf{M}_n = \mathbf{E}^n \mathbf{M}_0 \qquad (2)$$

CPMG and Its Solution (cont.)



$$
\begin{aligned}
f(n) &= \sum_{k=1}^{n} \left(\sqrt{M_{x,k}^2 + M_{y,k}^2} - \sqrt{M_{x,k-1}^2 + M_{y,k-1}^2} \right)^2 \\
&\equiv f(\phi, \omega, \gamma B_1, \tau, t_p)
\end{aligned}
$$

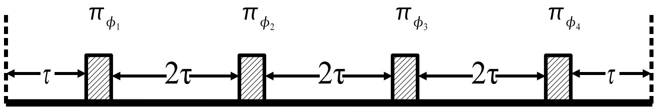
Mixed Integer Problem to Measure Oscillations

$$\min_{\phi\in\{0,1,2,3\}} \max_{\omega/\gamma B_1\in[-1/2,1/2],\tau/t_p\in[0,4]} f(\phi,\omega,\gamma B_1,\tau,t_p)$$

Solution: Maximum difference is 0.411 of phase 0 or 2.

Please note that the solution will depend on the initial magnetization. Here, we suppose the initial magnetization is along with the x axis.

Phase Variations of CPMG and Its Solution



$$\mathbf{E} = \mathbf{E}_{\text{fid}} \mathbf{E}_{\pi,\phi_4} \mathbf{E}_{\text{fid}} \mathbf{E}_{\text{fid}} \mathbf{E}_{\pi,\phi_3} \mathbf{E}_{\text{fid}} \mathbf{E}_{\text{fid}} \mathbf{E}_{\pi,\phi_2} \mathbf{E}_{\text{fid}} \mathbf{E}_{\text{fid}} \mathbf{E}_{\pi,\phi_1} \mathbf{E}_{\text{fid}}$$

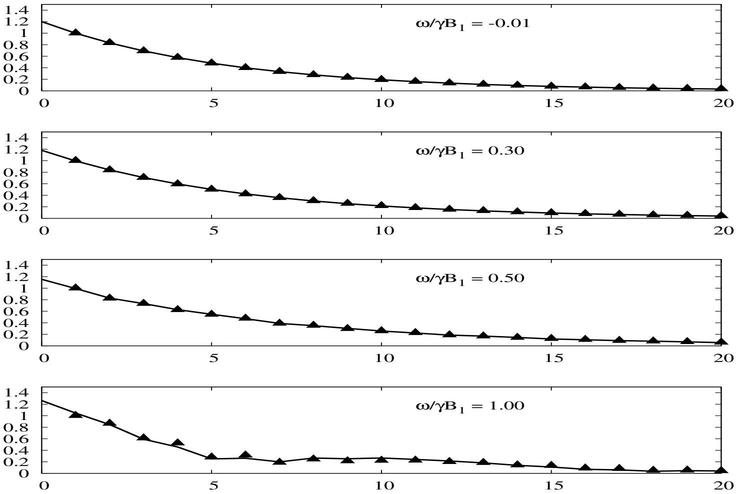
$$\mathbf{M}_n = \mathbf{E}^n \mathbf{M}_0$$

Mixed Integer Problem to Measure Oscillations for Phase Variations

$$\min_{\forall \phi_1, \cdots, \phi_K \in \{0,1,2,3\}} \max_{\omega/\gamma B_1 \in [-1/2, 1/2], \tau/t_p \in [0,4]} f(\phi_1, \cdots, \phi_K, \omega, \gamma B_1, \tau, t_p)$$

Solution: Maximum difference is 0.035 of using $\{0, 0, 1, 3\}$ for a group of 4 pulses.

Experiments



Effective Relaxation Rates of Using $\{0, 0, 1, 3\}$ for a group of 4 pulses

$$R_{2-eff}^{0013} = R_2 + \frac{(R_1 - R_2)t_p}{8\tau + 4t_p} + \frac{1 - e^{-(2\tau + t_p)(R1 - R2)}}{2\tau + t_p}\mu^2 + O(\mu^4)$$

where $\mu = \omega/\gamma B_1$.

$$R_2 = R_{2-eff} - \frac{t_p(R1 - R_{2-eff})}{8\tau + 3\,t_p} - \frac{4\left(1 - e^{\frac{-4(2\tau + t_p)^2(R1 - R_{2-eff})}{8\tau + 3\,t_p}}\right)}{8\tau + 3\,t_p}\mu^2 + O(\mu^4)$$

Fitting Problem

$$\min \sum_{i=1}^{n} \left| \left| M_{\text{meas}}(i) - I_0 \sqrt{M_{x,i}^2 + M_{y,i}^2} \right| \right|^2$$

Subject to:

$$\frac{d}{dt} \begin{pmatrix} M_x \\ M_y \\ M_z \\ M_e \end{pmatrix} = \begin{pmatrix} -R_2 & -\omega & \gamma B_1 \sin\phi & 0 \\ \omega & -R_2 & -\gamma B_1 \cos\phi & 0 \\ -\gamma B_1 \sin\phi & \gamma B_1 \cos\phi & -R_1 & R_1 \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} M_x \\ M_y \\ M_z \\ M_e \end{pmatrix}$$

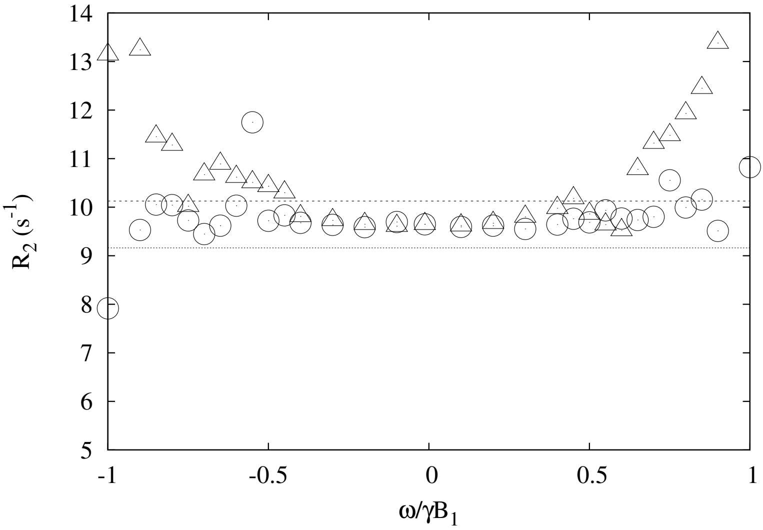
Unknown Variable: R_2

Reformed Fitting Problem

$$\min \sum_{i=1}^{n} \left|\left| M_{\text{meas}}(i) - I_0\sqrt{M_{x,i}^2 + M_{y,i}^2} \right|\right|^2$$

Subject to Eq. (2).

Comparison of Second-Order Formula and Exact Fitting



Conclusion

- An optimization model is proposed to quantify oscillations of measured intensities of CPMG experiments.
- Repeating one group of four pulses with different phases can significantly smooth the dependence of measured intensities on frequency offset in the range of $\pm\frac{1}{2}\gamma B_1$
- A second-order expression with respect to the ratio of offset to π-pulse amplitude is developed to describe the effective R_2 of CPMG experiments when using a group phase variation scheme.
- The second-order expression of the effective decay rate with phase variation is able to provide reliable estimates of R_2 when offsets are roughly within $\pm\frac{1}{2}\gamma B_1$.
- Most significantly, the more sophisticated optimization model using an exact solution of the discretized CPMG experiment extends, to $\pm\gamma B_1$, the range of offsets for which reliable estimates of R_2 can be obtained when using the preferred phase variation scheme.

Conclution (cont.)

Objective: Can we measure the relaxation time of all nuclei (^{15}N) of a protein at one carrier frequency?

Answer: **Yes, we can!**

Reference

1. *Alex D. Bain, Christopher Kumar Anand, Zhenghua Nie, Exact Solution of the CPMG Pulse Sequence with Phase Variation Down the Echo Train: Application to R_2 Measurements, Journal of Magnetic Resonance, 209 (2011) 183-194. (doi:10.1016/j.jmr.2011.01.009)*

2. *Alex D. Bain, Christopher Anand, Zhenghua Nie, Exact Solution to the Bloch Equations and Application to the Hahn Echo, Journal of Magnetic Resonance, 206 (2010) 227-240. (doi:10.1016/j.jmr.2010.07.012)*

Thanks!

Abstract

Accurately measuring relaxation time is a key process to investigate the dynamics of molecules. In this presentation, we demonstrate grouped phase variation in CPMG which removes oscillation and field-inhomogeneity effects and the exact CPMG simulation to fit the experiment data which provides reliable relaxation times in a wide range.