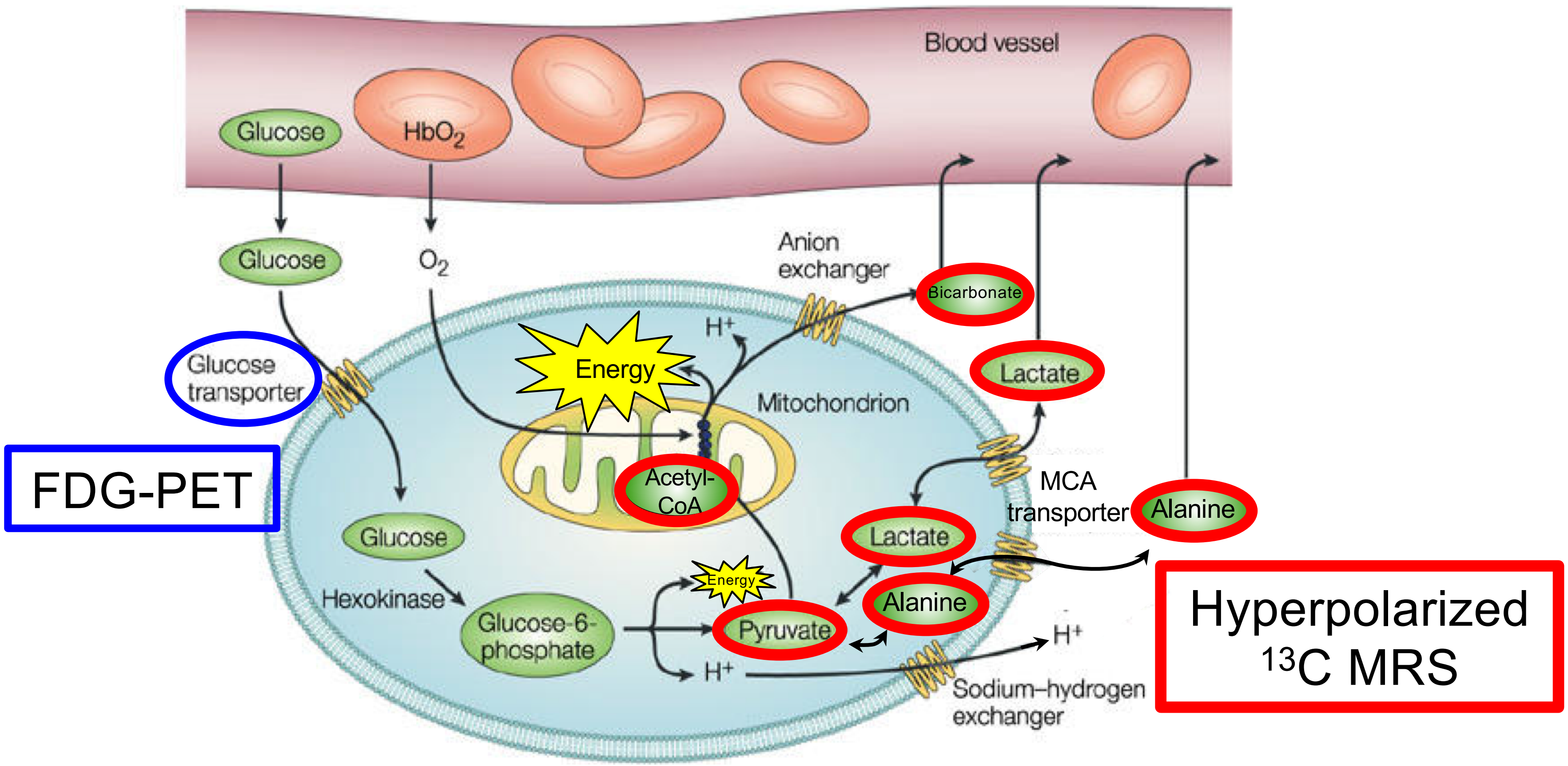
Lecture #9
Redfield theory: Examples

- Topics
  - Hyperpolarized ^{13}C-urea
  - Hyperpolarized ^{13}C-pyruvate
- Handouts and Reading assignments
  - Shang, et al., "Handheld Electromagnet Carrier for Transfer of Hyperpolarized Carbon-13 Samples", MRM, early view, 2015.
  - Lau, et al,. "A calibration-based approach to real-time in vivo monitoring of pyruvate C1 and C2 polarization using the JCC spectral asymmetry", NMR Biomed., 2013; 26.

Hyperpolarized ^{13}C MRS

- Images metabolism by performing an in vivo tissue assay.
- Key idea: inject a biological substrate and image both the substrate and its downstream metabolic products.



Key technology: A polarizer that magnetically prepares the substrate to boost its MR visibility by >10,000 fold.

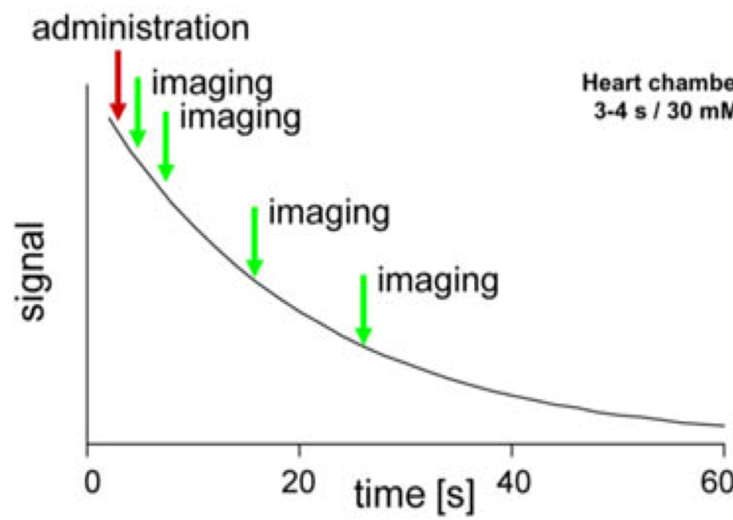
In Vivo Imaging Requirements

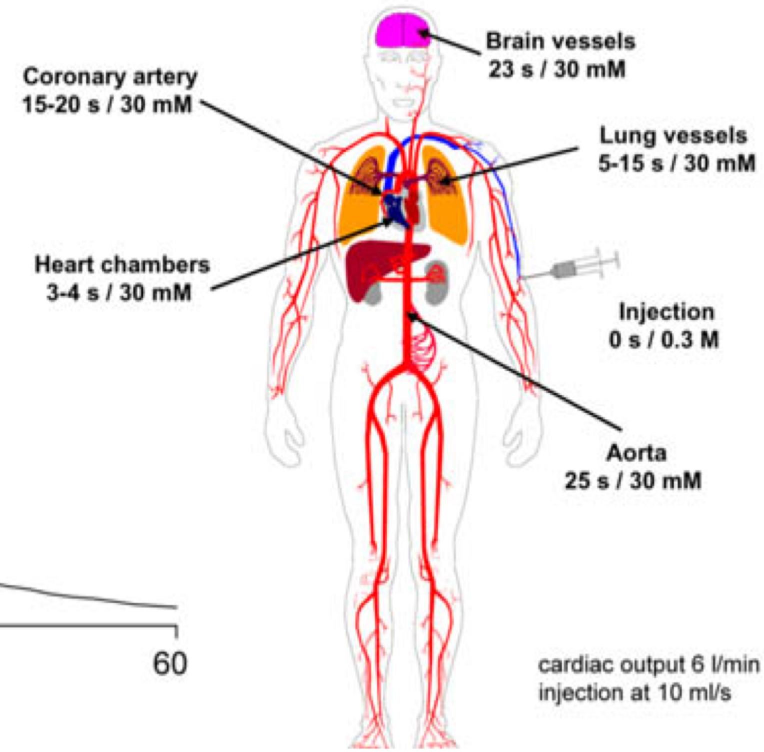
- Low toxicity (mM conc.)
- Long NMR relaxation times
- Chemical shift separation
- Rapid cellular uptake
- Rapid metabolism

Signal decays by relaxation and dilution

Polarization

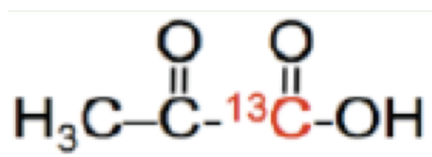
T_1 decay





➡ Focus on low molecular weight endogenous compounds.

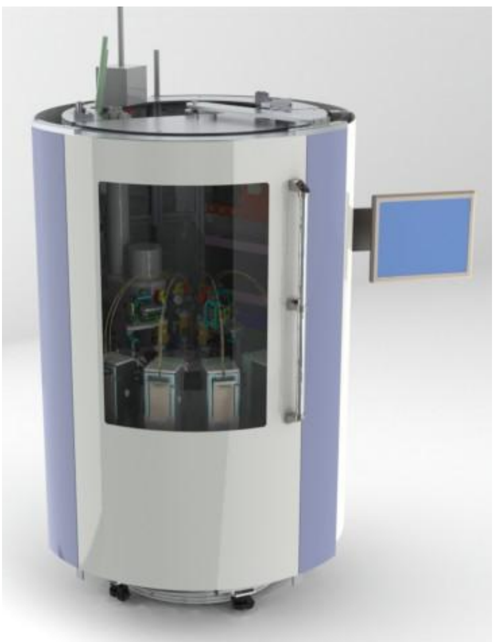
Example: [1-^{13}C]pyruvate



25% polarization ~ 30,000 fold signal gain!
In vivo T_1 = 30 s

Hyperpolarized Carbon-13 Experiment

Hyperpolarization → Run/walk and inject → Scan



1.5 - 3 hours

~30 seconds

1-2 minutes

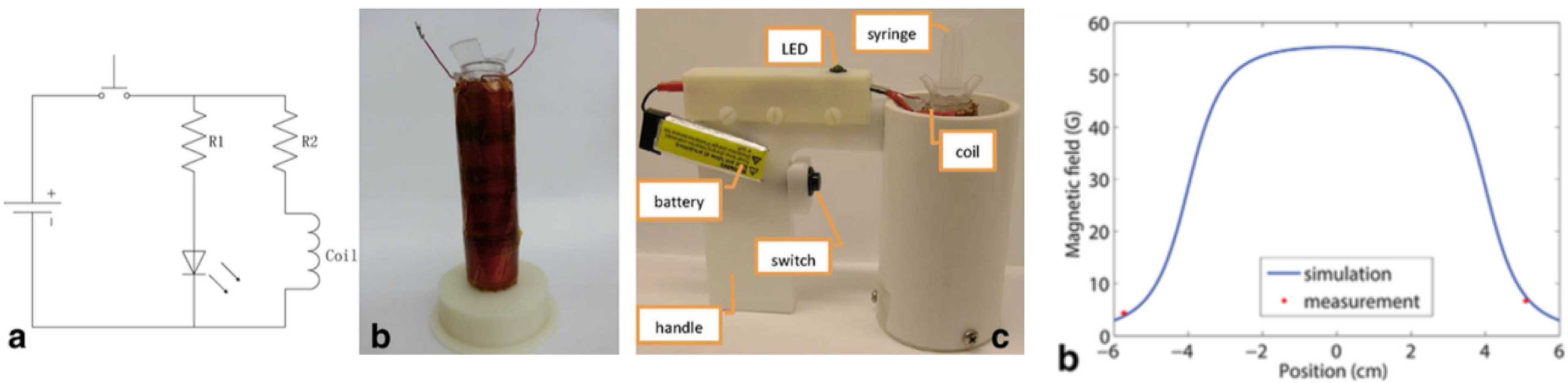
Example 1

NOTE

Magnetic Resonance in Medicine 00:00–00 (2015)

Handheld Electromagnet Carrier for Transfer of Hyperpolarized Carbon-13 Samples

Hong Shang,[1,2] Timothy Skloss,[3] Cornelius von Morze,[1] Lucas Carvajal,[1] Mark Van Criekinge,[1] Eugene Milshteyn,[1,2] Peder E. Z. Larson,[1,2] Ralph E. Hurd,[3] and Daniel B. Vigneron[1,2]*



Hyperpolarized ^{13}C MRS

- "Some HP ^{13}C substrates can lose polarization extremely quickly in low magnetic field when they are transferred between the polarizer and the MR scanner, reducing the SNR." – Shang, et al.

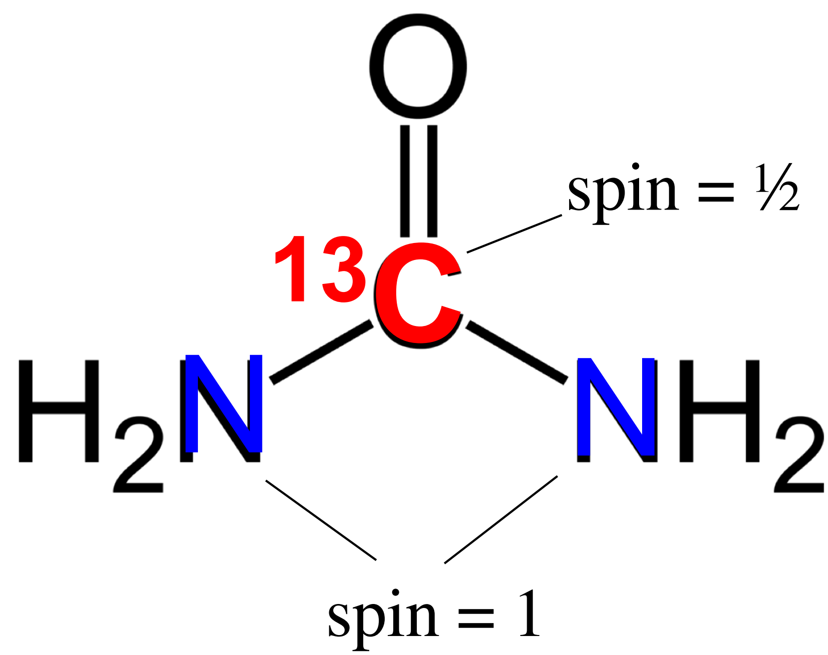
- Which substrates?

- Why is this a "low magnetic field" effect?

- How low is "low"?

[^{13}C]urea

- Hyperpolarized [^{13}C]urea of interest for measuring perfusion



- Scalar coupling between fast-relaxing spin 1 quadrupolar-coupled ^{14}N and spin ½ ^{13}C nuclei results in rapid loss of polarization at low field.

Scalar relaxation of the 2nd kind

- From the homework, we derived: $\frac{1}{T_{1,SC2}} = \frac{2(2\pi J)^2 S(S+1)}{3} \frac{T_{2,S}}{1+(\omega_I - \omega_s)^2 T_{2,S}^2}$

- For hyperpolarized [^{13}C-$^{14}N_2$]urea:

Extra factor of 2 due to two ^{14}N nuclei.

Compare to Shang, et al. Eqn [1].

$$\frac{1}{T_1} = \frac{1}{T_{1,0}} + \frac{2\cdot 8\pi^2 J^2 S(S+1)}{3} \frac{T_{2,N}}{1+(\gamma_C B_0 - \gamma_N B_0)^2 T_{2,N}^2} = \frac{1}{T_{1,0}} + \frac{32\pi^2 J^2}{3} \frac{T_{2,N}}{1+B_0^2(\gamma_C - \gamma_N)^2 T_{2,N}^2}$$

Relaxation from other mechanisms

- Some numbers…

$S = 1$

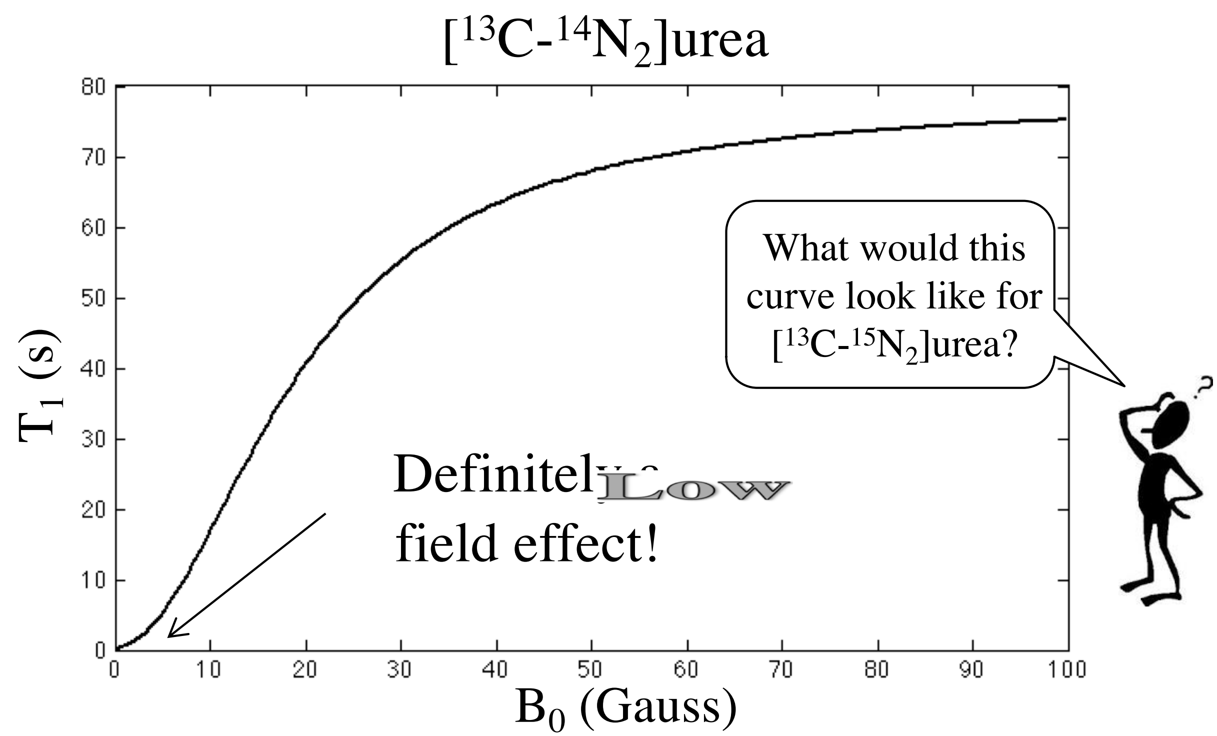
$J = 14.5$ Hz

$T_{1,0} = 78$ s

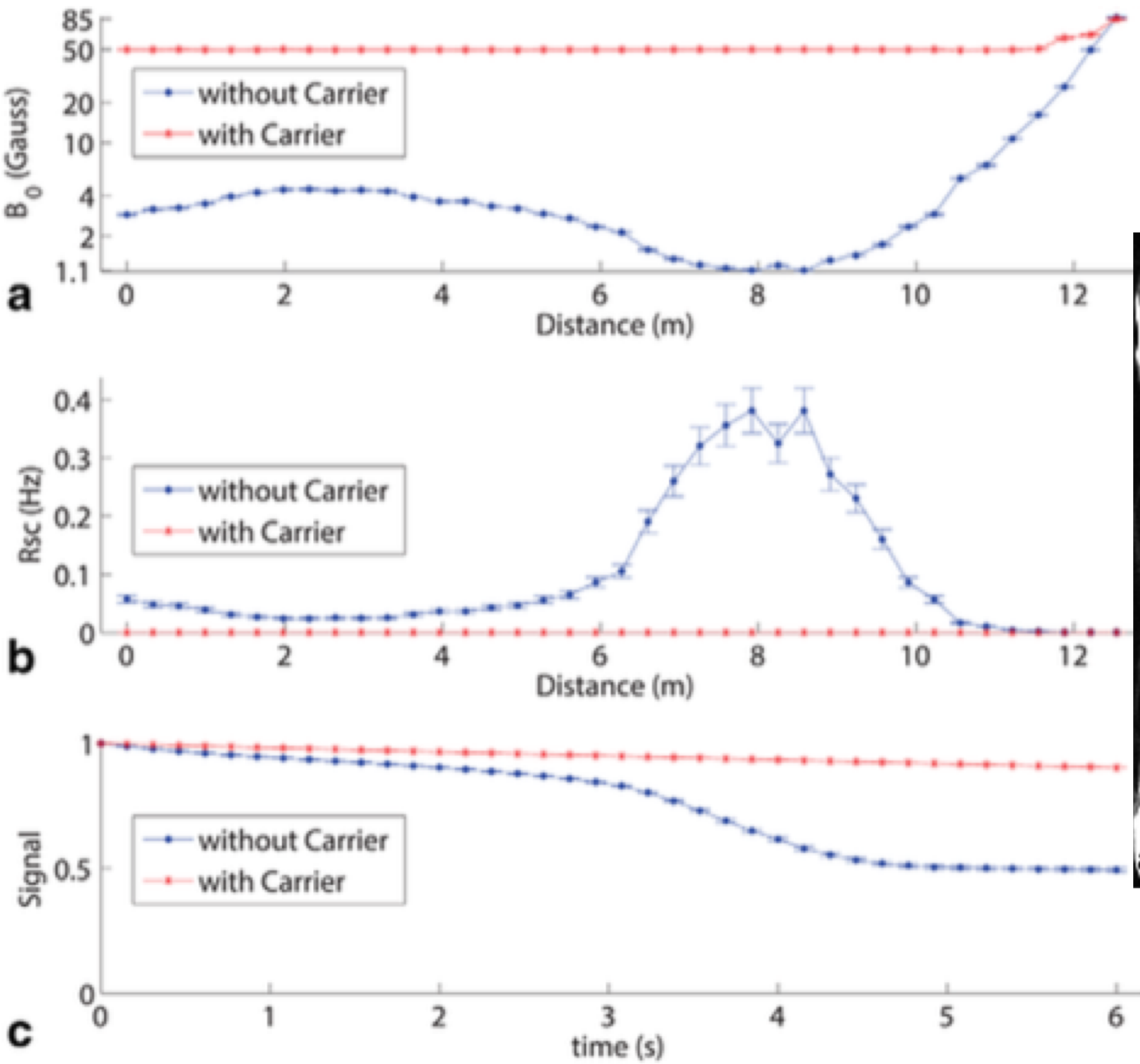
$T_{2,N} = 2\text{x}10^{-4}$ s

$\gamma_N = 19.331\text{x}10^6$ rad/s/Tesla

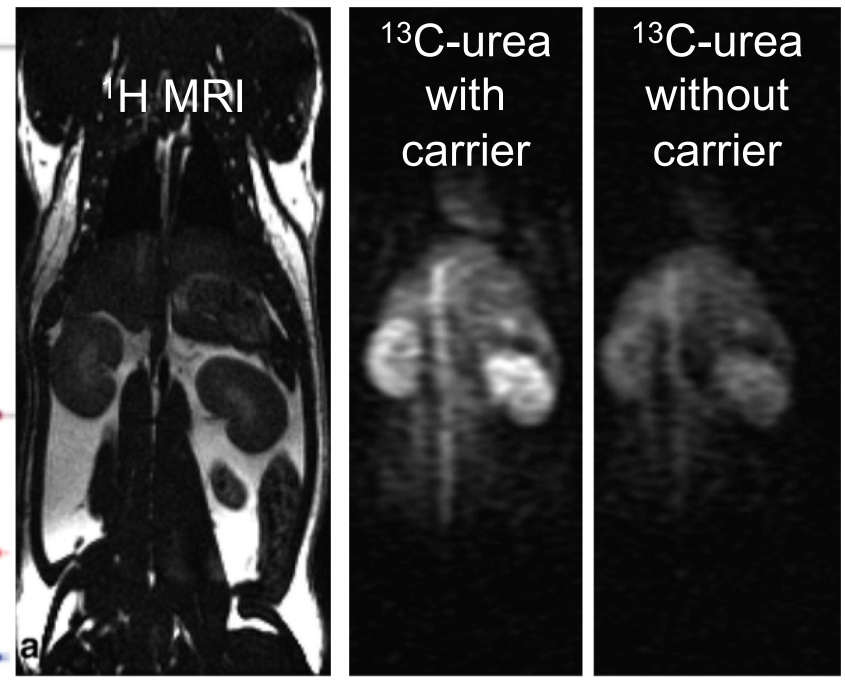
$\gamma_C = 67.262\text{x}10^6$ rad/s/Tesla



Hyperpolarized ^{13}C-urea

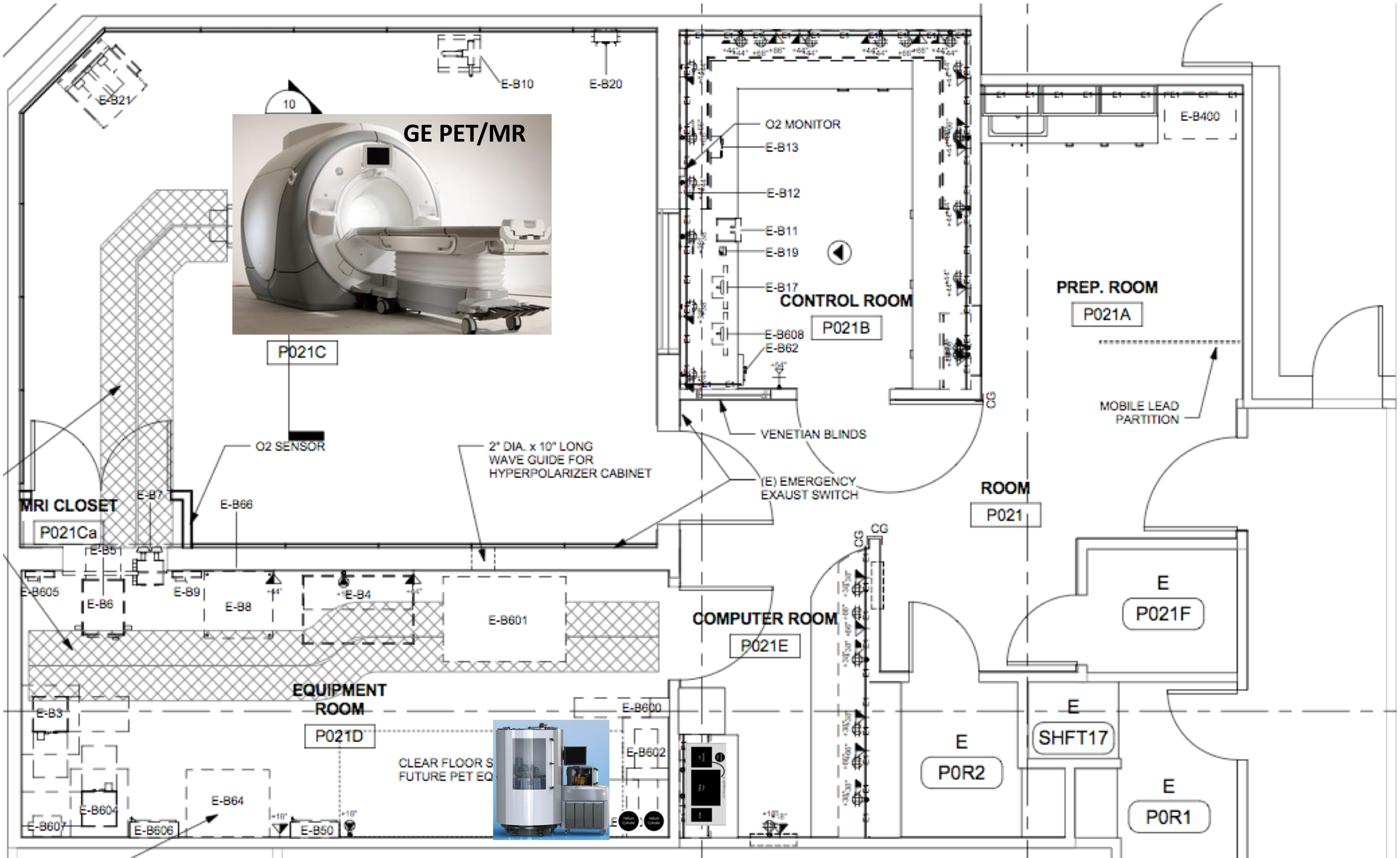


Rat



Shang, et al., "Handheld Electromagnet Carrier for Transfer of Hyperpolarized Carbon-13 Samples", MRM, early view, 2015

Lucas PET/MR Metabolic Service Center



GE Spinlab

PET/MR + Hyperpolarized MRS

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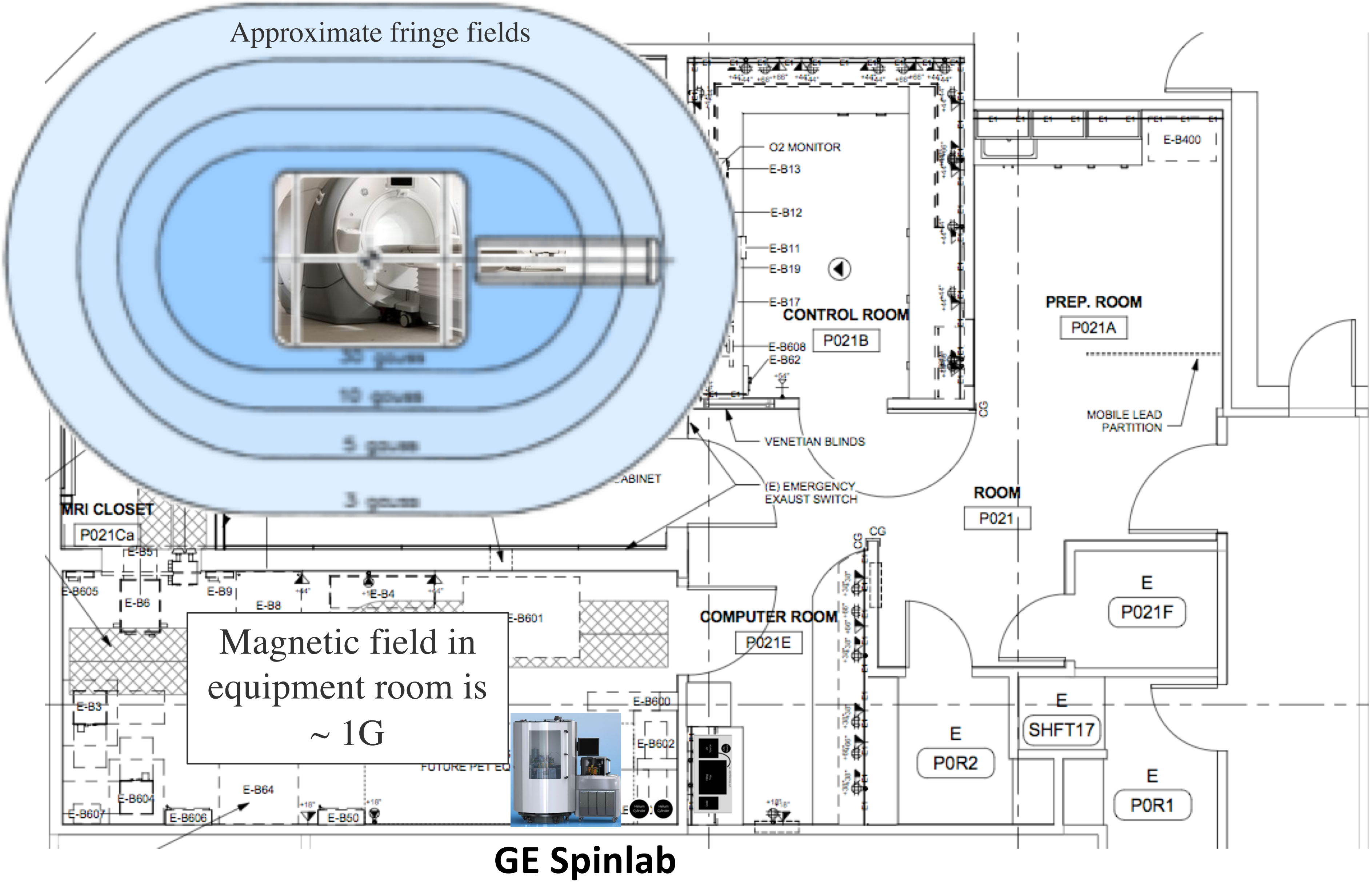

PET/MR + Hyperpolarized MRS

Ex 2: Hyperpolarized [1,2-^{13}C]Pyr

Research article

NMR IN BIOMEDICINE

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(wileyonlinelibrary.com) DOI: 10.1002/nbm.2942

A calibration-based approach to real-time *in vivo* monitoring of pyruvate C_1 and C_2 polarization using the J_{CC} spectral asymmetry

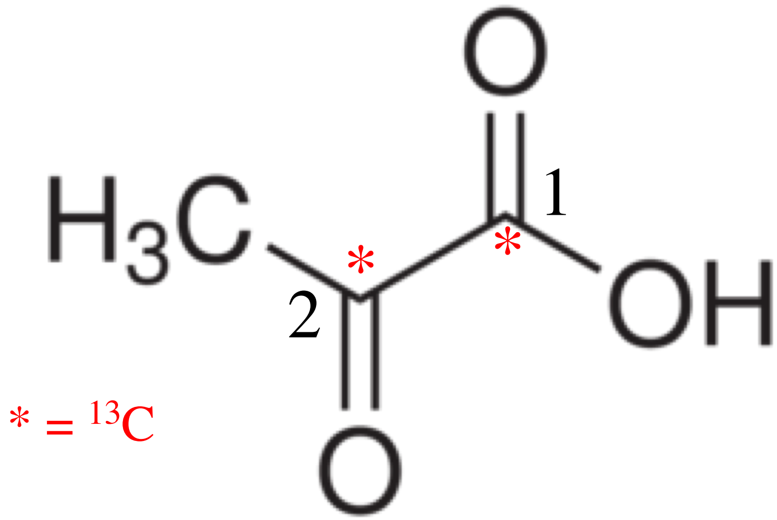
Justin Y. C. Lau[a,b], Albert P. Chen[c], Yi-Ping Gu[b] and Charles H. Cunningham[a,b]*

A calibration-based technique for real-time measurement of pyruvate polarization by partial integral analysis of the doublet from the neighbouring *J*-coupled carbon is presented. *In vitro* calibration data relating the C_2 and C_1 asymmetries to the instantaneous C_1 and C_2 polarizations, respectively, were acquired in blood. The feasibility of using the *in vitro* calibration data to determine the instantaneous *in vivo* C_1 and C_2 polarizations was demonstrated in the analysis of rat kidney and pig heart spectral data. An approach for incorporating this technique into *in vivo* protocols is proposed.

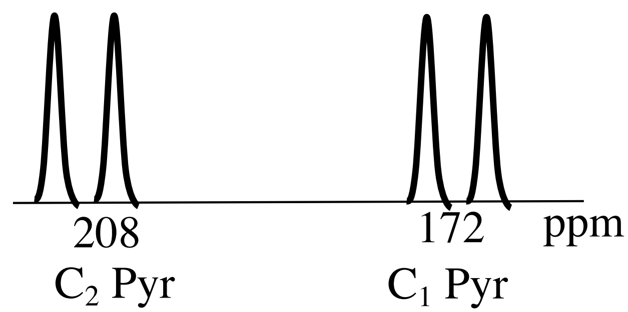
Keywords: hyperpolarized; pyruvate; DNP; carbon-13; polarization measurement; asymmetry

[1-^{13}C]Pyruvate

- 1% of [1-^{13}C]Pyr is actually doubly labeled [1,2-^{13}C]Pyr due to the natural abundance of ^{13}C.

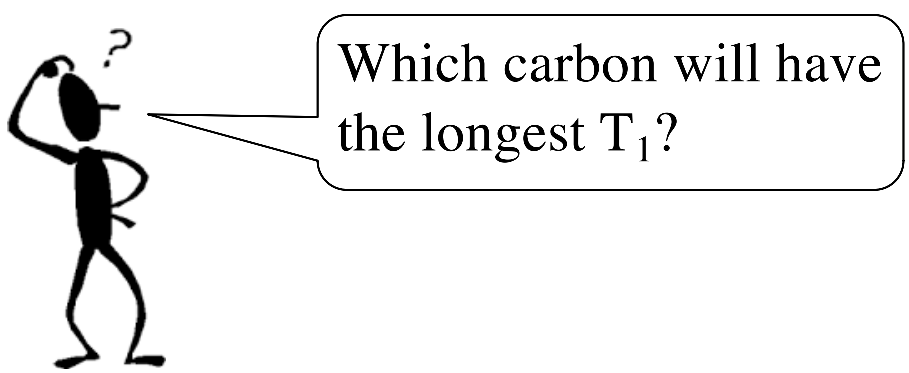


^{13}C MRS spectrum



- Carbon-carbon J-coupling of [1,2-^{13}C]Pyr leads to doublet resonances

- At standard temperatures, doublets are symmetric

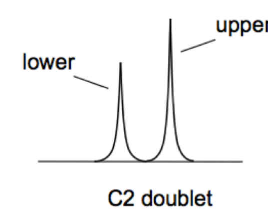


Doublet Asymmetry

- Hamiltonian: $\hat{H}_0 = -\omega_I \hat{I}_z - \omega_s \hat{S}_z + 2\pi J\left(\hat{\vec{I}} \cdot \hat{\vec{S}}\right)$
- Spin density operator: $\hat{\sigma}_0 \approx \frac{1}{4}\hat{E} + \frac{1}{2}P_C \hat{I}_z + \frac{1}{2}P_C \hat{S}_z + \frac{1}{2}P_C^2 2\hat{I}_z \hat{S}_z$ $\quad P_C$ = carbon polarization

- Consider an experiment where the initial carbon polarization is P_c and the flip angle for the C_1- and C_2-carbons of [1,2-^{13}C]Pyr is ϕ.

- The C_2 doublet (as well as the C_1 doublet) is asymmetric primarily due to the $2\hat{I}_z \hat{S}_z$ term generating an anti-phase signal (with a minor contribution from residual strong coupling effects).



- Defining an asymmetry parameter a_c = (upper peak – lower peak)/(upper peak + lower peak), one can show that at t = 0, a_c is given by:

$$a_C(0) \approx \; P_C \cos\phi + \sin\theta$$

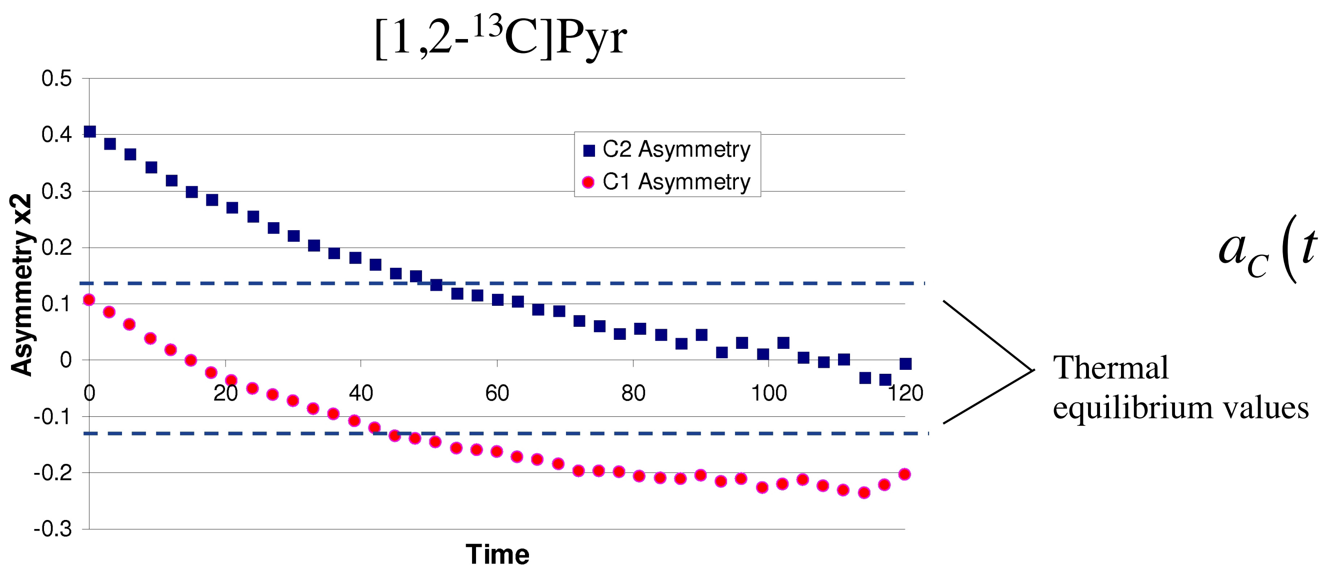
Residual strong coupling parameter = 0.056 for [1,2-^{13}C]Pyr at 3 T.

Doublet Asymmetry

- Given that P_c decays with the T_1 of C_2 pyruvate peak (~50 s in vitro at 3T), one would expect ac to exponentially decay with time constant T1 towards a thermal equilibrium value of 0.056.

$$a_C(0) \approx P_C \cos\phi + \sin\theta \Rightarrow a_C(t) \approx P_C e^{-t/T_1} \cos\phi + \sin\theta ?$$

- However, we observe something quite different!

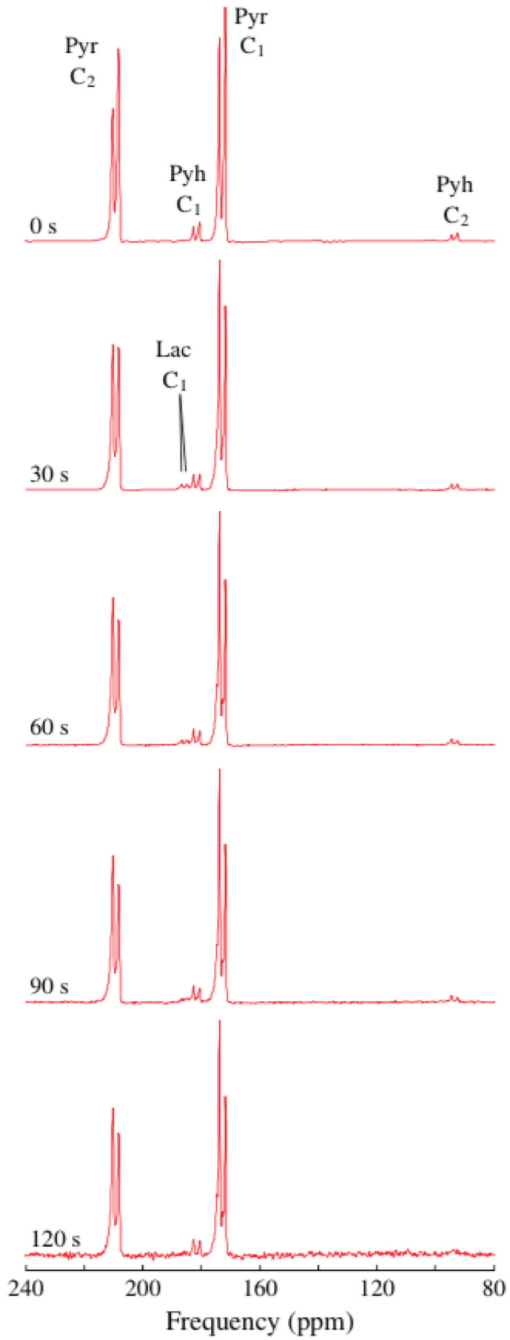


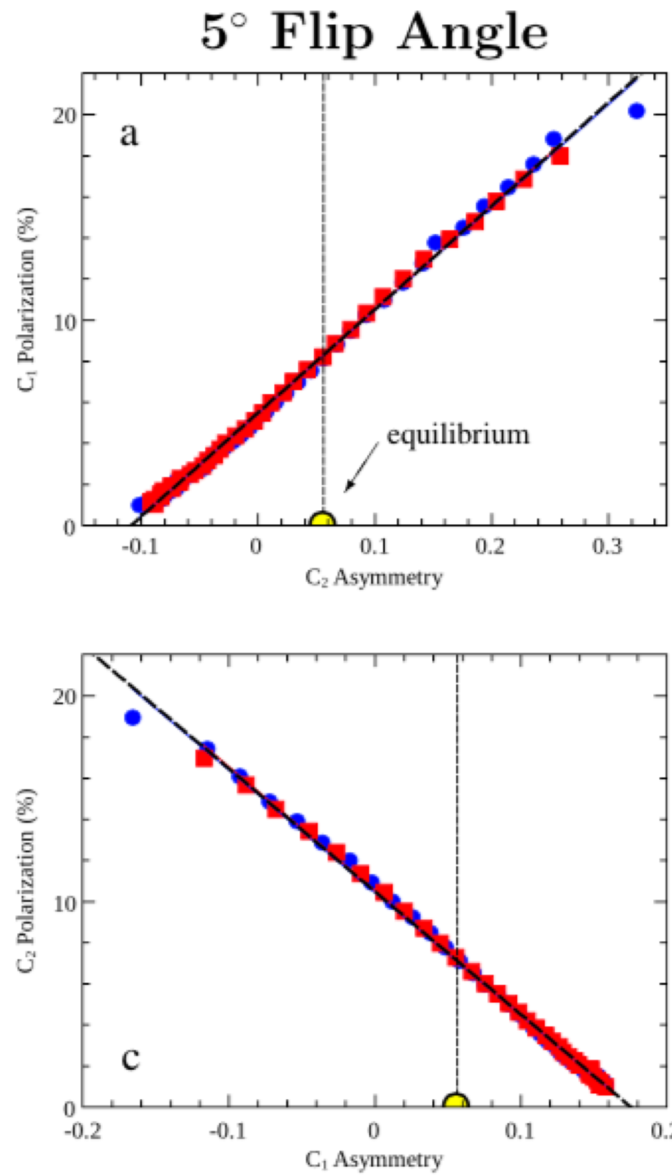
$$a_C(t) \neq P_C e^{-t/T_1} \cos\phi + \sin\theta$$

Hurd RE, Chen A, et al., Scalar Coupling Patterns In Hyperpolarized Spin Systems: JCC Spectral Pattern In Hyperpolarized 1,2-[13C]-Pyruvate, ENC, 2009.

Hyperpolarized [1,2-^{13}C]Pyr

Lau, et al.:

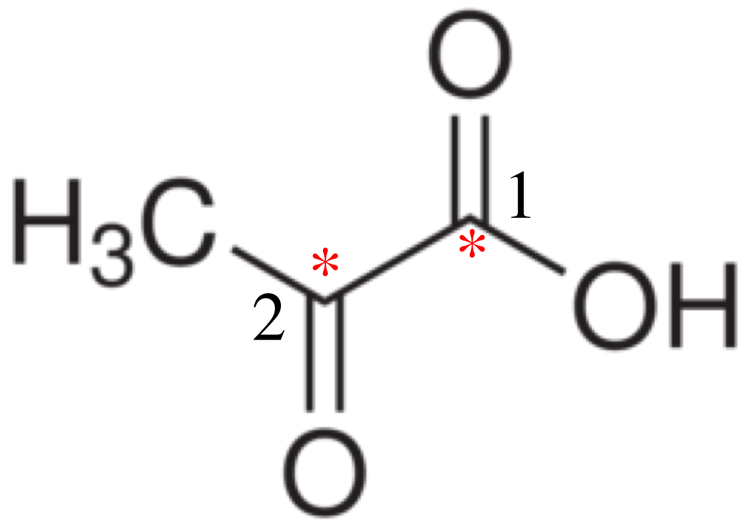




Data doesn't fit proposed analytic model.

$$a_C(t) \neq P_C e^{-t/T_1} \cos\phi + \sin\theta$$

[1,2-^{13}C]Pyruvate



* = ^{13}C

- If we write $a_C(t)$ in terms of the coherences, we get…

$$a_{C_2}(t) = \frac{\overline{\left\langle 2\hat{I}_z\hat{S}_z \right\rangle}(t)}{\overline{\left\langle \hat{S}_z \right\rangle}(t)}\cos\phi + \frac{1}{2}\frac{\left(\overline{\left\langle \hat{I}_z \right\rangle}(t) + \overline{\left\langle \hat{S}_z \right\rangle}(t)\right)}{\overline{\left\langle \hat{S}_z \right\rangle}(t)}\sin\theta.$$

- What are the possible relaxation mechanisms?

Time Evolution of Doublet Asymmetry

- Relaxation mechanisms to consider:
  1. C_1-C_2 dipolar
  2. C_1-H, C_2-H dipolar
  3. CSA of C_1 and C_2
  4. Combination of all of the above

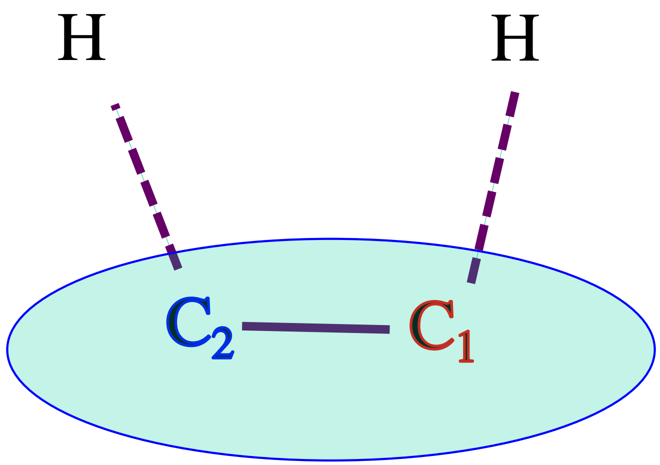
- In general…

$$\frac{d}{dt}\begin{bmatrix} \overline{\langle \hat{I}_z \rangle}(t) \\ \overline{\langle \hat{S}_z \rangle}(t) \\ \overline{\langle 2\hat{I}_z\hat{S}_z \rangle}(t) \end{bmatrix} = -\underbrace{\begin{bmatrix} R_{11} & R_{12} & R_{13} \\ R_{21} & R_{22} & R_{23} \\ R_{31} & R_{32} & R_{33} \end{bmatrix}}_{\text{RELAXATION MATRIX}} \begin{bmatrix} \overline{\langle \hat{I}_z \rangle}(t) - I_z^{eq} \\ \overline{\langle \hat{S}_z \rangle}(t) - S_z^{eq} \\ \overline{\langle 2\hat{I}_z\hat{S}_z \rangle}(t) - 2I_zS_z^{eq} \end{bmatrix}$$

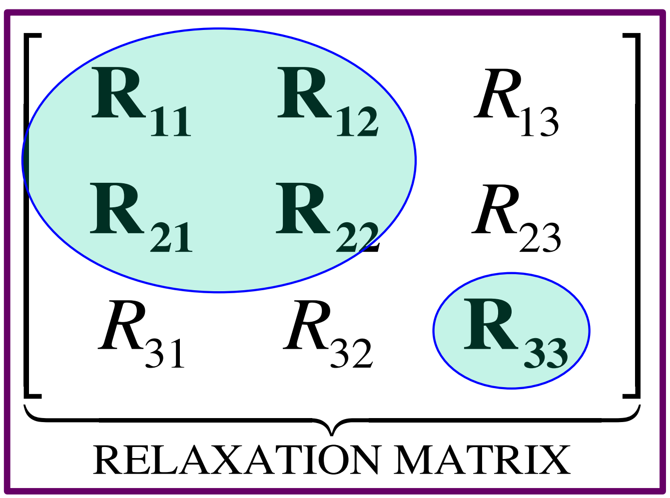
- Let's use Redfield relaxation theory to find analytic expressions for the R_{ij}s.

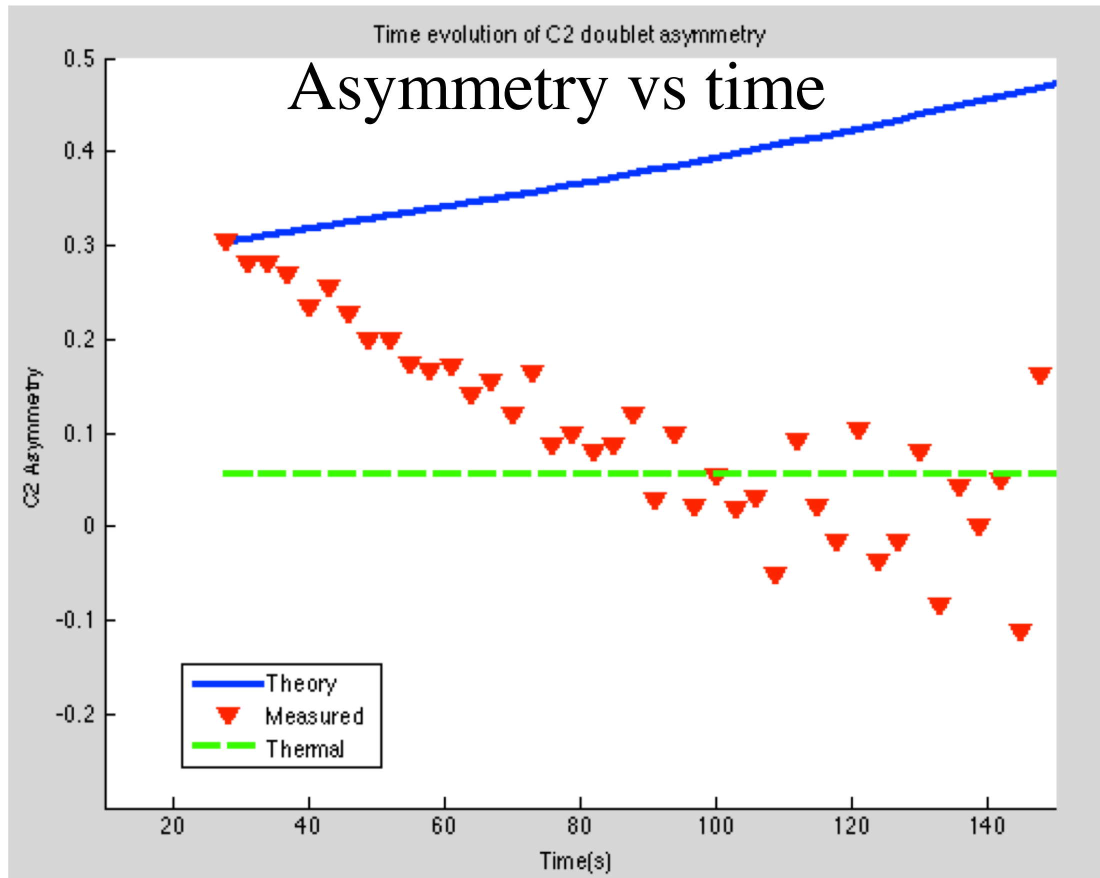
Note we'll use literature values for any unknown parameters such as τ_C=3ps,
r=1.1Å, $T_{1,DDCH}$=70s, $T_{1,CSA}$=200s.

C_1-C_2 Dipolar Coupling

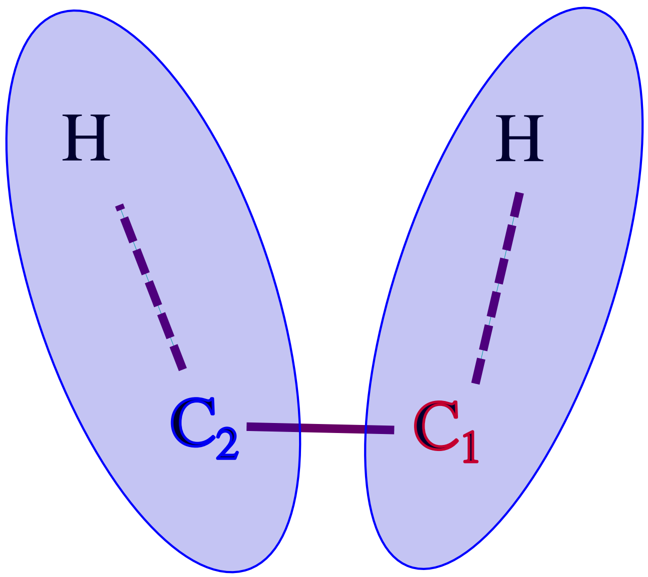


- Not a dominant source of relaxation
- Experimental T_1 values of C_1 in [1,2-^{13}C]Pyr similar to [1-^{13}C]Pyr

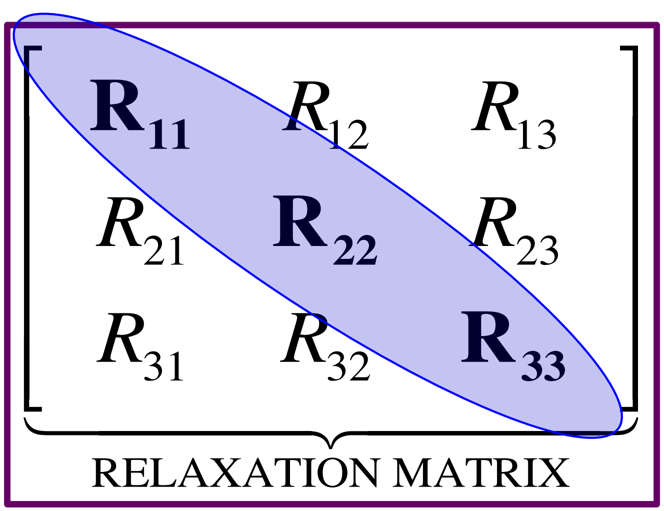


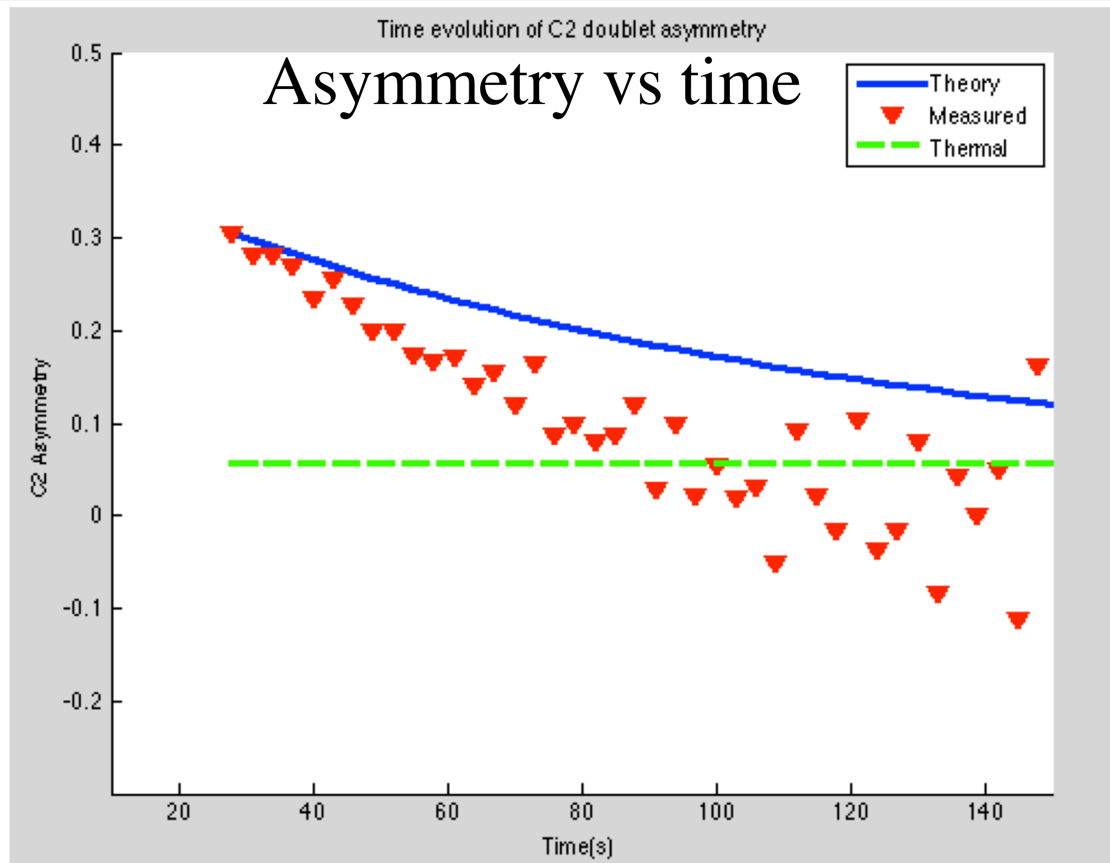


add C-H Dipolar Coupling

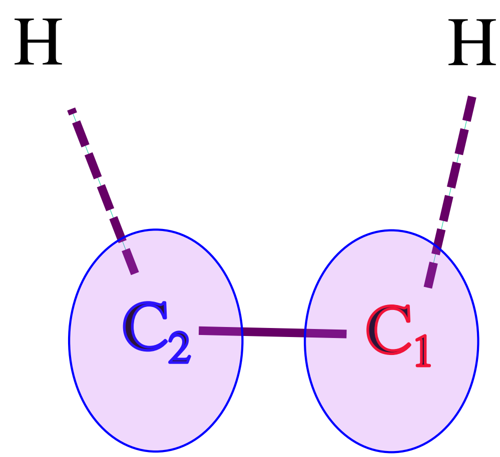


- A major source of relaxation for Pyr
- ^1H is a stronger magnet than ^{13}C
- $2I_zS_z$ coherence decays at twice the rate of I_z, S_z coherences
- No field dependence for small molecules

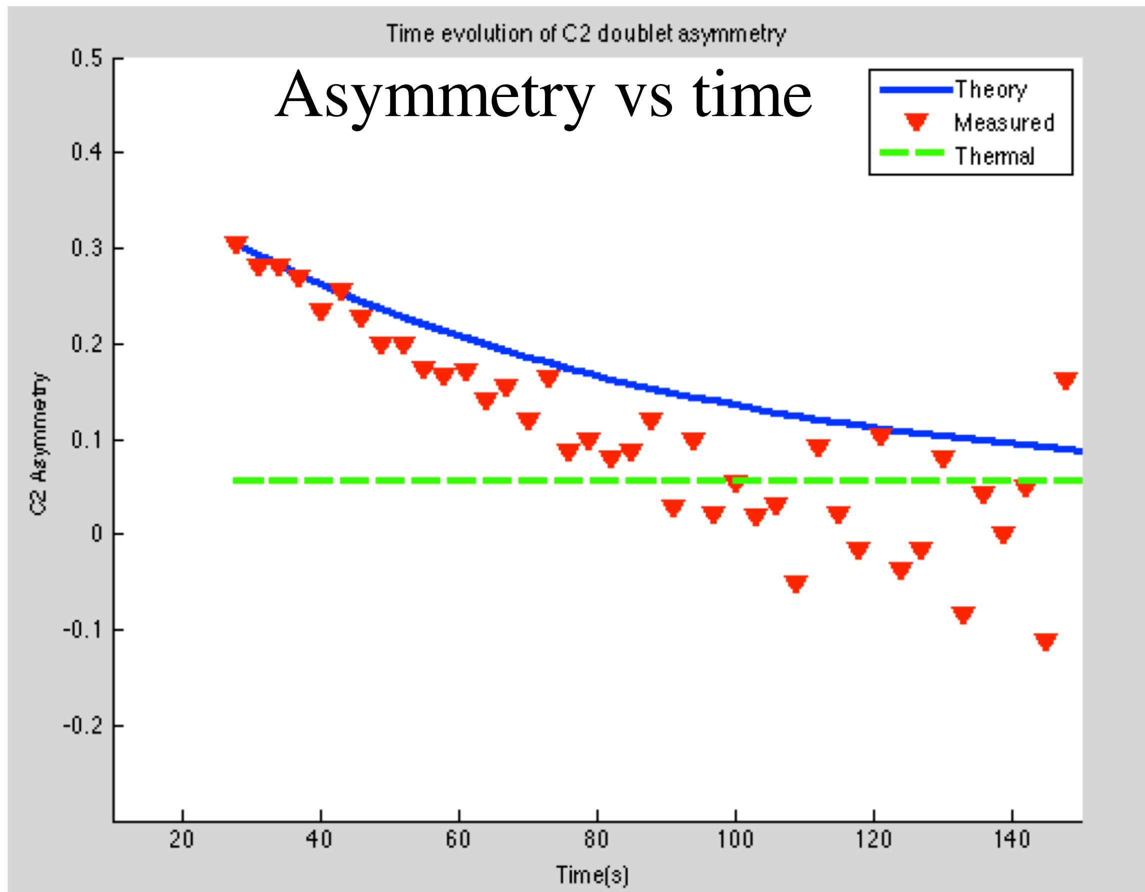




add Chemical Shift Anisotropy



- A moderate effect at 3T
- Effect is field dependent: $C_{1,2}$ T_1 values of [1,2-^{13}C]Pyr both decrease with ⇧B_0



$$\begin{bmatrix} \mathbf{R_{11}} & R_{12} & R_{13} \\ R_{21} & \mathbf{R_{22}} & R_{23} \\ R_{31} & R_{32} & \mathbf{R_{33}} \end{bmatrix}$$

RELAXATION MATRIX

Interference Effects

- When we consider the various relaxation mechanisms occurring simultaneously, some new terms can emerge…
- Consider the case of X = protons dipolar coupled to C_1 and Y=protons dipolar coupled to C_2

$$\hat{H}_{D_{IX}} = -\frac{\gamma_C \gamma_H \hbar}{r_{IX}^3} \sum_{q=-2}^{2} F_q \hat{A}_q \qquad \hat{H}_{D_{SY}} = -\frac{\gamma_C \gamma_H \hbar}{r_{SY}^3} \sum_{q=-2}^{2} F_q \hat{B}_q$$

$$\hat{A}_0 = \sqrt{\tfrac{1}{6}}\left(2\hat{I}_z \hat{X}_z - \tfrac{1}{2}\hat{I}_+ \hat{X}_- - \tfrac{1}{2}\hat{I}_- \hat{X}_+\right) \quad \hat{B}_0 = \sqrt{\tfrac{1}{6}}\left(2\hat{S}_z \hat{Y}_z - \tfrac{1}{2}\hat{S}_+ \hat{Y}_- - \tfrac{1}{2}\hat{S}_- \hat{Y}_+\right) \quad F_0 = \sqrt{\tfrac{3}{2}}\left(3\cos^2\theta - 1\right)$$

$$\hat{A}_{\pm 1} = \tfrac{1}{2}\left(\hat{I}_\pm \hat{X}_z + \hat{I}_z \hat{X}_\pm\right) \quad \hat{B}_{\pm 1} = \tfrac{1}{2}\left(\hat{S}_\pm \hat{Y}_z + \hat{S}_z \hat{Y}_\pm\right) \quad F_{\pm 1} = \pm 3 \sin\theta \cos\theta e^{\mp i\phi}$$

$$\hat{A}_{\pm 2} = \tfrac{1}{2}\hat{I}_\pm \hat{X}_\pm \quad \hat{B}_{\pm 2} = \tfrac{1}{2}\hat{S}_\pm \hat{Y}_\pm \quad F_{\pm 2} = \pm \tfrac{3}{2}\sin^2\theta e^{\mp 2i\phi}$$

then $\hat{\hat{\Gamma}} = \sum_q J_q(\omega_q)\left(\hat{\hat{A}}_{-q} + \hat{\hat{B}}_{-q}\right)\left(\hat{\hat{A}}_q + \hat{\hat{B}}_q\right)$, but $\left[\hat{A}_q, \hat{B}_q\right] = 0 \quad \forall q$ hence

$$\hat{\hat{\Gamma}} = \hat{\hat{\Gamma}}_A + \hat{\hat{\Gamma}}_B = \sum_q J_q(\omega_q)\hat{\hat{A}}_{-q}\hat{\hat{A}}_q + \sum_q J_q(\omega_q)\hat{\hat{B}}_{-q}\hat{\hat{B}}_q$$

and we can just independently sum the resulting relaxation rates.

Interference Effects

- But what about CSA and C_1-C_2 dipolar coupling?

$$\hat{H}_{D_{IS}} = -\frac{\gamma_C^2 \hbar}{r_{IS}^3} \sum_{q=2}^{2} F_q \hat{A}_q \qquad \hat{H}_{CSA1} = \gamma_C B_0 \Delta\sigma \sum_{q=-1}^{1} F_q \hat{B}_q \qquad \hat{H}_{CSA2} = \gamma_C B_0 \Delta\sigma \sum_{q=-1}^{1} F_q \hat{C}_q$$

$$\hat{A}_0 = \sqrt{\tfrac{1}{6}}\left(2\hat{I}_z\hat{S}_z - \tfrac{1}{2}\hat{I}_+\hat{S}_- - \tfrac{1}{2}\hat{I}_-\hat{S}_+\right) \qquad \hat{B}_0 = \tfrac{1}{3}\sqrt{\tfrac{3}{2}}\hat{I}_z \qquad \hat{C}_0 = \tfrac{1}{3}\sqrt{\tfrac{3}{2}}\hat{S}_z$$

$$\hat{A}_{\pm 1} = \tfrac{1}{2}\left(\hat{I}_\pm\hat{S}_z + \hat{I}_z\hat{S}_\pm\right) \qquad \hat{B}_{\pm 1} = \tfrac{1}{6}\hat{I}_\pm \qquad \hat{C}_{\pm 1} = \tfrac{1}{6}\hat{S}_\pm$$

$$\hat{A}_{\pm 2} = \tfrac{1}{2}\hat{I}_\pm\hat{S}_\pm$$

$$F_0 = \sqrt{\tfrac{3}{2}}\left(3\cos^2\theta - 1\right) \qquad F_{\pm 1} = \pm 3\sin\theta\cos\theta e^{\mp i\phi} \qquad F_{\pm 2} = \pm\tfrac{3}{2}\sin^2\theta e^{\mp 2i\phi}$$

In this case $\hat{A}_q, \hat{B}_q$, and $\hat{C}_q$ don't all commute. $\hat{\hat{\Gamma}} = \sum_q J(\omega_q)\left(\hat{\hat{A}}_{-q} + \hat{\hat{B}}_{-q} + \hat{\hat{C}}_{-q}\right)\left(\hat{\hat{A}}_q + \hat{\hat{B}}_q + \hat{\hat{C}}_q\right)$

and we get new cross relaxation terms such as:

$$R_{13} = R_{31} = \langle \hat{I}_z | \hat{\hat{\Gamma}} | 2\hat{I}_z\hat{S}_z \rangle = \frac{2}{5} q_{CC,CSA_1} J(\omega_C) \equiv \frac{1}{T_{Iz-IzSz-cross}} \qquad q_{CC,CSA_1} = \left(\frac{\mu_0}{4\pi}\right)\frac{\gamma_C^4 \hbar}{r_{CC}^3} B_0 \Delta\sigma_1.$$

$$R_{23} = R_{32} = \langle \hat{S}_z | \hat{\hat{\Gamma}} | 2\hat{I}_z\hat{S}_z \rangle = \frac{2}{5} q_{CC,CSA_2} J(\omega_C) \equiv \frac{1}{T_{Sz-IzSz-cross}} \qquad q_{CC,CSA_2} = \left(\frac{\mu_0}{4\pi}\right)\frac{\gamma_C^4 \hbar}{r_{CC}^3} B_0 \Delta\sigma_2.$$

The complete relaxation matrix

$$\frac{d}{dt}\begin{bmatrix} \overline{\langle \hat{I}_z \rangle}(t) \\ \overline{\langle \hat{S}_z \rangle}(t) \\ \overline{\langle 2\hat{I}_z\hat{S}_z \rangle}(t) \end{bmatrix} = -\underbrace{\begin{bmatrix} R_{11} & R_{12} & R_{13} \\ R_{21} & R_{22} & R_{23} \\ R_{31} & R_{32} & R_{33} \end{bmatrix}}_{\text{RELAXATION MATRIX}} \begin{bmatrix} \overline{\langle \hat{I}_z \rangle}(t) - I_z^{eq} \\ \overline{\langle \hat{S}_z \rangle}(t) - S_z^{eq} \\ \overline{\langle 2\hat{I}_z\hat{S}_z \rangle}(t) \end{bmatrix}$$

- Assuming extreme narrowing…

$$R_{11} = \frac{1}{T_{1,CSA_1}} + \frac{1}{T_{1,HC_1}} + \frac{1}{T_{1,CC}}$$

$$R_{22} = \frac{1}{T_{1,CSA_2}} + \frac{1}{T_{1,HC_2}} + \frac{1}{T_{1,CC}}$$

$$R_{33} \approx \frac{1}{T_{1,CSA_1}} + \frac{1}{T_{1,CSA_2}} + \frac{1}{T_{1,HC_1}} + \frac{1}{T_{1,HC_2}} + \frac{2}{5T_{1,CC}}$$

Direct relaxation

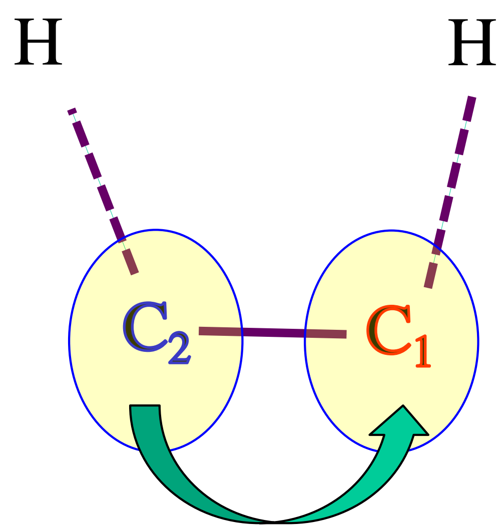
$$R_{12} = R_{21} \approx \frac{1}{2T_{1,CC}}$$

$$R_{13} = R_{31} \approx \sqrt{\frac{6}{5}}\sqrt{\frac{1}{T_{1,CC}T_{1,CSA_1}}}$$

$$R_{23} = R_{32} \approx \sqrt{\frac{6}{5}}\sqrt{\frac{1}{T_{1,CC}T_{1,CSA_2}}}$$

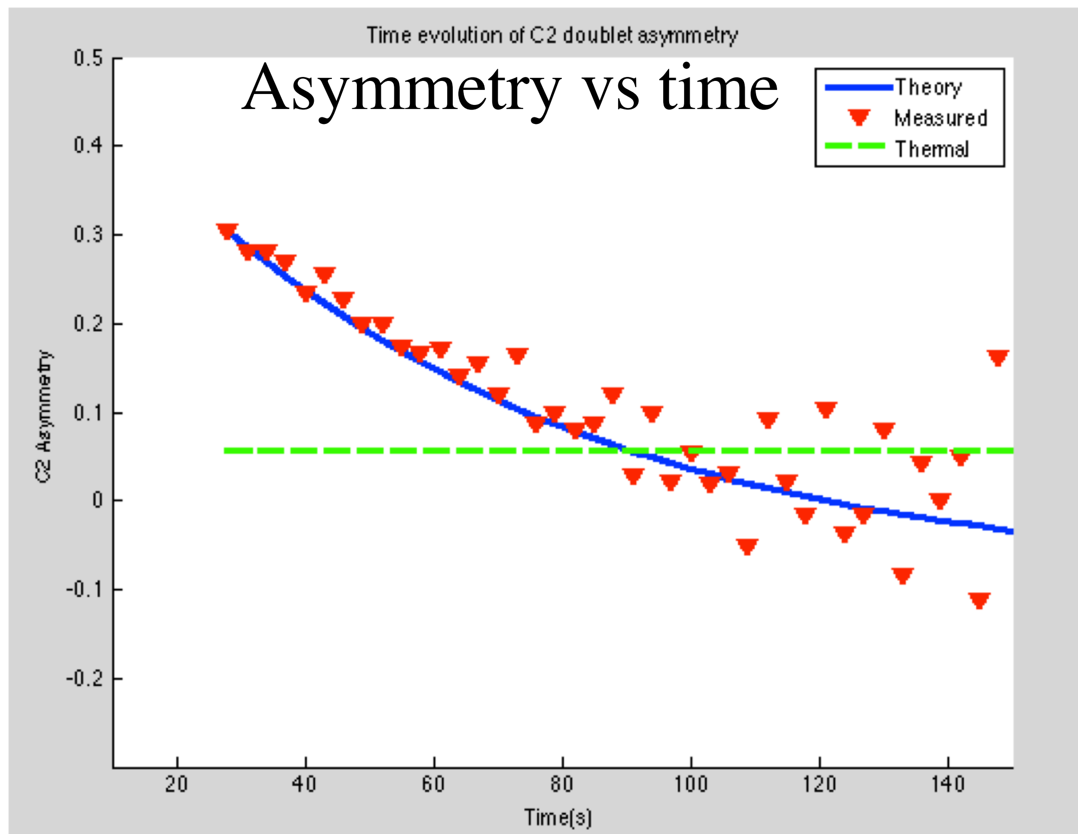
Cross relaxation

add Dipolar/CSA Interference

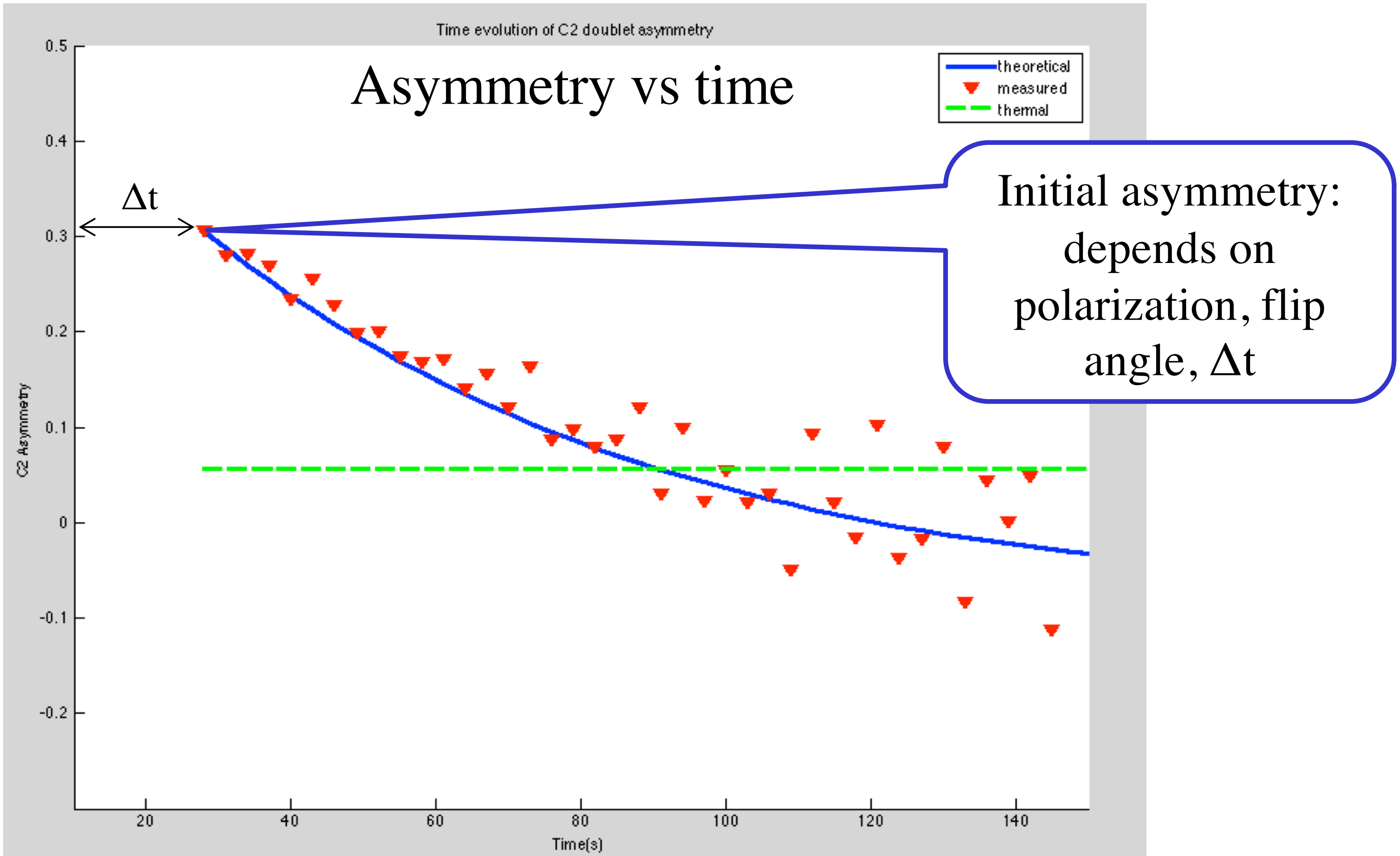


- Despite C-C coupling having a negligible direct effect, cross relaxation (via CSA interference effect) is very important!
- Explains asymmetry beyond equilibrium
- Like CSA, this effect is field dependent.

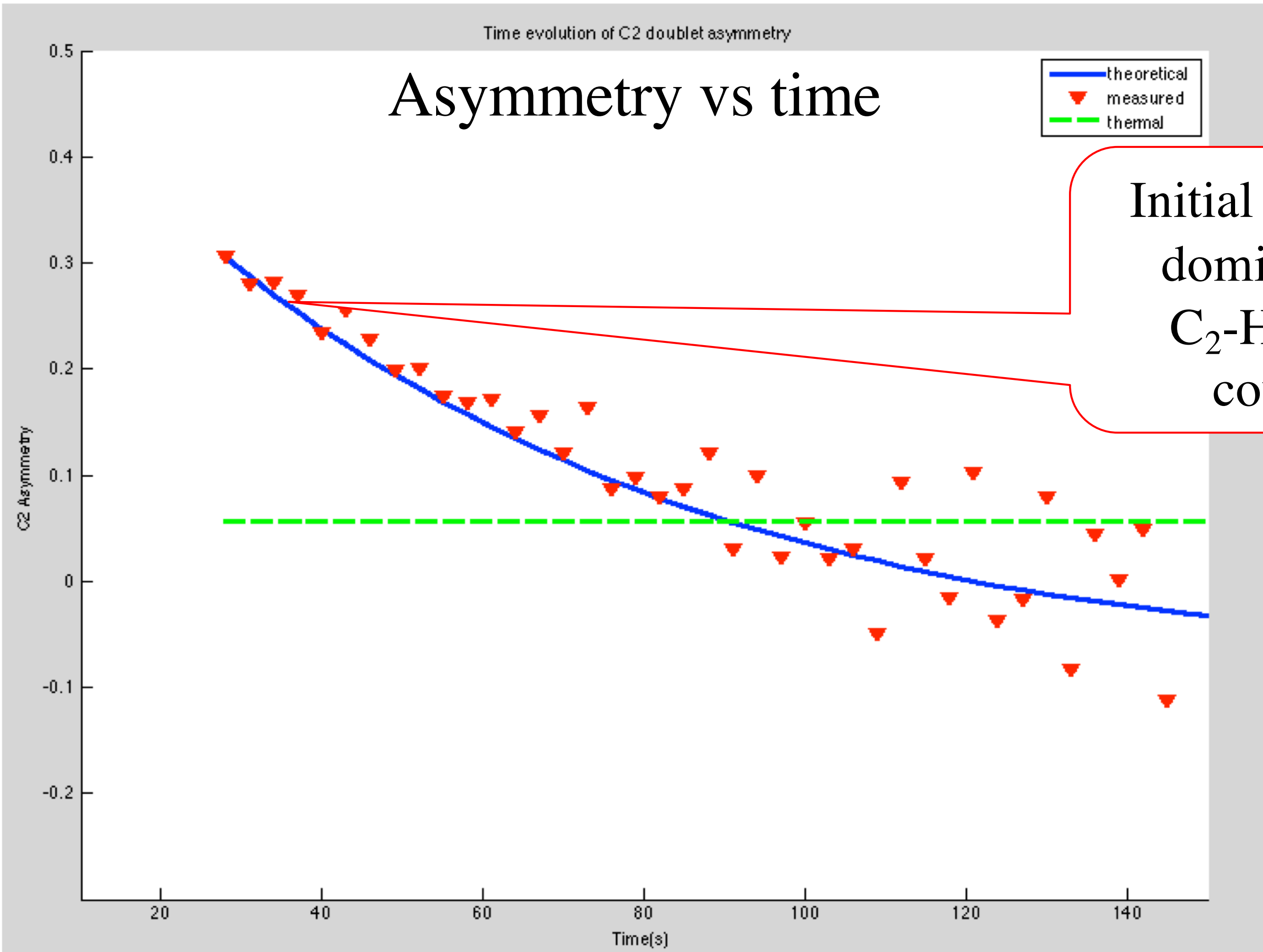
$$\underbrace{\begin{bmatrix} R_{11} & R_{12} & \mathbf{R_{13}} \\ R_{21} & R_{22} & \mathbf{R_{23}} \\ \mathbf{R_{31}} & \mathbf{R_{32}} & R_{33} \end{bmatrix}}_{\text{RELAXATION MATRIX}}$$



Doublet asymmetry verses time

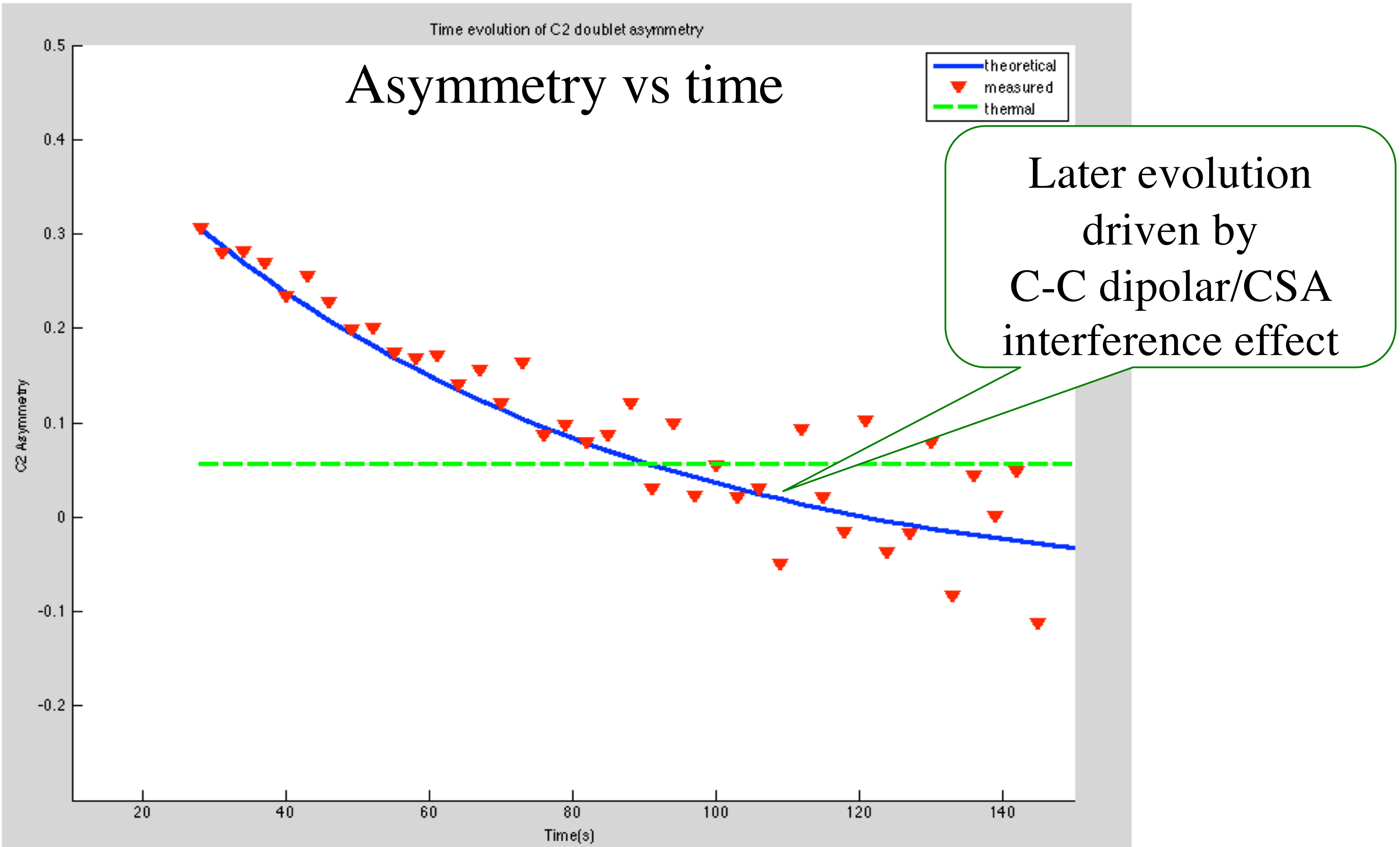


Doublet asymmetry verses time

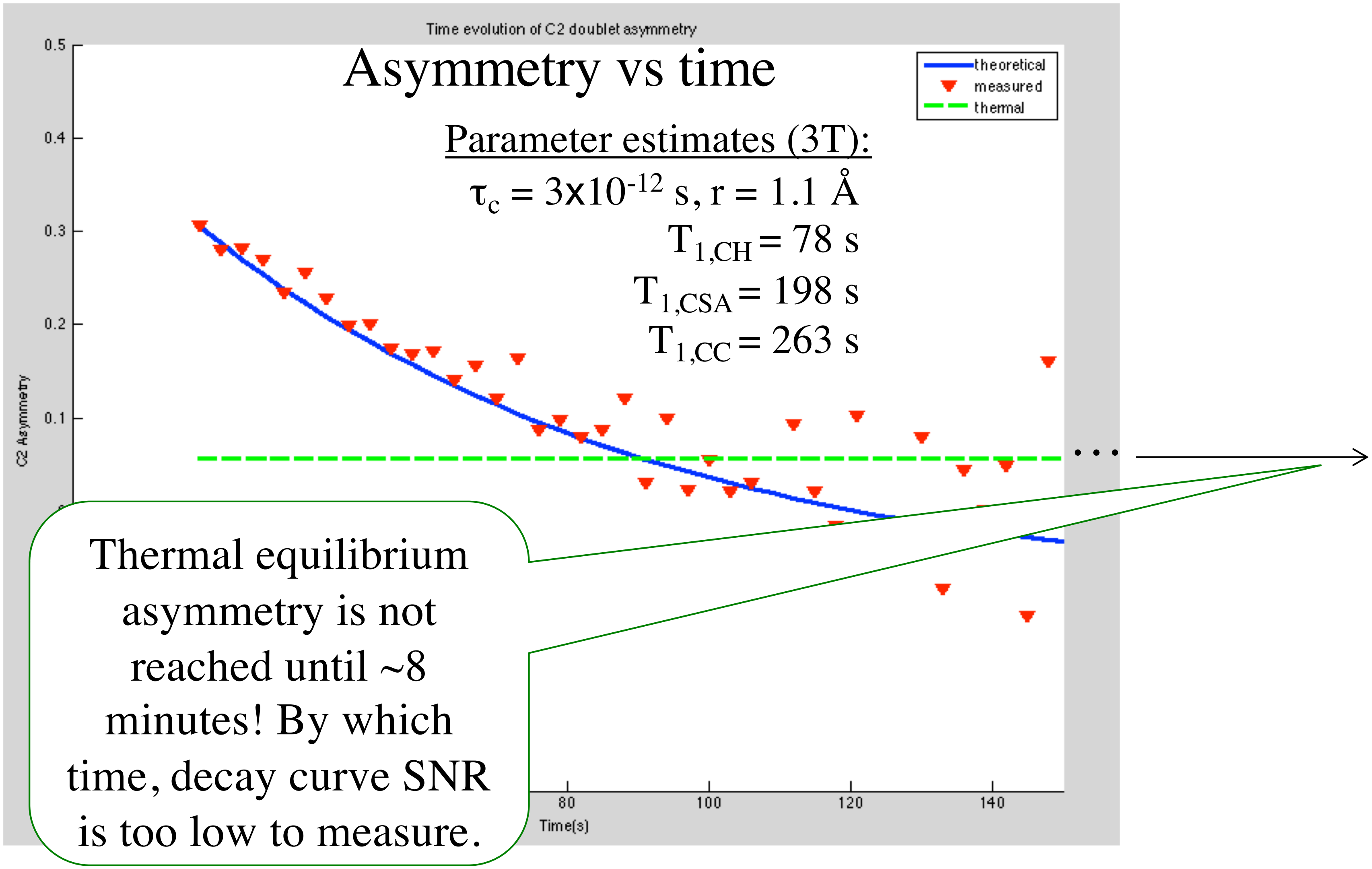


Initial evolution: dominated by C_2-H dipolar coupling

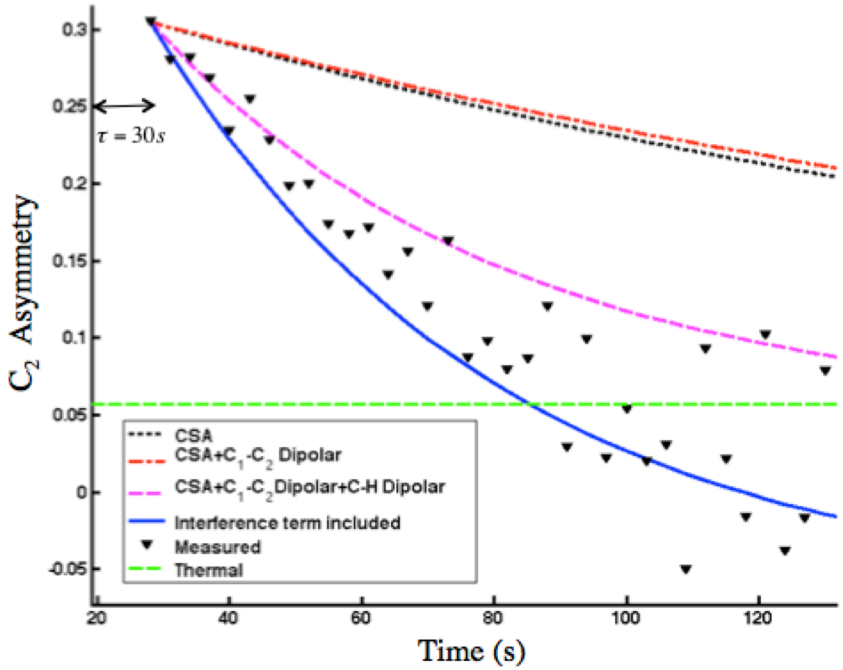
Doublet asymmetry verses time

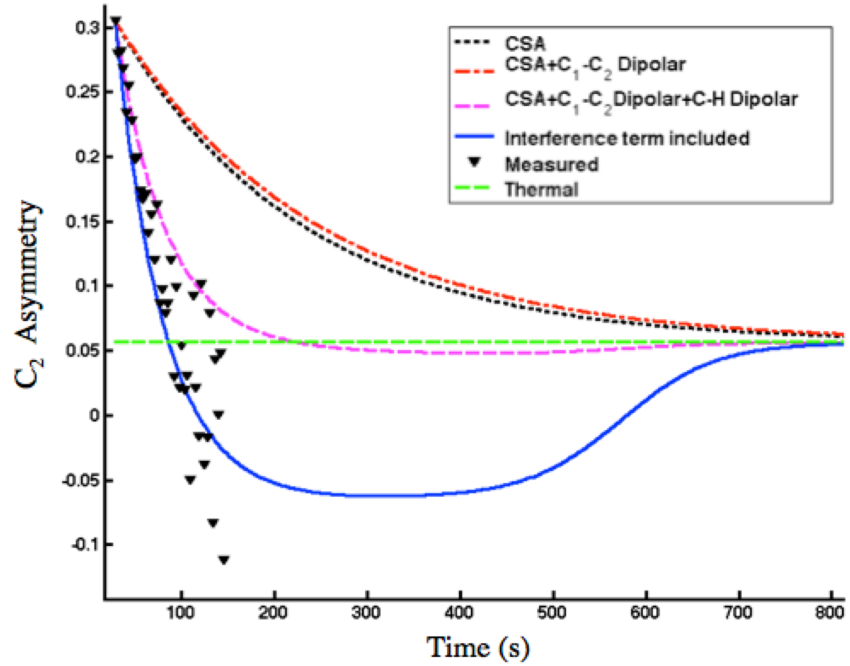


Doublet asymmetry verses time

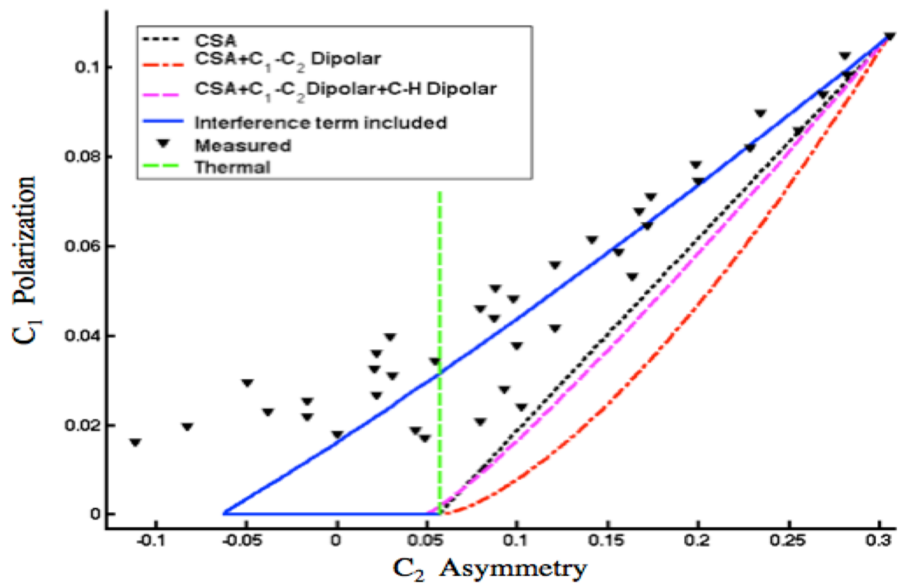


Doublet asymmetry verses time





C_1 polarization vs. C_2 doublet asymmetry



Example 2: Conclusions

- Simple experiment, confusing results.
- Explanation required use of three NMR relaxation mechanisms.
- Asymmetry driven by **three** primary sources.
  - $2I_zS_z$ direct relaxation
  - C-C dipolar coupling/CSA interference effect
  - Residual strong coupling effects
- Use of asymmetry metric to estimate instantaneous polarization requires:
  - Knowledge of initial polarization
  - Time history of the sample in low and high fields

Next Lecture: Spin lattice relaxation in the rotating frame ($T_{1\rho}$)