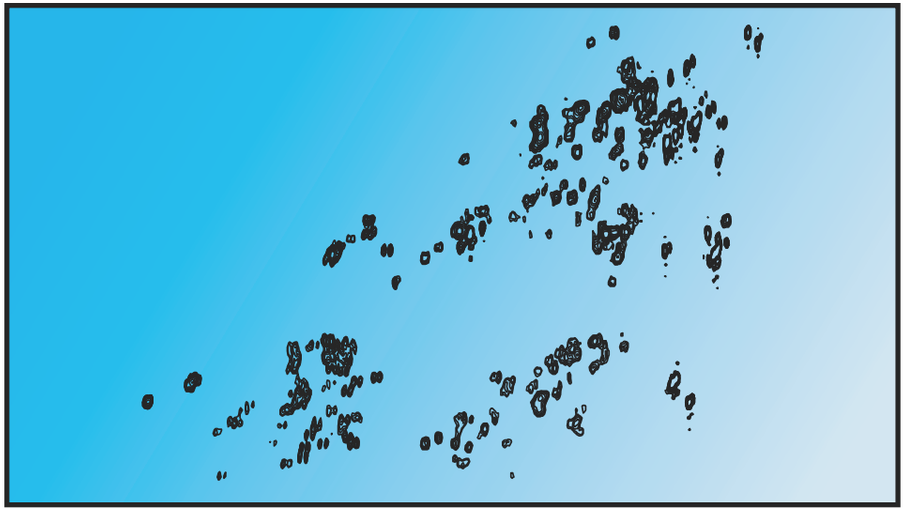
Numerical Methods for Pulse Sequence Optimisation

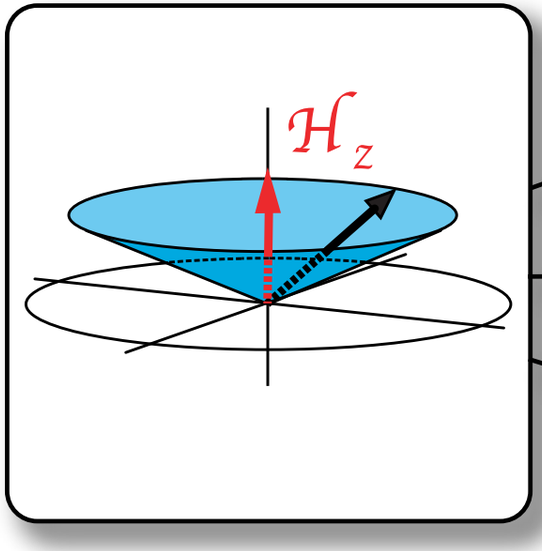


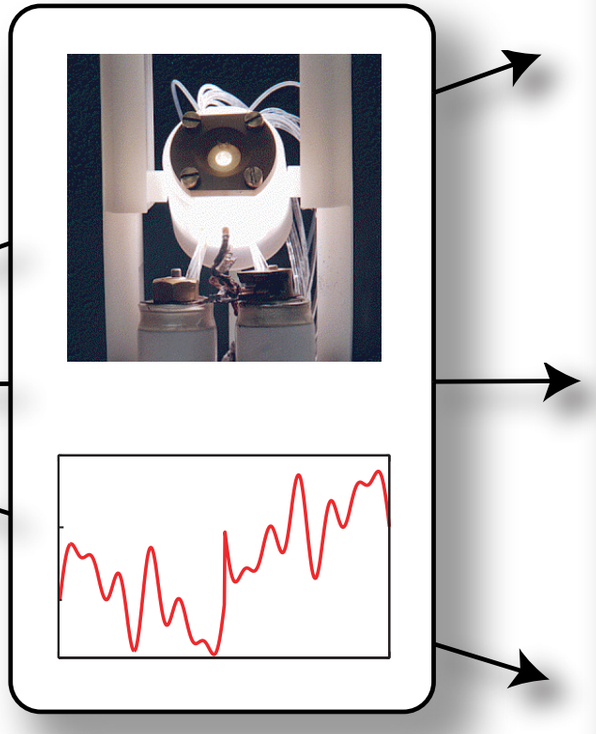
Lyndon Emsley,
Laboratoire de Chimie, Ecole Normale Supérieure de Lyon,
& Institut Universitaire de France

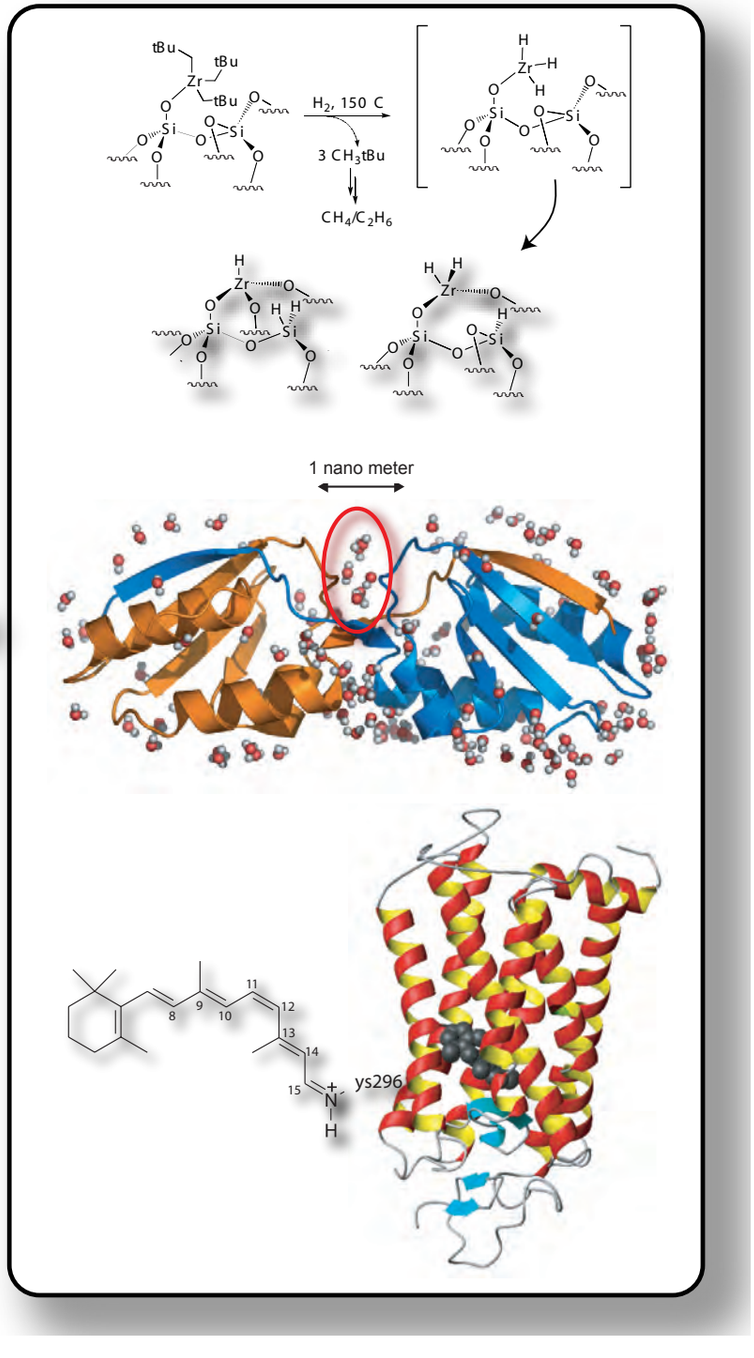
ECOLE NORMALE SUPERIEURE DE LYON

IUF

Dances with Spins: Whispered Messages from the Picometer World







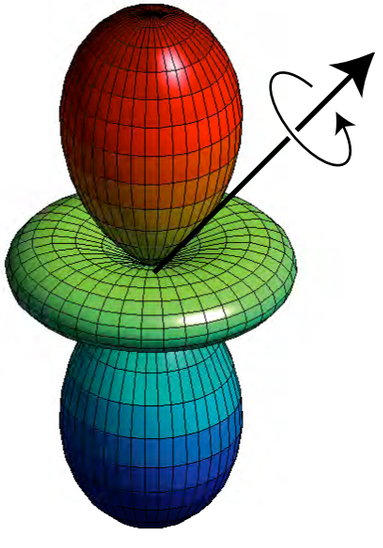
Dances With Spins

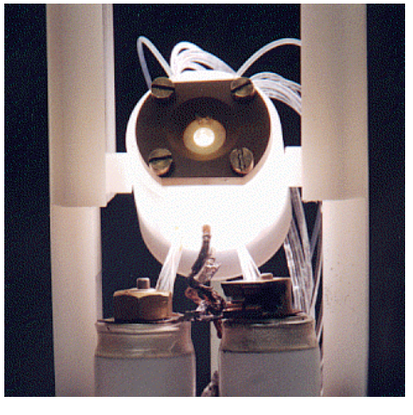
designing effective Hamiltonians

$$\mathcal{H} = \mathcal{H}_z + \mathcal{H}_Q + \mathcal{H}_D + \mathcal{H}_{cs} + \mathcal{H}_J + \mathcal{H}_{ext}$$

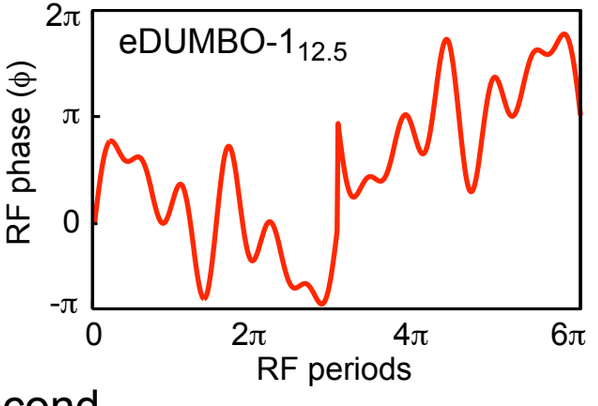
We can ***add rotations*** controlled by the experimentalist. If properly designed these rotations can ***selectively cancel out*** parts of the Hamiltonian.

Rotations in Laboratory Space
(*magic angle spinning*)





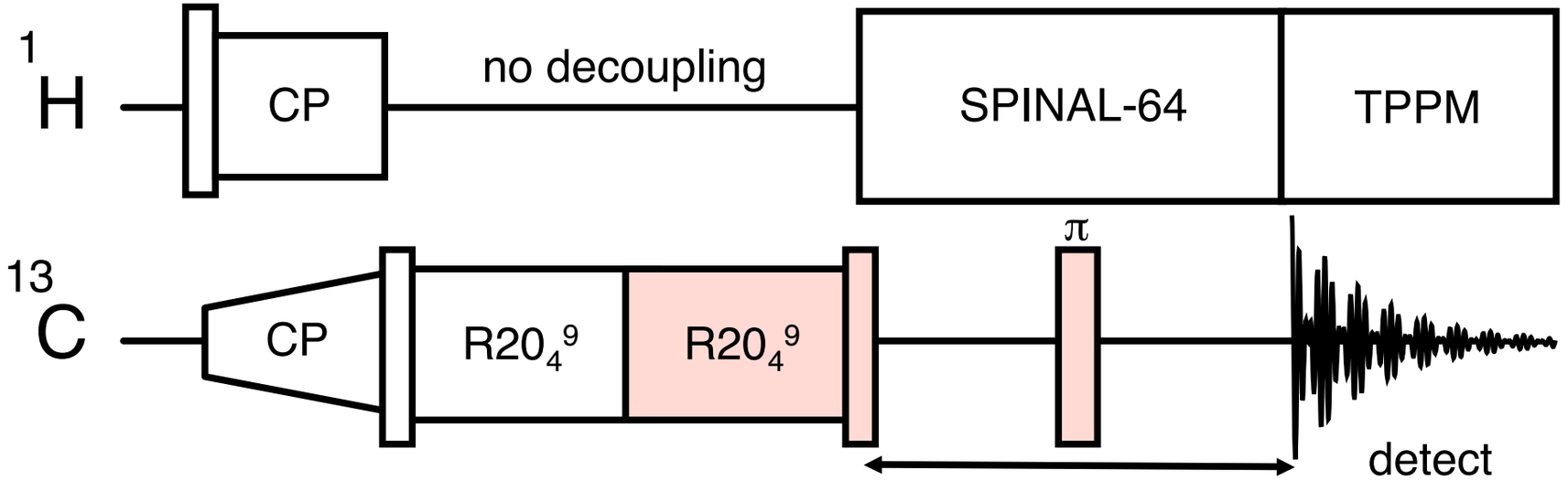
Rotations in Spin Space
(*radiofrequency pulses*)



Spatial rotation: 35 000 rev/second
Spin rotation: 150 000 rev/second

The Dance of the Spins

adapting the effective Hamiltonian to our needs



$\overline{\mathcal{H}} = \mathcal{H}_D$

to select only the pair of spins we are interested in

$\overline{\mathcal{H}} = \mathcal{H}_J$

to measure the J coupling

$\overline{\mathcal{H}} = \mathcal{H}_{CS}$

to detect a resolved spectrum

J. Am. Chem. Soc. **128**, 3878 (2006).

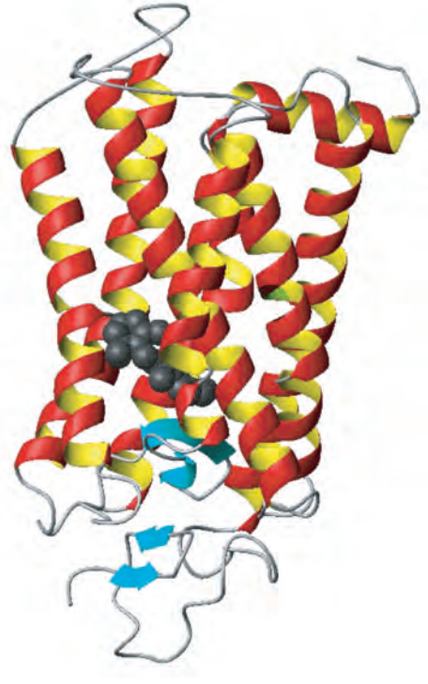
Structure of the Retinylidene Ligand in Rhodopsin

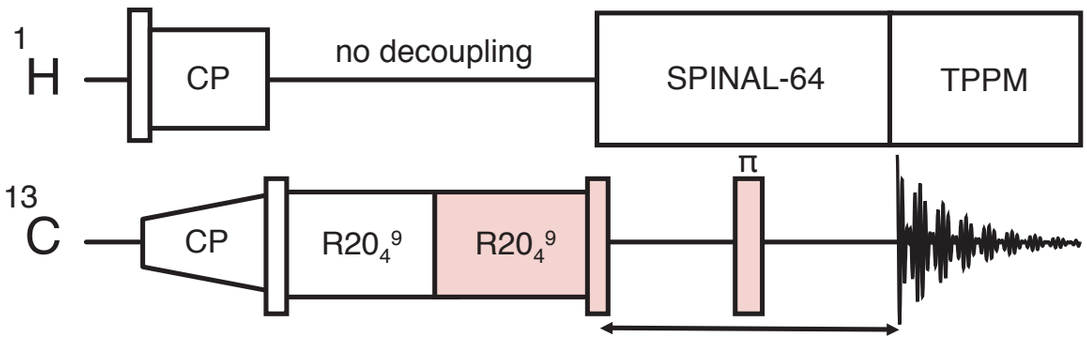
The Whispered Message:

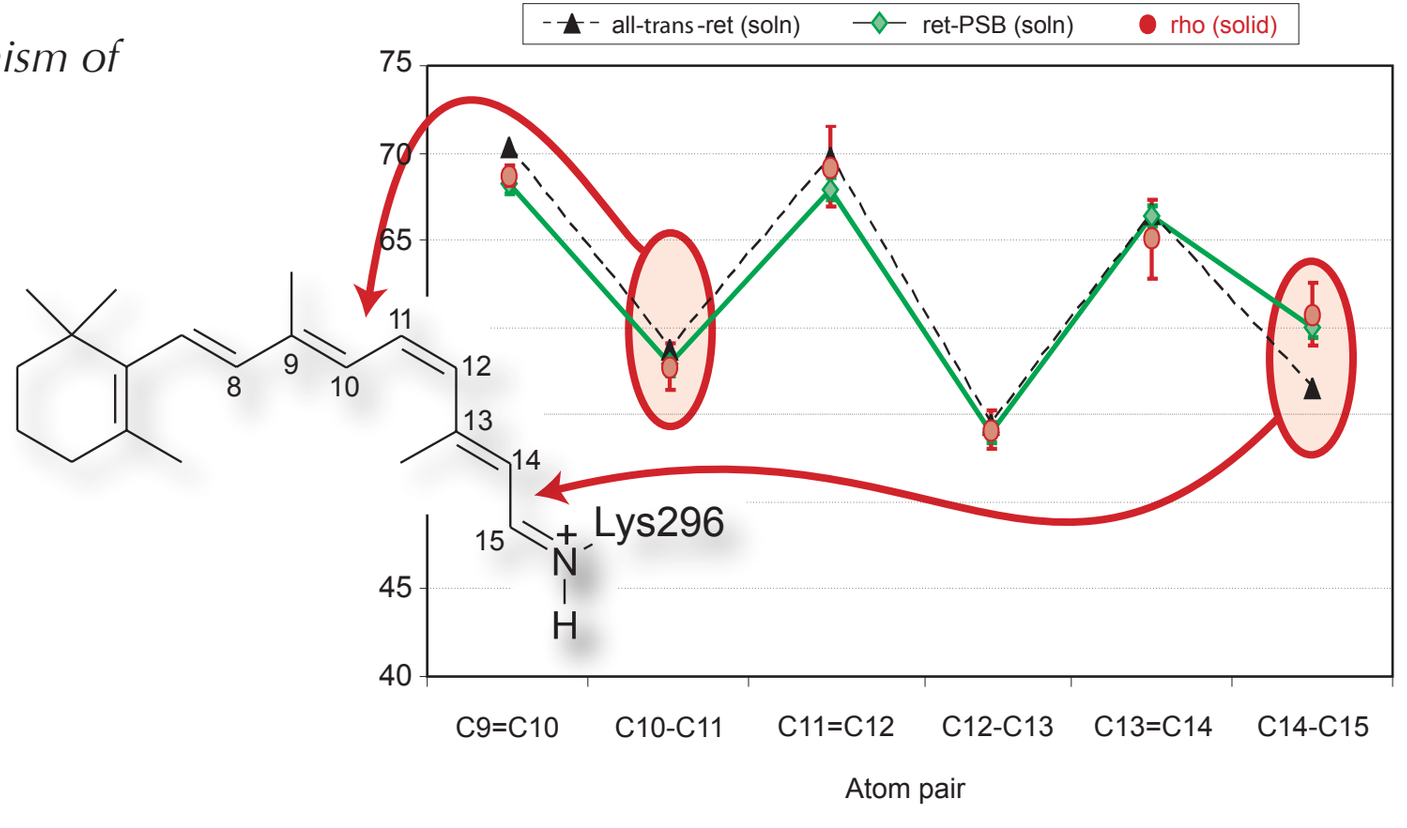
J couplings reveal ***no conjugation defects*** *around the isomerization site.*

They do detect the expected penetration of the PSB positive charge into the retinylidene chain

can be related to the mechanism of photoisomerization?

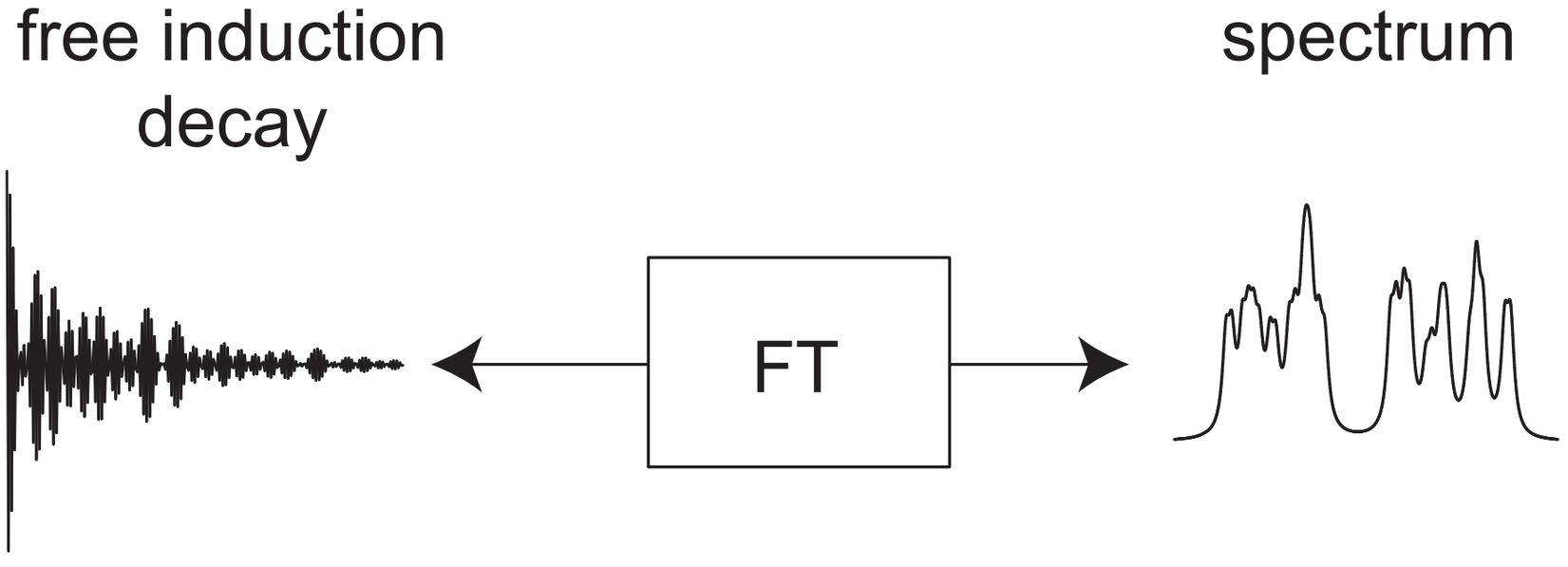






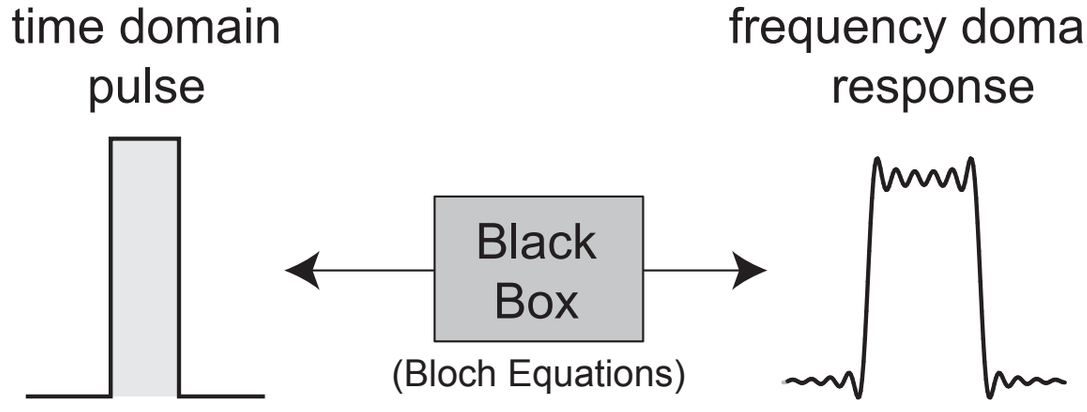
Levitt and coworkers, J. Am. Chem. Soc. **128**, 3878 (2006).

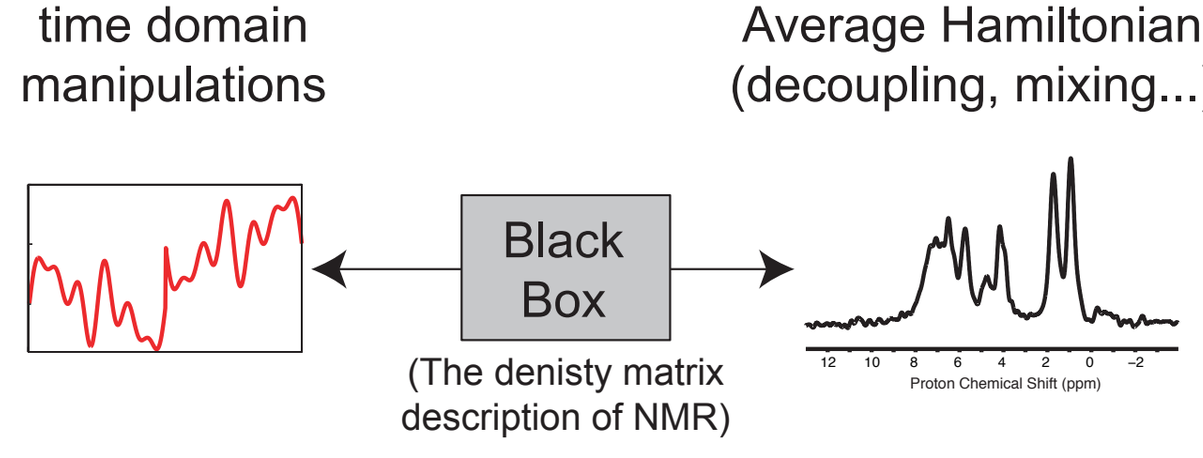
Where is the Problem in the Design of Effective Hamiltonians or Transformations?



Luckily we have an analytical and reversible transform that links the fid with the spectrum...

Where is the Problem in the Design of Effective Hamiltonians or Transformations?





.... more generally there is no analytical solution to the equation relating the pulse sequence to the spin system response. This is the general question of how does a radiofrequency field (light) interact with the nuclear spin system (matter) ?

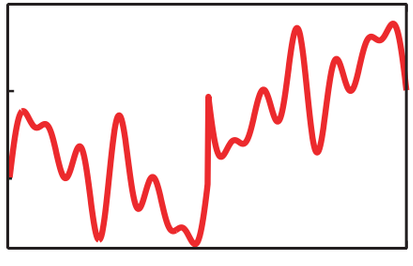
In general the forward transformation has no analytical solution

There are three main strategies for the forward calculation:

1. Find an analytical solution for a simplified case (rare, always difficult)

2. Use approximate methods: Average Hamiltonian Theory, Static Perturbation Theory, Floquet Theory

time domain manipulations



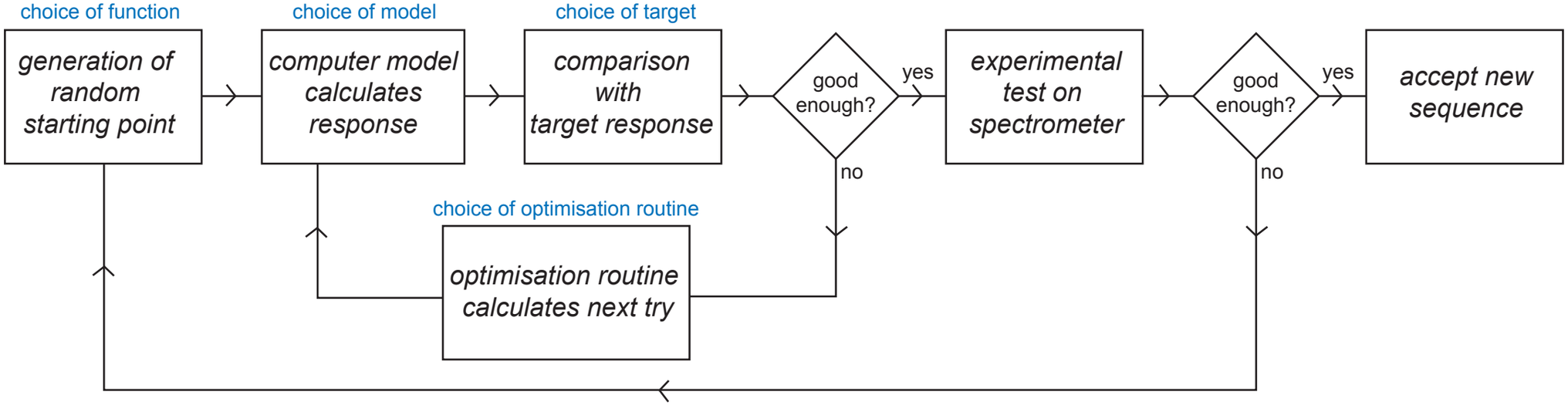
3. Solve the problem numerically

$$\frac{d}{dt}\sigma = -i[\mathcal{H},\sigma]$$

$$\overline{\mathcal{H}} = \cancel{\mathcal{H}_D} + \mathcal{H}_{cs} + \cancel{\mathcal{H}_J} + \cancel{\mathcal{H}_{ext}}$$

Average Hamiltonian
(decoupling, mixing...)

Numerical Methods for Pulse Sequence Optimisation

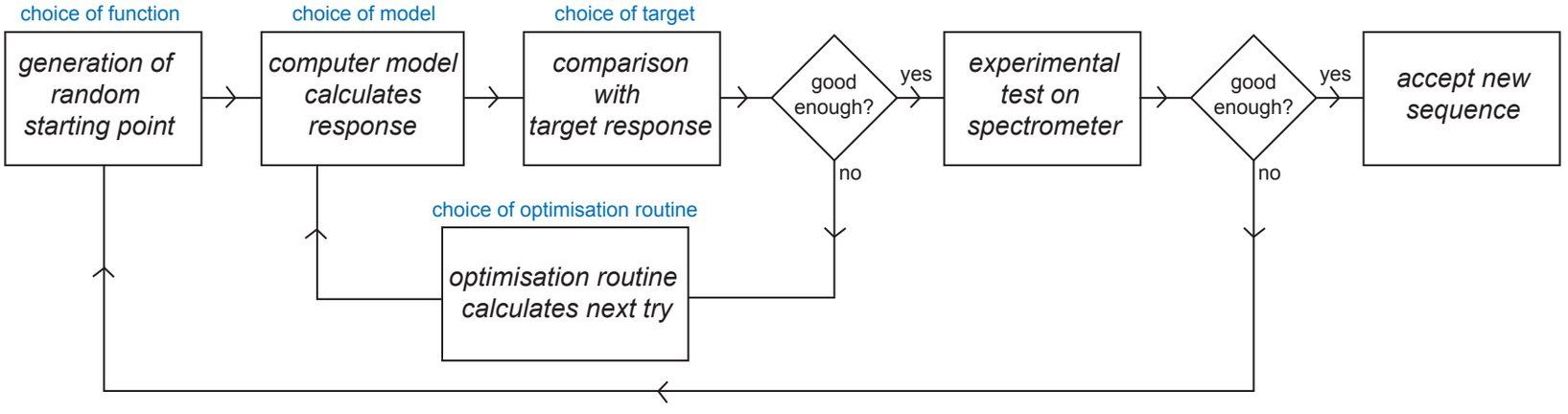


Has been used to generate pulses and sequences for:

- numerous MRI applications
- robust selective excitation and inversion (G3, BURP...)
- heteronuclear J decoupling (GARP, ...)
- homonuclear dipolar decoupling in solids (DUMBO)
- coherence transfer in liquids and solids (Optimal Control)

Key authors: Morris, Warren, Freeman, Emsley, Kupce, Glaser

Example: Broadband J Decoupling

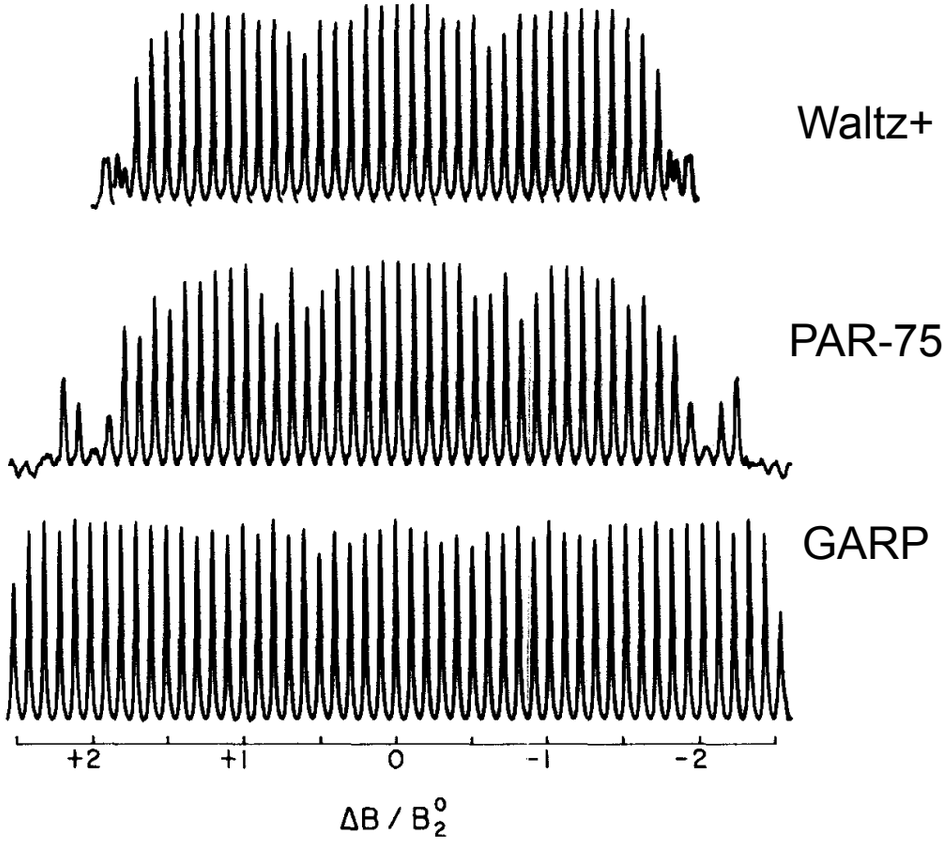


Model Spin System: One isolated spin, Bloch Equations, resonance offset or B_1 misset

Excitation Function: Pulse flip angles in periodic decoupling sequence.

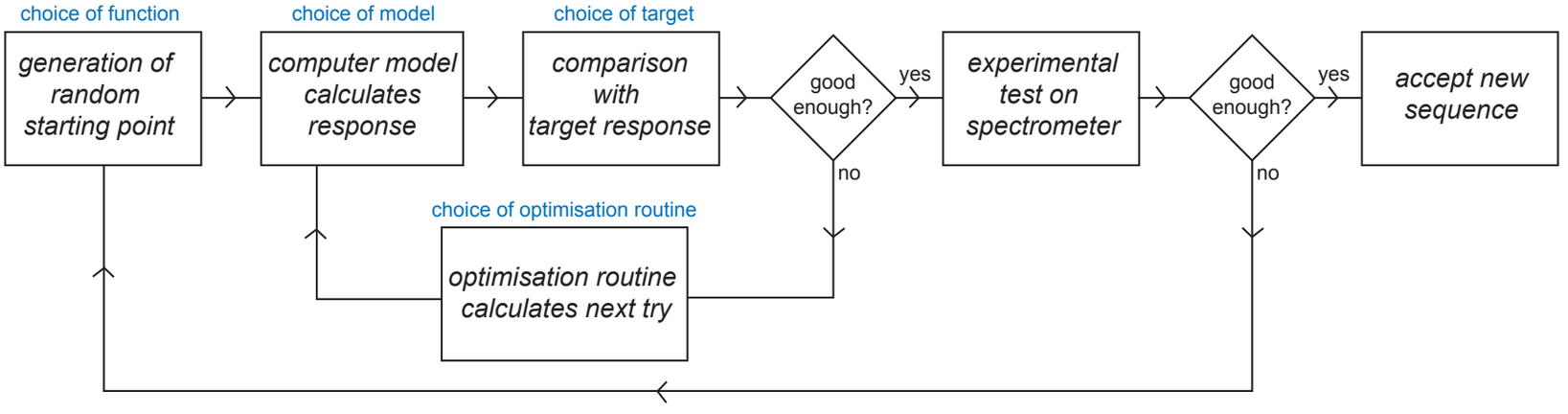
Target: Broadband (low power) J decoupling

Optimisation Routine:
Gradient descent



Shaka, Barker & Freeman, JMR **64**, 547 (1985)

Example: Selective Excitation in Liquids



Model Spin System: One isolated spin, Bloch Equations, resonance offset

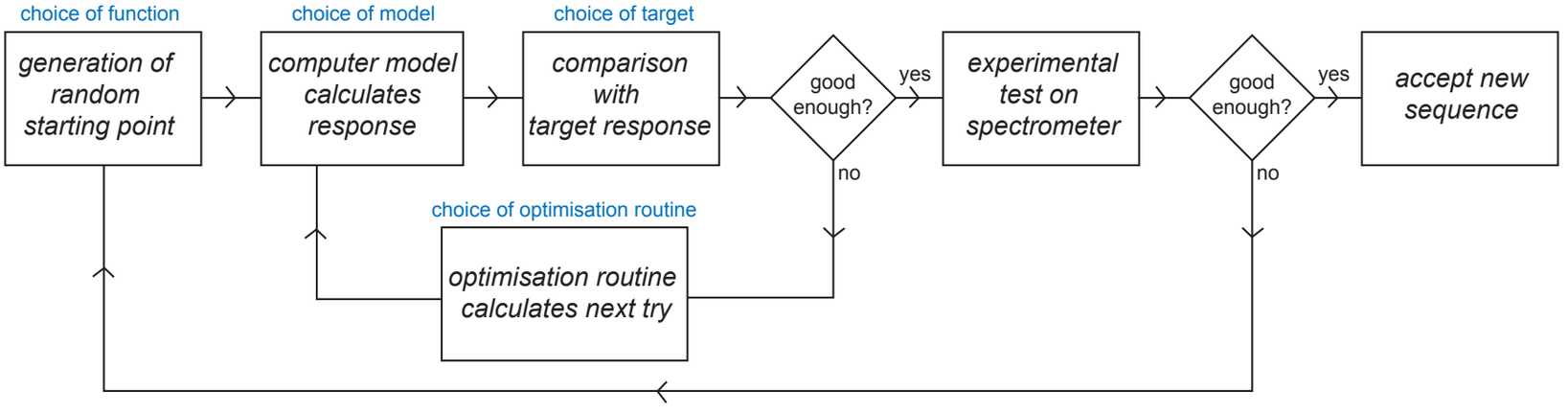
Excitation Function: Amplitude modulation described by a truncated Fourier series.

Target: In phase full excitation in bandwidth. No excitation out of bandwidth.

Optimisation Routine: Simulated annealing

Geen, Wimperis & Freeman, JMR **85**, 620 (1989)
Geen & Freeman, JMR **93**, 93 (1991)

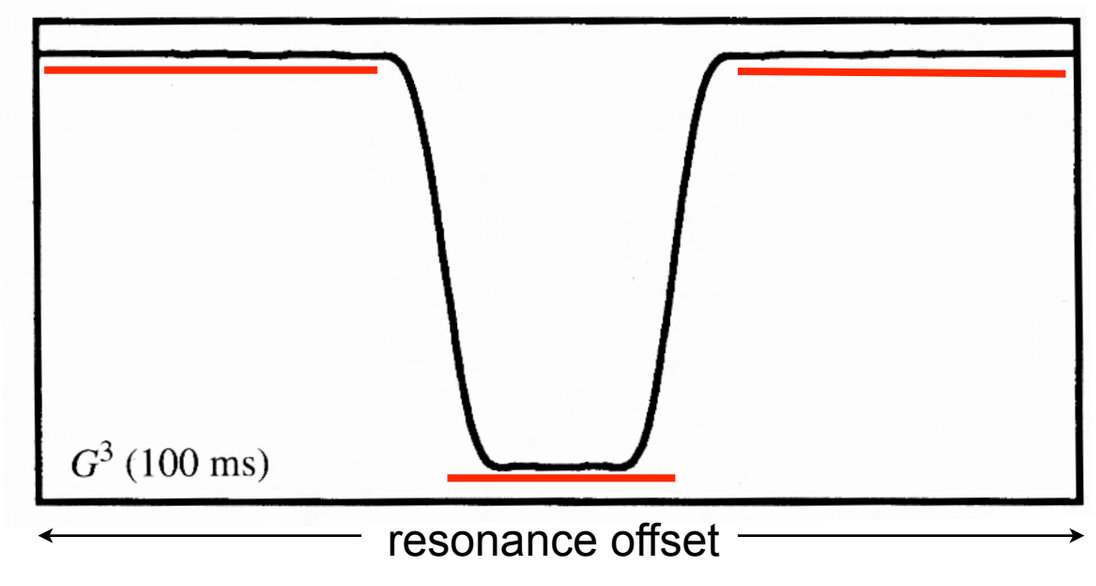
Example: Selective Inversion in Liquids



Model Spin System: One isolated spin, Bloch Equations, resonance offset

Excitation Function: Amplitude modulation described by a sum of Gaussians.

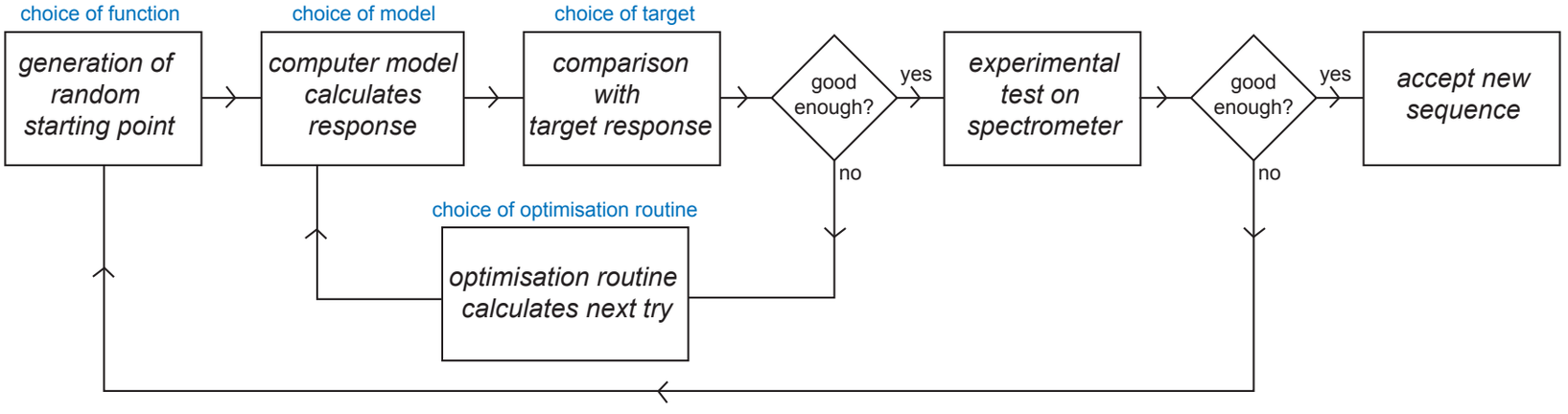
Target: Full inversion in bandwidth.
No effect out of bandwidth.



Optimisation Routine:
Gradient descent

Emsley & Bodenhausen, CPL **165**, 469 (1990)
Emsley & Bodenhausen, JMR **97**, 135 (1992)

More Challenging Examples?



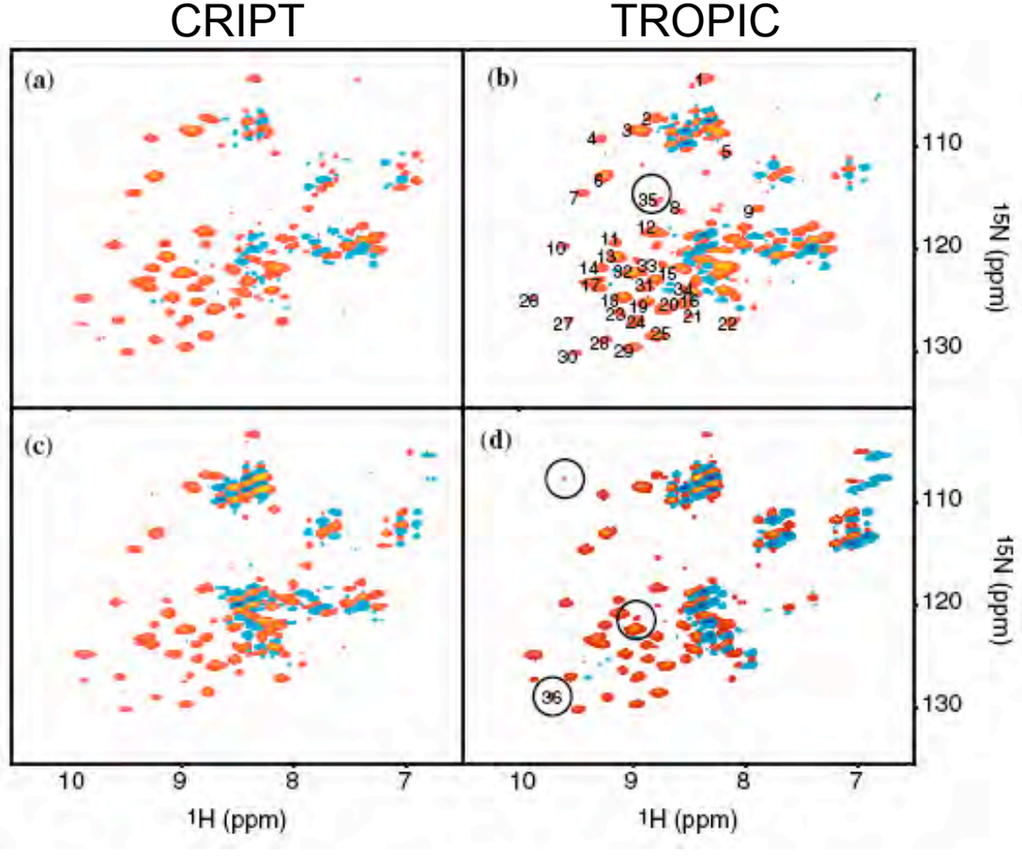
Model Spin System: Two J coupled spins, rapid relaxation

Excitation Function: Flip angles and delays in a multi-pulse sequence

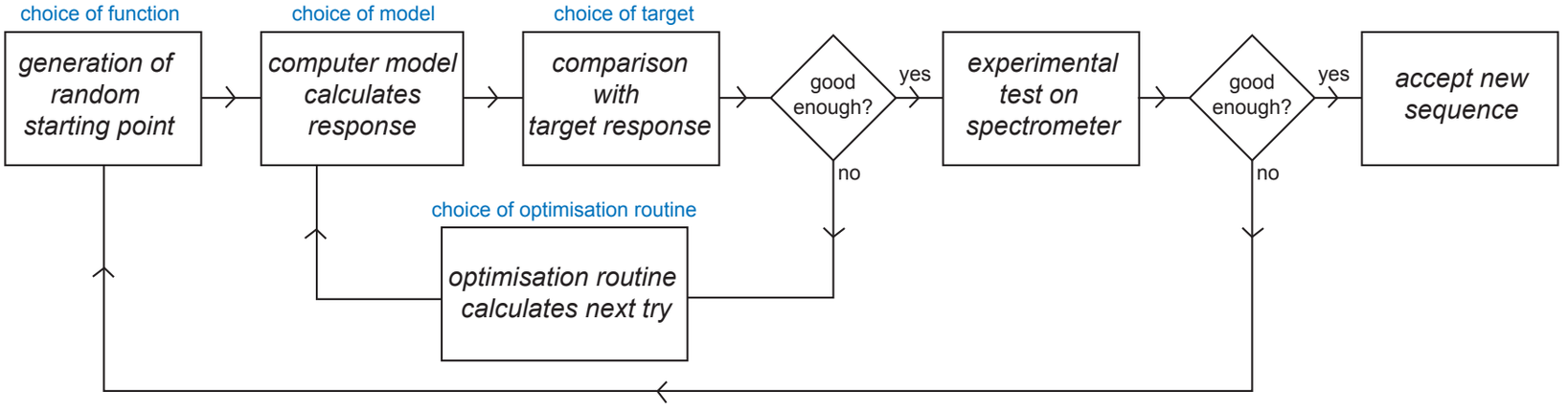
Target: Maximum coherence transfer

Optimisation Routine:
Optimal control

Frueh et al. J. Biomol. NMR **32**, 23 (2005)



More Challenging Examples?



Model Spin System: One spin, with quadrupolar coupling, under MAS in a powder

Excitation Function: Individual time steps in an amplitude and phase modulated continuous irradiation sequence.

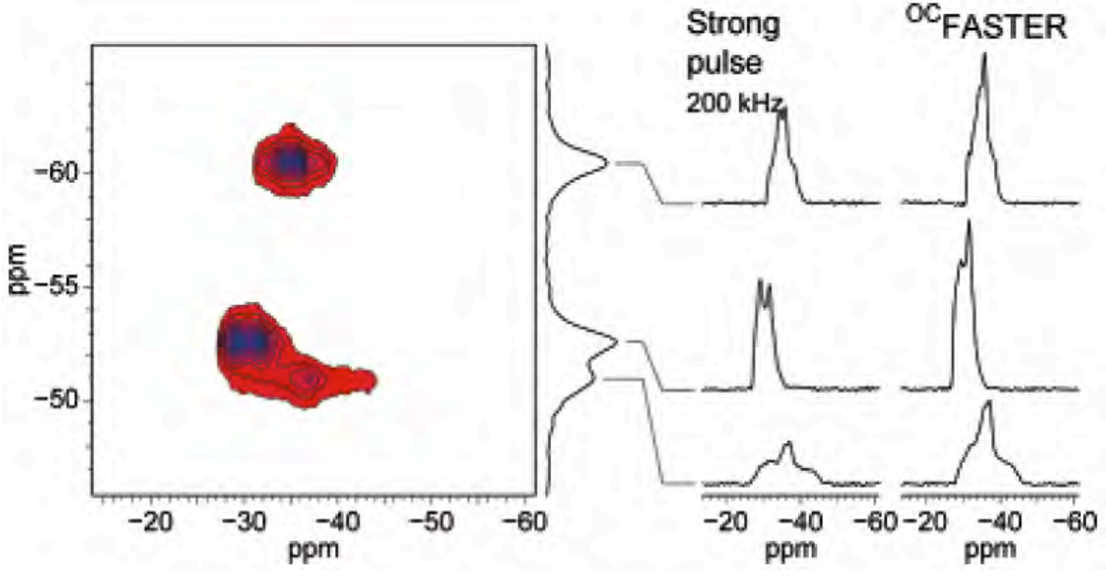
Target: Maximum excitation efficiency

Optimisation Routine:
Optimal control

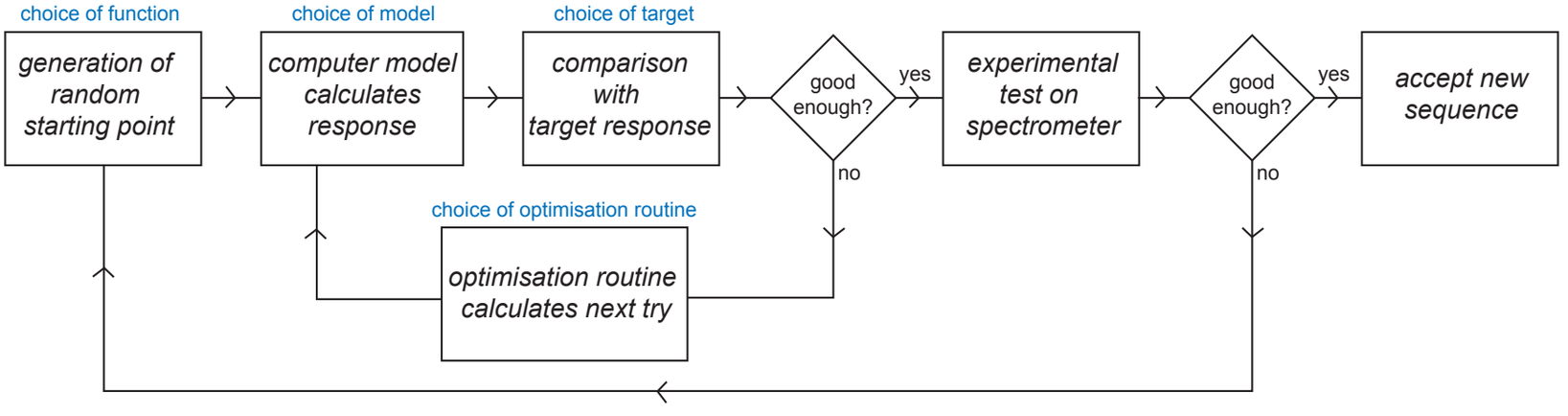
Vosegaard et al., JACS **127**, 13768 (2005)

+ many other examples for optimal control from Glaser, Khaneja and coworkers

Enhanced MQ MAS experiments



More Challenging Examples?

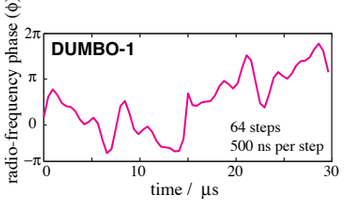


Model Spin System: Two dipolar coupled spins.

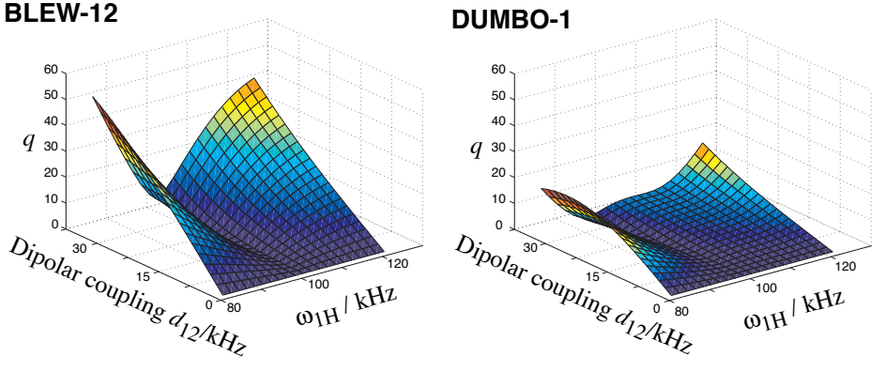
Homonuclear Dipolar Decoupling

Excitation Function: Continuous phase modulation defined by a truncated Fourier series

$$\phi(t) = \sum_{n=0}^{6} \left(a_n \cos(n\omega_c t) + b_n \sin(n\omega_c t) \right)$$



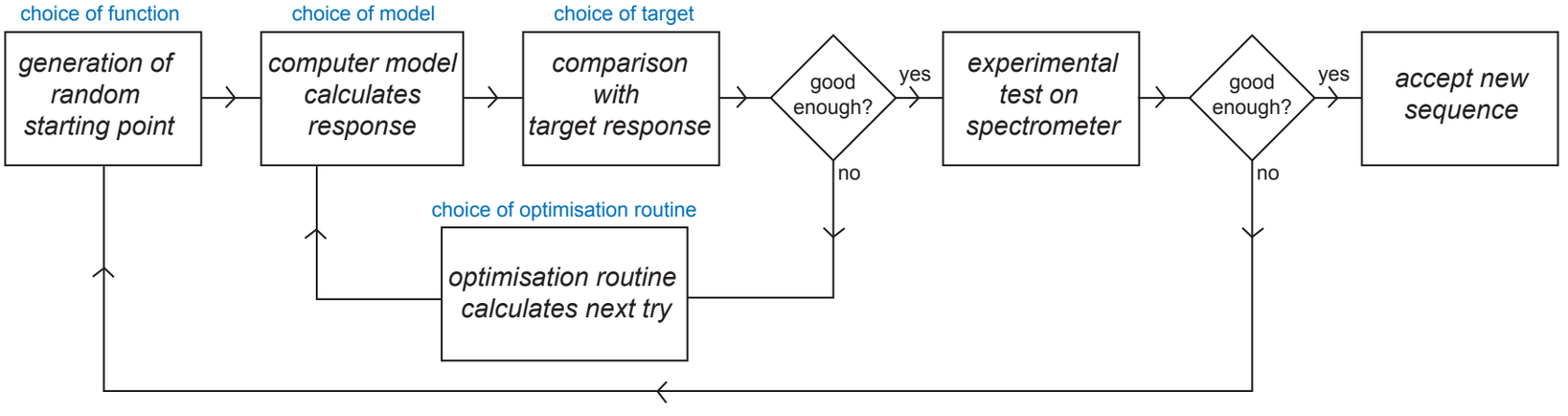
Target: Maximise the chemical shift, remove the dipolar coupling



Optimisation Routine:
Gradient descent

Sakellariou et al., CPL **319**, 253 (2000)

The Solution to All Your Problems?

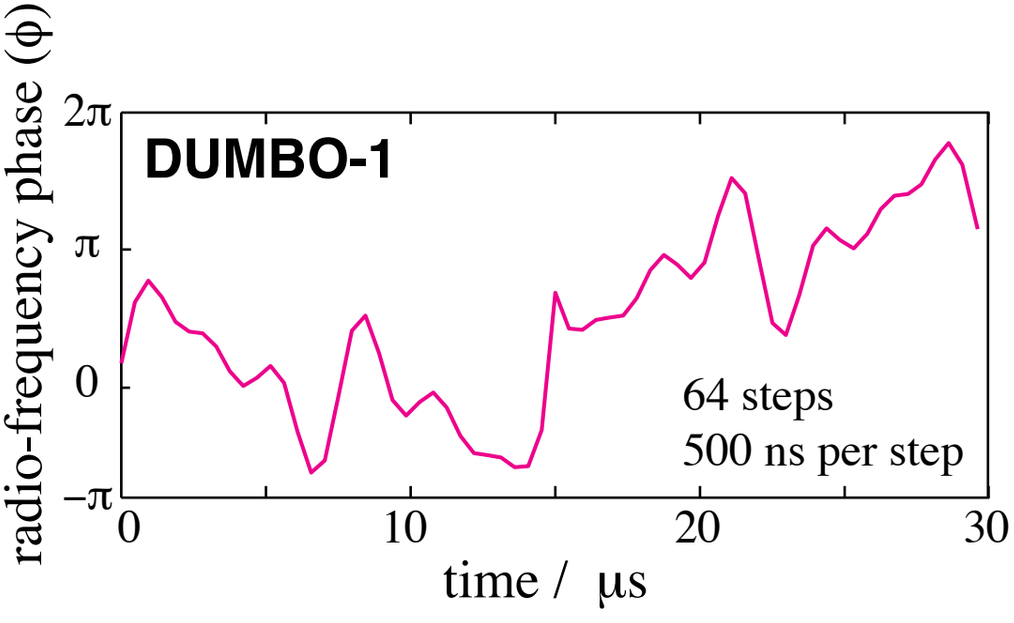


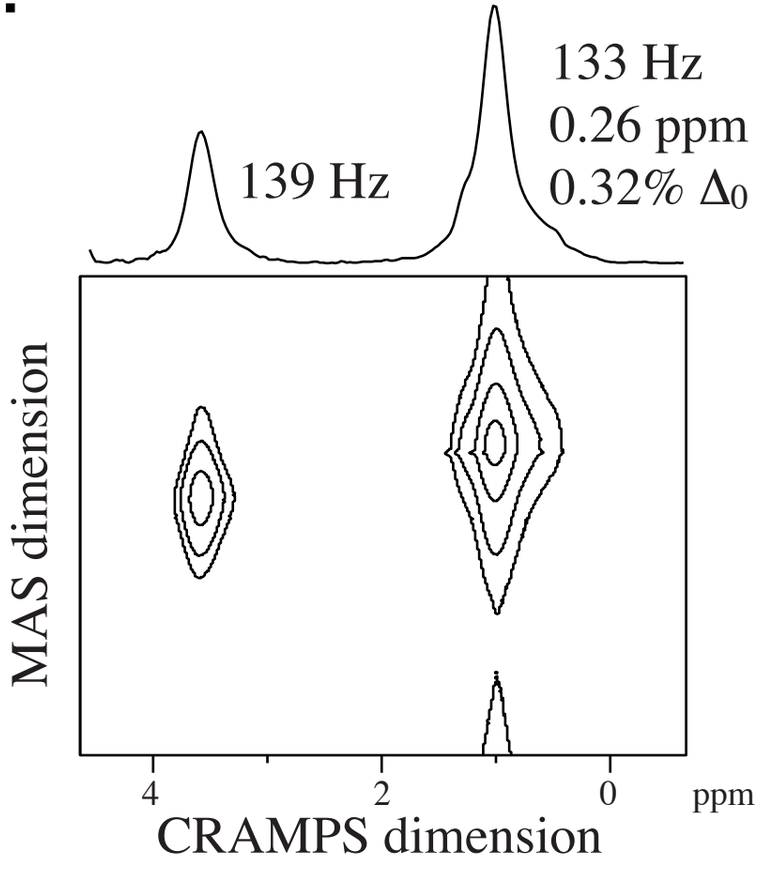
Model Spin System: Two dipolar coupled spins.

The weakness of numerical optimisation in that the computer is that the solution you obtain, by whatever method, ***is only as good as the accuracy with which the model system you set up actually reproduces experiment!***

"Out of many results, the 5-TR pulse sequence shown in Figure 1a yielded the highest 3Q coherence excitation."

What Next?





DUMBO-1 was developed using a computer simulation approach.
It works very well. But still not good enough for chemistry....!!

How can we do better than 0.32% residual?

How Can We Improve the Accuracy of the Predicted Spin System Response?

We need < 1% accuracy...

...we routinely adjust the B_0 homogeniety
to << 1% accuracy...

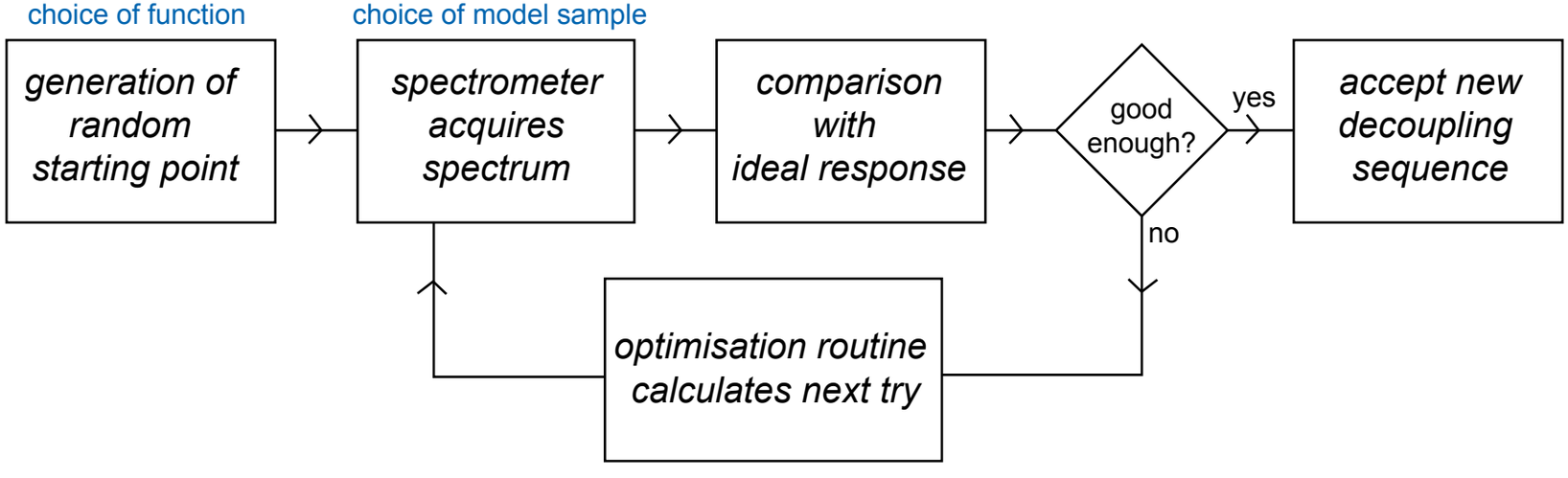
... by “shimming” directly on the NMR signal response.

We would never imagine shimming by first calculating the field map, to predict the best shim values, and then try them!!

The eDUMBO Approach

experimental Decoupling Uses Mind Boggling Optimization

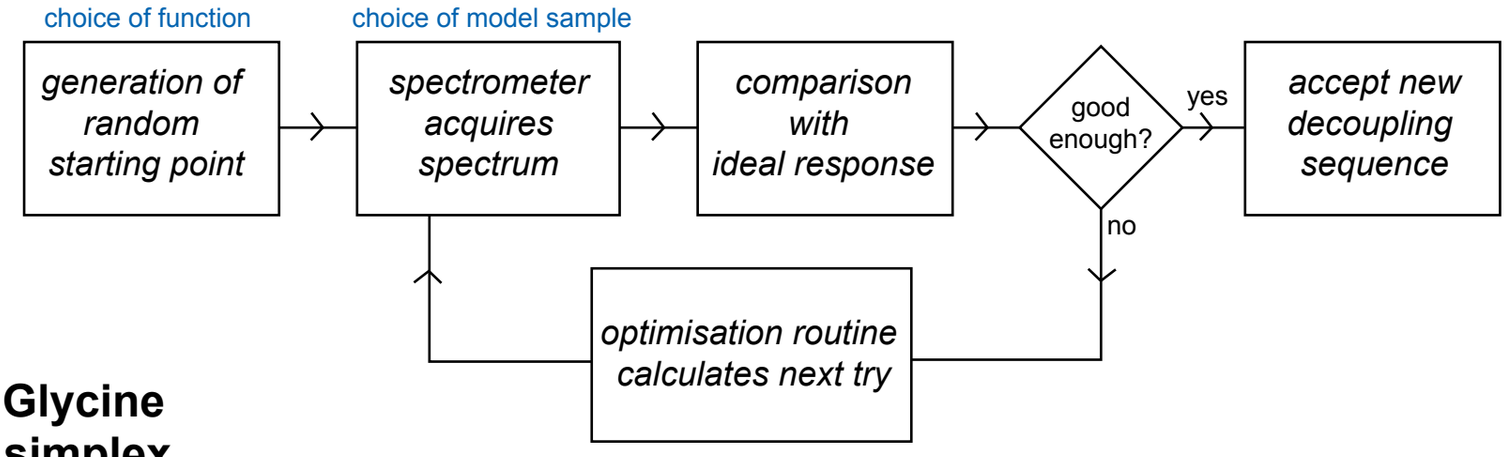
Use the NMR signal to find high-performance pulse sequences through iterative optimisation: “autoshimming” sequences.



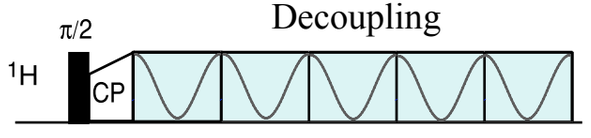
Has been used to generate pulses and sequences for:

- heteronuclear dipolar decoupling under MAS (CM)
- homonuclear dipolar decoulping under MAS (eDUMBO)
- increased carbon-13 transverse dephasing times T_2' (TDOP)
- increased sensitivty in solid-state ^{1}H-^{13}C INEPT & HSQC

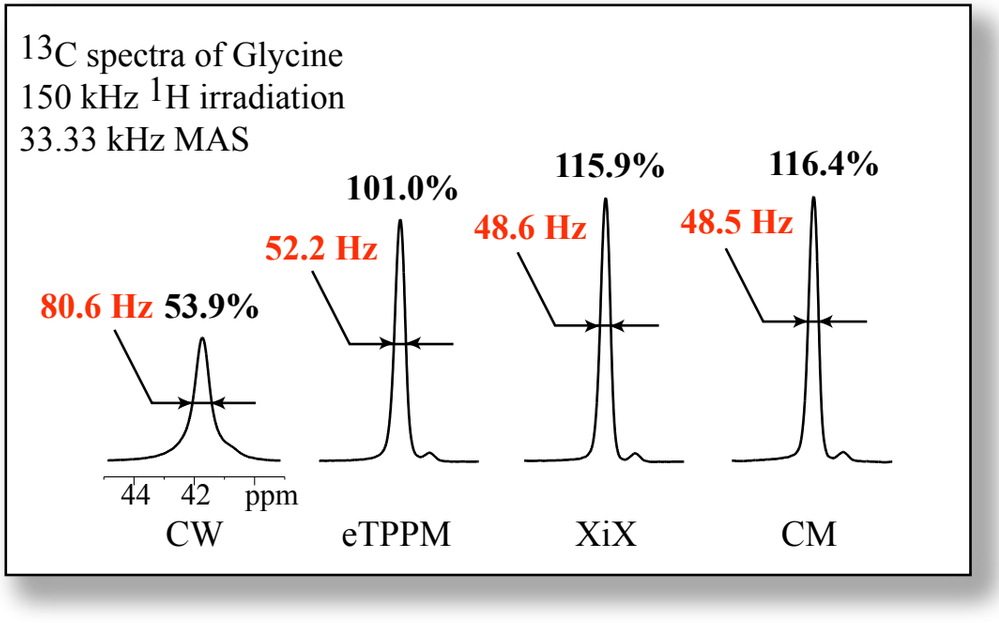
The eDUMBO Approach to Heteronuclear Dipolar Decoupling in Solids

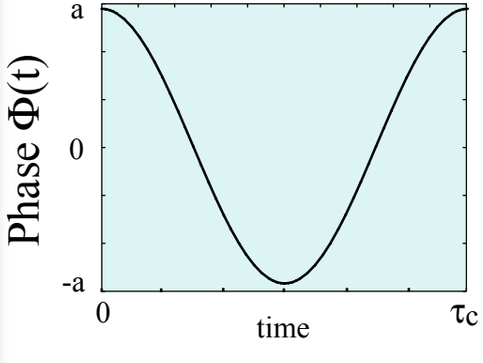


Model sample: **[2-^{13}C] Glycine**
Optimisation Method: **simplex**
Quality Factor: **intensity of the carbon-13 CPMAS peak**



Chem. Phys. Lett. 376 , 3-4 (2003).





Cosine Modulation (CM)

$\Phi(t) = a \cos(t/\tau_c)$

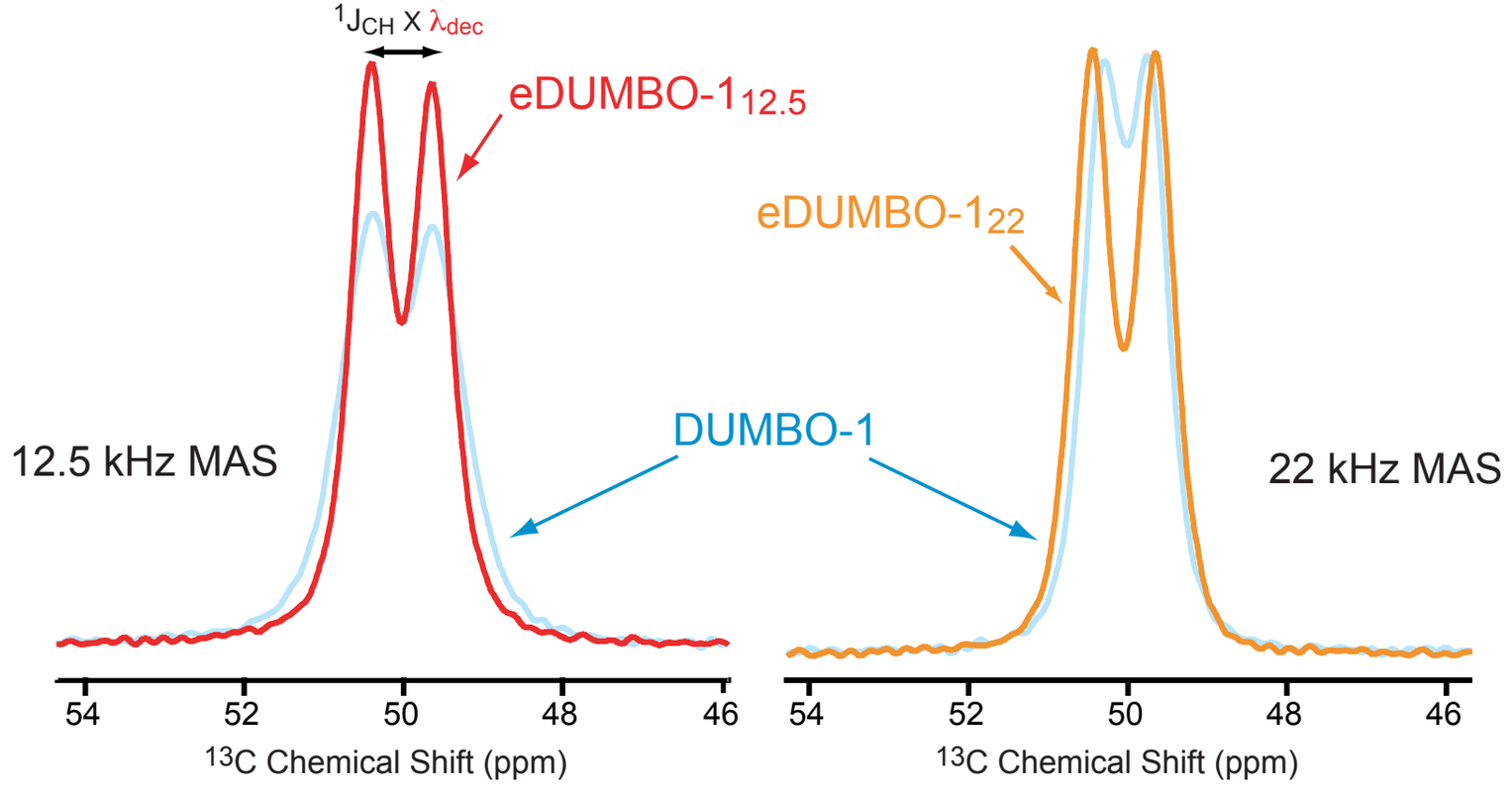
where τ_c and a are variables for optimisation.

High-Resolution Proton NMR Spectroscopy: eDUMBO-1

Model sample: **[2-^{13}C] L-Alanine**
Optimisation Method: **simplex**
Quality Factor: **resolution of the $^{1}J_{CH}$ doublet on carbon-13**

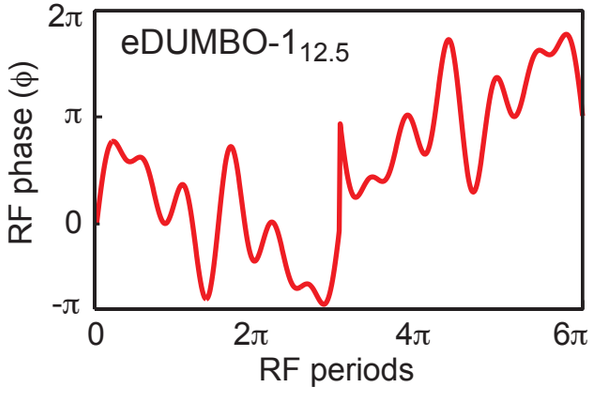
100 kHz ^{1}H-Homodecoupling

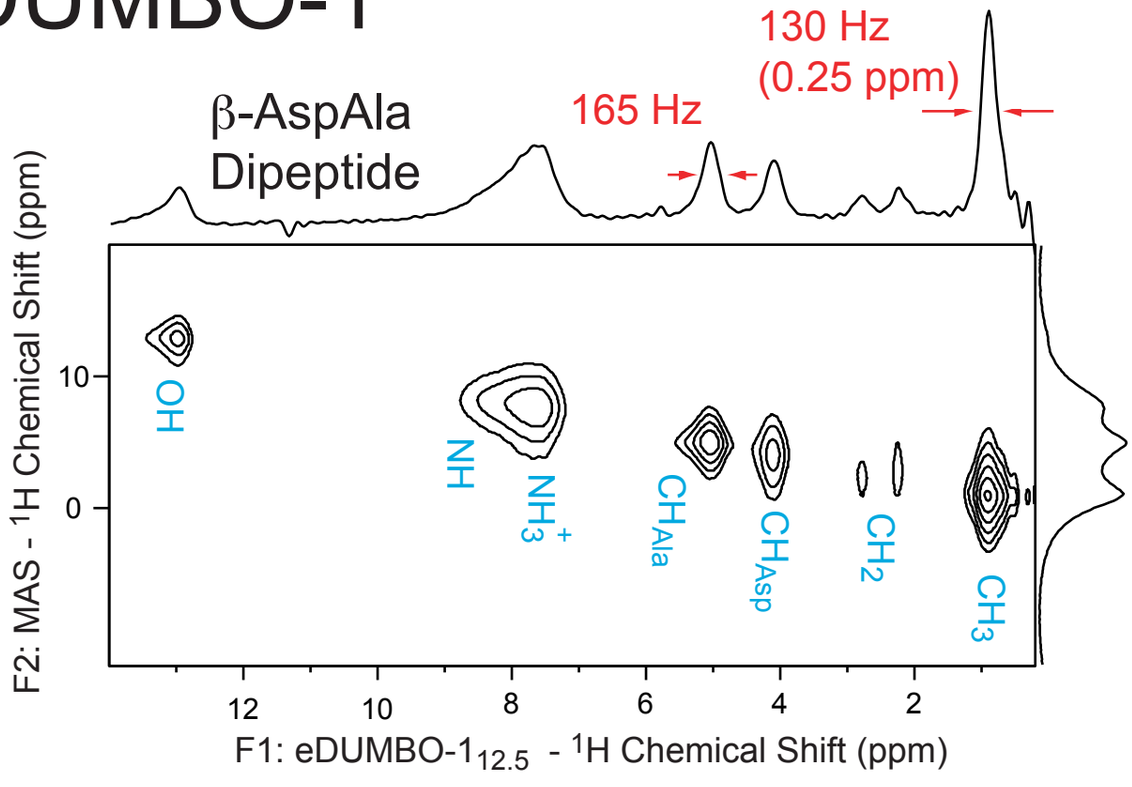
$$q = a\,(I_1 + I_2) - b\,|(\omega_1 - \omega_2) - J_{CH} \times \lambda_M|$$



Chem. Phys. Lett. **398**, 532 (2004).

High-Resolution Proton NMR Spectroscopy: eDUMBO-1





^{1}H linewidths (FWHH) - β-AspAla dipeptide

12.5 kHz MAS:

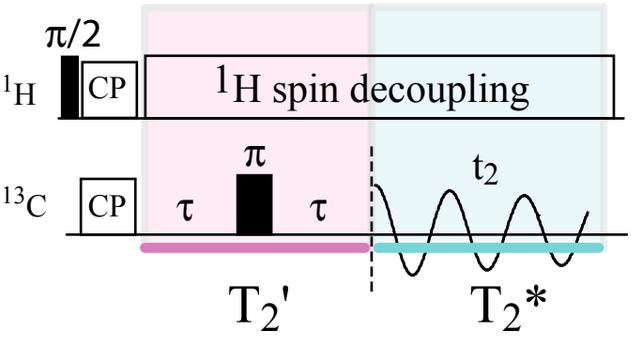
	$\Delta^*(CH_3)$	λ_{exp}	$\Delta^{cor}(CH_3)$
DUMBO-1	72 Hz	0.48	152 Hz (0.30 ppm)
eDUMBO-1$_{12.5}$	72 Hz	**0.56**	***129 Hz (0.26 ppm)***

22 kHz MAS:

	$\Delta^*(CH_3)$	λ_{exp}	$\Delta^{cor}(CH_3)$
DUMBO-1	82 Hz	0.48	171 Hz (0.34 ppm)
eDUMBO-1$_{12.5}$	88 Hz	0.55	161 Hz (0.32 ppm)
eDUMBO-1$_{22}$	80 Hz	**0.57**	***141 Hz (0.28 ppm)***

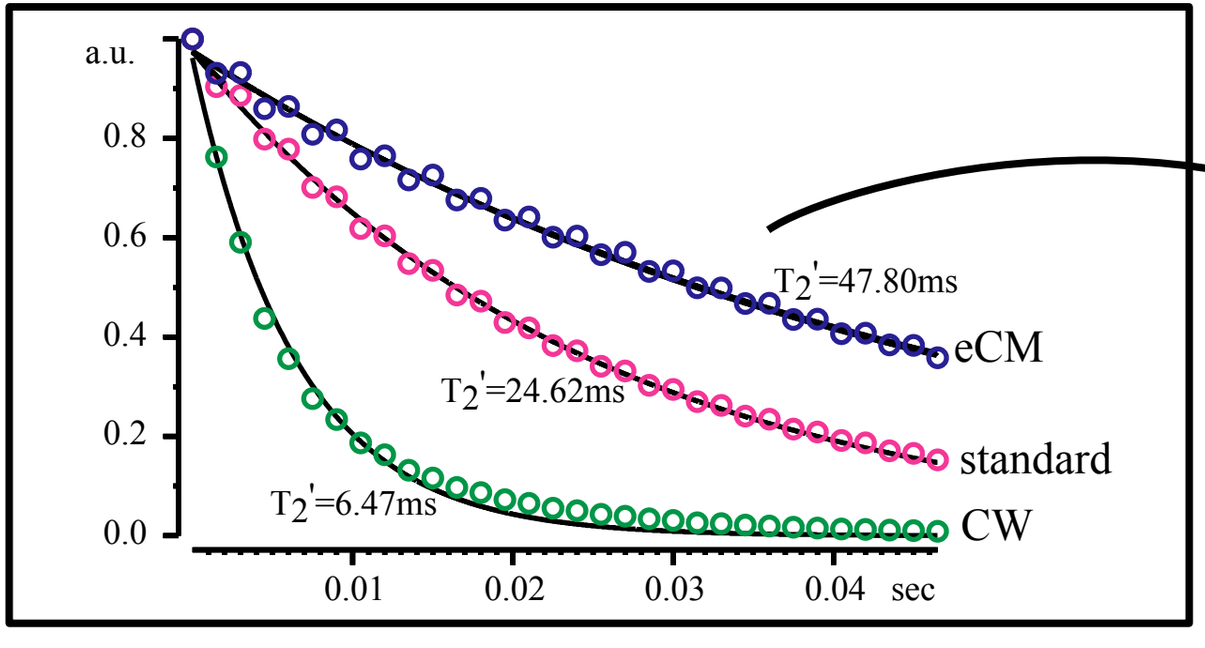
Intrinsic Linewidths in Solids:

Coherent Control of Transverse Dephasing Times

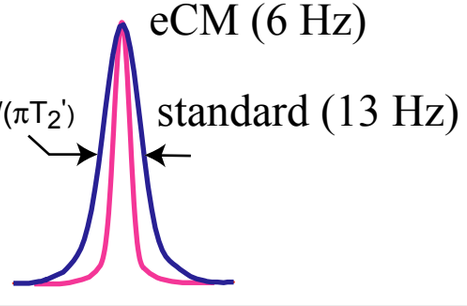


Model sample: **[2-^{13}C] Glycine**
Optimisation Method: **simplex**
Quality Factor: **intensity of the signal after a 30 ms spin echo**

Very small difference in unrefocused linewidths (<10 %)



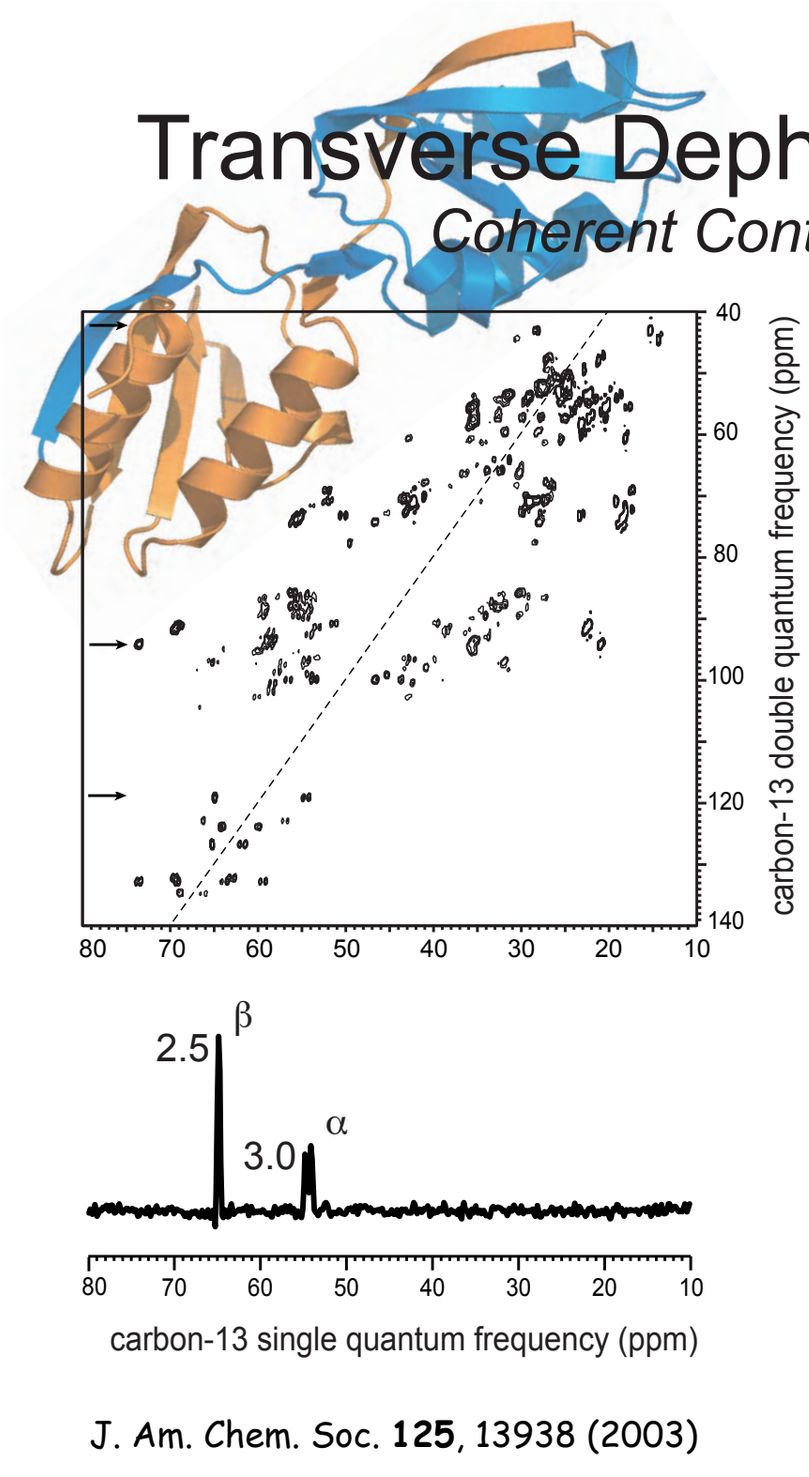
Very large difference in refocused linewidths (>50 %)



J. Am. Chem. Soc. **125**, 13938 (2003)

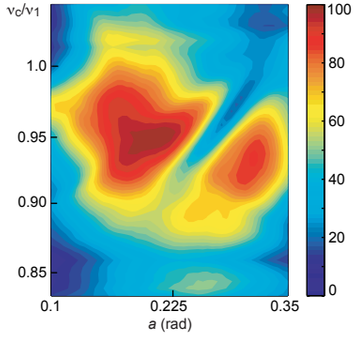
Transverse Dephasing Optimised Spectroscopy

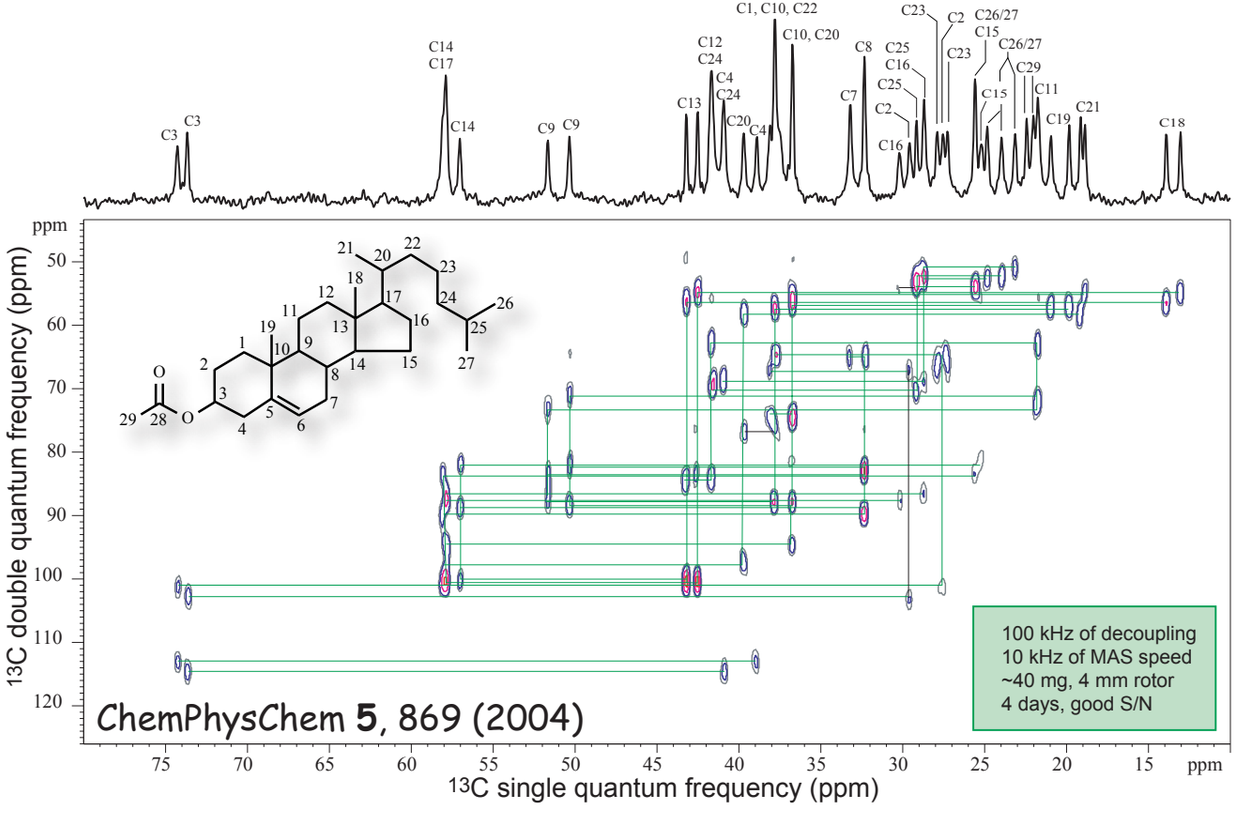
Coherent Control of Transverse Dephasing Times



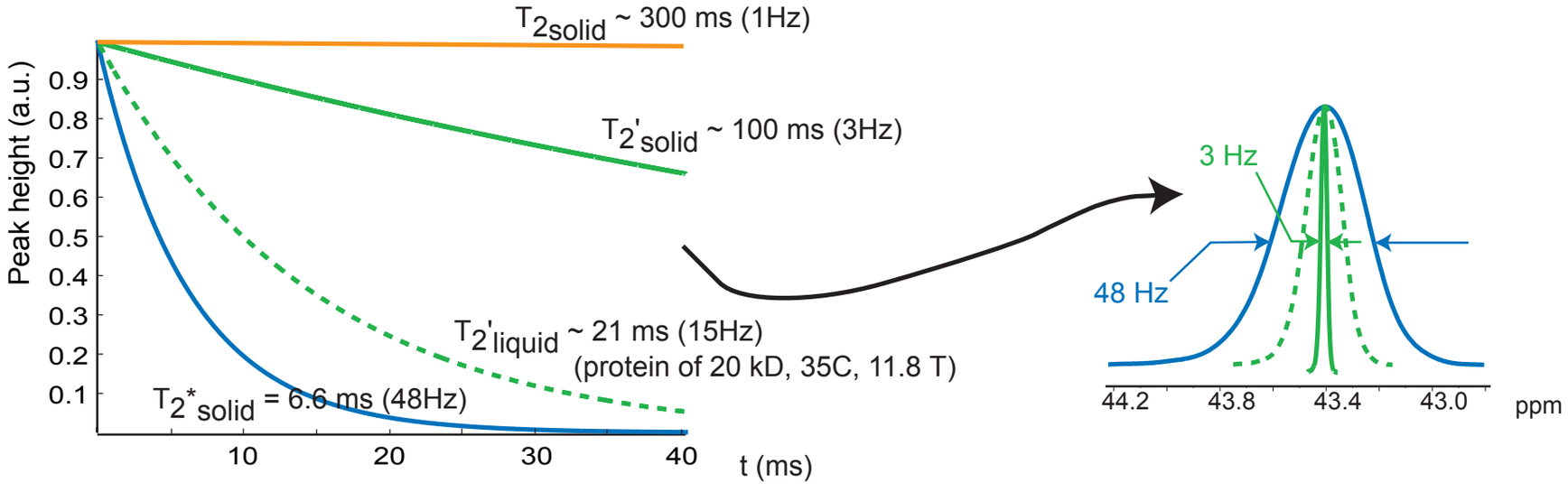
J. Am. Chem. Soc. **125**, 13938 (2003)

eOptimisation of the coherence lifetime essential to find the best decoupling conditions with CM or TPPM





"Decoherence Times": Liquids & Solids



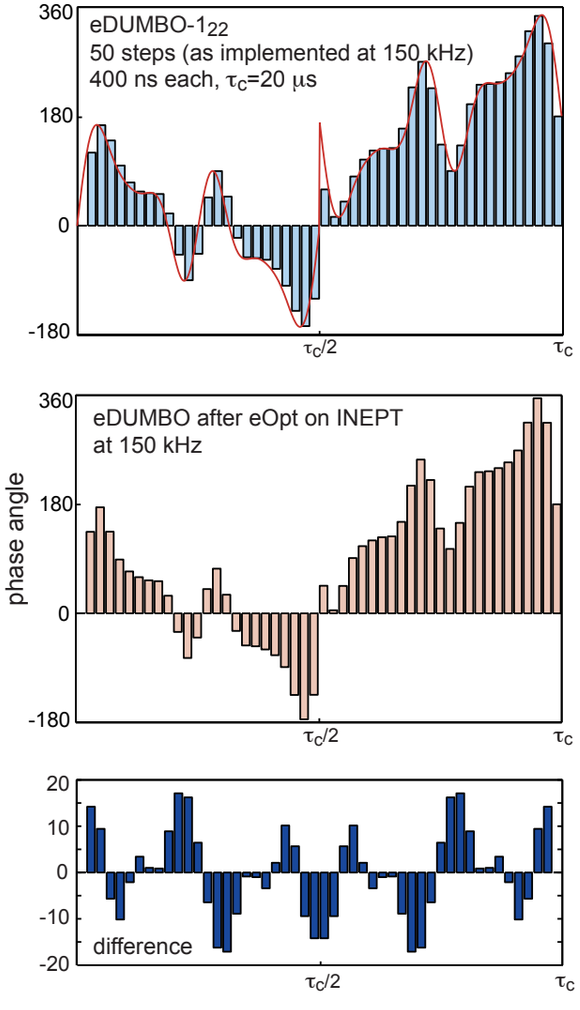
Apparent T_2	Refocused T_2	Incoherent T_2
$T_2^*_{solid}$	$\ll$ $T_2'_{solid}$	$<$ T_{2solid}
$\wedge\wedge$	$\vee$	$\vee\vee$
$T_2^*_{liquid}$	$<$ $T_2'_{liquid}$	$\sim$ $T_{2liquid}$

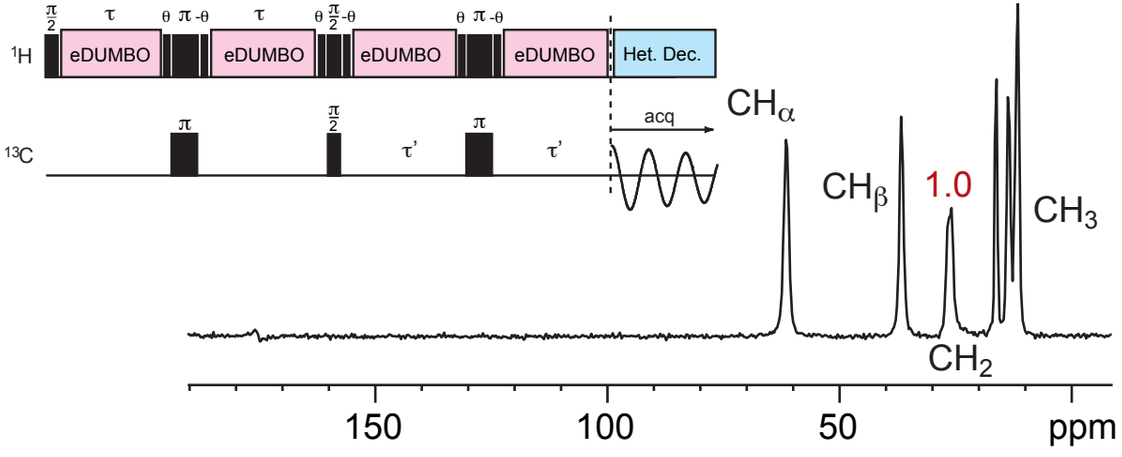
potentially very long, depends mainly on internal dynamics

decreases as a function of the molecular weight

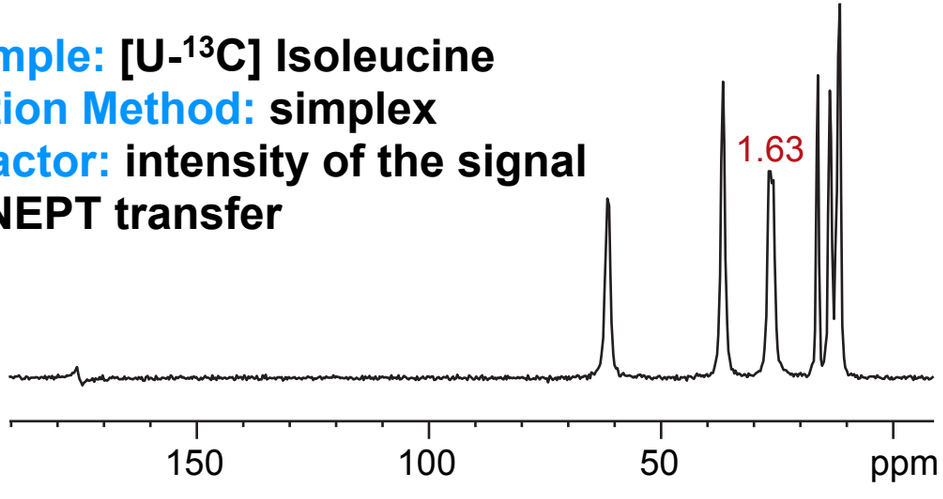
Effective coherence lifetimes in solids can be longer than in liquids!
SSNMR experiments can be more efficient than equivalent liquid-state experiments.

Direct eOptimisation of ^{1}H-^{13}C J-INEPT





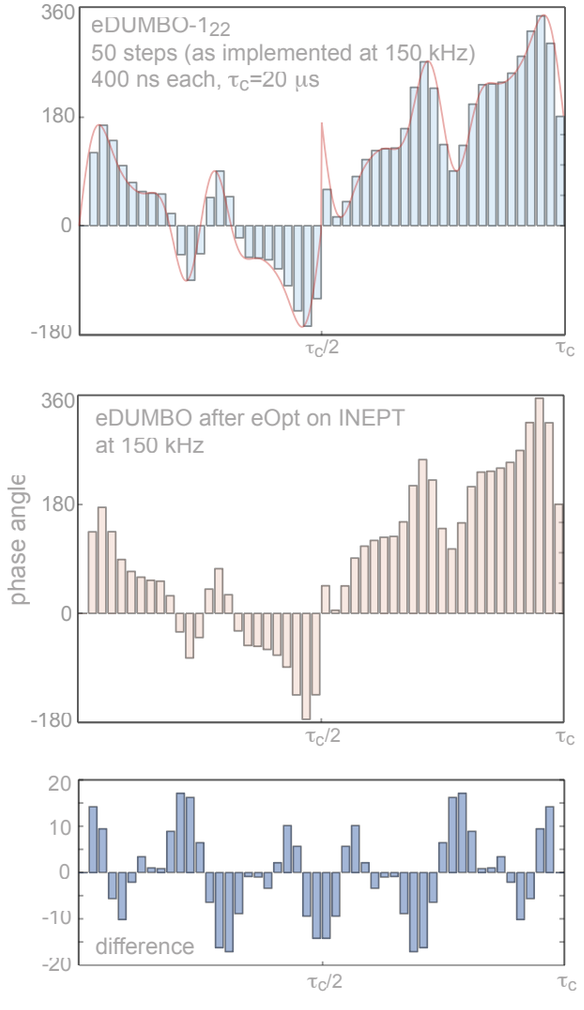
Model sample: **[U-^{13}C] Isoleucine**
Optimisation Method: **simplex**
Quality Factor: **intensity of the signal after an INEPT transfer**

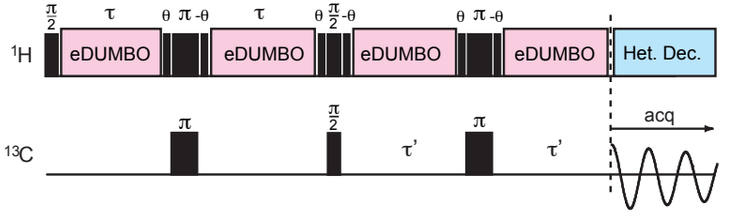


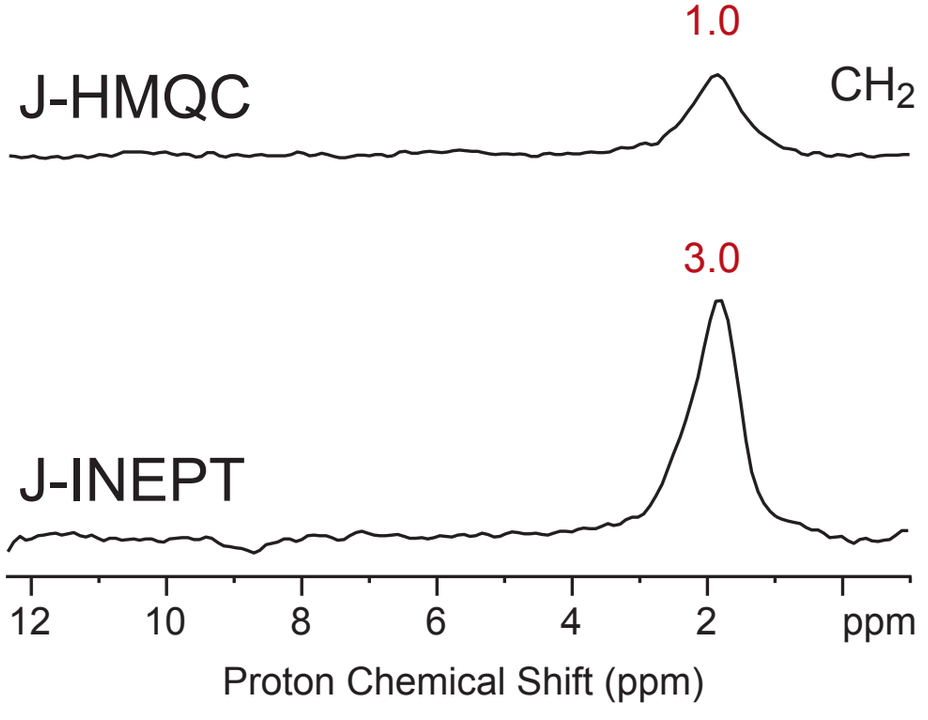
Direct experimental optimisation of the CH2 transfer efficiency increases the proton coherence lifetime, leading to a >60% increase in sensitivity.

J. Am. Chem. Soc. **127**, 17296 (2006).

Direct eOptimisation of ^{1}H-^{13}C J-INEPT





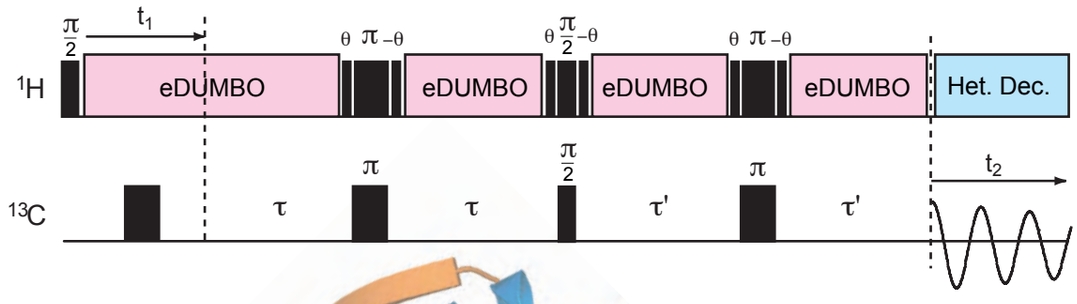


In carbon-13 labelled compounds, the efficiency of the transfer is far superior to that of the J-HMQC sequence.

J. Am. Chem. Soc. **127**, 17296 (2006).

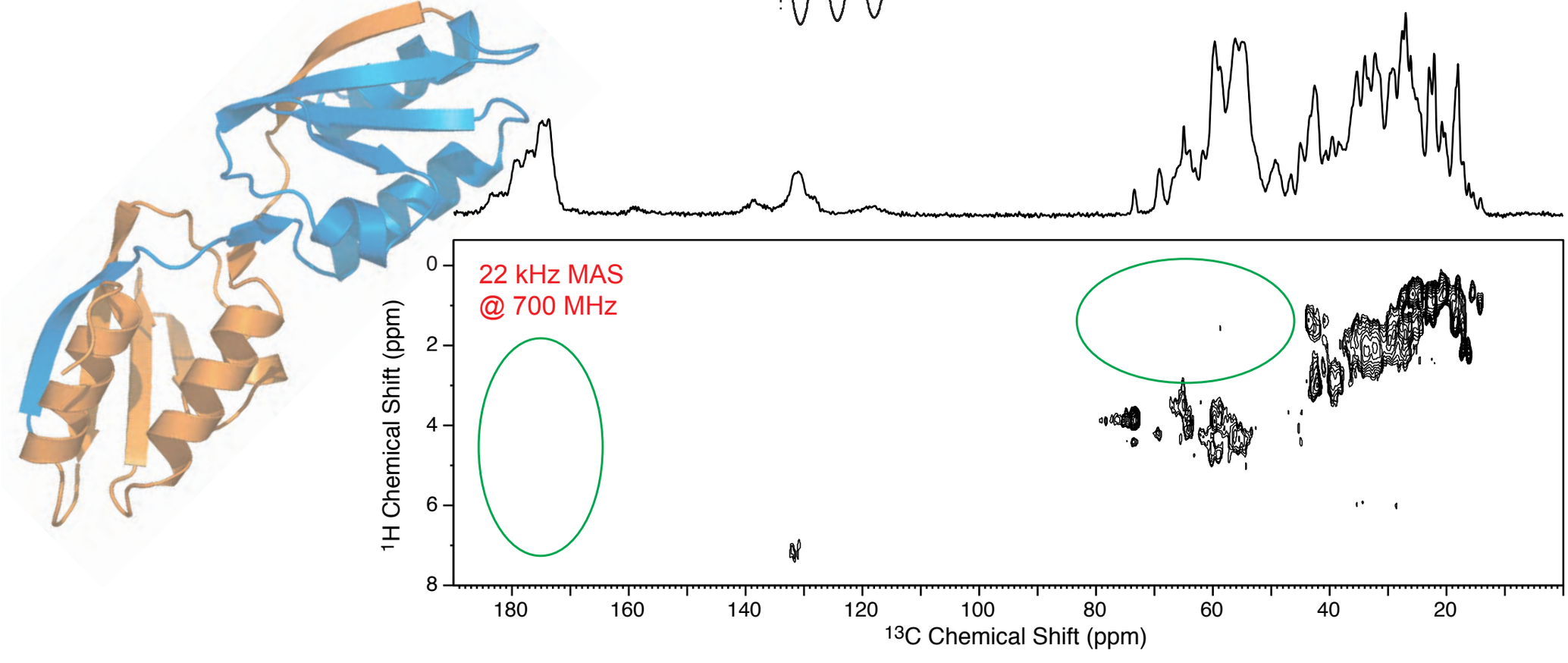
Through-Bond INEPT Based HSQC for Proteins

Solid-State Refocused ^{1}H-^{13}C INEPT experiment



3.2 mm MAS probe
192 scans
Total expt. time = 20 hours
100 kHz eDUMBO decoupling

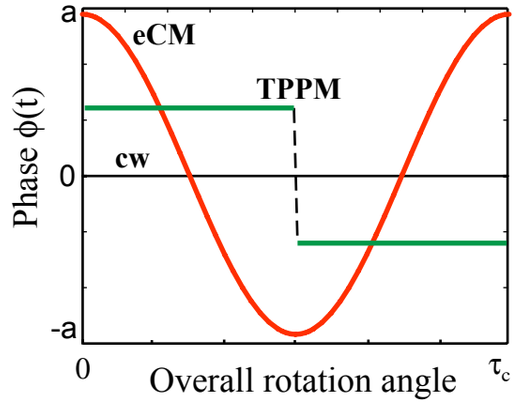
Sample temperature = 5 C
Sample cooling using nitrogen gas through the BCU-X
MAS using dry air

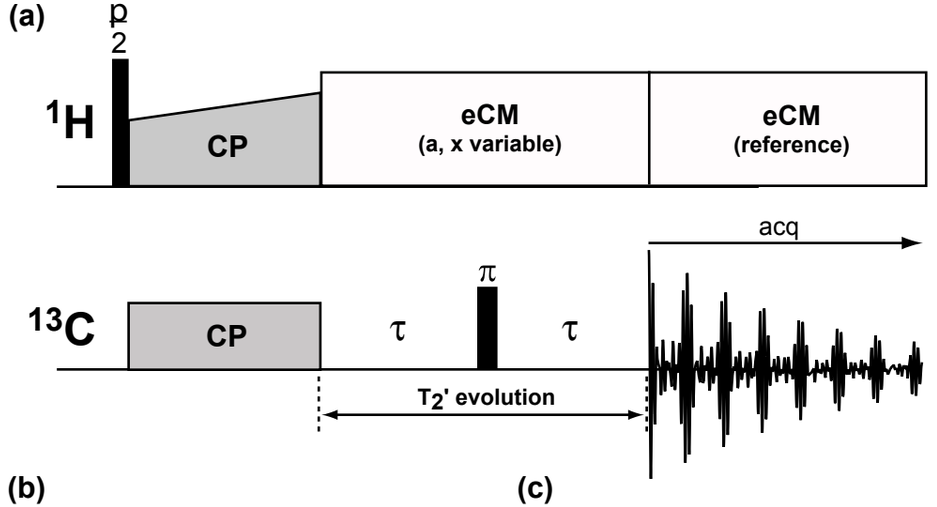


J. Am. Chem. Soc. **127**, 17296 (2005).

“I don’t like numerical methods, because they don’t provide any understandable result. It’s all too much of a black box.”

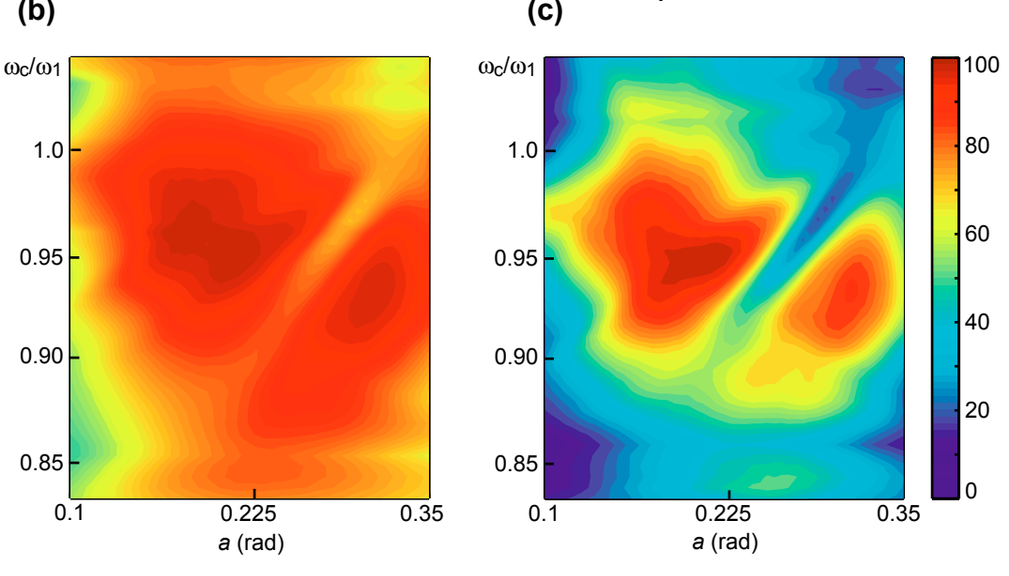
eOptimised Heteronuclear Decoupling





Numerical optimisation converges to a very simple answer for heteronuclear decoupling (a close cousin of TPPM), and demonstrates that the parameterisation is very sensitive.

Can we determine why it works?

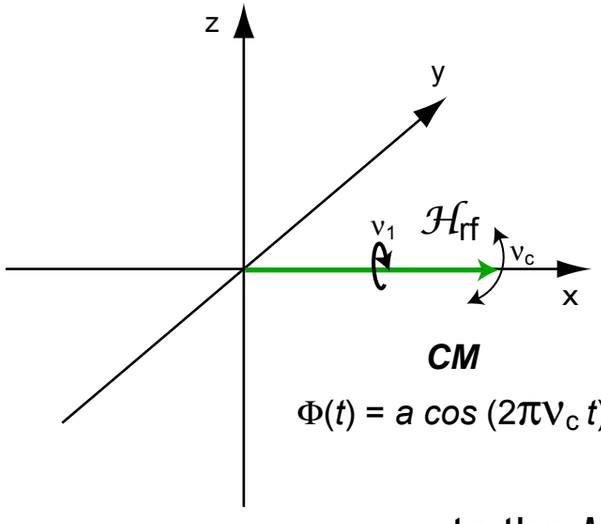


J. Chem. Phys. **121**, 3165 (2004)

Proton Decoupling: eCM & TPPM

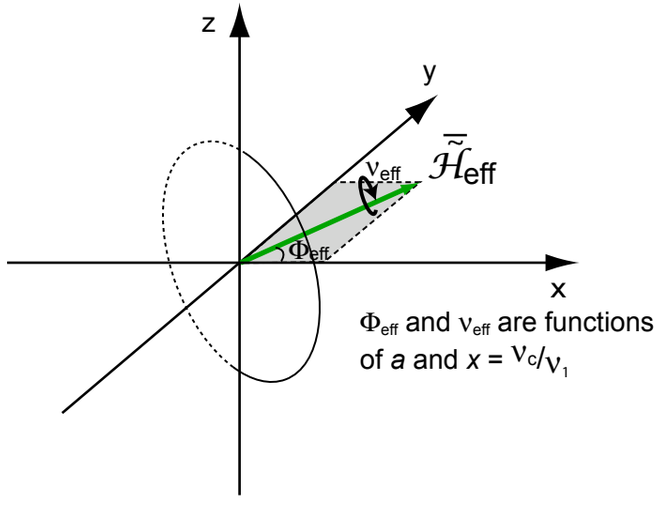
Modulation Frame HORROR Conditions

From the *Rotating* Frame ...

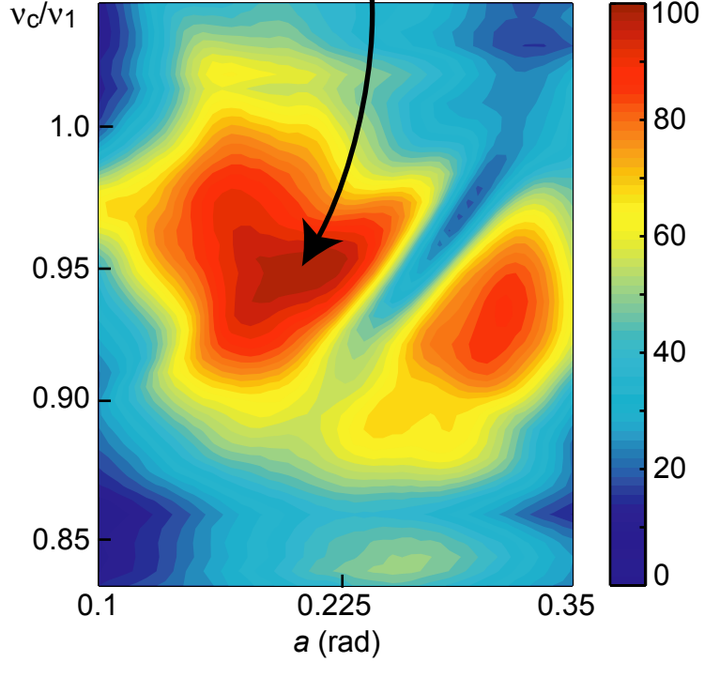


... to the *Modulation* Frame

(defined as the frame rotating around the mean axis x at the frequency of the modulation ν_c)



This point is found to be a modulation frame HORROR condition. *The numerical result provided the key to understanding the mechanism & parameterisation of TPPM !*



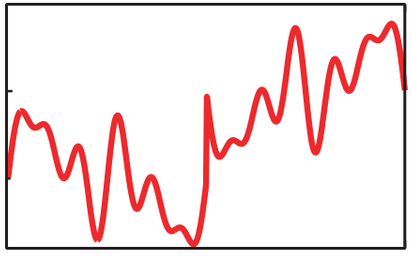
J. Chem. Phys. **121**, 3165 (2004).

Summary I

If the approximate analytical solution is sufficiently accurate, Average Hamiltonian Theory (and cousins) is a good platform for pulse sequence development. It provides a detailed understanding.

J decoupling in liquids is an excellent example of where AHT methods work very well to describe the experimental observations.

time domain manipulations



$$\frac{d}{dt}\sigma = -i[\mathcal{H},\sigma]$$

$$\overline{\mathcal{H}} = \cancel{\mathcal{H}_D} + \mathcal{H}_{cs} + \cancel{\mathcal{H}_J} + \cancel{\mathcal{H}_{ext}}$$

Average Hamiltonian (decoupling, mixing...)

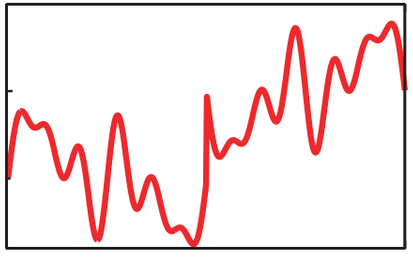
Summary I

If approximate methods fail, numerical methods can provide better solutions.

This is often the case where single spin dynamics are sufficient to describe the problem accurately.

Selective pulses are an excellent example of where numerical computer optimisation works well. Liquid state coherence transfer is another area where this approach works.

time domain manipulations



Methods using computer simulations of the spin system can only be as accurate as the simulation itself.

$$\frac{d}{dt}\sigma = -i[\mathcal{H},\sigma]$$

$$\overline{\mathcal{H}} = \cancel{\mathcal{H}_D} + \mathcal{H}_{cs} + \cancel{\mathcal{H}_J} + \cancel{\mathcal{H}_{ext}}$$

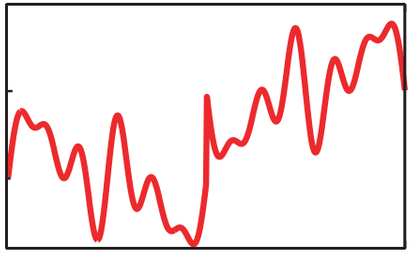
Average Hamiltonian
(decoupling, mixing...)

Summary I

In many cases, especially in solid-state NMR, computer simulations do not reproduce the experimental behavior sufficiently accurately to allow useful results.

In these cases, direct optimisation of the NMR signal naturally provides more accurate results, and can generate the best pulse sequences.

time domain manipulations



Homonuclear dipolar decoupling is an excellent example of where the experimental optimisation yields the best results.

$$\frac{d}{dt}\sigma = -i[\mathcal{H},\sigma]$$

$$\overline{\mathcal{H}} = \cancel{\mathcal{H}_D} + \mathcal{H}_{cs} + \cancel{\mathcal{H}_J} + \cancel{\mathcal{H}_{ext}}$$

Average Hamiltonian (decoupling, mixing...)

Summary II

eOptimisation: An Experimental Approach to Pulse Sequence Design

Weaknesses of eOptimisation:

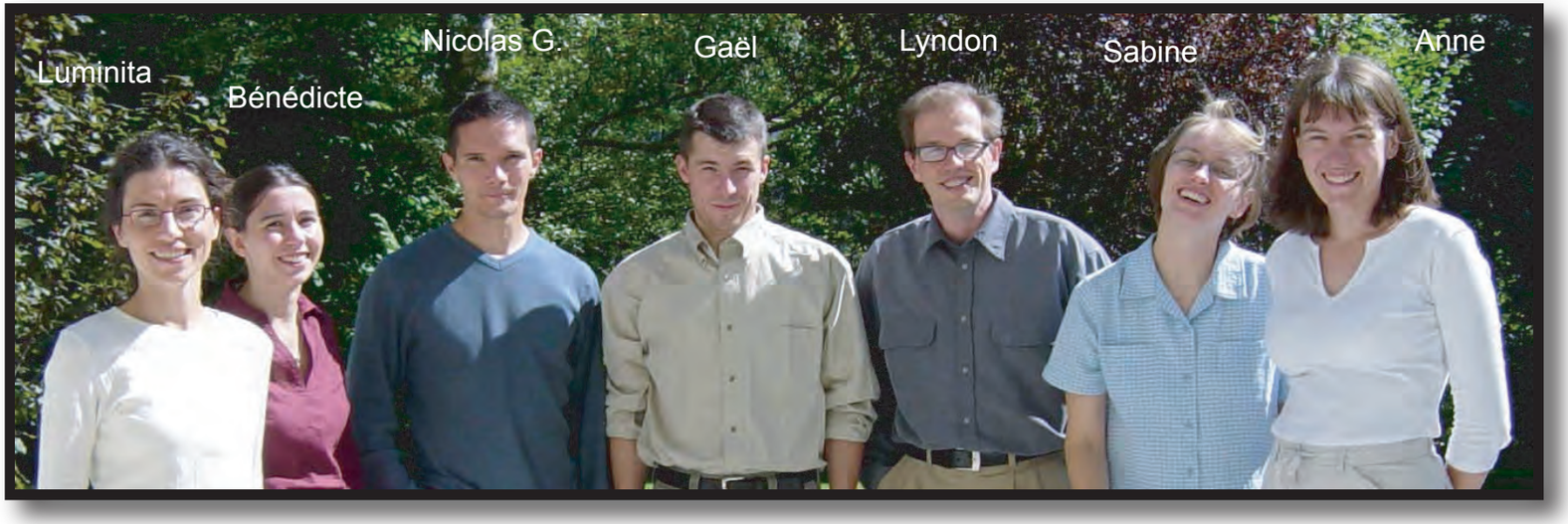
- sensitivity.
- needs a robust experimental quality factor that can be reliably calculated automatically.
- in most cases, does not provide feedback for understanding.
- needs a robust optimisation method that can deal with noise in the quality factor.

Summary II

eOptimisation: An Experimental Approach to Pulse Sequence Design

Advantages of eOptimisation:

- ☑ naturally integrates *all* the error terms.
- ☑ can be adapted to almost any problem, even when neither a theoretical nor a numerical description is available. Is easy to carry out.
- ☑ in some cases, may provide feedback for understanding.
- ☑ can be combined with any robust optimisation method.
- ☑ as long as the model compound is valid, no need for reoptimisation for each sample.
- ☑ it works!



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