Ultrafast NMR Workshop, 2013 SMASH, Santiago de Compostela, Spain

Principles of Ultrafast Multidimensional NMR

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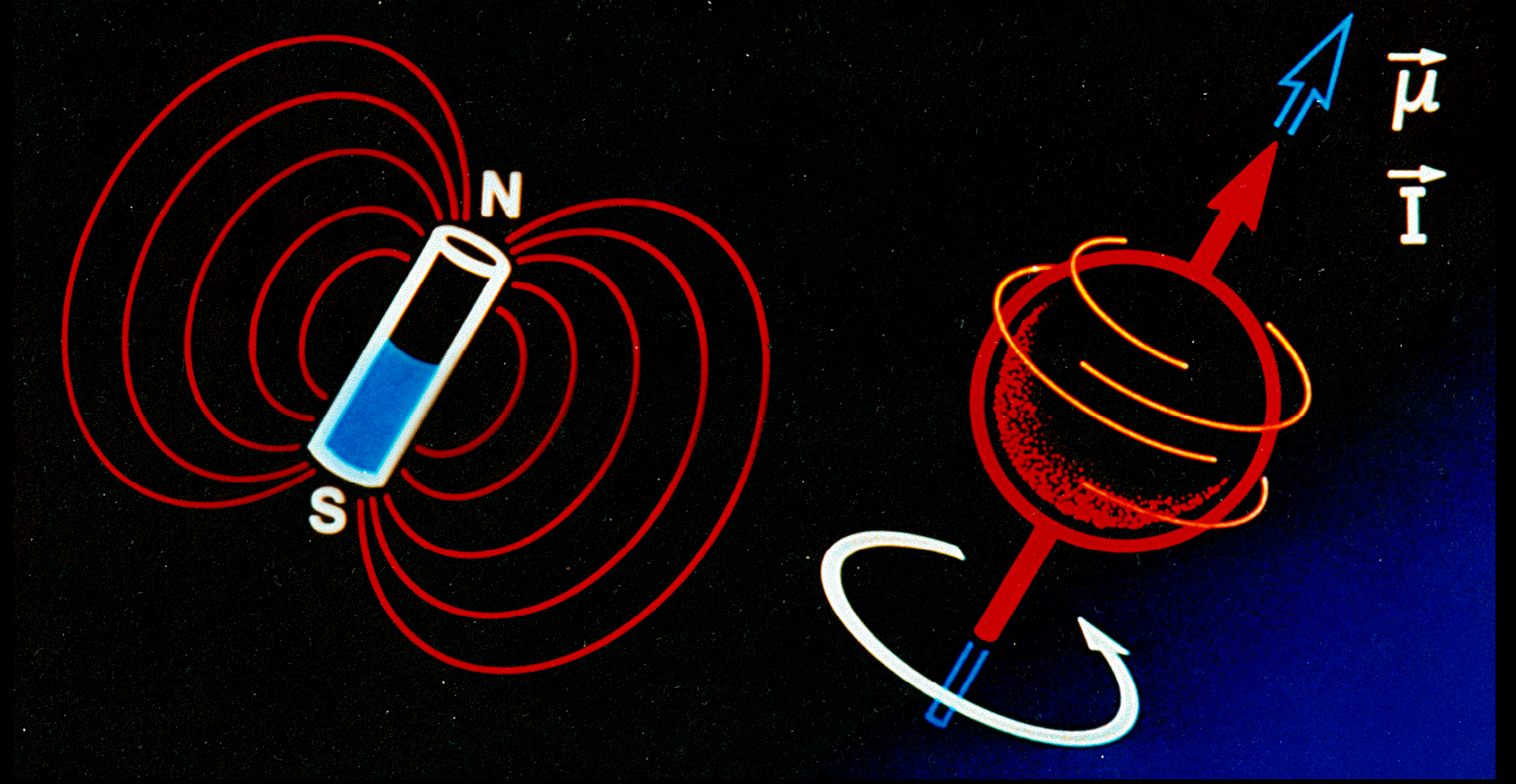
The cast in this play…

THE PRECESSING NUCLEAR SPINS



Quantum mechanical "Tops" (Spins) endowed with a magnetic moment μ *- will precess in a magnetic field at rates proportional to B_o's strength: Larmor frequency $\omega_o = \gamma B_o$*

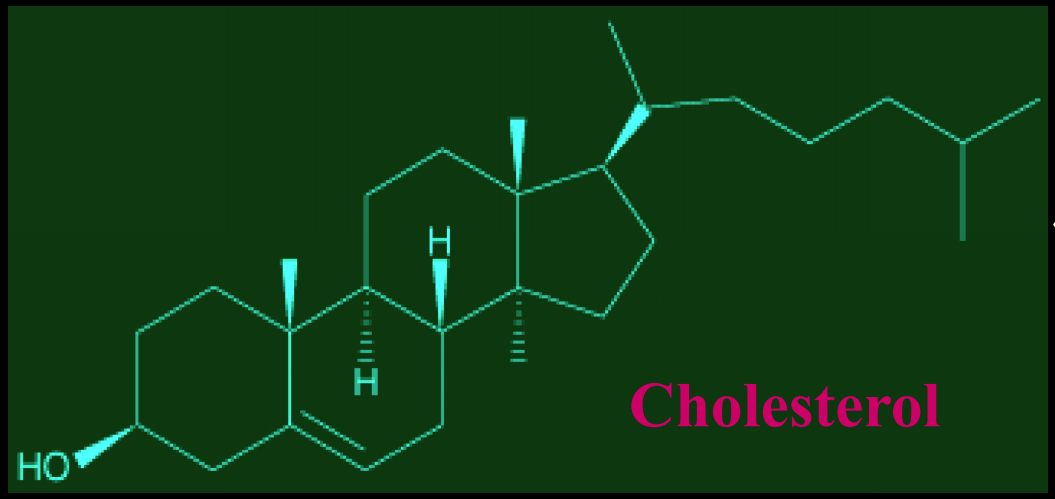
Why is it that we all love NMR?

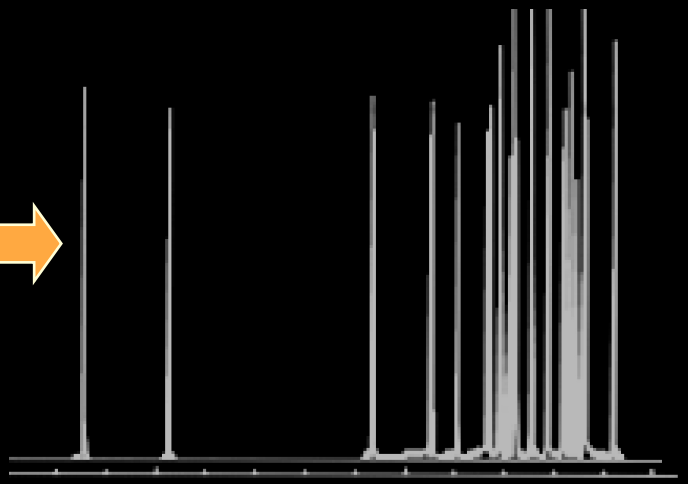
An NMR spectrum is very simple:

One Site - One Frequency - One Peak

Two Sites - Two Frequencies - Two Peaks

A direct atom-by-atom picture of a molecule, mapping Chemistry into sharp spectral peaks appearing at predictable/interpretable frequency positions



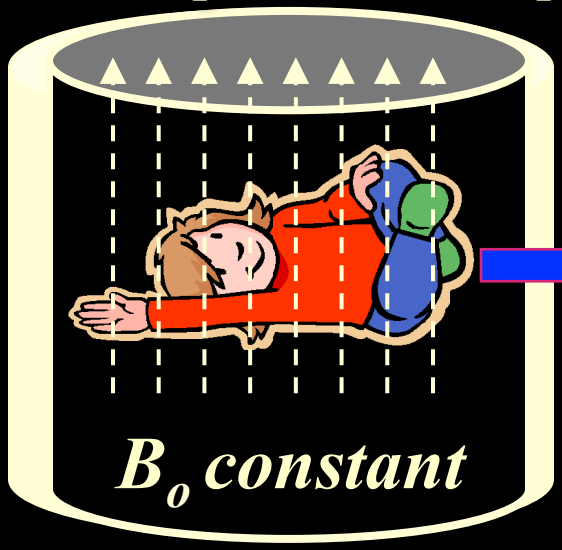


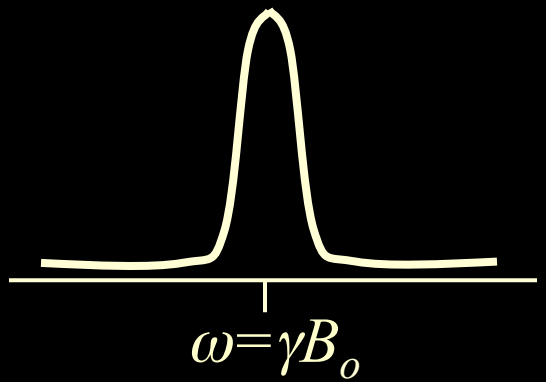
NMR Spectrum

NMR is nowadays exploited, most of the time, in a very different way: Towards the non-invasive localization of spins by field gradients (P. Lauterbur, 1973)

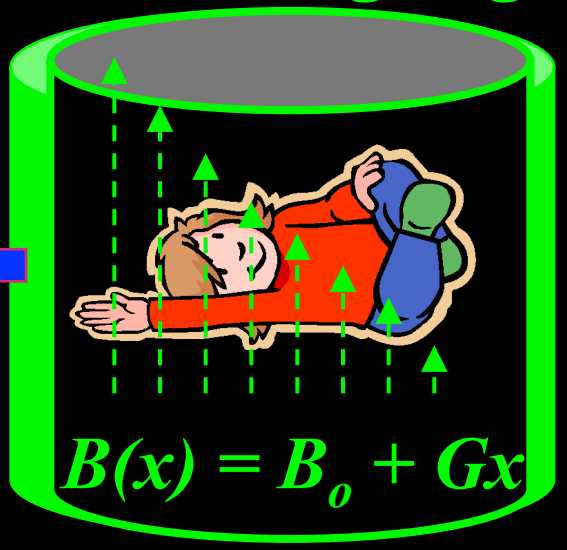
Magnetic Resonance Imaging (MRI)

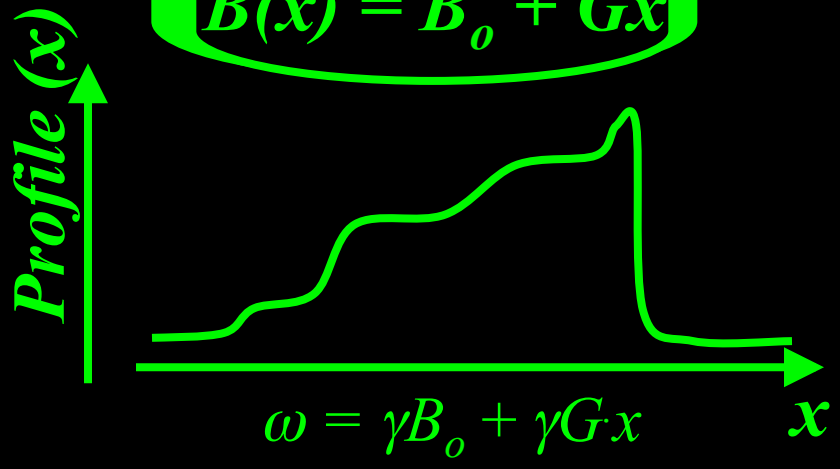
NMR Spectroscopy





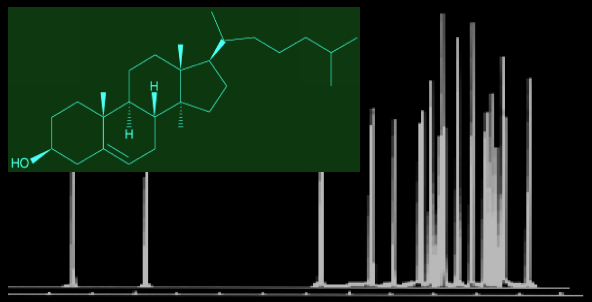
NMR Imaging





Sample (H_2O)

Acquisitions in Nuclear Magnetic Resonance



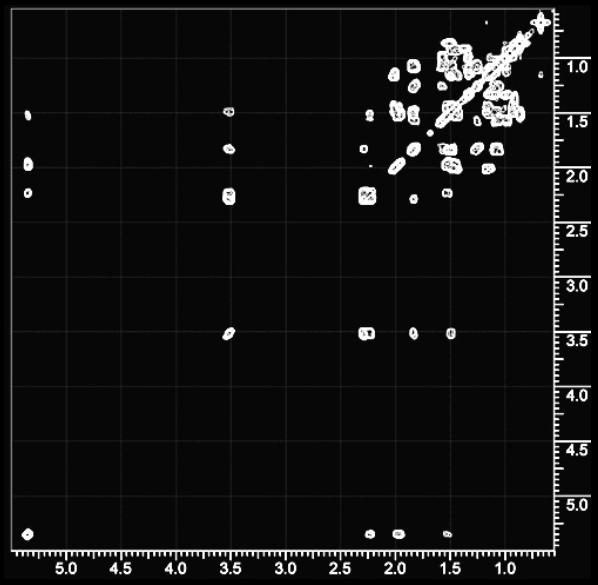
Chemical Fingerprint

Spectroscopy

1D measurements

Spatial Profile

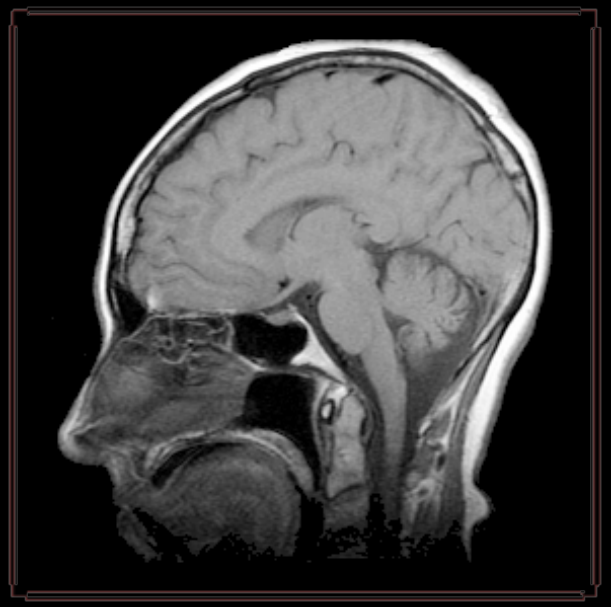
Imaging



Inter-site Correlations

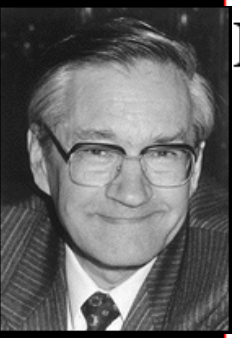
But much of NMR's power comes from

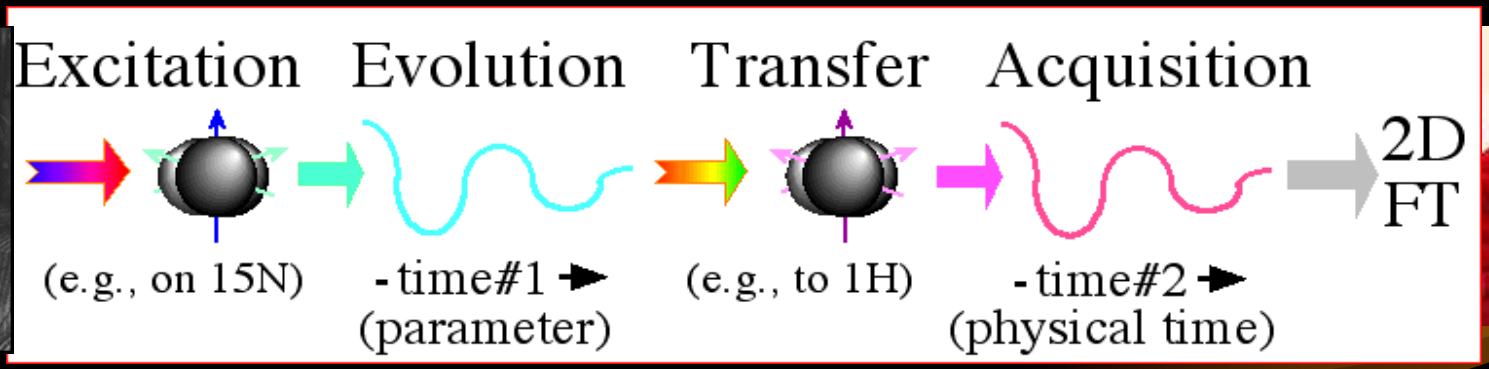
2D measurements



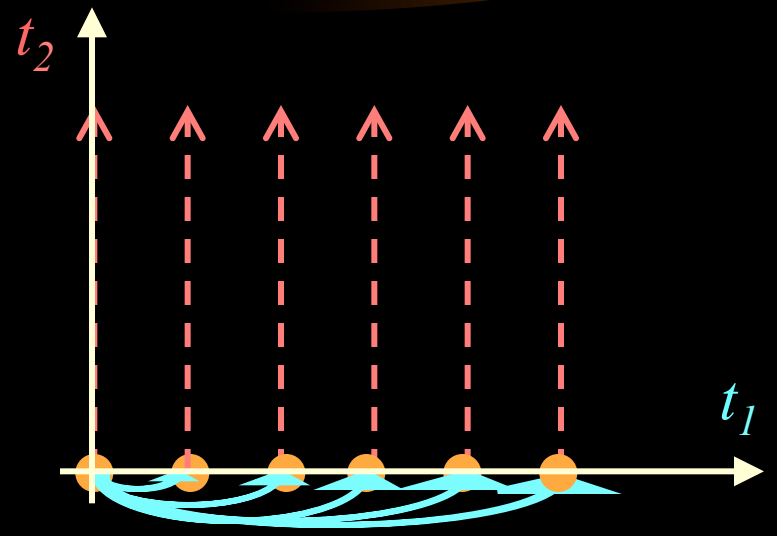
Non-invasive Images

2D MR is based on Jeener-Ernst classical scheme:





A 2D time-domain signal is sampled by two "extraction variables" whose roles are actually very different : t_2 is a physical time; t_1 is monitored in a point-wise, scan-by-scan fashion



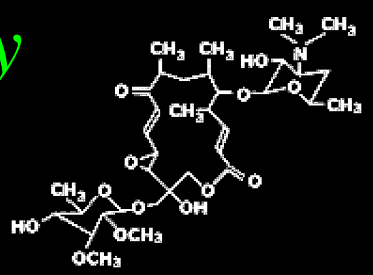
•1D NMR: Single-scan (sub-second)

•2D NMR: Series of 1D NMR acquisitions (minutes)

•3D NMR: Series of 2D NMR acquisitions (hours)

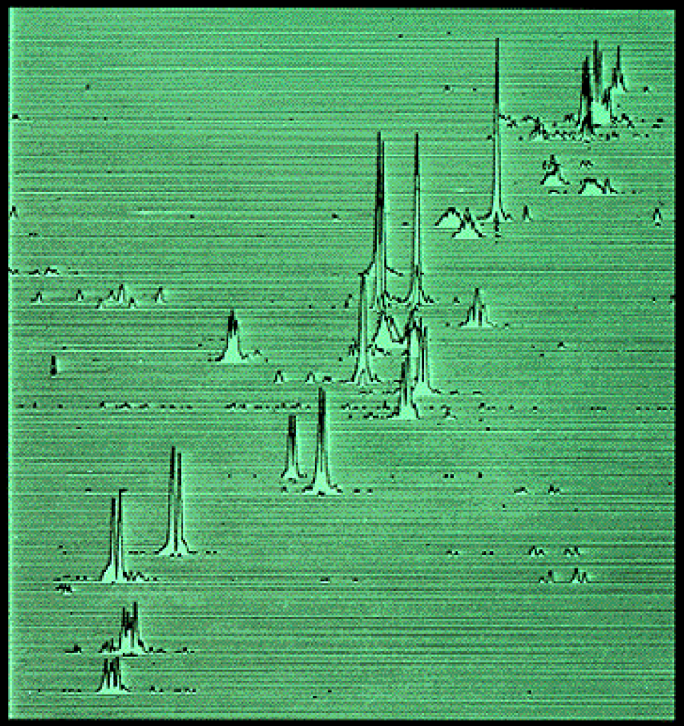
…

KURT WÜTHRICH - 2002 Nobel, Chemistry



The power of 2D NMR spectroscopy

"A typical investigation combines several types of 2D NMR methods (can be modified in many ways, resulting in hundreds of different types of 2D NMR experiments) and **even 3D or 4D experiments**. The accumulated information provides often a detailed picture of the molecular structure. The complete three-dimensional structure of many proteins and other biological macromolecules in solution has been determined in this way."



MRI's k-Space

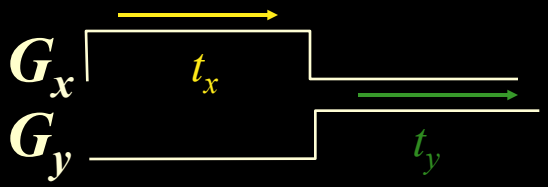
In MRI: It's the gradients that encode the "interactions"

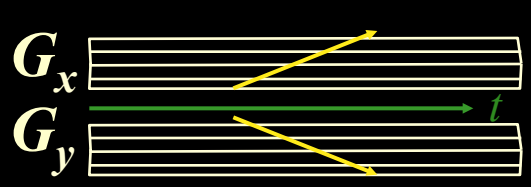
$k_x = G_x t_1$
$k_y = G_y t_2$

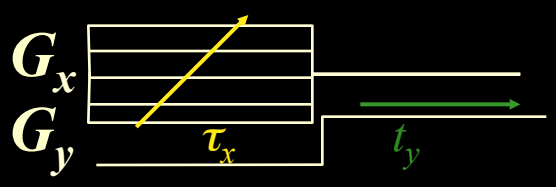
$$S(t_1,t_2) = \iint \rho(x,y)\, exp[i(t_1 \cdot G_x x + t_2 \cdot G_y y)]\, dxdy$$

$$\Rightarrow S(k_x,k_y) = \iint \rho(x,y) exp[i(k_x x + k_y y)] dxdy$$

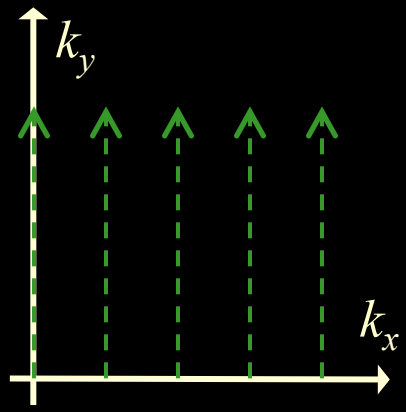
*Get the image by 2D FT vs k_x,k_y; **wavenumbers in reciprocal space***



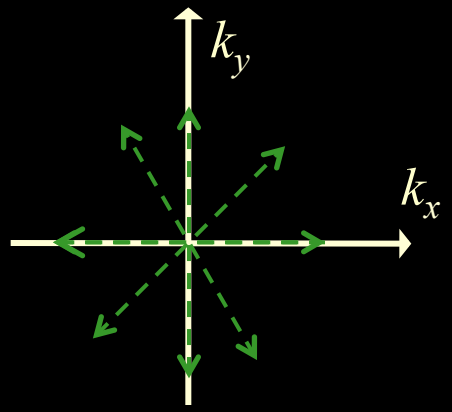




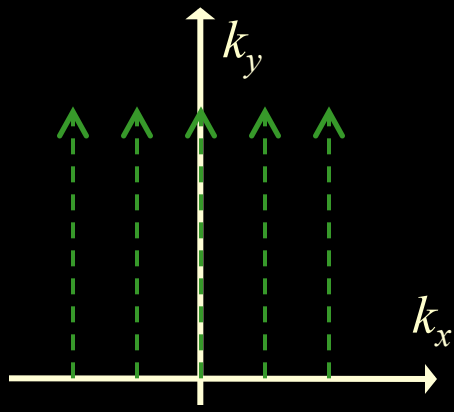
FT imaging



Back-Project

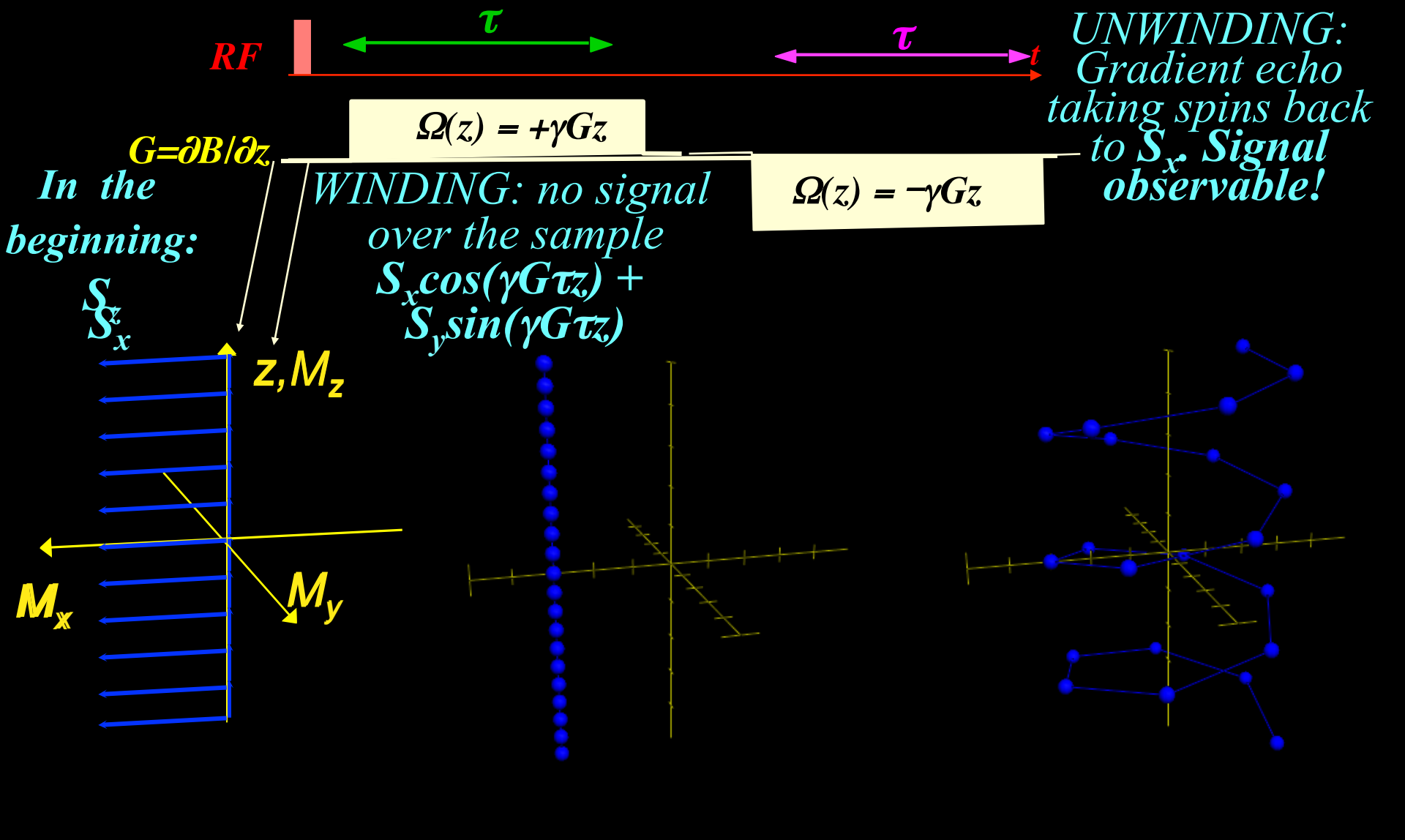


Spin-Warp



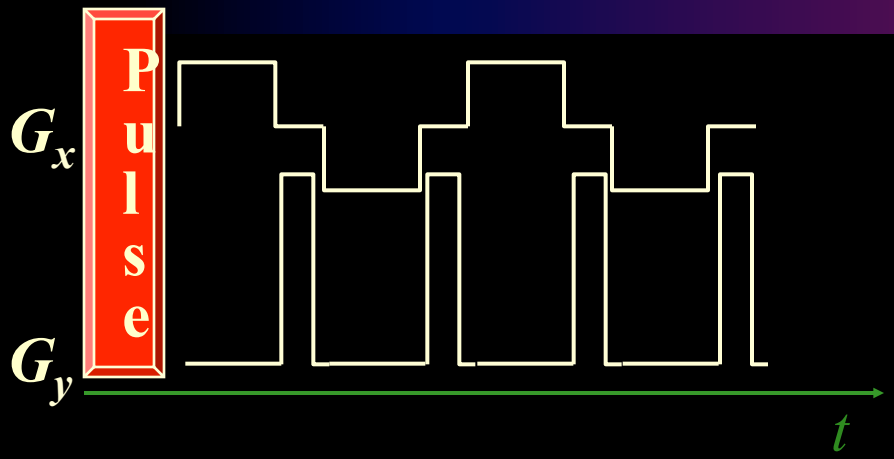
Gradients: Windings & Echoes

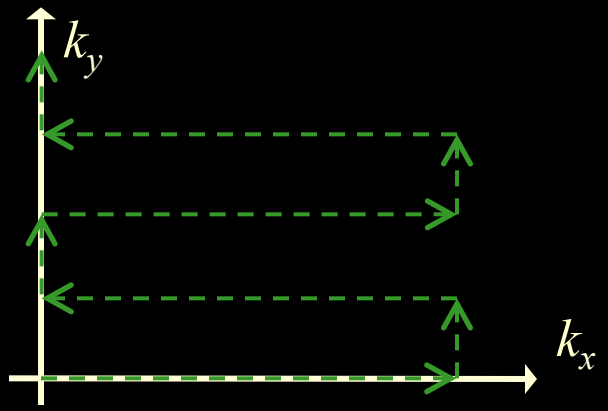
Due to their particular nature, MRI interactions are 100% reversible. This gives an opportunity to "echo" their effects:

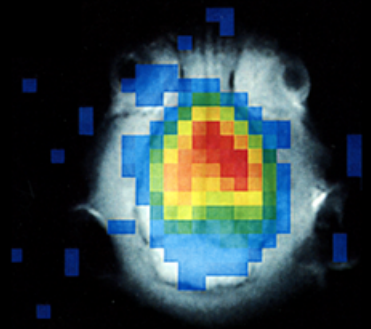


"Ultrafast" Imaging: 2D MRI in a single scan

(Mansfield, 1976; Nobel Prize in Medicine, 2003)







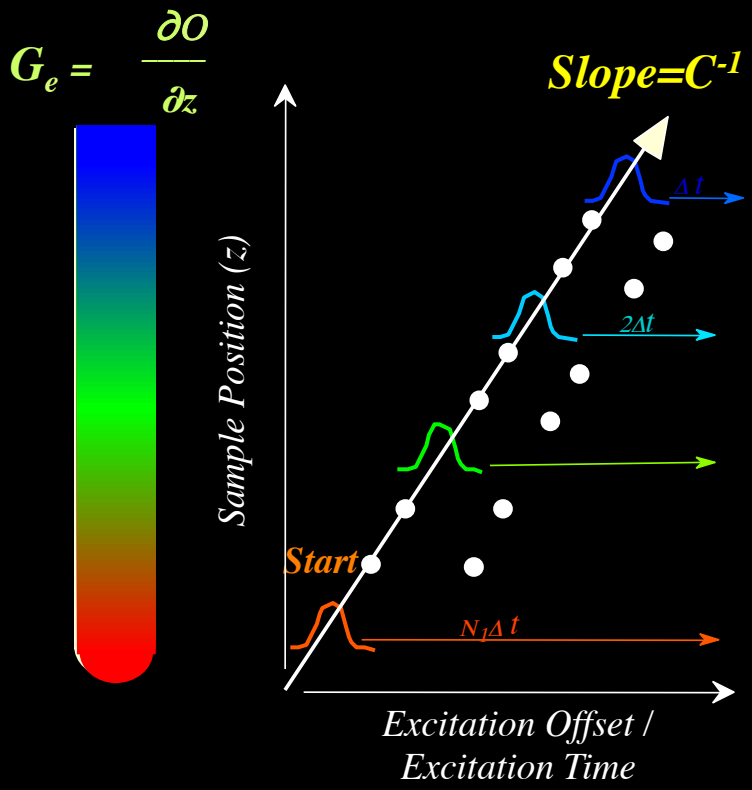
Echo Planar Imaging →→→→ Functional MRI

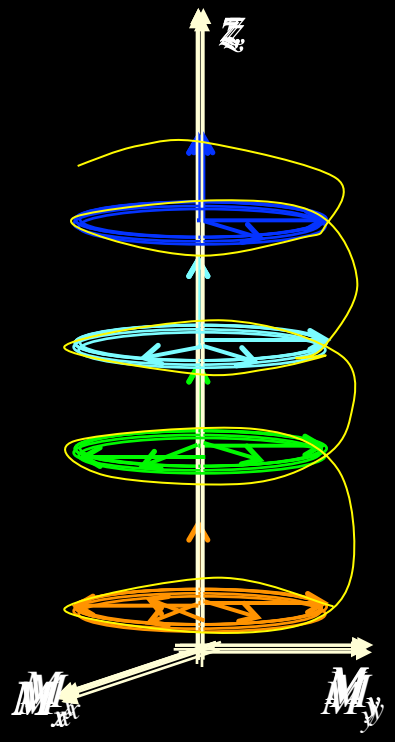
2D NMR spectroscopy can also be carried out "Ultrafast"

Starting point: An alternative way to collect 1D NMR data based on encoding the MR interactions along a Spatial Domain

The Principle: **Excite spins @ different z's as a function of t**

Spins are excited and begin evolving under the action of an internal Ω_1



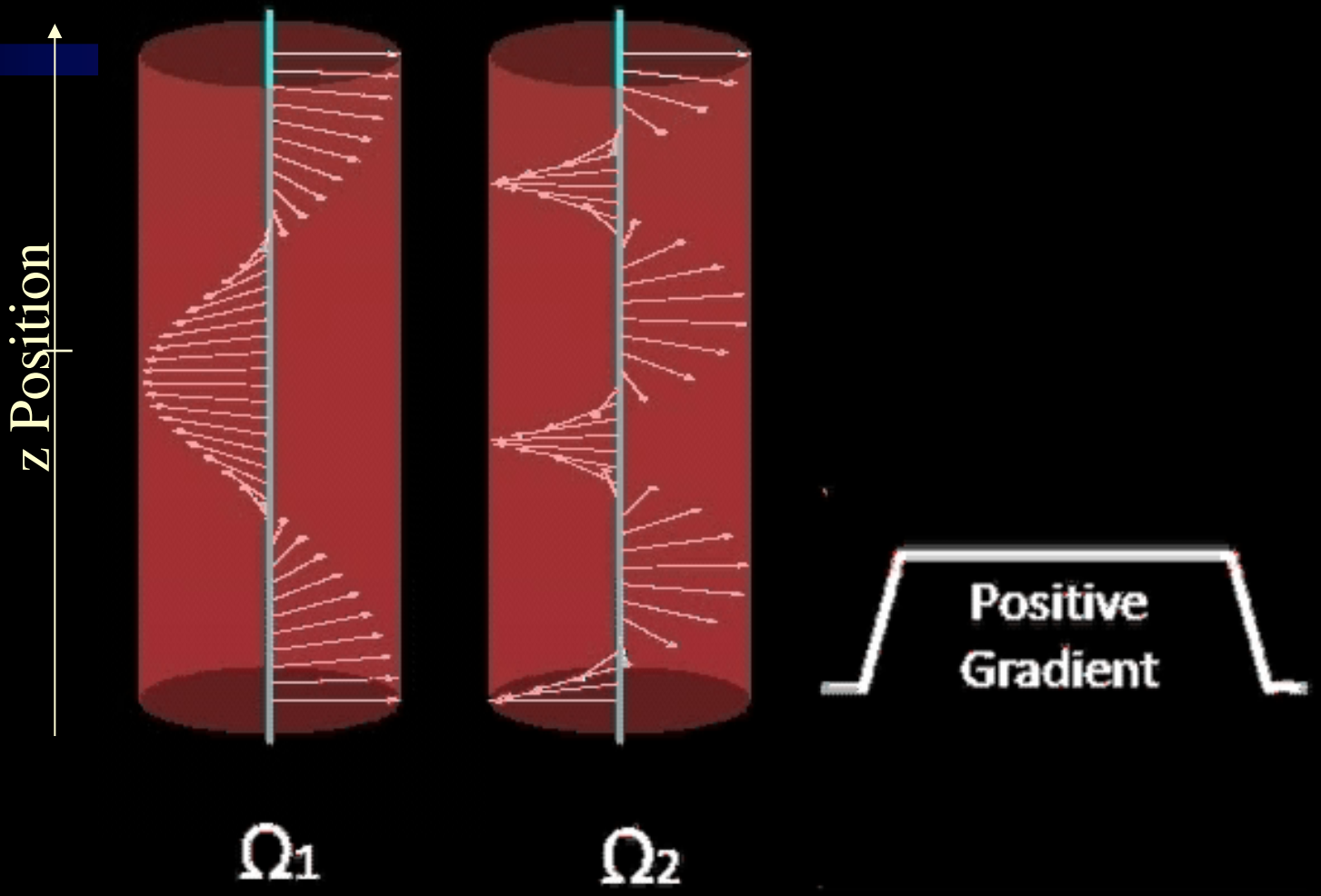


This process creates a shift-driven winding of the x-y magnetization:

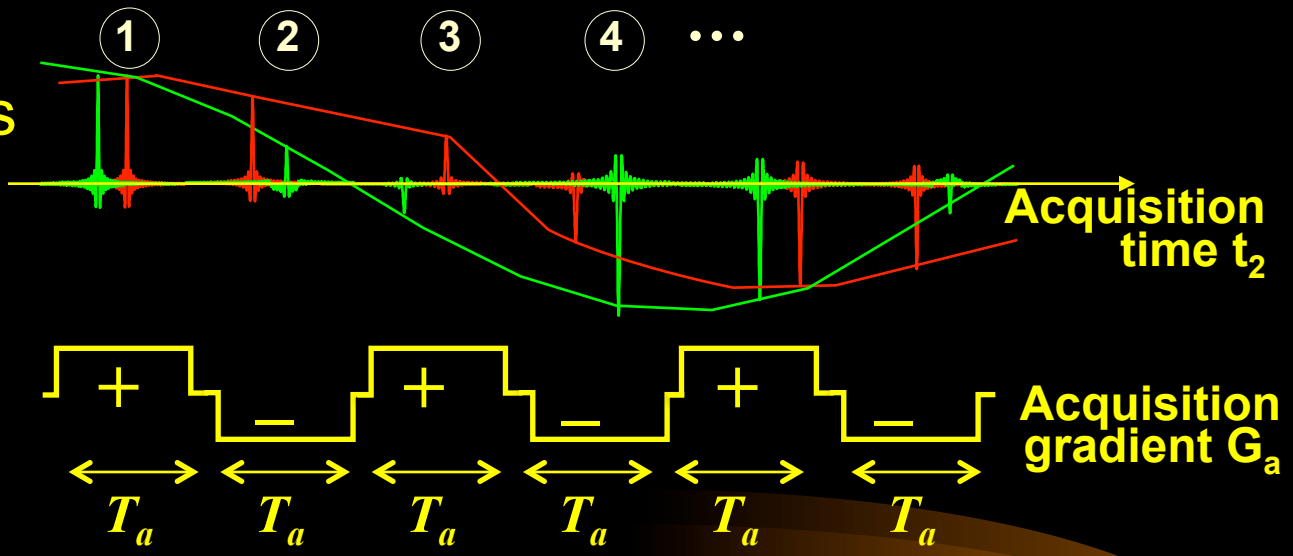
$$M_+(z) \approx \exp[iC\Omega_1 z]: \text{NO OVERALL SIGNAL}$$

*An acquisition gradient can then unravel the Ω evolution frequencies - **revealing them as echoes***

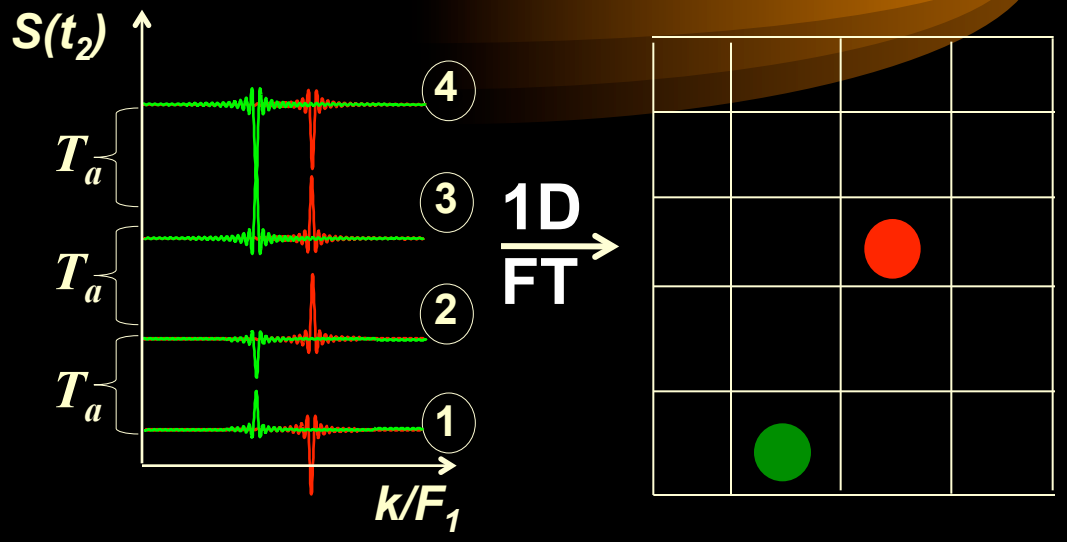
The "S(k)" time-domain signal manages to map the I(Ω) NMR spectrum being sought directly - no FT involved



Oscillating this gradient numerous times over the course of an acquisition time t_2 can unravel the direct-domain frequencies Ω_2



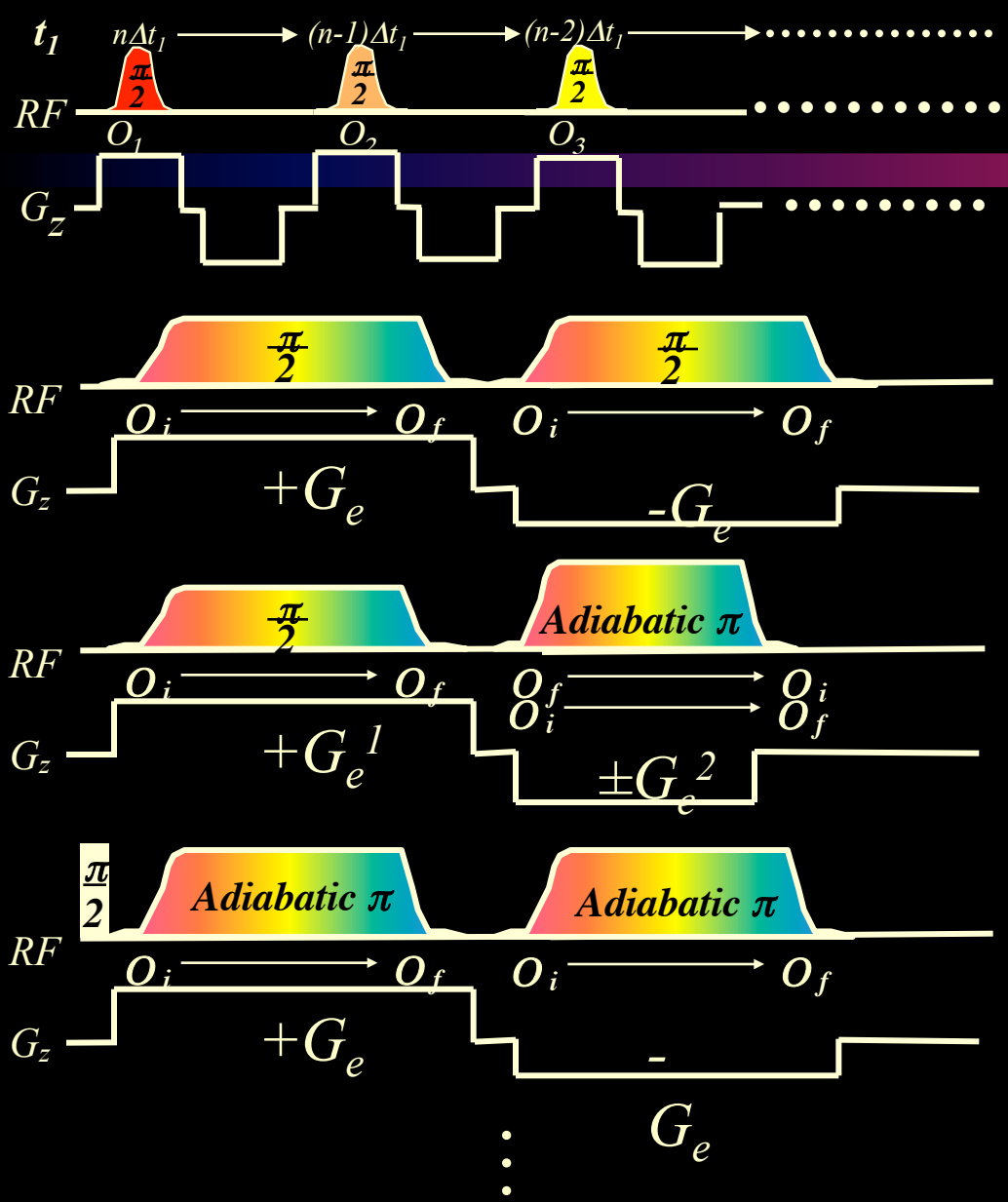
Finally, rearrangement of this interferogram in the correct k/F_1 & t_2 space & 1D FT vs t_2…



…provides a 2D NMR spectrum/image in 1 scan

Ultrafast 2D NMR:

Spatially-Encoding the Internal NMR Interactions



A Discrete Approach

A Continuous AM Approach

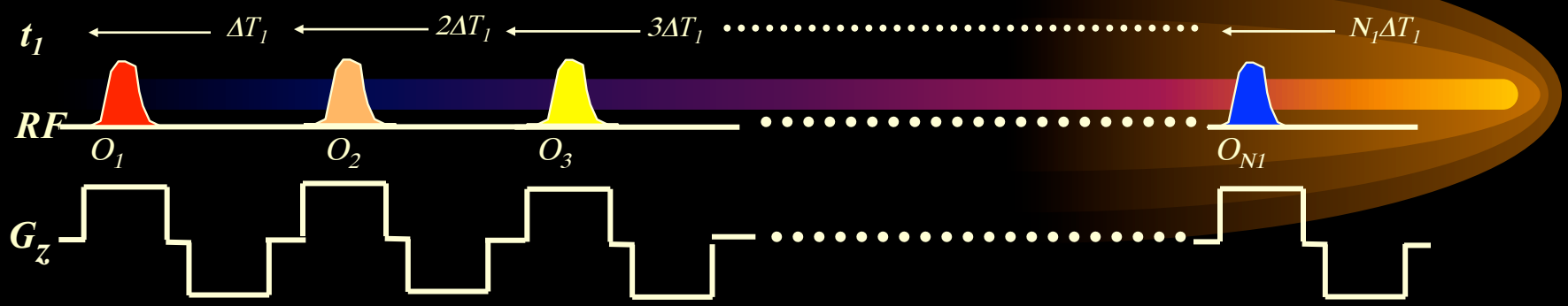
A Continuous PM Approach

A Continuous CT Approach

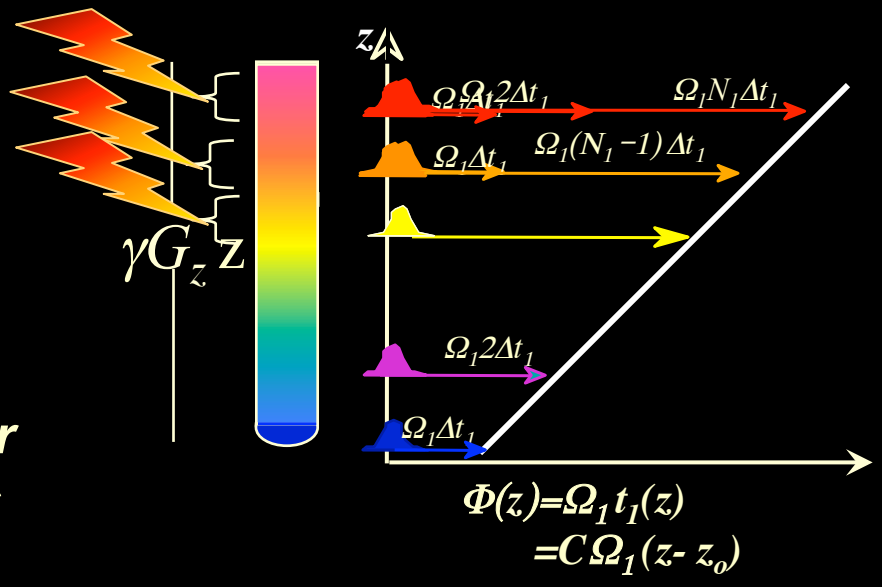
⋮ ⋮

The simplest way to understand the spatiotemporal encoding

The Discrete Encoding Approach



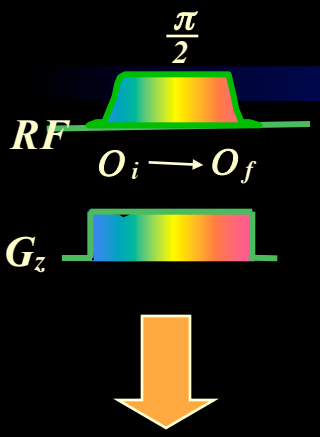
The combination of echoing field gradients & selective, time-incremented RF pulses, results in the encoding of a purely internal evolution over multiple t_1 increments within the same single-shot experiment.

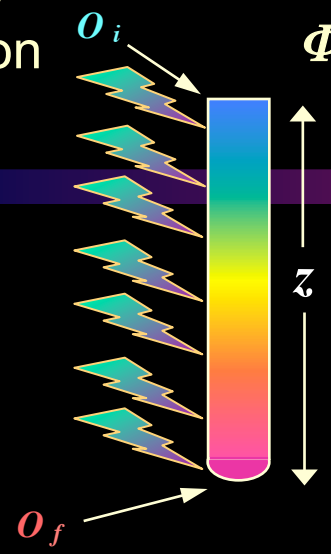


As in conventional NMR, the spectral resolution will be given by the maximum t_1^{max} time over which we allow isochromats to evolve

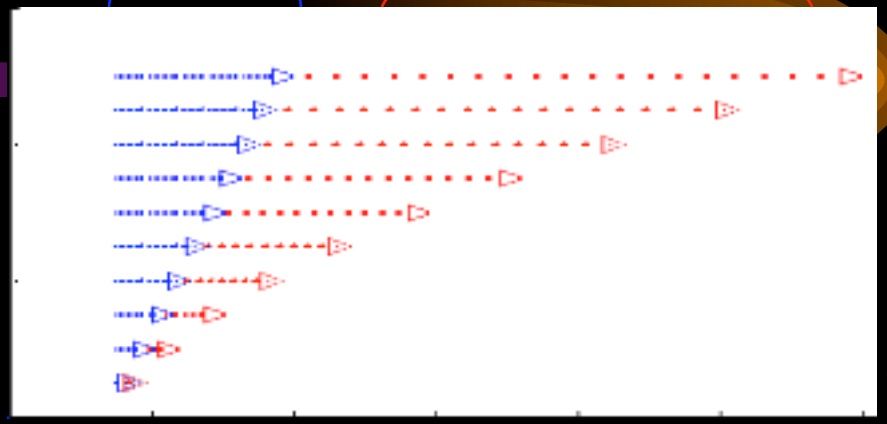
How do continuous approaches achieve a gradient-echo but avoid a shift-echo?

Begin with a frequency swept (chirped) excitation



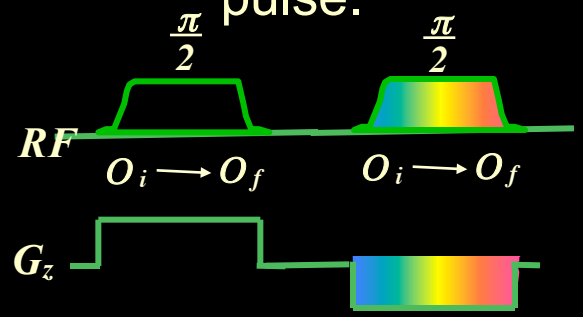


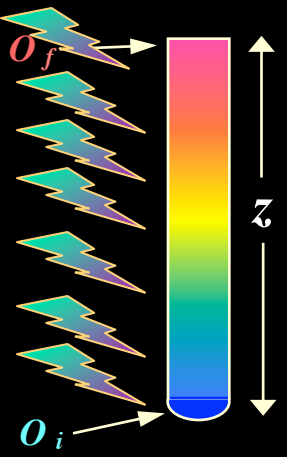
$$\Phi_{excite}(z) = \underbrace{\Omega_1\, t(z)}_{\alpha z} + \underbrace{\gamma G_z z\, t(z)}_{\beta z^2}$$



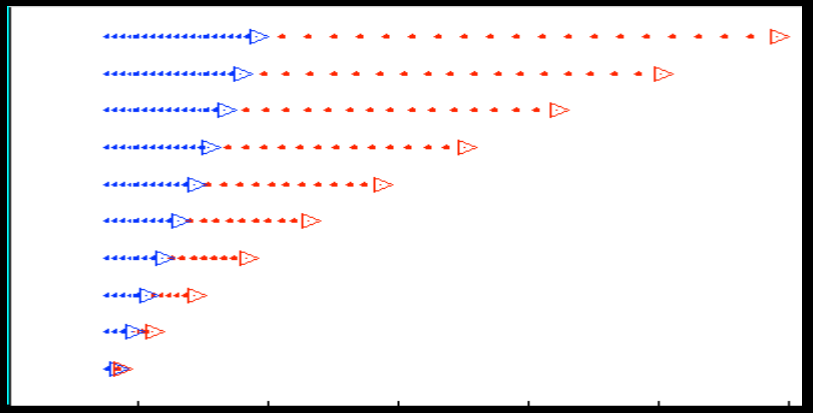
$\Phi(z)$

Conclude with a frequency-swept storage pulse.





$$+\Phi_{storage}(z) = \Omega_1\, t(z) - \gamma G_z z\, t(z)$$

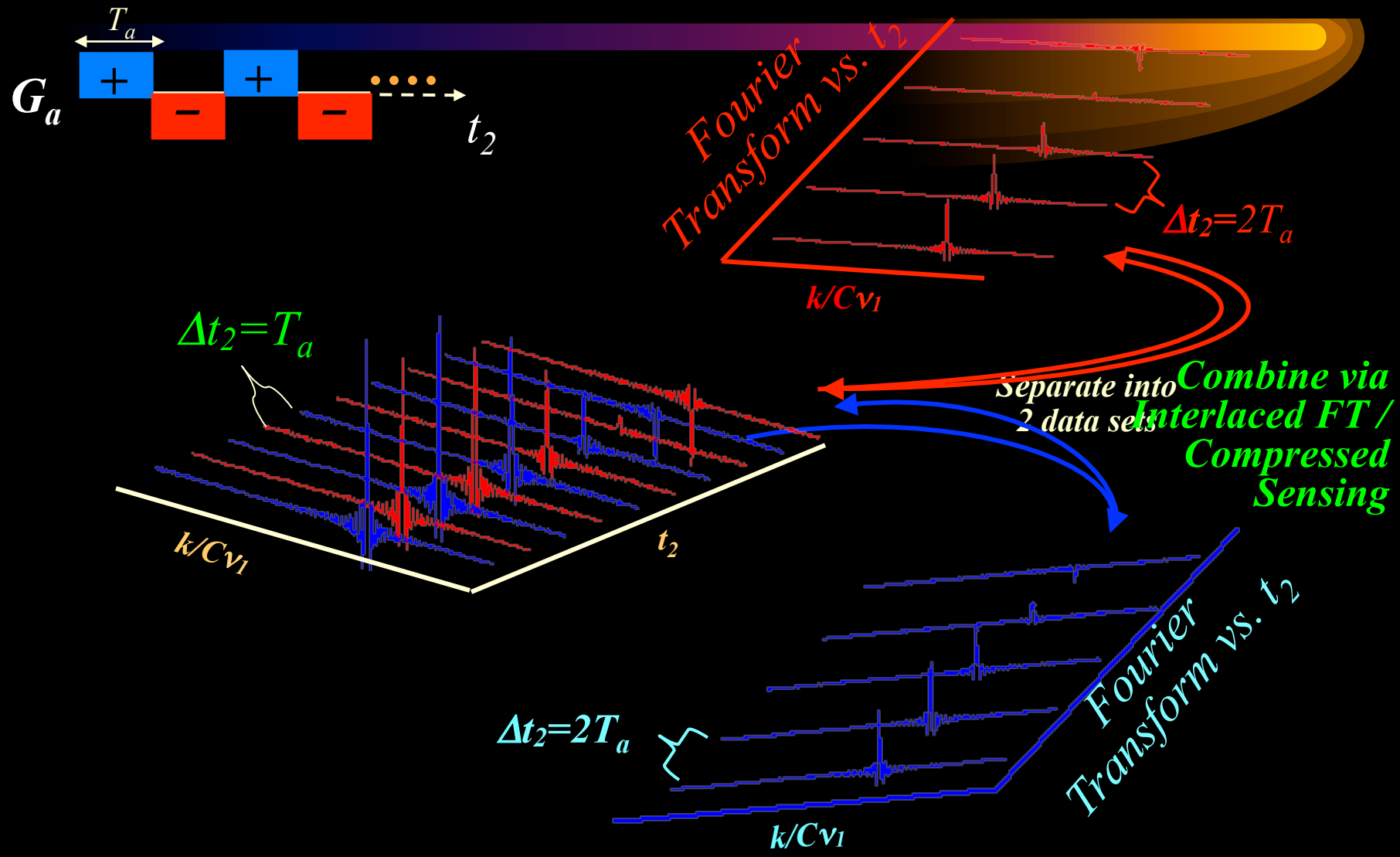


$$\Phi_{total}(z) = 2\Omega_1 t(z)$$

Acquisition and processing

Spatial decoding and the t_2 Fourier Transform

During the single-scan 2D NMR acquisition of a $(k/\nu_1,t_2)$ data set:



A closer look at two ways of retrieving 2D NMR spectra:

In traditional time-encoded 2D NMR

We detect $S(t_1,t_2) = \int_{all\ \Omega_2's} d\Omega_2 \left[\int_{all\ \Omega_1's} d\Omega_1 I(\Omega_1,\Omega_2) e^{i\Omega_1 t_1} e^{-t_1/T_2} \right] e^{i\Omega_2 t_2} e^{-t_2/T_2}$

and we get what we want by 2D FT $I(\nu_1,\nu_2) \propto \int_{all\ t_2's} dt_2 \left[\int_{all\ t_1's} dt_1 \{ S(t_1,t_2) \} e^{-i\nu_1 t_1} \right] e^{-i\nu_2 t_2}$

In spatiotemporal-encoded 2D NMR (where $t_1 = C \cdot z$)

We detect $S(k,t_2) = \int_{all\ z's} dz \left\{ \int_{all\ \Omega_2's} d\Omega_2 \left[\int_{all\ \Omega_1's} d\Omega_1 I(\Omega_1,\Omega_2) e^{i\Omega_1 Cz} e^{-Cz/T_2} \right] e^{i\Omega_2 t_2} e^{-t_2/T_2} \right\} e^{ikz}$

and we get what we want by calling $-k/C = \nu_1$, and doing a <u>1D</u> FT $I(\nu_1,\nu_2) \propto \int_{all\ t_2's} dt_2 \left[S(k/\nu_1, t_2) \right] e^{-i\nu_2 t_2}$

These relations lead to the Nyquist criteria & other characteristics of ultrafast 2D NMR spectra:

- $(2T_a)^{-1} \leq SW(\nu_2) \leq (T_a)^{-1}$

depending on whether conventional or interlaced $FT(t_2)$ is used

- $SW(\nu_1) = k_{max}/C \approx L \cdot (\gamma_a G_a T_a)/t_1^{max}$

the longer T_a can be made, the weaker of a G_a is needed

- **Peak shapes along ν_1: as in conventional 2D NMR**

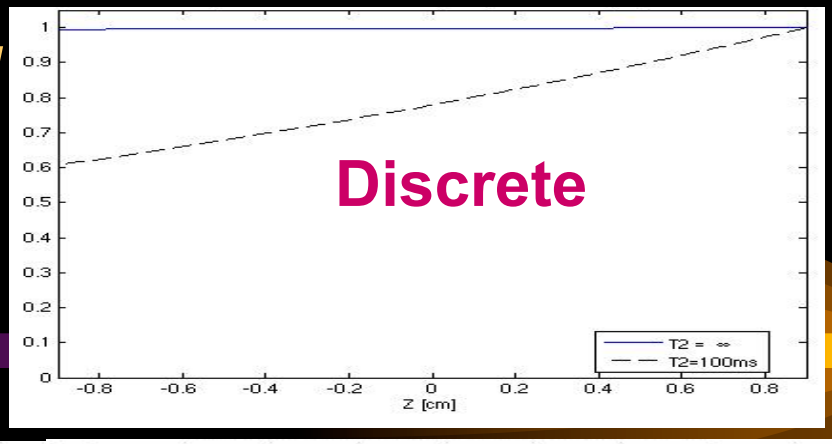
first order phase distortion may arise; line widths α $(T_2)^{-1}$, $(t_1^{max})^{-1}$

- **Purely absorptive line shapes are feasible**

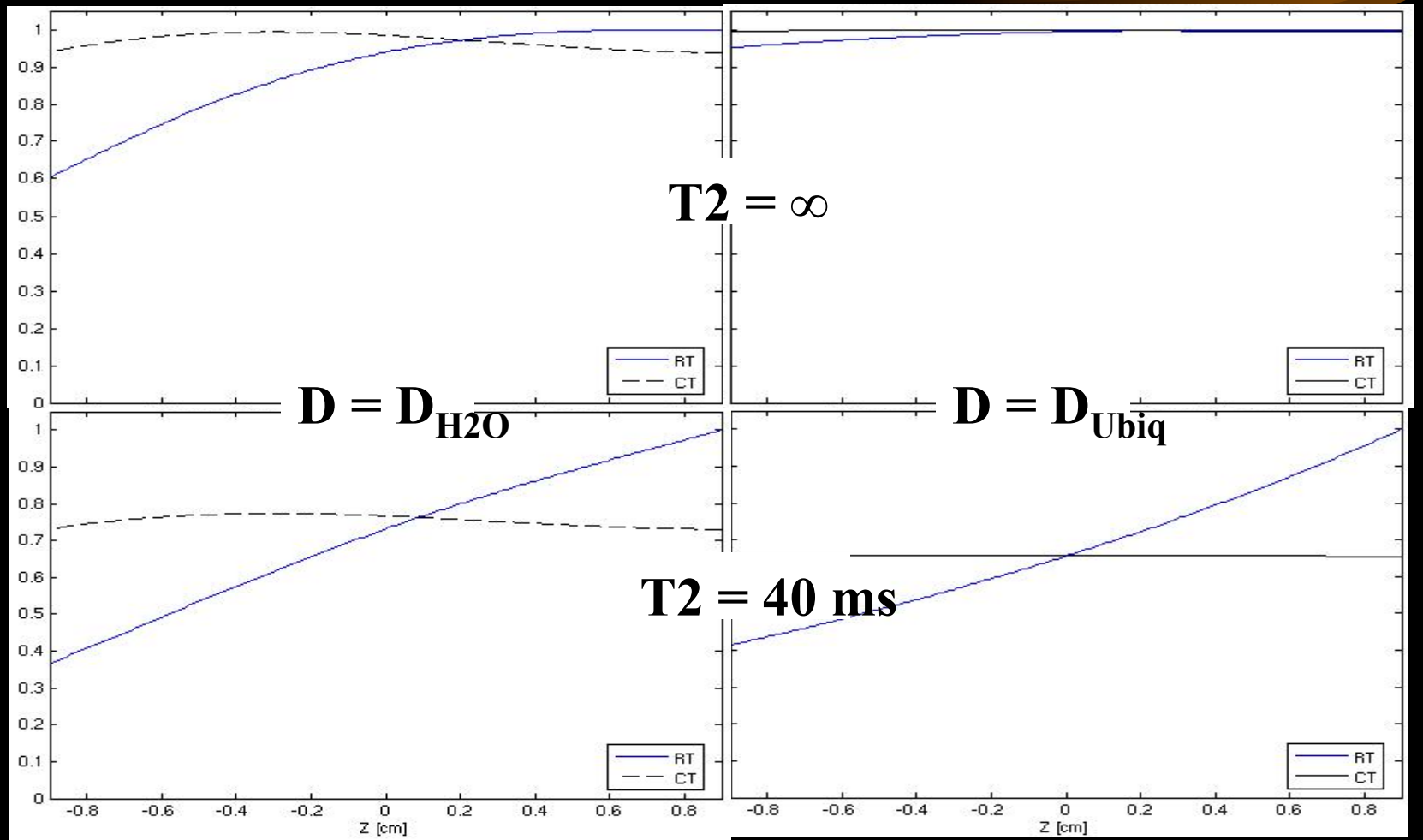
- $(S/N)_{optimized} \approx (S/N)_{1\text{-}scan} * \sqrt{[SW(\nu_2)/\gamma_a G_a L]}$

S/N per unit time is decreased, not because the signal is smaller, but because the noise is larger: The receiver bandwidth needs to accommodate a gradient-driven effect. With current state-of-the-art hardware, LODs ≈ 1-2mM/scan

Diffusion & T_2 during the spatial encoding are also sources of loss – and hence lineshape determining factors (HSQC example, t_1^{max}=40 ms)



Continuous

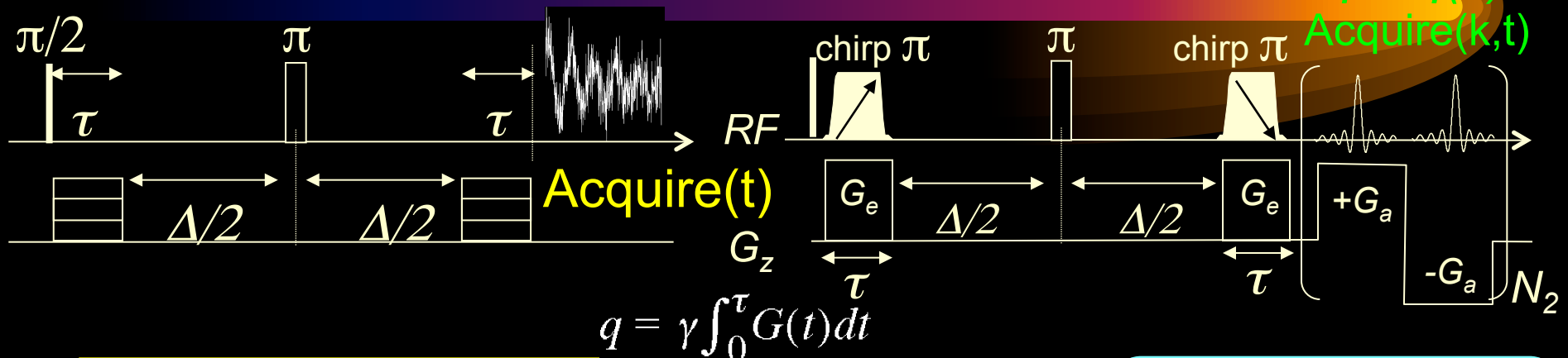


Within a high-resolution context, these losses can be exploited towards

Single-Scan 2D DOSY NMR

Conventional PGSE: q = incremented

"Ultrafast" PGSE: q = q(z)



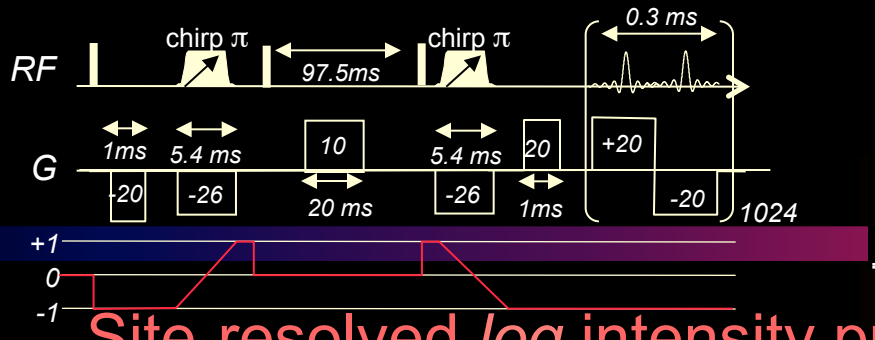
$$q = \gamma \int_0^{\tau} G(t)\,dt$$

$$\ln\left[\frac{A(q)}{A(0)}\right] = -q^2\left(\Delta - \frac{\tau}{3}\right)\cdot D$$

$$\ln\left[\frac{A(z)}{A(G_e = 0)}\right] = -q^2\left(\frac{2z}{L}\right)^2\left(\Delta + \frac{\tau}{2}\right)\cdot D$$

By fitting the quadratic z-dependence arising upon 2D FT of the FID vs (k,t), the D-coefficient becomes available for every chemical site

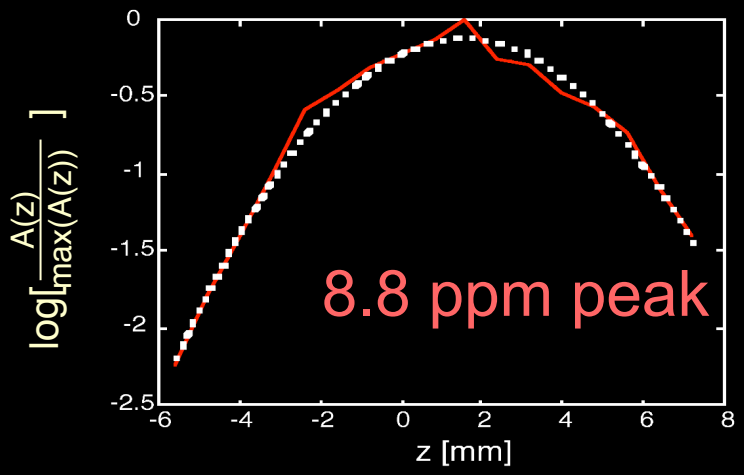
Stimulated-echo single-scan 2D DOSY sequence

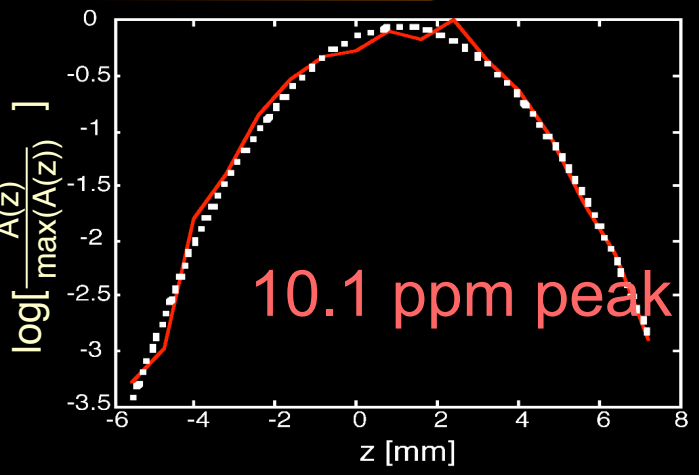


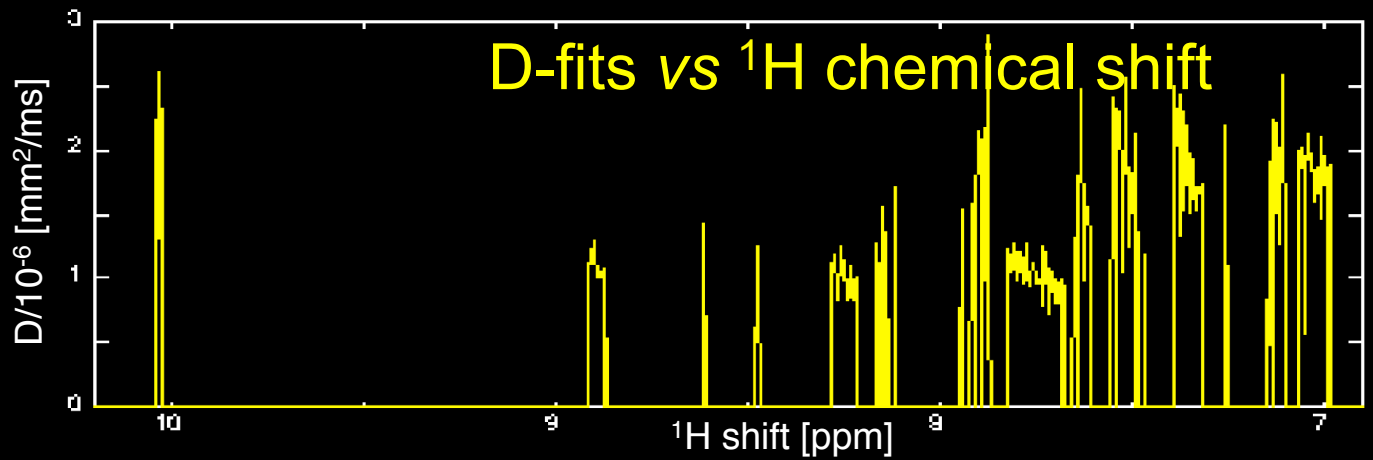
Example

Single-scan 2D DOSY character-ization of a Tetraphenyl-porphyrin + Benzaldehyd e + Diphenyl-ether solution in $CDCl_3$

Site-resolved *log* intensity profiles for different sites





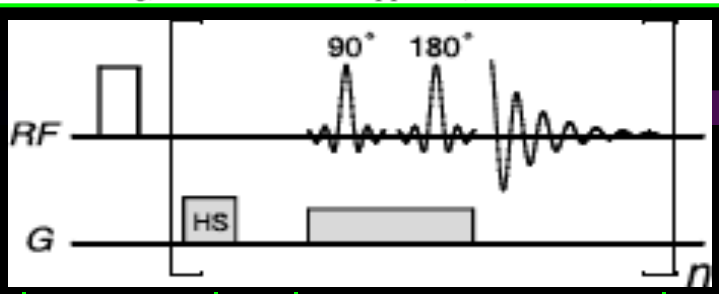


Single-scan 2D NMR: Encoding the Spins' Relaxation

Single-scan longitudinal relaxation measurements in high-resolution NMR spectroscopy

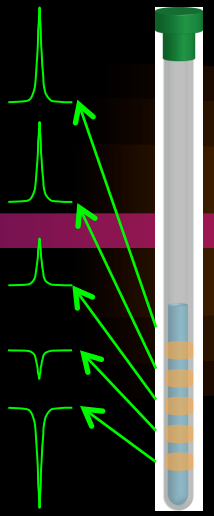
Journal of Magnetic Resonance 164 (2003) 321–328

Nikolaus M. Loening,[a,*] Michael J. Thrippleton,[b] James Keeler,[b] and Robert G. Griffin[a]



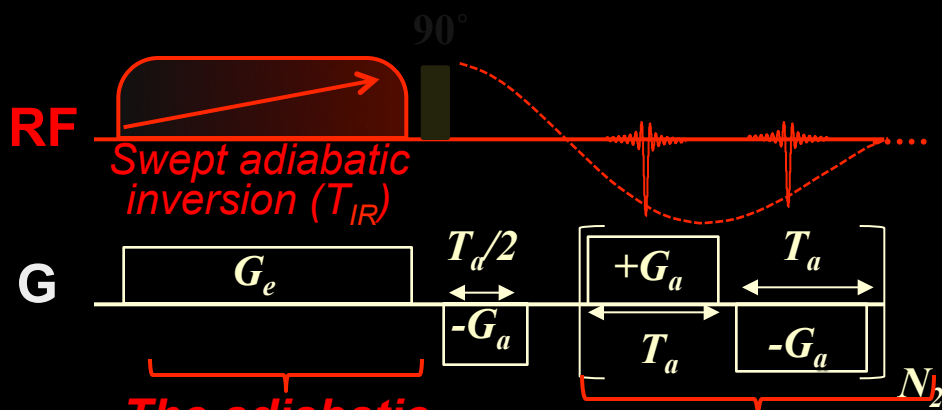
Inversion-recovery time

Slice selective excitation + acquisition vs time t_2



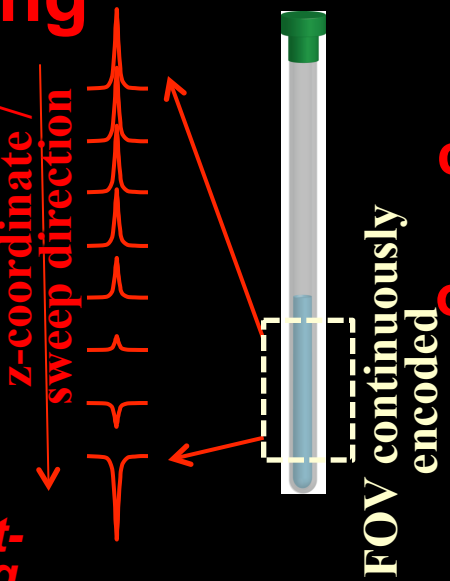
Non-selective Inversion followed by slice-selective recall & acquisitions: Suitable for T_1's >>T_2

Continuous, ultrafast inversion recovery with spatial decoding



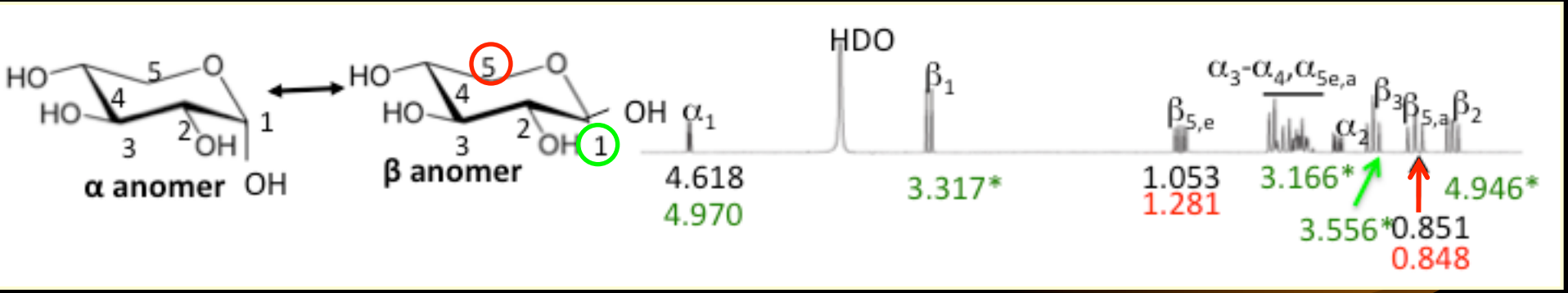
The adiabatic inversion defines the I-R time

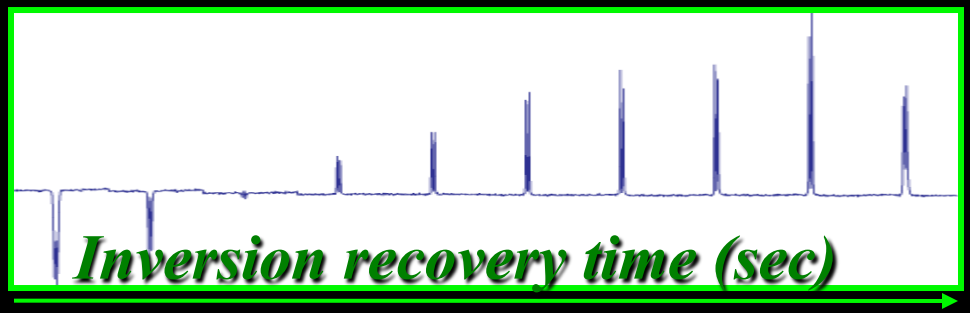
EPSI: Space- & Shift-dependent decoding



Inversion & Recovery encoded continuously & decoded by one full sample readout: Suitable for T_1≈T_2

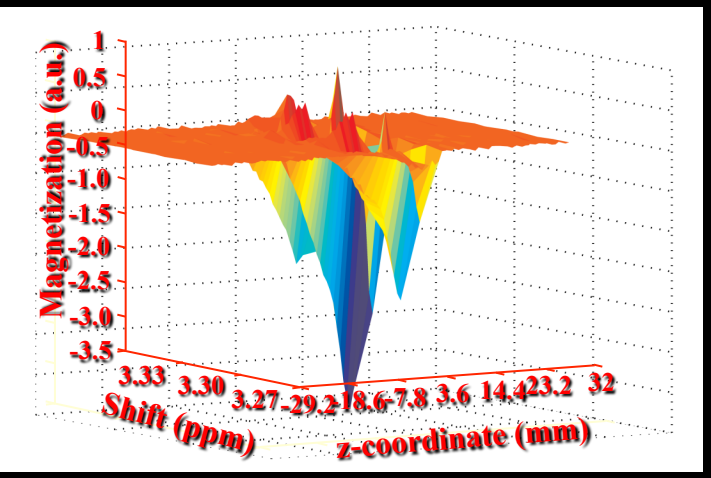
Single-scan T_1 measurements: Xylose

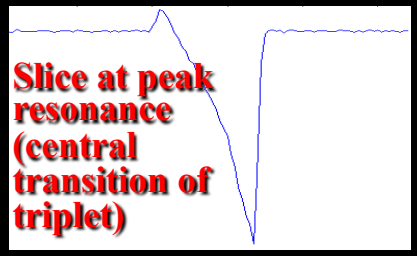


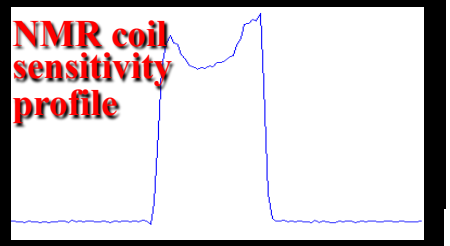


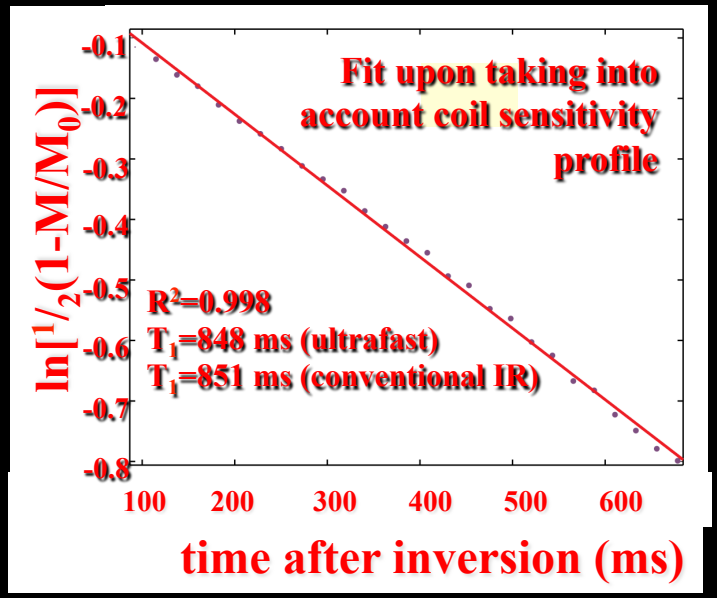
Multislice/multiacq on $H_{1,\beta}$

Single-scan on $H_{5a,\beta}$



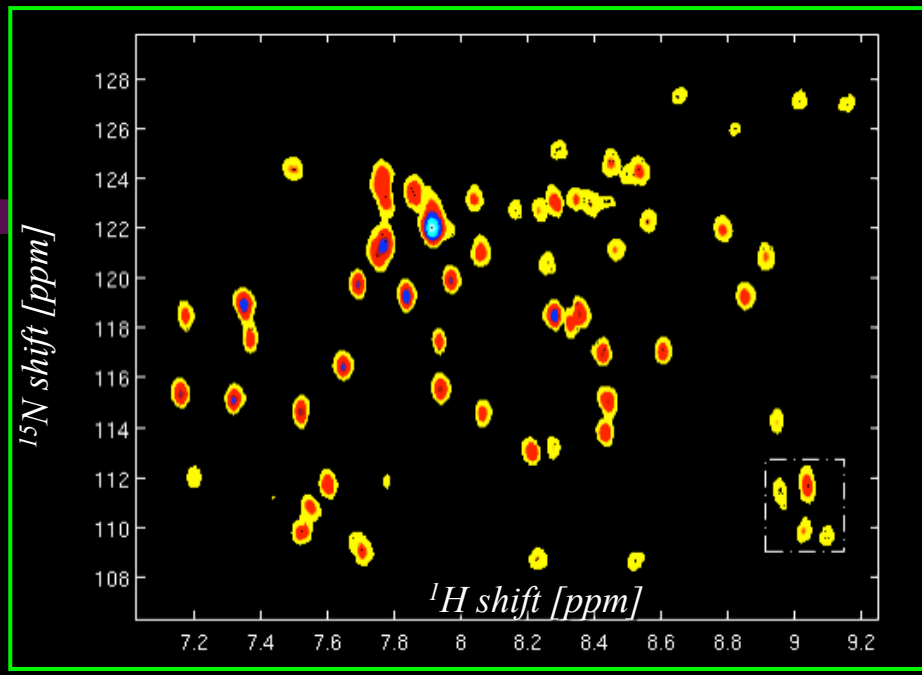


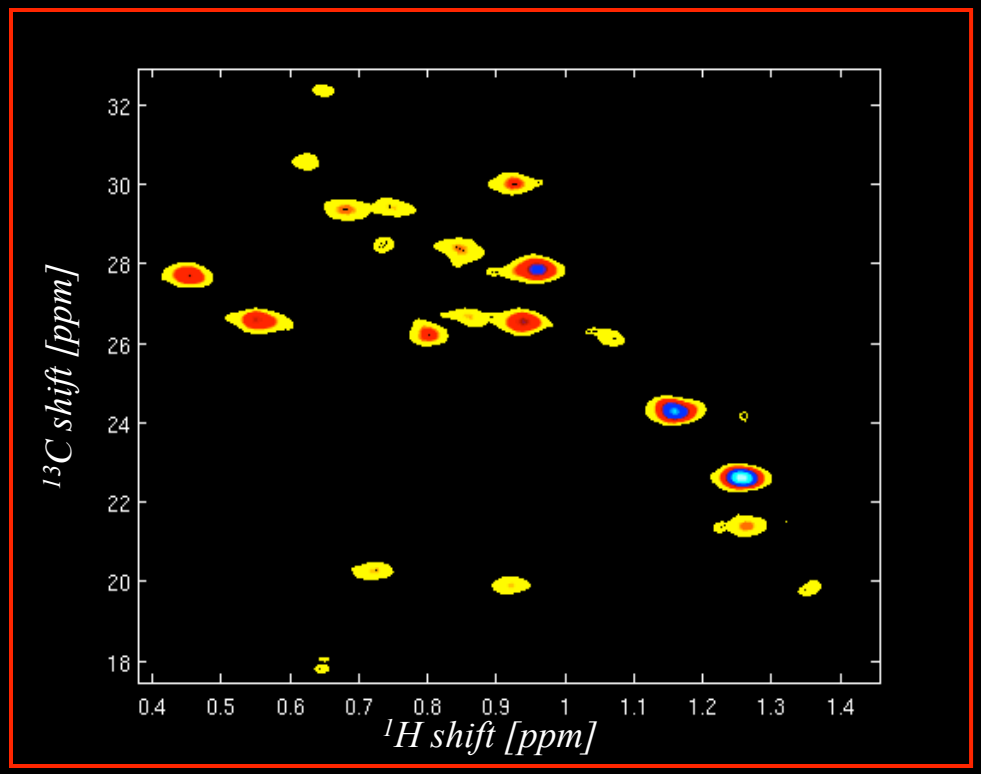




Single-scan 2D NMR - Biomolecular Examples

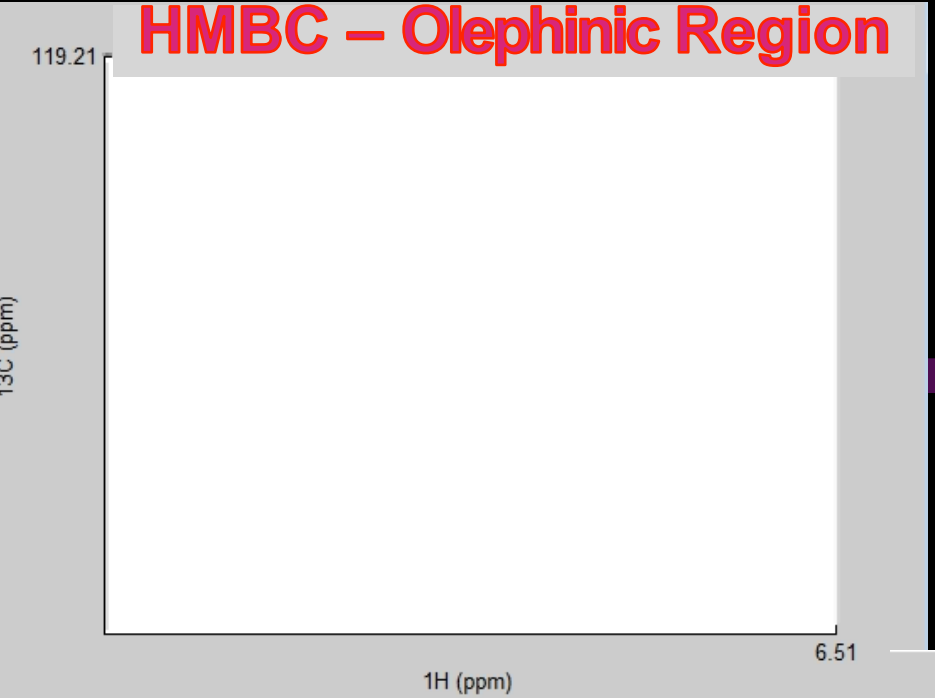
^{15}N-^{1}H 2D HMQC NMR spectrum; 2.3 mM ^{15}N-Ubiquitin *85 ms acquisition time*





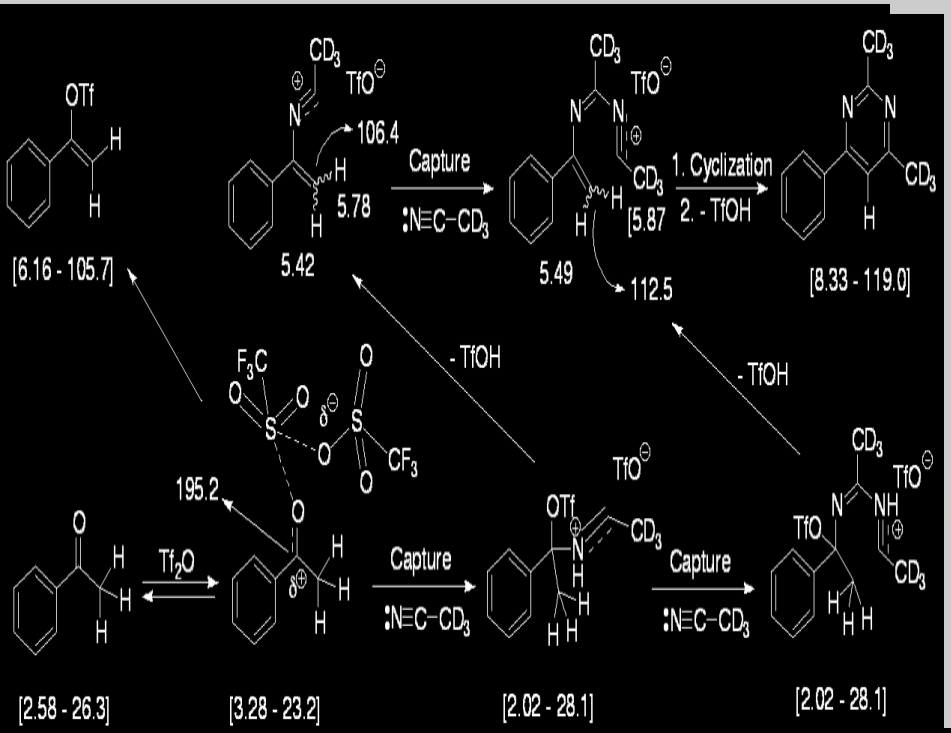
^{13}C-^{1}H 2D HSQC NMR spectrum; 1.0 mM U(^{15}N, ^{13}C)-protein A *60 ms acquisition time*

HMBC – Olephinic Region

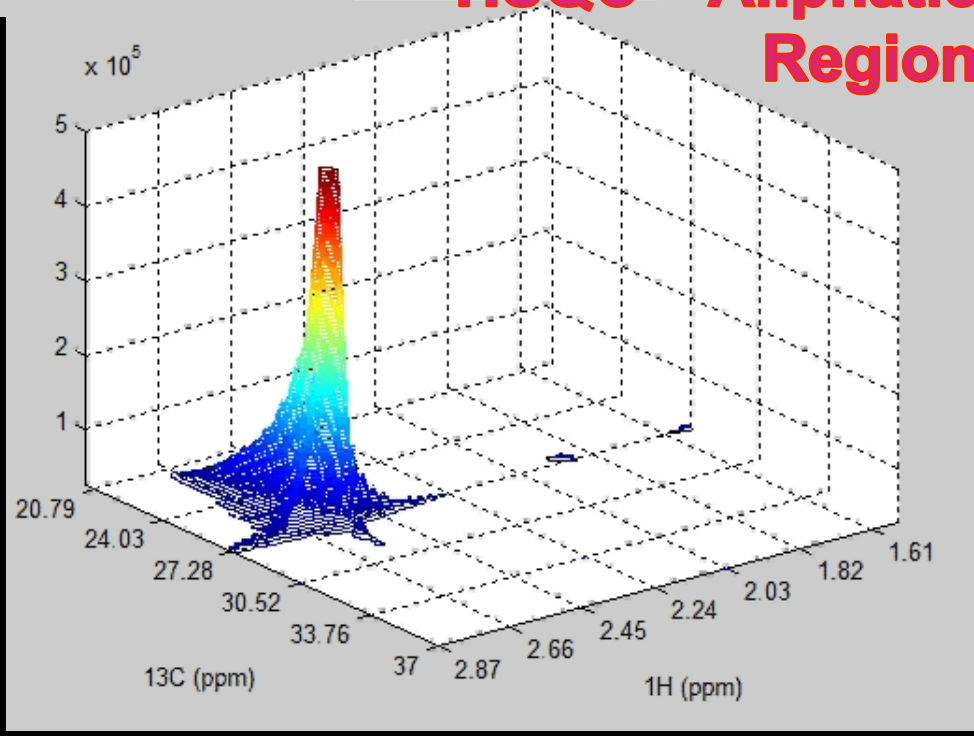


UF2D NMR can perform chemical analyses by examining real-time changes arising from 1000s of 2D NMR spectra in organic reactions

(G. Olsen, Z. Pardo in collaboration with A. Herrera et al, Madrid)

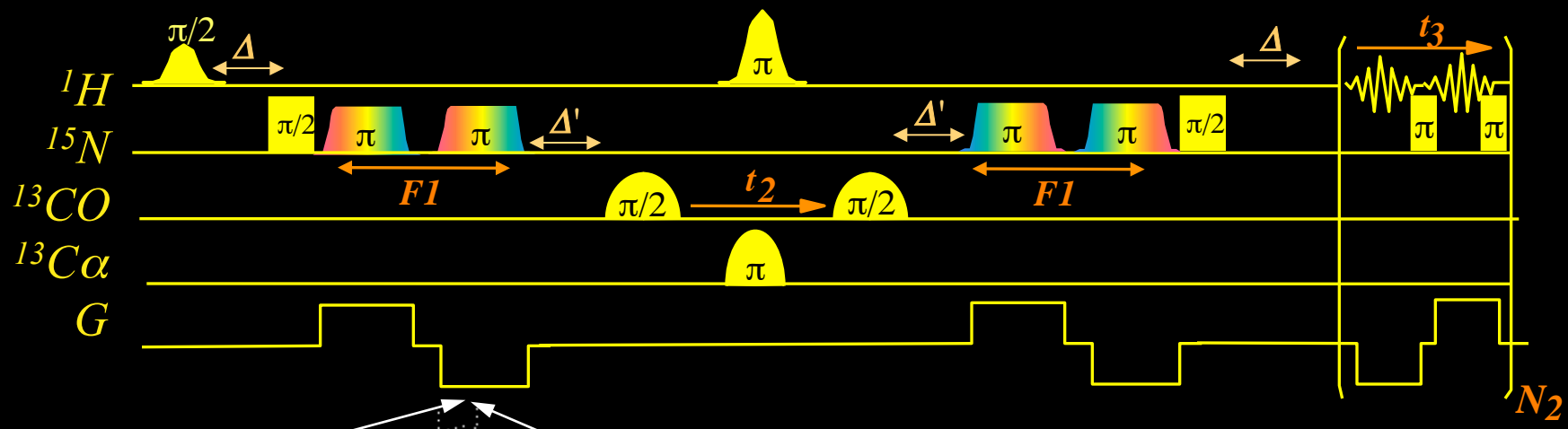


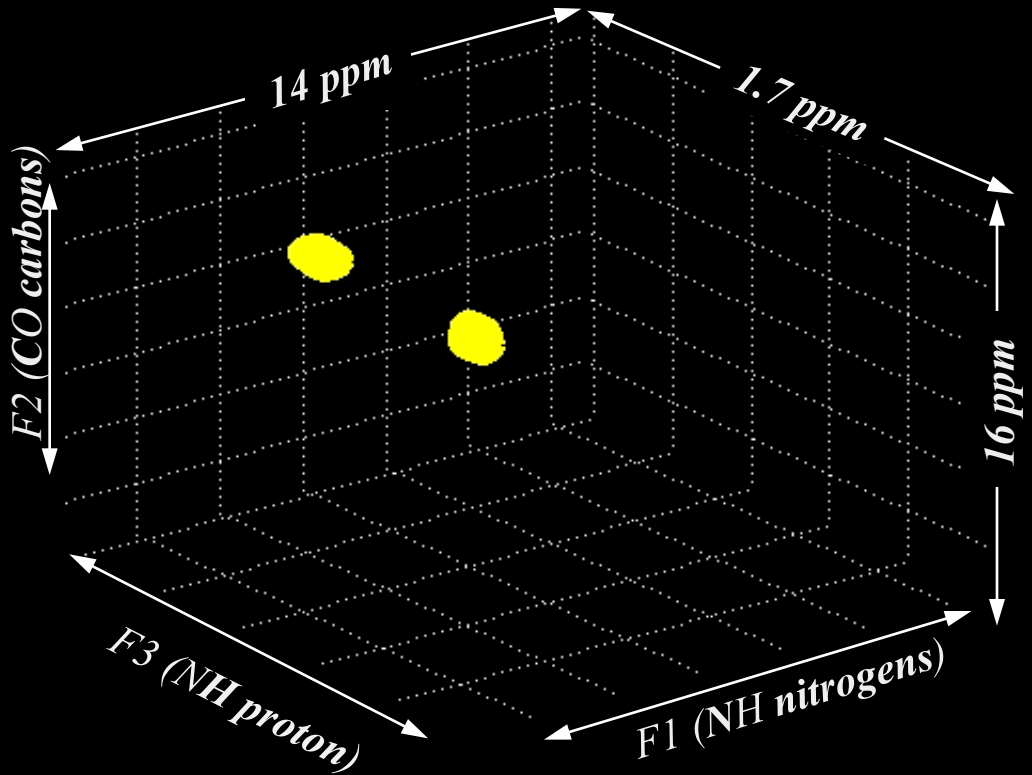
HSQC – Aliphatic Region



Ultrafast NMR and higher-dimensional acquisitions:

Accelerated 3D HNCO on a model tripeptide



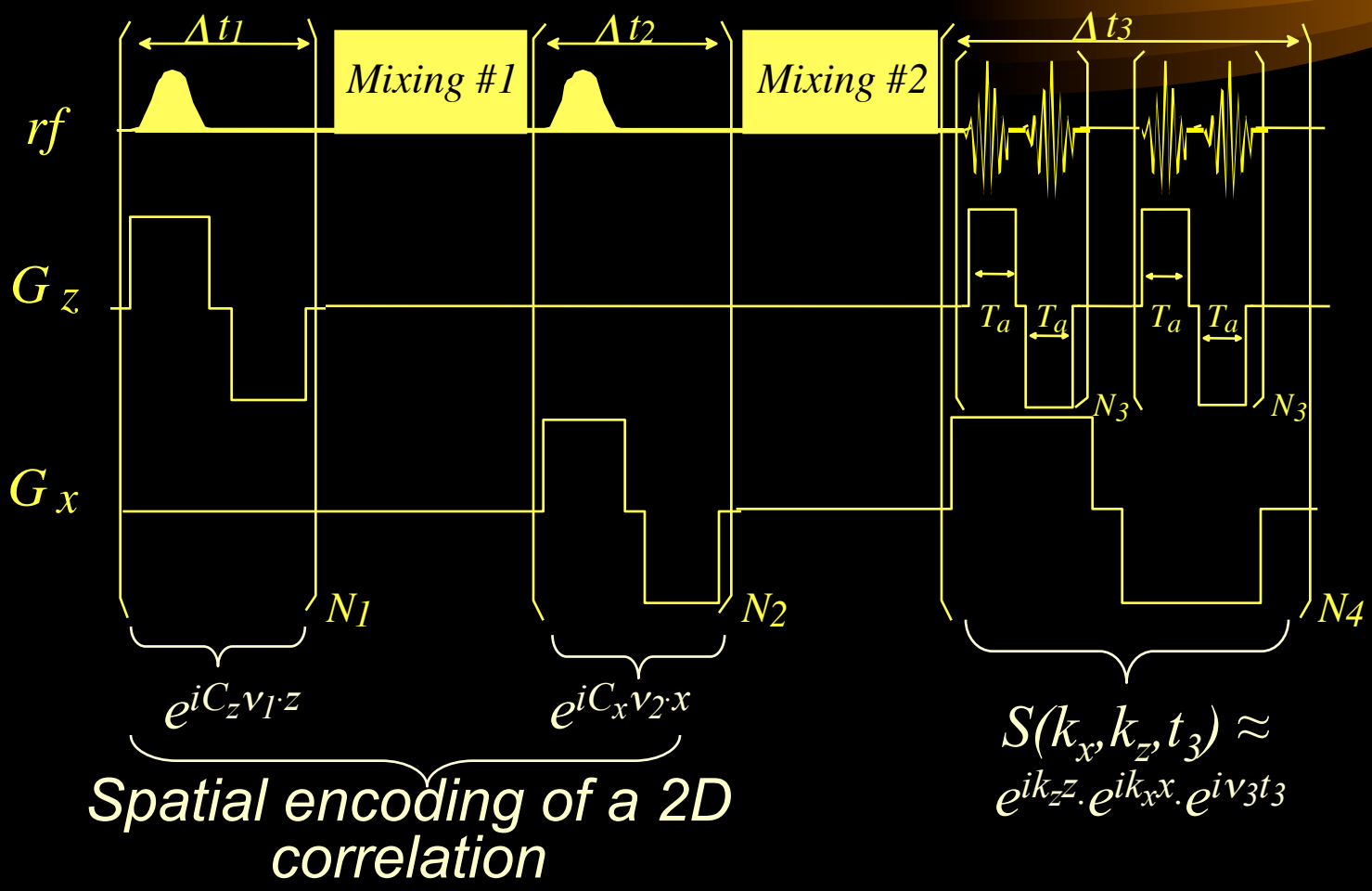


2 mM U-(^{15}N,^{13}C)-Leu-Ala-Phe
128 total scans
Amide region peaks

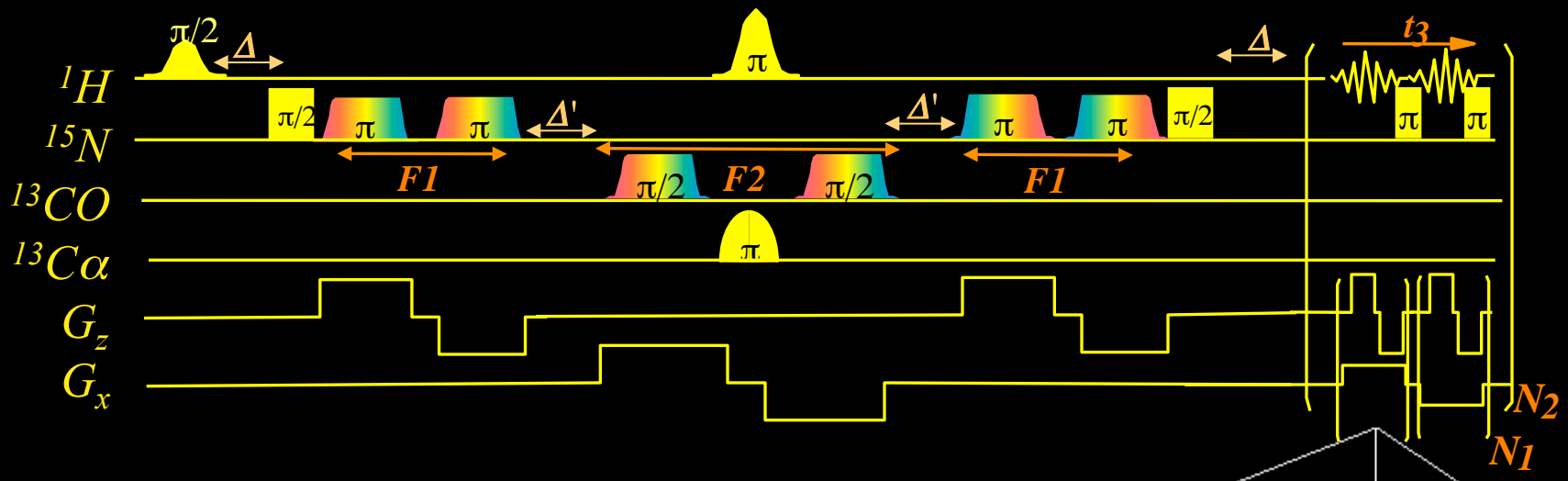
Acq time: 85 sec

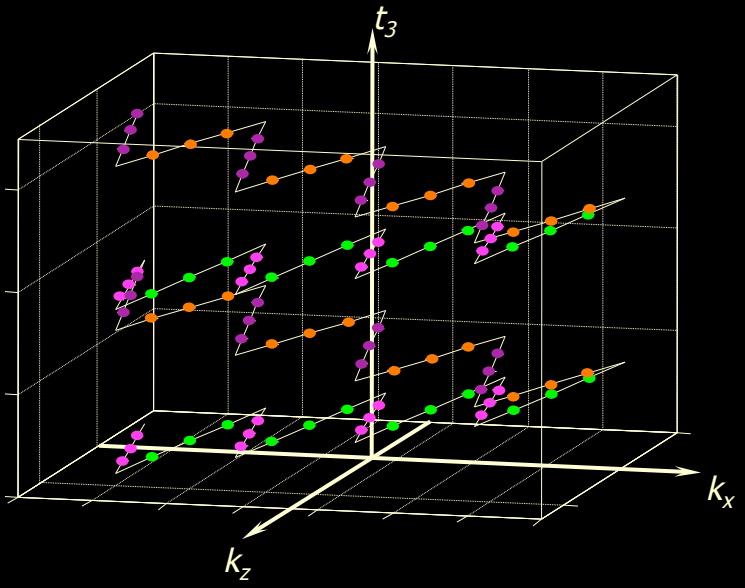
Yet another possibility:

3D NMR in a Single Scan

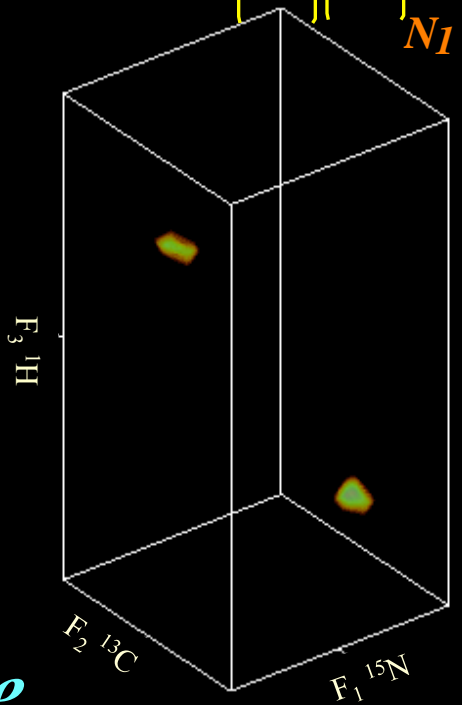


3D HNCO UFNMR of U-$^{15}N/^{13}C$ Leu-Ala-Phe





Interlaced FT: Integrated Processing of all Data



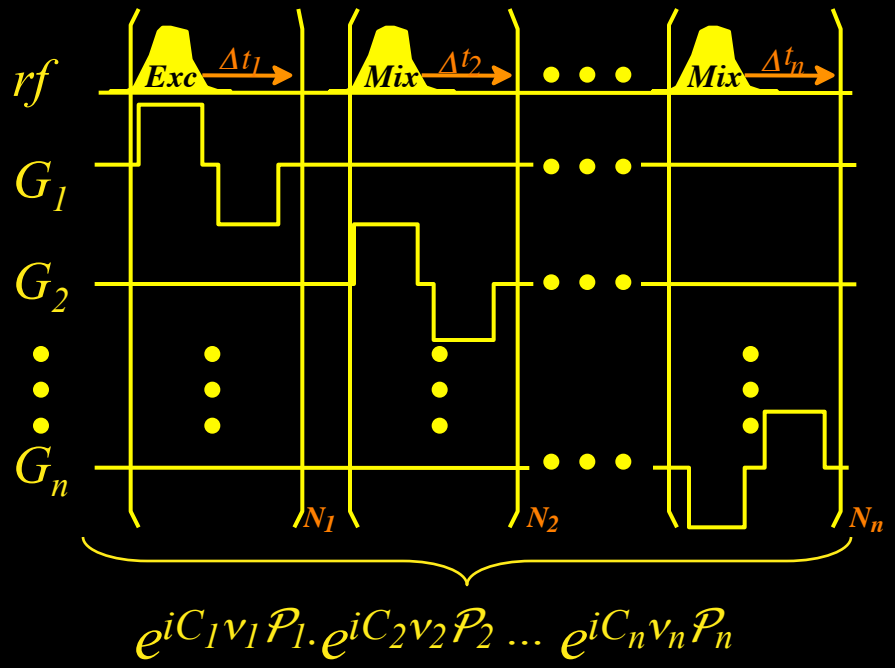
2 sec total acquisition time

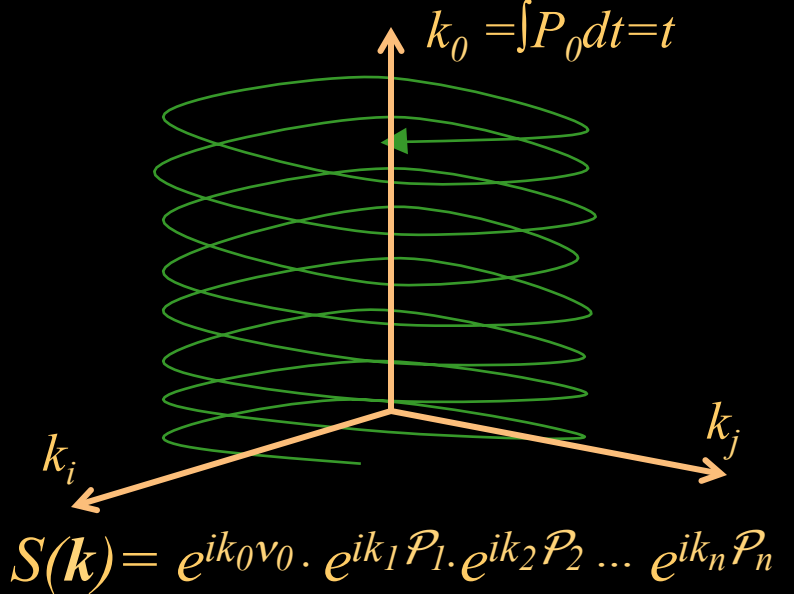
2 mM in d_6-DMSO; 2 phase-cycled scans @ 11.7 T

The ultimate multiplexing:

Given a gradient set $G_i = \{\partial B_o/\partial \mathcal{P}_i\}_{i=1\text{-}n}$, *based on* $\mathcal{P}_i(r)$ *geometries such that* $\int \mathcal{P}_i(r)\,\mathcal{P}_j(r)d^3r = \delta_{ij}$ *(as in shimming coils)*

Then the spatial encoding… and a $k_i = \int G_i(t')dt'$ ***sampling…***





…will furnish a signal from which an (n+1)D NMR spectrum could become available within a single scan

Summary

- **We have developed a new way of collecting magnetic resonance data**
  - Based on the spatial (rather than temporal) encoding of the MR interactions
  - Its read-out is based on field gradients whose effects can be done/undone nearly at will, enabling the parallelization of arbitrary nD NMR/MRI acquisitions into a single scan
  - The fact that the nD spectra can be collected in a single scan does not mean they will be visible in one scan: **SNR remains THE paramount obstacle to overcome**

- **Potential areas of applications**
  - Fast 2D NMR characterizations of real-time chemical kinetics, high-throughput DOSY/T1, new kinds of 2D NMR correlations, solid state NMR
  - New opportunities in higher-dimensional (≥3D) MR – alone or in combination with other emerging proposals in the field
  - New hyperpolarized ultrafast approaches enable new of *in vitro* and *in vivo* studies: analytical applications, metabolism, diagnose malignancy.

Acknowledgements

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Bio-NMR

COST Action TD1103

META ^{13}C FLUX

Kimmel Prize for Innovative Research

erc

European Commission 7th Framework Program Grants


Thanks for coming!
GRACIAS!