Benchtop NMR session at 2023 SNUG postgraduate meeting

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Applications Specialist
Oxford Instruments Magnetic Resonance

Benchtop NMR session

- Introduction to benchtop NMR
- What can benchtop NMR do?
- Applied relaxometry
- Summary

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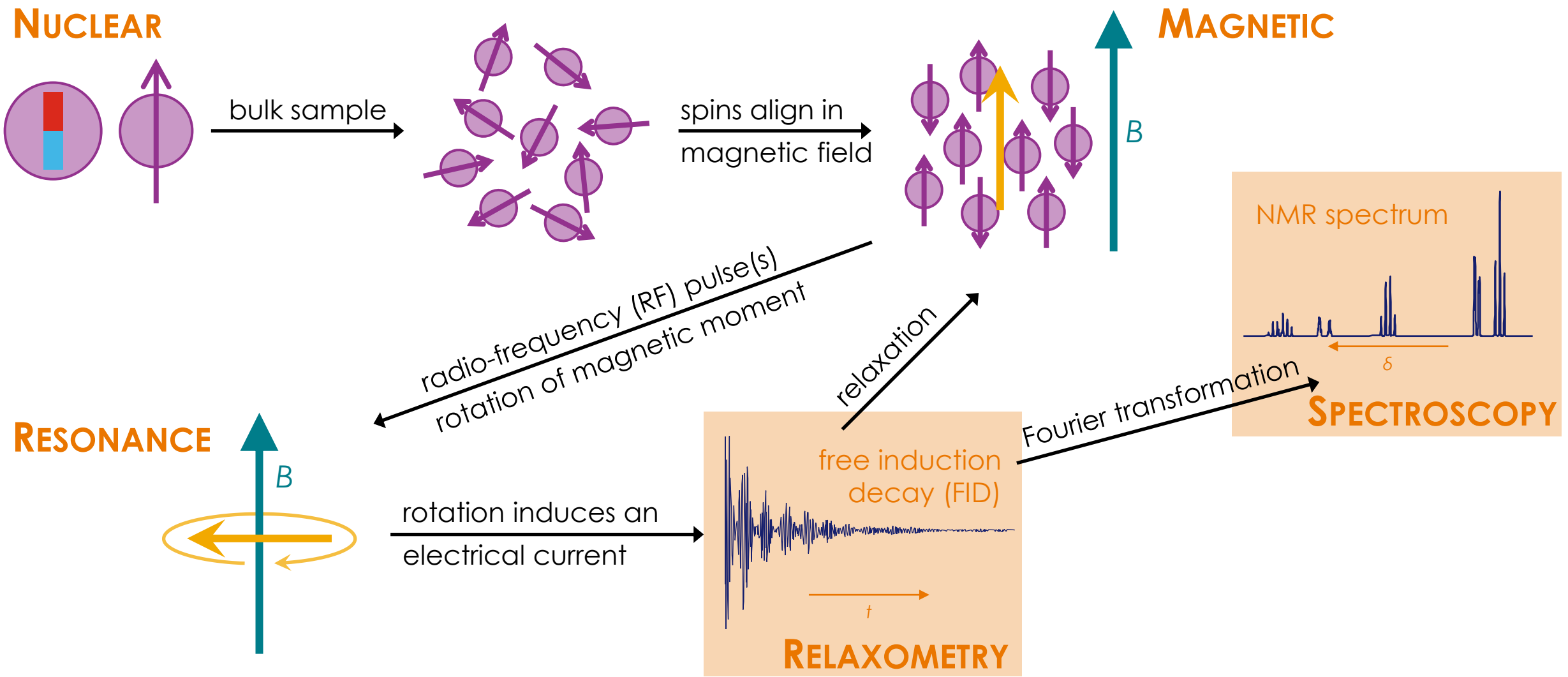
Introduction to benchtop NMR

What is NMR?



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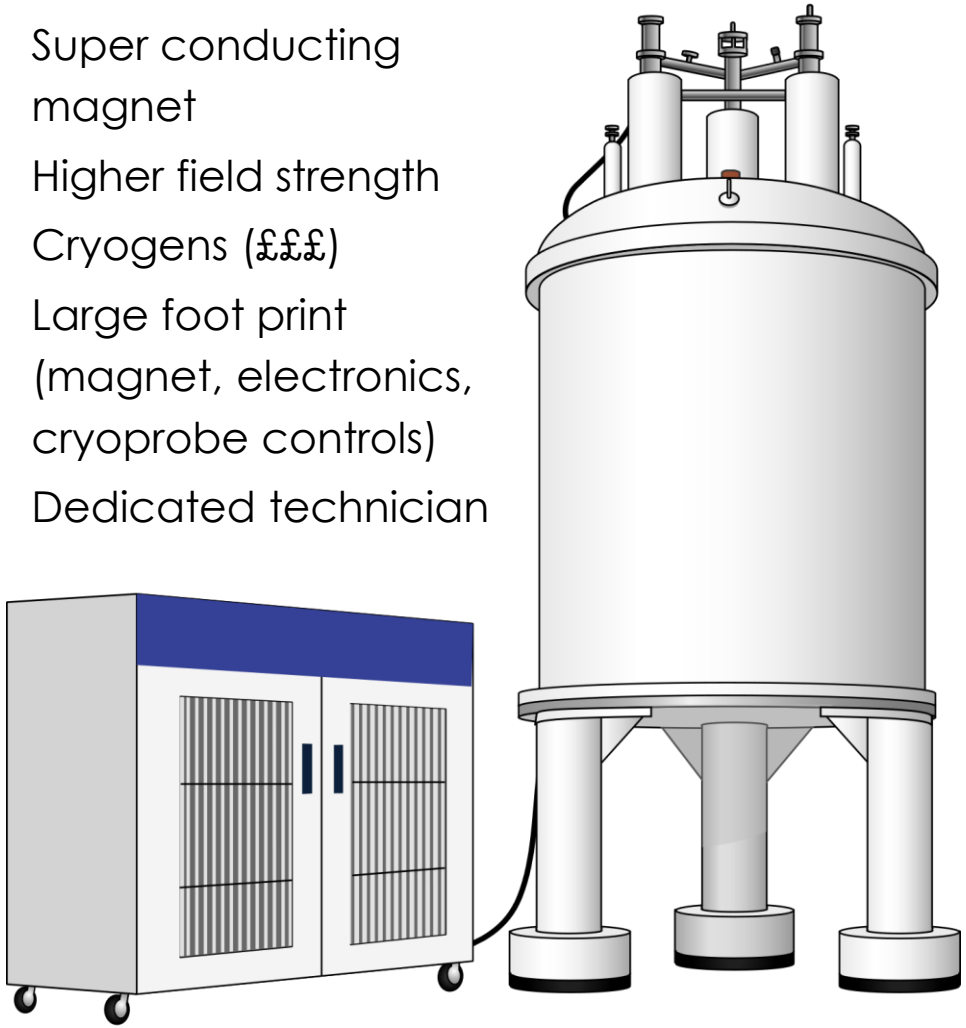
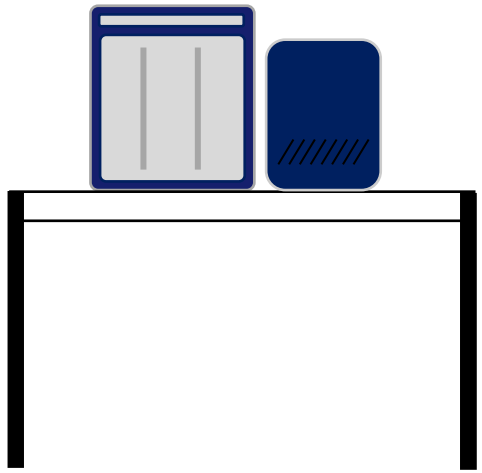
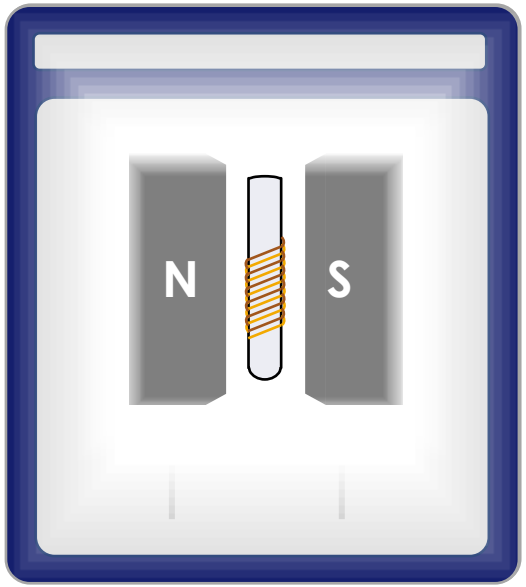
High-Field *versus* Benchtop NMR

- Super conducting magnet
- Higher field strength
- Cryogens (£££)
- Large foot print (magnet, electronics, cryoprobe controls)
- Dedicated technician



- Permanent magnet
- Lower field strength
- No cryogens
- Small foot print
- Minimal stray field





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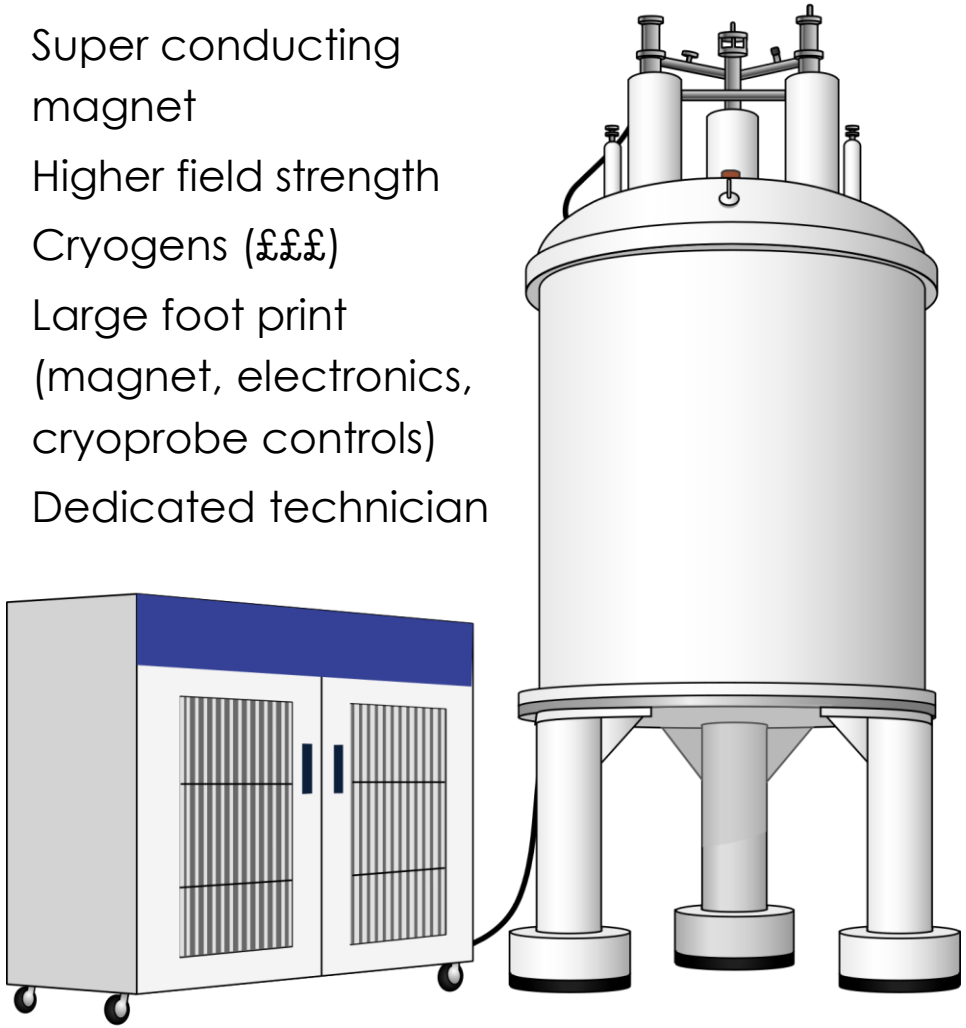

- Permanent magnet
- Lower field strength
- No cryogens
- Small foot print
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X-Pulse

- Separate electronics console for optimal performance
- Mobile workstation
- User removable probe

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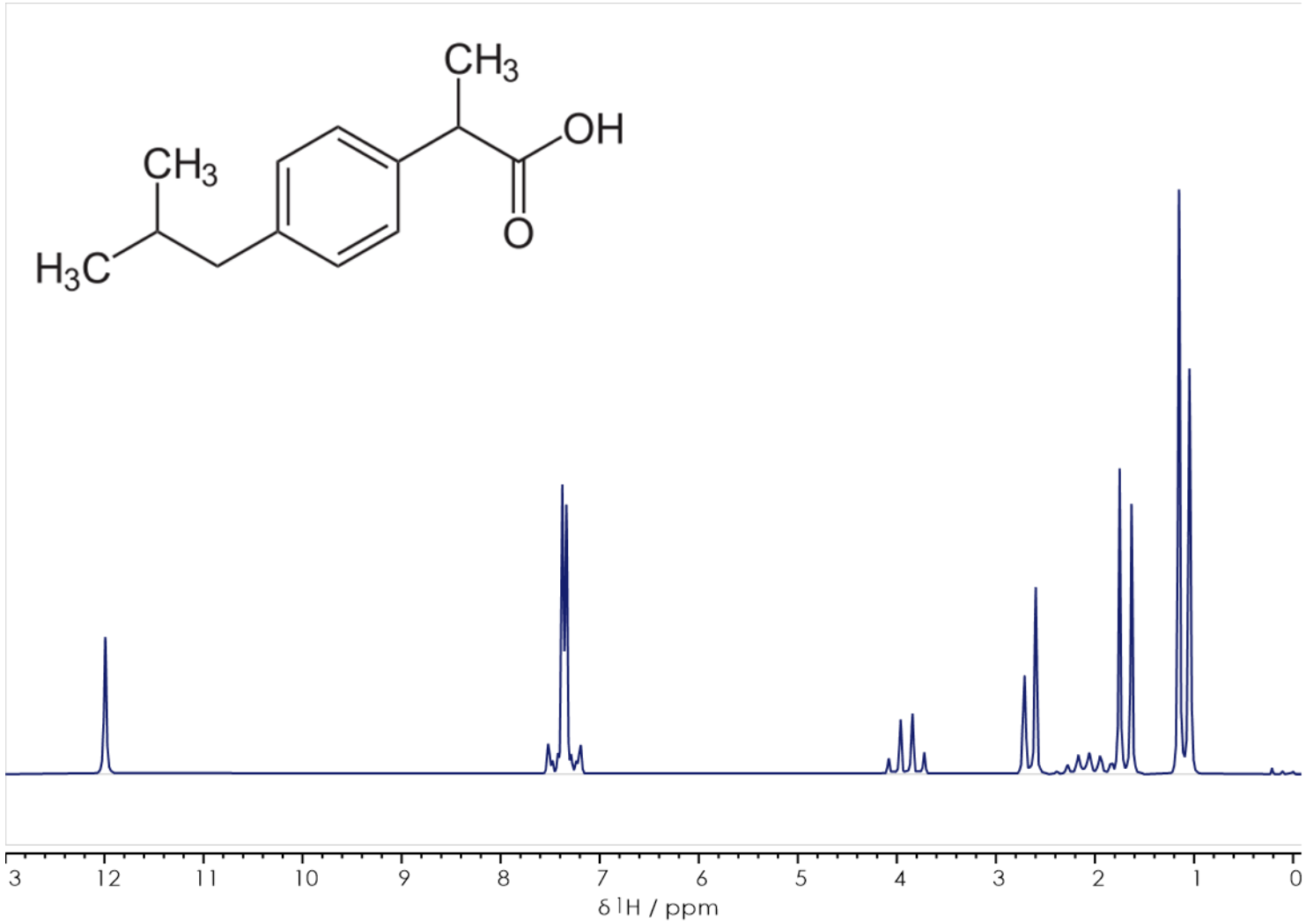
Benchtop NMR spectroscopy

What can benchtop NMR do?

Structural determination of small molecules

- Structural determination and identification
  - Integrals, chemical shifts, multiplets and *J*-couplings



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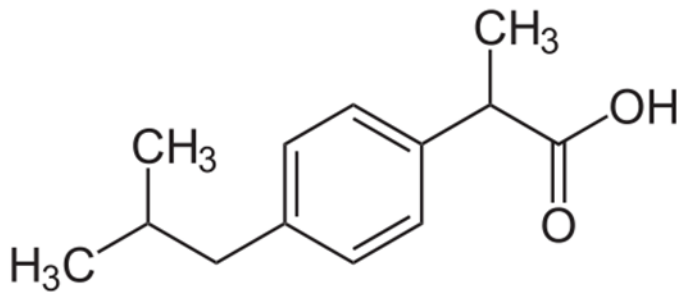
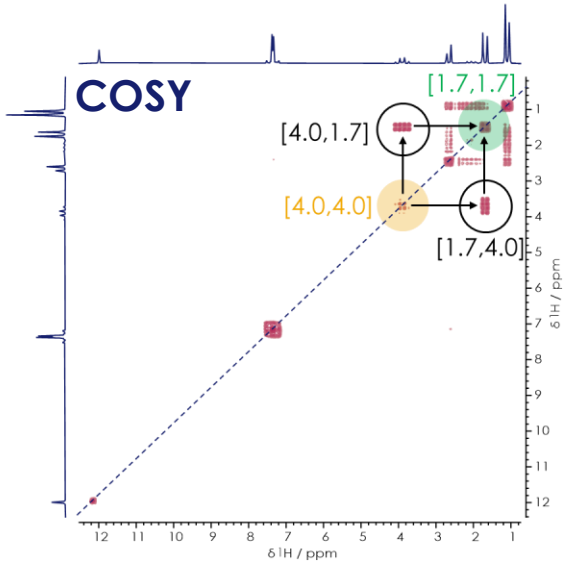
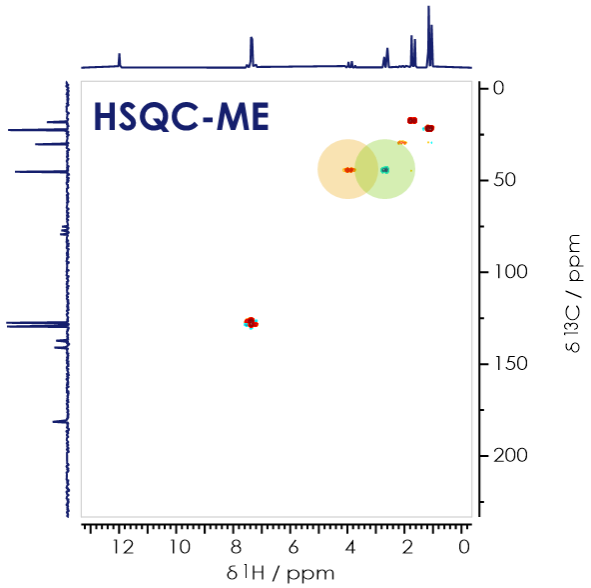
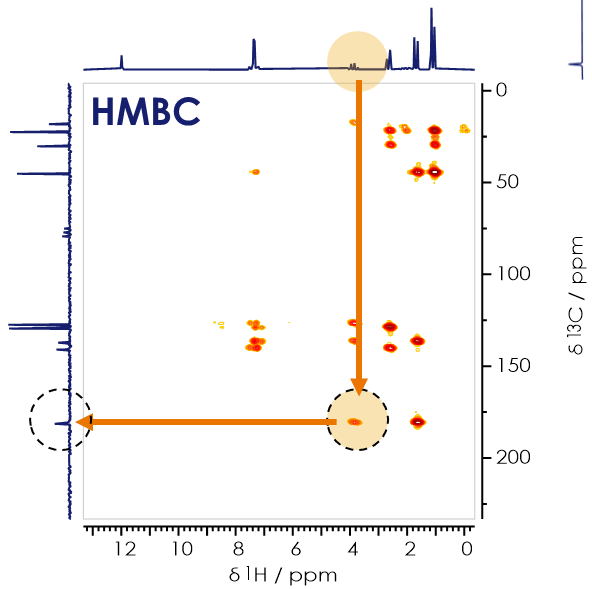
Structural determination of small molecules

- Structural determination and identification
  - Integrals, chemical shifts, multiplets and *J*-couplings
  - 2D NMR spectra









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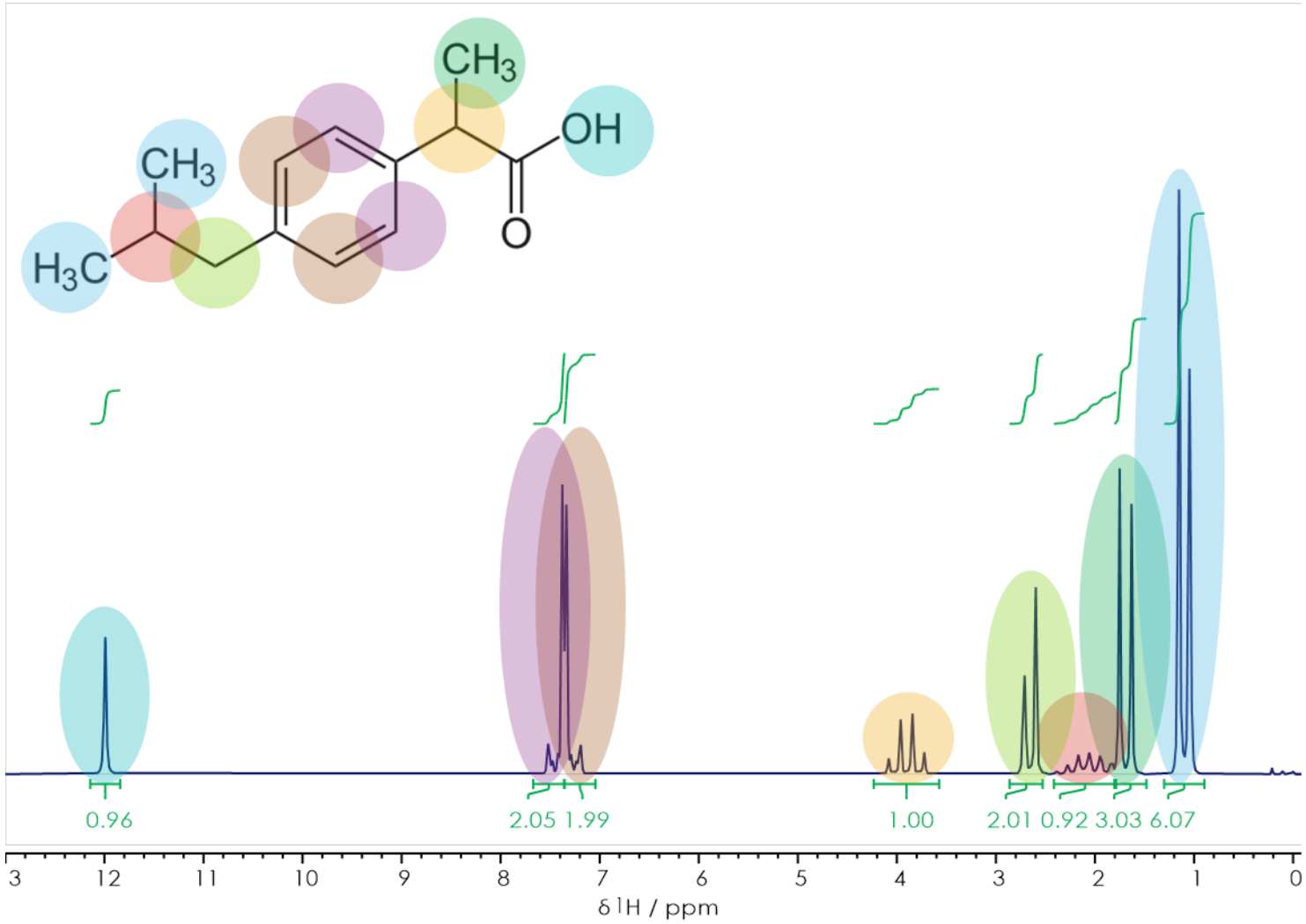
Structural determination of small molecules

- Structural determination and identification
  - Integrals, chemical shifts, multiplets and *J*-couplings
  - 2D NMR spectra
- Who?
  - Education
  - Research
  - Forensics
  - Pharmaceutical
  - Quality control



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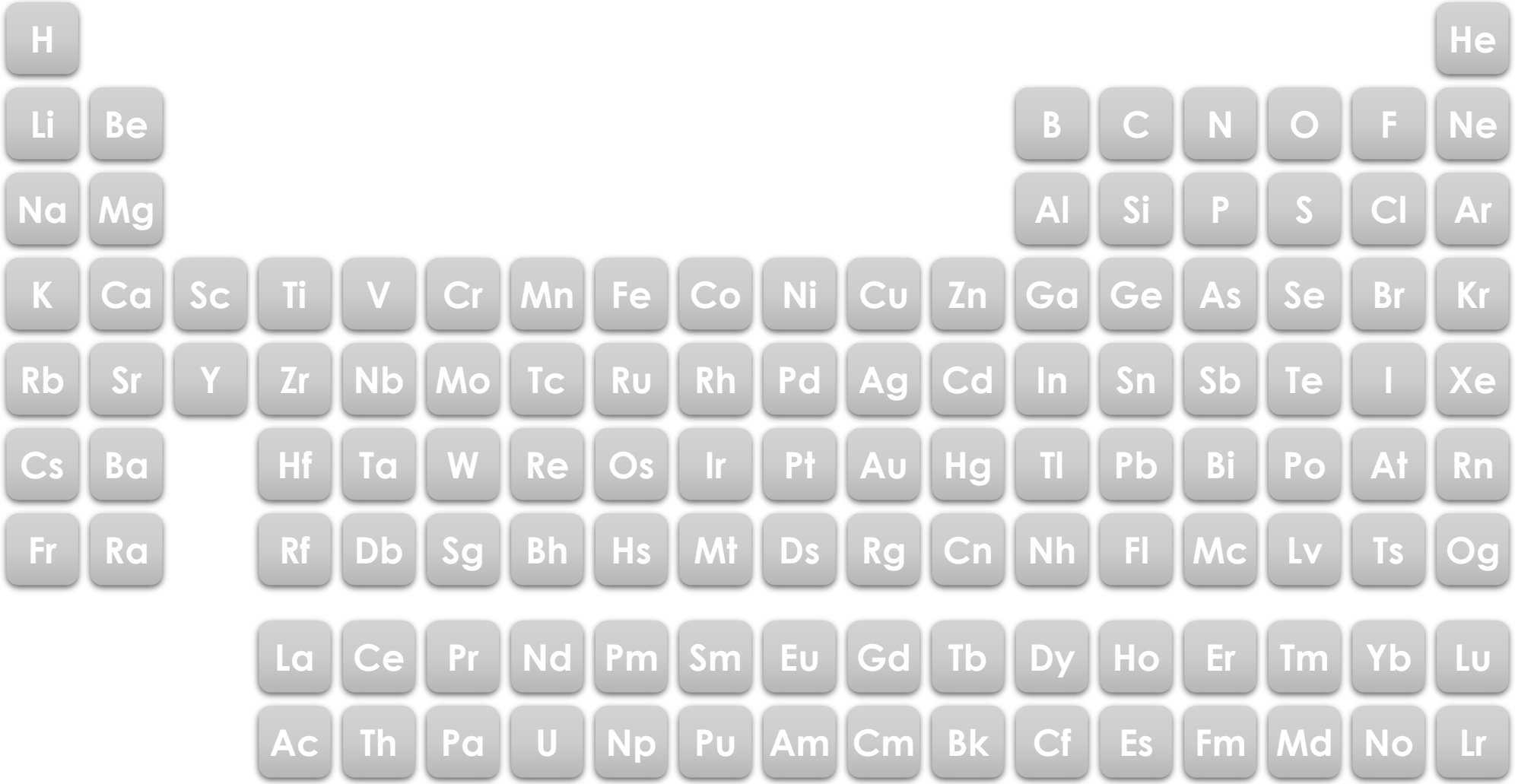
Heteronuclei

What if you work with something other than small organic molecules?

Periodic Table of the Elements



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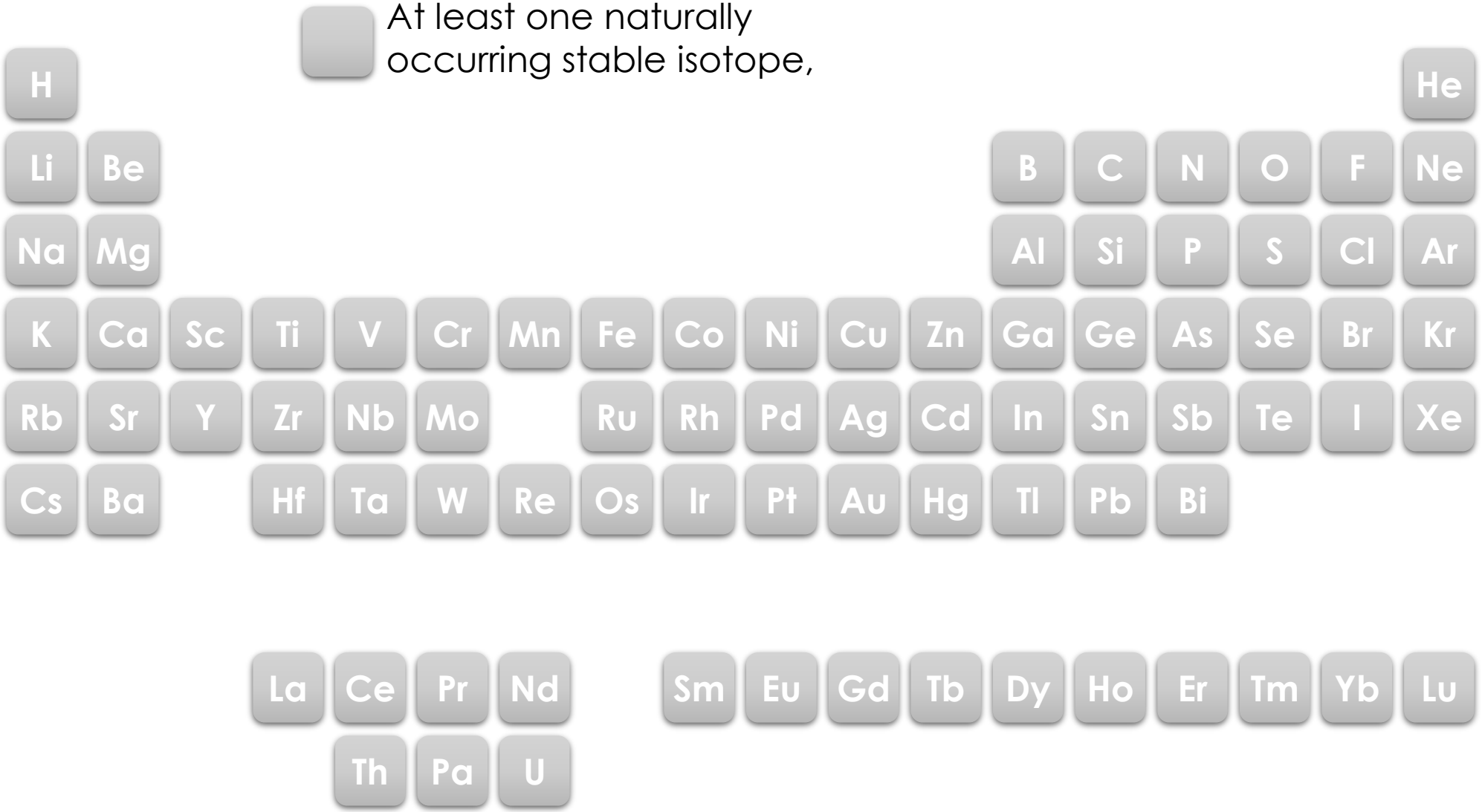

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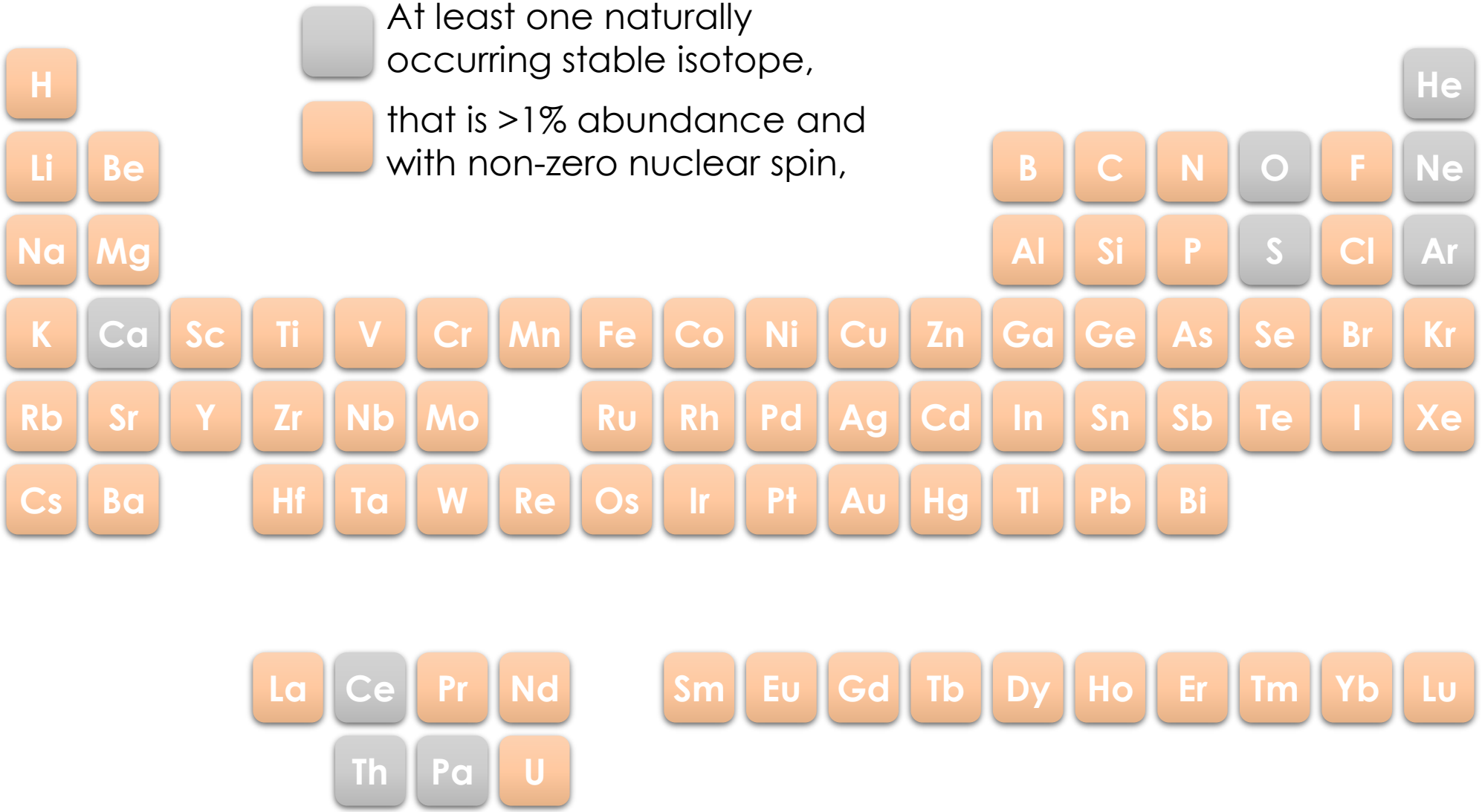
Periodic Table of the Elements, for NMR



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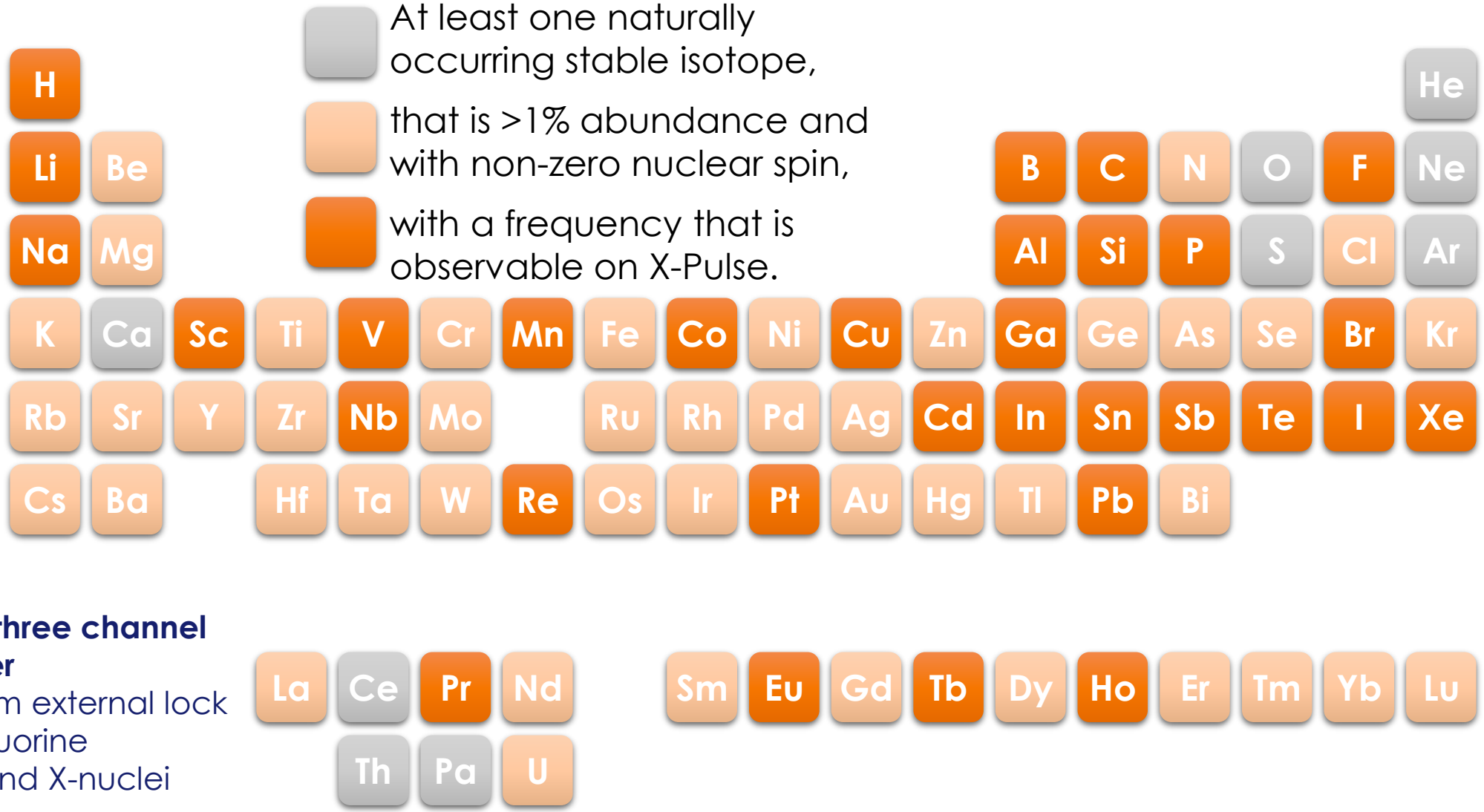

X-Pulse is a three channel spectrometer

1. Deuterium external lock
2. Proton/fluorine
3. Broadband X-nuclei

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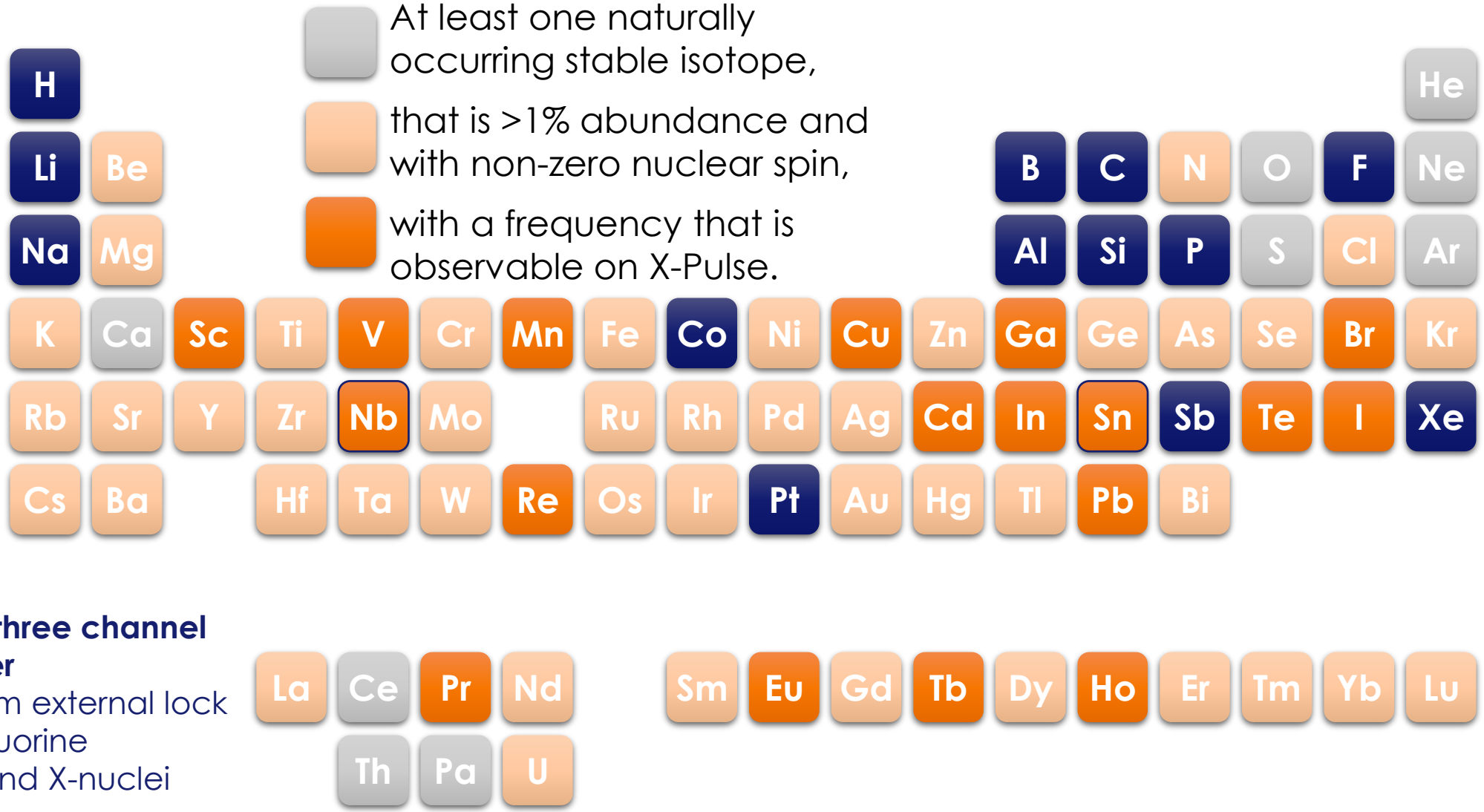
Periodic Table of the Elements, for NMR



X-Pulse is a three channel spectrometer

1. Deuterium external lock
2. Proton/fluorine
3. Broadband X-nuclei

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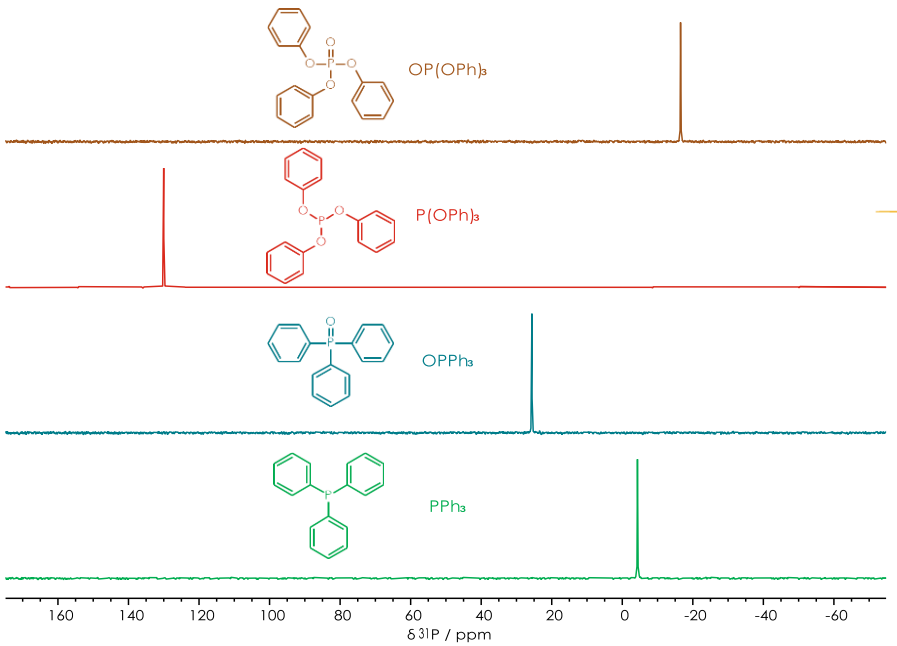
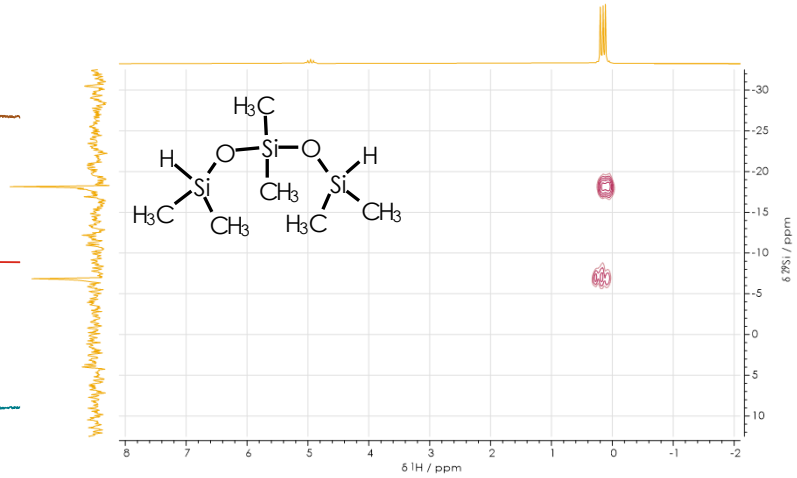
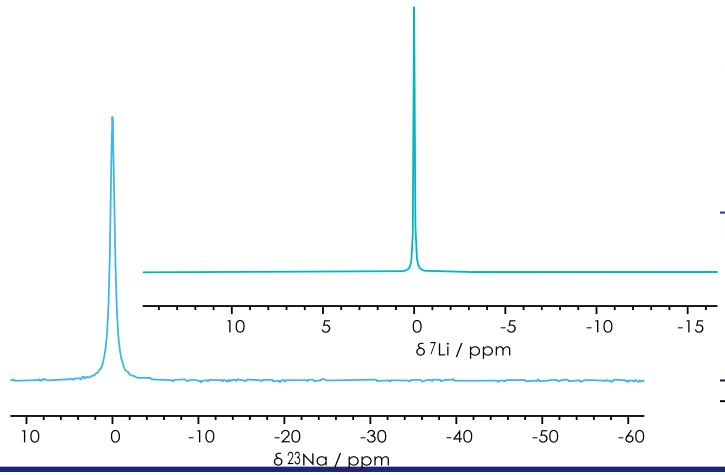
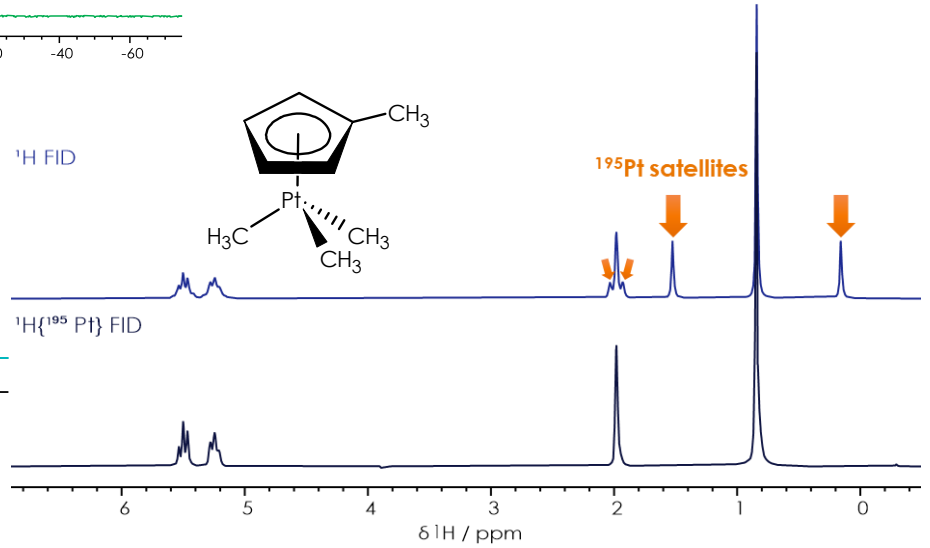
Heteronuclei: beyond ^{1}H and ^{13}C

- ^{31}P (100%)
  - catalysis
  - biologics
- ^{7}Li (92%) & ^{23}Na (100%)
  - organometallic compounds
  - salt content
- ^{29}Si (5%)
  - poly-siloxanes
- ^{195}Pt (34%)
  - anti-cancer drugs
  - homo- and heterogeneous catalysts









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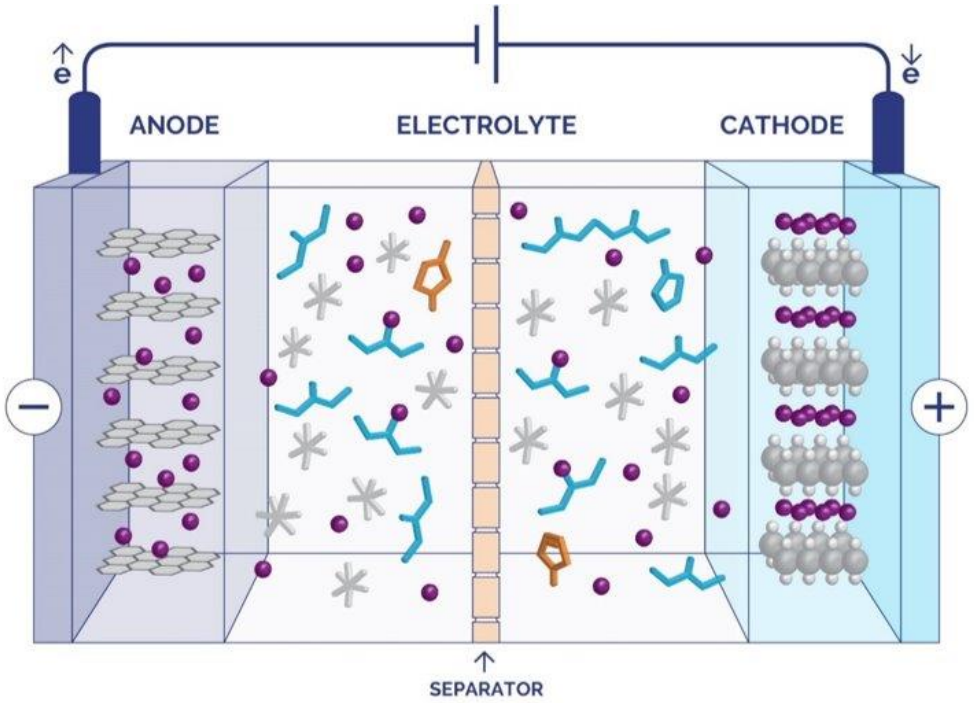
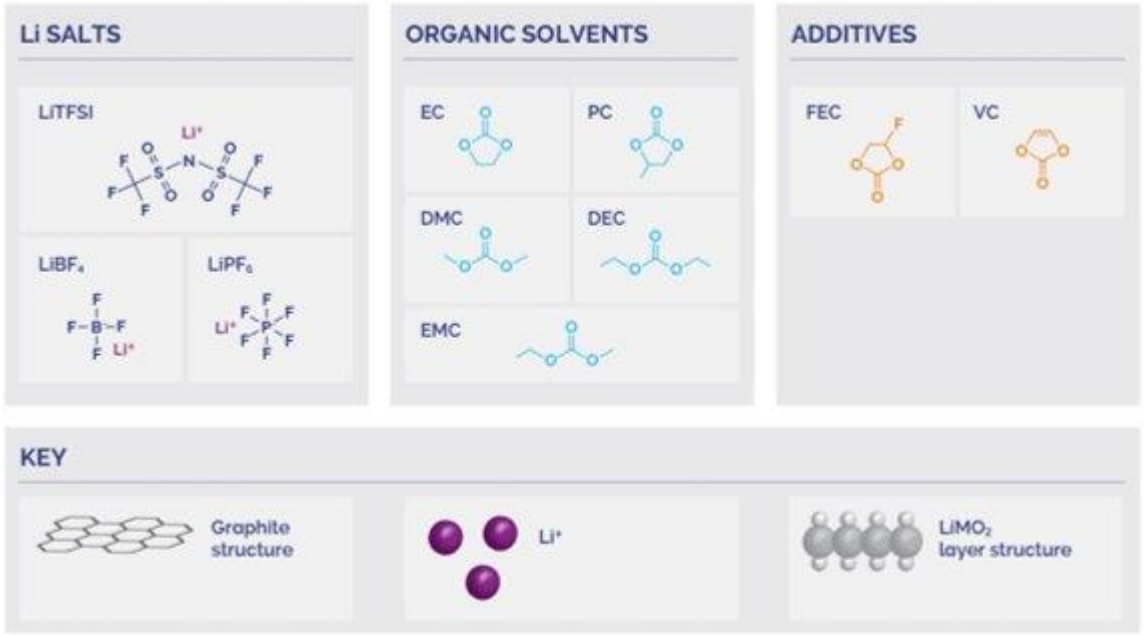
Diffusion

Battery characterisation





- Wide variety of nuclei
- Measuring diffusion coefficients can improve predictions of the electrolyte performance in a cell
- Measured using pulsed field gradient NMR (PFG-NMR)

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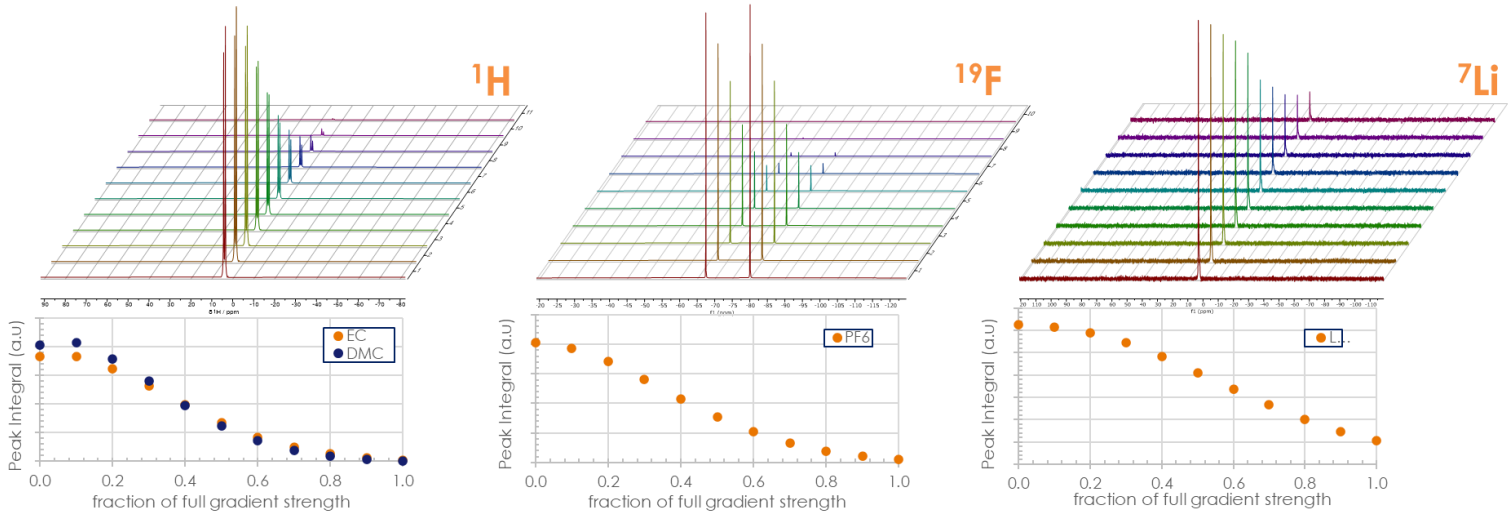
Battery characterisation

- ^{1}H for small organic solvents
- ^{7}Li for the Li^{+} cation
- ^{19}F for the $[PF_6]^{-}$ anion



Stejskal-Tanner equation

$D^{EC} = 6.41 \times 10^{-10} m^2/s$

$D^{DMC} = 7.41 \times 10^{-10} m^2/s$

$D^{PF6} = 4.46 \times 10^{-10} m^2/s$

$D^{Li} = 2.73 \times 10^{-10} m^2/s$

Ionic conductivity and cation transference → Battery performance

Air-sensitive samples: the X-Pulse benchtop NMR spectrometer at University of Oxford is installed in a glovebox in an inert argon atmosphere.

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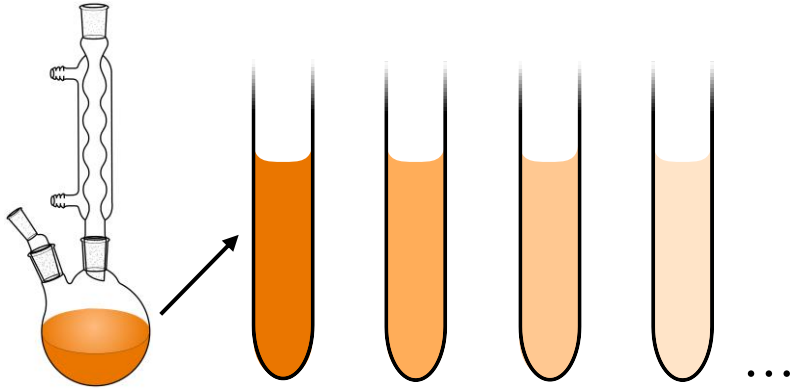
Reaction Monitoring

Reaction monitoring

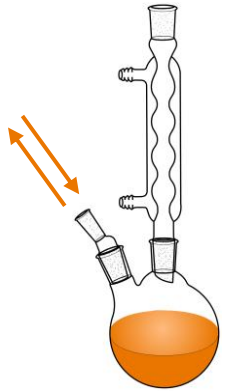
- NMR can be used to monitor reactions in a variety of ways:

Preparation of the reaction directly in an NMR tube

Take aliquots at specified times from a reaction vessel



Flow the reaction mixture directly from the reaction vessel through the spectrometer



- Placement flexibility and mobility allows for continuity of analysis
  - Lab fumehoods
  - Larger reaction vessel in process development
  - Manufacturing site

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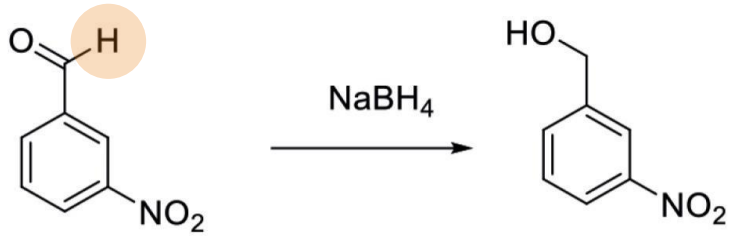
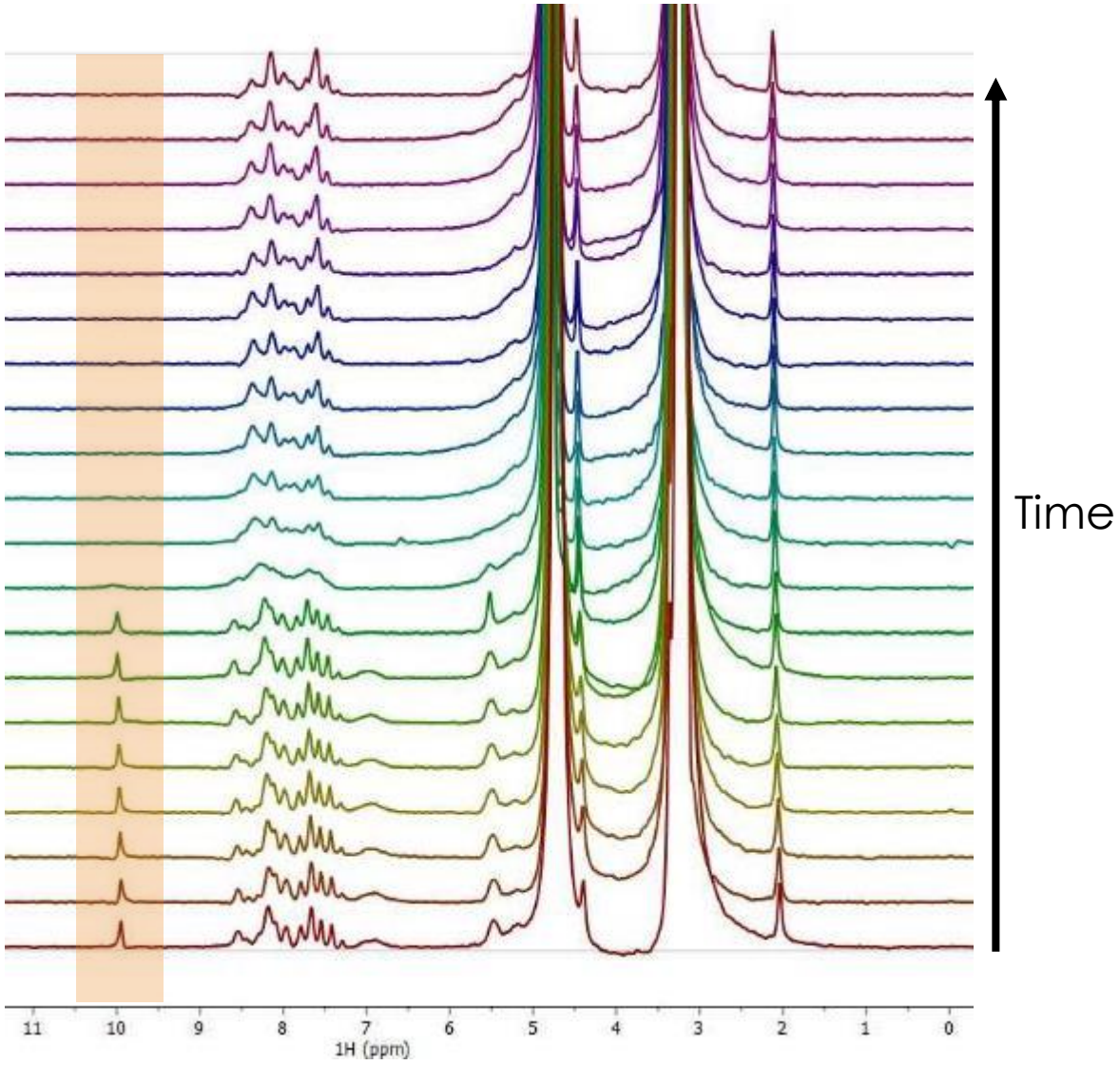
Reduction of Nitrobenzaldehyde



- Here we see the progression of a reduction reaction
- Integration of the CHO signal at 10 ppm indicates the reaction progress.
- When all the starting material is consumed the reaction can end.
- This provides all the information required for an optimisation procedure.



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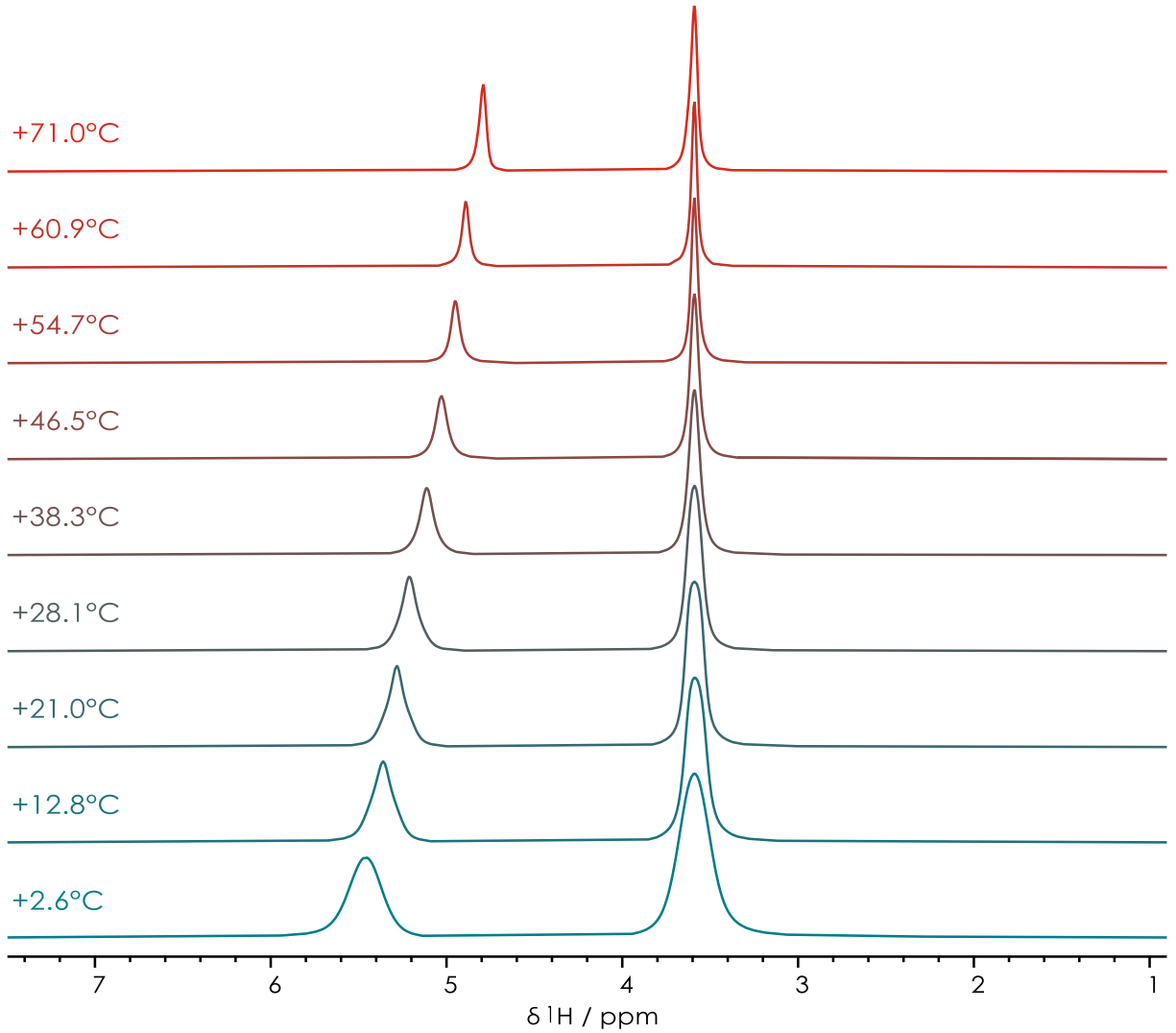
Variable Temperature

Variable Temperature - NMR Thermometer

- Reaction monitoring, kinetics, dynamic processes, physical properties.
- Chemical shifts of hydroxy groups are dependent on temperature
- Appropriately chosen compounds can therefore be used as a 'NMR thermometer'
  - Ethylene Glycol ($HOCH_2CH_2OH$)
    - $T(°C) = 193.35 - 102.00(\Delta\delta_H)$
      suitable range: 0 - +140 °C
  - Methanol (CH_3OH)
    - $T(°C) = 135.85 - 36.54(\Delta\delta_H) - 21.85(\Delta\delta_H)^2$
      suitable range: −95 - +57 °C

J. Magn. Reson., 1982, **46**, 319-321



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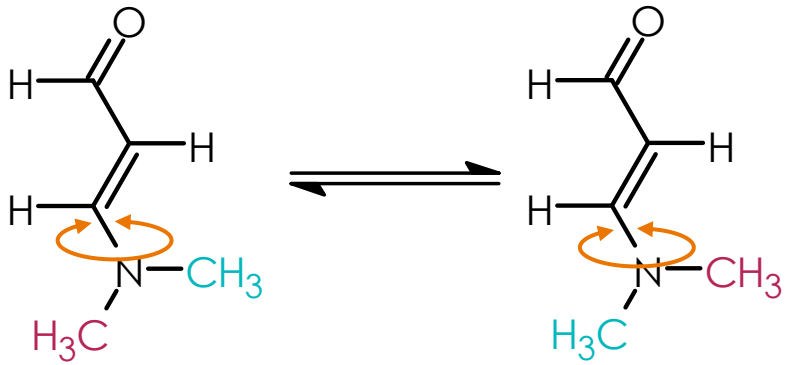
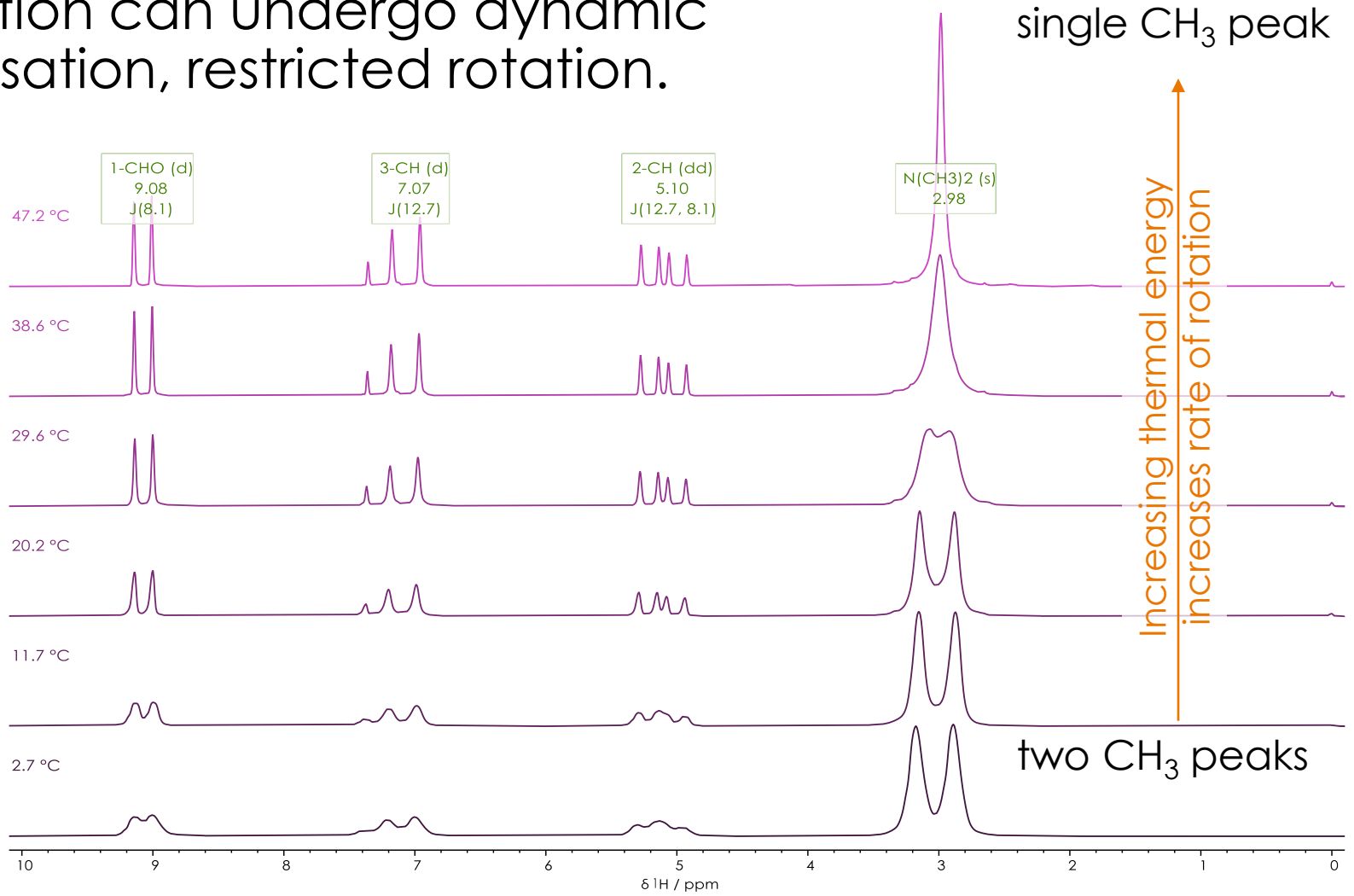
Solution state dynamic processes

- Chemical species in solution can undergo dynamic processes *e.g.* tautomerisation, restricted rotation.

- We can observe this by NMR for 3-dimethyl-aminoacrolein



- Two unique resonance at low temperature coalesce at high temperature



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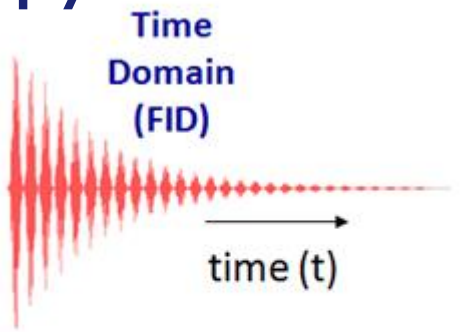
Applied relaxometry

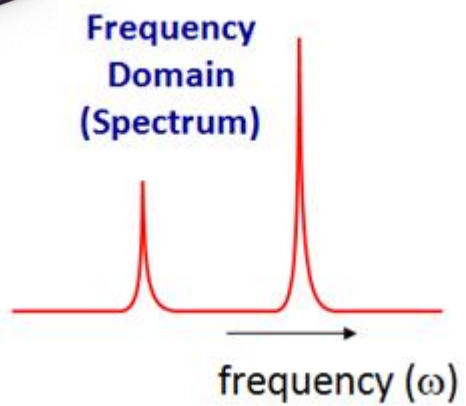
What about time domain NMR?

Relaxometry *versus* Spectroscopy data

Spectroscopy

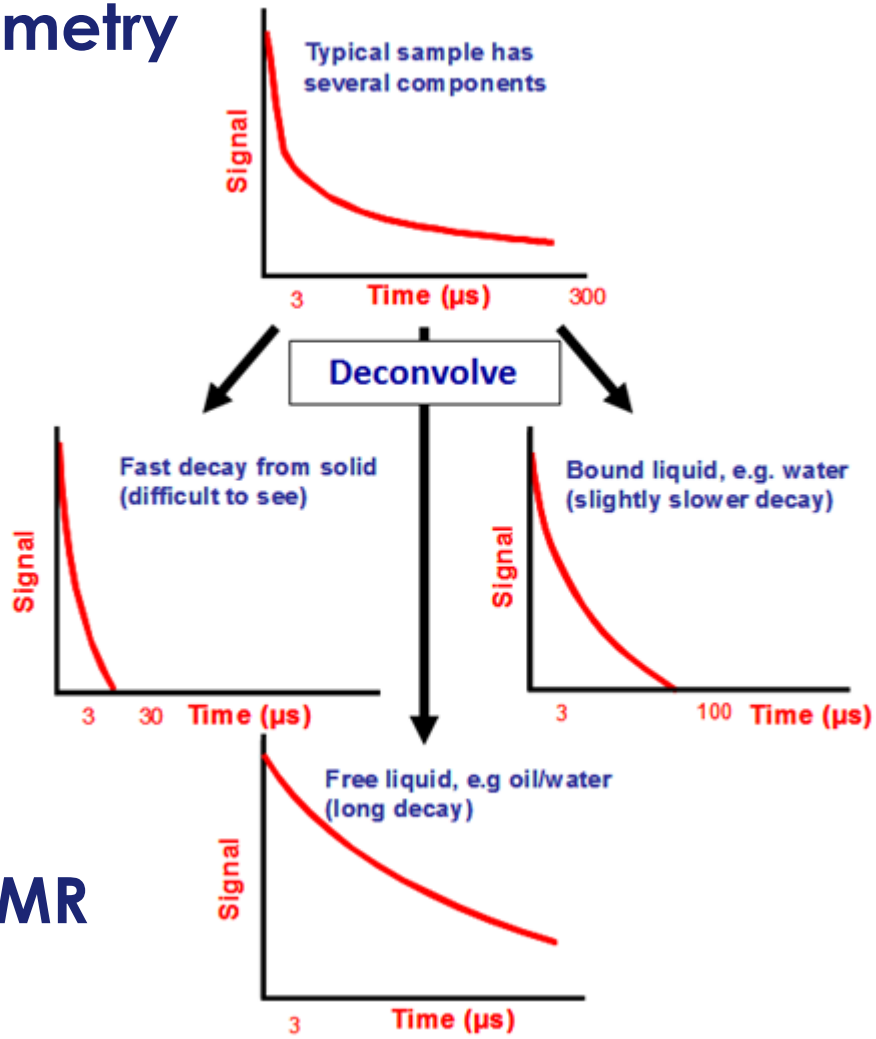


Fourier Transform



FT-NMR

Relaxometry



TD-NMR

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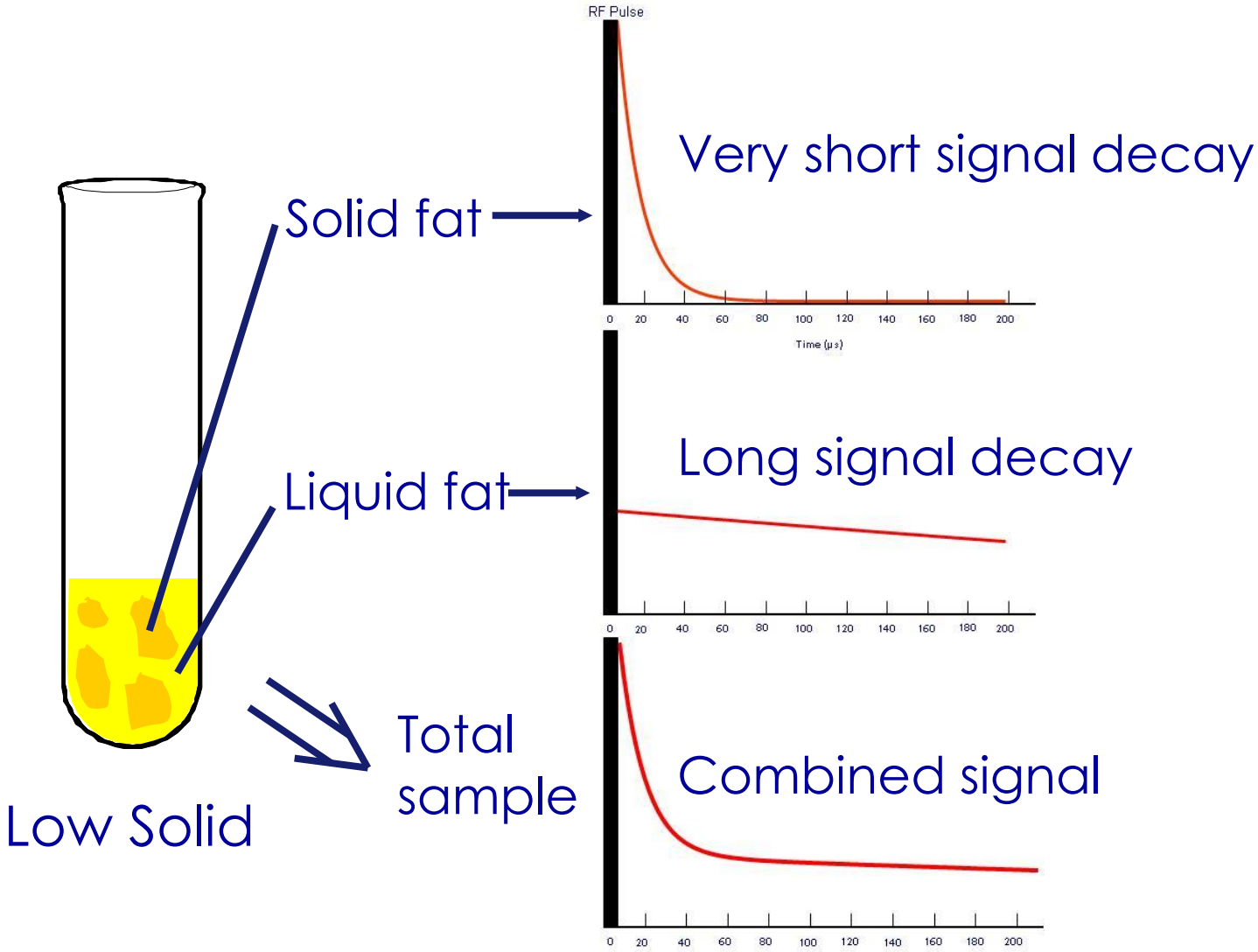
Solid Fat Content (SFC) Direct Method



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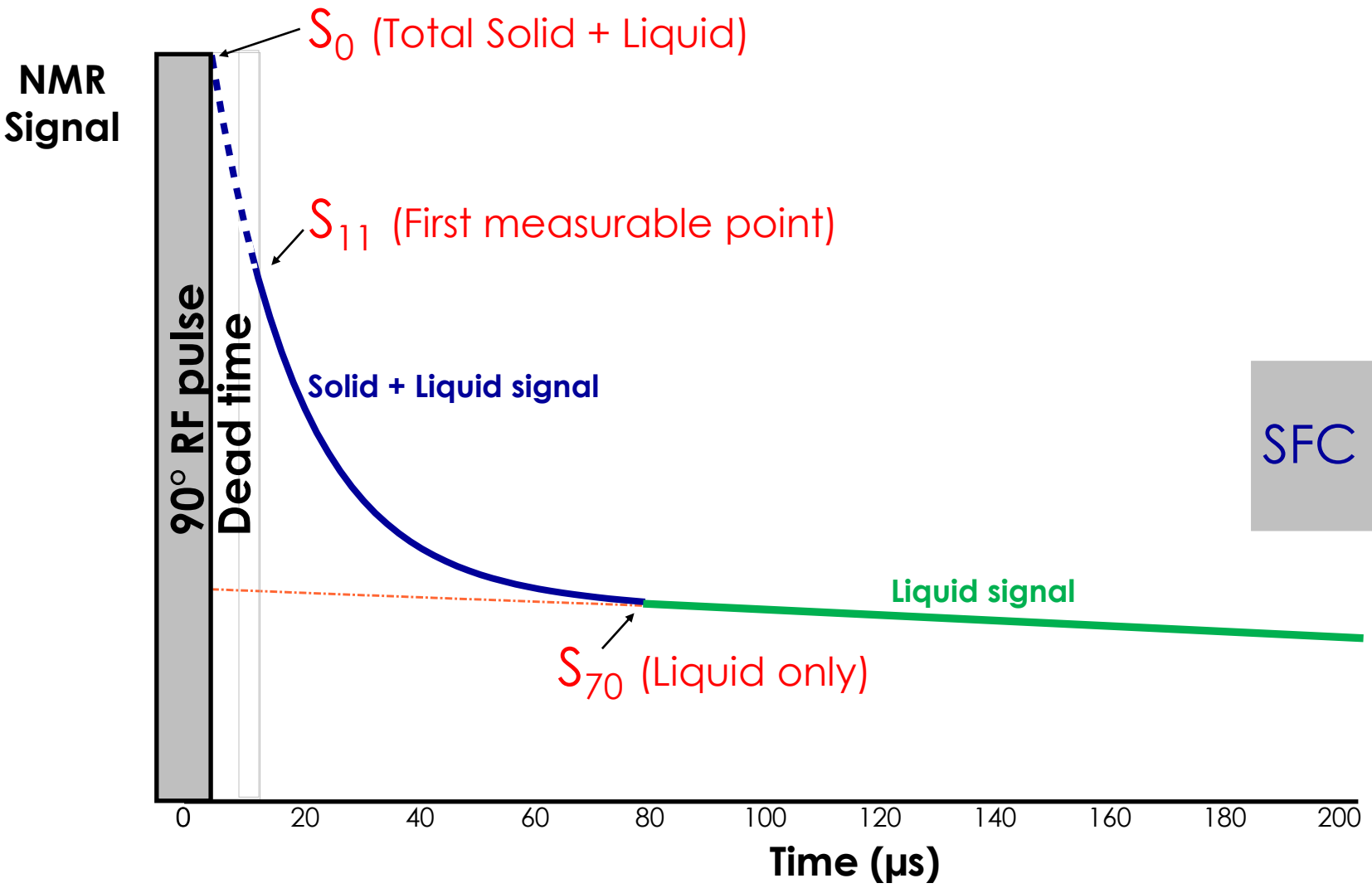
Solid Fat Content – Direct method



$$SFC\ (\%) = \frac{S_0 - S_{70}}{S_0} \times 100$$

$$S_0 = S_{70} + f \times (S_{11} - S_{70})$$

where *f* is an empirical factor

$$SFC\ (\%) = \frac{f \times (S_{11} - S_{70}) \times 100}{S_{70} + f \times (S_{11} - S_{70})}$$

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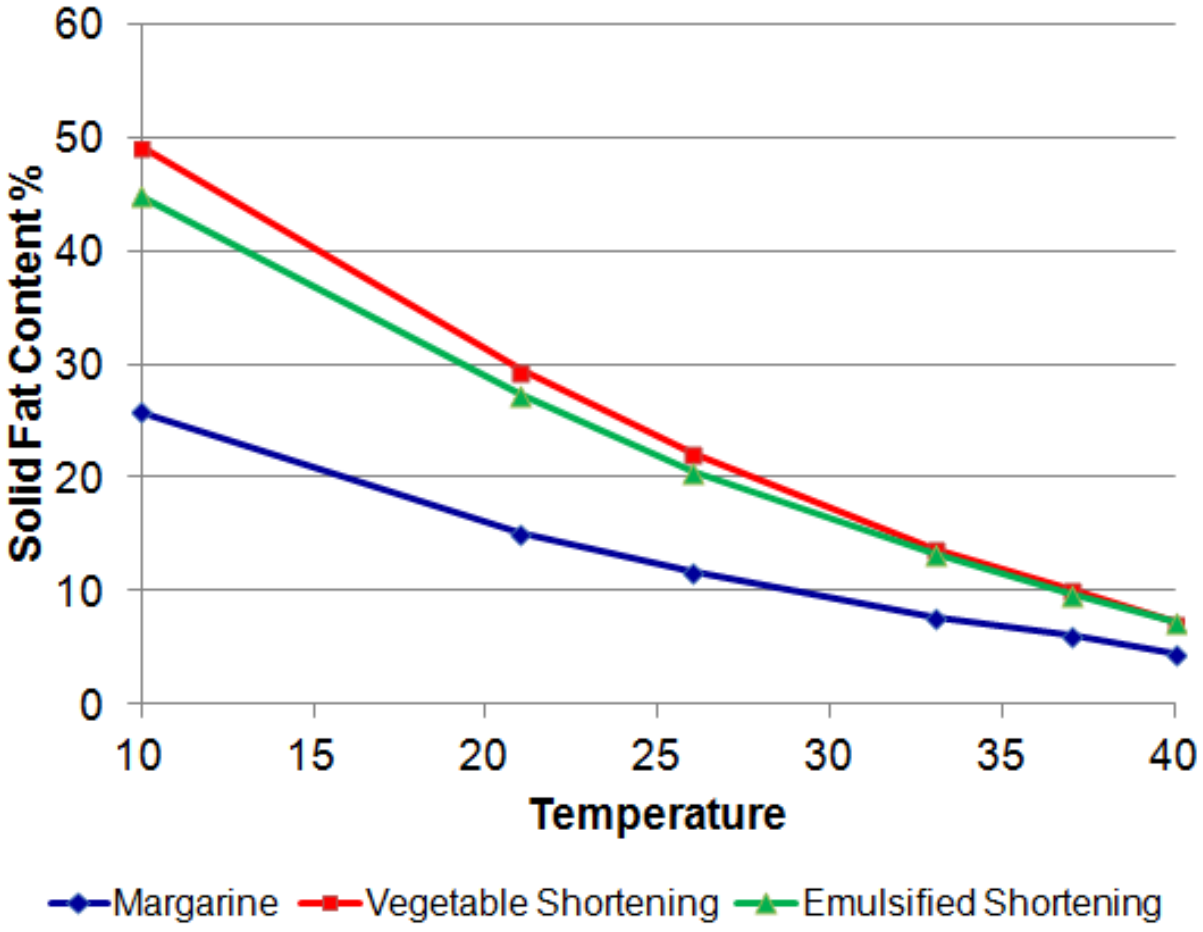
SFC Direct Method – Melting profiles



- Affects sensory and physical properties, such as spreadability, firmness, mouth feel, processing and stability which are specific to the application
- TD-NMR is internationally recognised for measurement of solid fat
  - AOCS Cd 16b-93, ISO 8292-1:2008 and IUPAC 2.150 methods

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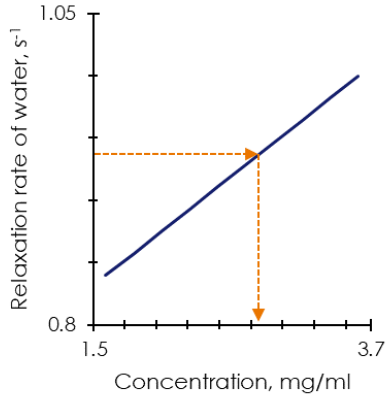
Non-destructive testing of pharmaceuticals



PROBLEM

Having the wrong fill level or wrong dose in a pharmaceutical product can lead to significant issues during administration of the drugs. Current testing methods rely on destructive testing of a small number of samples from large batches.

ANALYSIS

Time domain NMR can measure the relaxation time of the water component in an emulsion or suspension. This can be directly correlated with the fill level of the API.

SOLUTION

MQC+ can be used to directly measure the fill level without destroying the product ensuring a greater certainty in uniformity of pharmaceuticals.

AAPS PharmSciTech (2019) 20:189
DOI 10.1208/s12249-019-1405-0

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Summary

Summary

- Advanced NMR spectroscopy experiments including 2D NMR, selective pulses, gradient-based methods and solvent suppression
- Extensive range of nuclei
- Mobile with flexible placement
- Autosamplers
- Advanced flow and variable temperature capabilities
- Uses of benchtop NMR include:
  - structural elucidation and identification
  - quality control and quantification
  - measurement of physical properties

Throwback to SNUG PG 2019 benchtop NMR presentation

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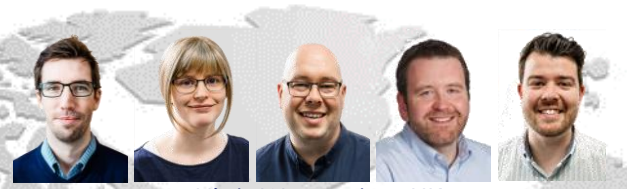
Oxford Instruments Magnetic Resonance Applications & Product Management Team



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Recruiting Now

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