The Role of Reaction Monitoring by NMR in the Pharmaceutical Industry

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Talk outline

- The need
- The utility of NMR
- Performing NMR experiments – options and examples
- Cheminformatics and statistical approaches

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Chemical process understanding

- PAT: a *process* centric focus on quality
- QbD: *designing* a process centric approach having quality built in

Quality

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Fundamental to success

- Greater understanding of reactions
  - Kinetics & mechanism
  - Establish reaction end points
    - Facilitate telescoped reactions
- Guide the design of synthetic route development
  - Improved yields
  - Cost savings
  - Reduce by-product formation or reaction quenching
  - Environmental impact

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Why NMR?

- All species will be seen
- Easier quantification – ‘NMR is a molar detector’
- Powerful tools available to determine structure
- Subtle effects are reported

Conventional methods

- Sampling for HPLC
- Vibrational spectroscopy (IR, NIR)

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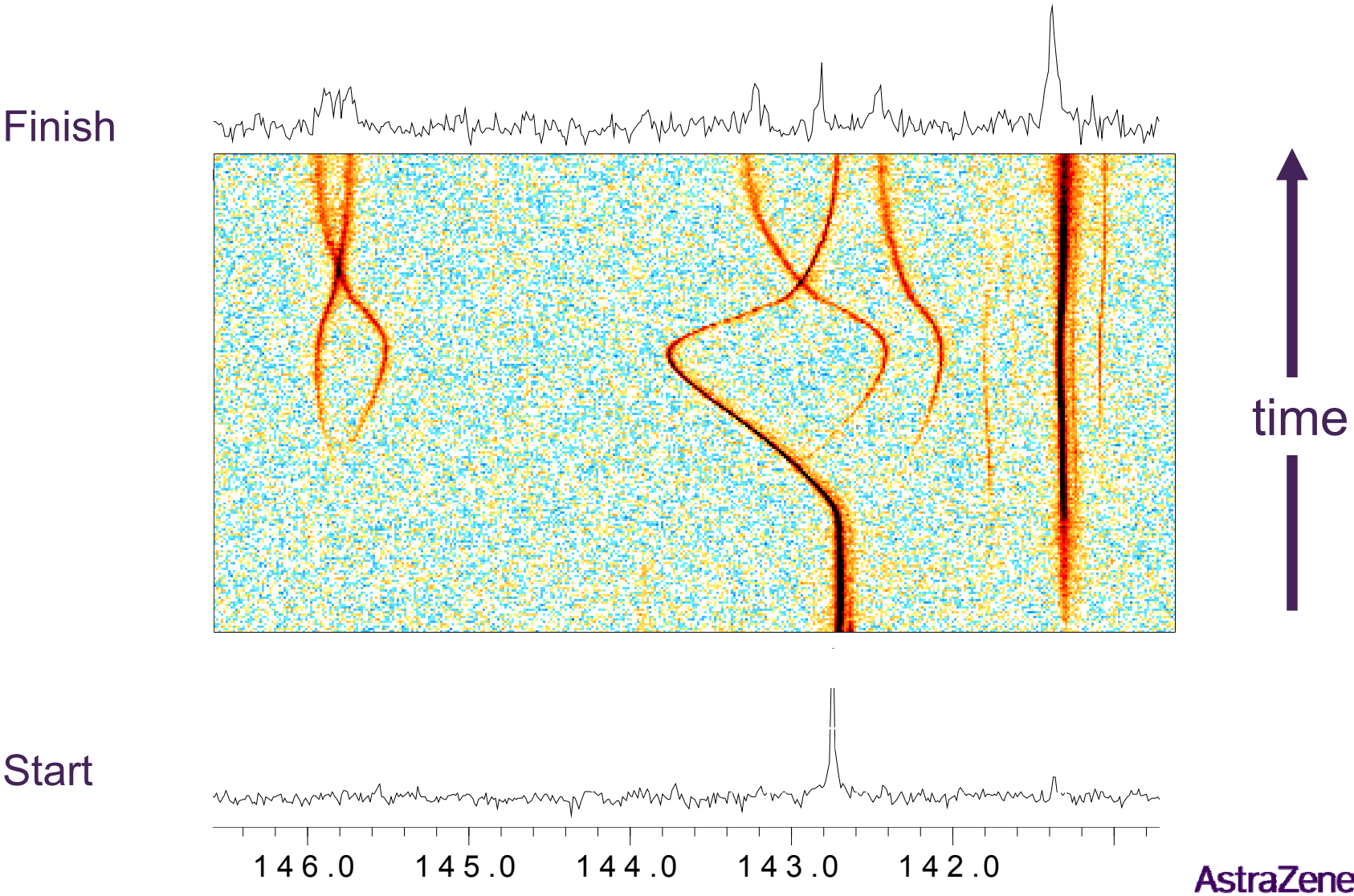
Time sliced NMR measurements



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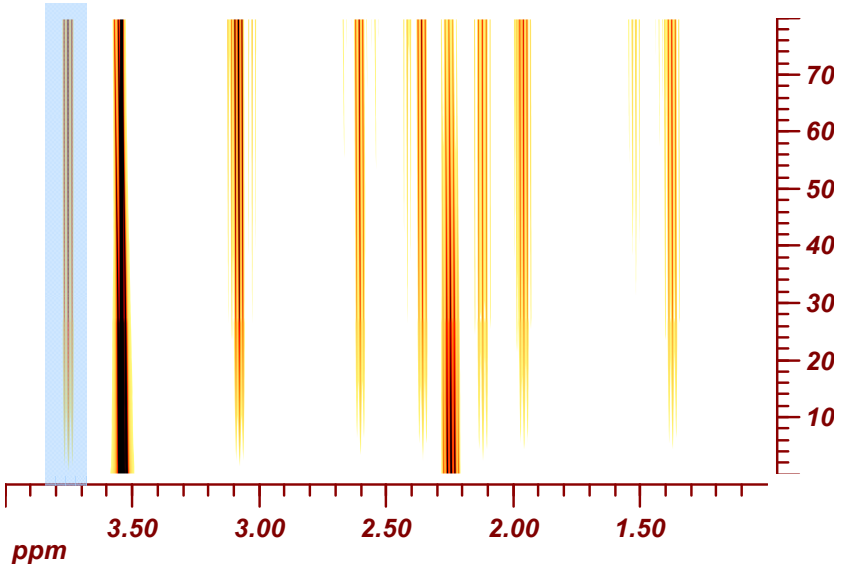
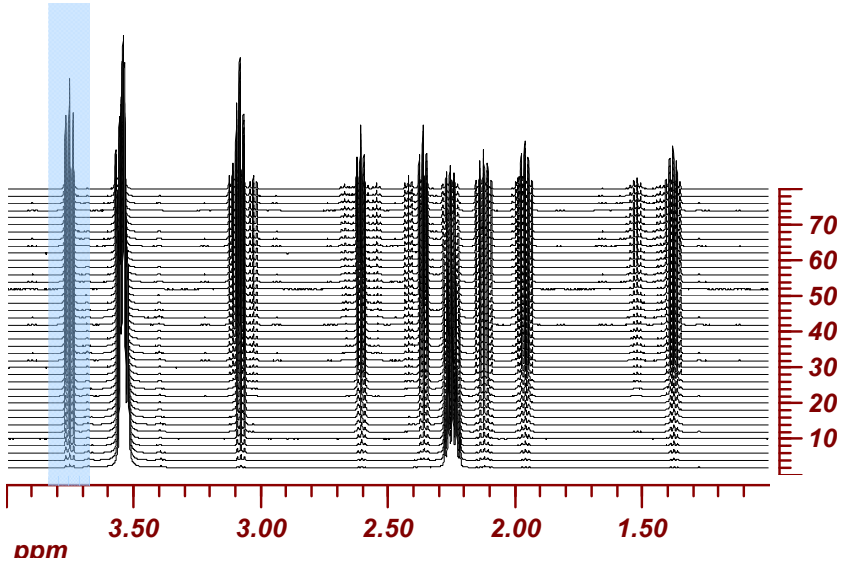
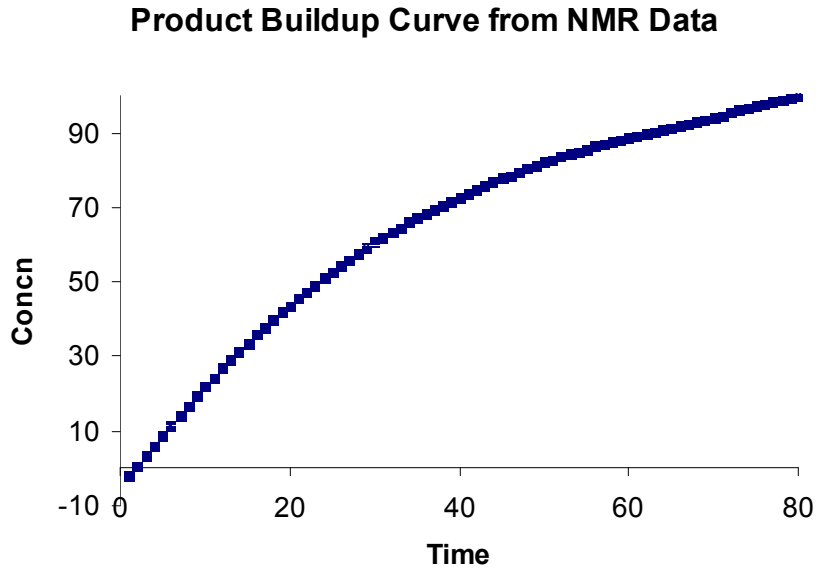
Simple data extraction







MestReNova software

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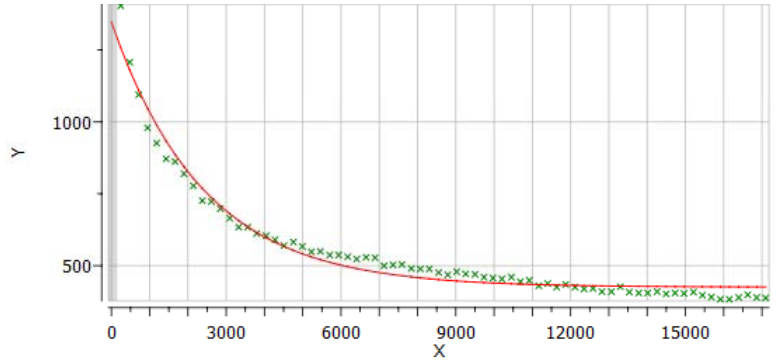
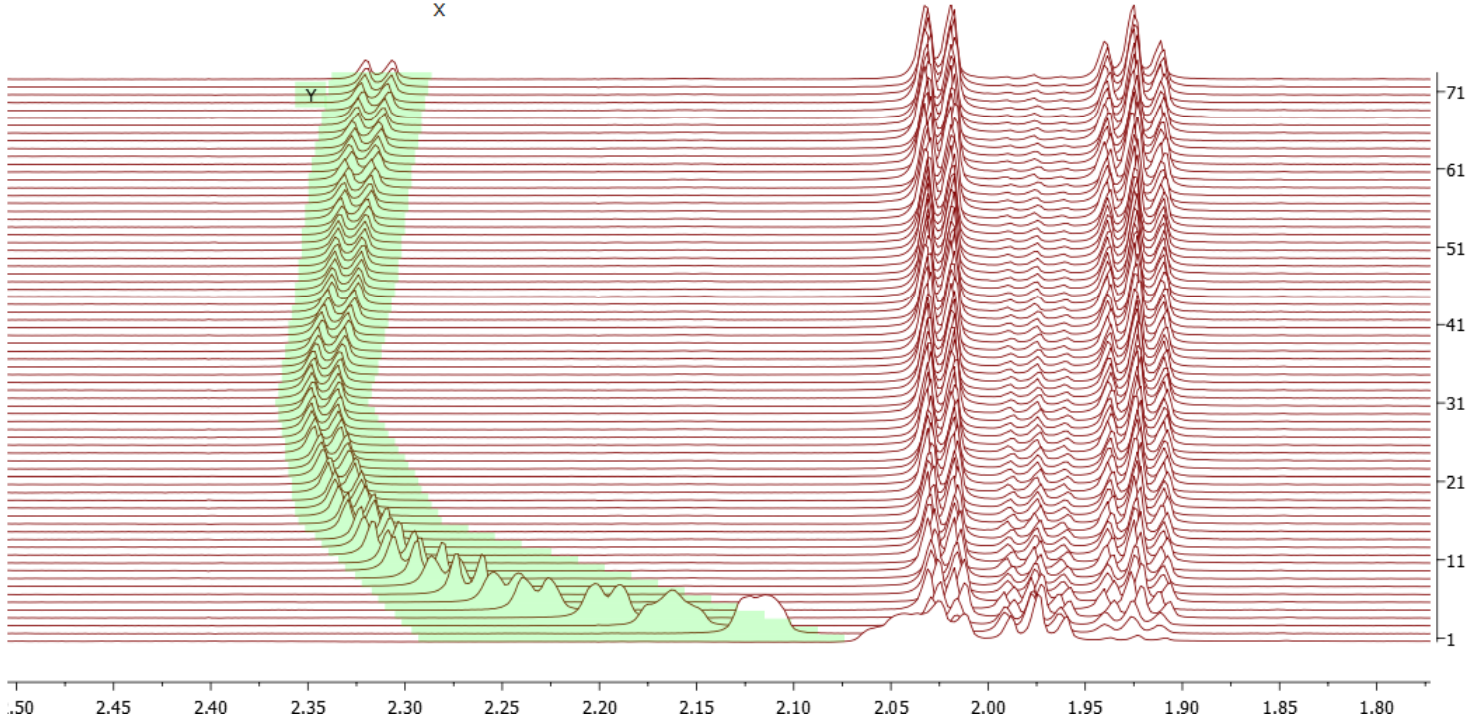
More complex data extraction





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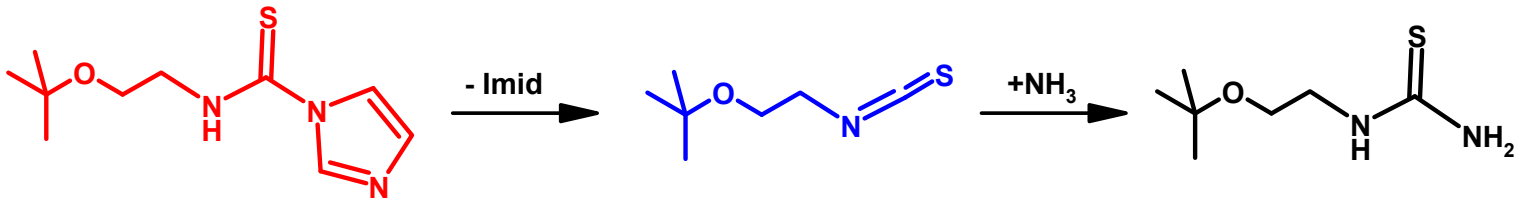
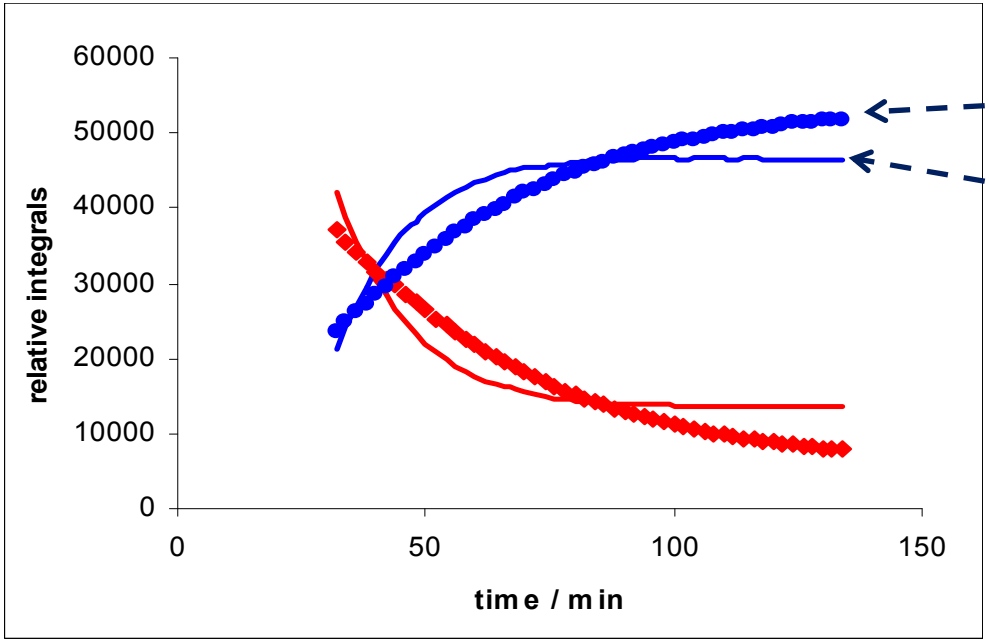
Optimising a telescoped reaction

A “quick look-see”: Identification of intermediates





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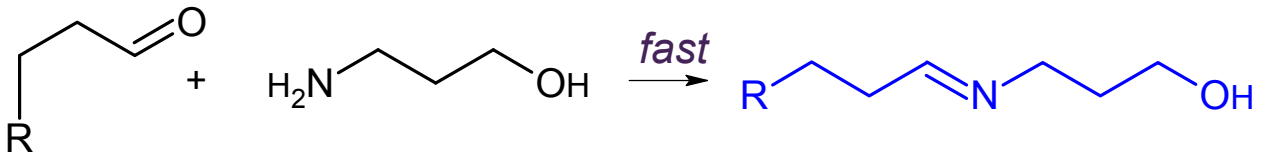
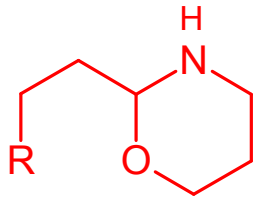
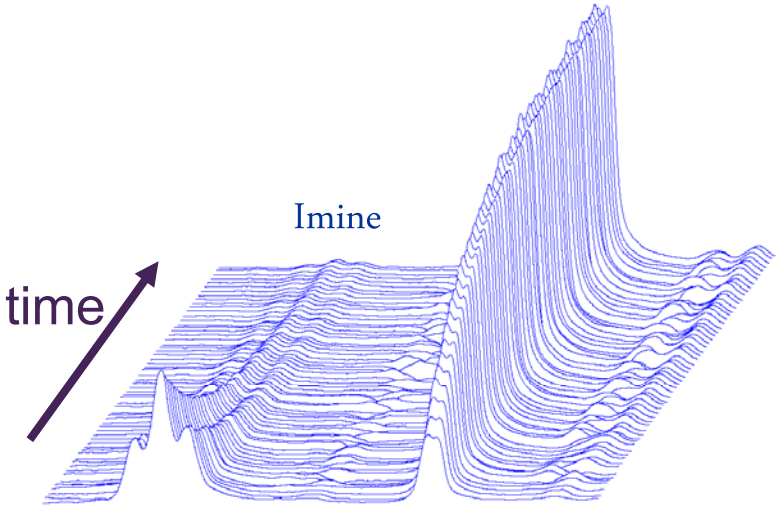
Speciation in condensation reaction

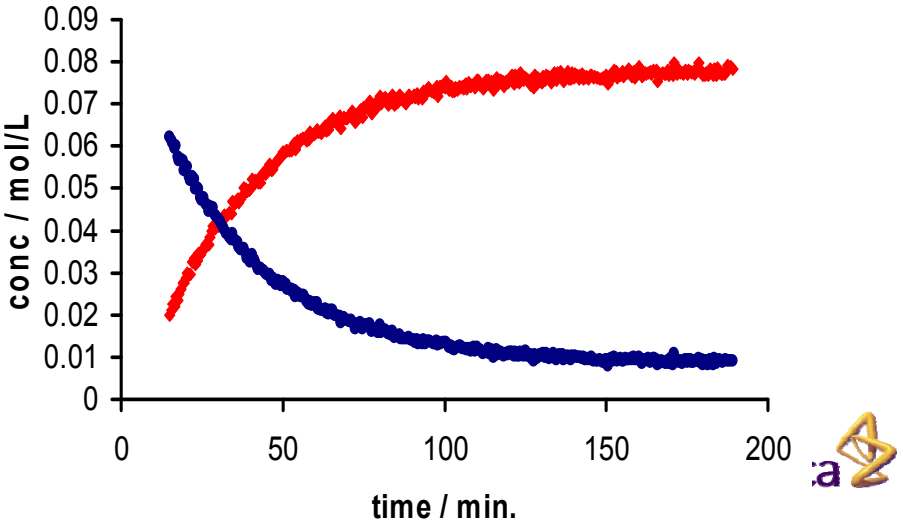


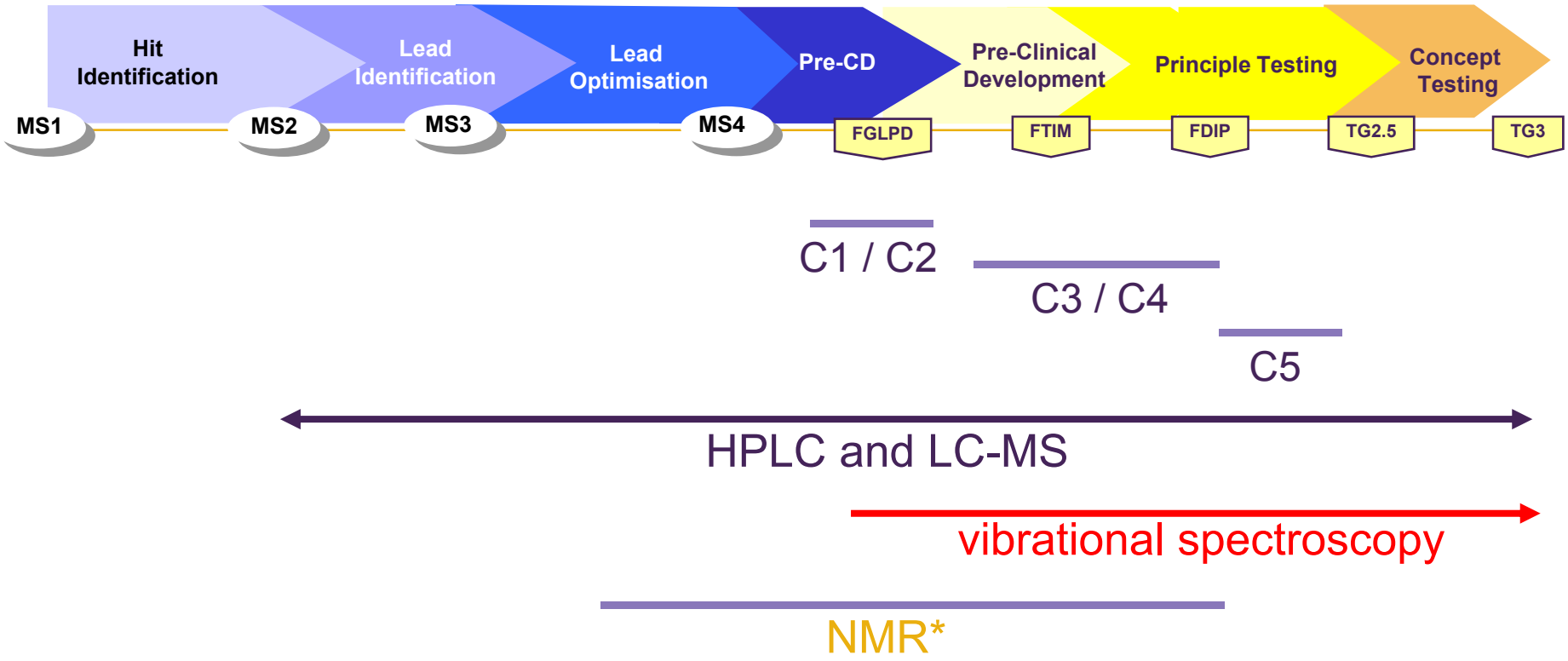
See by NMR

Marked solvent dependence









* high information content

- *Understand chemistry at early developmental stage*
- *Correlate e.g. NMR data to techniques that can be used easily at scale*

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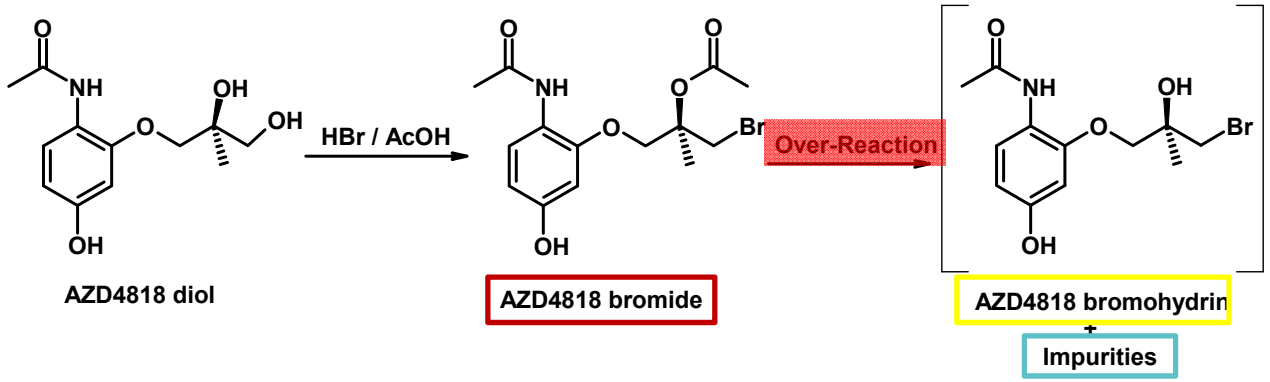
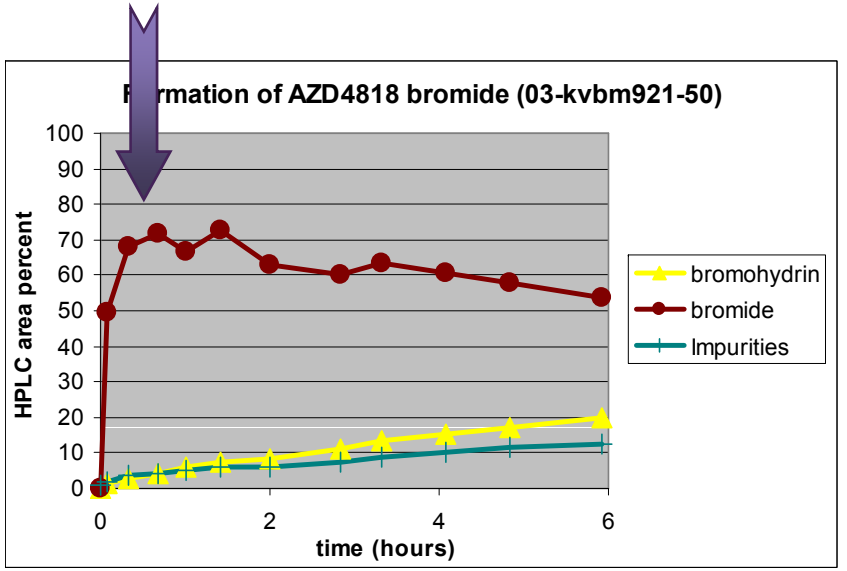
Bromination (over)reaction





- Route design for 40g – 40Kg scale
- Can we prove the over-reaction was occurring?
- Need for real time reaction monitoring in pilot plant

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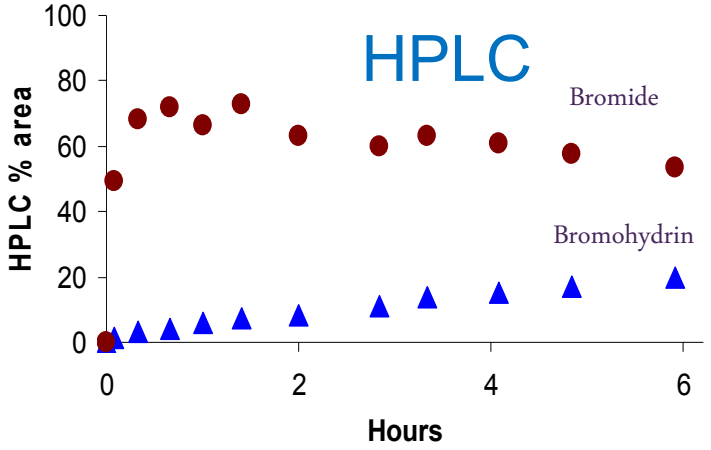
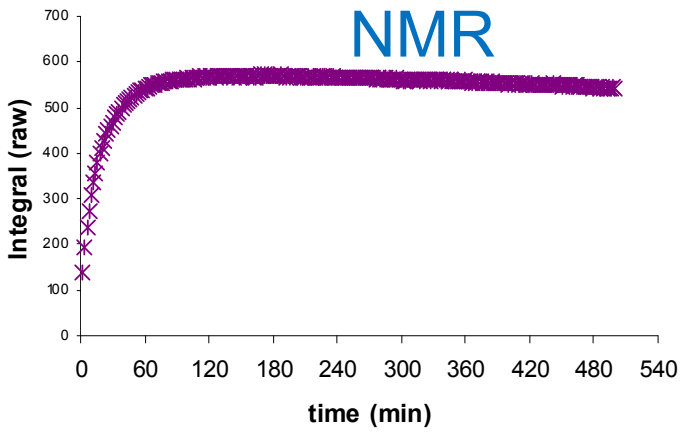
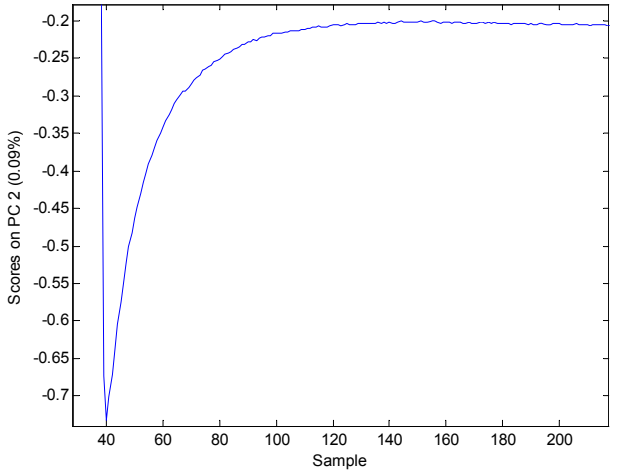
Bromination: overlapping technology



NMR provided initial in-depth structural work to complement HPLC



Near InfraRed



Profiles matched to NIR profiles for monitoring at scale.

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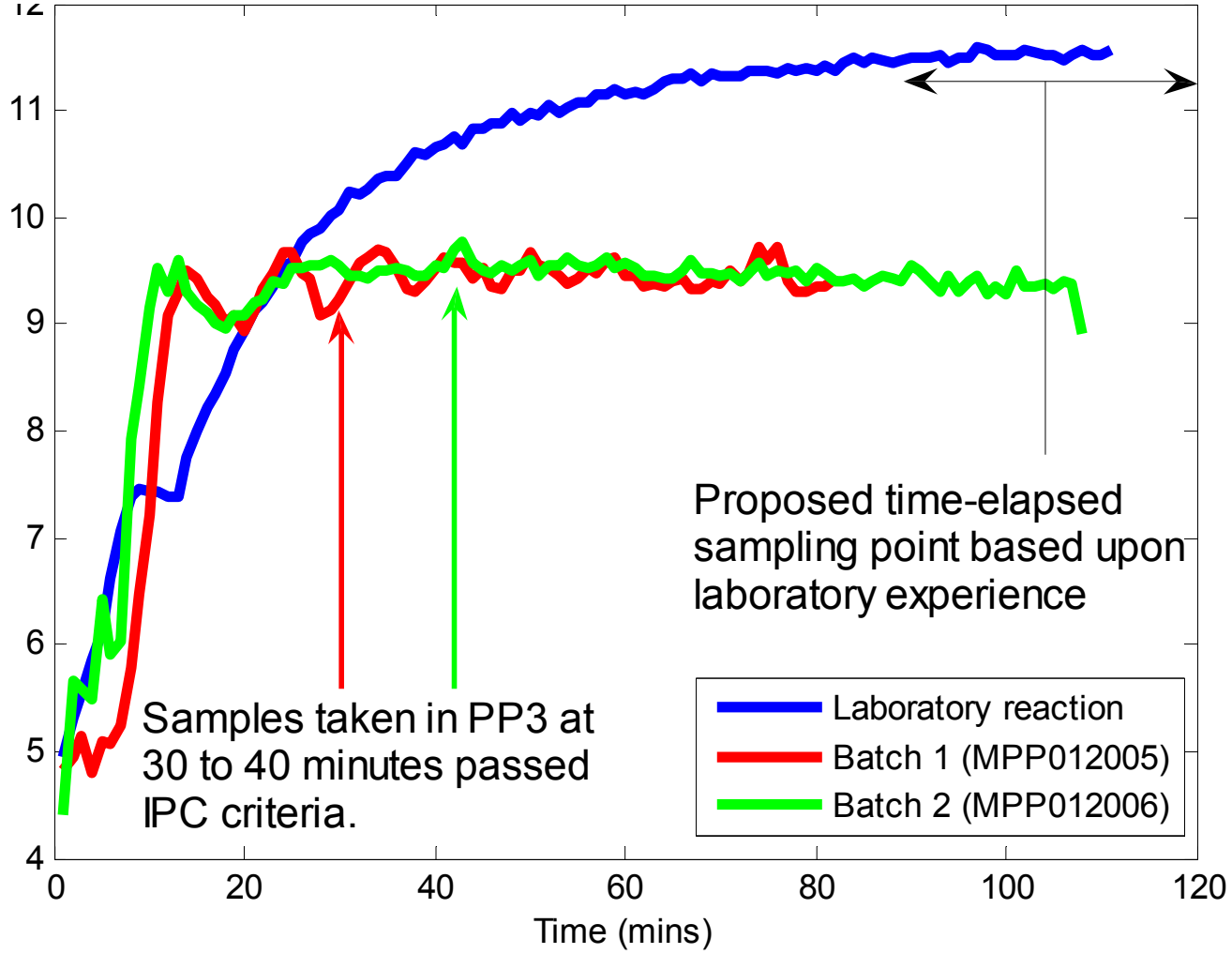
Bromination : NIR monitoring at scale



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NMR Analysers in Production

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Kinetics in an NMR tube

- Pros
  - quick and easy to set up
  - can use any available probe / observation nucleus
  - temperature control and good range
  - small amounts of material required (*ca*. 0.5 mL)

- Cons
  - no inerting
  - evaporation
  - no stirring
  - inhomogeneous reactions not tolerated

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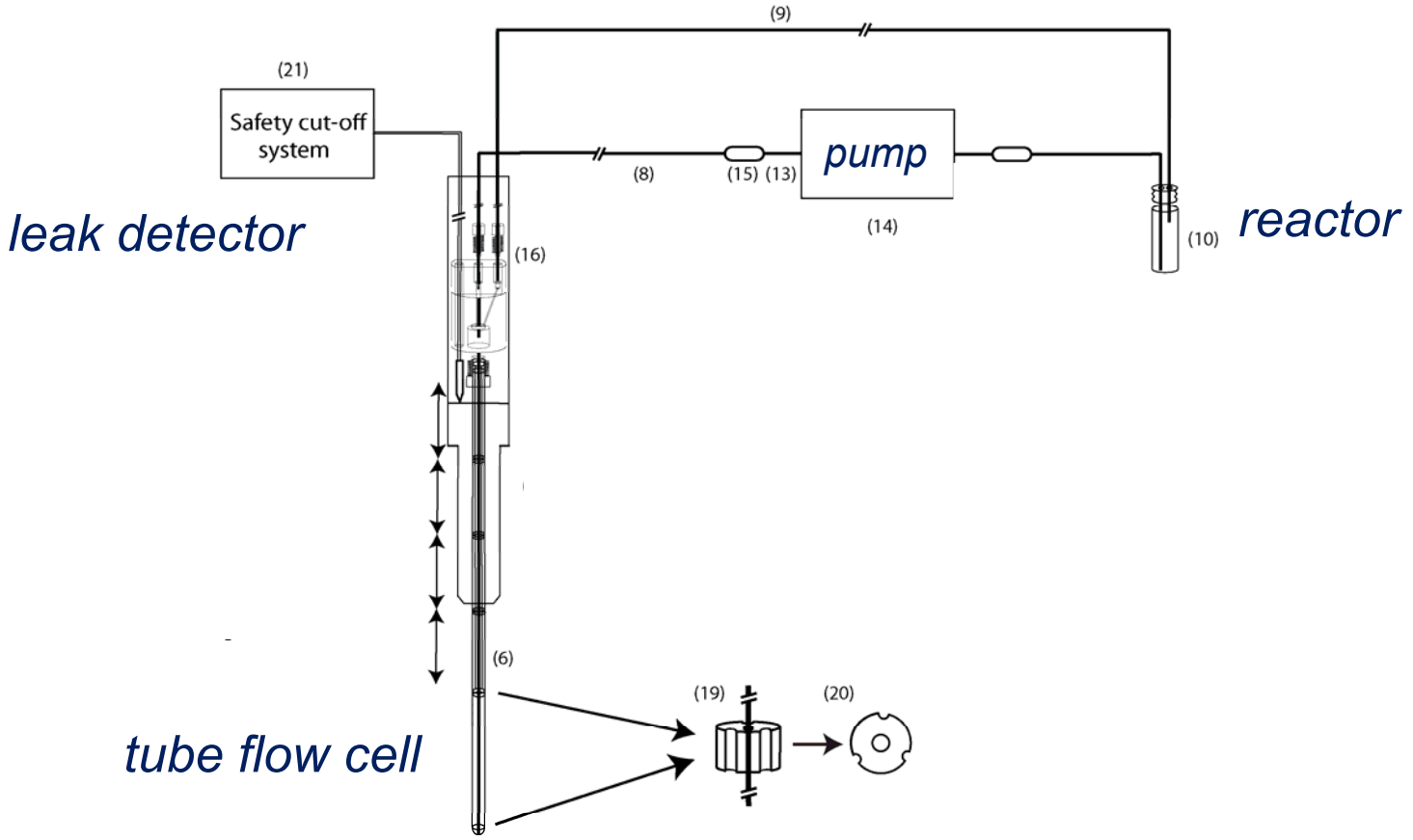
NMR on-flow: Sample limited

- A “flexible” NMR flow cell



M Khajeh, MA Bernstein, and GA Morris, *Magn Reson Chem*, **48** (2010) 516.

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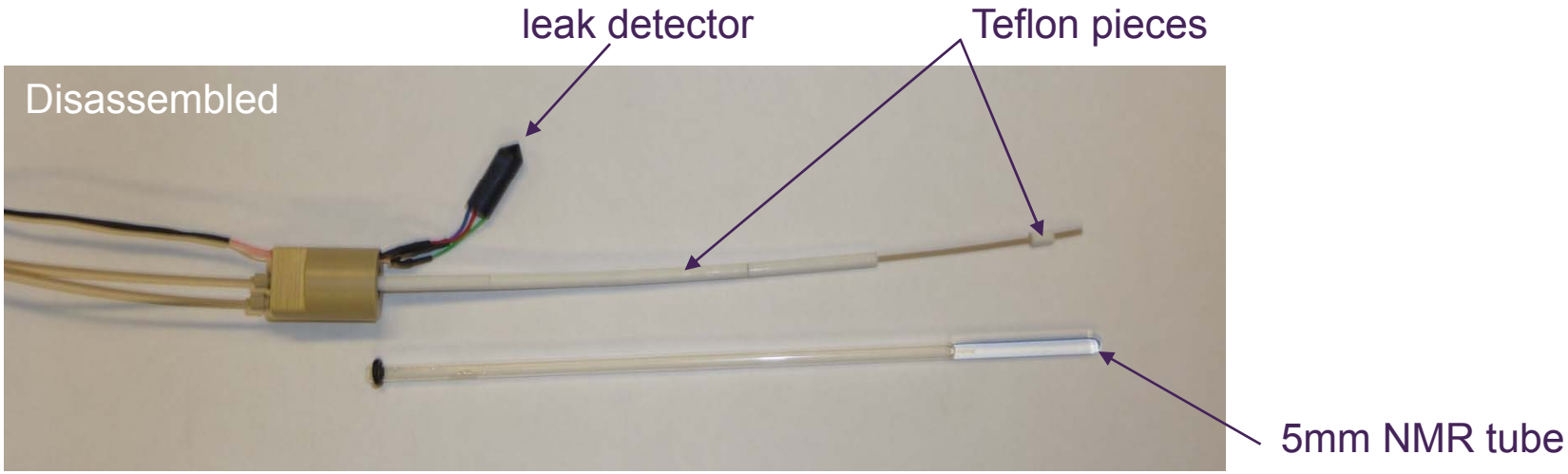

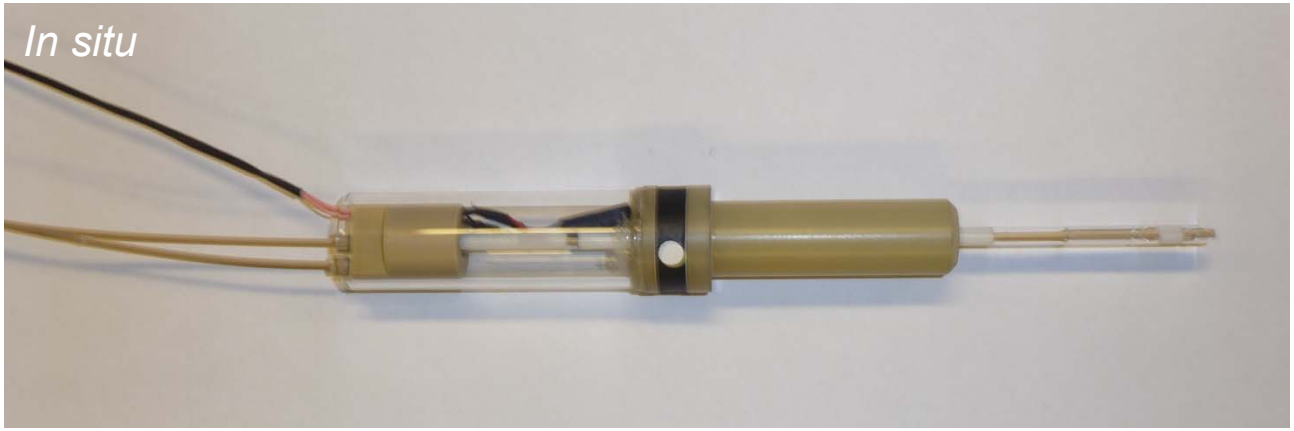

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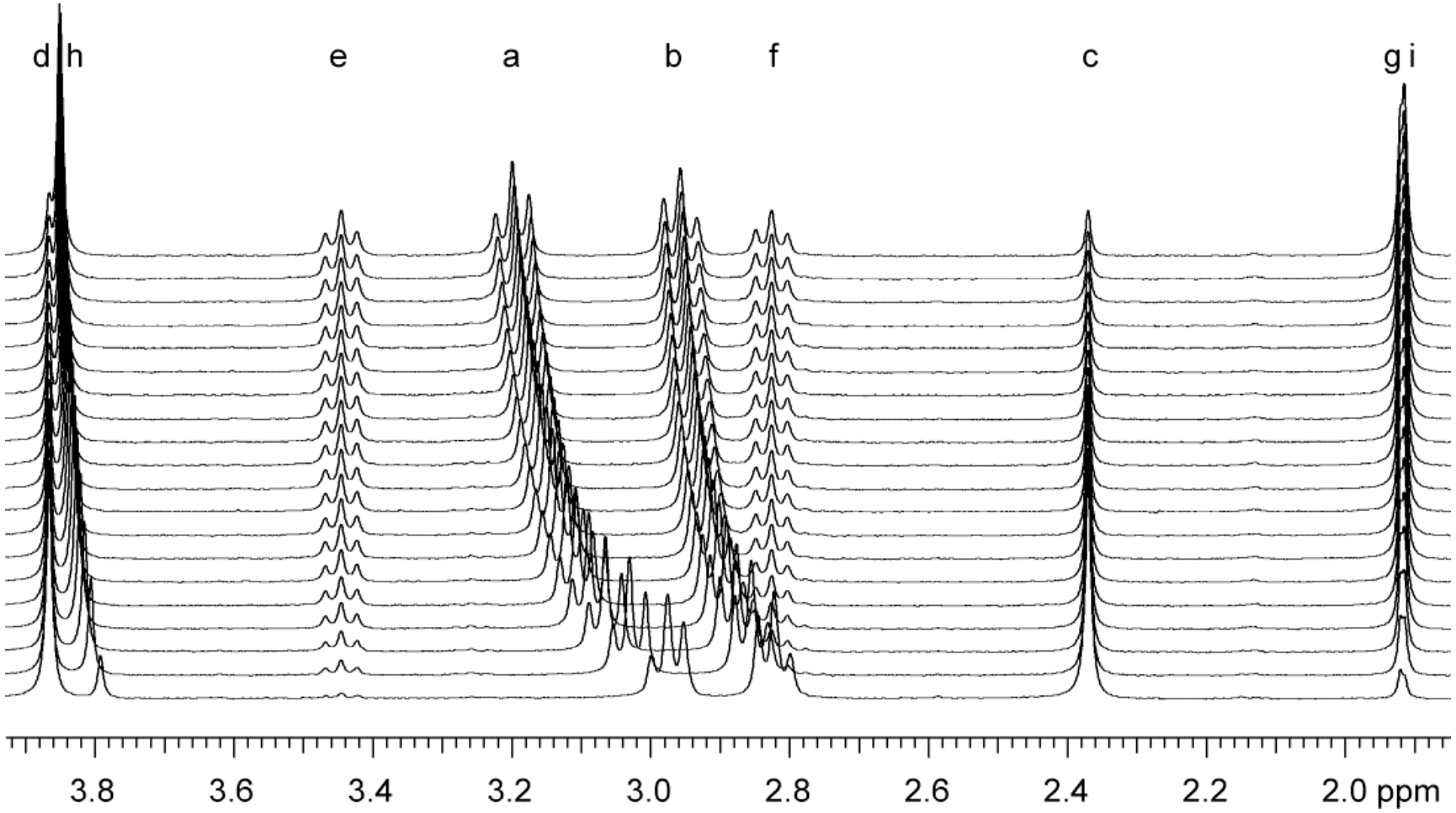
Reaction followed using flow tube



Data collected on-flow

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NMR on-flow using new flow cell Sample limited

- Pros
  - controlled reaction conditions
    - agitation, temperature control, inerting
  - relatively easy to set up
  - inhomogeneous reactions
  - carry out chemical reaction whilst monitoring by NMR
  - can use any NMR probe/nucleus available
- Cons
  - reaction done at laboratory scale
  - blockages are not tolerated
  - temperature control is imperfect

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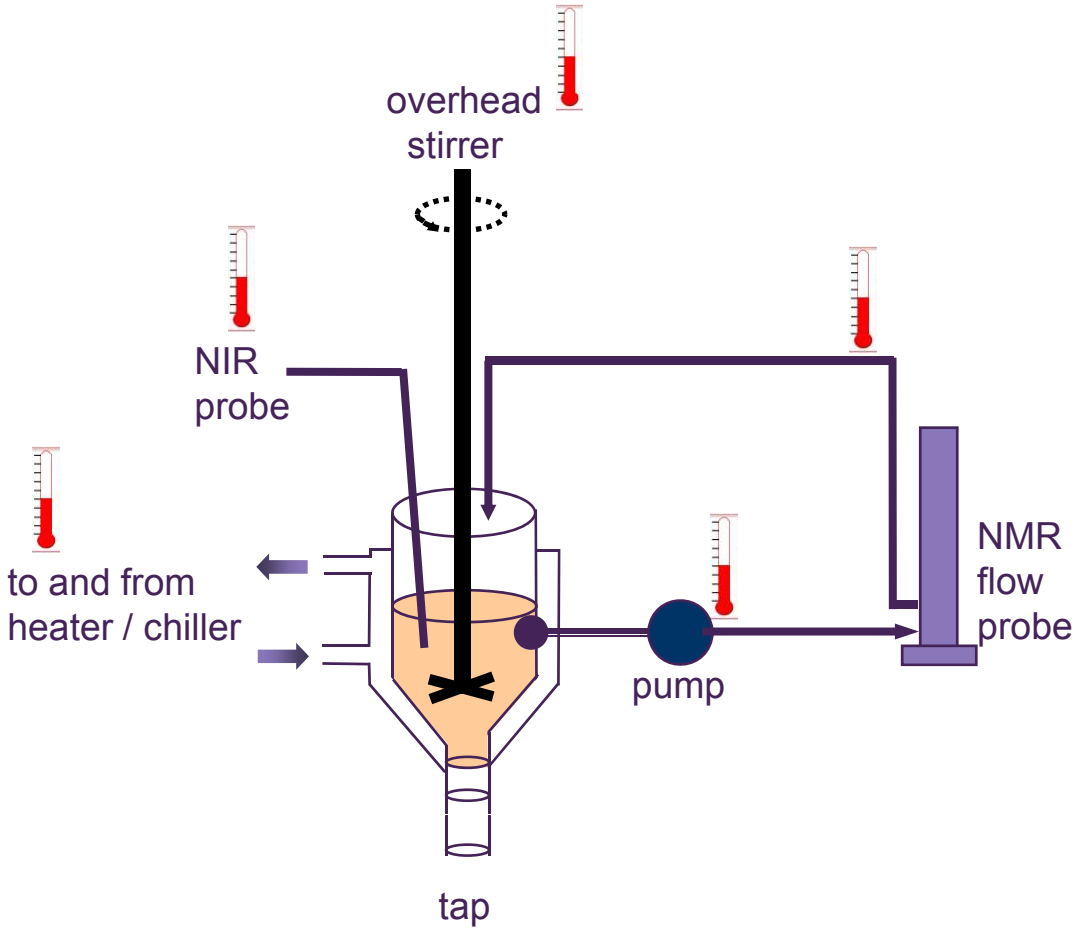
NMR monitoring with experiment control



Maiwald et al., *J Magn Reson* **2004**, *166*, 135

MA Bernstein, M Štefinović, C Sleigh, *Magn Reson Chem* **2007**, *45,* 564

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Implementation at AZ Charnwood

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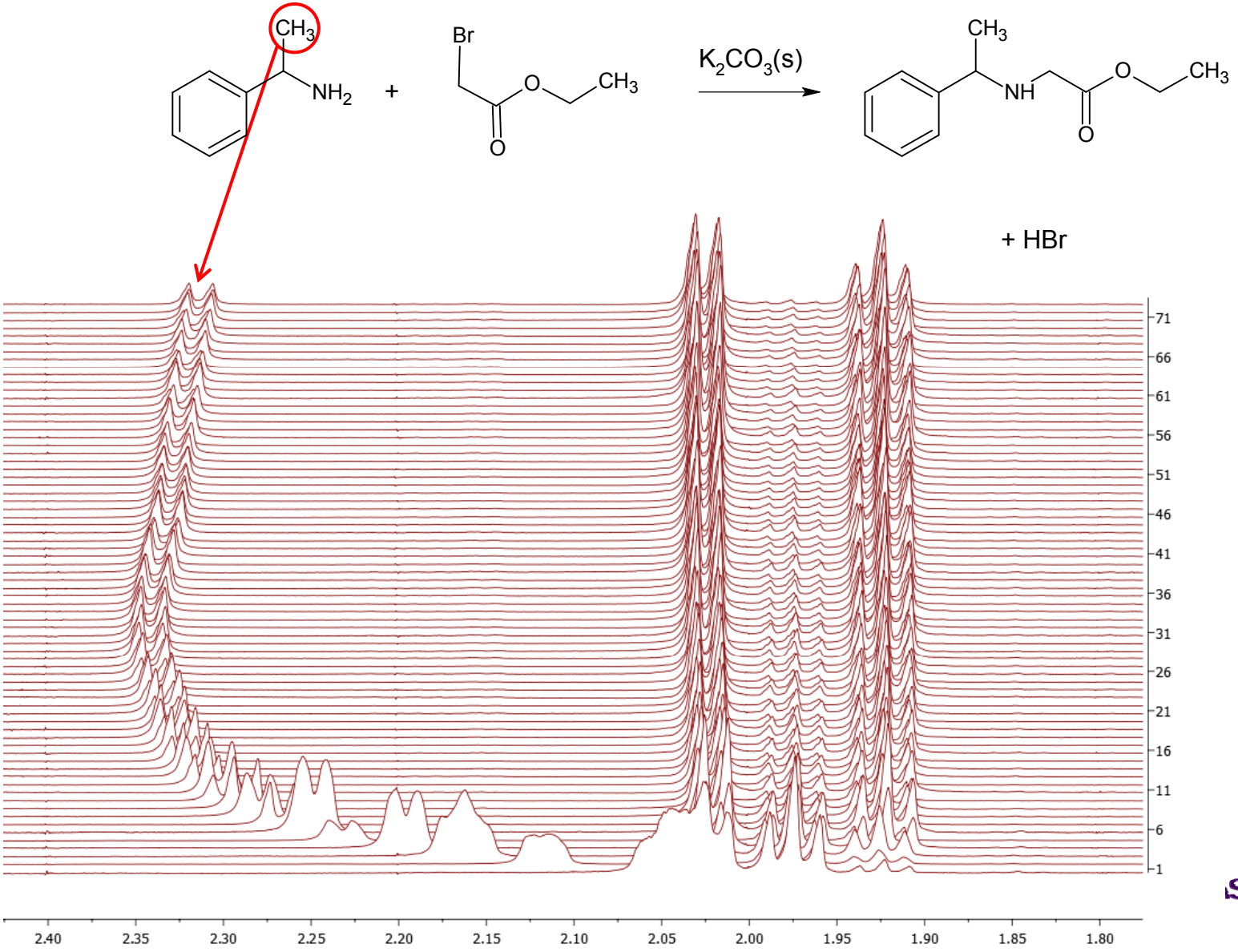
N-alkylation over K_2CO_3(s)



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NMR on-flow
Not sample limited

- Pros
  - closely-controlled reaction conditions
    - agitation, temp. control, inerting
  - inhomogeneous reactions
  - simultaneous monitoring
  - carry out chemical reaction
- Cons
  - relatively difficult to set up
  - reaction done at relatively large scale
  - blockages are not tolerated
  - restricted to one probe (^{1}H, ^{13}C observe)

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Using chemometrics

- A solution to the problem of signal overlap
- General applicability
- Better data integration across methods

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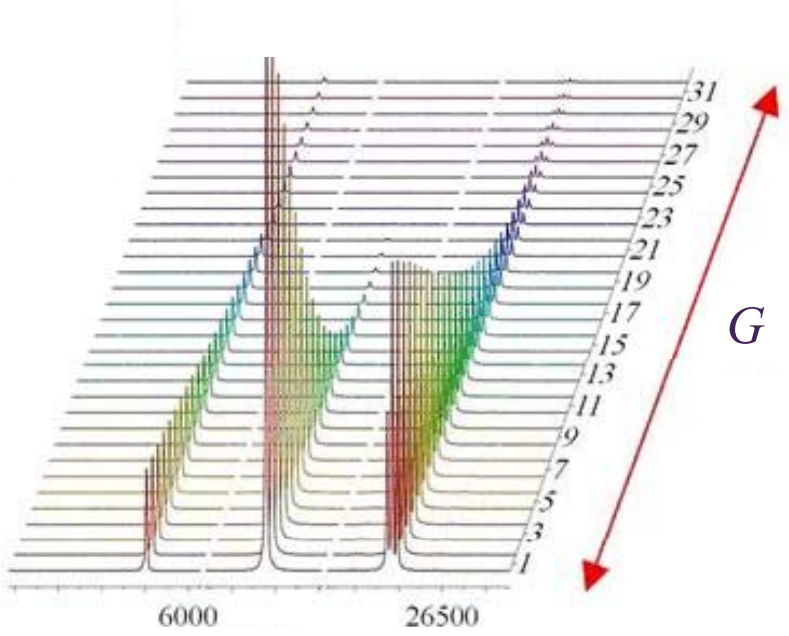
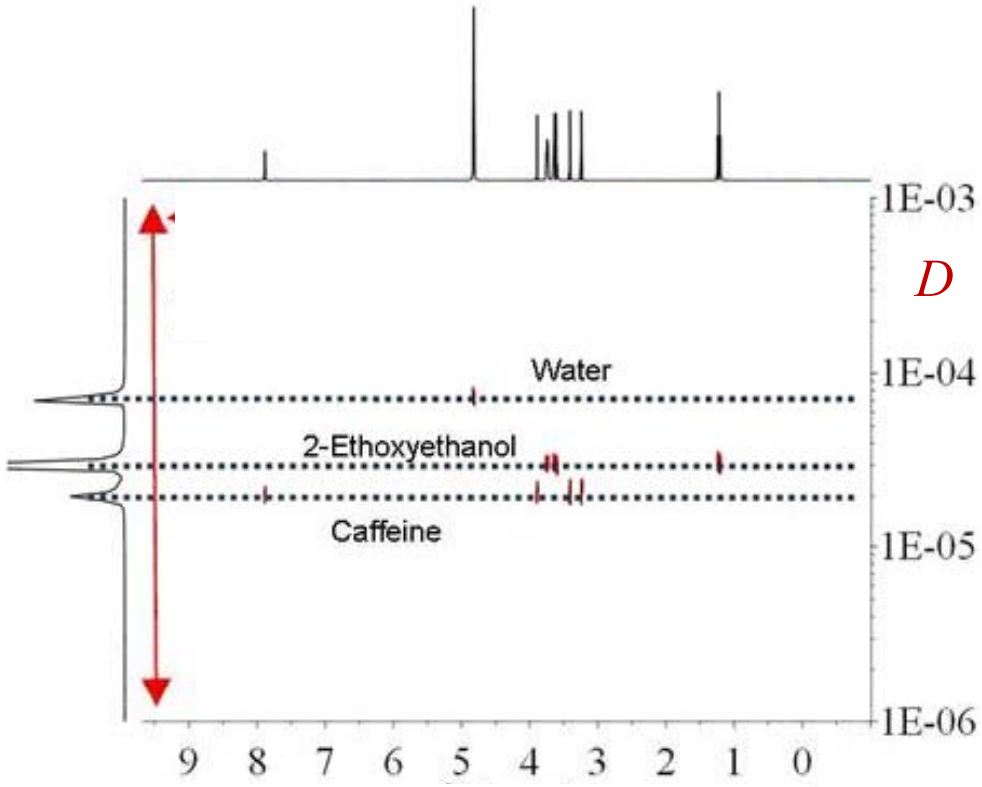
Measuring diffusion using NMR (DOSY)

Spectroscopic "separation" of a mixture based on diffusion rates

$$S(G) = S_0 e^{-D\gamma^2\delta^2G^2\Delta'}$$





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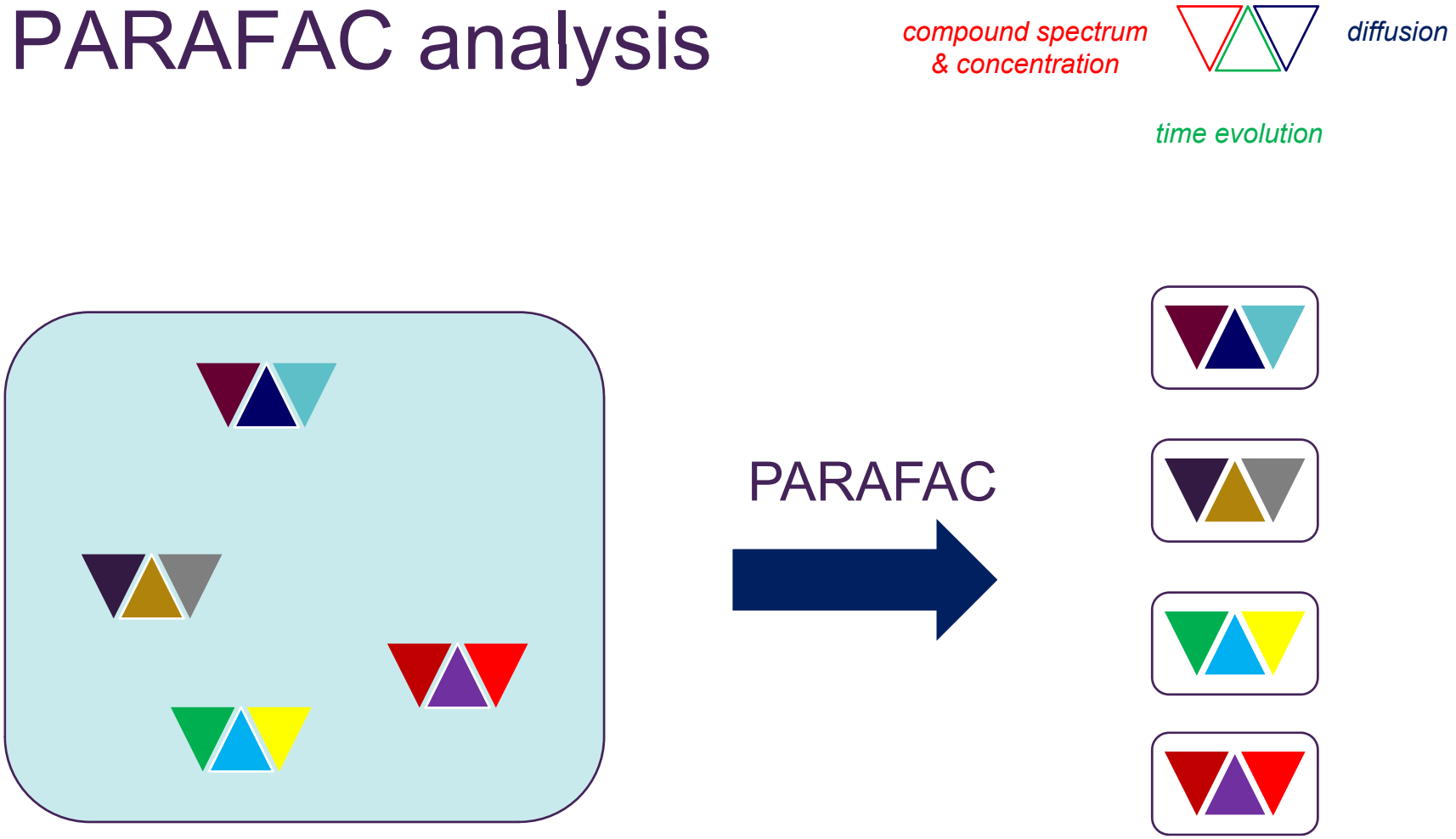
PARAFAC analysis



G Tomasi & R Bro, *Comput. Stat. Data Anal.* **2006**, *50*, 1700-1734

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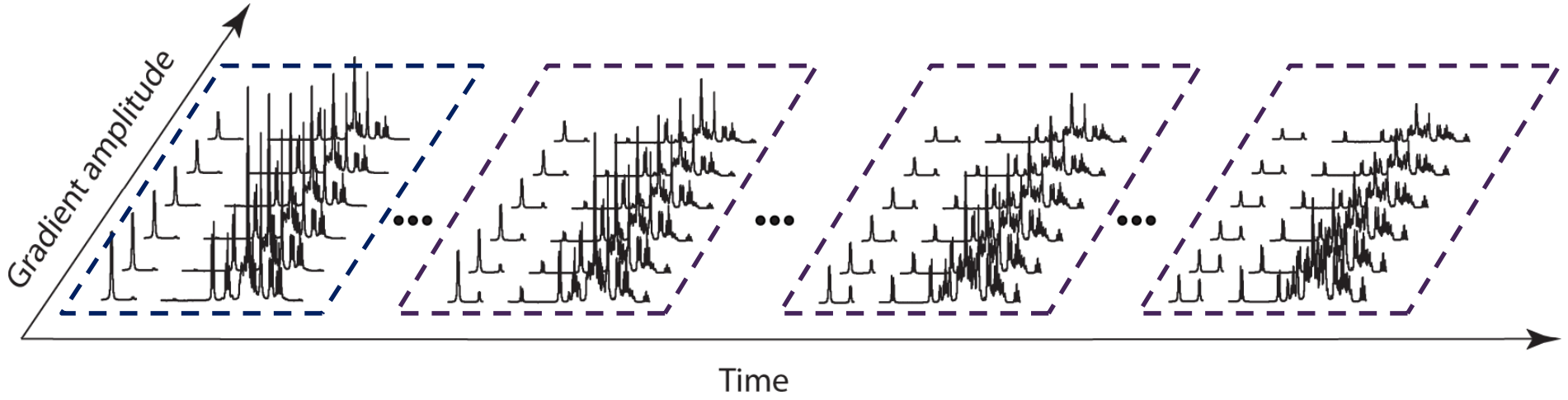
Practically...

- Perform a quick DOSY experiment at regular time points through the course of a chemical reaction



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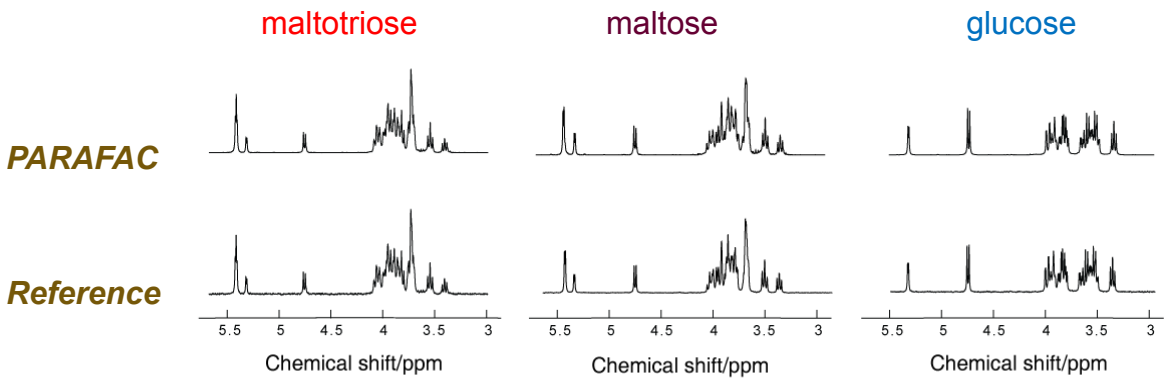
M Nilsson, M Khajeh, A Botana, MA Bernstein, & GA Morris, *Chem. Commun.*, **2009**, 1252–1254

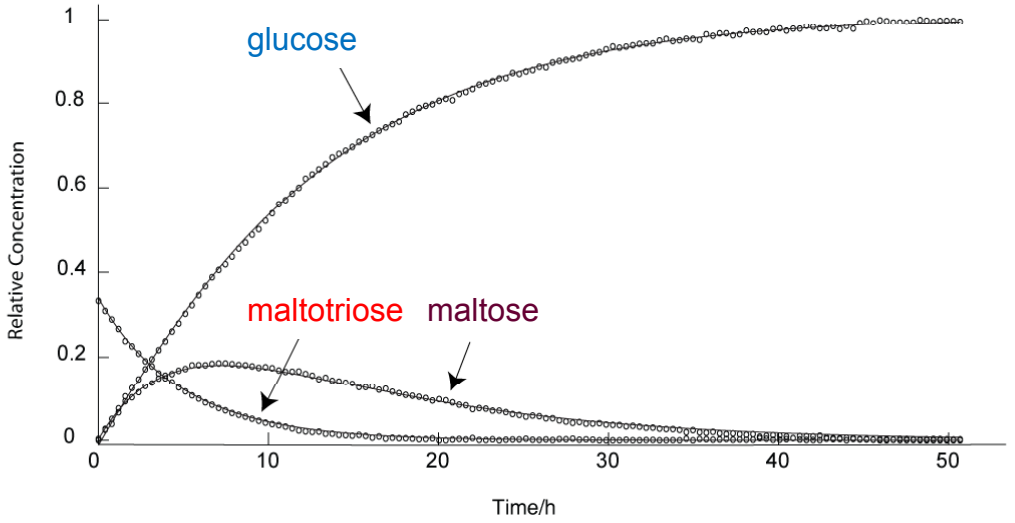
Maltotriose hydrolysis

maltotriose → glucose + maltose → 2 glucose

a



b



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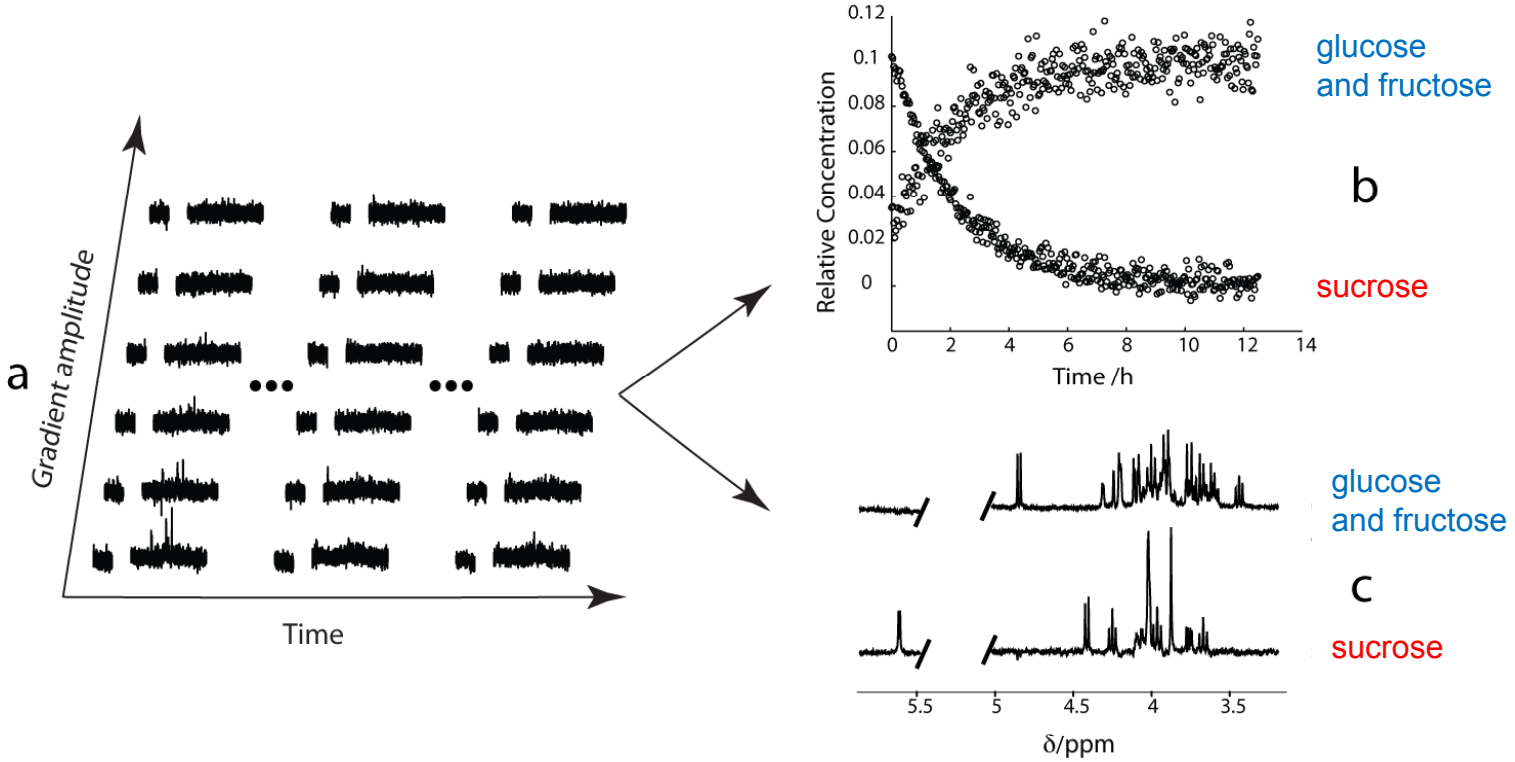
Species at low concentration

sucrose → glucose + fructose

1.1 mM



M Khajeh, A Botana, MA Bernstein, M Nilsson,* & GA Morris *Anal. Chem.* **2010**, *82*, 2102

Future prospects

- Wider use
  - Complete kinetic studies
  - Quick, chemistry assistance
- Impact on PAT and QbD
- Chemometrics
  - Integration with other measurements

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Acknowledgements and thanks

Chris Sleigh (Chemistry)

Marijan Štefinović

Steve Eyley

Dave Ennis

Dave Lathbury

Gareth Morris

Mathias Nilsson

Maryam Khajeh

Adolfo Botana