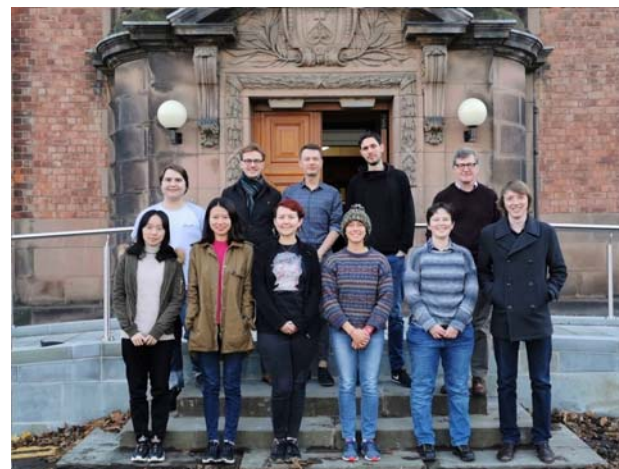


# NMR and Kinetics



Yael Ben-Tal  
SNUG Postgraduate NMR course  
03 Dec 2019

## Introduction

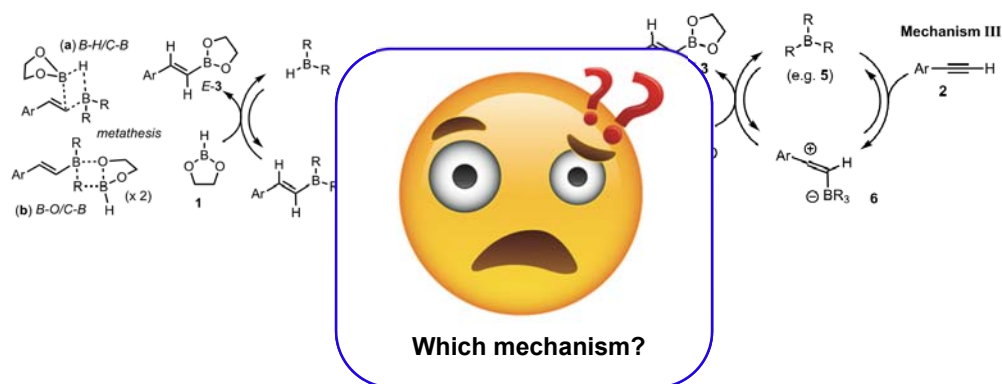


Mechanistic studies!

## Introduction



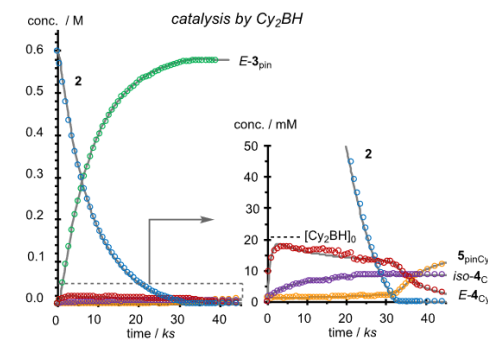
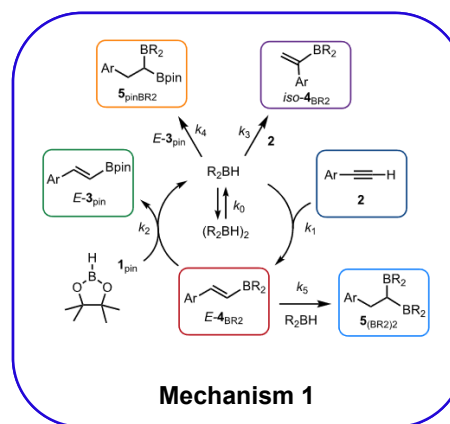
### Case study: Alkyne Hydroboration



## Introduction

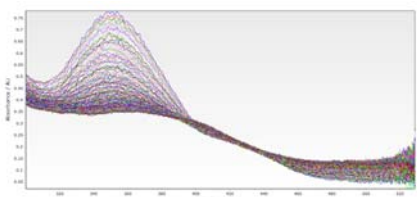
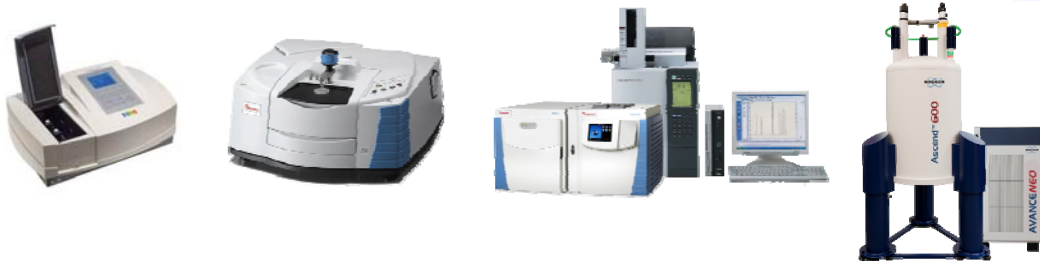


### Case study: Alkyne Hydroboration



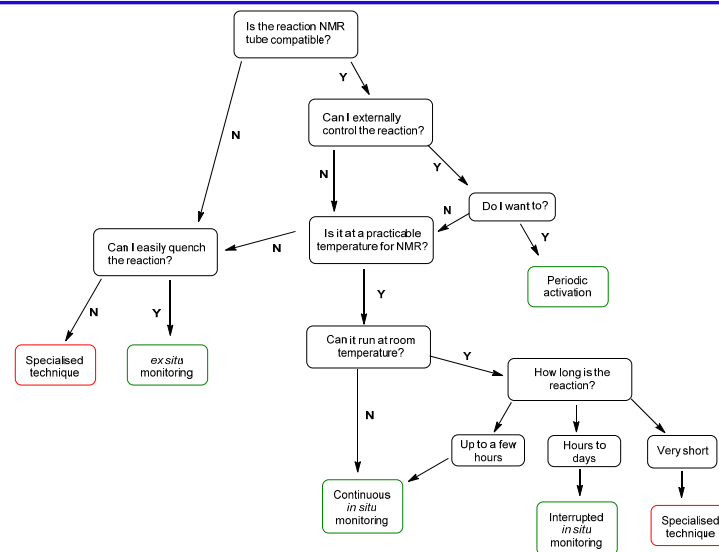
Many different kinetic experiments!

## Introduction

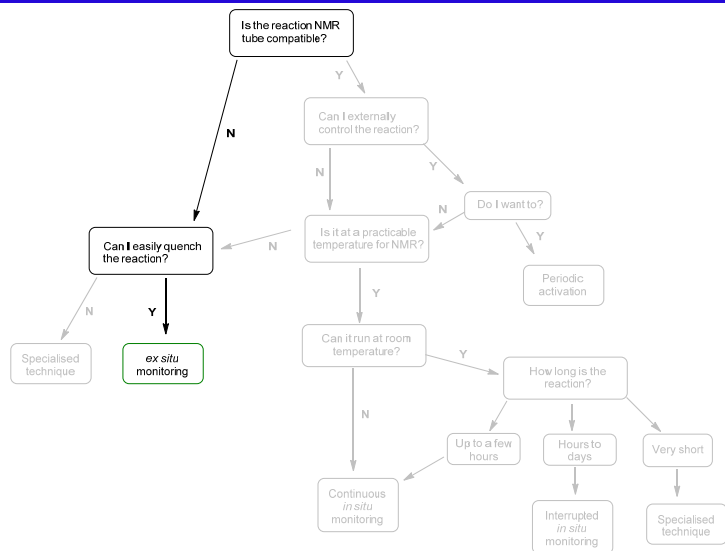


- High information density
- Non destructive

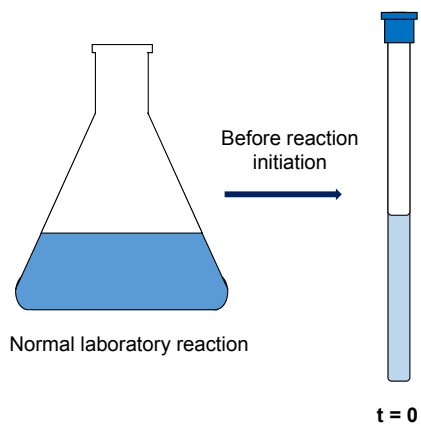
## Sampling Methods



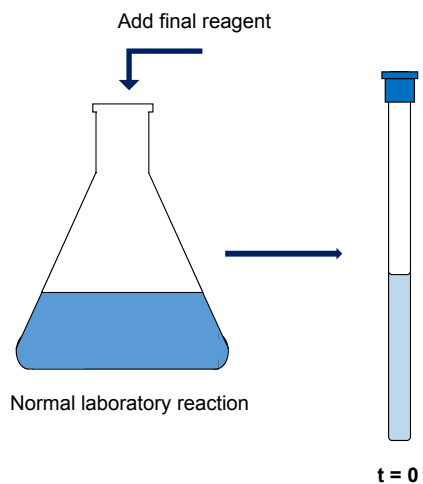
## Sampling Methods



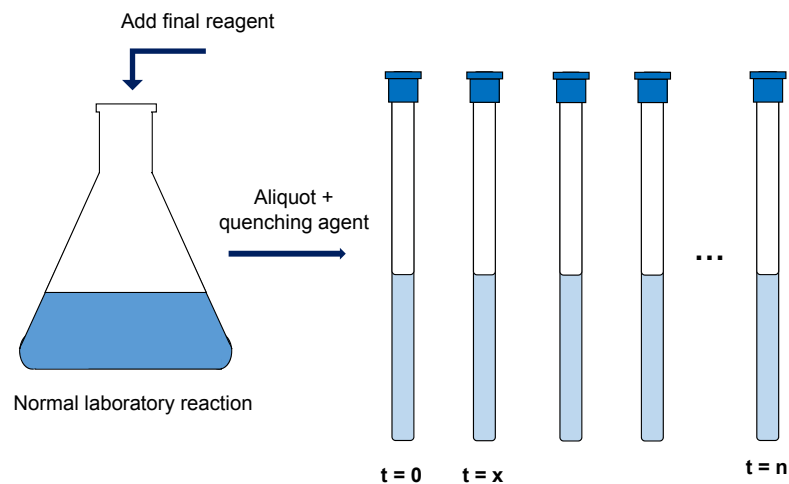
## Sampling Methods – *ex situ* Monitoring



## Sampling Methods - *ex situ* Monitoring

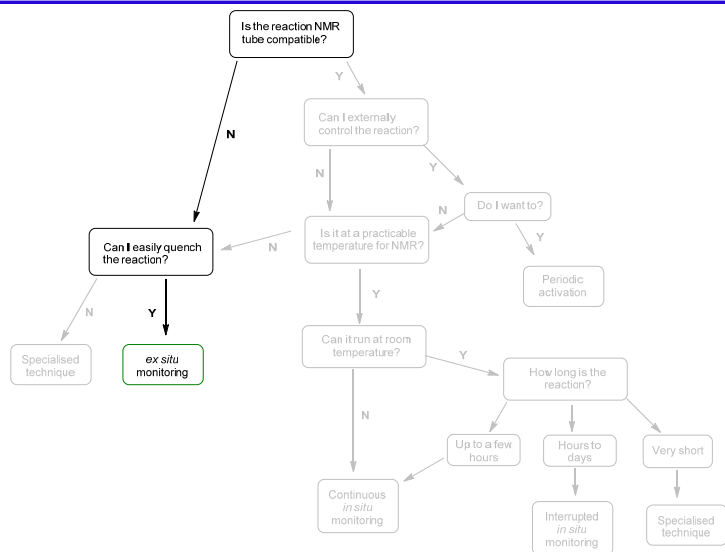


## Sampling Methods - *ex situ* Monitoring

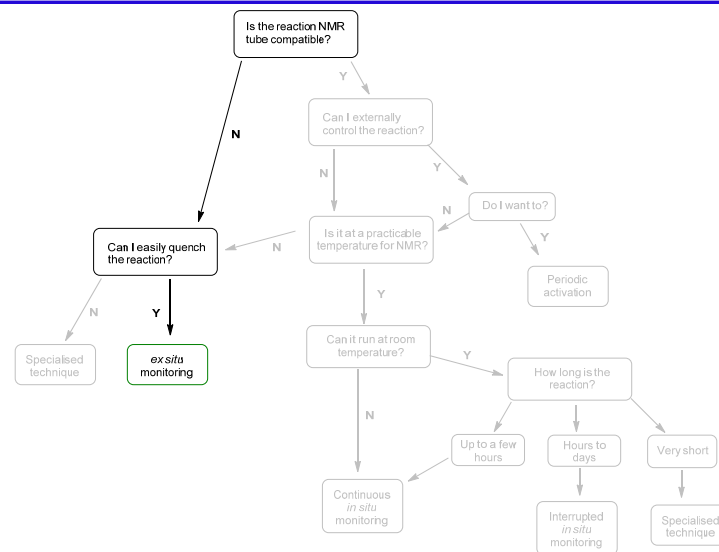


- Same conditions as lab
- Parallel experiments
- Labour intensive
- Long NMR experiments possible
- Lose transient/unstable intermediates
- Incomplete quenching
- Large reaction volume

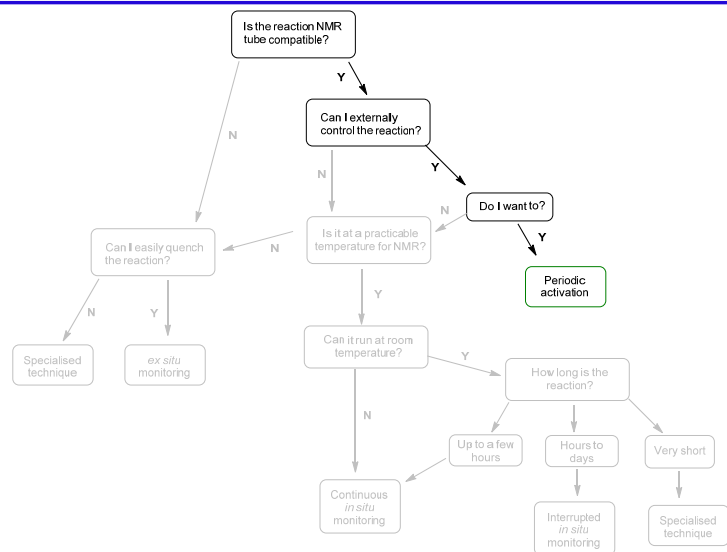
## Sampling Methods



## Sampling Methods

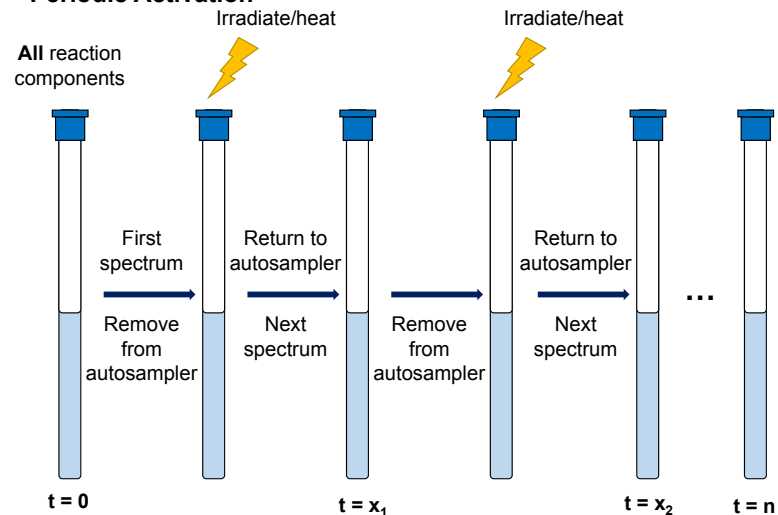


## Sampling Methods



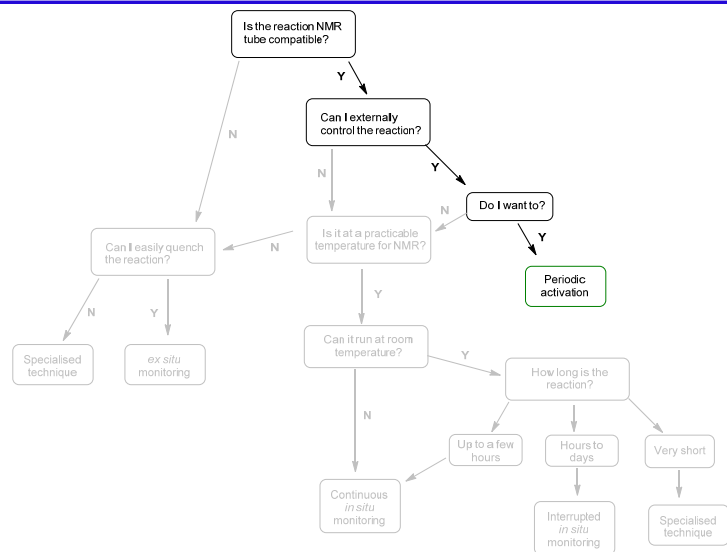
## Sampling Methods – *in situ* Monitoring

### Periodic Activation

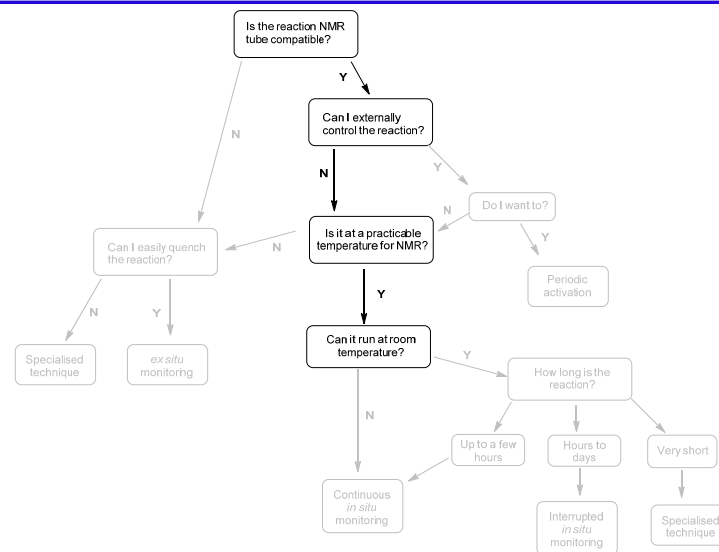


- Long NMR experiments possible
- Parallel reactions possible
- Labour intensive
- Possibly lose transient species
- Limited reaction compatibility

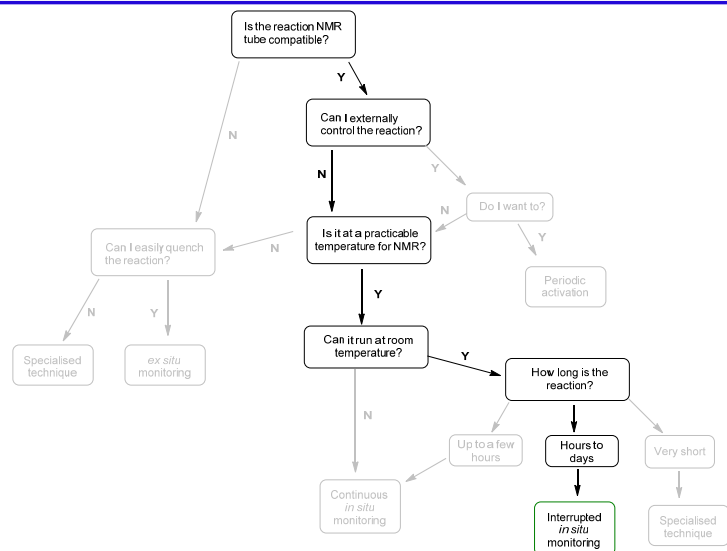
## Sampling Methods



## Sampling Methods

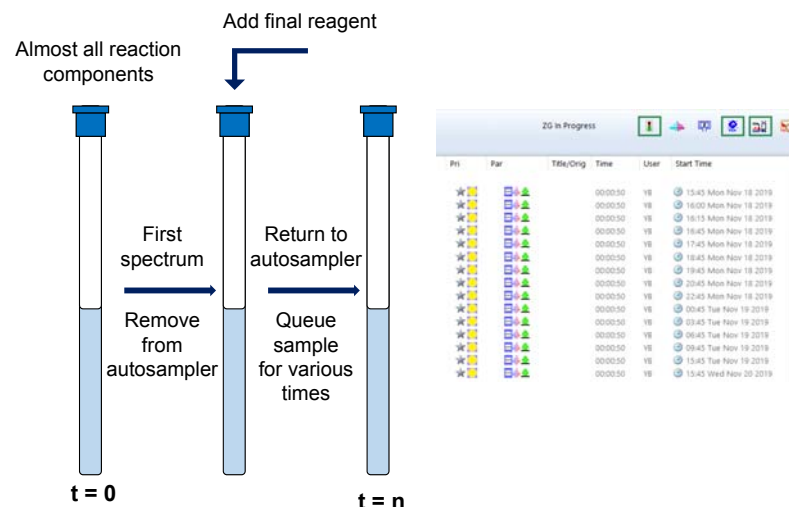


## Sampling Methods



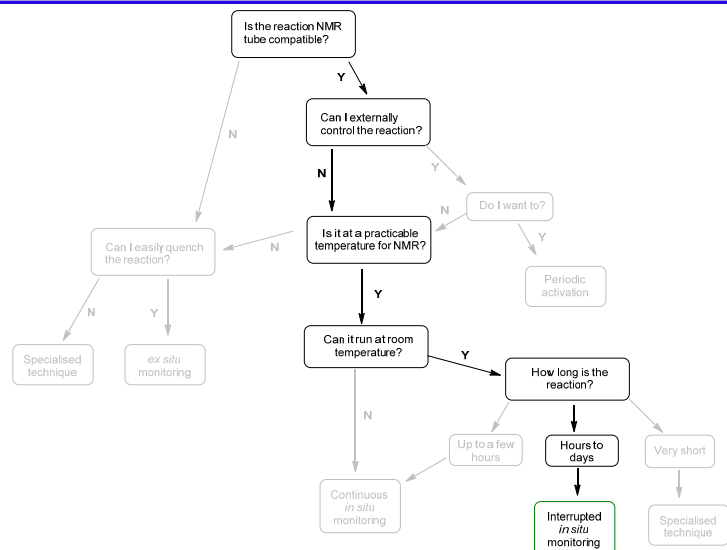
## Sampling Methods – *in situ* Monitoring

### 'Interrupted' Monitoring

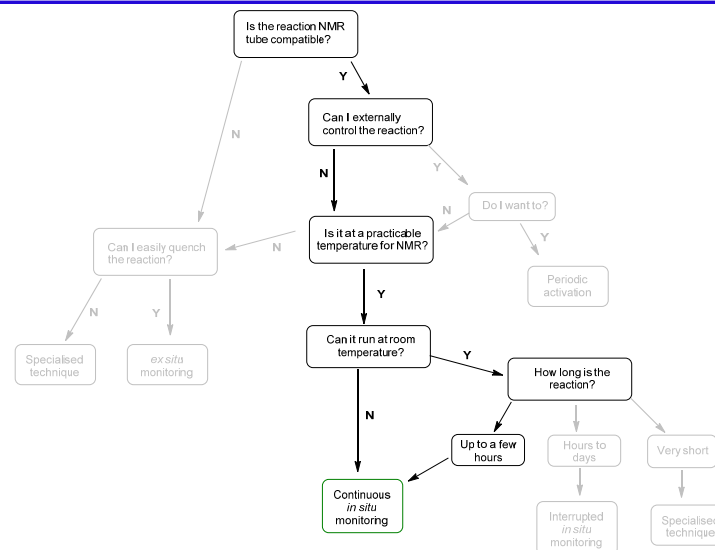


- Easy
- Parallel experiments
- Relatively slow reactions

## Sampling Methods

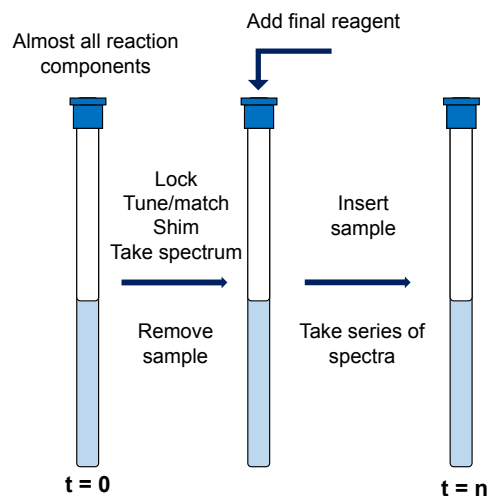


## Sampling Methods



## Sampling Methods – *in situ* Monitoring

### Continuous Monitoring

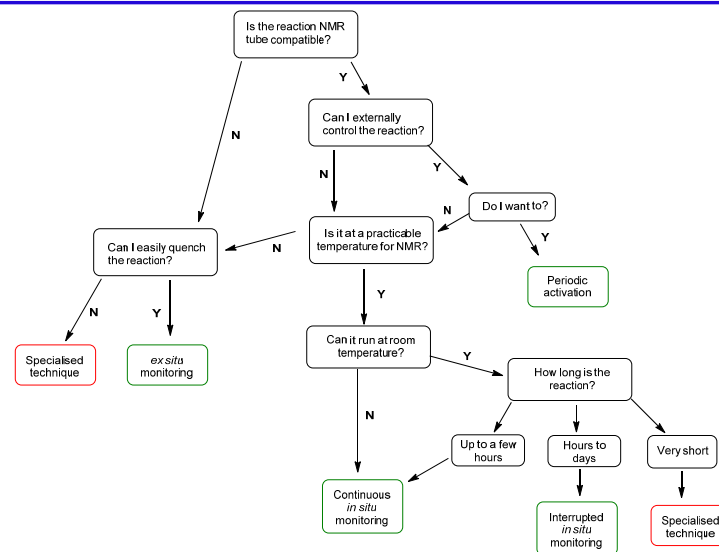


**Topspin commands:**

lock  
atma or atmm  
topshim  
rga  
zg  
multi\_zgvd

- Not labour intensive
- Uses entire instrument time
- Much faster reactions

## Sampling Methods

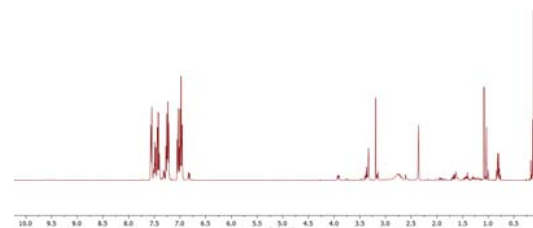


## Considerations – Nucleus

Nucleus	Abundance (%) / Sensitivity (% $^1\text{H}$ )	NMR experiment time	Level of structural information	Likelihood of presence in target system	Solvent
$^1\text{H}$	99.99 / 100	Fast	High	High	Deuterated
$^{19}\text{F}$	100 / 83	Fast	Medium	Medium	Non-deuterated
$^{31}\text{P}$	100 / 7	Slow	Medium	Medium	Non-deuterated
$^{29}\text{Si}$	4.68 / 0.03	Slow	Medium	Medium	Non-deuterated
$^{13}\text{C}$	1.07 / 0.017	Slow	Medium	High	Non-deuterated

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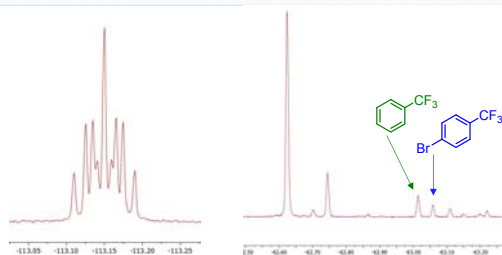


## Considerations – Nucleus



Nucleus	Abundance (%) / Sensitivity (% <sup>1</sup> H)	NMR experiment time	Level of structural information	Likelihood of presence in target system	Solvent
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- Coupling
- Highly sensitive to chemical environment
- Assignment by independent isolation



## Considerations – Nucleus



Nucleus	Abundance (%) / Sensitivity (% <sup>1</sup> H)	NMR experiment time	Level of structural information	Likelihood of presence in target system	Solvent
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<sup>13</sup> C	1.07 / 0.017	Slow	Medium	High	Non-deuterated

Sometimes very useful!

- Quenched reactions
- Slow reactions
- Equilibria

## Considerations – Solvent



### Deuterated solvent

- <sup>1</sup>H
- Expensive!

### Non-deuterated solvent

- Much cheaper!
- Non <sup>1</sup>H nuclei
- <sup>1</sup>H with solvent suppression - longer pulse sequence takes time

CDCl3	chloroform-d	Ne19F.zg30	1D Fluorine (128 scans) 7 m
DMSO capillary	For D6-DMSO in capillary		
Dioxane	dioxane-d8		
EtOH	ethanol-d6		
H2O	Water, non-deuterated		
H2O+D2O	90%H2O and 10%D2O		
H2O+D2O_salt	90%H2O and 10%D2O with salt		
DMSO	90%DMSO and 10%DMSO-d6		
Juice	fruit juice		
MeOD	methanol-d4		
None	no solvent		
Plasma	blood plasma		
Pyr	pyridine-d5		
TFAI	trifluoroacetic acid		
TFE	trifluoroethanol-d3		
THF	tetrahydrofuran-d8		

None	no solvent	Ne19F	1H (8 scans) 4min day
IMBIC	long range correlation 32min night		
ISQCROCKY	proton carbon ISQC-TOCSY 30 min night		
eMOSY_PURGE.noav.rd	MOSY 1H-1H correlation through space with purge 50 min night NO SW optimisation		
eMBC.noav.rd	long range proton carbon correlation NO SW optimisation		
IMANDQUATE	13C-13C correlation 6 hours night		
eCOSY.noSM	proton proton correlation 20 min day no SW optimisation		
eMISQ.ed.noSM	proton carbon correlation with DEPT editing NO SW optimisation		
eMISQ.noSM	proton carbon correlation NO SW optimisation		
eDpreat	Double preat for THF (16) day		
eDpreat.para	Double preat para THF (16) day		
eDpreat	Single preat for Dioxane, H2O, (16) day		
eDpreat.para	Single preat para for Dioxane, H2O, (16) day		
eDpreat	Triple preat for Pyridine, (16) day		
eDpreat.para	Triple preat para for Pyridine (16) day		
eDpreat.noavpyrid	1H spectrum with noav-preparation for H2O/D2O samples		
e1H.noSVT	1D Proton (16 scans) day 15-20 min for One Variable Temperature (OneVT) experiment non spin		
e1H.noSVT.no	1D Proton (16 scans) day 15-20 min for One Variable Temperature (OneVT) experiment non spin		
e13C.NoSVT	1D Carbon (256 scans) 2D-3D min day for One Variable Temperature (OneVT) experiment		
e13C.NoSVT.no	1D Carbon (256 scans) 2D-3D min day for One Variable Temperature (OneVT) experiment non spin		

## Considerations - Internal Standards

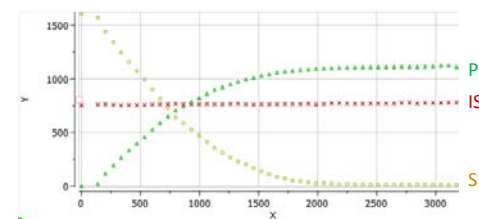


### Why?

- Reference chemical shift
- Integral normalisation

### Good internal standard

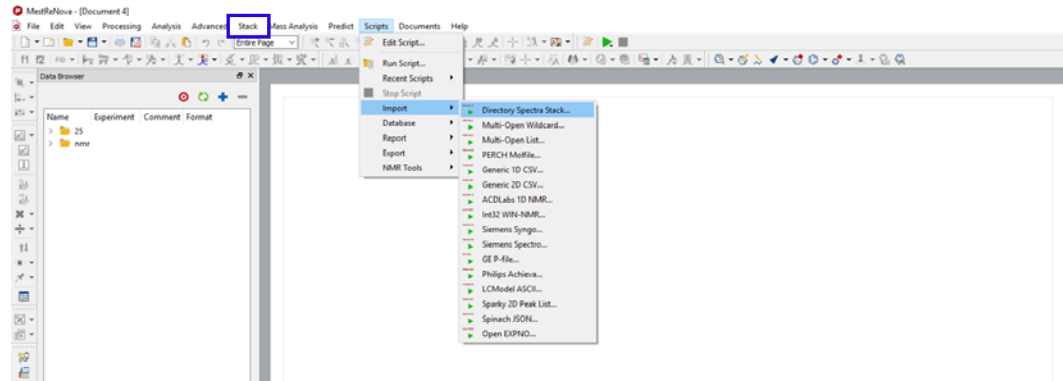
- Concentration stays fixed over reaction
  - (relatively) nonvolatile
  - innocent
- No signal overlap
- Similar  $T_r$  to reagents



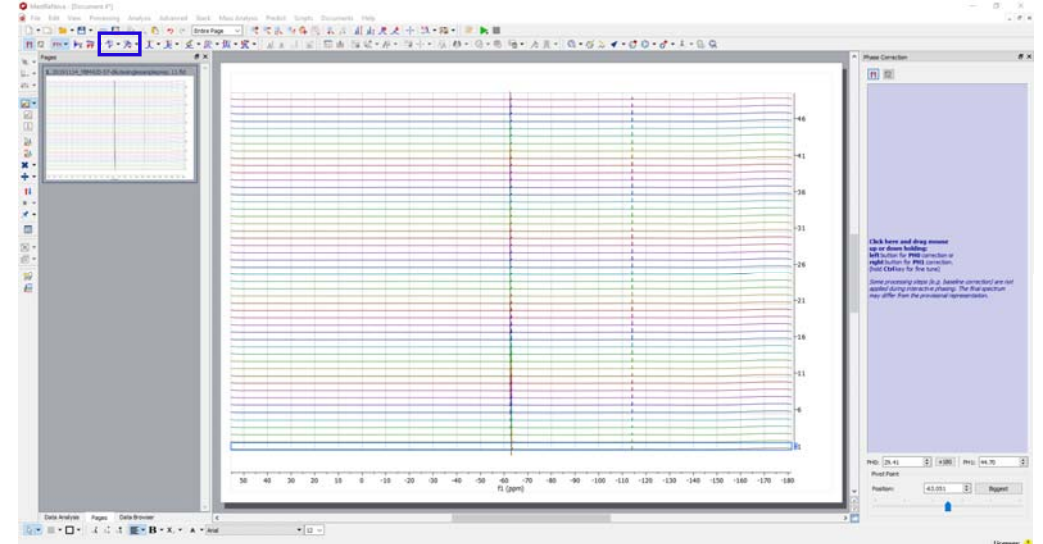
$$[A] = \frac{s(A)}{s(IS)} \times \frac{n(IS)}{n(A)} \times [IS]$$



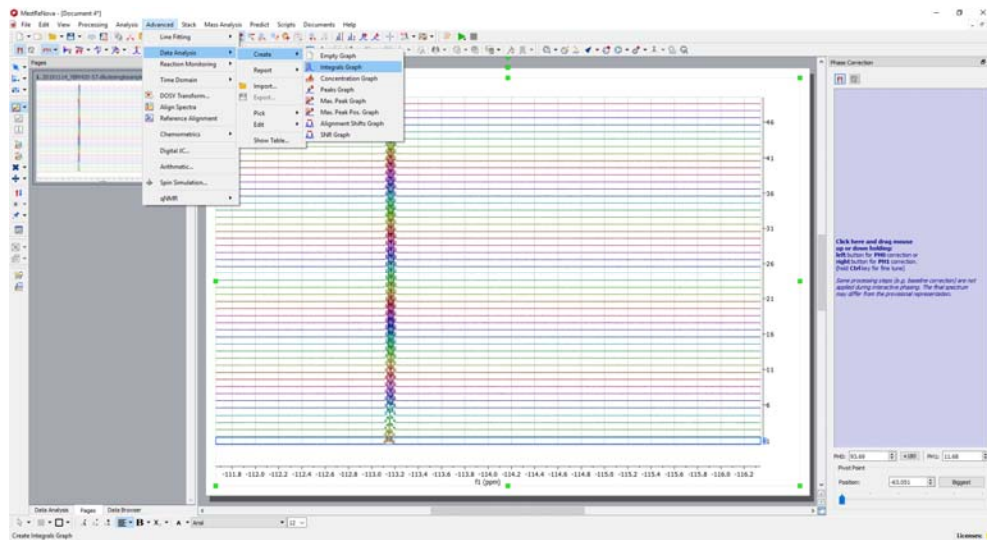
## Data Processing - Mestrenova



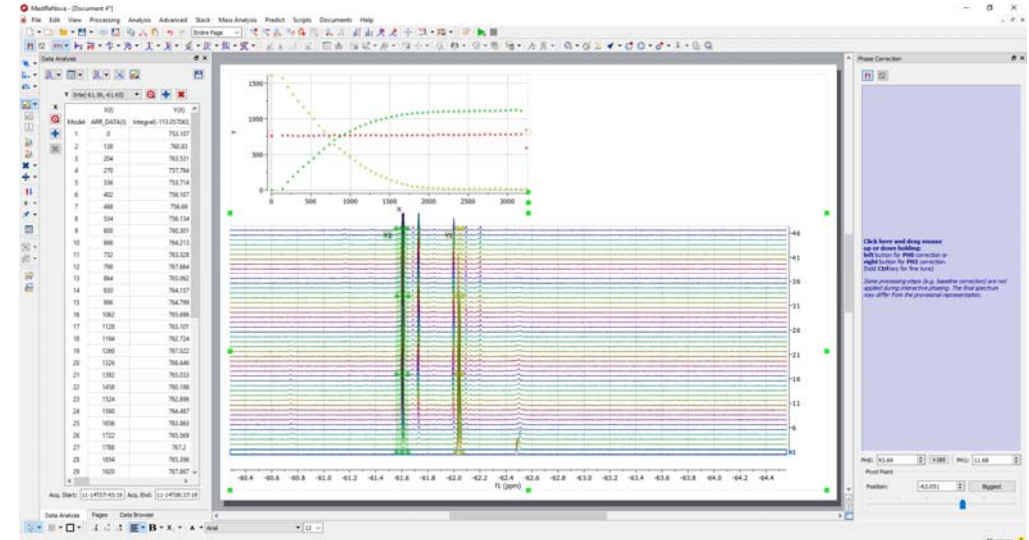
## Data Processing - Mestrenova



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## Data Processing - Mestrenova

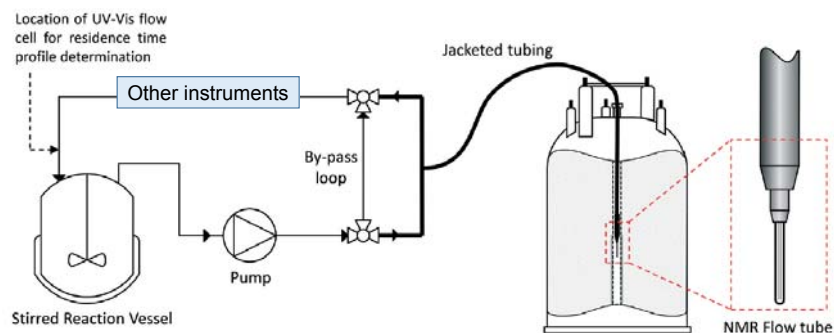




## Specialised Techniques – Flow NMR



### On-line monitoring

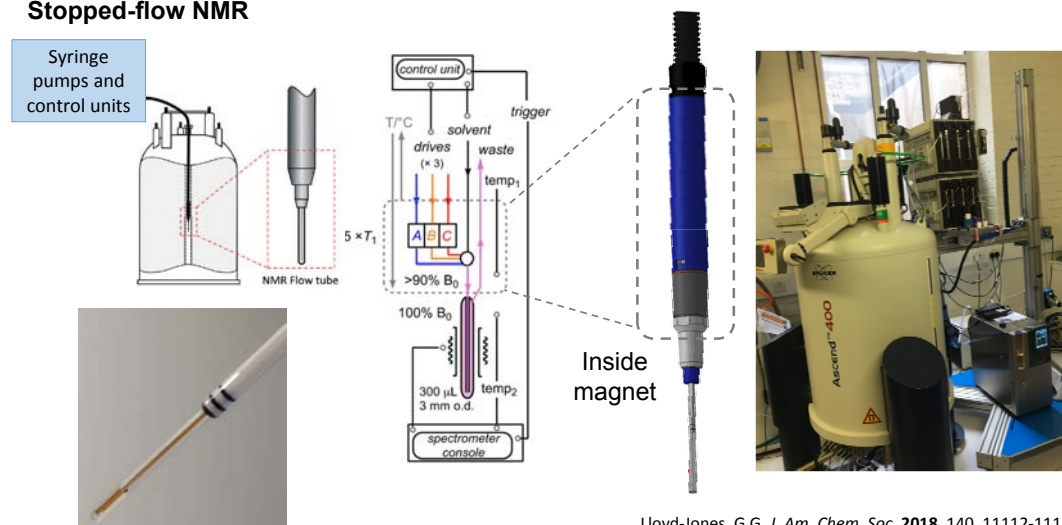


Hintermair, U. *Catal. Sci. Technol.* **2016**, *6*, 8406-8417.

## Specialised Techniques – Stopped-Flow NMR

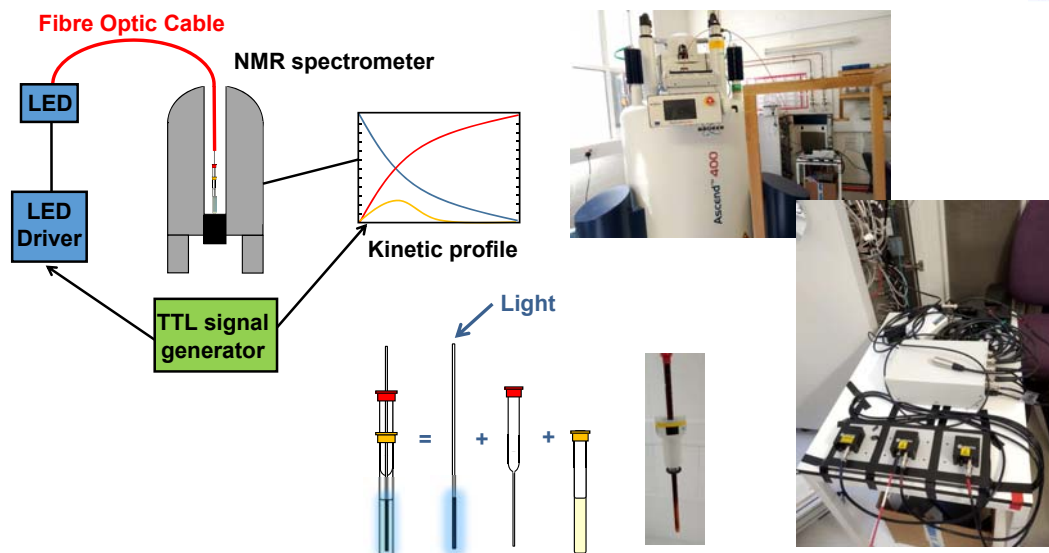


### Stopped-flow NMR




Lloyd-Jones, G.G. *J. Am. Chem. Soc.* **2018**, *140*, 11112-11124.

## Specialist Techniques – *in situ* Illumination

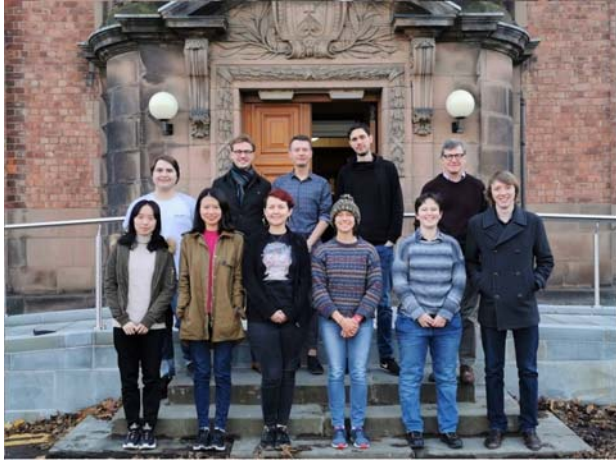


## Key Messages



- Lots of different ways to monitor kinetics by NMR
    - Sampling methods
    - Signal to monitor
  - Lots of different factors to consider
  - Often don't need specialised equipment
- 
- ... remember that other techniques exist too

## Acknowledgements



**Prof. Guy Lloyd-Jones FRS**

***Past members:***

**Eduardo Nieto Sepulveda**

***Current members:***

**Katie Grant**

**Andres Garcia Dominguez**

**Patrick Boaler**

**Hannah Hayes**

**Harvey Dale**

**Maciej Kucharski**

**Ran Wei**

**Yuan Gao**

**Pedro Helou**