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5th PANIC
Hilton Head Island, USA

Low Field NMR Spectroscopy for Sustainable and Flexible Production of High Quality Chemical Products

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CONSENS: Smart Online NMR Sensor for Advanced Process Control

Flexible Intensified Continuous Plant

Characteristics

Miniaturized equipment

Intensified heat & mass transfer

Possibly modular setup



Benefits

Product uniformity

Sustainability

Fast adaption to market demand

Innovative products

Containerized modular plant Source: INVITE GmbH



Reaction Monitoring on Lab Scale at BAM

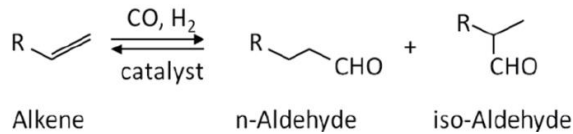
Process Analytical Technology for Intensified Processes



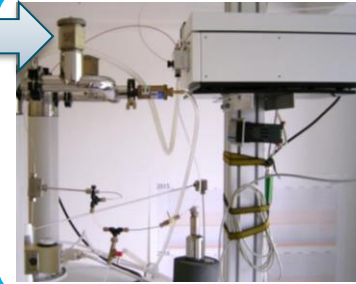
Examples from BAM



Catalysis:
Hydroformylations of C12-alkenes
in micro emulsions

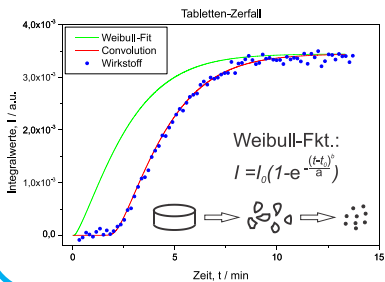


P3

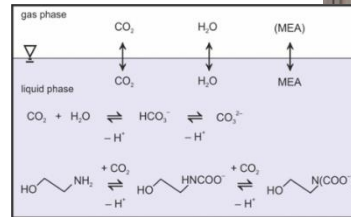


qNMR (Metrology):
Gases and
condensed phases
up to 1000 bar

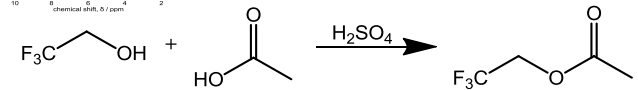
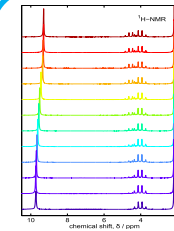
Pharmaceuticals:
Liberation kinetics



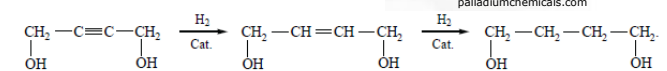
CO₂ scrubbing



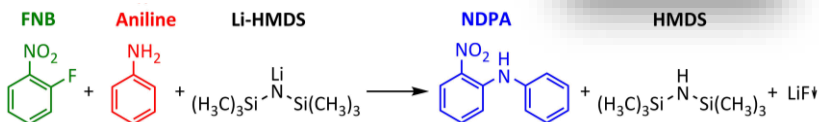
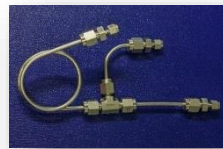
Method development:
Esterifications
(model reactions)



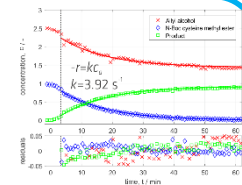
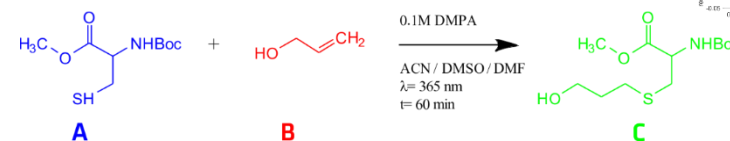
Catalysis:
Hydrogenations



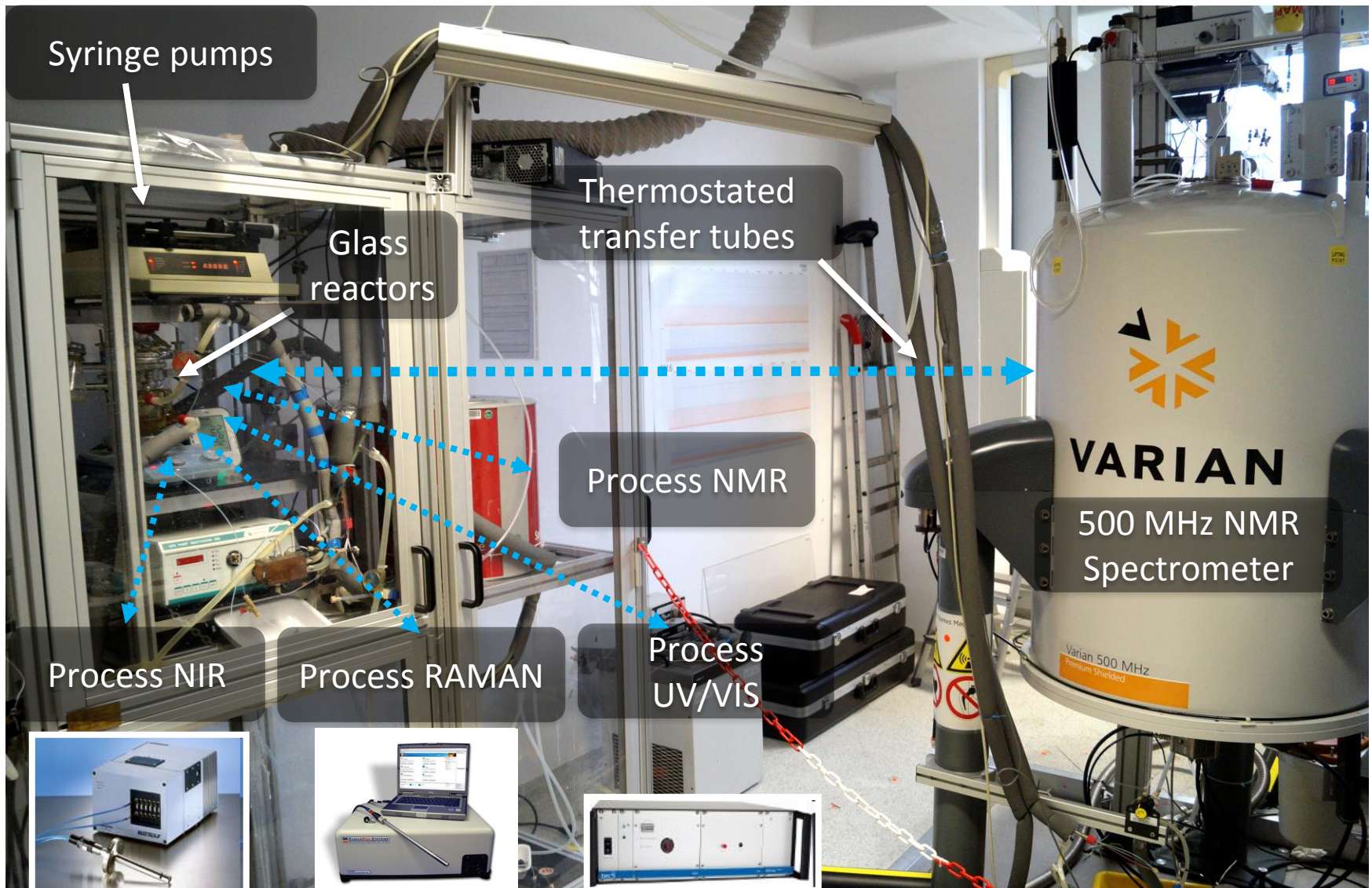
Reaction Engineering:
Lithiation reactions



Reaction Engineering:
Photo reactions („click chemistry“)



Reaction Monitoring in Lab-scale at BAM



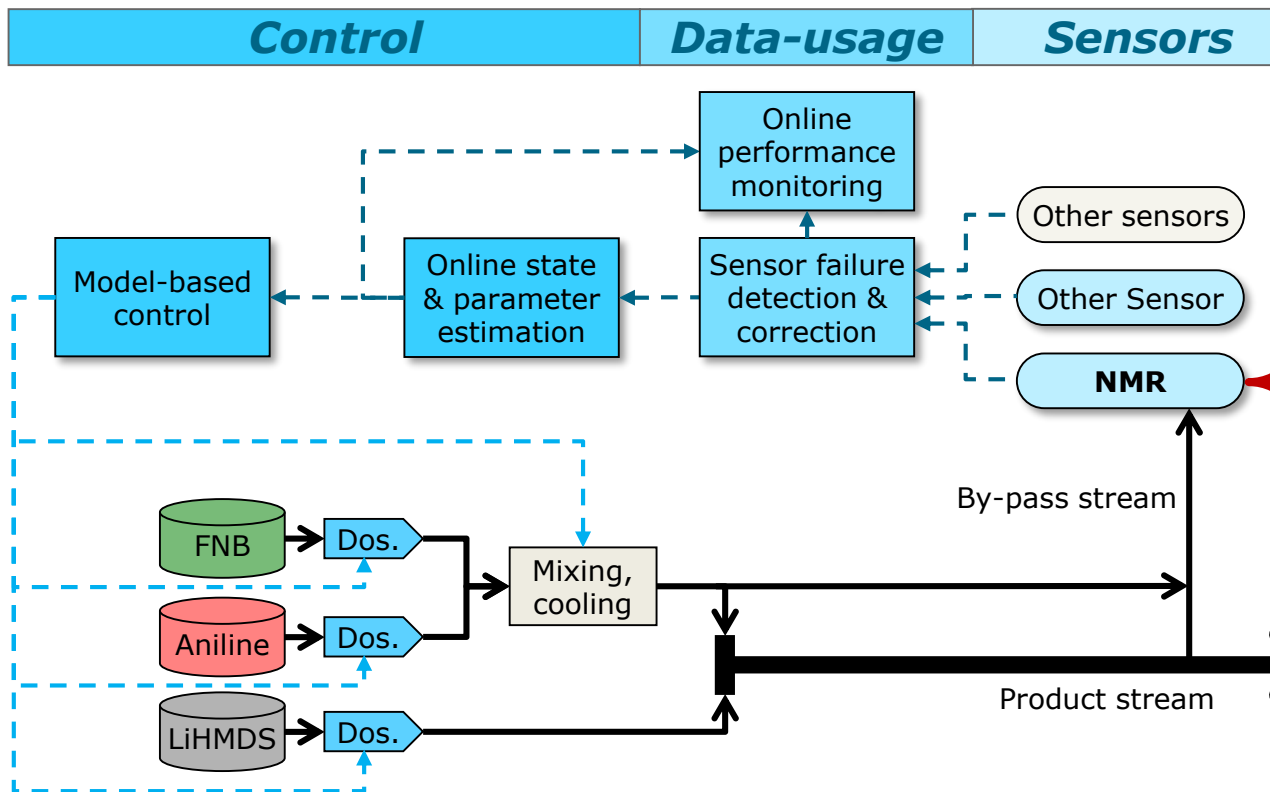
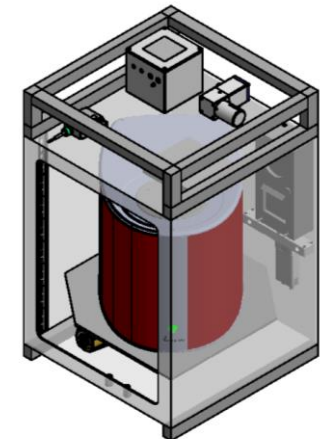
CONSENS: Case Study 1

Intensified Synthesis of Organic Compounds

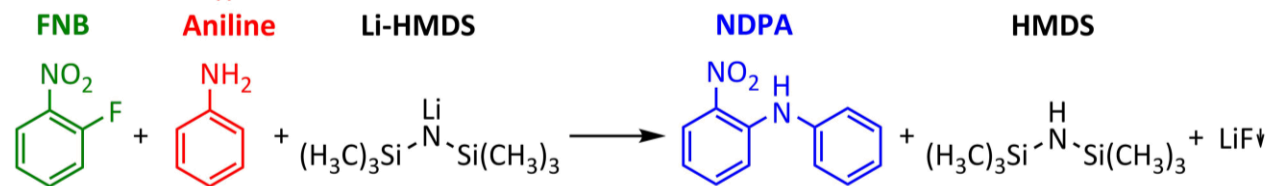


Source: INVITE GmbH

Explosion proof housing



Reaction Scheme:



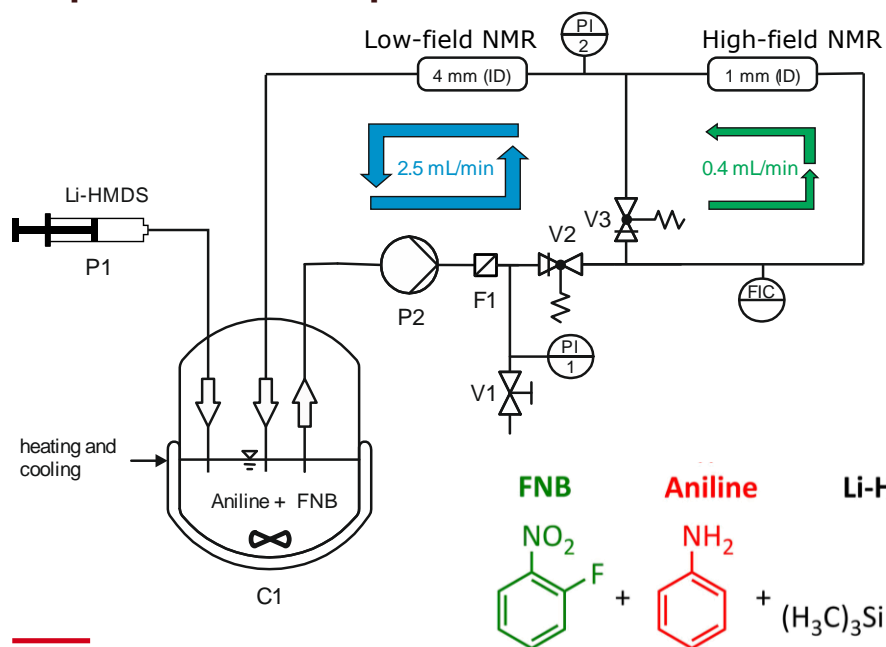
Reaction Characterization in Lab

Lab Experiments in Batch along Reaction Co-ordinate

- Data in parallel acquired with high-field and low-field spectrometer
- „Fast“ and „slow loop“
- Li-HMDS was dosed stepwise

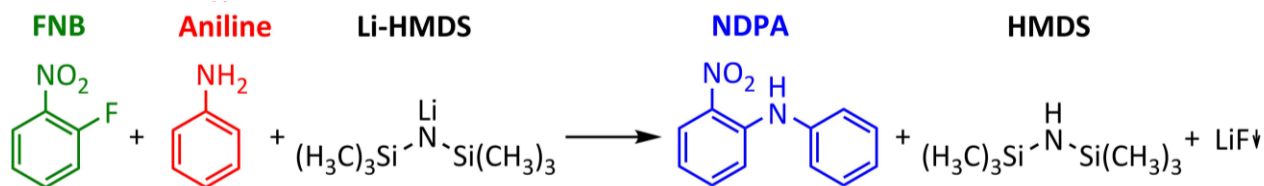


Experimental set-up

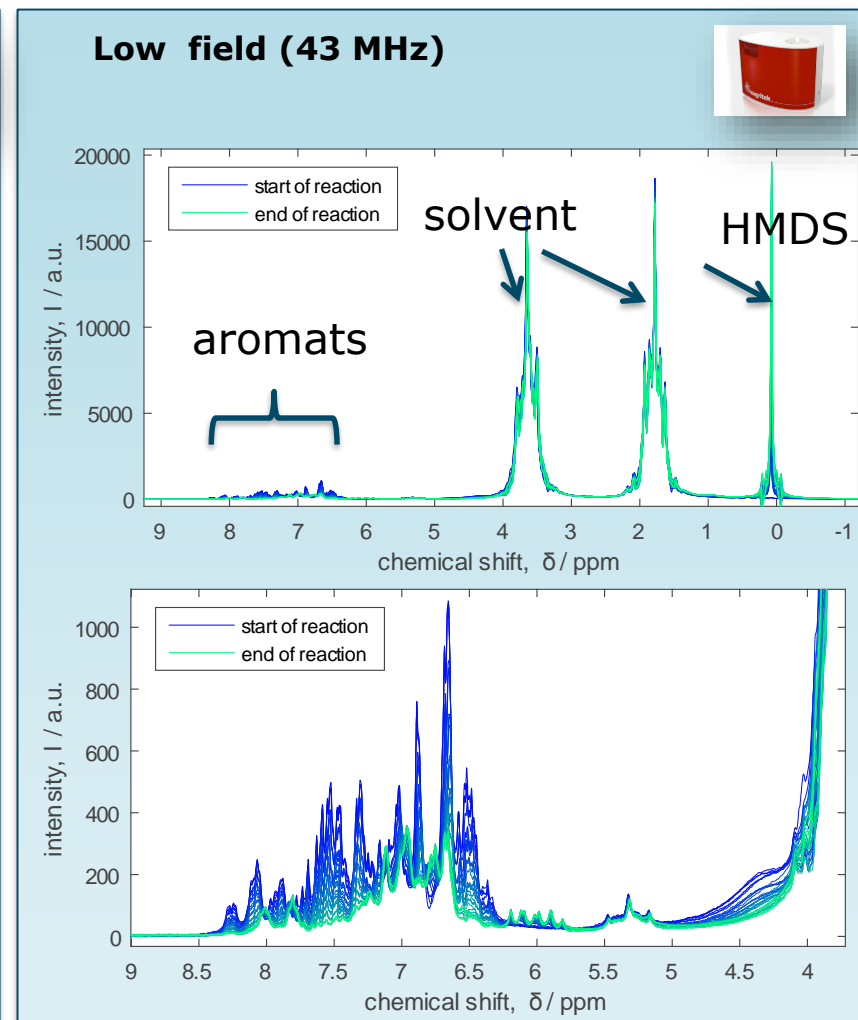
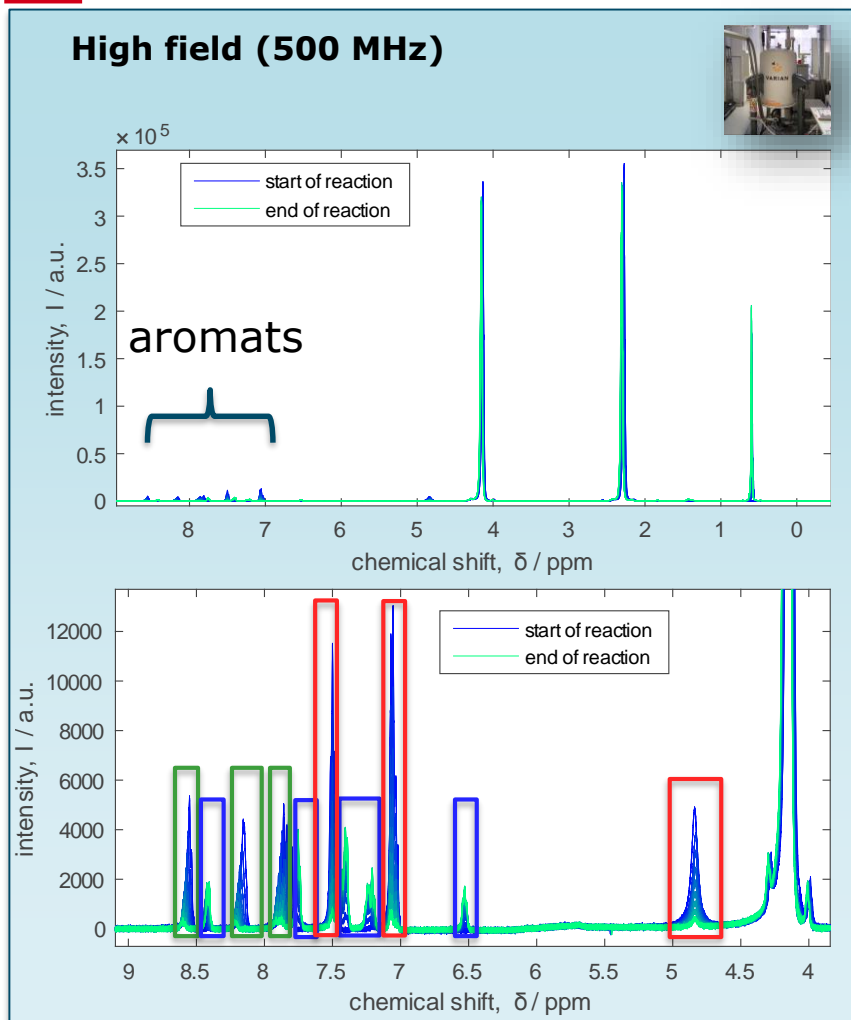


- Exothermic reaction
➔ required cooling (28.5 °C)
- Li-HMDS in two-fold excess

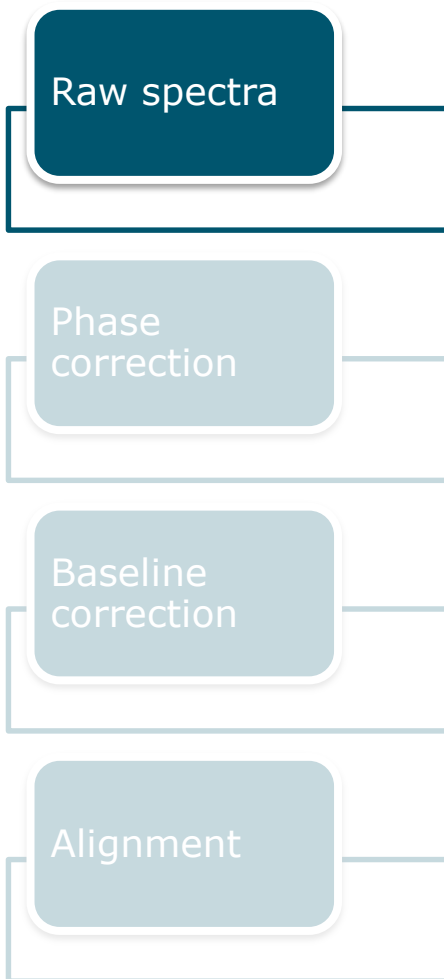
Reaction Scheme:



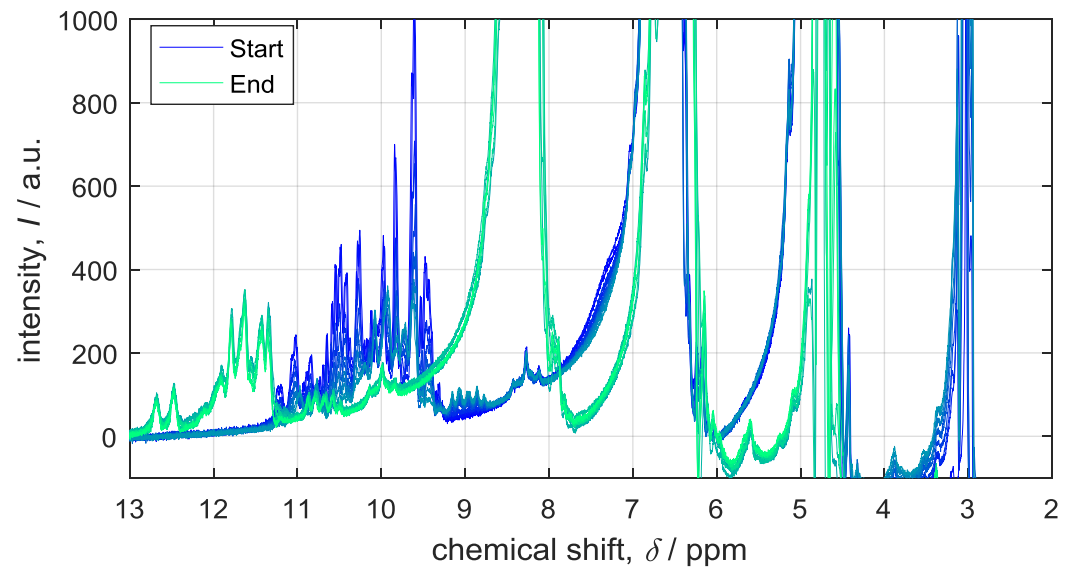
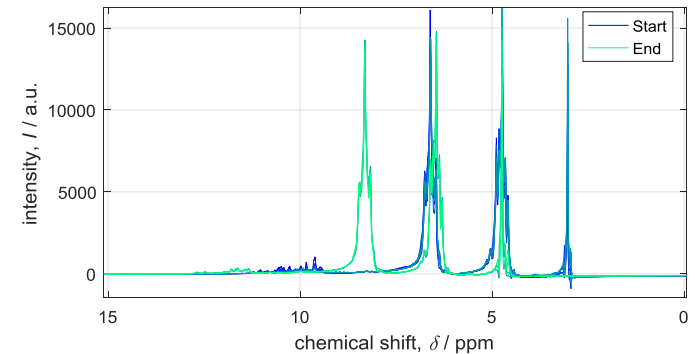
Online ^1H NMR Spectra of Lithiation Reaction Step



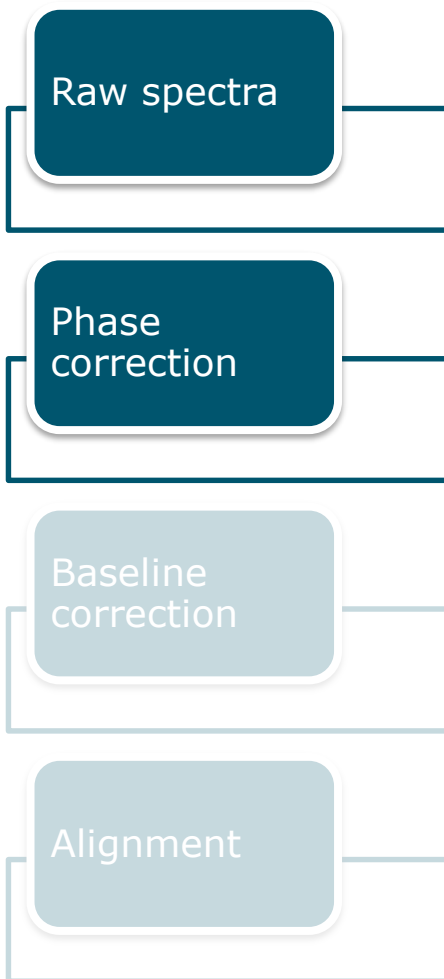
Data Processing for Low-field NMR in Matlab



**single scan
each 15s
in flow**

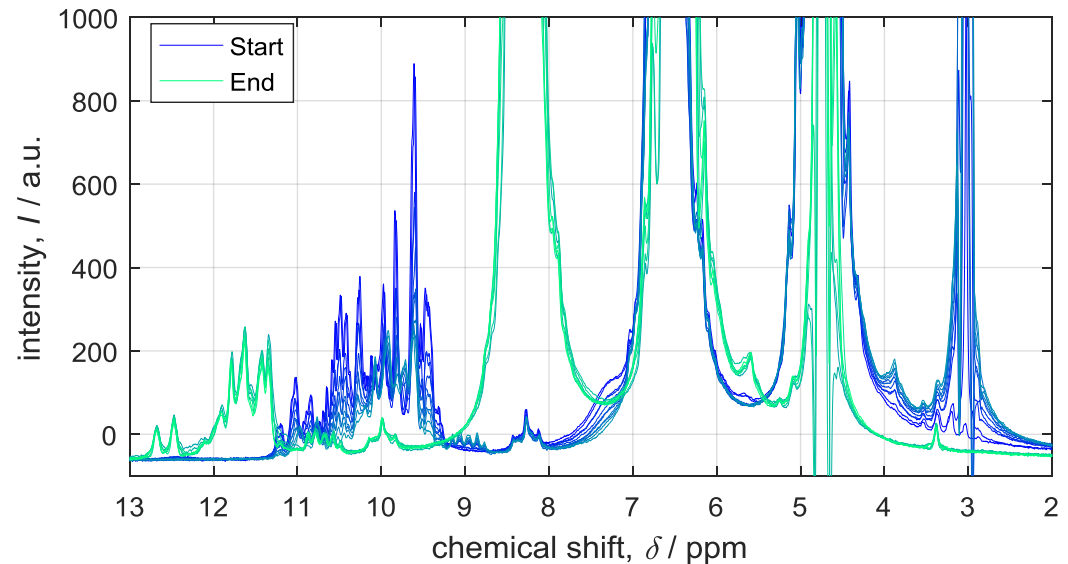
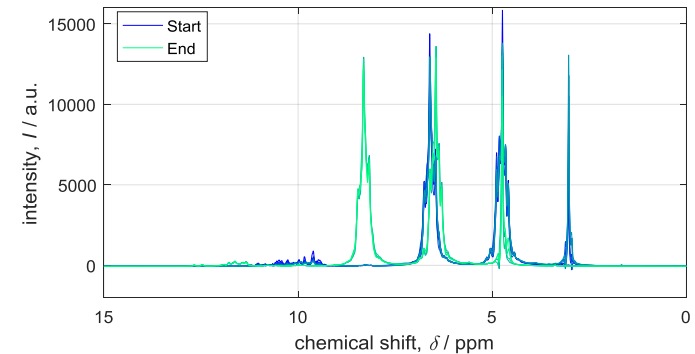


Data Processing for Low-field NMR in Matlab

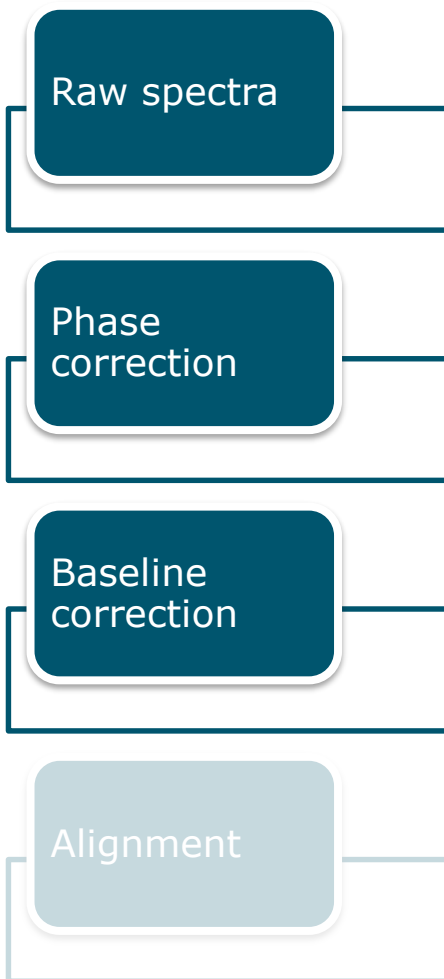


Entropy minimization method:

Chen et al., *J Magn Reson.*
2002, *158*, 164-168

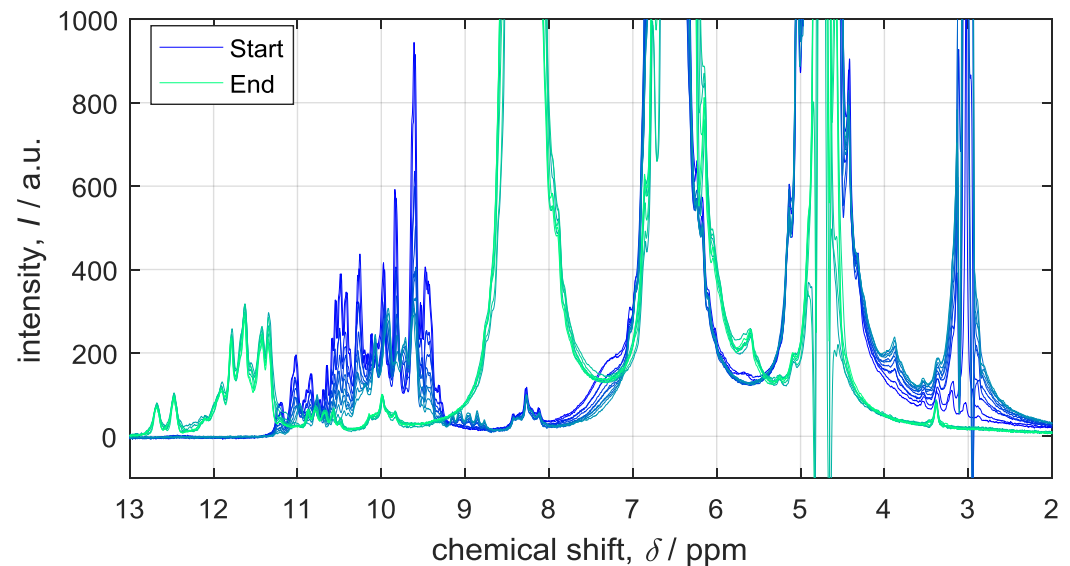
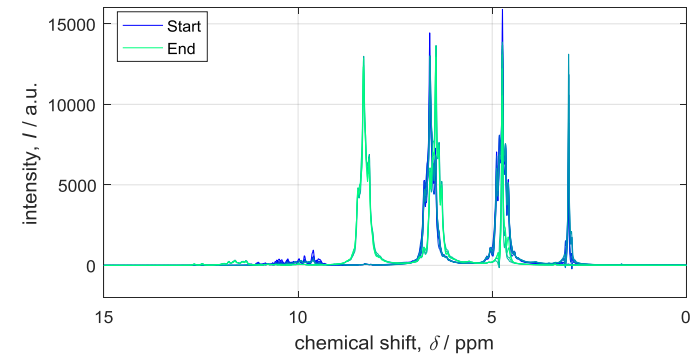


Data Processing for Low-field NMR in Matlab

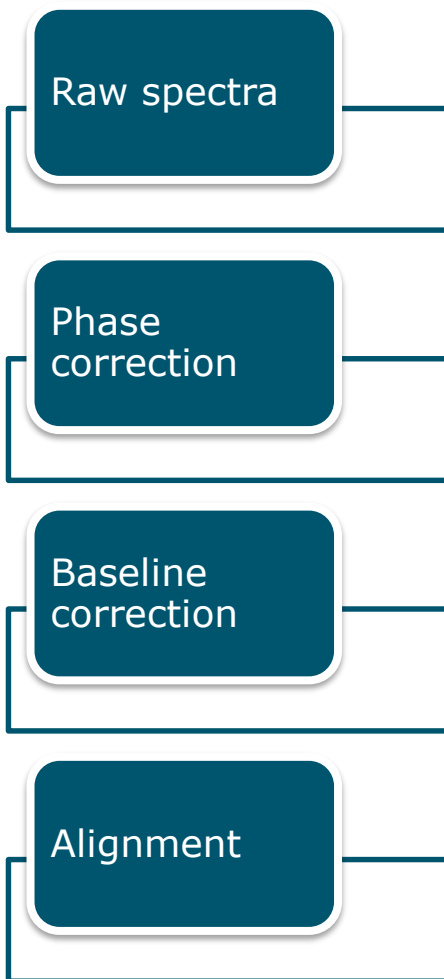


Low-order Polynomial fit:

Mazet et al., Chemometrics
Intell. Lab. Sys. **2005**, 76,
121-133.

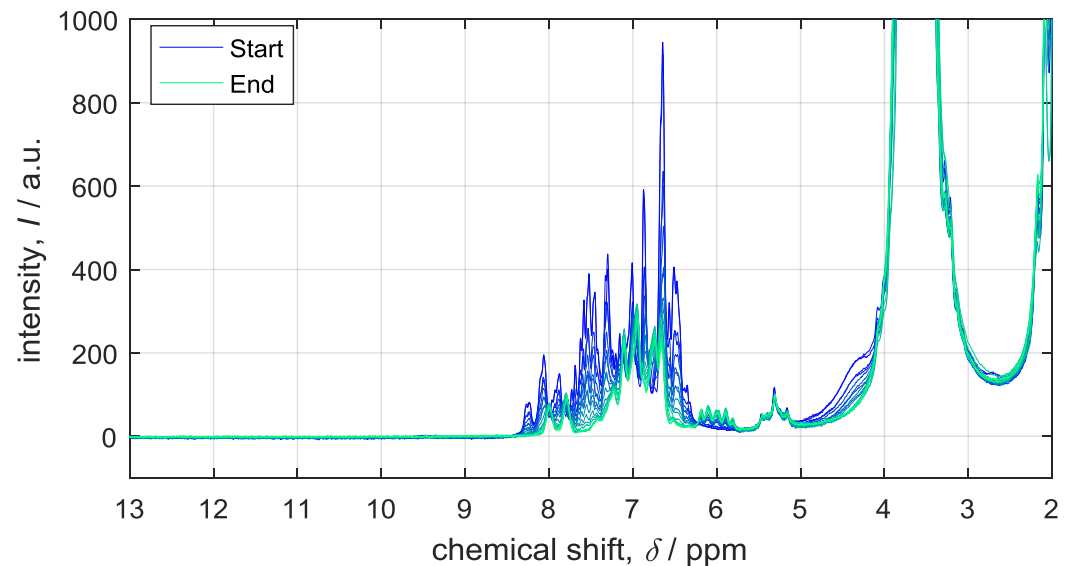
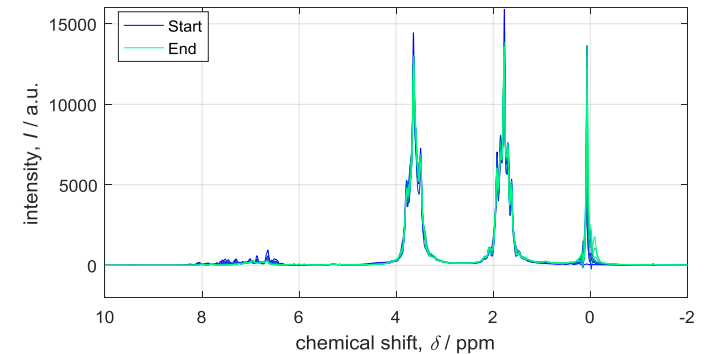


Data Processing for Low-field NMR in Matlab



Alignment to reference signal (THF) using *icoshift*:

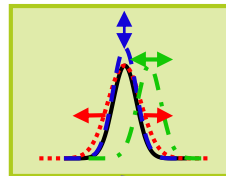
Savorani et al., J Magn Reson. **2010**, 2, 190-202



Modeling → peak fitting of pure component spectra → mixture model

Analysis → "component fitting" → calculation of component area

- » Group of peaks represent pure component spectra

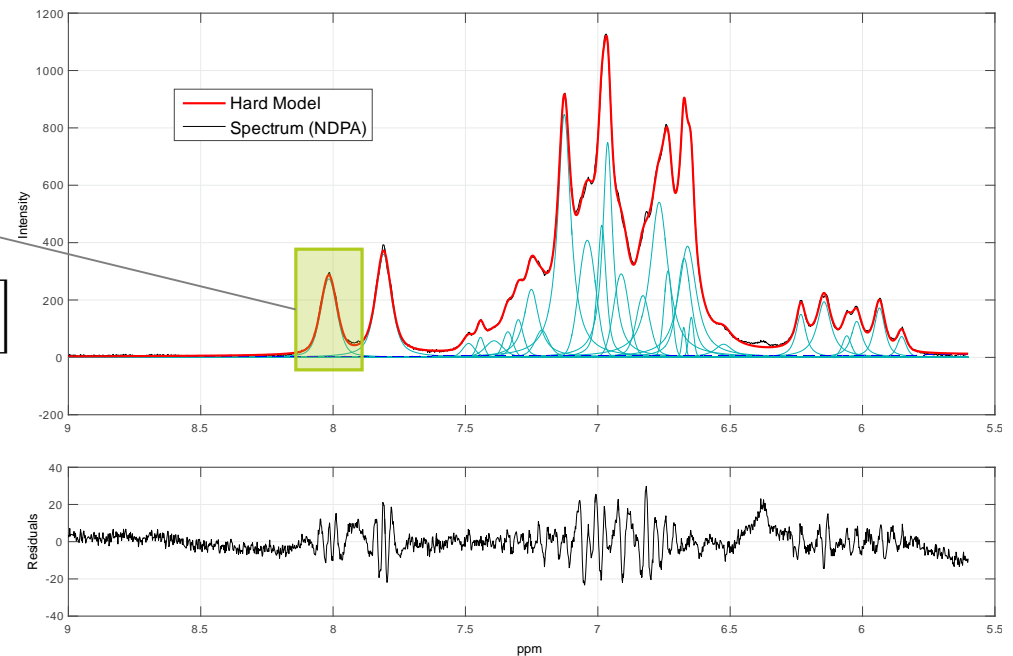


- » Pseudo-Voigt function

$$V = \alpha \left[\beta \cdot \exp\left(-\ln(2) \frac{(x - \delta)^2}{\gamma^2}\right) + (1 - \beta) \frac{\gamma^2}{(x - \delta)^2 - \gamma^2} \right]$$

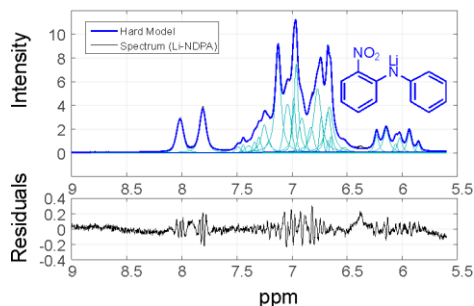
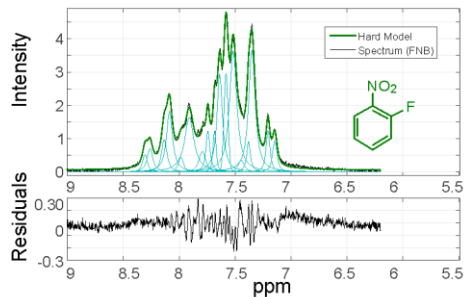
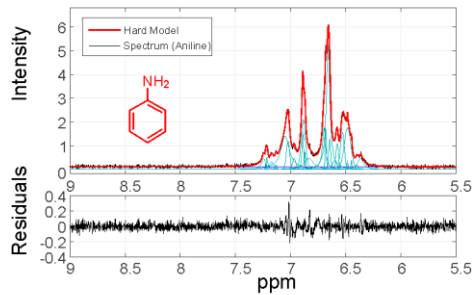
α = peak maximum
 β = Gaussian-Lorentzian-ratio
 γ = half width
 δ = center position

Hard model for pure components



IHM – „component fitting“

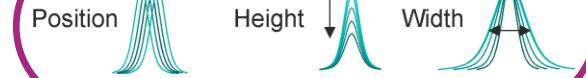
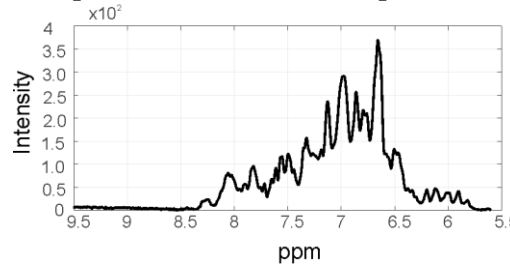
Pure component models



Mixture model

Component fitting

Experimental Spectrum



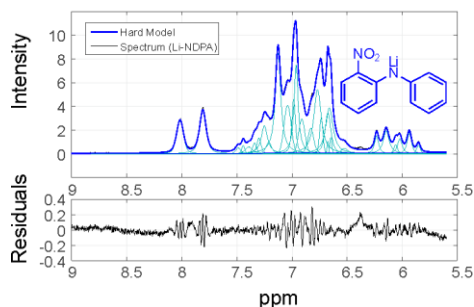
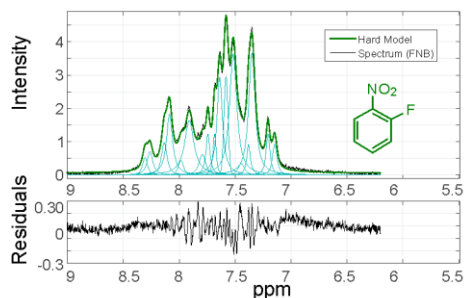
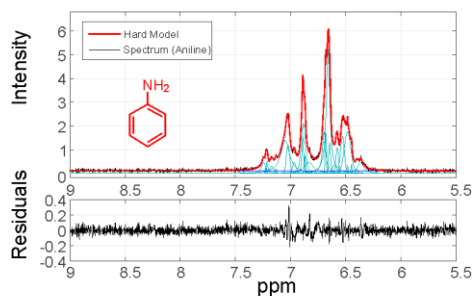
Modeling → Mixture model

No. components	3
Peaks per component	22, 21, 28
Degree of freedom (total free parameters)	292
Considered interacting peaks	25
Max. peak shift	0.01 ppm
...	...

Peak area ratio for each pure component model is kept constant!

IHM – „component fitting“

Pure component models

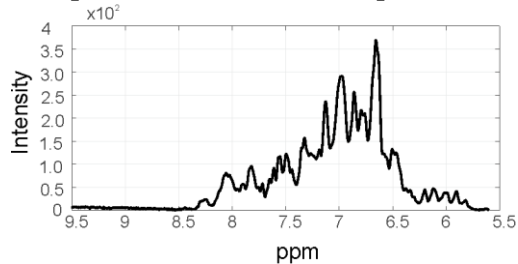


Analysis "component fitting"

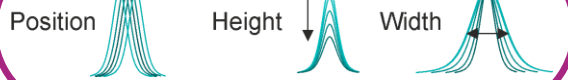
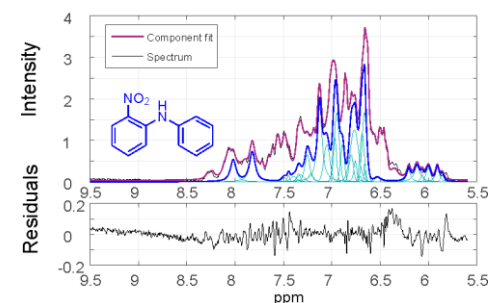
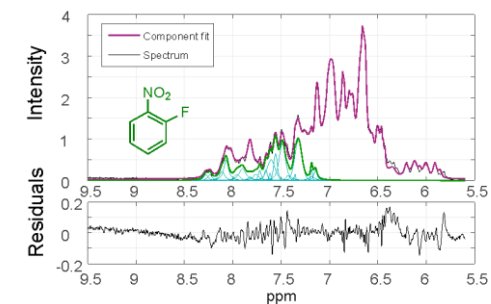
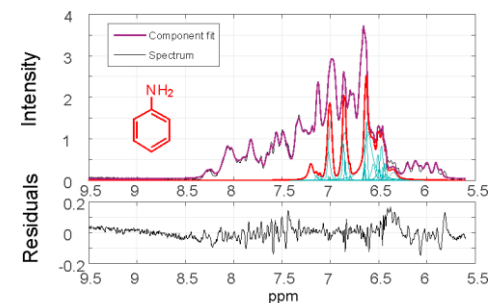
Mixture model

Component fitting

Experimental Spectrum



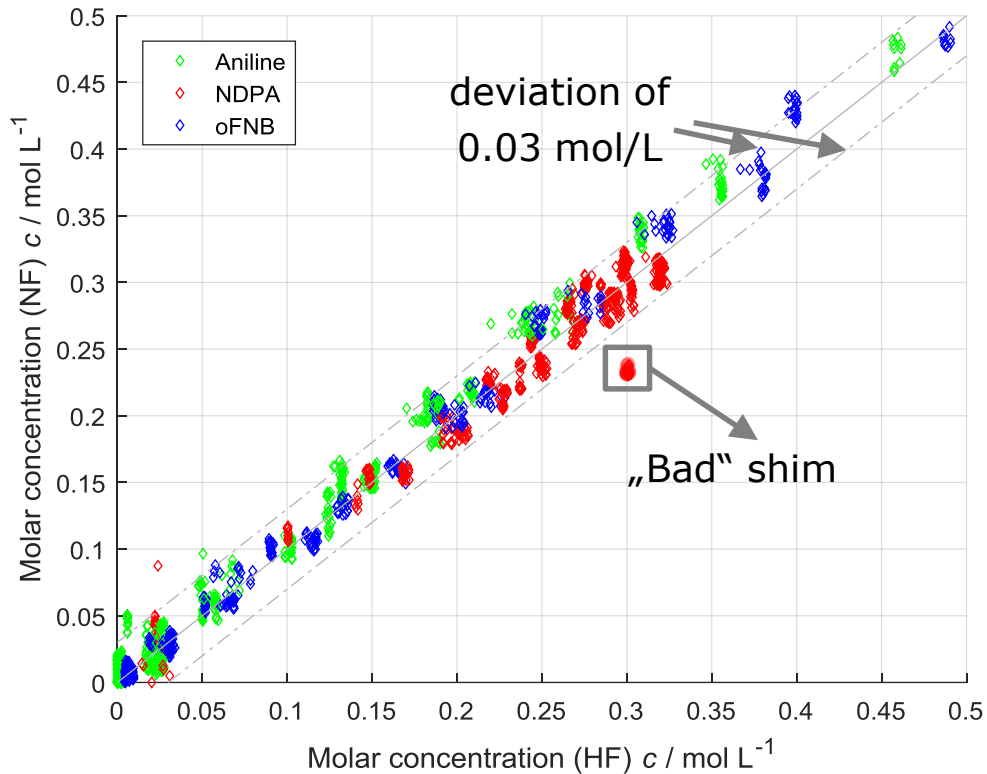
Deconvoluted spectrum



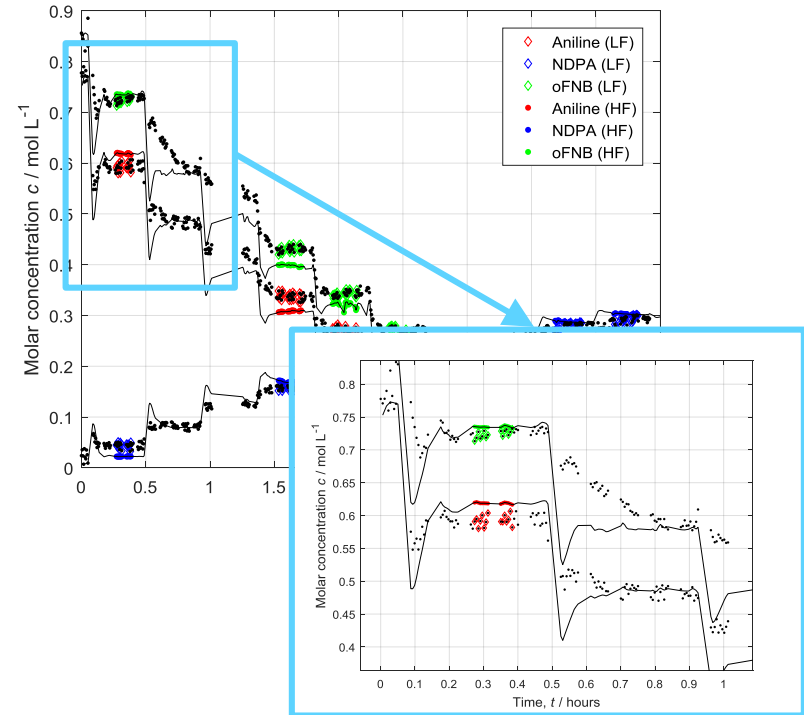
Results: Reaction Characterization

Lab Experiments in Batch along Reaction Co-ordinate

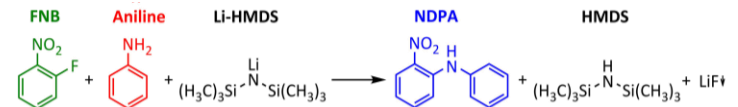
- 3 semi-batch reaction with varying starting concentrations
- 1500 Spectra for each HF- and NF-NMR



Classification of steady states

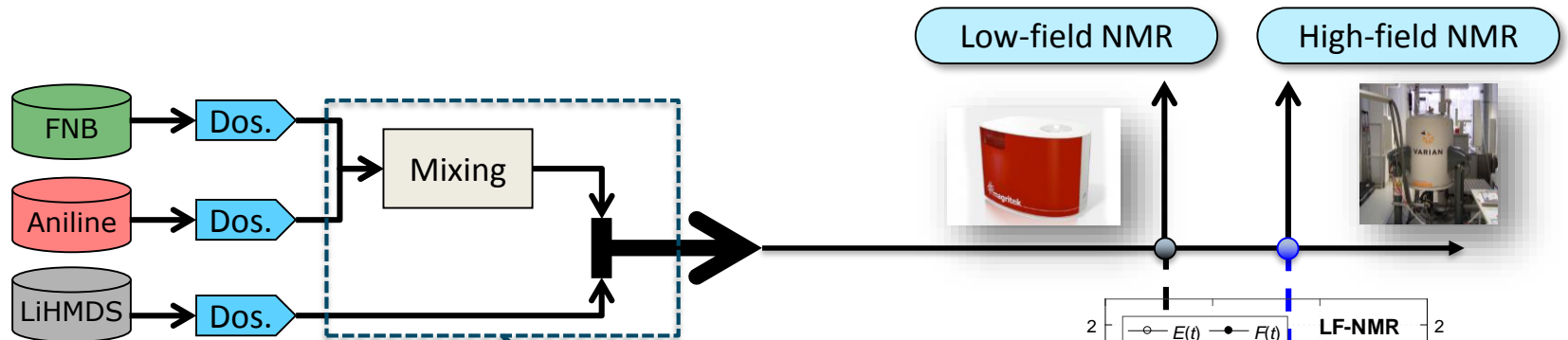


Reaction Scheme:

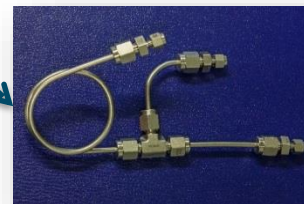


Validation of Lab Experiments in Tube Reactor

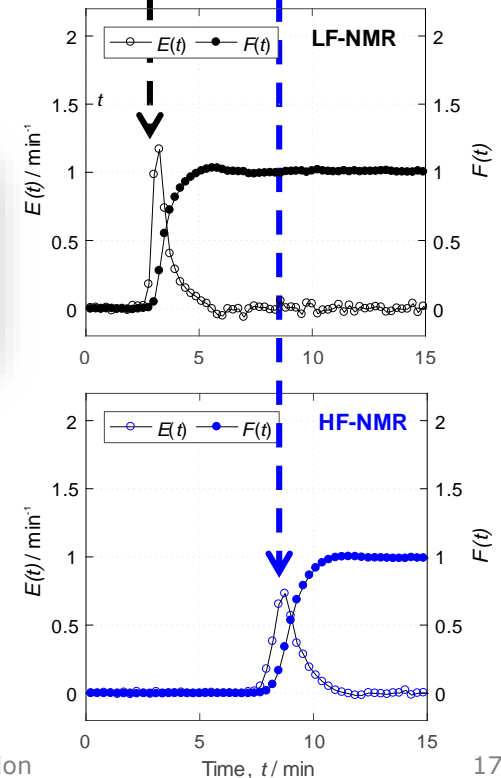
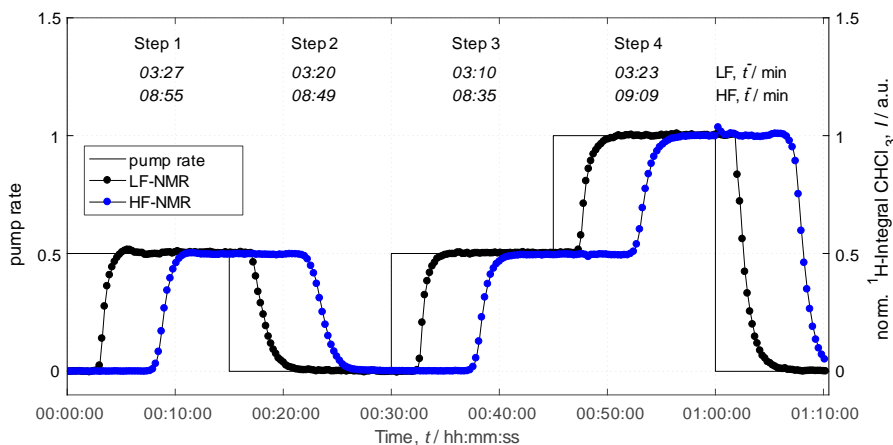
Continuous Lithiation Reaction Set-up at BAM



1/8" tube reactor



Step tracer experiments

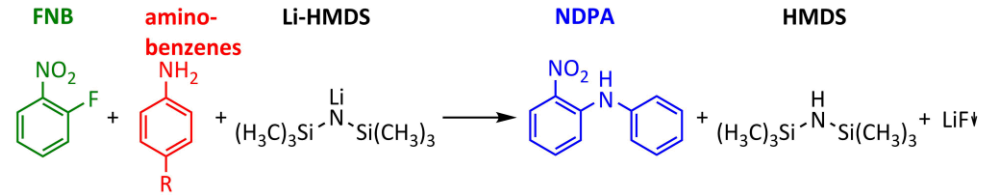


Experimental Design

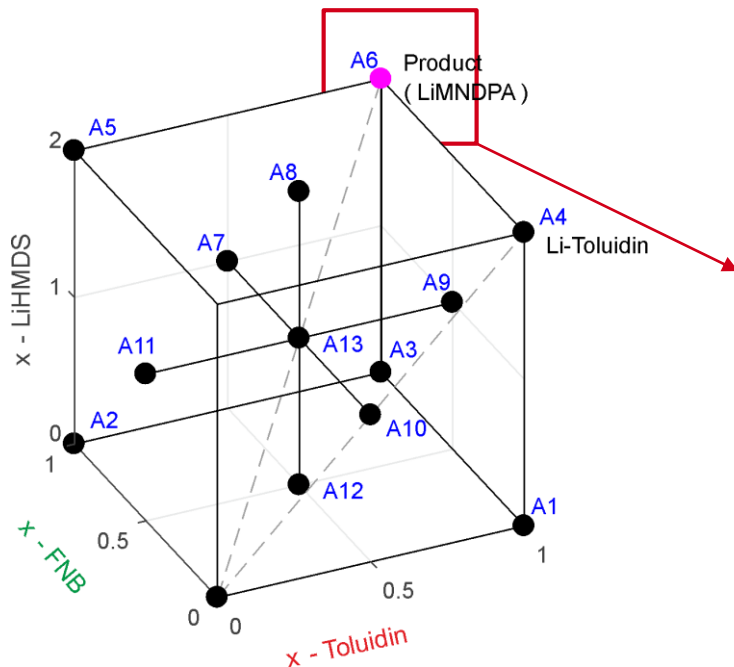
Continuous Lithiation Reaction Set-up at BAM

- Independent variation of flowrates / stoichiometric conditions

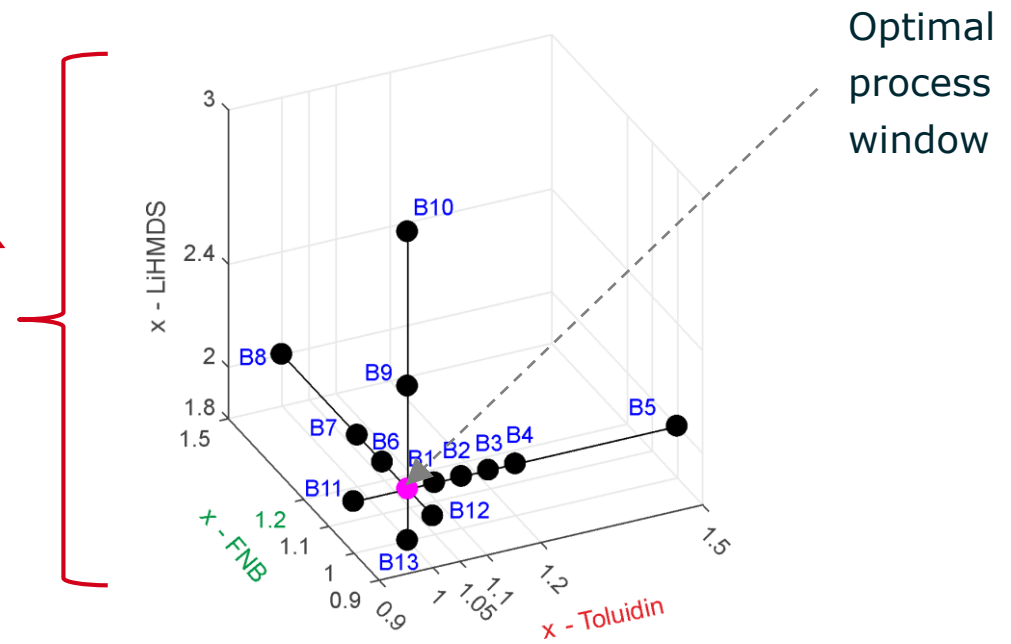
Reaction Scheme:



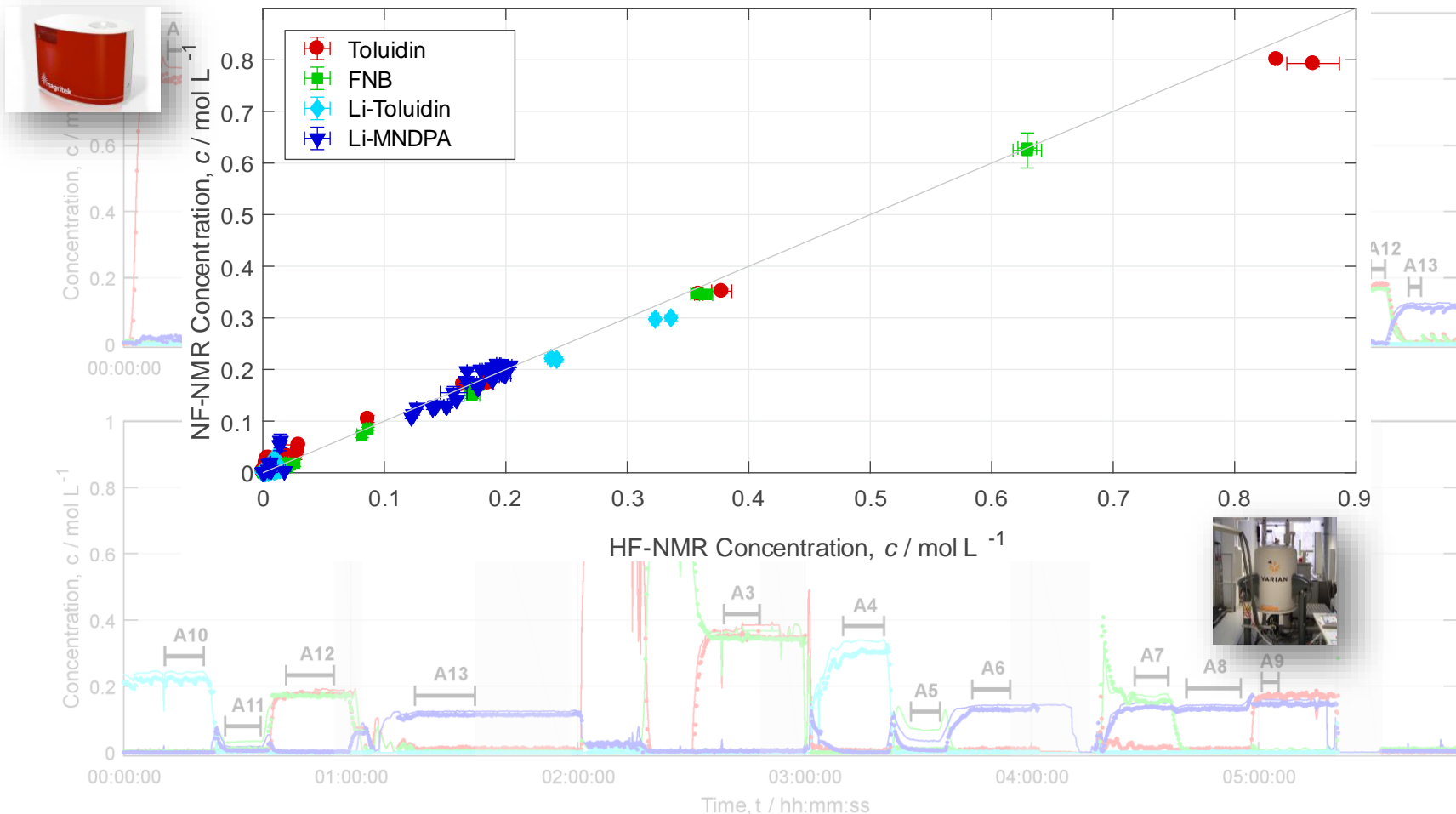
Coarse variation:



Fine variation:



Monitoring of Continuous Aromatic Substitution Reaction by Low Field NMR



Smart NMR Sensor Concept

CONSENS: Smart Online NMR Sensor for Advanced Process Control

Flexible Intensified Continuous Plant

Characteristics

Miniaturized equipment

Intensified heat & mass transfer

Possibly modular setup



Benefits

Product uniformity

Sustainability

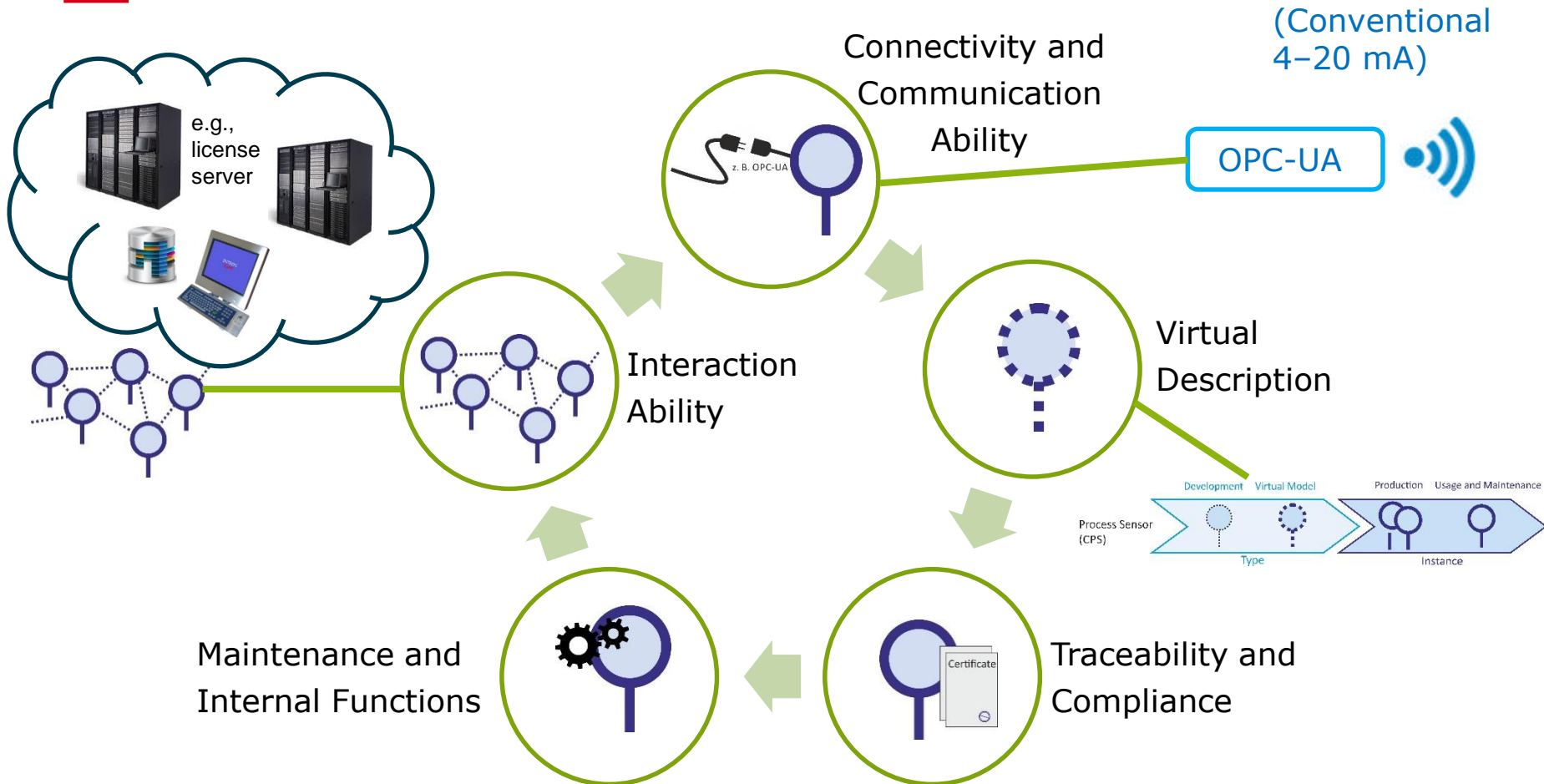
Fast adaption to market demand

Innovative products

Containerized modular plant Source: INVITE GmbH



Current and Future Requirements to Smart Process Sensors As Parts of Cyber-Physical Production Systems

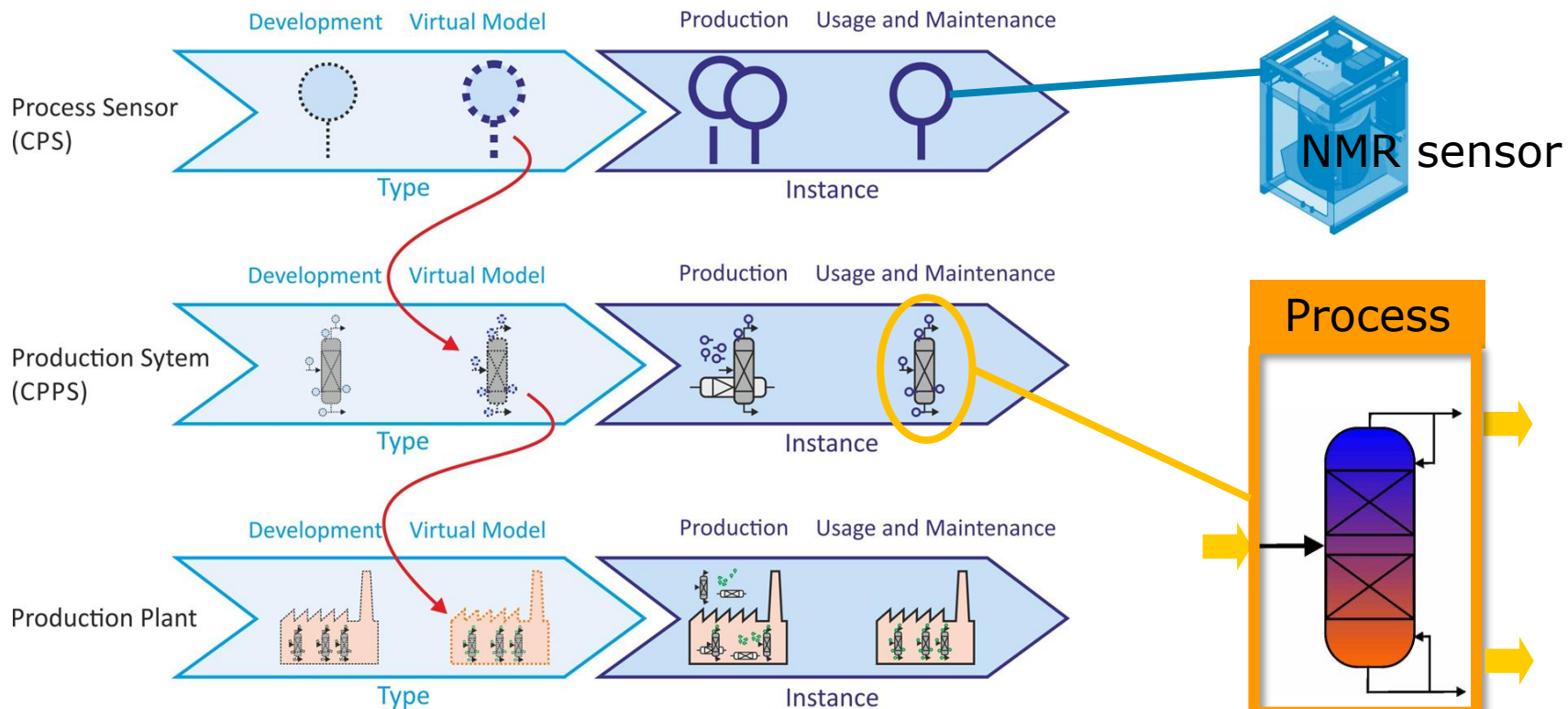


Contemporary Process Engineering

Towards Cyber-Physical Production Systems (CPPS)

“Cyber-Physical Systems (CPS) are integrations of computation with physical processes. Embedded computers and networks monitor and control the physical processes, usually with feedback loops where physical processes affect computations and vice versa”.

E. A. Lee, Cyber Physical Systems: Design Challenges, EECS Department, University of California, Berkeley, 2008



Smart NMR Sensor Concept

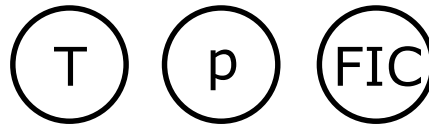
Module size:
850 x 570 x 570 mm



Safety devices

- Nitrogen purge control
- Leakage safeguard

Measuring Conditions



Data Acquisition

- Triggering
- Automated evaluation (Matlab)
- MySQL Database

Conventional
4–20 mA



**Programmable
Fieldbus
Controller**

www.wago.de



OPC-UA
Client



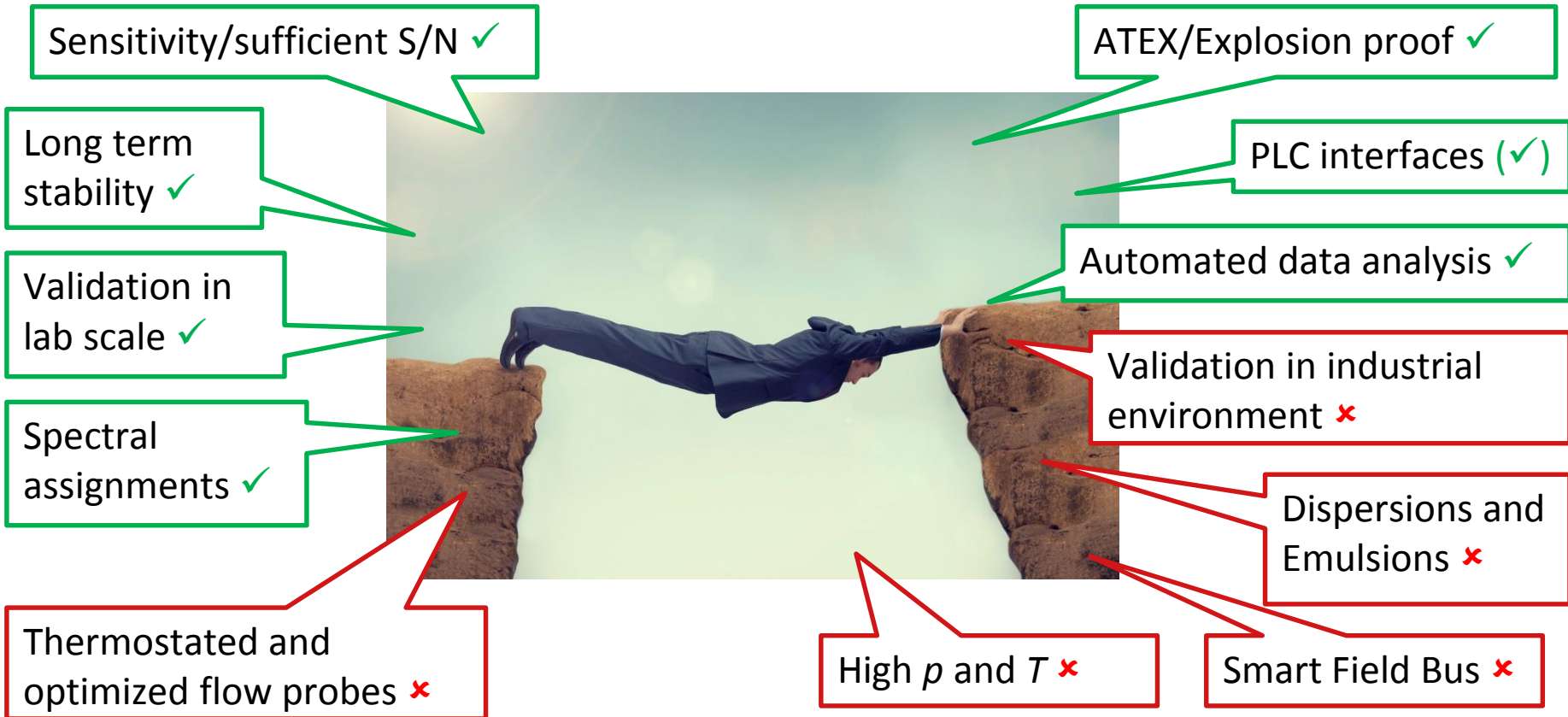
Ethernet

Closing the Gap ...

Key Attributes of Compact NMR Spectroscopy for Industrial Online Applications

Laboratory research

Chemical industry



THANK YOU!

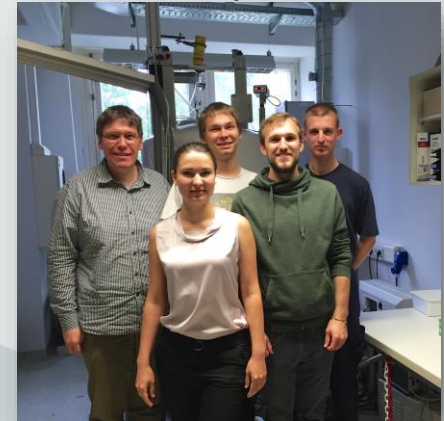
Jürgen Kolz
Ullrich Koch
Juan Perlo
Mike Bernstein

Magritek
Magritek
Magritek
MestreLab

Harald Pape
Clemens Minnich
Dirk Engel
Alfons Steil

PTB
S-Pact
S-Pact
PSG Petro Service

NMR Group at BAM




CONSENS – Integrated Control and Sensing for Sustainable Operation of Flexible Intensified Processes, funded by the European Union's Horizon 2020 research and innovation programme under grant agreement N° 636942.
www.consens-spire.eu

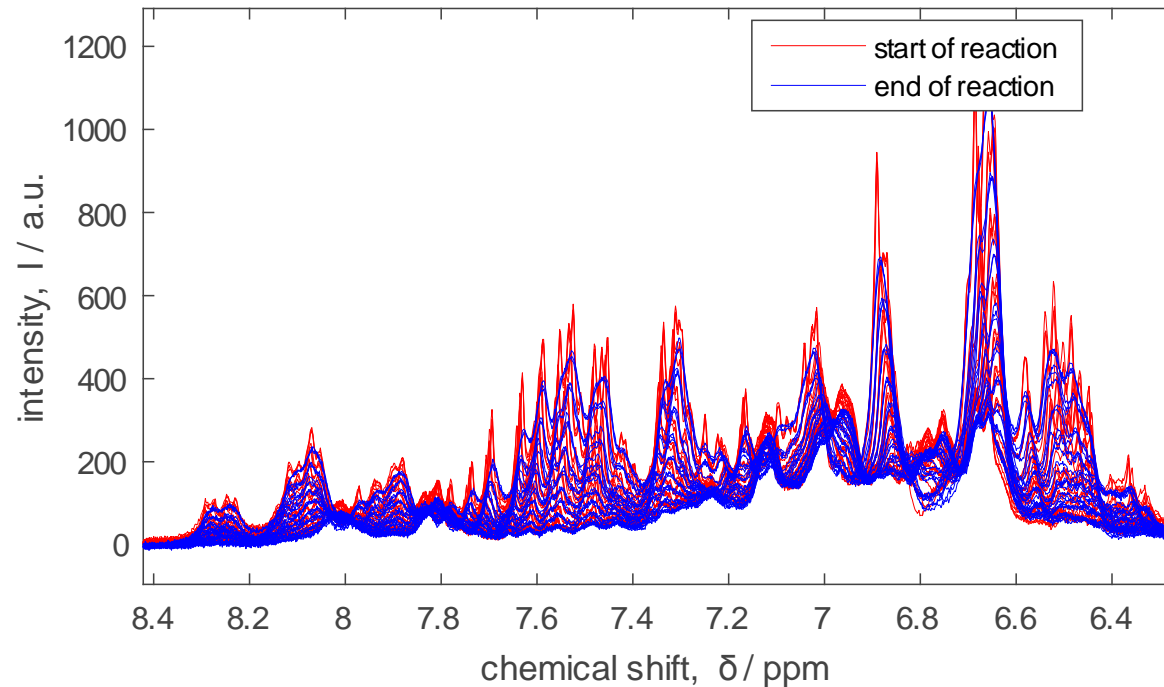
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- Spectra for repeated batches vary, e.g., due to the quality of the respective shim
- fundamental acceptance criteria for online NMR spectroscopy:

 robust data pretreatment and evaluation strategy with the potential for automation

Comparison of proton spectra of different runs



-
- K. Meyer, S. Kern, N. Zientek, G. Guthausen, M. Maiwald, Process control with compact NMR, *TrAC Trends in Analytical Chemistry*, October 2016, Vol.83:39–52, doi:[10.1016/j.trac.2016.03.016](https://doi.org/10.1016/j.trac.2016.03.016)
 - N. Zientek, C. Laurain, K. Meyer, A. Paul, D. Engel, G. Guthausen, M. Kraume, M. Maiwald, Automated data evaluation and modelling of simultaneous ^{19}F – ^1H medium-resolution NMR spectra for online reaction monitoring, *Magnetic Resonance in Chemistry*, 54 (2016) 513-520.
 - N. Zientek, C. Laurain, K. Meyer, M. Kraume, G. Guthausen, M. Maiwald, Simultaneous ^{19}F – ^1H medium resolution NMR spectroscopy for online reaction monitoring, *Journal of Magnetic Resonance*, 249 (2014) 53-62.
 - Meyer, K.; Ruiken, J. P.; Illner, M.; Paul, A.; Müller, D.; Esche, E.; Wozny, G.; Maiwald, M.; Process spectroscopy in microemulsions–Setup and multi-spectral approach for reaction monitoring of a homogeneous hydroformylation process. *Measurement Science and Technology* 2017, 28.