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LOW FIELD NMR SPECTROSCOPY FOR PROCESS CONTROL

Robust automated data preparation and analysis as prerequisites

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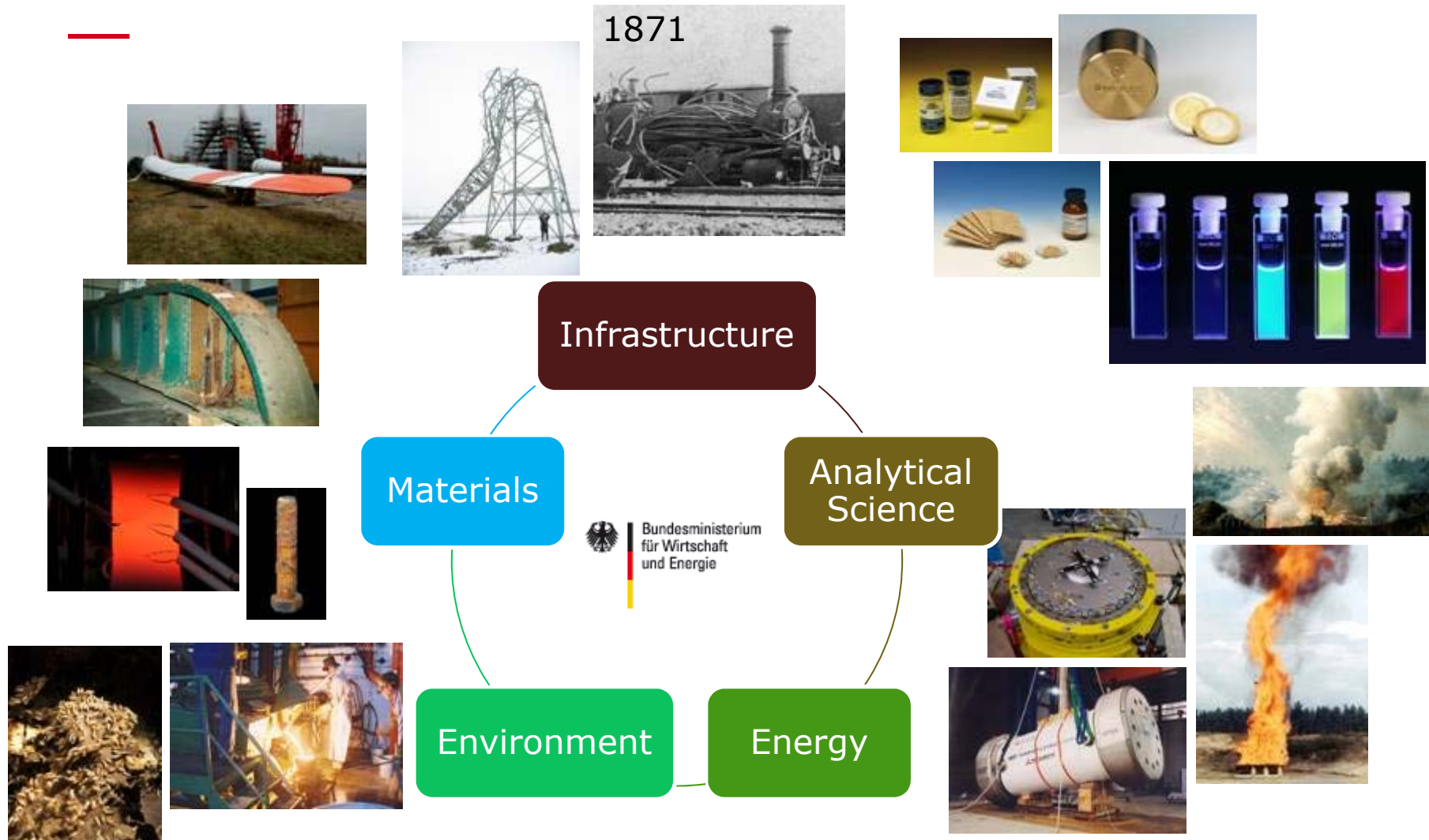


This project has received funding from the European Union's Horizon 2020
research and innovation programme under grant agreement N° 636942

Safety in Technology and Chemistry



Our Key Areas



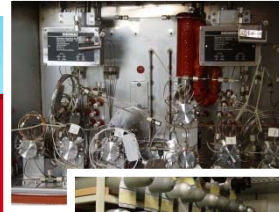
BAM is a senior scientific and technical Federal institute with responsibility to Federal Ministry for Economic Affairs and Energy

Division 1.4: Process Analytical Technology BAM

Our Key Areas

Gas Analysis

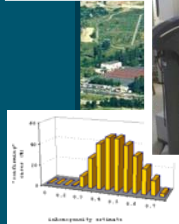
- Primary Reference Gas Mixtures
- Gas Analysis, Gas Metrology
- Certification of Sec. Gas Mixtures



Located in Berlin, Germany

Process Spectroscopy

- Online NMR Spectroscopy, qNMR
- Raman Spectroscopy and Microscopy
- NIR, MIR, FIR spectr., IR Microscopy
- Data Treatment: Statistics, Numerics
- Measurement Uncertainty Evaluation

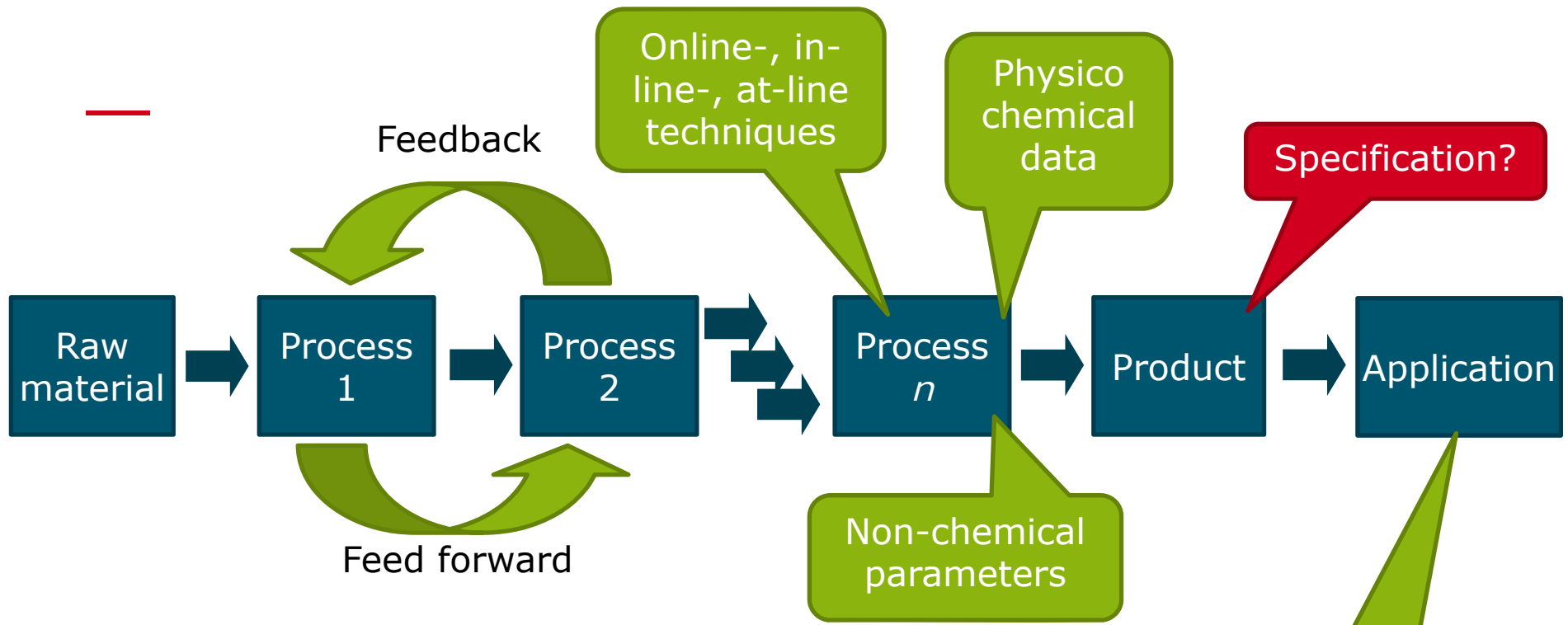


Inorganic Process Anal. Technol., XRF

- X-ray fluorescence Analysis (XRF)
- Laser-induced Breakdown (LIBS)
- Total Reflectance XRF (T-XRF)



Process Analytical Technology

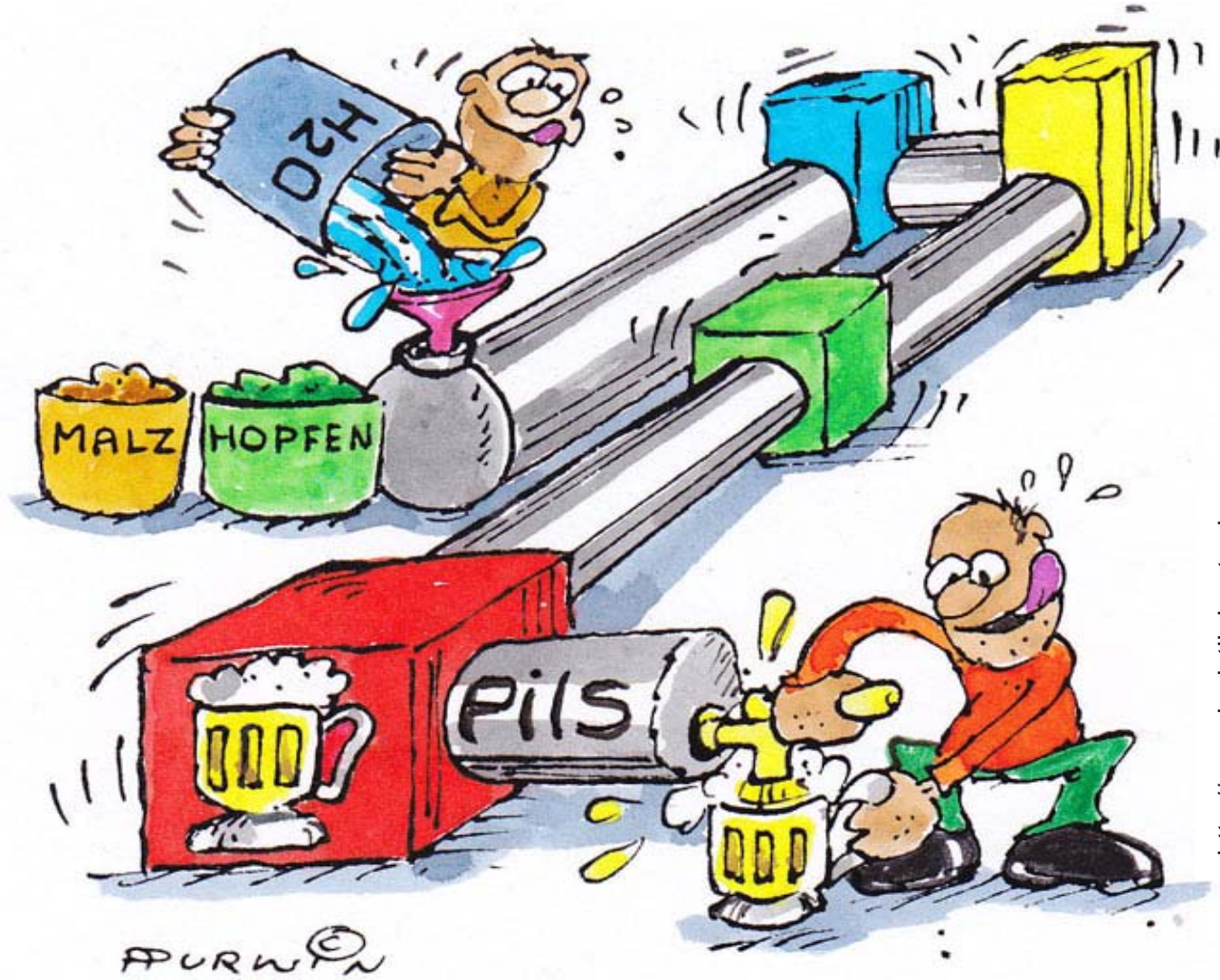


Motivation

- Optimal design ("quality by design")
- Demanded product quality with an optimum use of equipment, raw materials, and energy
- Affordable quality costs

Objective description of **quality**
→ comprehensive understanding

Process Analytical Technology



Raw material

- Motivati
- Optim
 - Dema
 - optim
 - mater
 - Afford

ification?

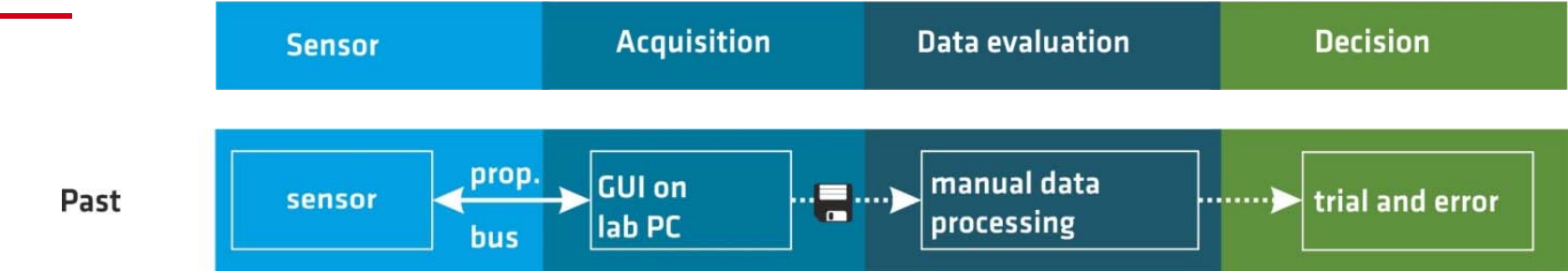
Application

<http://www.logistik-heute.de>
(07.01.2012)

n
ve
understanding

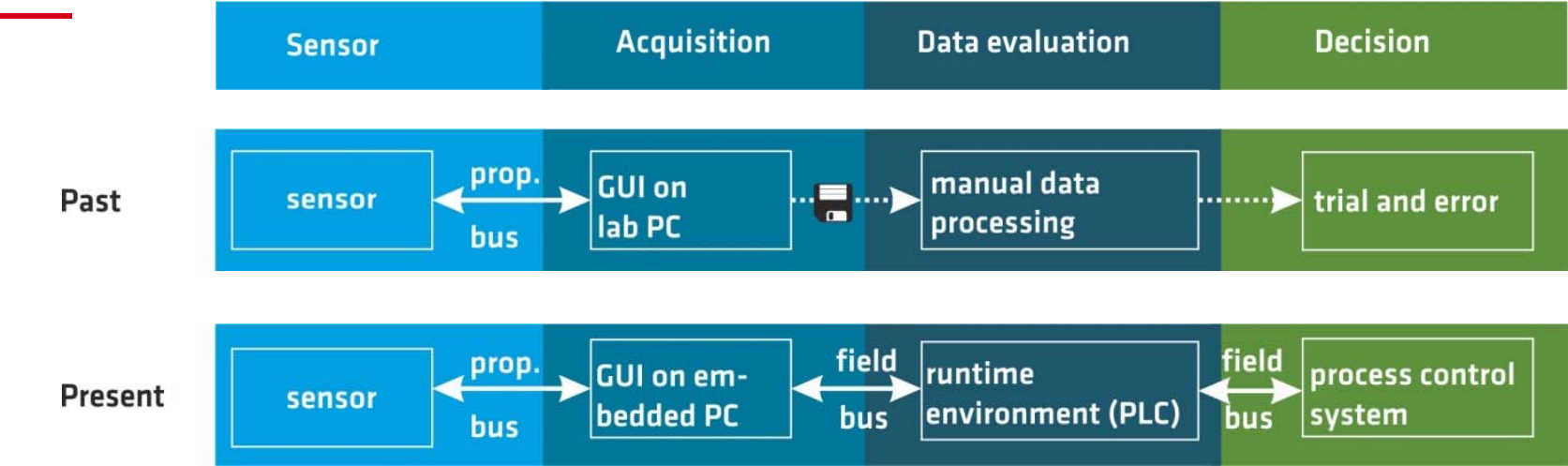
From Lousy Interfaces to "Industrie 4.0" BAM

Use of Runtime Environments



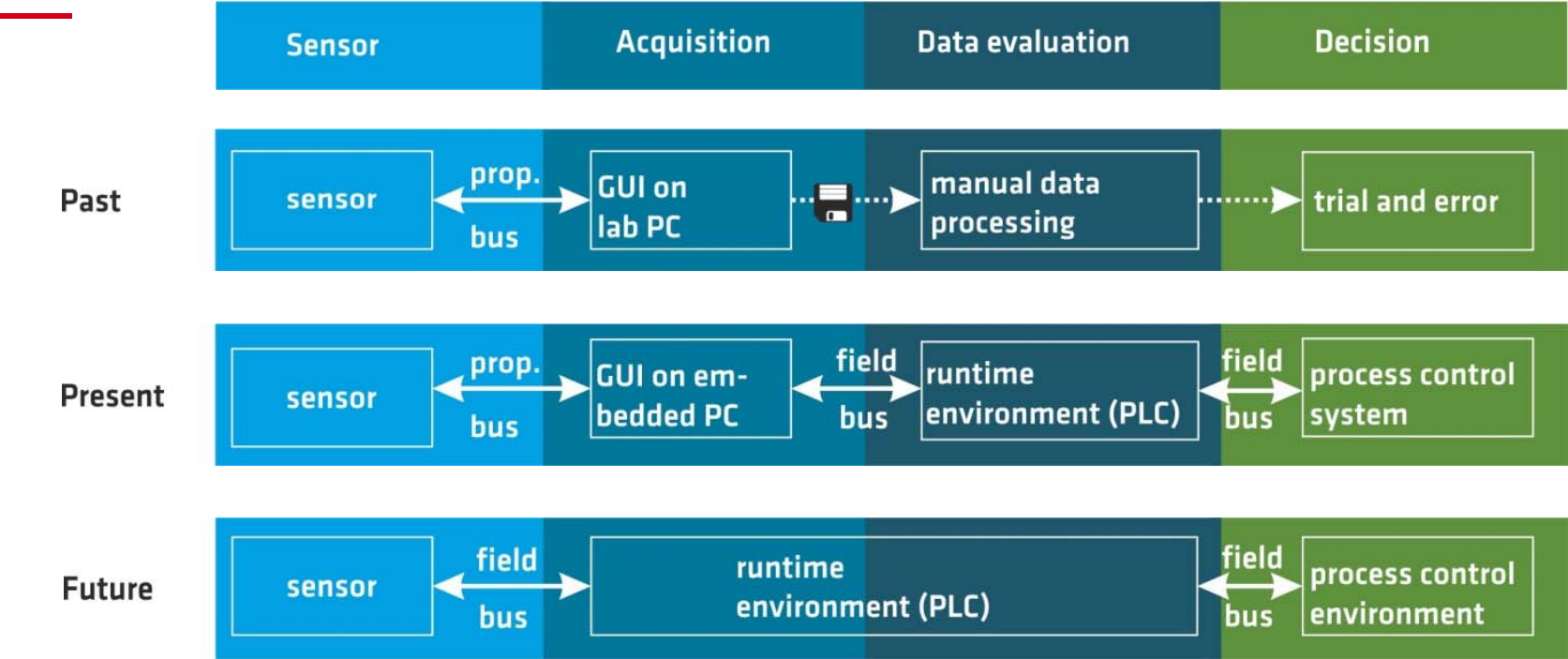
From Lousy Interfaces to "Industrie 4.0" BAM

Use of Runtime Environments



From Lousy Interfaces to "Industrie 4.0" BAM

Use of Runtime Environments



CONSENS: Smart Online NMR Sensor for Advanced Process Control



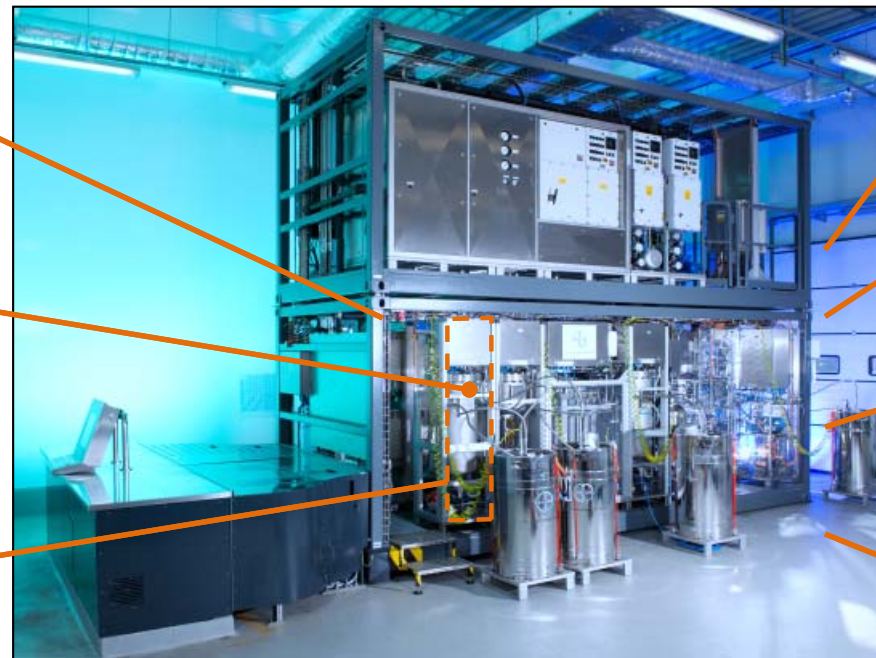
Flexible Intensified Continuous Plant

Characteristics

Miniaturized equipment

Intensified heat & mass transfer

Possibly modular setup



Benefits

Product uniformity

Sustainability

Fast adaption to market demand

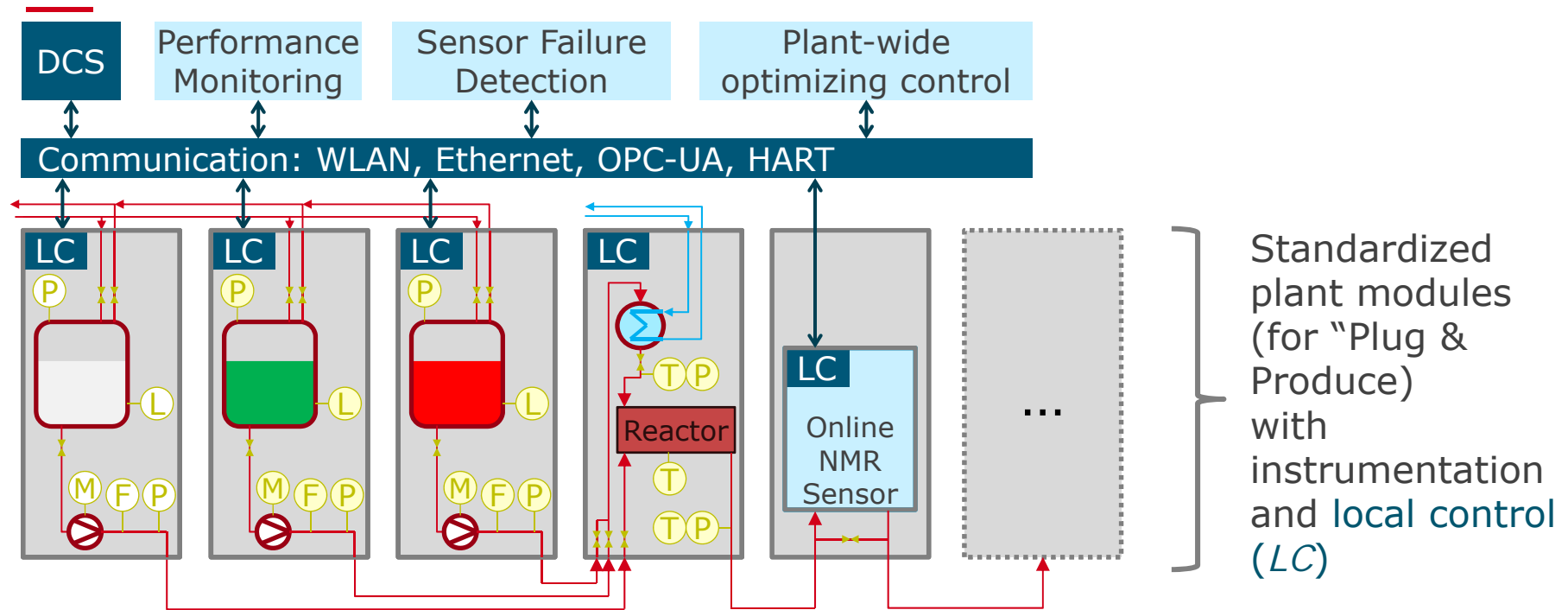
Innovative products

Containerized modular plant Source: INVITE GmbH



Continuous Lithiation Reaction Set-up

Flexible Intensified Continuous Plant



- Miniaturized flexible equipment
- Fast and complex exothermic reaction
- Hazardous and inflammable substances → Explosion protection!
- Prone to fouling & clogging
- Multi-objective constrained optimization

CONSENS: Case Study 1

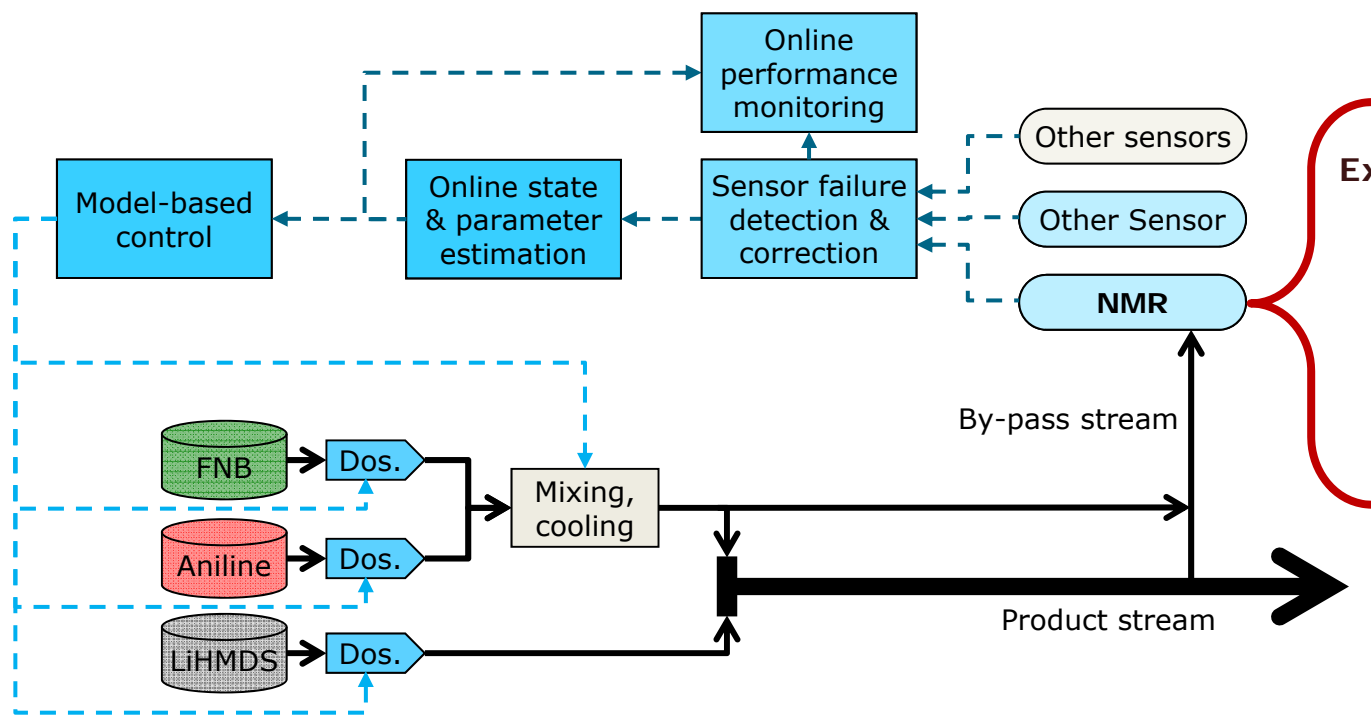
Intensified Synthesis of Organic Compounds



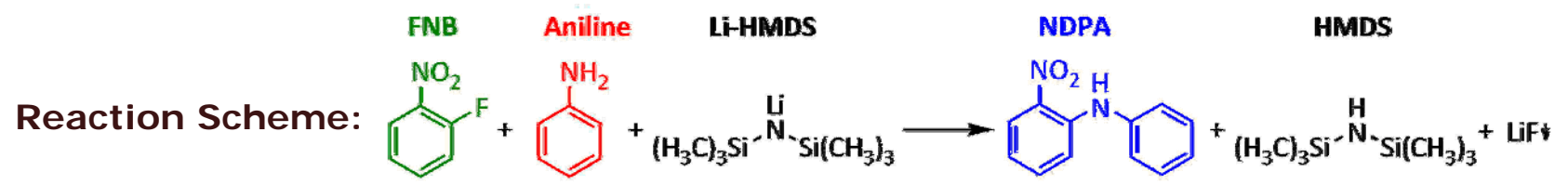
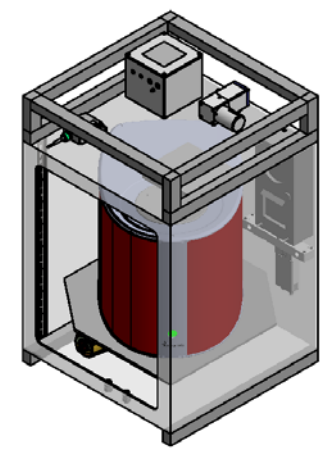
Modular plant



Source: INVITE GmbH



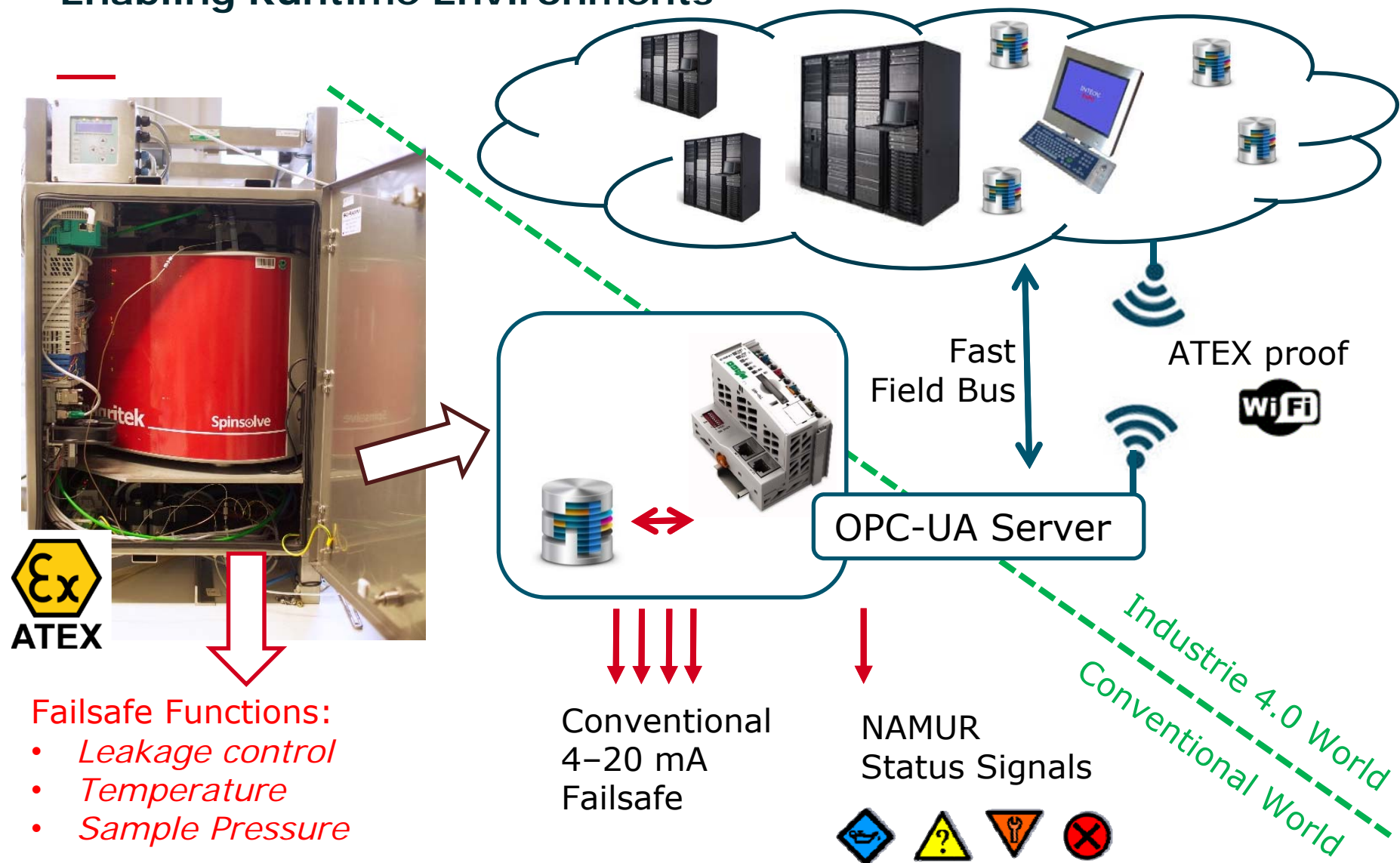
Explosion proof housing



Conventional and Smart Functions

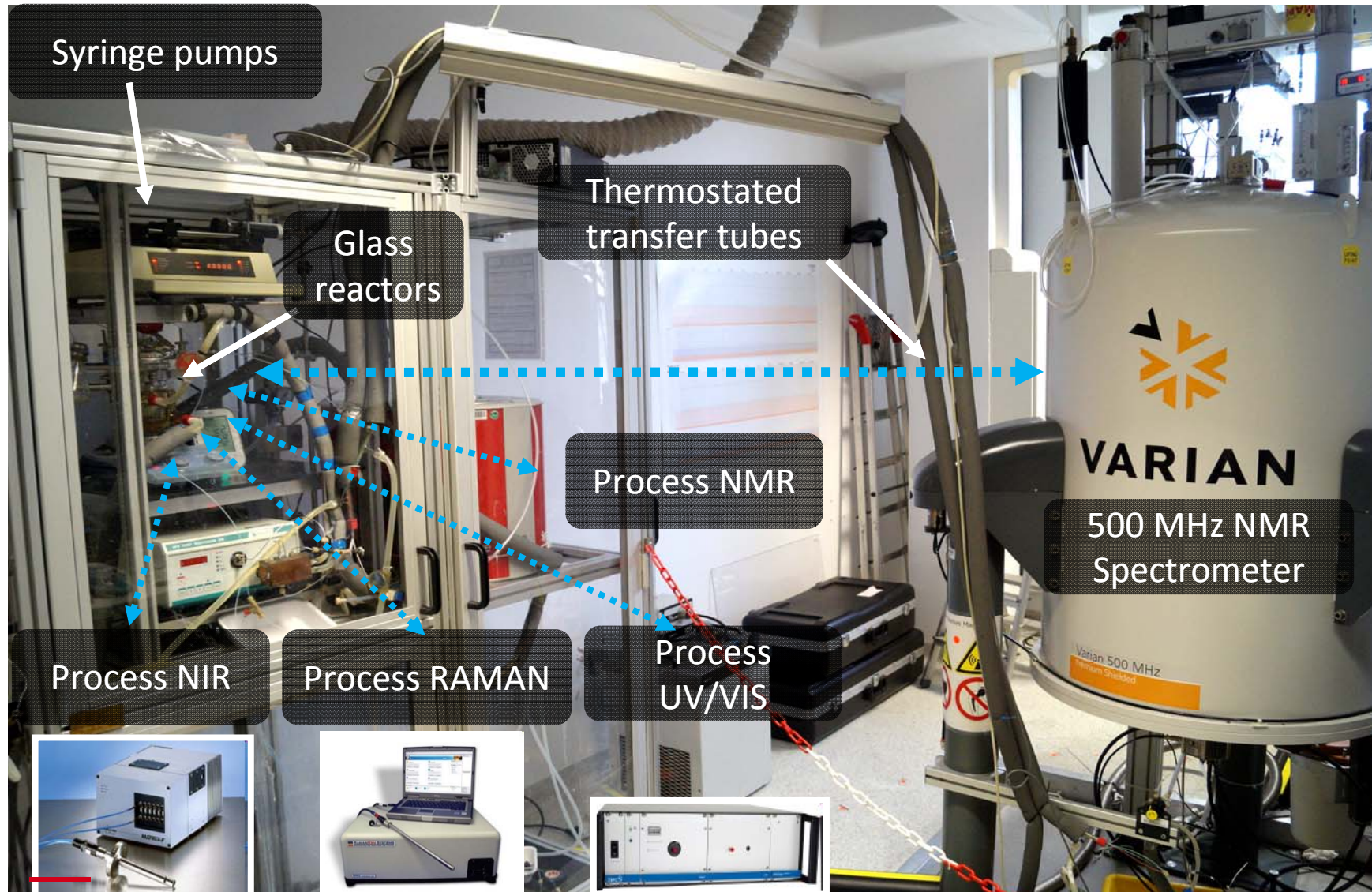


Enabling Runtime Environments



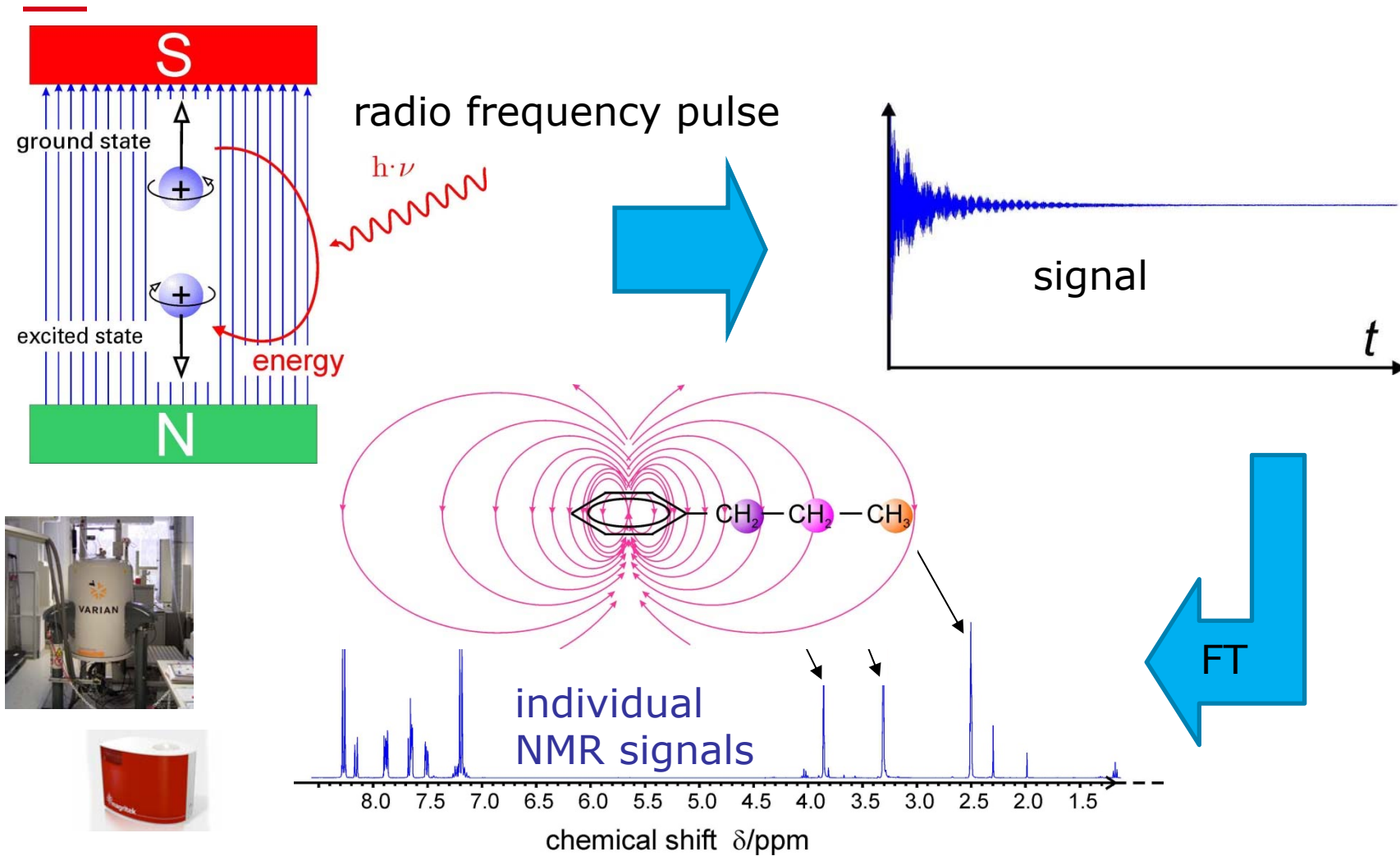
- Failsafe Functions:**
- Leakage control
 - Temperature
 - Sample Pressure

Reaction Monitoring in Lab-scale at BAM



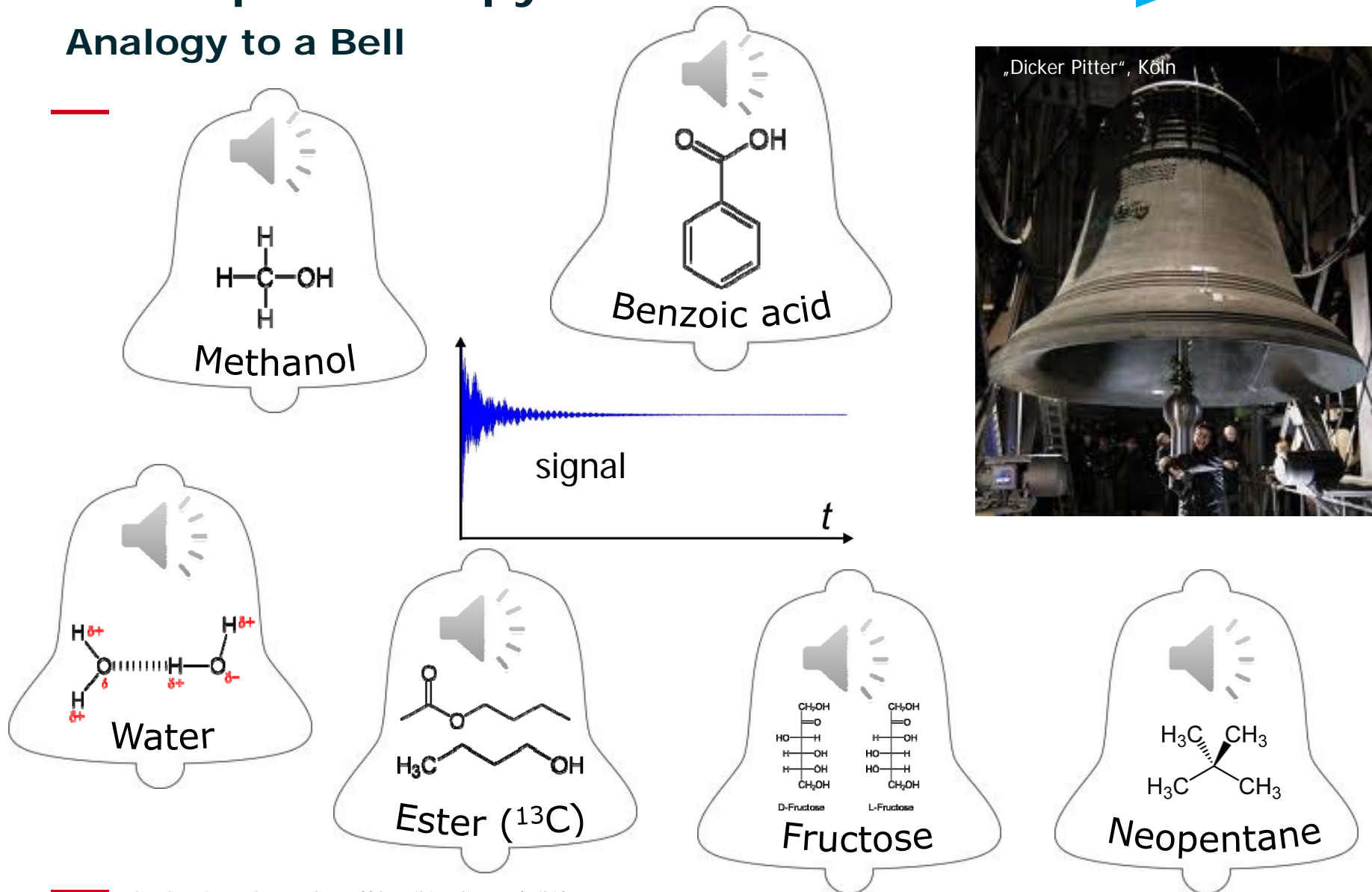
Nuclear Magnetic Resonance (NMR)

Direct Comparison Method → Calibration Free!



NMR Spectroscopy

Analogy to a Bell



The diagram illustrates the analogy of NMR spectroscopy to a bell. Six chemical structures are shown inside bell-shaped containers, each with a speaker icon, representing different 'sounds' or signals. A central graph shows a signal over time (t).

- Methanol:** CO
- Benzoic acid:** O=C(O)c1ccccc1
- Water:** O (with partial charges δ^+ and δ^-)
- Ester (^{13}C):** CCCCC(=O)OCC
- Fructose:** C(C1C(C(C(O1)O)O)O)O (D-Fructose and L-Fructose)
- Neopentane:** CC(C)(C)C



Strukturformeln von <http://de.wikipedia.org/wiki/>

Reaction Monitoring on Lab Scale at BAM

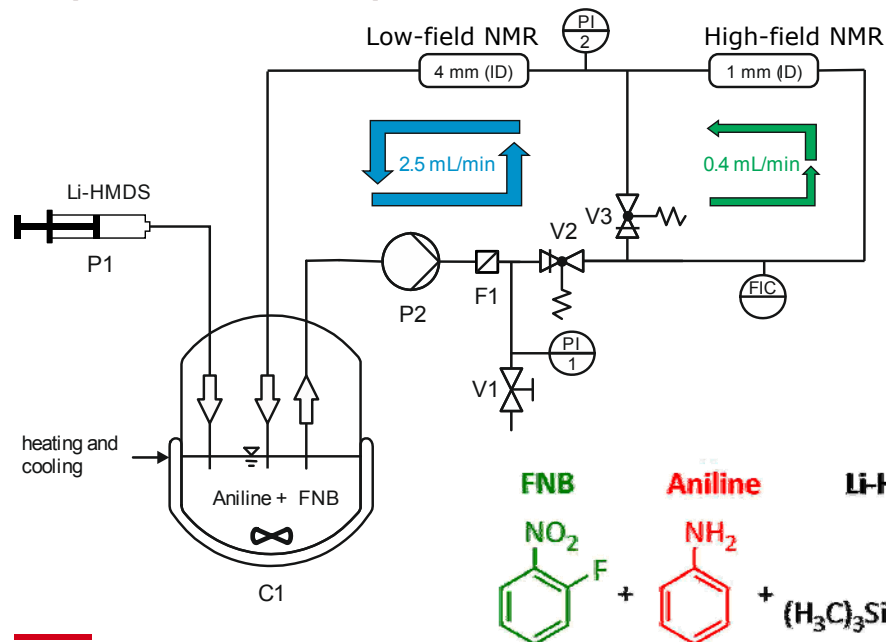
Reaction Characterization in Lab

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

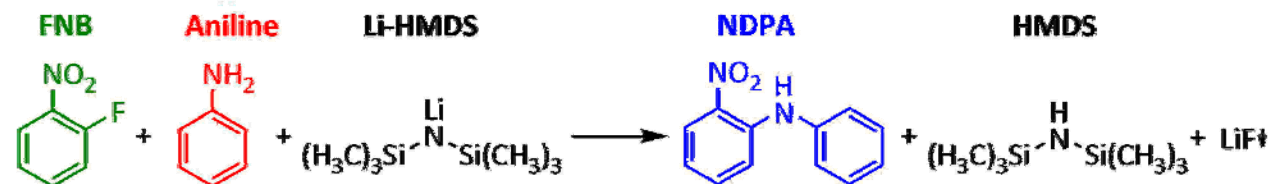


Experimental set-up

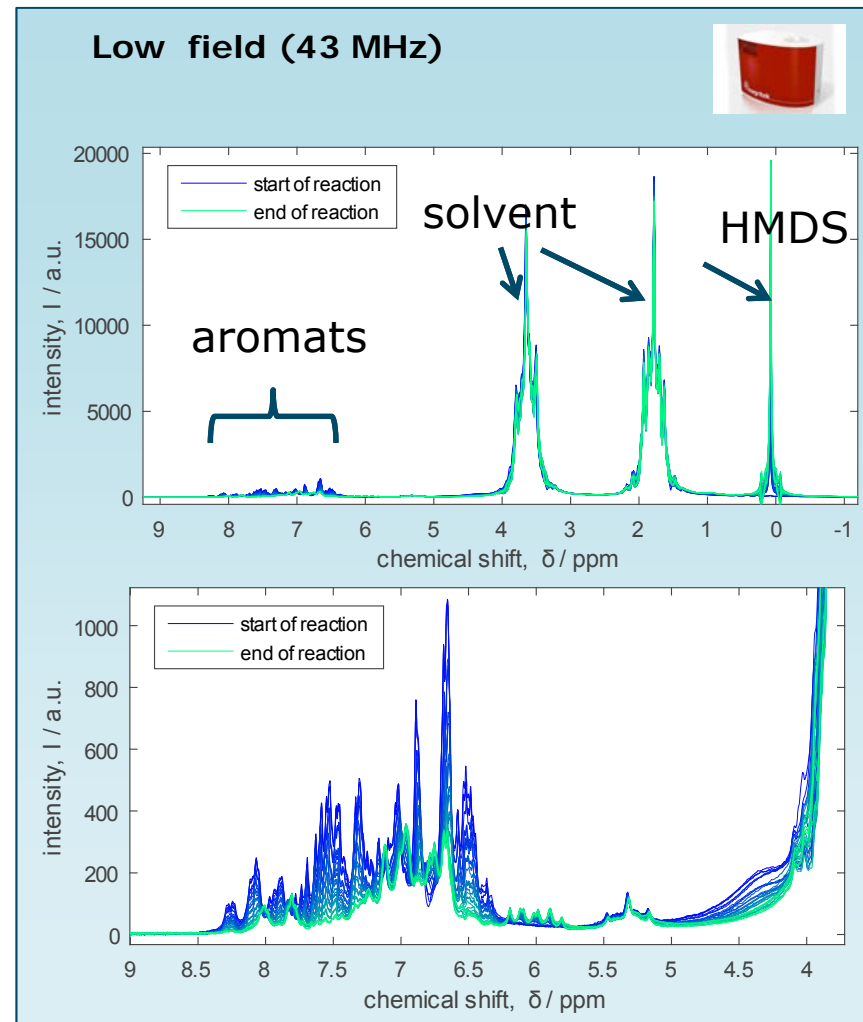
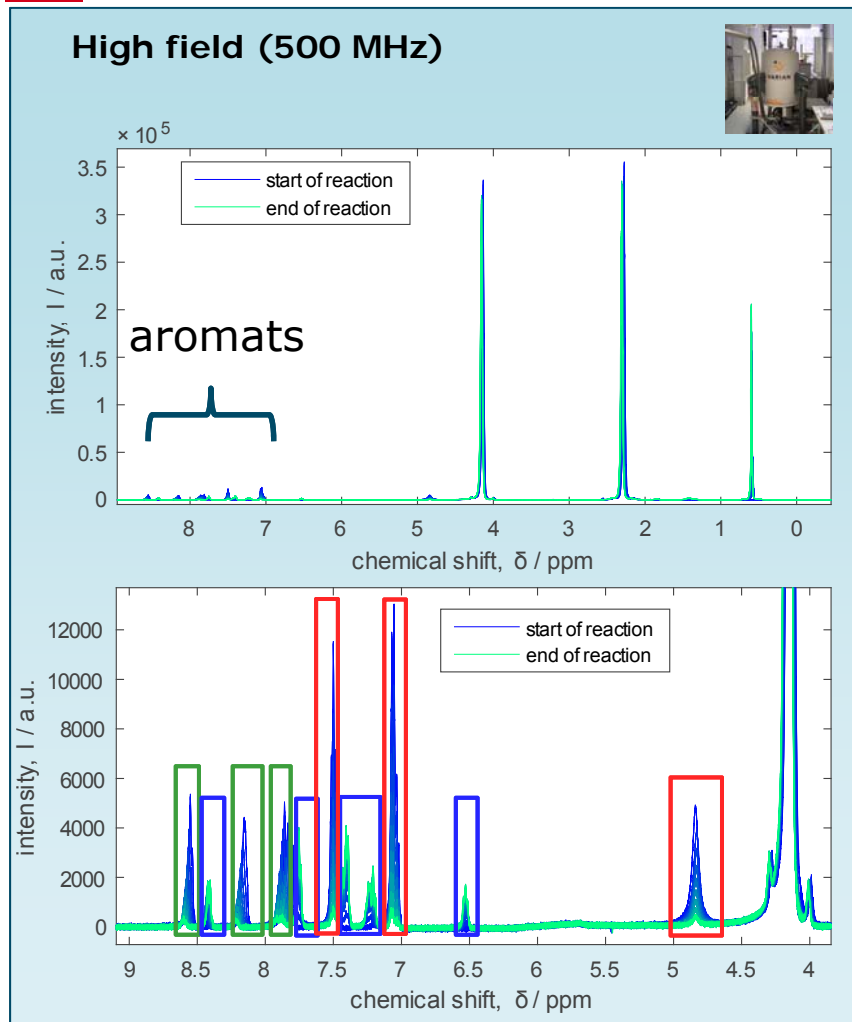


- Exothermic reaction
 → required cooling (28.5 °C)
- Li-HMDS in two-fold excess

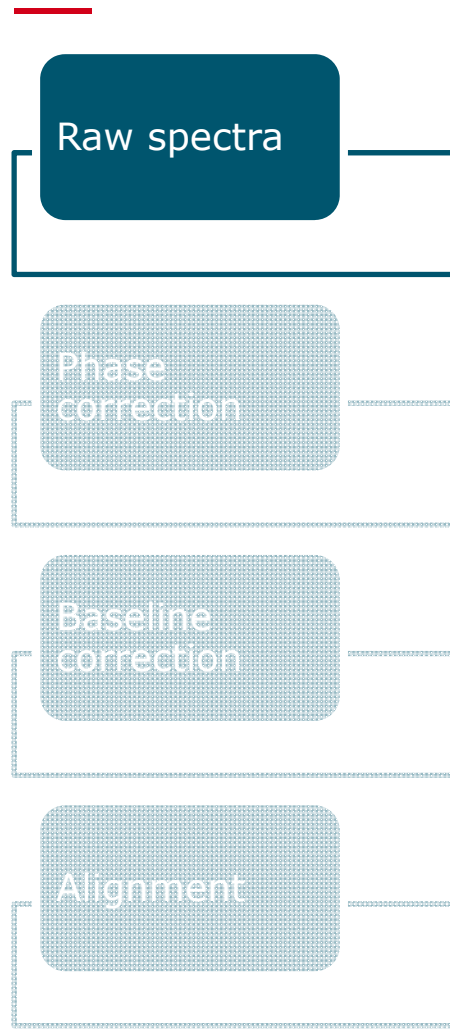
Reaction Scheme:



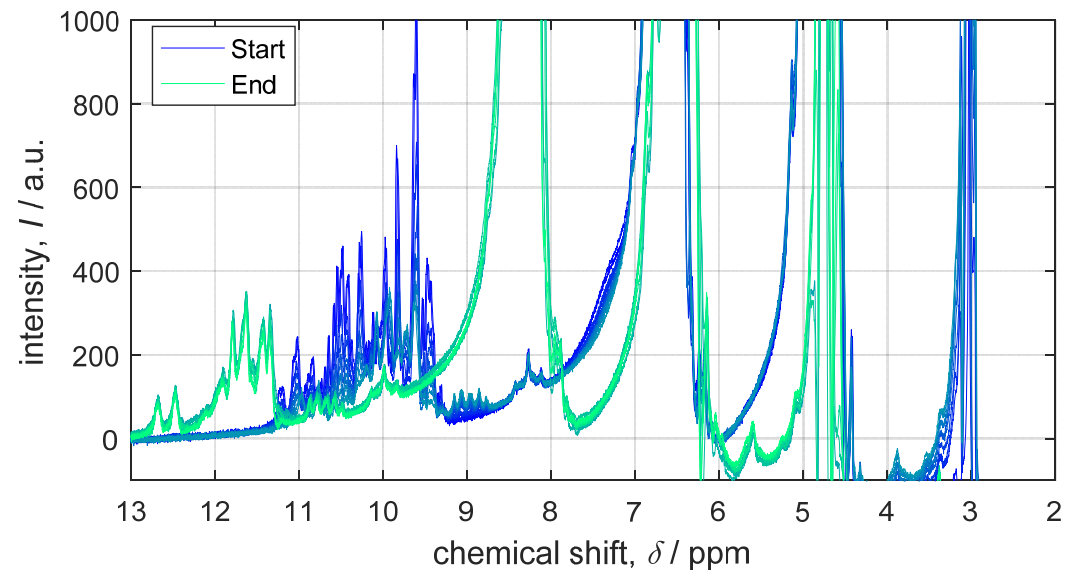
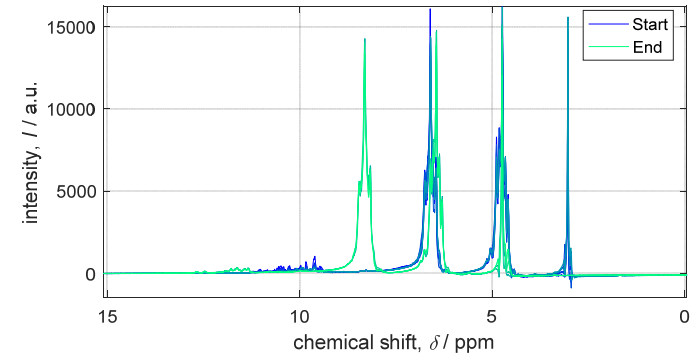
Online ^1H NMR Spectra of Lithiation Reaction Step



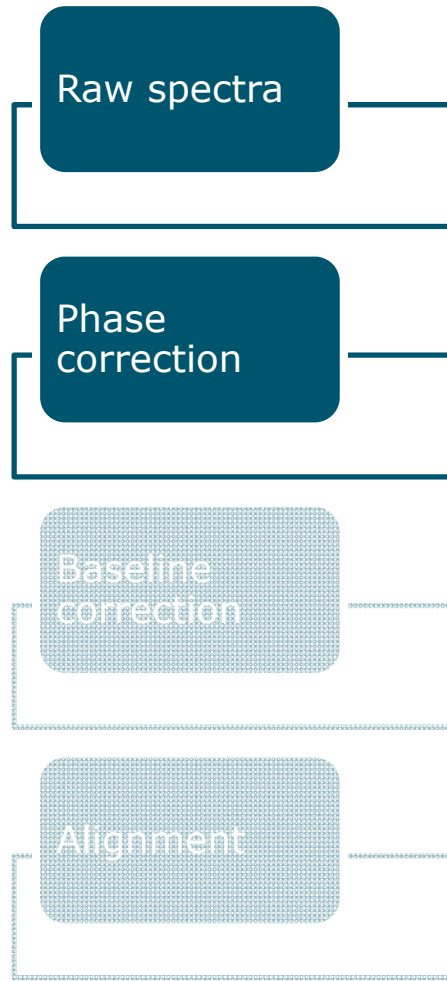
Data Processing for Low-field NMR in Matlab



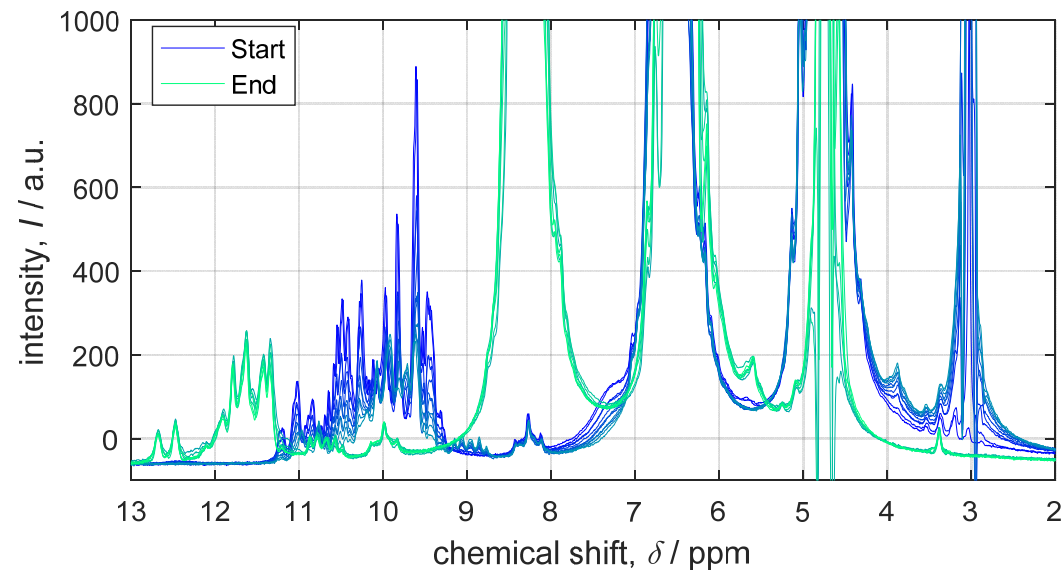
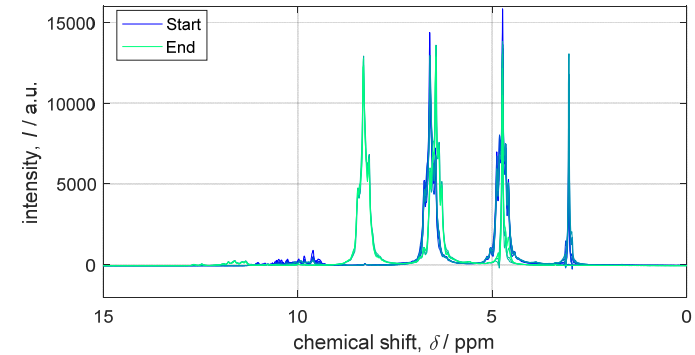
single scan
each 15s
in flow



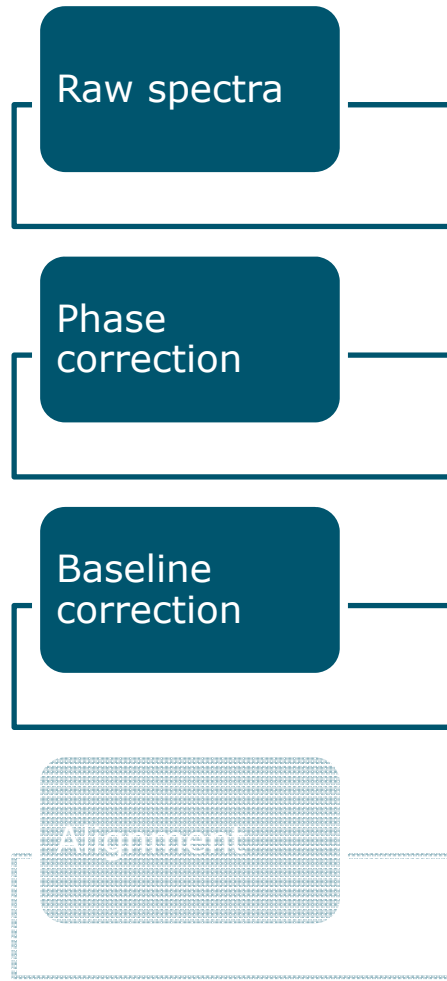
Data Processing for Low-field NMR in Matlab



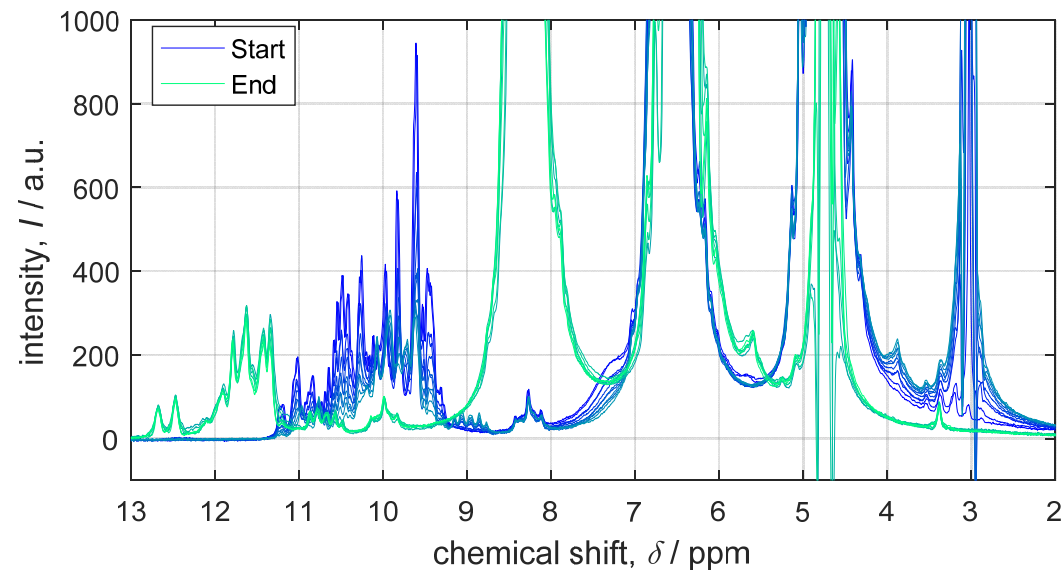
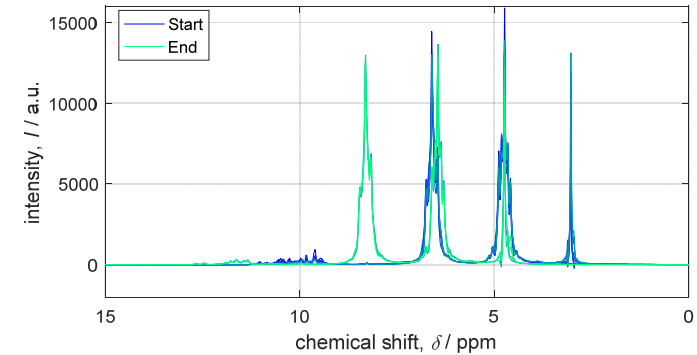
Entropy minimization method:
Chen et al., J Magn Reson.
2002, 158, 164-168



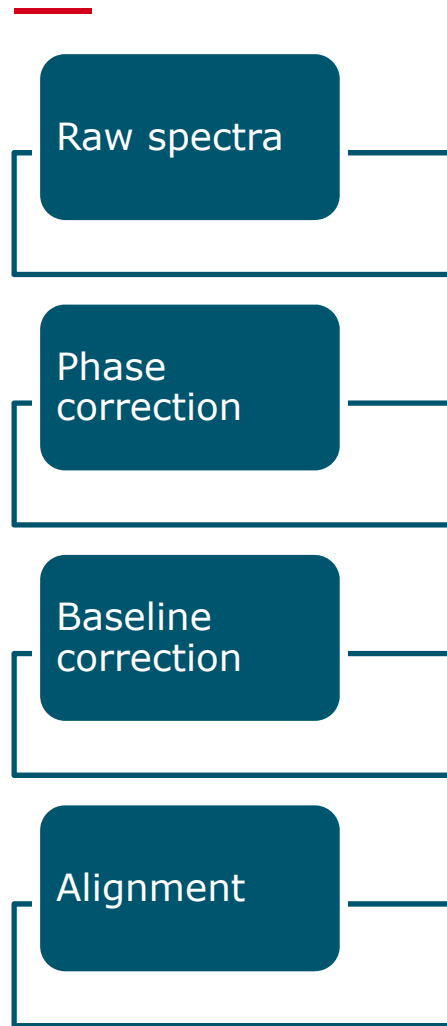
Data Processing for Low-field NMR in Matlab



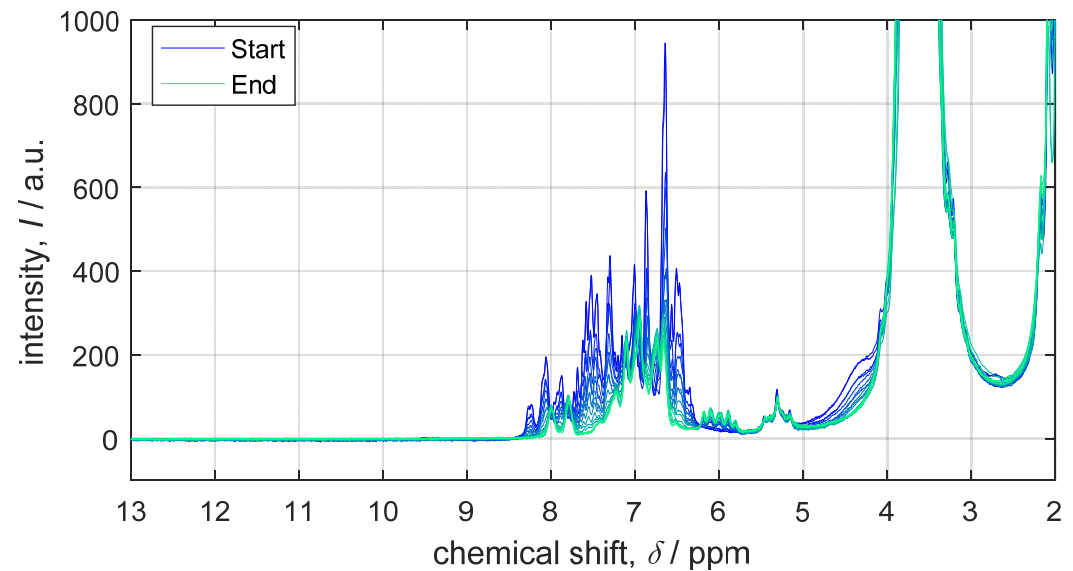
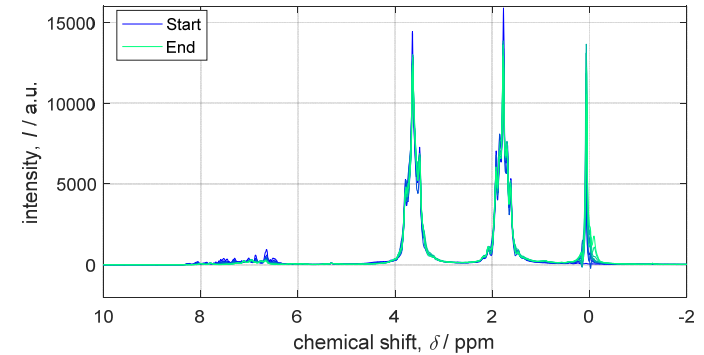
Low-order Polynomial fit:
Mazet et al., Chemometrics
Intell. Lab. Sys. **2005**, *76*,
121-133.



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



Challenges in Automated Data Analysis



Data pretreatment

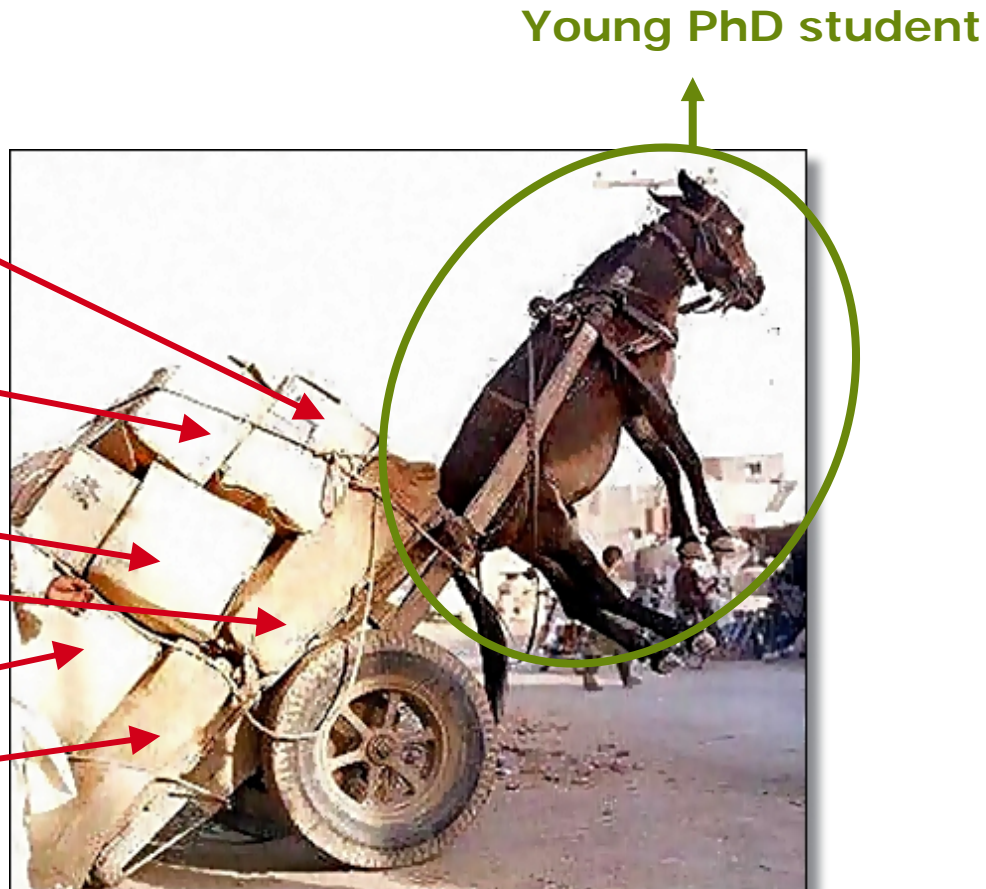
Integration

MCR

Binning/ PLS-R

GSD/ Edited Sum

IHM



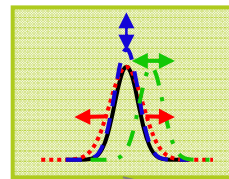
<http://collegeaffordology.com/>



Indirect Hard Modeling (IHM)

- Modeling → peak fitting of pure component spectra → mixture model
- Analysis → "component fitting" → calculation of component area

» Group of peaks represent pure component spectra

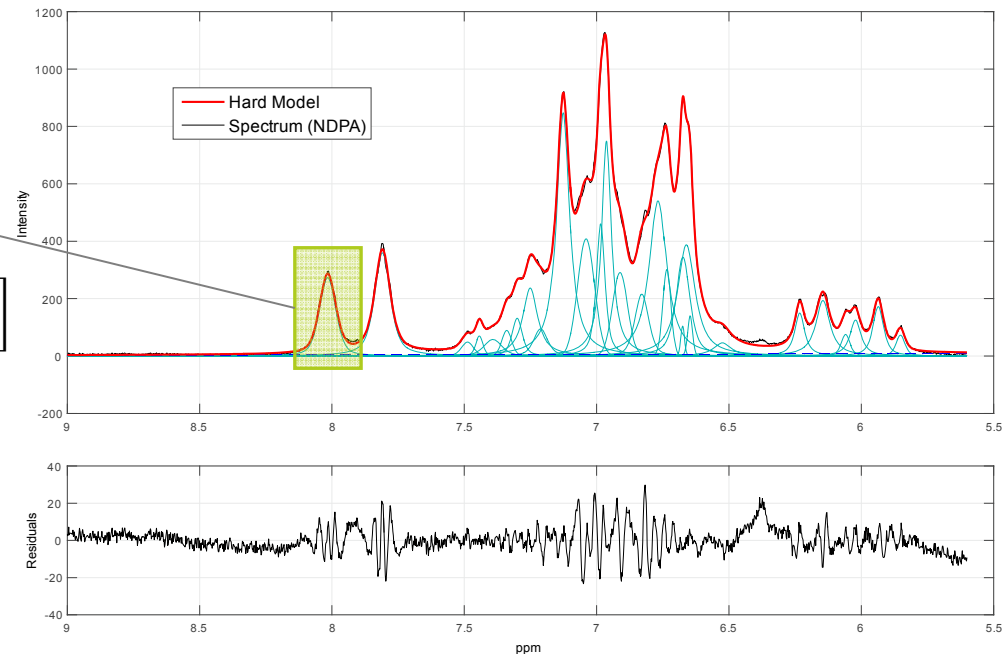


» Pseudo-Voigt function

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

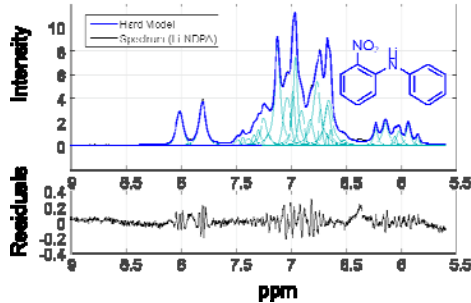
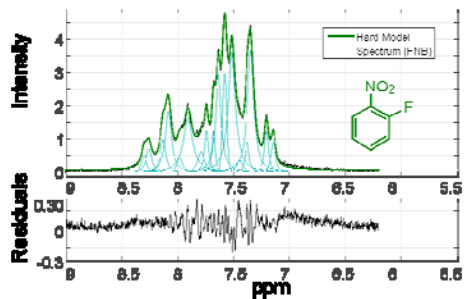
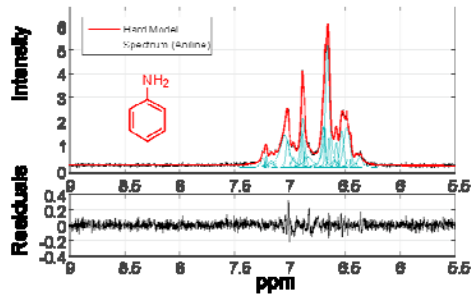
- α = peak maximum
- β = Gaussian-Lorentzian-ratio
- γ = half width
- δ = center position

Hard model for pure components



IHM – „component fitting“

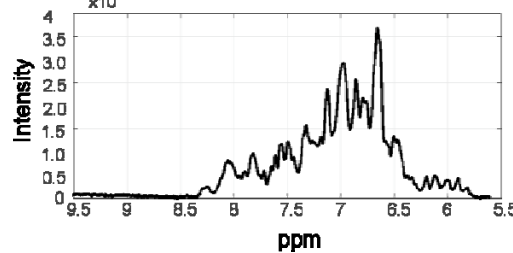
Pure component models



Mixture model

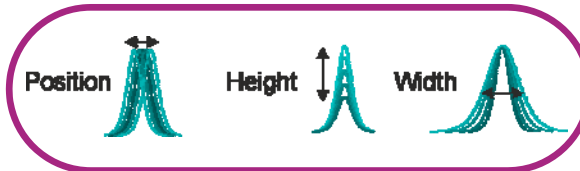
Component fitting

Experimental Spectrum



Modeling → Mixture model

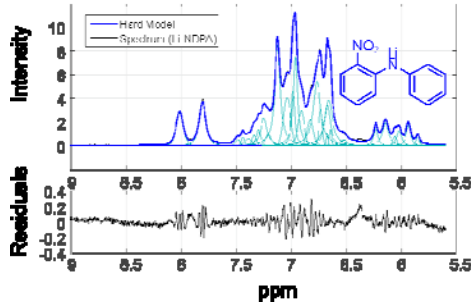
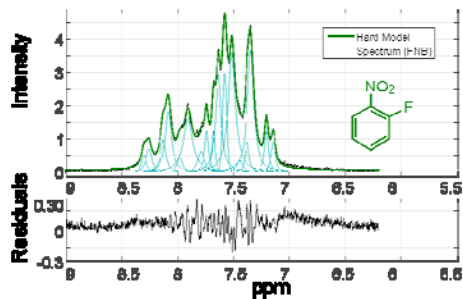
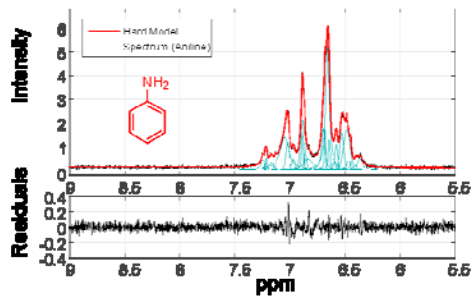
| | |
|---|------------|
| No. components | 3 |
| Peaks per component | 22, 21, 28 |
| Degree of freedom (total free parameters) | 292 |
| Considered interacting peaks | 25 |
| Max. peak shift | 0.01 ppm |
| ... | ... |



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

IHM – „component fitting“

Pure component models

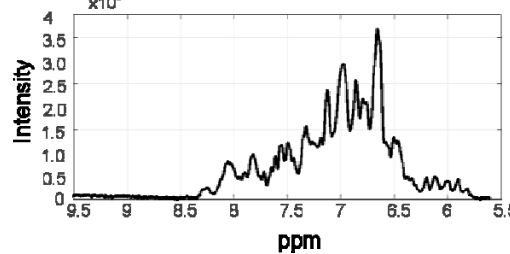


Analysis "component fitting"

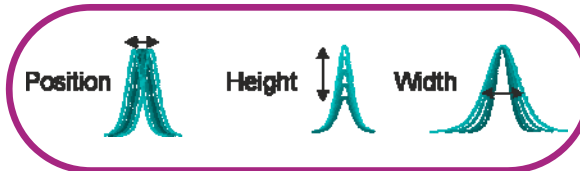
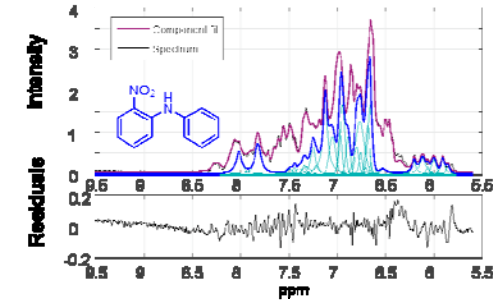
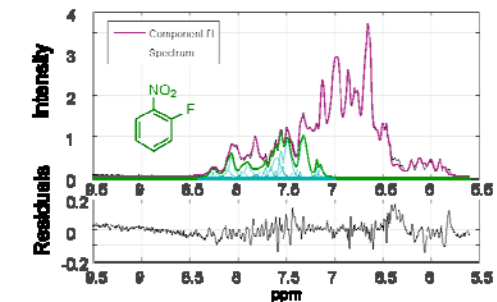
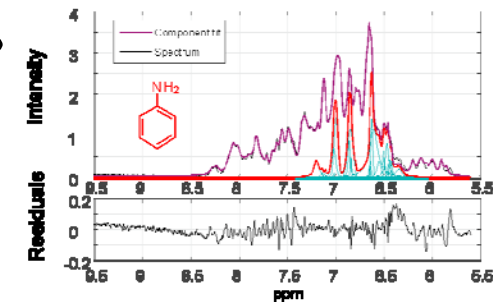
Mixture model

Component fitting

Experimental Spectrum



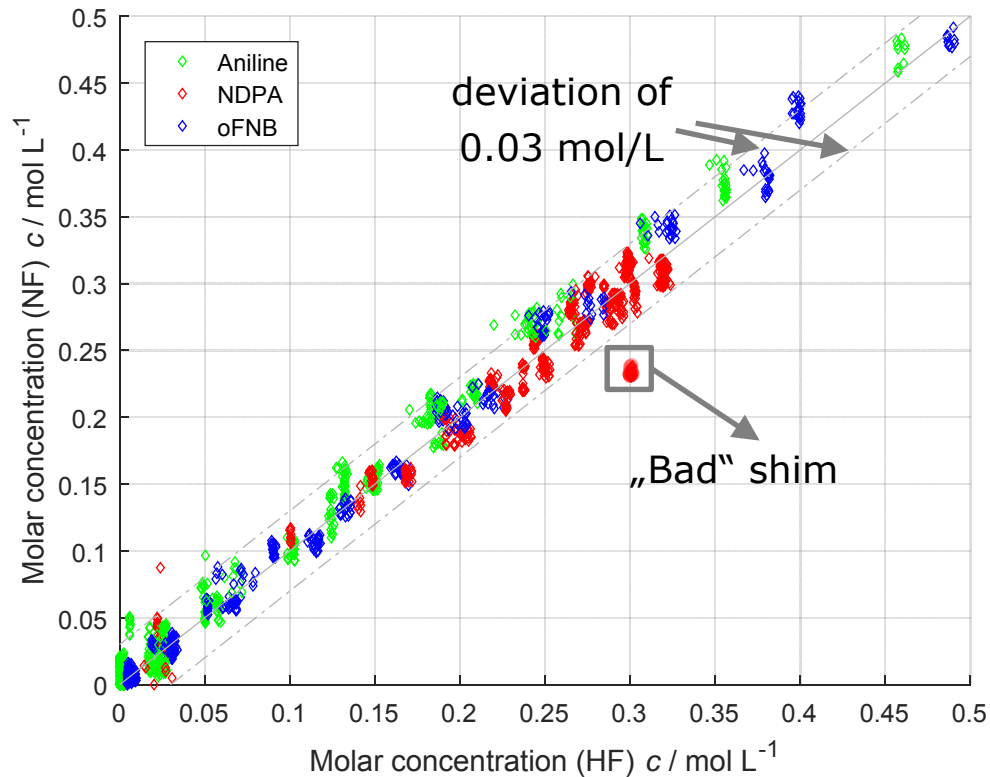
Deconvoluted spectrum



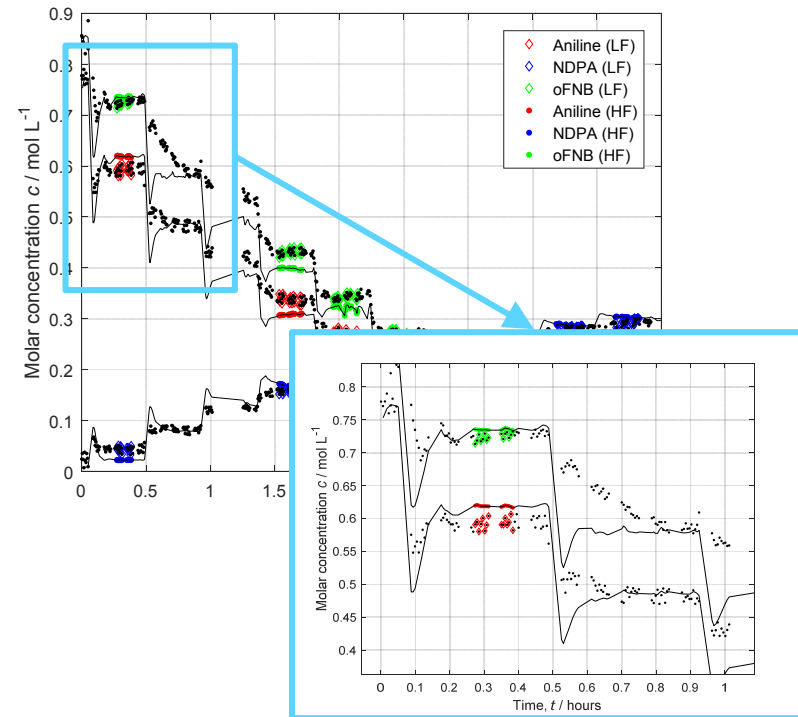
Results: Validation of IHM Model

Lab Experiments in Batch along Reaction Co-ordinate

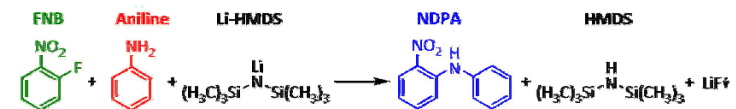
- 3 semi-batch reaction with varying starting concentrations
- 1500 Spectra for each HF- and NF-NMR



Classification of steady states

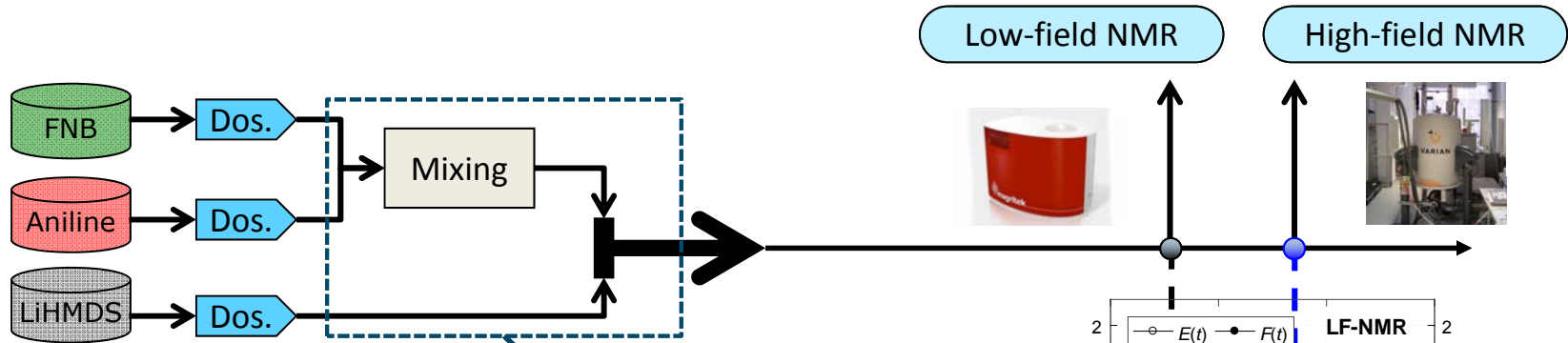


Reaction Scheme:

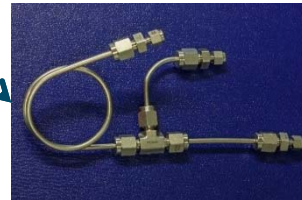


Results: Validation of IHM Model

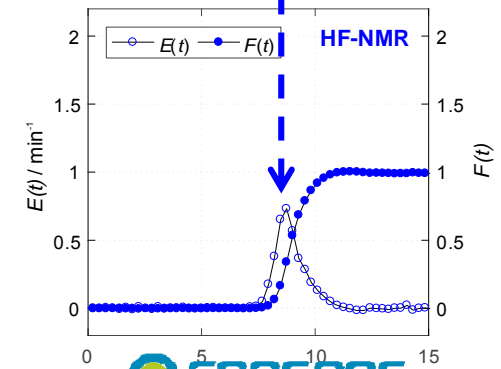
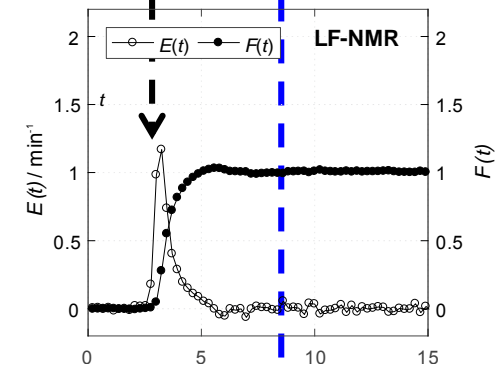
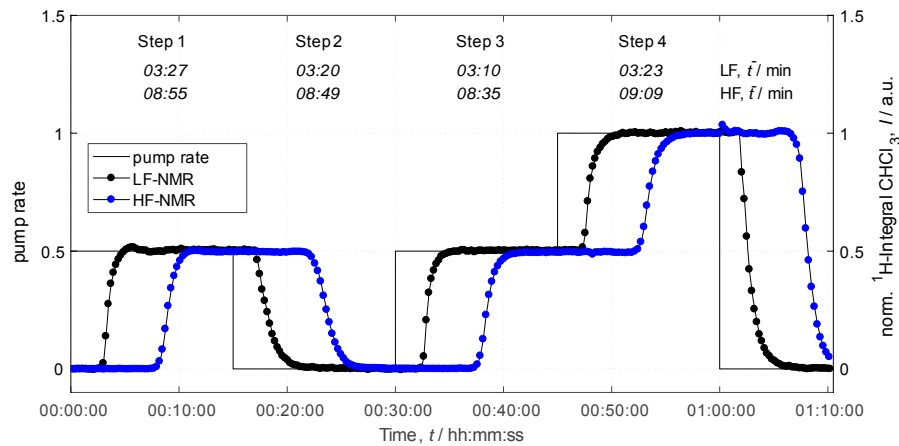
Lab Experiments in Batch along Reaction Co-ordinate



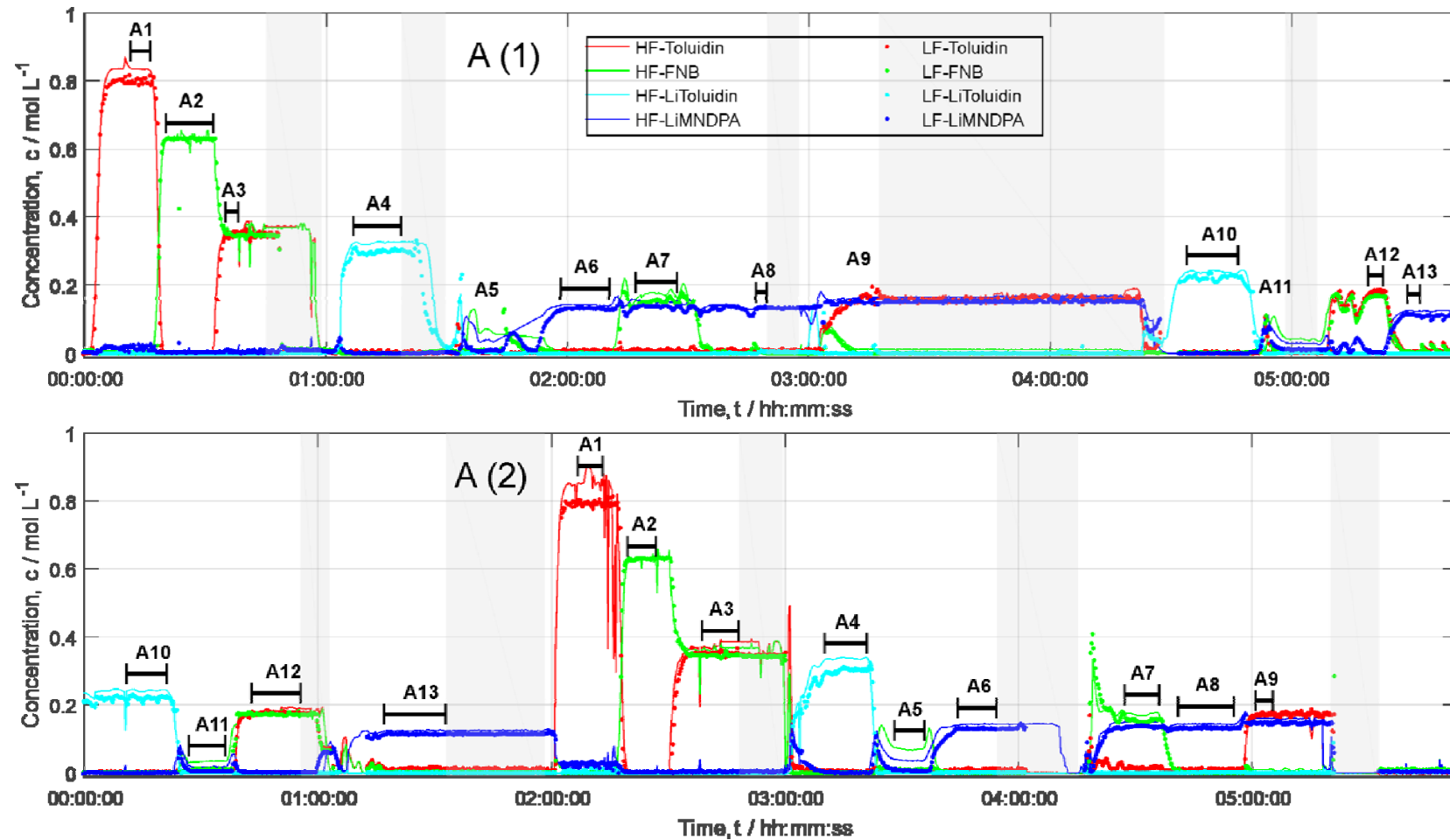
1/8" tube reactor



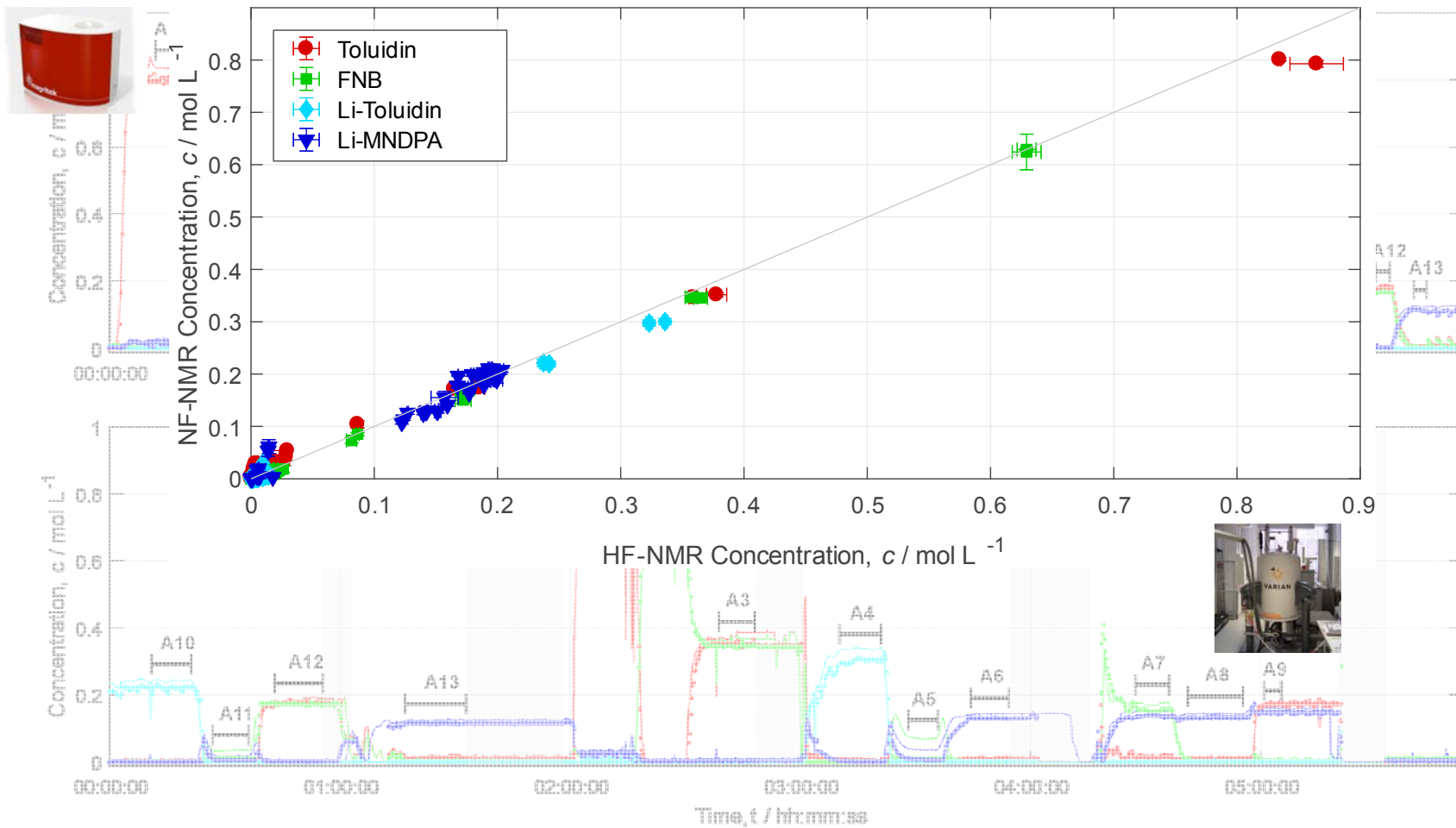
Step tracer experiments



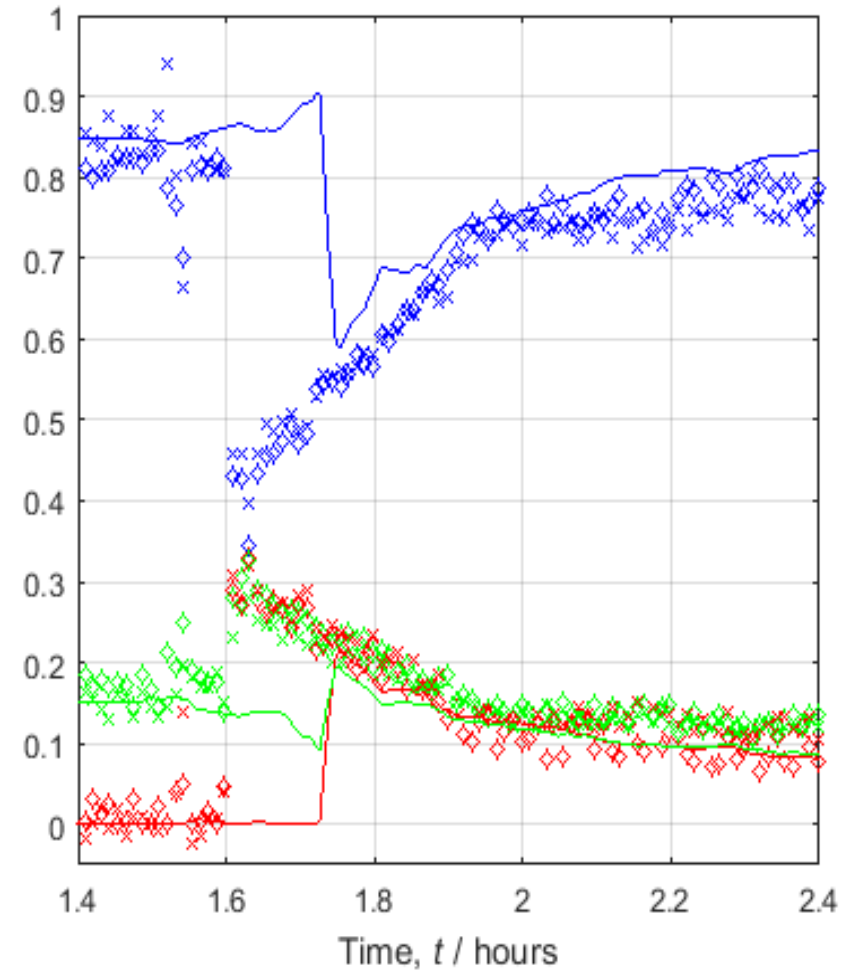
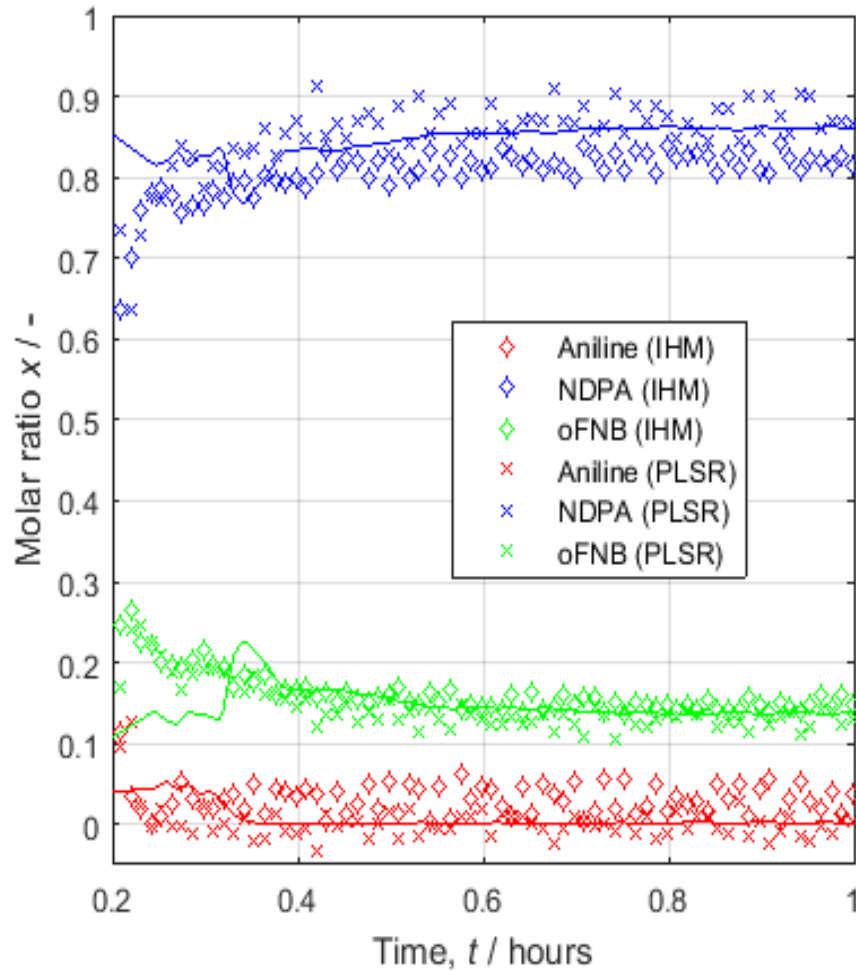
Monitoring of Continuous Aromatic Substitution Reaction by Low Field NMR



Monitoring of Continuous Aromatic Substitution Reaction by Low Field NMR



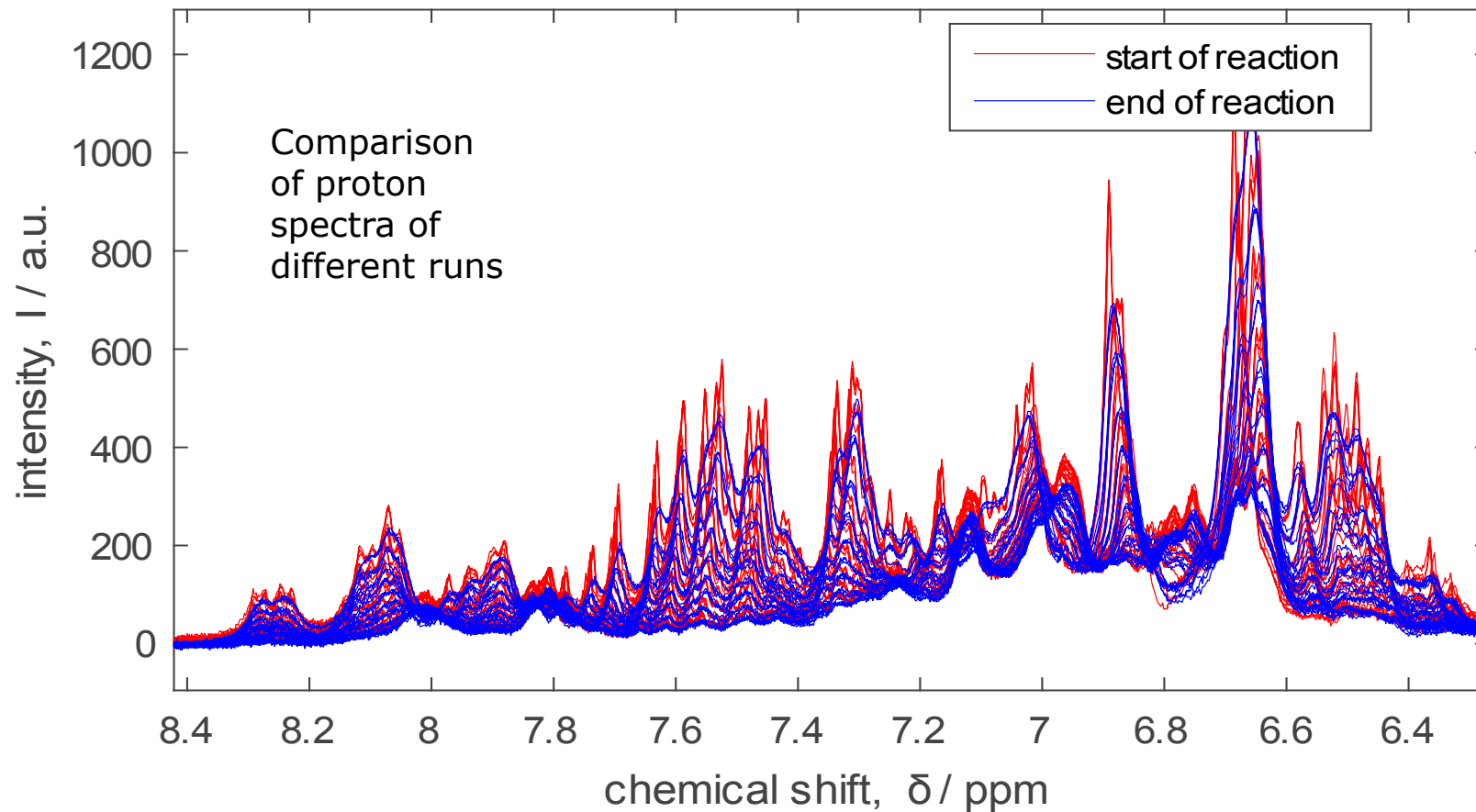
Problem: Overestimation of Components at Low Concentrations



Challenges in Industrial Scale

Varying Peak Width

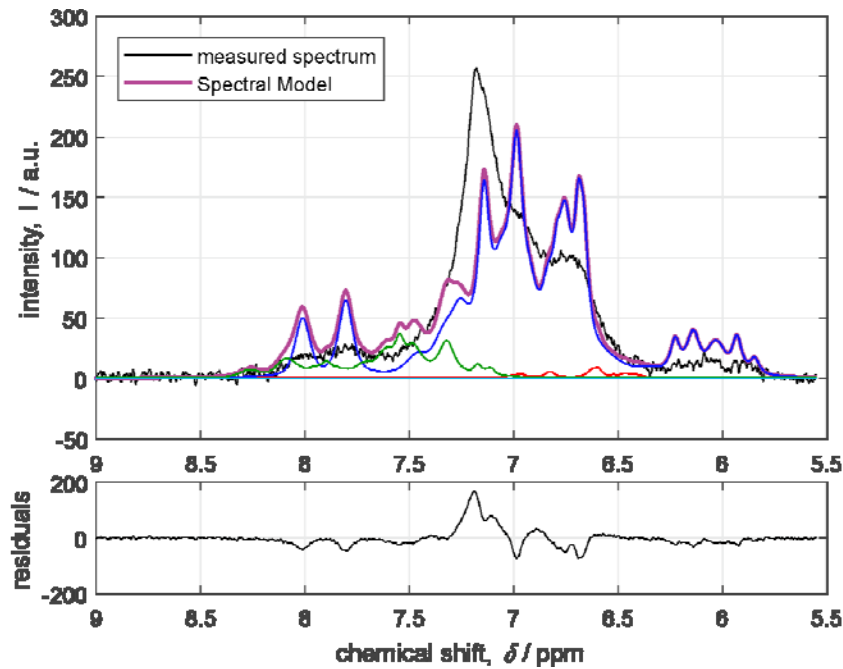
- Spectra for repeated batches vary, e.g., due to the quality of the respective shim



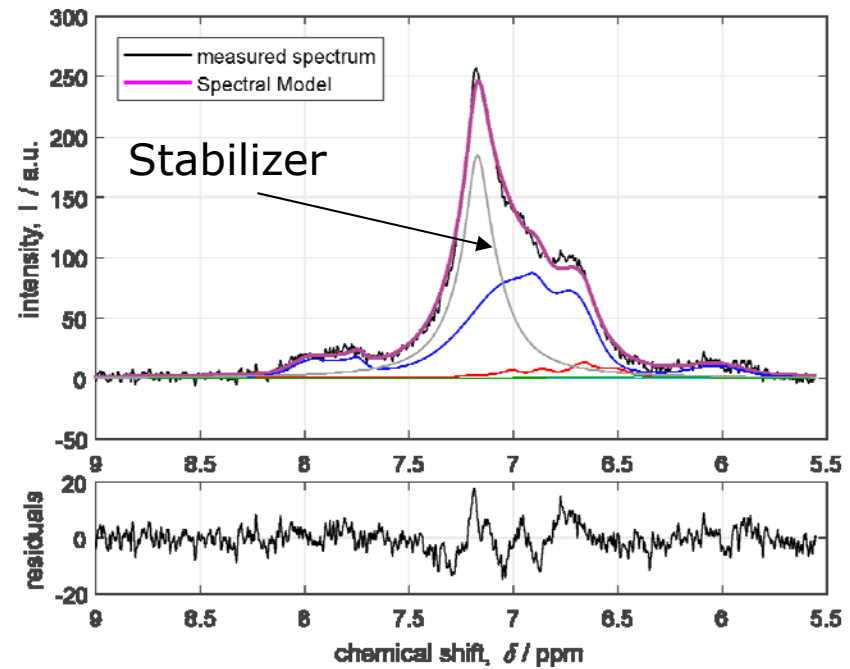
Challenges in Industrial Scale

Unknown Components

Model derived from Lab data



Model adaption to „process conditions“



THANK YOU!

Jürgen Kolz

Ullrich Koch

Juan Perlo

Mike Bernstein

Magritek

Magritek

Magritek

MestreLab

Harald Pape

Clemens Minnich

Dirk Engel

Alfons Steil

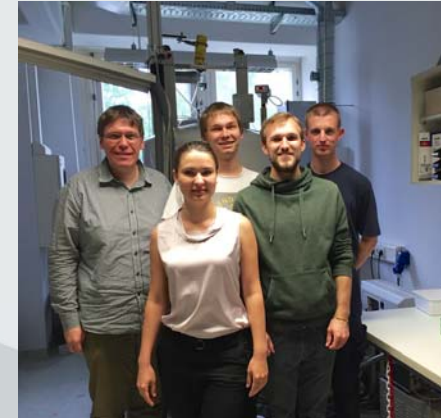
PTB

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

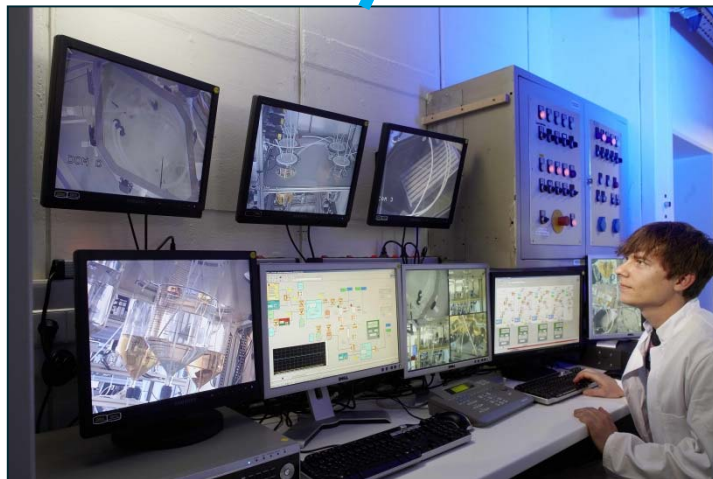
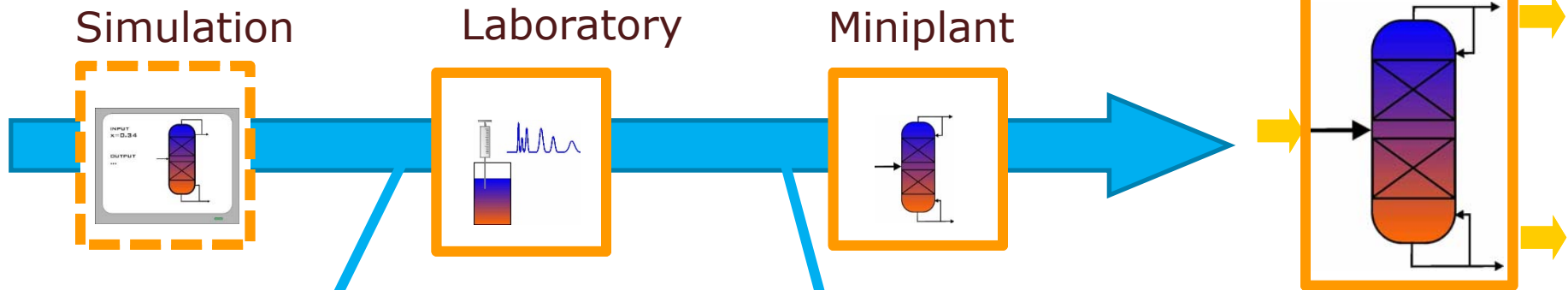
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Backup

Integrated Process Design and Intensified Processes

Current Trend: Hybrid Modular Plants



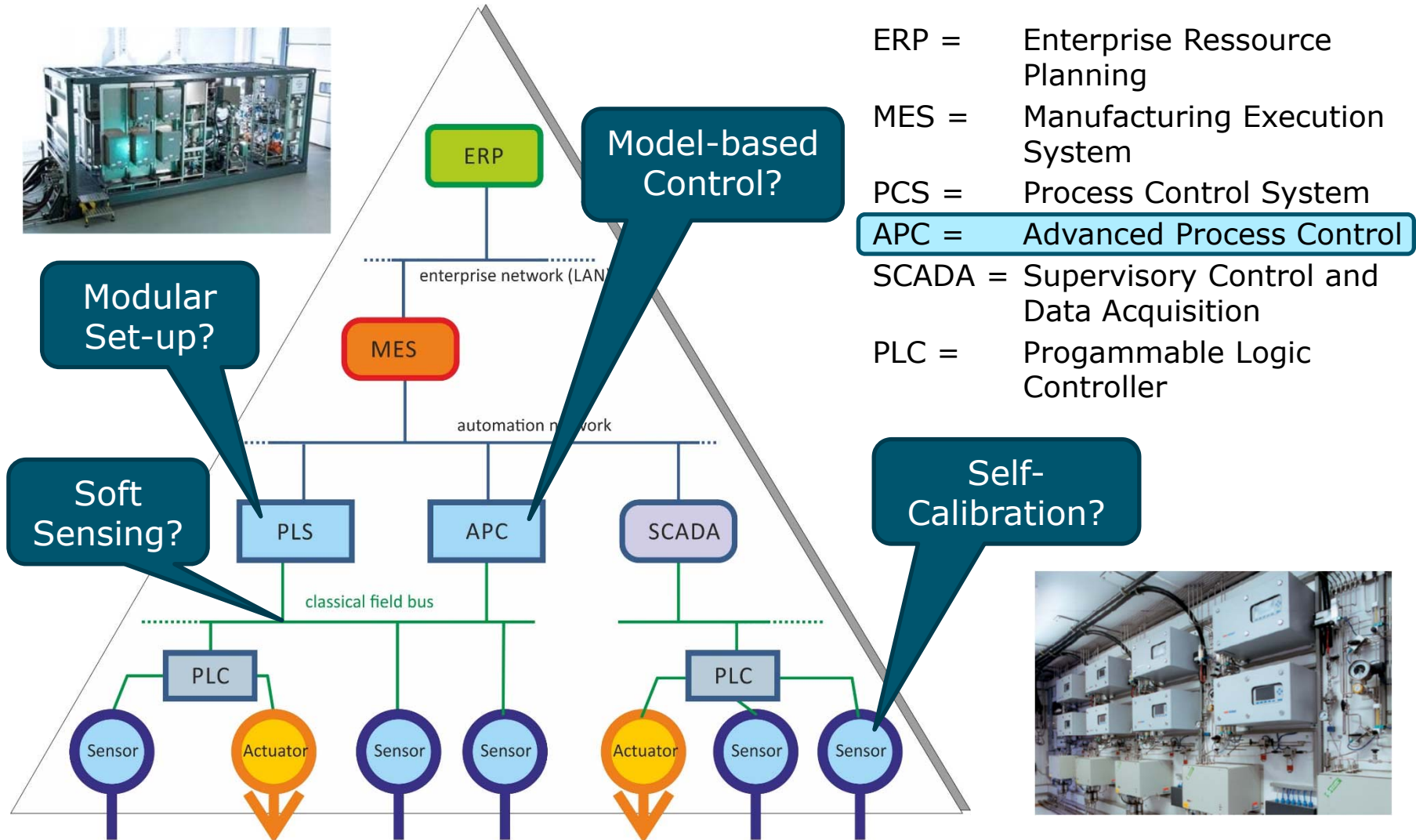
Micro Reaction Technology
(Example: Fraunhofer ICT, Pfinzta/D)



Modular Production
(Example: Foster Wheeler AG, Zug/CH)

Process Automation

The Classical Automation Pyramid → is Outdated!



- ERP = Enterprise Resource Planning
- MES = Manufacturing Execution System
- PCS = Process Control System
- APC = Advanced Process Control**
- SCADA = Supervisory Control and Data Acquisition
- PLC = Programmable Logic Controller



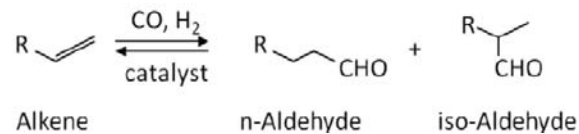
Process Analytical Technology for Intensified Processes



Examples from BAM

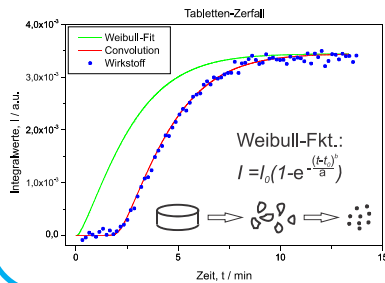


Catalysis:
Hydroformylations of C12-alkenes in micro emulsions

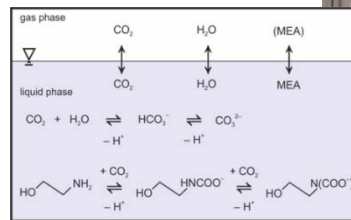


qNMR (Metrology):
Gases and condensed phases up to 1000 bar

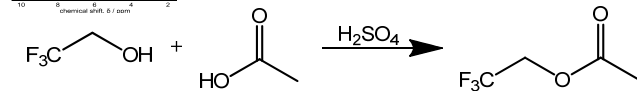
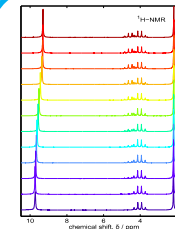
Pharmaceuticals:
Liberation kinetics



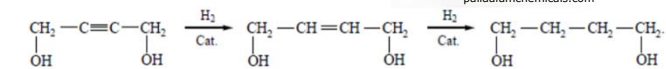
CO₂ scrubbing



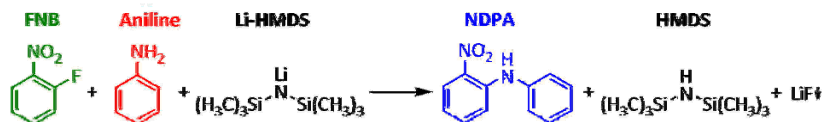
Method development:
Esterifications
(model reactions)



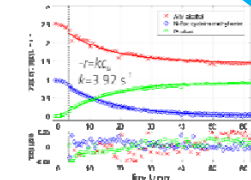
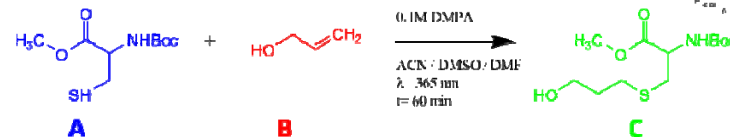
Catalysis:
Hydrogenations



Reaction Engineering:
Lithiation reactions



Reaction Engineering:
Photo reactions („click chemistry“)

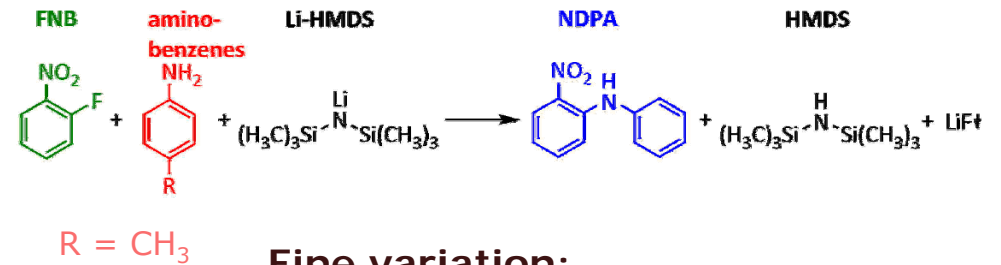


Experimental Design

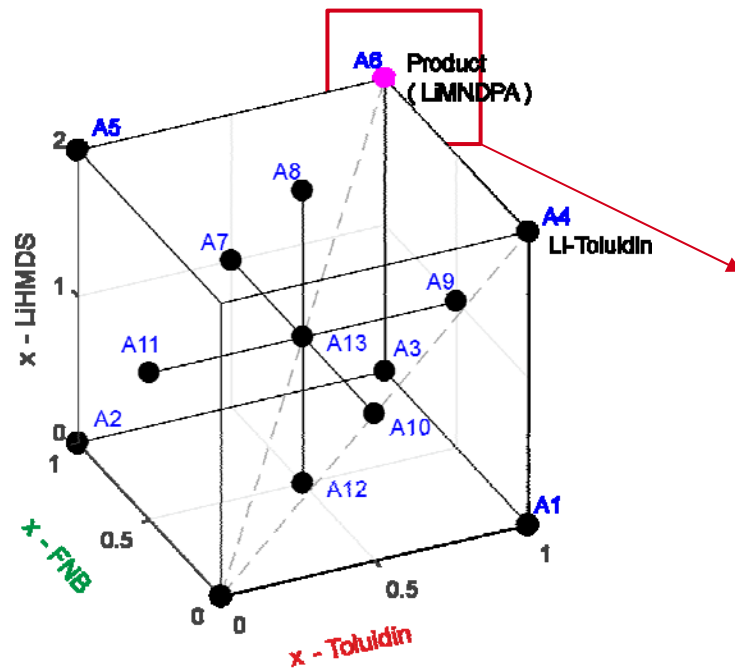
Continuous Lithiation Reaction Set-up at BAM

- Independent variation of flowrates / stoichiometric conditions

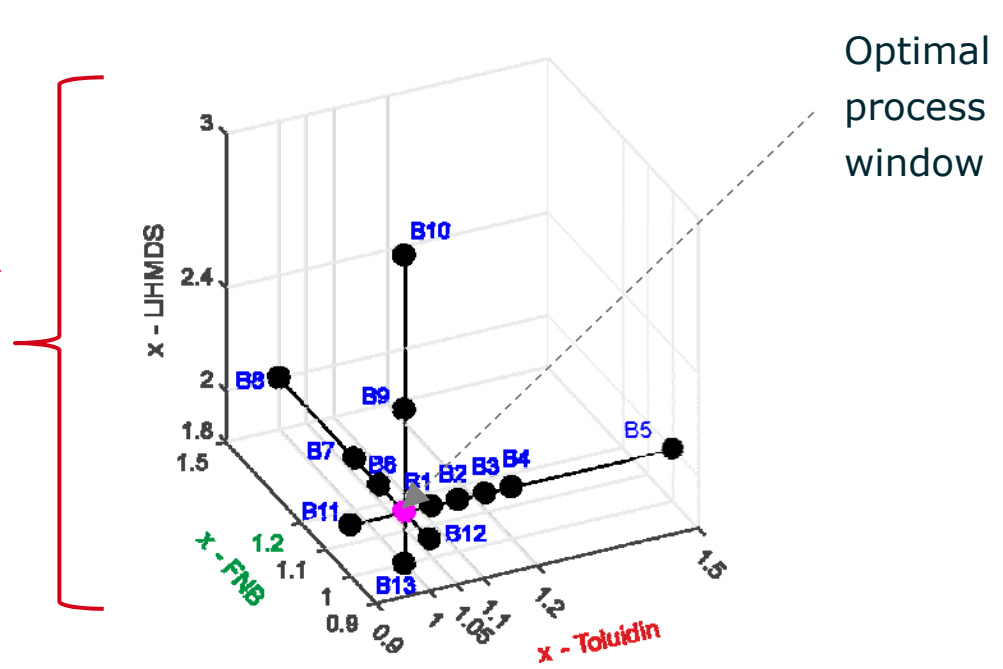
Reaction Scheme:



Coarse variation:



Fine variation:



Smart NMR Sensor Concept



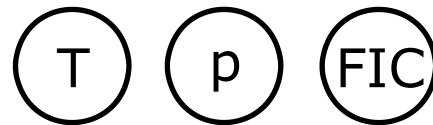
Module size:
850 x 570 x 570 mm



Safety devices

- Nitrogen purge control
- Leakage safeguard

Measuring Conditions



Data Acquisition

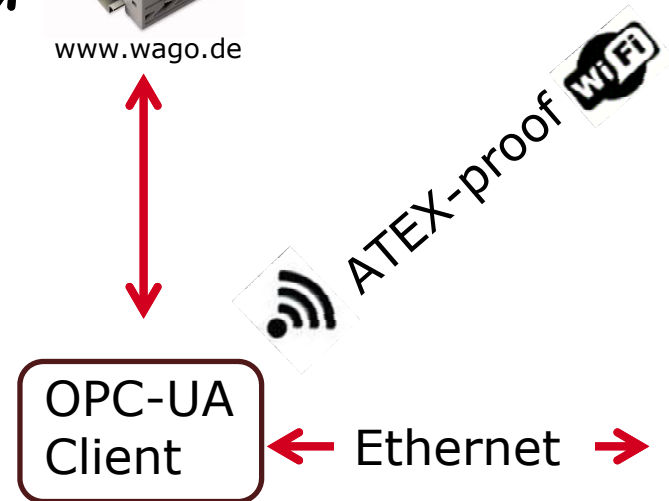
- Triggering
- Automated evaluation (Matlab)
- MySQL Database

Conventional
4–20 mA

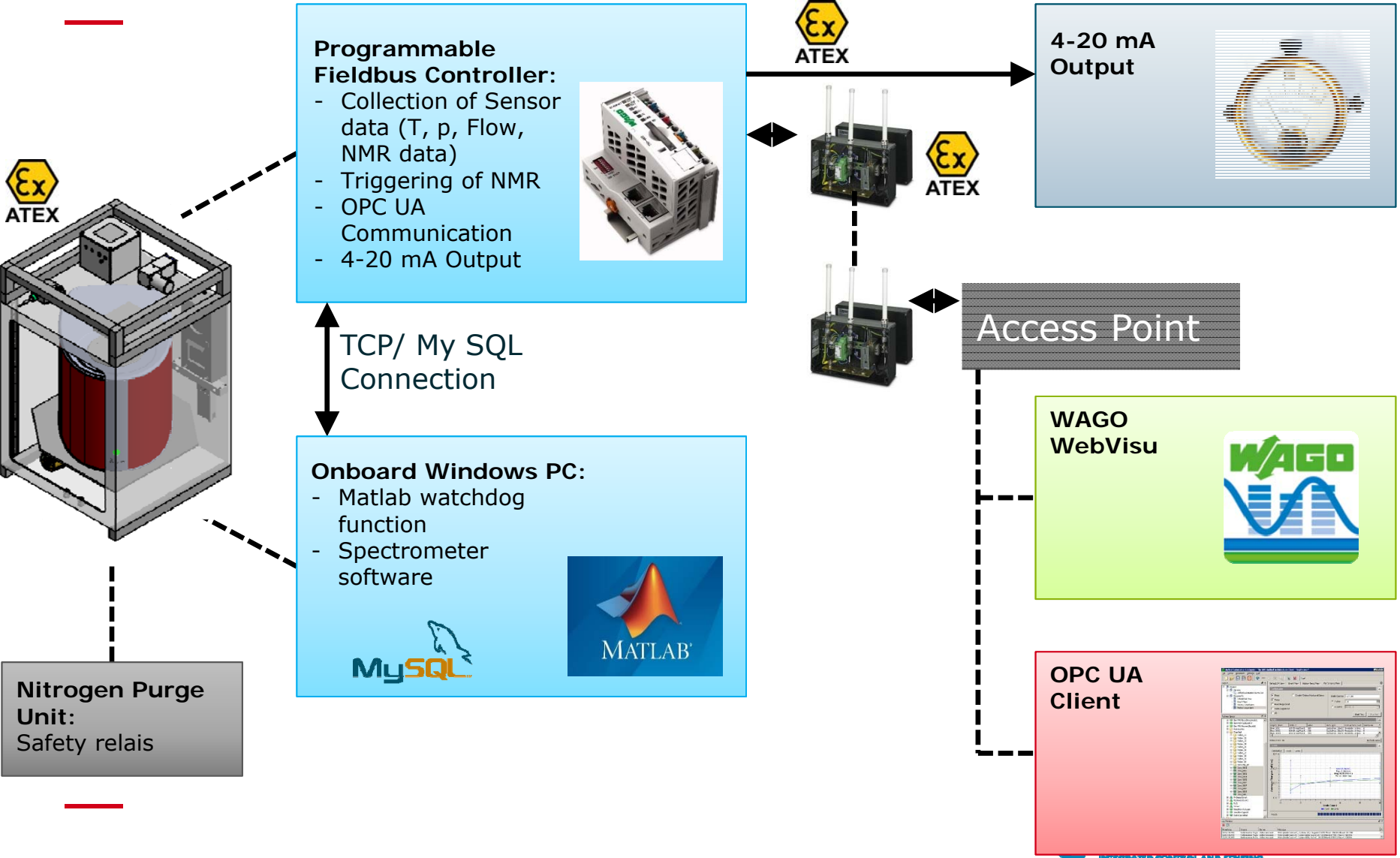


Programmable
Fieldbus
Controller

www.wago.de



Online NMR Module: Data flows



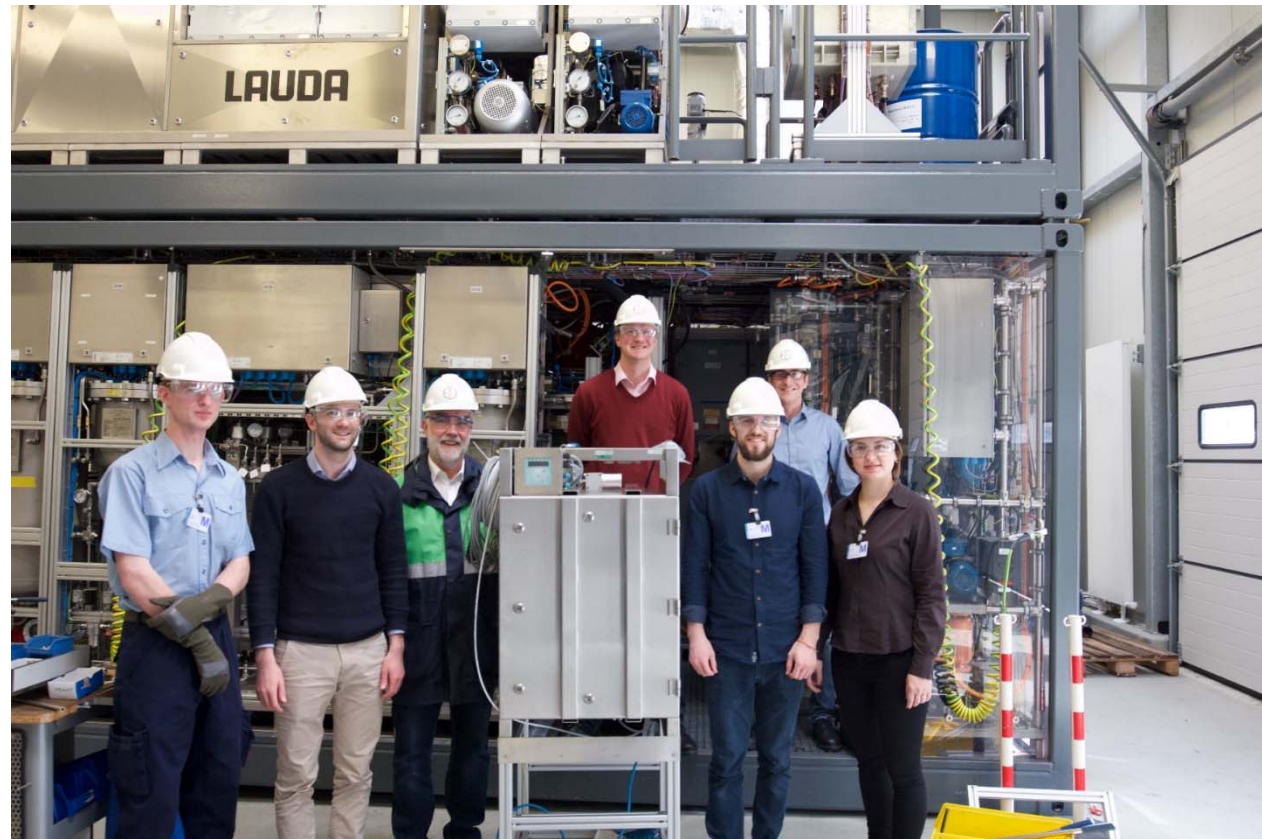
CONSENS: Deliverable of Fully Automated NMR Analyser



NMR Analyser at BAM

Set-up at INVITE, Leverkusen

Module size:
850 x 570 x 570 mm

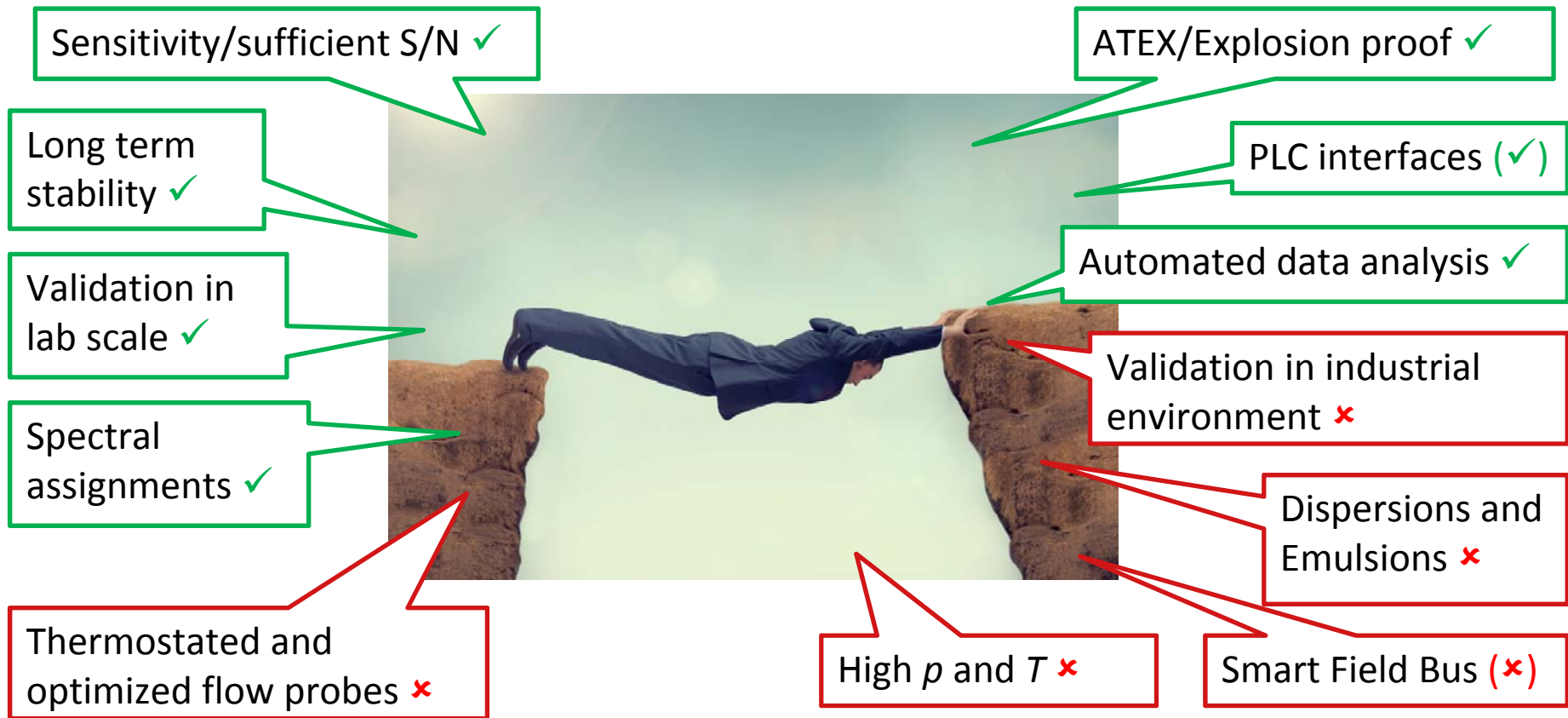


Closing the Gap ...

Key Attributes of Compact NMR Spectroscopy for Industrial Online Applications

Laboratory research

Chemical industry



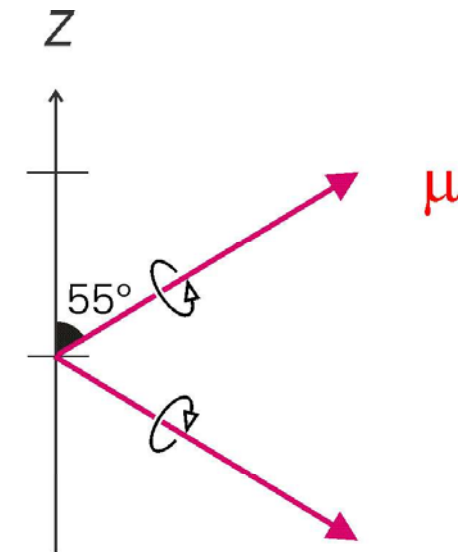
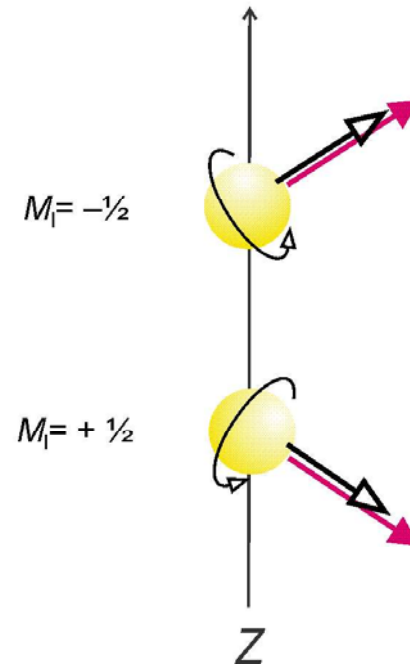
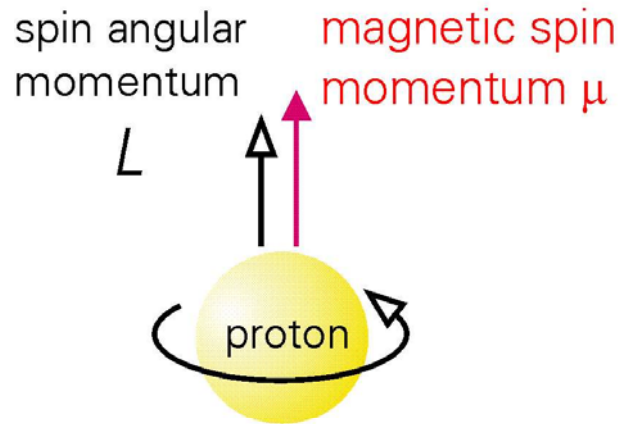
References



-
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 - 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.

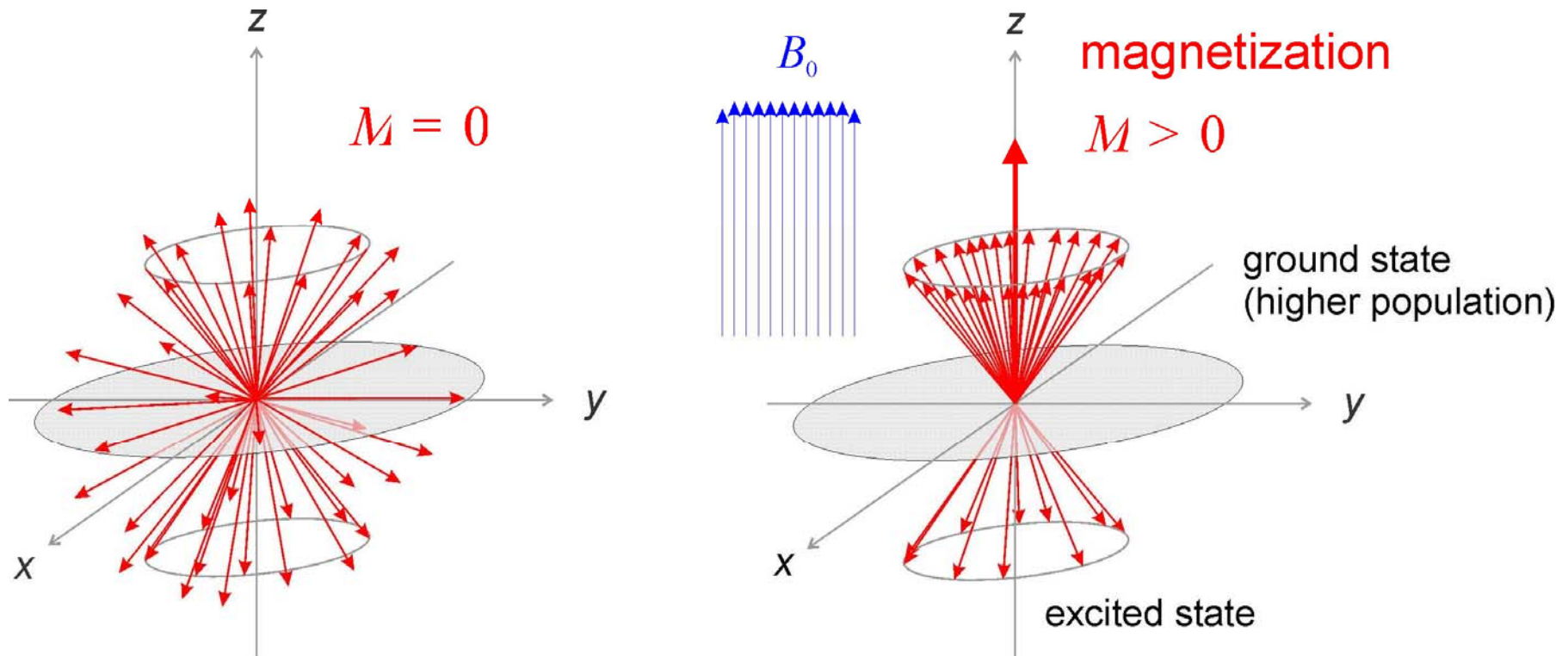
NMR-Grundlagen

Quantenmechanische Einschränkung

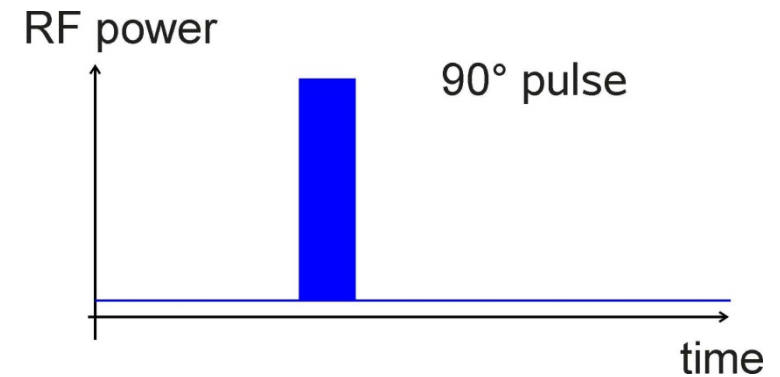
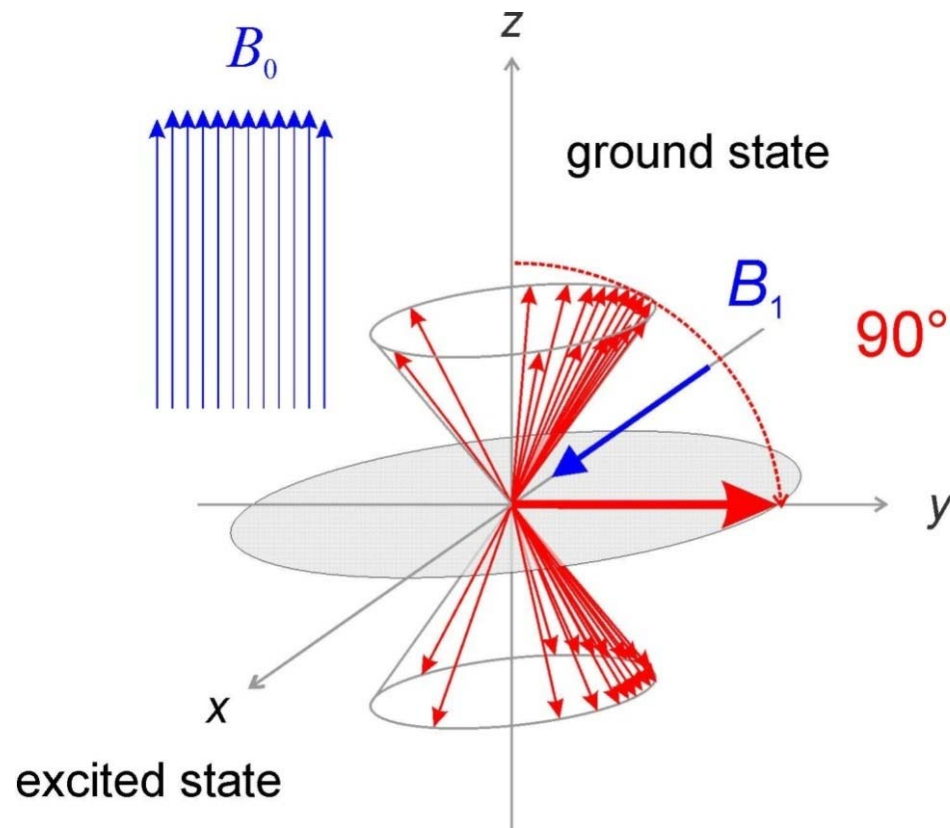


Quantenmechanische Einschränkung

Die Spins richten sich im Magnetfeld auf Kegelmänteln aus



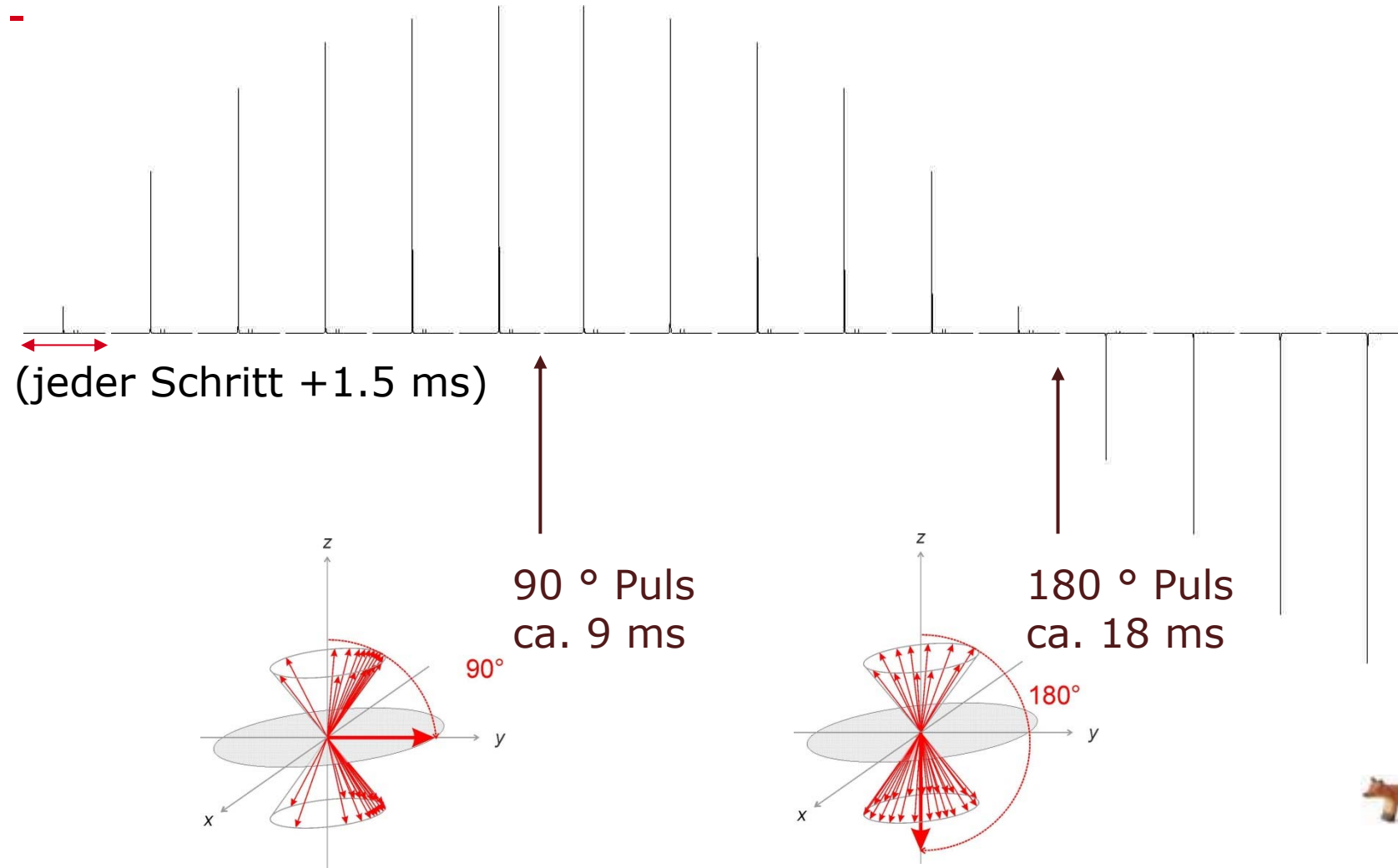
90°-Anregung mit Radiofrequenzpuls



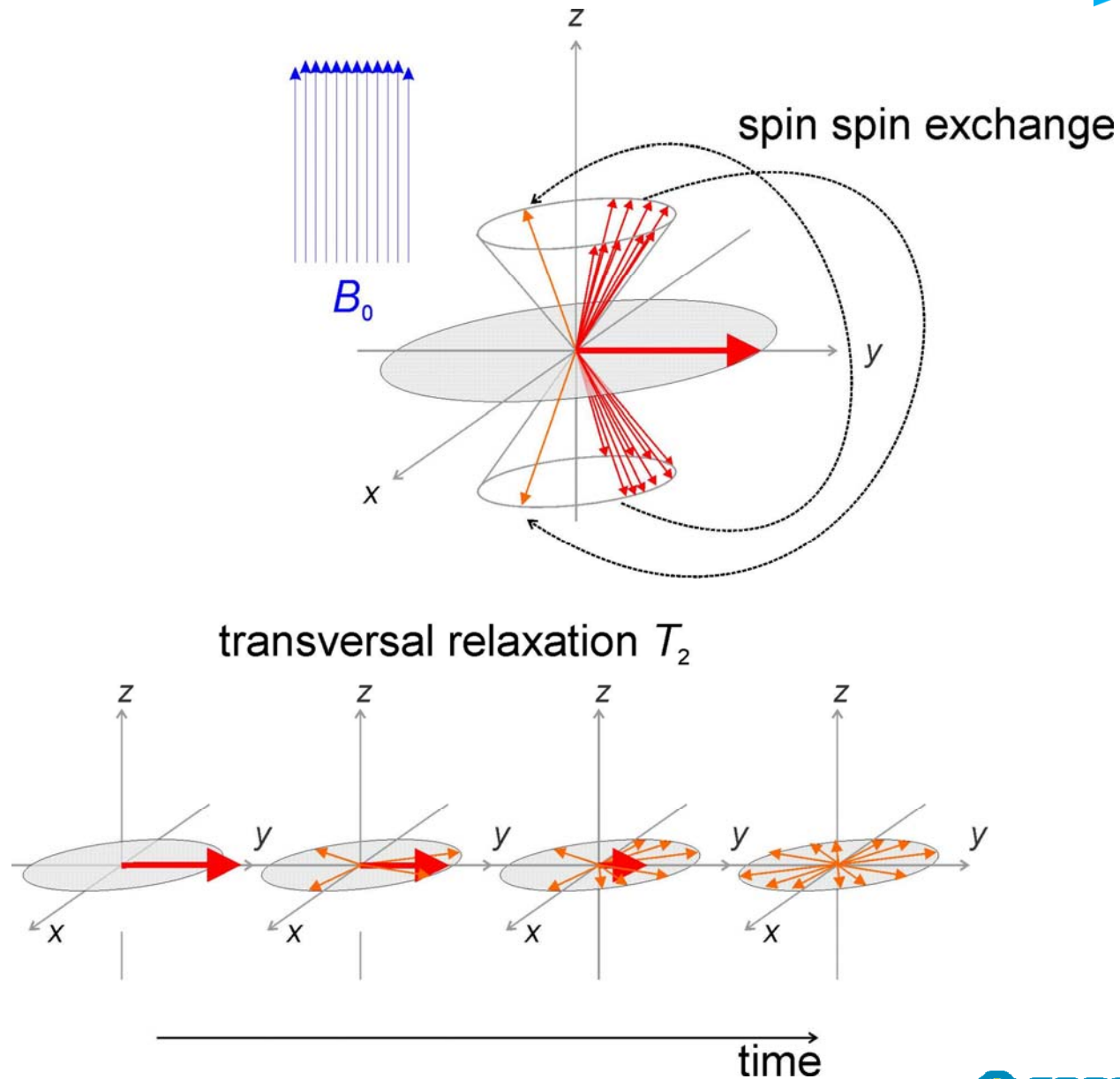
magnetization M shows into x-y-plane



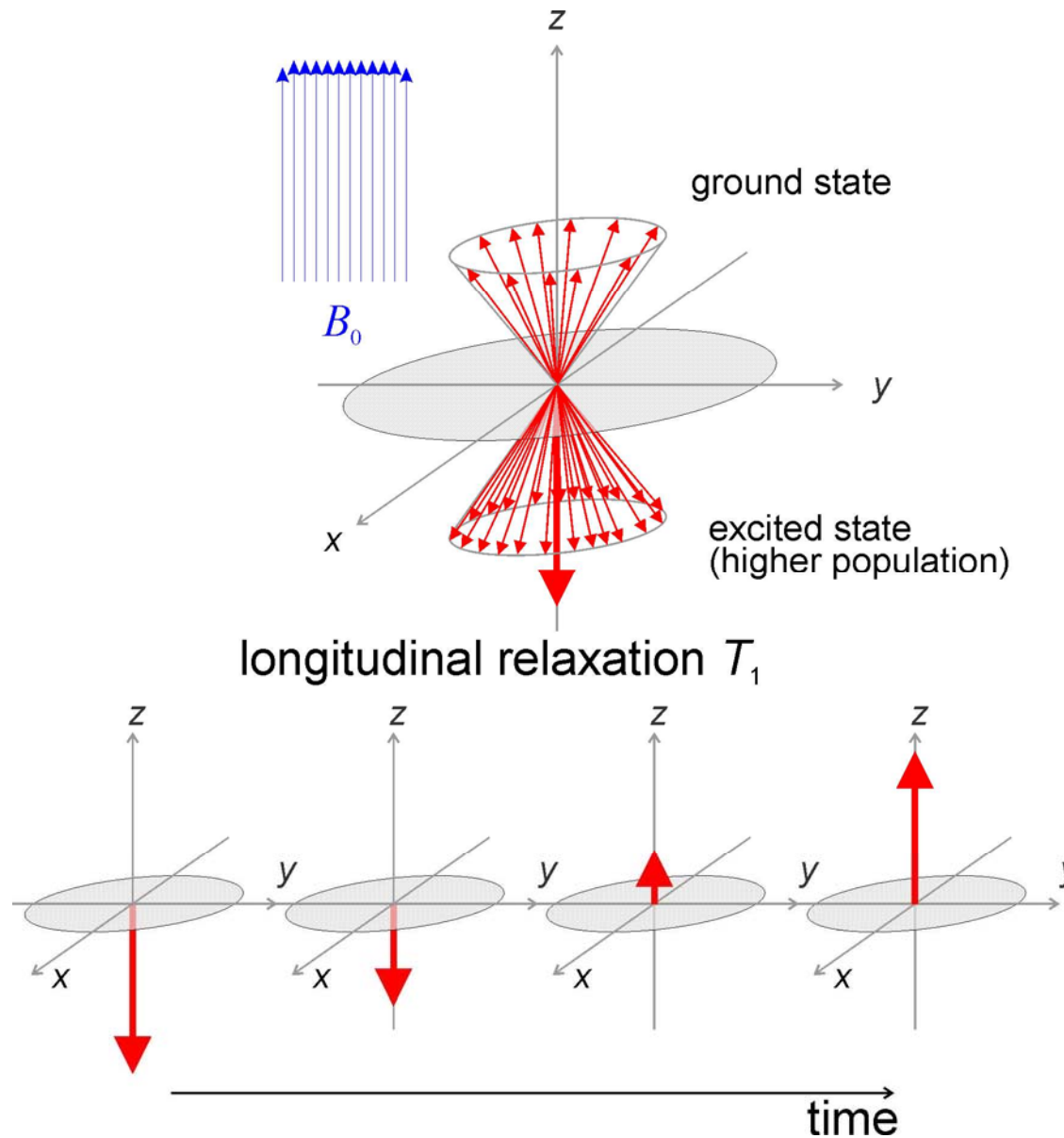
Variation der Pulslänge (Kalibrierung)



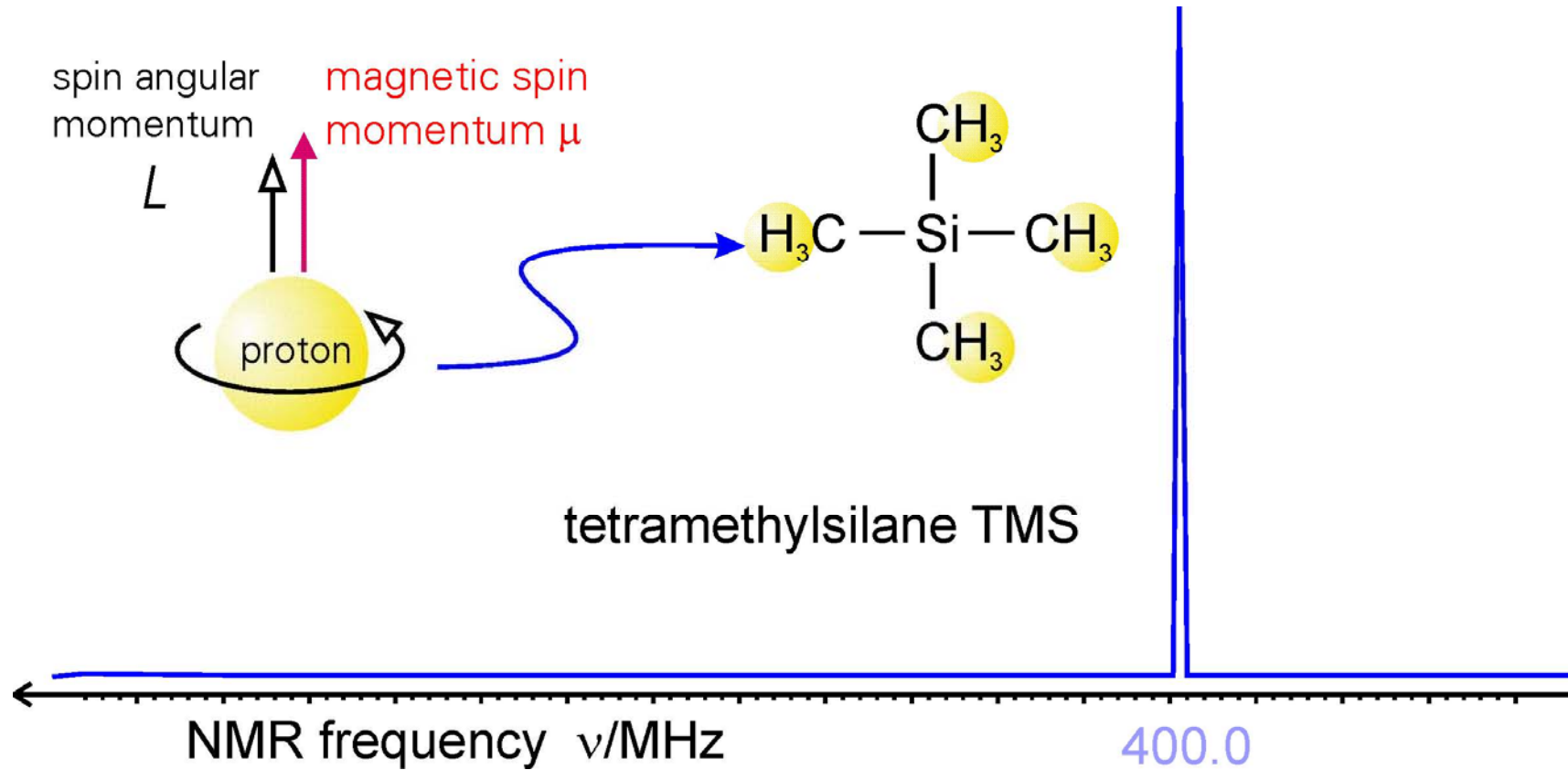
Relaxation



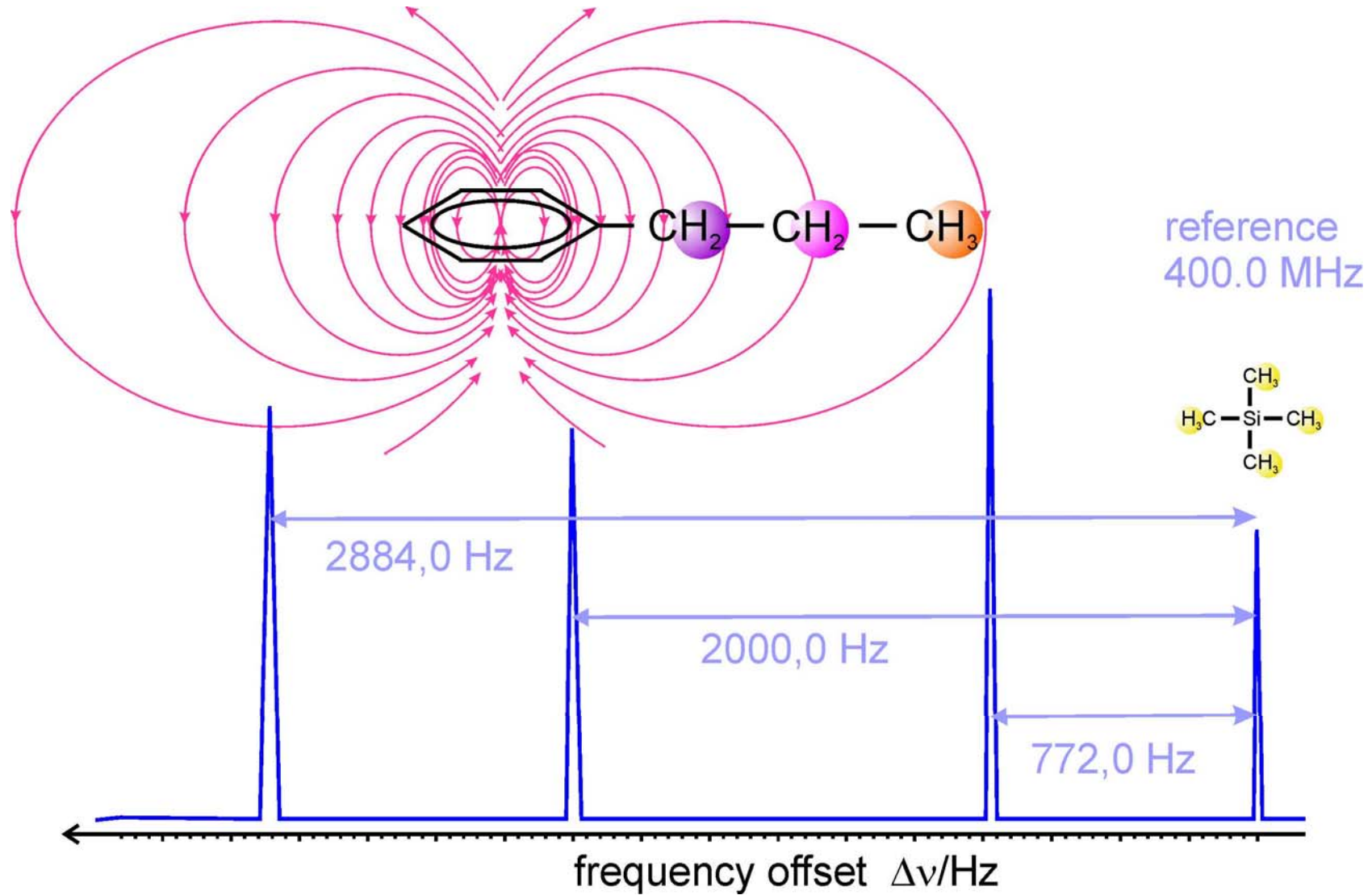
Relaxation



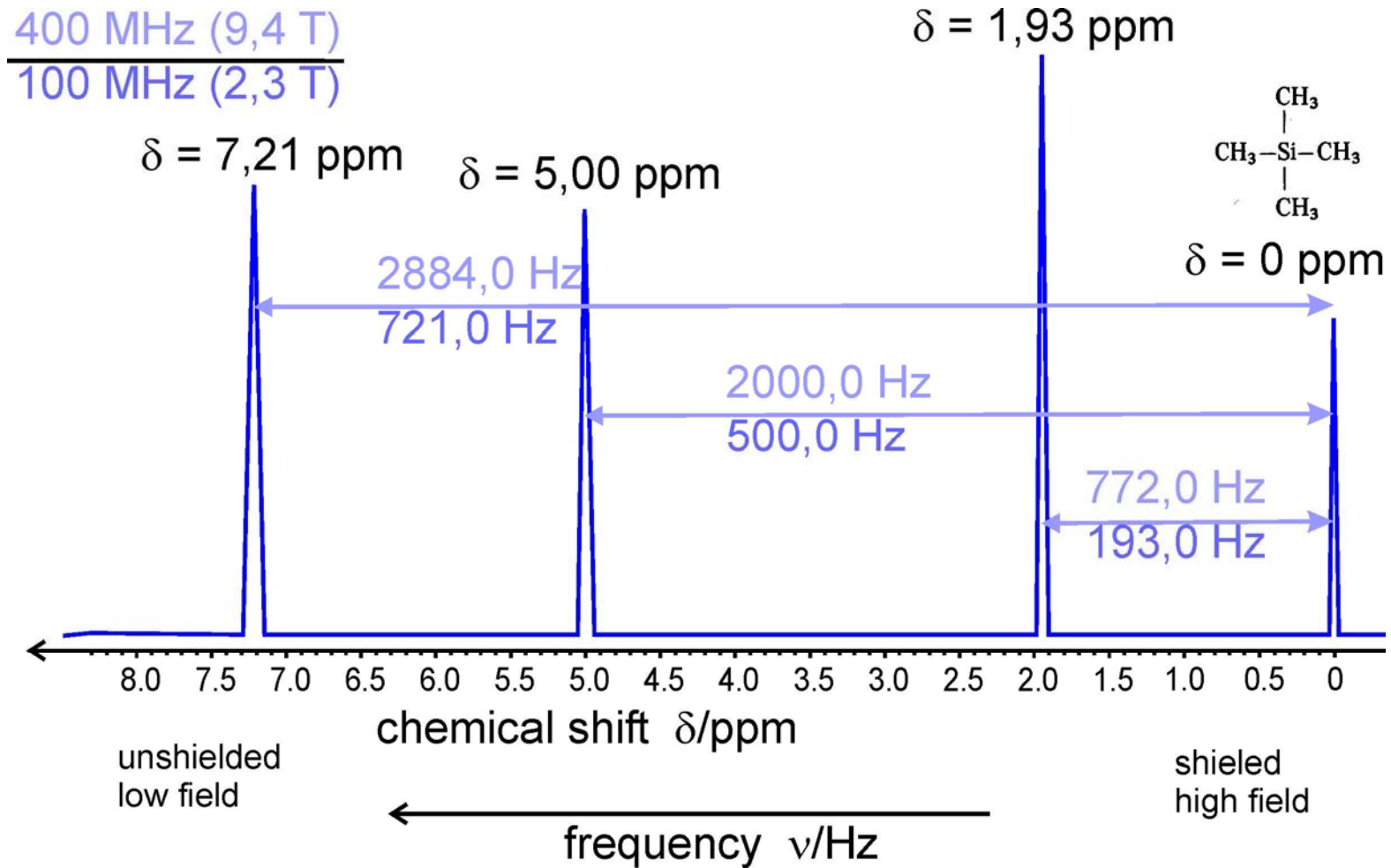
Chemische Verschiebung



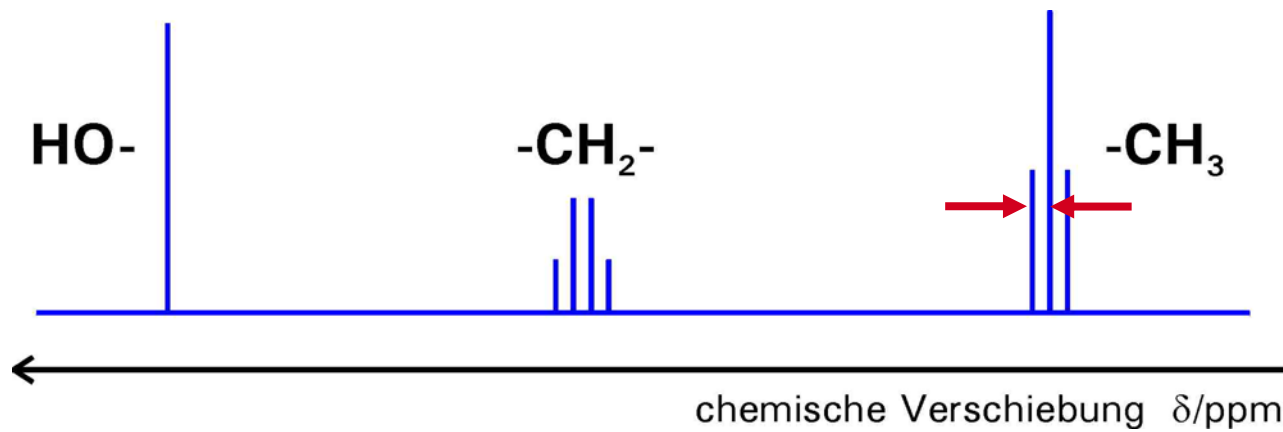
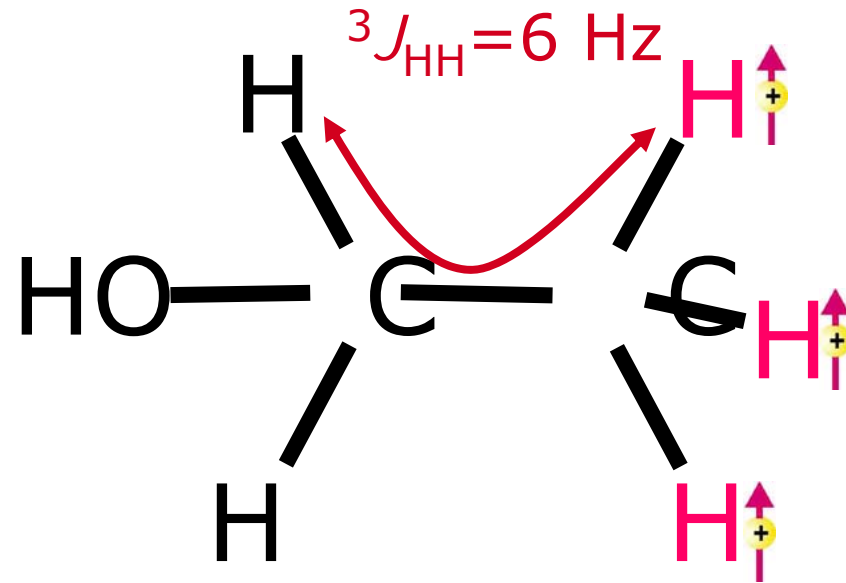
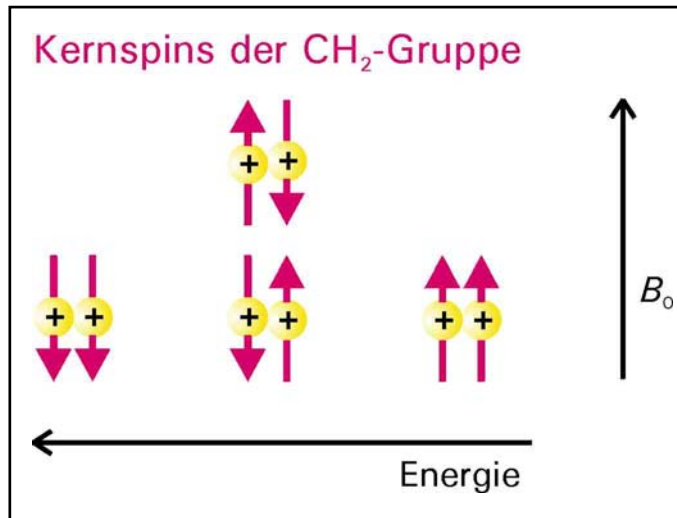
Chemische Verschiebung



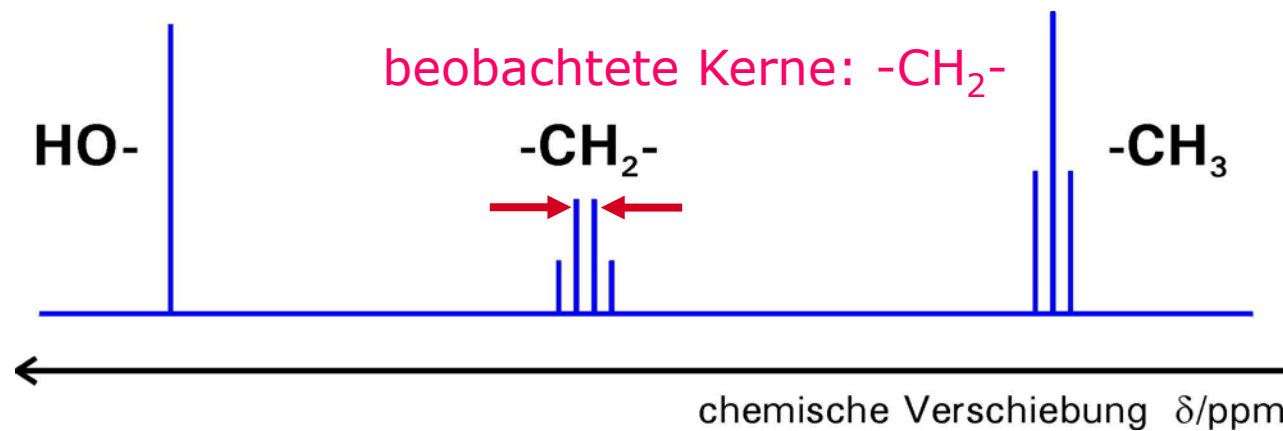
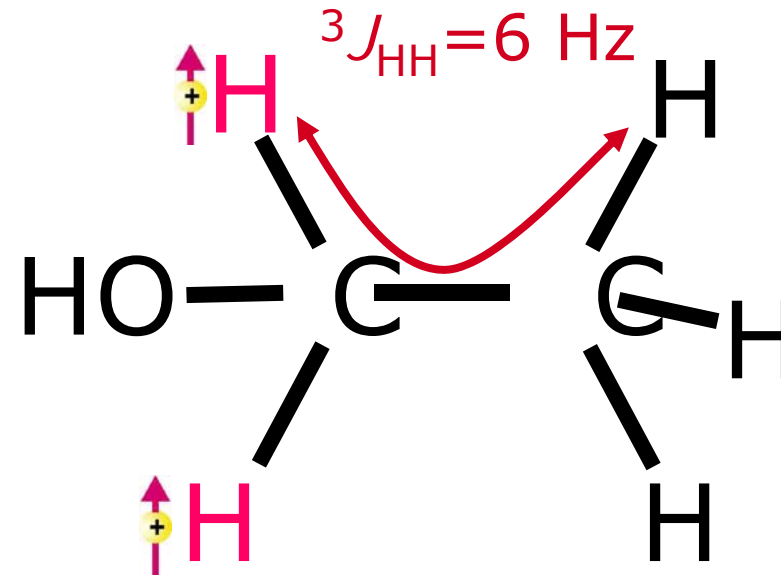
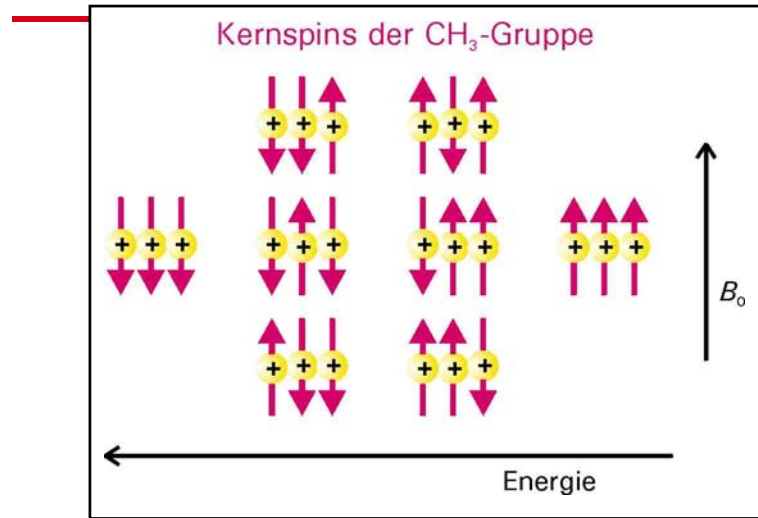
Chemische Verschiebung d-Skala



^1H -NMR-Spektrum von Ethanol



^1H -NMR-Spektrum von Ethanol



^1H -NMR-Spektrum von Ethanol

