

23.09.2015

AUTOMATED DATA EVALUATION AND MODELING OF SIMULTANEOUS ^{19}F - ^1H BENCHTOP NMR SPECTRA FOR ONLINE REACTION MONITORING

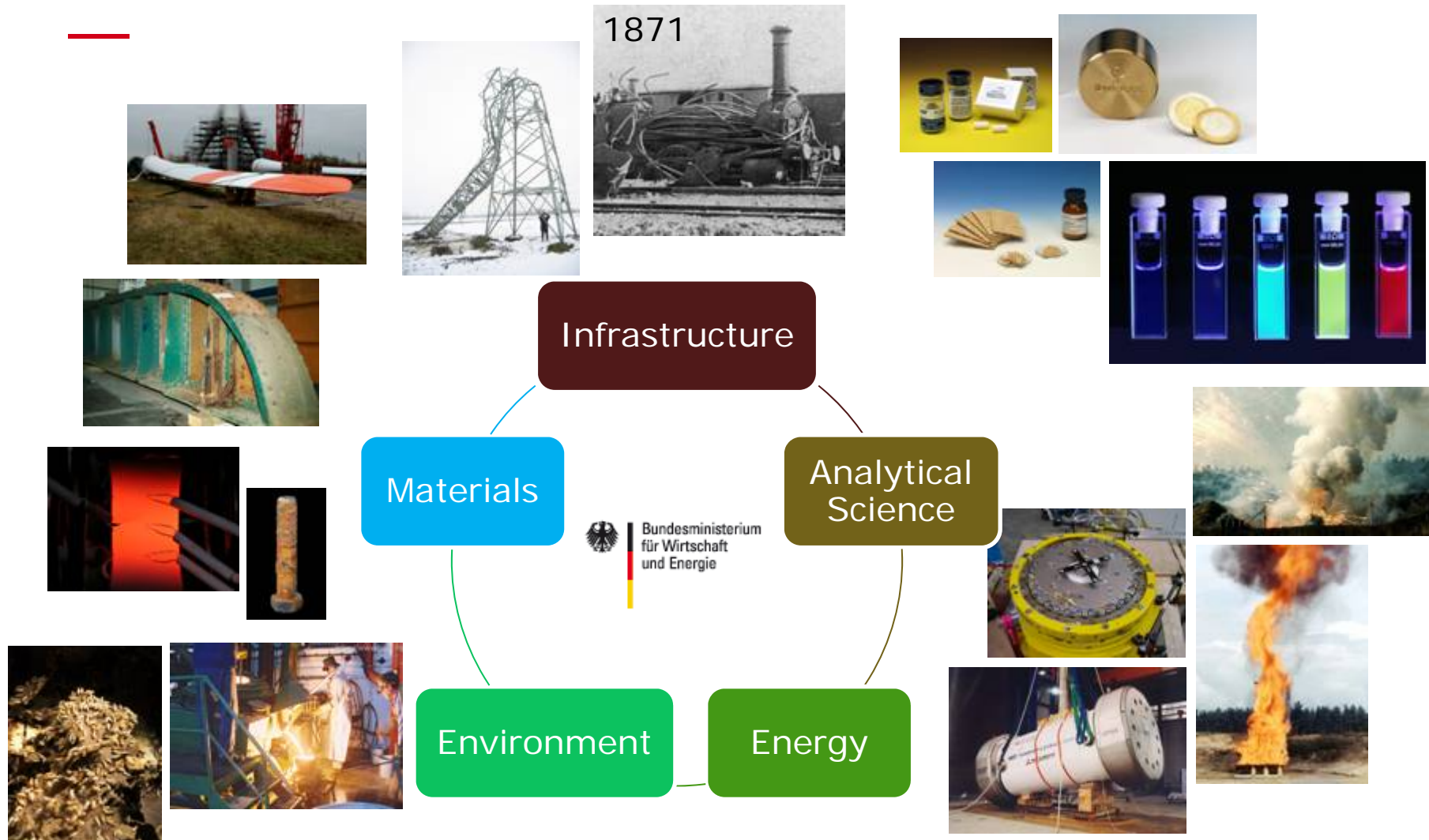
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Andrea Paul¹, Dirk Engel⁵, Matthias Kraume⁴, Gisela Guthausen³

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2. École Nationale Supérieure de Chimie de Lille, Villeneuve D'ascq Cedex, France
3. Pro2NMR, Institute of Mechanical Process Engineering and Mechanics and Institute of Biological Interfaces, KIT, Karlsruhe, Germany
4. Department of Chemical Engineering, Technische Universität Berlin, Berlin, Germany
5. S-PACT GmbH, Aachen, Germany

Safety in Technology and Chemistry

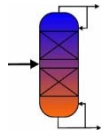


Our Key Areas



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

Workflow

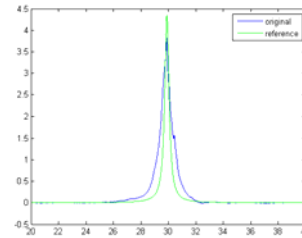


Processes

- Process Development
- Hybrid Plants
- Some Reactions

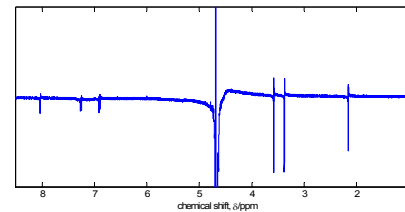
Instrument

- Stability
- Line Shape („enhancement“)
- Standards



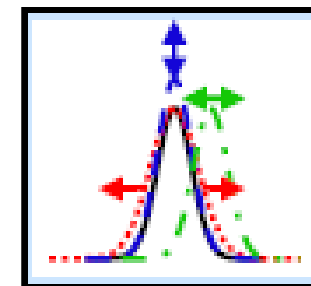
Data preparation

- Phasing

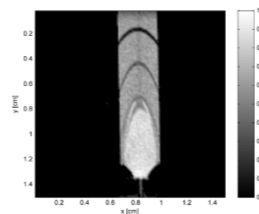
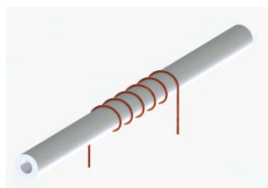
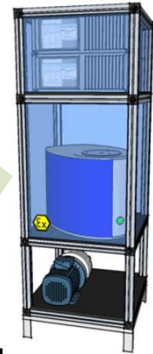


Data Modeling

- Direct Integration
- Line fit
- Indirect Hard Modeling
- Indirect Hard Modeling II
- PLS-R

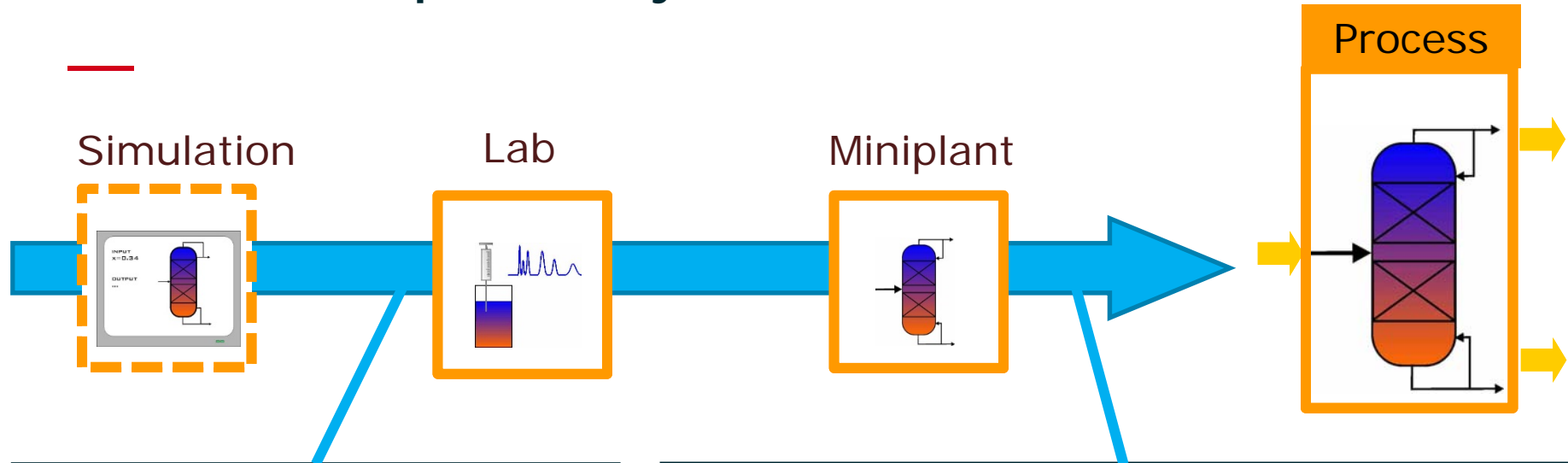


- PLC control
- ATEX



Process Development

Current Developments: Hybrid Plants



Micro reaction technology
(Example: Fraunhofer ICT, Pfinztal/D)



Container Concept
(Example: INVITE, Leverkusen/D)

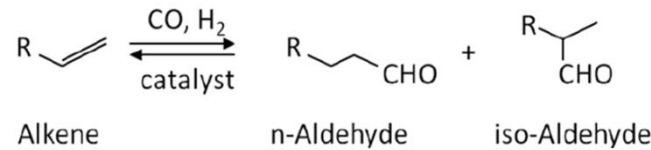
Process Understanding



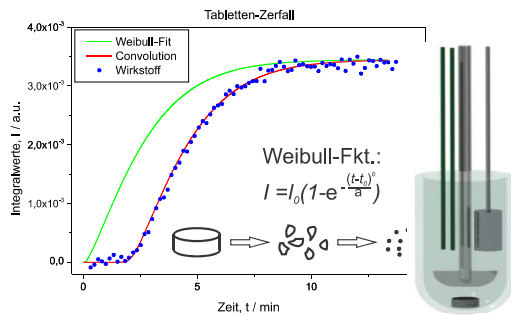
Examples for online NMR reaction monitoring



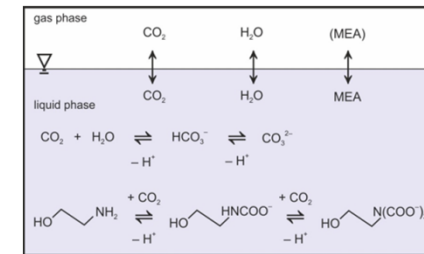
Catalysis:
Hydroformylation
of C12-alkenes



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

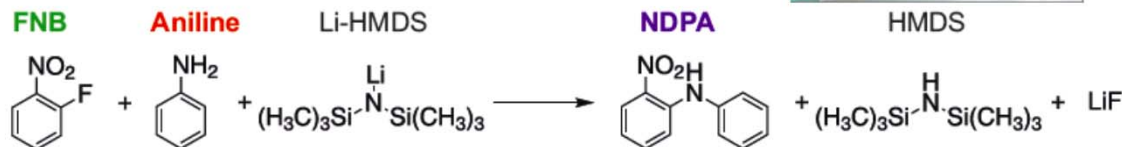


Method development:
Esterification
(model reactions)

$$F_3C-CH_2-OH + HO-C(=O)-CH_3 \xrightarrow{H_2SO_4} F_3C-CH_2-O-C(=O)-CH_3$$


Pharmaceuticals:
Liberation kinetics

Reaction Engineering:
Lithiation reaction



CO₂ scrubbing

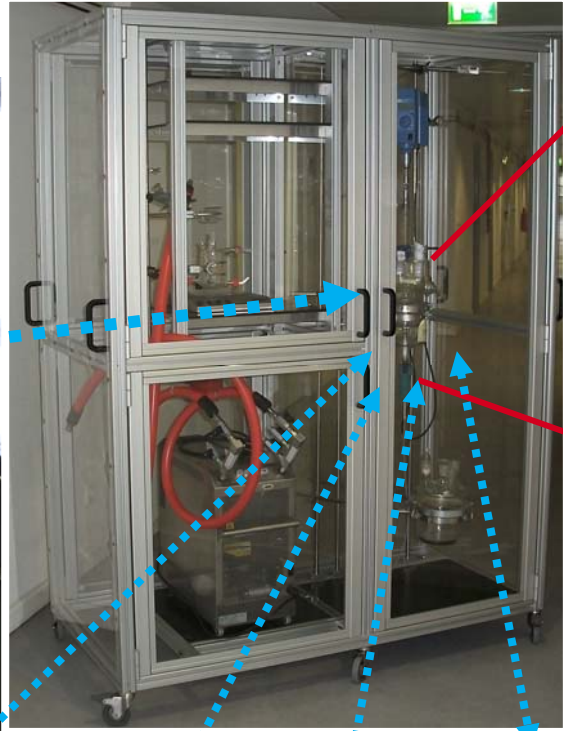


Online NMR Spectroscopy as Reference

Hyphenation to reactors and devices



500 MHz
Online NMR



reactors

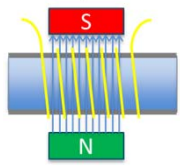


Complex reacting multicomponent mixtures

- quantitative information
- qualitative („chemical“) information
- highest possible dispersion

Direct coupling to reactors

- fast and direct sample transfer
- automation
- extended pressure range



Process NMR



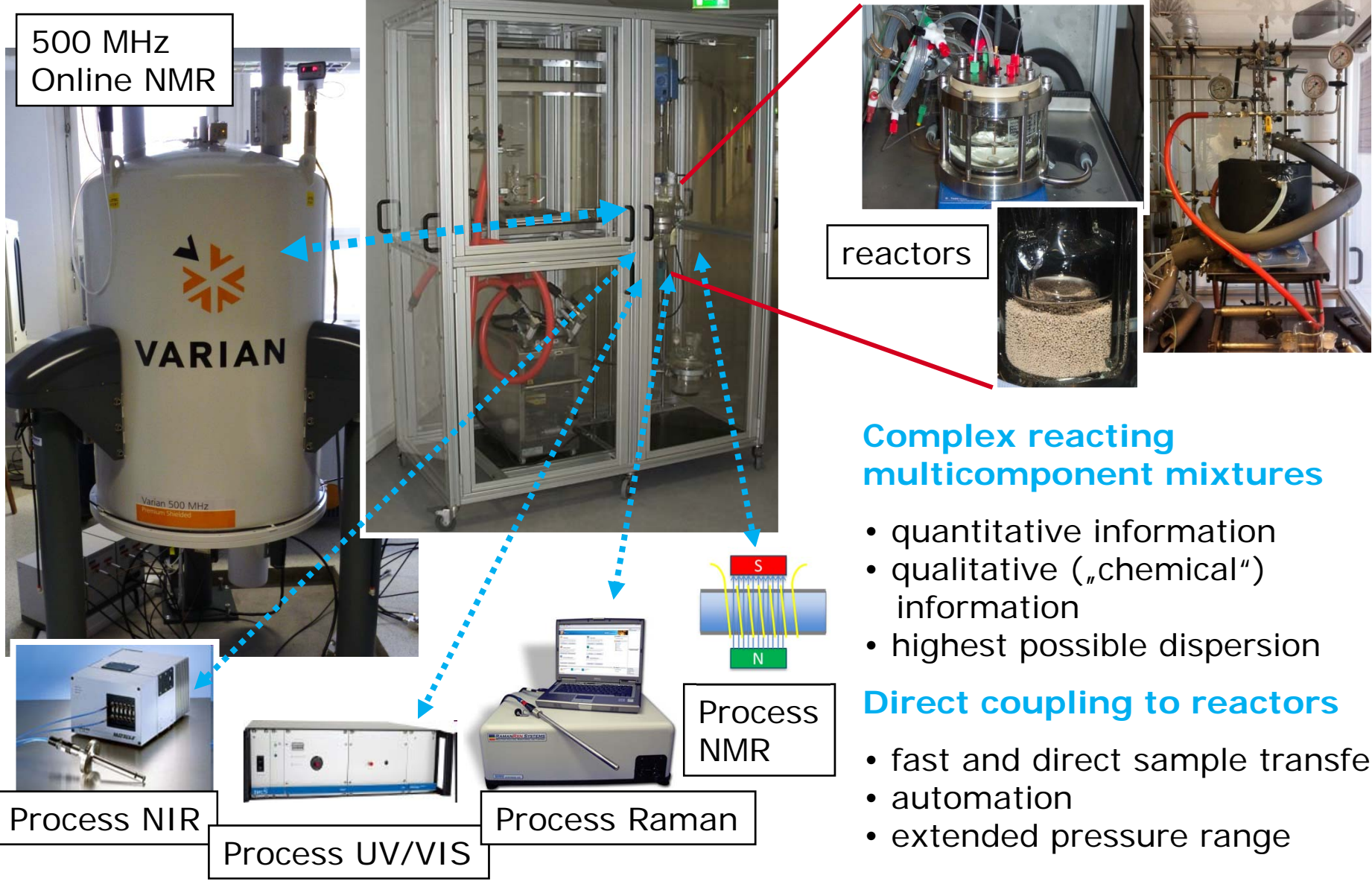
Process NIR



Process UV/VIS

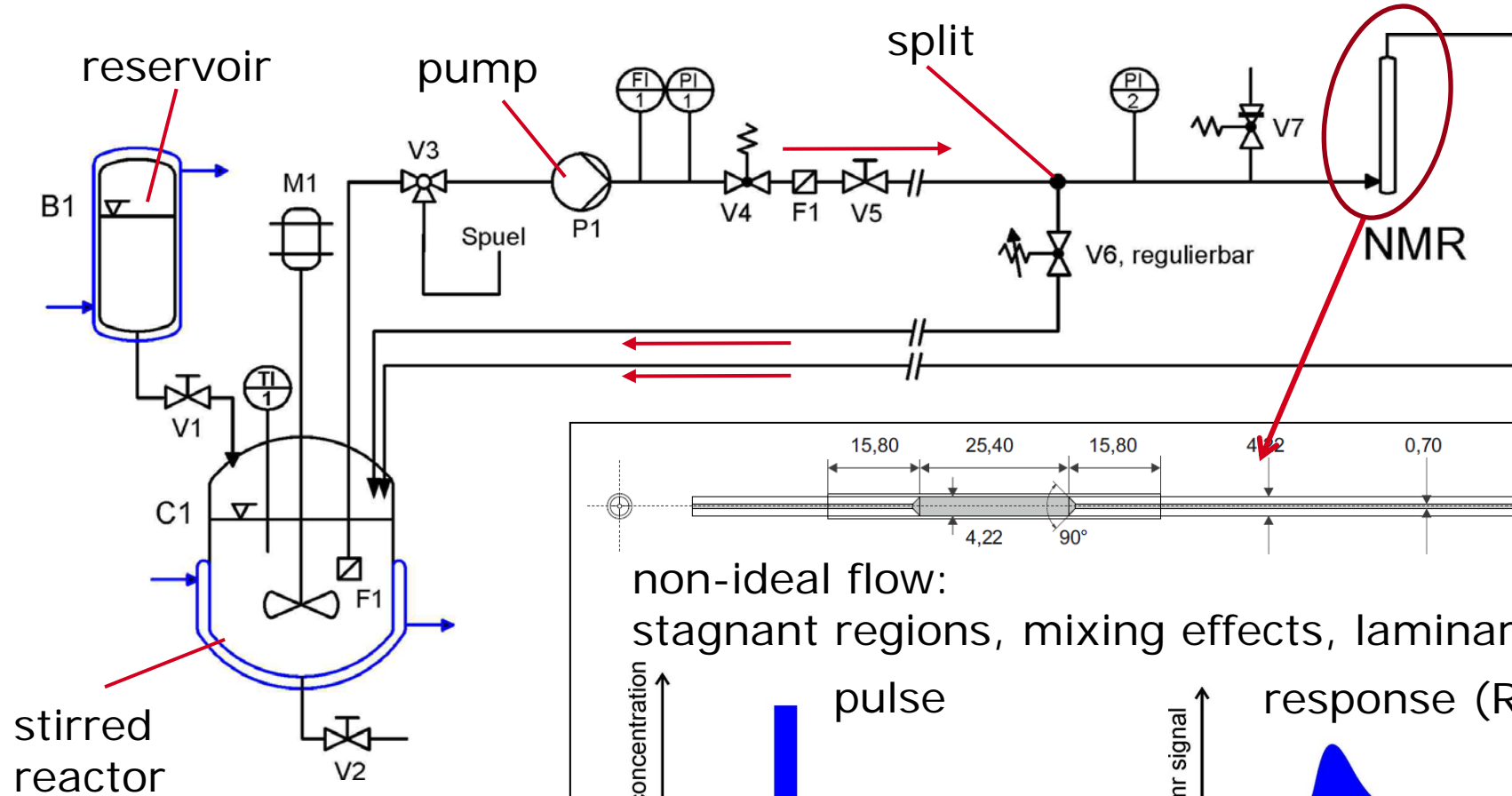


Process Raman



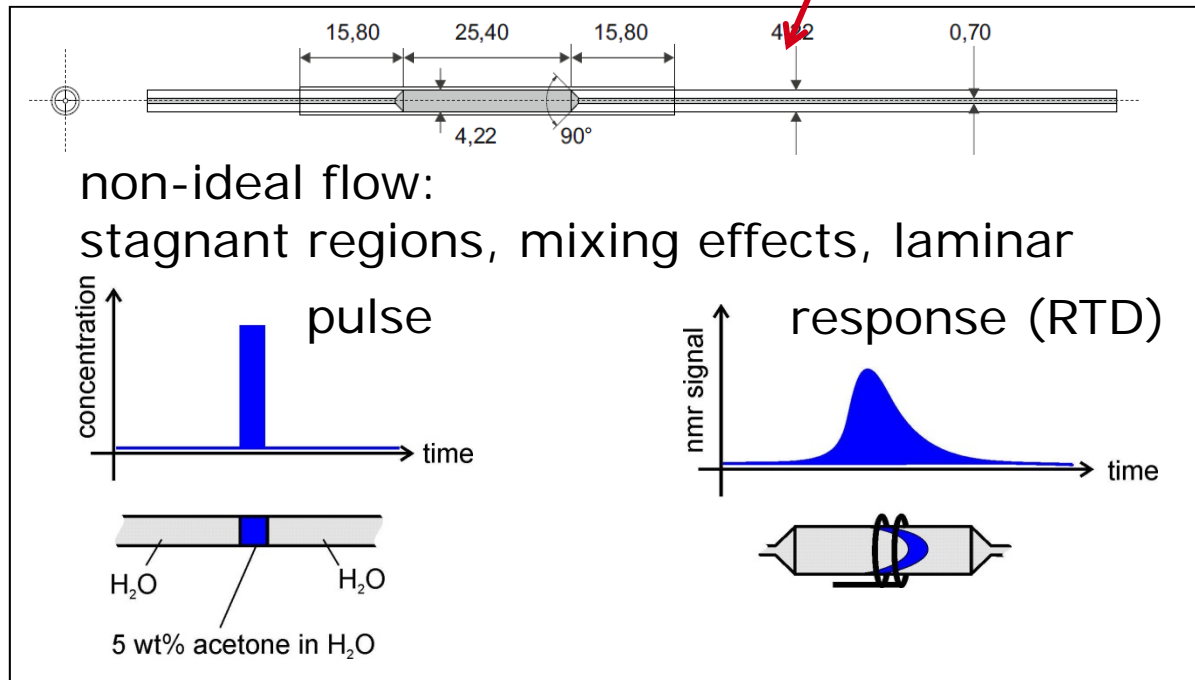
Online NMR Spectroscopy

Flow scheme, thermostated bypass



Tubing:

- PEEK 0.25–0.75 mm ID
- liquid thermostated



Online NMR Spectroscopy

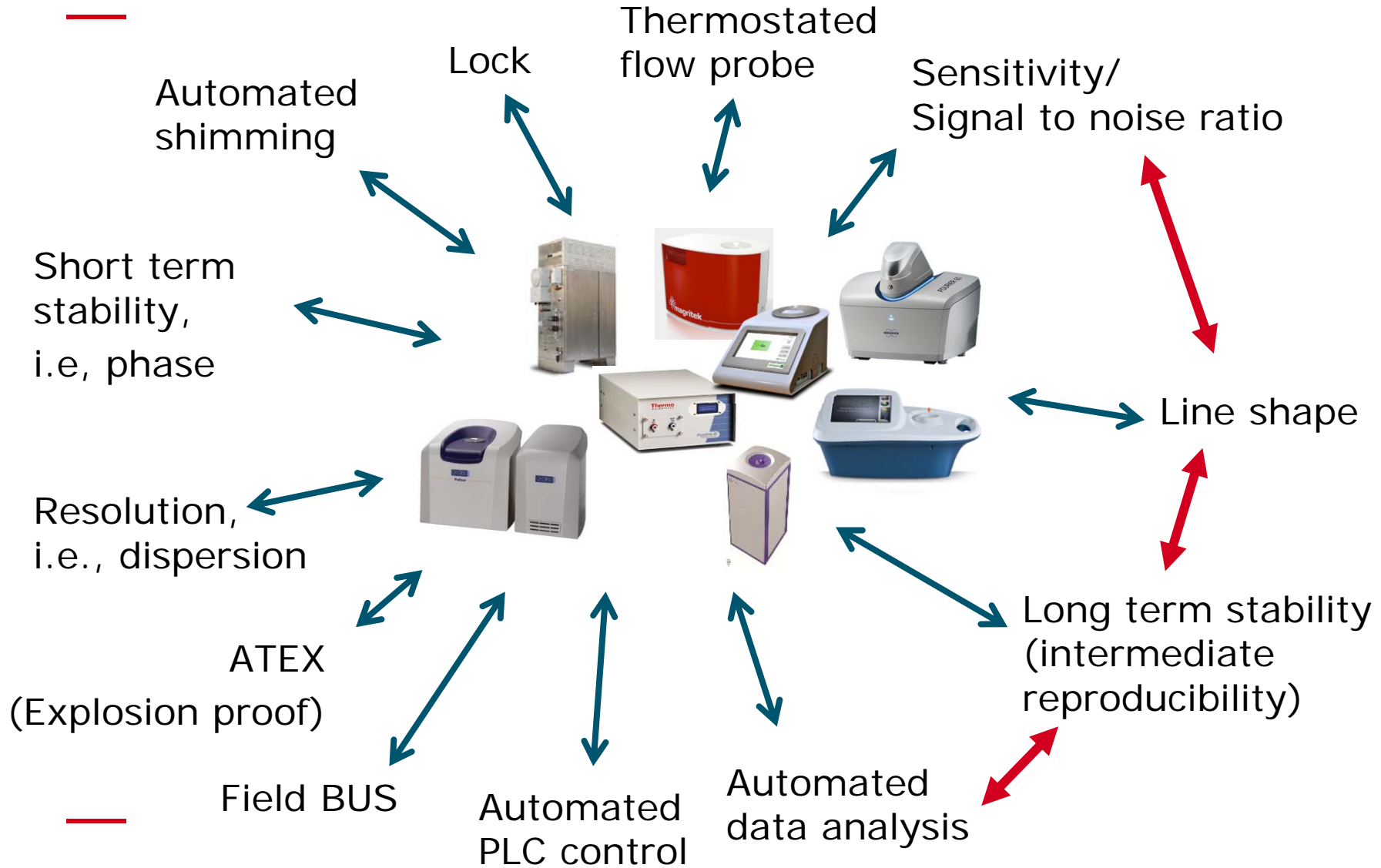
Hyphenation of process spectrometers to reactors and devices



Benchtop NMR Instruments



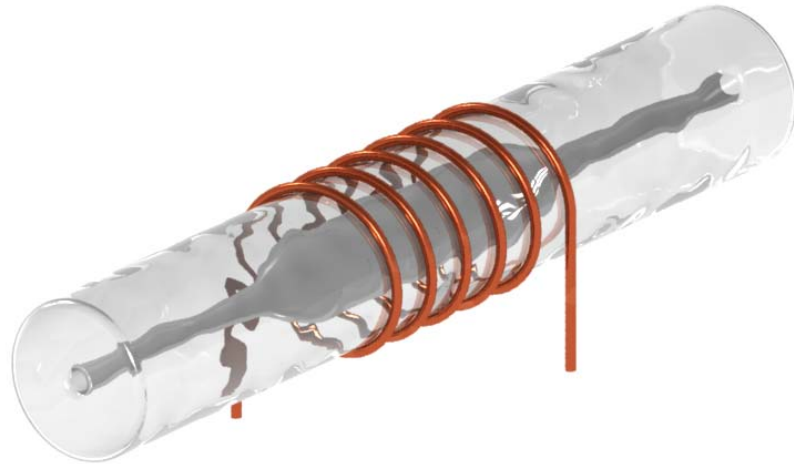
Key issues for industrial online applications



Concepts for flow cells

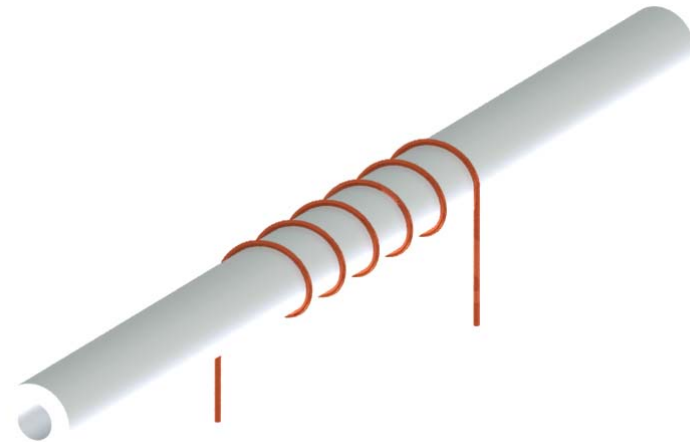


Glas Flow cell



- 😊 optimized geometry
- 😊 chemical and thermal resistance
- 😊 thermally decoupled coil
- 😞 low mechanical resistance
- 😞 junctions glass to tubing

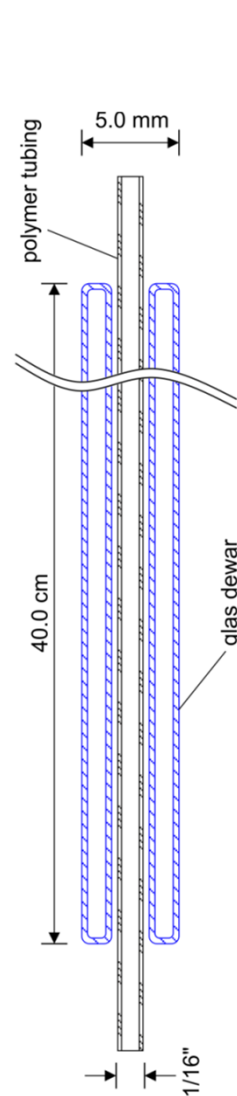
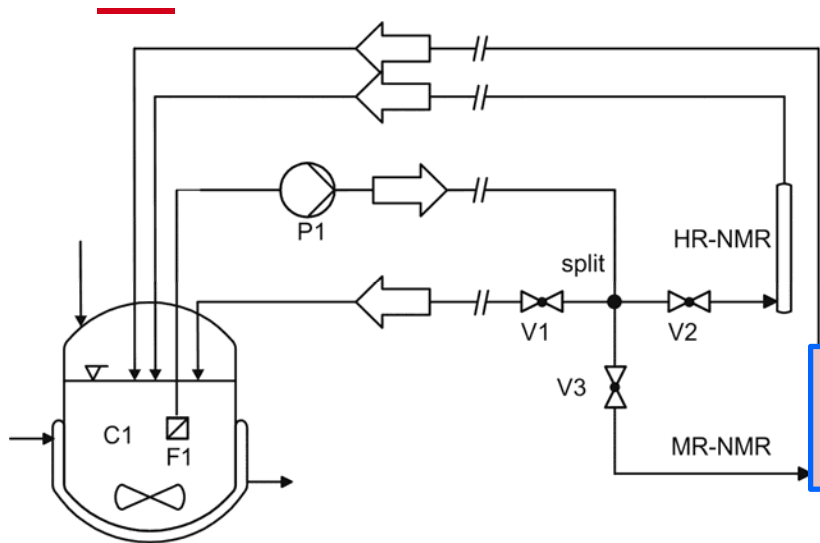
Tubing



- 😊 commercially available
- 😊 industrial manufacture
- 😞 geometry not optimal

Simple Dewar Flow Cell

Concept of a Flow Cell 1/16" PFA Tubing (ID 1 mm)



Advantages

- 😊 durable polymer tubing
- 😊 thermally decoupled

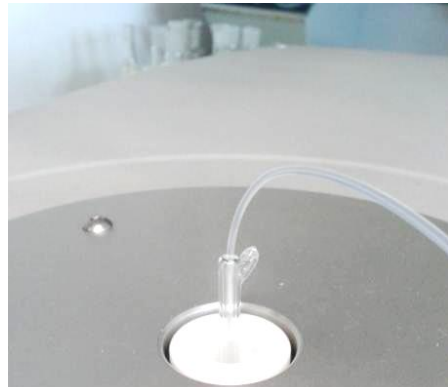
Disadvantage

- 😞 geometry not optimised

Zientek, N. et al. *J. Magn. Reson.*, **249**: 53-62 (2014)

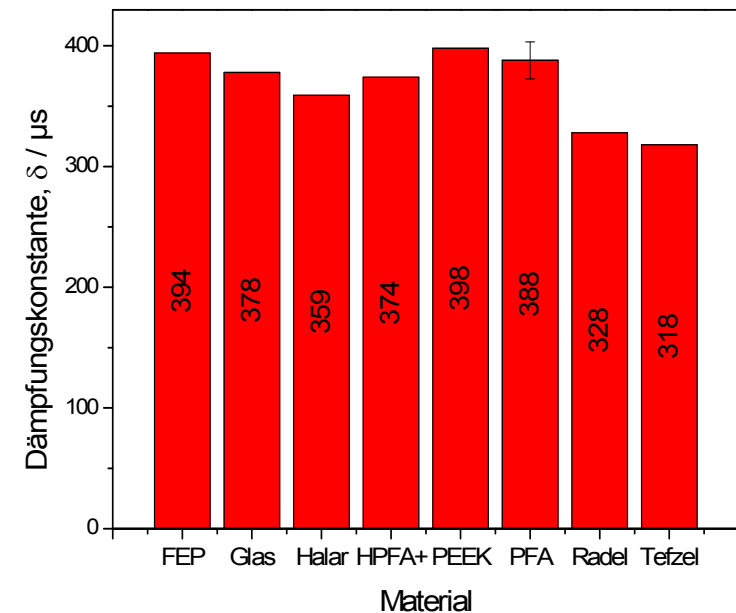
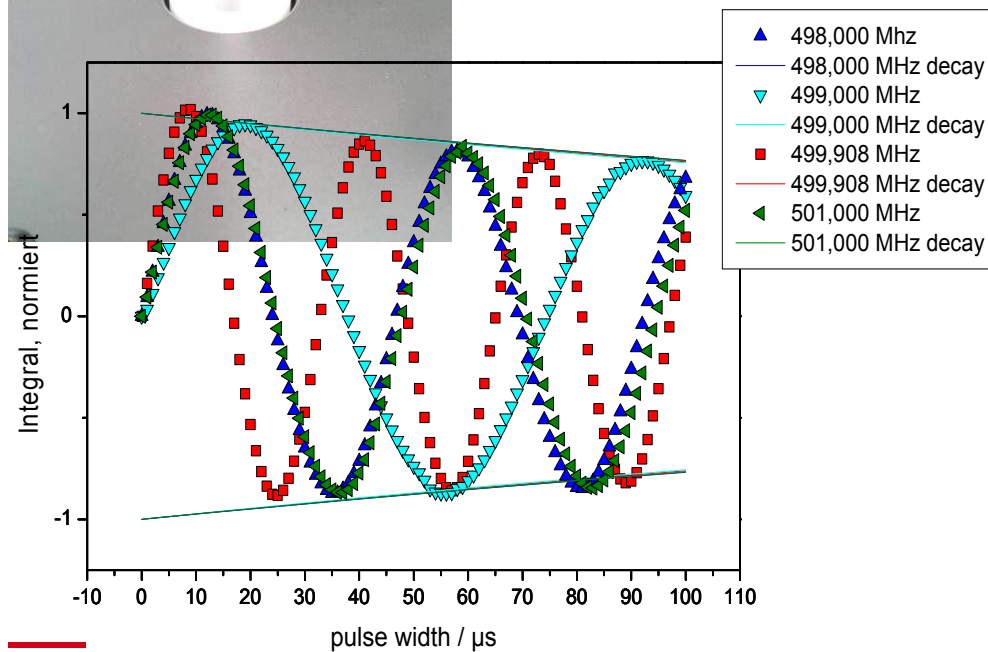
Simple Dewar Flow Cell

Concept of a Flow Cell 1/16" PFA Tubing (ID 1 mm)



$$M = M_0 + A \cdot \exp\left(-\frac{t_p}{\delta}\right) \cdot \sin\left(\pi \frac{t_p - t_{p,0}}{\omega}\right)$$

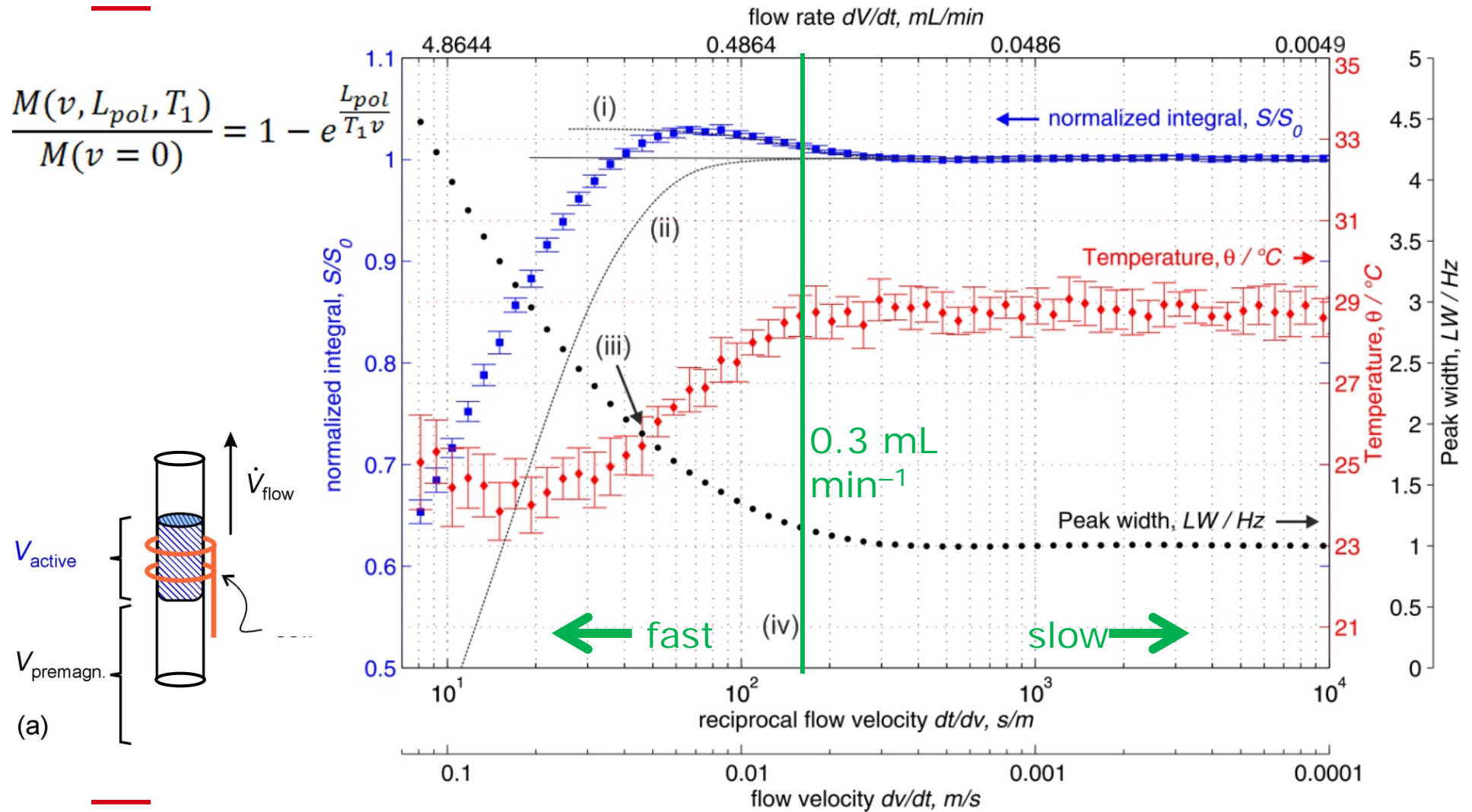
Damping constant



Nicolai Zientek 2013

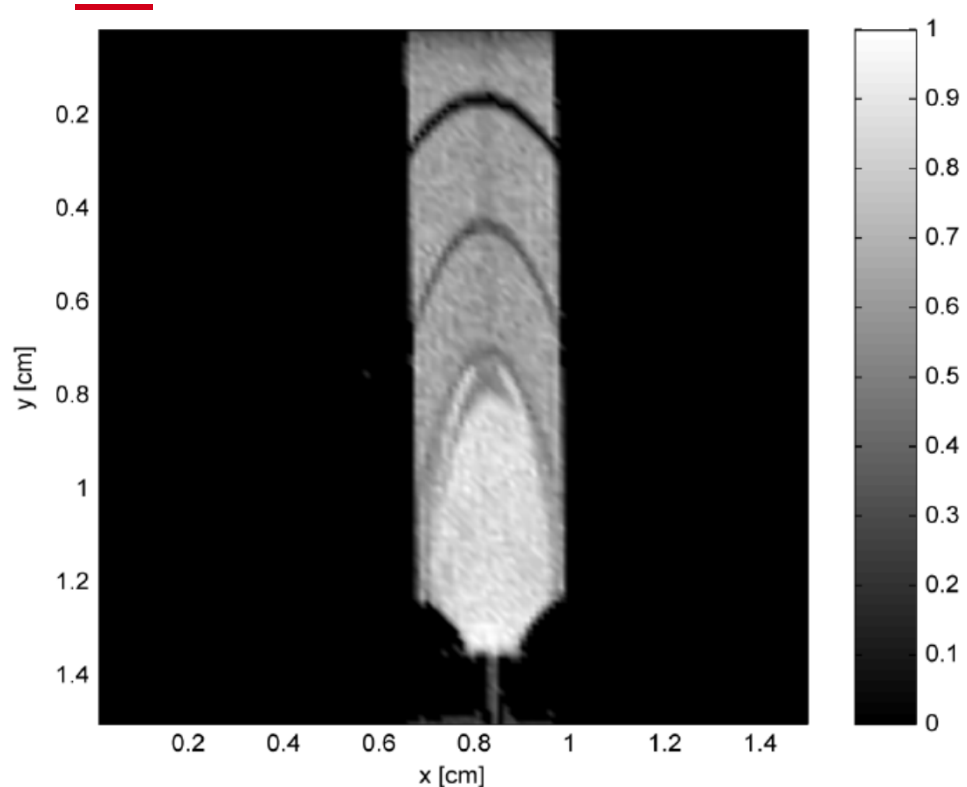
Influence of flow on polarisation

Experiments with flowing EtOH

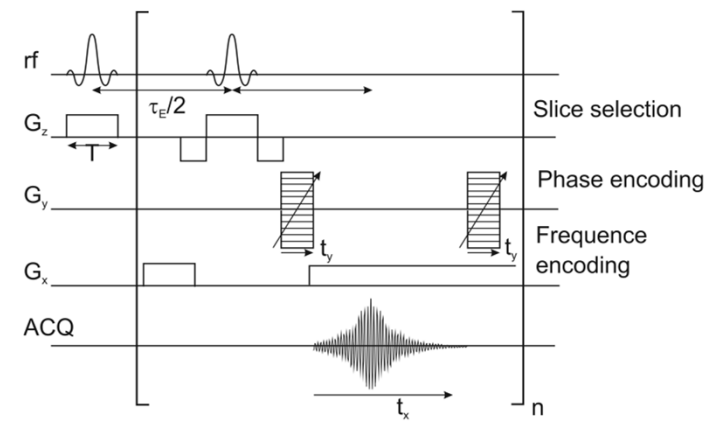


Flow NMR Spectroscopy

MSME experiments on flow profile

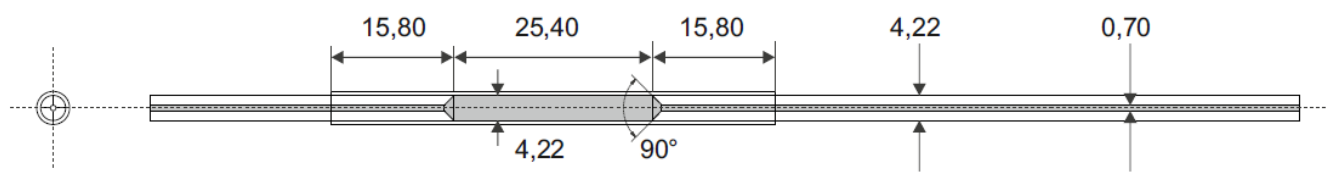


MSME = Multi Slice Multi Echo
 fast Time-of-flight-Method, produces visible profiles
 (Exp.: 2011, KIT Karlsruhe, Bruker Avance 200 MHz Tomograph)



MSME experiment: 5 ml/min Olive oil

Varian NMR flow cell:



Flow NMR Spectroscopy

CFD Calculation of Magnetisation Buildup

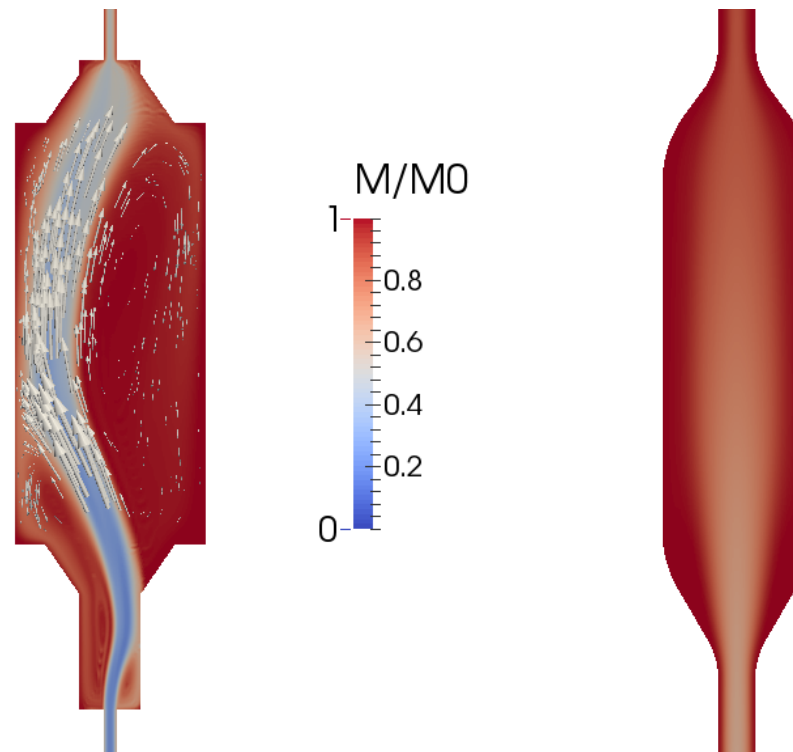
Flow Cells :

PTFE 1

$V_{\text{mean,in}} = 13.8 \text{ mm/s}$

PTFE 2 / Glass Dewar

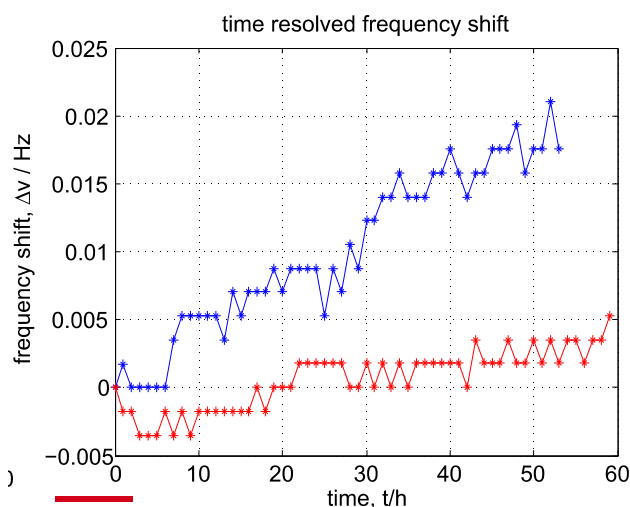
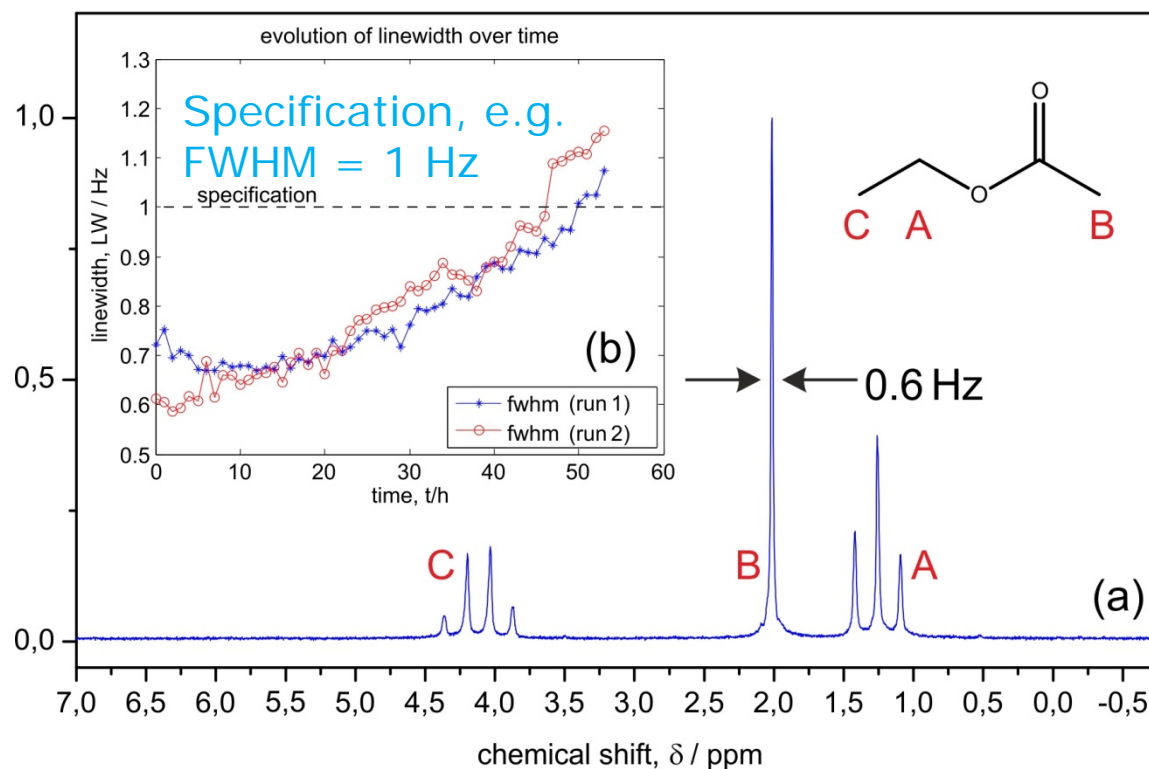
$V_{\text{mean,in}} = 31.8 \text{ mm/s}$



Long term stability and field drift



Long term stability
(intermediate
reproducibility)



1/16" PFA Tubing (ID 1 mm)

Field drift

$\Delta\delta/dt < 0.02$ Hz / h
(externally locked, ^{19}F)

Line shape and line shape stability

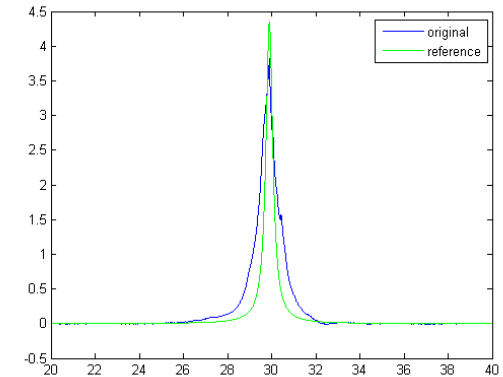
„What you see is what you get“



Conventional line shape test

→ limited in technical applications ☹️

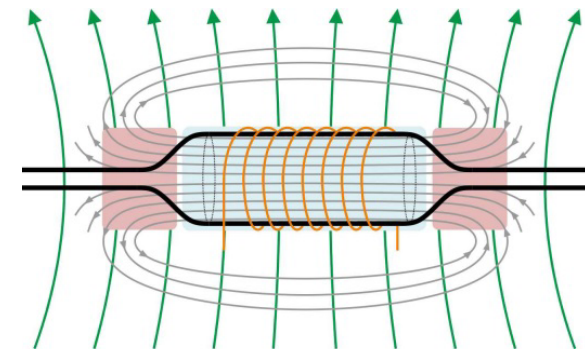
Distribution moments → not defined for ideal Lorentzian signals ☹️



Real world line shapes (non-exponential decay)

$$s(t) = M_0 \cdot [\cos(2\pi\nu t) - i \cdot \sin(2\pi\nu t)] \cdot e^{-\frac{t}{T_2}} \cdot a(t)$$

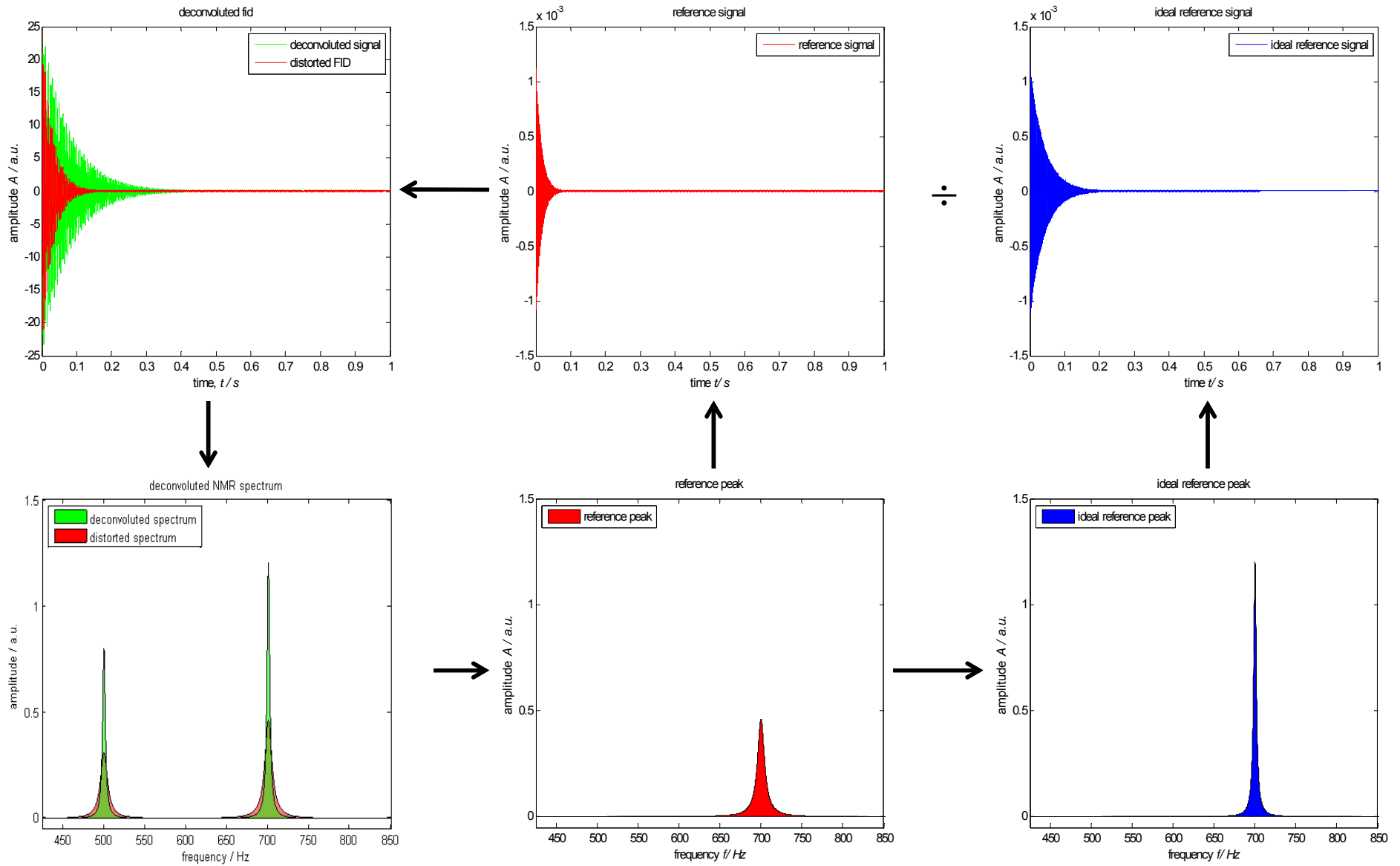
Instrument function



homogeneous B_1
 inhomogeneous B_1
 B_0 field
 B_1 field

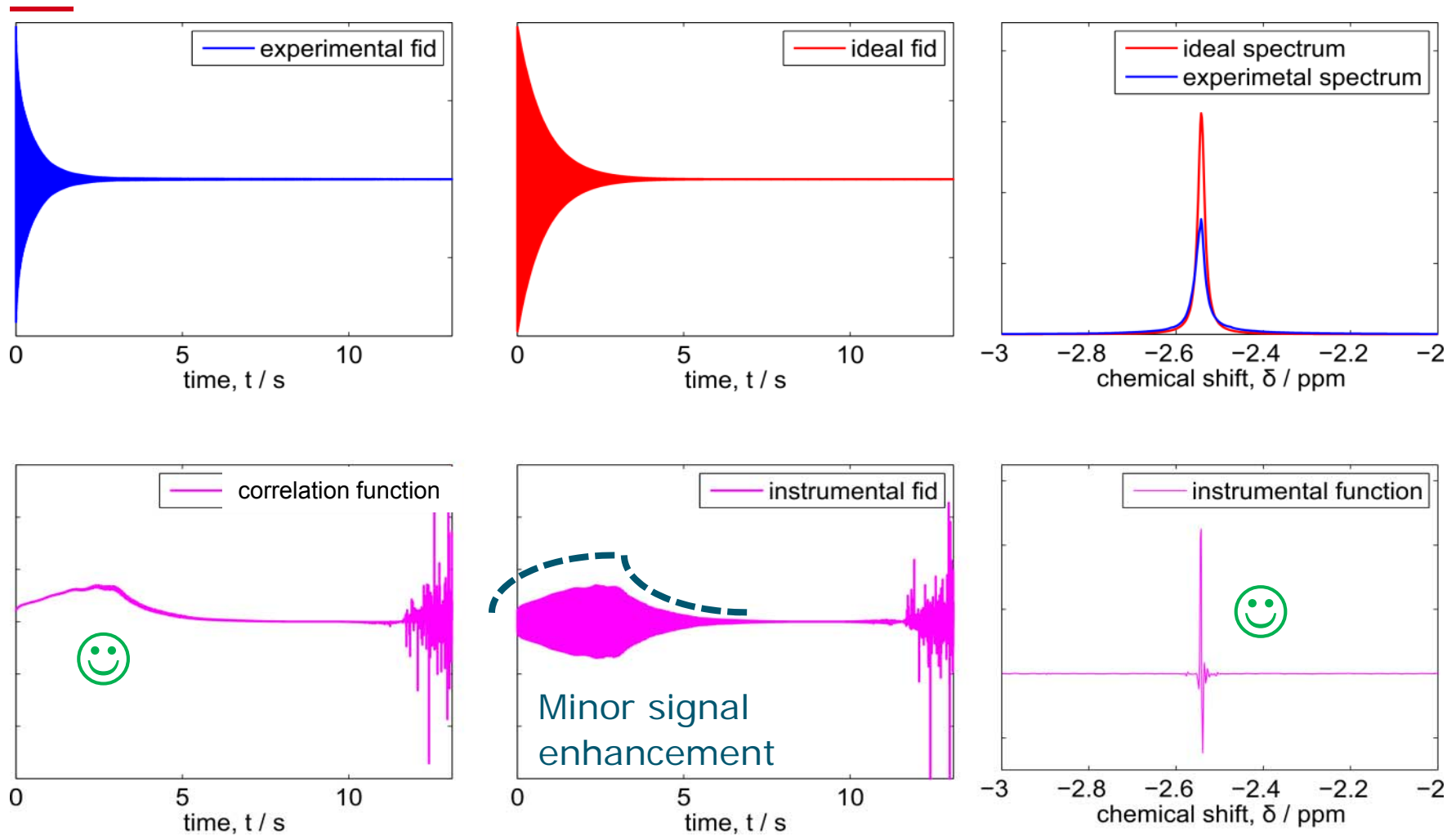
Line Shape Deconvolution Algorithm (LSDA) 😊

Reference Deconvolution



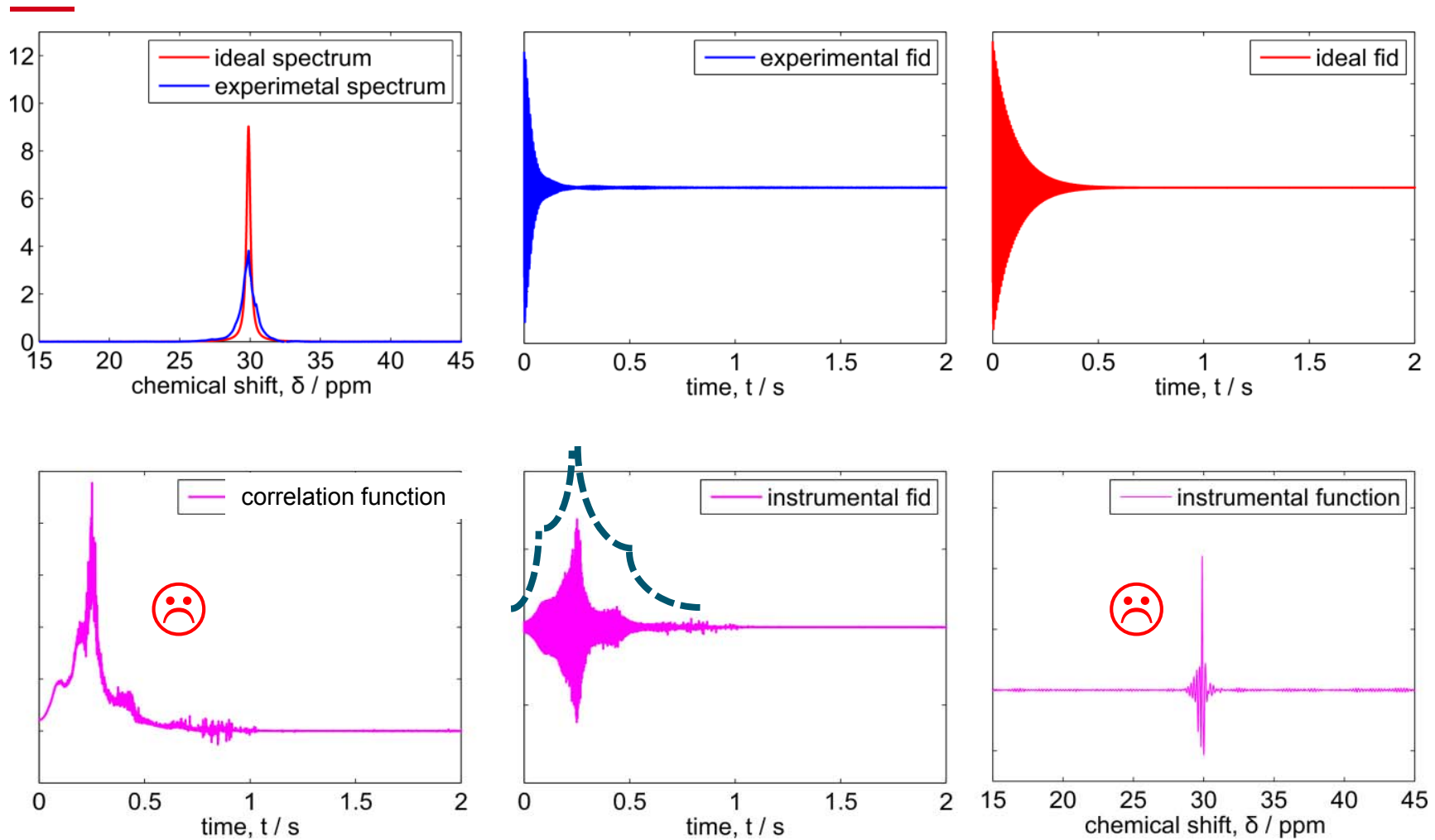
Instrument Functions $a(t)$

Performance of hardware adequate



Instrument Functions $a(t)$

Performance of hardware



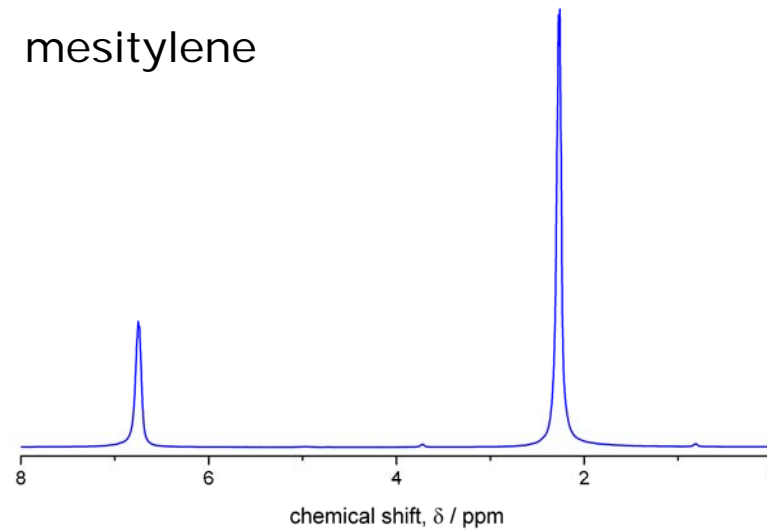
Practical MR NMR Standards

- Usable in open system
- Readily available
- No deuterated compounds

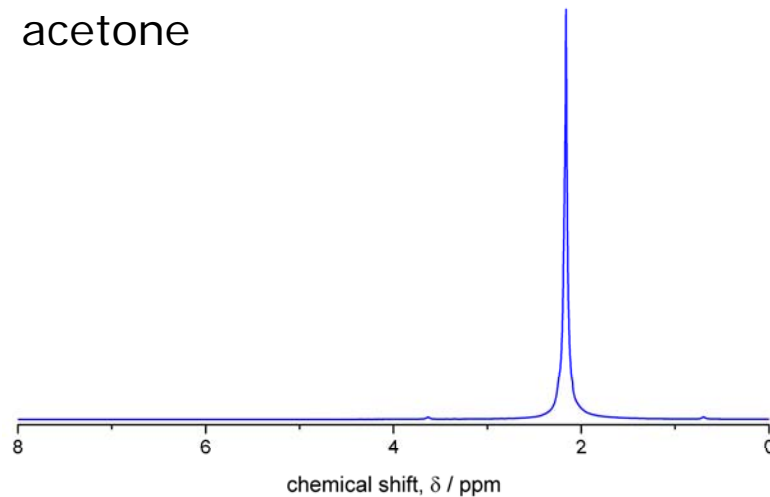
Others

- water
- cyclohexane
- chloroform

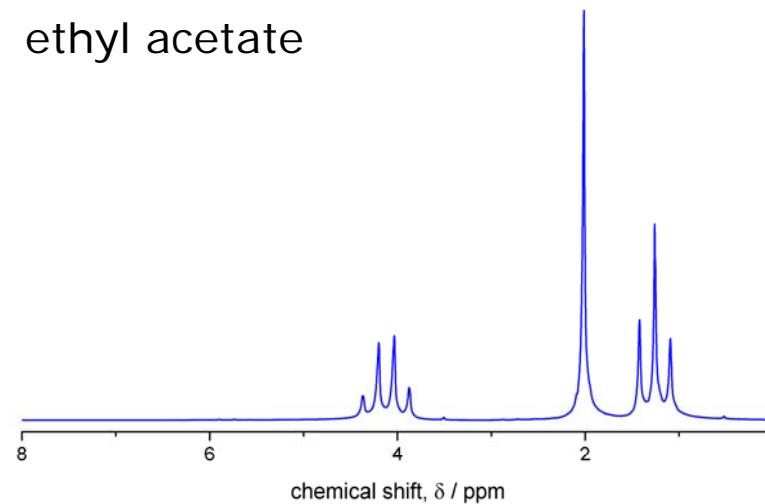
mesitylene



acetone



ethyl acetate



Instrument Functions $a(t)$



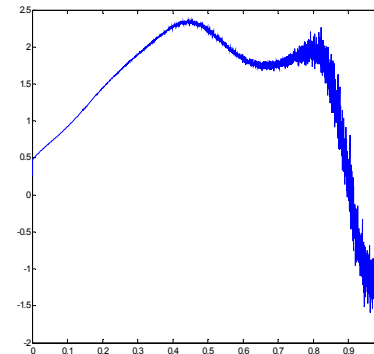
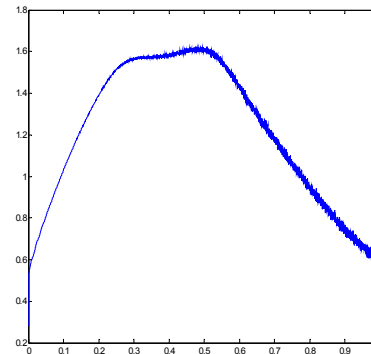
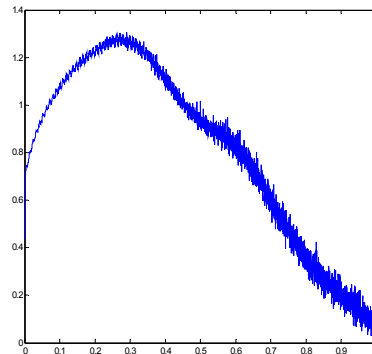
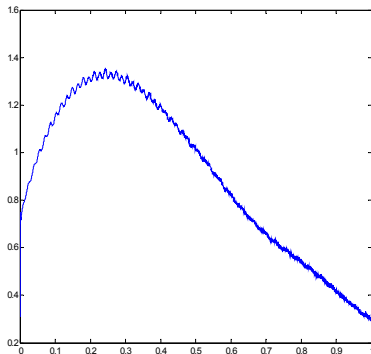
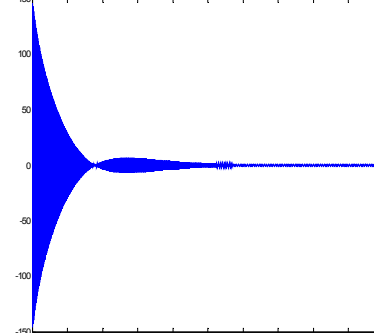
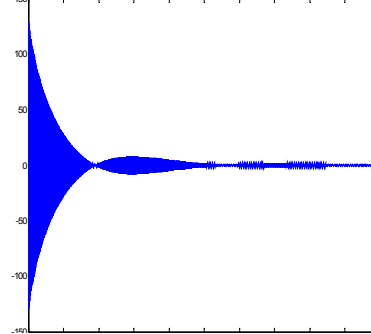
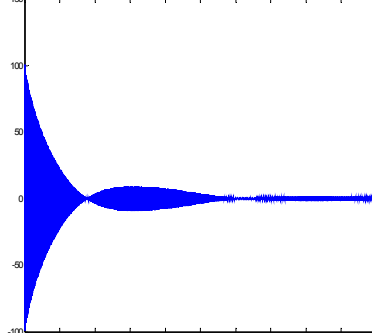
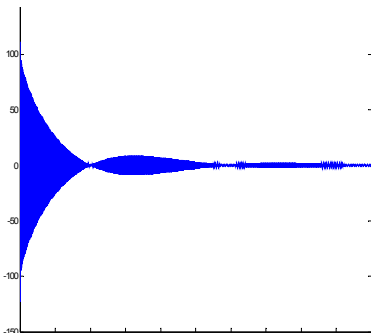
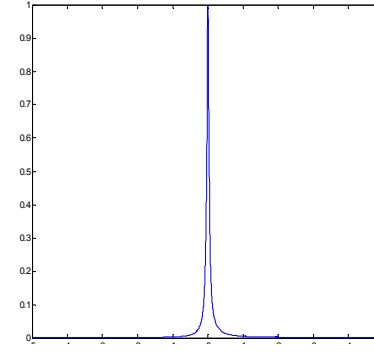
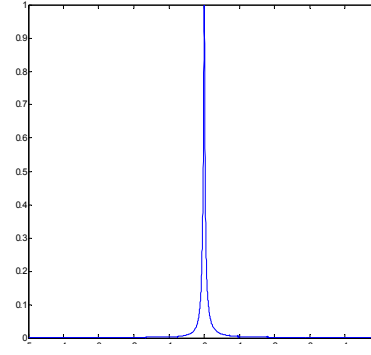
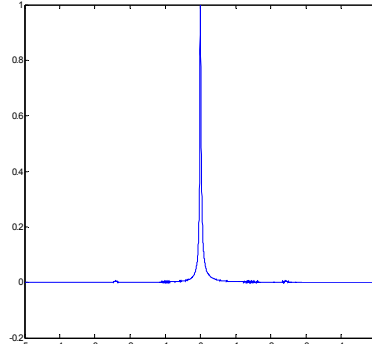
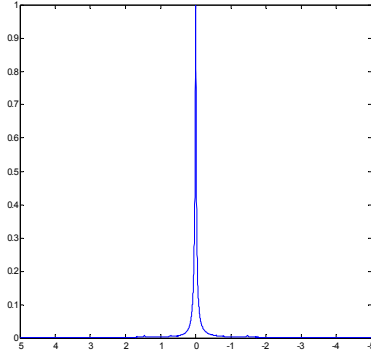
Comparison of different solvents

acetone

chloroform

cyclohexane

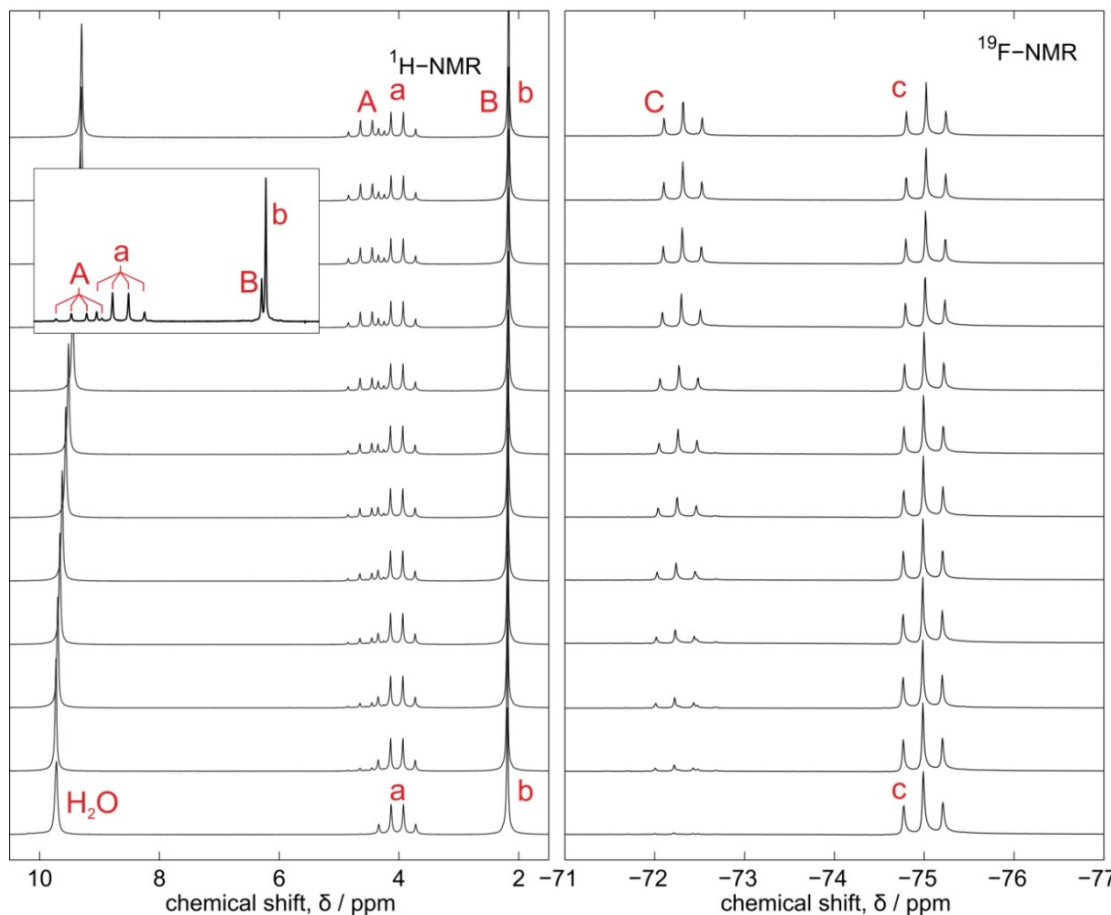
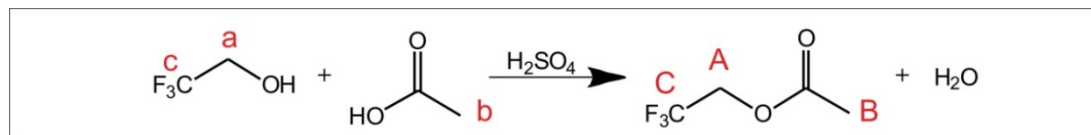
water



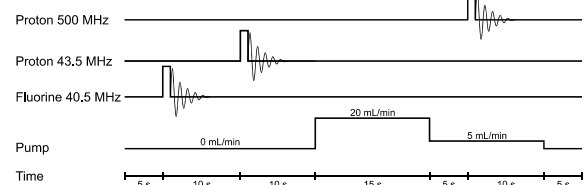
¹H- and ¹⁹F-NMR MR-NMR

Quasi-parallel acquisition

- relative sensitivity of ¹⁹F-NMR: ~85 %
- 30% of important industrial chemicals and pharmaceuticals contain fluorine



Pulse sequence



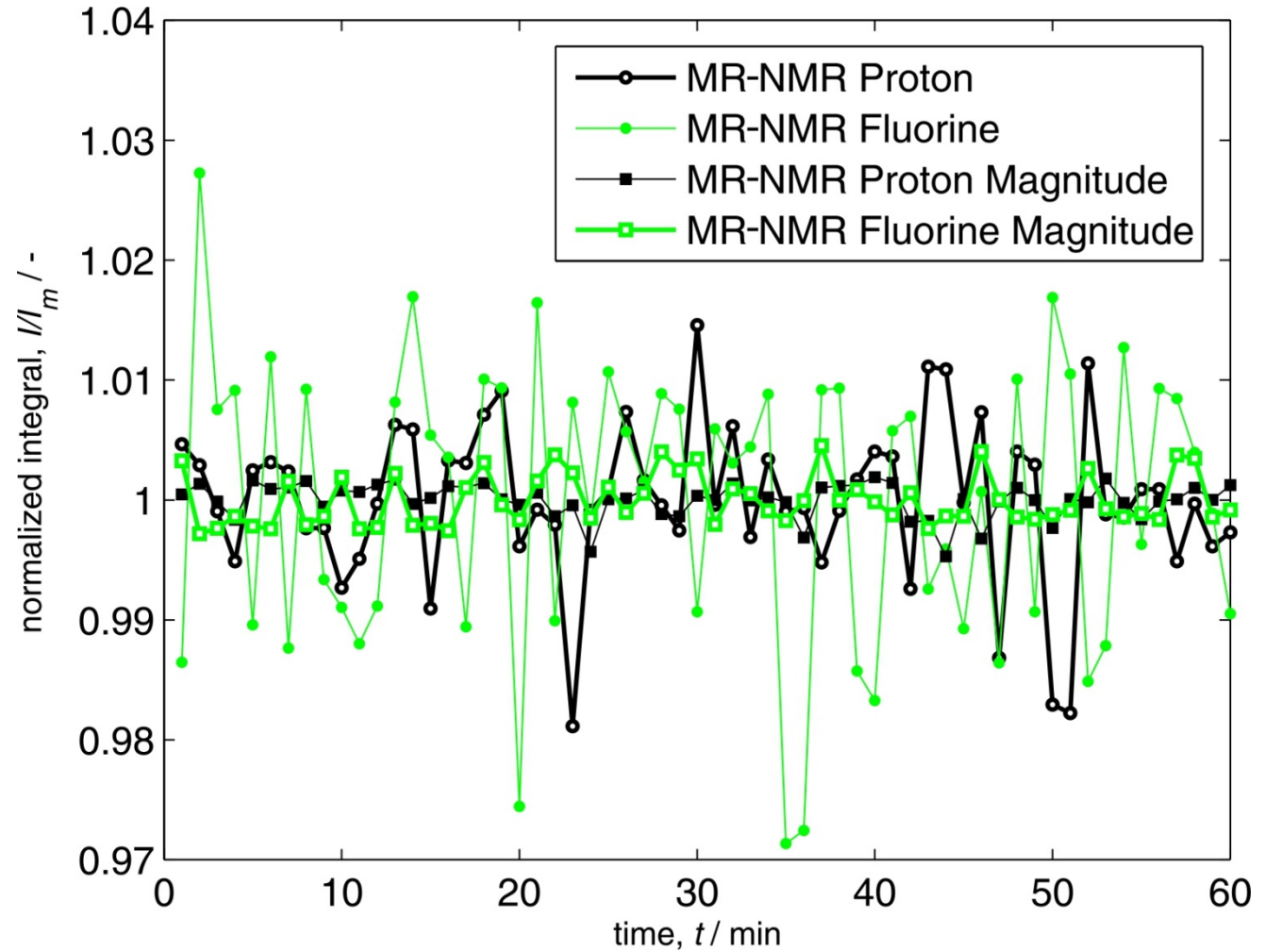
1 minute

NMR Data Acquisition



Phase stability ^1H and ^{19}F

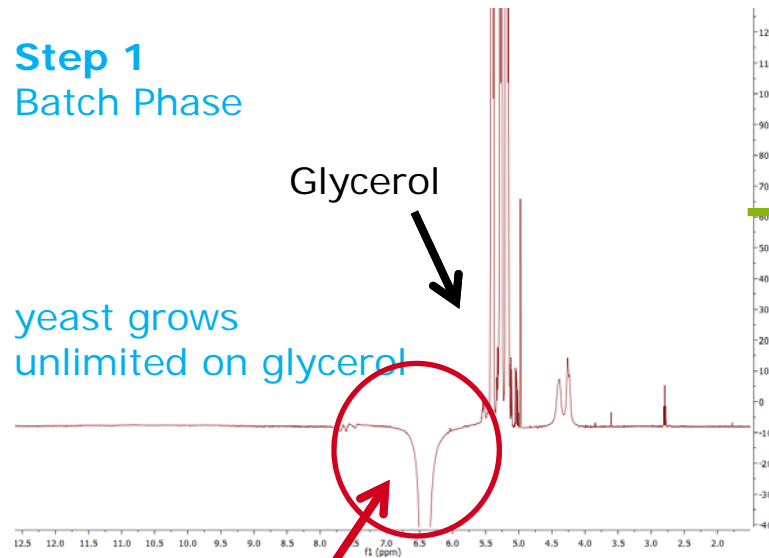
—
 ^1H and ^{19}F
phase scatter
over 60 repeated
experiments



Monitoring of yeast based process via high resolution online NMR spectroscopy

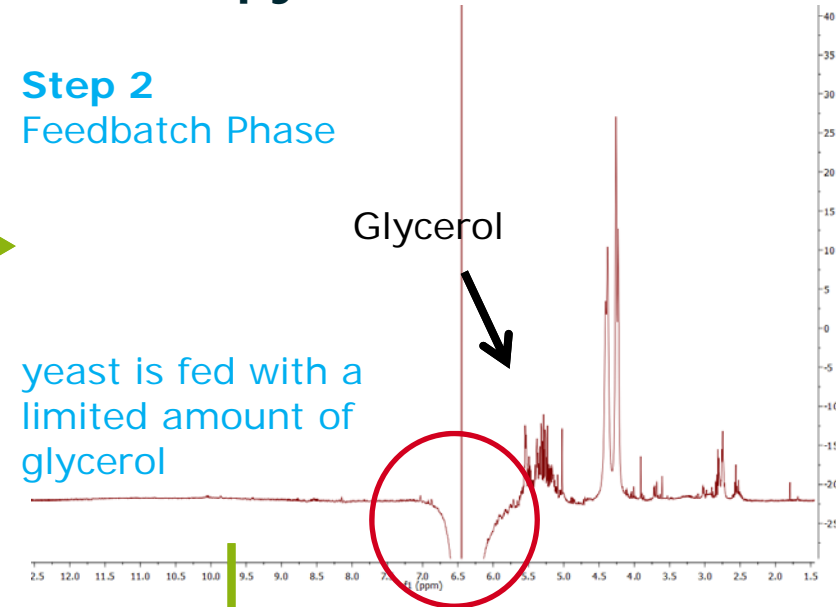


Step 1 Batch Phase

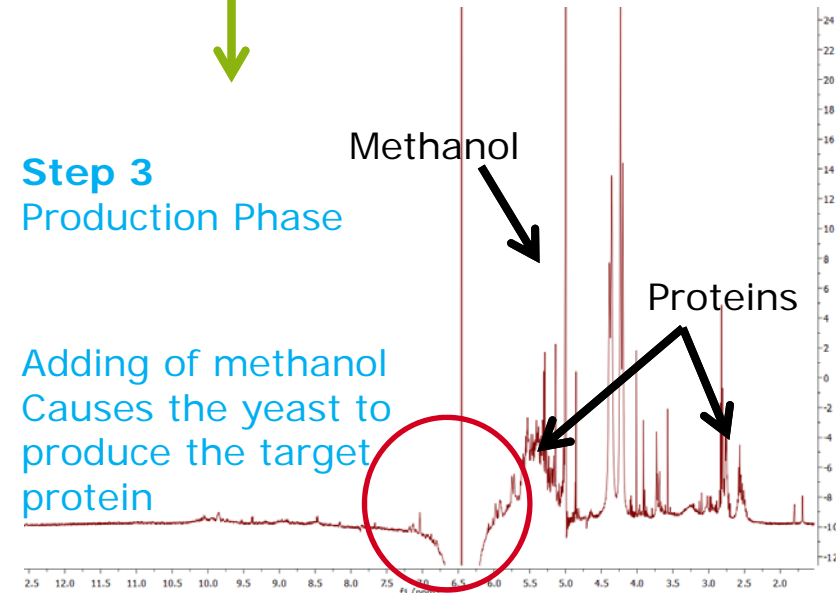


Remaining
Water signal
(WET)

Step 2 Feedbatch Phase



Step 3 Production Phase



Korvin Walter, Jan-Patrick Voß
Andrea Paul, Michael Maiwald

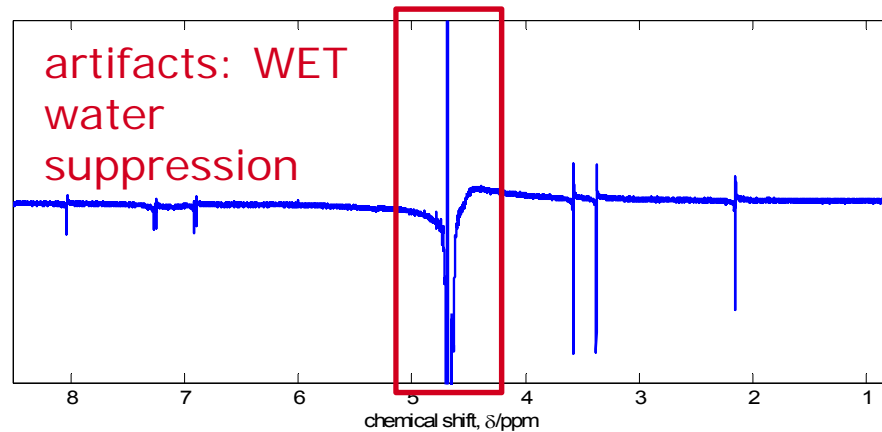
Automated Phase Correction



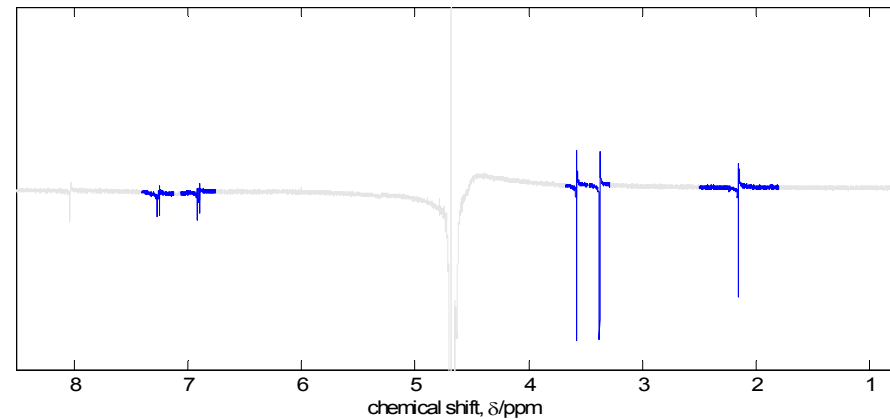
Phase Optimisation using Entropy Minimisation [1]

[1] Chen et. al, Journal of Magnetic Resonance **2002**, 158, 164-168

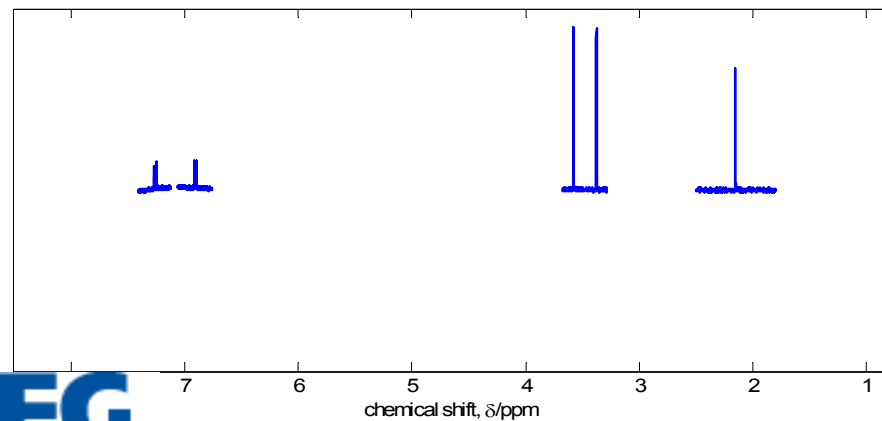
standard phase correction



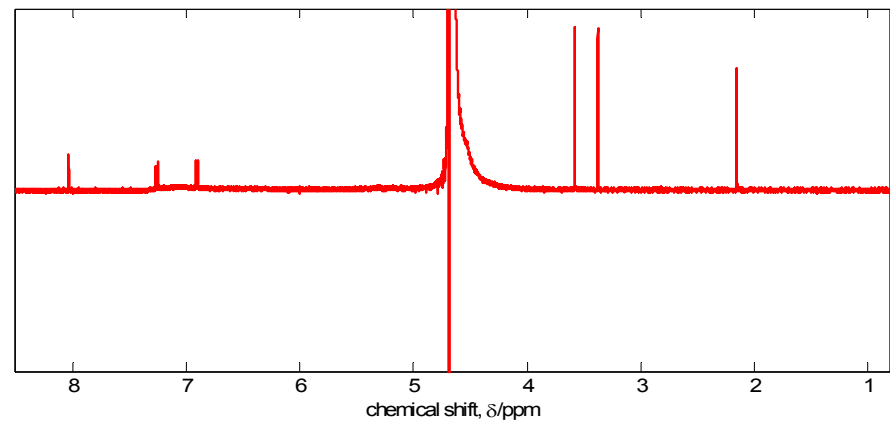
selective signal selection



calculate optimal phase (MinEnt)



apply phase values to entire spectrum

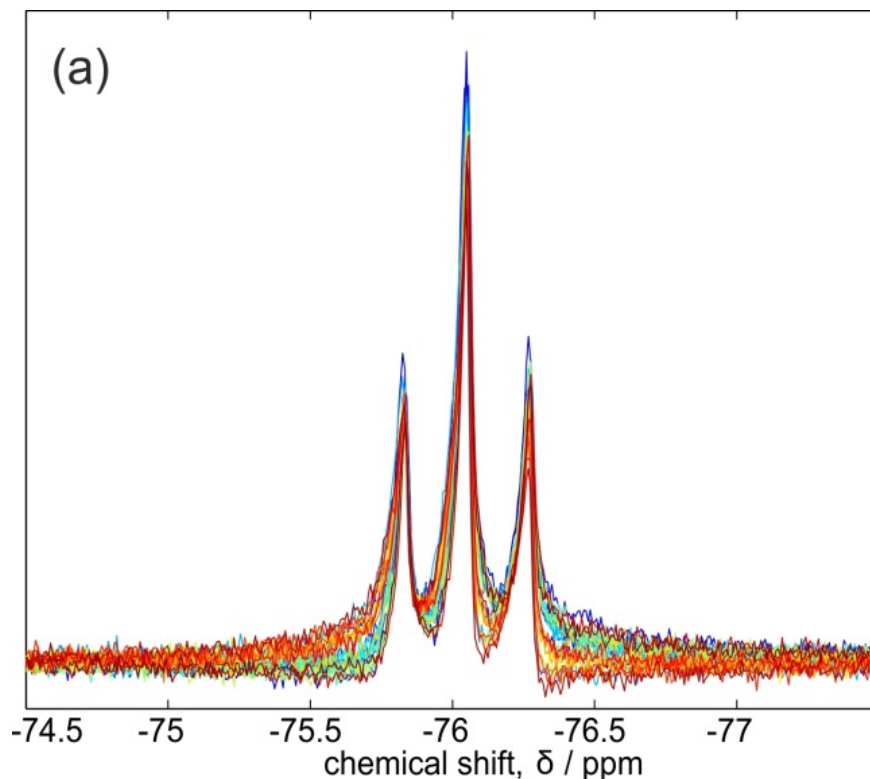


NMR Data Preparation

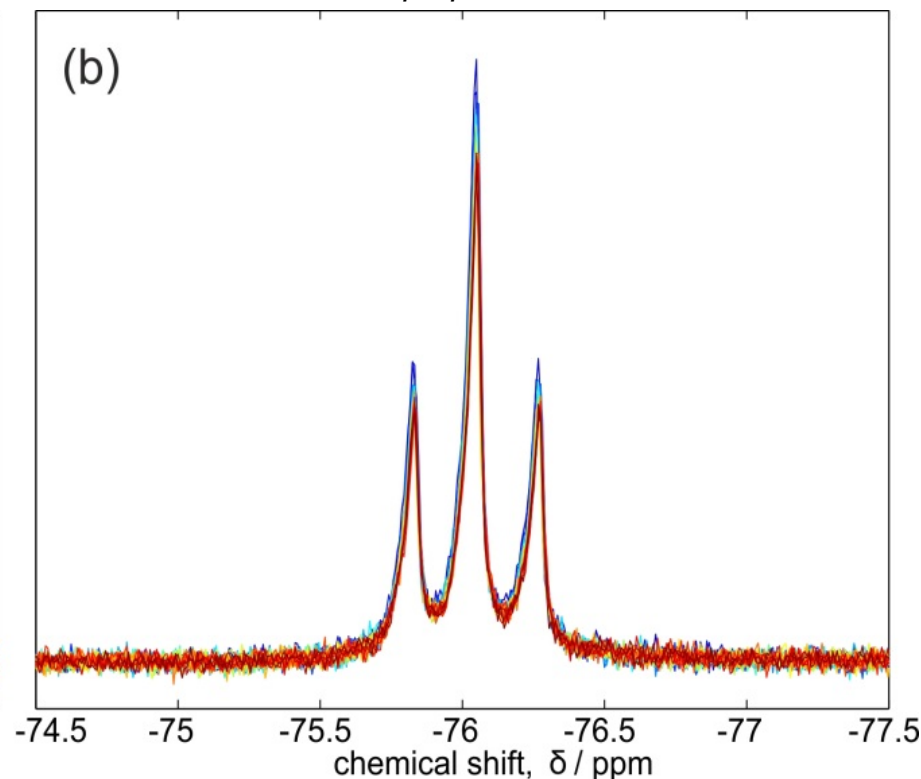


Phase Correction: Superimposed ^{19}F NMR spectra

2,2,2-trifluoroethanol

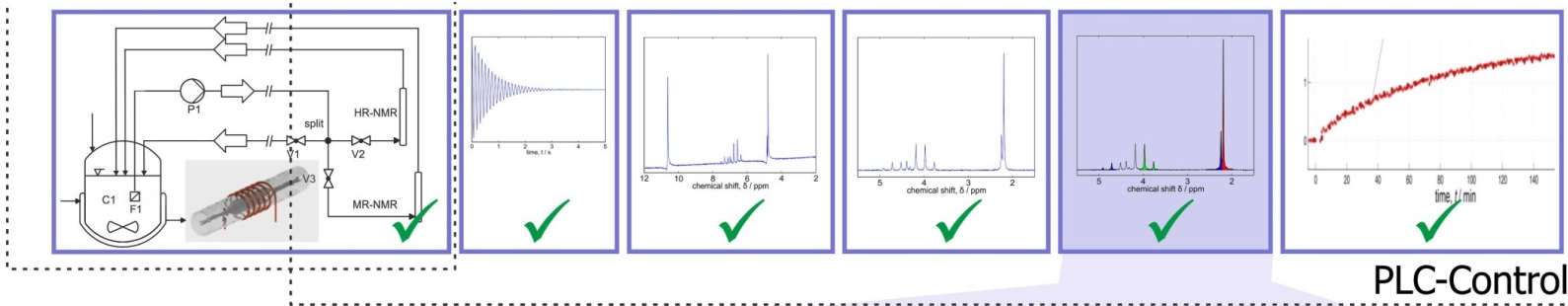


(a) auto-phased and baseline-corrected NMR spectra using vendor NMR software and

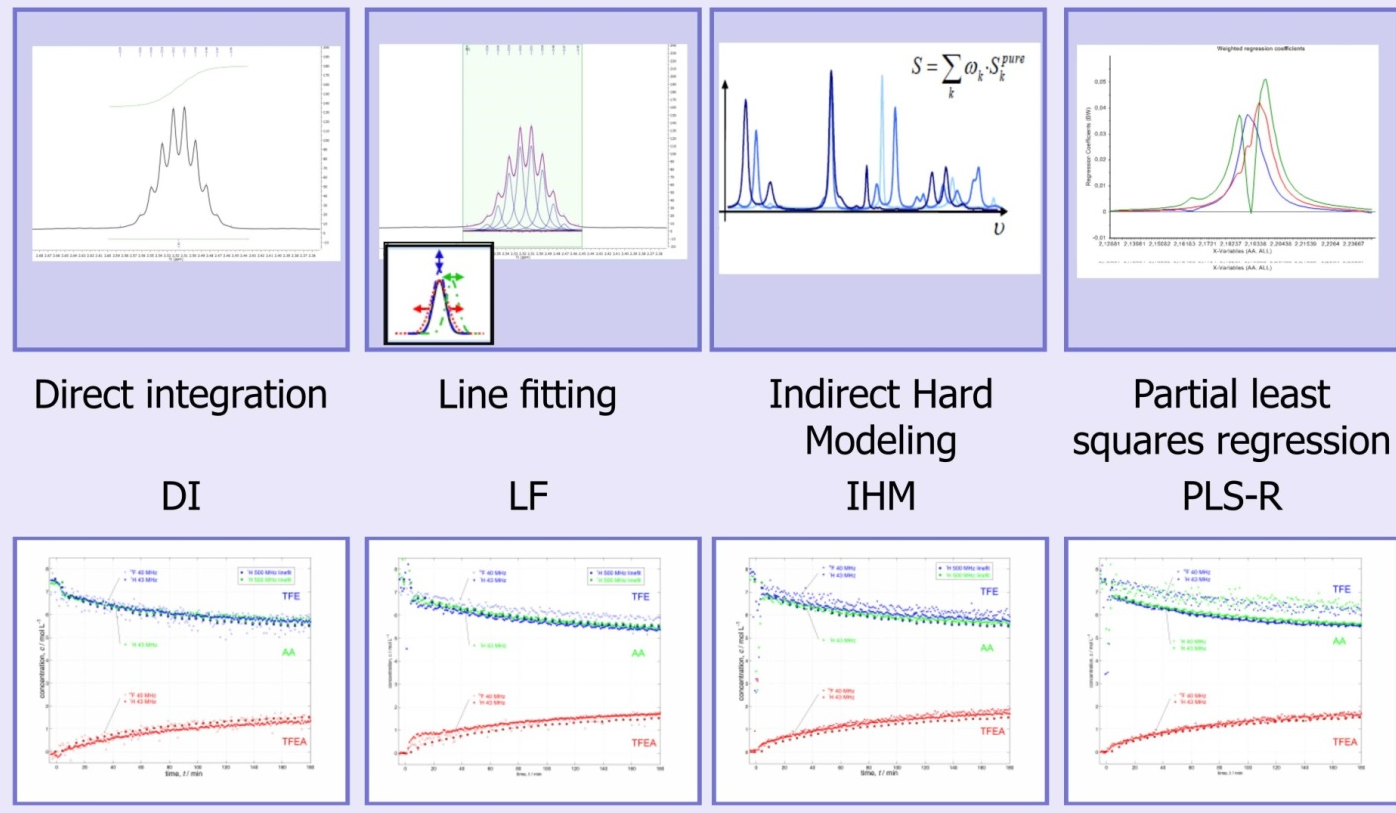


(b) baseline-corrected and automatically phased using the minimum entropy phase correction

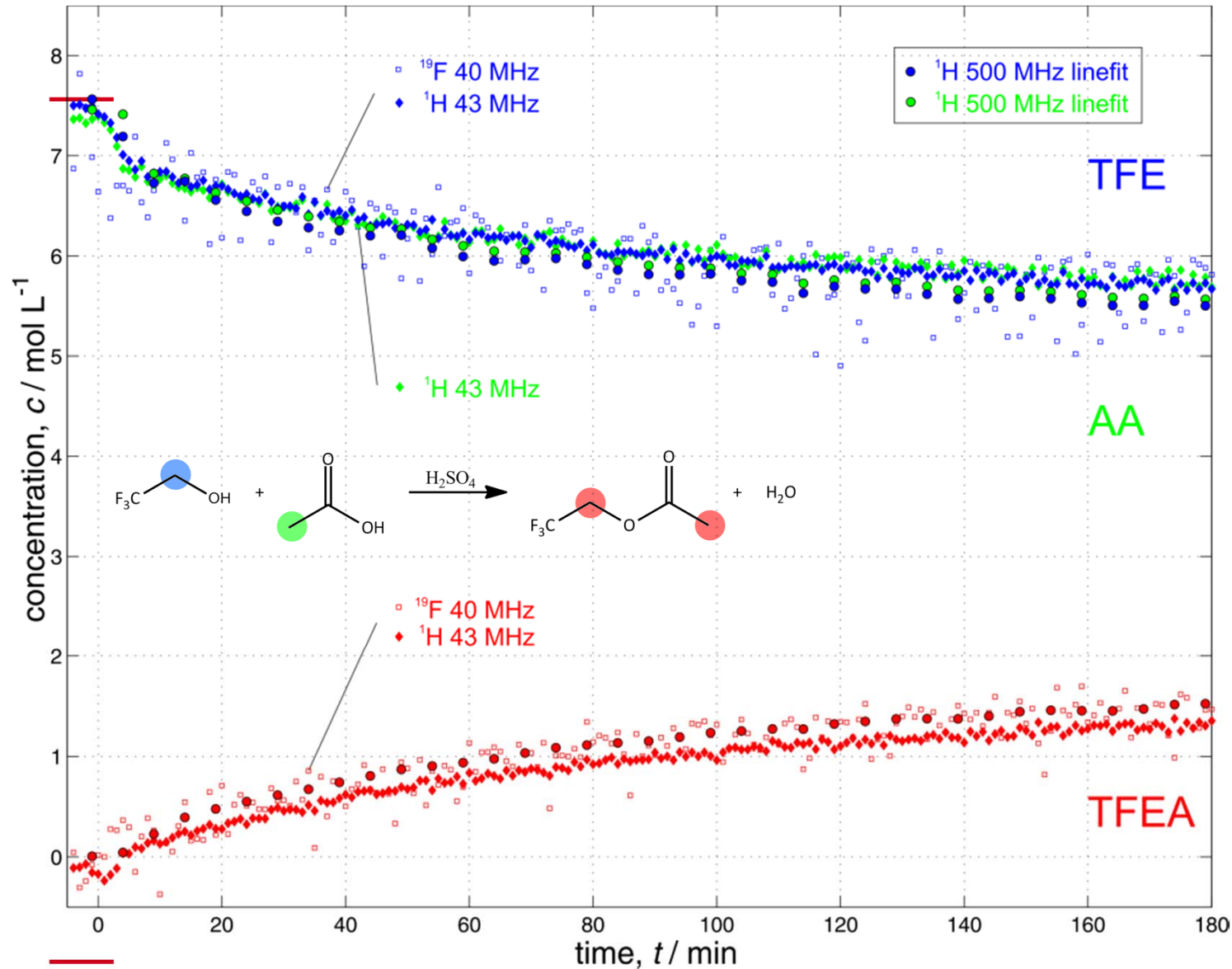
Data Analysis - Overview



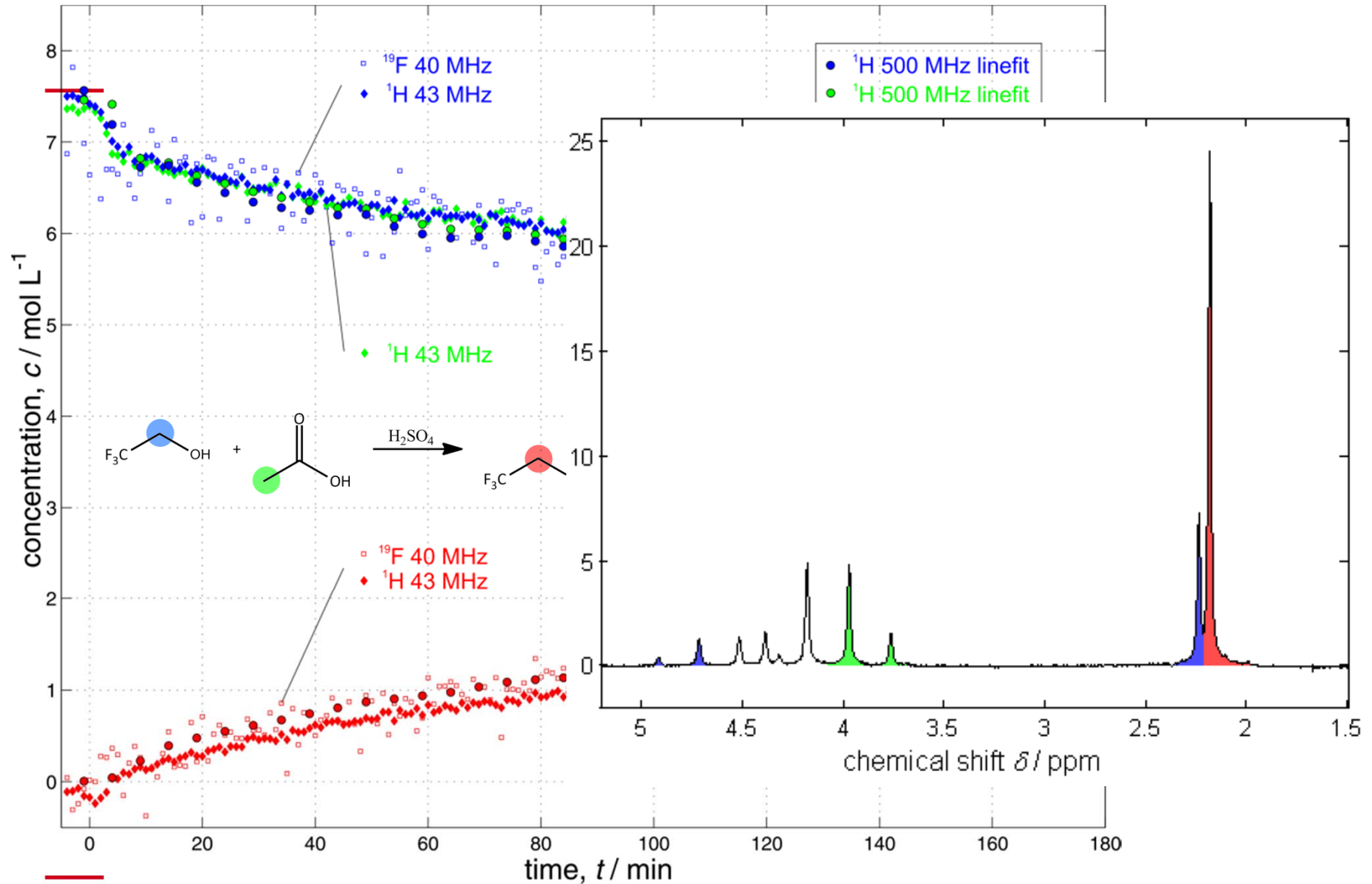
process → instrument → FID → raw data → corr. data → model → decision



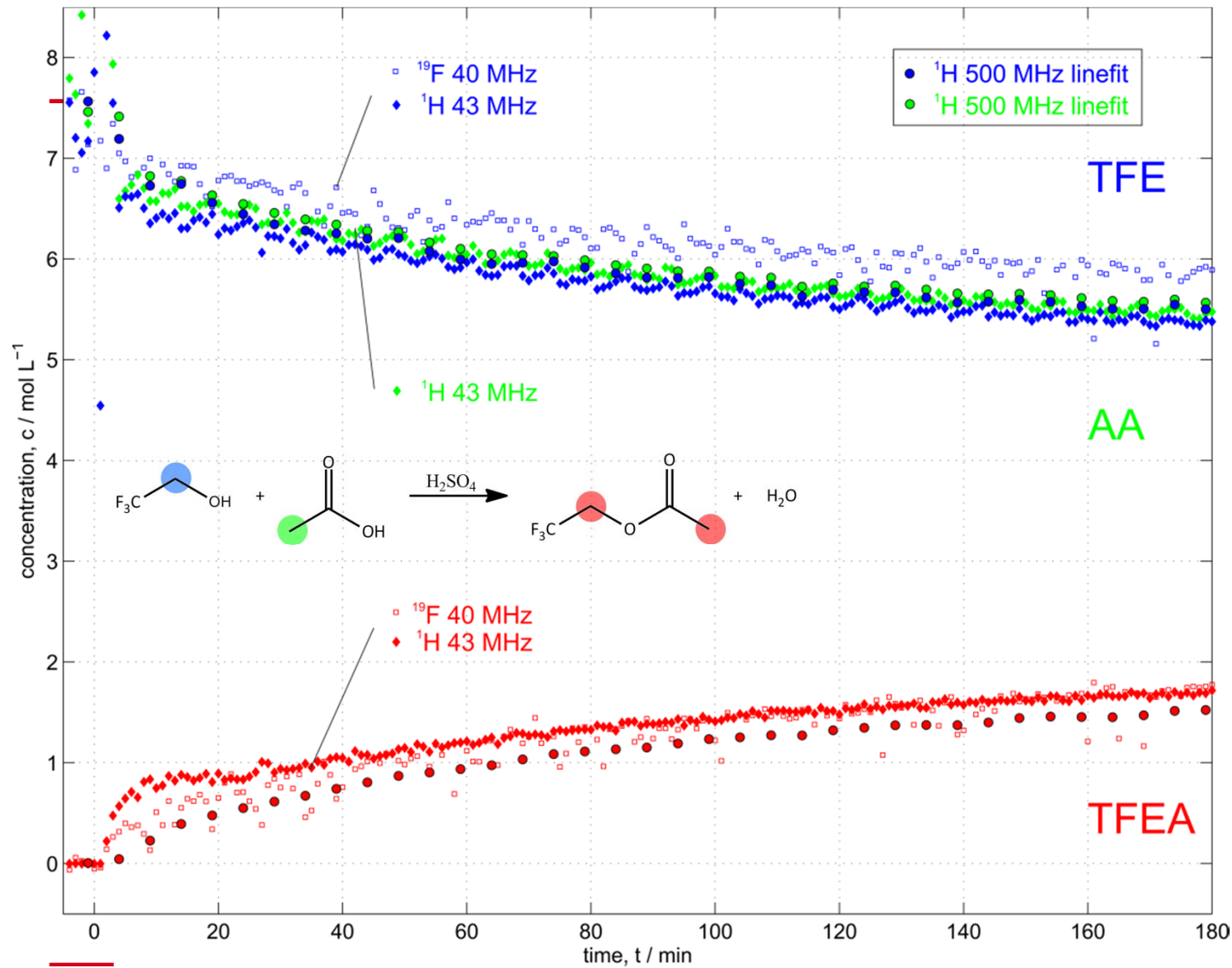
Method 1: Direct Integration



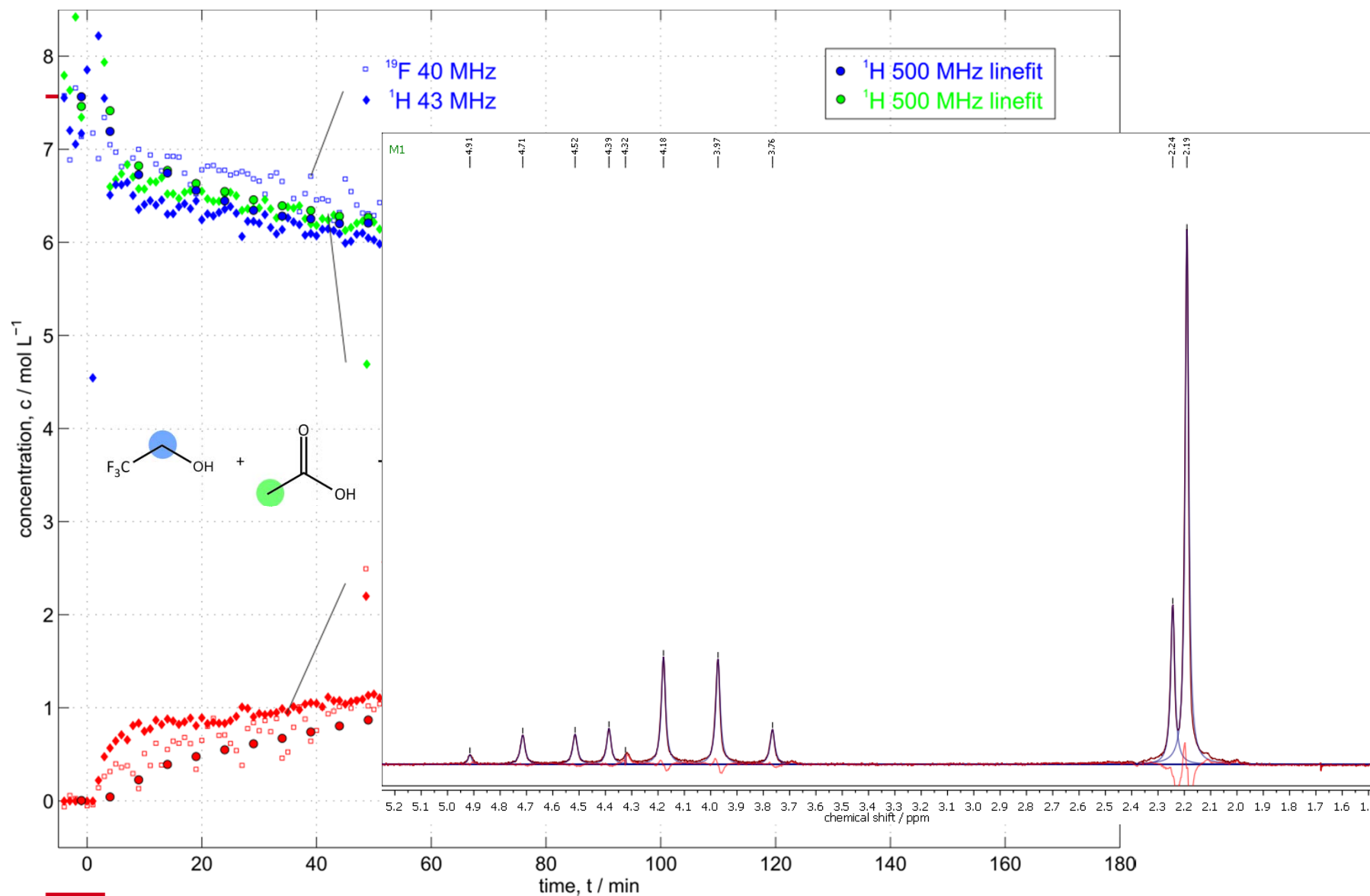
Method 1: Direct Integration



Method 2: Line Fitting

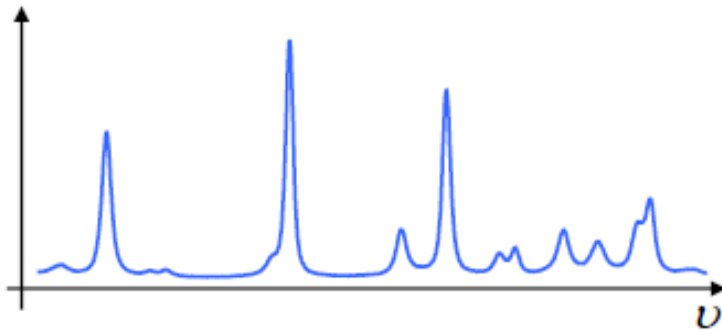


Method 2: Line Fitting

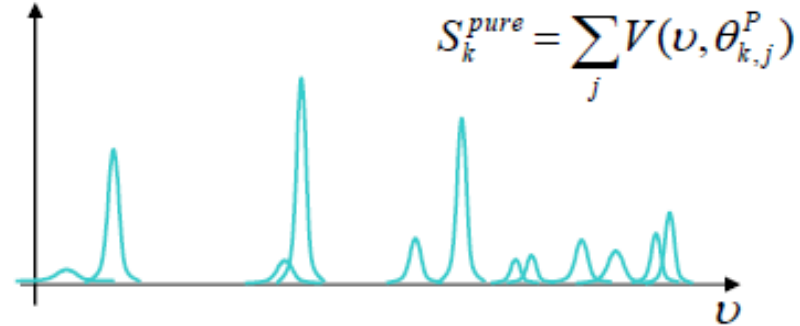


Indirect Hard Modeling

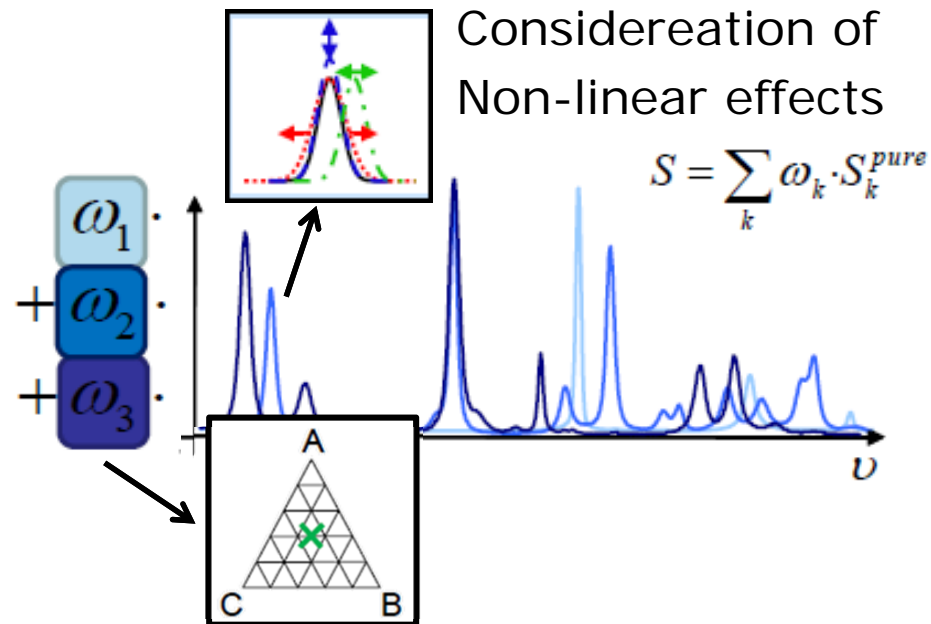
1. Pure Component Spectra



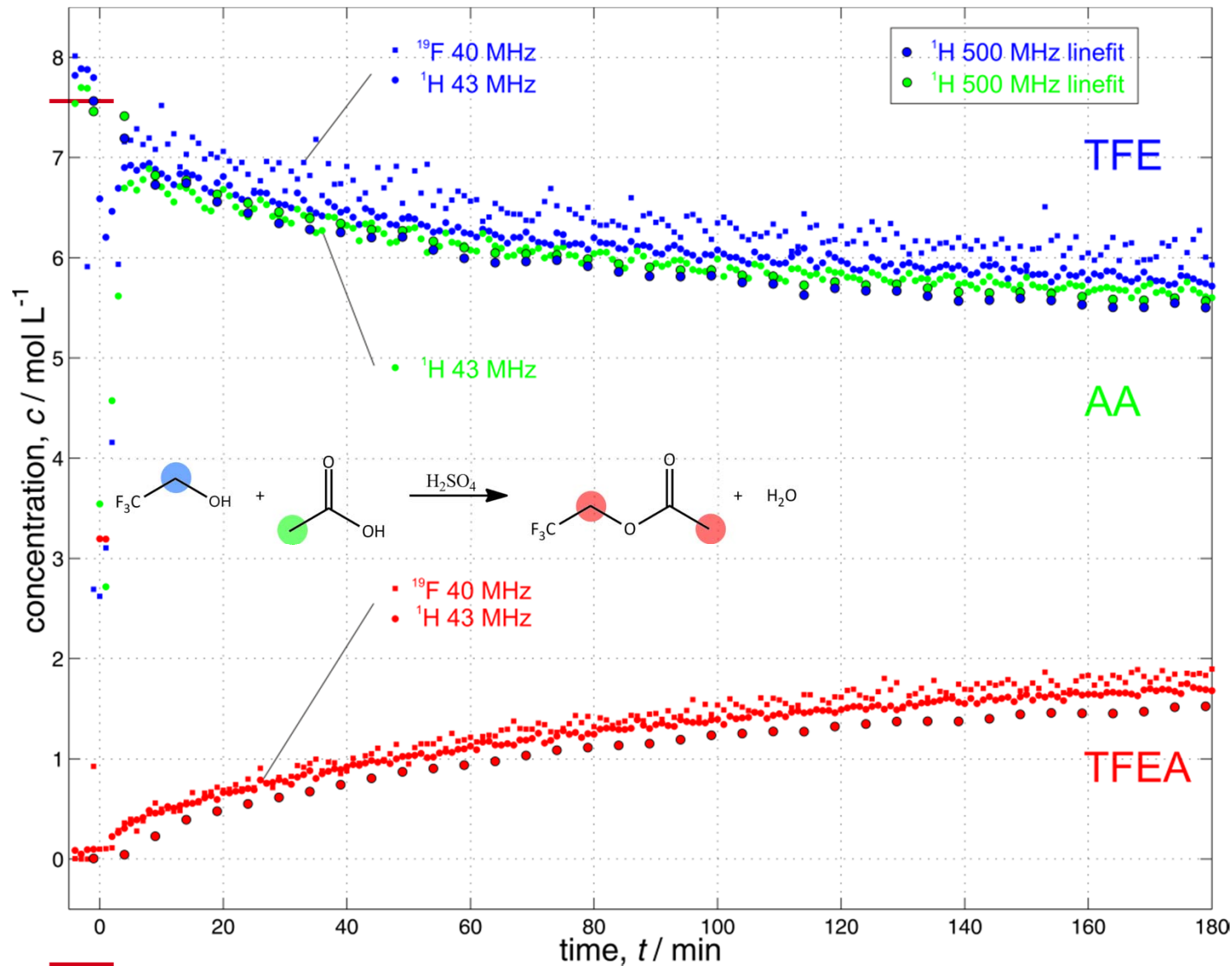
2. Hard Model: Sum of peak-shaped curves



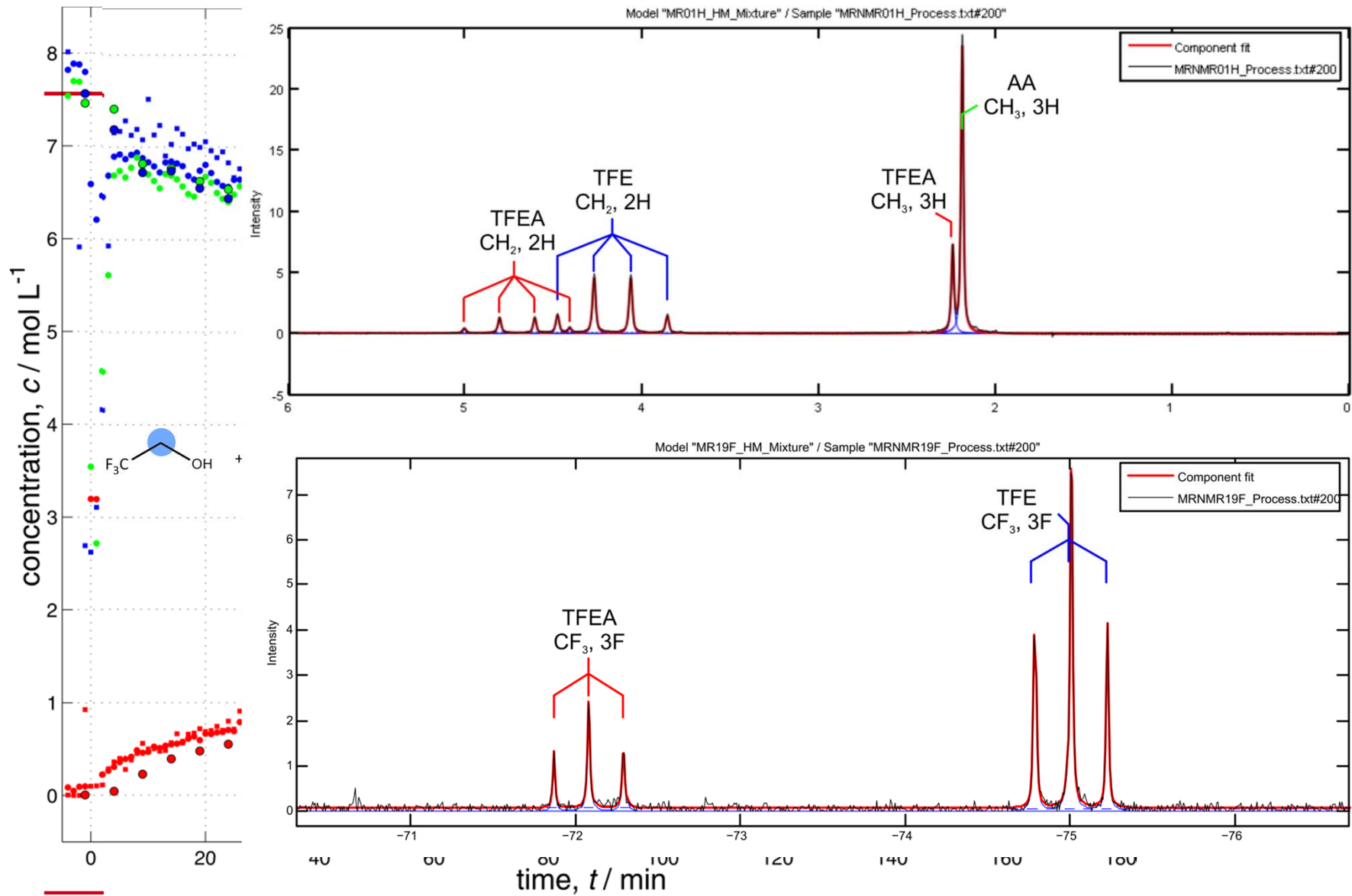
3. Measured Spectrum



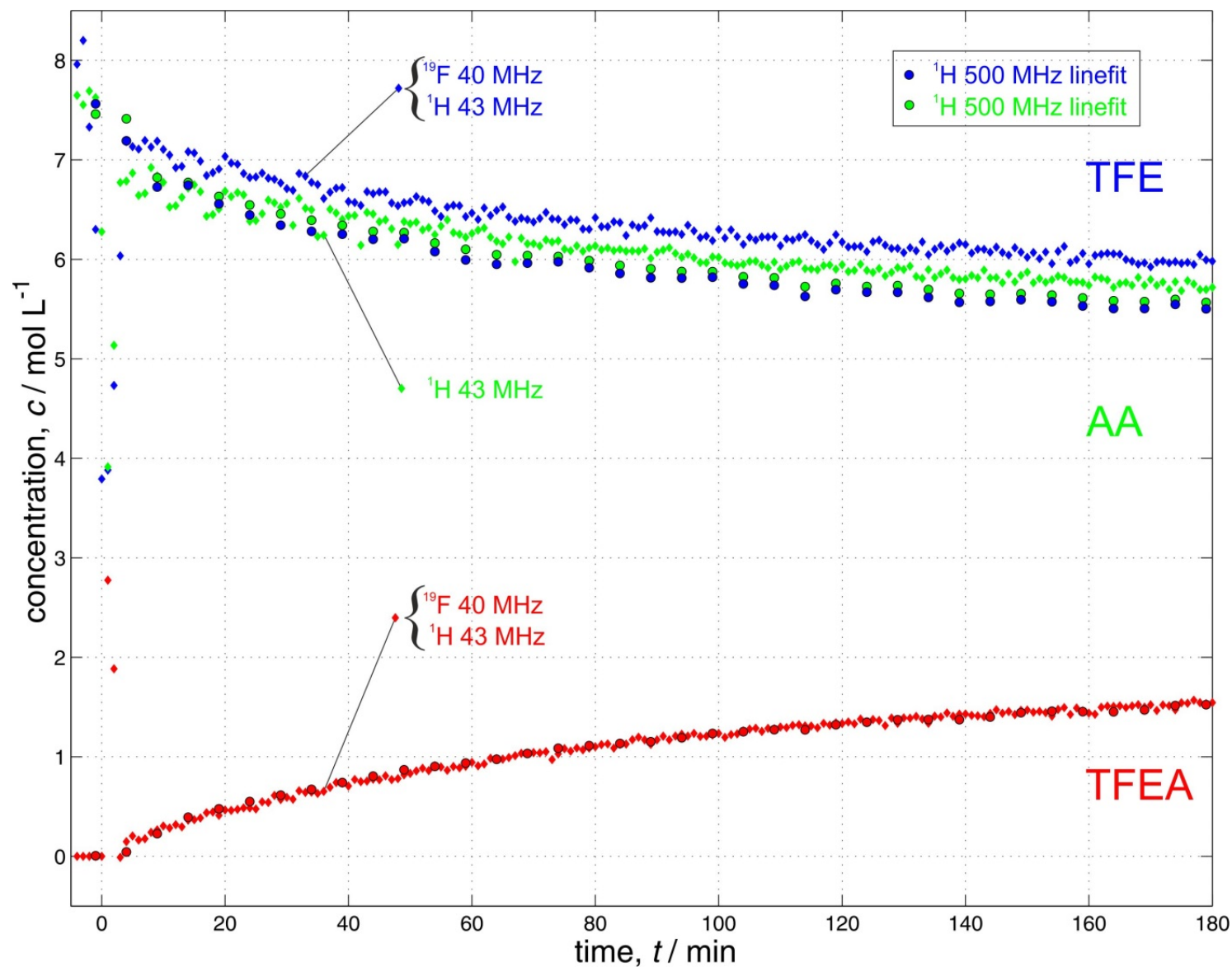
Method 3: IHM #1



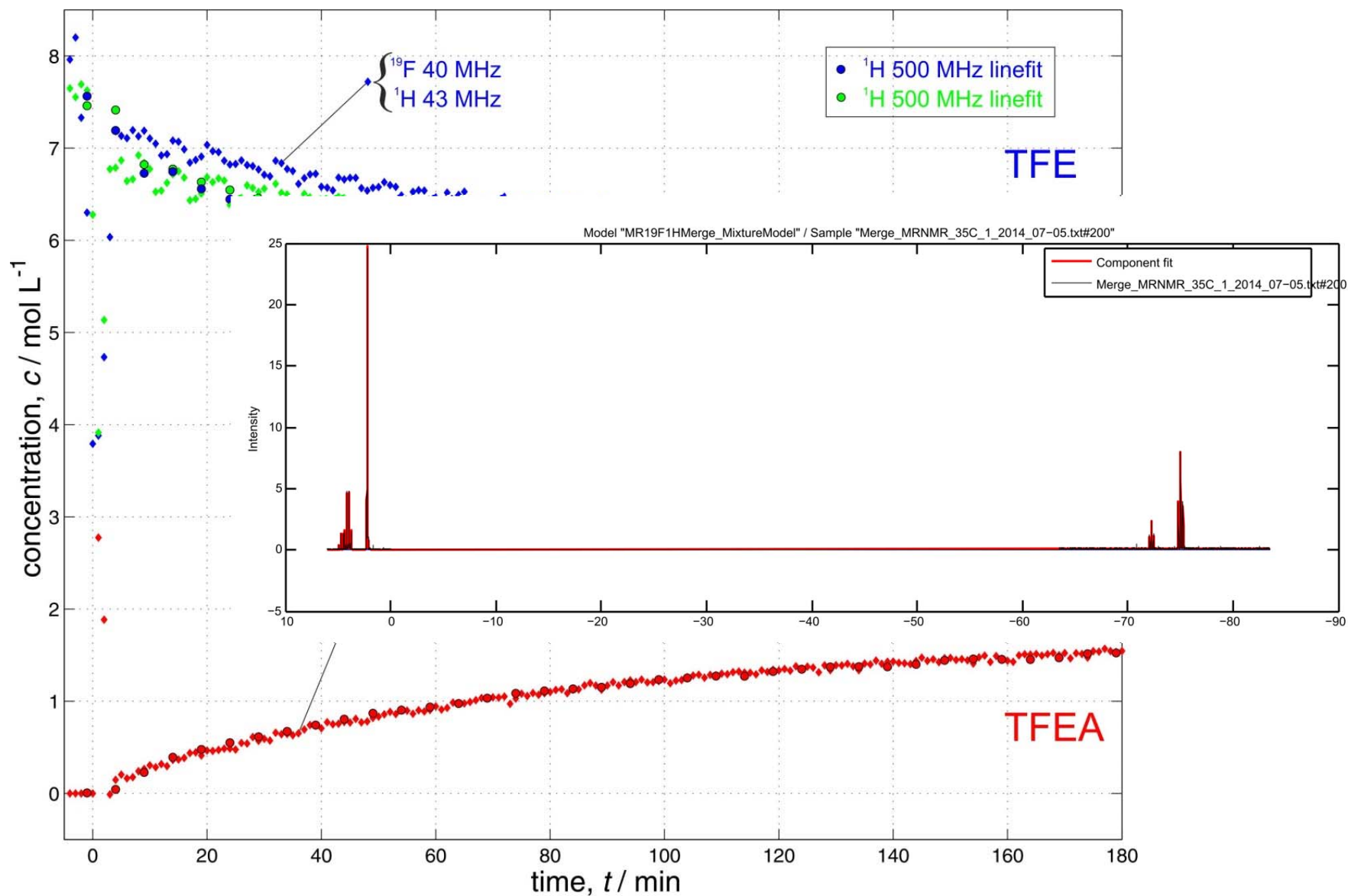
Method 3: IHM #1



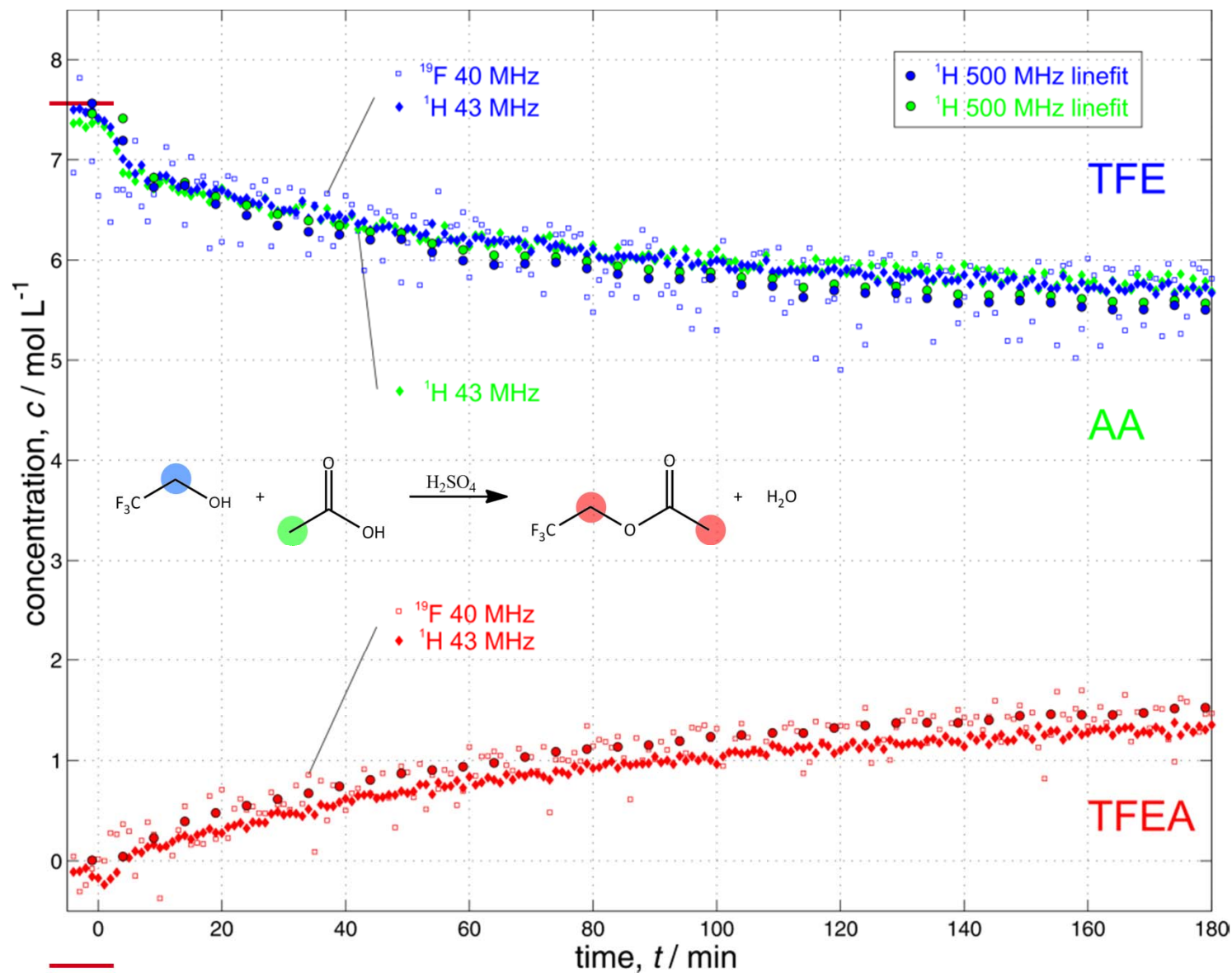
Method 3: IHM #2, combined model



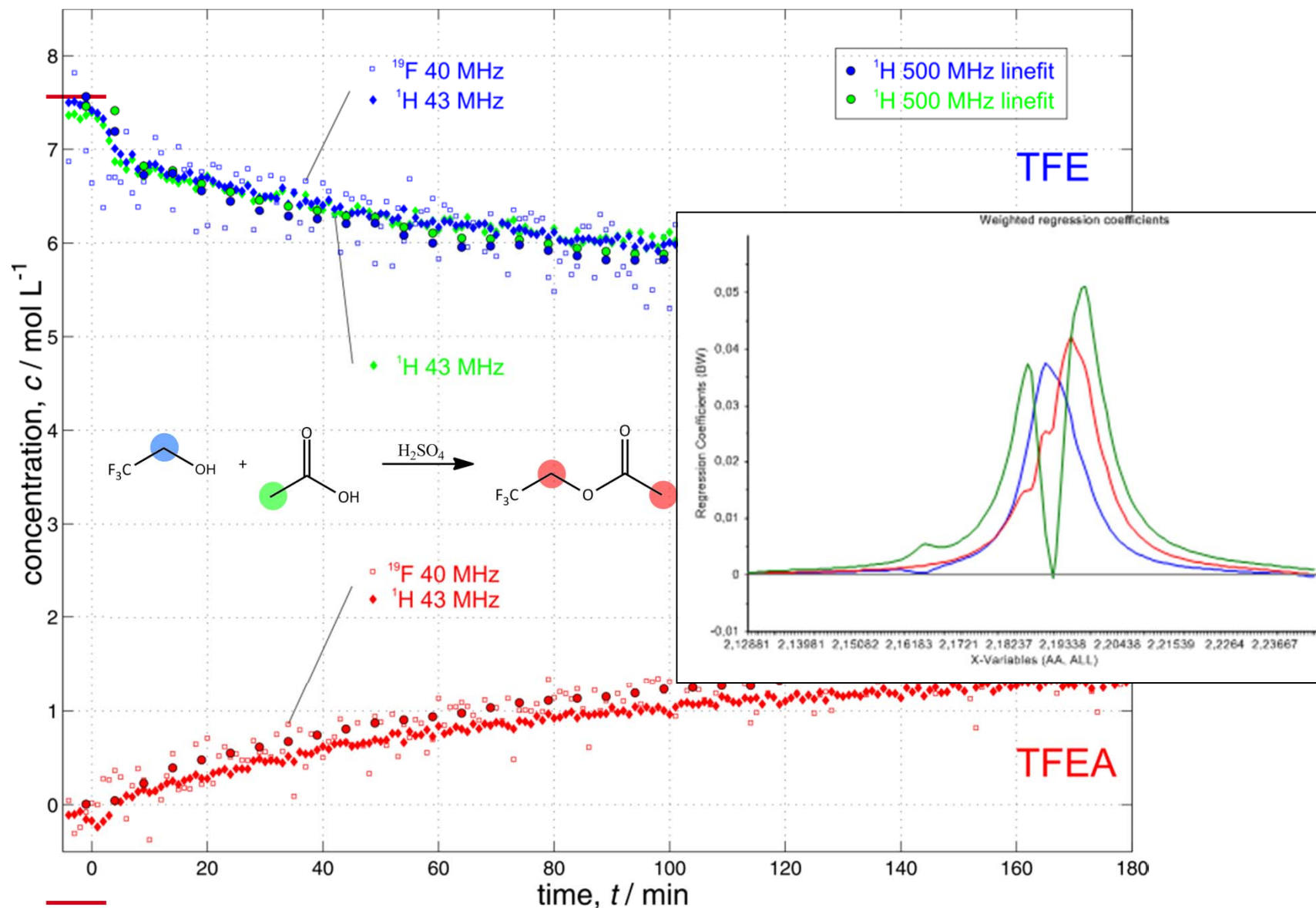
Method 3: IHM #2, combined model



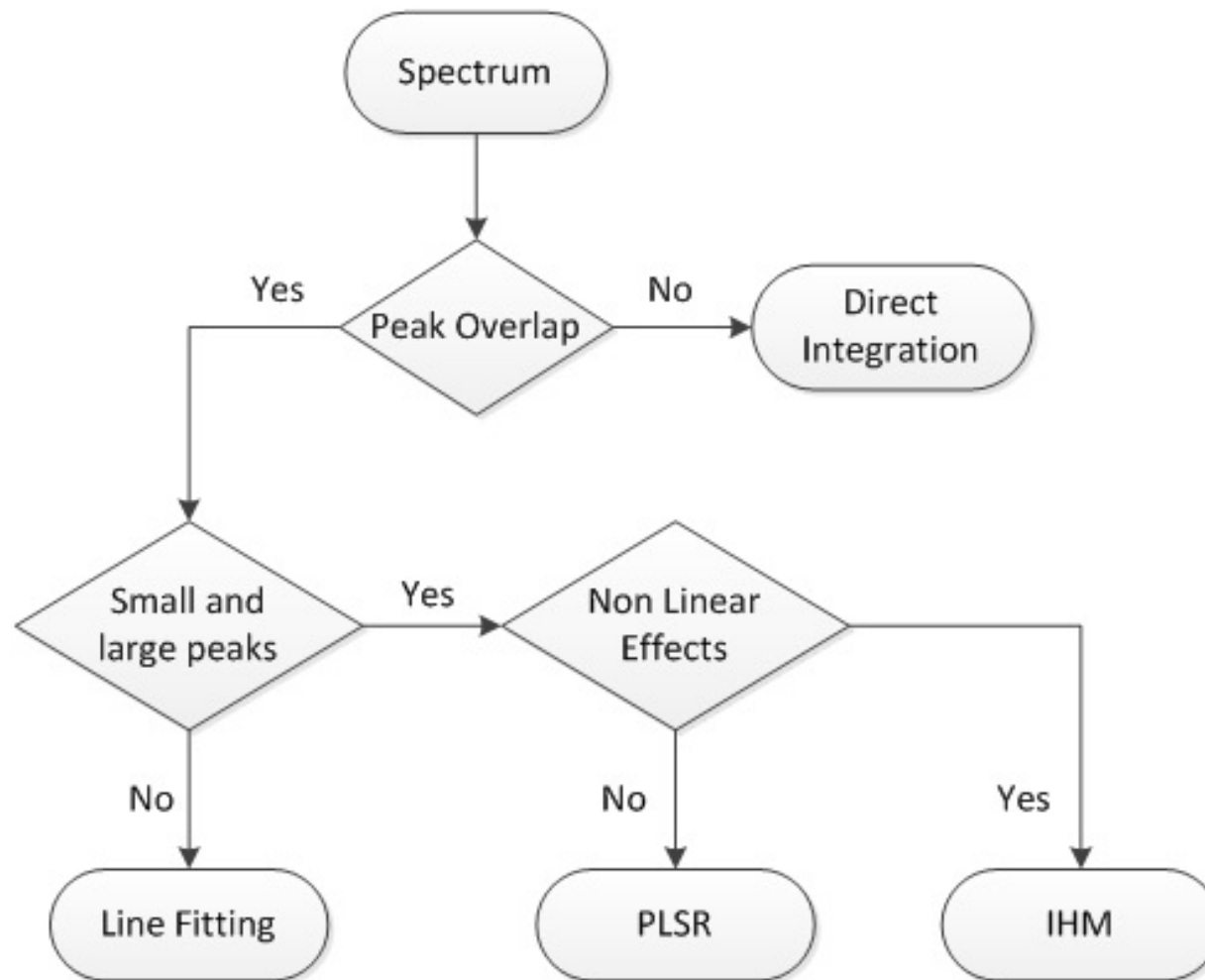
Method 4: PLS-R



Method 4: PLS-R

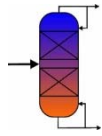


Decision tree



Conclusion

Go ahead

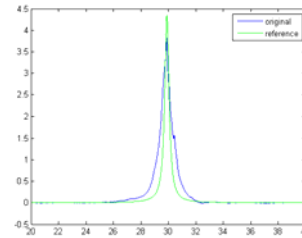


Processes

- Process Development
- Hybrid Plants
- Some Reactions

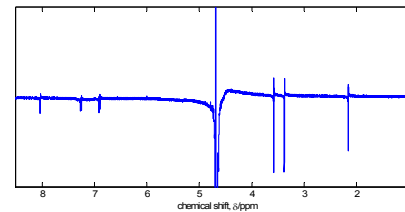
Instrument

- Stability
- Line Shape („enhancement“)
- Standards



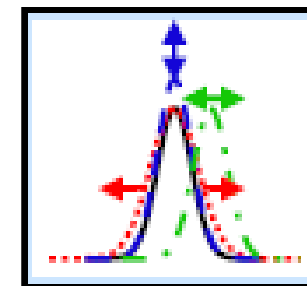
Data preparation

- Phasing

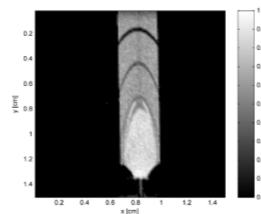
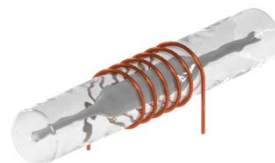
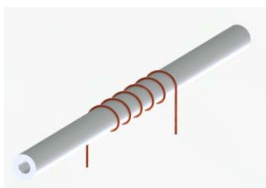
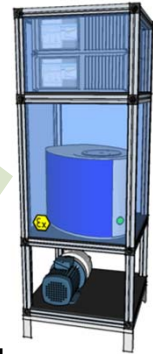


Data Modeling

- Direct Integration
- Line fit
- Indirect Hard Modeling
- Indirect Hard Modeling II
- PLS-R



- PLC control
- ATEX





About the project

- **Start Date:** 1st January 2015
- **Duration:** 36 Months, until 31st December 2017
- **Budget:** 6 million €
- **Project web site:** www.consens-spire.eu
(in construction)
- **Coordinator:** Manuel A. Pereira Remelhe,
BAYER TECHNOLOGY SERVICES
- **Consortium members:** see next page

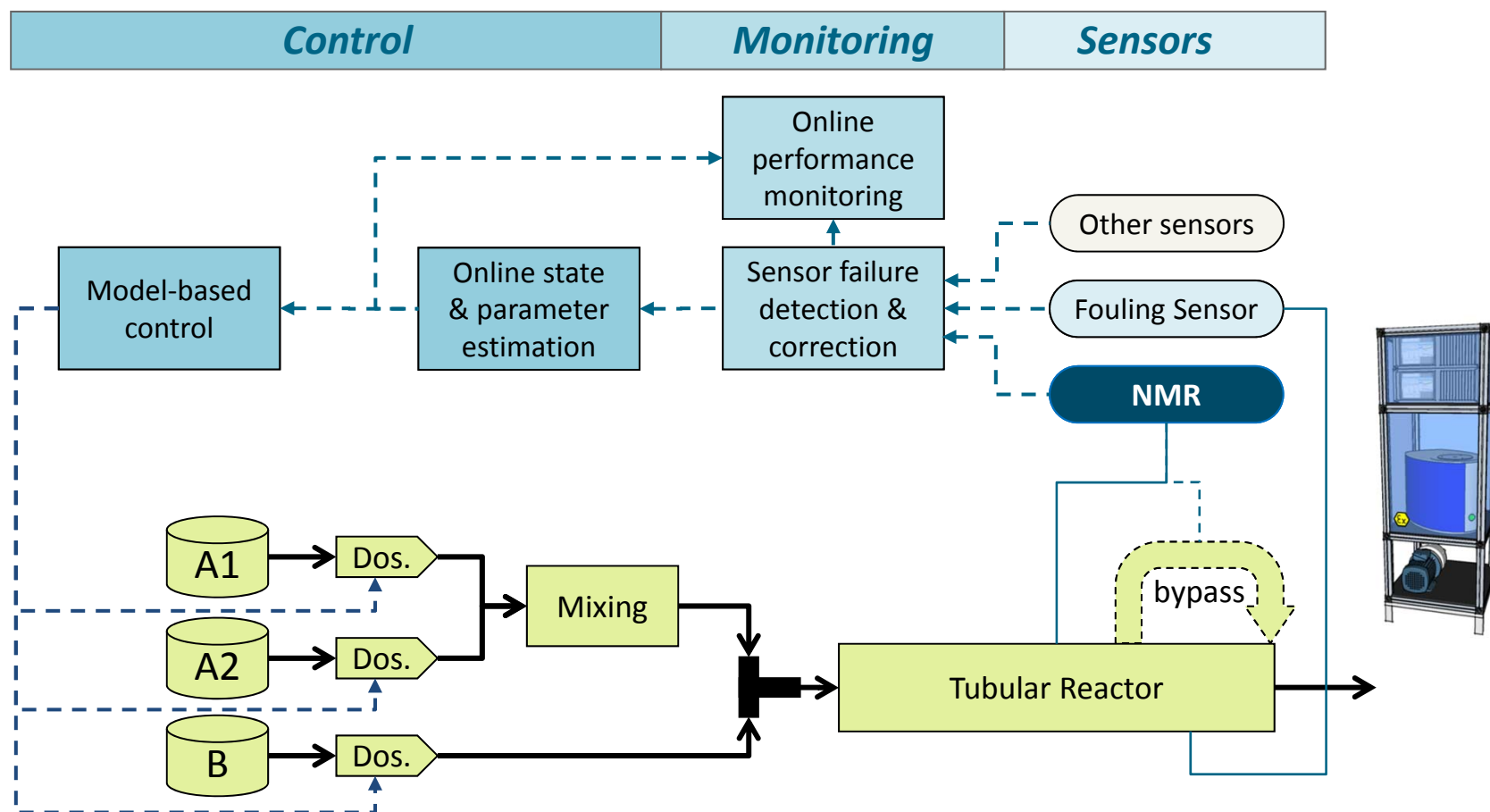


2015-2017



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

Example for integrated validation: Intensified synthesis of organic compounds



Acknowledgements



Thank you!

Ulrich Panne
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Andrew Coy
Juan Perlo
Federico Casanova

Magritek GmbH, Aachen

Mike Bernstein
Santi Dominguez

Mestrelab Research



Backup



NMR Process Monitoring

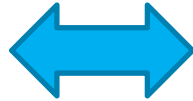
Towards an automated field integration



spectrometer hardware

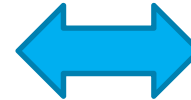
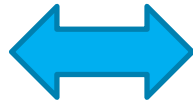
spectrometer software

user control and data storage



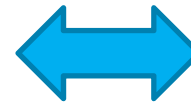
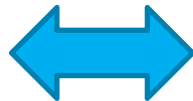
manual data analysis

GUI on PC in lab



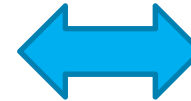
analysis method selected by user

„DLL“ on server farm



database

„DLL“ on PLC



analysis method implemented in PCS

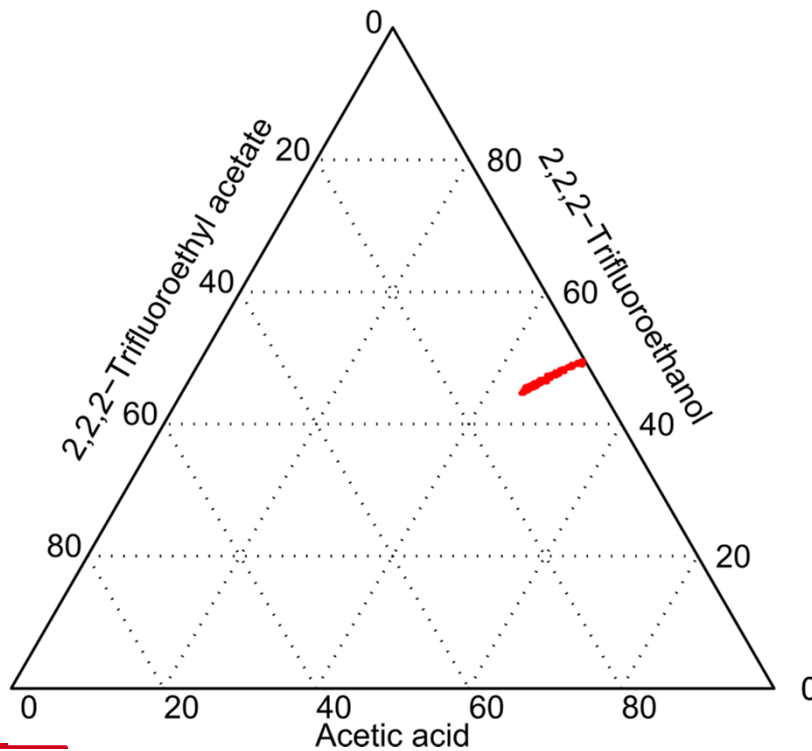


database

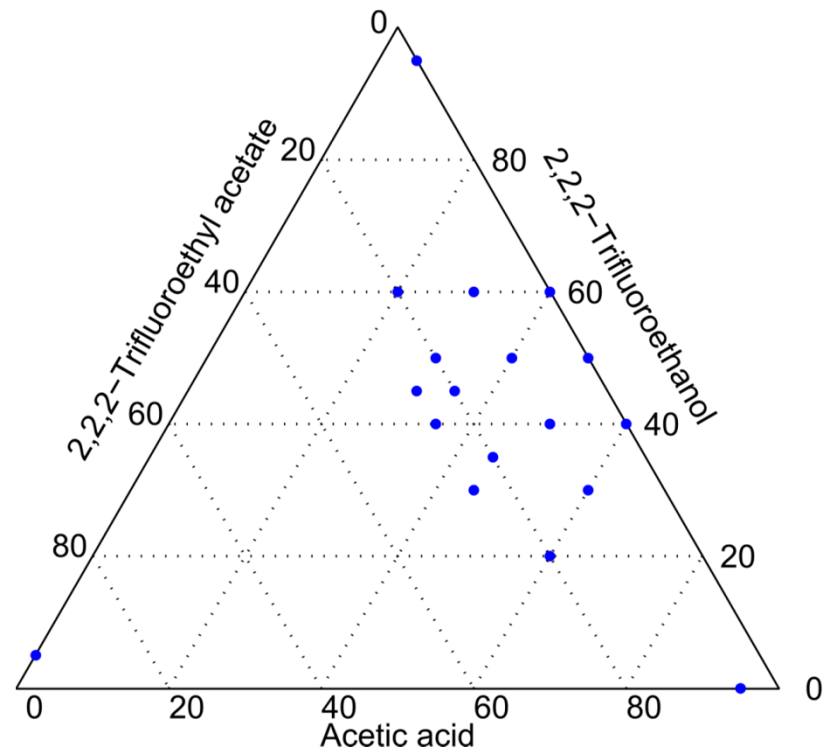
Offline Calibration

Preparing Ternary Mixtures of the Reactants
(projection into ternary diagram)

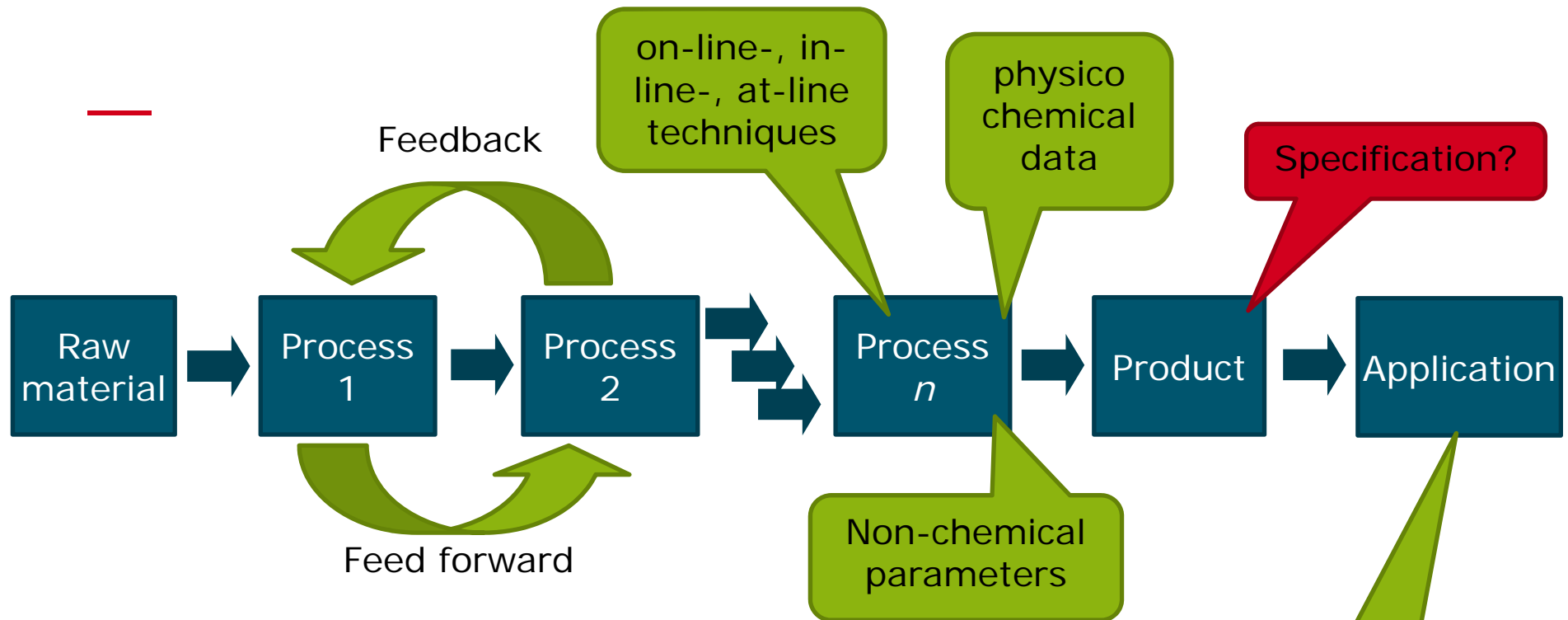
Course of reaction



20 Calibration mixtures



Process Analytical Technology



Motivation

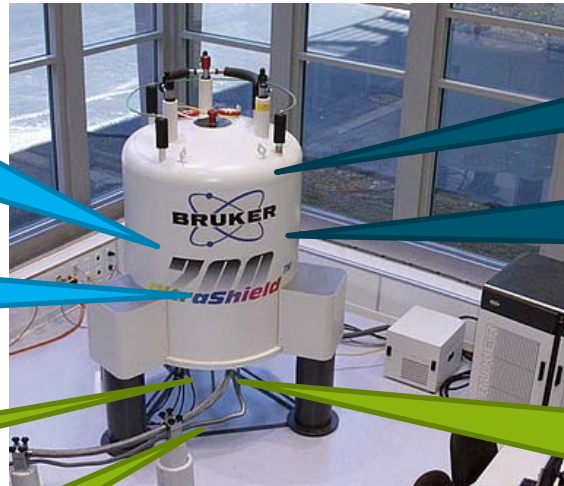
- optimal design ("quality by design")
- demanded product quality with an optimum use of equipment, raw materials, and energy

Quality by design

objective description of **quality**
→ comprehensive understanding

NMR Spectroscopy

Continuous improvement of acquisition time, stability, and linearity



PFG techniques
(*pulsed field gradient*)
▶ time improvement

shaped pulses
▶ selective excitation

cryo/cold probes
▶ sensitivity x 3

flow through probes
▶ direct hyphenation

parallel
NMR acquisition
▶ synchronous
NMR experiments

high-field NMR > 950 MHz
▶ highest dispersion

Ultra-shielded cryo
magnets
▶ no stray field

Improvement of
coil design
▶ sensitivity

^1H field mapping
▶ technical solvents
possible

direct digital detection
▶ no more artefacts

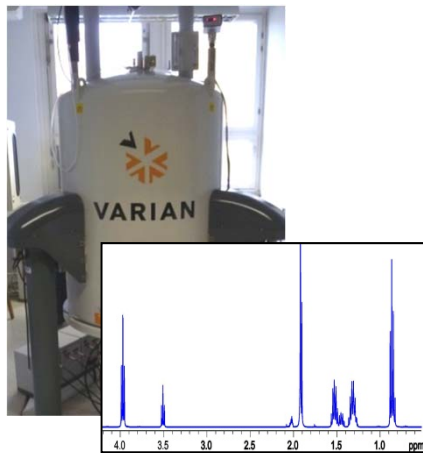
improved console concept
▶ no dead times



Quantitative Online NMR Spectroscopy



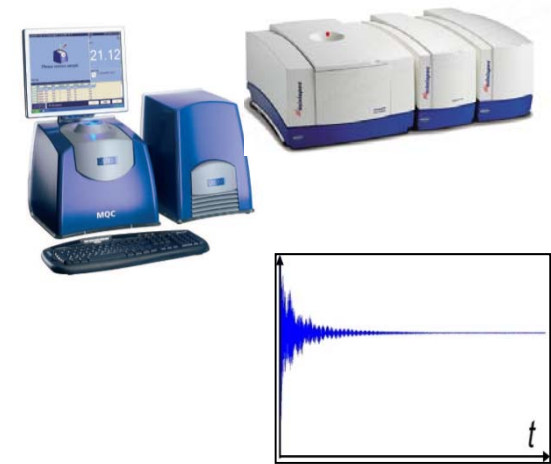
High resolution (HR) NMR
300–1.000 MHz



Benchtop NMR
30–90 MHz



Time Domain (TD) NMR
5–60 MHz



HR NMR 500 MHz
kryo magnet

- structure determination
- (bio) chemistry

Benchtop NMR 30–90 MHz
permanent magnet

- petro chemistry
- reaction observation

TD NMR 5–60 MHz
permanent magnet

- food quality control
- petro chemistry

Where are the limits for qNMR?



Physics and instrument

- S/N: dependent on
 - field (ω_0)
 - filling factor
 - volume (V_C)
 - filling factor (V_S / V_C)
 - temperature of coil (T_C)

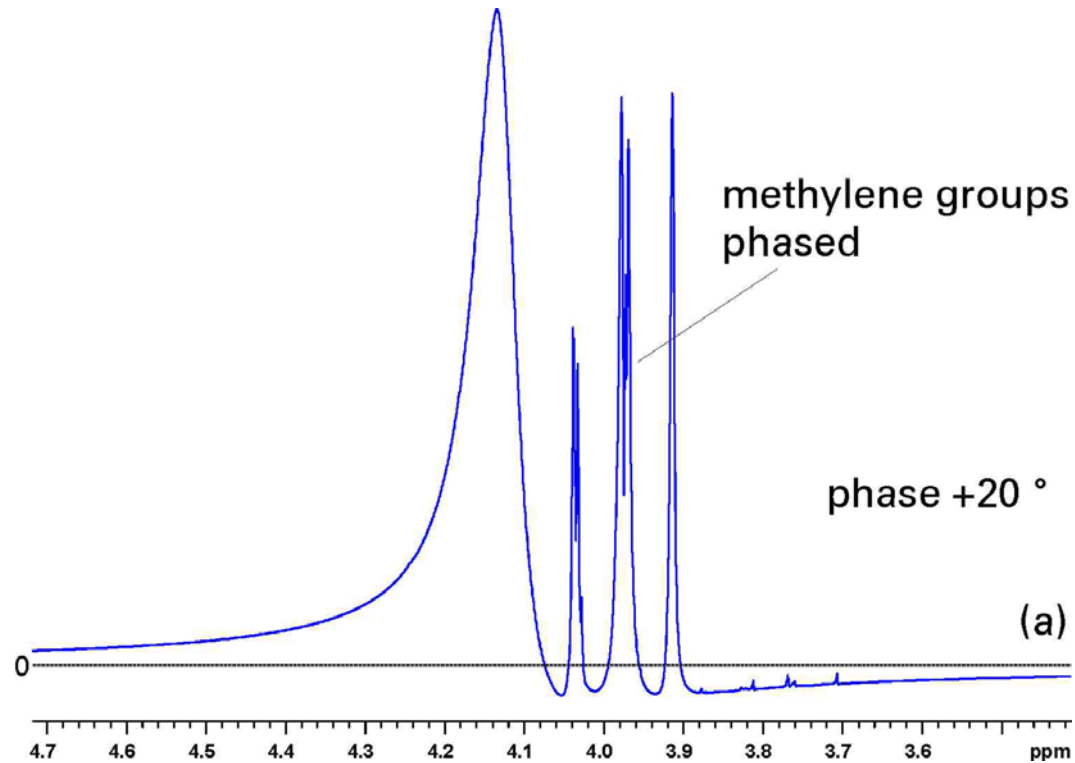
Hoult, D. I.; Richards, R. E.
J Magn Res **24**, 71 (1976)

$$\frac{S}{N} = \underbrace{V_S \omega_0^{\frac{7}{4}} \frac{N_S \gamma \hbar^2 I(I+1)}{3k_B T_S}}_{\frac{\chi_0}{\gamma}} \underbrace{(B_1/i)_{xy} \left(\frac{p}{k_B T_C \sigma l} \right)^{\frac{1}{2}} \left(\frac{1}{\mu_r \mu_0 \rho} \right)^{\frac{1}{4}}}_{coil} \underbrace{\left(\frac{1}{\Delta f} \right)^{\frac{1}{2}} \frac{3}{5.05}}_{probe}$$

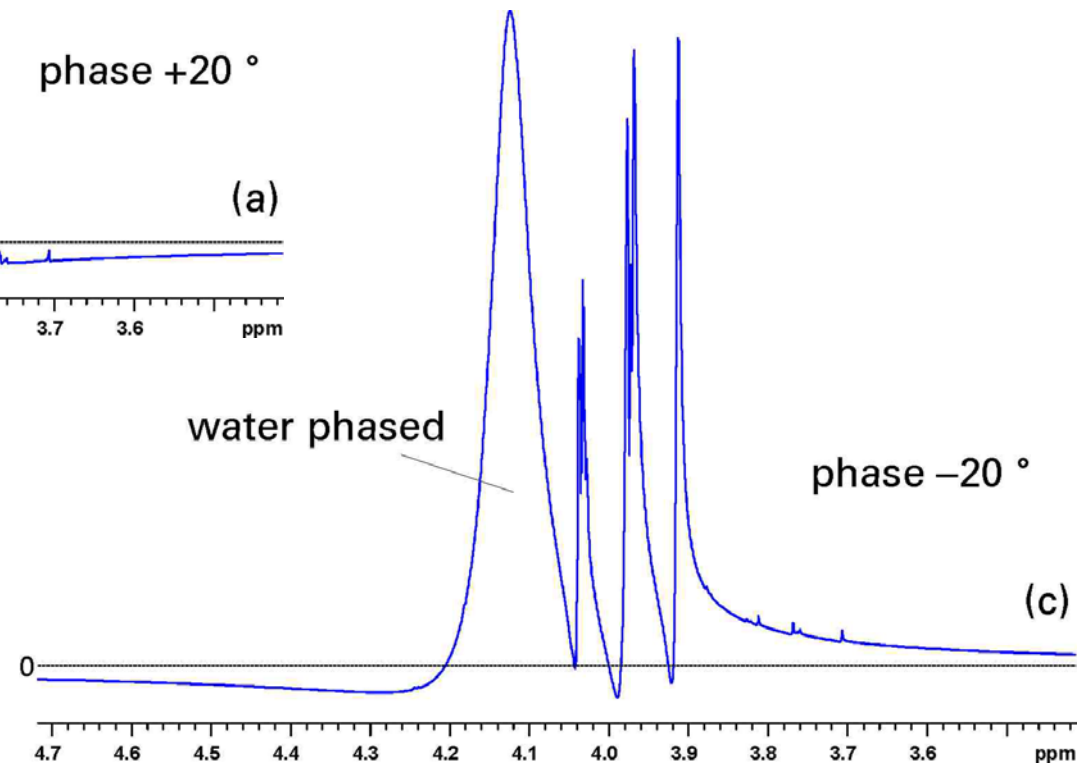
- Instrument electronics (amplifier circuits)
 - T-control of NMR console
 - Miniaturization
- Sample density (temperature dependent)
 - T-control of probe

Radiation damping

in technical mixtures: "ugly non-linear phase jumps"



Formaldehyde in water
 $w(\text{FA}) = 0,3401$, $T = 293 \text{ K}$, pH 2
400 MHz ^1H -NMR



Radiation damping in technical mixtures



- intensive NMR signals can induce current in receiver coil
- produced RF field speeds up relaxation
- time constant $T_{RD} = (2\pi \eta Q \gamma M_0)^{-1}$

filling factor η , quality factor $Q = \omega L/R$,
magnetogy. ratio. γ , equilibrium magnetization M_0

- leads to
 - line broadening and phase shifts
 - problems in high field nmr (e.g.,. effective water suppression)
 - errors in relaxation time measurements T_1 and T_2
 - errors in pulse width calibration
 - artifacts in 2D nmr spectroscopy
 - unexpected echoes in spin echoe experiments

Suryan, G.: *Current Sci. (India)* **18** (1949), 203

Bloom, A. L.: *J. Appl. Phys.* **28** (1957), 800–805

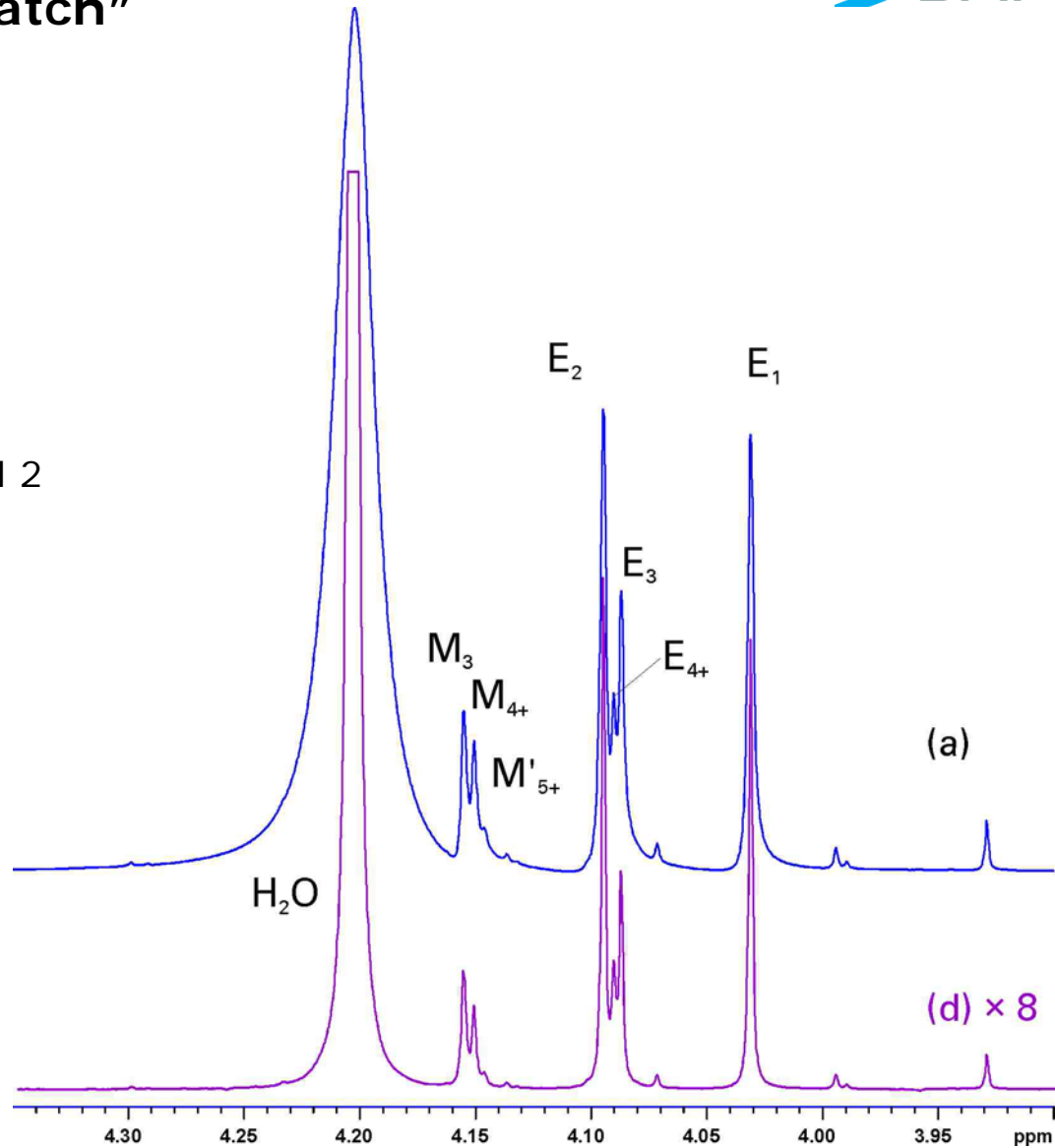
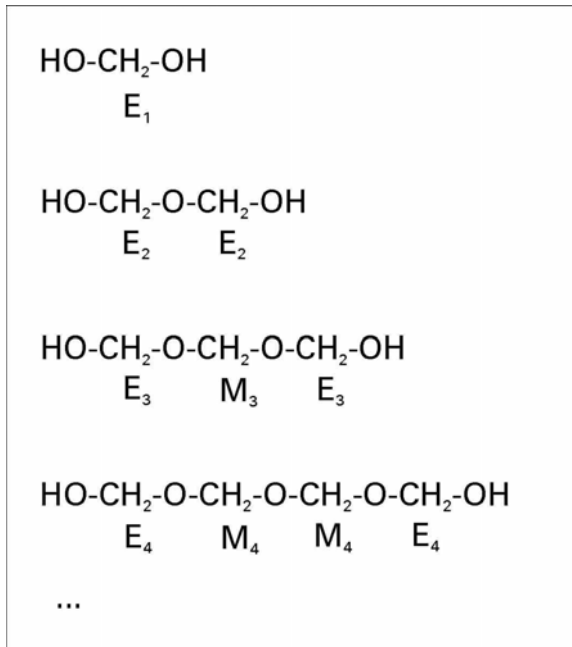
Freeman, R.: *A Handbook of Nuclear Magnetic Resonance*, Essex : Longman 1988

Augustine, M. P.: *Prog. NMR Spectroscopy* **40** (2002), 111–150

Radiation damping

Reduce by "tuning mismatch"

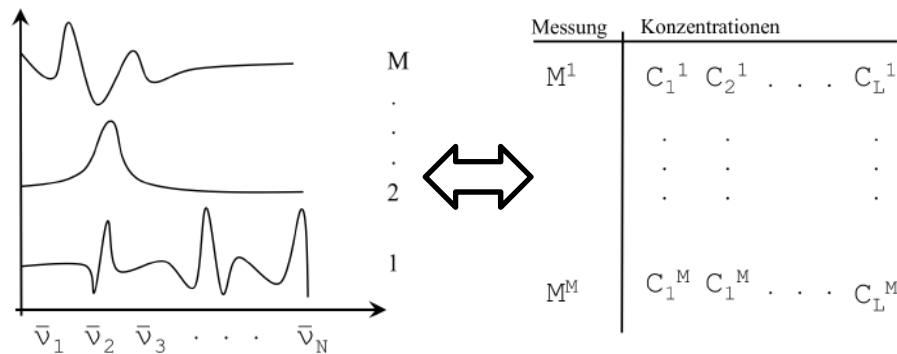
Formaldehyde in water
 $w(\text{FA}) = 0,3401$, $T = 293 \text{ K}$, $\text{pH } 2$
 400 MHz $^1\text{H-NMR}$



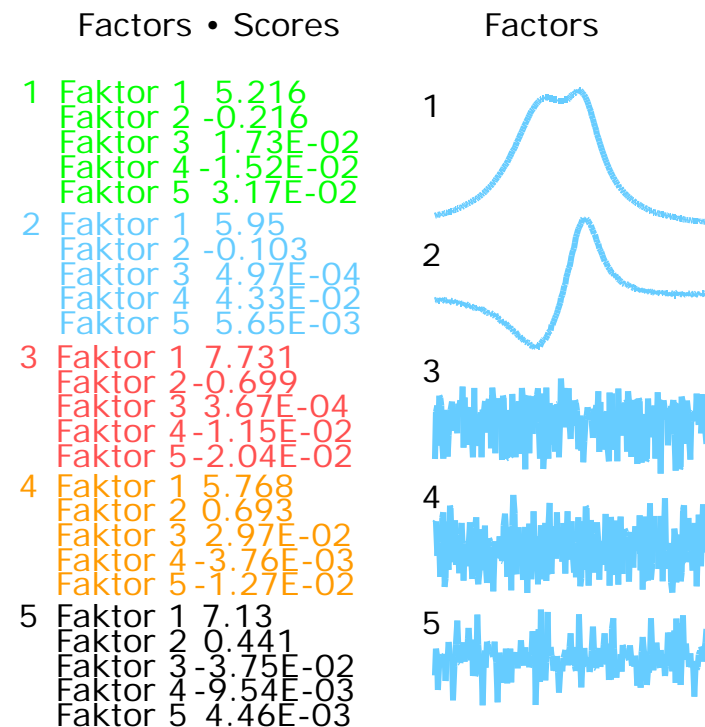
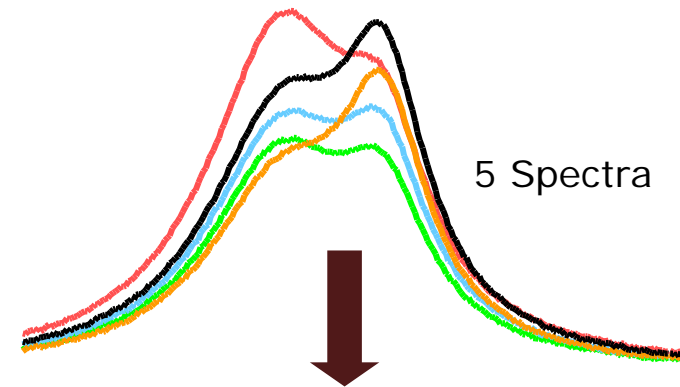
Method 4: PLS-R

Multivariate Data Analysis – Principal Component Analysis (PCA)

Spectra are decomposed into factors cf. Principal components and the associated weights of these factors (scores).



This results in a reduced data set where all characteristics of the spectra are conserved in individually weighted factors. This is done by exchanging the spectrum matrix and the concentration matrix.

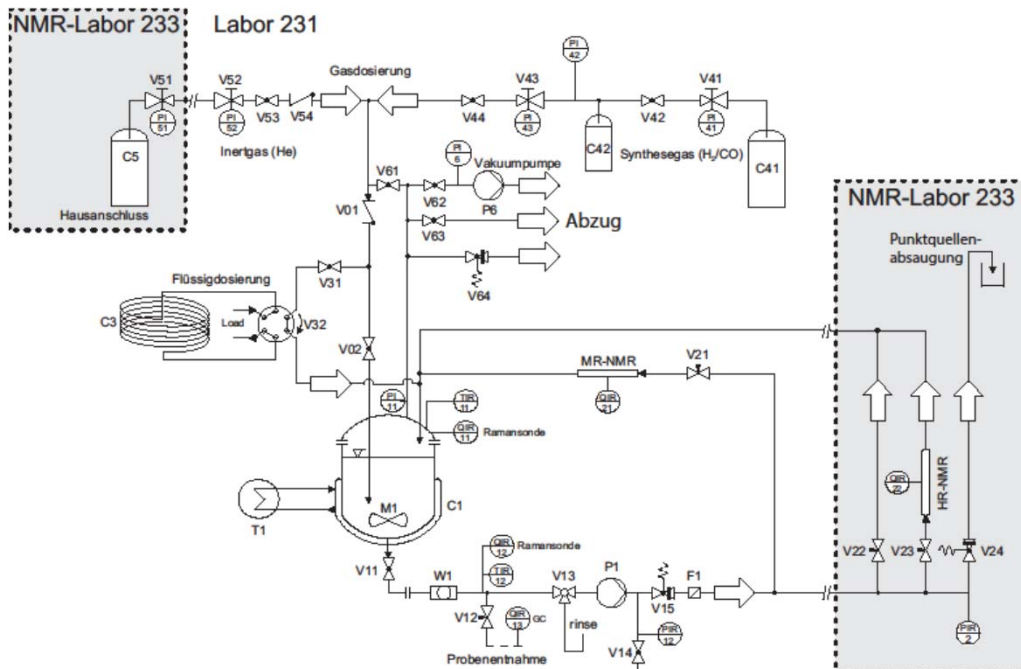
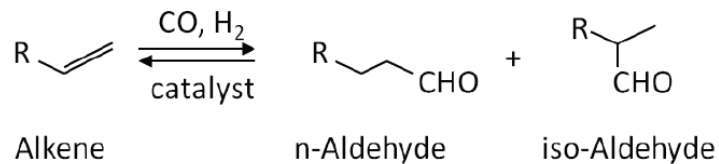


Example: Hydroformulation

Hydroformylation of long-chained alkenes in microemulsions

InPROMPT: Integrated chemical processes in liquid multiphase systems, hydroformylation of C12 – Alkenes [1]

Standard industrial process for aldehyde production



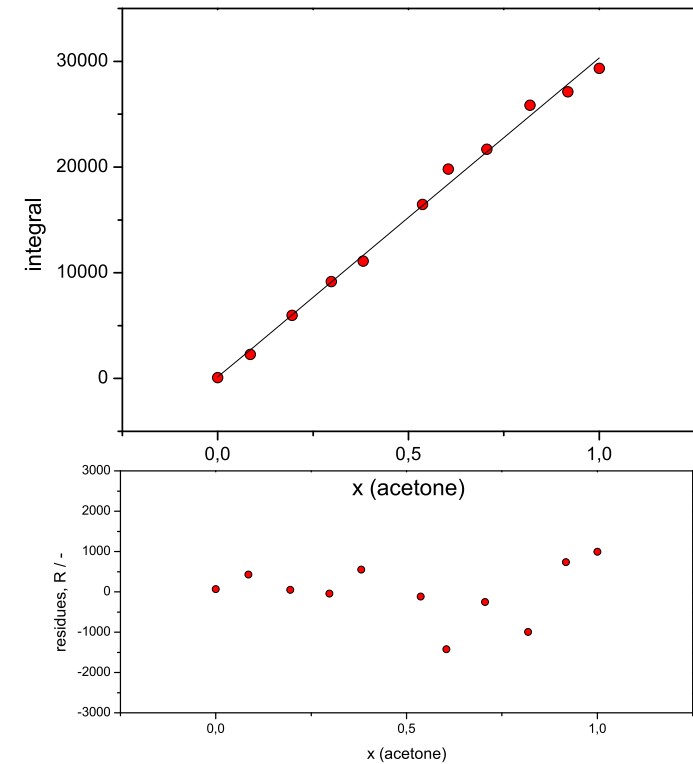
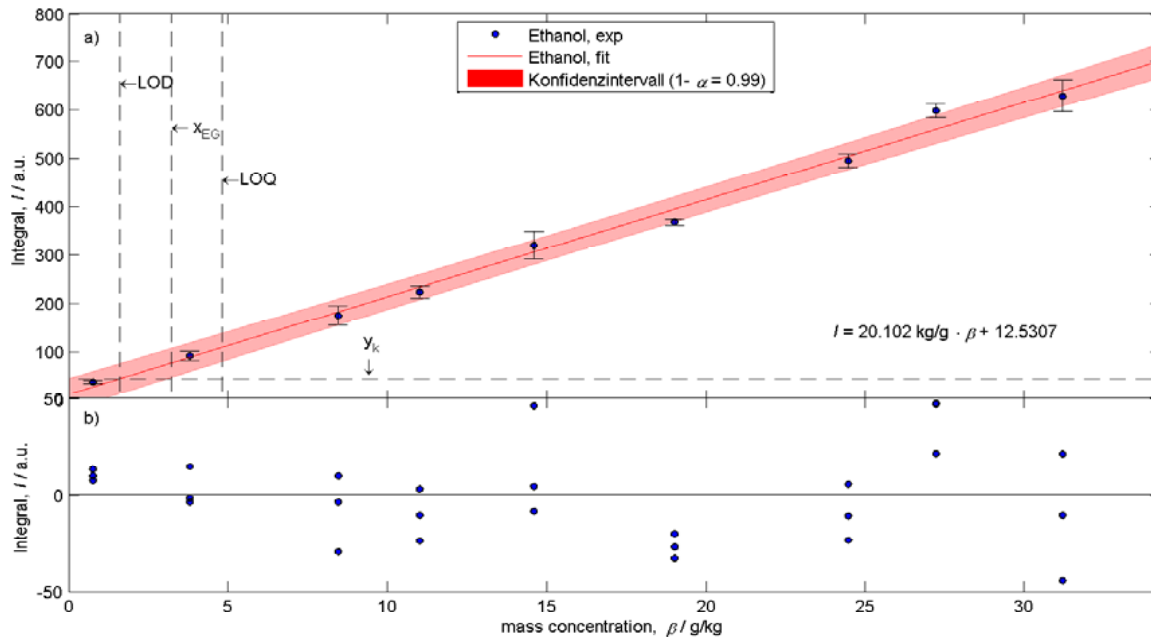
Characterisation

Limit of Detection and Quantification



Linearity

Acetone in Acetone-d6



	1/16" tube (43.5 MHz)	5mm tube (43.5 MHz)	500 MHz
LOD	17.7 g/kg	1.6 g/kg	3.2 mg/kg
LOQ	53.2 g/kg	4.8 g/kg	10.9 mg/kg