LOW FIELD NMR SPECTROSCOPY FOR PROCESS CONTROL

Robust automated data preparation and analysis as prerequisites

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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

Our Key Areas

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

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)

Located in Berlin, Germany
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

Quality by design
- Objective description of quality
  → comprehensive understanding

Specification?

Online-, in-line-, at-line techniques
Physico chemical data
Non-chemical parameters

Feed forward
Feedback

Raw material → Process 1 → Process 2 → Process n → Product → Application

Objective description of quality
→ comprehensive understanding
Process Analytical Technology

**Motivation**
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- Affordable quality costs

**Objective description of quality**
- Comprehensive understanding

**Parameters**
- Physicochemical data
- Non-chemical parameters

**Techniques**
- Feed forward
- Online-, in-line-, at-line

**Quality by design**
- Motivation
- Demanded product quality with an optimum use of equipment, raw materials, and energy
- Affordable quality costs

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

12.07.2017 S. Kern, M. Maiwald
Low field NMR spectroscopy for process control
From Lousy Interfaces to "Industrie 4.0"
Use of Runtime Environments

Sensor  Acquisition  Data evaluation  Decision

Past

sensor  prop. bus  GUI on lab PC  manual data processing  trial and error

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Use of Runtime Environments

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Past

- Sensor
- prop. bus
- GUI on lab PC
- Manual data processing
- Trial and error

Present

- Sensor
- prop. bus
- GUI on embedded PC
- Field bus
- Runtime environment (PLC)
- Field bus
- Process control system

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Present

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Future

- Sensor
- field bus
- runtime environment (PLC)
- field bus
- process control environment
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

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Low field NMR spectroscopy for process control
Continuous Lithiation Reaction Set-up
Flexible Intensified Continuous Plant

- Miniaturized flexible equipment
- Fast and complex exothermic reaction
- Hazardous and inflammmable substances  → Explosion protection!
- Prone to fouling & clogging
- Multi-objective constrained optimization
CONSENS: Case Study 1
Intensified Synthesis of Organic Compounds

Control  Data-usage  Sensors

Model-based control  Online state & parameter estimation  Sensor failure detection & correction

NMR

Other sensors

Sensor failure detection & correction

Online performance monitoring

Other sensors

Online state & parameter estimation

Explosion proof housing

By-pass stream

Product stream

Reaction Scheme:

FNB

Aniline

LiHMDS

NDPA

HMDS

Source: INVITE GmbH

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Conventional and Smart Functions
Enabling Runtime Environments

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

**Conventional 4–20 mA Failsafe**

**NAMUR Status Signals**

**ATEX proof**

**Fast Field Bus**

**OPC-UA Server**

**Industrie 4.0 World**

**Conventional World**
Reaction Monitoring in Lab-scale at BAM
Nuclear Magnetic Resonance (NMR) 
Direct Comparison Method → Calibration Free!

- Individual NMR signals
- FT
- Radio frequency pulse
- Ground state
- Excited state
- Energy

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Low field NMR spectroscopy for process control
NMR Spectroscopy

Analogy to a Bell

- Methanol
- Benzoic acid
- Water
- Ester (\(^{13}\)C)
- Fructose
- Neopentane

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

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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 $^1$H NMR Spectra of Lithiation Reaction Step

High field (500 MHz)

- Start of reaction
- End of reaction

Low field (43 MHz)

- Start of reaction
- End of reaction

aromats

solvent

HMDS
Data Processing for Low-field NMR in Matlab

Raw spectra

Phase correction

Baseline correction

Alignment

single scan each 15s in flow
Data Processing for Low-field NMR in Matlab

- Raw spectra
- Phase correction
- Baseline correction
- Alignment

**Entropy minimization method:**
Chen et al., J Magn Reson. **2002**, 158, 164-168
Data Processing for Low-field NMR in Matlab

- Raw spectra
- Phase correction
- Baseline correction

Low-order Polynomial fit:
Mazet et al., Chemometrics
Data Processing for Low-field NMR in Matlab

- Raw spectra
- Phase correction
- Baseline correction
- Alignment

Alignment to reference signal (THF) using $i$coshift: Savorani et al., J Magn Reson. 2010, 2, 190-202

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Challenges in Automated Data Analysis

Data pretreatment
Integration
MCR
Binning/ PLS-R
GSD/ Edited Sum
IHM

http://collegeaffordology.com/

Young PhD student
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

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

\( a \) = peak maximum
\( \beta \) = Gaussian-Lorentzian-ratio
\( \gamma \) = half width
\( \delta \) = center position

Hard model for pure components

- Group of peaks represent pure component spectra
- Pseudo-Voigt function

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Pure component models

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

Deconvoluted spectrum

Analysis “component fitting”

Mixture model

Component fitting

Experimental Spectrum

Position Height Width
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

![Graph showing molar concentration deviations](image)

- "Bad" shim

Reaction Scheme:

![Chemical reaction scheme](image)

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Results: Validation of IHM Model
Lab Experiments in Batch along Reaction Co-ordinate

Step tracer experiments

1/8” tube reactor

Low-field NMR
High-field NMR

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Low field NMR spectroscopy for process control
Monitoring of Continuous Aromatic Substitution Reaction by Low Field NMR
Monitoring of Continuous Aromatic Substitution Reaction by Low Field NMR

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9
NF-NMR Concentration, c / mol L\(^{-1}\)

Toluidin
FNB
Li-Toluidin
Li-MNDPA

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9
HF-NMR Concentration, c / mol L\(^{-1}\)

Concentration, c / mol L\(^{-1}\)

00:00:00
01:00:00
02:00:00
03:00:00
04:00:00
05:00:00

Time, t / hr:mm:ss

A10 A11 A12 A13 A14 A15 A16 A17 A18 A19

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Problem: Overestimation of Components at Low Concentrations

![Graphs showing molar ratio over time for Aniline (IHM), NDPA (IHM), oFNB (IHM), Aniline (PLSR), NDPA (PLSR), oFNB (PLSR).]
Challenges in Industrial Scale
Varying Peak Width

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

Comparison of proton spectra of different runs.
Challenges in Industrial Scale

Unknown Components

Model derived from Lab data

Model adaptation to „process conditions“

Stabilizer
THANK YOU!

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Juan Perlo  Magritek
Mike Bernstein  MestreLab

Harald Pape  PTB
Clemens Minnich  S-Pact
Dirk Engel  S-Pact
Alfons Steil  PSG Petro Service

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Backup
Integrated Process Design and Intensified Processes

Current Trend: Hybrid Modular Plants

- Simulation
- Laboratory
- Miniplant

Micro Reaction Technology
(Example: Fraunhofer ICT, Pfinztal/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

- Modular Set-up?
- Soft Sensing?
- Model-based Control?
- Self-Calibration?

Enterprise Network (LAN)
Classical Field Bus
Automation Network
Process Analytical Technology for Intensified Processes

Examples from BAM

Catalysis:
Hydroformylations of C12-alkenes in micro emulsions

\[
\begin{align*}
\text{Alkene} & \xrightarrow{\text{CO}_2, \text{H}_2} \text{Aldehyde} + \text{iso-Aldehyde} \\
\text{Catalyst} & \quad \text{Aldehyde} + \text{iso-Aldehyde}
\end{align*}
\]

Pharmaceuticals:
Liberation kinetics

CO\(_2\) scrubbing

Reaction Engineering:
Lithiation reactions

Method development:
Esterifications (model reactions)

Reaction Engineering:
Photo reactions ("click chemistry")

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

Catalysis:
Hydrogenations

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:

Optimal process window
Smart NMR Sensor Concept

Safety devices
- Nitrogen purge control
- Leakage safeguard

Measuring Conditions
- Triggering
- Automated evaluation (Matlab)
- MySQL Database

Data Acquisition
- Conventional 4–20 mA
- Programmable Fieldbus Controller

Module size: 850 x 570 x 570 mm

OPC-UA Client

Ethernet

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Online NMR Module: Data flows

Programmable Fieldbus Controller:
- Collection of Sensor data (T, p, Flow, NMR data)
- Triggering of NMR
- OPC UA Communication
- 4-20 mA Output

Onboard Windows PC:
- Matlab watchdog function
- Spectrometer software

Nitrogen Purge Unit:
Safety relais

4-20 mA Output

Access Point

TCP/ My SQL Connection

WAGO WebVisu

WAGO OPC UA Client
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**

- Sensitivity/sufficient S/N ✓
- Long term stability ✓
- Validation in lab scale ✓
- Spectral assignments ✓
- Thermostated and optimized flow probes ✗

**Chemical industry**

- ATEX/Explosion proof ✓
- PLC interfaces ✓
- Automated data analysis ✓
- Validation in industrial environment ✗
- Dispersions and Emulsions ✗
- High p and T ✗
- Smart Field Bus ✗


NMR-Grundlagen
Quantenmechanische Einschränkung

spin angular momentum

magnetic spin momentum $\mu$

$L$

proton

$M_l = -\frac{1}{2}$

$M_l = + \frac{1}{2}$

$Z$

$\mu$

55°
Quantenmechanische Einschränkung

Die Spins richten sich im Magnetfeld auf Kegelmänteln aus

\[ M = 0 \]

magnetization

\[ M > 0 \]

ground state
(higher population)

excited state
90°-Anregung mit Radiofrequenzpuls

magnetization $M$ shows into $x$-$y$-plane
Variation der Pulslänge (Kalibrierung)

(jeder Schritt +1.5 ms)

90 ° Puls ca. 9 ms

180 ° Puls ca. 18 ms
Relaxation

spin spin exchange

transversal relaxation $T_2$

$B_0$

time
Relaxation

longitudinal relaxation $T_1$
Chemische Verschiebung

Spin Angular momentum $L$ → Magnetic spin momentum $\mu$

$tetramethylsilane TMS$

NMR frequency $\nu$/MHz

400.0
Chemische Verschiebung

reference
400.0 MHz

2884,0 Hz
2000,0 Hz
772,0 Hz

frequency offset $\Delta v$/Hz
Chemische Verschiebung d-Skala

400 MHz (9,4 T)  
100 MHz (2,3 T)

δ = 7,21 ppm  δ = 5,00 ppm

2884,0 Hz  721,0 Hz

δ = 1,93 ppm

2000,0 Hz  500,0 Hz

δ = 0 ppm

772,0 Hz  193,0 Hz

unshielded low field

shielde high field
$^1$H-NMR-Spektrum von Ethanol

Kernspins der CH$_2$-Gruppe

Energie

chemische Verschiebung $\delta$/ppm

beobachtete Kerne: -CH$_3$

$^3J_{HH}=6$ Hz

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Low field NMR spectroscopy for process control
$^1$H-NMR-Spektrum von Ethanol

Kernspins der CH$_2$-Gruppe

beobachtete Kerne: -CH$_2$-

chemische Verschiebung $\delta$/ppm

$^3$J$_{HH}$=6 Hz

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$^{1}$H-NMR-Spektrum von Ethanol

$^{3}J_{HH} = 6 \text{ Hz}$