Man proposes, God disposes

Robert Fludd (1574–1637)
Micocosm (1619)

Utriusque cosmi maioris scilicet et minoris [...] historia, tomus II (1619), tractatus I, sectio I, liber X, De triplici animae in corpore visione.
de.wikipedia.org
Man proposes, 
God disposes

Corporate Microcosm

Sensors

Models

Knowledge Undestanding Technical rules

Process Control

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Contemporary process engineering
Towards Cyber-Physical Production Systems (CPPS)

Process engineering focuses on the design, operation, control, and optimization of chemical, physical, or biological processes.

- Involves creating production facilities that translate raw materials into value-added products along the supply chain
- Conversions typically take place in repeated reaction and separation steps – either in batch or continuous processes.
- Computer aided tools: mass transfer, thermodynamic, kinetic, and other physical properties of treated materials
- Sufficient understanding of such properties is available and implemented in dynamic numeric models.
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.

Integrated process design and intensified processes

- Intensified continuous processes

Motivation
- Continuous Processing
- Standardized modular equipment
- Numbering-up on demand
- Fast response to marked change

More efficient and flexible low to medium scale production of specialty chemicals

Intensified production concepts require for adaptive sensor and process control technology
- Short set-up times
- Modular control strategies
Integrated process design and intensified processes

Example: Flow Chemistry

A. Adamo, R. L. Beingessner, M. Behnam et al., On-demand continuous-flow production of pharmaceuticals in a compact, reconfigurable system, Science Science 352(6281), 2016, 61-67

Process analytical technology for intensified processes

Examples from BAM

Catalysis:
Hydroformylations of C12-alkenes in micro emulsions

Pharmaceuticals:
Liberation kinetics

CO₂ scrubbing

Reaction Engineering:
Lithiation reactions

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

Method development:
Esterifications (model reactions)

Catalysis:
Hydrogenations

Reaction Engineering:
Photo reactions ("click chemistry")
Validation lab experiments in tube reactor

Continuous Lithiation Reaction Set-up at BAM

Data usage

Control
- Online performance monitoring
- Online state & parameter estimation
- Sensor failure detection & correction

Sensors
- Other Sensor
- NMR
- Low field NMR
- High-field NMR

- Experimental design for validation of spectral models
- Full conversion was achieved

- same residence time as pilot plant

Reaction Scheme

Proton NMR Spectra 500 MHz vs 43 MHz

Lab experiments in batch along reaction co-ordinate
Model Building: IHM and PLS-R
Lab experiments in Batch Along Reaction Co-ordinate
Validation with HF-NMR

Indirect Hard Modeling (IHM)
How it works

Pure component models

Deconvoluted spectrum

Experimental Spectrum

Position

Height

Width

Mixture model

Component fitting
Model Building: IHM and PLS-R

Lab experiments in Batch Along Reaction Co-ordinate

Current Limitations

- Model limitations for low concentration of Aniline
- Prediction uncertainty 5–7 % relative, i.e., 0.25–0.35 % absolute
Model Validation
Lab Experiments (DoE) in Continuous Tube Reactor

- Two series covering 1 : 1 : 2.3 (FNB : Aniline : Li-HMDS)
- Additional experiments, e.g., concentration variation in THF etc.

<table>
<thead>
<tr>
<th></th>
<th>-50 %</th>
<th>-20 %</th>
<th>-10 %</th>
<th>0 %</th>
<th>+20 %</th>
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</table>

- Model Building: IHM and PLS-R
Lab experiments in Batch Along Reaction Co-ordinate

Current Limitations

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Model Building: IHM and PLS-R
Lab experiments in Batch Along Reaction Co-ordinate

Current Limitations

- Model limitations for low concentrations of Aniline
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DoE: 10% less Li-HMDS, Ratio 1:1:2.6
(Anilin : FNB : Li-HMDS)
Concentration FNB and Anilin 0.6 mol/L

Model Validation
Variation of Substituents in Continuous Tube Reactor

- Various substituents
- Fast adaption of spectral models to various substituents
- Calibration-free

\[ R = H, \text{CH}_3, \text{F} \]
"Click" analytics for "click" chemistry – a simple method for calibration-free evaluation of online NMR spectra

Reaction mechanism of the thio-ene coupling monitored with online NMR spectroscopy:

\[ \text{H}_2\text{C} = \text{CH} \text{NHBoc} + \text{HO} - \text{CH} = \text{CH}_2 \xrightarrow{\text{ACl} / \text{DMSO} / \text{DMF}} \text{HO} - \text{CH} = \text{CH}_2 \text{NHBoc} \]

Recorded online spectra:

Kinetic information for various solvents:

Summary: Low Field Reaction Monitoring
And it’s Way to Industrial Automation

Todos

Processes
- Dispersions
- Emulsions
- Technical conditions in T and p

Flow Probe
- Thermo-stating
- Optimized pre-magnetisation
- Pressure resistance
- Optimized probe design

Instruments
- Automated shimming
- Stable lock
- Line shape stability
- Long-term stability
- Lab remote control

Data Preparation
- Automated phasing
- Automated baseline correction
- Data quality evaluation

Data Analysis
- Spectral Modeling
- Sensor fusion
- "Semantic" models
Current and future requirements to process sensors

Sensors go smart

- Smart process sensors are important parts of cyber-physical production systems and generate new business cases for users, instrument manufacturers, and service providers.
- "Smart" sensors provide services within networks and use information out of the network.

- Use of "complicated" sensors has to be simplified towards "plug and play"
Communication Concept

- Safety Information
  - Leakage, T, p

NAMUR status signals
Conventional 4-20 mA

OPC-UA Client

ATEX-proof WiFi

Fast field bus

Smart Sensors

ERF = 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
From Lousy Interfaces to "Industrie 4.0"
Use of Runtime Environments

Past:
- Sensor
- Acquisition
- Data evaluation
- Decision

- Sensor → prop. bus → GUI on lab PC → manual data processing → trial and error

Present:
- Sensor
- Acquisition
- Data evaluation
- Decision

- Sensor → prop. bus → GUI on embedded PC → field bus → runtime environment (PLC) → field bus → process control system
From Lousy Interfaces to “Industrie 4.0”
Use of Runtime Environments

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**Past**
- Sensor: prop. bus
- GUI on lab PC

**Present**
- Sensor: prop. bus
- GUI on embedded PC
- Field bus: runtime environment (PLC)

**Future**
- Sensor: field bus
- Runtime environment (PLC)
- Field bus: process control environment

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Dirk Engel    S-Pact

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
Process Control

- Contemporary process engineering
- Integrated process design and intensified processes
  - Intensified continuous processes
  - Integrated processes
  - Towards continuous pharmaceutical manufacturing
  - Flow chemistry
- Contemporary automation and process control
- Current and future requirements to process sensors

Integrated process design and intensified processes
Towards continuous pharmaceutical manufacturing

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<th>Presently Targeted Approach</th>
<th>Future Vision</th>
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<td>Quality by Design (QbD)</td>
<td>Continuous Manufacturing (CM)</td>
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<td>Studies with particular parameter variations</td>
<td>ICH Guideline Q8 „Design Space“</td>
<td>„Real Time Release“ (RTR)</td>
</tr>
<tr>
<td>Defined Processes and Specifications (ICH Q6)</td>
<td>ICH Guideline Q9 „Quality Risk Management“</td>
<td>Flexible hook-up of small production facilities</td>
</tr>
<tr>
<td>„Quality by Testing“ (QbT)</td>
<td>ICH Guideline Q10 „Pharmaceutical Quality Systems“</td>
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<td>ICH Guideline Q11 „Development and Manufacture“</td>
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Contemporary automation and process control

- Current focuses of research are closed-loop adaptive control concepts for plant-wide process control, which make use of specific or non-specific sensors along with conventional plant instruments.
- Such advanced control solutions could give more information than only control information, such as
  - sensor failure detection
  - control performance monitoring
and improve simulation-based engineering.

Motivation
- processes can automatically be driven much closer to the optimal operating limit
- adaptation during the life cycle of the process
- potential to automatically cope with changes of the raw-materials as well as process conditions

Model Building: IHM and PLS-R
Lab experiments in Batch Along Reaction Co-ordinate

Current Limitations

- High field NMR as reference method (RTD corrected)
- Calibration free (100 % method)
- Molar concentration calibration

DoE: 50 % less Li-HMDS, Ratio 1:1:2,6 (Anilin : FNB : Li-HMDS);
Concentration of FNB and Anilin 0,6 mol/L