Attributes of Real-time Micro-Analytical Systems to Fully Exploit the Potential of Microscale Processing

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Definition of real-time chemical analyzer

A device that is able to characterize a chemical system that is undergoing change. The device needs to provide an analysis of the chemical system at known points in time. This information should be able to be converted to knowledge about the performance of the unit operation.
Univariant and multivariant analysis

Univariant measurement provides one variable to characterize a system. Temperature, pH, pressure, and flow rate are examples. Simple sensors

Multivariant measurements provide several variables to describe a system. Chromatography, spectroscopy, as well as multiple univariant measurements are examples.
Reasons for real-time characterization of microscale processing

1. Optimization of hardware design
2. Determination of system operating characteristics (the system operates as designed; for example, detection of unexpected flow characteristics)
3. Detection of system failures
4. Advanced control approaches
5. Reaction characterization
6. Quantitative reaction analysis for process dev.
7. Quality assurance (operation within design space)

Will point out examples of each reason though focus will be on 5 and 6
Analyzer system (sample conditioning, analyzer and data analysis) parameters

• Measurement time including sample conditioning
• Degree of compound speciation required
• Sensitivity and dynamic range of measurement
• Resolution of measurement
• Measurements span the variable space
• Reliability, automation, size and cost

Analyzer system requirements change with reason for use
The reasons for measurement and the parameters of the measurement are actually the same as for any scale unit operation.

However, there are key advantages for their use with *microscale* equipment.

- Rapid heat and mass transfer makes understanding underlying chemical rates easier, no back mixing in plug flow systems.
- Rapid response to new process conditions enables sophisticated control.
- Requires small amount of reactants.
- Much wider range of operating conditions.
- Safer system operation.
Real-time analysis of continuous micro-scale unit operations enables rapid process characterization

- Flowing streams enable rapid and easy real-time process analysis e.g. taking a sample
- Automation is easier
- Standard flow path technology enables the use of multiple analytical techniques
- Real time data enables the use of dynamic Design of Experiments

Plug flow reactors can be modeled as batch reactors
Optimization of reactor design for desired performance characteristics; Typically this is done by vendors but may be needed for special uses; first reason
Dow developed a polymer research characterization system that provides an example of reaction characterization for better process understanding of the chemistry using simple sensors.

This section is focused on the analyzer part of the analyzer system.
Principle

Electrical Resistance

Steel Tubing

Temperature

Tracking the voltages along the tube at known current gives temperature

C. A. Nielsen, D. D. Beigzadeh, Novel Tubing Microreactor for Monitoring Chemical Reactions, Spring 2006 AIChE meeting
Principle

“Steel Tube as Both Heater & Sensor Array”

Voltage Taps
(Sense Temp Profile Along Tubing)

Reactant Flow

Precision DC Supply
(High Current at Low Voltage)

C. A. Nielsen, D. D. Beigzadeh, Novel Tubing Microreactor for Monitoring Chemical Reactions, Spring 2006 AIChE meeting
A pulse of catalyst is added to a preheated, pressurized solution of reactant in a solvent. Released heat from the reaction is monitored downstream via the voltage taps.

C. A. Nielsen, D. D. Beigzadeh, Novel Tubing Microreactor for Monitoring Chemical Reactions, Spring 2006 AIChE meeting
Examples of reasons

2. Operating characteristics

3. Failure detection

4. Rapid response for enhanced control

5. Reaction characterization

**Figure 3.** Electrothermal microreactor (ETMR) as configured for ethylene polymerization. The glovebox affords a subparts-per-million oxygen environment to protect the catalysts. The arrangement of Figure 2 is highlighted in the lower right of this figure. Note the PEEK unions installed to provide electrical isolation.

Typical Results from an Ethylene Polymerization Showing all Seven “Zones” Temperatures in Response to a Catalyst Injection

The catalyst injector is closest to “Zone1” so the exotherm is detected first here and subsequently moves towards higher numbered “zones” as the catalyst pulse works its way through the reactor.

C. A. Nielsen, D. D. Beigzadeh, Novel Tubing Microreactor for Monitoring Chemical Reactions, Spring 2006 AIChE meeting
Combined Zone Areas Give Polymer Mass

Output response is the combined areas (Δ₀°C•s) of the seven zones. Therefore, conversion can be obtained on-line from the total area.

C. A. Nielsen, D. D. Beigzadeh, Novel Tubing Microreactor for Monitoring Chemical Reactions, Spring 2006 AIChE meeting
Comparison of Results for Ethylene Polymerization Using Two Different Catalysts at 155 C

Relative rate data are quickly measured in the Tubing Microreactor given 10 runs/hour. In contrast only 4-6 runs can be made per day in standard 2 L batch reactors.

C. A. Nielsen, D. D. Beigzadeh, Novel Tubing Microreactor for Monitoring Chemical Reactions, Spring 2006 AIChE meeting
Goals for utilizing micro-reactors in process research

• Characterize process parameter impact on chemical reaction
• Provide data to develop control model. For example if an impurity is detected should temperature be raised or lowered, or should the feed rate be changed, or agitation rate changed.

Quantitative characterization of chemistry needed by reaction engineer for process development

• Determine rate expression and parameters of chemical reaction e.g. heat flows
• Determine mechanism of reaction.

Use of multivariate sensors for enhanced understanding
Dow described a system designed to provide the quantitative characterization (reason 6) of chemistry needed by reaction engineering for process development.

- Determine rate expression and parameters of chemical reaction
- Determine mechanism of reaction
- Define optimal reactor design and operating conditions to maximize objective function (e.g. economic profit)

Microreactor system for reaction characterization; Hickman and Sobeck; Micro-Instrumentation for High Throughput Experimentation and Process Intensification – A Tool for PAT
Lab System design objectives

• Maximum experimental throughput
• Minimal material consumed
• Minimize data uncertainty
• Maximize parameter space sampled such as residence time, temperature, pressure and concentration
• Automated operation
• Built in safety checks

Microreactor system for reaction characterization; Hickman and Sobeck; Micro-Instrumentation for High Throughput Experimentation and Process Intensification – A Tool for PAT
Criteria for system component selection

• Minimum residence time 10 sec
• Maximum residence time several hours
• Reactor volume 20 X mixing tee
• Isothermal throughout reactor
• Mixing time ¼ minimum residence time
• Pressure drop at min residence time 100 psi
• Min. 60 sec. at 99% steady state

Microreactor system for reaction characterization; Hickman and Sobeck; Micro-Instrumentation for High Throughput Experimentation and Process Intensification – A Tool for PAT
Microreactor system for reaction characterization; Hickman and Sobeck; Micro-Instrumentation for High Throughput Experimentation and Process Intensification – A Tool for PAT
High quality analytical data is required for effective process development.

A standard LC experiment gave a standard deviation of 5.5%.

An error propagation analysis suggests that a commercial reactor would need a 31% larger design volume to insure desired conversions.

Analytical precision can be improved by the square root of the number of measurements which are easy to repeat in microscale equipment.

This section is focused on the data analysis part of the analyzer system.
Applying Chemometrics to Process GC

Need to address speed
GCs are not used in true process control settings. The information derived from GC analysis is either hands-on during a process transition/calibration or is automated to confirm normal operation in the near-past or a post-mortem to understand past events.

- Impact on signal processing
  Correcting for retention shift
- Automating the data interpretation
  Classification and quantitative analysis
- Data management
  Mining a database

This work is describing Process GC’s in refinery applications

The Chemometrics Role in Process GC, Brian Rohrback, Infometric, inc., CPAC Summer Institute, 2009
C_{1} - C_{9} Raw Chromatograms

This is describing the impact of time variations on component ID

The Chemometrics Role in Process GC, Brian Rohrback, Infometric, inc., CPAC Summer Institute, 2009
$C_1 - C_9$ After Chemometric Alignment

The Chemometrics Role in Process GC, Brian Rohrback, Infometric, inc., CPAC Summer Institute, 2009
Gating Problem

This is describing the impact of time variations on quantitation

The Chemometrics Role in Process GC, Brian Rohrback, Infometric, inc., CPAC Summer Institute, 2009
Gating Problem Solved

The Chemometrics Role in Process GC, Brian Rohrback, Infometric, inc., CPAC Summer Institute, 2009
In the future it should be possible to use PAT enhanced microscale reaction characterization to implement QbD for protein therapeutic production.

For example rapidly develop new post bioreactor chemical modifications:

- Rapid mixing in a low shear environment
- Rapidly determine rate expression
- Evaluate the impact of pH, ionic strength, solvent, catalysts, temperature and other parameters on the reaction

This section mentions issues with the sample conditioning part of the analyzer system.
Pfizer group has recently demonstrated the value of QbD to the production of protein therapeutics

(This work did not use microreactors but the work appears to be compatible with microreactor use for reaction characterization)

Optimization of the copper catalyzed oxidation of monomer to dimer for a new atherosclerotic plaque reduction drug

Cysteine (or RSH) $\rightarrow k_1 \rightarrow$ Cysteine Dimer (RS-SR)

Cysteine (or RSH) $\rightarrow k_2 \rightarrow$ Cysteine Sulfonate (RSO3H) + H2O2

(Pfizer Group)
Note timing and sample complexity

Reason 7; Operation in design space

Thus, as pointed out earlier the parameters of the measurement must be matched to the rates of the reaction being studied to be useful for real time analysis.

For post translational modification analysis current approaches are too slow. Fortunately Paul Watts has demonstrated that microscale technology can also be used to speed sample conditioning. Thus he has shown that the protein digests needed for analysis can be done in minutes rather than hours.
Conclusions

• The use of continuous micro-reactors will enable the rapid automated characterization of chemical reactions to develop process models.
• The same concepts should enable the characterization of other unit operations such as separations.
• Post fermentation modifications of proteins should be possible to study with continuous microscale equipment
• PAT enables better control to insure operation in the Design Space for the process