

# Utilization of microreactor technology for reaction characterization

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University of Washington

# The need for new process characterization and development capability

- More efficient processes are needed to reduce production costs and especially to reduce the energy needed for purification.
- New sources of raw materials are beginning to appear, especially bio-sourced materials.
- Distributed processing for global expansion and proximity to raw materials would benefit from intensified processing.
- Process development groups are disappearing.

Pilot scale is expensive for optimization

# Also to satisfy the critical elements of advanced process understanding envisioned by the FDA in the QbD program

- Critical Quality Attributes (CQAs) linked to patient needs
- Critical Process Parameters (CPPs)
- A Process Model
- Design Space
- Process and Measurement Control

More broadly these same QbD concepts are used for each part of the process and will require more characterization capabilities

- Qualification of raw materials including excipients
- Reactor characterization
- Bioreactor characterization
- **API purification steps**
- Formulation and tableting

# Advantages of using continuous micro-reactors/microscale equipment for process characterization

- Rapid heat and mass transfer makes understanding underlying chemical rates easier, no back mixing.
- Rapid response to new process conditions.
- Requires small amount of reactants
- Much wider range of operating conditions
- Safer system operation

Plug flow reactor segments can be modeled as micro-batch reactors

# Potential problems with using micro-reactors for process characterization

- Problems with solids in the process
- Problems with viscous solutions
- Use of corrosive materials
- Use of catalysts; homogeneous and heterogeneous
- Multiple phases
- Equilibrium driven reactions

However, most of these can be handled

# Goals for process research utilizing micro-reactors

- Characterize 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

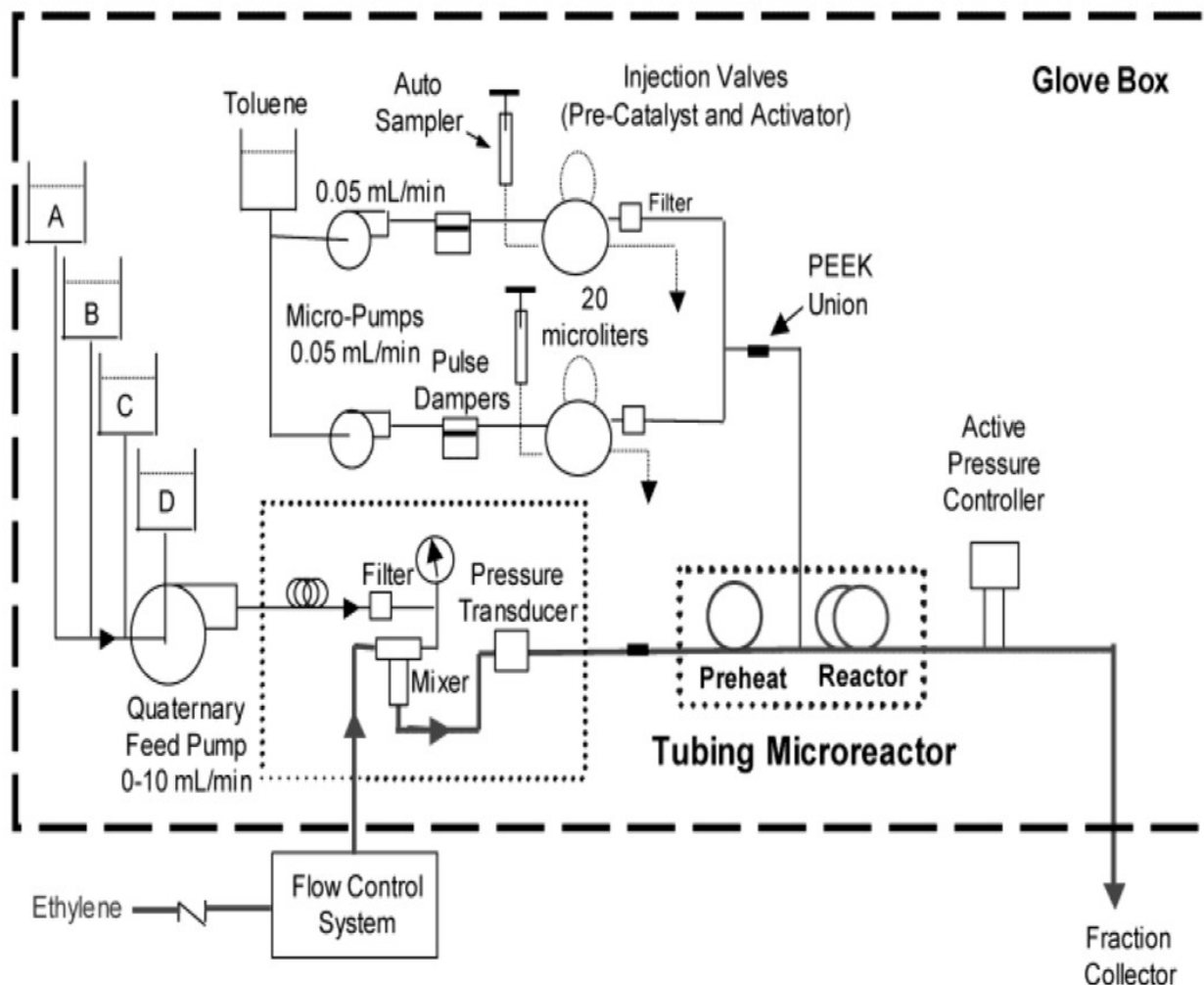
- Determine rate expression and parameters of chemical reaction.
- Determine mechanism of reaction.

# Real-time analysis of continuous micro-reactors enables rapid process characterization (Key focus of presentation)

- Flowing streams enable rapid and easy real-time process analysis
- Standard flow path technology enables the use of multiple analytical techniques
- Real time data enables the use of dynamic Design of Experiments

Sample conditioning such as dilution, filtering or reaction quenching may be required

Dow developed a polymer characterization system that provides an example of reaction characterization for better understanding of the chemistry using simple sensors

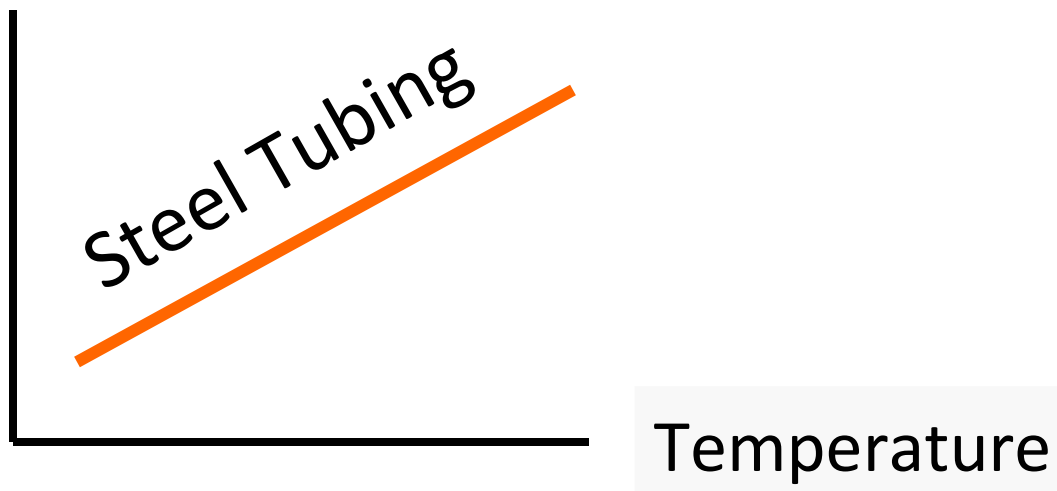


**Figure 3.** Electrothermal microreactor (ETMR) as configured for ethylene polymerization. The glovebox affords a subparts-per-million oxygen environment to protect the catalysts. The arrangement of Figure 2 is highlighted in the lower right of this figure. Note the PEEK unions installed to provide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

**Novel Tubing Microreactor for Monitoring Chemical Reactions, Charles A. Nielsen, Ray W. Chrisman, Robert E. LaPointe, and Theodore E. Miller, Jr.,** The Dow Chemical Company, Corporate R&D, 1712 Building, Midland, Michigan 48674  
*Anal. Chem.* **2002**, *74*, 3112-3117

# Principle

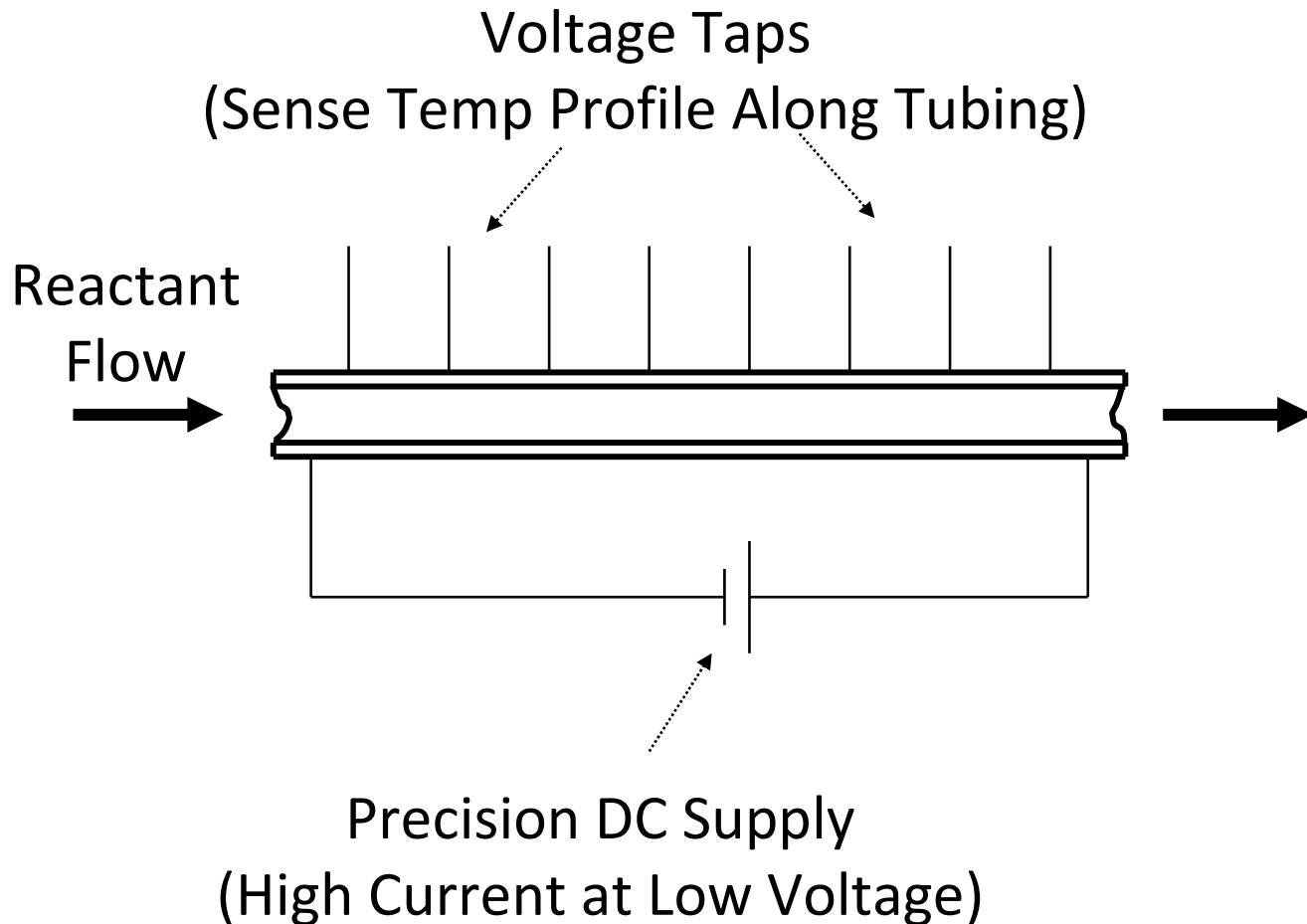
Electrical  
Resistance



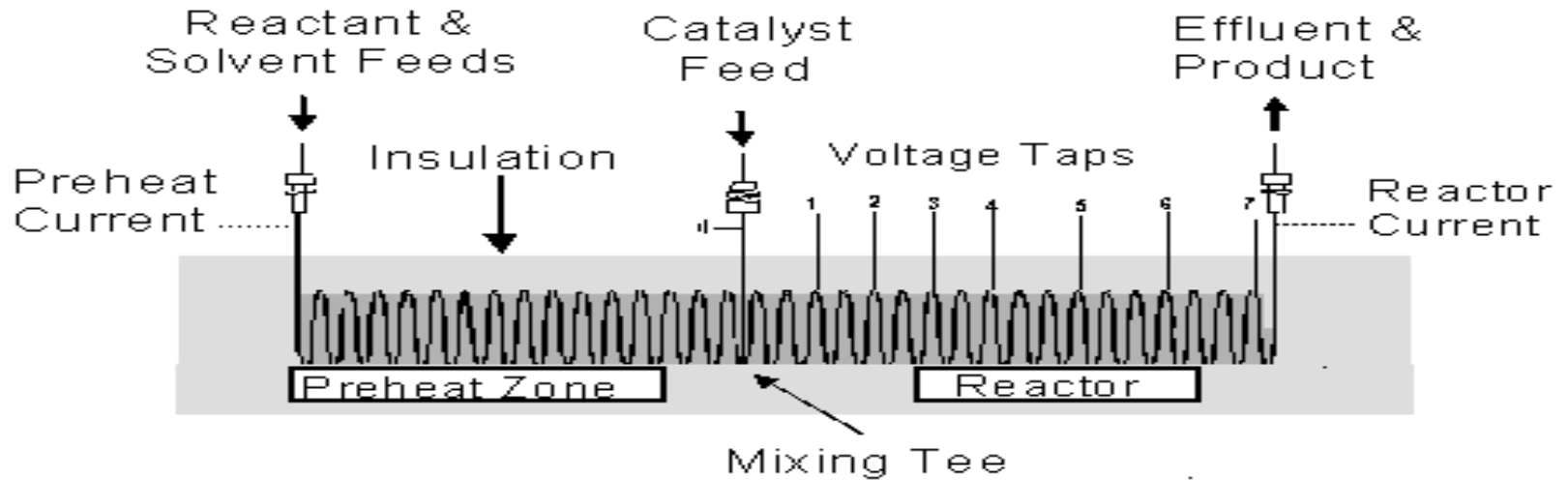
Tracking the voltages along the tube at  
known current gives temperature

# Principle

“Steel Tube as Both Heater & Sensor Array”

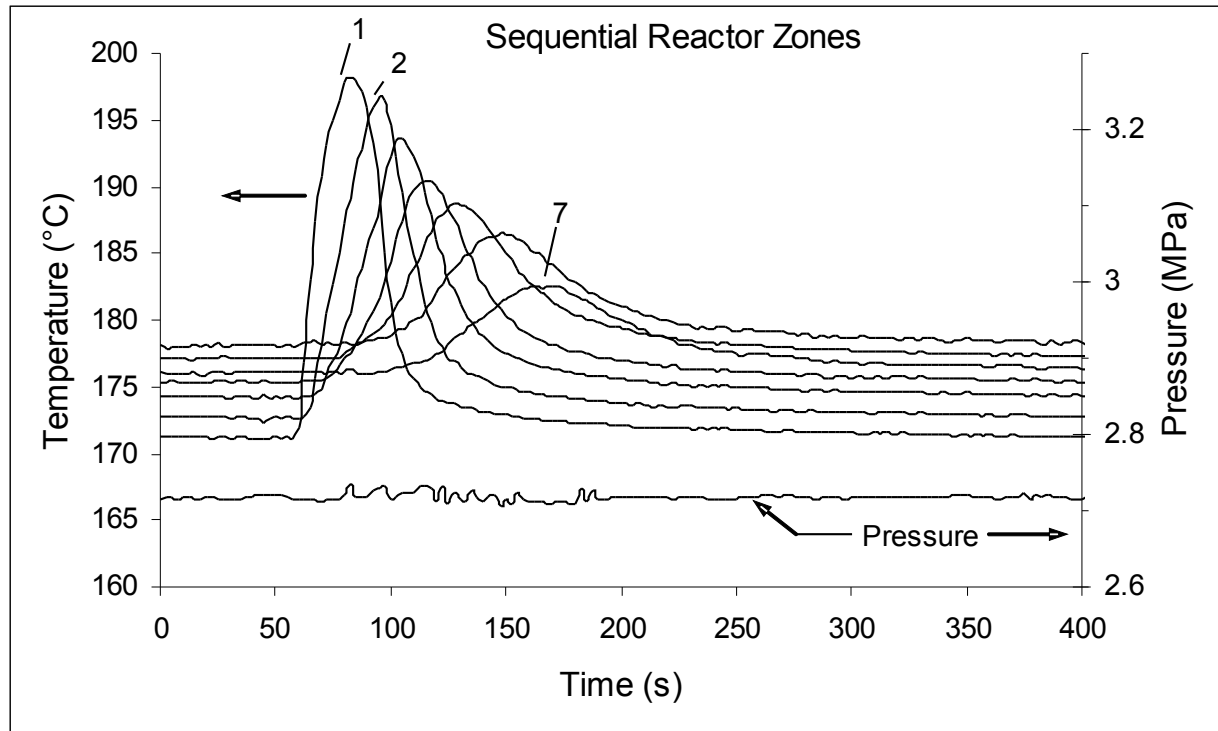


# Reactor Configuration



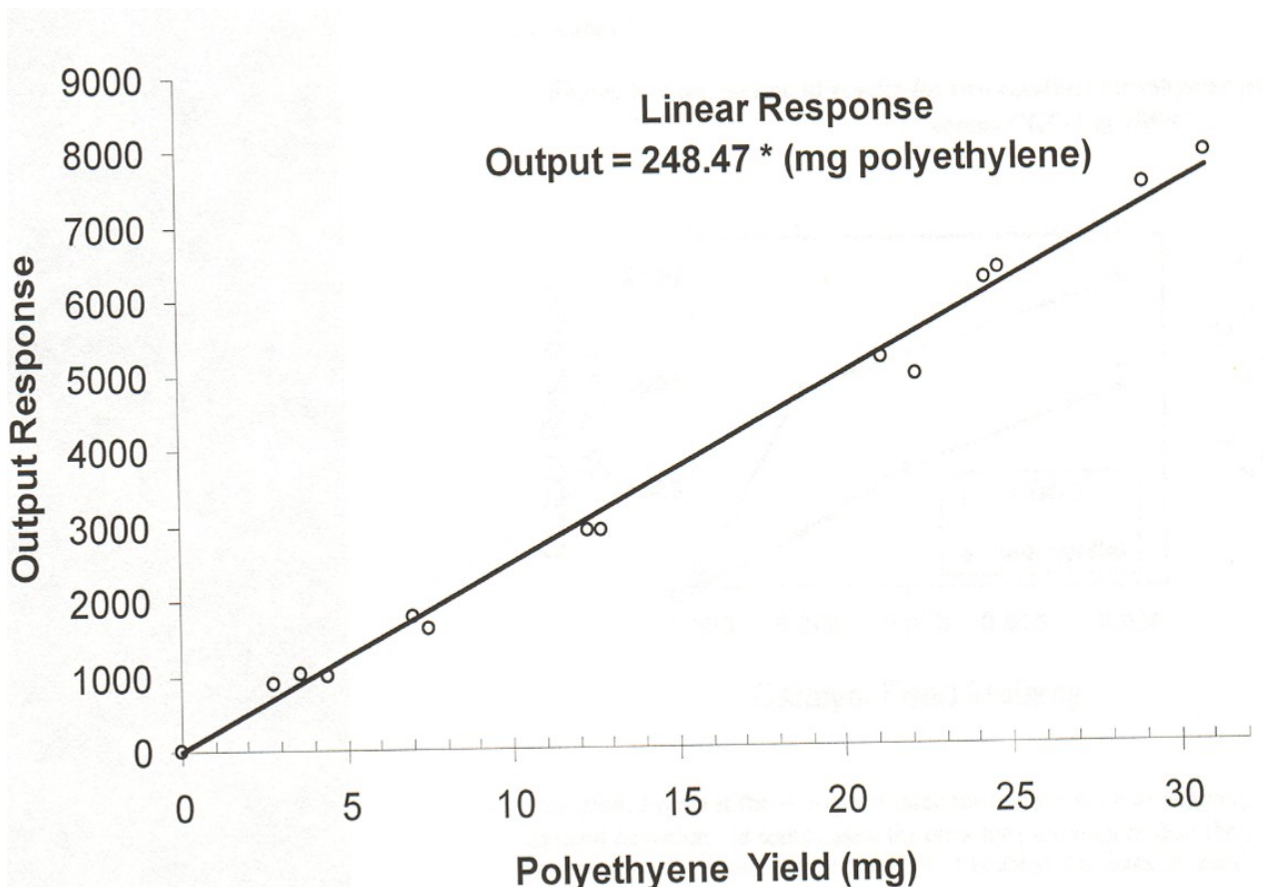
**A pulse of catalyst (or reactant) is added to a preheated, pressurized solution of reactant in a solvent. Released heat from the reaction is monitored downstream via the voltage taps.**

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



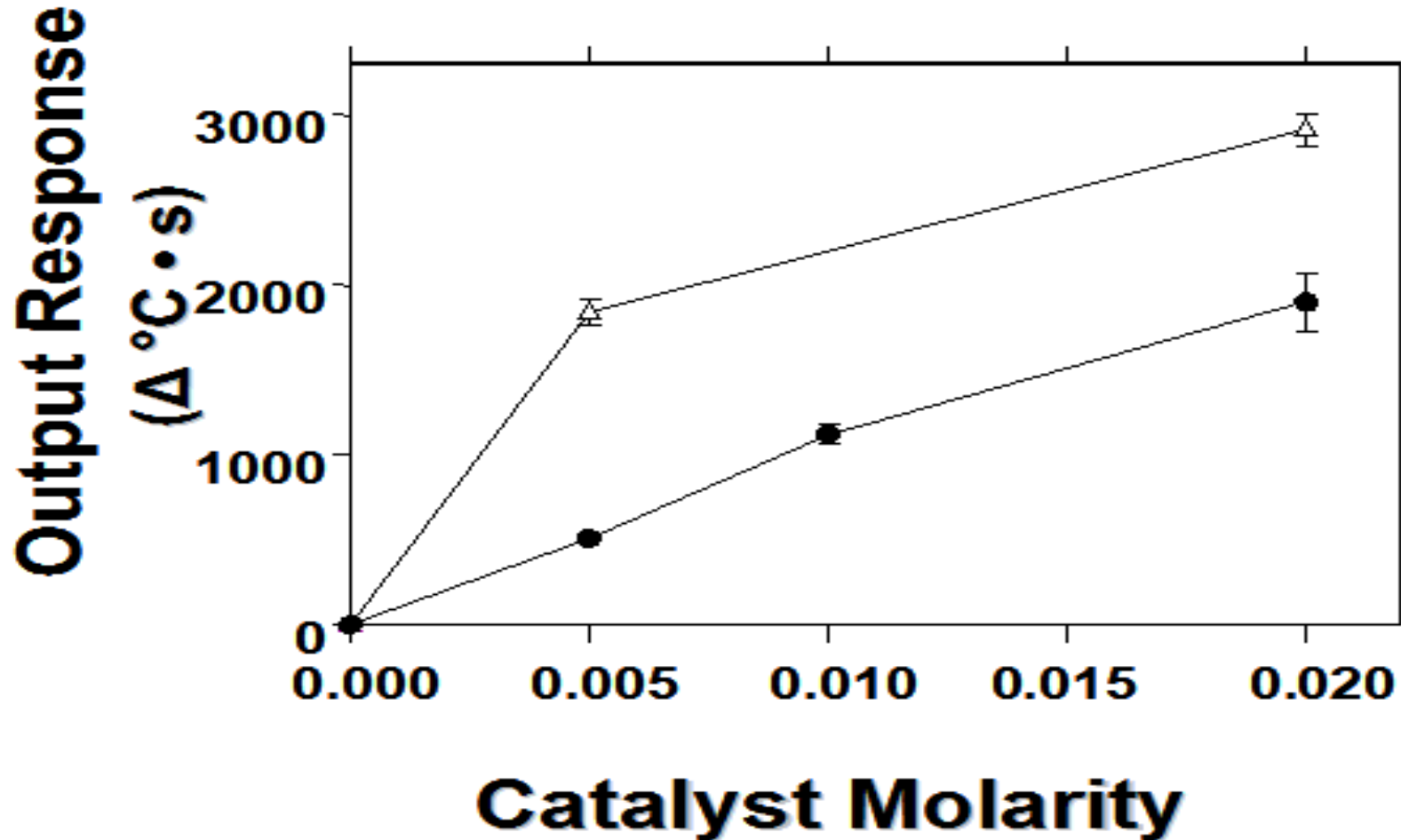
The catalyst injector is closest to “Zone1” so the exotherm is detected first here and subsequently moves towards higher numbered “zones” as the catalyst pulse works its way through the reactor.

## Combined Zone Areas Give Polymer Mass



**Output response is the combined areas ( $\Delta^{\circ}\text{C}\cdot\text{s}$ ) of the seven zones. Therefore, conversion can be obtained on-line from the total area.**

# Comparison of Results for Ethylene Polymerization Using Two Different Catalysts at 155 C

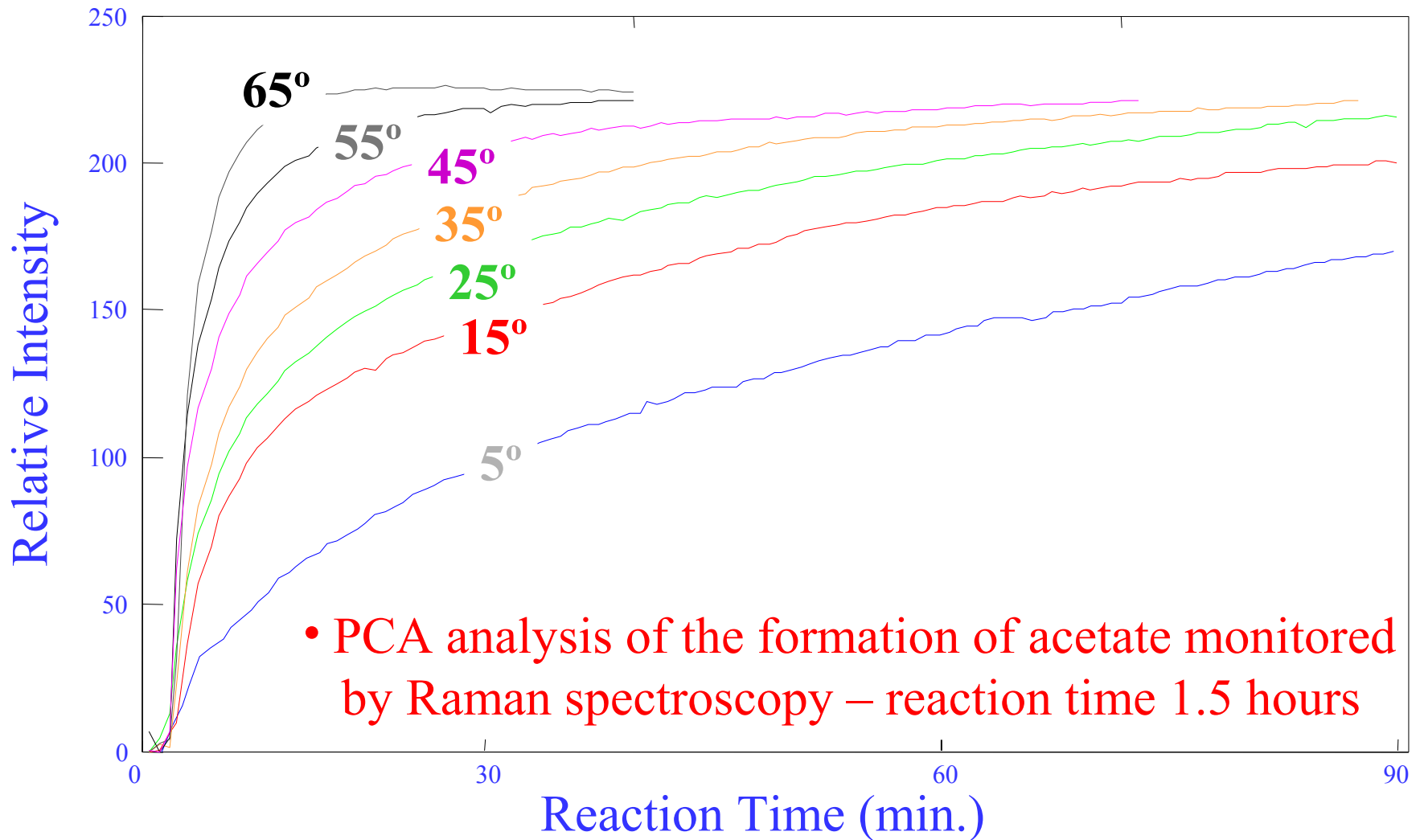


Relative rate data are quickly measured in the Tubing Microreactor given 10 runs/hour. In contrast only 4-6 runs can be made per day in standard 2 L batch reactors.

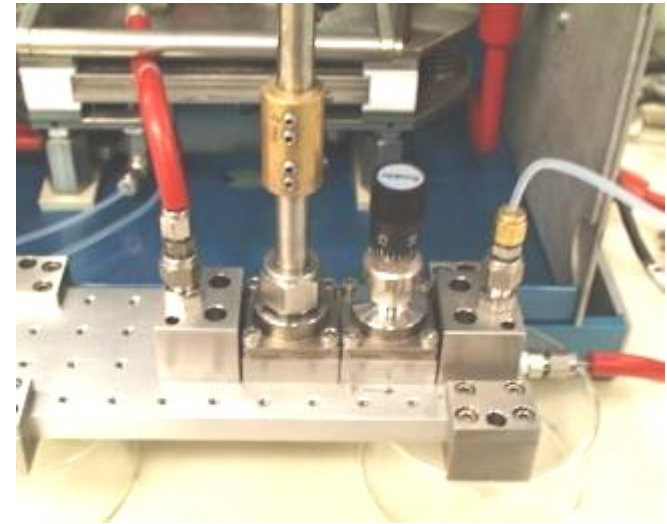
Real-time compositional analysis  
provides even more insight into  
reaction chemistry

Following few slides are from Brian  
Marquardt's group at CPAC

# Traditional Batch Formation of Methyl Acetate at Different Temperatures

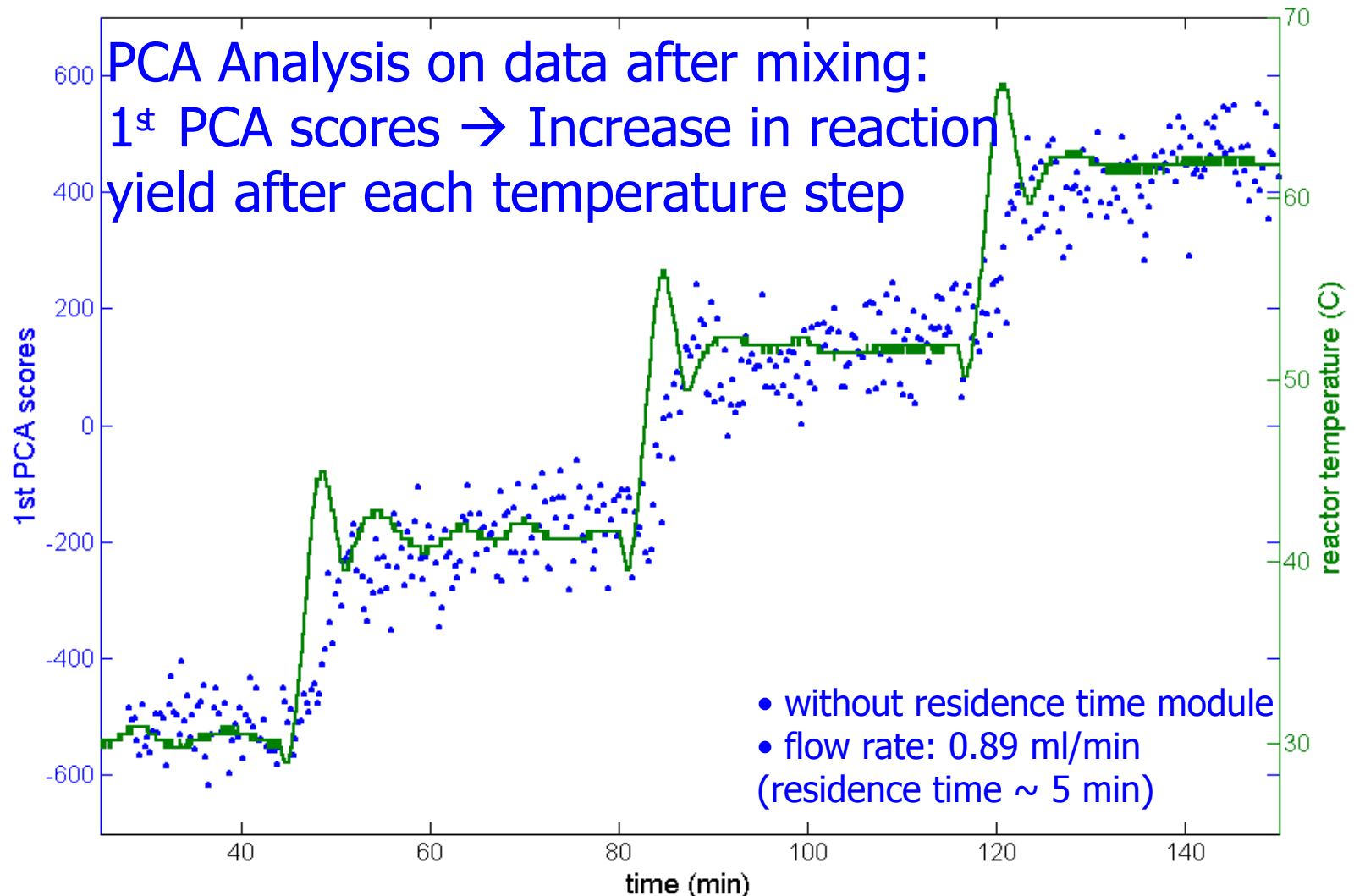


# NeSSI Raman Sampling Block

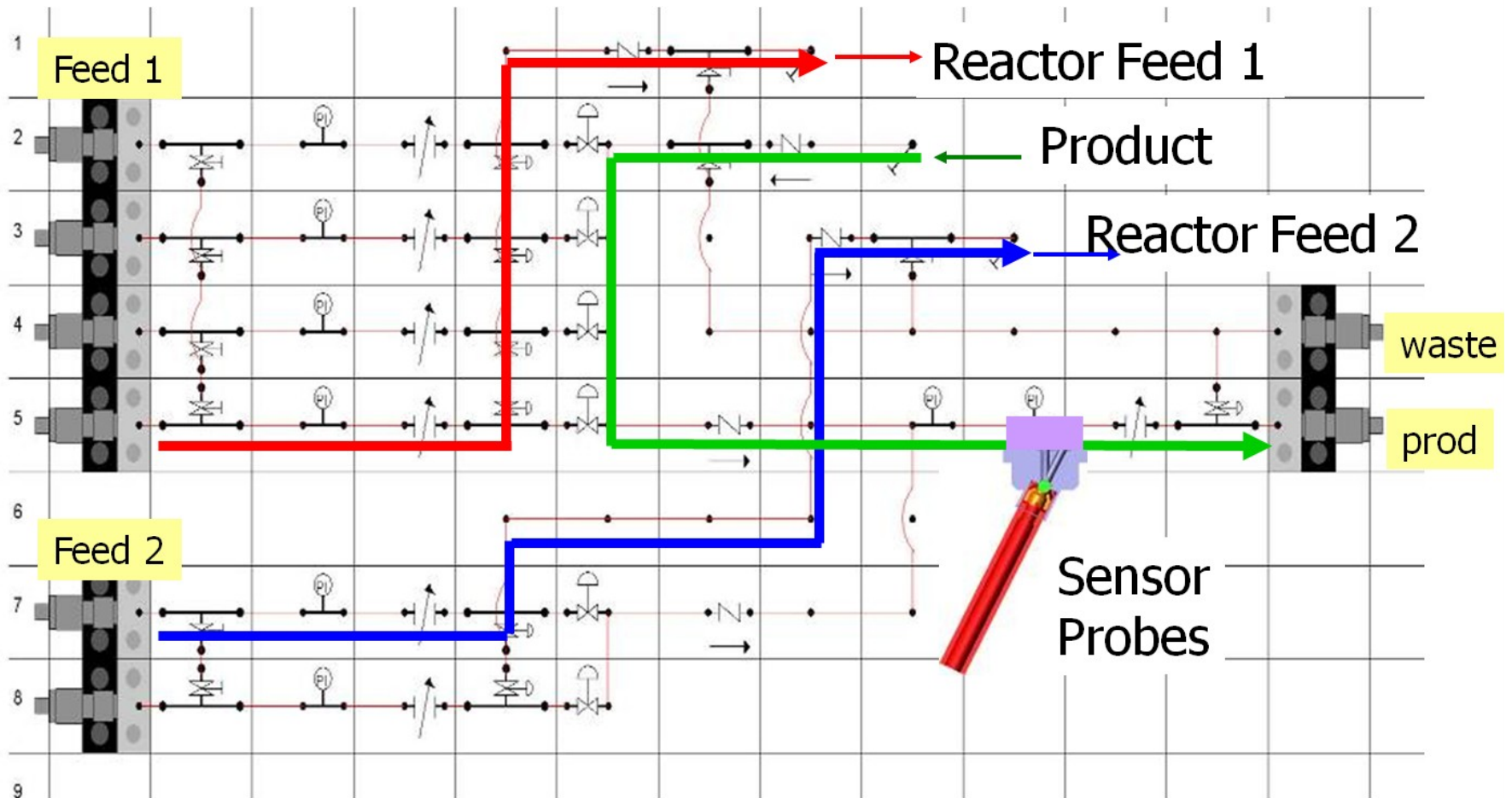


- Parker Intraflow NeSSI substrate
- Sample conditioning to induce backpressure to reduce bubble formation and the heated substrate allows analysis at reactor conditions

# Scores Plot vs. Temperature Steps from 30-60°C



# NESSI Membrane Sampling /Calibration System



# Real-time analytical provides a better understanding of the chemistry of the process

- Reactants and products can be determined as a function of process conditions
- Intermediates can be detected and characterized
- Formation of impurities can be detected and characterized as a function of process conditions

# Real-time analytical data also detects system problems

- Mixing may not be as fast as expected
- Back mixing may be occurring
- Surface effects can change the system characteristics
- Enables detection of system malfunctions

Dow described a system designed to provide the quantitative characterization 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

# System design objectives

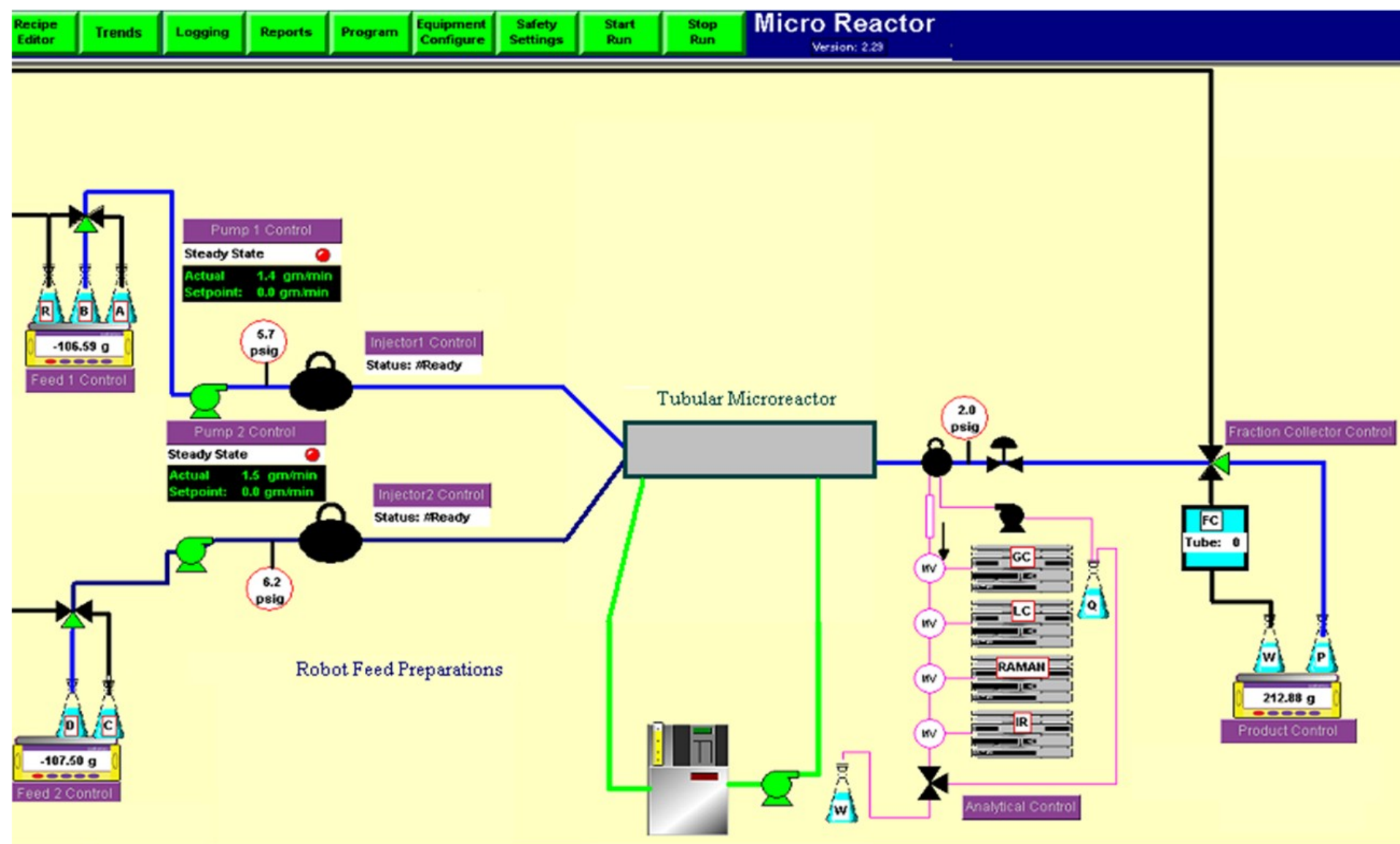
- Maximum experimental throughput
- Minimal material consumed
- Minimize data uncertainty
- Maximize parameter space sampled such as residence time, temperature, pressure and concentration
- Automated operation
- Built in safety checks

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  $\frac{1}{4}$  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 Sobek; 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

# Applying Chemometrics to Process GC

## Need to address speed

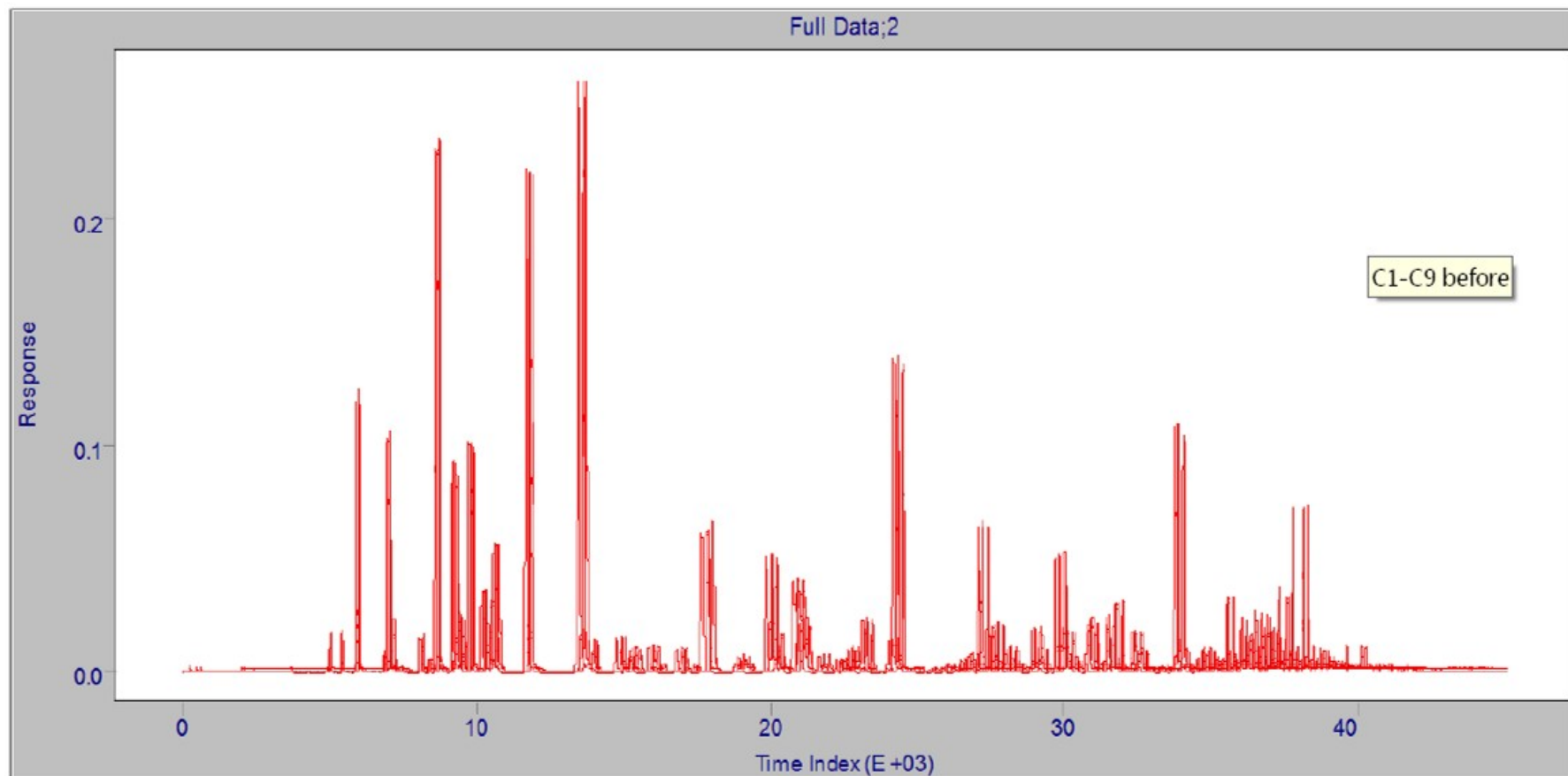
GCs are not used in true process control settings. The information derived from GC analysis is either hands-on during a process transition/calibration or is automated to confirm normal operation in the near-past or a post-mortem to understand past events.

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

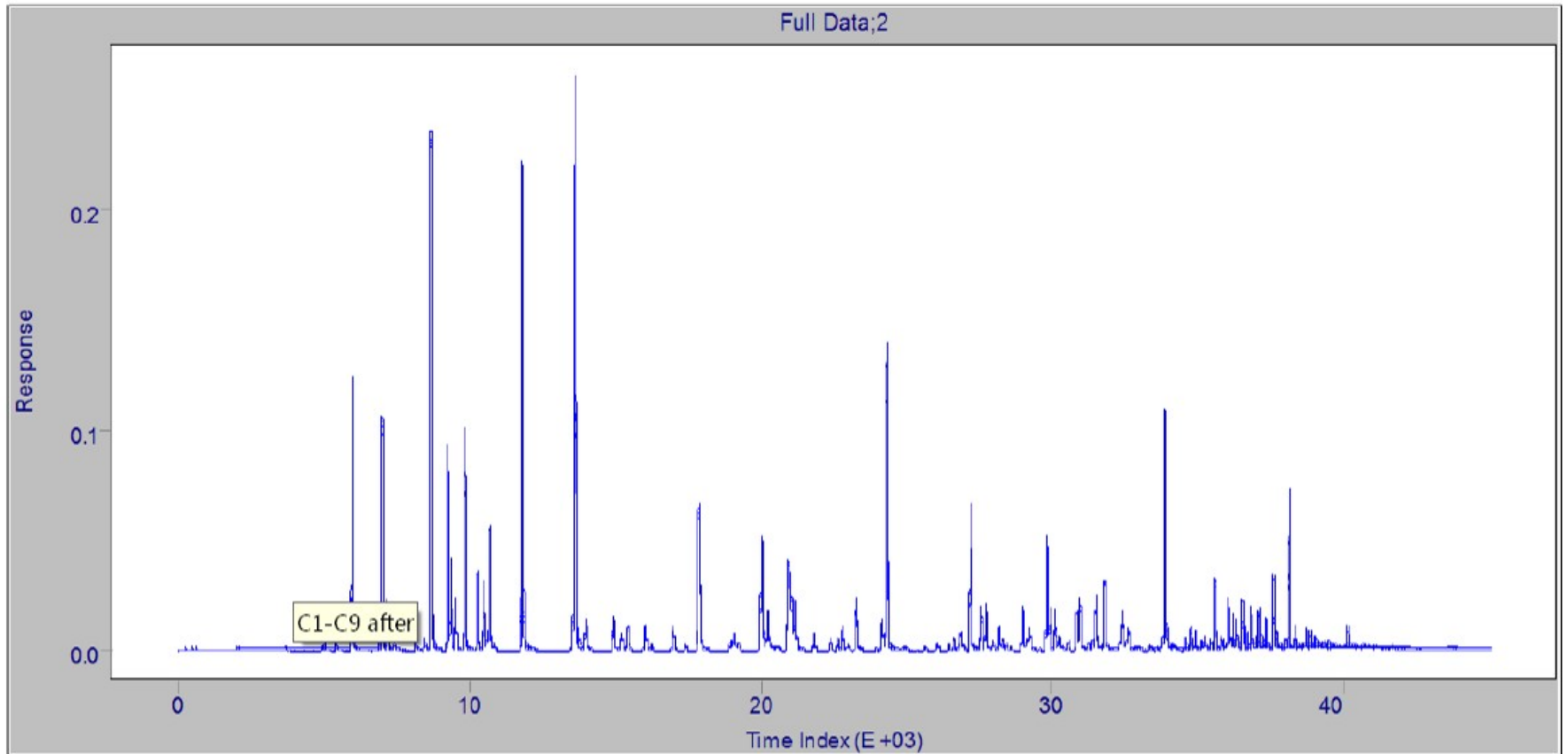
Trick is to make all GCs look as much alike as possible.

Interchangeability  
common interpretive base

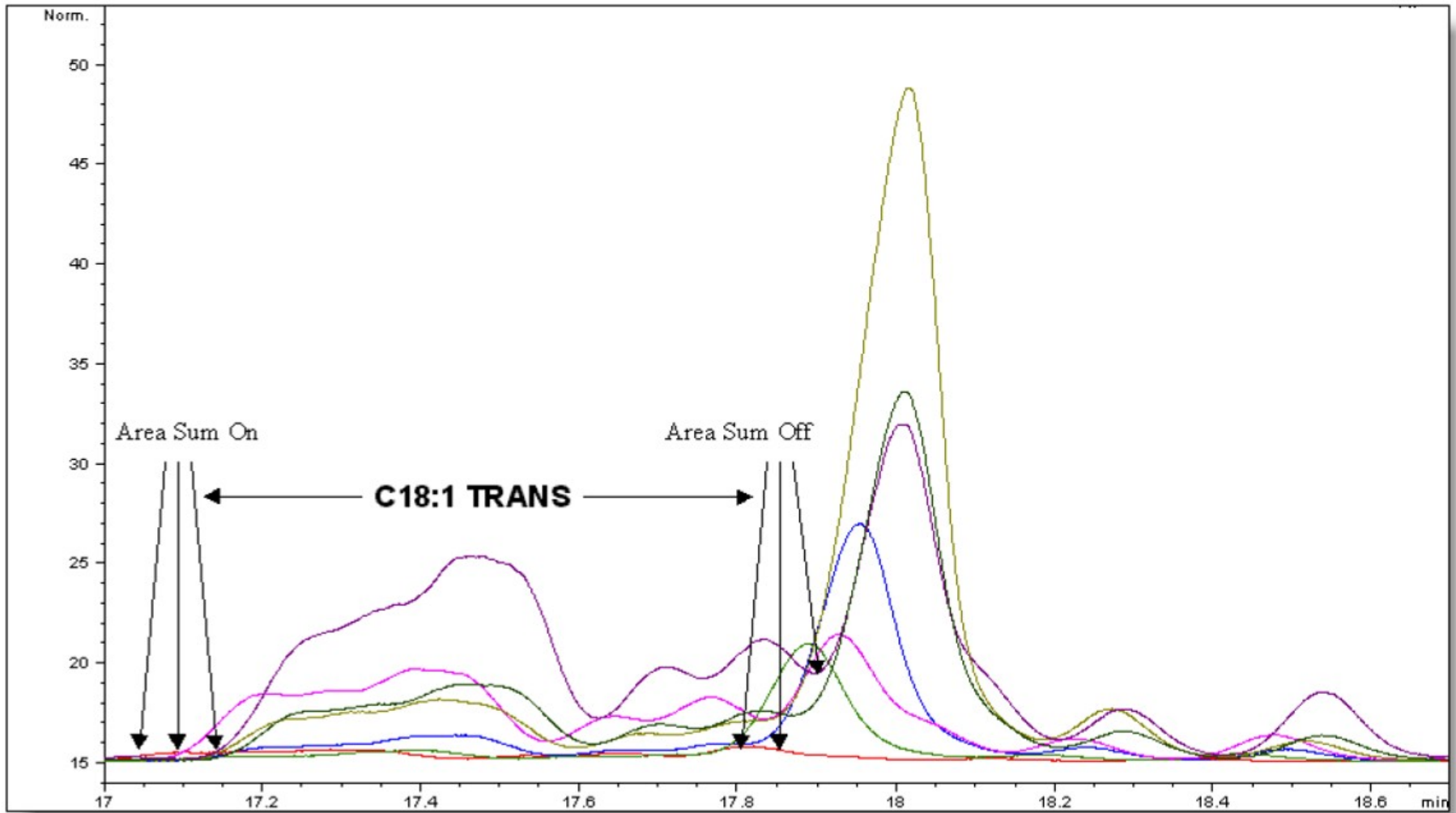
# C<sub>1</sub> - C<sub>9</sub> Raw Chromatograms



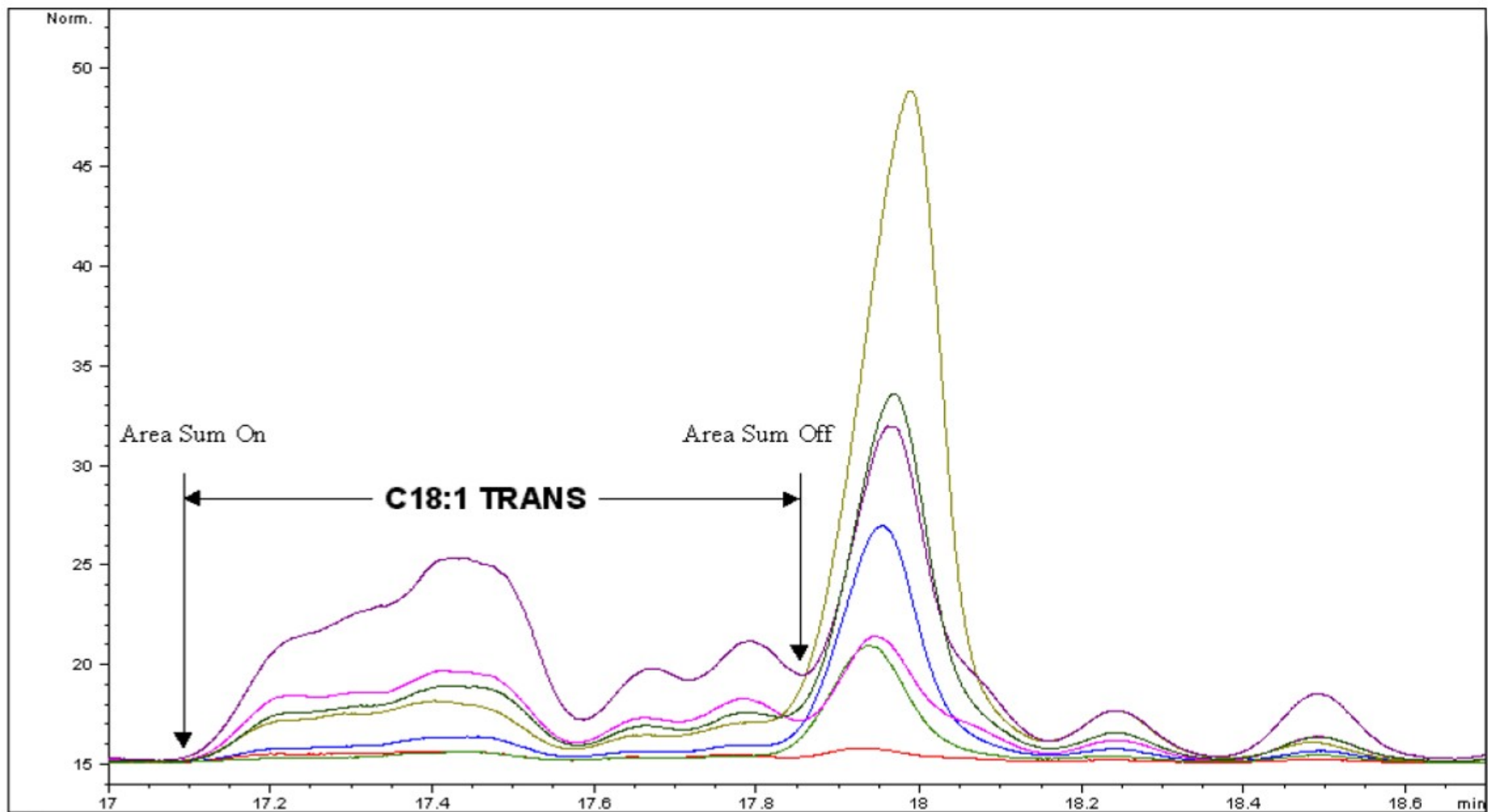
# C<sub>1</sub> - C<sub>9</sub> After Chemometric Alignment



# Gating Problem



# Gating Problem Solved



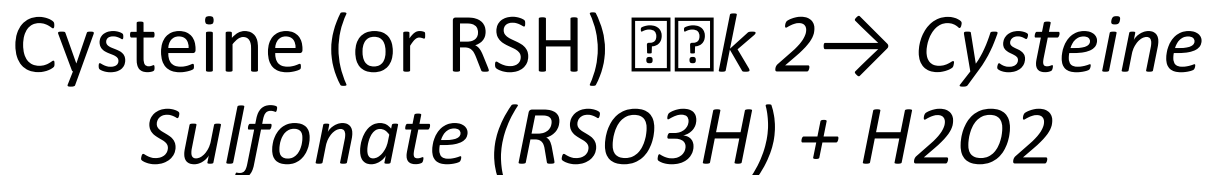
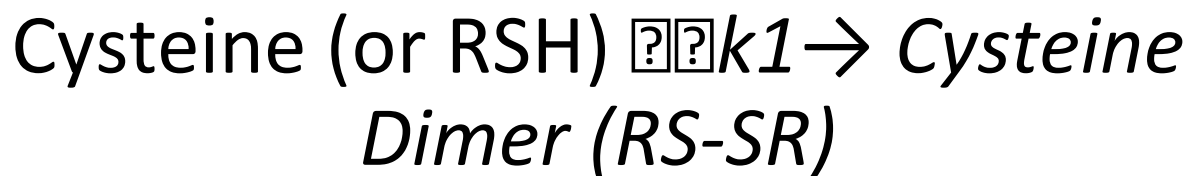
# Utility of PAT enhanced microscale characterization for QbD

- Rapidly determine rate expression
- Characterize reaction temperature dependence
- Evaluate the impact of pH, ionic strength, solvent, catalysts and other parameters on the reaction
- Rapidly develop new post bioreactor chemical modifications
- Optimize process separation technology as well as other unit operations

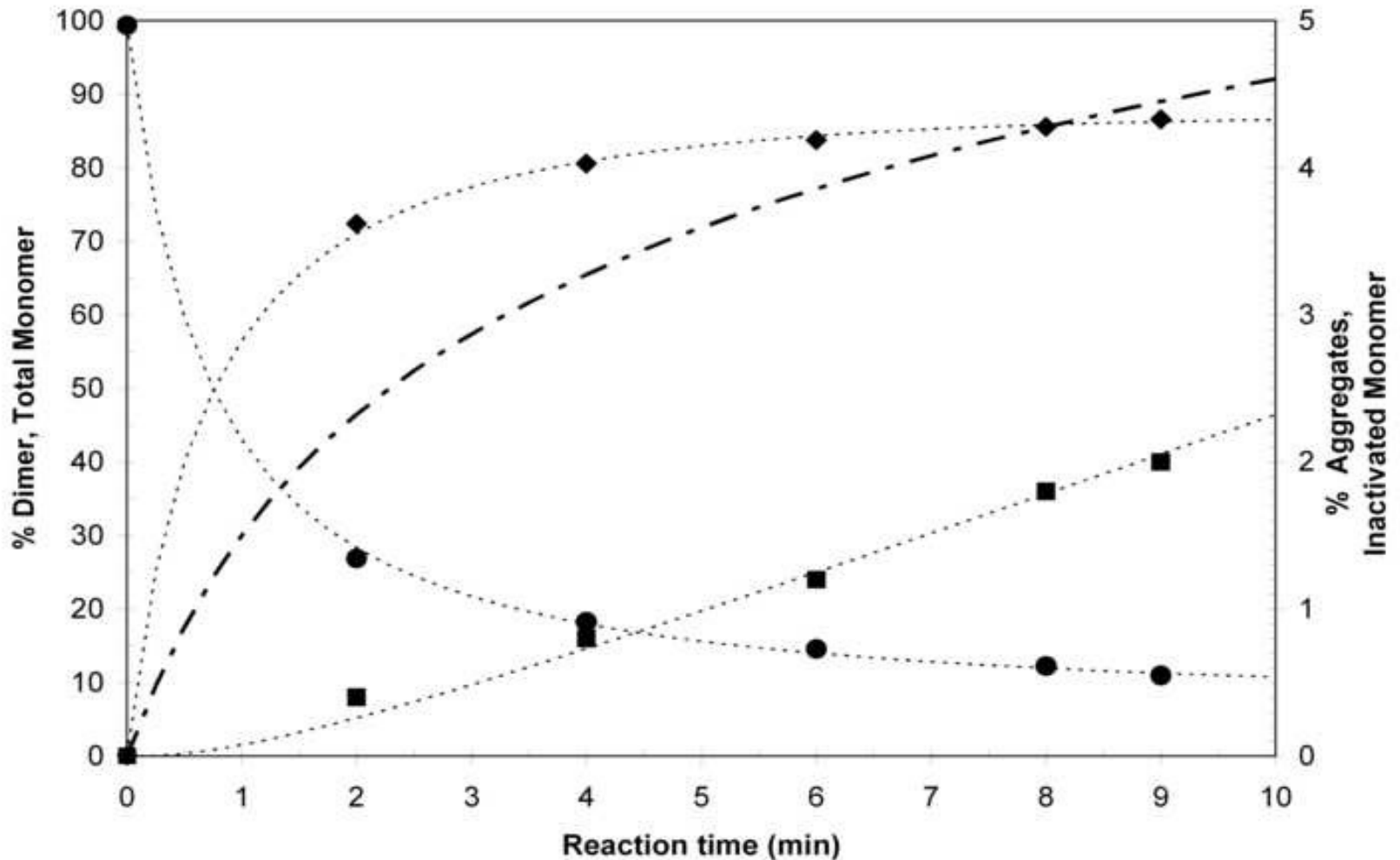
Pfizer group has recently demonstrated the value of QbD to the production of protein therapeutics

(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

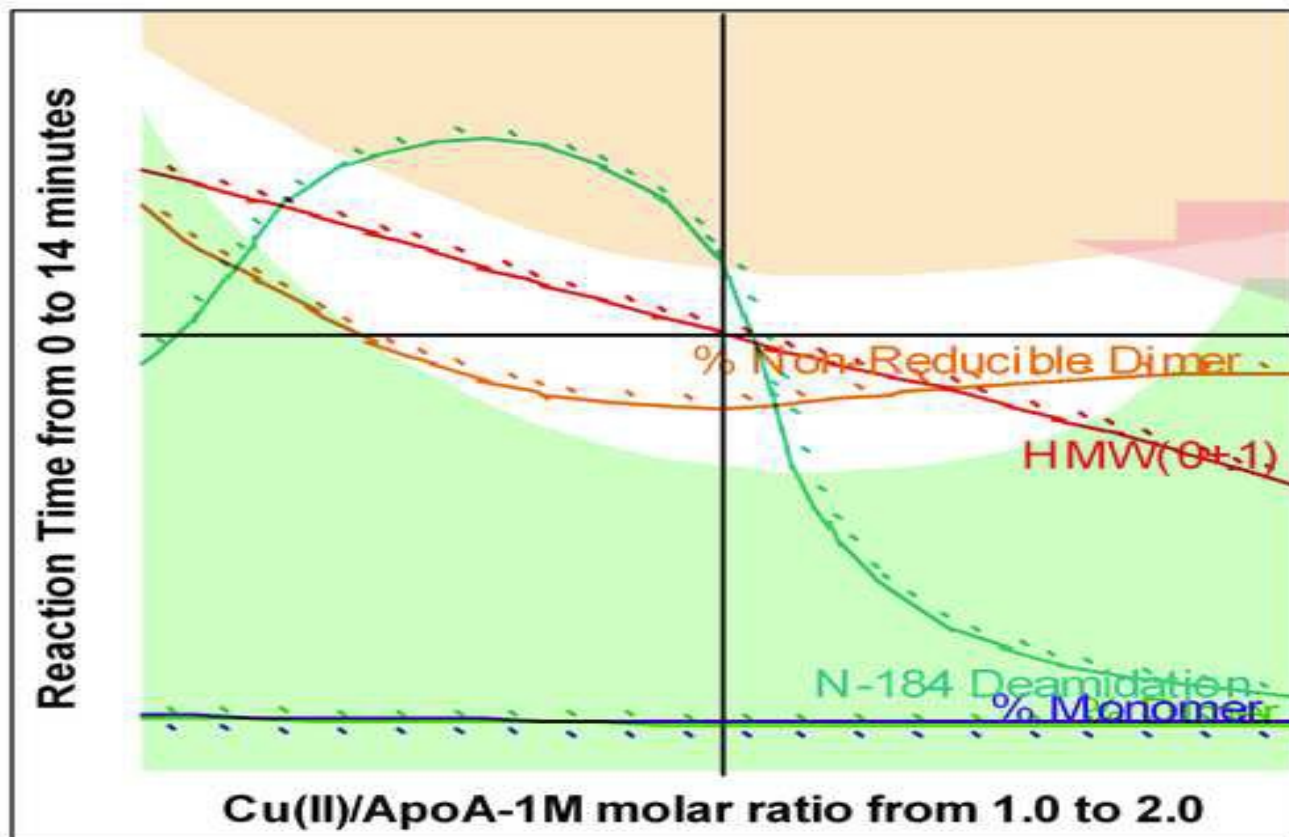


(Pfizer Group)



SA V. HO, JOSEPH K. MCLAUGHLIN, KRISTEN E. THOMAS, ERIC SUDA, JOHN T. HERBERG, ROBERT L. DUFIELD AND ALAN K. HUNTER, REACTION KINETICS AND OPTIMIZATION OF THE COPPER-CATALYZED OXIDATION OF APOA-1M, *CHEMICAL ENGINEERING SCIENCE* (2009), DOI:10.1016/J.CES.2009.02.035

<b>Window of Operation:</b>	<b>white area</b>
<b>Dimer</b>	<b>&gt; 85%</b>
<b>Aggregates</b>	<b>&lt; 3%</b>
<b>Non-reducible dimer</b>	<b>&lt; 3%</b>



SA V. HO, JOSEPH K. MCLAUGHLIN, KRISTEN E. THOMAS, ERIC SUDA, JOHN T. HERBERG, ROBERT L. DUFIELD AND ALAN K. HUNTER, REACTION KINETICS AND OPTIMIZATION OF THE COPPER-CATALYZED OXIDATION OF APOA-1M, *CHEMICAL ENGINEERING SCIENCE* (2009), DOI:10.1016/J.CES.2009.02.035

# Conclusions

- The use of continuous micro-reactors will enable the rapid automated characterization of chemical reactions to provide process models.
- The same concepts should enable the characterization of other unit operations such as separations.
- Bio-processes should also be possible to study