Using Data-Rich Experimentation to Enable the Development of Continuous Processes

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Nalas Engineering Services

• Located in Centerbrook, CT, ca. 25 employees
• Approx. equal mixture of chemists and chemical engineers.
• Contract research for chemical process R&D
• Scale: up to 50 liter reactors (current) and 200 gallon (Fall 2015)
Functionalities at a Glance

- Process Development
- Custom Synthesis
- Process Safety
- Process Understanding/Design Space
- Chemistry and Synthesis
- Chemical Engineering
- Reaction Kinetics and Modeling
- Analytical
- Solid-State Chemistry
- Crystallization Design
- Process Design
- Scale-Up
- Kilo-lab Manufacturing
- Testing Services
With the compressed timelines typical of Process R&D work, getting as much data from each experiment is critical to delivering on time and within budget.

- Automated reactor platform (Mettler Toledo)
  - Heat flow, controlled (and documented) reagent doses
- In situ spectroscopy (Mettler Toledo, Kaiser Optical Systems)
  - Kinetics, identity of reaction intermediates
- In situ particle measurements (Mettler Toledo)
  - Crystallization kinetics, in situ determination of particle size and morphology
Automated Reactors

**EasyMax**

**RC-1**

**Heat Flow - dimethoxypyrazine**

**Nitration of DMP to DMDP**

Watts/Kelvin

\[ Q_r \]

\[ T_r - T_j \]

**Continuous Dose of DMP at 30˚C**

\[ Q_r \text{ Max}=7.29 \text{W or ~ 90 W/liter} \]

**Dose of DMP**

**Qr=435 kJ/moles of DMP**

\[ 	ext{Our 50-liter reactor can remove 30 W/liter} \]
Online Reaction Monitoring

Experiment NAL-003-0136
Start of 1st and 2nd dose of reducing agent

FTIR

Raman

PVM

FBRM

Distribution Public Release
Mettler Toledo iC Suite

• iControl (EasyMax, OptiMax, RC1)
  – Monitor reactor, jacket temperatures, pH, pressure, etc. and control agitator and dosing pumps.

• Software for in situ probes:
  – iC IR
  – iC Raman
  – iC FBRM
  – iC PVM

• Software makes it much easier to understand what is occurring in the reactor: overlay heat flow with Raman peak intensity, for example.
Mettler Toledo iC Suite

Raman Trends

Tr (red) and Tj (blue) from EasyMax reactor

$H_2O_2$ solution dose (automated syringe pump)
Online Reaction Monitoring

• Direct observation: no interference of quench for offline sampling.

• Correlate other observations with the species present in the reactor: color changes, crystallizations, gas evolution.

• When possible, validate the method using an established offline method, such as GC, HPLC, or NMR spectroscopy.
Why Collect Kinetics Data?

• Reaction understanding: rate-limiting step(s), induction periods, catalyst deactivation.
• Process development: optimize the reaction to achieve the desired cycle times and sizing of continuous reactor systems.
Kinetics for Reaction Understanding

• How do reagent and catalyst concentrations influence rate, and what does that imply about the mechanism?
• Is there a catalyst decomposition pathway?
• Mechanistic understanding is the only way to make a true breakthrough in reaction improvement!
Identifying “Funny Business” in Catalysis

Klausen and Jacobsen *OL* 2009, 11, 887.

Kinetics for Process Development

• **Cycle times**: accurately predict cycle times for meaningful cost estimates as processes scale up to manufacturing.

• **Continuous reactor system sizing**: determine the reactor size and flow rate necessary to achieve the desired level of conversion.

• **Optimize key process parameters** (**loadings of reagents and catalysts, temperatures**) to reduce cost and meet schedules.
Kinetics: It Doesn’t Have to be Hard!

• Only collect the data that you need!
• We collect data and develop models to answer the specific questions that we are interested in.
• Stop when you have enough, and save your time to work on the next big challenge for your reaction.
DynoChem Kinetic Models

• Straightforward to build sophisticated kinetic models for networks of chemical reactions.

• Can accommodate real-world conditions:
  – Slow doses of reagents
  – Slow mass transfer (gas-liquid, solid-liquid)
  – Temperature changing during reaction
  – Decomposition pathways

• Just scratching the surface! This is a very powerful tool.
Example: Oxidation of Amine to Nitro

\[
\begin{align*}
R-NH_2 + H_2O_2 & \rightarrow R-NHOH + H_2O & \text{Amine to Hydroxylamine} \\
R-NHOH + H_2O_2 & \rightarrow R-NO + 2H_2O & \text{Hydroxylamine to Nitroso} \\
R-NO + H_2O_2 & \rightarrow R-NO_2 + H_2O & \text{Nitroso to Nitro} \\
R-NH_2 + R-NO & \rightarrow R-N=N-R + H_2O & \text{Azo: undesired} \\
R-NHOH + R-NO & \rightarrow R-N=N(O)-R + H_2O & \text{Azoxy: undesired} \\
2H_2O_2 & \rightarrow O_2 + 2H_2O & \text{Background } H_2O_2 \text{ decomp.}
\end{align*}
\]

- 3 equiv. $H_2O_2$ required for desired transformation
- Subtle changes in conditions can change selectivity to form azo- and azoxy-bridged dimers
- Dimers are often straightforward to separate by differences in solubility
Building a Kinetic Model

\[
\text{H}_2\text{O}_2 \text{ data from in situ Raman spectroscopy. R-} \text{NH}_2 \text{ and R-NO}_2 \text{ from HPLC analysis of aliquots.}
\]
Advantages of Continuous Production

• Control of residence time: allows for manufacturing-scale production using chemistry where the product is somewhat unstable in reaction mixture.
• Excellent heat transfer (greater surface area per unit volume).
• Limit inventory of hazardous chemistry.
• Often smaller footprint (but consider isolation steps as well!)
Equipment for Continuous Processing

Continuous Stirred Tank Reactor (CSTR):

• Use reactors already on hand for batch production
• Use pumps to transfer from one reactor to the next
• Handle slurries well (limited by pumps and mixing)
• Easy to work with
• Good mixing and heat transfer for most processes
• Mixing independent of flow rate

Plug Flow Reactor (PFR):

• Use tubing as a reactor
• Use static mixers to mix (minimum flow rate requirement for mixing!)
• Smallest possible footprint
• Potential for exceptionally good heat transfer (materials selection)
• Gas generation can be challenging (diminished available reactor volume)
• Prone to clogging
Lab Scale Demo of Continuous Production

2x 100-mL CSTR

Peristaltic pumps

- CSTRs: use whatever is available. 100-mL EasyMax reactors are convenient and allow for collection of some heat data, pH feedback loops, etc.
- Pumps: Ismatec peristaltic pumps work very well. Set dip tube at desired reactor fill volume and pump faster than desired flow rate. Continuous or pulsed pumping.

A
B

Product!
Designing Continuous Processes: The Levenspiel Plot

• Devised by Prof. Octave Levenspiel (Oregon State) as a simple tool for determining reactor size necessary for a continuous process.
• Two inputs: molar feed rate $F$ and reaction rate $r$ (as a function of conversion, $X$).

Using Kinetics to Design a Continuous Process

Projection for Continuous Process with Six 100 mL CSTRs in Series:

\[ F = 7.7 \text{ g/hour (rxn run in 15 volumes)} \]

\[ F \text{ [=} \text{ mol/s}; \quad r \text{ [=} \text{ M/s} = \text{ mol/(L*s)} \Rightarrow F/r \text{ [=} \text{ L}} \]
Plug Flow Reactors

• The best solution for:
  – Extremely exothermic reactions: best surface area to volume ratio
  – Superheated reaction mixtures/reactions with gas reagents under pressure: much easier to maintain elevated pressure in a tube vs. in a large reactor

• Using off-the-shelf equipment: requires engineering design each time the process is scaled up to ensure adequate mixing, heat transfer.

• Commercially available solutions reduce the amount of engineering required. Best in class for extremely fast and exothermic chemistry: the Corning Advanced-Flow Reactor (AFR).
Corning Advanced-Flow™ Reactor Design

- Glass plate sandwich!
- Modular and flexible
- Similar mixing through each system with flow rates of 2 mL/min to >100 kg/h (LF – G4)
- Similar heat exchange through each system (LF-G4)
- Limitations—at the mercy of reaction kinetics
# Heat Transfer Comparison

<table>
<thead>
<tr>
<th>Reactor</th>
<th>Heat Transfer Coefficient U (W/m²*K)</th>
<th>Specific Cooling Area (m²/m³)</th>
<th>ΔT Required on Jacket to Cool 30 W/Liter (K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Round Bottom Flask</td>
<td>200</td>
<td>86</td>
<td>2</td>
</tr>
<tr>
<td>Jacketed Lab Reactor</td>
<td>150</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>250 Liter</td>
<td>250</td>
<td>6.8</td>
<td>16</td>
</tr>
<tr>
<td>1000 Liter</td>
<td>250</td>
<td>4.6</td>
<td>26</td>
</tr>
<tr>
<td>6300 Liter</td>
<td>250</td>
<td>2.6</td>
<td>44</td>
</tr>
<tr>
<td>Corning G4 AFR</td>
<td>2500</td>
<td>400</td>
<td>&lt;&lt;1</td>
</tr>
</tbody>
</table>

Manufacturing-scale production with **better** heat transfer than in the lab scale!
Process Development for the AFR

• Turns batch scale-up on its head: you can rely on excellent heat transfer and mass transfer up to the plant scale.

• Design processes to be as fast as possible, regardless of the heat output.

• Possible to run reactions near decomposition temperature with little chance of triggering.

• Even in the event of a runaway reaction (chiller failure), consequences diminished by the small reactor volume (0.1-4 liters).
Process Development Rig for AFR
## The Voice of Scale-Up Experience

<table>
<thead>
<tr>
<th>Do</th>
<th>Don’t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborate</td>
<td>Add solids to a reaction</td>
</tr>
<tr>
<td>Log</td>
<td>Evaporate to dryness</td>
</tr>
<tr>
<td>Sample</td>
<td>Use “all in &amp; heat”</td>
</tr>
<tr>
<td>Safety test &amp; review</td>
<td>Rely on critical timing</td>
</tr>
<tr>
<td>Use test</td>
<td>Do hot filtrations</td>
</tr>
<tr>
<td>Keep it simple</td>
<td>Risk all in one batch</td>
</tr>
</tbody>
</table>

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No problem with a continuous process!

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McConville, F. X., CEP 103 (2007) 18-19

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https://workspace.imperial.ac.uk/memtide/Public/Brechtelsbauer.pdf
5000 L reactor
4000L Liquid Holdup

G4 reactor
4L Liquid Holdup
Questions?