Process Modeling and Control Challenges in the Pharmaceutical Industry

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Outline

• Introduction: What do pharma engineers do?
• Current Practice: what do we do for modeling and control now?
  – Reaction engineering
  – Crystallization
  – Drying
• Better Practice: What are we working towards?
• Some examples
• Needs
  – infrastructure
  – technical
Realities of Pharmaceutical Processes: High Attrition, Few Campaigns

- Numerous early stage candidates which will not survive from Phase I to Phase II/III
- Early objectives (first plant, large scale lab campaigns)
  - enable chemistry
  - not much eng input
- Over 80% of batches in our pilot plants are one-off
- Perhaps only 5-6 total campaigns prior to filing
- Late stage objectives (Phase II supply and beyond)
  - develop detailed models
  - determine critical parameters
  - understand equipment limitations

Early Toxicology, Phase I (30-50 candidates)
Phase III/NDA (1-3 candidates)
Introduction: Pharmaceutical Research and Development

• We are a batch process industry
  – essentially no continuous processes
  – why?
    • Many products don’t make it to market
    • Batch reactors offer flexibility over continuous reactors in that they are adaptable for many products and unit operations
    • Volumes continuously change through the lifetime of a product. Again, batch reactors are adaptable
    • GMP

• We are an industry dominated by chemists
  – many plant campaigns are one-off; little engineering needed
  – sometimes difficult to get sufficient eng. Input to projects
In general, chemists dictate the way processes are conceived and executed. Engineering input is often secondary.
Process Engineering - Input Level to Projects

Chemical Engineering Activity

Process design optimisation
- Heat/mass transfer
- Crystallization/particle eng.
- Separations
- Environmental, etc.

Unit operation optimisation

Rte optimisation

P.A.T.

Time

Synthetic Chemistry Activity

Route Design

Chemistry Optimisation

Robustness Studies
Key Unit Operations - Synthetic Chemicals

- Extractions: In general, every process stage has an average of greater than 1 extraction.
- Distillations (Batch): on average, 1 distillation per stage
- Reactions: A given chemical stage has 1-4 chemical transformations
- Crystallizations: Critical for defining physical properties of final drug product
- Filtration: Both final product and intermediates
- Drying: Every final product is dried. Probably most empirical field.
- Environmental: solvent recovery, biotreatment, incineration
- Chromatography: infrequent currently, but becoming more common
Key Unit Operations: Biopharmaceuticals

- Fermentations - most critical step. Determines complexity of separations chain and product yield
- Ultrafiltration - removes cellular material from fermentation broth
- Exclusion chromatography - purification by size separation
- Ion chromatography - purification by ionic charge
- Dialysis - buffer exchanges
Manufacturing Limitations to Complex Control Strategies
We are in general “Low Tech” with respect to Reaction Engineering

• Many of our vessels in pilot plant and manufacturing are jack of all trades, but master of none
  – nearly 70% of existing GSK vessel capacity is glass lined, radial impeller (e.g., retreat curve, crow’s foot, cryobat)
  – little flexibility for difficult mixing problems

• Roughly 50% of our manufacturing capacity relies on crude control
  – “banded” control using following options: steam, hot water, cold water, fridge, jacket hold, jacket drain

• We have little in the way of sophisticated process analytics which might provide opportunity for better control.
Current Practice: Reaction Engineering

- Collect kinetic data, often semi-quantitative
- Estimate parameters, or determine boundary conditions
- Determine crude optimum either graphically, through DOE
- Program DCS Sequence to obtain crude optimum

- Do to large number of early phase compounds, expedient but not perfect methods required (80% engineering)
- We often use sub-optimal data (IR traces, reaction calorimetry, HPLC PAR’s) and model in these domains
- While parameter estimation is often numerically performed (not always!), optimization tends to be crude
- Tools: MatLab, HiQ, DynoChem
“Crude” Modeling: Using ReactIR data to improve a reaction

- Rate constant $k_1$ (formation of methylthiol product and rate constant of impurity formation $k_2$: $k_1 / k_2 \approx 75$
  - Improve ratio of rate constants by changing reaction temperature.

For 100% conversion of starting thiol:
- 1.048 eq Mel
- 94.4% Product
- 5.6% Impurity

More MeI only increases di-Methyl impurity %

$$\text{Ar-SH} \xrightarrow{\text{KOH, MeI}} \text{Ar-SMe} + \text{KI} + \text{H}_2\text{O}$$
Desired Practice: Reaction Engineering

- Would like to improve level and quality of modeling
- Will never be “perfect” due to time constraints, but better optima, better extrapolation possible
- Broaden use of optimization tools?

Collect kinetic data, quantitative → Estimate statistically significant parameters, or determine boundary conditions → Use parameters to define an optimal operating policy → Improve optimization based on further experimentation → Program DCS Sequence to obtain optimum
Biopharmaceutical fermentations tend to be very complex systems, with many potentially important parameters:
- shear
- dissolved gas levels (CO$_2$, O$_2$)
- pH
- fermentation by-products

Many side reactions possible for proteins: similar reactive sites (e.g., a monoclonal antibody may have multiple histidine groups)

Downstream purification operations are extensive: perhaps 10-20 unit operations to get fermentation product into a formulated product

Single batches typically run for ~ 15 days. End value of batch can be 1 million US for 1000 L fermentor
Biopharmaceutical Modeling Problem: Deamidation of a Protein

Many unknowns in model: how do various parameters affect cell growth rate constant (different for almost any two experiments)

How would optimum harvest time vary across natural variability of $k_0$
Need for new process analytical technologies: mechanistic inferences, potentially kinetic information to drive model development. Example: electrospray mass spectrometry, real-time data
Typical Setup for Reaction Monitoring by ES/MS
Proposed Reaction Mechanism Using Observed Intermediate
Reaction Mechanism proposed to be that proposed by Knoevenagel, rather than that proposed by Hann and Lapworth

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Current Practice: Crystallization

- Semi-quantitatively driven
  - analytical issues: what is particle size?
- Data collection techniques: probably underdeveloped relative to other fields
Solubility Measurement:
Example of basic collected data using IR methods. Automated, rapid, accurate, and routine.

System calibrated in 0.5 days for 4 solvents; PLS fit to calibration standards. ~ 6 g material required, ~ 4 g recovered. In ~24 hours, solubility mapped out in 4 solvents.
Kinetic Information: Qualitative Desupersaturation Monitoring

- For a typical crystallization design, crystallization monitoring occurs after measuring solubility, MSZW.
- Time scales for crystal growth under different seeding, cooling conditions are inferred from turbidity, Lasentec, and IR signals.
- From this basis, boundary conditions are determined.
- Qualitative Design.
• Need for improved analytical methods for data collection
• While we may never be able to model accurately in the domain of FDA accepted particle size methods, we can use models to indicate sensitivity of process to changes. This would improve robustness of process.
• Due to high value of product at this stage, active control strategies on plant would attract investment
• Some good academic activity in this area (Rawlings, Braatz)
Drying: The forgotten field

• Drying influences product sizes perhaps more strongly than crystallization unit operations, yet there is very little research in drying modeling

• How do we explain/correlate particle breakage in filter dryers (f(mechanical properties, geometry))

• How do we explain agglomeration phenomena?
Industry Needs: Infrastructure

- More hiring of graduates from control and modeling programs
  - ChE hires tend to be from crystallization, chemistry oriented programs ---> tend to have weaker math/modeling skills
- Integration of best practice optimization algorithms, approaches into commercial software (e.g. MatLab)
- Training and implementation sessions from modeling and control community
Industry Needs: Technical (1)

- Integration of detailed mixing effects into modeling
- Consideration of pharma used process analytical tools (Raman, IR, Lasentec?, NIR) in development of control schemes: how would we take complex data, reduce it quickly, and allow its feedback?
- Some academic effort into modeling drying processes
- Close work with PAT community to improve model development and control strategies for crystallization and reaction engineering
- New PAT’s to enable better models: electrospray MS? Ultrasound? Etc...
Industry Needs: Technical (2)

- Additional resource into crystallization modeling and control
- Detailed consideration of biopharmaceutical reaction engineering: how to best model cellular systems
Summary

- As an industry, we are in general not state of the art in modeling and control
- Pharma is chemistry rather than engineering driven
- Significant scale-up constraints due to plant configurations
- Significant infrastructure and technical needs that can be addressed by modeling and control community
- Advancement in modeling is relatively straightforward; advancement in control is longer term