Achieving Excellence in Continuous Manufacturing:

Using Process Models for Process Development and Understanding Process Dynamics

By

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Overview

- Flowsheet models
- Applications to process design
- Applications to risk assessment and validation
- Applications to process control
- Way forward – HME, capsule filling, predictive material property databases, and real time optimization
What is flowsheet modeling?

- Flowsheet modeling uses differential, algebraic and integral equations to describe the physics and dynamics of processing unit operations.
- Unit operations can be combined in sequence to represent a complete manufacturing process – this is a flowsheet model.
- Process responses calculated in one unit become inputs to the next unit.
- Sensors and control loops can be included to describe the dynamics of the entire system.

**FEEDERS:**
- **Model:** Delay Differential Equation
  - Powder properties, Flowrate set point
  - rpm, tooling

**MIXER:**
- **Model:** Residence time distribution (RTD)
  - Powder properties, Flowrate in
  - rpm, geometry
  - Blend powder properties, Flowrate out

**DIRECT COMPACTION**

**Hopper:**
- **Model:** Delay Differential Equation
  - Blend properties
  - Powder properties, Flowrate in
  - geometry
  - Blend powder properties, Flowrate out,
  - Mass holdup

**Tablet press:**
- **Model:** RTD, Heckel or Kawakita compression equation
  - Blend powder properties, Flowrate in
  - feed frame speed, compression force, fill depth
  - tablet production rate, tablet weight, tablet hardness, disso.
Why flowsheet modeling?

- Flowsheet models can be applied to pharmaceutical processes in order to:
  - Conduct preliminary design evaluation
  - Identify potential bottlenecks
  - Compare control strategies
  - Identify potential critical process parameters
  - Explore design space
  - Enhance process understanding
Building a unit operation model

- Each unit operation can be described by a system of equations that relates process inputs to process outputs.
- The model should represent the major phenomena associated with the transformation of inputs to outputs. For example:
  - A blender model should relate blend homogeneity (RSD, segregation intensity) to relevant operating parameters like rpm and raw material flowrates.
  - A tablet press model should incorporate compression equations relating inlet bulk density to tablet porosity via applied compression force.
Building a unit operation model

- Unit operation models should also account for process dynamics. For instance:
  - The dynamic response of the system to a change in operating conditions should be captured through transfer functions.
  - Residence time in each unit operation should be considered so that the response of the system to transient disturbances can be accurately captured.

\[ \tau \frac{dy}{dt} + y = y_{\text{set}} \]

\[ y(t) \]

\[ \text{Material in at } t=t_0 \]

\[ \tau - \text{mean residence time} \]

\[ \text{Material out at } t=t_0+\tau \]

\[ \tau - \text{time constant} \]

\[ y_{\text{set}} - \text{flowrate set point} \]
Continuous tablet manufacturing pilot-plant

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Enable: Continuous FLEXIBLE multipurpose platform

Validation of Continuous Processes

- What does validation mean for a continuous process?
  - Traceability of materials through process
  - Understanding of process dynamics
  - Identification of critical parameters
  - Design and implementation of control strategies to ensure product quality

- How can flowsheet modeling contribute to continuous process validation?
  - Understand variability propagation
  - Identify potential CPPs and control variables using uncertainty and sensitivity analysis
  - Predict traceability of raw materials through a system
  - Determine design space and evaluate process robustness using Flexibility and Feasibility Analysis
Disturbance Propagation in Continuous Systems

- Continuous manufacturing processes are integrated systems
  - Interconnected series of unit operations
- Transient disturbances propagate from one unit operation to the next
- Downstream processing may attenuate or filter out variability
- Poorly designed feedback controls can amplify perturbations
- Dynamic simulation and uncertainty analysis can be used to understand propagation of variability in continuous systems
Tracking response to step changes

Simulate step changes in mixer RPM

Monitor hopper fill-level to avoid overfilling

Tracking variability in RSD in response to changes in mixer RPM

RSD

max
Evaluating response to transient disturbances

An **unavoidable perturbation** in a continuous manufacturing process is a feeder refill.

This disturbance is propagated to downstream unit operations - distribution changes due to RTD in the system.

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**Component Feed Rate**

- API flowrate
- Excipient flowrate
- Lubricant flowrate

**Relative Standard Deviation**

- Hopper RSD
- Mixer RSD
- Tablet RSD
Propagation of uncertainty in granulation flowsheet - uncertain inputs

- gSOLIDS template is used for this case study of a 3 component mixture being granulated and milled
- Significant inputs are chosen:
  - Material properties (bulk densities)
  - API flowrate
  - Breakage parameters in milling
- These inputs are sampled according to known distributions and their effects on process outcomes are observed
Group Uncertainty propagation-Direct Compaction case study

- Total number of 2048 scenarios were simulated in parallel (gPROMS) and analyzed in SIMLAB
- Example of questions we aim to answer:

  “Does the uncertainty in the feed flow rate cause variability at the outlet of the blender?”
Sensitivity Analysis

• Process of attributing variance in process responses to sources of variability in the process and/or model

• Local – one at a time variation of parameters
• Global – simultaneous variation of parameters
  – Appropriate to complex systems with parameter interactions

• Sensitivity metrics indicate the magnitude of the effect of a process variable on a particular process response

• Applications for pharmaceutical process development
  – Identification of critical process parameters
  – Potential control variables and development of control strategies
Which factors contribute most significantly to variability in process outcomes?

Partial Rank Correlation Coefficient

Eliminate parameters that are less significant for subsequent analysis
- For variance-based methods, the number of samples required to estimate indices increases with the number of inputs considered
- Parameters related to lubricant properties or feeding
- Univariate input-response relationships
  - FF rotation rate
  - Tablet press compression force
  - Hopper aperture

Identify potential critical parameters
- Material properties (API, Excipient)
- Feeder parameters
  - Screw rpms
  - Feeder gain parameter
Conclusions for Direct Compaction Case Study

Potential CPPs
- API and Excipient physical properties including $d_{50}$ and bulk density
- Interaction between API and Excipient properties is also significant – consideration when determining design space
- Feeder tooling and sizing – interacts with operating parameters
  - Important to consider design variables when optimizing process operations

Potential Manipulated Variables
- API and Excipient feeder screw rpms
- Mixer rpm – interacts with API and excipient feed rates

Applications
- Quality risk assessment
- Control strategy design
- Design space determination
Direct compaction - traceability

Input: Total throughput, formulation, feeder hopper sizes and refill strategy:
- Individual feeder rpm
- Hopper fill level
- Time of refill → causes peak in feedrate

Discard tablets during:
- [0-800], [5000-5250], [9400-10000], [13900-14400] and [18000-19500] seconds

96% Avicel, 3% Acetaminophen, 1% MgSt, 100 kg/hr, refill level 20%
The Challenge of defining a “Batch”

Material traceability in a batch process is well-understood. Continuous still has a gap between understanding and regulatory acceptance.
RTD of Each Unit Operation
Identifying sources of variability

- Downspout Accumulation
- Feeder Bearding
- Feeder Fluctuations
- Disturbances (Feeder hopper refill)
Detect and Trace Disturbances

- 0.25 g Pulse
- 30 kg/hr
- 6% API

Blender:
- MRT: 41.6s
- StdDev: 12s
Determine System Robustness

1 g Pulse
30 kg/hr
6% API

Blender:
MRT: 41.6s
StdDev: 12s
Reconfigure Blender to increase backmixing

1 g Pulse
30 kg/hr
6% API

Blender:
MRT: **71.7s**
StdDev: **24.9s**
Determining Adequate PAT Sensor Frequency

\[ t_m = \int_{0}^{\infty} tE(t) dt \]

\[ \sigma^2 = \int_{0}^{\infty} (t - t_m)^2 E(t) dt \]

Sensor at least 3-5 times faster than standard deviation should have decent resolution allowing for detection of pulse variability.

Mean Residence Time: 71.7s

Standard Deviation: 24.9s

Sample Time Interval: 8.3s
Introduction to process control

Why needed?
1. To achieve the desired predefined end product quality
2. To manufacture the product safely
3. To satisfy the flexible market demands
4. To reduce the manufacturing expenses (e.g., labor cost)
5. To assure consistent manufacturing of desired quality product
Process dynamics

Step change

$u(t)$

$t$

Process

? 

Process inputs example:

- Feeder screw rotational speed.
- Blender RPM.
- Feed frame speed.
- Blend density.
- Material properties.

Product quality assurance:

- Drug concentration?
- RSD?
- Tablet weight?
- Tablet hardness?
- Tablet dissolution?
Advanced supervisory control system

- API feeder
- Excipient feeder
- Lubricant feeder

Control variables:
- API composition
- Powder level
- Tablet weight
- Tablet hardness

MPC

API flowrate

Fill depth

(Restrain gauge)

Weight

Hardness

(Composit)

Coater

Tablet press

D-RTO

API composition

Powder level

Tablet weight

Tablet hardness
Way forward

• Expand model library
  • More models, better models
    • Feeders, hoppers, coating pans, granulators
  • More methods for designing, optimizing, controlling, validating, assessing risk
  • More processes – HME, capsule filling, biologicals

• Predictive libraries of material properties for formulation design

• Two way communication between the process and the model to enable real time optimization