Real Time Release in Continuous Solid Dose Manufacturing:
Systematic Characterization of Material Properties, and Optimal Design of Sensing and Control Methods

Fault tolerant control for safe plant operation

Qinglin Su, Mariana Moreno, Jianfeng Liu, Gintaras V. Reklaitis, Zoltan K. Nagy
School of Chemical Engineering

November 10, 2016
Content

- Introduction
  - Systematic framework for control design & analysis
  - Example: continuous feeder & blender system
  - Summary & conclusions
- **Batch vs. continuous manufacturing**

**A typical batch manufacturing process**

- **Synthesis**
  - Test & Storage
- **Crystallization**
  - Test & Storage
  - Shipping

**Region 1**

**Blending**
- Test & Storage

**Granulation & Sizing**
- Test & Storage

**Tablet press & Coating**
- Test & Tablets

**Region 2**

**Months**

**A conceptual integrated continuous manufacturing process**

- **Synthesis**
- **Crystallization**
- **Blending**
- **Granulation & Sizing**
- **Tablet press & Coating**

**At one site: (1) small equipment; (2) short supply chain.**

**Days**

---

Continuous manufacturing in pharma.

- FDA Quality Related Guidance Initiatives
  - e.g. PAT Guidance (2004)
  - e.g. OPQ Standup and ETT Formation (2015)

- Flexible demand
- Precise medicine
- Competitiveness

- Smaller production facilities
- Minimizing manufacturing cost
- Enhancing reliability and flexibility
- **Monitoring & control**
  - drug quality on a continuous basis rather than through post-production, batch-based testing
Continuous manufacturing pilot plant

Potter B36 in Purdue University
Demands for efficient process monitoring & control

- Implementation layer
- Final quality assurance

Challenges:
- Model-plant mismatch
- PAT calibration
- Process disturbance
- System interactions
- Process nonlinearity
- Plant start-up
- Plant shut-down
- Controllability
- Stability
- Robustness
- Self-adaptiveness
- Controller tuning
Content

- Introduction
- Systematic framework for control design & analysis
- Example: continuous feeder & blender system
- Summary & conclusions
- **C1 Material library**
  - Material database
  - Process characterisation
  - Feasible formulation space

- **C2 Sensing & RTR strategy**
  - Control variables
  - Control set points

- **C3 Process Monitoring & Control**
  - Process parameters
  - Unit operations

- **C4 System Performance & Verification**
  - Operating cost
  - Process maintenance

- **Project objectives & outlines**

- **Pilot plant**

- **Process model**
Systematic framework for control design & analysis (1)

Layer 0
- Built-in control systems by manufacturers at unit operation level
- Simple PID control
- Single unit operation

Layer 1
- Based on PAT to measure CQAs and closed loop control (PFC)
- PID based more advanced control schemes
- Single or multiple unit operations

Layer 2
- Use of dynamic models for prediction
- Model Predictive Control, Adaptive Control, Gain Scheduling, etc.
- Integrated across multiple unit operations

Hierarchical control architecture
- Risk levels & failure mode
  - R0 Low
  - R1 Medium
  - R2 High
  - Risk levels & failure mode
    - T2P, M2P, MRI

Evaluation & regulatory filling
- Continuous improvement
  - e.g. Good Manufacturing Practices (GMP) guidelines
    - Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.
    - Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary.

Sensor accuracy, precision, sampling time
Sensor location
Control architecture reconfiguration
Control method
Controller tuning
Formulation optimization
Process reconfiguration

- Systematic framework for control design & analysis (2)
- **Hierarchical three-layer control**

**MES:** Manufacturing execution system
- MPC-1
- MPC-2
- RTO
  - Production control
  - Optimization
  - Plant scheduling

**SCADA:** Supervisory control and data acquisition
- Cascaded multiple SISO loops with PID controller
- Tools for pairings, tuning, etc.
- Single/multiple unit operations
- Control CQAs with PAT tools

**Layer 2**
- **Layer 1**
- **Layer 0**

**Layer 0**
- PLC-1
  - SISO & PID
  - Single unit
  - Control CPPs
- PLC-2
- PLC-3
- PLC-4

**Layer 1**
- OPC

**Layer 2**
- MPC-1
- MPC-2
- RTO

**Diagram Elements:**
- Feeder
- Blender
- Hopper
- Tablet press
LO & L1 control design

- Mostly decentralized SISO PI/PID control loops
- Interactions among parallel control loops are important
- Interactions among hierarchical control loops

1. Selection of input/output variables
   • Input and Output Effectiveness
   • Controllability e.g., condition number (CN), relative gain array (RGA)
   • Resilience e.g., Morari’s Resilience Index (MRI)

2. Pairing and interaction analysis
   • Pairing selection e.g. RGA, relative interaction array (RIA), Niederlinski Index (NI), singular value decomposition (SVD)
   • Interaction e.g., Dynamic Interaction Measure (DIM)

3. Close-loop control system evaluation
   • Stability e.g., Nyquist’s stability criterion, Characteristic Loci Plots
   • Robustness e.g., SVD, µ-based method
   • Dynamic simulation e.g., MATLAB, Simulink

L2 model-based control / real-time optimization

Model $Y = f(x, u)$

- Control algorithm
- Sensors
- Process
- Measurement

Objective $J$

Input $U$

Output $Y$

- $U(k+i)$
- $U(k)$
- $Y(k)$

$x$: system state variables

$i = 1, 2, \ldots, N_c, \ldots, N_p$

- $N_c$: control horizon
- $N_p$: prediction horizon

- Model update
- State estimator
- Kalman filter
- Extended Kalman filter
- Unscented Kalman filter
- Moving horizon state estimator
- ...
L2 MPC real-time implementation strategy

\[ Y(k) \quad \text{Past} \quad K-1 \quad k \quad K+1 \quad K+2 \quad K+N_C \quad k+N_p \quad \text{Future} \]

\[ Y(k+1) \]

\[ u(k \mid t=k-1) \]

\[ u(k+1 \mid t=k) \]

\[ U(k+1: k+N_p \mid t=k) \]

\[ U(k: k+N_p-1 \mid t=k-1) \]

\[ \text{MPC} \quad U(k+1: k+N_p \mid t=k) \]

Computation time \( \leq \) sampling time
Risk analysis and control evaluation
Content

- Introduction
- Systematic framework for control design & analysis
- Example: continuous feeder & blender system
- Summary
Continuous dry granulation process

- Loss-in-weight Feeders
- Continuous Blender
- Roller Compactor
- Mill
- Lube
- Tablet Press
### Feeder & blender control system

<table>
<thead>
<tr>
<th>Unit operation</th>
<th>Process output (y)</th>
<th>Process input (u)</th>
<th>Control Layer</th>
<th>Controller type</th>
</tr>
</thead>
<tbody>
<tr>
<td>API feeder</td>
<td>API flowrate</td>
<td>Screw rotation speed</td>
<td>L0</td>
<td>PID</td>
</tr>
<tr>
<td>Exp. feeder</td>
<td>Exp. flowrate</td>
<td>Screw rotation speed</td>
<td>L0</td>
<td>PID</td>
</tr>
<tr>
<td>Blender</td>
<td>API composition</td>
<td>API flowrate</td>
<td>L1/2</td>
<td>PID, Ratio, MPC</td>
</tr>
<tr>
<td></td>
<td>Powder flowrate</td>
<td>Excipient flowrate</td>
<td>L1/2</td>
<td>PID, MPC</td>
</tr>
<tr>
<td></td>
<td>API mixing RSD</td>
<td>Rotation speed</td>
<td>L1/2</td>
<td>PID, MPC</td>
</tr>
<tr>
<td></td>
<td>Rotation speed</td>
<td>Motor current</td>
<td>L0</td>
<td>PID</td>
</tr>
</tbody>
</table>

![Feeder and Blender CONTROL SYSTEM](image)

**a** Feeder and mixer system with control panel. **b** Feeder and mixer system with control panel.
System identification: state-space models

Continuous-time identified state-space model

\[
\frac{dX}{dt} = A_cX(t) + B_cU(t)
\]

\[
Y(t) = C_cX(t) + D_cU(t) + e(t)
\]

\[
G = C^{-1}(SI - A)B + D
\]

L1 control design

decoupled control design
e.g., condition number
Niederlinski index
relative gain array
Morari’s resilience index
...

Discrete-time identified state-space model

\[
X(k + 1) = A_dX(k) + B_dU(k)
\]

\[
Y(k) = C_dX(k) + D_dU(k) + e(k)
\]

\[
\min_{\Delta U} J = \|Y_{sp} - \hat{Y}\|_2 + w_u \|\Delta U\|_2
\]

\[
e(k) := w_e e(k - 1) + (1 - w_e) e(k)
\]

L2 control design

Linear MPC design
Sampling time: 4s
Kalman filter design
State estimation
...

PURDUE UNIVERSITY
*System identification: training data*

- API flow (kg/hr)
- Exp. flow (kg/hr)
- API Comp.
- Blender flow (kg/hr)

*Sampling time of 4 second for all measurements, only 4 measurements shown here*
• **System identification: validation data**

![Graph showing time response comparison with API Comp, Amplitude, Powder Flow, and API RSD over time (seconds). The graph indicates a sampling time of 4 sec for all measurements.](image)

*Sampling time of 4 sec for all measurements*
• L1 control design & analysis: a check list

Command Window

STEP ONE: Input/Output Variables Sets

[S1-1] Condition Number: 18.23057
[S1-2] Morari Resilience Index: 0.07729
[S1-3] The lower bound of minimized condition number: 1.00000
   The upper bound of minimized condition number: 2.00000

STEP TWO: Input/Output Pairing

[S2-1] RGA pairing is successful:
   0.8768  0
   0  0.8768

[S2-2] Niederlinski Index (>0): 1.14
   Diagonal SISO controllers may be stable!

[S2-3] KTA pairing is successful:
   0.1406  0
   0  0.1406

STEP THREE: Performance Measures for Fixed Input/Output Pairing

[S3-1] Dynamic Interaction Measure (DIM): 45.00368
   Compensation to reduce the interaction is needed!

[S3-2] Diagonal Dynamic Interaction Measure (DIM): 88.33010
   Compensation to reduce the interaction is needed!

[S3-3] Moore pairing is successful:
   1  0
   0  1

[S3-4] μ Interaction measure: 2.66713
   The decentralized controller may not be stable.

[S3-5] Performance Interaction Measure (PIM) (0-2): 0.72692
   Smaller Τao indicates lower performance interaction

✓ >> |
Control architecture

**SP**: Set point

**MV**: Measured variable

**FT**: Flowrate transducer

**CC**: Composition control

**FC**: Flowrate control

**RSD**: Relative standard deviation

**RC**: Ratio control

**MC**: Motor control

**L0**: Level 0 equipment control

**L1**: Level 1 supervisory control

**MW/NIR**: Microwave/near infrared
**LO/2 control for feeder & blender system**

Control architecture:
- **SP**: Set point
- **MV**: Measured variable
- **FT**: Flowrate transducer
- **FC**: Flowrate control
- **CC**: Composition control
- **RSD**: Relative standard deviation
- **MPC**: Model predictive control
- **MC**: Motor control
- **LO**: Level 0 equipment control
- **L1**: Level 1 supervisory control
- **MW/NIR**: Microwave/near infrared

Diagram:
- **API feeder**
- **Excipient feeder**
- **Continuous blender**
- **L0-FC-1**: PID control
- **L0-FC-2**: PID control
- **L0-MC-1**: N/A control
- **L2-MPC**: Model predictive control
- **FT**: Flowrate transducer

Definitions:
- **API comp.**: API composition
- **RSD**: Relative standard deviation
- **Blend flowrate**: Blend flow rate
- **Blender RPM**: Blender RPM
Feeder & blender simulation in Simulink/MATLAB

Sampling time:
- FT: 1.0 s
- NIR: 2.0 s
- L0/1: real time
- L2 MPC: 4.0 s

L0.CTRL Blender Control Panel

L1/L2.CTRL Feeder & Blender Control

API flow sensor

Exciptent flow sensor

Powder flow sensor

API Comp sensor

Hopper fill

Blender

FT

NIR

FT
Risk Analysis for feeder & blender: R0 & R1

R0 risk: mass flow disturbances due to feeder reloading
R1 risk: calibration errors in the feeders
Risk Analysis for feeder & blender: R2

R2 risk: material flowability changed due to humility while a step change on the powder flow rate was also executed.
Performance evaluation based on the API composition.
+ Indicators based on API mean composition; * Indicators based on API mixing RSD.

<table>
<thead>
<tr>
<th>Control</th>
<th>D2R (s)</th>
<th>M2P (%)</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R2</td>
<td>R0</td>
<td>R1</td>
</tr>
<tr>
<td>L0</td>
<td>176⁺</td>
<td>Fail</td>
<td>Fail</td>
</tr>
<tr>
<td>L1</td>
<td>97⁺</td>
<td>238⁺</td>
<td>494*</td>
</tr>
<tr>
<td>L2</td>
<td>81⁺</td>
<td>183⁺</td>
<td>259*</td>
</tr>
</tbody>
</table>

* **Blender D2P**: Duration to reject, s; **M2P**: Magnitude to product, %
Risk Analysis for feeder & blender: R2 PAT gross error

**Layer 0 control:** no feedback control based on the PAT tools.

The PAT tool of NIR for API composition measurement drifted from 40 to 100 seconds and suffered the gross error from 100 to 240 seconds before it was corrected.
Layer 1 control: The PAT tool with gross error detoured the API mean composition and its mixing uniformity from their set points.
Layer 2 control: The Kalman filter with data reconciliation can reject the measurement gross error when large model-plant mismatches detected.

\[ x[k|k] = x[k|k - 1] + M(y[k] - y[k|k - 1]) \ R \]

\[ R = diag\left(\exp\left(-\frac{e_i^2}{c\sigma_i^2}\right)\right) \]
Summary & conclusions

- The primitive systematic framework for control design and analysis based on SIMULINK platform has been developed.

- L0 control loops response fastest to measurable R0 disturbances but fail to response to the unmeasurable disturbance R1.

- L1/2 control loops are capable of intermediate product quality control. L2 control based on MPC is beneficial but the maintenance cost is also high.