Robust model-based control for safe pharmaceutical manufacturing

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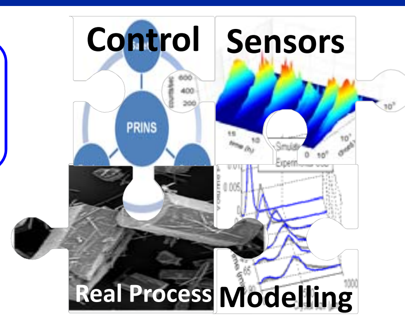
May 3, 2017

Purdue Process Safety and Assurance Center (P2SAC)

Advanced Process Control of Complex Systems

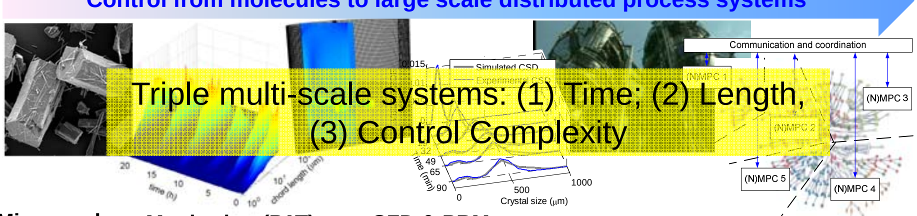
Aim:

Development of systems approaches & tools for improved (particulate) product design and optimal process operation (control)



Control from molecules to large scale distributed process systems

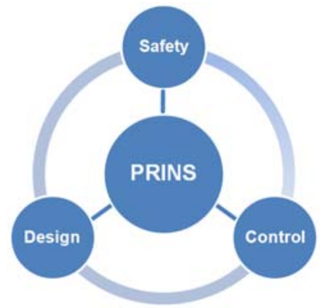
Triple multi-scale systems: (1) Time; (2) Length, (3) Control Complexity



Micro scale | **Monitoring (PAT)** | **CFD & PBM** | **Integrated and distributed systems**

Overall Project Objectives

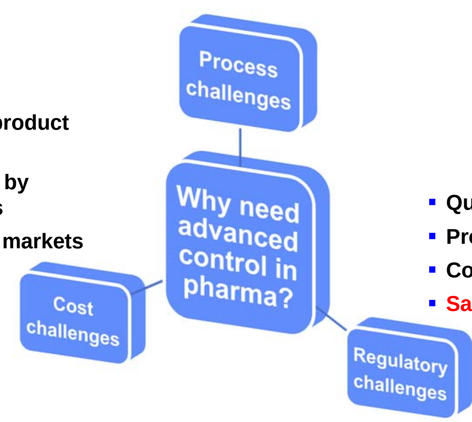
- Develop a methodology for integrated Design-Control-Safety (DCS) platform for pharmaceutical processes
- Control for Safety: Fault tolerant control (FTC) for safe plant operation
  - risk-based control system design and validation
- Improve process performance and safety via continuous manufacturing of pharmaceuticals or continuous batch-to-batch process improvement



Why do we need to use advanced control techniques in the pharmaceutical industries?

- **Lack of real-time measurements**
- **Lack of models**
- **Lack of actuators**

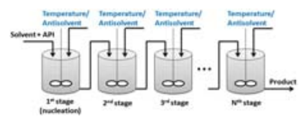
- **Large variations in product pipeline**
- **Downward pressure by healthcare providers**
- **Growth in emerging markets**



- **Quality assurance**
- **Process validation**
- **Continuous verification**
- **Safety**

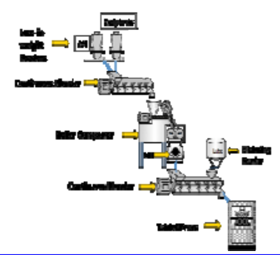
Past and Present
Target Processes for Implementation

- **Batch crystallization**
- **Continuous crystallization**



  - MSMPR (cascade of MSMPRs)
    - **Advantages:** equipment in place, easier use of PAT
    - **Disadvantage:** similar to batch processes (large residence time distribution, low heat transfer area/volume ratio)

  - Plug flow crystallizers (PFC) – different technologies
    - **Advantages:** faster, smaller volume, higher product consistency
    - **Disadvantage:** need for new equipment, difficulty of using PAT
- **Continuous tablet manufacturing**



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Targeted Safety Problems in Pharmaceutical Manufacturing

- Loss of controllability, attainable regions for desired quality and safety constraints during operation and start up
- Fouling (loss of heat/mass transfer, overheating, impurities, etc.)
- Production off-spec product due to fault or large disturbances (wrong bioavailability, reduced dosing, side effects, etc.)
- Batch-to-batch continuous process improvement for better quality and safety
- Advanced purity control (decreased toxicity, etc.)

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- Fault tolerant control framework for continuous tablet manufacturing
- Systematic framework for risk-based analysis and design of control strategies for continuous pharmaceutical manufacturing
- Simulation and practical implementation on pilot plant

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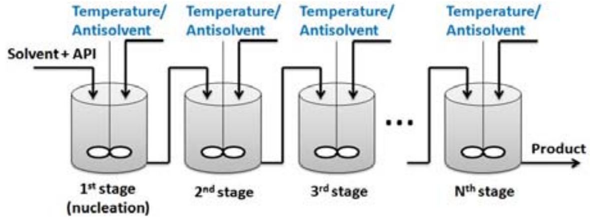
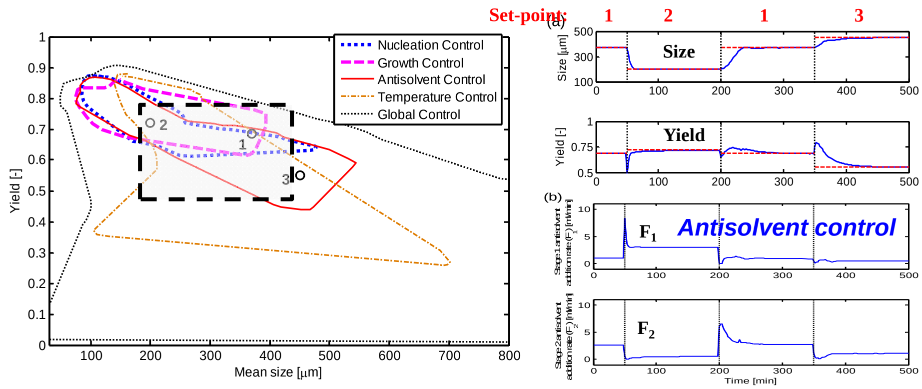
Cascade MSMPR system



NMPC – attainable regions for control for safety

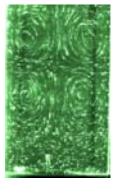


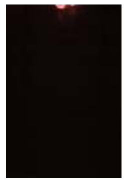
Point	Yield	Size
1	Medium	Medium
2	High	Small
3	Low	Large

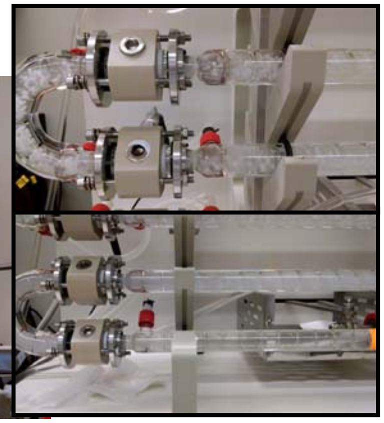
- Tradeoff between yield and size
- Attainable region depends on control approach
- **Depending on safety constraints control change of control structure needed**
- Robust fault-tolerant control

Continuous plug flow crystallization systems

Process Integration and Intensification through Oscillatory Baffled Crystallizer and Spherical Crystallization



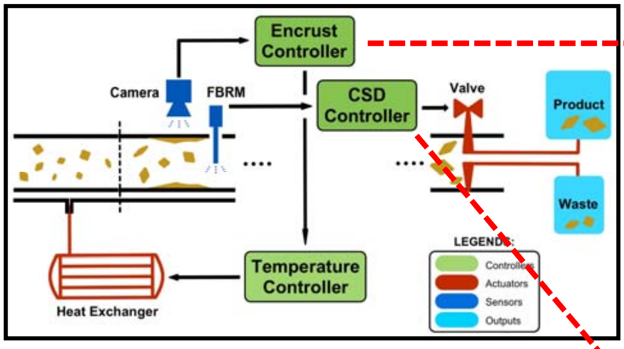


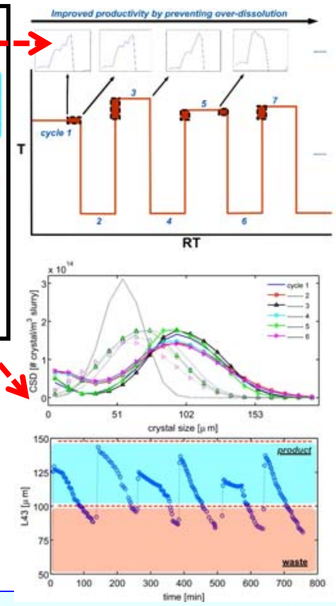


Fouling or encrustation

- Encrustation is a process by which solute (API) deposits on to the crystallizer surface.
- Encrust **reduces heat transfer**, and subsequently product quality and yield.
- Causes **non-steady state** process and leads to **blockage**.

On-Off Fault-tolerant Feedback Control





- The Encrust and CSD controller assures **state of control**.
- The CSD feedback controller detects the **upper and lower bounds** and trigger the point of collection (blue).
- **Example of level-1 control**, in which an active process control system is used to monitor CQAs in real-time.
- Process will work indefinitely due to **QbC** approach despite fault due to encrustation

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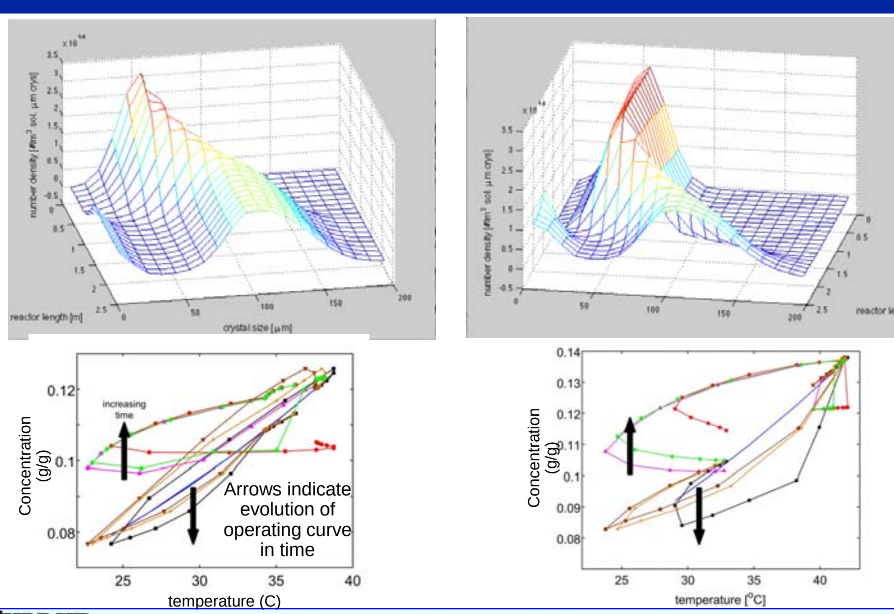
Response of Periodic AFC



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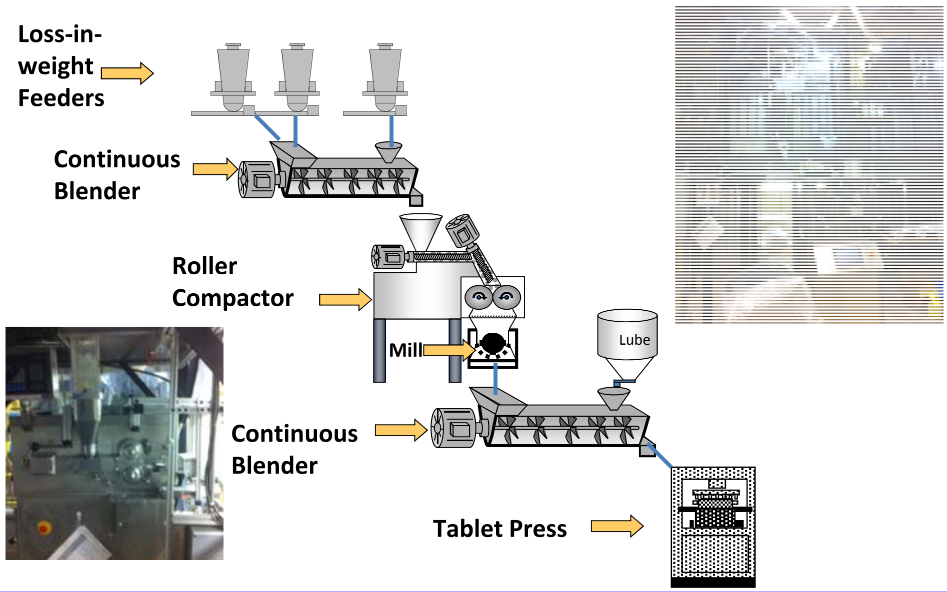
Continuous dry granulation process



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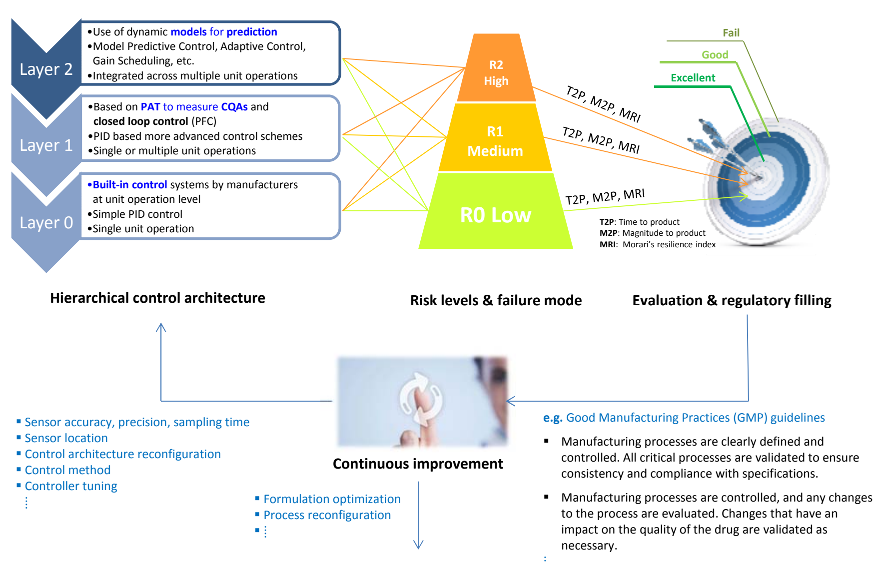
Systematic design and analysis of feedback control strategies for continuous tablet manufacturing processes



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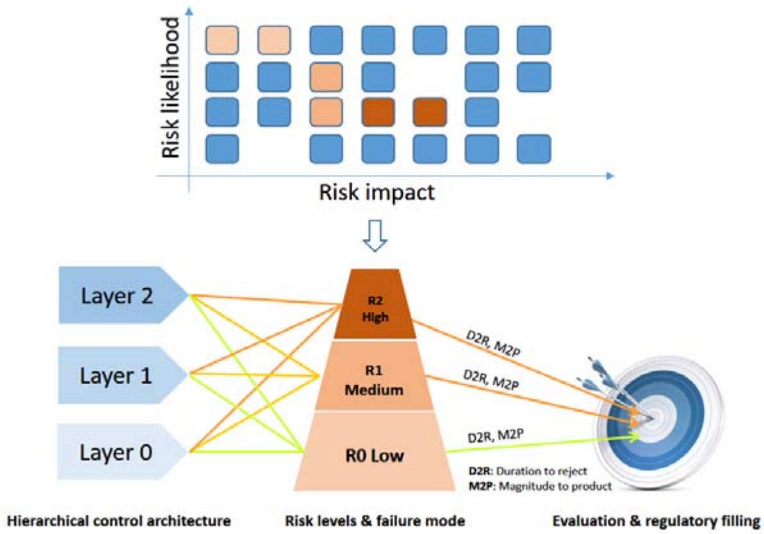
Risk analysis and control evaluation

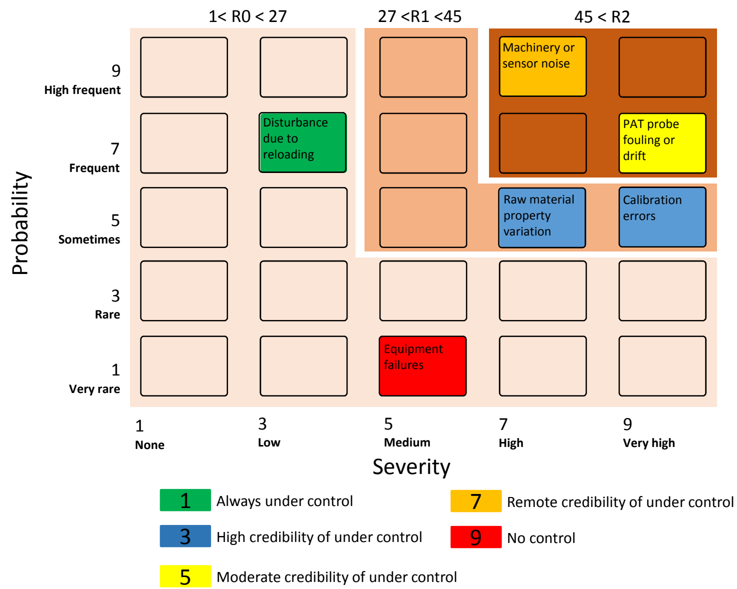


Risk scoring for RTR process control

A risk mapping, from the perspective of process control, will be designed based on scores of severity and probability of risks during continuous manufacturing, upon which the proposed real-time release control strategies will be evaluated to give corresponding controllability scores for each risk.

Rate	Severity		Probability		Controllability	
1	No effect	None	< 1 occurrence during the continuous production in 5 years (e.g., control instrument failure)	Very rare	All the applicable measurements & controls are in place	Always under control
3	No patient effect Process performance decreasing (e.g., divert of non-conforming product)	Low	1 occurrence during the continuous production in 1 to 2 years (e.g., calibration errors)	Rare	Most of the applicable measurements & controls are in place	High credibility of under control
5	No patient effect Process performance decreasing (e.g., large amount of non-conforming product, process shut-down)	Medium	< 1 occurrence during a single continuous production campaign (e.g., variance in raw material properties)	Sometimes	Some of the applicable measurement & controls are in place	Moderate credibility of under control
7	Potential patient effect (e.g., large variance in critical quality attributes)	High	> 1 occurrence during a single continuous production campaign (e.g., raw material reloading)	Frequent /No information	Few of the applicable measurements & controls are in place	Remote credibility of under control
9	Significant patient effect (e.g., large variance in target product quality profile, loss of clinical performance)	Very high	At any time during the continuous operation (e.g., machinery vibration)	High frequent	None of the applicable measurements & controls are in place	No control

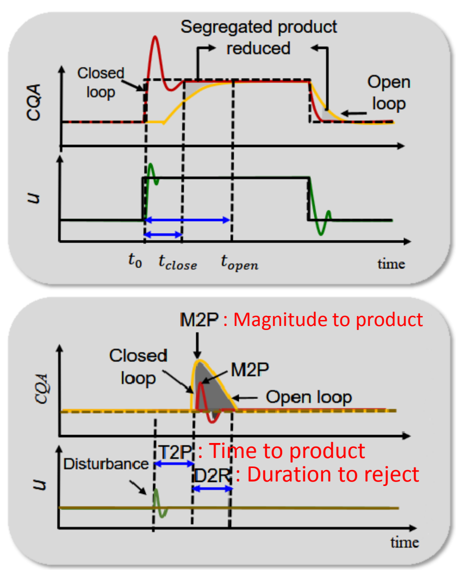
[1] Potter C. PQLI application of science- and risk-based approaches (ICH Q8, Q9, and Q10) to existing products. Journal of Pharmaceutical Innovation. 2009;4(1):4-23.



Control performance evaluation

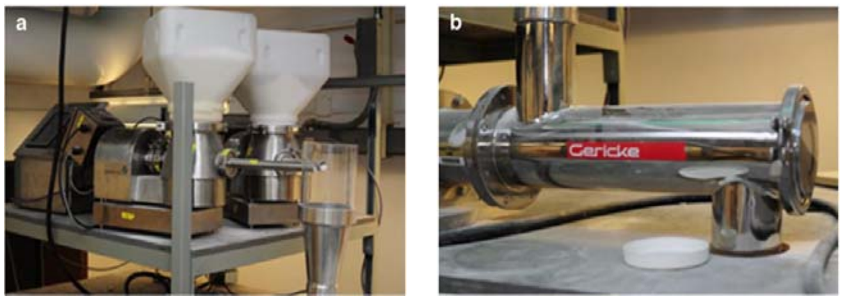
The control design should be robust enough to maintain the quality under common process disturbance, and efficient enough for servo regulation purpose.

KPI: process capability index
M2P: the magnitude the product quality deviates the set point.
T2P: How long it takes for a disturbance to affect the final product quality.
D2R: How long it needs to reject the non-conforming product.

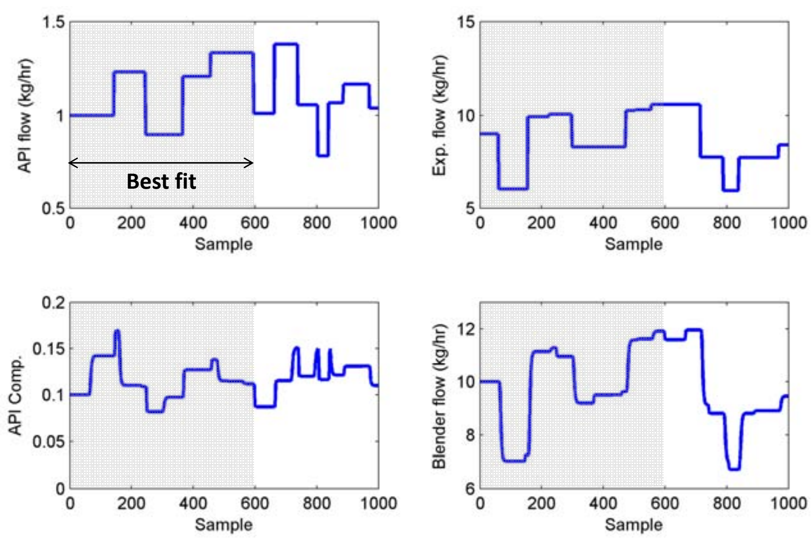


Feeding & blending control system in Purdue Pilot plant

Unit operation	Process output (y)	Process input (u)	Control Layer	Controller type
API feeder	API flowrate	Screw rotation speed	L0	PID
Exp. feeder	Exp. flowrate	Screw rotation speed	L0	PID
Blender				
	Rotation speed	Motor current	L0	PID

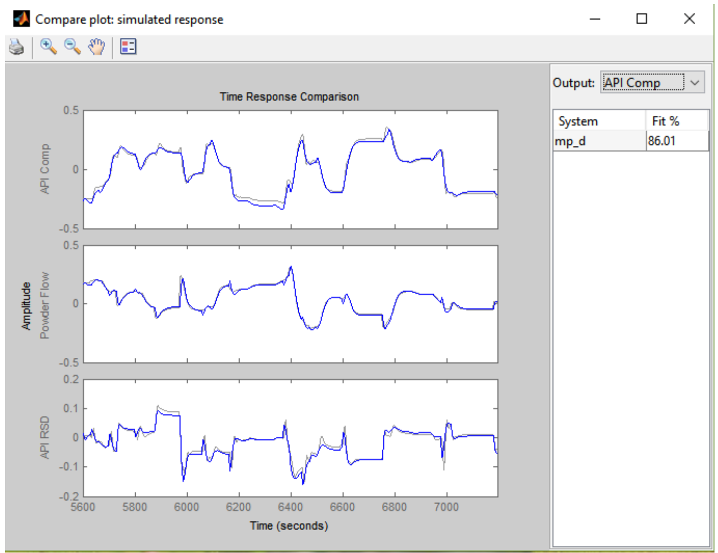


System identification: step test

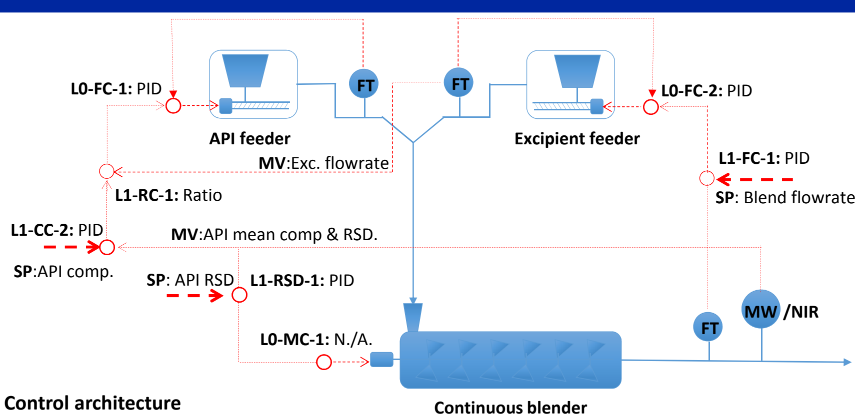


*Sampling time of 4 second for all measurements, only 4 measurements shown here

System identification: validation data



L1 control for feeder & blender system



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

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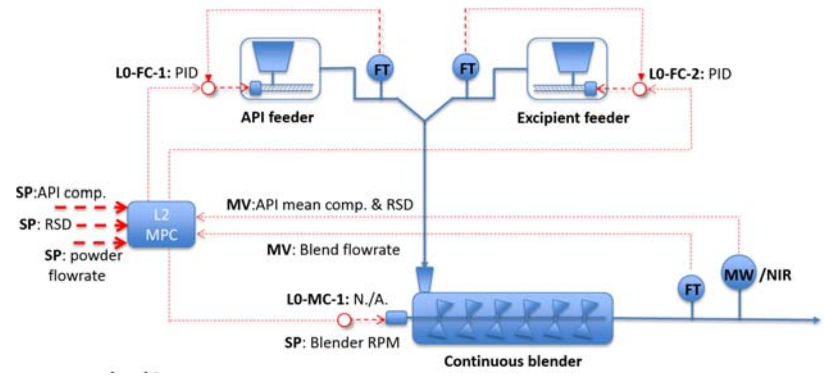
L0/2 control for feeder & blender system



Control architecture

- **SP**: Set point
- **MV**: Measured variable
- **FT**: Flowrate transducer
- **CC**: Composition control
- **FC**: Flowrate control
- **RSD**: Relative standard deviation
- **MPC**: Model predictive control
- **MC**: Motor control
- **L0**: Level 0 equipment control
- **L1**: Level 1 supervisory control
- **MW/NIR**: Microwave/near infrared

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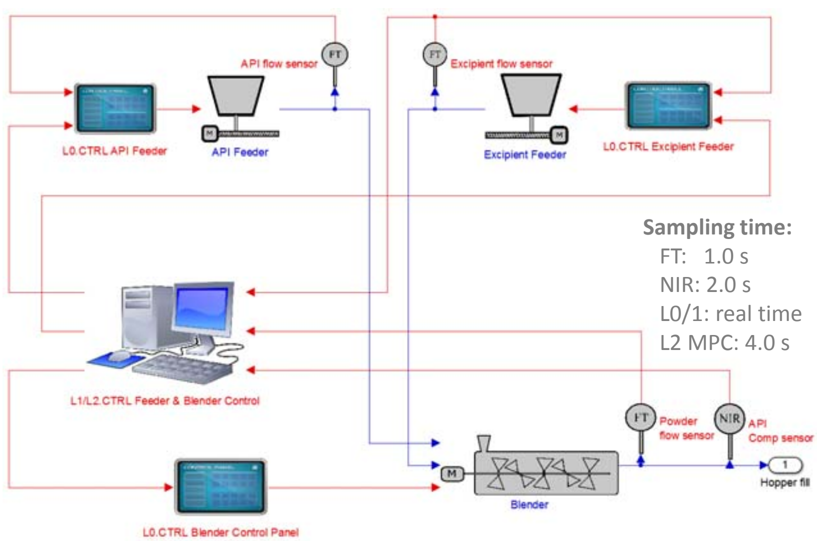
Feeding & blending simulation in Simulink/MATLAB



Sampling time:

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

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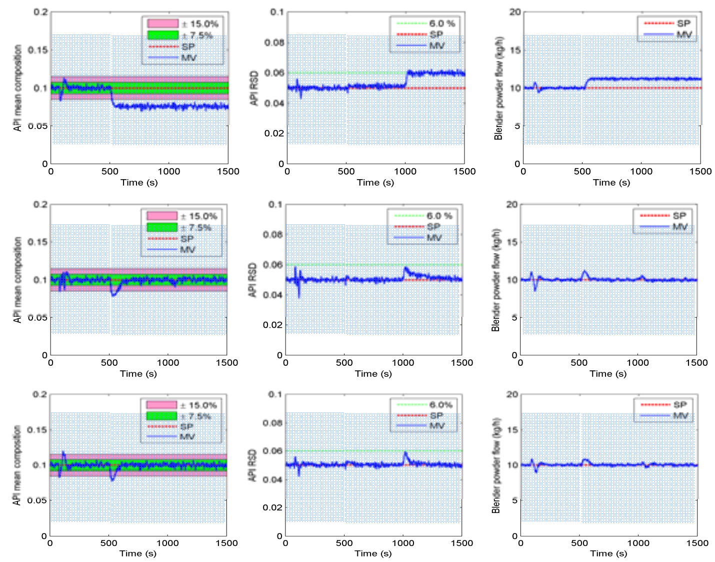
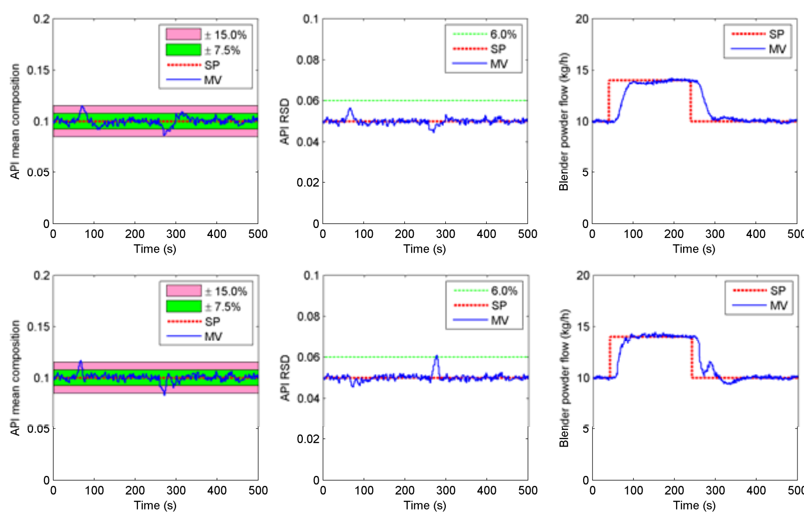
Risk Analysis for feeder & blender: R0 & R1



R0 risk: mass flow disturbances due to feeder reloading
R1 risk: calibration errors in the feeders or change in the material flowability

Risk Analysis for feeder & blender: R2



R2 risk: material flowability changed due to humidity while a step change on the powder flow rate was also executed, meaning large model-plant mismatch for system identification.

Risk Analysis summary

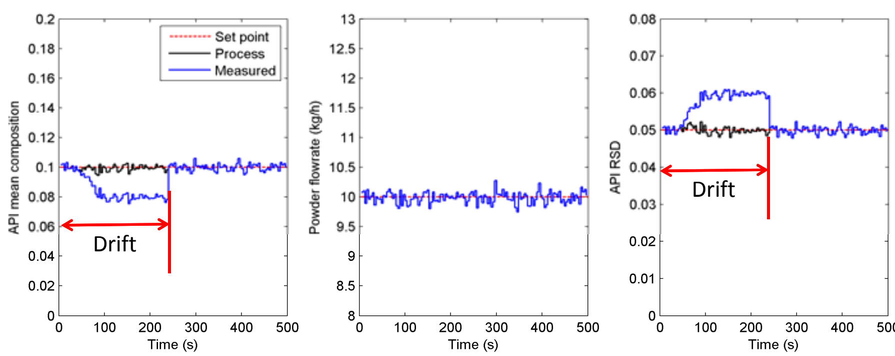
Performance evaluation based on the API composition.
+ Indicators based on API mean composition; * Indicators based on API mixing RSD.

Control	D2R (s)			M2P (%)			Remark
	R0	R1	R2	R0	R1	R2	
L0	176+	Fail	Fail	0.65+	Fail	Fail	Failure for R1 & R2
L1	97+	238+	494*	0.38+	1.52+	0.48*	Long D2R for R2
L2	81+	183+	259*	0.65+	2.30+	0.46*	High M2P for R1

* **Blender D2P**: Duration to reject, s; **M2P**: Magnitude to product, %

Risk Analysis for feeder & blender: R2 PAT gross error

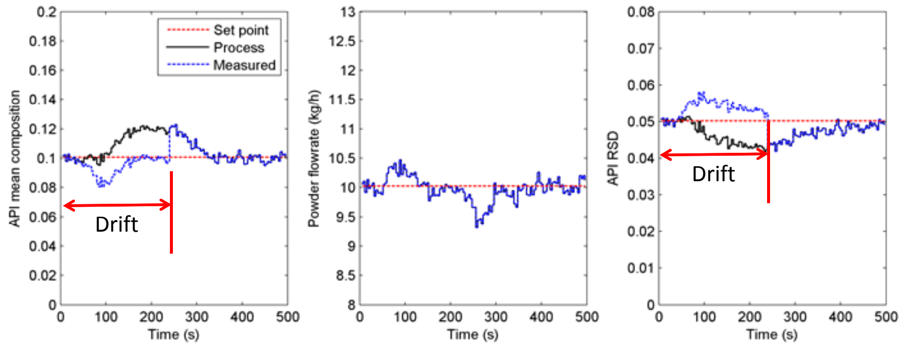
Layer 0 control only: no feedback control based on the PAT tools.



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.

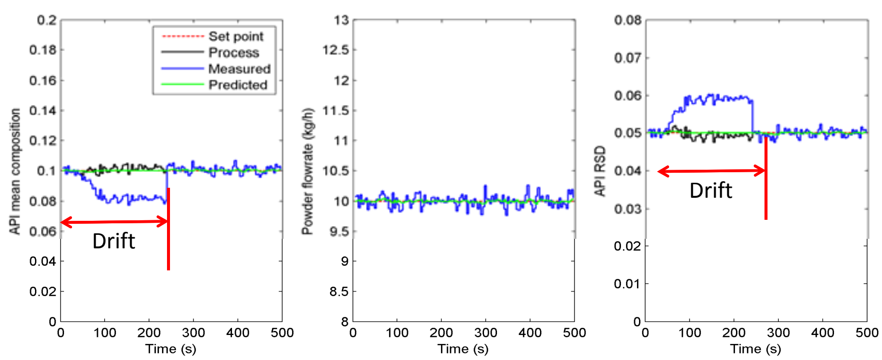
Risk Analysis for feeder & blender: R2 PAT gross error

Layer 1 control: The PAT tool with gross error detoured the API mean composition and its mixing uniformity from their set points.



Risk Analysis for feeder & blender: R2 PAT gross error

Layer 2 control: The Kalman filter with data reconciliation can reject the measurement gross error when large model-plant mismatches detected.



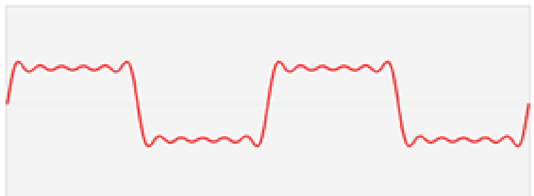
The Kalman filter with data reconciliation

$$\mathbf{x}[k|k] = \mathbf{x}[k|k-1] + \mathbf{M}(\mathbf{y}[k] - \mathbf{y}[k|k-1])\ \mathbf{R}$$

$$\mathbf{R} = diag\left(\exp(-\left(\frac{e_i}{c\sigma_i}\right)^2\right)$$

Frequency Domain Analysis

A time-domain graph shows how a signal changes over time, whereas a frequency-domain graph shows how much of the signals lies within each given frequency band over a range of frequencies.



The Fourier transform relates the function's time domain, shown in red, to the function's frequency domain, shown in blue. The component frequencies, spread across the frequency spectrum, are represented as peaks in the frequency domain.

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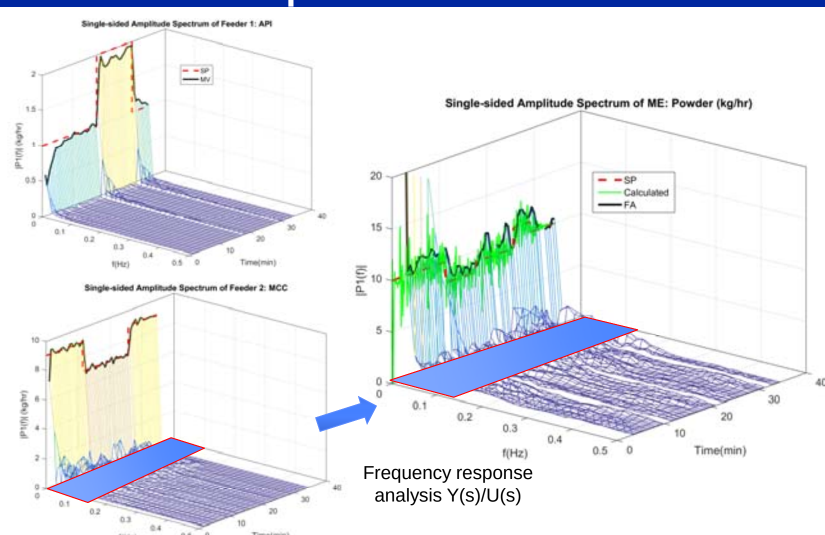
Fourier transform of the API, MCC, and powder flowrates



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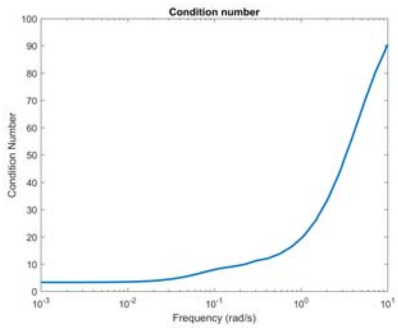
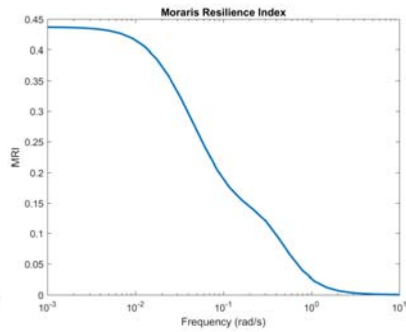
Process control design and analysis in frequency domain

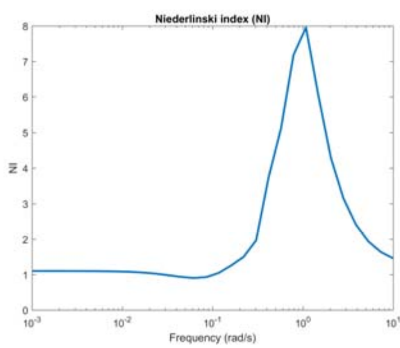
- The condition number and Moraris resilience index both indicate the degraded control performance at higher frequency variations.
- This can help to choose a better sampling time interval and control tuning.

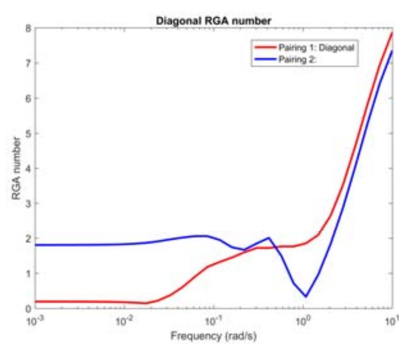




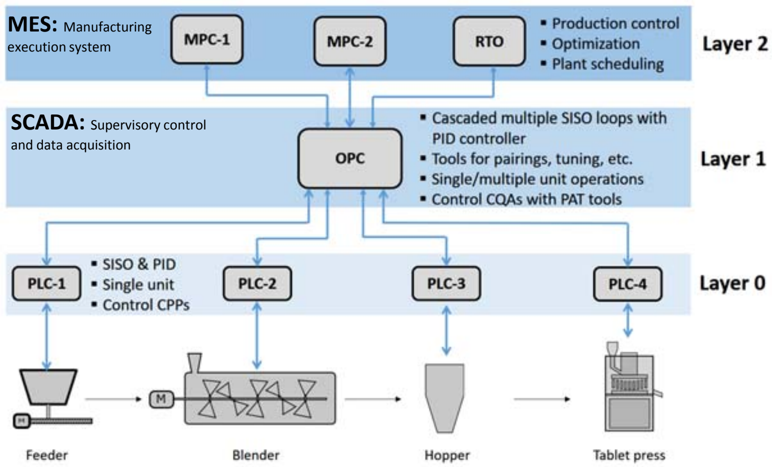
Process control design and analysis in frequency domain

- The system is stable as indicated by the NI number as a necessary condition.
- The RGA pairing changed at higher frequency for a 3 by 3 feeding-blending control system.





A hierarchical three-layer control structure



PLC: Programmable Logic Control

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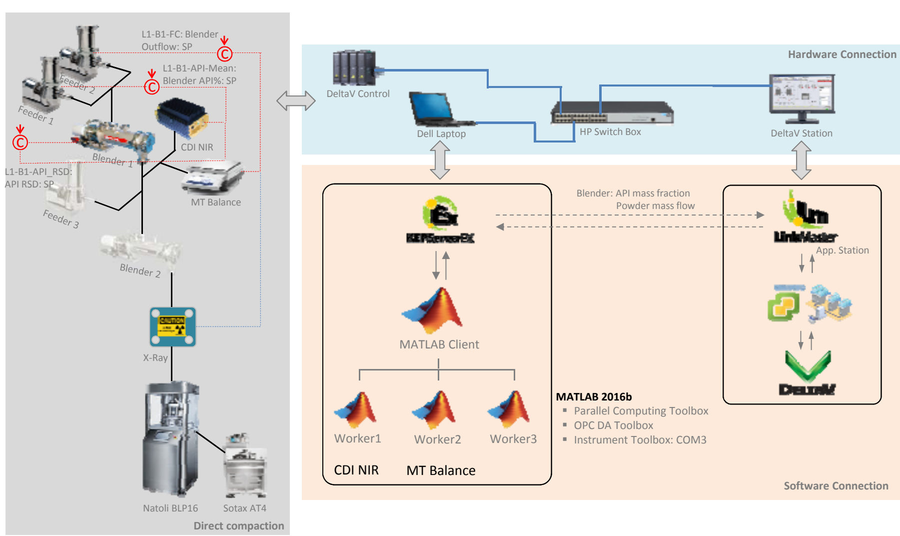
▪ Direct Compaction Monitoring and Control



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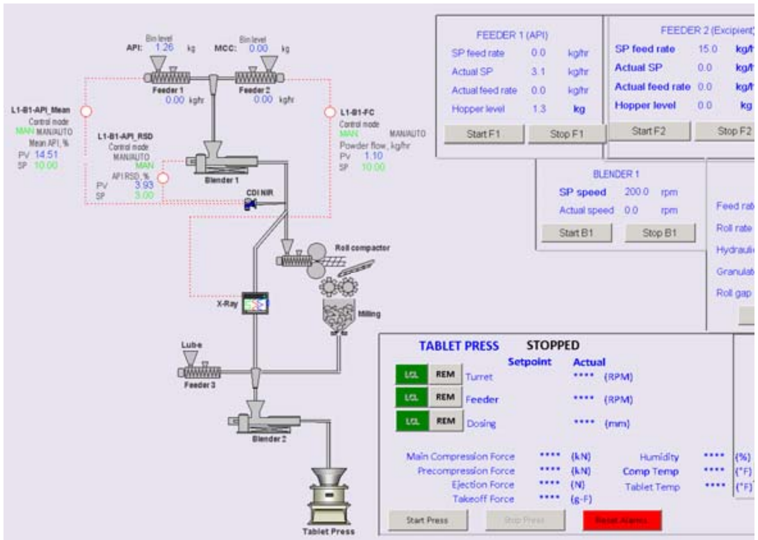
- **DeltaV Operator interface for the Continuous Manufacturing Pilot Plant**



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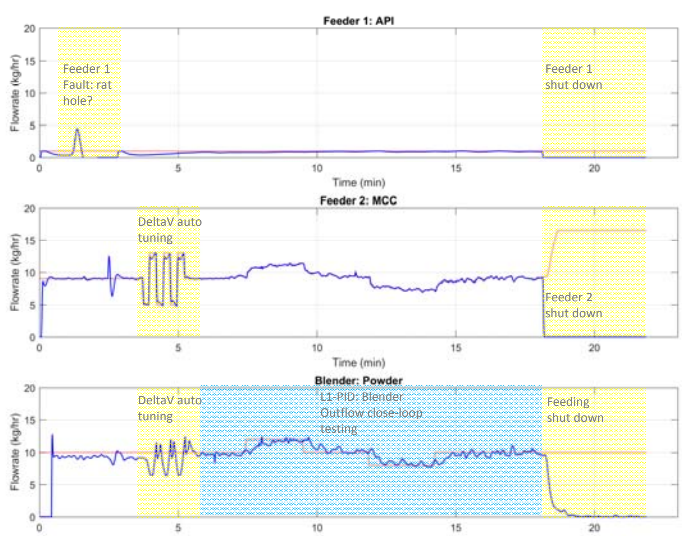

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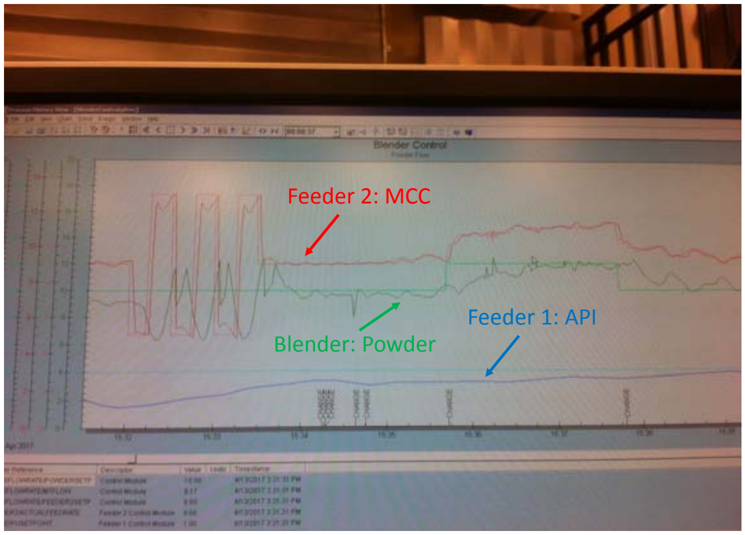
- **Blender powder mass flow control**



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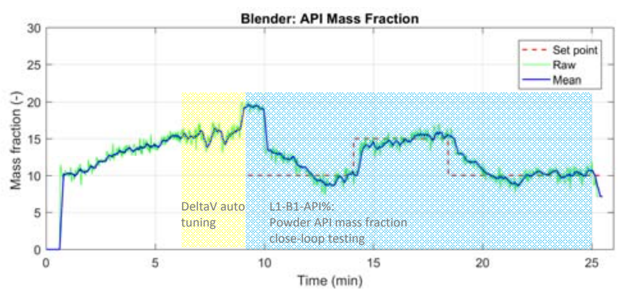

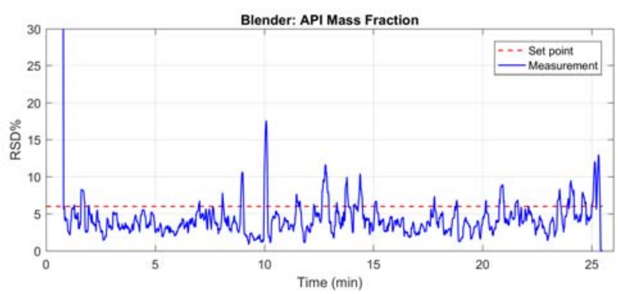

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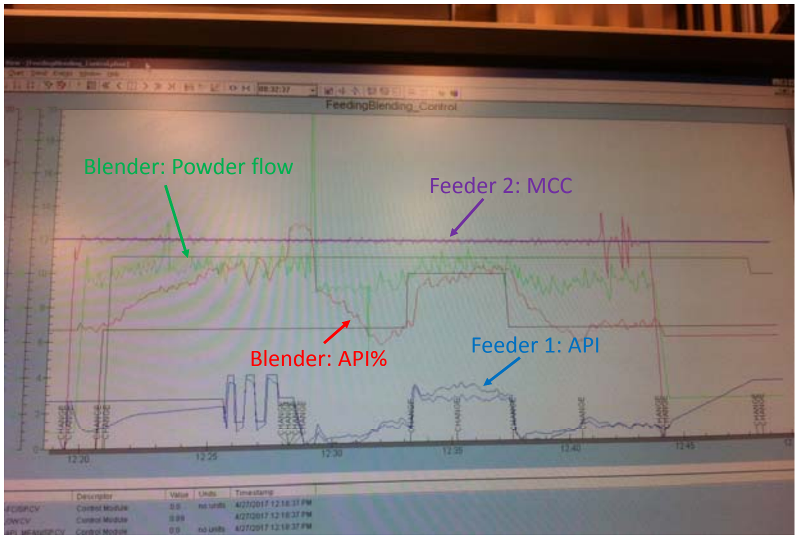
- **Blender API mean mass fraction control**



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Safety and runaway prevention in batch and semibatch reactors

BASF in Oppau,
21.9.1921

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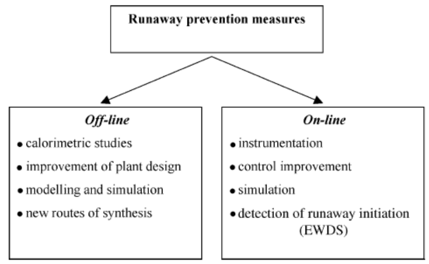
Prime causes of batch reactor incidents and prevention measures

Table 1. Prime causes of batch reactor incidents (Verwijs, 1994).

	1962–1984	1962–1987	1986–1990
	References*		
Incident cause	Nolan and Barton (1987)	Barton and Nolan (1989)	Etchells (1993)
Thermo-reaction chemistry	21.4%	20.1%	14.8%
Raw material quality	7.9%	8.9%	9.8%
Maintenance/other factors	22.3%	21.3%	22.2%
Temperature control	22.2%	18.9%	13.9%
Loss of mixing/agitation	9.5%	10.1%	13.1%
Mischarging of reactants	16.7%	20.7%	26.2%
Incident rate (#/month)	0.46	0.54	2.03

*Data obtained from Health and Safety Executive records (HSE, UK).



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Objectives

- Enhance safety both by **design** and **control.**

1. Use novel reactor technology for batch operation (inherent safety)
2. Investigate the safety impact of moving from batch to continuous
3. Apply advanced control (robust nonlinear model predictive control

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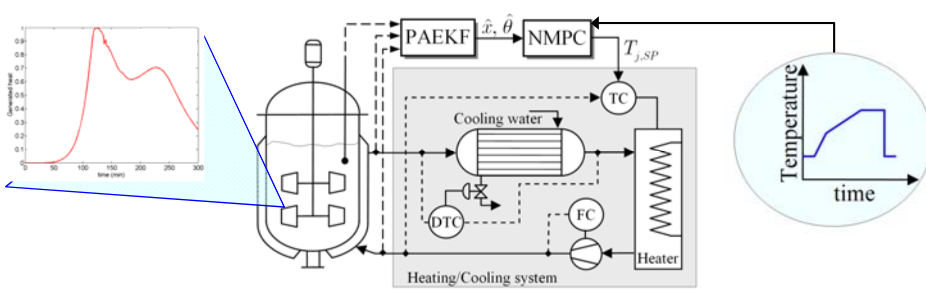
Runaway reaction in Moving Baffle – Oscillatory baffled reactor (MB-OBR)

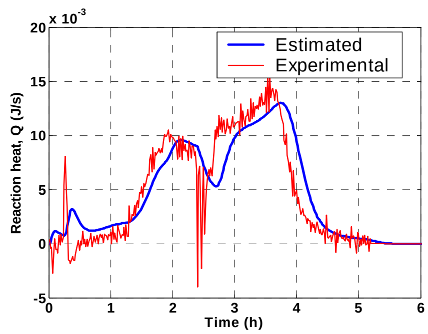
- Higher S/V ratio than stirred tank
- More intensive/uniform mixing
- Currently on going
  - Equipped with PAT (ATR-FTIR), calibration ongoing
  - Conversion from batch to continuous
  - Investigation of RTD
  - CFD and kinetic model development

Typical Temperature Control of Batch Reactor



- Control Objective: Follow temperature profile, while rejecting disturbances
- Major disturbance: Heat generation due to reaction (strongly exothermic)
- Measurements: Temperatures (reactor, jacket in/out, heating/cooling)
- Estimation: Parameter Adaptive MHE
- NMPC input: Jacket inlet temperature (setpoint)
- Complex heating/cooling system → large transport delay

Estimation: Constrained MHE



$$\min_{x_0,p}\left\{\sum_{j=k-N+1}^{k}\left\|y_j-y_j^{meas}\right\|_{W_y}^2+\left\|x_0-\hat{x}_0\right\|_{W_0}^2\right\}$$

$$x_j = f(x_{j-1},u_{j-1};p)$$

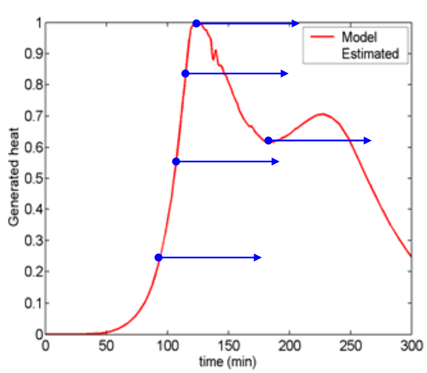
$$y_j = g(x_j,u_{j-1};p)$$

$$h(x_j,\,u_{j-1};\,p)\le 0$$

$$j=k-N+1,\ldots,k$$

- **Incorporates state constraints**
  - **Can eliminate local optima**
  - **States within physical constraints (robustness against numerical failure)**
- **Explicitly uses nonlinear model**
- **Optimizes over a trajectory of states and measurem.**

Experiment: model without kinetic model



- **Prediction is performed with current estimated reaction heat**

Generic approach: NMPC of batch reactors with exothermic (unknown) kinetics

$$\dot{n}_M = -Q_r / \Delta H_r$$

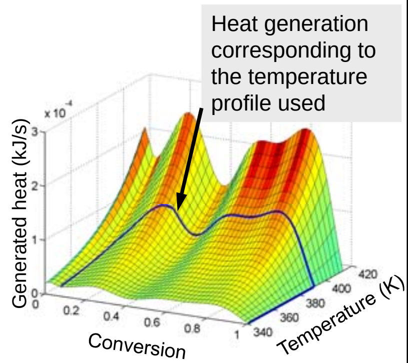
$$\dot{T}_{r,k} = (Q_r + U_w A_w (T_{w,k} - T_{r,k}) - (UA)_{loss,r}(T_{r,k} - T_{amb})) / (m_M c_{p,M} + m_P c_{p,P} + m_{water} c_{p,water})$$

$$\dot{T}_{w,k} = (U_j A_j (T_{j,k} - T_{w,k}) - U_w A_w (T_{w,k} - T_{r,k})) / m_w / c_{pw}$$

$$\dot{T}_{j,k} = (N F_j \rho_j c_{p,j} (T_{j,k-1} - T_{j,k}) - U_j A_j (T_{j,k} - T_{w,k}) - (UA)_{loss,j}(T_{j,k} - T_{amb})) / (m_j c_{p,j})$$

$$\dot{T}_{j,0} = K / \tau u(t) - T_{j,0} / \tau \qquad u(t) = T_{j,setpoint}$$

$$Q_r = f(X,T) \quad \text{with} \quad k = 1,\ldots,N$$



- **Energy balance based model**
- **UwAw estimated => accounts for model/plant mismatch**
- **Controller => Q is predicted from heat generation function (HGF)**
- **HGF = summ of Gaussians from detailed model (experimental data)**

Key problem in practical NMPC = Control-relevant modeling

Two Steps modeling ⇒ Control-relevant model

❶ **Derive detailed first-principles model**

Detailed first-principles model: $x_1, x_2, \ldots, x_m, x_{m+1}, \ldots, x_n$

⇒ Open-loop optimal control

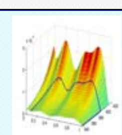
Setpoint

❷ Derive control-relevant model

- Systems theoretical properties (observable, controllable, etc.)
- Real-time feasibility

Control-relevant (hybrid) model

Nonlinear map



$\mathbf{y} = \mathbf{f}(x_1, x_2, \ldots, x_m)$

⇔

Reduced first-principles model: $x_{m+1}, \ldots, x_n, \mathbf{y}$

⇒ Closed-loop NMPC

NMPC formulation with safety constraints

$$\min_{u(t)} \int_{t_k}^{t_F} ((T_r(t) - T_r^{ref}(t))^2 + R_{\Delta u} du(t)^2) dt$$

$u_{\min} \le u(t) \le u_{\max}$ ⇐ Bounds on NMPC manipulated input

$\dot{u}_{\min} \le \dot{u}(t) \le \dot{u}_{\max}$ ⇐ Bounds on the variation of the NMPC manipulated input

$Q_g \le Q_g^{\max}$ ⇐ **Maximum heat transfer (safety constraint)**

$0 \le PV_{PI} \le 100$ ⇐ Bounds on predicted PI controller output

$\dot{x}(t) = f(x(t), u(t); \theta)$

$y(t) = g(x(t), u(t); \theta)$ ⇐ Model equations

$$u(t) = T_{j,in}^{SP}(t)$$

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NMPC = repeated open-loop optimization

Obtain measurements y

↓

Estimate state x

↓

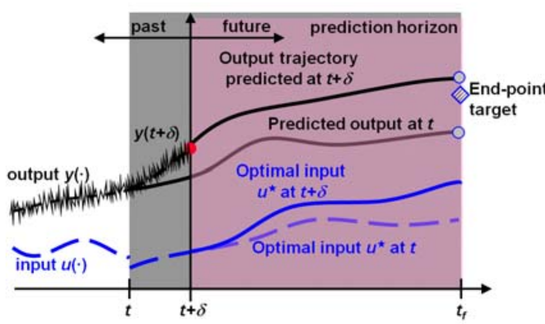
Solve optimal control problem

$$\min_{u(t) \in \mathcal{U}} \mathcal{H}(x(t), u(t), \theta)$$

Subject to: model equations
constraints

↓

***Implement input u* for first sampling period**



- **Receiding/shrinking horizon approach**
- **Efficient implementation**
  - **Multi-stage formulation**
  - **Real-time iteration scheme**

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Distributional robust nonlinear model predictive control (DR-NMPC)

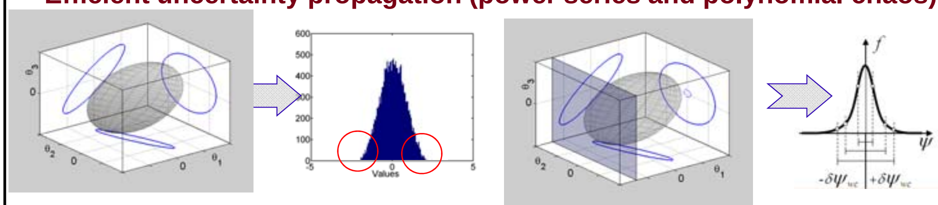
- **Uncertainty in model parameters:** $\theta = \hat{\theta} + \delta\theta$
- **Described by a hyper-ellipsoid:** $\varepsilon_\theta = \{\theta : (\theta - \hat{\theta})^T \mathbf{V}_\theta^{-1} (\theta - \hat{\theta}) \le \chi_n^2(\alpha)\}$
- **Uncertainty in output:** $\psi = \hat{\psi} + \delta\psi$ **characterized by** $\mathcal{E}[\psi]$ **and** V_ψ

$$\min_u \{(1-w)\underbrace{\mathcal{E}[\psi(x(t_F);\theta)]}_{\text{Performance term (Expected value)}} + w\underbrace{V_\psi(t_F)}_{\text{Robustness term (Variance)}}\}$$

Subject to: $S(x(t), u(t); \theta) \le 0,\ \ S_F(x(t_F); \theta) \le 0,\ \ u \in \mathcal{U}$

- **Multi-objective optimization**
- **Tradeoff between performance and robustness set by *w***
- **Back-off term for constraints**

- **Efficient uncertainty propagation (power series and polynomial chaos)**



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Solution via Probability Safety Constraints

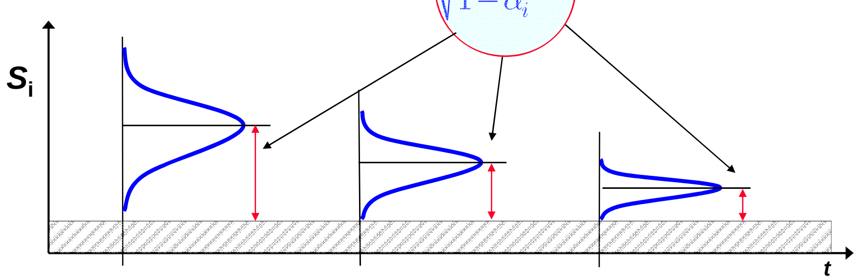
- **Inequality constraints must be satisfied for all $\theta \in \Theta$**
- **Impose inequality constraints in probabilistic sense**

$$\mathbb{P}(S_i(x, u; \theta) \le 0) \ge \alpha_i$$

α_i - given desired confidence level

- **Using one-sided Chebyshev inequality:**

$$\mathbb{P}(S_i \le 0) \ge \alpha_i \quad \Leftarrow \quad \mathcal{E}(S_i) + \sqrt{\frac{\alpha_i}{1-\alpha_i} V_i} \le 0, \quad i = 1, \ldots, n_S$$



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Efficient uncertainty propagation

- **Approximation of model along the input trajectory**
- **Power Series Expansion (PSE)[1]:**

$$\delta\psi = L\delta\theta + \frac{1}{2}\delta\theta^T \mathbf{M}\delta\theta + \dots$$

$$L(t) = \left(\frac{\partial \psi(t)}{\partial \theta}\right)_{\hat{\theta},u(t)} \qquad \mathbf{M}(t) = \left(\frac{\partial^2 \psi}{\partial \theta^2}\right)_{\hat{\theta},u(t)}$$

$$\dot{L} = \mathbf{J}_x L + \mathbf{J}_\theta$$
$$\mathbf{J}_x = df/dx \in \mathbb{R}^{n_x \times n_x}$$
$$\mathbf{J}_\theta = df/d\theta \in \mathbb{R}^{n_x \times n_\theta}$$

- **Polynomial Chaos Expansion (PCE):**
  - **Model output described as an expansion of orthogonal polynomial (Hermite) functions (Γ) of parameters**

$$\psi = \underbrace{a_0\Gamma_0}_{\text{constant}} + \underbrace{\sum_{i_1=1}^{n} a_{i_1}\Gamma_1(\theta_{i_1})}_{\text{first order terms}} + \underbrace{\sum_{i_1=1}^{n}\sum_{i_2=1}^{i_1} a_{i_1 i_2}\Gamma_2(\theta_{i_1},\theta_{i_2})}_{\text{second order terms}} + \underbrace{\sum_{i_1=1}^{n}\sum_{i_2=1}^{i_1}\sum_{i_3=1}^{i_2} a_{i_1 i_2 i_3}\Gamma_3(\theta_{i_1},\theta_{i_2},\theta_{i_3})}_{\text{third order terms}} + \dots$$

- **Both approaches are able to provide analytical expression for** V_ψ
- **Similar formulation for constraint sensitivity calculation**

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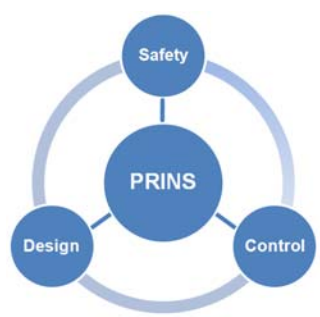
Conclusions

- Developed integrated approaches that use design, measurement and control to improve safe operation in pharmaceutical manufacturing
- Drug substance and drug product



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