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

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Content

- Introduction
- Systematic framework for control design & analysis
- Example: continuous feeder & blender system
- Summary & conclusions

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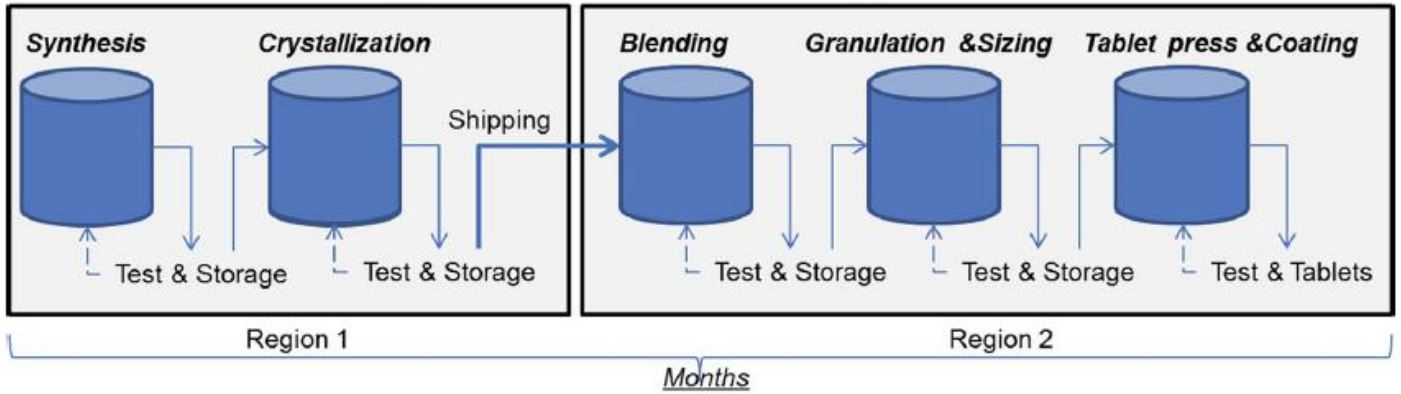
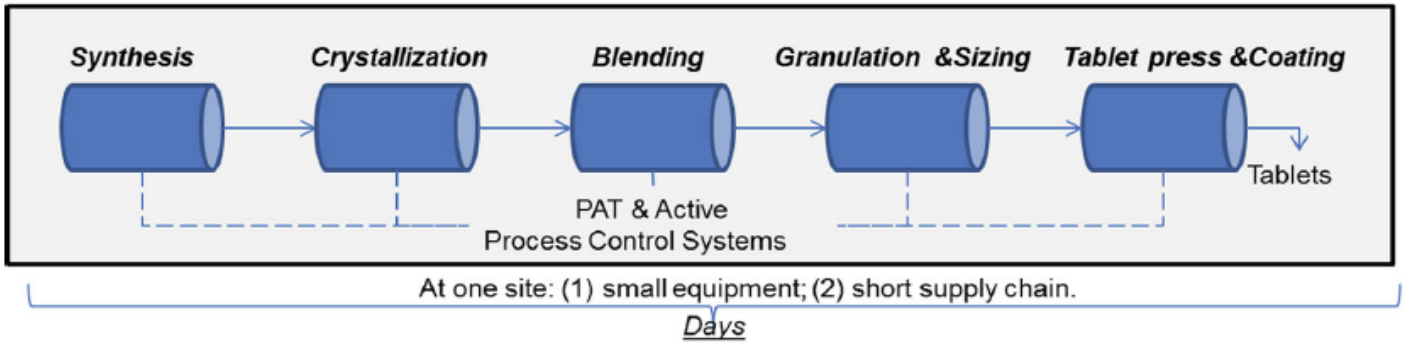
Batch vs. continuous manufacturing

A typical batch manufacturing process



A conceptual integrated continuous manufacturing process



[1] Lee SL, O'Connor TF, Yang X, Cruz CN, Chatterjee S, Madurawe RD, Moore CMV, Yu LX, Woodcock J. Modernizing pharmaceutical manufacturing: from batch to continuous production. Journal of Pharmaceutical Innovation. **2015**;10:191-199.

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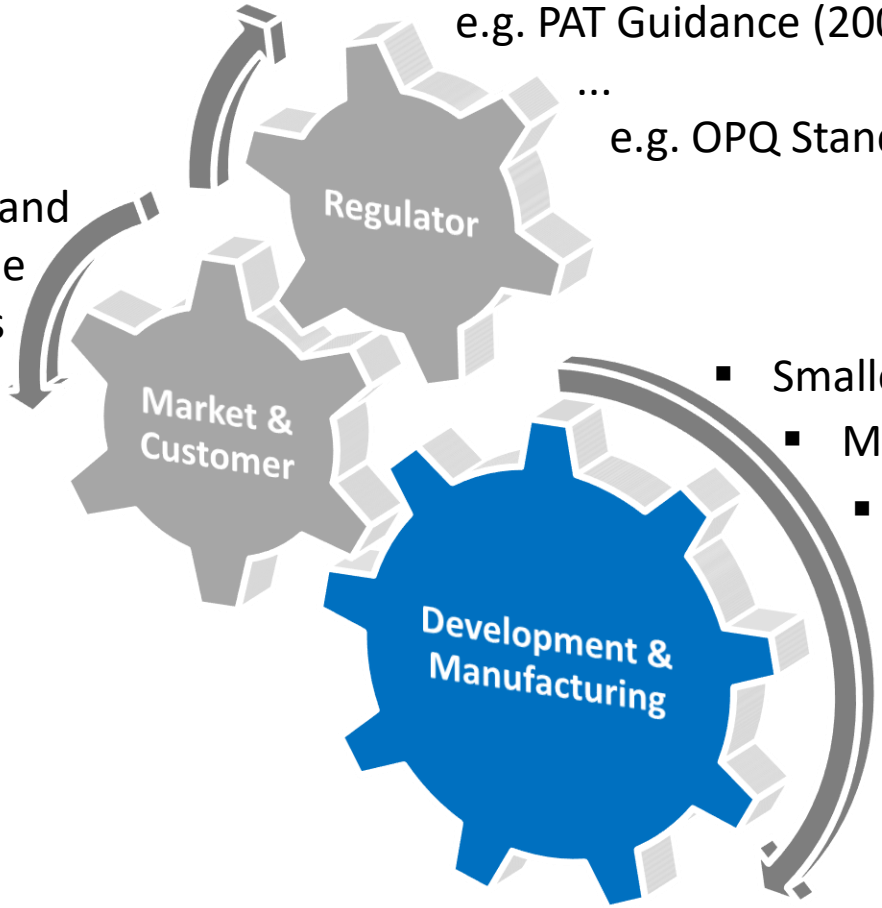
▪ Continuous manufacturing in pharma.

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

Flexible demand
Precise medicine
Competiveness
...



- 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

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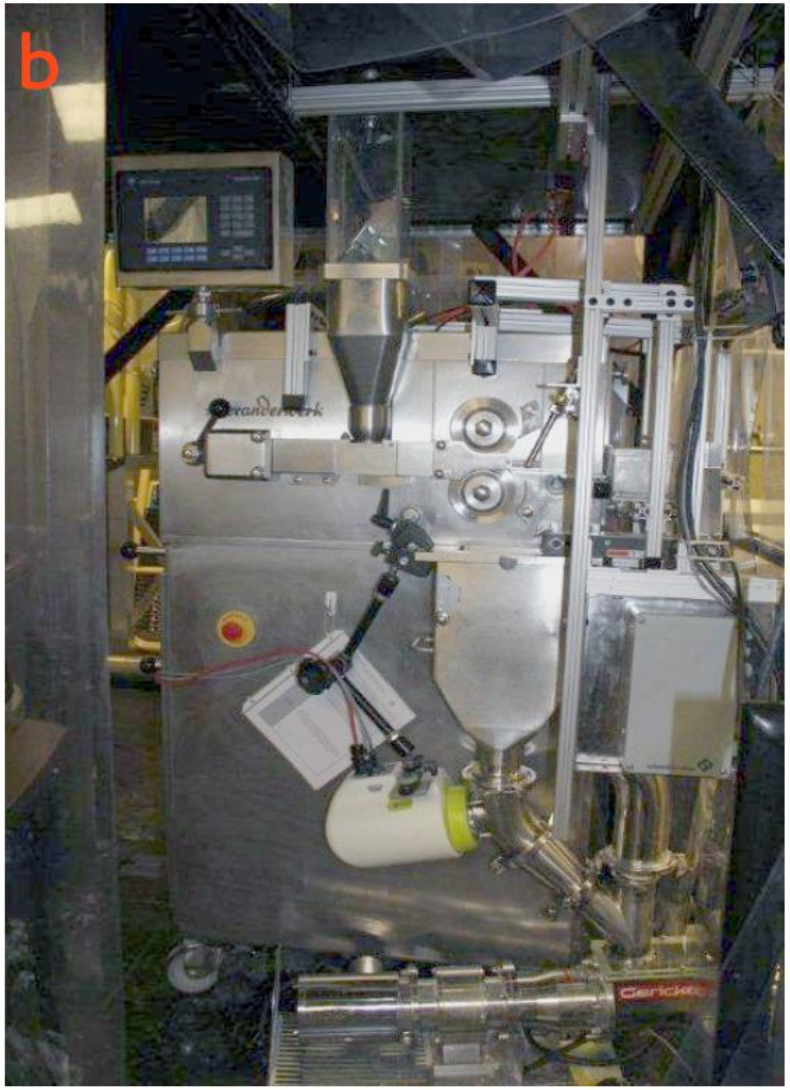
▪ Continuous manufacturing pilot plant



Potter B36 in Purdue University

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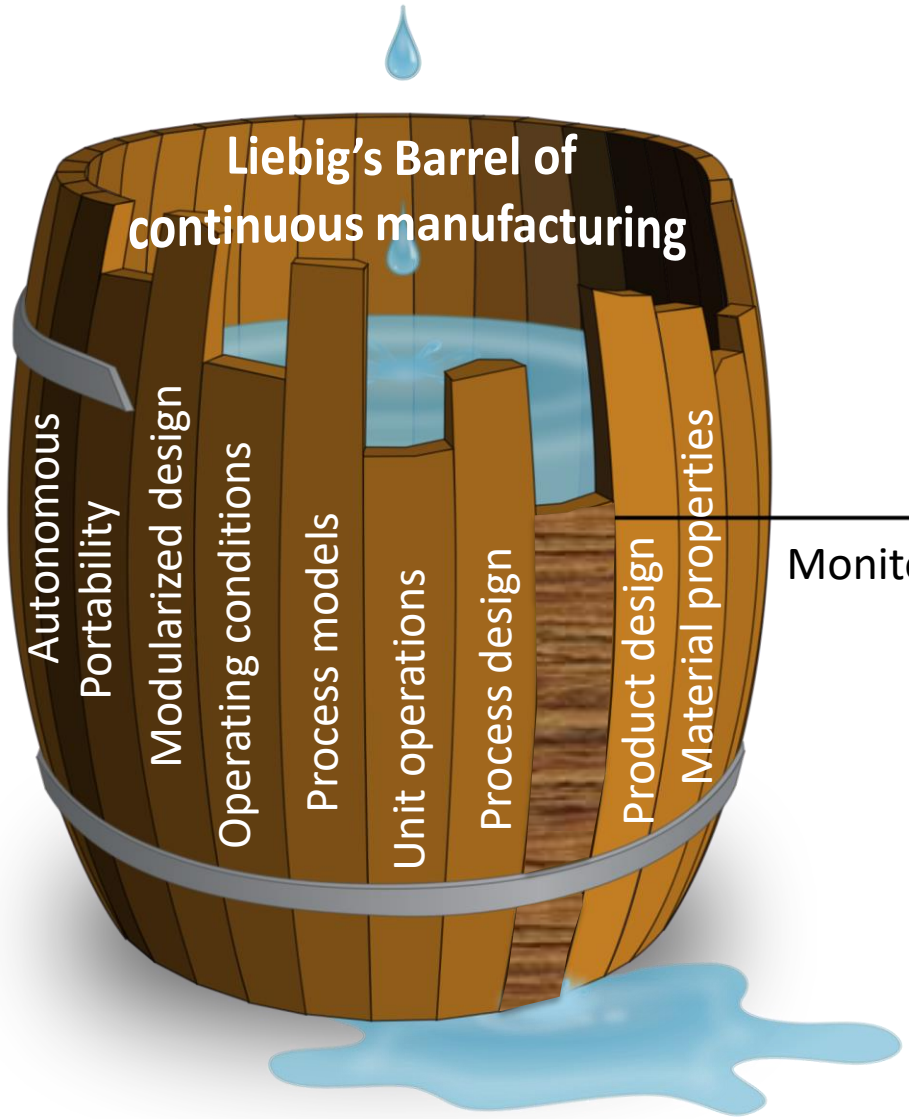
▪ Demands for efficient process monitoring & control



Minimum

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

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▪ Project objectives & outlines

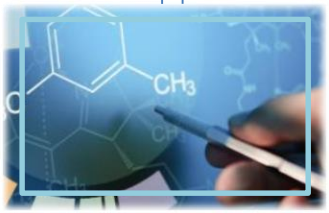
C4 System Performance & Verification

- Operating cost
- Process maintenance
- ⋮

- Material database
- Process characterisation
- Feasible formulation space
- ⋮

- Control variables
- Control set points
- ⋮

Process model



C1 Material library

C2 Sensing & RTR strategy

Pilot plant

- Process parameters
- Unit operations
- ⋮

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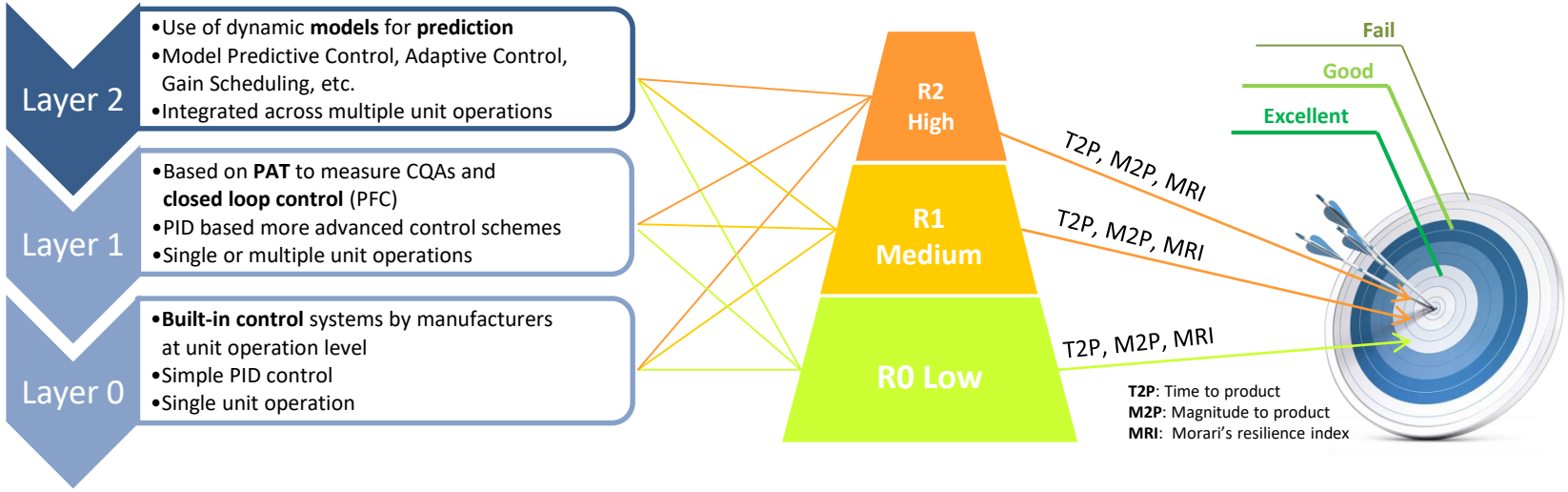
Systematic framework for control design & analysis (1)



Hierarchical control architecture

Risk levels & failure mode

Evaluation & regulatory filling

Continuous improvement

- Sensor accuracy, precision, sampling time
- Sensor location
- Control architecture reconfiguration
- Control method
- Controller tuning

⋮

- Formulation optimization
- Process reconfiguration
- ⋮

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.

⋮

[1] Morari M. *Chem. Eng. Sci.*, 1983;38:1881-1891.

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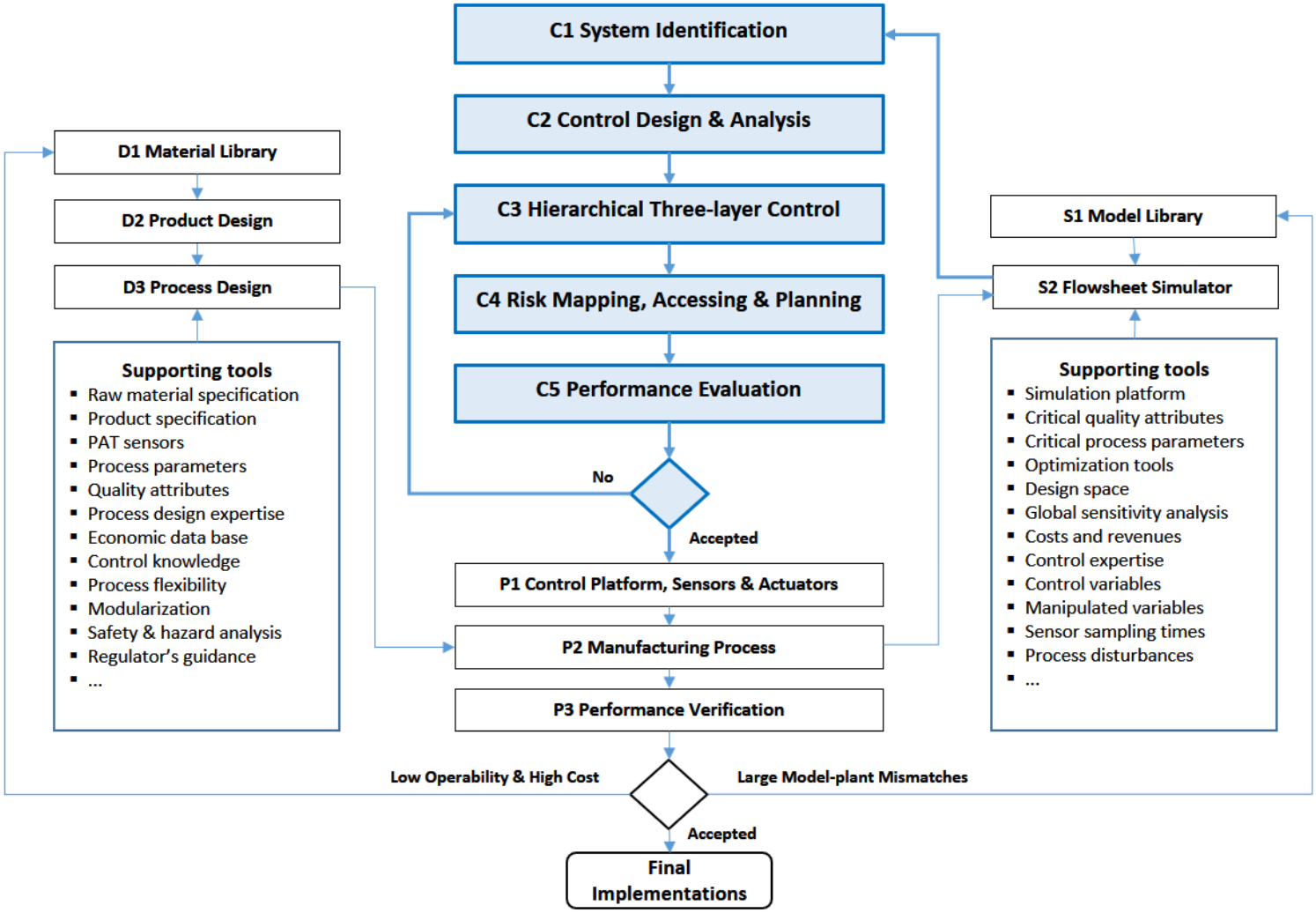
Systematic framework for control design & analysis (2)



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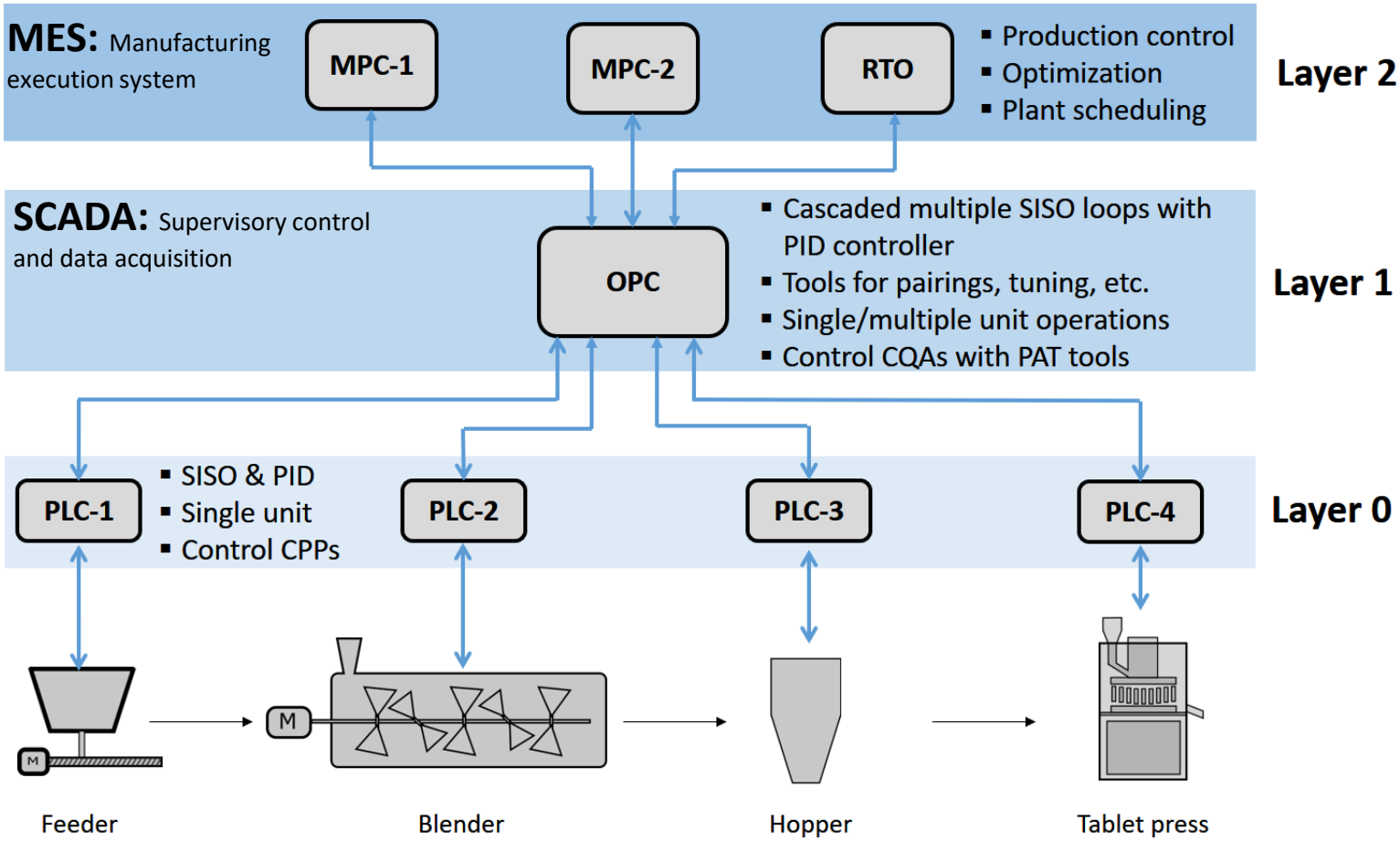
Hierarchical three-layer control



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L0 & 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

[1] Asmar BN. Control of a two-stage refrigeration system. PhD Dissertation. University of Nottingham, 1999

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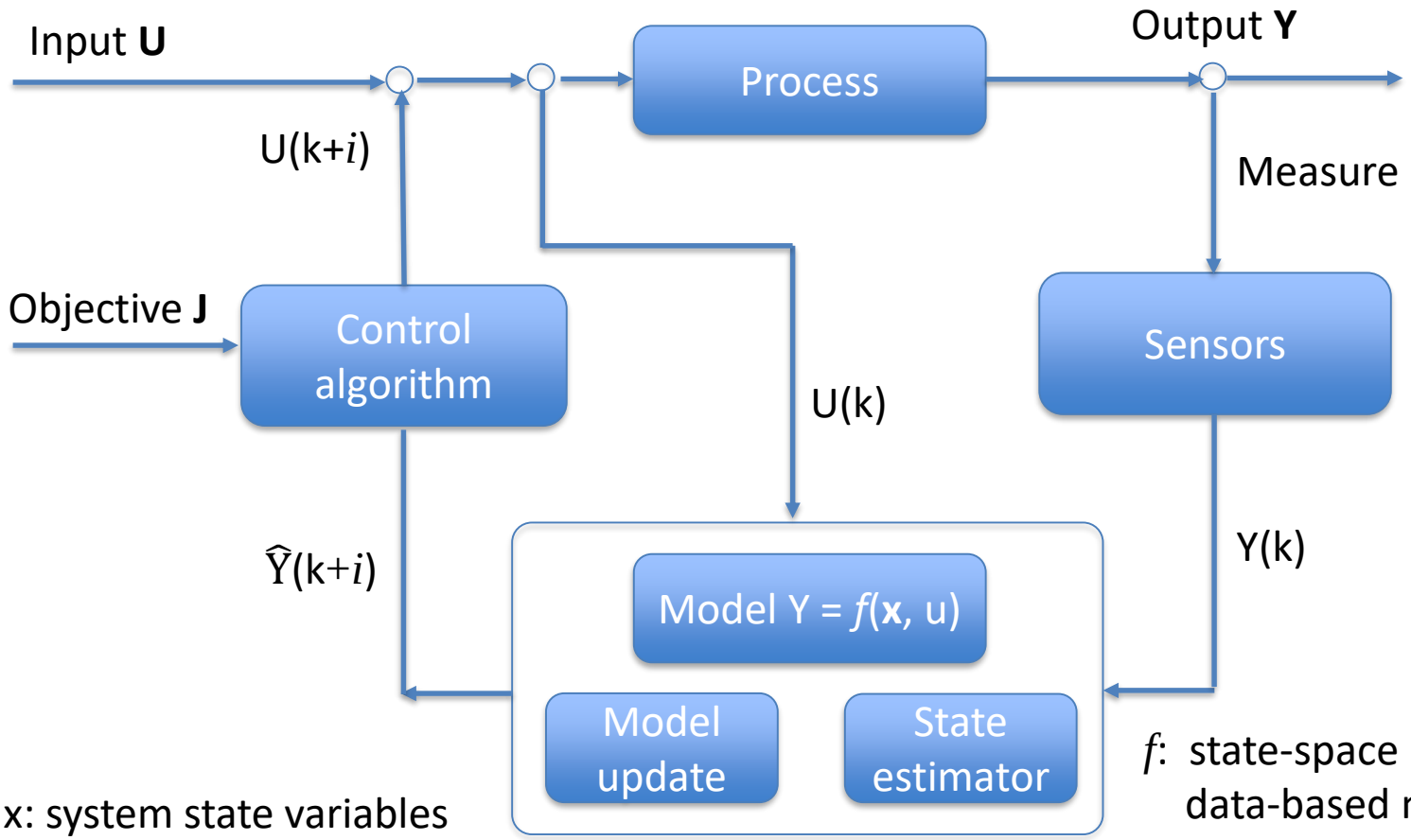
▪ L2 model-based control / real-time optimization



x: system state variables
i = 1,2,..,Nc,...,Np
Nc : control horizon
Np: prediction horizon

Kalman filter
Extended Kalman filter
Unscented Kalman filter
Moving horizon state estimator
....

f: state-space model
data-based model
empirical model
First-principles model
...

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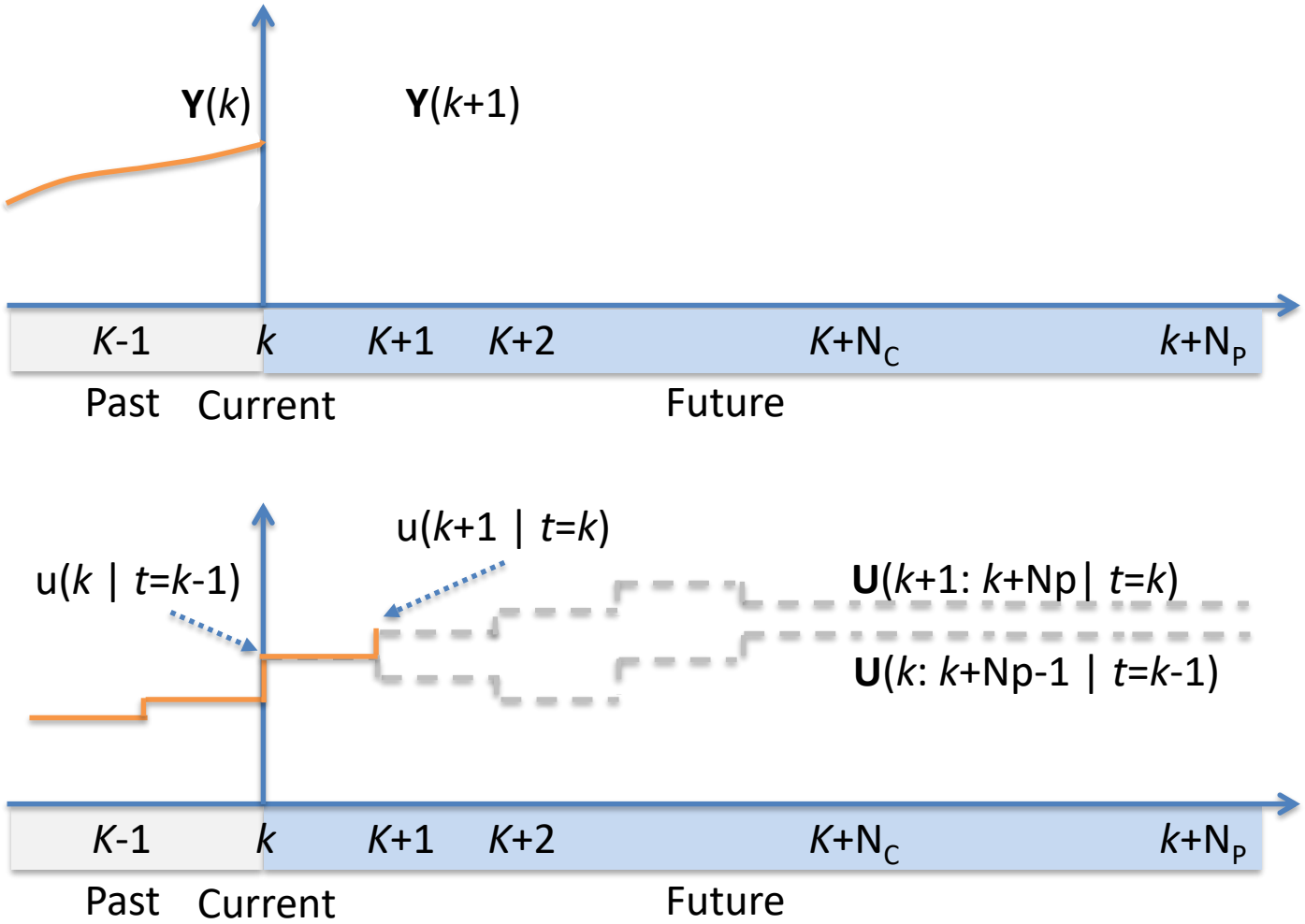
L2 MPC real-time implementation strategy



MPC **U**(*k+1*: *k*+Np | *t*=*k*)

→ Computation time ≤ sampling time

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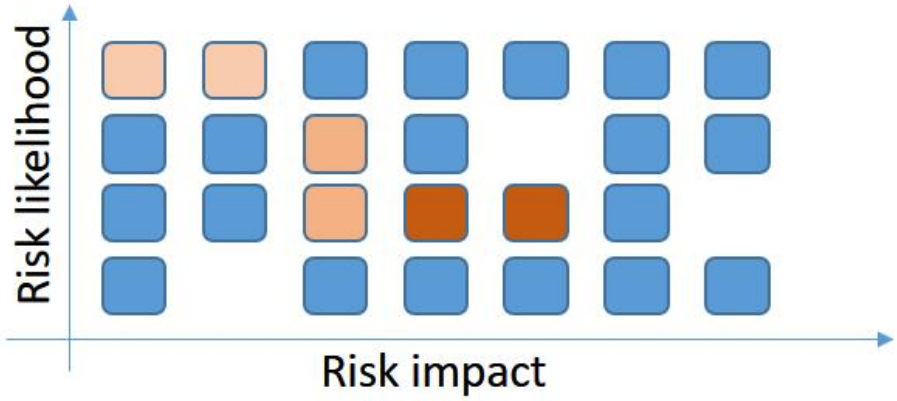
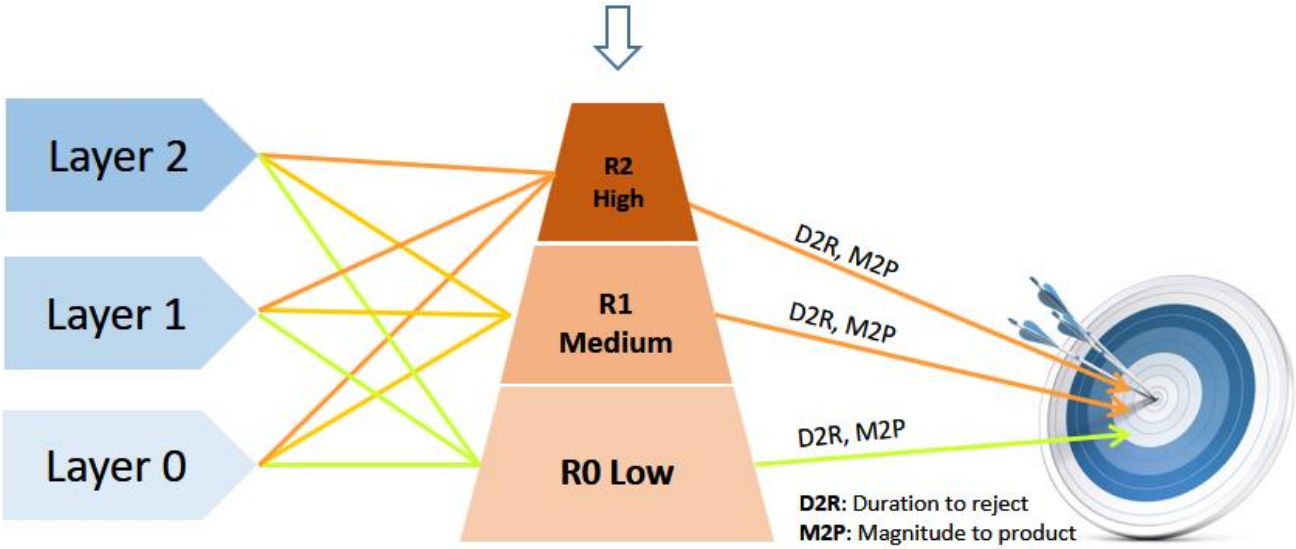
Risk analysis and control evaluation





Hierarchical control architecture **Risk levels & failure mode** **Evaluation & regulatory filling**

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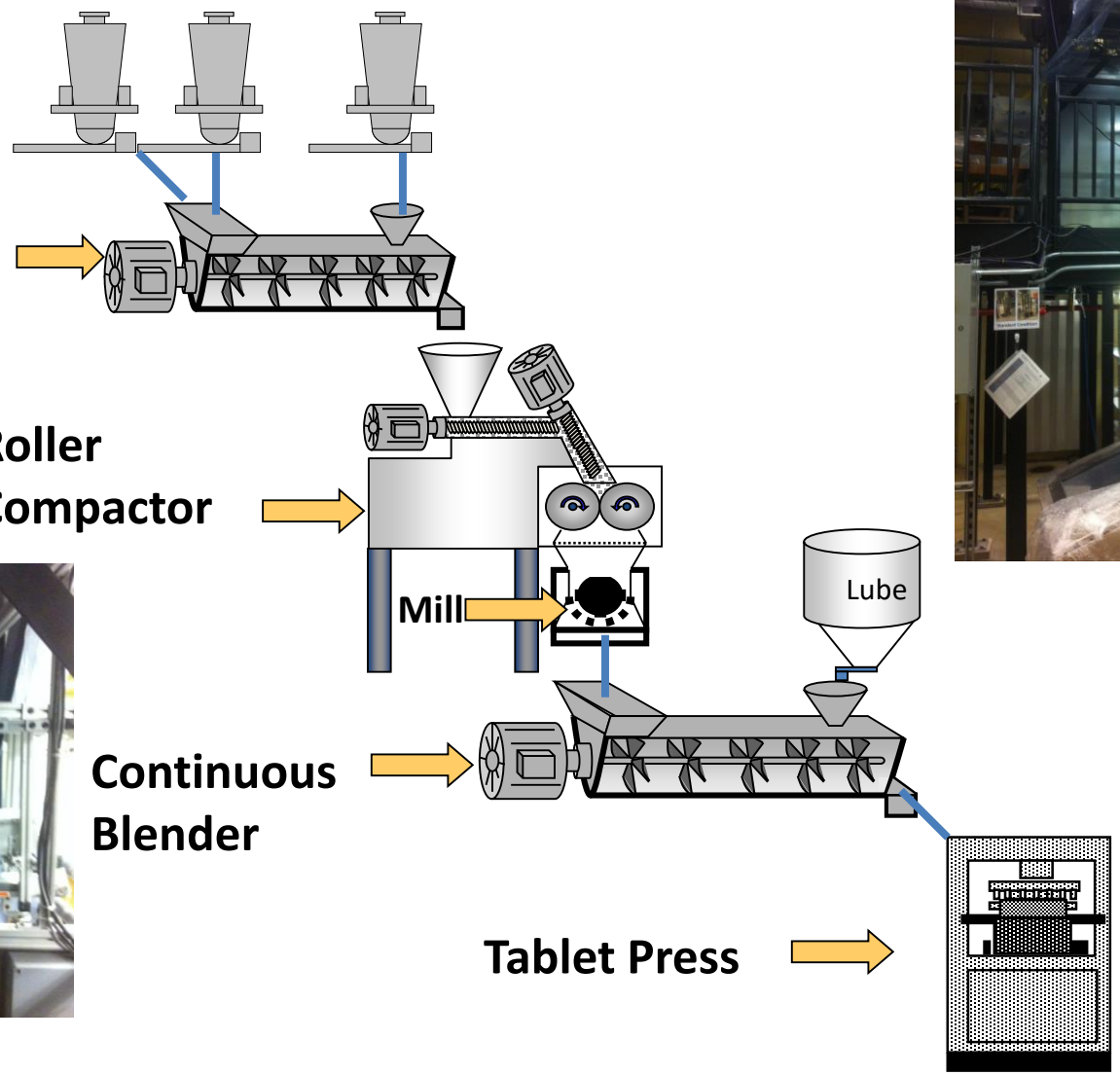
Continuous dry granulation process



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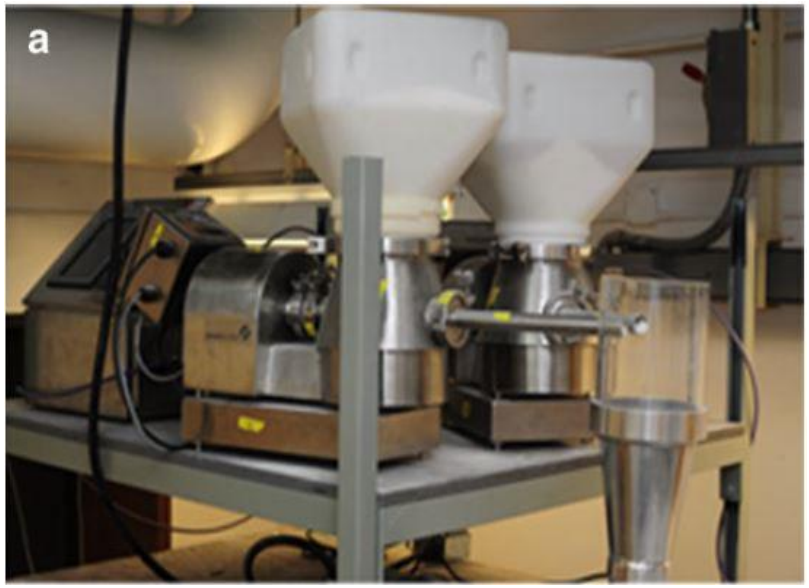
Feeder & blender control system

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	API composition	API flowrate	L1/2	PID, Ratio, MPC
	Powder flowrate	Excipient flowrate	L1/2	PID, MPC
	API mixing RSD	Rotation speed	L1/2	PID, MPC
	Rotation speed	Motor current	L0	PID



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System identification: state-space models

Continuous-time identified state-space model	L1 control design
$$\frac{dX}{dt} = A_c X(t) + B_c U(t)$$ $$Y(t) = C_c X(t) + D_c U(t) + e(t)$$ $$G = C^{-1}(SI - A)B + D$$	decoupled control design e.g., condition number Niederlinski index relative gain array Morari's resilience index …

Discrete-time identified state-space model	L2 control design
$$X(k+1) = A_d X(k) + B_d U(k)$$ $$Y(k) = C_d X(k) + D_d U(k) + e(k)$$ $$\min_{dU} J = \left\| Y_{sp} - \hat{Y} \right\|_2 + w_u \|\Delta U\|_2$$ $$e(k) := w_e e(k-1) + (1 - w_e) e(k)$$	Linear MPC design Sampling time: 4s Kalman filter design State estimation …

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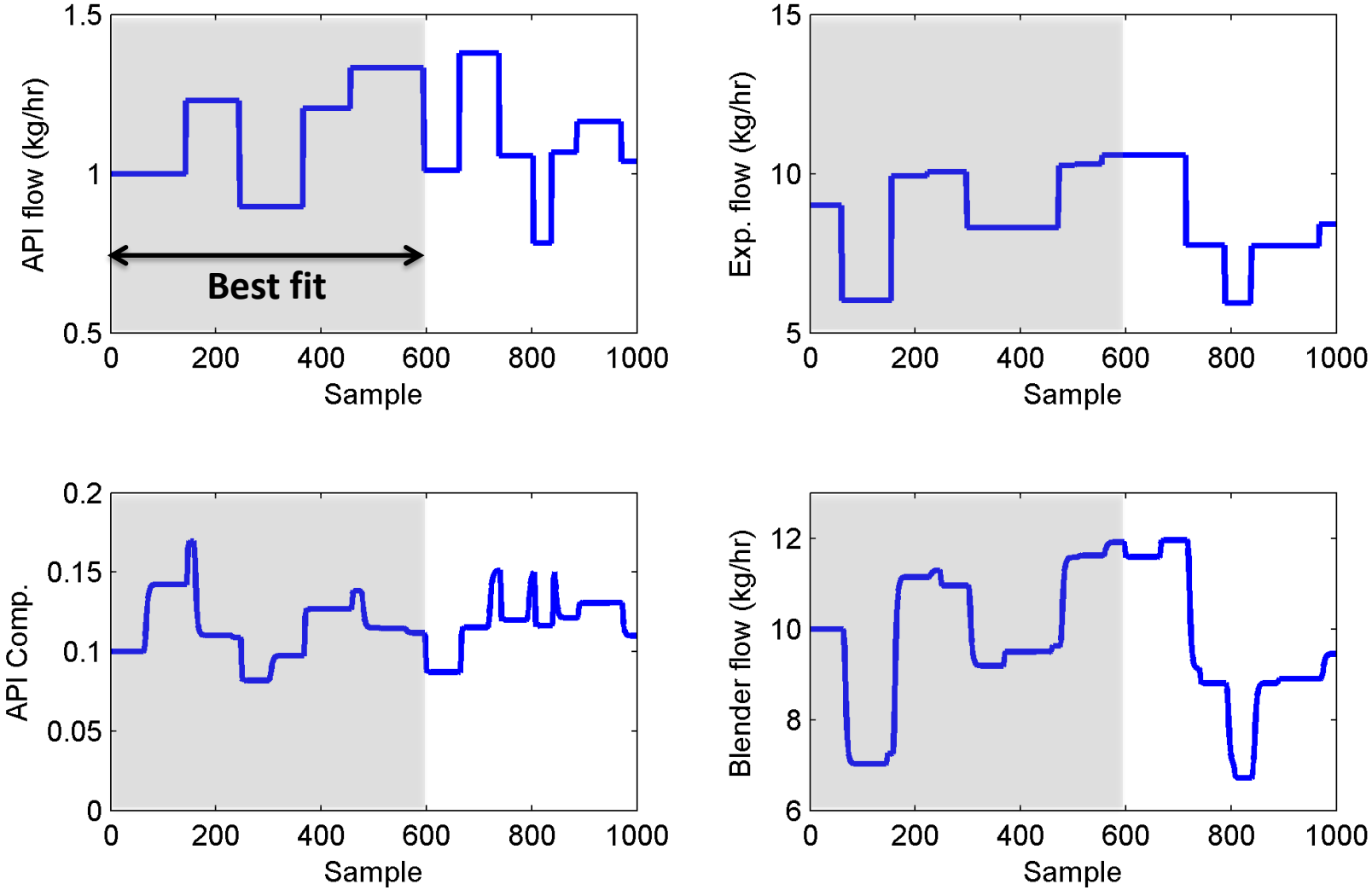
System identification: training data



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

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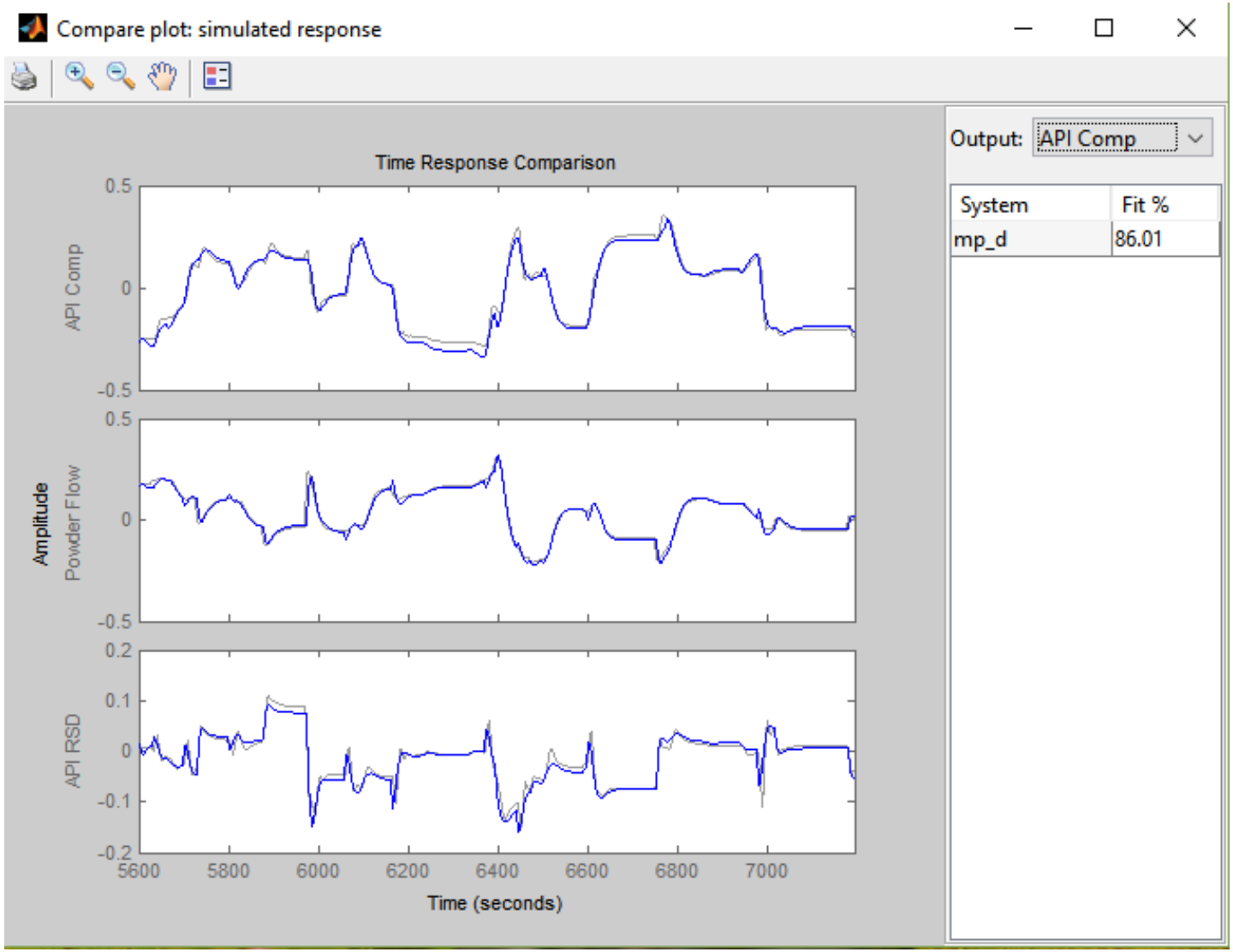
System identification: validation data



*Sampling time of 4 sec for all measurements

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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]RIA pairing is successful:
    0.1406         0
         0    0.1406


          STEP THREE: Performance Measures for Fixed Input/Output Pairing

[S3-1]Dynamic Interaction Measure (DIM): 45.03688
      Compensation to reduce the interaction is needed!

[S3-2]Diagnoal 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]mu Interaction measure:  2.66713
      The decentralized controller may not be stable.

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

Step one

Step two

Step three

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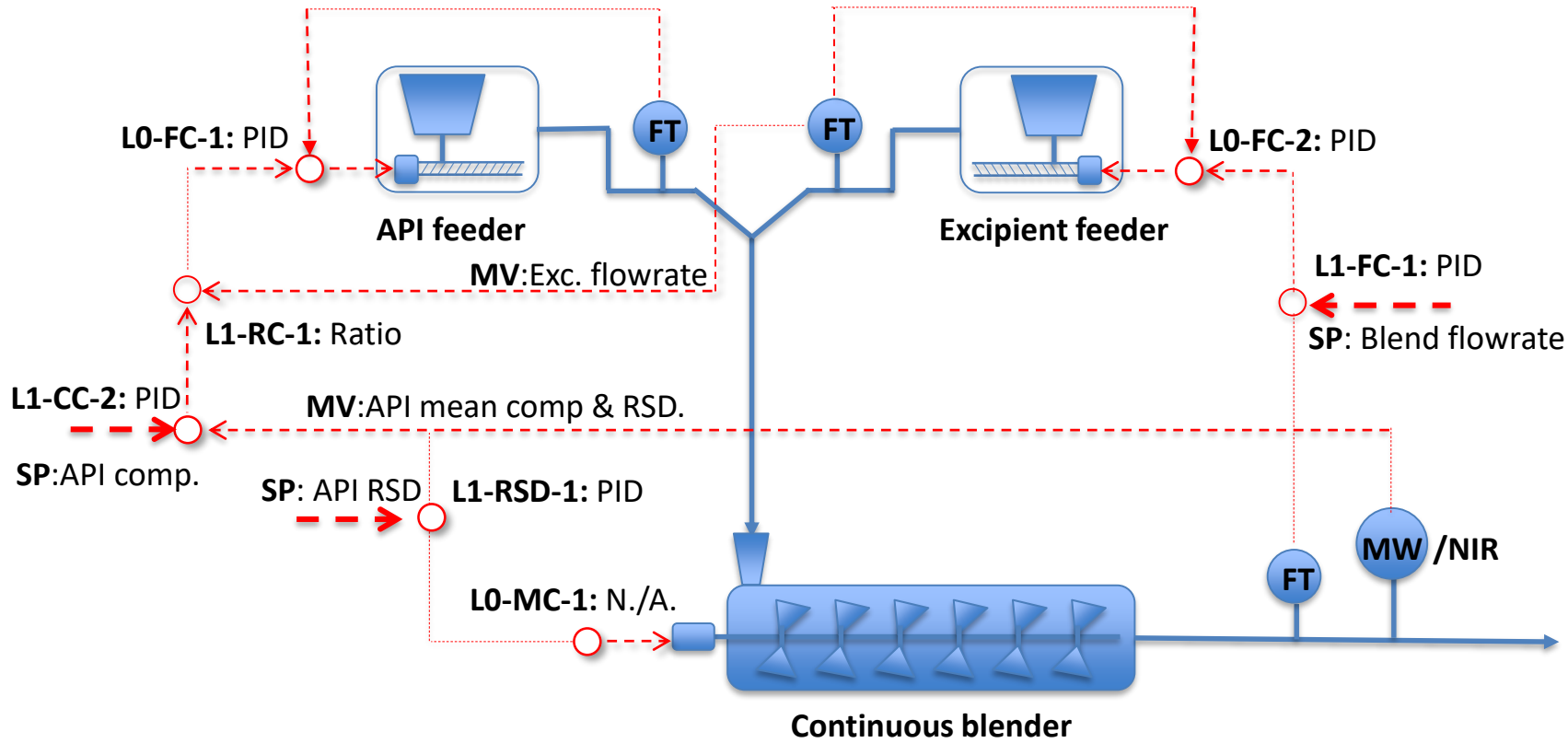
▪ L1 control for feeder & blender system



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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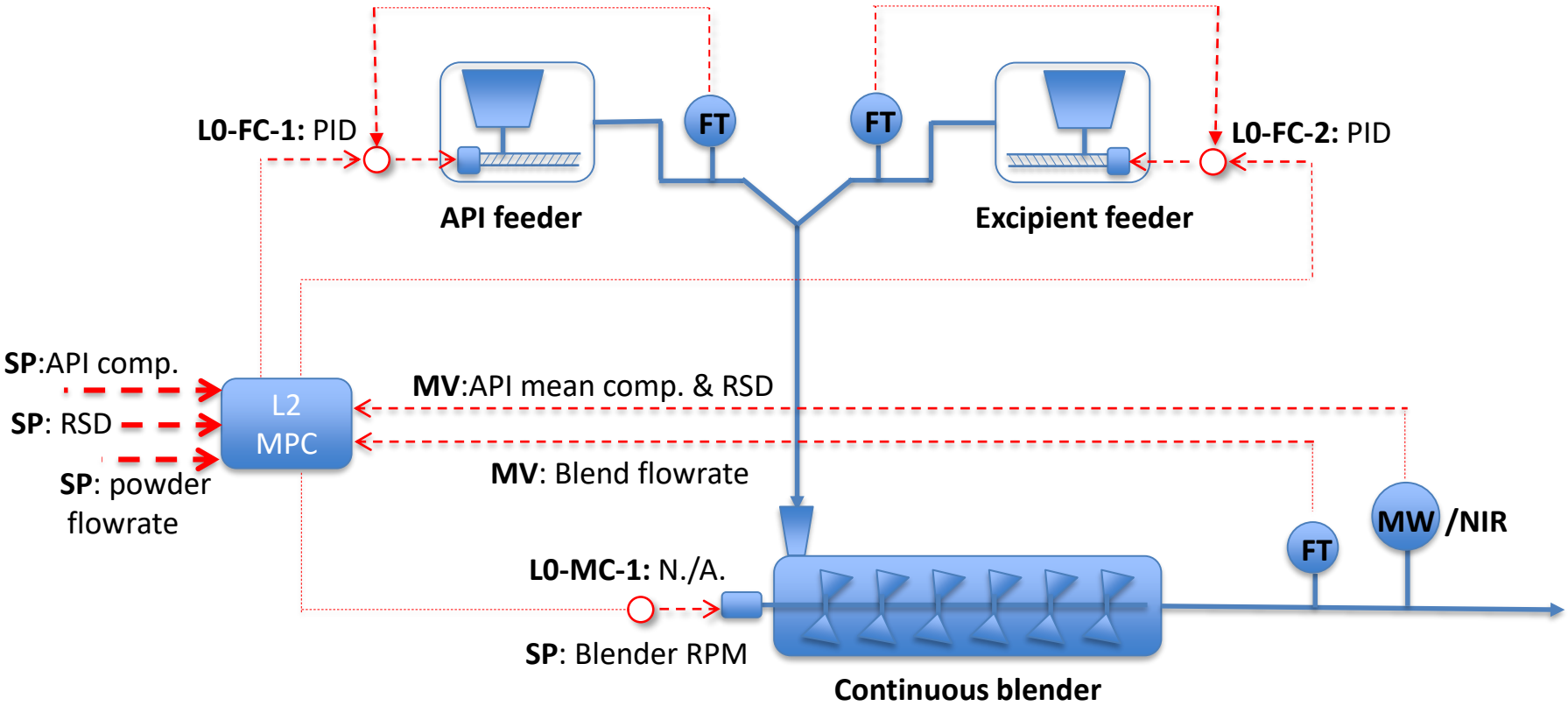
L0/2 control for feeder & blender system



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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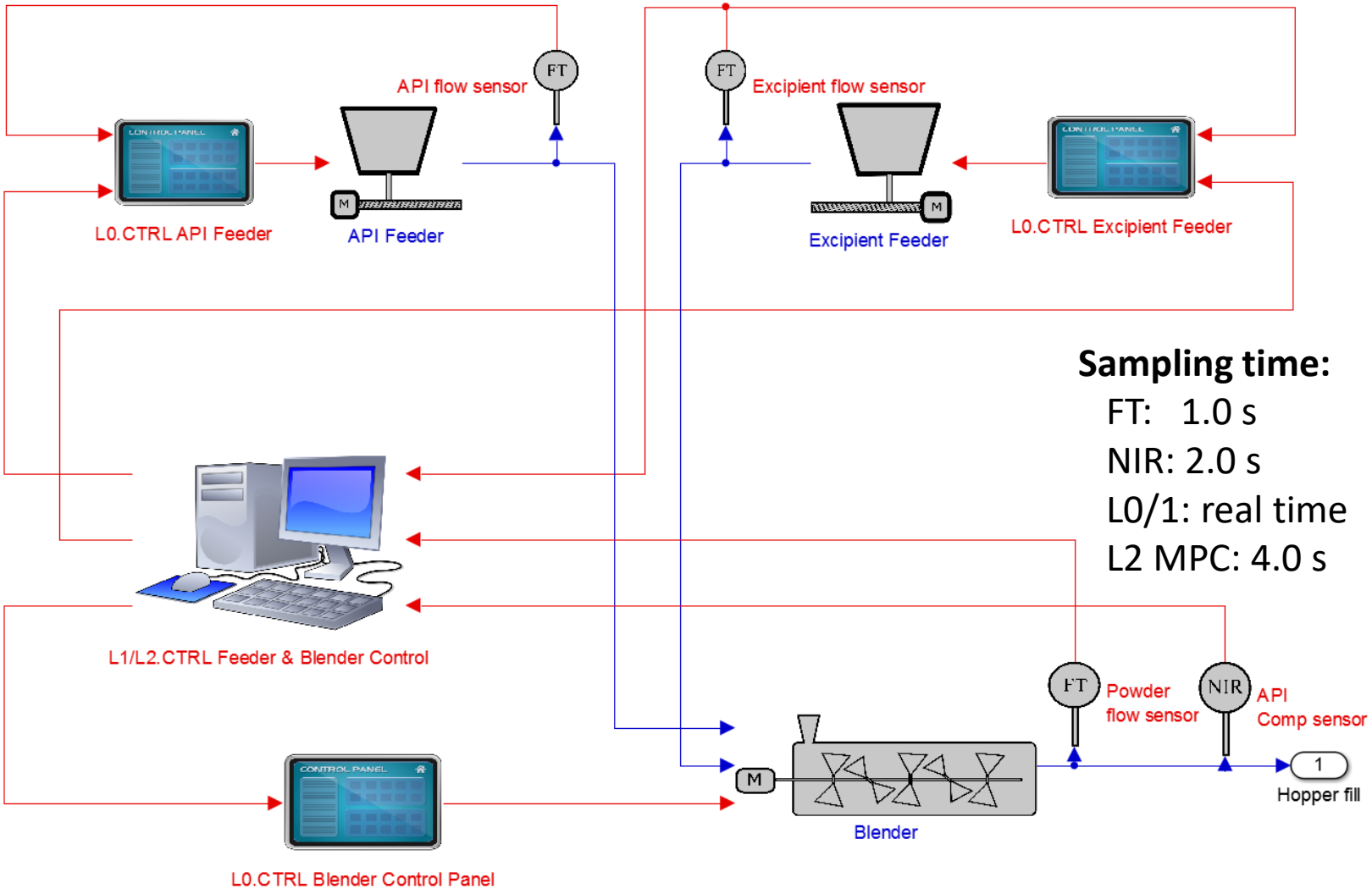
▪ Feeder & blender simulation in Simulink/MATLAB



Sampling time:

FT: 1.0 s

NIR: 2.0 s

L0/1: real time

L2 MPC: 4.0 s

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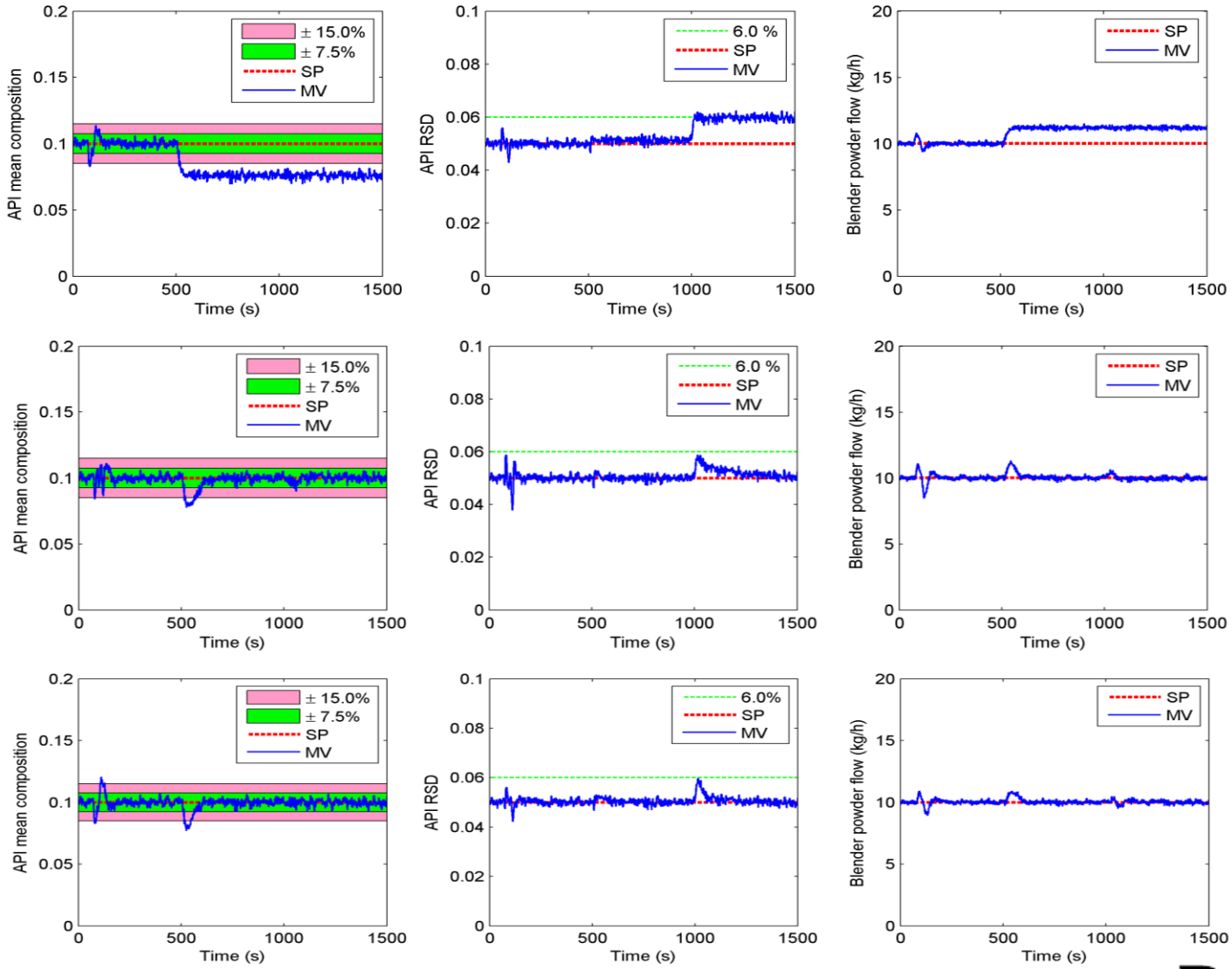
Risk Analysis for feeder & blender: R0 & R1

L0

L1

L2



R0 risk: mass flow disturbances due to feeder reloading

R1 risk: calibration errors in the feeders

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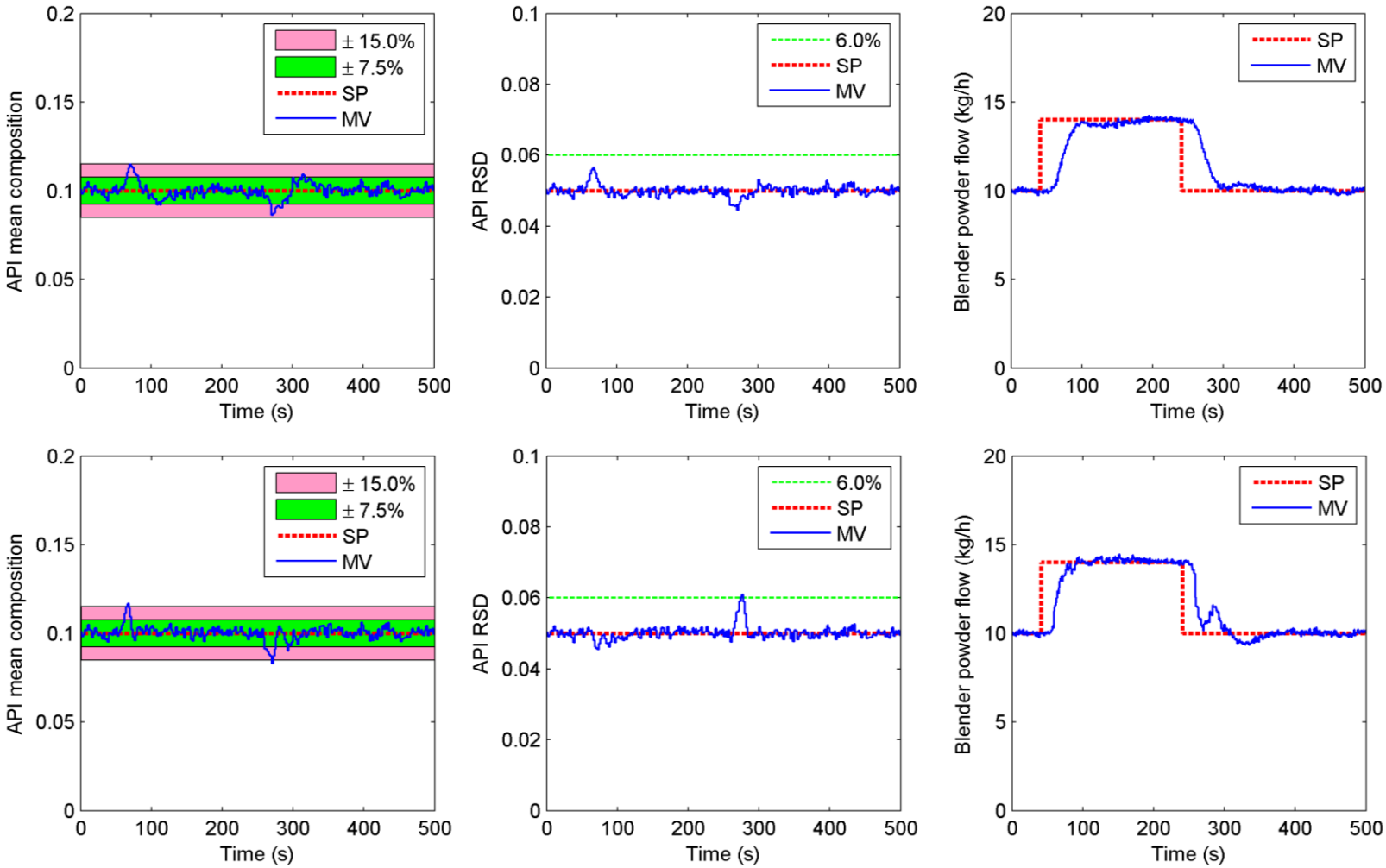
Risk Analysis for feeder & blender: R2

L1

L2



R2 risk: material flowability changed due to humility while a step change on the powder flow rate was also executed.

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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	Fail 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, %

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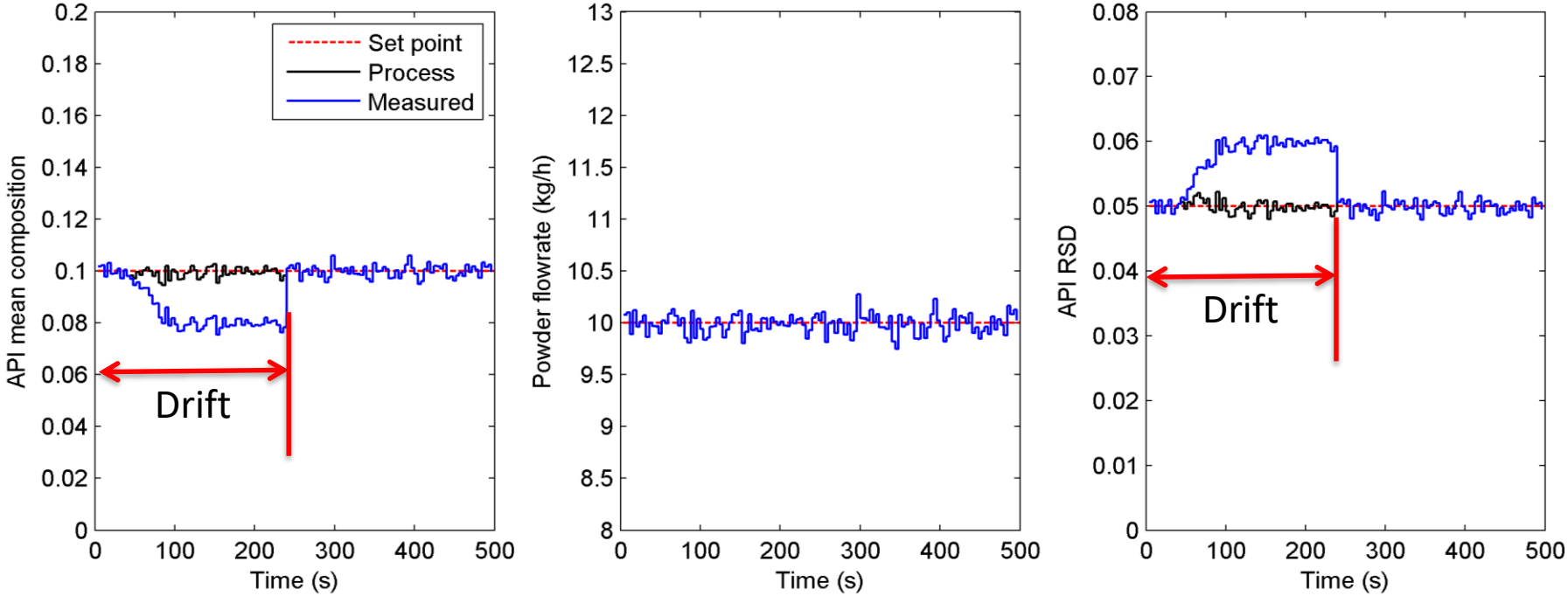
▪ Risk Analysis for feeder & blender: R2 PAT gross error

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.

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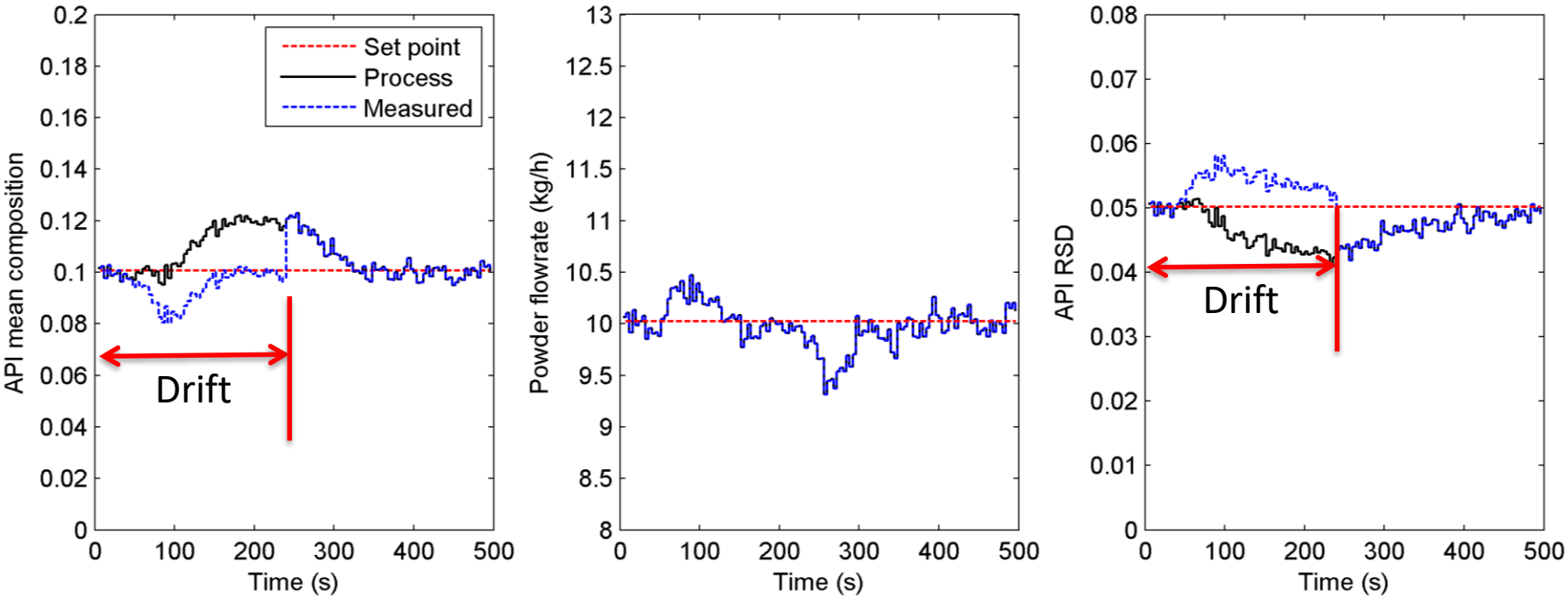
Layer 1 control: The PAT tool with gross error detoured the API mean composition and its mixing uniformity from their set points.



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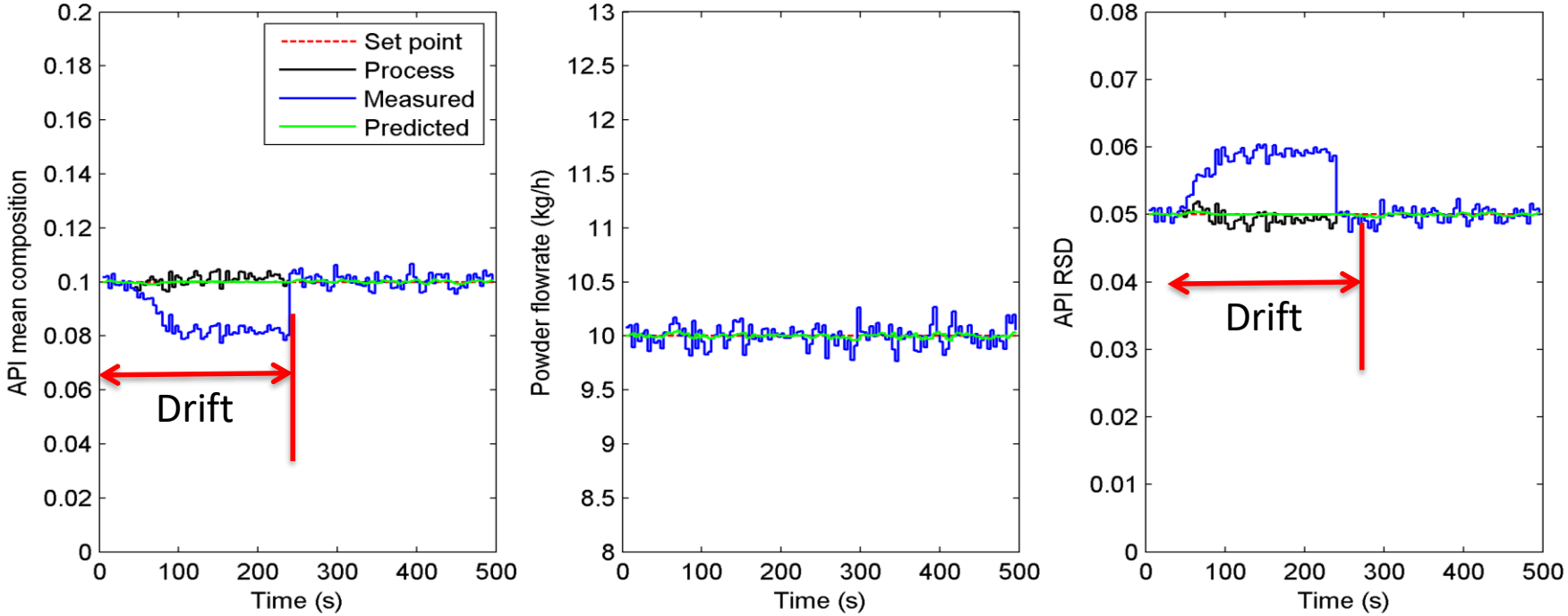
Layer 2 control: The Kalman filter with data reconciliation can reject the measurement gross error when large model-plant mismatches detected.



The Kalman filter with data reconciliation

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

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

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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.