ERC: C-SOPS capabilities towards continuous manufacturing of solid based drug products

Marianthi Ierapetritou
Ravendra Singh, Zilong Wang,
Sebastian Escotet, Fernando Muzzio

Department of Chemical & Biochemical Engineering
Rutgers University, USA

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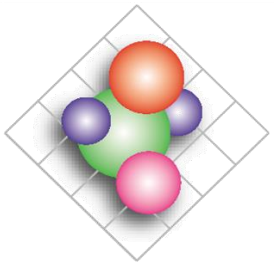

ENGINEERING RESEARCH CENTER FOR
STRUCTURED **O**RGANIC **P**ARTICULATE **S**YSTEMS

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Presentation Outline

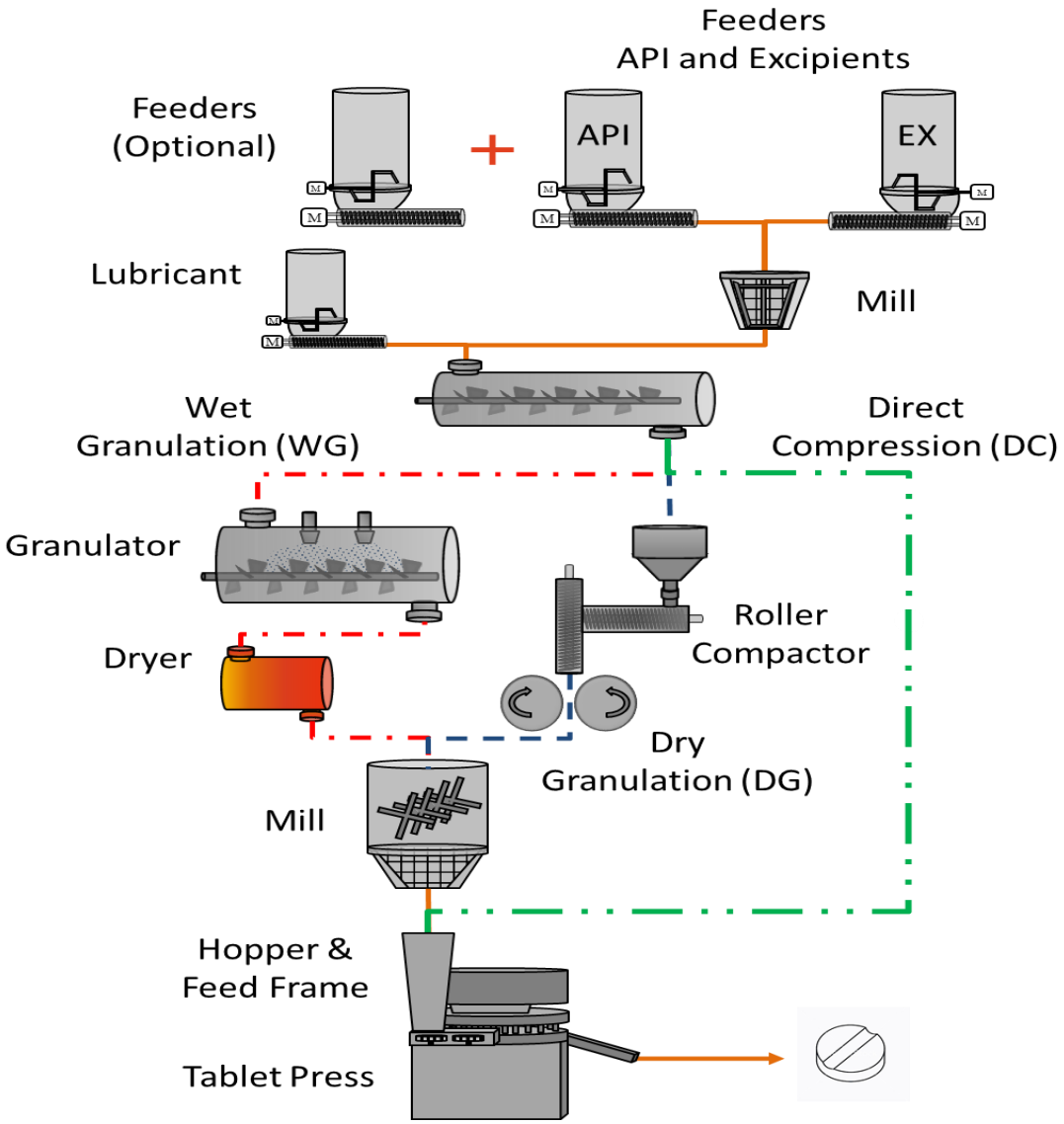
- **Use of gPROMS at C-SOPS**
- **Rutgers Models for Continuous Direct Compression (CDC)**
  - Feeder
  - Blender
  - Feed Frame & Tablet Press
- **Sensitivity and Feasibility Analysis**
  - Global Sensitivity of CDC
  - Feasibility analysis
- **Controls and Implementation**
  - Feed Forward/Feed Back Controls
  - Implementation at Rutgers
- **Conclusions**
- **Questions and Answers**

Use of gPROMS at C-SOPS

- FDA – development of modeling tools for risk based assessment of continuous processes
- FDA - detailed studies of integrated systems; exploring system robustness and control, RTR, and the links to material and process characterization and risk assessment
- Janssen – development of models to support Inspire line
- Janssen – development of models to support Mirror lines (ConSigma)
- Bosch – modeling development and training for new CM equipment design and development
- Usage based on Center project output (D2, D5):
  - Janssen
  - Lilly
  - Pfizer
  - Bosch
  - FDA

Rutgers Models for Continuous Direct Compression (CDC)

Routes of Manufacturing In Continuous



There are 3 major routes of manufacturing in pharmaceutical processes

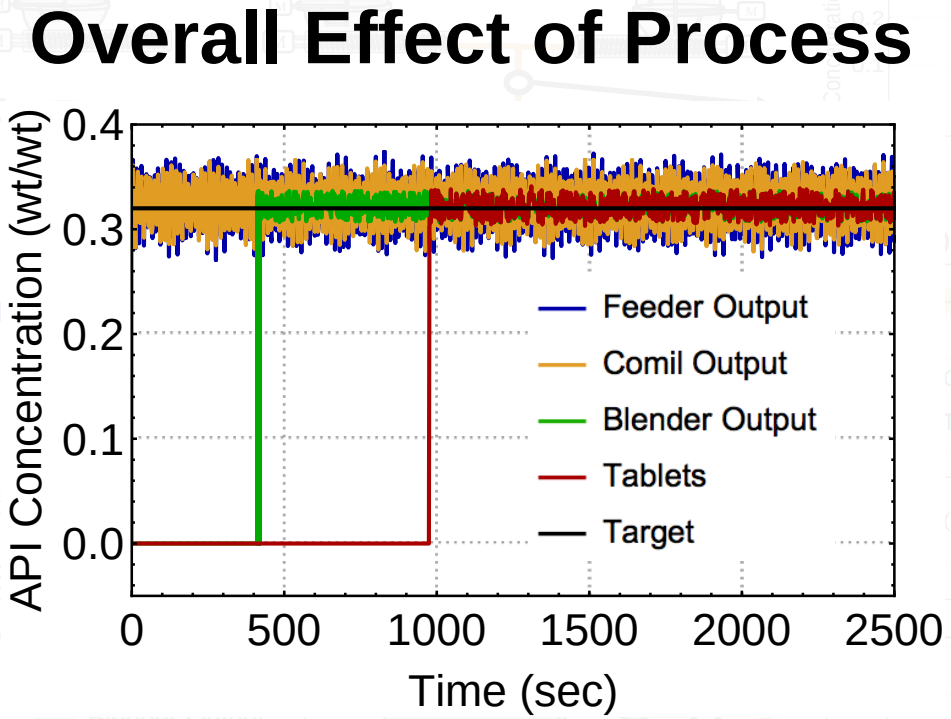
- Direct compression
- Dry granulation
- Wet granulation

At Rutgers we work on all 3 methods, but focus primarily at continuous direct compression

We study the individual unit operations and focus on developing flowsheet models for the complete lines

Rutgers Continuous Direct Compression Line

The objective of our models are to study the overall effects of the system as a function of time



Rutgers Continuous Direct Compression Line

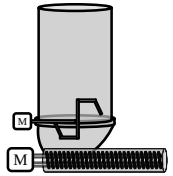
Mathematical models for feeders and comil have been based on semi empirical and empirical equations based on the characterization of equipment

Model based on the characterization of the feed factor of a material: mass of material per screw revolution – Allows for the calculation of flow rate as a function of volume displaced by the screws in the feeder

Screw Feeder: Flow Rate

Mass Balance & Volumetric Displacement

Feed Factor Characterization



$$\dot{V}_{out}(t) = w(t)\ V_{screw\ flight}$$

$$\dot{m}_{out}(t) = ff(t)\ w(t)$$

$$ff(t) = V_{screw\ flight}\ r_{apparent}(t)$$

$$w_{Set}(t) = \dot{m}^{Set}_{out}(t) \Big/ ff(t)$$

$$\rho_{apparent}(t) \approx \rho_{saturated} + \Delta\rho_{process}\ Exp\left(-\frac{g\ k\ M(t)}{A_{feeder}}\right)$$

$$\Delta\rho_{process} = \left(\rho_{saturated} - \rho_{empty}\right)$$

$$\rho_{saturated} \approx \rho_{bulk}\left(1-\varepsilon\right)$$

Mass in hopper

Since working in a DC, there are no major changes in the particle size. Therefore this unit is treated as a simple mixing unit with no PBMs

Comil: Mixing – No major Particle Size Change

Perfect Mixing Model and Mass Balance

$$C_{in}(i,t) = \frac{\dot{m}_{in}(i,t)}{\sum_{i=1}^{No.\ Inlets} \dot{m}_{in}(i,t)}$$

$$\dot{m}^{in}_{total}(t) = \sum_{i=1}^{No.\ Inlets} \dot{m}_{in}(i,t)$$

$$M_{ss}(t) = \bar{t}(t)\ \dot{m}^{in}_{total}(t)$$

$$\bar{t}\frac{dM(t)}{dt} = Mss - M(t)$$

$$\dot{m}^{out}_{total}(t) = \left(\dot{m}^{in}_{total}(t) - \frac{dM(t)}{dt}\right)$$

$$\dot{m}_{out}(i,t) = \dot{m}^{out}_{total}(t)\, C_{out}(i,t)$$

$$\bar{t}(t) = t_{\max}\left(1 - Exp\left(-\frac{a}{w - w_{\min}} - \frac{b}{\dot{m}^{in}_{total}(t)}\right)\right)$$

$$\frac{d\left(C_{out}(i,t)\,M(t)\right)}{dt} = \dot{m}_{in}(i,t) - \dot{m}_{out}(i,t)$$

NSF Engineering Research Center for Structured Organic Particulate Systems (C-SOPS)

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Rutgers Continuous Direct Compression Line

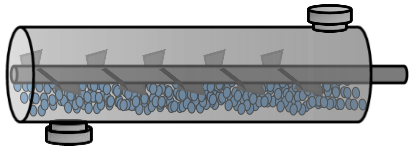
Mathematical models for blenders and tablet presses have been based on semi empirical equations that are based on the characterization efforts for each unit

Model based on the use of RTD for calculating concentration at the blender's outlet given a concentration profile coming from the feeders

Blender: Concentration Output

Residence Time Distribution Model

CSTR-in-Series and Taylor Dispersion



$$E_{Blender}(t) = Unit\ Step\ [\mathrm{t}-\mathrm{t}_{plug}]\ \frac{(t-t_{plug})^{n-1}\ Exp[-\frac{t-t_{plug}}{\tau}]}{(n-1)!\ \tau^{n}}$$

$$n = \mu_n + a_n\ \mathrm{MFR} + b_n\ \mathrm{RPM} + c_n\ \mathrm{MFR}^2$$

$$\tau = \mu_T + a_T\ \mathrm{MFR} + b_T\ \mathrm{RPM} + c_T\ \mathrm{MFR}^2$$

$$t_{Plug} = \mu_D + a_D\ \mathrm{MFR} + b_D\ \mathrm{RPM} + c_D\ \mathrm{RPM}^2$$

$$\tau\frac{\partial C_{out}(Z,i,t)}{\partial t} = \frac{1}{Pe}\frac{\partial^2 C_{out}(Z,i,t)}{\partial Z^2} - \frac{\partial C_{out}(Z,i,t)}{\partial Z}$$

$$C_{out}^{final}(i,t) = C_{out}(Z=1,i,t)$$

$$C_{out}(Z=0,i,t) = C_{in}(i,t)$$

$$\frac{\partial C_{out}(Z=1,i,t)}{\partial Z} = 0$$

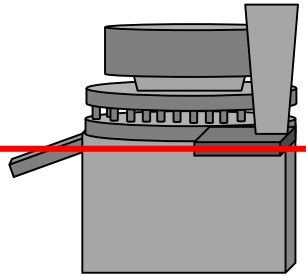
$$Z = \frac{z}{L}$$

$$\tau = \frac{L}{v}$$

Feed Frame & Tablet Press: Mixing and Compression

Perfect Mixing Model and Mass Balance

Kawakita and Kuentz & Luenenberger Model



$$CP_{pre} = \frac{b(V_0 - V_{pre})}{(V_0(\varepsilon_0 - 1) + V_{pre})}$$

$$CP_{main} = \frac{b^*(V_{pre} - V)}{(V_{pre}(\varepsilon_{main} - 1) + V)}$$

$$V_{pre}\ \varepsilon_{main} = V_{pre} - (1-\varepsilon_0)V_0$$

$$V_{solid}(t) = V_{fill}(t)(1-\varepsilon_{in}(t))$$

$$\rho_{relative}(t) = \frac{V_{solid}(t)}{V_{tablet}}$$

$$\lambda_{hardness}(t) = Log\left(\frac{1-\rho_{relative}(t)}{1-\rho_{critical}}\right) \qquad \rho_{critical} < \rho_{relative}(t) < 1$$

$$H_{tablet}(t) = H_{\max}\left(1 - Exp\left(\rho_{relative}(t) - \rho_{critical} + \lambda_{hardness}(t)\right)\right)$$

A two part model that comprises a mass balance and perfect mixing for the Feed Frame and a set of compression models for the turret of the TP

Rutgers Continuous Direct Compression Line

Material properties have become of interest for our center in terms of being able to predict the behavior of blends from raw material properties. Currently we use the following material properties calculated as weighted average based on the composition

- **Bulk Density:** flow rate and fill level
- **True Density:** calculate powder porosity
- **Particle Size:** granulation units and compression models
- **Cohesion Value:** blending models
- **Angle of Repose**: transfer pipe and feeder models
- **Compressibility Coefficient:** compression models
- **Flow Function Coefficient:** blending models
- **Hausner Ratio:** feeding and compression models
- **Angle of Internal Friction:** feeding models

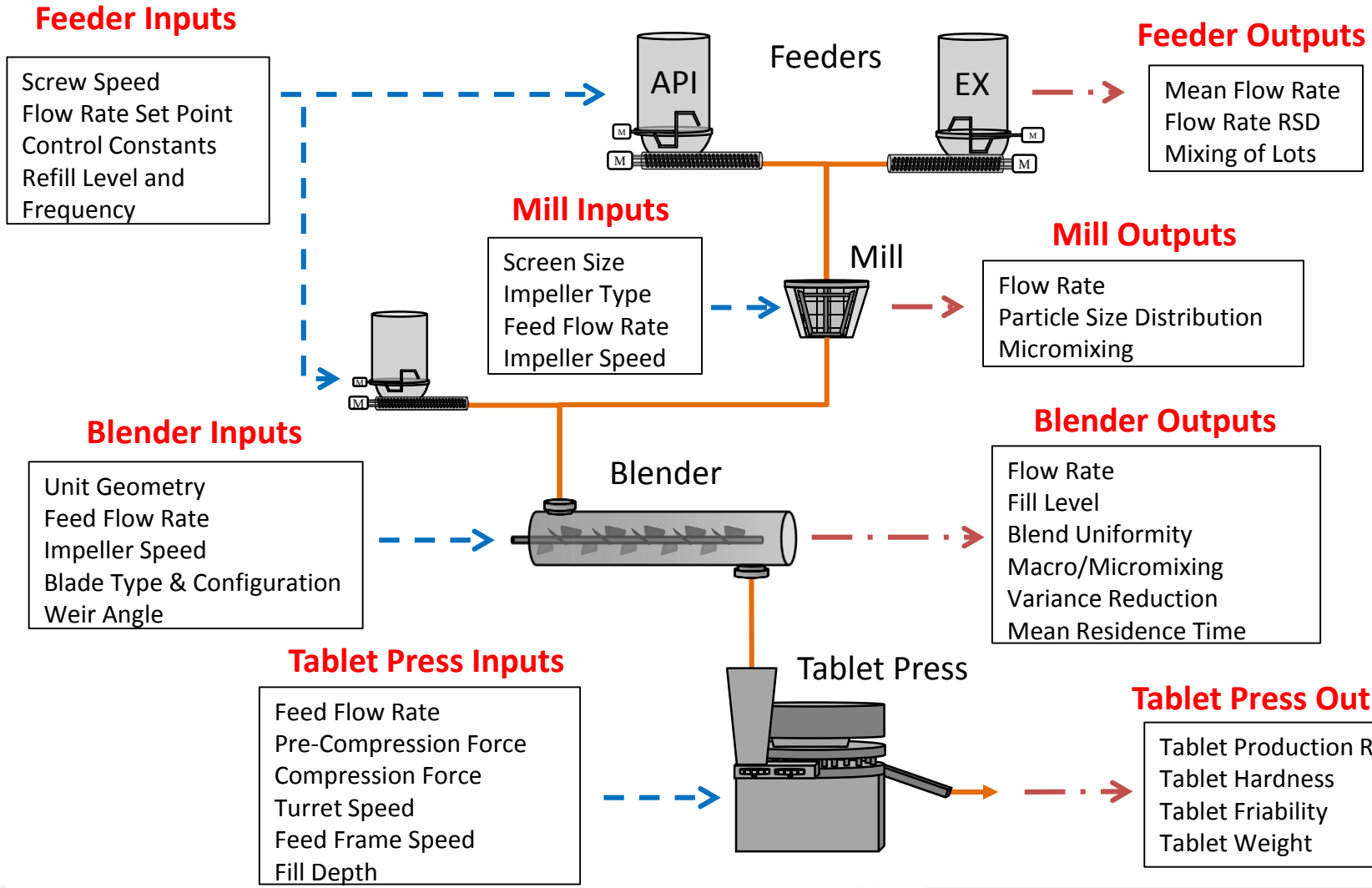
The objective of the center is to study raw material properties and correlate them to their behavior as blends using surrogate models to replace weighted averages

- Principal Component Analysis and Regression (PCA & PCR)
- Partial Least Squares (PLS)

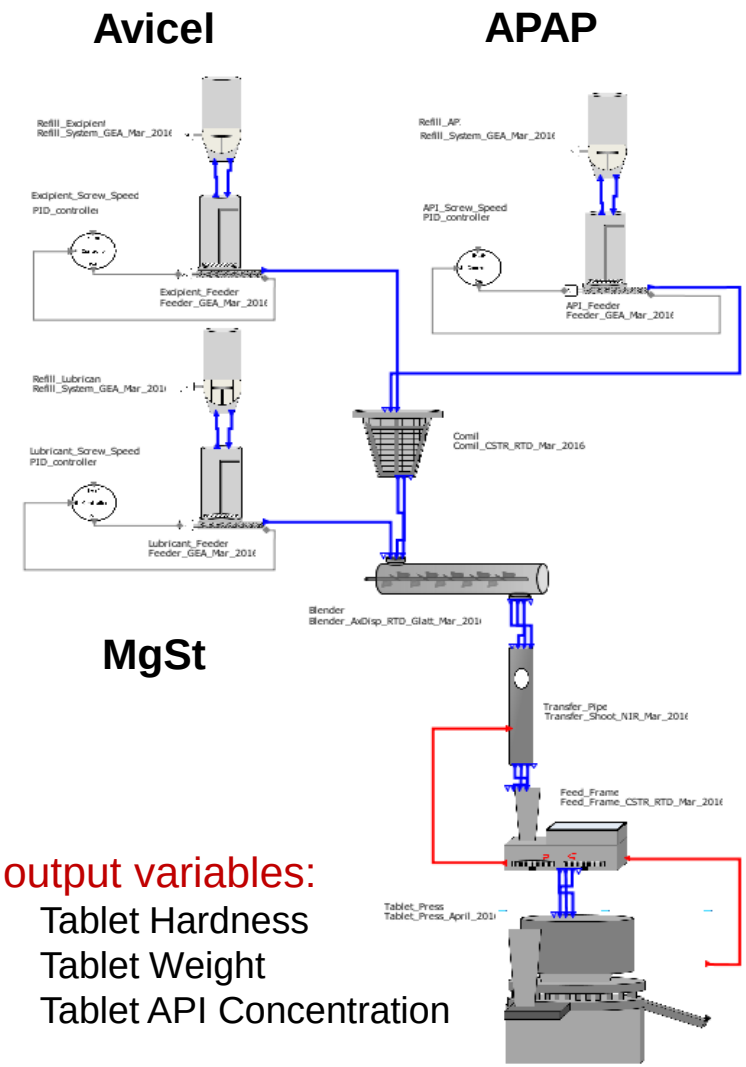
Sensitivity Analysis

Understanding How Inputs Affect Outputs

Each of our models has several inputs for each set of equations. Understanding the relationships between these models is critical for process development and control



Application Sensitivity Analysis (SA) to CDC



Taken the models for the unit operations of the CDC line, we can select distributions for the input parameters

Ranges for 16 input factors:

1. Tablet fill depth setpoint ~ Unif (8e-3, 10e-3) [m]
2. Tablet thickenss setpoint ~ Unif (3.2e-3, 3.7e-3) [m]
3. APAP Hausner Ratio ~ Unif (1.149, 1.167)
4. APAP flowrate setpoint ~ Unif (2, 2.4) [kg/h]
5. APAP bulk density ~ Unif (633, 643) [kg/m3]
6. APAP mean particle size ~ Unif (385, 405) [micron]
7. Avicel Hausner Ratio ~ Unif (1.5, 1.553)
8. Avicel flowrate setpoint ~ Unif (12.4, 12.8) [kg/h]
9. Avicel bulk density ~ Unif (280, 290) [kg/m3]
10. Avicel mean particle size ~ Unif (90, 110) [micron]
11. MgSt Hausner Ratio ~ Unif (1.682, 1.787)
12. MgSt flowrate setpoint ~ Unif (0.1, 0.2) [kg/h]
13. MgSt bulk density ~ Unif (160, 170) [kg/h]
14. MgSt mean particle size ~ Unif (18, 28) [micron]
15. Comil blade speed ~ Unif (1000, 1100) [rpm]
16. Blender blade speed ~ Unif (240, 260) [rpm]

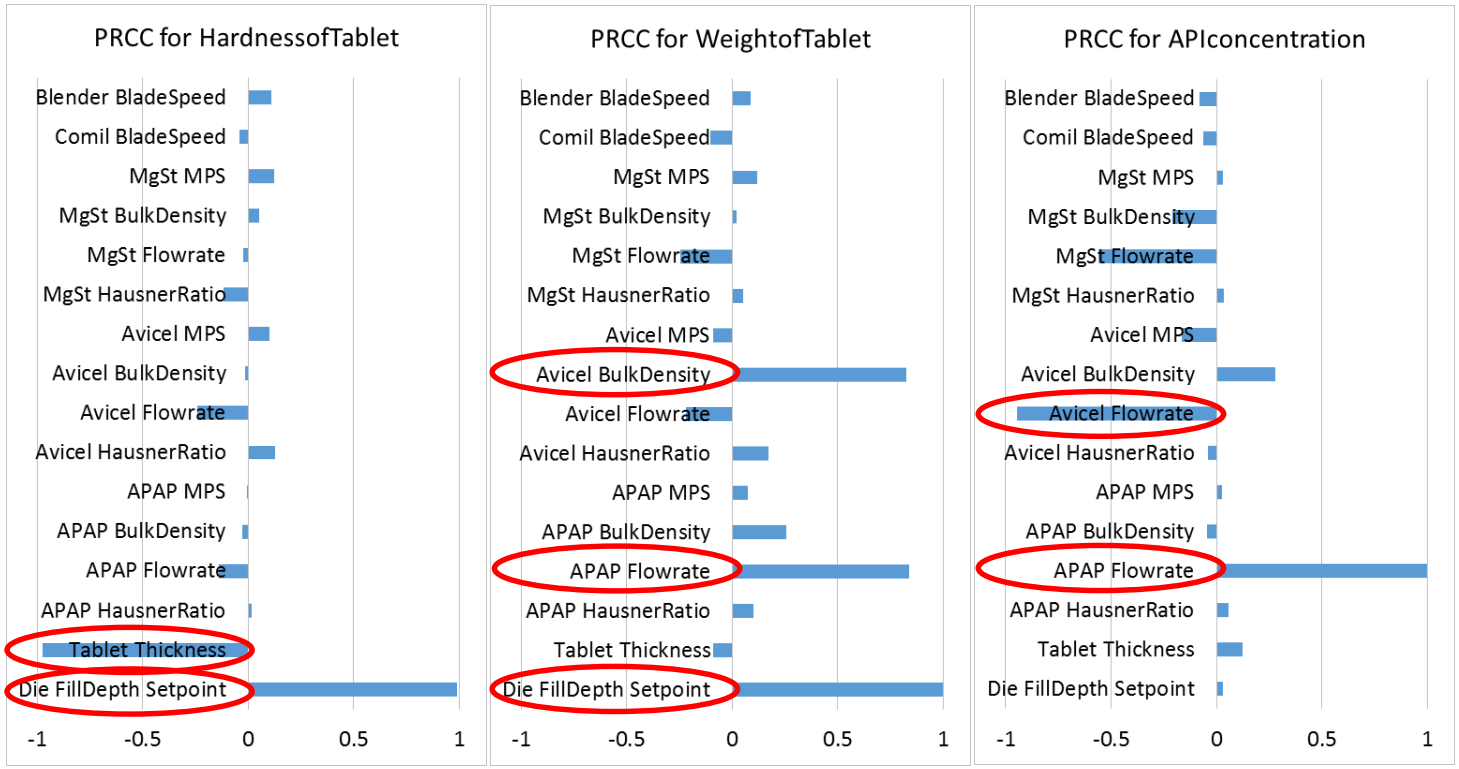
3 output variables:

1. Tablet Hardness
2. Tablet Weight
3. Tablet API Concentration

Results of PRCC SA Methodology

In order to determine which are the most influential terms for the simulation a less computationally demanding PRCC method is applied. The analysis reveals that:

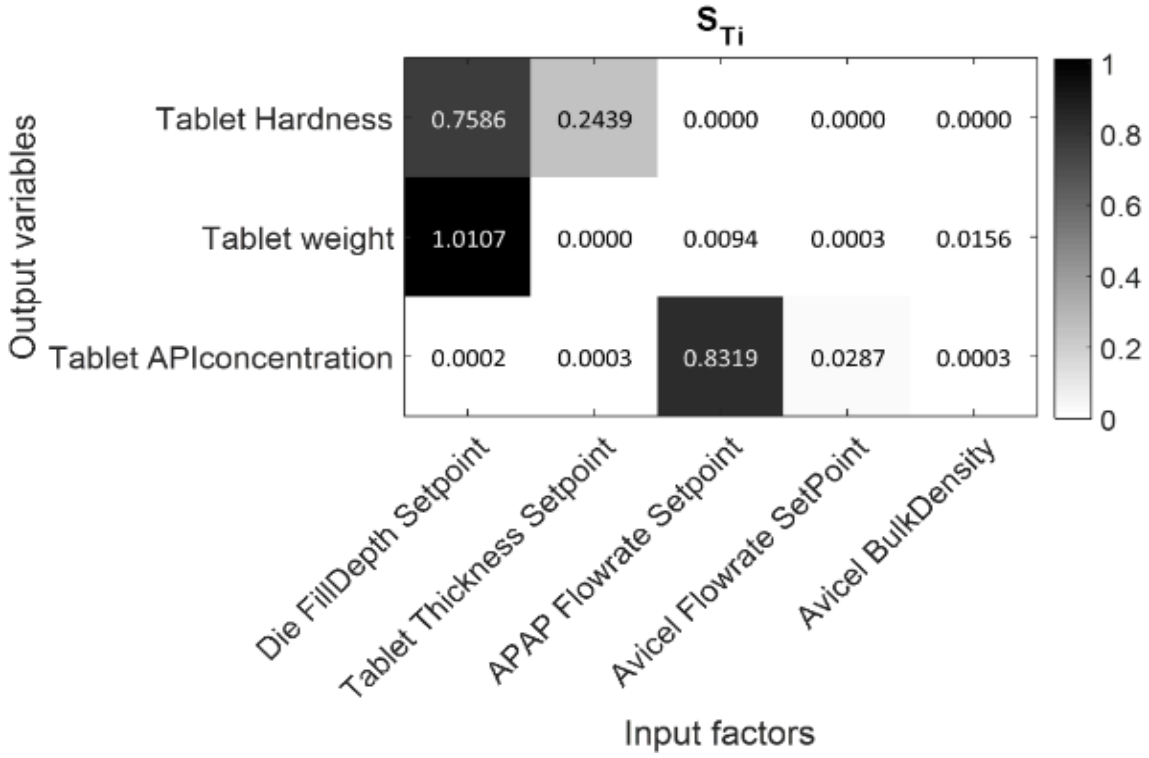
- Tablet hardness is affected by the tablet thickness and fill depth of the die at the tablet press
- The weight of the tablets is affected by the bulk density, flow rate, and fill depth of the die
- The API concentration in tablets is affected by the flow rate of the excipient and the API



Results of Sobol's SA Methodology

From the application of the Sobol's method for global sensitivity we can observe that:

- Tablet hardness is highly dependent on the fill volume die at the tablet press (i.e., the fill volume of powder to make the tablet) and the thickness set point of the tablet (compressing more material into a smaller compact)
- Tablet weight depends highly on the fill volume of the die (because allows more powder)
- Tablet API concentration is found to obviously be correlated with the flow rate set point of the feeders



Feasibility Analysis: Determining the Design Space

Feasibility analysis is to identify the region where a process satisfies all operating, quality and production constraints under uncertainty

Feasibility Function $\psi(d,\theta) = \max_{j \in J} \{ f_j(d,\theta) \}$

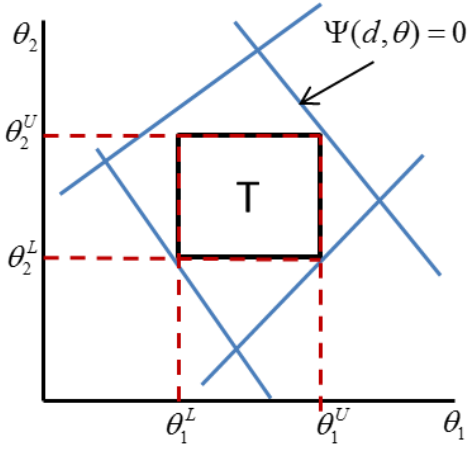
$$\psi(d,\theta) = \max_{u} u$$

$$s.t.\ f_j(d,\theta) \le u, \quad \forall j \in J$$

where

d : design variables (e.g. equipment size)

θ : uncertain parameters (inlet conditions)



Feasible design $\chi(d) \le 0$

Surrogate-based adaptive sampling method

- Surrogate model is constructed to reduce simulation time and guide the search of samples
- Adaptive sampling is used to efficiently sample new points near feasible region boundary and uncertain areas.

Grossmann I E, et al. Computers & Chemical Engineering, 2014, 70: 22-34.
Rogers A, Ierapetritou M. *Chemical Engineering Science.* 2015;137:986-1004.

Feasibility Analysis of Tablet Press Model

Problem statement: Under certain process parameters, find the feasible region within uncertain ranges (Table 1) that can result in qualified tablets with properties within specified ranges (Table 2)

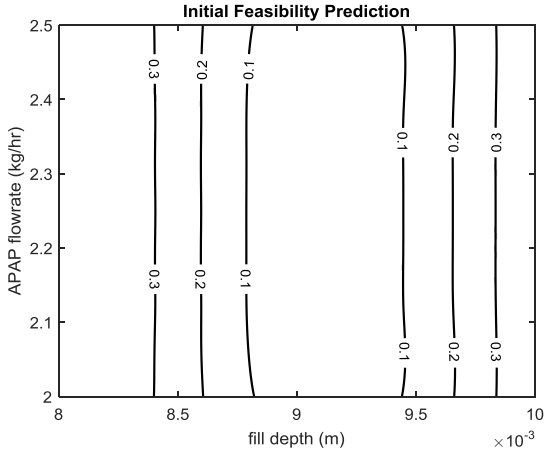
Table 1. Ranges of uncertain variables

	lower bound	upper bound
API flowrate [kg/hr]	2	2.5
Tablet die fill depth [m]	0.008	0.01

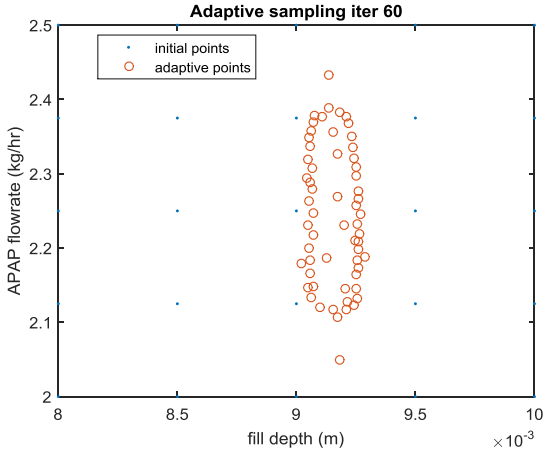
Table 2. Tablet quality constraints

	Nominal values	Lower bound (-5%)	Upper bound (+5%)
Tablet hardness [N]	70	66.5	73.5
Tablet weight [kg]	3.40E-04	3.23E-04	3.57E-04
Tablet API concentration [w/w]	0.15	0.1425	0.1575

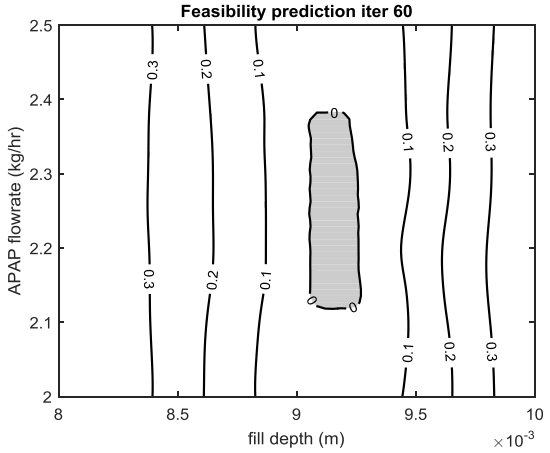
Step 1. Initial surrogate



Step 2. Adaptive sampling



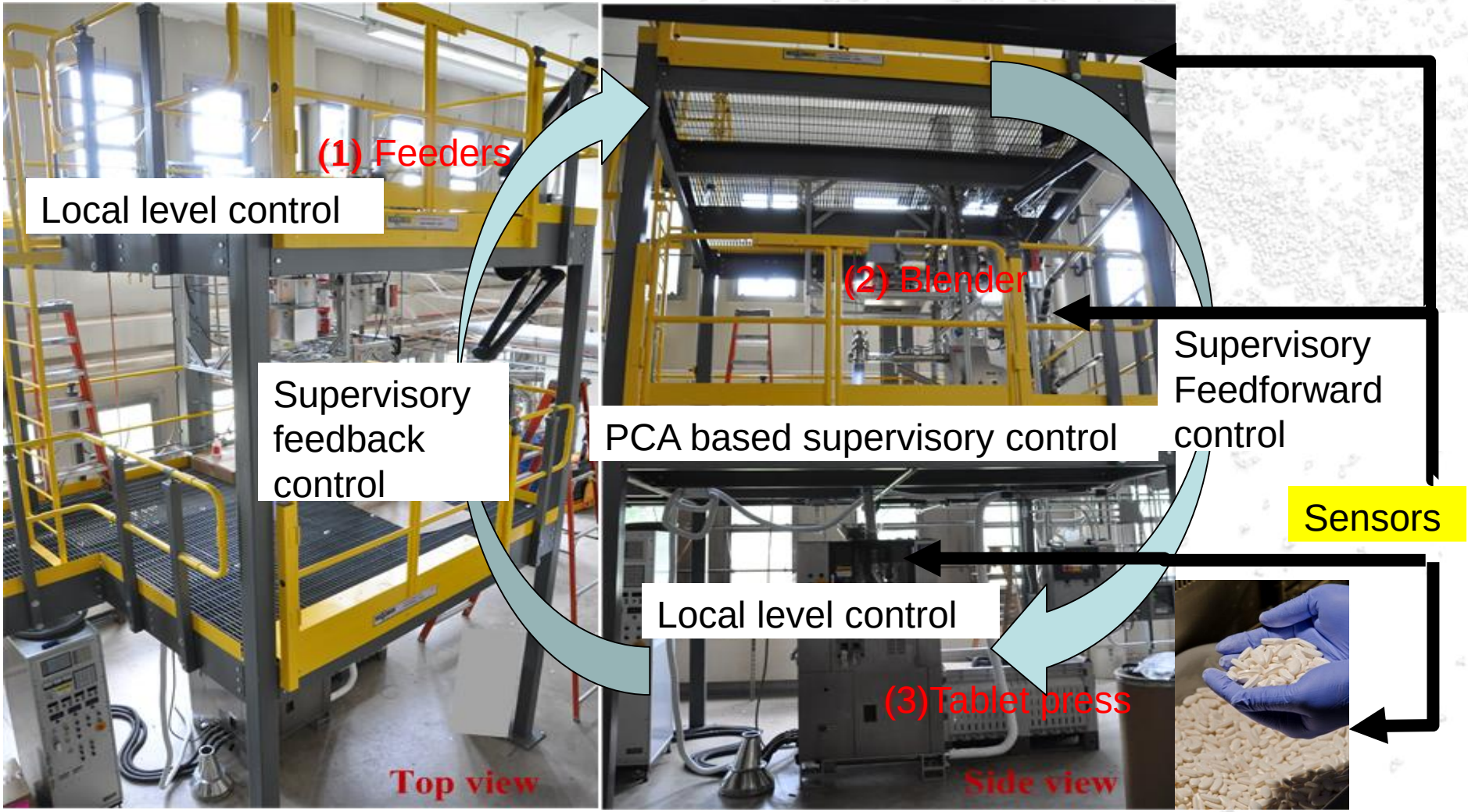
Step 3. Feasible region identified



Accuracy:
99.98% correctly identified
0.02% not conservative

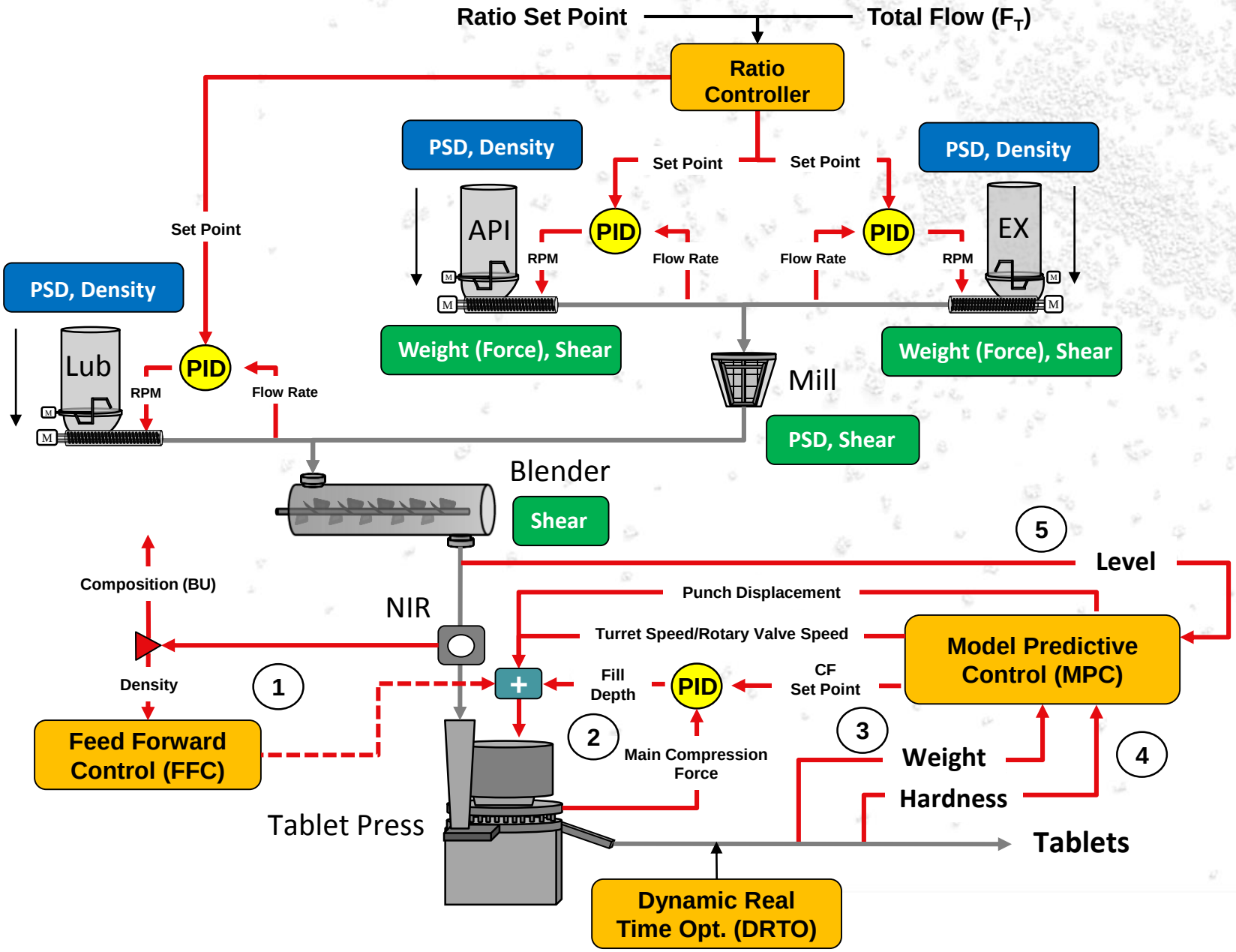
Control and Implementation

Continuous tablet manufacturing pilot-plant

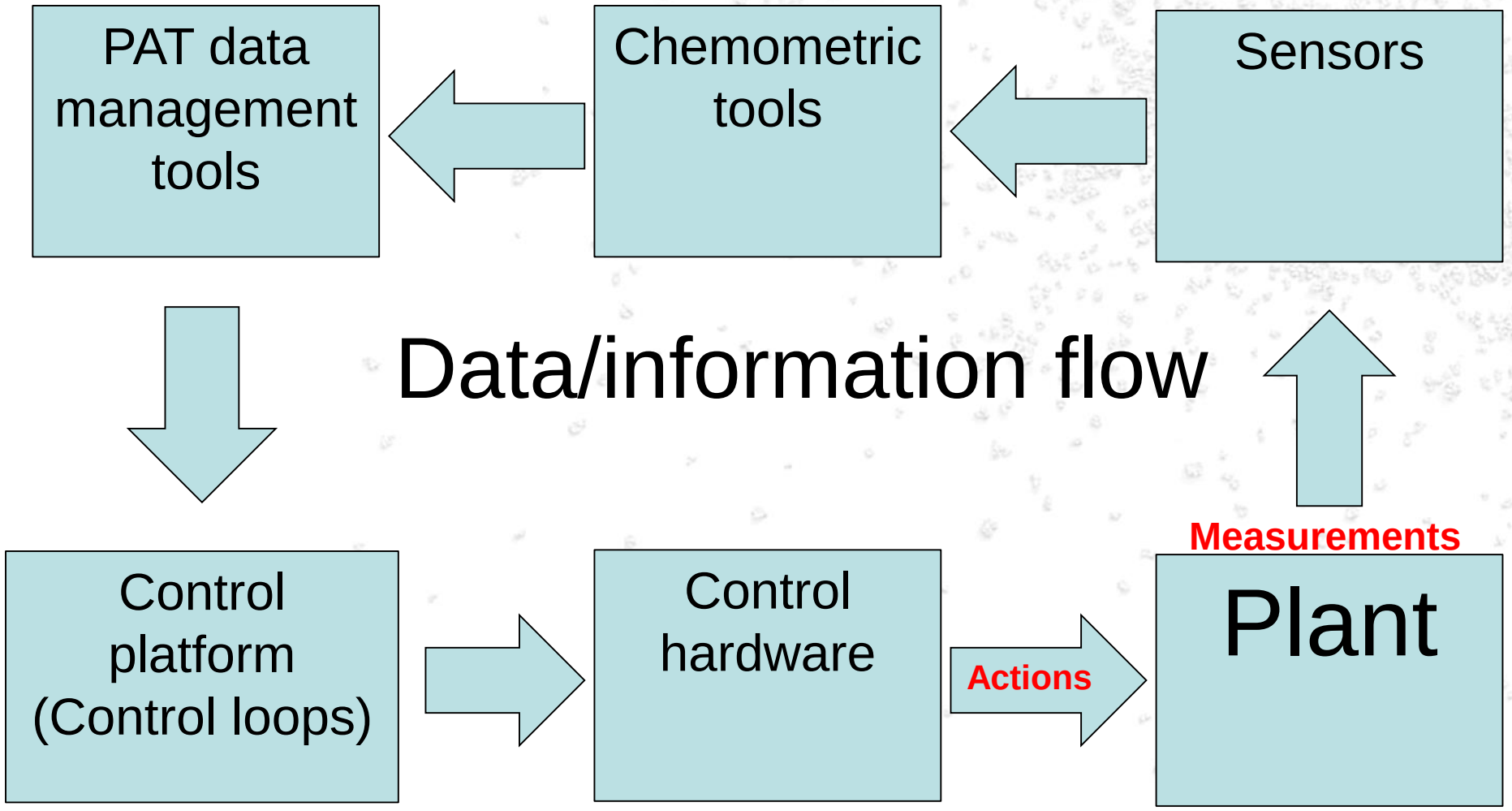


Singh, R., Boukouvala, F., Jayjock, E., Ramachandran, R. Ierapetritou, M., Muzzio, F. (2012). Flexible Multipurpose Continuous Processing. PharmPro Magazine, 28 June, 2012,

Feed-Forward/Feed Back Control System

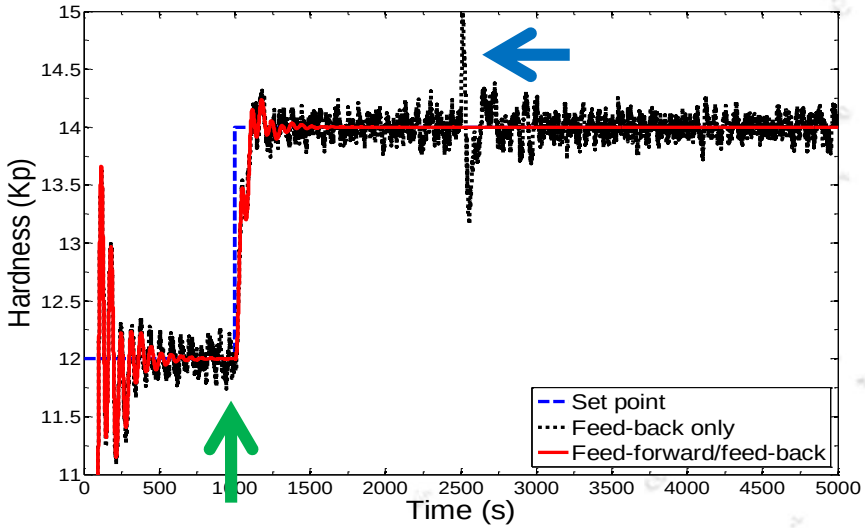


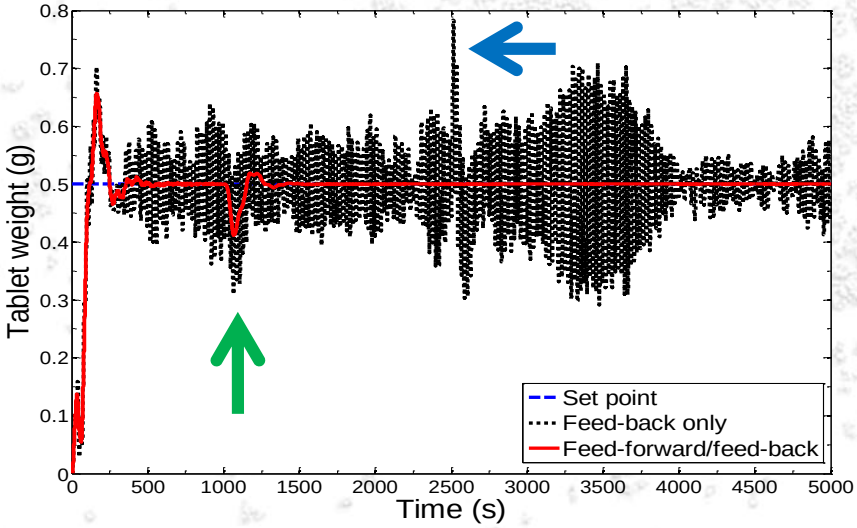
Control System Implementation



Feedforward/feedback control of hardness

- Random disturbances in blend density were introduced to test the controls

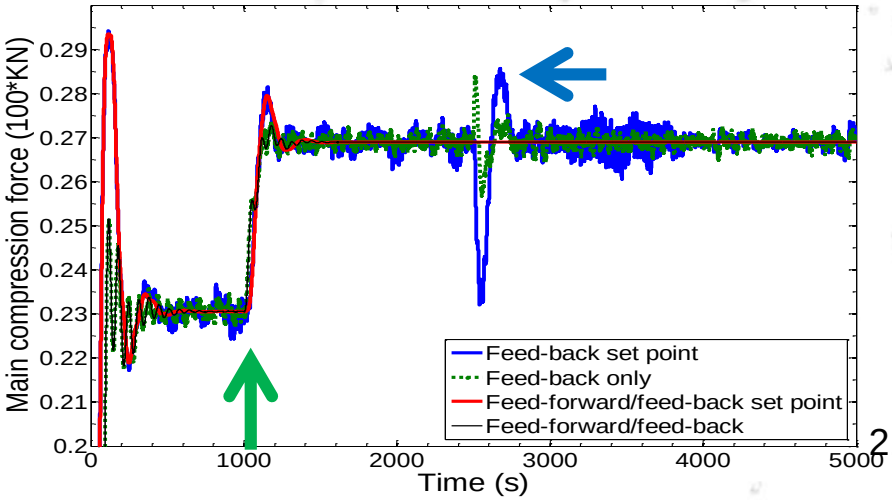




Disturbance Legend

Step change in hardness set point

Step change in blend density



Optimization

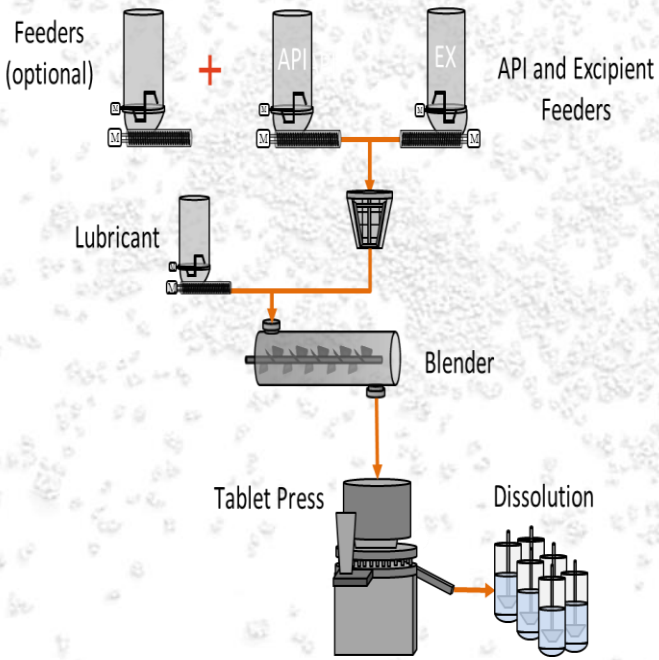
Process Optimization

Modeling of powder flow: expensive flowsheet models

Output can be stochastic:

- Probability of particles of different size to collide, interact, break, form aggregate govern bulk powder properties
- Material properties are described by distributions

Pharmaceutical tablets must satisfy quality constraints.



$$\min_x f(x)$$

Expensive objective function

$$s.t.$$

$$g_i(x) \le 0$$

Black-Box constraints

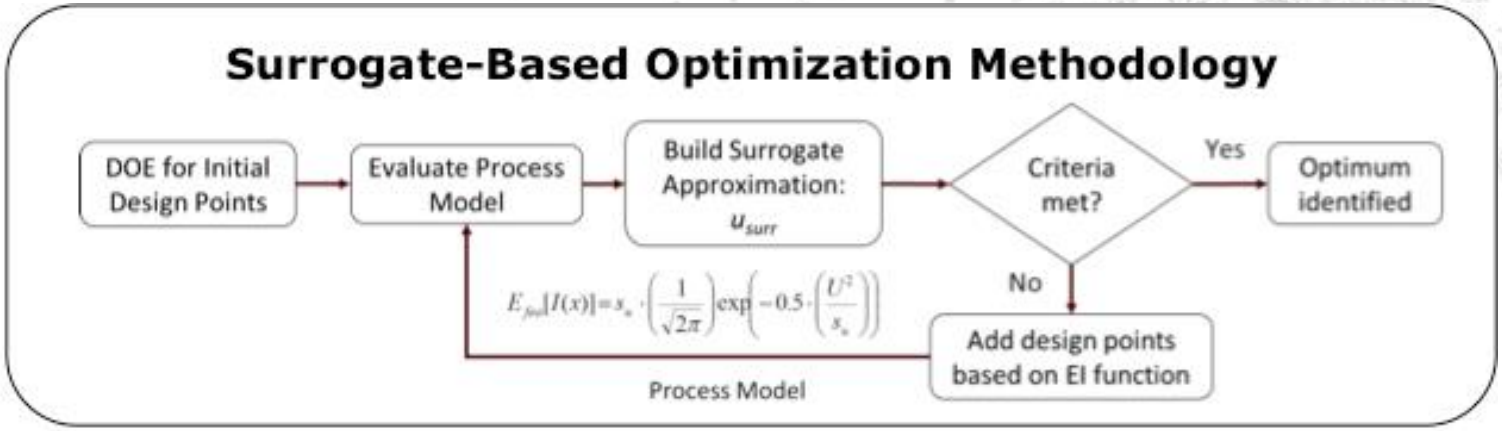
- expensive
- no assumptions about the form of the feasible region

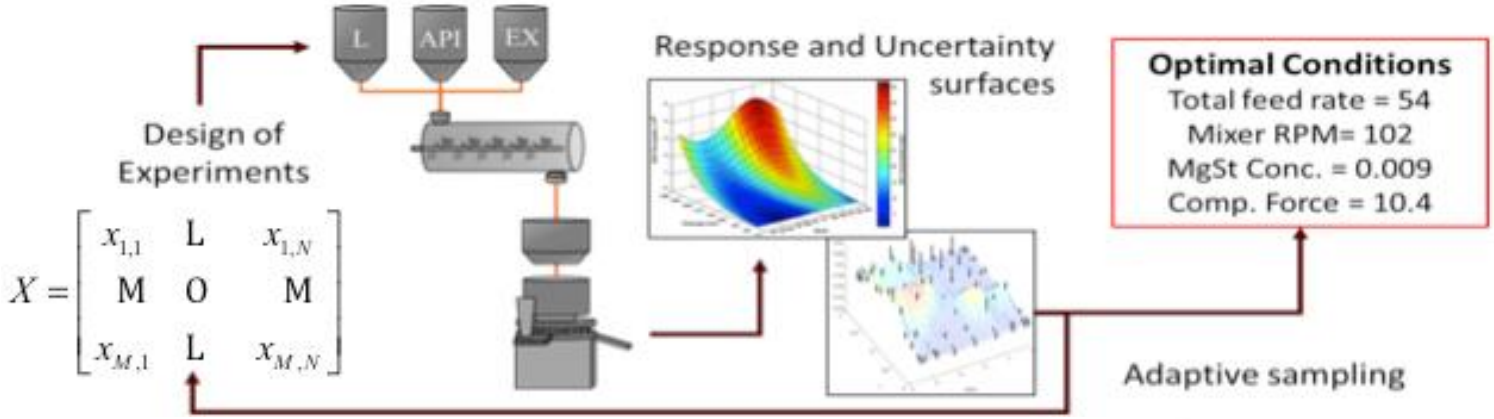
$$x_k^{lb} \le x_k \le x_k^{ub}$$

SIMULATION-BASED, DERIVATIVE-FREE OPTIMIZATION using SURROGATE APPROXIMATIONS

Process Optimization Case Study

- **OBJECTIVE:** minimize cost of a 1 day operation of continuous direct compaction
- **DECISION VARIABLES:** process capacities, operating conditions, throughput, refill strategy
- **SUBJECT TO:** Process capacity bound constraints, Product quality constraints, Minimum production requirement.





Conclusions

- Models for unit operations for the continuous direct compression line at Rutgers have been developed
- An integrated model was used to determine the impact of each unit operation on the powder stream
- Sensitivity analysis was performed in order to quantitatively assess the effect of inputs on outputs of the simulation
- Feasibility was done in order to determine the design space
- New methods for real time monitoring of powder level and powder bulk density have been developed.
- Advanced control architecture has been developed and implemented into continuous tablet manufacturing pilot-plant.
- Surrogate models can be built from evaluation of simulations in order to map responses in a lower dimensional space
- Optimization methods can be applied and additional points can be included using an adaptive sampling strategy

Thank you!

QUESTIONS?

Acknowledgements

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