Process Intensification: Application in Pharmaceutical Manufacturing

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Current state of Pharmaceutical Industry

- **Process development challenges**
  - Time pressure for clinical supply delivery
  - Uncertainty throughout development process
  - Unique physical properties of APIs
  - Sequential scale-up of batch processes

- **Economic challenges**
  - Up to 27% of revenues spent on manufacturing costs
  - Increased global competition, generics manufacturers

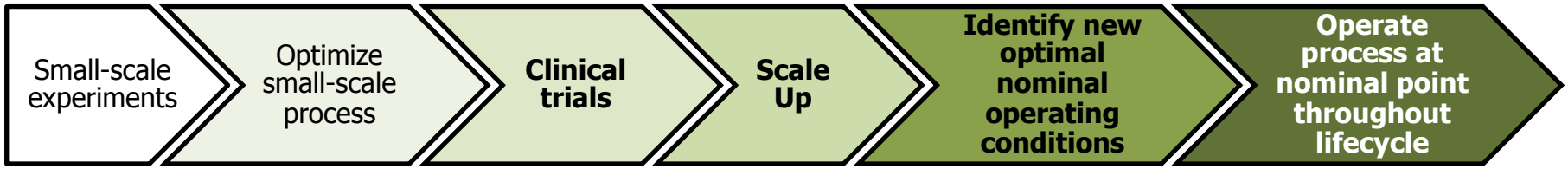
- **Regulatory concerns**
  - Quality by Design (QbD) – companies need increased process understanding
  - Inherent variability in performance and sampling

Need efficient and robust manufacturing strategies in order to remain competitive

McKenzie, P. K et al. AIChE Journal 2006, 52 (12).
Buchholz, S. Chem Eng Process 2010, 49 (10), 993-995
Basu, P. et al. J Pharm Innov 2008, 30-40.
Shah, N. Comput Chem Eng 2004, 28 (6-7), 929-941

Current state of Pharmaceutical Industry

- Pharmaceutical industry is innovative in development of new drugs **BUT manufacturing is primitive** compared to other chemical industries
- Given a **new** formulation/product:



- Production predominantly in **BATCH** mode
- A batch is produced → samples are tested → batch FAILS/PASSES

Sample only a few

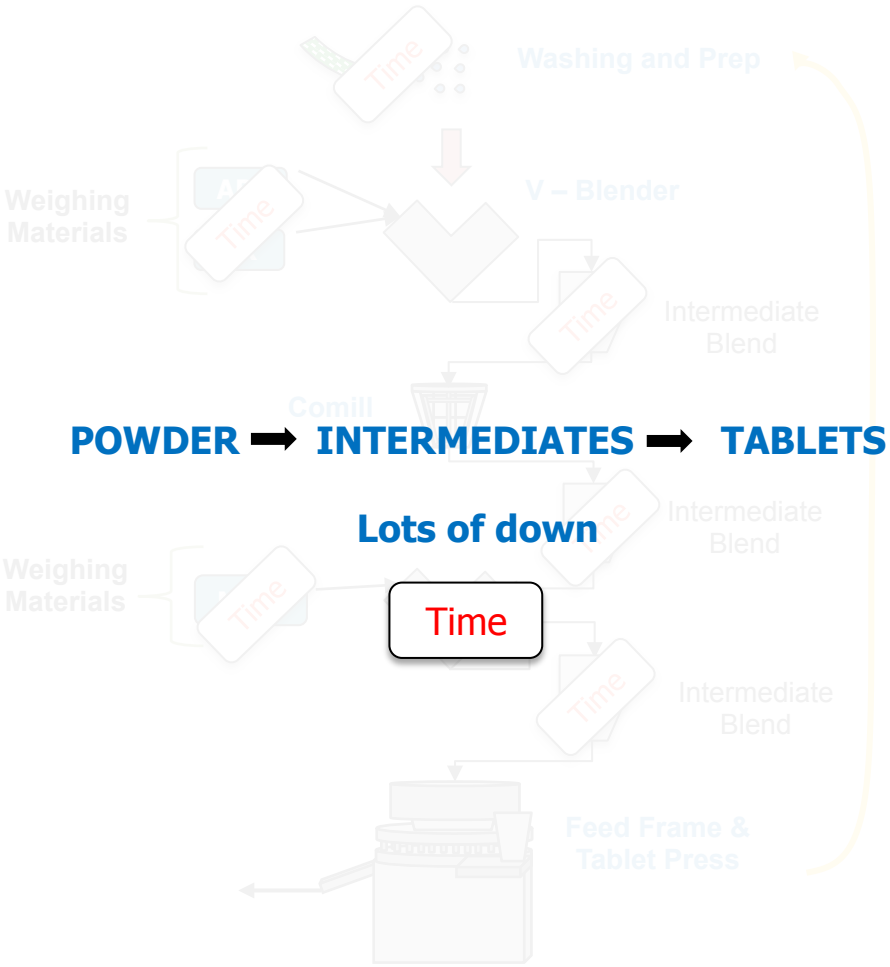
Waste and cost!

Is quality for rest of the tablets the patient will take **captured** ?

Batch vs. Continuous Processes

- **Intermediate steps** in batch, not continuous

Batch Process



POWDER ➡ INTERMEDIATES ➡ TABLETS

Lots of down

Time

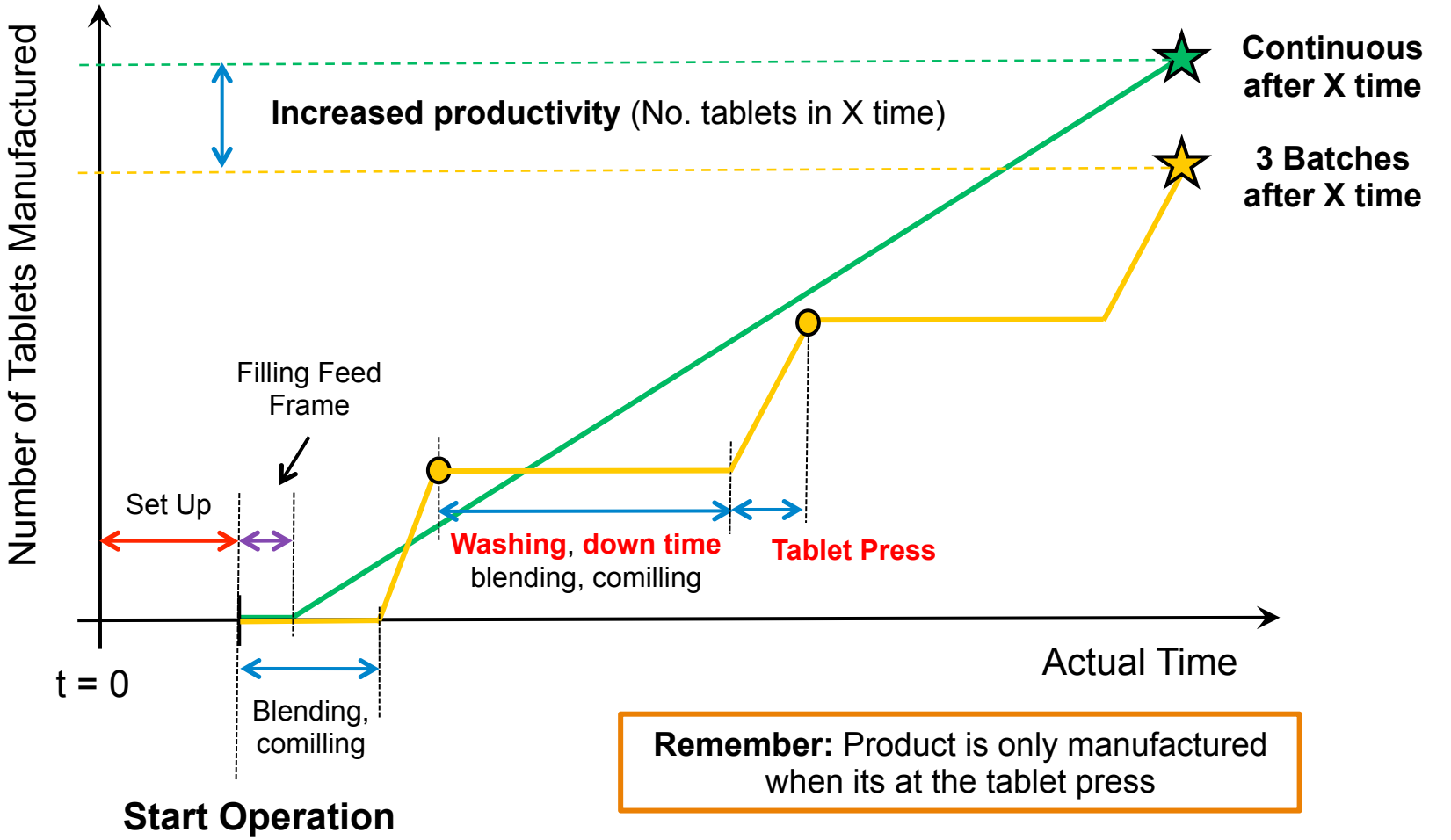
Continuous Process

POWDER ➡ TABLETS

No intermediate blends or steps

Batch vs. Continuous Processes

- Continuous manufacturing has no lag times in production, while batch has delays due to washing, blending and comilling between batches (no product being made)



Batch vs. Continuous Processes

- **Batch**

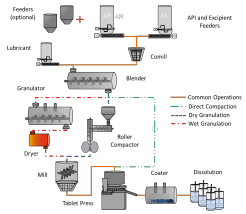
Cons

- Productivity is low
  - Down time
- Set process design and operation
- Powder exposure during process
- Scale-up necessary
  - Time and new equipment
- Harder to control
  - Wasted batches
  - Within-batch variability
- Multiple operators required

Pros

- Many products are produced in smaller quantities
- Existing 'know-how' and fillings

- **Continuous**



Cons

- Novel method
  - Few regulatory fillings
- Requires engineering understanding

Pros

- High Productivity
  - No down time in process
- Set design, but varying parameters
  - Flexible operation
- Enclosed powders = no exposure
- Less scale-up studies
  - Extended operation = scale up
- Better control
  - No failed batches
- Automated process = less operators
- Smaller footprint and equipment

Advantages of Continuous Processes

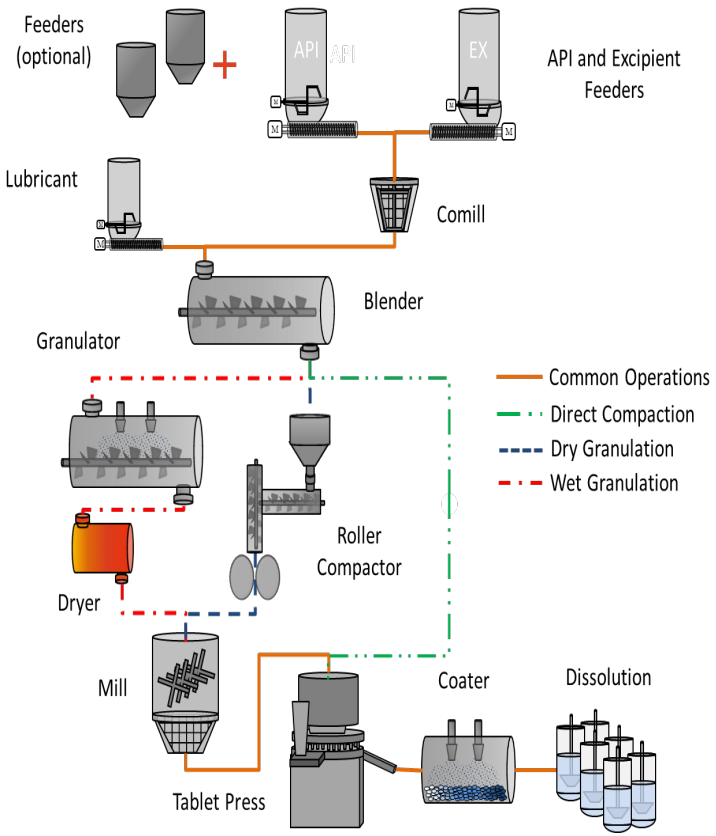
Some of the major advantages of continuous systems include:

- **Increased productivity**
  - Eliminate down time during operation
- **Fewer scale-up studies**
  - Parallelization, increased throughput[3]
  - Reduced time to market
- **Small and compact equipment**
  - Reduced capital cost and utilities requirement[1,2]
  - Small area footprint
- **Ability to implement control strategies[4]**
  - Real-time feedback control, Model Predictive Control (MPC)
  - Enhanced process robustness
- **Advanced computational tools – process systems engineering[5]**

1. Seifert, T. et al. *Chem Eng Process* **2012,** *52*, 140-150.
2. Schaber, S. D et al. *Ind Eng Chem Res* **2011,** *50* (17), 10083-10092.
3. Plumb, K., *Chem Eng Res Des* **2005,** *83* (A6), 730-738.
4. Singh, R.; et al. *Int J of Pharm* **2012,** *438* (1-2), 307-26.
5. Gernaey, K. V. et al. *Comput Chem Eng* **2012,** *42*, 15-29.

Process Systems Engineering

- **Process modeling capabilities**
  - Supplement experimental work during process development[1]
  - Design and test control strategies
  - Flowsheet models[2], Discrete element method[3]
- **Process analysis**
  - Sensitivity analysis[4] – identify critical process parameters, control variables
  - Flexibility and feasibility analysis[5] – design space and process robustness
- **Process optimization**[6]
  - Determine optimal process design and operating conditions subject to product quality and process operating constraints



1. Gernaey, K. V. et al. *Comput Chem Eng* **2012,** *42*, 15-29.
2. Boukouvala, F et al. *J Pharm Innov* **2013,** *8* (1), 11-27.
3. Sarkar, A.; Wassgren, C. R.. *Powder Technology* **2012,** *221*, 325-336.
4. Rogers, A et al. *Ind Eng Chem Res* **2013**, 131015102838009.
5. Boukouvala, F.; Ierapetritou, M. G., *Comput Chem Eng* **2012,** *36*, 358-368.
6. Boukouvala, F.; Ierapetritou, M. In AIChE Annual Meeting, Pittsburgh, PA, AIChE: Pittsburgh, PA, 2012.

Challenges for a flowsheet model for solids

Critical material properties

- Lack of **universal** set throughout processes and industries
- Inherent **variability** in powder material properties & **distributed** parameters
- Lack of technology for **monitoring** desired material properties online

Critical process operating variables

- Lack of **correlation** between operating variables and material properties
- No **control** strategies

Modeling work

- Majority: Discrete Element Method (DEM) simulations→ computationally expensive
- In recent literature: plethora of experimental studies & empirical correlations of certain inputs/outputs & specific materials
- Dynamic reduced order models are needed:
  - First-principle based
  - Population balance models
  - Data based models

Werther, J., et al. *Computers & Chemical Engineering* **23**(11-12) 1773-1782
Boukouvala, F. et al. *Computers & Chemical Engineering*. **42**(11) 30-47

Ideal Development of a Pharmaceutical Process

Given a Formulation

↓

Characterize Powders using Universal Tests

↓

Evaluate Unit Operation Models using Powder Properties

↓

Create the Design Space for Individual Unit Ops

↓

Design the Process

↓

Build a Flowsheet Model

↓

Develop the Design Space of the Overall Process and **Optimize**

↓

Determine Operating Parameters and Control Strategies

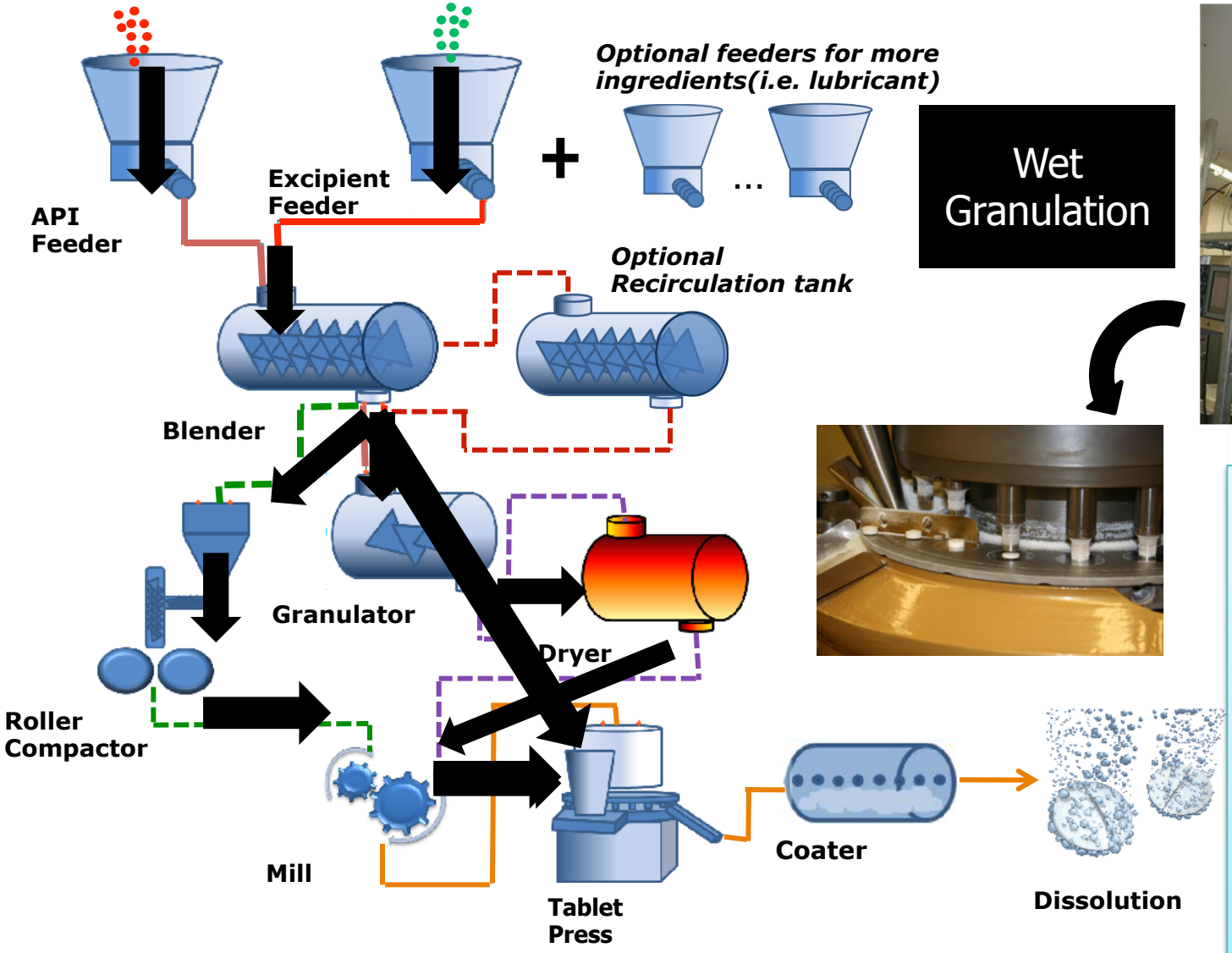
↓

Validate using Experimental Data

↓

Asses Process Sensitivities and Risks

Integrated Process Models



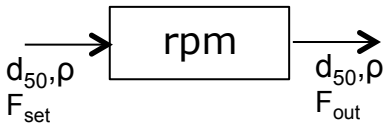
Continuous flexible **multipurpose** platform

- Process simulation
- Sensitivity analysis
- Design space evaluation
- Optimization

Unit Operation Models: Direct Compaction

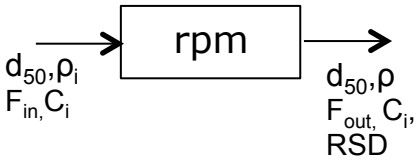
FEEDERS:

Model: Delay Differential Equation

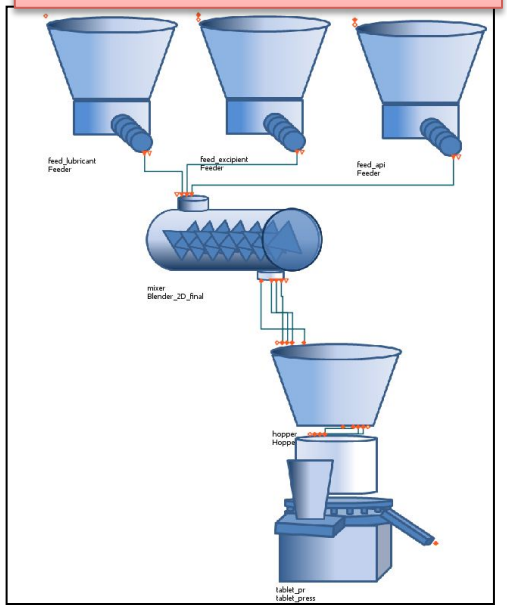


MIXER:

Model: Population Balance model

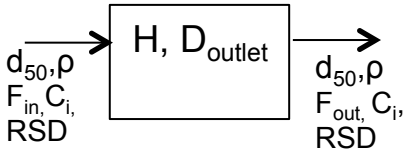


DIRECT COMPACTION



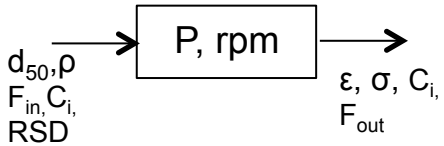
HOPPER:

Model: Mass flow buffer tank model



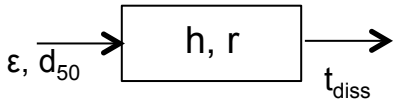
TABLET PRESS:

Model: Heckel equation & feed frame residence time model



DISSOLUTION:

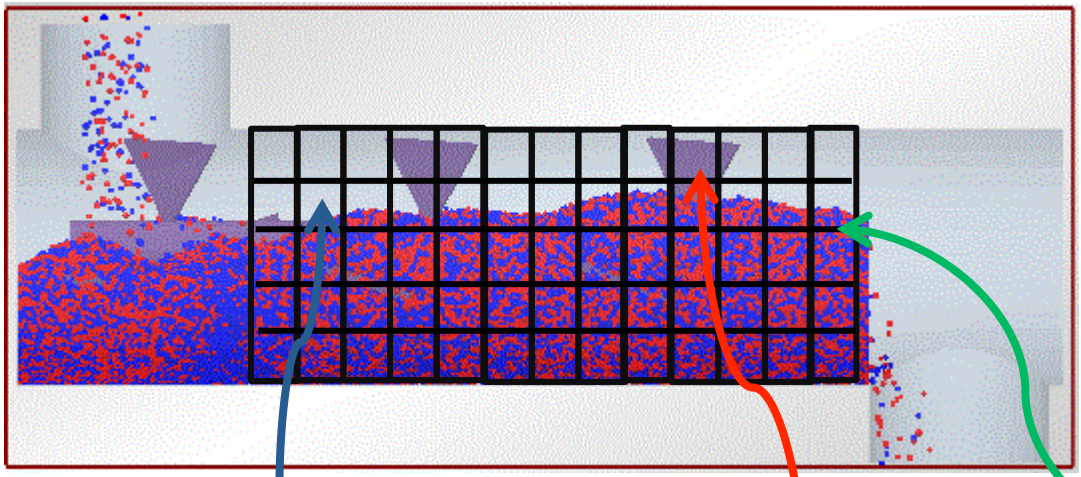
Model: Fick's second Law



- Individual unit operation models consist of a series of equations meant to describe process physics and dynamics
- Unit operation equations can be combined sequentially to represent entire manufacturing processes

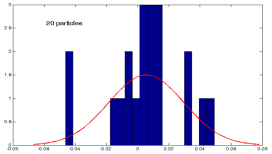
Latent Variable ROM based on DEM

- In CFD simulation: Discretize into finite elements→ solve set of equations for specific element→ calculate continuous variable values (T,P).
- In a DEM simulation→ discrete elements (particles)→ How do we extract information???
  - Discretize geometry and extract **average** information about number of particles inside each compartment. Consider "unreliable means" as **missing**



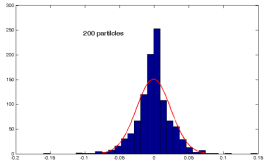
BUT how to discretize?
✓Dense enough to capture spatial variation
✓Coarse enough to have large number of particles inside each element

Few number of particles:
Consider as missing data
(impute)



Very few or no particles:
Set equal to zero

Large enough number of particles:
Use average value

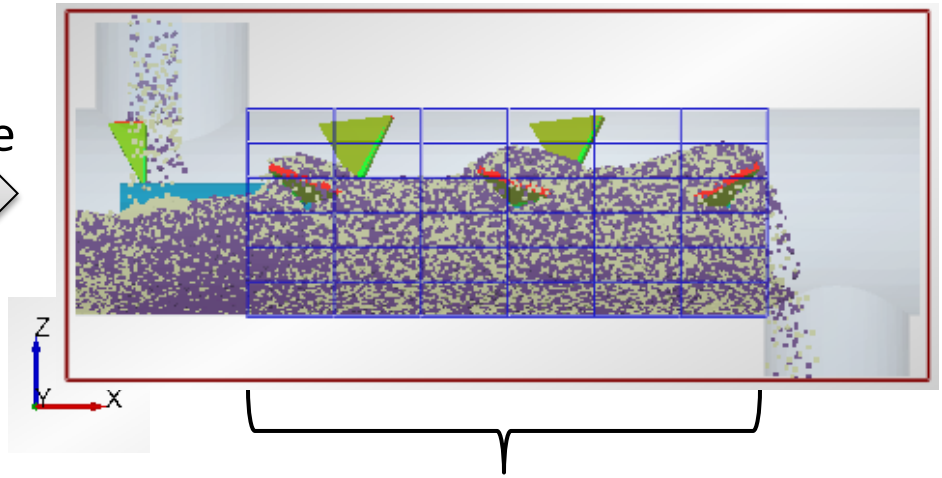


Discrete Element Reduced-Order Modeling Methodology

1. DOE – parameter variation
2. Discretize process geometry
3. Extract state data (*Z*)
4. Obtain response data (*Y*)
5. Pre-process state and response data

Input Space

$X \in \Re^{Nxn}$



State Space $Z \in \Re^{Nxp}$

Output Space

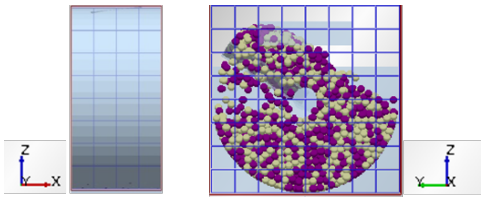
$Y \in \Re^{Nxm}$

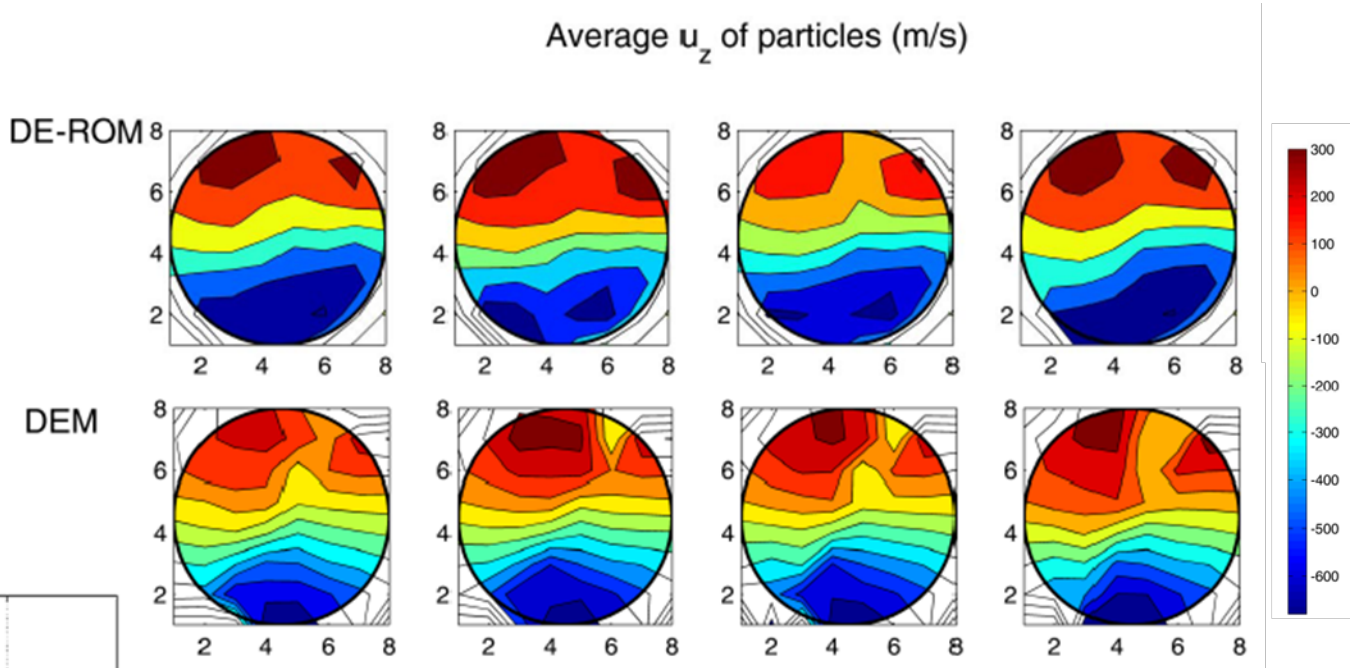
6. Reduce dimensionality of state data (PCA)
7. Develop a mapping between input space *(X)* and reduced state space *(PCA scores)*

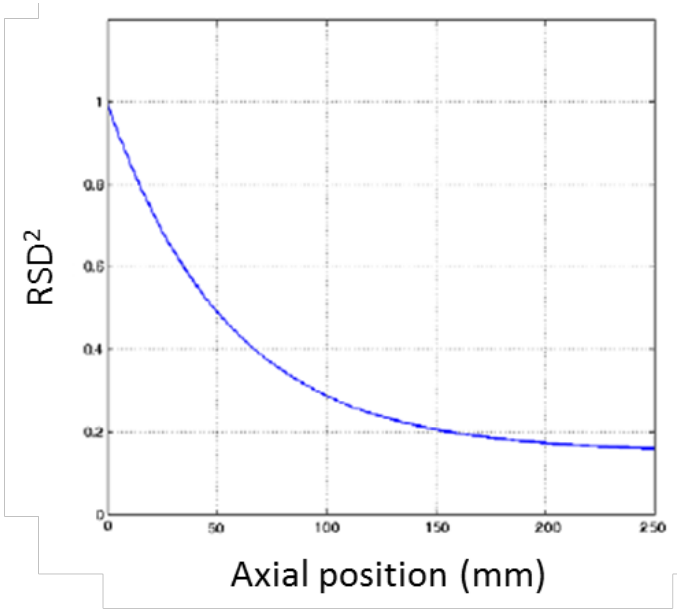
$$X \rightarrow T$$

8. Develop a mapping between input parameters *(X)* and output space *(Y)*

Steady State Case Study



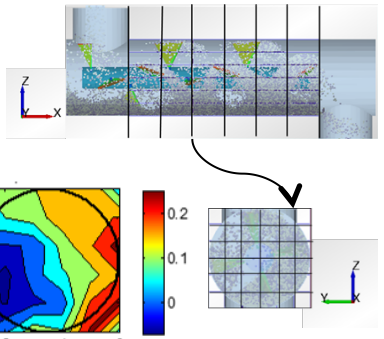




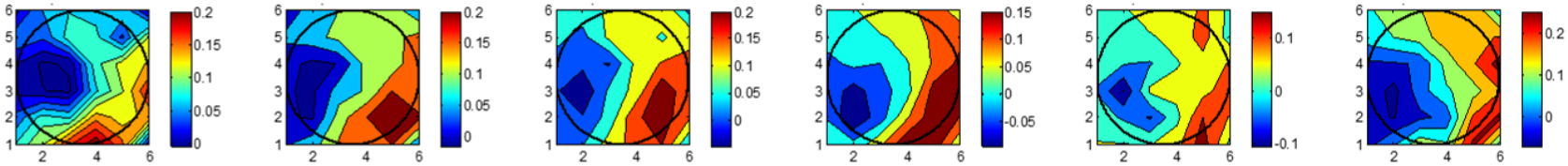
	Ux	Uy	Uz
% MSE	28%	19%	21%

Prediction error for RSD (1 case): 1%

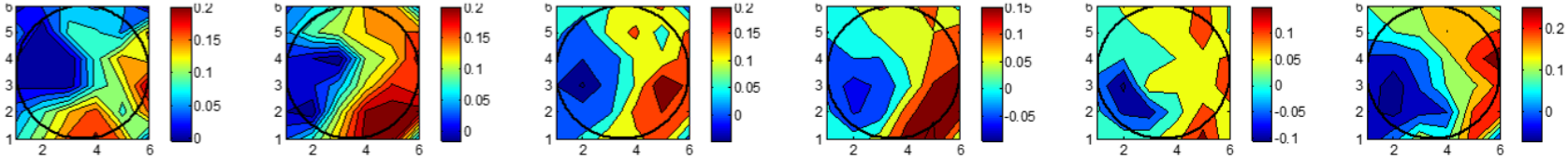
Dynamic Case Study



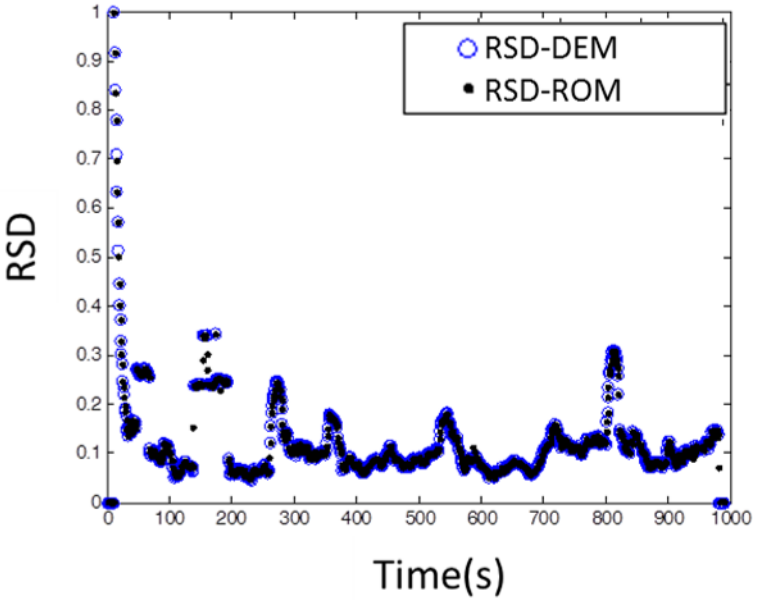
Velocity predicted by ROM



Velocity obtained from DEM



Predicted u_x vs. u_x obtained from DEM 23 seconds after change from 160 to 250 rpms



- Velocity and RSD predictions have good accuracy
- Velocity prediction can be used directly in PBM model
- Prediction of RSD can be used for surrogate-based modeling or sensitivity analysis applications

	Ux	Uy	Uz	RSD
% MSE	0.55%	0.96%	1.13%	1.07%

DESIGN SPACE

How much **uncertainty** can a process tolerate?

FDA's "Design Space" vs. PSE's Process Flexibility

Design Space

- *"..The multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality..."*

J Pharm Innov (2008) 3:79–87
DOI 10.1007/s12247-008-9034-2

PRODUCT QUALITY LIFECYCLE IMPLEMENTATION (PQLI) INNOVATIONS

PQLI Design Space

John Lepore · James Spavins

Published online: 17 May 2008
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Abstract This paper describes progress made by the Design Space Task Team within the ISPE Product Quality Lifecycle Implementation (PQLI) initiative. It is intended to provide approaches to the rational development of Design Space, as well as background on Design Space, its historical origins and how it fits within the wider PQLI initiative. The focus of this paper is on the technical elements of Design Space development.

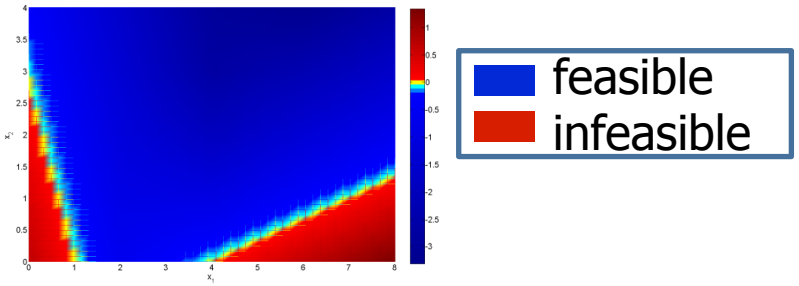
The general engineering and technical design processes discussed here have been widely used by many types of industries in addition to the pharmaceutical industry (including aerospace, food, computer, civil and mechanical engineering and medical devices) and the use of risk based analyses to determine design constraints and then determine appropriate controls is a foundational process to the advancement of science and technology. Accordingly, it is appropriate for the pharmaceutical industry to expand the

- *No clearly defined method about how to identify a process DS*[3]

?

Flexibility

- *"Flexibility of a process is defined as its capability to maintain **feasible operation** for a **range of uncertain conditions** that may be encountered during operation"*[1,2]



$$\max_{d,z,x} / \min \; P(d,z,x,\theta)$$

$$s.t.$$

$$h(d,z,x,\theta) = 0$$

$$g(d,z,x,\theta) \le 0$$

Vast literature on formulation of optimization problems which to find max acceptable deviations under uncertainty

[3] *Lepore, J., & Spavins, J. Journal of Pharmaceutical Innovation, 2008*
[4] *Boukouvala et. al, Journal of Pharmaceutical Innovation, 2010*

[1] *Halemane et al. (1983), AIChE Journal.*
[2] *Floudas et al. (2001), IECR*

Black-box Process Feasibility

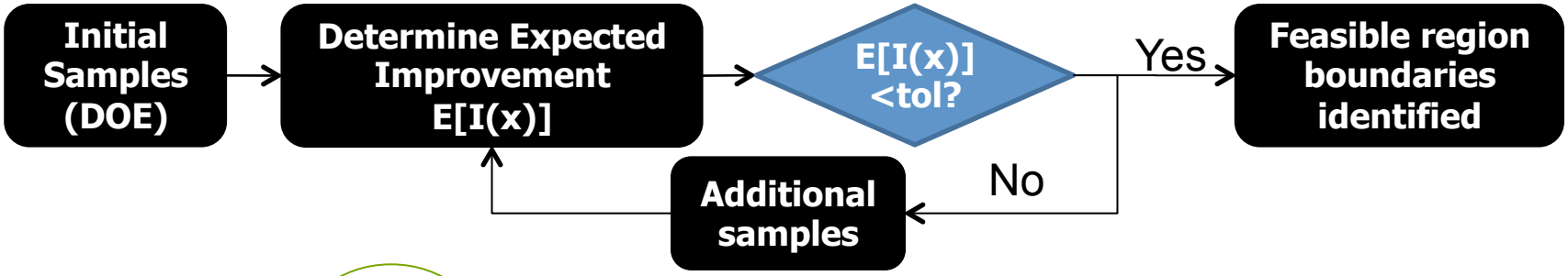
Goal is to locate boundaries of feasible operation:

- *When multiple constraints are present*
- *Closed form expression for constraints may not be available*
- *When discrete designs are possible*

Feasibility function – process is feasible when u≤0

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

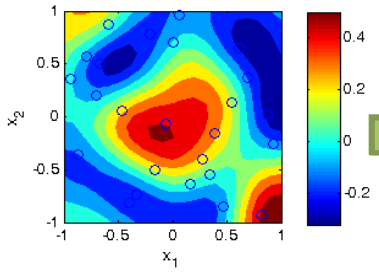
$$s.t. g_j(d,z,\theta) \le u, \quad j \in J$$

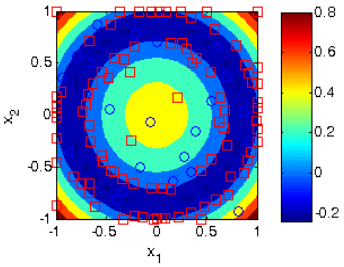


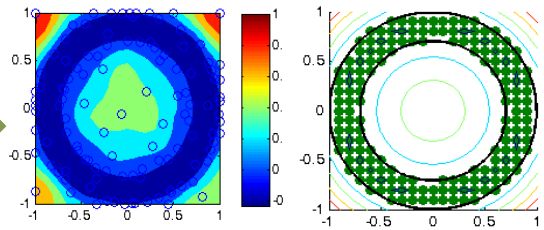
$$E[I(x)]_{feas} = s\phi\left(\frac{0 - y_{pred}}{s}\right)$$

Probability of $u=0$: boundary

Model uncertainty







Initial sampling

Refined sampling

Predicted feasible region

$$x_1^2 + x_2^2 \le 1^2$$

$$\vdash x_1^2 + x_2^2 \ge 0.5^2$$

$$\Downarrow$$

$$\max \; u$$

$$x_1^2 + x_2^2 - 0.5^2 \le u$$

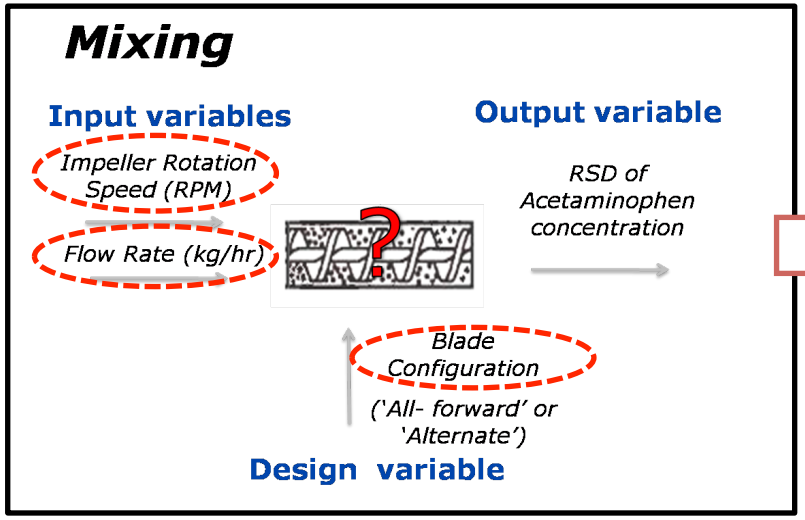
$$x_1^2 + x_2^2 - 1^2 \le u$$

$$0.5^2 - x_1^2 - x_2^2 \le u$$

[1]Jones et al. 1998

[2]Boukouvala et. al, Computers and Chemical Engineering, (36), 2012

Design Space of Continuous blender



We define feasibility:

- Since we want to minimize the output RSD, we set a maximum threshold value that can be tolerated (RSD_{max})
  - *If the predicted output is lower, it's feasible*
  - *If the predicted output is higher, it's infeasible*

Introduce binary variables for each design (m) and form a MINLP problem:

$$\min/\max \sum_i^m y_i x_i$$

$$s.t. \sum_{i=1}^m y_i = 1$$

$$y_i \in \{0,1\}^m$$

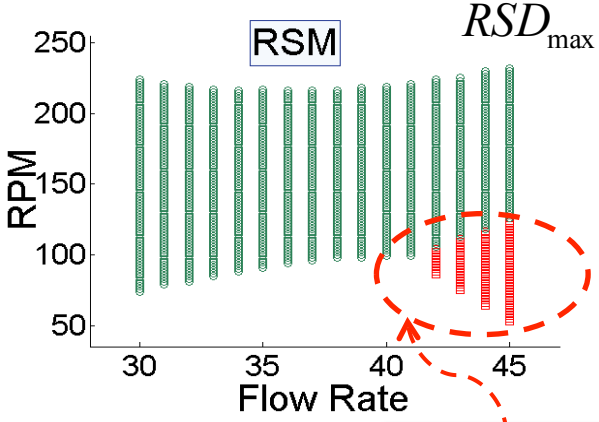
$$z_j^{(i)lo} \le z_j^{(i)} \le z_j^{(i)up} \qquad i = 1...m, j = 1...k$$

Where:
i: design
m: total number designs
n: number of input variables
β_j: *RSM coefficients*
z_j: *input variables*
x_i: response surface produced for each design *i*

Constraint to make sure only one design is chosen

$$x_i = \beta_o + \sum_j^n \beta_j z_j + \sum_{j<k}^n \beta_{jk} z_j z_k + \sum_j^n \beta_{jj} z_j^2$$

$RSD_{max} = 0.1$

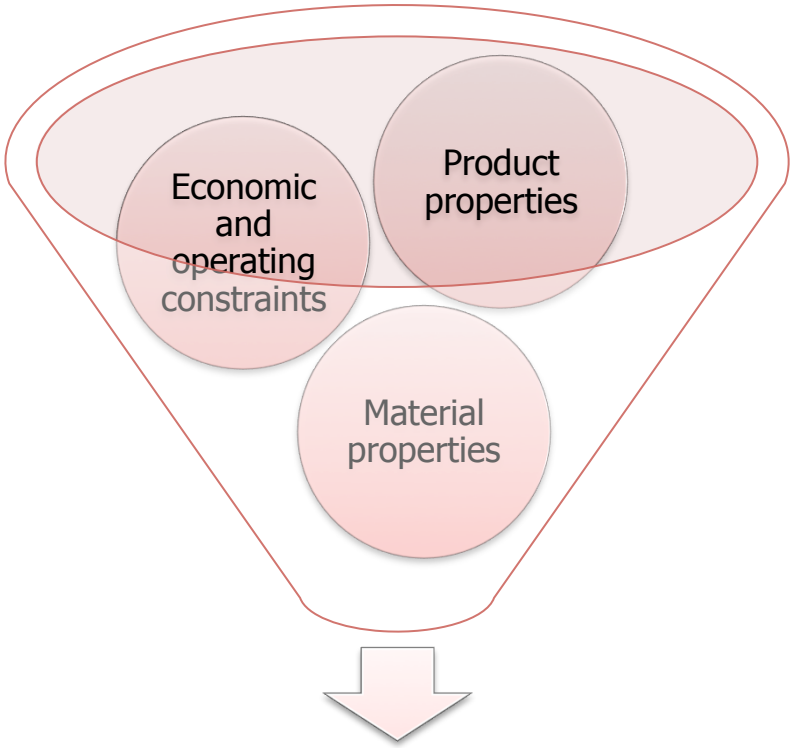


At high Flow Rates, low RPM→ use forward blade configuration

Boukouvala et. Al, Journal of Pharmaceutical Innovation, 2010

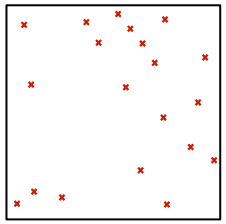
OPTIMIZATION

Inverse problem:
Based on desired properties, what should the design of the flowsheet be?



Surrogate Based Optimization: Proposed Methodology

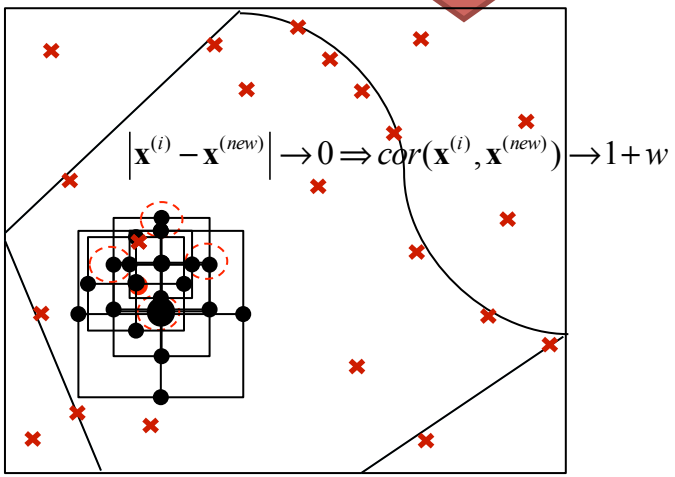
- Combination of global search (initially) with local search (final stage)
- Incorporation of a black-box feasibility stage to identify form of feasible region
- Final local trust-region approach by allowing multiple starting points if clusters of promising feasible points is identified
- Alleviation of noise effects through a stochastic kriging model
  - heteroscedastic variance case



Initially sample entire region

$$E[I(x)]_{feas} = s\phi\left(\frac{0-y_{pred}}{s}\right)$$

Refine in boundary regions to map feasible region



Boukouvala, F., Ierapetritou, M AIChE Journal. Volume 60, Issue 7, pages 2462–2474, July 2014.

Process Optimization

- **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
- Leads to an optimization of an expensive-to-evaluate model, with complex constraints and uncertainty: *SURROGATE SIMULATION-BASED OPTIMIZATION*

Step 1: Formulate objective and constraints

Step 2: Flowsheet simulations for different conditions based on DOE

Step 3: Build surrogate model and optimize. Approximate uncertainty

$$\min_{F_{total}, rpm_{mixer}, C_{MgSt}, RL, V_{hopper}, V_{mixer}, P_{compr}} C_{equipment} + C_{operation} + C_{waste}$$

s.t.

$$F_{total}^{lo} \le F_{total} \le F_{total}^{up}$$

$$rpm_{mixer}^{lo} \le rpm_{mixer} \le rpm_{mixer}^{up}$$

$$0.99 C_{MgSt}^{nominal} \le C_{MgSt} \le 1.01 C_{MgSt}^{nominal}$$

$$0.1 \le RL \le 0.6$$

$$V_{hopper}^{lo} \le V_{hopper} \le V_{hopper}^{up}$$

$$V_{mixer}^{lo} \le V_{mixer} \le V_{mixer}^{up}$$

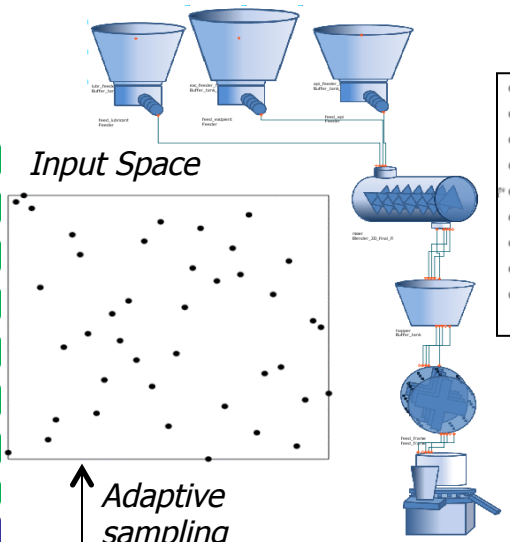
$$P_{compr}^{lo} \le P_{compr} \le P_{compr}^{up}$$

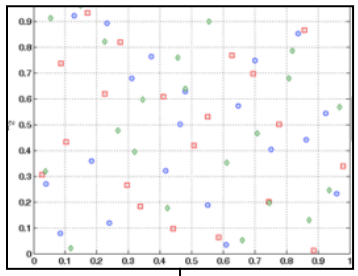
$$hardness^{lo} \le hardness \le hardness^{up}$$

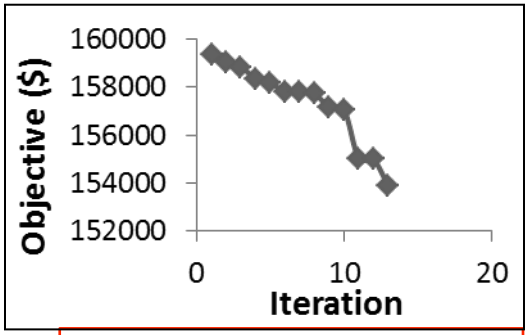
$$\varepsilon^{lo} \le \varepsilon \le \varepsilon^{up}$$

$$t_{diss}^{lo} \le t_{diss} \le t_{diss}^{up}$$

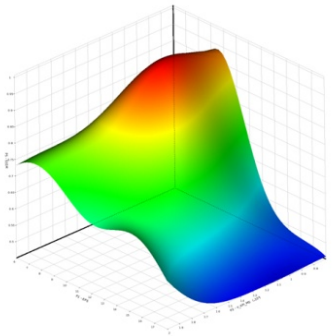
$$Tablet\_prod_{\min} \ge Tablet\_prod_{diss}$$

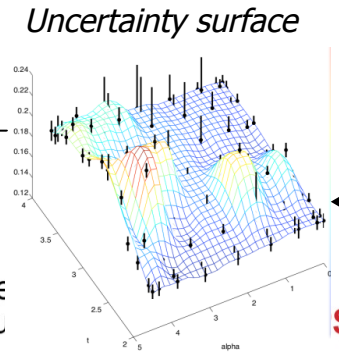






Optimal cost: $ 153892





Variable	Optimum
F_{total}(kg/h)	54
Mixer rpm	102
C_{MgSt} (w/w)	0.0092
RL(%)	54
V_{hopper} (m^3)	0.03
P_{comp}(Pa)	1042

Conclusions and future goals

- As the industry is moving to advanced manufacturing solutions, process intensification will be in the center of attention.
- There is a need for predictive models for optimization of process design and operations
- Reduced order modeling techniques are needed, due to the complexity of models necessary for complex pharmaceutical processes
- Technologies are transferrable to other powder processing industries such as food, consumer goods.
- As flowsheet models are being used, flowsheet synthesis framework will be developed to design process for any new formulation

Process Modeling and Optimization of Biorefinery

Zhaojia Lin

Motivation: Exhausting petroleum resources have prompted the development of sustainable *biorefinery* to produce *biofuel and bio-chemicals* from biomass feedstocks.

Objectives:

- Perform techno-economic analysis on the productions of biobased chemicals and estimate the minimum cost of the products
- Apply life cycle assessment to evaluate the environmental impacts
- Implement process synthesis and optimization to achieve an optimal process diagram

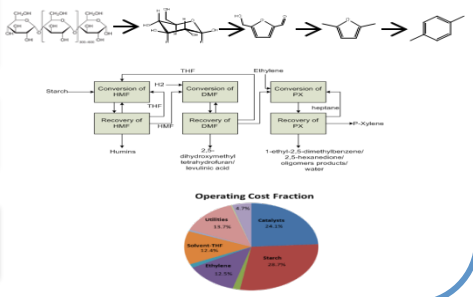
Accomplishments:

Techno-Economic Analysis

Experimental Data

Process Design

Discounted Cash Flow



Life Cycle Assessment

Aspen plus simulation

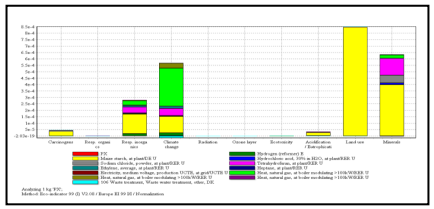
LCA software

Inventory

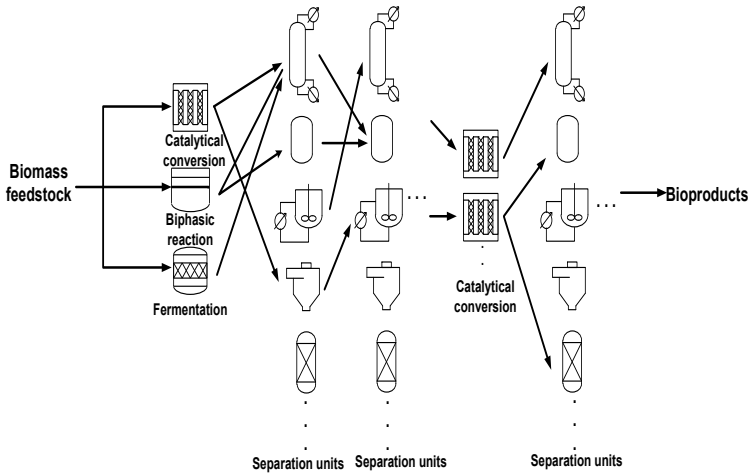
Energy flow

HEN

Aspen Energy Analyzer



Process Synthesis and Optimization



- Black-Box optimization and synthesis

Acknowledgements :

Funding provided by the ERC (NSF-0504497, NSF-ECC 0540855)

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