

**PURDUE**

ENGINEERING

CHEMICAL ENGINEERING

# A Holistic Approach for the Model-based Control of Crystal Size, Shape and Purity in Integrated Continuous Crystallization – Wet Milling – Classification System

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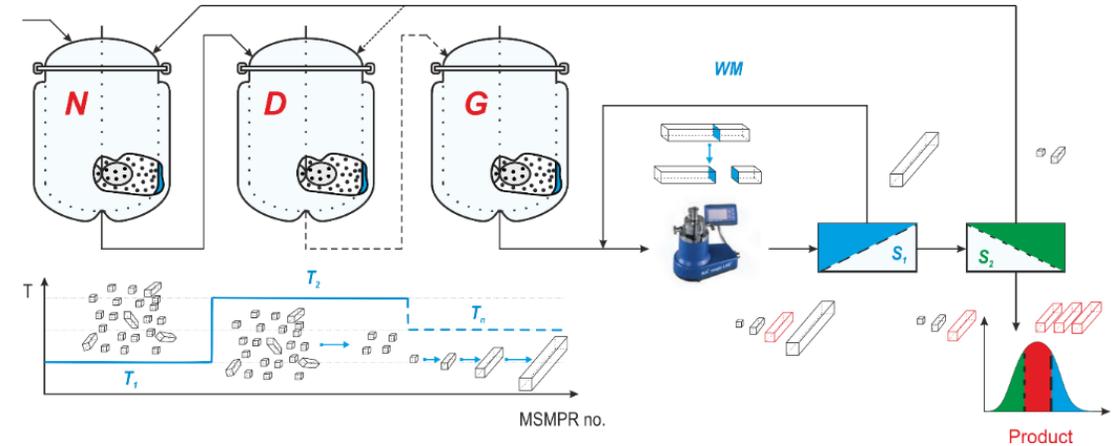
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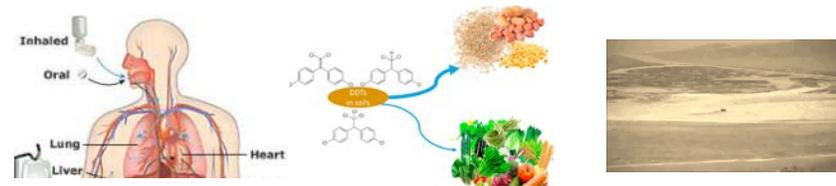
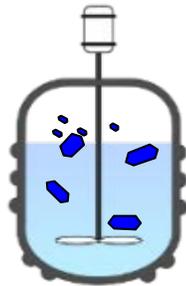
# Presentation RoadMap

- Introduction
  - Background
  - Motivation
  - Previous accomplishments and current work
- Models developed for all units of operations (crystallizer, wet mill, classifier)
  - Design Space for wet mill and classifier
- Design Space
  - Comparing the cascade of MSMPRs with addition of different units
  - Dynamic design space
- Application of crystallizer network
  - Scale-up
- Short Term Future Plans



# Project Objective

- Many technology and economic drivers
- 70% of all solid products & 90% of APIs involve a crystallization step
- Control of crystalline properties (CSD, shape, polymorphic form, purity, etc.) important
  - Product effectiveness (dissolution, bio-availability, tablet stability)
  - Efficient downstream operations (filtration, drying)



Crystallization

Downstream processes

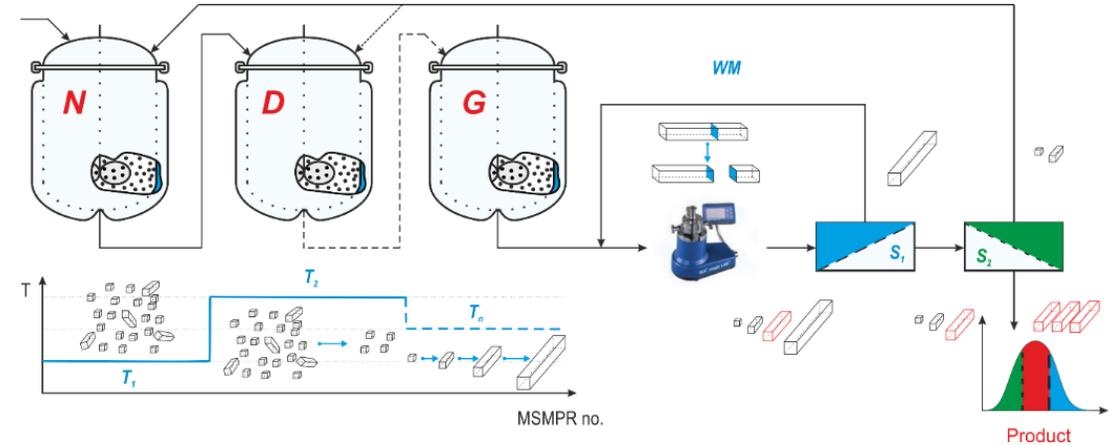
Final product

**Control of crystal properties is critical for product functionality and operational efficiency**



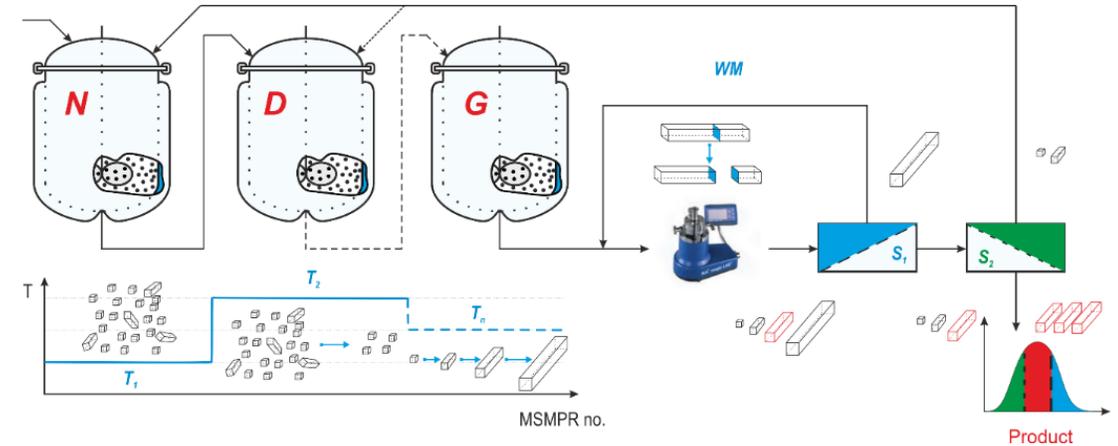
# In Previous Years...

- Detailed 1D and 2D model development for crystallizers
  - Nucleation, growth, agglomeration, breakage
- Detailed 1D and 2D model development for wet mill
  - Immersion, external
- 1D parameter estimation and soft sensor development



# In Previous Years...

- Detailed 1D and 2D model development for crystallizers
  - Nucleation, growth, agglomeration, breakage
- Detailed 1D and 2D model development for wet mill
  - Immersion, continuous
- 1D parameter estimation and soft sensor development



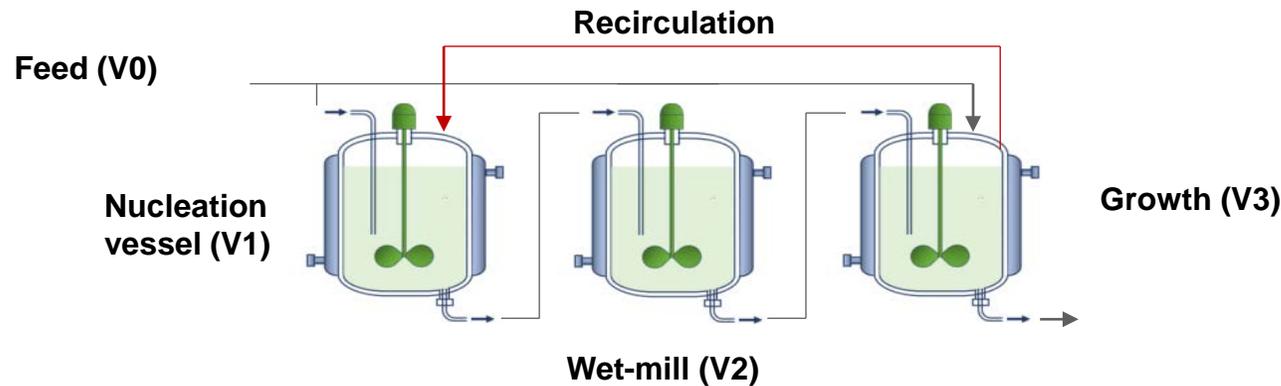
## This Year...

- Development of integrated system model:
  - A cascade of multi-stage continuous crystallizers connected to a downstream wet mill and classification system with recirculation
- Effect of recycle on crystal size, **purity** and dynamics (startup time)
- Finding an attainable region for crystal quality attributes
- Creating a flexible framework to generalize the system to other potential applications (e.g. scale-up)



# MSMPR Network

- Model-equations populated based on adjacency matrices that defines the connectivity
- The active crystallization mechanisms set for each MSMPR
- The vessels can represent any unit i.e. crystallizer, wet mill, classifier etc.

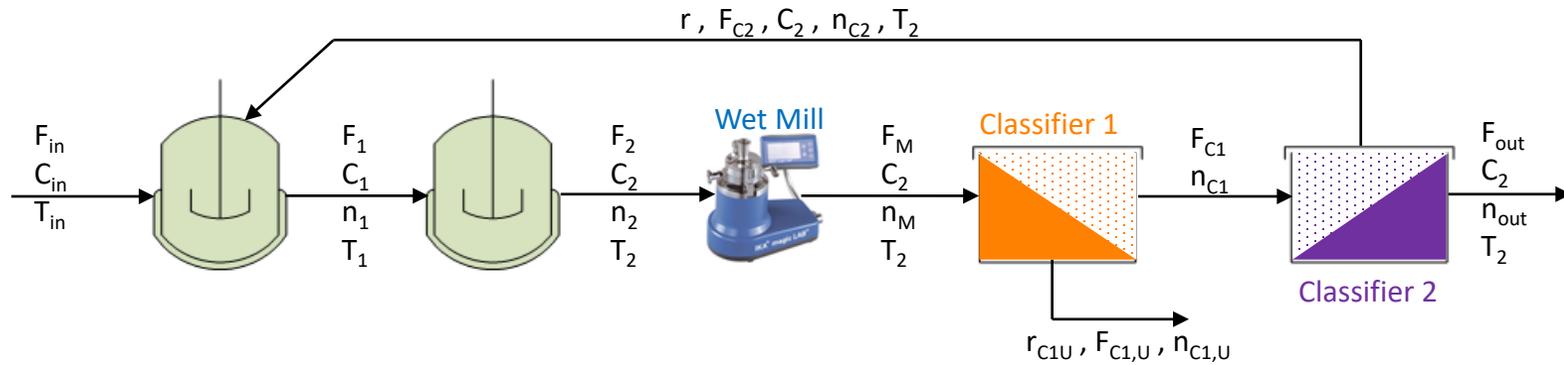


	V0	V1	V2	V3	
V0	0	1	0	1	▪ Example: definition of connectivity between the MSMPRs
V1	0	0	1	0	▪ "1" in a cell means that there is a flux <u>from</u> the crystallizer in the given line <u>to</u> the crystallizer of the given column
V2	0	0	0	1	▪ Similar adjacency matrices are applicable for the definition of other operating conditions (e.g. flowrates)
V3	0	1	0	0	

# Connectivity Flow Matrix for our integrated system

- Connectivity matrix for flow rates used in population balance equations

	$V_{in}$	Crys. 1	Crys. 2	WM	Class. 1	Class. 2
$V_{in}$	0	$F_{in}$	0	0	0	0
Crys. 1	0	0	$F_1$	0	0	0
Crys. 2	0	0	0	$F_2$	0	0
WM	0	0	0	0	$F_M$	0
Class. 1	0	0	0	0	0	$F_{C1}$
Class. 2	0	$F_{C2}$	0	0	0	0

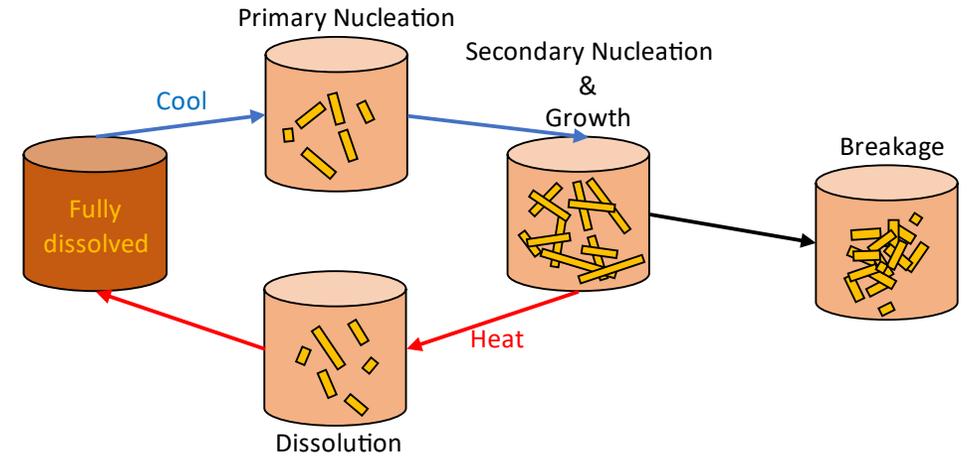


- The column for each vessel represents the inlet flows into that vessel
- The row for each vessel represents the outlet flows



# Mechanisms considered in the system

- Primary nucleation
- Secondary nucleation
- Growth
- Dissolution
- Breakage in wet mill



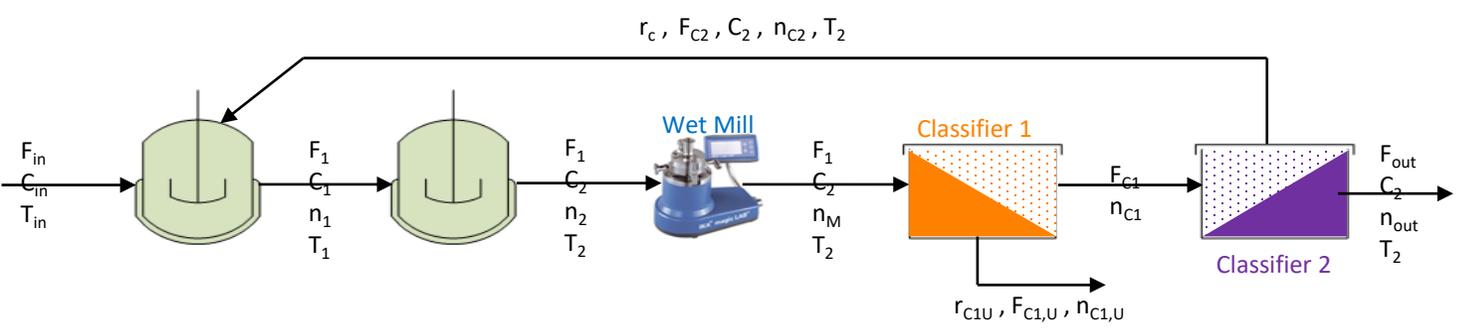
- Population Balance model is written in respect to the mechanism occurring + inlet and outlet flows using the connectivity matrix:

$$\frac{dn_i}{dt} = \text{mechanism} + \text{column}_i(FM) * \mathbf{n} - \text{row}_i(FM) * \mathbf{n}$$

$$\frac{dc_i}{dt} = \text{mechanism} + \text{column}_i(FM) * \mathbf{c} - \text{row}_i(FM) * \mathbf{c}$$

$$\mathbf{n} = \begin{bmatrix} n_{in} \\ n_1 \\ n_2 \\ n_M \\ n_{c1} \\ n_{c2} \end{bmatrix} \quad \mathbf{c} = \begin{bmatrix} c_{in} \\ c_1 \\ c_2 \\ c_2 \\ c_2 \end{bmatrix}$$

# Impurity Modeling



At steady state, once thermodynamics equilibrium is reached:  
Mass balance for impurity is written as

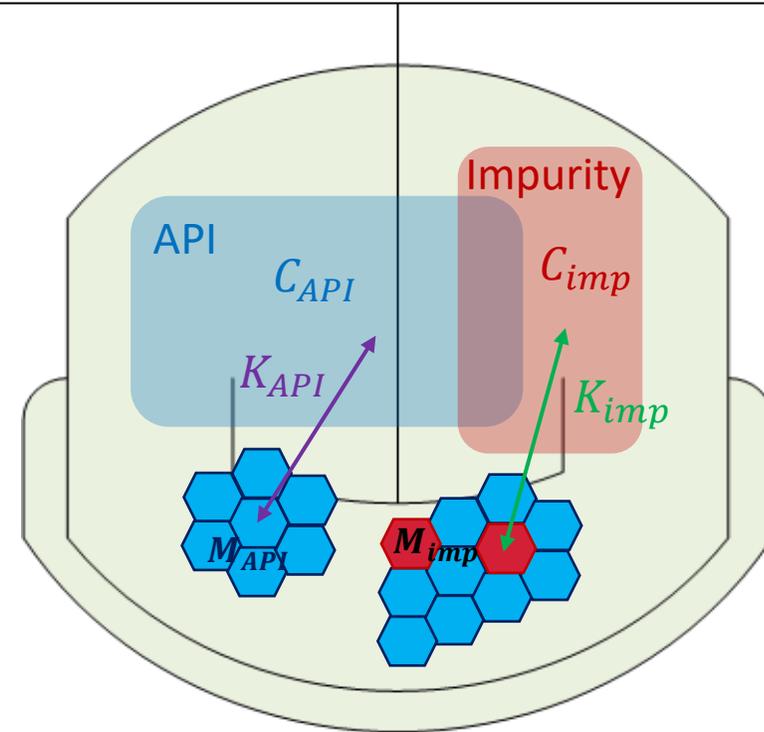
$C_i$  = concentration of liquid phase (kg/m<sup>3</sup> soln)  
 $M_i$  = concentration of solid phase (kg/m<sup>3</sup> soln)

- $F_{in}C_{imp,in} + F_{C2}C_{imp,2} + F_{C2}M_{imp,C2} - F_1C_{imp,1} - F_1M_{imp,1} = 0$
- $F_1C_{imp,1} + F_1M_{imp,1} - F_2C_{imp,2} - F_2M_{imp,2} = 0$

$$\alpha_i = \frac{K_{imp,i}}{K_{API,i}} \quad K_{imp,i} = \frac{M_{imp,i}}{C_{imp,i}} \quad K_{API,i} = \frac{M_i}{C_i}$$

$$\rightarrow M_{imp,i} = \alpha_i K_{API,i} C_{imp,i}$$

$\alpha$  : partition coefficient  
K : relates solid phase to liquid phase



# Classifiers

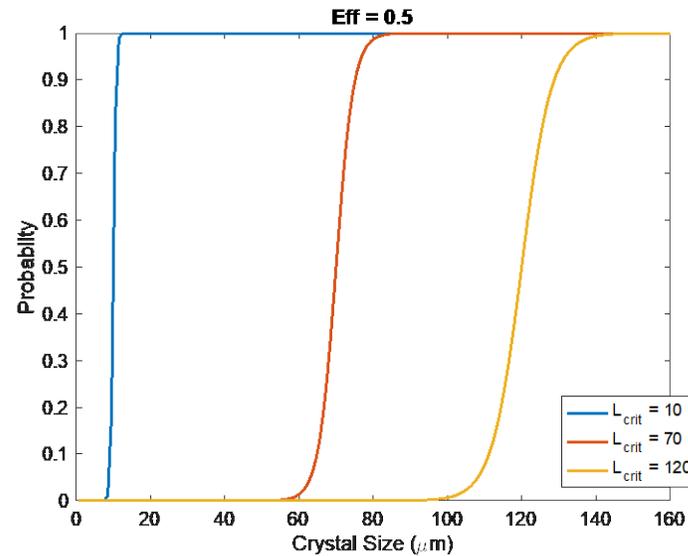
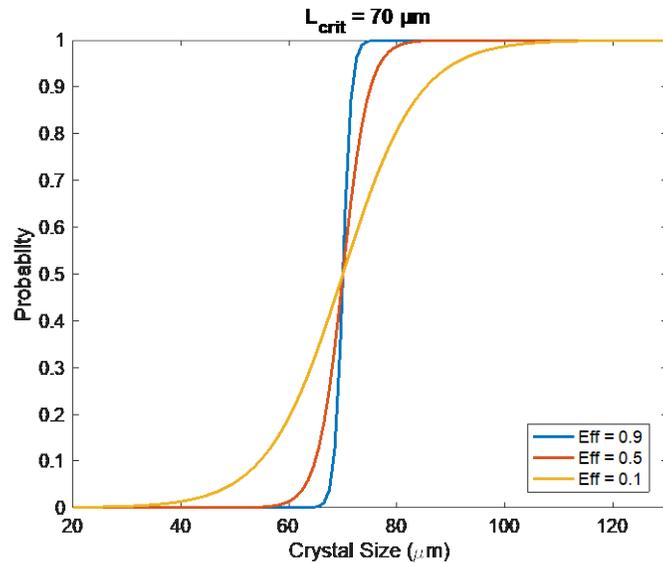
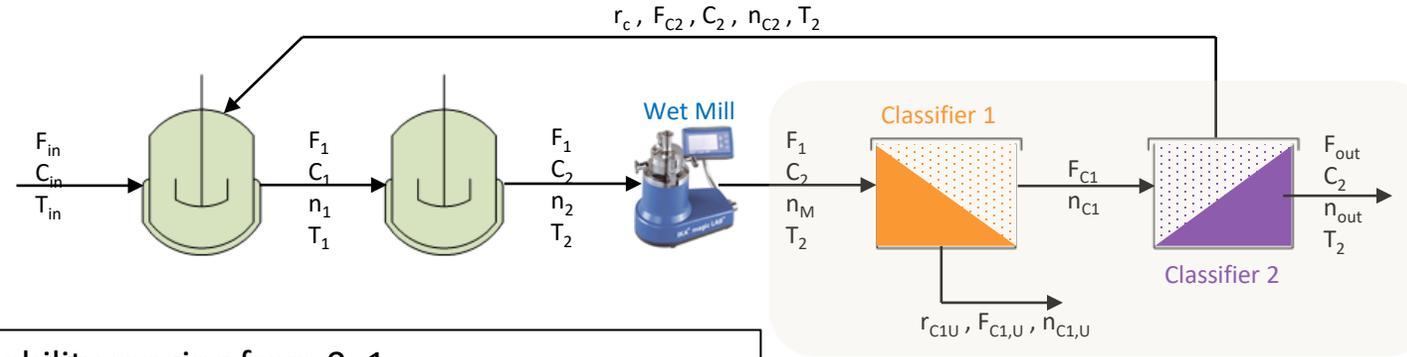
## Lynch and Rao's Model

- $S = \frac{e^{EX} - 1}{e^{EX} + e^{E-2}}$

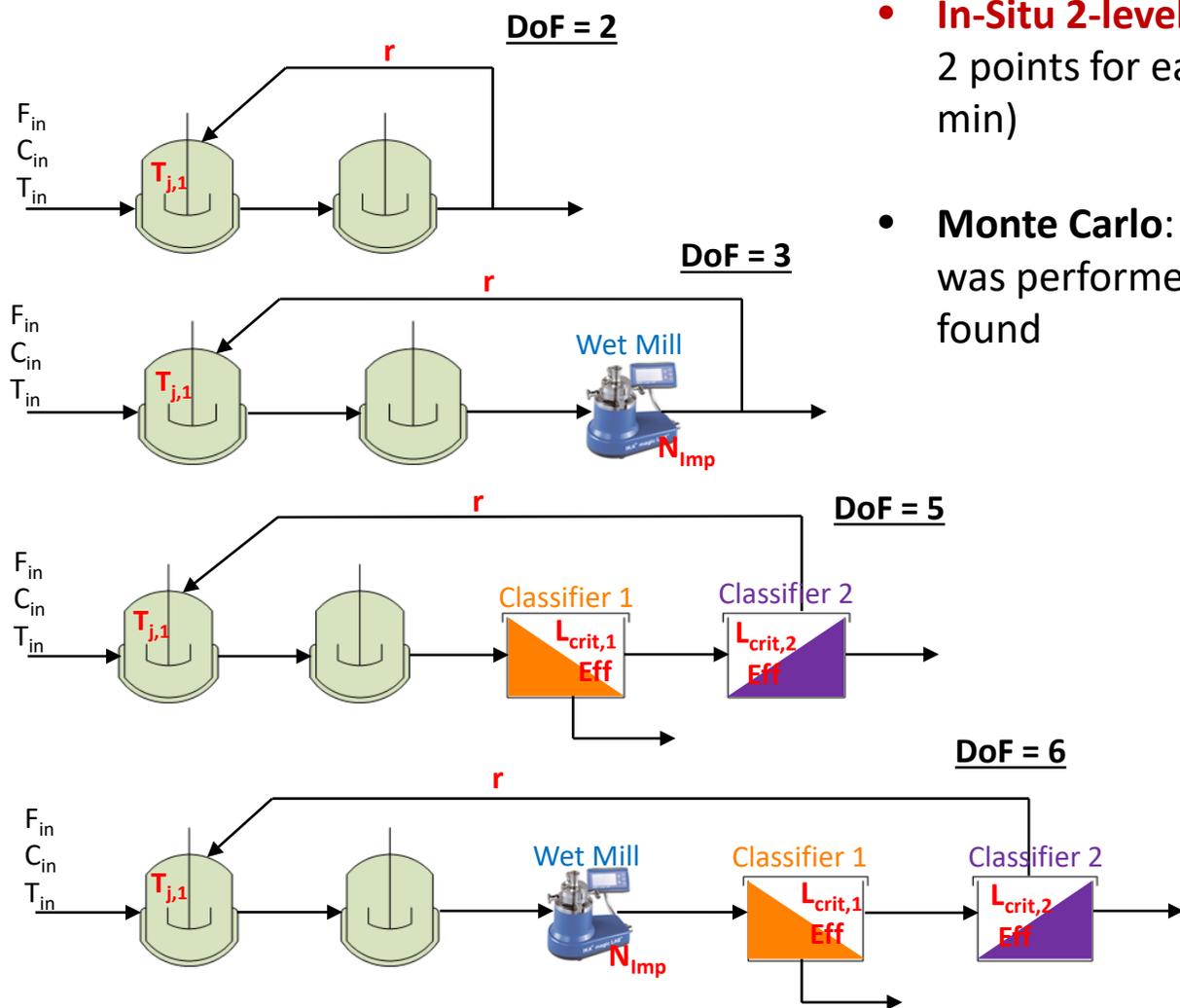
U: underflow  
O: overflow

- $n_U = S n_{in}$
- $F_{in} n_{in} = F_U n_U + F_O n_O$

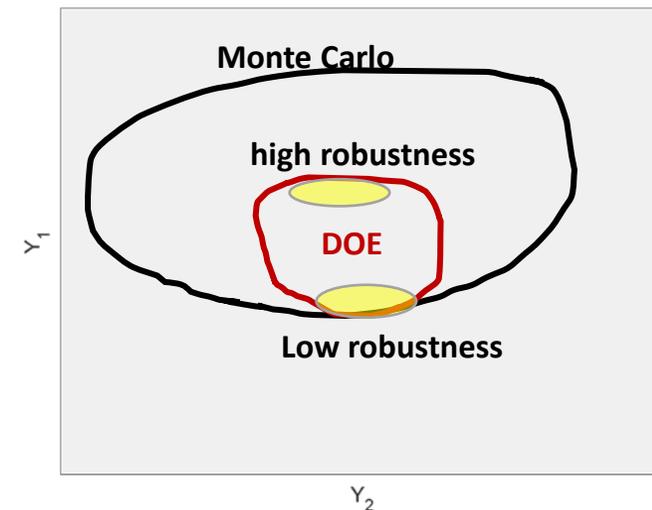
S: probability ranging from 0–1  
X: normalized size distribution  $X = \frac{L}{L_{crit}}$   
E: model parameter measuring sharpness of separation (classification efficiency)



# System Setups



- **In-Situ 2-level Design of Experiment (DOE):** 2 points for each variable was chosen (max, min)
- **Monte Carlo:** Detailed sensitivity analysis was performed and attainable region was found



## Operating Variables

- $10^{\circ}\text{C} \leq T_{j,1} \leq 40^{\circ}\text{C}$
- $5000 \leq N_{imp} \leq 20000$       WM impeller speed
- $0 \leq r \leq 0.9$
- $0.1 \leq E_1 = E_2 \leq 0.9$       Classifier Efficiency
- $100\mu\text{m} \leq L_{crit,1} \leq 180\mu\text{m}$
- $10\mu\text{m} \leq L_{crit,2} \leq 90\mu\text{m}$       } Classifier Critical Length

# Design Space Figures – DOE vs. Monte Carlo

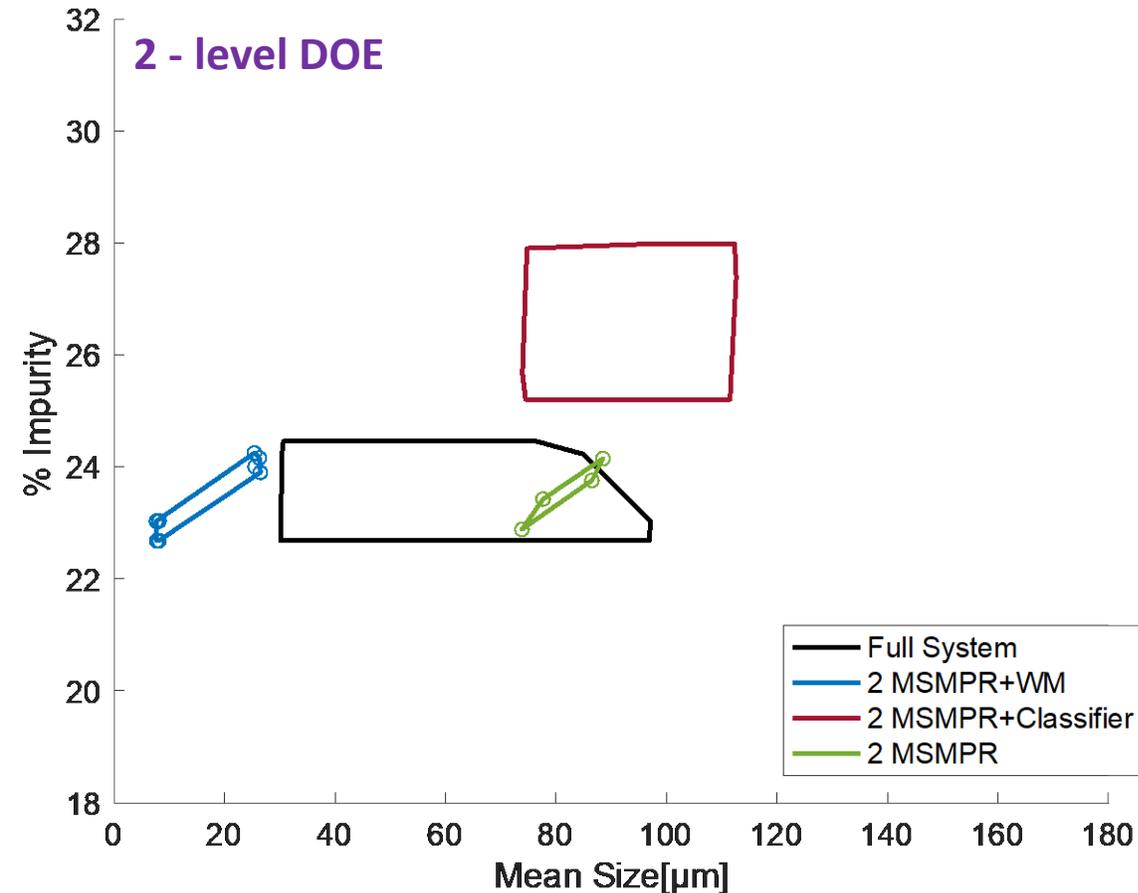
Full Sys :  $2^6 = 64$  points (experiments)

2MSMPR+Classifier:  $2^5 = 32$  points

2MSMPR+WM:  $2^3 = 8$  points

2 MSMPR :  $2^2 = 4$  points

2 - level DOE



The scatter points shown are found from DOE

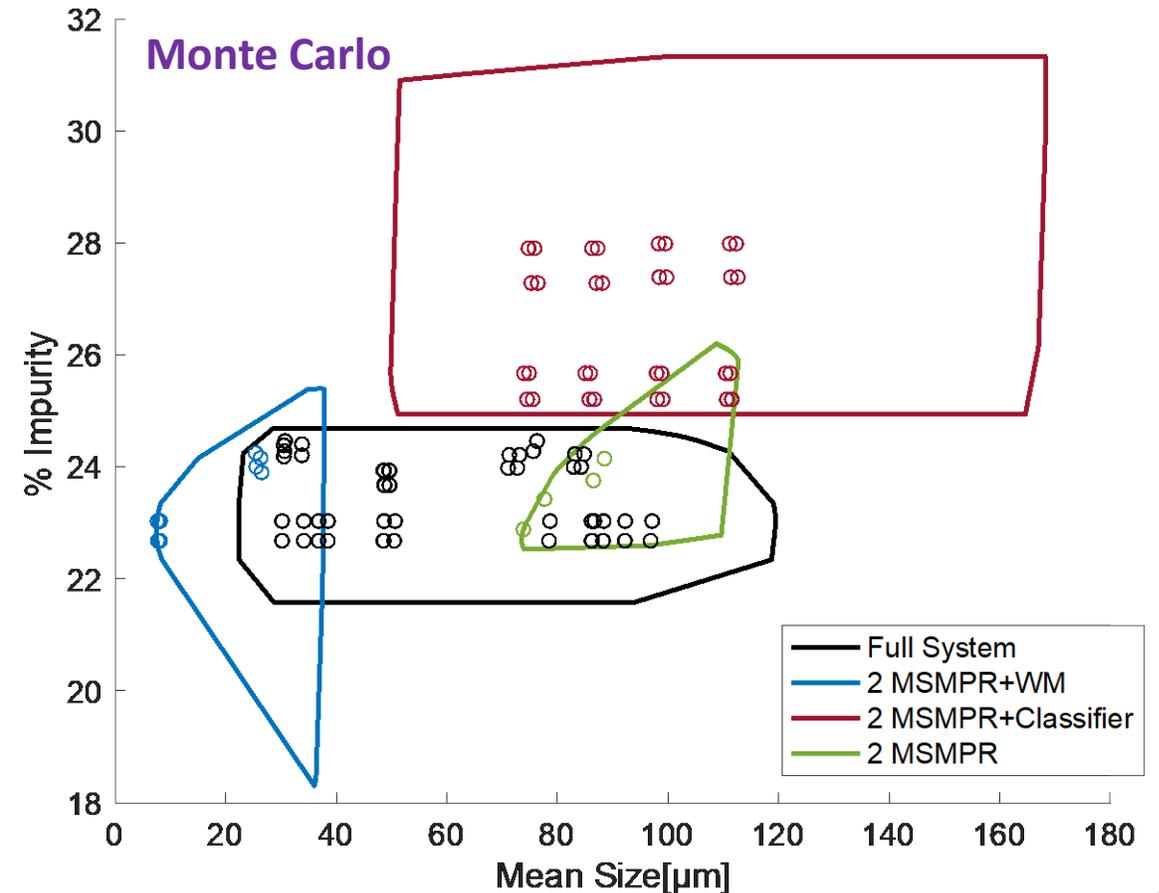
Full Sys : 10,500 points

2MSMPR+Classifier: 6,300 points

2MSMPR+WM: 420 points

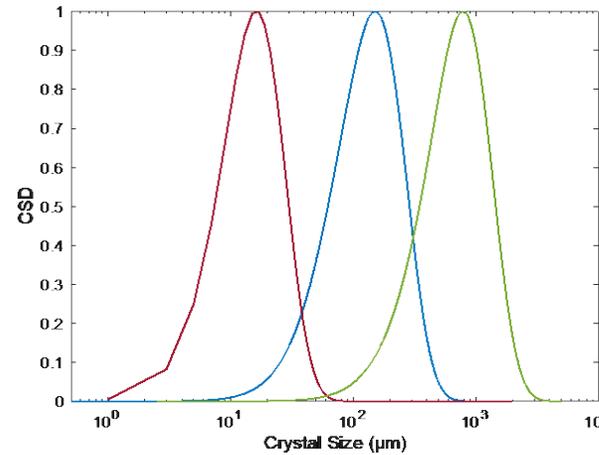
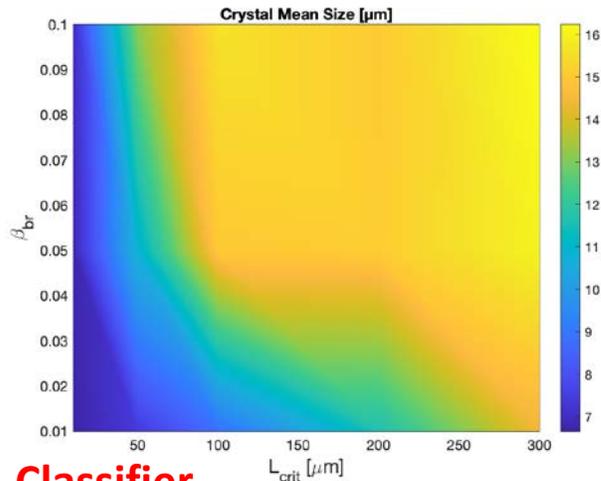
2 MSMPR : 160 points

Monte Carlo

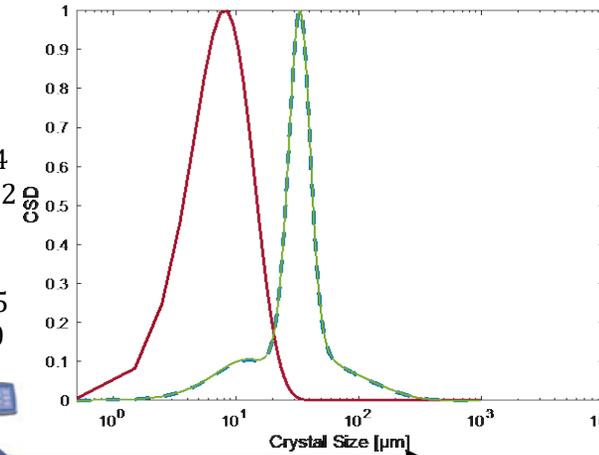


# Effect of each unit added to the system

## Wet Mill

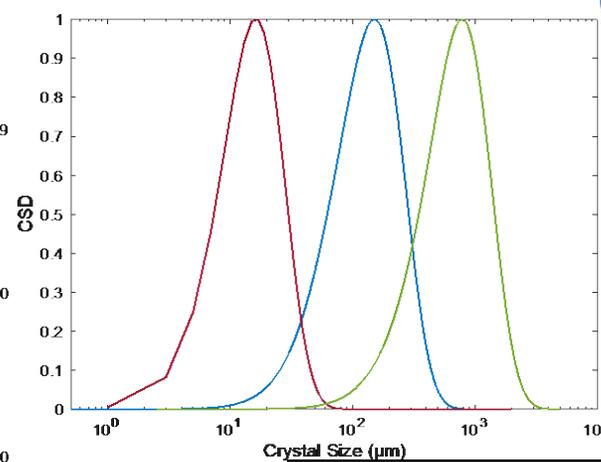
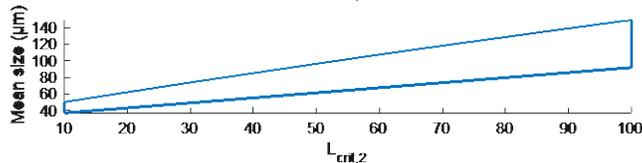
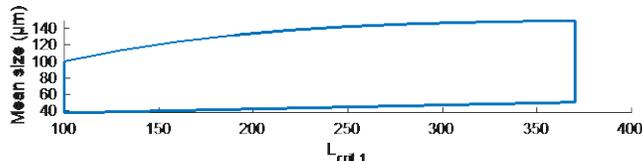
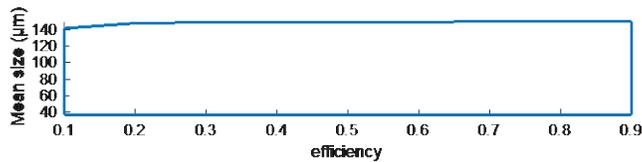


$$\begin{aligned}
 k_a &= 1E-4 \\
 k_{br} &= 1E-2 \\
 N_{Imp} &= 15,000 \\
 \beta_{br} &= 0.05 \\
 L_{crit} &= 50
 \end{aligned}$$

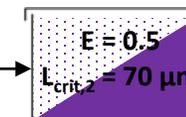
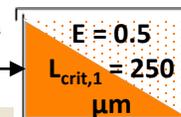
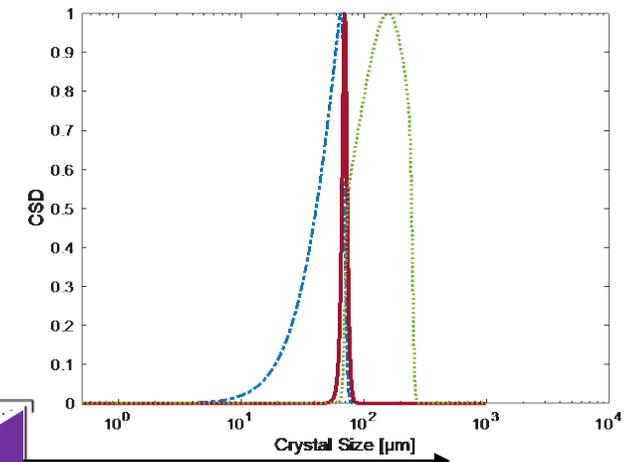


v.b. D <sub>50</sub> In (μm)	v.b. D <sub>50</sub> Out (μm)
10.80	10.75
204.20	69.16
808.48	70.15

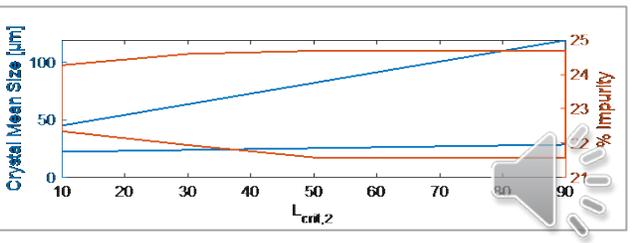
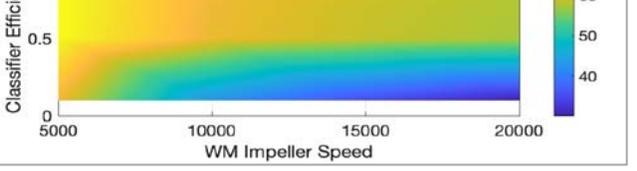
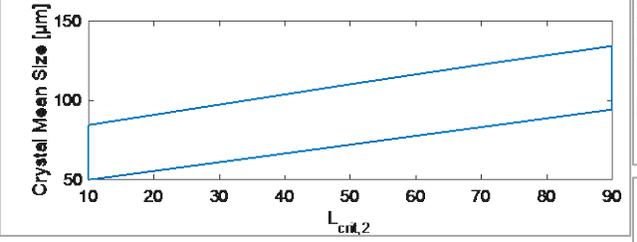
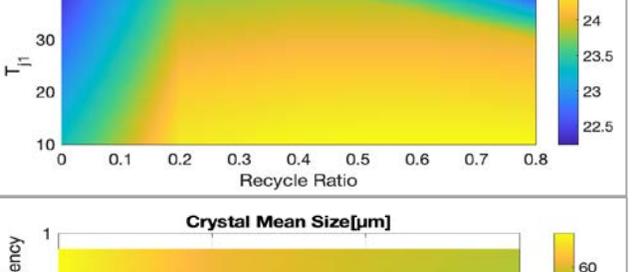
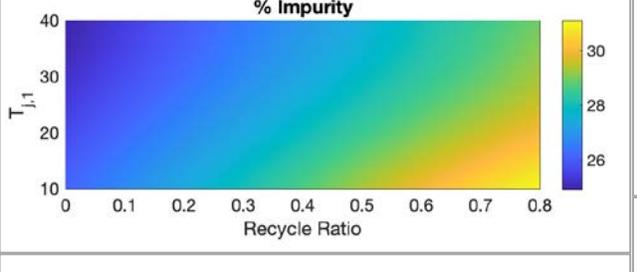
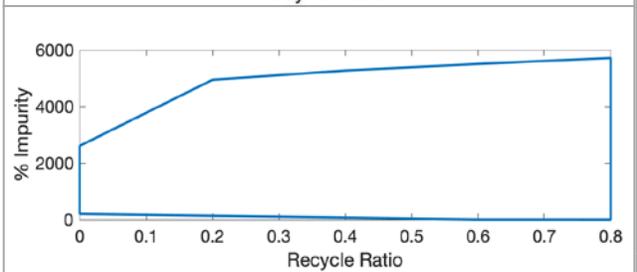
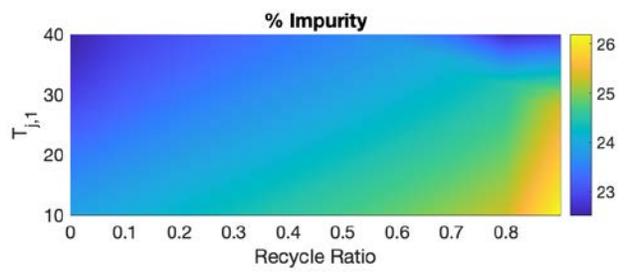
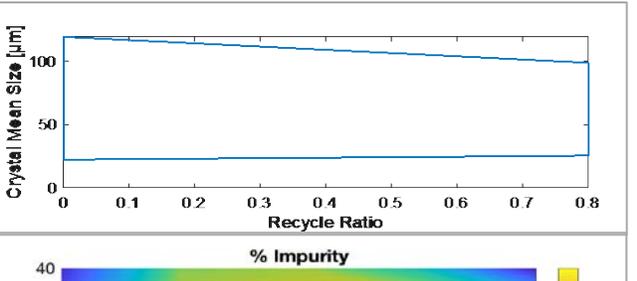
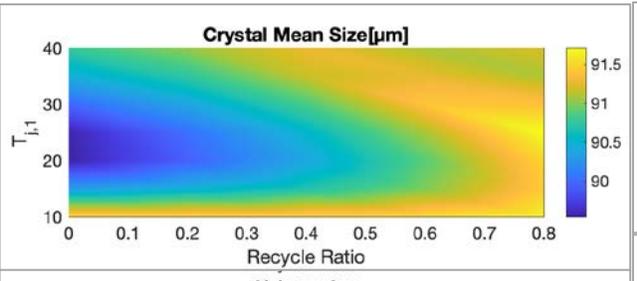
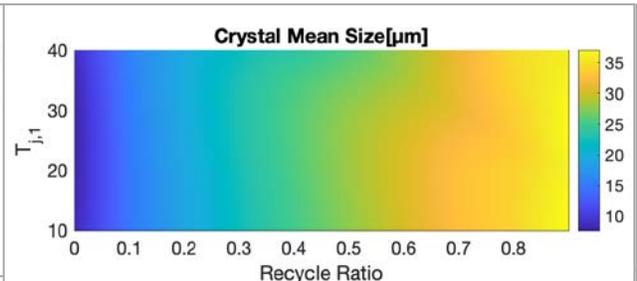
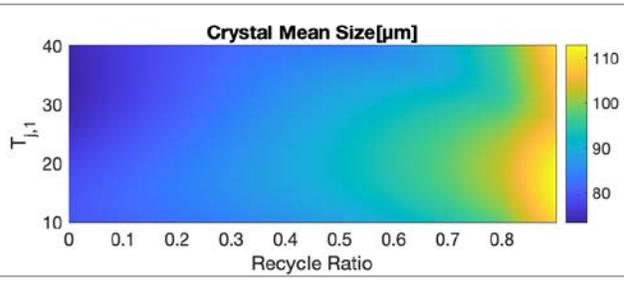
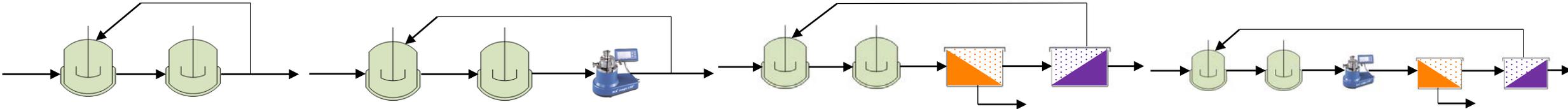
## Classifier



v.b. D <sub>50</sub> In (μm)	v.b. D <sub>50</sub> Out (μm)
10.80	69.03
204.20	51.72
808.48	161.88



# Effect of variables on CQAs



	2 MSMPR		2 MSMPR + WM		2 MSMPR + Classifier		Full System	
	Impurity	Size	Impurity	Size	Impurity	Size	Impurity	Size
r	✓	✓	✓	✓	✓	✓	✓	✓
T <sub>j,1</sub>	✓	✓	✗	✓	✓	✓	✓	✗
N <sub>Imp</sub>			✗	✗	✗	✗	✗	✓
Eff					✗	✗	✗	✓
L <sub>crit,1</sub>					✗	✗	✗	✗
L <sub>crit,2</sub>					✗	✓	✓	✓

# Startup Time

Plot drawn at:

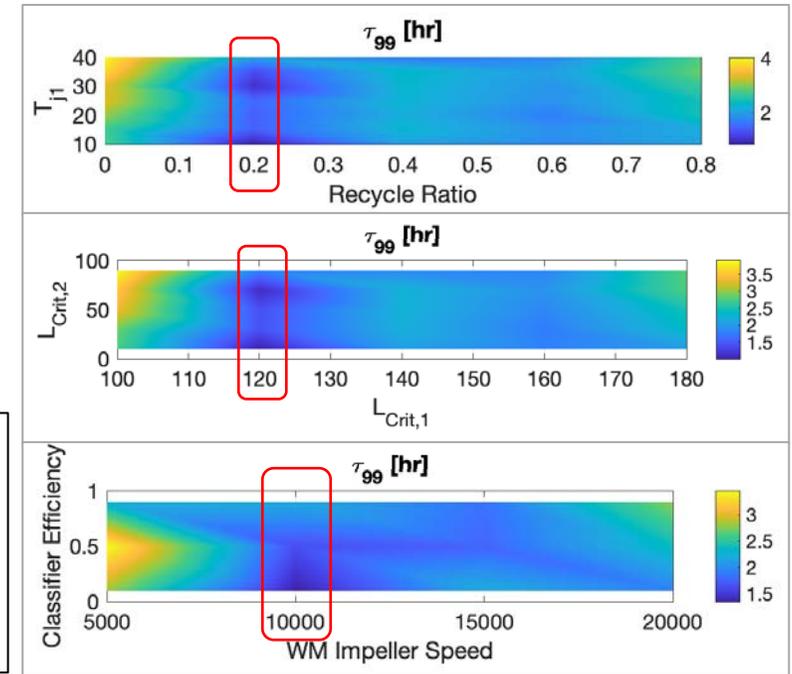
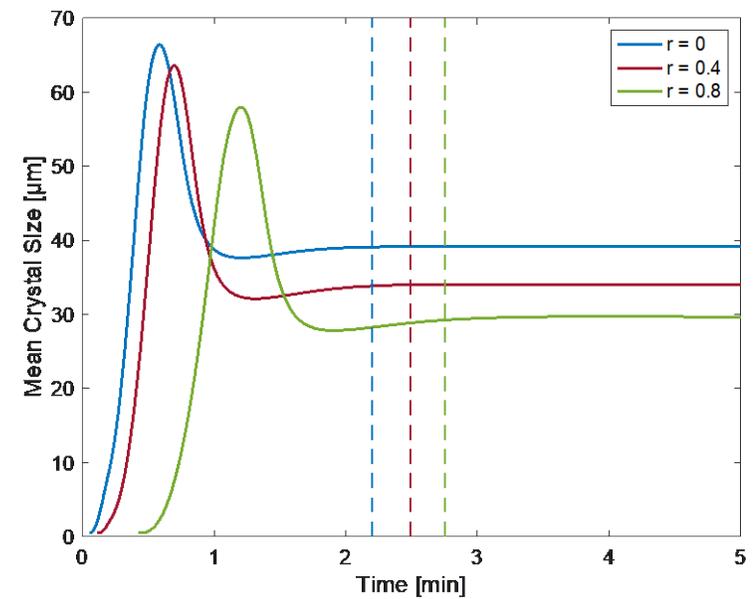
$$T_{j1} = 20^{\circ}\text{C} \quad N_{\text{imp}} = 15,000$$

$$E_1 = E_2 = 0.5$$

$$L_{\text{crit},1} = 140\mu\text{m} \quad L_{\text{crit},2} = 50\mu\text{m}$$

In continuous crystallization:

- The crystal properties are inconsistent until steady state is reached
- So, time and products are wasted
- shorten the startup duration time and reduce waste
- $t_{99}$  : time required for the system to reach a steady state of operation with less than 1% variations.

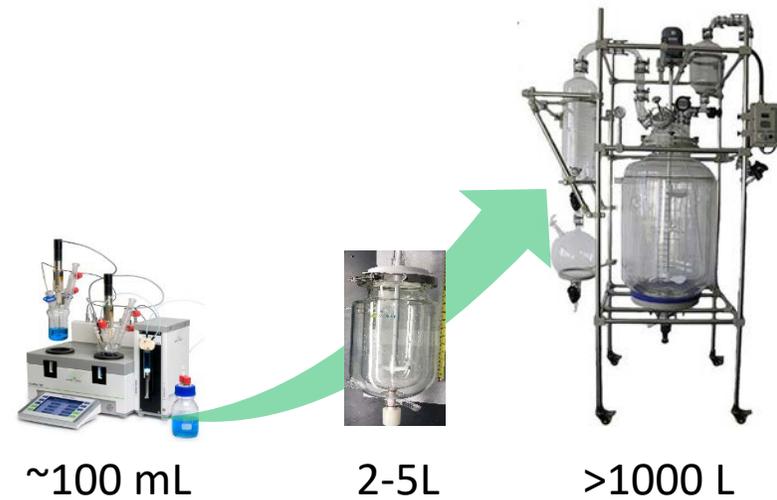


There is a local minima for startup time at:  
 $r = 0.2$   
 $L_{\text{crit},1} = 120 \mu\text{m}$   
 WM impeller speed = 10,000

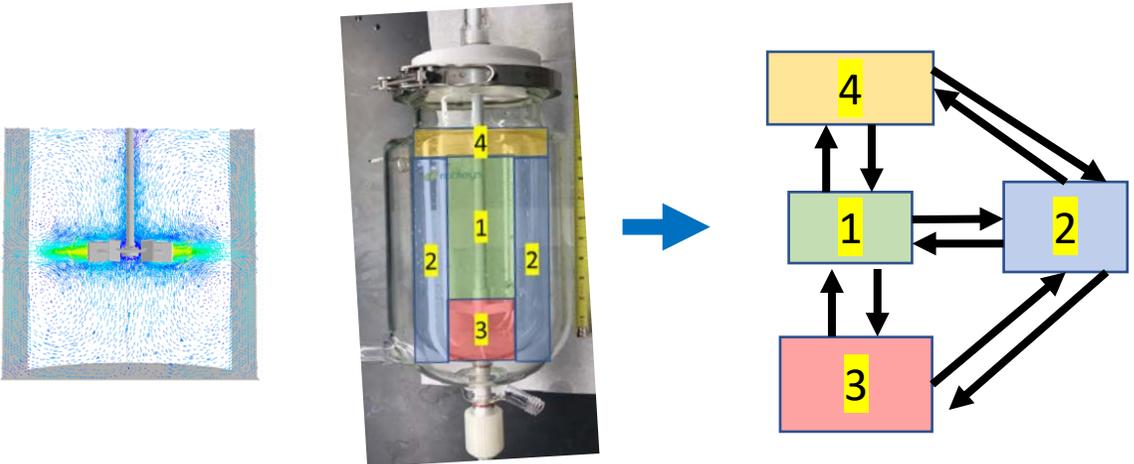
# Application of crystallizer network in compartmental modeling

- Batch crystallization scale-up issues:
  - Crystallizer geometry, scale, and operating conditions change

Phenomenon	Effects	Compartment
Wall temperature gradient	Undesired nucleation	2
Impeller properties	Attrition	3
Surface effects	Artificial cooling	4
Feed pipes	High local supersaturation	-



- Use crystallizer network to mimic flow of reactor compartments



Connection=

Comp.	1	2	3	4
1	0	1	1	1
2	1	0	1	1
3	1	1	0	0
4	1	1	0	0

Flow=

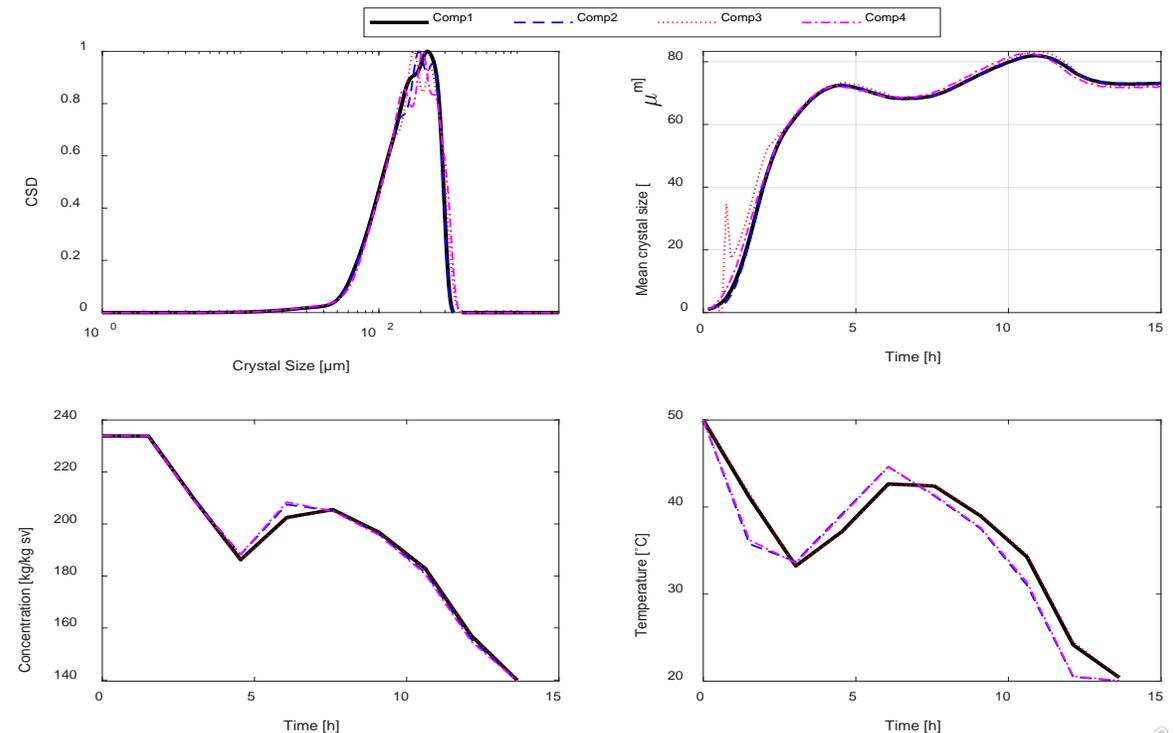
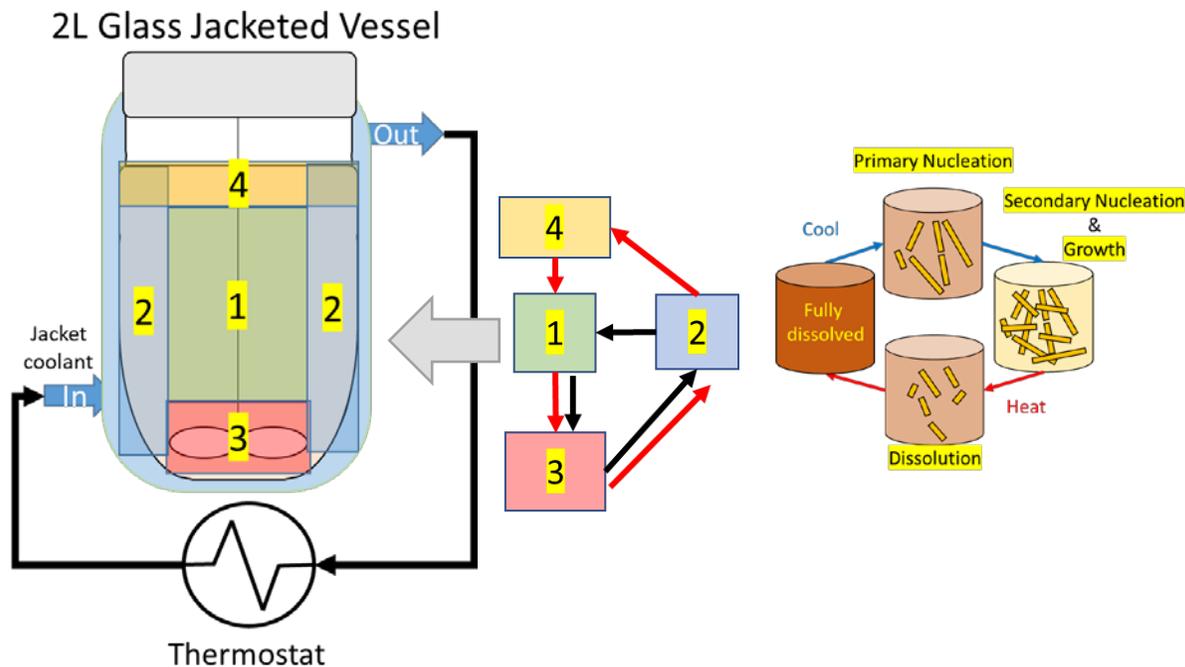
Comp.	1	2	3	4
1	0	$F_{1,2}$	$F_{1,3}$	$F_{1,4}$
2	$F_{2,1}$	0	$F_{2,3}$	$F_{2,4}$
3	$F_{3,1}$	$F_{3,2}$	0	$F_{3,4}$
4	$F_{4,1}$	$F_{4,2}$	$F_{4,3}$	0

Connectivity matrix connects from row to column!

# Preliminary application/ proof of concept

- Model down-pumping impeller in 2L crystallizer
- Two major regions of circulation
  - Reduced connectivity for simple case
- Coupled with PBM, mass, and energy balances
  - Obtained kinetics and flow velocity values from literature

- Batch thermocycling temperature profile
  - Heat transfer delayed in compartment 1 (bulk phase) and compartment 3 (impeller)
- Next steps will investigate flow profile from CFD simulations and incorporate attrition at impeller



# Short Term Future Plans (~1 year)

- Experimental validation of overall system for model system and commercial active ingredient
- Other applications of the crystallizer network
  - Flow profile from CFD simulations
  - Incorporating attrition at impeller
- Model based quality by control (QbC)
  - Developing a moving horizon estimation (MHE) based nonlinear model predictive control using the full PBMs for size, shape and inferential purity control

The background of the slide is a microscopic view of numerous small, blue-tinted crystals. These crystals are irregular in shape, with some appearing as simple cubes and others as more complex, multi-faceted structures. They are scattered across the frame, with some in sharp focus and others blurred in the background, creating a sense of depth. The lighting is bright, highlighting the facets and edges of the crystals.

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