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

Rojan Parvaresh, Dr. Zoltan K. Nagy
School of Chemical Engineering
Purdue University, West Lafayette, IN

PURDUE UNIVERSITY

PURDUE CHEMICAL ENGINEERING

Outline

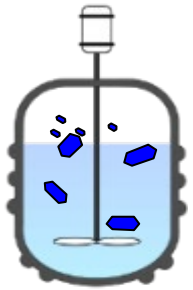
- **Project objectives**
  - *… and main deliverables*

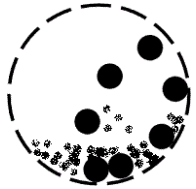
- **Summary of deliverables**
  - *… in a nutshell*

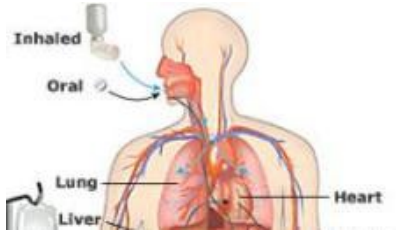
- **Progress summary and application**
  - *… given what we know, what could we do*

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)



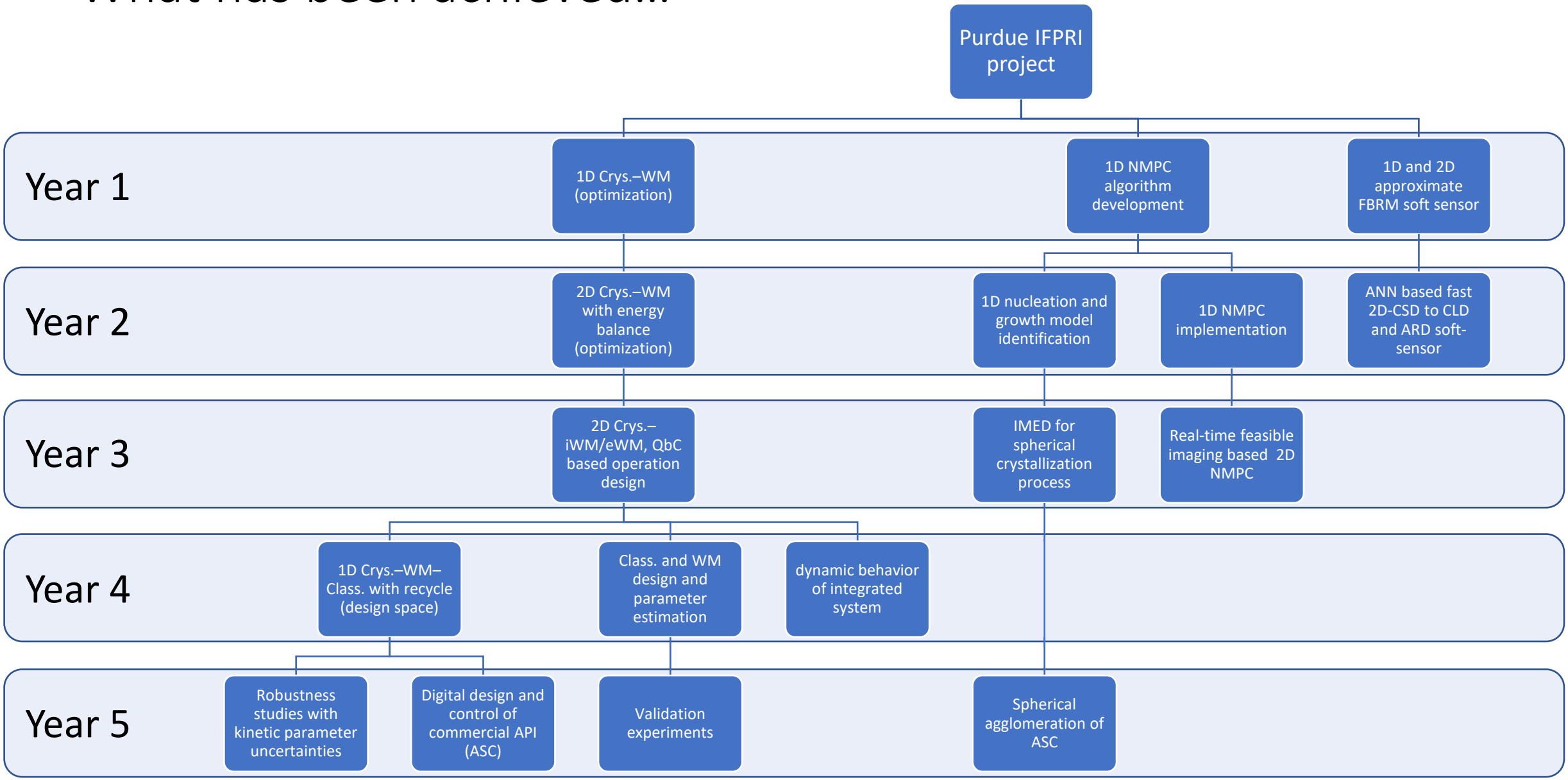




Crystallization → **Downstream processes** → **Final product**

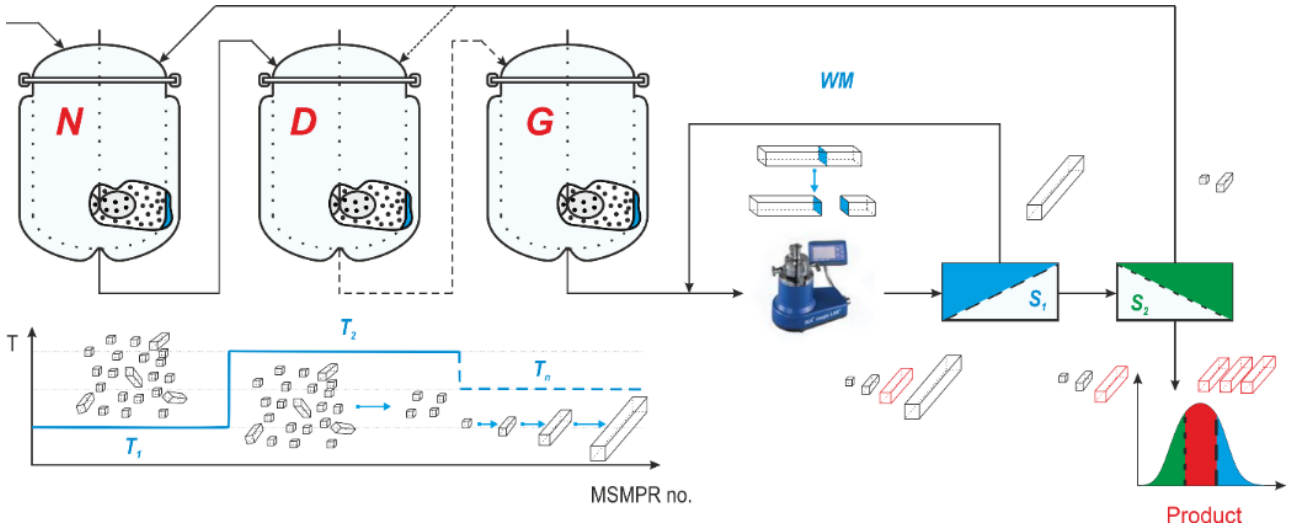
Control of crystal properties is critical for product functionality and operational efficiency

What has been achieved…



Continuous Integrated System

- **Crystallization-Milling-Classifier-Recycle systems (Crys.–WM–Class.–R).**
- Main questions to answer:
  - How different integration of the system affects the design
  - Can framework be applied to other API?
  - Robustness of the system

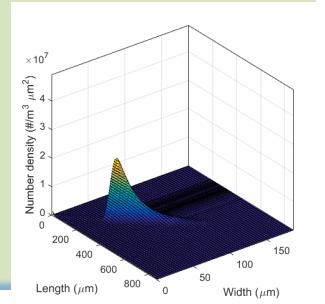


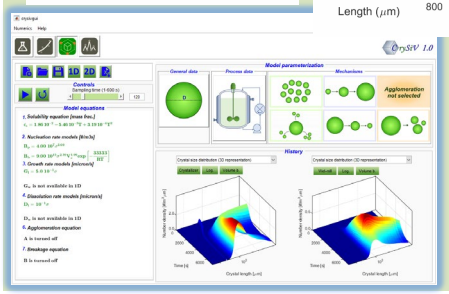
Population Balance Modeling and Mechanism in the simplified System

Case study
paracetamol in ethanol

Crystallizer

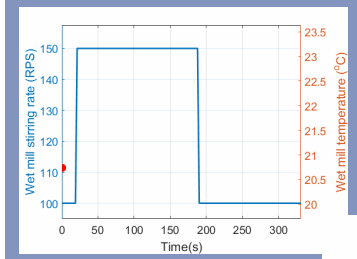
- 1D/2D PBM
- Nucleation, growth, agglomeration, breakage
- Effects of impurity
- Crysiv

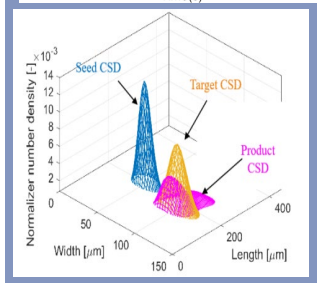


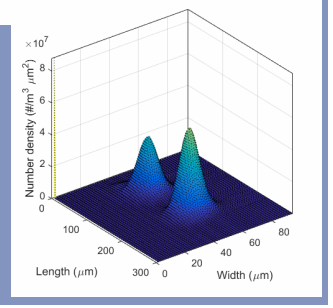


Wet Mill

- 1D/2D PBM
- Integrated Crys. – WM
- Attrition, breakage
- Energy balance
- Optimization

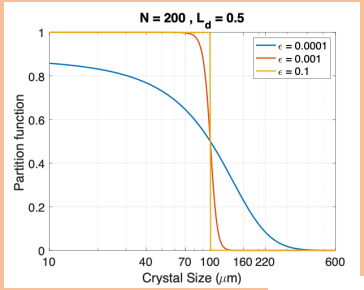


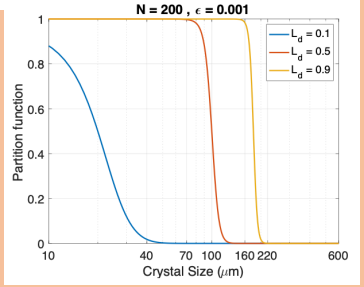




Classifier

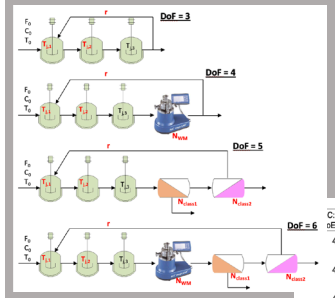
- 1D PBM
- Partition curve using sigmoid function
- Parameter estimation

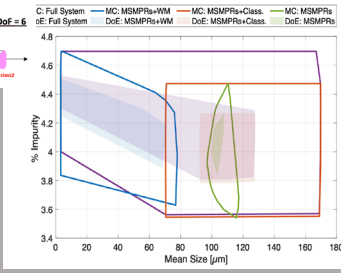




Fully integrated simplified system

- Applied to commercial products (Takeda, Corteva, ASC)
- Effect of recycle on size, impurity and dynamics
- Validation experiments
- Robustness studies

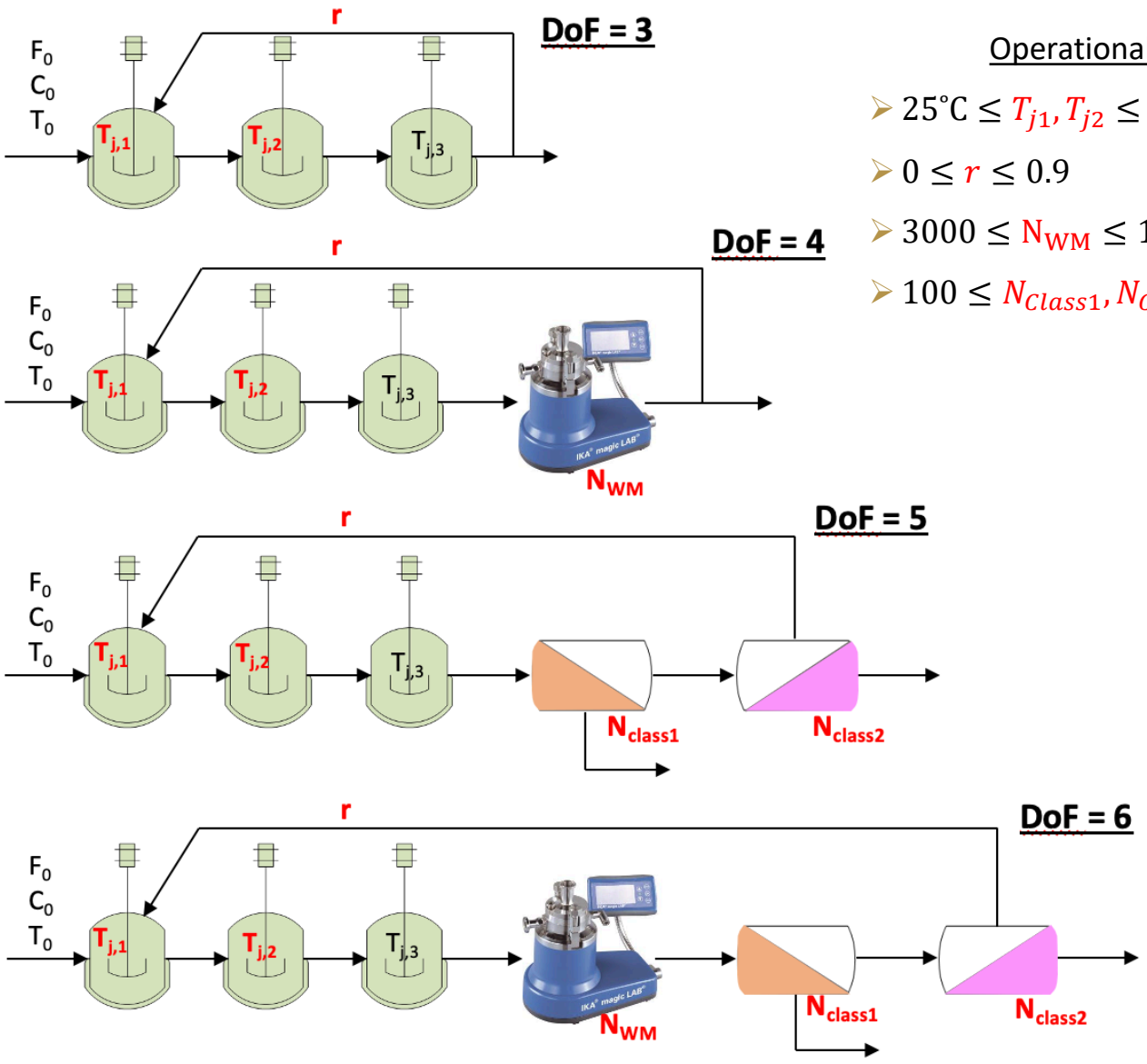




Leveque, Elsevier **(2002);** Van Leer et al. Compt. Phys. **(1974);** Liu & Nagy, Springer **(2020);** Nagy et al., Springer **(2020);** Randolph & Larson, Academic Press **(1971);** Jones, Elsevier **(2002)**; N Mitchell et al. *J Cryst Growth*. **(2011)**; P Frawley et al. *Chem Eng Sci.* **(2012)**; N Mitchell et al. *J Cryst Growth* **(2010)**

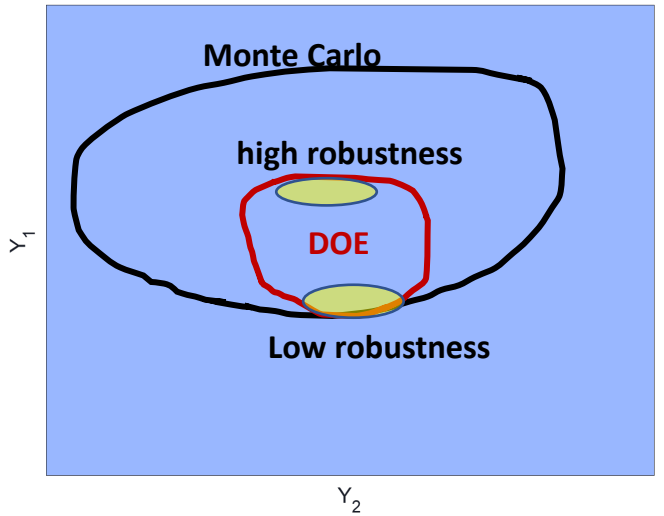
System Setups and Flow Diagrams

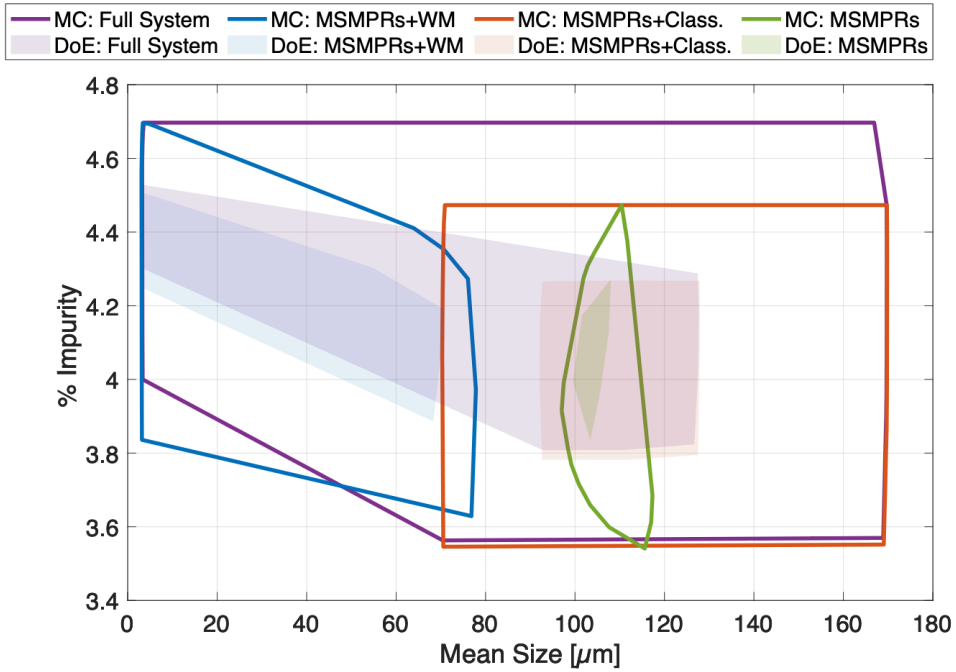
- In-Situ 2-level Design of Experiment (DOE)
- Monte Carlo



Operational Variables

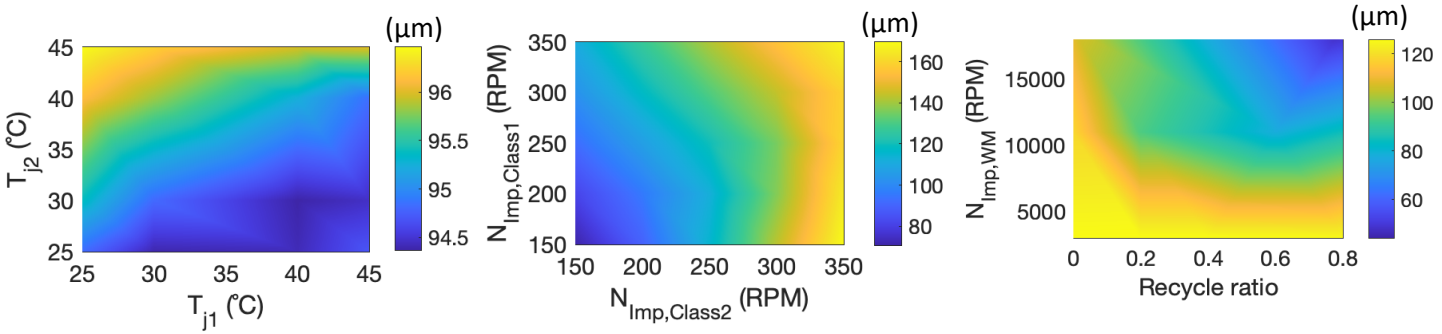
- $25^{\circ}C \leq T_{j1}, T_{j2} \leq 45^{\circ}C$
- $0 \leq r \leq 0.9$
- $3000 \leq N_{WM} \leq 19000$ RPM
- $100 \leq N_{Class1}, N_{Class2} \leq 350$ RPM





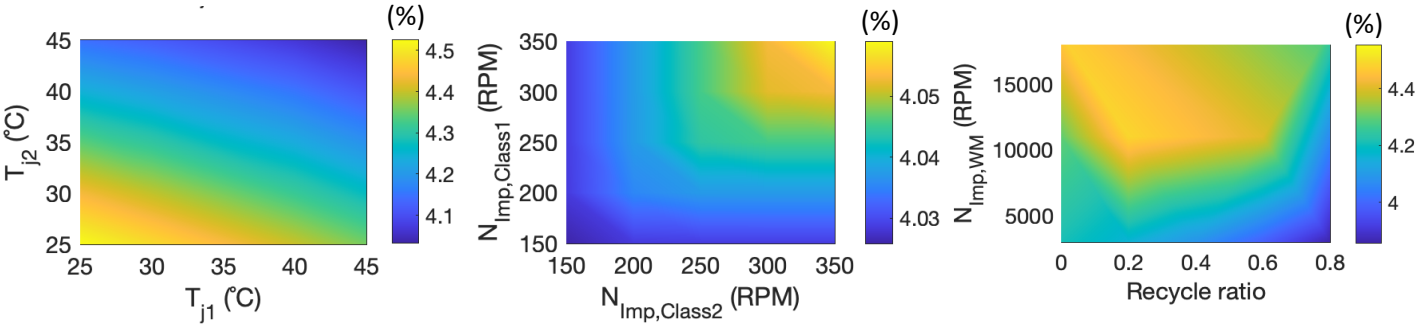
Sensitivity of Design Variables & Startup

Crystal Mean Size:



$$N_{Imp,Class2} > N_{Imp,WM} > r > T_{j2} > T_{j1} > N_{Imp,Class1}$$

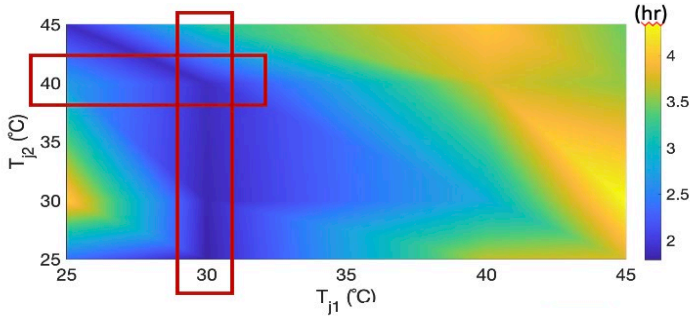
Impurity:

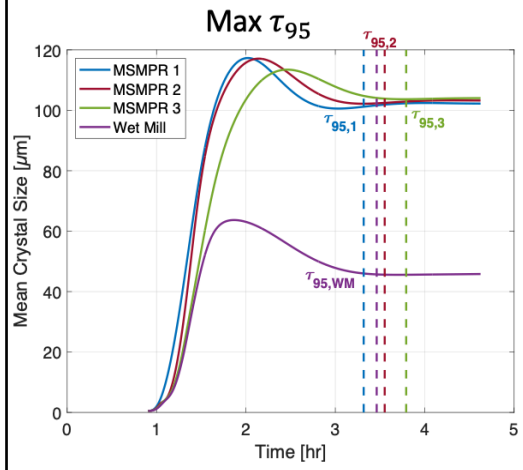


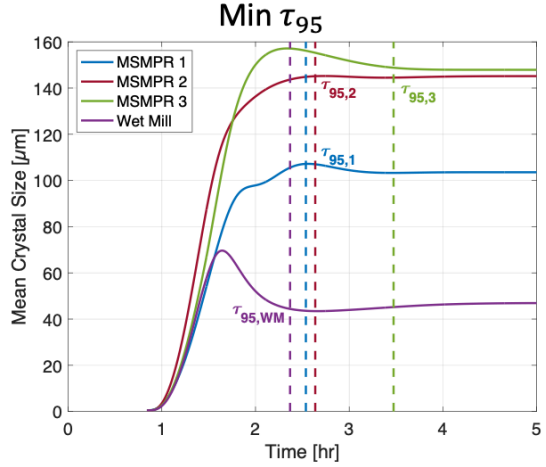
$$T_{j2} > N_{Imp,WM} > r > T_{j1} > N_{Imp,Class2} > N_{Imp,Class1}$$

<u>In continuous crystallization:</u>

- Crystal properties are inconsistent until steady state
  - Time and material wasted
  - Conditions for optimized startup can be identified

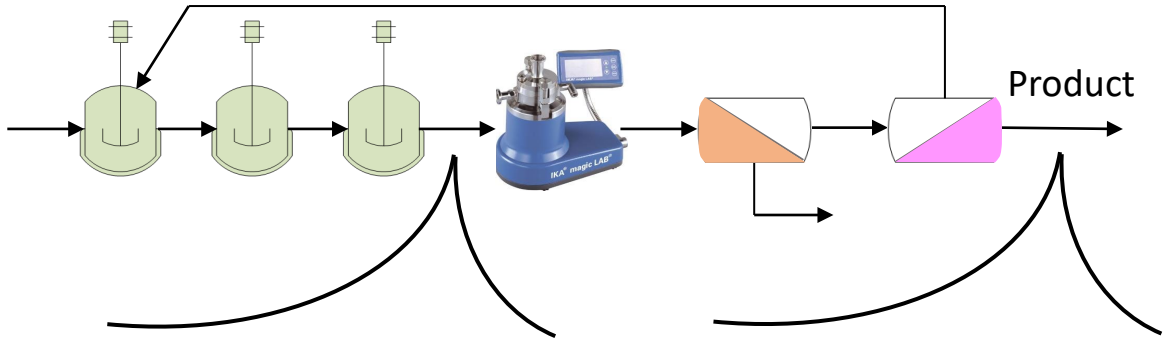


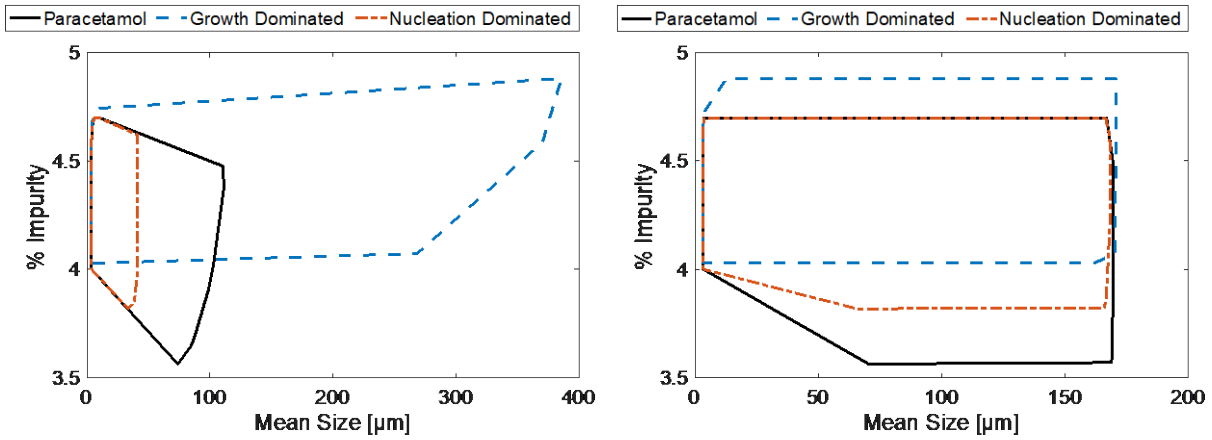




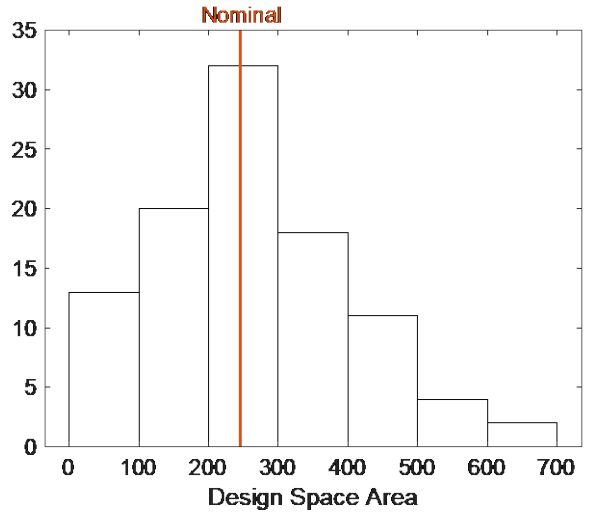
Robustness Design Space Studies

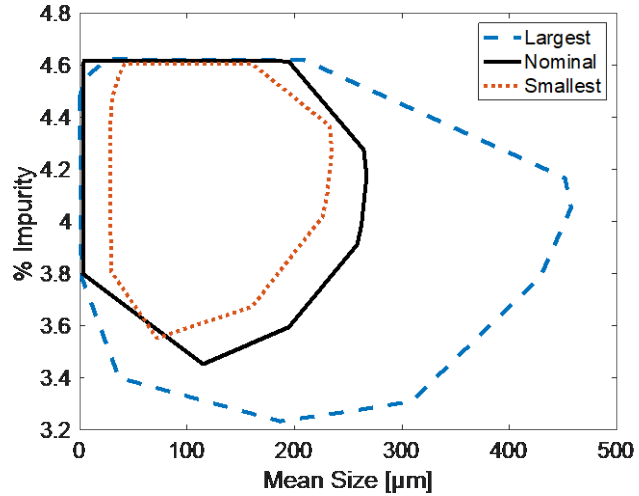
- Case study : B or G dominated process
- Growth Dominated : B, G*100
- Nucleation Dominated : B*100, G





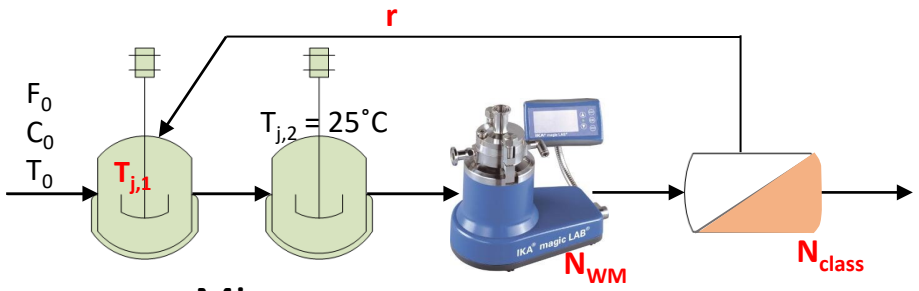
- General kinetic parameter uncertainties
  - 7 parameters for Crystallizer: $k_p, p, k_s, s, k_p, k_g, g, E_a$
  - 5 for wet mill: $k_{br}, k_a, \beta_{br}, L_{c,br}, x_n$
  - 2 for classifier: ε, l_d
- A confidence hyper-ellipsoid was generated

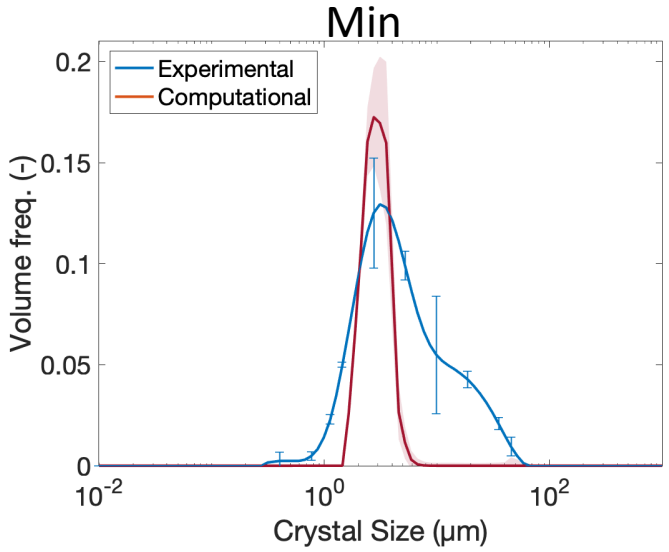


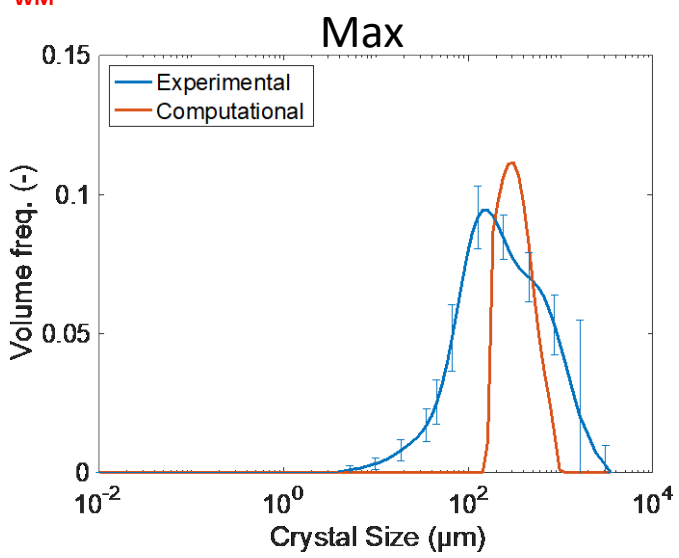


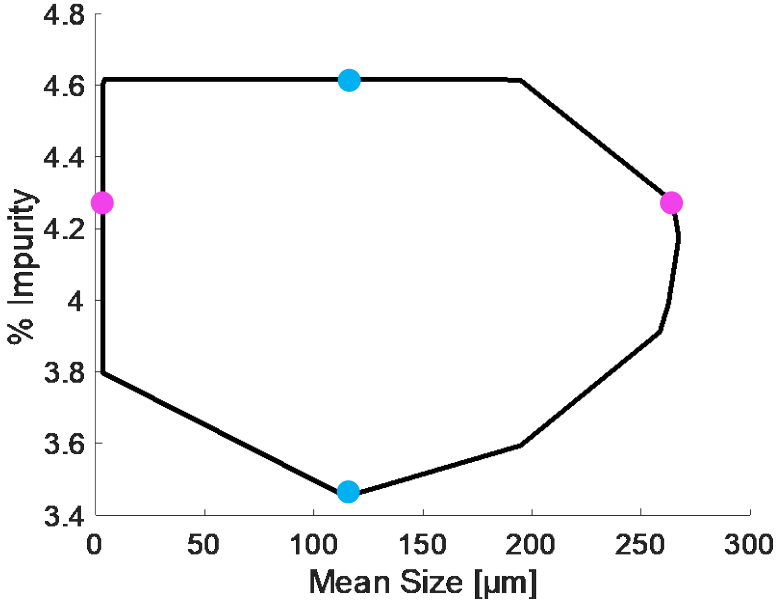
Experimental Validation (Paracetamol)

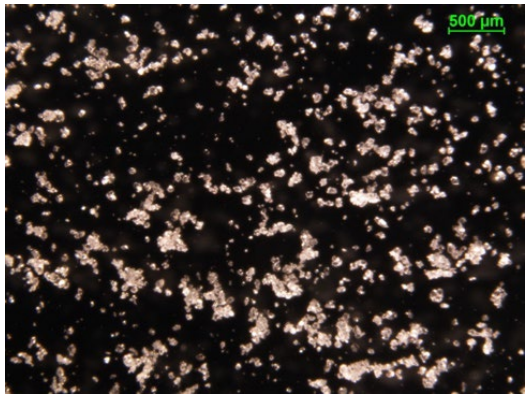
		$T_{j,1}$ (°C)	N_{WM} (RPM)	r	$N_{Classifier}$ (RPM)
Size	Min	25	19000	0.9	150
	Max	30	3000	0	350
Impurity	Min	45	3000	0.8	150
	Max	25	15000	0.2	150

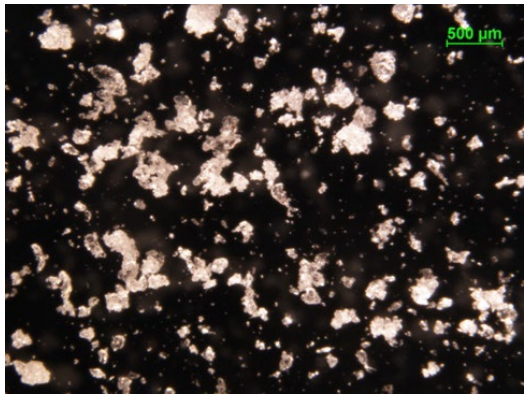








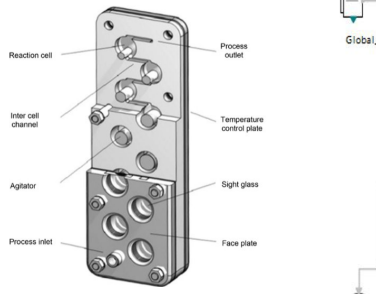


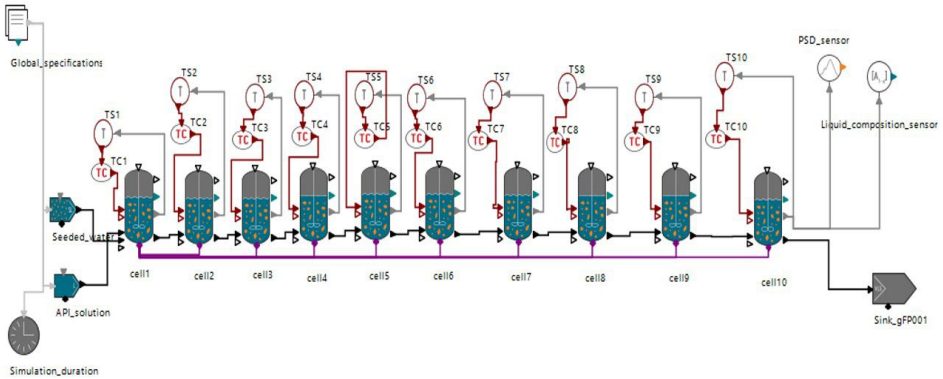


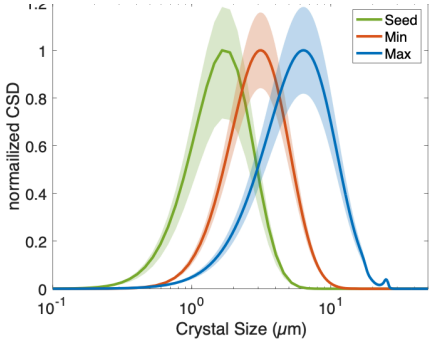
	Min	Max
Experimental	3.95 ± 0.031 %	6.33 ± 0.012 %
Simulation	3.45 ± 0.016 %	4.62 ± 0.0086 %

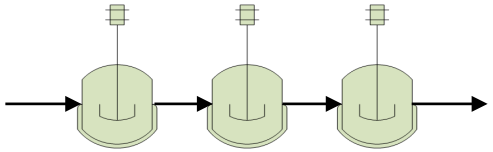
Applied to Commercial API (Atorvastatin calcium (ASC))

ACR: seed generation









Main goal:

- Digital design and control of integrated continuous crystallization of Atorvastatin calcium (ASC)
- Crystallization and spherical agglomeration of ASC
- End-to-end manufacturing of ASC

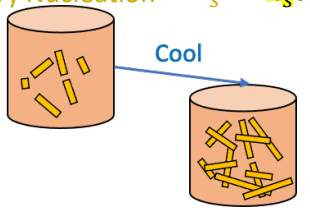
Parameter	Definition	Value
k_g	Growth rate constant (μm/s)	110.95 ± 10.0373
g	Growth rate exponent (-)	2.1060 ± 0.9831
Ea, g	Growth activation energy (J/mol K)	8.0784E+04 ± 9.1311
k_p	Secondary nucleation coefficient (#/m³ s)	6.8645E+10 ± 107.8764
p	Secondary nucleation exponent (-)	2.3986 ± 0.1937
k_s	Secondary nucleation coefficient (#/m³ s)	1.932E+07 ± 18.3982
s	Secondary nucleation exponent (-)	1.5275 ± 0.1937

- Parameter estimation of continuous crystallization of ASC
- Attainable region of an integrated continuous system
- Uncertainty in kinetic parameters and initial operating conditions
- Robust design space for the 2 different uncertainties

Primary Nucleation $B_p = k_p \sigma^p$

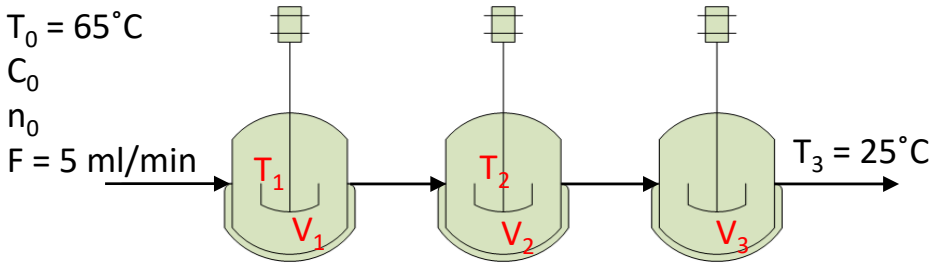
&

Secondary Nucleation $B_s = k_s \sigma^s V_c$

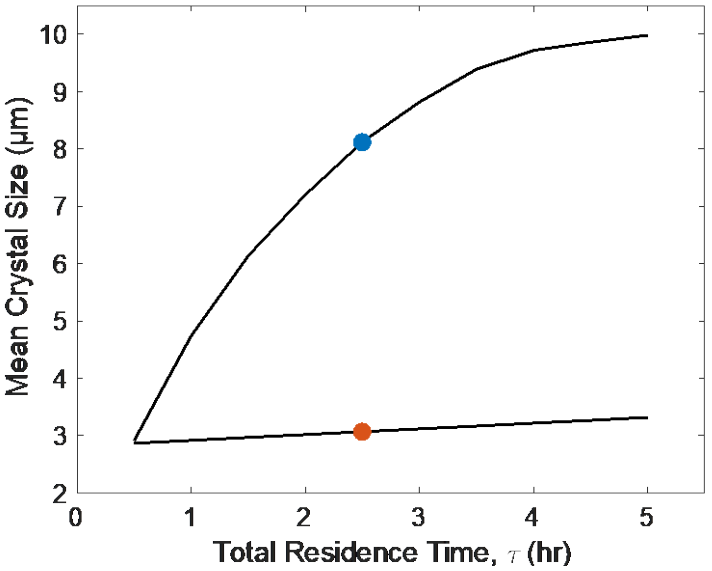


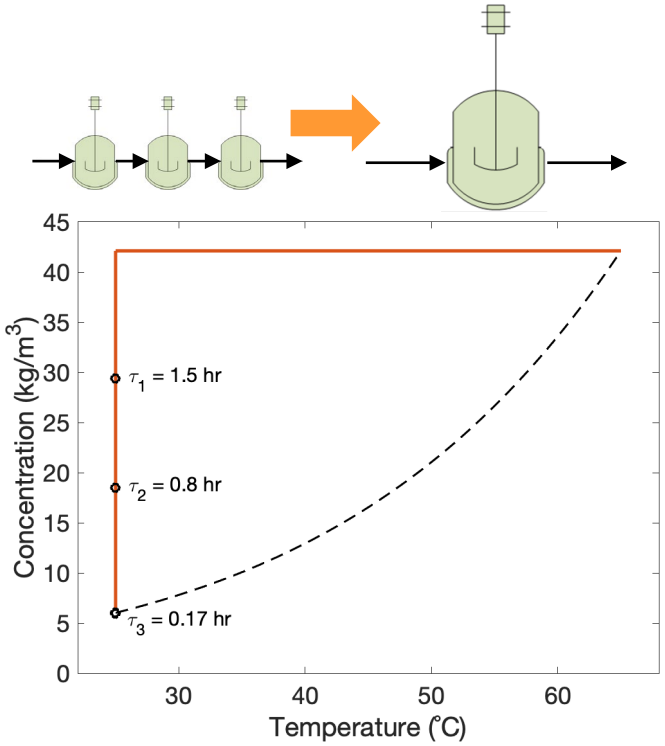
Growth $G = k_g e^{\left(-\frac{Ea,g}{RT}\right)} \sigma^g$

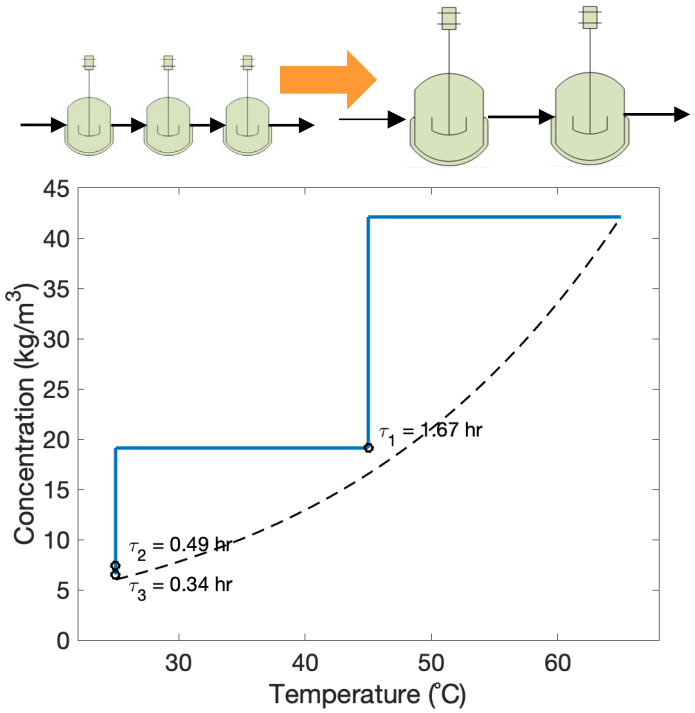
Digital Design and Control of Atorvastatin Calcium

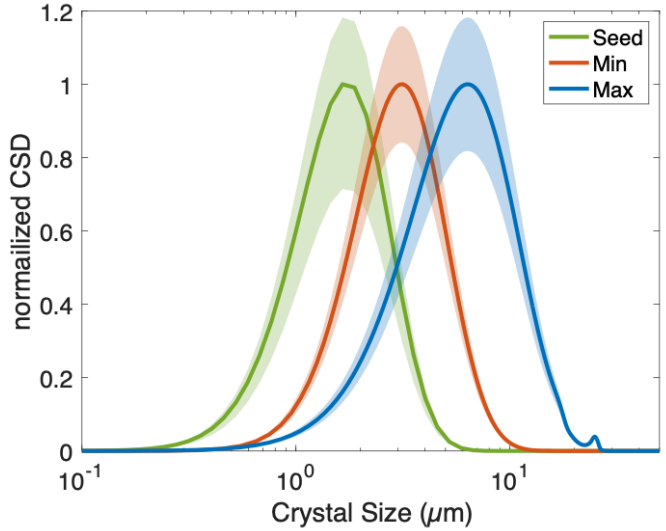


$$\min_{V_i, T_i} / \max \bar{L} \quad s.t. \sum_{i=1}^{3} \tau_i = \tau_{tot}, \quad T_3 \le T_2 \le T_1 \le T_0, \quad Y \ge 0.9 Y_{theoretical}$$





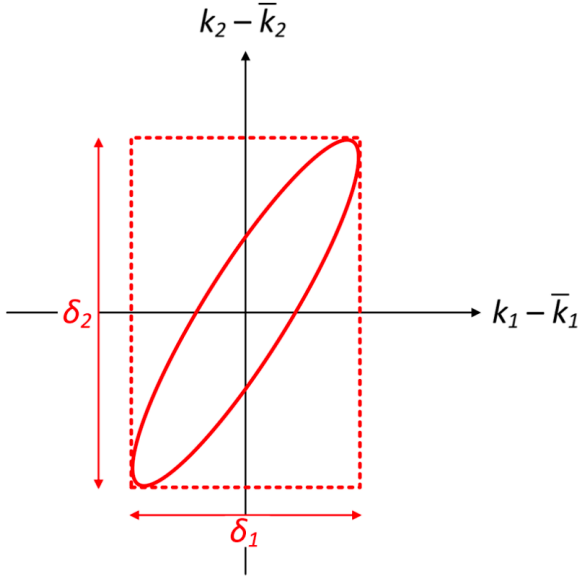


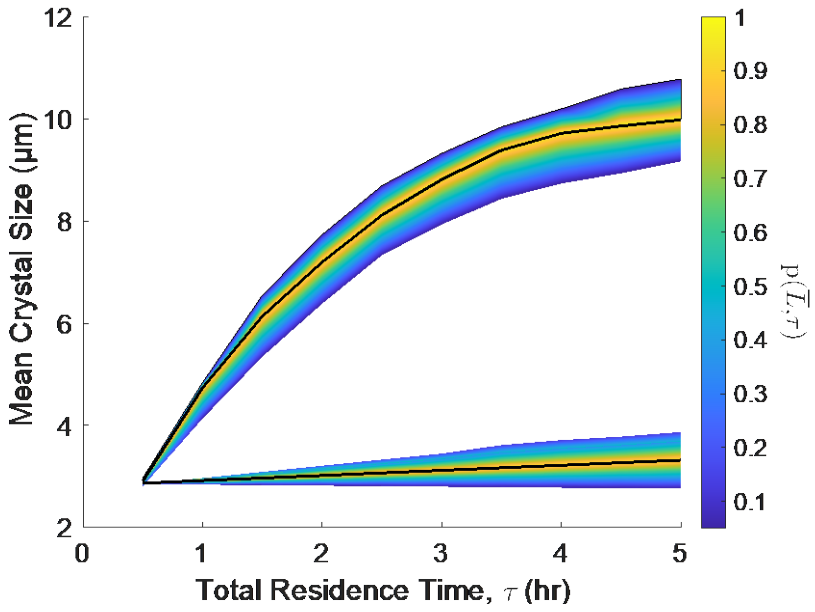


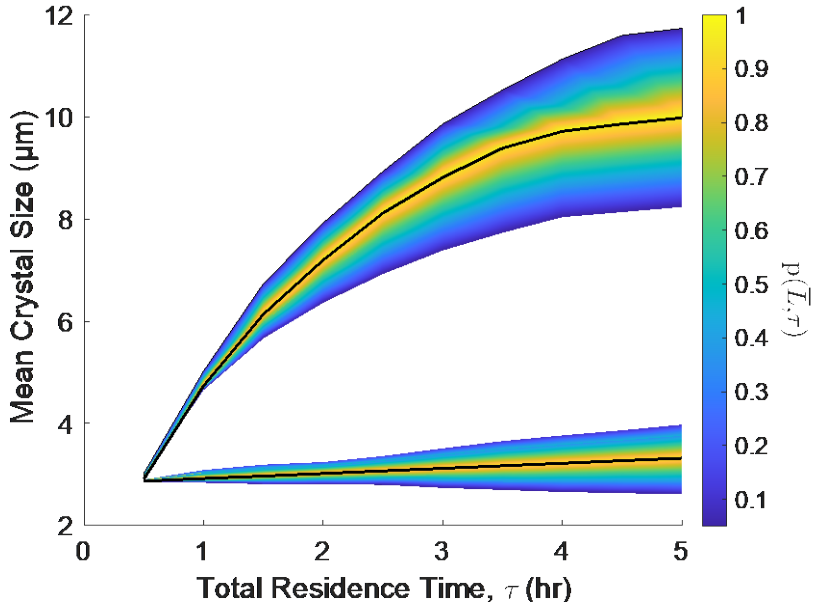
Robustness Studies

- Kinetic parameter uncertainties
  - 7 parameters: $k_p, p, k_s, s, \ k_g, g, E_a$
- 150 combinations of random values for each optimization

- Fit inlet CSD to a gamma probability density function
  - 95% confidence limits
- Inlet seed distribution uncertainties
  - 2 parameter: a, b

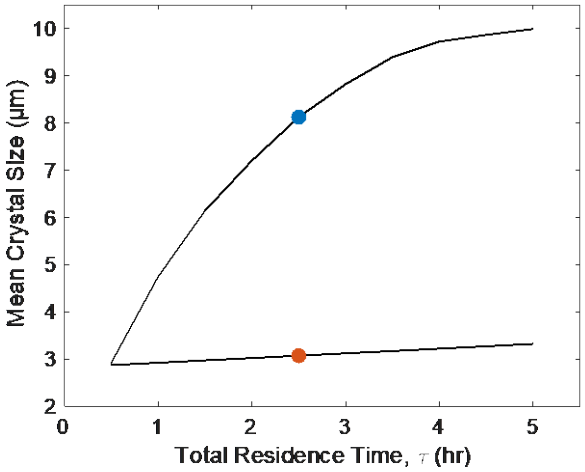


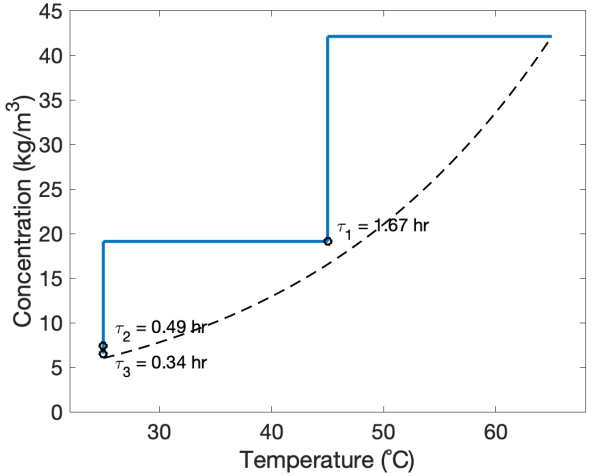




Parameter	Definition	Values
a	Shape parameter (-)	2.0727 ± 0.18
b	Scale parameter (-)	0.4255 ± 0.0027

Integrated Crystallization and Spherical Agglomeration

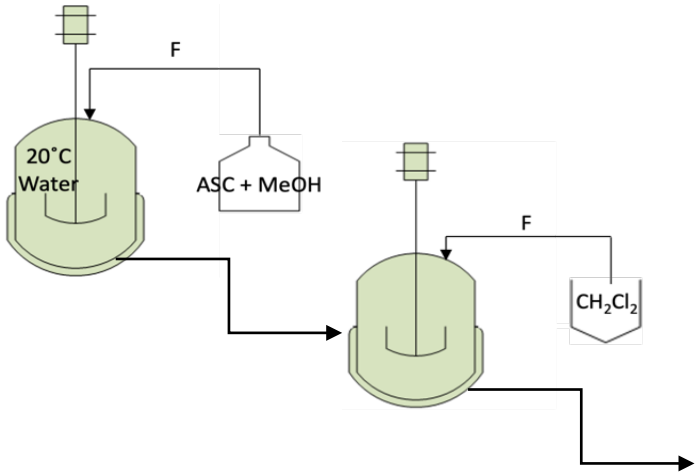


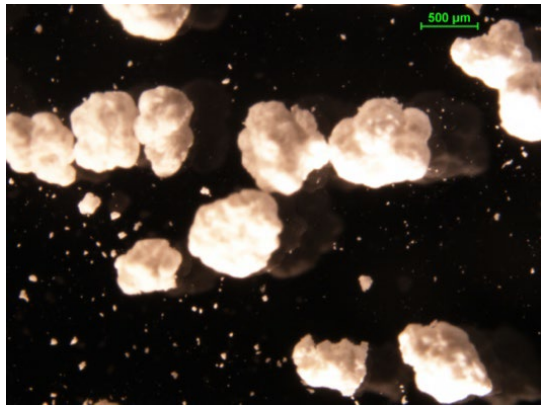


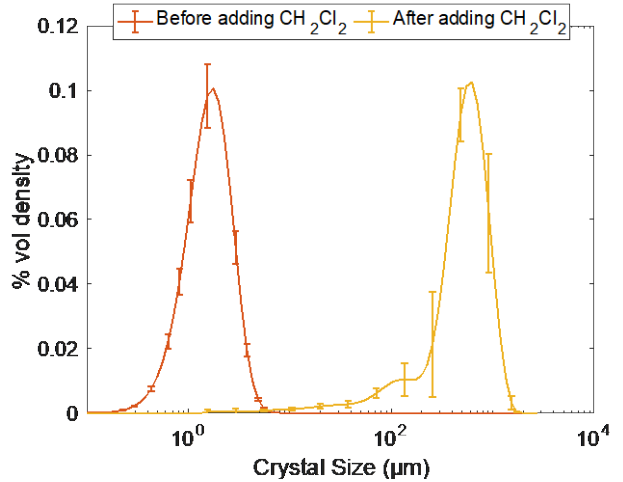
- 3 stage crystallizer cold only produce crystals up to 10 μm
- Only 2 crystallizers were used

  → An integrated 2 stage crystallization–spherical agglomeration system

1st stage: antisolvent crystallization and stable polymorphic form I
2nd stage: adding bridging solvent (CH_2Cl_2) to form spherical agglomerates

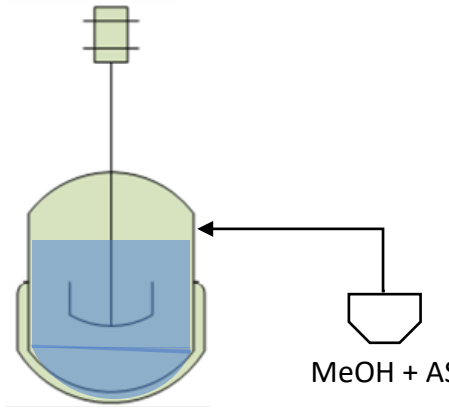






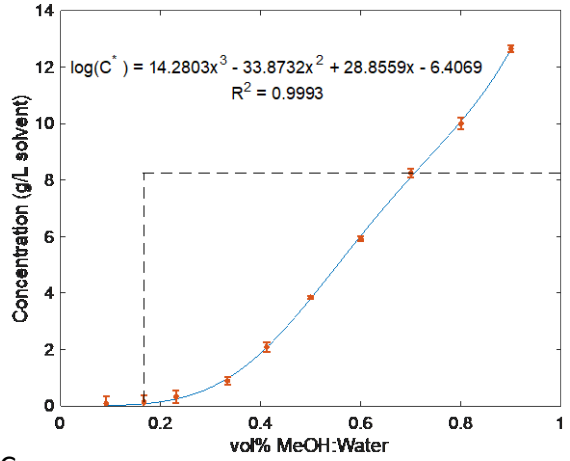
Design of Experiments

Crystallization step



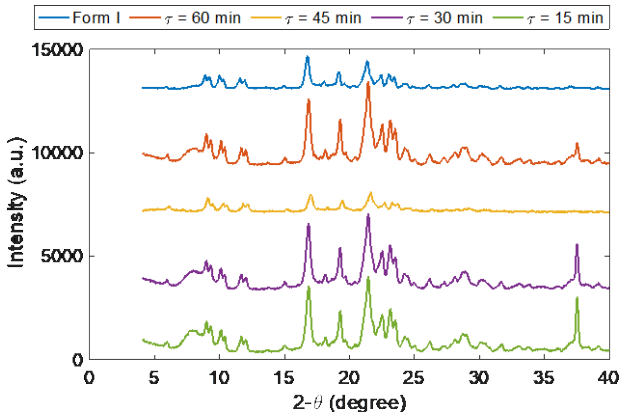
MeOH + ASC

300 ml water
20˚C

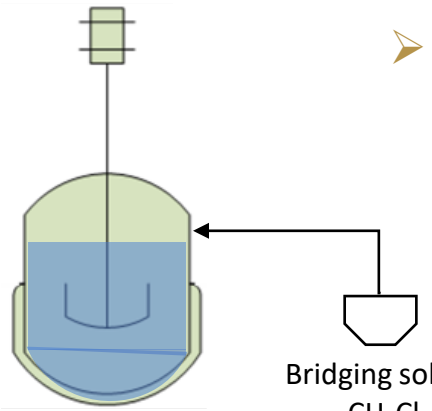


- Design variables:
  - RPM
  - Residence time

RPM	residence time (min)	Form I?
250	100	Form I
250	60 and lower	Amorphous
300	60	Form I
300	45	Form I
300	30	Form I
300	15	Form I



Spherical agglomeration step

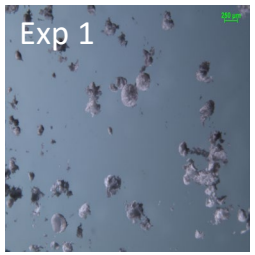


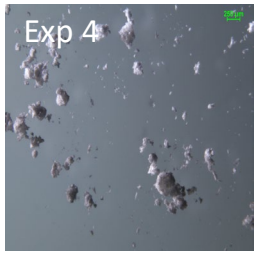
Bridging solvent
CH_2Cl_2

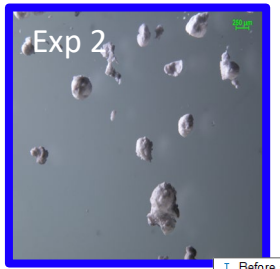
300 ml water
20˚C

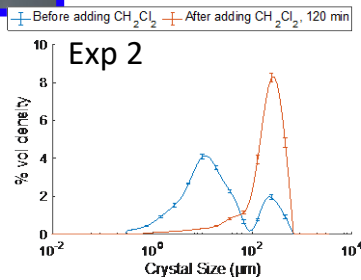
- Design variables:
  - Bridging solvent ratio ($BSR = \frac{V_{CH_2Cl_2}}{V_{AVS}}$)
  - RPM

Exp. #	BSR	RPM	Spherical?
1	6	350	Spherical
2	6	250	Spherical
3	4.5	350	not spherical
4	4.5	250	Spherical
5	3	350	not spherical
6	3	250	not spherical



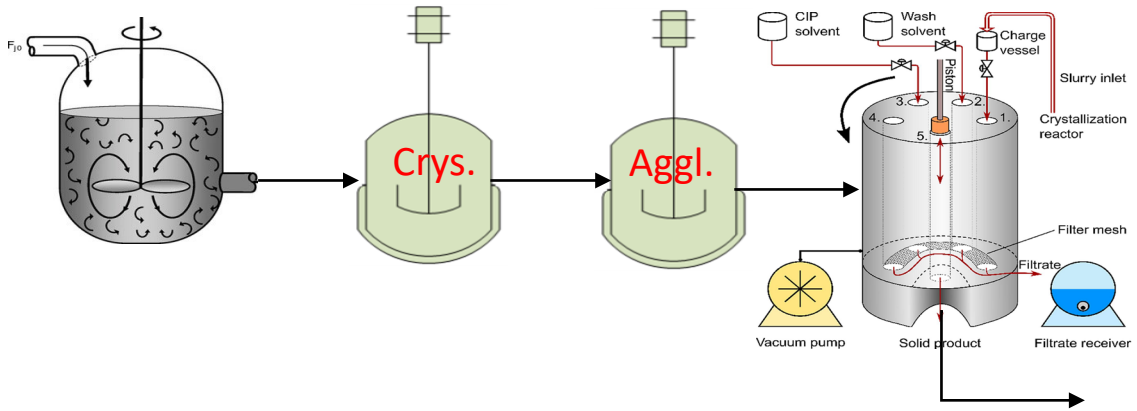






Future Work

- Continuous operation of integrated system
- Crystal characterizations
  - Flowability
  - Filtration and drying time
  - Compaction and tableting
  - Dissolution
- End-to-end continuous manufacturing of ASC
  - Reaction + crystallization–spherical agglomeration + continuous filtration and drying (CFC)



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

Rojan Parvaresh, Dr. Zoltan K. Nagy
School of Chemical Engineering
Purdue University, West Lafayette, IN

PURDUE UNIVERSITY

PURDUE CHEMICAL ENGINEERING