Utilization of Population Balance Models to Develop a Continuous Crystallization Process: Process Design and Optimization

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Answers That Matter.

Motivation

Pharma has recently “rediscovered” continuous processing.

Crystallization:

- Workhorse for separations.
  - Undesired impurities are preferentially removed (potency and purity)
  - Acceptable yield is achieved
  - Desired crystal form is maintained
  - Target particle size (or specific surface area)
  - Morphology (crystal shape)

Moving from Batch to Continuous Crystallization Process Development.

- 2012 APM Forum “Tailoring API Physical Properties through Crystal Engineering: Moving from Batch to Continuous Crystallization Development”
- How to integrate continuous process development into a traditional batch process development environment?
  - Desire to deliver same/better potency, impurity profile, particle size and morphology
- *How to achieve this in the same development timeframe?*
- *How to achieve the same (or better) physical properties?*

Outline

- Introduction to crystallization process development.
- Crystallization kinetic models.
- Kinetic experiments.
- Parameter regression.
- Model validation or confirmation.
- Process optimization.

- Opportunities.

Supersaturation

- Concentration driving force:

$$\Delta c = c - c^*$$

- Supersaturation ratio:

$$S = \frac{c}{c^*}$$

- Relative or absolute supersaturation:

$$\sigma = \frac{\Delta c}{c^*} = S - 1$$

- Thermodynamic supersaturation.
  - Driving force for crystallization is the difference in chemical potentials.

$$\Delta\mu = \mu_{solution} - \mu_{crystal}$$

$$\mu = \mu_0 + RT \ln a$$

$$\frac{\Delta\mu}{RT} = \ln\frac{a}{a^*} = \ln S$$

$$S_a = \exp\left(\frac{\Delta\mu}{RT}\right) = \frac{a}{a^*} = S\frac{\gamma_c}{\gamma_c^*}$$

Symbol	Definition
c	Solution concentration
c^*	Solubility
μ	Chemical potential
$a = \gamma_c c$	Activity
γ_c	Activity coefficient

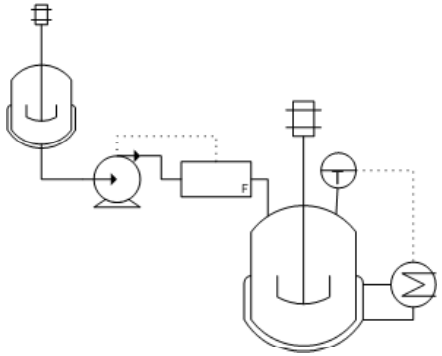
In general, base *S* on molal units (mol/kg solvent) as it is more practical and less temperature dependent.

Mullin, J.W. (2001). *Crystallization*. (4th ed.), Elsevier Butterworth-Heinemann, Amsterdam.

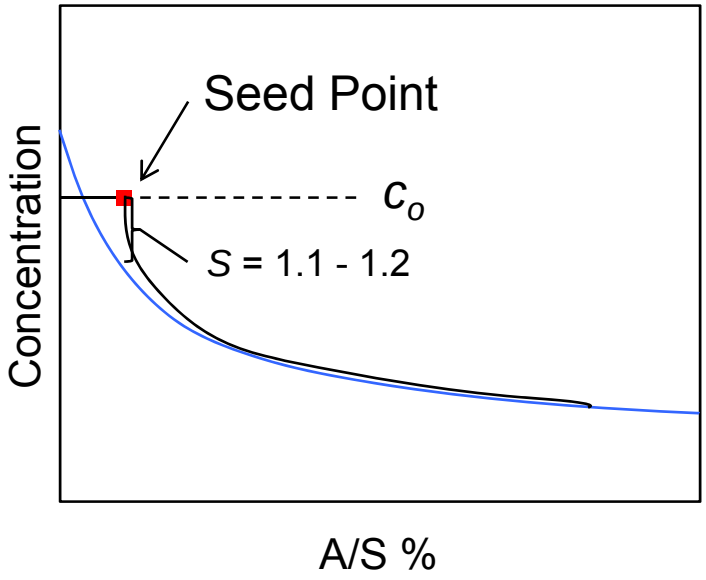
Typical Batch Crystallization Development

1) Choose solvent system
   - Solvent screening
   - Solubility modeling
2) Collect solubility data
   - Data drives choice of: thermal, A/S, combo
3) Choose seed point
   - c/c^* = 1.1 to 1.2
4) Follow solubility curve
   - *eg.* c/c^* = const
   - $c - c^*$ = const
5) Equilibrate and isolate

- Seeded, growth dominated crystallization.
- Time frame for design is accepted.



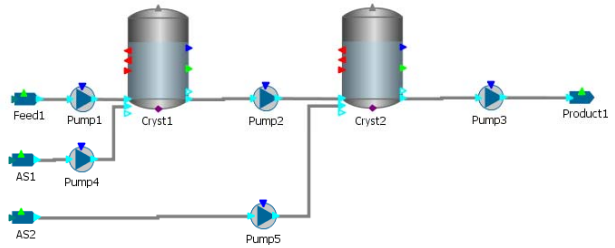
Example Crystallization



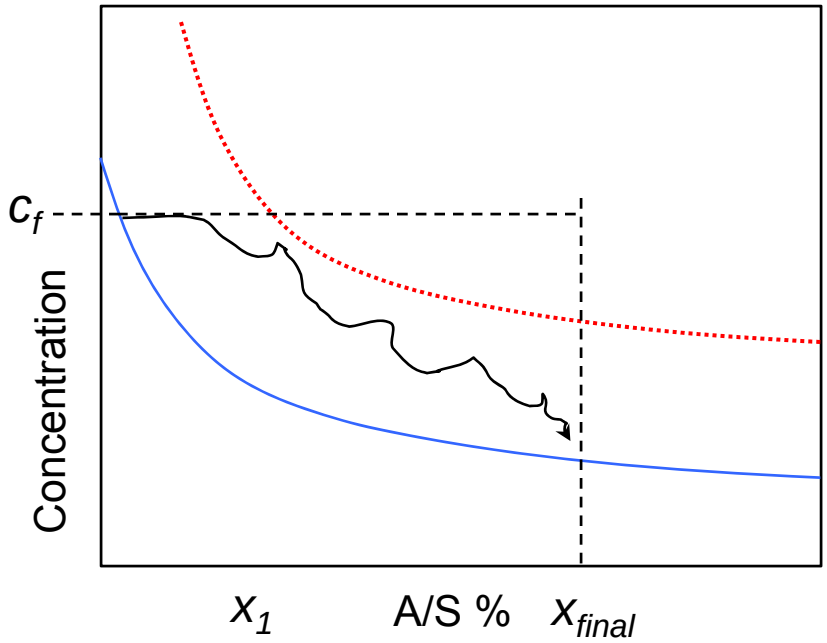
Continuous Crystallization Design

1) Choose solvent system
2) Collect solubility data
   - Data drives choice of: thermal, A/S, combo?
3) (startup: generate initial seed bed)
4) Traverse the solubility curve
5) Isolate

- Choose feed concentration based on prior process steps.
- Choose final composition based on yield and total solvent volumes.



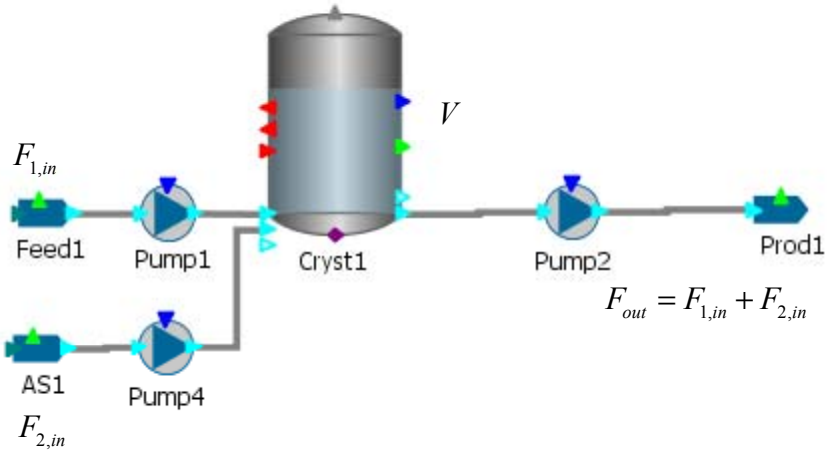
Example Crystallization

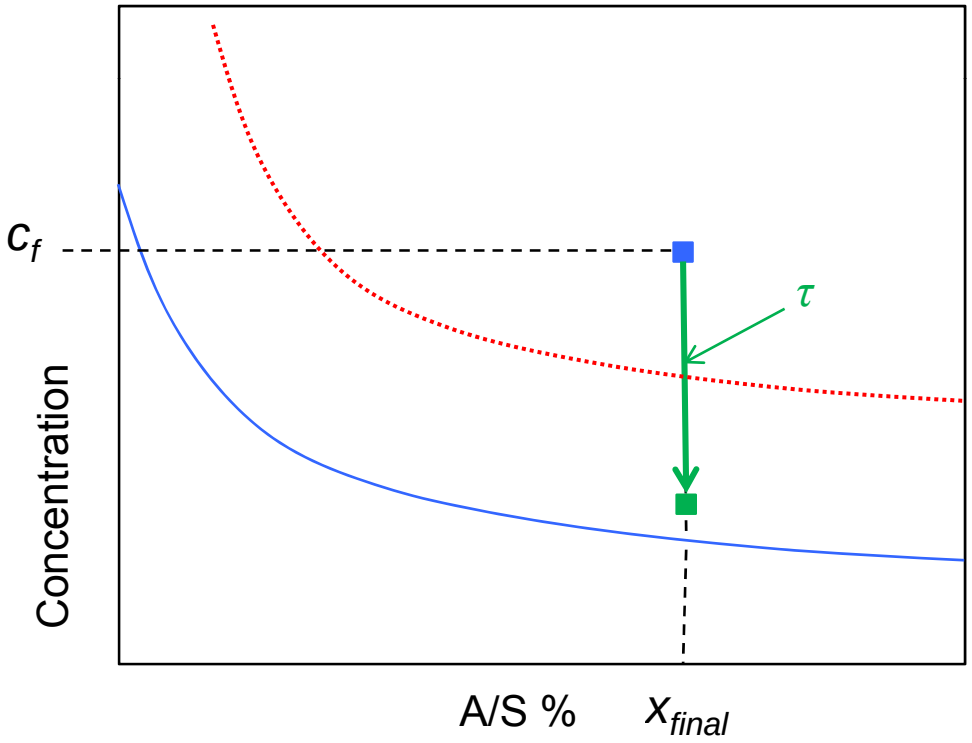


Continuous Anti-Solvent Crystallization Development Example – Single MSMPR

- Mixed Suspension, Mixed Product Removal – *Think CSTR*
- 1 variable – Residence Time (τ)
- 3 levels (low, medium, high), 1 day per experiment
- ~1 week to get probe process space.
- Prone to oiling, fouling, or agglomeration

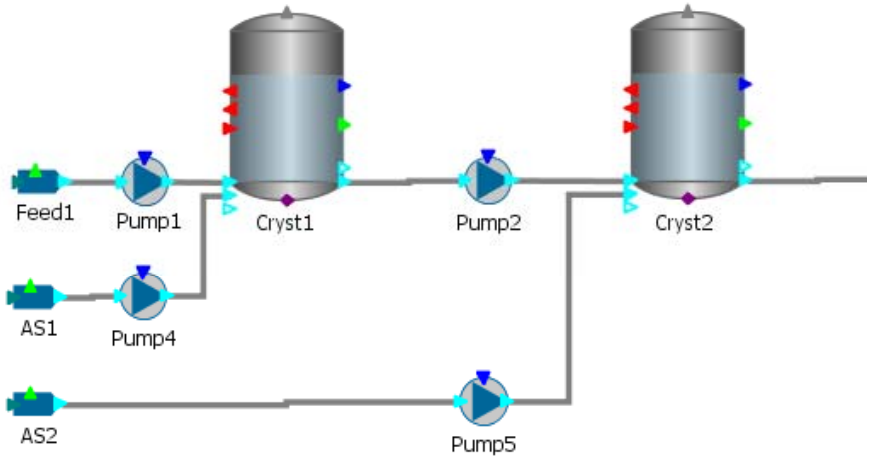
$$\tau = \frac{V}{F_{out}}$$

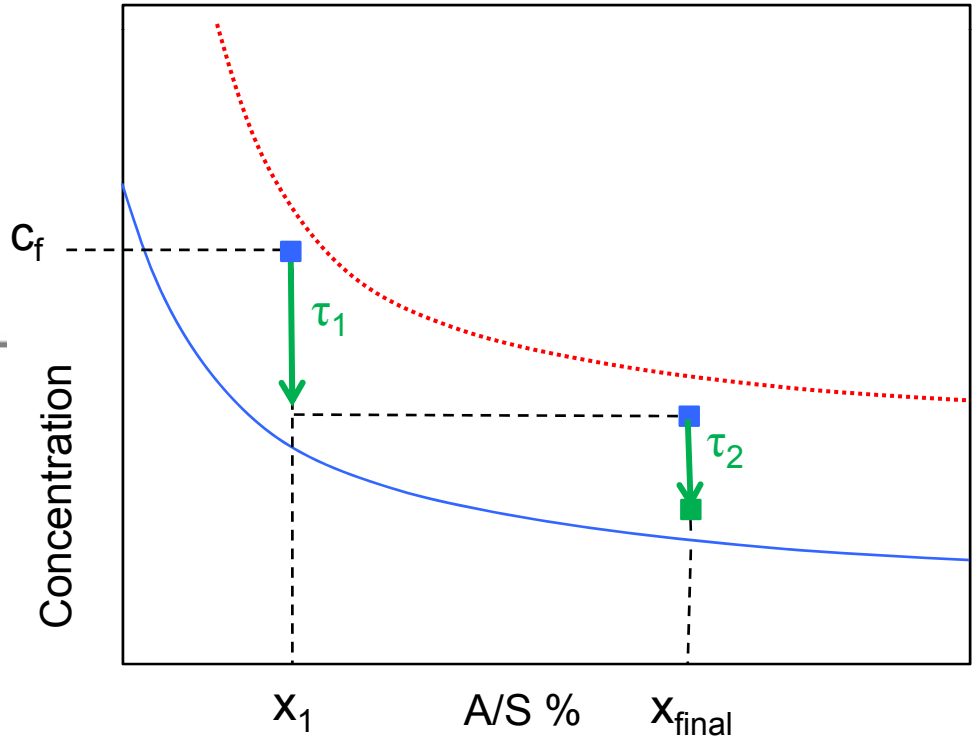




Continuous Anti-Solvent Crystallization Development Example – Two MSMPRs

- 3 variables – τ_1, τ_2, x_1
- 3 levels, 27 total experiments, 4 experiments/wk
- ~7 weeks





Accelerating Continuous Crystallization Development

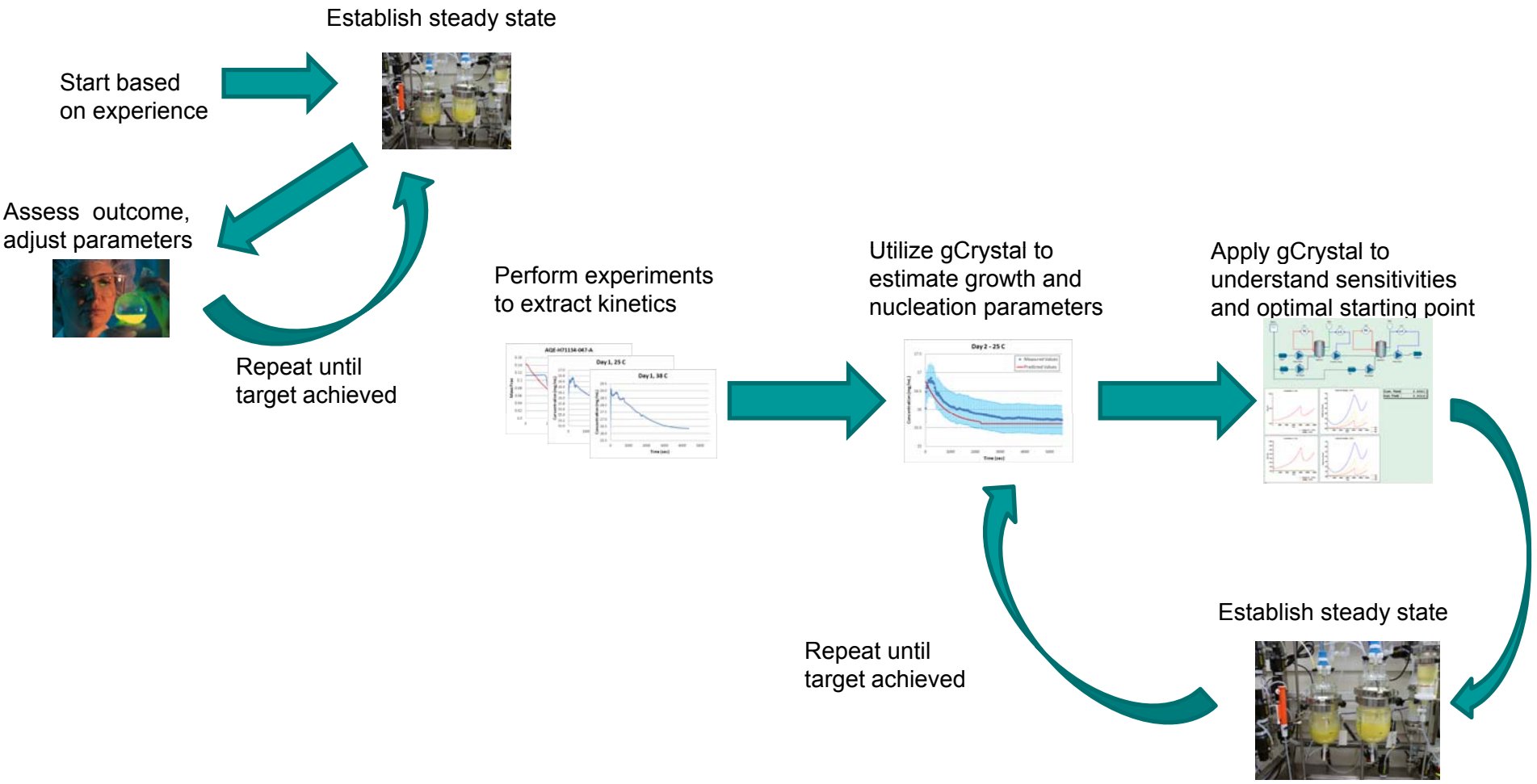
1) Time
   - Six to ten residence times to reach steady state.

2) Material
   - Small scale MSMPR requires 20 g to 50 g of product per condition.

3) Knowledge
   - Understanding crystallization kinetics using population balance models significantly increases process knowledge.

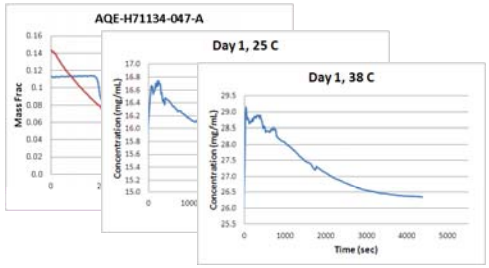
- *Modeling provides for a rational starting point for the experimental phase of process development.*

Continuous Crystallization Development Workflow

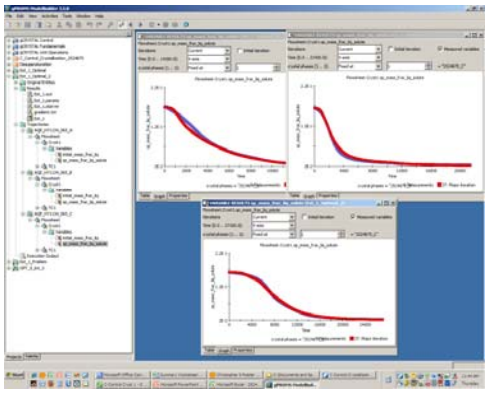


Development Cycle

Perform experiments to extract kinetics

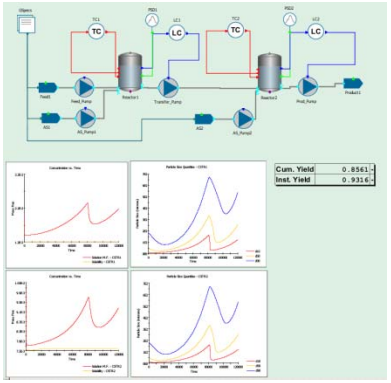


Determine growth and nucleation parameters



Apply appropriate kinetic model

Determine optimal process conditions



Establish steady state

Utilize new data to update model

Crystallization Modeling

Nucleation

Formation of initial particle

Growth

Increase in crystal mass

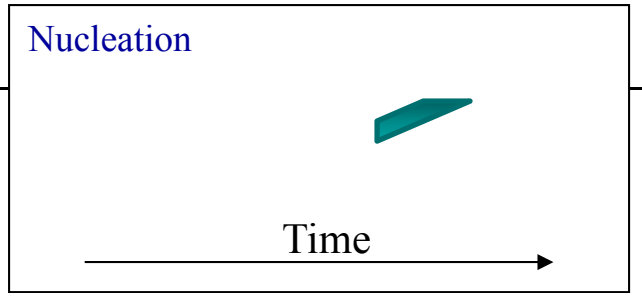
Attrition

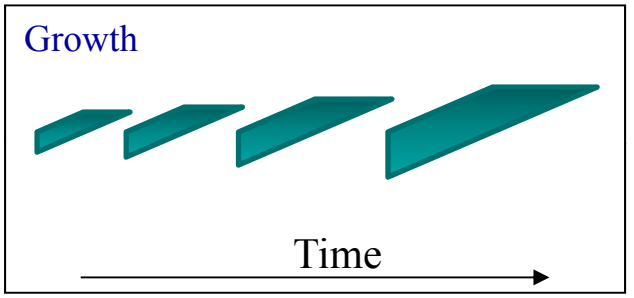
- Particle-particle collisions
- Turbulence and shear

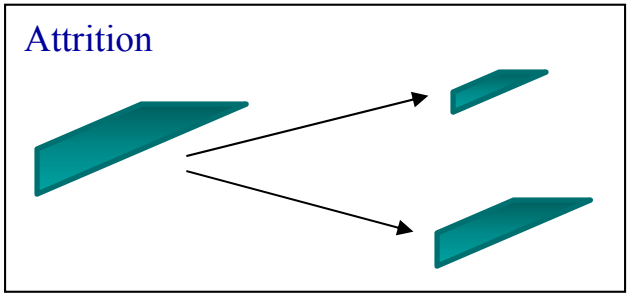
Agglomeration

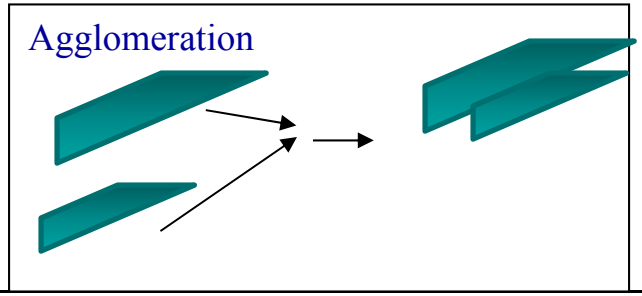
- Particle-particle collisions
- Adhesion of particles

$$\frac{\partial n(L,t)V}{\partial t} = F_{in}n_{in} - F_{out}n(L,t) - \frac{V\partial\left(G(C)n(L,t)\right)}{\partial L}$$
$$+V(B-D)$$



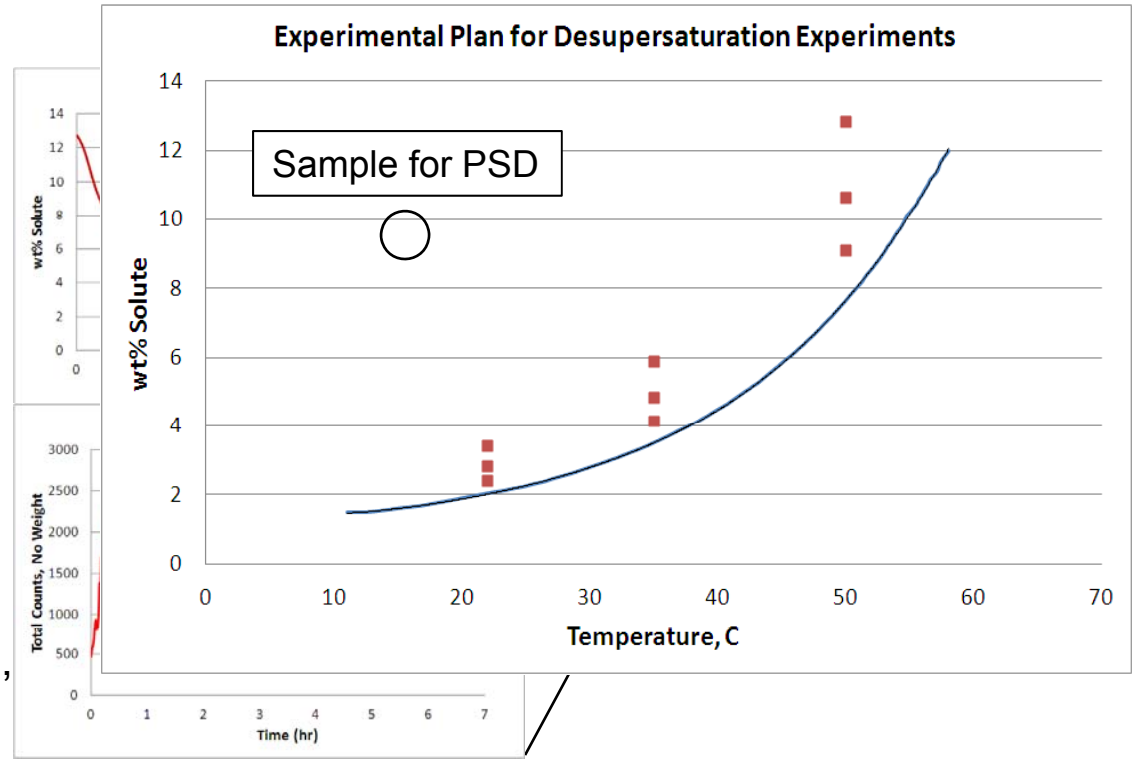






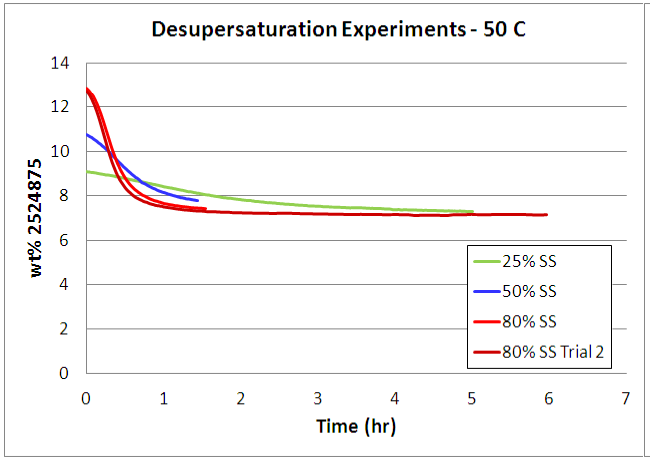
Experimental Growth and Nucleation Kinetics

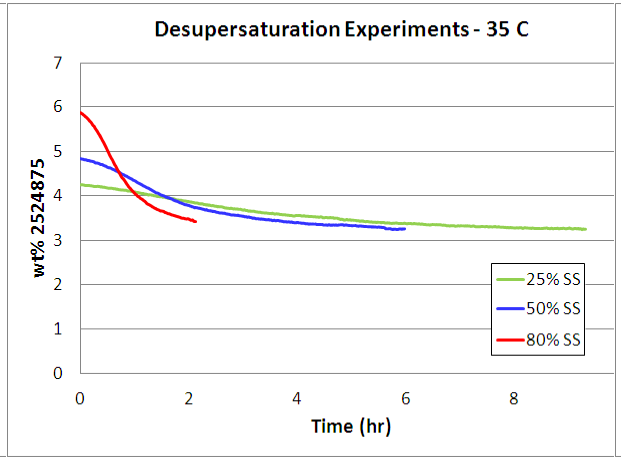
- De-supersaturation experiments[1] were conducted over a range of temperature and supersaturation.
- Seeded with well characterized seed.
  - 1 wt%
- De-supersaturation monitored .
  - ReactIR (ATR-IR).
  - FBRM.
- Sample for particle size.
- Repeat:
  - Add solvent to adjust the total solute composition.
  - Dissolve material by heating, cool to the next seed point.

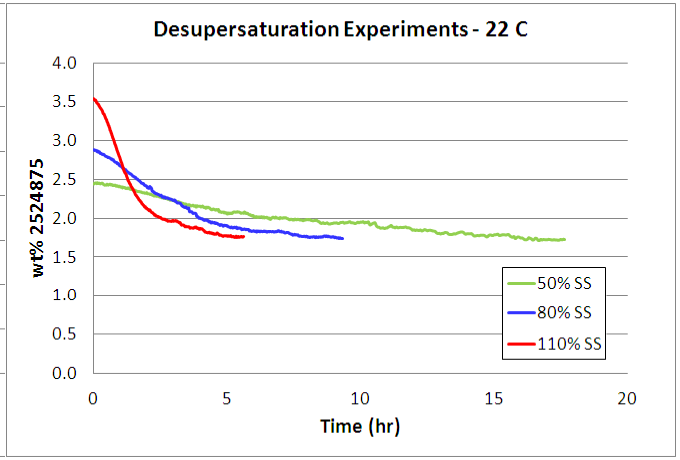


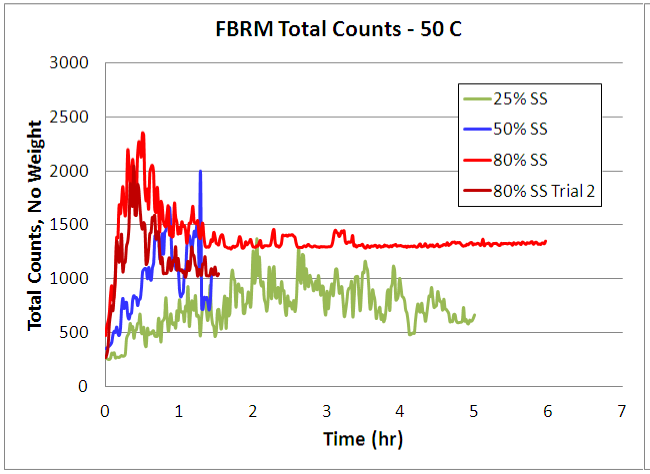
[1]Garside, J., Mersmann, A., Nyvlt, J. *Measurement of Crystal Growth and Nucleation Rates* 2nd ed. **2002**

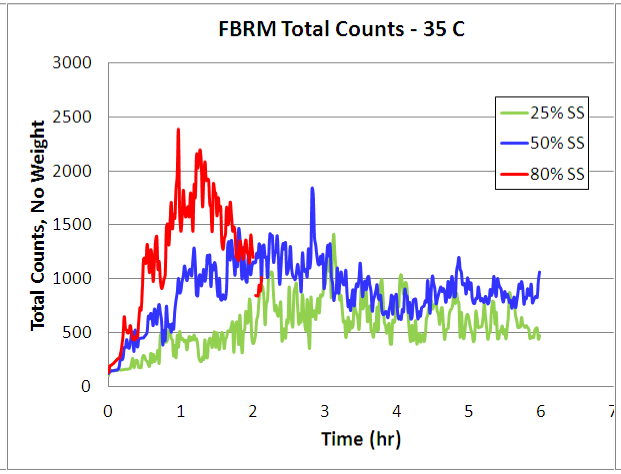
De-supersaturation Experiments

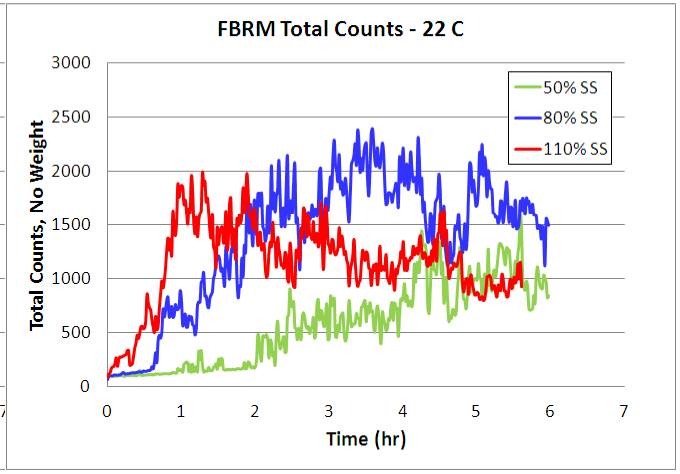




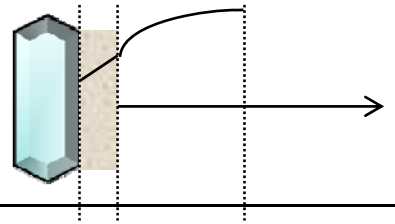








Growth Models



Two step growth

- Mass transfer to an interface: $$G(L) = k_d(T, L)\left(\frac{C - C_i(L)}{\rho_c}\right)$$
- Surface Integration
  - Two different driving forces (ΔC versus σ) were explored for surface integration.

$$G(L) = k_g \exp\left(\frac{-E_{A,g}}{RT}\right)\left[\frac{C_i(L) - C^*}{\rho_c}\right]^g$$

Delta C model (gCRYSTAL 2.0 built-in)

$$G(L) = k_g \exp\left(\frac{-E_{A,g}}{RT}\right)\left[\frac{C_i(L) - C^*}{C^*}\right]^g$$

Rel. supersaturation model

[2]Aoun, M., et al. *Chem. Eng. Sci.* **54** (1999) 1161-1180.
[3]Nagy, Z., et al. *Ind. Eng. Chem. Res.* **47** (2008) 1245-1252.
[4]Nancollas, Z., *J. Cryst. Growth* **3,4** (1968) 335-339.
[5]Zipp, G.L., et al. *Int. J. Pharm.* **51** (1989) 147-156.
[6]Kougoulos, E., et al. *J. Cryst. Growth* **273** (2005) 520-528.
[7]Mangood, A., et al. *J. Cryst. Growth* **290** (2006) 565-570.

Three Different Secondary Nucleation Models Were Compared

1. Secondary nucleation models based on the Evans model (built in to gCRYSTAL 2.0).
2. Modified model adds an Arrhenius dependence to the proportional factor, k_n.
3. Power law model.

- Primary nucleation assumed negligible.

$$B = k_n \sigma^n \frac{N_Q}{N_P} k_v \rho_c \varepsilon \int_{L_{\min}}^{\infty} nL^3 dL$$

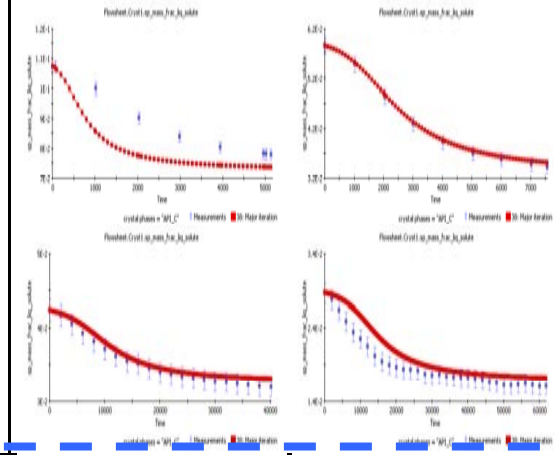
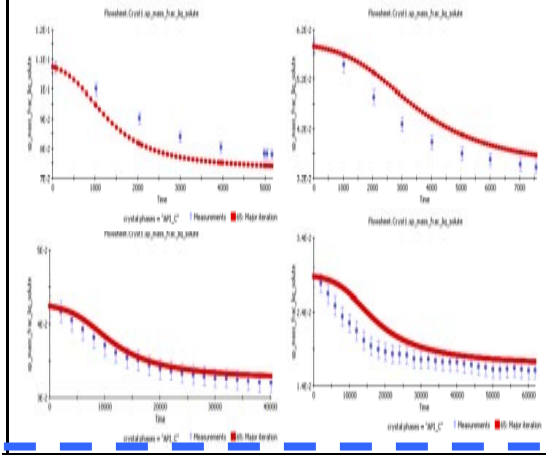
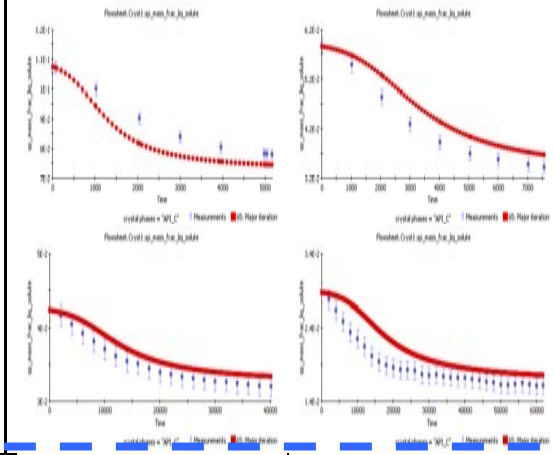
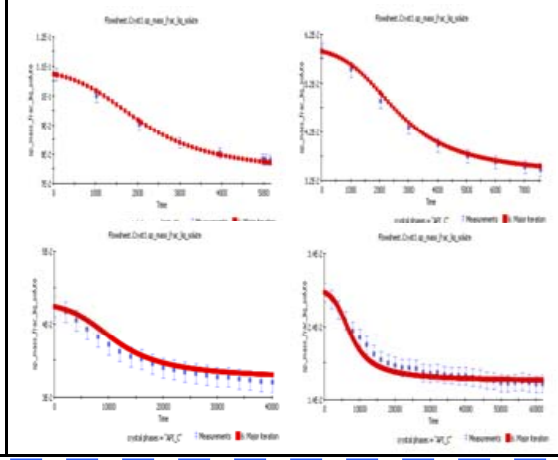
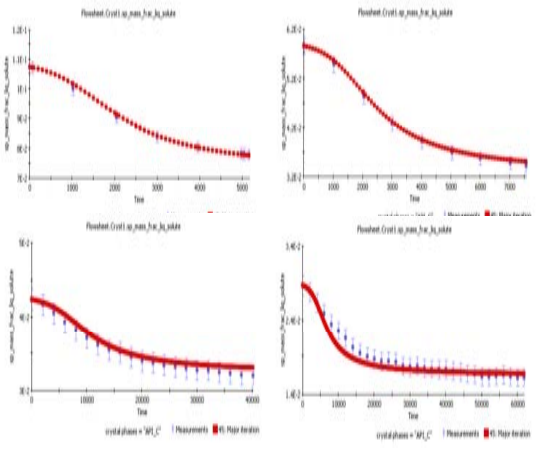
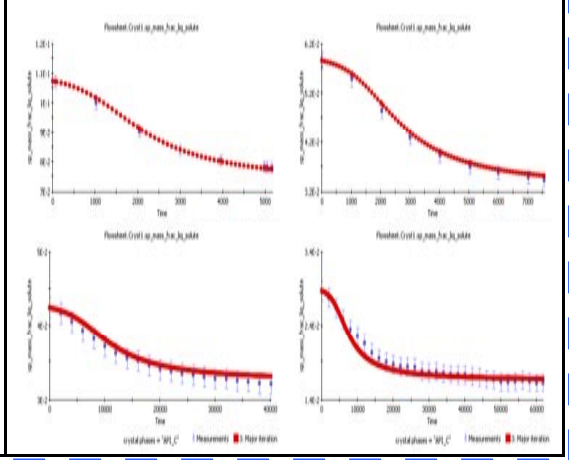
$$B = k_n \exp\left(\frac{-E_{A,n}}{RT}\right) \sigma^n \frac{N_Q}{N_P} k_v \rho_c \varepsilon \int_{L_{\min}}^{\infty} nL^3 dL$$

$$B = k_n \left(\frac{\Delta C}{\rho_c}\right)^n \exp\left(\frac{-E_{A,n}}{RT}\right)$$

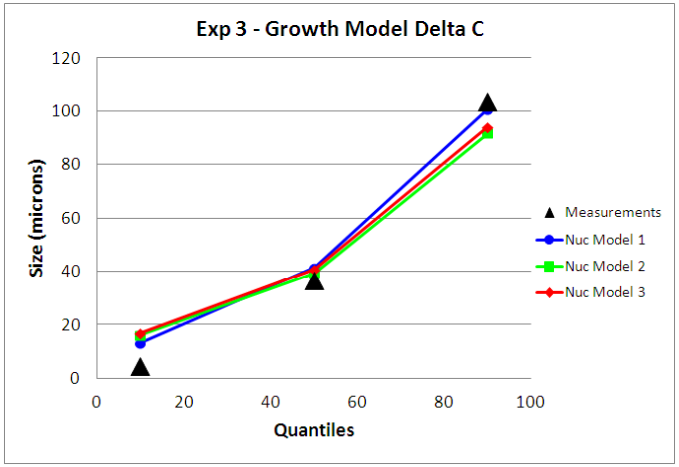
k_n = proportional factor
σ = relative supersaturation = S – 1
n = supersaturation dependence of the secondary nucleation rate
N_Q = Impeller pumping number
N_P = Impeller power number
kv = Volumetric shape factor
ρc = Mass density of crystals
ε = Energy dissipation rate
n = Number density of particles
L_{min} = Particle size above which particles are prone to attrition

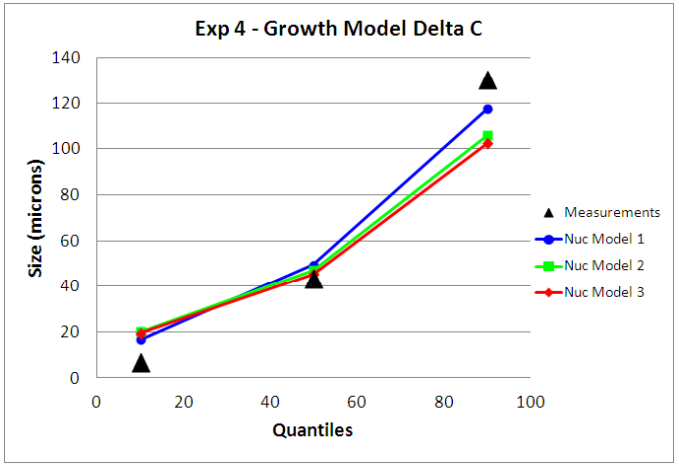
[8]Evans et. al., *AIChE Journal* ***20*** (1974) 959-966.

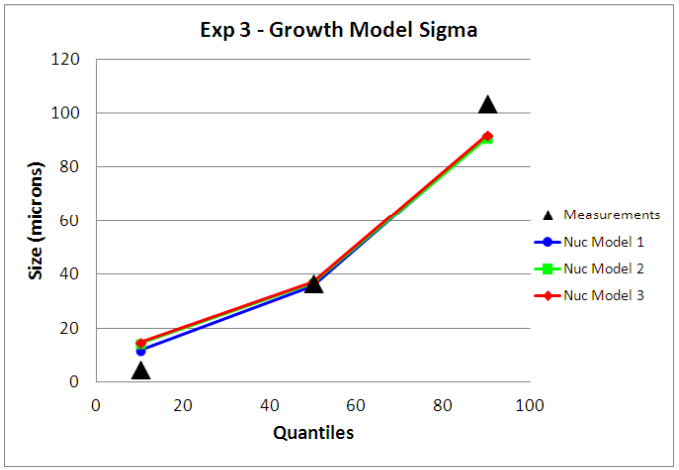
Solute Concentration vs. Time Fits

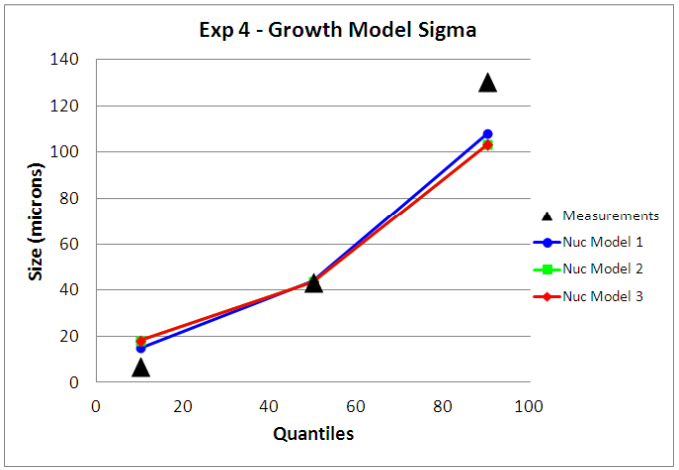
Growth Model ↓	Nucleation Model: Nuc Model 1 (Evan's)	Nuc Model 2 (w/T Dep.)	Nuc Model 3 (Power Law)
ΔC			
σ			

Particle Size Quantile Fits









Observations

- Nucleation Model 1 predicts broader PSD (lower d10, higher d90) across the board. This is more representative of the measured values.
- Predictions using relative supersaturation growth model less dependent on nucleation model choice.
- Nucleation Models 2 and 3 predict very similar values.

Parameter Estimation Results and Statistics

		Nucleation Model		
Model Parameter	Growth Model	Nuc Model 1	Nuc Model 2	Nuc Model 3
$E_{a,g}$ (J/mol)	ΔC	27851 (6.123)	35131 (6.00)	32905 (5.49)
$E_{a,n}$ (J/mol)		---	27761 (4.282)	1578.9 **(0.2299)**
k_g		1.153 **(0.5234)**	11.336 **(0.3593)**	9.1718 **(0.3445)**
$\ln(k_n)$		22.326 (179.1)	27.333 (10.36)	19.239 (8.177)
g	$k_g \exp\left(\frac{-E_{A,g}}{RT}\right)(c-c^*)^g$	1.9607 (17.17)	1.8557 (13.24)	1.9995 (12.8)
n		-0.16224 **(1.146)**	0.090871 **(0.5048)**	0.38055 (4.098)
$E_{a,g}$ (J/mol)	σ	55120 (20.97)	53924 (18.17)	55839 (19.34)
$E_{a,n}$ (J/mol)		---	38763 (8.465)	2389.6 **(0.6768)**
k_g		25.514 **(0.9168)**	15.686 **(0.8405)**	30.778 **(0.8535)**
$\ln(k_n)$		23.018 (118.2)	32.821 (17.82)	21.846 (17.47)
g	$k_g \exp\left(\frac{-E_{A,g}}{RT}\right)\left(\frac{c-c^*}{c^*}\right)^g$	1.8436 (18.52)	1.8292 (19.02)	1.7807 (18.87)
n		0.53625 (3.857)	1.2394 (8.994)	0.71874 (9.882)

$$J_{\text{sec}} = k_n \sigma^n \frac{N_Q}{N_P} k_v \rho_c \varepsilon \int_{L_{\min}}^{\infty} n \; L^3 \, dL$$

$E_{a,n}$ implemented as $k_n = k_{n,0} * \exp(E_{a,n}/RT)$

- Six simulations results are shown above. (T-test values in parenthesis).
- T-test values shown in red indicate the parameter is insignificant at a 95% confidence level.

Parameter Estimation Results and Statistics

- Lack of fit tests for each model reveal that the two most appropriate models are relative supersaturation with Nuc Model 1 and Nuc Model 2.
- As the weighted residual gets lower, model is more representative of the system.

Weighted Residual

	Nucleation Model		
Growth Model	Nuc Model 1	Nuc Model 2	Nuc Model 3
delta C	1138.6	1244.8	1256.9
Sigma	454.96	475.65	561.87

Chi Squared (95% Confidence)

	Nucleation Model		
Growth Model	Nuc Model 1	Nuc Model 2	Nuc Model 3
delta C	256.68	255.6	255.6
Sigma	256.68	223.16	255.6

Fitted Crystallization Model

- A full population balance model was fit to a series of de-supersaturation experiments.
  - Two-step growth.
  - Secondary nucleation.
  - No primary nucleation.
  - No agglomeration.
- Two models will be considered:

Parameter	Model 1	Temp. Dep. 2nd Nucleation
$E_{a,g}$ (J/mol)	55120	53924
$E_{a,n}$ (J/mol)	---	38763
k_g	25.5	15.7
$\ln(k_{n,0})$	23.0	32.8
g	1.84	1.83
n	0.536	1.24

Crystal Growth Model (MassTransfer-Surface Integration)

$$R_G = k_d \left(C - C_{\text{int}}\right)$$ k_d = calculated diff. coefficient

$$R_G = k_g \exp\left(\frac{-E_{A,g}}{RT}\right)\left(\frac{C_{\text{int}} - C^*}{C^*}\right)^g$$

Secondary Nucleation (Evans)

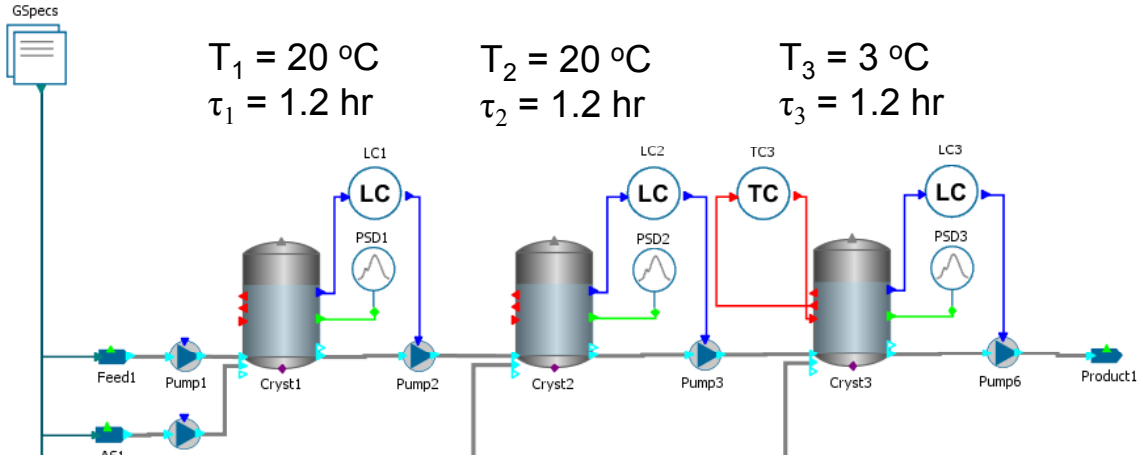
$$J_{\text{sec}} = k_n \sigma^n \frac{N_Q}{N_P} k_v \rho_c \varepsilon \int_{L_{\min}}^{\infty} n \; L^3 \, dL$$

k_n = constant
n = supersaturation dependence of the secondary nucleation rate
N_Q = Impeller pumping number
N_P = Impeller power number
kv = Volumetric shape factor
ρc = Mass density of crystals
ε = Energy dissipation rate
n = Number density of particles
L_{min} = Particle size above which particles are prone to attrition

Evans et al. *AIChE Journal* 1974, *20, 959–966.*

Model 1: $k_n = k_{n,0}$ | Model 2: $k_n = k_{n,0} * \exp(E_{a,n}/RT)$

gCRYSTAL Model Verification – Steady State Conditions, Iteration 1



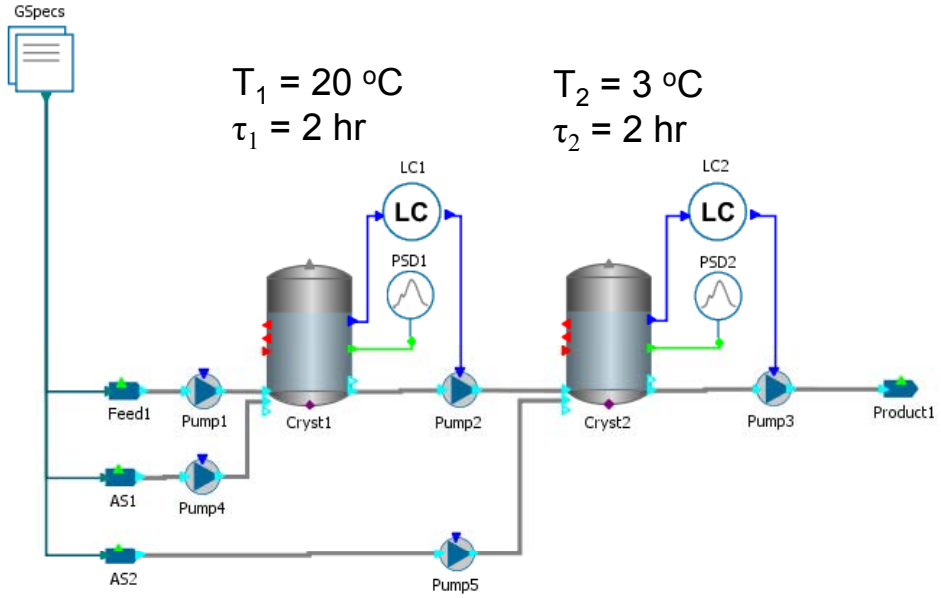
A/S_1 = 5 L EtOH/kg Solute

A/S_2 = 0.9 L H2O/kg Solute

A/S_3 = None

Value	Actual	Model 1	Model 2
Solubility MSMPR 1 (wt%)	5.7	5.7	5.7
Solubility MSMPR 2 (wt%)	1.2	1.2	1.2
Solubility MSMPR 3 (wt%)	0.76	0.73	0.73
Solute in Solution MSMPR 1 (wt%)	**7.9**	**8.2**	10
Solute in Solution MSMPR 2 (wt%)	**1.7**	**1.6**	2.0
Solute in Solution MSMPR 3 (wt%)	**0.83**	**0.86**	1.0
Rel. Supersaturation MSMPR 1 (%)	40	44	78
Rel. Supersaturation MSMPR 2 (%)	35	29	63
Rel. Supersaturation MSMPR 3 (%)	9.2	18	41

gCRYSTAL Model Verification – Steady State Conditions, Iteration 2



A/S_1 = 2 L (85/15 EtOH/H2O)/kg Solute

A/S_2 = 2 L (85/15 EtOH/H2O)/kg Solute

Value	Actual	Model 1	Model 2
Solubility MSMPR 1 (wt%)	7.5	7.5	7.5
Solubility MSMPR 2 (wt%)	1.9	1.8	1.8
Solute in Solution MSMPR 1 (wt%)	**8.8**	**10.**	13
Solute in Solution MSMPR 2 (wt%)	**2.0**	**2.4**	3.4
Rel. Supersaturation MSMPR 1 (%)	18	32	69
Rel. Supersaturation MSMPR 2 (%)	6.5	34	85

Optimization Problem Statement

Potential Objectives

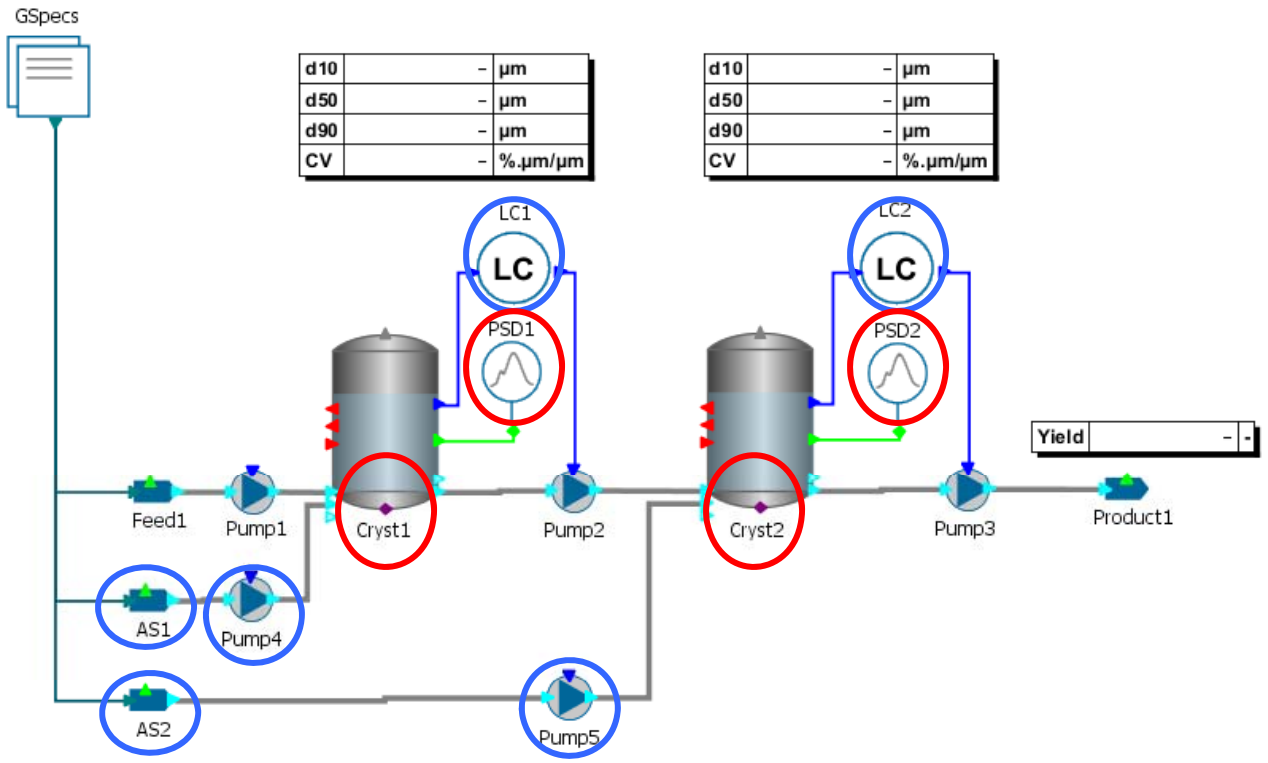
- Simple
  - Maximize Yield
  - Minimize Impurities
    - Need impurity model…
- Compound
  - Combine simple objectives
    - Maximize yield but penalize volume
    - penalize impurities
    - penalize deviation from target particle sizes
- Explicit Cost
  - Assign costs to product loss, solvent use, equipment time, etc.

Potential Constraints

- Equipment Size
- Solute Concentrations
  - Prevent process problems such as oiling, agglomeration, encrustation
- Physical Properties
  - Bounds on PSD quantiles
    - d10 > x (prevent excess fines)
    - d90 < x (bioavailability)
    - d90 – d10 < x (powder flow)
- Impurity levels
  - Need impurity models…

2-MSMPR Optimization

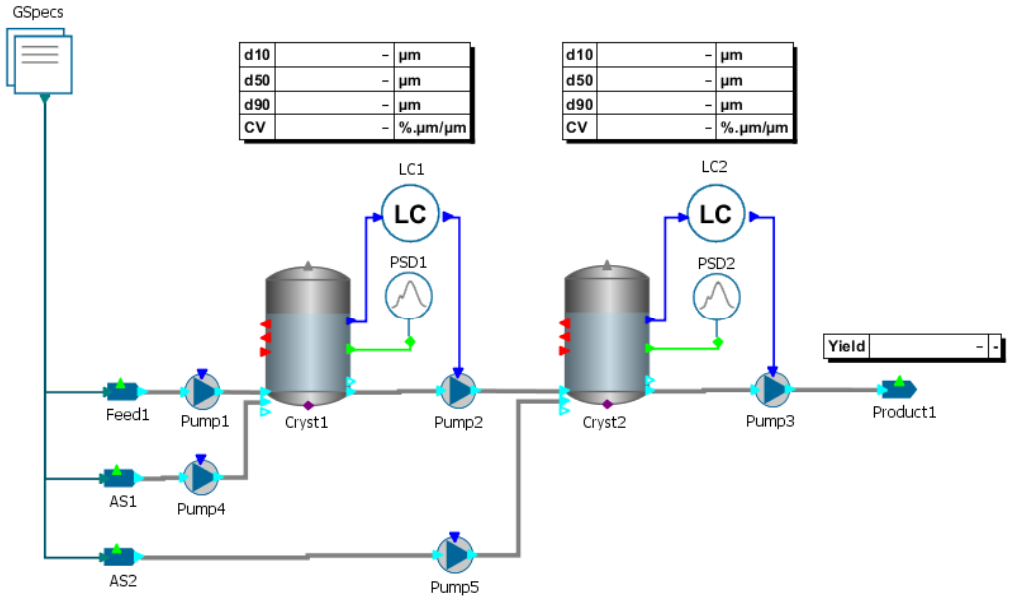
- Objective Function: Max[Yield – (Residence Time MSMPR1 + Residence Time MSMPR2) / Scaling Factor]
- Yield is a fractional amount, residence time is in minutes and Scaling Factor = 2000
  - (20 minutes = 1% yield)
- Controls:
  - AS1 Composition
  - AS2 Composition
  - Pump4 Rate
  - Pump5 Rate
  - LC1 Volume
  - LC2 Volume
- Constraints:
  - Cryst1 σ < 1
  - Cryst2 σ < 0.2
  - d10 > 10 µm
  - d90 < 200 µm
- Optimization maximizes yield with a penalty on equipment size
- Constrain on particle size, supersaturation.



2-MSMPR Optimization

- Effect of particle size constraint, d_{90} < 200 µm
- Feed basis ~5.5 g product/hr

Parameter	Value
AS1 EtOH w/w%	88.1%
AS2 EtOH w/w%	80% (lower bound)
Crystallizer 1 Vol.	30 mL (low bound)
Crystallizer 2 Vol.	524 mL
Cryst1 Res. Time	**47 min**
Cryst2 Res. Time	**~6 hours**
AS1 Flowrate	~4 L/kg feed
AS2 Flowrate	~8.5 L/kg feed
Steady-State Yield	89.9 %

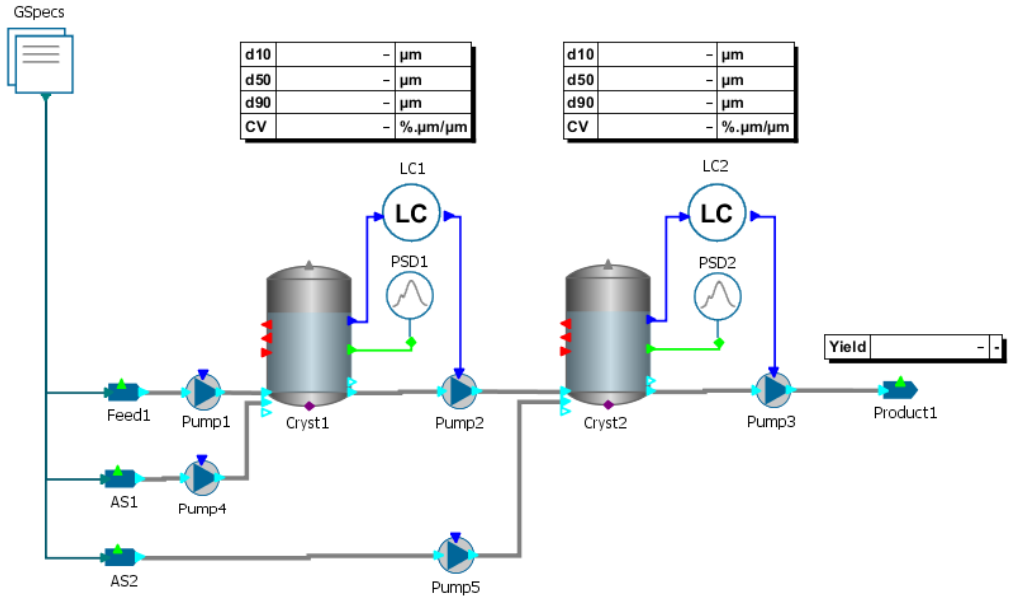


- Particle size bounded by the maximum constraint.
- σ bounded by the upper limit in each MSMPR.

2-MSMPR Optimization

- Effect of particle size constraint, d_{90} < 190 µm.

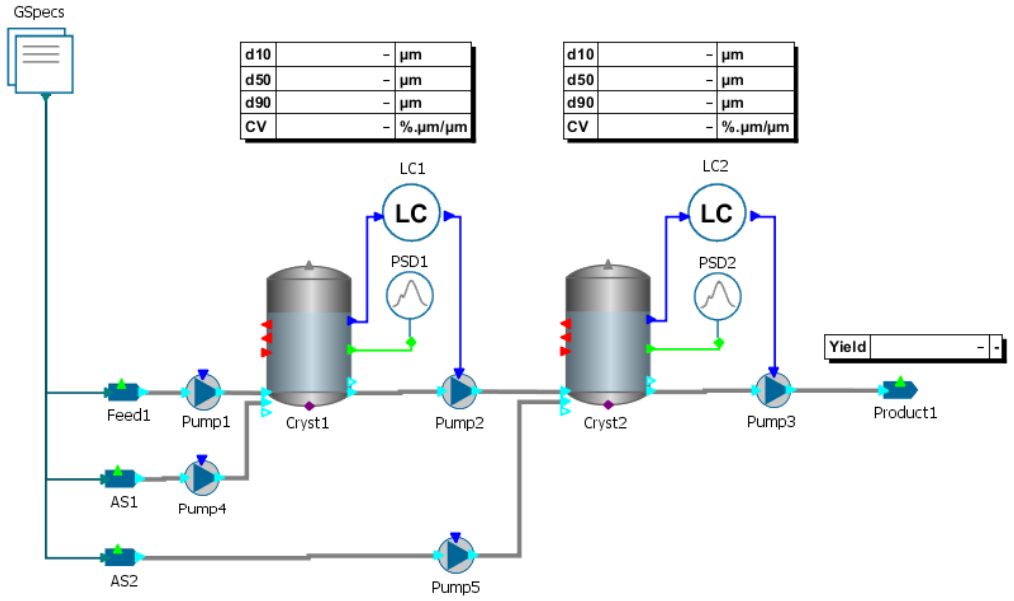
Parameter	Value
AS1 EtOH w/w%	91.3% ↑
AS2 EtOH w/w%	80% (lower bound)
Crystallizer 1 Vol.	30 mL (low bound)
Crystallizer 2 Vol.	727 mL
Cryst1 Res. Time	**45 min** ↓
Cryst2 Res. Time	**~7 hours** ↑
AS1 Flowrate	~4.2 L/kg feed ↑
AS2 Flowrate	~11 L/kg feed ↑
Steady-State Yield	89.7 % ↓



2-MSMPR Optimization

- Effect of particle size constraint, d_{90} < 175 µm

Parameter	Value
AS1 EtOH w/w%	95.3% ↑
AS2 EtOH w/w%	80% (lower bound)
Crystallizer 1 Vol.	30 mL (low bound)
Crystallizer 2 Vol.	977 mL
Cryst1 Res. Time	**42 min** ↓
Cryst2 Res. Time	**~8.3 hours** ↑
AS1 Flowrate	~4.8 L/kg feed ↑
AS2 Flowrate	~13 L/kg feed ↑
Steady-State Yield	87.5 % ↓



Summary of Trade-Offs

Limit – d_{90} max (µm)	Cryst1 τ (hr)	Cryst2 τ (hr)	Total Process Volume (L/kg)	Yield (%)
200	0.78	6	14	90
190	0.75	7	17	90
175	0.70	8.3	20	87

- Particle sizes is tunable
- Smaller size requires:
  - Larger equipment size (residence time)
  - More anti-solvent
  - Results in lower yields.

Conclusions

De-supersaturation experiments were determine growth and nucleation kinetics.

Multiple models for growth and nucleation considered.

- Generated significant process insight for process design and optimization.

Verification of the predictive capability of the different secondary nucleation models.

Process optimization was performed for a 2 MSMPRs.

- Resulted in much different residence times in each from initial experimental development.

Model was used to provide directional guidance on how to manipulated process variables to achieve desired results.

Utilization of population models for continuous crystallization does speed process development time.