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

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# Outline

**Project objectives**

*… and main deliverables*


**Progress summary**

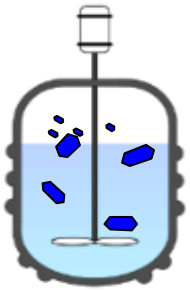
*… in a nutshell*

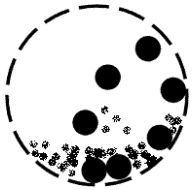
**Next steps**

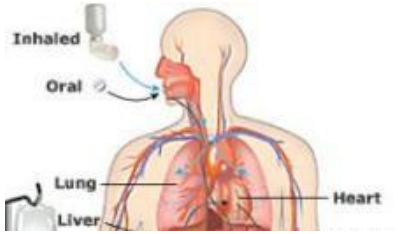
*… given what we know, what could we do*

# Project objectives

- 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**

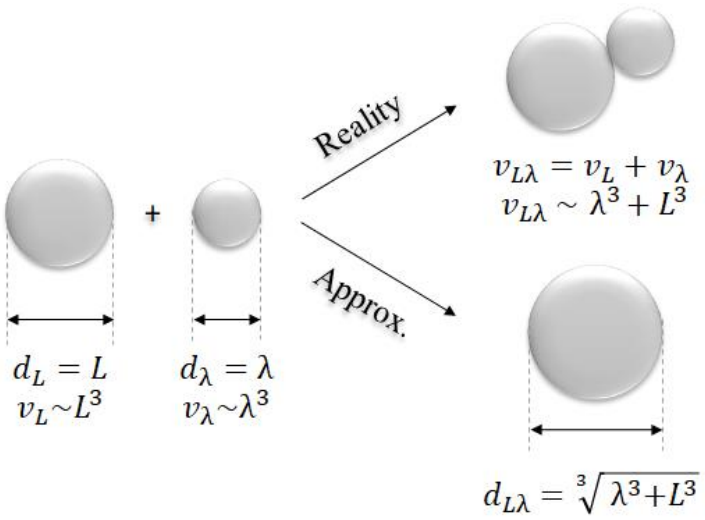
# *1D agglomeration and breakage models and solvers*

# Agglomeration modeling in crystallization (1D)

- **Agglomeration often spontaneously occurs during crystallization.**
- **“Forced agglomeration”: spherical agglomeration.**
- **Granulation processes fully governed by agglomeration.**

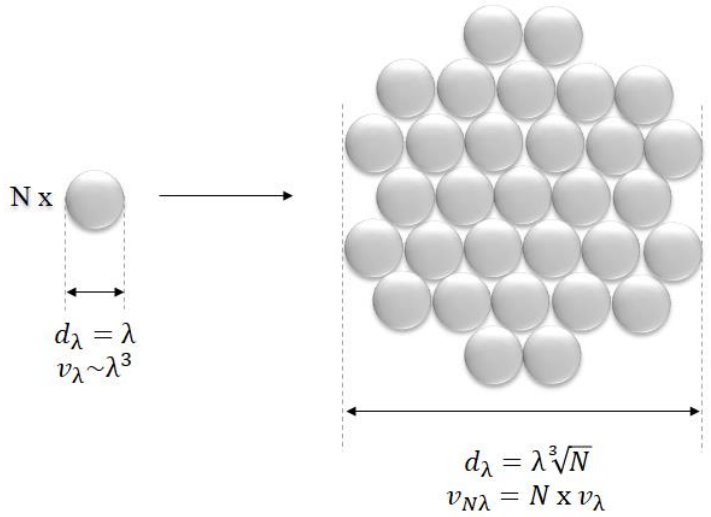
### Agglomeration of two primary particles

- Volume conservation
- No shape conservation. Modeling practice: sphere equivalent diameter




### Agglomeration of multiple particles

- Volume conservation
- Quasi shape-conservation. Modeling practice: sphere equivalent diameter



# Agglomeration modeling in crystallization (1D)

The agglomeration population balance model-equation:

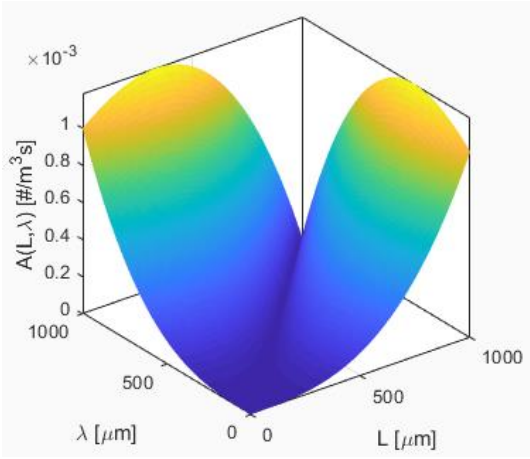
$$\frac{\partial n(L,t)}{\partial t} = \frac{L^2}{2}\int_0^L \frac{\beta\left[(L^3-\lambda^3)^{1/3},\lambda\right]}{(L^3-\lambda^3)^{2/3}} n\left((L^3-\lambda^3)^{1/3},t\right) n(\lambda,t)d\lambda - n(L,t)\int_0^{L_{max}} \beta(L,\lambda)n(\lambda,t)d\lambda$$

Birth rate of $L$-size particles by agglomeration

Death rate of $L$-size particles by agglomeration

$\beta(L,\lambda)$: agglomeration kernel. Implemented:

| Name | $\beta(L,\lambda)$ |
|---|---|
| Constant | $k_{ag}$ |
| Brownian motion | $k_{ag}\frac{(L+\lambda)^2}{L\lambda}$ |
| Sum | $k_{ag}(L^3+\lambda^3)$ |
| Hydrodynamic | $k_{ag}(L+\lambda)^3$ |
| Differential force | $k_{ag}(L+\lambda)^2\lvert L-\lambda\rvert^2$ |




Differential force ($k_{ag} = 10^{-12}$)



$k_{ag}$: might depend on temperature, stirring conditions, growth rate etc.

# Breakage modeling in crystallization (1D)

- **Attrition often occurs during crystallization processes.**
- **Fragmentation might also occur.**
- **Wet milling: governed by particle breakage.**
- **Breakage: volume conserving. Not shape conserving (there are exceptions, as high aspect-ratio crystals)**

The breakage population balance model-equation:

$$\frac{\partial n(L,t)}{\partial t} = \int_{\lambda}^{L_{max}} b(L|\lambda) n(\lambda,t) S(\lambda) d\lambda - S(L) n(L,t)$$

Birth rate of $L$-size particles by breakage

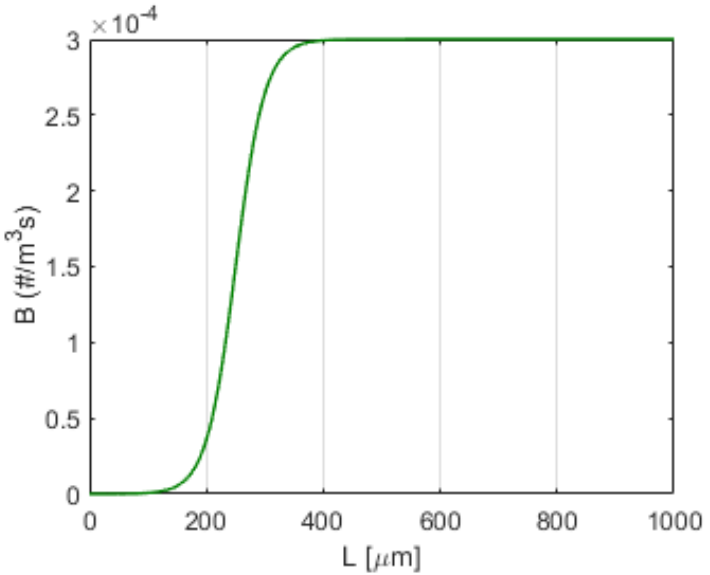
Death rate of $L$-size particles by breakage

# Breakage modeling in crystallization (1D)

## Breakage selection function ($S(L)$)

- Probability that an $\boldsymbol{L}$ size crystal breaks up
- Numerous functions. Implemented: constant, power-law and hyperbolic tangent

$$S(L) = k_{br}\frac{1}{2}\left(\tanh\left(k(L_c - L)\right) + 1\right)$$

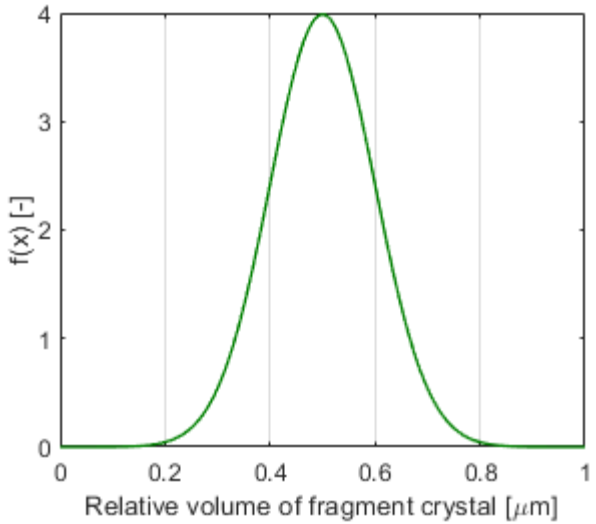



Parameters: $k_{br}$ = 0.0003; $k$ = 0.02; $L_c$ = 250 μm

## Fragment distribution function ($b(L|\lambda)$)

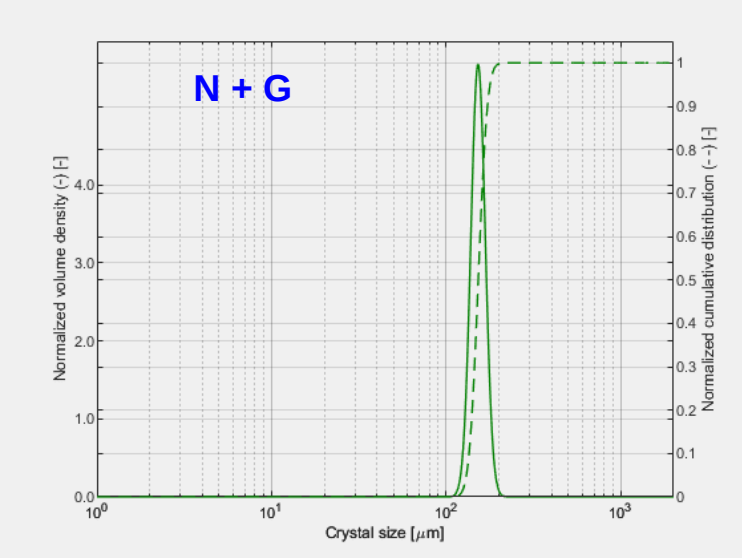
- Probability that $\boldsymbol{L}$ sized crystal is produced from the breakage of a $\boldsymbol{\lambda}$ size crystal
- Implemented: symmetric fragmentation, uniform distribution, normal distribution

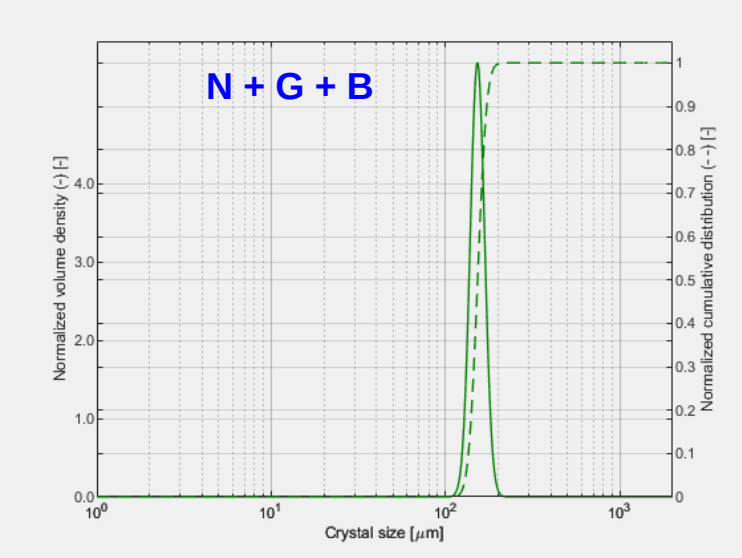
$$b(L|\lambda) = \frac{1}{\sigma\sqrt{2\pi}}\exp\left(-\frac{(L-\mu)^2}{2\sigma^2}\right)$$

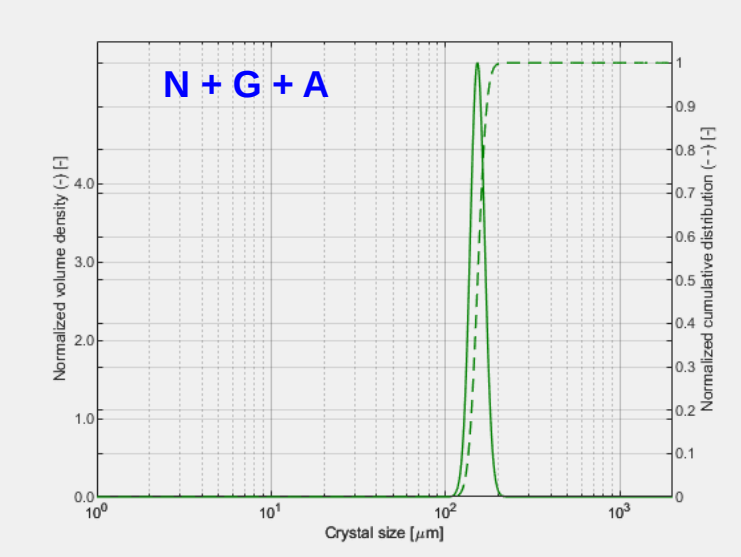


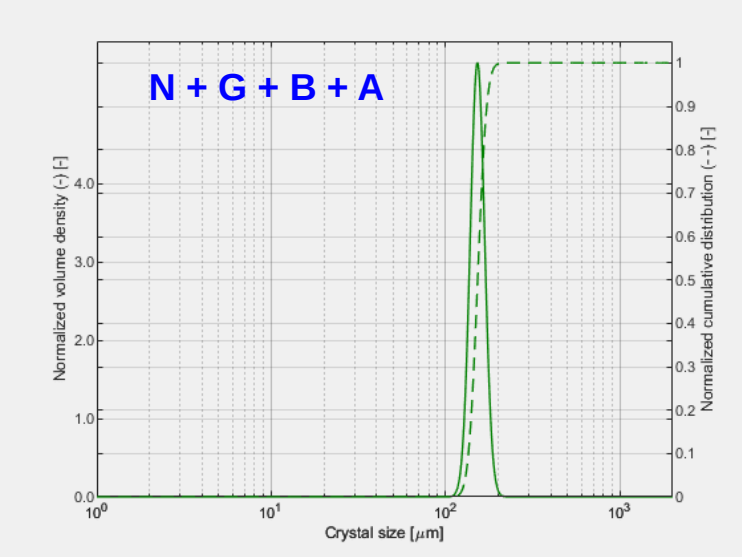

Parameters:$\sigma$= 0.1$\boldsymbol{\lambda}$; $\mu$= 0.5 $\boldsymbol{\lambda}$

# Implementation in the generic 1D solver



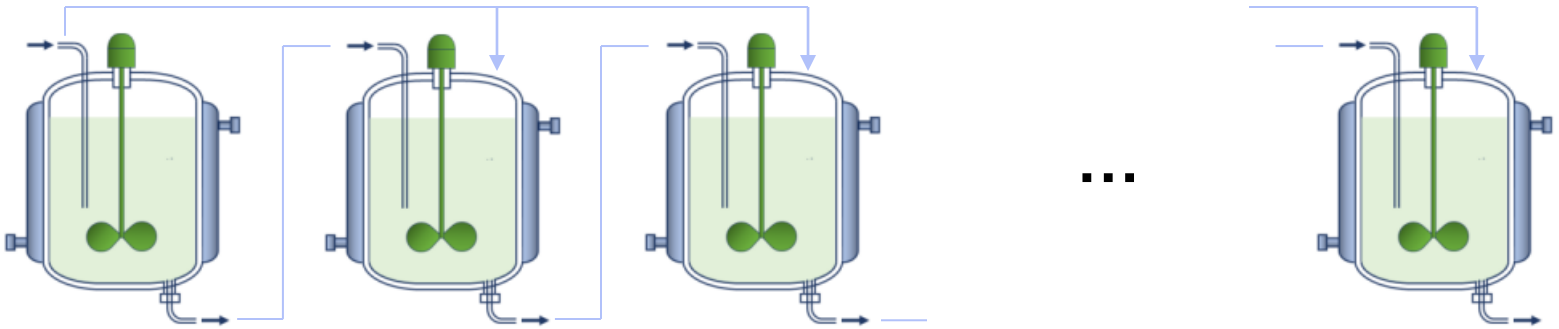



# *Integrated system model development: MSMPR cascade and it's applications*

# MSMPR cascades

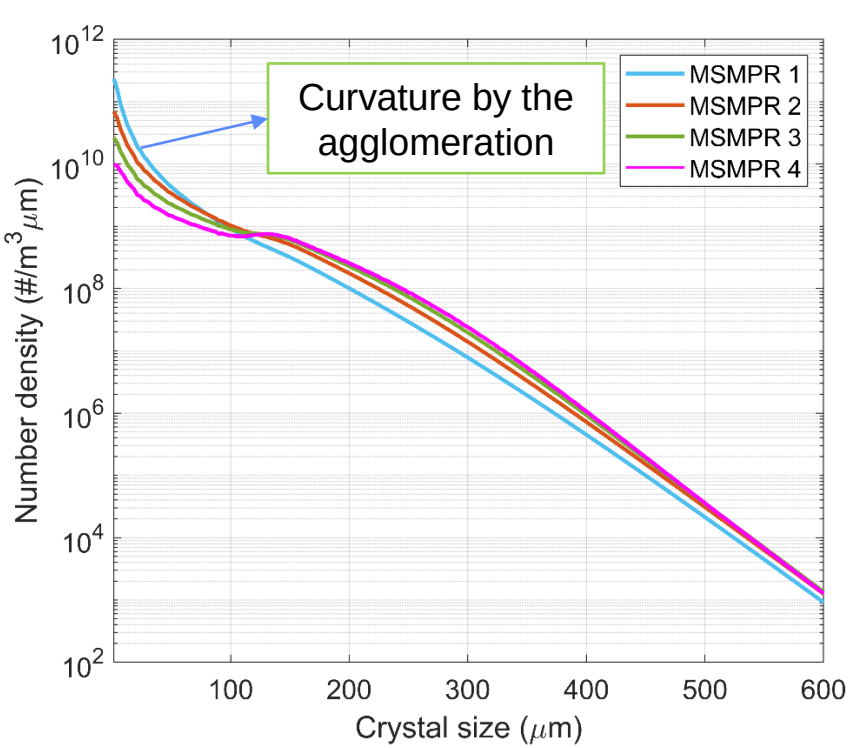
- First step in the flexible crystallization network development.
- Mechanisms: 1D nucleation, growth, dissolution, breakage, agglomeration
- System types: cooling, antisolvent, combined cooling and antisolvent

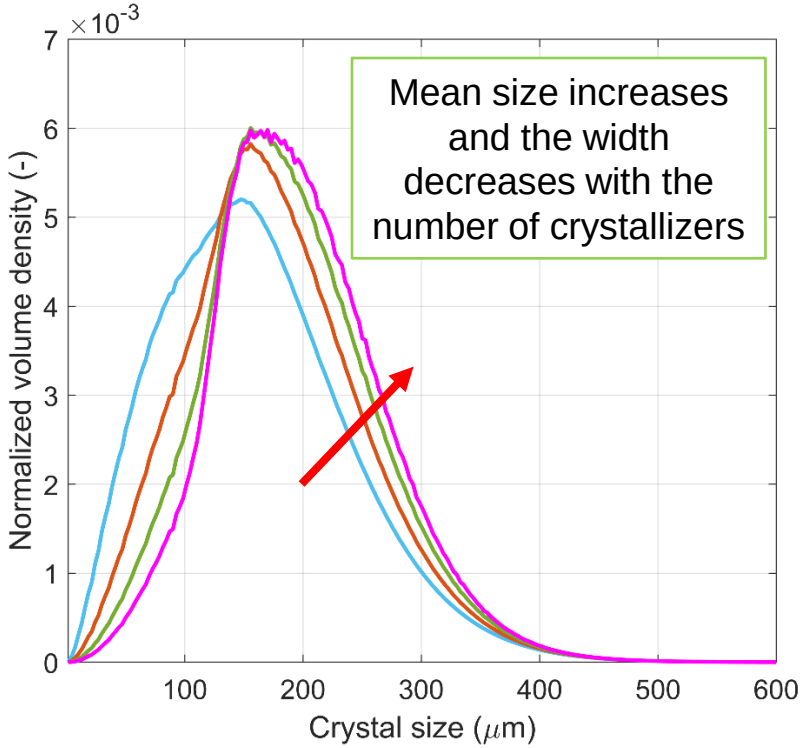



- Flexible number of crystallizers (no upper limit)
- Operating conditions configured individually for each crystallizer

# MSMPR cascades: modeling and simulation

- Quick example: pure cascade of four MSMPRs. Model-equations were populated and solved automatically for each crystallizer
- Cooling crystallization with identical yields and mean residence times

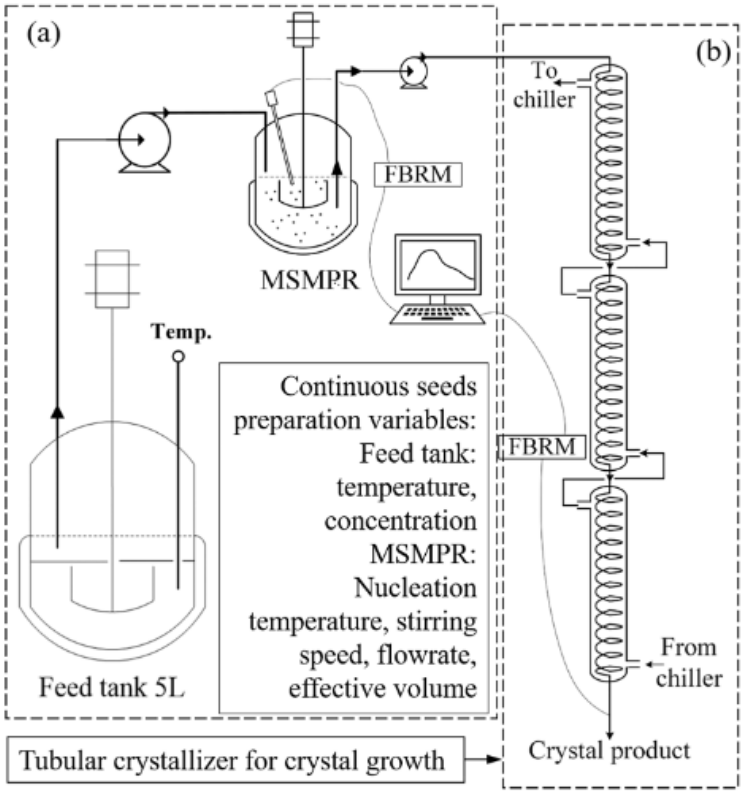


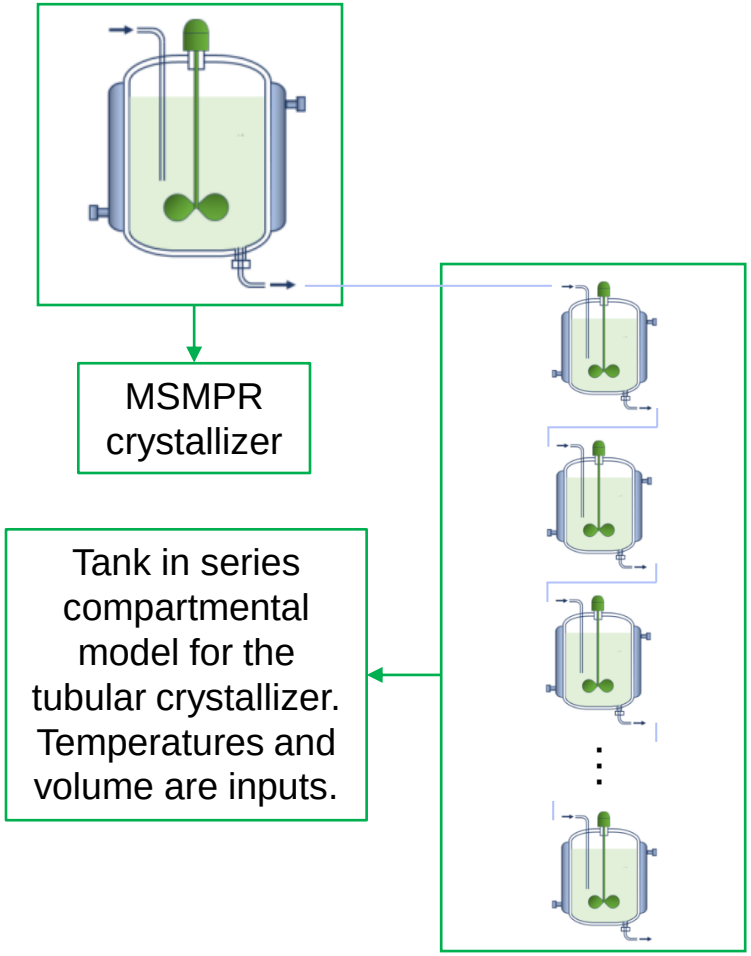

**Typical MSMPR cascade simulation with nucleation, growth, agglomeration and size dependent breakage (~10 s, 3 μm grid size, 2400 μm max. size)**

# Flexible MSMPR cascade model: further applications

- Integrated MSMPR-tubular crystallizers are promising devices. In MSMPR in-situ seed generation happen.




Scheme of an integrated continuous MSMPR-tubular crystallizer system for polymorphic crystallization *

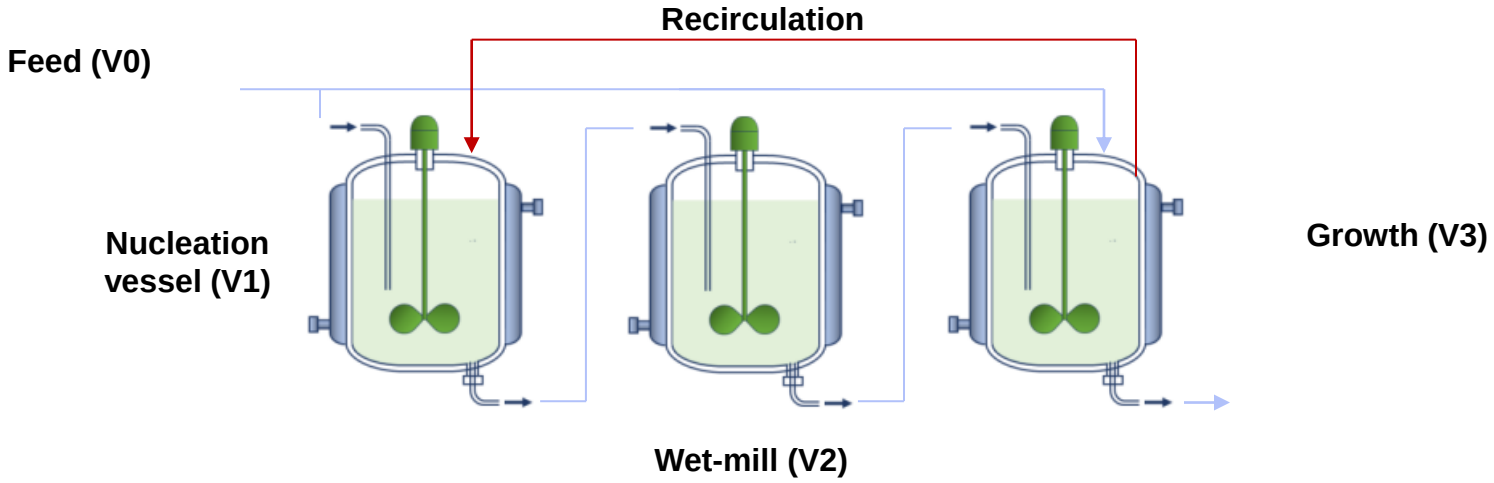





* Z. Gao et al., Journal of Crystal Growth, 507, 334-351

# Extension to MSMPR network (in progress)

- Model-equations populated based on adjacency matrices that defines the connectivity
- The active crystallization mechanisms set for each MSMPR




| | V0 | V1 | V2 | V3 |
|---|---|---|---|---|
| V0 | 0 | 1 | 0 | 1 |
| V1 | 0 | 0 | 1 | 0 |
| V2 | 0 | 0 | 0 | 1 |
| V3 | 0 | 1 | 0 | 0 |

- *Example*: definition of connectivity between the MSMPRs
- "1" in a cell means that there is a flux from the crystallizer in the given line to the crystallizer of the given column
- Similar adjacency matrices are applicable for the definition of other operating conditions (e.g. flowrates)

# *Parameter estimation: a novel way of using FBRM data and it's application to 1D and 2D crystallization kinetics estimation*

# How to use the FBRM count data for PE?

**Repeating question, because:**

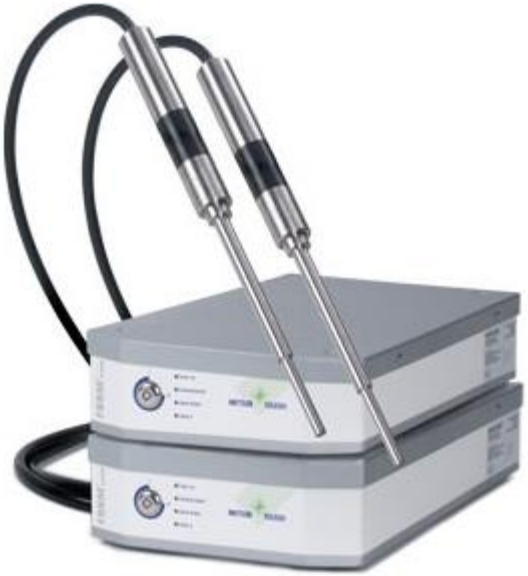
- FBRM became routine tool in crystallization monitoring
- Great for qualitative measurements, indirect feedback control on particle size (DNC)
- Difficult to quantify
- Inaccurate CSD-CLD transformations
- Generally not used for PE

$$\boldsymbol{O(KP)} = f(\Delta C) + wf(\Delta D) + uf(\Delta N)$$

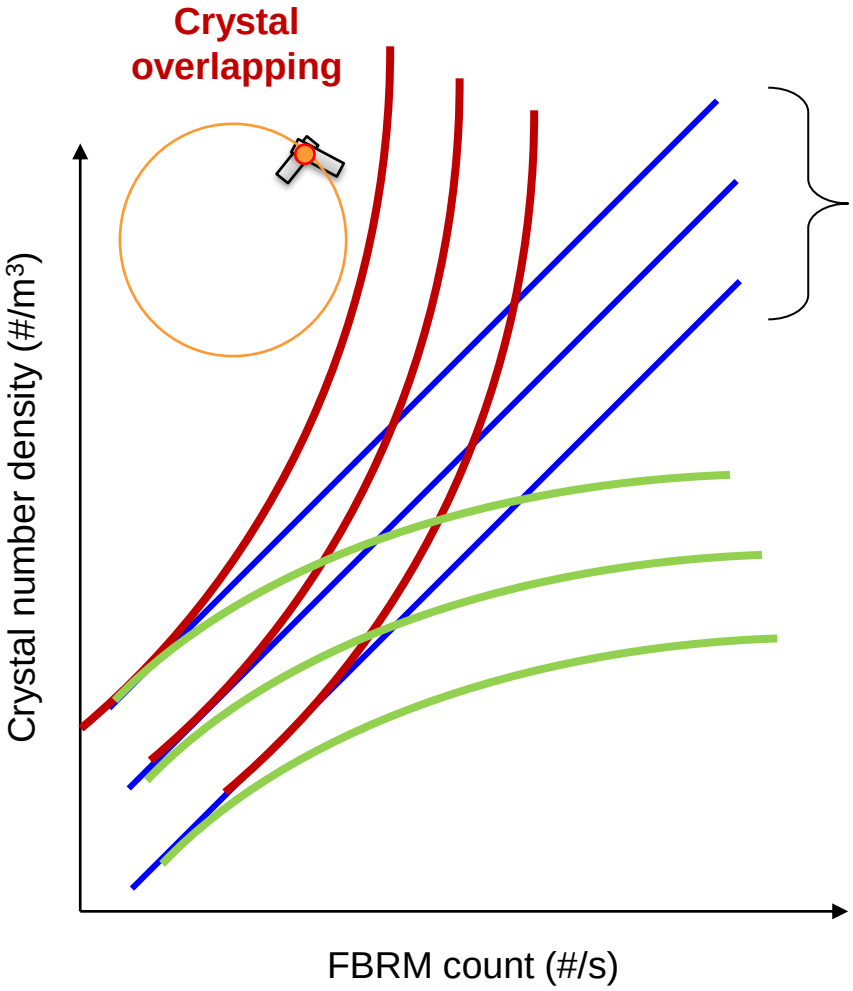
$\Delta C$ sum-squared error of concentrations

$\Delta D$ sum-squared error of CSDs

$\Delta N$ FBRM term (generally not used)

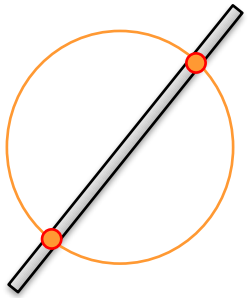


# Correlation between count and number density?




(low solid loading, spherical crystals…)

FBRM placement, stirring rate etc.



Double counting of high AR crystals

# How to use the FBRM data for PE?

**Repeating question, because:**

- FBRM became routine tool
- Great for qualitative measurements
- Hard to quantify
- Inaccurate CSD-CLD transformations
- Generally not used for PE

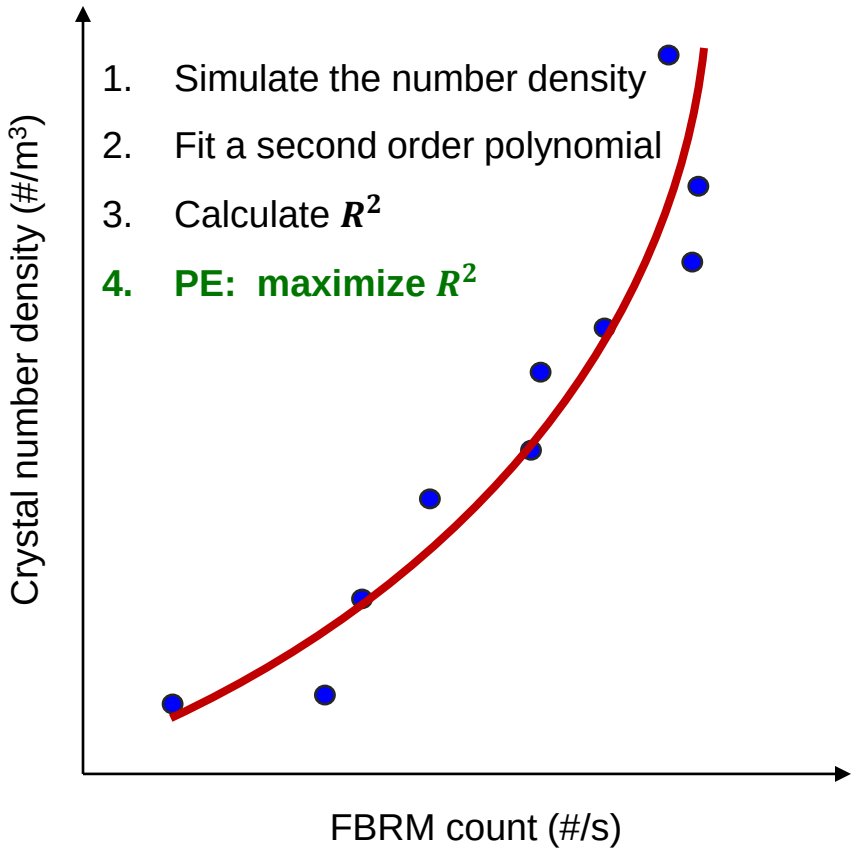
$$\boldsymbol{O(KP)} = f(\Delta C) + wf(\Delta D) + uf(\Delta N)$$

$\Delta C$ sum-squared error of concentrations

$\Delta D$ sum-squared error of CSDs

$\Delta N$ FBRM term (generally not used)

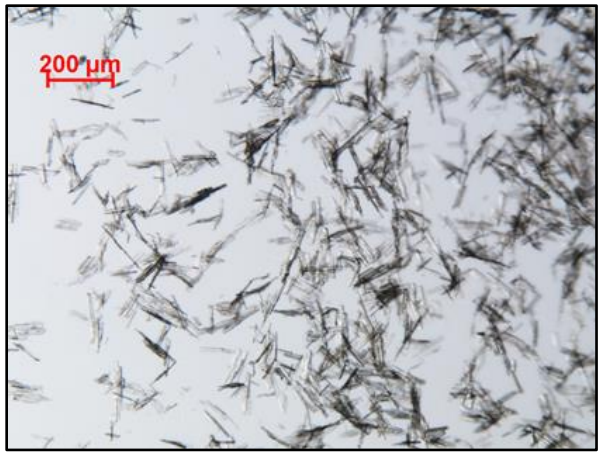
$$\Delta N = -\boldsymbol{R^2}$$



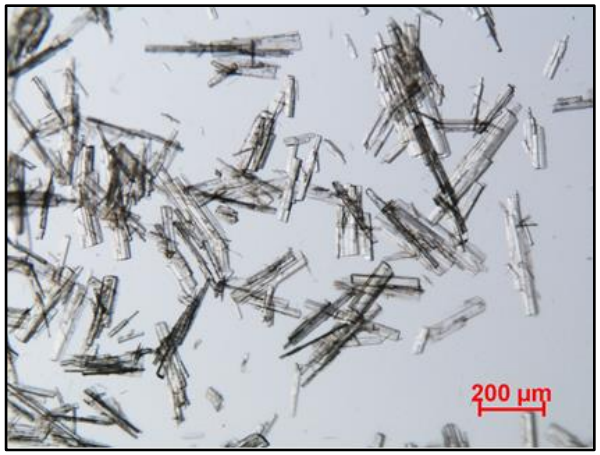

**New assumption: The FBRM count correlates with the true number density, which can be captured with a second order equation**

# Crystallization kinetics of a model API: 1D case

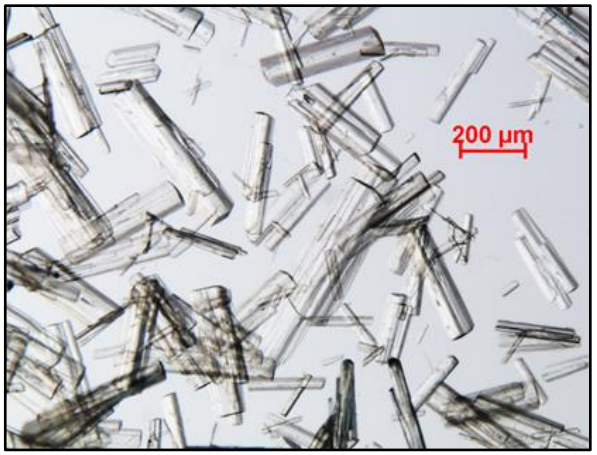
- 1D demonstration to introduce a novel size dependent growth expression and the count correlation based parameter estimation.
- Model API (“Compound A”, real API candidate).
- Slow-growing high aspect ratio crystals, nucleation-dominated process.
- Temperature cycles are required to obtain sufficiently large crystals.
- The model would enable direct optimization and *in-silico* DOEs




Linear cooling *




One temperature cycle *




Three temperature cycles *

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*** Identical batch time, operating temperature range and initial conditions**

# Numerical solution: 2D HR-FVM

- **1D PBM with nucleation and growth**

$$\frac{\partial n(L,t)}{\partial t} + \frac{\partial G(S)n(L,t)}{\partial L} = B(S)\delta(L - L_n)$$

- **Numerical solution: HR-FVM on non-uniform grid**
- **The kinetics** (fitting parameters)

$$B = k_b \sigma^b V_c$$

$$D = k_d \sigma (1 + d_d L)^{-d_e}$$

$$G = k_g \sigma^g \exp\left(-\frac{E_A}{RT}\right) G(L)$$

**Model 1:** $G(L) = (1 + c_1 L)^{c_2}$

**Model 2:** $G(L) = 1 - \exp(-c_1(L + c_2))$

Size dependent growth models generally used to fit steady-state MSMPR CSD data

**Model 3:** $G(L) = 0.5(\tanh(c_1(L - c_2)) + 1)$

**Model 4:** $G(L) = 0.5(\tanh(c_1(L - c_2)) + 1)(1 + c_3 L^{c_4})$

Size dependent growth models proposed in this case to capture size dependency in the Kolmogorov scale

# Crystallization kinetics of a model API: 1D case

- PE using 6 calibration and 2 validation experiments.

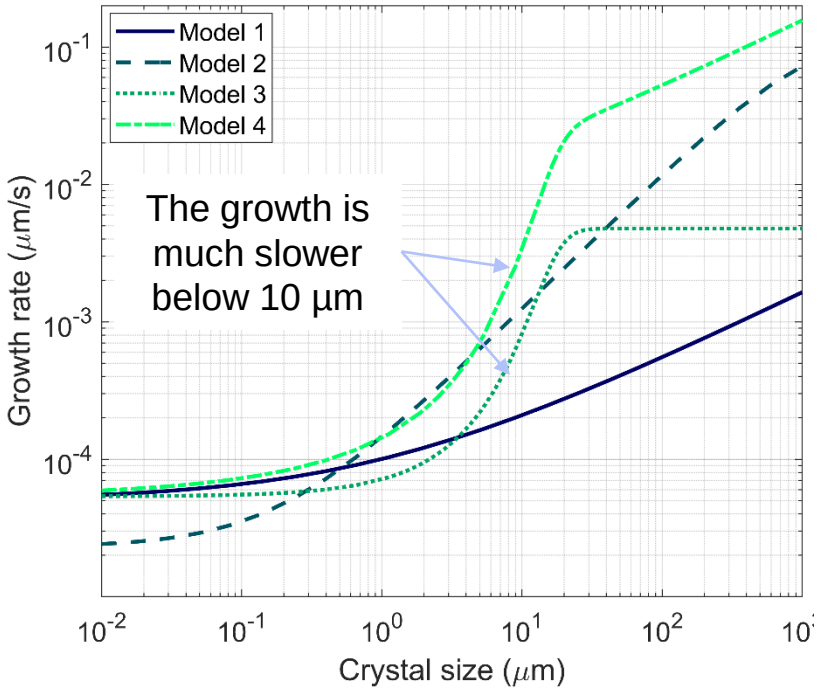
| $\min_{P \in R_+^0} O(P)$ | With FBRM data | | | | Without FBRM data | | | |
|---|---|---|---|---|---|---|---|---|
| | Model 1 | Model 2 | Model 3 | Model 4 | Model 1 | Model 2 | Model 3 | Model 4 |
| **Calibration** | 29237.2 | 2682.7 | 495.0 | 232.6 | 11543.6 | 1804.3 | 278.8 | 129.3 |
| **Validation** | 6018.6 | 1462.8 | 212.9 | 90.0 | 4593.8 | 1083.3 | 145.1 | 67.1 |

## Much narrower CI-s for Model 4 by FBRM

| Parameter | Nominal parameters (± C.I. limits) | |
|---|---|---|
| | W.O. FBRM | W. FBRM |
| $\log10(k_s)$ | -2.77 ± 8.6 | -3.06 ± 0.21 |
| $s$ | 2.19 ± 14.0 | 2.25 ± 0.37 |
| $\log10(k_g)$ | 10.83 ± 53.5 | 10.79 ± 0.79 |
| $g$ | 1.12 ± 4.9 | 1.04 ± 0.17 |
| $\log10(E_A)$ | 4.91 ± 2.0 | 4.92 ± 2.4 $10^{-2}$ |
| $\log10(\mathbf{c_3})$ | -0.75 ± 0.74 | -0.90 ± 0.39 |
| $\mathbf{c_4}$ | 0.97 ± 0.17 | 0.84 ± 0.14 |
| $\log10(\mathbf{c_1})$ | | |
| $\log10(\mathbf{c_2})$ | | |
| $\log10(k_d)$ | | |
| $\log10(\mathrm{d_d})$ | -3.10 ± 2.2 $10^4$ | -3.19 ± 105.6 |
| $\mathrm{d_e}$ | 1.2 $10^{-3}$ ± 61.76 | 1 ± 237.6 |

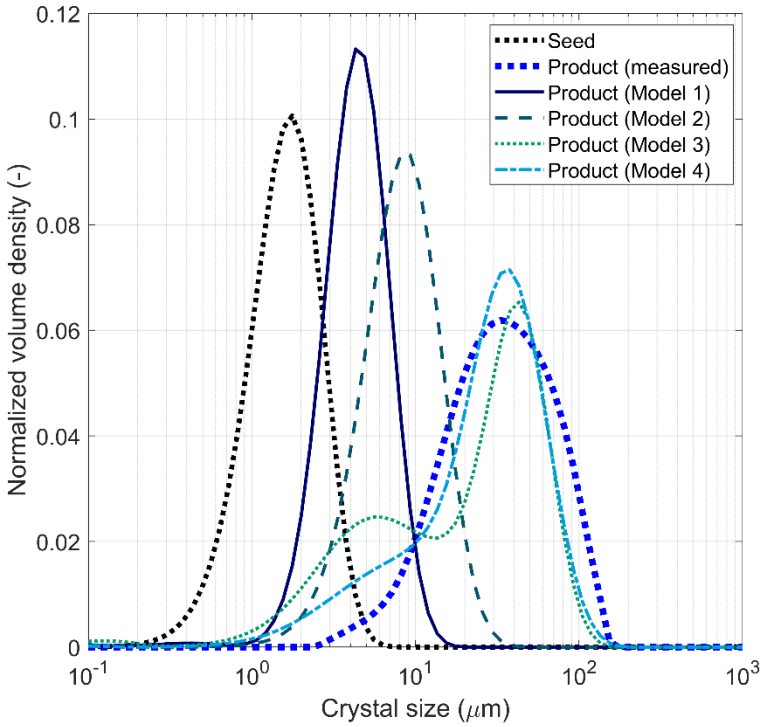
Quasi size-independent dissolution

## Different SDG shapes in the small range

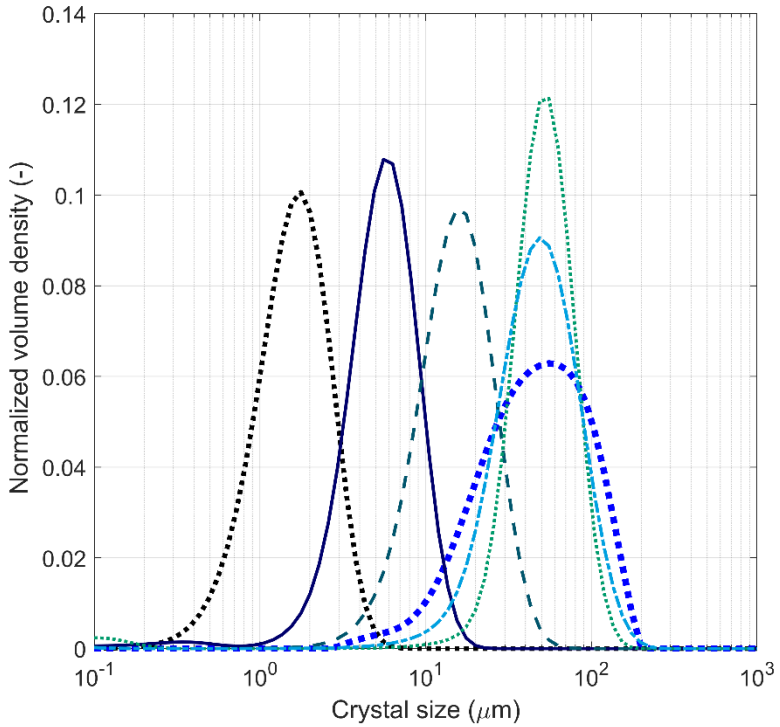


# Crystallization kinetics of a model API: 1D case

- Hyperbolic tangent growth models (Model 3 and Model 4) gave superior performance compared to the traditional SDG models.
- Model 1-3 has the same number of parameters (no over-fitting).




Validation experiment # 1: simulated and measured product CSDs




Validation experiment # 2: simulated and measured product CSDs

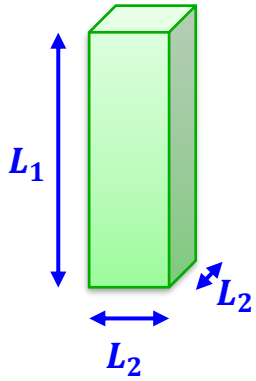
# The need for a 2D model in this case

Mean aspect ratio of product crystals obtained in different experiments. There is a strong variation.

| Expt. # | Seed type | Product mean AR |
|---|---|---|
| 1 | Type 1 | 7.78 |
| 2 | | 7.33 |
| 3 | | 4.81 |
| 4 | | 6.25 |
| 5 | Type 2 | 4.79 |
| 6 | | 4.41 |
| 7 | | 4.48 |
| 8 | | 3.62 |
| 9 | Type 3 | 4.91 |
| 10 | | 5.44 |

**Nucleation:**

$$B = k_b \sigma^b V_c$$




**The growth rate equation:**

$$G_i = G(L_1, L_2) k_{g,i} \sigma^{g_i} \exp\left(-\frac{E_A}{RT}\right)$$

$$G(L_1, L_2) = 0.5\left(\tanh\left(c_1(D_e - c_2)\right) + 1\right)\left(1 + c_3 D_e^{c_4}\right)$$

$$D_e = \frac{6}{\pi}\sqrt[3]{k_V L_1 L_2^2}$$

**Dissolution:**

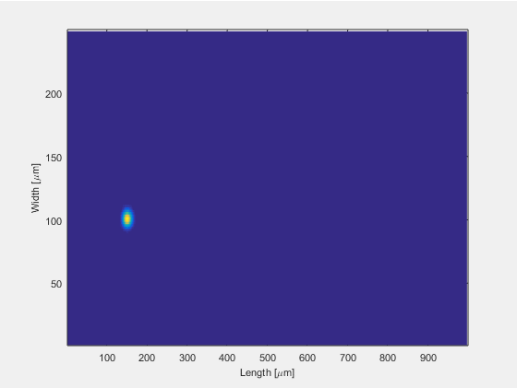
$$D_i = D(L_1, L_2) k_{d,i} \sigma$$

$$D(L_1, L_2) = \frac{1}{(1 + d_d D_e)}$$

# Numerical solution: 2D HR-FVM

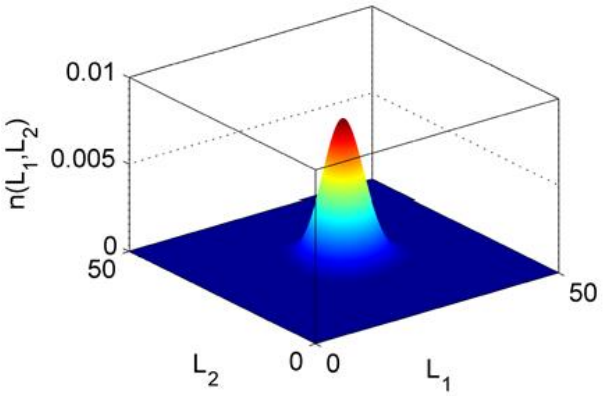
## ❑ 2D PBM with Nucleation and Growth

$$\frac{\partial n(L_1,L_2,t)}{\partial t}+\frac{\partial G_1(S)n(L_1,L_2,t)}{\partial L_1}+\frac{\partial G_2(S)n(L_1,L_2,t)}{\partial L_2}=B(S)\delta(L_1-L_{1n})(L_2-L_{2n})$$

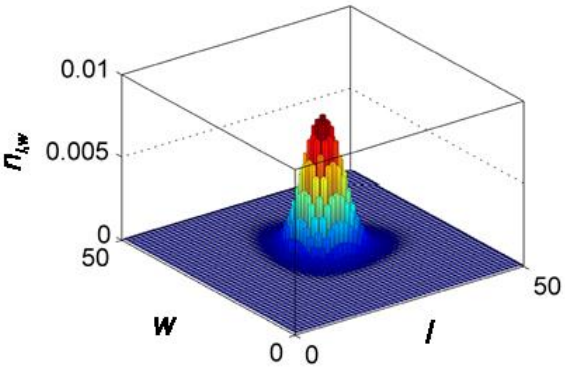



2D CSD dynamics in seeded batch crystallization with N and 2D Growth

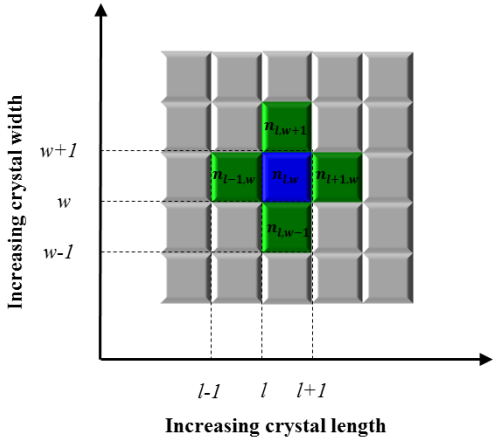
## ❑ Numerical solution: 2D HR-FVM on GPU




**Step 1.** Continuous 2D population density function (PDF)




**Step 2.** Finite volume discretization of the 2D PDF




**Step 3.** Number balance based on PBM for every cell

# Crystallization kinetics of a model API: 2D case

## Proposed objective function for 2D parameter estimation

$$O(\boldsymbol{KP}) = f(\Delta C) + wf(\Delta D) + uf(\Delta L) + zf(\Delta N)$$

- $f(\Delta C)$: Concentration fit
- $f(\Delta D)$: CSD fit
- $f(\Delta L)$: Shape fit
- $f(\Delta N)$: Count correlation maximization

## Why these many terms?

$f(\Delta C)$: coupled $N$, $G_1$ and $G_2$ information

$f(\Delta D)$: partly decouples $N$ from $G_1$ and $G_2$

$f(\Delta L)$: provides relative $G_1$ and $G_2$ information

$f(\Delta N)$: influenced majorly by $N$ and fines dissolution

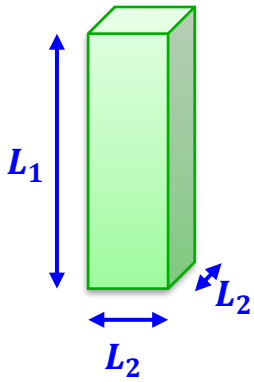
## However, there is also more sensor-specific error…



$\boldsymbol{KP}$: vector of kinetic parameters to be estimated

# Seed CSD approximation

- 2D CSD of seeds must be approximated from 1D size and shape measurement (inverse problem)
- Solved by optimization, assuming sum of 2D correlated normal distributions

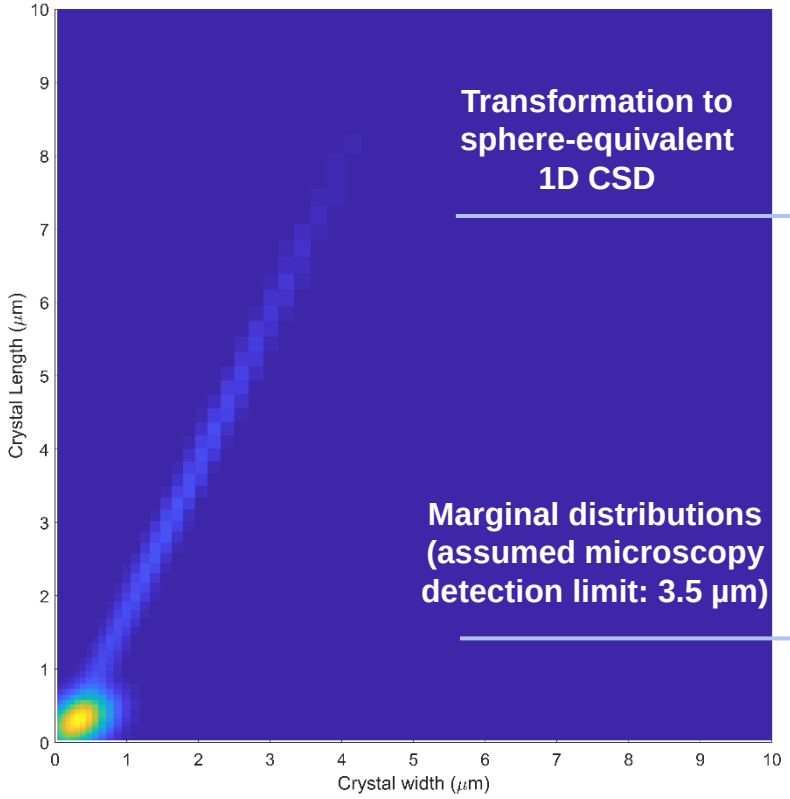


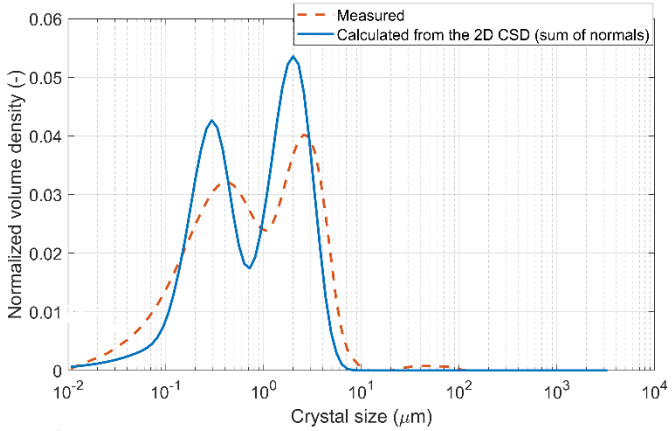

$$V_{Cr} = k_V L_1 L_2^2$$

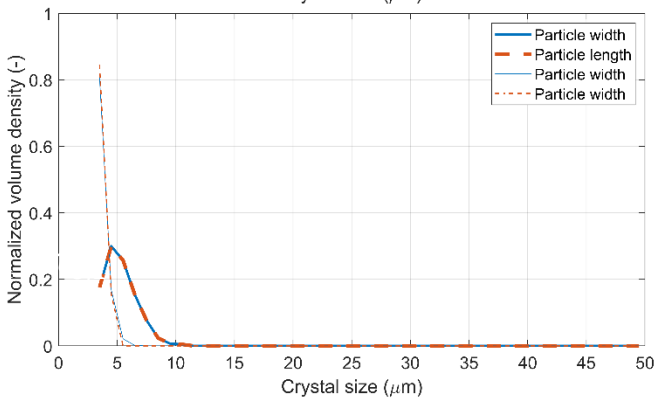
$$n_0 = n_{0,1} + w n_{0,2}$$

$k_V$ = 0.153

$w$ = 4.98



# 2D case, intermediate results

- 2D crystallization kinetics: dissolution and size dependent growth along the length and with was considered in the first step
- Under extension to nucleation rate model

The considered size dependent growth rates:

$$G_i = G k_{g,i} \sigma^{g_i} \exp\left(-\frac{45000}{RT}\right)$$

$$G = 0.5\left(\tanh\left(c_1(D_e - c_2)\right) + 1\right)\left(1 + c_3 D_e^{c_4}\right)$$

$D_e$ is the sphere-equivalent diameter:

$$D_e = \frac{6}{\pi}\sqrt[3]{k_V L_1 L_2^2}$$

The considered size independent dissolution rates:

$$D_i = k_{d,i}\sigma$$

Nominal values and 95 % confidence interval limits *

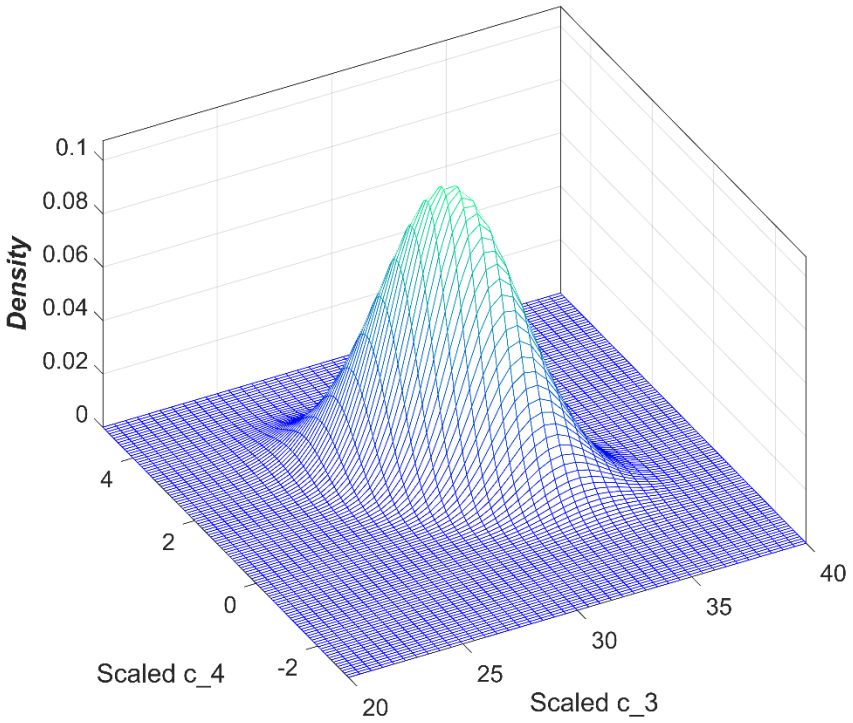
| P | Nom. | L.B. | U.B. |
|---|---|---|---|
| $k_{g,1}$ | 110420 | 37229 | 327480 |
| $k_{g,2}$ | 24429 | 5218 | 114370 |
| $g_1$ | 1.80 | 1.34 | 2.25 |
| $g_2$ | 1.42 | 0.98 | 1.86 |
| $k_{d,1}$ | 0.032 | 0.02 | 0.51 |
| $c_1$ | 0.072 | 0.054 | 0.097 |
| $c_2$ | 14.02 | 9.60 | 20.47 |
| $c_3$ | 2.99 | 1.25 | 7.16 |
| $c_4$ | 0.807 | 0.51 | 1.14 |



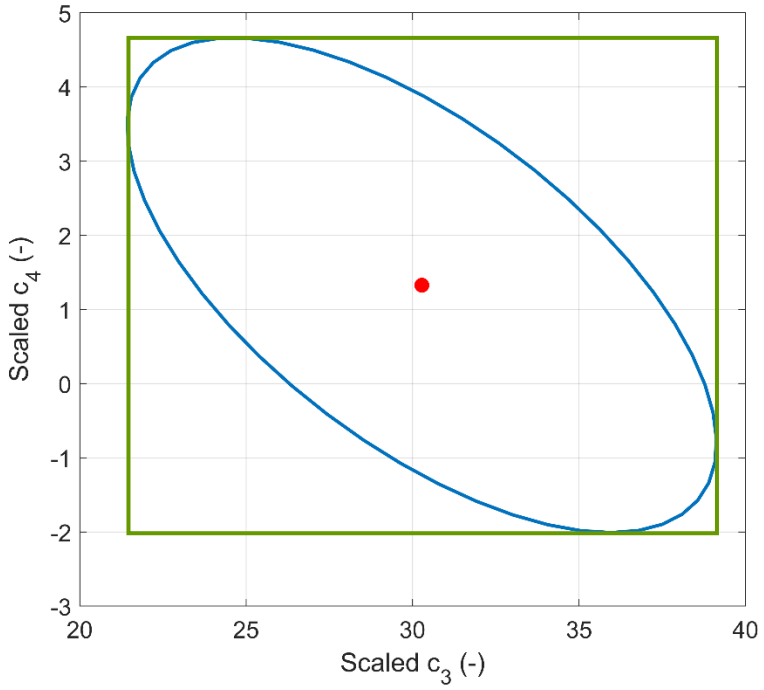
* $k_{d,2}$ was fixed to 0.005

# 2D case, intermediate results

- Basic uncertainty analysis (as we have many fitting parameters)
- Monte-Carlo sampling of kinetics assuming multivariable correlated normal CSD (left hand side figure). 150 random kinetic parameter combinations

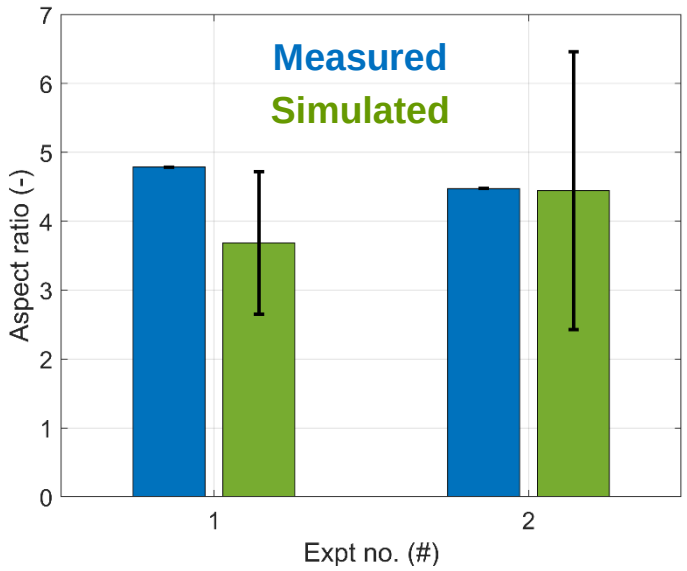


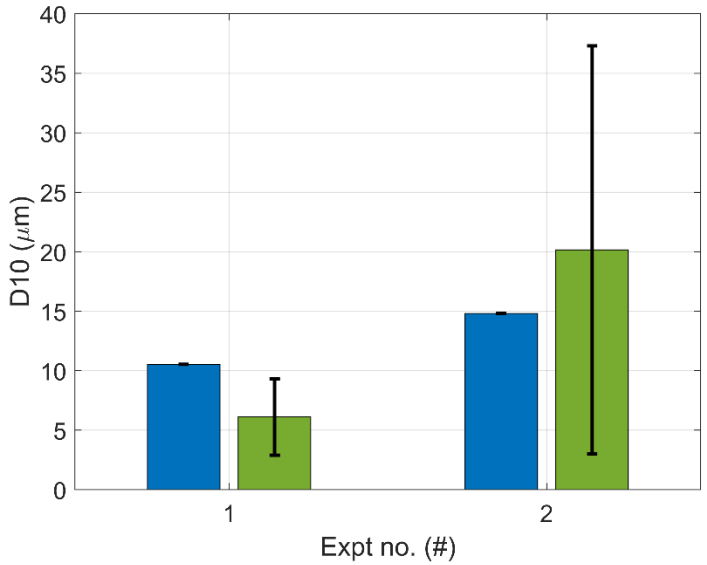

**Correlation between $c_3$ and $c_4$**

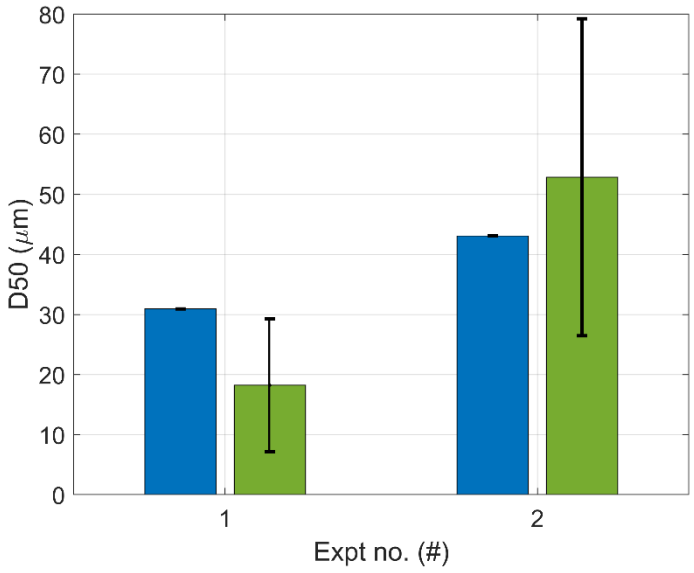


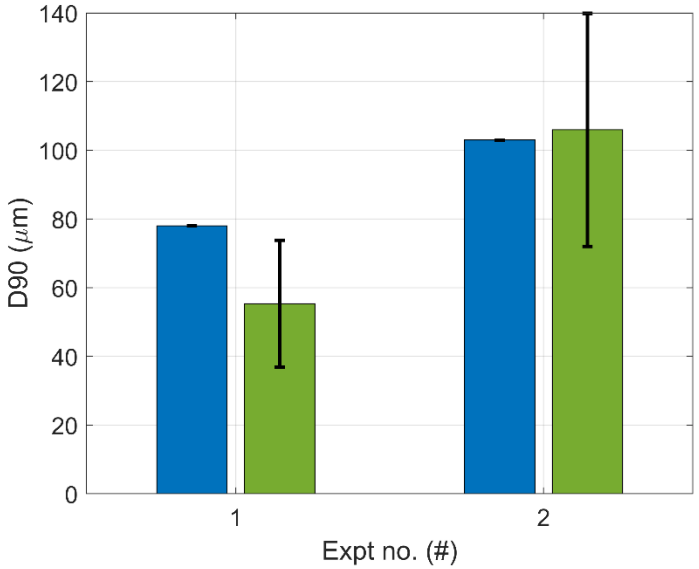

**Nominal value, confidence ellipsoid and box (confidence intervals)**

# 2D case, intermediate results. Validation runs




*Mean and standard deviation of 150 simulation with kinetics sampled randomly

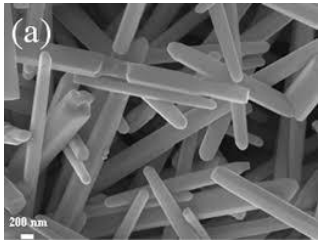
# Short term plans (~1 year)

## Flexible MSMPR network

*… with dedicated wet-mills and recirculation streams*

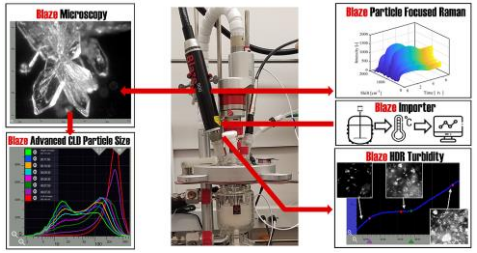

## 2D crystallization

*… Finishing the 2D parameter estimation*




## Blaze probe acquisition

*… and comparing it to the Metler's EasyViewer probe*



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

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