Micro-scale process development and optimization for crystallization processes

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Introduction

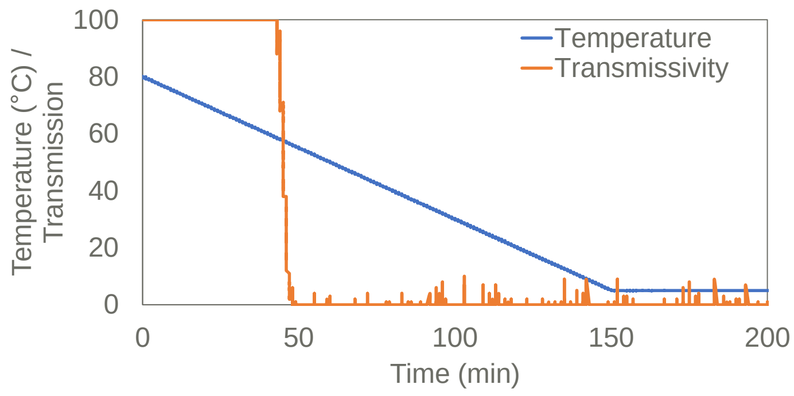
Initial crystallisation experimental phases commonly carried out in small scale (1 – 5mL) high throughput instruments. Such as Crystal16 and Crystalline from Technobis Crystallization Systems. Commonly used for solubility measurements. But can also produce a wealth of other data that is not currently utilised for process model development.

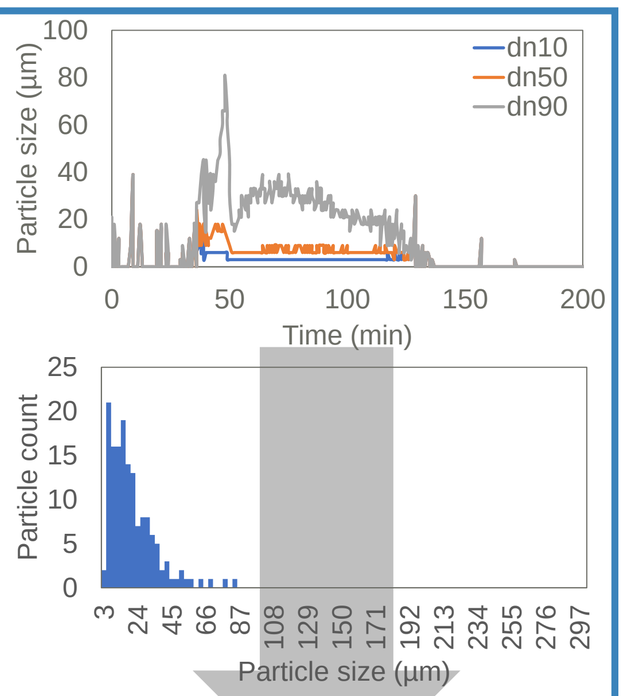
Research questions:

1. Can suitable data be extracted from a Crystalline experiment to allow for the estimation of process model parameters?
2. Can mechanism evaluation be performed? i.e. empirical power laws vs. mechanistic parameters

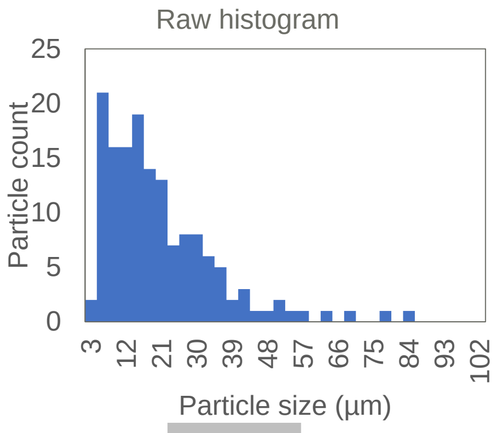
Typical raw Crystalline data

Sample turbidity and block temperature are recorded throughout. Addition of *in situ* camera module allows for the imaging of suspended particles and the determination of particle size distribution (PSD) through image analysis

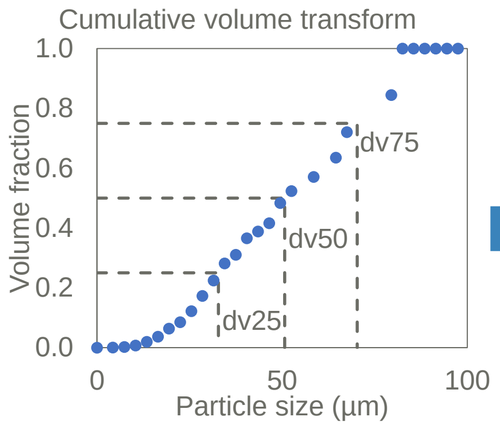




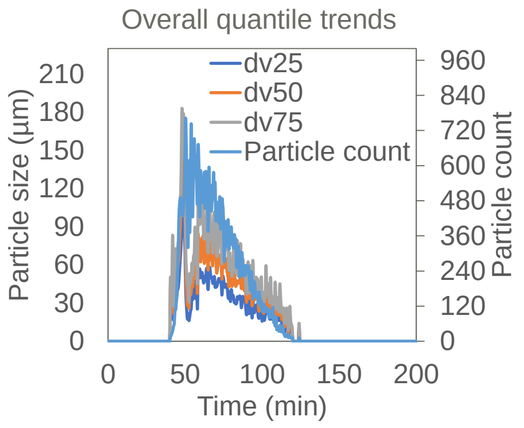
Data extraction



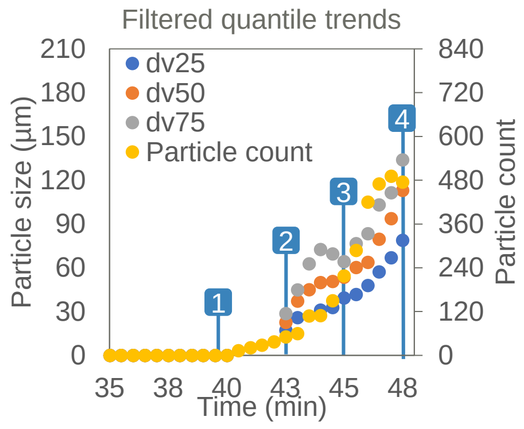
Raw output from Crystalline software. Number based histogram with 3 µm linearly spaced bins.



Converted to volume weighted cumulative distribution assuming spherical particles and geometric mean of bin bounds.



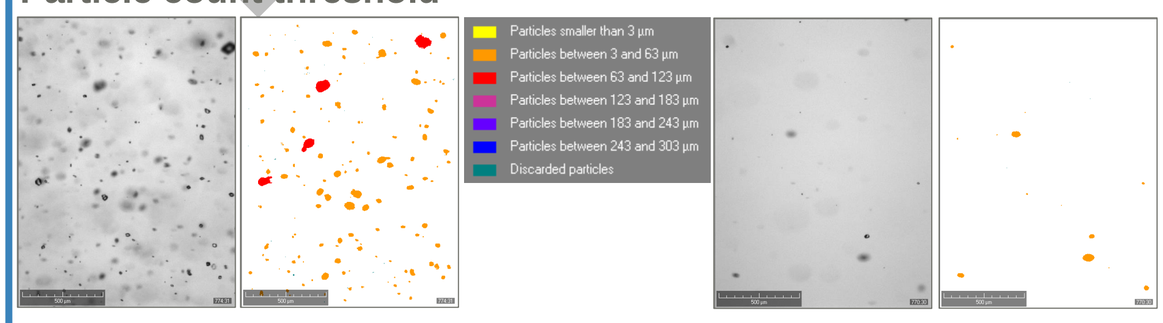
Region which data is feasible to use is limited due to low particle number or particle overlap, see below.

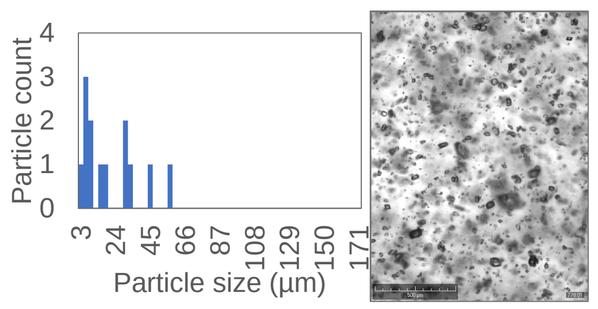


Features:

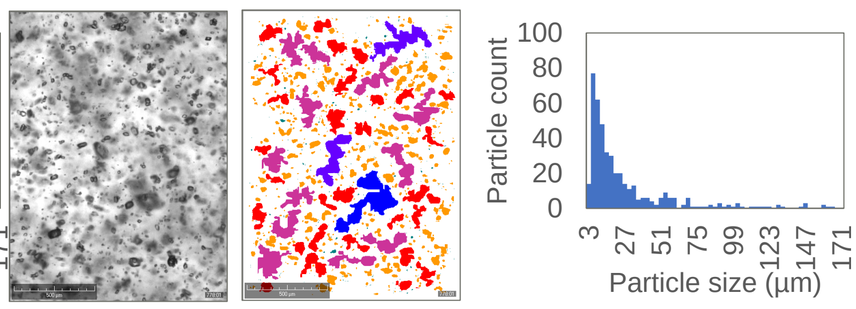
1 Last point of no crystal mass
1 to 2 Particles present but density too low for accurate PSD
2 Accurate PSD possible
3 PSD accuracy decreases due to overlapping particles (>200 particles)
4 PSD inaccurate due to too high particle density

Particle count threshold





Less than 10 particles. Clear segregation of particles. Insufficient particles for statistical PSD



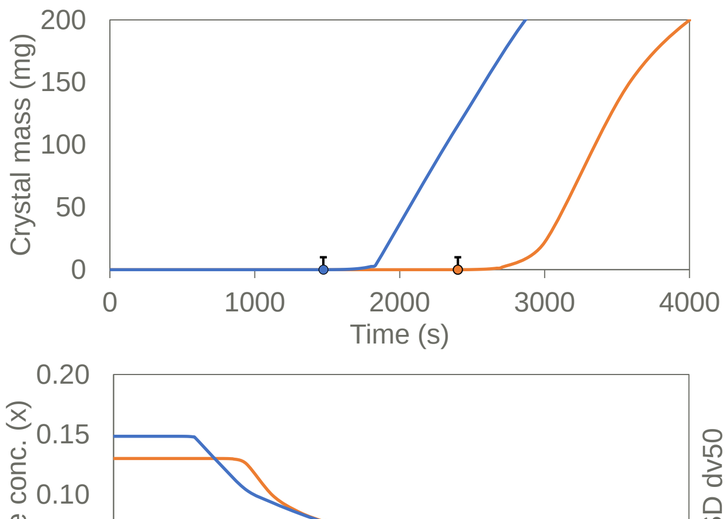
Greater than 200 particles. Significant probability of particle overlap. Sufficient particles for statistical PSD.

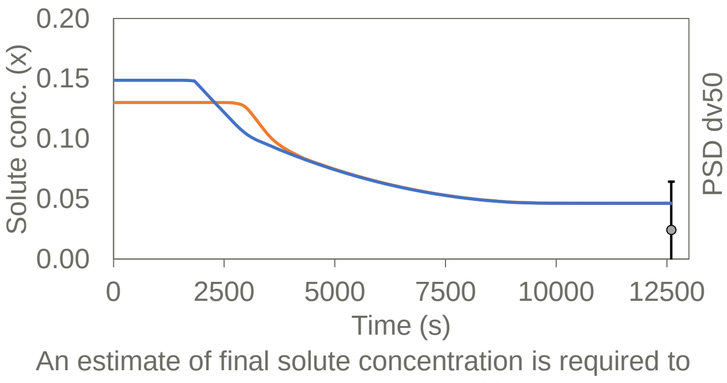
Parameter estimation

Experiments from solubility measurements

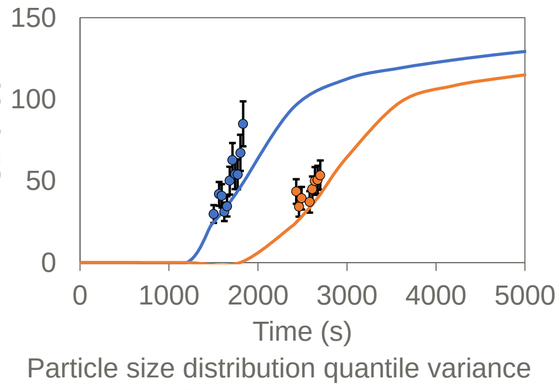
Exp.	Vial	Clear point (°C)	Conc. (x)	Cloud Point (°C)	Volume (ml)
StYe_02	F	72.8	0.1302	67.9	5.54
StYe_02	G	78.1	0.1486	68.7	5.45
StYe_13	F	72.4	0.1300	60.4	5.54
StYe_13	G	77.1	0.1486	68.7	5.45

Example fits





An estimate of final solute concentration is required to help complete the material balance. However, a large variance is placed on this as it is unknown if the solution reached equilibrium.



Particle size distribution quantile variance based on ISO standard errors for particle sizing from image analysis.

Primary nucleation – Classical (Mullin)
Crystal growth – Two step (Classical)

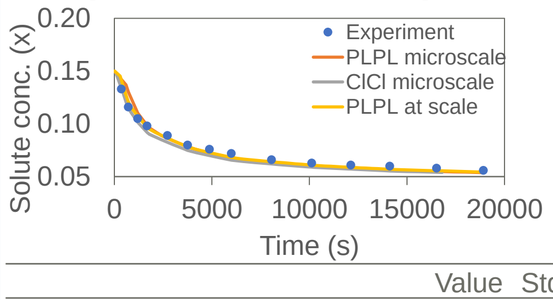
	Value	Std. dev.
Growth activation energy, $E_{A,g}$	7275.4	1.24E+05
Growth rate constant, k_g	3.69E-05	0.001176
Growth order with S, g	1.6431	4.2
Effective diffusivity correction, α	0.0359957	0.09528
Nucleation rate constant, A_0	19.5766	4.875
Surface energy correction, α	0.178425	0.131
Weighted residual	92.4875	
χ^2 value (95%)	125.458	

Primary nucleation – Power law
Crystal growth – Power law

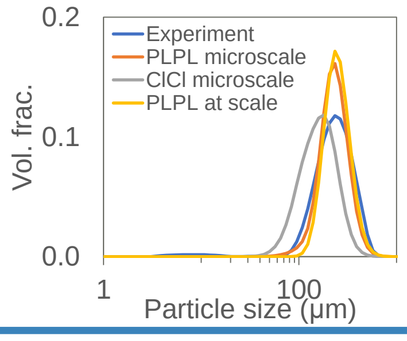
	Value	Std. dev.
Growth activation energy, $E_{A,g}$	4220.7	4162
Growth rate constant, k_g	0.000455	0.001002
Growth order with S, g	1.80085	0.2913
Nucleation activation energy, $E_{A,n}$	0	
Nucleation rate constant, k_n	29.9996	7.687
Nucleation order with S, n	3.66314	1.86
Weighted residual	84.4168	
χ^2 value (95%)	126.574	

Fits based on residuals are good but parameters are statistically weak. Additional datasets from solubility could improve this. Future work to investigate global system sensitivity to estimated parameters.

Comparison to at scale parameter estimation



Parameters estimated at microscale used to predict response at 1 L scale. Also compared to power law growth parameters estimated at scale.



	Value	Std. dev.
Growth activation energy, $E_{A,g}$	0	
Growth rate constant, k_g	0.000368	0.002782
Growth order with S, g	4.12663	3.505
Weighted residual	2.51615	
χ^2 value (95%)	38.8851	