Material-Sparing Methods for Early Crystallization Development Using the Technobis Crystalline™

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Technobis Crystallization Workshop: Nucleation, Applications and Process Optimization

October 4, 2023

Agenda

- Challenges in Early Crystallization Process Development
- Material-Sparing Workflow for Kinetic Screening in a Crystalline
- Generation of a Kinetic Map to Inform Early Process Design

Challenges in Early Crystallization Development

Industrial Crystallization

Most active pharmaceutical ingredients (APIs) are solids.

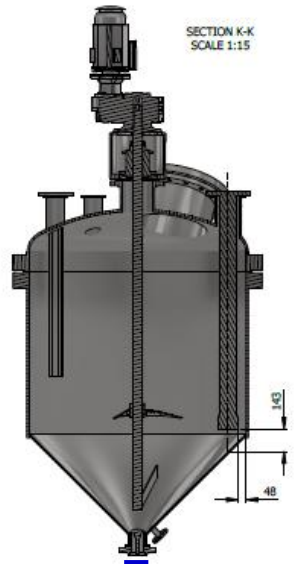
Why do we use crystallization?

- **SEPARATION** of a solid mass from solvents/solutions, reaction mixtures
- **QUALITY CONTROL** Removal of impurities and control of the right polymorph
- **PARTICLE ENGINEERING** to enhance downstream unit operations like filtration and drying, and address drug product requirements

Crystallization

Impacted By

- Nucleation Rates
- Crystal Growth Rates
- Crystal Morphology
- Mass Transfer (Mixing)
- Heat Transfer
- Thermodynamics



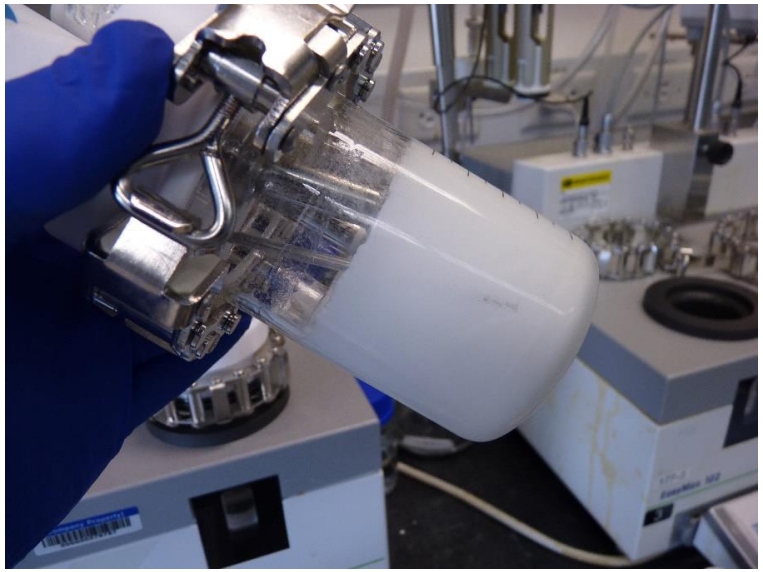
Unit Operations Post Crystallization
Filtration> Drying> Milling

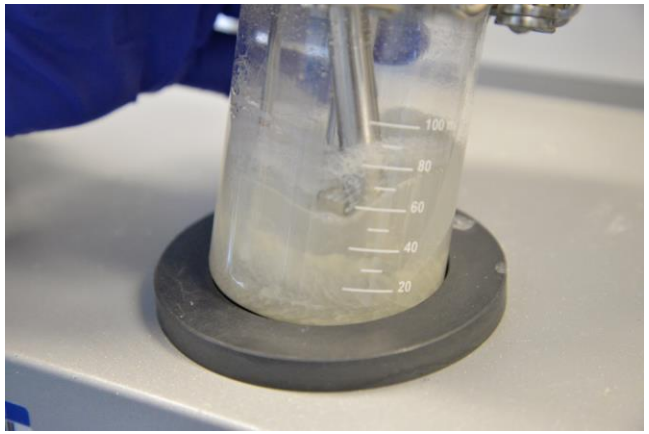
Formulation

Impacts

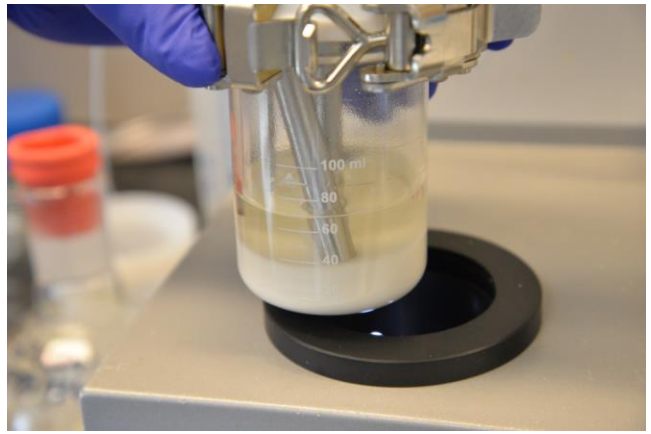
- Process Yields
- Impurity purge
- Polymorphic / crystalline form behavior
- Mixing & segregation in crystallizer
- Filtration times
- Drying times
- Caking properties in storage
- Bulk density
- Dissolution rates
- Milling and subsequent formulations

What Can Happen if Crystallization is Not Designed Well



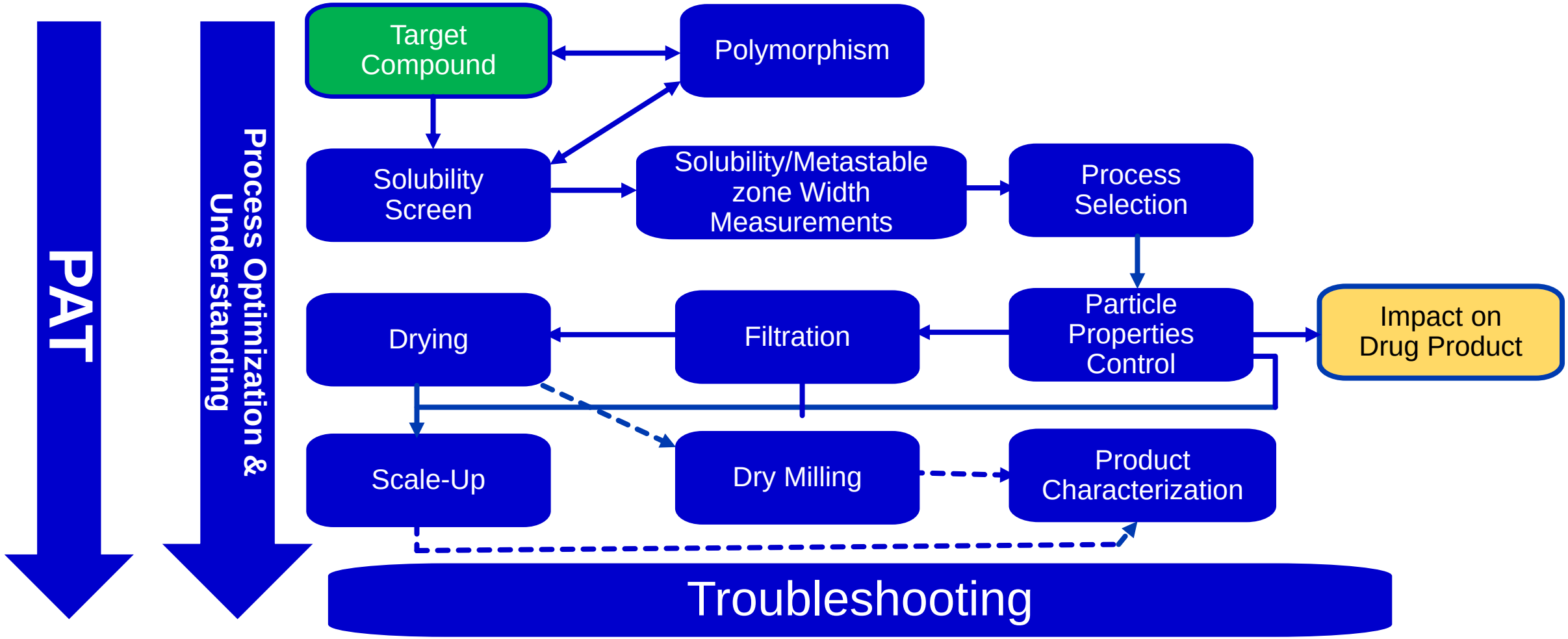


Fast cooling, no seeding



Multistage cooling profile with seeding

Crystallization Development Road Map



Thermodynamic and Kinetic Aspects of Crystallization

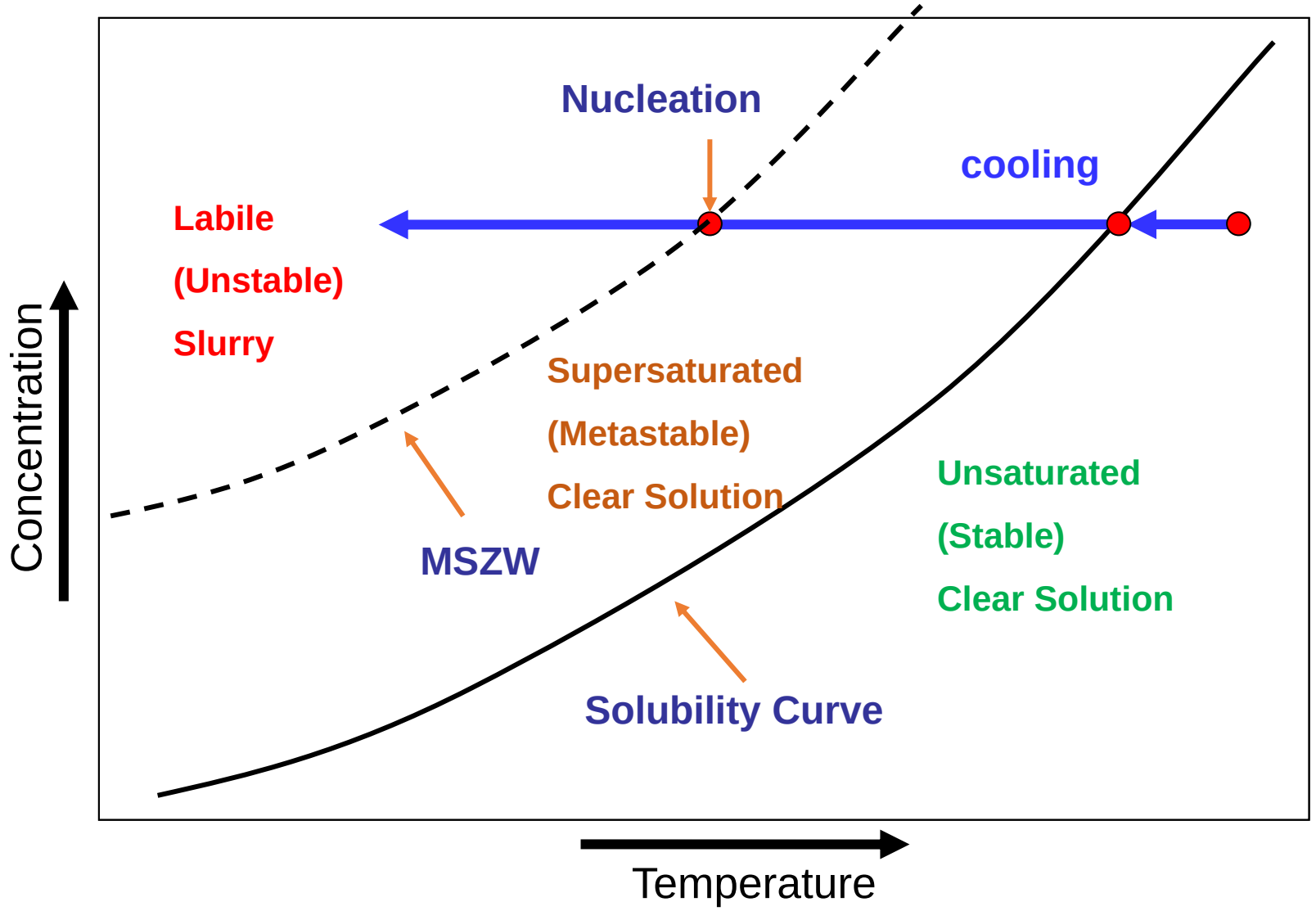
Thermodynamics:

- Provide the driving force for crystallization (chemical potential).
- Often simplified as equilibrium solubility.
- Phase diagrams are the maps we use to design crystallizations.
- Helpful for knowing maximum yield and polymorphic forms.

Kinetics:

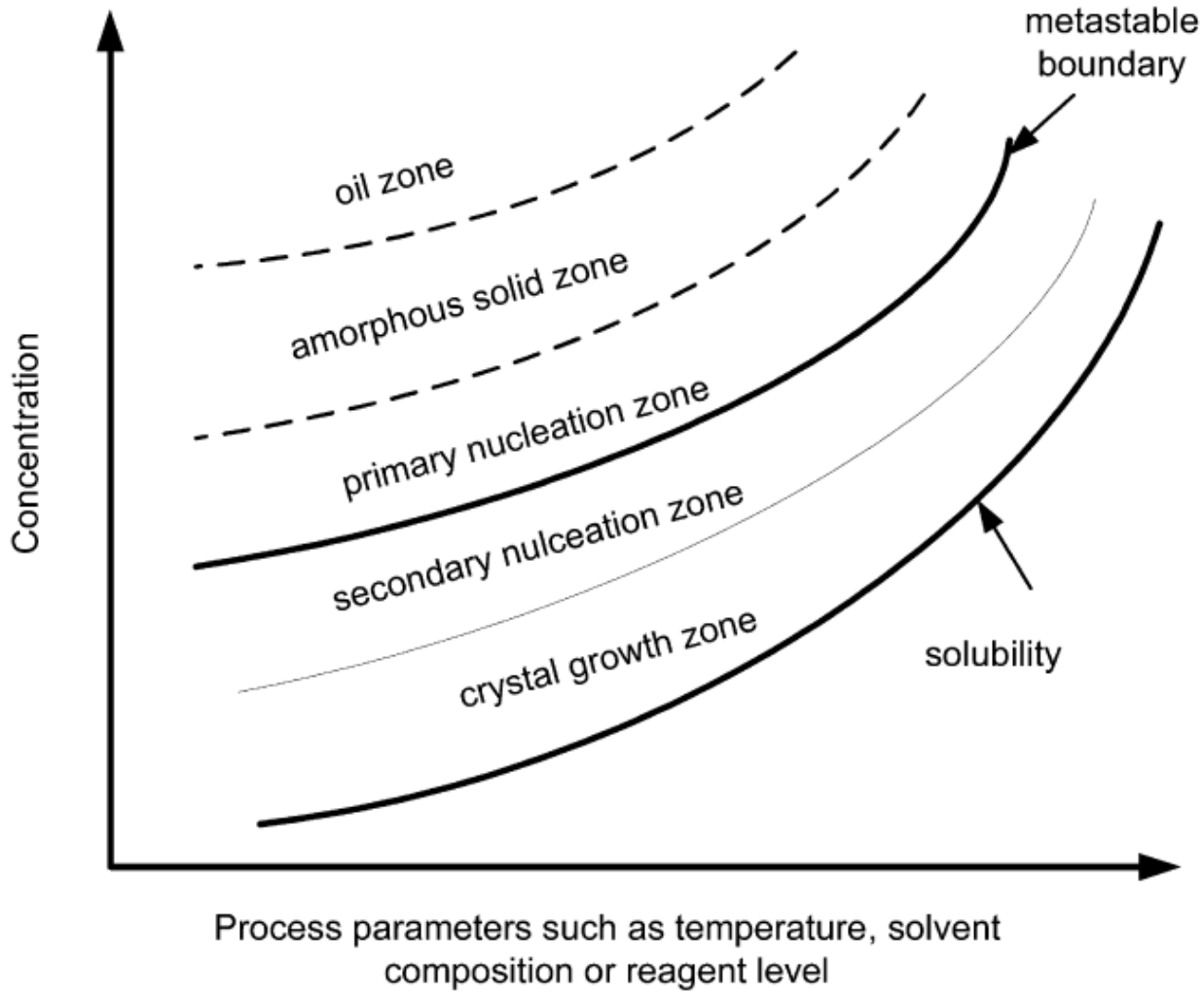
- Describe how fast things will happen.
- Rate equations that depend on supersaturation.
- Helpful for knowing particle characteristics such as size, shape, and filterability.

Solubility Curve and Metastable Zone Width Measurement



We all wish for this simple curve using crystal 16 data but often encounter complicated profiles

The Real-Life Phase Diagram…



Metastable Limit

Primary nucleation point (aka ‘cloud point’)

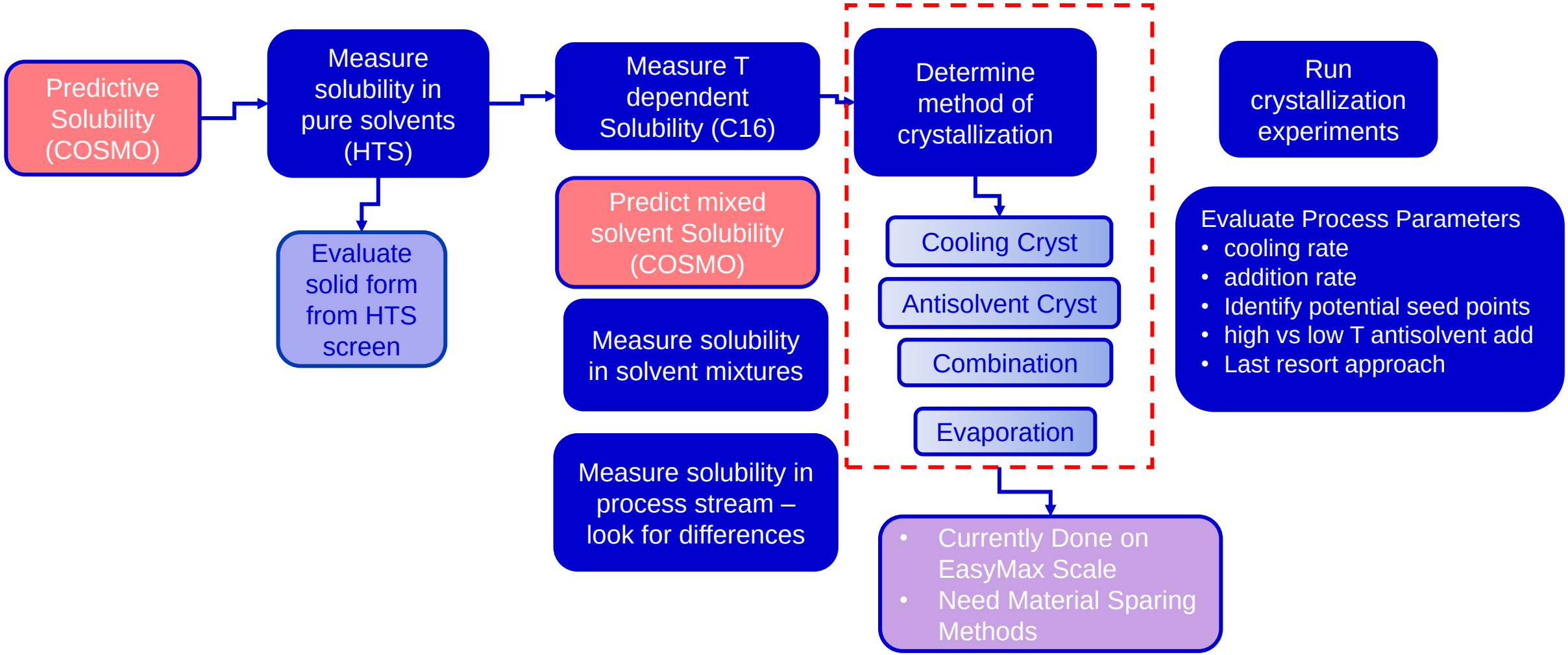
Kinetic Event

Dependent on route to the end conditions

- Temperature rates
- Addition rates
- Agitation / mixing
- Foreign matter / seed
- Reactor shape / size

H-H. Tung, *Org. Proc. Res. Dev. 2013,* 17, 445

Crystallization Design Workflow



Problem Statement

- It’s very difficult to accurately predict crystallization behavior without performing extensive experimental screenings.
- Polymorphism, changes across different scales, changing kinetic values of growth and secondary nucleation, impurities, stability, processability, dissolution behavior, stirring effects, etc.

Approach Explored

- Crystalline™-based experiments allow for greater amounts of data and information to be collected for the early development of crystallization processes in a material sparing fashion.
- We explored these methods on two compounds through Pfizer-Rowan collaboration.

Material-Sparing Workflow to Measure Kinetics in the Crystalline

CRYSTAL GROWTH & DESIGN

pubs.acs.org/crystal

Article

Automated and Material-Sparing Workflow for the Measurement of Crystal Nucleation and Growth Kinetics

Ryan J. Arruda, Paul A.J. Cally, Anthony Wylie, Nisha Shah, Ibrahim Joel, Zachary A. Leff, Alexander Clark, Griffin Fountain, Layane Neves, Joseph Kratz, Alpana A. Thorat, Ivan Marziano, Peter R. Rose, Kevin P. Girard, and Gerard Capellades*

Cite This: *Cryst. Growth Des.* 2023, 23, 3845−3861

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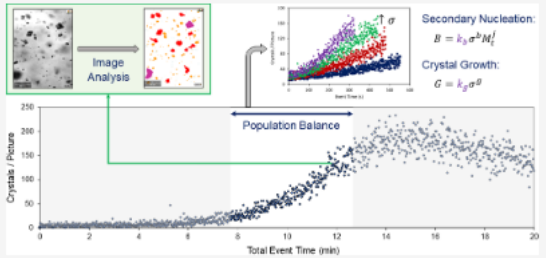
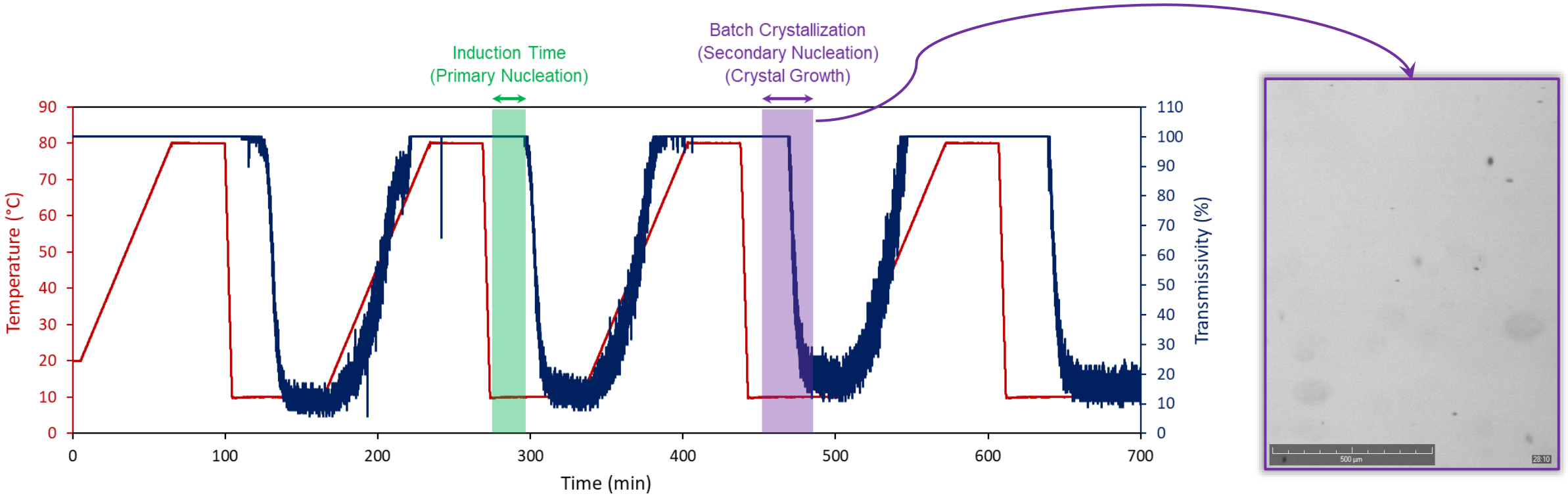
ABSTRACT: The development of digital twins for model-based crystallization process development is often limited by the associated material-intensive and time-intensive experimental screenings. Methods for measuring primary nucleation rates are well established and common practices for academic studies; however, methods for the measurement of secondary nucleation and crystal growth rates are often inconsistent due to differing strategies in the selection of supersaturation models, particle size measurement techniques, and investigated scales. We hereby provide a workflow of automated methods for the experimental screening, data analysis, and parameter estimation for secondary nucleation and crystal growth kinetics in solution crystallization. The methods have been integrated with common experimental protocols in the determination of induction times for primary nucleation and with the use of commercially available tools that can be found in crystallization laboratories across academia and industry. These tools include a Technobis Crystalline as well as process simulation software, currently tailored to gPROMS FormulatedProducts. The methods have been demonstrated for two well-known model systems: antisolvent crystallization of acetaminophen from ethanol−water mixtures and cooling crystallization of a metastable polymorph of L-glutamic acid from water. The presented workflow will serve as a basis to standardize the analysis of crystallization kinetics for new systems, generating kinetic trends using similar methods that would aid in early process development as well as in academic studies.



Data Collection

Data Collection

Collecting imaging data near the onset of nucleation:

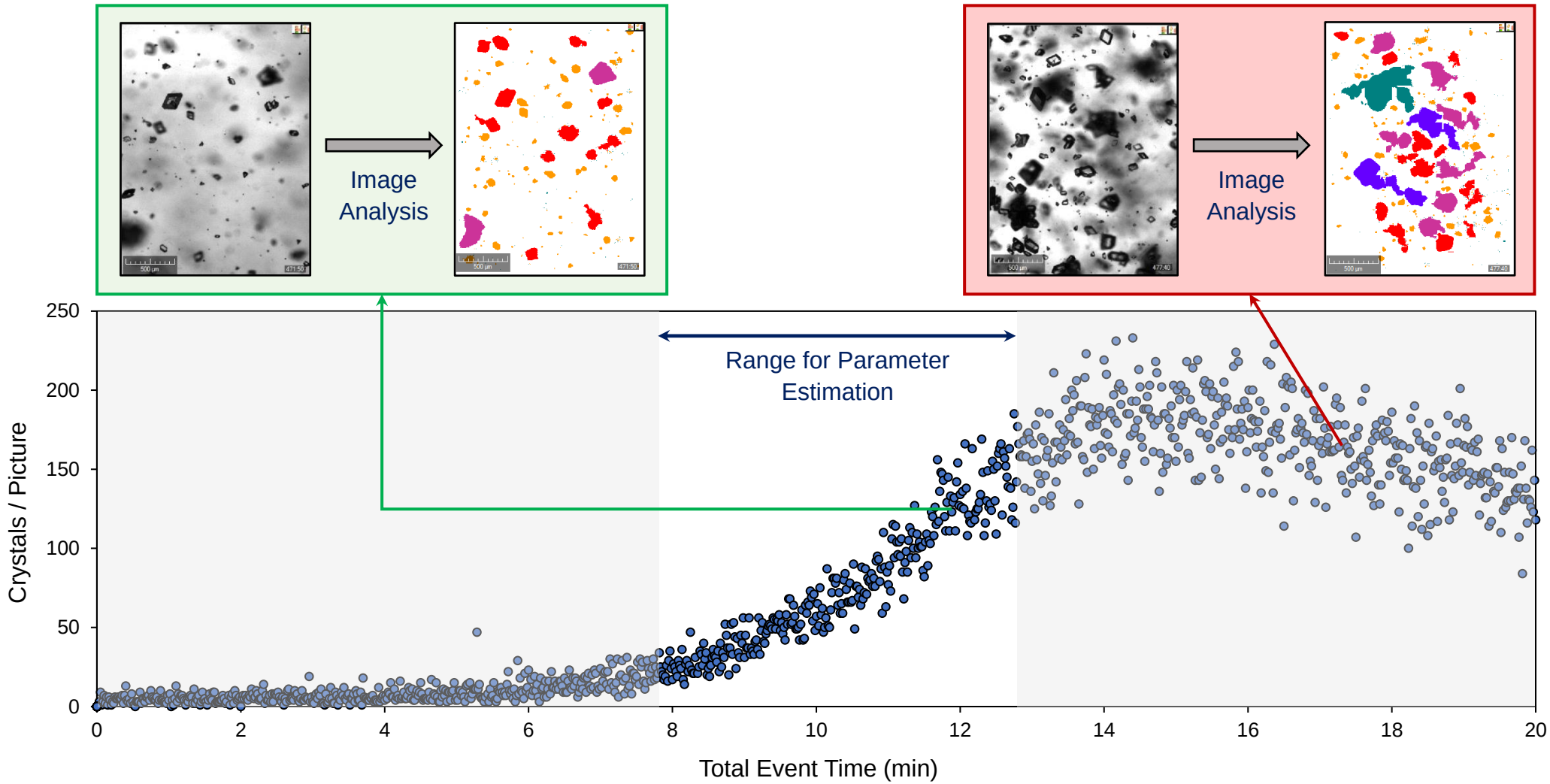


- Capture rates of 1 image/second.
- Analysis to obtain the total number and size of crystals in a picture.

R.J. Arruda, P.A.J. Cally, A. Wylie, N. Shah, I. Joel, Z.A. Leff, A. Clark, G. Fountain, L. Neves, J. Kratz, A.A. Thorat, I. Marziano, P.R. Rose, K.P. Girard, G. Capellades. *Crystal Growth & Design* 2023, 23, 3845-3861.

Navigating Crystal Overlap

As crystallization progresses, overlapping crystals will be seen as a single entity – not representative anymore!



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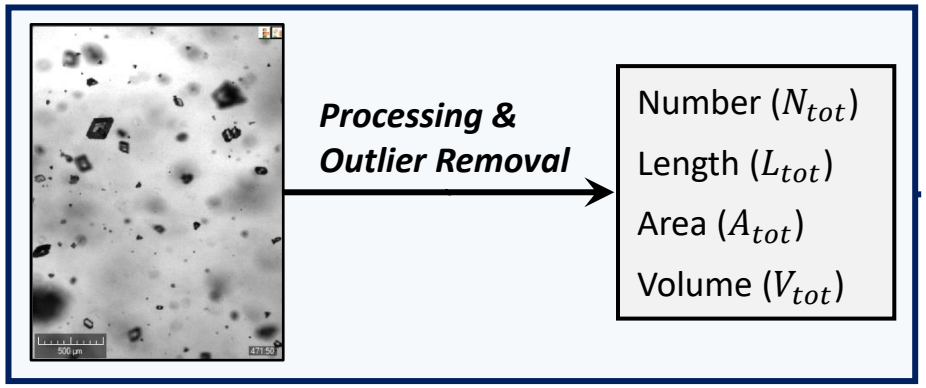
Data Flow – What Do We Need?



Processing & Outlier Removal

- Number (N_{tot})
- Length (L_{tot})
- Area (A_{tot})
- Volume (V_{tot})

Imaging Trends (Kinetic Screening)

Time-Dependent Trends (N_{tot} and A_{tot} Only)

Initial Conditions (N_{tot}, L_{tot}, A_{tot}, V_{tot})

gPROMS Model

- Kinetics
- Population Balance
- Supersaturation Model
- Mass Balance

Experimental Conditions:

- Solute Concentration
- Temperature

Secondary Nucleation Constant: k_b

Crystal Growth Constant: k_g

Solubility Curve (Empirical)

$$x_{sat} = \alpha \cdot exp(\beta T)$$

From Isothermal or Polythermal Screening

Solute Properties

From Literature or Solid-State Analysis

- Density
- Molar Mass
- Melting Point
- Enthalpy of Fusion
- Solvate/Hydrate Stoichiometry

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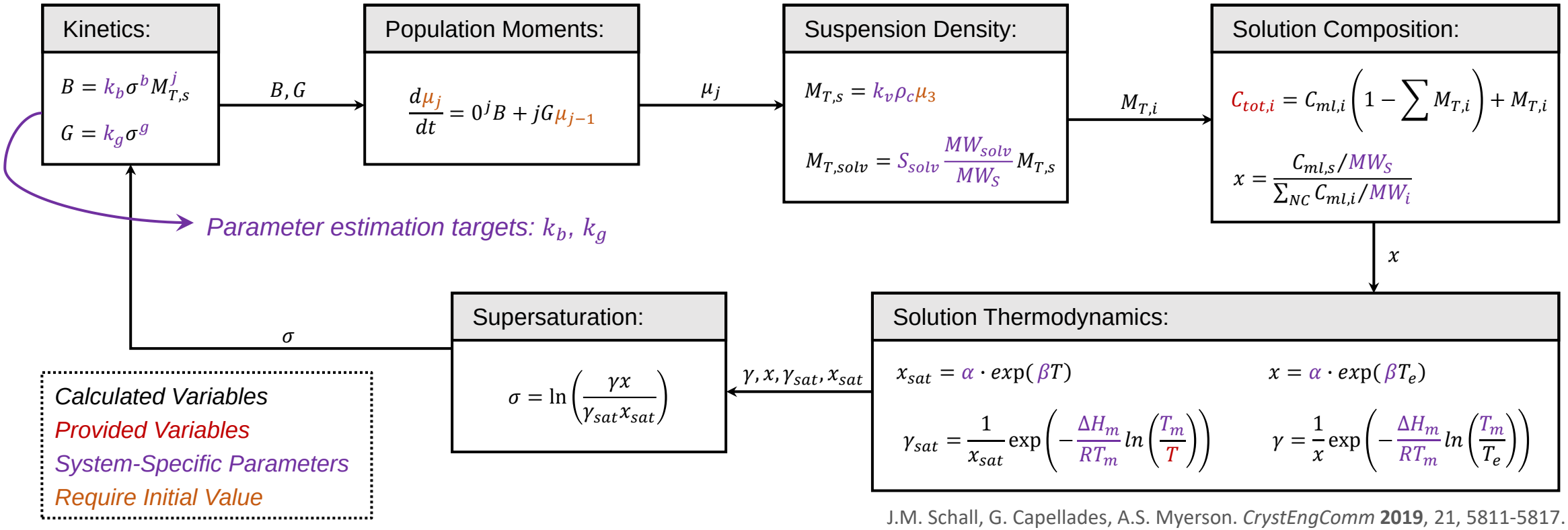
Model Description

General Batch Crystallization Model

The Crystalline experiment can be tracked using a general population balance model for batch crystallization (initial conditions for the moments needed):



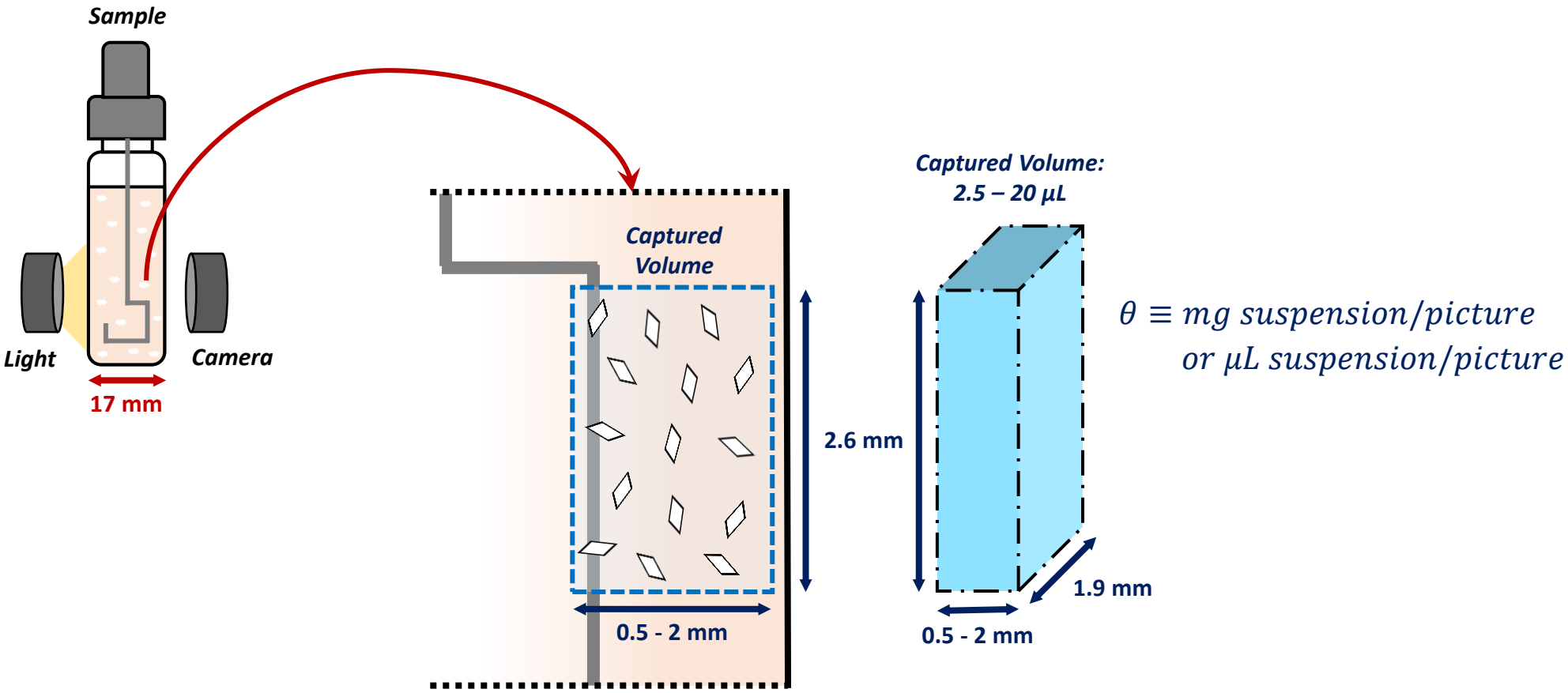
J.M. Schall, G. Capellades, A.S. Myerson. *CrystEngComm* **2019**, 21, 5811-5817.

- Problem: the Crystalline does not measure population moments, only their projections as crystal number and size!

Moments on Camera

The 8 mL vials used for the Crystalline have external dimensions of 17 x 60 mm.

Camera captures a small volume within. We'll call this θ.



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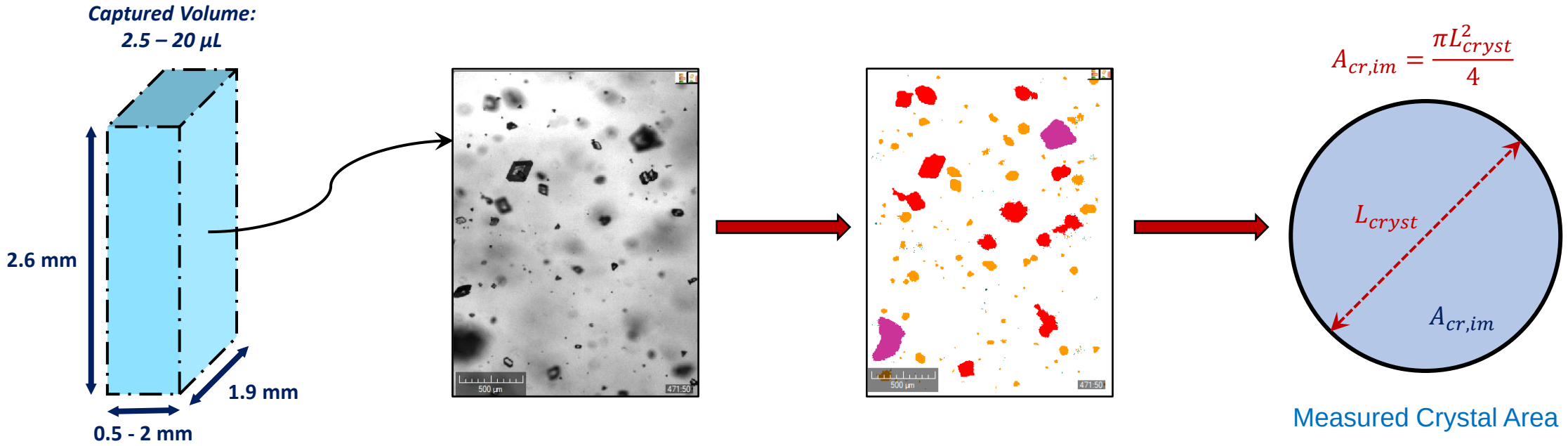
Moments on Camera

The captured volume is much larger than that found in most PATs (back lighting, large capture area, large image depth). We get a 2D projection containing >100 crystals, with a certain size.

- The crystalline provides a particle size distribution, where size is the diameter of the equivalent circle:



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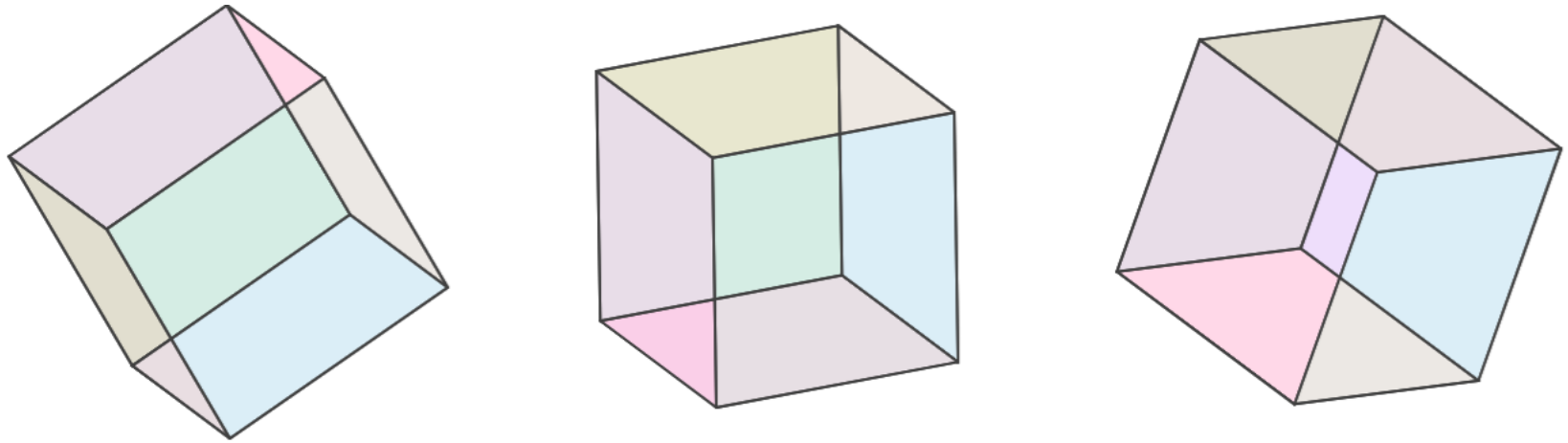
Moments on Camera

Assuming crystals have cubical habit (requirement for the presented methods), their 2D projection on camera is not a strong function of their orientation:



http://www.malinc.se/math/linalg/rotatecubeen.php

- We can estimate area (k_a) and volume (k_v) shape factors, that translate size from the Crystalline (L, as equivalent circle diameter) into area and volume of the cubical crystals:

$$k_a = \frac{3}{2}\pi \qquad k_v = \left(\frac{\pi}{4}\right)^{3/2}$$

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Moments on Camera → Overall Crystallizer Moments

For each image, we can now calculate the number, length, area, and volume of the crystals on camera (making the cubical habit assumption to get the projection of the crystal in the third dimension):

$$N_{tot} = \sum_{i\ channels} N_i$$

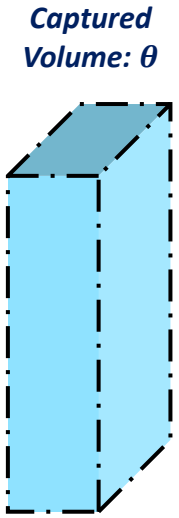
$$L_{tot} = \sum_{i\ channels} N_i L_i$$

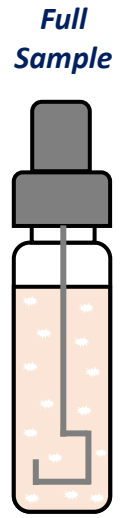
$$A_{tot} = \sum_{i\ channels} k_a N_i L_i^2$$

$$V_{tot} = \sum_{i\ channels} k_v N_i L_i^3$$

$\theta \equiv \mu L\ suspension/picture$

Scale adjustment, assuming representative PSD





$$\mu_0 = \frac{N_{tot}}{\theta}$$

$$\mu_1 = \frac{L_{tot}}{\theta}$$

$$\mu_2 = \frac{A_{tot}}{k_a \theta}$$

$$\mu_3 = \frac{V_{tot}}{k_v \theta}$$

- Note: Because the crystalline only measures counts and size, L_{tot}, A_{tot} and V_{tot} are not independent!

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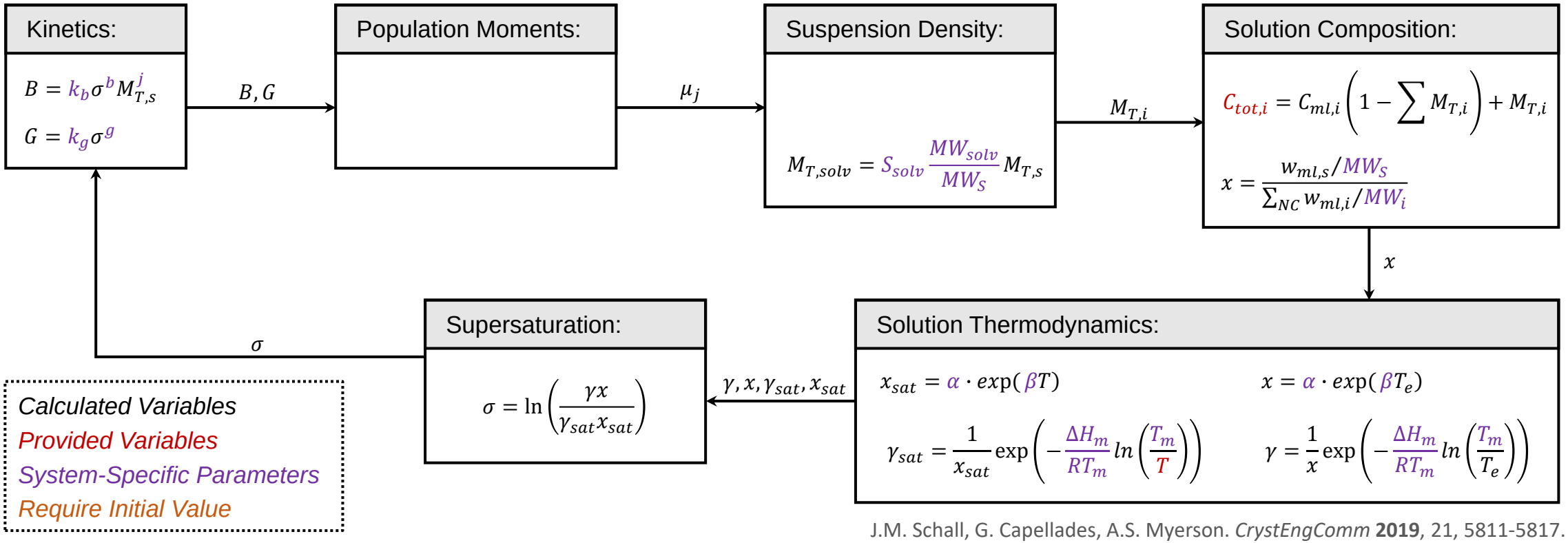
General Crystallization Model → Crystalline™ - Specific Model

We can now adapt the batch crystallization model to use those projected moments instead:



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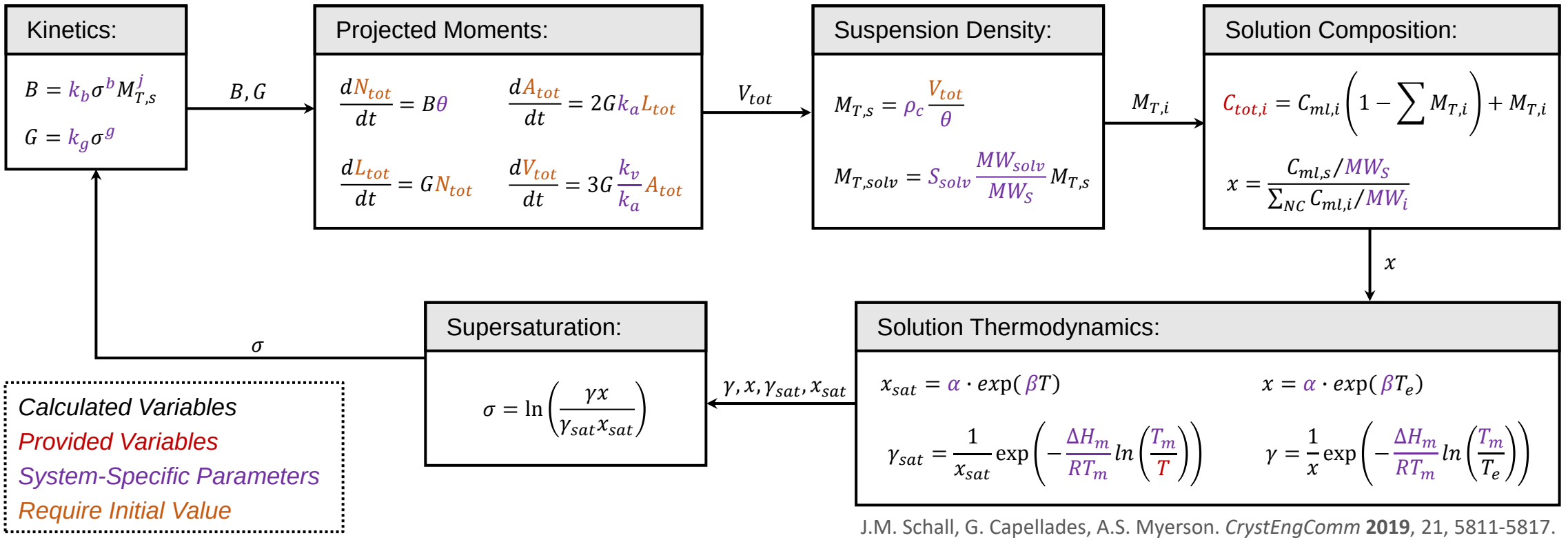

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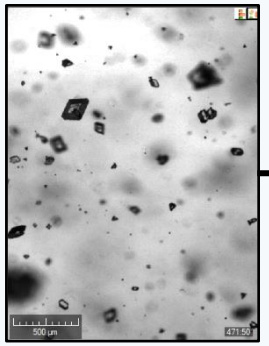
Data Processing

Back to the Data Flow

Imaging Trends (Kinetic Screening)



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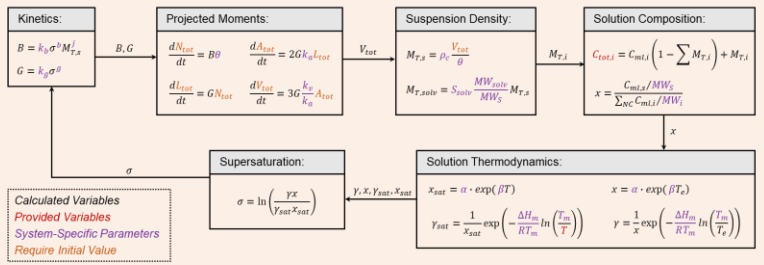
Time-Dependent Trends (N_{tot} and A_{tot} Only)

Initial Conditions (N_{tot}, L_{tot}, A_{tot}, V_{tot})

How?

Can we automate this?

gPROMS Model



Experimental Conditions:

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Solubility Curve (Empirical)

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From Isothermal or Polythermal Screening

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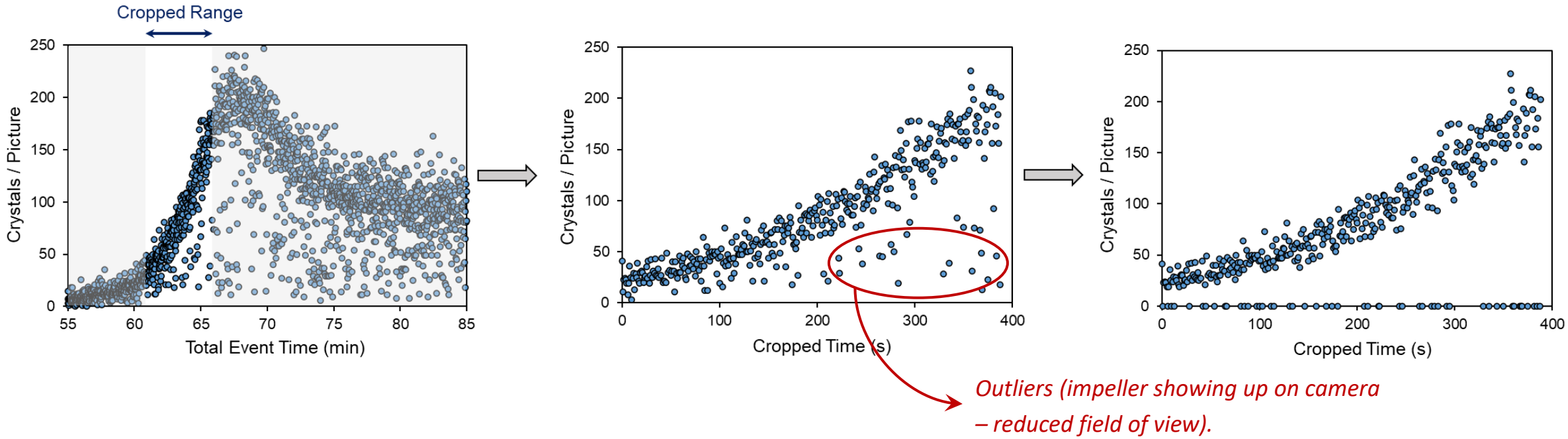
Processing Crystalline Data

To ensure that the methods are not user-sensitive, we have automated data cropping, outlier detection, and calculation of initial conditions for parameter estimation.



- Cropped range covering 70% of the event, from base line to the highest crystal count.
- Outlier removal based on deviation from a moving average.

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Processing Crystalline Data – Excel Template

Assumptions / Comments

Crystalline measures particle size as the diameter of the equivalent circle with the same projected area as the crystal

Although it reports particle size, area is the most reliable reading, which can be re-calculated as $A_i = \Sigma N_i * (3/2) * \pi * L_i^2$

Methods rely on the samples collected on camera being representative of the crystal concentration and size in suspension, on working with cubical crystals, and on the assumptions of constant habit and negligible agglomeration

Especially when using the overhead hook for stirring, the stirrer may show up on camera and decrease the signal in certain pictures. An outlier removal algorithm has been implemented that removes pictures with less than 70% of the crystals from a moving average (see 3b below).

How to Use

1 - Export the PSD data from the Crystalline, only at the region where the temperature was constant. It does not need to start right at the point where temperature became constant. You just need a range that captures the crystallization event. This should give one file per crystallization event.

2 - Copy and paste the Crystalline PSD output in the highlighted cells, one tab per crystallization event. Check that temperature was constant throughout

3 - Compare the plotted figures - was the event captured correctly? Is there any change in slope or an increase in noise towards the end of the event that would have to be cropped? Was that cropped right by the template?

3.a - if the outlier removal is too severe, you can adjust the percent change allowed here (default is 30% deviation from moving average):

Accepted deviation from moving average:	30%	(recommend 30%, use 100% to turn off outlier removal)
Correction factor:	0.7	

3.b - Note that outlier removal is set on a moving average

4 - Copy the values in columns DR and DT to gPROMS for parameter estimation - you'll be using number and area only, but still need initial conditions for N, L, A, and V. Your initial conditions, as the average of the first ten points, are in rU20 - U23. For fast crystallizing systems, make sure those avera

Results:

Average number of crystals (N):

Baseline	1.5
Max. Change	201.0
Start Value	21

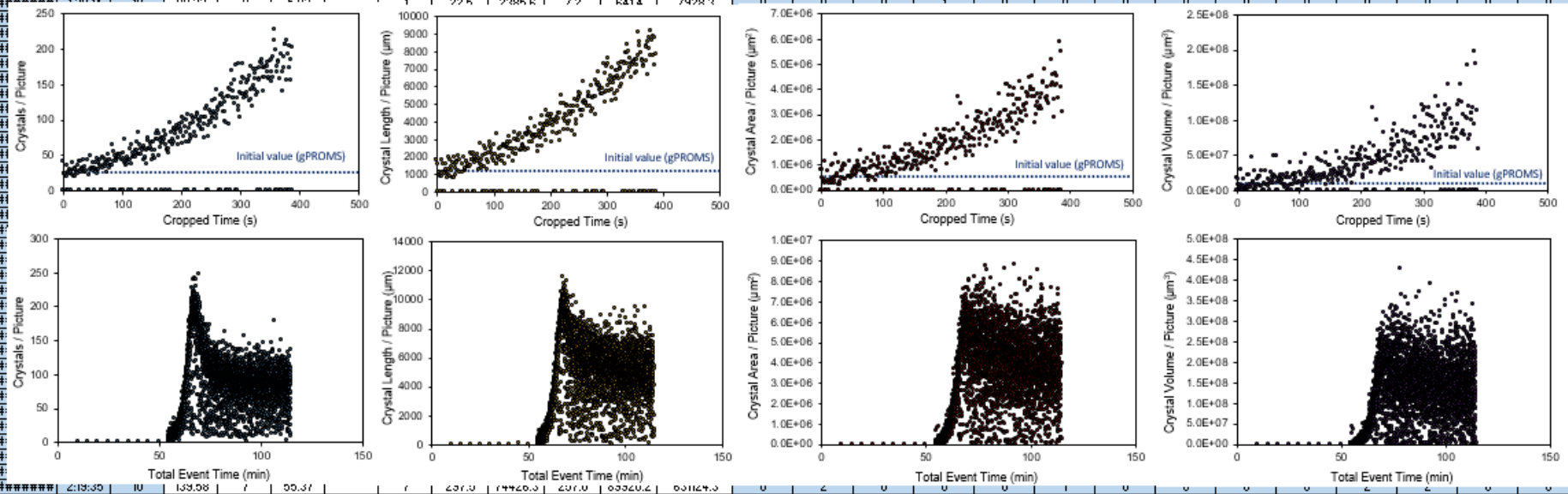
Adjust the values for t0 and tend if you disagree with the automated cropping (may be needed for fast

tend	66.6	<-- for the bottom plot, this is the last time value that will be used for parameter estimation
tmax	68.2	<-- this is the approximate time when the number of crystals per picture peaks
t0	60.1	<-- for the bottom plot, this is the first time value that will be used for parameter estimation

Initial Conditions (gPROMS)

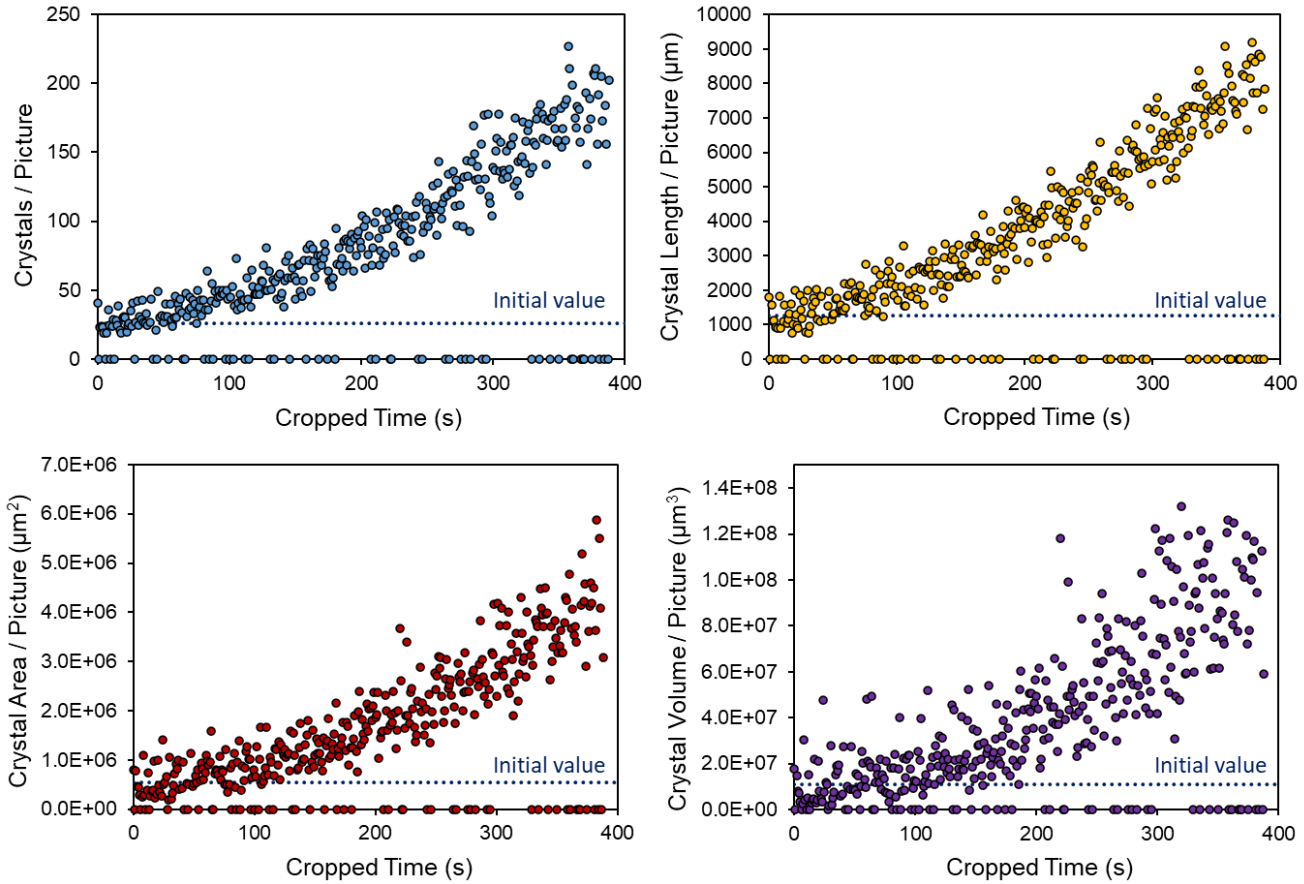
N	26	
L	1.3E+03	µm
A	5.5E+05	µm²
V	1.1E+07	µm³

Date time	Decimal time	Actual temperature	Total Experiment Time (min)	N Moving Avg	Total Event Time (min)	Adjusted Time [t-t0] (c)	Crystals/Picture, N	Total L (µm)	Total A (µm²)	L Moving Avg (µm)	A Moving Avg (µm²)	Total V (µm³)	bin0Size	bin1Size	bin2Size	bin3Size	bin4Size	bin5Size	bin6Size	bin7Size	bin8Size	bin9Size	bin10Size	bin11Size	bin12Size	bin13Size	bin14Size
	(mins)	(Â°C)											5	10	15	20	25	30	35	40	45	50	55	60	65	70	75
##########	1:24:13	10	84.22	0	0.00		1	12.5	736.3	7.2	688.5	1359.5	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
##########	1:24:14	10	84.23	0	0.01		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:15	10	84.25	0	0.02		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:16	10	84.27	0	0.03		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:17	10	84.28	0	0.05		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:18	10	84.30	0	0.07		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:19	10	84.32	0	0.08		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:20	10	84.33	0	0.10		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:21	10	84.35	0	0.12		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:22	10	84.37	0	0.13		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:23	10	84.38	0	0.15		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:24	10	84.40	0	0.17		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:25	10	84.42	0	0.18		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:26	10	84.43	0	0.20		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:27	10	84.45	0	0.22		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:28	10	84.47	0	0.23		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:29	10	84.48	0	0.25		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:30	10	84.50	0	0.27		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:31	10	84.52	0	0.28		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:32	10	84.53	0	0.30		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:33	10	84.55	0	0.32		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:34	10	84.57	0	0.33		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:35	10	84.58	0	0.35		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:36	10	84.60	0	0.37		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:37	10	84.62	0	0.38		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:38	10	84.63	0	0.40		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:39	10	84.65	0	0.42		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:40	10	84.67	0	0.43		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:41	10	84.68	0	0.45		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:42	10	84.70	0	0.47		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:43	10	84.72	0	0.48		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:44	10	84.73	0	0.50		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:45	10	84.75	0	0.52		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:46	10	84.77	0	0.53		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:47	10	84.78	0	0.55		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:48	10	84.80	0	0.57		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:49	10	84.82	0	0.58		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:50	10	84.83	0	0.60		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:51	10	84.85	0	0.62		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:52	10	84.87	0	0.63		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:53	10	84.88	0	0.65		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:54	10	84.90	0	0.67		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:55	10	84.92	0	0.68		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:56	10	84.93	0	0.70		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:57	10	84.95	0	0.72		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:58	10	84.97	0	0.73		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:24:59	10	84.98	0	0.75		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:00	10	85.00	0	0.77		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:01	10	85.02	0	0.78		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:02	10	85.03	0	0.80		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:03	10	85.05	0	0.82		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:04	10	85.07	0	0.83		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:05	10	85.08	0	0.85		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:06	10	85.10	0	0.87		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:07	10	85.12	0	0.88		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:08	10	85.13	0	0.90		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:09	10	85.15	0	0.92		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:10	10	85.17	0	0.93		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:11	10	85.18	0	0.95		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:12	10	85.20	0	0.97		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:13	10	85.22	0	0.98		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	1:25:14	10	85.23	0	1.00		1	22.5	2385.6	7.2	6414	7928.3	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
##########	2:19:35	10	139.58	7	55.37		7	297.9	74428.3	297.0	63320.2	651124.3	0	2	0	0	0	1	0	0	0	0	2	2	0	0	0



Processed Data

We get trends for number, length, area, and volume of crystals on camera:



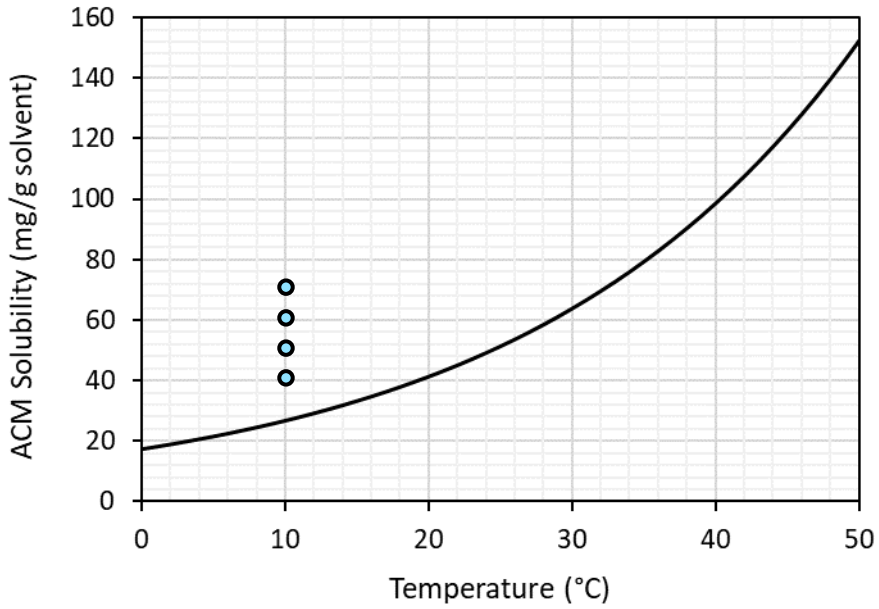
- Because length, area, and volume are not independent (all calculated from the crystal area that the equipment sees), only number and area are used for parameter estimation.

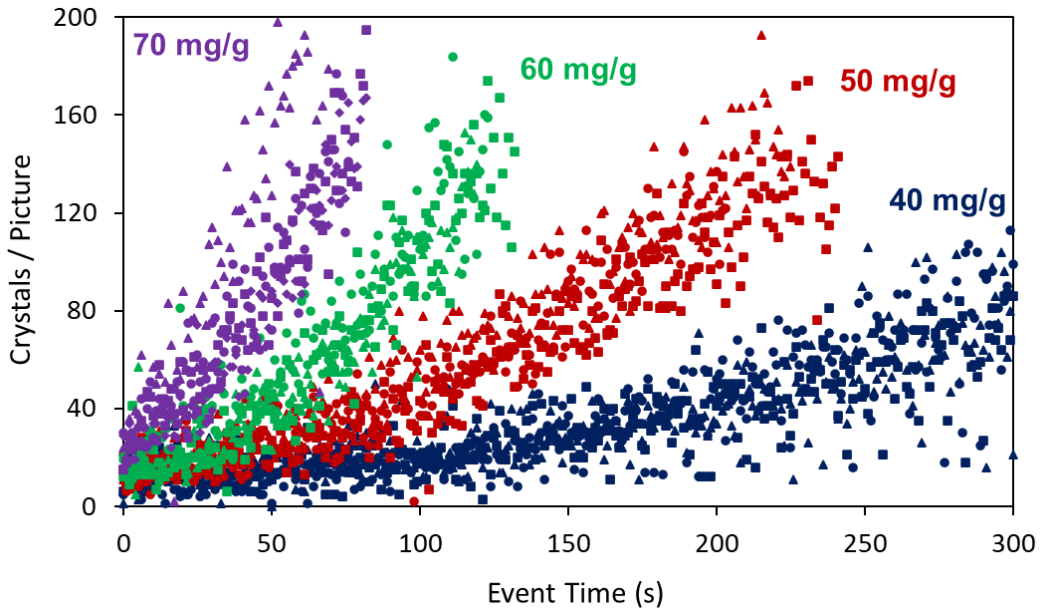
R.J. Arruda, P.A.J. Cally, A. Wylie, N. Shah, I. Joel, Z.A. Leff, A. Clark, G. Fountain, L. Neves, J. Kratz, A.A. Thorat, I. Marziano, P.R. Rose, K.P. Girard, G. Capellades. *Crystal Growth & Design* 2023, 23, 3845-3861.

Parameter Estimation - Example

Acetaminophen from Ethanol-Water

Kinetic data collected at 10 °C, at constant solvent composition (25% ethanol in water), for different starting supersaturations. 4 replicate events at each concentration:





- With 4 camera modules, the entire screening can be completed in one day (4 concentrations x 4 replicates -> 16 events).
- While data is noisy, trends with supersaturation can be clearly seen beyond the repeatability of the methods.

R.J. Arruda, P.A.J. Cally, A. Wylie, N. Shah, I. Joel, Z.A. Leff, A. Clark, G. Fountain, L. Neves, J. Kratz, A.A. Thorat, I. Marziano, P.R. Rose, K.P. Girard, G. Capellades. *Crystal Growth & Design* 2023, 23, 3845-3861.

Parameter Estimation

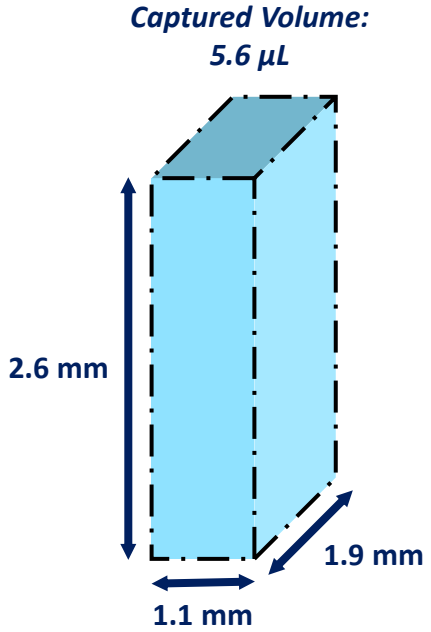
Best fit and parameters for Acetaminophen in Ethanol-Water:

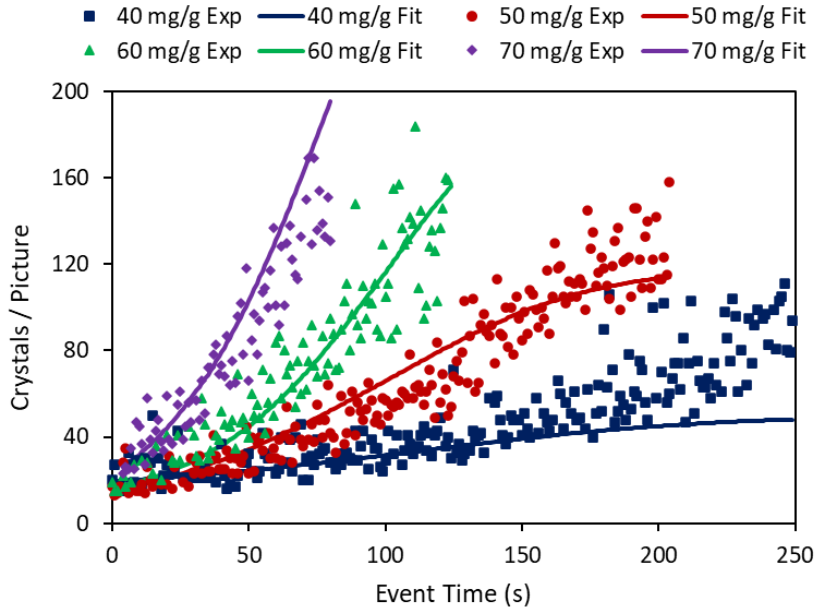
Parameter	Value	Units
k_b	(2.08 ± 0.03) · 10^5	$g^{-1}s^{-1}$
b	2	-
j	1	-
k_g	2.31 ± 0.02	µm/s
g	1	-
θ	5.45 ± 0.09	mg/picture

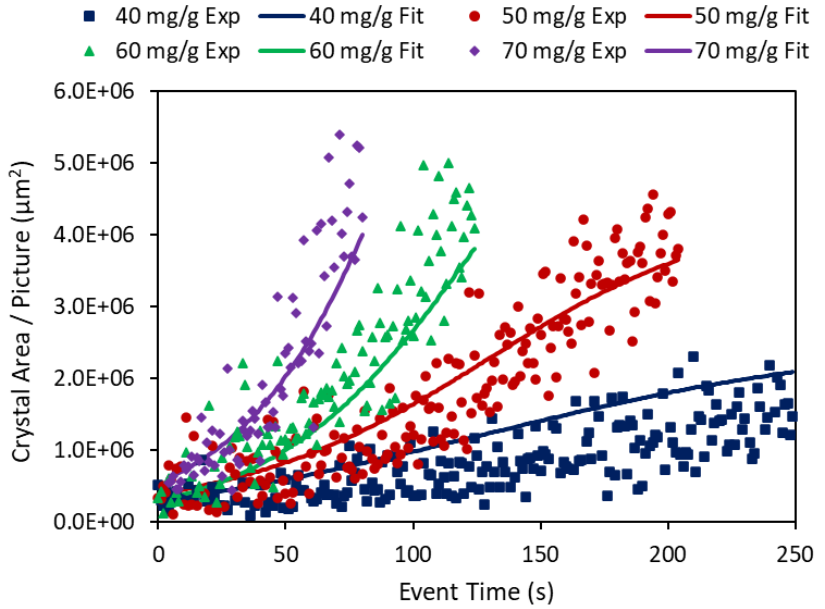
$$B = k_b \sigma^b M_{T,s}^j$$

$$G = k_g \sigma^g$$

- Estimated θ is reasonable when converting from mass to volume.
- Note: depth may be underestimated, as effective 2D area is not 2.6 mm x 1.9 mm (crystals at picture's edges may not be analyzed)





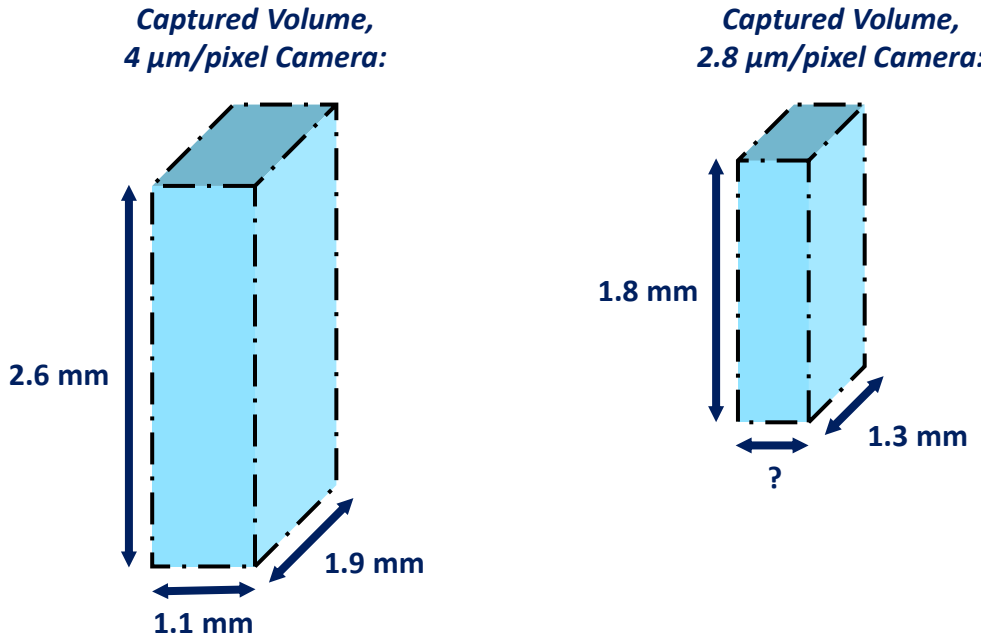


R.J. Arruda, P.A.J. Cally, A. Wylie, N. Shah, I. Joel, Z.A. Leff, A. Clark, G. Fountain, L. Neves, J. Kratz, A.A. Thorat, I. Marziano, P.R. Rose, K.P. Girard, G. Capellades. *Crystal Growth & Design* 2023, 23, 3845-3861.

Model Validation

To validate reproducibility, experiments were repeated at the Pfizer site (Groton, CT), with their Crystalline:

- Camera magnification is 2.8 µm/pixel instead of our 4 µm/pixel. New dimensions:

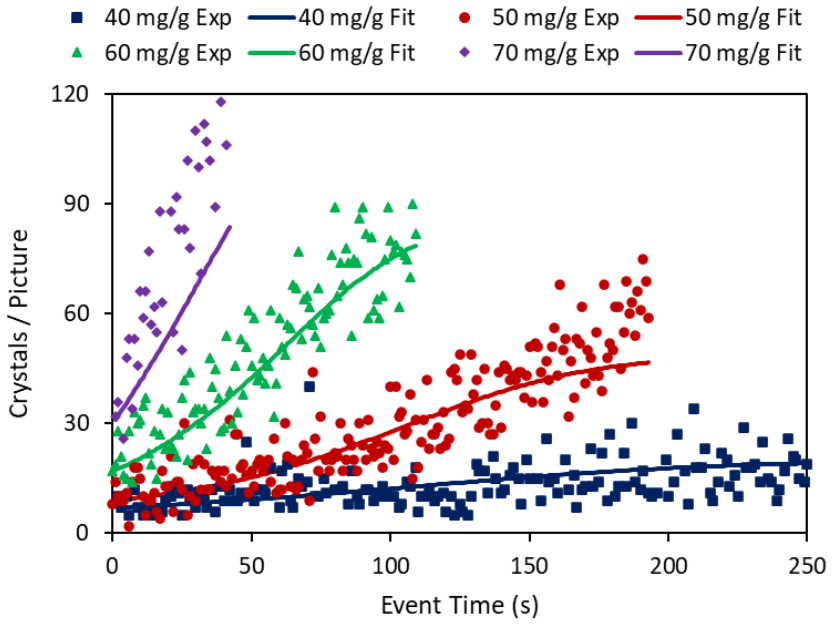


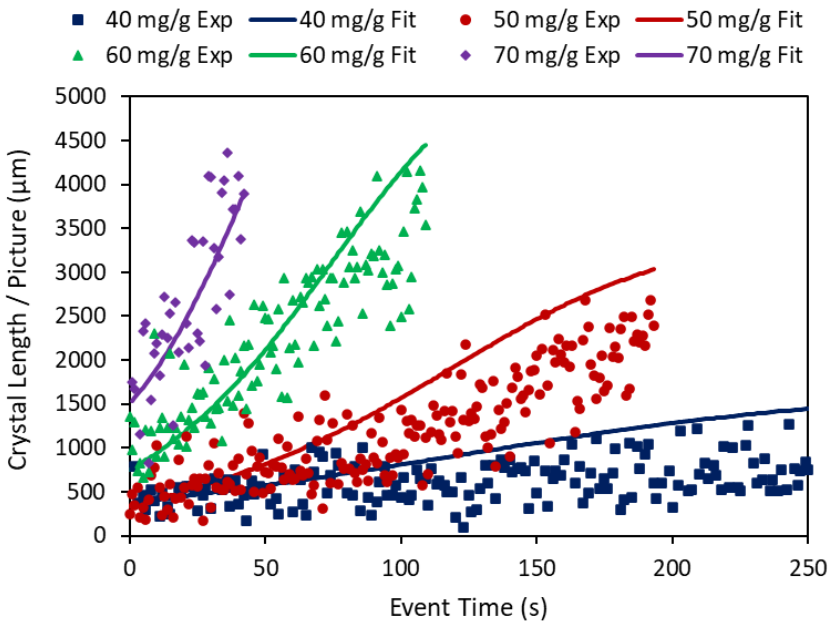
- The 2D area being captured is 2.4 mm^2 instead of 4.9 mm^2 (effective area may be lower, edge effect). We expect θ to drop by at least 50%.

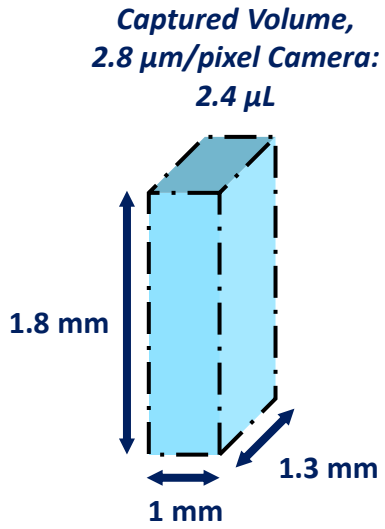
Model Validation

To validate reproducibility, experiments were repeated at the Pfizer site (Groton, CT), with their Crystalline:

- Using parameters estimated at Rowan to predict Pfizer data (adjusting θ only):

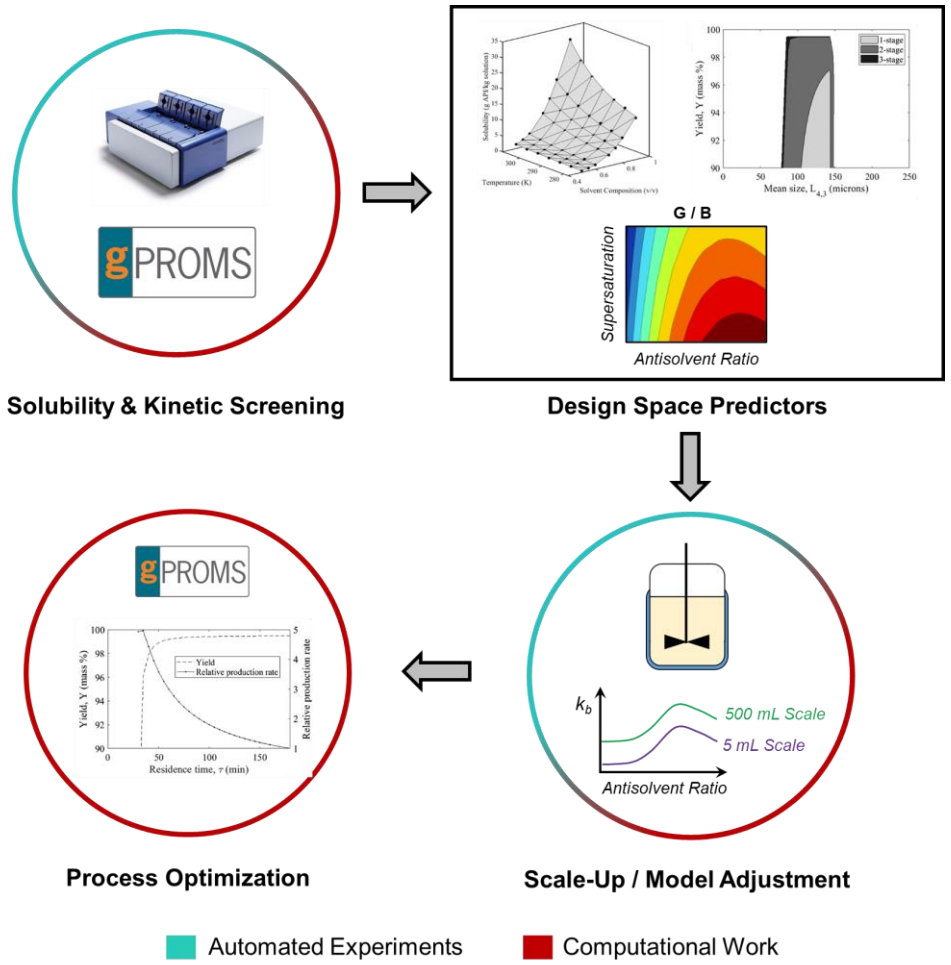






- θ for the 2.8 µm/pixel magnification converged at 2.26 ± 0.02 mg/picture.
- 59% drop in θ when capture area drops by 51% → Effects of different depth, and edge effects.

Application: Systematic Process Development



Systematic Crystallization Process Development

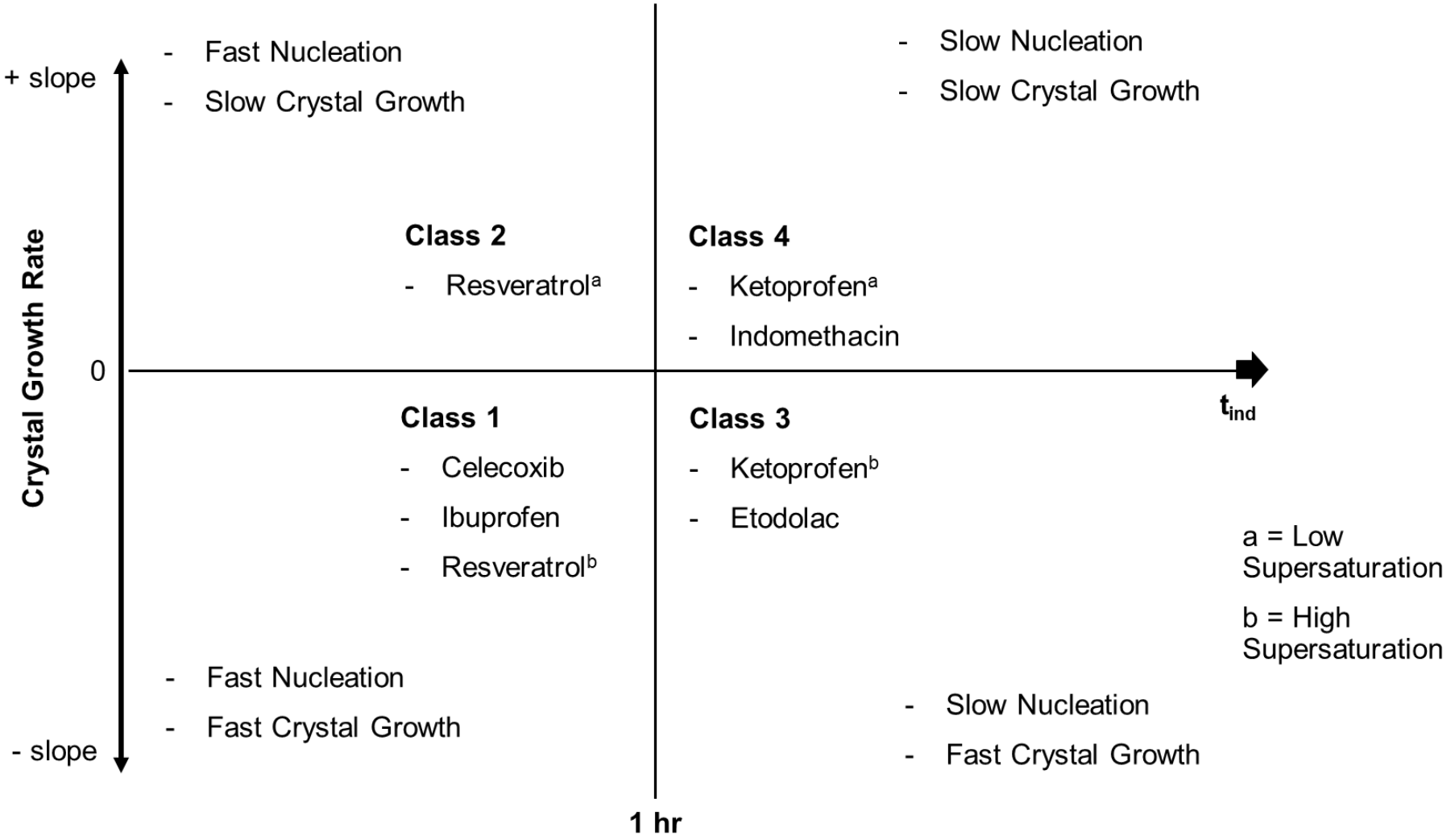
- Classifying APIs by their kinetic properties using Crystalline™-based experiments allows greater amounts of data and information to be collected for the early development of crystallization processes in a material sparing fashion.
- gPROMS FormulatedProducts™-based modeling allows for the development of a parameter estimation framework that can provide quick and accurate k_b and k_g values for nucleation and growth respectively.

Objectives

Can we use k_b and k_g (nucleation and growth constants) to model crystallization behavior independent of supersaturation and suspension density?

- Reduce the number of unknowns and variables.
- Model crystallization events.
- Identify trends.
- Make data-based predictions.

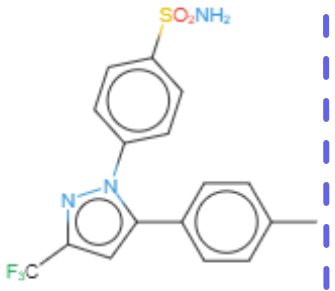
API Selection



Model Compounds

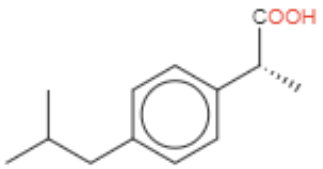
Celecoxib

- PF-00345549
  - MP: 160.9°C
  - MW: 381.87 g/mol
  - Density: 1.43 g/mL
  - ΔH_{fus}: 34.35 kJ/mol



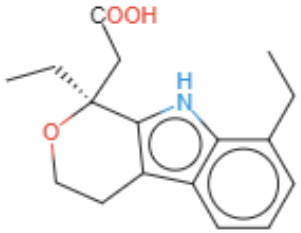
Ibuprofen

- MP: 74.5°C
- MW: 206.28 g/mol
- Density: 1.03 g/mL
- ΔH_{fus}: 27.94 kJ/mol



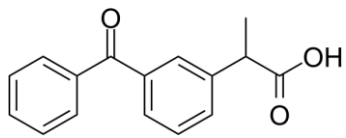
Etodolac

- PF-00345040
  - MP: 145°C
  - MW: 287.35 g/mol
  - Density: 1.193 g/mL
  - ΔH_{fus}: 26.175 kJ/mol



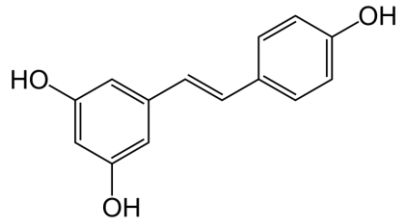
Ketoprofen

- MP: 94°C
- MW: 254.28 g/mol
- Density: 1.2 g/mL
- ΔH_{fus}: 37.3 kJ/mol



Resveratrol

- MP: 254°C
- MW: 228.24 g/mol
- Density: 1.359 g/mL
- ΔH_{fus}: 37.65 kJ/mol

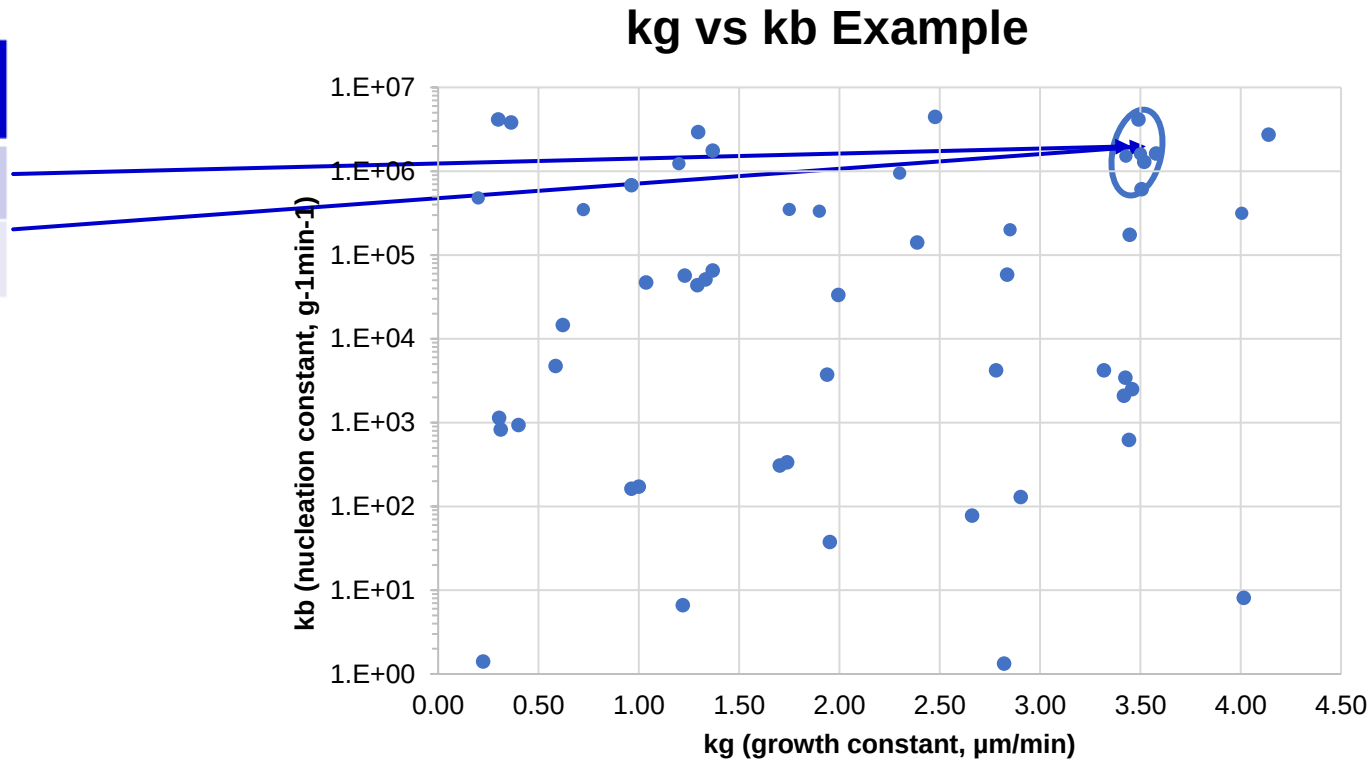


The Workflow

Initial Characterization and Solubility → Crystalline™ Data Collection → Excel Cropping → gPROMS™ Parameter Estimation → k_b and k_g Plotting

	k_b [#crystals/(s·g suspension)]	k_g [$\mu m/s$]
System 1	1514061.53	3.42765
System 2	1610515	3.5

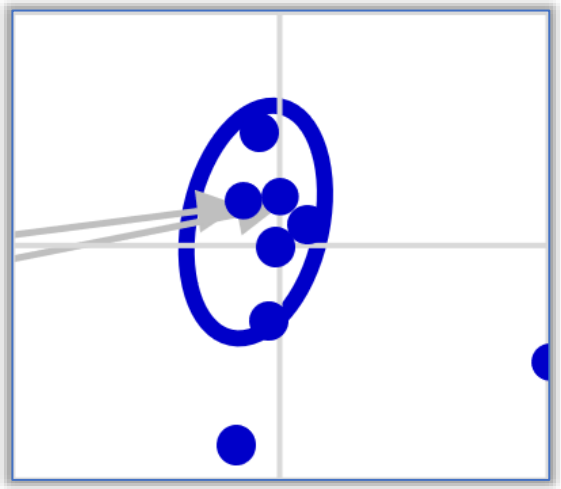
T = 10°C
Stirring = 1000rpm
Scale = 5 mL



Big Picture – Systematic Crystallization Process Development

Trends between k_b and k_g values plotted against each other for different systems could tell a variety of stories.

- How similar are solvent-dependent kinetics, compared to differences across solutes?
- Pure solvents vs mixed solvents – how much difference is there in kinetic effects?
- How much of a correlation exists between nucleation and growth?
- Quick comparison of new compounds with established systems
- Residence time and initial pot conditions for continuous crystallization
- Identification of critical parameters, and streamlining development stages: are solvent or temperature effects significant for this compound? Do we need to investigate those at the larger scale?



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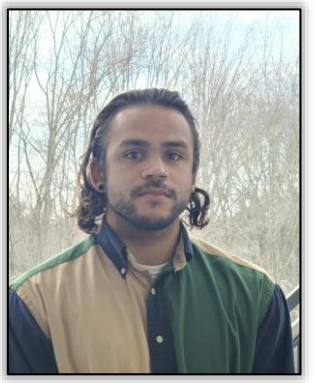

Griffin Fountain

Pfizer Advising Team:

- Kevin Girard
- Peter Rose
- Ivan Marziano