From Fundamentals to Process: Automated Crystallisation Workflows for Agrochemicals

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Acknowledgements:
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Adam Keates
Alan Collier
Peter Burland
Katie Foster
David Bowskill

Classification: PUBLIC

June 2026

57,000

people across more than 100 countries

$33.4bn

annual sales

Syngenta Group

UK footprint

syngenta Crop Protection	syngenta Seeds	ADAMA	Syngenta Group China
Weed control	Seeds	Weed Control	Crop Protection
Disease Control	Traits	Disease Control	Seeds
Insect Control	Corn & Soybean	Insect Control	Crop Nutrition
Seed Treatment	Vegetables	Consumer & Professional Solutions	Ingredients & Intermediates
Professional Solutions	Diverse Field Crops	Ingredients & Intermediates	Former Services
Biologicals	Flowers		Digital Agricultural Solutions
Digital Solutions			

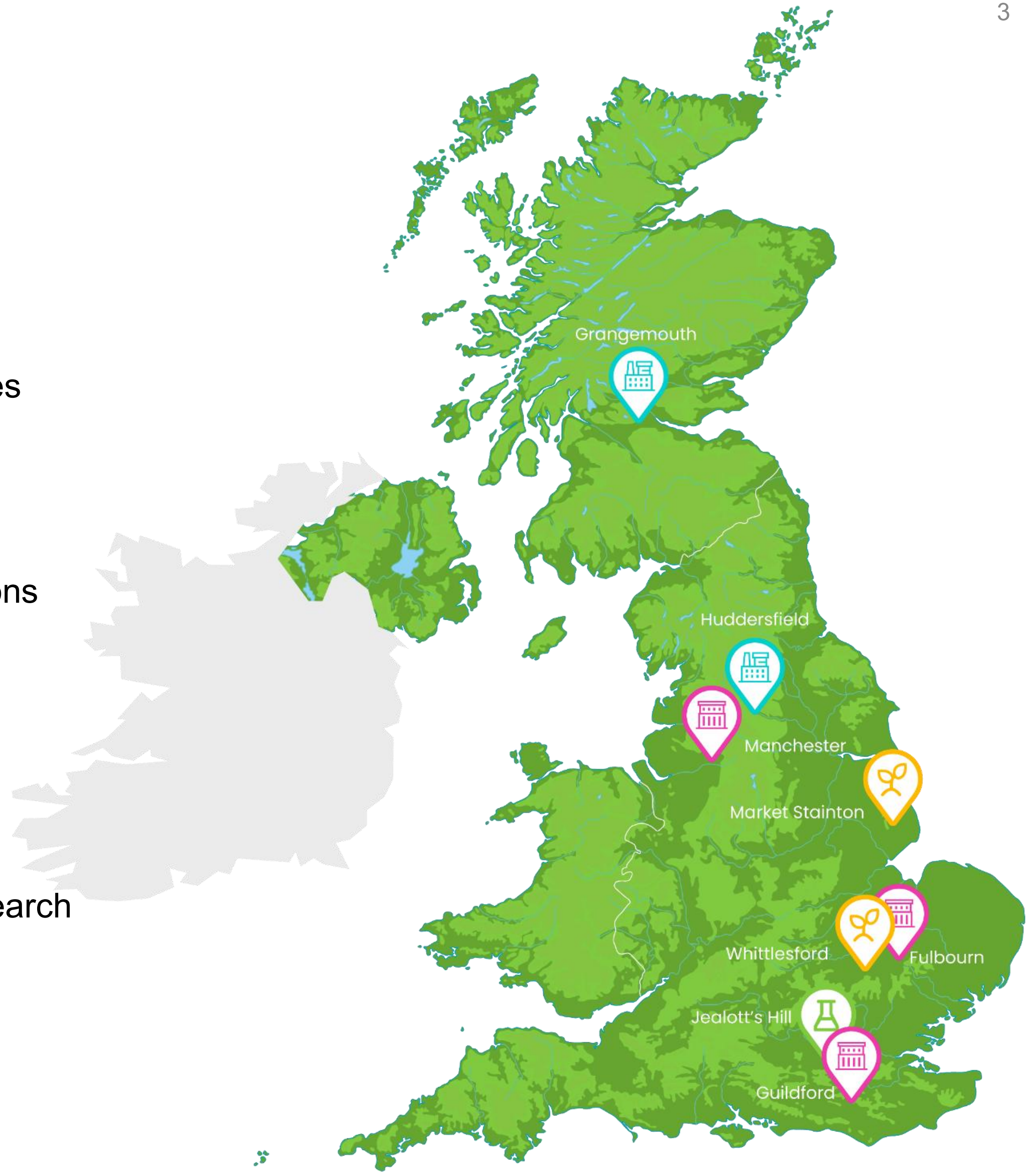
Over **2000** employees across **NINE SITES**

Manufacturing sites

Commercial & corporate operations

Seeds sites

International Research Centre



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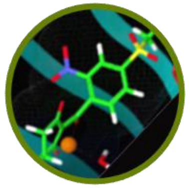
Jealott's Hill Capabilities



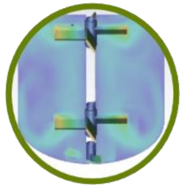
Research Chemistry:
Design, model, synthesise and optimise novel and sustainable chemical compounds

Research Biology:
Generate biological data to support projects

Bioscience:
Deliver fundamental understanding of biological systems to guide innovation in CP R&D

Biologicals:
Discover microbial biocontrols and biostimulants

Product Technology & Engineering:
Develop new formulations for Active Ingredients



Process Studies Group:
Provide fundamental understanding of the physical science that underpins our processes and products

Seeds R&D Doubled Haploid:
Develop new winter wheat and barley varieties

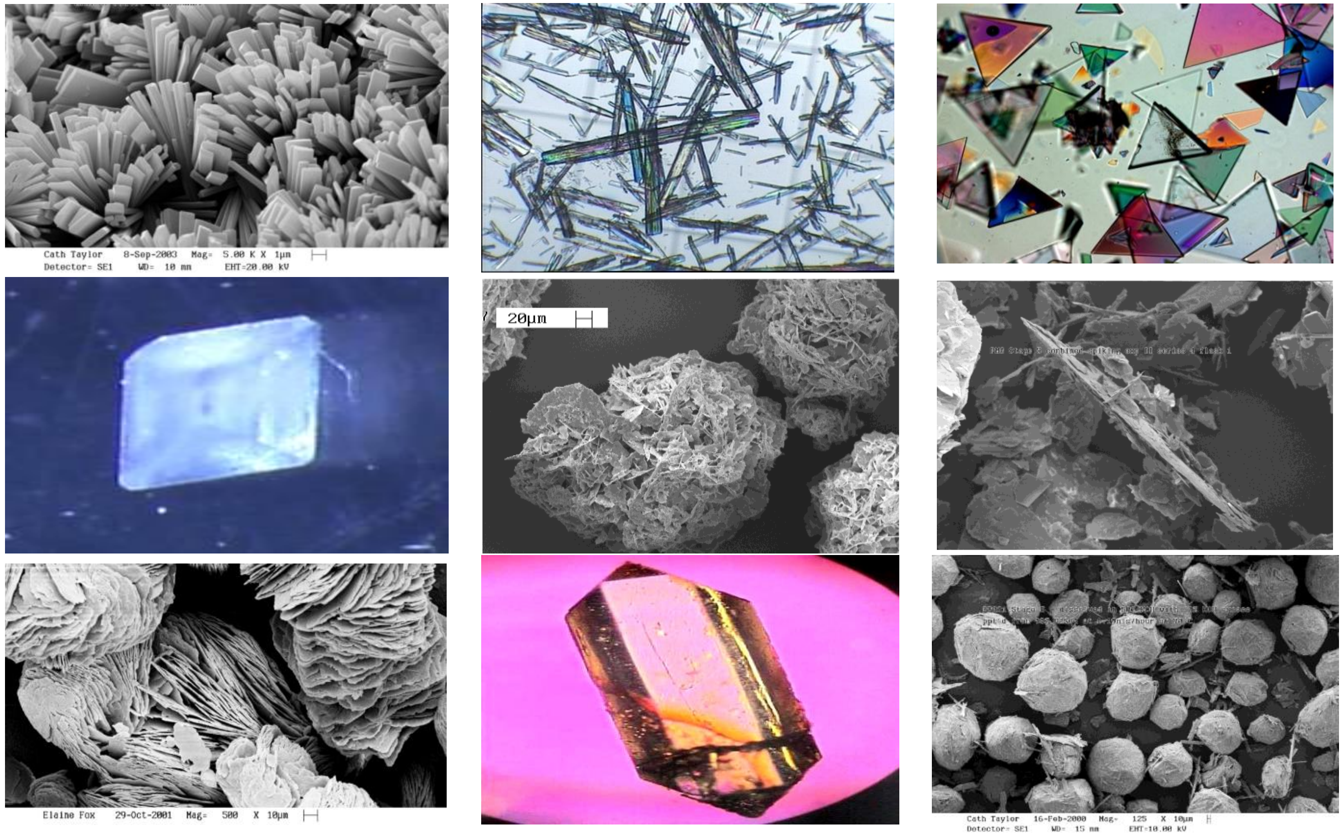
Technology & Digital Integration:
Identify and assess new technologies and capabilities

R&D IT:
Design, build and improve digital tools & systems

Product Safety:
Ensure our products and technologies are safe for both humans and the environment

Syngenta Crop Protection Crystalline Organic Particles

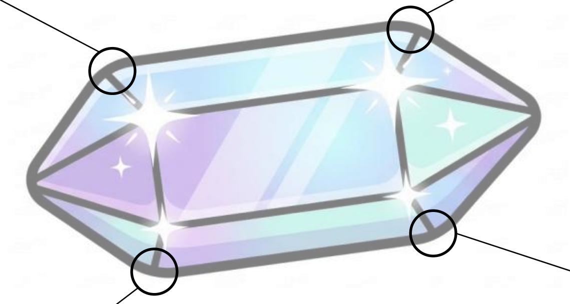
- Manufacture of the agrochemical active ingredients (AIs) can vary between **10 to 10000s** of tonnes per annum (depending on the product).
- A large proportion of Syngenta active ingredients are isolated by a final **crystallisation step**.



Why should crystallisation be controlled?

Slow filtration can become the **bottleneck** if particle size + shape are not controlled

Optimising the cooling profile leads to **reduced batch time** and **higher productivity**



Fine particles lead to significant **compaction** issues during **storage** & **transportation**

Low **Minimum Ignition Energy (MIE)** of fine powders

Why is automation important?

Increases productivity by freeing up the experimentalist's time spent on manual actions

Perform actions and acquire data when the experimentalist cannot be in the lab

Improved safety by reducing interaction with hazardous chemicals

Aids data storage and management, making analysis more efficient

For crystallisations:

- React to events based on kinetic mechanisms (e.g. nucleation)
- More precise control of process conditions (cooling profile → supersaturation)
- Improved repeatability of batches

Crystallisation studies workflow (at lab-scale)

- Solvent Selection
- Solubility Measurement
- Concentration Model Calibration
- Scoping Crystallisations
  - Unseeded
  - Seeded
  - Varied Process Conditions
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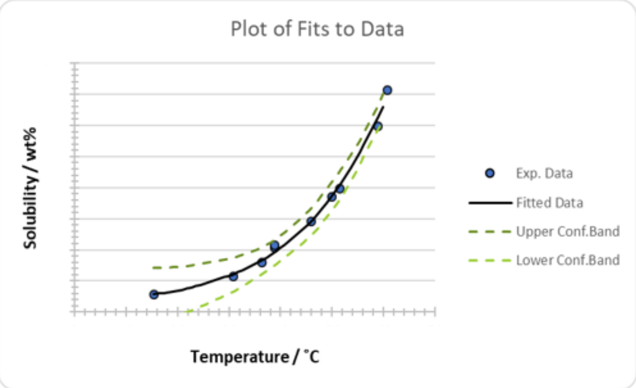
- Initial solvent screening based on reaction step, modelling etc.

- Solubility measurement in selected solvent(s)
  - Assess most suitable solvent for yield/purity
  - Determine temperature/loading range for calibration and crystallisation DoE

What is needed for efficient and robust solubility measurement?

- High throughput (min. 4 data points)
- Confidence of dissolution point
- Good temperature control

- Digital tools can support with fitting solubility data to widely used models
  - Statistics help explain observations during crystallisation, e.g. final yield
  - Accurate fitted expression is required for process modelling tools, e.g. gPROMS (Siemens)



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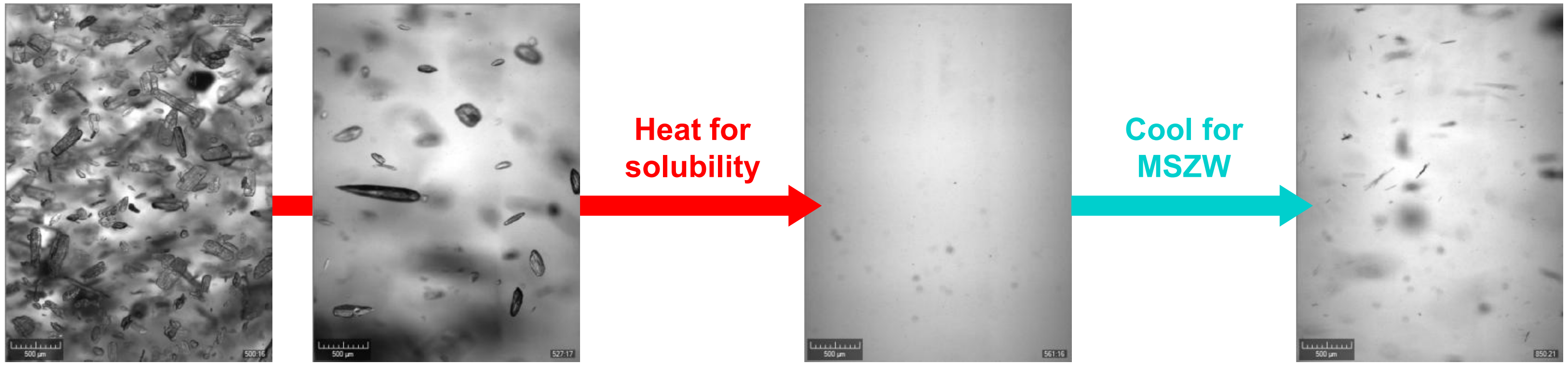
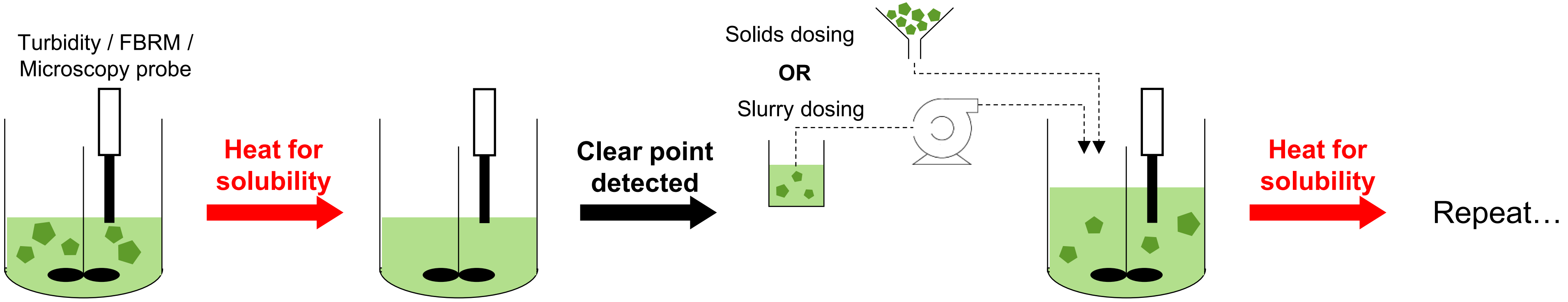
Solubility measurement

- **Crystalline** (Technobis) system commonly used for high throughput (8 x 8 ml vials), combination of images/turbidity



- *Alternative*: any size vessel with **automated solids/slurry dosing** – ideally requires a way of detecting the dissolution point in-situ (e.g. turbidity, particle counts)



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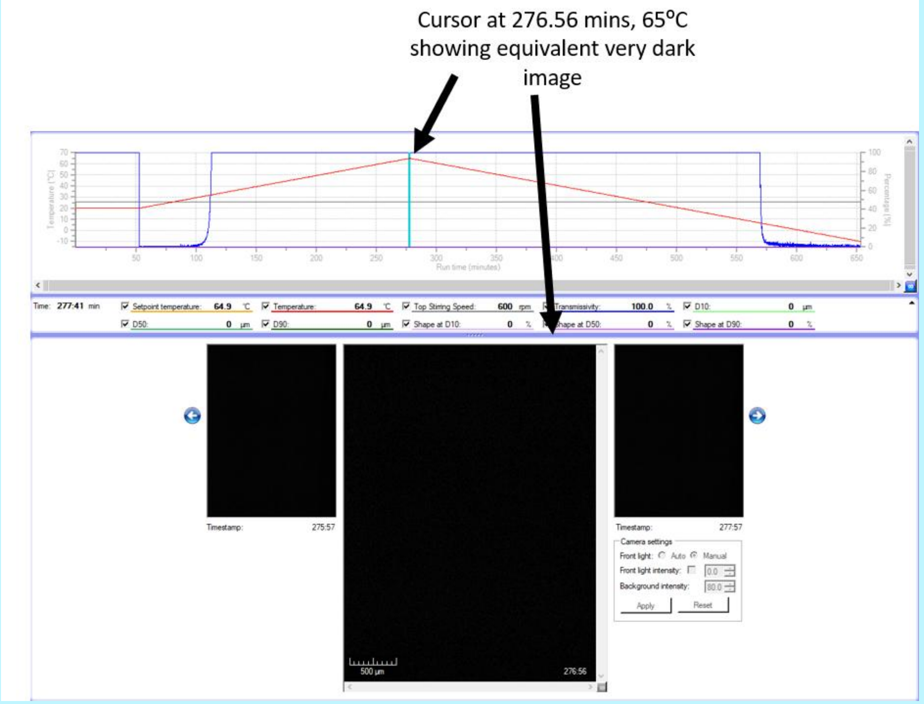
Case studies: Crystalline v2 trial for solubility/MSZW

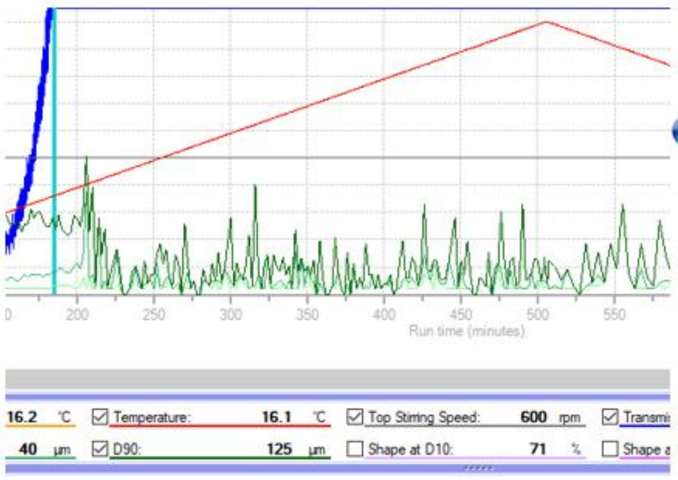
- Impure solutions may be very turbid/dark, and therefore difficult to image

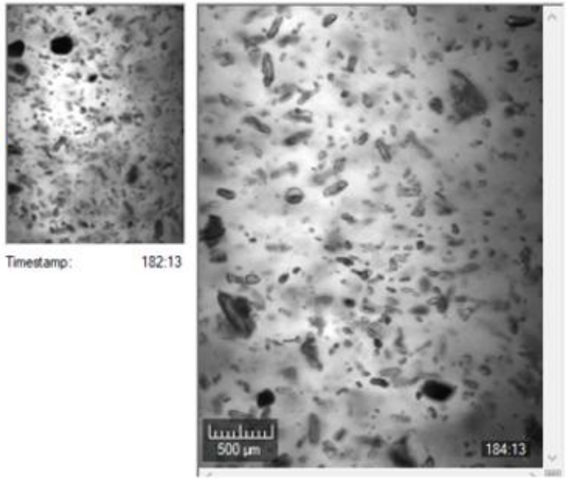
Crystalline V1

- Camera can't see, relying only on transmissivity to monitor dissolution



- Even in clearer solutions, transmissivity alone cannot always be trusted – 100% transmissivity measured when many particles still present!





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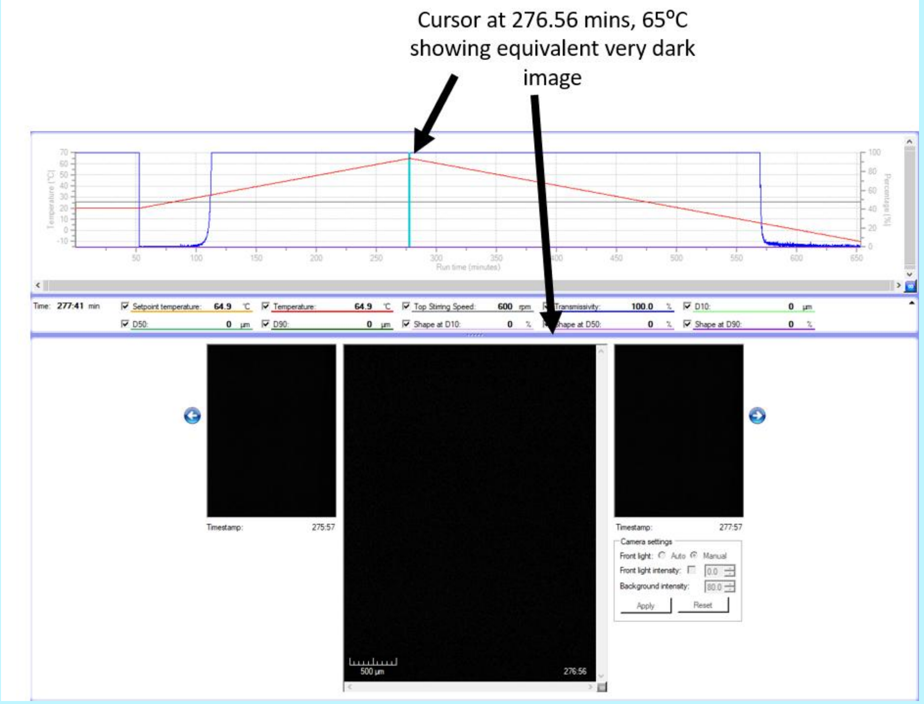
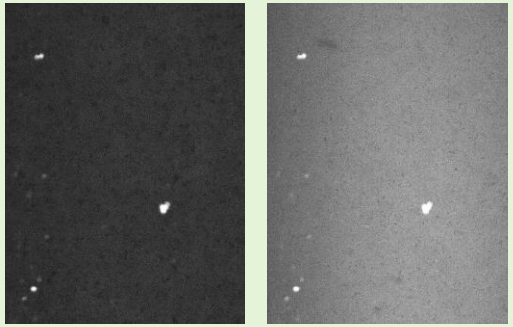
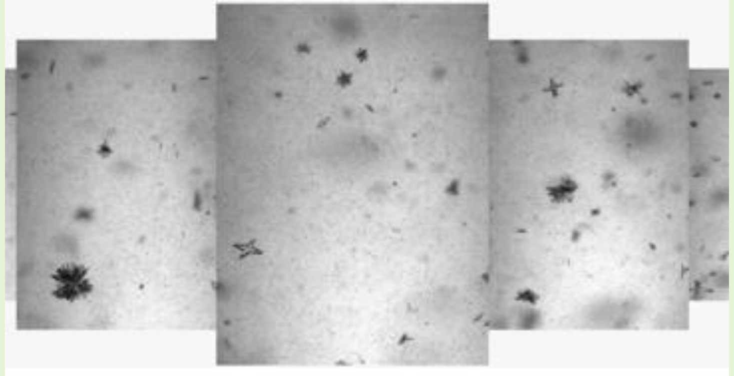


Crystalline V2

- Clearer dissolution point



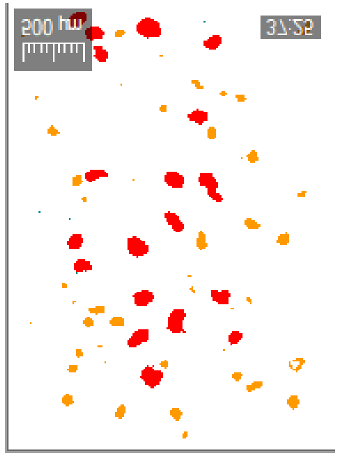
- Nucleation of impurities observed

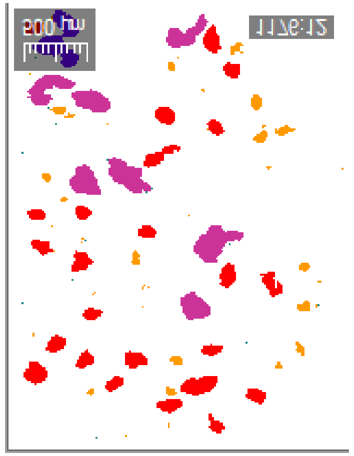


Case studies: Crystalline v2 trial for crystal growth (PSD analysis)

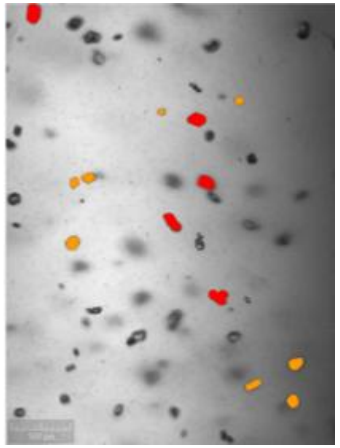
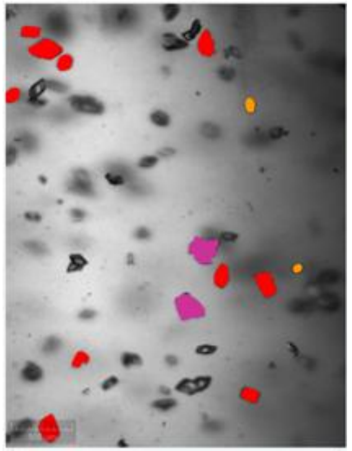
Seed | Post Growth

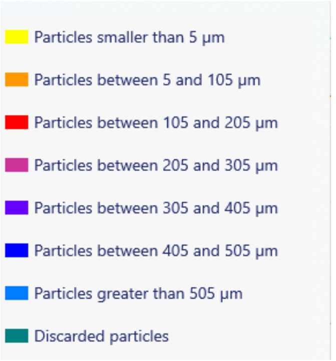
Legacy V1



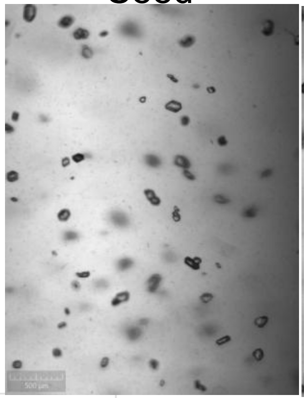
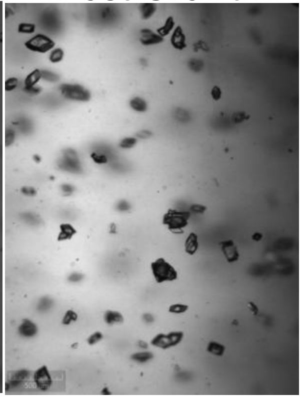


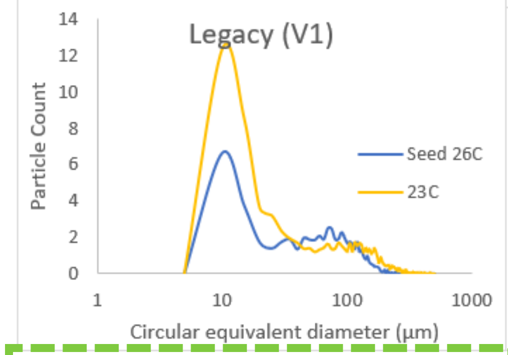
Ai V2

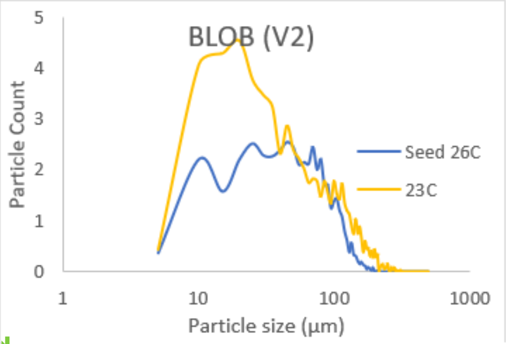



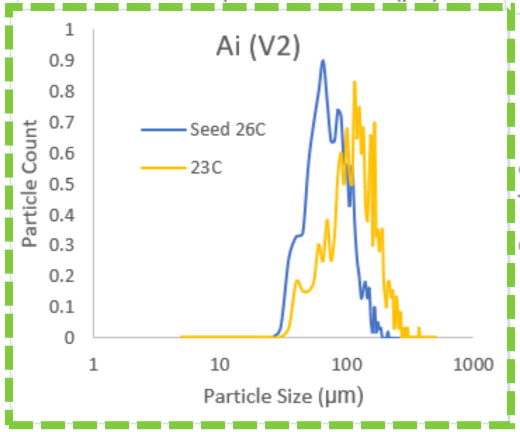


Seed | Post Growth







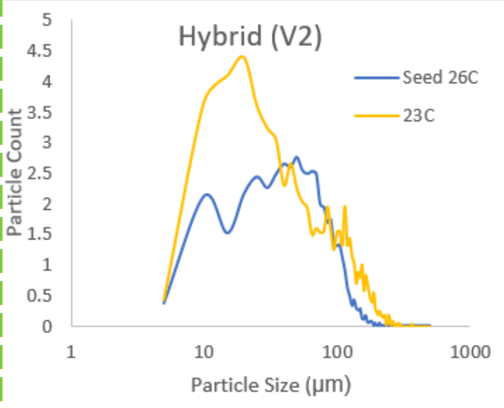
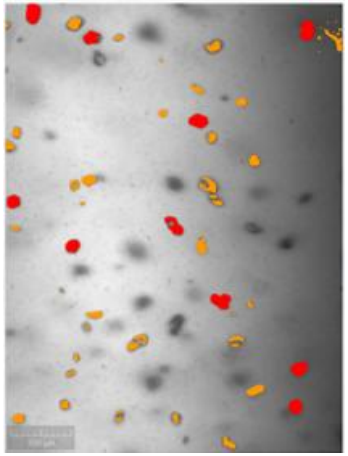
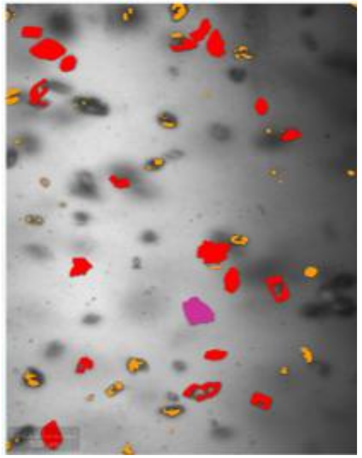


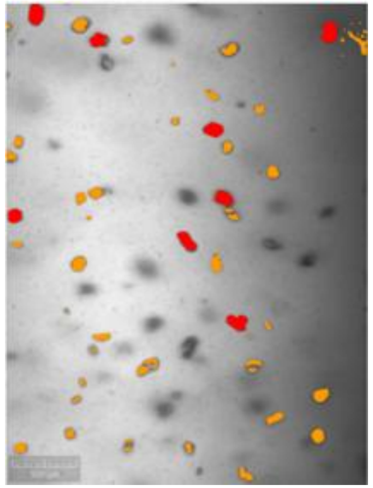
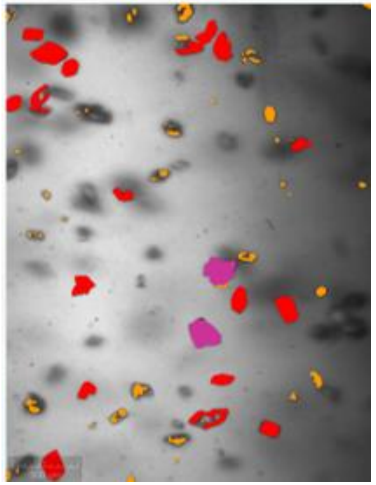
Figure 27: Averaged PSD data from the four image analysis techniques on the ~40 images at the end of seed generation at 26°C and end of isothermal growth experiment at 23C°.

Seed | Post Growth

Blob V2

Hybrid V2

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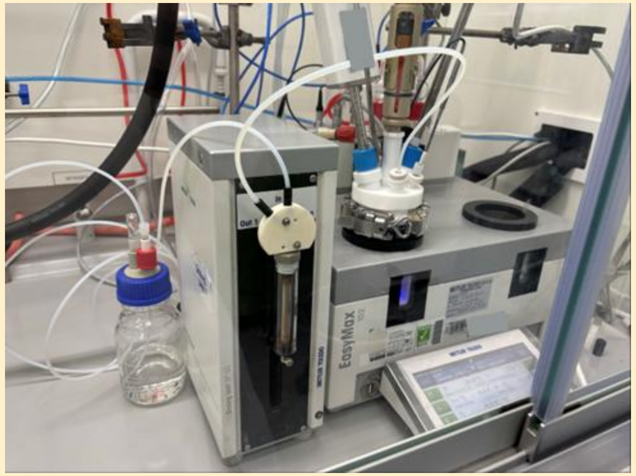
- Calibration of process analytical technology (PAT) for in-situ solution concentration measurement (IR, UV-Vis, etc.)

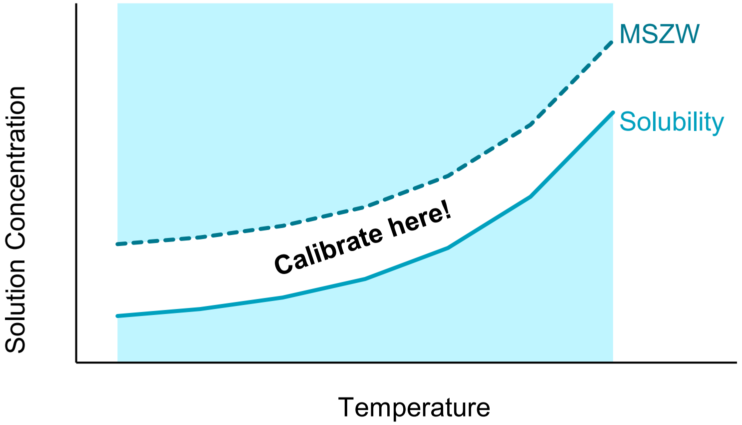
What is needed for automated collection of calibration data?

- Suitable size vessel for PAT probes
- Capable of dilution to new concentrations
- Good temperature control

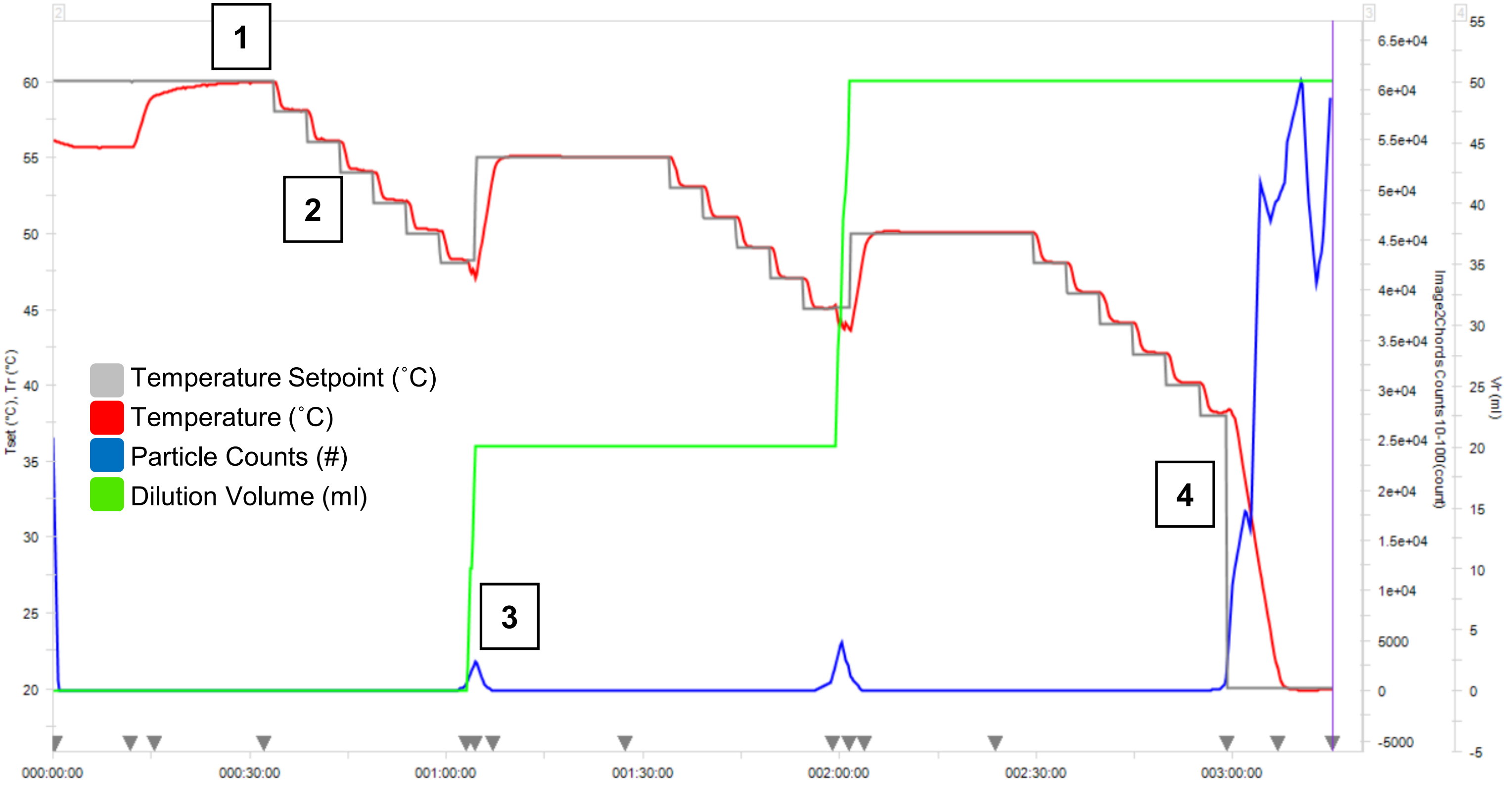
Small-scale vessels e.g. **EasyMax** (Mettler) provide best control over temperature, plus dosing capability (e.g. syringe pump)



- Crystallisations will usually be supersaturated, but below the metastable limit:

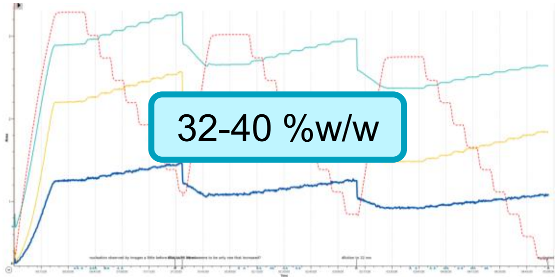


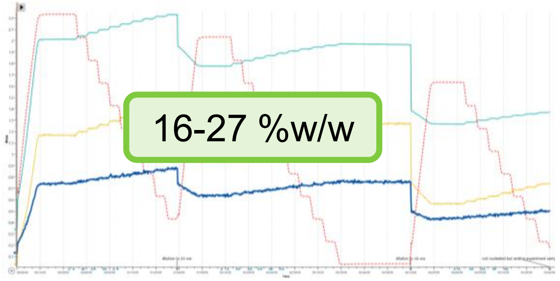
Example: Automated IR calibration experiments

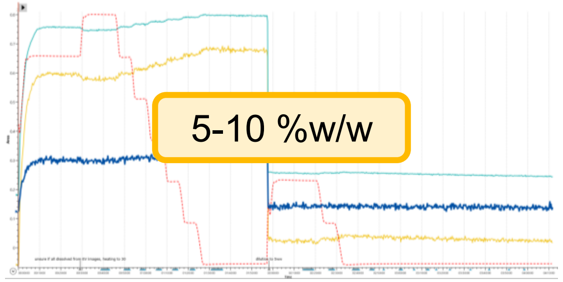


1. Prepare the initial concentration (highest %w/w)
2. Step-down cooling – better confidence of temperature IR spectra are measured at
3. Nucleation occurs (counts measured by FBRM or in-situ microscopy), system is diluted and reheated
4. Repeated until no more dilutions possible

- Multiple experiments may be required to cover the entire crystallisation process range (dilution volume limited)







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Understanding crystallisation mechanisms

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- Scoping Crystallisations
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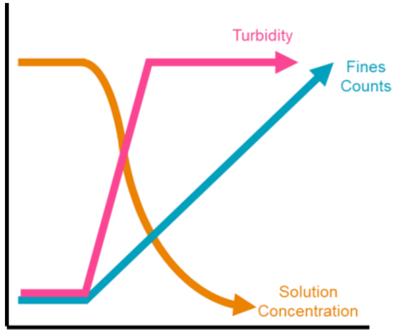
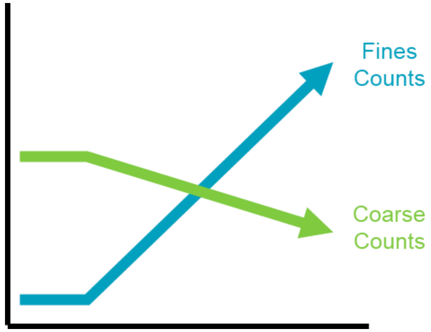
- Scoping crystallisations to observe the crystallisation behaviour
  - Identify mechanisms using trends from in-situ PAT probes:

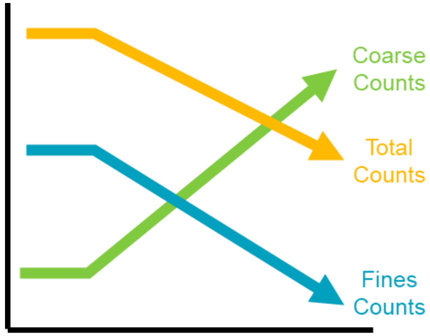
Primary Nucleation

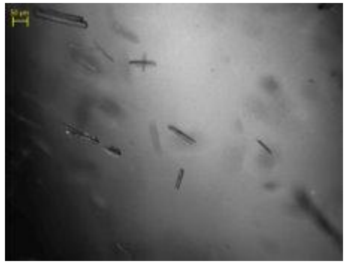


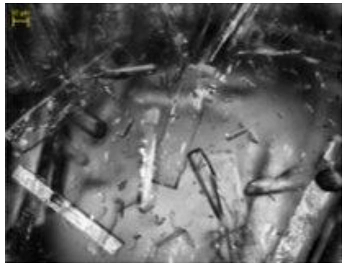
Secondary Nucleation (Attrition)

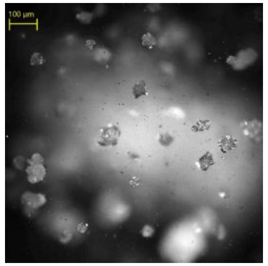


Agglomeration





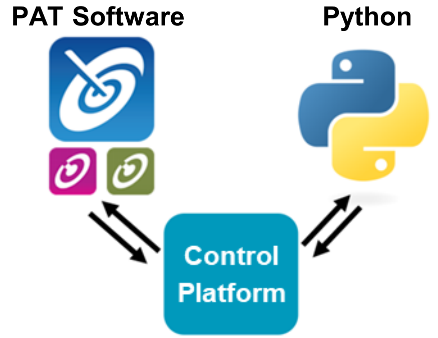




Images help validate!

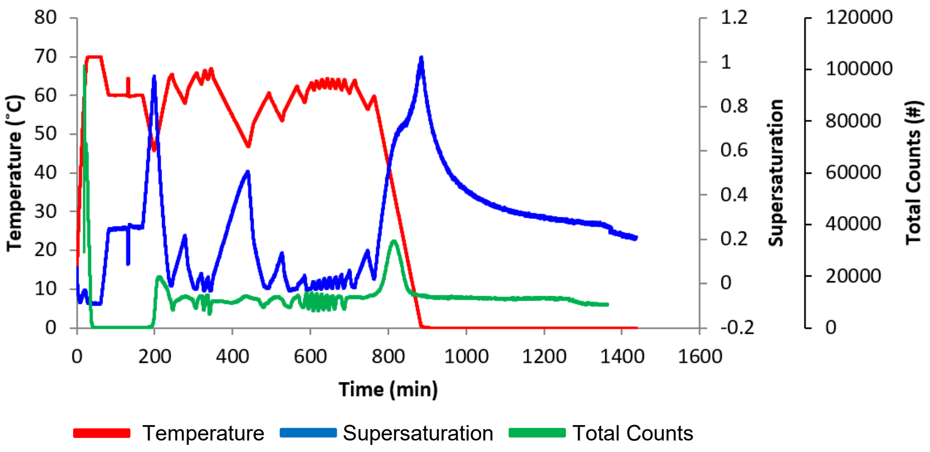
- Automated crystallisations for deeper understanding of mechanisms and quantify kinetics for modelling
  - Direct nucleation control (DNC) for nucleation
  - Iso-supersaturation control (SSC) for growth

Example: Automated crystallisation control

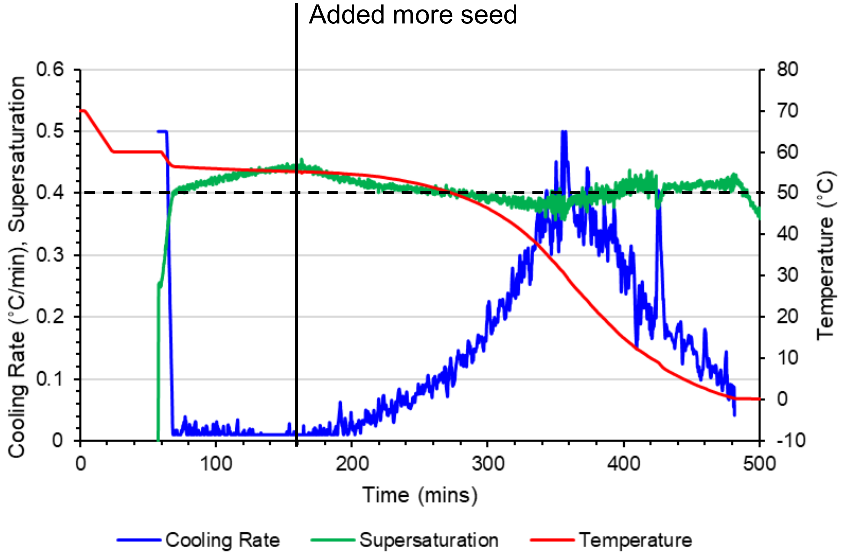


- Secondary nucleation and growth kinetics investigated deeper through **direct nucleation control (DNC)** and **supersaturation control (SSC)**, controlled with Python scripts and an automation scheduling platform:

- DNC controlled total particle counts with heating/cooling cycles, but could not reach final temperature
- **Key learning**: secondary nucleation is consistent and difficult to avoid



- SSC initially struggled to reduce supersaturation with slow cooling, required more seeds (i.e. surface area for growth)
- **Key learning**: slow growth rate, keeping supersaturation low is unreasonable



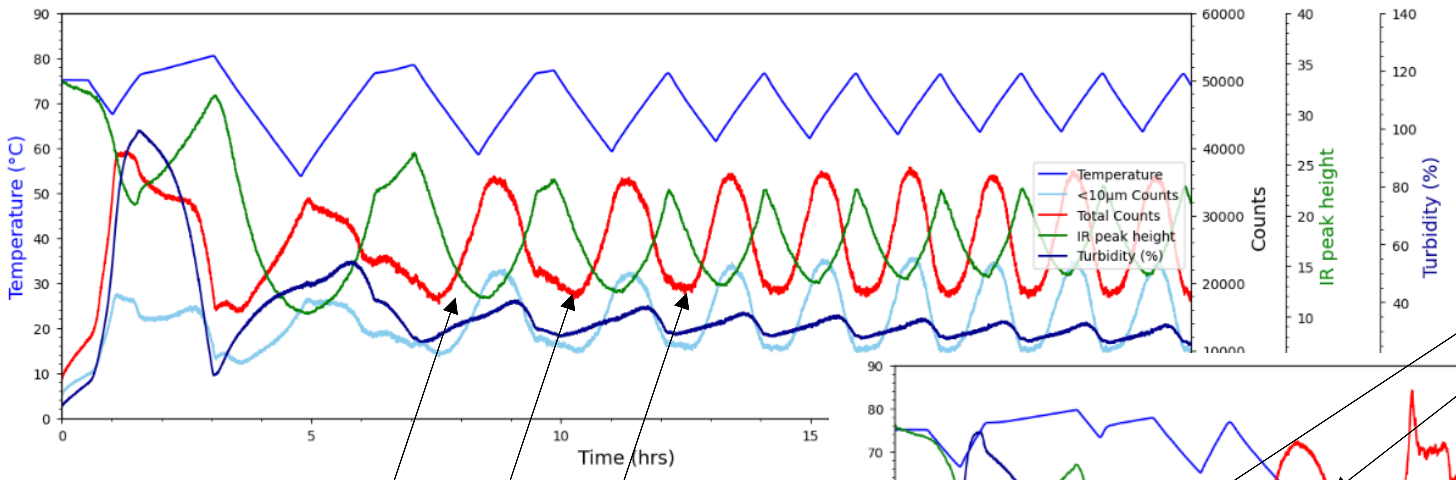
Conclusions:

- Secondary nucleation should be promoted to reduce batch time
- Adapting for continuous crystallisation seems feasible

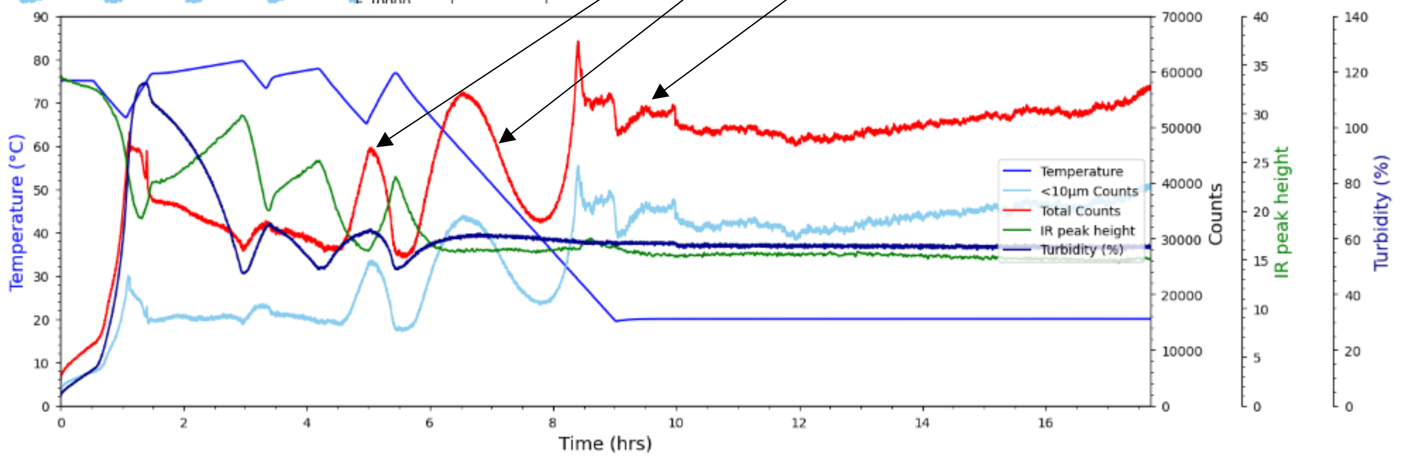
Example: PAT for automation at production scale

- DNC with FBRM control was unable to converge for impure systems, detection of false nucleation events due to fouling
- Algorithm robustly converged using turbidity control

Benefit:
Turbidity sensors could be implemented more easily than other PAT at **production scale**, enabling more **advanced control of the PSD**



FBRM Controlled
- Algorithm unconverged after >24 hours due to cyclic behaviour



Turbidity Controlled
- Crystallisation well controlled and terminates

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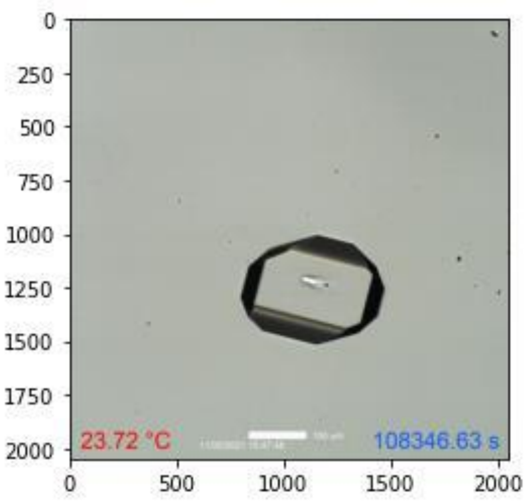
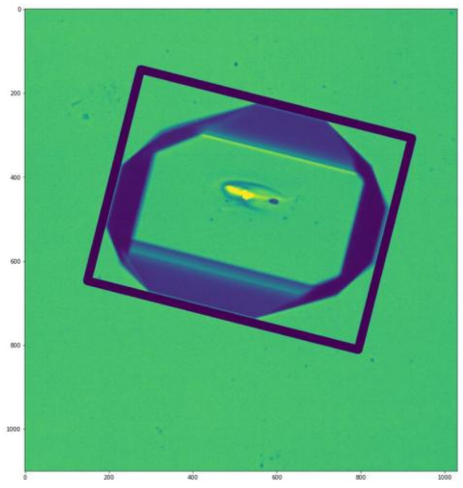
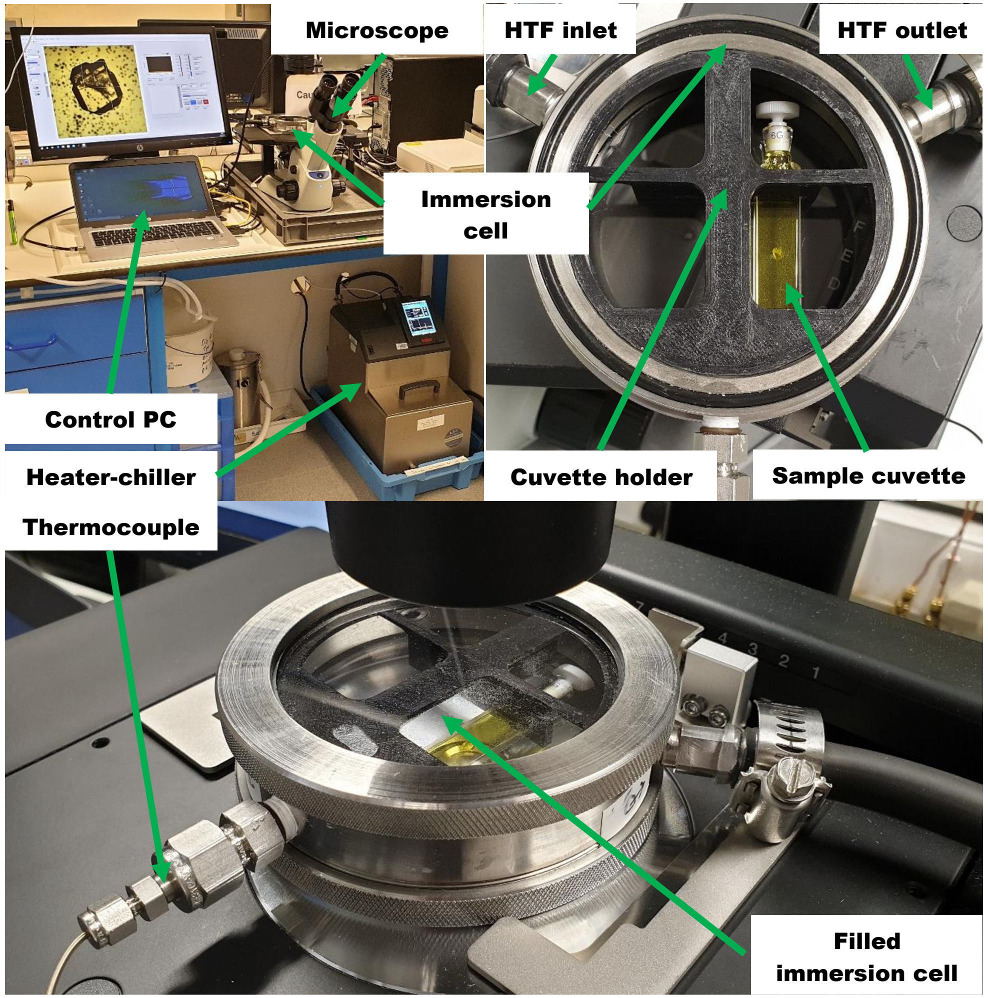
Measuring growth rate kinetics: Immersion cell

- Single crystal growth rates at different temperatures and supersaturations measured in a microscopy cell
- Automation of temperature cycles via scripting
- Change in particle length and width over time measured using image analysis
  - Growth kinetics along the length and the width of the particle measured independently







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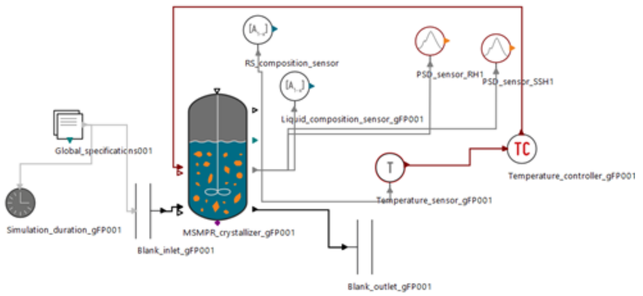
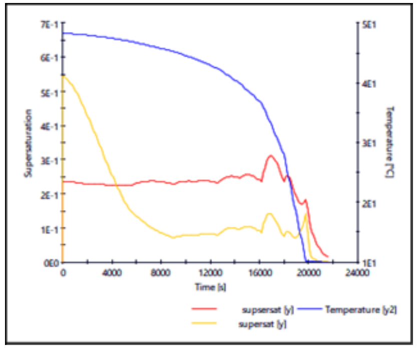
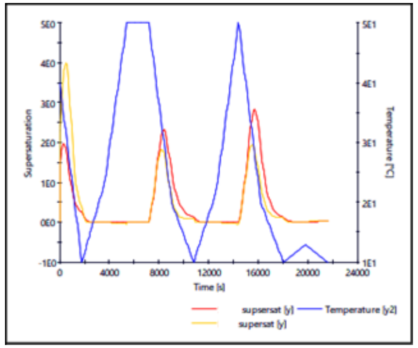
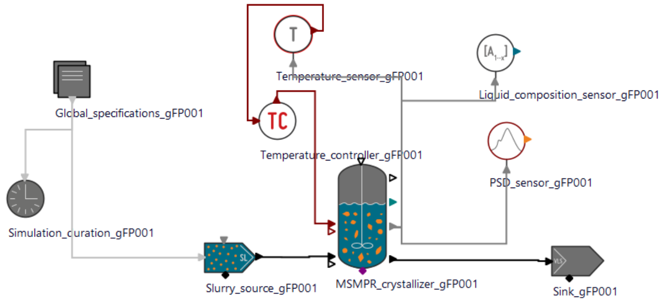
- Crystallisation data used to parameterize a population balance model (PBM), often using commercial tools e.g. gPROMS (Siemens)
  - Model batch crystallisations to optimize the process (yield, PSD)

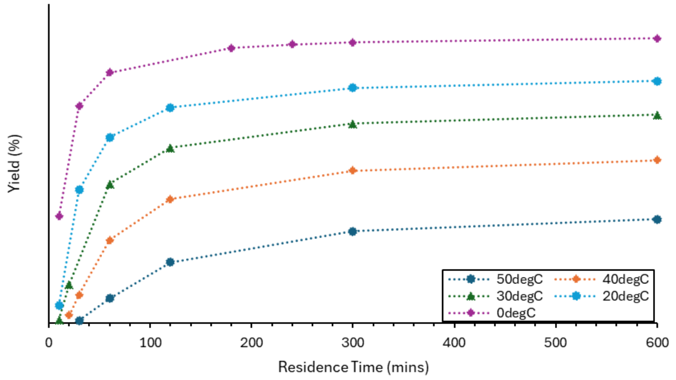






  - Adapt model for different processes, e.g. semi-batch/continuous crystallisation to assess feasibility





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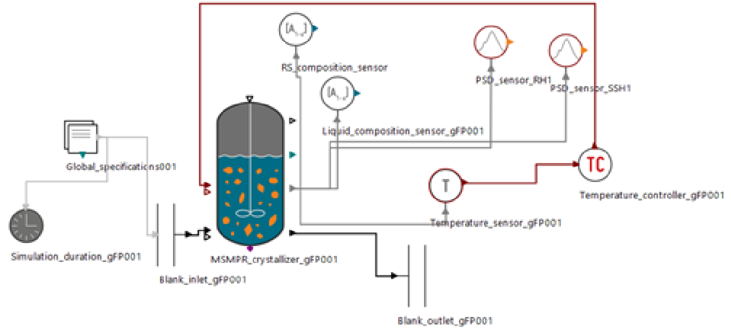
  - Unseeded
  - Seeded
  - Varied Process Conditions
- Crystallisations for Kinetics
  - DNC (Nucleation)
  - SSC (Growth)
  - Varied Process Conditions
- Process Modelling
- Crystallisations for Model Validation
  - Optimised Process

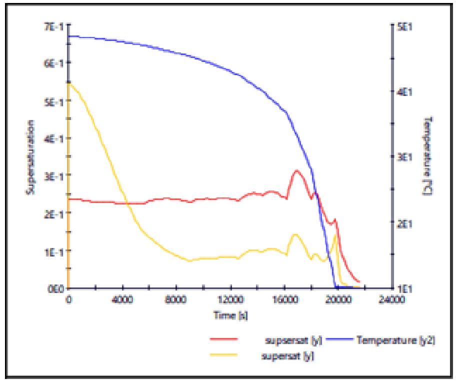
- Crystallisation data used to parameterize a population balance model (PBM), often using commercial tools e.g. gPROMS (Siemens)

1 **Batch** crystallisation model to optimize the process (yield, PSD):

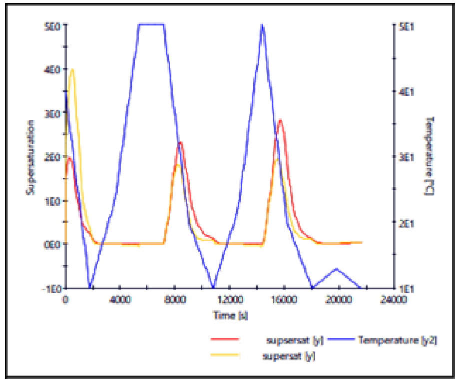
Minimize aspect ratio…



Maximise needle length…



Optimised temperature / supersaturation profiles



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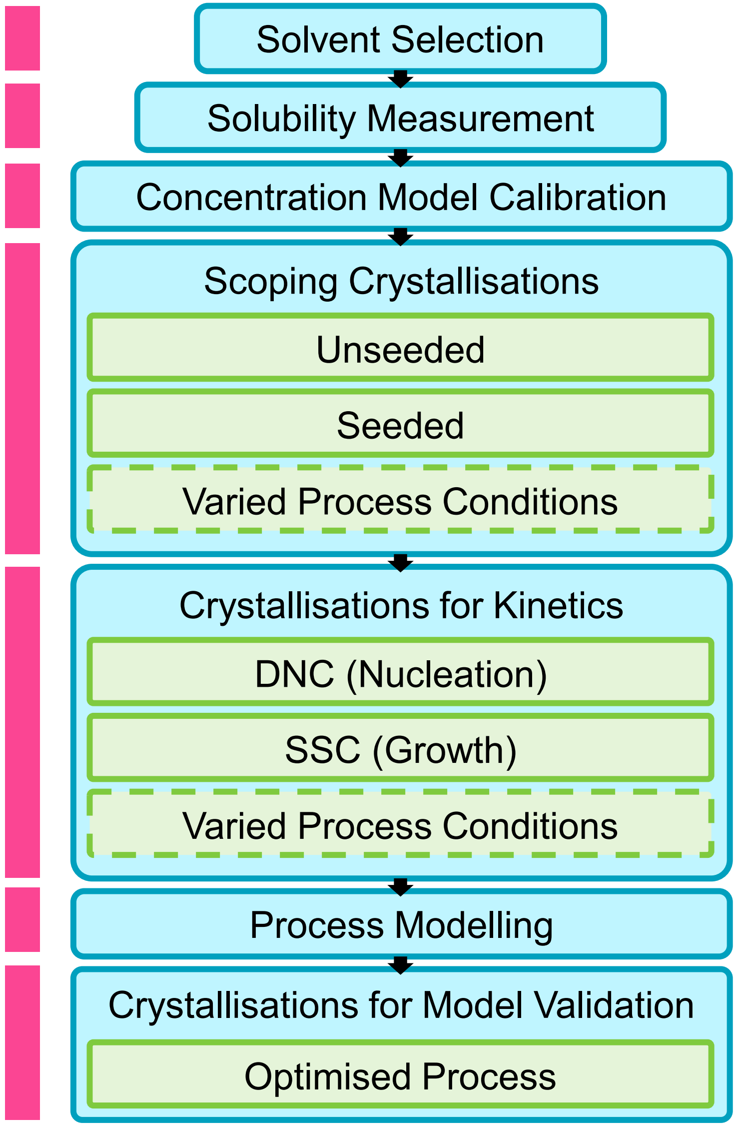
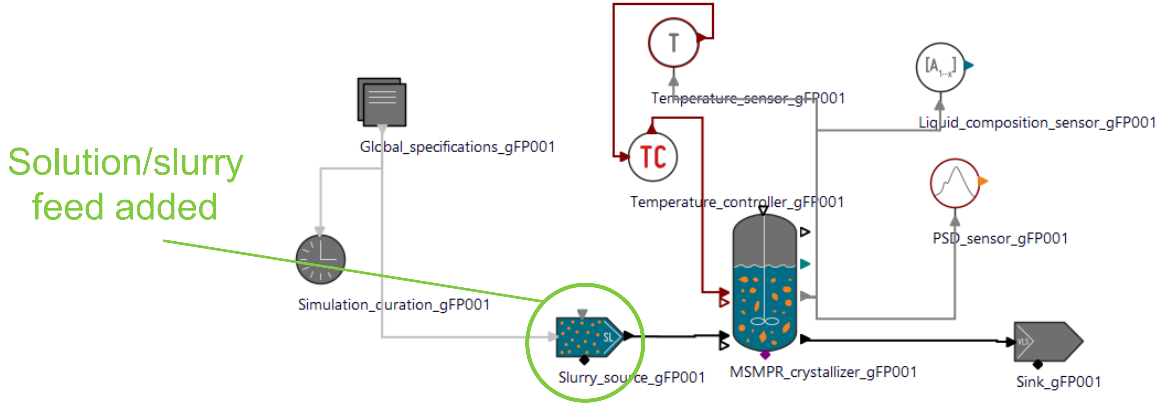
Crystallisation process modelling

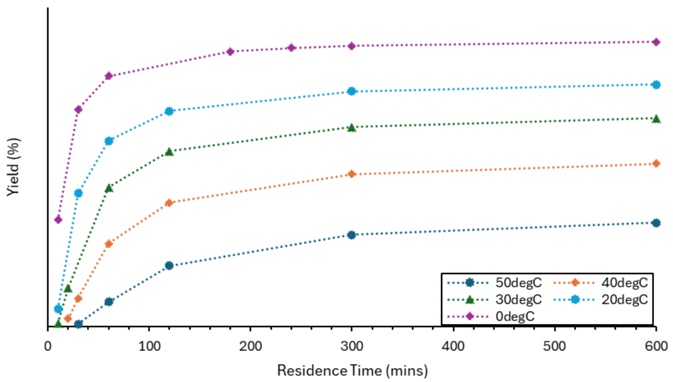


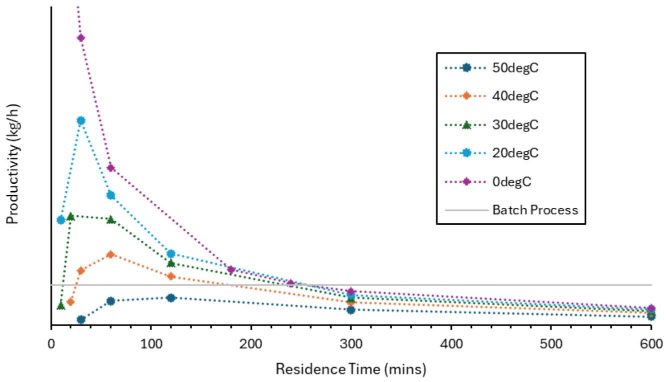
- Crystallisation data used to parameterize a population balance model (PBM), often using commercial tools e.g. gPROMS (Siemens)

2 **Semi-batch / Continuous** crystallisation model to assess feasibility



Vary temperature + residence time…





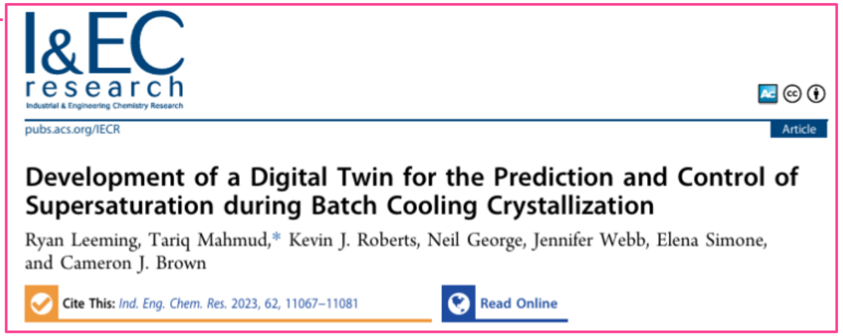
Predicted yield and productivity

Further use of automation/digital tools for crystallisation

- Exploring technology for expanding lab automation capability:

Wet milling | Seeding (solids/slurry dosing) | Sampling

- Model-based methods for improving control of crystallisation parameters:
  - Model predictive control (MPC)
  - AI / machine learning approaches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Article

Development of a Digital Twin for the Prediction and Control of Supersaturation during Batch Cooling Crystallization

Ryan Leeming, Tariq Mahmud,* Kevin J. Roberts, Neil George, Jennifer Webb, Elena Simone, and Cameron J. Brown

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- 2D/3D/Morphological PBMs to optimise crystallisation of complex shapes

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