Control of Size and Shape Distribution in Continuous Crystallisation Systems

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Overview

- **Introduction**
- **Composite-PAT array (CPA) and CryPRINS**
- Continuous real-time monitoring of crystallization processes
- CSD control via tailored dissolution in batch crystallisation (model-based and model-free)
- Model-based control of CSD in continuous crystallizers
- Control of shape distribution using growth modifiers
- Conclusions

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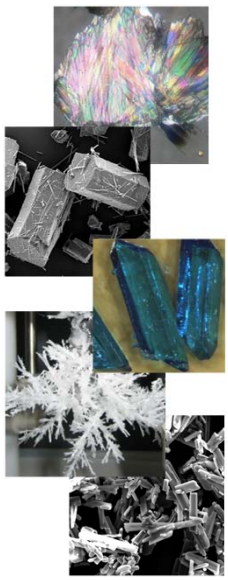
Monitoring and Control of Crystallisation Processes - Motivation

- **Many technology and economic drivers**
- **70% of all solid products & 90% of APIs involve a crystallization step**
- **Control of crystal properties important**
  - Efficient downstream operations (filtration, drying)
  - Product effectiveness (tablet stability, bio-availability)
- **Strict regulatory requirements related to variation of quality**
- **High economic penalty of producing off-spec product (£1-2 million/batch)**
- **Quality-by-design, fast scale up and product consistency**



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Continuous Crystallisation

- **Has been identified as a key paradigm shift with high potential of improving pharmaceutical production [1]**
- **Continuous processing has the advantages:**
  - Consistency in product quality
  - Reduction of cost by asset utilization
  - Shorter down time
  - Ease of scale up
  - Achieve operating conditions unattainable in batch processes
- **Continuous processing is impossible without suitable control strategies**

[1] **Chen et al., Cryst. Growth Des., 2011, 11, 887-895**

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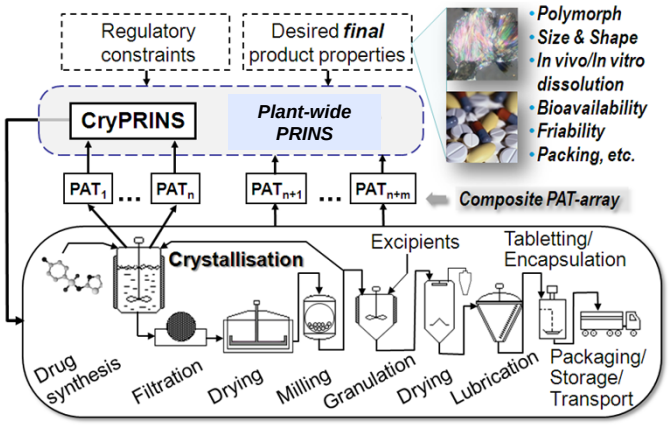
Key role of monitoring and control in process intensification and integration

New generation of integrated, intensified & intelligent crystallization systems with drastically improved flexibility, predictability, stability & controllability.

erc CrySys

Manipulated inputs:

- *Seed addition*
- *Cooling profile*
- *Antisolvent*
- *Growth/nucleation modifiers*



- *Integrated, intensified & reconfigurable plant*
- *Batch versus continuous manufacturing*

Nagy&Braatz, Handbook of Ind. Cryst., 2012; Nagy&Braatz, Annu. Rev. Chem. Biomol. Eng., 2012

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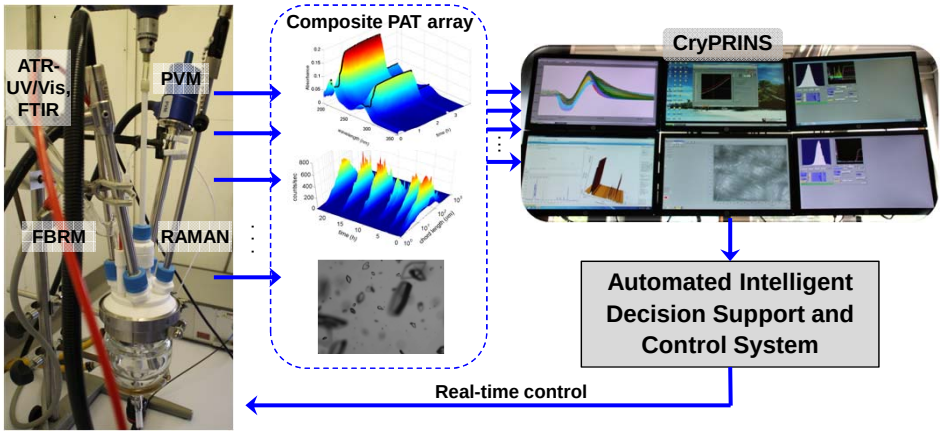
Crystallization product engineering via real-time feedback control



- Continuous real-time monitoring
- Full characterisation of crystallisation state in the phase diagram using CPA
- Complementarity & redundancy in measurements → robust control
- Automated/adaptive operation to ***design particles with tailored made properties***
- Model-based and model-free crystallization design & control approaches

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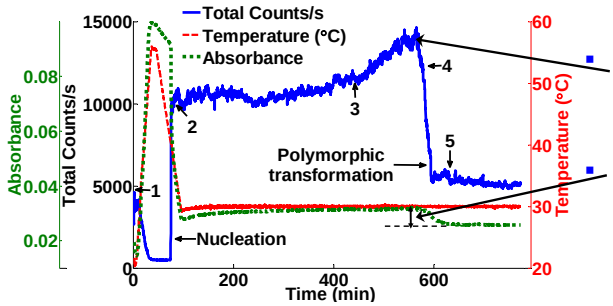
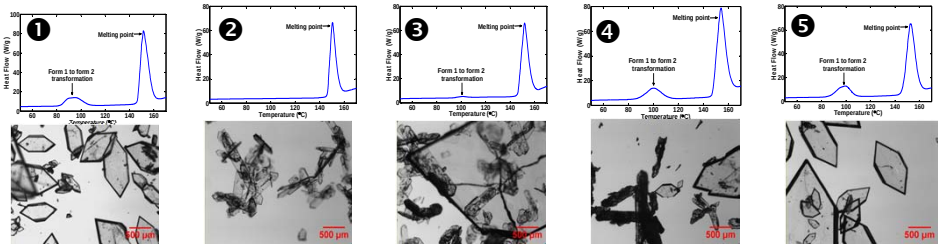
FBRM for detection of OABA polymorphism



- Surface roughness due to polymorphic transformation
- Solubility difference between polymorphs



Form 1 (raw) | Form 2 (nucleation) | Form 2 + 1 (starts) | Form 2 + 1 | Form 1

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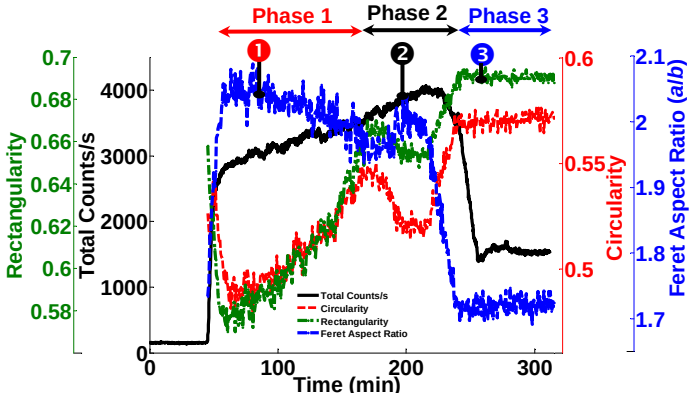
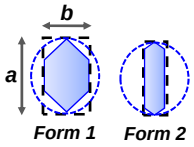
Image analysis (IA) for monitoring polymorphic transformation of OABA





- Decrease in aspect ratio
- Increase in circularity
- Increase in rectangularity → agglomeration

Form 2 nucleates | *Mixture of forms 2+1* | *Form 1*

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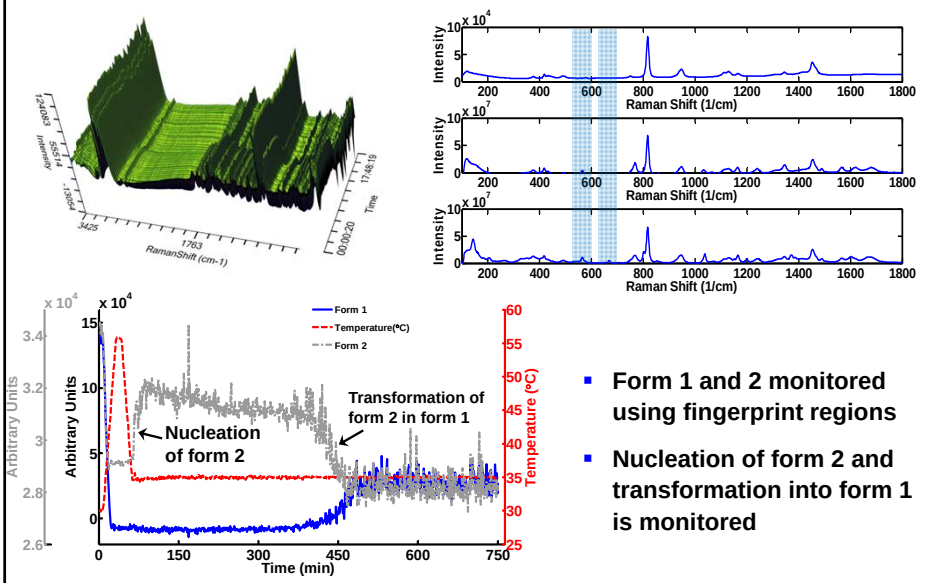
Monitoring polymorphic transformation OABA using process Raman Spectroscopy



- Form 1 and 2 monitored using fingerprint regions
- Nucleation of form 2 and transformation into form 1 is monitored

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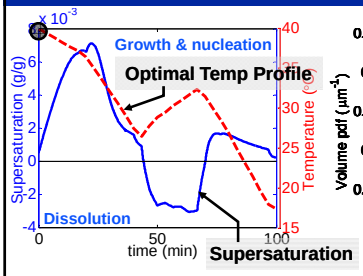
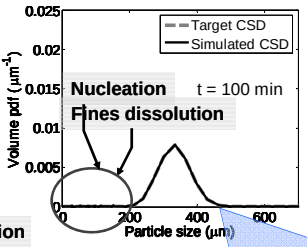
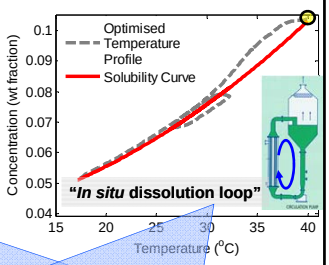
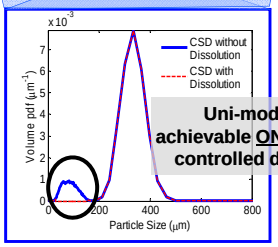
In situ fine removal via controlled dissolution







- Optimal temperature includes heating stage
- Use of controlled dissolution for programmed fine removal
- Fine removal via control rather than equipment design
- Suitable control strategy can eliminate design limitations
- Model-free approach: DNC



Uni-modal CSD achievable ONLY by using controlled dissolution

Nagy et al., CGD 2011; Nagy, CACE 2009

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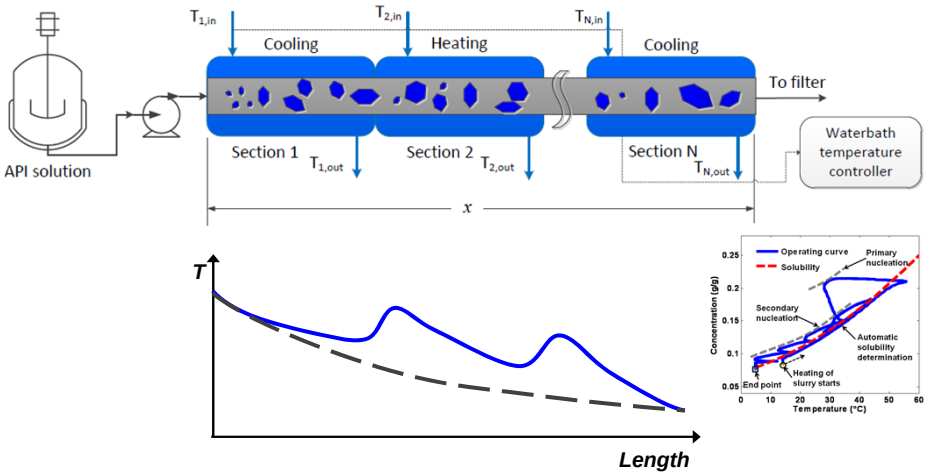
Continuous plug flow crystallizer with controlled dissolution segments



- Spatially distributed operating profile (heating/cooling or antisolvent/solvent)
- Alternating nucleation-growth-dissolution segments

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PBM of the Continuous Plug Flow Crystallizer

Steady state model equations

- Population balance equation (PBE) is used to model the crystallization process
- Steady state PBE for growth and nucleation

$$u_x \frac{\partial n}{\partial x} + \frac{\partial Gn}{\partial L} = B\delta(L - L_0);\ \ S \geq 0$$

- PBE for dissolution

$$u_x \frac{\partial n}{\partial x} - \frac{\partial Dn}{\partial L} = 0;\ \ S < 0$$

- Kinetics

$$G(t) = k_g S^g (1 + \gamma L)^p;$$

$$D(t) = \frac{k_d}{L^q}(-S)^d;$$

$$B = k_b S^b;\ S = (C - C_{sat})$$

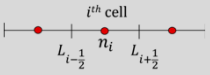
- Mass balance

$$u_x \frac{dC}{dx} = -3\rho_s k_v G \int L^2 n dL$$

High resolution technique for solving PBEs

- Efficient, accurate and captures discontinuity
- Define the cell average in each cell

$$n_i = \frac{1}{\Delta L}\int_{L_{i-\frac{1}{2}}}^{L_{i+\frac{1}{2}}} n dL\ ;$$



- The PBE becomes a set of ODEs

$$\frac{dn_i}{dx} = -\frac{1}{\Delta L}\left(F_{i+\frac{1}{2}} - F_{i-\frac{1}{2}}\right);$$

$$F_{i+1/2} = G_{i+1/2} n_{i+1/2}$$

- Flux reconstruction in cell boundary

$$n_{i+\frac{1}{2}} = n_i + \frac{1}{2}\phi\left(r_{i+\frac{1}{2}}\right)(n_{i+1} - n_i)$$

- van Leer flux limiter to remove oscillation near discontinuity

$$\phi\left(r_{i+\frac{1}{2}}\right) = \frac{\left|r_{i+\frac{1}{2}}\right| + r_{i+\frac{1}{2}}}{1 + \left|r_{i+\frac{1}{2}}\right|};$$

$$r_{i+1/2} = \frac{n_i - n_{i-1}}{n_{i+1} - n_i}$$

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Optimization Problem: CSD shaping in continuous crystallisation

- Temperature profile along the crystallizer with dissolution for fine removal
- Objective function to be minimized:

$$\min_{T(k)} \left\{ J = \sum_{i=1}^{N} \lambda_i (f_{v,i}^{t} - f_{v,i})^2 \right\};$$

Target CSD — Predicted CSD

- Gradient based methods are often caught in local minima due to high nonlinearity of the problem
- A stochastic technique genetic algorithm (GA) is used to solve the optimization problem
- Allows also to optimize number of segments needed → MINLP
- Combined design and control of crystallisation processes

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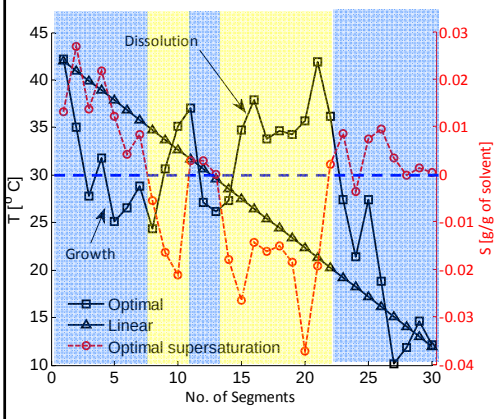
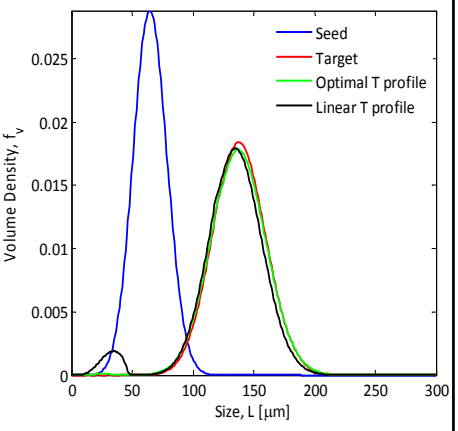
Spatially distributed control of product CSD with fines removal





- Linear temperature profile produces large amount of fines
- The optimal profile alternates between growth and dissolution eliminate fines
- Three growth and 2/3 dissolution clusters
- Optimal profile also needed within clusters

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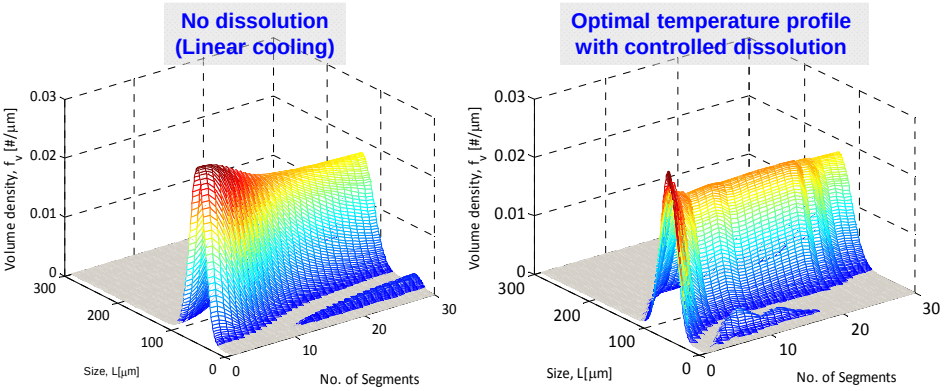
Spatial evolution of CSD



- Linear temperature profile produces lots of fines
- The optimal profile alternates between growth and dissolution to eliminate fines

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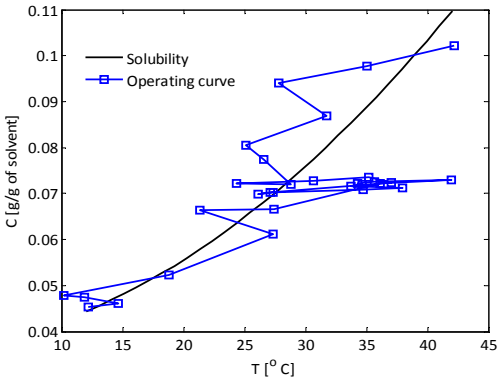
Spatial operating profile in the phase diagram



- Spatial optimal profile can be represented in the phased diagram
- Optimal operating profile both in the supersaturated and under saturated region
- Dissolution rate is also manipulated
- For poorly soluble compounds large under-saturation needed

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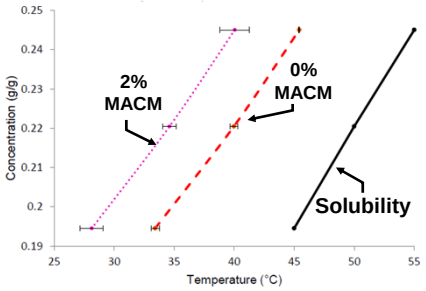
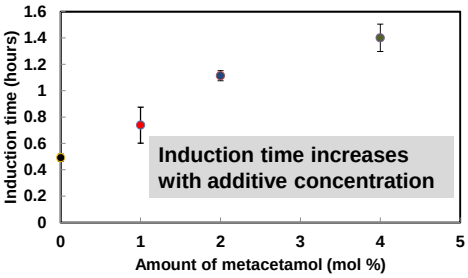
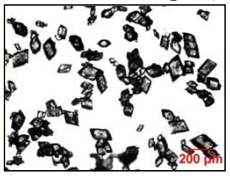
Effect of additives on nucleation and crystal shape of Paracetamol

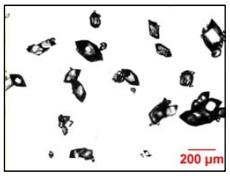




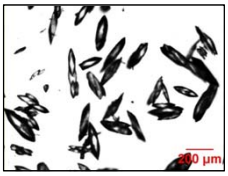
0% Metacetamol (pure)



2% Metacetamol



4% Metacetamol



- **Significant increase in aspect ratio**
- **Influence on both CSD and shape**

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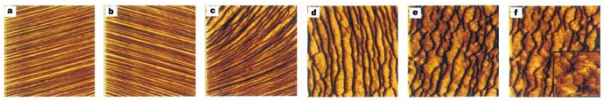
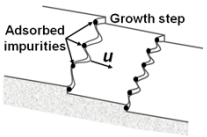
Multi-dimensional PBM with the effect of impurities/additives (growth modifiers)

- **Step velocity decreases with time leading to degradation of crystal surface**



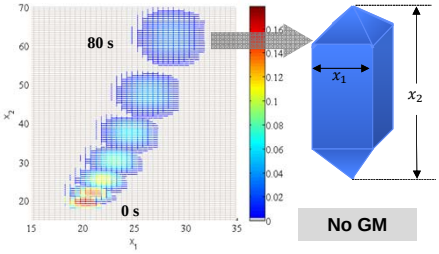
KDP grown in the presence of Fe^{3+} (Terry et al. Nature, 1999)



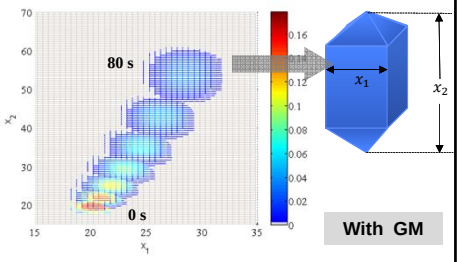
- **"Poisoning effect" of impurities → growth reduction (unsteady-state adsorption)**

$$G(t) = G_0(t)(1-\alpha\frac{KC_i}{1+KC_i}(1-\exp(\frac{t}{\tau})))$$

Use additives to achieve & control product properties (shape, polymorph, etc.)



No GM



With GM

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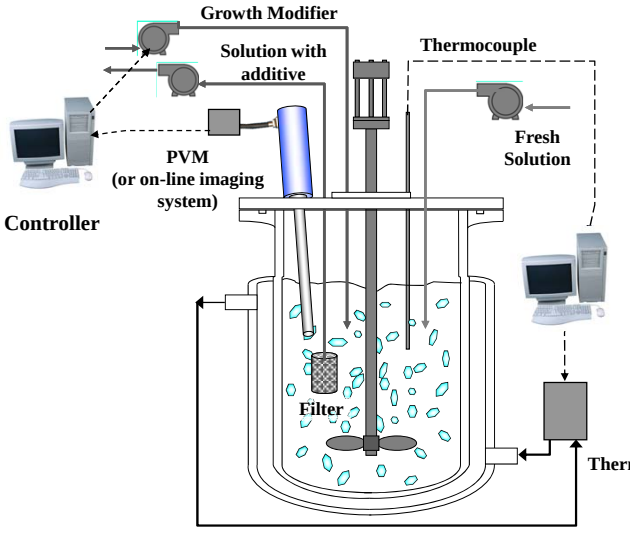
Hybrid Continuous-batch crystallisation setup for shape distribution control using additives (growth modifiers)



- **Control Mean Aspect Ratio (MAR)**
- **2D CSD measured in-situ or on-line**
- **Manipulate additive concentration**
- **Flow through system with constant volume**
- **Continuous operation for liquid phase (can dynamically manipulate GM concentration)**
- **Batch operation for solid**

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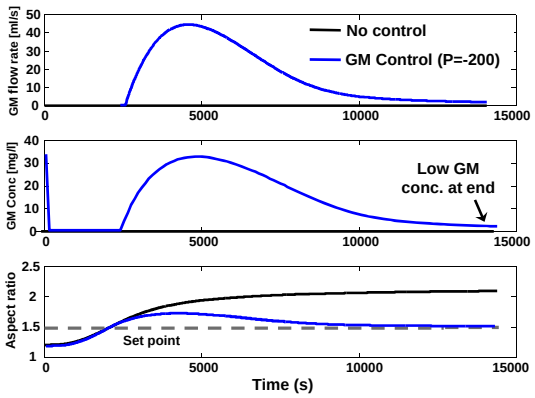
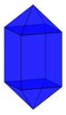
Dynamic GM feedback control of mean aspect ratio





Mean aspect ratio=2.1
(No control)

Mean aspect ratio=1.5
(With GM control)

- Hybrid operation allows dynamic manipulation of GM concentration
- Mean aspect ration significantly reduced (~30%)
- GM concentration high during middle of batch but very low at the end (no contamination of product)

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Summary

- Many economic drivers for better control of CSD and shape
- Concept of composite sensor array (CSA) and CryPRINS allow continuous and real-time full characterisation of the crystallisation
- Model based optimal control and design can significantly improve the pharmaceutical production process
- Novel control approach for continuous crystallisation with spatially distributed controlled dissolution for fine removal
- Shape distribution control using GM and hybrid continuous-batch crystallisation operation

Thank You

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