EPSRC

Centre for Innovative Manufacturing
in Continuous Manufacturing and Crystallisation

High resolution video imaging as a crystallization tool

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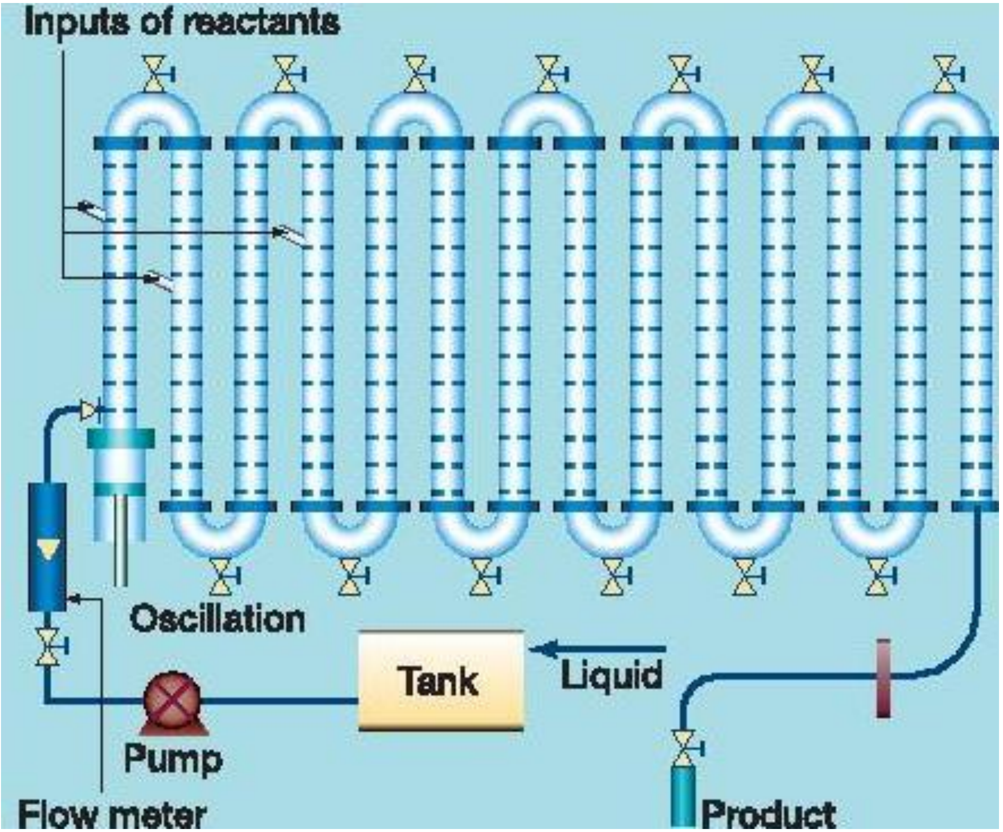
1) Objective

- Develop a process analytical tool for continuous oscillatory baffled crystallizers which complements the existing tools

- Criteria:
  - Locatable at any point in the COBC
  - Does not hinder or disrupt flow of fluid within the COBC
  - Able to monitor crystallization process
  - Determine key crystallization parameters
  - Low cost

2.1) Background – Continuous oscillatory baffled crystallizer (COBC)

- Increased specific area per volume for heat transfer
- Plug flow conditions
- Linear scale up
- Decrease in API crystallization time
- Uniform mixing
- Consistent fluid mechanic conditions
- Crystals of consistent quality



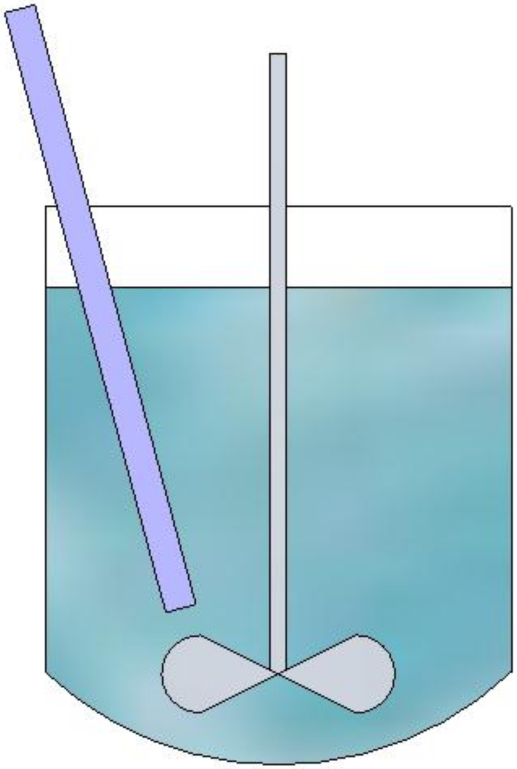
2.2) Background – Current tools

Tool	Parameter
Turbidity	Solid concentration, nucleation point
IR	Solution concentration, nucleation point
FBRM	Characteristic crystal dimension, number of crystals, nucleation point, crystal growth kinetics
PVM	Crystal size, nucleation point, crystal growth kinetics
UV	Solution concentration, nucleation point

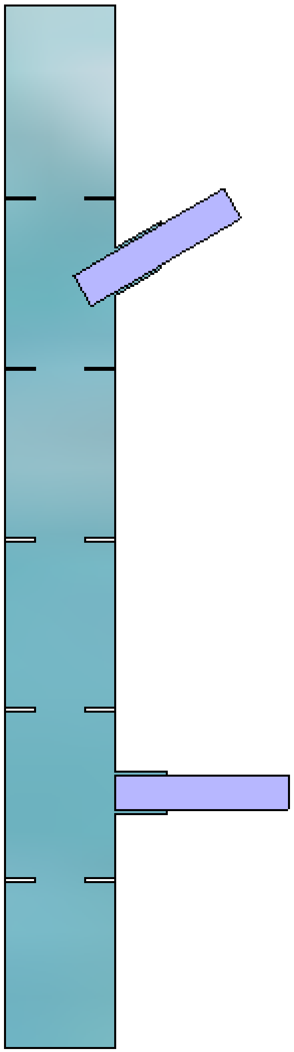
- All require an internal probe
- Size can range from 6 mm+ in diameter
- Typical COBC internal diameter 10 – 15 mm

2.2) Background – Current tools

- Probes added to stirred tank crystallizers:
  - Have little effect on hydrodynamics on large scale tanks
  - Can actually improve mixing on lab scale by acting as baffle
  - In poorly mixed large scale tanks it might not truly measure the bulk concentration/temperature etc.
  - Probes are seldom used in industrial scale



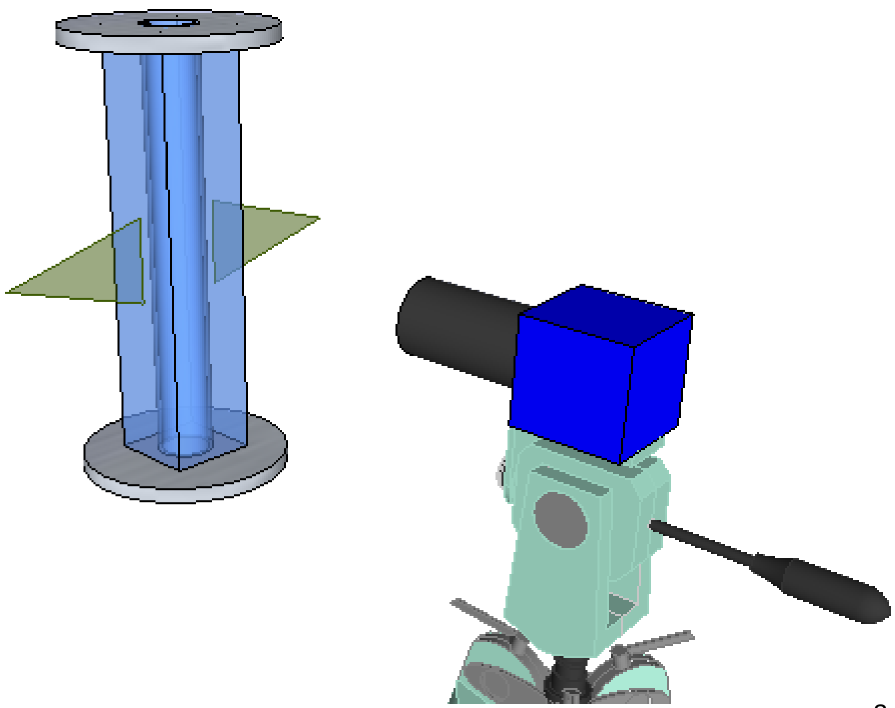
2.2) Background – Current tools



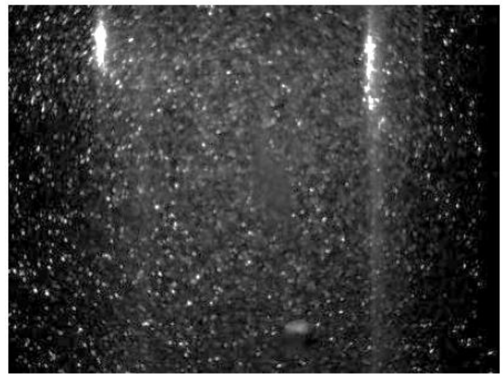
- Adding probes to a COBC:
  - protruding into the flow could alter local fluid dynamics
  - even fitting flush with the wall could potentially provide areas for cross contamination
- Non-invasive would be ideal

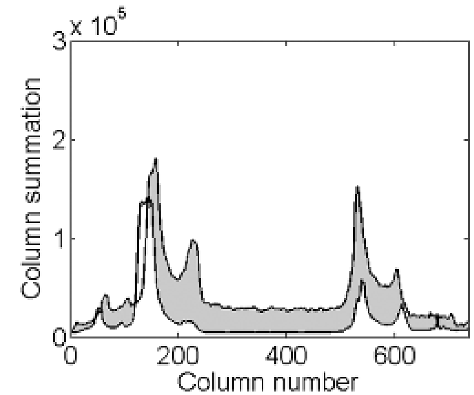
3.1) Setup

- Video imaging already shown to be a possible tool for monitoring crystallization (Simon *et al.,* 2009, Larsen & Rawlings, 2009)
- Camera can record crystals in-situ non-invasively
- Small crystals require powerful illumination to be captured within a reasonable exposure time to prevent distortion
  – Laser light sheets
- All off the shelf components



3.2) What can it measure?



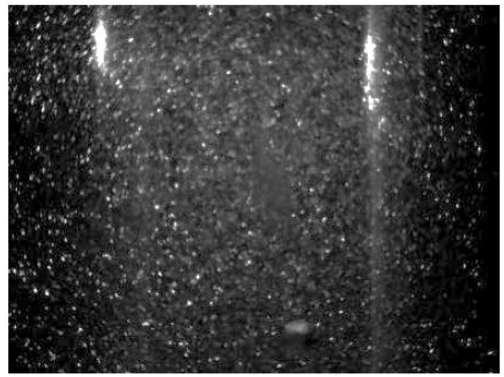


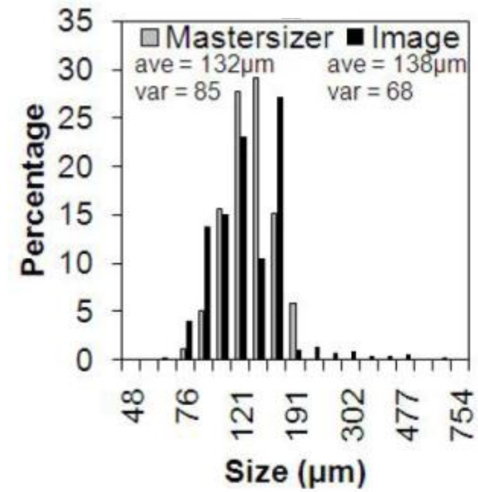
- Image with no crystals predominately black
- Crystals present scatter light towards the camera
- Image shows an increase in white pixels
- Summation of pixel values (0 for black, 255 for white) along image width gives a distribution of white pixels
- Integral of this distribution proportional to concentration of crystals
  - Intensity Distribution Integral (IDI)
    - Analogous to absorbance for turbidity measurements

3.2) What can it measure?

- Camera has a minimum detectable crystal size of 11 µm
  - Dependant on:
    - COBC / camera distance
    - Lens
    - Focus area
- Overall crystallization rate (combination of nucleation and growth) can be determined from this size upwards
- Indication of onset of nucleation or dissolution
  - Solubility
  - Metastable zone width (MSZW)
    - Nucleation kinetics

3.2) What can it measure?

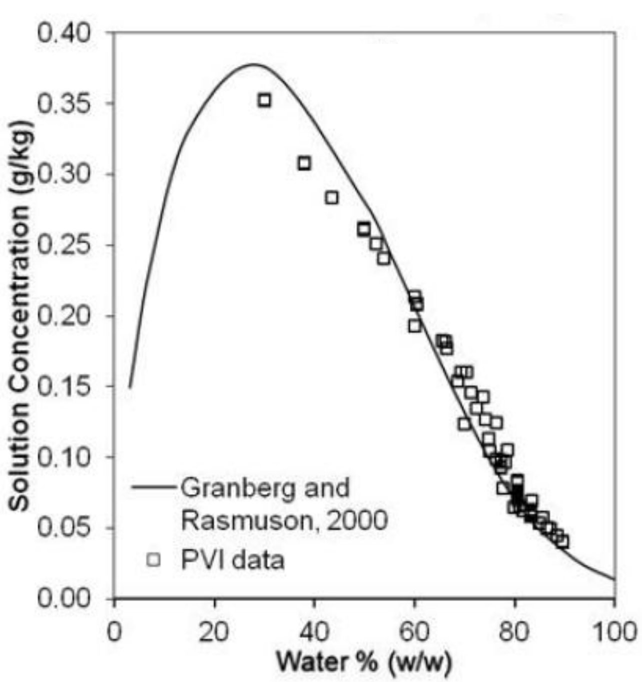


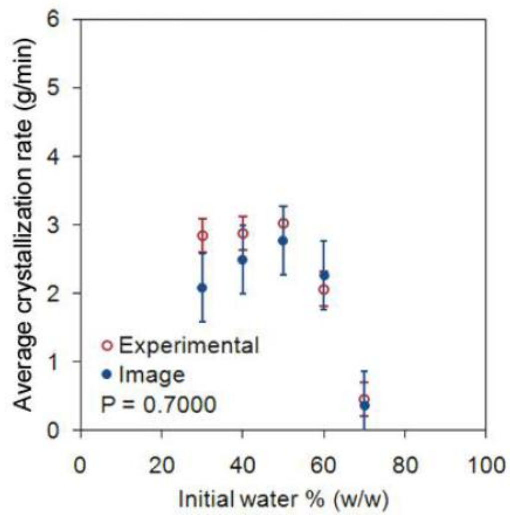


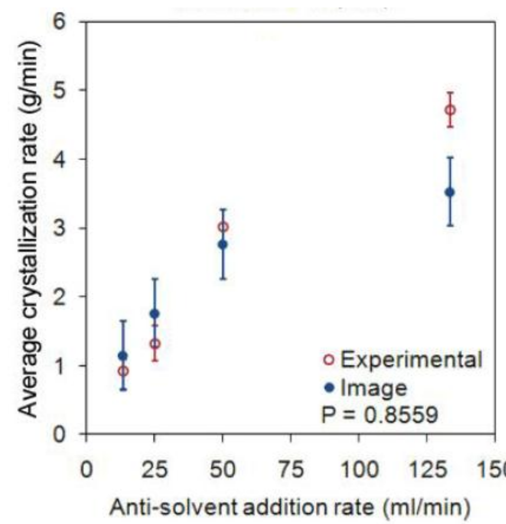
- Each region of white pixels can have the area and perimeter calculated
- Pixel Region Measurement (PRM)
  - Equivalent diameter = (4 x area) / (perimeter)
- Crystal size distribution > 11 µm
  - Mean crystal size
    - Growth kinetics

3.3) How accurate is it? - IDI

- Valid technique by comparing:
  - Calculated solubility to existing data:
  - Experimental sampling:

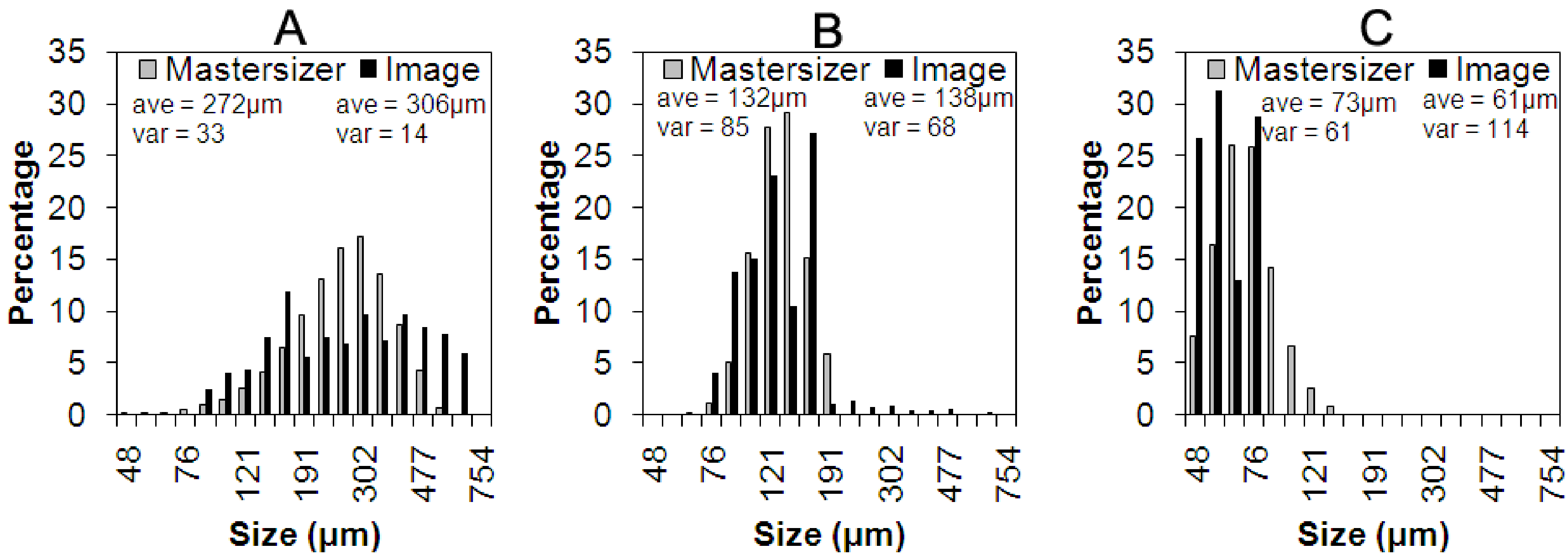






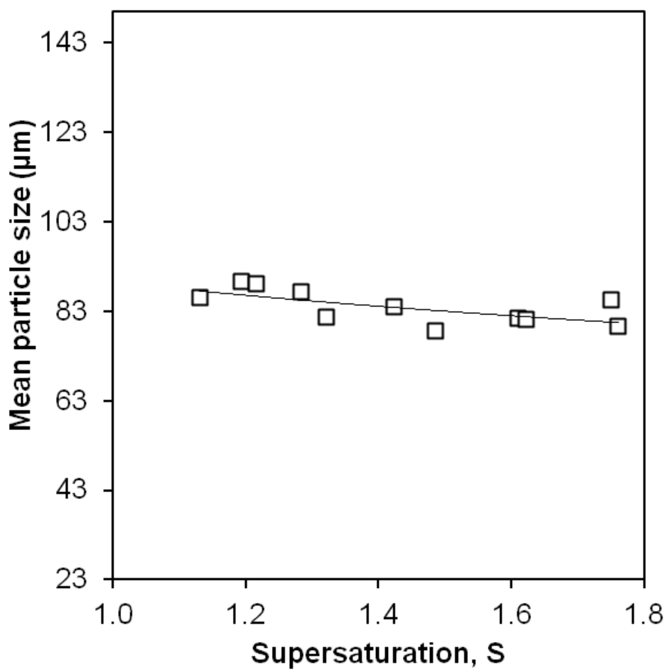
3.3) How accurate is it? - PRM

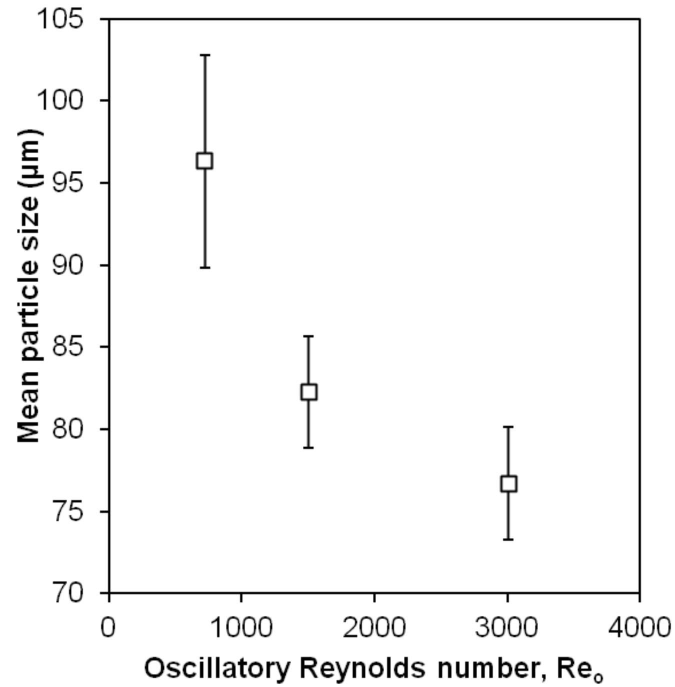
- Valid technique by comparing:
  - To know particle size distribution:



3.4) Results - PRM

- Mean crystal size (paracetamol/water cooling crystallization):

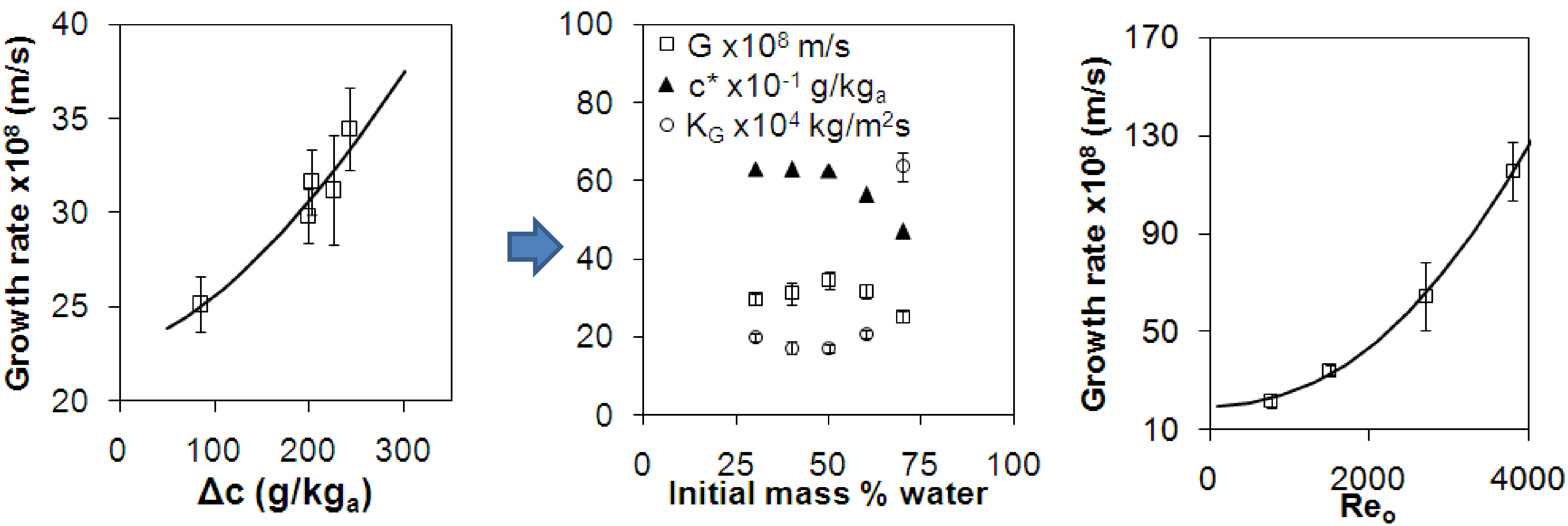




- Low dependence on supersaturation
- High dependence on mixing intensity

3.4) Results - PRM

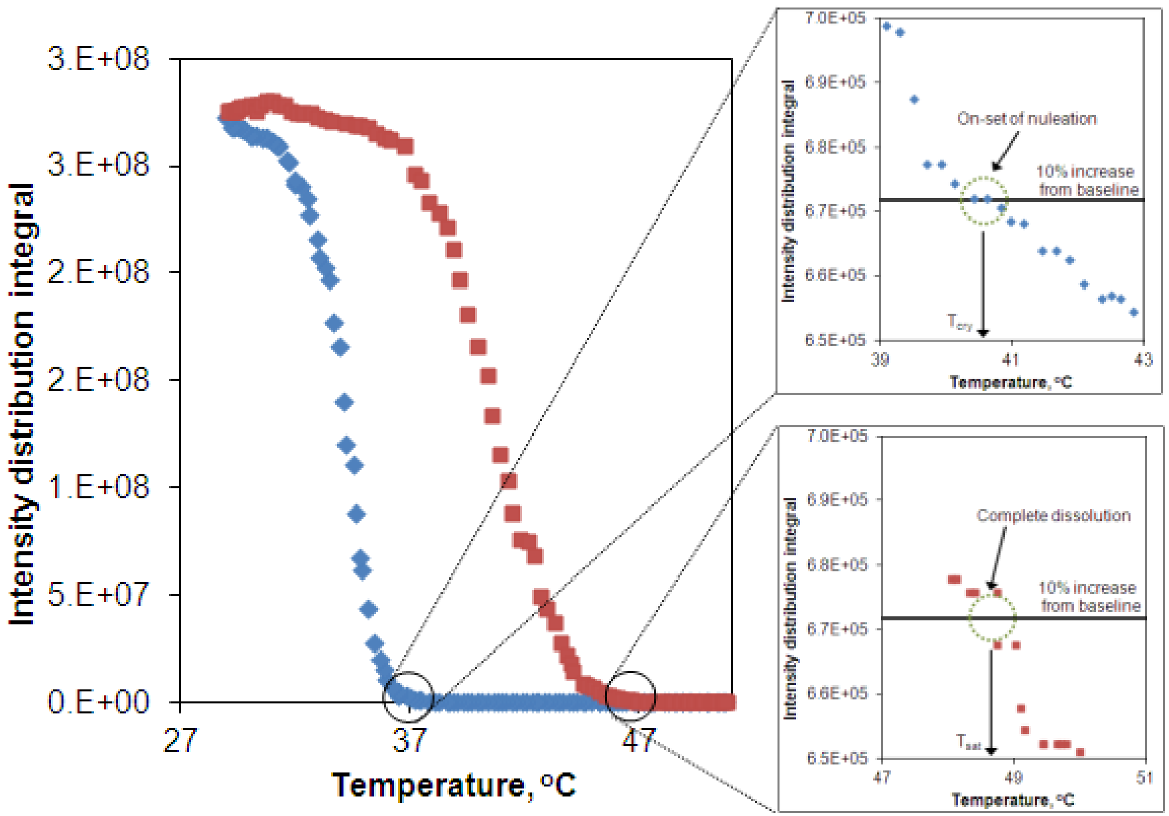
- Growth rate (paracetamol/water/acetone anti-solvent crystallization)



- Highly dependant on both Δc and mixing intensity

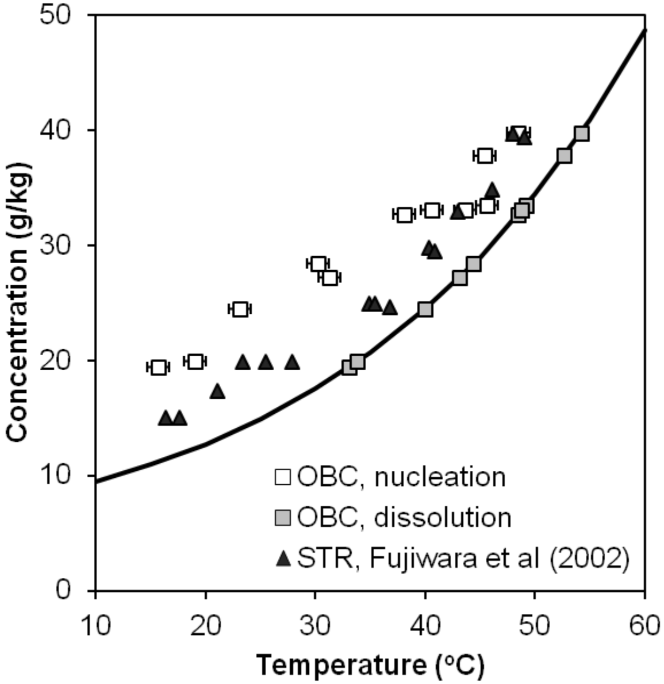
3.4) Results - IDI

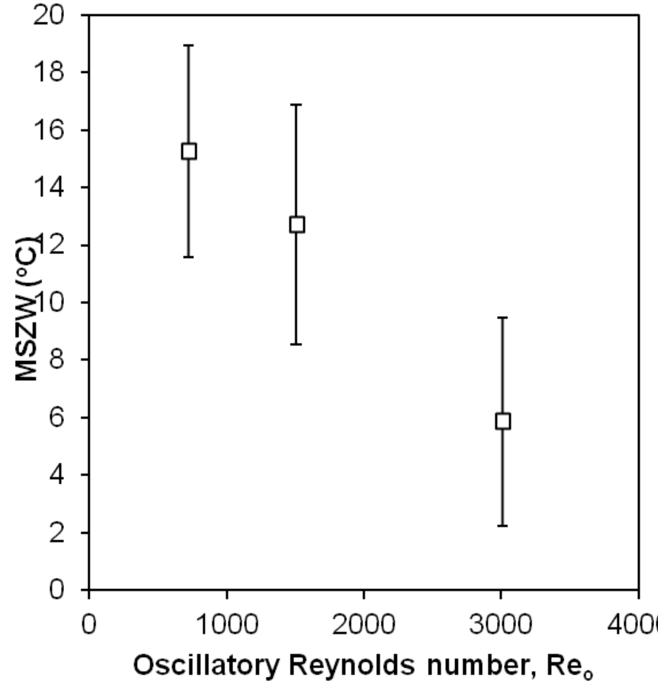
- Metastable zone width (paracetamol/water cooling crystallization):



3.4) Results - IDI

- Metastable zone width (paracetamol/water cooling crystallization):





- MSZW looks wider in OBC vs. STR but is highly dependant on other variables (impurities, degree of filtration etc.)
- MSZW decreasing significantly with mixing intensity

3.4) Results – How accurate is it? Part 2

- Proposed nucleation kinetics can be determined from MSZW measurements (Kubota, 2008):

$$\log \Delta\theta_{max} = \frac{1}{n+1}\log\left[\left(\frac{N_m}{V}\frac{1}{k_n}\right)(n+1)\right] + \frac{1}{n+1}\log\beta$$

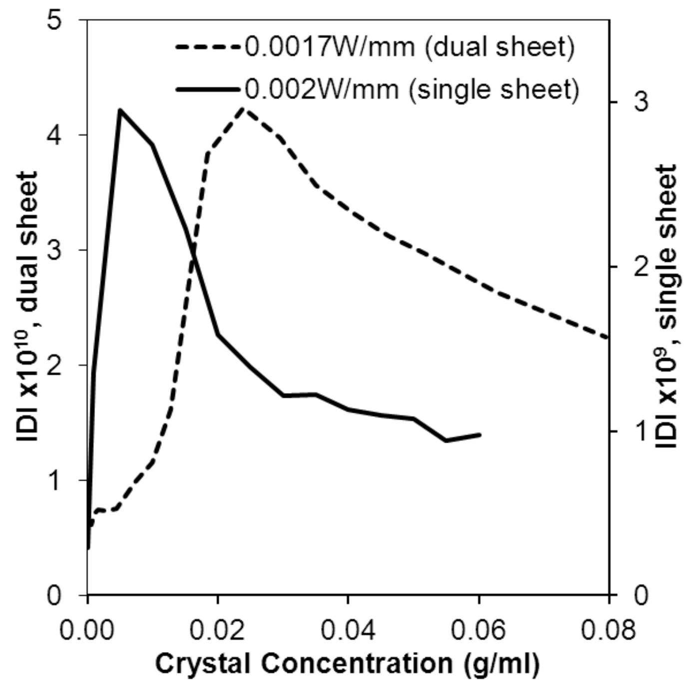
- Detectable number density, N_m/V depends on technique used to detect onset of nucleation
  - Smaller value the more sensitive the measurement

Technique	N_m	V	N_m/V
Turbidity	$1x10^{7}$	$1x10^{-4}$	$1x10^{11}$
FBRM	5	$2.32x10^{-9}$	$2.16x10^{9}$
Imaging	540	$2.76x10^{-7}$	$1.95x10^{9}$

- As sensitive as an FBRM but non-invasive

3.5) Limitations

- Minimum detectable crystal size
  - Nuclei must grow to certain size before detection (true for any optical technique)
  - Unable to decouple nucleation from growth
- Maximum solid concentration
  - Eventually images with show completely white
  - Unable to determine any crystal size or concentration
  - Must operate below this limit



3.6) Conclusions

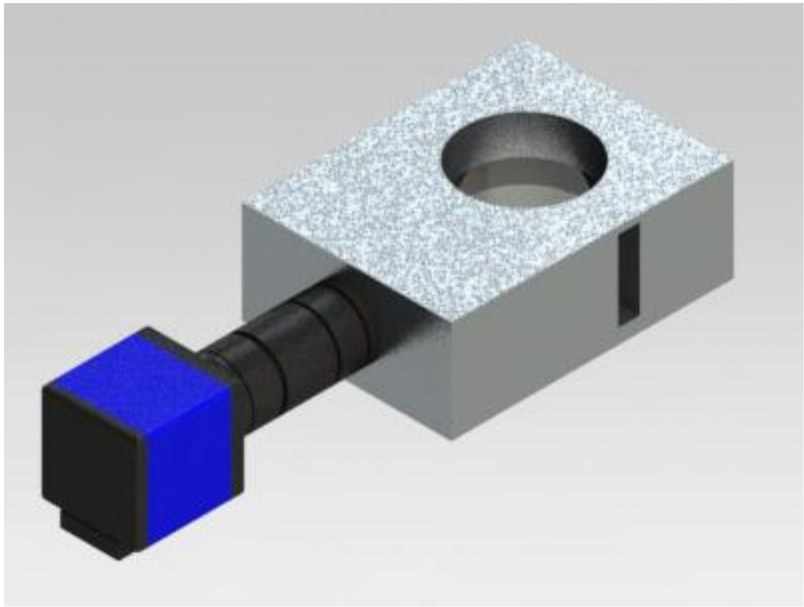
- Can determine:
  - Onset of nucleation
    - As sensitively as current techniques
  - Crystal size distribution
    - Key for downstream processing
  - Growth kinetics
    - Affect crystal size distribution

3.6) Conclusions

- Compare to criteria:
  - Locatable at any point in the COBC
    - Laser/camera alignment tricky
  - Does not hinder or disrupt fluid of fluid within the COBC ✓
  - Able to monitor crystallization process ✓
  - Determine key crystallization parameters ✓
  - Low cost ✓
    - Off the shelf components kept total cost under £10K

4) On-going work

- Develop single camera/optics/illumination unit for COBC
  - Currently prototyping
- Improvements to optics and illumination to decrease minimum detectable crystal size and increase maximum crystal concentration
- Establish the full profiles of crystal size and concentration along the length of a COBC
- Creation of COBC crystallization model based on those profiles



Acknowledgements

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Thank you

Questions?