Optimierung von Kristallisationsprozessen mittels in-situ Messtechnik

Kolloquium Prozessanalytik

16. November 2007

Dr. Jochen Schöll

Dr. Paul Barrett

METTLER TOLEDO

Overview

Brief introduction of MT PAT tools

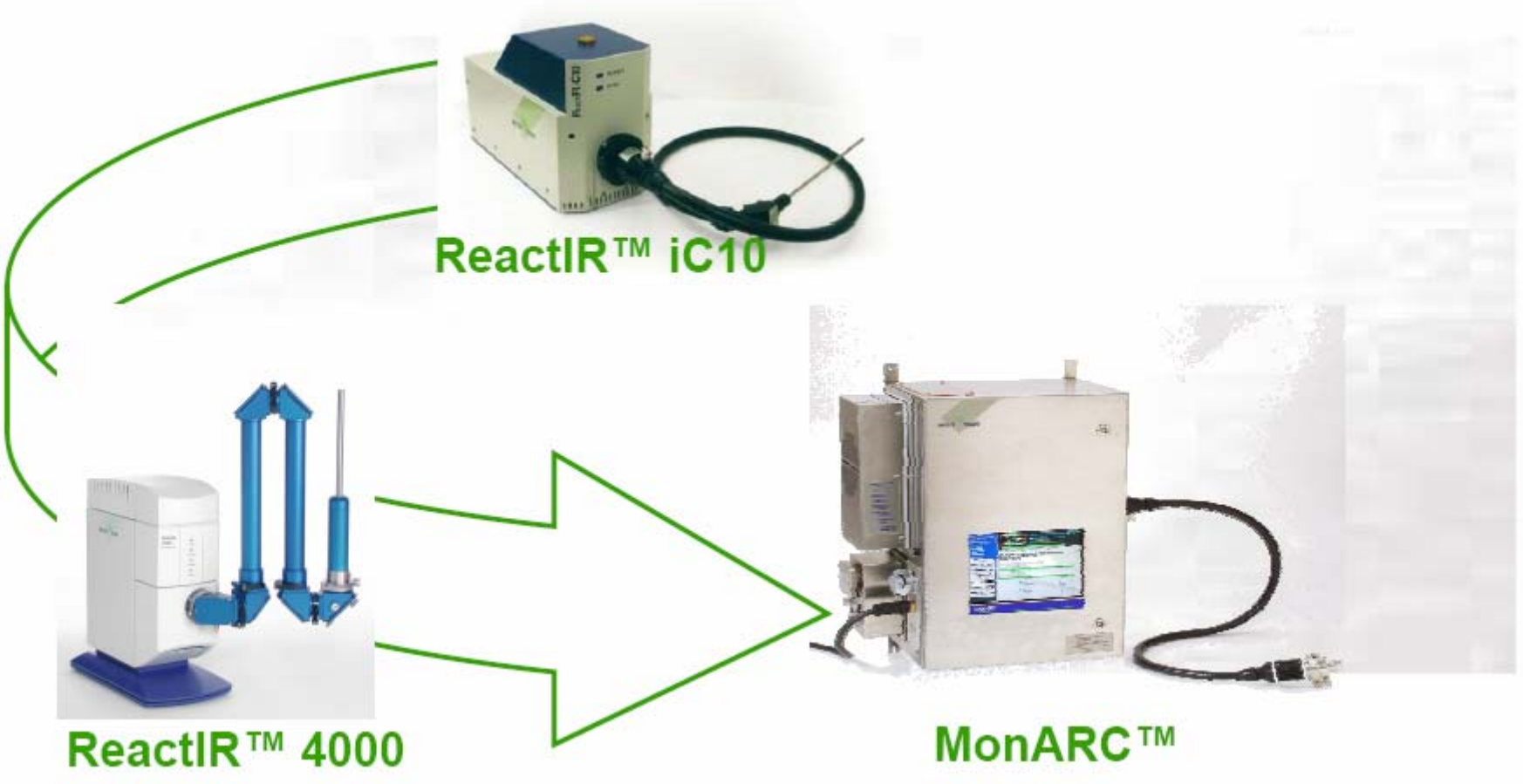
- PAT tools in crystallization process development
  - Process understanding
  - Process control
  - Scale-up and production
- Conclusions

Why PAT for Crystallization Processes?

- Crystallization:
  important unit operation for purification and formulation
- Issues with offline analysis:
  - Sampling & sample preparation
  - Temperature sensitive
  - Sample tends to agglomeration / segregation
  - Provides no process dynamics
  - etc.
- **Therefore:**

Introduction: ReactIR® and MonARC®

ReactIR – the online in-situ reaction analysis system for the characterization, optimization and control of chemical processes

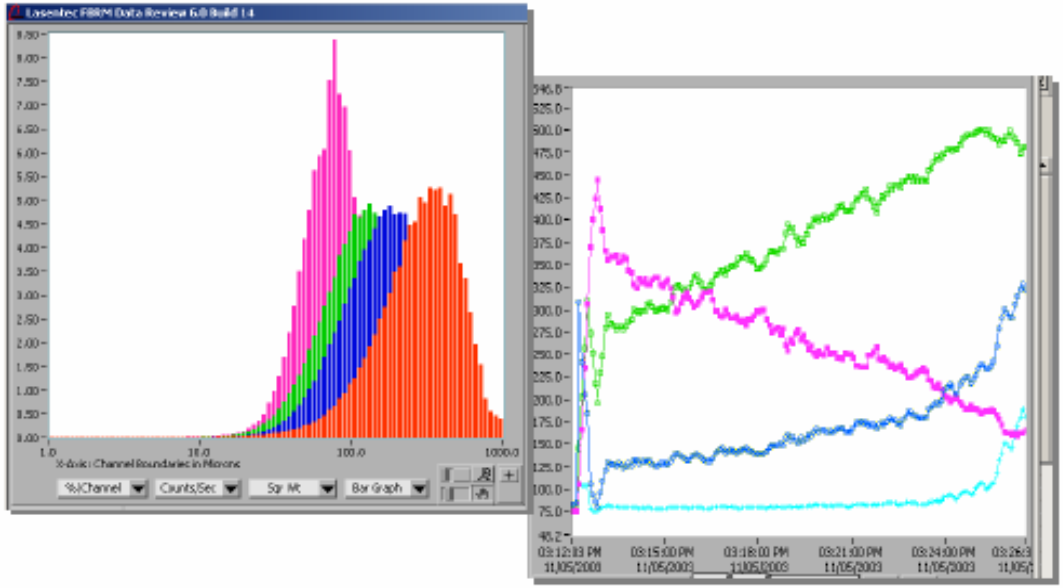


Introduction: FBRM® and PVM® Technologies

FBRM:

Focused
Beam
Reflectance
Measurement

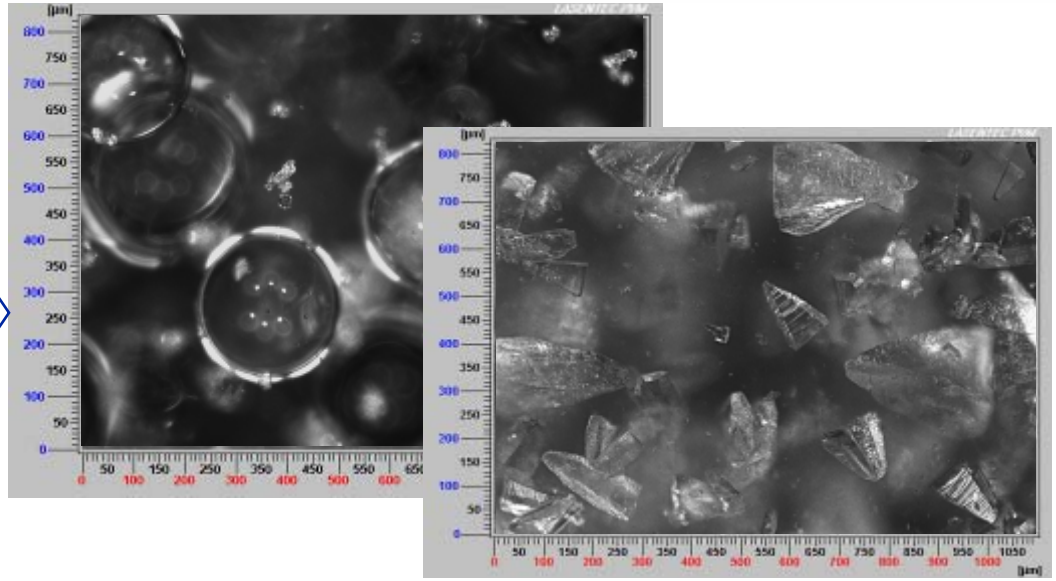
Sensitive measurement of change in Particle Dimension & Number



PVM:

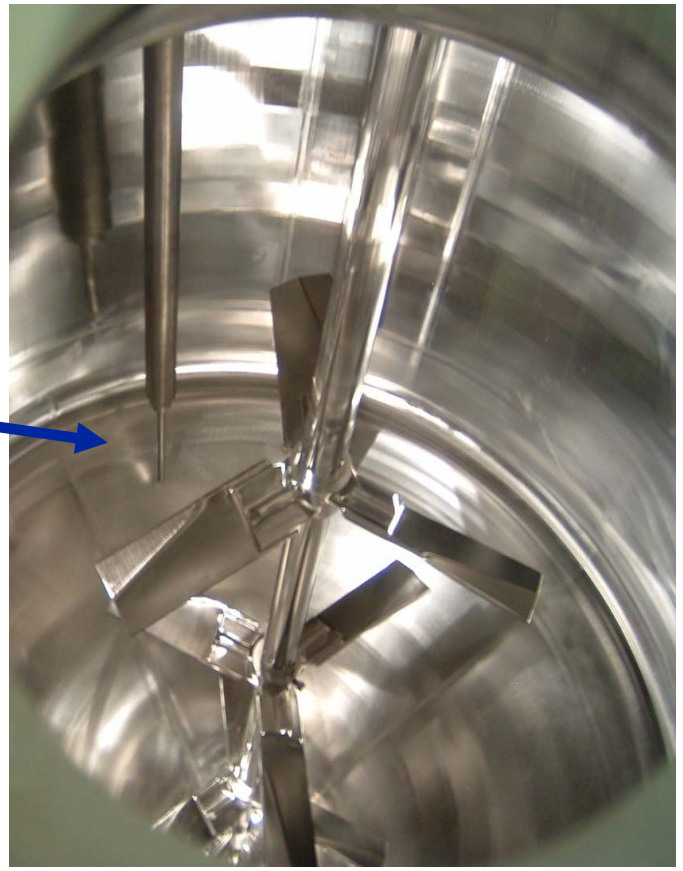
Particle
Video
Microscopy

See your particles as they naturally exist in process.



Lasentec® : Award-Winning Innovation

D600R

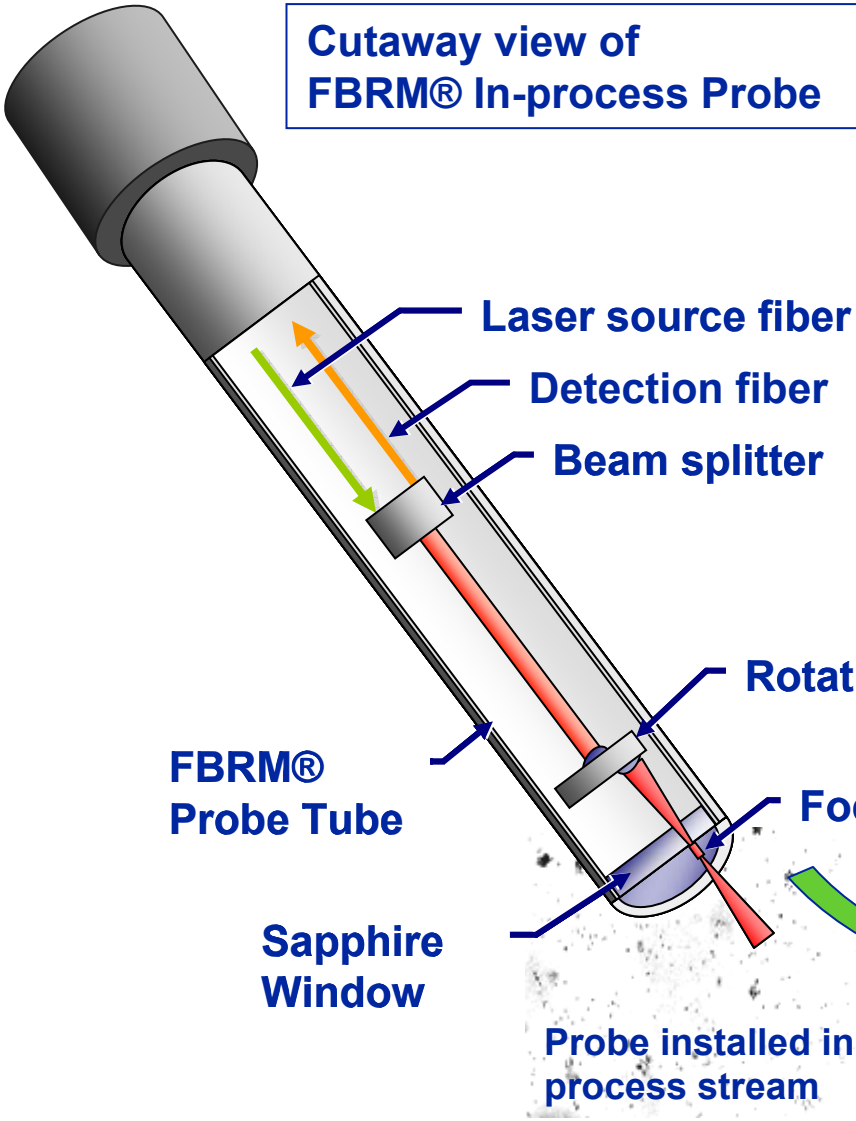


S400

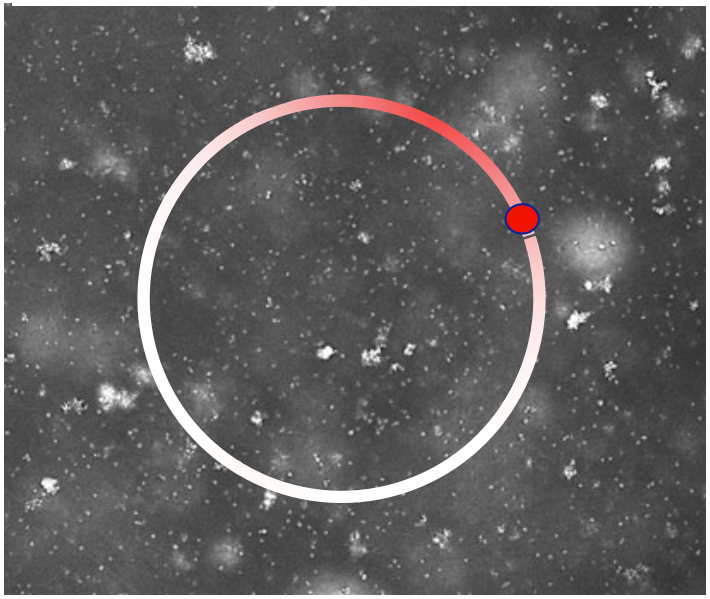
D600L

FBRM® Method of Measurement

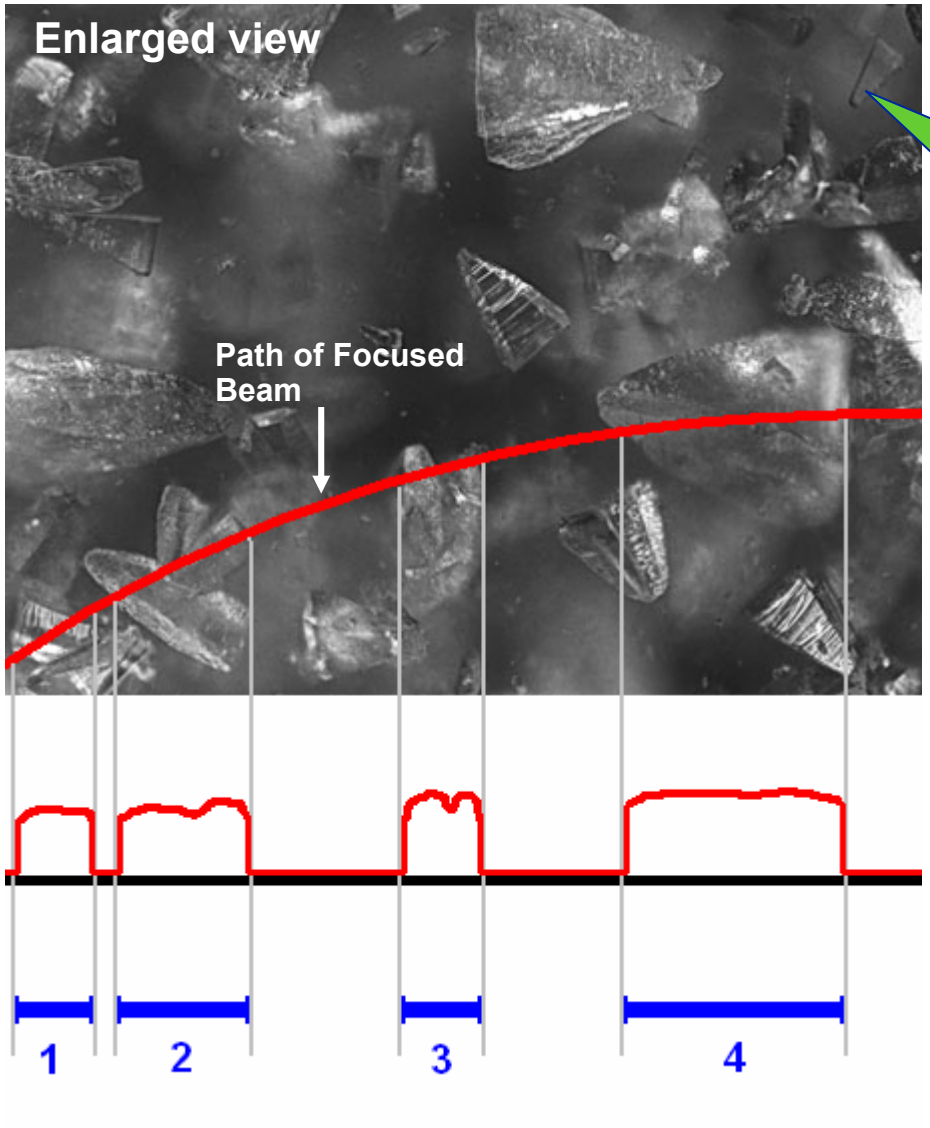
Cutaway view of
FBRM® In-process Probe



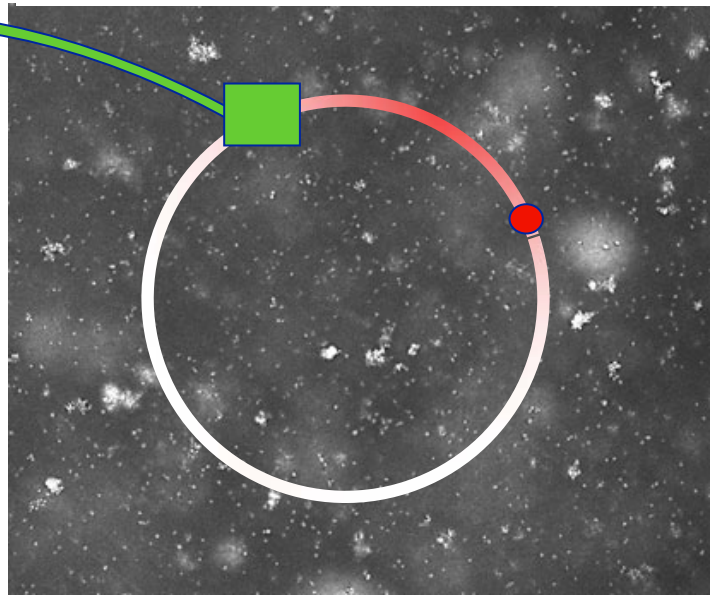
PVM® image illustrating the view
from the FBRM® Probe Window



FBRM® Method of Measurement



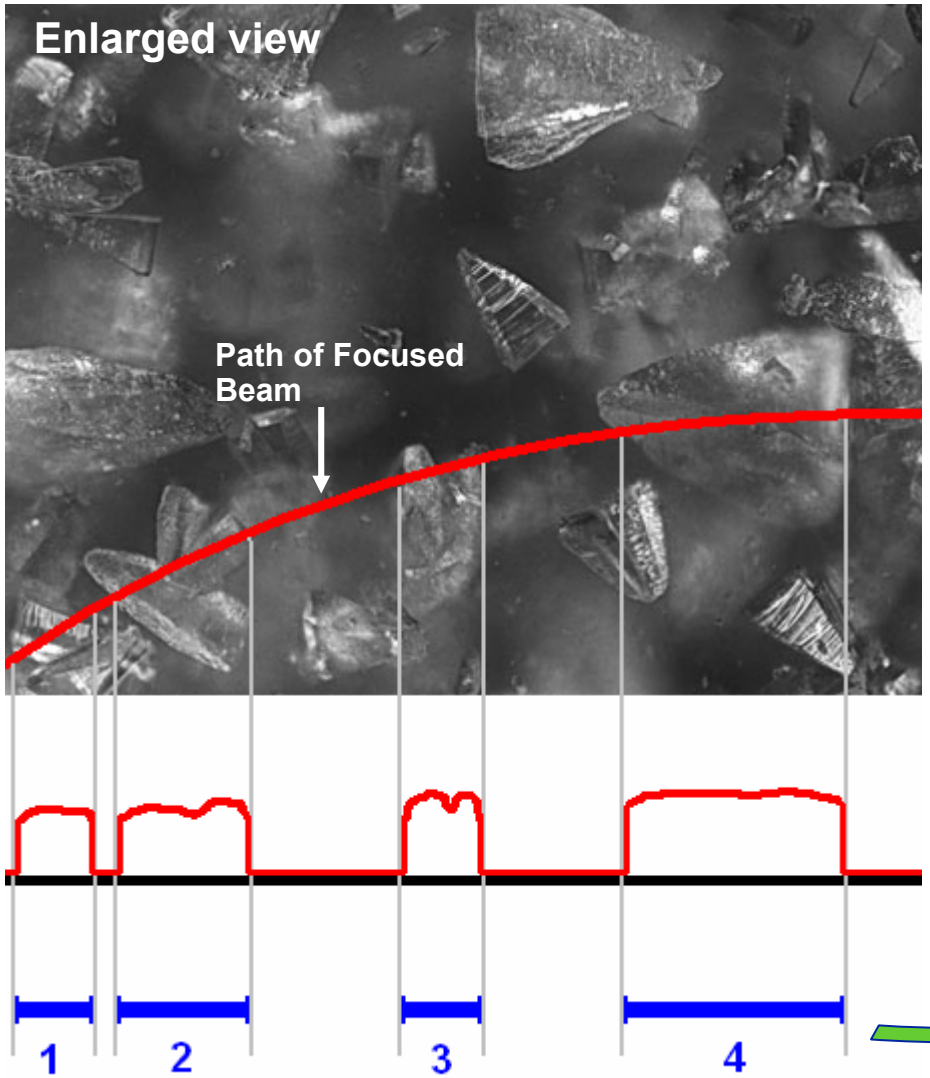
PVM® image illustrating the view from the FBRM® Probe Window

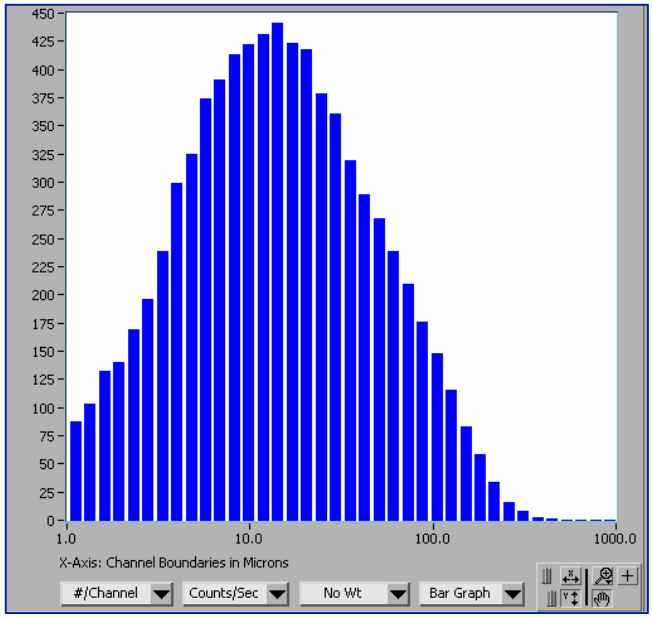


Probe detects pulses of Backscattered light

And records measured Chord Lengths

FBRM® Method of Measurement

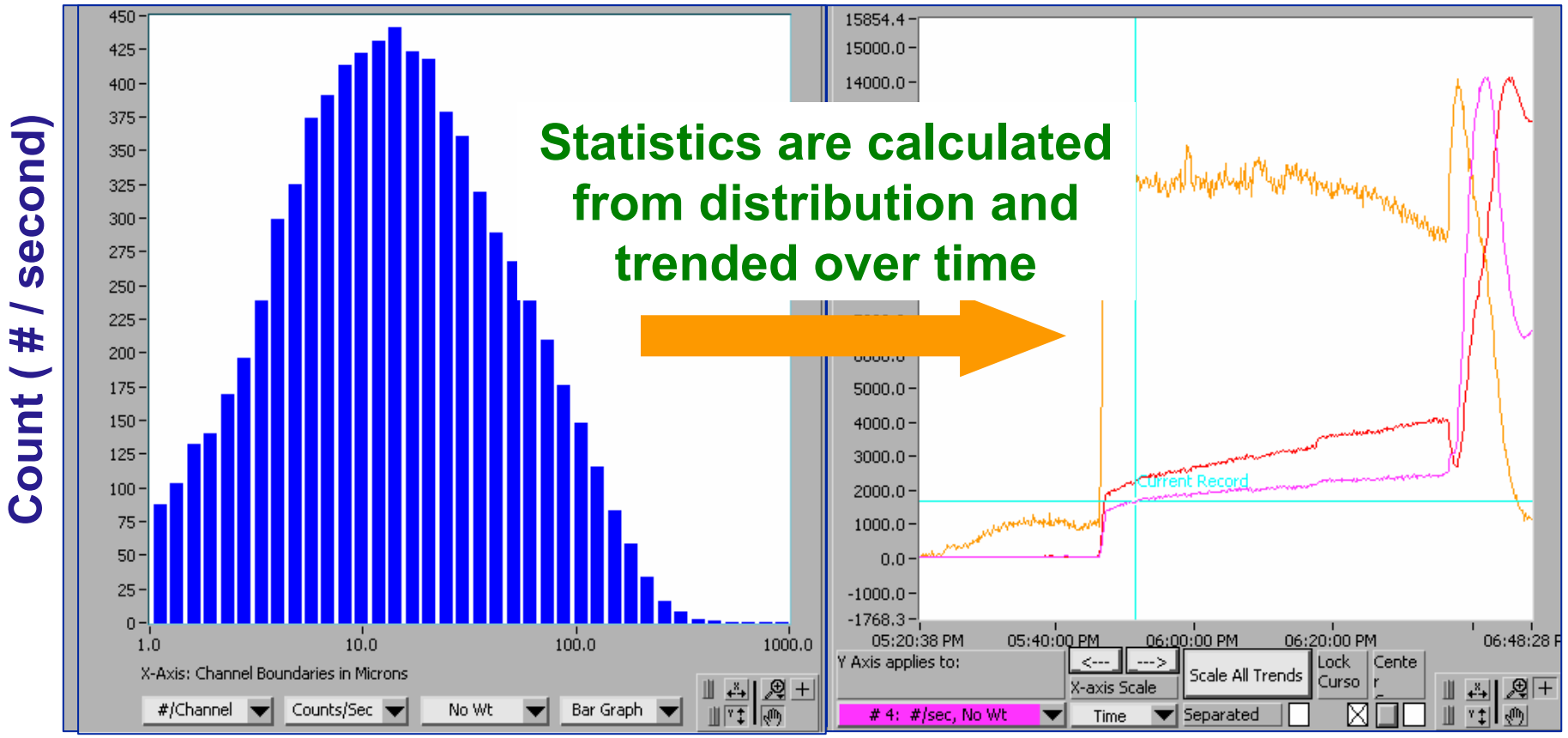




Thousands of Chord Lengths are measured each second to produce the FBRM® Chord Length Distribution :

The FBRM® Chord Length Distribution

Real-time measurement of number and dimension



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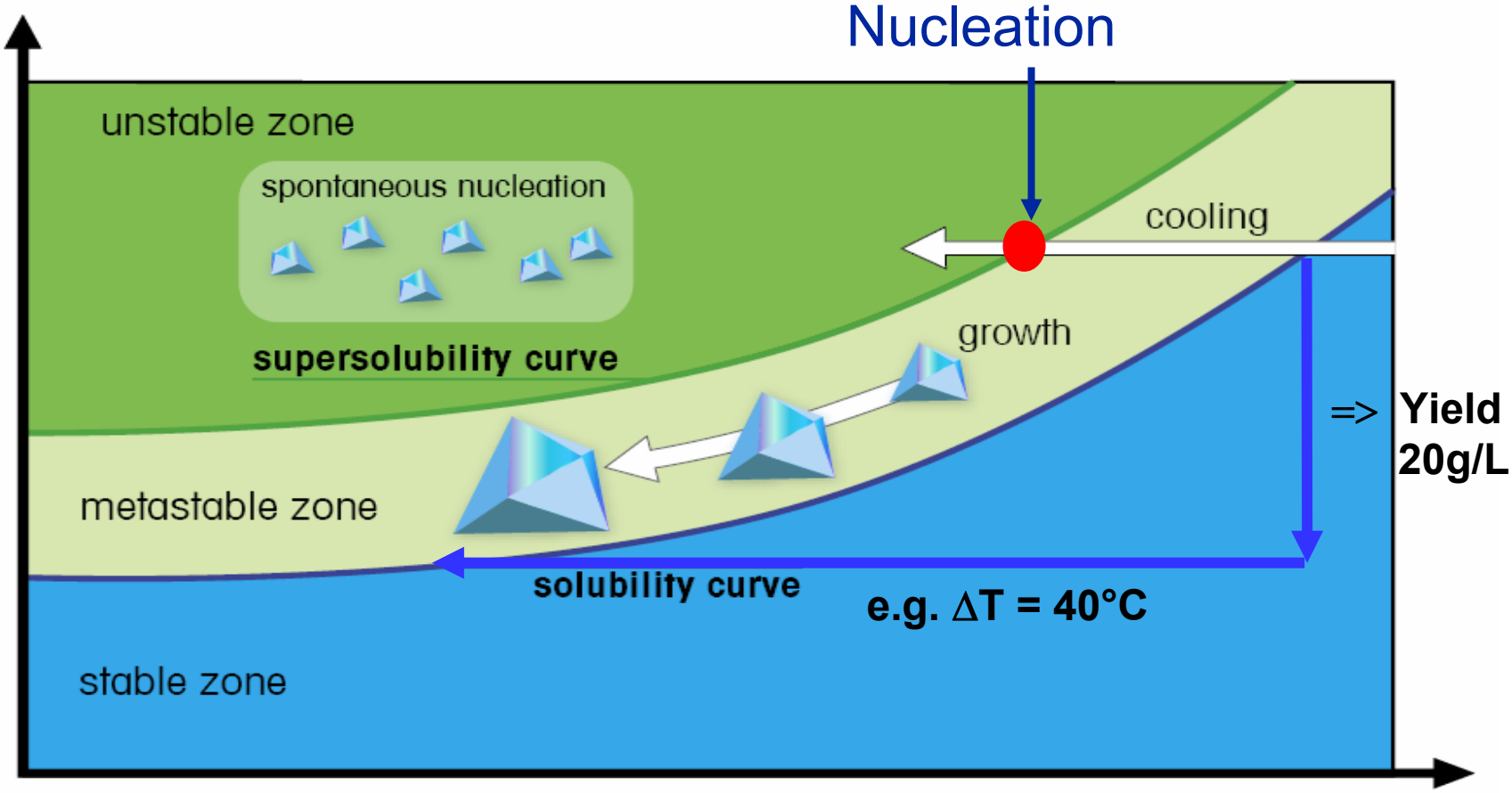
Solubility and Metastable Zone Width (MSZW)

- The **solubility** of a substance in a solvent as a function of temperature and/or solvent composition is the **fundamental thermodynamic information** that lays the foundation for any crystallization process development.
- The Metastable Zone Width (MSZW) characterizes the ability of a system to remain in a supersaturated state without exhibiting spontaneous nucleation. The MSZW is a **kinetic information** depending both on nucleation and growth kinetics.
- The **fast and reliable determination** of solubility and MSZW by combining FBRM and an automatic lab reactor will be shown in the following slides.

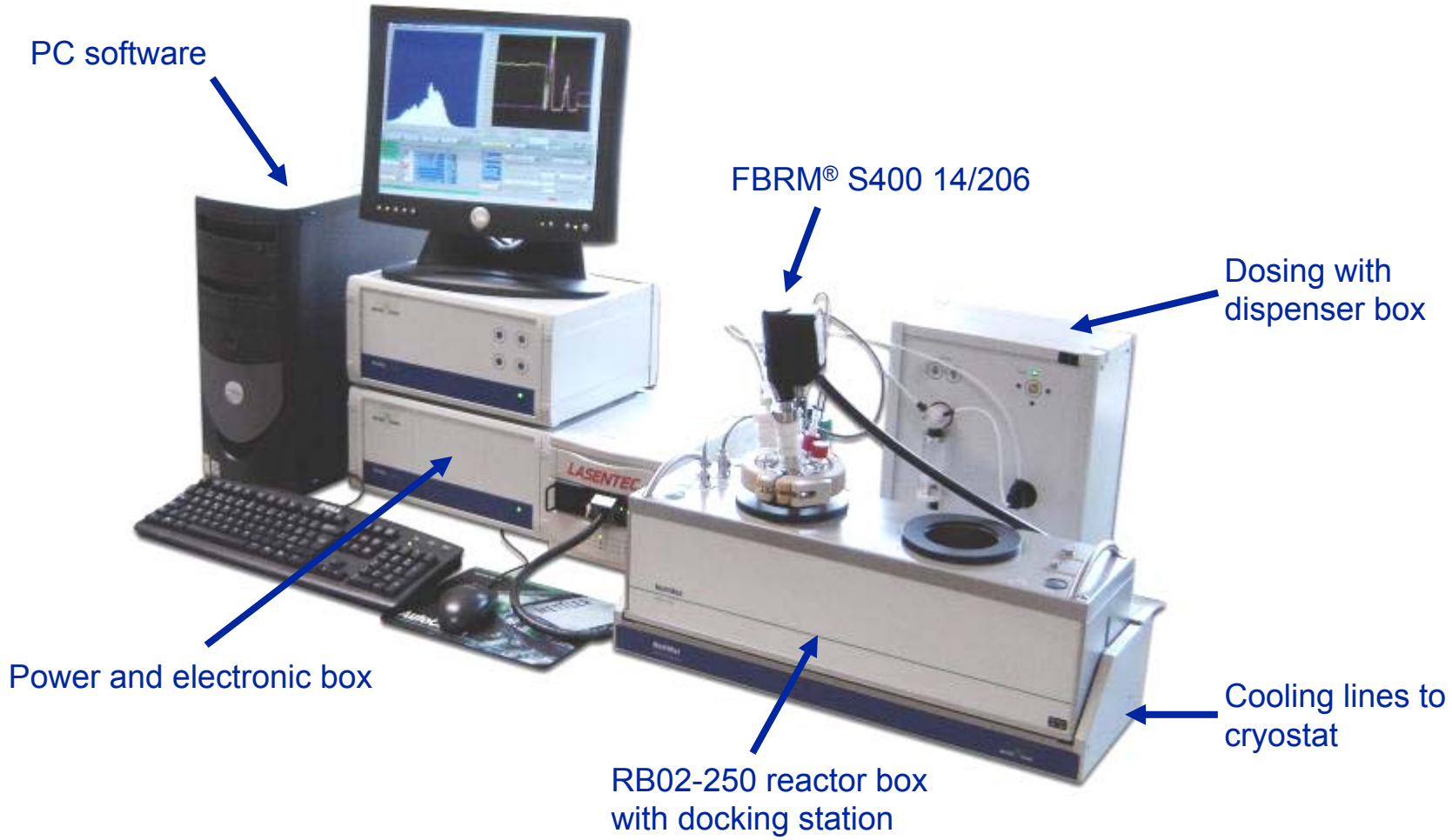
The Metastable Zone Width concept



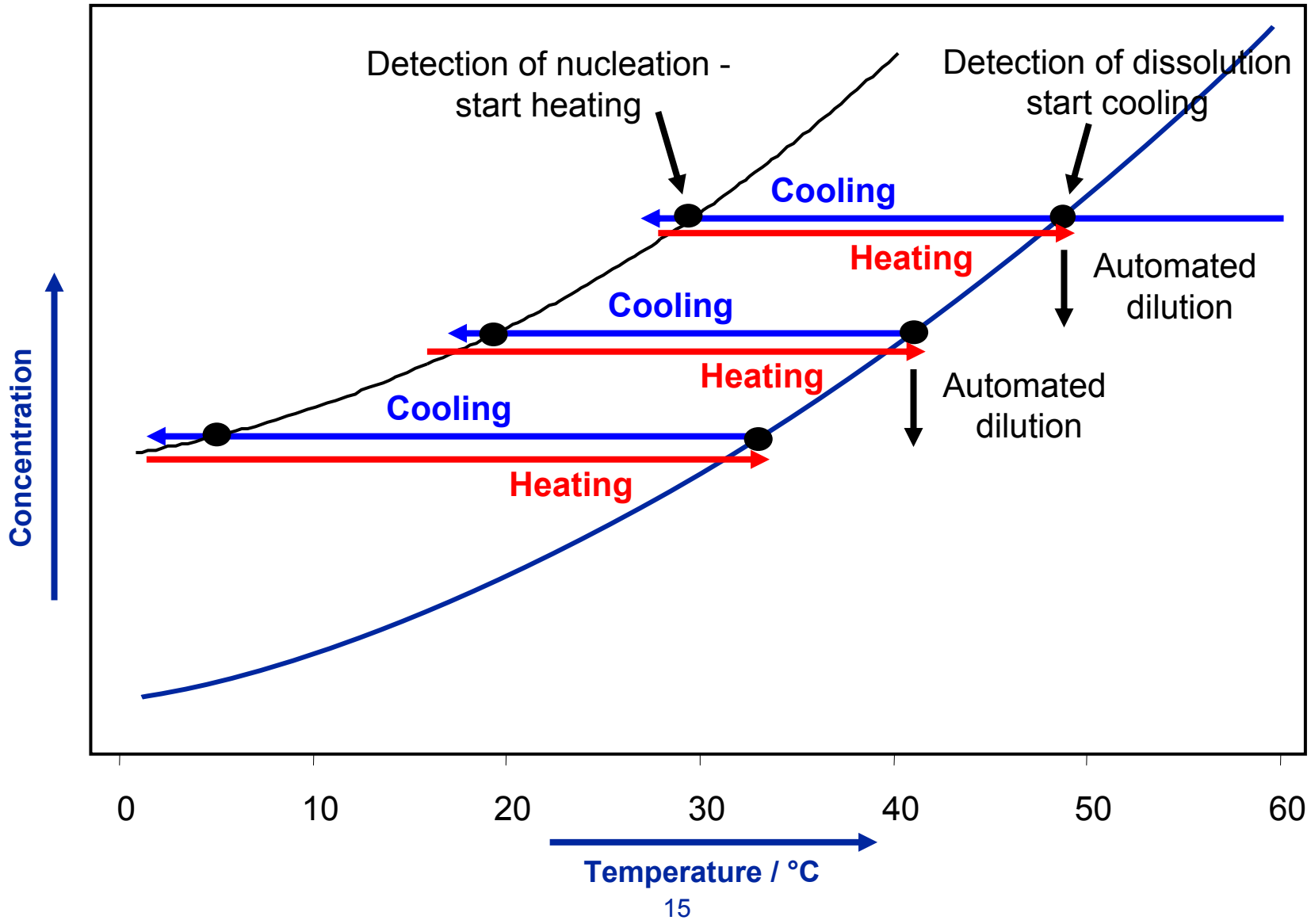
Recommendation for robust crystallization process development:
Seed half-way in the MSZ and apply controlled cooling profile

Automated and in parallel

- Automated MSZW determination combining FBRM and ALR



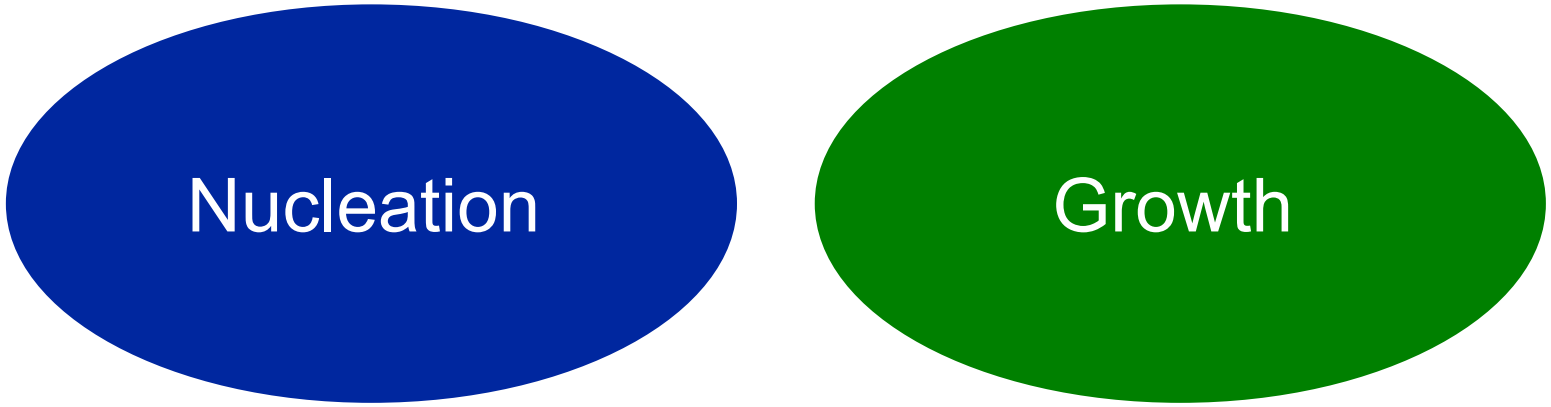
How is it done?



Supersaturation controlled crystallization

One step further: crystallization kinetics

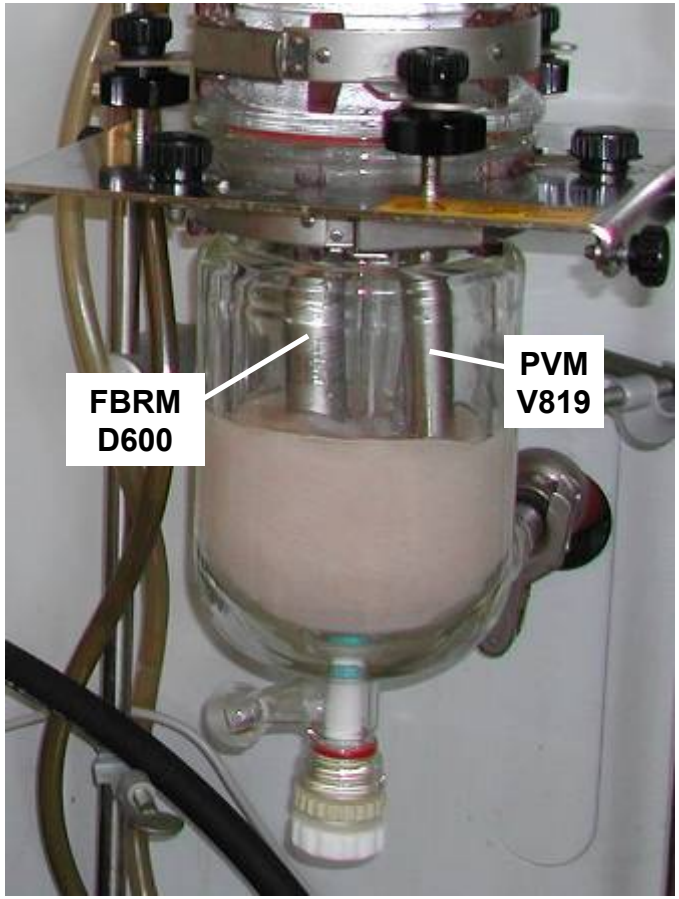
- Nucleation or growth?
  Besides the thermodynamic properties of a system, mainly the **kinetics of the fundamental mechanisms** are determining the properties of a given system. Hereby, nucleation and growth play a significant role, since they are mainly depending on the driving force, i.e. supersaturation



- The following example highlights how the combined use of FBRM and PVM allows for the fast and reliable characterization of the underlying fundamental kinetics of a crystallization .

Quantifying crystallization kinetics

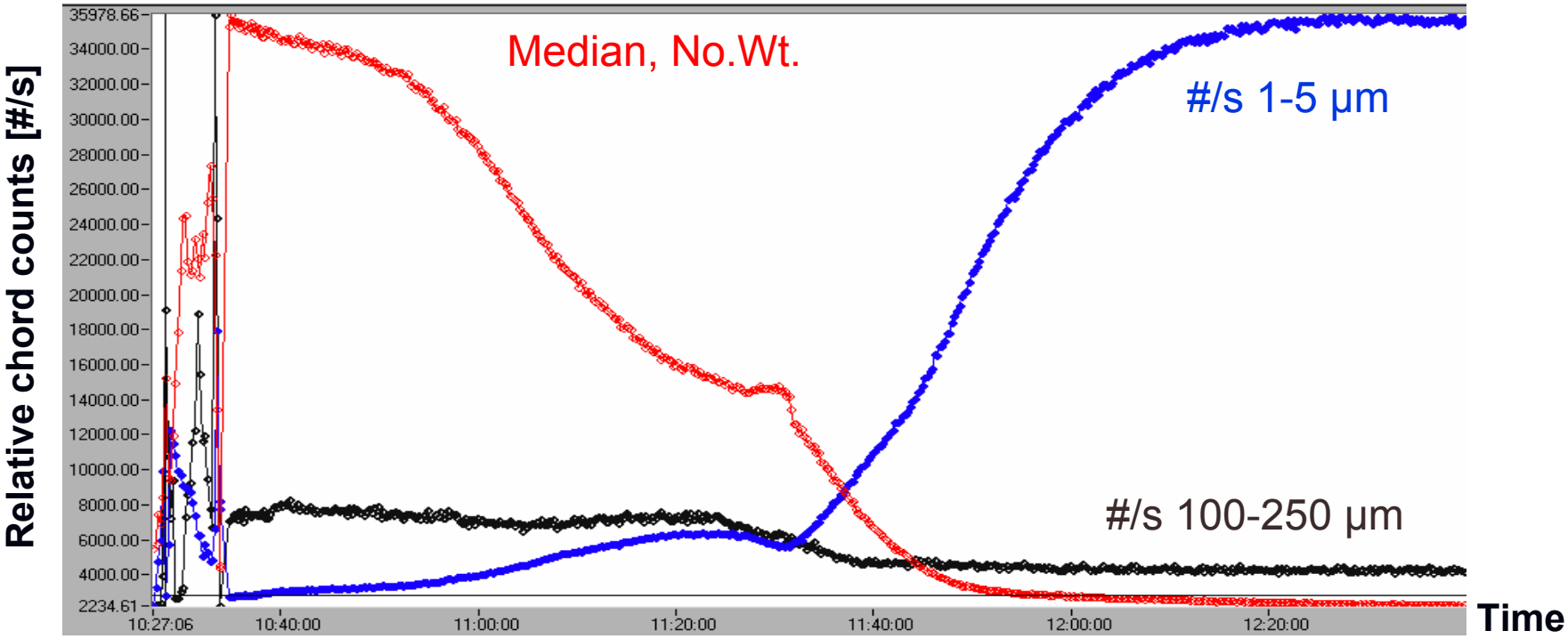
- The dependence of nucleation and growth kinetics on the driving force, i.e., supersaturation, can be directly quantified for a given system using in situ monitoring tools, as will be shown in the following example.
- In this example, we will see a seeded drowning-out crystallization:
  - Mother liquor with crystal seeds
  - Linear antisolvent addition at constant T
- To simplify the example, the same experiment was repeated at two different reactor temperatures.



Typical crystallization set-up featuring FBRM and PVM in an automated lab reactor

FBRM trends of Run1

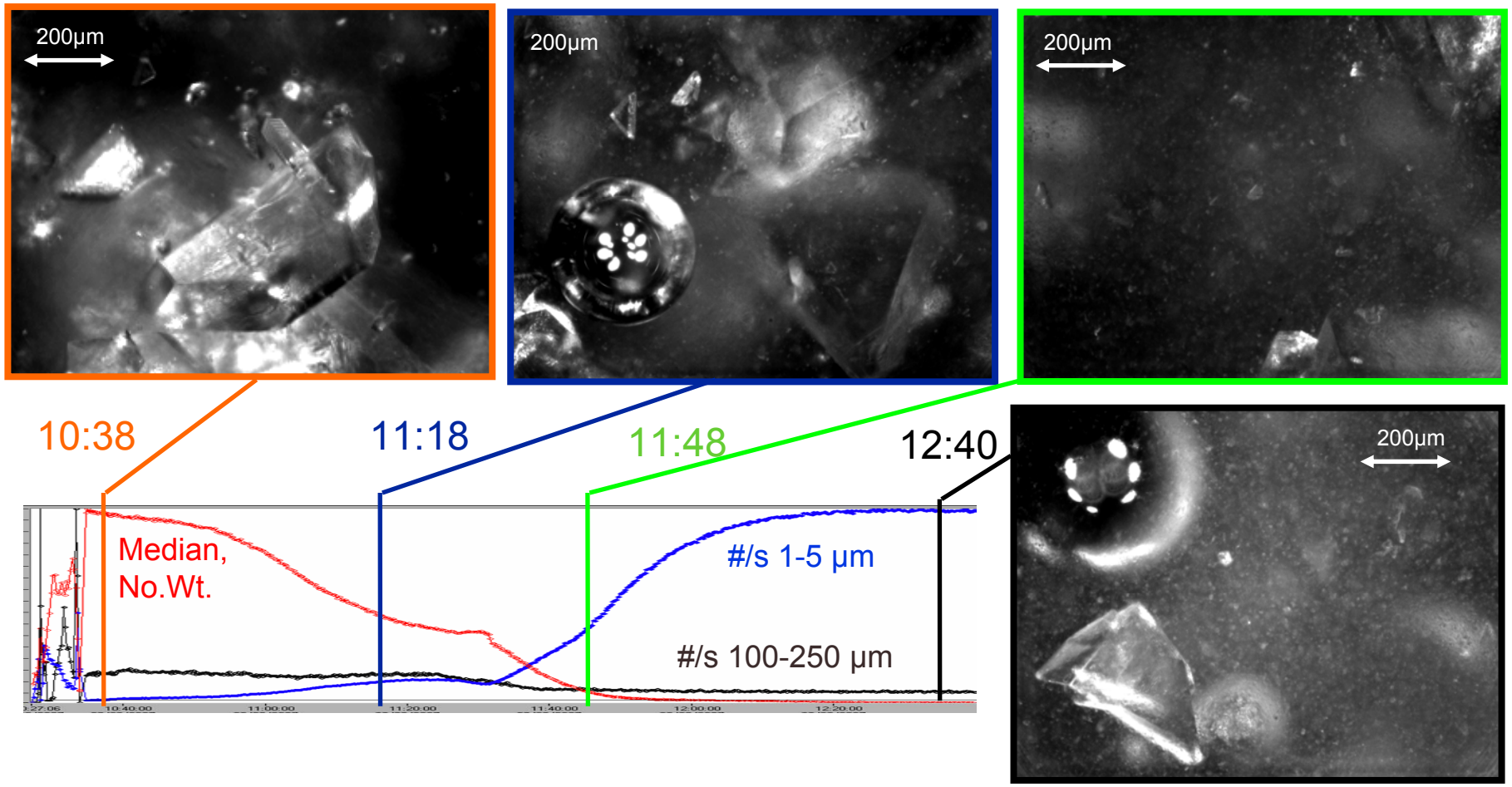
- FBRM trends of Run1 at lower temperature (T=25°C)



- Initially small, later steep increase of fine particles (1-5µm)
- Decrease in the number of coarse particles (100-250µm)
- Median is decreasing throughout the process

PVM images of Run1

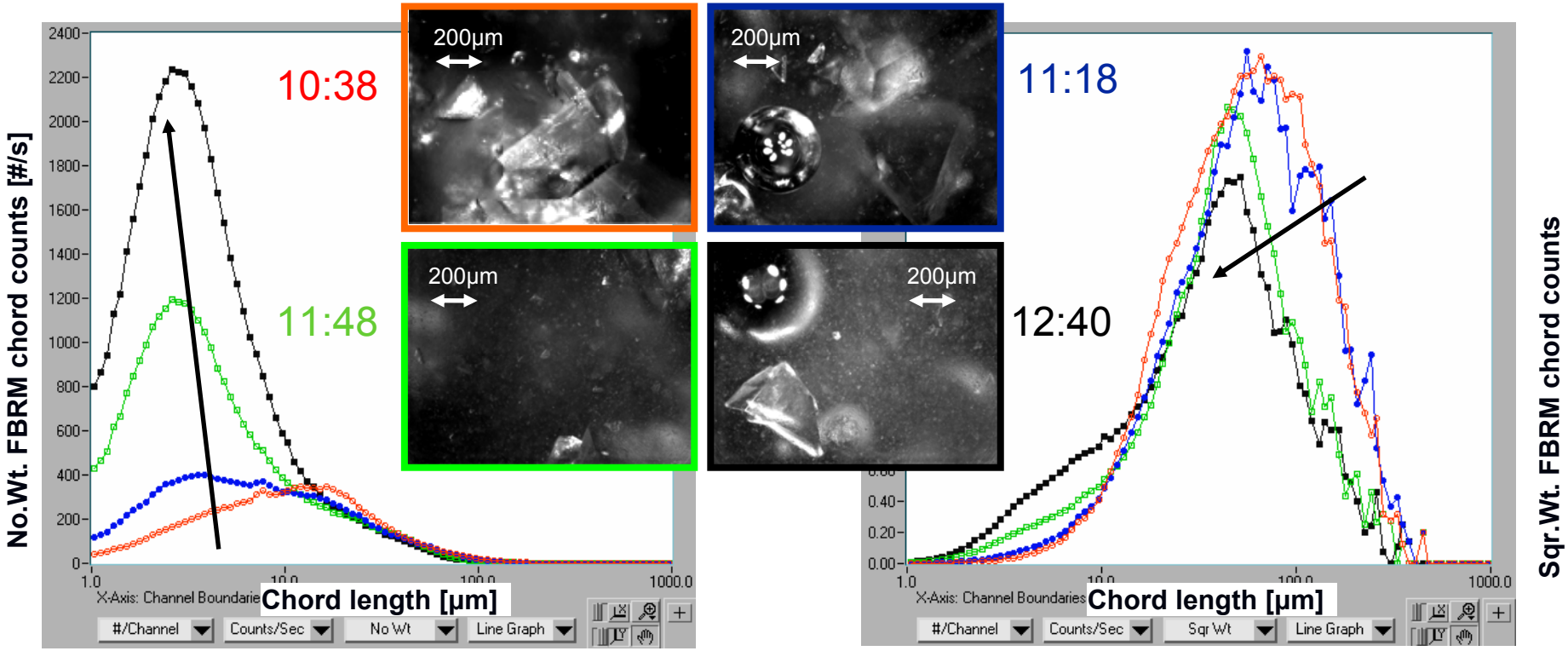
- FBRM trends and PVM images of Run1 at T=25°C



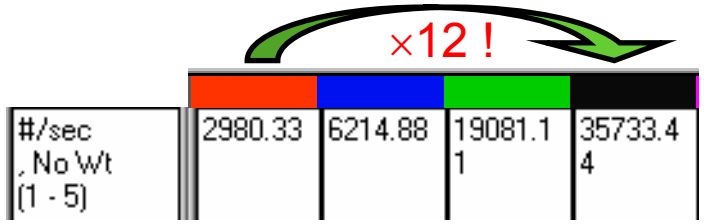
- PVM images visualize FBRM measurement data

Distribution comparison of Run1

- FBRM CLDs and PVM images of Run1 at T=25°C

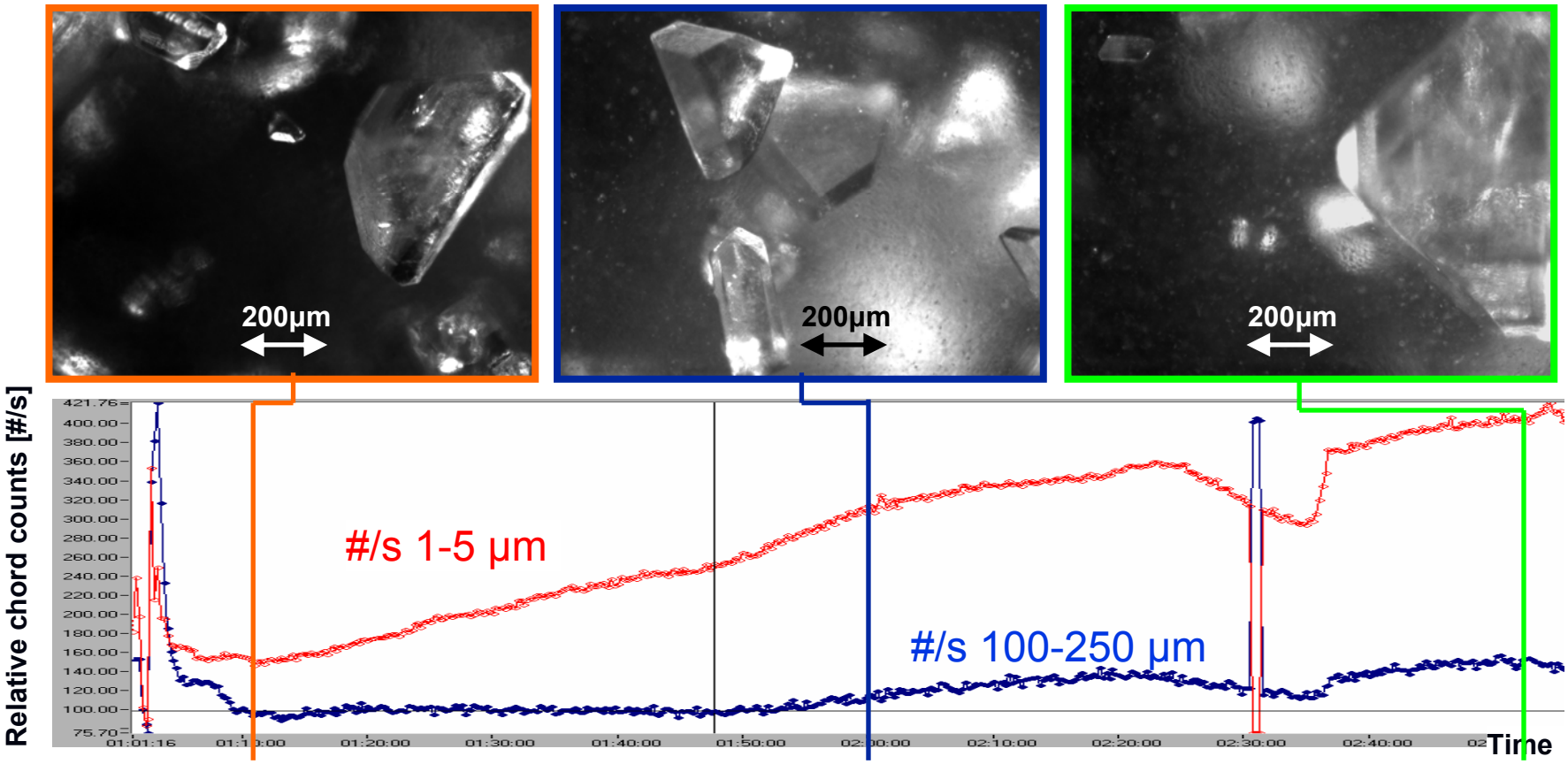


- Increase in fines highlighted on the left in No.Wt. CLD
- Slight decrease in size can be seen on the right in Sqr.Wt. CLD
- Quantification of fines increasing using statistics:



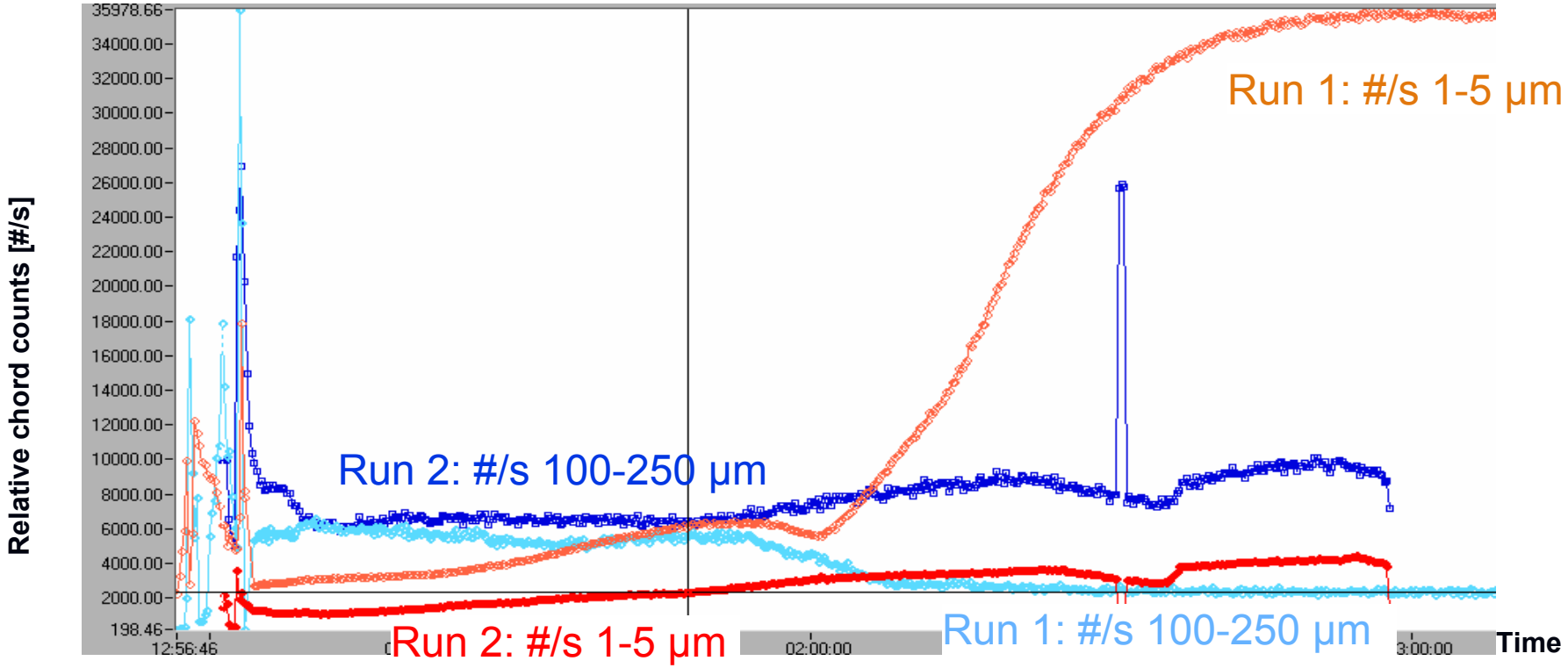
FBRM trends of Run2

- FBRM trends and PVM images of Run2 at 45°C



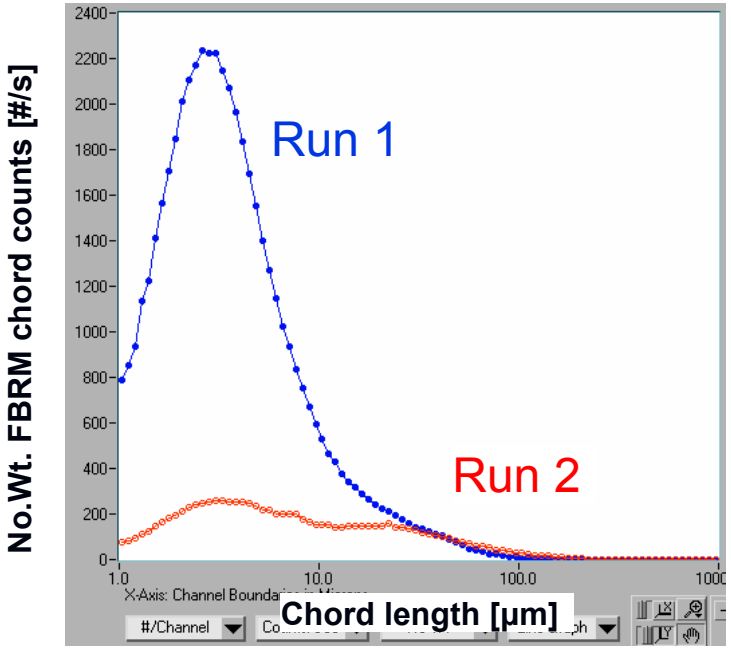
- Similar trends as observed in Run 1; however, fines generation less pronounced.
- PVM images confirm the slight increase of fine particles.

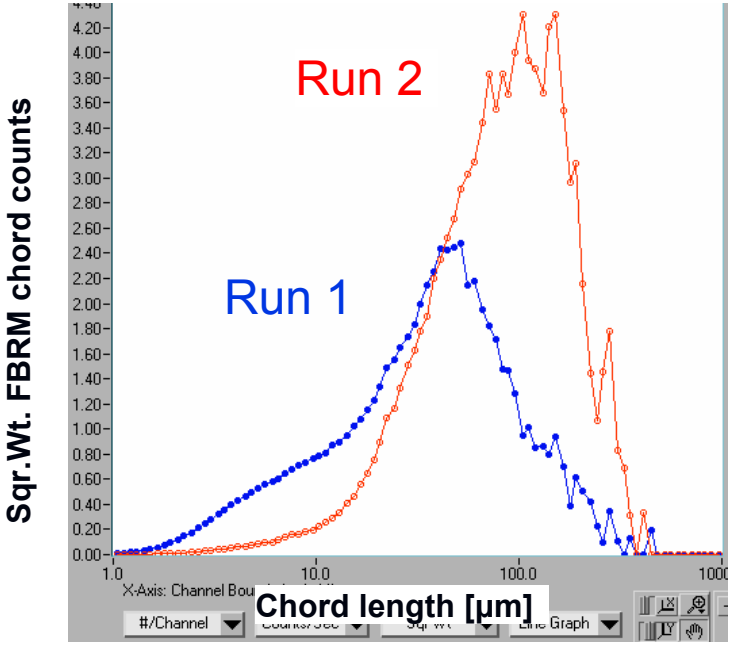
Comparison of Run1 and Run2



- Less increase of fine particles at higher temperature.
- Increase instead of decrease in the number of coarse counts at higher temperature.

Comparison of endpoint distribution





- Main results: Run1 features more fines and less coarse material than Run2
- Main effects of higher process temperature:
  - Lower supersaturation at higher temperature generates less nuclei
  - Higher temperature accelerates crystal growth

Both effects lead ultimately to a coarser and more homogeneous product

Quantifying crystallization kinetics

In situ FBRM and PVM are valuable tools for the relative quantification of nucleation and growth kinetics for a series of experiments

- For the determination of the dependence of nucleation and growth kinetics on supersaturation additional information is needed, e.g., the liquid phase concentration as monitored via ATR-FTIR spectroscopy.
- Following publications describe protocols to determine the kinetics of
  - **Nucleation:** J. Schöll et al., *Chem. Eng. Technol.*, 29(2), 257-264, 2006.
  - **Crystal growth:** J. Schöll et al., *Faraday Discuss.*, 136, 247-265, 2007
  - **Agglomeration:** C. Lindenberg, J. Schöll, L. Vicum, J. Brozio, and M. Mazzotti, “Precipitation of L-glutamic acid: agglomeration effects”, submitted to *Crystal Growth and Design*.
  - **Polymorph transformation:** J. Schöll et al., *Cryst. Growth Des.*, 6(4), 881-891, 2005.

Once these kinetics are known, they can be used together with Population Balance Modeling to simulate the process under different conditions.

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In-Situ Supersaturation Monitoring & Control of Crystallization Processes

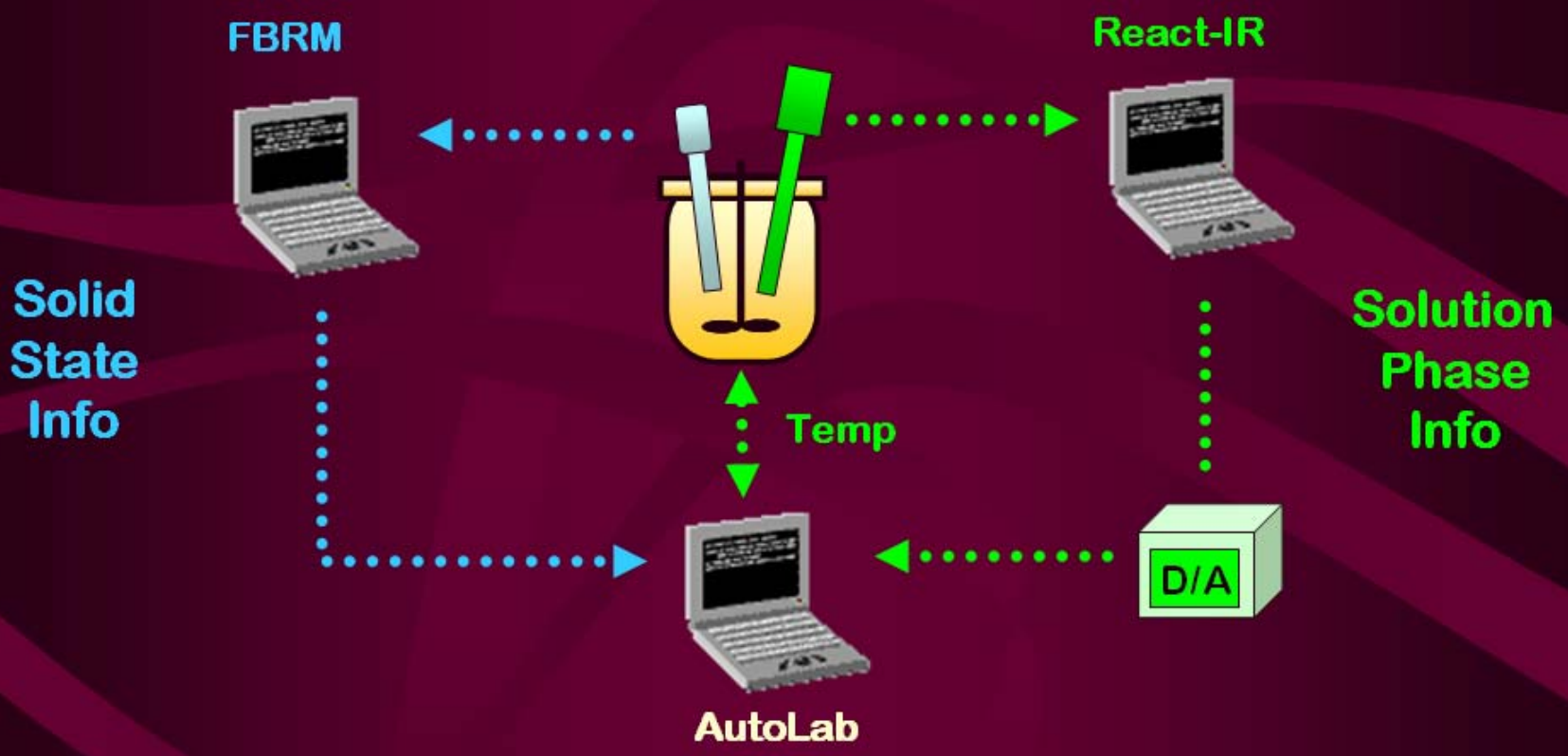
Vince Liotta, Ph.D. & Vijay Sabesan

Schering-Plough Research Institute

Real-Time Analytics Users Forum
February/March 2005

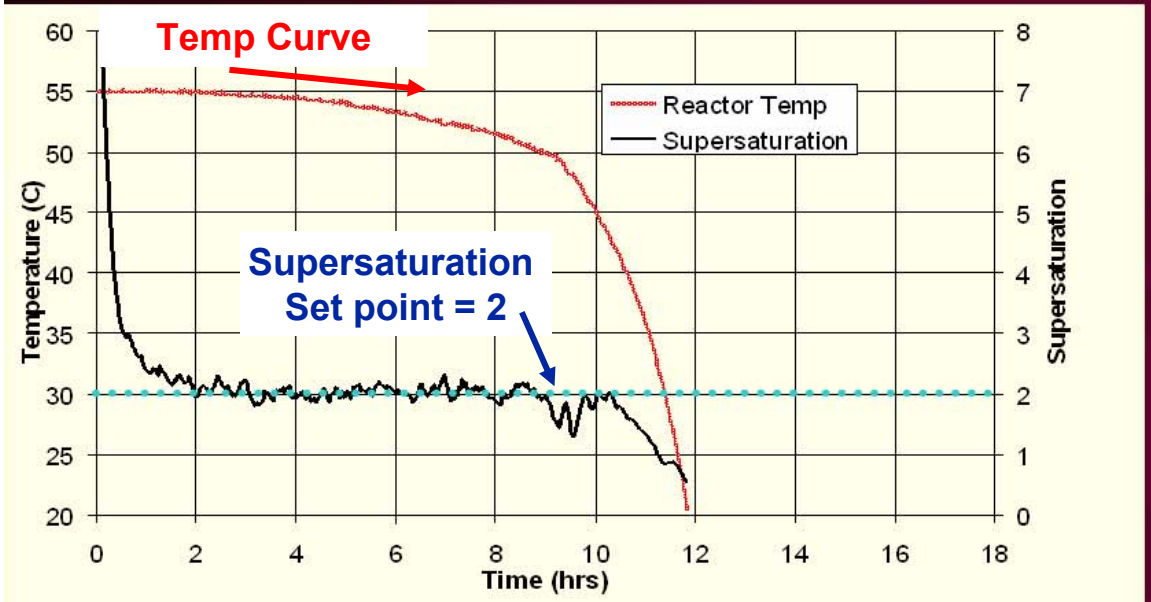
Experimental Setup

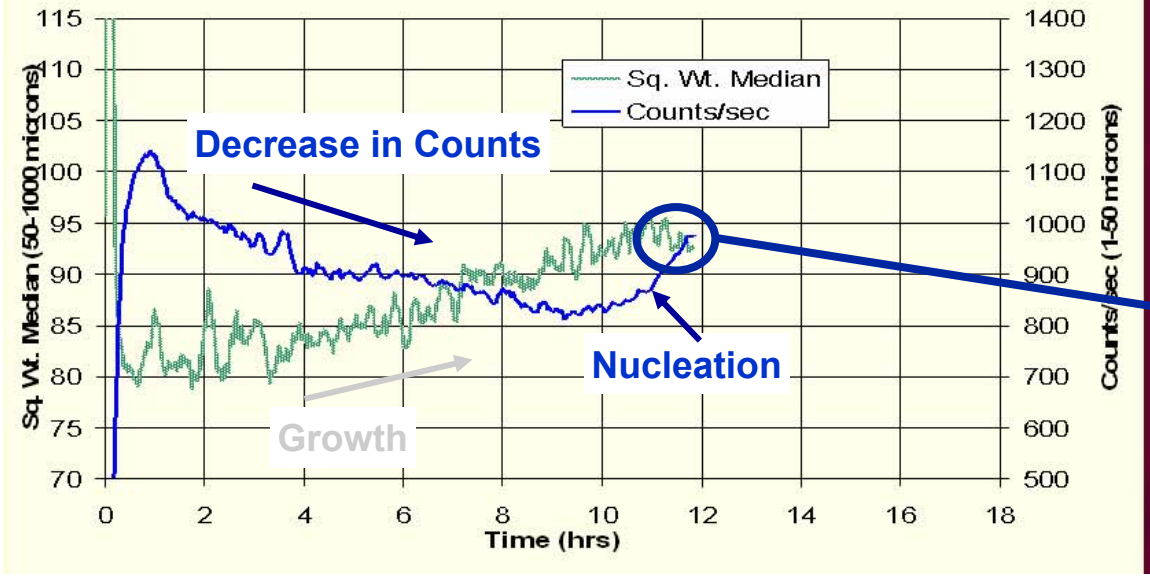
Crystallization Monitoring



Supersaturation Control

at S=2 =ΔC

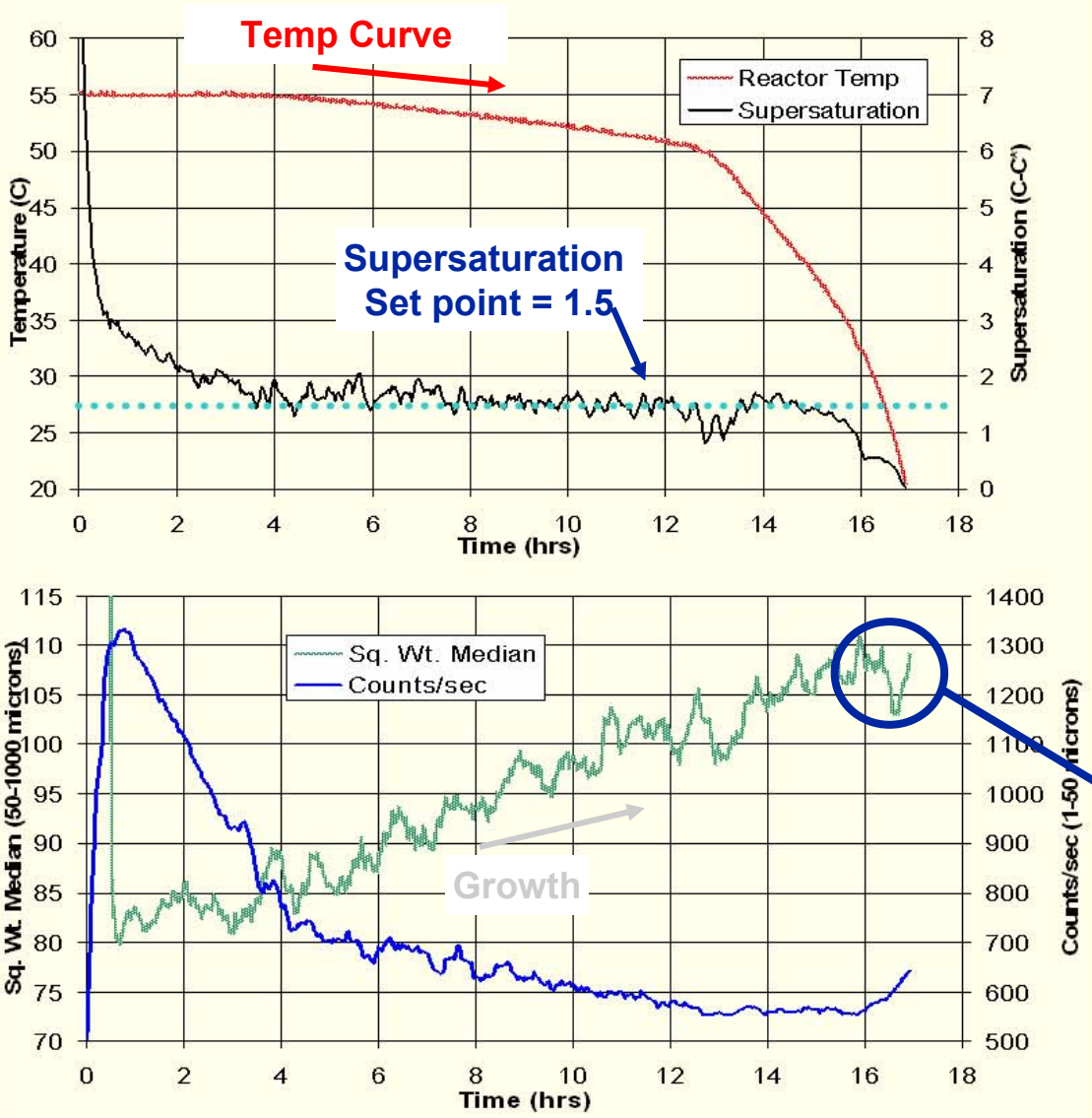




Temperature &
Calculated FTIR Data

Lasentec FBRM Data
Mean at Endpoint = 95µm

Supersaturation Control
at S=1.5 =ΔC

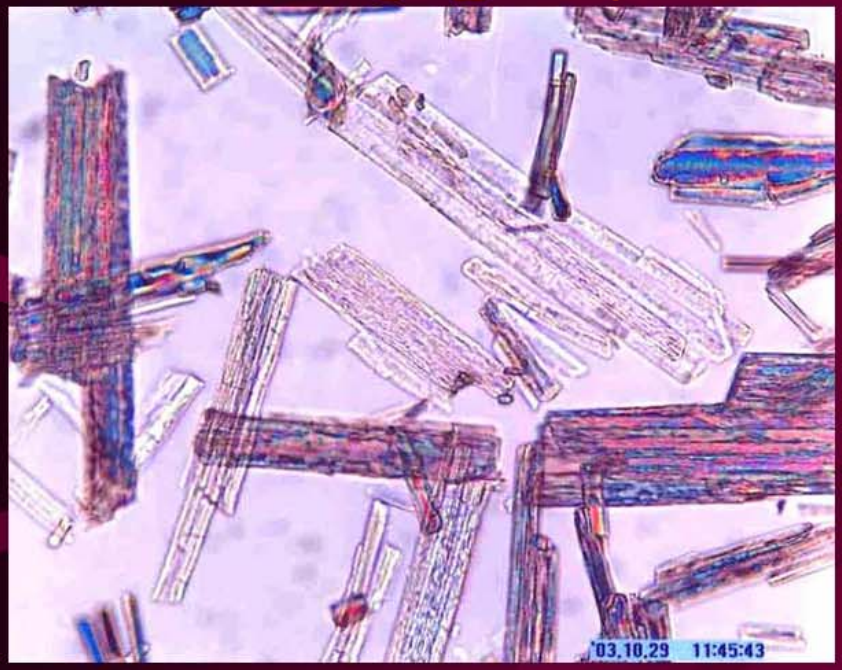


Temperature &
Calculated FTIR Data

Lasentec FBRM Data
Mean at Endpoint = 107μm

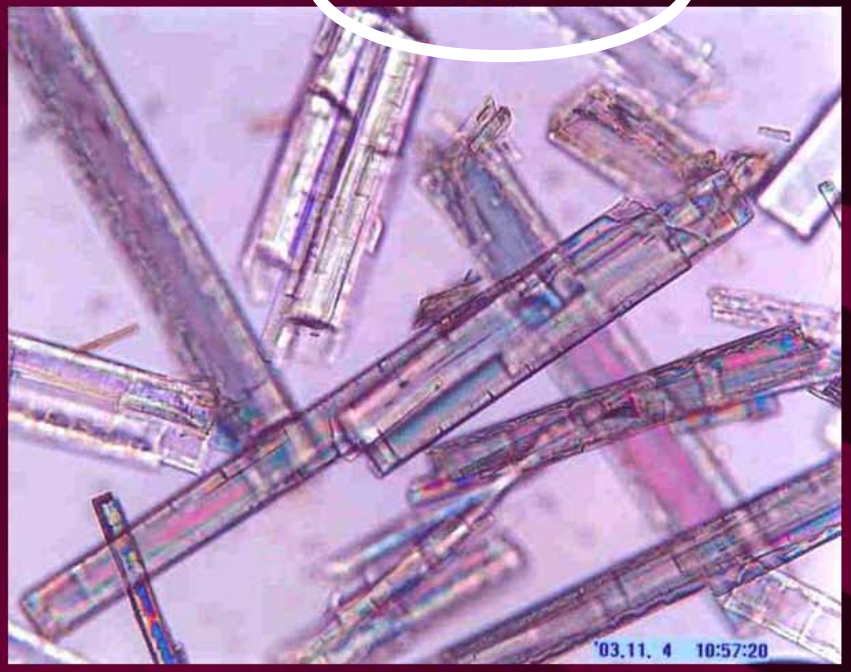
Crystal Size Results

S=2 =ΔC



Sq Wt Median = 95μm

S=1.5 =ΔC



Sq Wt Median = 107μm

Lower Supersaturation yielded larger Crystals

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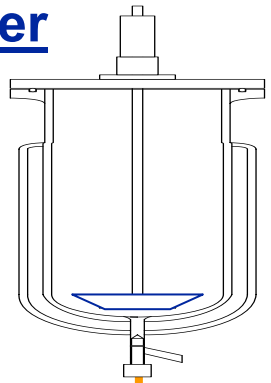
Possible downstream processing issues

Crystallizer



Filter

Dryer

Mill

Product

- Inconsistency batch to batch
- Batches difficult to stir and filter
- Yield, purity or polymorph issues

- Poor Filtration rates
- Crystals damaged in the filter
- Excessive washing dissolves product

- Long drying times & Attrition in the dryer

- Multiple Mill pass required
- Mill time not optimized

- Poor product handling/storage
- Inconsistent product qualities

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PAT from Lab-scale to Production: a Lasentec Approach

André Ridder – 12.06.2007

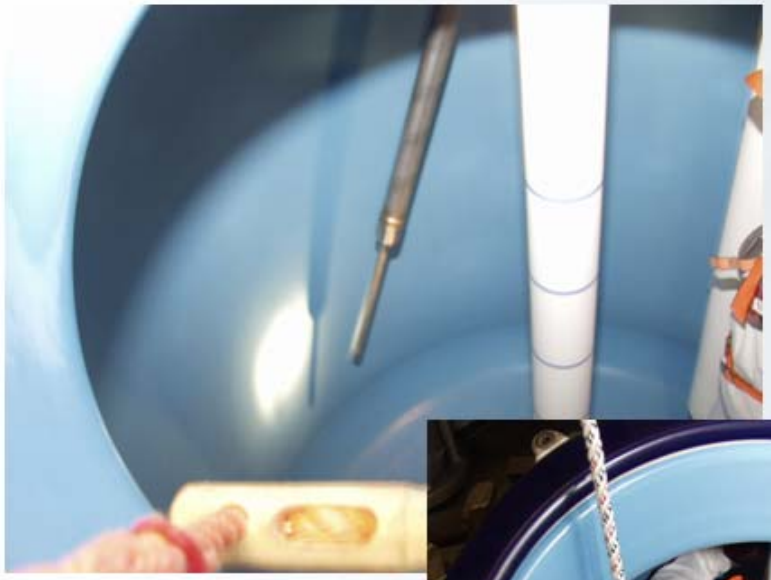
Group Leader Process Development/PAT Champion

Heumann *PCS*, Pfizer PGM, Feucht, Germany

Why are we Dealing with PAT at Feucht?

- Continuous quality monitoring
- Supporting health and safety
- *Saving money*

Pictures from the Plant Implementation



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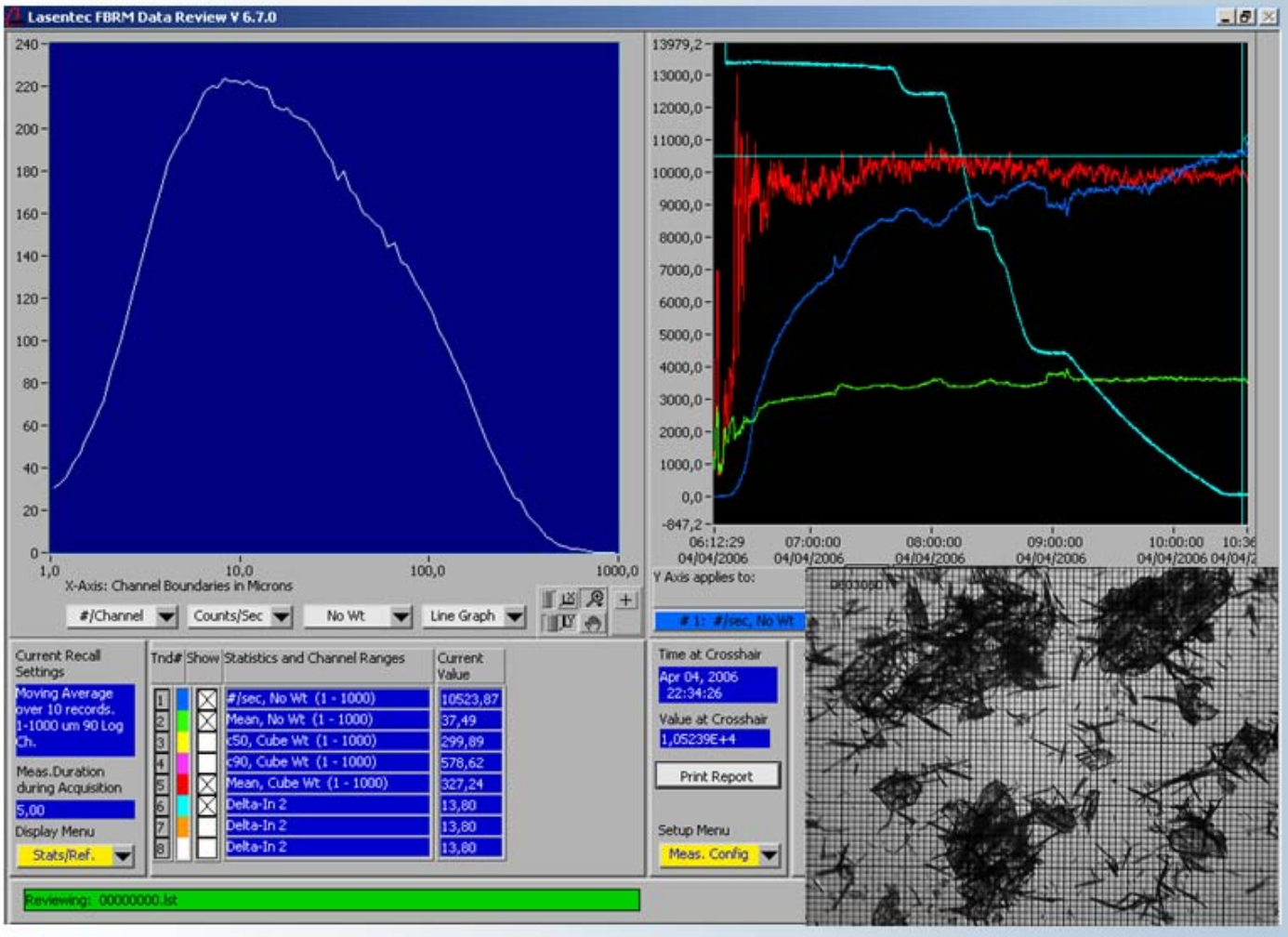
Old Process: Crystallization



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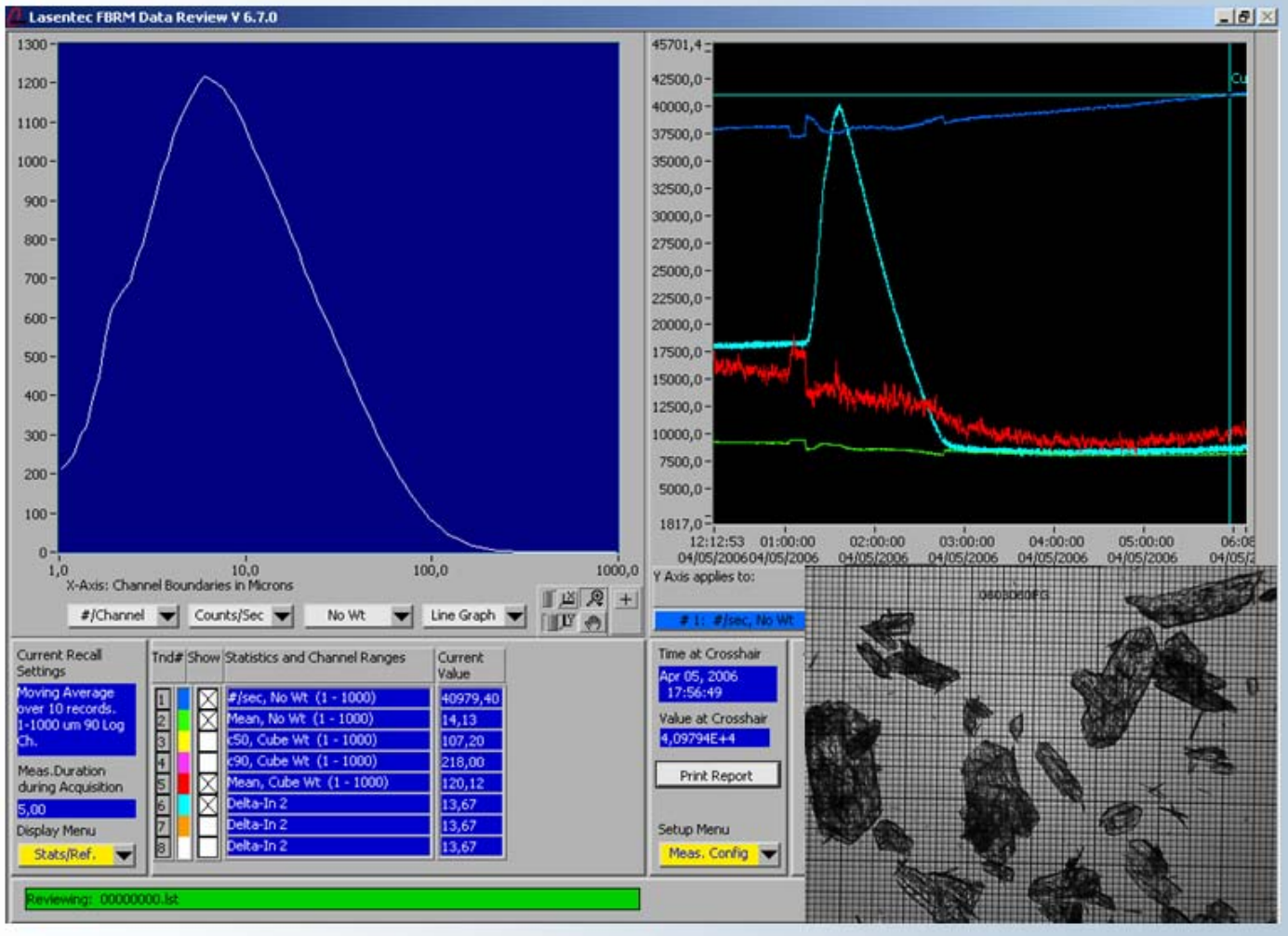
Old Process: Water Wash



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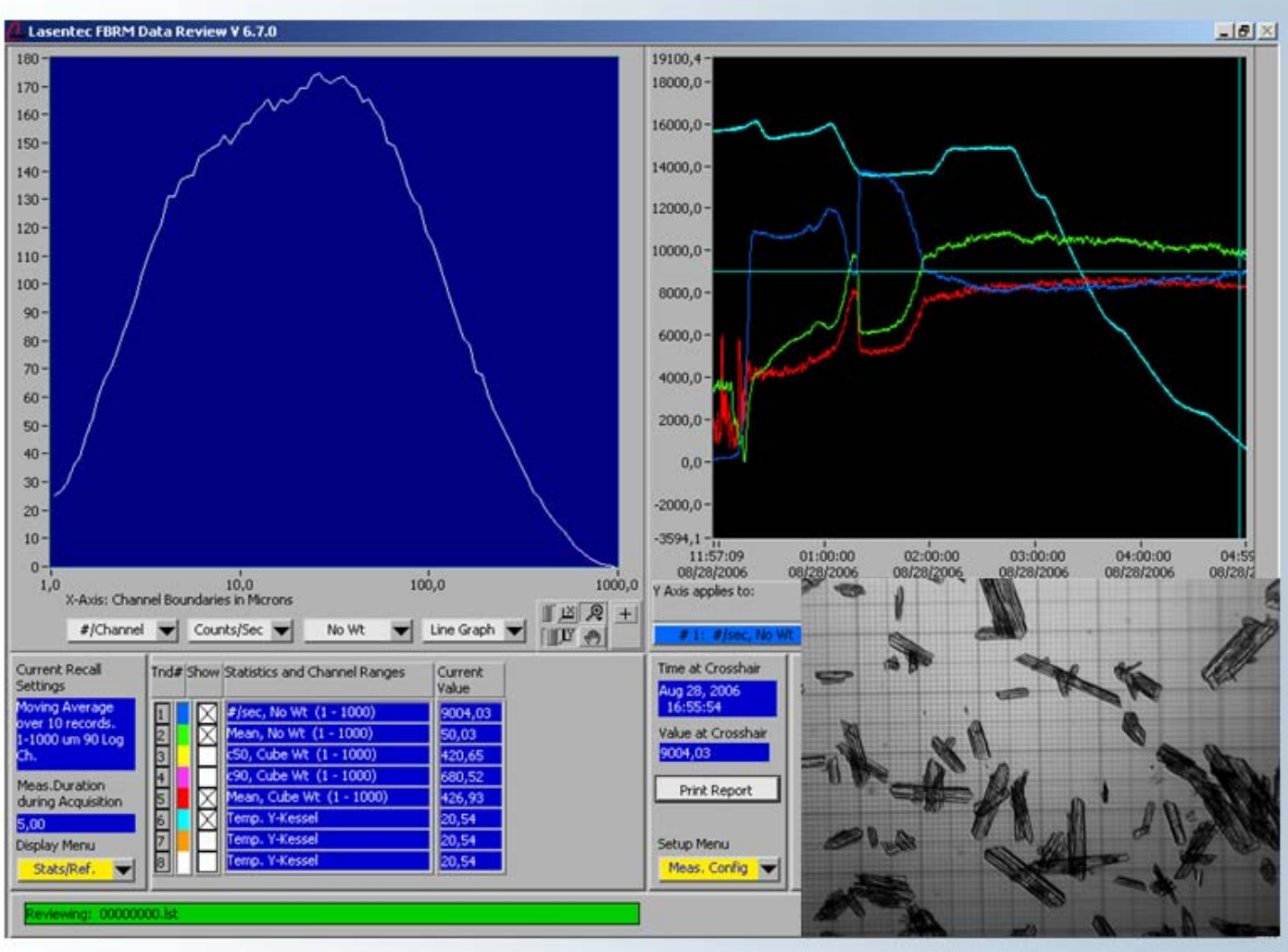
New One-Pot Procedure



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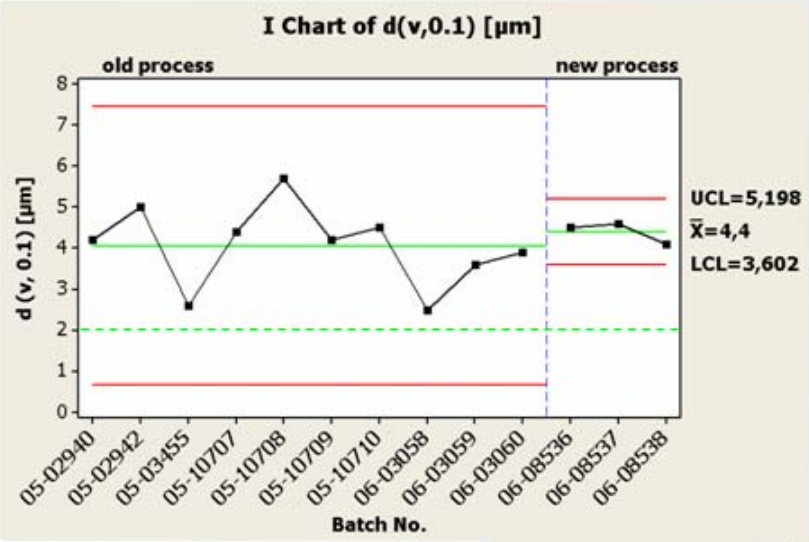
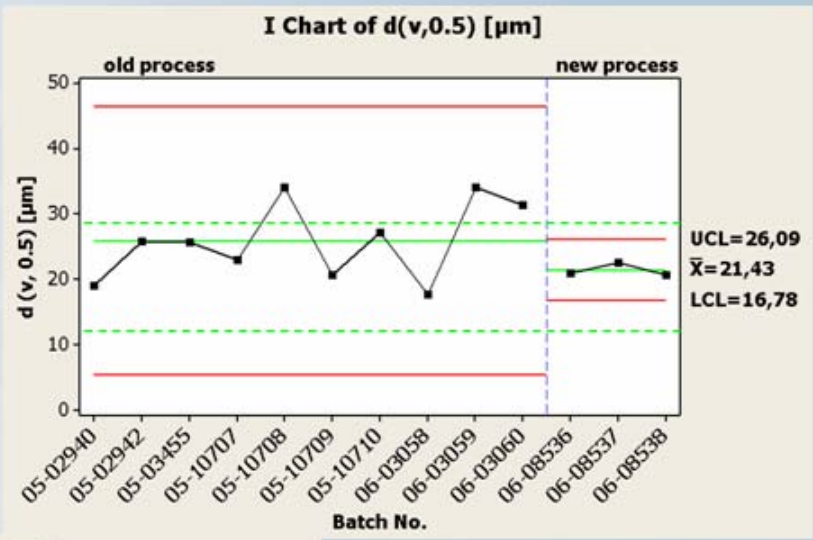
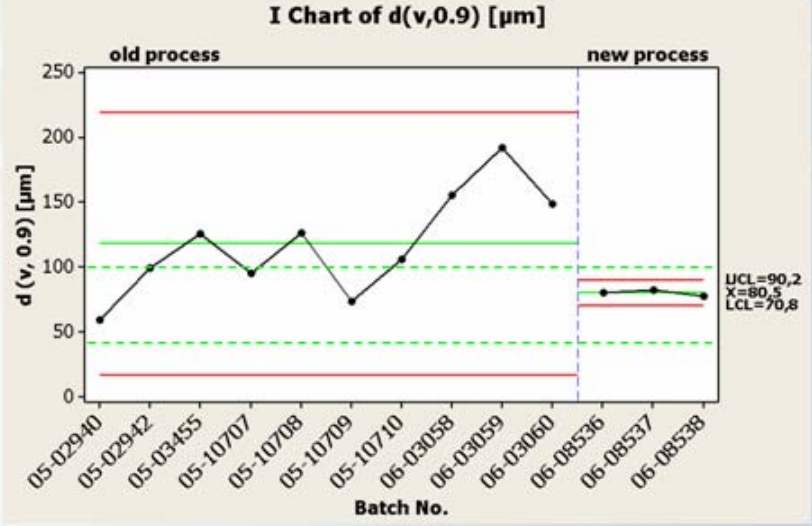
Product Particle Size Distribution







Alphapharm Specification:

d(v,0.1) > 2 µm

d(v,0.5) = 12-28 µm

d(v,0.9) = 44-100 µm

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Conclusion and Outlook

- Feucht was capable to optimize the process with Lasentec FBRM® on plant scale among the first at Pfizer
- Stable process with an extremely narrow particle size distribution
- Cycle time reduction of 16 hours
- Yield improvement by 10% due to better crystallization
- Cost reduction by 20%

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Conclusions

- In situ PAT tools such as ATR-FTIR, FBRM and PVM are valuable for the fast and reliable determination of thermodynamic and kinetics properties of a given crystallization process and thus allow for a rigorous process development and optimization.
- PVM allows for the detection of multiple phases, components, shapes, and polymorphs while avoiding any sampling problems. The online microscopic images recorded by PVM can offer unexpected improvements in process understanding.
- FBRM chord length distributions can be used as a fingerprint at the end-point of the particulate process, thus it can help to ensure batch-to-batch consistency and simplifies scale-up.
- Finally, FBRM and PVM have an enormous potential for process optimization with respect to downstream issues and product properties and therefore assure fast ROI.

Questions and answers

For further application, product and technology information visit

www.mt.com/crystallization

OR

Contact us at autochem.marketing@mt.com

OR

+ 1.410.910.8500

Visit www.mt.com/webinars2007 for the AutoChem webinar schedule.