Process Analytical Technologies (PAT) and Quality by Design

- the Impact for Process Systems Engineering

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"To Honour the Life-long Contribution of
Professors Anastasios Karabelas and Stavros Nychas
to Chemical Engineering in Greece"

Symposium on New Frontiers in Chemical & Biochemical Engineering, Thessaloniki, 26-28 Nov 2009

Overview of Presentation

- An overview of some of the pharma-sector challenges
- Process Analytical Technologies:
  - Where have we come from? Where are we now?, Where are we going?
- Some challenges in spectroscopic data pre-processing and modelling
  - Applications in Crystallisation and other industrial problems
- Variability - Different Product Formulations, Recipes, Processing Units, Production Sites, Spectroscopic Probe Locations, ….
- Closing the Analytical Control Loop
- Closure

The EU provides 32% of the worlds chemicals manufacturing through some 25,000 enterprises of which 98% are SMEs which account for 45% of the sectors 'added value', and 46% of all employees are in SME

What does PAT, QbD and Real-Time-Release mean to an SME?

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Benchmarks for Pharmaceuticals Companies

PHARMACEUTICAL BENCHMARKS			
KPI's	**Present Pharmaceutical Industry**	**A Winning Pharmaceuticals Plant**	**A World Class Pharmaceuticals Manufacturing Plant**
Stock Turn	3 to 5	14	50
OTIF	60% to 80%	97.4%	99.6%
RFT	85% to 95%	96%	99.4%
CpK	1 to 2	3.5	3.2
OEE	30%	74%	92%

Stock Turn - this is the total turnover on the site at manufacturing price divided by all the stocks on the site on the same basis. Stocks include finished goods, work in progress, and purchased raw materials; ***On Time in Full (OTIF) delivery*** - this is the percentage of orders that are satisfied on time in full with zero defects; ***Right First Time (RFT) -*** this is the percentage of the products that at the point of manufacture are delivered right first time with no defects; ***CpK -*** is a statistical process measure on the variability of the product; ***Overall Equipment Effectiveness (OEE) -*** this measures how effectively the manufacturing equipment is used.

Benson R.S, From World Class Research to World Class Manufacturing: the Challenges, Pharmaceutical Eng. Sept/Oct 2005

PAT and QbD

- **QbD:** "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management."

  Definition in ICH Q8R, Annex to ICH Q8: 'Pharmaceutical Development'

- **PAT:** "A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality."

  Definition in ICH Q8: 'Pharmaceutical Development'

Courtesy Staffan Folestad AstraZeneca, APACT09

Design Space and Quality

- **Design Space:** "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. …Design space is proposed by the applicant and is subject to regulatory assessment and approval.."

  Definition in ICH Q8: 'Pharmaceutical Development'

- **Quality:** "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity."

  From ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

Courtesy Staffan Folestad AstraZeneca, APACT09

Real Time Release (RTR)

- "**Real Time Release Testing**: The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls."

  ICH Q8(R1), Nov 2008

- …emerging revision of CPMP Guidance on Parametric (incl Real-Time Release)…

Courtesy Staffan Folestad AstraZeneca, APACT09

The Principles of a 'Process' Systems Base Approach

- RTR is a Systems Approach to *Designing and Building in Quality (i.e. QbD)*
- Key is a *Mechanistic Process Understanding*
- As an outcome of a *Risk Assessment* an *In-Process Control Strategy* can be implemented. Models are developed to verify process outputs and product parameters can be predicted
- The *Quality of the Product* can be assured by evaluation of an *RTR Scheme* based on *Risk Assessment*

Courtesy Staffan Folestad AstraZeneca, APACT09

Where are we in

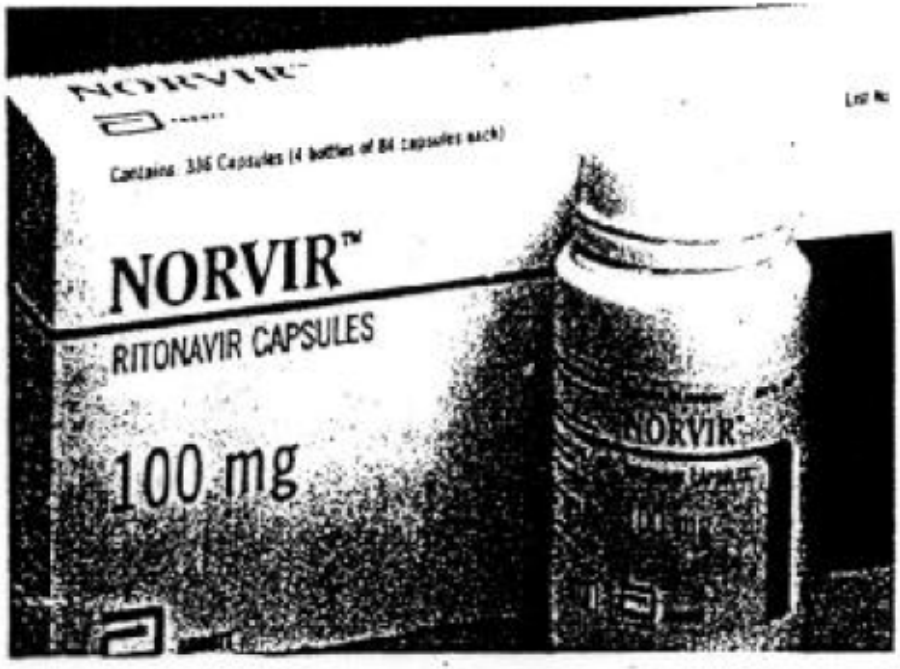
Process Analytics and Control Technologies?

Heterogeneity

- Heterogeneity can be influenced by the manufacturing process.
  - Different product variants arising
    - from varying raw materials
    - from upstream processing issues
    - from downstream processing changes
    - from utilities issues
    - ……

Impurities and Polymorphism (Where we were in 1998)

Capsules of Abbott Laboratories' protease inhibitor Norvir (ritonavir) are likely to become unavailable by the middle of August. The company has a problem with the manufacture of the anti-HIV capsules which it cannot resolve at present.



Capsules unlikely to be available from mid-August

The problem relates to "undesirable" crystal formation. Abbott says that a series of recent production batches of Norvir capsules failed the approved test for dissolution, and were not released for marketing. Investigation of the reason for the failure showed the presence of a new crystalline form of ritonavir which affects the way it dissolves, and possibly its absorption. Retained samples from a number of marketed batches of capsules were examined and there was no evidence of the unwanted crystalline form.

Mr Mark Haywood (managing director, Abbott Laboratories) said that teams were working round the clock to try to resolve the issue, but at present the company had no idea why the problem was occurring.

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Impurities and Polymorphism

- Impurities effect nucleation and growth processes, and hence can stabilise meta-stable polymorphic forms.

- As product purity improves during process chemistry work-up, the “stable” polymorphic form can change !

- e.g. RITONOVIR aids drug which changed from anhydrous to hydrate crystal after launch:

  - with lower solubility and hence bio-availability.

  - **product was withdrawn for a year and reformulated.**

  - new FDA approval needed – **mega cost implication !**

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Atlanta District Office
60 8th Street, N.E.
Atlanta, Georgia 30309

1. Failure to establish and follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess as required by 21 CFR § 211.100(a).

. Product testing alone is not sufficient to assure that a process consistently produces a product with predetermined specifications. Adequate process design; knowledge and control of factors that produce process variability: and successful process validation studies, in conjunction with product testing, provide assurance that the process will produce a product with the required quality characteristics.

Also, it is not acceptable to disregard the findings in one of the lots by stating that another lot made under the same process had sample results that met the criteria. To the contrary, this is an indication that you have not identified, and are unable to control, those factors that cause variability in the process. This also indicates that you lack a robust process design. Consequently, you do not have a high level of assurance that the process is in a state of control and is capable of consistently producing a product

The Impact of Multi-dimensionality

Variability with Different Scales,

Product Formulations / Recipes,

Different Spectroscopic Probe Locations,

Different Processing Units,

Across Different Production Sites, …

Multi-Recipe (Formulation) Data

- ***Industrial challenge – one weeks production:*** 50 different products. 40 different recipes, 5 different production units. Example application of multiple group PCA and PLS with two formulations. Each process mixer is also considered as a separate *'formulation'*, hence the process model has 4 distinct groups.

Recipe	Group	Mixer	Number of Batches	Raw Materials	Quality Variables	Process Variables
1	1 (☆)	1	19	23	1	120
	2 (+)	2	21	23	1	120
2	3 (o)	1	20	17	1	90
	4 (x)	2	29	17	1	90

- **Note:** Formulation 2 has fewer raw materials and fewer process variables than Formulation 1

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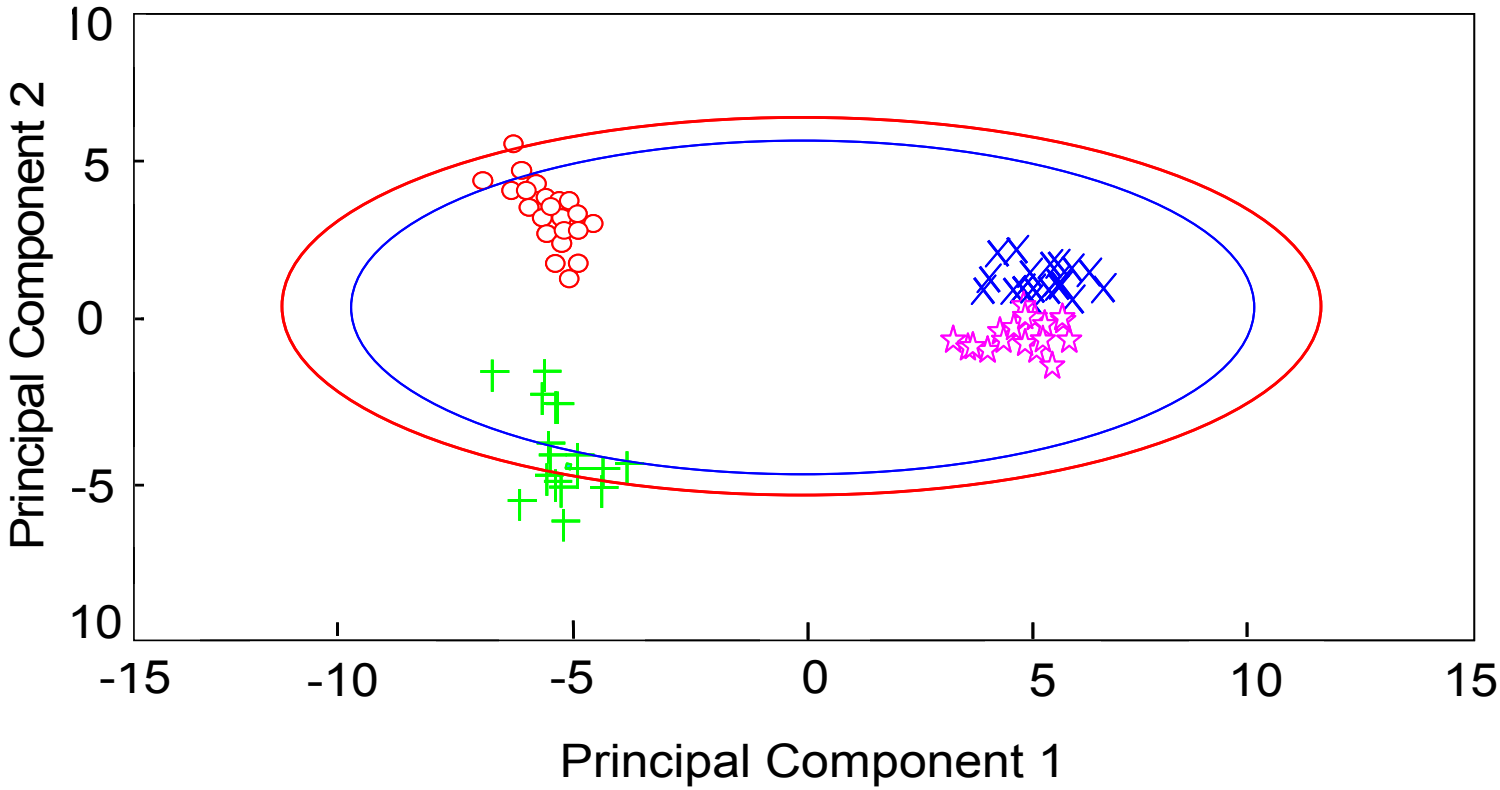
Impact of Different Formulations

- The model contains within and between group variation.
- Subtle process events cannot be detected; the greater the number of distinct groups in the data set, the greater the impact of between group variation.

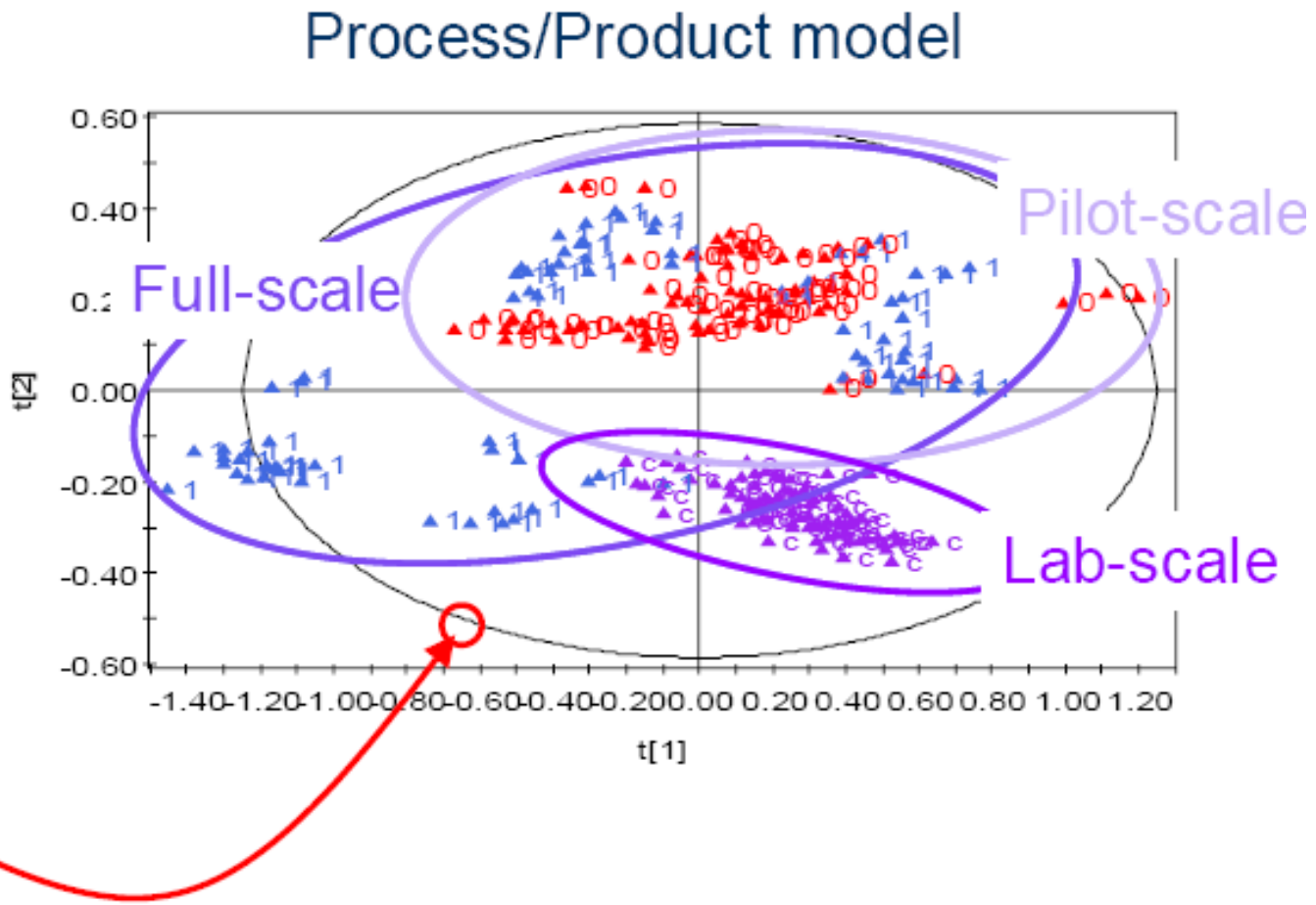


Courtesy Unilever, Vlaardingen

The Impact of Multidimensionality in PAT, QbD (Hence a Process Systems approach)

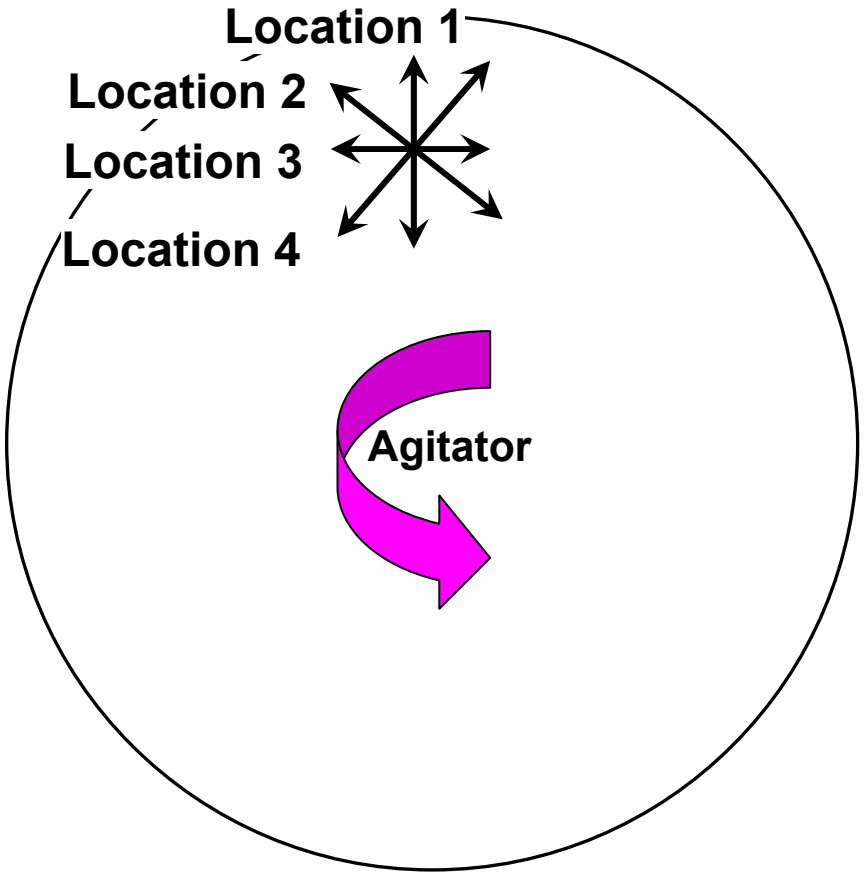
Example of multivariate model where all batches manufactured at three different scales (lab, pilot, full production) yield product of intended Quality!

Designs Space is thus significantly wider than the confidence interval In this example!

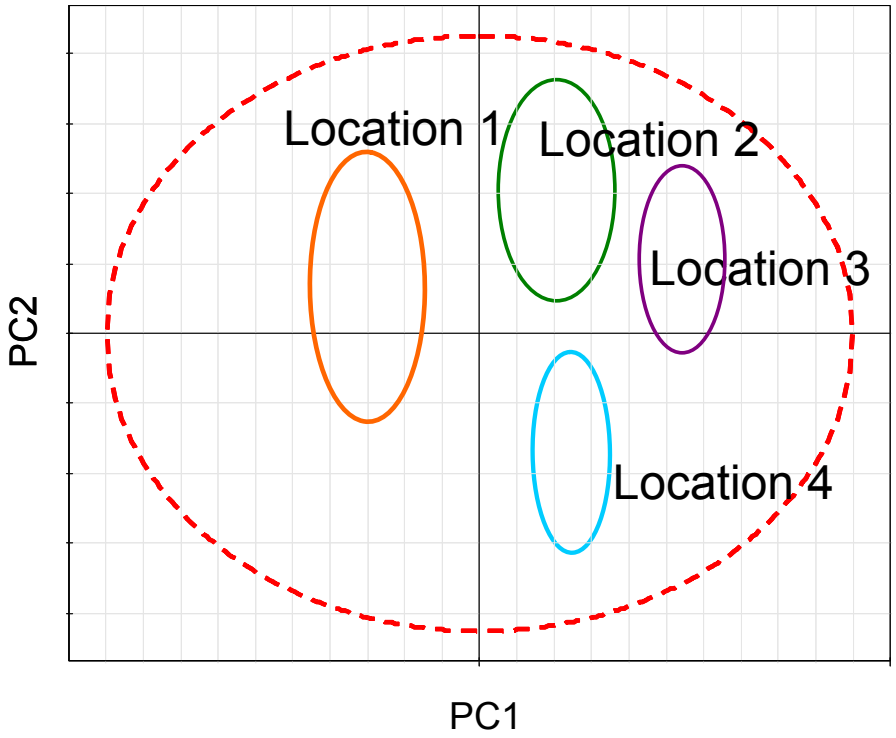


Courtesy Staffan Folestad AstraZeneca, APACT09

Impact of Spectroscopic Probe Location in a Reactor Vessel



Spectroscopic Probe Location



PCA Plot of Measured Spectra

A multi-group ‘generic’ calibration model can help overcome probe location issues

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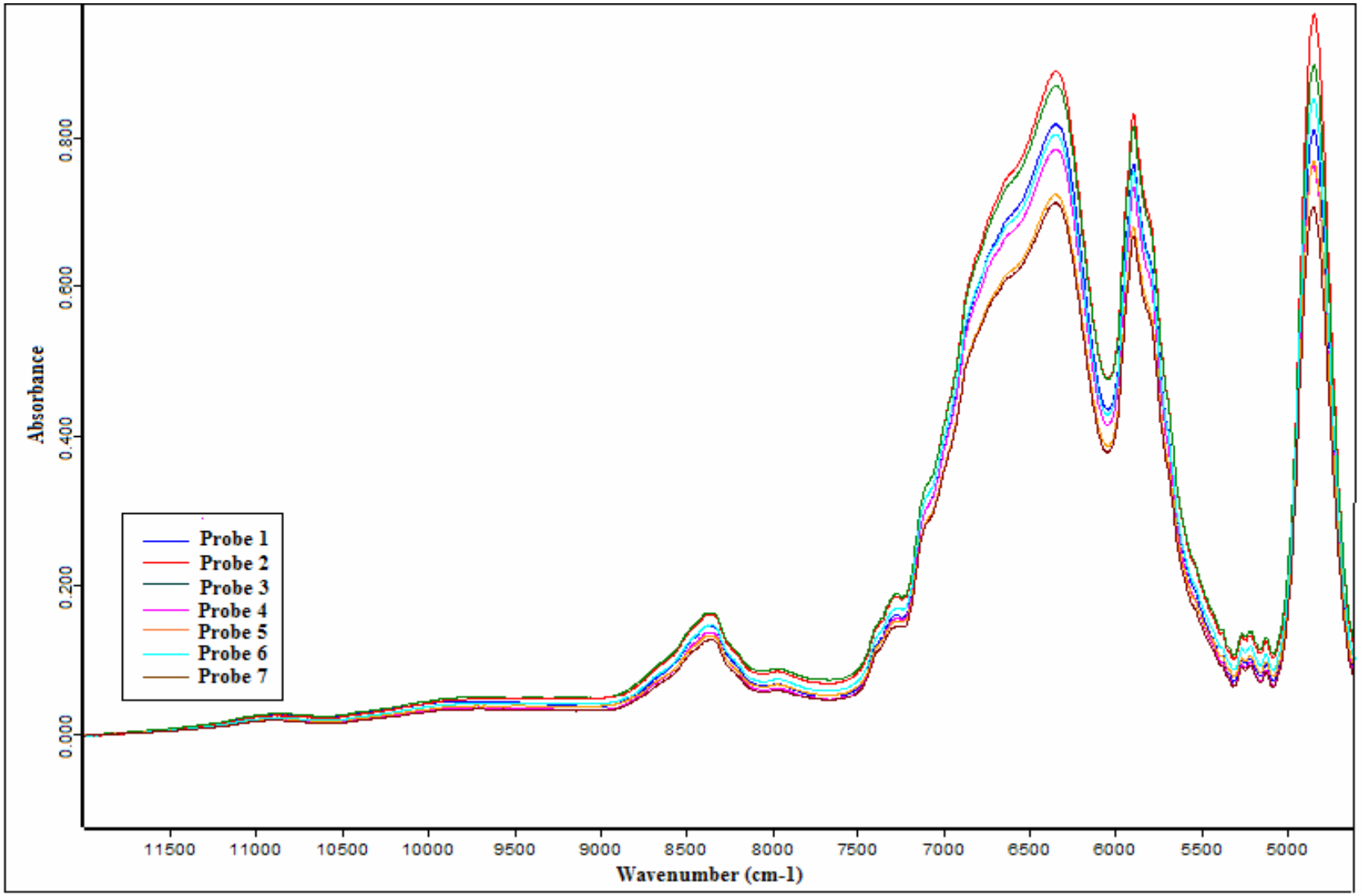
The Impact of Inter-probe Variability



- Spectra from different probes are distinct
- Inter-probe variability is the greatest source

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Variability – Modelling and Calibration Challenges

- **Process Issues:**
  - Scaling up and reactor size and characteristics issues
  - Multiple or changing formulations (recipes)
  - Cell improvement; cell line changes; media changes
  - Equipment characteristics; site-to-site process differences, etc
  - Fluctuations in both control and external process variables
  - Limited experimental data due to time and cost limitations – hence small data sets from which to build models – learn from medical statistics and statistics used in clinical trials.

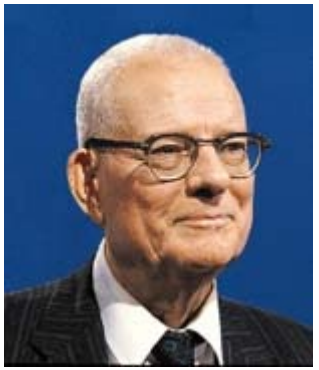
- **Analytical Issues:**
  - Separating absorbance from multiplicative light scattering effects caused by the variations in optical path length
  - Inter probe variability: impact of component variance on PLS calibration – can probe differences be accomodated or eliminated?
  - Can calibration models be made generic for different production unit operations / production lines?

Variability (or PAT) by Edwards Deming

Cease reliance on mass inspection to achieve quality.

Eliminate the need for mass inspection by building quality into the product in the first place.

Dr W. Edwards Deming
(Circa 1980s)



“Learning is not compulsory, …

…. Neither is survival”

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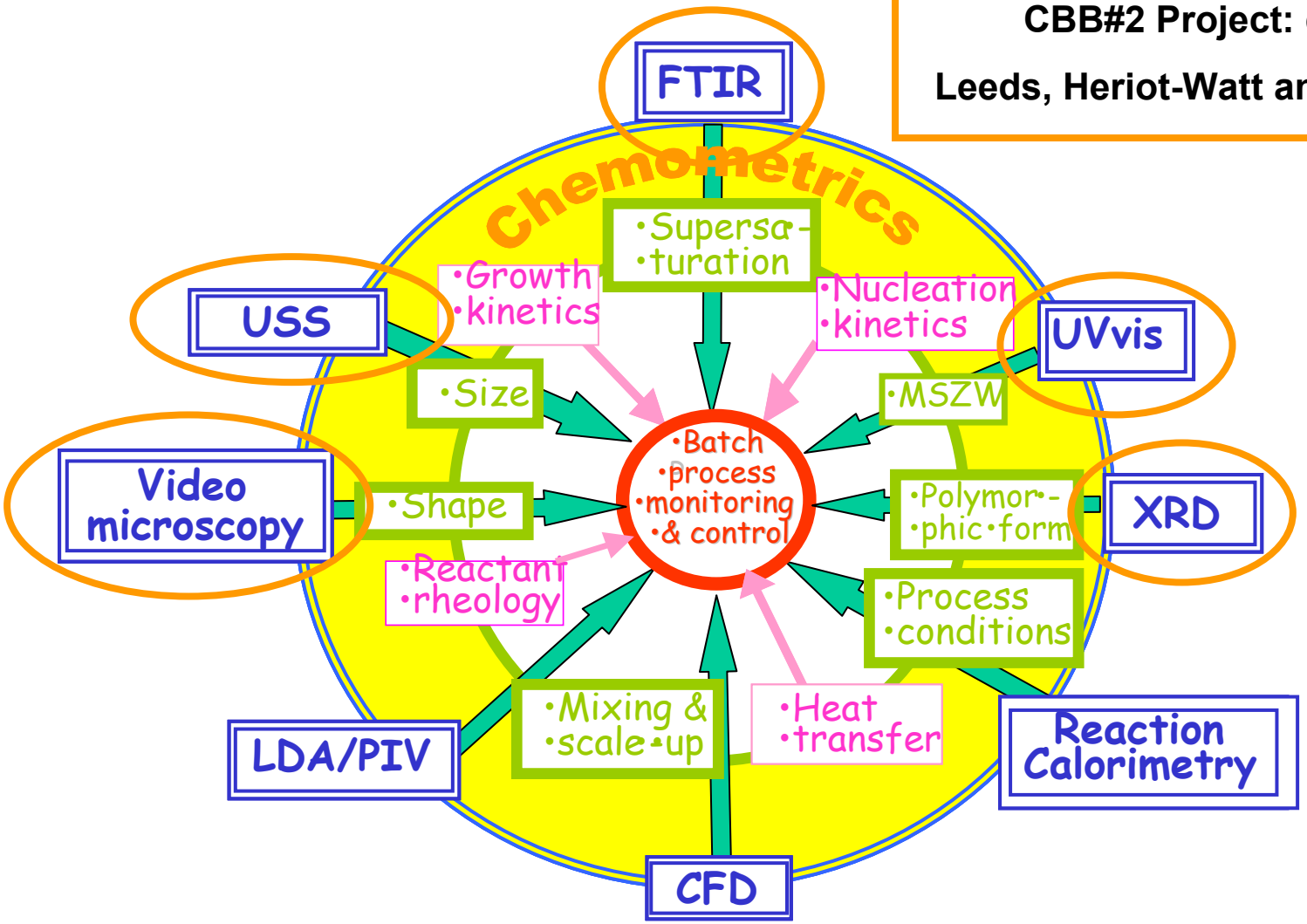
In-Process Analytics & Process Control

CBB#2 Project: collaboration with

Leeds, Heriot-Watt and Newcastle University



Partners

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BNFL
Clairet Scientific
DTI
EPSRC
GlaxoSmithKline
HEL
Malvern Instruments
Pfizer
Syngenta

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Issues in Down-Stream Production Processes (e.g. in Crystallisation)

- ***Multi-sourced*** materials properties making up feed-stocks impact on product processability:
  - hence on the properties of any formulated products made downstream.
  - I.e. variability in feedstock results in variability of products.

- Important solid-form properties:
  - physical - particle size / shape, hardness, density and plasticity
  - chemical - purity, polymorphic form, crystallinity, hygroscopicity

- **Clear need for flexible processes developed through QbD and controlled using PAT to ensure reproducible processes producing highly consistent quality product suitable for Real-Time-Release into the Patient.**

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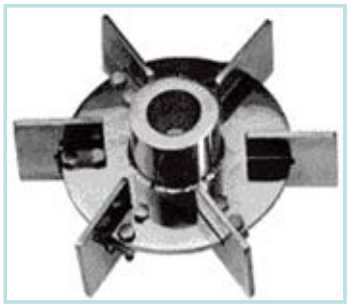
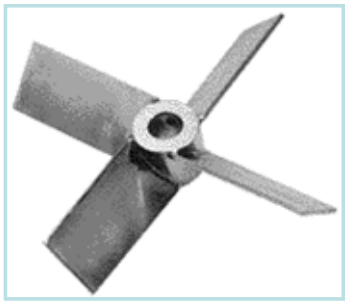
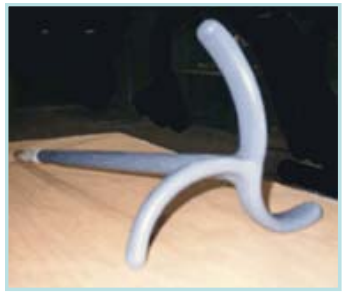
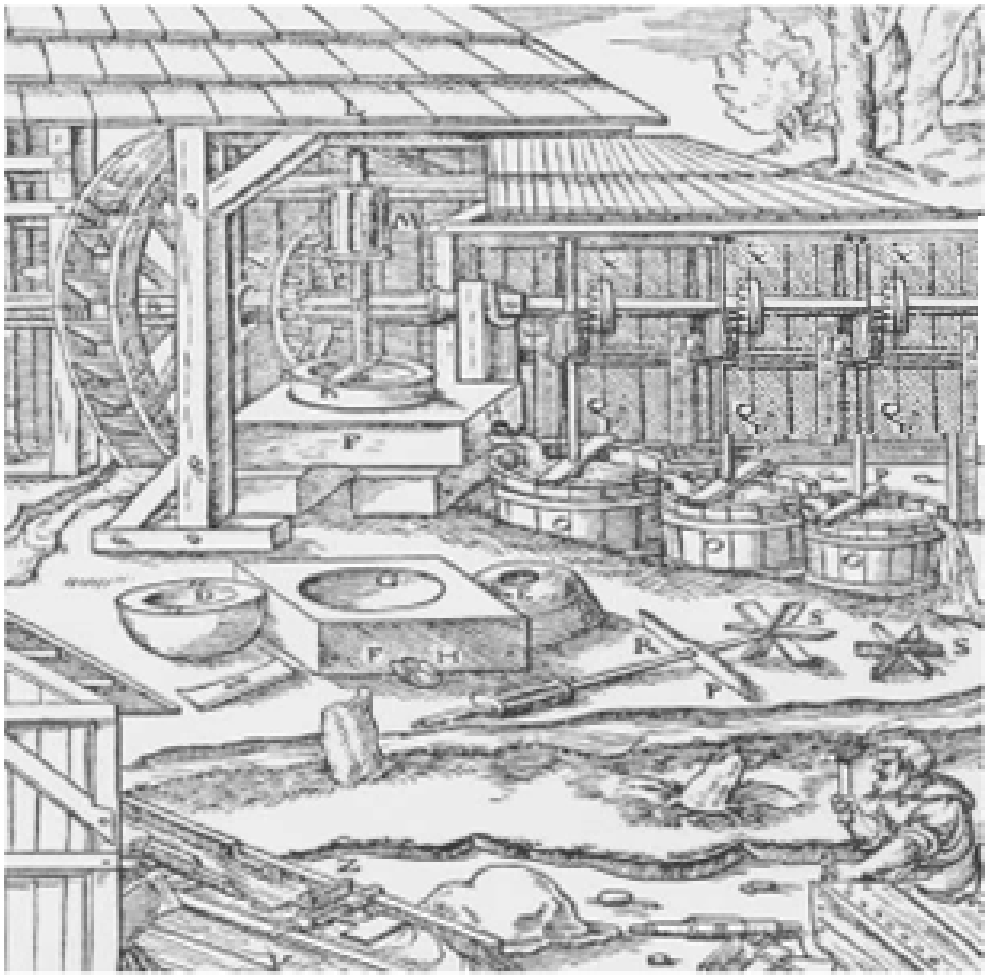
Reactor Scale-Up: Effects on Nucleation Processes

- Nucleation promoted via sites within crystallisation reactor such as at:
  - Walls of vessel & at liquid free surfaces
  - Stirrer and reactor internals such as baffle surfaces and impellers

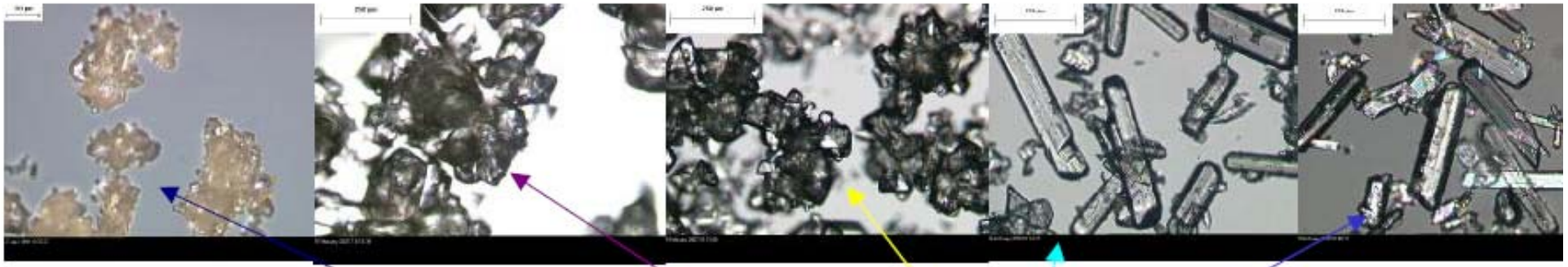




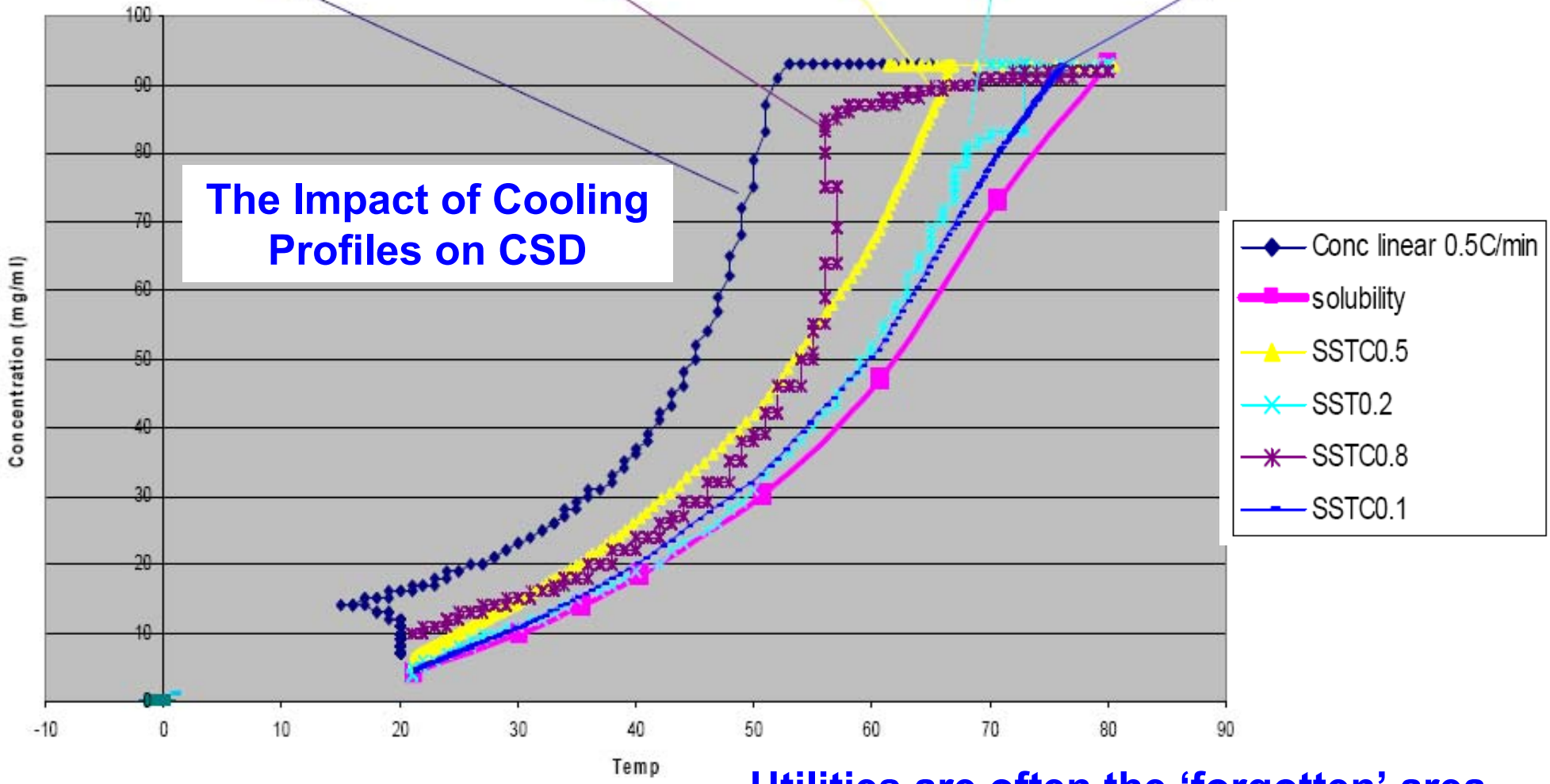




- Hetero-nuclei, e.g. impurities, particulates, seeds etc.
- Particle/particle and reactor/particle collision attrition fragments
- Process in-homogeneities due hydrodynamics and reactor mixing



The Impact of Cooling Profiles on CSD



Utilities are often the 'forgotten' area

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Advanced Chemometric Methods
For Assured Process Analytics Applications

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Fluctuations in External Variables on Calibration Models

- In process analytical applications, spectral measurements can be subject to changes in process temperature, flow turbulence, compactness, and other external variations.

- Typically, variations of external variables influence spectral data in a non-linear manner which leads to the poor predictive ability of bilinear calibration models on raw spectral data.

- The influence of external variables on spectral data we classify into two different modes:
  - **multiplicative influential mode, and**
  - **composition-related influential mode**

- A new chemometric method, Extended Loading Space Standardization (ELSS), has been developed to explicitly model these two kinds of influential modes.

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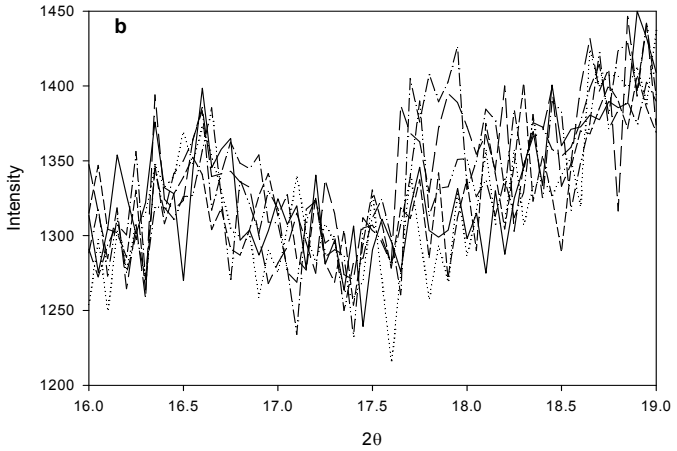
Spectral Calibration Issues

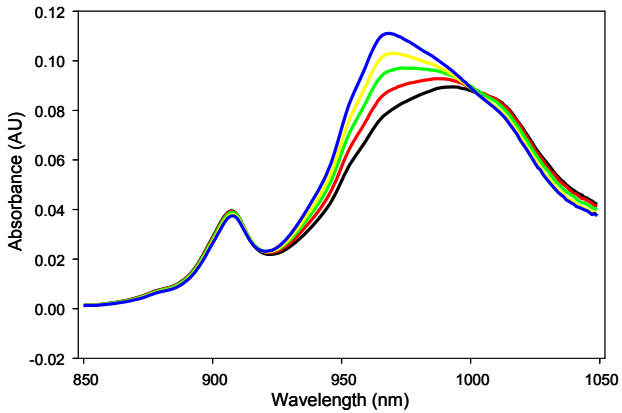
- Spectroscopic measurements in chemical and pharmaceutical processes are always liable to fluctuations in both control and external process variables.
- This can result in noisy spectra, non-linear shifts, broadening in spectral bands and multiplicative light scattering perturbations.

Noisy spectra



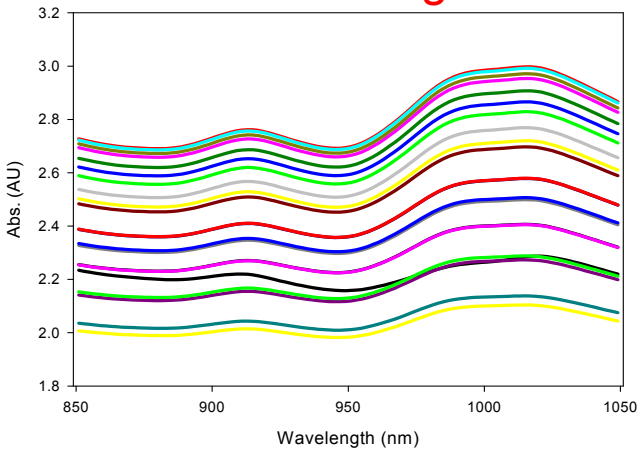
X-ray diffraction profiles of mannitol-methanol suspensions with the content of mannitol varying from 0.0% to 5.0% g/ml.

Shift and broadening in spectral bands



Five NIR spectra for a ternary mixture sample measured at five different temperatures

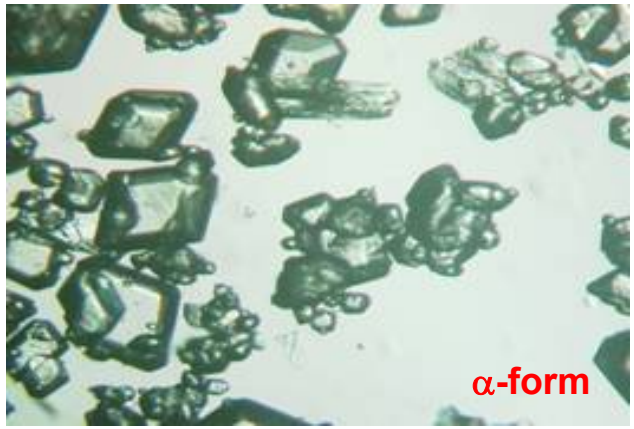
Multiplicative light scattering



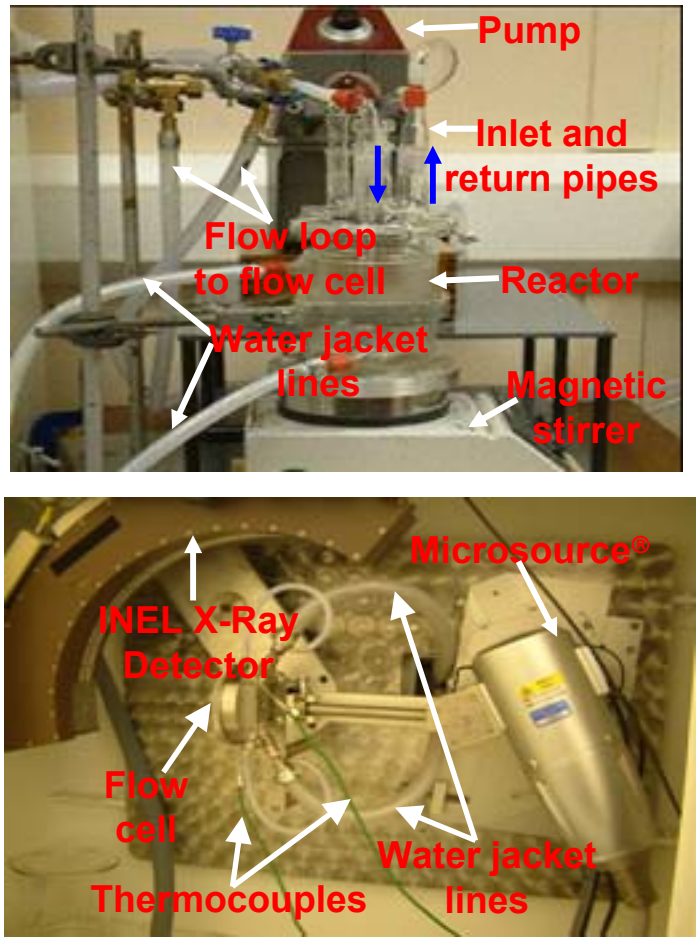
20 NIR spectra of a powder mixture measured under different sample compactness

Smoothed Principal Component Analysis (SPCA)

- **SPCA:** Enhancing the Signal to Noise Ratio of X-ray Diffraction Spectra of Glutamic acid-methanol suspensions system.



L-Glutamic acid morphology: prismatic α-form and needle-like β-form crystals



Experimental set-up and on-line X-ray diffraction system

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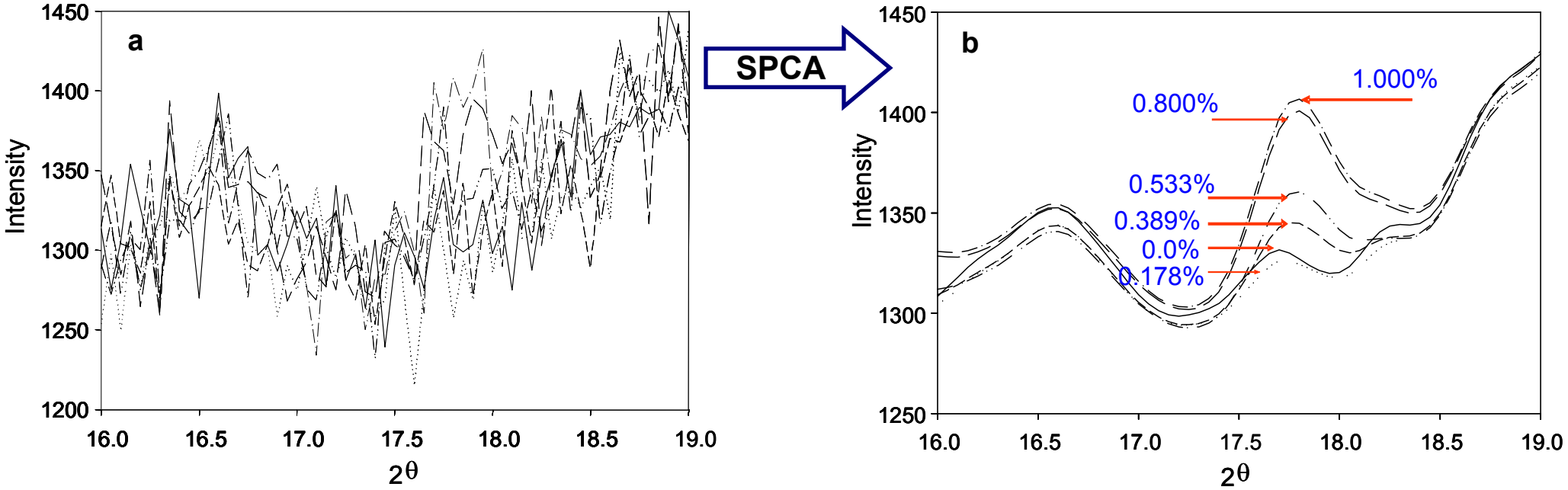
Smoothed Principal Component Analysis (SPCA)

- ***Enhancing signal-to-noise ratio***

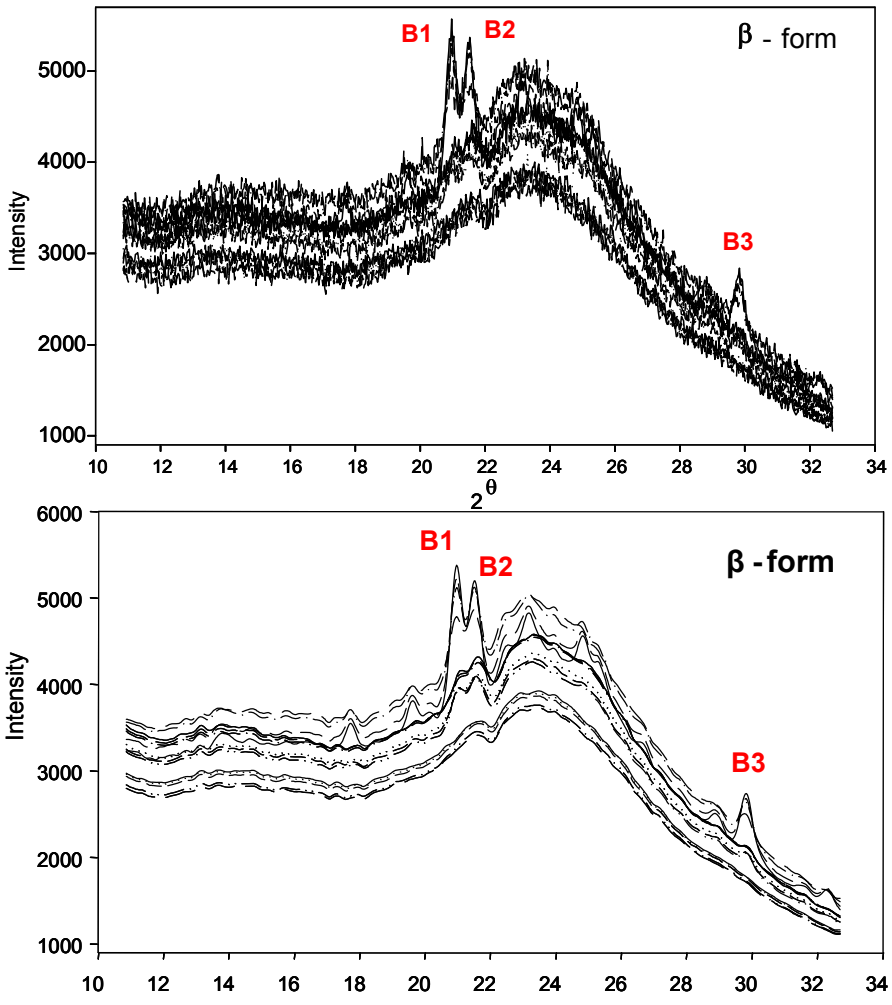
$$\mathbf{X}^{\mathrm{T}}\mathbf{X}\mathbf{r}_i = \lambda_i \times (\mathbf{I} + k \times \mathbf{Q}^{\mathrm{T}}\mathbf{Q})\mathbf{r}_i \qquad i = 1, 2, \cdots, m$$

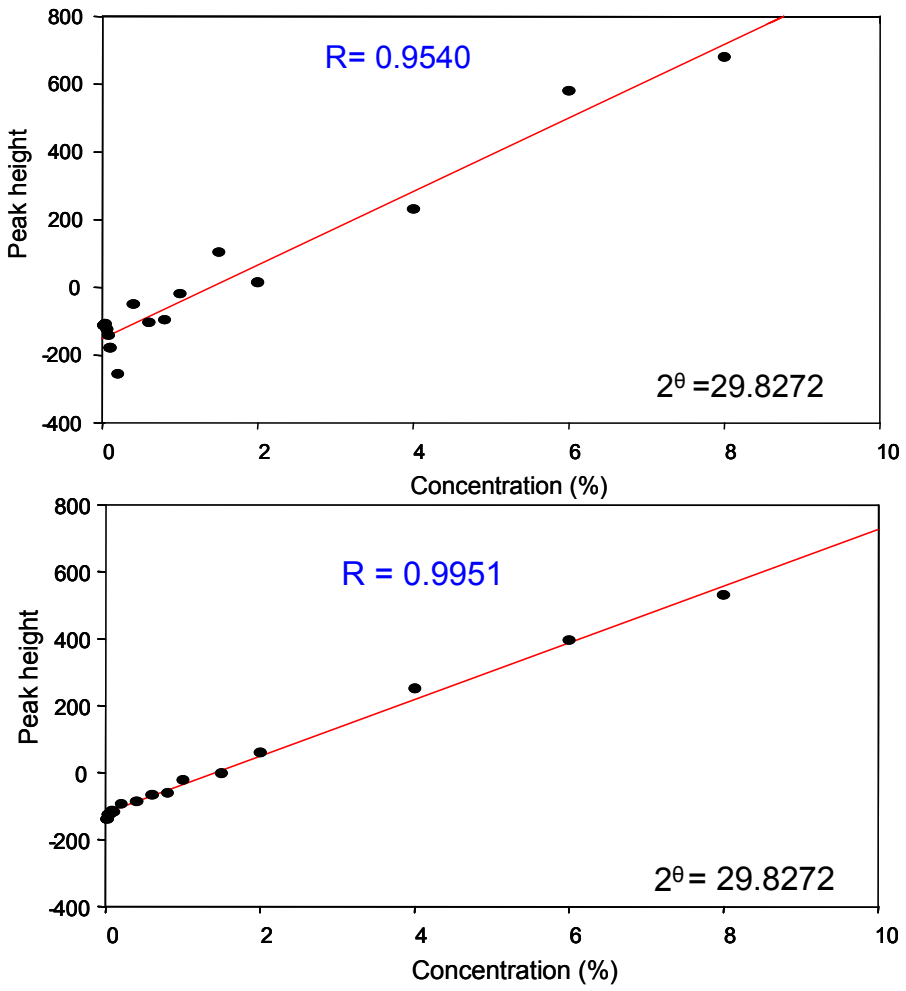
$$\mathbf{F} = [\mathbf{r}_1, \mathbf{r}_2, \cdots \mathbf{r}_c] \times [\mathbf{r}_1, \mathbf{r}_2, \cdots \mathbf{r}_c]^{+} \qquad \mathbf{x}_F = \mathbf{F}\mathbf{x} = \mathbf{F}\mathbf{x}_s + \mathbf{F}\mathbf{x}_n$$



Raw (a) and Processed (b) XRD profiles (by SPCA) for 6 XRD data sets of mannitol-methanol suspensions with the contents of mannitol equalling to 0.0%, 0.178%, 0.389%, 0.533%, 0.8% and 1.0% g/ml, respectively

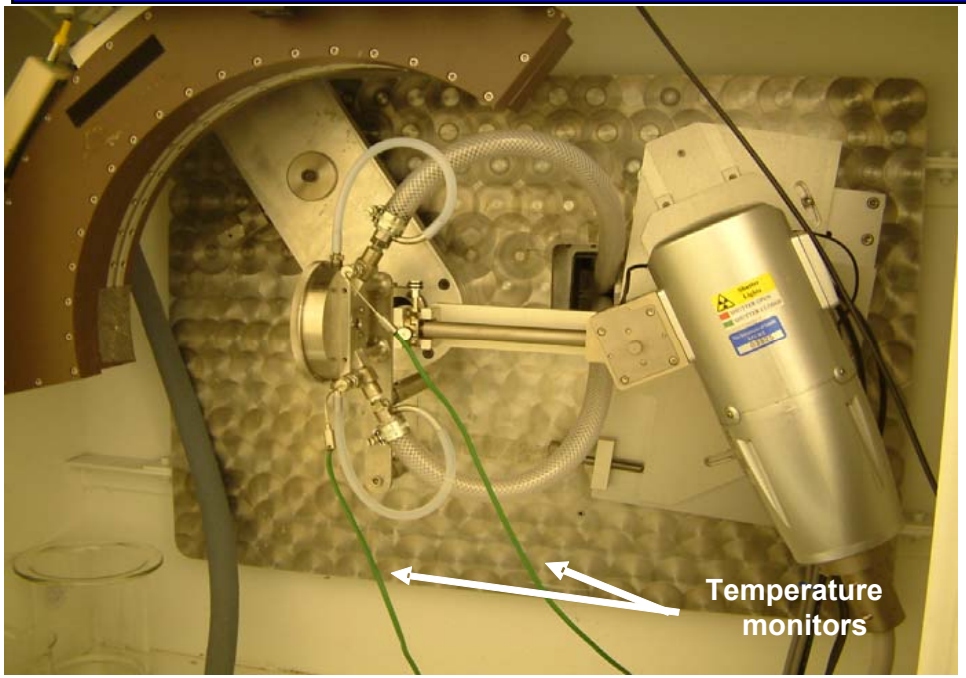
Case – SPCA in Morphology Monitoring





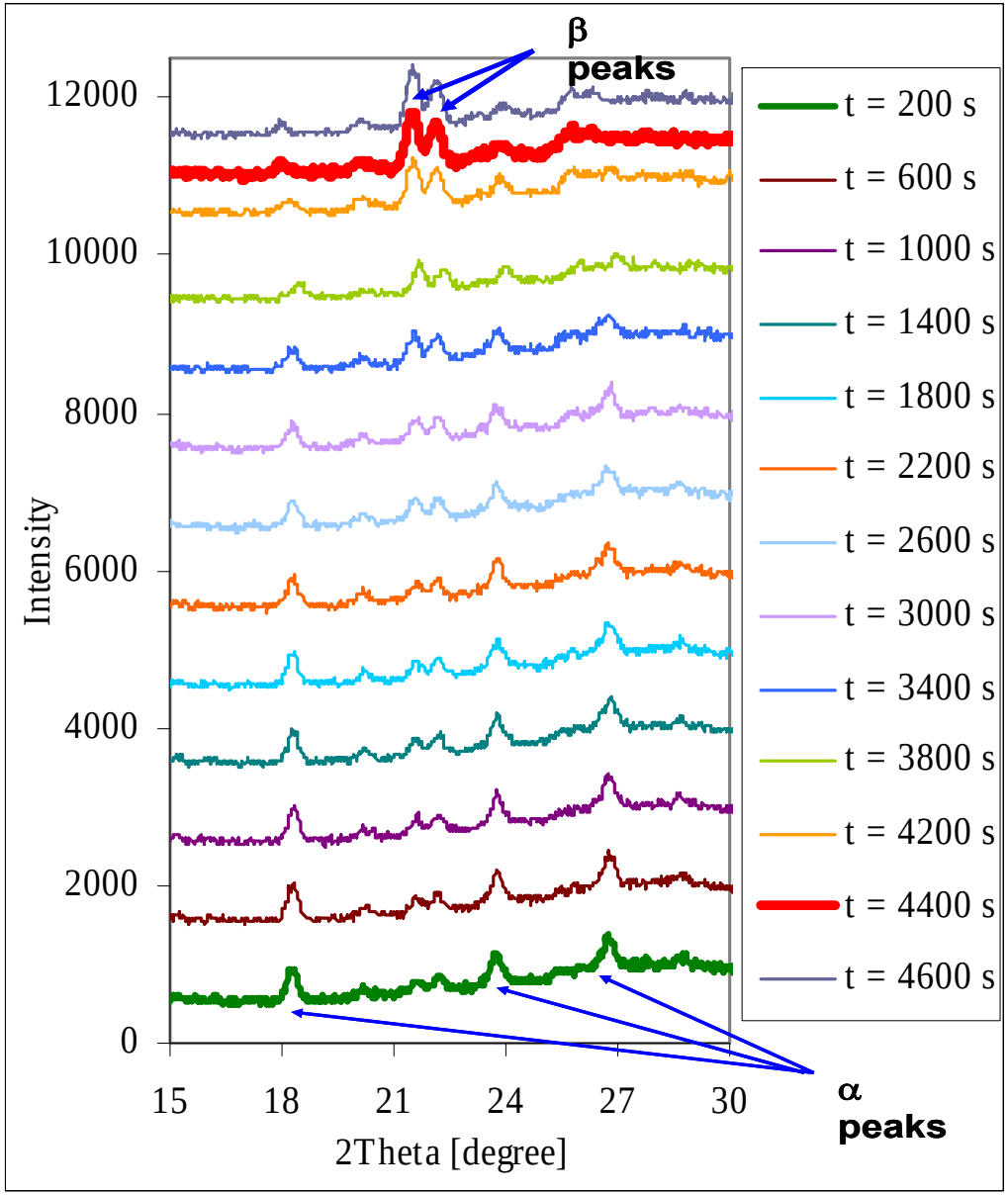
The raw (a) and pre-processed (b) XRD profiles of the beta form of GA-methanol slurries with concentration varying from 0.02% to 8.00%; The relationships between concentrations and peak heights at peaks B3 of the raw (c) and processed (d) spectra.

Bede MONITOR™ In-process XRD
Crystal Polymorph Monitoring & Control



System provides capability to monitor polymorphic form “in-process”, i.e. that unaffected by product separation prior to analysis.

Typically circa 1 wt % detectable via in-process XRD, much lower with advanced chemometric analysis (Smoothed PCA)



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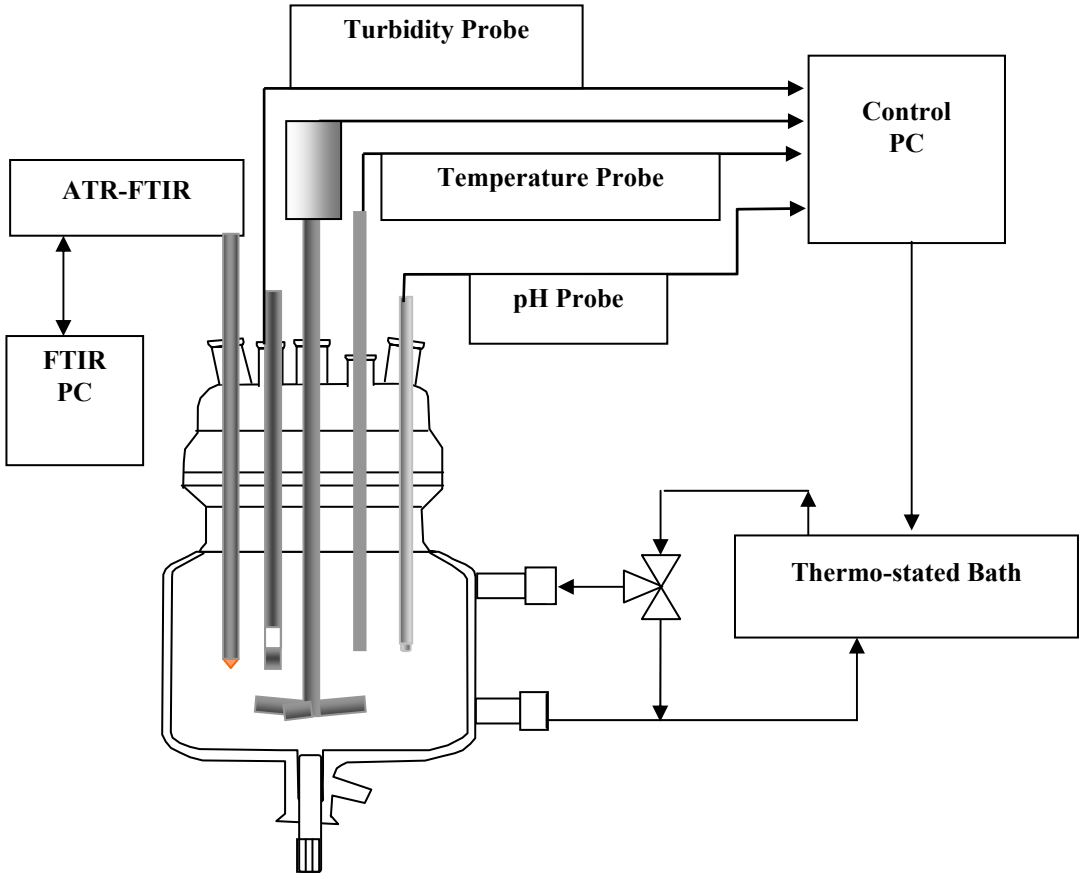
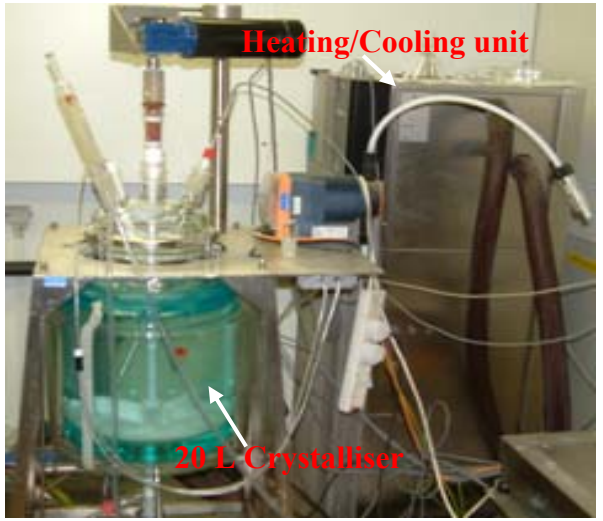
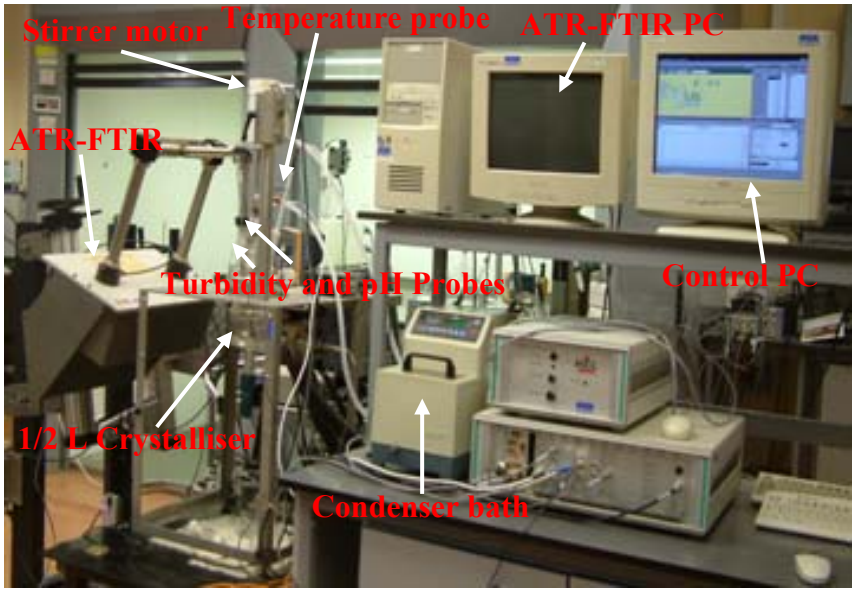
Loading Space Standardisation (LSS)

- Correcting temperature-induced spectral variations for ATR-FTIR data in crystallization process monitoring.







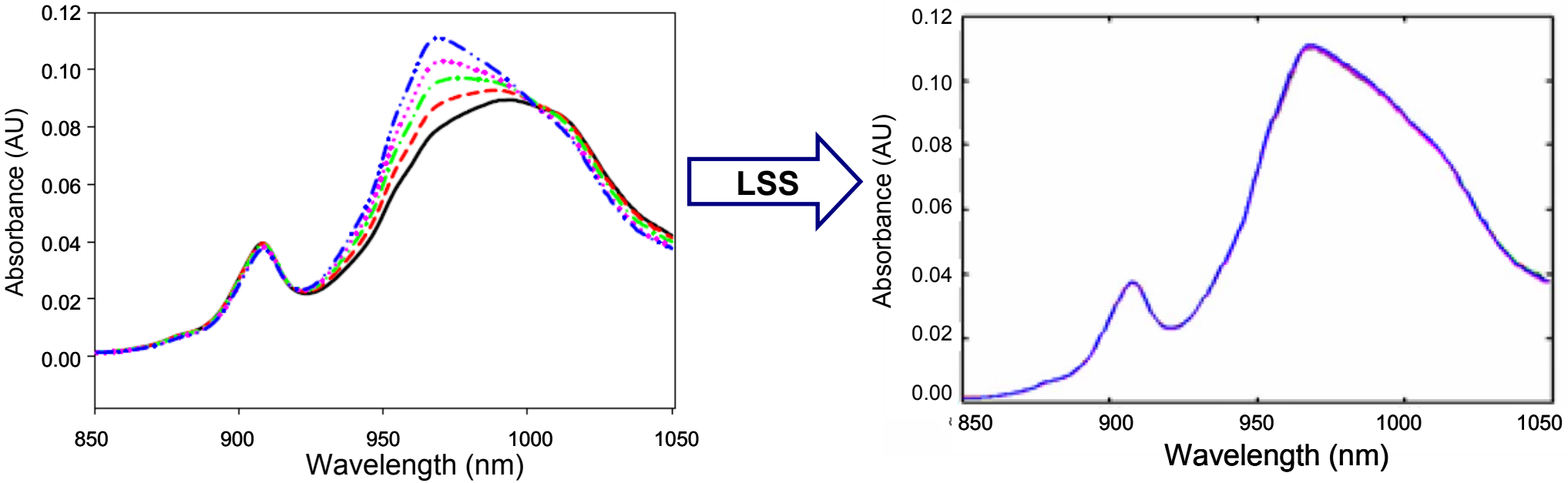
Loading Space Standardisation (LSS)

- ***Correcting non-linear shift and broadening in spectral bands caused by temperature fluctuations:***

$$\mathbf{x}_i(t_i) = \sum_{k=1}^{K} c_{i,k}\mathbf{s}_k(t_i) + \mathbf{e}_i(t_i)$$

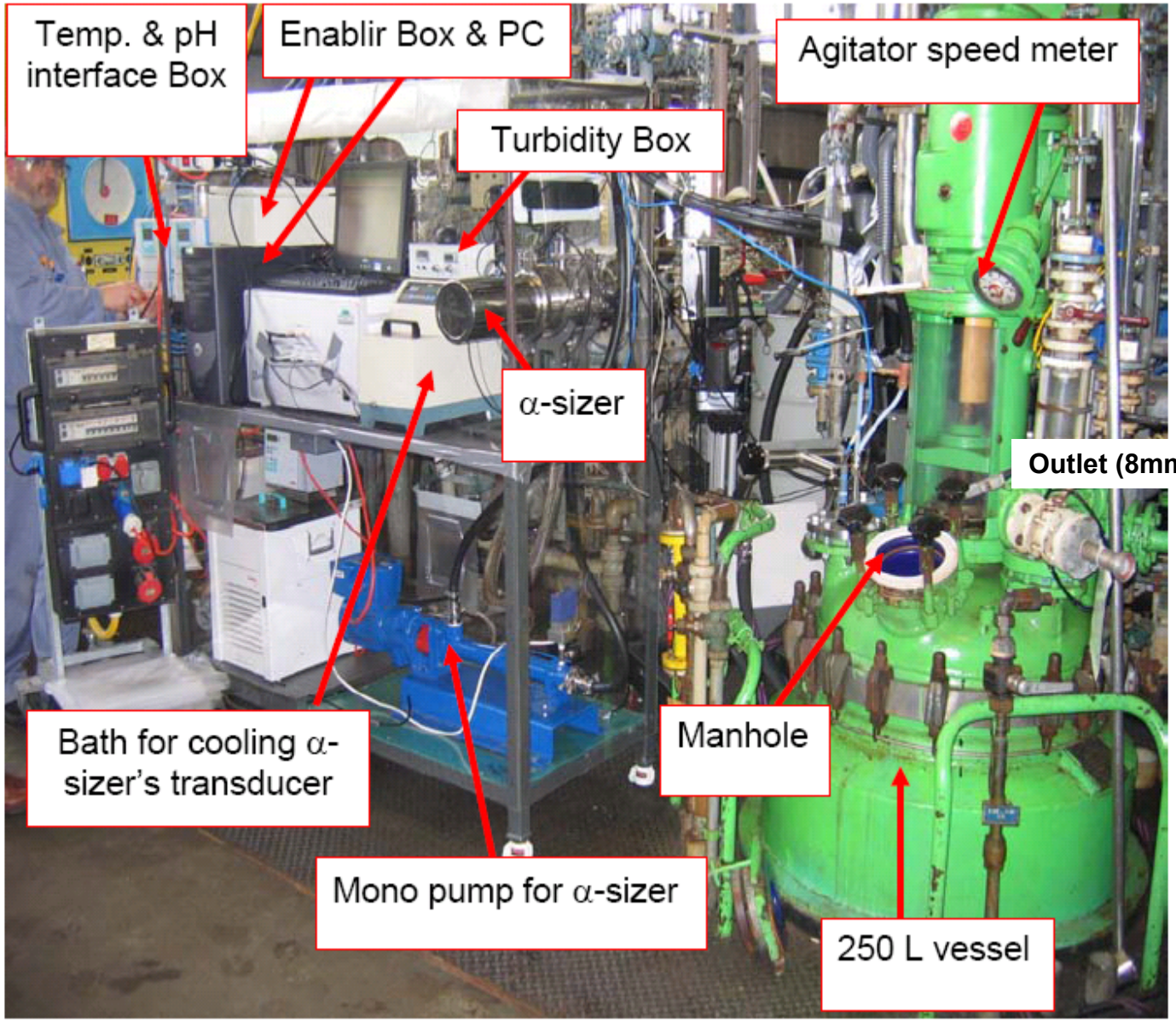
$$\mathbf{X}(t_1) \xrightarrow{PCA} \mathbf{TP}'(t_1)$$
$$\vdots \qquad \vdots \qquad \vdots$$
$$\mathbf{X}(t_m) \xrightarrow{PCA} \mathbf{TP}'(t_m)$$

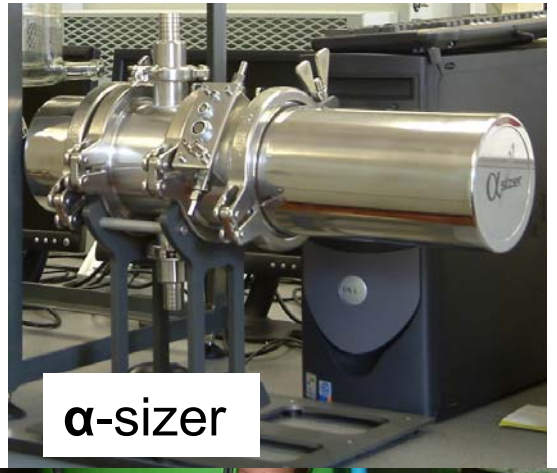
$$\mathbf{P}(t_i) \sim t_i \Rightarrow LSS \qquad \mathbf{x}(t_{test}) \xrightarrow{LSS} \mathbf{x}(t_{ref})$$

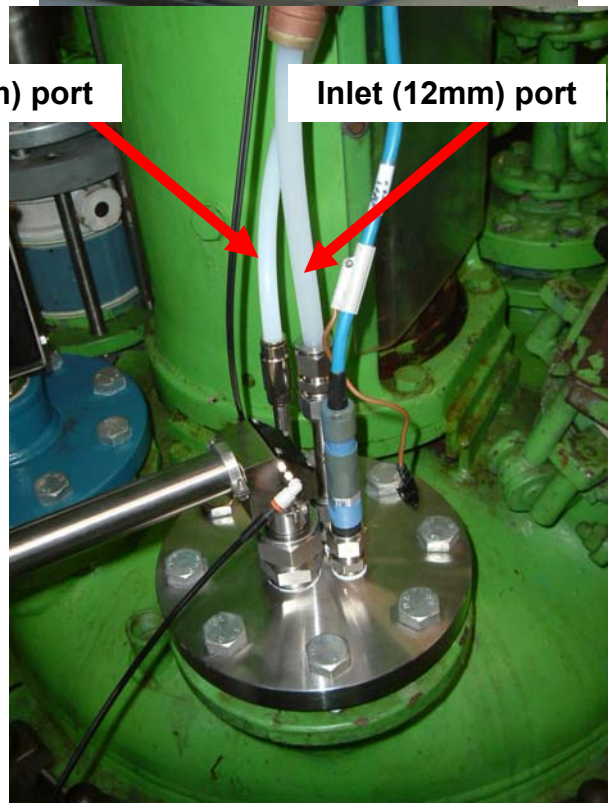


Ternary mixture 5 spectra measured at 5 different temperatures (black solid line: 30°C, red dash line: 40°C, green dash-dot line: 50°C, pink dotted line: 60°C, blue dash-dot-dot line: 70°C)

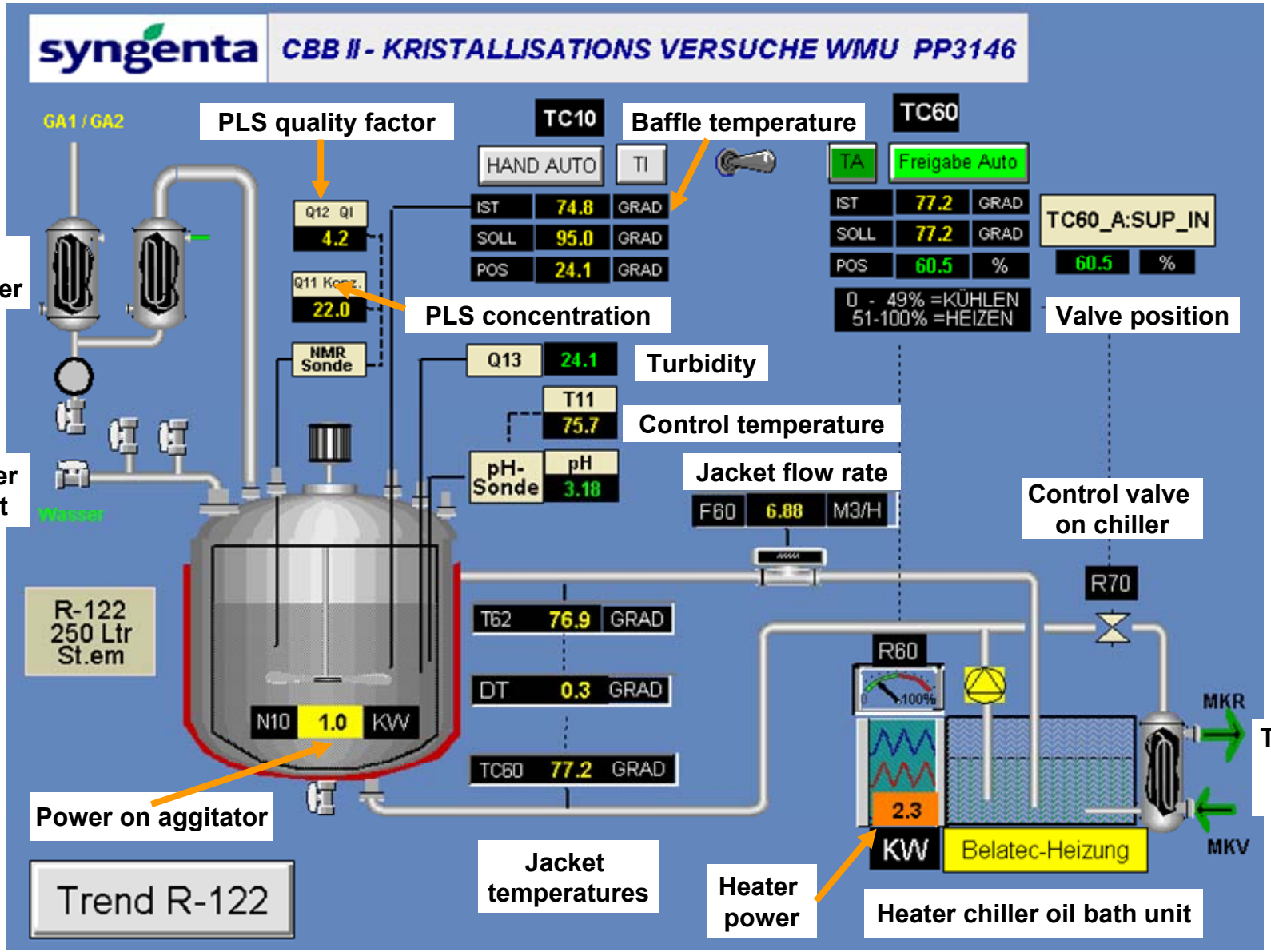
250l Pilot Plant Batch Agitated Vessel



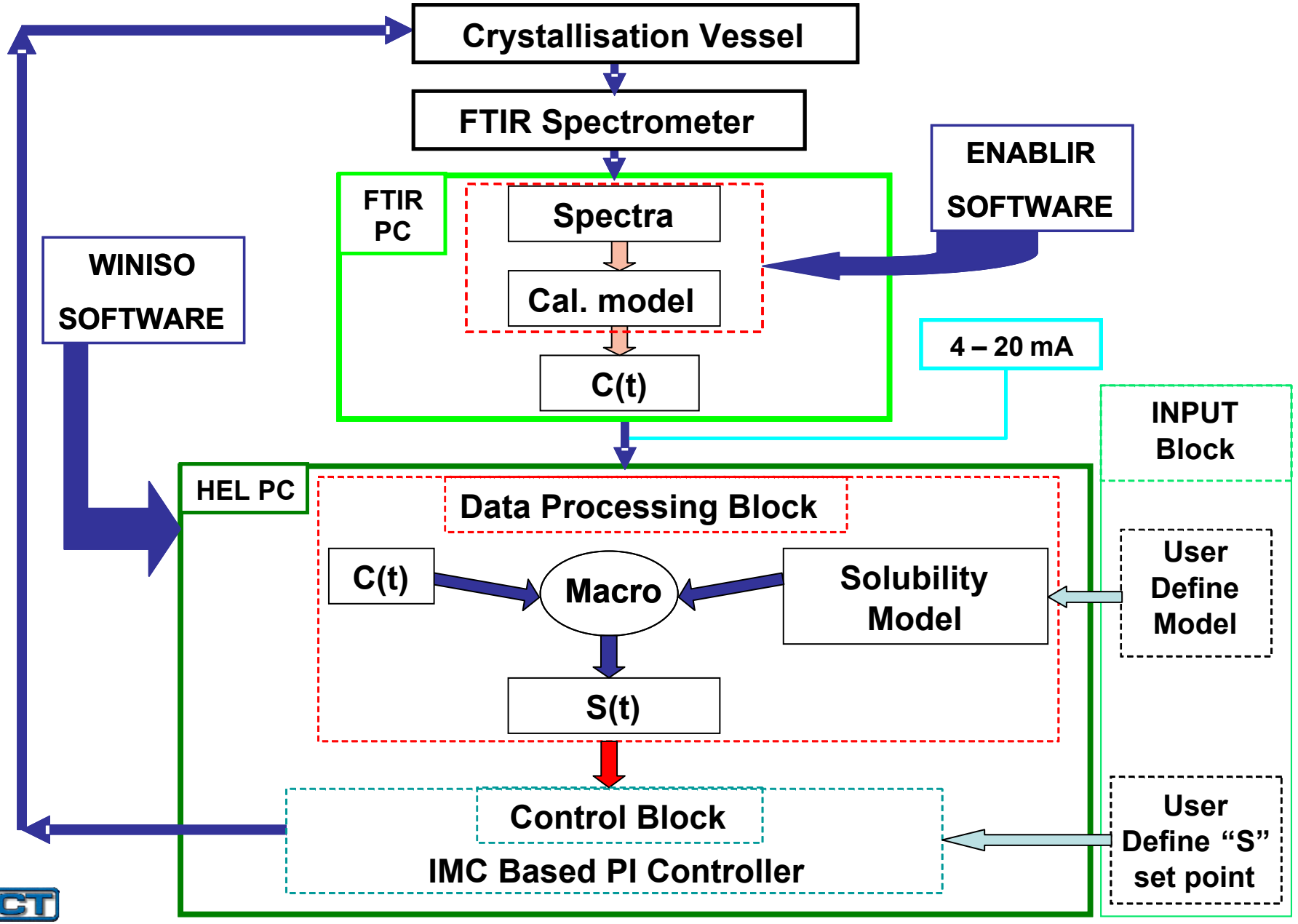




Münchwilen Foxboro Control System as Set-Up for CBBII Trial on 250 Litre Reactor R-122



Supersaturation Control System Upgrade to PI Capability



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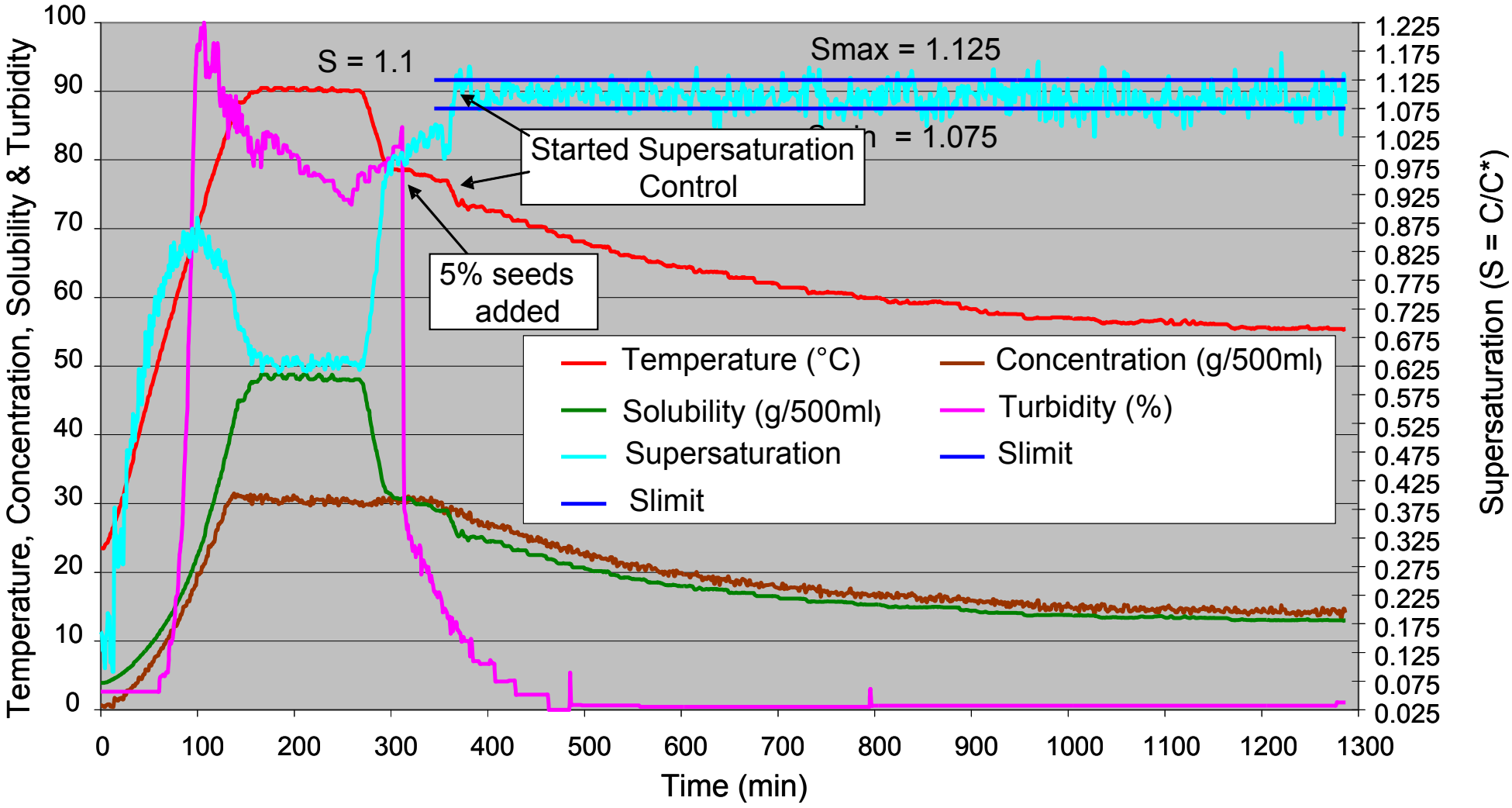
Supersaturation Control of L-Glutamic Acid
250 litre Plant Crystalliser



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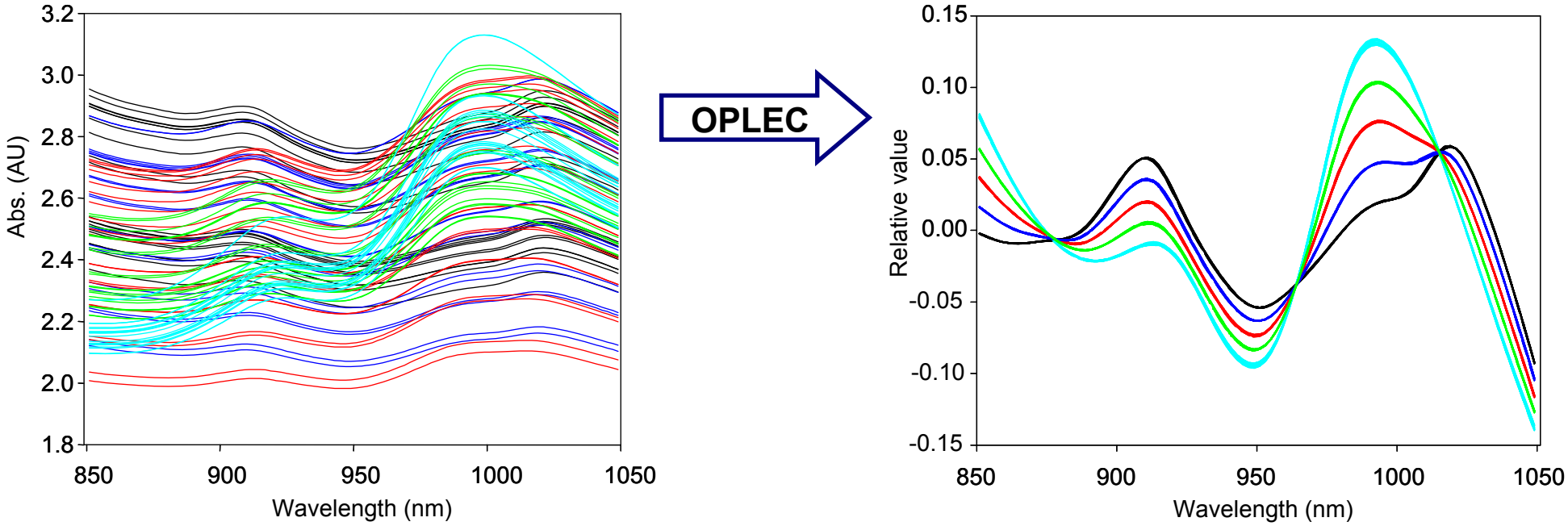
Optical Path-Length Estimation and Correction (OPLEC)

- ***Separating absorbance from multiplicative light scattering effects caused by the variations in optical path length***

$$\mathbf{x}_i = b_i \sum_{j=1}^{J} c_{i,j}\mathbf{s}_j + \boldsymbol{\varepsilon}_i$$

b_i - multiplicative parameter

$$b_i = OPLEC(\mathbf{X}, \mathbf{c}_j),\ \mathbf{X} = [\mathbf{x}_1, \mathbf{x}_2, \cdots, \mathbf{x}_m],\ \mathbf{c}_j = [c_{1j}, c_{2j}, \cdots, c_{mj}]$$



NIR spectra of five gluten/starch mixtures in 20 replicates (left) with different compactness and the corresponding NIR spectra processed by OPLEC (right)

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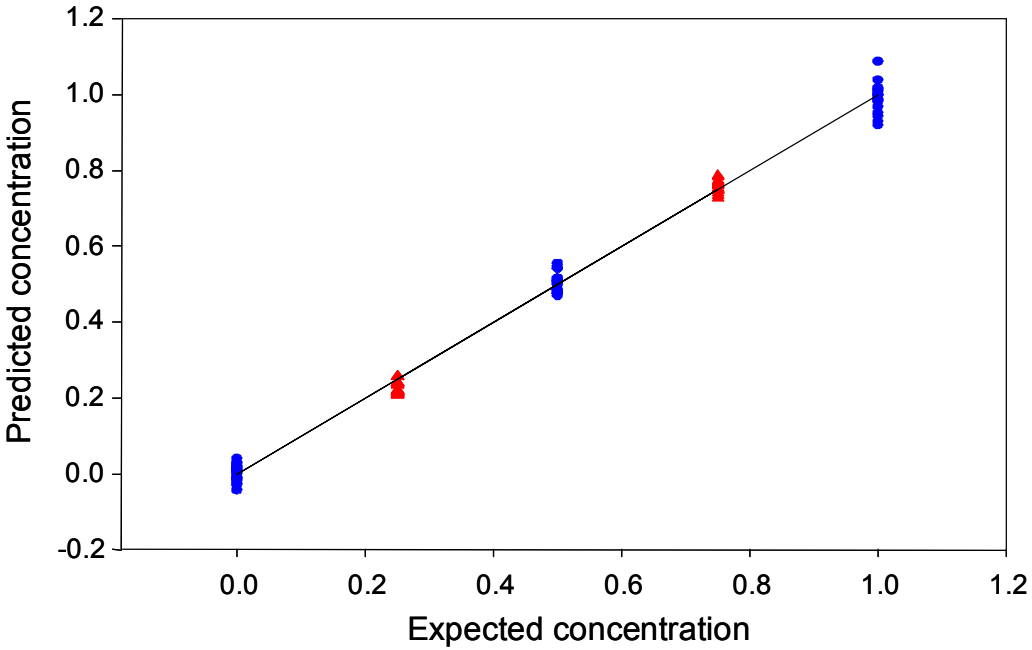
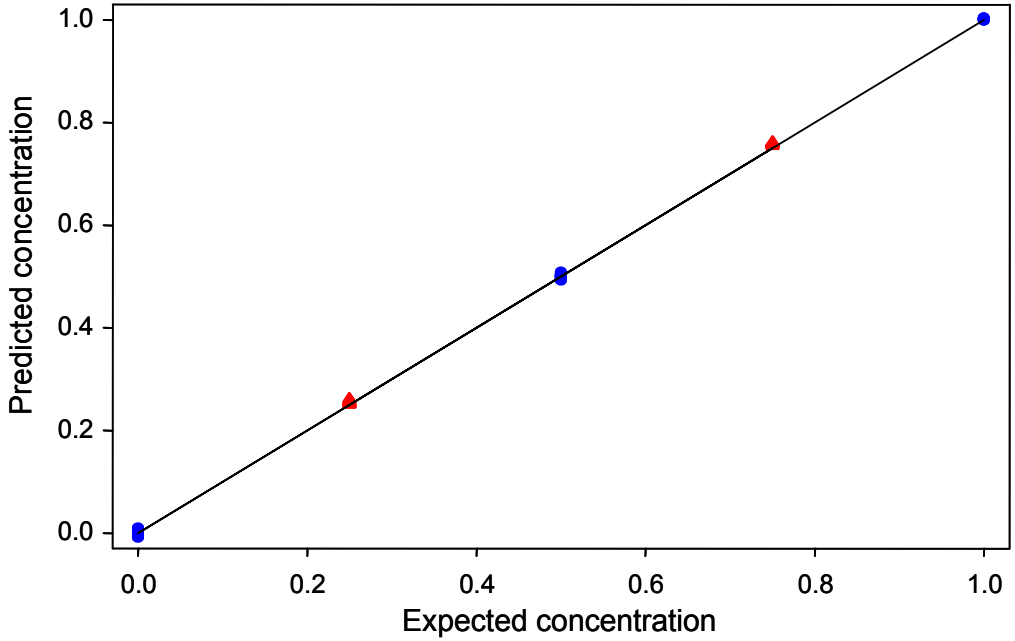
OPLEC has recently been applied in Raman Scattering applications

9-component PLS Model on Raw Spectral Data 2 versus 2-component PLS Model Pre-processed by OPLEC

- Predictions for the calibration set
- Predictions for the independent test set



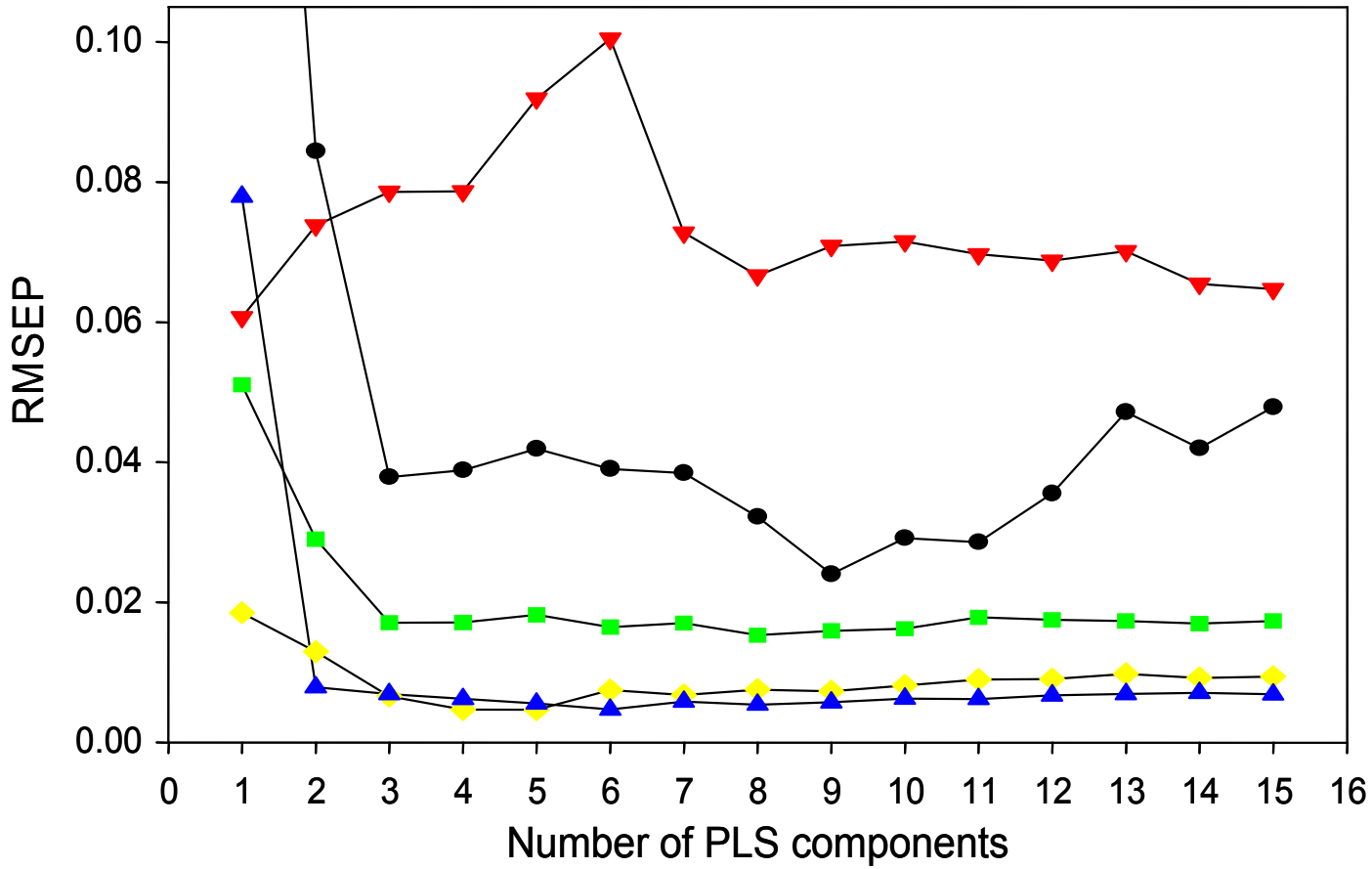
- Predictions for the calibration set
- Predictions for the independent test set



Predictive Performance of the PLS Models

● Standard PLS model; ▲ Calibration spectra pre-processed by OPLEC

◆ Martens EMSC Selection 1; ▼ Martens EMSC Selection 2; ● EISC



EMSC - Extended Multiplicative Scatter Correction; EISC - Extended Inverted Signal Correction

Closing the Analytical Control Loop

Incorporating PAT Sensors into Real Time Process Control

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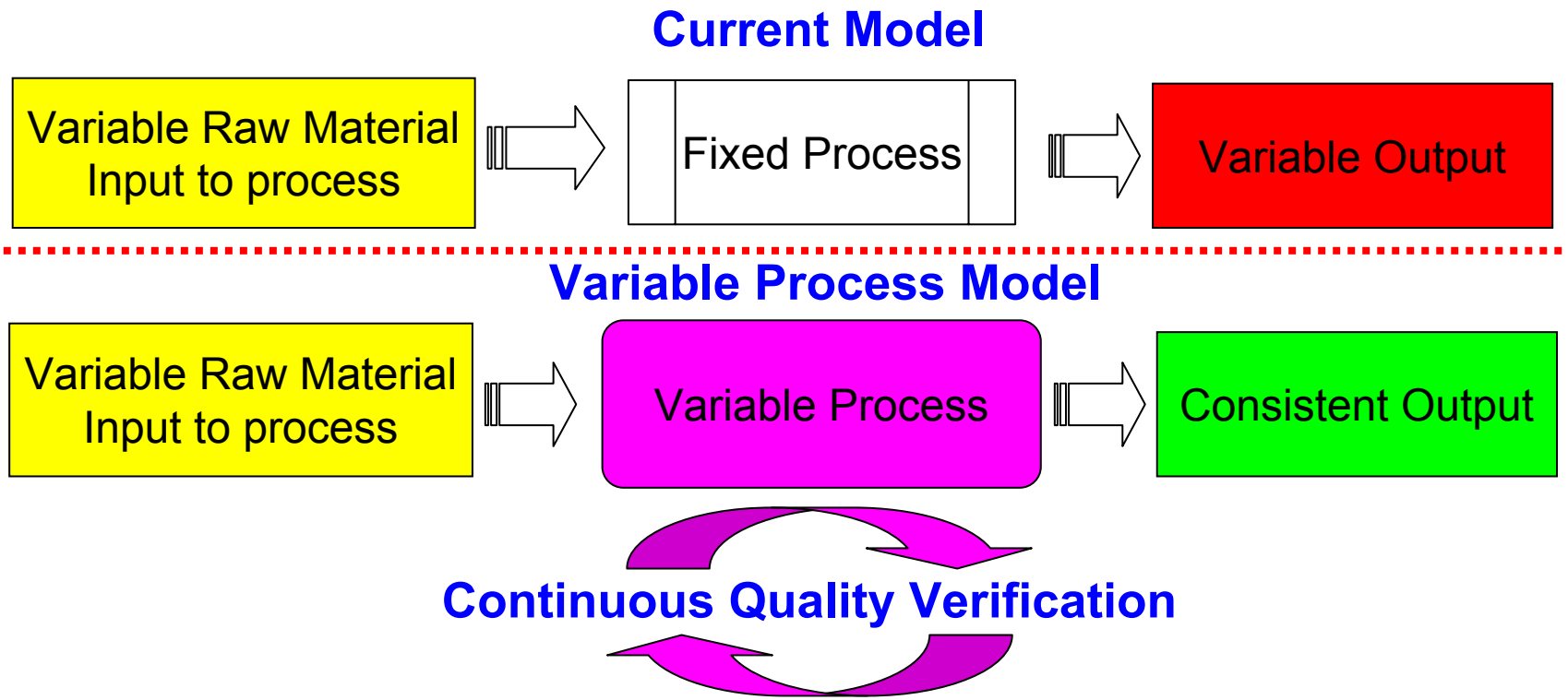
PAT and Advanced Process Control - Why we're here



- PAT is part of a tool box to optimise the way pharmaceuticals are manufactured
- Provide greater understanding of the process and what to control
- Potentially provide a means to control "Critical Attributes" by monitoring and adjusting "Critical Parameters" in real time
- Provides some of the ability to reduce the risk of process variability effecting process capability and product quality

Data Quality Monitoring

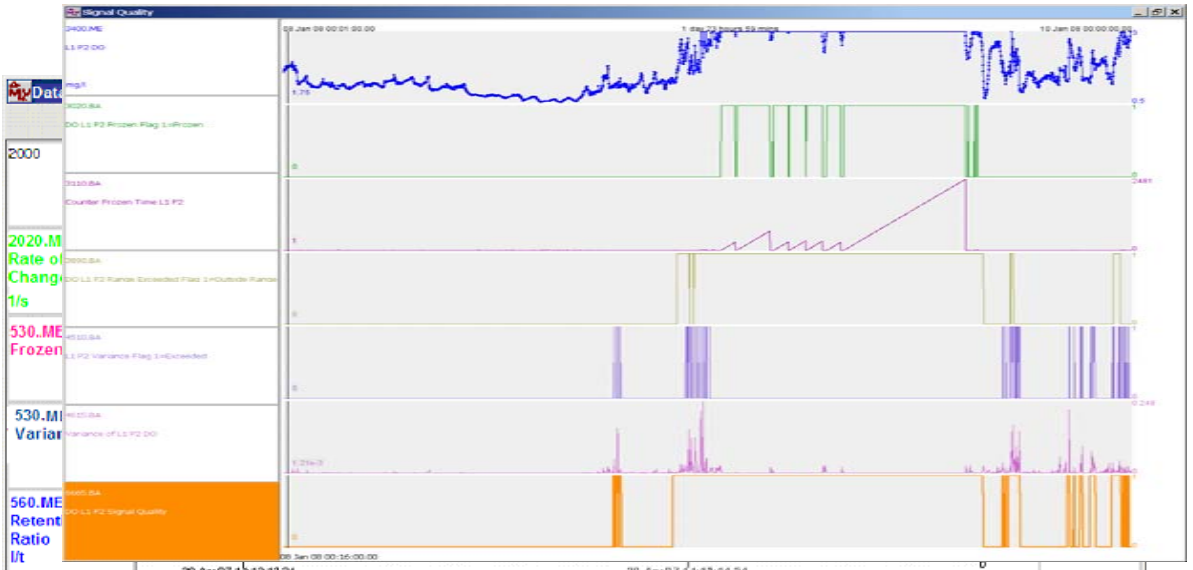
Univariate Data Quality Monitor:

Individual Signal Validation

- Logical Checks
- Statistical checks

Multivariate: Using Robust PCA

- Outlier detection
- Outlier Identification
- Data Quality Monitoring



Signal	Desc	Value	Quality	OPC Quality	Rate of Change	Frozen	Low Limit	High Limit	T-Test	Q-Test	Variance
1000.ME	Steam Flow	5.5	Bad				25	30		0.45	
1010.ME	BOD	202	Suspect		2.1	0	20	210	0.98		86
1020.ME	Dissolved Oxygen	2.3	Bad		0.34	240			0.35		43
1030.ME	Ammonia	2.1	Suspect	Calibration Error			1	3			
1040.ME	Sensor 5	1237.5	Good				500	1400			
1050.ME	Product flow	4342	Bad		14		3000	5000			

Signal	Desc	Display	Sample Interval	ROC Time	ROC Threshold	Frozen Threshold	Frozen Time	Use OPC Quality	Range Limit Low	Range Limit H
1000.ME	Steam Flow		40 s						0	0
1010.ME	BOD	☐	40 s	80s	10	0.01	160s	☐		
1020.ME	Dissolved Oxygen	☑	40 s	160s	20	0.2		☑	1	10
1030.ME	Ammonia	☑	40 s					☑		
1040.ME	Sensor 5	☑	40 s					☑		
1050.ME	Product flow	☐	40 s	80s	13			☑		

21 CFR Part 11 Records

Data Quality Records Underpin the Validity of the System – Critical in a Validated Environment

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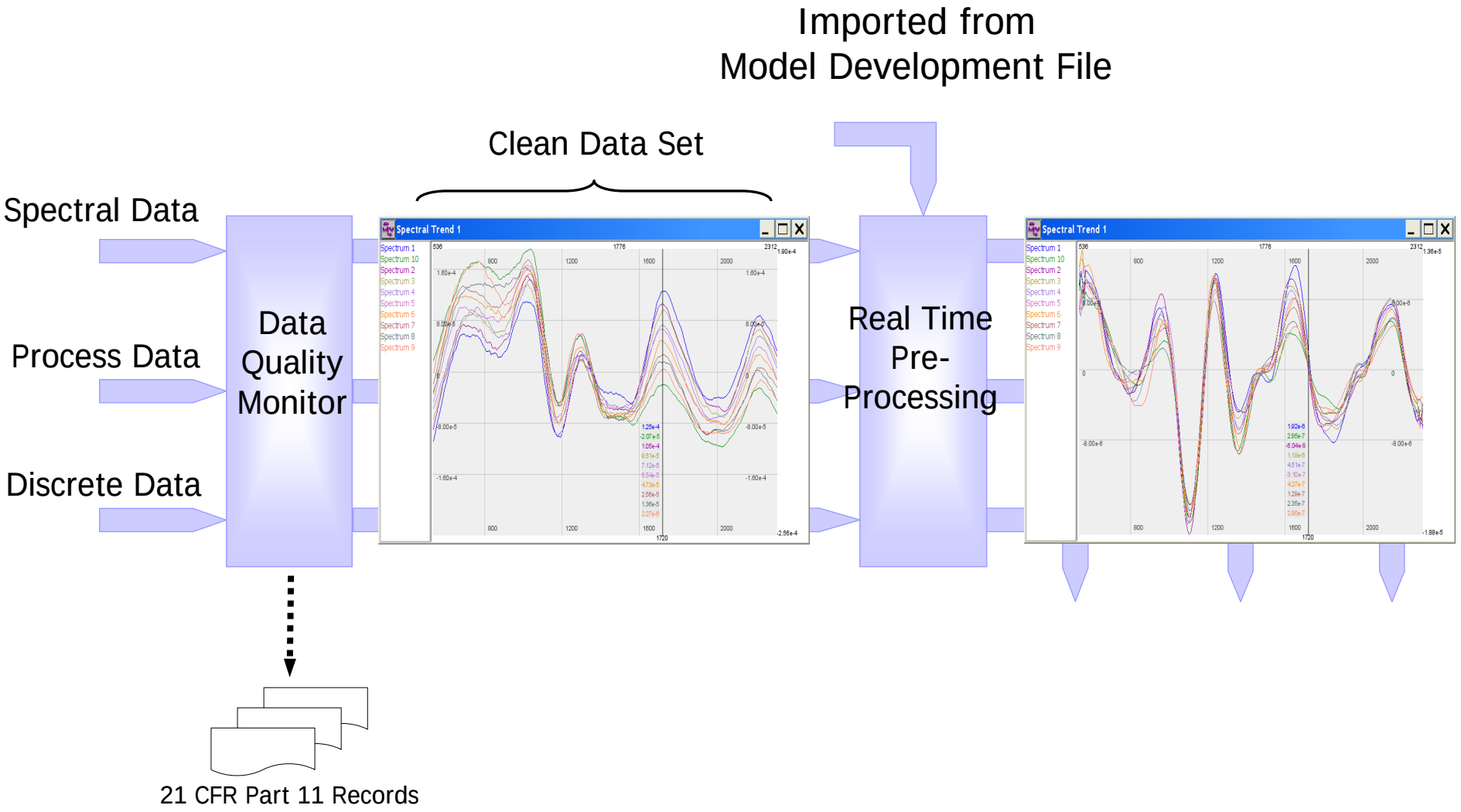
Courtesy Perceptive Engineering

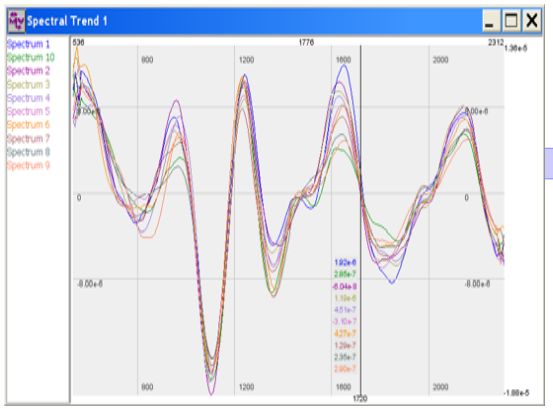
Real Time Quality Control (Using Spectral Data)



Real Time Quality Control and Integrated Data Management

Real time pre-processed data

Spectral Data



Process Data

Discrete Data

PLS/PCA Calibration Model

Dynamic PCA Controller

Control Space

Design Space

C-t-Q Parameters

- Continuously measured **OR**
- a-periodically measured **OR**
- real time value Inferred from calibration model **OR**
- end-point value inferred from calibration model **OR**
- scores of calibration model are C-t-Q parameters

Courtesy Perceptive Engineering

PAT in Closed Loop Process Control - Some Challenges

- Real-time management of process and spectroscopic data.
- Real time robust fit-for-purpose ‘transferable’ calibration models.
- No control system is going to control a spectrum of several hundred simultaneous values; so what is important?
  - Is there is a robust fit-for-purpose calibration model to infer specific product properties?
  - Are there particular features / segments of the spectrum of interest?
- What is the impact of process control on spectroscopic calibration & modelling? e.g. temperature, light scattering effects, etc on control loop performance?
- What is the impact of auto correlated data on the reliability and fitness-for-purpose of spectroscopic calibrations and on-line statistical performance monitoring models on product and process understanding and manufacture
  - the usual assumptions that the observations are Independent and Identically Distributed (IID), are inappropriate

Process Analytics – An Observation

A FTIR – €100,000

Costs the same as

A Mercedes S Class - €100,000

and a Process Oxygen Analyser costs €15,000

While

Lambda Sensor
Mercedes S Class costs €100!

Process Analysis is restricted to large companies while 98% of chemicals manufactured in Europe is by SME's, primarily in Batch Plants

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Courtesy Professor Roger Benson EUROPACT 2008

So, Where do We Need to Go ?

Smart PAT, QbD and RTR
is Smart Process Systems Engineering

And Needs

Smart Miniaturised Process Analytics
Smart Modelling / Smart Chemometrics
Smart Process Control and Optimisation

& Smart (Responsive, Flexible, Intensified) Processing

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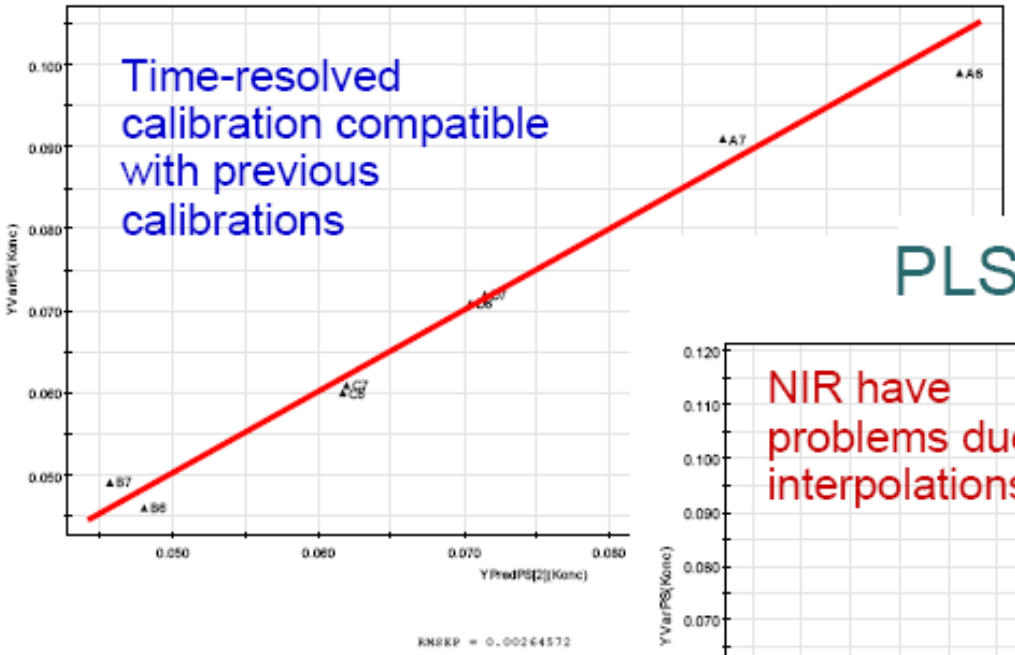
Process Analytics - 2020

- Miniaturised, self-cleaning, selective wavelength spectroscopy systems the standard at very competitive costs.
- Open spectral data handling software across all analysers.
- Much better use made of the spectral data integrated with process data.
- Specific calibration built into each analysers with the ability to identify changes and proactively update.
  - and for SME manufacturers, all remotely monitored, checked, validated and re-calibrated.
  - ***e-Pharmaceuticals Manufacturing***
- Opportunities for measurements and standards - Molecules to Manufacturing.

Advances in PAT Tools

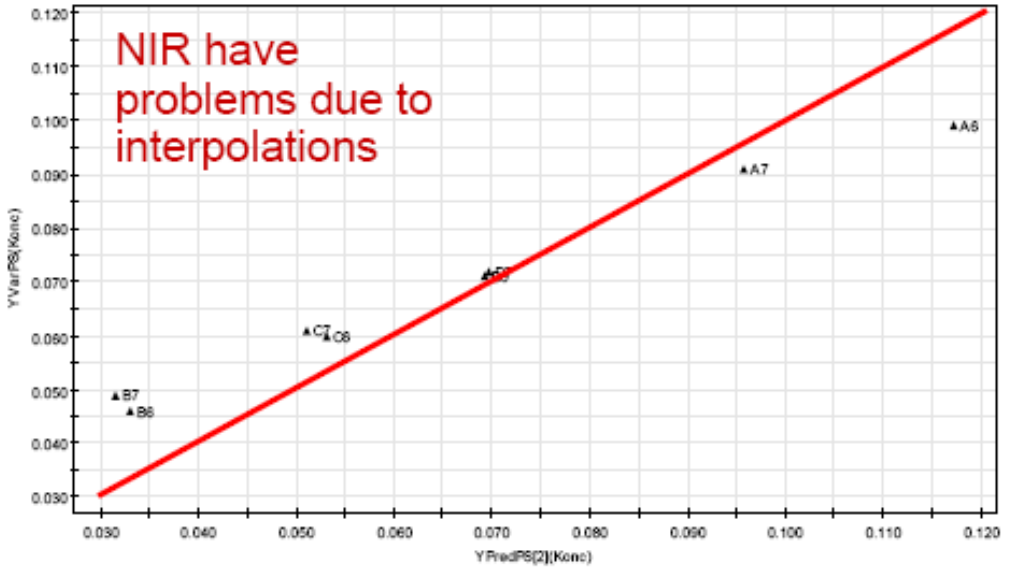
Time Resolved NIR Spectral Data extends spectroscopy into the time domain

Photon Migration



training set:
2 thicknesses
prediction set: remaining
thickness group

PLS Robustness



With time-resolved we can go outside the calibration space!

C. Abrahamsson et al., Anal. Chem. 77, 1055-1059 (2005)

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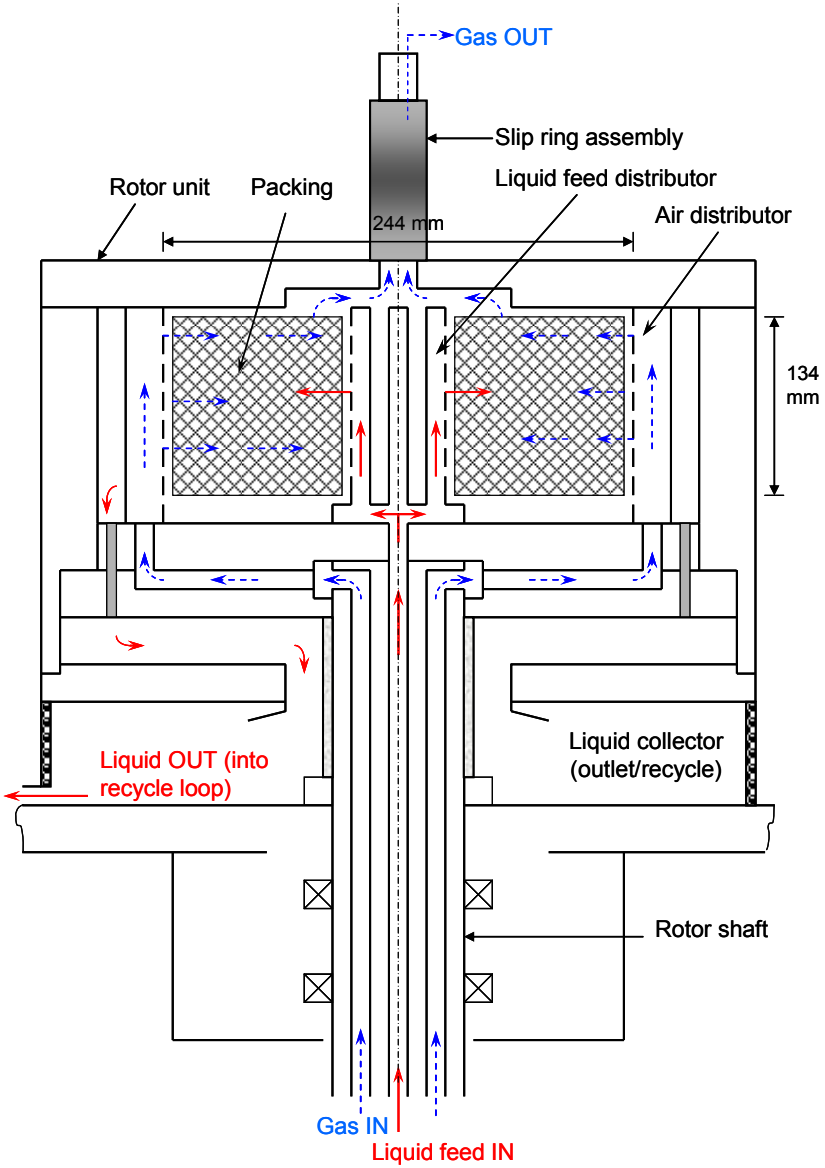
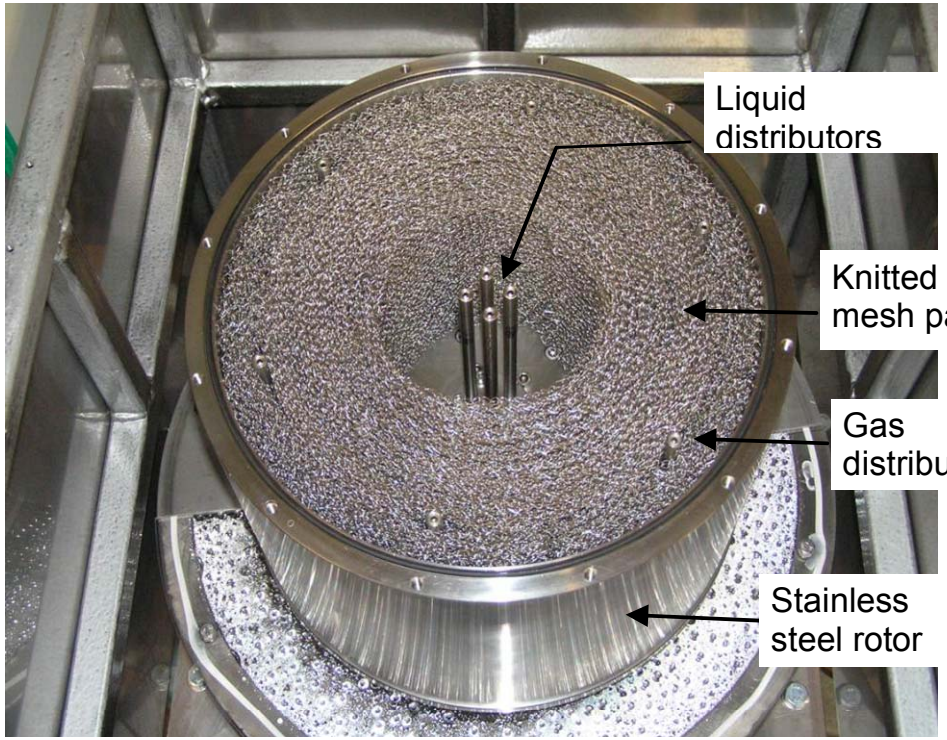
Courtesy Staffan Folestad AstraZeneca, APACT09

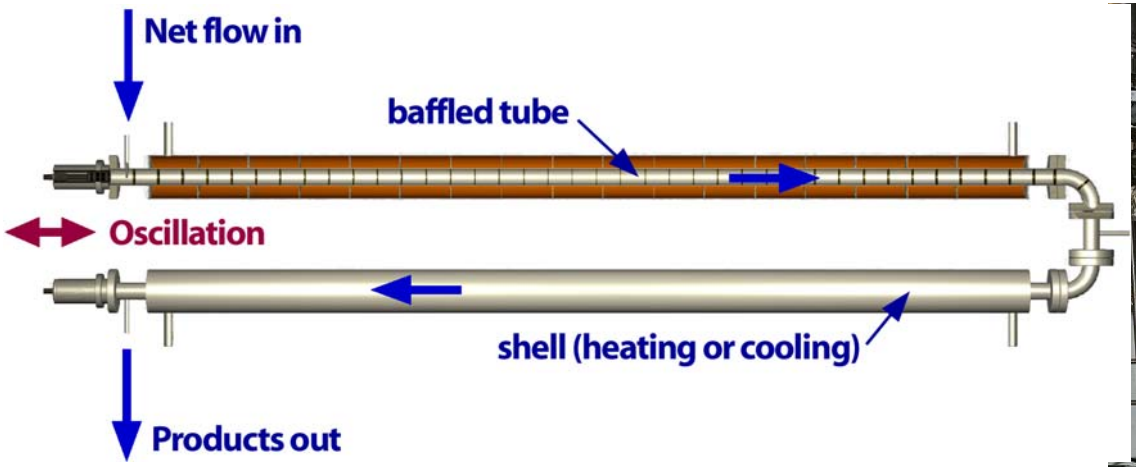
Intensified Processing - Bioproduction

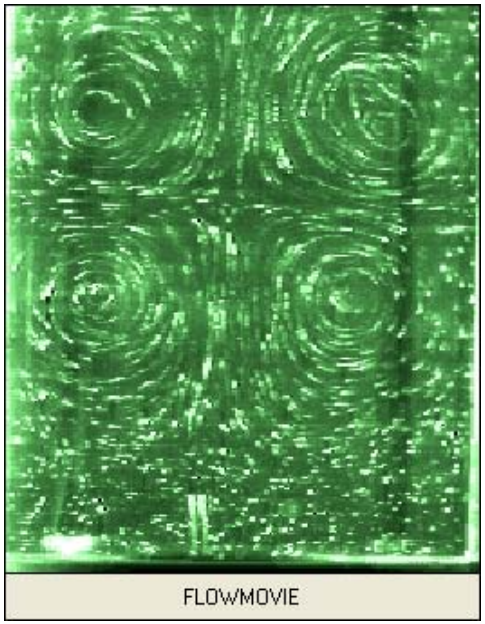




Rotating Packed Bed Hi-G Bioreactors

Intensified Processing - Bioproduction





Oscillatory Baffled Bio-reactor

Courtesy CPI

Potential Savings with PAT in Bio-pharma

- Assumptions:
  - 20 batches attempted per year, $20M annual budget
  - $1,000,000 total cost per batch, 50% in purification ($500,000/batch)
  - 90% overall batch success rate – 18 batches/yr, 2 fail due to bioburden
  - Cycle time of off-line bioburden assay: 14 days; to bulk: 7 days
  - Cost of lost batches if processed all the way to bulk: $2,000,000/year
  - Cost of lost batches if stopped at harvest: $1,000,000/year

Potential Savings with on-line bioburden assay: $1,000,000 / year

Courtesy P Galliher, Potential Benefits of PAT for Biomanufacturing, IFPAC 2005

Closure and Thanks

- In this talk, I have tried to…
- Introduced the concept of PAT, QbD and RTR within a Process Systems Engineering framework leading to faster scale-up (scale-down), assured product quality and reproducibility and enhanced manufacturing.
- Highlighted some Process Analytical Technologies through work aiming to improve the understanding of process variability resulting in enhanced calibration models, enhanced process understanding and assured closed loop process monitoring and control.
- Shown the utility of combining a number of process analytical technologies for real-time closed loop batch cooling crystallisation monitoring and control in an industrial pilot plant, and other key industrial issues.
- …. And I hope, shown how they might contribute to moving:

"From Shake Flask to Multi-kilos – Faster, Better and Sustainably Through a Process Systems Approach"

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north east england

Passionate people. Passionate places.

nis

die

sor

& Stavros Nychas on their well deserved retirement

I w **o attem**

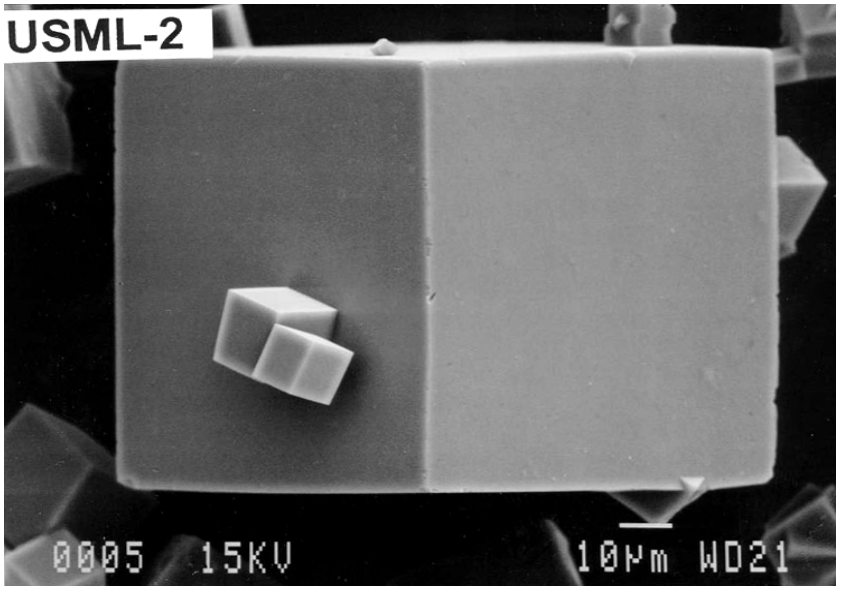
Ac *P Sustain*

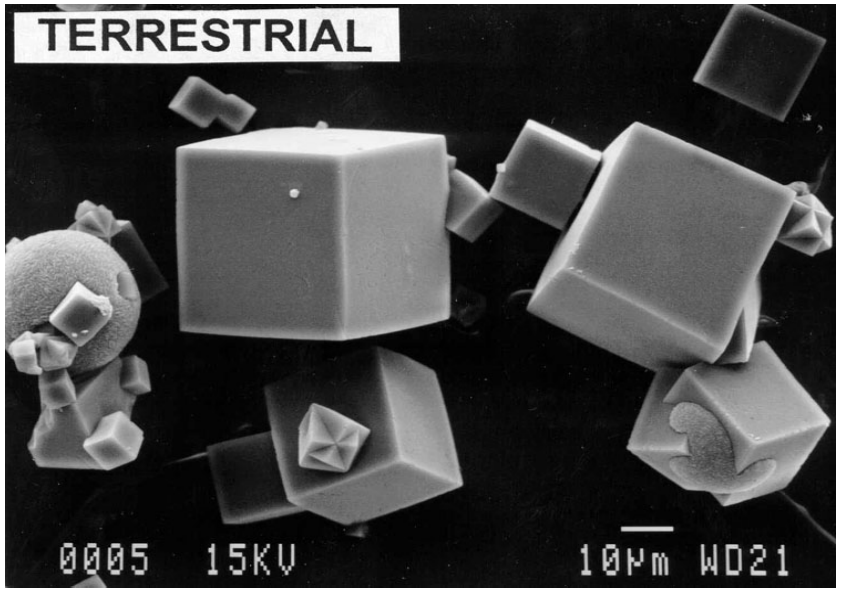
Pr *nal Mater*

CP *t and pres*

CPAC

Proteins Grown in Space Can Help Understand Disease





Courtesy Prof Al Sacco & Dr Catherine Coleman,
Space Scientists

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