Batch Statistical Process Control (BSPC): a powerful multi-level risk & process analytics tool

AgroStat 2016
March 21-24, 2016
Lausanne

Sébastien Preys
Ondalys
France
Consulting and Training in Chemometrics

- Exploratory analysis – Data-mining
- Multivariate modeling
- Multi-block analysis
- Experimental designs

- UV-VIS-NIR-MIR spectroscopy
- Mass spectrometry
- Imaging
- Sensory data

How to get the best from your data
Research and Industrial Customers

Technical & Research Centers

Agro-Food industry

Pharmaceutical Industry

Petro-chemical Industry

Miscellaneous

PAT initiative
I – What is the PAT initiative?

II – Focus on Batch Statistical Process Control (BSPC): benefits and challenges?

III – Discussion and round table …
Process

- Inputs and outputs: raw materials / in-process products / end-products
- Specifications = Quality Control on end-products ⇒ product release
- Intermediate measurements = CQA (Critical Quality Attributes)
- Process parameters to be controlled = CPP (Critical Process Parameters)
Historically: **PAC** (Process Analytical Chemistry)

- « to supply quantitative and qualitative information about a chemical process, … not only to monitor and control processes, but also to optimize its efficient use of energy, time and raw materials »

- = monitoring and control of key process parameters to provide the desired quality of the end-product
Process Analytical Technology (PAT)

More recently (2004): PAT (Process Analytical Technology)

« Process Analytical Technology (PAT) – A framework for innovative pharmaceutical development, manufacturing and quality assurance »

« A system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality »

Benefits

- This risk-based concept enables:
  - Process understanding
  - Continuous process optimization
  - Improvement of the process robustness, especially during the development phase, using Quality by Design (QbD) methodology
  - Replacing classical quality control on the end-product by in-process real time quality control or Real Time Release (RTR)
Tools

- **Process analyzers** (sensors): at-line, on-line or in-line, including classical process measurements and multivariate sensors

- **Process control tools**: to monitor the state of a process, by measuring the Critical Quality Attributes (CQA), and manipulate the Critical Process Parameters (CPP) to maintain a desired state

- **Multivariate tools for design, data acquisition and analysis**: Design of Experiments (DoE), MultiVariate Data Analysis (MVDA)

- **Continuous improvement and knowledge management**: using information technology infrastructure, in order to justify post-approval changes towards the regulatory authorities
Multivariate tools: different levels

- **PAT – 1**: Multivariate calibration on CQA, using rapid analytical measurements (spectra,...)

- **PAT – 2**: Multivariate Statistical Process Control (MSPC) to decide if the samples are in-control or out-of-control using multivariate measurements

- **PAT – 3**: Batch Statistical Process Control (BSPC) to decide if the trajectory of a batch is in-control or out-of-control using multivariate measurements

- **PAT – 4**: Multi-block analysis to combine multivariate data of all the critical unit operations (steps) of a process

- **PAT – 5**: Control procedure by feedback loops using multivariate models

*Wold, 2006*
SPC vs. MSPC

Temperature

Pressure

Abnormality not detected in univariate!
False alert in univariate!
Outline

I – What is the PAT initiative?

II – Focus on Batch Statistical Process Control (BSPC): benefits and challenges?

III – Discussion and round table …
Data structure

Initial conditions
- pH setpoint
- Temperature setpoint
- ...

Process parameters
Offline:
- Concentrations
- ...

Online:
- pH
- Temperature

End quality
- Specifications
Methodology

- Batch Evolution Modelling (BEM) – Selection of reference batches
  - Use of initial variable trajectories (line plots)
  - Use of score trajectories (line plots)
Methodology

- BEM - Selection of reference batches

Process variables:
- 12
- 48
- ...
- ...

Time:
- 1

PLS (Multi-way)
Methodology

- BEM – Selection of reference batches
  - Use of score trajectories (scatter plots)

- Use of multivariate control charts ($T^2$, $Q$)
Methodology

- Batch Level Modelling (BLM) using reference batches
  ➤ Check batch selection

TRAINING SET
(Reference batches)

40

Initial conditions + Scores (3) x time

3 x time

PCA
Multi-blocks
Methodology

- Batch Level Modelling (BLM) using reference batches
  - Use of score plot
Methodology

- Batch Level Modelling (BLM) using reference batches
- Response modelling

**TRAINING SET**  
(Reference batches)

40

| 7 |

3 x time

40

Initial conditions + Scores (3) x time

2

PLS

MB-PLS

40

End quality
Methodology

- Batch Level Modelling (BLM) using reference batches
- Response modelling

![Graph showing Y Measured against Y CV Predicted with R² = 0.84, 3 Latent Variables, RMSECV = 0.18]
Methodology

- Process monitoring
Multi-level applications

- Process understanding
- Process optimization
- Real-time process monitoring and fault diagnosis
Challenges

- Different batch kinetics (latency, time-lags,...) and durations
- Missing data
- Noise
- Different frequencies of data acquisition (on-line, off-line)
- More indices needed (ratios, speed,...)?
Outline

I – What is the PAT initiative?

II – Focus on Batch Statistical Process Control (BSPC): benefits and challenges?

III – Discussion and round table …