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

AgroStat 2016
March 21-24, 2016
Lausanne

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ondalys

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

- IFV – Institut Français de la Vigne et du Vin
- cirad
- IRD
- Cemagref
- cnrs – dépasser les frontières
- cea
- CRA-W Gembloux
- INRA

Agro-Food industry

- Danisco – First you add knowledge..
- Moët & Chandon – Champagne
- Dow
- Imperial Tobacco
- Limagrain – United Kingdom
- Royal Canin – Connaissance et respect

Pharmaceutical Industry

- gsk – GlaxoSmithKline
- sanofi aventis – L'essentiel c'est la santé.
- sanofi pasteur – La division vaccins du Groupe sanofi-aventis.
- Servier
- Abbott – A Promise for Life
- Cephalon – Insights into medicine

Petro-chemical Industry

- Total
- Arkema – The world is our inspiration
- Chevron
- Oronite
- CERTECH – CEntre de Ressources TEchnologiques en CHimie

Miscellaneous

- Chanel
- L'Oréal
- I.N.P.S. – Institut National de Police Scientifique
- bertin Technologies
- EADS Sodern
- Cedre

PAT initiative

ondalys – Multivariate Data Analysis

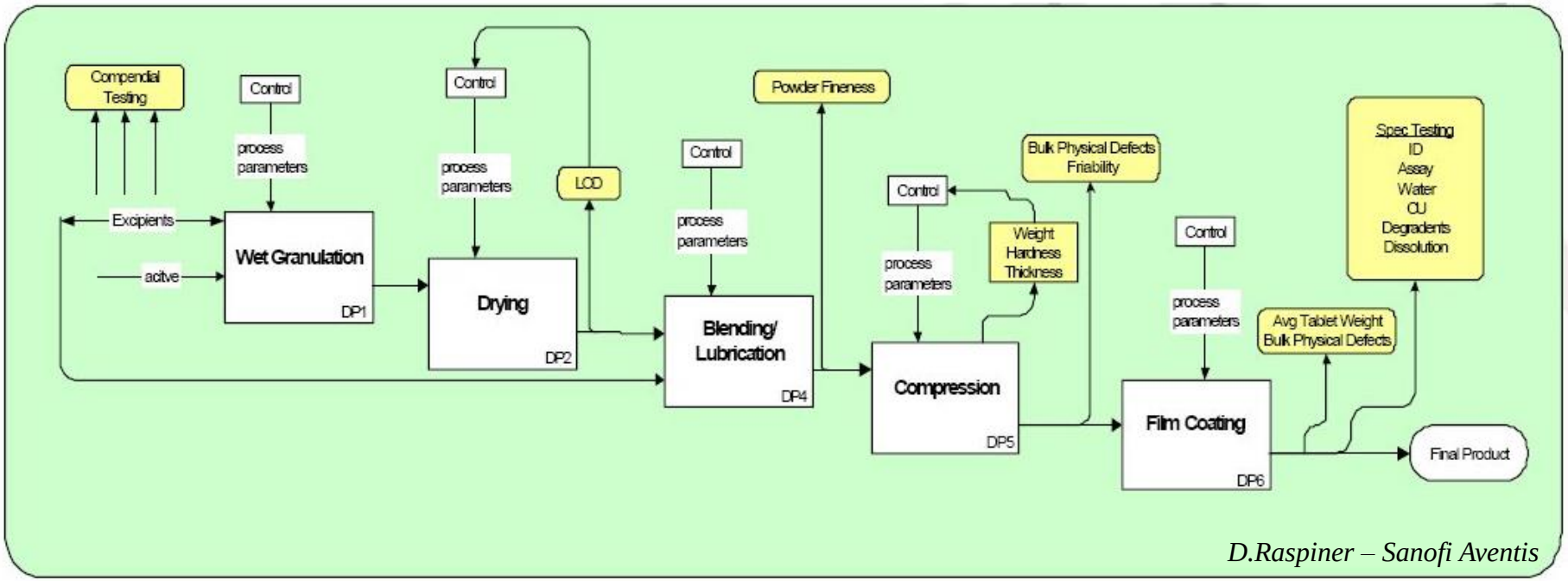
Outline

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 controled = CPP (Critical Process Parameters)

Process Analytical Chemistry (PAC)

- 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 »

Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, FDA, September 2004.
http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070305.pdf

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)

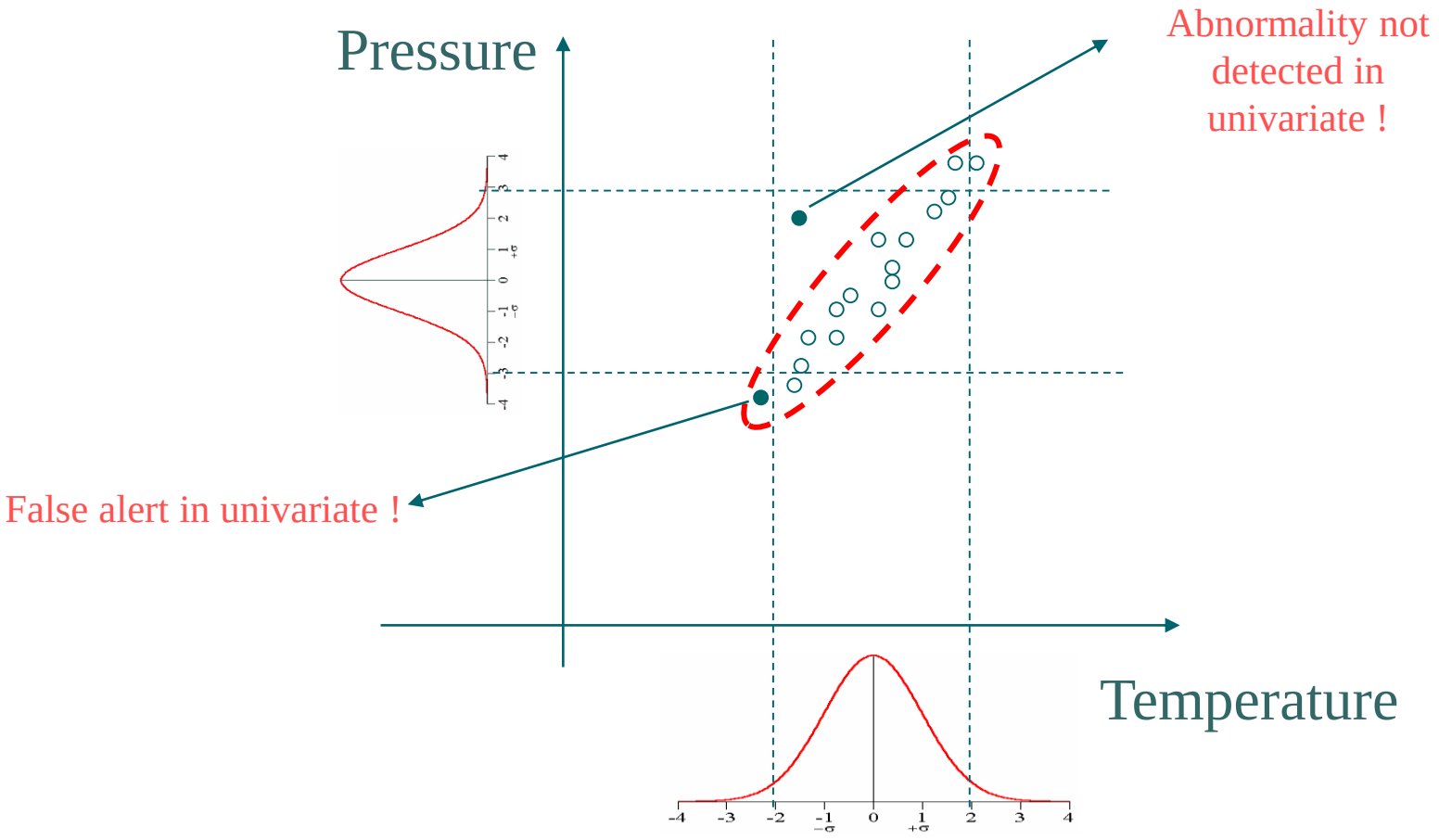
- **Continuous improvement and knowledge management**: using information technology infrastructure, in order to justify post-approval changes towards the regulatory authorities

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 he multivariate models

Wold, 2006

SPC vs. MSPC


Pressure
Abnormality not detected in univariate !
False alert in univariate !
Temperature
-4 -3 -2 -1 0 1 2 3 4
−σ
+σ

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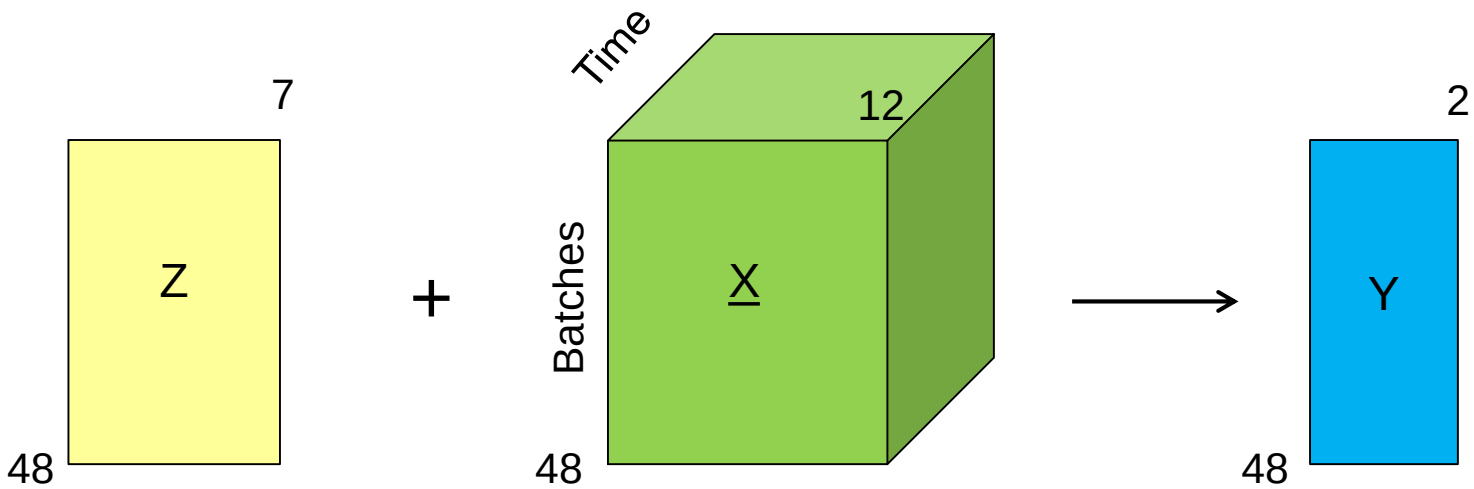
Data structure



Initial conditions

- pH setpoint
- Temperature setpoint
- …

Process parameters

Offline :
- Concentrations
- …

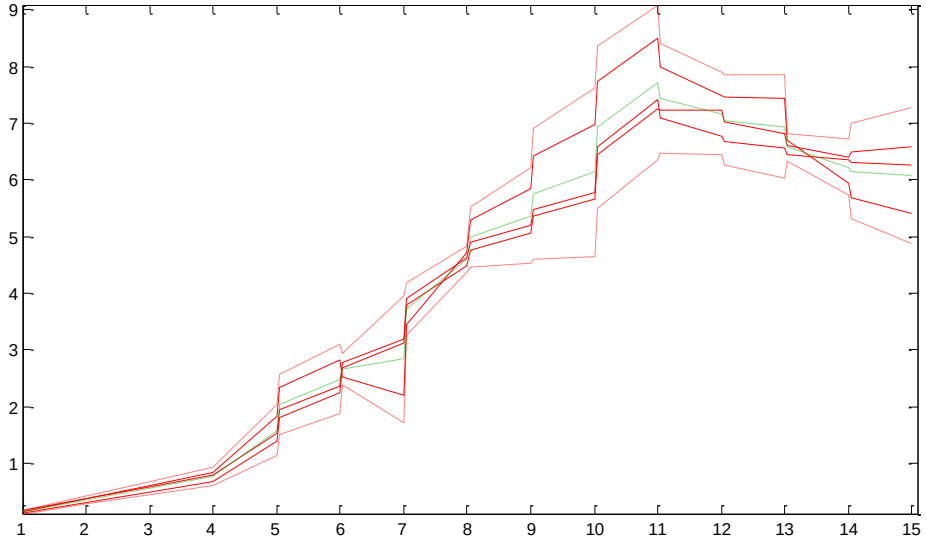
Online :
- pH
- Temperature

End quality

- Specifications

Methodology

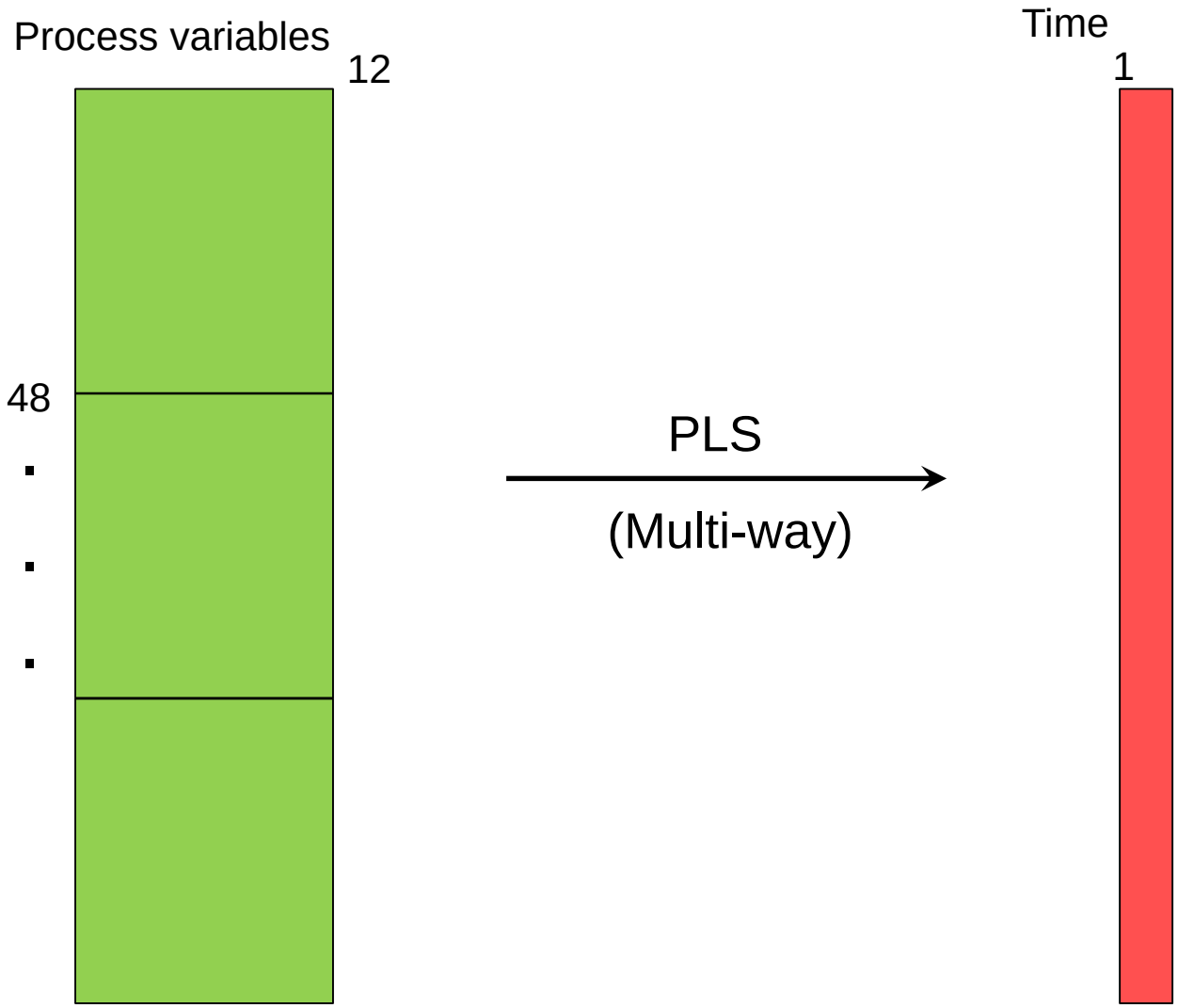
- Batch Evolution Modelling (BEM) – Selection of reference batches
  - Use of initial variable trajectories (line plots)



  - Use of score trajectories (line plots)

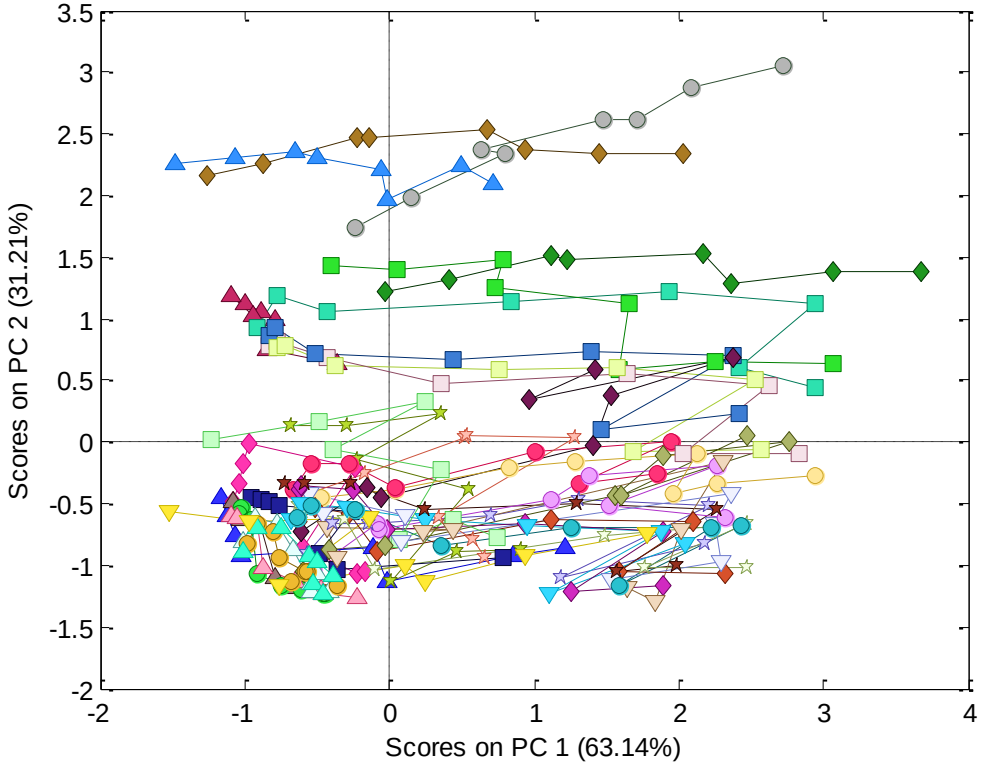
Methodology

- BEM - Selection of reference batches



Methodology

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

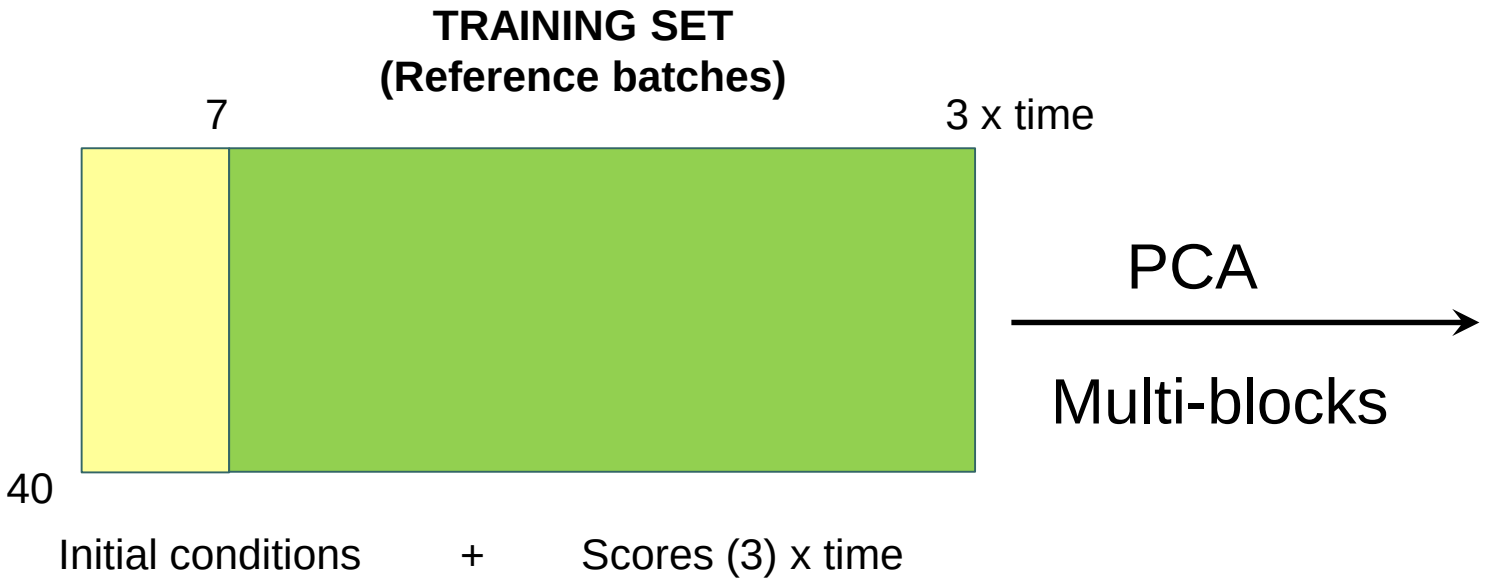


  - Use of multivariate control charts (T^2, Q)

Methodology

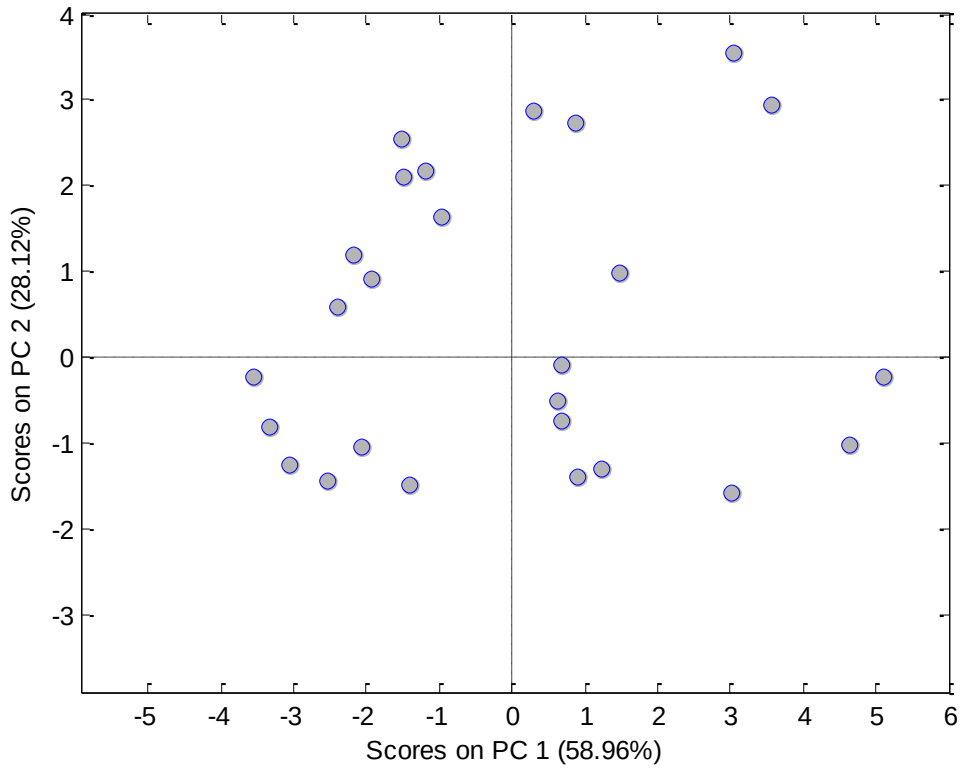
- ❑ Batch Level Modelling (BLM) using reference batches

➔ Check batch selection



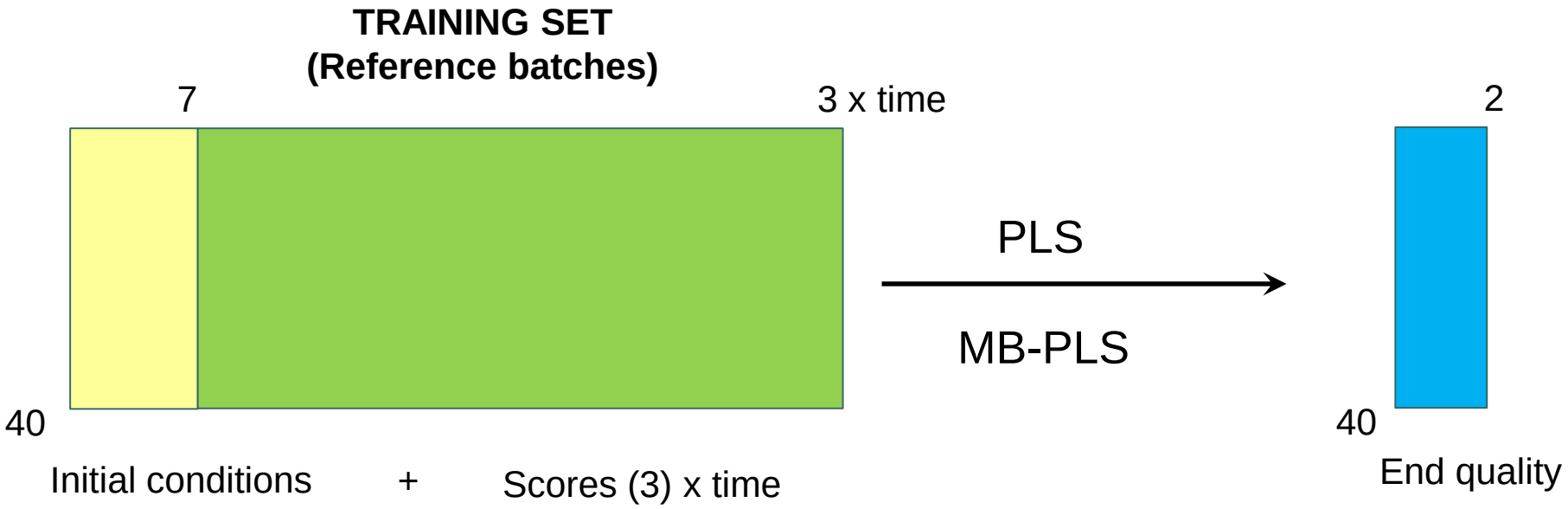
Methodology

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



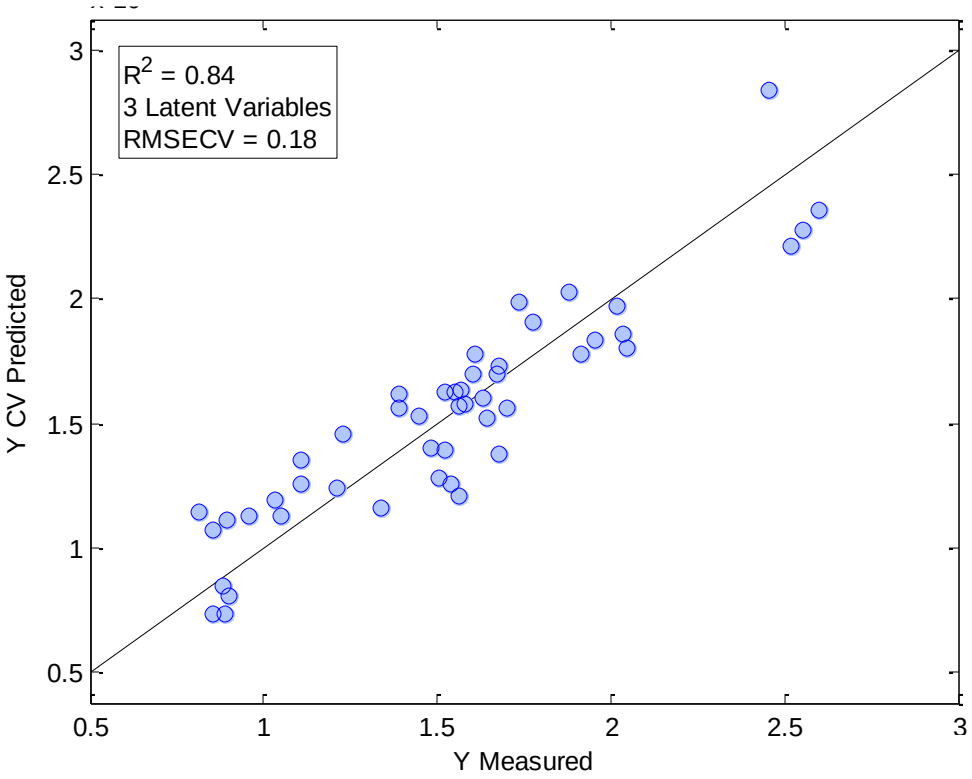
Methodology

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



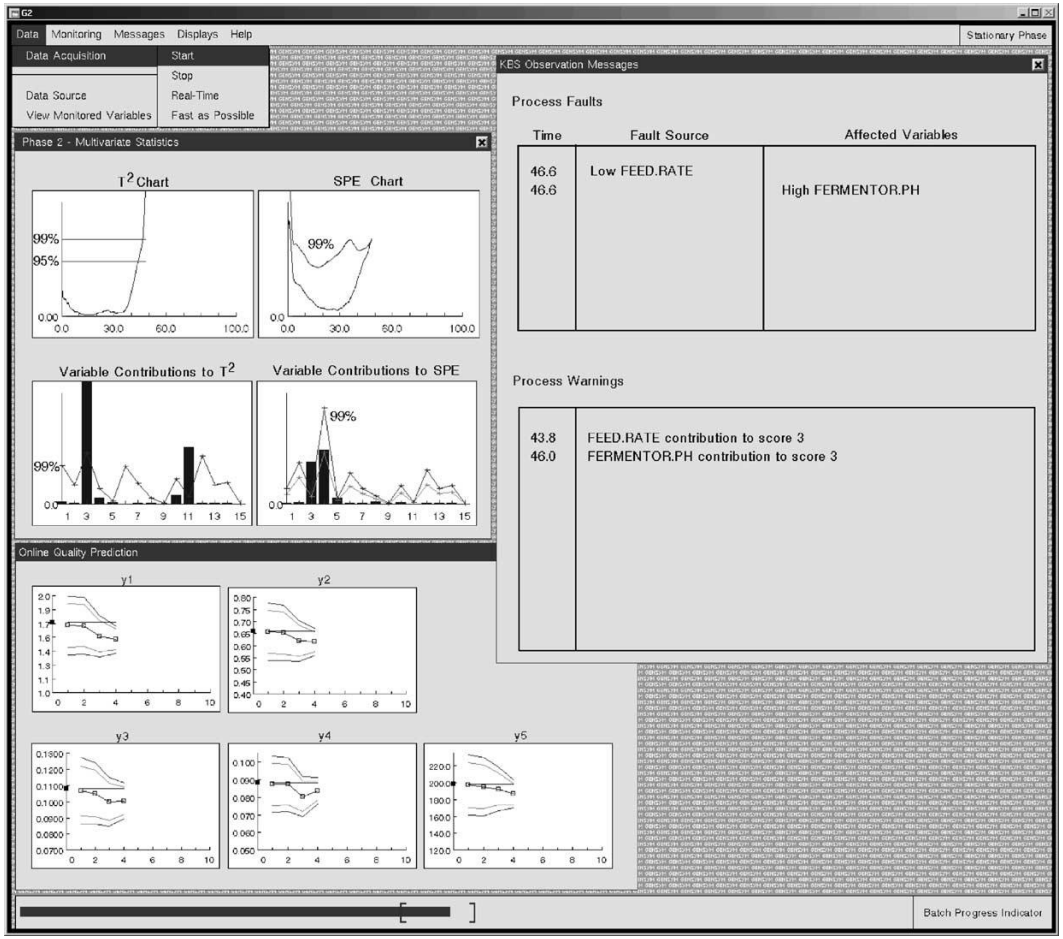
Methodology

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



Methodology

- Process monitoring



C. Ündey et al. / Journal of Biotechnology 108 (2004) 61–77

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,…) ?

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