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

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Abstract
The Food and Drug Administration (FDA) initiative in the USA recommended in 2004 the implementation of Process Analytical Technology (PAT) in the pharmaceutical industry, in order to improve the risk and process control. Within the PAT framework, the BSPC (Batch Statistical Process Control) or batch monitoring approach is a high added value method to monitor and control batch processes. The principles and methodology will be presented.

Keywords: Process; batch; monitoring; multivariate; Batch Statistical Process Control (BSPC).

Mots-clés : Procédé ; batch ; supervision ; multivarié ; Maîtrise Statistique des Procédés (MSP).

1. Introduction

The Food and Drug Administration (FDA) initiative in the USA recommended in 2004 the implementation of Process Analytical Technology (PAT) in the pharmaceutical industry, in order to improve the risk and process control. Ten years after, PAT has been developed, tested and implemented in numerous R&D and industrial sites all over the world.
The first part of this presentation gives details on PAT goals and implementation. The second part focuses on one important field of application of PAT with high added value, i.e. batch monitoring or Batch Statistical Process Control (BSPC) using multivariate data analysis.

2. Principles of Process Analytical Technology (PAT)

2.1 Goals

PAT is described as 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, FDA*).
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).

2.2 Tools

PAT is implemented by using different kinds of tools:

- Process analyzers (sensors): at-line, on-line or in-line, including classical process measurements, such as pH-meters, manometers…, biological, chemical and physical attributes, and multivariate sensors, such as NIR or Raman spectrometry
- 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.

3. Batch Statistical Process Control (BSPC)

The BSPC or batch monitoring approach is a method to monitor and control batch processes, within the PAT framework.

3.1 Data structure

The data structure for BSPC applications includes 3 blocks:

- Initial conditions, characterizing raw materials and experimental design
- Process parameters, univariate or multivariate
- End quality parameters, characterizing the end-products.

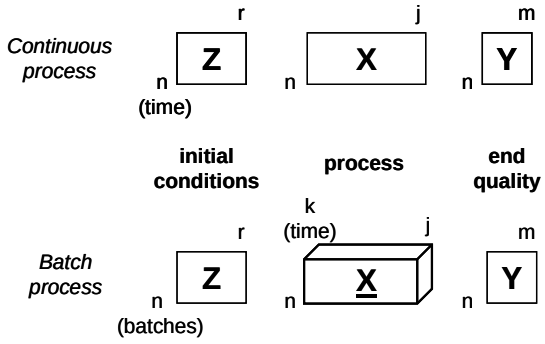

Figure 1: Data structure for MSPC (top) and BSPC (bottom) (*O'Donnell et al.*).

Data for BSPC applications generally requires a long and complex phase for data cleaning and preparation, including missing data handling, pre-treatments, noise reduction, data alignment…

3.2 Methodology and illustration

The general methodology for BSPC includes 2 steps (*Wold et al.*):

- A first observation level models the **X** matrix, i.e. the batch evolution, according to column-wise unfolding, where each row represents an observation
- The second level, called the batch level, corresponds to row-wise unfolding, where each row represents a batch, and models **Z**, **X** and **Y** simultaneously, i.e. the final batch results.

The first observation level enables the selection of the "golden batches", using univariate and multivariate trajectories.
The second batch level is based on these "golden batches" to build a multivariate model for multi-level applications:

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

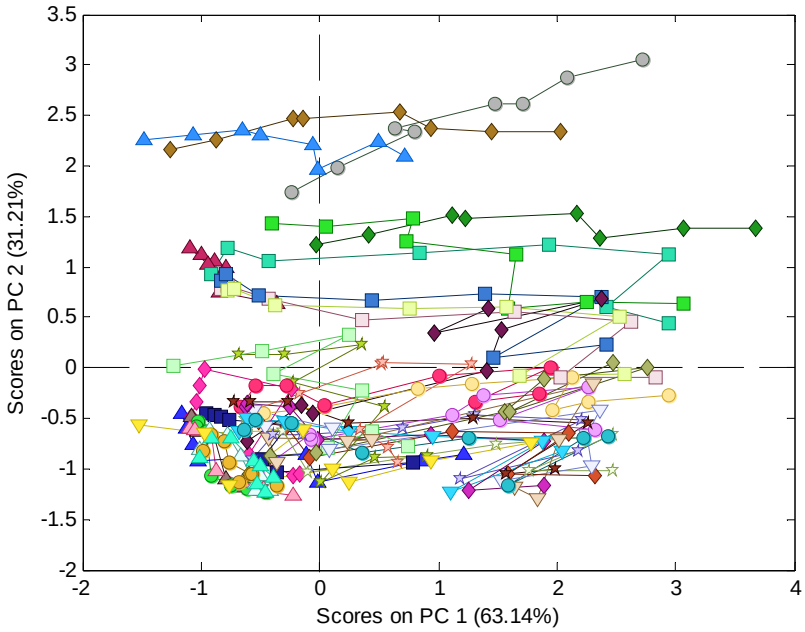

Figure 2: Multivariate trajectories based on the process parameters of the batches.

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