Applications of Multivariate Data Analysis

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Novartis values from MVDA for PAT & QbD

Increase of **process understanding**
- Identification of influential process parameters
- Identification of correlation pattern among the process parameters
- Generation of process signatures
- Relationship between process parameters and quality attributes

Increase of **process control**
- Enabling on-line early fault detection
- Support for time resolved design space verification (real time quality assurance)
- Predicting quality attributes based on process data
- Excellent tool for root cause, trending analysis and visualization

**Business Challenge**
- Reduction of dimensionality
- Conformity check
- Real time release testing
- Trend analysis
- Root cause analysis

**Solution**

**Results and Benefits**
- Ability to be proactive rather than reactive to variation or poor quality.
- Saving batches
- Reducing OOS
- Helping to optimize the process
Topics

• Introduction: MVDA in the context of pharmaceutical production
• Case studies for MVDA I
  – Process monitoring of a granulation process in pharmaceutical production
• Case studies for MVDA II
  – Statistical Process Control Biopharmaceutical Production for optimization
• Short real-time demonstration

Using PI Server, PI Batch and PI Event Frame & PI Interface for SIMCA-online
Umetrics

- Part of ~1Billion conglomerate
- The market leader in software for multivariate analysis (MVDA) & Design of Experiments (DOE)
- 25+ years in the market
- Off line analysis tools
- On-Line process monitoring and fault detection
- 700+ companies, 7,000+ users
- Pharmaceutical, Biotech, Chemical, Food, Semiconductors and more
- Worldwide Presence with MKS
- Close collaboration with universities in USA, Sweden, UK and Canada
SIMCA-online

With SIMCA-online, you have the power to monitor manufacturing evolution in real time providing quality information before the product is finished. SIMCA-online makes this possible using multivariate techniques combined with conventional SPC (Statistical Process Control), underpinned by a seamless graphical interface. Finally, you have the ability to react to quality issues as they happen.

SIMCA-OnLine

BY UMETRICS

Average Overall Rating

★ ★ ★ ★ ★ (1 Reviews)

Write a Review

Features & Benefits

- Increase manufacturing efficiency & quality using proven statistical methods
- Optimize process to reach desired quality target while reducing risk
- Very fast return on investment, often from the first major production deviation alert
- Provides information for engineering to make continuous improvements in the process

Industry

- Oil & Gas
- Chemical & Petrochemicals
- Materials, Mines, Metals & Metallurgy
- Pharmaceuticals, Food & Life Sciences
- Pulp & Paper
- Power & Utilities
- Critical Facilities, Data Centers & IT

Solution Area

- Process Characterization and Analytics
- Process Control/Optimization
- Visualization

Region Sold

- Africa
Building a capable process

- **DOE** is a knowledge building tool for process development
- **MVDA** is used both for process understanding and process monitoring
Our Customers’ Goals in Pharma

• The goal in Pharma production is to help take advantage of data present in the development labs, and the production environments all the way from API to the final product. = ROI
The Need for Multivariate I

The information is found in the correlation pattern - not in the individual variables!
The Need for Multivariate I
The Need for Multivariate II

- Data explosion, more process measurements than ever before, reduce false alarms

- Spectrometers
  - NIR, FTIR, RAMAN, UV, LLSD
  - MS, GC, HPLC

- Process Sensors
  - Acoustic, Video
  - P, T, Flow, pH
  - pO₂ pCO₂

- Require MVDA methods to visualise and extract reliable information from raw data

- MVDA handles noise, missing data, correlation and visualize in graphs
This control chart is familiar to you?

\[ \text{SMI} = x_1 \cdot \text{Novartis} + x_2 \cdot \text{Roche} + x_3 \cdot \text{Merck} + x_3 \cdot \text{FB} \ldots \]
So this control chart is easy to understand....

\[ t_1 = x_1 \text{Temperature} + x_2 \text{Pressure} + x_3 \text{Agitation speed} \] ....
MSPC

Observation Level

- Example of a drying step

Control limits

Average (signature) of all batches

New batch assessed by the model
Statistical Process Control

BATCH CONTROL CHART

average of all batches

control limits (± 3σ from avg.)

Batch Process Signature
Work and Data flow

For Method Development

Final Model
Batch Level
Observation Level
All Process Parameters

Reduction of Dimensionality

Individual Probes

Aims:
- Creation of batch signature
- Identify correlation patterns
Work and Data flow

For Routine Use in Production

Aims:
- Conformity check
- Real time release testing
- Trend analysis
- Root cause analysis

Increase of level of detail

SIMCA-online

Batch Level

Observation Level

Identification of responsible Parameter(s)

Investigation on process data
MVDA applied to granulation

*Example for a qualitative model used for MSPC*

- High Shear Granulation (Production Scale)
- Four phases
  - Dry Mixing
  - Wet mixing
  - Water addition
  - Granulation
- Variables
  - Power consumption and torque
  - Product temperatures
  - Granulator and chopper speed
  - Pump properties and flow parameters
Key consideration for method development

• Which observations should be included?
  – Sufficient number of batches to cover **natural variability**
  – **DoE Data** for special cause variations
  – Exclusion of anomalous, unsteady, discontinuous data (spikes)

• Which variables should be included?
  – Exclusion of variables with no impact and low reliability
  – Weighting and transforming of variables
  – How many scores should be considered

• Data alignment and synchronization
  – Definition of start/stop conditions and phases
  – Merger of variables with different acquisition rates
  – Normalization of time based maturity variables vs. absolute time
Granulation Process

Data Setup

Input: Initial conditions

Variable initial conditions:
- Amount of granulation liquid
- Granulation time

X₀

Output: Quality Attributes

IPC results:
- LOD
- PSD

Dry Mixing Water Addition Kneading

1. Power consumption
2. Power consumption rate
3. Torque
4. Product Temperature
5. Mixer Speed
6. Chopper Speed
7. Water addition rate
8. Flow Liquid Speed
9. Liquid Speed Pump
Example Granulation

Results of DoE investigation

- Different phases during granulation are monitored
- Process variability are reflected by the red lines
- Clustering of DoE batches can be visualised
- Common cause vs. special cause variation
Loadings

Identification of process parameters contributing to process variability

- Which parameters are most influential?
- How do the variables correlate to each other?
First experience in production

Preventive maintenance

-10 0 10 20 30
-20 -10 0 10 20

Ellipse: TCrit (95%) = \(x^2/19.9118^2 + y^2/17.1288^2 = 1\)

Last campaign
This campaign
Last batch after liquid feed tube change
Root cause analysis

Liquid feed pump speed trajectory during the latest 2 campaigns

Campaign with OOC

After liquid feed tube changed
Root Cause: Worn out liquid feed tube

By replacing the tube, # batches were saved.

$ XXXXXXXX saved
Cell cultivation process

- **Motivation**: established process, not fully characterized, most of process understanding based on experience
- **Modeling**: > 80 DS batches, fully meeting release specifications but some variability in main fermentation yield is observed
- Defined reference (golden) batches, i.e. batches which provided the highest total amount of antibody during cell culture
Statistical Process Control for cell cultivation process

Perfusion Start

All the variables for each batch are summarized into one quantity (carrier of the information) - process signature

REFERENCE (i.e. avg of golden batches)

±3 sd from ref.
Improve Process Understanding

Compared the other batches ("non-golden") against the "golden" to establish which are the variables responsible for the observed differences.
MVDA learning

- Generated useful process knowledge
  - Enhanced process understanding supported by data
  - Improved process consistency
- Established key parameters for cell cultivation
  - medium feeding rate
  - inoculation cell density
  - cells aeration
- No correlation between cell behavior and DS quality attributes
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