Umetrics SIMCA-online: Complex Analytics Applied to PI System™ Data

Lorenz Liesum, Novartis

Presented by

Petter Möree, Umetrics

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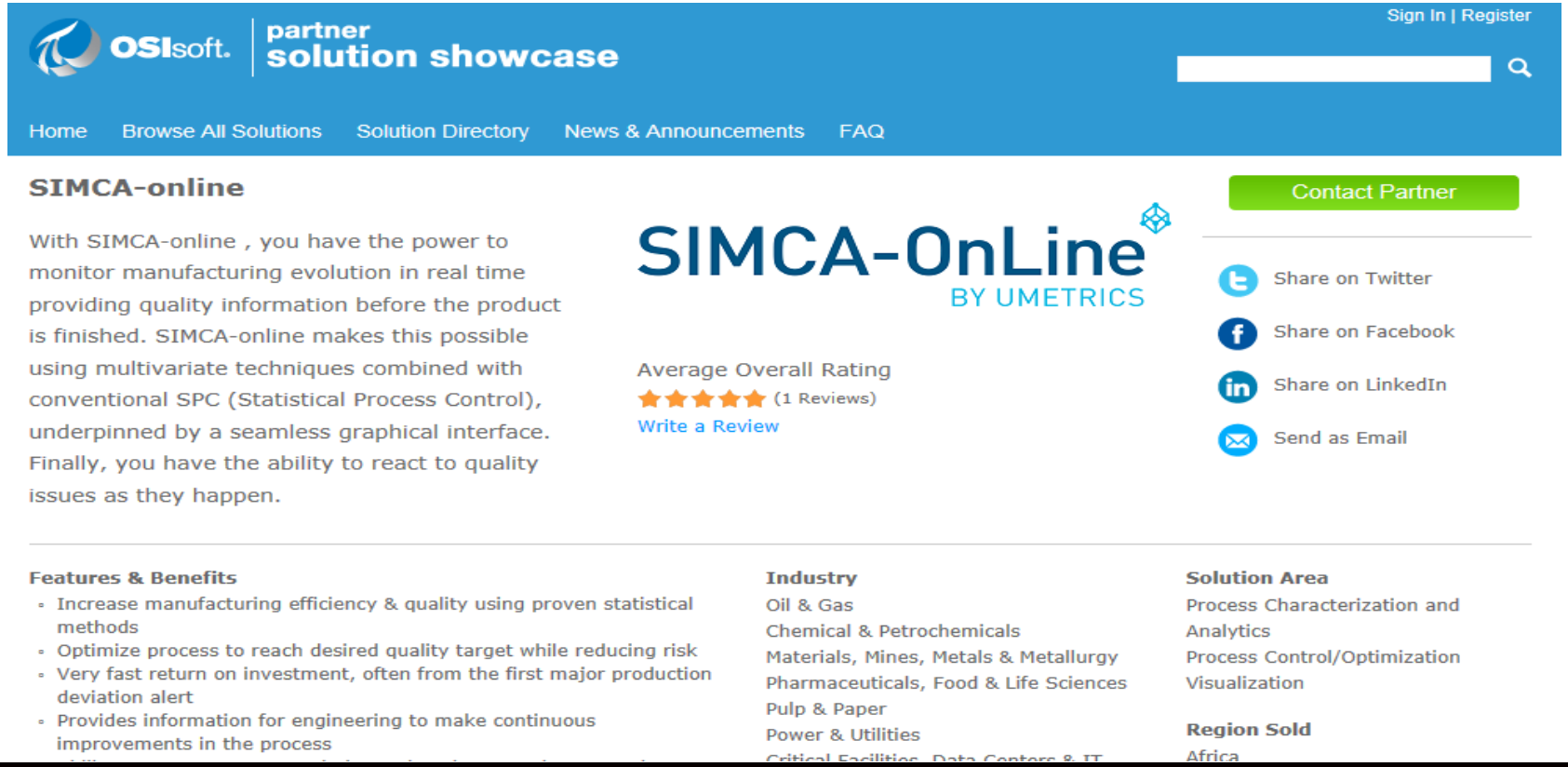

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“Our mission is to maximize the Value our customers get from our product and services”

Novartis provides healthcare solutions that address the evolving needs of patients and societies.

UMETRICS
AN MKS COMPANY

Founded in 1987 to provide consulting/teaching services based on multivariate data analysis and design of experiments by a group from the Department of Organic Chemistry, from Umeå University, Sweden.

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On-line Process Monitoring and Complex Statistics applied to PI Systems in Pharmaceutical Production at Novartis

Lorenz Liesum

Global Pharma Engineering, Novartis

OSIsoft Webinar

17th July 2013

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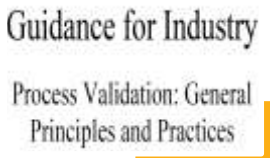
About Novartis

Novartis provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on healthcare, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care products, cost-saving generic pharmaceuticals, consumer health products, preventive vaccines and diagnostic tools. Novartis is the only company with leading positions in each of these areas.

Business Driver for on-line monitoring and control

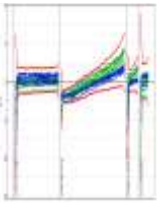
Production Cost

- Reduction of end product testing
- Throughput times decrease
- Higher level of Automation



Regulatory Expectations

- QbD (Quality by design)
- New Process Validation Guidance
- Less Failures
- Valuable for investigations



Innovation

- More efficient process control
- Better Process understanding
- Continuous Manufacturing

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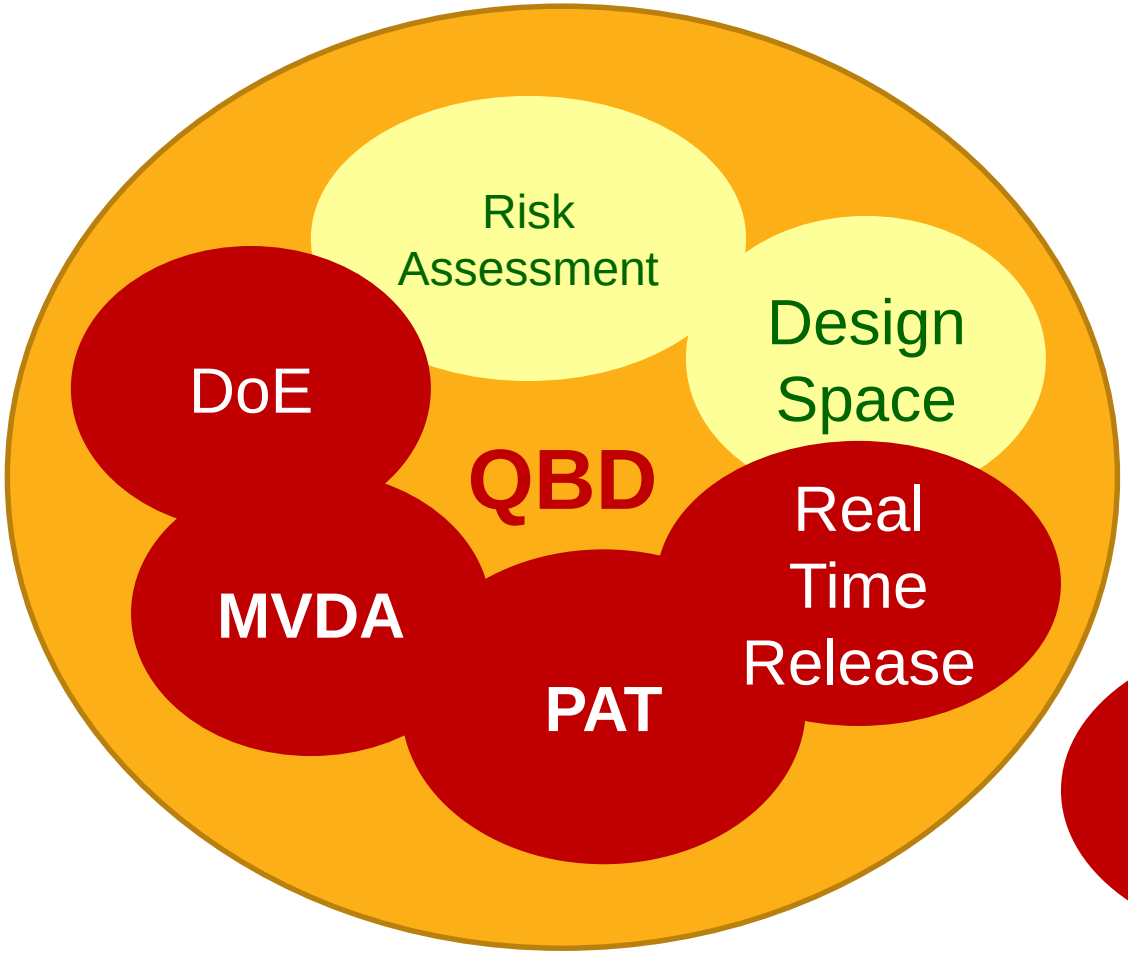
Definition QbD (Quality by Design)

Paradigm shift to develop and control processes and the quality of the products



With Chemometrics High Data flow

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Type of data

Input X and output Y

- **Input data X**
  - Critical material attribute: CMA , e.g. type of excipient/catalyst
  - Critical process parameter: CPP, e.g. pH, temperatures or pressure
  - In process control: IPC, e.g. water or solvent measurement
- **Output data Y**
  - Critical Quality Attributes: Assay, Dissolution, degradation products

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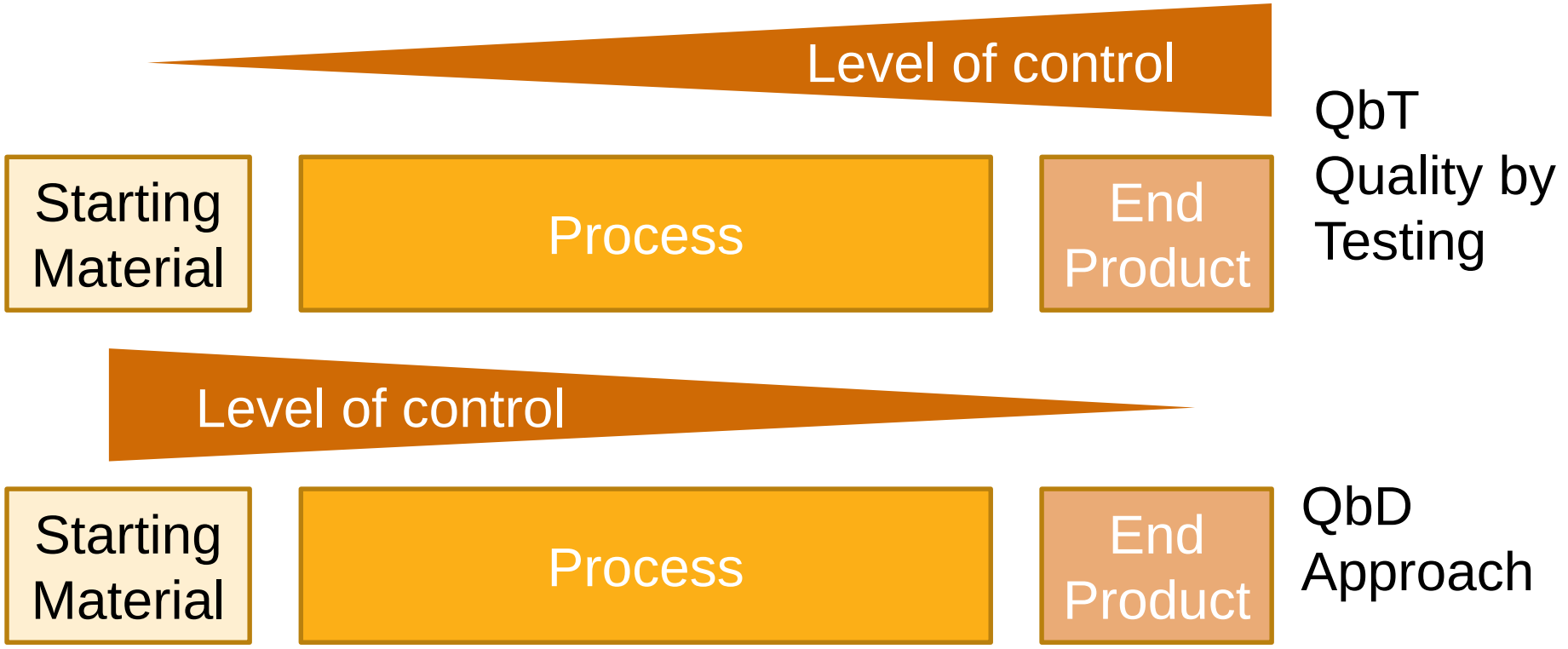
Real Time Release (RTR) „testing“

- *„...Quality cannot be tested into the product, i.e., quality should be built in by design.“ (ICH Q8)*



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PAT@Novatis

„Soft and hard“ PAT

- Process sensors (PAT):
  - Measure a physical or chemical property on-line
    - Process Spectrometer (Near Infrared spectro
    - Process Chromatography
    - Process Mass Spectrometry (MS)

Getting Data

- Process data evaluation (**M**ulti **V**ariate **D**ata **A**nalysis):
  - Evaluation system to cope with huge data amount to extract information out of data in real time
    - Multivariate statistical process control (MSPC) enabled by MVDA

Evaluating Data

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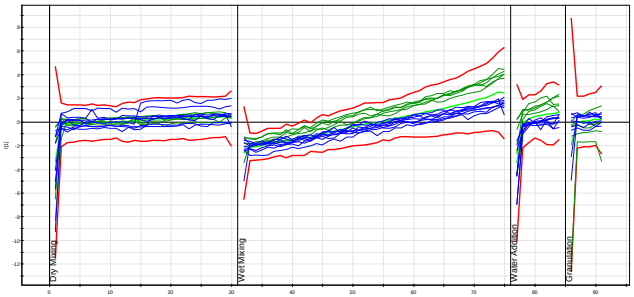
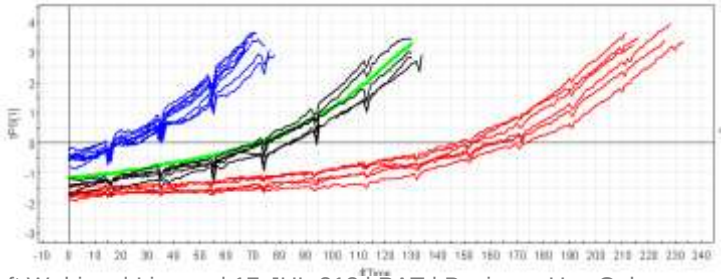
QbD Control Strategy (Real Case Study)

Pharmaceutical Process for a Solid Dosage Form, Mix of soft and hard PAT

Granulation | Drying | Blending | Compression





MVDA Models

Blend Uniformity by NIR

Content Uniformity by NIR

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In alignment with EMA process validation guideline

of CQA and Critical Process Parameter (CPP) trends. Process analytical technology applications such as NIR spectroscopy with or without feedback loop (e.g. end point determination of blend homogeneity, determination of granules surface area, determination of content uniformity with large sample size) and multivariate statistical process control (MSPC) can be viewed as enablers for continuous process verification.

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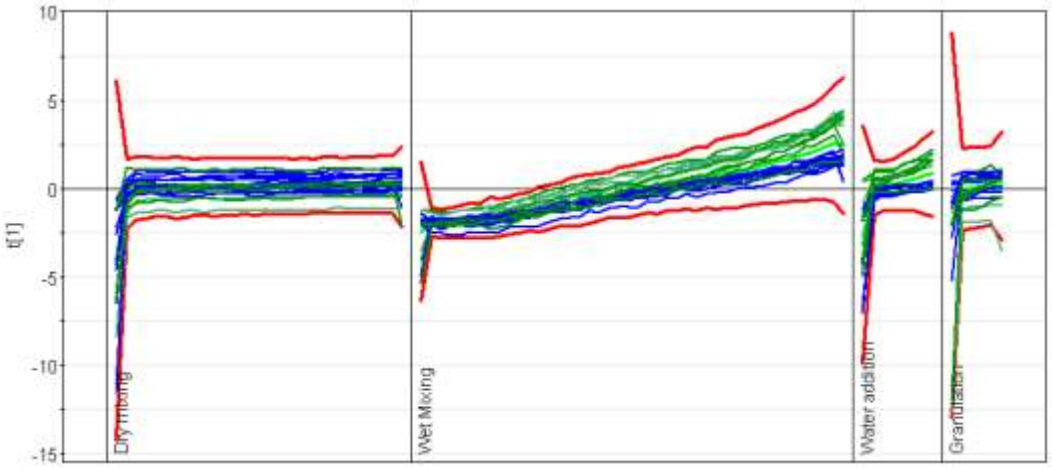
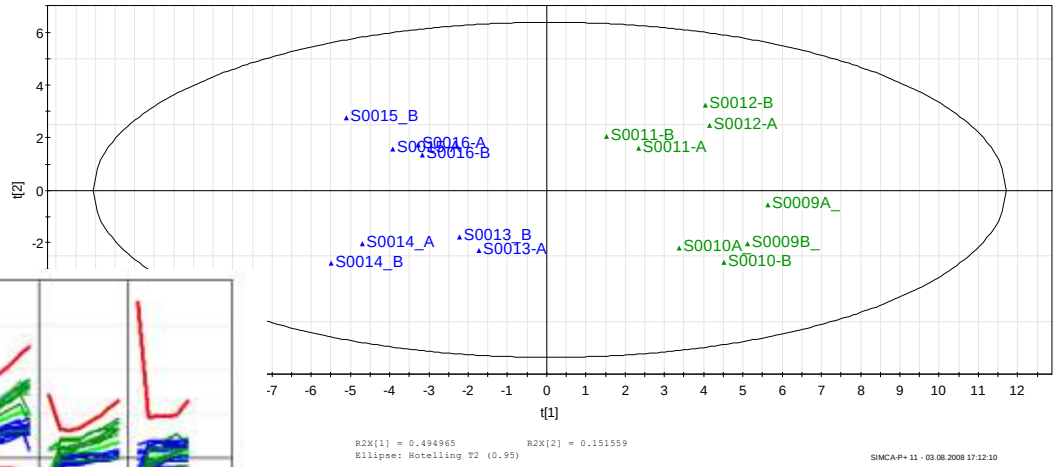
Use of Multivariate Data Analysis (MVDA) for Statistical Process Control (SPC)





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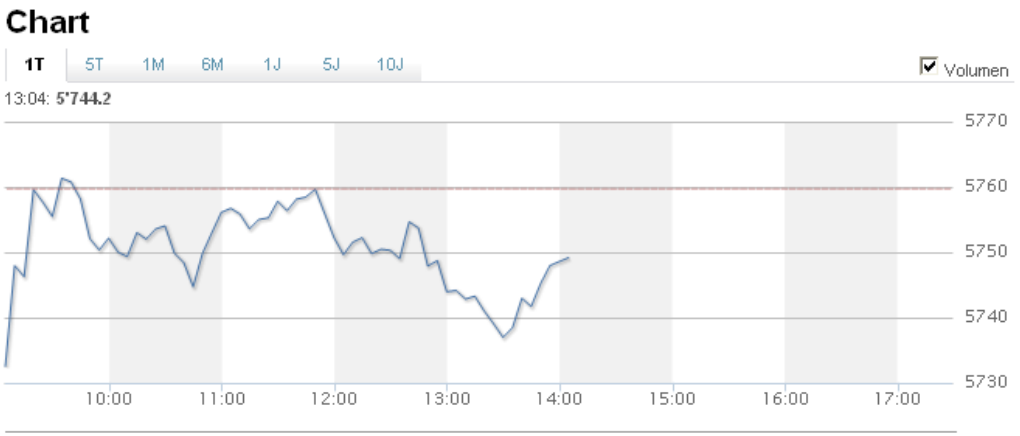
This control chart is familiar to you ?



SMI= x1*Novartis + x2*Roche + x3*USB ....

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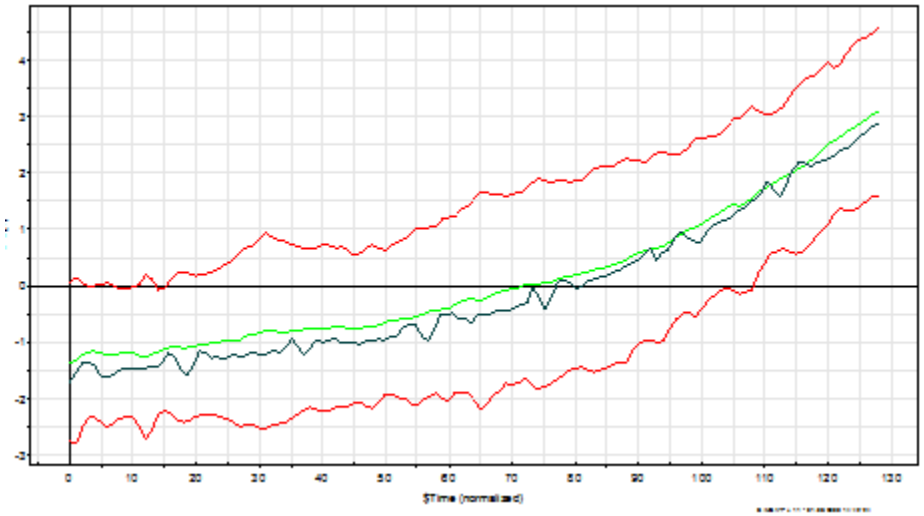
So this control chart is easy to understand....



t_1= x1*Temperature + x2*Pressure + x3*Agitation speed ....

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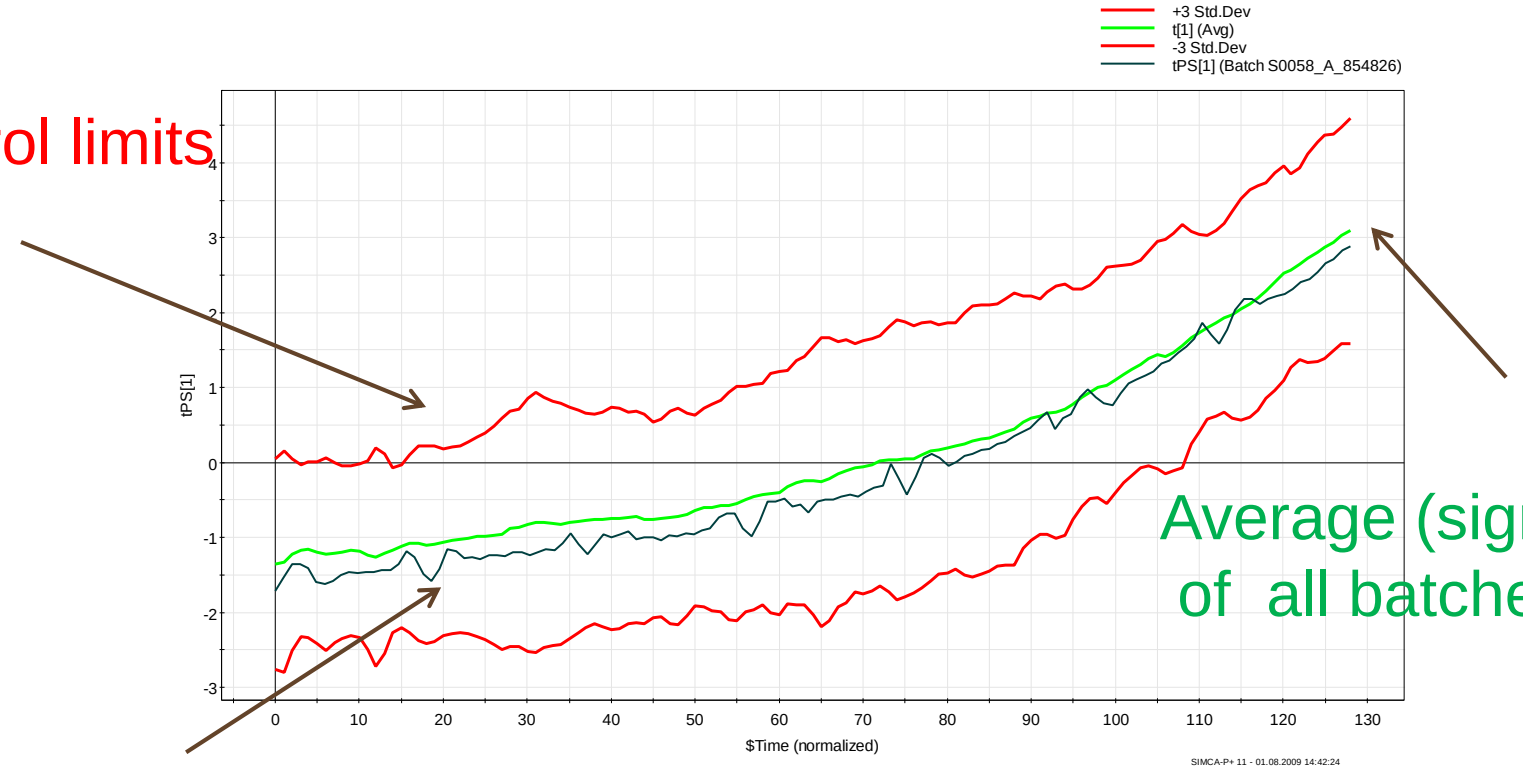
MSPC

Observation Level

- Example of a drying step

Control limits



Average (signature) of all batches

New batch assessed by the model

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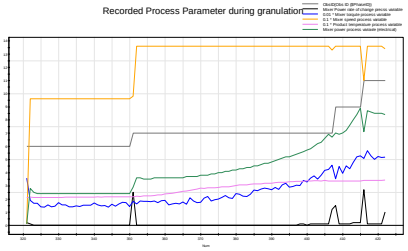
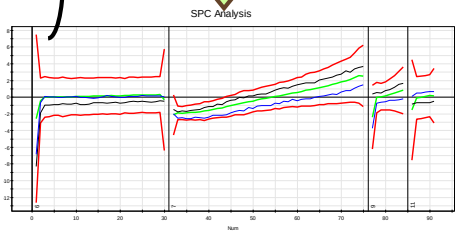
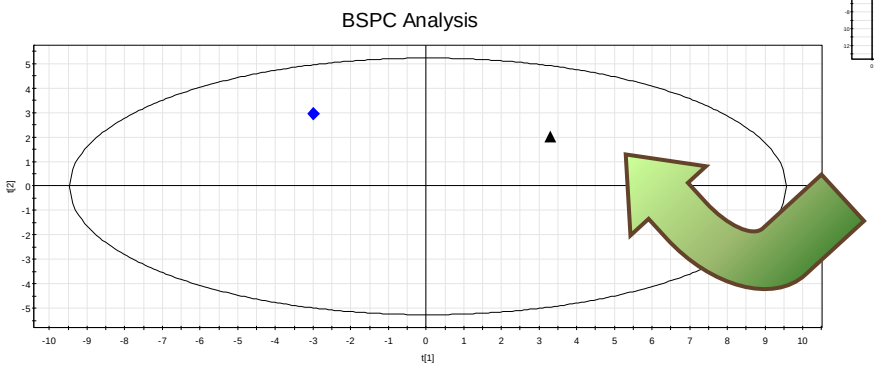
SPC (Statistical Process Control) & BSPC (Batch-level SPC)



Process parameters are summarized in one quantity (process signature)





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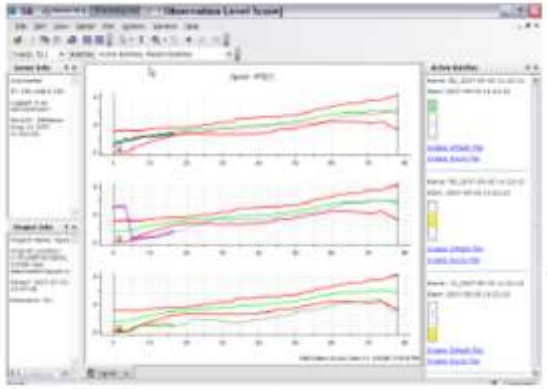
Data Flow and Aggregation



MVDA Analysis

PI System

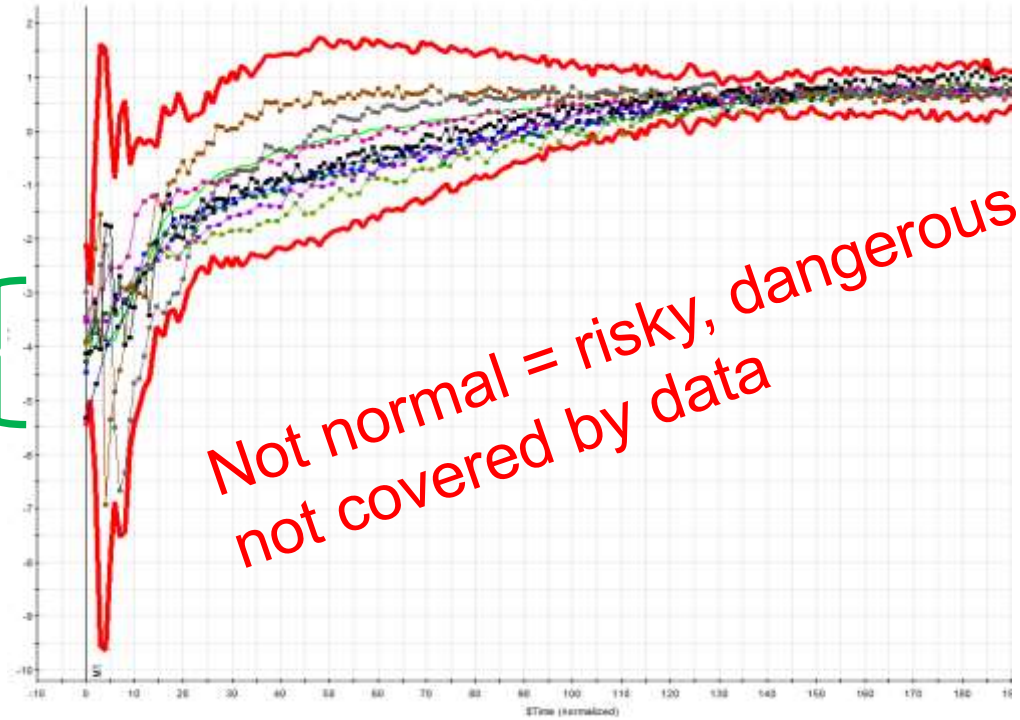
SCADA

Equipment with physical and chemical sensors (PAT)

Monitoring and Trending

Assurance of normal operational conditions

Not Normal



Non normal behavior requires root cause analysis and an explanation.

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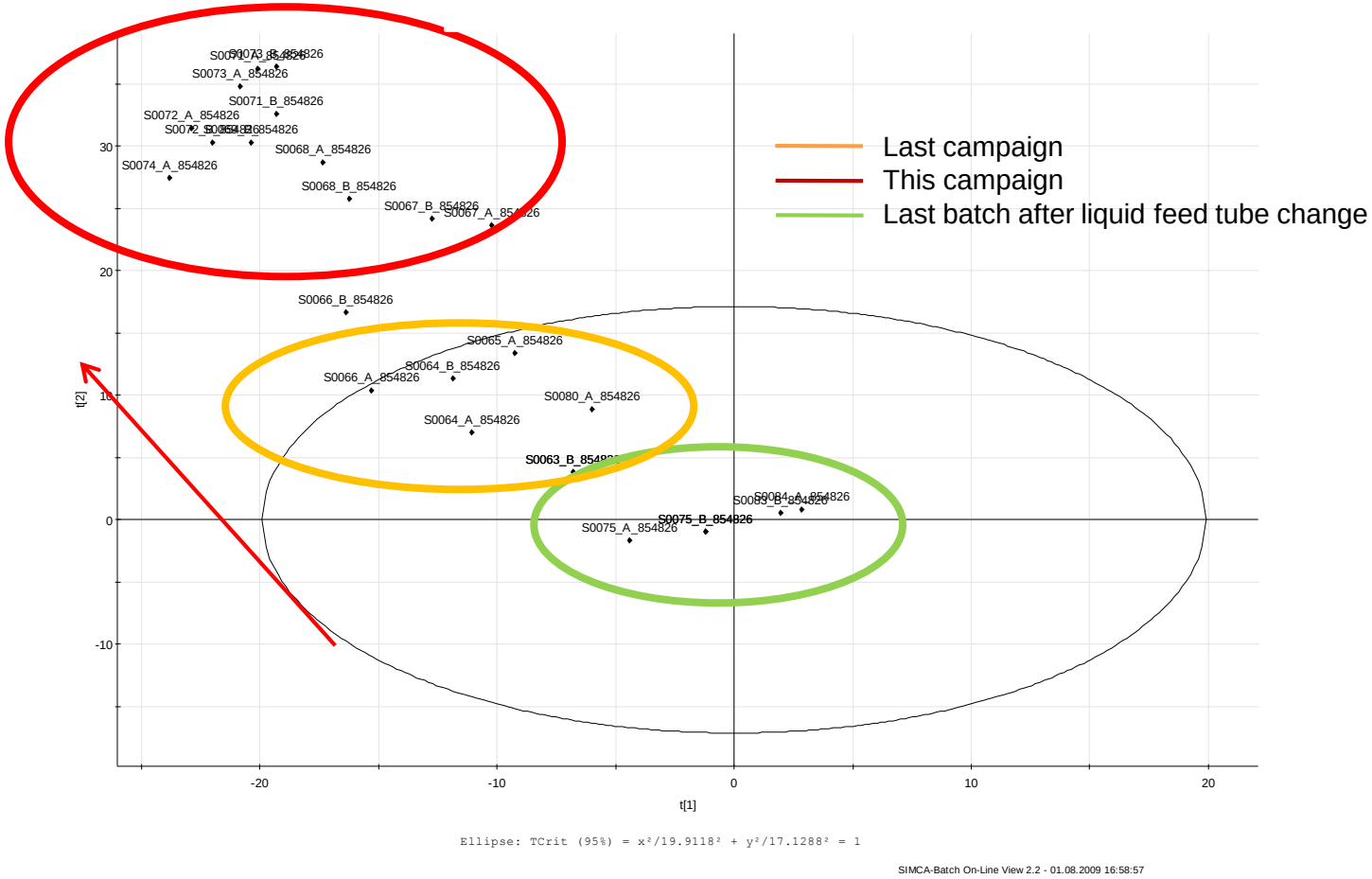
MVDA example
Early Fault Detection



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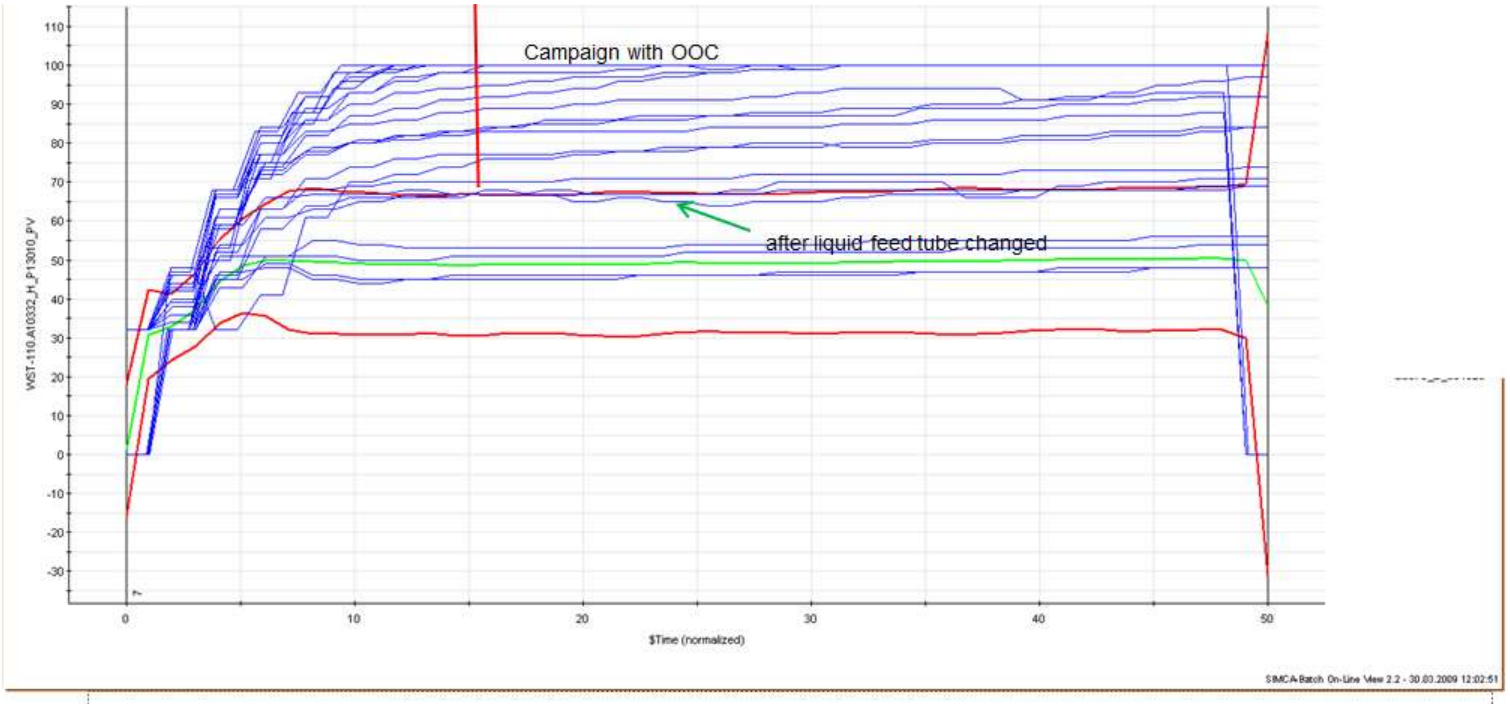
MVDA example

Early Fault Detection



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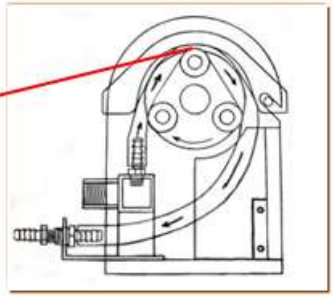
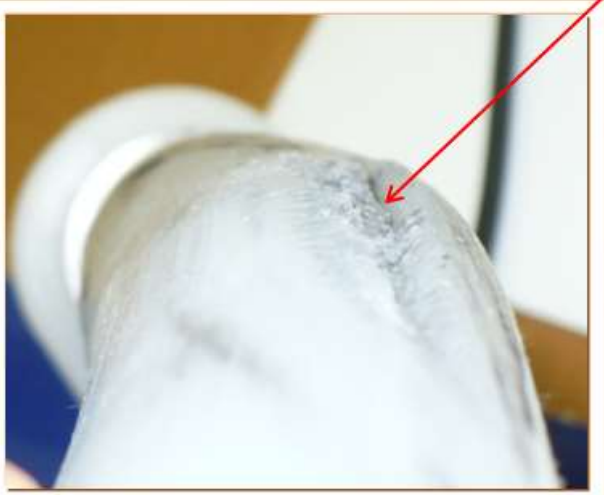
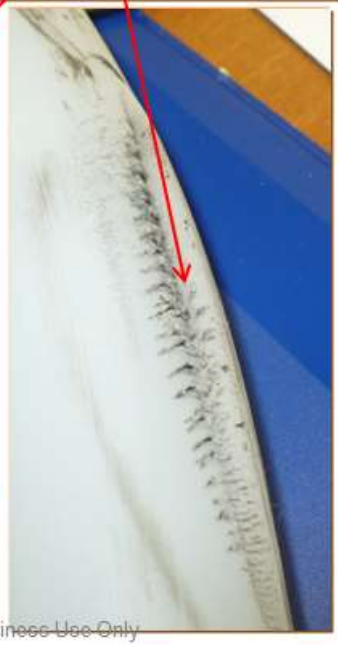
MVDA example

Root cause Analysis







Root Cause:
Worn out liquid feed tube

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M(ultivariate) TC in the production shop floor

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Case Example for PROCES CONTROL

Controlling a process using on-line MVDA

- Tags from the PI System
  - Temperatures:
    - Internal Drying Temperature
    - Jacket Temperature
    - Dryer Vapor Temperature
  - Pressures
    - Pressure in the dryer
  - MS
    - Acetone concentration measured by MS in the headspace
- Batch data:
  - More than 30 historical batches produced at target conditions reflecting normal behavior

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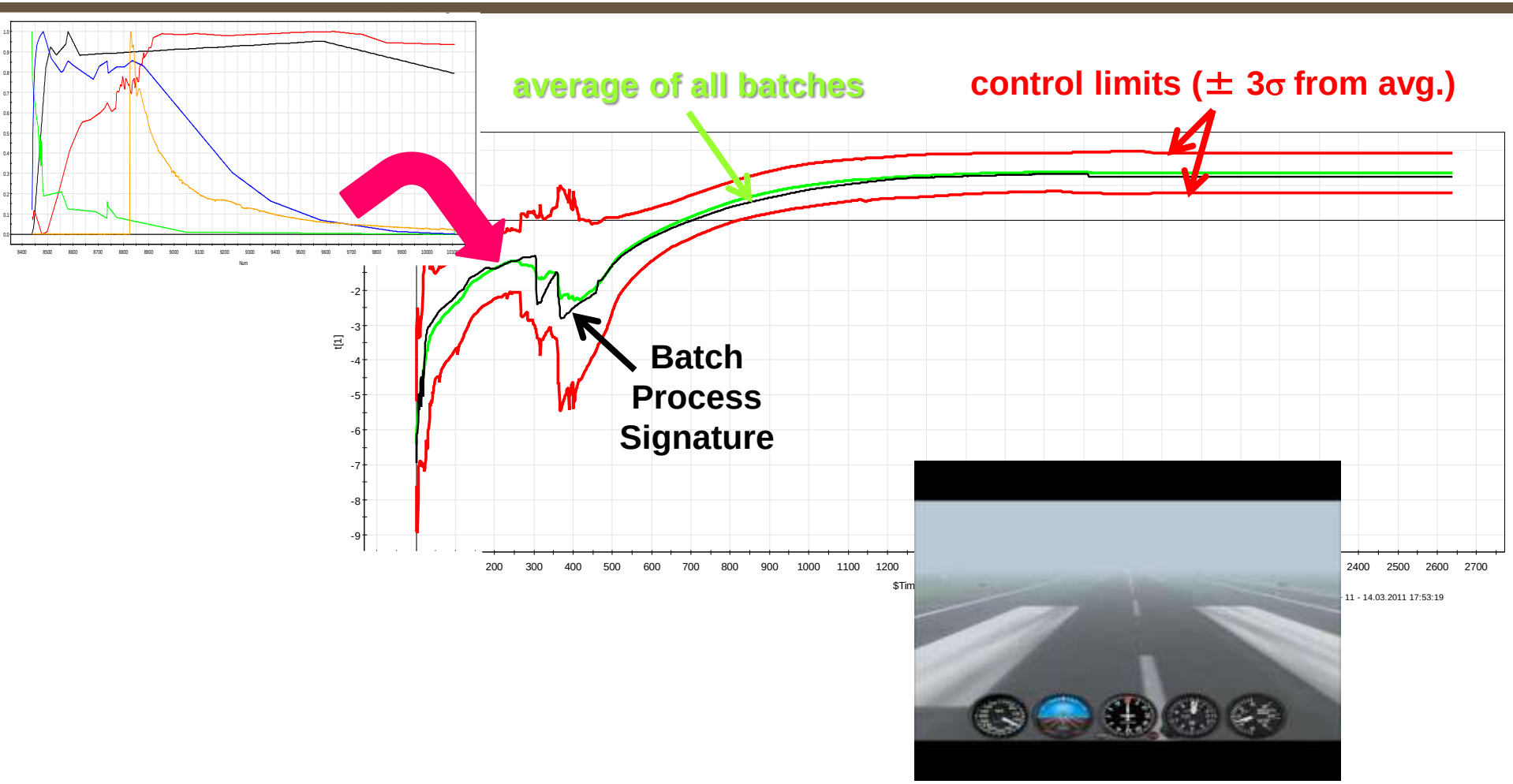
Statistical Process Control of a drying step



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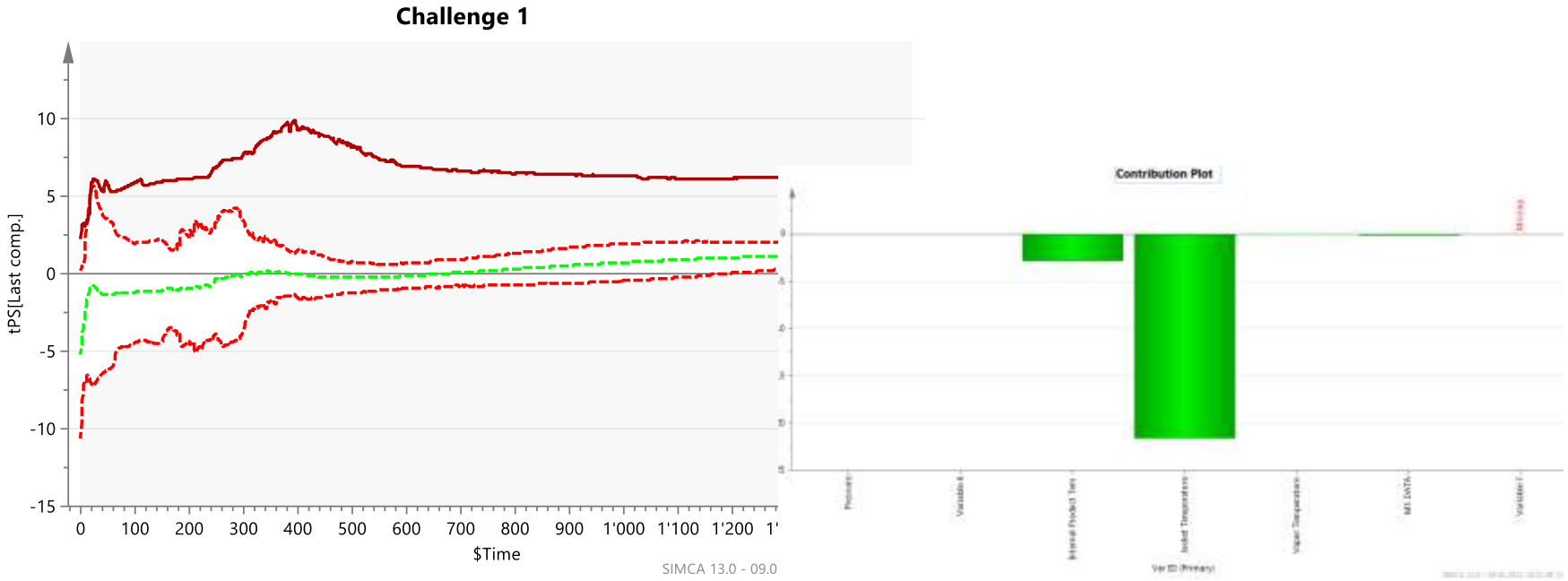
Challenge

Batches that showed an unusual behavior



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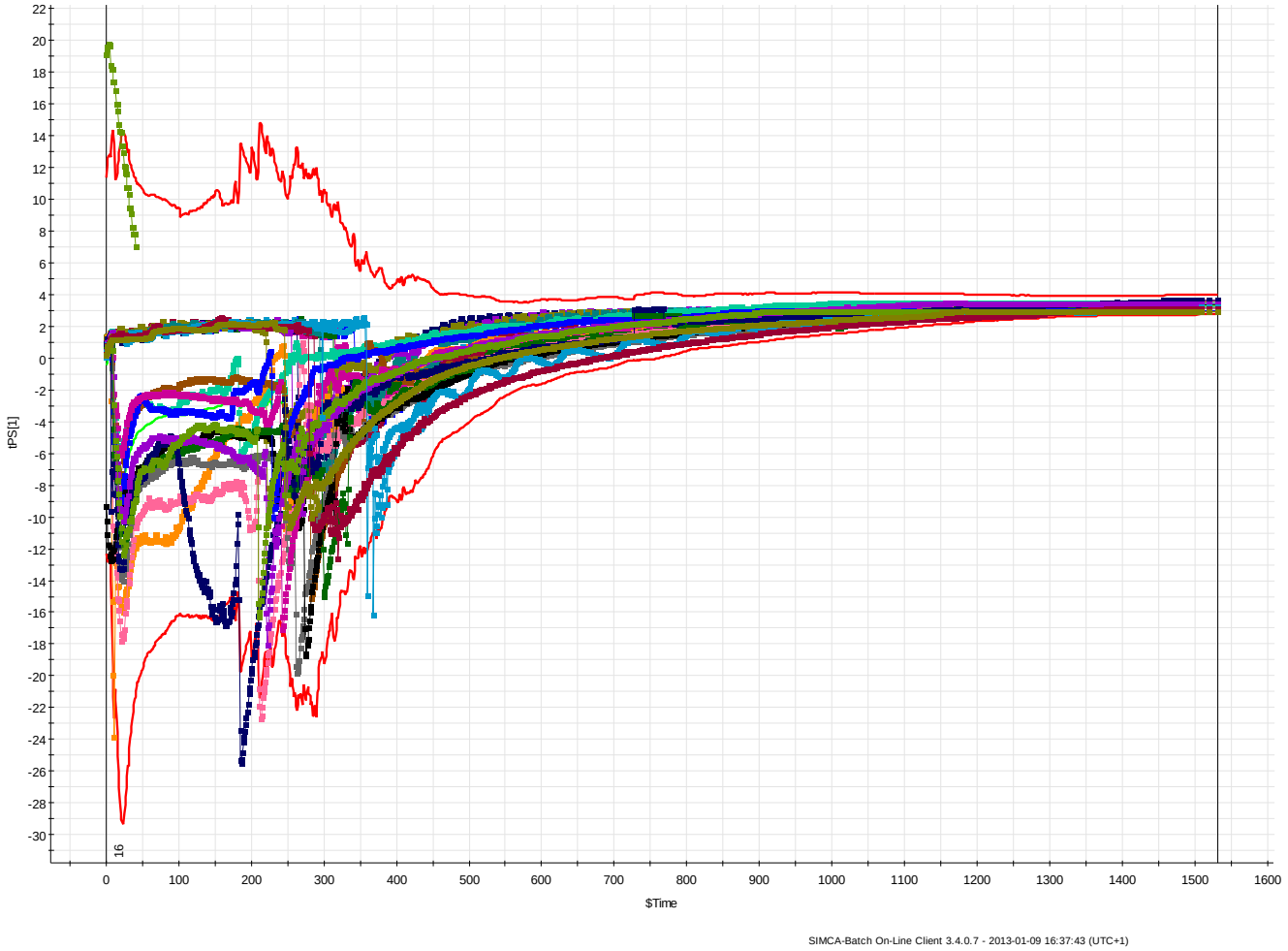
Experience from daily routine

Recently produced batches



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Conclusions

- Important aspects to be considered
  - Convince people in QA and production for a change in mindset
  - A state of the art automation and IT infrastructure is a prerequisite
  - A PAT project is not completed right after validation, then it actually starts with automation, maintenance and using it at a daily basis
  - and ....

PATience

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Thank you for you attention !

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mks
Technology for Productivity

Umetrics

Company Presentation

Petter Mörée

Director Product Management

Umetrics, The Company

- Part of **~1Billion** conglomerate
- The **market leader** in software for multivariate analysis (MVA) & 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
- Offices: Umeå & Malmo, Sweden
  - London, England
  - Boston & San Jose, USA
  - Japan, Israel & More
- Close collaboration with universities in USA, Sweden, UK and Canada

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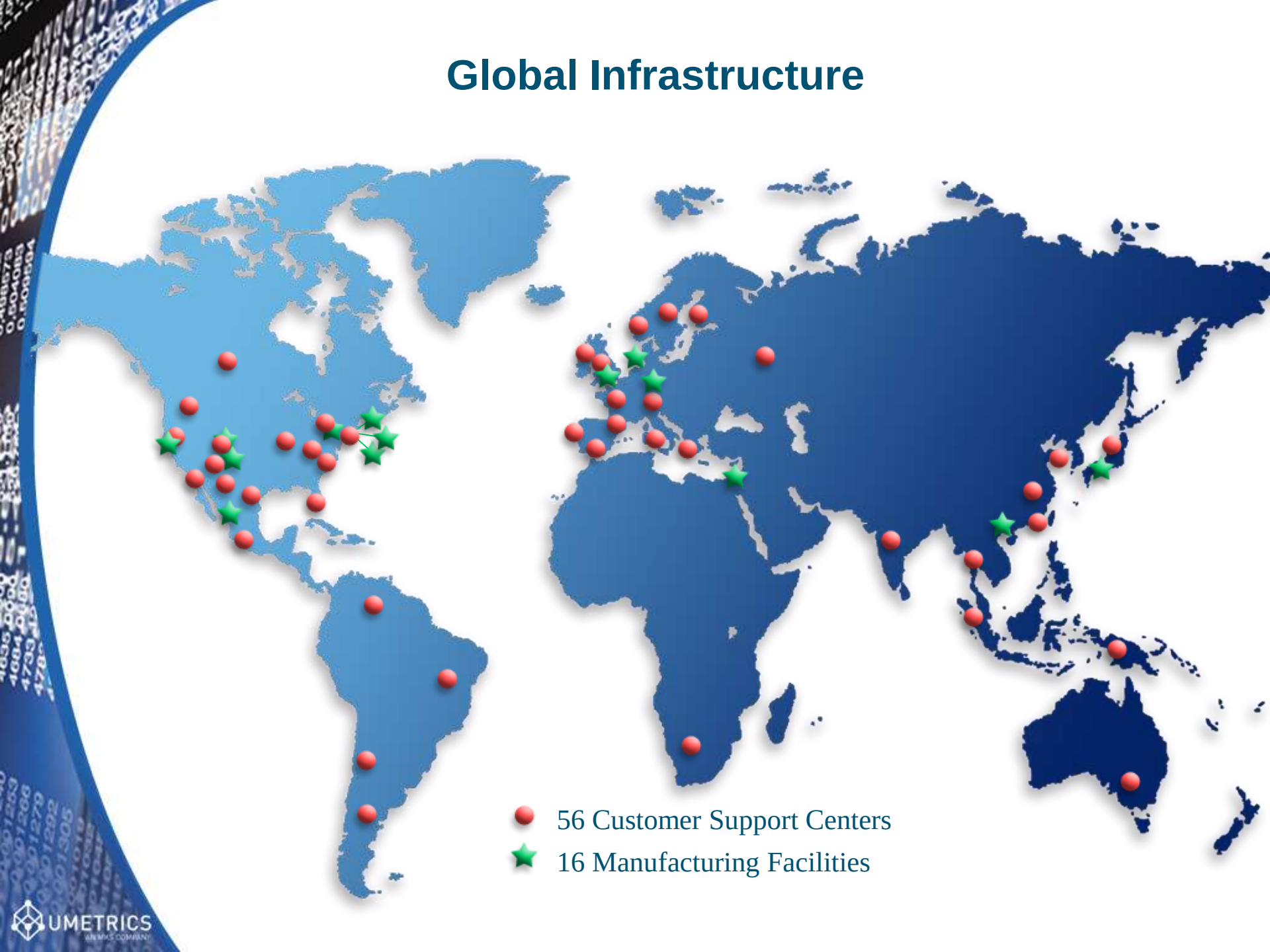
Global Infrastructure



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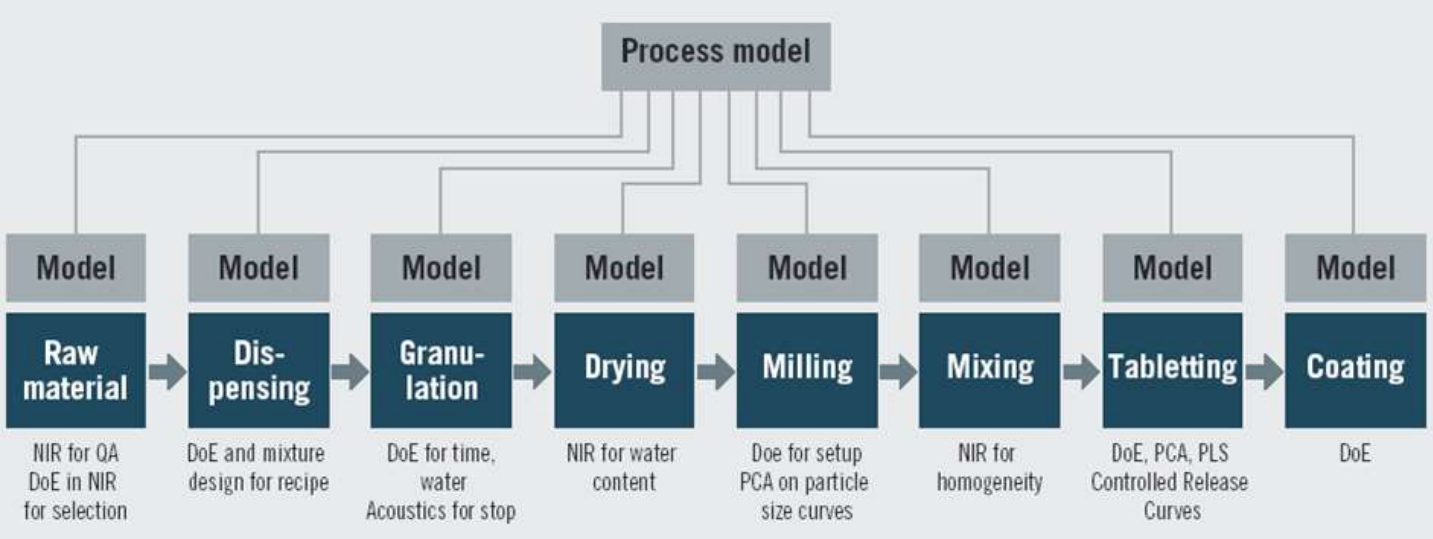
Our Customers' Goals in Pharma

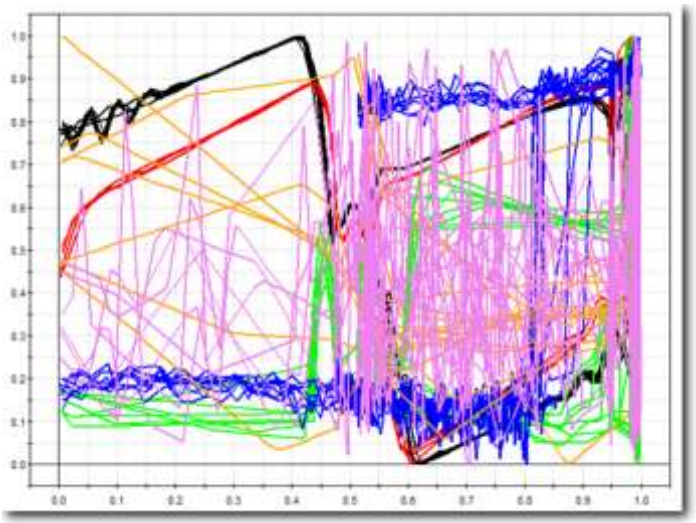
- The goal in Pharma production is to help take advantage of data present (automation and spectral data) in the development labs, and the production environments all the way from API to the final product. **= ROI** (Return of Investment)



The Need for Multivariate

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

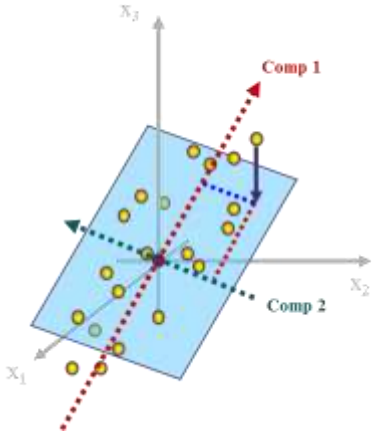
- Spectrometers
  - NIR, FTIR, RAMAN, UV, LLSD
  - MS, GC, HPLC
- Process Sensors
  - Acoustic, Video
  - P, T, Flow, pH
  - pO2 pCO2



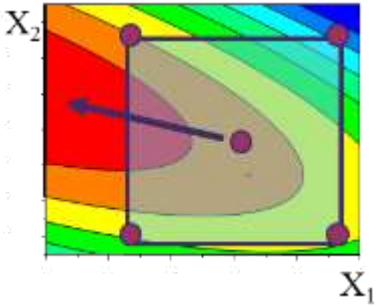
- Require MVA methods to visualise and extract reliable information from raw data

The Technology

- **Multivariate Analysis**
  - Reduces complexity when multi parameters are measured
  - BUT takes into account ***ALL variables***
  - Convert ***data*** into ***information (pictures)***
  - How far is an observation from the model
  - Minimum false alarms



- **Design of Experiments**
  - Tools to design experiments
  - Use for process analysis and optimisation
  - Quick, powerfull, easy to use
  - ***Maximize*** information
  - ***Minimize*** No of experiments
  - Minimise the cost



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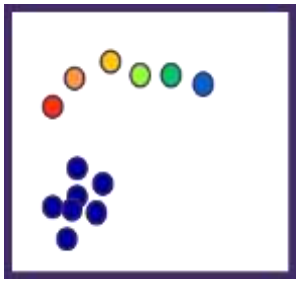
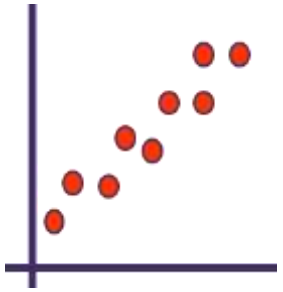
The Basic Multivariate Methods

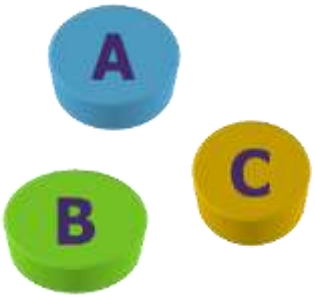
- **Overview** (PCA – Principal Component Analysis)
  - The objective maybe an overview, find out if any observation has any abnormal values, making it atypical, and an ***outlier***. You may want to look at their similarity and dissimilarity.



- **Relationships** (PLS - Partial Least Squares)
  - A model of predict measurements base on exiting observations. Can predict Quality / Purity, Biological Activity, Toxicity, Reactivity and much more.

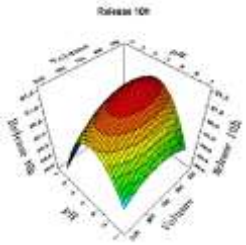


- **Classification** (PLS-DA)
  - Finally you may have collected different types of objects and you want to understand whether the types are truly different and if so which measurements make them different.

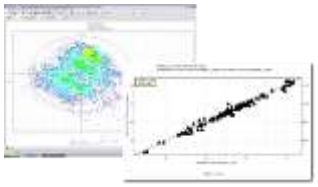


Umetrics Solutions

MODDE – Software for Design of Experiments (DOE), Optimization and Design Space Estimation.

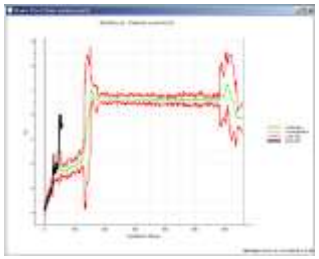


SIMCA - Software for multivariate analysis (MVA) and modeling. For development of process models and spectral calibration models.

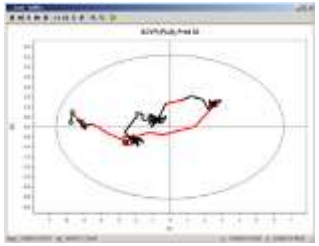


Real-time/On-line solutions:

SIMCA-Q – Real-time multivariate modeling and prediction engine software for integration with other systems (i.e. SIPAT, xPAT, SynTQ, Waters, Sartorius). Allows execution of MVA models for process monitoring, quality prediction etc..



SIMCA-online (SOL) – Real-time multivariate monitoring of batch or continuous processes. Allows continuous monitoring of batch evolution for multiple unit operations. Provides a tool for early fault detection and real-time quality prediction.



All Umetrics software have

- User-friendly point-and-click interface developed for use by engineers, scientist and operators
- Been fully tested and validated to ensure quality expected from Pharma industry

Services

- Technical support
- Consulting/Feasibility studies
- Training: MVA, DoE, Process Development, Manufacturing, PAT, Spectral applications etc….

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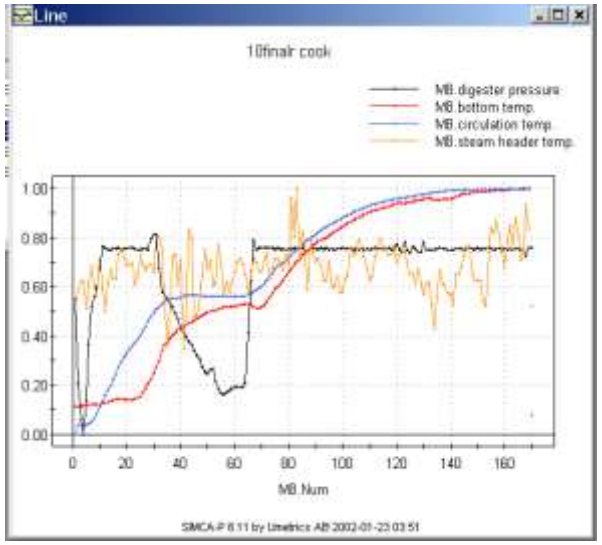
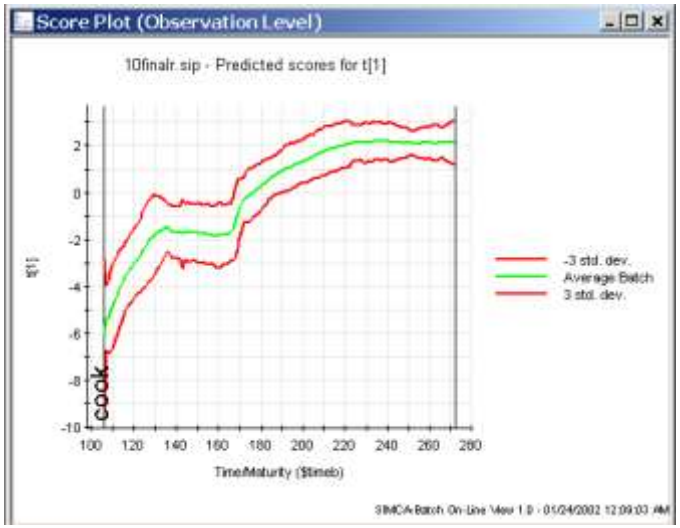
MVA-Batch Technology

- We summarize the variables measured during the evolution of “good batches” into a few new variables (the scores).
- Many individual variable plots reduce to a few Score Plots.



BECOME



Many variables of one batch are plotted.

All the variables of same batch plotted

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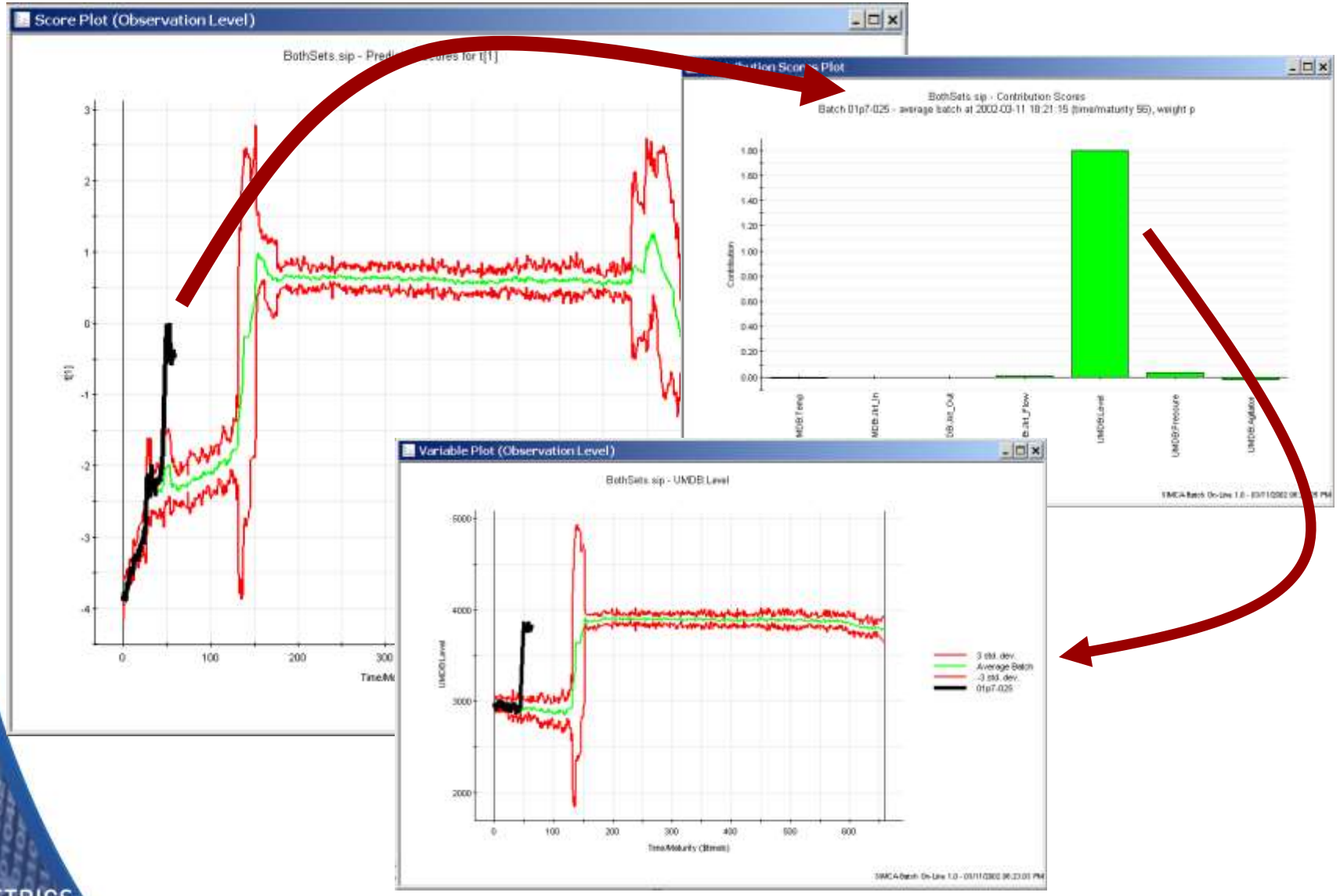
Multivariate Process Monitoring (BSPC)
* Easy of Use *



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Overview of Umetrics Solution

Starting material

400 l

2000 l

10000 l

Down Stream

Lab QA

Process sensors

Instruments

LIMS

Process Historians (PI Server)

Spectra

SimApi

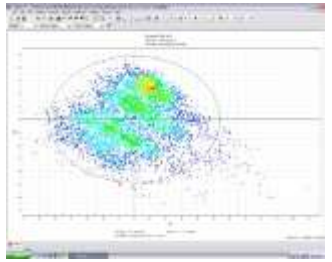
SimApi

SimApi

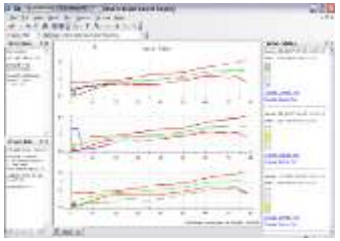
Data Integration Layer

SIMCA - offline

- Historical Data Analysis
- Model Building
- Process Characterization
- Process Investigation



SIMCA process model



SIMCA-online (Real Time)

- Monitoring
- Prediction
- Fault Diagnosis

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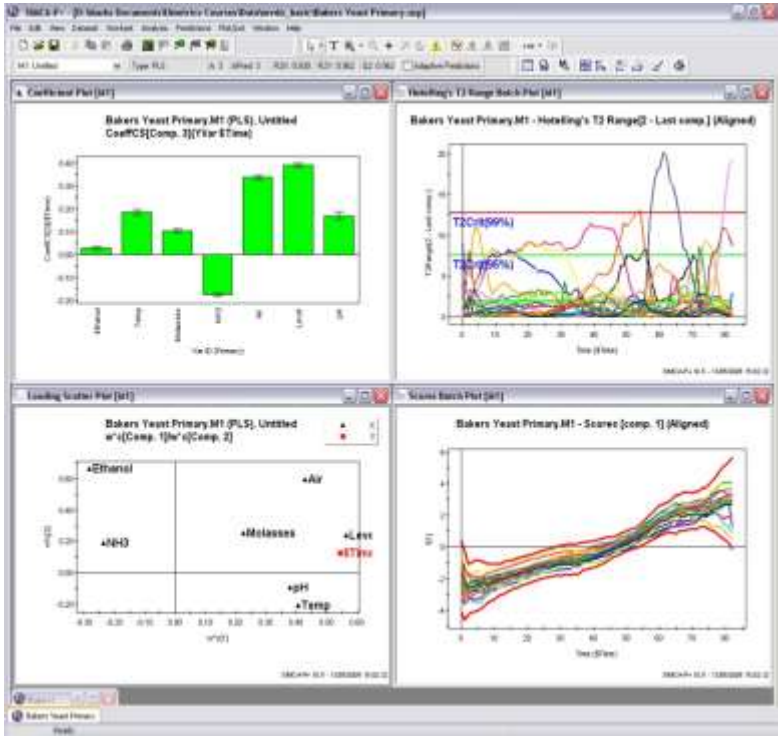
DEMO
SIMCA-online 13

Multivariate Modeling Applications

- Process Mapping and Process Monitoring
- Identification of Critical Quality Parameters
- Prediction of Metrology
- Prediction of Quality
- Process Classification
- End-point detection
- Trouble shooting
- Capacity Improvement
- Calibration



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Implementation Phases

- **Training**
  - Multivariate methods
  - PAT
- **Feasibility Study**
  - Quantify information in data
  - Understand variability sources
  - Return on investment
  - Review data infrastructure

Learning/Scoping Phase

Test/Trial Phase

- **On-line Pilot**
  - Run models in on-line production environment
  - Review issues, ROI, etc…
  - Validation

Corporate Adoption Phase

- **Site/Corp Buy-in**
  - Verify validation, ROI, monitoring, data infrastructure etc…
  - Corp sales agreement
- **Spread to other sites or product lines**

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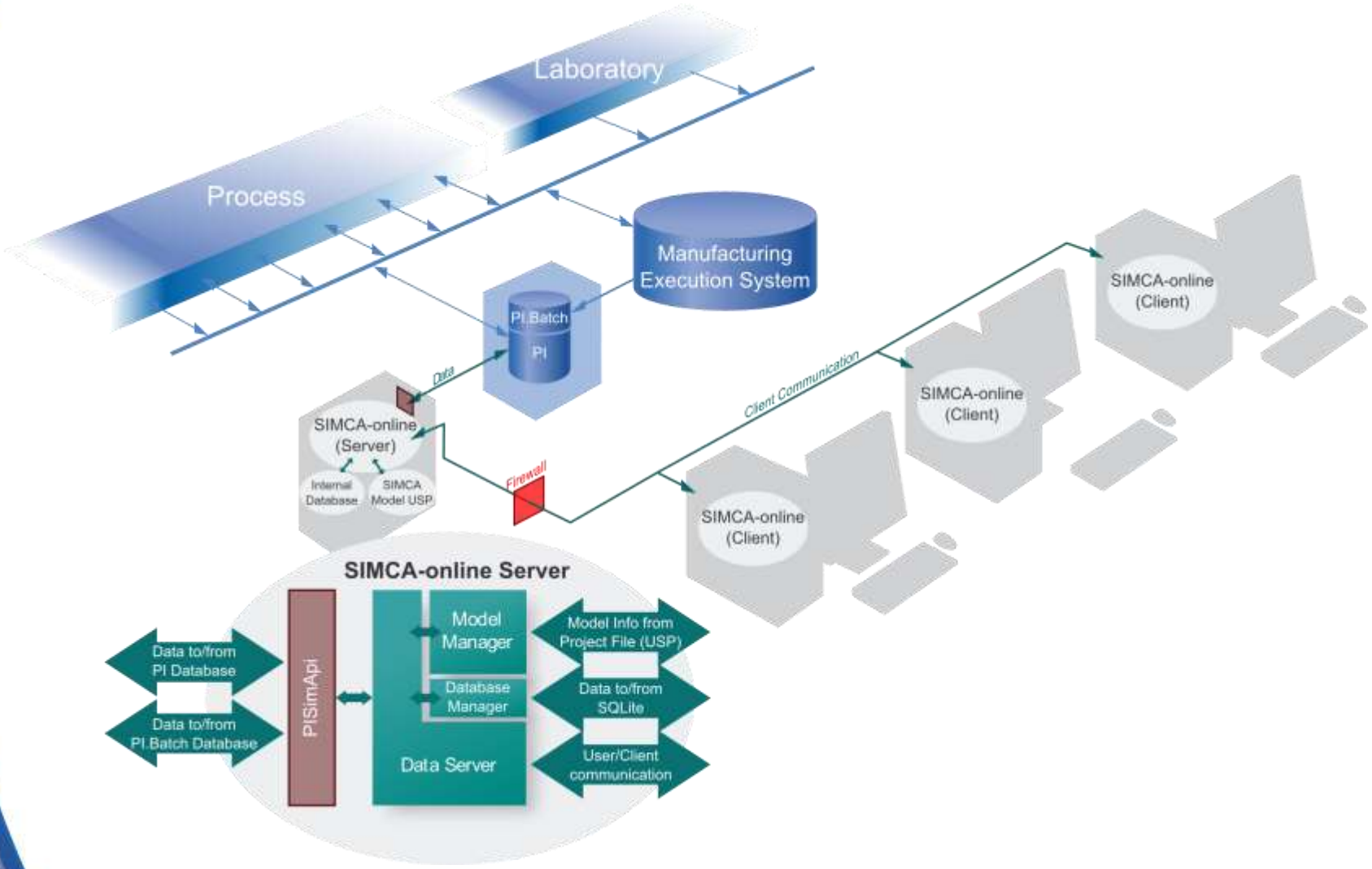
Umetrics and OSIsoft

SIMCA-online and the PI System set the standard for real-time multivariate monitoring, prediction and control

Relationships

- More than 80% of Umetrics install base uses PI System with SIMCA-online.
  - Corporate installations with e.g Novartis, Biogen, Amgen, Merck etc.
- Close partnership between the companies for more than 8 years
- Documentation is available by both companies
- Support has escalated channels via OSIsoft
- Supports batch processes & continuous processes
- Full support for catch-up, re-prediction, export and reporting

Architecture – Umetrics SIMCA-online and the PI System



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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

Contact Partner

Share on Twitter

Share on Facebook

Share on LinkedIn

Send as Email

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

Documentation and support by OSIsoft

OSIsoft.

Best Practice Integration Guidance: Integrating Umetrics SIMCA-Batch On-Line with PI

Version 1.0

References

Reference	Source
SIMCA-Batch On-Line Interface to the PI System, Version 2.1.1.3	OSIsoft User Manual [LINK TO DOCUMENT]
User Guide to SIMCA-Batch On-Line, Version 3.3	Umetrics User Guide [LINK TO UMETRICS WEB SITE]

Version History

Version	Date	Author(s)	Description
1.0	May 06, 2009	Todd Brown	First Approved Version
2.0	Dec 27, 2011	Umetrics On-Line Support	Non OSIsoft approved updates to reflect recent changes in the Umetrics system

System Overview and Architecture

This section will describe the systems overview and architecture for implementing Umetrics SBOL on top of PI.

System Overview

The OSIsoft SIMCA-Batch On-Line Interface is not a typical OSIsoft Interface. While most OSIsoft Interface primarily focus on bringing data from external systems into PI as their primary function, the SBOL Interface exposes PI data to the Umetric's SBOL application via their SimApi programmatic interface. SimApi does allow multivariate parameter data from SBOL to be sent back to the PI Server and stored in PI tags.

Figure 1 below describes the systems overview and overall process for setting up the model (USP file) and then configuring that model within SBOL. The *PI DB* is the PI server that collects data from the manufacturing automation systems and PLCs in real-time and histories that data. In order to create the model within SIMCA-P+, a file containing a raw data dump in a spreadsheet format must be generated by the customer from the source historical PI data that includes the variables and data that will be used within the model. The format of the data within this file is defined within the various Umetics documentation but in general it must contain data including the Batch ID(s), Phase IDs/Names, optionally Umetrics sub-batches, and data for each variable at the same interpolated sampling interval. Once the source file is generated, it is imported into SIMCA-P+ where the model is generated (USP file in diagram). The model is then imported into SBOL where there is a mapping of variables defined in the model with actual PI tags. In addition, active tags are mapped within SBOL to PI Unit Batch .ACTIVE tags and PI Subbatch .ACTIVE tags. The SimApi (OSIsoft SBOL Interface) is used to provide this functionality within SBOL. After the model is created and running within SBOL, the SimApi (OSIsoft SBOL Interface) is used to allow the SBOL application to read and write snapshot data in PI, read archive data from PI, and read a subset of batch data from the PI Batch DB.

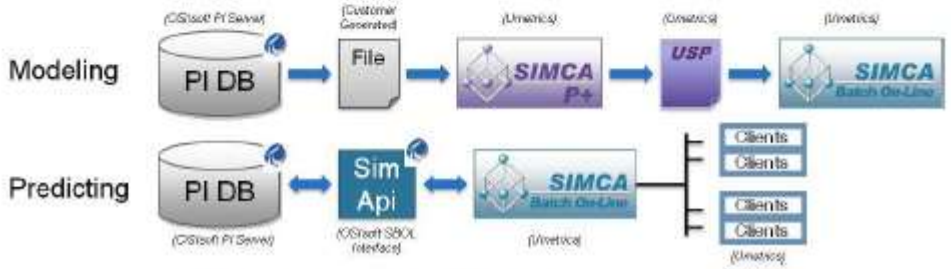

Figure 1 – Umetrics SBOL and OSIsoft PI System Overview

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Regulatory References

- Umetrics is in close relation with regulatory
- Performed 3 day trainings for inspectors and assessors in MVA, Batch MVA and DOE.
- Regular review submissions.

afssaps
Agence française de sécurité sanitaire des produits de santé

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

FDA U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Quality

- All Umetrics products are tested and validated.
- Validation reports are available
- Complete validation package is available
- Entire QA team has long expereince in testing and validation
  - They have GMP5 and CFR 21 part 11 training
- Audits performed at Umetrics
  - Beiersdorf AG 1996
  - AZ 2000, 2003, 2006
  - GSK 2004
  - Novartis 2005
  - Biogen 2006
  - TEVA 2011
  - Baxter 2012

Some of Umetrics Customers

Business drivers of PAT/QbD

Improve Existing Process

- Gain new process understanding
- Process optimization
- Process consistency
- Reduced cost of quality
- Raw material specifications
- Real Time Release

New Product Development

- Real Time Release (RTR)
- Fast time to market
- Fast scale-up
- Clinical batches
- Process optimization
- Reduced cost of quality

Validation Optimization

- Validation needs understanding
- Integral part of project
- Built validation into process

Site to Site transfer

- Accelerate transfer
- Design space
- Reduce validation effort
- Mitigate transfer risk
- Move manufacturing to most effective site

End of life-cycle

- Transferability of process
- Scale down

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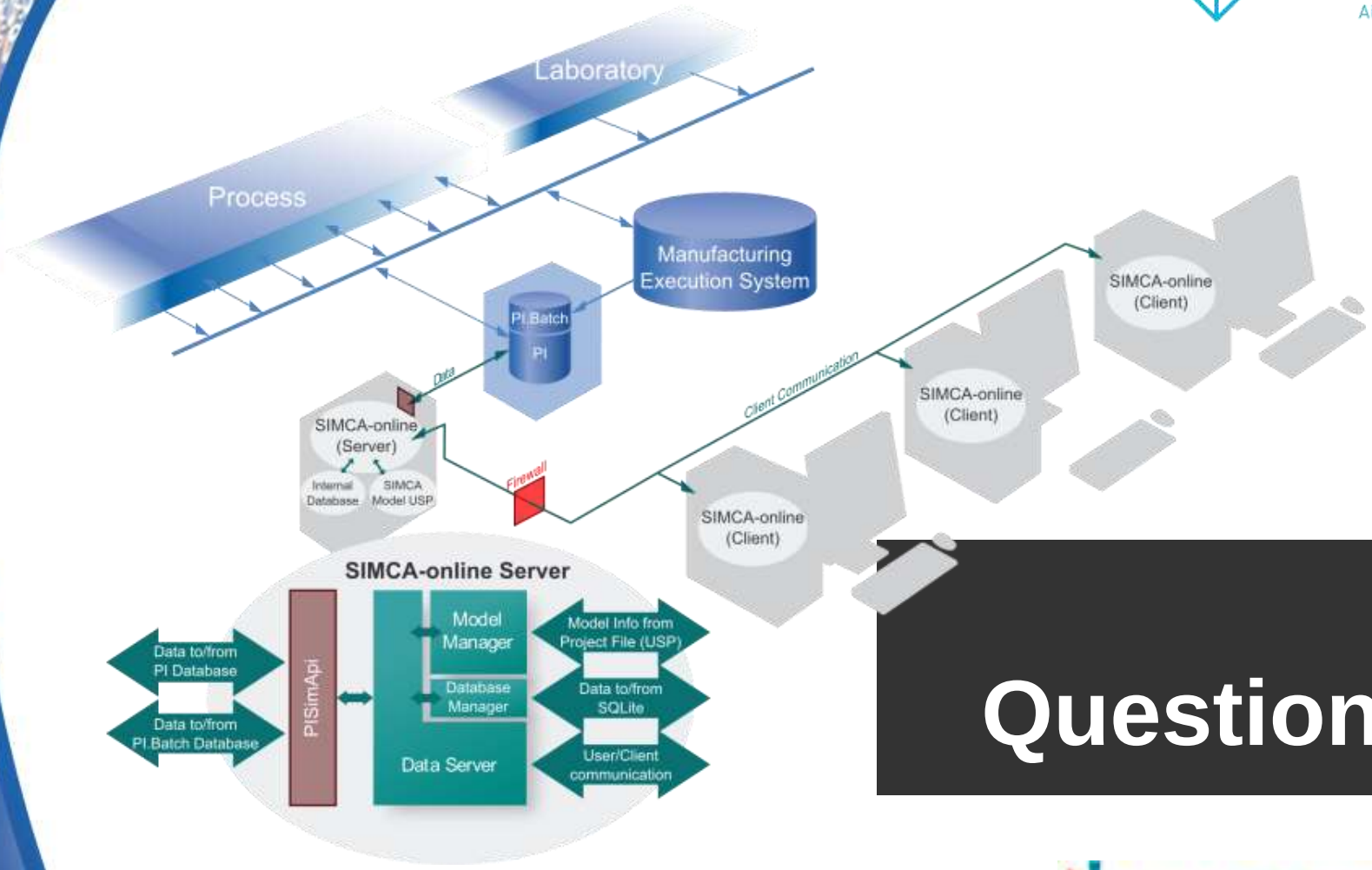

Questions?

NOVARTIS

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Contacts – Follow up

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  Email: eferguson@osisoft.com

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Content: In august 2013, the RasGas office computer systems were struck by an unknown virus attack that caused the company to disconnect its plant automation systems from the corporate network to insure operations were not disrupted by the virus. The result of disconnecting the plant and business networks was an interruption of information flow from the production networks to the business networks….

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Thank you

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