

Multivariate Chemometric and Statistic Software Role in Process Analytical Technology

Camo Software Inc
For IFPAC 2007

By Dongsheng Bu and Andrew Chu

The Unscrambler®



Delivering Tomorrow's Innovations, Today

PAT Definition

A system

- Understand the Process
 - Design experiments
 - Study and analyze process data
 - Build models
- Control the Process
 - Timely measurement
 - Analyze with the models
 - Feedback loop

Achieving the Goal of Ensuring
Final Product Quality



PAT Application

- Pharmaceutical

Improve quality and reduce costs in applications such as:

- blending
- granulation
- drying
- tableting
- coating

Measure parameters such as:

- moisture
- hardness
- density
- impurities
- polymorphism
- crystallinity

Other Verticals:

Food and Beverage, Agriculture, Oil and Gas, Chemicals, Materials, etc...

The Unscrambler®

PAT Adds Business Value

- Reduce Safety Risk
 - Reduce exposure to process hazards
 - Ensure raw materials are correct in use
- Reduce Cost
 - Reduce process variability
 - Higher product yield and quality
 - Lower production of waster streams
- Improve Process Understanding
 - Enables process control to be optimized
 - Enables improvement in process design or operation
 - Shortens development time for new product and process

With manufacturing costing a quarter of revenue, even a 1% improvement in efficiency can produce significant financial benefits.

The Unscrambler®



Delivering Tomorrow's Innovations, Today

Process Analytical Technology Tools – by FDA

- **Multivariate** data acquisition and **analysis** tools
(Unscrambler®, PLS_Toolbox/Solo, Pirouette, Umetrics...)
- Modern process analyzers or **process analytical chemistry** tools
- Process and endpoint **monitoring** and control tools
- Continuous improvement and knowledge management tools (Symbia, GE, Honeywell...)

Scientific, risk-managed means

Effective and efficient means

Continuous improvement means

Information and knowledge management means

<http://www.fda.gov/cder>

Chemometrics Software

Direct Hits

- Multivariate data analysis tools
- Process and endpoint monitoring and control tools
- Critical parameter identification and variation reduction
- Improvement in process design or operation
- Development of new product and process

The Unscrambler®



Delivering Tomorrow's Innovations, Today

Unscrambler® and Online Monitoring Tools

- The Unscrambler®
 - Design of Experiments
 - Exploratory data analysis (PCA, Cluster Analysis)
 - Regression and Prediction (PLS, PCR, MLR)
 - Data pretreatments (Derivatives, MSC, SNV, etc)
- On-Line Prediction and Classification
 - OLUP/OLUC-OEM and Unscrambler-Online (UO)
 - *for continuous real-time process monitoring and quality control*
- Product Optimizer
 - *for formulation and process analysis and optimization*

The Unscrambler®

DOE Case: Optimizing Tablet Manufacturing Process

- Main Objective:
Change the shape of a well-known tablet formulation.
- Question:
Is it possible to produce tablets with the new shape without losing quality?
- Design of Experiment for Study and Optimize
 - Identify the most important process variables.
 - Find optimum process settings
 - Process variables: Pressure, Pre-Press, and Velocity
 - Measured qualities: Disintegration, Dissolution at 10 minutes and Dissolution at 20 minutes

The Unscrambler®



Delivering Tomorrow's Innovations, Today

Using Central Composite Design (CCD) in the Unscrambler®

Process factor/attributes in consideration:

	(-) low	(+) high
pressure	3.07	4.73
pre press	1.16	3.10
velocity	100000	150000

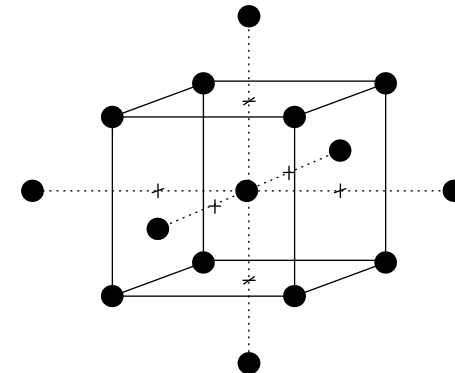
The measured tablet qualities:

Disintegration (>450)

%dissolution_10min (75-85)

%dissolution_20min (>95)

weight variation



5 levels for each variable

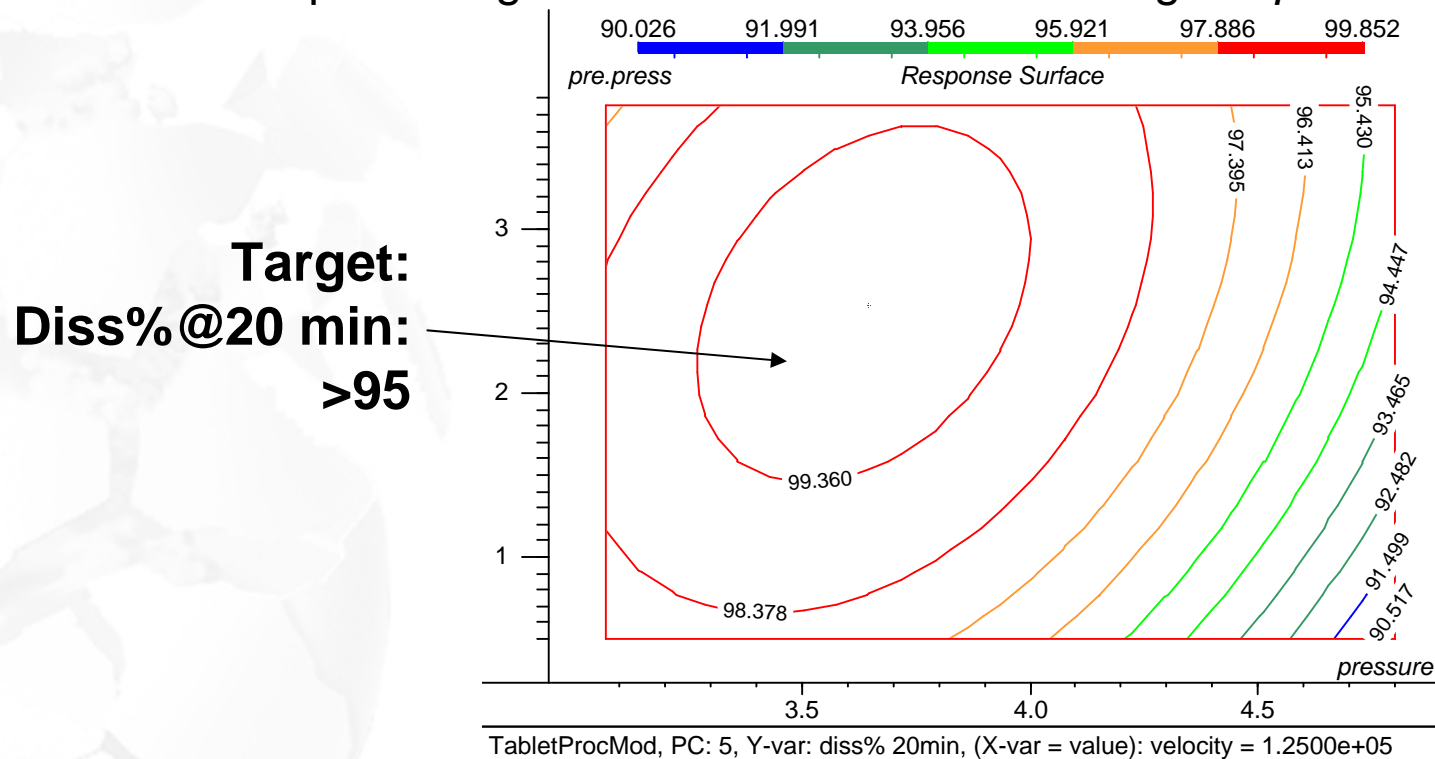
Unscrambler has 7 standard, easy-to-use DOE designs to maximize the chances of obtaining the desired information at the least cost



Modeling in the Unscrambler®

Response Surface Plot

Dissolution percentage at 20 minutes over the change of *pressure* and *pre.press*



The Unscrambler is the leading software package for Analysis of Effect, Modeling and Visualization Plotting in DOE applications.



CAMO
Delivering Tomorrow's Innovations, Today

Obtain Solution Using the Product Optimizer software

3X						
Factor	Lower bound	Min	Max	Upper bound	Opt Value	Response Chart
pressure		2.504112	4.8		4.110949	
pre.press		0.49866095	3.761339		2.4624665	
velocity		82955.18	167044.83		125000.01	

3Y						
Factor	Main goal	<= Target <=	Min	Max	Predicted Value	
disintegration		450	inf	305.0	778.0	450.0
diss% 10min		75	85	42.9	90.0	84.19928
diss% 20min	y	95	inf	73.3	101.0	98.87596

Recommended solution

Product Optimizer utilizes models building in the Unscrambler, and provides suggested solution based on targets and constraint settings. It is an efficient way to solve multi-objective, equality/inequality optimization problems.



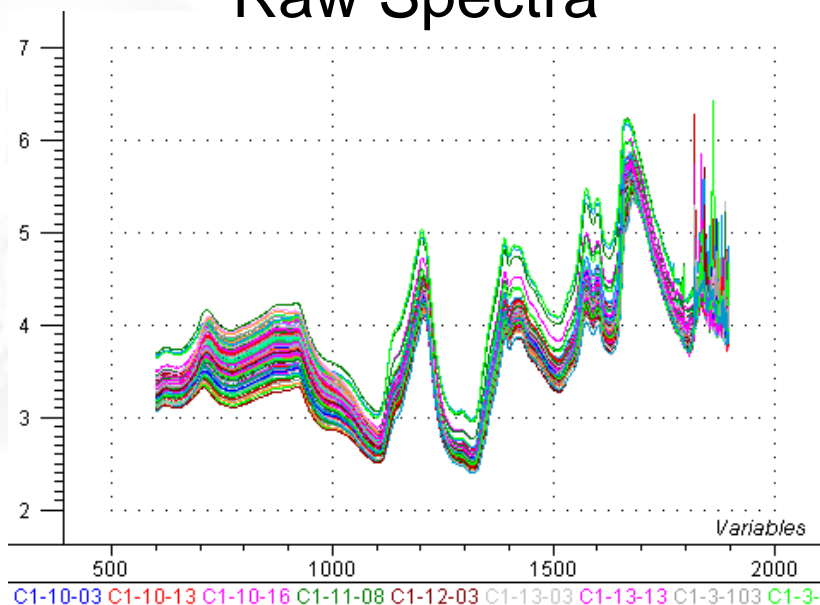
Prediction Case: Tablet API Monitoring by NIR

- 152 tableted samples
- Active ingredient was not disclosed
- X-data: NIR transmittance spectra recorded in the range of 600-1980 nm in 2 nm increments
- Y-data: Concentration of active ingredient in each tablet measured by High Performance Liquid Chromatography (± 1.3 mg with a nominal value of 200 mg per tablet).

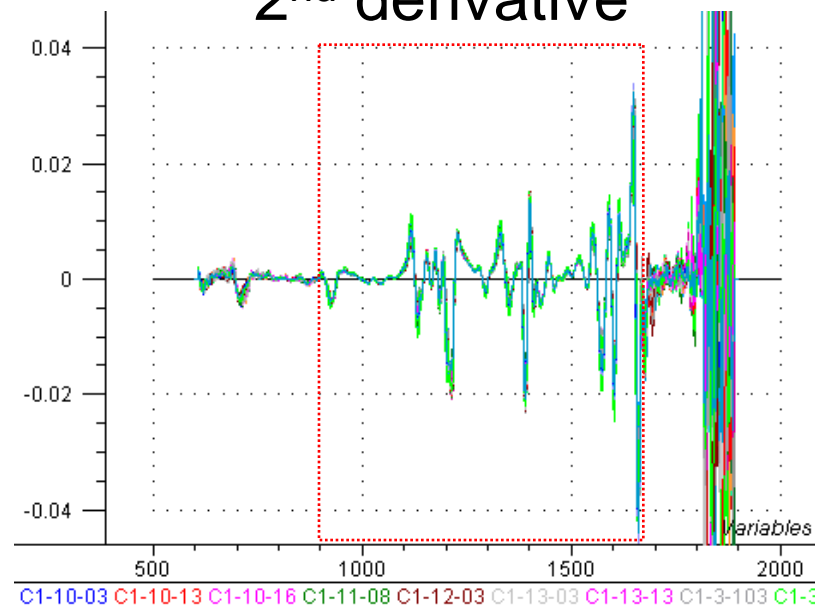
The Unscrambler®

Modeling - Spectral Check and Preprocessing

Raw Spectra



2nd derivative



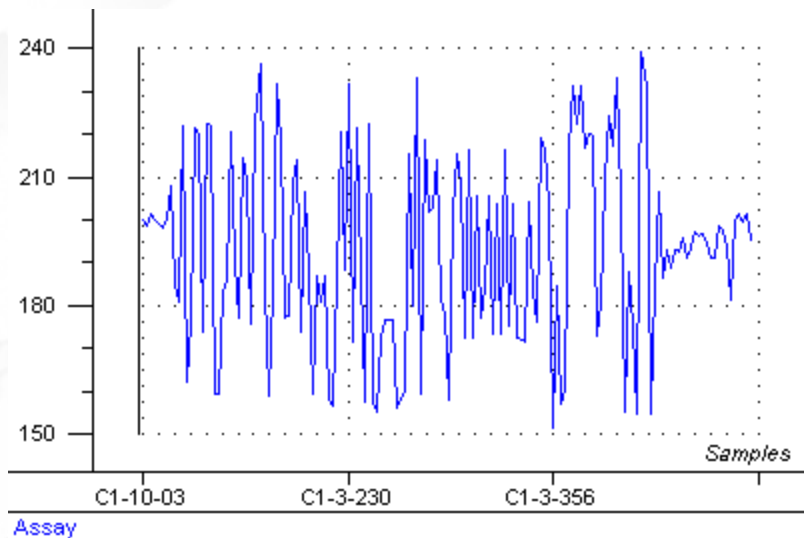
Check:

- Measurement quality
- Batch-to-batch variation
- Pre-treatment selection
- Wavelength selection

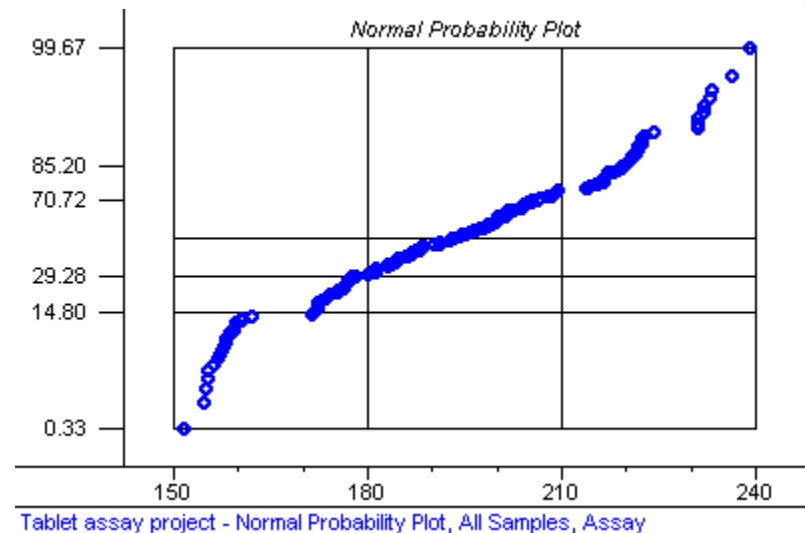


Modeling - HPLC API Reference

Line Plot



Normal Probability Plot



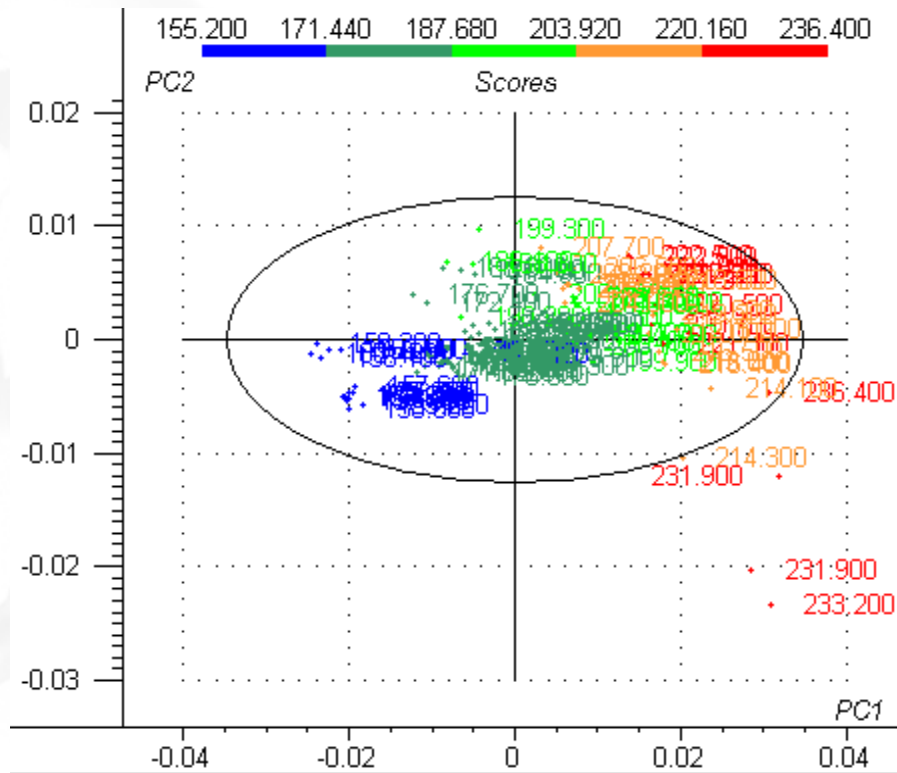
Check:

- Representative region
- Balanced Distribution
- Sampling order/pattern/correlation

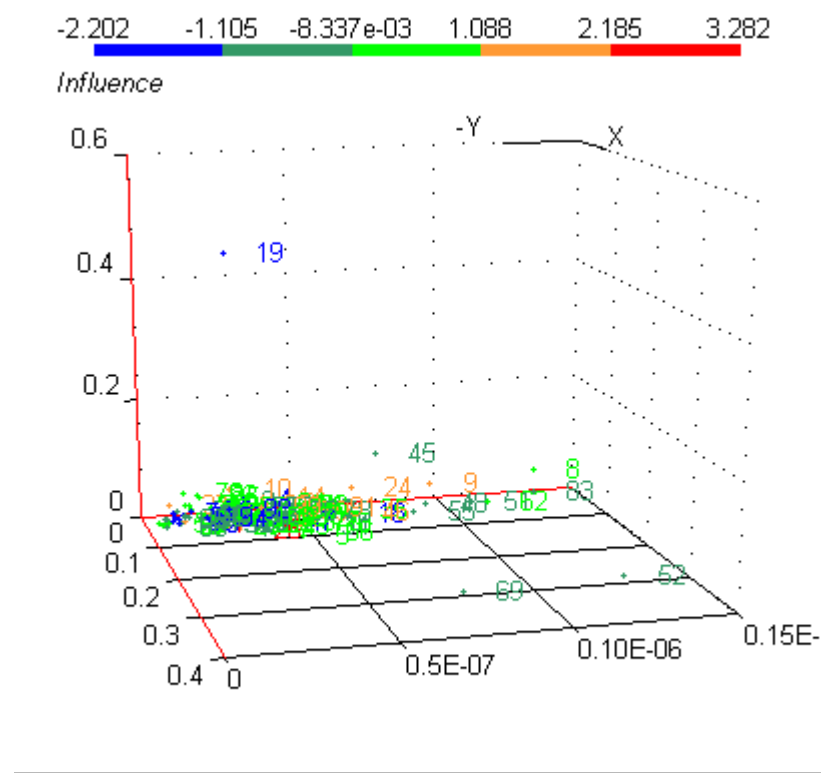


Modeling - Outlier Visualization & Detection

From Scores Plot



From Leverage Plot



Unscrambler provides reliable tool to identify outlier samples and study the causes for better modeling.



Modeling and Validating Strategy

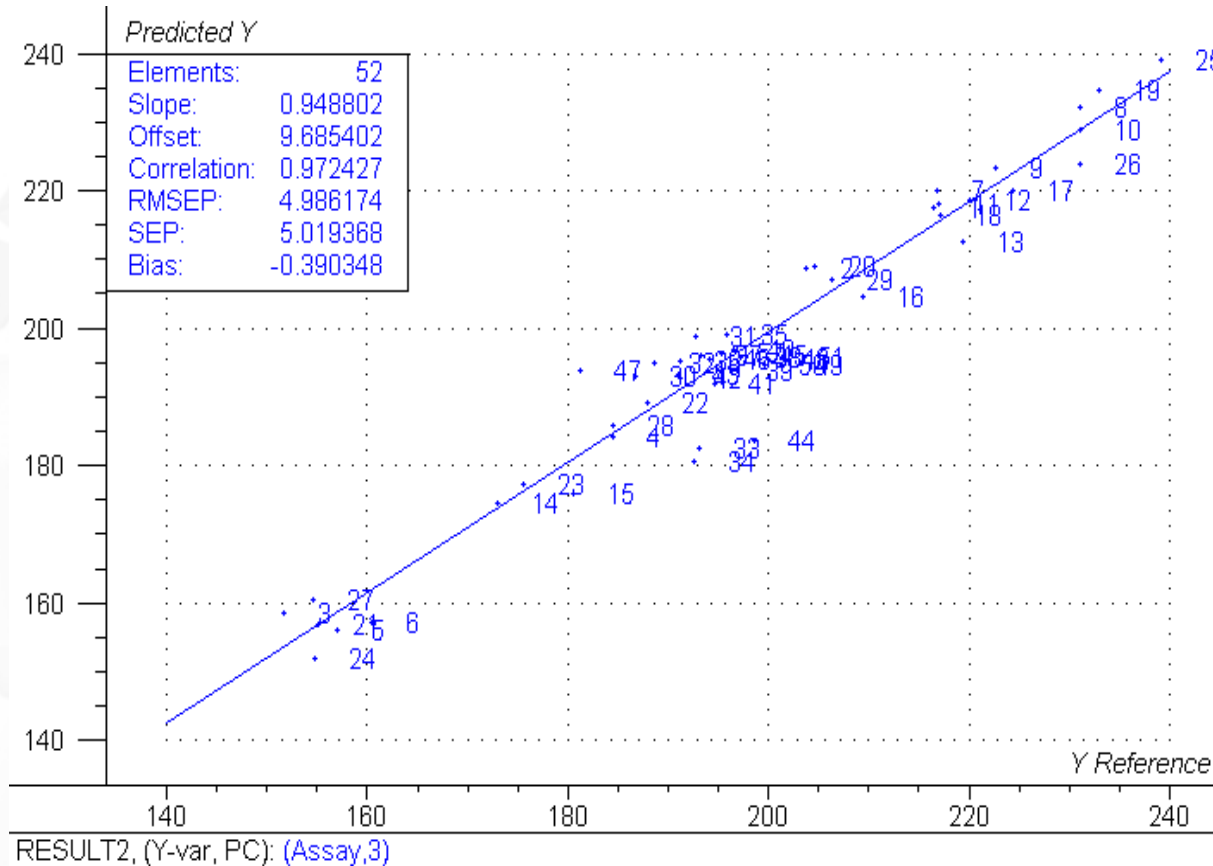
- Training/Calibration set requirements
 - Representative of target population
- Variable selection
 - Refer FTIR/NIR/ chart
 - Pure chemical measurement
 - Avoid interference variables
- Outlier sample detection
- Non-linearity correction
- Test/validation set requirements
 - Not in the model, however Not “unknown” (Reference is available)
 - Representative of future prediction samples

The Unscrambler®



Delivering Tomorrow's Innovations, Today

Statistic Results (RMSEP, R², Bias) Provide Model Validations

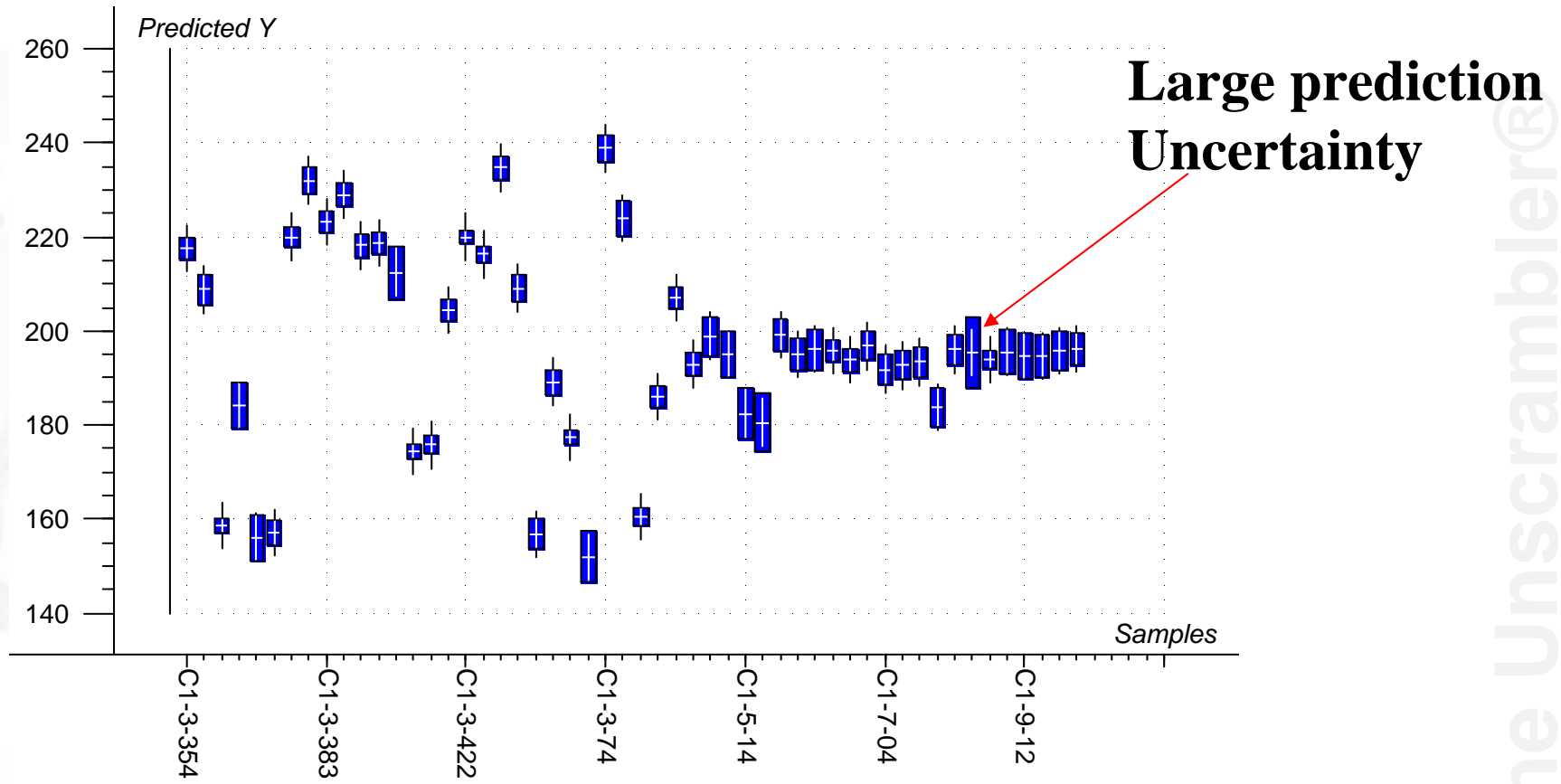


***If the validation error is close to the modeling error,
then the model can be trusted.***



Prediction - Data QC

y-Deviation, Hotelling T², etc



Testset, (Y-var, PC): (Assay,3)

Unscrambler provides prediction uncertainty results in addition to predicted values



Delivering Tomorrow's Innovations, Today

More Multivariate Chemometric Modeling Applications

- Utilized SIMCA approach to successfully classify 18 raw materials by NIR in a pharmaceutical company
- PCA on a set of process data to identify failure driven factors in a biotech company
- Real-time Blend Uniformity Monitoring by NIR
- Tracking density of oil before shipment by NIR
- Wheat protein content
- Milk %Fat
- Polymer composition

The Unscrambler®

Another Type of PAT Tools -Multivariate Analyzers

- Spectroscopy-based
UV/Vis, IR, **NIR**, Raman, NMR, XRF, fluorescence
- Separation-based
Chromatography, mass spec, GC, HPLC
- Array of Sensors
T, P, flow, density. pH, O₂, viscometers,
moisture, color, etc.

The Unscrambler®



Delivering Tomorrow's Innovations, Today

OEM Partners Analyzer Providers

CAMO works closely with OEM partners to assist them in finding the easiest way to incorporate CAMO software products and solutions.

The Unscrambler® from CAMO can work with data from NIR, IR, FT-IR, UV, UV/VIS, NMR, LC, GC, HPLC, DAS, CE, Raman and Mass Spectroscopy instruments.

Thermo
ELECTRON CORPORATION



BRIMROSE



Perten
INSTRUMENTS



CAMO
Delivering Tomorrow's Innovations, Today

The Unscrambler®

PAT Implementation Stages

There could be four stages (by S. Wold)

1. Off-line chemical analysis in labs to large extent substituted by *at-line* analysis - spectroscopy, fast chromatography, and sensor arrays. Multivariate calibration used to convert PAT data to traditional space, e.g., concentrations, disintegration rate
2. The at-line PAT data are used directly without conversion back to the traditional space
3. *On-line* PAT: Data are measured also during the batch evolution of each production step - on-line MSPC
4. Over-all on-line PAT: Putting data from all steps and raw materials together for a total view of the process.



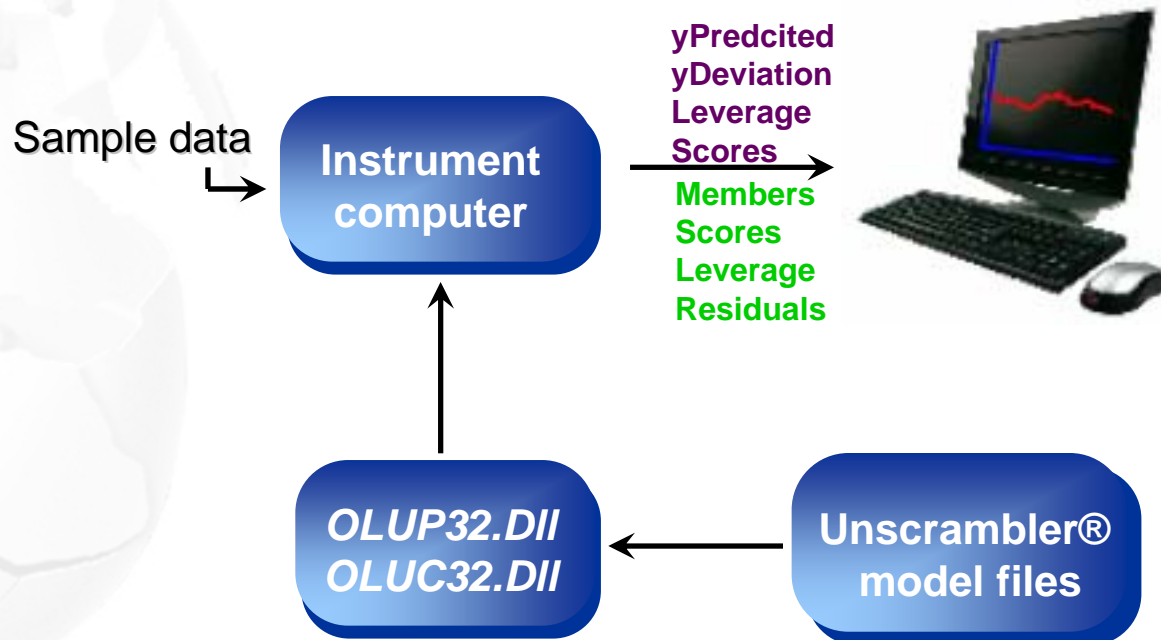
CAMO

Delivering Tomorrow's Innovations, Today

The Unscrambler®

Unscrambler-Online, On-Line Predictor and Classifier for Stage 3 &4

Provide tools to perform prediction and classification using Unscrambler regression/classification models in real-time.



The Unscrambler®

Unscrambler-Online

- A revolutionary, plug 'n' play product designed for end-users across industry verticals
- Enables full utilization of PLS-R and PCR models for prediction, and PCA for classification

Support auto pretreatments

Support multiple models

e-Signature

- Internally authenticated with identical values for both Username and Password

e-Record

- Batch name and date to identify the operation
- Raw data intact saved

Traceability

The Unscrambler®



Delivering Tomorrow's Innovations, Today

Software Validation Document Overview

SECTION A: Product Development in Camo Software AS

SECTION B: Product Changes History

SECTION C: Functional Requirement Specifications

SECTION D: Testing

SECTION E: Error Reporting and Tracking

SECTION F: Release Process

SECTION G: Traceability and Secure Electronic Recordings

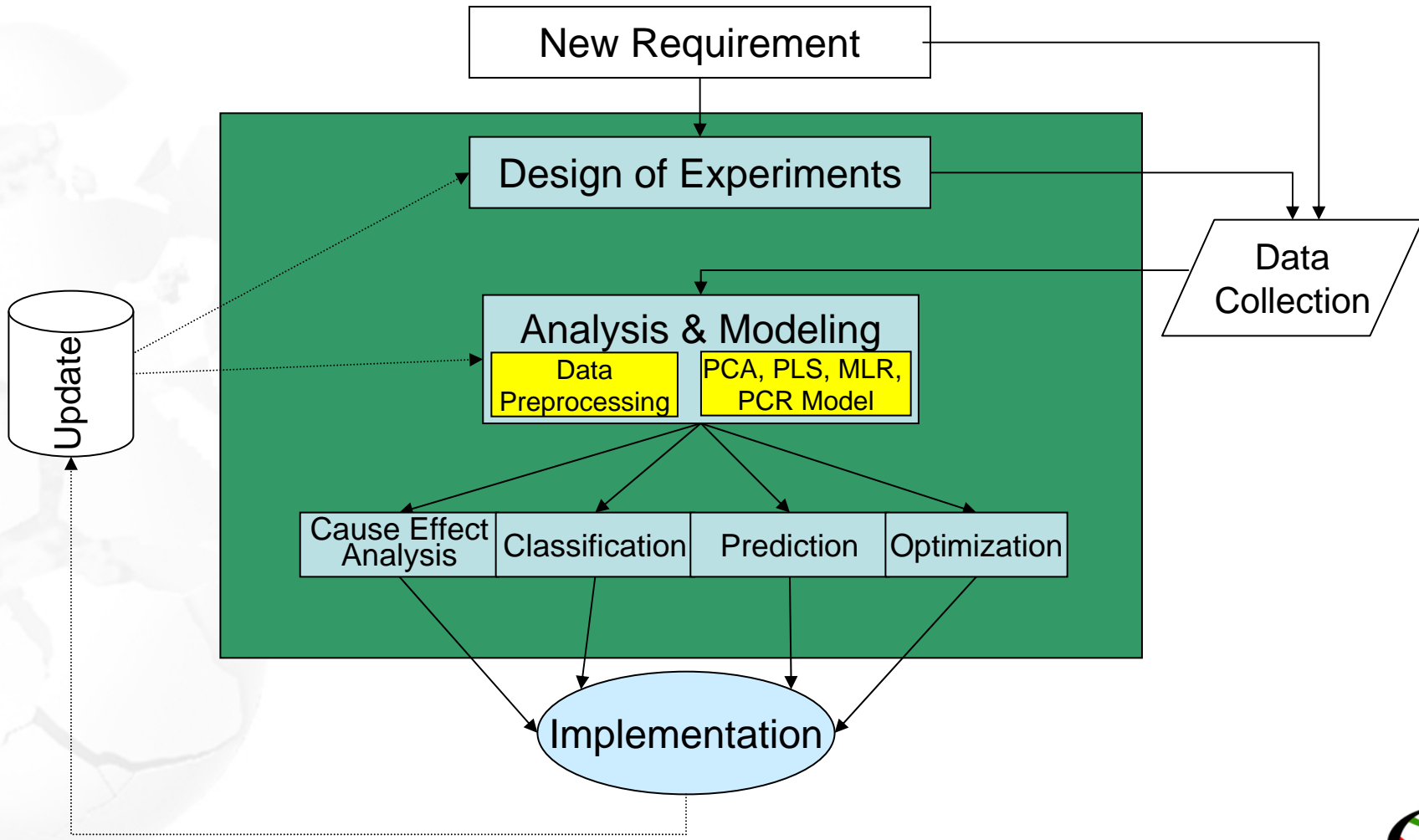
Overview of the compliance of The Unscrambler® to the FDA's 21 CFR Part 11 guidelines.

SECTION H: Qualification Workbook

Recommended procedures for Installation Qualification (IQ)

Recommended procedures for Operational Qualification (OQ)

Addressing Product and Process Quality with Bundled Solutions



The Unscrambler®



CAMO
Delivering Tomorrow's Innovations, Today

Setting Standards in Multivariate Data Analysis

Thank You!

www.camo.com

732-602-8886 Ext 32



The Unscrambler®



Delivering Tomorrow's Innovations, Today