Electronic Chromatogram Review at Biogen Idec: Past, Present, ad Future

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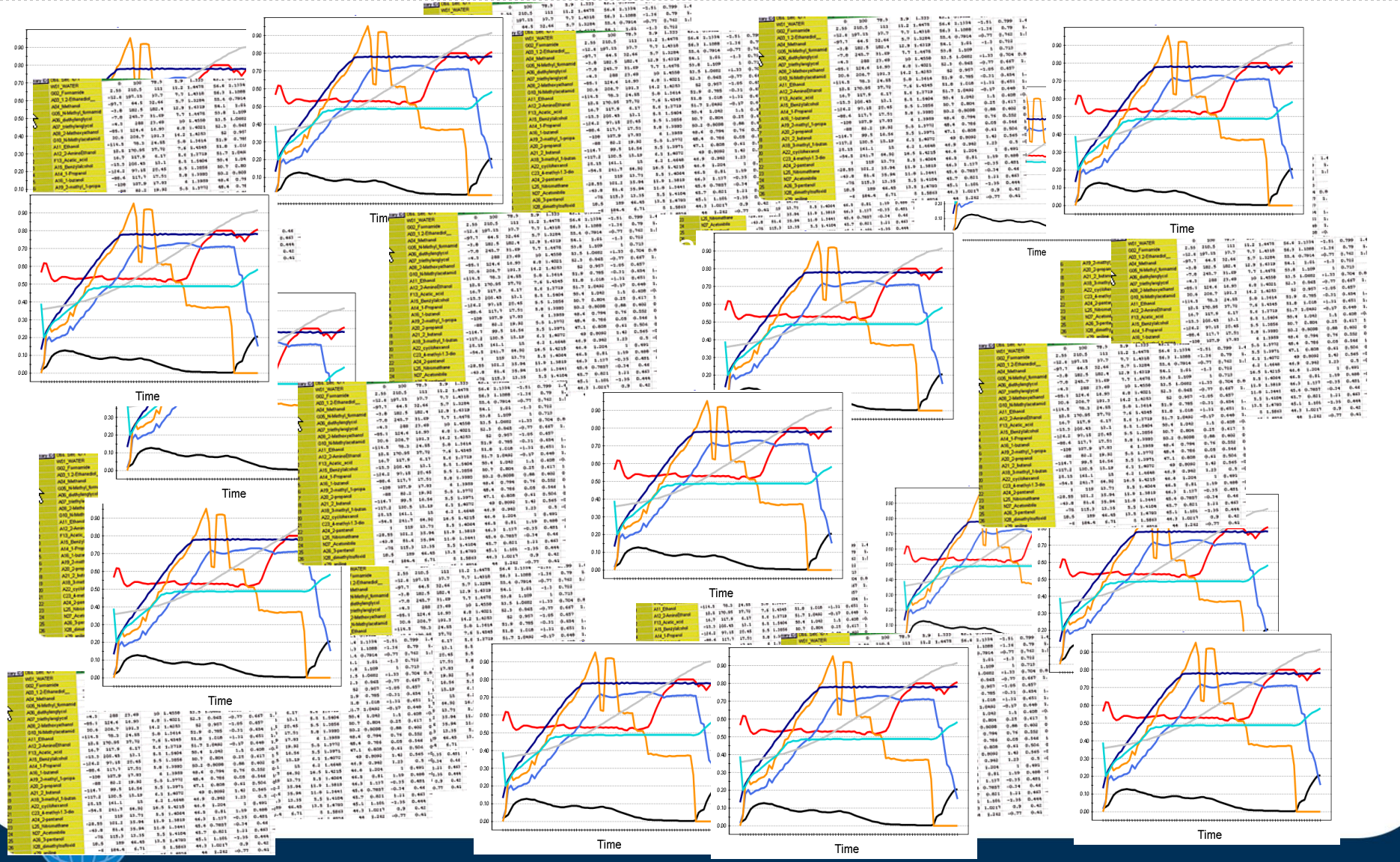
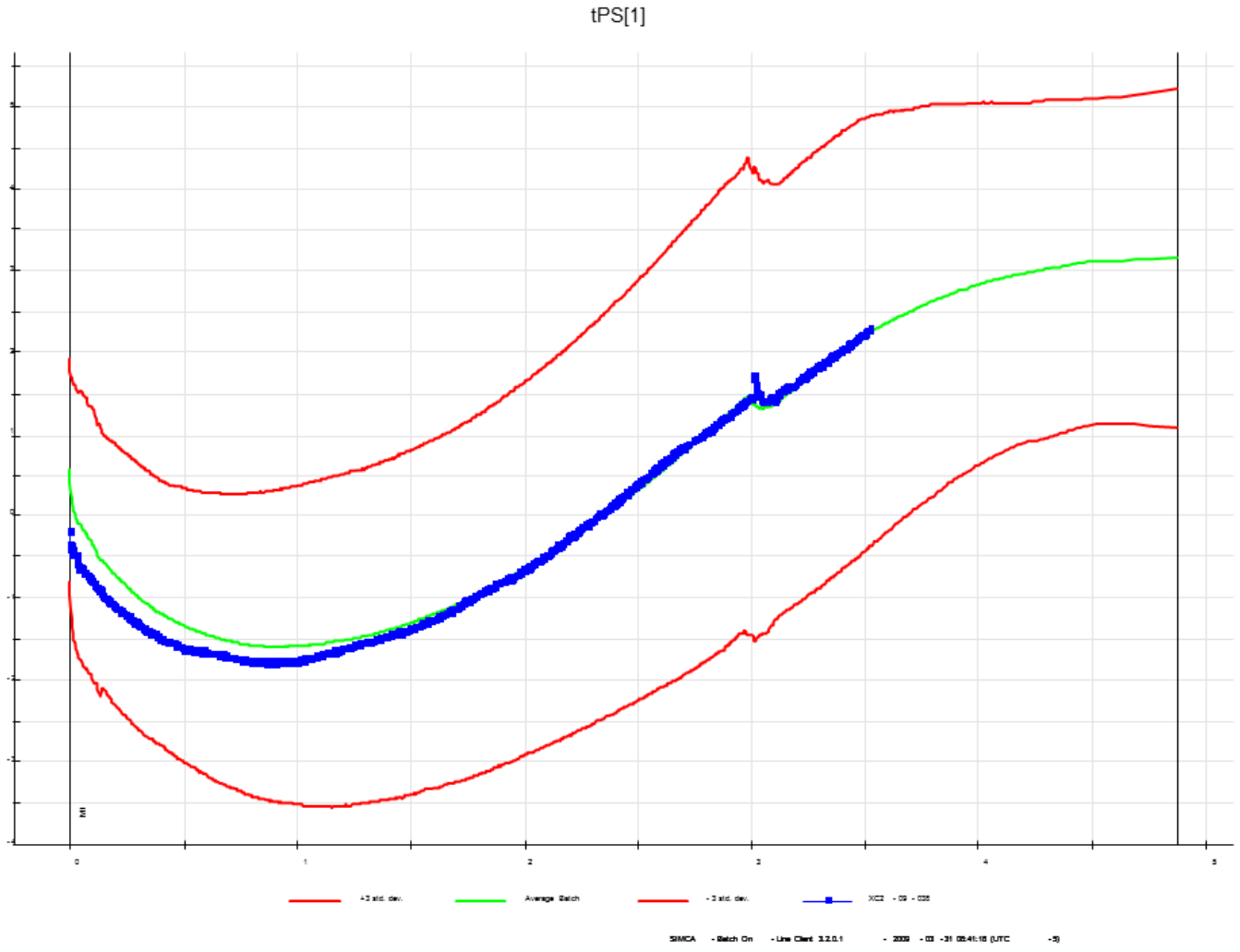
Outline

- Introduction
- Biogen Idec Multivariate Analysis Journey
- Case Studies
- Summary

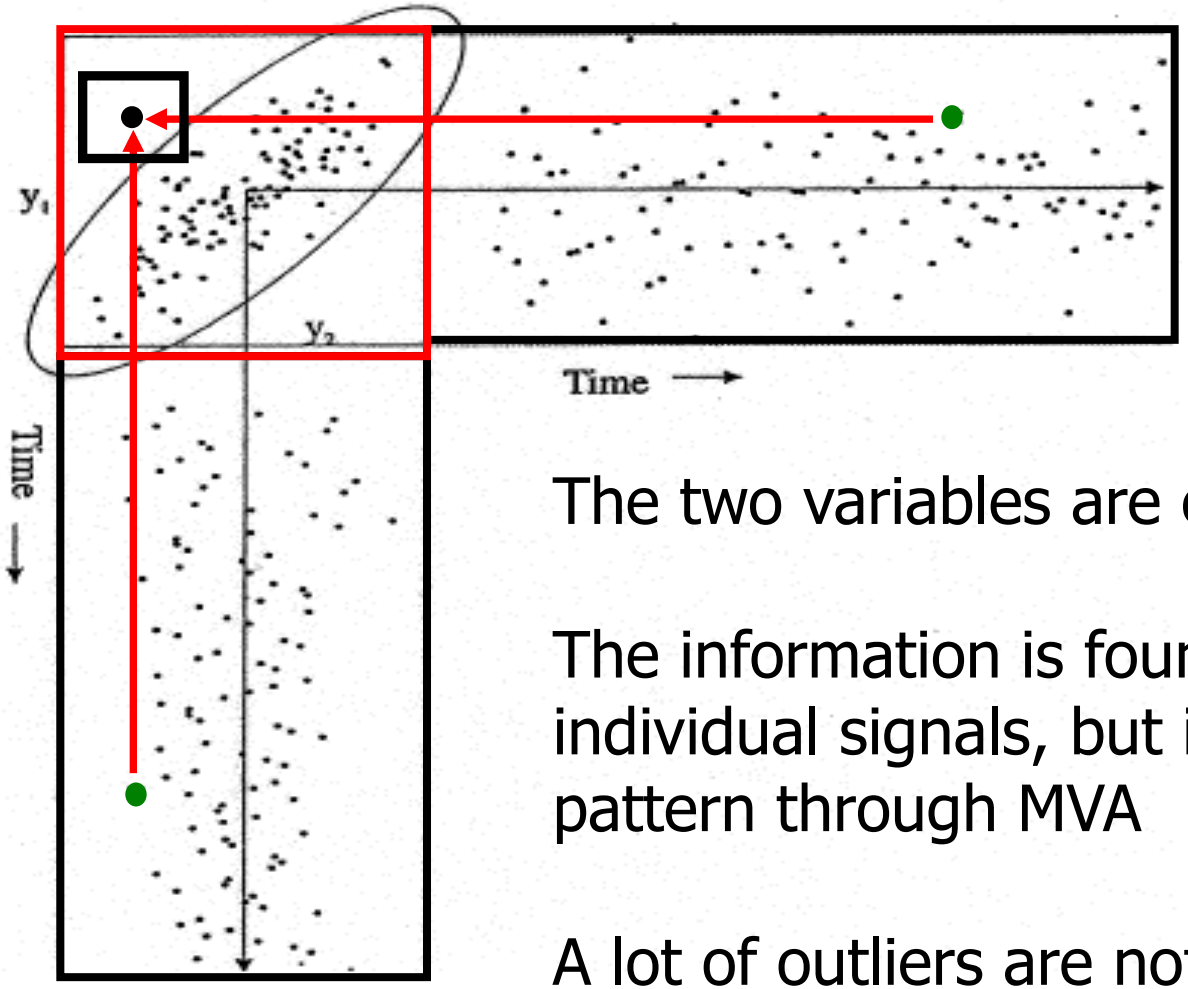
Inundata-ed



This Looks Better



Multivariate Analysis: What & Why



The two variables are correlated

The information is found NOT in the individual signals, but in the correlation pattern through MVA

A lot of outliers are not detected unless all the variables are analysed together

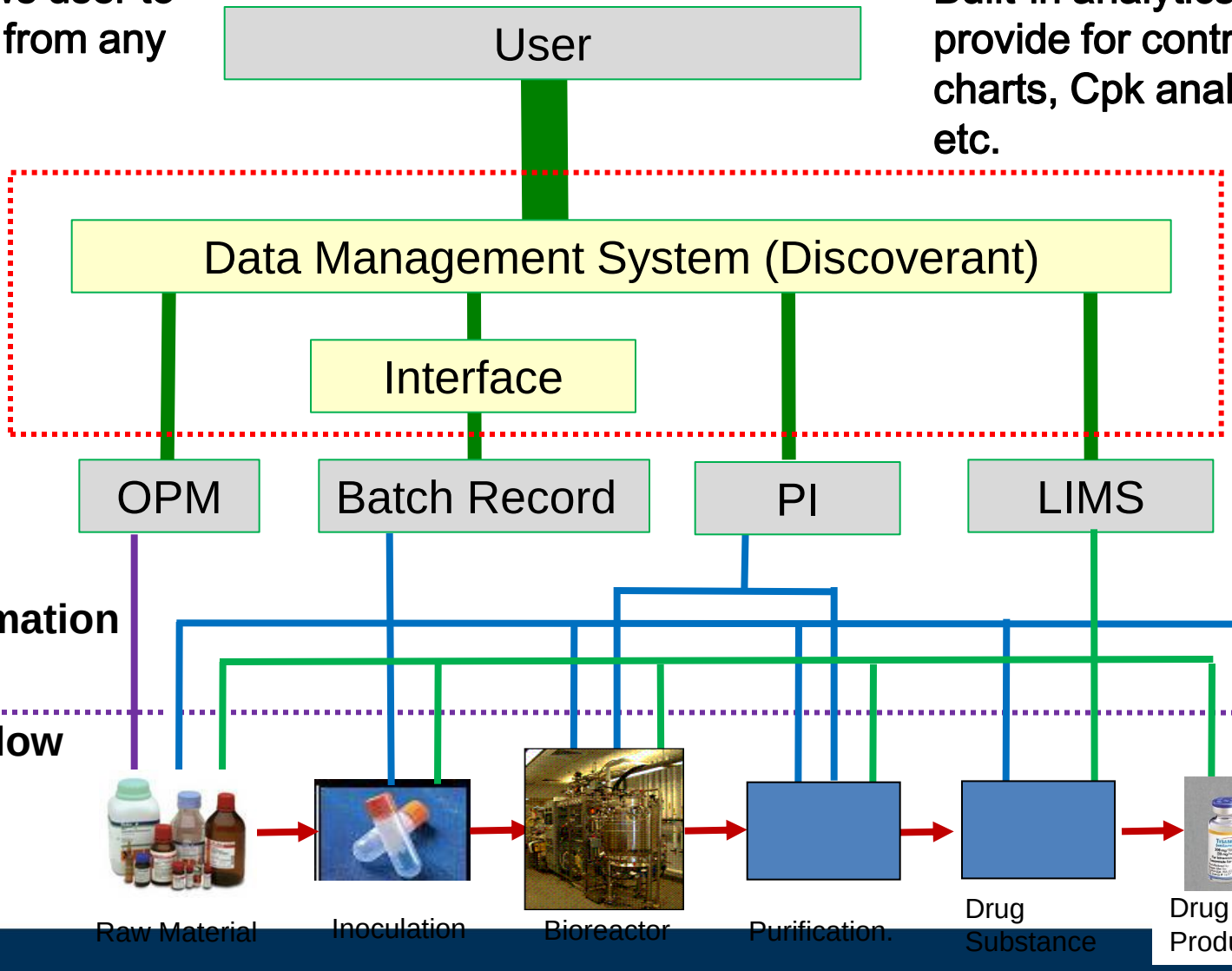
Biogen Idec Advanced Process Control

- Established an infrastructure for data centralization and real time process monitoring
  - Achieved full scale utilization of Disoverant and SBOL
    - 2003: 1st Discoverant Hierarchy & 1st Cell Culture SBOL
    - 2006: SBOL on Manufacturing Floor
    - 2007: 1st Purification SBOL model
    - 2013: Approved patent on “Systems and Methods for Evaluating Chromatography Column Performance”, US008410928B2, 02Apr2013
- Built a culture of advanced process monitoring
  - Shift Trend Review + Routine Trend Review

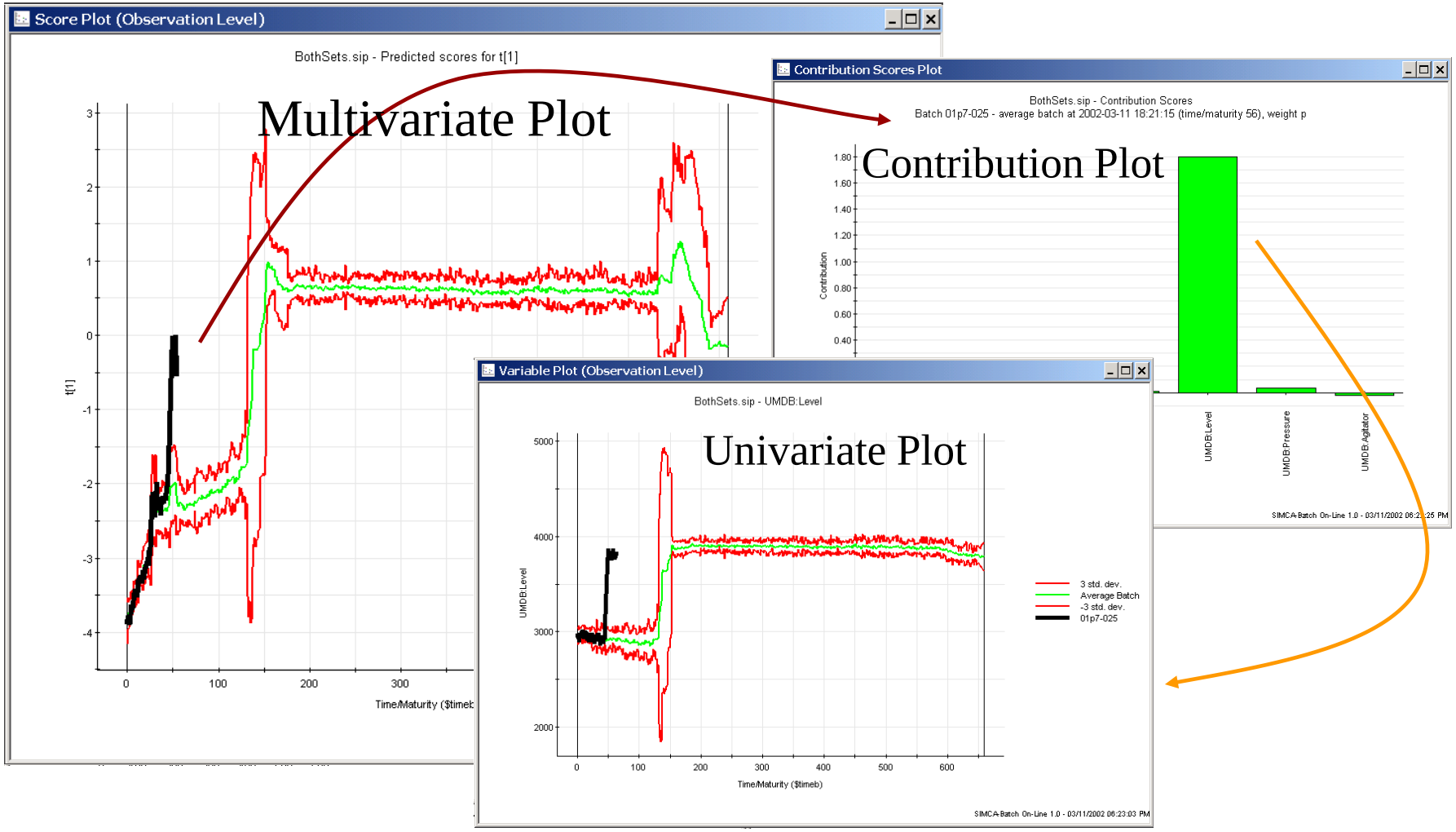
Centralized Data Management System

System allows user to access data from any system

Built-in analytics provide for control charts, Cpk analysis, etc.



Multi-variate Monitoring System - SBOL

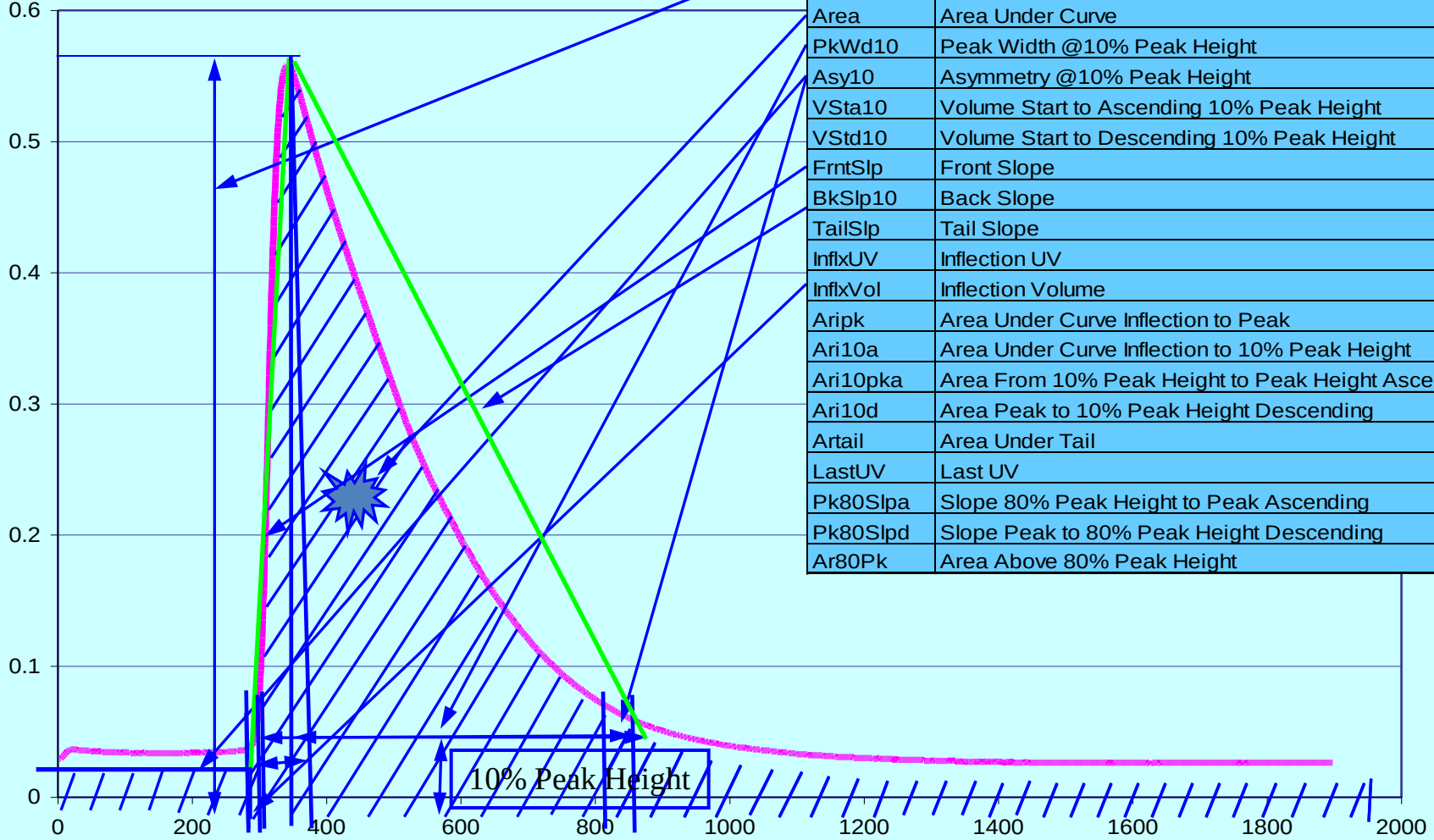


Multivariate Chromatogram Analysis

- Motivation
  - Chromatograms contain a lot of information that we are not utilizing
  - Exploit already available continuous data
    - UV, conductivity, pH, pressure, volumetric flow
- Goals
  - Non-subjective, quantitative method for evaluating chromatograms
- Example: Analysis of elution peak UV tracing
  - MVA model using discrete parameters that describe the characteristics of the elution UV peak

MVA of Chromatograms

Elution Peak Parameters



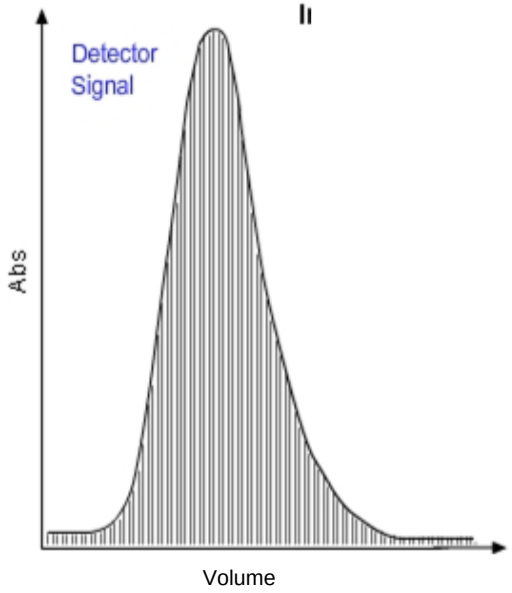
Alias	Description
PkHt	Peak Height
VolMid	Volume at Peak Height
Area	Area Under Curve
PkWd10	Peak Width @10% Peak Height
Asy10	Asymmetry @10% Peak Height
VSta10	Volume Start to Ascending 10% Peak Height
VStd10	Volume Start to Descending 10% Peak Height
FrntSlp	Front Slope
BkSlp10	Back Slope
TailSlp	Tail Slope
InflxUV	Inflection UV
InflxVol	Inflection Volume
Aripk	Area Under Curve Inflection to Peak
Ari10a	Area Under Curve Inflection to 10% Peak Height
Ari10pka	Area From 10% Peak Height to Peak Height Ascending
Ari10d	Area Peak to 10% Peak Height Descending
Artail	Area Under Tail
LastUV	Last UV
Pk80Slpa	Slope 80% Peak Height to Peak Ascending
Pk80Slpd	Slope Peak to 80% Peak Height Descending
Ar80Pk	Area Above 80% Peak Height

Case Study #1: AUP

- Area under peak (AUP) of elution UV peak was proposed as an alternative to quantify protein concentration
- Ratios of AUP to total offline A280 across manufacturing sites were shown to be different
- Investigation was Launched
  - To understand root cause and harmonize practice

Background

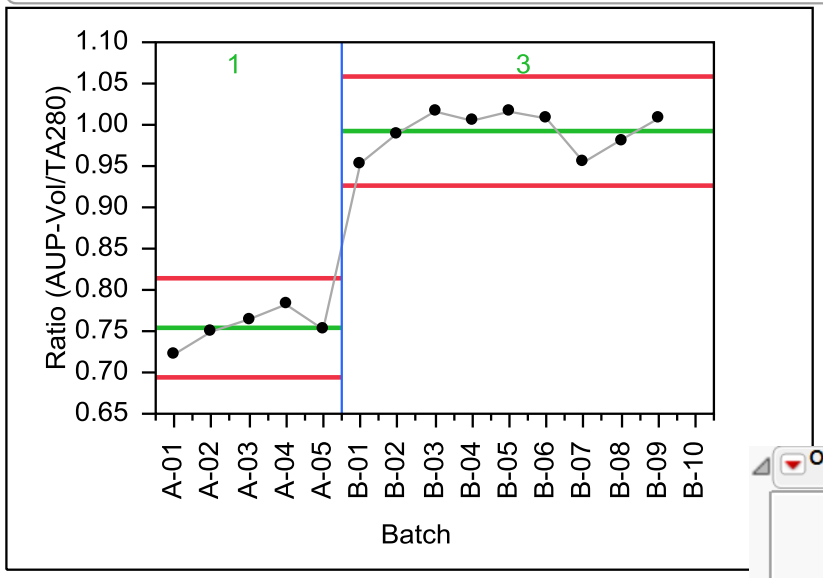
- Current practice: offline sampling for TA280
- TA280 information is contained in the elution peak
  - $\int$A280 *d* V = TA280
  - Concept has been used in the past to assess incorrect A280 sampling deviations
  - Assumption: A280 signal is proportional to protein concentration



Inconsistent Ratios X-Site (Before)

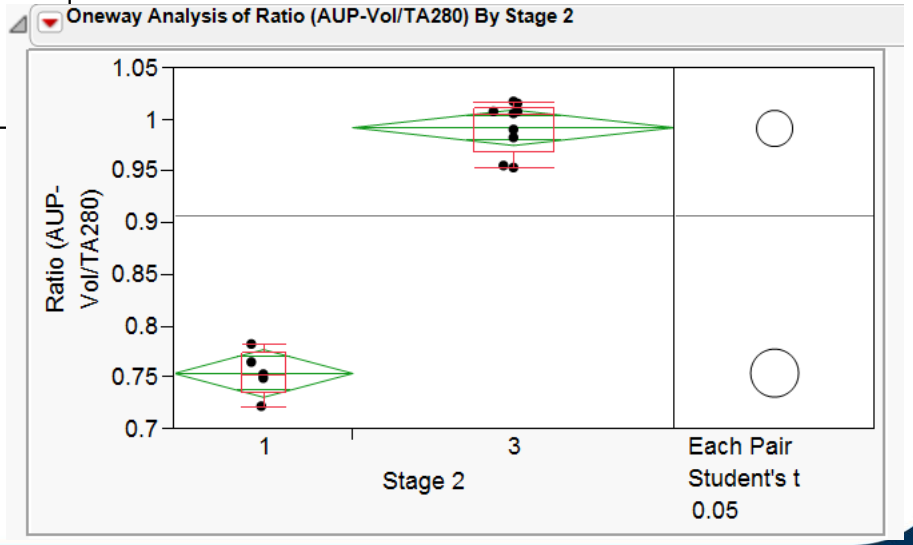
Control Chart

Individual Measurement of Ratio (AUP-Vol/TA280)



Phase Limits

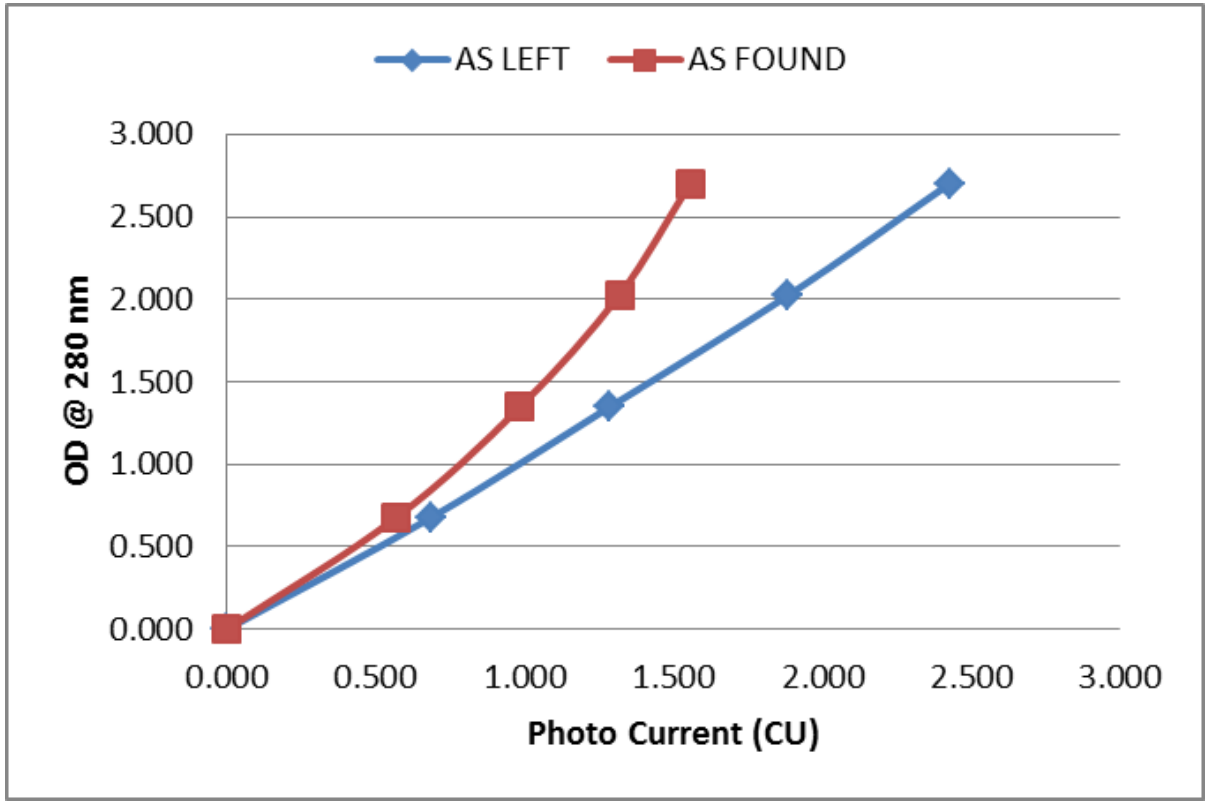
Phase	LCL	Avg	UCL
1	0.694062	0.754089	0.814115
3	0.926336	0.992396	1.058455



1: Data from site A per “As Found” linearization curve

3. Data from site B – Linearization curve normal

Root Cause - Linearization Curve Not Linear

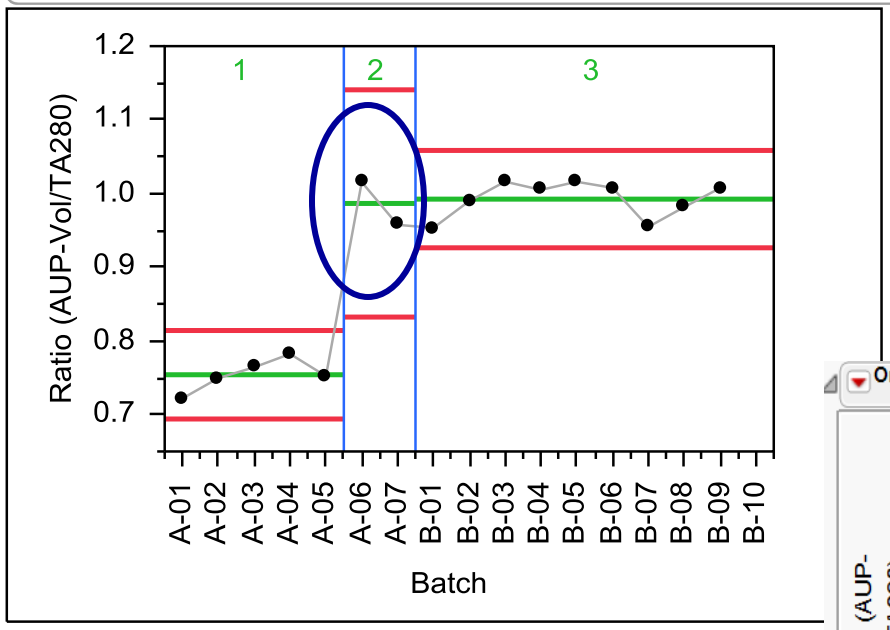


- "As Found" curve was not linear
- "As Left" curve returned to linear after replacing interference filter

Consistent AUP/TA280 X-Site (After)

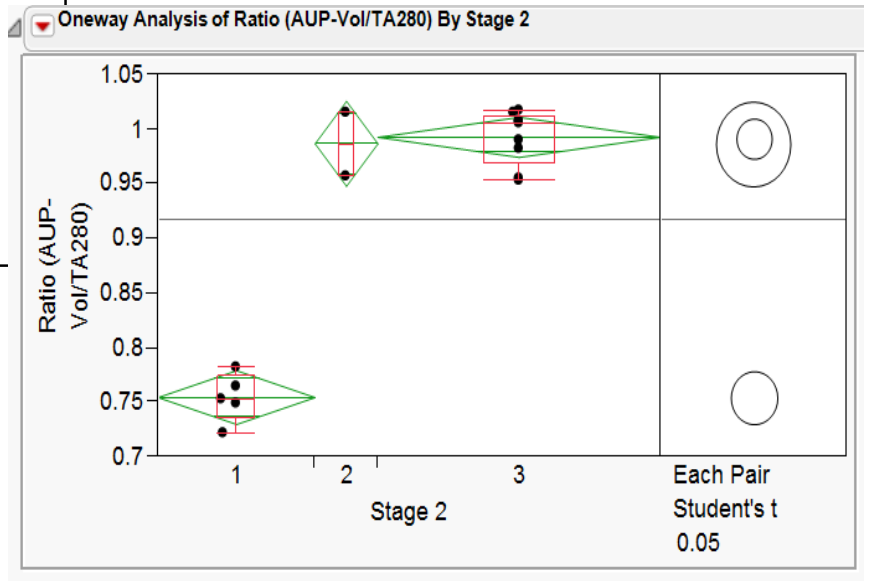
Control Chart

Individual Measurement of Ratio (AUP-Vol/TA280)



Phase Limits

Phase	LCL	Avg	UCL
1	0.694062	0.754089	0.814115
2	0.832367	0.986524	1.140681
3	0.926336	0.992396	1.058455



1. Data from site A per “As Found” linearization curve
2. Data from site A per “As Left” linearization curve
3. Data from site B – Linearization curve normal

Lessons Learned

- Area under peak of elution could add significant value to real time chromatography performance monitoring
- Question: Is UV representative of protein concentration?
- Answer: Correct linearization table is critical to UV meter performance and success of Chromatogram analysis (including AUP)

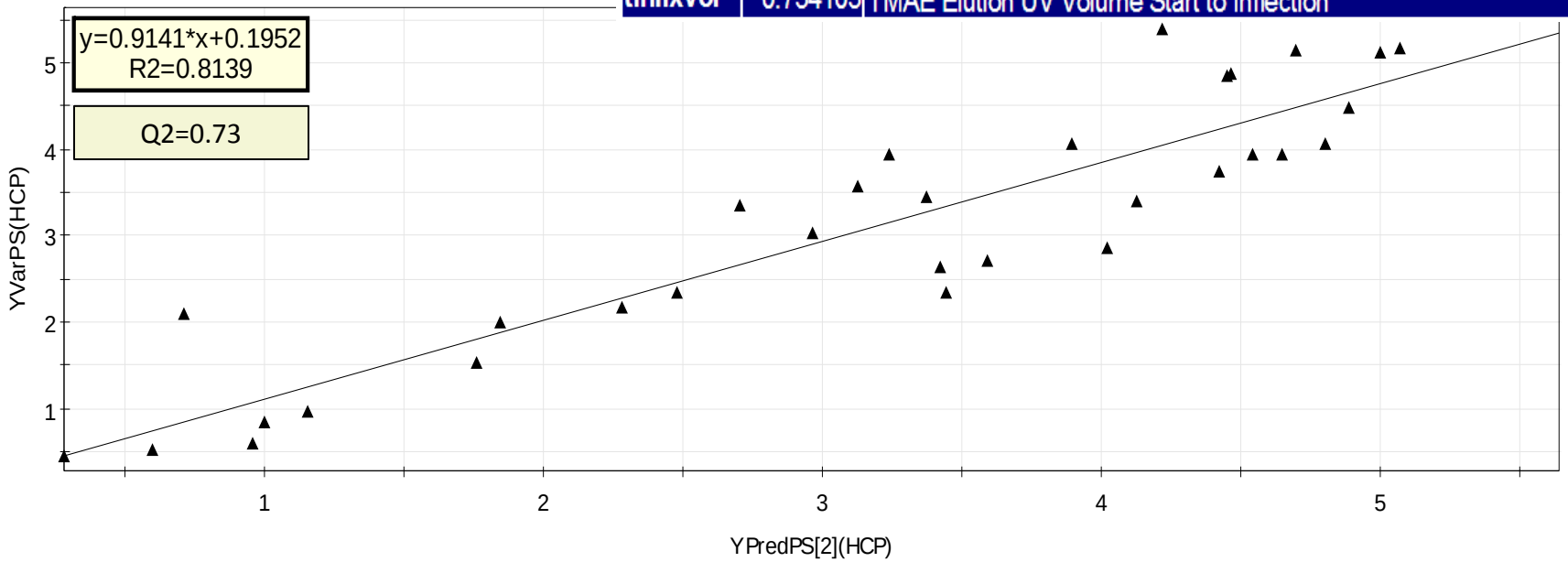
Case Study #2 – Elution UV Chromatogram Analysis

- Residual host cell protein was showing a gradual upward trend in the drug substance
- AIEX step (column 2) was suspected root cause
- Investigation was launched
  - Started by building a multivariate process model (approximately 60 variables covering cell culture and purification)

AIEX PLS Model to Predict HCP

- Eight chromatogram parameters predicts well HCP level in the Drug Substance

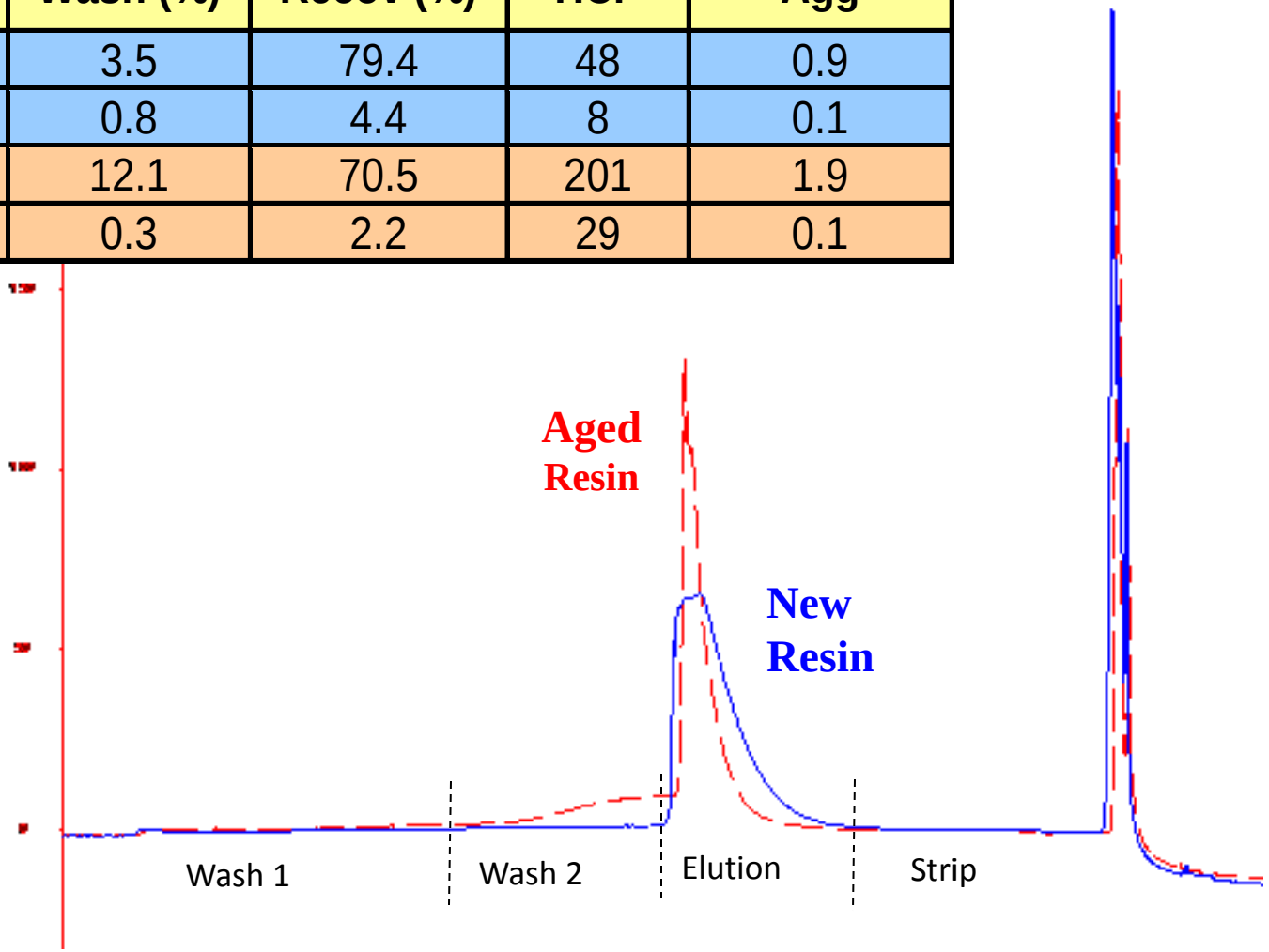
Var ID (Primary)	M10.VIP[2]	
tFrntSlp	1.16213	TMAE Elution UV Front Slope
tPkHt	1.14422	TMAE Elution UV Peak Height
tBkSlp10	1.13214	TMAE Elution UV Back Slope (Pk to 10% Pk Height Decending)
tVolMid	1.00968	TMAE Elution UV Volume Start to Peak Max
tVStd10	0.961922	TMAE Elution UV Volume Start to 10% Peak Height Decending
tPkWd10	0.944189	TMAE Elution UV Volume @ 10% Peak Height
tTailSlp	0.826636	TMAE Elution UV Slope 10% Peak Height Decending to End
tInflxVol	0.734103	TMAE Elution UV Volume Start to Inflection



Further correlation analysis indicated: Chromatogram shapes changed as resin aged

Confirmation via Lab Studies: Change in Chromatogram Shape due to Resin Age

Resin		Wash (%)	Recov (%)	HCP	Agg
New	Average	3.5	79.4	48	0.9
	S.D.	0.8	4.4	8	0.1
Aged	Average	12.1	70.5	201	1.9
	S.D.	0.3	2.2	29	0.1



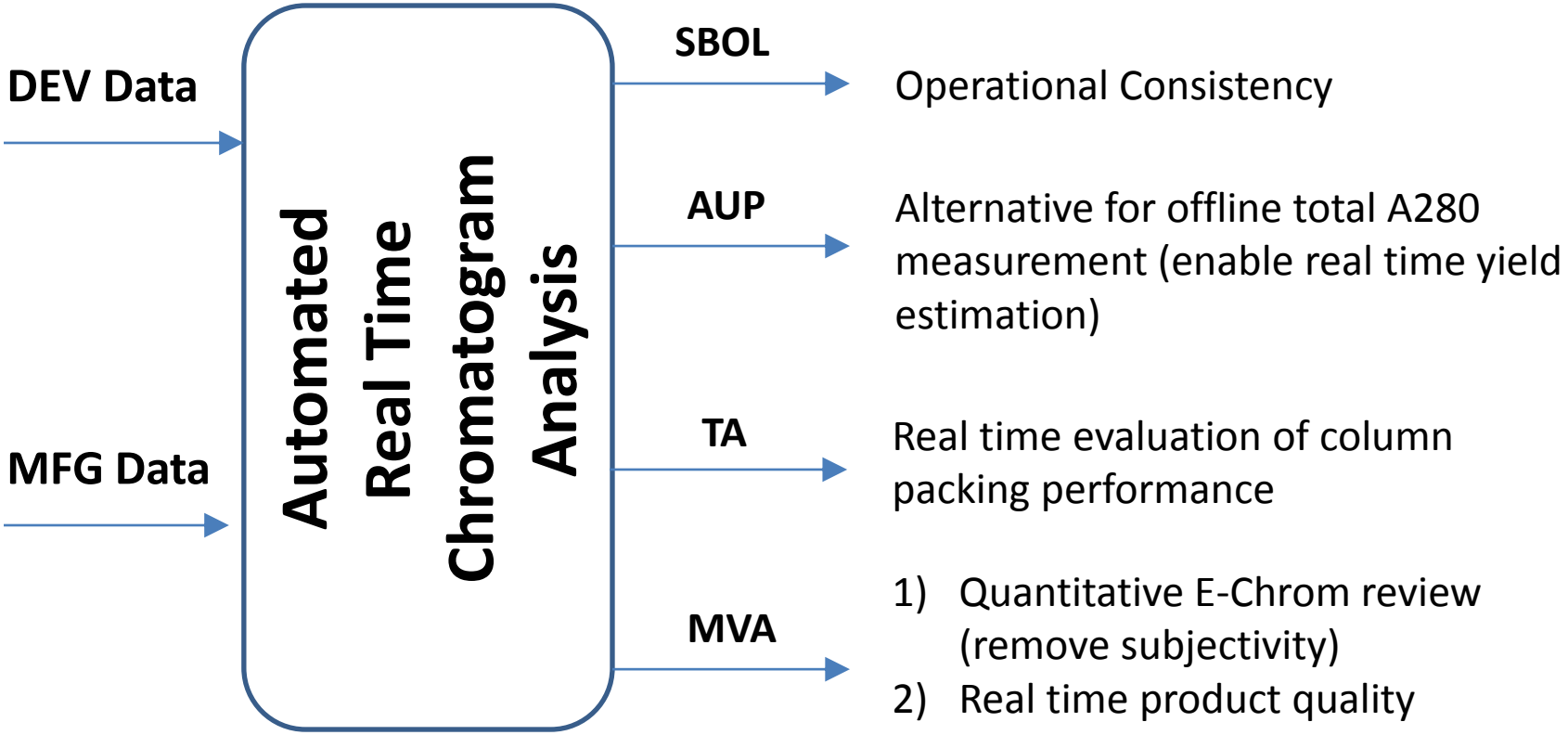
Chromatogram MVA Summary

- Chromatogram MVA enabled successful root cause investigation of the HCP upward shift
  - Multivariate analysis of cell culture and chromatogram parameters indicated that chromatogram parameters were strongly correlated with HCP
  - Further correlation analysis indicated that resin age contributed to the chromatogram shape shift
  - Lab studies confirmed that resin age contributed to the column performance shift and the gradual upward trend of HCP

Summary and Conclusions

- Biogen Idec's E-Chrom Review
  - Our Goal is to develop non-subjective, quantitative method for evaluating chromatograms
- Data Accuracy is Key
  - Adequate instrument calibration/maintenance ensures accurate data and successful electronic chromatogram analysis
- Multivariate Chromatogram Review
  - More objective and quantitative than visual inspection
  - Relates chromatogram characteristics to column performance and product quality attributes

Future of Chromatogram Review at Biogen Idec



Operational Consistency

Alternative for offline total A280 measurement (enable real time yield estimation)

Real time evaluation of column packing performance

1) Quantitative E-Chrom review (remove subjectivity)
2) Real time product quality prediction
3) Real time column life cycle validation

Challenges:

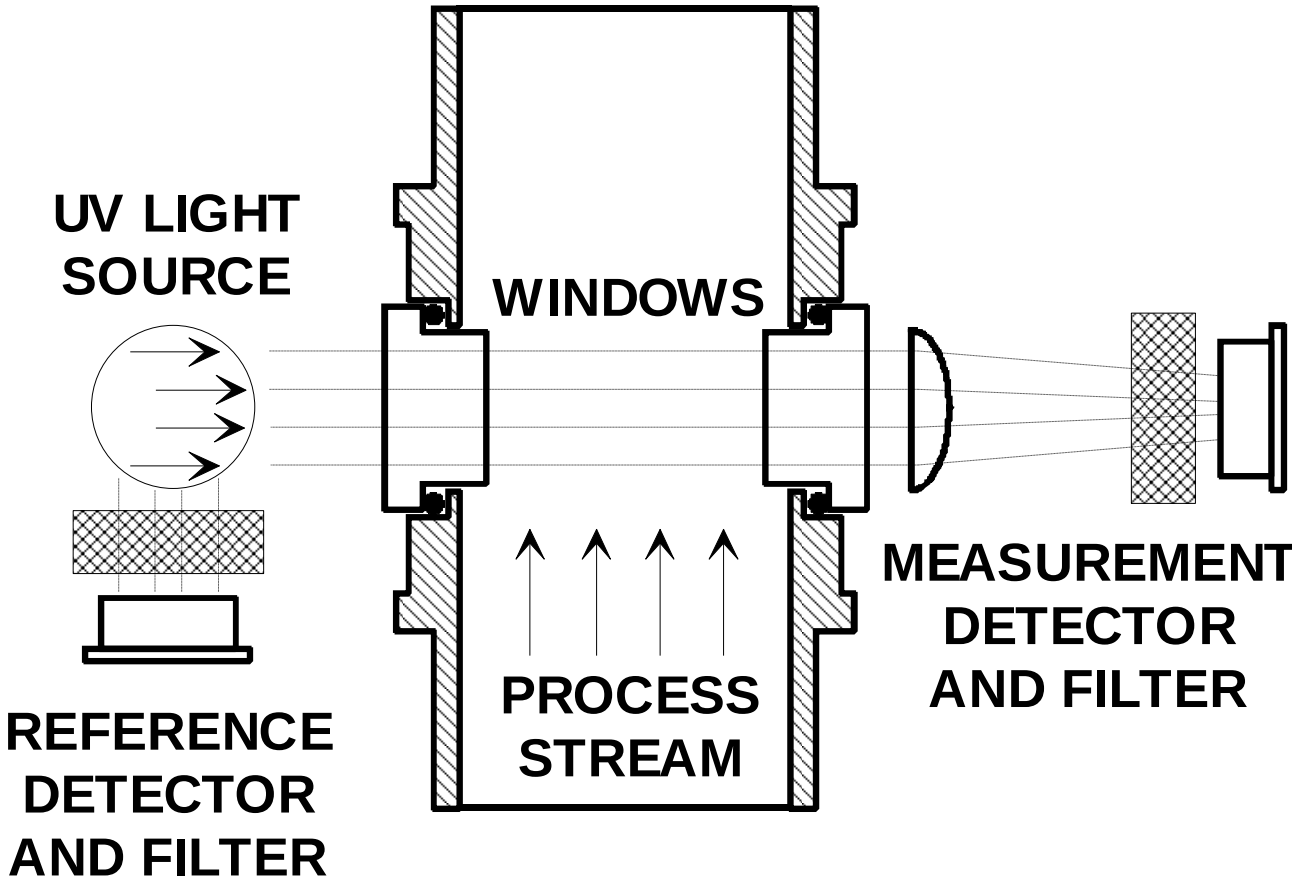
Equipment design, Instrument, and interaction of solution to resin

Acknowledgement

- Doug Cecchini
- Joydeep Ganguly
- Robert Genduso
- Ben Gilbert
- John Pieracci
- Jeff Simeone
- Jorg Thommes
- Andre Walker
- Sarah Yuan

Excess slides

UV Absorbance



MVA Principal Component Analysis

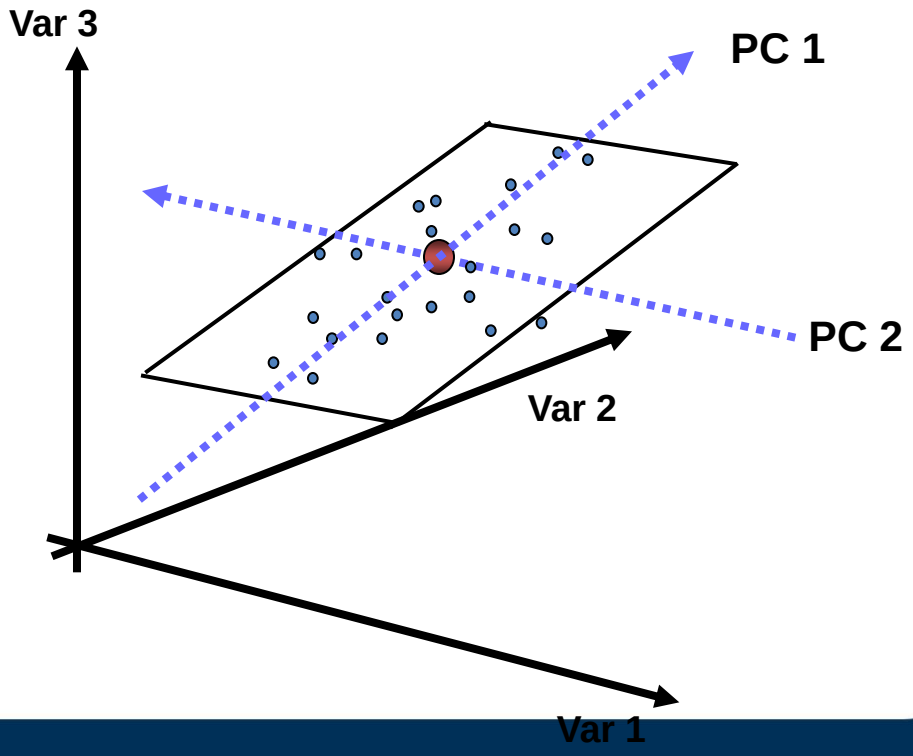
	Variables				
N	1	X_1	X_2	X_3	X_4
	2	X_1	X_2	X_3	X_4
	3	X_1	X_2	X_3	X_4
	4	X_1	X_2	X_3	X_4
	5	X_1	X_2	X_3	X_4
	6	X_1	X_2	X_3	X_4
	7	X_1	X_2	X_3	X_4
	8	X_1	X_2	X_3	X_4
	9	X_1	X_2	X_3	X_4
	10	X_1	X_2	X_3	X_4

Scores	
$t_{1\text{-}1}$	$t_{2\text{-}1}$
$t_{1\text{-}2}$	$t_{2\text{-}2}$
$t_{1\text{-}3}$	$t_{2\text{-}3}$
$t_{1\text{-}4}$	$t_{2\text{-}4}$
$t_{1\text{-}5}$	$t_{2\text{-}5}$
$t_{1\text{-}6}$	$t_{2\text{-}6}$
$t_{1\text{-}7}$	$t_{2\text{-}7}$
$t_{1\text{-}8}$	$t_{2\text{-}8}$
$t_{1\text{-}9}$	$t_{2\text{-}9}$
$t_{1\text{-}10}$	$t_{2\text{-}10}$

Weight				
	$P_{1\text{-}1}$	$P_{1\text{-}2}$	$P_{1\text{-}3}$	$P_{1\text{-}4}$
	$P_{2\text{-}1}$	$P_{2\text{-}2}$	$P_{2\text{-}3}$	$P_{1\text{-}4}$

SIMCA-P+ (Umetrics)

- Data is scaled and centered
- Plotted in K dimensional space
- Fit 1st Principal components (least squares)
- Fit 2nd Principal components (least squares)
- Project data onto two dimensional plane



Score Plot (t1 vs t2)