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Leveraging large data sets in continuous chromatography applications: Monitoring critical process parameters using MVDA

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Pall

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Capturing the value of Continuous Bioprocessing through MVDA

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Pall Life Sciences

Integrated Continuous Biomanufacturing II
Berkeley (CA), November 2015

Continuously Improving **Bioprocesses**

Enabling Technologies

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Cadence™ Inline Concentrator

BioSMB® Continuous Multi-Column Chromatography
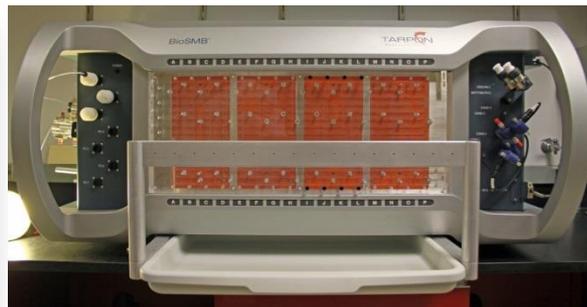
Acoustic Wave Separation

Cadence™ SPTFF

Stax™ Hyperion Flow Technology
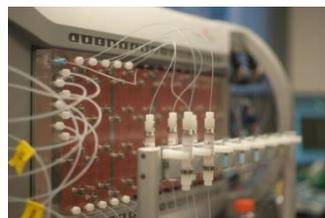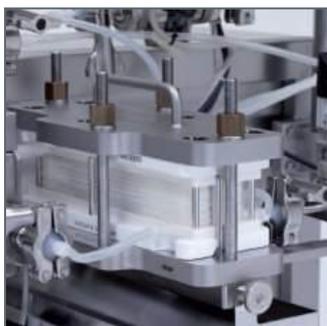
Pegasus™ Virus Filters

Mustang® Membrane Chromatography
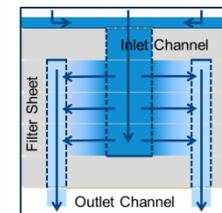
+ New Development Pipeline

Trends in Continuous Bioprocessing
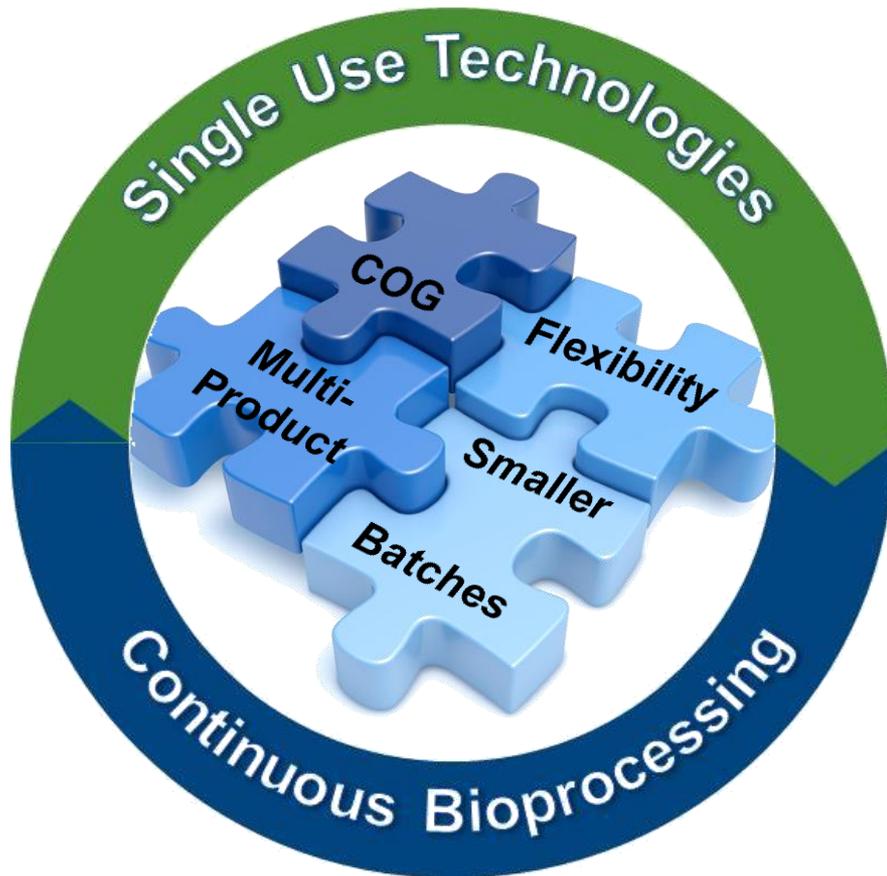
- **Process economics:**
  - Improved capital utilization
    - Reduced facility footprint
  - Reduction of operating expenses
  - Increased capacity utilization

- **Process control:**
  - Improved safety
  - Improved product quality control

BioSMB® Technology

Key Benefits:

- ✓ Improved specific productivity
- ✓ Improved utilization of resin capacity
- ✓ Significant reduction in buffer consumption
- ✓ Enabler for integrated continuous bioprocessing
- ✓ Enabler for integrated single-use manufacturing
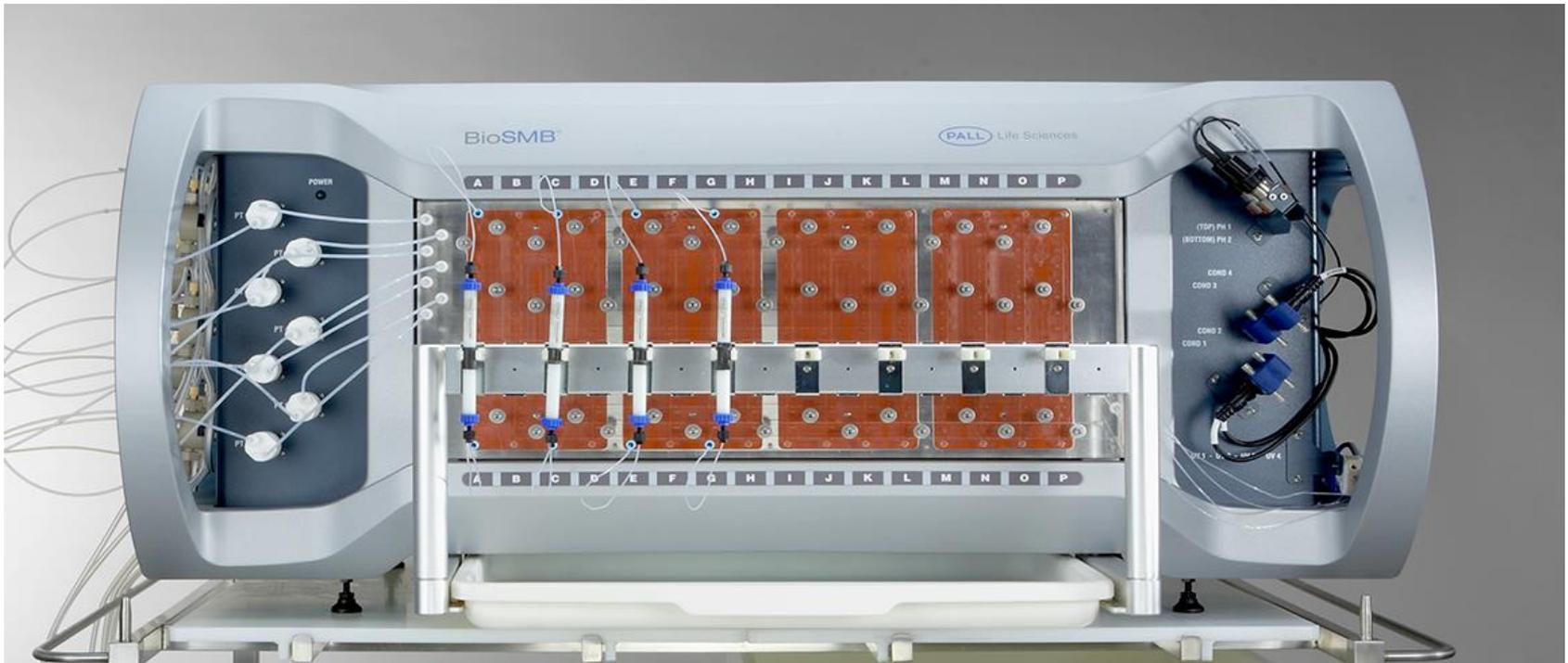
BioSMB Technology

Highlights:

- Multiple columns work together to allow continuous feed

- Columns travel through the process (or actually vice versa)

- Each column results in one elution peak every cycle
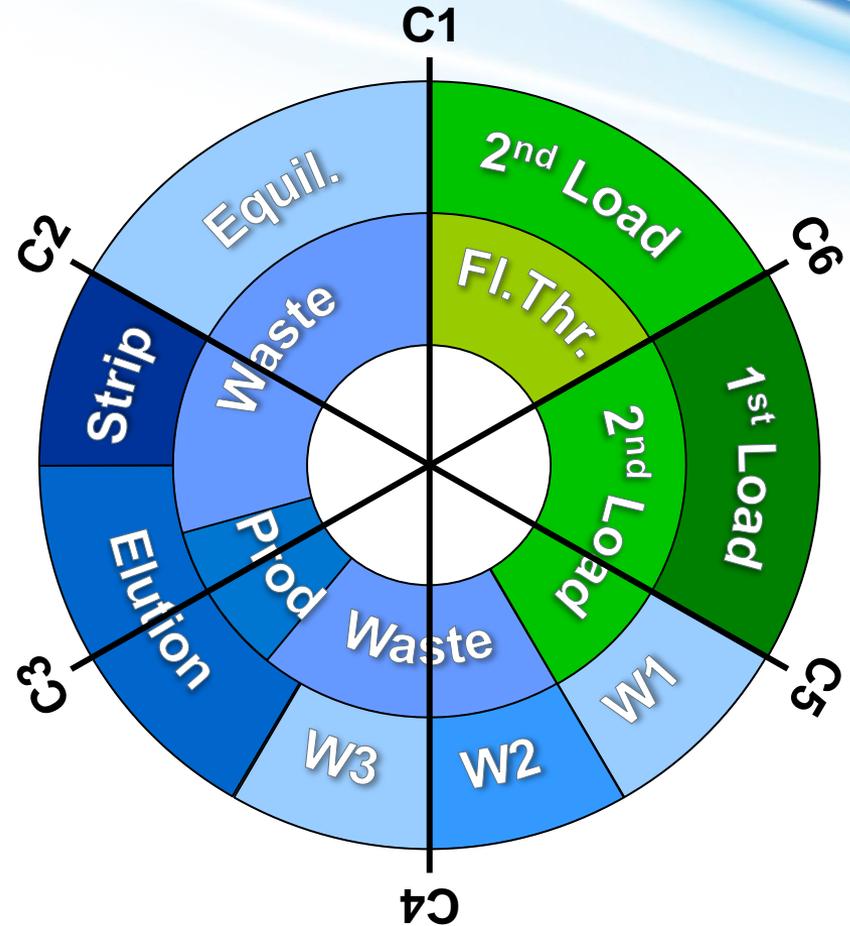
UV Absorbance in Product Outlet

Evaluation of Chromatographic Performance

**Traditional chromatography process monitoring:**

Process performance monitoring	Comment
Column characterization (HETP and asymmetry)	Prior to process start
Critical parameters (pool volumes, yields, etc.)	Off-line analyses
Review of chromatographic peaks: • Visual review • Moment analysis	Based on on-line data

This Strategy may need to be reconsidered for Continuous Bioprocessing

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# Using old Tools for a new Approach

Multivariate Data Analysis (MVDA):

✓ A mathematical tool for data reduction

✓ Very strong for recognizing patterns in large and complex datasets

➢ **Principal Components Analysis (PCA)**

Raw Data	1st PC	2nd PC

Courtesy: Umetrics (http://www.umetrics.com)
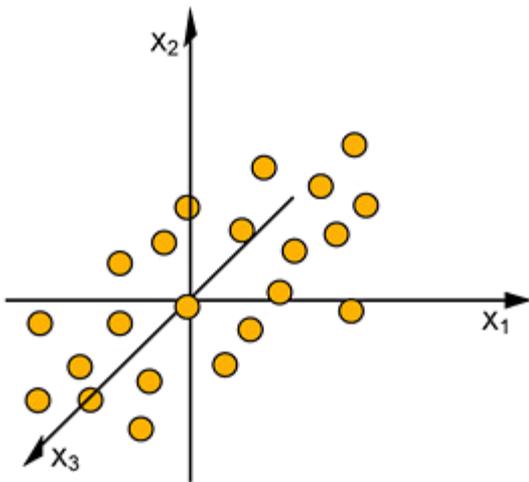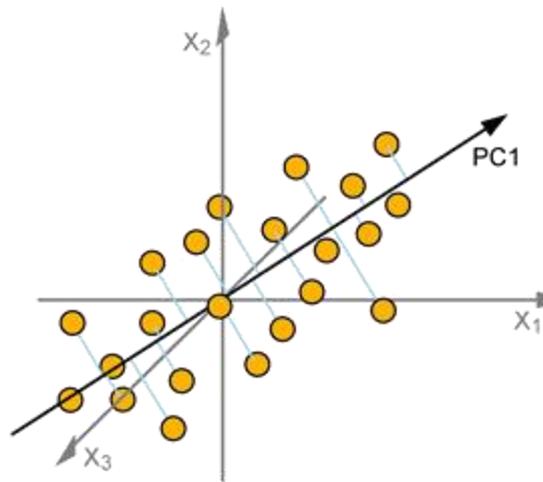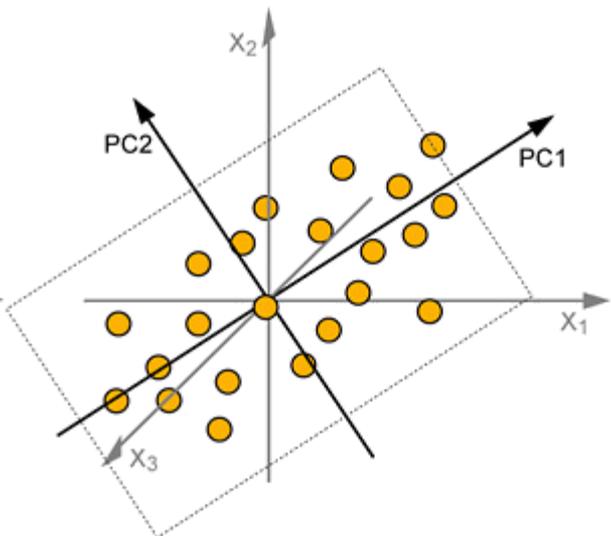
PCA for Chromatography

The correlation between the Principal Components (PC1 & PC2) and the physical characteristic of the chromatography peak...

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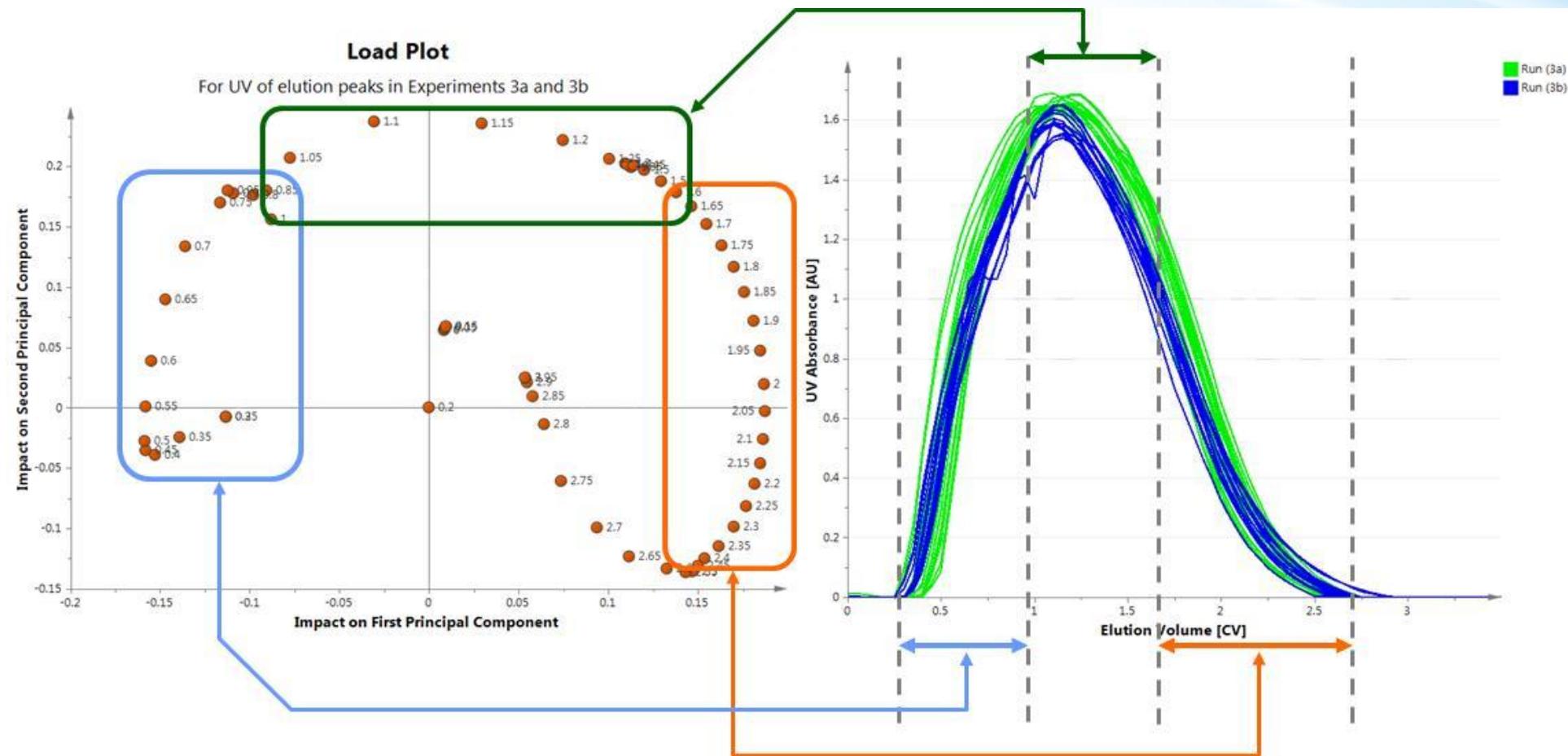
Case Study 1: Column to Column Variations

Monovariate Analysis	Multivariate Analysis

Protein A Elution Peaks (UV)
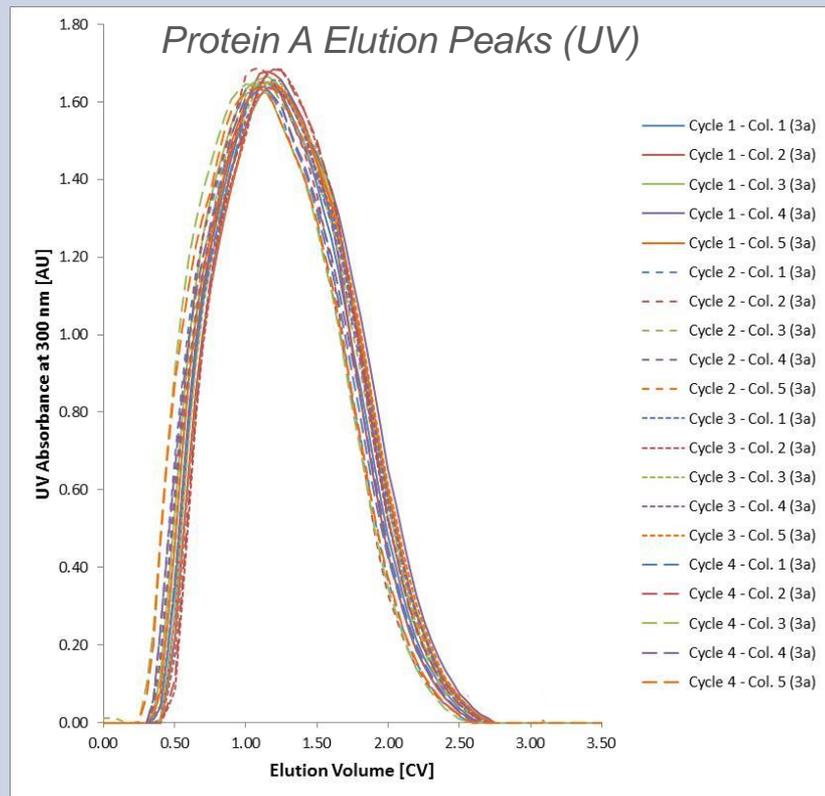
No significant variations detectable

Main source for variation: Column-to-column variations

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Case Study 1: Batch to Batch Variations

Monovariate Analysis	Multivariate Analysis

Protein A Elution Peaks (UV)

Start-up behaviour: excluded from analysis
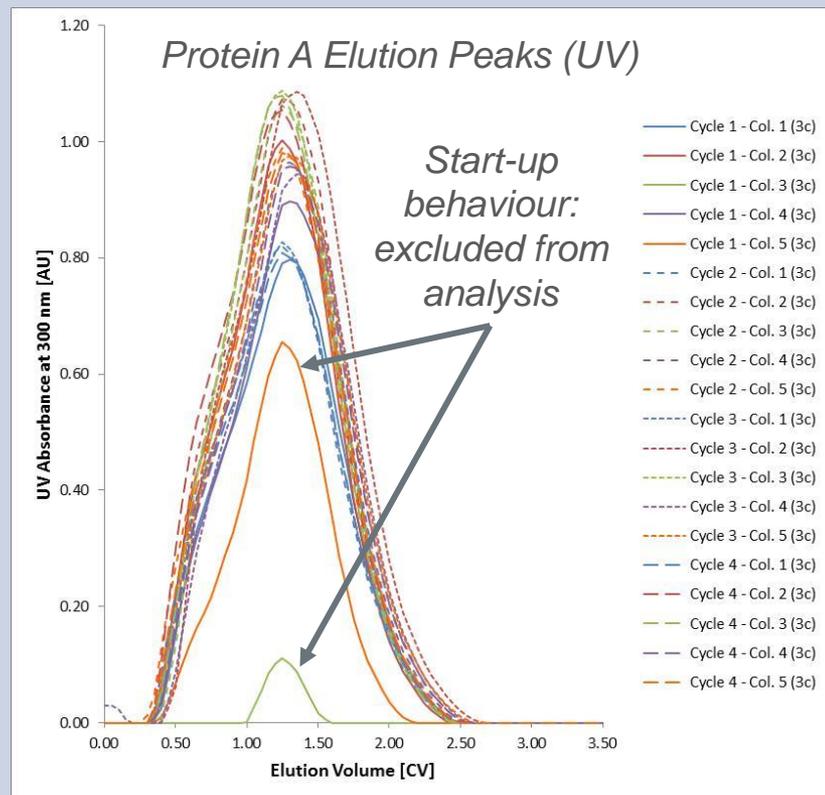
No significant variations detectable
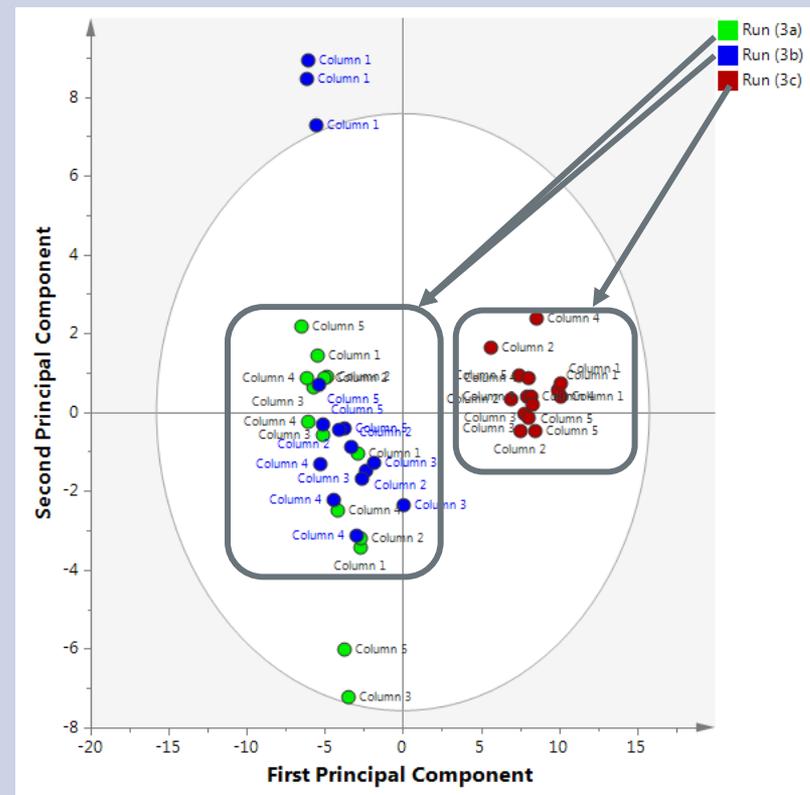
Reasonable consistency for two, but large variation for third batch

Case Study 1: Batch to Batch Variations

Monovariate Analysis	Multivariate Analysis

Protein A Elution Peaks (UV)

Three different clouds
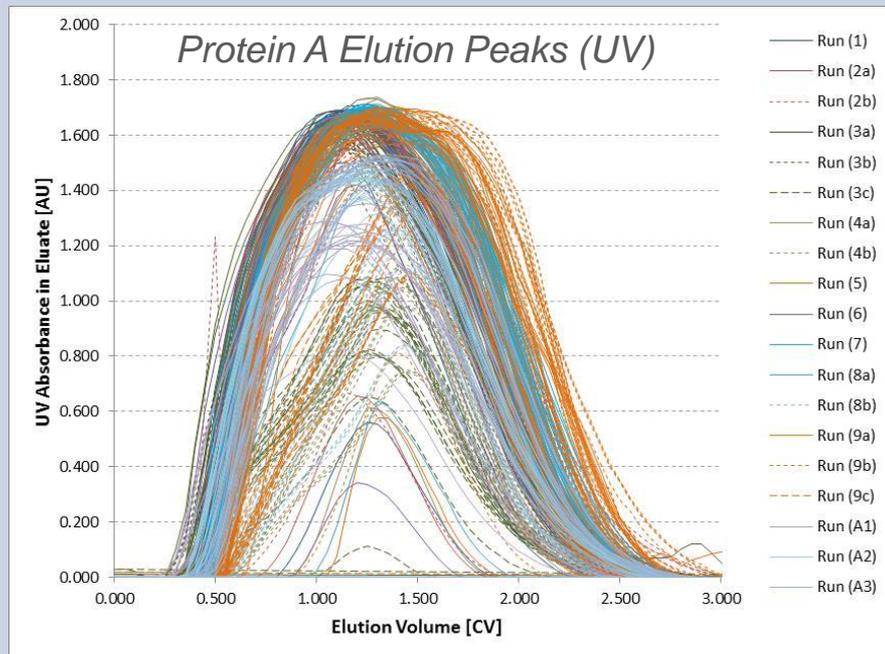
Too much data to make any sense
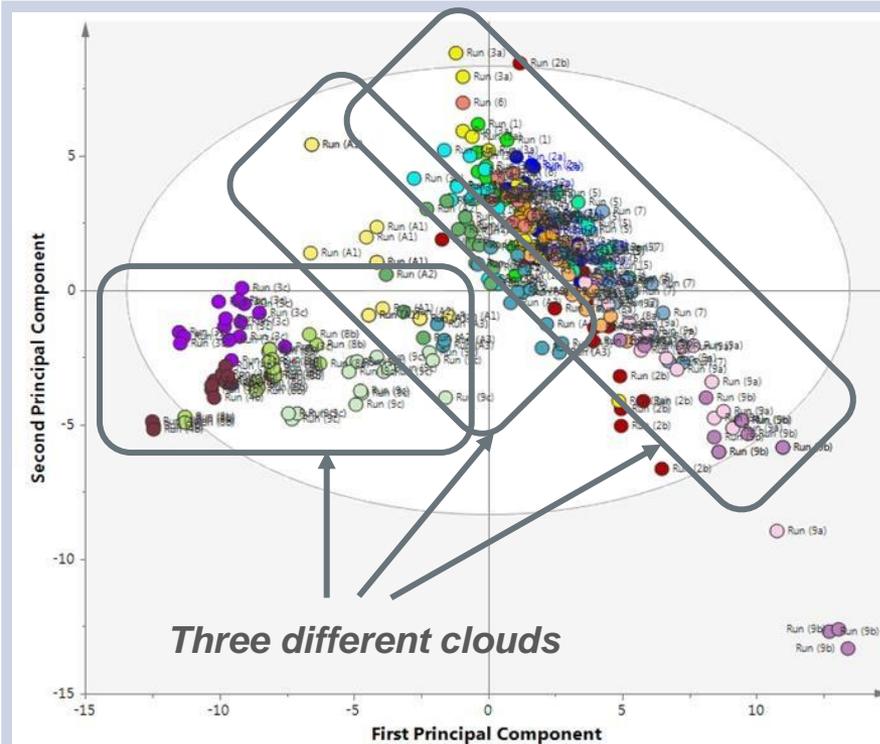
Harvest procedures impacted the PCA of PrA elution peaks

Case Study 2: Column Malfunctioning

Monovariate Analysis	Multivariate Analysis

Protein A Elution Peaks (UV)

Protein A Elution Peaks (UV)

Note: Performance decay in Column 5 was most likely related to inadequate cleaning conditions (not to the separation and/or technology itself)
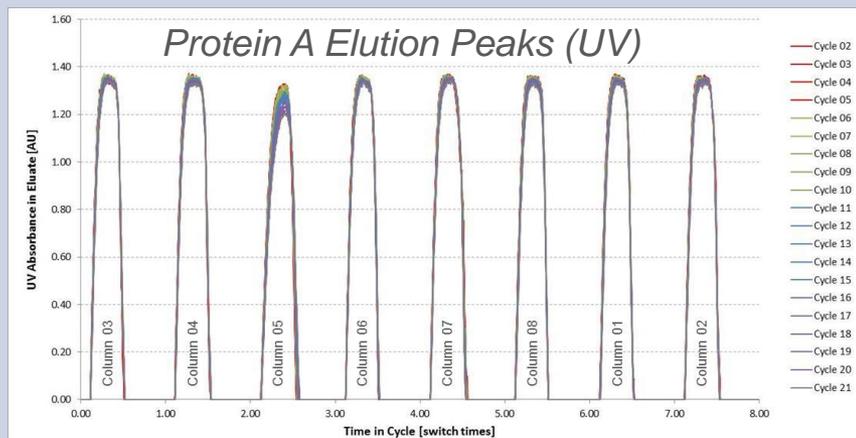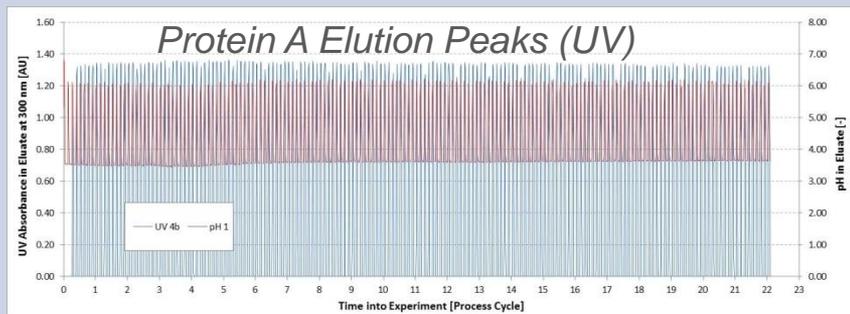
Cycle-to-cycle overlay shows some effect in Column 5

Column 5 shows deviations from start of run

Case Study 3: Comparing Processes

Monovariate Analysis	Multivariate Analysis

Eight tests:

- Two monoclonal antibody products
- Same chromatography media and buffer system
- Slight differences in load capacity
- Different column configurations in load zone
- Elution peaks looked very similar

Collect BI data.M2 (PCA-X)
Colored according to Obs ID (Obs. Sec. ID:1)

Molecule B

Molecule A

[1] = 0.713   R2X[2] = 0.121   Ellipse: Hotelling's T2 (95%)

| Overall process performance was consistently acceptable	Small differences process conditions become clearly visible
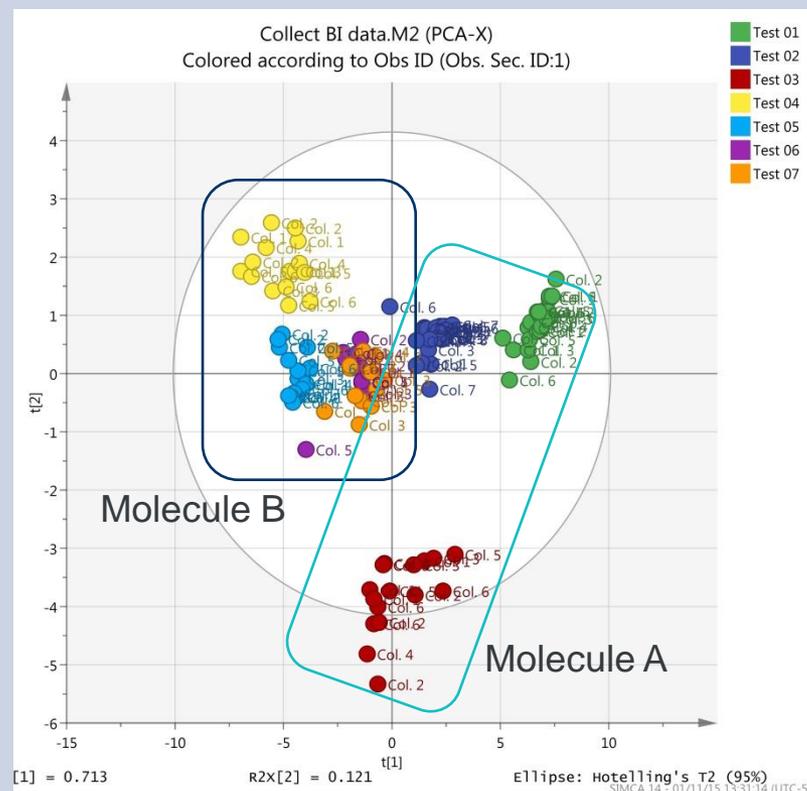
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Case Study 4: Process upsets

Monovariate Analysis	Multivariate Analysis
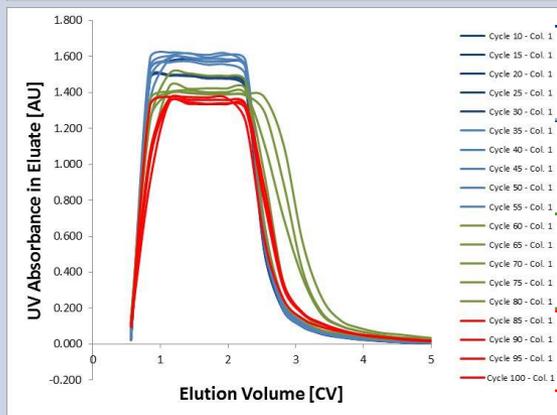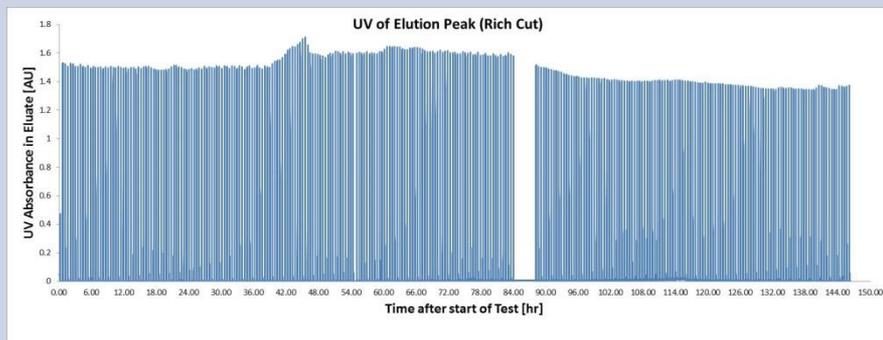
Several process interruptions for changing feed solutions and buffers
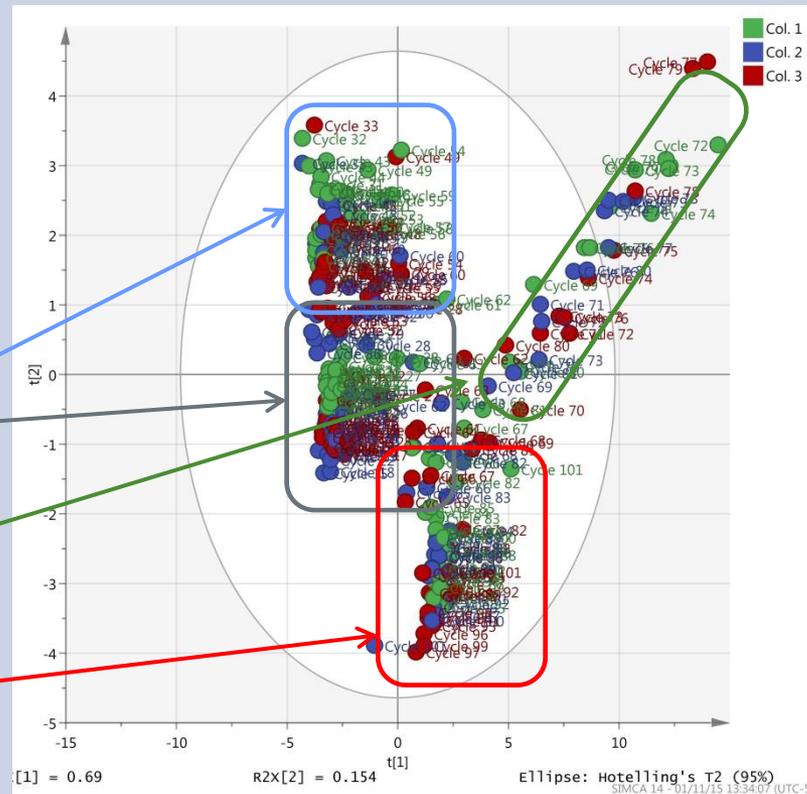
Excursions in PCAs correlated with changing feed solutions

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Opportunities

MVDA offers numerous opportunities for monitoring process consistency:

Opportunity (examples only)	Potential Approach
On-line column characterization	PCA on ΔP across columns (e.g. during equilibration or wash step)
Monitoring bed packing consistency	PCA on conductivity as column moves through different wash steps

Forward looking:

- Correlating response from MVDA to product attributes (CQA's) will bring us one step closer to parametric release

- Integrated process control (Process Analytical Technologies)

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Conclusions

- Multivariate Data Analysis (MVDA) turns large datasets into (visual) information, thereby capturing the value of continuous bioprocessing

- Principal Components Analysis (PCA) can detect small deviations in peak shapes before traditional methods can:

  - Monitor process consistency (cycle-to-cycle reproducibility)

  - Detect column-to-column variations

  - Detect column failures and other trends before they become problematic

> ✓ **MVDA will help end-users providing evidence that they're in control of their process**
> ✓ **MVDA can be used to build effective process monitoring and control strategies**

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- Brian To
- Mark Strawn

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