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Capturing the value of Continuous Bioprocessing through MVDA

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Biopharmaceutical Manufacturing

- Biopharmaceutical industry is relatively young in terms of manufacturing operations

- Not all product attributes can be measured (at any given time)

"The process is the product"

- Process validation is an inherent part of product quality control
- Dominated by batch manufacturing

… but changes are coming!

Continuous Manufacturing

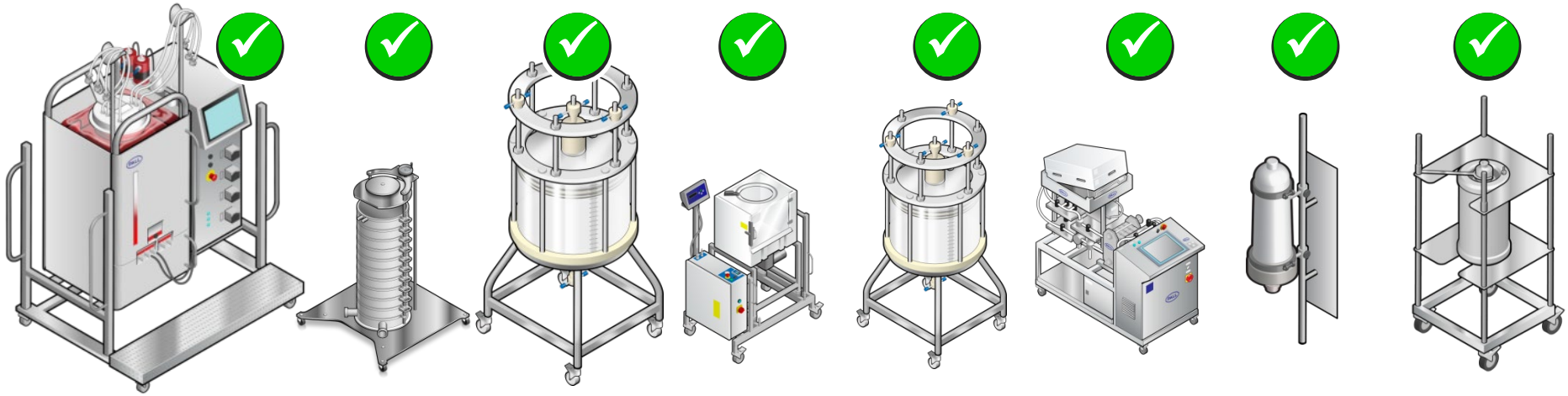
Why are many mature industries moving towards continuous processing:

- Process economics:
  - improved capital utilization
  - reduction of operating expenses
- Process control:
  - Improved safety
  - Improved product quality control

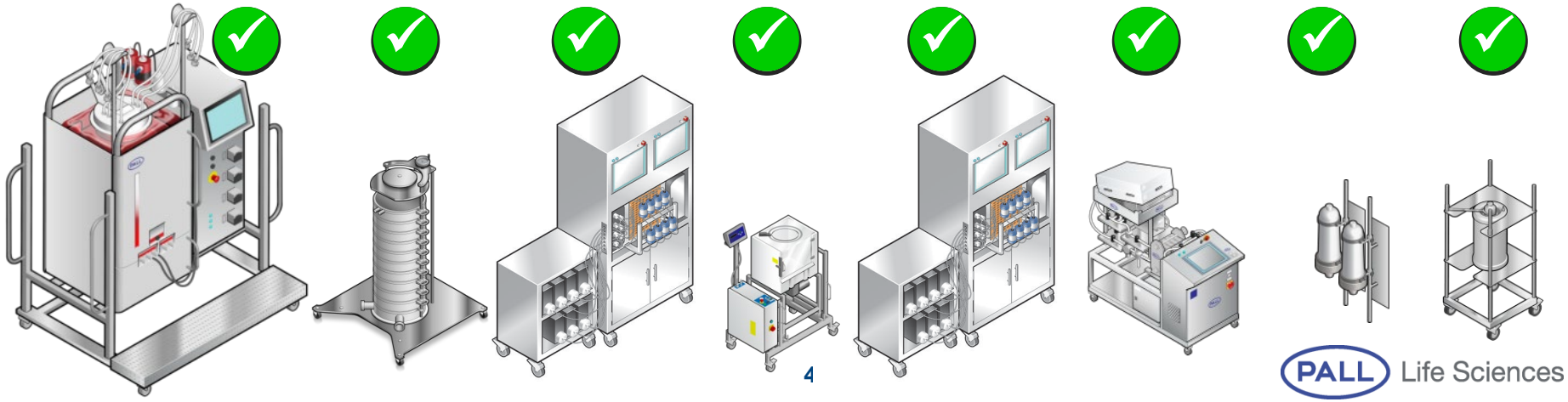
Compelling arguments for Biopharmaceutical Industries

Integrated Continuous Bioprocessing

Fed Batch USP + Batch DSP



Fed Batch USP + Continuous DSP



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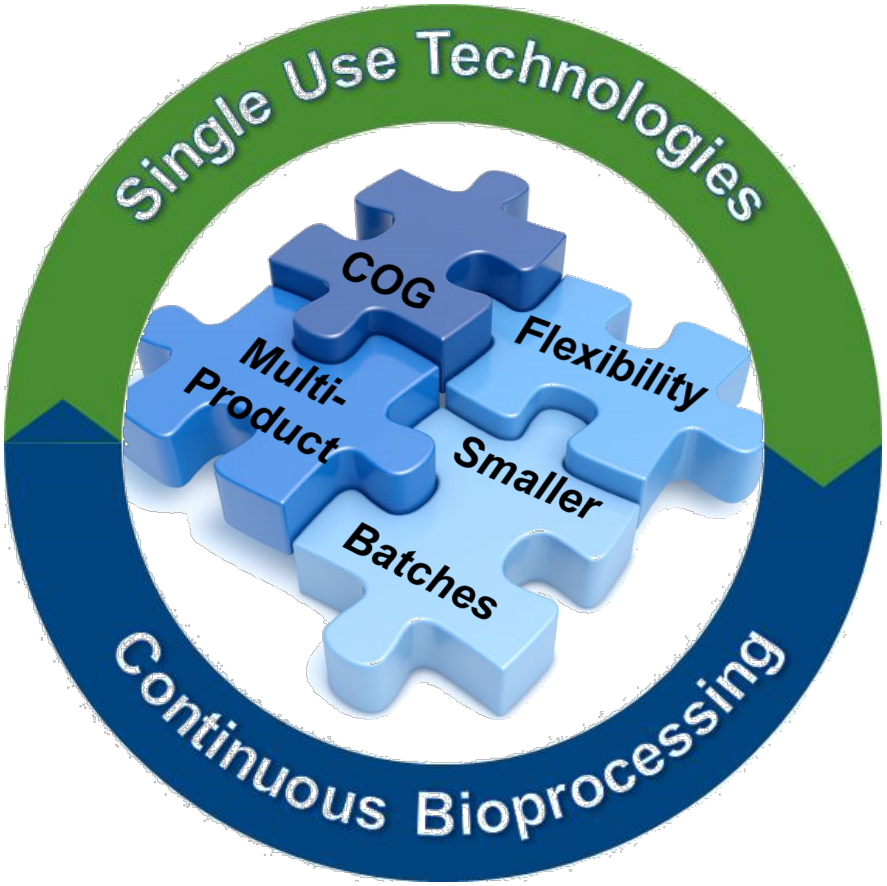
Trends in Continuous Bioprocessing

Industry Trends



Considerations:

Most DSP steps are compatible with continuous bioprocessing:

- Filtration steps
- Flow-through chromatography steps

Key Enabling Technology:

- Multicolumn Chromatography (e.g. BioSMB®) for bind/elute chromatography

BioSMB® Technology

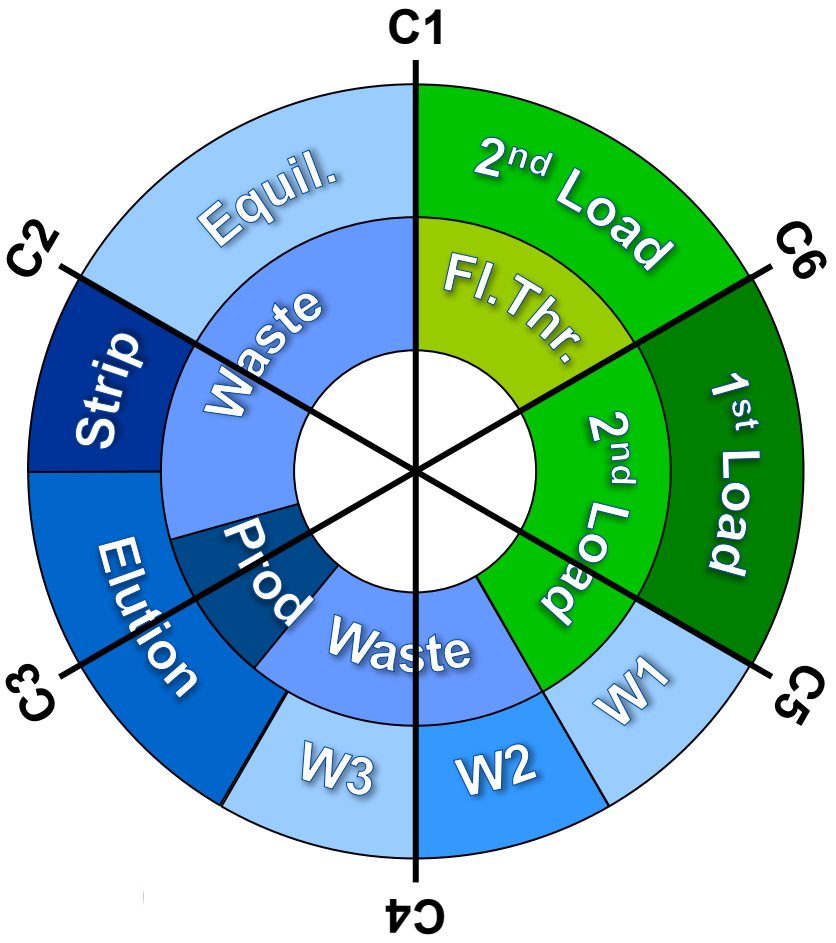
Key Benefits:

- 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

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

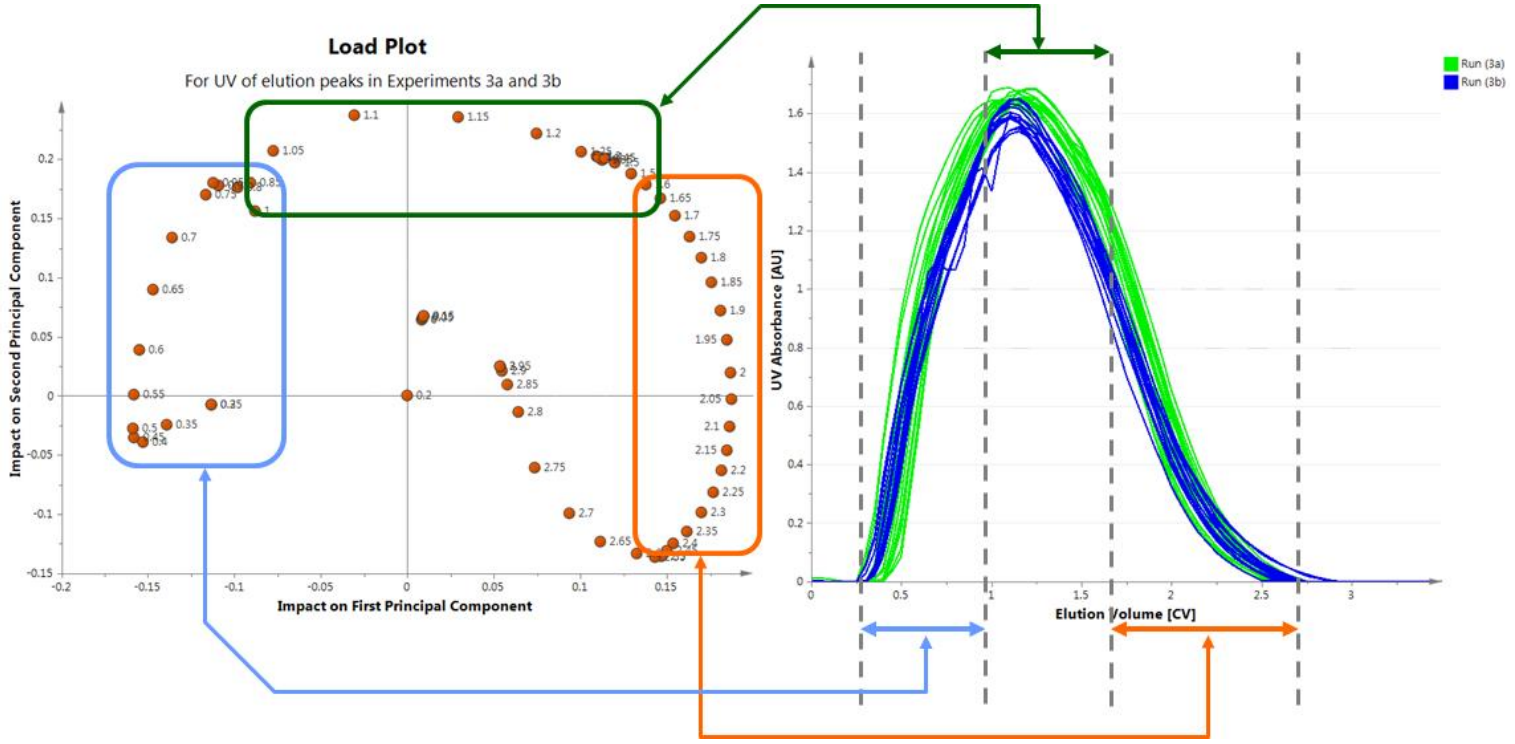
In this study, we will limit the MVDA to:

Principal Components Analysis (PCA):

- Not new: PCA was first described (invented) in 1901
- Mathematical transformation of data into orthogonal (principal) components

PCA for Chromatography

The Principal Components do not (necessarily) represent a physical characteristic of the chromatography peak, but...



The correlation between load plot and chromatography peak changes with the data set.

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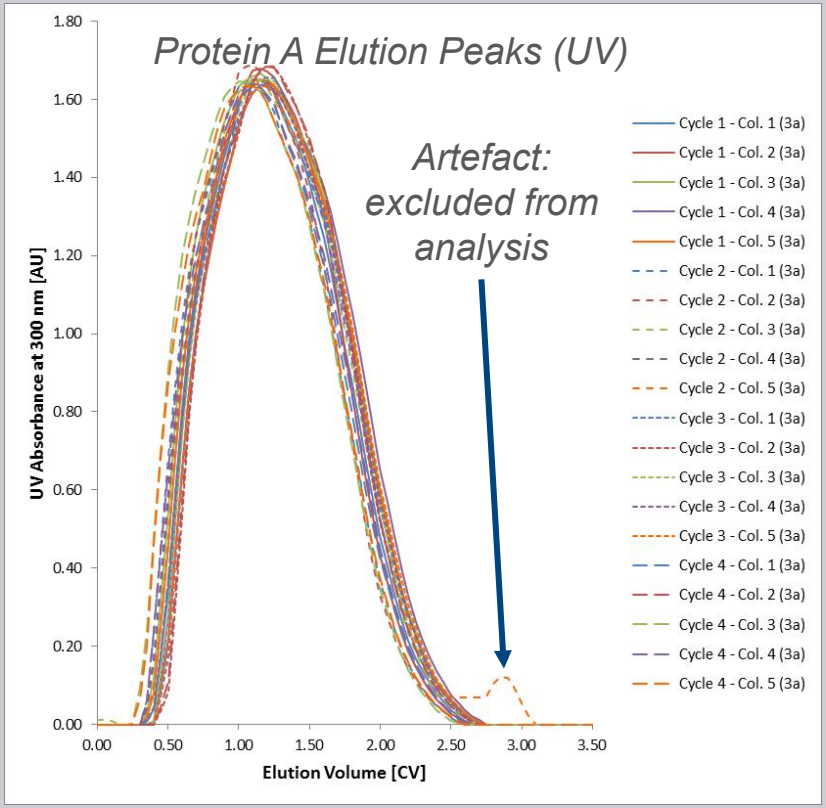
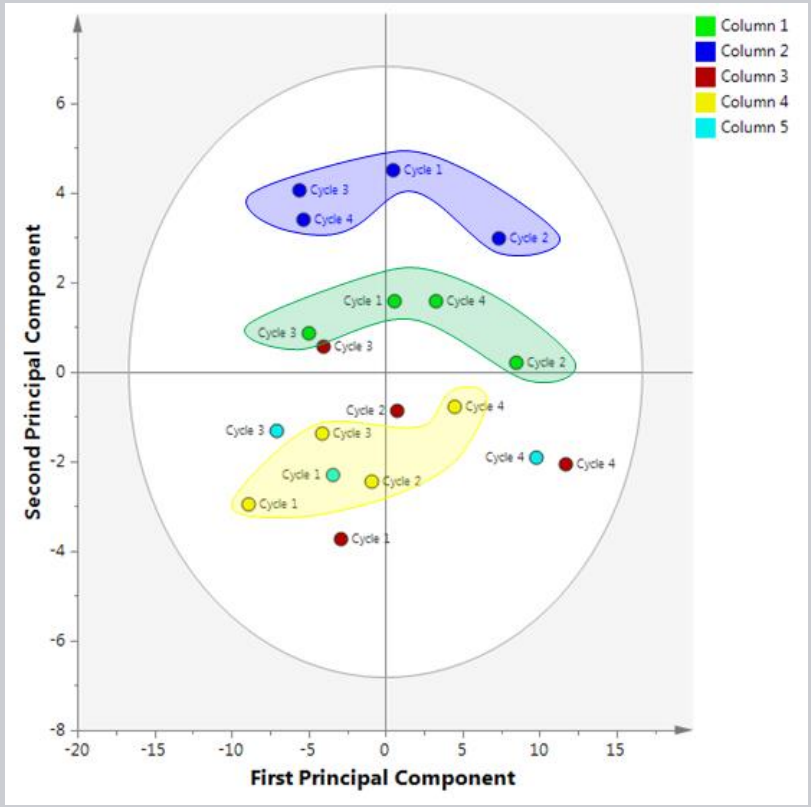
Case Study 1: Column to Column Variations

Monovariate Analysis



No significant variations detectable

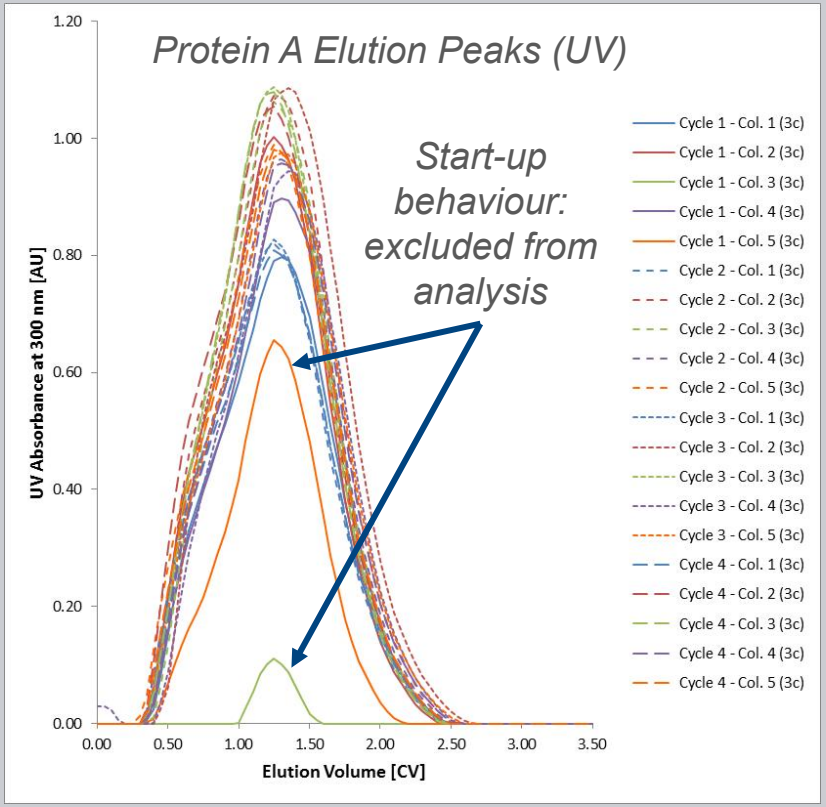
Multivariate Analysis



Main source for variation: Column-to-column variations

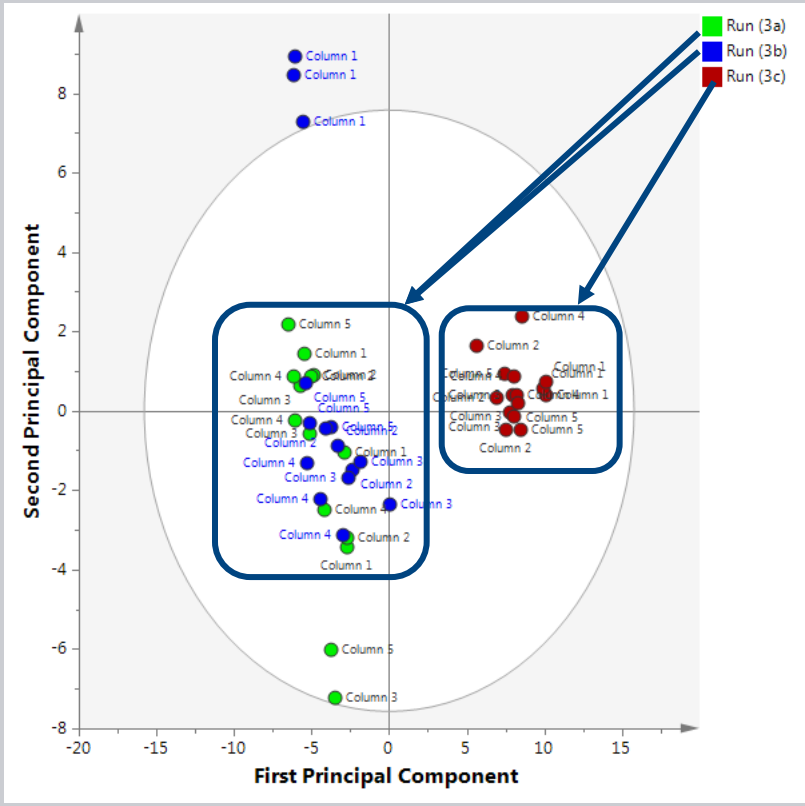
Case Study 1: Batch to Batch variations

Monovariate Analysis



No significant variations detectable

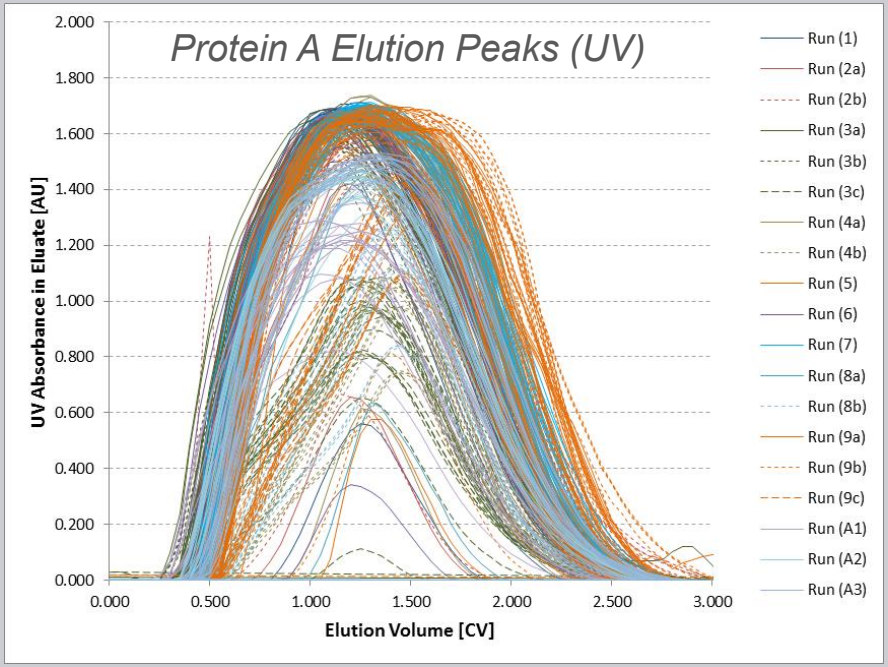
Multivariate Analysis



Reasonable consistency for two, but large variation for third batch

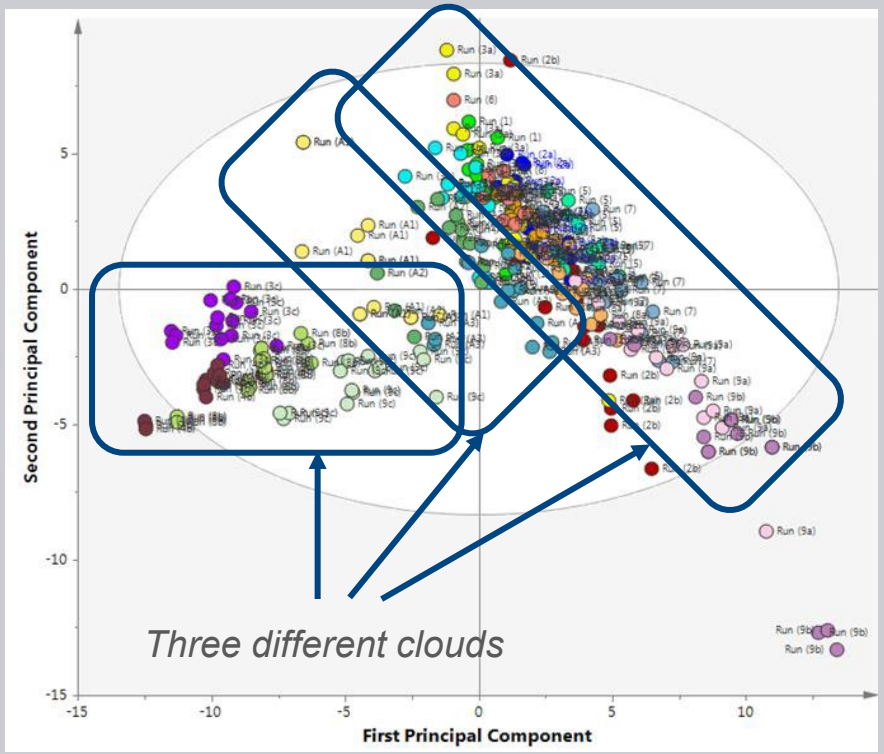
Case Study 1: Batch to Batch variations

Monovariate Analysis



Too much data to make any sense

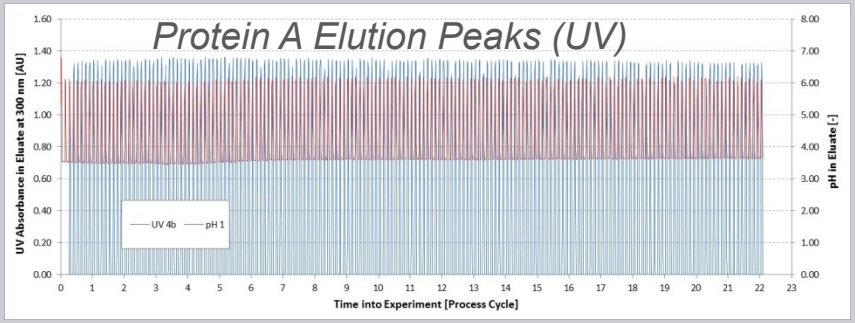
Multivariate Analysis

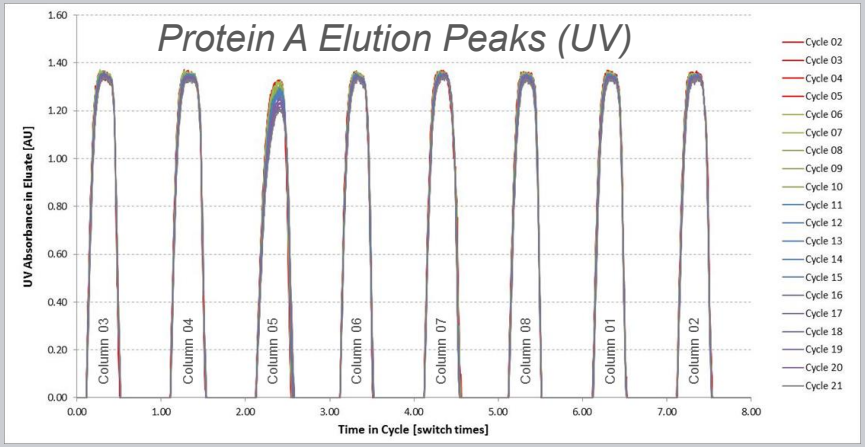


Harvest procedures impacted the PCA of PrA elution peaks

Case Study 2: Column Malfunctioning

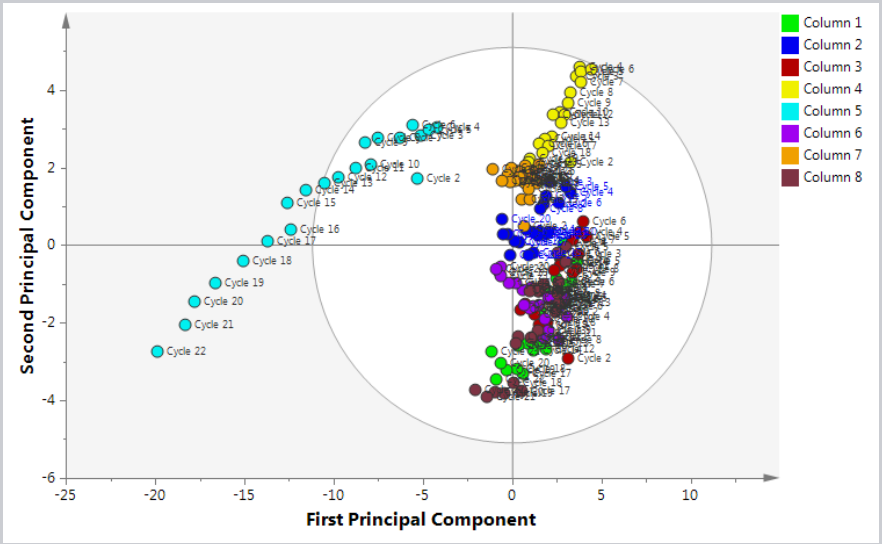
Monovariate Analysis





Cycle-to-cycle overlay shows some effect in Column 5

Multivariate Analysis



Note: Performance decay in Column 5 was most likely related to inadequate cleaning conditions (not to the separation and/or technology itself)

Column 5 shows deviations from start of run

Data generated at Sanofi-Aventis, Höchst, Germany (courtesy)

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 (QCA's) will bring us one step closer to parametric release
- Integrated process control (Process Analytical Technologies)

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 becomes problematic

MVDA will help end-users providing evidence that they're in control of their process

Acknowledgements

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