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Advanced technologies and computational modeling in continuous bioprocessing Heather Brooke, Pall Corporation, USA

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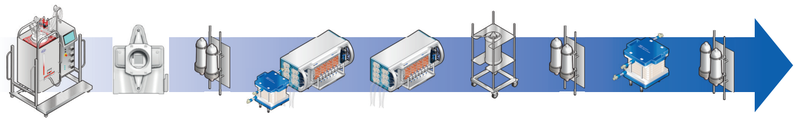
INTRODUCTION

Advanced technologies and computational modeling is an overall capability upgrade to be used in conjunction with our existing and planned continuous bioprocessing toolbox to enable on-line and at-line real time continuous process analytical technology (PAT) and automation of the continuous products.

Pall Corporation is developing new PAT tools including both instrumentation and computational techniques. This overall capability upgrade will be used in conjunction with both batch and continuous processes to enable real time on-line and at-line monitoring, as well as advanced automation approaches.

PAT adds value to batch processes and paves the way for continuous manufacturing through timely measurements of critical process parameters (CPPs) and critical quality attributes (CQAs) across both raw and in-process materials, allowing better process understanding and optimized control.

Pall's continuous laboratory in Westborough, MA, USA



Increased Efficiency, Greater Flexibility, Higher Quality, Reduced Cost, Smaller Facility Footprint

PROBLEM STATEMENT

Gaining a better process understanding during biotherapeutics process development will reduce the cycle time for deviation investigations, problem analysis and implementation of corrective actions:

- During process development, we seek to understand the CQAs needed to achieve the desired product
- Process that uses quality-by-design (QbD) principles is followed:
  - Understanding how CPPs affect the CQAs
  - Gain understanding of the relationship between CQAs and CPPs
  - Develop a multivariate model that defines how variability of the CPPs affects the CQAs in order to produce a quality product

Once relationship between CPPs and CQAs is achieved, PAT-based measurements, monitoring and control can be used to ensure quality and increase overall manufacturing performance.

BENEFITS

- Increase product quality and robust overall manufacturing performance
- Enable end-to-end continuous process by implementing lean and flexible biomanufacturing
- By reducing off-line analytical testing, ultimately time to perform the analysis of critical attributes in real-time is increased and quality is improved

USING PAT TO SET MONITORING AND CONTROL STRATEGIES

- **Identify CQAs that affect the product quality in the continuous process**
  - Cell density, protein concentration, aggregation, host cell protein (HCP), glycosylation, etc.
- **Identify CPPs that affect CQAs during the continuous process**
- **Implementation of PAT-based measurements and controls (in addition to sensors)**
  - Analytical instrumentation capable of characterizing CQAs of interest
  - Develop chemometric models by using chemometric tools
  - Software for PAT method development, data management, and system integration

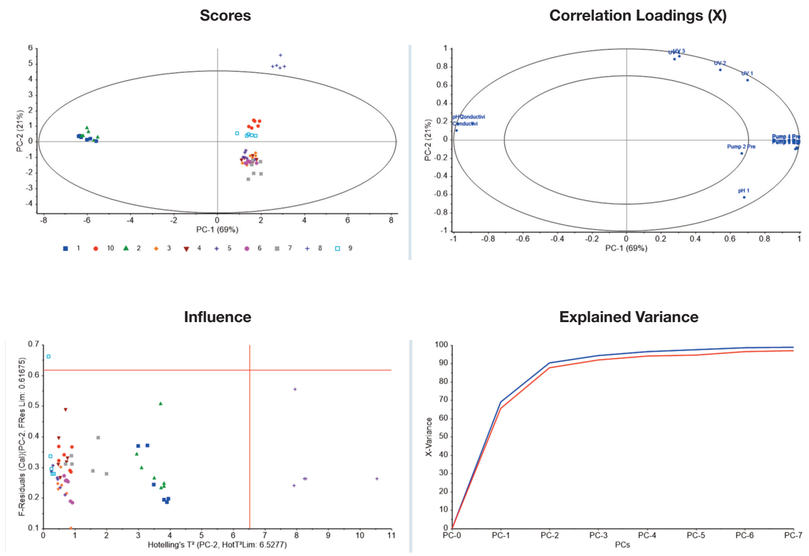
CHEMOMETRIC MODELS FOR CONTINUOUS BIOPROCESSING

Qualitative Process Monitoring via Principal Components Analysis (PCA)

- Runs 1 and 2 were known deviations, with different resin and buffer, high conductivity noted in the final CQAs. This PCA model confirms that as runs 1 and 2 have low scores on the principal component (PC) 1, which has a strong influence by conductivity in the loadings plot.
- When a model was built with batches without any deviations, these batches are flagged as outliers, one can drill down in the residuals to determine that the conductivities were high. Having this knowledge in real-time can allow operators to make adjustments immediately and move the process back into the 'golden batch zone'.

Figure 1

PCA of 10 runs during protein capture. The explained variance plot (lower right) shows that 2 components cover 90% of the total variation in the measured variables. The correlation loading plot shows that the PC1 explains the variations in pump pressures, pH, and conductivity, and the PC2 is mostly the UV responses. High conductivity was noted for runs 1 and 2, which is confirmed in the scores plot.



CHEMOMETRIC MODELS FOR CONTINUOUS BIOPROCESSING *(Continued)*

The media was spiked with common metabolites or chemicals ($CaCl_2$ [shown], glutamax, glucose, NaOAc, and IgG) found in the bioreactor, and Raman spectra was collected to build preliminary partial least square (PLS) models.
This proof-of-concept shows that Raman has the potential for qualitative analysis during an upstream bioreactor run.

Figure 2

Raman spectra of media spiked with $CaCl_2$ ranging from 0.625 g/L to 10 g/L, also pure $CaCl_2$. There are differences seen in the bands from ~1300 cm^{-1} to ~1550 cm^{-1}, which corresponds well with the pure component spectra.

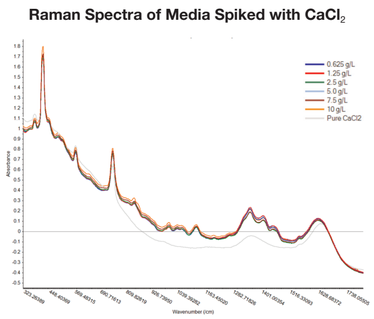
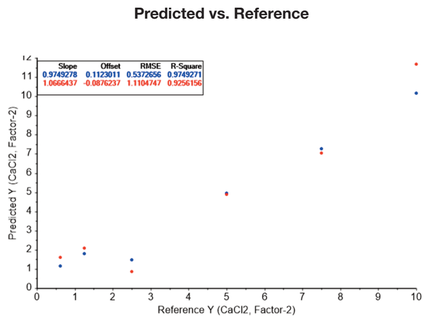


Figure 3

A PLS model was created based on a gravimetric method for reference.
We see a good linearity across the full range, with the exception on the 2.5 g/L sample.

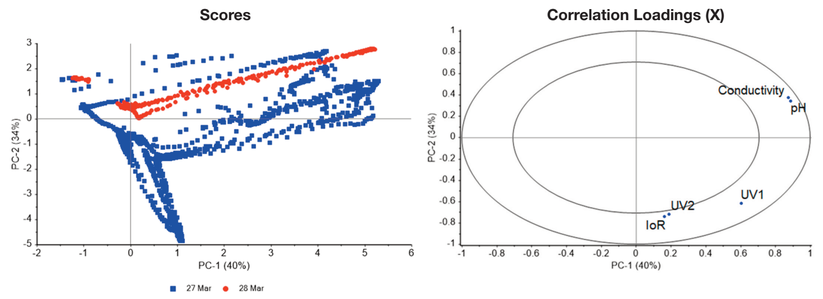


Identifying and Comparing New Technologies

A new technology using refractive index was compared with the current ultraviolet-visible spectroscopy (UV/Vis) approach for measuring the protein content during capture. The loadings shown here prove that the index of refractivity (IoR) is highly correlated with the UV results, and is not affected by conductivity or pH due to the fact that each PC is by definition orthogonal to the others.

Figure 4

A PCA model was built on data from 2 days of experiments of the protein capture unit operation. The loadings plot shows that the IoR corresponds well to the UV2 response, and is not affected by changes in the conductivity or pH.



OUTLOOK

The ideal continuous controls platform combines analytics and process control strategy, empowering users to execute advanced processes with excellence in quality, yield, and return on investment

Value of PAT / multivariate data analysis (MVDA) implementation:

- Ensure consistent product quality and increase robust overall manufacturing performance, reducing heterogeneity
- Enable end-to-end continuous process by implementing lean and flexible biomanufacturing
- Advanced computational tools support continuous monoclonal antibody production
- Process time and cost savings can be achieved through automation and continuous integration in existing facilities

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