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PAT concepts for the process monitoring and control of continuous biomanufacturing

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PAT CONCEPTS FOR THE PROCESS MONITORING AND CONTROL OF CONTINUOUS BIOMANUFACTURING

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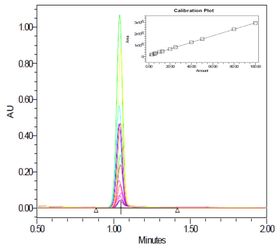
Introduction

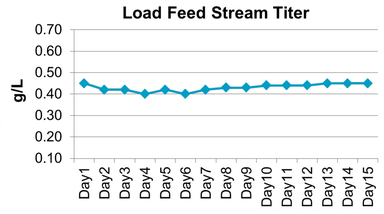
- Process Analytical technologies (PAT) are a key component to fully leverage the success of continuous manufacturing.
- The timely measurement of critical quality attributes and critical process parameters assures that the desired product quality is being consistently manufactured and non-conforming material being identified. PAT tools can be utilized to meet the expectations for in-process monitoring, and allows for identification and isolation of undesired in-process materials.
- It further supports process development, as continuous and fast response of process to factor changes allows efficient experimentation and increases process understanding within the range of conditions studied during development. Ultimately, PAT will allow Real Time Release (RTR), reduce cost, timelines and manufacturing risk.

On-line Titer Analysis of Permeate

The PATROL® Process Analysis System from Waters is an on-line UPLC instrument, providing access to real-time, chromatographic-quality analysis for in-process samples.

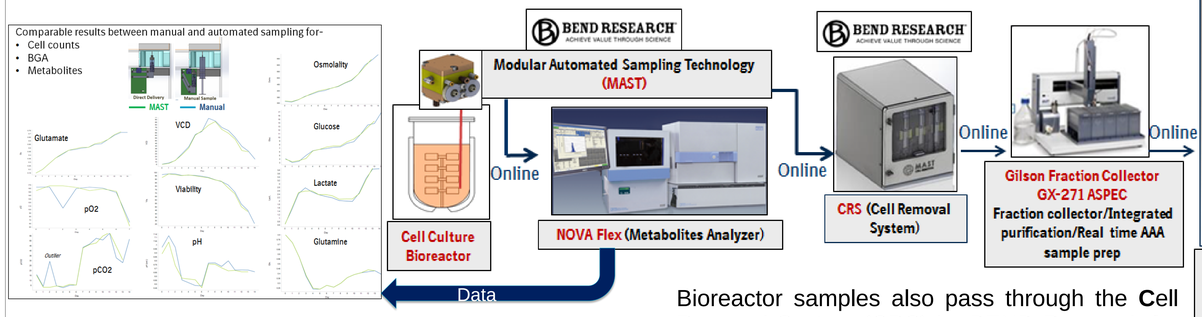


In this study, the PATROL® system was connected directly to the load feed-stream (HCCF permeate) of an ÄKTA chromatography system for continuous protein A (ProA) purification. Continuous sampling and monitoring of titer has been successfully demonstrated.



Integrated PAT Concept for Bioreactor Monitoring

We are presenting an integrated PAT concept for the analysis of cell culture performance, titer and product quality parameters for bioreactor performance.



Daily samples were drawn from bioreactors using the **M**odular **A**utomated **S**ampling **T**echnology (MAST) units by BEND Research. Bioreactor samples were directed to a NOVA Flex unit for online metabolite analyses. A god correlation to manual samples has been established.

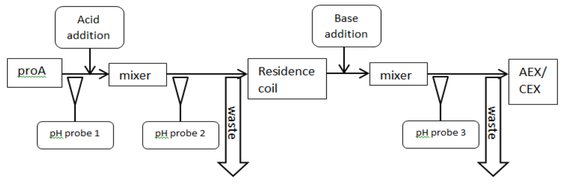
Bioreactor samples also pass through the **C**ell **R**emoval **S**ystem (CRS) by BEND Research for delivery of cell free samples to the Gilson fraction collector for further sample preparation, e.g. for AAA analysis or ProA purification. Retains can be collected for additional at-line/offline analysis. POC for the integral part of the CRS and Gilson is on-going.

From here, the Waters PATROL® system can perform on-line AAA analysis or PQ analysis of proA purified samples, e.g. SEC for size analysis or CEX for charge variants.

Continuous Low pH Virus Inactivation

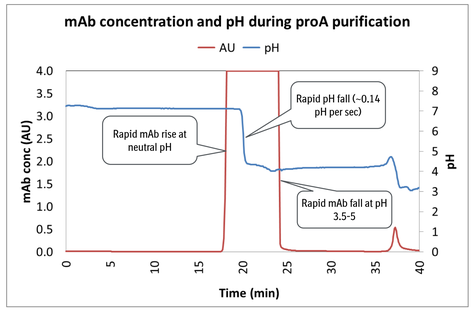
Example process (feed forward control)

1. Measure pH at probe 1 ➔ result controls acid addition.
2. Measure pH at probe 2 ➔ if pH good, flow through ≥1 hr. residence coil; if not, divert to waste.
3. Add base.
4. Measure pH at probe 3 ➔ if pH good, flow to AEX/CEX; if not, divert to waste.

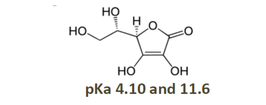


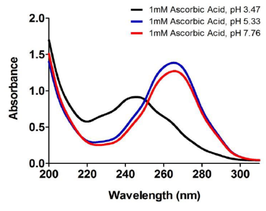
pH probe requirements:

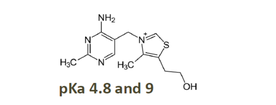
- 25 day process ➔ system sterility required ➔ probes sterility required
- Should not need removal for maintenance, must tolerate SIP/CIP.
- Fast response to add correct amount of inactivation acid.
- Accuracy (± 0.10 in 3.0-3.8 range) over time to ensure adequate pH values.

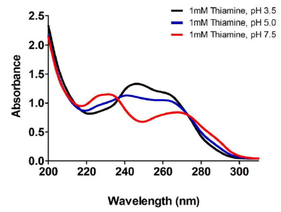


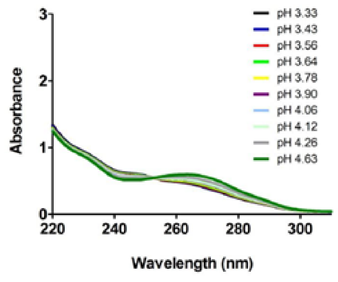
Though potentiometric pH probes are commonly used in downstream processes, the potential drawbacks of the need for periodic recalibration (with consequent risk of product stream contamination), susceptibility to human calibration error, and slow response time, are of concern for sterile, continuous manufacturing systems over long periods of time. Thus, we established POC of spectral pH measurement as an alternative approach as PAT application during low pH virus inactivation within the desired accuracy (±0.10). We researched chromophores that are on the FDA inactive ingredient list or GRAS list, UV absorbing, colorless, and have pKa values in desired pH range. **Ascorbic acid** and **thiamine** met the requirements and gave a strong UV signal dependent on pH. The applied multivariate model showed **±0.07 pH accuracy in the 3.3-4.5 range**.

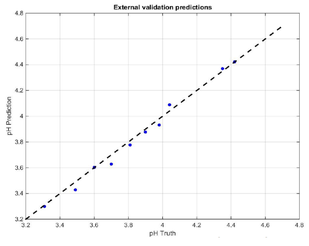












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