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Protein Refinery Operations Lab (PRO Lab): A sandbox for continuous protein production & advanced process control

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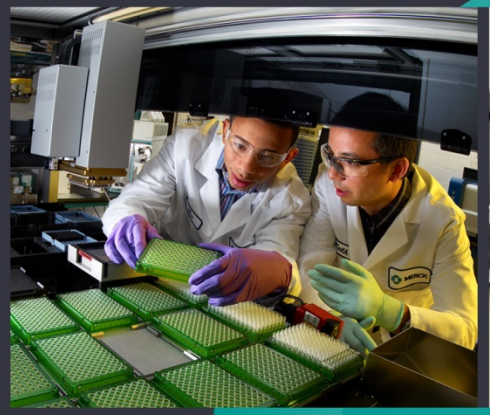

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BioProcess Development
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Kenilworth, NJ

ECI Integrated Continuous Biomanufacturing II
Berkeley, CA
01-05 November 2015

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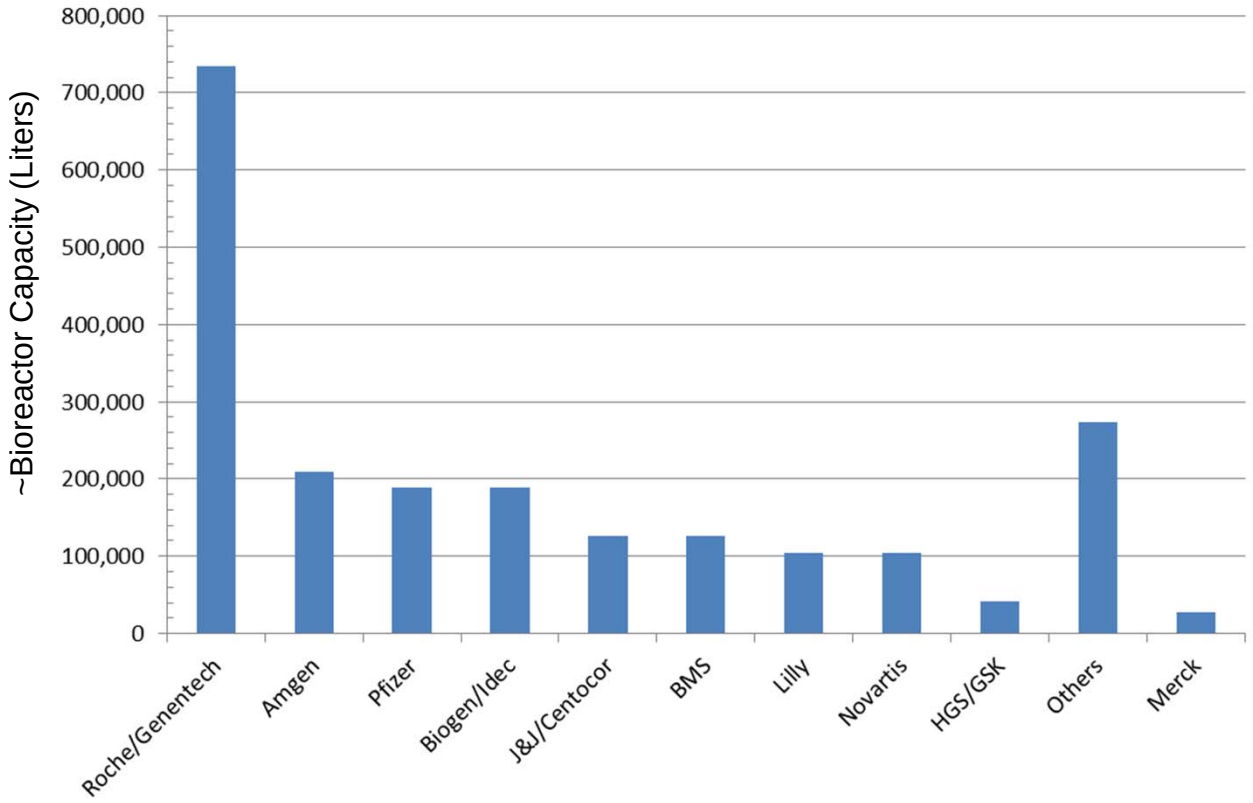
Merck's Motivation



- Merck lags other major biopharma companies on installed SS bioreactor capacity*
- Can this "disadvantage" be leveraged into a competitive advantage?

* Source: BioPlan 10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production

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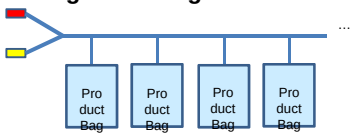
Facility of the Future

CHO mAb Processing Vision at Merck

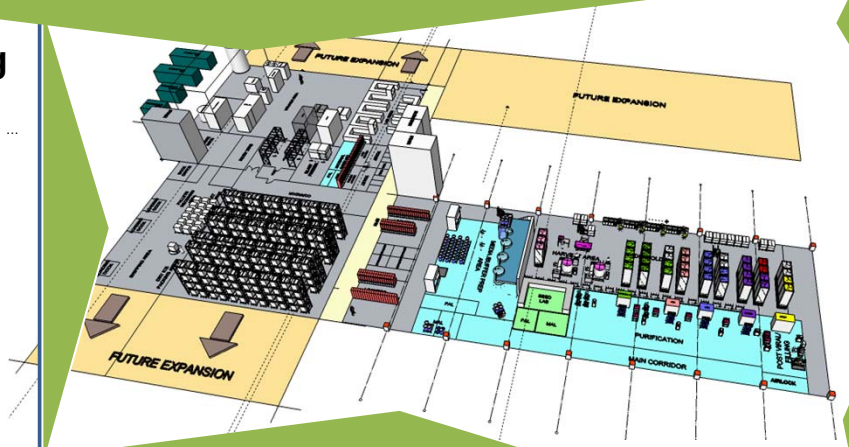
Automated Continuous Processing

Component Engng

'lego' building blocks

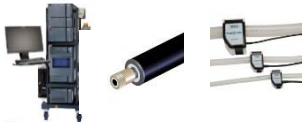


Molded parts

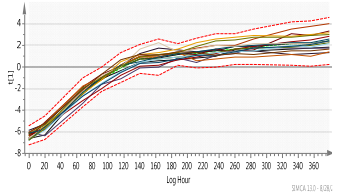


Adaptive Process Control

PAT tools



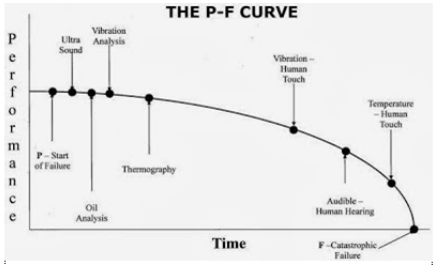
Predictive MDVA models



Real Time Release Testing

Equipment Performance Real time Monitoring

Examples:
Real time sensing of Pump seal failure, PAT sensor performance
•Proactive preventative maintenance to limit failures
•Eqpt redundancy strategy
•Process flow strategy for deviations



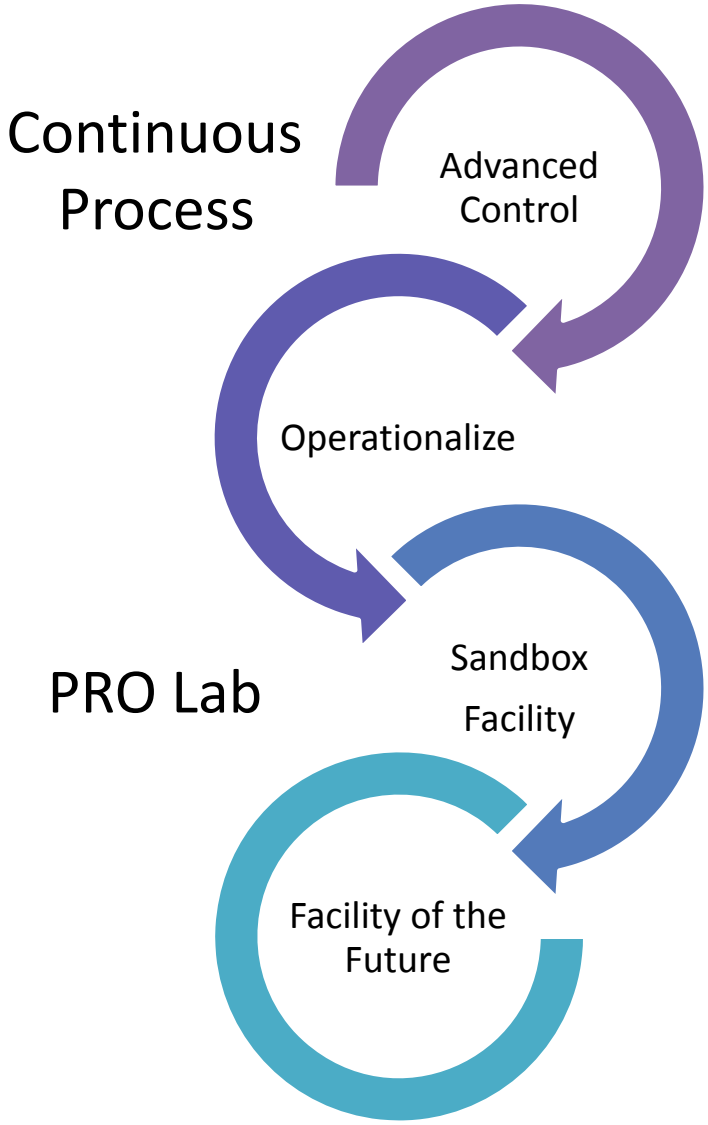
SU operations

Automated Inventory management

Single use Workflows
Buffer supply
Fluid flow management

A Sandbox for the Facility of Future

Protein Refinery Operations (PRO Lab)



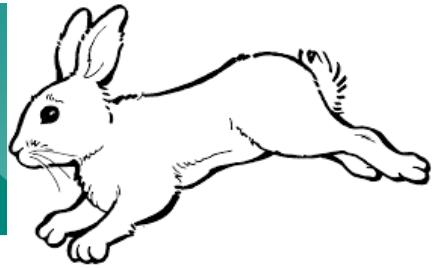
- PAT & sampling integration
- Process monitoring and MVDA modeling
- Adaptive/feedback unit operation control
- Robust control strategies

- Connections and piping
- Component engineering
- Component change-outs (filters etc.)
- Liquid and RM management

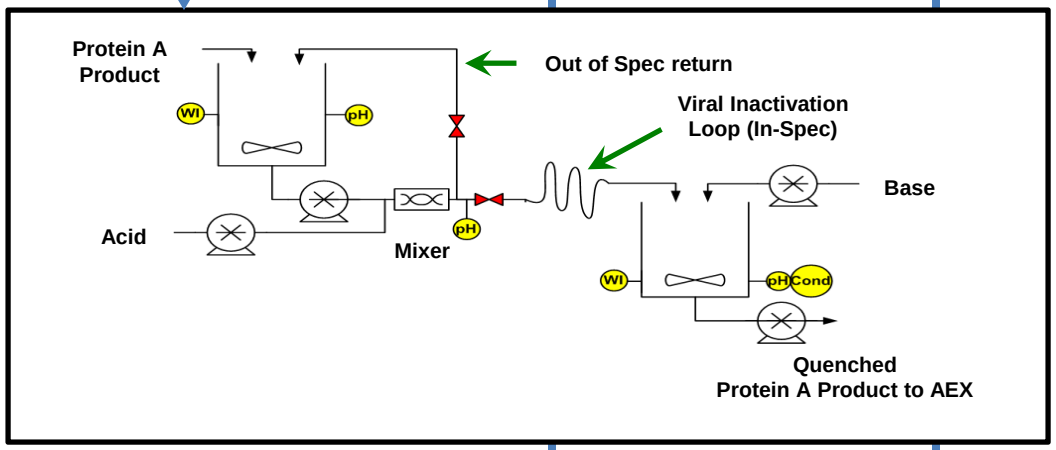
- Medium-scale operation
- PAT & control implementation
- Batch demonstrations
- Applying facility of the future principles

- Robust manufacturing platform

PRO Lab Timeline



1H 2014 → 2H 2014 → 1H 2015 → 2H 2015 → 1H 2016



B#1
40 Days
Debugging

B#2
50-70 Days
(On-Going)

$ Define Base Control Strategies & Order Components

$ Order & Install Components

MVDA Modeling
& Perturbation Analysis

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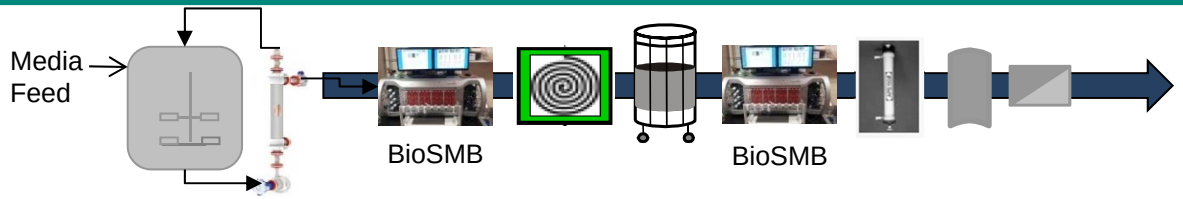
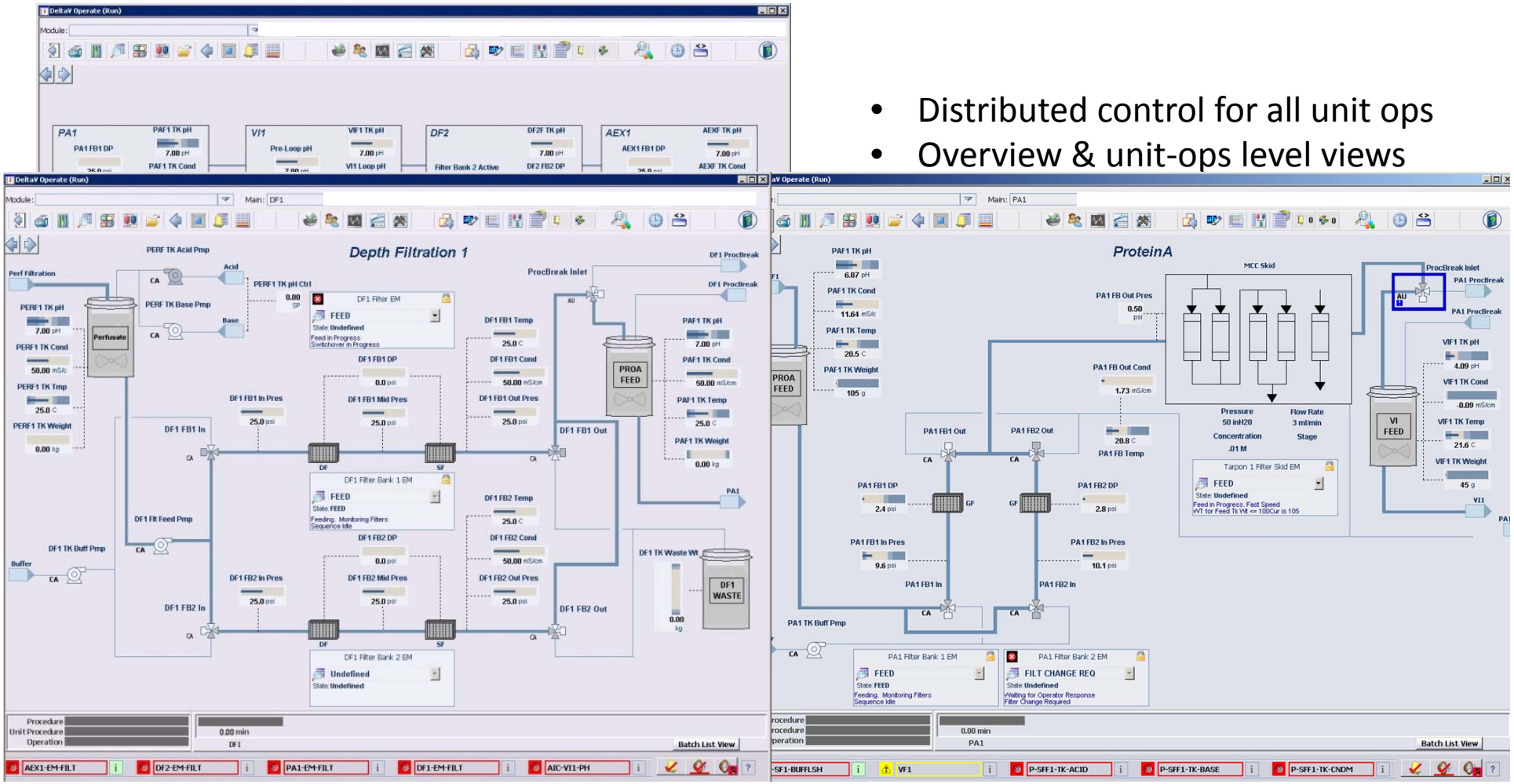
PRO Lab:

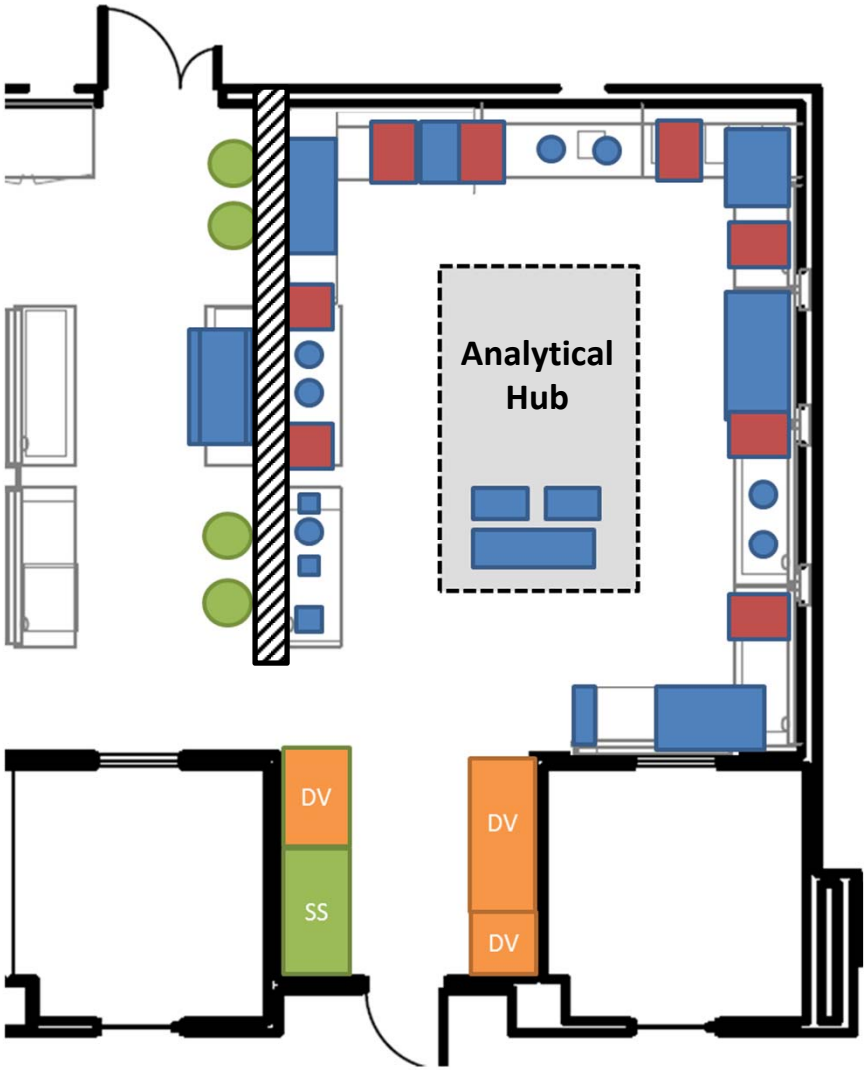
Fully automated mAb drug substance



- Distributed control for all unit ops
- Overview & unit-ops level views



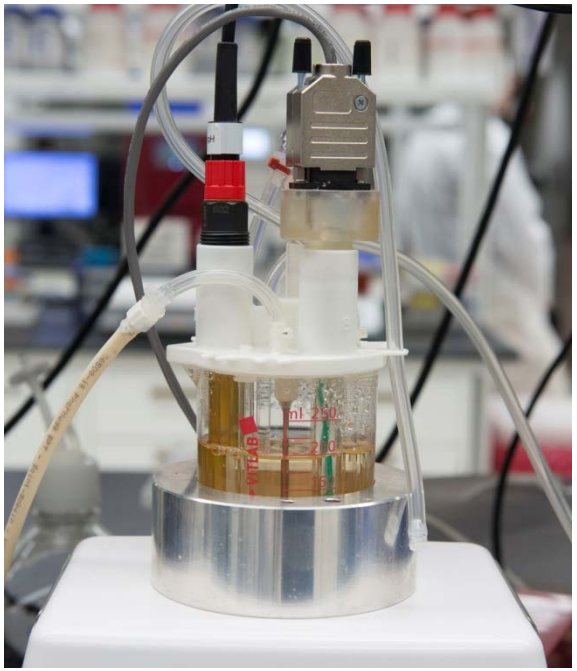
PRO Lab Layout



- Upstream area for perfusion bioreactor
- Downstream unit operations in connected “U” shape
- Routine operations at 10L bioreactor
- Analytical hub
- Buffer/media holds outside of process area
- Hardware agnostic

Operating Principles

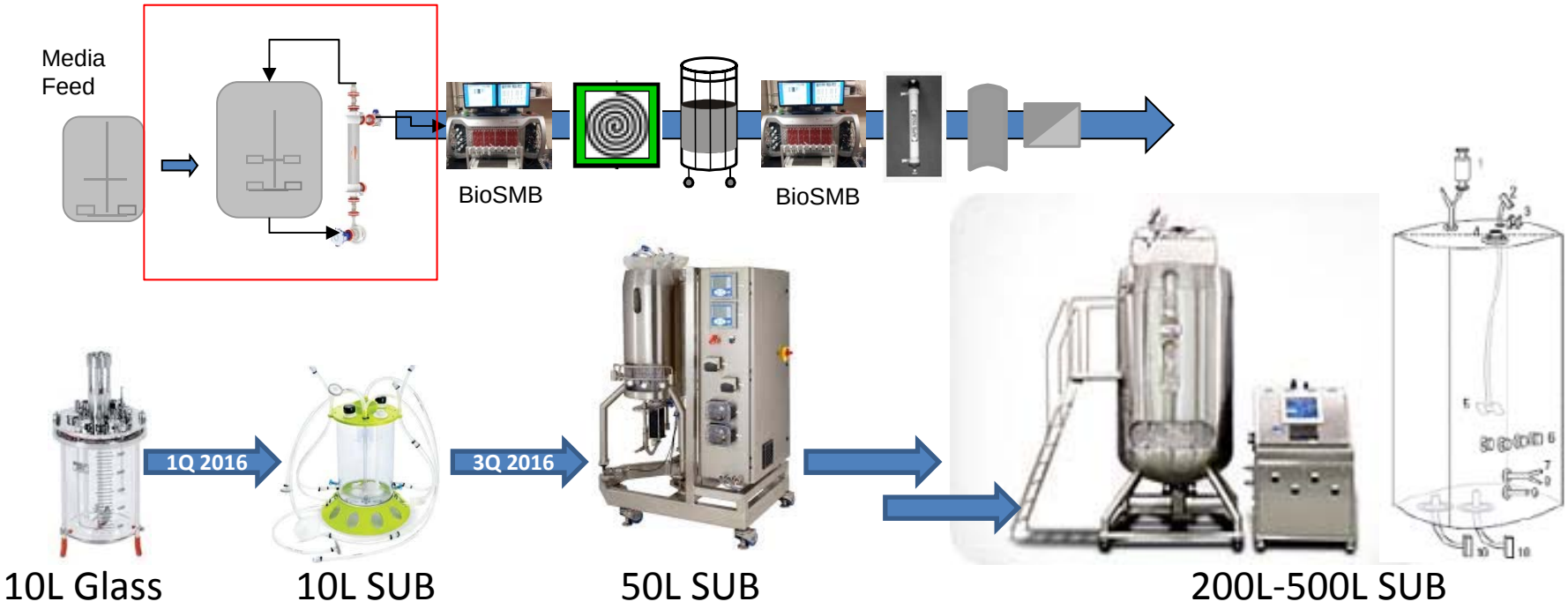
A Lights-Out Approach



- Each unit operation represented
- Surge vessels used to collect and feed next unit operation
- Stream adjustments & sampling in surge vessels
- Redundant filters
- Speed compensated methods with breakpoints
- SU/closed processing methodology

Upstream

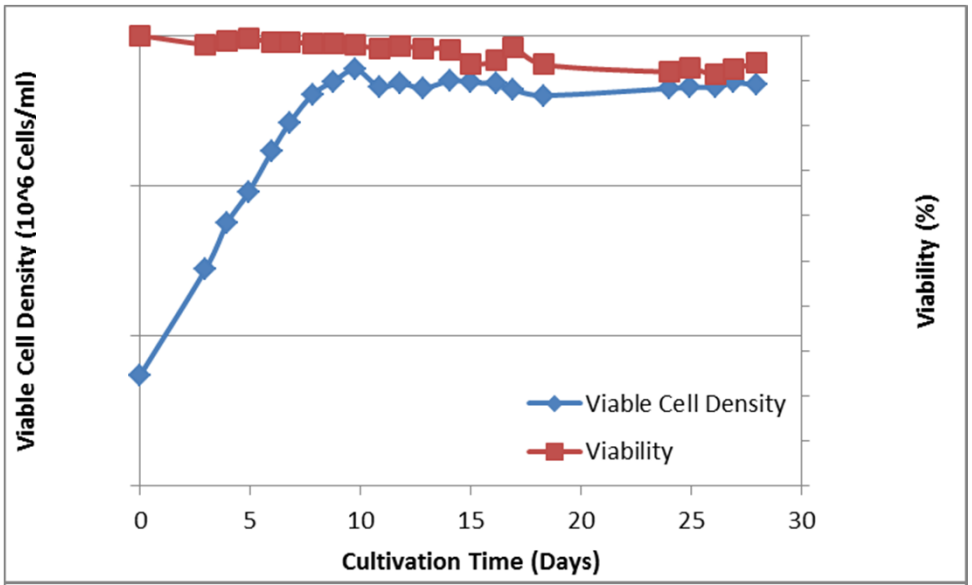
Perfusion Operations

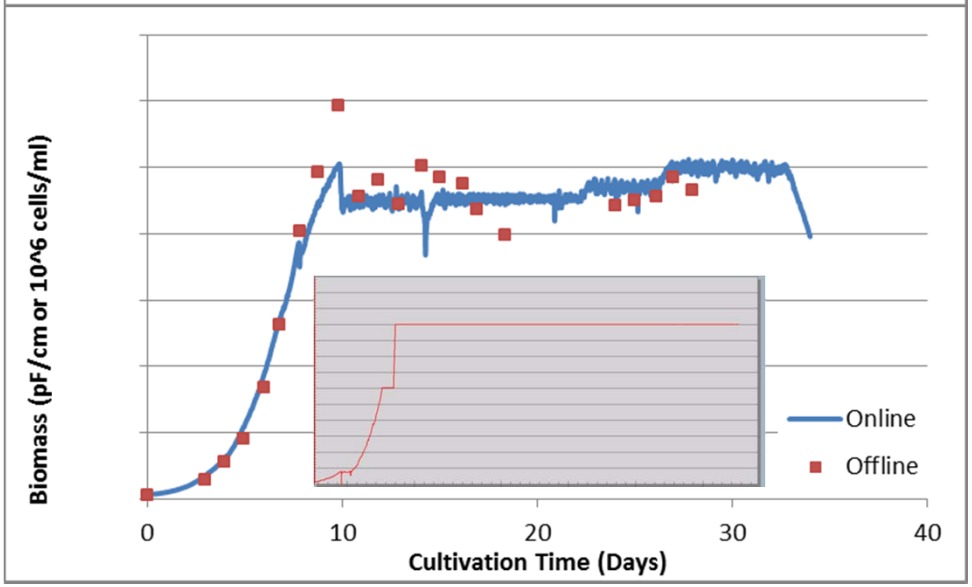


- Routine operation at 10L scale
- 50L scale-up demonstrations
- SU AutoTFF cell retention device
- Weldable filter replacements

Upstream Operation Performance

Cell Culture Operation





Baseline Perfusion Performance

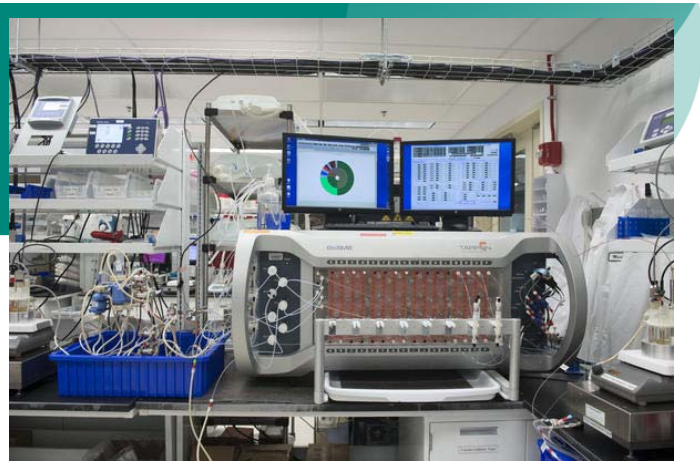
- Stable cell density
- Viability maintained >99%
- Productivities > 1g/(L·Day)
- Membrane fouling and antibody sieving
- Significant cell lysis

Capacitance Measurement

- Capacitance for “in-vivo” biomass monitoring
- Correlation of online and offline biomass measurement
- Used to automate cell bleed and maintain constant biomass

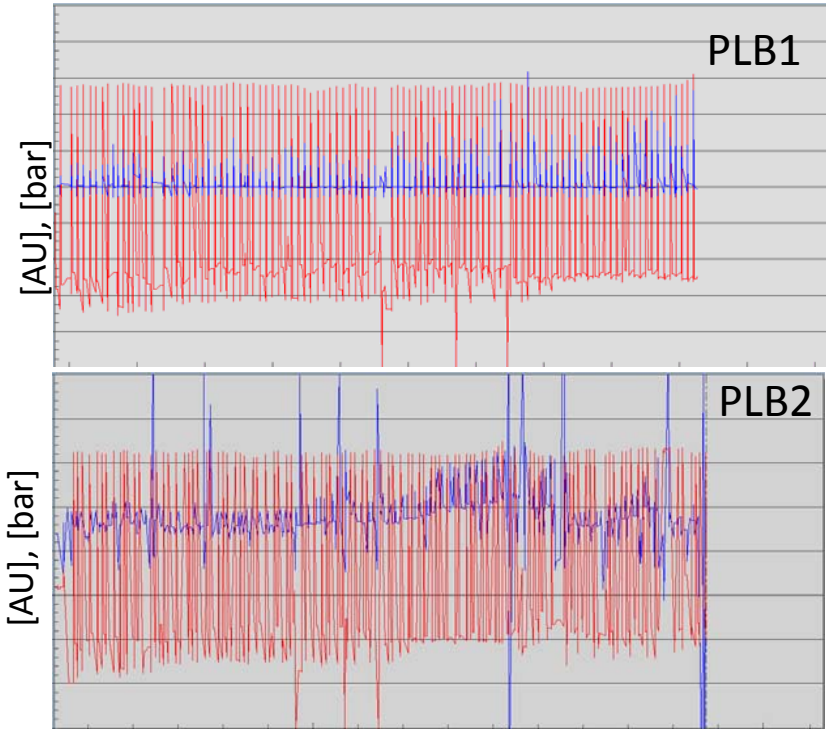
*Kistler, Napoli, Chen, Xu

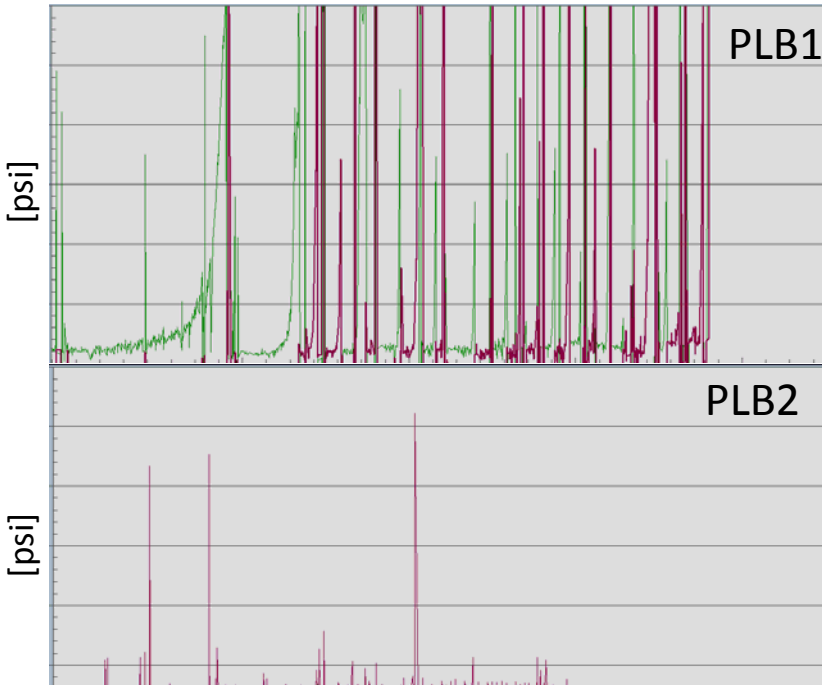
Downstream Operations
Protein A Chromatography



Protein A Chromatography

- Predictable reproducible elution
- Low feed pressure
- Accelerated column lifetime

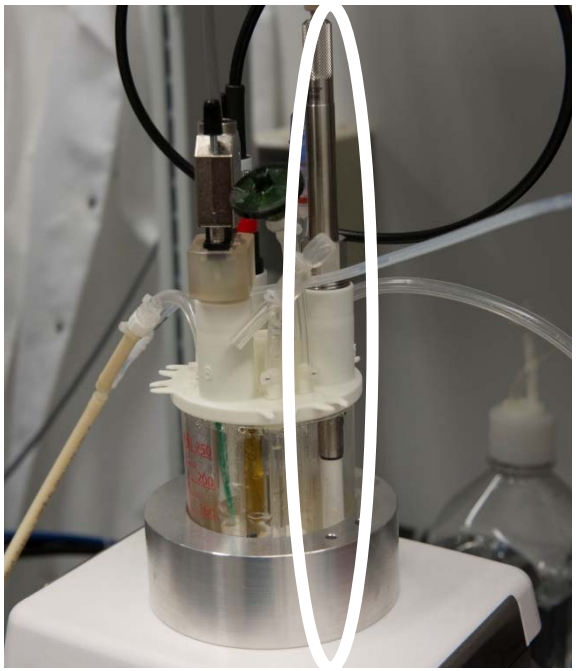




Systems Closure

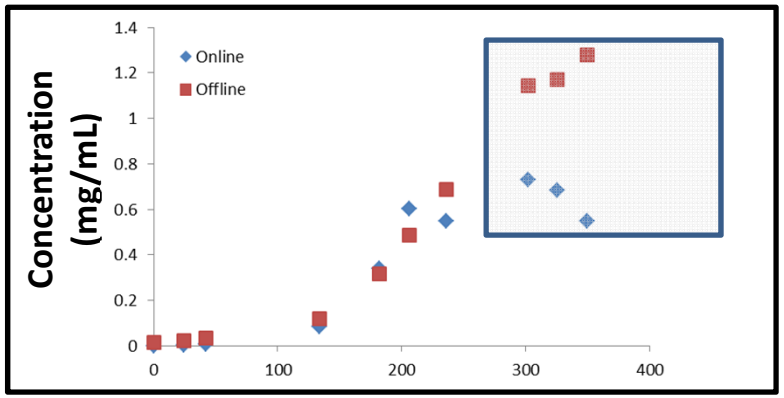
- Guard Filter Performance
  - 1 Guard filter per day→ 1 guard filter per batch
  - Volume based filter switching

Automated Sample Collection & Analysis



In-tank clarification

- Ceramic membrane sampling device
- Automated sample management
- Integration with 3rd party analytics
- Sieving of product with surface fouling



External clarification

- Sanitized sample port
- Cell removal device
- Automated sample management & integration with 3rd party analytics

- Hybrid solution targeted January 2016

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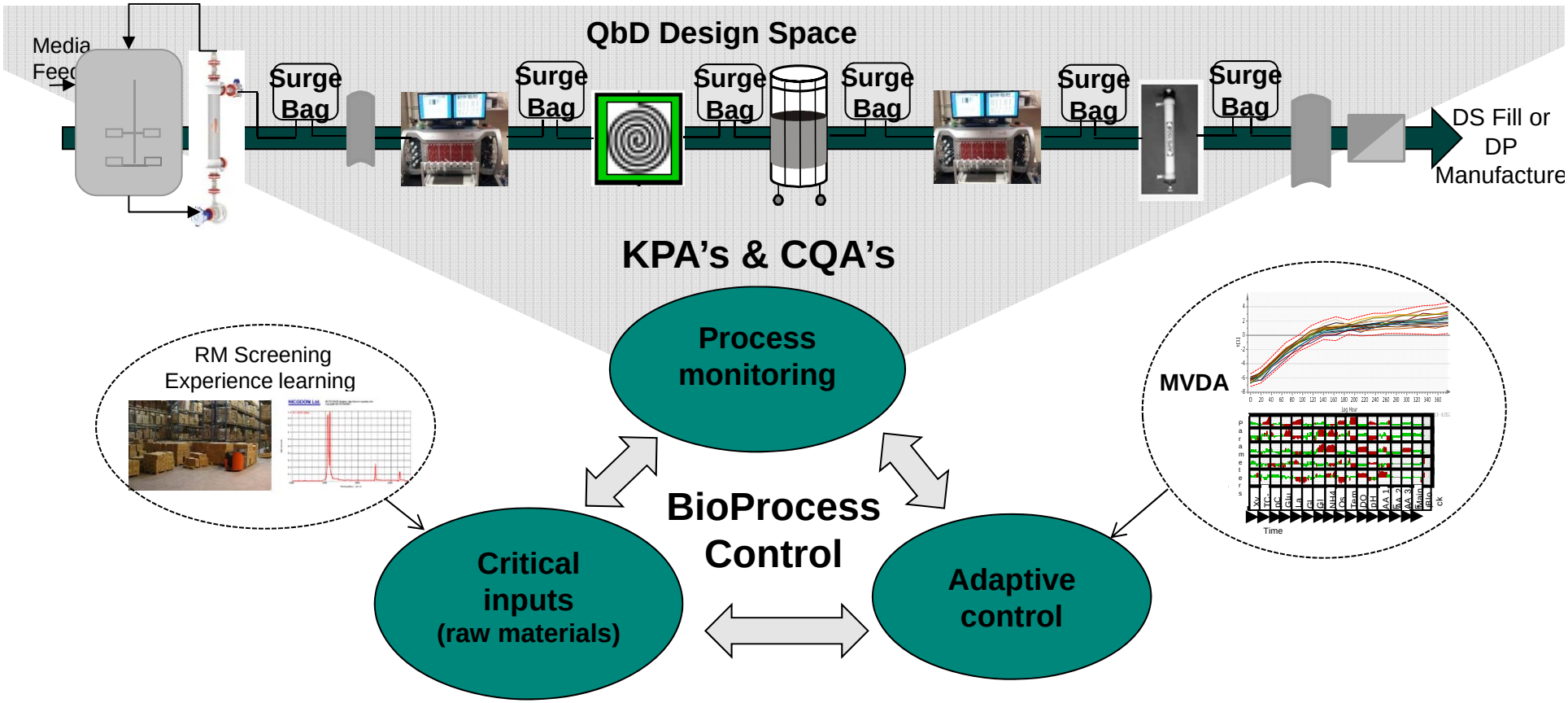
Continuous Processing:

PAT, Automated Control & Real Time Release



- End Product Testing transition to Real Time Release Testing
- Real time automated control: process responds to variability & disturbances
  - End to end prediction models for complete process
  - RM control ➡ Process input ➡ Product quality & yield

Multi Attribute Method via Peptide Mapping

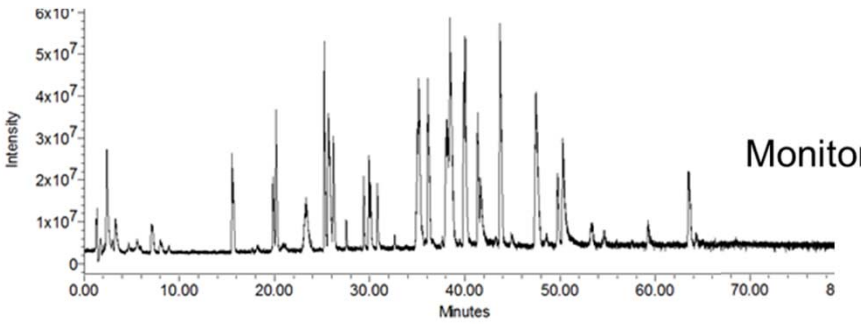
"Direct measurement of CQA's at molecular level"

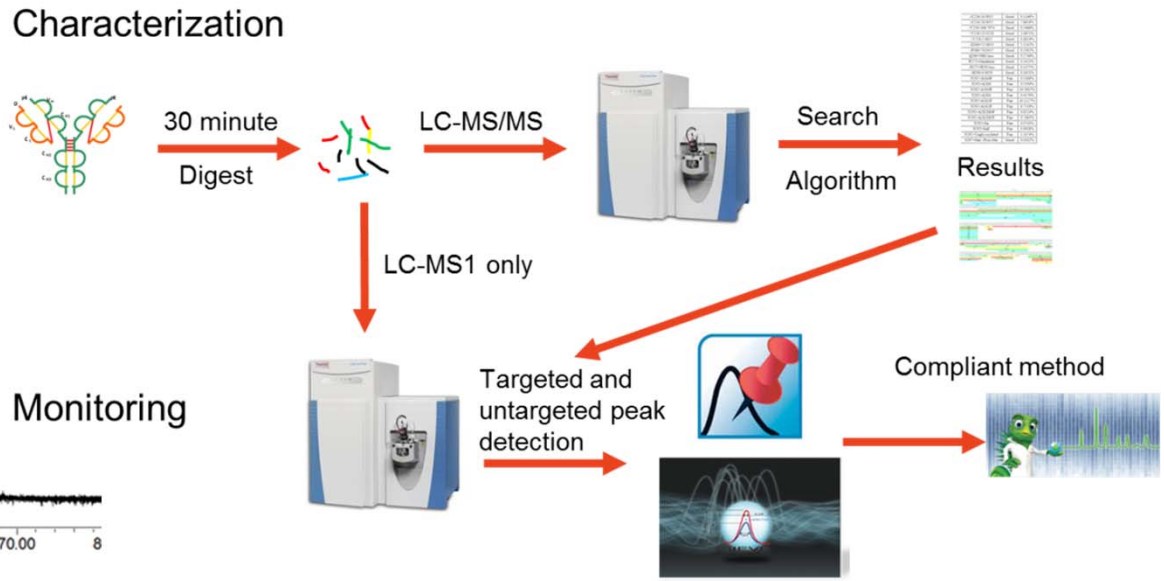
Quality Attribute	Current Method
Identity	Immunoassay
Glycans	HILIC-Fluor
Charge Variants	CEX-HPLC
Oxidation	HIC
Clips	rCE-SDS
Process Impurities	HCP/ProA ELISA

MAM
Peptide Mapping

Thermo Q-Exactive LC-MS

LC-MS TIC





30 min Tryptic digest—Ren, D. et. al. Anal Biochem. 2009 Sep 1;392(1):12-21
MAM—Rogers, R. S. et. al. mAbs 2015 Sep 3;7(5):881-90

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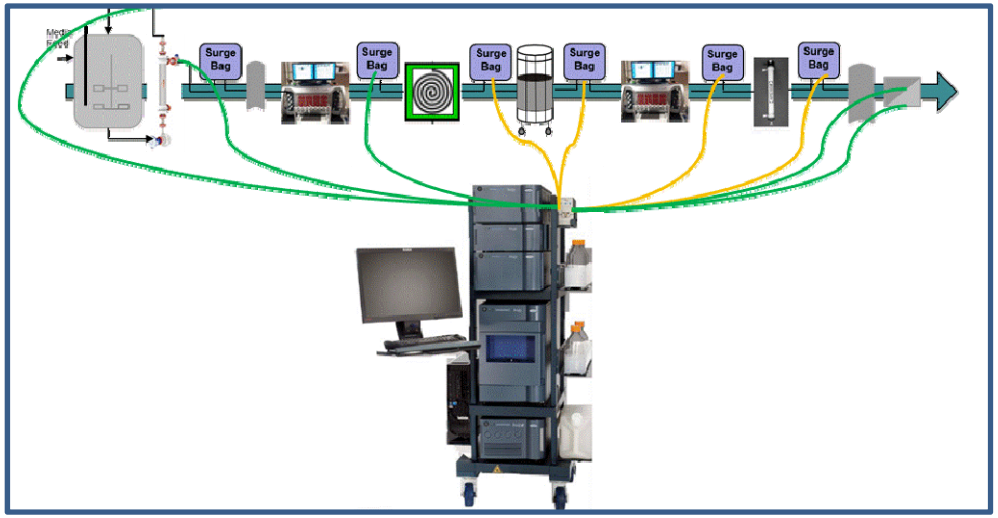
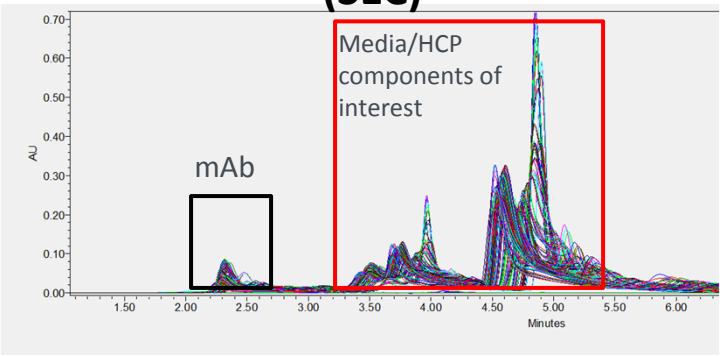
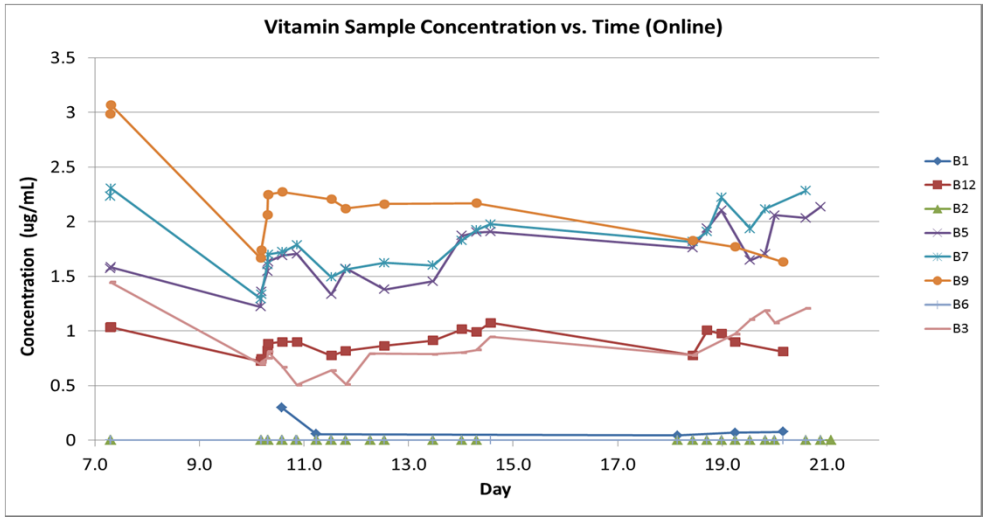
PAT UPLC Process Monitoring



Perfusion profile monitoring (SEC)





- SEC quality and permeate monitoring
- Water soluble vitamins with QDA MS Detector
- Multi-attribute peptide mapping methods installation in 1Q 2016

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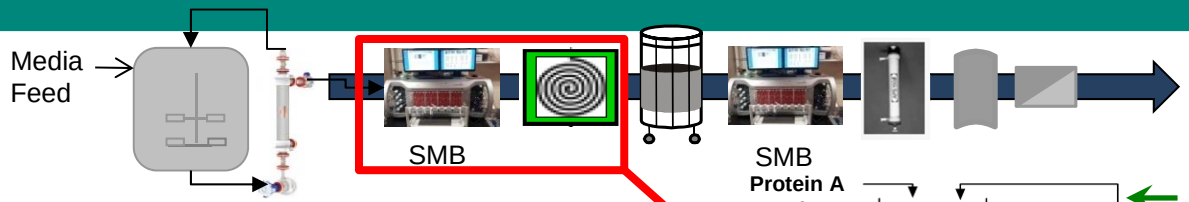
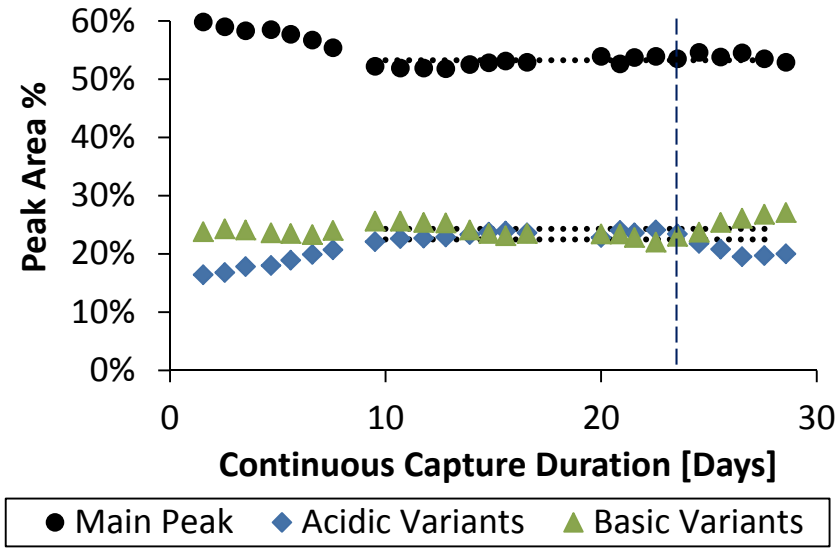
Continuous Process Performance

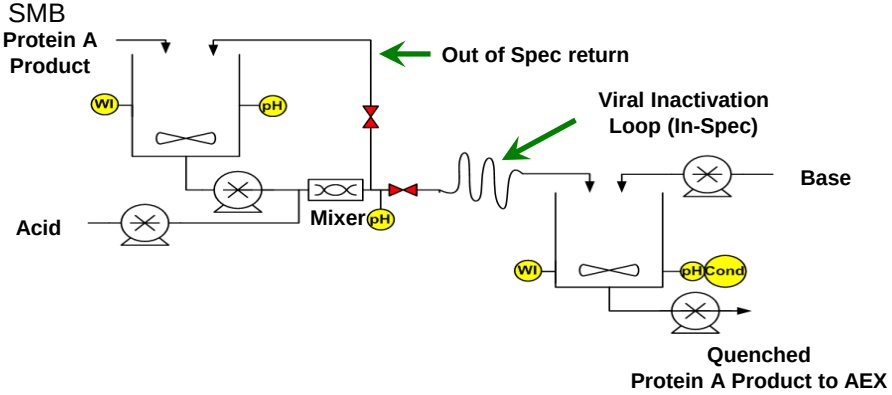
Perturbation Analysis

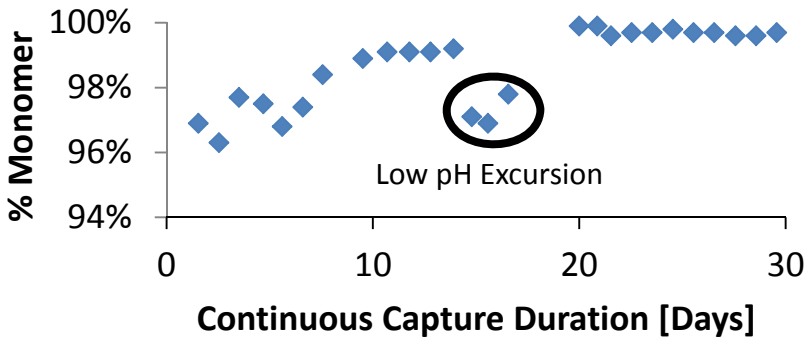


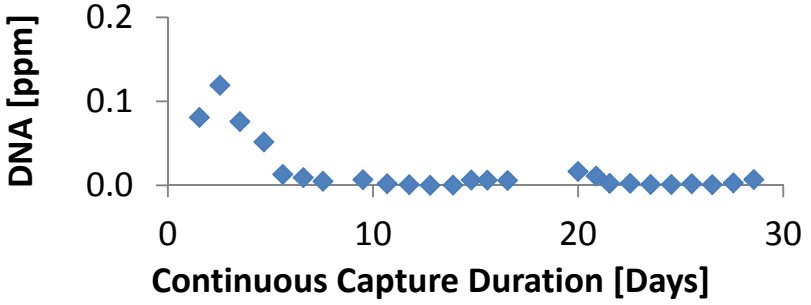
Upon reaching steady state, purity and quality attributes remain consistent



- More complex perturbation analysis expected with MAM method
- Predicting outcomes from indicator process intermediates







Conclusions

- A fully automated continuous bioprocessing suite has been established at Merck with distributed control via DeltaV
- The facility has been designed using “lights out” and closed processing approaches
- Two perfusion batches have been demonstrated in the lab to date achieving steady state cell densities for >50 days
- PRO Lab will serve as a sandbox for new sampling, PAT and MVDA strategies with ultimate feedback and adaptive control

Acknowledgements

- Adrian Gospodarek
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