PALL CORPORATION

Automation and Control of an Integrated Continuous Bioprocess

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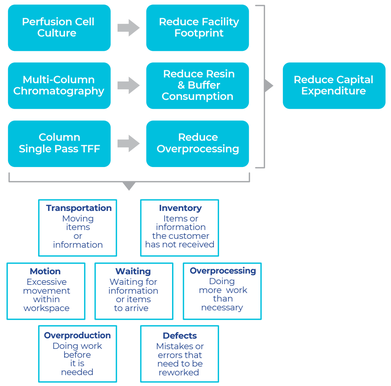
PROCESS INTENSIFICATION THROUGH AUTOMATION OF A DOWNSTREAM mAb PURIFICATION PROCESS

What is Continuous Bioprocessing?

- A way to intensify your process
- A way to decrease manufacturing cost by reducing:
  - Resin consumption
  - Buffer consumption
  - Facility footprint
  - Capital expenditure
  - Waste



DEMONSTRATION OF A NOVEL END-TO-END AUTOMATED CONTINUOUS DOWNSTREAM PLATFORM FOR THE PURIFICATION OF MONOCLONAL ANTIBODIES

Pall Continuous Lab in Westborough, MA, USA

At Pall, a continuous downstream processing laboratory located at our Westborough Massachusetts New England Center of Excellence is used to evaluate new technologies and control strategies in the area of process intensification.

Risk Assessment-Based Approach

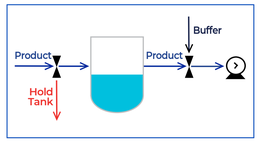
Within the context of a fully integrated end-to-end continuous downstream platform, there are a variety of risks that must be considered. A risk assessment-based approach coupled with identifying a suitable design space through design of experiments is imperative. Some of the major risks the team sought to mitigate included:

- Filter or membrane fouling
- Out-of-specification product
- Mismatching flow rates between unit operations

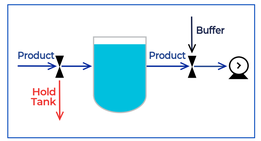
Automation is used to mitigate these risks and reduce inconsistencies between a multitude of processes at two different scales and overall process durations.

Universal Valve Strategy

The control strategy implemented in the lab was centered around a small surge tank associated with each unit operation in the process sequence. The level of the surge tank, measured via balance, dictated the flow rate as well as the valve configuration. A universal valving approach was implemented with user configurable flow paths and control strategies for each unit operation type. These flow paths and control types are selected within the control software and associated control strategy is automatically applied to the system.



Default Steady – State Flow Rate



High Flow Rate – Prevent Overfilling

Control Strategy

The setpoints associated with the control of the valving and pump speeds are shown in Figure 1.

The Platform Process Implemented in the Pall Continuous Lab

Process Unit Operations

- *In-Line Concentration*
- *Affinity Capture*
- *Virus Inactivation*
- *Depth & Sterile Filtration*
- *AEX*
- *CEX*
- *Virus Filtration*
- *In-Line Diafiltration*
- *In-Line Concentration*
- *Sterile Filtration*

Chromatography with ÄKTA♦ pccs

- ***Capture***: MCC with MabSelect♦ PrismA
- ***AEX***: Mustang® Q capsules
- ***CEX***: Capto♦ S ImpAct

Filtration

- ***Depth***: K100P Supracap™ 50 capsules
- ***Virus Filtration***: Pegasus™ Protect and Pegasus Prime filters
- ***Sterile***: Supor® EKV filters

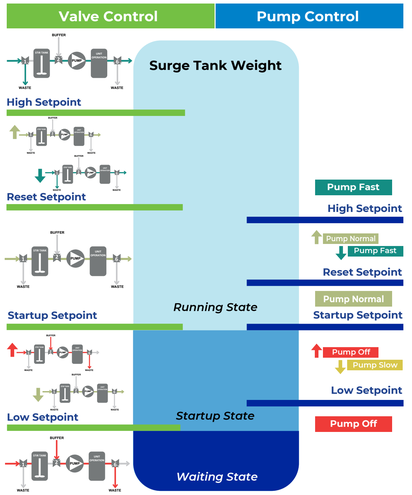
In-Line TFF

- ***Concentration***: Cadence® ILC Modules
- ***Diafiltration***: Cadence ILDF Modules

This representative mAb process was used to show that Pall and Cytiva products could deliver an end-to-end Danaher solution for process intensification. The chromatographic unit operations were executed with the Cytiva ÄKTA pcc system. A 3-column approach was used for the protein A capture step while alternating 2-column chromatography was implemented for the polishing chromatography steps. The single pass TFF modules, the Cadence ILC and ILDF were both 30 kDa MWCO.

Figure 1

Valving and pump control strategy with setpoints



Setpoints and associated valving and pump speeds under those conditions

EXPERIMENTAL PARAMETERS

Automated Processes Performed for a Range of Duration and Flow Rates / Column Sizes

Table 1

Process parameters for 4 processes

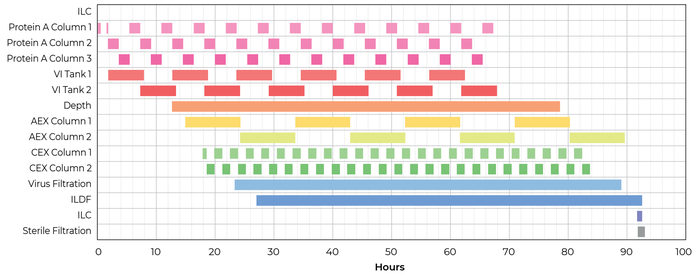
Run Number	Process Scale (Protein A Sizing)	Target Duration	Loading Titer (g/L)
1	Small scale (8.8 mL)	Short duration (24 hours)	1.2
2	Small scale (8.8 mL)	Long duration (96 hours)	1.2
3	Large scale (100 mL)	Short duration (24 hours)	1.2
4	Large scale (100 mL)	Short duration (24 hours)	2.4 *(pre-Pro A ILC)*

Subsequent downstream unit operations and their associated consumables were scaled based on process flow models. Having multiple runs with these different parameters demonstrated the robustness of this control strategy through scale-up.

Process models were used for identifying startup and shutdown times for each unit operation in the process sequence.

Figure 2

Example model from our 4-day process. This modeling approach accounts for flow rates, hold up volumes, surge tank filling, etc. This tool was scalable for all processes.

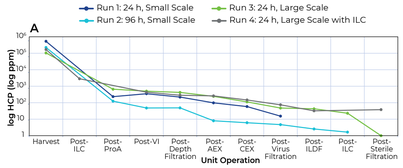


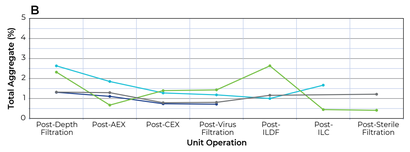
PROCESS ROBUSTNESS

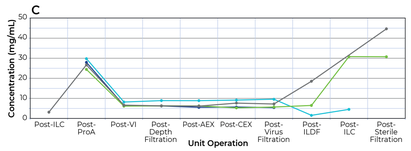
Four processes were executed to test the performance of the continuous lab.

Figure 3

*Process comparison. **A**: HCP removal where we achieve sufficient reduction of HCP to less than 80 ppm for all processes. **B**: Aggregate content where we achieve sufficient reduction of aggregates to less than 1.5% for all processes, as demonstrated during our process development. **C**: Product concentration through the four processes where we achieve comparable performance regardless of process duration or scale.*







SUMMARY & CONCLUSIONS

- Four end-to-end downstream processes were conducted to evaluate technologies and strategies for continuous bioprocessing
- Automation can control and coordinate complex processes and handle deviations without human intervention while maintaining product quality

Key Takeaways

- A risk assessment-based approach, with flexibility and modular construction in mind, should be used to design automation strategies
- Predictive and reactive models are key for integrated automation

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