Development of Single Pass Tangential Flow Filtration for Continuous End-to-End mAb Bioprocessing

Chaz Goodwine[1], Michelle Najera[1], Beth Larimore[1]

[1] *Just-Evotec Biologics Inc., 401 Terry Avenue N, Seattle, WA, 98109*

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Introduction

- End-to-end (E2E) continuous manufacturing enables efficient, compact, multiproduct facilities while also reducing the costs, labor, and waste of bioprocessing.
- Single Pass Tangential Flow Filtration (SPTFF, also known as In Line Concentration [ILC]) allows for process stream concentration to be performed in a continuous manner as an alternative to traditional UF/DF. Multiple devices are available commercially for performing SPTFF at various scales. Two systems are evaluated within this work: an SPTFF device with a 'tree' shaped configuration of TFF membranes with decreasing stage surface area in a 3/2/1/1 assembly, and an SPTFF device with a constant stage surface area configuration in a 1/1/1 assembly.

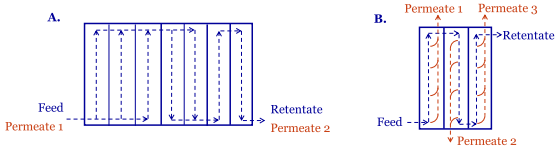
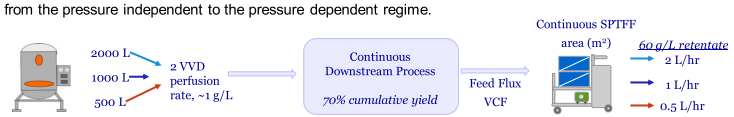


Figure 1: Diagrams of SPTFF devices investigated, highlighting the locations of the feed, retentate, and permeate ports and the flow path for retained product material. A) 3/2/1/1 SPTFF assembly, and B) 1/1/1 SPTFF assembly.

- End-to-end continuous processing often operates at low flow rates for long durations (several weeks) in contrast to typical batch bioprocessing. For example, for bioreactor scales of 500 L to 2000 L, process flow rates after concentrating product to 60 g/L are all less than 2 L/hr for a typical end-to-end continuous downstream process.
- For continuous operation, operation of SPTFF devices in a pressure-independent regime is preferred. Operating in the pressure-independent (membrane-dependent) regime ensures perturbations in pressure have minimal impact on permeate flux.
- Commercially available SPTFF products designed for GMP manufacturing generally have membrane areas greater than 0.5 m^2. At these surface areas, the resulting feed fluxes for end-to-end continuous processes are below the typical ranges for pressure-independent operation, requiring either operation in a pressure-dependent regime or the use of smaller devices that are not appropriately designed for GMP manufacturing.
- This study closes the gap for end-to-end processing by investigating operation of SPTFF systems at these low flow rates and identifying process parameters at the transition from the pressure independent to the pressure dependent regime.



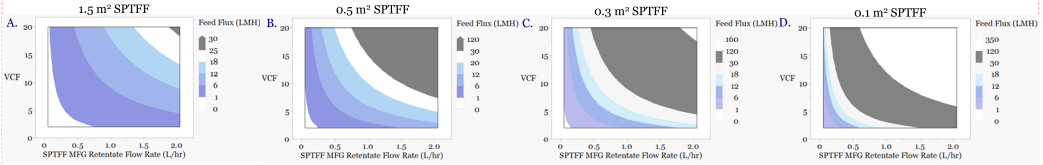


Figure 2: Feed flux for various SPTFF device membrane areas is plotted against volumetric concentration factor (VCF) and the SPTFF retentate flow rate for a manufacturing scale system, assuming a fixed retentate concentration. The feed flux range of 30 – 120 LMH is plotted in grey, and represents the general range recommended by vendors for operating in a pressure-independent regime. The feed flux range of 1 – 18 LMH for is filled in shades of blue, and represents the range evaluated in this study.

Methods

Format	Feed concentration	VCF target
3/2/1/1	13.0, 8.4	4.5, 7.2
1/1/1	11.5, 7.2, 4.2	5.7, 9.0, 15.6

- Purified IgG mAb at concentrations between 4 and 13 g/L in a 100 mM sodium acetate, pH 5 buffer
- Two commercially obtained SPTFF systems, configured according to the manufacturers' specifications, were used in this study, both utilizing regenerated cellulose membranes with a 30 kD pore size:
  - A 'tree' configuration of membranes with 7 total membranes arranged over 4 stages in a 3/2/1/1 assembly and having a total membrane area of 0.065 m^2. Inline pressure probes were attached directly to the four ports of the system: feed, retentate, permeate 1, and permeate 2. During operation, a two-way valve would seal the outlet of permeate 1, directing all permeate out permeate 2.
  - A 'constant stage area' configuration of membranes with 3 membranes arranged over 3 stages in a 1/1/1 assembly and having a total membrane area of 0.33 m^2. Inline pressure probes were attached directly to the four feed side ports of the system. The three permeates were attached together then monitored with an inline pressure probe.
- Under full recirculation, feed and retentate flow rates were investigated at a constant VCF to target a retentate concentration of 65 g/L. After allowing time for equilibration, feed and retentate concentration were measured and pressures recorded.

Results

- Both SPTFF systems successfully achieved target VCFs across the range of feed flux and feed concentrations screened. The systems demonstrated different relationships between their feed and retentate pressures across the feed flux design space.
  - In the 3/2/1/1 SPTFF system, at feed flow rates below 10 LMH the feed and retentate pressures align at the VCFs evaluated. Above 10 LMH, both the feed and the retentate pressures diverge, and the pressure drop from feed to retentate becomes smaller compared to lower VCFs.
  - In the 1/1/1 SPTFF system, the profiles for feed flux vs feed and retentate pressure across the three VCFs investigated align. This observation further suggests that the pressure-dependent region for the 1/1/1 assembly may extend to higher feed fluxes than the 3/2/1/1 SPTFF system.

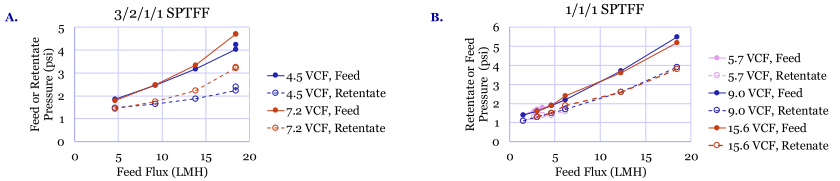


Figure 4: Feed and retentate pressure are plotted against the feed flux at various retentate flow controlled VCF conditions for A) a 3/2/1/1 SPTFF device, and B) a 1/1/1 SPTFF device.

- Considering a typical TMP vs permeate flux curve, both SPTFF systems exhibited pressure trends indicative of the pressure-dependent regime within the design space evaluated. Transmembrane pressure (TMP) is evaluated below and was calculated as:

$$TMP_{3-2-1-1} = \frac{P_{feed}+P_{retentate}}{2} - \frac{P_{Permeate1}+P_{Permeate2}}{2} \qquad TMP_{1-1-1} = \frac{P_{feed}+P_{retentate}}{2} - P_{Permeate}$$

  - The 3/2/1/1 SPTFF device shows similar trends in TMP at permeate rates below 13 LMH at the VCFs evaluated. Above 13 LMH, the higher VCF condition of 7.7 begins to show curvature indicative of a transition towards the pressure-independent region.
  - The pressure-flux profiles for the 1/1/1 SPTFF device at the three VCFs screened align and exhibit linear trends, suggesting that the pressure-dependent region may extend through a larger design space than for the 3/2/1/1 SPTFF system.

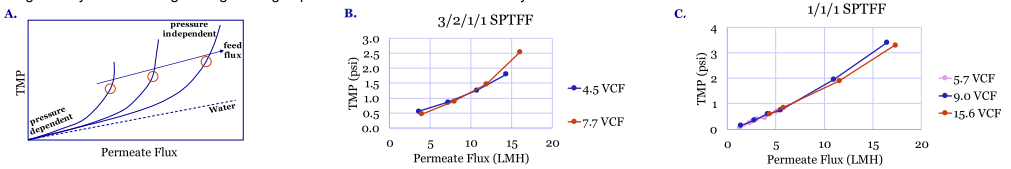


Figure 3: A) a typical flux-pressure-flowrate relationship is shown for an SPTFF system under TMP controlled operation. In contrast, permeate flux for these evaluations is plotted against resultant transmembrane pressure at various retentate flow controlled VCF conditions for B) a 0.065 m^2 3/2/1/1 SPTFF device, and C) a 0.33 m^2 1/1/1 SPTFF device.

Conclusions and Next Steps

	3/2/1/1 SPTFF	1/1/1 SPTFF
Achieved desired VCFs required for end-to-end manufacturing:	✓	✓
No fouling observed within design space evaluated:	✓	✓
Pro/Cons of operating on devices at low flux compared to operating on smaller scale manufacturing systems:	- Reduced shear stress with low flow - Operating in a pressure-independent regime requires luer-lock connectors	- Reduced shear stress with low flow - Operating in pressure-independent regime requires a stainless steel holder (non-single use)

- Future work aims to further evaluate the feasibility of commercial scale SPTFF devices in end-to-end continuous bioprocessing, including the investigation of load challenge and process response to system perturbations, and integration of in-line concentration measurements.

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Acknowledgements

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