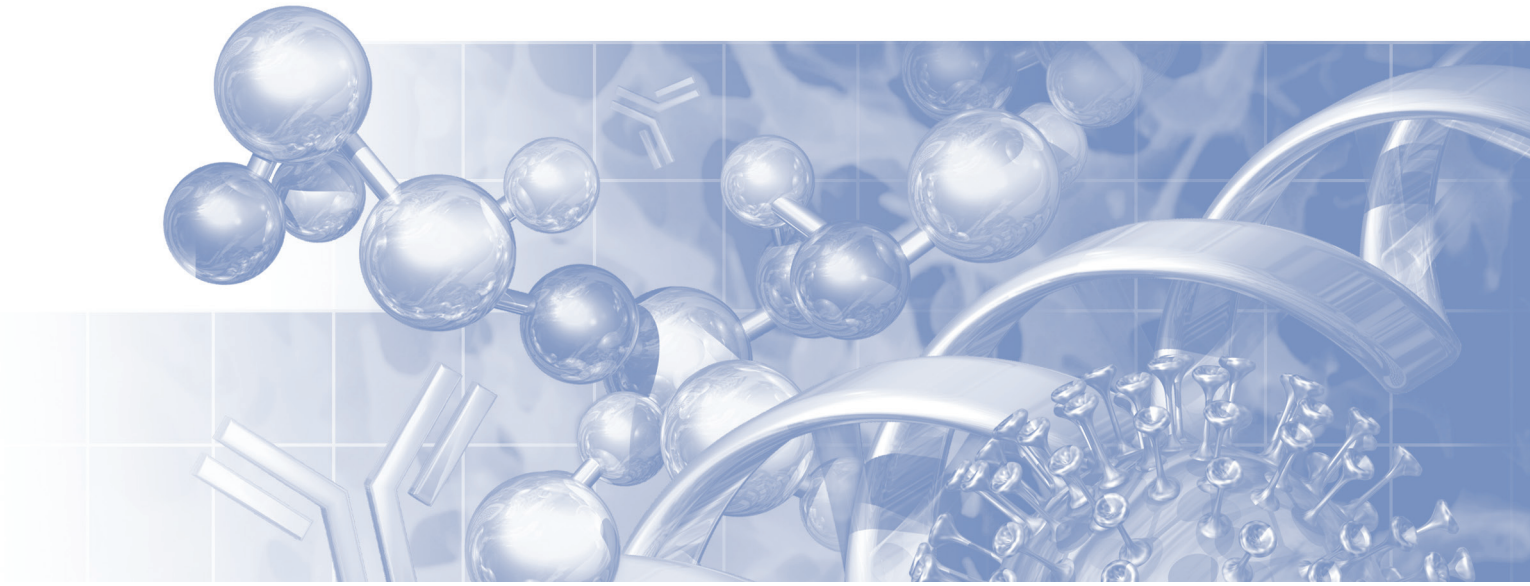
PALL Life Sciences

White Paper

USD3127

Understanding Single-Pass Tangential Flow Filtration and the New Era of Bioprocessing

Engin Ayturk, Ph.D.; BioPharm Applications R&D; Pall Corporation, 20 Walkup Drive, Westborough, MA 01581 USA



Introduction

Single-pass tangential flow filtration (SPTFF) technology from Pall Corporation is revolutionizing current and future bioprocessing platforms with its implementations in biotech, vaccine and plasma industries. Its features are protected by a portfolio of patents[1-6]. Common applications of the Cadence™ SPTFF technology extend to but are not limited to inline volume reduction and/or concentration, in-process dilution/de-salting, high concentration formulations, and processing of fragile molecules. In this context, SPTFF technology is not only an important addition to the process development tool-box for platform process evaluation but also a crucial enabler of integrated, streamlined and continuous bioprocessing initiatives.

Within the diverse filtration portfolio of Pall Life Sciences, this breakthrough technology is made available in a variety of building blocks that utilize different membrane types and configurations to provide a comprehensive solution package that will meet end-user's processing needs and targets over wide range of applications[7-17]. For example, Cadence Inline Concentrator (ILC) modules are holder-less SPTFF devices equipped with a built-in fixed retentate restrictor, which greatly simplifies SPTFF process control and achieves high conversion separations with the simplicity of direct flow filtration.

Adopting SPTFF at process development (PD), pilot, clinical and commercial manufacturing scales has major advantages over conventional approaches. Some of key benefits can be summarized as follows:

- Provides flexible manufacturing through process integration/coupling and continuous upstream and downstream processing,
- Reduces processing volumes, system sizing and facility footprint and leads to novel facility fit solutions and overcomes manufacturing bottlenecks,
- Enables disposable and/or single-use technology utilization and therefore, increases productivity and eliminates non-value added processing steps and improves workflow,
- Achieves high product recoveries and increases yield through utilization of smaller, more compact systems,
- Enables high concentration factors and processing of highly shear-sensitive products,
- Provides major savings in capital expenditure, materials, labor and facility operating costs.

SPTFF Protected Domain

In order to better understand the SPTFF technology, its applications and coverage in biopharmaceutical applications, it is noteworthy to refer to the terminology used in the issued patents[1-6] (hereafter "SPTFF Patents"). This innovative approach to conventional tangential flow filtration (TFF) includes a plurality of stages, each stage having a plurality of channels providing at least one serial flow path that is configured either internally or externally, by the use of spacers, manifolds, staging plates and/or similar[1-6].

Among many other performance attributes, the novelty and protected domain of the SPTFF technology is specified by two quantitative parameters that define the structure of the SPTFF channel, the specific membrane area of the channel, σ_C, expressed as the ratio of the membrane area to the void volume of the channel, in cm^{-1}, (Equation 1) and the dimensionless length, λ, which is the product of channel length and the specific membrane area for a given stage and/or a system (Equations 2 and 3).

$$\sigma_C = \frac{\text{Membrane Area of Flow Channel } [cm^2]}{\text{Void Volume of Flow Channel } [cm^3]} \quad (1)$$

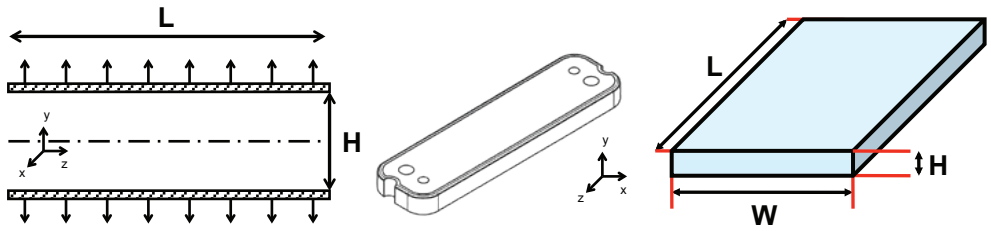
$$\lambda_{Stage} = \text{Specific Membrane Area } (\sigma_c) \times \text{Channel Length}) \ (L_{Stage}) \quad (2)$$

$$\lambda_{System} = \text{Specific Membrane Area } (\sigma_c) \times \text{Channel Length}) \ (L_{Total}) \quad (3)$$

The range of the specific membrane area of the channel, shown in Equation 1, is specified in the SPTFF Patents to be greater than about 40 cm^{-1} for at least one channel[1-6] for the flow channel depicted in Figure 1.

Figure 1

Flow channel of a TFF device



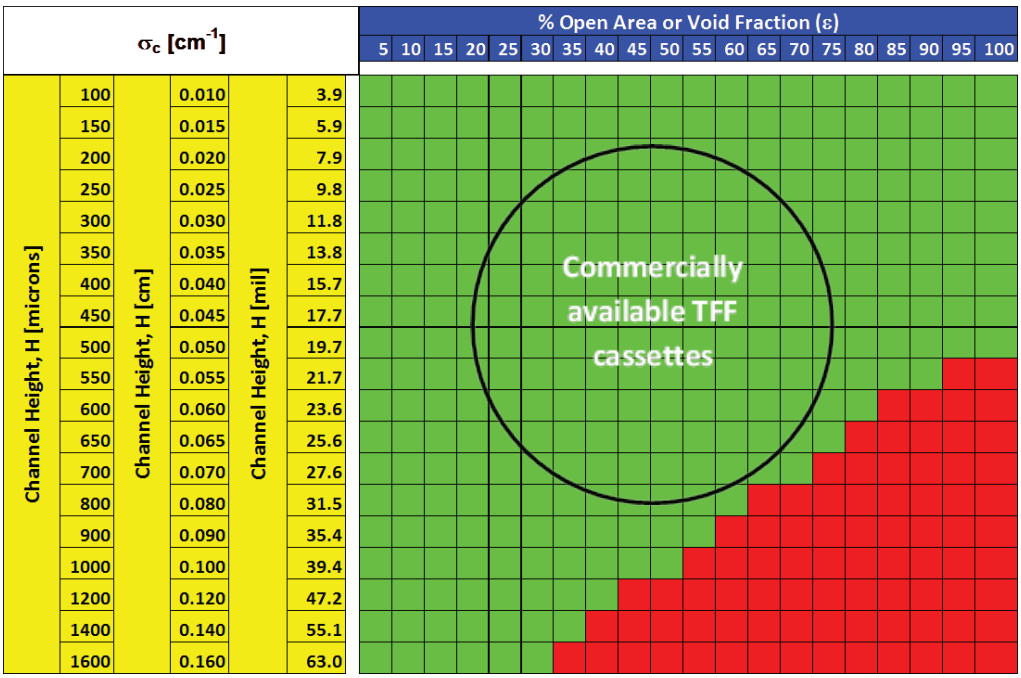
For a TFF cassette (shown in Figure 1), with known width (W), length (L), channel height (H), which is dictated by the thickness of the feed screen used in the channel, and screen void fraction (also referred to as percent open area) ε, Equation (1) reduces to:

$$\sigma_C = 2WL/\varepsilon WHL = 2/\varepsilon H \geq 40\ cm^{-1} \quad (4)$$

Equation (4) can be used to graphically describe the domain protected by the SPTFF Patents over a wide range of feed screens and void fraction values, as shown in Figure 2. Please note that the majority of the commercially available TFF cassettes[21] with varying void fractions, screen types, feed channel widths and thicknesses are annotated by the circle within the green region ($\sigma_C \geq 40\ cm^{-1}$)[1-6], that represents the SPTFF protected domain.

Figure 2

Specific membrane area σc feasibility map covered highlighting the design space for the SPTFF Patents[1-6], where green ≥ 40 cm^{-1} and red < 40 cm^{-1} (1 mil = 1/1000th of an inch).

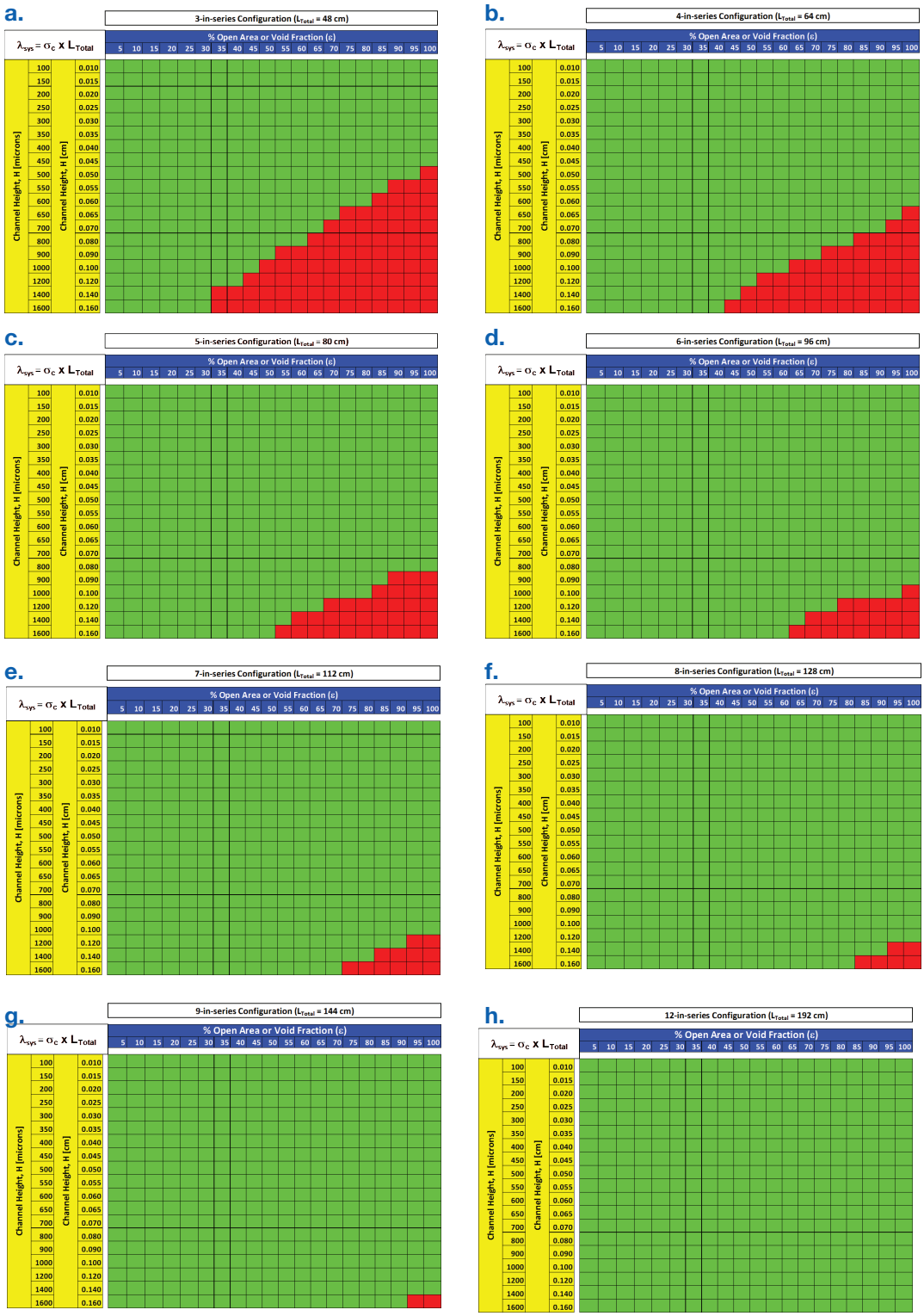


Furthermore, it should be noted that the dimensionless length of a stage (Equation 2) is the sum of the dimensionless lengths of each channel in the longest serial flow path in the stage that is less than about 6,000 and the dimensionless length of the system (Equation 3) is the sum of the dimensionless lengths of the plurality of stages that is greater than about 2,000[1-6].

To simplify the terminology, similar analysis can be extended to map the dimensionless length of the system, λ_{sys}, for various SPTFF configurations in order to fully capture the impact of the flow path as shown in Figure 3. The GREEN regions depict the space protected by the SPTFF Patents, in contrast to the RED regions, which belongs to the prior art.

Figure 3

Graphic representation of the dimensionless length of the system, λ_{sys}, per SPTFF configuration [a] 3-in-series, [b] 4-in-series, [c] 5-in-series, [d] 6-in-series, [e] 7-in-series, [f] 8- in-series, [g] 9-in-series, and [h] 12-in-series (Green ≥ 2,000, Red < 2,000).



PALL Life Sciences

Figures 2 and 3 describe clearly and accurately the design space protected by the SPTFF Patents with respect to the specific membrane area, σ_C, and the dimensionless length, λ, in contrast to interpretations found elsewhere[18-19], which are vague and even misleading. The regions marked/highlighted with "RED" in Figure 3 lie outside of σ_C and λ specifications, thus the space protected by SPTFF Patents. However, these regions typically correspond to devices that will result in poor mass transfer properties and, therefore, poor performance. In summary, SPTFF systems having a path length equivalent to three (3) or more standard- cassettes in-series have dimensionless length greater than 2000, and therefore, covered by the SPTFF Patents.

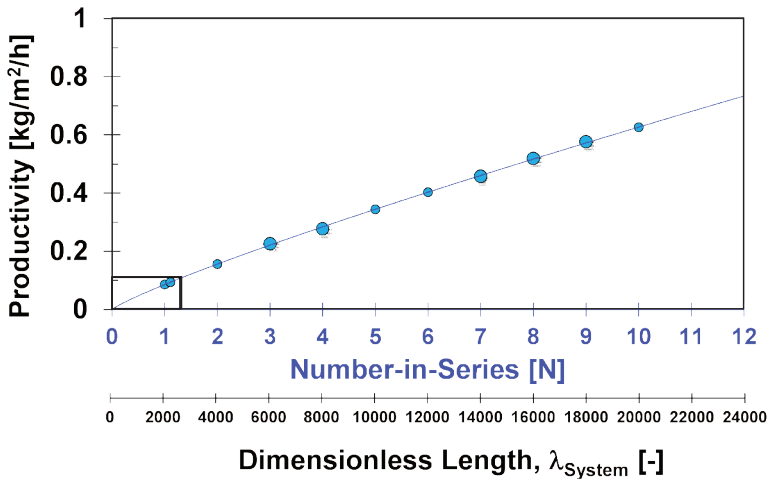
Also, another aspect of the SPTFF Patents is the use of Christmas tree staging in combination with the protected parameters, $\sigma_C \geq 40$ cm^{-1} and $\lambda_{sys} \geq 2{,}000$. It is important to highlight that the SPTFF design space is independent of the type of staging used (i.e., "Christmas tree" or so-called "equal area") but rather it is a direct function of the total path length that is expressed as the dimensionless length of the system[1-6], in other words, number of cassettes in series.

Mapping Productivity, Performance and Process Stability

The productivity is defined as the mass throughput of the SPTFF device in kg/m^2/h ("KMH"). Figure 4 shows the impact of path-length, expressed both as the number-of-cassette- channels in-series and the dimensionless length of the system, λ_{sys}, on productivity for the case of a 50 g/L feed stream concentrated to 225 g/L. The productivity increases as the path length increases (i.e., 9-in-series v. 3-in-series). Such effect is more pronounced especially for applications targeting high final concentrations. Also noteworthy to mention that, SPTFF devices with path lengths greater than 2-cassettes in-series fall within the domain protected by SPTFF Patents[1-6] (with $\sigma_C \geq 40$ cm^{-1} and $\lambda \geq 2{,}000$). Indeed, the 9- or 10-in-series flow- path for the application depicted in Figure 4 produces more than 3-times the productivity of SPTFF devices (i.e., 2-in-series), that are not covered by the SPTFF Patents. In summary, SPTFF systems operating with 1 or 2 cassettes in-series have significantly inferior performance to SPTFF systems using cassettes having optimal path lengths of 3 or more cassettes in-series.

Figure 4

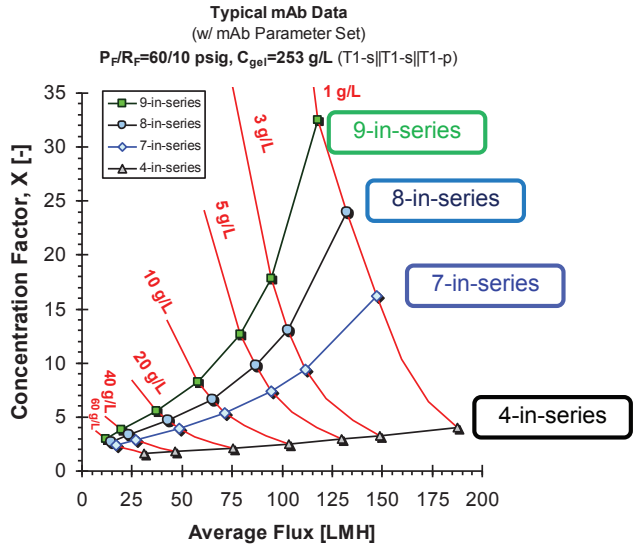
Impact of number-in-series and/or dimensionless length, λ_{System}, on Productivity (SPTFF configurations with 20 mil spacer, 35% void fraction, 50 g/L feed concentration, concentration factor of 4.5x and a final retentate concentration of 225 g/L).



The robustness of the SPTFF device performance to achieve high conversion separations is enabled by the thin, long channels that are configured via the proprietary serial- and/or parallel- arrangement of the flow path and more importantly, dictated by the optimized feed flow rate, residence time and the pressure drop during processing. Figure 5 shows the design curves and/or so-called web-plots consisting of lines of constant concentration for SPTFF modules with short-to-long flow paths that depict the operating space for the target application.

Figure 5

Performance benchmarking of commercially available SPTFF modules with short- to-long path length configurations at varying mAb feed concentrations between 1 and 60 g/L.



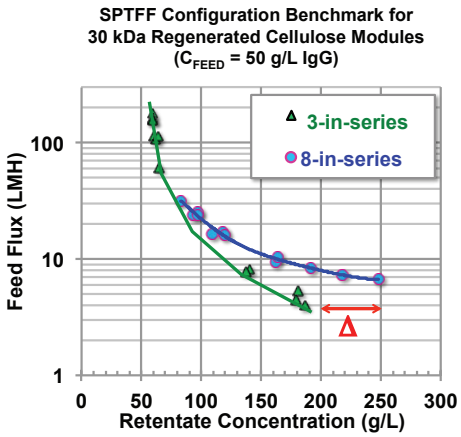
As outlined in Figure 5, better utilization of SPTFF design principles enable module designs with longer flow path configurations (i.e., 7-, 8-, or 9-in-series), which manifests itself with a wider operational window and a design space, thus resulting in higher concentration factors. This aspect of operation is utmost critical to process stability and is a key determinant for evaluating the time-to-reach steady-state, especially during high concentration applications.

Therefore, understanding process transients and appropriate management of flow and pressure profiles at high concentrations are essential for designing scalable, reproducible and robust single-pass processes. Such built-in flexibility and customization is provided by the Cadence single-pass TFF product portfolio.

In order to better illustrate this point, a benchmark study between 3- and 8-in-series modules was undertaken to evaluate their respective performances for a final concentration application of ~50 g/L IgG feed, as shown in Figure 6 and summarized in Table 1. Upon testing over the typical operational window shown in Figure 6, benefits of utilizing a longer flow path module (i.e., 8-in-series) was amply demonstrated via significantly higher final concentration of 250 g/L, ~2-fold higher fluxes, productivity and/or ~2-fold shorter processing times with a wider operating window (high DP). This clearly indicates better utilization of feed channel pressure drop during protein testing and therefore, resulted in stable processing conditions with no process transients (Table 1).

Figure 6

SPTFF configuration benchmark between 3- and 8-in-series modules to process 50 g/L Polyclonal Bovine IgG with 30 kDa regenerated cellulose membranes over a operational window of 10-60 psig.



PALL Life Sciences

Table 1

Performance Summary for SPTFF Configuration Benchmark Study

SPTFF Config.	Initial Concentration, C_{FEED} (g/L)	Final Concentration, $C_{Retentate}$ (g/L)	Feed Flux (LMH)	Productivity (kg/m²/h or KMH)	Feed Pressure (psig)	Pressure Drop* (psid)	Stable Process (?)
3-in-series	50	190	4	0.2	63	2	NO
8-in-series	50	250	7	0.35	37	28	YES

** Feed channel pressure drop measured during protein processing.*

Also worth noticing that the feed channel pressure drop (DP) of 2 psid during protein processing for the 3-in-series module was significantly lower than the hydraulic DP of the individual cassettes (8-12 psid) used to build this flow path. Coupled with the high feed pressure of 63 psig, shown in Table 1, such discrepancy is further evidence indicating that the device has potentially reached its capacity and the 3-in-series configuration is not a suitable configuration for achieving the targeted high concentration application. In summary, poor utilization of the flow channel pressure drop with the 3-in-series configuration results in inferior performance compared to optimal 8-in-series configuration in multiple respects:

a. It is unstable;

b. It has half the productivity; and

c. It is unable to reach the target final concentration of 250 g/L.

Conclusions

This study is intended to provide a thorough analysis of the key terminology and the protected space that defines and qualifies a single-pass TFF process for biopharmaceutical applications. Then, a data-driven approach was taken in order to further elucidate the impact of single-pass flow path on key processing conditions and various performance attributes and subsequent technology selection criteria's. It was demonstrated that designing scalable, reproducible, and robust single-pass TFF processes requires in-depth understanding of processing conditions and design space, requires built-in flexibility, customization, ease-of- use, and a product portfolio to provide appropriate mitigation strategies against process transients. Such holistic approach and technical mastery is essential to leverage the key benefits of single-pass TFF technology at PD, pilot, clinical and commercial scales, as we re-shape and re-define the future of bioprocessing.

Acknowledgements and Remarks

Authors greatly acknowledge Leon Mir and Gastón de les Reyes of SPF Innovations LLC and the dedicated team of Pall R&D and Applications R&D scientists and engineers who have worked and collaborated diligently since 2007 to commercialize this pioneering technology for biopharmaceutical applications.

SPTFF Technology is protected by U.S. Patents No. 7,384,549; 7,510,654; 7,682,511; 7,967,987; 8,157,999; 8,231,787; 8,231,788; 8,847,669 and is covered by other pending U.S. and international patent applications.

Pall Corporation (Port Washington, NY) has an exclusive licensing agreement with SPF Innovations LLC for the manufacturing, marketing, and sale of SPTFF Products for biopharmaceutical applications.

References

[1] Gaston de los Reyes and Leon Mir. Method and apparatus for the filtration of biological solutions, US Patent 7,384,549 B2 (June 10, 2008).

[2] Leon Mir and Gaston de los Reyes. Tangential flow filtration system, US Patent 7,510,654 (March 31, 2009).

[3] Gaston de los Reyes and Leon Mir. Method and apparatus for the filtration of biological solutions, US Patent 7,682,511 B2 (March 23, 2010).

[4] Gaston de los Reyes and Leon Mir. Method and apparatus for the filtration of biological solutions, US Patent 7,967,987 B2 (June 28, 2011).

[5] Gaston de los Reyes and Leon Mir. Method and apparatus for the filtration of biological solutions, US Patent 8,157,999 B2 (April 17, 2012).

[6] Leon Mir and Gaston de los Reyes. Tangential flow filtration system, US Patent 8,231,787 (July 31, 2012).

[7] Casey, C., Gallos, T., Alekseev, Y., Ayturk, E., and Pearl, S. Protein concentration with Single-Pass Tangential Flow Filtration, Journal Membrane Science, 384(1-2) (2011) 82-88.

[8] Pall Application Note (USD2789): Cadence™ Systems Employ New Single-Pass TFF Technology to Simplify Processes and Lower Costs (2011).

[9] Dizon-Maspat, J., Bourret, J., D'Agostini, A. and Li, F. Single Pass Tangential Flow Filtration to Debottleneck Downstream Processing for Therapeutic Antibody Production. Biotechnology and Bioengineering, 109(4) (2011) 962-970.

[10] Casey, C. and Ayturk, E., Pall Application Note (USTR 2913): Volume Reduction and Process Optimization with Cadence™ Single-Use Inline Concentrator (2013).

[11] Forespring, C., Ayturk, E., El-Agib, D., Casey, C., Bender, J. and Kuriyel, R. "Manufacturing Technologies and Case Studies to Increase Efficiency in Clinical or Commercial Production", Poster Presentation at BioProcess International Conference and Exhibition, October 26-29, 2015, Boston, MA, USA.

[12] Casey, C., Rogler, K., Gjoka, X., Gantier, R. and Ayturk, E. "Continuous Downstream BioProcessing by Coupling Cadence™ Single-Pass TFF with Chromatography Steps", Poster Presentation at BioProcess International Conference and Exhibition, October 26-29, 2015, Boston, MA, USA.

[13] Schofield, M., Rogler, K., Gjoka, X., Ayturk, E., and Gantier, R. Pall Application Note (USD3002): Productivity and Economic Advantages of Coupling Single-pass Tangential Flow Filtration to Multi-Column Chromatography for Continuous Processing (2014).

[14] Casey, C. Rogler, K., Gjoka,X., Gantier, R. and Ayturk, E. Pall Application Note (USD3003): Cadence™ Single-pass TFF Coupled with Chromatography Steps Enables Continuous Bioprocessing while Reducing Processing Times and Volumes (2015).

[15] Casey, C. and Ayturk, E. Pall Application Note (USD3004): Scalability of Cadence™ Inline Concentrator Module for Bovine IgG Processing (2015).

[16] Casey, C., Haberman, P., Ayubali, M., and Ayturk, E. Pall Application Note (USD3005): Cleanability and Re-usability of Cadence™ Inline Concentrator Modules (2015).

[17] Engin Ayturk and Rene Gantier, "Process Economics of Continuous mAb Processing with Single- Pass Tangential Flow Filtration", Presented at 249th American Chemical Society National Meeting and Exposition, March 23-26, 2015, Denver, CO, USA.

[18] Zou, Y., Ngan, C., Hillier, B., Parrella, J., and Kozlov, M. New technologies for high concentration protein ultrafiltration: High Viscosity TFF Cassettes and Single-Pass TFF (2014).

[19] Millipore Application Note (AN5572EN00_EM): Single-pass tangential flow filtration (2014).

PALL Life Sciences

Corporate Headquarters
Port Washington, NY, USA
+1.800.717.7255 toll free (USA)
+1.516.484.5400 phone
biopharm@pall.com e-mail

European Headquarters
Fribourg, Switzerland
+41 (0)26 350 53 00 phone
LifeSciences.EU@pall.com e-mail

Asia-Pacific Headquarters
Singapore
+65 6389 6500 phone
sgcustomerservice@pall.com e-mail

Visit us on the Web at www.pall.com/biopharm
E-mail us at biopharm@pall.com

International Offices
Pall Corporation has offices and plants throughout the world in locations such as: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, India, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Poland, Puerto Rico, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, the United Kingdom, the United States, and Venezuela. Distributors in all major industrial areas of the world. To locate the Pall office or distributor nearest you, visit www.pall.com/contact.

The information provided in this literature was reviewed for accuracy at the time of publication. Product data may be subject to change without notice. For current information consult your local Pall distributor or contact Pall directly.