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Application Note

Best Practices for Permeate-Controlled Tangential Flow Filtration

Process Development and Optimization

Introduction

Tangential Flow Filtration (TFF) is widely used in bioprocessing. The diverse range of membrane nominal Molecular Weight Cutoffs (MWCO) from 1 kDa to 1,000 kDa, and pore sizes from 0.1 µm to 5 µm, make TFF membranes ideal for purifying a variety of therapeutics of different modalities.

The most common TFF operations in bioprocessing are Ultrafiltration (UF) for concentration and separation of molecules based on size, and Diafiltration (DF) for buffer exchange.[1] For UF/DF operations, most membrane MWCOs range from 1 kDa to 100 kDa, and the process is usually controlled using transmembrane pressure (TMP).[2] On the other hand, for open-TFF applications such as clarification of bioreactor harvests or purification of viral and gene therapies, membrane MWCOs greater than 100 kDa are commonly used, requiring a control of the permeate flux (J) to achieve the best performance.[3] **Figure 1** outlines general guidelines for TFF control, dependent on membrane MWCO.

This document provides technical information and best practices for process development scientists and biomanufacturers aiming to develop a robust permeate-controlled TFF process using microfiltration and/or open-ultrafiltration membranes.

Background and Applications

In UF/DF, most membrane MWCOs range from 1 kDa to 100 kDa, resulting in a relatively low permeability. When operating with a low TMP, a small fraction of the crossflow is converted into permeate, resulting in poor process performance and high filtration area requirements. Thus, TMP is usually set and maintained at an optimal operating point by a retentate valve. Permeate flux is monitored for performance.

$$TMP = \frac{P_{Feed} + P_{Retentate}}{2} - P_{Permeate}$$

Where:

- TMP is the transmembrane pressure, expressed in bar or psi
- P_{Feed}, $P_{Retentate}$ and $P_{Permeate}$ are feed, retentate and permeate pressure respectively, expressed in bar or psi

$$J = \frac{q_{Permeate}}{A}$$

Where:

- J is the permeate flux, expressed in L/m²/h
- $q_{Permeate}$ is the permeate flow rate, expressed in L/h
- A is the filtration area, expressed in m²

TMP-controlled operations
Less than 100 kDa

- TMP control as the most reliable operating mode
- Cover many modalities (monoclonal antibodies, ADC, human blood plasma, etc.)
- Commonly refered as ultrafiltration

Flexible area
100 kDa to 300 kDa

- Both TMP control and permeate control to be assessed
- Viral and gene therapies as main modalities
- Commonly refered as open-ultrafiltration

Permeate-controlled operations
Above 300 kDa

- Permeate control as the most reliable operating mode
- Mostly used for clarification, perfusion or cell harvest
- Commonly refered as microfiltration

Figure 1. Guidelines for TFF control as a function of membrane properties

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Open-TFF applications are performed with devices having high intrinsic permeability (500-15,000 L/m²/h/bar, or 35-1,035 L/m²/h/psi) so almost all crossflow is converted to permeate even at very low applied TMP (<0.2 bar or <3 psi).[4] Although the short-term impact may be seen as positive, since the process starts with very high initial permeate flux, there may be a dramatic flux decay due to premature membrane fouling, which risks membrane damage or inconsistent filtration performance. Therefore, operating under a constant permeate flux rather than a constant TMP is recommended for open-TFF applications to avoid excessive membrane fouling. Constant permeate flux can be achieved using a pump or valve at the permeate side to limit flow rate, **Figure 2**. Thus, under permeate control, with the flux held constant, the process endpoint is often determined by an increase of the TMP to a maximum threshold or by a reduction in retention/sieving of a product or contaminant. Additionally, permeate control offers more control over the formation of the boundary layer within a TFF module, enabling improved impurity clearance for certain processes.[5]

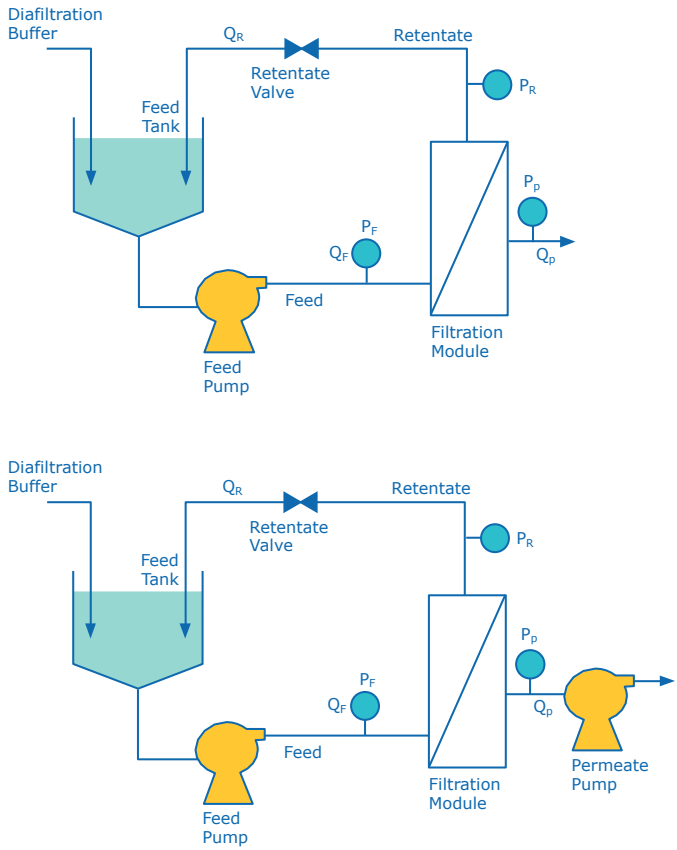

Figure 2: The top diagram illustrates the standard setup while the bottom diagram depicts the permeate-controlled setup, highlighting the differences in operation. A permeate pump (shown on the right) facilitates effective control of permeate flux.

Permeate-controlled TFF is used for many applications. The technique has been historically implemented for microfiltration, using membranes ranging from 0.1 µm to 0.65 µm for clarification of bioreactor harvests or to run perfusion applications in intensified upstream processing.

The emergence of newer modalities such as viral and gene therapies, with active molecules having a size greater than the typical immunoglobulin of monoclonal antibody (mAb) therapies, prompted the development of TFF devices with larger MWCOs, which will likely need to be run using permeate flow restriction.

Preliminary Work

Success criteria

The first step is the determination of quantified and prioritized success criteria, **Table 1**. Success criteria should be adapted to the application and the following considerations:

- Product quality and yield
- Process time
- Process operational expenditures
- System limitations: pump capacity, footprint, equipment availability

Table 1: Typical success criteria by application

Application	Example of success criteria
Clarification/removal of cells, cell debris and particulates	• Product yield (permeate) • Permeate turbidity • Capacity of downstream membrane filter (V_{max})
Cell harvest/recovery of cells containing intracellular product and buffer exchange	• pH • Conductivity
Perfusion/retention and concentration of viable cells	• Viable cell density • Effluent product concentration • Perfusion lifetime or rate
Open-ultrafiltration/concentration and buffer exchange	• Volumetric concentration factor (VCF) • Yield • pH • Conductivity • Impurity percentage

Development of a robust scale-down model

A key point for successful development of a permeate-controlled TFF operation is a robust scale-down model. Many parameters are easily scalable and can ensure consistency from bench to manufacturing scale:

- Recommended operating parameters include constant normalized crossflow rate and permeate flow rate expressed in L/m²/min and L/m²/h respectively.
- Permeate throughput (volume of permeate per unit of filtration area, L/m²), is a strong indicator of filter capacity.
- For flux-controlled processes, TMP is not a directly controlled parameter but a measured value for process monitoring (this contrasts with TMP-controlled TFF processes where TMP is directly optimized and controlled).

Materials

System consideration

System design and instrument specifications should be adapted to permeate-controlled operations. Requirements can slightly differ from typical TMP-controlled ultrafiltration. **Table 2** highlights key system differences:

Table 2: System consideration for TMP control and permeate control

Component	Permeate control	TMP control
Feed pump	• Should match with the application and device selected • 4 – 7 L/m²/min for 100 kDa to 500 kDa membranes • 10 – 15 L/m²/min for microfiltration with screened cassettes	• Usually 3 – 7 L/m²/min
Pressure management	• Feed, retentate and permeate pressure monitoring mandatory • Typical sensor range: 0 – 2.5 bar (0 – 36 psi) • Recommended accuracy: 0.05 bar (0.8 psi) max	• Feed and retentate pressure monitoring mandatory • Permeate pressure is recommended but can be assumed as approximately 0 bar (or 0 psi) relative for small scale systems (atmospheric pressure) • Typical sensor range: 0 – 5.5 bar (0 – 80 psi) • Recommended accuracy: 0.05 – 0.1 bar (0.8 – 1.5 psi)
Permeate flow management	• Accurate permeate control is mandatory • Permeate pump or flow-controlled valve should be implemented	• No specific control needed • Permeate line can be isolated when needed
Mixing	• Mandatory, to ensure product homogeneity and avoid particulate sedimentation (if present)	• Mandatory, to ensure product homogeneity
Transfer pump (or vacuum)	• Usually recommended for product transfer, fed-batch, washing and diafiltration	• Usually recommended for product transfer, fed-batch and diafiltration

Device selection

The main drivers for device selection are feed stream characteristics and module pressure drop. Permeate flux control will result in permeate pressure increase, then TMP decrease. However, TMP limitation cannot be successful without reducing the upstream (*i.e.* feed and retentate) pressure. This can be achieved by selecting a channel geometry with a lower pressure drop. **Table 3** lists modules available for process development and optimization.

Table 3: Modules available for process development

Application	Type of module	Main characteristics	MWCO or pore size available
Microfiltration	• Open channel devices (e.g. Prostak™) • Hollow fibers	• Very low feed channel pressure drop • Bioprocessing of challenging feed streams at very low TMP • Mostly operated in series • Adapted to perfusion, can be sterilized and reused	• 0.1 – 0.65 µm • 1,000 kDa (cassettes only)
	• Screened cassettes (e.g. Pellicon® 2 V-screen)	• Low feed channel pressure drop • High productivity • Low footprint • Easily scalable • Operated in parallel • Can be reused	
Open-ultrafiltration	• Screened cassettes (e.g. Pellicon® 2 C-screen)	• High mass transfer coefficient • Low footprint • Easily scalable • Operated in parallel • Can be reused	• 100 – 500 kDa
	• Capsules (Pellicon® Capsule portfolio)	• Scalable with Pellicon® cassettes • Single-use • Enables closed processing • Minimize pre- and post-processing workload	• 100 kDa and 300 kDa

Regardless of the device selected, it is recommended to perform process development work using the smallest filtration area possible to minimize feed stream requirements.

Process Development Lifecycle

The first three experiments, referred to as critical flux assessment and capacity assessment (x2), are performed sequentially to identify ideal operating parameters.[6] Results are then considered in the context of realistic manufacturing parameters to design the process simulation.

Table 4: Experimental plan

Sequence	Purpose
1. Critical flux assessment/mass flux optimization	• First assessment of membrane capacity • Feasibility assessment • Calculation of 50% and 75% of the critical flux ($J_{50\%}$ and $J_{75\%}$ respectively) to be used afterwards • Evaluation of the sieving of the component to be washed out
2a. Capacity assessment at $J_{50\%}$ 2b. Capacity assessment at $J_{75\%}$	• Generating data on filter capacity • Determination of the optimum flux
3. Process simulation at the optimum flux	• Bench-scale evaluation of process efficiency

Set-up and Installation Procedure

Refer to the appropriate User Guide when setting up and installing the filtration device.

1. Assemble the TFF system as shown in **Figure 2** and according to bill of materials, **Table 5**.
2. Install the filtration device in the appropriate holder or stand.
3. Flush and sanitize the module. Pre-use integrity testing can be performed.

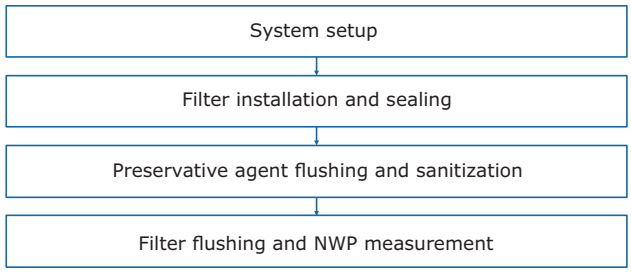

Figure 3: Typical pre-processing lifecycle

Table 5: Bill of materials

Component/cleaning agent	Specification
Feed pump	According to targeted crossflow, e.g. up to 60 L/h for 0.1 m² ultrafiltration devices Up to 150 L/h for 0.1 m² microfiltration devices
Permeate pump	According to targeted permeate flux, e.g. 8 – 250 mL/min for 0.1 m² microfiltration devices
Filtration holder with appropriate device	XX42PMINI holder with Pellicon® mini cassette filtration module PCX001 capsule stand with appropriate Pellicon® Capsule XXPXLSTND stand for Pellicon® XL50 devices
Feed, retentate, and permeate pressure sensors	0 – 2.5 bar (0 – 36 psi) Two decimal reading
Retentate valve and permeate valve (unless permeate pump head can isolate permeate line)	Manual handling membrane valve Automated pressure-controlled valve when using integrated system
Feed vessel with appropriate stirring	3 – 10 L depending on application
Feed and retentate tubing	As per targeted crossflow
Permeate tubing	As per targeted permeate flux
Cleaning agent	As per membrane chemistry, typically NaOH or NaOCl

Cleaning and NWP Measurement in Permeate-Controlled Operations

Once the filter has been sanitized and flushed, the Normalized Water Permeability (NWP) should be measured to have a baseline for the cleaning assessment.

$$NWP = \frac{q_p * TCF}{A * TMP}$$

Where:

- NWP is the normalized water permeability, expressed in L/m²/h/bar or L/m²/h/psi
- q_p is the permeate flow rate, expressed in L/h
- TCF is the temperature correction factor determined according to the water temperature (no dimension, correlation tables available in Pellicon® User Guides)
- A is the filtration area, expressed in m²
- TMP is the transmembrane pressure, expressed in bar or psi

The following considerations apply when running permeate-controlled operations:

- Consistent measurements are difficult to perform because of the device's intrinsic high permeability – NWP values are more influenced by resistance within the system since, as the membrane MWCO increases, the membrane resistance decreases and no longer acts as the dominating resistance in the flow circuit. Therefore, NWP becomes one factor in a holistic evaluation (including Total Organic Carbon, product carryover, bioburden, etc.) of membrane cleanability.
- Pressure sensor accuracy should capture small variations of TMP so that the NWP measurement remains repeatable.
- NWP drop after first product run is sharper with open membranes. This does not necessarily mean a performance decrease as process permeate fluxes are significantly lower than water permeability. Alert limit definition should be adapted accordingly.
- NWP should be always done at the same feed flow rate.

Process development experiments are particularly harsh for devices with open MWCO because the nature of open TFF process development purposefully pushes devices to a fouled, or nearly fouled, state. Therefore, it is mandatory to clean the filtration device between each experiment or, alternatively, utilize a new device in lieu of cleaning.

Process Development Work

Determining the critical flux

The critical flux is the permeate flux at which the process becomes unstable[6]: the TMP begins to steadily rise with time and, eventually, the filter will foul prematurely and the permeate flux will decline.

Although important for process development, the critical flux is not an operating parameter by itself. It serves as an indicator of the filter suitability and a prerequisite value for the next steps of process development.

The experiment for defining the critical flux should be run with the smallest scalable filtration device, in a total recirculation configuration. The procedure is described hereafter:

1. Pour the process fluid inside the feed vessel and initiate active mixing.
   Note: active mixing is highly important for every TFF unit operation to ensure homogeneity, and also to avoid any tank bypass and short circuiting.
2. With the permeate line closed, ramp up the feed pump to the desired crossflow rate (check vendor recommendations for a given device). The equation for crossflow rate can be seen below[5]:

$$J_{Crossflow} = \frac{1}{A}\left(\frac{q_F + q_R}{2}\right) = \frac{1}{A}\left(q_F - \frac{q_p}{2}\right)$$

Where:

- $J_{crossflow}$ is the average crossflow normalized with the filtration area, expressed in L/m²/min
- A is the filtration area, expressed in m²
- q_F, q_R and q_P are the feed, retentate and permeate flow rates respectively, expressed in L/min

3. After 5 minutes of stabilization, apply a slight retentate pressure of 0.3 – 0.5 bar (4 – 8 psi) by closing the retentate valve slightly. Further details on applying retentate pressure are listed on page 9.
4. After 5 – 10 minutes of stabilization, slowly ramp the permeate pump to the first permeate flux to assess. It is recommended that the user starts at low flux, typically 5 – 10 L/m²/h. The feed pump should be adjusted accordingly to ensure that the desired crossflow rate is maintained.
5. Record feed, retentate, and permeate pressures 3 to 4 times over a period of 10 to 20 minutes (typically; $t_{0\ min}$, $t_{5\ min}$, $t_{10\ min}$ and $t_{15\ min}$). Use the feed, retentate, and permeate pressures to calculate TMP for each time point.
6. Monitor stability of TMP during the given period: a rapid increase in TMP indicates membrane fouling. Take samples of feed and permeate at the end of the period and analyze for product and impurity concentrations. This analysis can be used to determine sieving/retention data for a given process setpoint.
7. If the TMP is stable over the time period, increase the permeate flux to a higher value. Typically, 5 – 15 L/m²/h increments are used depending on the feed stream. Adjust the retentate valve

to maintain the target retentate pressure utilized at the onset of the study. When increasing the permeate flux, it is normal to see an immediate TMP increase as the permeate pressure will decrease under higher flux rates. However, the resulting TMP should remain constant during the period 10 – 20 min if the setpoint is stable.

8. Repeat steps 5 – 7 until the critical flux is obtained. Critical flux assessment can be qualitative (continuous permeate pressure decreases and inlet pressure increases) or quantitative (a +20%/min TMP increase can be used for instance, and/or when TMP is equal to 1.5 – 2x the TMP recorded at the beginning of a 20-min period).

When the critical flux is obtained, stop the permeate pump (or close the permeate flow control valve) and fully open the retentate valve.

During experimentation, it is possible that the permeate flux is high enough that the permeate pressure is null or negative. If this occurs, stop the experimentation. The value at which this occurred can be considered the critical flux.

Figure 4 shows analysis from a critical flux experiment. When TMP is plotted against time for each flux setpoint, a stepwise increase in TMP is observed as the permeate flux is ramped up, followed by a plateau highlighting pressure stability. In this example, the critical flux is reached at 60 L/m²/h, as the TMP is no longer stable over time.

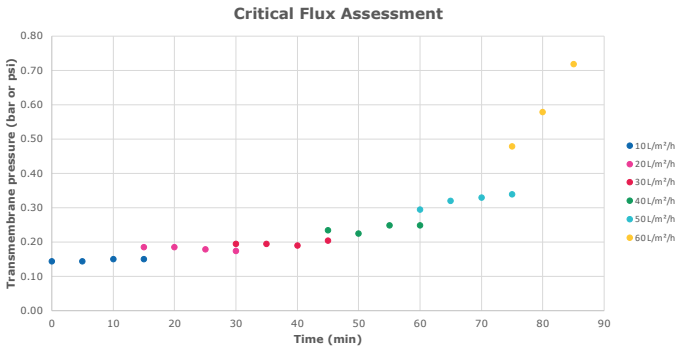

Figure 4: Critical flux assessment outcome

Mass flux optimization

Feed and retentate sampling analyses can also be used to determine the trial endpoint. The polarization of the membrane is function of the membrane flux and crossflow. As the flux rate changes for a given crossflow, the polarization of that membrane also changes. This can have implications for the retention (or wash out) of species within a particular system. Excessive permeate flux can also accelerate fouling and impact the membrane retention profile. By sampling at the end of each flux setpoint, one can characterize the sieving and retention of species for that given setpoint and better optimize the system if a particular separation is desired. Mass flux can be used for such optimization[5], balancing membrane sieving (or retention) performance and area-time requirement:

$G = J*C_p = J*C_b*S$

Where:

- G is the solute of interest mass flux, expressed in g/m²/h
- J is the permeate flux set, expressed in L/m²/h
- C_p is the permeate concentration of the solute of interest, expressed in g/L
- C_b is the bulk concentration of the solute of interest, expressed in g/L
- S is the sieving coefficient of the solute of interest (no dimension)

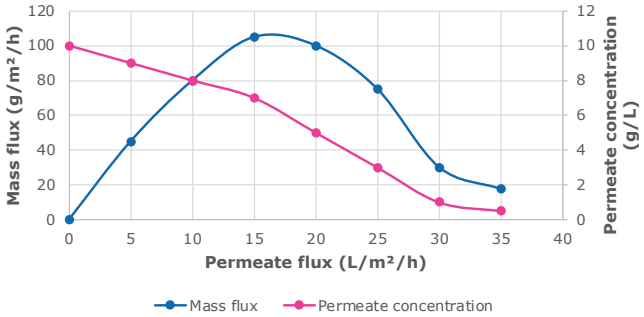

Figure 5: Optimizing mass flux (Lutz, 2015)

In the example shown on **Figure 5**, the optimal mass flux of 108 g/m²/h (peak of the blue curve) corresponds to a permeate flux of 15 L/m²/h.

After the experiment, the filter should be cleaned, ready for re-use at full capacity. Alternatively, a new membrane can be installed, prepared, and equilibrated for use in subsequent steps.

If desired, the critical flux experiment can be repeated at different crossflow rates.

Capacity assessment based on the critical flux

Capacity assessment[6] should be performed to understand the relationship between the filter capacity (expressed in L/m²) and the permeate flux set point.

For the capacity assessment, at least two experiments should be run. The product is concentrated using the crossflow rate and the retentate pressure set for the critical flux assessment. Permeate flux is a variable that should be set below the critical flux. Operational permeate flux values can be defined as:

- A permeate flux set at 50% of the critical flux ($J_{50\%}$)
- A permeate flux set at 75% of the critical flux ($J_{75\%}$)

A permeate flux setpoint of 25% of the critical flux can also be considered if desired.

The critical fluxes, $J_{50\%}$ and $J_{75\%}$, are not operating parameters for manufacturing scale but intermediate values needed to define the optimum flux through experimentation.

Example of calculation:

Considering a critical flux determined at 60 L/m²/h; $J_{50\%}$ and $J_{75\%}$ are then:

- $J_{50\%}$ = 60 * 0.50 = 30 L/m²/h
- $J_{75\%}$ = 60 * 0.75 = 45 L/m²/h

Capacity assessment procedure is described hereafter:

1. Set the system in total recirculation configuration.
2. Pour the product inside the feed vessel[1] and start the stirring.
3. With the permeate line closed, ramp up the feed pump to the desired crossflow rate.
4. After 5 minutes of stabilization, apply a slight retentate pressure (0.3 – 0.5 bar or 4 – 8 psi as per critical flux assessment) by closing the retentate valve.
5. After 5 – 10 minutes of stabilization, slowly ramp the permeate pump to the desired flux ($J_{50\%}$ or $J_{75\%}$) and divert it into the permeate collection vessel.
6. Immediately start a stopwatch and record, at least, the following parameters as outlined in **Table 6**:
   - Feed, retentate, and permeate pressures
   - Permeate volume collected
7. Calculate at least the following parameters:
   - Device pressure drop[2] and TMP
   - Permeate throughput[3]
   - Volumetric concentration factor[4]

Table 6: Example of data collection sheet

Time (min)	Feed flow rate (L/m²/min)	Permeate flow rate (L/m²/h)	Feed pressure (bar or psi)	Retentate pressure (bar or psi)	Permeate pressure (bar or psi)	Permeate volume (mL)	TMP (bar or psi)	Permeate throughput (L/m²)
–	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–

8. Monitor stability of TMP during the concentration. End the concentration by closing the permeate line when the TMP reaches TMP_{max} or an alternative process endpoint. TMP_{max} can be defined as a maximum allowable TMP for the system – this can be product dependent, but generally a value of 0.7 – 1 bar (10 – 15 psi) can be used. Another process endpoint that can be used is a ≤0 bar (or ≤0 psi) permeate pressure. The permeate throughput read at this moment is the filter capacity ($V_{Capacity\text{-}J50\%}$ or $V_{Capacity\text{-}J75\%}$), expressed in L/m².
9. Repeat the experiment with the second permeate flux to obtain the second capacity. Ensure the device has been properly cleaned between uses or install and prepare a new device as per the procedures listed previously.
10. If time and resources allow it, additional fluxes (inside or outside of the 50 to 75% range) can be assessed.

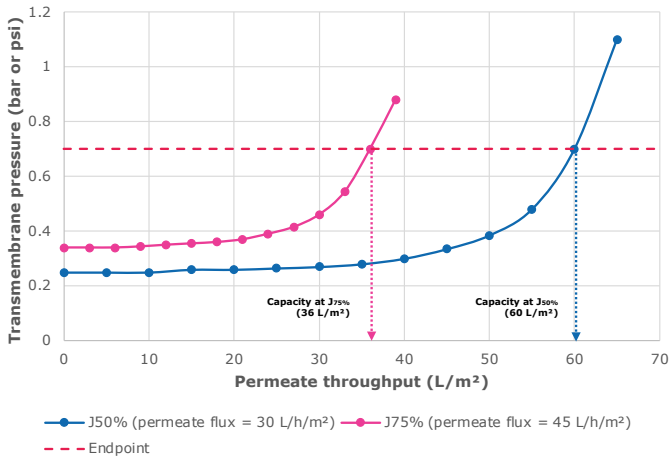

Figure 6: Capacity assessment outcome

[1]Typically, 30 to 70 L/m² for microfiltration application. For open ultrafiltration, volume should be defined according to VCF target.

[2]$\Delta P = P_{Feed} - P_{Retentate}$

[3]Permeate throughput = Permeate volume / filtration area

[4]Volumetric concentration factor = Initial volume / (initial volume – current permeate volume)

Data interpretation and determination of the optimum flux

Capacity assessment confirms that membrane capacity increases as permeate flux decreases. Optimum flux is a balanced value fulfilling the time and membrane area objectives, with respect to membrane capacity and can be determined as follows[6]:

1. Calculate, for each experiment, A_1 and A_2 values:

$$A_1 = \frac{V_b}{V_{capacity}}$$

$$A_2 = \frac{V_b}{J * t_b}$$

Where:

- A_1 is the estimated membrane area based on capacity, expressed in m²
- A_2 is the estimated membrane area based on time objectives, expressed in m²
- V_b is the volumetric goal, expressed in L:
  - The batch size when not running diafiltration
  - The expected permeate throughput when running diafiltration
- J is the permeate flux, expressed in L/m²/h
- $V_{Capacity}$ is the process capacity, expressed in L/m²
- t_b is the process time, expressed in hours

Table 7 lists A_1 and A_2 values from the example above, considering a batch size of 1,000 L and a process time of 5 h:

Table 7: Example of calculation for A_1 and A_2 values

Trial	$V_{capacity}$ (L/m²)	A_1 (m²)	A_2 (m²)
$J_{50\%}$	60	16.7	6.7
$J_{75\%}$	36	27.8	4.4

2. Plot on a chart the following series:
   - A_1 values as function of the permeate flux
   - A_2 values as function of the permeate flux
3. Draw and extrapolate a linear trendline from each series until they meet

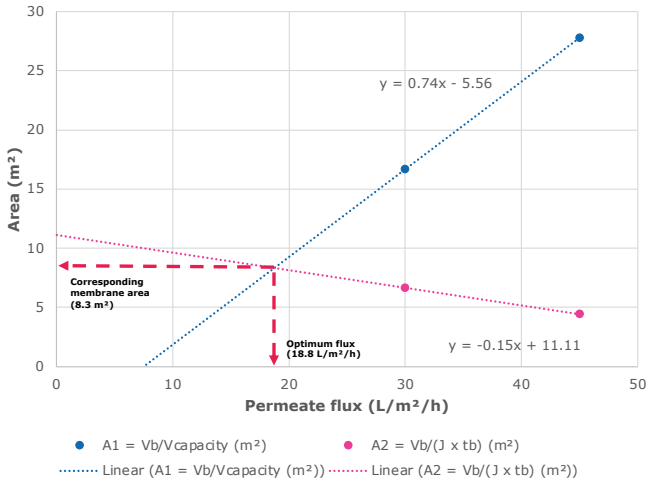

Figure 7: Optimum flux determination

Optimum flux is read on the x-axis when trendlines meet, *i.e.* $A_1 = A_2$. This means that membrane capacity meets time and area requirements.

Optimum flux is associated with a filtration area to be read on the y-axis, also when A_1 and A_2 trendlines meet.

In this example, considering the two linear functions f_1 and f_2 associated with data points:

f_1: $y_1 = 0.74x - 5.56$

f_2: $y_2 = -0.15x + 11.1$

One can solve for $y_1 = y_2$ i.e.: $0.74x - 5.56 = -0.15x + 11.1$ or $x = 18.8$ L/m²/h,

Solving then f_1 or f_2 using $x = 18.8$ L/m²/h gives $y = 8.33$ m².

Process Simulation

Process simulation should be run with a new cassette, and feed and retentate analyses should be performed to confirm that retention and impurity clearance targets are met.

The optimum flux found from previous experiments should be used to design a full process simulation.

Batch size and filtration area should be selected according to filter capacity and expected permeate throughput. Expected number of diavolumes should be included.

Table 8: Operating and monitoring parameters for process simulation

Parameter	Target
Feed flow rate	As per critical flux and capacity assessment
Retentate pressure	As per critical flux and capacity assessment
Permeate flow rate	Optimum flux
Membrane area	Usually 0.1 m²
Batch size	According to filter capacity and expected permeate throughput (including diafiltration)
Transmembrane pressure	Should not exceed 1.5 – 2x initial value or 0.7 – 1.0 bar (10 – 15 psi)
Process time	As per target
Yield and contaminant removal	As per target

Following process simulation, confirmation runs can be done at intermediate scales to secure the implementation at manufacturing scale.

Applying retentate pressure

Although it contributes to TMP increase, applying retentate pressure of 0.3 – 0.5 bar (or 4 – 8 psi) is necessary to increase the initial feed and permeate pressures to enable the critical flux evaluation.

It should also be noted that large-scale systems are never free from pressure drop (pipe length, valve design, etc.). Having no retentate backpressure may result in unobtainable TMP at manufacturing scale.

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