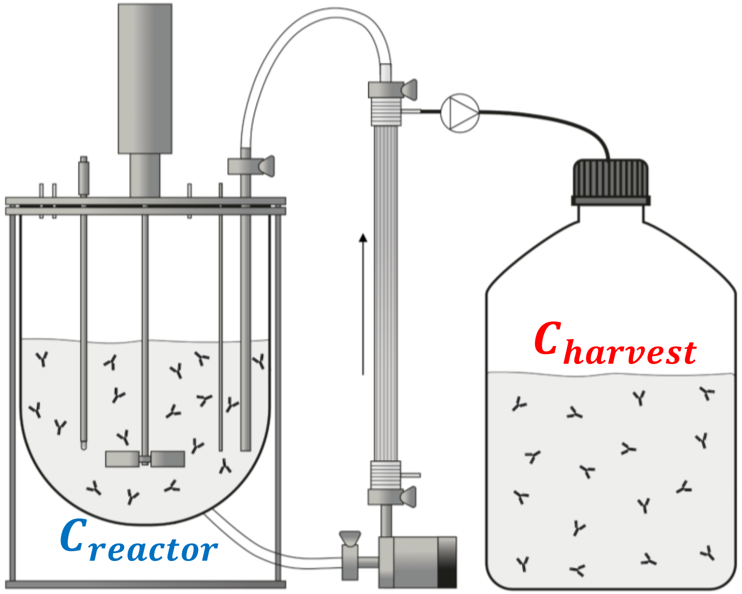
Co-current Filtrate Flow in TFF Perfusion Processes: Decoupling Transmembrane Pressure from Crossflow to Improve Product Sieving

Levitronix Bioprocessing Conference 2024

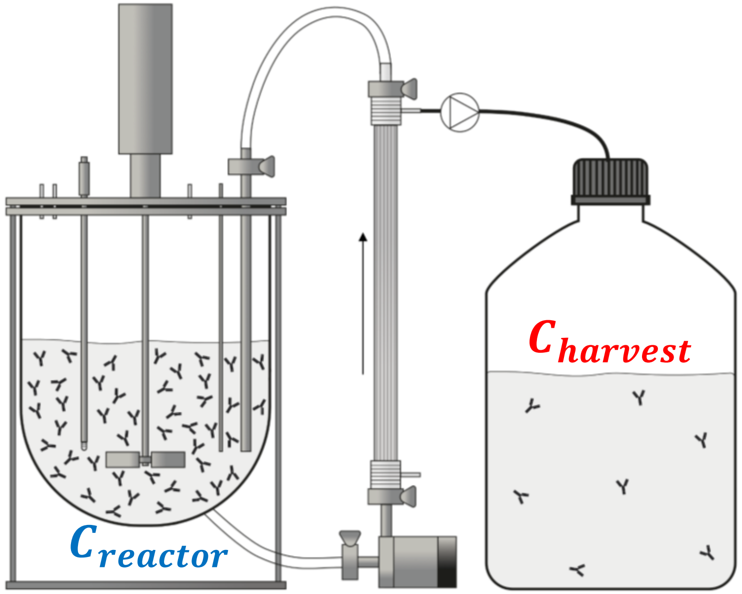
Dr. Patrick Romann

The Sieving Challenge in Perfusion

High Product Sieving



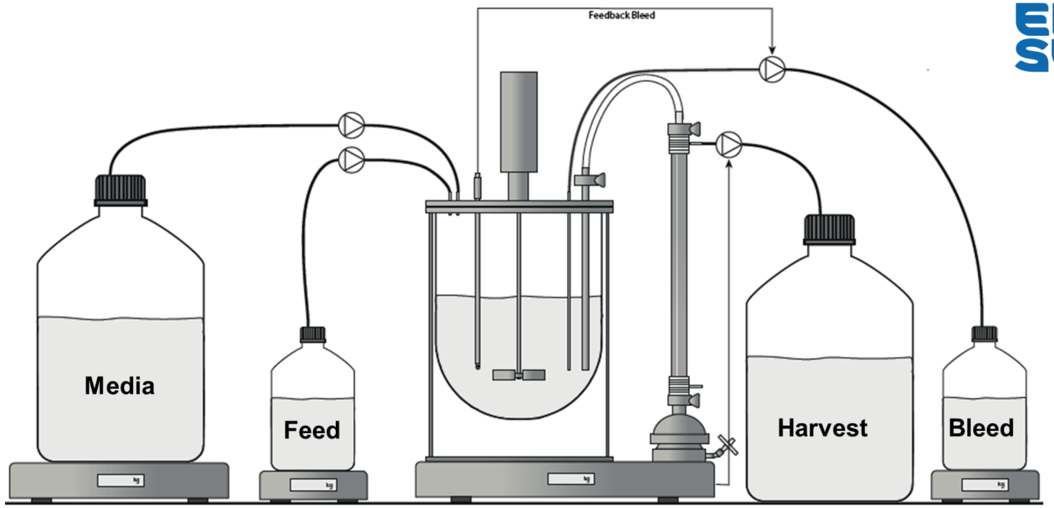
Low Product Sieving



$$Sieving = \frac{c_{harvest}}{c_{reactor}} \times 100$$

- TFF systems with hollow fibers are most common cell rentention devices
- Product retention is one of the major bottle necks in USP

Context: Exploring Novel Technologies to Improve High Density Perfusion Processes



- EMD Serono Platform process
- Steady-state perfusion (ATF / TFF)
- 10-30% biomass (20-100 mio. cells/mL)
- Run duration: 42 days or longer

Goal: Exploring alternative Cell Retention Technologies

Reference: Romann, P., Giller, P., Sibilia, A., Herwig, C., Zydney, A. L., Perilleux, A., Souquet, J., Bielser, J.-M., & Villiger, T. K. (2023). **Co-current filtrate flow in TFF perfusion processes: Decoupling transmembrane pressure from crossflow to improve product sieving.** Biotechnology and Bioengineering, 1–15. https://doi.org/10.1002/bit.28589

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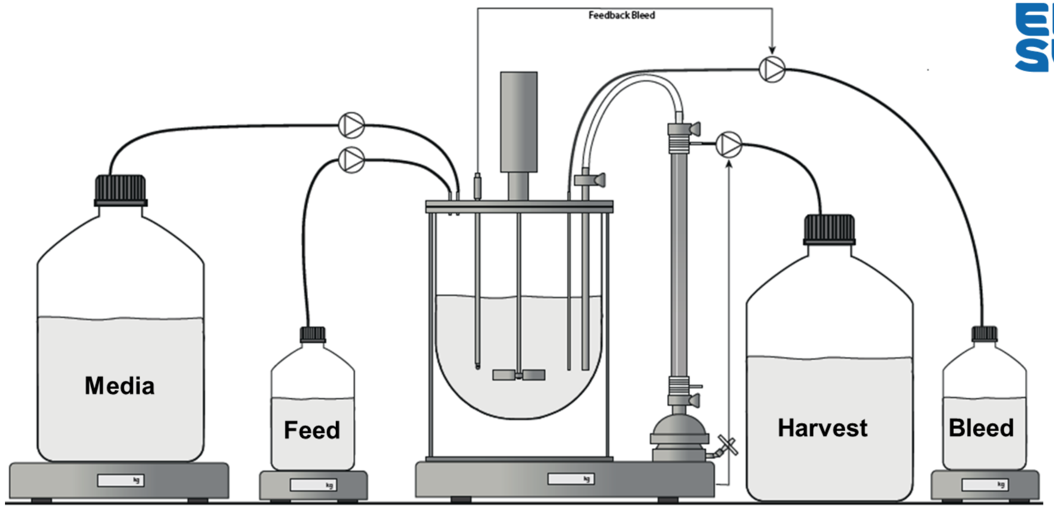

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Targets to Optimize Tangential Flow Filtration

Sieving Optimization

→

Filter Characteristics

- **Module and Fiber Design**
  - Lumen ID
  - Length
  - Pore size …
- **Membrane Chemistry**
  - Membrane material
  - Membrane symmetry
  - …

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System Operation

- **Operating Parameters**
  - Crossflow (Shear)
  - Permeate Flux
  - Residence Time in loop
- **System Design**
  - TFF
  - ATF / reverse TFF (rTFF)
  - Co-current TFF (ccTFF)

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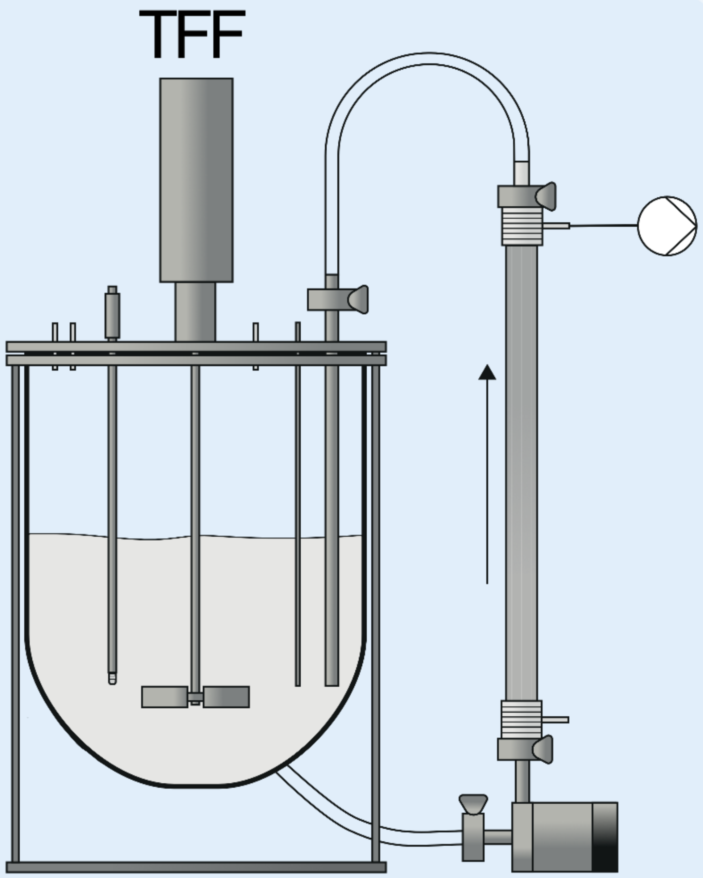
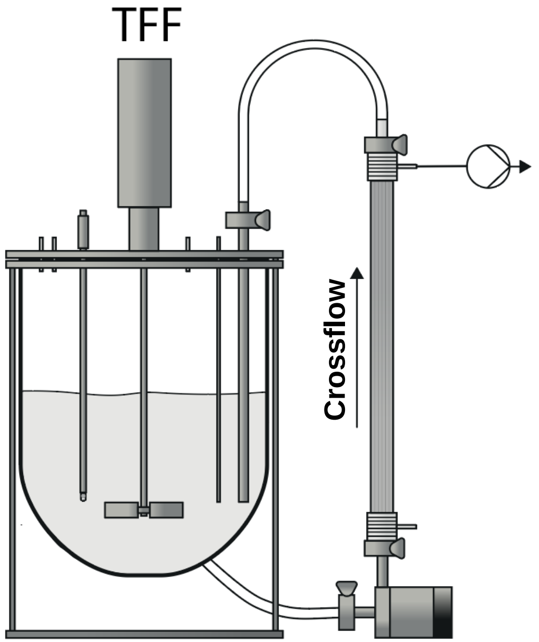
Standard TFF

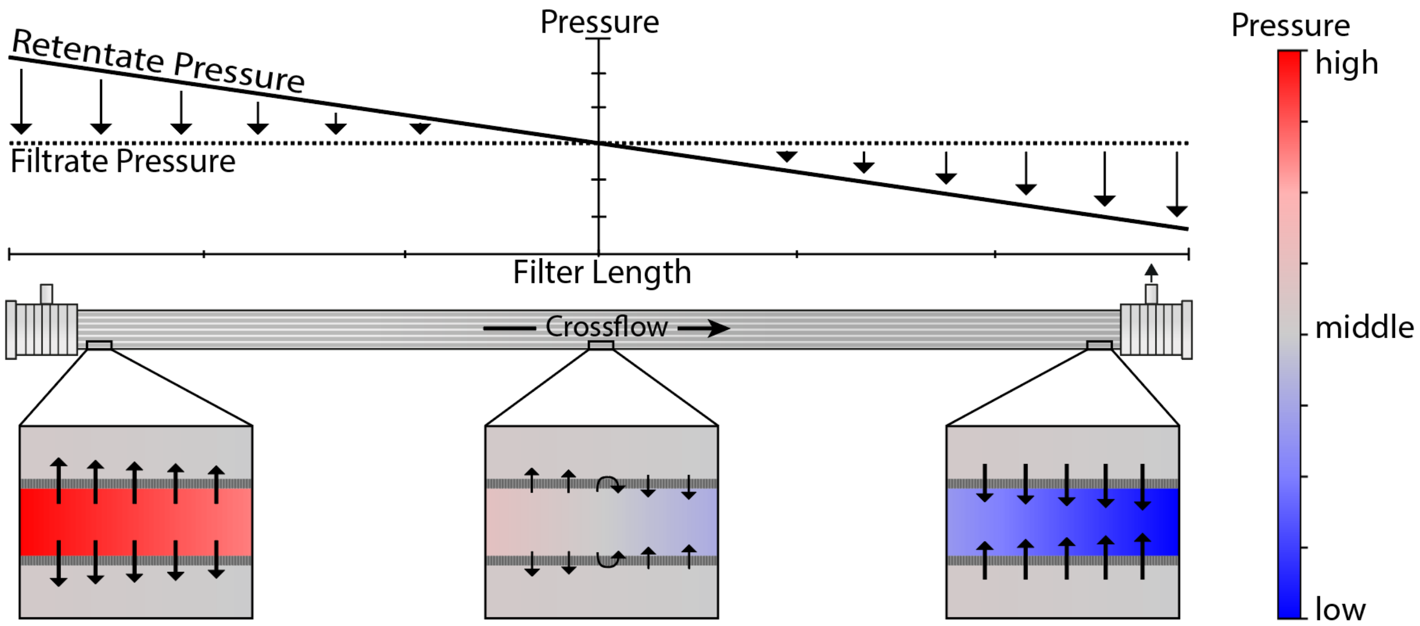


TFF Setup:

- Most simple system
- Unidirectional crossflow

A closer Look at Pressure Profiles in TFF





- Pressure drop along filter module → TMP changes

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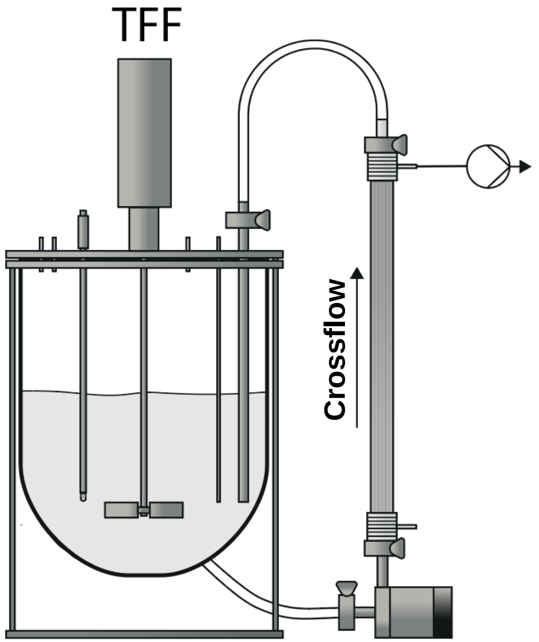

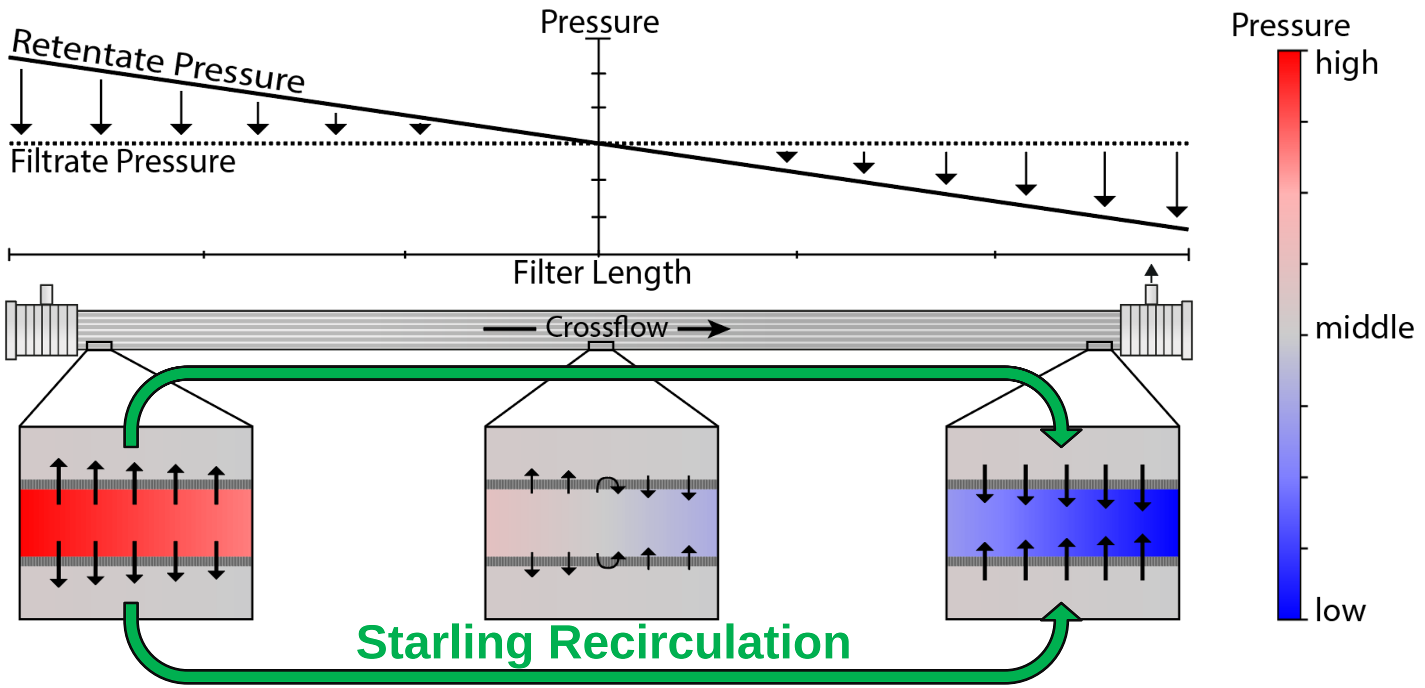

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- Starling Recirculation (**backflush**, but comes with **much higher filtrate flux**)

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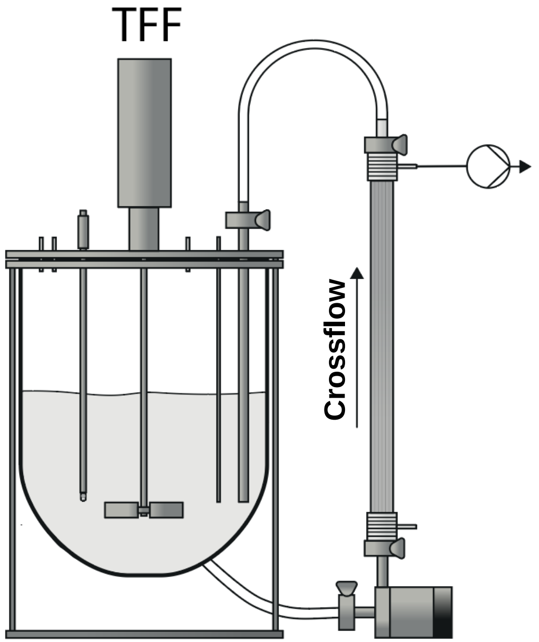
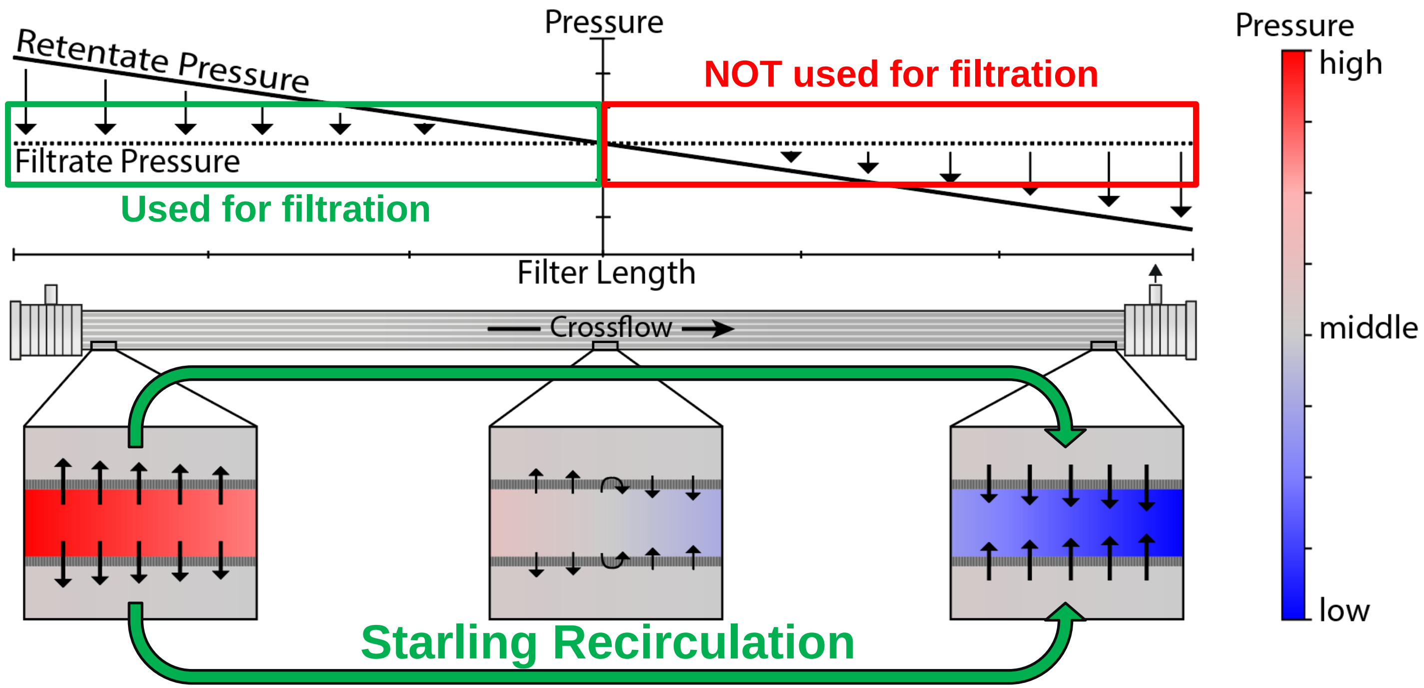
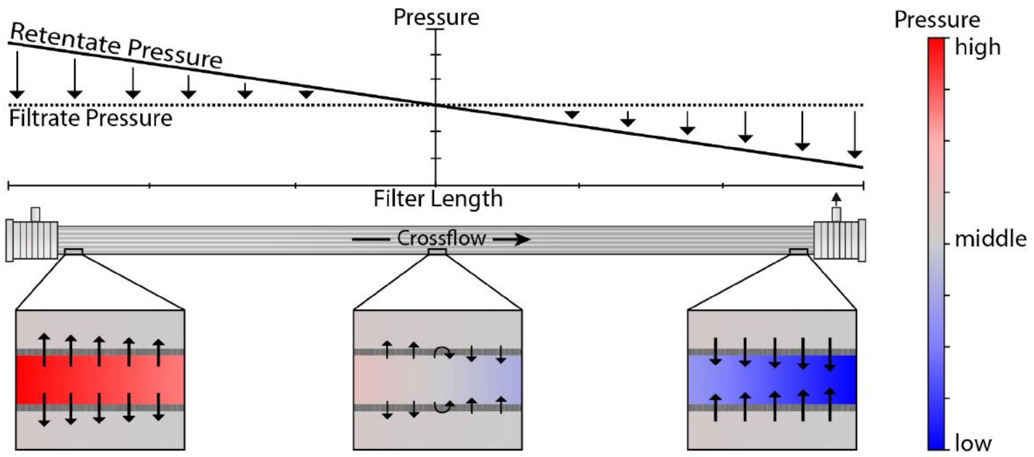




- Pressure drop along filter module → TMP changes
- Starling Recirculation (**backflush**, but comes with **much higher filtrate flux**)
- Unidirectional crossflow: only first half of filter used

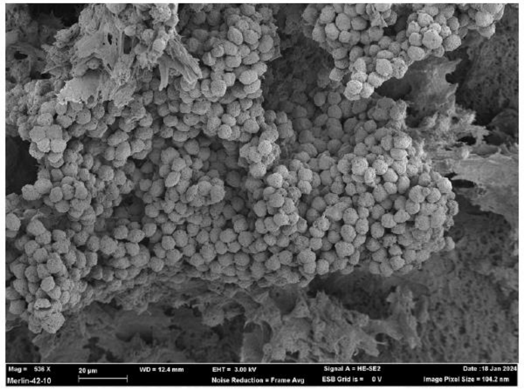
SEM pictures of TFF after several weeks

Also shown with computational fluid dynamics ([1] Radoniqi et al, 2018)

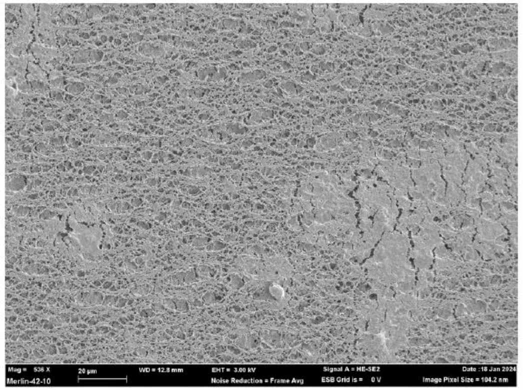


Runtime of several weeks with dynamic perfusion

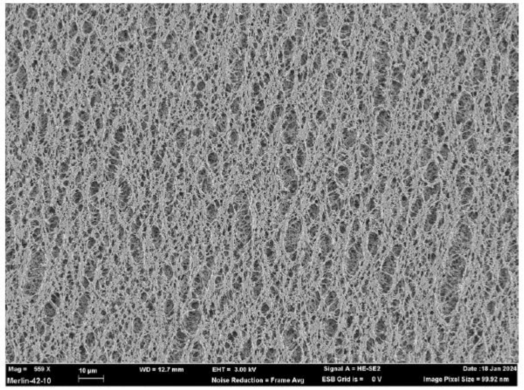
Inlet



Middle



Outlet

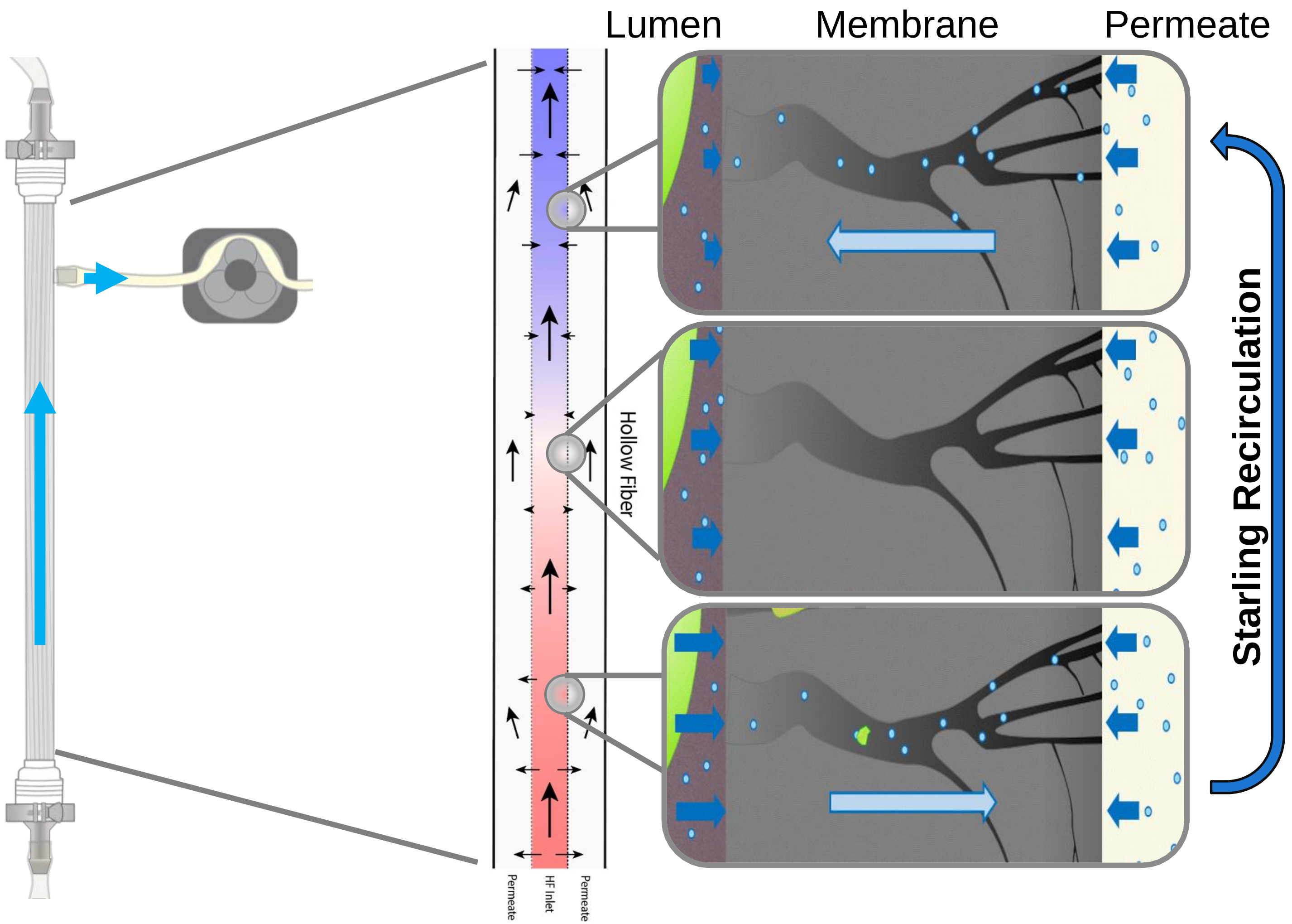


Images acquired by Alexandra Graff (FMI)

New cell retention technologies 5

SEM picture reference: Dominik Schieman, "Product sieving understanding in different TFF operation modes in dynamic perfusion cultures" in “Recovery & Purification", BPI Vienna, (2024).

Starling Recirculation in TFF



Filter Outlet:

- Strong backflush

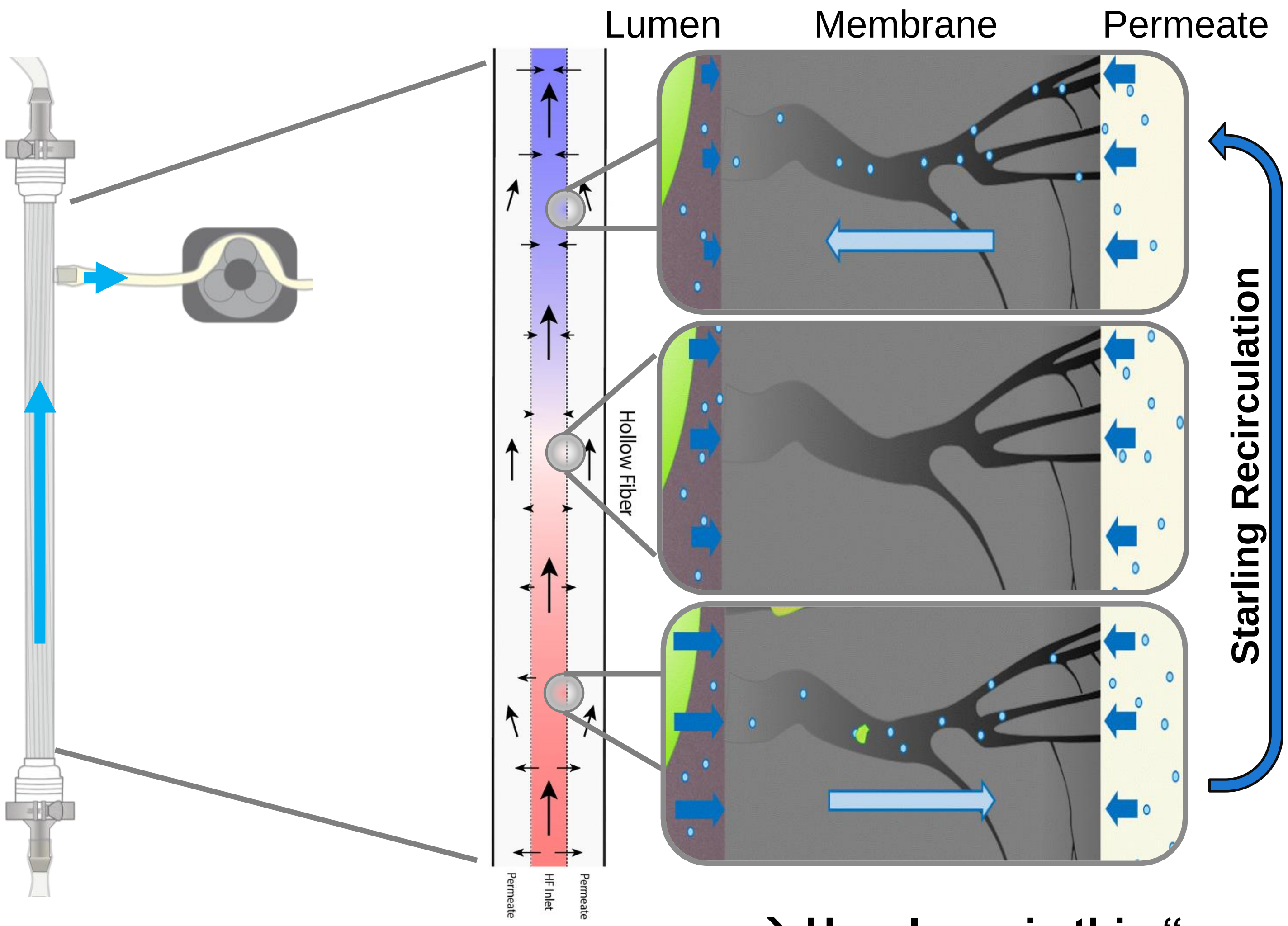
Middle Section:

- Neglectable filtration

Filter Inlet:

- Strong filtration

Starling Recirculation in TFF



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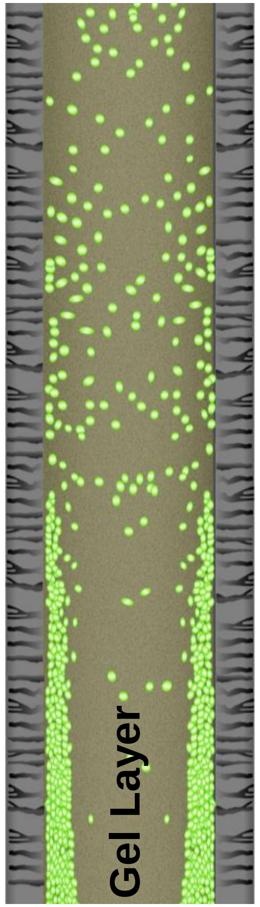


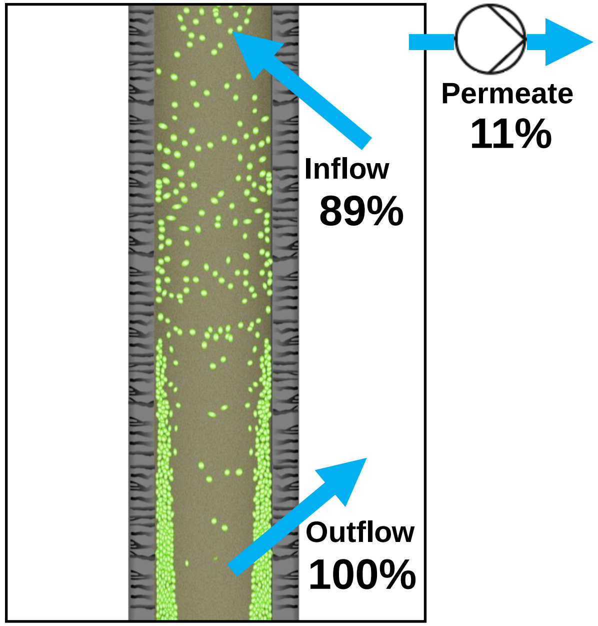
→ How large is this “unnecessary” flux across membrane?

Starling Flow Quantification

Feed Solution	Cross flow velocity ($m \cdot s^{-1}$)	Pressurized phase: Outflow ($ml \cdot min^{-1}$)	Inflow ($ml \cdot min^{-1}$)	Avg. Permeate flow rate ($ml \cdot min^{-1}$)
Water	0.11	0.077	0.056	0.021
	0.22	0.151	0.130	0.021
	0.70	0.190	0.170	0.021

Note. Outflow: permeate flow out of the lumen; inflow: permeate flow back into the lumen.

Radoniqi F, Zhang H, Bardliving CL, Shamlou P, Coffman J. Computational fluid dynamic modeling of alternating tangential flow filtration for perfusion cell culture. Biotechnology and Bioengineering**. 2018**;115: 2751–2759. https://doi.org/10.1002/bit.26813



Study summary:

- 20 cm hollow fiber filter used
- 0.7 m/s corresponds to 1000 s-1
- 2 L/m2/h permeate flux

→ 89% Inflow, only 11% Permeate

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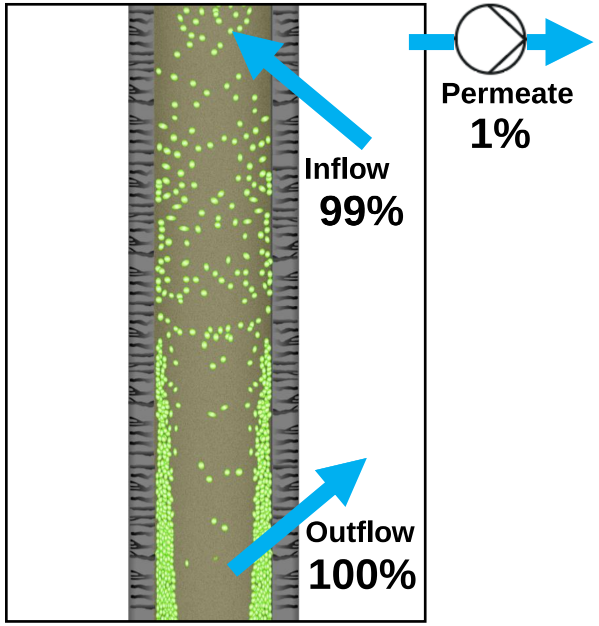

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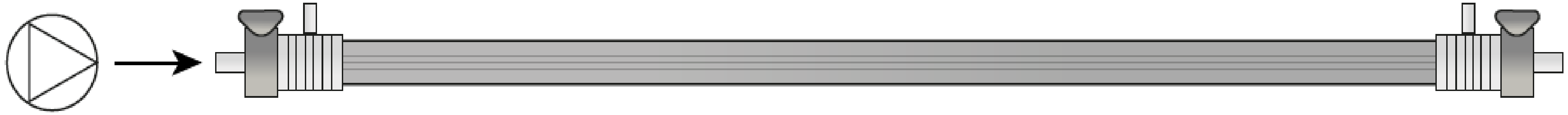
More common scenario:

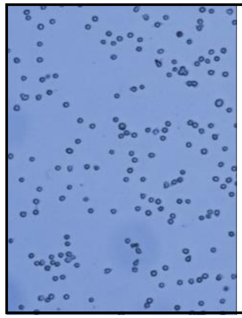
- 60+ cm hollow fiber filter
- 1000 - 2000 s-1

→ Permeate < 1-5%

→ **Starling Recirculation: 95 - 99%**

How to reduce Starling Recirculation?





Culture Viscosity:

- Increases pressure drop

→ **Reduce viscosity**

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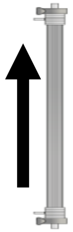

Crossflow Velocity:

- Increases pressure drop
- Limitation: restriction to low crossflows

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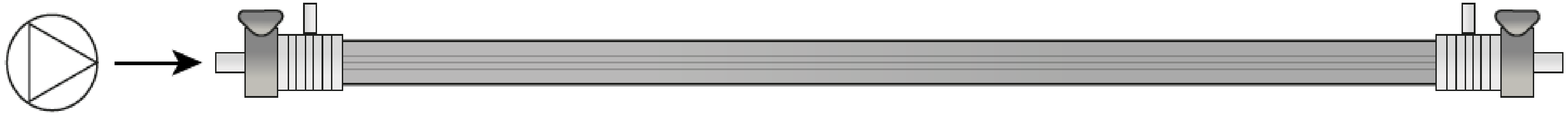

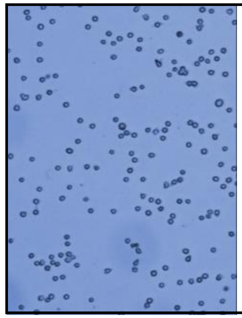

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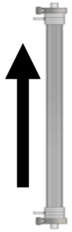

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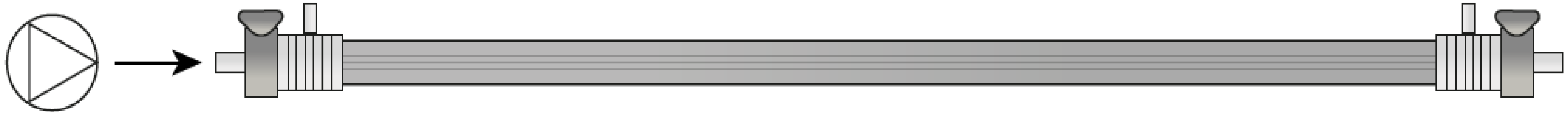

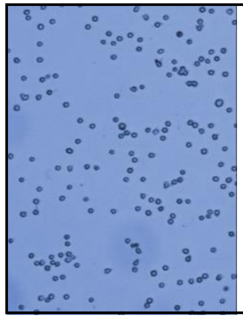

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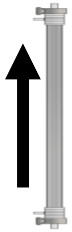

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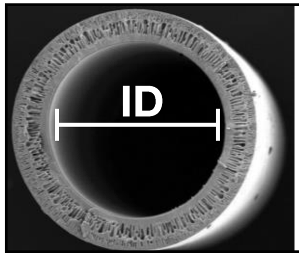
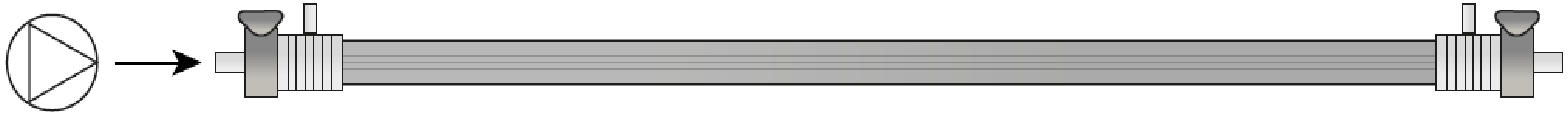
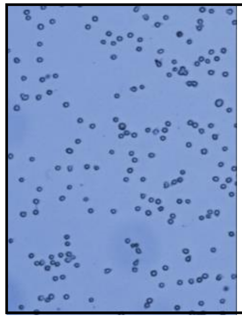


Fiber Lumen Diameter:

- Small diameters increase pressure drop
- Large diameters reduce membrane surface

→ **Increase lumen diameter**





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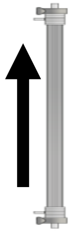

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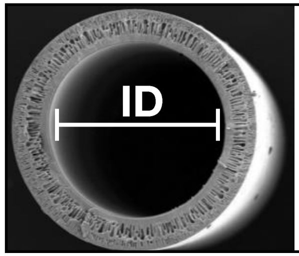

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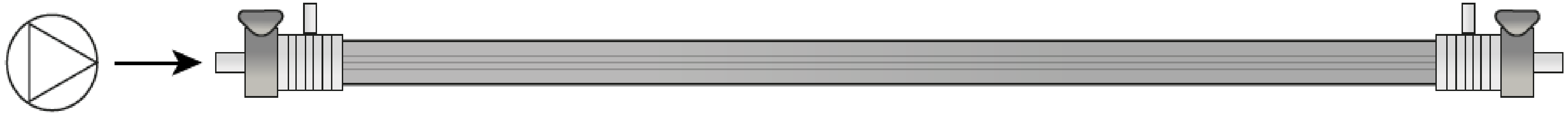

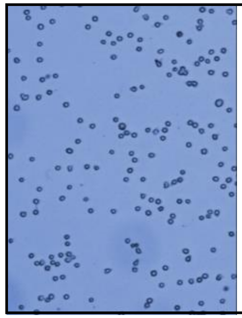

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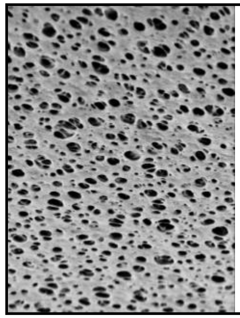


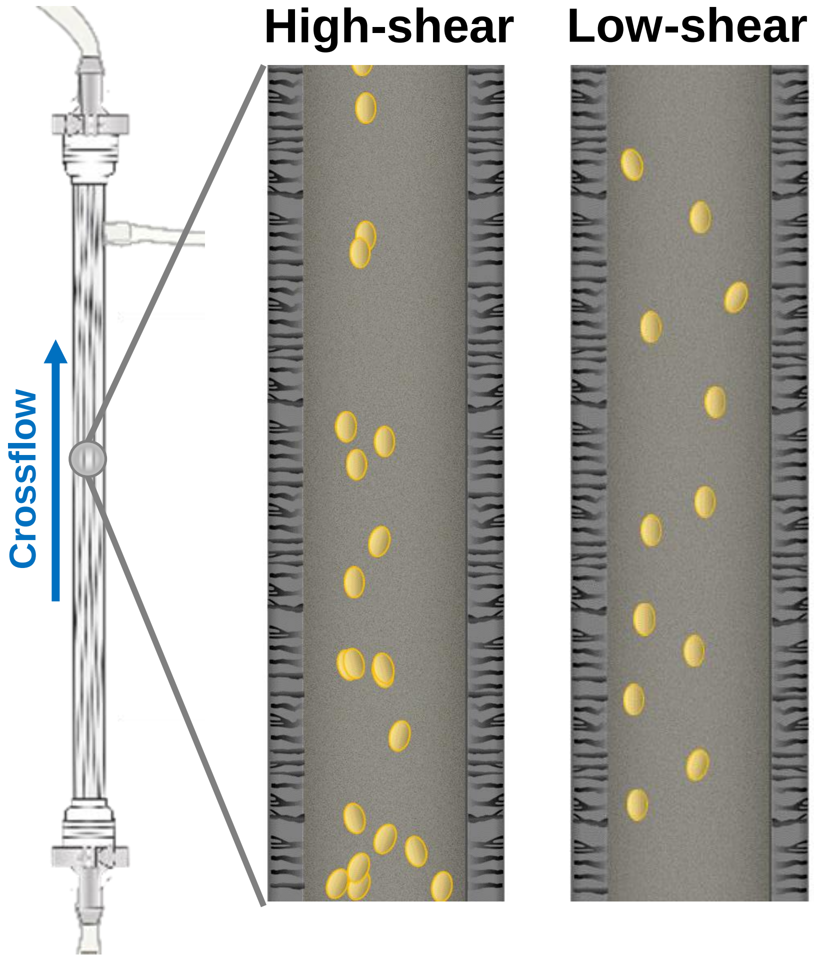
Membrane Pore Size:

- Larger pores reduce membrane resistance
- Increase in Starling flow

→ **Reduce pore size**

→ We are very restricted with changing the above factors

Crossflow: High vs. Low-shear TFF



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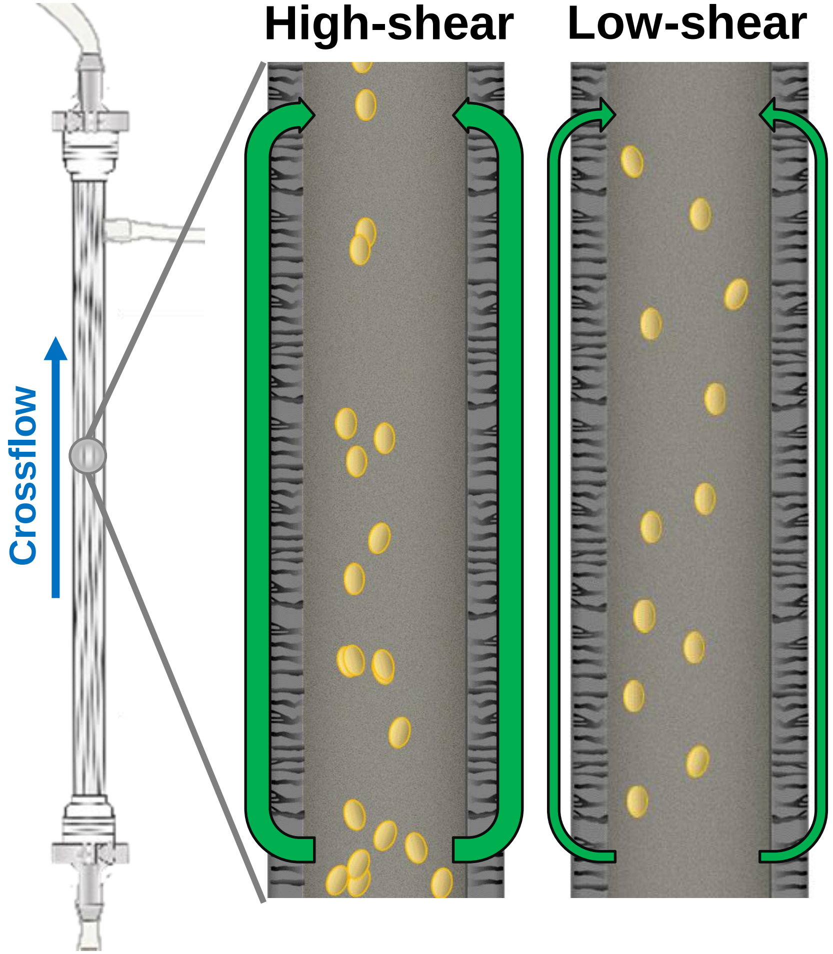

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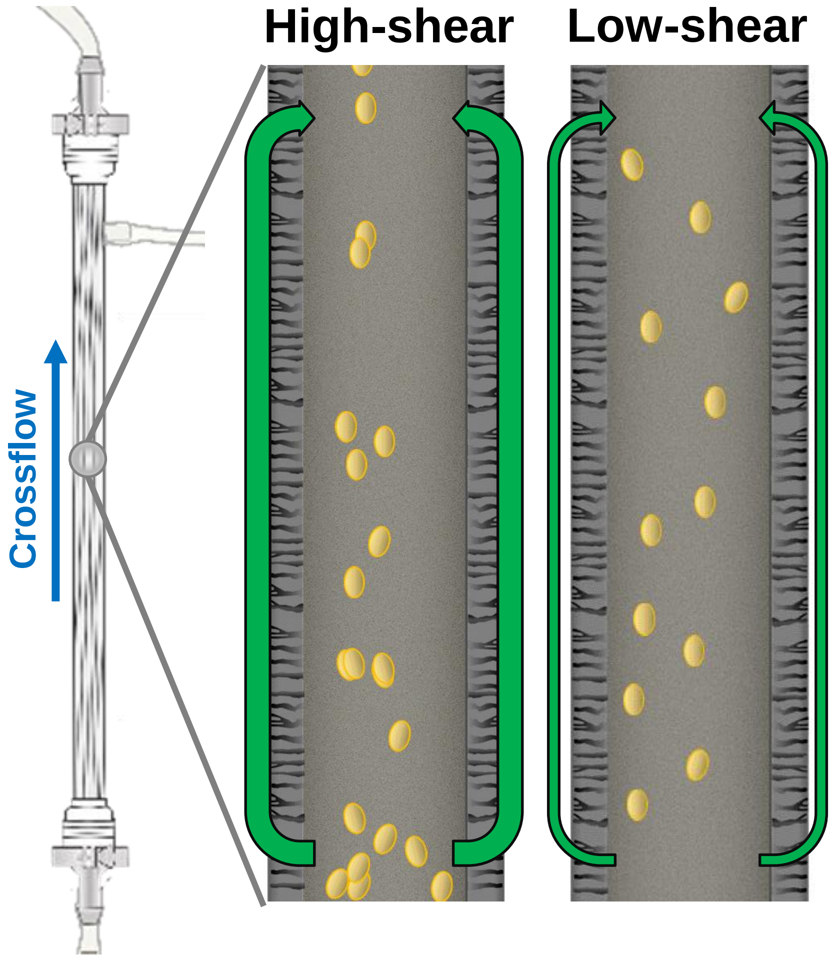
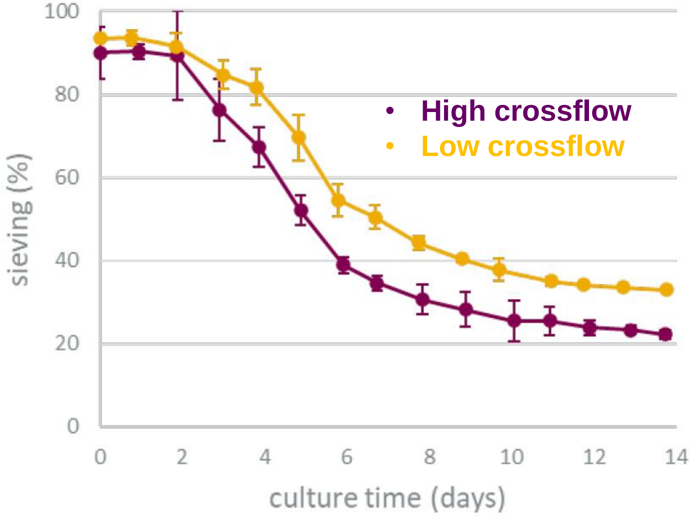
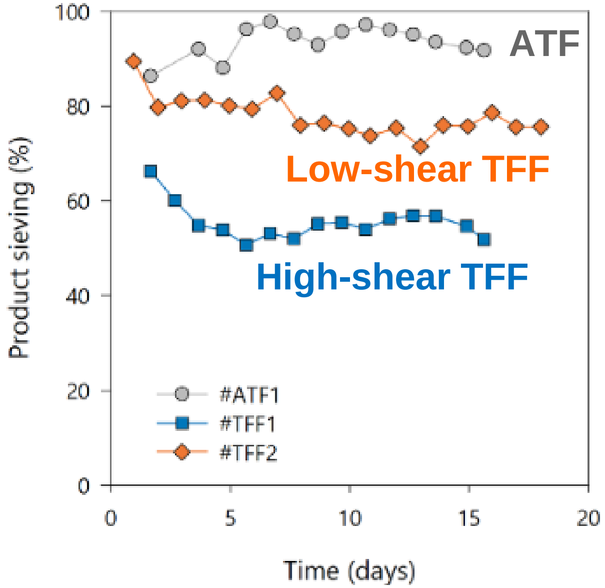




Reference: Kenneth Lee, "**Design considerations when scaling from 3-L to 3000-L or larger**" in "Integrated Continuous Biomanufacturing V", ECI Symposium Series, (2022). https://dc.engconfintl.org/biomanufact_v/74



Reference: Pappenreiter, M., Schwarz, H., Sissolak, B., Jungbauer, A., & Chotteau, V. (2023). **Product sieving of mAb and its high molecularweight species in different modes of ATFand TFF perfusion cell cultures.** Journal of Chemical Technology and Biotechnology, 1-15, https://doi.org/10.1002/jctb.7386

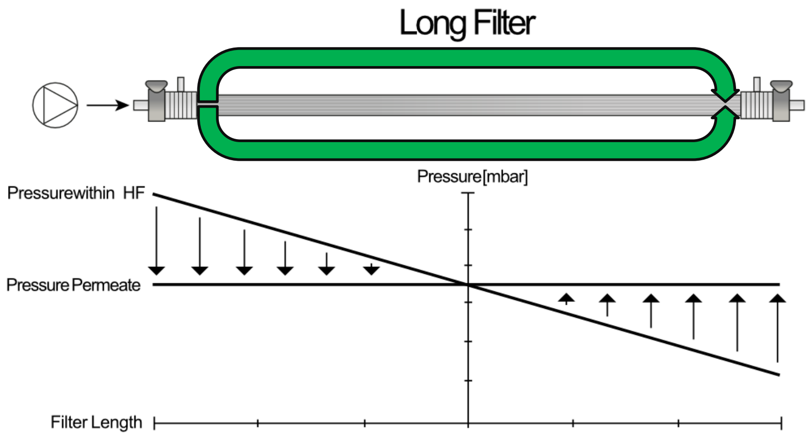
Summary:

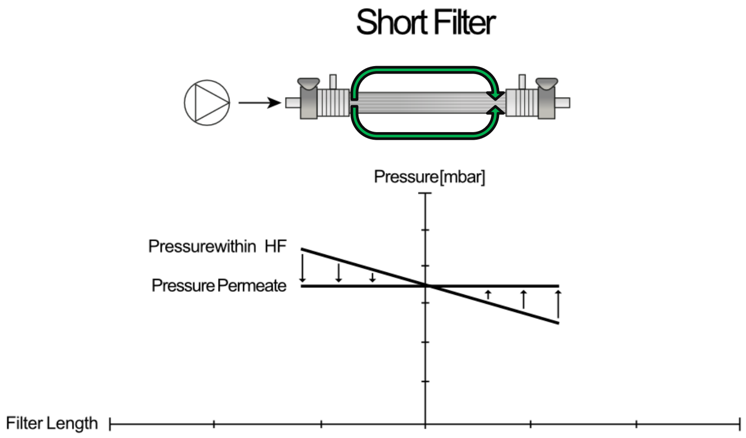
→ Low-shear outperforms high-shear in perfusion application

→ Magic number 2000 s-1 gets challenged

→ Shear rates < 1000 s-1 are getting of interest

Filter Length: Impact on TFF Performance





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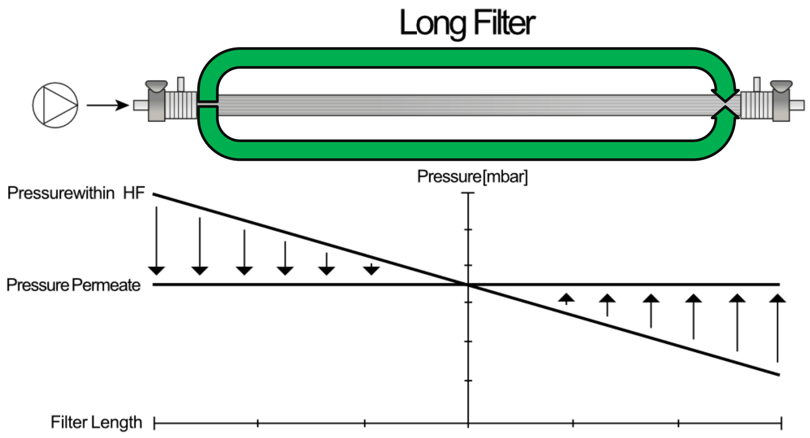

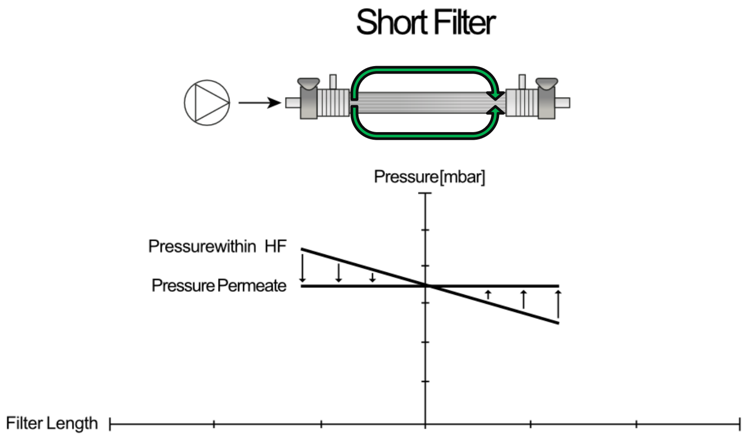

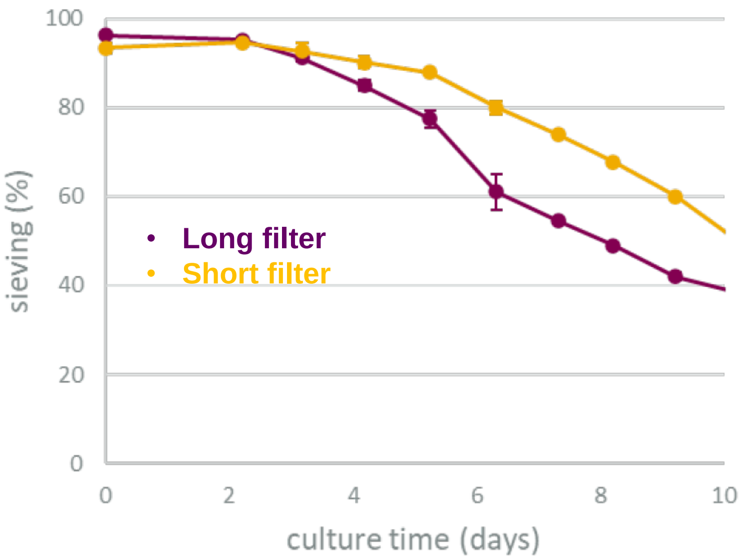

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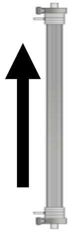
Summary:

→ Longer filter increases pressure drop (and Starling recirculation)

→ Long filter leads to reduced sieving

We should minimize Starling Recirculation in TFF



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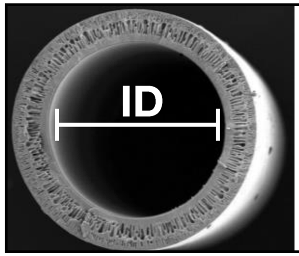
→ **Reduce Crossflow**



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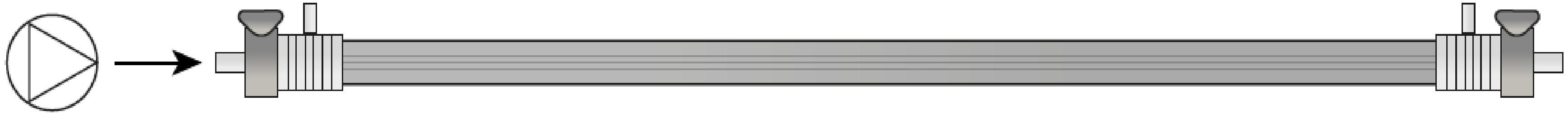
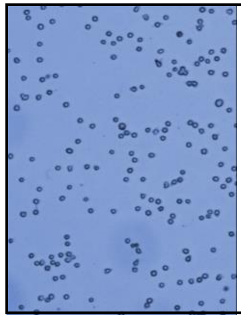




Culture Viscosity:

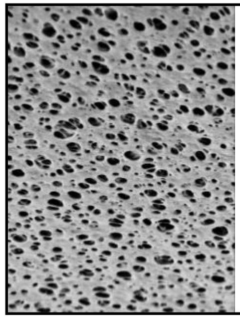
- Increases pressure drop

→ **Reduce viscosity**

Filter Length:

- Increases pressure drop
- Limitation: restriction to shorther filters / parallel setups

→ **Reduce filter length**



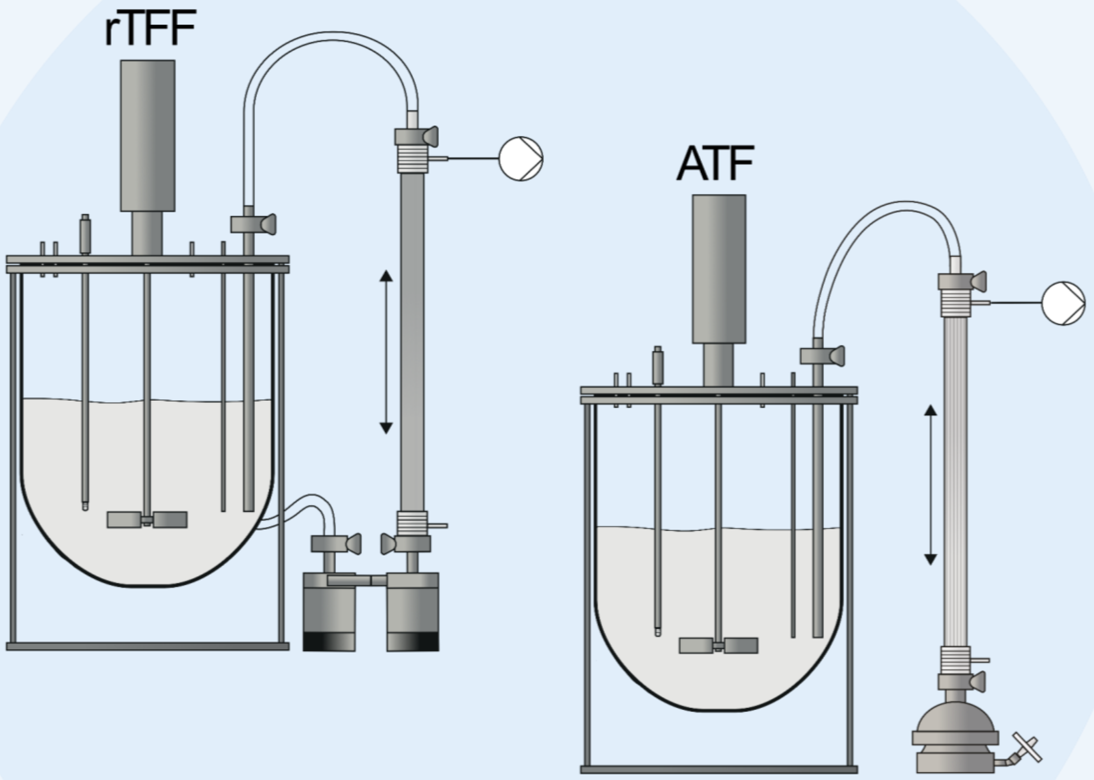
Membrane Pore Size:

- Larger pores reduce membrane resistance
- Increase in Starling flow

→ **Reduce pore size**

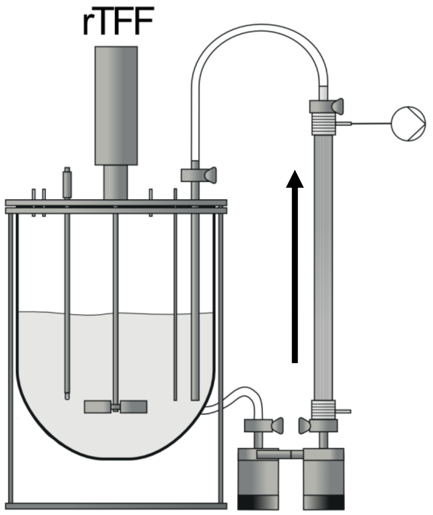
→ We are very restricted with changing the above factors

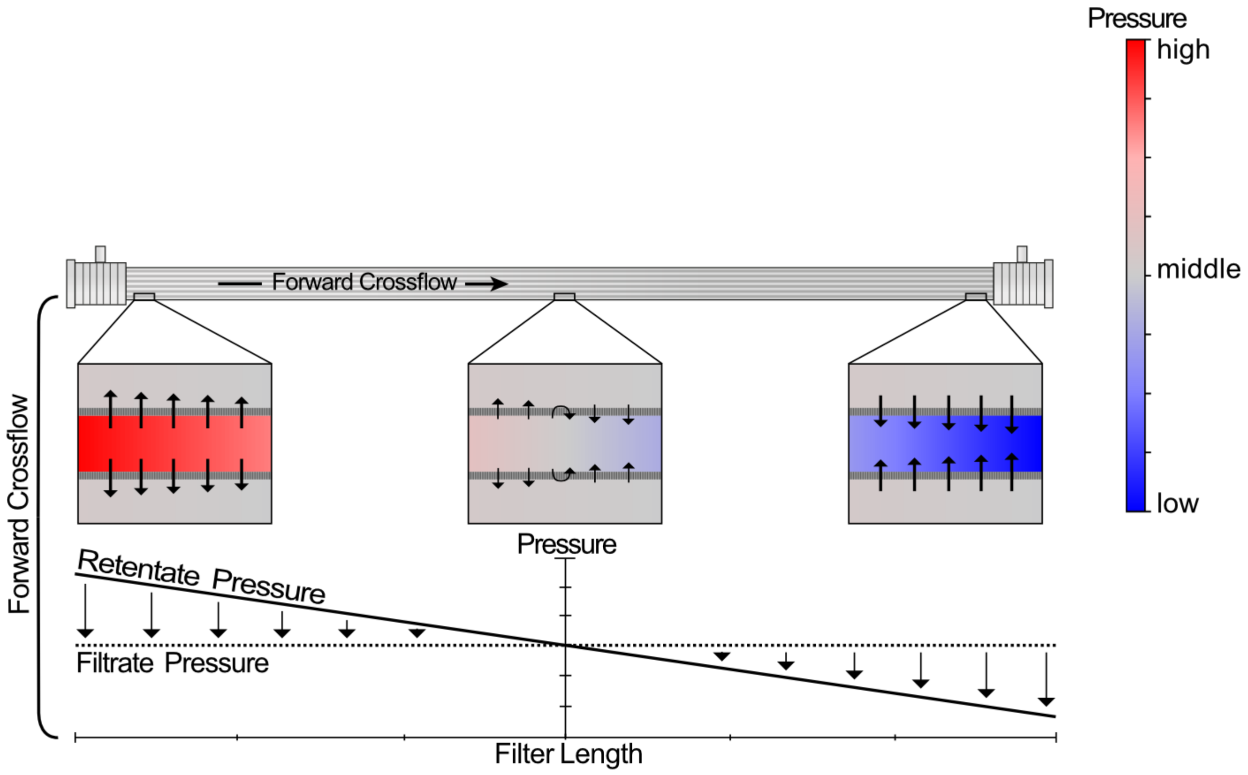
Alternating Tangential Flow Filtration



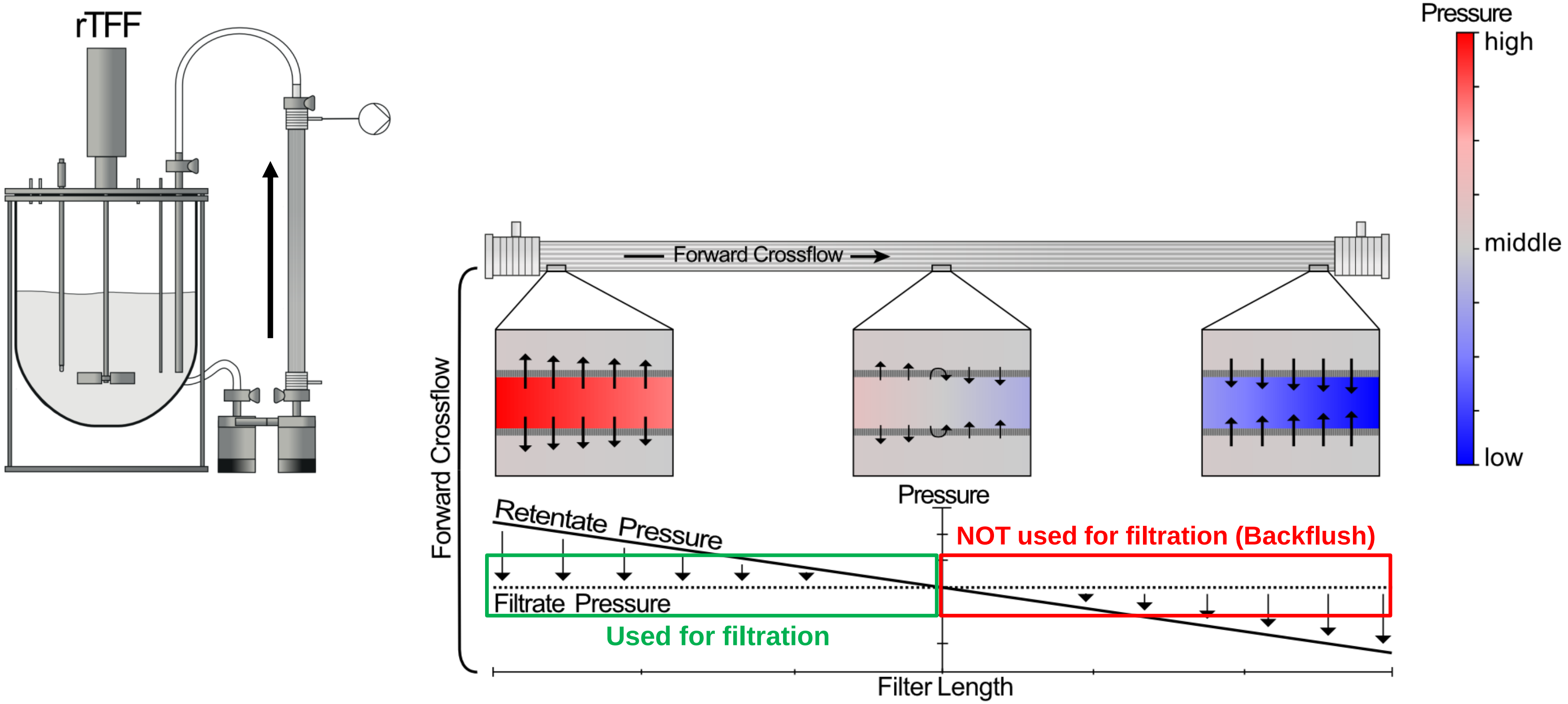
→ **Alternating crossflow (2 cycles)**

A closer Look at Pressure Profiles in ATF/rTFF

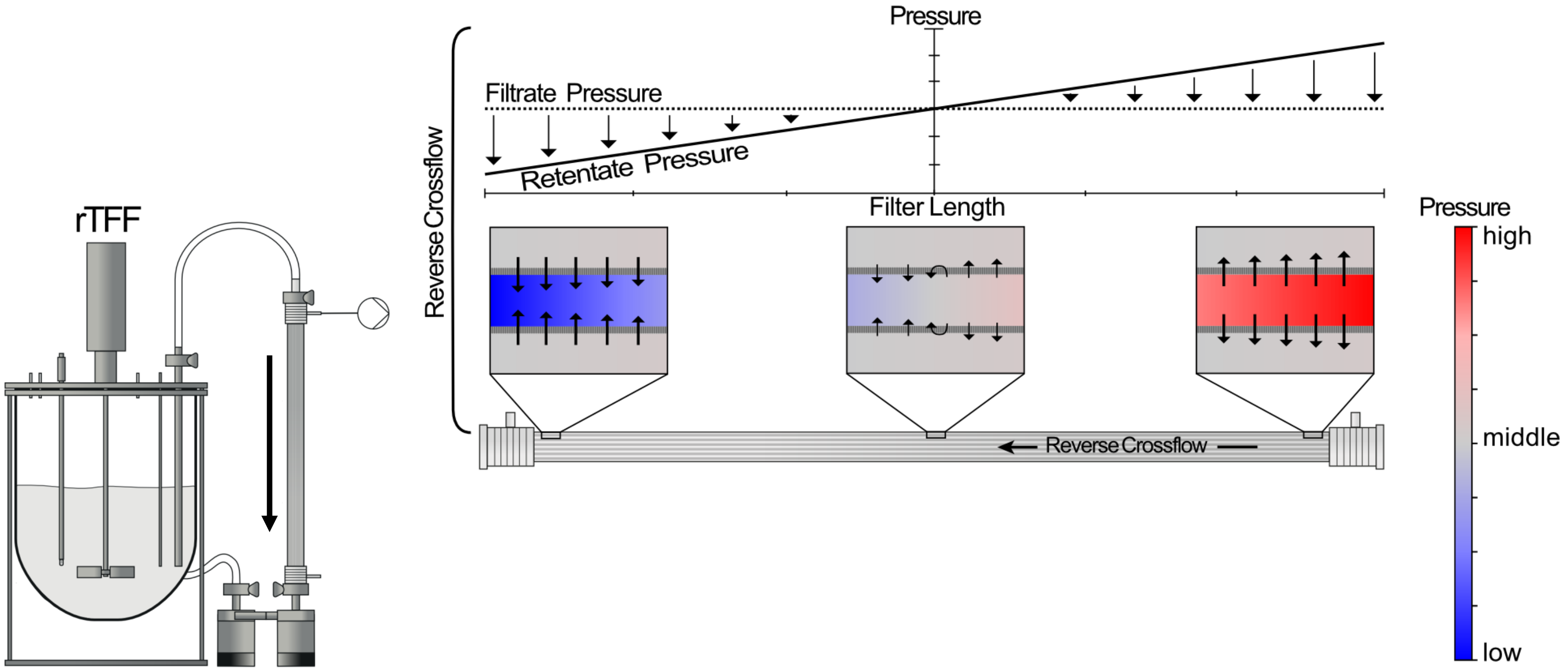




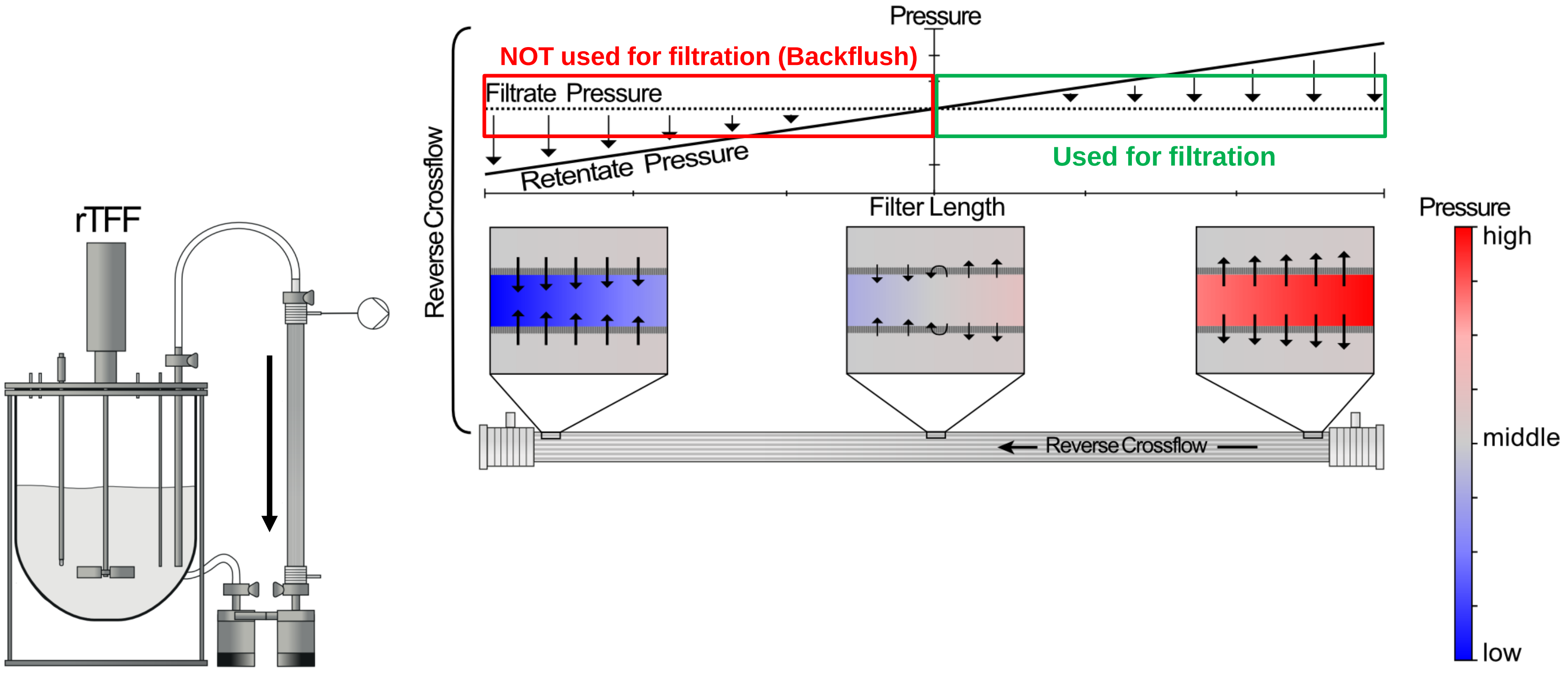
A closer Look at Pressure Profiles in ATF/rTFF



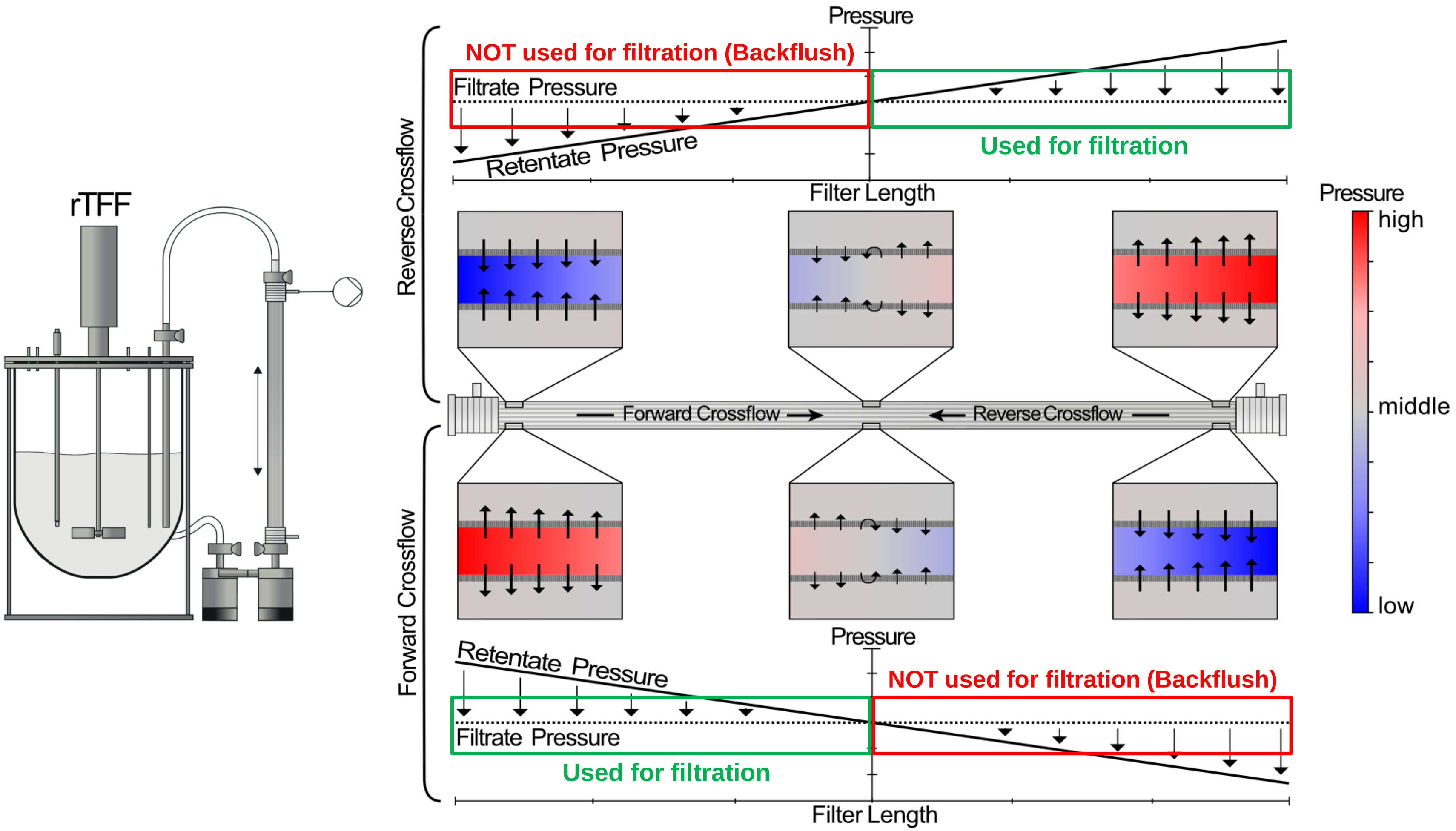
A closer Look at Pressure Profiles in ATF/rTFF



A closer Look at Pressure Profiles in ATF/rTFF



A closer Look at Pressure Profiles in ATF/rTFF



Similar to TFF:

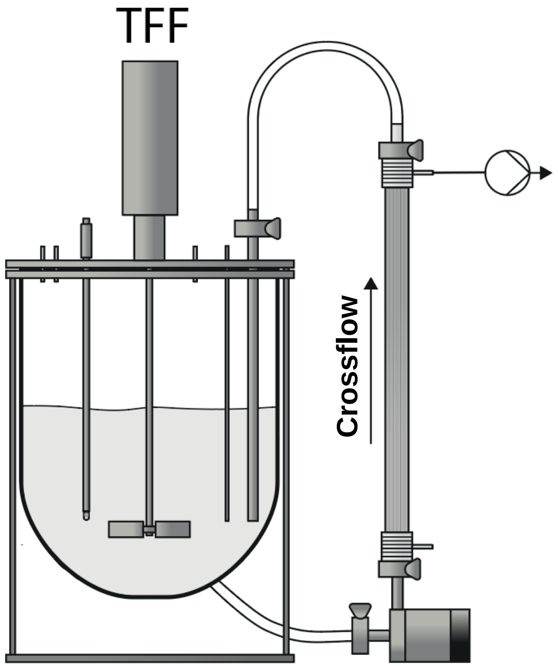
- Pressure drop along filter
- Starling Recirculation

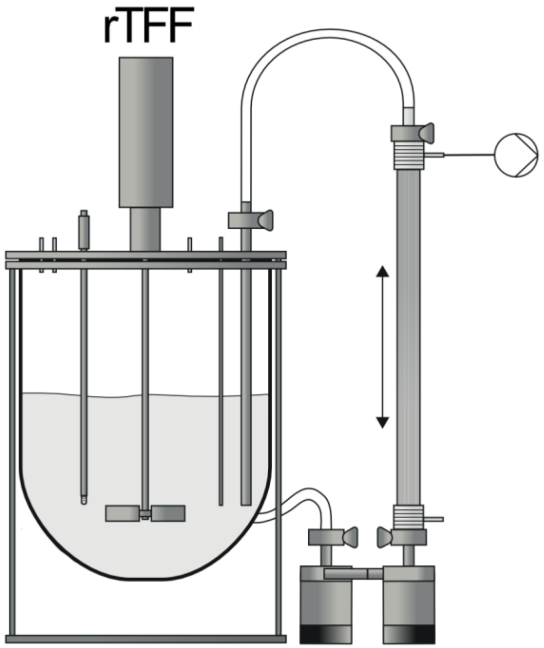
Difference to TFF:

- Alternating Crossflow
- Alternating Starling Recirculation (Backflush)

Steady-state Perfusion: TFF vs. rTFF

rTFF = reverse TFF





TFF:

- 1 pump
- Unidirectional flow

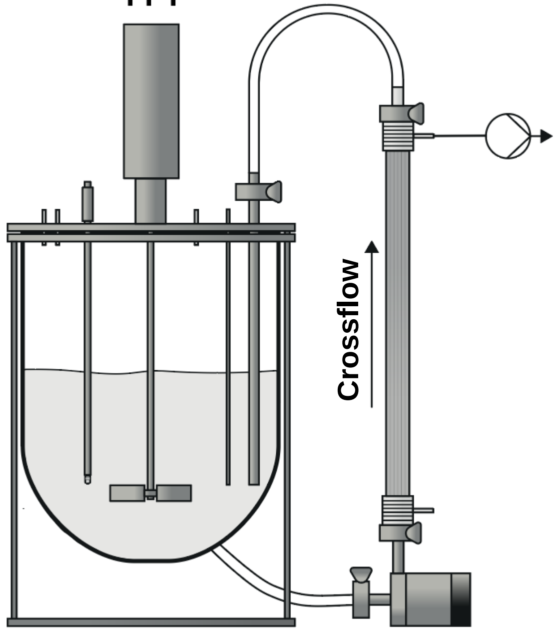
rTFF (basically ATF):

- 2 pumps
- Alternating flow

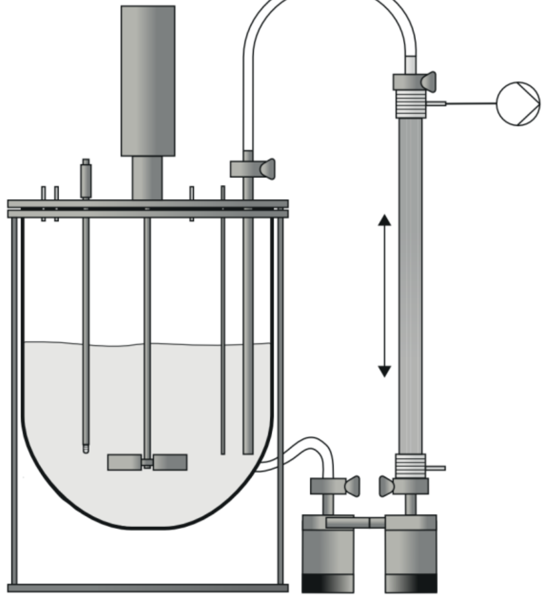
Steady-state Perfusion: TFF vs. rTFF

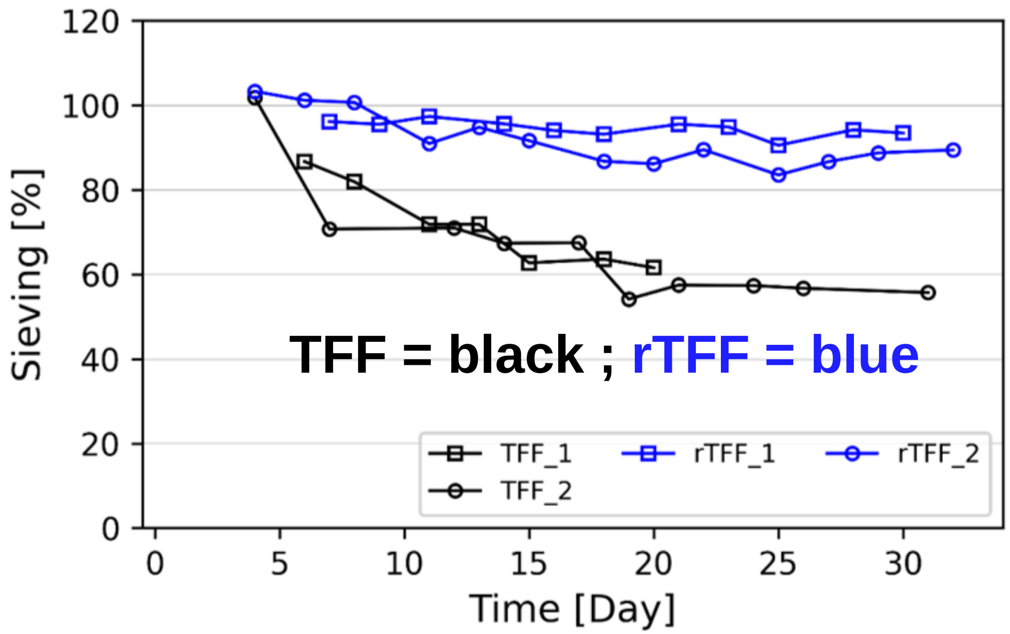
rTFF = reverse TFF

TFF



rTFF





TFF:

- 1 pump
- Unidirectional flow

rTFF (basically ATF):

- 2 pumps
- Alternating flow

Product Sieving:

- rTFF: Much higher product sieving

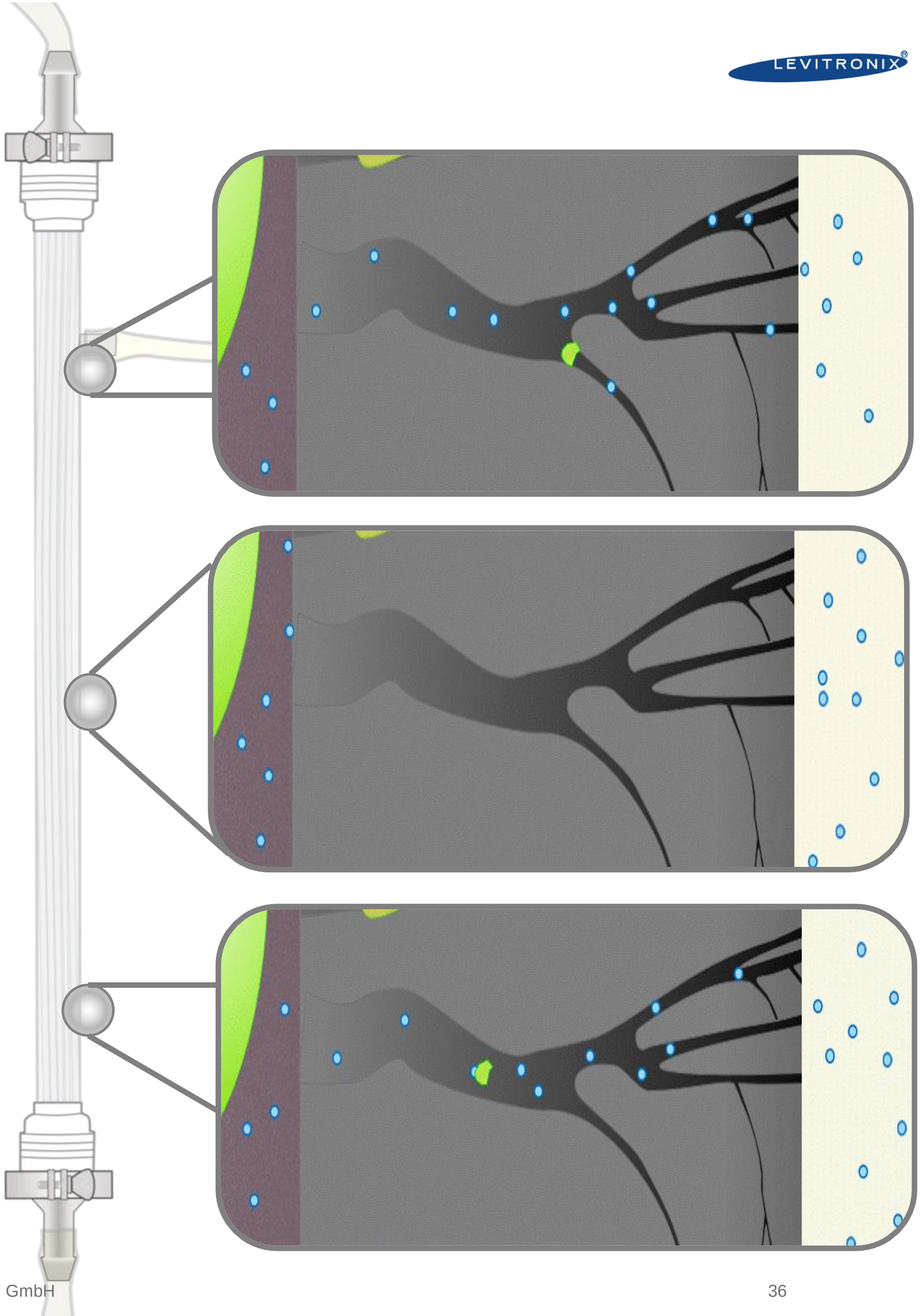
Reference: Romann, P., Giller, P., Sibilia, A., Herwig, C., Zydney, A. L., Perilleux, A., Souquet, J., Bielser, J.-M., & Villiger, T. K. (2023). **Co-current filtrate flow in TFF perfusion processes: Decoupling transmembrane pressure from crossflow to improve product sieving.** Biotechnology and Bioengineering, 1–15. https://doi.org/10.1002/bit.28589

Backflushing is not for free!

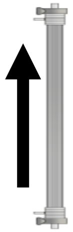
The price for backflushing:

- Everything that flows back must be filtered at the other filter side
- High filtration flux might cause pore blocking
- Controlling Starling Recirculation can be beneficial

→ Do we really need such a high Starling Recirculation (Backflush)?



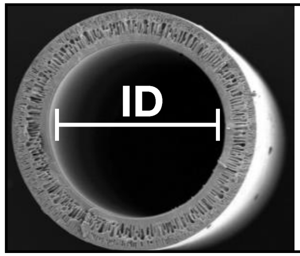
Should we also minimize Starling Recirculation in rTFF?



Crossflow Velocity:

- Increases pressure drop
- Limitation: restriction to low crossflows

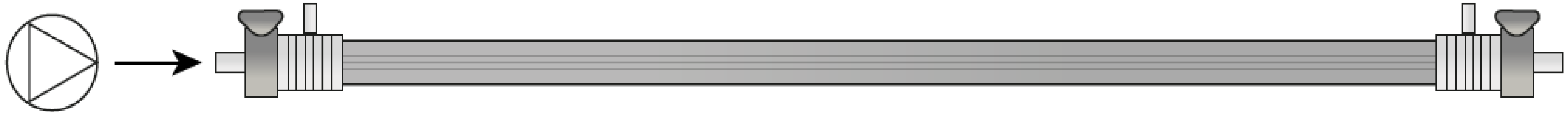
→ **Reduce Crossflow**

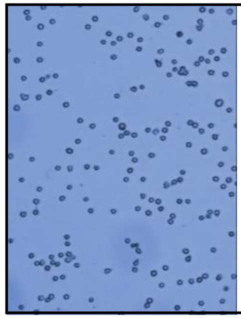


Fiber Lumen Diameter:

- Small diameters increase pressure drop
- Large diameters reduce membrane surface

→ **Increase lumen diameter**





Culture Viscosity:

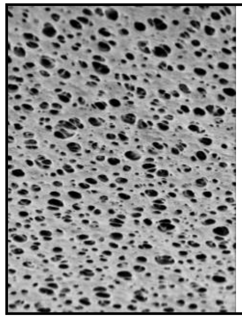
- Increases pressure drop

→ **Reduce viscosity**

Filter Length:

- Increases pressure drop
- Limitation: restriction to shorther filters / parallel setups

→ **Reduce filter length**



Membrane Pore Size:

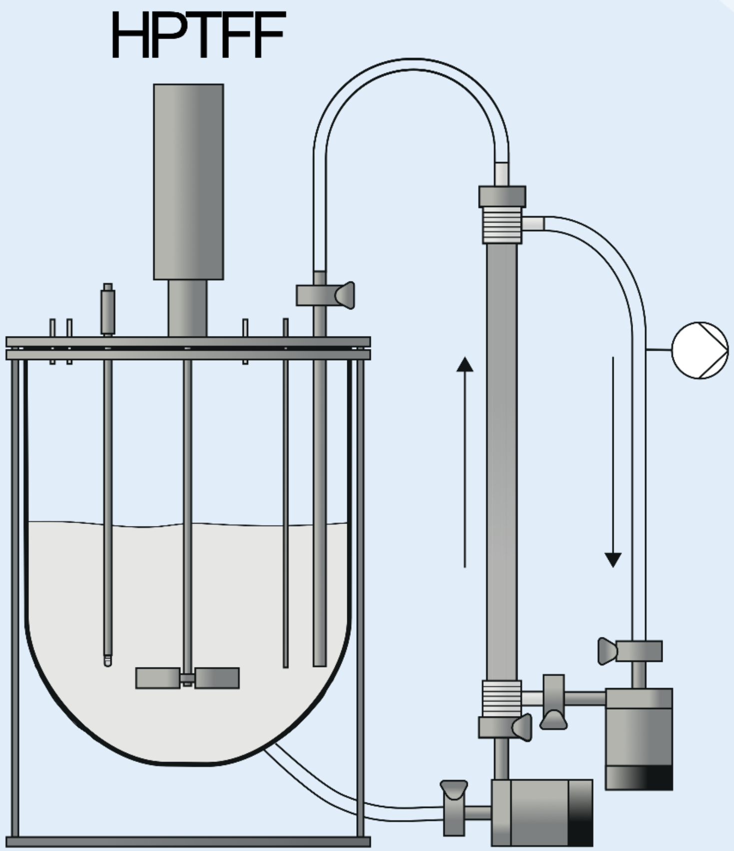
- Larger pores reduce membrane resistance
- Increase in Starling flow

→ **Reduce pore size**

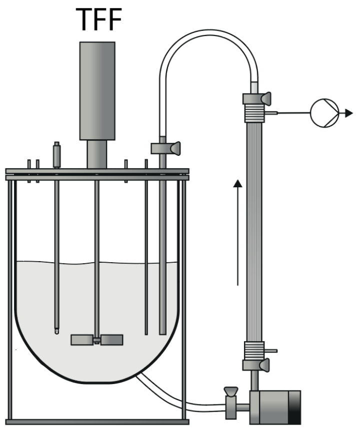
→ We are very restricted with changing the above factors

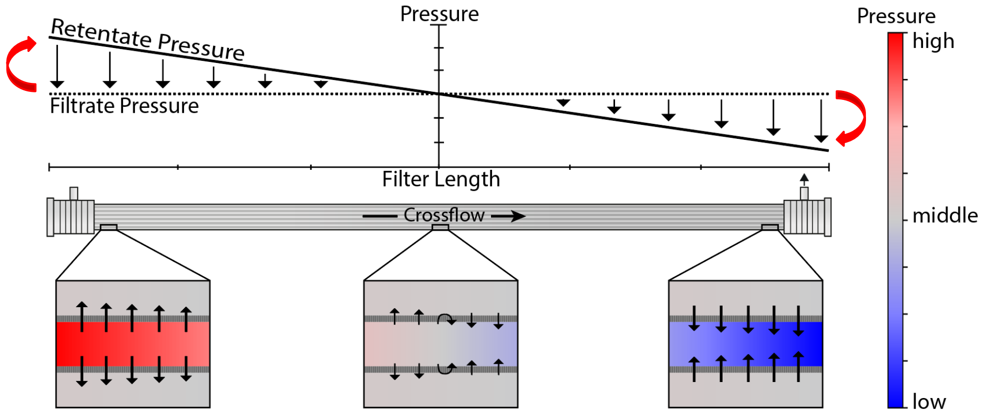
High-Performance TFF (HPTFF)

→ **Removing Starling Flow completely**



Removing Starling Recirculation





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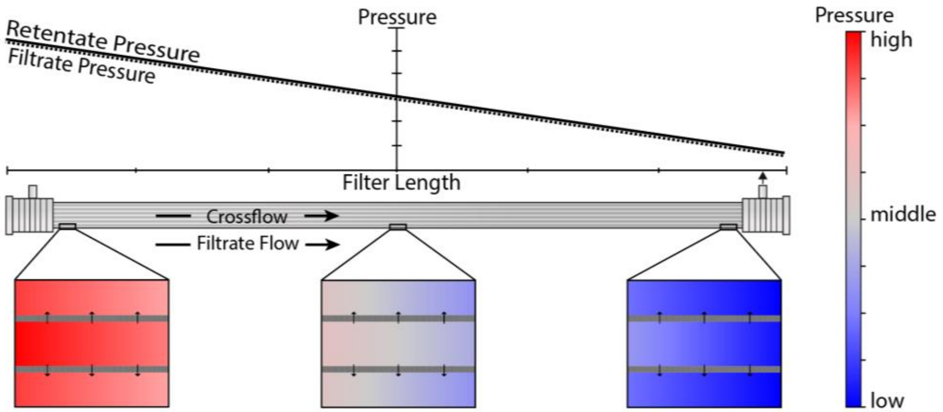


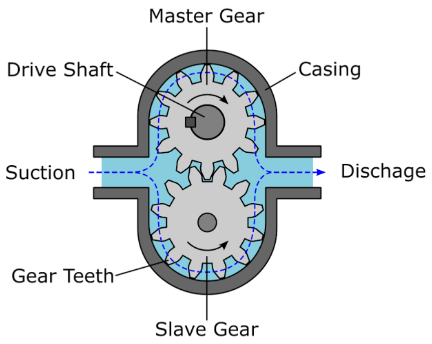
Idea:

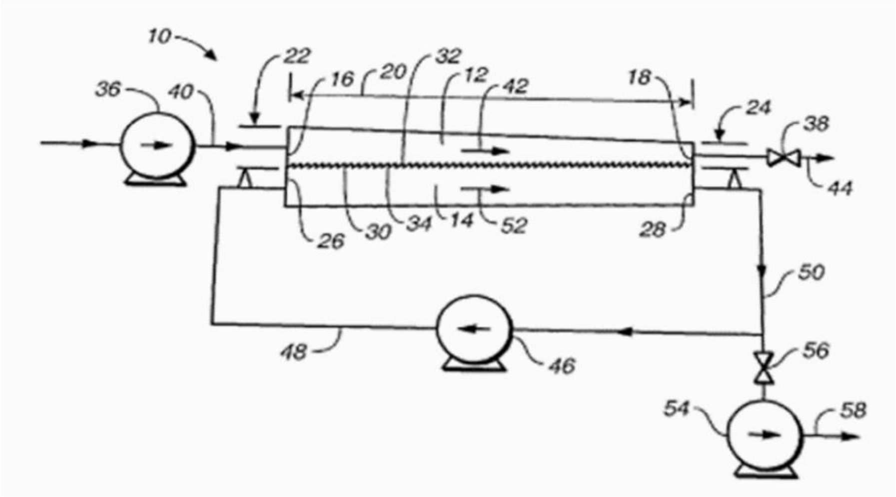
- Establish filtrate pressure gradient
- Match filtrate and retentate pressure
- Eliminate Starling Recirculation

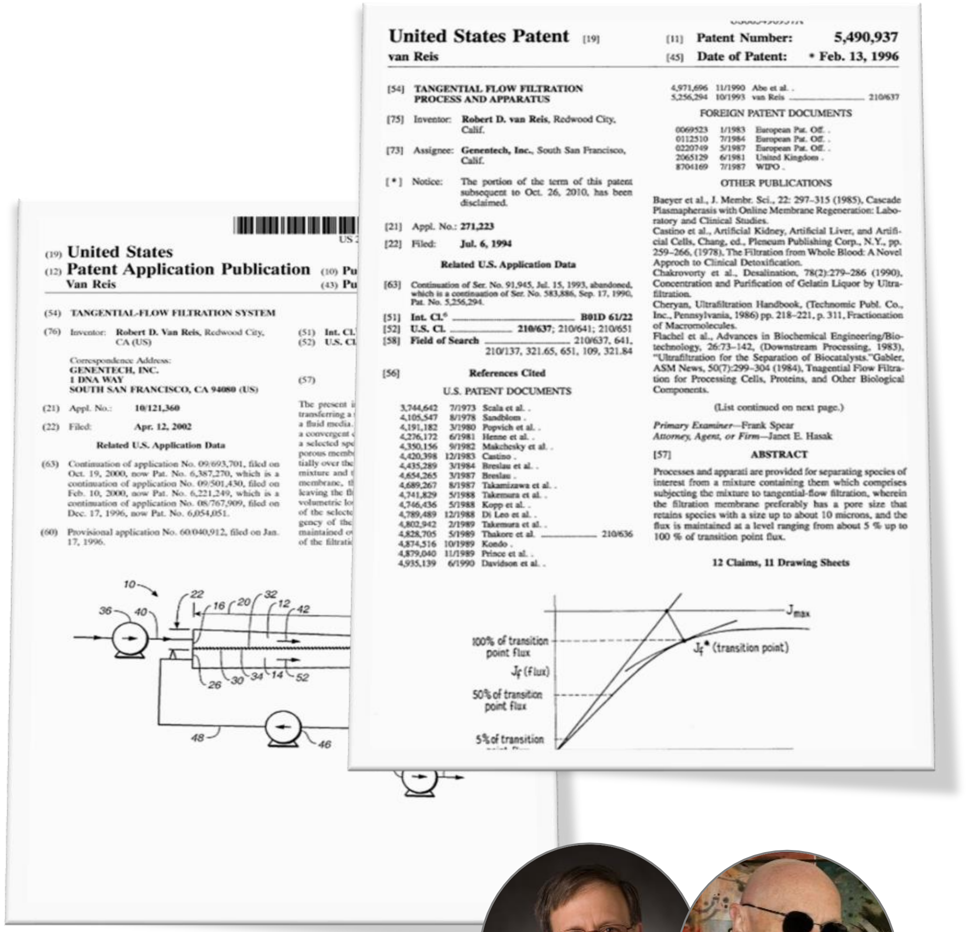
HPTFF, a Sleeping Beauty

Patents 5,490,937 & US 2002/0108907

- 1996 patented for DSP
- Idea to create uniform TMP
- Goal to separate proteins by size
- Realized with gear pumps







(19) United States
(12) Patent Application Publication
Van Reis

(54) TANGENTIAL-FLOW FILTRATION SYSTEM

(76) Inventor: Robert D. Van Reis, Redwood City, CA (US)

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SOUTH SAN FRANCISCO, CA 94080 (US)

(21) Appl. No.: 10/121,360

(22) Filed: Apr. 12, 2002

Related U.S. Application Data

(63) Continuation of application No. 09/693,701, filed on Oct. 19, 2000, now Pat. No. 6,387,270, which is a continuation of application No. 09/501,430, filed on Feb. 10, 2000, now Pat. No. 6,221,249, which is a continuation of application No. 08/767,909, filed on Dec. 17, 1996, now Pat. No. 6,054,051.

(60) Provisional application No. 60/040,912, filed on Jan. 17, 1996.

United States Patent [19]
van Reis

[11] Patent Number: 5,490,937
[45] Date of Patent: * Feb. 13, 1996

[54] TANGENTIAL FLOW FILTRATION PROCESS AND APPARATUS

[75] Inventor: Robert D. van Reis, Redwood City, Calif.

[73] Assignee: Genentech, Inc., South San Francisco, Calif.

[*] Notice: The portion of the term of this patent subsequent to Oct. 26, 2010, has been disclaimed.

[21] Appl. No.: 271,223

[22] Filed: Jul. 6, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 91,945, Jul. 15, 1993, abandoned, which is a continuation of Ser. No. 583,886, Sep. 17, 1990, Pat. No. 5,256,294.

[51] Int. Cl.[6] B01D 61/22
[52] U.S. Cl. 210/637; 210/641; 210/651
[58] Field of Search 210/637, 641, 210/137, 321.65, 651, 109, 321.84

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Chakrovorty et al., Desalination, 78(2):279–286 (1990), Concentration and Purification of Gelatin Liquor by Ultrafiltration.
Cheryan, Ultrafiltration Handbook, (Technomic Publ. Co., Inc., Pennsylvania, 1986) pp. 218–221, p. 311, Fractionation of Macromolecules.
Flachel et al., Advances in Biochemical Engineering/Biotechnology, 26:73–142, (Downstream Processing, 1983), "Ultrafiltration for the Separation of Biocatalysts."Gabler, ASM News, 50(7):299–304 (1984), Tnagential Flow Filtration for Processing Cells, Proteins, and Other Biological Components.

(List continued on next page.)

Primary Examiner—Frank Spear
Attorney, Agent, or Firm—Janet E. Hasak

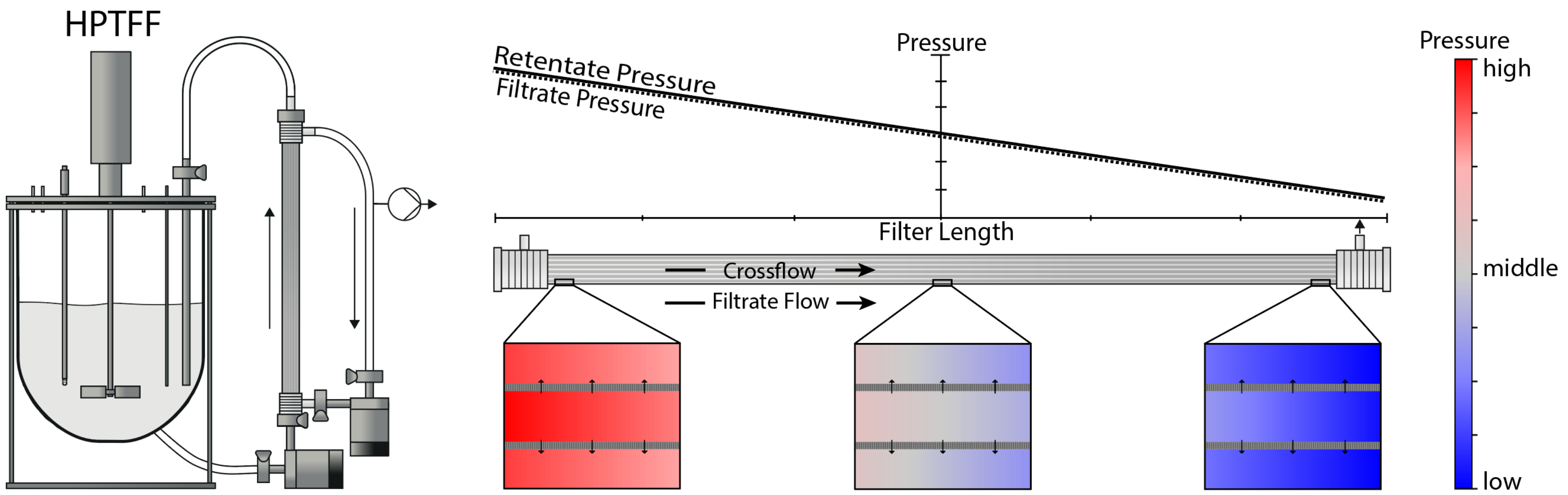
[57] ABSTRACT

Processes and apparati are provided for separating species of interest from a mixture containing them which comprises subjecting the mixture to tangential-flow filtration, wherein the filtration membrane preferably has a pore size that retains species with a size up to about 10 microns, and the flux is maintained at a level ranging from about 5 % up to 100 % of transition point flux.

12 Claims, 11 Drawing Sheets

Source1: https://worldwide.espacenet.com/patent/search/family/024334996/publication/US5490937A?q=pn%3DLV11283A
Source 2: https://worldwide.espacenet.com/patent/search/family/026717592/publication/US2002108907A1?q=pn%3DUS2002108907A1
Source 3: https://marinerspointpro.com/gear-pump-working-types-constructions-parts-applications/

High-Performance TFF (HPTFF)

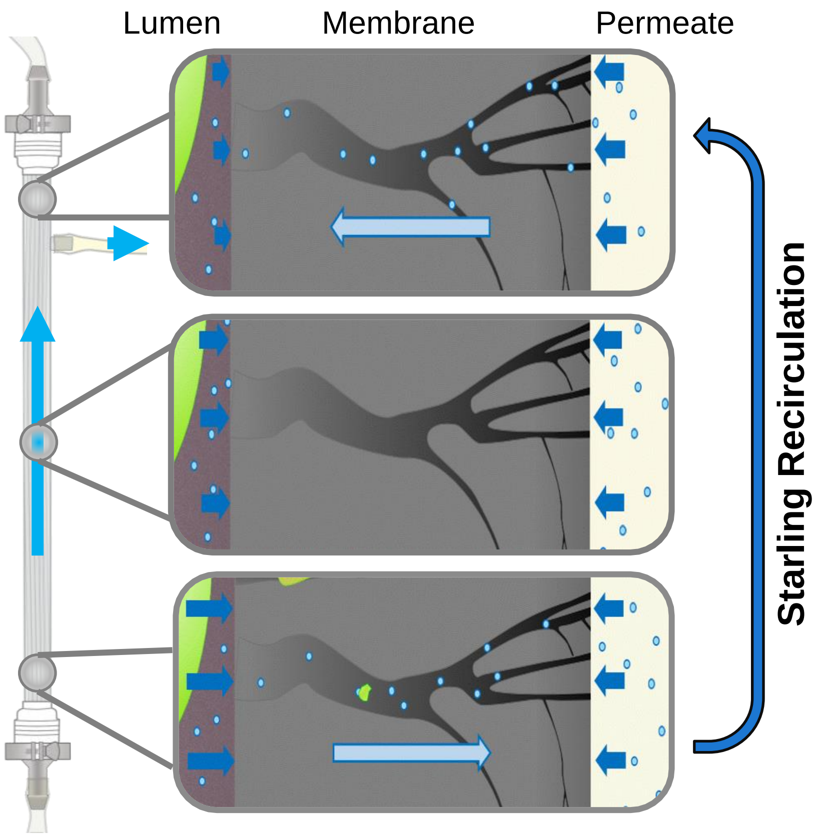


- Co-current filtrate flow (centrifugal pump)
- Pressure drop on filtrate side
- No TMP across entire membrane (almost)

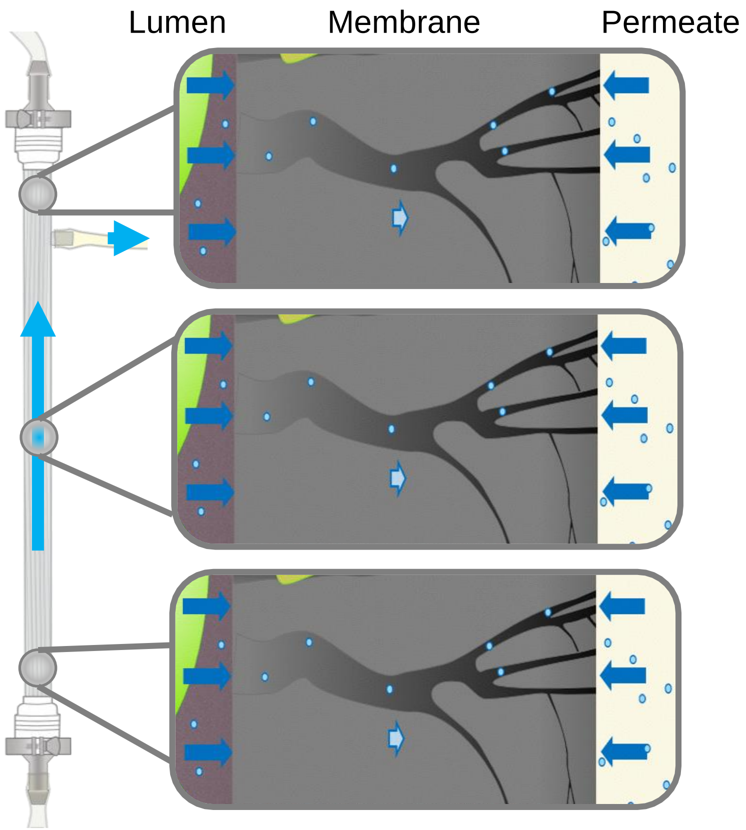
→ **No Starling Recirculation**

Removing Starling Recirculation

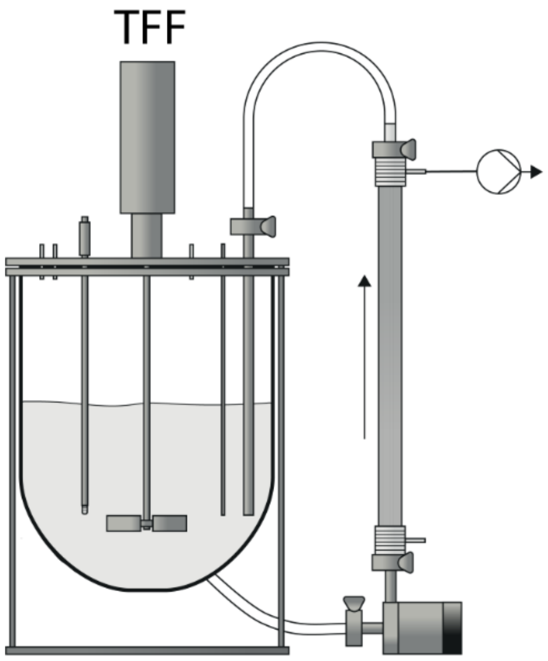
TFF

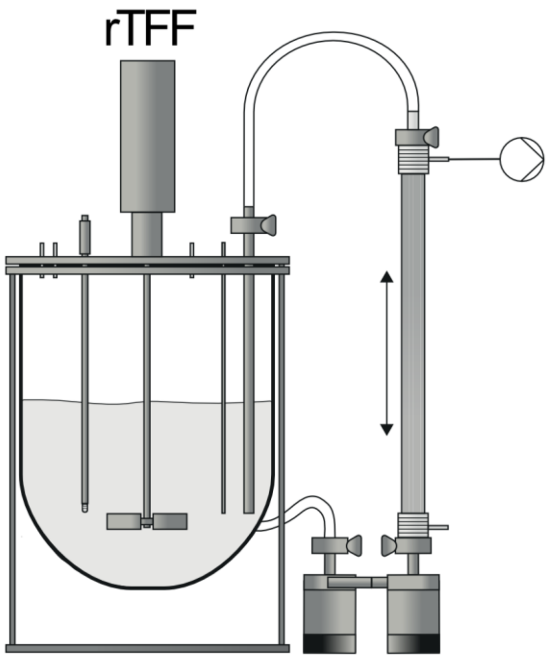


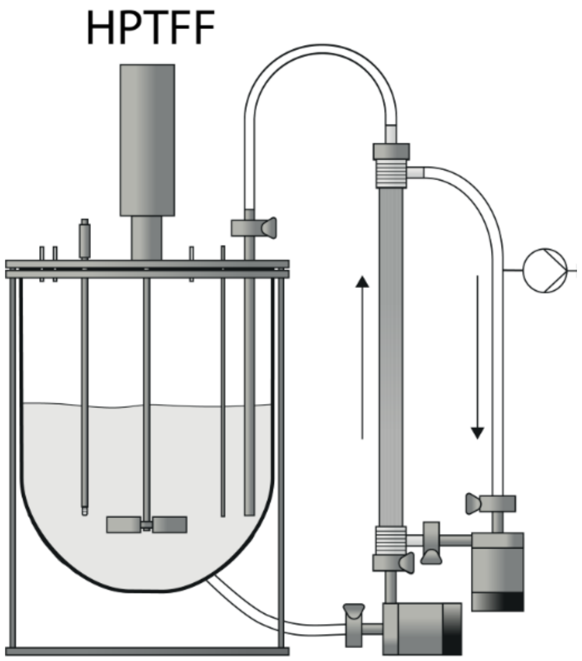
HPTFF



SS Perfusion: TFF vs. rTFF vs. HPTFF







TFF:

- 1 pump
- Unidirectional flow

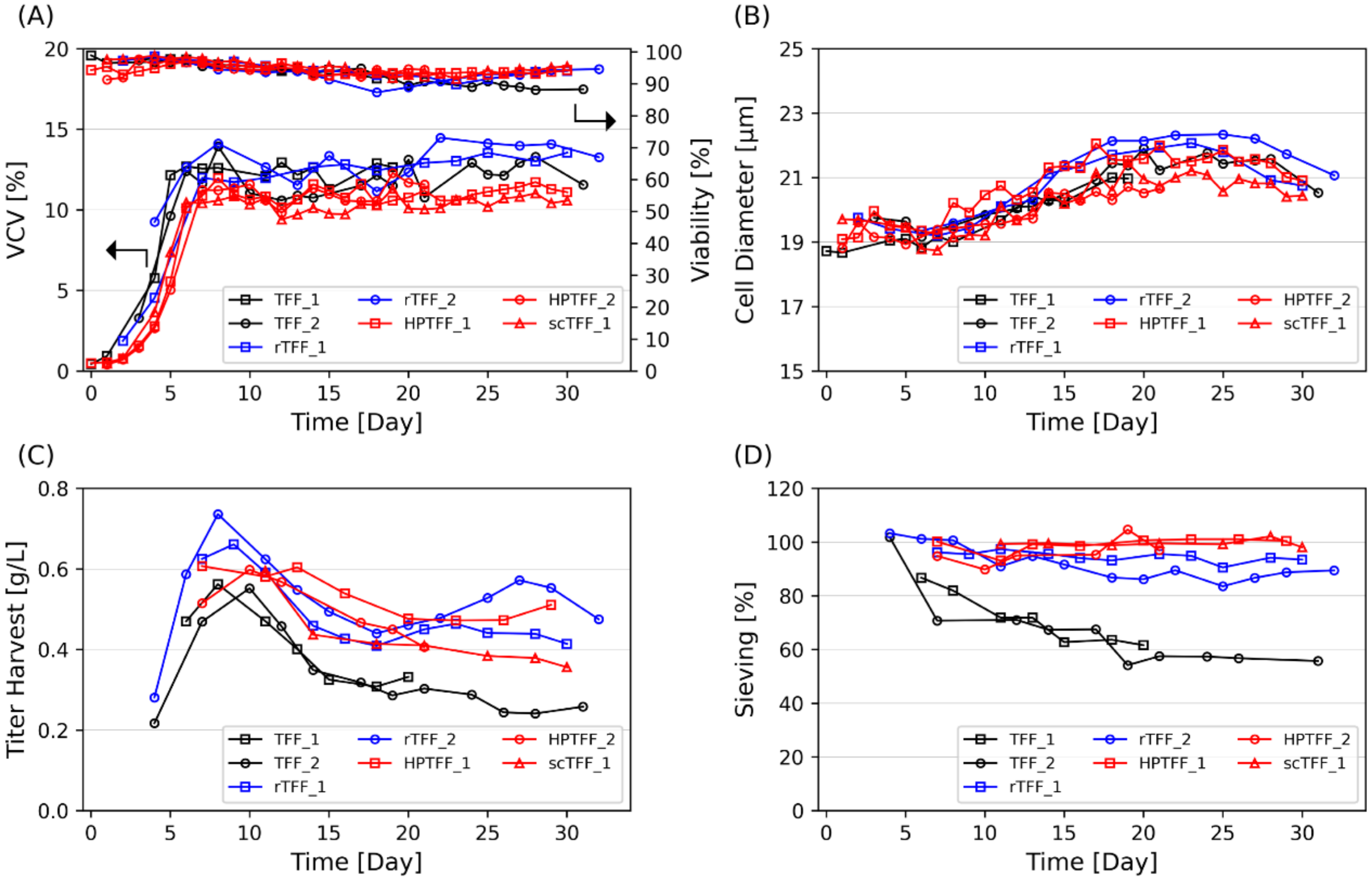
rTFF (basically ATF):

- 2 pumps
- Alternating flow

HPTFF

- 2 pumps (Co-current filtrate flow)
- Unidirectional flow
- No Starling Recirculation

Case-Study: Steady-state Perfusion



TFF = black

rTFF = blue

HPTFF = red

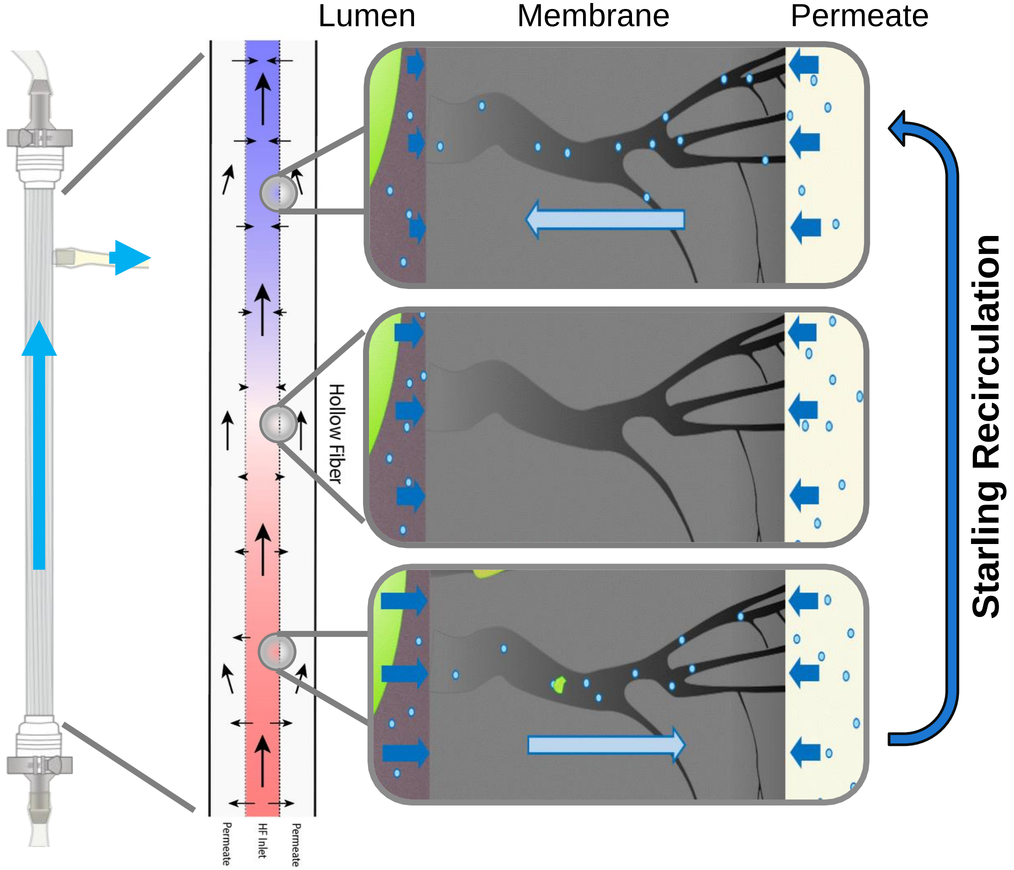
Results HPTFF:

- Better Sieving than TFF and rTFF

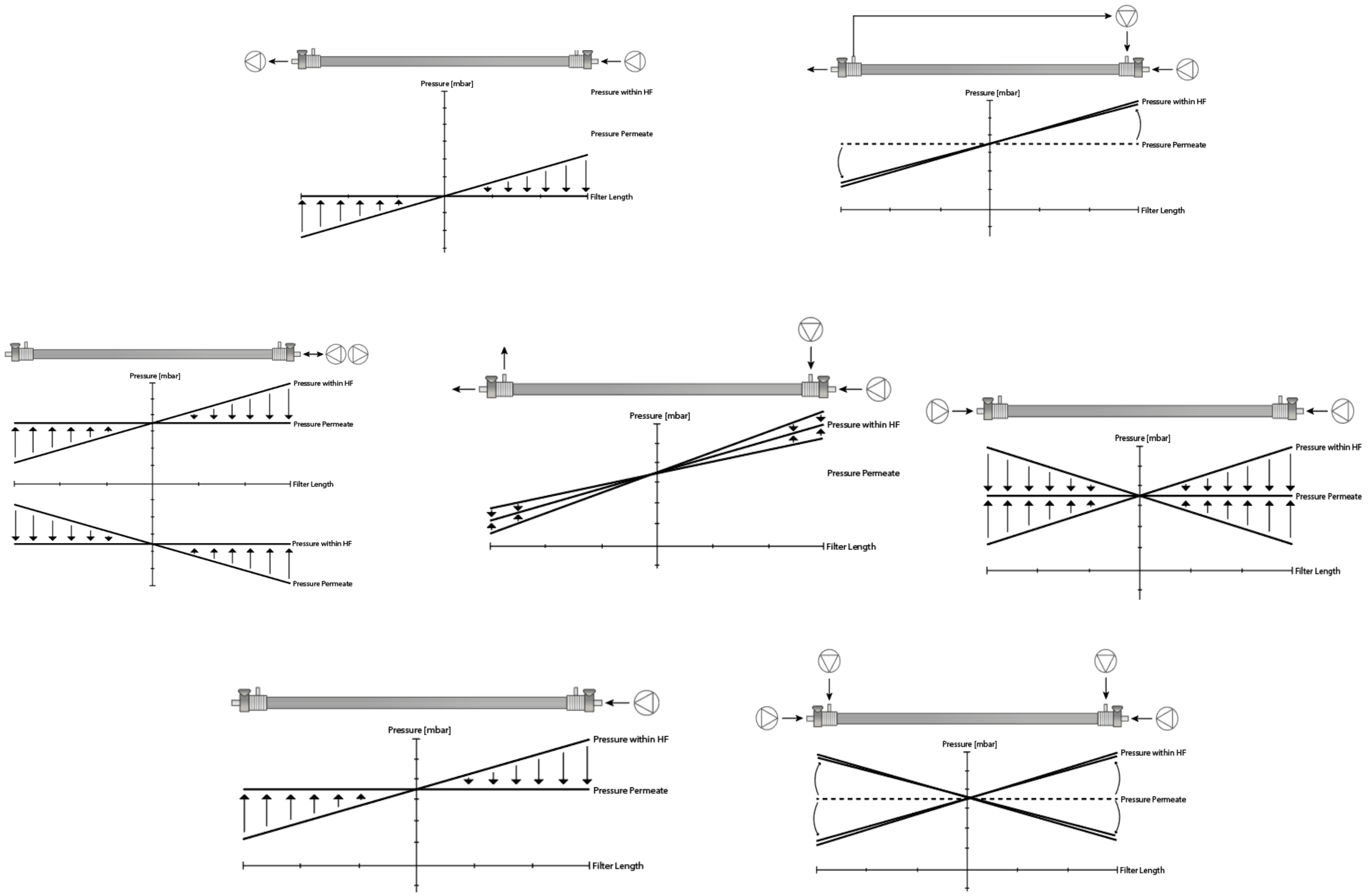
Reference: Romann, P., Giller, P., Sibilia, A., Herwig, C., Zydney, A. L., Perilleux, A., Souquet, J., Bielser, J.-M., & Villiger, T. K. (2023). **Co-current filtrate flow in TFF perfusion processes: Decoupling transmembrane pressure from crossflow to improve product sieving.** Biotechnology and Bioengineering, 1–15. https://doi.org/10.1002/bit.28589

Conclusion

- Starling Recirculation is a consequence of pressure drop
- Intensity of Starling Recirculation strongly influences filtration performance
- Solutions to Sieving Challenge:
  - Option 1: **Reducing** Starling Recirculation (TFF/rTFF)
  - Option 2: **Eliminating** Starling Recirculation (HPTFF)



Outlook



and many more …

Acknowledgements

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- Loic Chappuis
- Alexandre Chatelin
- Arnaud Périlleux, Dr. Jonathan Souquet
- BTI and Analytics Team

Levitronix

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- Lorenz Schüssler
- Philipp Campos
- Knut Kuss

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- Prof. Dr. Oliver Spadiut
- Prof. Dr. Christoph Herwig

External Support

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- Dominik Schiemann (Novartis)

Q&A

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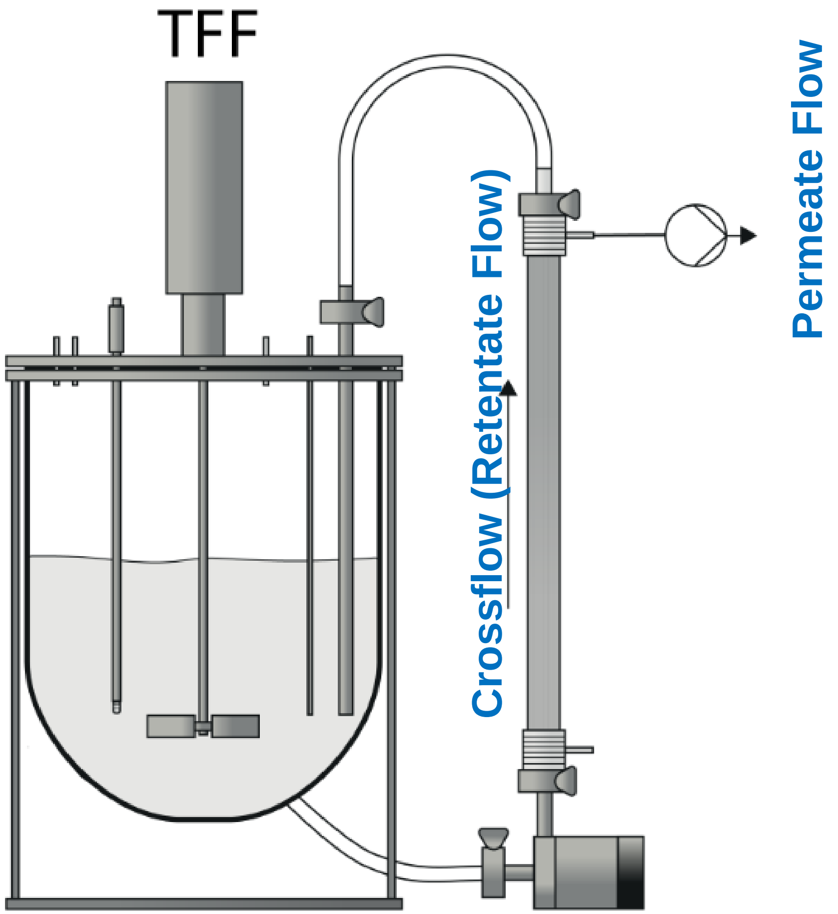
Additional Information

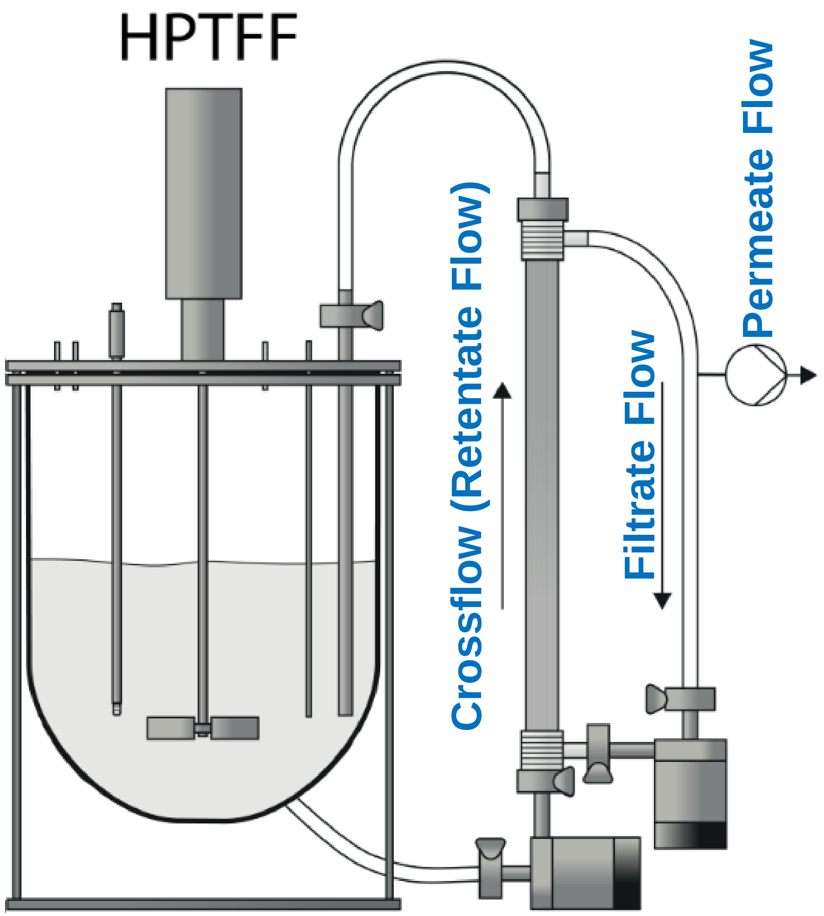
HPTFF: System Setup



System Setup:

- Retentate pump (centrifugal)

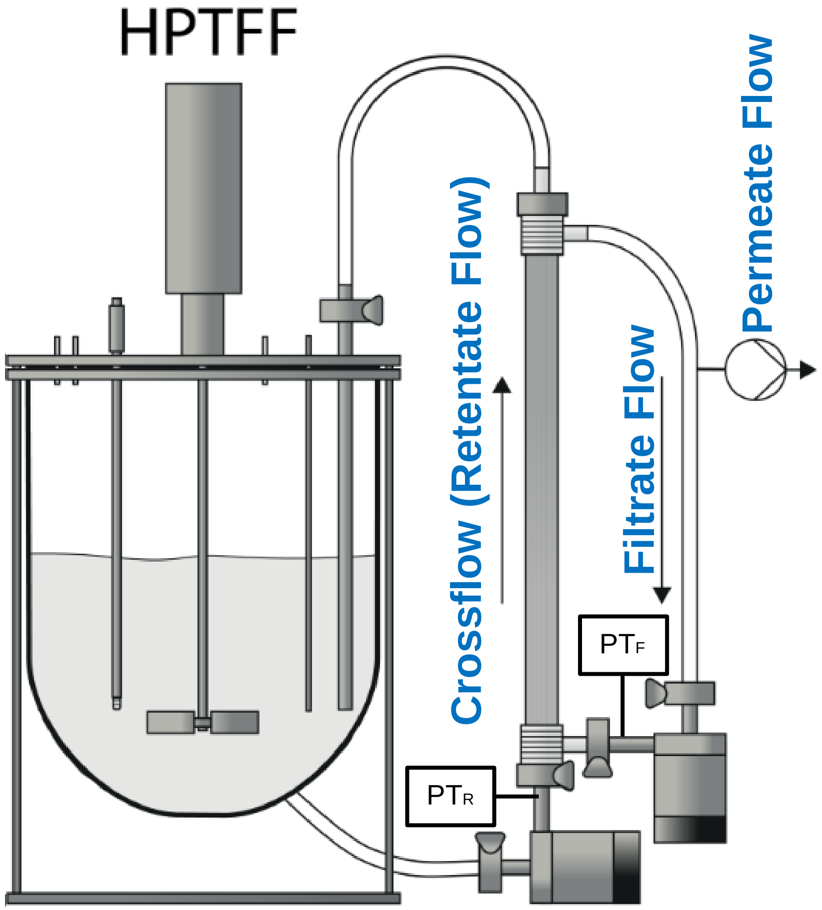
HPTFF: System Setup



System Setup:

- Retentate pump (centrifugal)
- Filtrate Loop Pump (centrifugal)

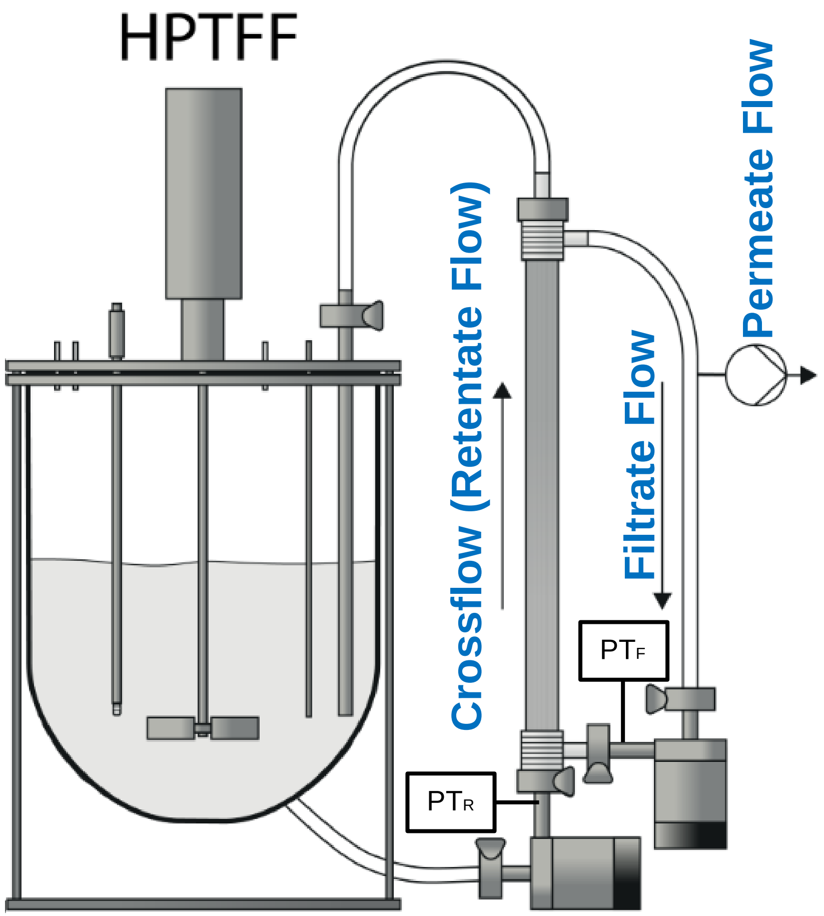
HPTFF: System Setup



System Setup:

- Retentate pump (centrifugal)
- Filtrate Loop Pump (centrifugal)
- Pressure Sensors:
  - PT_{Rin}: Retentate Inlet
  - PT_{Fin}: Filtrate Inlet

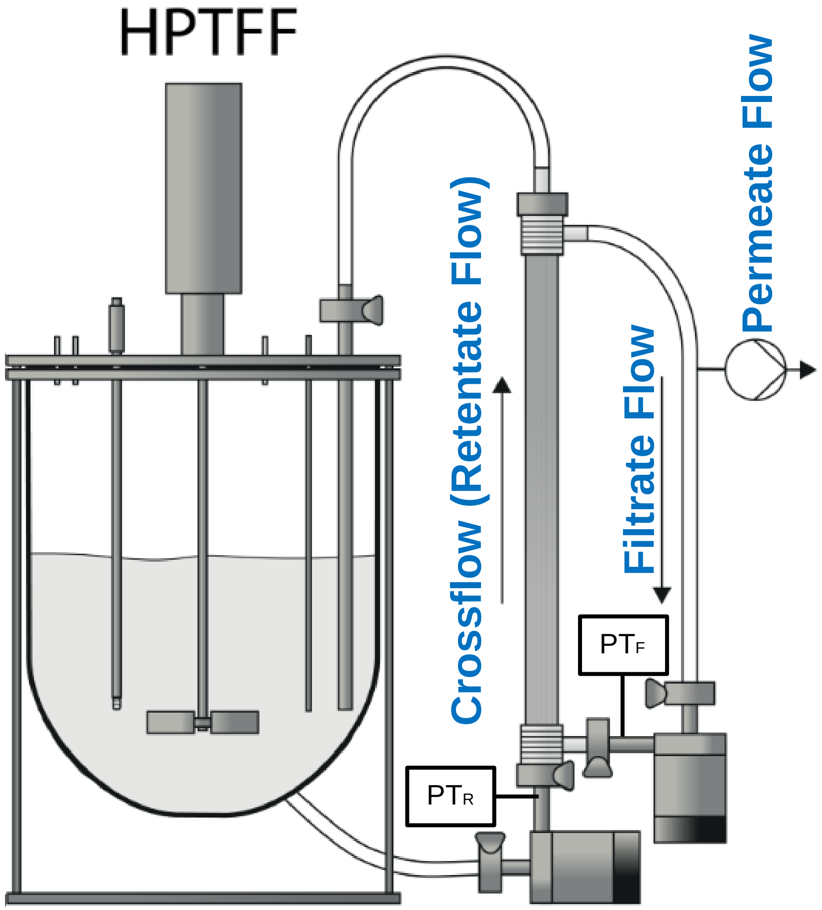
HPTFF: System Setup

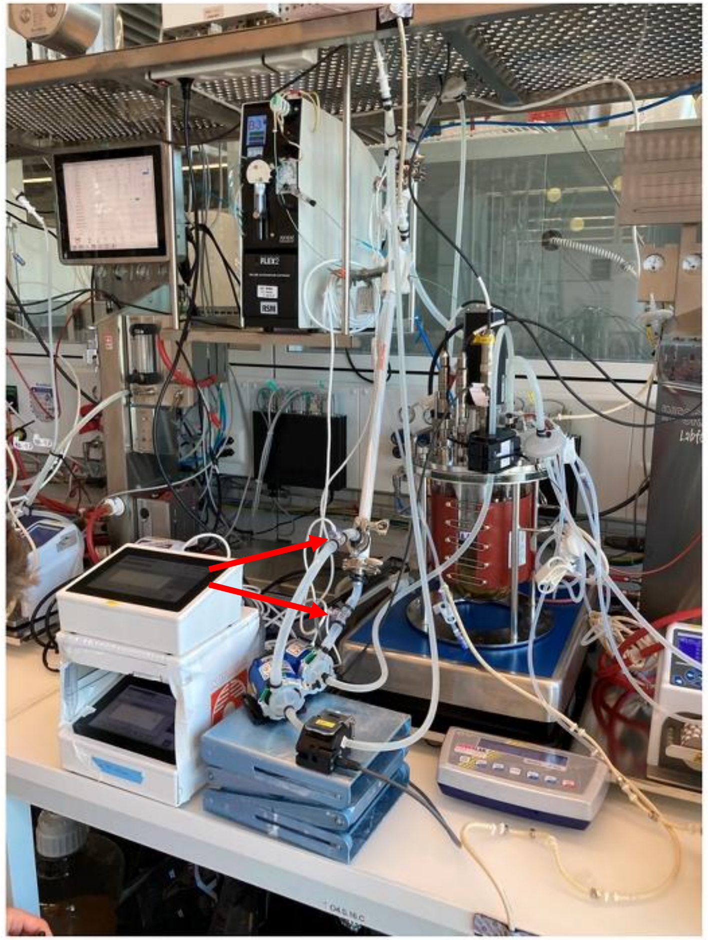


System Setup:

- Retentate pump (centrifugal)
- Filtrate Loop Pump (centrifugal)
- Pressure Sensors:
  - PT_{Rin}: Retentate Inlet
  - PT_{Fin}: Filtrate Inlet
- Optional:
  - Flow Sensors
  - Further Pressure Sensors

HPTFF: System Setup

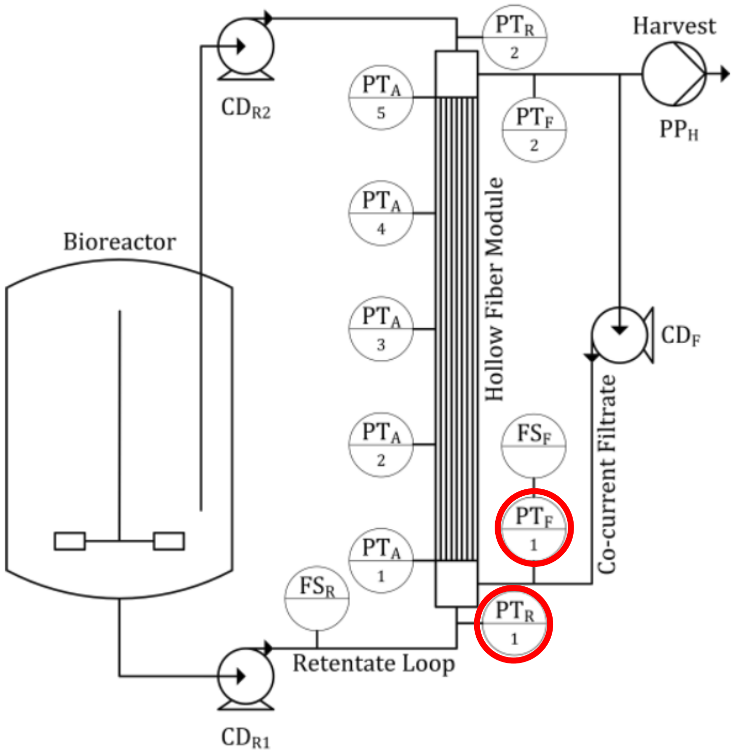


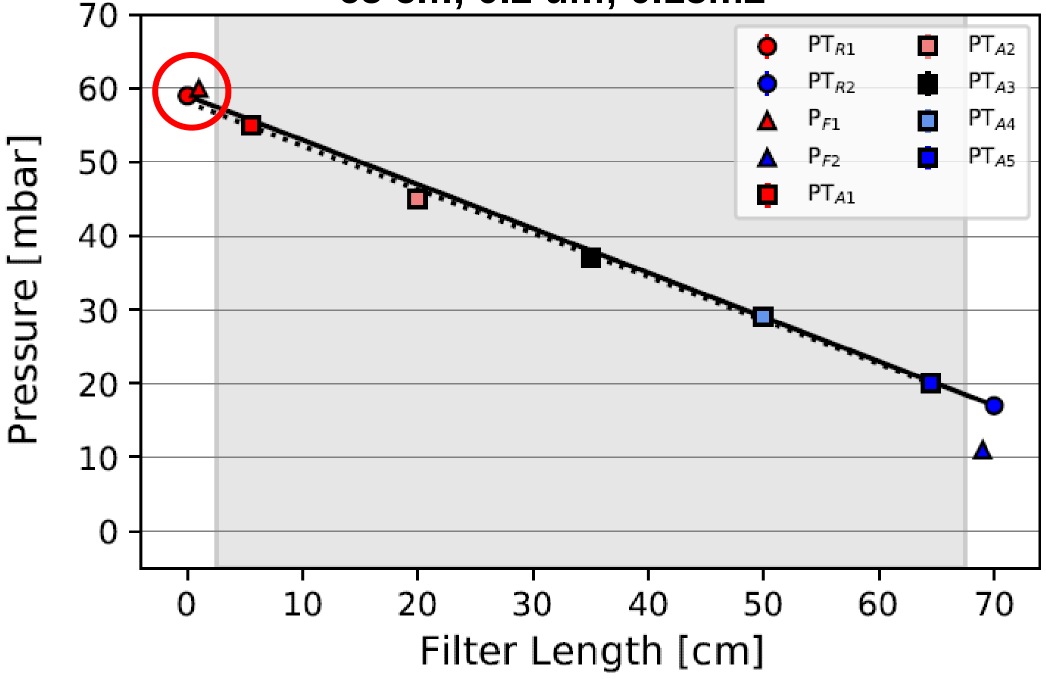


HPTFF Control Strategy: Delta Pressure

→ Delta Pressure Setpoint must be determined! (water characterization)

Characterization Setup

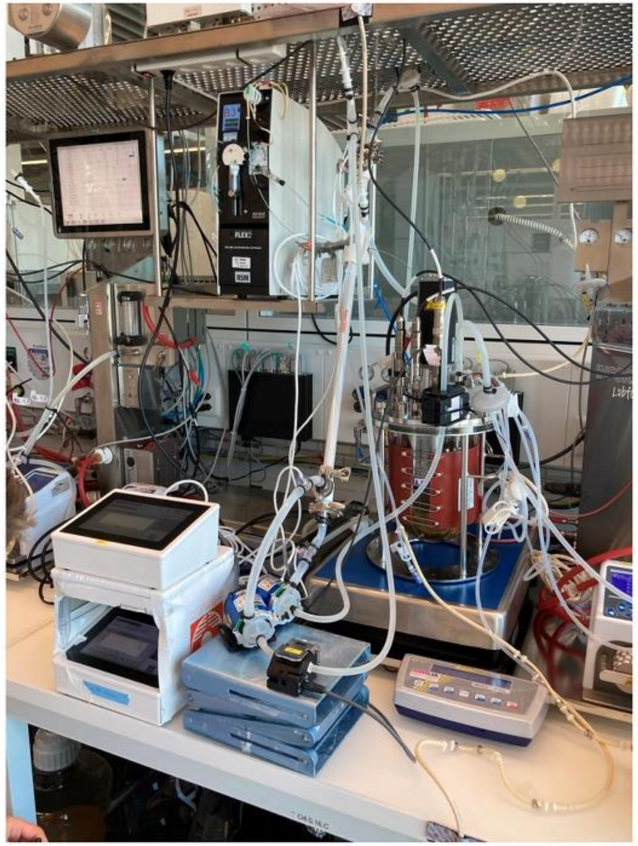




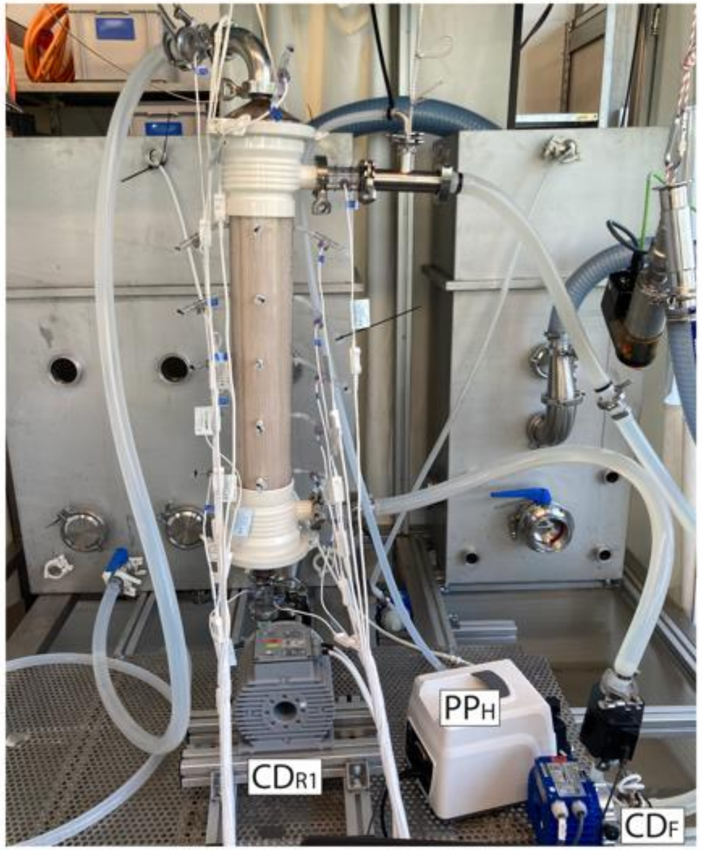
→ Delta Pressure Setpoint = 0 mbar

Lab-scale and Large-scale Filter for HPTFF

S06-P20U-10-N, Repligen
65 cm; 0.2 um; 0.15m2

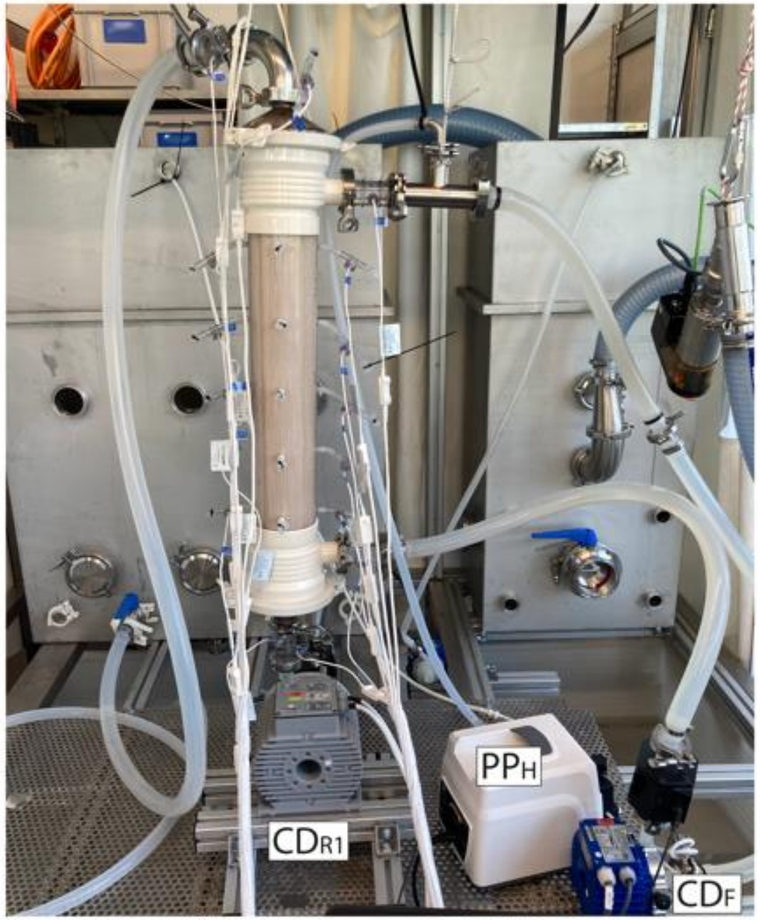


X06-P20U-10, Repligen
70 cm; 0.2 um; 7.15m2

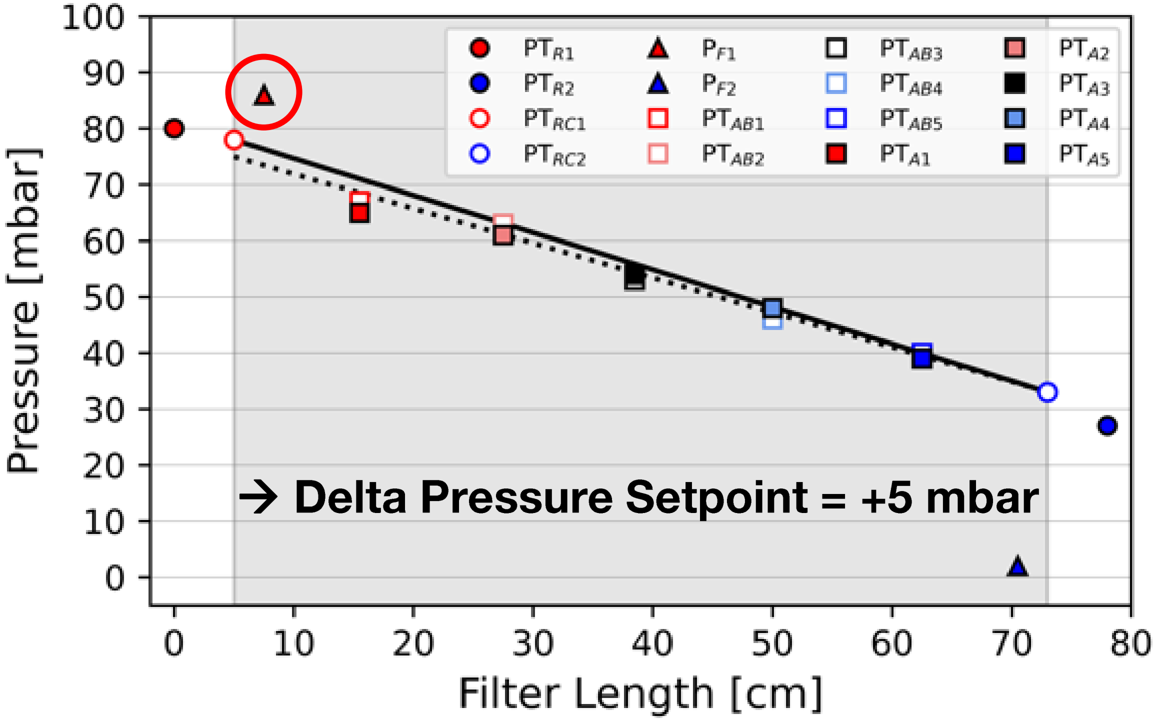


Large-Scale: Delta Pressure

→ Delta Pressure Setpoint must be determined! (water characterization)

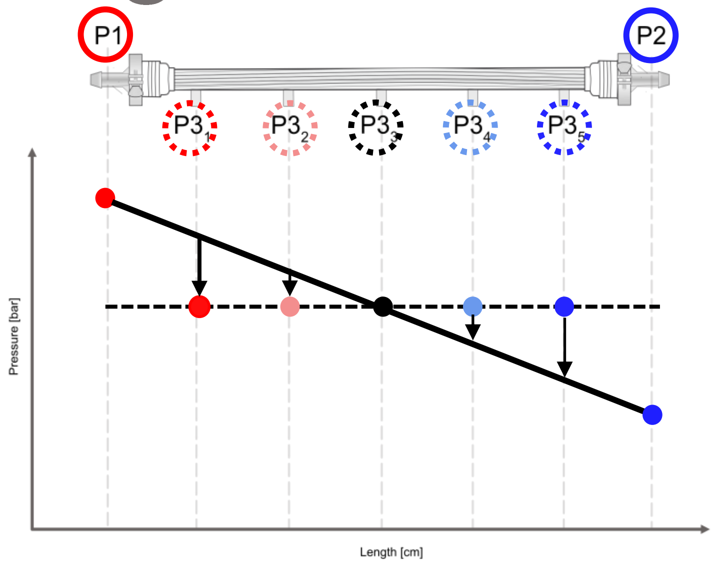


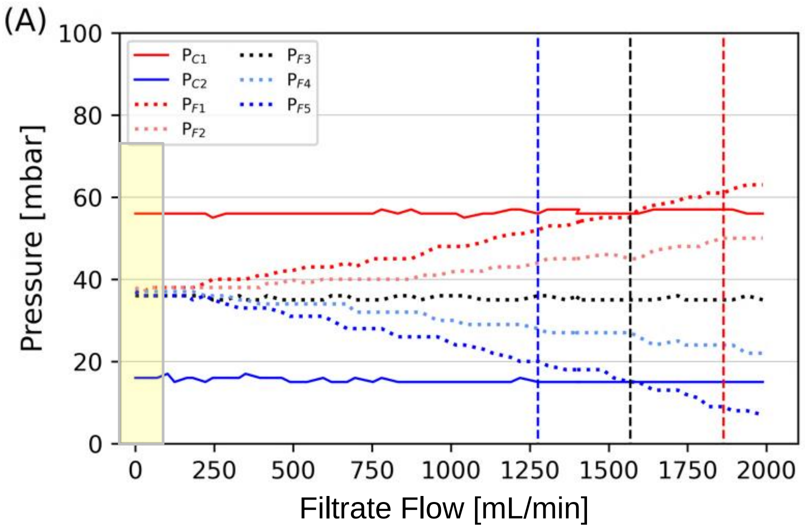
X06-P20U-10, Repligen
70 cm; 0.2 um; 7.15m2



→ turbulences might be responsible for pressure drifts (not fully understood)

Stepping co-current TFF



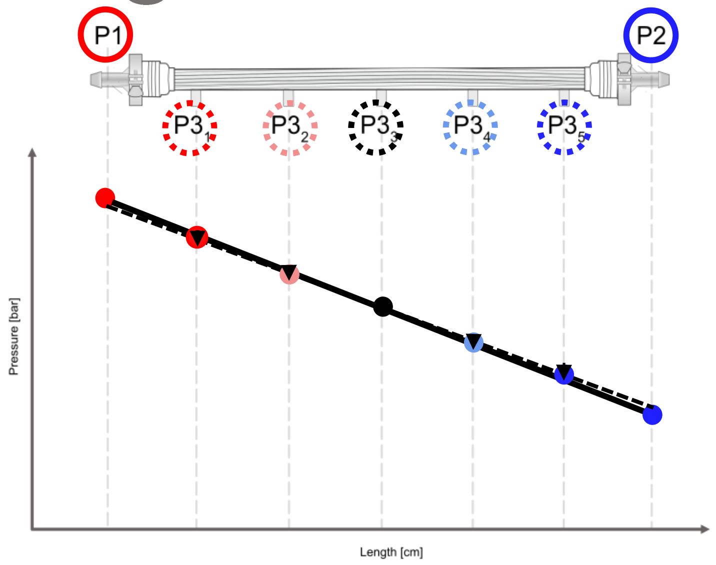


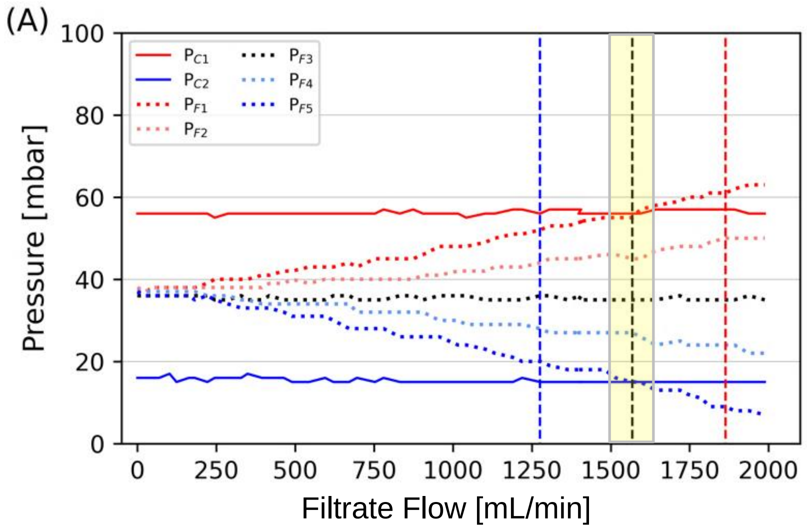
Standard TFF:

- No co-current filtrate flow

LEVITRONIX

Stepping co-current TFF

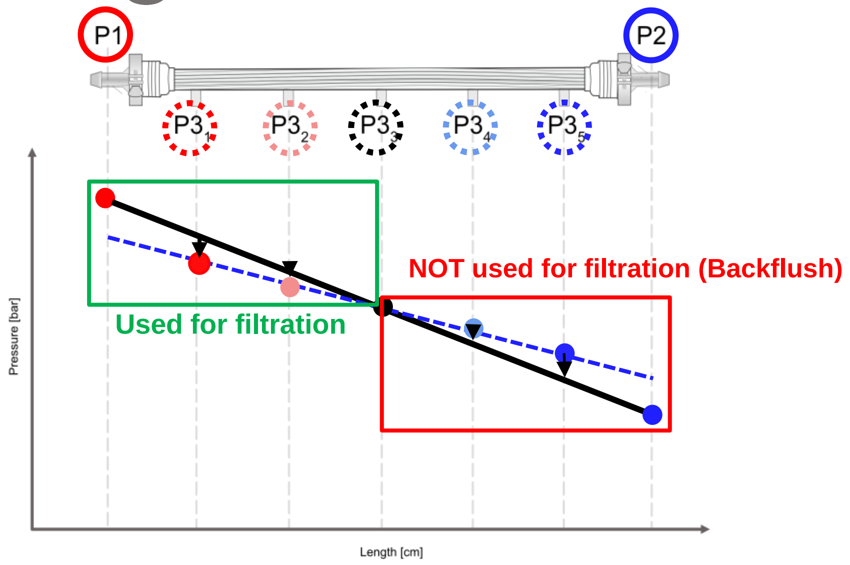


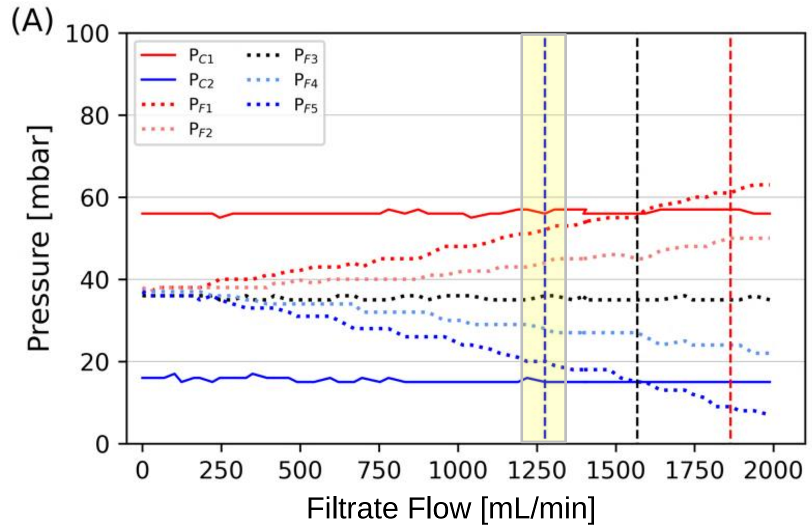


HPTFF:

- Co-current filtrate flow to match P1 and P3
- No TMP along fibers (almost)

Stepping co-current TFF

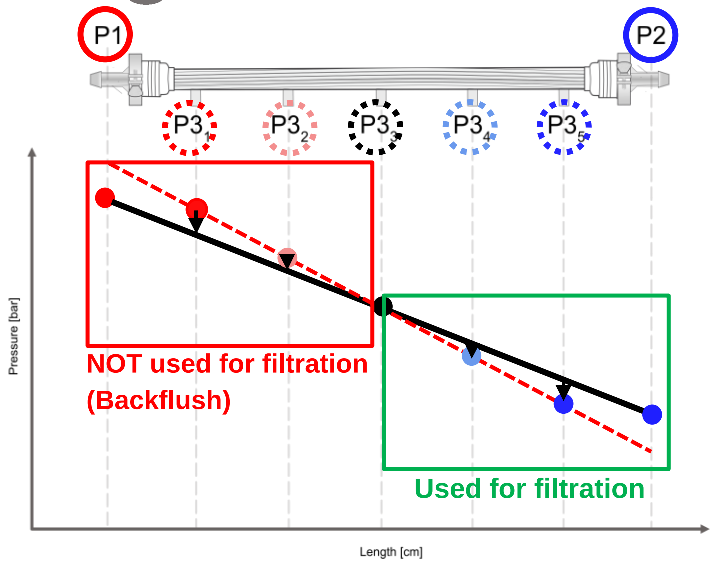


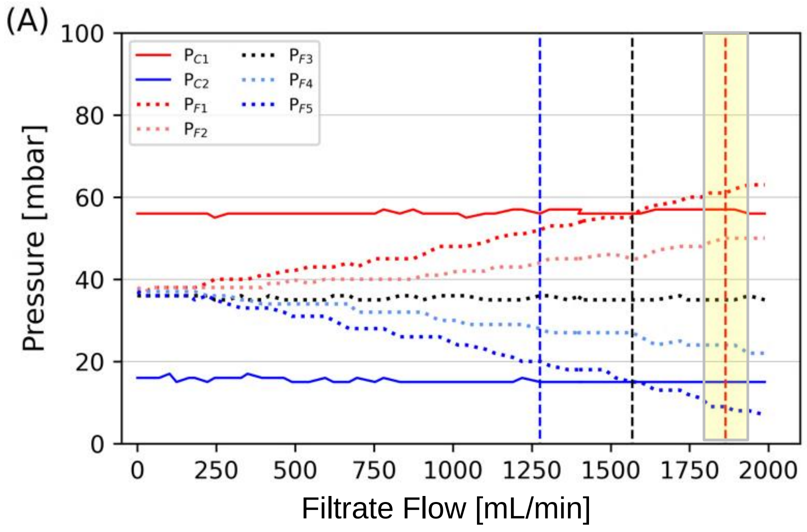


scTFF (Phase 1):

- Coflow < HPTFF Coflow
- Backflush 2nd half of filter

Stepping co-current TFF





scTFF (Phase 2):

- Coflow > HPTFF Coflow
- Backflush 1st half of filter