High Flux Tangential Flow Filtration for Perfusion Harvest Scale Up

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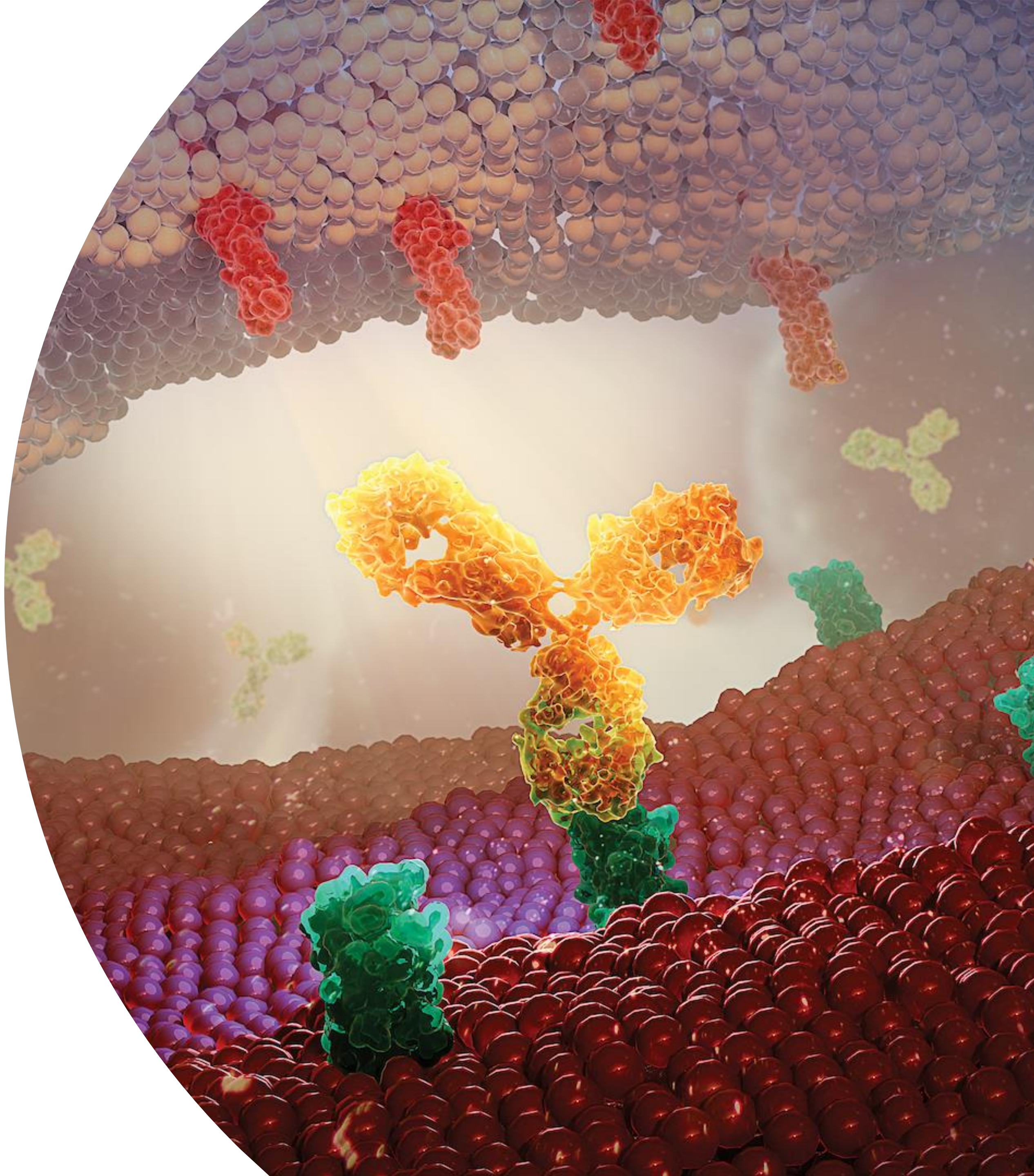
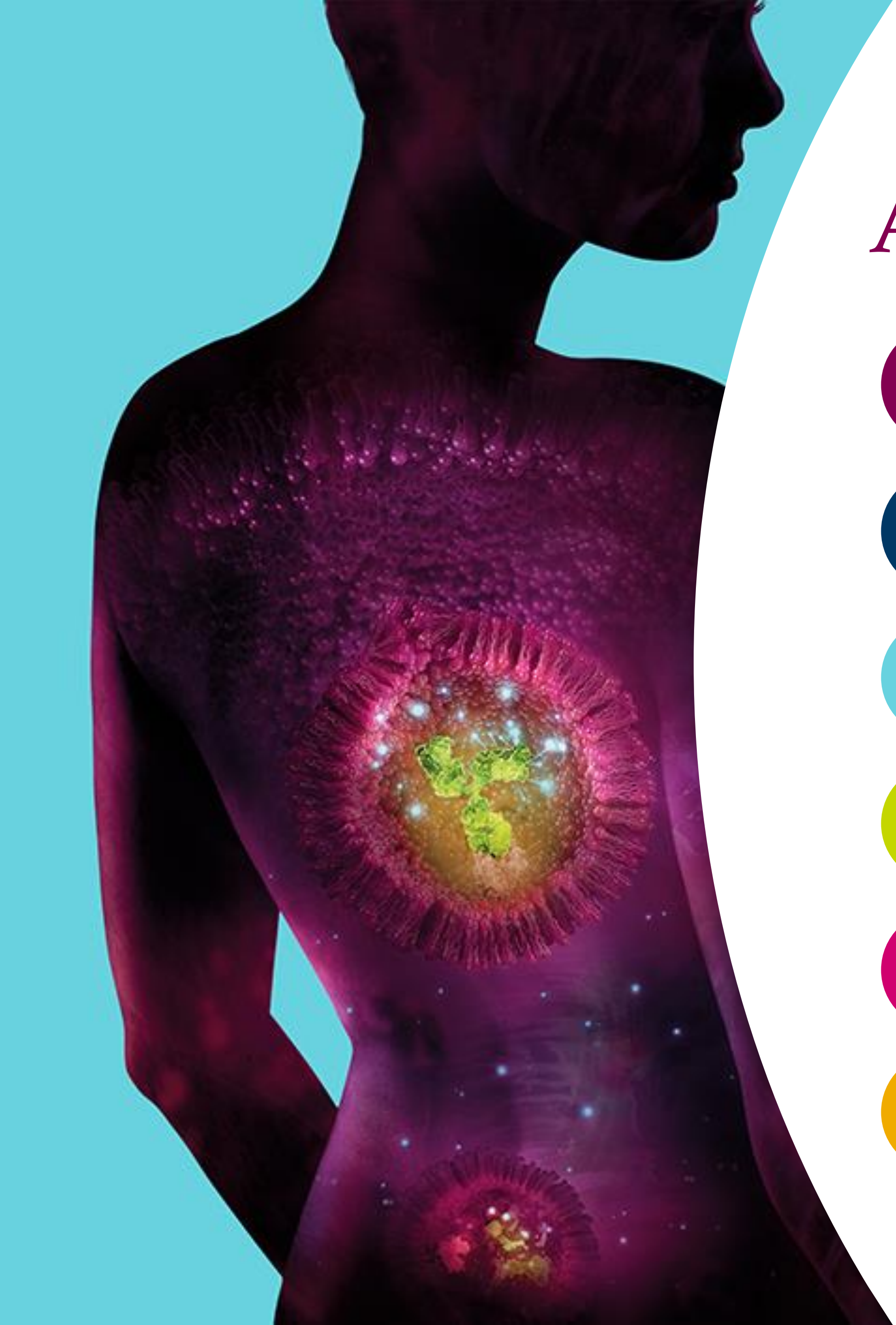
20Jun24



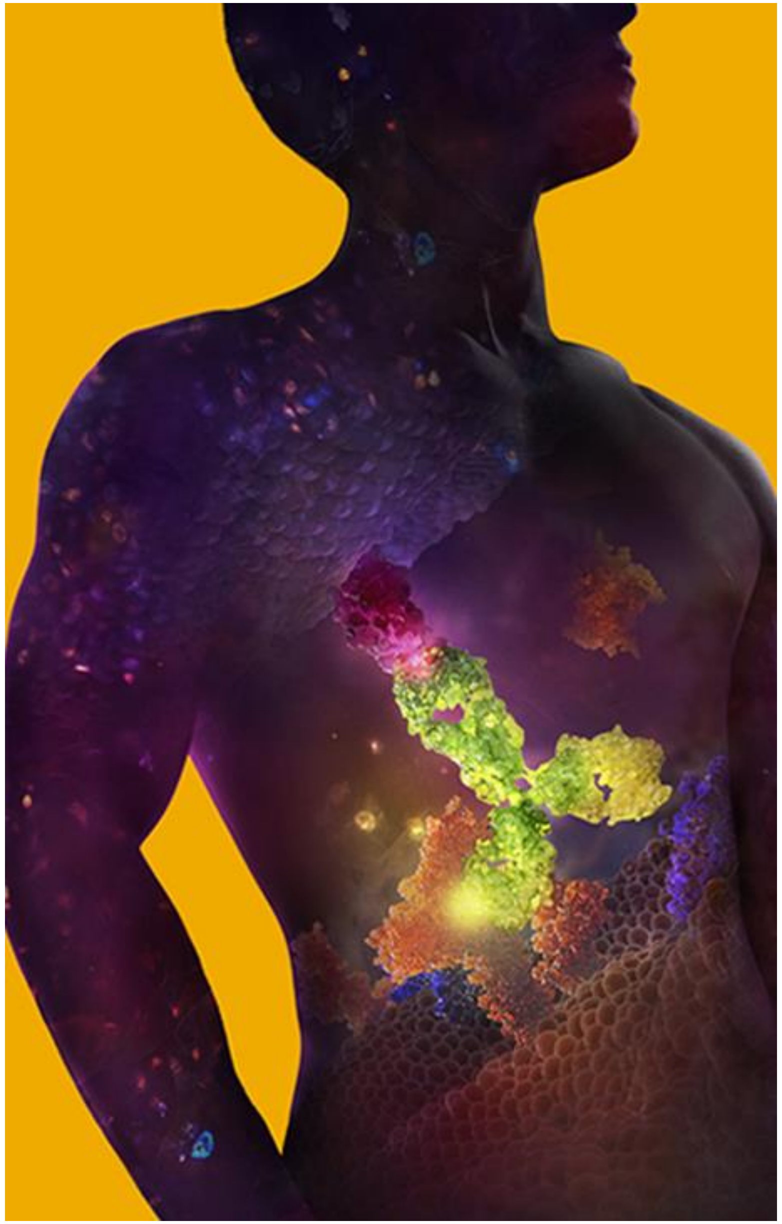


Agenda

1. What is NGM at AstraZeneca?
2. Platform NGM Upstream Process
3. Scaling Concerns/Strategies
4. Why High Flux?
5. High Flux Results
6. Conclusion

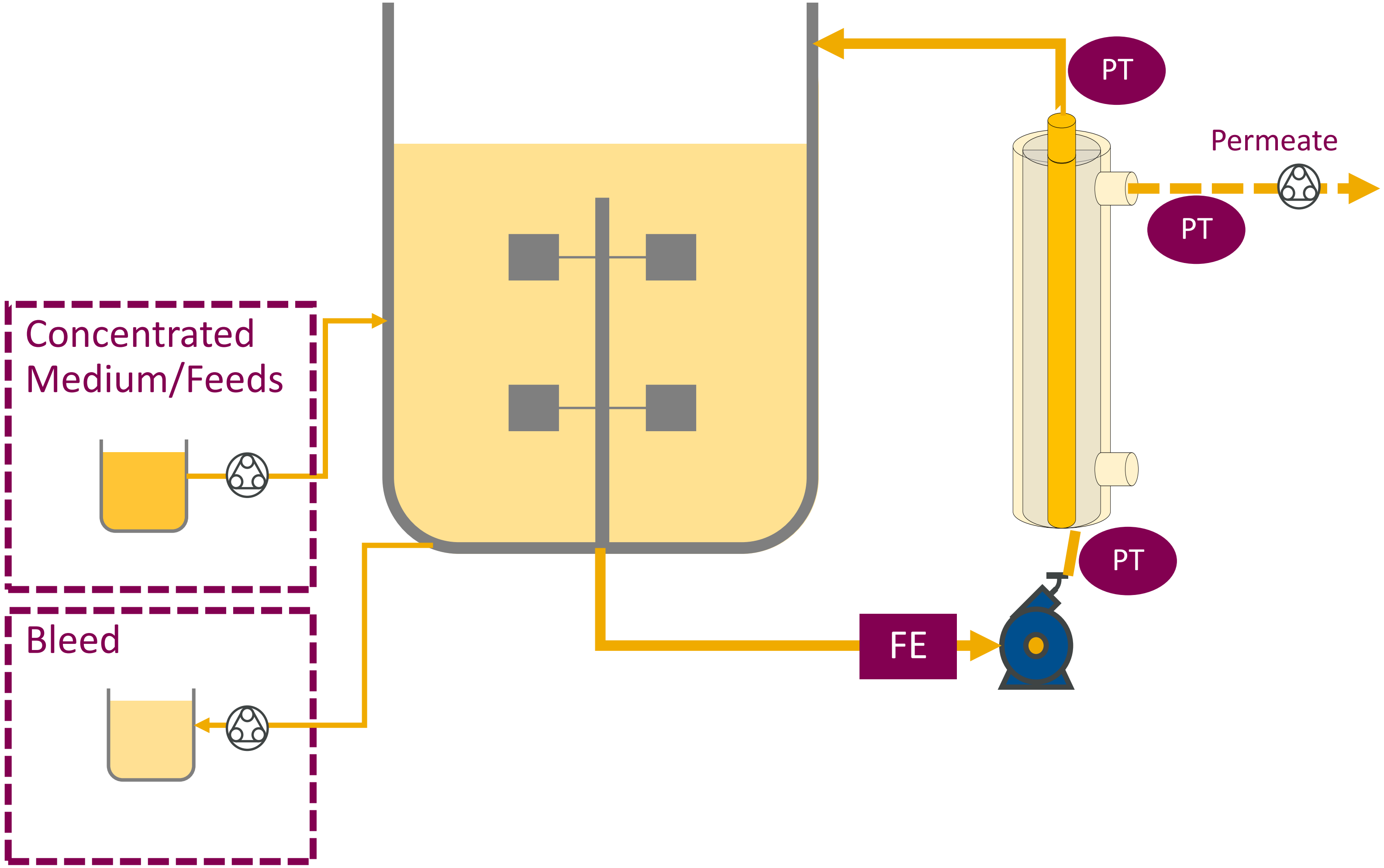
What is NGM at AstraZeneca?

- "Next Generation Manufacturing" is a fully continuous process from bioreactor to drug product
  - Defined unit operations are identifiable from fed-batch but continuous



Platform NGM Upstream Process

- Multiple concentrated feeds
- TFF cell retention
  - Levitronix pump
- Perfusion Rate = Bleed Rate + Permeate Rate
- Feed flowrates based on consumption rate

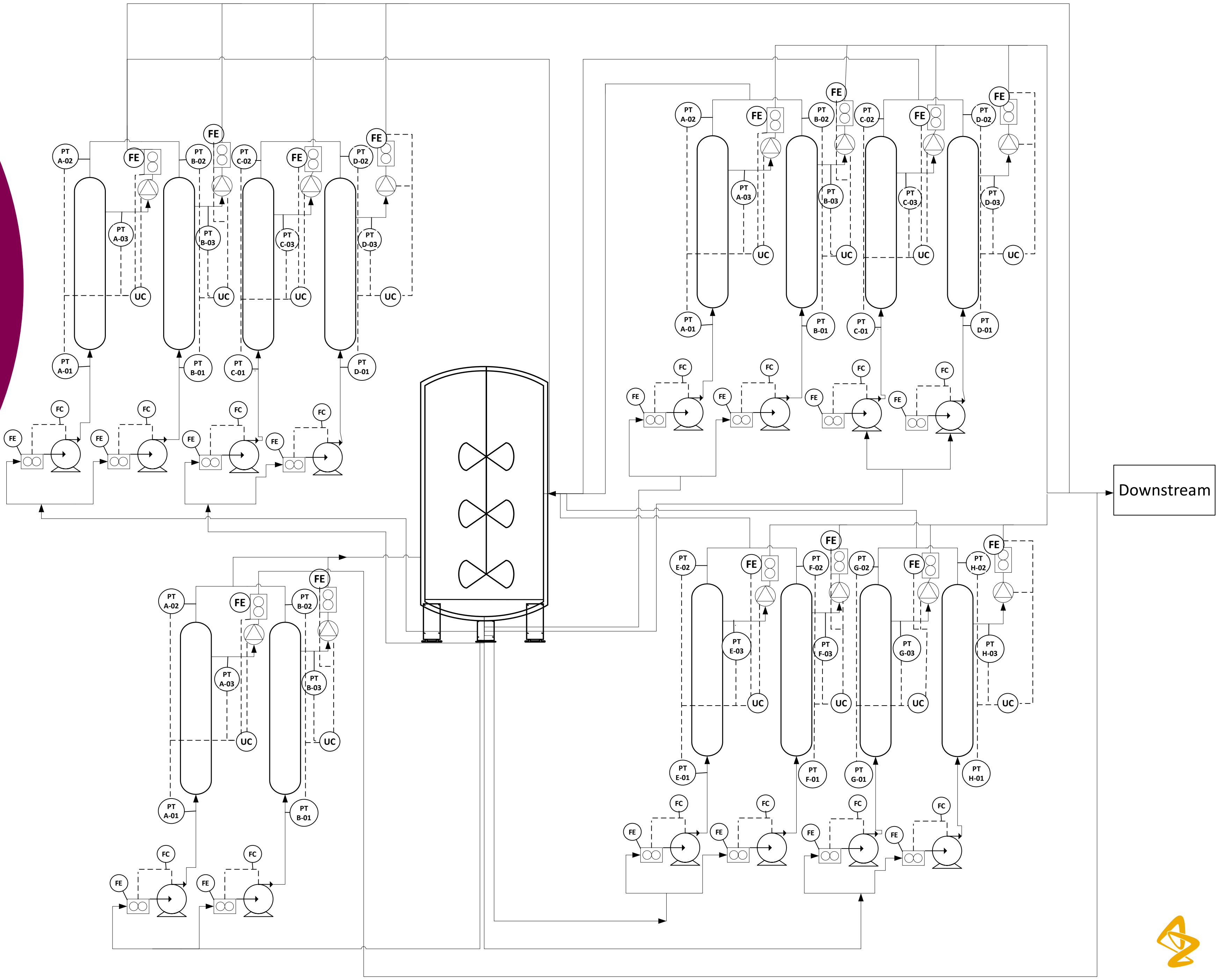


Scaling Concerns

- Current platform at large scale would require 14 filters for one large-scale bioreactor
  - Excessive number of outlet/inlet ports on BRX bag
  - Large footprint required
  - Numerous retentate/permeate pumps
  - High demand on operators

Scale	Small	Medium	Large
Membrane Chemistry	PES	PES	PES
ID (mm)	1.0	1.0	1.0
SA per filter (m2)	0.098	7.16	7.16
No. of Filters Required per Run	1	4	14

Manufacturing Outlook



Scaling cell retention device

Reduce ΔP

- Increased fiber ID
- Decreased fiber length

Filter Stacking

Filter Changeout

- Returned sieving %

High Performance Tangential Flow Filtration (HPTFF)

High Flux

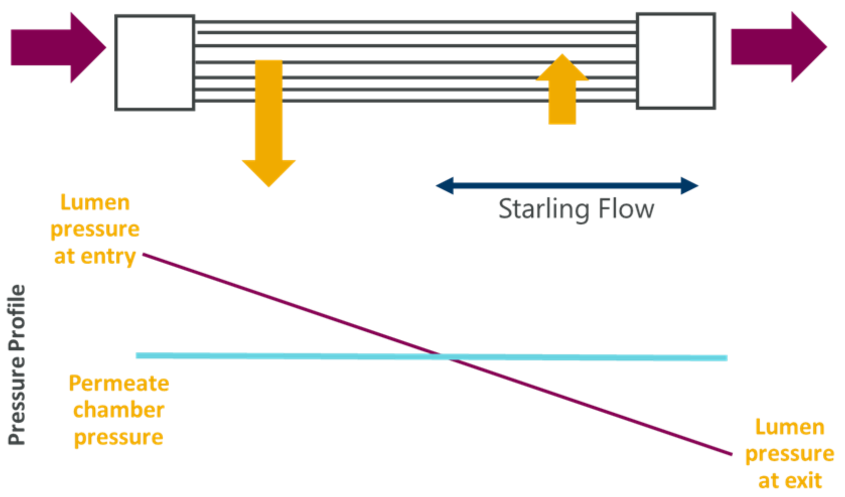
- Increased filter capacity

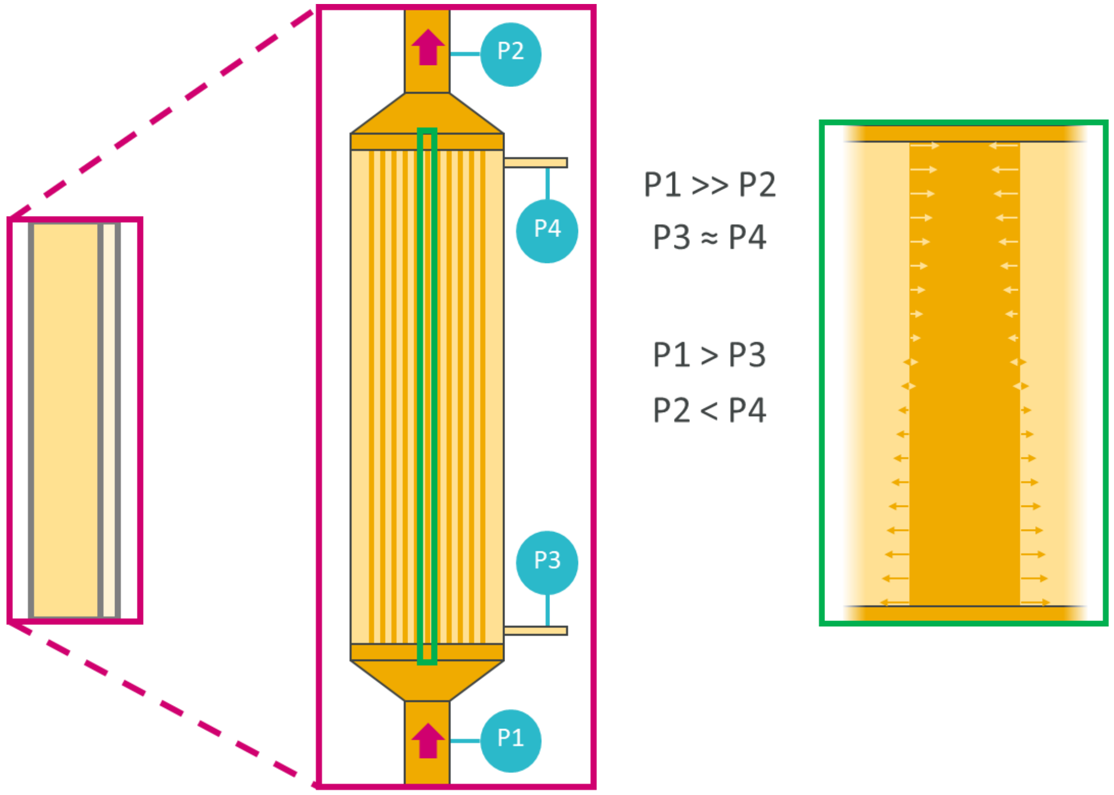
What is Starling Flow?

- Starling Flow = Undesired permeate flow back into lumen caused by transmembrane pressure transition from positive to negative along length of fiber.

Hagen Poiseuille Equation:

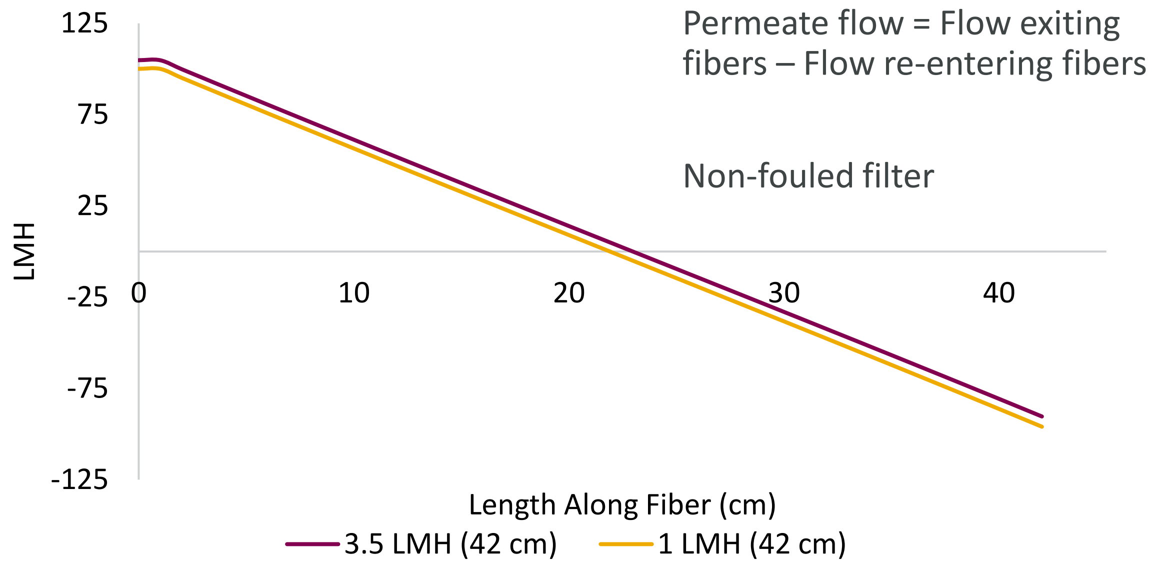
$$\Delta P = \frac{8\mu L Q}{\pi R^4}$$





Why High Flux?

- Higher flux = Higher filter capacity
  - Greater area of positive pressure across filter length compared to low flux



$$\frac{Q_s}{Q_p} = Ratio\ of\ flow\ rate\ exiting\ fibers\ to\ net\ permeate\ flow\ rate$$

For 42 cm fibers:

- 1 LMH = Ratio of 10.3
- 3.5 LMH = Ratio of 3.3

High Flux Considerations

- As run progresses:
  - Viscosity increases
    - Begins to act as a Non-Newtonian fluid
  - Fouling Increases
    - Flux begins to act unpredictable
- As net flux is held constant and viscosity increases, TMP begins to rise
  - Risk of passing critical flux point

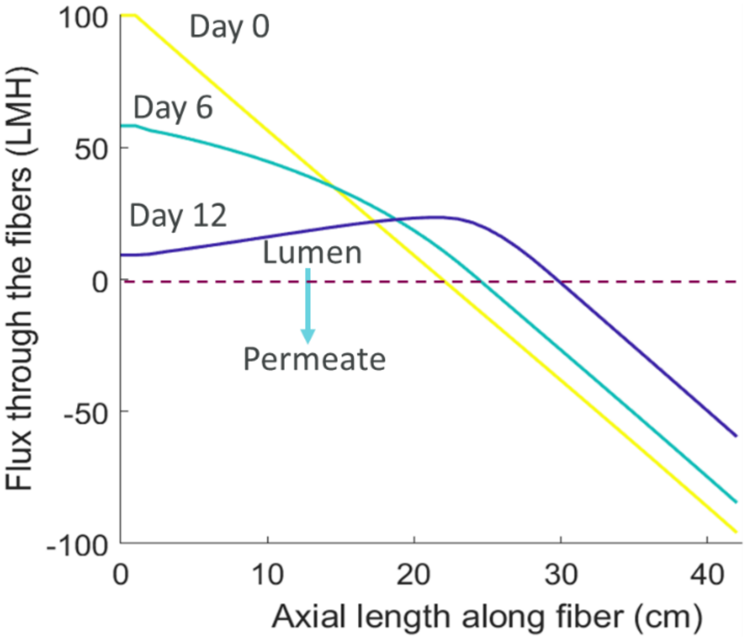
Assuming cylindrical pores, the resistance (Rt) based on the Darcy's equation is:

$$J = \frac{TMP}{\mu R_t}$$

$$R_t = \frac{8\delta_m}{r_p^2 \varepsilon}$$

δ_m = membrane thickness
ε = membrane porosity
μ = viscosity
r_p = pore radius

A.)



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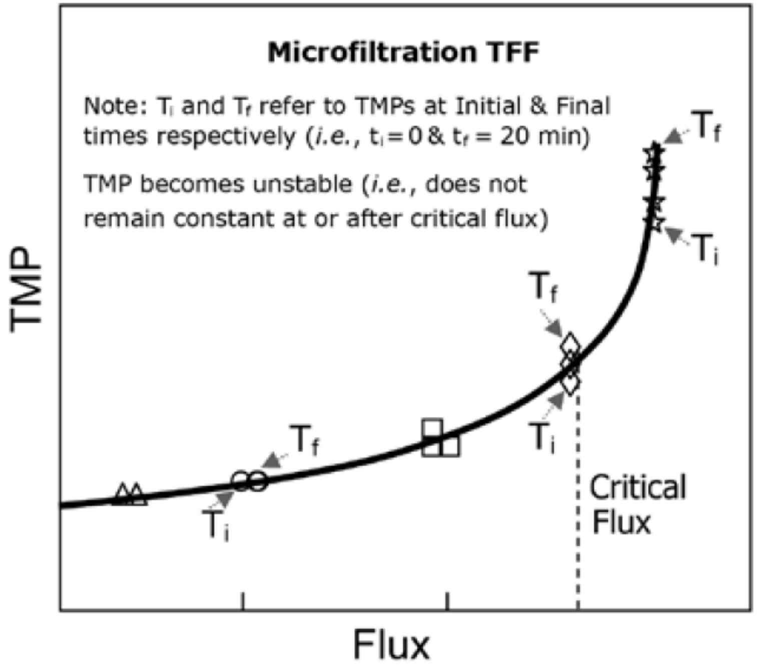
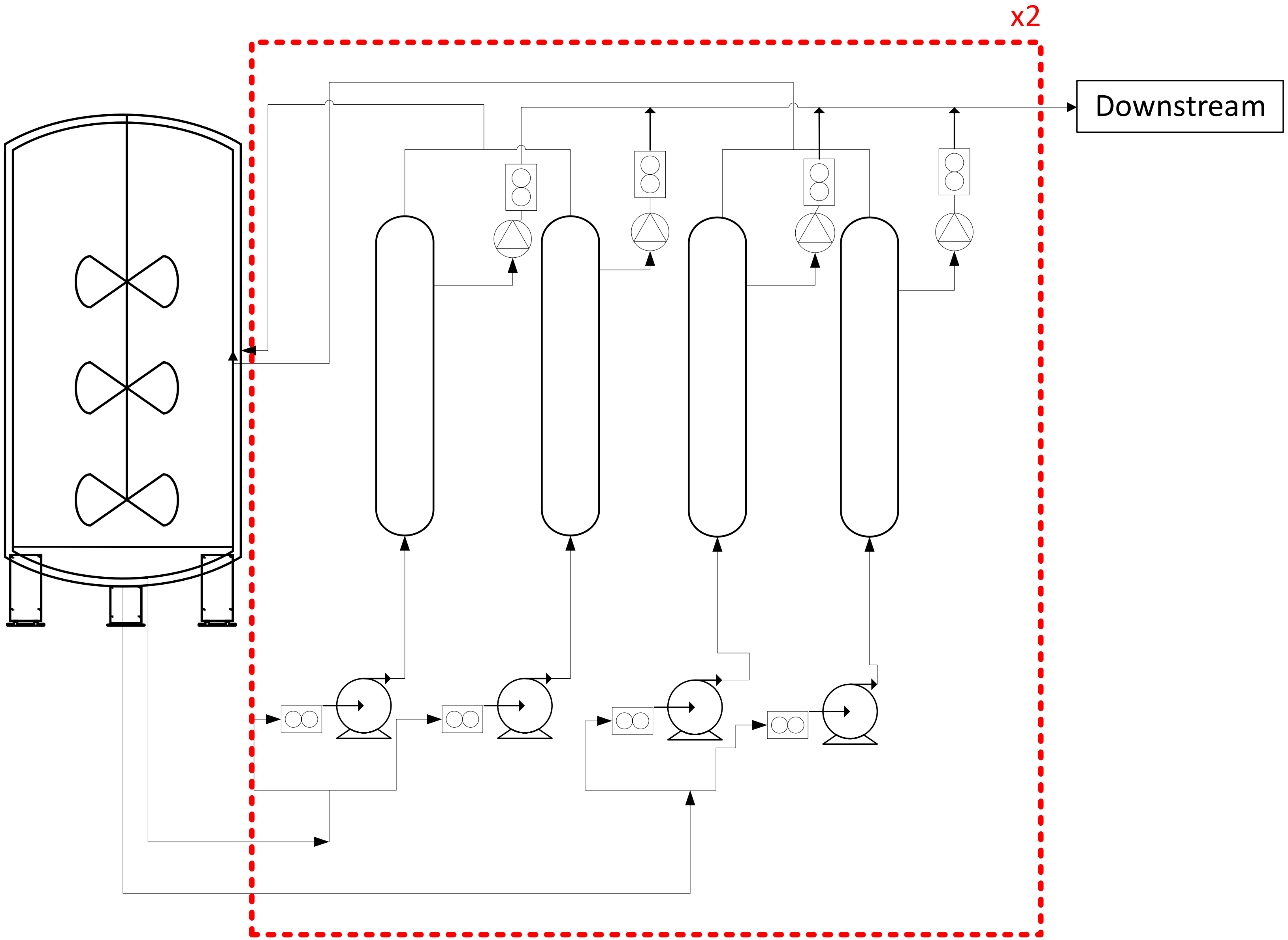


A.) Ashna Dhinga B.) Raghunath, Bala & Wang, Bin & Pattnaik, Priyabrata & Janssens, Jeroen. (2012). Best Practices for Optimization and Scale-Up of Microfiltration TFF Processes. BioProcessing Journal. 11. 30-40. 10.12665/J111.Raghunath.

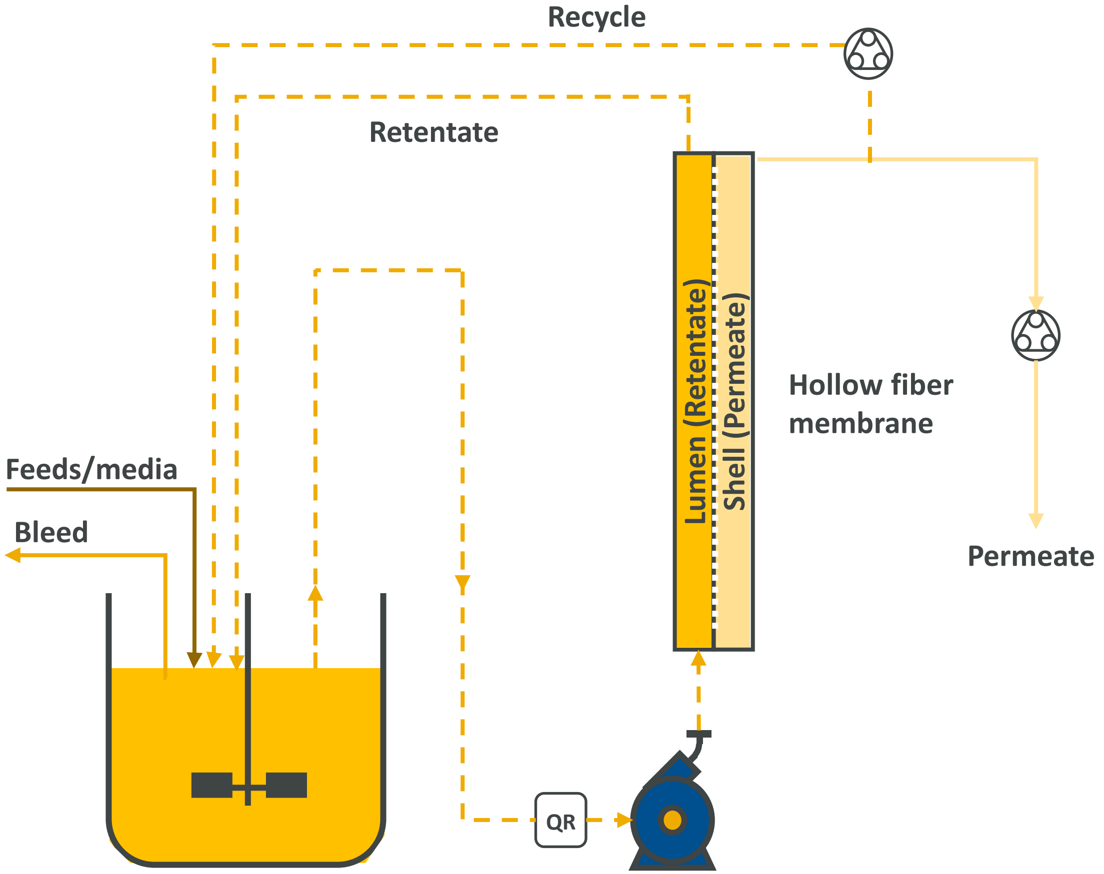
Manufacturing Outlook: High Flux High Capacity TFF



3L High Flux Experiment

- Varied High Flux Conditions
  - Split permeate line into constant recycle stream (return to bioreactor) and permeate
- Perfusion Rate = Permeate Rate + Bleed Rate
- Fixed Recycle Rate
- Assessed Harvest Throughput at Varied Flux Rates utilizing different membrane chemistries

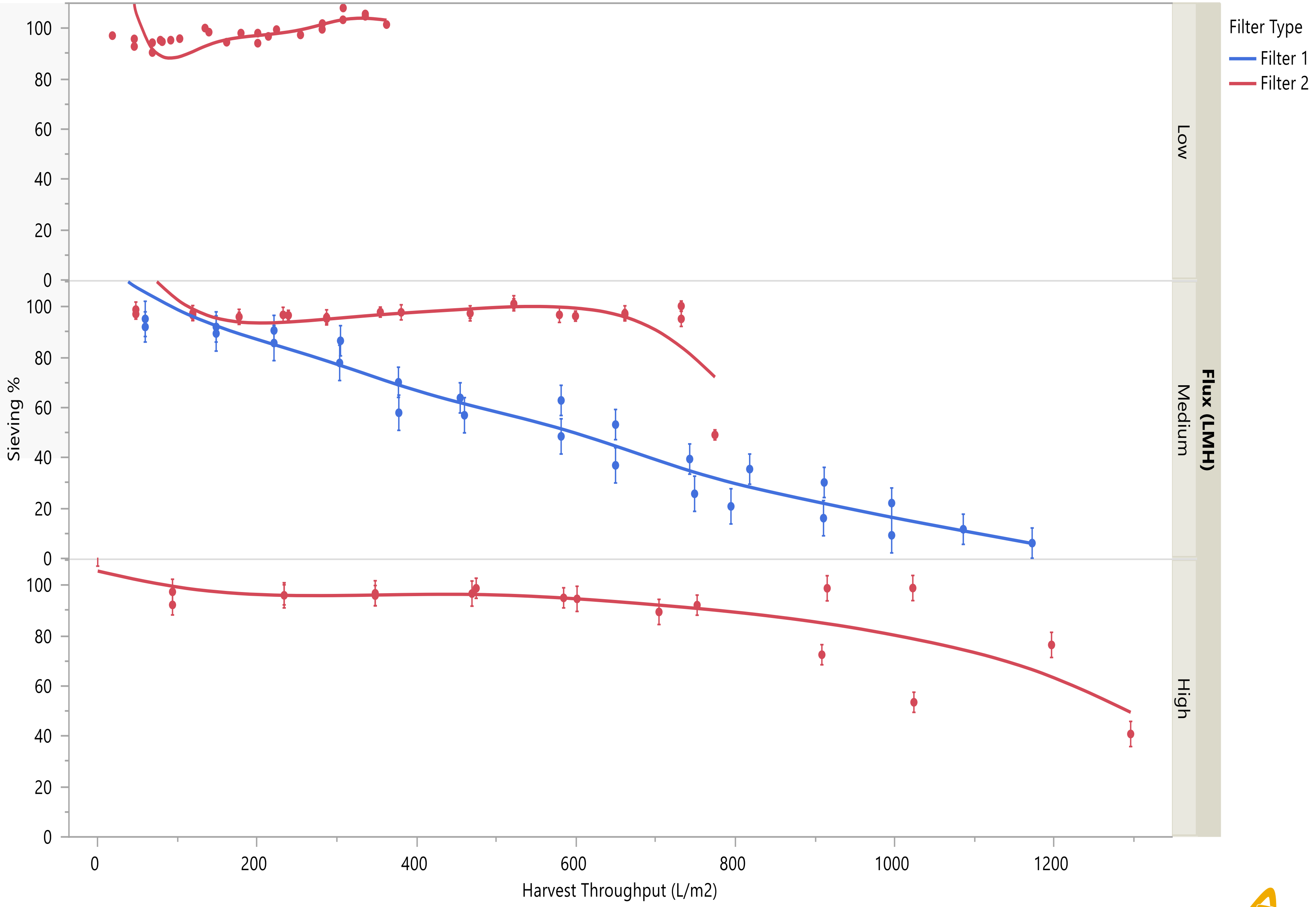
	Filter 1	Filter 2
Chemistry	PES	PVDF
ID (mm)	1.0	1.4
# of Fibers	75	100
Surface Area (m^2)	0.098	0.09
Length (cm)	41.5	19.8



Filter Performance

- Filter 2 filter shows higher sustained sieving performance in till critical flux is reached
- Filter 1 has a steady sieving decline as fouling increases
- Capacity estimation determined by mixture of critical failure and sieving reaching approximately 50%
- Filter 1 capacity:
  - Medium Flux= 550-650 L/m^2
- Filter 2 capacity:
  - Low Flux= Not reached
  - Medium Flux= 700 – 800 L/m^2
  - High Flux= 900-1000 L/m^2

    Changeout filter mid run results in lower capacity due to High VCD load



Conclusion

Increased flux results in increased filter capacity for both Filter 1 and 2

Filter 2 displayed higher yield and sustained sieving over Filter 1

High flux can reduce both filters demand at large scale by approximately half

Acknowledgements

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Questions?

Confidentiality Notice