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Design considerations when scaling from 3-L to 3000-L or larger

Kenneth Lee
AstraZeneca, USA, ken.lee@astrazeneca.com

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Ken Lee

Bioprocess Technologies & Engineering,
BioPharmaceuticals Development, R&D,
AstraZeneca, Gaithersburg, US

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What is AstraZeneca's continuous process?

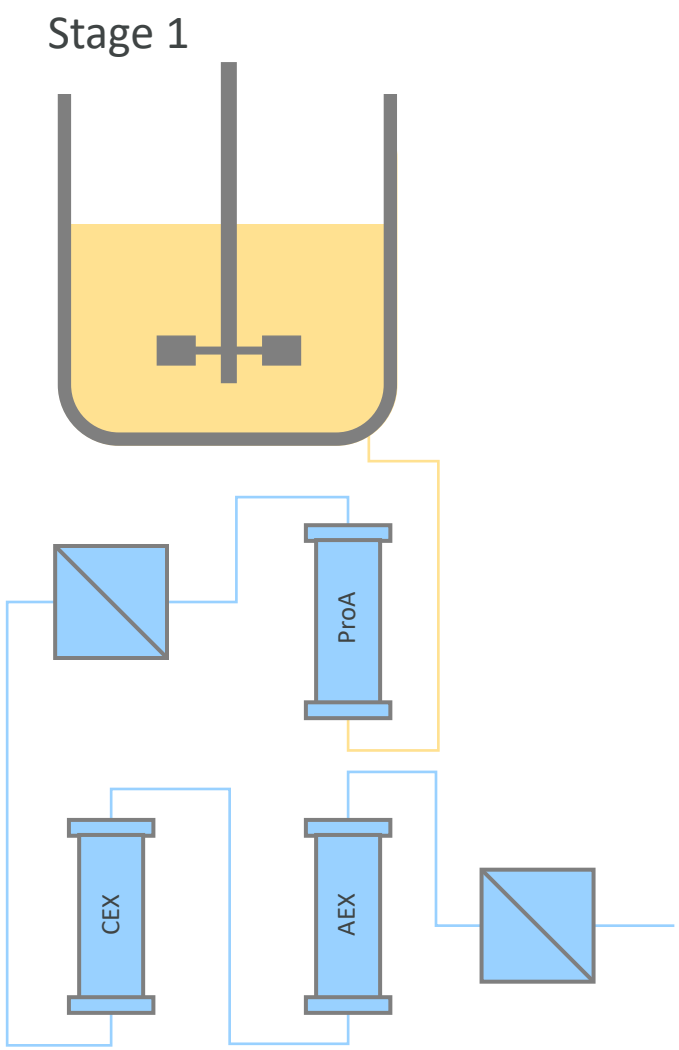
- Fully continuous process for Drug Substance
- First iteration is analogous to batch processing – just continuous!
  - Defined unit operations are still identifiable

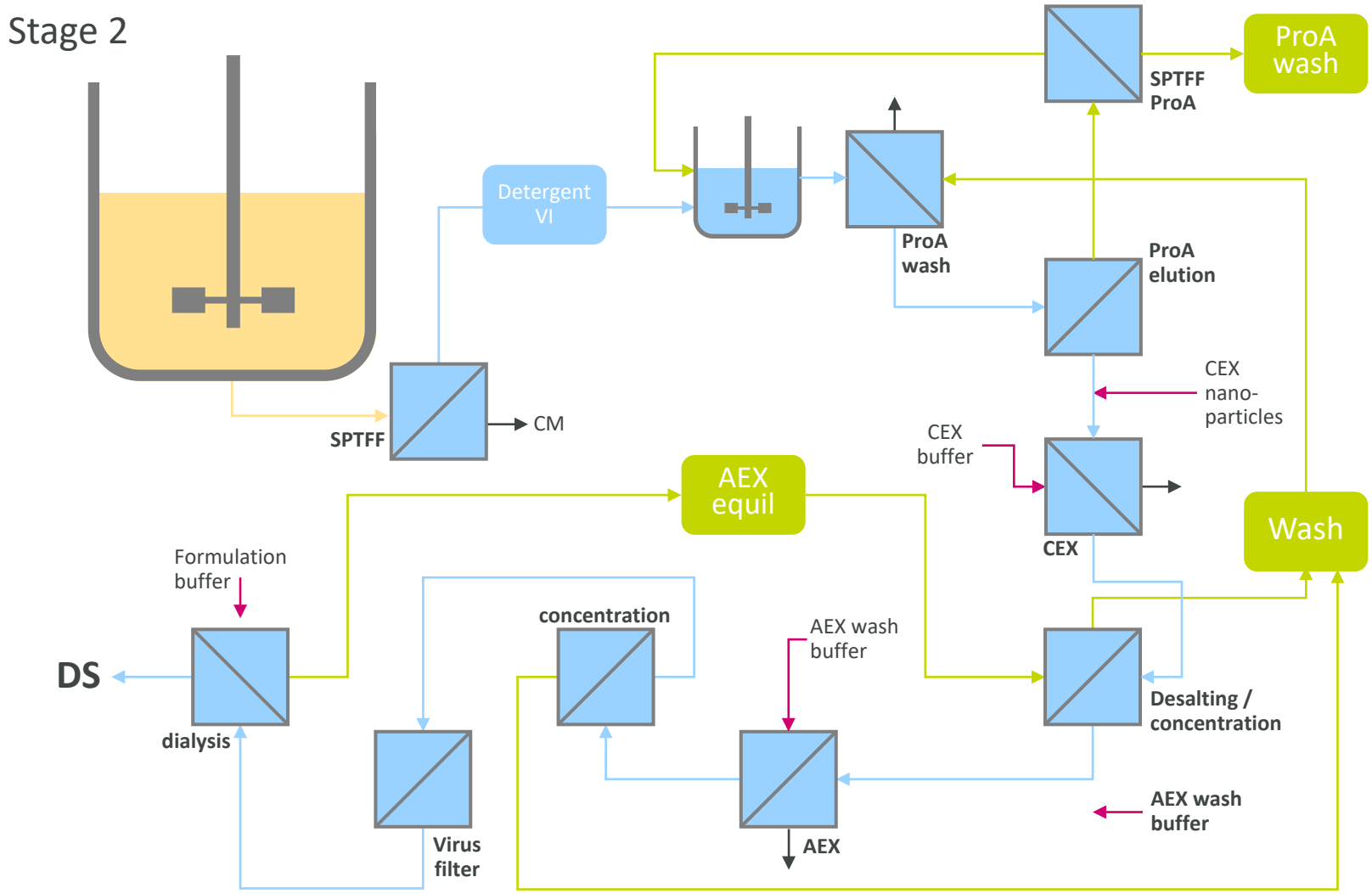
- **Platform continuous process defined to enable entire portfolio**

“Why aren’t we doing this with every molecule?”

Pascal Soriot, CEO of AZ

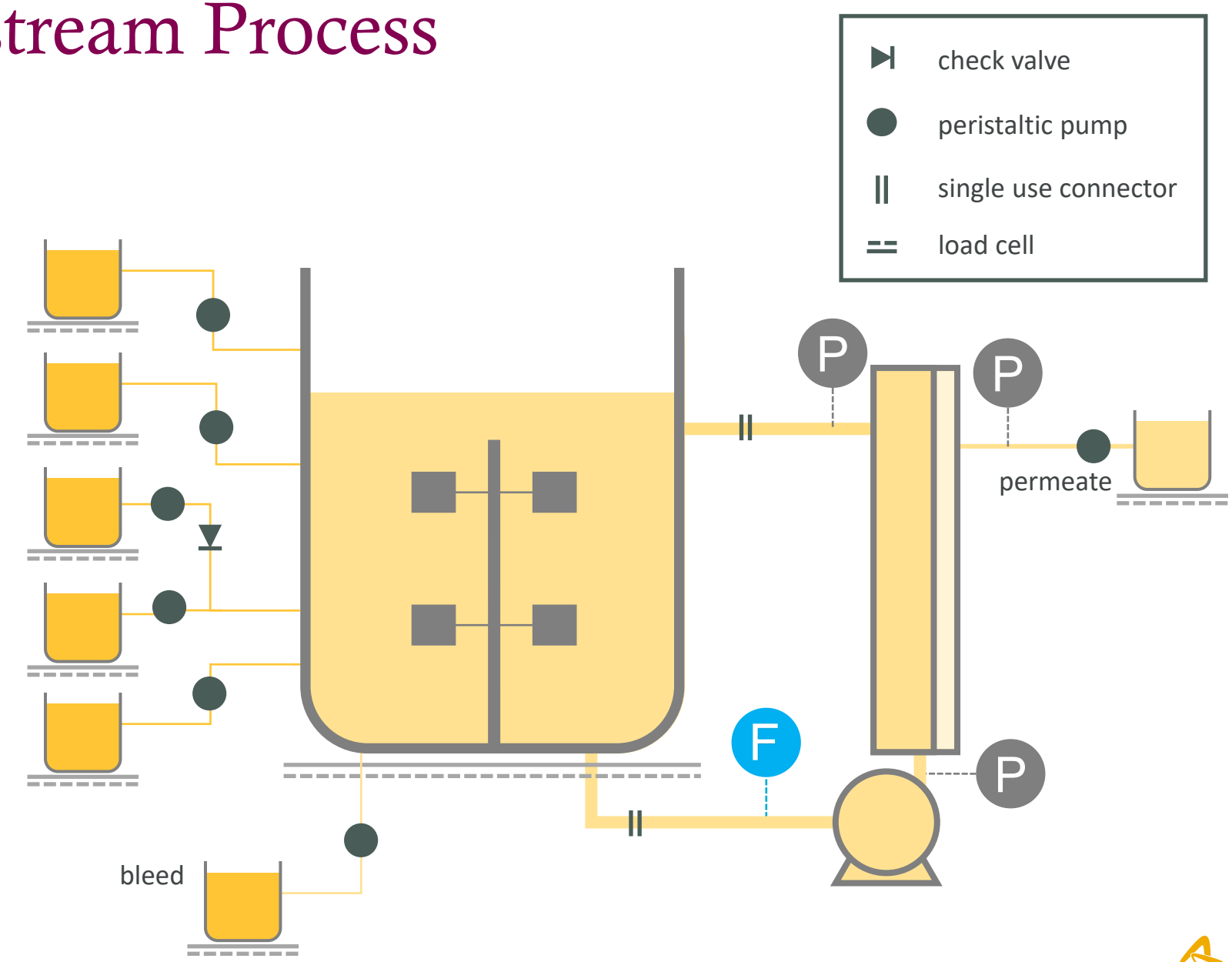
What does AZ's continuous process look like?





Platform NGM Upstream Process

- Multiple concentrated feeds
- TFF cell retention
  - Levitronix pump
- Fixed perfusion rate
- Feed flowrates based on consumption rate



Scaling bioreactors

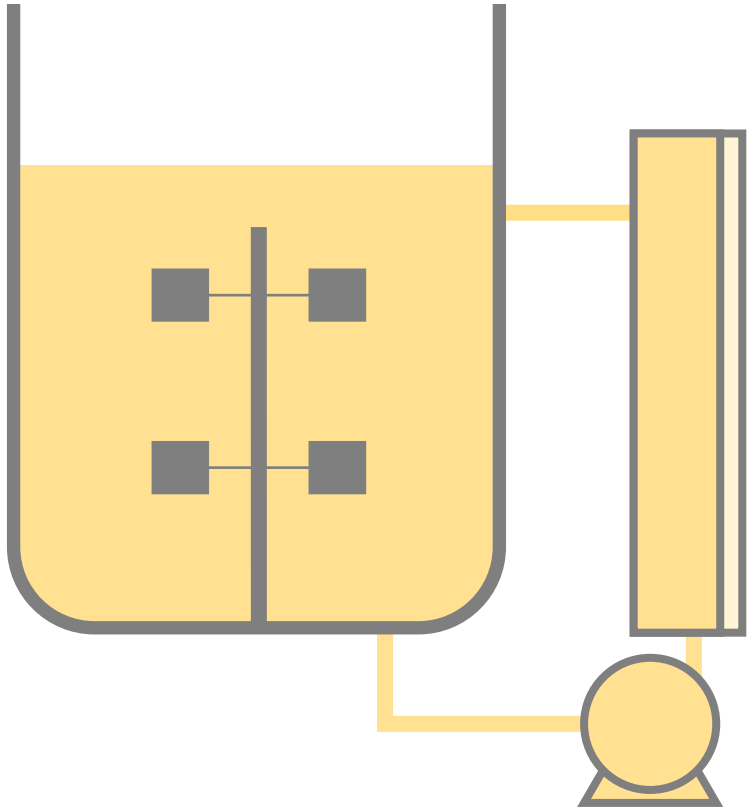
- Lots of knowledge in scaling bioreactors!
  - P/V
  - k_La
  - OUR
  - mixing time
- Cooling
  - Assuming 25 pW/cell [1]
    - 2.2 °C/hr @ 10^8 cells/mL if no cooling
- antifoam usage, and foam-out mitigations

[1] R. B. Kemp, 1993, Thermochimica Acta

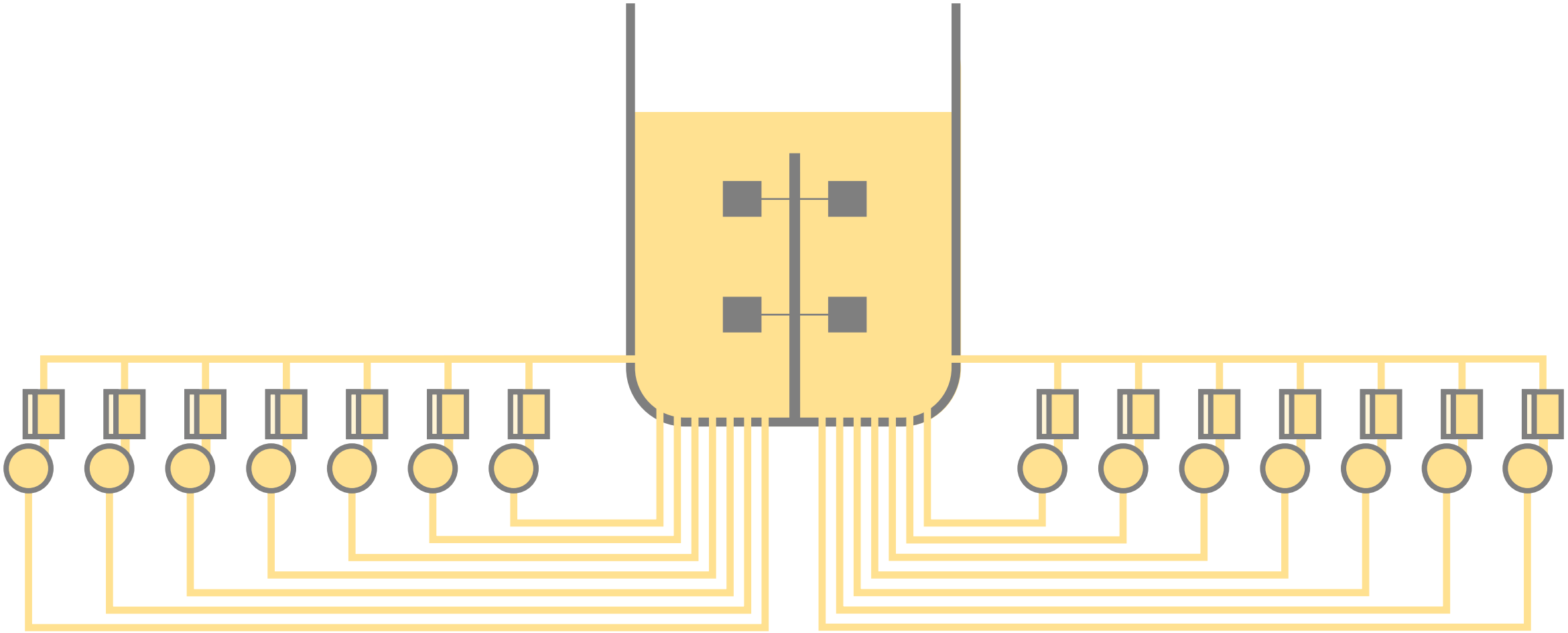
Scaling cell retention device – from 3L

- Scale by filter area

Scale (L)	Working volume (L)	Filter area (m^2)
3	2	0.098
3000	3000	147.0



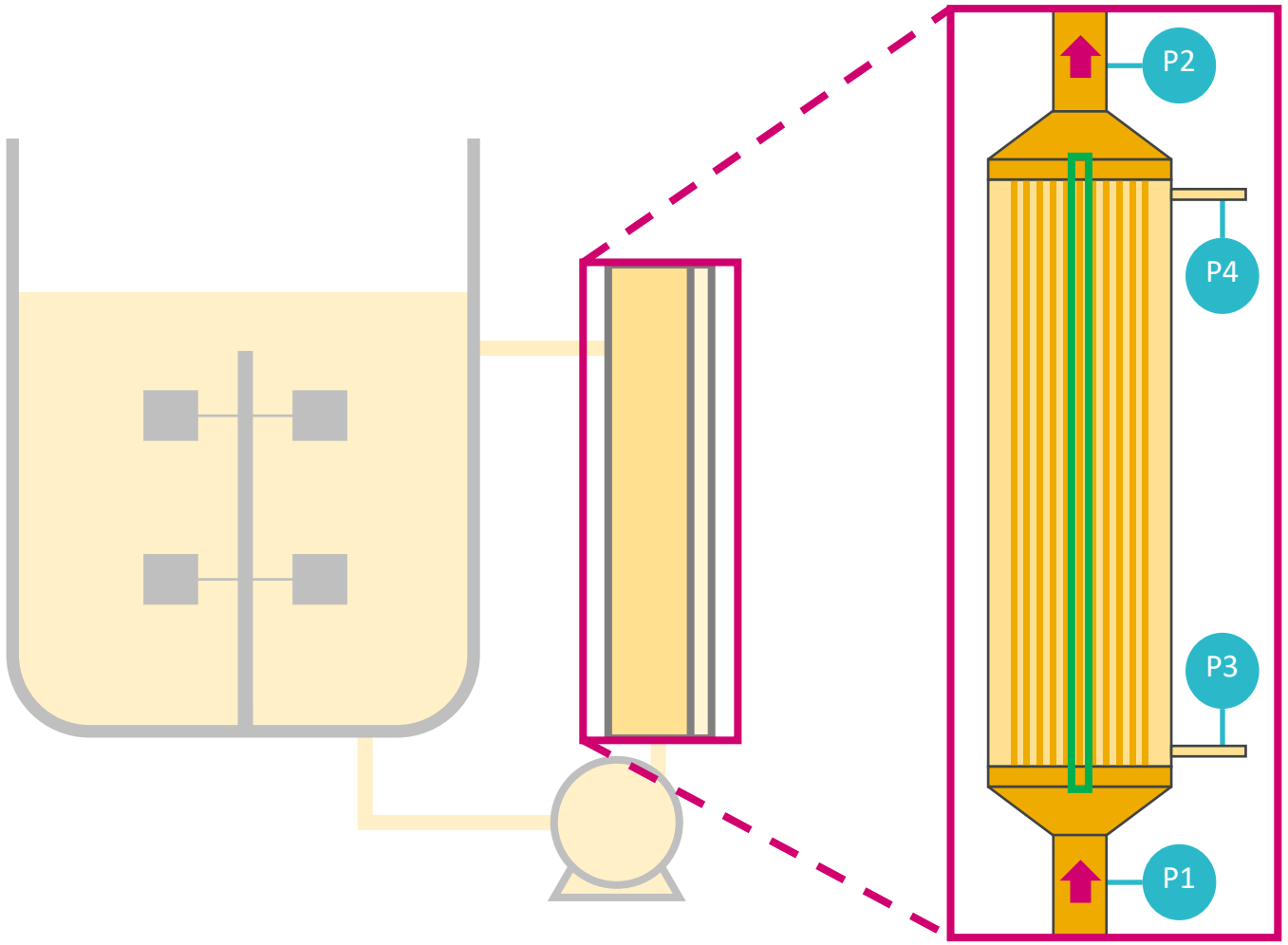
Scaling cell retention device – from 3L



Scaling cell retention device – from 3L

Scaling cell retention device

can we scale differently?

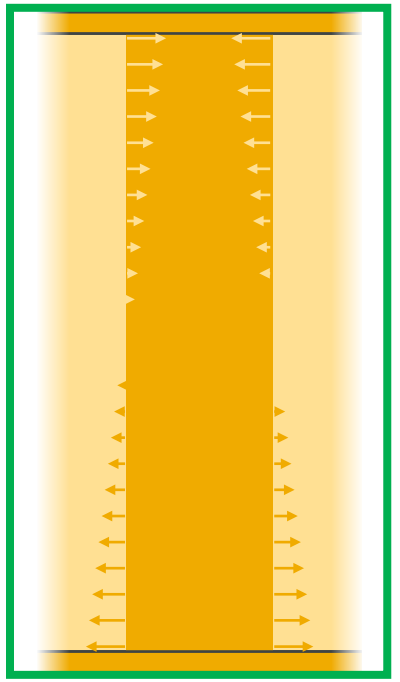


P1 >> P2

P3 ≈ P4

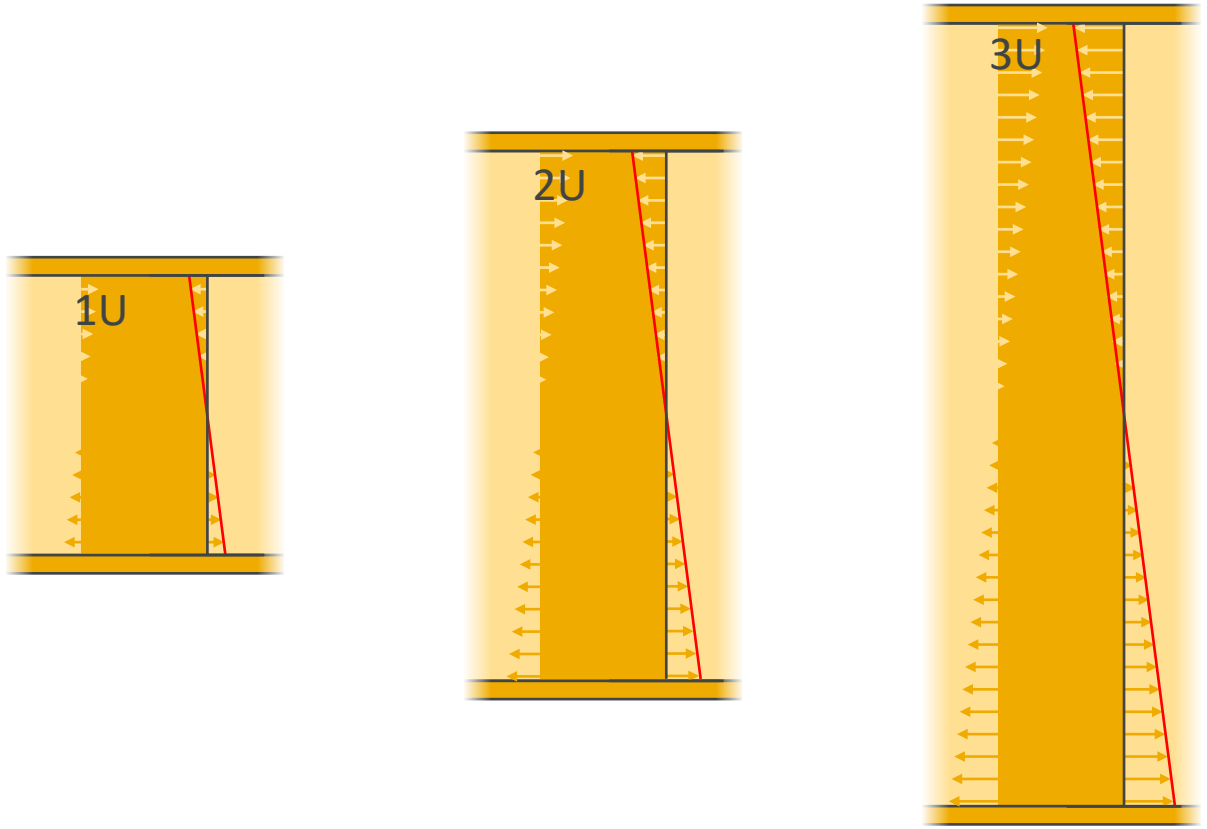
P1 > P3

P2 < P4



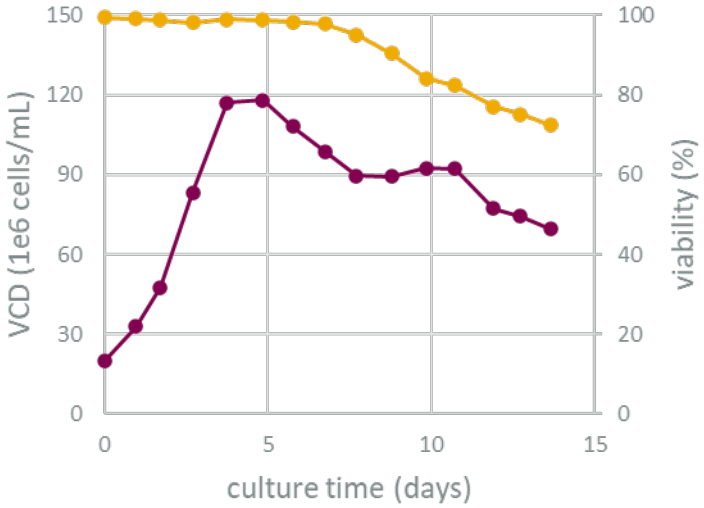
Scaling cell retention device

- Increasing hollow fiber length exacerbates the problem

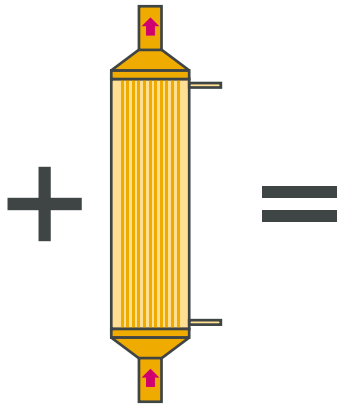


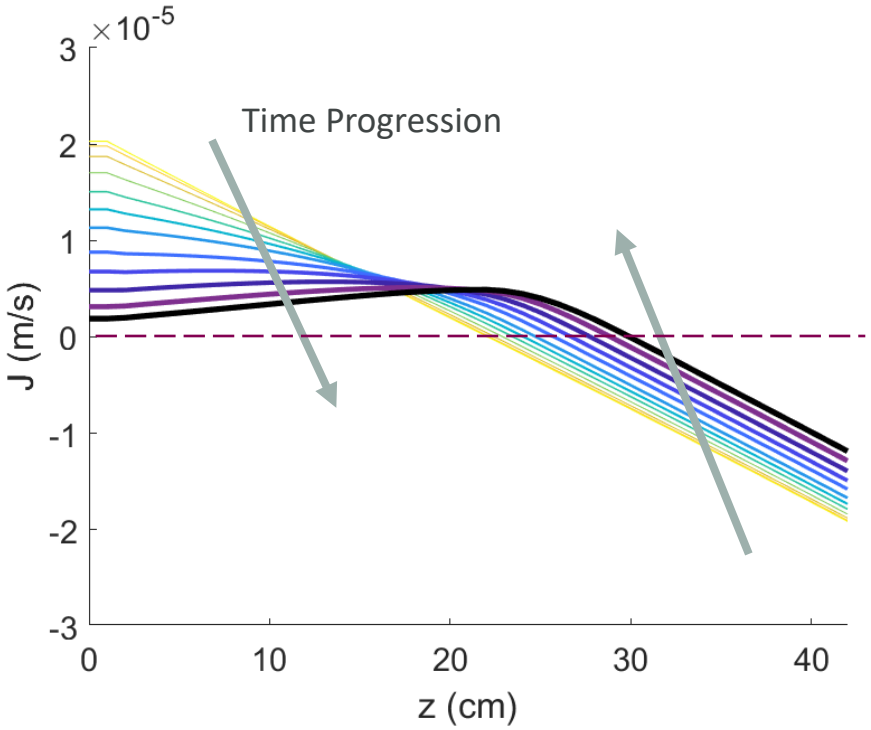
Scaling cell retention device

- Increasing hollow fiber length exacerbates the problem
- Once fouling starts flux changes unpredictably

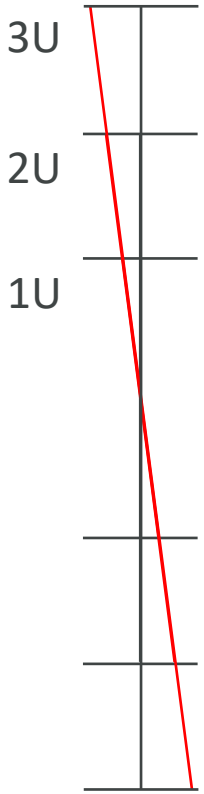


Data from Dominique WuDunn



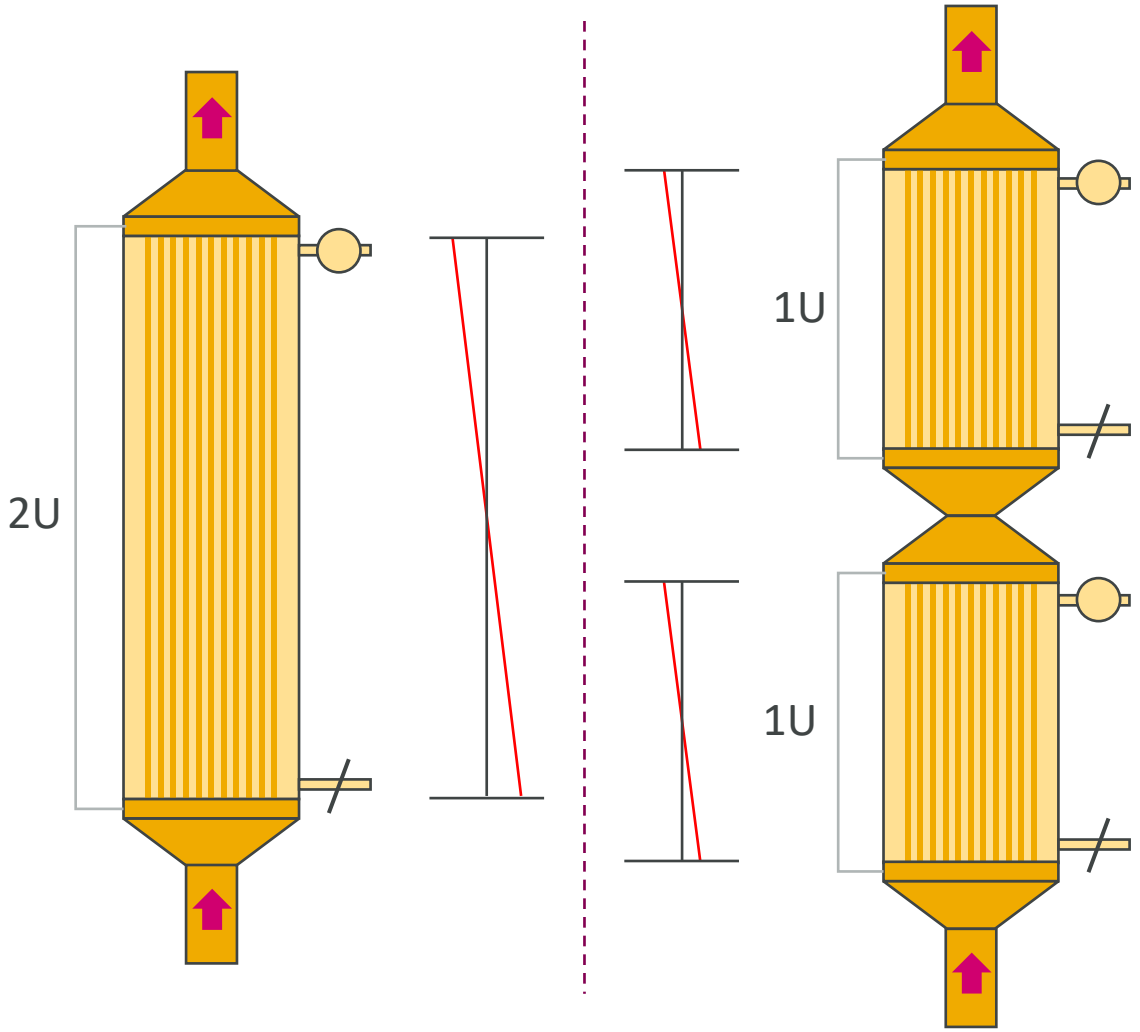


Data from Ashna Dhingra

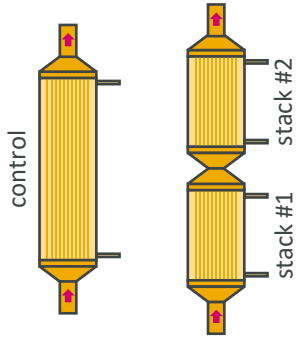


Reduce ΔP at inlet and outlet

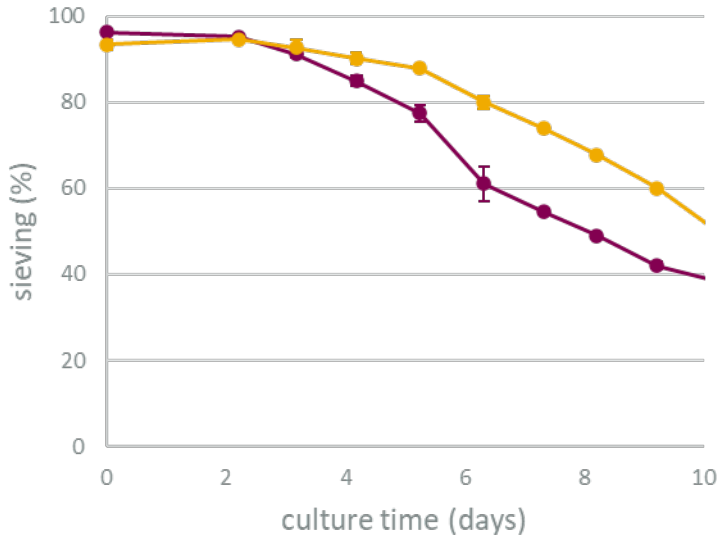
- Change the way hollow fibers are configured
  - Reducing hollow fiber length will increase overall lifetime of the filter

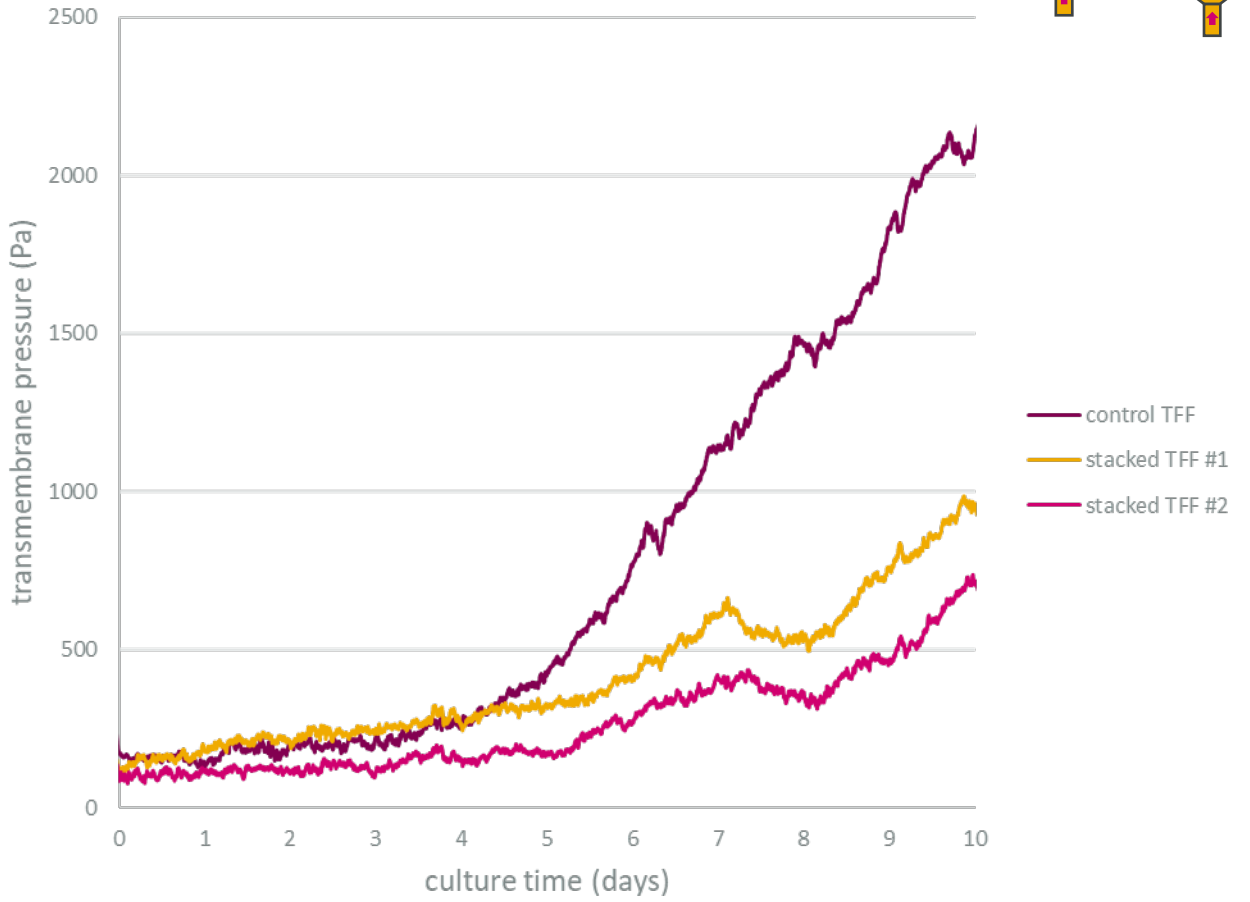


Change hollow fiber configuration



- Reducing hollow fiber height reduces TMP significantly
- Improves product sieving

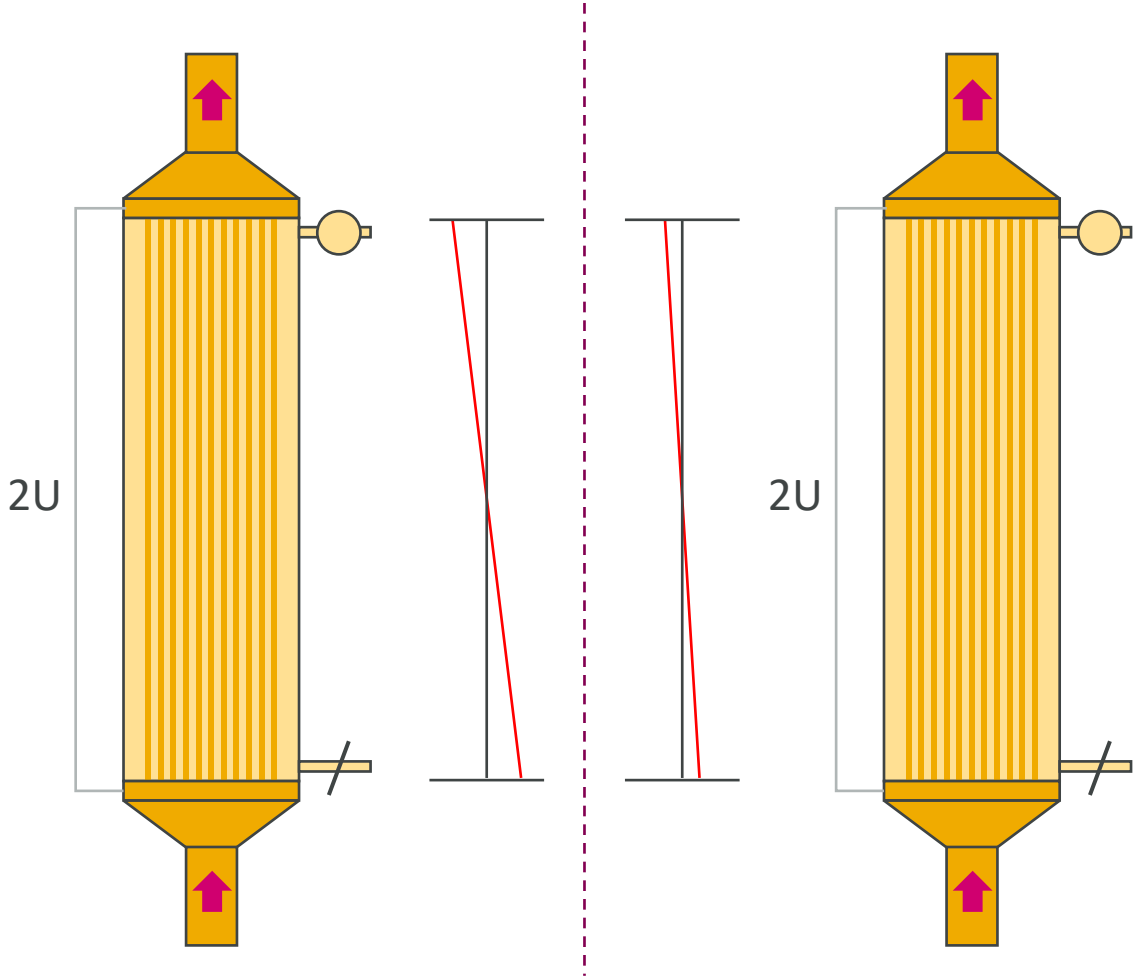




data from Jimmy Vu

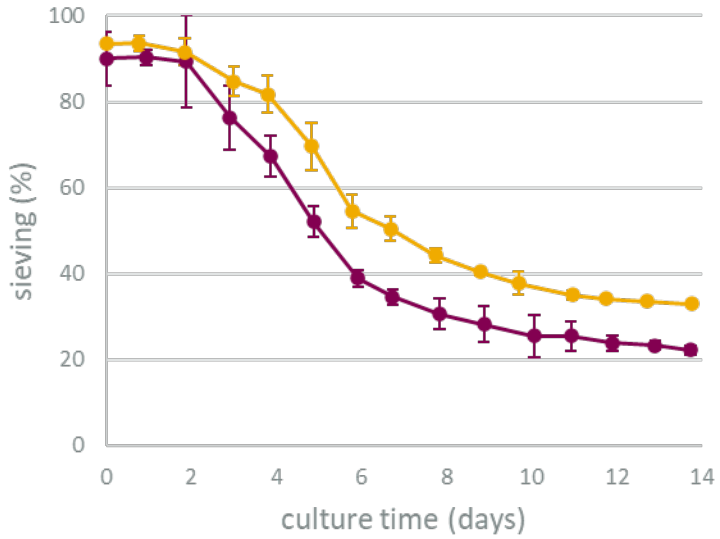
Reduce ΔP at inlet and outlet

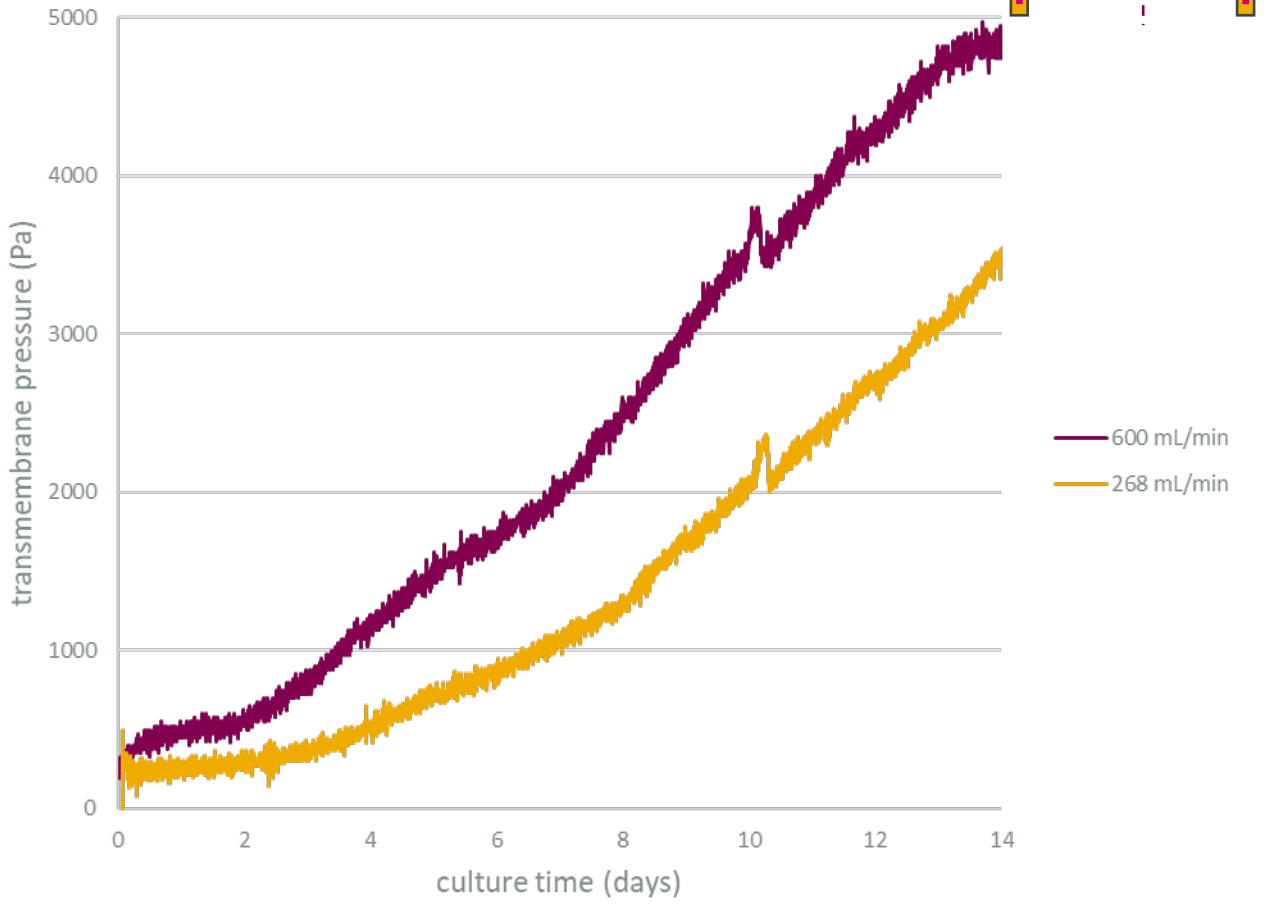
- Change the way hollow fibers are configured
  - Reducing hollow fiber length will increase overall lifetime of the filter
- Reduce flowrate
  - Reduces TMP at the extremes



Reduce flowrate

- Lower flowrate improves sieving
- Simple to implement

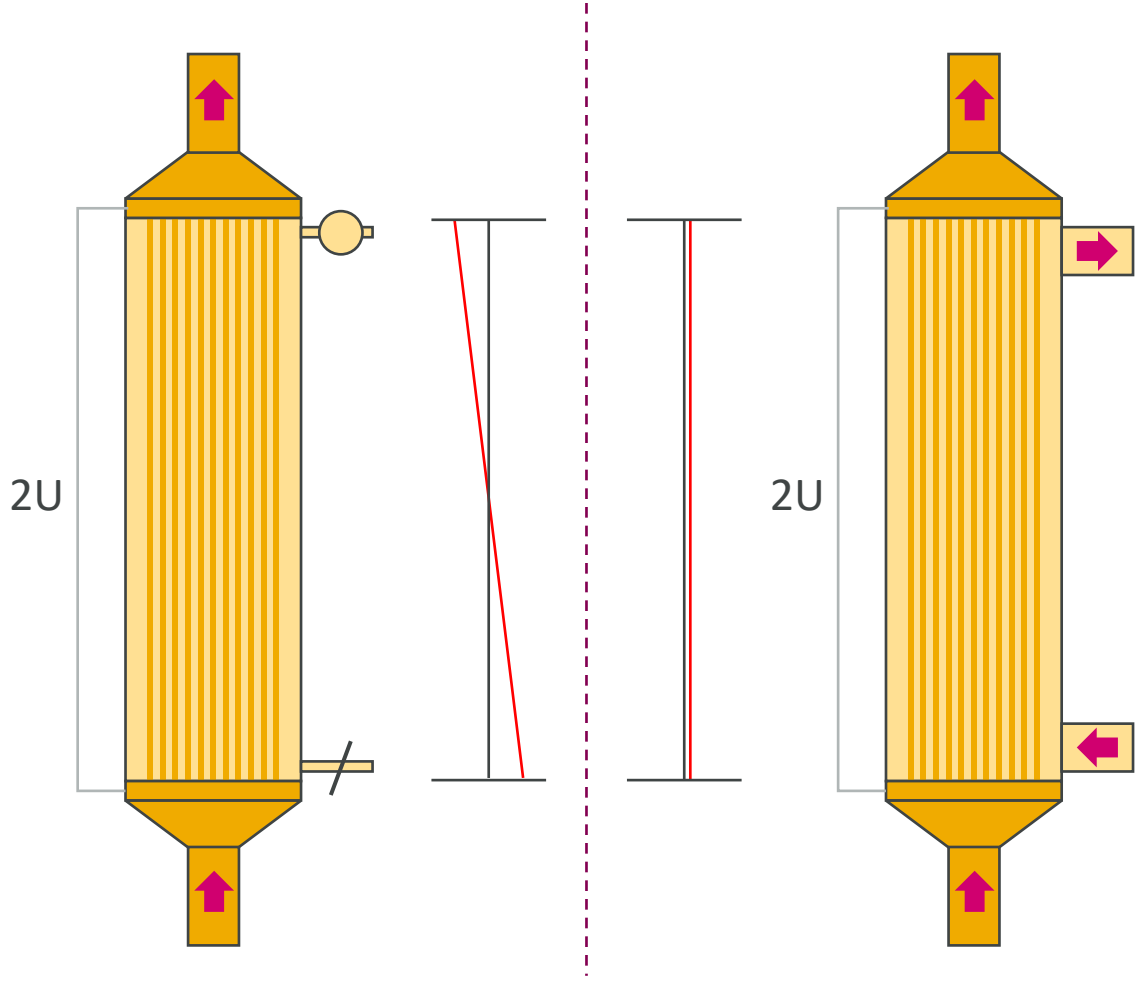




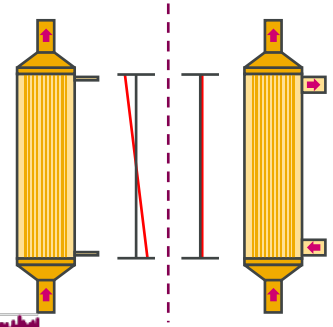
data from Andrea Squeri

Reduce ΔP at inlet and outlet

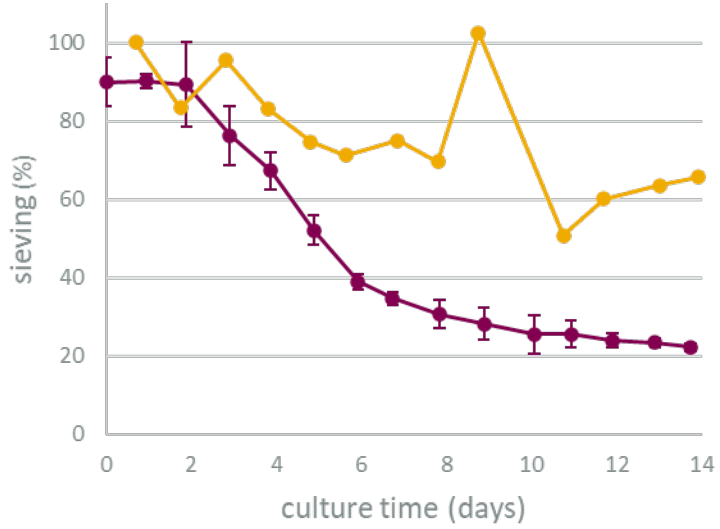
- Change the way hollow fibers are configured
  - Reducing hollow fiber length will increase overall lifetime of the filter
- Reduce flowrate
  - Reduces TMP at the extremes
- Exert equal pressure on the permeate
  - Significantly reduce Starling flow / Darcy flow

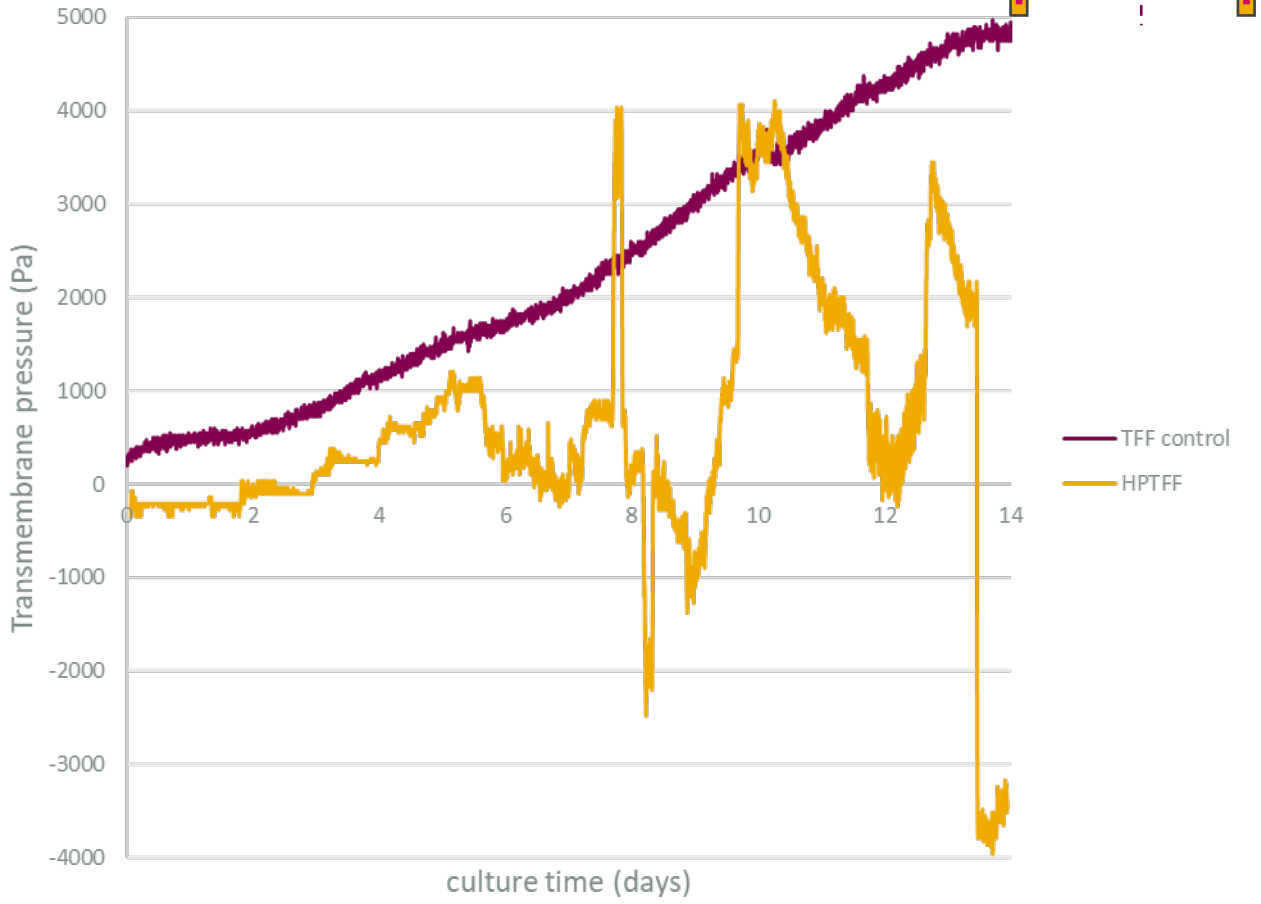


Exert equal pressure on the permeate: HPTFF



- Based on work by Robert van Reis[1]
- Hypothesis works in principle
- Requires more complex control system





data from Jimmy Vu

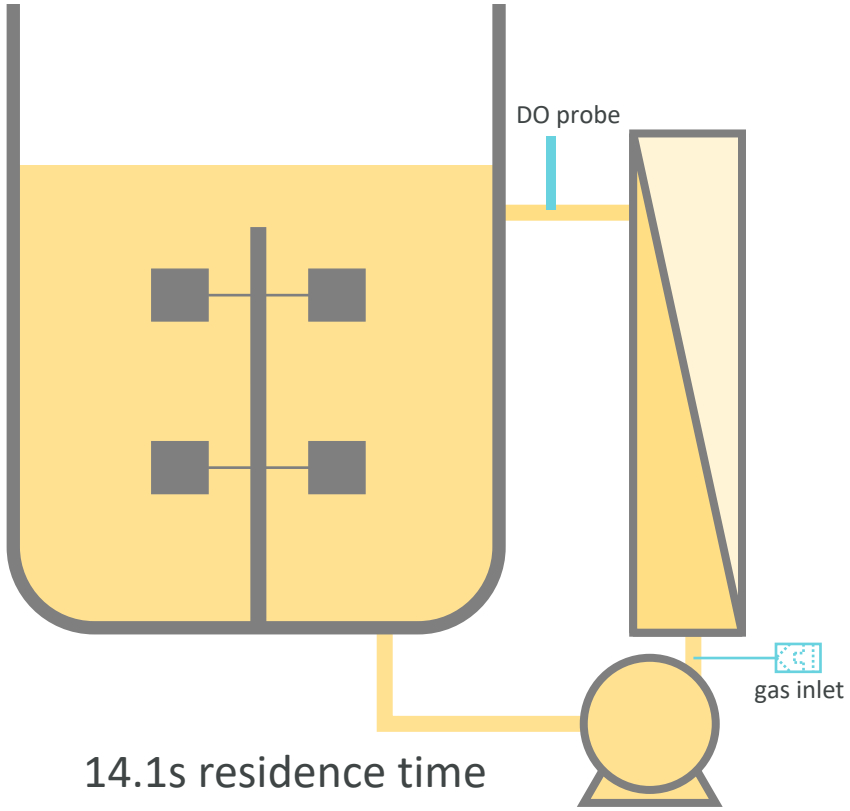
[1] *van Reis et al., 1997, Biotechnol Bioeng*

Strengths and weaknesses

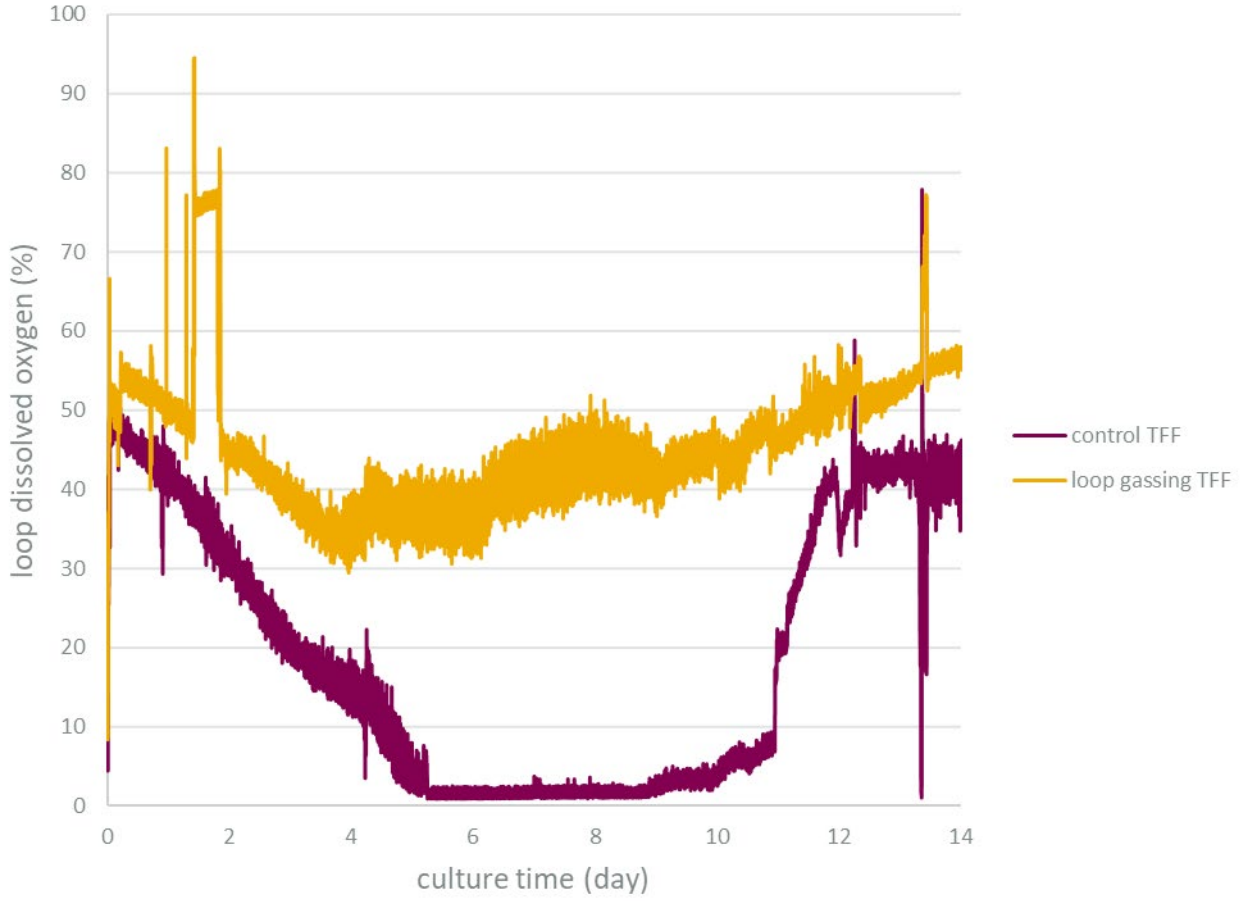
Configuration	Strength	Weakness
Stacked fibers	• Simple implementation • Moderate improvement to sieving	• More hardware: permeate pumps • Increased pressure head = increased shear rate
Low flowrate	• Simple implementation • No additional hardware required	• Significant oxygen limitation
HPTFF	• Significant improvement to sieving	• Significantly more complex implementation

Additional to ICB2022 presentation: increasing lumen diameter also reduces pressure across the hollow fiber and therefore reduces Starling flow / Darcy flow

Addressing DO exhaustion



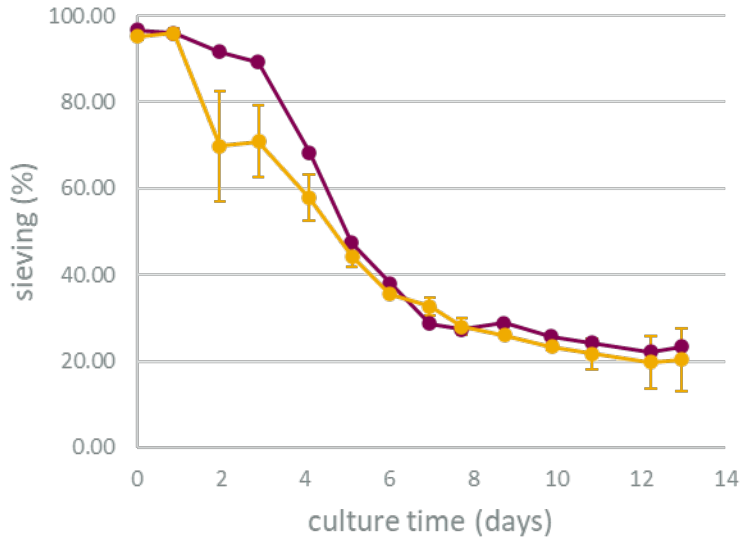
14.1s residence time

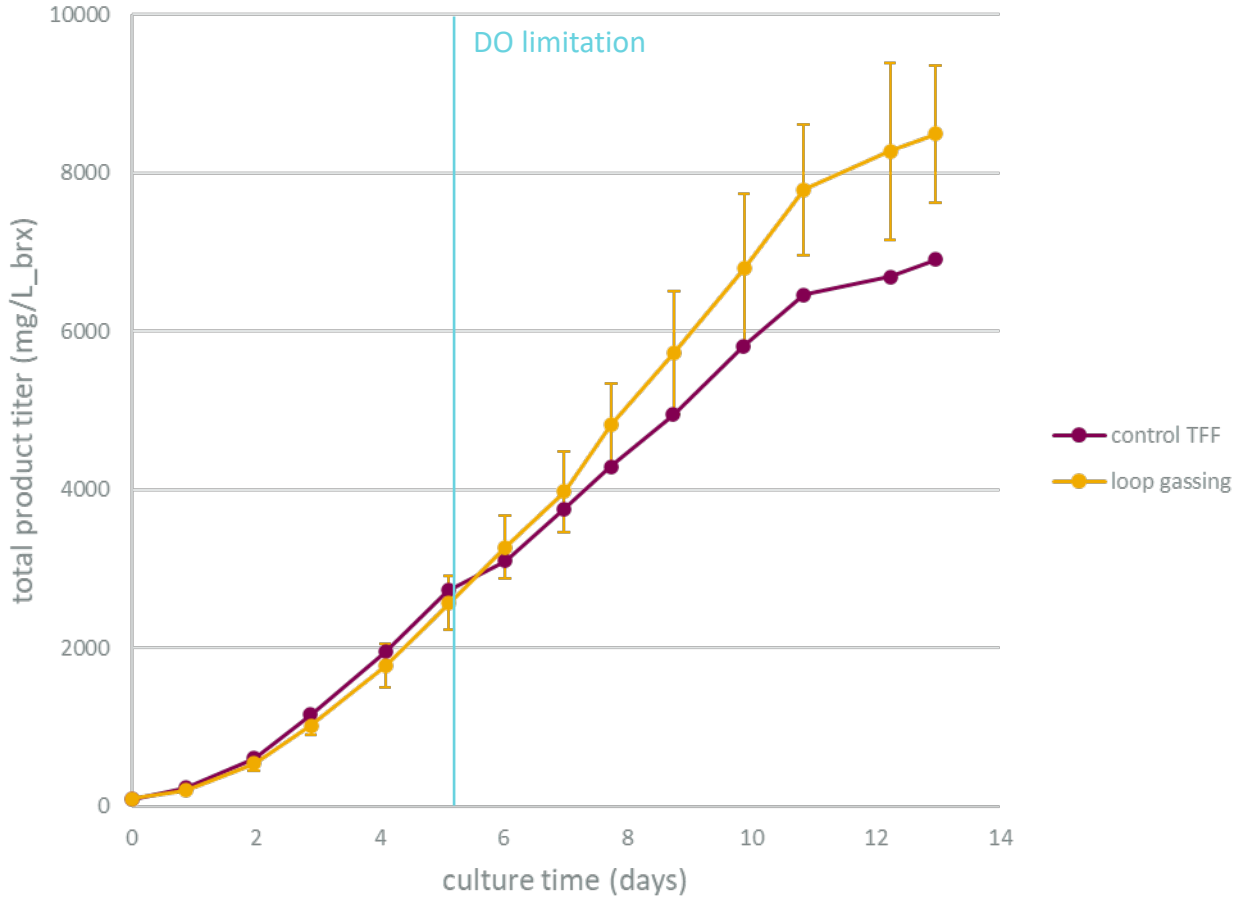


data from Andrea Squeri

Addressing DO exhaustion

- Improving DO in the recirculating loop also helped improve productivity
- Does not affect sieving

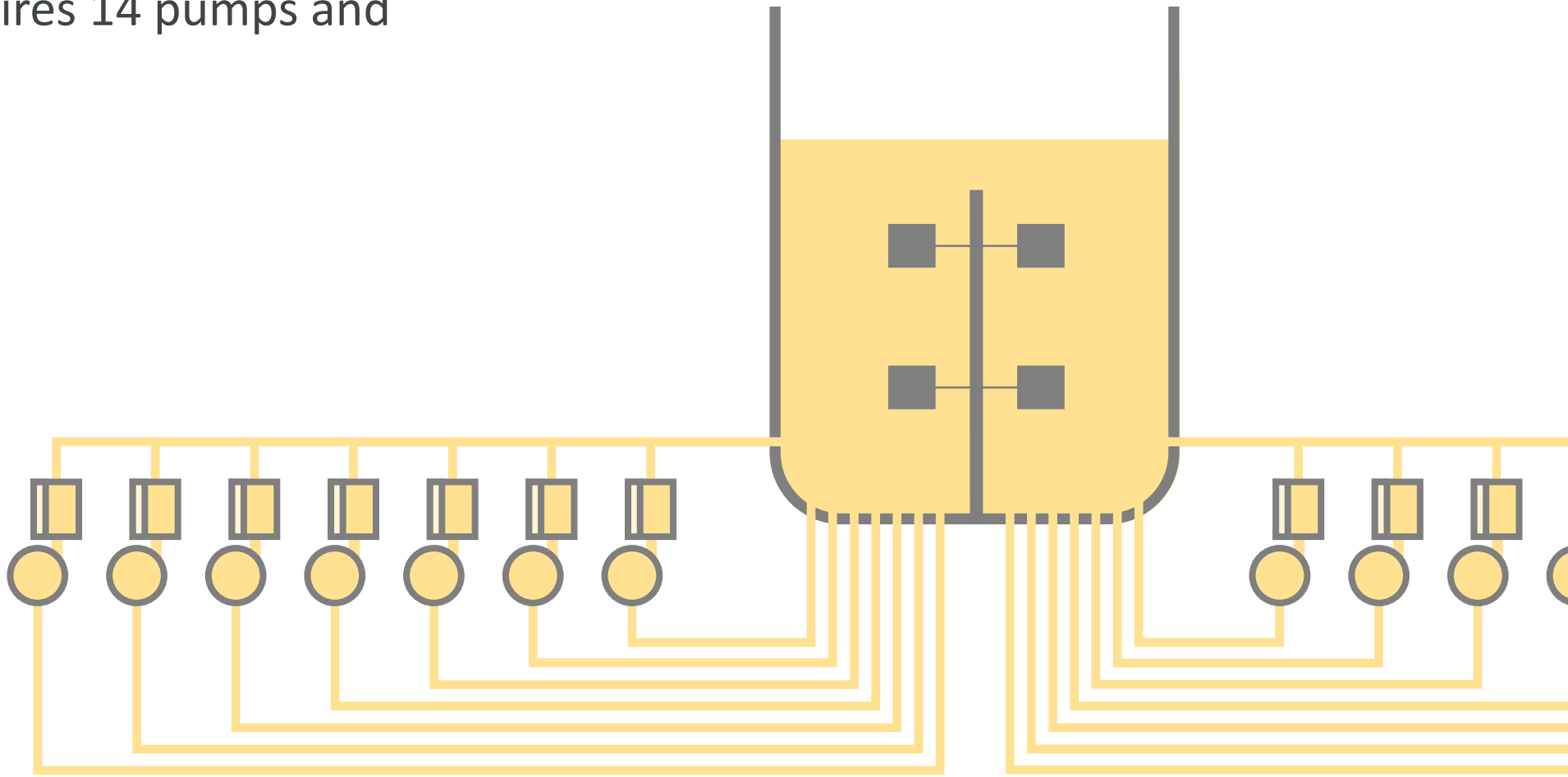




data from Andrea Squeri

Standard configuration

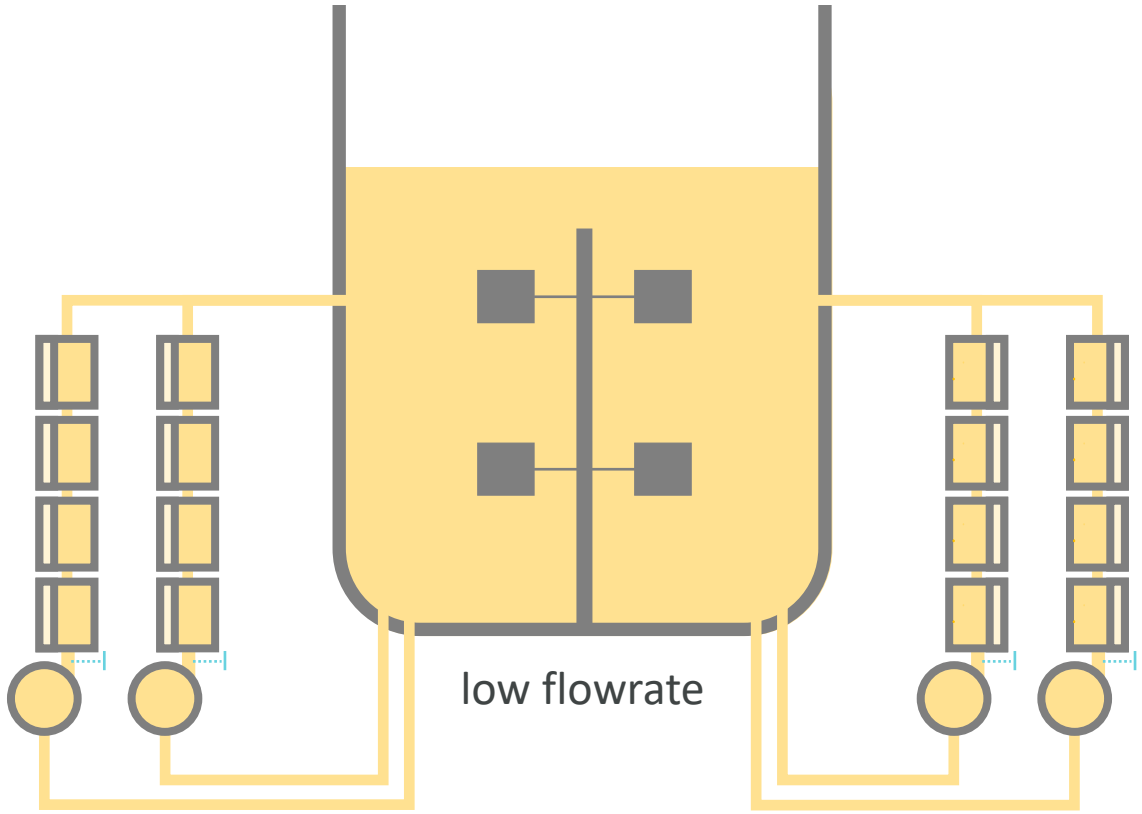
- Original setup requires 14 pumps and 14 hollow fibers



Combining everything – stage 1

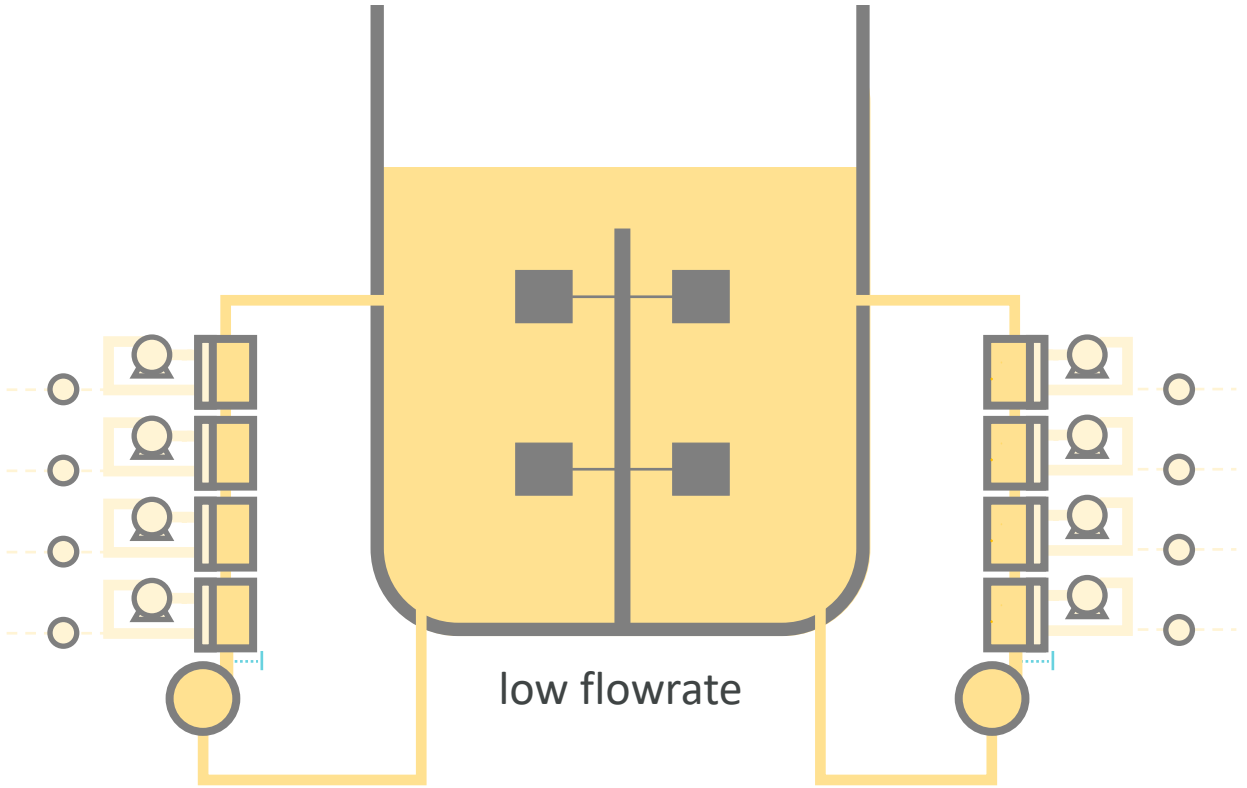
- Stage 1 enables reduced recirculating pumps
  - Stacking hollow fibers

- stacked hollow fibers increase residence time
  - Introduce gas flow into recirculating loop



Combining everything – stage 2

- Stage 2 enables further reduction in recirculation pumps
- Higher residence times mitigated by loop gassing



acknowledgements

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