

10-12-2022

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

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### Recommended Citation

Kenneth Lee, "Design considerations when scaling from 3-L to 3000-L or larger" in "Integrated Continuous Biomanufacturing V", Ana Azevedo, Técnico Lisboa, Portugal; Jason Walther, Sanofi, USA; Rohini Deshpande, Amgen, USA Eds, ECI Symposium Series, (2022). [https://dc.engconfintl.org/biomanufact\\_v/](https://dc.engconfintl.org/biomanufact_v/)  
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# Design considerations when scaling from 3L to 3000L or larger

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12 October 2022

# 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**

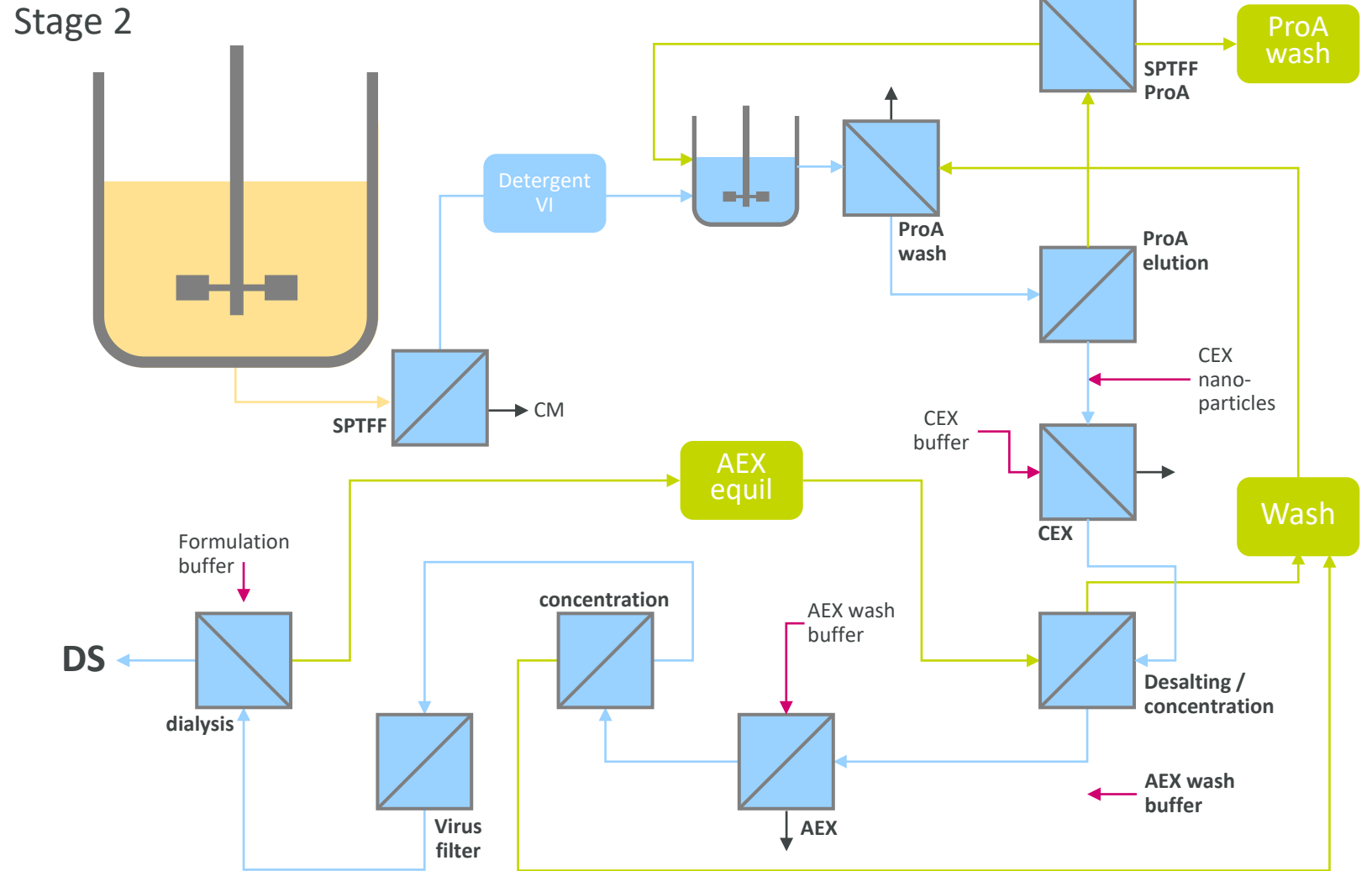
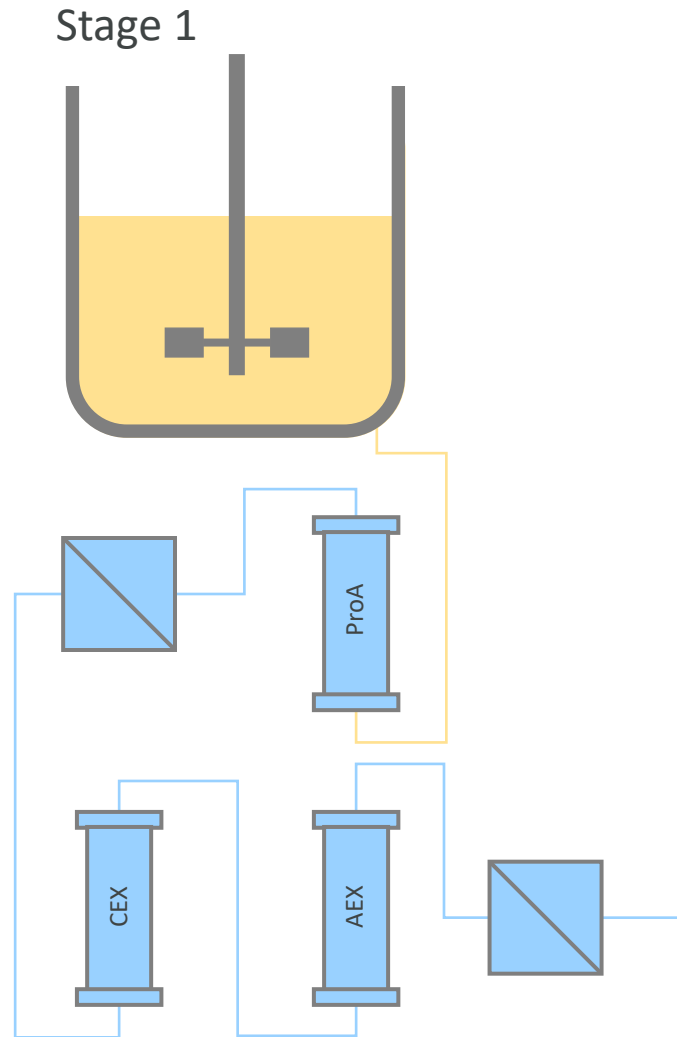




“Why aren’t we doing this  
with every molecule?”

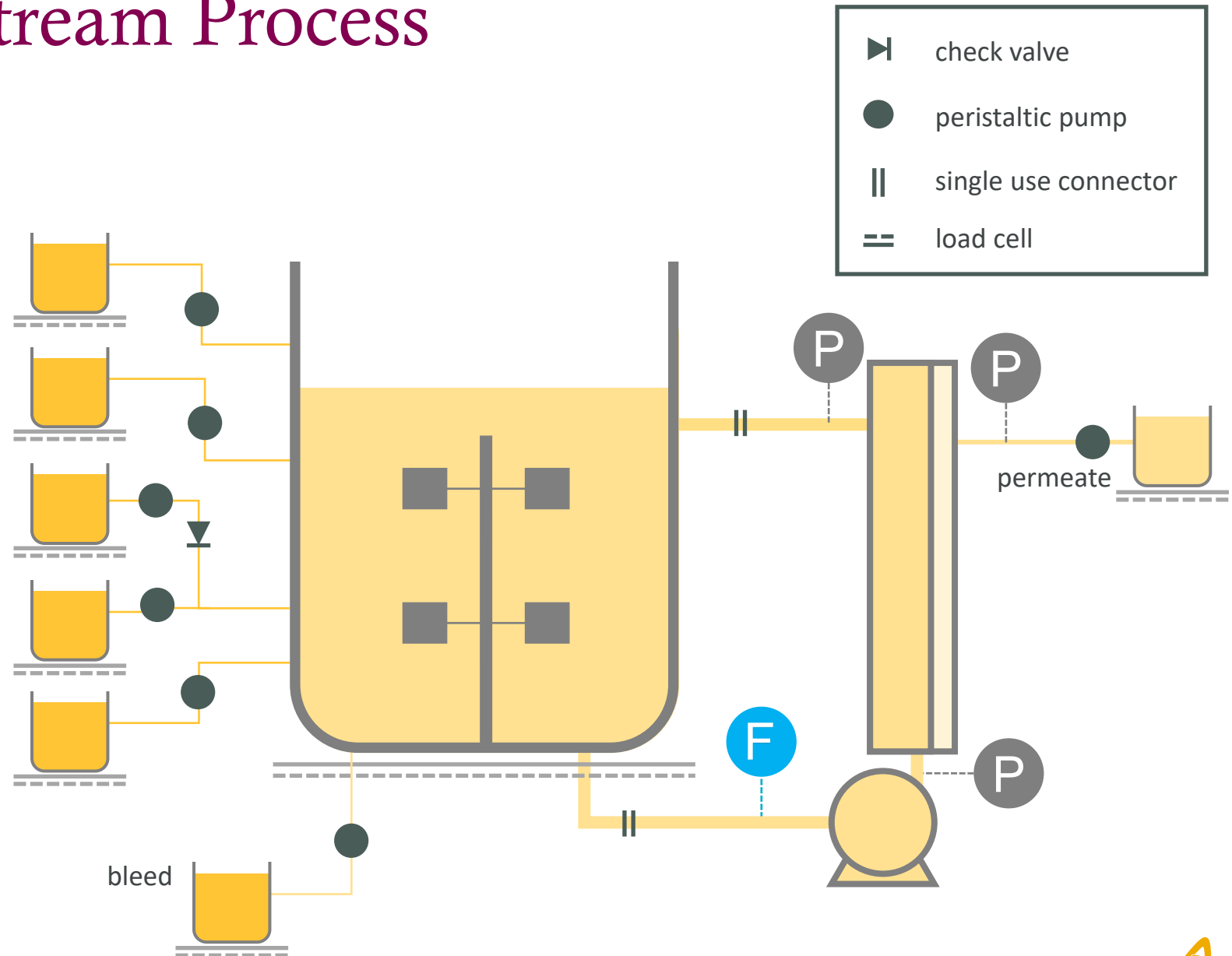
Pascal Soriot, CEO of AZ

# 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!
  - $P/V$
  - $k_L a$
  - OUR
  - mixing time
- Cooling
  - Assuming 25 pW/cell <sup>1</sup>
    - 2.2 °C/hr @  $10^8$  cells/mL if no cooling
- antifoam usage, and foam-out mitigations

<sup>\*1</sup> R. B. Kemp, 1993, *Thermochimica Acta*

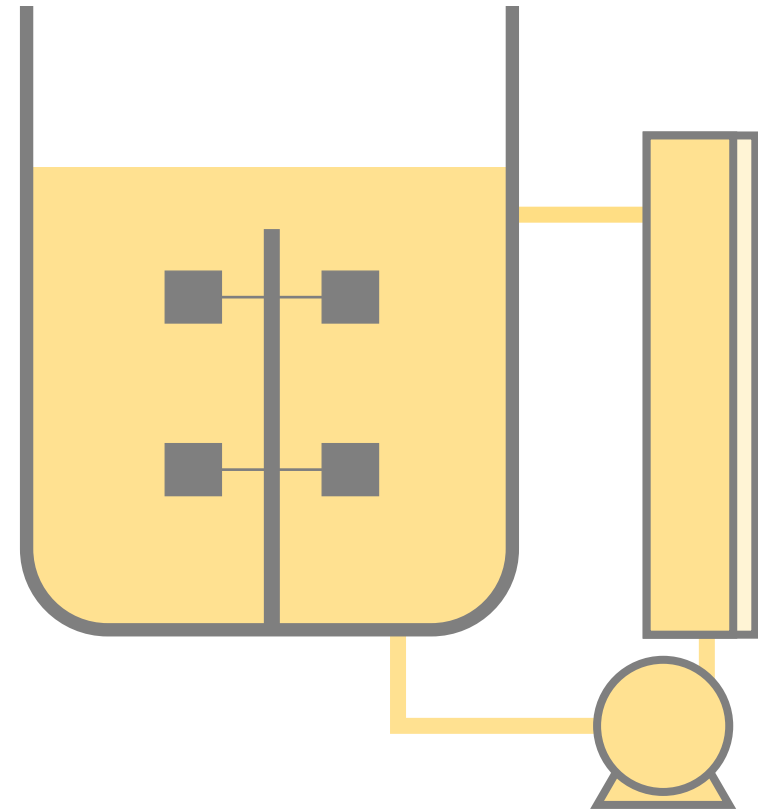


# Scaling cell retention device – from 3L



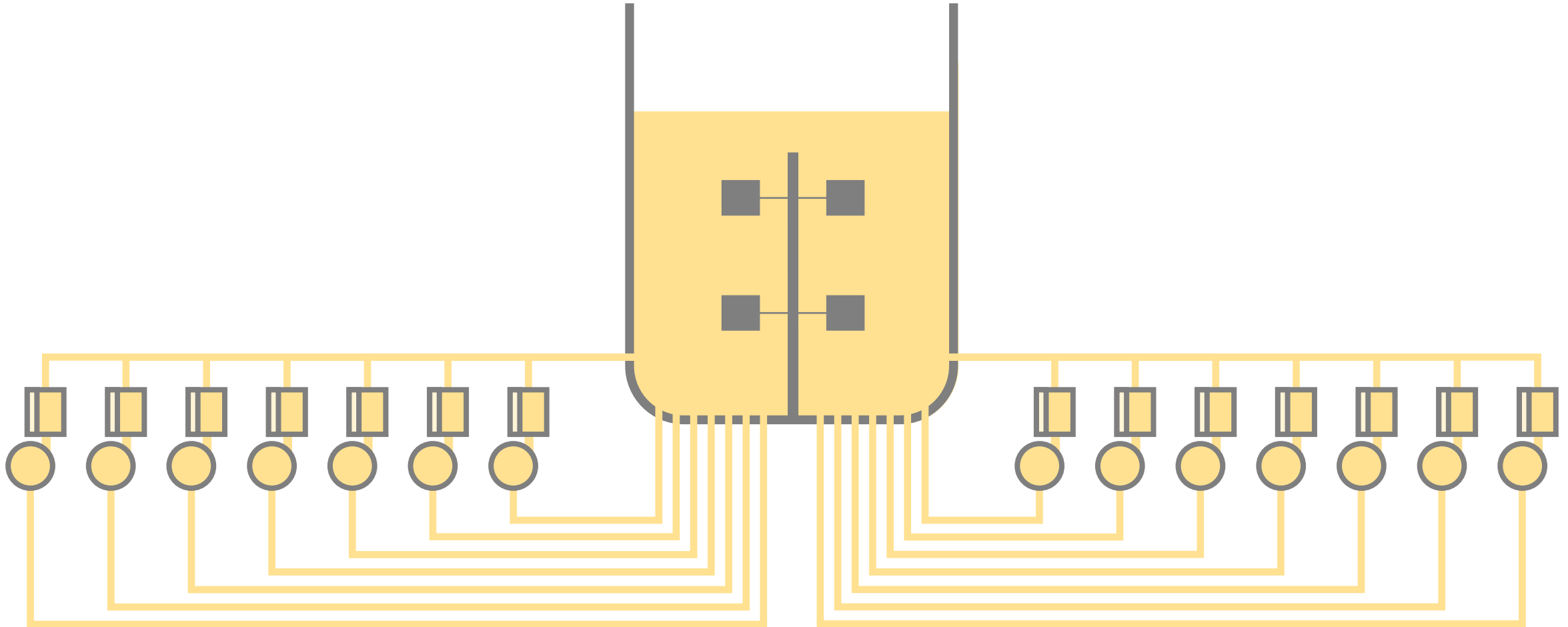
- Scale by filter area

Scale (L)	Working volume (L)	Filter area (m <sup>2</sup> )
3	2	0.098
3000	3000	147.0





# Scaling cell retention device – from 3L



# Scaling cell retention device – from 3L

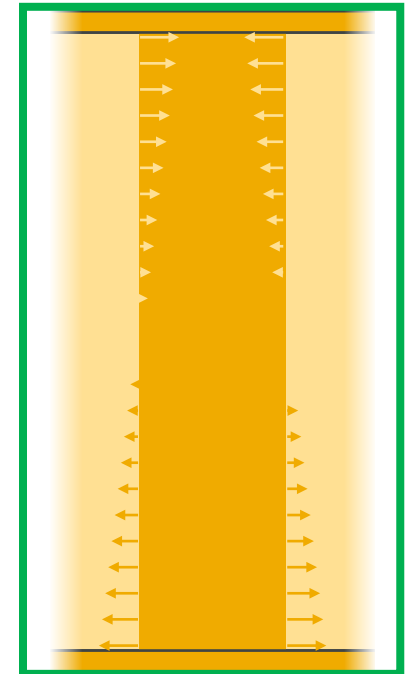
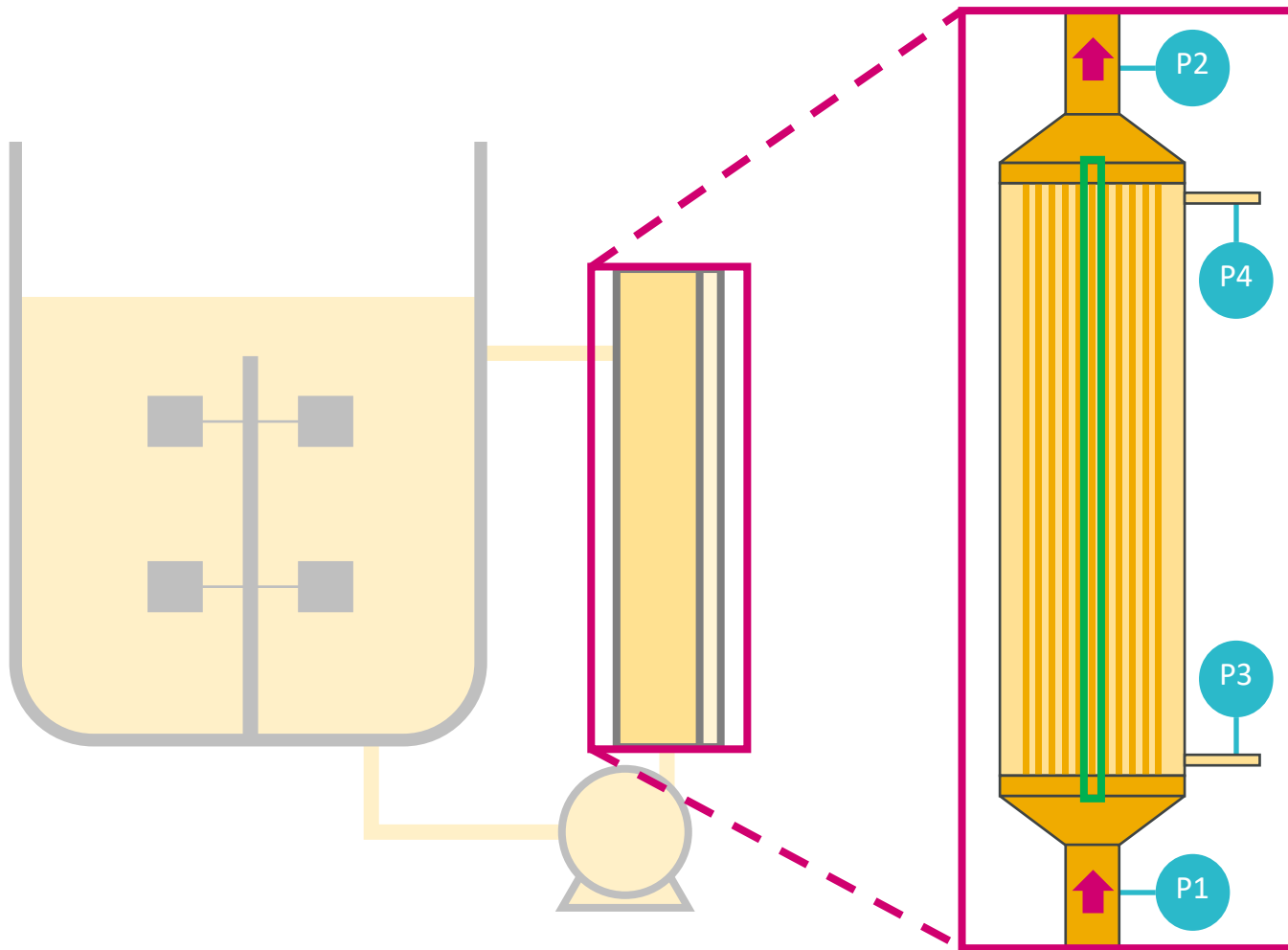


Image by Andree Wallin



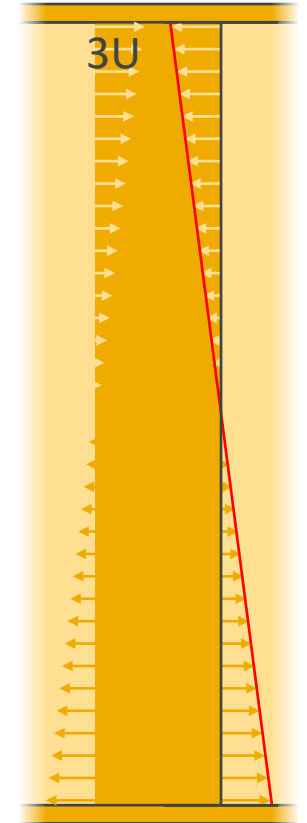
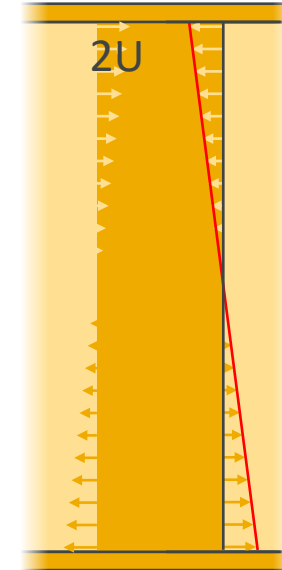
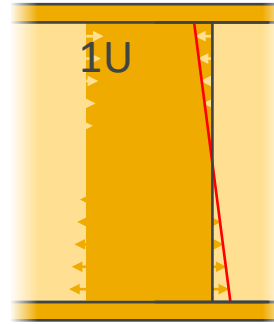
# Scaling cell retention device

*can we scale differently?*



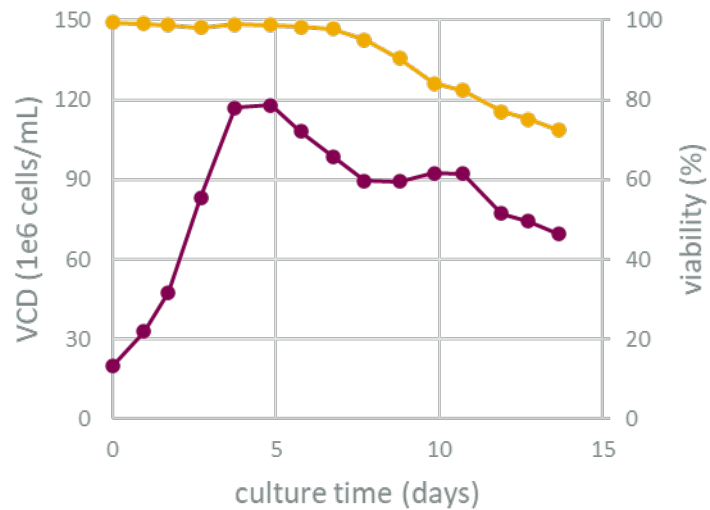
# Scaling cell retention device

- Increasing hollow fiber length exacerbates the problem

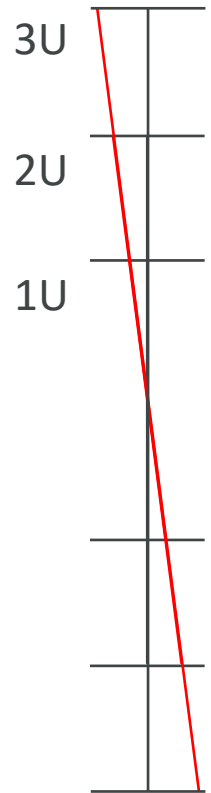
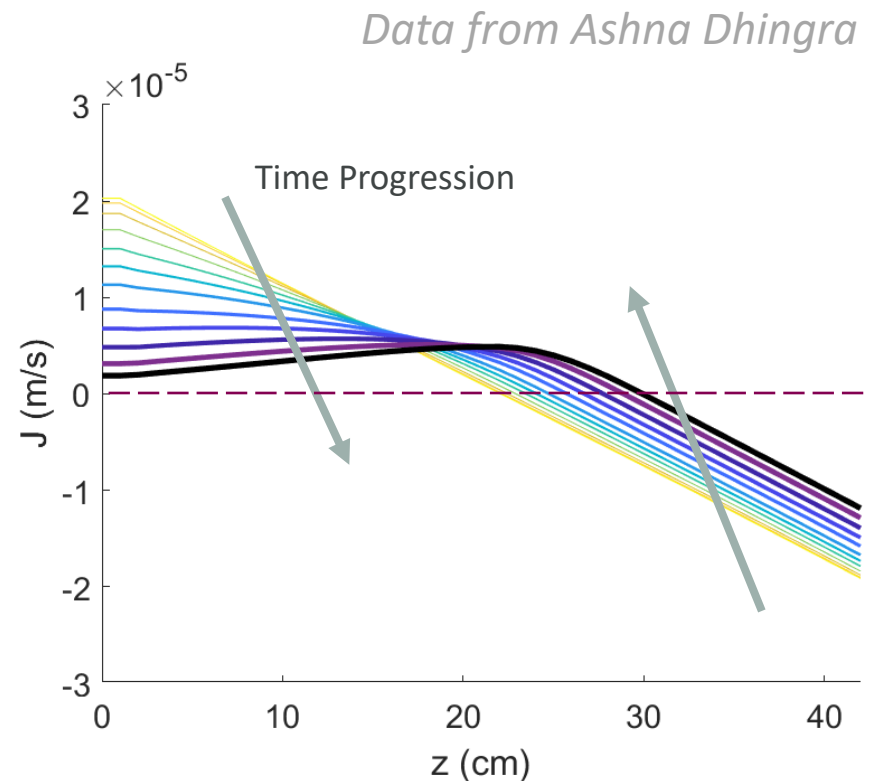
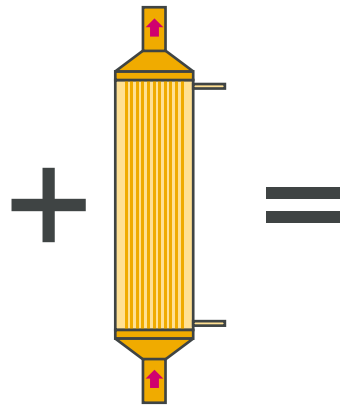


# Scaling cell retention device

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

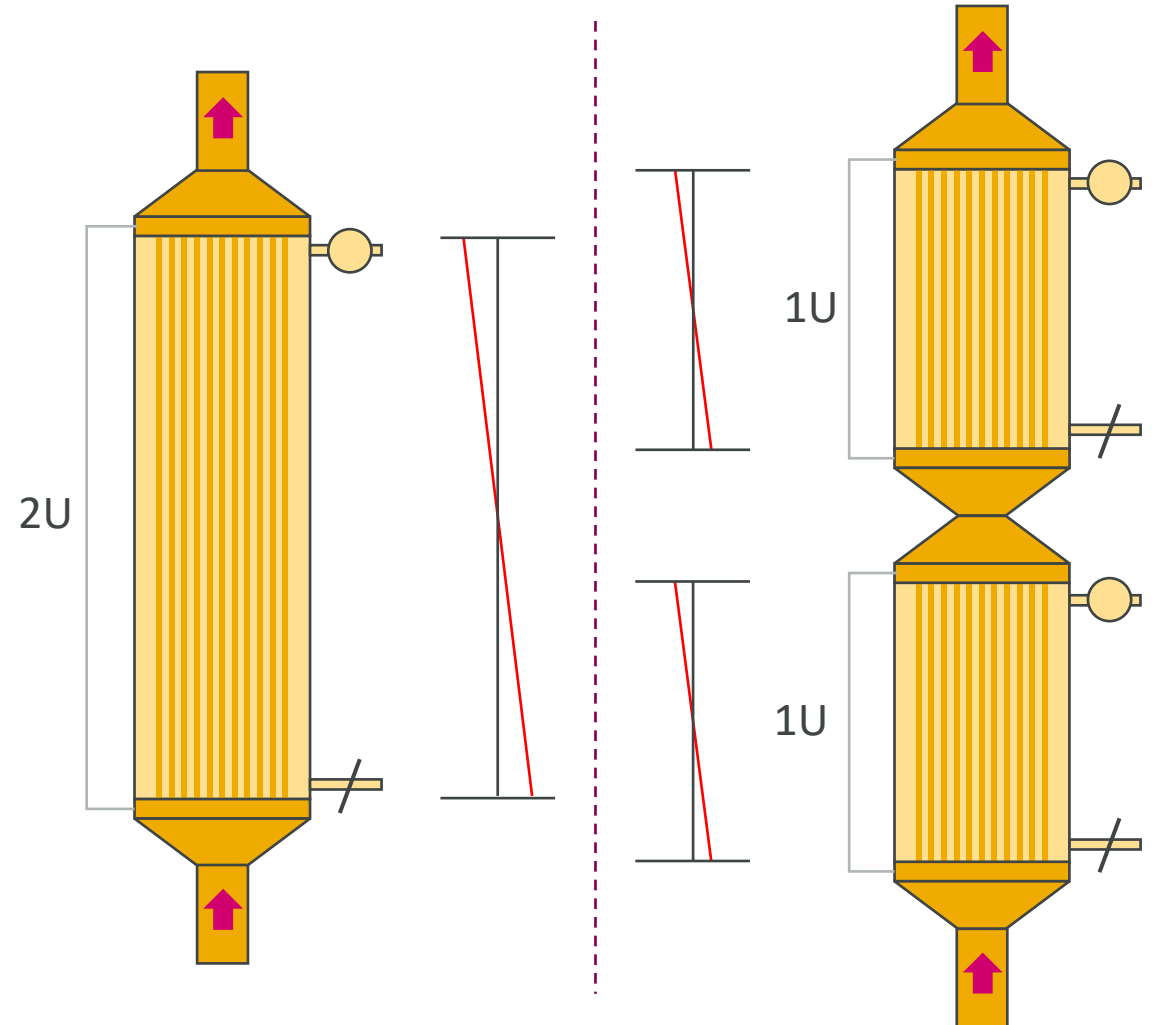


*Data from Dominique WuDunn*



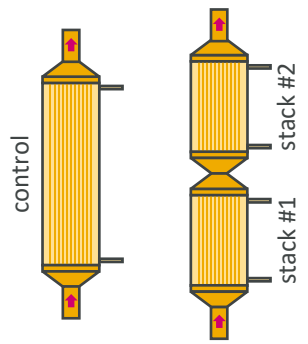
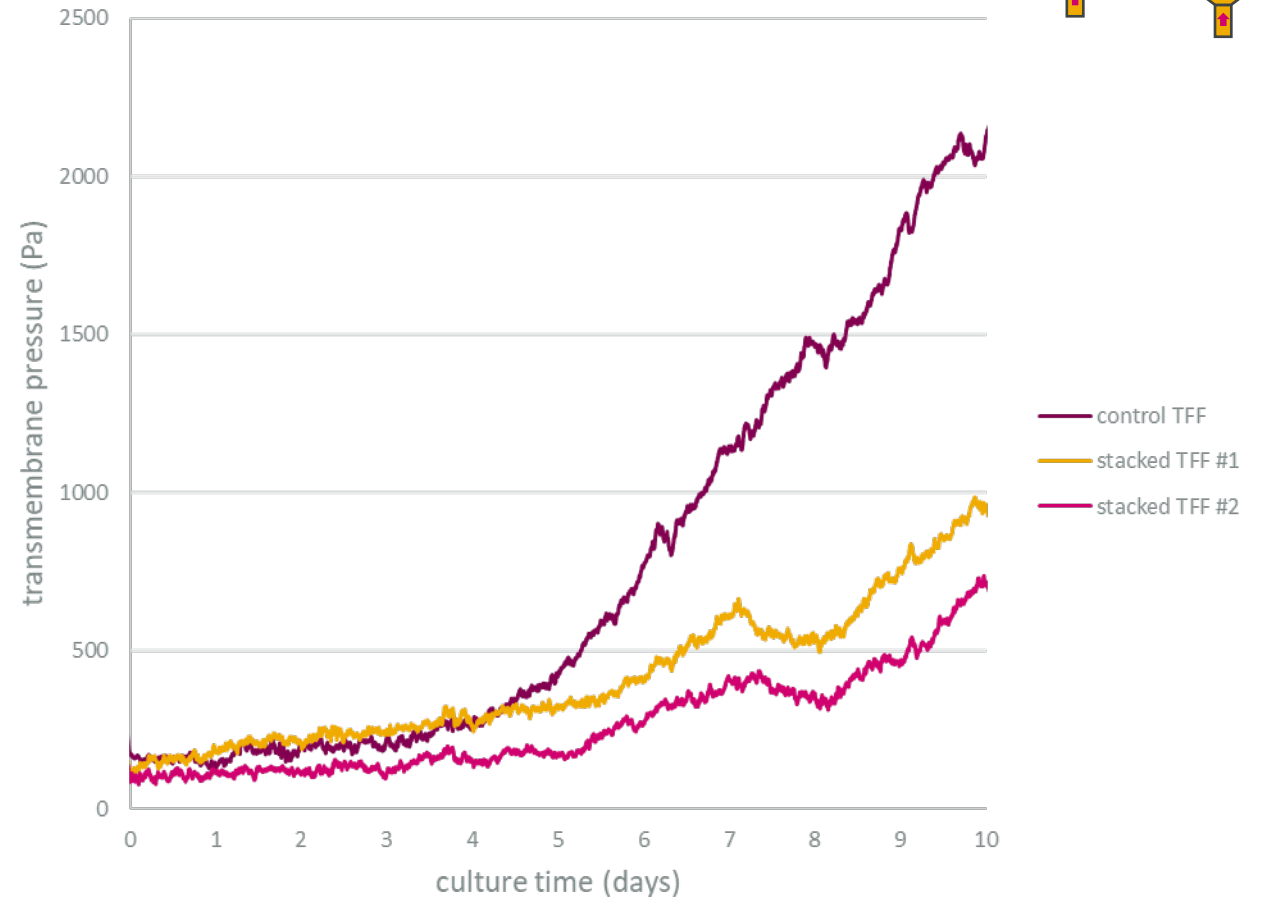
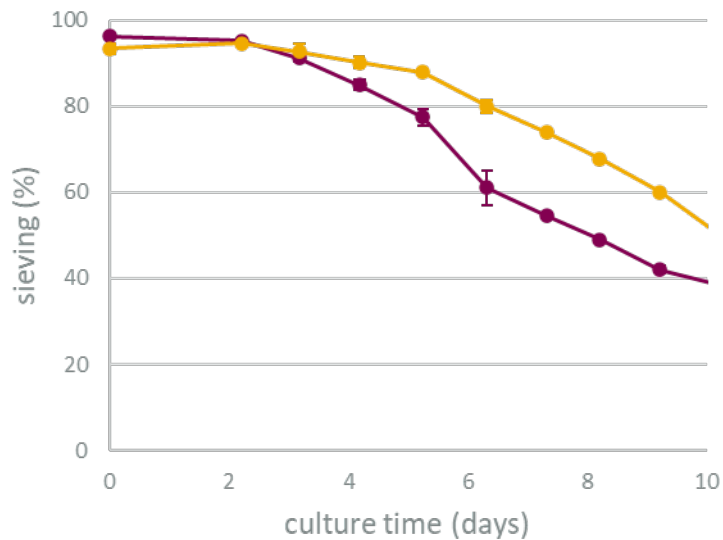
# Reduce $\Delta P$ at inlet and outlet

- 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

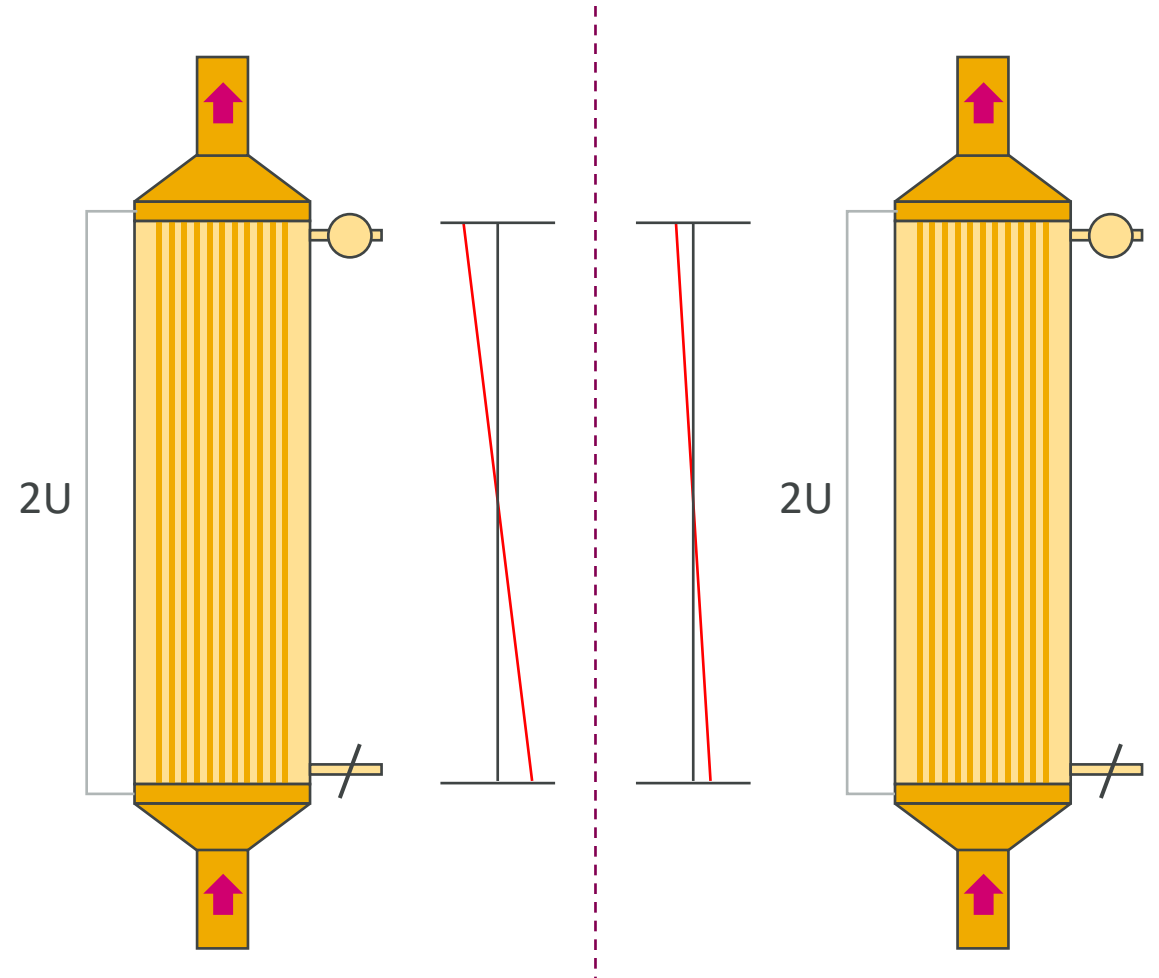


*data from Jimmy Vu*



# Reduce $\Delta P$ at inlet and outlet

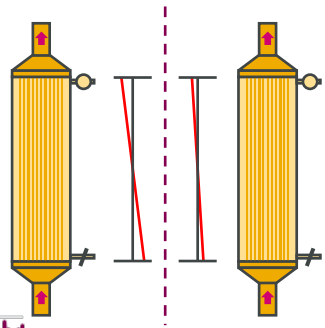
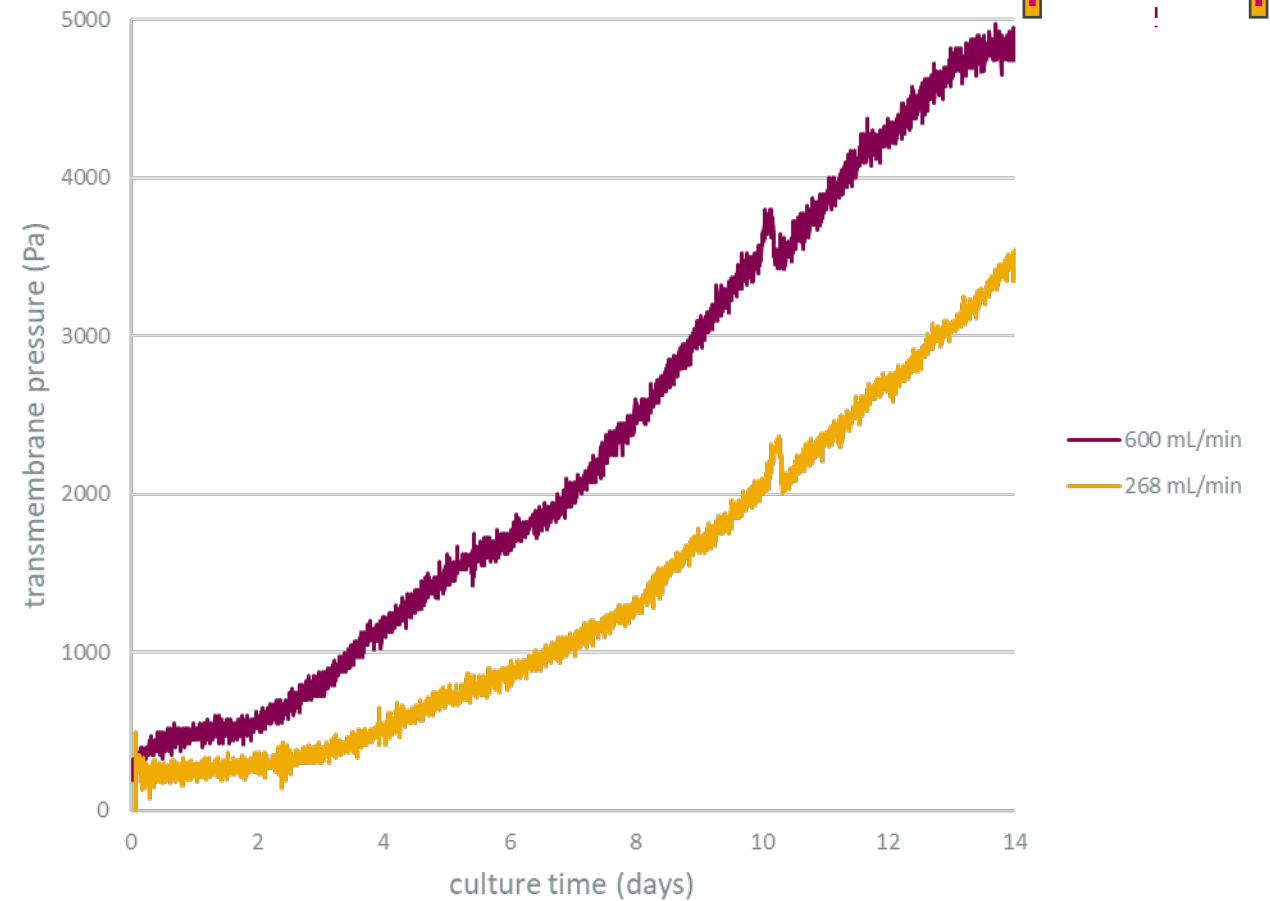
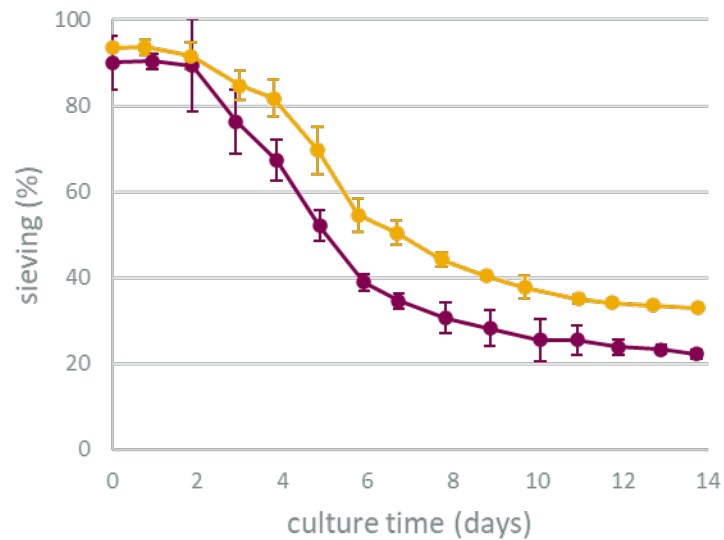
- Change the way hollow fibers are configured
  - Reducing hollow fiber length will increase overall lifetime of the filter
- Reduce flowrate
  - Reduces TMP at the extremes





# Reduce flowrate

- Lower flowrate improves sieving
- Simple to implement

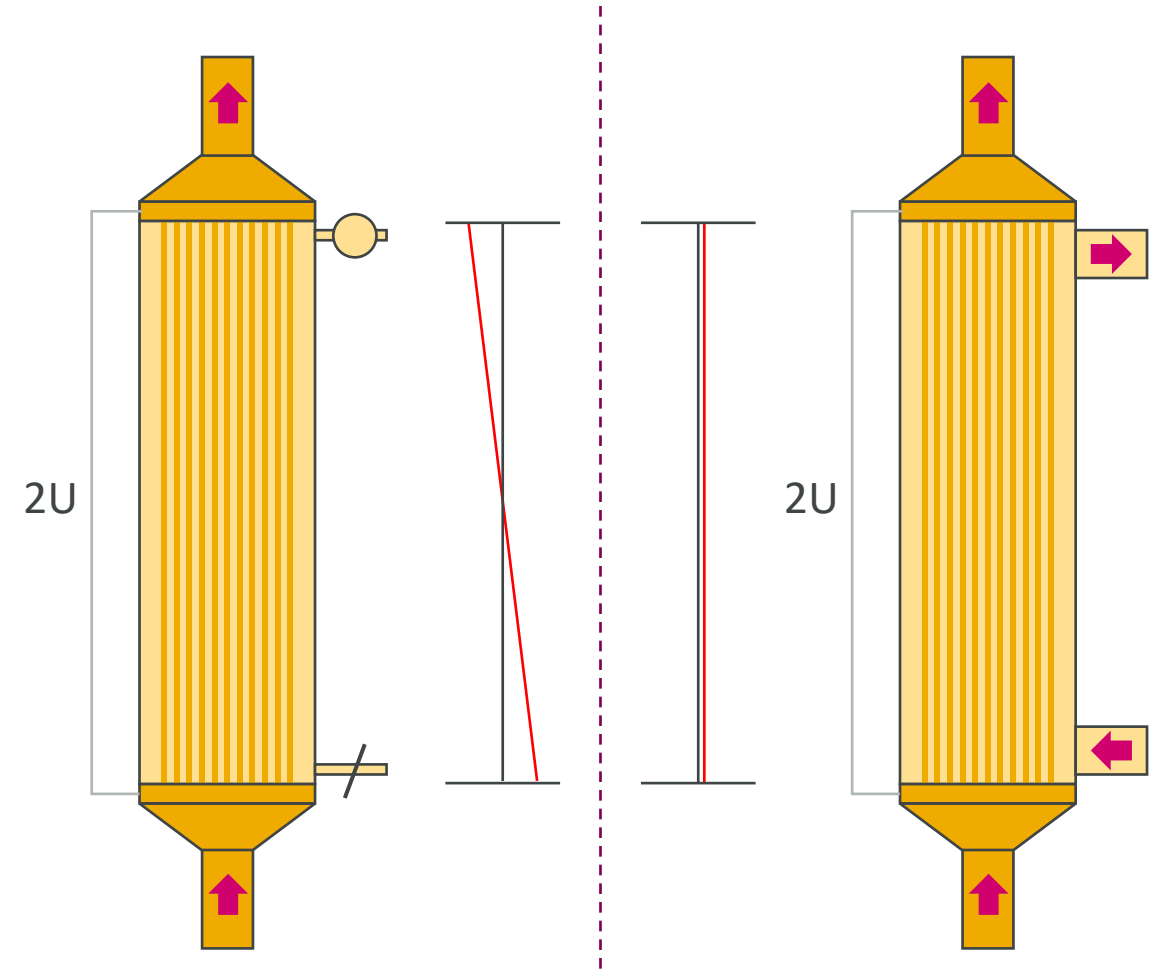


*data from Andrea Squeri*



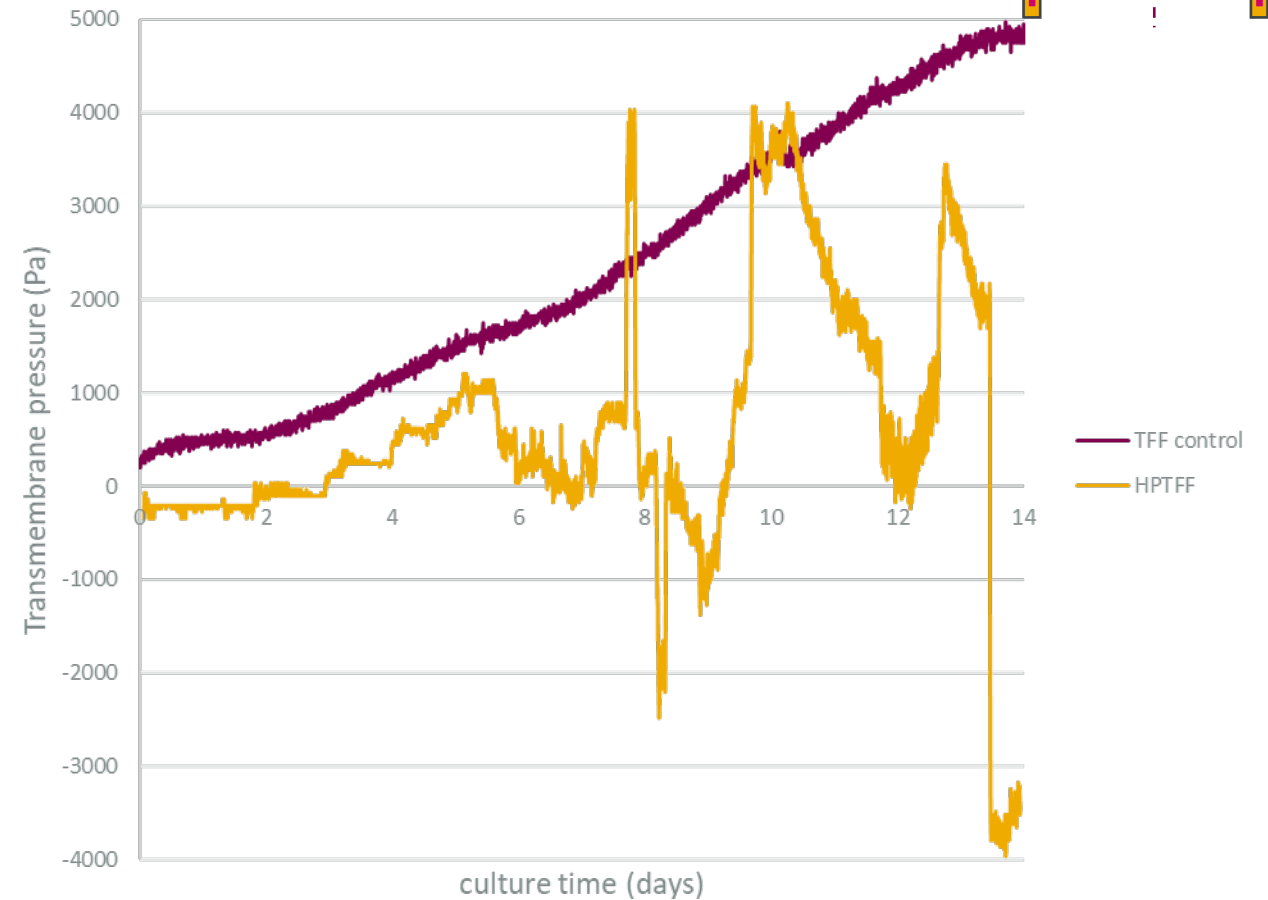
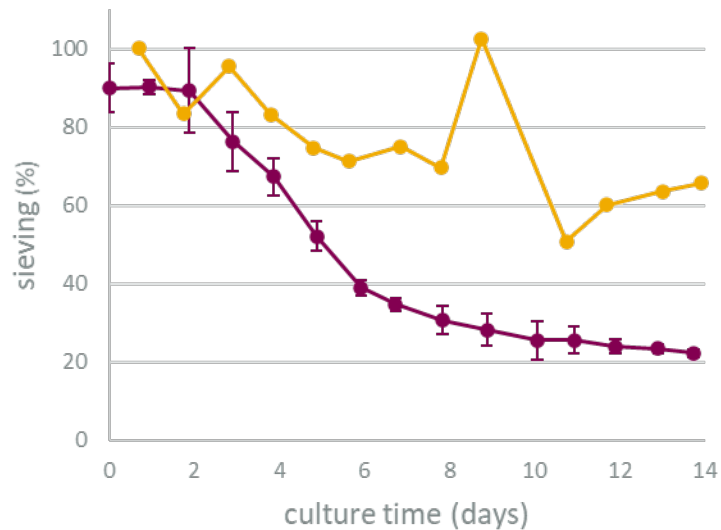
# Reduce $\Delta P$ at inlet and outlet

- 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<sup>1</sup>
- Hypothesis works in principle
- Requires more complex control system



*data from Jimmy Vu*

<sup>1</sup> van Reis et al., 1997, *Biotechnol Bioeng*



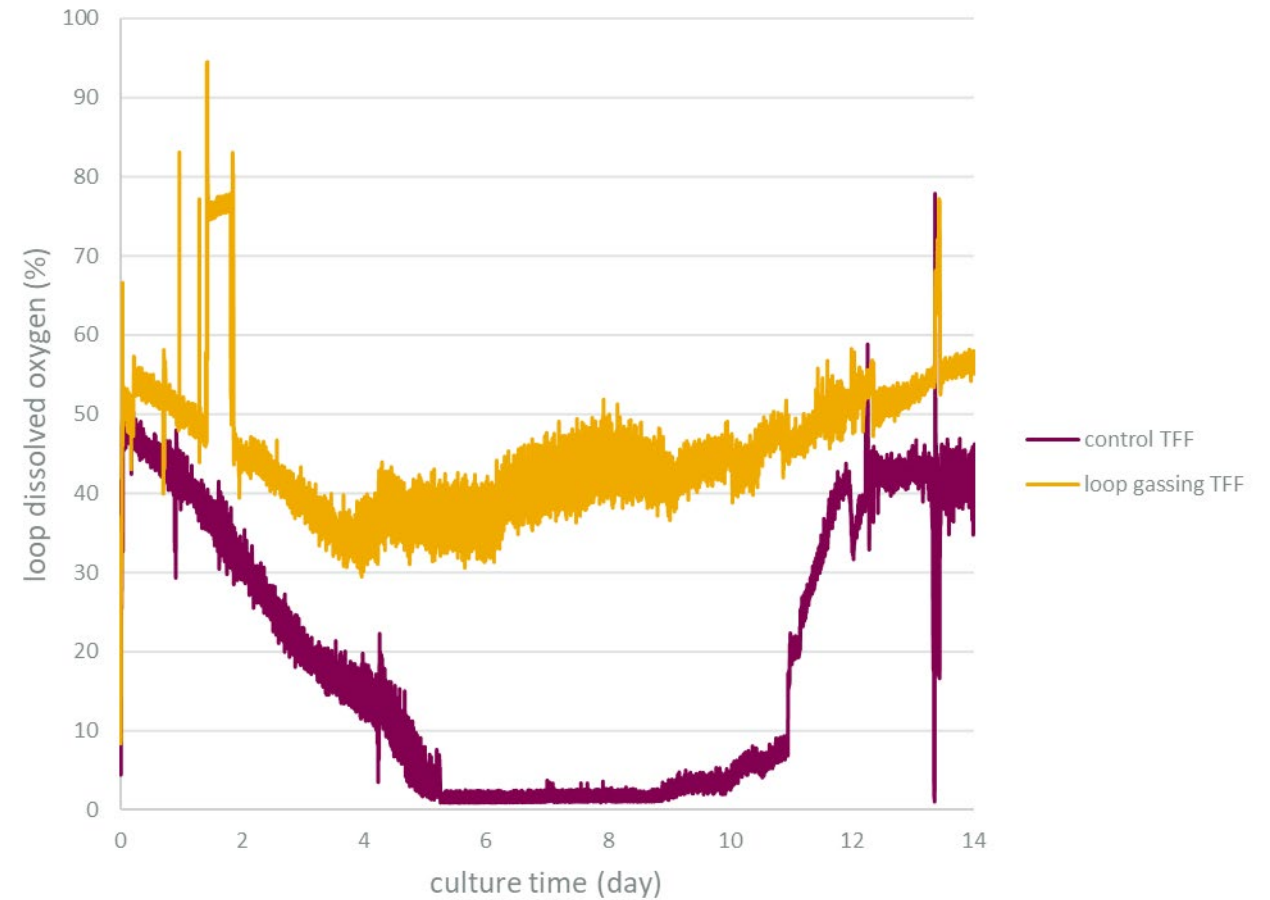
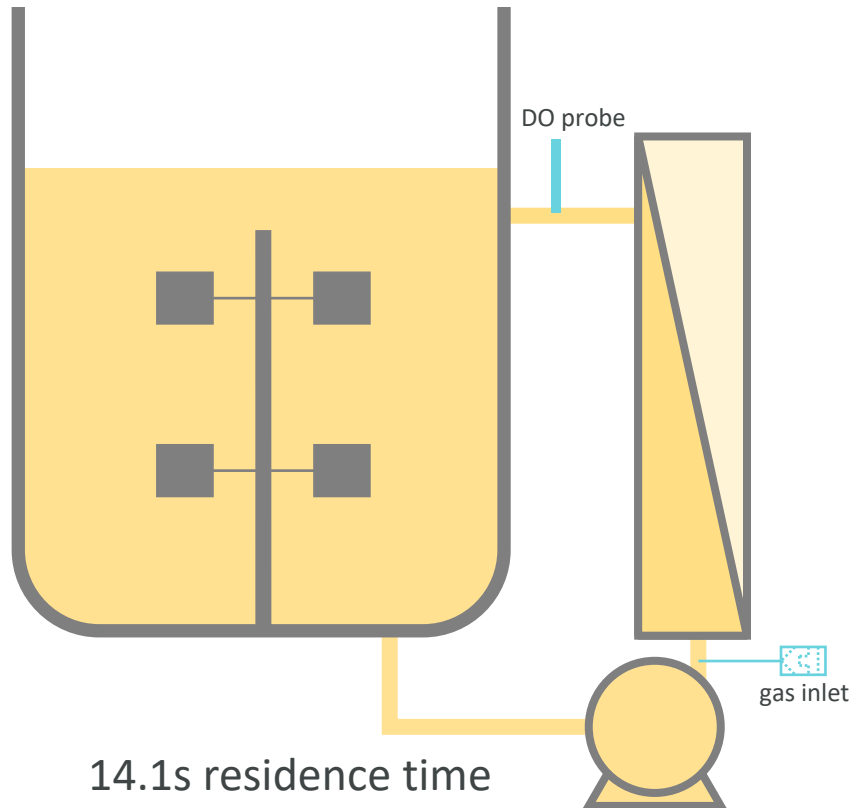
# Strengths and weaknesses

Configuration	Strength	Weakness
Stacked fibers	<ul style="list-style-type: none"><li>• Simple implementation</li><li>• Moderate improvement to sieving</li></ul>	<ul style="list-style-type: none"><li>• More hardware: permeate pumps</li><li>• Increased pressure head = increased shear rate</li></ul>
Low flowrate	<ul style="list-style-type: none"><li>• Simple implementation</li><li>• No additional hardware required</li></ul>	<ul style="list-style-type: none"><li>• <b>Significant oxygen limitation</b></li></ul>
HPTFF	<ul style="list-style-type: none"><li>• Significant improvement to sieving</li></ul>	<ul style="list-style-type: none"><li>• Significantly more complex implementation</li></ul>

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



# Addressing DO exhaustion

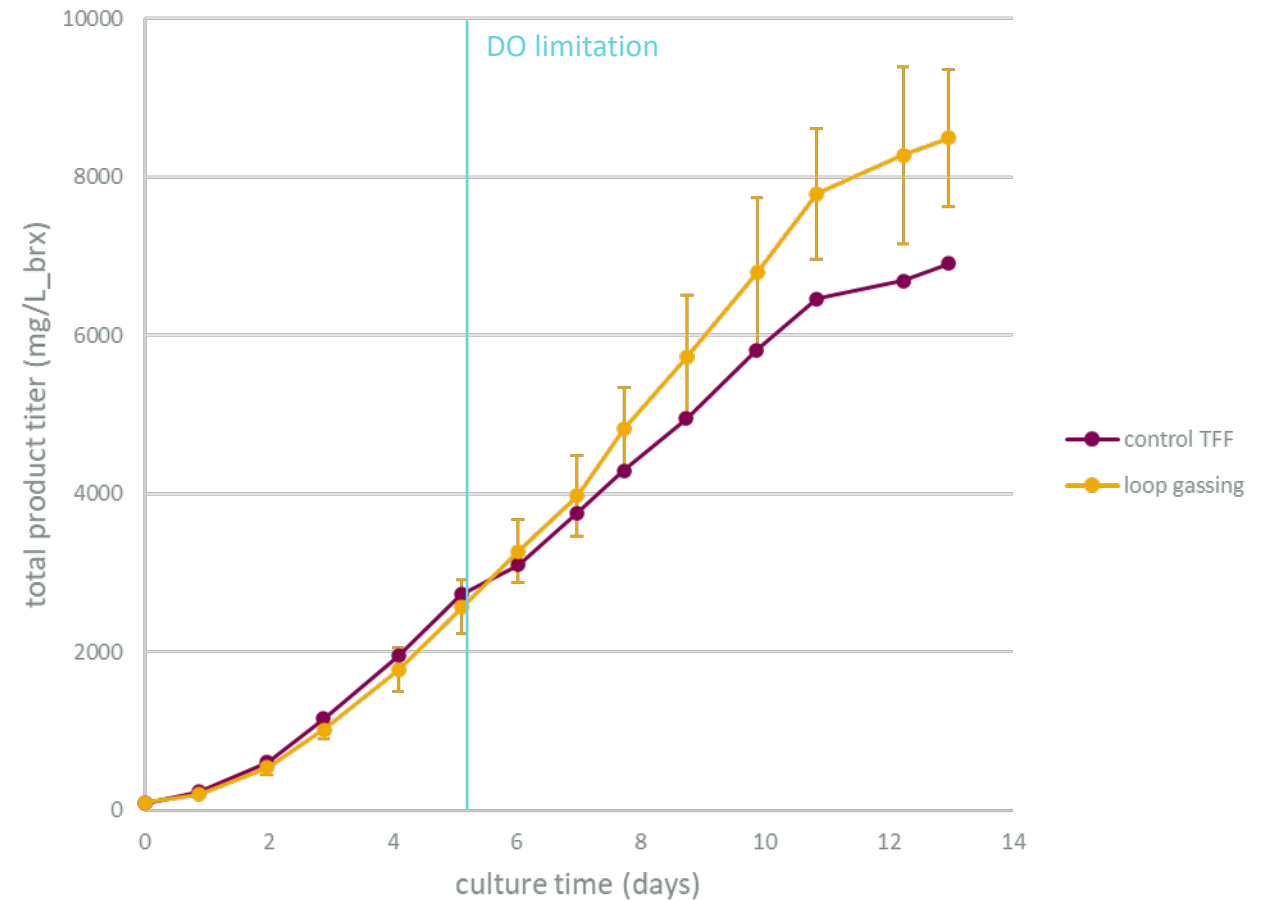
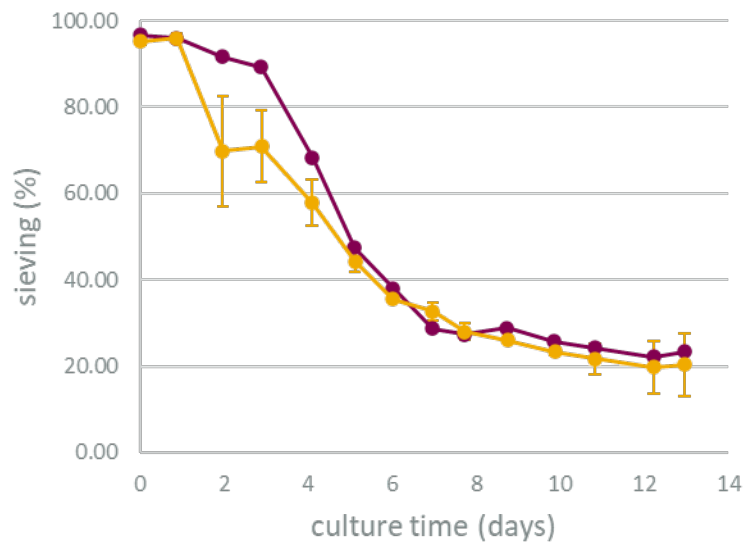


*data from Andrea Squeri*



# Addressing DO exhaustion

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

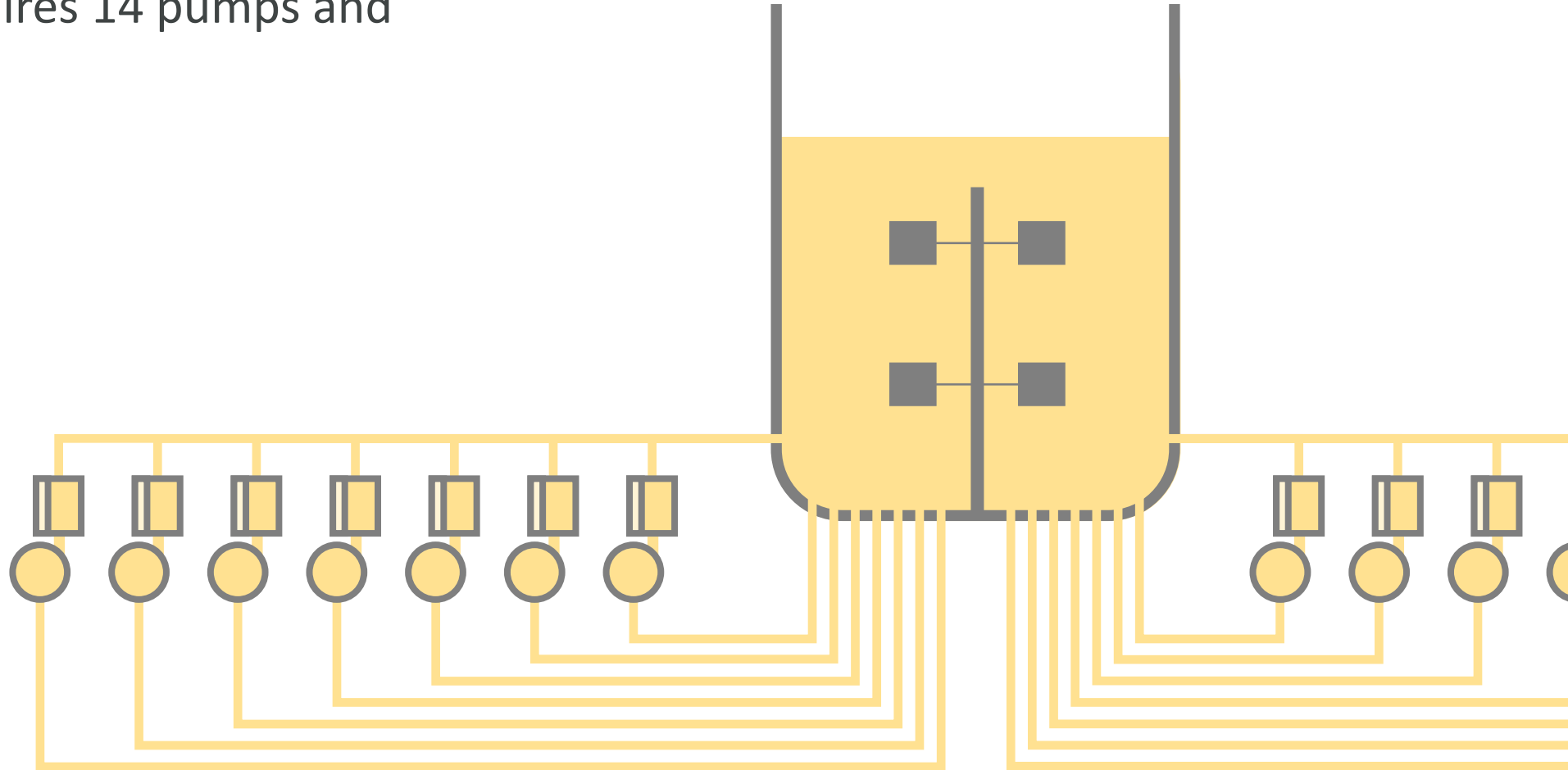


*data from Andrea Squeri*



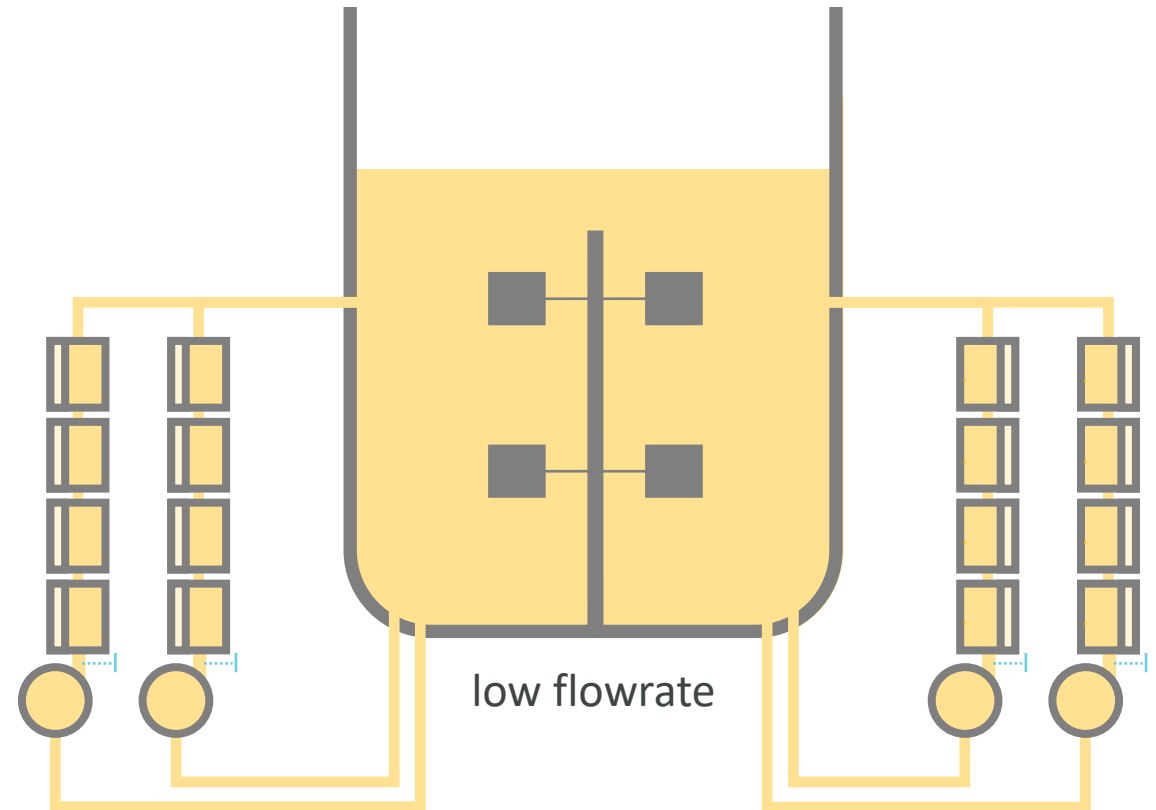
# Standard configuration

- Original setup requires 14 pumps and 14 hollow fibers



# Combining everything – stage 1

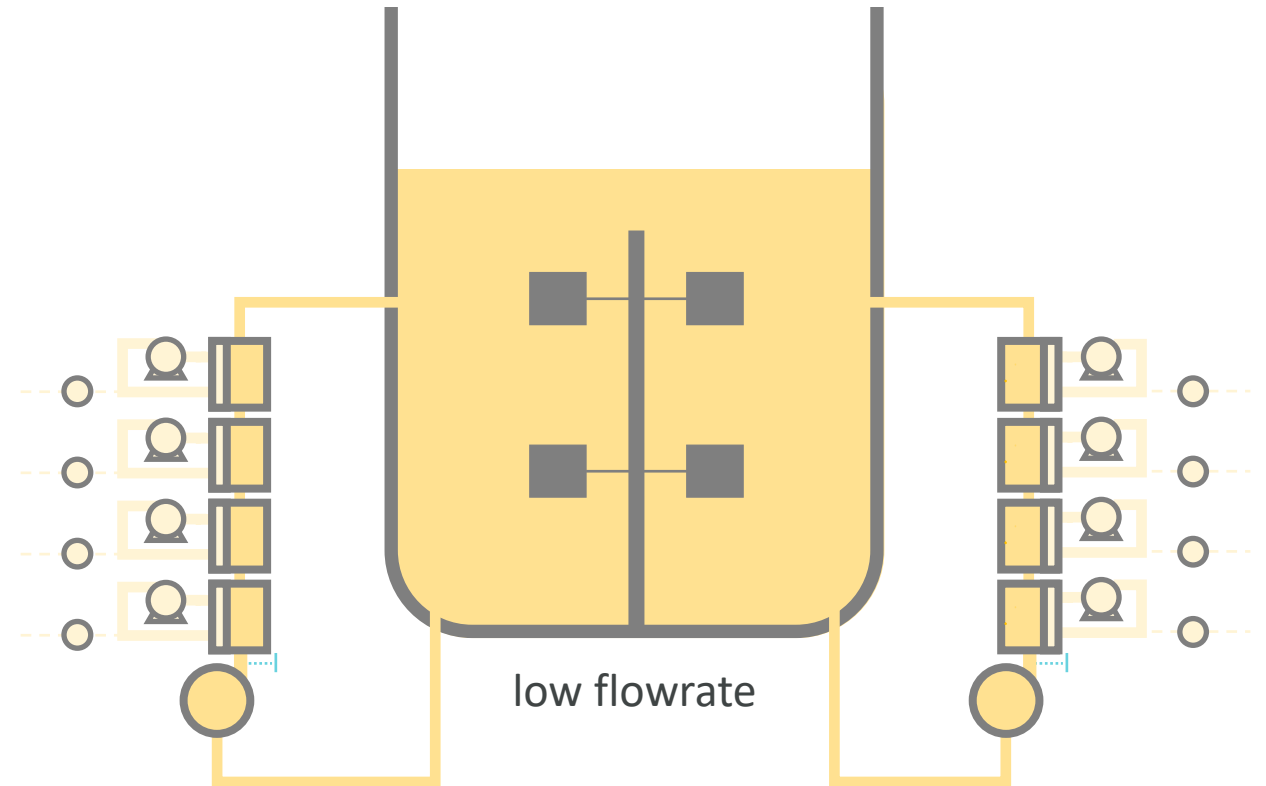
- Stage 1 enables reduced recirculating pumps
  - Stacking hollow fibers
- stacked hollow fibers increase residence time
  - Introduce gas flow into recirculating loop





# Combining everything – stage 2

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



# acknowledgements

- BTE-Upstream
  - **Andrea Squeri**
  - **Jimmy Vu**
  - Sam Preza
  - Alex Gadberry
  - **Dominique WuDunn**
- BTE-Downstream
  - Irina Ramos
  - Ujwal Patil
  - Nikunj Sharma
- BTE-Modelling
  - Mike Mollet
  - **Ashna Dhingra**
  - Nick Guros
  - Adrian Joseph
- Support functions
  - Media prep
  - Bioreactor prep
- Sponsors
  - Jon Coffman
  - Venkat Raghavan



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