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

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

Ken Lee

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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?

Stage 1

Stage 2

ProA wash

SPTFF

ProA elution

ProA

Wash

DS

Formulation buffer

Dialysis

Concentration

Virus filter

AEX wash buffer

AEX

SPTFF

CM

Desalting / concentration

AEX wash buffer

AEX

AEX equil

CEX

Detergent VI

ProA wash

ProA

Nano-particles

Wash

Concentration

Virus filter

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CEX
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 $^1$
    • 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

<table>
<thead>
<tr>
<th>Scale (L)</th>
<th>Working volume (L)</th>
<th>Filter area (m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2</td>
<td>0.098</td>
</tr>
<tr>
<td>3000</td>
<td>3000</td>
<td>147.0</td>
</tr>
</tbody>
</table>
Scaling cell retention device – from 3L
Scaling cell retention device – from 3L

Image by Andree Wallin
Scaling cell retention device

can we scale differently?

- $P_1 >> P_2$
- $P_3 \approx P_4$
- $P_1 > P_3$
- $P_2 < P_4$
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 Ashna Dhingra

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\(^1\)
• Hypothesis works in principle
• Requires more complex control system

\(^1\) van Reis et al., 1997, Biotechnol Bioeng
## Strengths and weaknesses

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

**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
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
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