Up-scaling in Cross Flow Filtration Processes
Design for Fermentation Broths

SYNPOL’s Course on “Industrialization of Biotechnological Processes”
Auditorio Fundación Parque Científico
Murcia, 23 October 2015

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1. Membranes for separation processes
   a) Filtration concept
   b) Fields of application in biotechnology industry
   c) Modules/materials of commercial membranes
   d) Operating modes/configurations

2. Methodology and scaling up
   a) Meaning of KPIs
   b) Life cycle of scaling up a process

3. Case study

4. Conclusions
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4. Conclusions
Selective barrier (porous membrane) between two solutions. By applying pressure at one of the membrane sides, the components are transported towards the membrane surface. There, some of them will pass through it while the rest will be retained, depending on their size.

≠ f (osmotic pressure)
Physical screening

= f (osmotic pressure)
Chemical affinity “solute-water-membrane”

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1.b) Examples of application fields

**BEVERAGES**
Clarification/Concentration

**DAIRY**
Clarification/Division/Concentration

**PHARMA/BIOTECH**
Screening/Concentration
Purification

Extraction
Clarification/Concentration

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1.c) Modules/Materials

<table>
<thead>
<tr>
<th></th>
<th>Cassettes</th>
<th>Tubular</th>
<th>Hollow fiber</th>
<th>Spiral</th>
</tr>
</thead>
<tbody>
<tr>
<td>m²/volumen</td>
<td>MEDIUM</td>
<td>LOW</td>
<td>HIGH</td>
<td>VERY HIGH</td>
</tr>
<tr>
<td>Tolerance to solids</td>
<td>MEDIUM</td>
<td>VERY HIGH</td>
<td>LOW</td>
<td>LOW</td>
</tr>
<tr>
<td>Easy scaling up</td>
<td>VERY HIGH</td>
<td>HIGH</td>
<td>MEDIUM</td>
<td>MEDIUM</td>
</tr>
<tr>
<td>Tolerance to viscosity</td>
<td>HIGH</td>
<td>VERY HIGH</td>
<td>MEDIUM</td>
<td>LOW</td>
</tr>
</tbody>
</table>

Polymeric:
- PVDF
- PS
- PES
- CR
- CN
- PTFE
- CA

Inorganics:
- Ceramics

- Resistant to high T and pH
- Long lifetime
- Limited to MF, UF, fine UF
1.d) Operating modes/configurations

**Dead-end mode**
- Perpendicular feed to surface.
- All the fed fluid is withdrawn as permeate.
- Premature blockage of pores.
- Rapid loss of performance.

**Cross-flow mode**
- Parallel feed to surface.
- Certain feed fraction sweeps along particles.
- Surface cleaning effect.
- Performance more stable over time.
1. OPEN LOOP configuration

- Batch mode operation
- Small volumes
- Double purpose pump (Q and ΔP)
- Diafiltration for cleaning the product
2. CLOSED LOOP configuration

- Continuous and batch mode
- Big volumes
- Two pumps for two purposes (Q and ΔP)
- Diafiltration for cleaning the product
1.d) Operation/configuration modes

3. MULTI-STEP configuration

- Continuous operation
- Two pumps for two purposes (Q and \( \Delta P \))
- Consecutive concentrations

**SERIES**
- Feed
- Permeate
- Concentrate

**PARALLEL**
- Feed
- Permeate
- Concentrate

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When the product of interest is in the supernatant, two filtration steps can be coupled in series, decreasing membrane pore size, to concentrate and clean the permeate generated in the first pass.
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2. Methodology and scaling up
   a) Meaning of KPIs
   b) Life cycle of scaling up a process

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4. Conclusions
2.a) Meaning of KPIs

What we stand for KPI? → “Key Performance Indicator”

<table>
<thead>
<tr>
<th>KPI</th>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permeate flux (L/h/m²)</td>
<td>$$\frac{Q_P}{A}$$</td>
<td>Fraction of the feed stream that is obtained as filtrate per hour and membrane area.</td>
</tr>
<tr>
<td>Transmembrane pressure, TMP (bar)</td>
<td>$$\frac{P_1 + P_2}{2} - P_p$$</td>
<td>Average pressure throughout the membrane.</td>
</tr>
<tr>
<td>Cross flow velocity (m/s)</td>
<td>$$\frac{Q_{feed}}{S_{paso}}$$</td>
<td>Ratio of feed flow and the cross membrane section.</td>
</tr>
<tr>
<td>Product losses (%)</td>
<td>$$\frac{m_{p_fin}}{m_{p_in}}$$</td>
<td>Fraction of the interest product which is lost with the rejected stream.</td>
</tr>
<tr>
<td>Volumetric concentration factor (VCF)</td>
<td>$$\frac{V_{in}}{V_{fin_conc}}$$</td>
<td>Ratio of total fed volume and the final concentrate volume.</td>
</tr>
<tr>
<td>Diaphragmation factor (DF)</td>
<td>$$\frac{V_{buffer}}{V_{fin_conc}}$$</td>
<td>Ratio of total volume of buffer solution added and the final concentrate volume.</td>
</tr>
</tbody>
</table>
2.b) Life cycle of scaling up a process

Customer -> Bionet -> Are any user requirements created?
2.b) Life cycle of scaling up a process

- **Type of product:** fermentation broth, enzymatic process, dairy product, etc.
- **Aim of filtration:** clarification, concentration, etc. and *Specification Sheet* of the product (if possible or if it makes sense).
- **Size of the interest product.**
- **Characterization of the feed stream:** % solids, viscosity, density, allowable temperature and pH, etc.
- **Target KPI:** minimum VCF and product losses.
2.b) Life cycle of scaling up a process

Customer ➔ Bionet ➔

NO

ARE ANY USER REQUIREMENTS CREATED?

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2.b) Life cycle of scaling up a process

Customer → Bionet → User requirements?

Are KPIs available?

Establish KPIs at lab/pilot scale?

Which is the amount of sample available?

Lab scale

V ≈ 4-6 L

Pilot scale

V ≈ 60-80 L
2.b) Life cycle of scaling up a process

Customer → Bionet → User requirements?

- NO
  - Are KPIs available?
    - YES → Experimental design bases
    - NO → Establish KPIs at lab/pilot scale?
      - YES → Assumption of design bases
      - NO

- YES
  - Experimental design bases

✓ Cross flow velocity
✓ Permeate flux
✓ TMP
✓ VCF
2.b) Life cycle of scaling up a process

Optimization of design bases

1. Determination of the optimal cross-flow velocity and TMP

- Permeate and concentrate streams are recycled back to the feed tank.
- Set filtration temperature.

<table>
<thead>
<tr>
<th>Feed flow</th>
<th>Time</th>
<th>TMP</th>
<th>Permeate flux</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>⋮</td>
<td>⋮</td>
<td>⋮</td>
</tr>
<tr>
<td></td>
<td>⋮</td>
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<td>⋮</td>
<td>⋮</td>
<td>⋮</td>
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<tr>
<td>2</td>
<td>⋮</td>
<td>⋮</td>
<td>⋮</td>
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<tr>
<td></td>
<td>⋮</td>
<td>⋮</td>
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</tr>
<tr>
<td></td>
<td>⋮</td>
<td>⋮</td>
<td>⋮</td>
</tr>
<tr>
<td>3</td>
<td>⋮</td>
<td>⋮</td>
<td>⋮</td>
</tr>
</tbody>
</table>

Diagram:
- Permeate flux vs. TMP
- Optimal point indicated

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2. Determination of the optimal permeate flux

- Concetrate is recycled and permeate is sent to another reservoir
- Set cross-flow velocity and TMP previously optimized
- Trial finishes: max VCF achieved or pumping limitation

<table>
<thead>
<tr>
<th>Q2 = constant</th>
<th>Time</th>
<th>Permeate flux</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP = constant</td>
<td>....</td>
<td>....</td>
</tr>
<tr>
<td>T = constant</td>
<td>....</td>
<td>....</td>
</tr>
</tbody>
</table>

![Graph showing optimization of permeate flux over time](image-url)
2.b) Life cycle of scaling up a process

- Customer
  - Bionet
    - User requirements?
      - NO
      - YES
        - Are KPIs available?
          - NO
          - YES
            - Establish KPIs at lab/pilot scale?
              - NO
              - YES
                - Experimental design bases
                  - Cross-flow velocity
                  - Permeate flux
                  - TMP
                  - VCF
                - Assumption of design bases

- Murcia, 23th October, 2015
2.b) Life cycle of scaling up a process

Customer → Bionet → User requirements?

- Are KPIs available?
  - NO → Experimental design bases
  - YES → Establish KPIs at lab/pilot scale?
    - NO → Technically feasible?
      - NO → Discard the technology
      - YES → Assumption of design bases
    - YES → Experimental design bases

✓ Bad filtrability:
- Low permeate flux
- Long filtration times
- High TMP
2.b) Life cycle of scaling up a process

Customer → Bionet → User requirements?

- **YES** → Are KPIs available?
  - **YES** → Establish KPIs at lab/pilot scale?
    - **YES** → Technically feasible?
      - **YES** → Assumption of design bases
      - **NO** → Discard the technology
    - **NO** → Experimental design bases
  - **NO** → Trials report

- **NO** → Scaling-up

**Notes:**
- Establish KPIs at lab/pilot scale based on user requirements.
- Technically feasible decision based on experimental design bases.
- Discard the technology if technically not feasible.
2.b) Life cycle of scaling up a process

Scaling-up a process

✓ Which operation modes are preferred by the customer: batch or continuous?
✓ Determine the volume or flow of product the customer wants to process
✓ Time required to do the filtration, work day

\[
V_{\text{permeate}} = V_{\text{feed}} \cdot \left(1 - \frac{1}{VCF}\right)
\]

\[
A_{\text{membrane}} = \left(\frac{V_{\text{permeate}}}{\text{time}}\right) \rightarrow m^2 \rightarrow m^2 \text{ total}
\]

 CONFIGURATION PROPOSAL
2.b) Life cycle of scaling up a process

Customer → Bionet → User requirements?

- Yes
  - Are KPIs available?
    - Yes → Establish KPIs at lab/pilot scale?
      - Yes → Technical feasibility?
        - Yes → Assumption of design bases
        - No → Discard the technology
    - No → Conceptual Engineering
  - No → Experimental design bases
    - Yes → Technically feasible?
      - Yes → Assumption of design bases
      - No → Discard the technology

- No → Conceptual Engineering
  - Yes → Economic model (CAPEX & OPEX)
  - No → Discard the technology
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4. Conclusions
1. **Objective:** Clarify yeast fermentation broth to separate the supernatant, which contains an extracellular enzyme that wants to be isolated and concentrated.

2. **Broth characterization:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspended solids (% v/v)</td>
<td>40-50</td>
</tr>
<tr>
<td>Viscosity (cP)</td>
<td>2-3 (at 20ºC)</td>
</tr>
<tr>
<td>Density (g/L)</td>
<td>1000</td>
</tr>
<tr>
<td>Max allowable temperature (ºC)</td>
<td>40</td>
</tr>
</tbody>
</table>

3. **Size of the microorganism:** > 0,6 µm

4. **Size of the interest product:** 60 kDa

5. **Sample volume:** 65 L
3) Case study: Enzyme concentration

Double pass: ceramic membrane + hollow fiber membrane

Fed broth → Concentrated bacteria

MICROFILTRATION: 0.45 µm

Enzyme

ULTRAFILTRATION: 10 kD

Permeate free of enzyme
3) Case study: Enzyme concentration

1. **MF**: optimization of **CF velocity**, **TMP** and **permeate flux**

![Graph showing permeate flux vs. TMP and Time](image)

- **CFV**: 4.5 m/s
- **TMP**: 2.65 bar
- **Average flux**: 72 L/h/m²
- **VCF**: 3.4

**Graph details**:
- Permeate flux (L/h/m²) vs. TMP (bar)
- Permeate flux (L/h/m²) vs. Time (h)
- Line graph for permeate flux with CFV: 5.5 m/s and 4.5 m/s
- Dotted line indicating average flux = 72 L/h/m²
3) Case study: Enzyme concentration

2. **UF**: optimization of **shear rate**, **TMP** and **permeate flux**

- **Shear rate**: 5000 s⁻¹
- **TMP**: 1.5 bar
- **Flux**: 25 L/h/m²
- **VCF**: 10

---

Average flux = 25 L/h/m²
2. Scaling-up

- **V_{feed}:** 1000 L (en modo “batch”)
- **Total filtration time:** 8 h

**After pilot trials (MF):**

- **V_{CF}:** 4 / **Flux:** 72 L/h/m²
- **V_{permeate}:** 750 L
- **Time:** 5.5 h
- **Total area:** 1.9 m² → 2.2 m²

(security factor 20%)
2. Scaling-up

- **V_{feed}:** 1000 L (en modo “batch”)
- **Total filtration time:** 8 h

---

**After pilot trials (MF):**

- **V_{CF}:** 4 / **Flux:** 72 L/h/m²
- **V_{permeate}:** 750 L
- **Time:** 5.5 h
- **Total area:** 1.9 m² → 2.2 m²

(security factor 20%)

---

**After pilot trials (UF):**

- **V_{CF}:** 10 / **Flux:** 25 L/h/m²
- **V_{permeate}:** 675 L
- **Time:** 2.5 h
- **Total area:** 10.7 m² → 12.8 m²

(security factor 20%)
3) Case study: Enzyme concentration

2. Scaling-up

After pilot trials (UF):

- **VCF:** 10 / **Flux:** 25 L/h/m²
- **V_{permeate}:** 675 L
- **Time:** 2.5 h
- **Total area:** 10.7 m² → 12.8 m²

(security factor 20%)
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4. Conclusions
4) Conclusions

1) **Membrane** filtration has to be recognized as one of the main technologies to consider in the first steps of the downstream in the *biotech industry*. It is really helpful (depending on the product of interest) to clarify, separate or concentrate.

2) Before thinking in what membrane technology design and install, the most important issue is to define the **User Requirements**.

3) **Pilot trials**, with a well defined methodology, provide important information with low execution time. They are a great tool to *reduce* process **uncertainties** and **starting up times**.
THANKS FOR YOUR ATTENTION!

QUESTIONS?

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