Bioprocess Modeling of Fouling Phenomena in Cross-flow Filtration of Viable Bacteria

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Microbiological Analytical Methods

Sample Preparation + Detection = SCREENING METHOD

Sample Preparation + Detection + Isolation Identification = CONFIRMATION METHOD

2 to 4 hours + 3 to 4 hours = 5 to 8 hours

24 to 48 hours + 2 to 4 hours + 24 to 48 hours = 2 to 4 days

FDA 101, May 13, 2015
Goal: Reduce time to detection from 24 hrs to 8 hours

Sample → USDA and FDA approved Molecular biology based method (PCR)

Days 0 → 24 hours

Non-selective Enrichment

Detection

Proposed protocol

Sample → Enzyme incubation *(Salmonella enrichment)* → Pre-filtration → Microfiltration and centrifugation → *Salmonella* detection (PCR)
Trying to Shift a Core Assumption

Shaker Flask

Petri Dish

Hollow Fiber Module

Single Hollow Fibers

200 μM

Feed Stream

Permeate
Schematic of Cross Flow HF Filtration

Concentrate Volume = Initial feed – Permeate – System (Dead) Volume

As fluid is recycled, volume decreases

Concentrate and recovered microorganisms must be viable
Hollow fiber membrane module

Ferrules

Tubing

Tee junctions

Tubing

Tubing

Tee junctions

Hollow fiber
(No. =12, Polysulfone, 0.2 micron)

Surface area to volume ratio (28 cm²/0.2 cm³)
Flux per unit volume of membrane module (51 mL/(mL·min))
Continuous operation minimizes manual handling
Microfiltration

Practiced for 70 years.

Fouling is a consistent challenge (short membrane life, long processing times, decreases in flux)

Many interacting mechanisms cause reduced product yield upon filtration or microfiltration.

Our work:

- addition of enzyme to reduce membrane fouling, achieve consistent fluxes and maximize membrane re-use.
- recovery of microorganisms in a viable state
- control of flow velocities on retentate and permeate sides of membrane modules to maximize fluxes
- processing of biological materials to disrupt biofilms and recover microbial cells
Controlling Flow Velocities to Maximize Flux

Traditional Crossflow Filtration

Our Crossflow System

Concepts packaged into C3D research prototypes fabricated in our laboratory
Start microfiltration of enzyme treated spinach extract
2 samples being run in parallel
Spinach Extract - 4 minutes later - approaching end of run
At 6 minutes sample collected in plastic tube
Sample tube removed from instrument
Decant into centrifuge tube
Centrifuge for 10 min
PCR result for initial cell concentration of 1 CFU/G spinach

Initial volume of 500 mL with 3 hr enrichment (lactose then RV) Automated microfiltration followed by centrifugation = $10^3$ CFU/g in final volume of 1 mL for samples S1, S2, and S3.

PC = positive control. NC = negative control
Microfluidic Transport across Hollow Fiber Membrane
Model for Micro-filtration

Dynamic growth and compaction of deposit layer

\[
\int_0^t (2\pi (r_i - \delta) \partial z) (u - v_s) \phi_b \partial t = \pi (r_i^2 - (r_i - \delta)^2) \partial z \phi
\]

- \( u = \frac{r_i}{r_i - \delta} J \)
- \( v_s = \frac{0.05u_0 \bar{d}_p^2}{4(r_i - \delta)^2} \)
- Convective transport by permeation
- Shear induced back transport

Resistance of deposit layer

\( R_d = \alpha r_i \ln \frac{r_i}{r_i - \delta} \)

Compaction of deposit layer

\( \alpha = \alpha_0 \left( 1 + \frac{\Delta P_d}{\Delta P_0} \right)^n \)
# Model

**Filtration through a porous medium**

\[
J = \frac{(P_F - P_P)}{\mu(R_m + R_d)}
\]

(Darcy’s law)

## Axial pressure drop

- **Retentate side**
  \[
  \frac{\partial P_F}{\partial z} = -\frac{8\mu Q}{\pi r_i^4 N_0}
  \]
  (Hagen–Poiseuille equation)

- **Permeate side**
  \[
  \frac{\partial P_P}{\partial z} = -\frac{8\mu (r_M + N_0 r_o)^2}{\pi (r_M^2 - N_0 r_o^2)^3} U
  \]
  (modified Hagen–Poiseuille equation)

## Axial flow rate

- **Retentate side**
  \[
  \frac{\partial Q}{\partial z} = -2N_0\pi r_i J
  \]
  (Continuity equation)

- **Permeate side**
  \[
  \frac{\partial U}{\partial z} = -\frac{\partial Q}{\partial z}
  \]
  (Mass balance)
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Value</th>
<th>Unit</th>
<th>Physical meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_i$</td>
<td>$1.4 \times 10^{-4}$</td>
<td>m</td>
<td>inner radius of a single hollow fiber</td>
</tr>
<tr>
<td>$r_o$</td>
<td>$1.8 \times 10^{-4}$</td>
<td>m</td>
<td>outer radius of a single hollow fiber</td>
</tr>
<tr>
<td>$r_M$</td>
<td>$1.02 \times 10^{-3}$</td>
<td>m</td>
<td>inner radius of membrane module</td>
</tr>
<tr>
<td>$N_0$</td>
<td>12</td>
<td></td>
<td>number of hollow fiber</td>
</tr>
<tr>
<td>$A_c$</td>
<td>$7.4 \times 10^{-7}$</td>
<td>m$^2$</td>
<td>overall cross section area of hollow fiber bundle</td>
</tr>
<tr>
<td>$L$</td>
<td>0.27</td>
<td>m</td>
<td>length of hollow fiber</td>
</tr>
<tr>
<td>$L_{ext1}$</td>
<td>0.4</td>
<td>m</td>
<td>length of the extended tubing at the retentate port</td>
</tr>
<tr>
<td>$L_{ext2}$</td>
<td>0.3</td>
<td>m</td>
<td>length of the extended tubing at the permeate port</td>
</tr>
<tr>
<td>$r_{ext1}$</td>
<td>$1.0 \times 10^{-3}$</td>
<td>m</td>
<td>inner radius of the extended tubing at the retentate port</td>
</tr>
<tr>
<td>$r_{ext2}$</td>
<td>$1.0 \times 10^{-3}$</td>
<td>m</td>
<td>inner radius of the extended tubing at the permeate port</td>
</tr>
<tr>
<td>$\mu_o$</td>
<td>$1.0 \times 10^{-3}$</td>
<td>Pa$\cdot$s</td>
<td>dynamic viscosity of shell side fluid</td>
</tr>
<tr>
<td>$\mu$</td>
<td>$1.2 \times 10^{-3}$</td>
<td>Pa$\cdot$s</td>
<td>viscosity of permeate</td>
</tr>
<tr>
<td>$\phi_b$</td>
<td>$1.0 \times 10^{-4}$</td>
<td></td>
<td>solid fraction in bulk flow</td>
</tr>
<tr>
<td>$R_m$</td>
<td>$4.7 \times 10^{11}$</td>
<td>m$^{-1}$</td>
<td>intrinsic membrane resistance</td>
</tr>
<tr>
<td>$\alpha_0$</td>
<td>$6.0 \times 10^{14}$</td>
<td>m$^{-1}$</td>
<td>normalized specific film resistance</td>
</tr>
<tr>
<td>$n$</td>
<td>0.85</td>
<td></td>
<td>compressibility factor</td>
</tr>
<tr>
<td>$\phi$</td>
<td>0.5</td>
<td></td>
<td>solid fraction of deposit layer</td>
</tr>
</tbody>
</table>

**Parameters**

- Direct measurement/manufacturing information
- Pure water flux
- Fitting model to experimental data
Validation (BSA, Single Pass)

Inlet $\Delta P_0$ vs. $t$

$Q_p$ vs. $t$

- Calculated
- Measured

$kPa 
\times 10^{-7} m^3/s

Time (min)

Time (min)
Optimization of Membrane Geometry: Deposit Layer

Deposit layer thickness

\[ \delta_{ave} \]

\[ \times 10^{-5}\text{ m} \]

Based on chicken extract

\[ Q_0 \times 10^{-6}\text{ m}^3/\text{s} \]

Defining

\[ \lambda = \frac{L}{r_M} \]

Non-uniformity of layer

\[ (\delta_{max} - \delta_{min})/\delta_{ave} \]

Increasing deposition

Increasing fiber length

Increasing flowrate

Fiber length / radius
Conclusions
Fouling Phenomena in Cross-flow Filtration of Viable Bacteria

Hydrodynamic model
- developed/validated for hollow fiber, crossflow microfiltration
- correlated with membrane length to radius diameter for transmembrane pressure, flux and deposit layer formation.
- extrapolated to obtain flux, pressure and deposition layer thickness as a function of time and volumetric flow rate of feed suspension for different hollow fiber lengths
- used to identify local optima of membrane geometric design

Experimental Validation and Applications
- Food pathogen detection in 8 hrs
- Homogenized meats and vegetables (disrupts biofilms)
- Fruit, water, leafy greens