Tangential Flow Filtration

Methods For Successful Scale up

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Presentation Overview

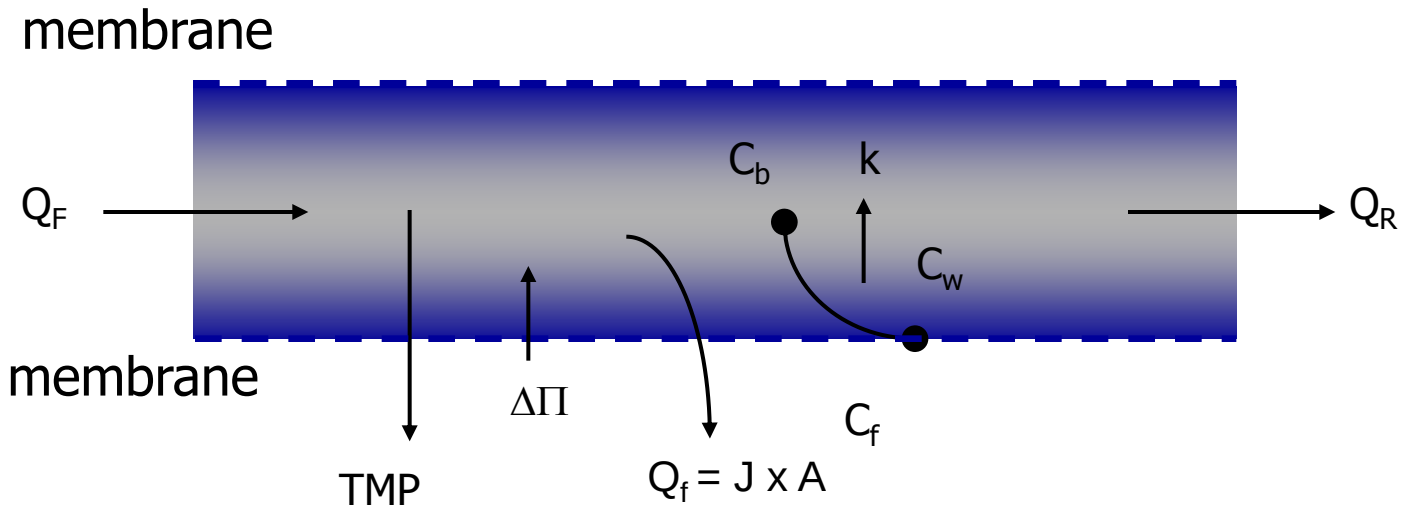
- Scale-up considerations in TFF
  - Scaling Rule and its Implementation
  - Various Practical Adaptations of the Scaling Rule
  - Considerations for Membrane/Module Scale-up
- TFF Scale-up
  - System Design Considerations
  - Operational Considerations

TFF Scaling Rule

- Ensure ‘similar’ concentration profiles at small and large scales

- What are these concentration profiles and how do we express them?

Concentration Profiles in a TFF Process



$$\frac{C_{wall/gel}}{C_{bulk}} = 1 - R^{Obs}\left\{1 - \exp\left(\frac{J}{k}\right)\right\}$$

Polarization Profile

$$\frac{C^{f}_{bulk}}{C^{o}_{bulk}} = \exp\left\{\underbrace{-\left(1-R^{Obs}\right)N}_{DF} + \underbrace{R^{Obs}\ lnX}_{UF}\right\}$$

Operating Profile

Polarization Profile

- Results from steady-state mass transfer considerations
  - Also called concentration polarization
- Determines
  - Stability of flux, polarization
- Affected by
  - Membrane retention
  - Flux
  - Cross flow rate
  - Module Geometry

} Affect ‘k’

$$\frac{C_{wall/gel}}{C_{bulk}} = 1 - R^{Obs}\left\{1 - \exp\left(\frac{J}{k}\right)\right\} \qquad \text{where } k = \frac{D}{\delta}$$

Polarization profile is a vital characteristic of a TFF process

Operating Profile

- Represents mass balance
  - Establishes perm, retentate volumes during the step
- Establishes concentration profile as a function of
  - Time
  - Area
  - Flux (processing velocity)

$$\frac{C^{f}_{bulk}}{C^{o}_{bulk}} = \exp\left\{-\left(1-R^{Obs}\right)N + R^{Obs}\,\ln X\right\}$$

Note that X and N can be expressed as function of flux (J), processing time (t) and process loading (V/A)

$$X = \left(\frac{1}{1-\frac{J_{1avg}At_1}{V_0}}\right) \qquad N = \frac{J_{2avg}At_2}{V_0}\left(\frac{1}{1-\frac{J_{1avg}At_1}{V_0}}\right)$$

'Executing' the Scaling Rule for TFF Processes

- For equivalent polarization profile $C_{wall/gel}/C_{bulk}$, maintain constant
  - J or production rate (liters/m^2-hr)
  - K or mass transfer coefficient
- For equivalent operating profile, maintain constant
  - X, N
  - Order or sequence of X, N

Production Rate → Area Requirements

- Constant production rate criterion helps establish membrane area requirements (‘size’) :

Large Scale (LS)	=	Experimental Scale (ES)
Production Rate		Production Rate

$$LS \cdot Area = ES \cdot Area \times \frac{LS \cdot Volume_{Filtered}}{ES \cdot Volume_{Filtered}} \times \frac{ES \cdot Time}{LS \cdot Time}$$

$\leftarrow 1/J_{ES}$

Adaptations of Scaling Rule

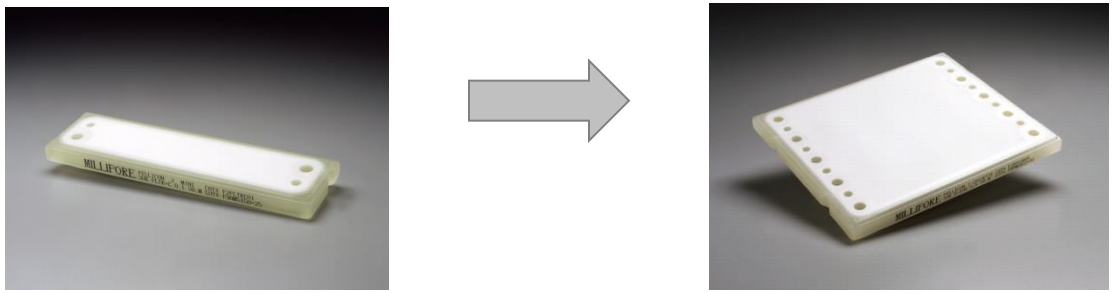
- Equivalent concentration profiles at different scales may be achieved by maintaining
  - Same polarization, same operating profile **Linear**
  - Same polarization, similar operating profile **Variation of Linear**
  - Similar average polarization & similar average operating profile **Serial**
  - Similar theoretical polarization & similar average operating profile **Theoretical**
- UF: 'Variation of linear' scaling ('lab' scale) followed by linear (pilot) scaling is most common
- MF: 'Serial module' scaling ('lab' scale) followed by linear scaling (pilot) is commonly used

Linear Scaling

- Characteristics – same ‘everything’ (well ‘almost’)
  - Same membrane material, MWCO, device format
  - Same flux (Production Rate)
  - Same k (Cross Flow Rate, Module Geometry: h, L)
  - Same processing time or Volume/Area loading
  - Only Module width, w, changes from small to large scale

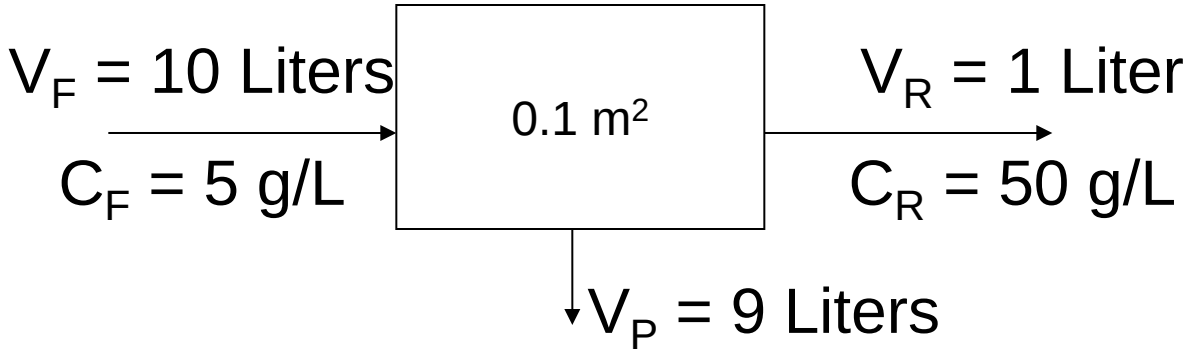
Same Polarization Same Operating Profile

- Need
  - Linearly Scale-down Device for process development
  - Large volume for process development



Example of Linear Scaling

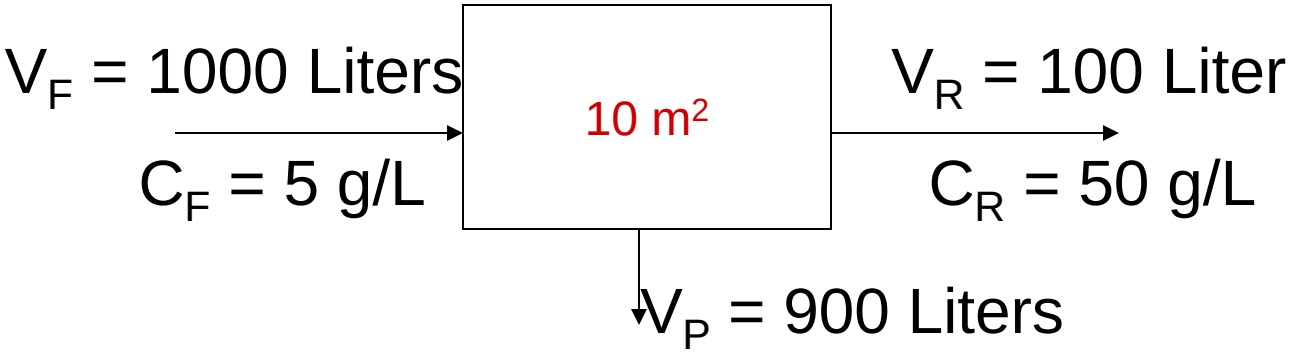
UF Process



X = 10,
J = 40 lmh, √
t_P = 135 min, √
Loading = 100 L/m² √

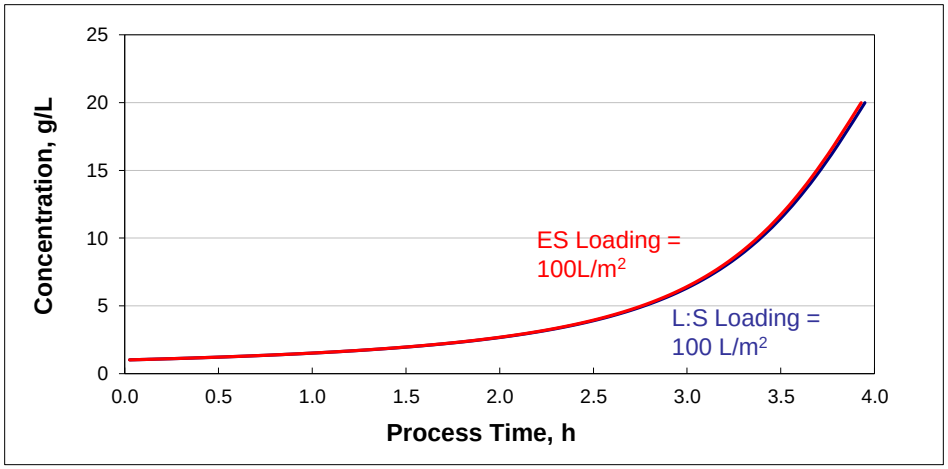
Same 'Fouling' risk

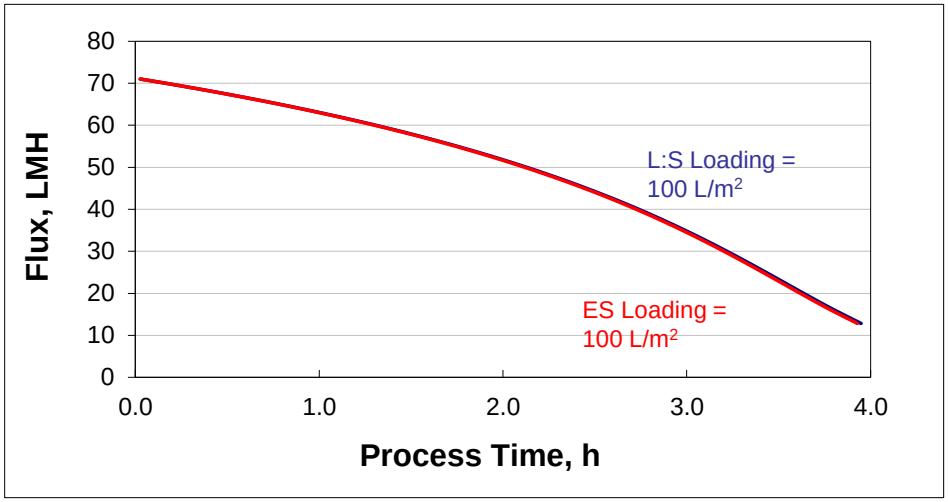
$$LS \cdot Area = 0.1 \times \frac{900}{9} \times \frac{135}{135}$$



X = 10,
J = 40 lmh, √
t_P = 135 min, √
Loading = 100 L/m² √

Concentration and Flux Profiles – Linear Scaling



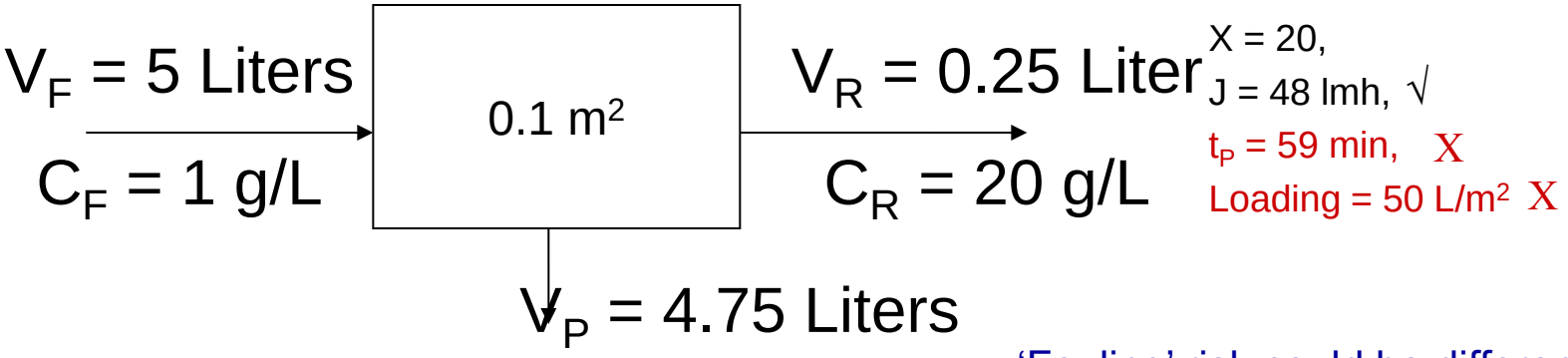


Variation of Linear Scaling

- Characteristics
  - Meets all criteria for linear scaling except processing time or volume/area loading i.e.
    - Same membrane material, MWCO, device format
    - Same average flux (Production Rate)
    - Same k (Cross Flow Rate, Module Geometry: h, L)
    - ~~Same processing time or Volume/Area loading~~
    - Module width, w, changes from small to large scale
  - Works well for UF-DF processes within limits
    - Limit < 2 fold process time extension
    - Requires considerably less volume for process development
    - Development time is short
  - Should not be used for MF-DF processes

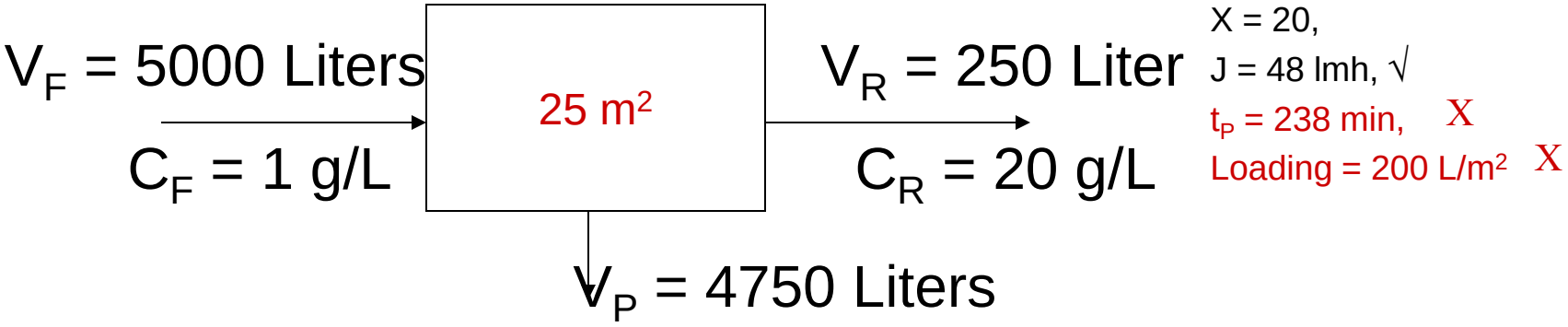
Example: Variation of Linear Scaling

UF Process

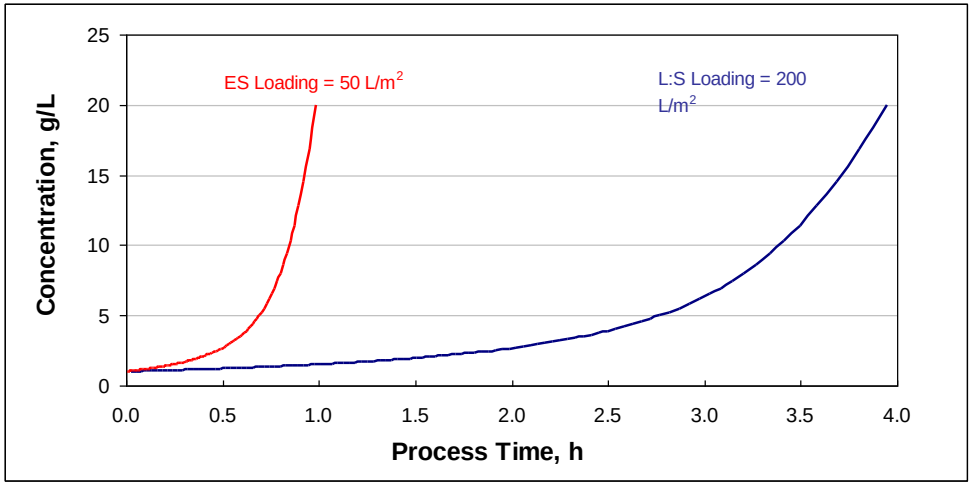


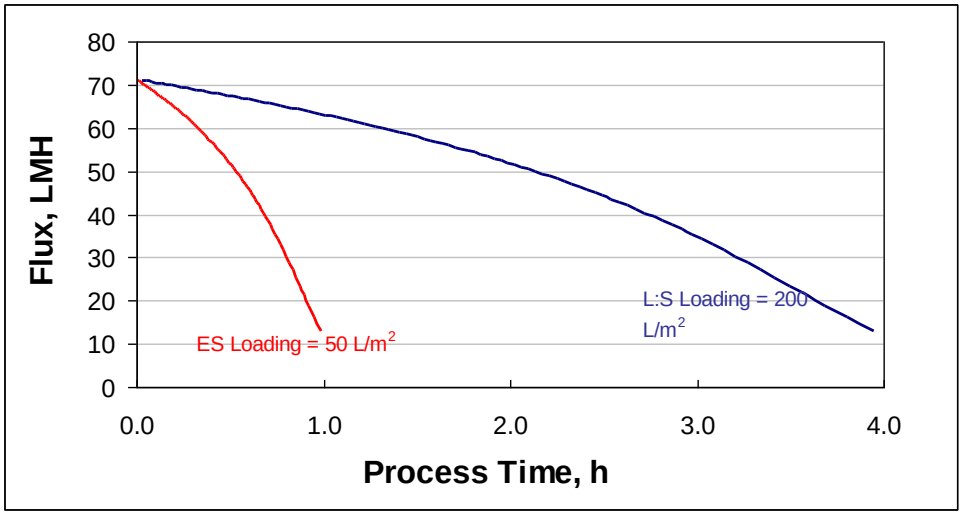
'Fouling' risk could be different due to different processing times

$$LS \cdot Area = 0.1 \times \frac{4750}{4.75} \times \frac{59}{238}$$



Concentration And Flux Profiles – Variation of Linear Scaling





Linear Scaling: Implications for Module Design

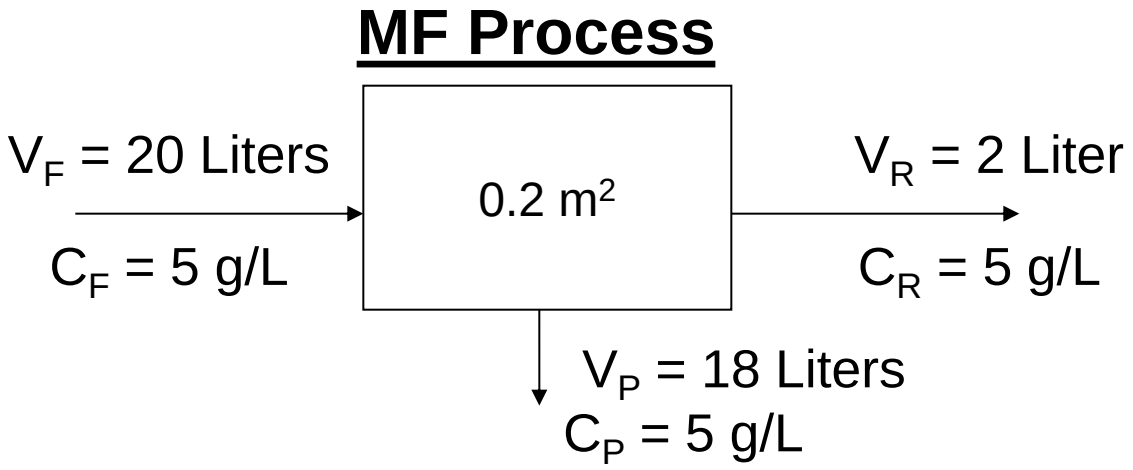
- Feed Channel Length
  - Constant for all device sizes
- Entrance/Exit Effects
  - Consistent inlet/outlet porting between sizes
- Channel Compression
  - Stable channel height
  - Controlled manufacturing

'Geometric Similarity' is essential to ensure equivalent velocity, concentration and temperature profiles!

Serial Module Scaling

- Characteristics
  - Stack multiple modules in series to reduce cross flow (pump size) and system size (piping size etc)
    - Fluid flow Path length, $L_{effective}$, changes
    - Cross-flow in a serial bank of modules is same as that for a single module
    - Widely used for MF processes with open channel devices: Prostak, Hollow Fibers
  - Same membrane material, MWCO, device format
  - ~~Same~~ similar average flux (Processing Rate)
  - ~~Same~~ similar k (Cross Flow Rate, Module Geometry: h, L)
    - $L_{effective}$ is changed
  - Same processing time or Volume/Area loading
    - For MF process
    - Not so for UF process
  - Module width, w, changes from small to large scale

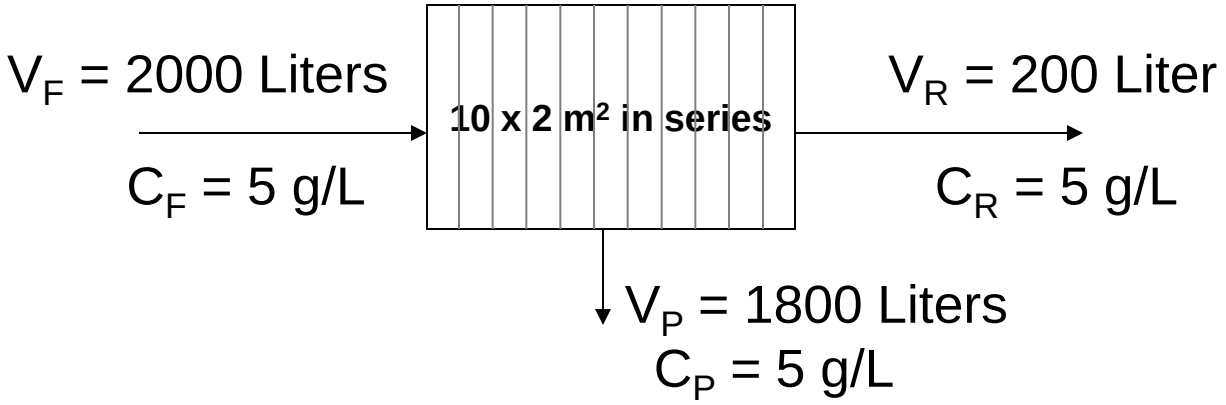
Example: Serial Module Scaling



X = 10,
J = 30 lmh, √?
t_P = 180 min, √
Loading = 90 L/m² √

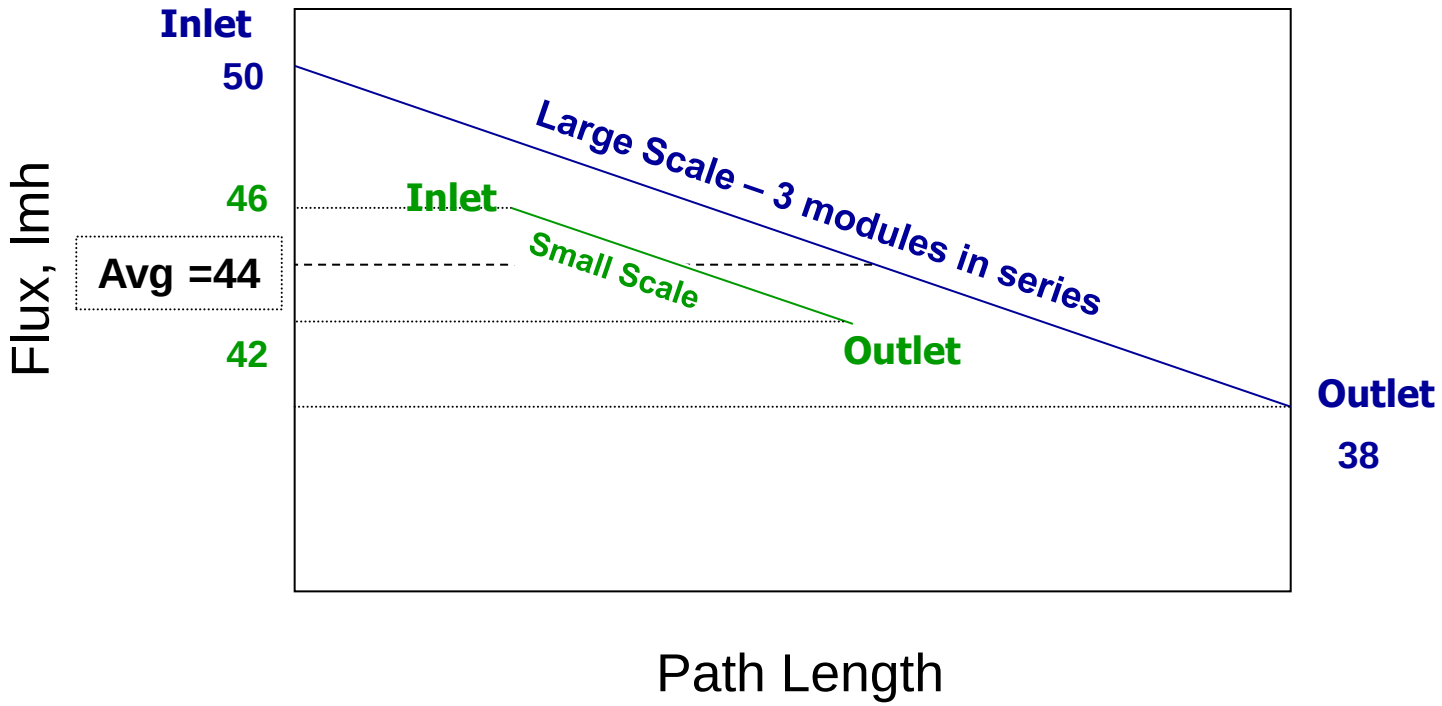
$$LS \cdot Area = 0.2 \times \frac{1800}{18} \times \frac{180}{180}$$

Different Fouling risk, DP,
Flux/TMP Profile → Must be accounted
For during Scale-up



X = 10,
Avg J = 30 lmh, √ ?
t_P = 180 min, √
Loading = 90 L/m² √

Potential Issues with Serial Module Scaling



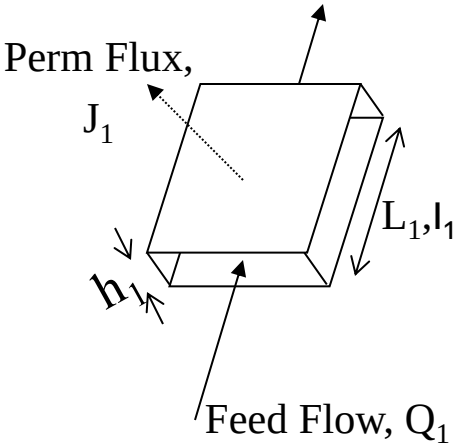
- How much variation in Flux, TMP is considered acceptable?
  - Depends on the process, fluid, module construction – need good process characterization data
  - Up to 3-5 in-series for UF; Up to 10 for MF
    - Always test the serial configuration in a scale-down format for confirmation

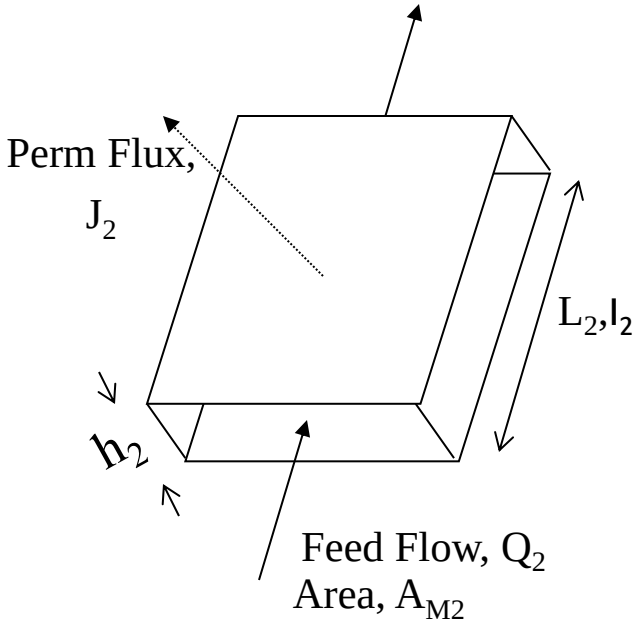
Non Linear/'Model-Based' Scaling

Uses predictions to estimate performance at different scales

- For Similar Geometry
  - Modules are geometrically similar
    - Ex Hollow Fiber or flat sheet with d_1, $L_1 \rightarrow d_2$, L_2
  - Same membrane material, MWCO, device format
  - Same average flux (Processing Rate)
  - ~~Same k (Cross Flow Rate, Module Geometry: h~~, L)
    - Equivalent k is obtained using mass transfer scaling correlations
  - ~~Same processing time or Volume/Area loading~~
  - Module width, w, may change from small to large scale
- For Dissimilar Geometry
  - Ex. Flat sheets to Spirals scale-up/scale-down
  - Not Recommended

Example: Non-Linear Scaling with Similar Geometry





For Equivalent Polarization, maintain same J (Flux) and k (mass transfer coefficient):

Use $J_1 = J_2$ and $\frac{Q_2}{Q_1} = \left[\frac{N_2+1}{N_1+1}\right] * \left[\frac{N_1}{N_2}\right] * \frac{A_{M2}}{A_{M1}} * \left(\frac{h_2}{h_1}\right)^2 * \frac{L_2}{L_1} * \left[\frac{l_1}{l_2}\right]$

TFF Scale-up:

System Design Considerations

The ‘Non-Linear’ aspects of the Process

Pump Effects

- Issues:
  - Pump configuration and number of pump passes
  - Final working volume
- Pump configuration:
  - Avoid micro-cavitation (air-liquid interface)
  - Minimum pressure at inlet of pump should equal manufacturer's specification (NPSH requirements)
    - Inlet line to the pump need to be properly sized

Quality

Pump Selection

- Pump Style
  - Circumferential piston displacement style is most common in biotech for large-scale
    - Waukesha and Viking are the major players – single and dual-lobe
  - Quattro-Flow is a relatively new option for smaller scale (4-chamber diaphragm)
    - Gentle protein processing
- Rotor Clearance
  - Don’t specify heat-tolerant rotors unless required – greater slip
  - Rotor clearance does not scale linearly with pump size
    - More protein damage likely in smaller pumps because clearance (slip) is a larger percentage of the total displacement

Pump Selection

- RPM and Sizing
  - Typical target is 400 – 500 rpm for protein processing, lower for cell processing
  - Design flowrate typically ~ 80% of pump maximum
- System Integration
  - Minimize distance and equipment from tank outlet to pump and use adequate ID's to avoid starving the pump
  - Target developing a cleaning protocol that uses the same feed flowrate as the process so that the pump (and piping) does not have to be oversized just to accommodate cleaning!

Tank Design

- Characteristics of a good tank design
  - Low Holdup Volume
  - Able to function at high (20-100 fold) volumetric reduction
    - No foaming or air entrainment
  - Good Mixing at low levels
    - Ensures homogeneous concentrations
    - Prevents retentate short circuit
  - No spray ball shadows
    - Efficient CIP

Yield

Quality

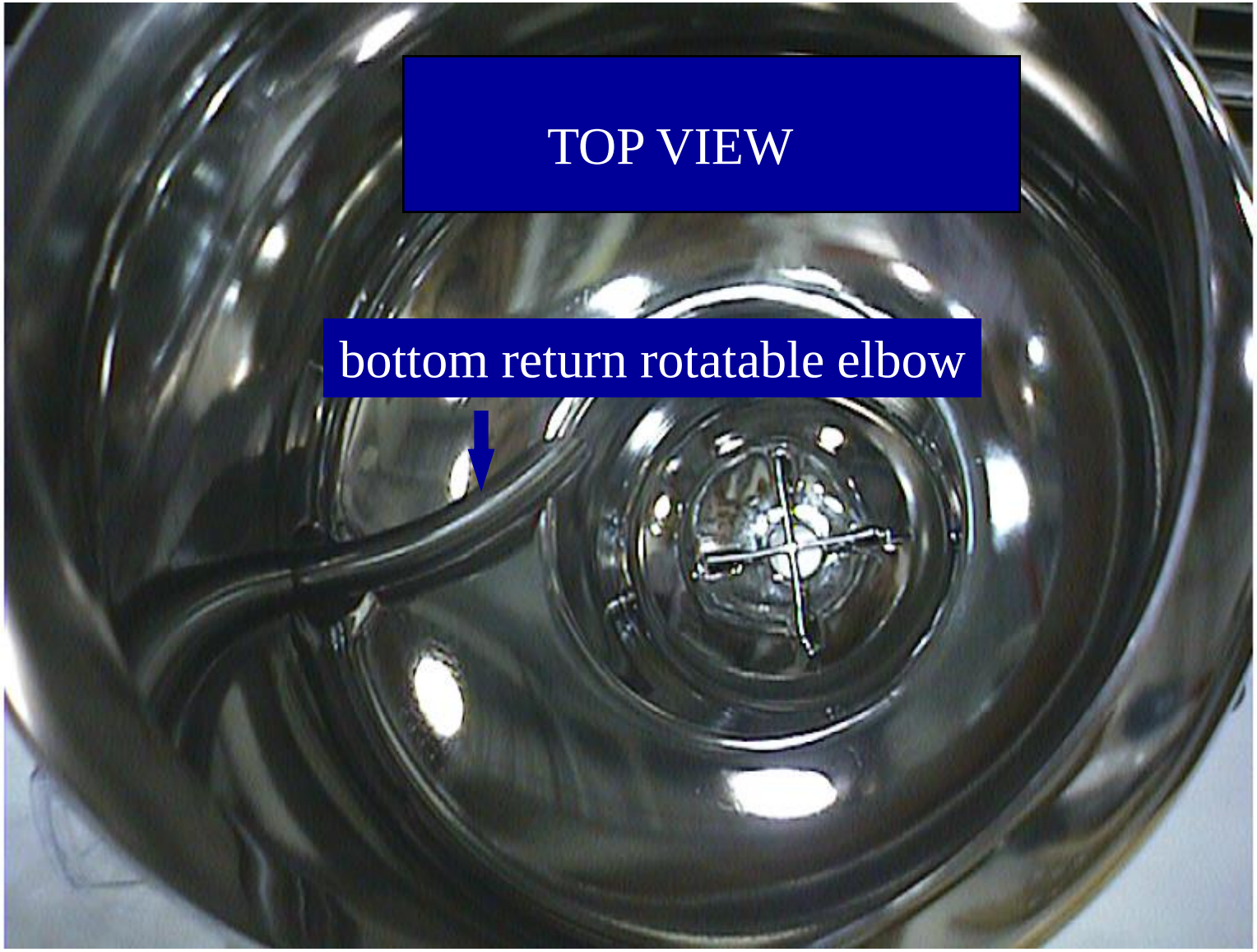
Purity

Tank Design Guidelines

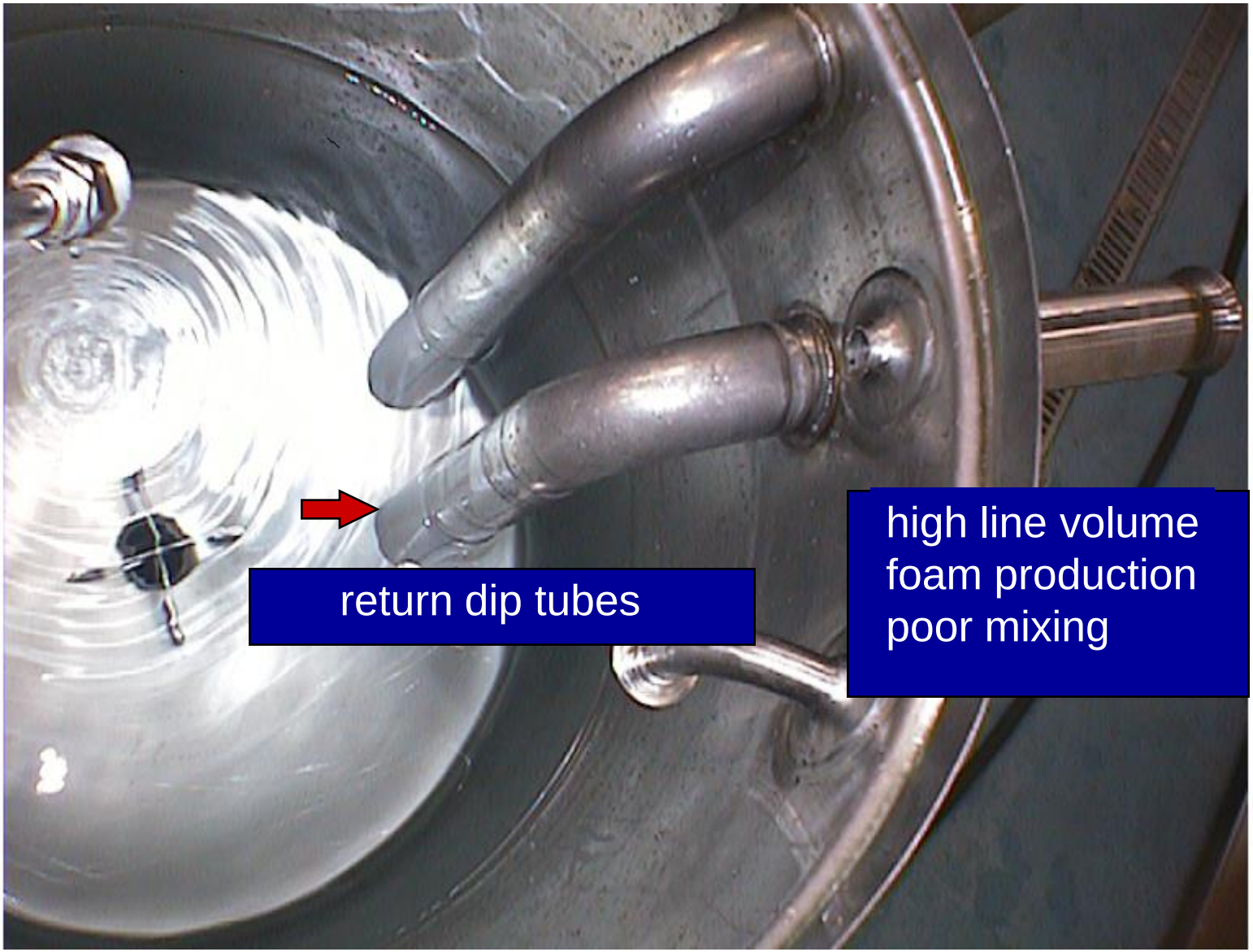
- Sizing
  - Maximum volume based on both a reasonable fed-batch ratio and on a reasonable cleaning solution volume
    - FBR ~ 4-5, cleaning flush ~ 10 L/m2
- Retentate entry
  - Very low on the tank sidewall to minimize retentate piping and also enable low tank volume operation
  - Design of dip tube is important to ensure good mixing and low turbulence
- Lots of experience with two key tank design types
  - Reduced bottom well (tulip style)
  - Conical bottom
  - Both can achieve low working volumes and good mixing
    - Conical may have an edge for cleanability, mixing, and level measurement

Tank Designs

Recirculation Tank



Example of Improper Tank Design



Integration of tank and recirc loop

Other Considerations

- Minimize hold-up
  - Minimize volume in piping
    - Fitting to fitting connections when possible
    - Instrument blocks incorporated onto membrane holders
    - Return dip tube into sidewall of recycle tank
  - Slope all lines to a low-point recovery port (1/16” per ft)
    - Tank on top of a vertically-mounted pump works well
    - Include a high-point air port for blowdown
- Avoid air/liquid interfaces
  - Very damaging to proteins
  - Vortexing in recycle tank (air entrainment)
    - design of diptube return and agitator placement/speed
- Ensure a well-mixed process stream
  - Agitator design and placement
  - Retentate dip-tube return and DF buffer stream entry
    - Ensure that DF buffer doesn’t float at top of tank while retentate short-circuits into feed intake

Other Consideration (Cont'd)

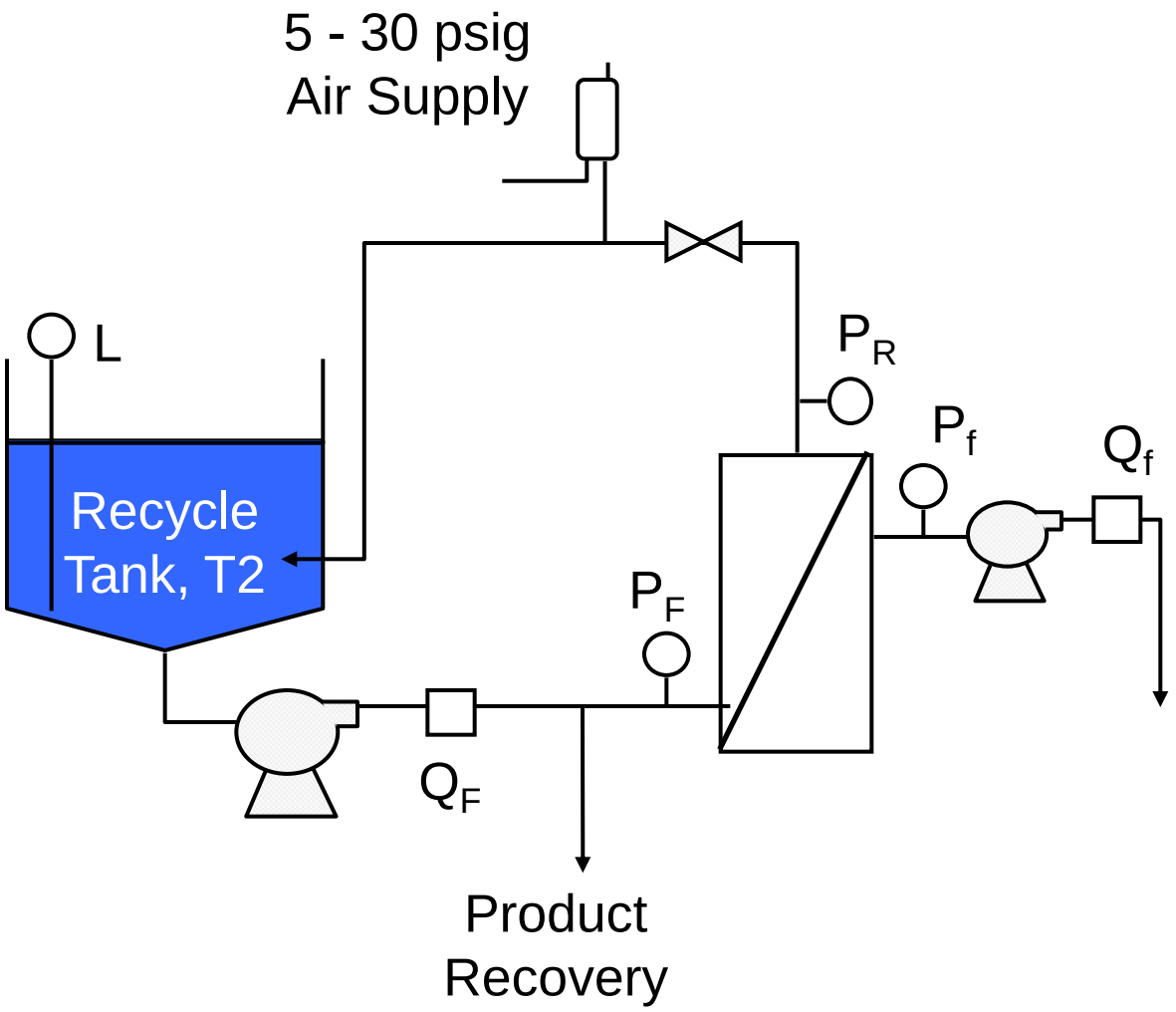
- Minimize deadlegs and contamination points:
  - Use short pull T's, NA connects, and zerostatic valves
  - Avoid flex lines
  - Minimize clamp connections
- System Size Flexibility
  - Trying to be too flexible compromises the system design for all scales of operation
  - Recommend a maximum of approximately 4-fold membrane area or flow range on a single system (2-fold is better)
- Line size:
  - Balance between pressure drop and holdup considerations
  - Maintain turbulent flow (5-7 ft/sec during CIP)
- Temperature control:
  - Jacketed tank vs in-line heat exchanger

Operational Considerations

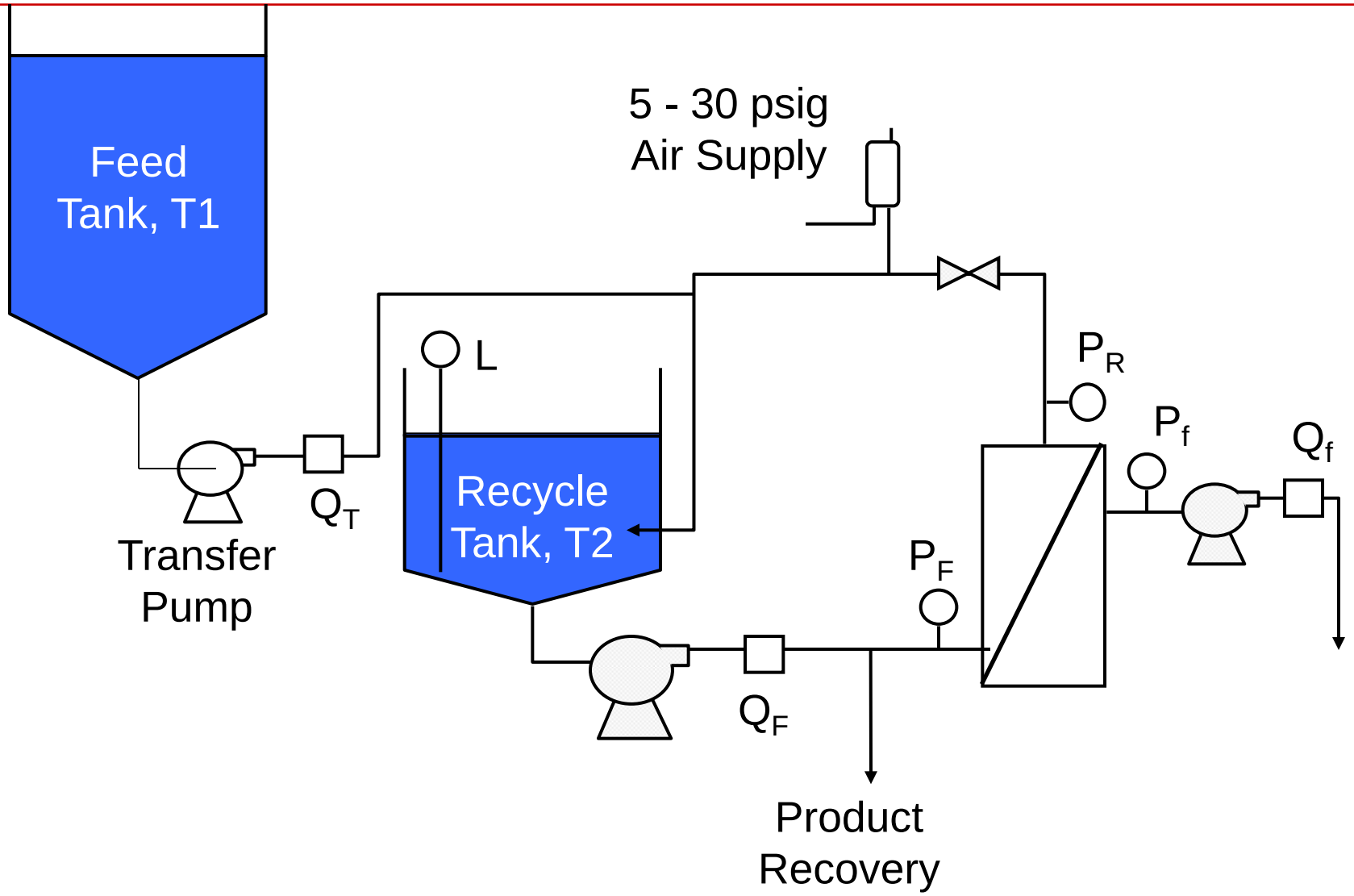
Operational Considerations

- Batch Vs Fed Batch
- Scale-up of process steps:
  - Module Installation, flushing storage solution, Integrity testing, NWP testing, Buffer Equilibration, Product Recovery, Cleaning/storage, Reuse
- Process Control

Batch


5 - 30 psig
Air Supply
L
Recycle
Tank, T2
P_R
P_f
Q_f
P_F
Q_F
Product
Recovery

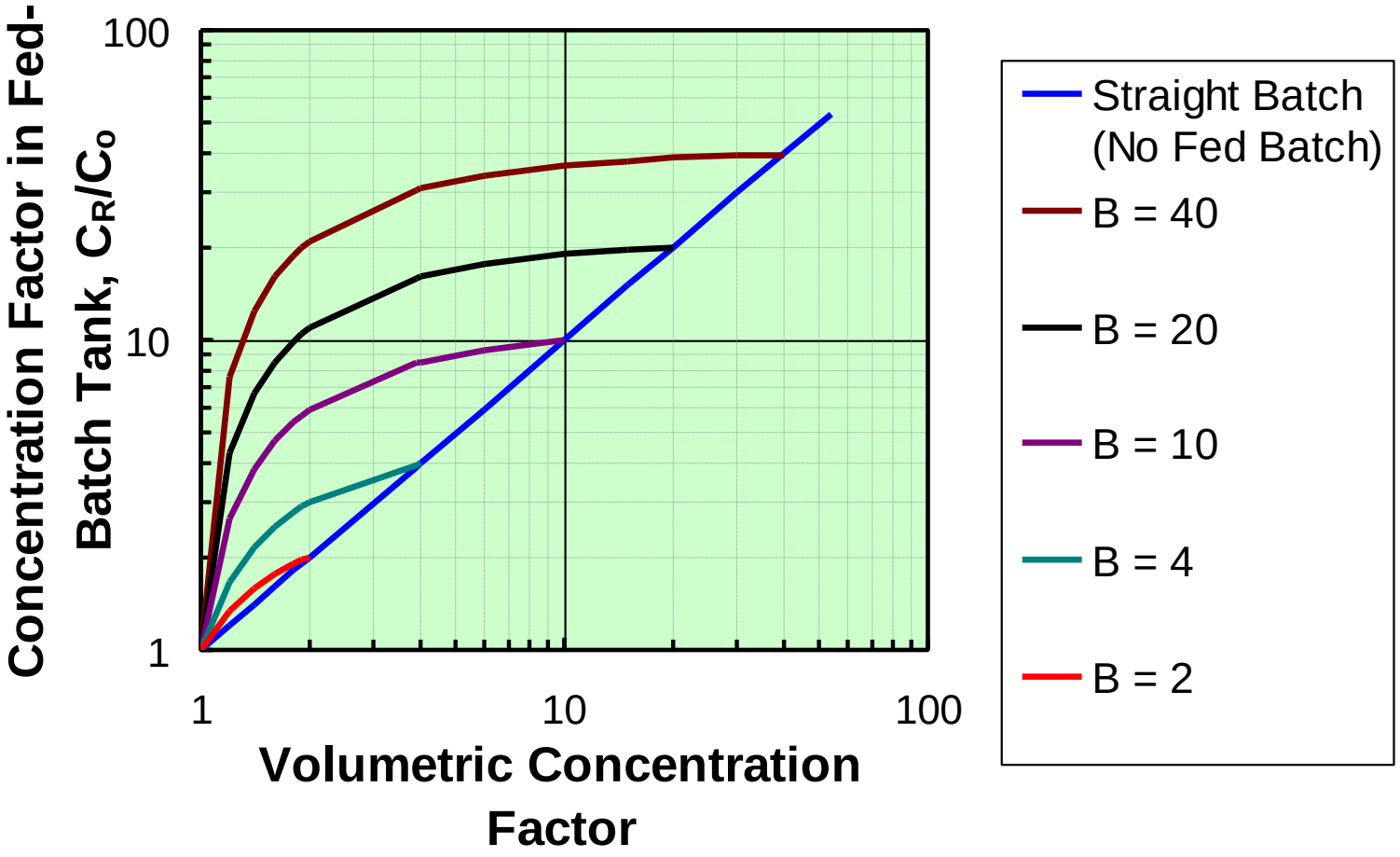
Fed-Batch


Feed
Tank, T1
5 - 30 psig
Air Supply
L
P_R
P_f
Q_f
Q_T
Recycle
Tank, T2
Transfer
Pump
P_F
Q_F
Product
Recovery

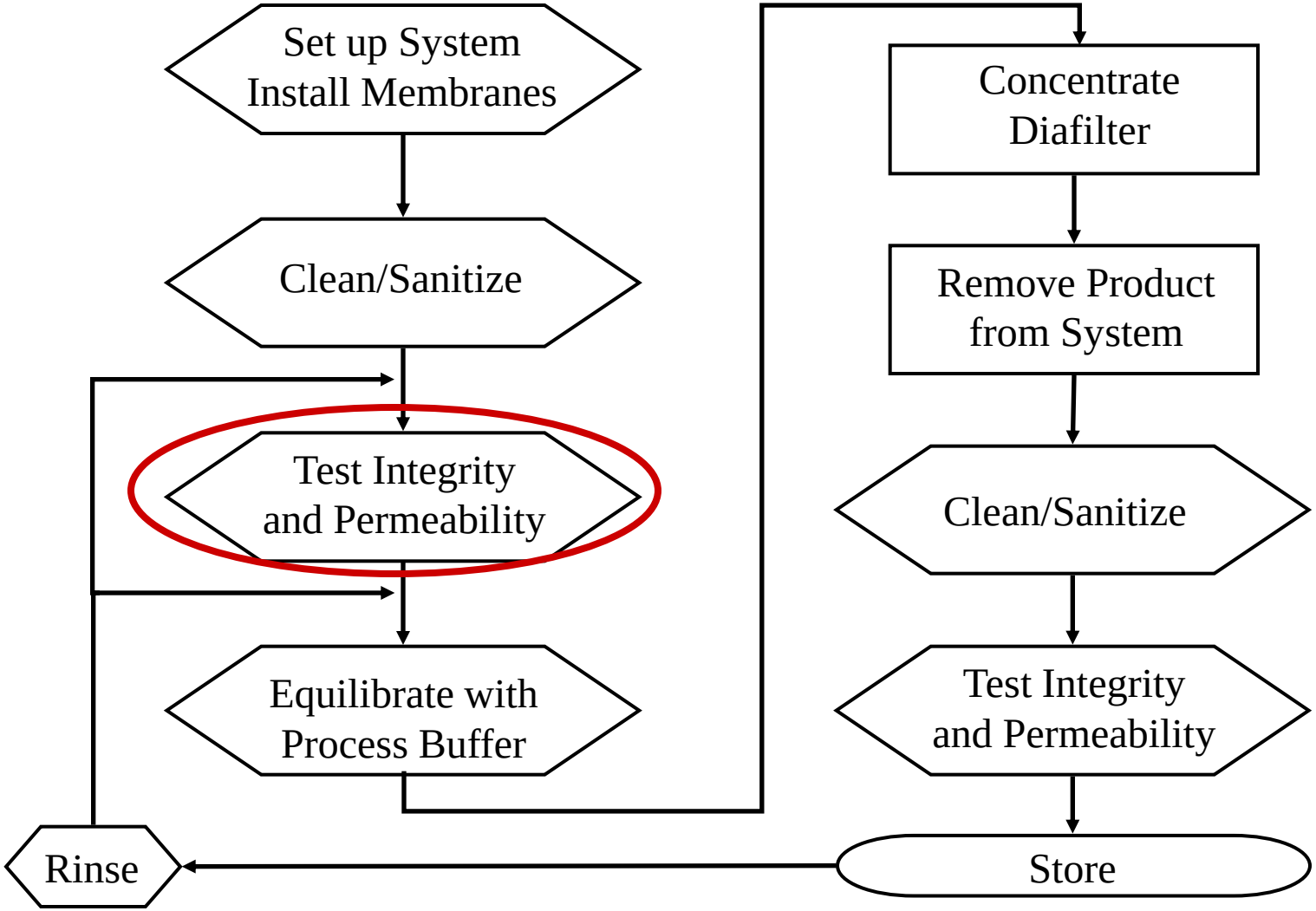
Batch versus Fed-Batch UF

- Batch UF is preferable whenever possible
  - Simplest system and control scheme
  - Feed is at lower Cavg → so less membrane area
  - Maximum achievable VCF ~ 20X
    - System or hardware limits:level measurement, mixing are reached
- Fed-Batch UF
  - Usually required for VCF > 10 - 15X
  - Minimize fed-batch ratio (= Total V_o / Recycle tank V) as much as possible to minimize membrane area
  - Maximum achievable VCF ~ 50 - 100X
  - Test process performance using proposed fed-batch ratio

Effect of Fed-Batch Ratio on Concentration in Recycle Tank



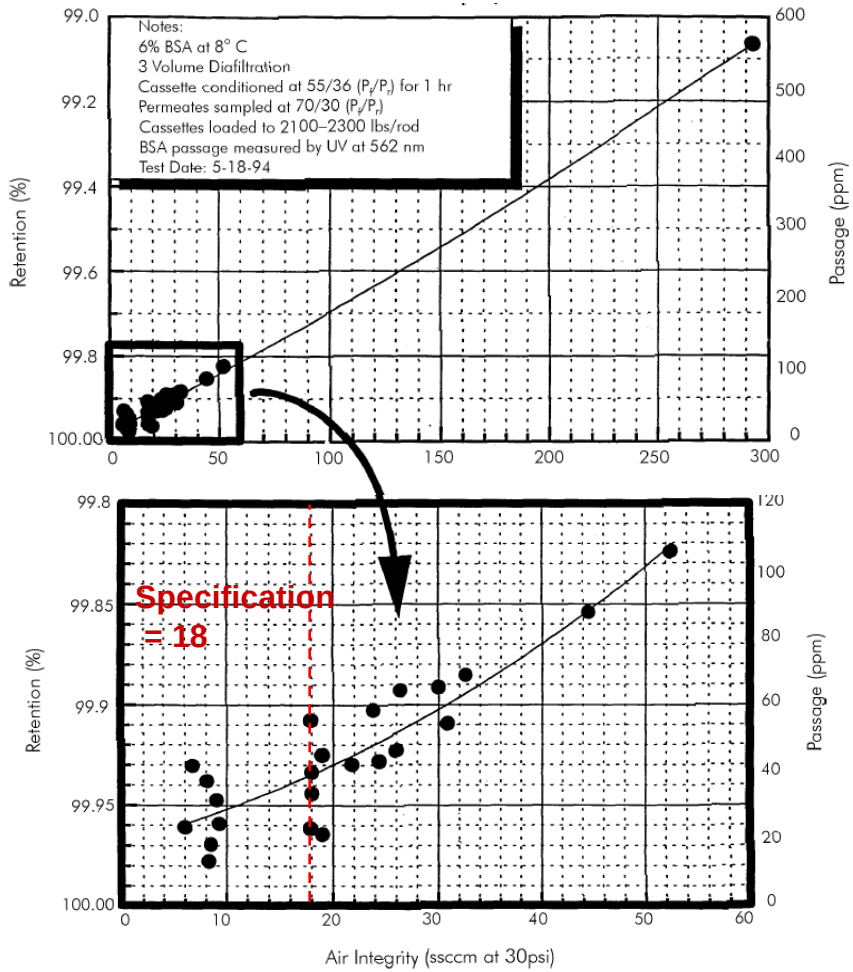
A Typical Process Sequence



Integrity Testing

- Many UF/MF processes use Air-Diffusion ‘integrity’/leak test prior to processing
  - Convenient and non-destructive way to check/confirm
    - Proper module installation
    - Damage during shipping/handling etc
    - Provides a gross measure of system integrity
  - Issues:
    - False Integrity failures can occur due to
      - Incomplete Cleaning
      - Lack of adequate wetting

Correlation to Protein Retention?



Integral Modules:

R_{BSA} > 99.9% at Air Flow < 25 scc/min

Non-Integral Modules:

R_{BSA} > 99% at Air Flow = 270 scc/min

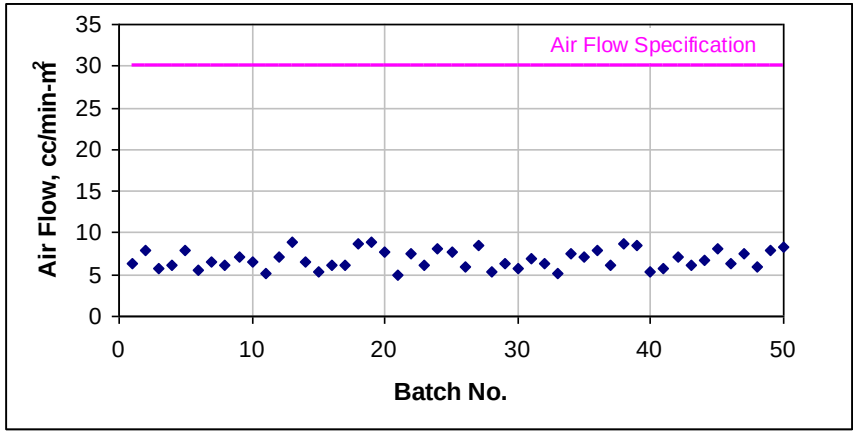
For X=20, N =5 , this represents an additional yield loss of 6.3%

Gross difference in air flow may indicate issues

Integrity Specification

$$\text{Specification} = N_{\text{Modules}} \times \text{Specification}_{\text{Individual Module}}$$

- For large installations, risk of letting a non-integral module go ‘undetected’
  - Reduce risk by trending diffusion values over batch runs
  - Alternate Spec. based on statistics
    - ‘Limited benefit for added the effort’
    - Risk of false failures
  - Other complementary tests: permeate sampling for product etc



Integrity Testing – Practical Aspects

- It is useful to have a single module holder in hand to individually test modules in the event of a failure
- Cassette devices rely on ‘sealing force’ to seal feed from permeate
  - Often a torque specification is provided by the manufacturer
    - The torque is a function of tie-rod type, thread, nut-size etc
    - The torque may be converted into sealing force as:
      - F = T/(u x d) where F = Force, T = Torque, u = friction factor, d = thread diameter
  - Many large scale systems have hydraulic closure mechanisms
    - Here, the sealing force is a function of the seal pressure resulting from the cylinders
      - Force = Effective Cylinder Area x Cylinder Pressure
  - Need to carefully review these factors when installing one set of filters into holders built by a different manufacturer

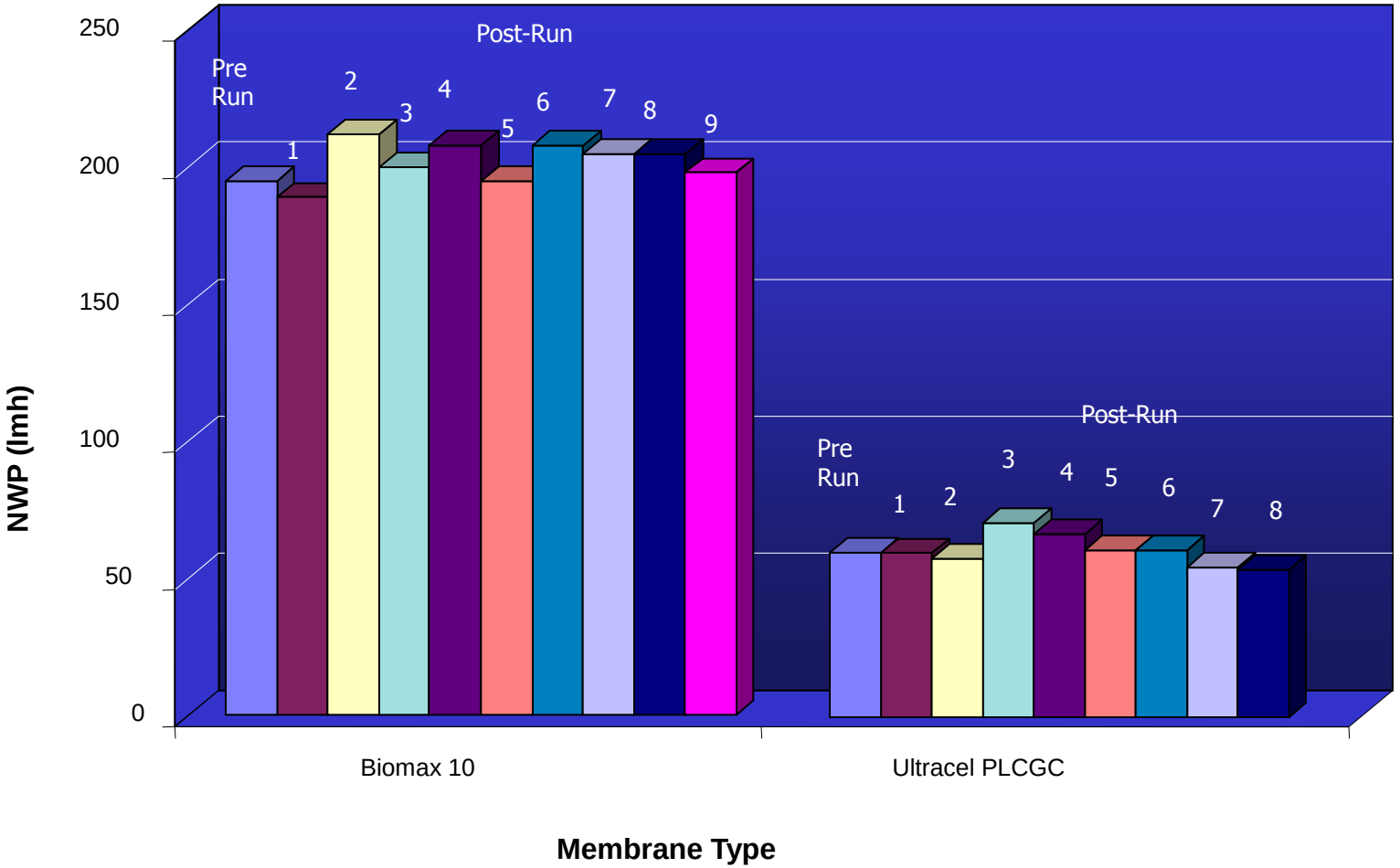
Membrane Permeability Testing

- Easy and nondestructive means of confirming the effectiveness of cleaning procedures and process consistency
- Strict definition is normal water permeability (NWP), but any solution is OK as long as you're consistent
  - Best if test solution is similar to water (viscosity)
  - Testing on storage solution is convenient
- Record temperature for accuracy
  - As well as flows and pressures

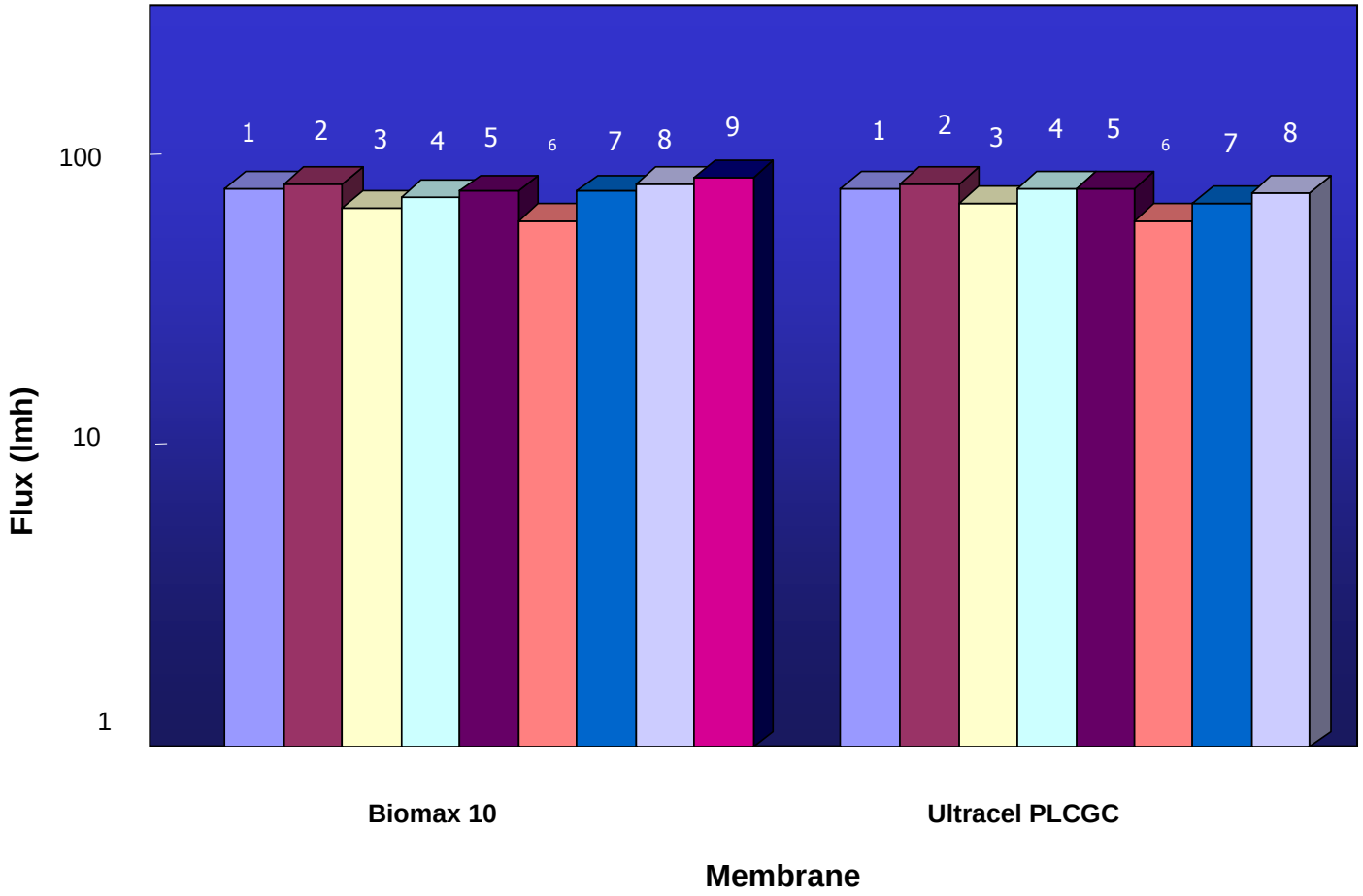
NWP – Practical Aspects

- Must be correctly used to serve as a ‘cleanliness’ indicator
  - Reliable as an indicator for tighter UF membranes (~ ≤ 300 kD)
  - For more open UF membranes & MF membranes, use NWP as a guideline rather than a specification:
    - Pressure gauge accuracy at low TMPs
    - Process permeability & TMP are stronger indicators of performance consistency
- Specification: Select NWP of the system after new filters are installed, flushed & cleaned to remove preservatives
  - Choose a ± range for acceptance criteria (varies between 60 - 80%)
- For improved reliability:
  - Use measurements at multiple TMPs (5, 10, 15 psi)

NWP Recovery after Cleaning



Process Permeability versus Batch Cycle



Product Recovery

- Product recovery strategy is often ignored at the small scale
  - Manual recovery procedures are employed (may include unclamping the unit at critical points to recover product)
  - Protein retention close to 100% is deemed a sufficient indicator for yield
- For large scale process, product recovery strategy is critical to ensure high yield
  - Gravity drain & buffer flush are often used to recover product
  - Product may still be trapped in the ‘unrecoverable’ holdup in the system and may contribute to significant yield loss
  - Enhanced product recovery techniques may be employed to boost yield

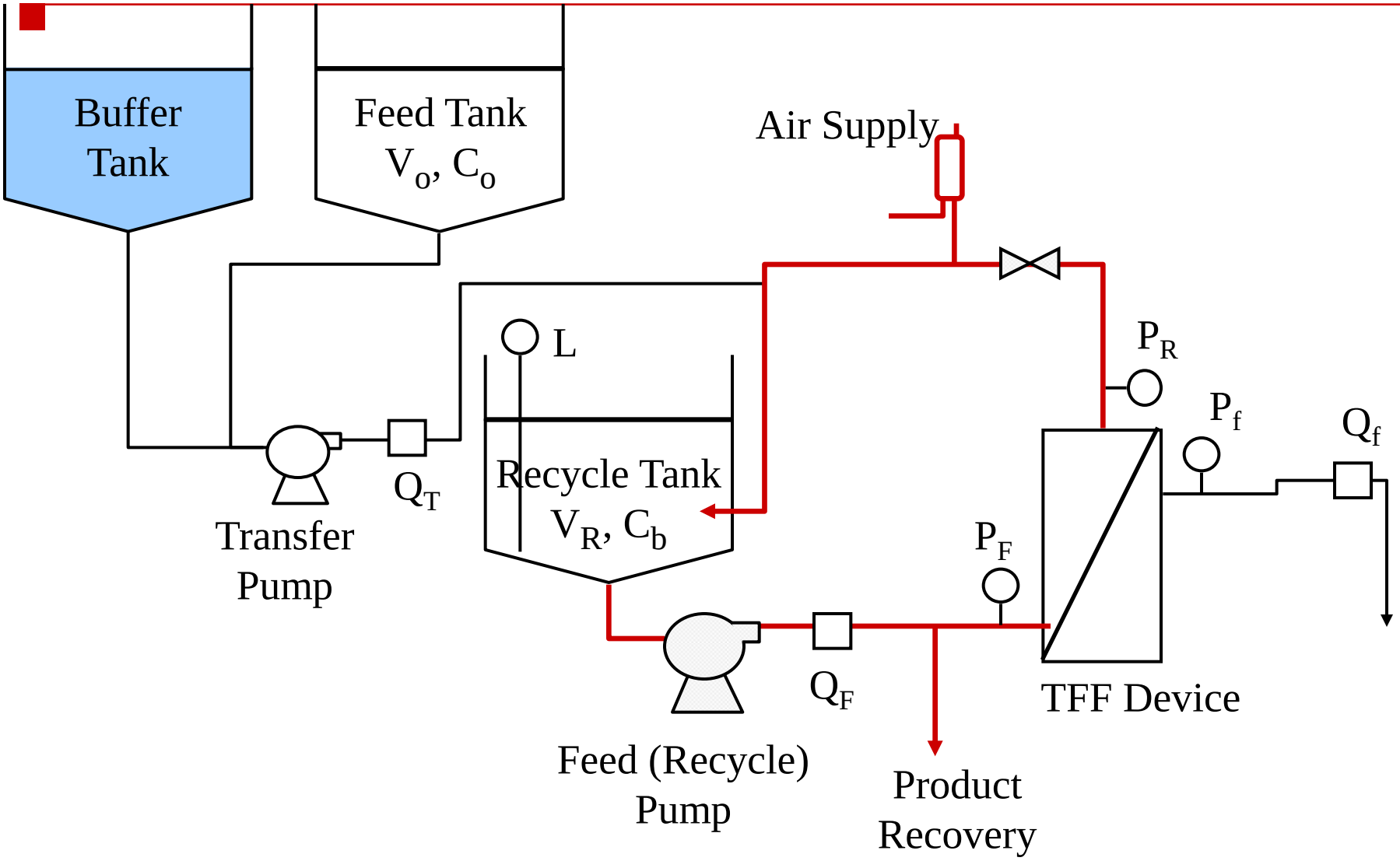
Product Recovery Techniques

- First, release polarization layer and mix feed
- Then, five recovery options to consider
  - System drain
  - System blowdown
  - Buffer flush
  - Buffer recirculation

Simple Product Recovery Options

- System Drain
  - Simplest!
  - Most effective if system has low-point drain port
  - Usually used in combination with another option
  - Works better for some devices than others
- System Blowdown
  - Air-pressure assisted drain
  - Most effective if system has high-point air port
  - Most effective to use low (5 psig) air pressure
    - Once an air path exists, recovery is finished

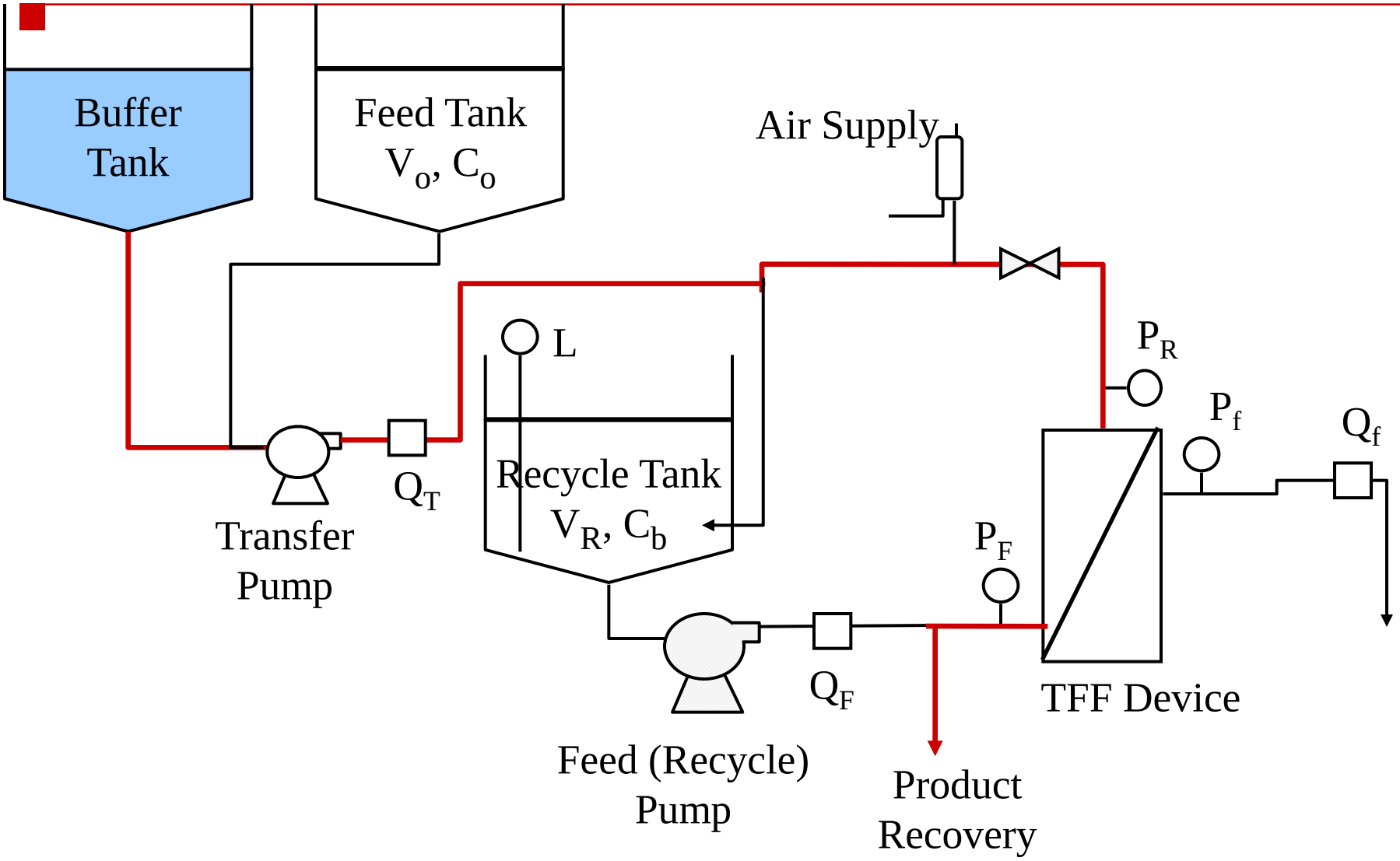
Drain and Blowdown Flowpath



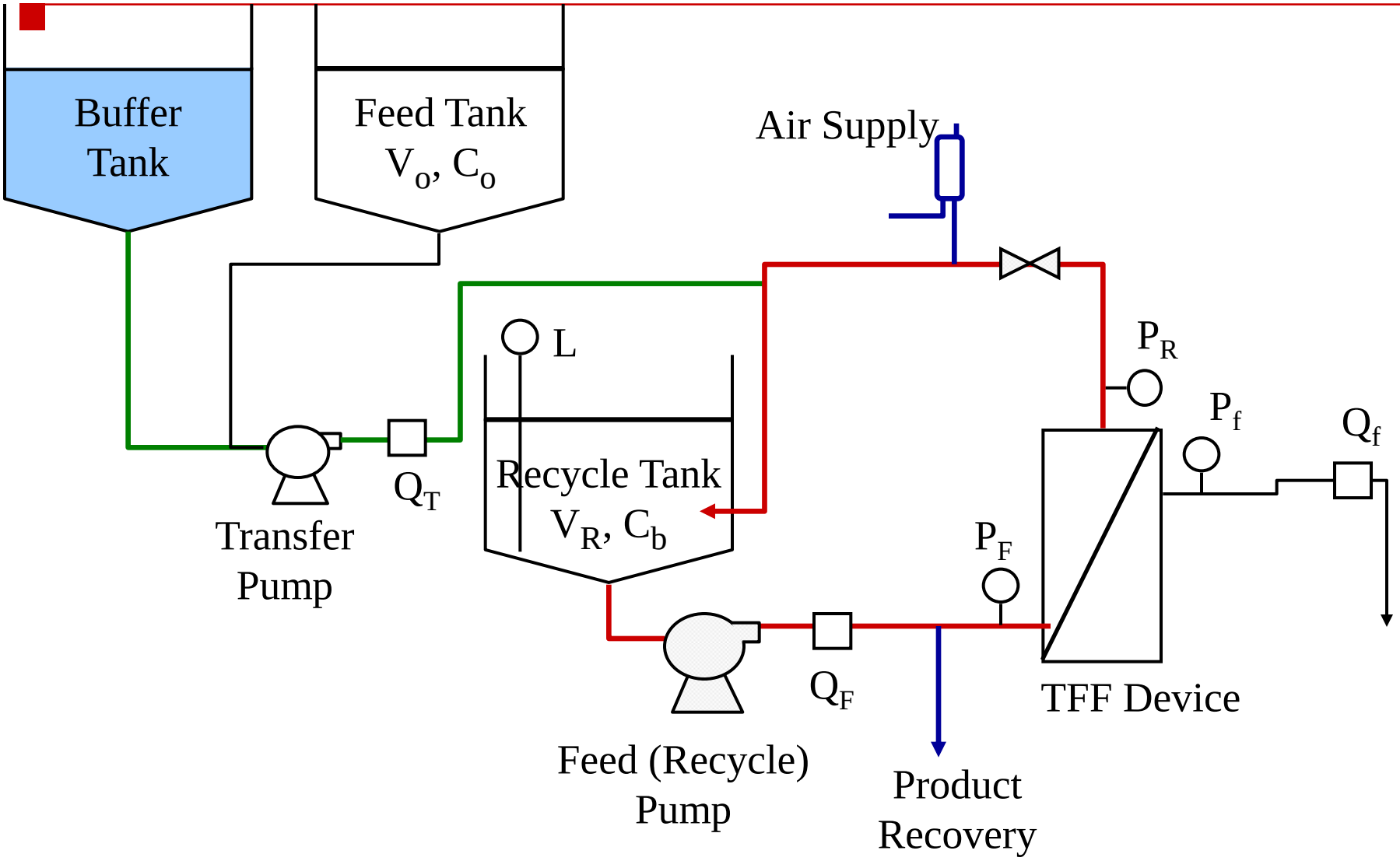
Buffer Flush or Recirculation

- These are very commonly used
- Buffer Flush
  - Flush buffer in single pass, through drained system
  - Approximately one system volume of buffer is required
  - Entire volume of buffer is added to product, so dilution must be acceptable
- Buffer Recirculation
  - Add buffer to empty recycle tank, recirculate through empty system, then recover
  - same dilution concerns as with buffer flush

Buffer Flush Flowpath



Buffer Recirculation Flowpath



Cleaning/Storage Considerations

- Establish a robust cleaning procedure:
  - Cleaning solution make-up:
    - If dosing with a high concentration stock solution, select the dosing point carefully → Ex. downstream of retentate line to maximize the probability of thorough mixing.
  - Allow NO significant lag time between end-of-processing (conc/recovery) and cleaning → ideally < 1 hr
  - Ensure CIP chemicals are 'clean'
  - Ensure there are no dead legs, paths during the CIP cycle.
  - Provide for partial 'flush' with cleaning solution before recirculation
  - Allow adequate distribution of flow between retentate and permeate side → target 30% conversion
    - Permeate restriction for MF and open UF membranes
    - Adequate TMP for tight UF membranes

Reuse Considerations

- Validation Requirements: Ensure
  - Reproducible process
    - Demonstrate performance consistency
      - Flux, TMP, crossflow, Yield, NWP, Integrity test
  - Contaminant clearance
    - Flush water residuals – measure TOC, sample for cleaning/sanitizing agents
    - Lot-to-lot product or contaminant carryover levels
  - System is free of bioburden
    - Live bacteria, mold, spores, etc
    - Endotoxin levels (measured by LAL test) are below spec.
- Economic Tradeoff
  - Membrane cost per run decreases with increasing number of uses
  - However, validation effort can become oppressive

Full or partial data from small scale

Demonstrate at large scale to # Of reuses

Process Control

Objective: Key process parameters need to be consistently maintained at fixed setpoints

- Crossflow Control
  - Creates the tangential flow (sweeping action)
- Retentate Pressure Valve Control
  - Creates driving force through the membrane to cause flux
- Other Control
  - Filtrate Control
    - Required to moderate the flux on large pore size UF and all MF systems
  - Level, Temperature

Crossflow Control Options

- Modulate the feed pump speed throughout a process to maintain:
  - Pressure Drop setpoint
  - Feed Rate setpoint

Crossflow Control by Constant Pressure Drop

- Simplest to implement (least expensive!)
  - Only pressure gauges required for control
- Actual crossflow is unknown
  - Less process information
  - Crossflow changes if viscosity changes significantly during run
- Lot-to-lot & within-run pumping requirements vary
  - Must have adequate high and low-end pumping capacity to span the potential range
- Scaleup / scaledown pump sizing more difficult

Crossflow Control by Constant Feed Rate

- Actual crossflow is known
  - More information on system performance
  - Crossflow is maintained if viscosity changes during run
- Lot-to-lot and within-run pumping req's are constant
  - Maximum pumping capacity need is known
- Scaleup / scaledown pump sizing is straightforward
  - Simple ratio of membrane area difference
- Requires feed flow measurement

Retentate Pressure Valve Control Options

- Modulate the retentate valve position throughout a process to maintain:
  - Pressure setpoint
    - Retentate pressure
    - TMP
  - Flux setpoint
    - Constant
    - Variable throughout run

Retentate Valve Control Using a Pressure Setpoint

- Retentate Pressure Setpoint
  - Simplest, robust control scheme for most UF processes - most widely used
  - Requires only retentate pressure measurement
- Transmembrane Pressure Setpoint
  - More complex than simple retentate pressure setpoint
  - For processes with constant ΔP, no real advantage
  - Maintains more constant pressure during viscosity changes
  - On-line TMP calculation required for an automated system

Retentate Valve Control Using a Flux Setpoint

- Constant Flux setpoint
  - More typical for MF and Virus-TFF processes than UF (often via a filtrate pump)
- Variable Flux setpoint
  - Sophisticated UF control scheme to maintain constant protein concentration at membrane surface (Cwall) regardless of bulk concentration or membrane permeability
  - Impossible to implement on manually-controlled system
- Both schemes require filtrate flow measurement

Filtrate Control

- Most UF processes (< 100kD)
  - free flow filtrate is the standard
  - no control and no restriction in filtrate line
  - permeability is low enough so that only a portion (<30%) of the feed flow converts to filtrate
- All MF processes and UF >100kD
  - filtrate flow must be regulated (restricted) to avoid most or all of the feed flow converting to filtrate
  - minimizes fouling, polarization, and over-concentration
  - results in pressure on the filtrate lines, reduced TMP
  - NEVER use with standard cellulose membrane!

Filtrate Control Options

- Regulate the filtrate flow to a fixed, robust setpoint throughout a process through the use of a:
- Pump
- Flow Control Valve

- Flux setpoint is most common
  - TMP setpoint is also possible but less robust, especially for MF

Level Control

- Maintain level in recycle tank constant throughout a fed-batch UF or a DF step
- Modulate either a transfer pump speed or a flow control valve position to maintain either:
  - Constant recycle tank level (+/- deadband)
  - Transfer flowrate equal to filtrate flowrate
- Considerations
  - Effects of pressurizing transfer tank contents
  - Degree of control required
  - Confidence in equivalency of 2 different flowmeters

Useful Equations

Process Step	Concentration	Yield
Concentration Step	$C_R = C_o\left(\frac{V_o}{V}\right)^r = C_o(X)^r$	$Yield_{\text{Retentate}} = \frac{(V_R C_R)}{V_O C_O} = X^{-(1-r)}$
Constant Volume Diafiltration Step	$C_{RN} = C_R e^{-(1-r)N}$	$Yield_{\text{Retentate}} = \frac{(V_{RN} C_{RN})}{V_R C_R} = e^{-(1-r)N}$
Concentration plus constant Volume Diafiltration Step	$C_{RN} = C_O e^{[-(1-r)N + r\ln X]}$	$Yield_{\text{Retentate}} = \frac{(V_{RN} C_{RN})}{V_O C_O} = e^{-(1-r)(N+\ln X)}$

Membrane Area:

$$FS \cdot Area = ES \cdot Area \times \frac{FS \cdot Volume_{Filtered}}{ES \cdot Volume_{Filtered}} \times \frac{ES \cdot Time}{FS \cdot Time} = \frac{Avg \cdot FS \cdot production \cdot rate}{Avg \cdot ES \cdot flux}$$

Number of Pump Passes:

$$NPP = \frac{N + \ln X}{\left(Q_P / Q_F\right)}$$