EPFL minor in Biotechnology

Module ChE-437
Part 3: Downstream Processing

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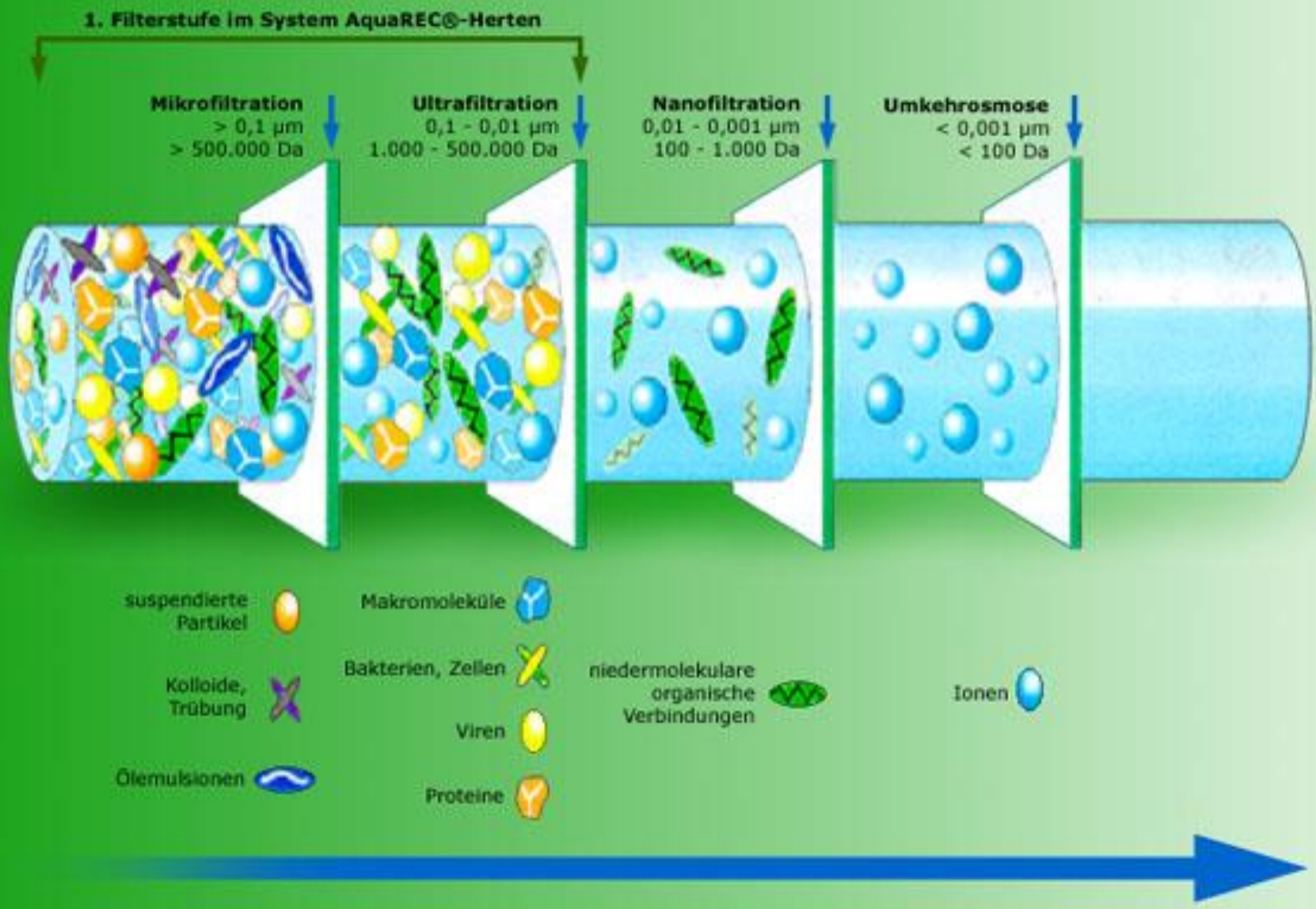
Lecture 3 – Membrane separations

3.1 Membrane basics
3.2 UF, DF …

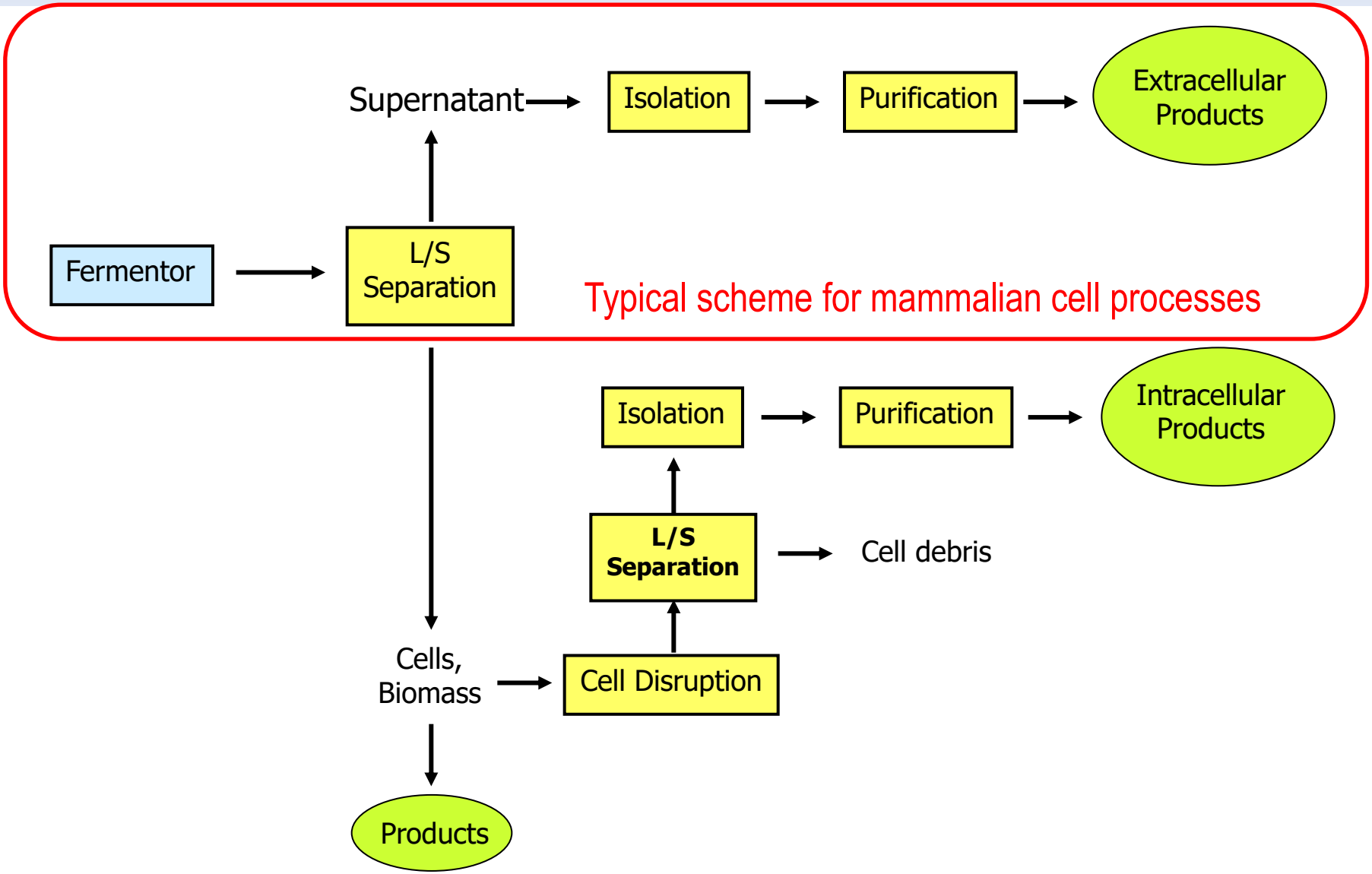
Lecture plan

- **Lecture 1:** Anatomy of a bioprocess, overview of biotech products and DSP in biotechnology; Analytical aspects. Production of mAbs. Purification platforms
- **Lecture 2:** Clarification, L/S separation: centrifugation, filtration
- **Lecture 3:** Membrane separation, chromatography part 1
- **Lecture 4:** Chromatography part 2, viral clearance
- **Lecture 5:** Reserve time (and possibly: continuous biomanufacturing, precipitation, crystallization, stability assessment)

Membranes: what is retained, what is not?



Common pathways for the isolation of products



3.1 Ultrafiltration membranes

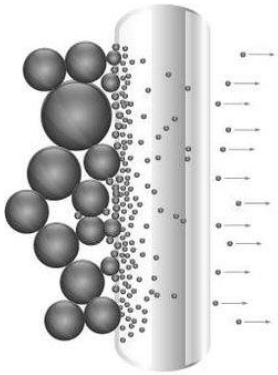
A bit of nomenclature and definitions

- **Membrane:** film-like barrier separating two fluids
- **CFF, TFF:** Cross Flow, resp. Tangential Flow Filtration
- **Retentate:** Mixture that remains upstream of the membrane
- **Permeate:** liquid and solutes passing through the membrane (equivalent of filtrate)
- **Retention (or rejection) factor**: $R = 1-(C_P/C_R)$
- **(Nominal) molecular weight cut-off (MWCO or NMWC):** molecular weight of a globular protein that has a retention factor R of 0.9.
- **Osmotic pressure:** the pressure that needs to be applied to a solution to prevent the inward flow of water across a semipermeable membrane
- **Transmembrane pressure (TMP):** average pressure drop between retentate and permeate side of the membrane
- **Diavolume:** permeate volume equal to the volume in the retentate tank and circulation loop
- **LMH (Liters per square meter and per hour):** non-SI unit traditionally used in the membrane trade to express the flux of permeate

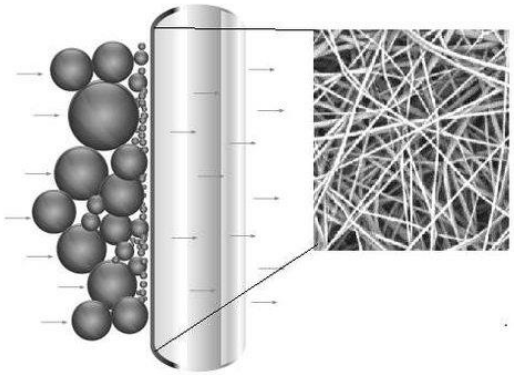
$$\mathbf{1\ LMH = 2.778 \cdot 10^{-7}\ m^3 \cdot m^{-2} \cdot s^{-1}}$$

Membrane filtration: the very basics

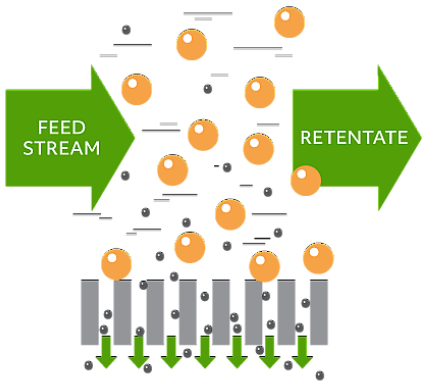
- Membrane filtration belongs to the **surface filtration** type
- The great majority of membrane techniques rely on the **Cross Flow (or Tangential Flow) Filtration** technique
- With membrane filtration it is possible to …
  - **Concentrate** a solution of a retained molecule
  - **Fractionate** (separate) molecules of different sizes
  - **Exchange buffers** (diafiltration)



a) Depth Filtration



b) Surface Filtration with Nanofibers

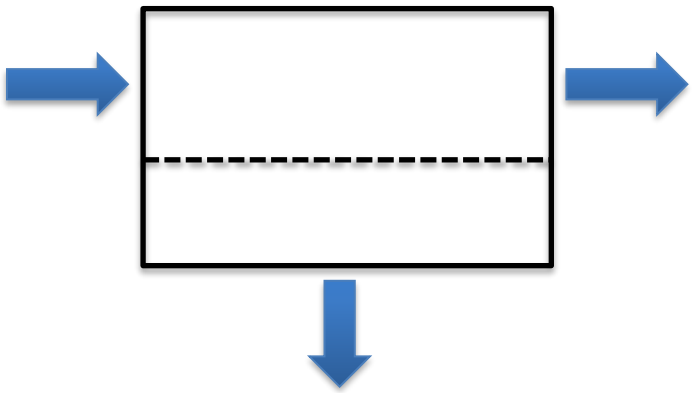


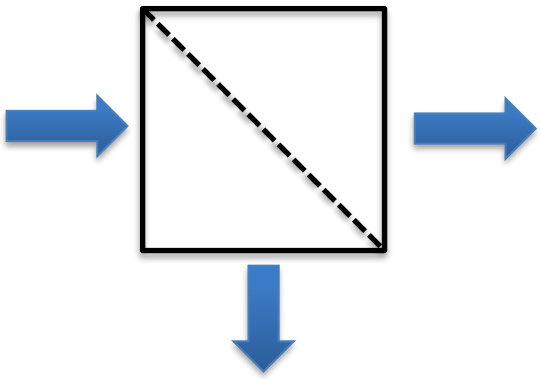
Tangential Flow Filtration (TFF)

Dead-End Filtration

3.1 Introduction (1/2)

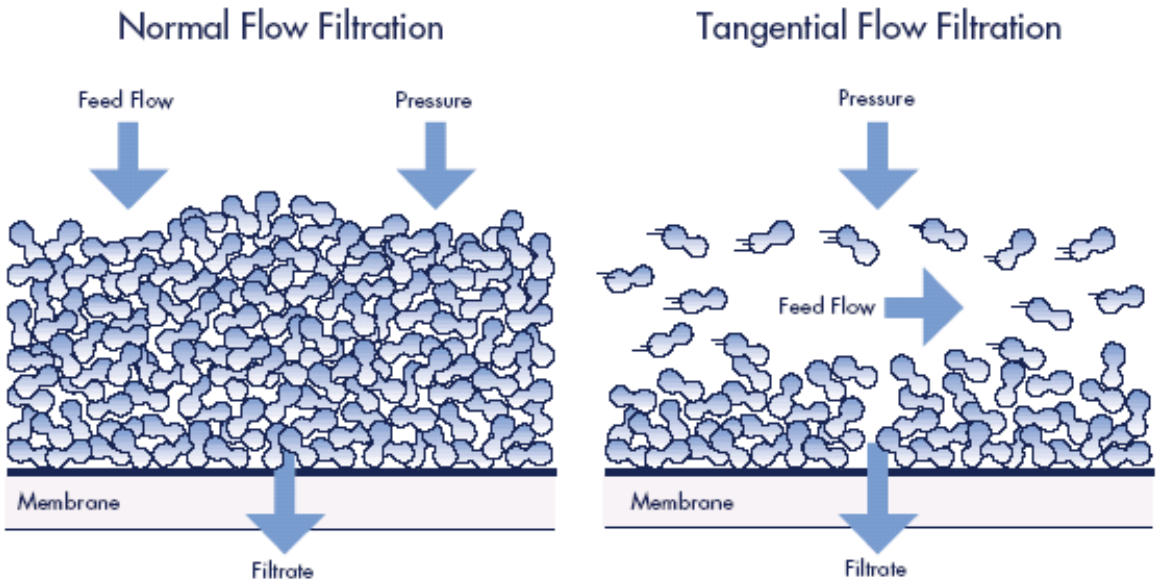
- All membrane filtrations are physical separation techniques based on size discrimination. They are used in **many industrial applications**
- **Solid/liquid suspensions** as well as **solutions** containing molecules of different sizes can be handled in a membrane filtration unit
- Like for «classical» filtration, **the driving force is a pressure difference Δp** between the compartments situated on each side of the separation element, i.e. the membrane. The higher this Δp, the higher the flow through the membrane
- A **tangential flow filtration module** is usually drawn in one of these two ways:



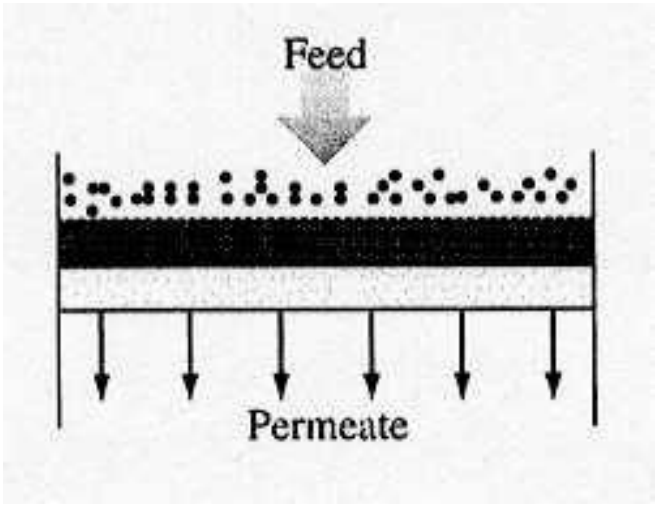


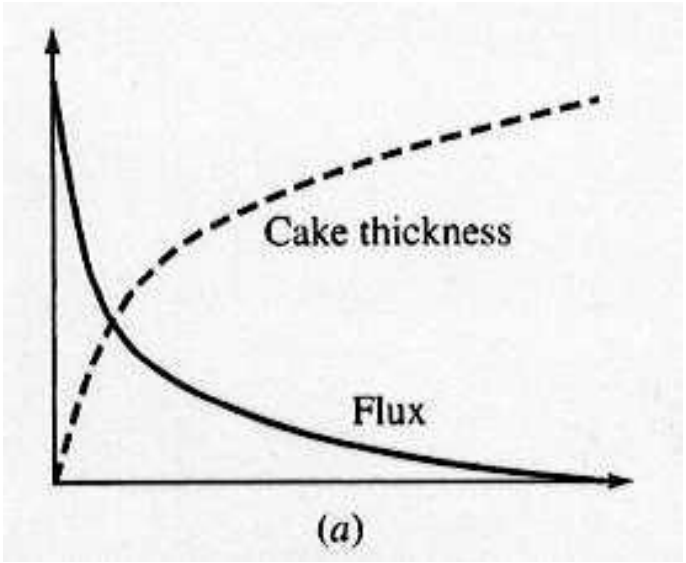
3.1 Introduction (2/2)

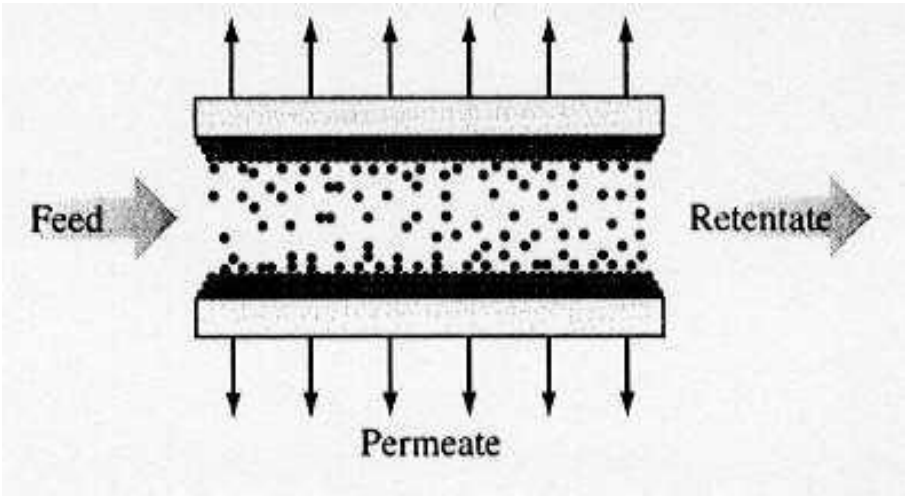
- The core element of the unit is the membrane, which pore size defines the type of particle/molecule that will be retained and the operation that will be performed:
  - Microfiltration (particle filtration)
  - Ultrafiltration
  - Nanofiltration
  - Reverse Osmosis

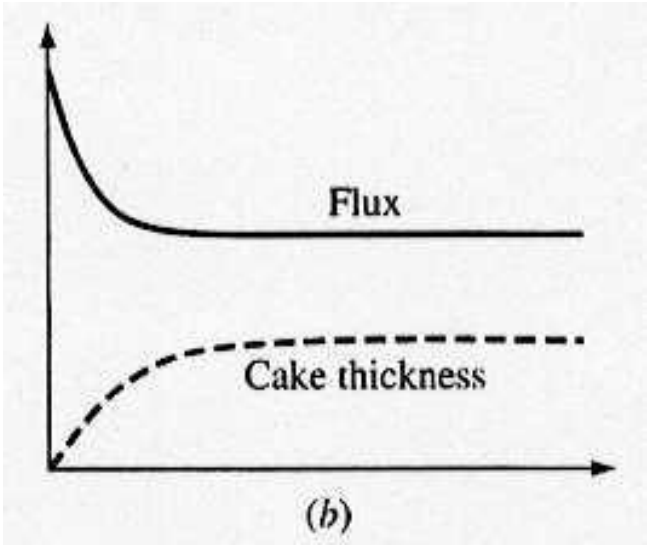


Frontal and tangential flow filtrations (seen already)

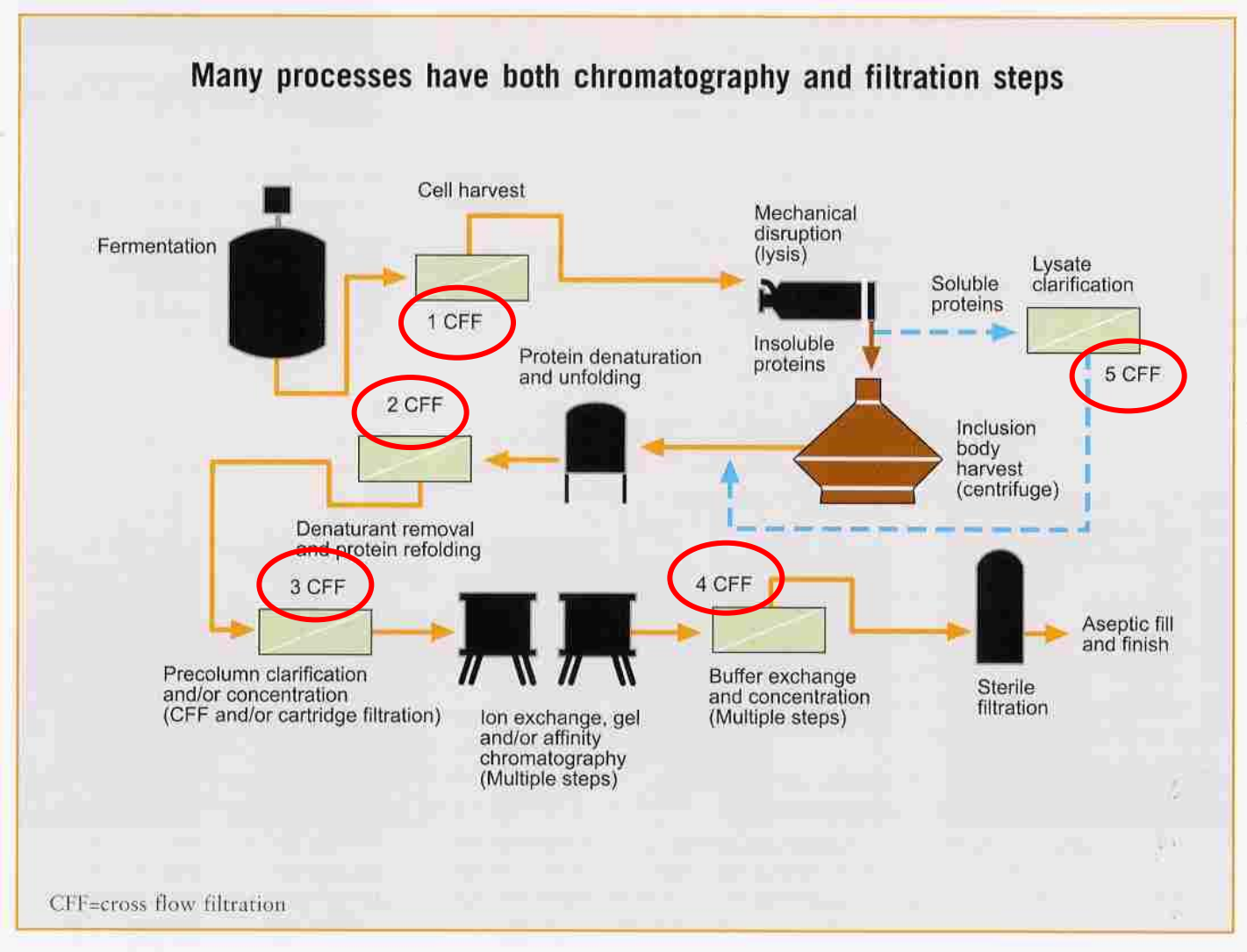








Many bioprocesses combine centrifugation, UF and chromatography for DSP



3.2 Membrane manufacturers and suppliers

3M

Whatman
Part of GE Healthcare

CUNO
a 3M company

cytiva

PALL
Pall Corporation

MERCK

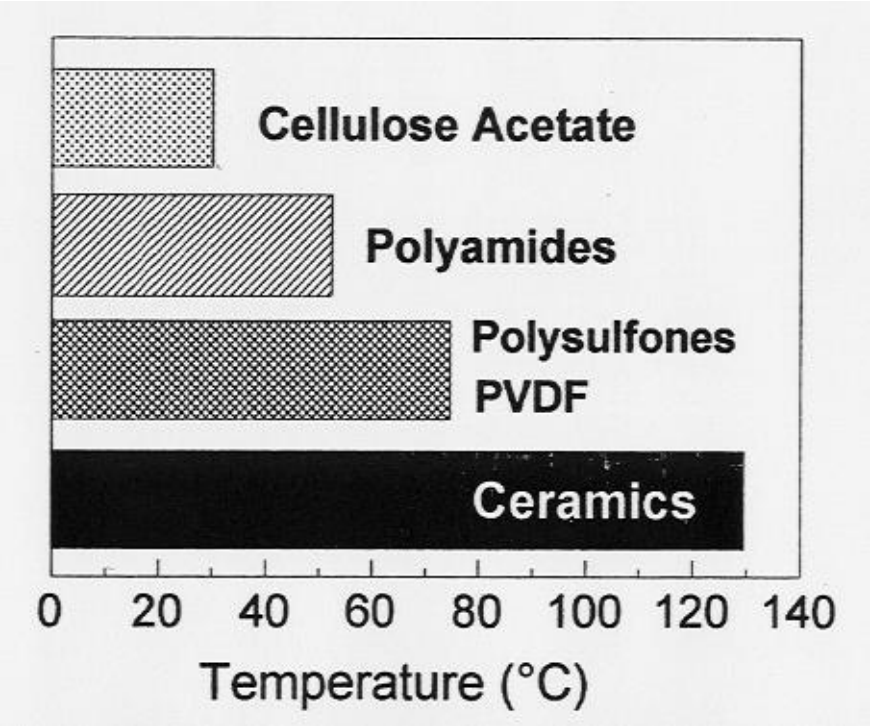
sartorius

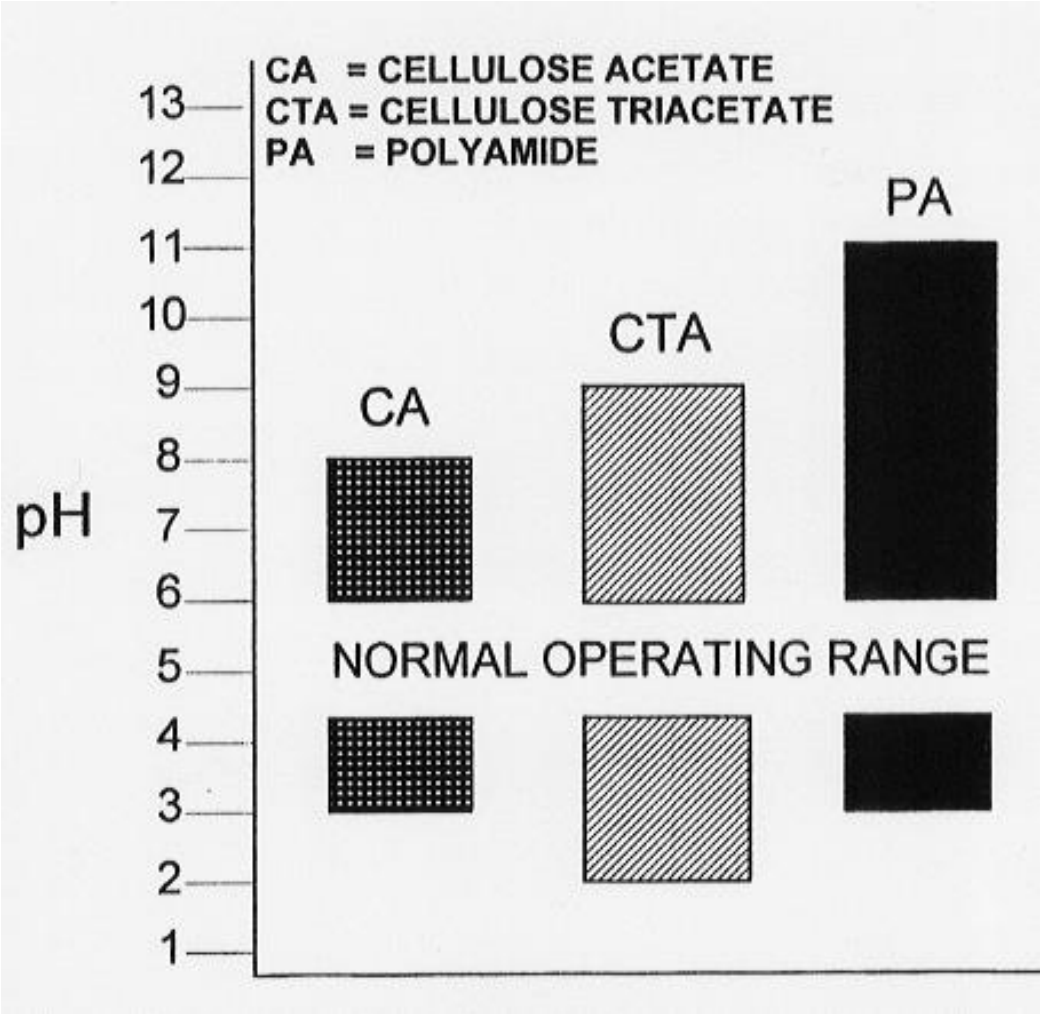
Commonly used materials for membranes

Since bioprocess liquid media are mostly aqueous, the most commonly used materials for membranes are of a hydrophilic nature

Material	MF	UF	RO
Alumina	X		
Cellulose esters (mixed)	X		
Polytetrafluoroethylene (PTFE)	X		
Sintered stainless steel	X		
Cellulose regenerated	**X**	**X**	
Ceramic composites (zirconia on alumina)	X	X	
Polyacrylonitrile (PAN)	X	X	
Polyethersulfone (PES)	**X**	**X**	
Cellulose acetate (CA), -triacetate (CTA)	**X**	**X**	
Polyimide		X	X
CA-CTA blends			X
Polyetherimide (PEI)			X

Temperature and pH resistance of various materials



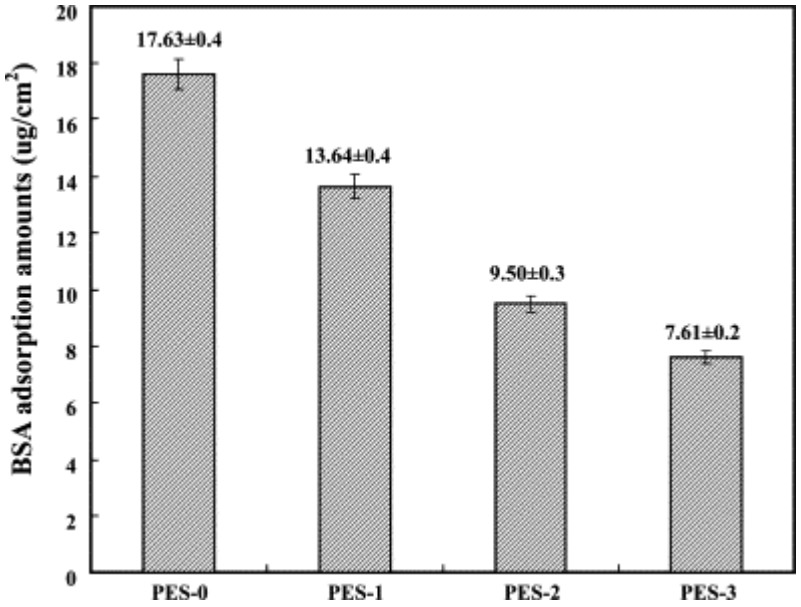


Common ranges for UF working parameters

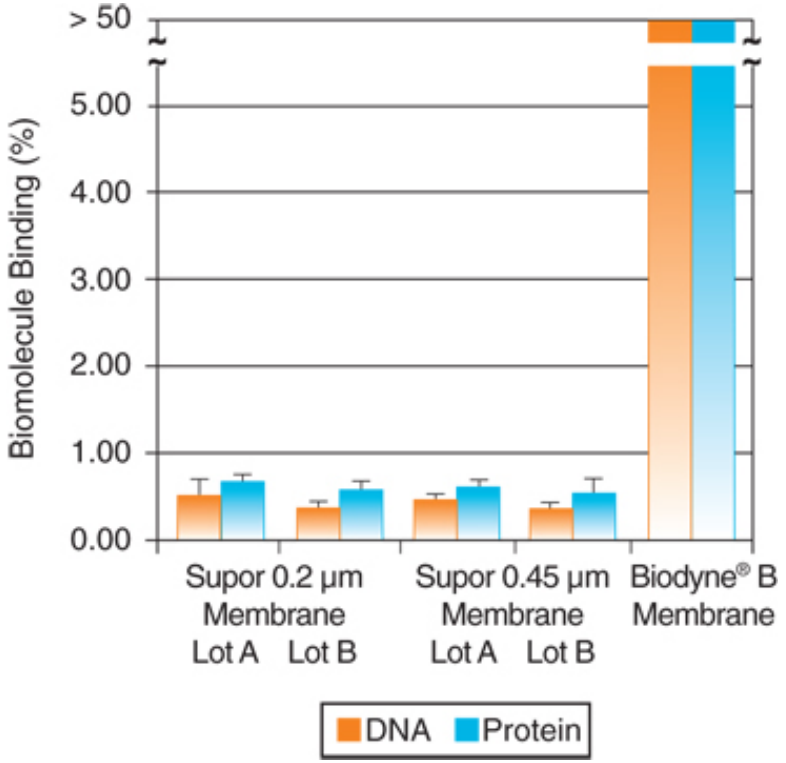
- Temperature: 0-60 °C (depending on the type of material)
- pH: 3-8 (depending on the type of material)
- Pressure: 0-10 bar
- Permeate flux J_P: 20-100 [$l \cdot m^{-2} \cdot h^{-1}$]
- Membrane surface: from a few hundreds cm^2 up to several hundreds m^2

Non-specific adsorption is the supplier's concern

(but it might become yours)



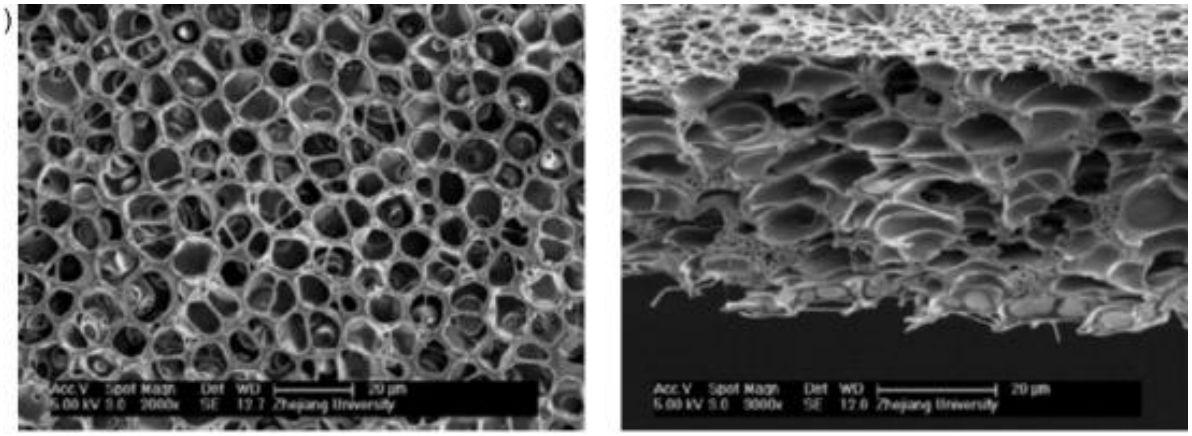
D. Wang, W. Zou, L. Li, Q. Wei, S. Sun, C. Zhao: Preparation and characterization of functional carboxylic polyethersulfone membrane. J. of Membrane Science 374 (1-2), 93-101 (2011)



Membrane manufacturing technologies

OPTIONAL

Manufacturing technology	Material
Phase inversion induced by: Organic solvents Evaporation Change in temperature Precipitation	Polymers: Cellulose (tri)acetate Polypropylene Polysulfone, nitrocellulose
Stretching of partially crystallized polymers	PTFE
Irradiation and chemical etching	Polycarbonates, polyesters
Fusion and sintering of powders	Ceramics, metal oxides, PTFE, polymethylene



SEM picture of a cellulose nitrate membrane

H. Sun et al., J. Membrane Science 295 (1-2), 2-10 (2007)

Internal structure of membranes

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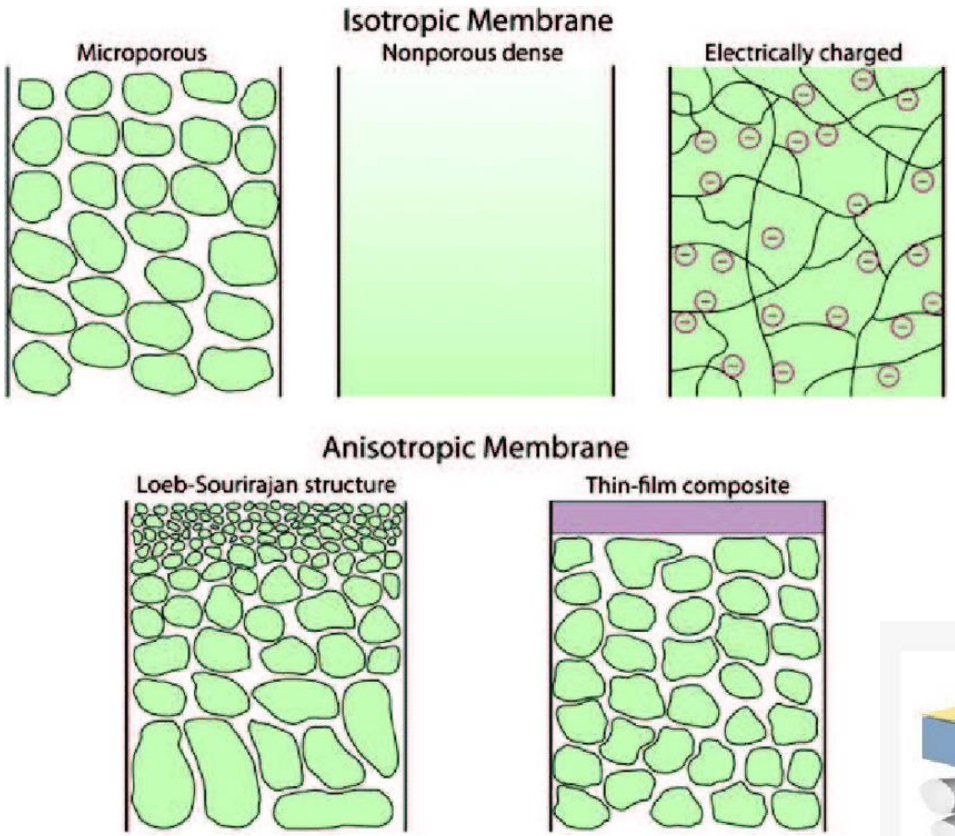

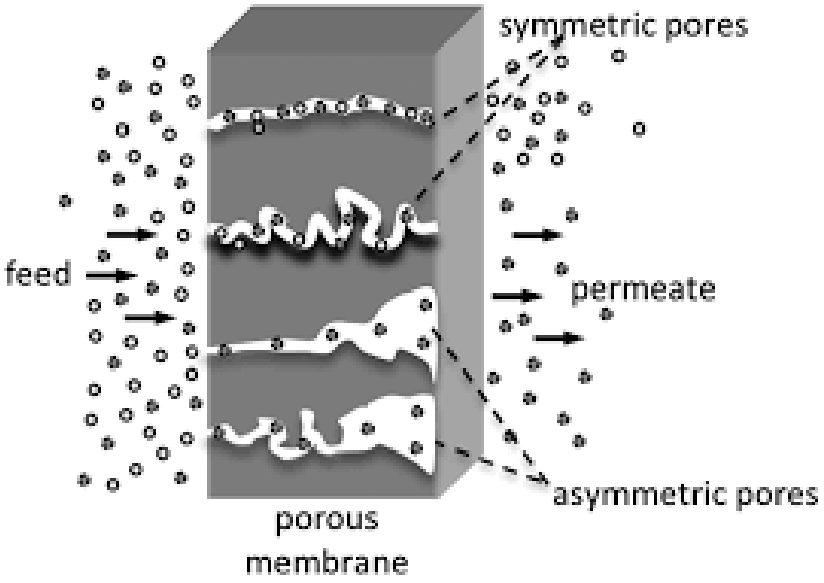

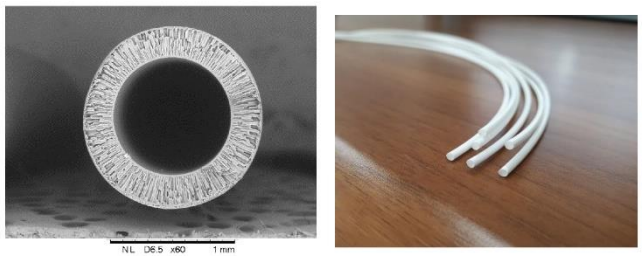

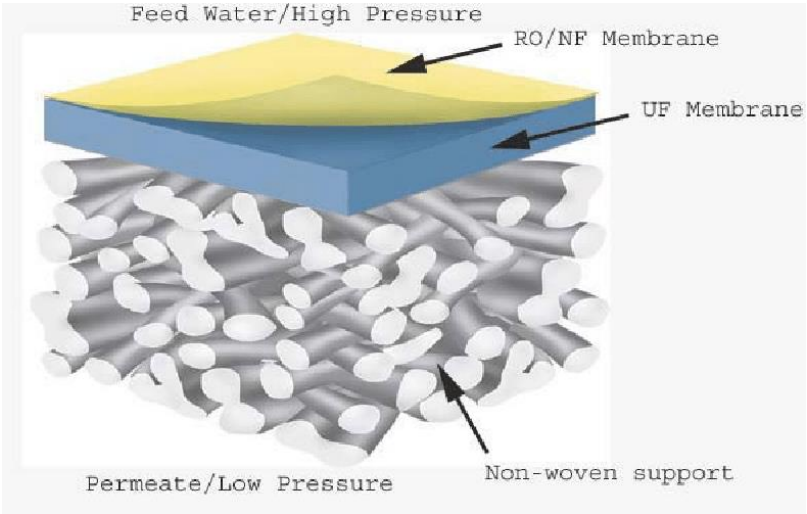

Thin film composite (TFC) membranes

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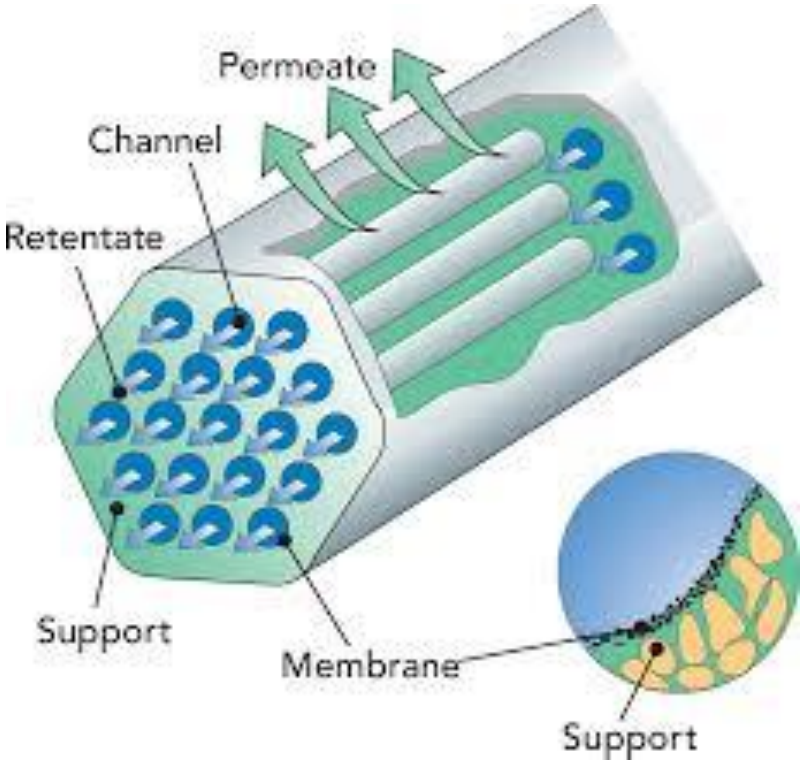
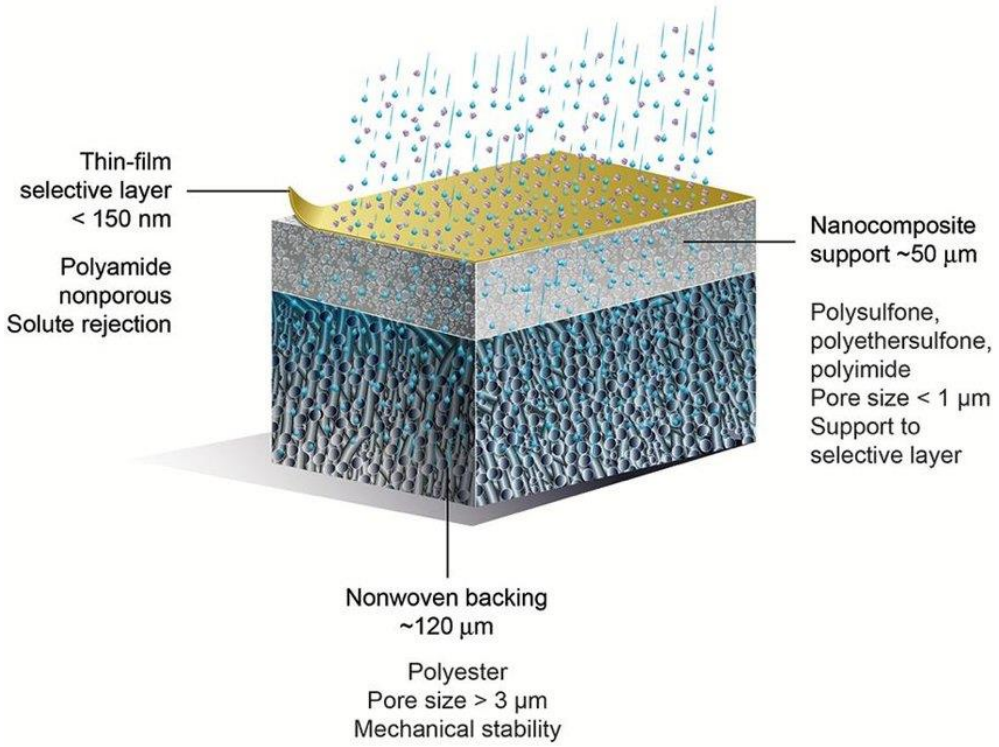
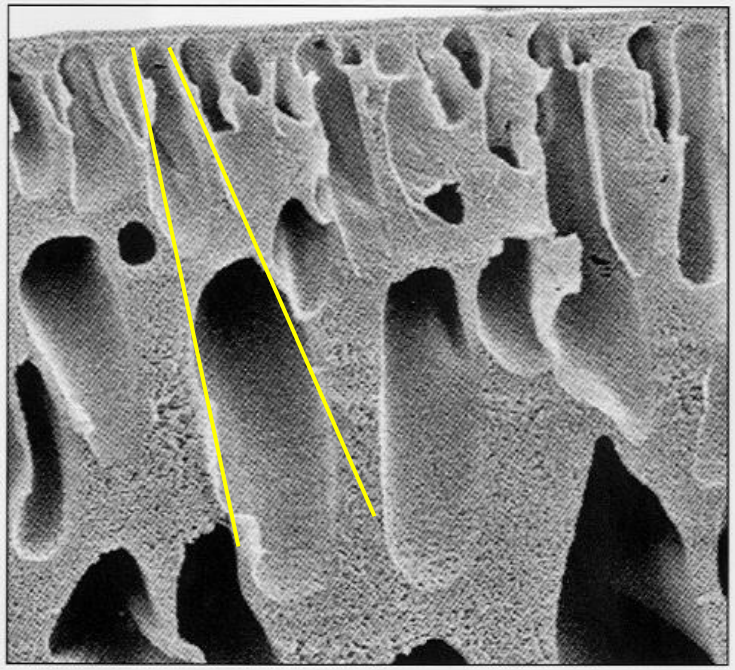
In the TFC type, the membrane responsible for the separation often consists in a thin layer on the surface of a carrier material



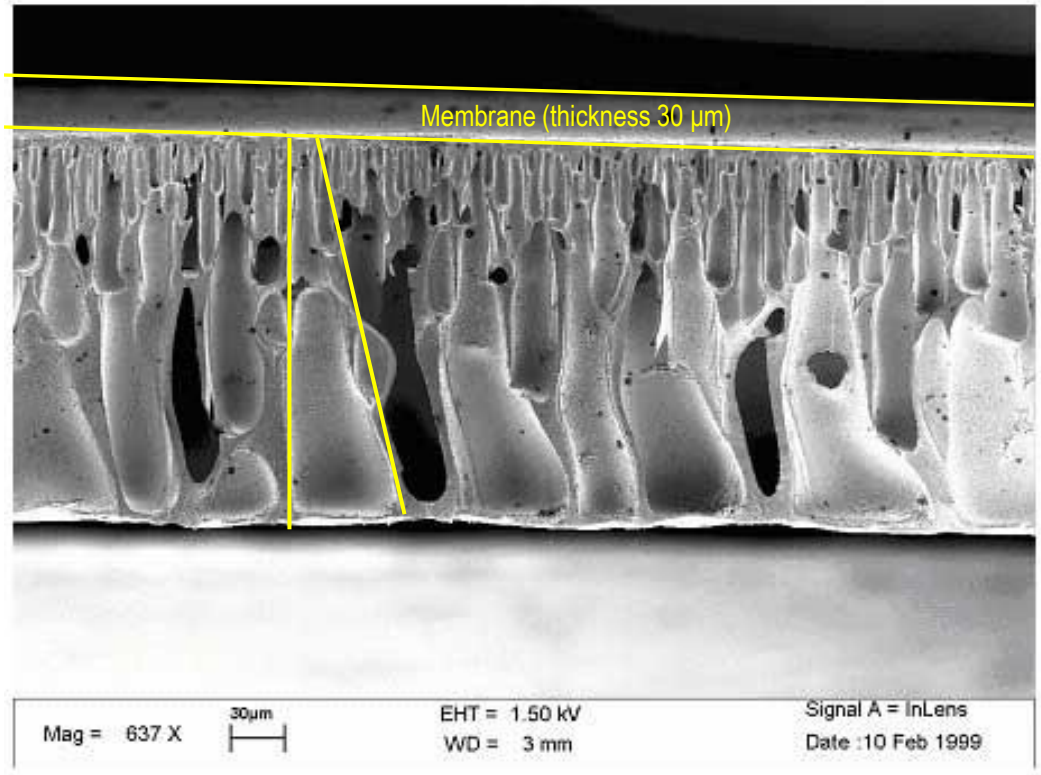


A closer view at membranes (1/3)

OPTIONAL



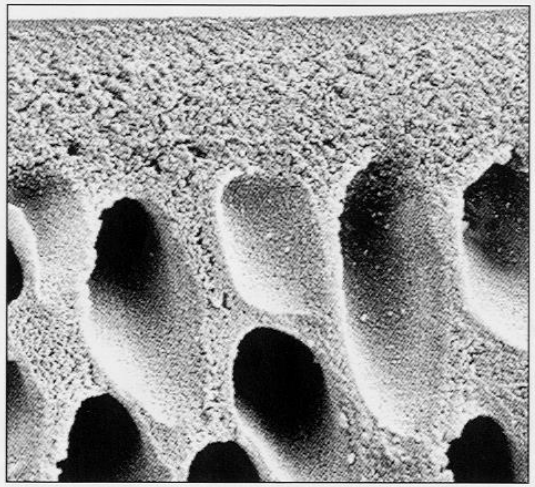
Macrovoid structure



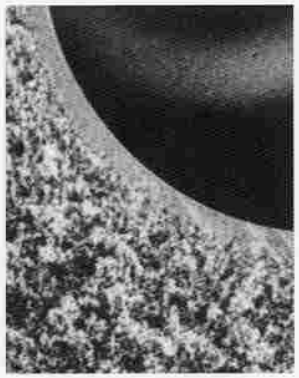
These pictures show the **asymmetric pores** (yellow lines), that grow larger after the thin membrane layer. That enables an easy, unobstructed flow of the permeate

A closer view at membranes (2/3)

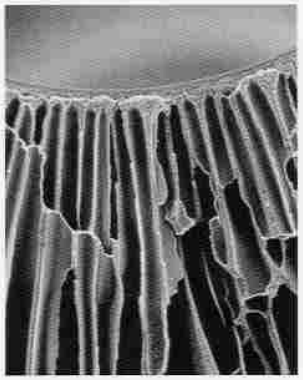
OPTIONAL



Foam structure



No Macrovoids
Advanced Amersham Biosciences
UF Membrane Structure



Macrovoids
Traditional UF
Membrane Structure

Hollow-Fiber Membrane

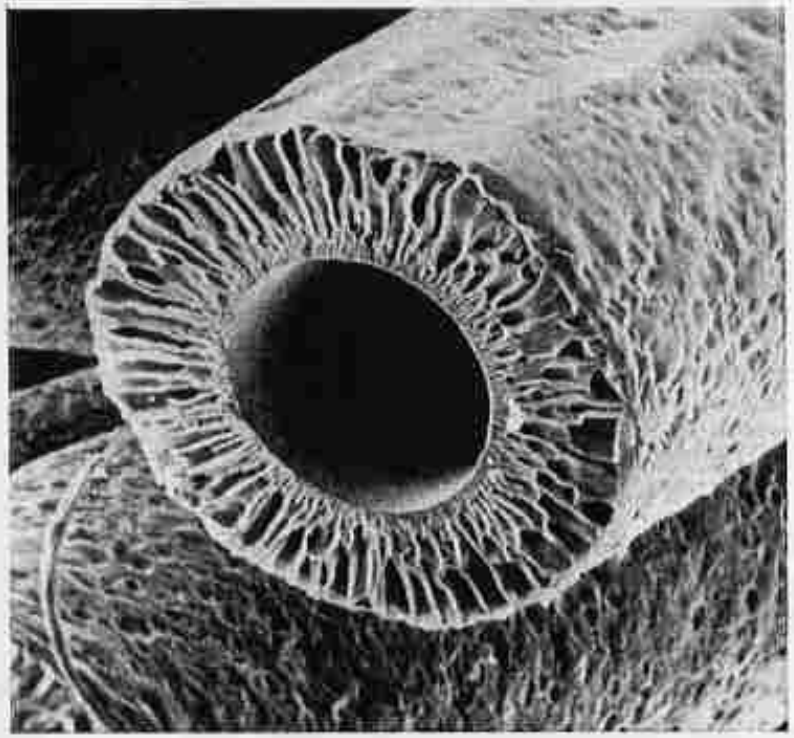
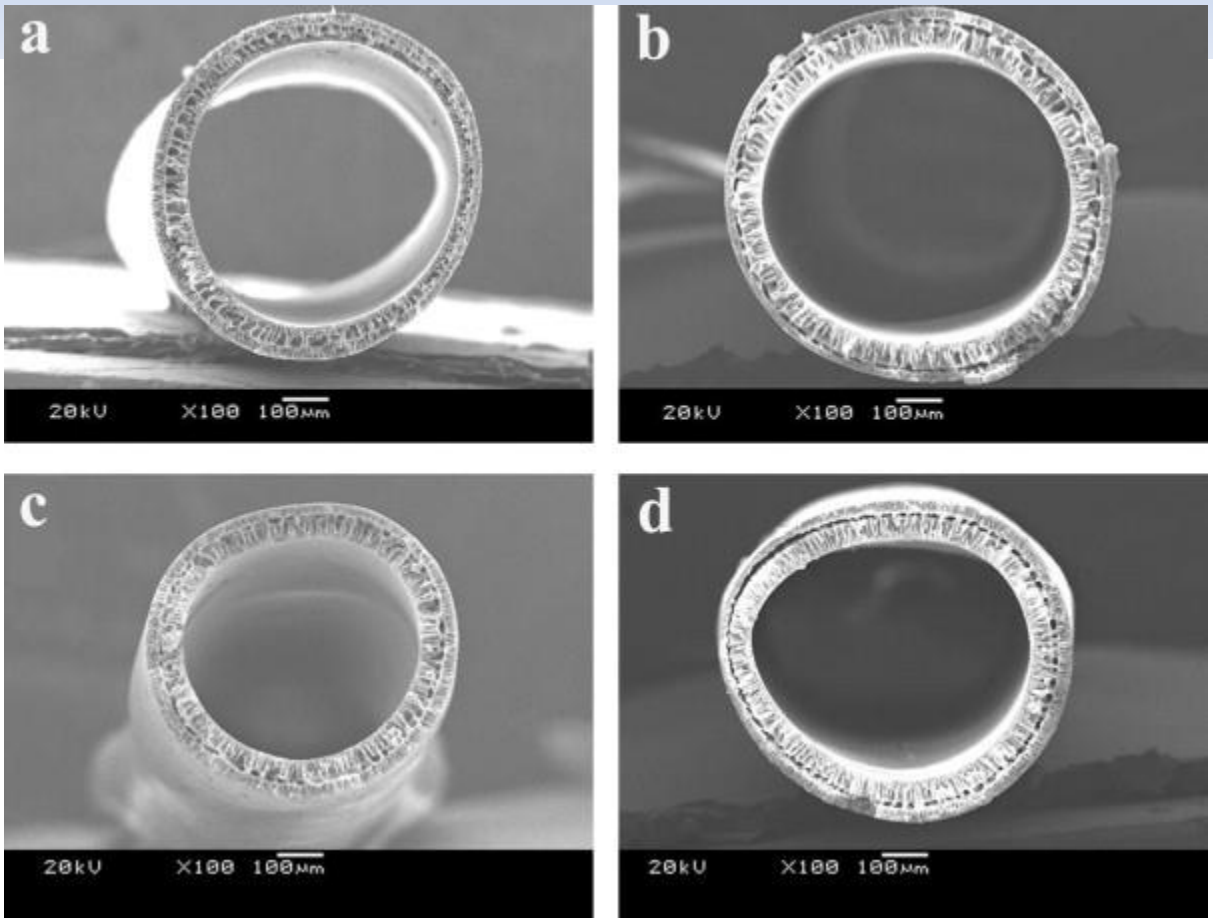


Figure 3.23 Scanning electron micrograph of the end of an asymmetric support membrane structure, with a pore-limiting skin (inner part of fiber). The thick wall of the hollow fiber imparts strength, while the skin or active membrane (0.1 micron thick) gives the controlled pore size. Flow occurs on the inside of the hollow fiber (diameter of 0.5 mm) in a direction parallel to the axis (i.e., along the length of the tube) and generates a sheer force that minimizes concentration polarization of the solute retained on the inside of the fiber. The support structure enables intermittant backflushing to be used (see Figure 3.25) to periodically force removal of foreign materials (i.e., foulants) and the flux inhibiting layer away from the membrane (skin) surface. Courtesy of Rhomicon.

A closer view at membranes (3/3)

OPTIONAL



Characterization of membrane pore size (distribution)

- There is a variety of techniques for the determination of membrane pore size distribution
  - Microscopy (visual observation)
  - Bubble point
  - Mercury porosimetry
  - Sorption measurements

The above methods have limited range of application and their results are not always comparable

The narrower the pore size distribution, the sharper the NMWC

Mercury porosimetry

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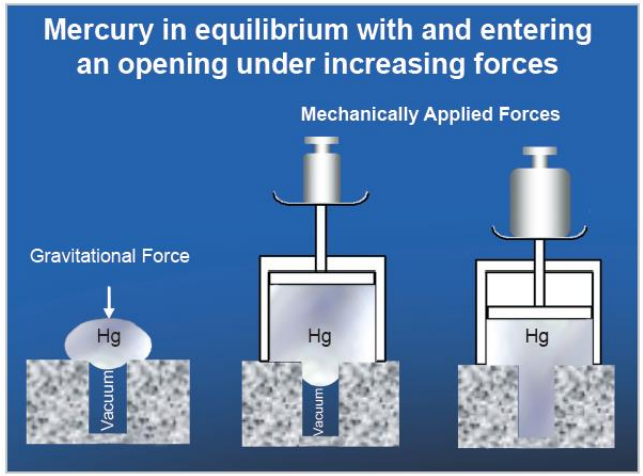
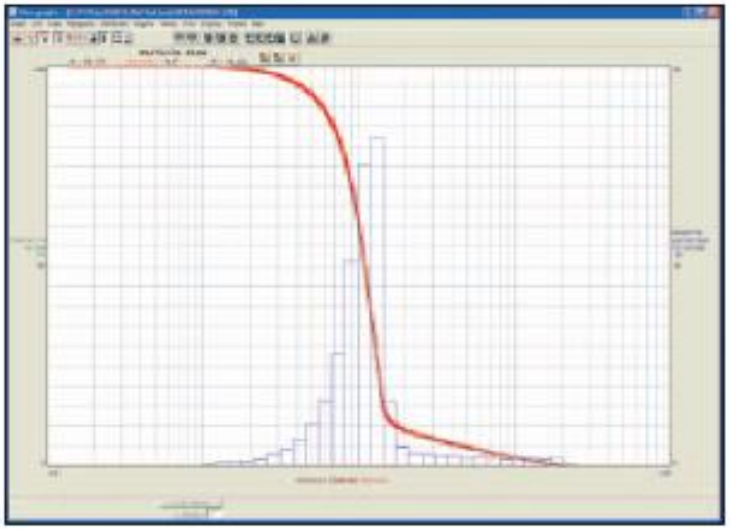


Illustration of mercury filling the sealed sample cup with sample present



The Washburn equation

$$d_p = \frac{-4 \cdot \gamma \cdot \cos \psi}{P}$$

P = Pressure [Pa]

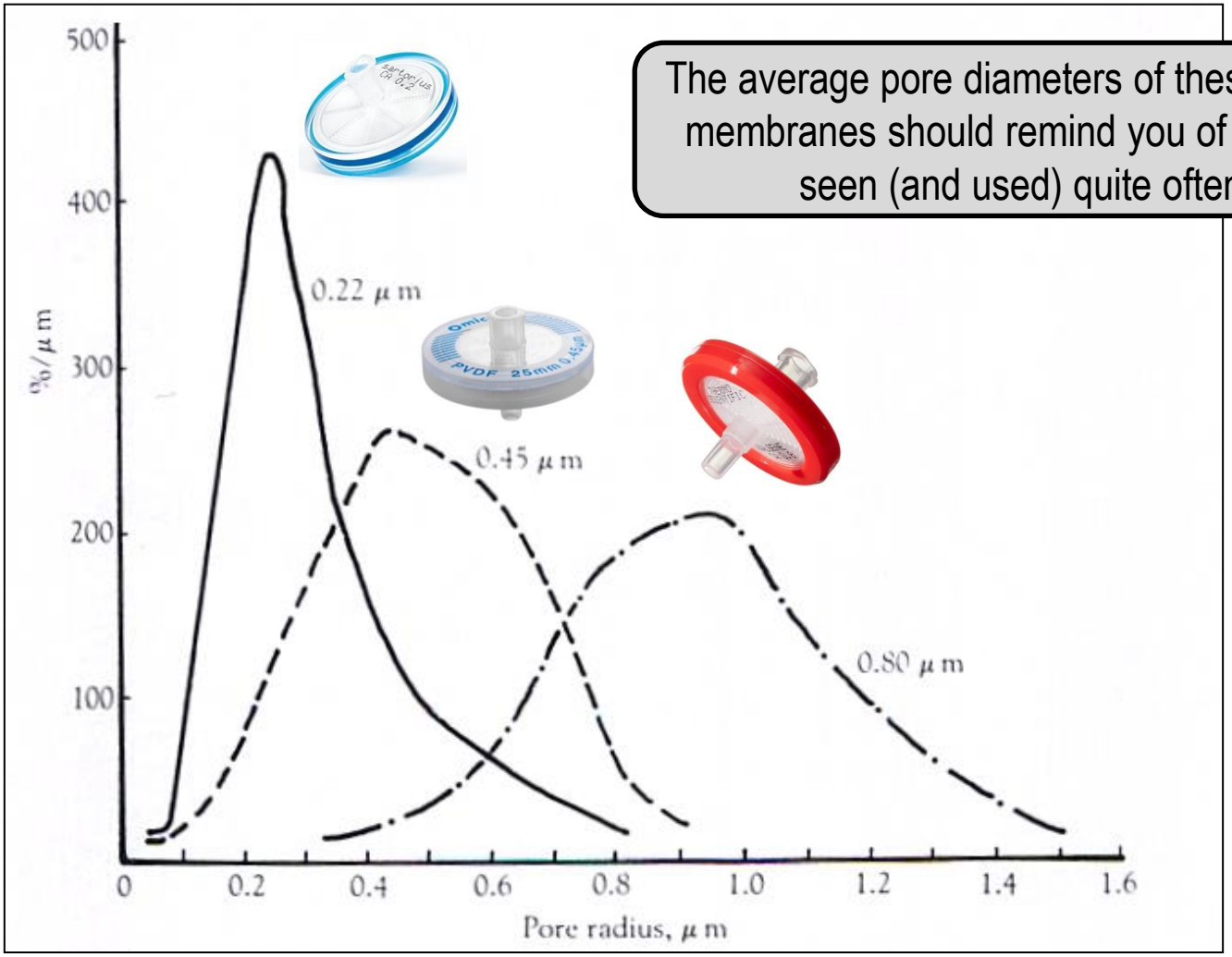
d_p = Pore diameter [m]

γ = Interfacial tension [N/m] (0.48 N/m)

γ (1 N/m = 1000 dyne/cm)

ψ = Solid/liquid contact angle (140 °)

Pore size distribution of microporous membranes
(measured by Hg porosimetry)



The average pore diameters of these three microfiltration membranes should remind you of something you have seen (and used) quite often in the lab …

Membrane: what is retained, what is not?

Determination of the retention factor R

- R is determined by measuring the concentration of the substance in the retentate (C_R) and in the permeate
- The retention (or rejection) factor is then defined as:

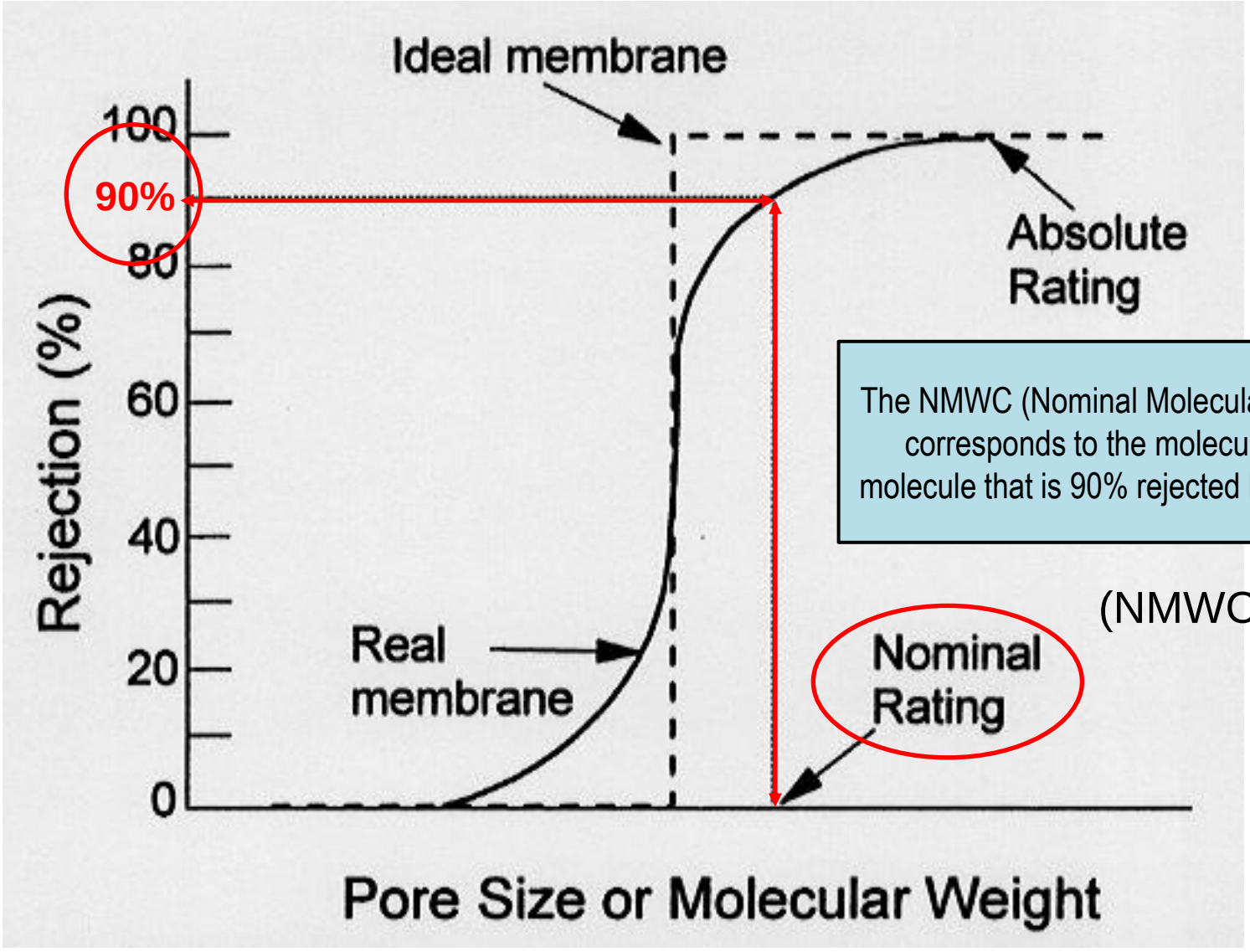
$$R = 1 - \left(\frac{C_P}{C_R} \right)$$

If for a given solute C_P=C_R, then R = 0 and there is no retention at all. That means the membrane is fully permeable to this molecule.

On the other hand if the molecule cannot be detected in the permeate (C_P = 0), that means R is equal to 1 (or 100%) and this molecule is completely retained by the membrane.

Rejection factor R and NMWC (1)

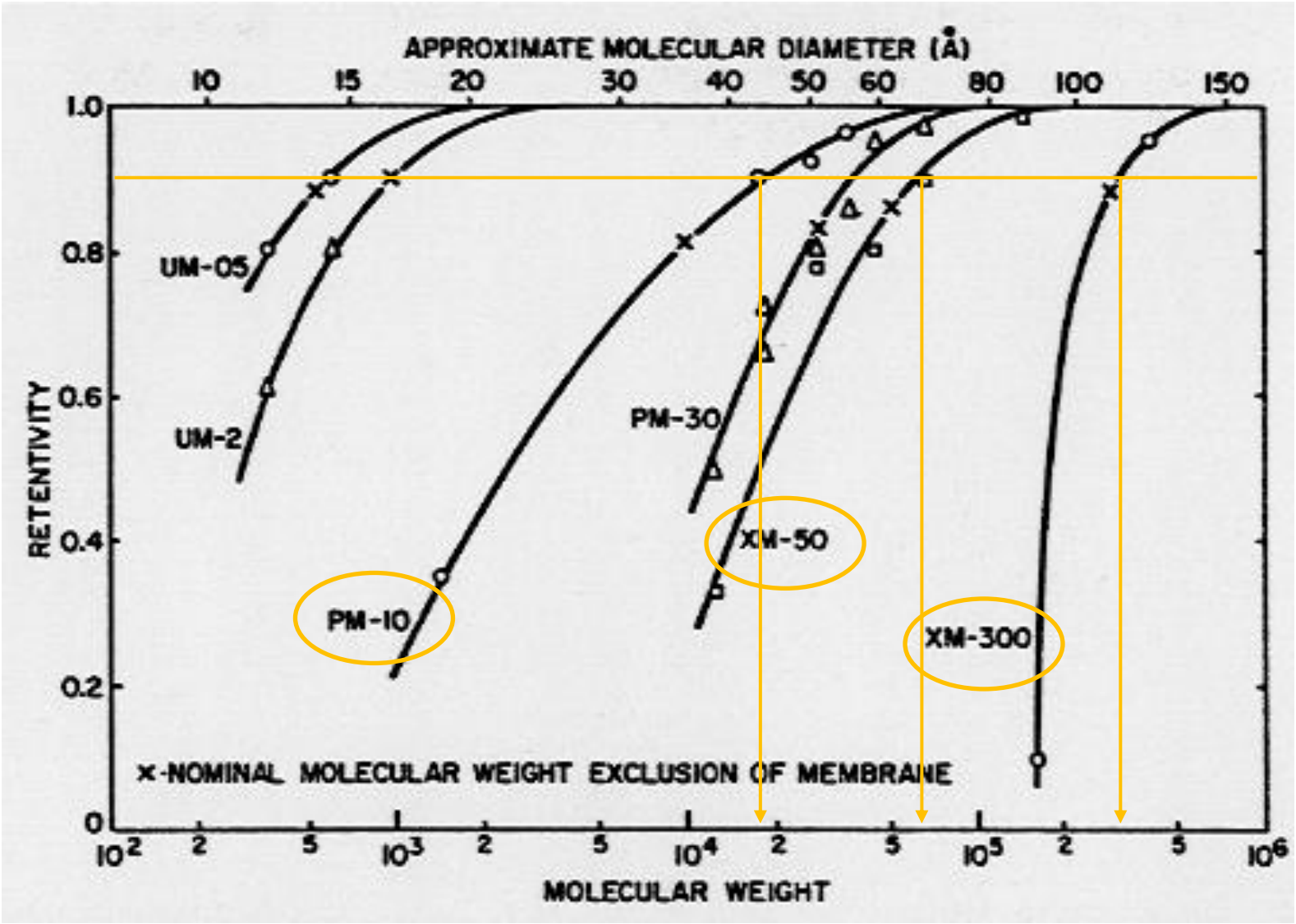
(1) Nominal Molecular Weight Cutoff



The NMWC (Nominal Molecular Weight Cut-off) corresponds to the molecular weight of a molecule that is 90% rejected by the membrane

(NMWC)

Retention factor, MW and molecular diameter



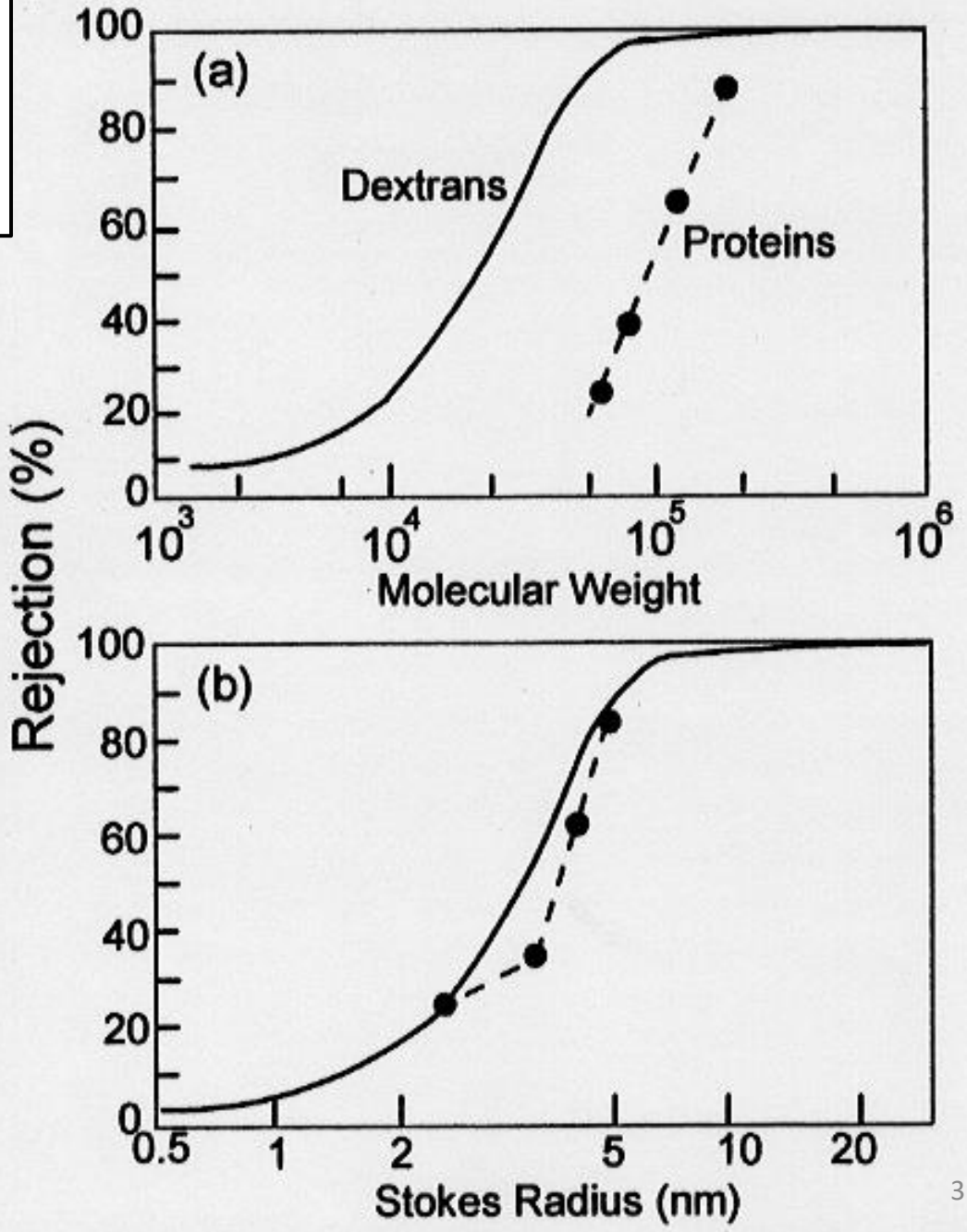
Influence of the solute's geometry on the retention (or rejection) factor

Molecular weight (MW) is not the only factor determining the retention factor.

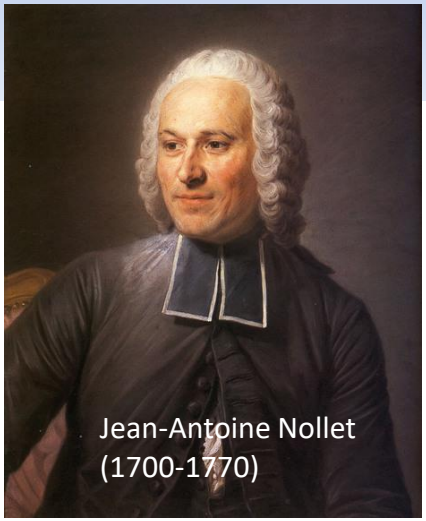
Like for size exclusion chromatography, the geometry of the molecules plays an important role as well.

This is shown here by comparing globular proteins and dextran, a linear polysaccharide.

The MW geometry can be taken into account by considering the Stokes radius of the solutes.



Nollet, Gibbs, van't Hoff …


Jean-Antoine Nollet
(1700-1770)

- The chemical potential μ is defined as

$$\mu_i = \left(\frac{dG}{dn_i}\right)_{p,T,n_{j\neq i}}$$

G Gibbs free enthalpy
n amount of i

- The chemical potential μ for water (compound 1) is lowered by the presence of another solute (compound 2)

$$\mu_1 = \mu_1^0 + RT \cdot \ln(\gamma_1 x_1)$$

R gas constant
T temperature
x_1 mole fraction of compound 1
γ_1 activity coefficient

Calculation of osmotic pressure Π

- Gibbs equation:

$$\Pi = -\frac{R \cdot T}{v_1} \cdot \ln \gamma_1 x_1$$
$$= -\frac{R \cdot T}{v_1} \cdot \ln \gamma_1 (1 - x_2)$$
$$\approx -\frac{R \cdot T}{v_1} \cdot \ln(1 - x_2) \;\; for \; x_2 \ll 1$$

- The van't Hoff equation is a particular case of the Gibbs equation when $x_1 >> x_2$ (i.e. for dilute solutions) and resembles the ideal gas law:

Index 1 is for water, index 2 for the solute

c_i : concentration of compound i $\left[\frac{\mathrm{mol}}{\mathrm{m^3}}\right]$
n_i : amount [mol] of compound i in the mixture
R: gas constant $\left[\frac{\mathrm{J}}{\mathrm{mol\ K}}\right]$
T: temperature [K]
v_i : molar volume of compound i $\left[\frac{\mathrm{m^3}}{\mathrm{mol}}\right]$
V_i : volume of compound i $[\mathrm{m^3}]$
x_i : mole fraction of compound i in the mixture [-]

$$\Pi = c_2 \cdot R \cdot T = \frac{n_2}{v_1 \cdot n_1} \cdot R \cdot T$$

Watch for the difference between v_i and V_i !!!

$$\Pi \cdot V = n_2 \cdot RT \qquad \text{(van't Hoff)}$$

Deviations from the van't Hoff equation

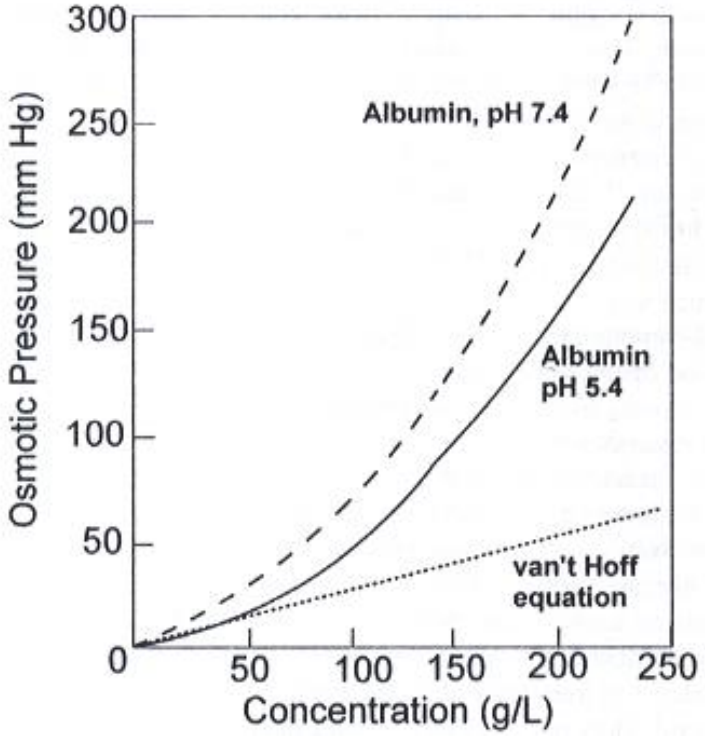
Values for sucrose solutions at 30 °C

		Osmotischer Druck (atm)		
Konzentration (% w/w)	Molarität	van't Hoff Gleichung	Gibbs Model	Experimentelle Daten
25,31	0.991	20,3	26,8	27,2
36,01	1,646	30,3	47,3	47,5
44,73	2,366	39,0	72,6	72,5
52,74	3,263	54,2	143,3	144,0
58,42	4,108	54,2	143,3	144,0
64,58	5,332	61,5	199,0	204,3

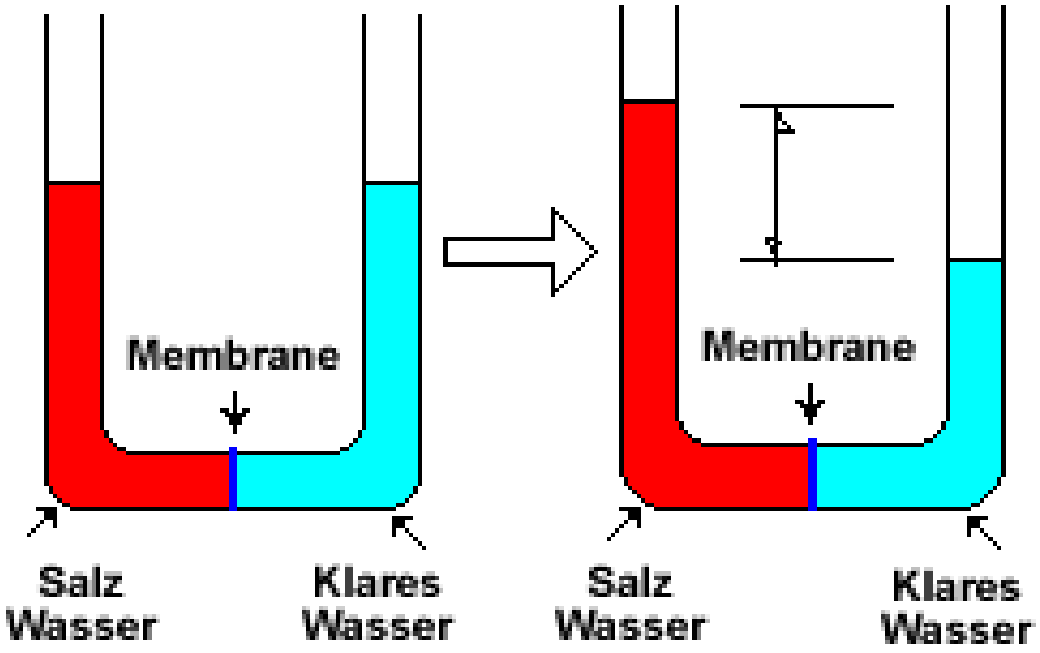
It is worth reminding here that the van't Hoff equation is better suited to the description of dilute solutions.

Some remarks on osmotic pressure

- The van't Hoff equation is valid for (highly) dilute solutions:
- The **oncotic pressure** is the fraction of osmotic pressure that is due to proteins
- Based on van't Hoff's equation, the molecular weight of proteins can be determined by measuring Π at various protein concentrations
- However, macromolecules such as proteins form strongly non-ideal solutions. The equation for osmotic pressure thus becomes more complex and includes a virial expansion that takes molecular interactions into account



Osmotic pressure



Alternative definition of Π:
Minimal pressure to be applied to prevent the passage of solvent from a less concentrated to a more concentrated solution through a semi-permeable membrane.

A classical question: on which side of the membrane is the osmotic pressure higher?
On the left (red, salt solution compartment) or on the right (blue, pure water compartment)?

In membrane technology (MF, UF, NF, RO) you always have to work against the osmotic pressure generated by the solutes that are retained by the membrane

Osmotic pressure of various solutions

Table 1.5. Osmotic pressure of foods at room temperature.

Food	Concentration	Osmotic Pressure (psi)
Milk	9% solids-not-fat	100
Whey	6% total solids	100
Orange juice	11% total solids	230
Apple juice	15% total solids	300
Grape juice	16% total solids	300
Coffee extract	28% total solids	500
Lactose	5% w/v	55
Sodium chloride	1% w/v	125
Lactic acid	1% w/v	80
Sweet potato wastewater	22% total solids	870
Perilla anthocyanins	10.6% total solids	330

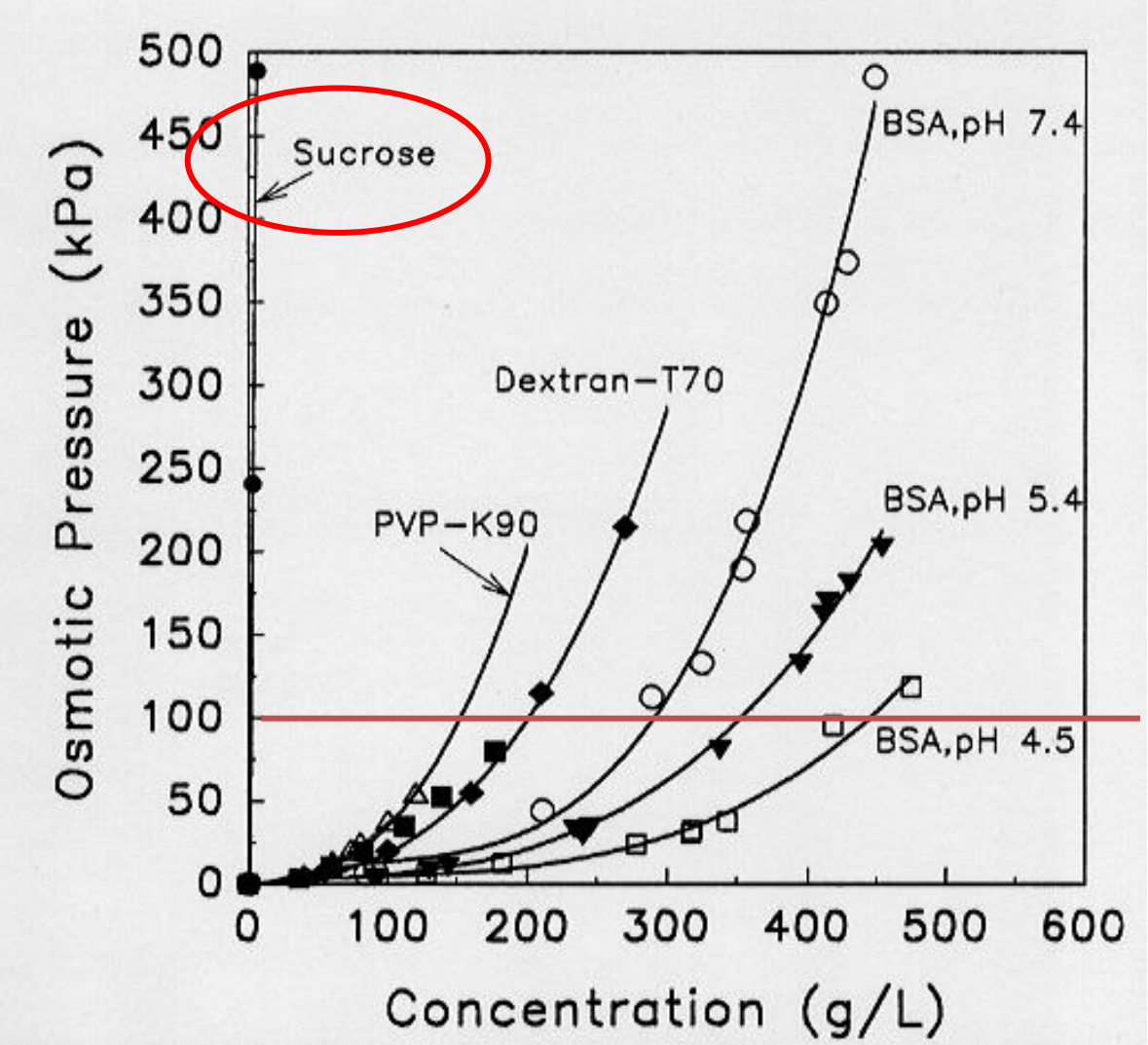
1 psi = 6.895 kPa = 0.0689 bar

Osmotic pressure of sea water approaches 25 bar

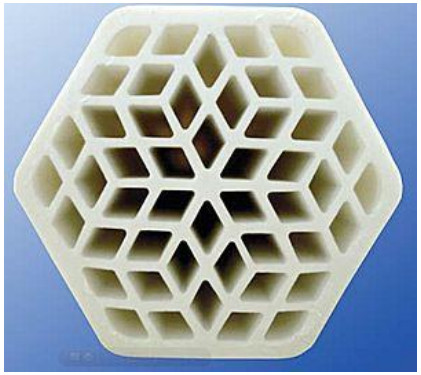
Due to the higher intracellular concentration of electrolytes, yeast cell walls must typically resist osmotic pressures of 3 to 5 bar

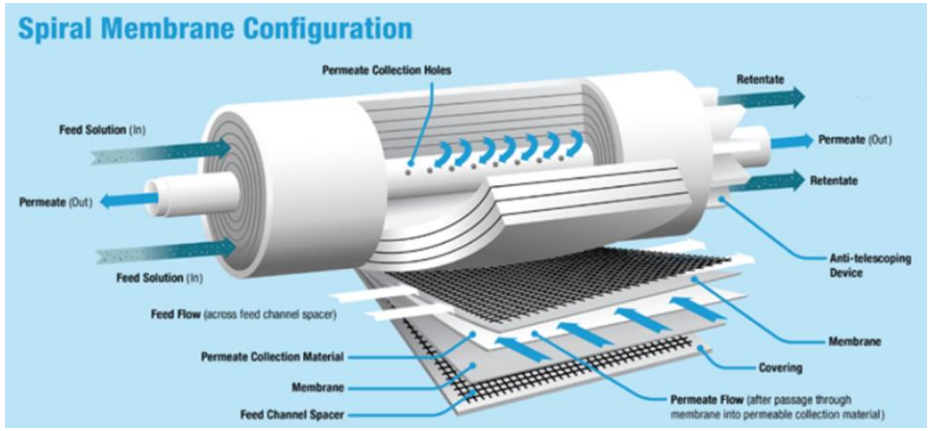
Component	Molecular Weight (*M*)	Number of Ions (*i*)	Osmotic Pressure (psi)
NaCl	58.50	2	125
Lactose	342	1	10
Casein	25,000	1	0.28

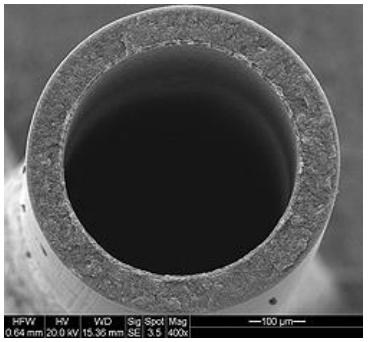
Osmotic pressure for solutes of different sizes

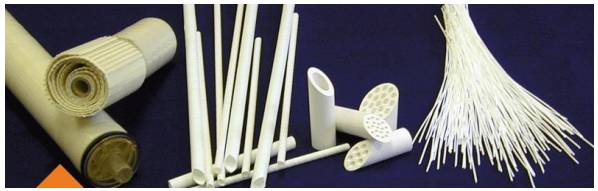


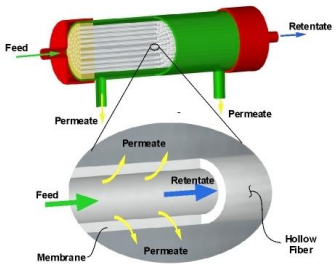
Membrane configurations

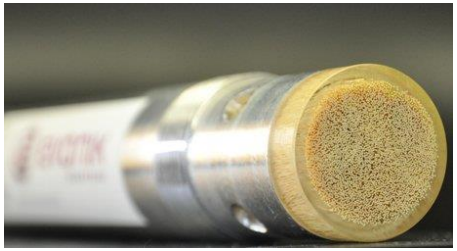












Spiral-wound module

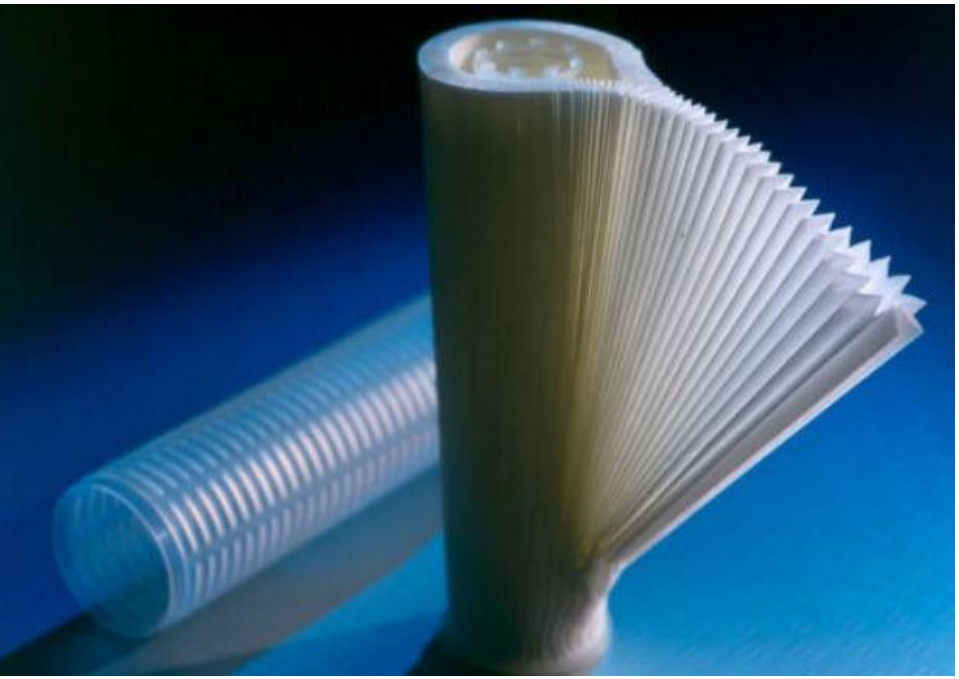
Ceramic membrane

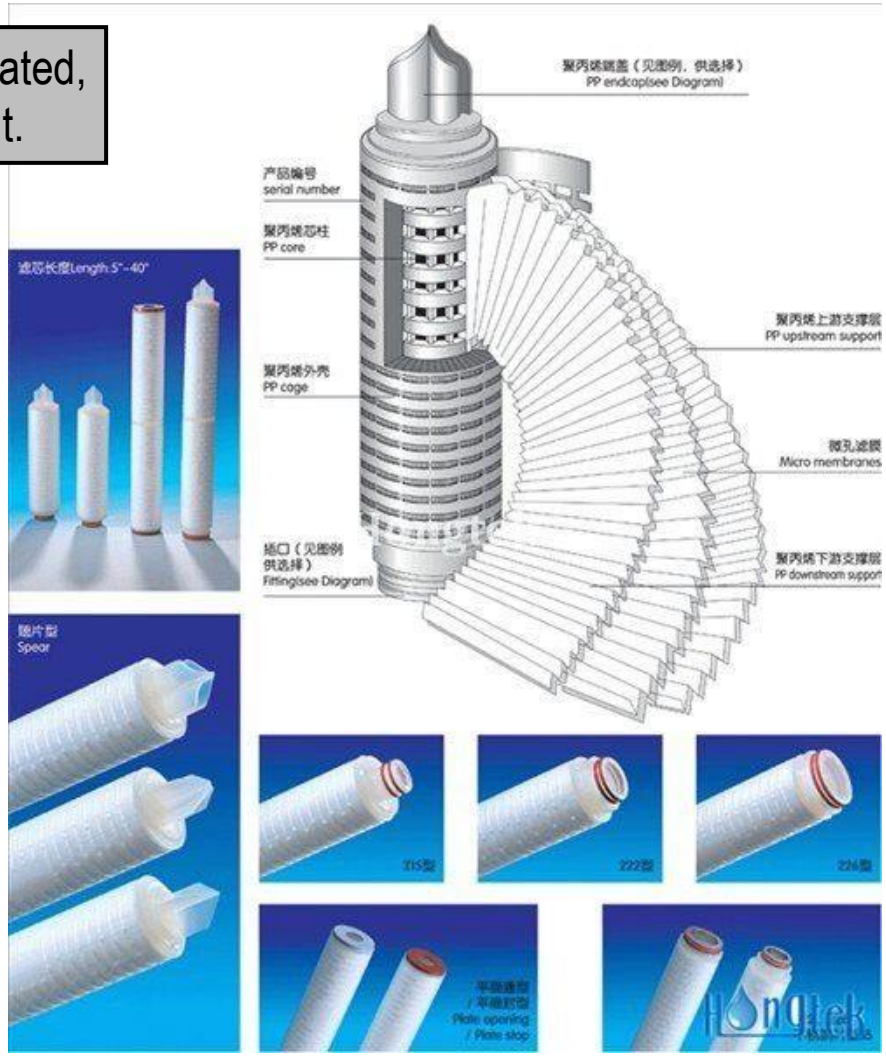
Membrane cassettes

Hollow fiber module

Pleated membranes in cartridges

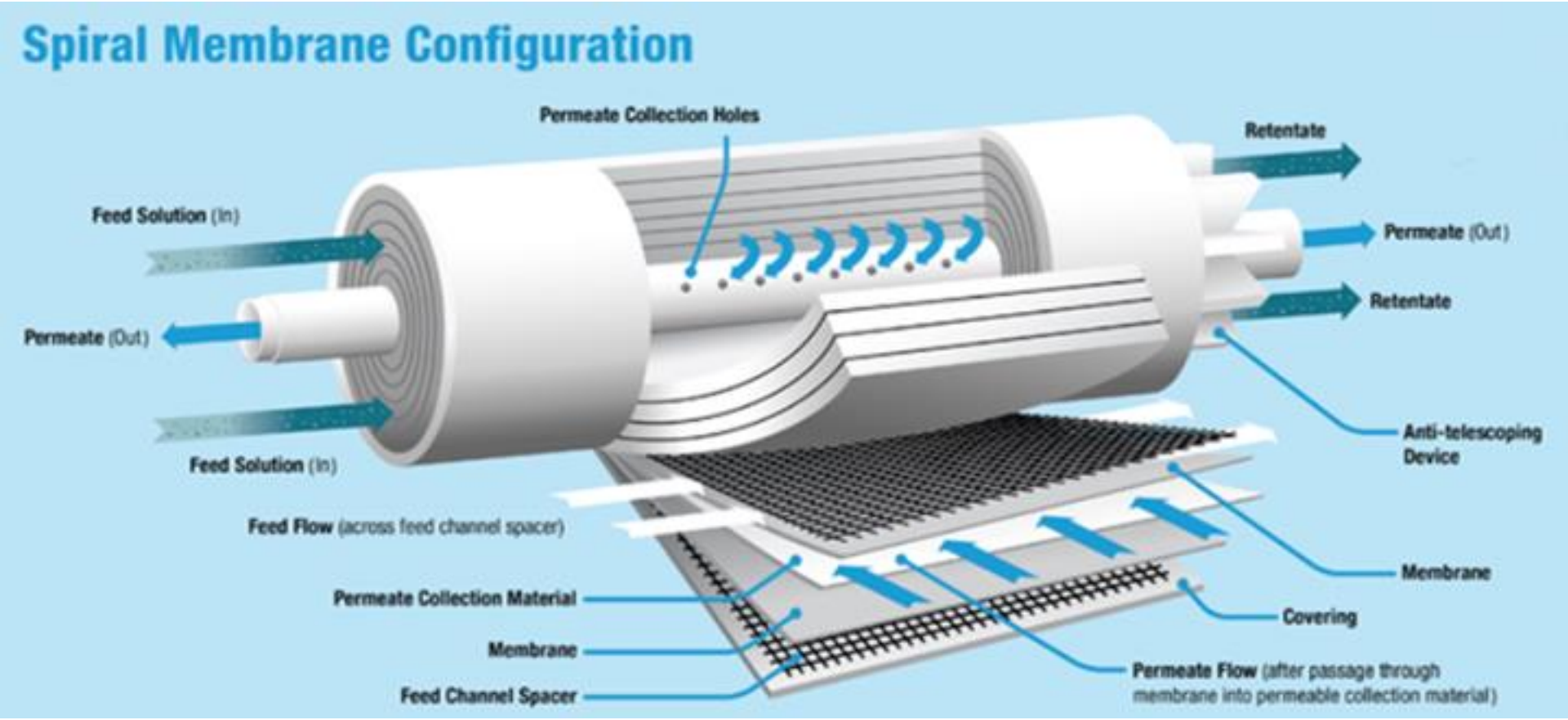
In a way similar to candle filters, the membrane is pleated, thus providing a large surface of filter for a small footprint.





Ceramic membranes

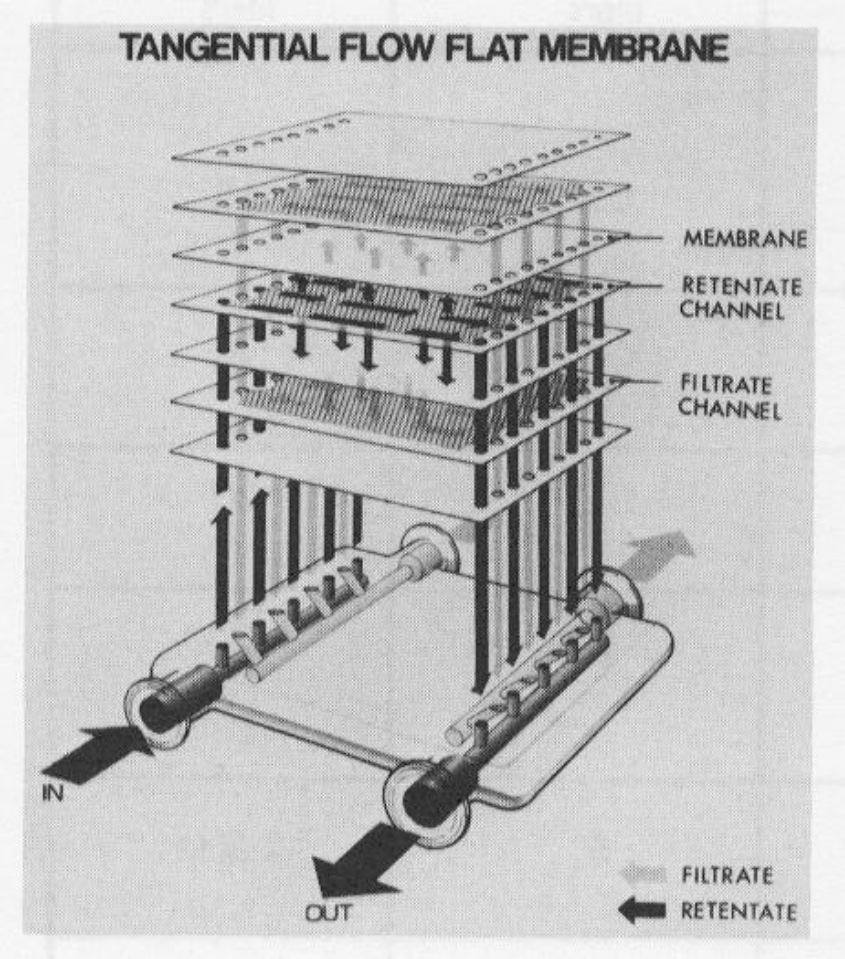
Spiral wound modules

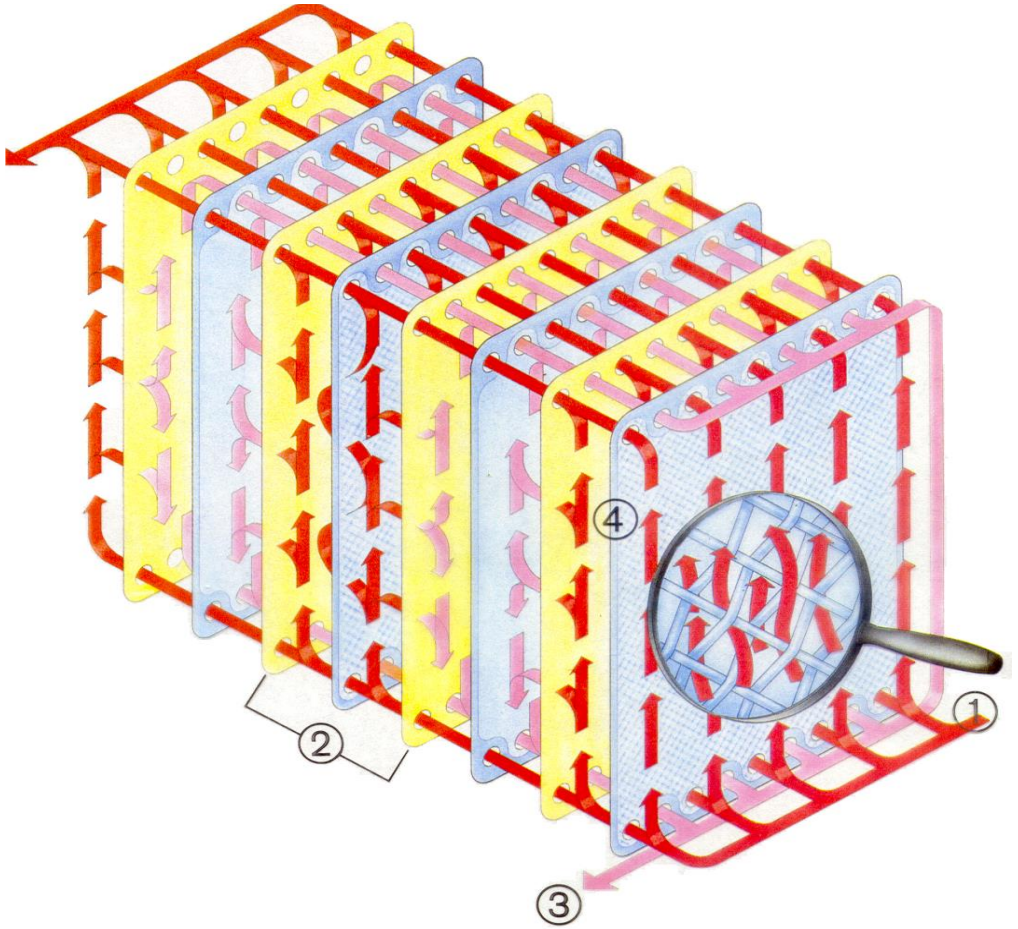


https://www.youtube.com/watch?v=gmGpPwSfhK0

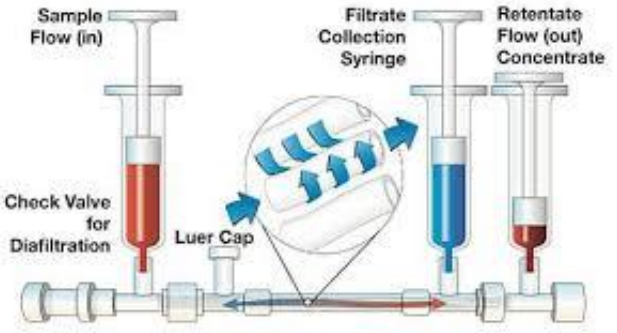
Cassette modules

Circulation of retentate and permeate in a cassette



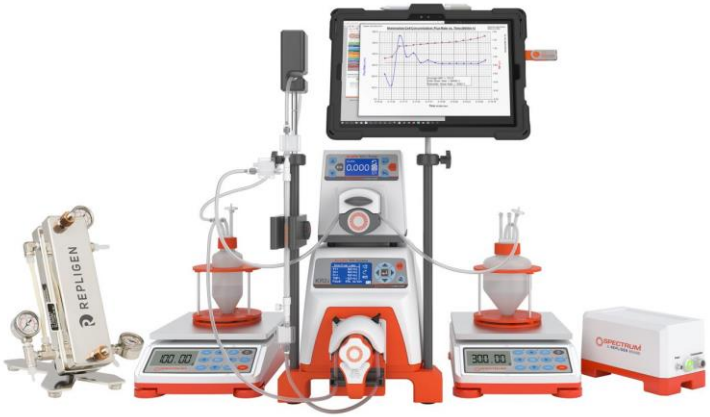


Hollow fiber modules



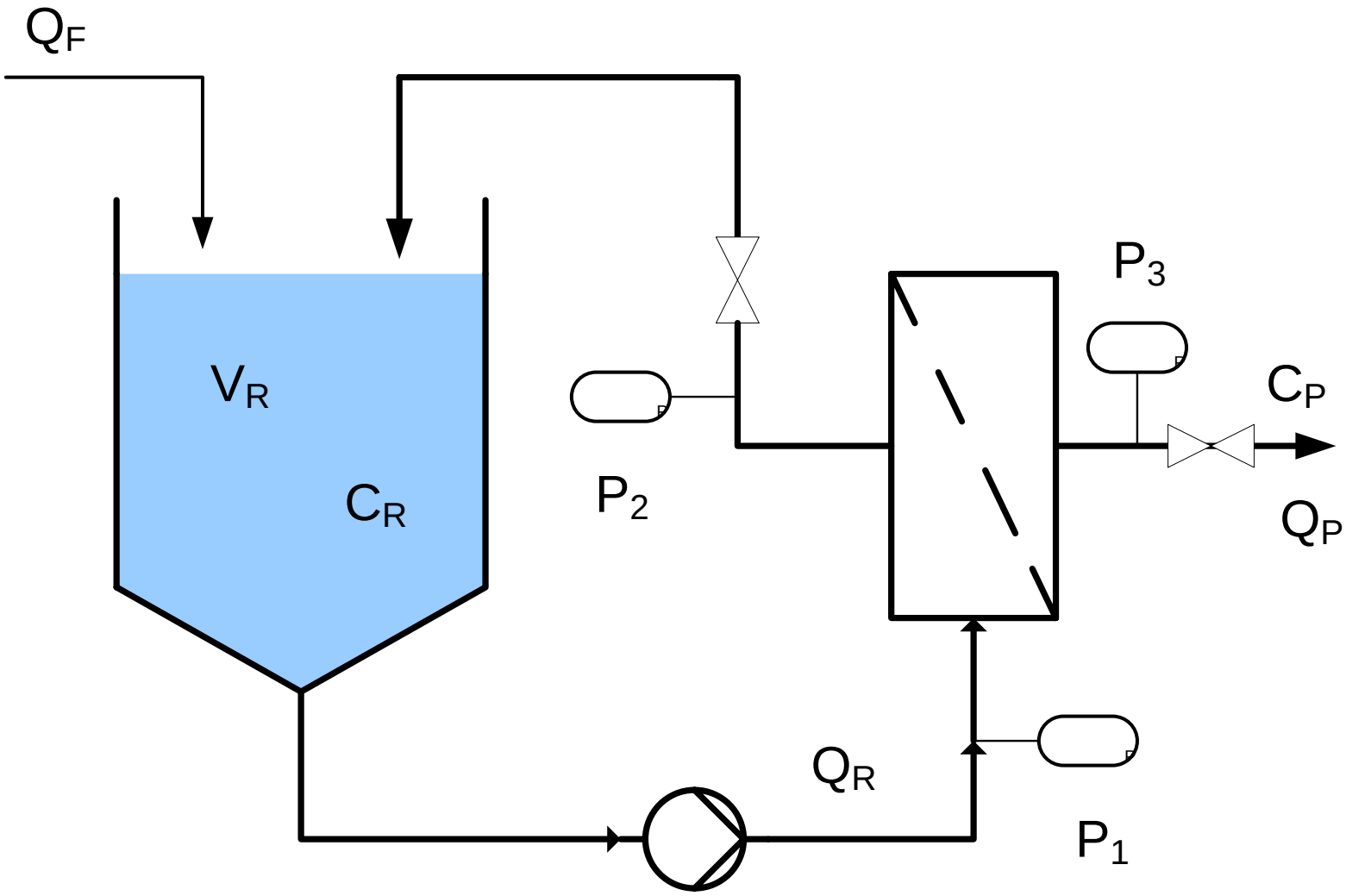
3.2 Ultrafiltration systems

Various ultrafiltration devices



These equipments have different sizes and configurations, but identical components

Drawing of a generic ultrafiltration equipment

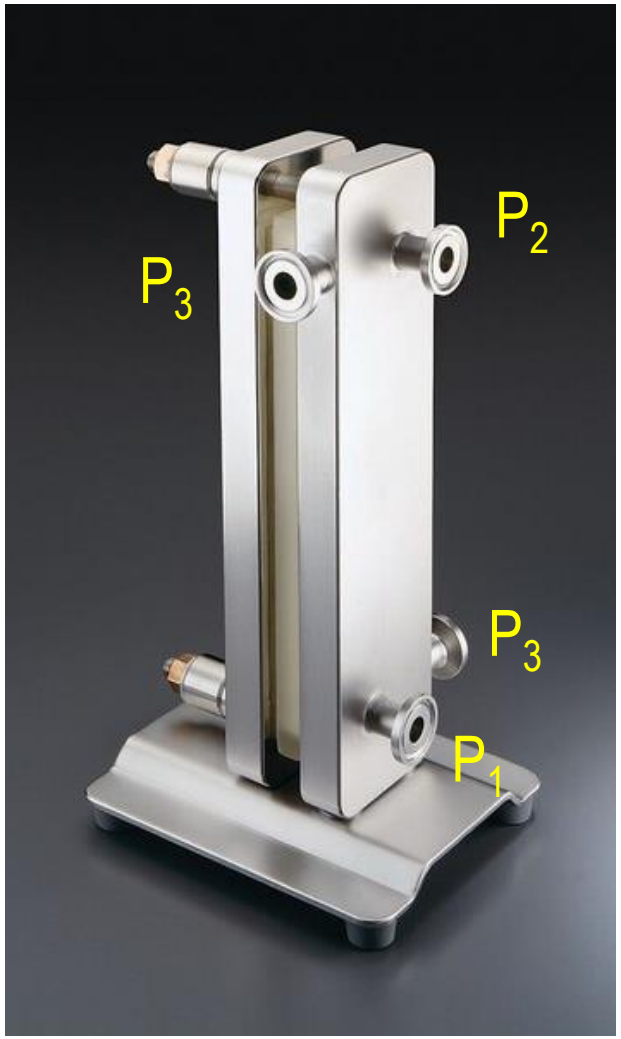


Which is the meaning of the TMP ?

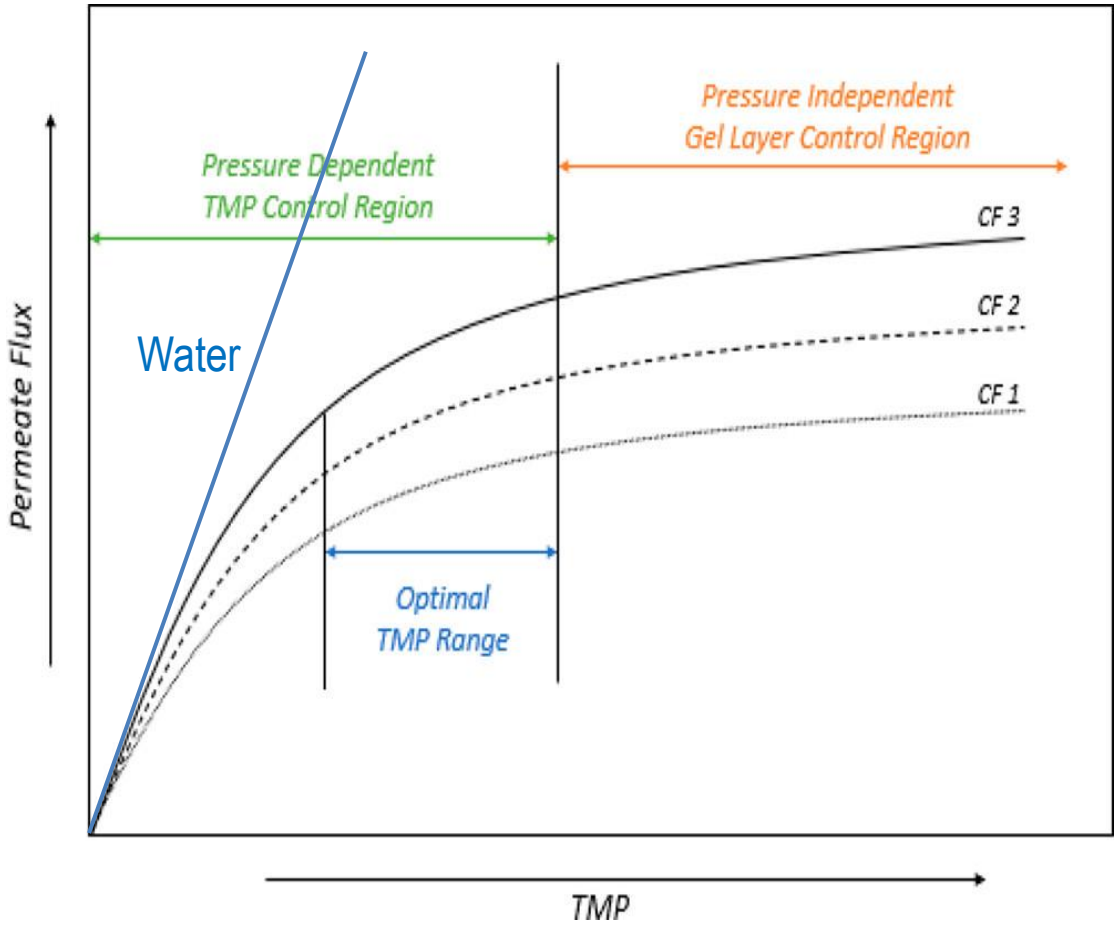
$$TMP = \left(\frac{P_1 + P_2}{2} - P_3\right)$$

(* transmembrane pressure)

- The UF module generates a loss of pressure, hence $P_2 < P_1$
- The permeate flux increases with the ΔP across the membrane
- ΔP amounts to P_1-P_3 at the entrance and to P_2-P_3 at the exit of the UF module
- TMP is hence nothing else than the average value of ΔP along the module (provided it varies linearily with distance)



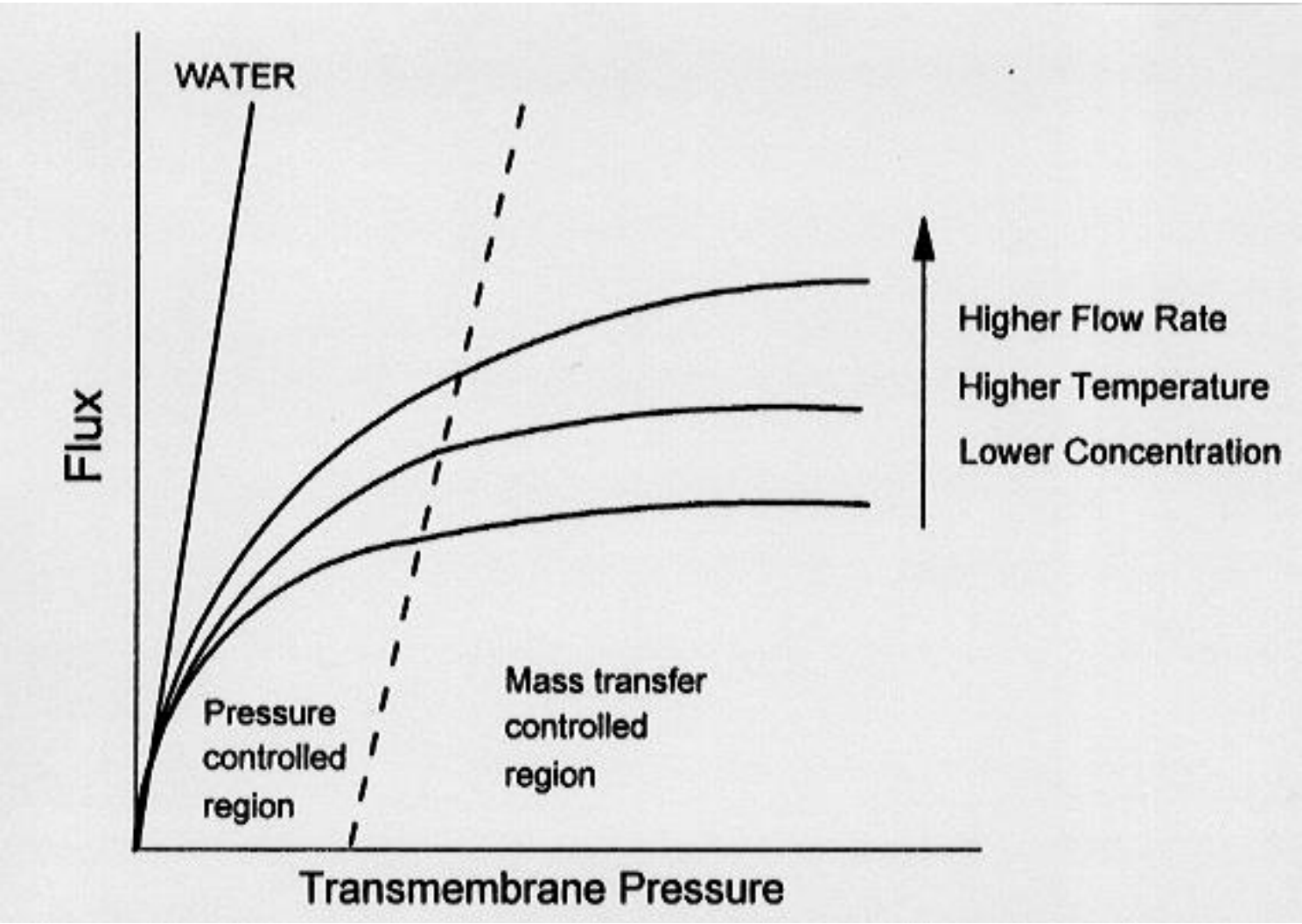
The gel (or polarization) layer model



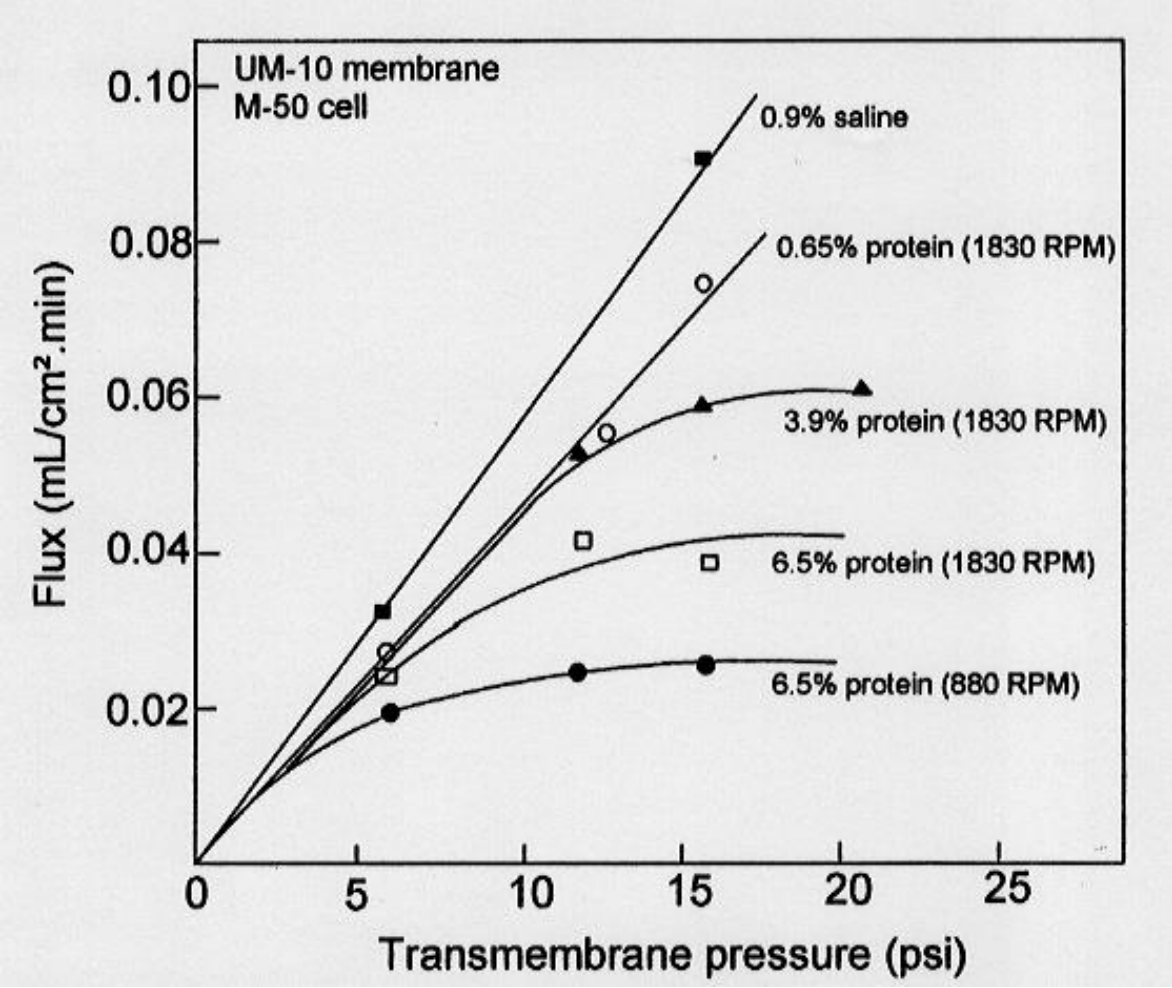
In the domain controlled by the gel (or polarization) layer, an increase in transmembrane pressure does not increase the permeate flux.

The optimal transmembrane pressure is in the transition zone between the area controlled by the TMP and the area controlled by the gel (or polarization) layer

Factors helping improve permeate flux



Permeate flux and transmembrane pressure

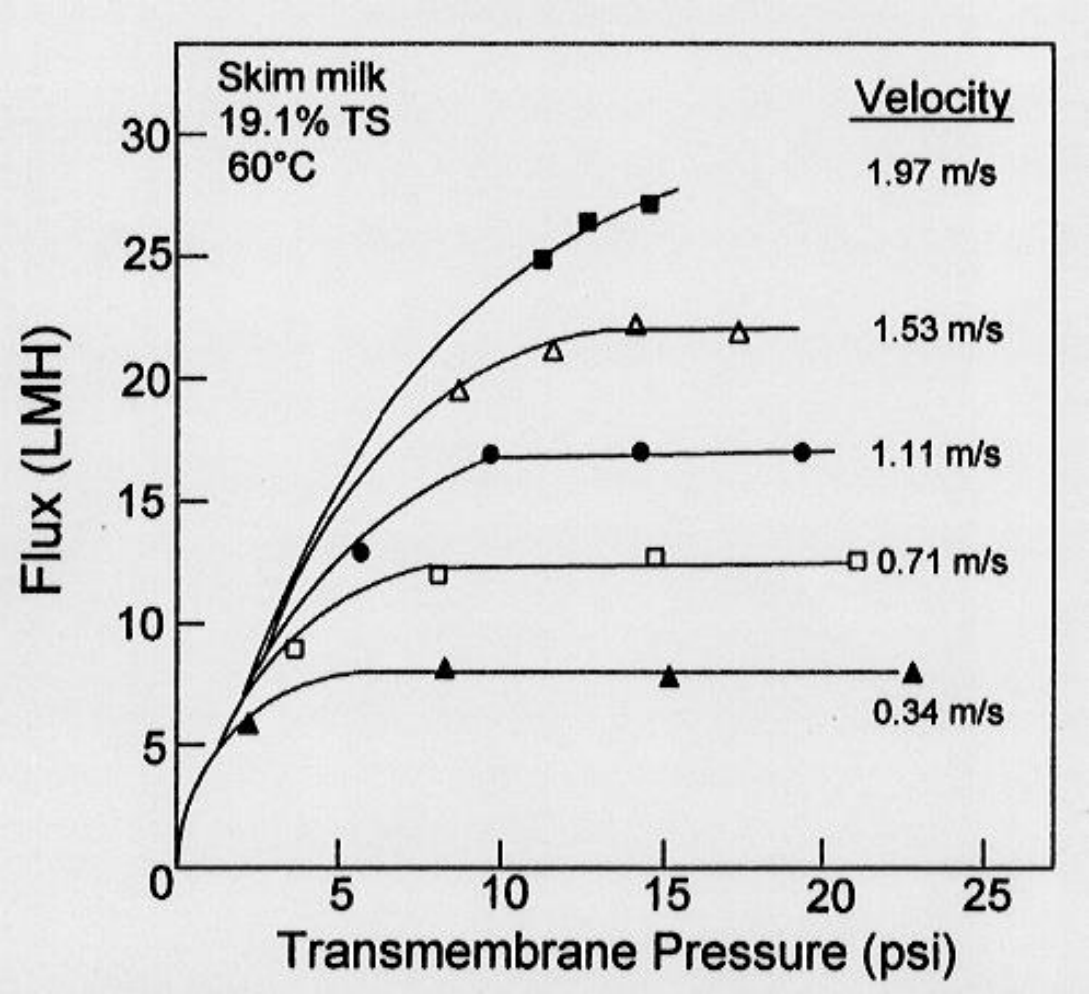


This graph shows the deviation from ideality (i.e. the straight line obtained with 0.9% saline) when a retained molecule is present in the mixture.

The higher its concentration and the lower the recirculation rate in the retentate circuit (RPM), the bigger the deviation.

Parameters that influence the permeate flux: retained solute molecular weight and concentration, presence of solid particles, composition and viscosity of the liquid, pH, temperature, ionic strength,

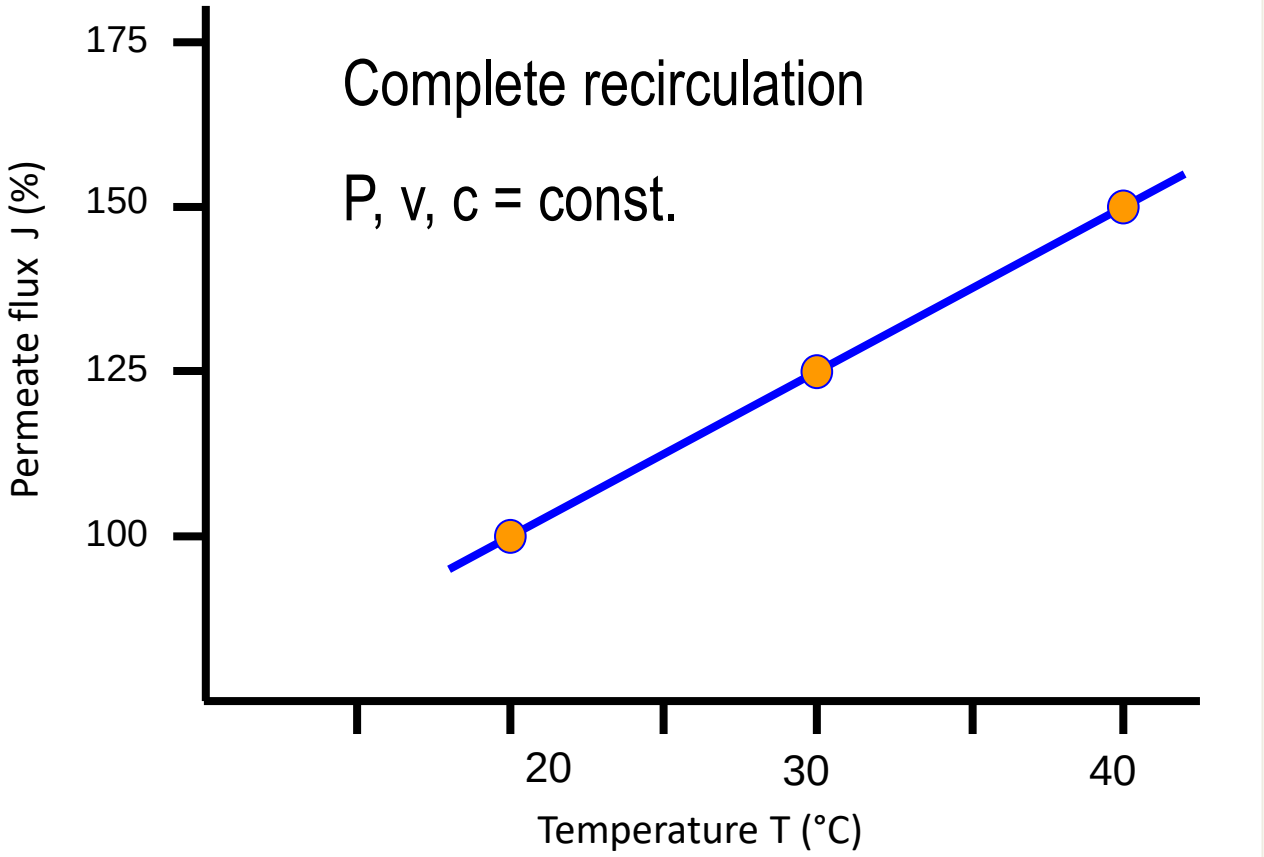
Influence of the tangential flow velocity



By increasing the velocity of the tangential flow, the range controlled by the TMP can be extended.

This enables working at higher values of the TMP, and leads to higher permeate fluxes

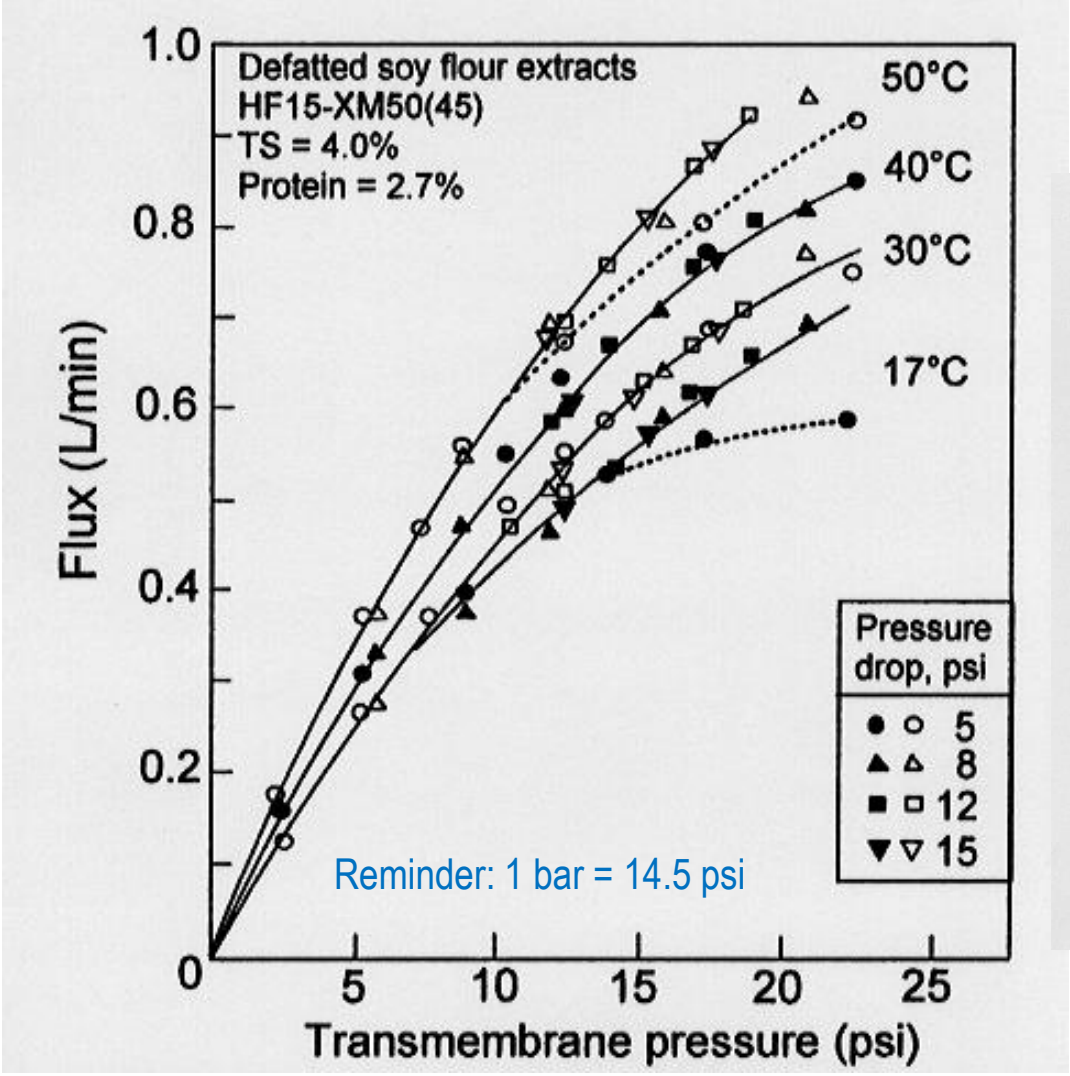
Influence of temperature

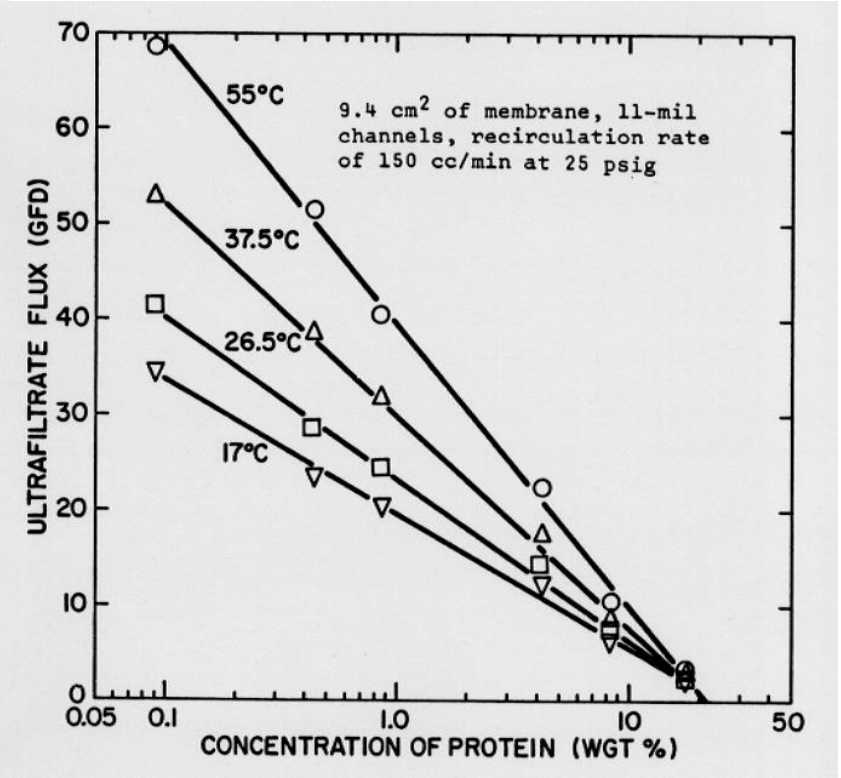


Higher temperatures are advantageous because they lower the viscosity of the treated solutions and suspensions

However, the maximum working temperature is limited by the type of module, the stability of the product and the increased risk of contamination.

Influence of temperature





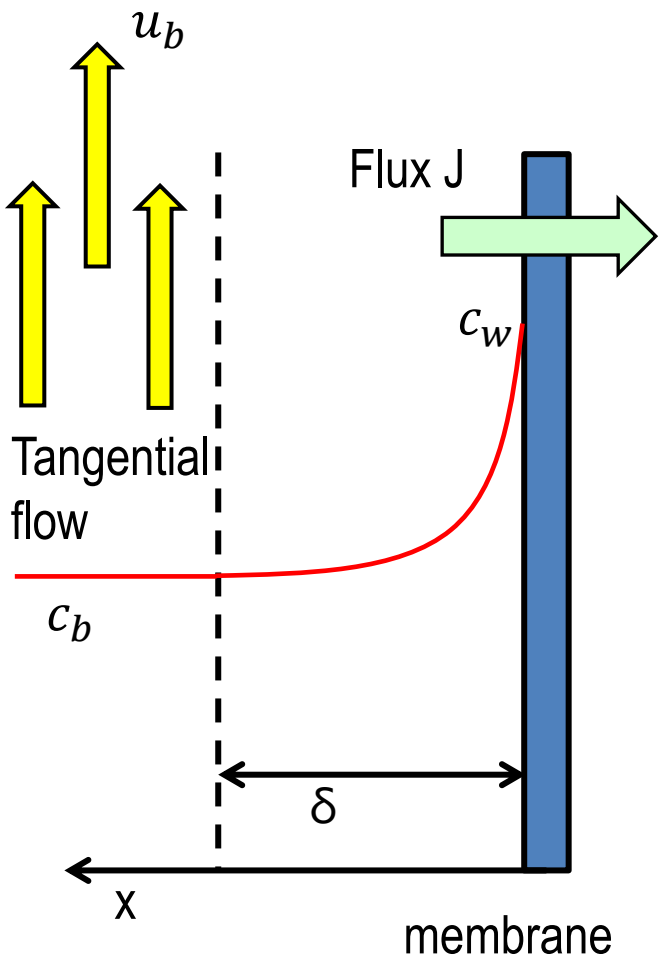
What happens in the membrane vicinity?

OPTIONAL

- When a solution of macromolecules is filtered through a UF membrane, the convective flow through the membrane causes retained material to accumulate in its vicinity
- This accumulation can go as far as the formation of a precipitate on the surface of the membrane. This gel layer can strongly reduce – or even block - the permeate flow *(see previous slide)*
- Even without precipitation, the increase in osmolarity near the membrane generates a solvent gradient that counteracts (in part at least) the pressure difference Δp across the membrane
- This higher concentration C_w at the membrane than in the solution (C_b) is called concentration polarization

Schematic description (1/2)

OPTIONAL



c_w, c_b	Wall resp. bulk concentration $[\mathrm{mol/m^3}]$
J	Permeate flux $\left[\frac{\mathrm{m}}{\mathrm{s}}\right]$
D	Diffusion coefficient $\left[\frac{m^2}{s}\right]$
δ	Film thickness [m]
u_b	Bulk tangential velocity $\left[\frac{m}{s}\right]$

Schematic description (2/2)

OPTIONAL

- Under stationary conditions, the rate of convective transfer of the solute from the bulk to the membrane must be equal to the diffusional transport from the membrane to the bulk

$$J \cdot c = -D \frac{dc}{dx}$$

- For a stagnant film (a.k.a. boundary layer) with thickness δ [m], the solution to the above equation is:

$$\frac{c_w}{c_b} = \exp\left(\frac{\delta}{D} J\right) = \exp\frac{J}{k}$$

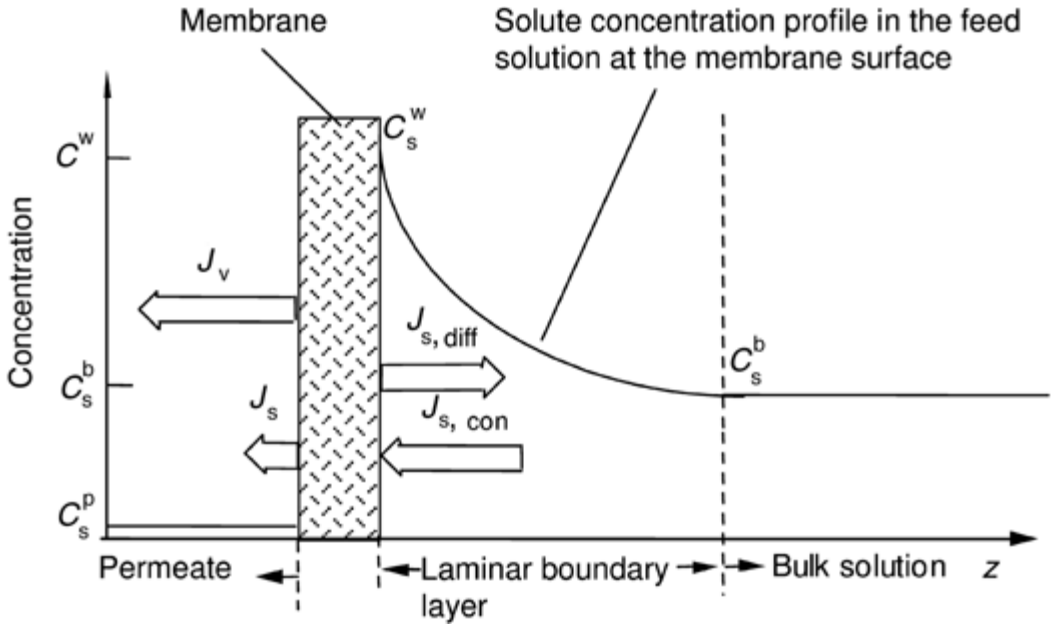
- $\left(\frac{\delta}{D}\right)^{-1} = \frac{D}{\delta}$ can be seen as a mass transfer coefficient k $\left[\frac{m}{s}\right]$.

- The ratio $\frac{c_w}{c_b}$ is sometimes called polarization modulus

In the membrane vicinity (when R<1)

OPTIONAL

- This situation where molecules are only partially retained by the membrane is relatively complex, hence it will not be treated in this chapter
- For a detailed review of this process, please refer to the following book: C. J. Geankoplis: Transport processes and separation process principles. Prentice Hall, 4th edition, 2003, p. 892-897



Source: H. Strathmann, Ullmann's Encyclopedia of industrial chemistry (2011)

Case of a laminar tangential flow

OPTIONAL

- For macromolecules with low diffusivities and permeable membranes (with high permeate fluxes J), the polarization modulus can reach high values ($\frac{c_w}{c_b}$ >10)
- A graph of the flux J as a function of log(C_b) often yields a straight line with a negative slope that cuts the horizontal axis (J=0) at concentration values that are a good approximation of c_w, the protein concentration at the membrane
- Correlations have been developed for the mass transfer coefficient k. In the case of a laminar flow:

$$k = 0.816\left(\gamma_w \frac{D^2}{L}\right)^{\frac{1}{3}}$$

- For a rectangular slit of height 2h:

$$g_w = \frac{3u_b}{h}$$

- For a circular tube of diameter d_t:

$$g_w = \frac{8u_b}{d_t}$$

γ_w fluid shear rate at the membrane surface [s^-

u_b bulk velocity $\left[\frac{m}{s}\right]$

L channel length [m]

k mass transfer rate $\left[\frac{s}{m}\right]$

For a turbulent tangential flow

OPTIONAL

- Empirical equations/correlations have been developed, that can help determine the mass transfer coefficient in the turbulent regime.
- They are based on the dimensional analysis of the mass transfer induced by forced convection in a closed channel:

$$Sh = \frac{k \times d_h}{D} = f(Re, Sc, \frac{L}{d_h}) \qquad \text{e.g.} \qquad Sh = \frac{k \times d_h}{D} = 0.082 \times Re^{0.69} \times Sc^{0.33}$$

NB: in this case, the influence of L/d_h is neglected

$Re = \frac{r \times u_b \times d_h}{m}$ Reynolds number (-)

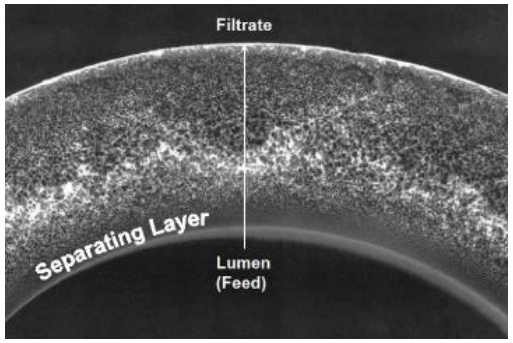
$Sc = \frac{m}{r \times D}$ Schmidt number (-)

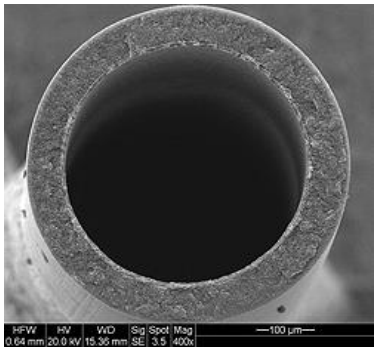
d_h	equiv. diameter of the channel = 4·cross section area/wetted perimeter	[m]
u_b	velocity of the tangential flow	[m/s]
μ	liquid dynamic viscosity	[Pa·s]

Polarization modulus: example

OPTIONAL

- Low molecular weight contaminants are being removed from a protein solution by diafiltration at constant volume through a hollow fiber type of ultrafiltration module
- The fibers have an internal diameter d_h = 1 mm and are 1m long
- The protein has a diffusion coefficient $D = 9.0 \cdot 10^{-7}$ cm^2/s. The solution has a viscosity μ = 1.2 mPa·s and a density ρ = 1.1 g/cm^3
- The velocity of the tangential flow inside the fibers is u_b = 300 cm/s
- Under these conditions, determine the value of the polarization modulus if the flux through the membrane amounts to 45 $L/(m^2 \cdot h)$





Exemple de calcul dans Harrison, Todd, Rudge & Petrides, p. 114-117

Detailed calculations

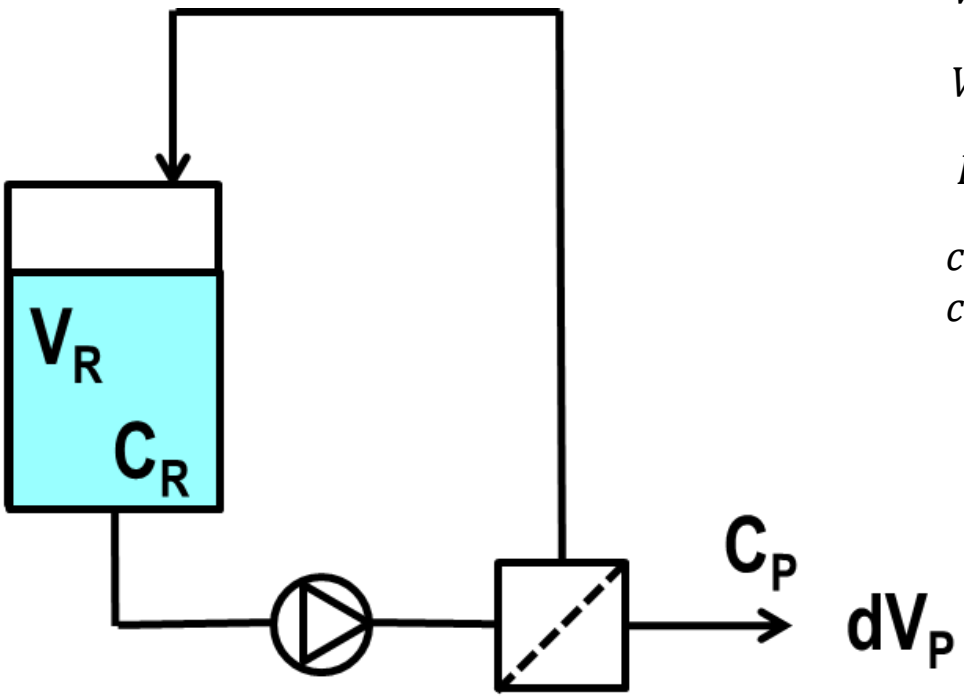
OPTIONAL

- The Reynolds is easily calculated and amounts to 2750 ⇒ *flow is turbulent*
- For a turbulent flow we need to know the value of the Schmidt number. It is determined at approximately Sc = 12'100
- The mass transfer coefficient k is contained in the Sherwood number Sh. The latter's value can be calculated using one correlation of the form Sh=f(Re, Sc, L/d_h)
- We find $k = (D \cdot Sh)/d_h = 3.88 \cdot 10^{-5}$ m/s

$$Sh = \frac{k \cdot d_h}{D} = 0.082\, Re^{0.69} Sc^{0.33}$$

- Knowing that $J = (D/\delta) \cdot \ln(C_w/C_b) = k \cdot \ln(C_w/C_b)$ ⇒ $C_w/C_b = 1.38$
- This value indicates that <u>the concentration polarization is not too severe in this case</u>

Characterization of a batch concentration



V_r	Retentate volume	$[\mathrm{m}^3]$
V_p	Permeate volume	$[\mathrm{m}^3]$
R	Rejection factor	$[-]$
c_R, c_P	Concentration in retentate/permeate	$\left[\frac{\mathrm{kg}}{\mathrm{m}^3}\right]$

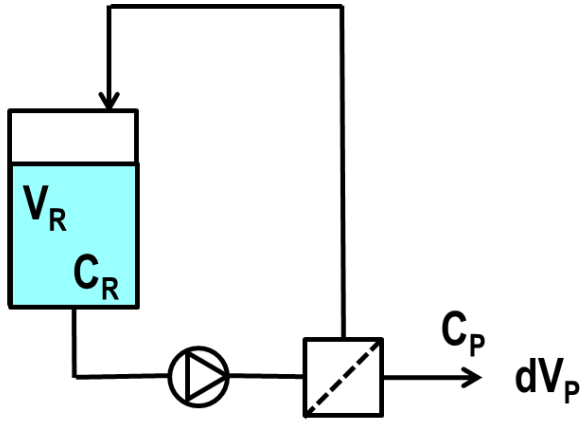
V_0	Initial retentate volume	$[m^3]$
c_0	Initial concentration	$\left[\frac{kg}{m^3}\right]$
$F_c = \frac{V_0}{V_R} = \frac{V_0}{V_0 - V_P}$	volumetric concentration factor	$[-]$
$\mathrm{L} = 1 - Y$	Loss	$[-]$
Y	Yield	$[-]$

General case: concentration of a solution

- Global mass balance on the solute:

$$V_r \cdot c_r = (V_r - dV_r) \cdot (c_r - dc_r) + c_p \cdot dV_p$$

Clearly, we can also write: $dV_r = dV_p = dV$



- Introducing the retention factor:

$$R = 1 - \frac{c_p}{c_r} \quad \Rightarrow \quad c_p = c_r \cdot (1 - R)$$

- We can thus eliminate C_p

$$V_r \cdot c_r = (V_r - dV_r) \cdot (c_r - dc_r) + c_r \cdot (1 - R) \cdot dV_r$$

- Development and integration

Note: the terme $dV_r \cdot dC_r$ can be considered as negligible

Due to time constraints we will spare ourselves the development and focus on the result

Concentration of a solute: result

- If the target molecule is not 100% retained (R<1), part of it will be lost in the permeate during the volume reduction
- Evolution of concentration in the retentate

$$c_R = c_0 \cdot \left(\frac{V_0}{V_R}\right)^R = c_0 \cdot \left(\frac{V_0}{V_0 - V_P}\right)^R = c_0 \cdot (F_C)^R$$

- Loss L upon concentration:

$$L = 1 - \frac{c_R}{c_R^*} = 1 - \left(\frac{V_0}{V_R}\right)^{(R-1)} = 1 - (F_C)^{(R-1)}$$

Discuss what happens in extreme situations where R=0 or R=1

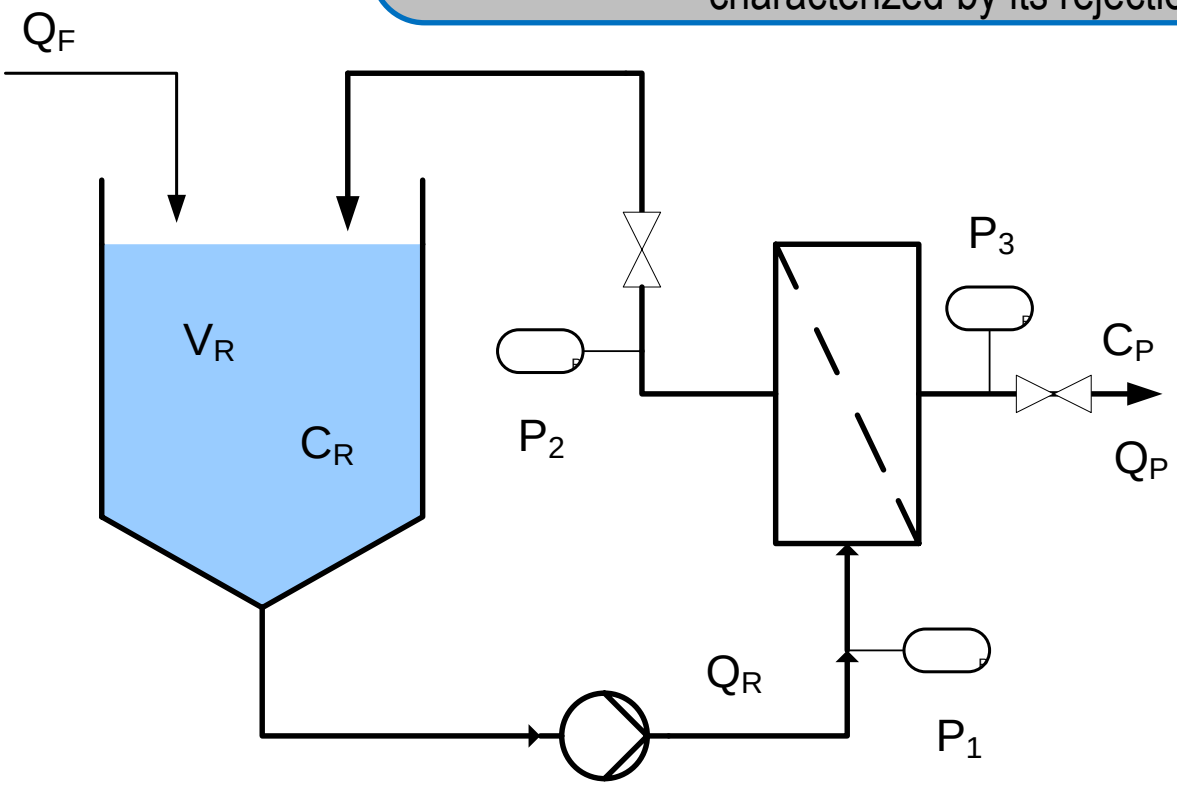
Where $C_R^* = C_R * F_c$ = theoretical concentration in the retentate if R=1

Diafiltration for desalting or buffer exchange

(at constant volume of retentate)

Exercise

Based on a differential mass balance, develop an expression for the evolution of the concentration in the retentate C_R for any substance as a function of time t or the volume of collected permeate V_P. Each substance is characterized by its rejection coefficient R.



Influence of the retention factor

- Loss upon a concentration trial

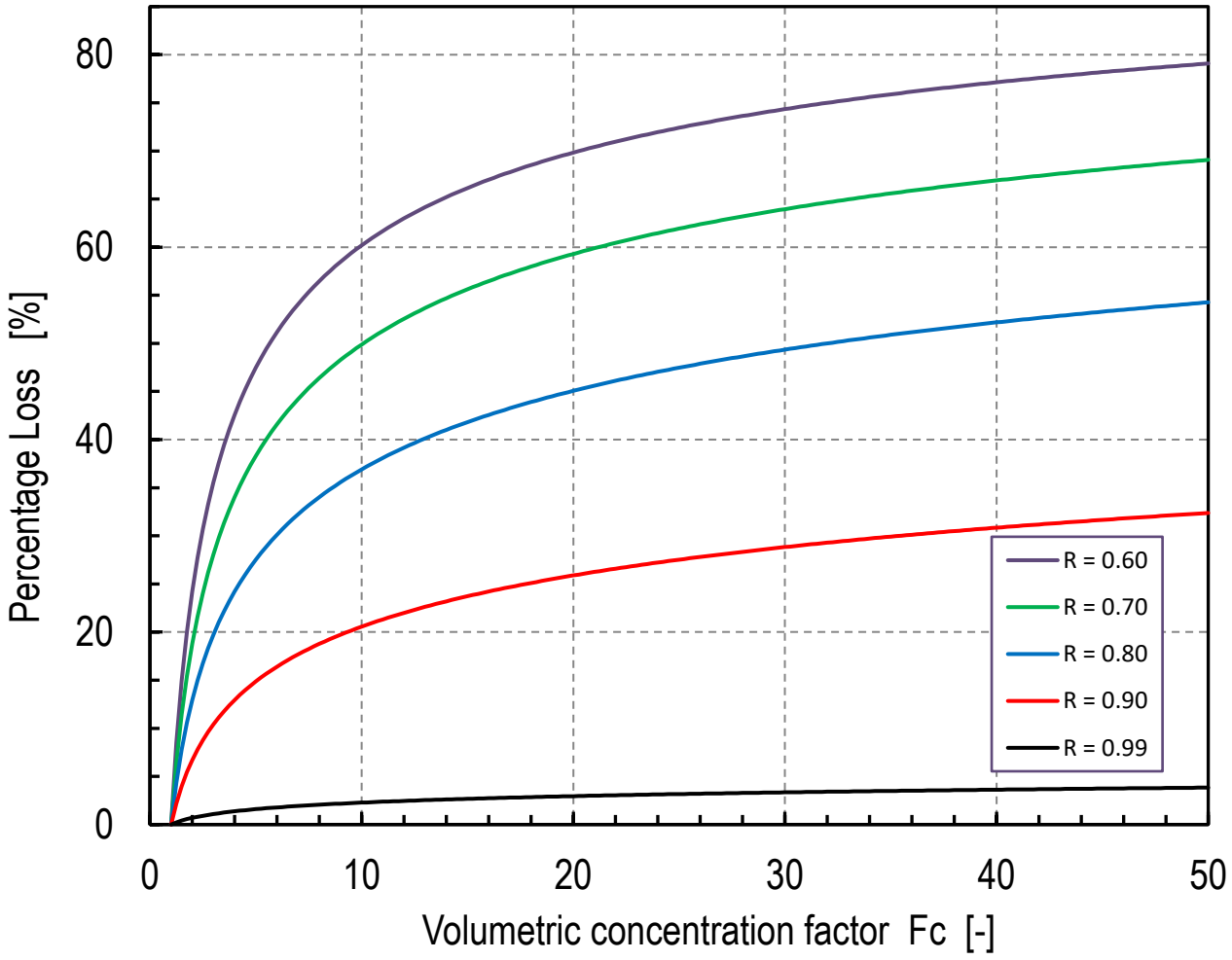
$$L = 1 - (F_c)^{(R-1)}$$

- Loss upon a diafiltration step

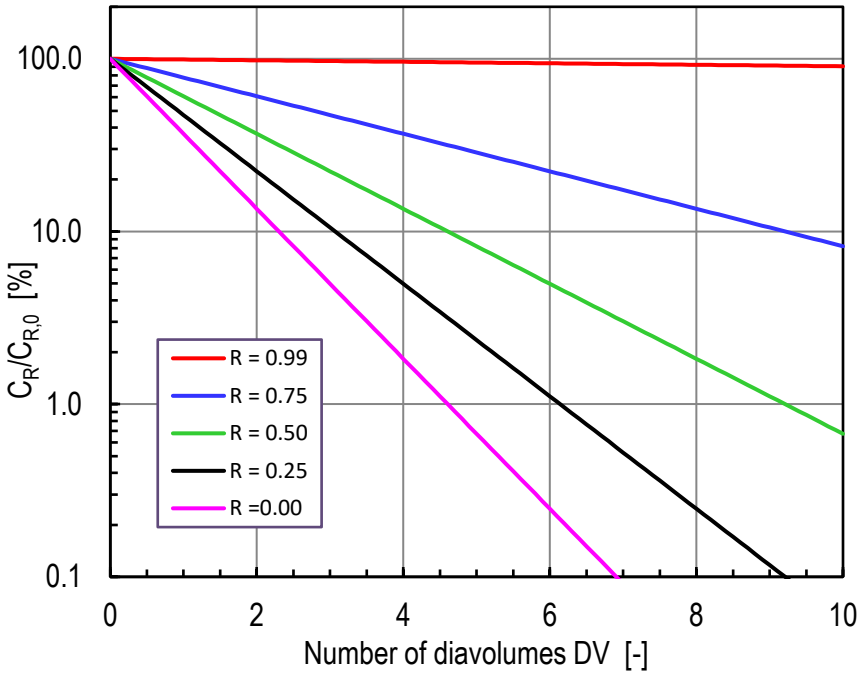
$$L = 1 - \exp\big((R-1) \cdot DV\big)$$

R	Retention factor	[-]
L	Loss	[-]
F_C	Volumetric concentration factor = $V_{R,final}/V_{R,0}$	[-]
DV	Number of diavolumes = $V_{Perm}/V_{R,0}$	[-]

Loss during a concentration step

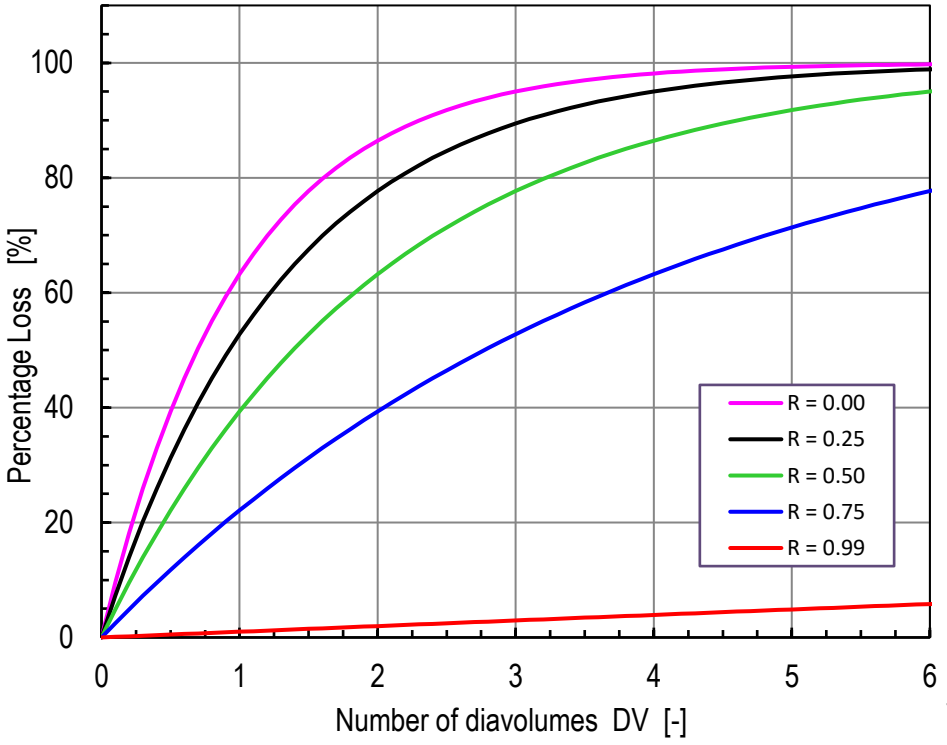


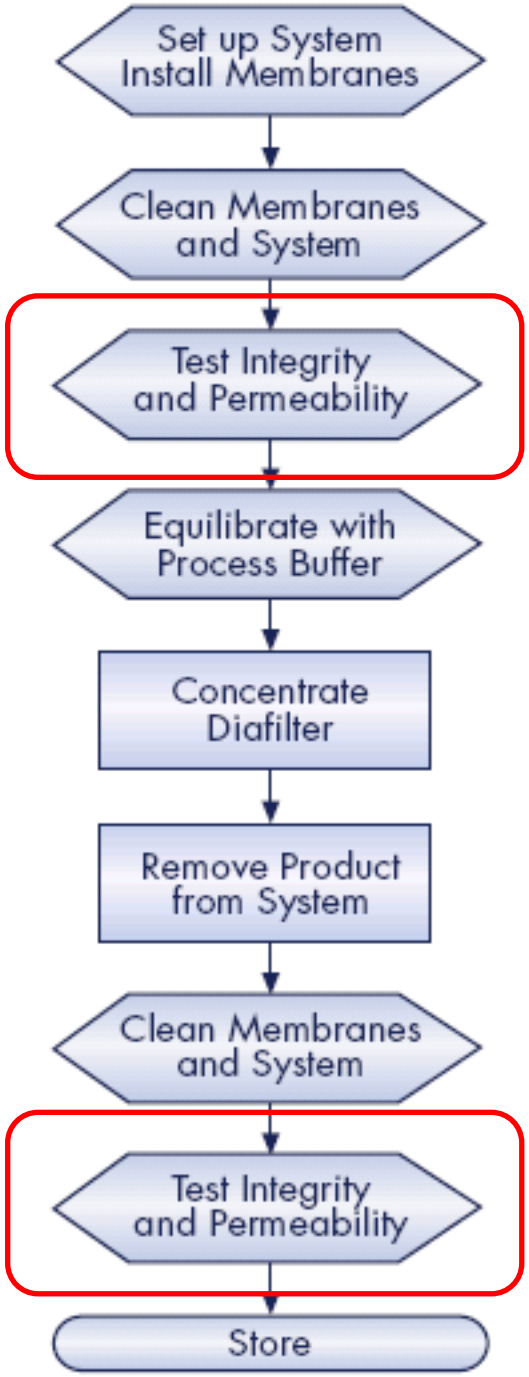
Concentration profile and loss upon diafiltration



The left graph shows the disappearance of molecules with different rejection factors from a diafiltration retentate. Please note the logarithmic scale of the vertical axis. All curves start from 100%, and as seen in the lab it takes 5 diavolumes to remove 99%

The graph on the right shows the amount of material that is lost if the rejection factor of the molecule is smaller than 1. Depending on the number of diavolumes to be removed, selecting the highest possible R value will minimise losses.





A typical protocol for carrying out membrane filtration trials

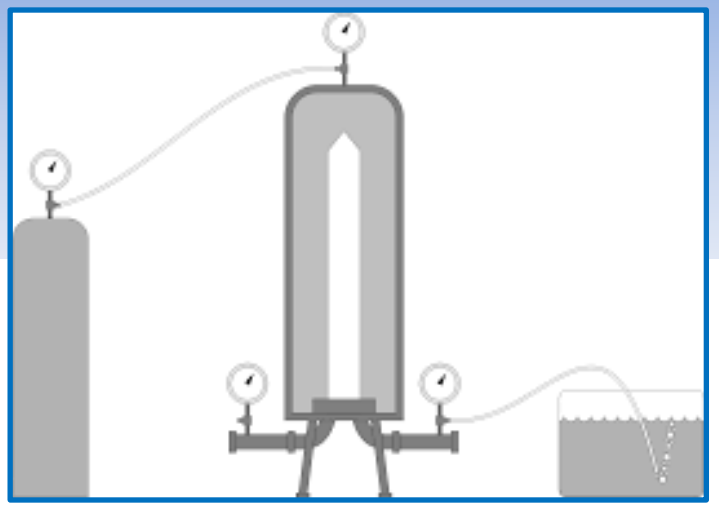
Testing the integrity of the membrane before the trials and after the cleaning are important steps

They help guarantee that the module is not damaged and that no loss of product will occur due to a defective membrane

To this effect there are several techniques and protocols available, depending on the type of application and the membrane supplier:

- Challenge test for contamination (*Clostridium*)
- Bubble point
- Gas diffusion test
- Pressure holding test

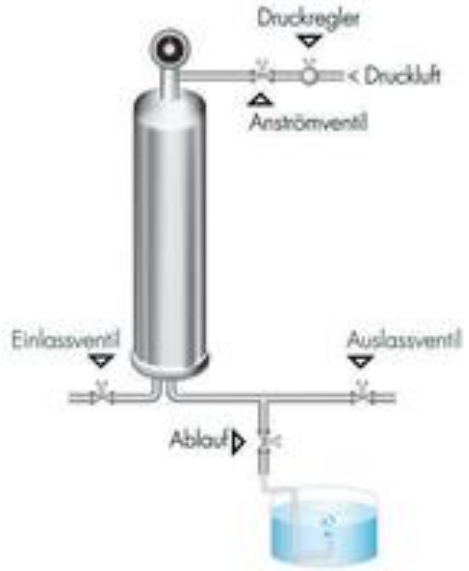
Bubble point test



- Non-destructive testing, the most commonly used in the industry
- Principle: liquid is trapped in the pores of the filter by capillary forces and surface tension
- The pressure is increased until it can push the liquid out of the pores
- Bubble point is reached when bubbles appear in a water bath (see illustration)
- The bubble point pressure P_b can be connected to the pore diameter:

$$P = \frac{4 \cdot \gamma \cdot \cos \psi}{d_p}$$

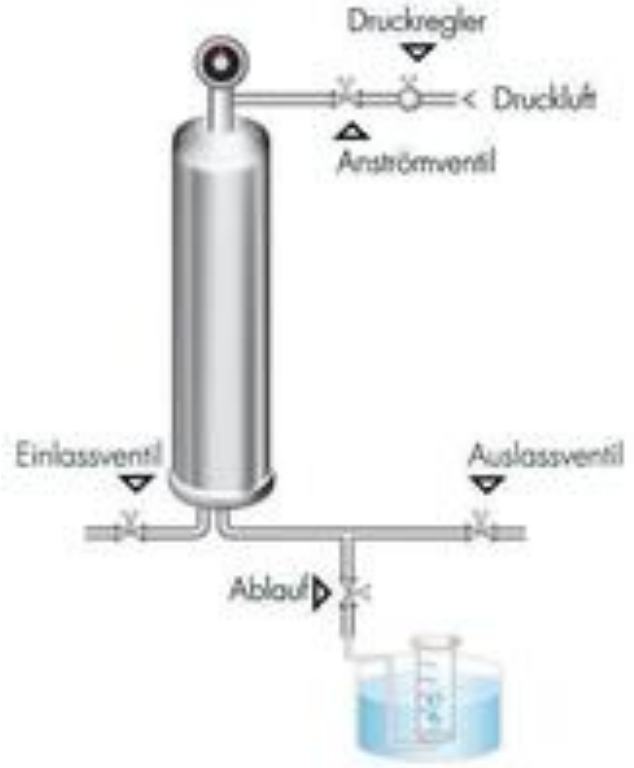
- If P_b is too low the membrane might be pierced and if it is too high it might be clogged



P_b = bubble pressure [Pa]
d_p = pore diameter [m]
γ = surface tension [N/m]
ψ = liquid/solid contact angle

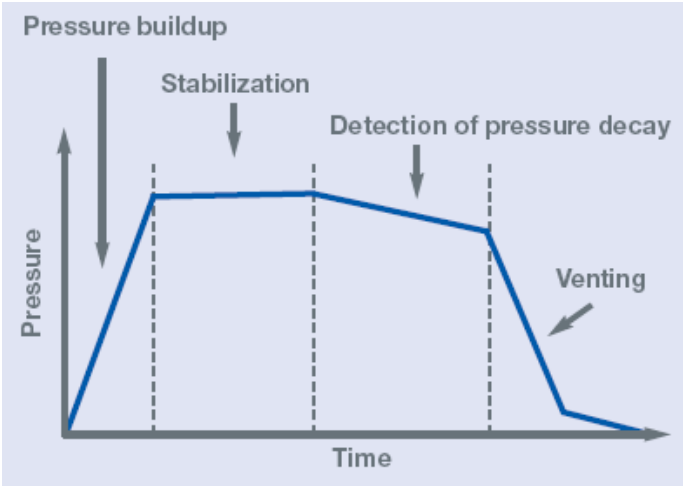
Diffusion test

- A gas pressure corresponding to about 80% of the bubble point pressure P_b is applied above the wetted membrane
- The quantitiy of gas that diffuses through the membrane is measured over a given period of time
- This quantity must remain smaller or at the maximum equal to specification so that the membrane can be considered intact



Pressure holding test

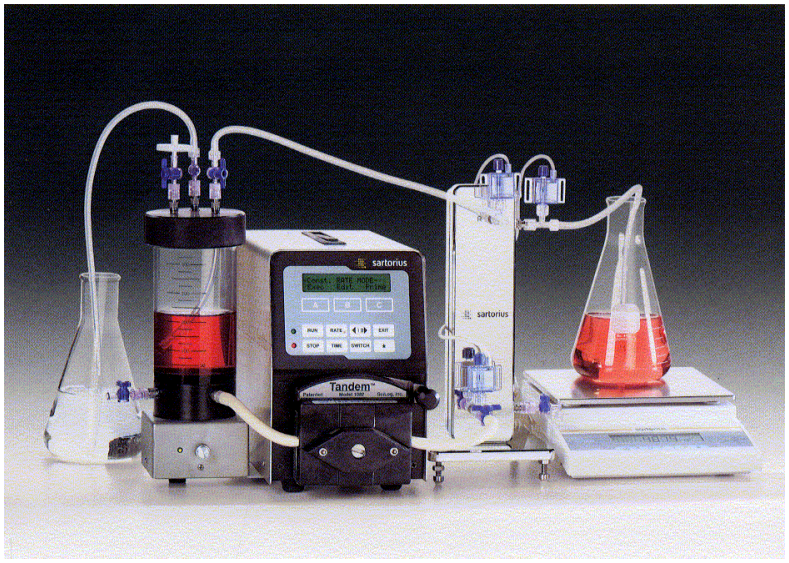
- Also known as pressure drop test
- This protocol is a variant of the diffusion test
- It requires the use of a highly precise manometer that enables the measurement of pressure decrease due to the diffusion of gas through the membrane
- Since no measurement of gas flow is performed on the permeate side of the membrane, the latter is easier to maintain sterile and it is less likely to be contaminated

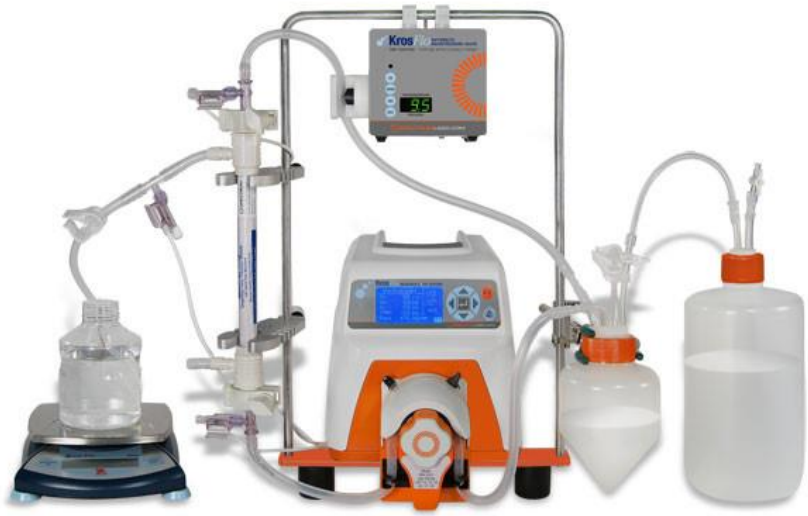


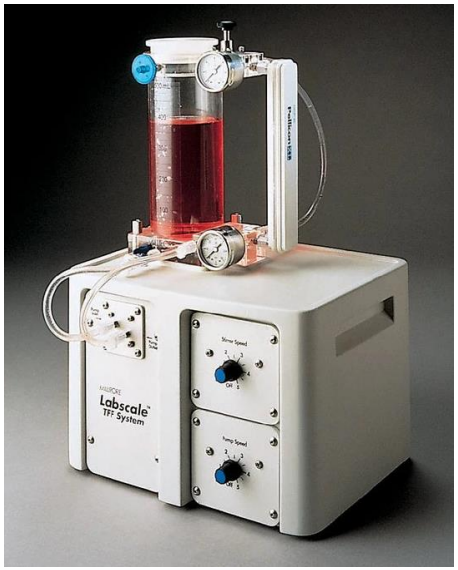
These measurements can be automatized and performed under traceable conditions

Again, whatever we saw is valid from lab scale …

CAUTION: pictures are not to scale







… going through pilot plant …

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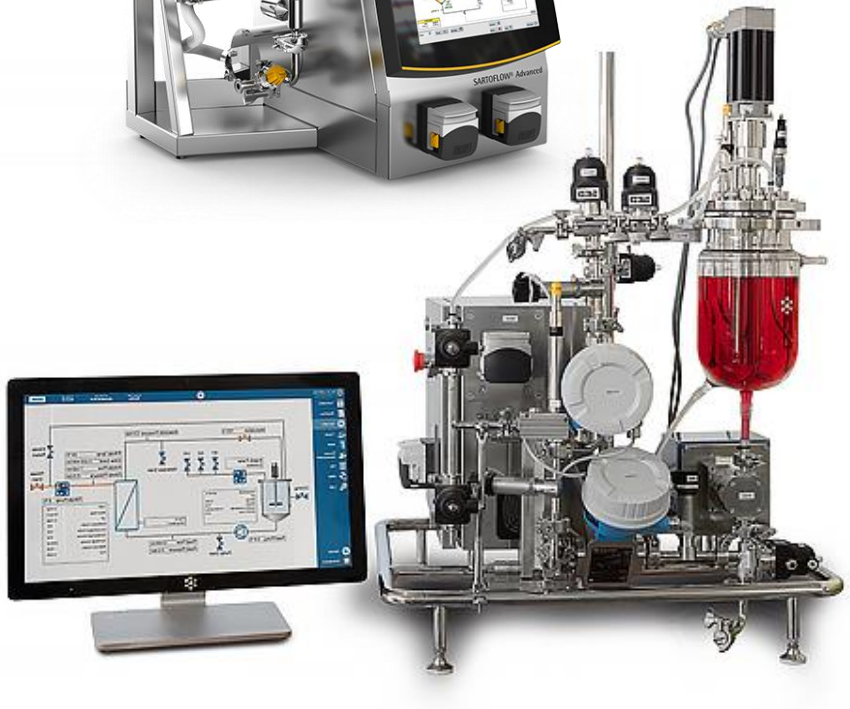

… and all the way to production scale

CAUTION: pictures are not to scale