High Performance Ultrafiltration Membranes: Pore Size, Geometry and Charge Effects

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Membranes for Clean Energy and Water
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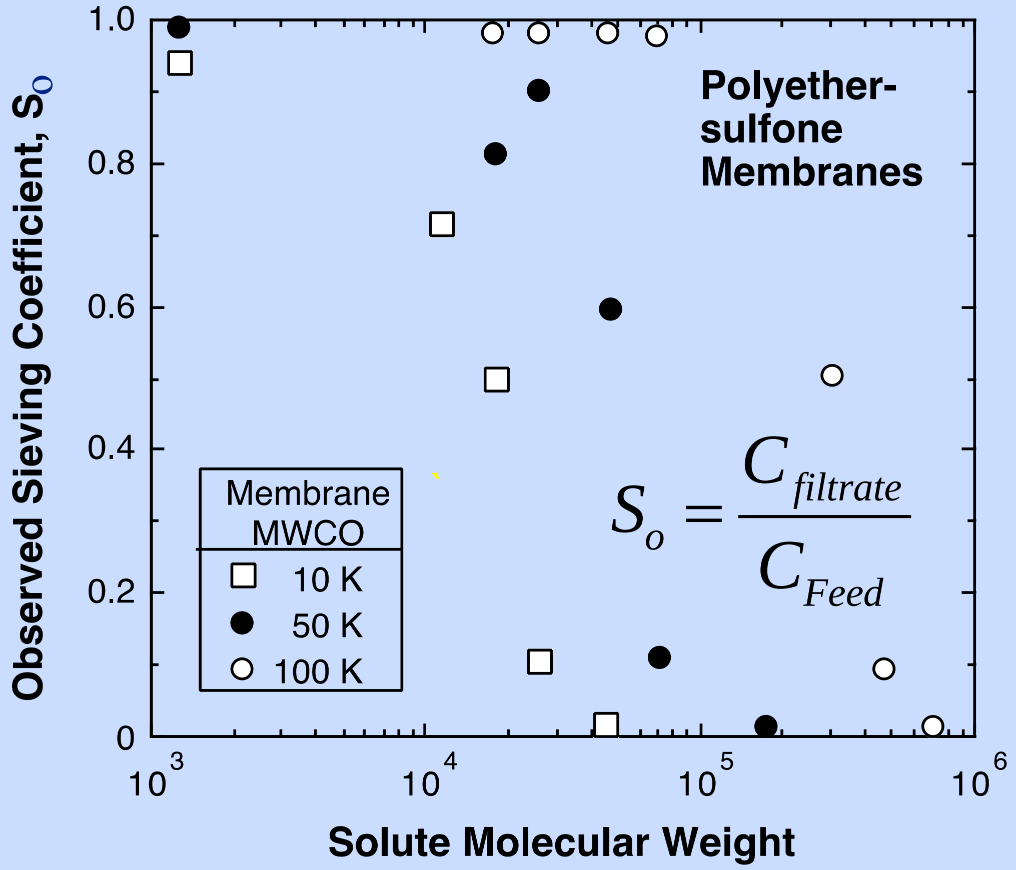
Ultrafiltration

- Ultrafiltration is used extensively for protein concentration and buffer exchange
  - Final formulation of recombinant protein products
  - Pre-conditioning of protein solutions
- Ultrafiltration is increasingly used in water treatment applications
  - Pretreatment before reverse osmosis
  - Removal of natural organic matter, viruses, etc.

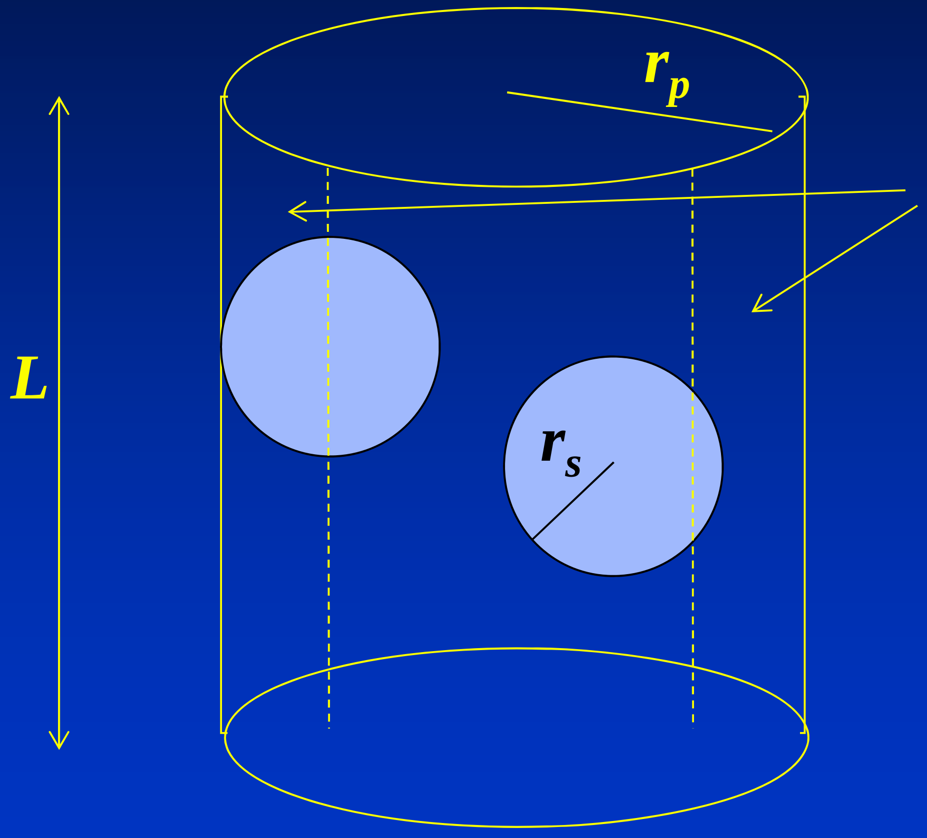
UF Membranes



$$S_o = \frac{C_{filtrate}}{C_{Feed}}$$

Data from Filtron Separation Product Profile

Steric Exclusion



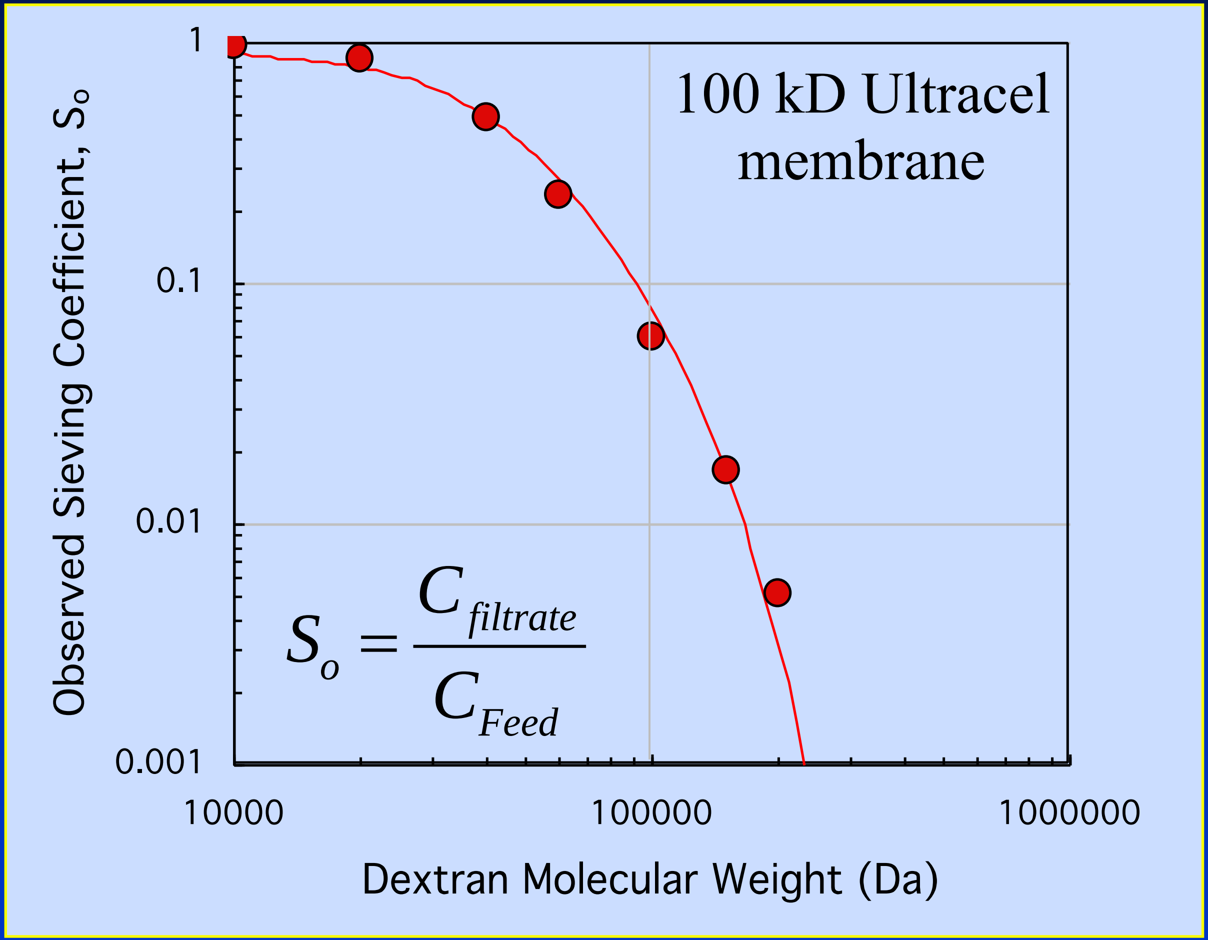
Cylindrical Pore

Excluded Volume

$$S \approx \frac{\pi\left(r_p - r_s\right)^2 L}{\pi r_p^2 L}$$

$$S \approx \left(1 - \frac{r_s}{r_p}\right)^2$$

UF Membrane Sieving



from Zydney and Xenopoulos, J. Memb. Sci. 291: 180 (2007).

Molecular Weight Cut-Off

- UF membranes charcterized by nominal MWCO
  - Molecular weight of solute with 90% retention

$$R = 1 - S_o = 1 - \frac{C_{filtrate}}{C_{Feed}}$$

- No standardization in method
  - Choice of solute (protein, dextran, PEG, etc)
  - Choice of conditions (pressure, flux, cross-flow)

Permeability - Selectivity Tradeoff

- Nominal MWCO provides only a single parameter describing membrane -> insufficient
- Key factors are the filtrate flux (related to permeability) and selectivity

Permeability:

$$L_p = \frac{Q_{filtrate}}{A\Delta P}$$

Selectivity:

$$\alpha = \frac{Flux\ of\ Impurity}{Flux\ of\ Product} = \frac{S_{impurity}}{S_{product}}$$

UF Selectivity

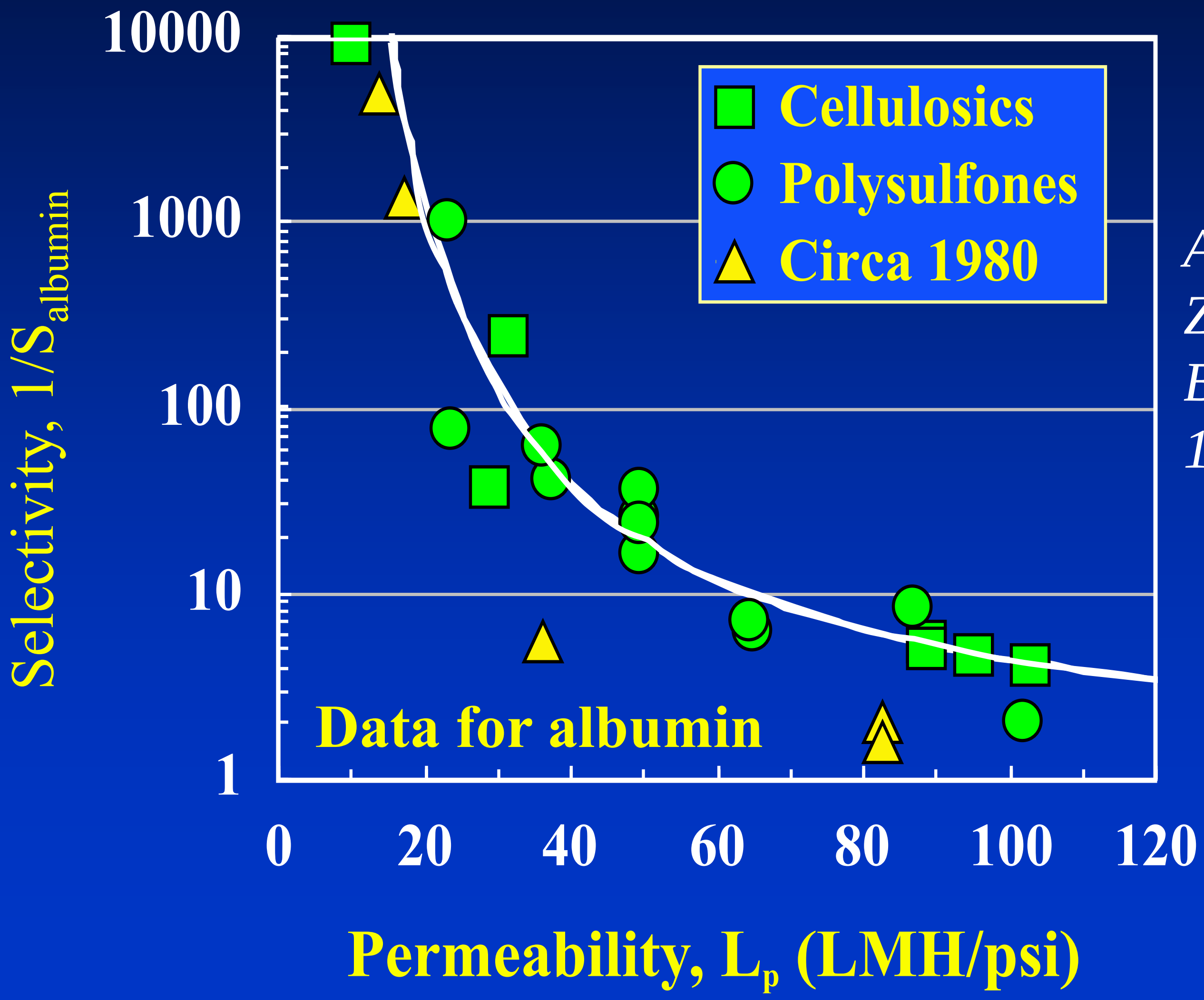
- For protein ultrafiltration, the impurity is typically a small buffer component with S ≈ 1

$$\alpha = \frac{S_{impurity}}{S_{product}} = \frac{1}{S_{protein}}$$

- For water treatment applications (product is in permeate):

$$\alpha = \frac{S_{water}}{S_{impurity}} = \frac{1}{S_{impurity}}$$

Permeability - Selectivity Tradeoff



Adapted from Zydney, Biotech Bioeng, 103, 227 (2009)

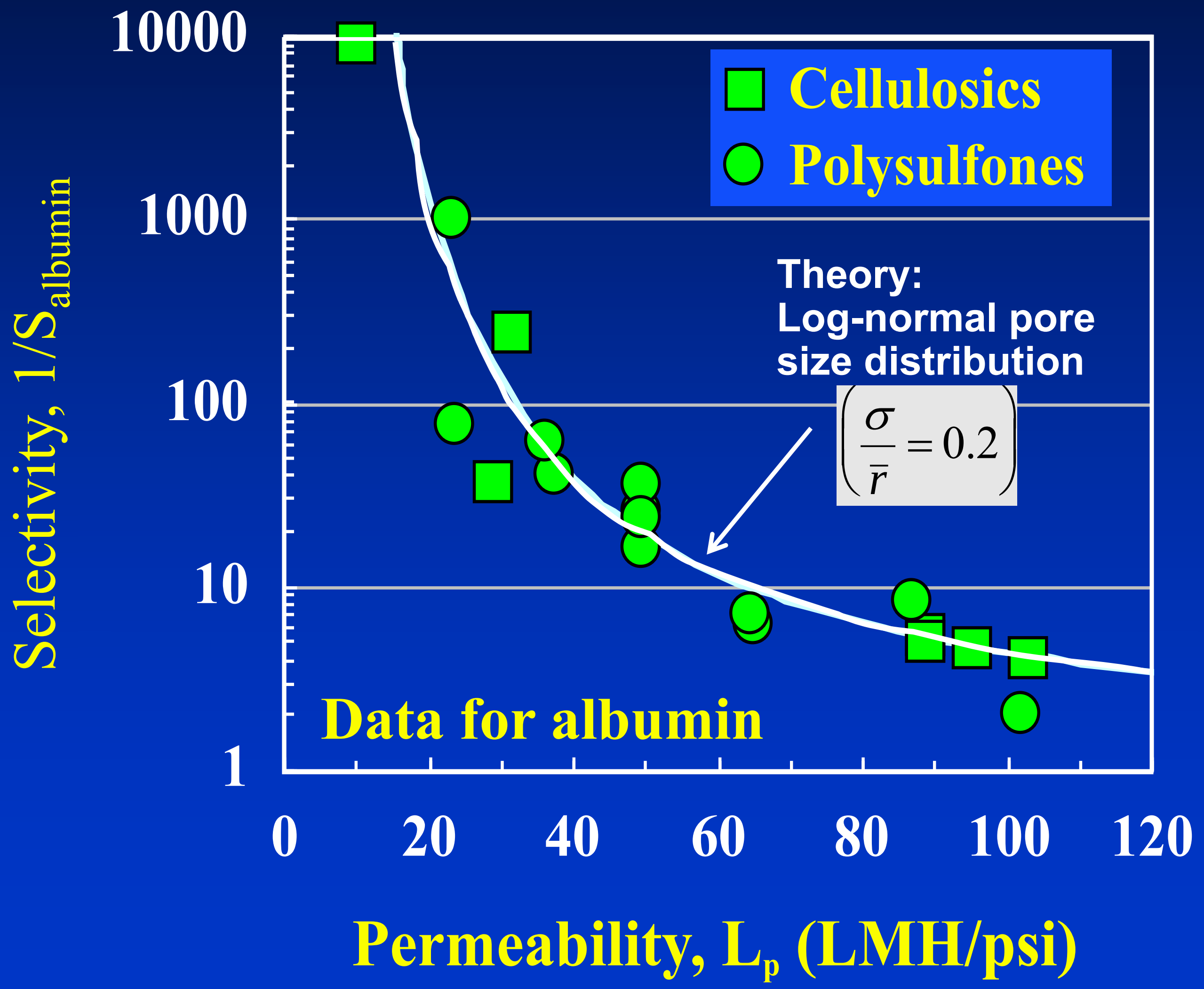
UF Tradeoff: Theory

- Membrane modeled as a parallel array of cylindrical pores with log-normal distribution

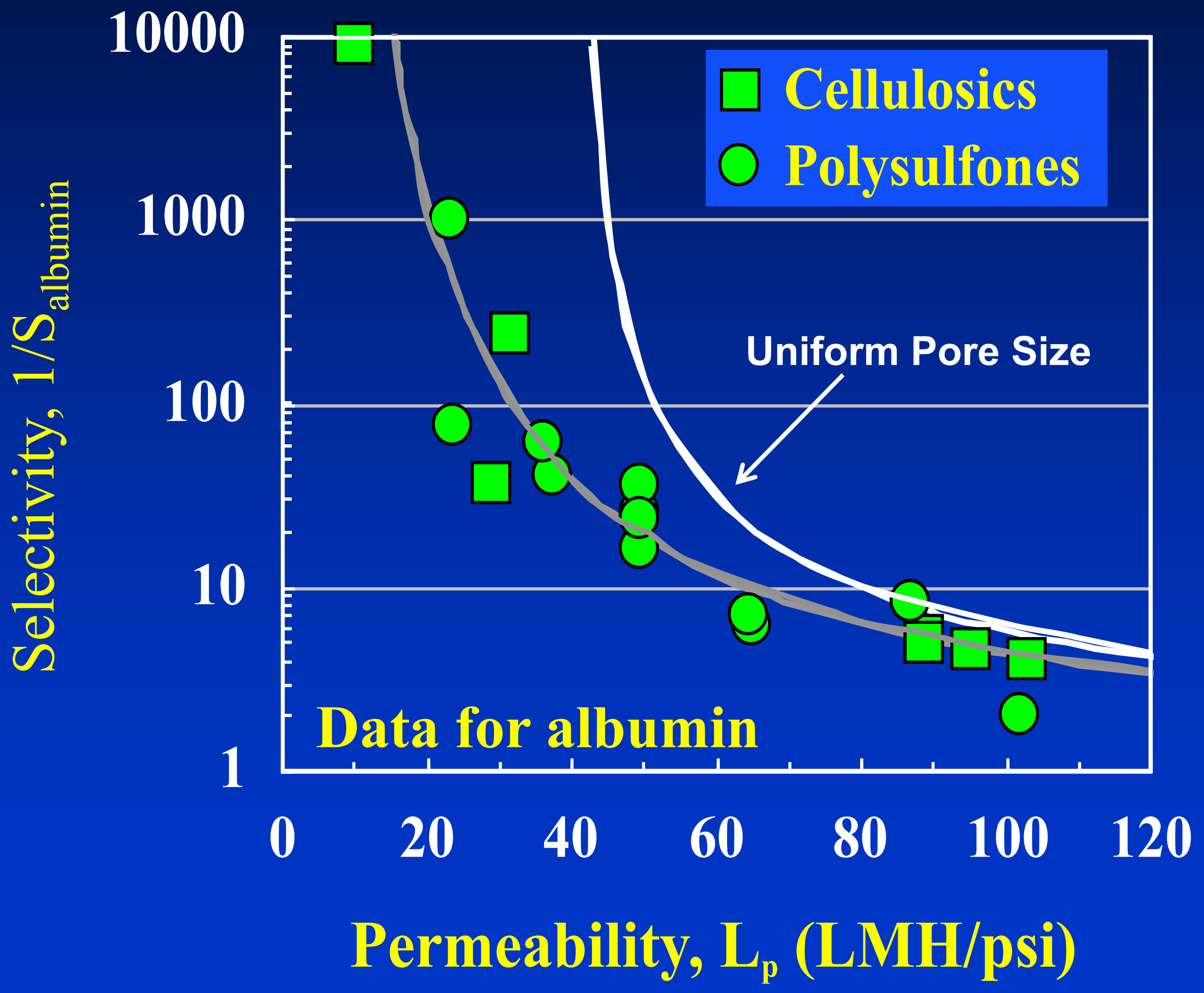
Mean = $\bar{r}$ Standard Deviation = $\sigma/\bar{r}$

- Permeability evaluated assuming Poiseuille flow through porous array
- Sieving coefficients evaluated using available hydrodynamic models by integrating over pore size distribution

Permeability - Selectivity Tradeoff



Permeability - Selectivity Tradeoff



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UF Membrane Development

- **Traditional Approach** -- Develop membranes with narrow pore size distributions by changing casting conditions, additives, or polymers --> fairly limited opportunity

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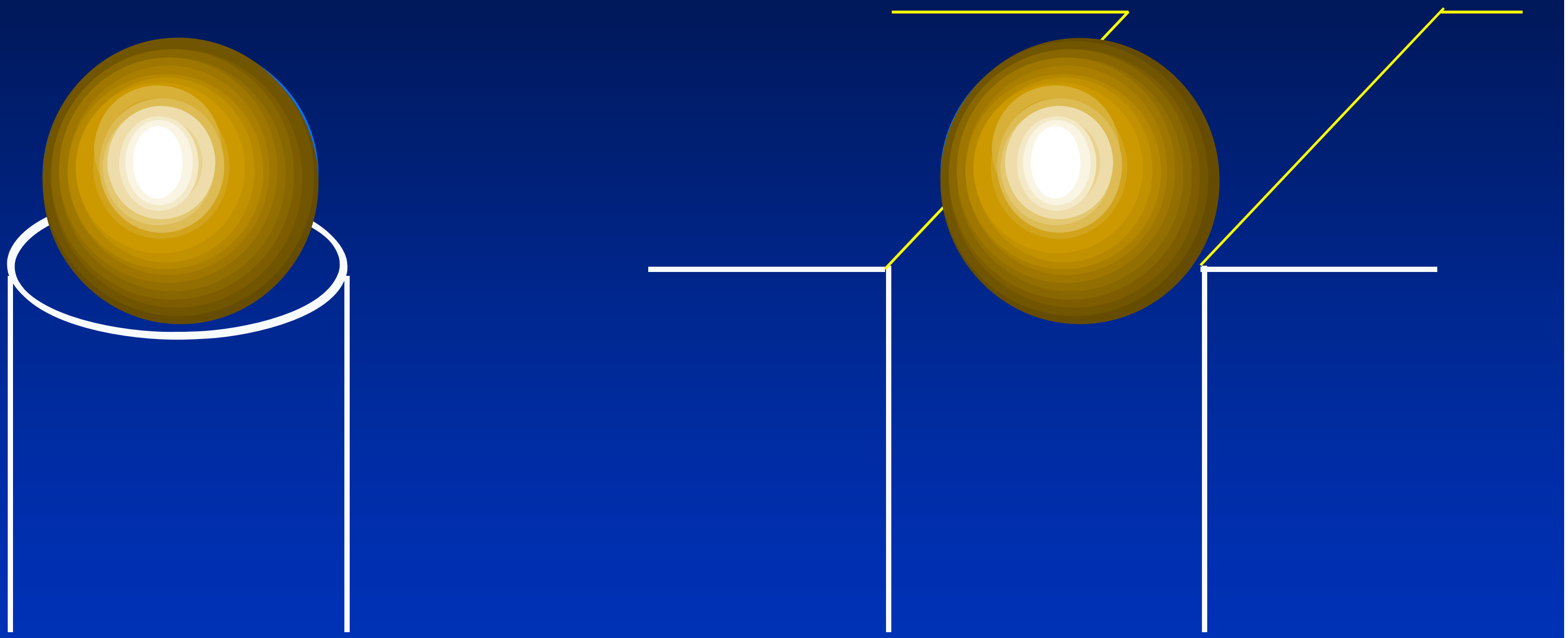
- **New Opportunities**
  - Pore morphology (slit-pores)
  - Electrically-charged membranes

Slit-Shaped vs Cylindrical Pores



Significant hydrodynamic interactions with entire surface of pore

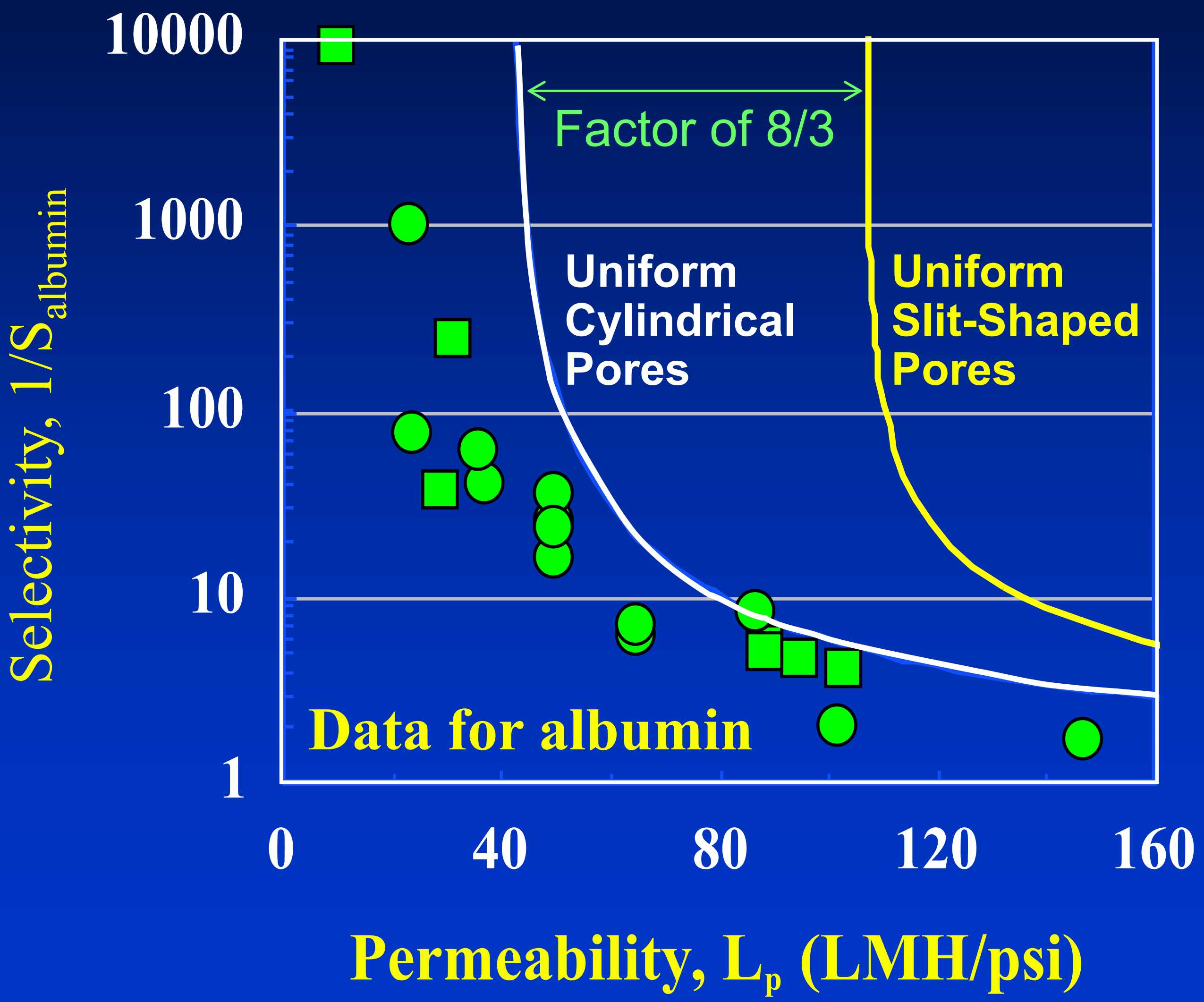
Reduced hydrodynamic interactions due to smaller wetted area

Slit-Shaped vs Cylindrical Pores

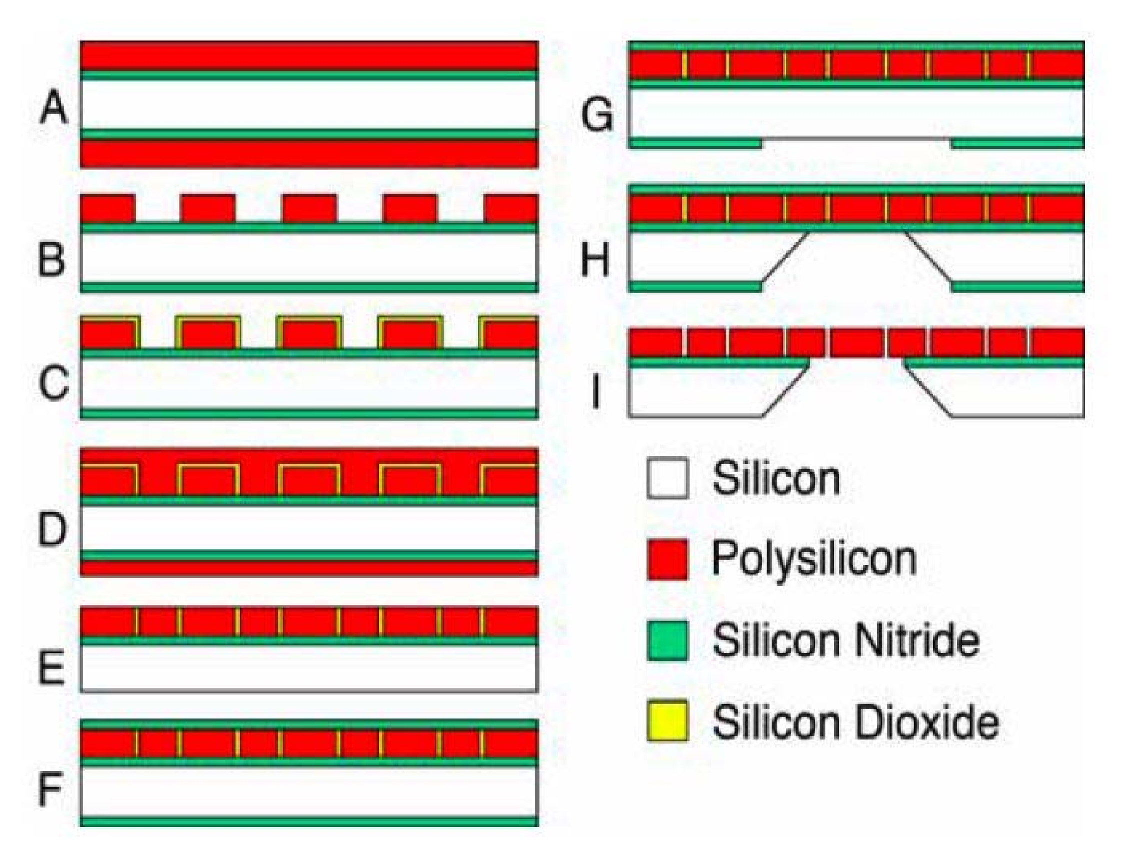
	Cylinder	**Slit Pore**
Pressure Drop:	$\Delta P = \frac{8Q\mu\delta_m}{N\pi R^4}$	$\Delta P = \frac{3Q\mu\delta_m}{2Nwh^3}$
Membrane Porosity:	$\varepsilon = \frac{N\pi R^2}{A}$	$\varepsilon = \frac{N2wh}{A}$
Permeability:	$L_p = \frac{\varepsilon R^2}{8\mu\delta_m}$	$L_p = \frac{\varepsilon h^2}{3\mu\delta_m}$

δ_m= pore length, R = pore radius, h = pore slit half-width

Permeability - Selectivity Tradeoff



Silicon Nanolithography for Membranes



A) A 400 μm-thick silicon wafer is coated with silicon nitride (500 nm) followed by polycrystalline silicon (5 μm)

B) Polysilicon layer is patterned by photolithography and reactive ion etching to create ~50 μm-long lines / spaces

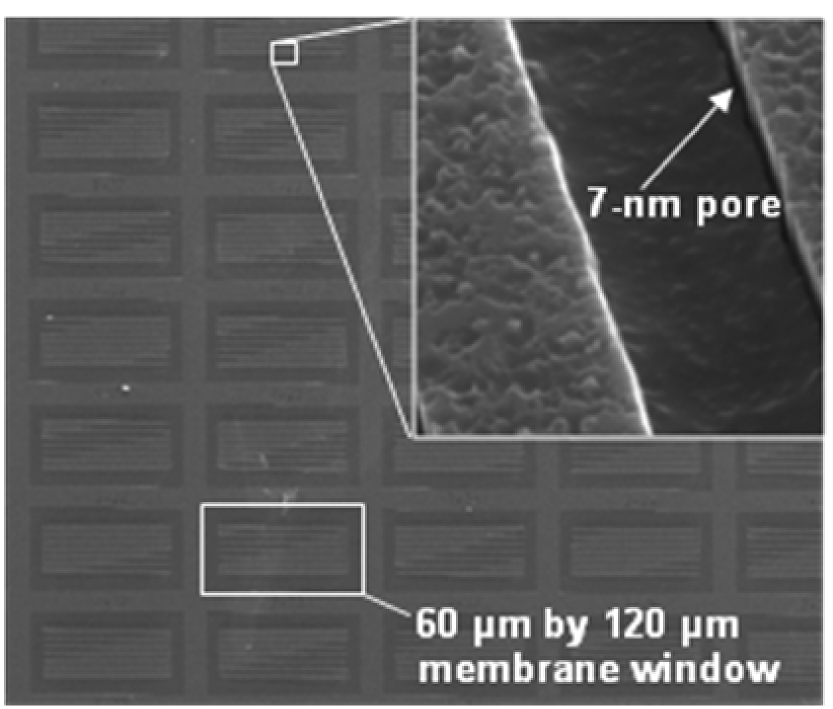
C) A thin conformal SiO_2 film is grown by thermal oxidation which defines the pore size

D) Deposition of 4 μm thick polysilicon layer

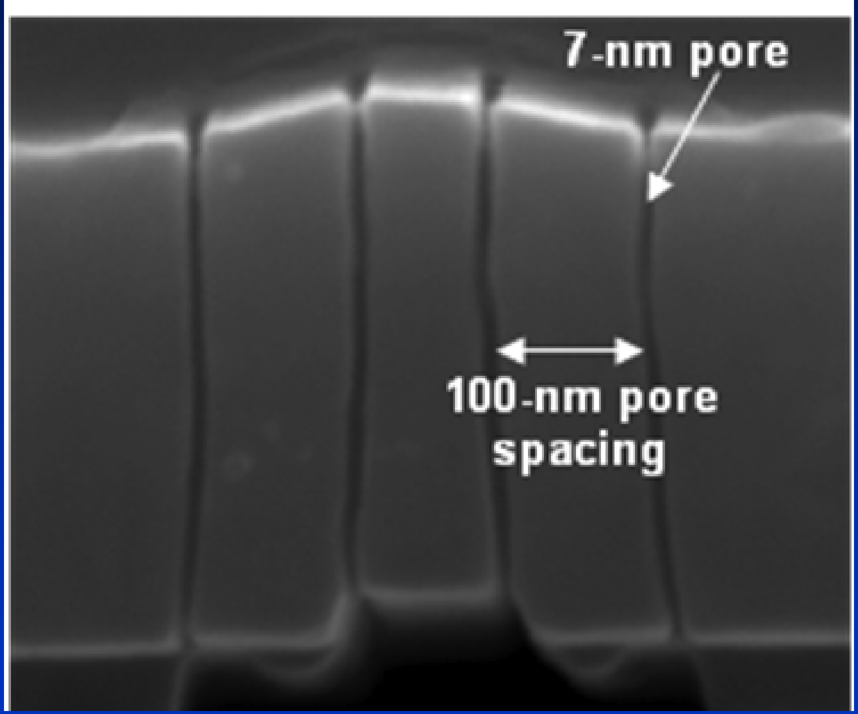
E) Chemical-mechanical polishing exposes nanopore regions on front side

Fissell et al., High-performance silicon nanopore hemofiltration membranes, J. Membrane Sci., 326, 58 (2009)

Silicon Lithographed Membranes

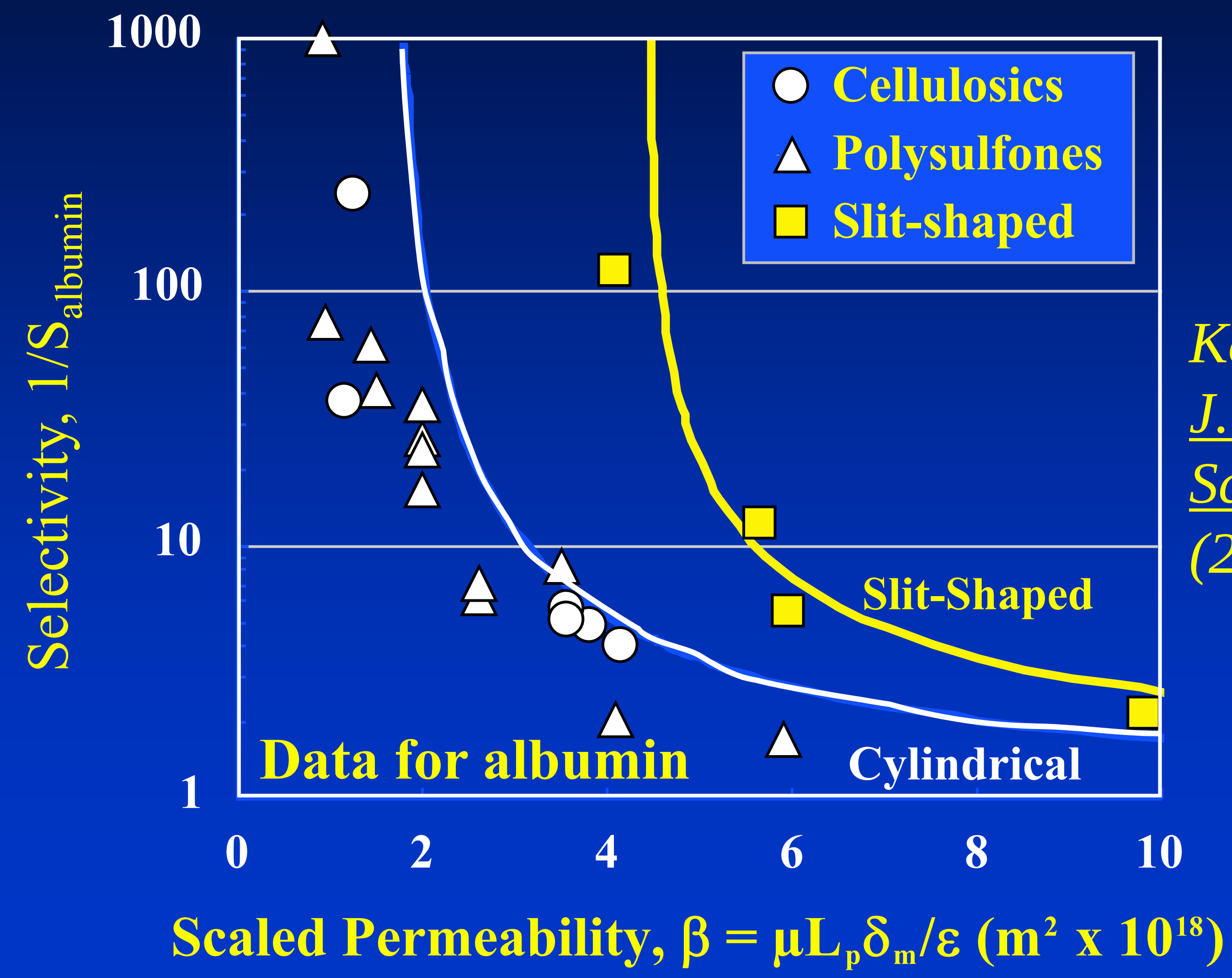


Upper Surface



Membrane Cross-Section

Permeability - Selectivity Tradeoff



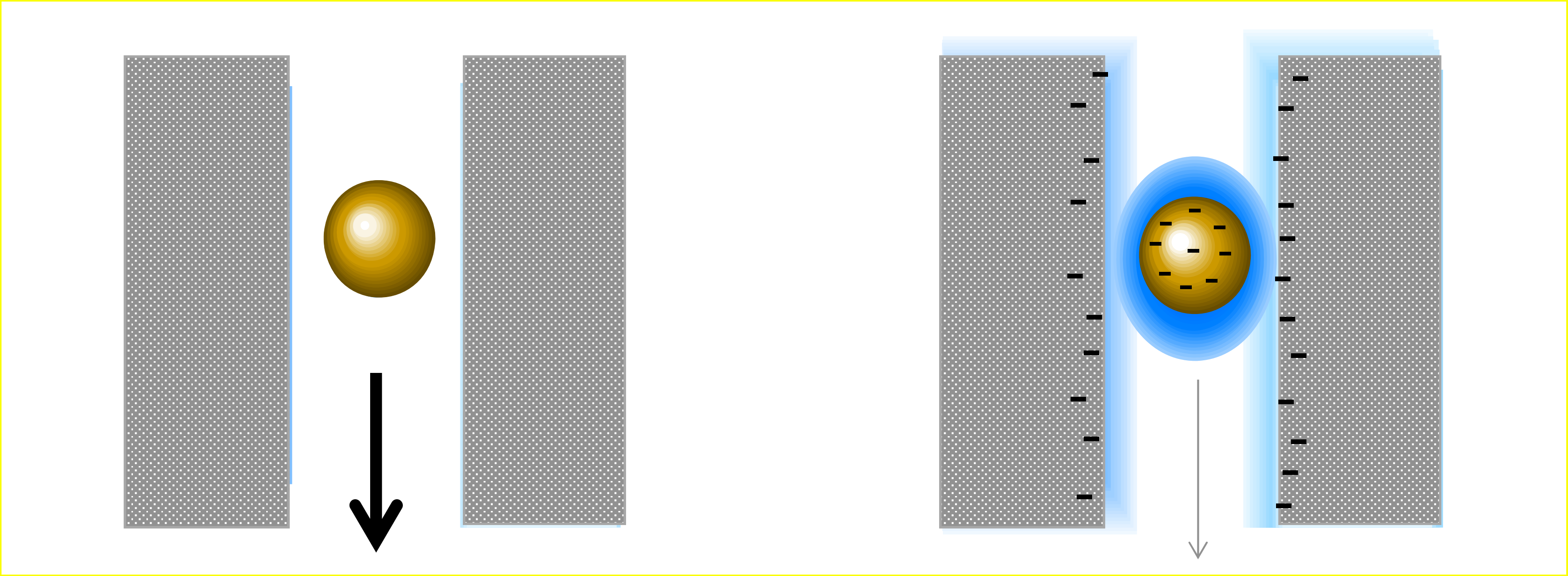
Kanani et al., J. Membrane Sci., ***349***, *405 (2010).*

Charged Membranes

- **Hypothesis:** Electrically-charged membranes can provide high retention of like charged proteins while giving high permeability (and rapid removal of small impurities)

- **Electrically-charged membranes**
    - – Sulfonic acids --> negative membrane
    - – Quaternary amines --> positive membrane

Electrostatic Interactions



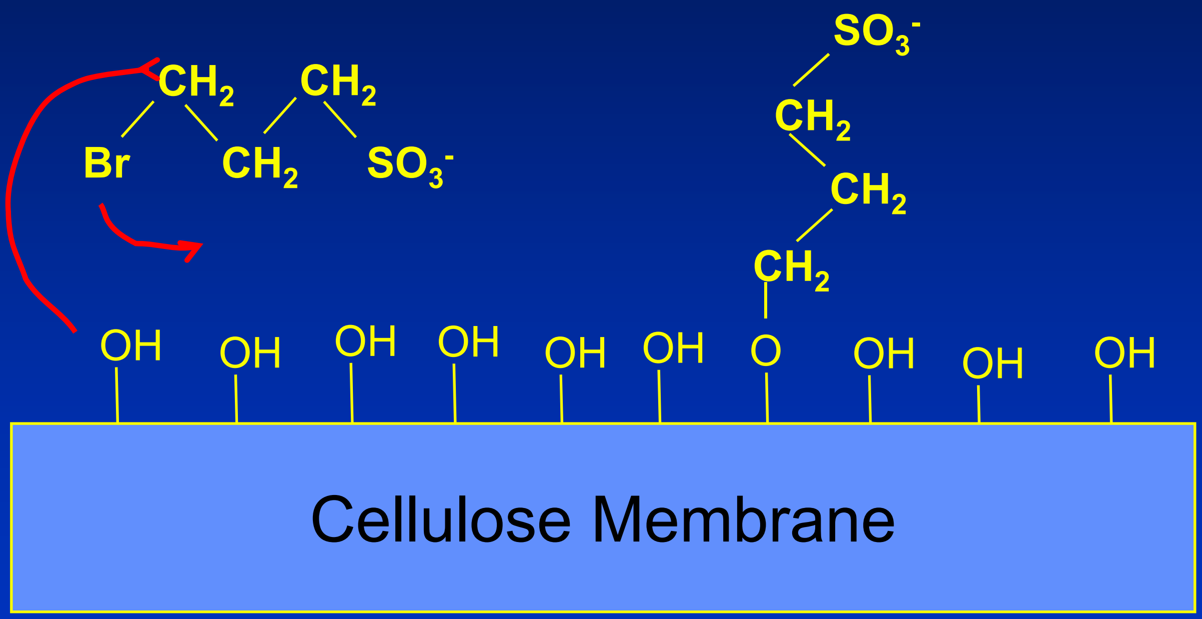
Significant Protein Transmission

Energetic Penalty due To Electrostatic Effects

Minimal Transmission

Charge-Modified Membranes

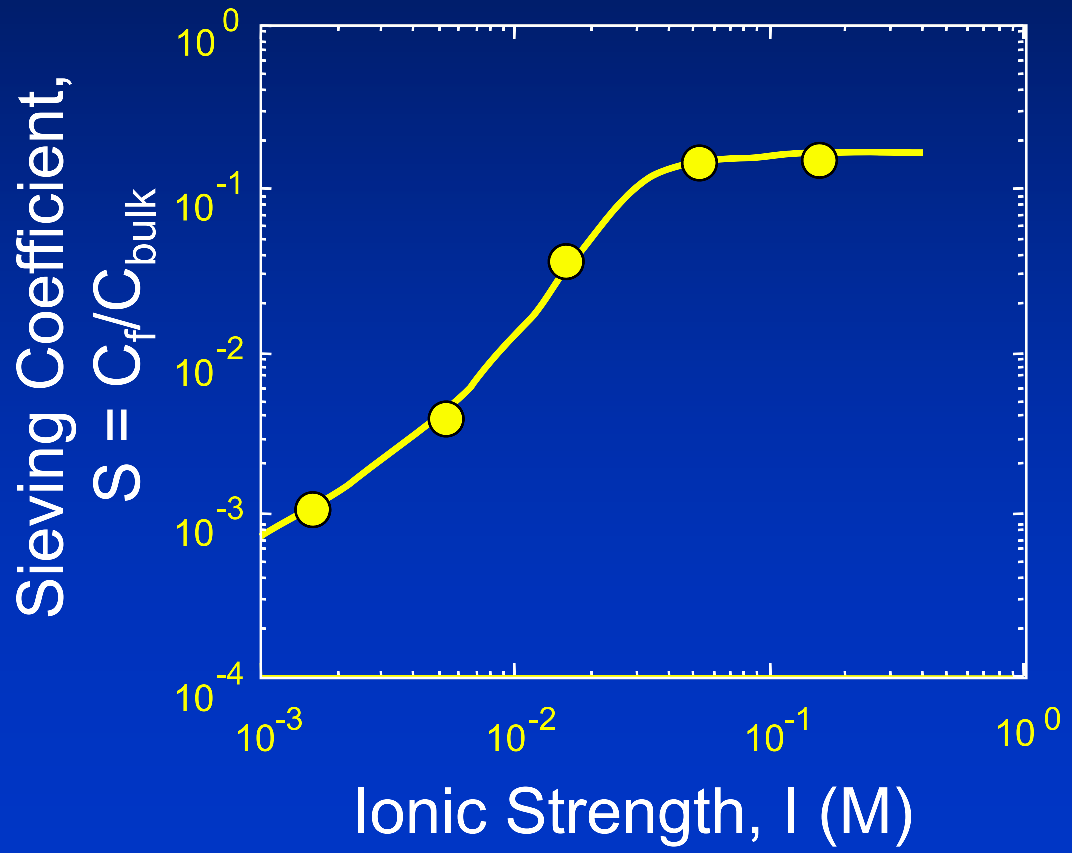
Base-Catalyzed Reaction



van Reis, R., USA patent WO 01/08792 A2 (2001)
Charged filtration membranes and uses therefor.

Electrostatic Interactions

Bovine Serum Albumin,
Biomax 100 kD Membrane, pH 7.0



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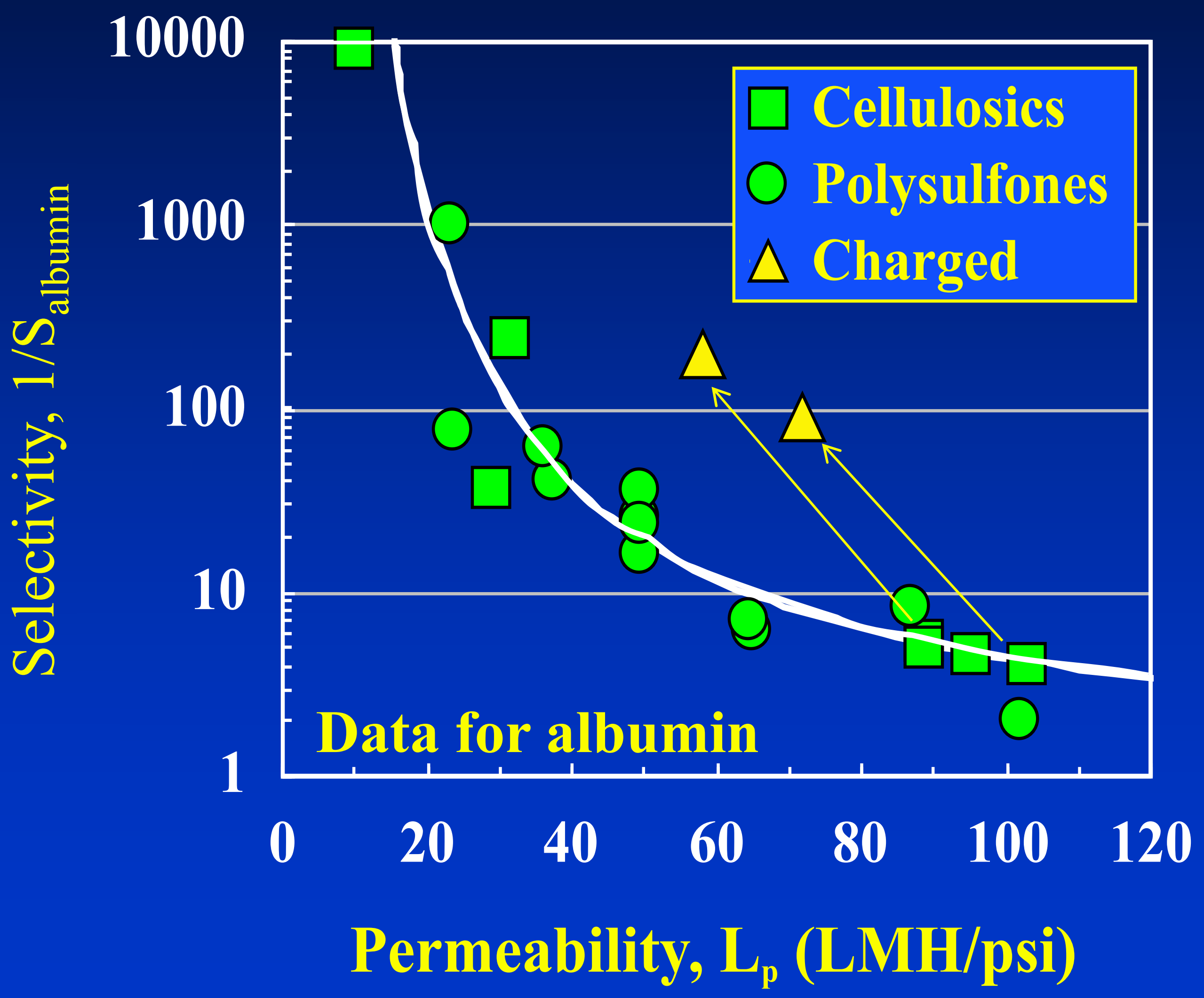
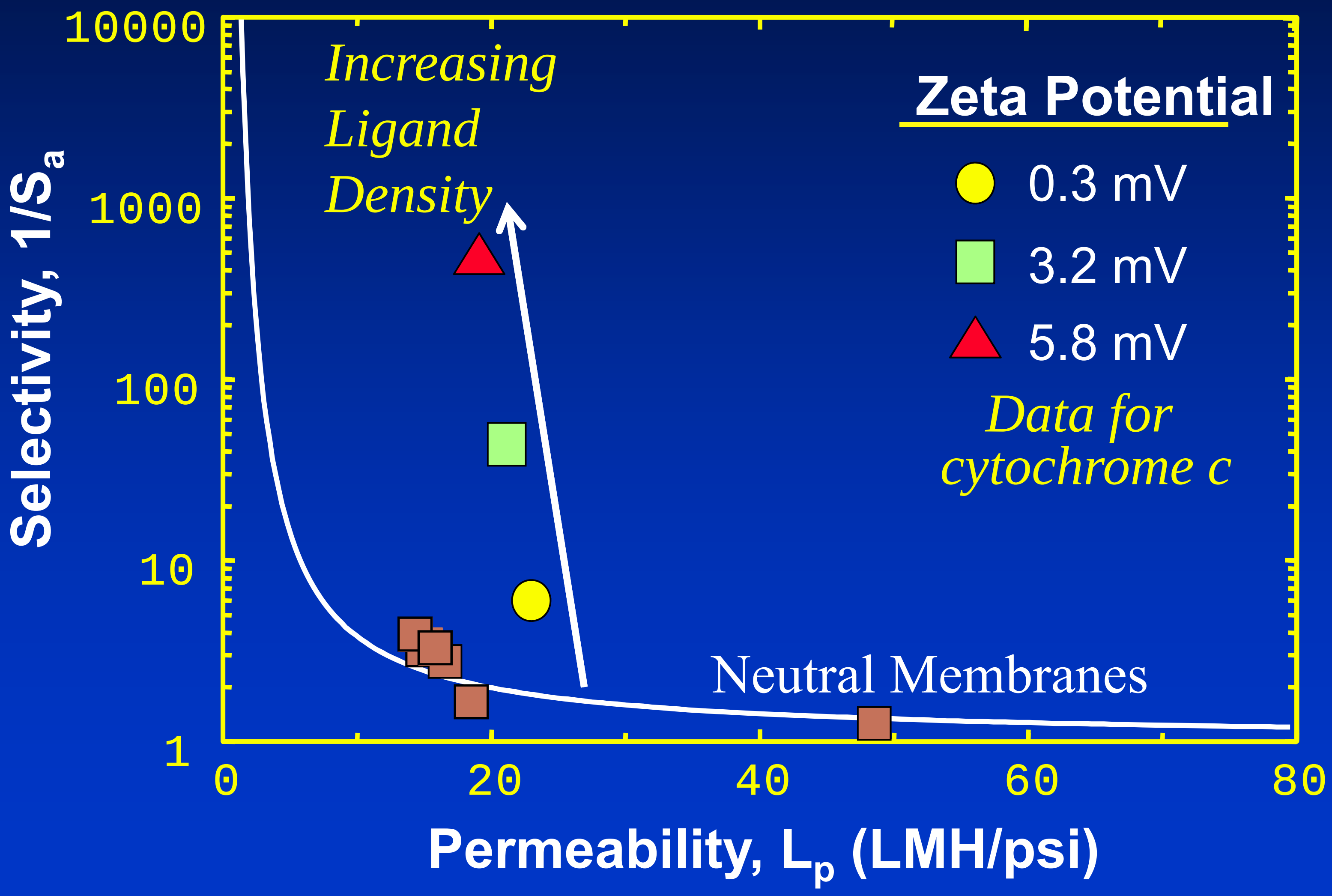
Permeability - Selectivity Tradeoff



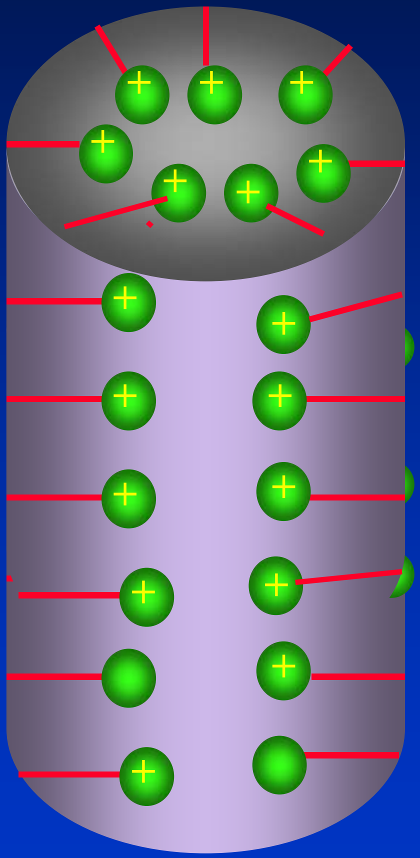
Charged UF Membranes

- **Nature of Charge Groups**
  - Weak versus strong acid / base
  - Detailed ligand and linkage chemistry
- **Location of Charge Groups**
  - Effect of spacer arm length / branching
- **Number of Charge Groups**
  - Surface charge density
  - Use of ligands with multiple charge groups

Effect of Ligand Density

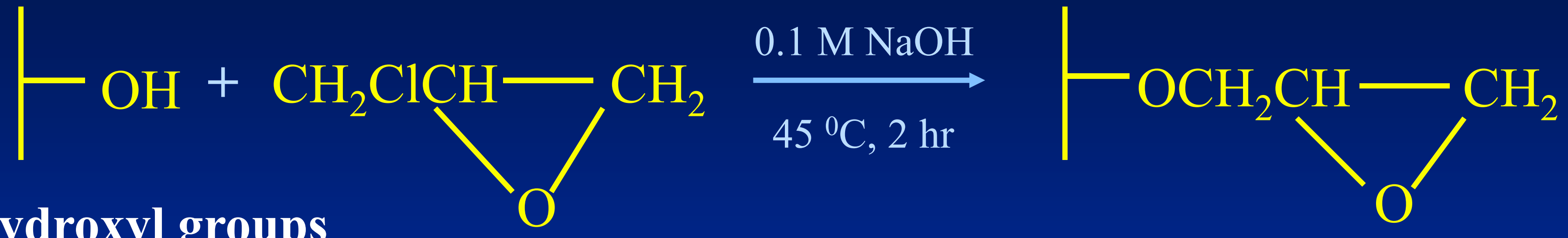


Spacer Arm Effects



- Longer spacer arms may increase electrostatic exclusion effects while maintaining high fluid flow rates (and solute removal)
- Possibility of using multiple charge groups along length of ligand to further enhance electrostatic exclusion

Epichlorohydrin Activation

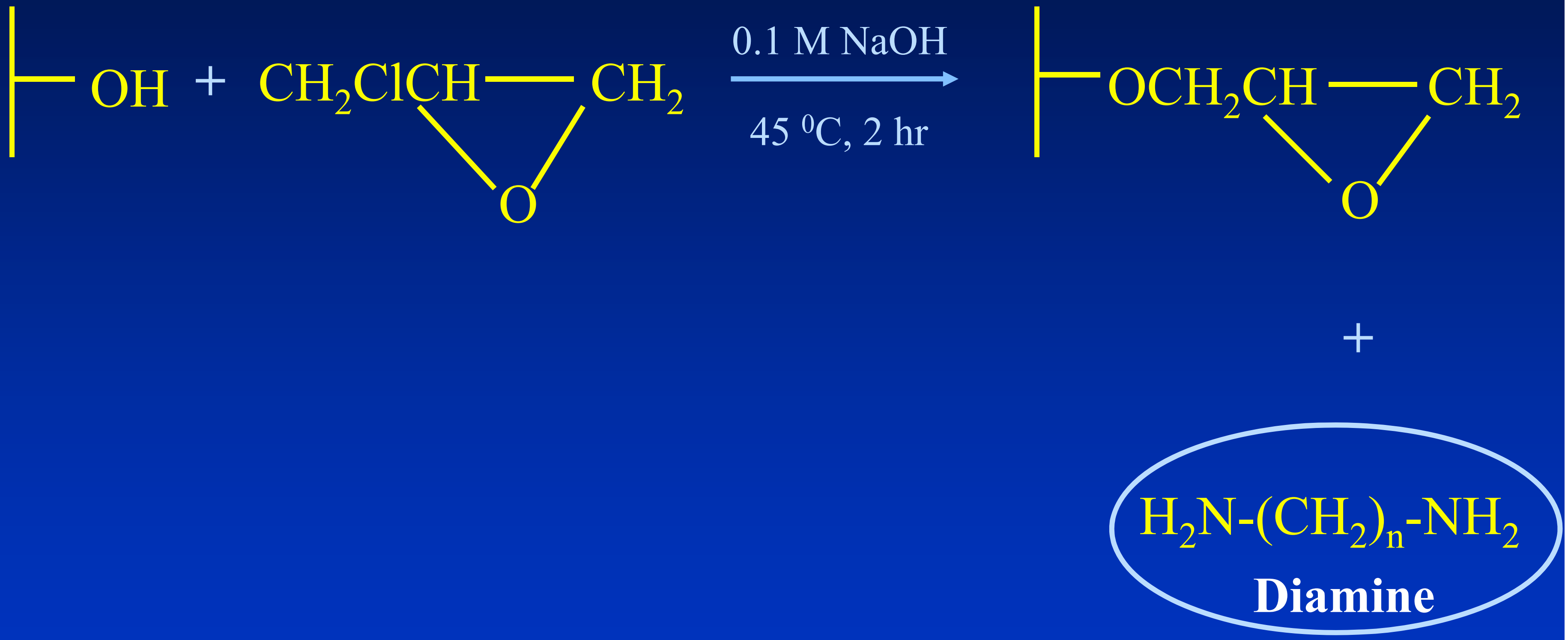


Hydroxyl groups on cellulose

Epichlorohydrin

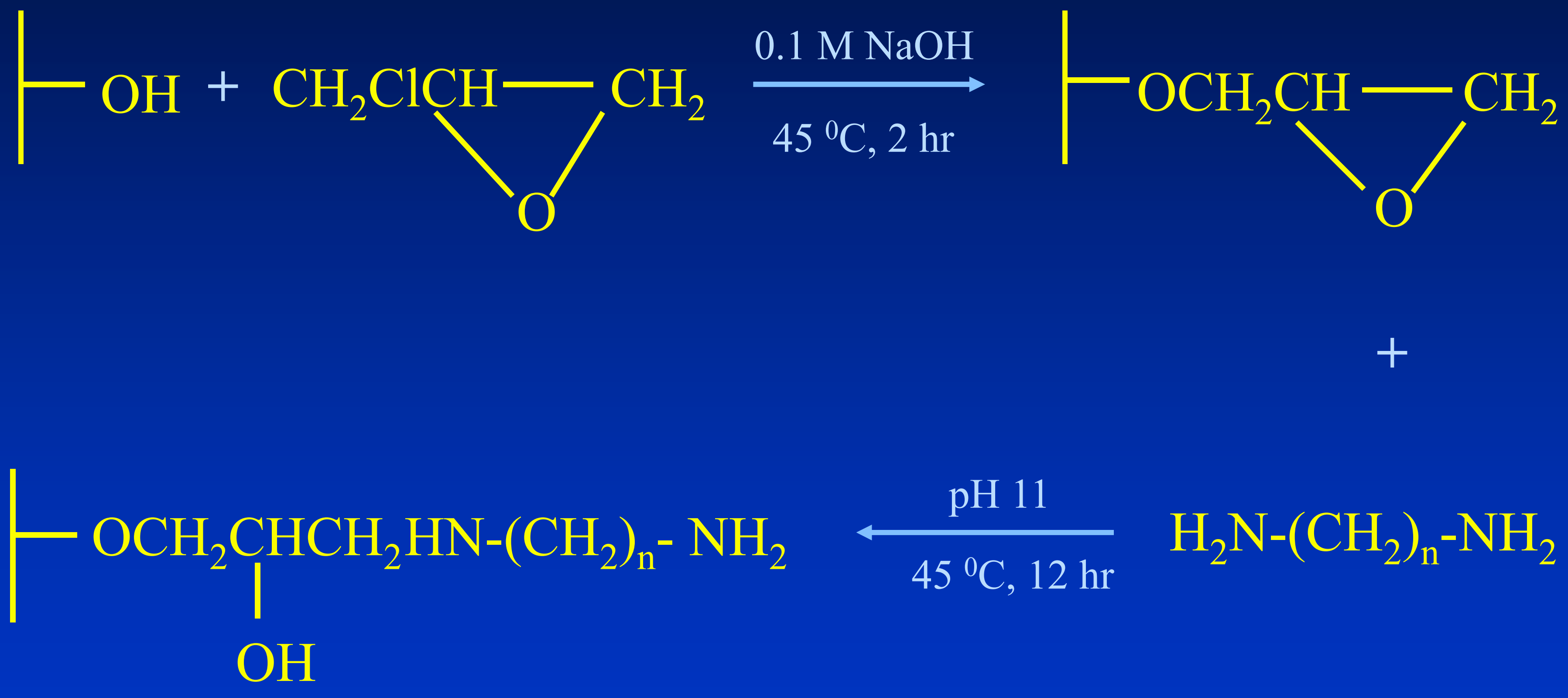
Activated Membrane

Diamine Addition



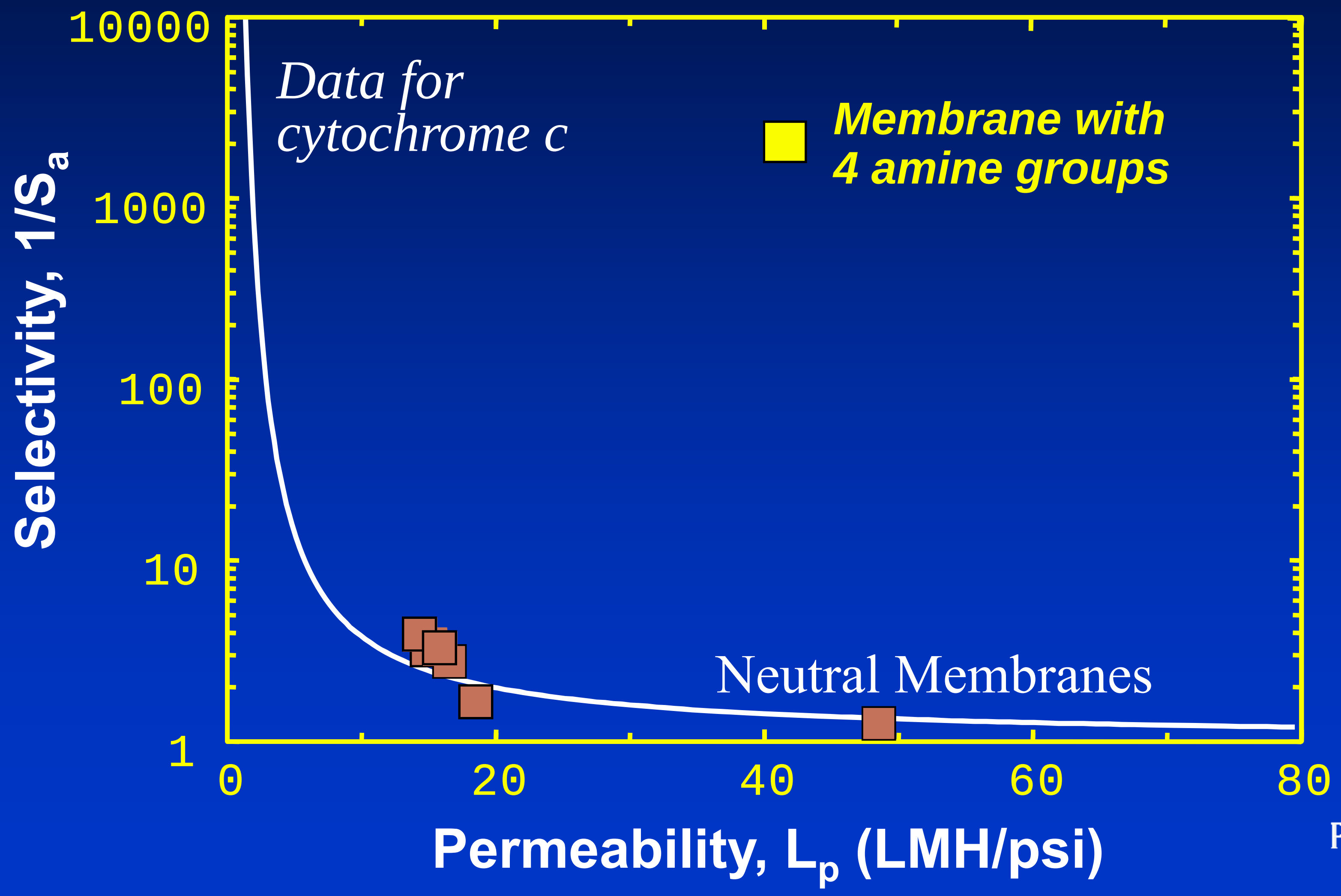
Variable n determines spacer length

Charge - Modified Membrane

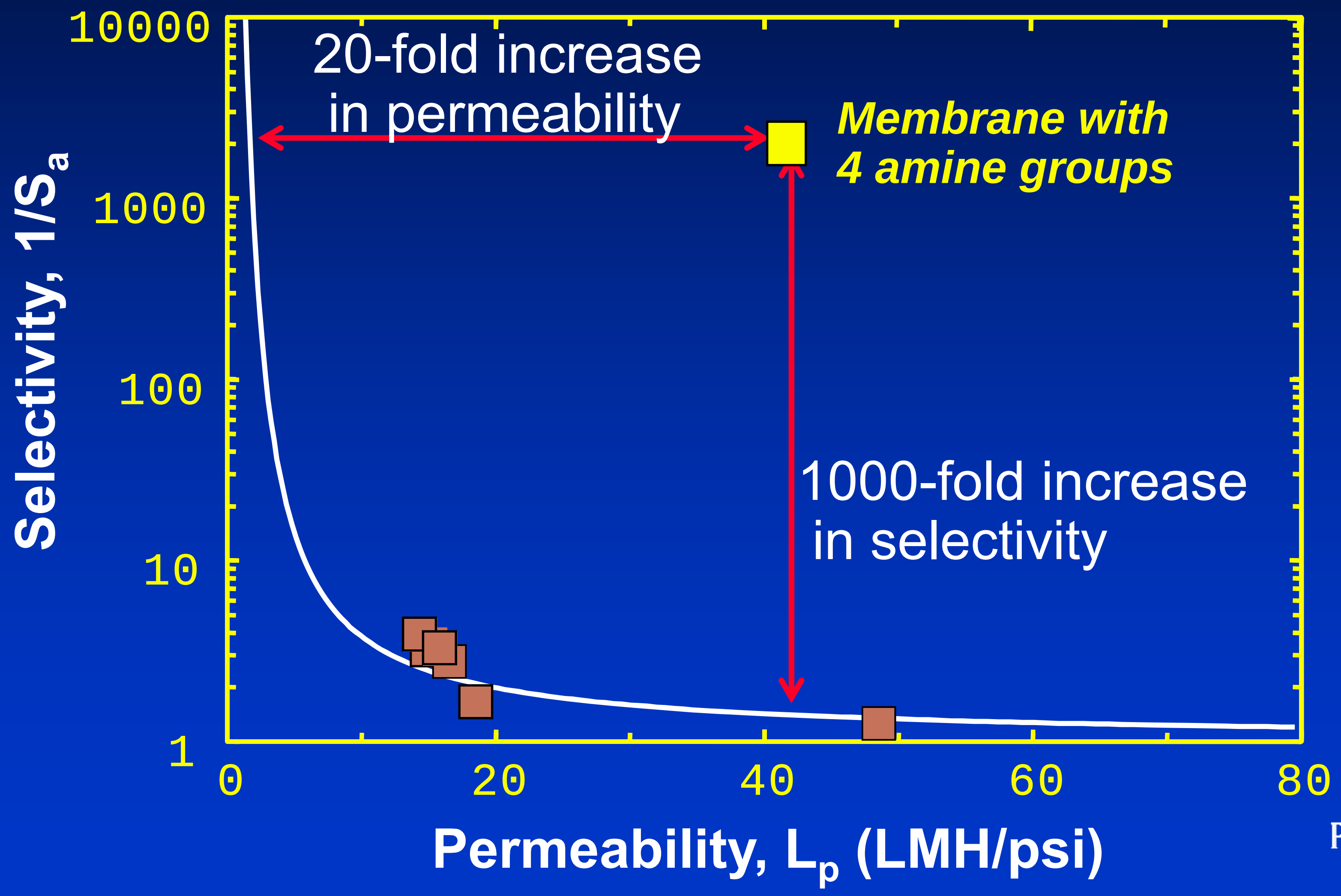


Charge-Modified Membrane

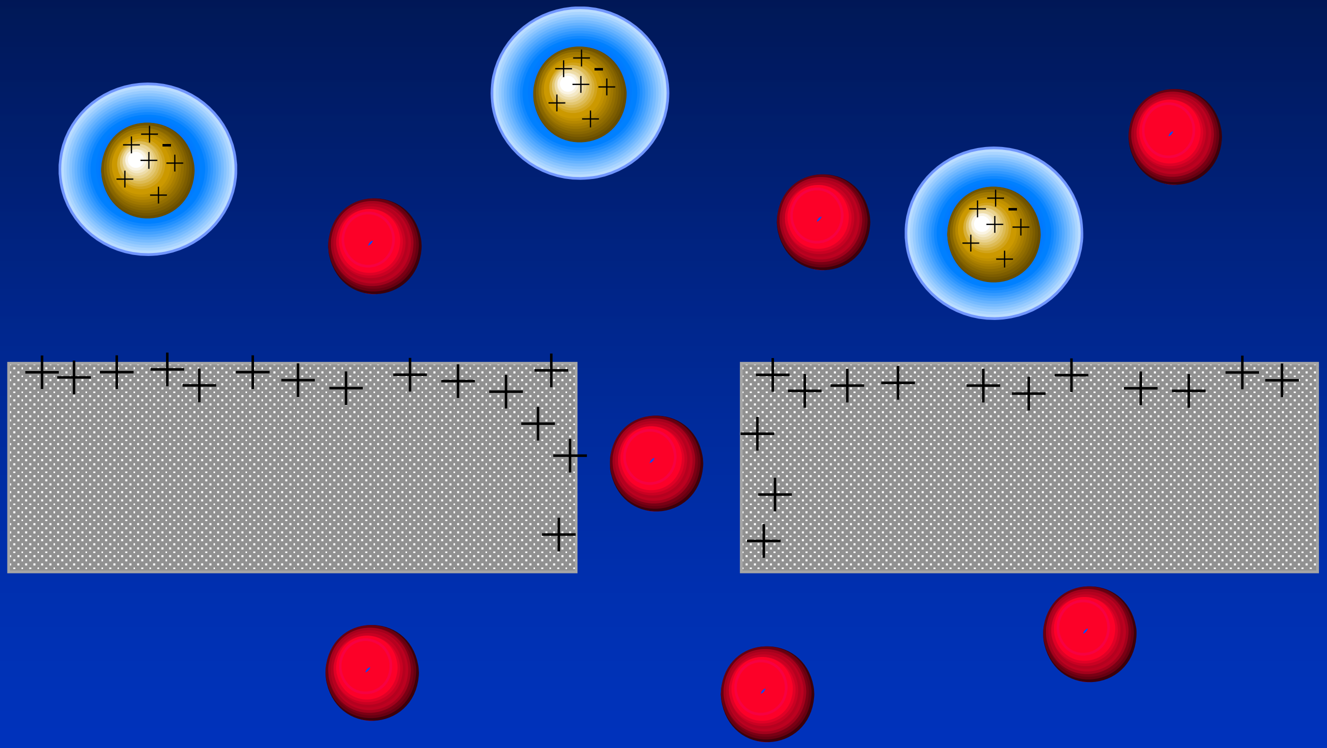
Multiple Charge Groups



Multiple Charge Groups



High Resolution Separations



- charged protein retained by electrostatic + steric interactions
- uncharged protein passes through membrane

Protein Variants

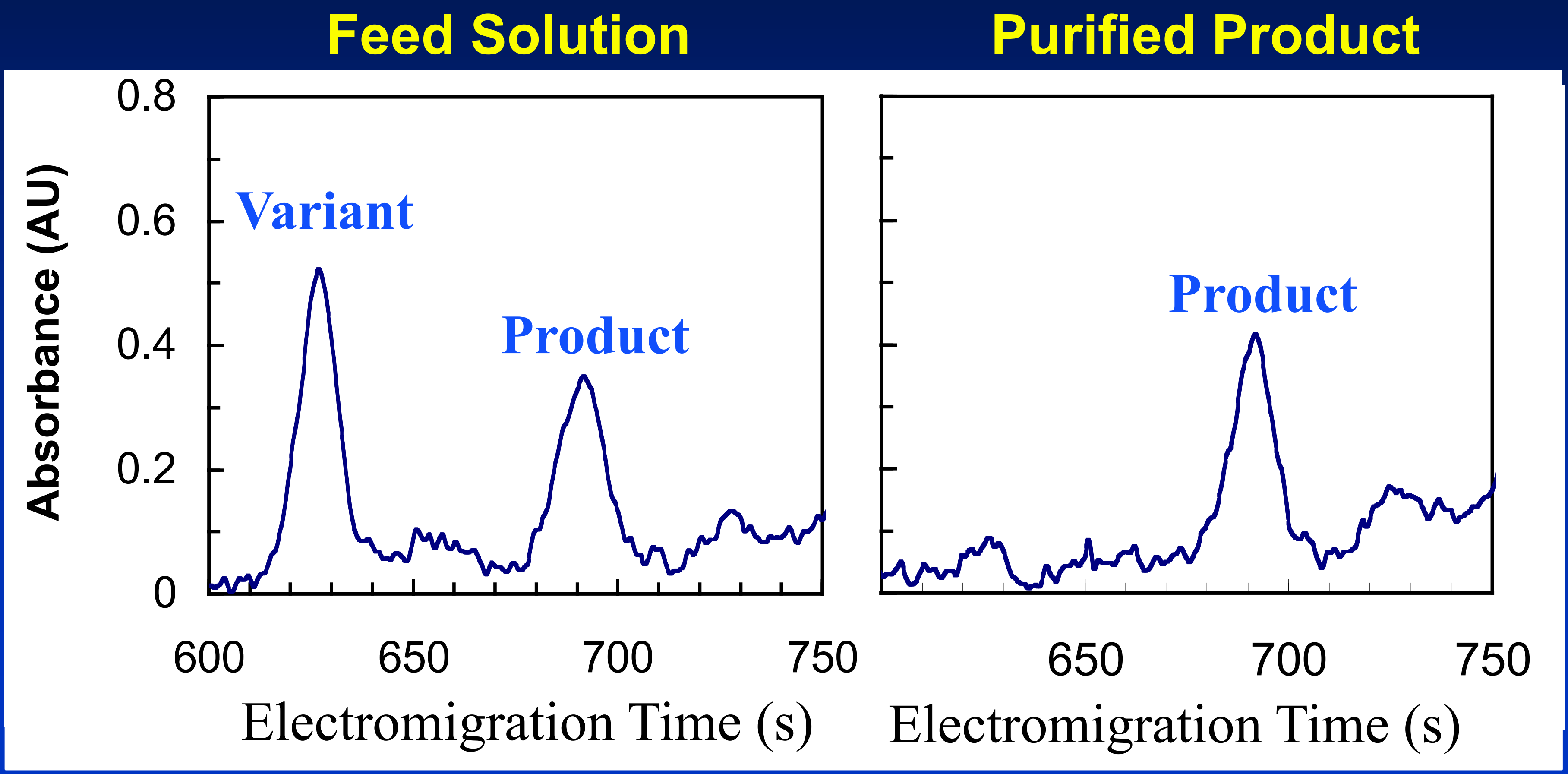
- A variety of post-translational modifications (deamidation, oxidation of methionine, carbamylation, etc) can occur during manufacture and processing
  - Resulting variants can have different activity and immunogenicity even though they differ at only one amino acid
- Variant removal is usually done as part of final purification (highly pure streams)

Myoglobin Sequence

GLSDGEWQQV LNVWGKVEAD
IAGHGQEVLI RLFTGHPETL
EKFDKFKHLK TEAEMKASED
LKKHGTVVLT ALGGILKKKG
HHEAELKPLA QSHATKHKIP
IKYLEFISDA IIHVLHSKHP
GDFGADAQGA MTKALELFRN
DIAAKYKELG FQG

Chemical modification of single lysine amino acid

Separation of Myoglobin Variants



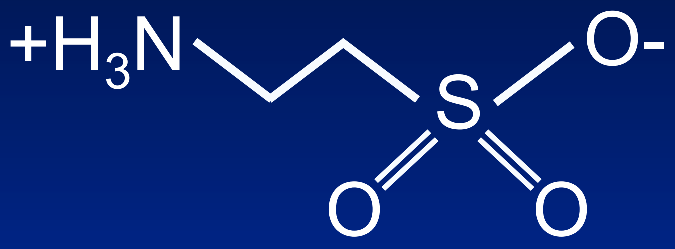
Ebersold and Zydney, Biotech Prog, 20, 543 (2004)

Zwitterionic Membranes

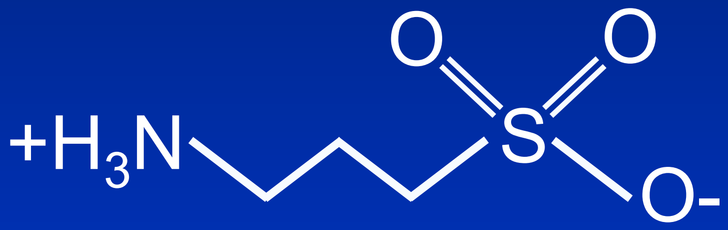
- Charged membranes provide dramatic improvements in permeability-selectivity tradeoff, but fouling can be an issue, particularly with oppositely charged species
- Zwitterionic surfaces are highly resistant to protein adsorption
  - Cell membranes contain zwitterionic phospholipids
  - Highly biocompatible materials (Whitesides et al.)
  - Limited studies with membranes (Jiang et al.)

Zwitterionic Ligands

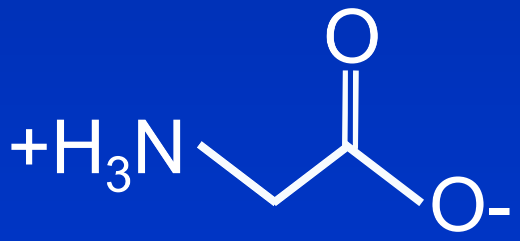
- Taurine:



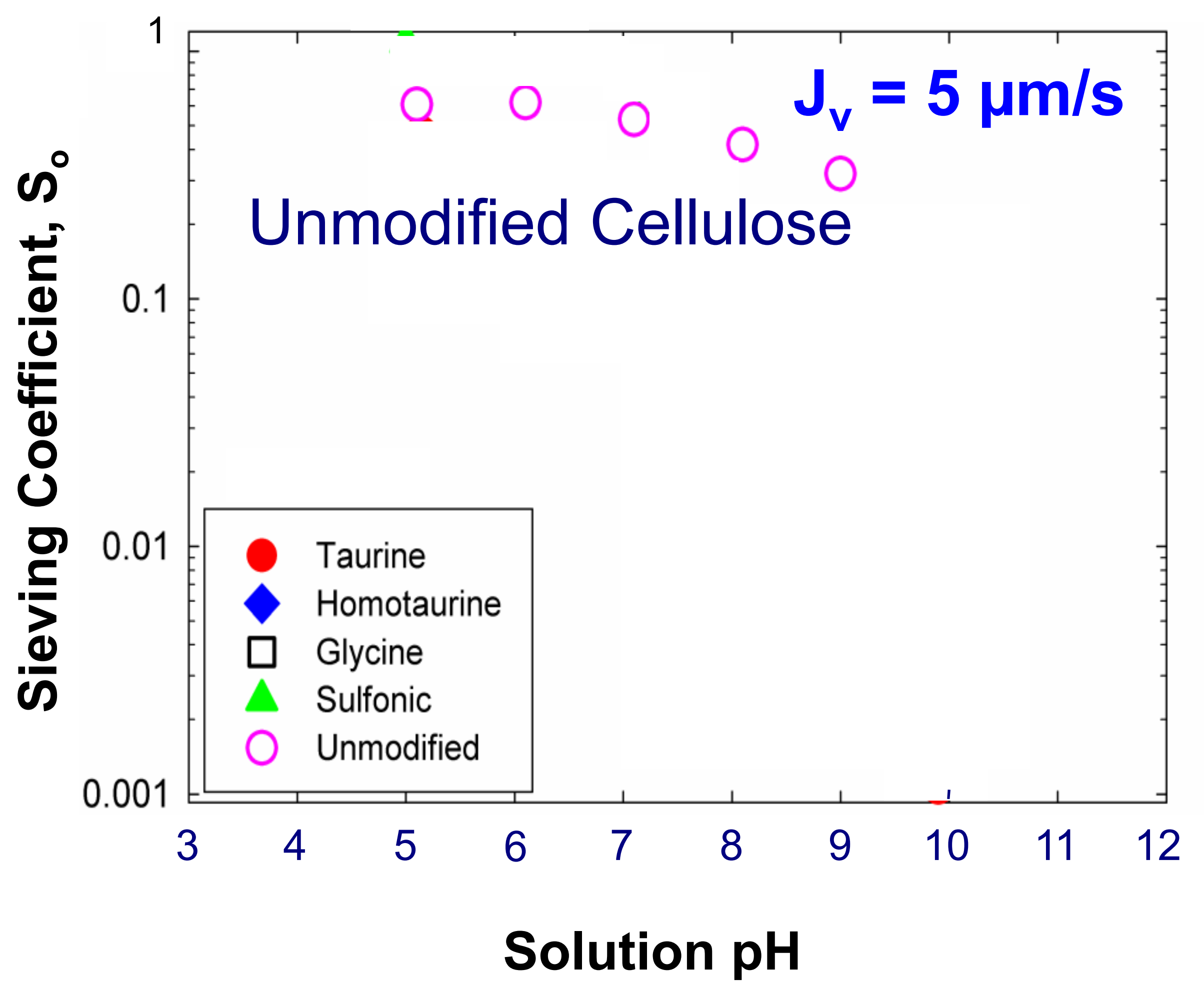
- Homotaurine:



- Glycine:



Myoglobin (pI ≈ 7) Sieving



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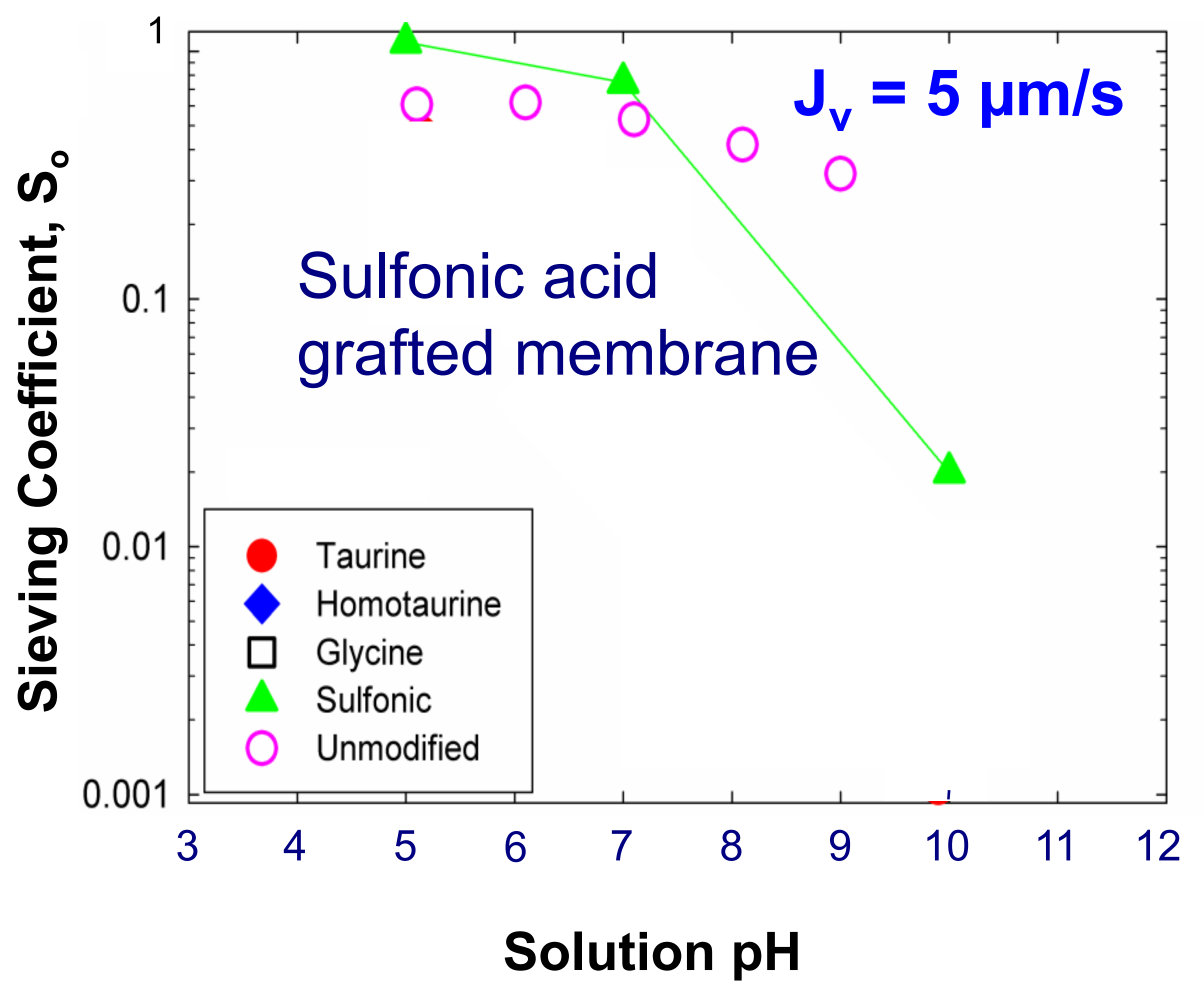

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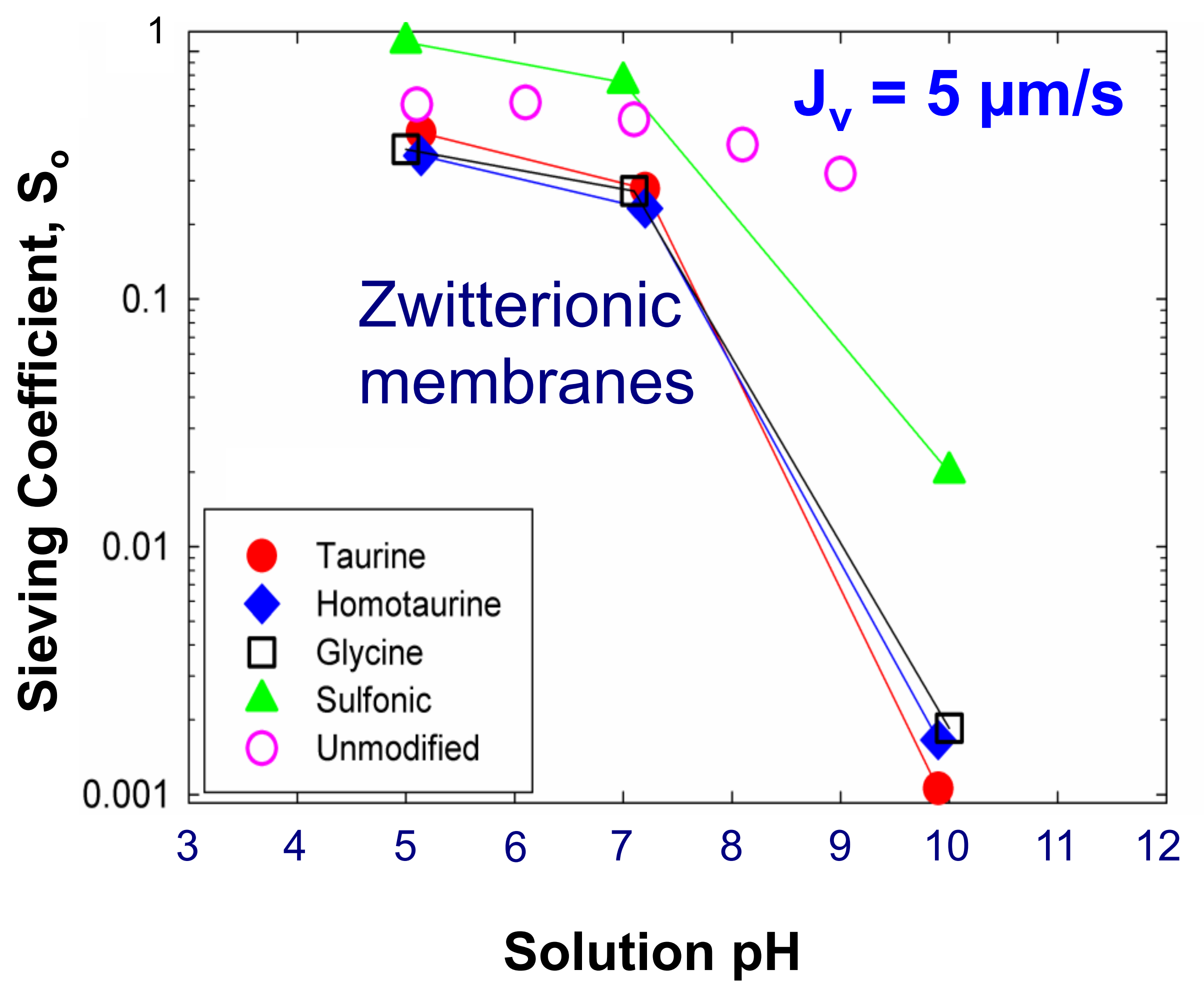
Myoglobin (pI ≈ 7) Sieving



No fouling observed even when protein and membrane were oppositely charged

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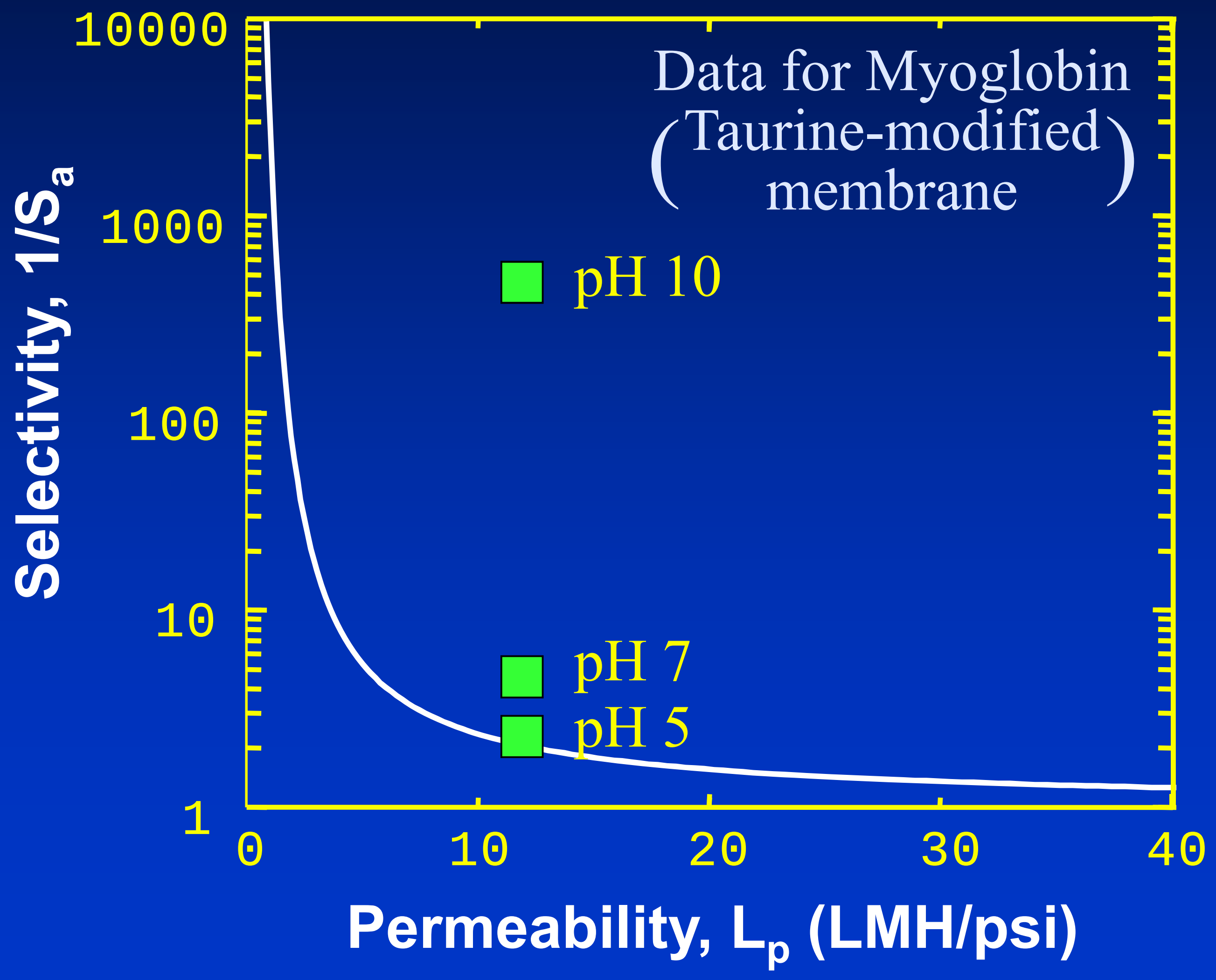
Permeability - Selectivity Plot



Strong pH dependence due to variation in effective charge of zwitterionic membrane

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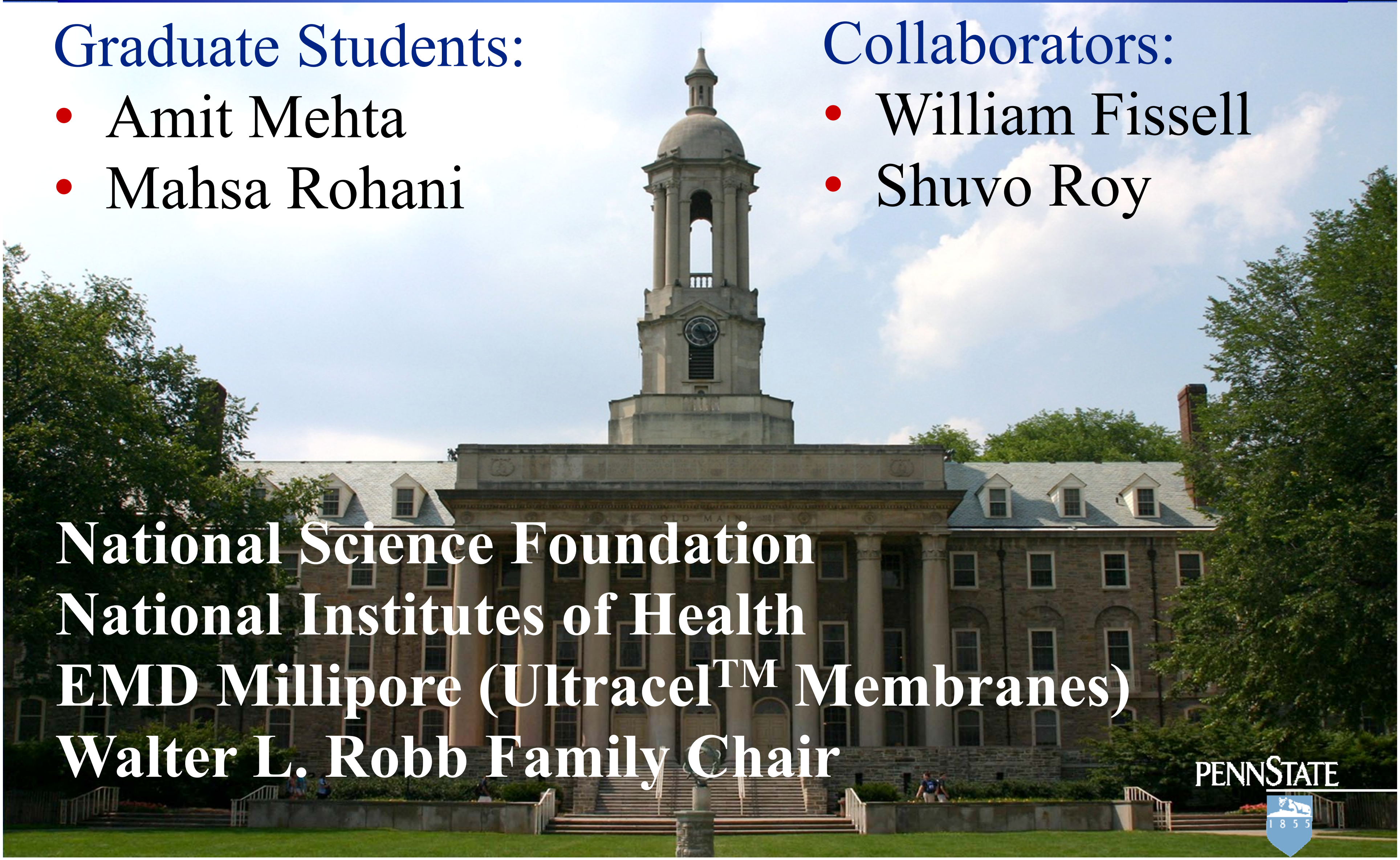
Summary

- Permeability - selectivity trade-off provides framework for analysis of existing UF membranes and evaluation of new membranes
- Significant opportunities for membrane development:
  - Slit-shaped pores (nanoporous silicon)
  - Charge-modified membranes (electrostatic interactions)
  - Zwitterionic (low fouling) membranes

Acknowledgements



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- Mahsa Rohani

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