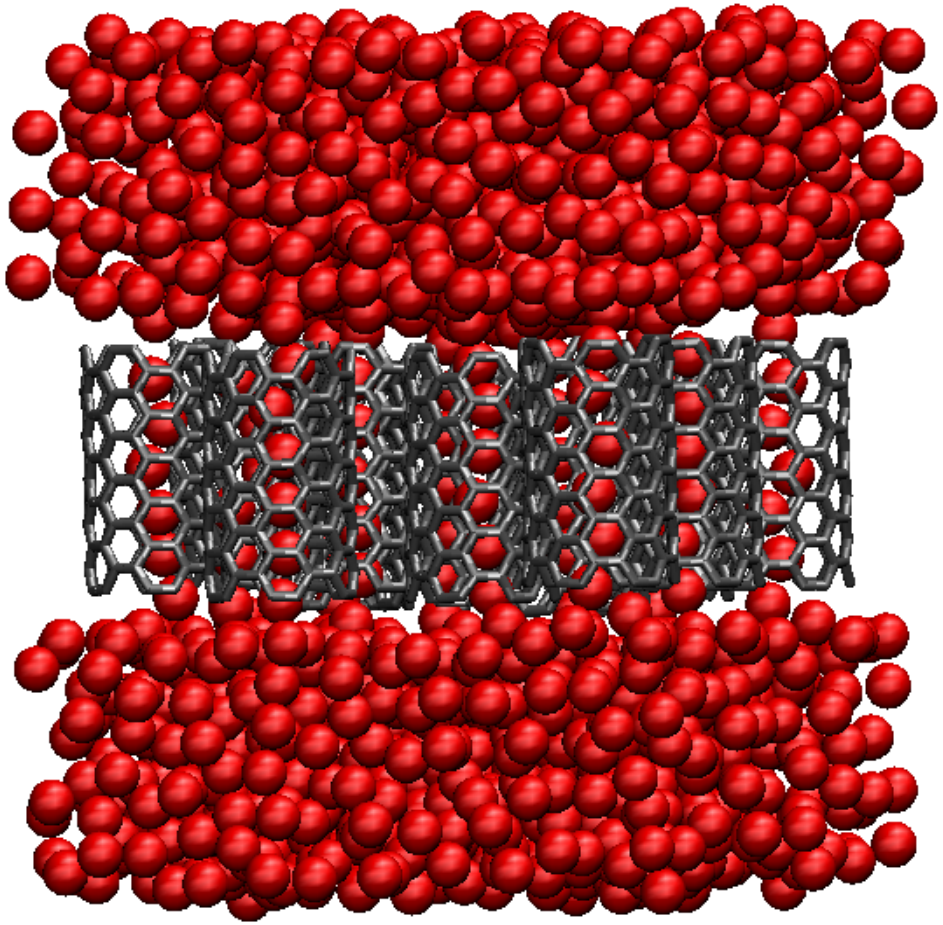
Molecular Dynamics Simulation of Membrane Channels

Part III. Nanotubes
Theory, Methodology

Summer School on Theoretical and Computational Biophysics
June 2003, University of Illinois at Urbana-Champaign
http://www.ks.uiuc.edu/training/SumSchool03/

Carbon Nanotubes
Hydrophobic channels - Perfect Models for Membrane Water Channels

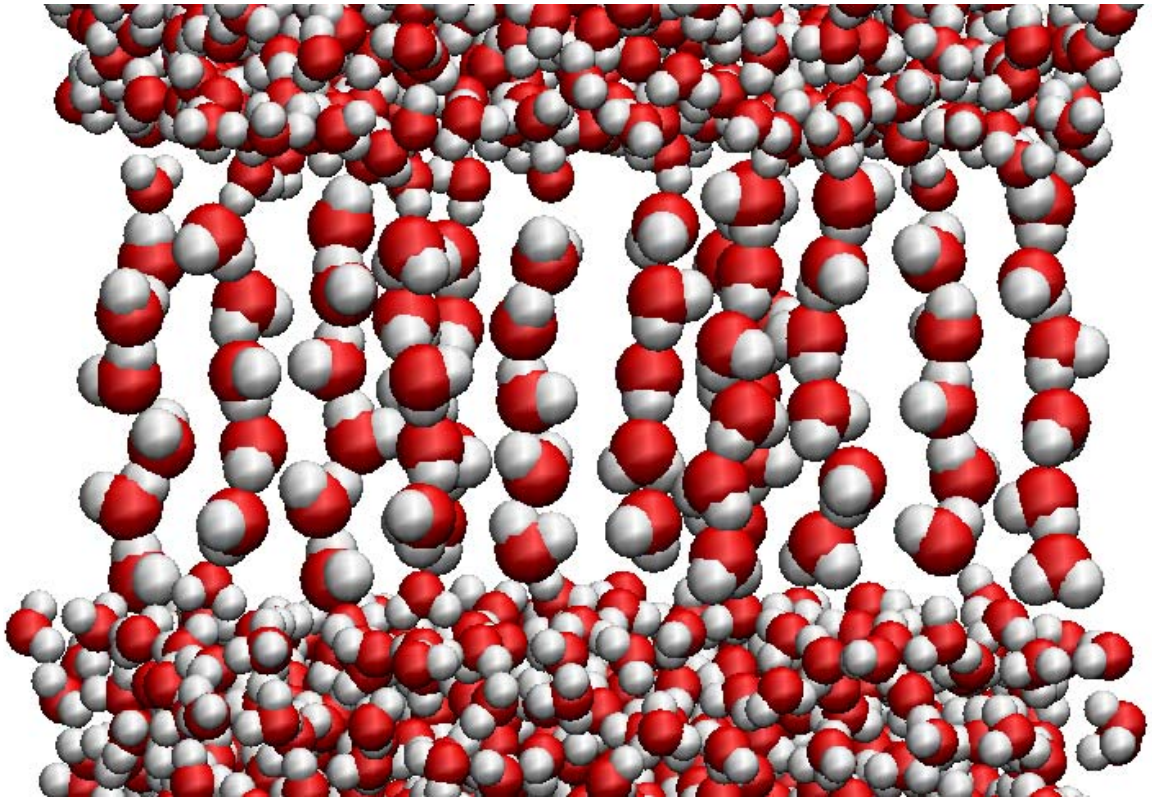


A balance between the size and hydrophobicity

Carbon Nanotubes
Hydrophobic channels - Perfect Models for Membrane Water Channels

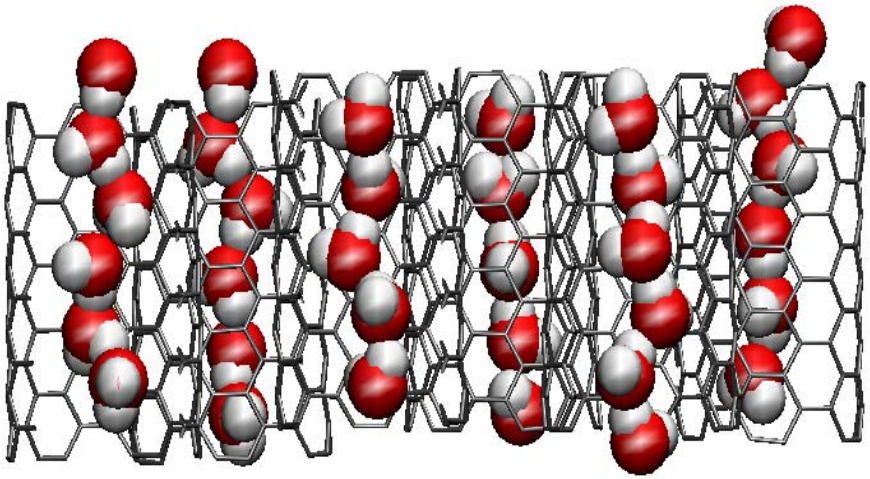
- Much better statistics
- No need for membrane and lipid molecules

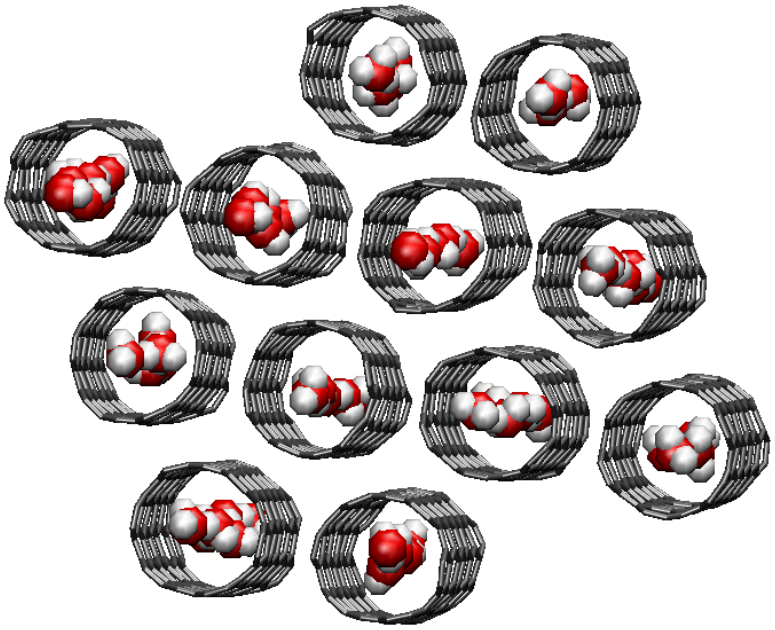
Carbon Nanotubes
Hydrophobic channels - Perfect Models for Membrane Water Channels



- Much better statistics
- No need for membrane and lipid molecules

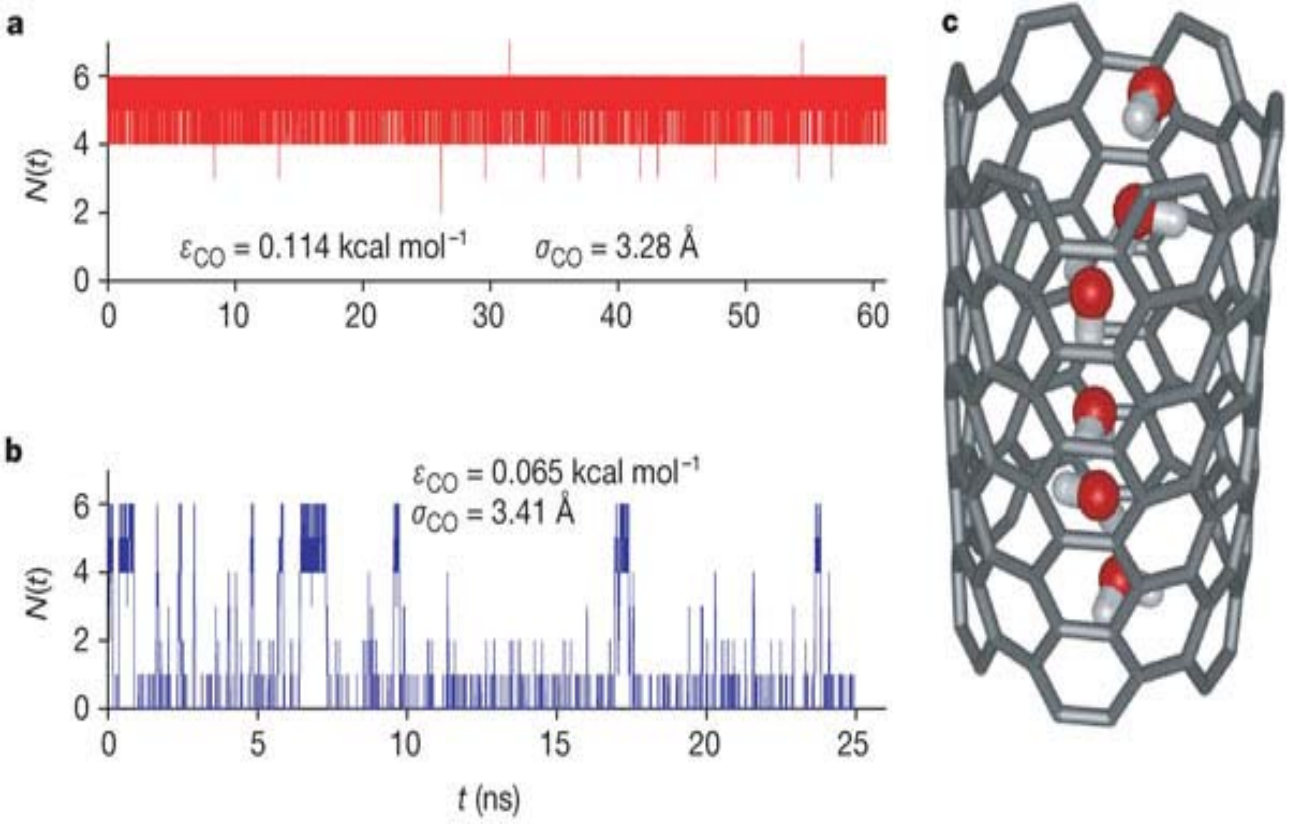
Water Single-files in Carbon Nanotubes





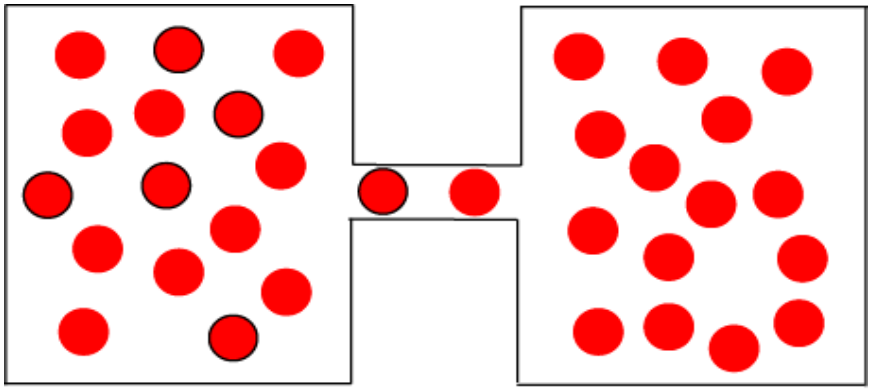
Water files form polarized chains in nanotubes

Water-Nanotube Interaction can be Easily Modified



Hummer, et. al., Nature, 414: 188-190, 2001

Calculation of Diffusion Permeability from MD

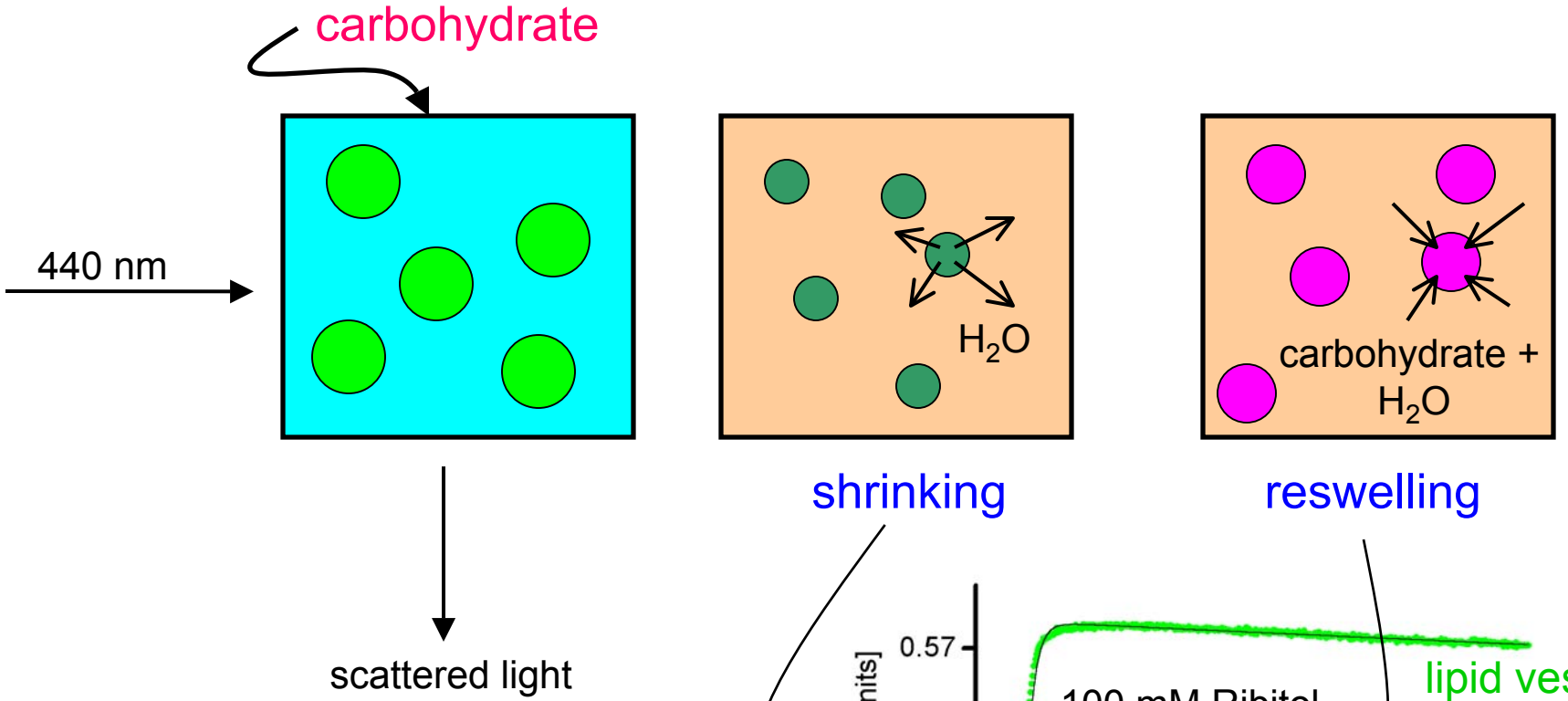


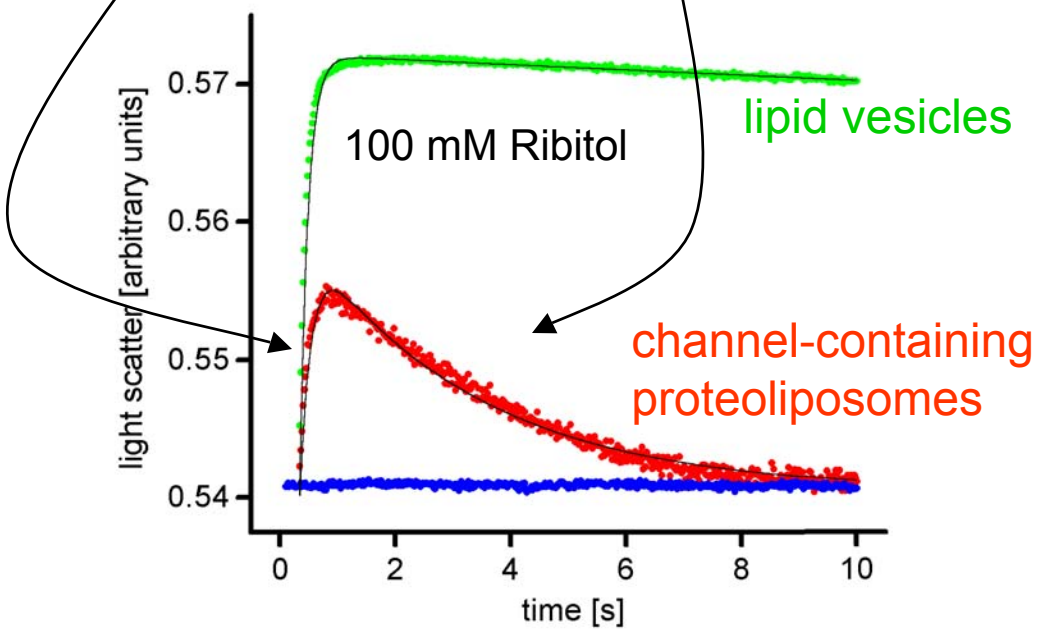
Φ_0: number of water molecules crossing the channel from the left to the right in unit time

$$p_d = \frac{V_w}{N_A}\Phi_0$$

Φ_0 can be directly obtained through equilibrium MD simulation by counting "full permeation events"

Liposome Swelling Assay





GlpF is an aquaglyecroporin: both water and carbohydrate can be transported by GlpF.

Chemical Potential of Water

$$\mu_w = \mu_w^o + RT \ln X_w + PV_w$$

$X_w = 1 \Rightarrow \ln X_w = 0$

μ_w^o : standard chemical potential of water

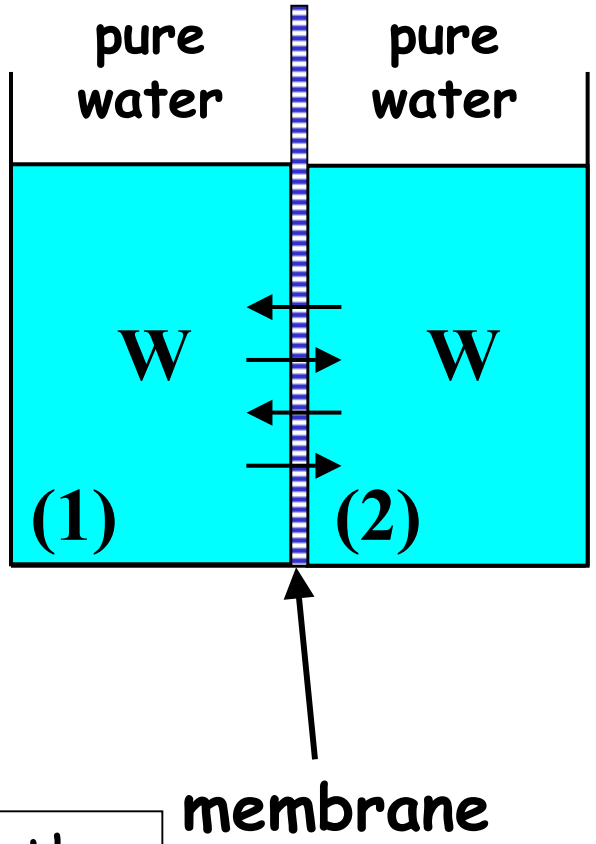
X_w : molar fraction of water

R : the gas constant

T : temperature

P : pressure

V_w : molar volume of water



Water flow in either direction is the same, i.e., no net flow of water.

Solutes Decrease the Chemical Potential of Water

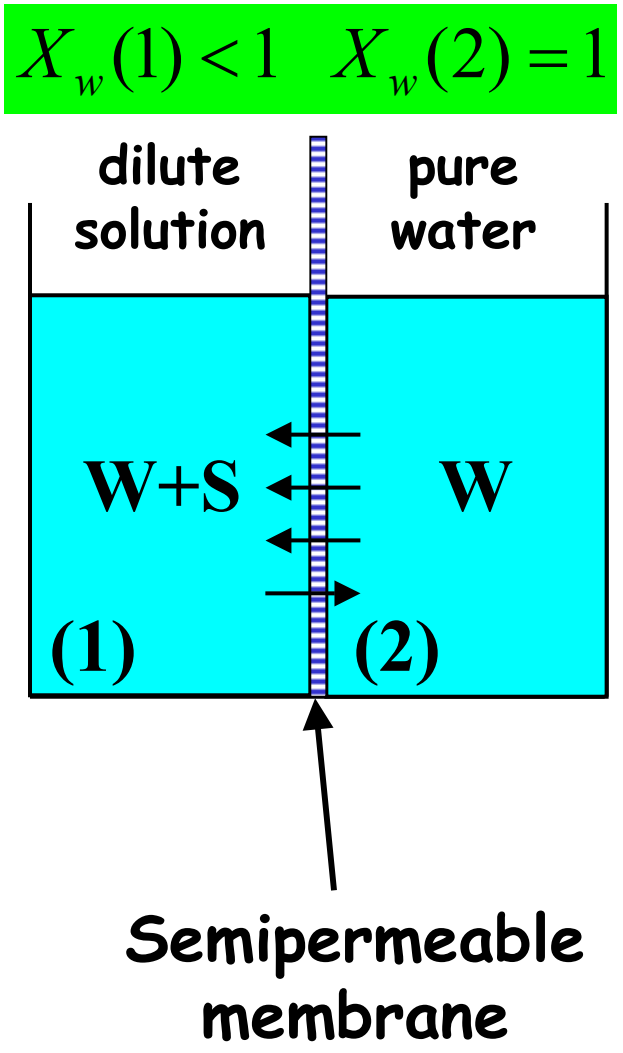
$$\mu_w = \mu_w^o + RT \ln X_w + PV_w$$

Addition of an impermeable solute to one compartment drives the system out of equilibrium.

$$RT \ln X_w(1) < RT \ln X_w(2)$$

$$\Rightarrow \mu_w(1) < \mu_w(2)$$

Water establishes a net flow from compartment (2) to compartment (1).



Establishment of Osmotic Equilibrium

$$@\text{equilibrium}: \mu_w(1) = \mu_w(2)$$

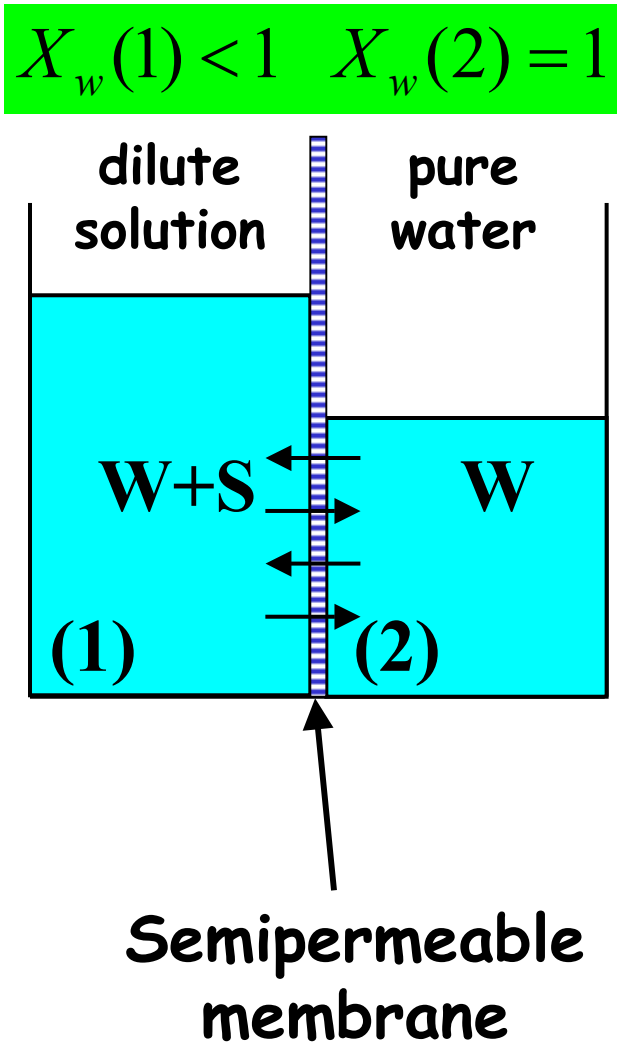
At equilibrium, the chemical potential of any species is the same at every point in the system to which it has access.

$$\mu_w^o(1) + RT \ln X_w(1) + P(1)V_w =$$

$$\mu_w^o(2) + RT \ln X_w(2) + P(2)V_w$$

$$RT \ln X_w(1) + P(1)V_w = P(2)V_w$$

$$\Delta \boldsymbol{PV_w} = -\boldsymbol{RT} \ln \boldsymbol{X_w}(1)$$



Establishment of an Osmotic Equilibrium

$$\Delta \boldsymbol{PV}_{\boldsymbol{w}} = -\boldsymbol{RT} \ln \boldsymbol{X}_{\boldsymbol{w}}(1)$$

Solute molar fraction in physiological (dilute) solutions is much smaller than water molar fraction.

$$X_w + X_s = 1 \;;\; X_s << 1$$

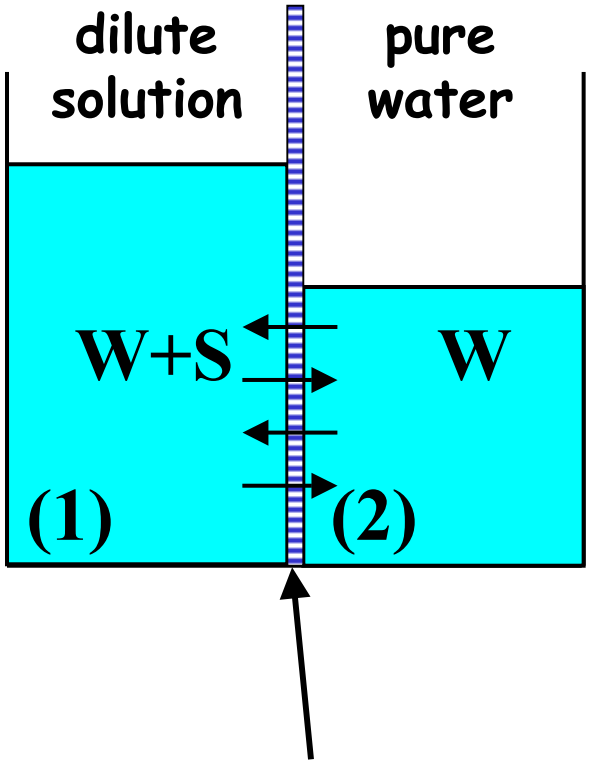
$$\Rightarrow \ln X_w = \ln(1 - X_s) \cong -X_s$$

$$\Delta \boldsymbol{PV}_{\boldsymbol{w}} = \boldsymbol{RTX}_{\boldsymbol{s}}$$

$$\Rightarrow \prod = \Delta P = \frac{RT}{V_w} X_s$$

Osmotic pressure

$X_w(1) < 1 \quad X_w(2) = 1$



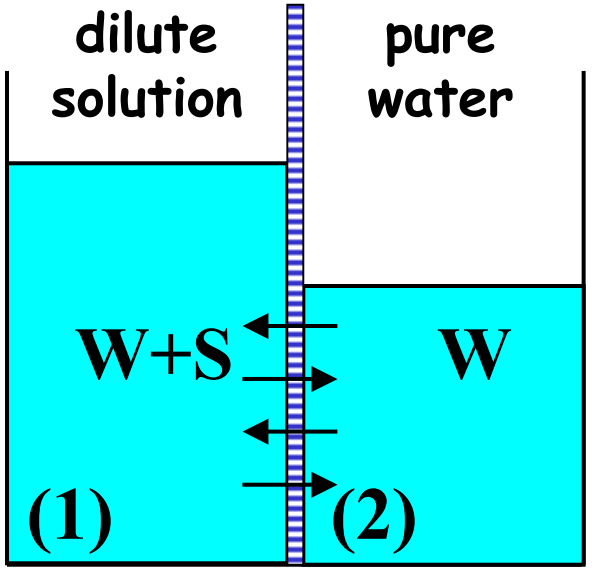
Semipermeable membrane

Establishment of an Osmotic Equilibrium

$$\prod = \Delta P = \frac{RT}{V_w} X_s$$

$X_w(1) < 1 \quad X_w(2) = 1$

Solute concentration (~0.1M) in physiological (dilute) solutions is much smaller than water concentration (55M).



$$X_s = \frac{n_s}{n_s + n_w} \approx \frac{n_s}{n_w} = \frac{n_s}{n_w}\frac{V_w}{V_w}$$

$n_s << n_w$

$$= \frac{n_s}{V_{tot}} V_w = C_s V_w$$

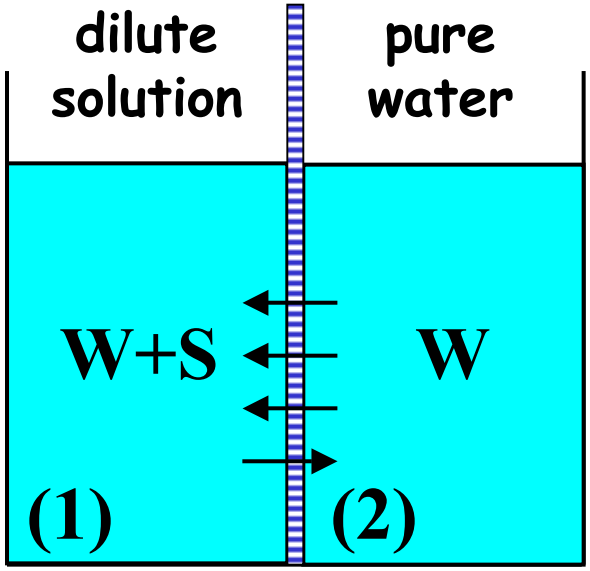
$$\Pi = \Delta P = \frac{RT}{V_w} C_s V_w = RTC_s$$

$$\Delta\Pi = \Delta P = RT\Delta C_s$$

Osmotic Flow of Water

@equilibrium: $\Delta P - \Delta\Pi = 0$

Net flow is zero



$$J_v \sim \Delta P - \Delta\Pi$$

$$J_v = L_p(\Delta P - \Delta\Pi)$$

Volume flux of water

Hydraulic permeability

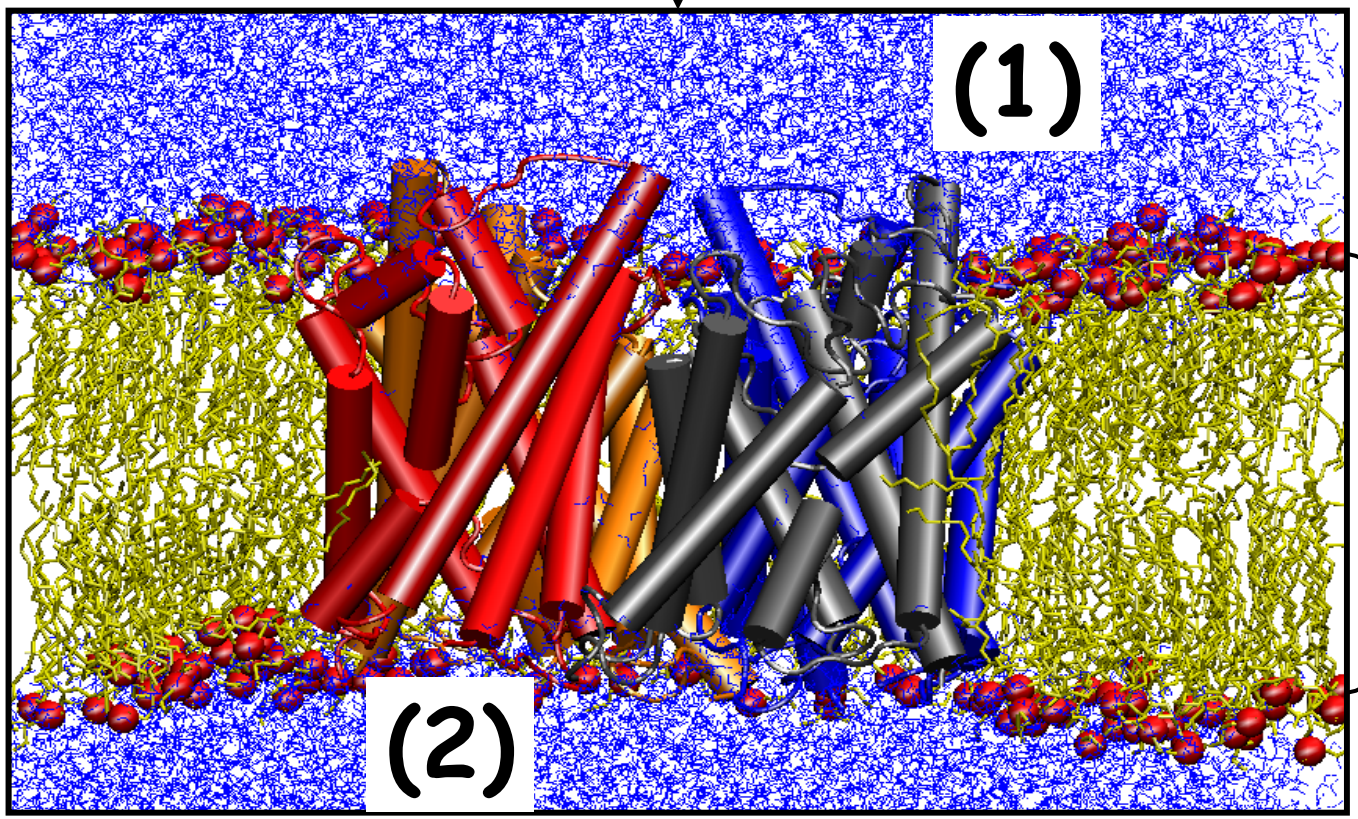
Osmotic permeability

Molar flux of water

$$\Phi_w = \frac{J_v}{V_w} = P_f A\left(\frac{\Delta P}{RT} - \Delta C_s\right)$$

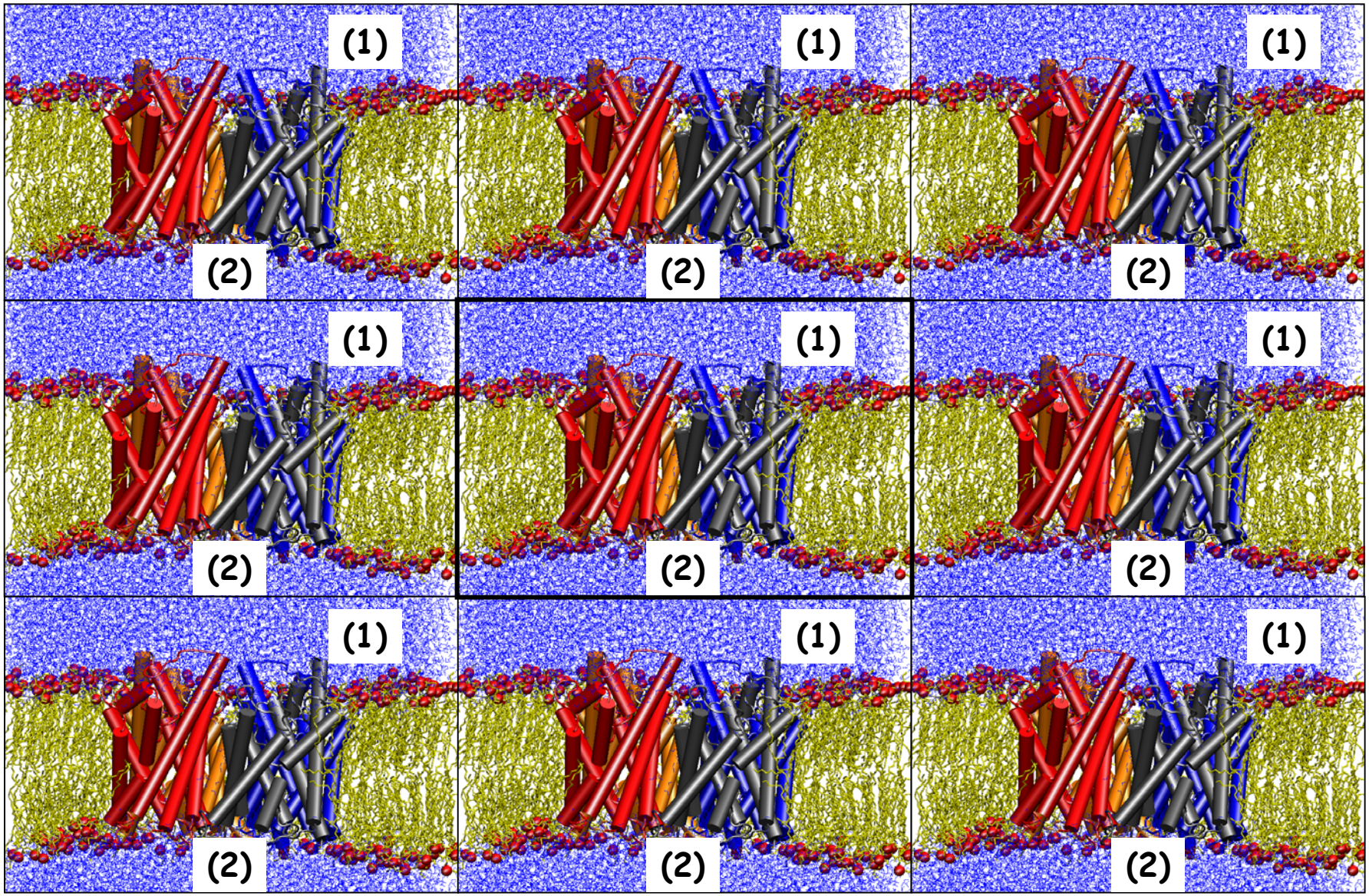
Simulation of osmotic pressure induced water transport may be done by adding salt to one side of the membrane.

$NaCl \rightarrow Na^+ + Cl^-$



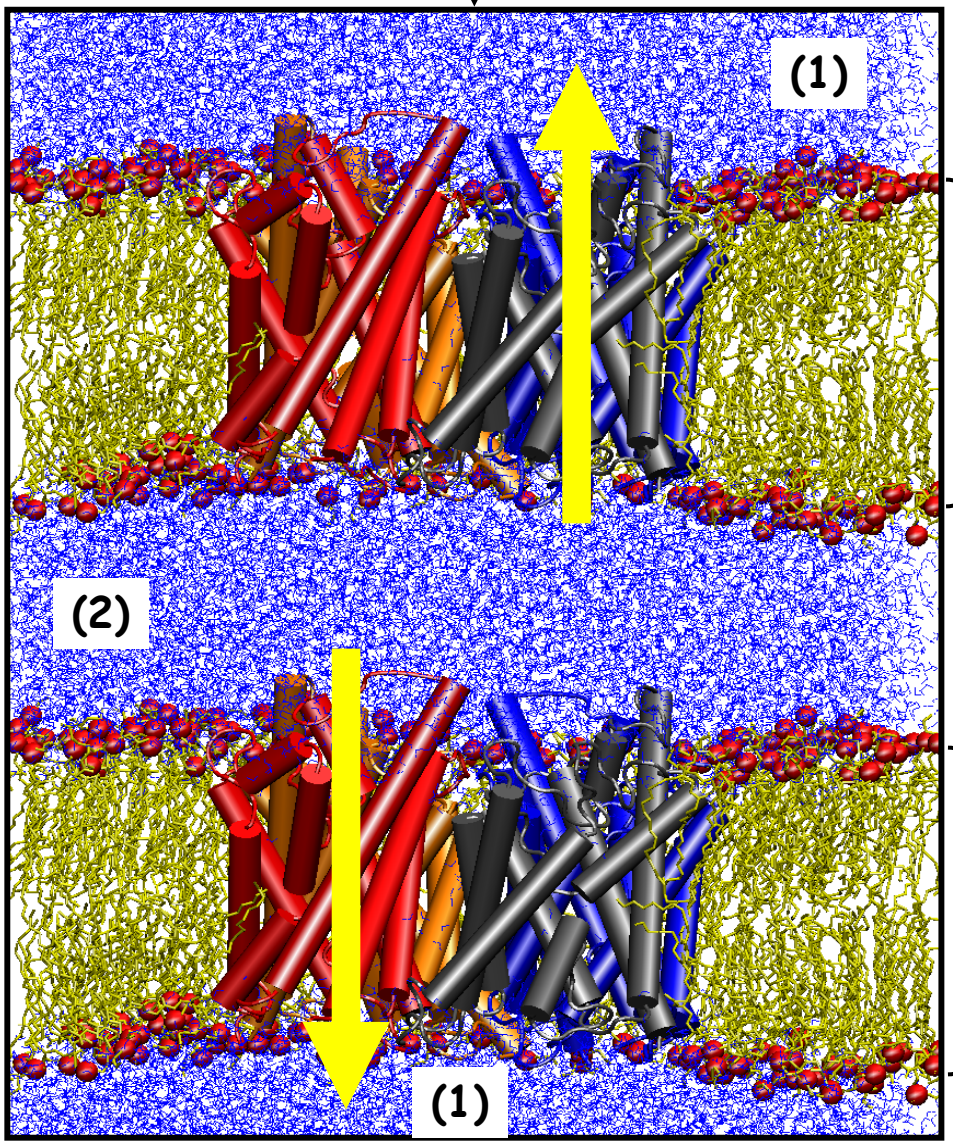
There is a small problem with this setup!

Problem: The solvents on the two sides of a membrane in a conventional periodic system are connected.



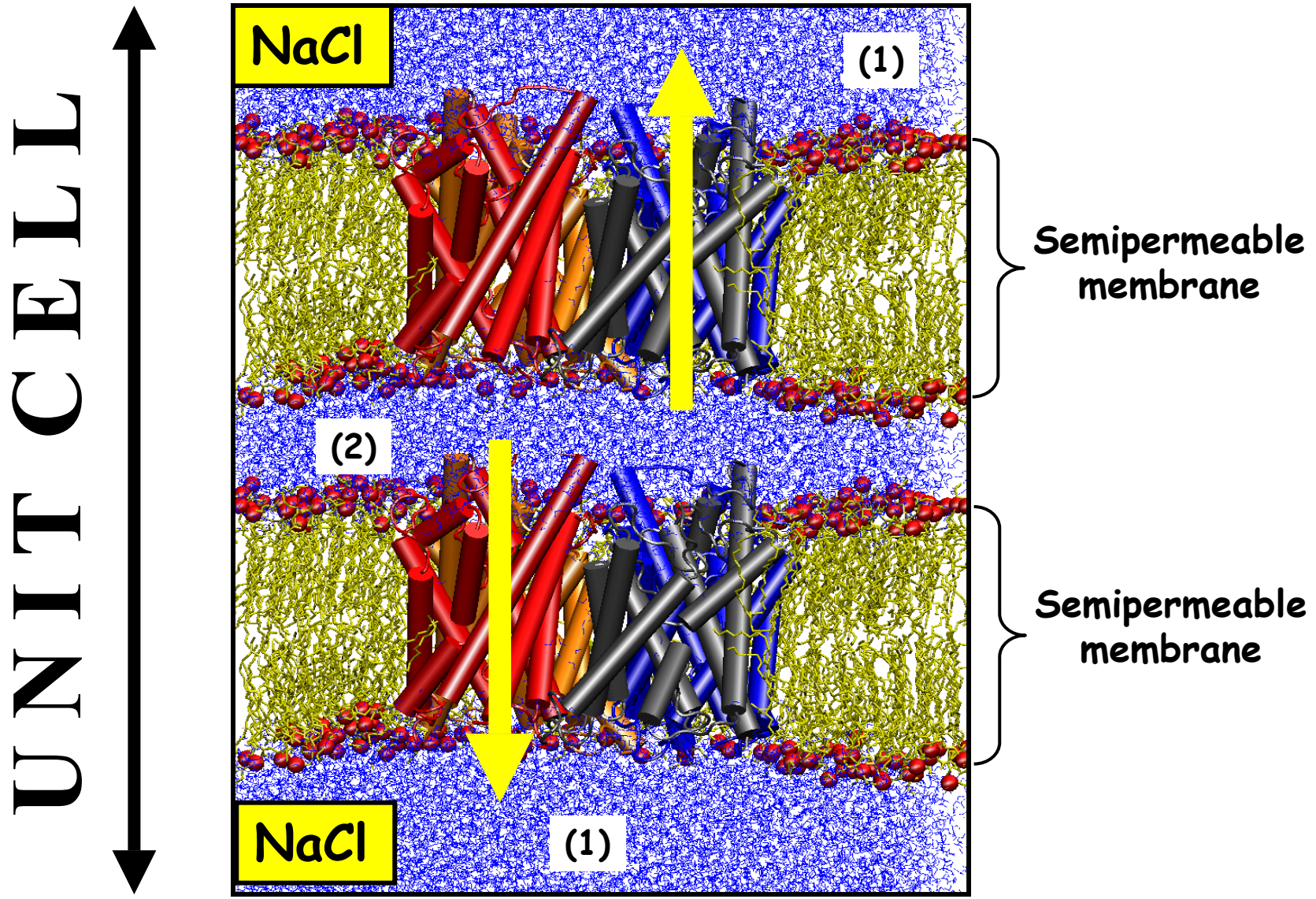
We can include more layers of membrane and water to create two compartment of water that are not in contact

NaCl



Semipermeable membrane

Semipermeable membrane

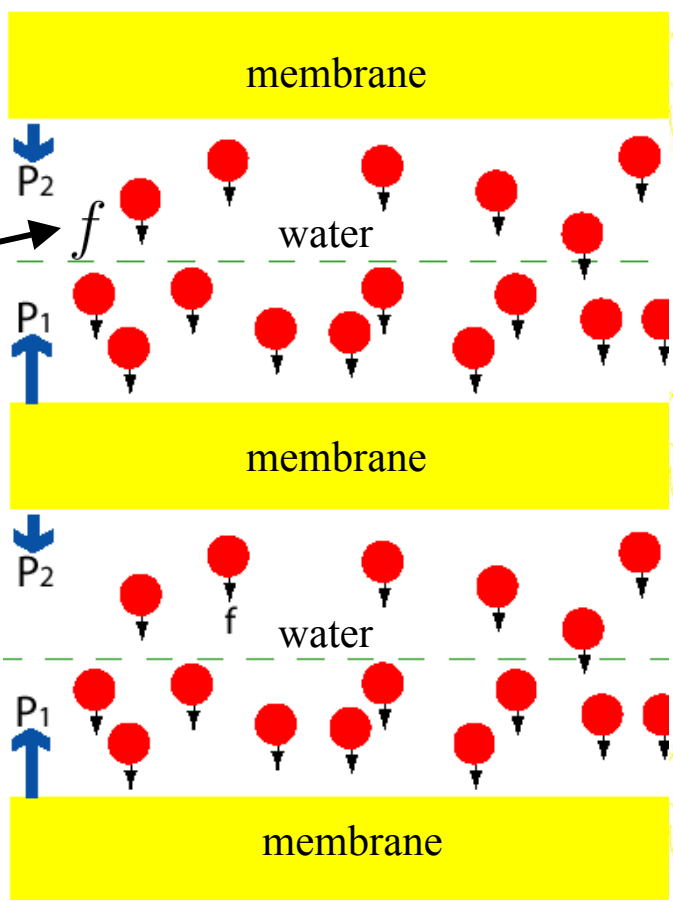

UNIT CELL
NaCl
(1)
Semipermeable membrane
(2)
Semipermeable membrane
NaCl
(1)

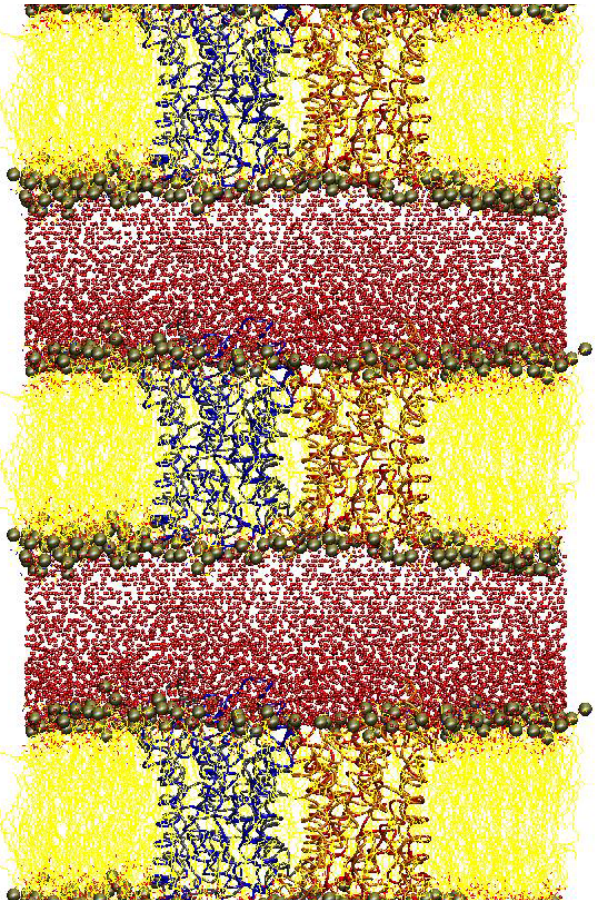
Realizing a Pressure Difference in a Periodic System

$$P_1 = P_2 + nf \Rightarrow \Delta P = nf / A$$

Fangqiang Zhu

f is the force on each water molecule, for *n* water molecules



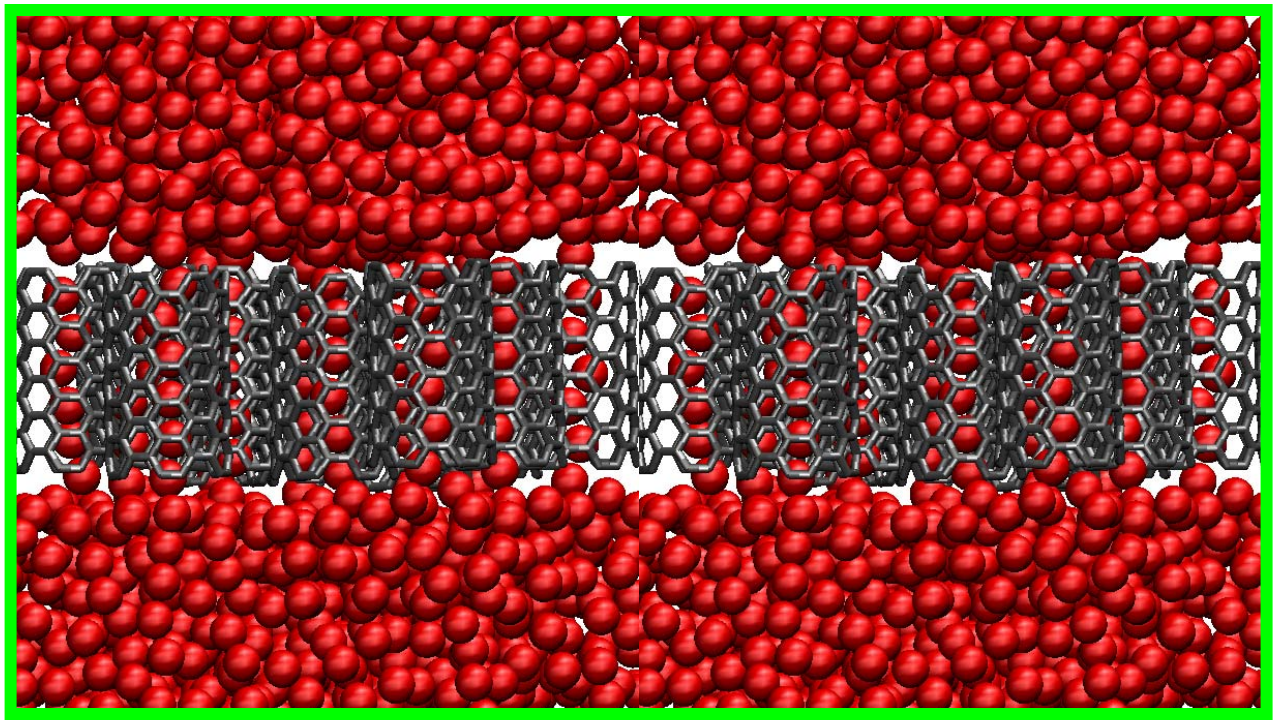


The overall translation of the system is prevented by applying constraints or counter forces to the membrane.

F. Zhu, et al., *Biophys. J.* 83, 154 (2002).

Applying a Pressure Difference Across the Membrane

$$\Delta P = nf / A$$

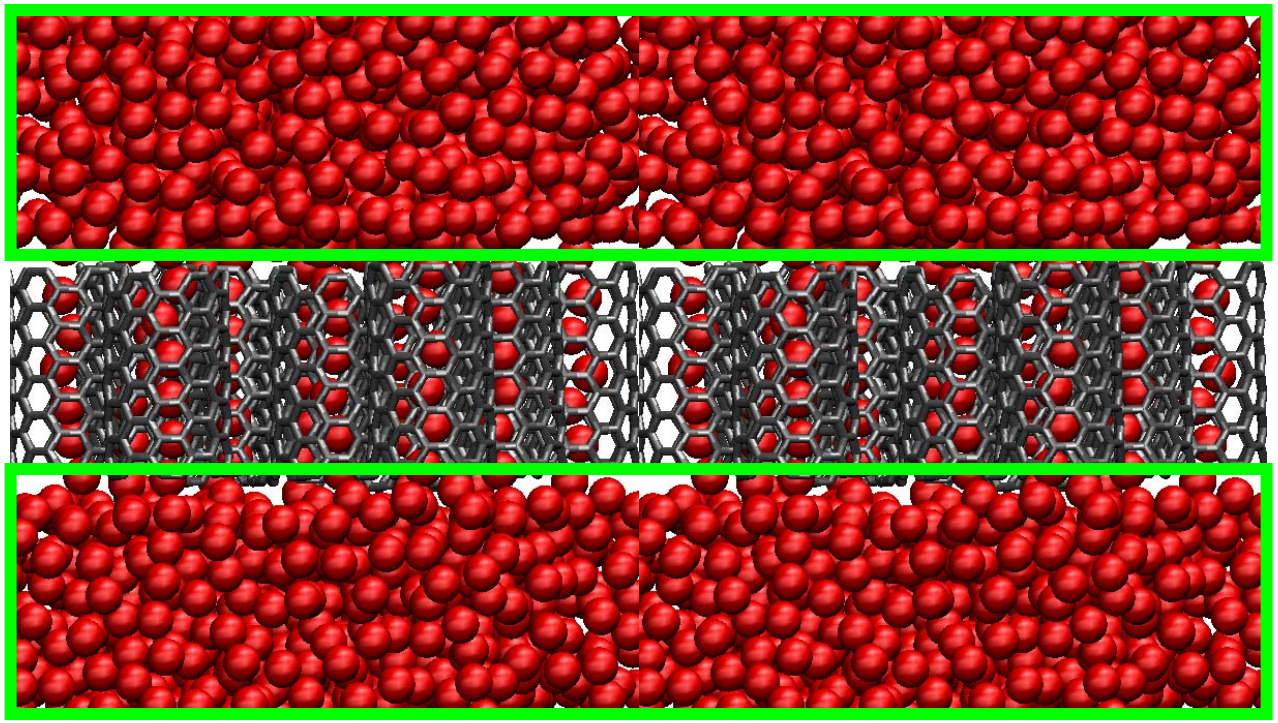


Applying force on all water molecules.

Not a good idea!

Applying a Pressure Difference Across the Membrane

$$\Delta P = nf / A$$

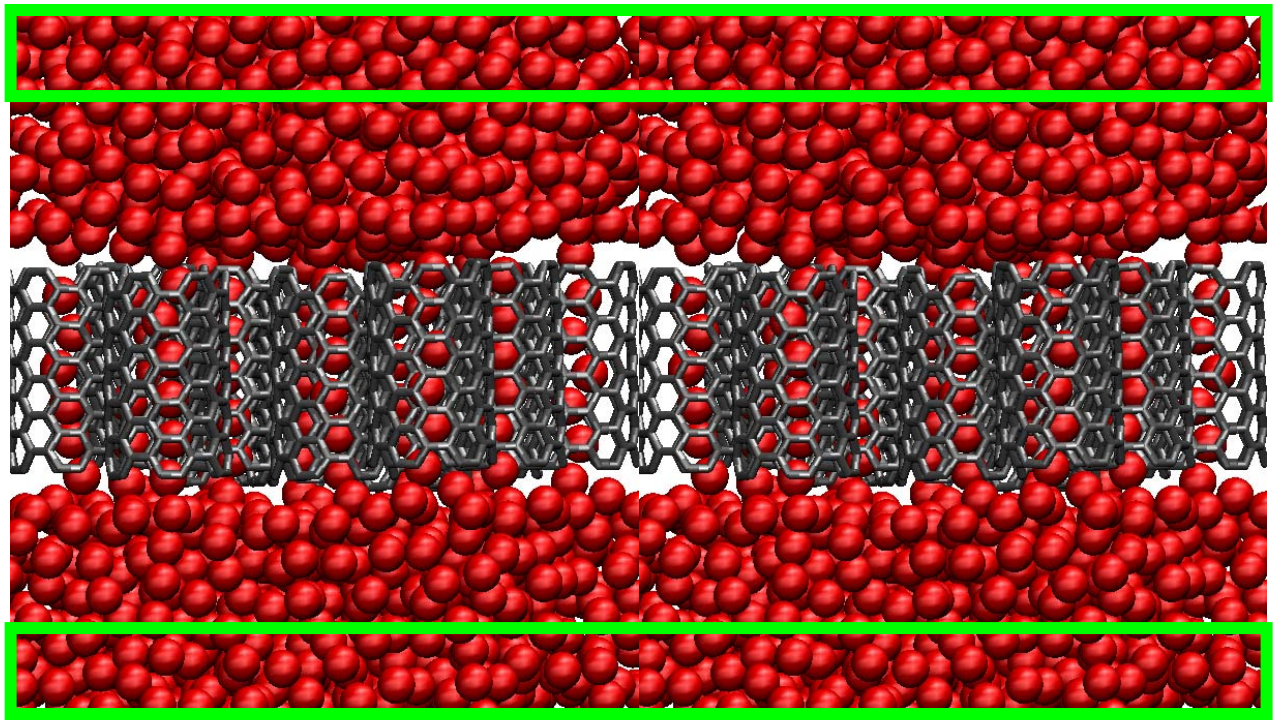


Applying force on bulk water only.

Very good

Applying a Pressure Difference Across the Membrane

$$\Delta P = nf / A$$



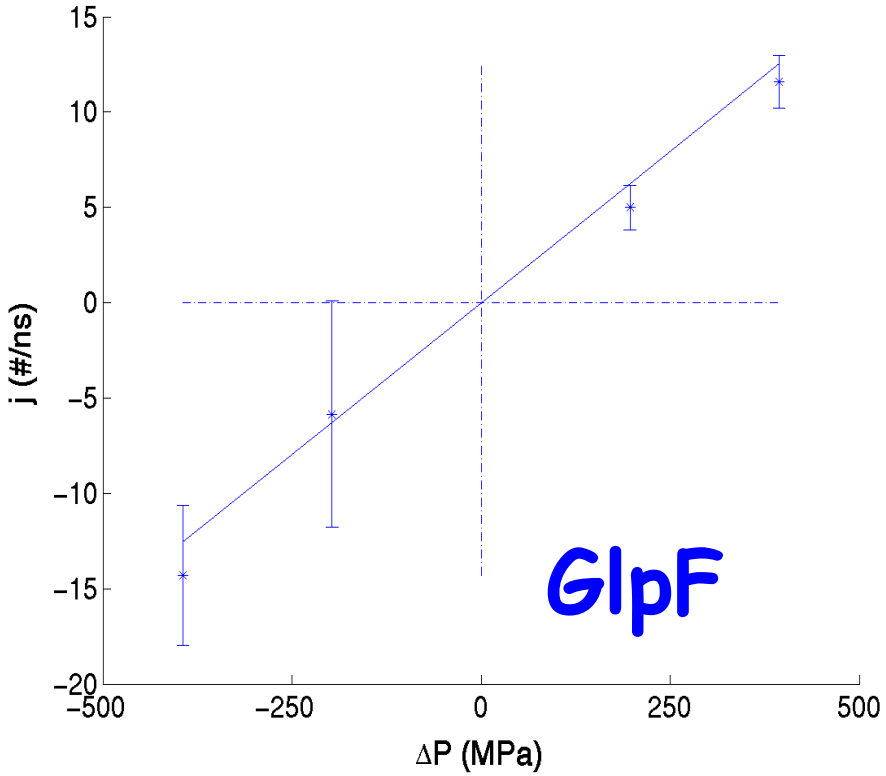
Applying force only on a slab of water in bulk.

Excellent

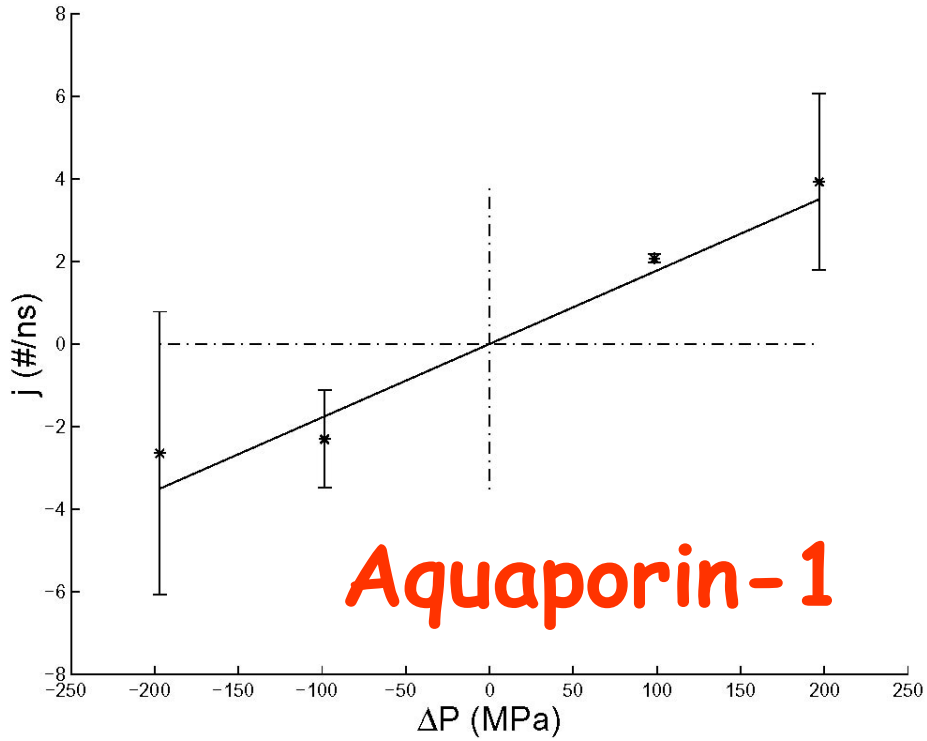
P_f can be calculated from these simulations

$$\Phi_w = P_f A(\frac{\Delta P}{RT} - \Delta C_s)$$

Calculation of osmotic permeability of water channels

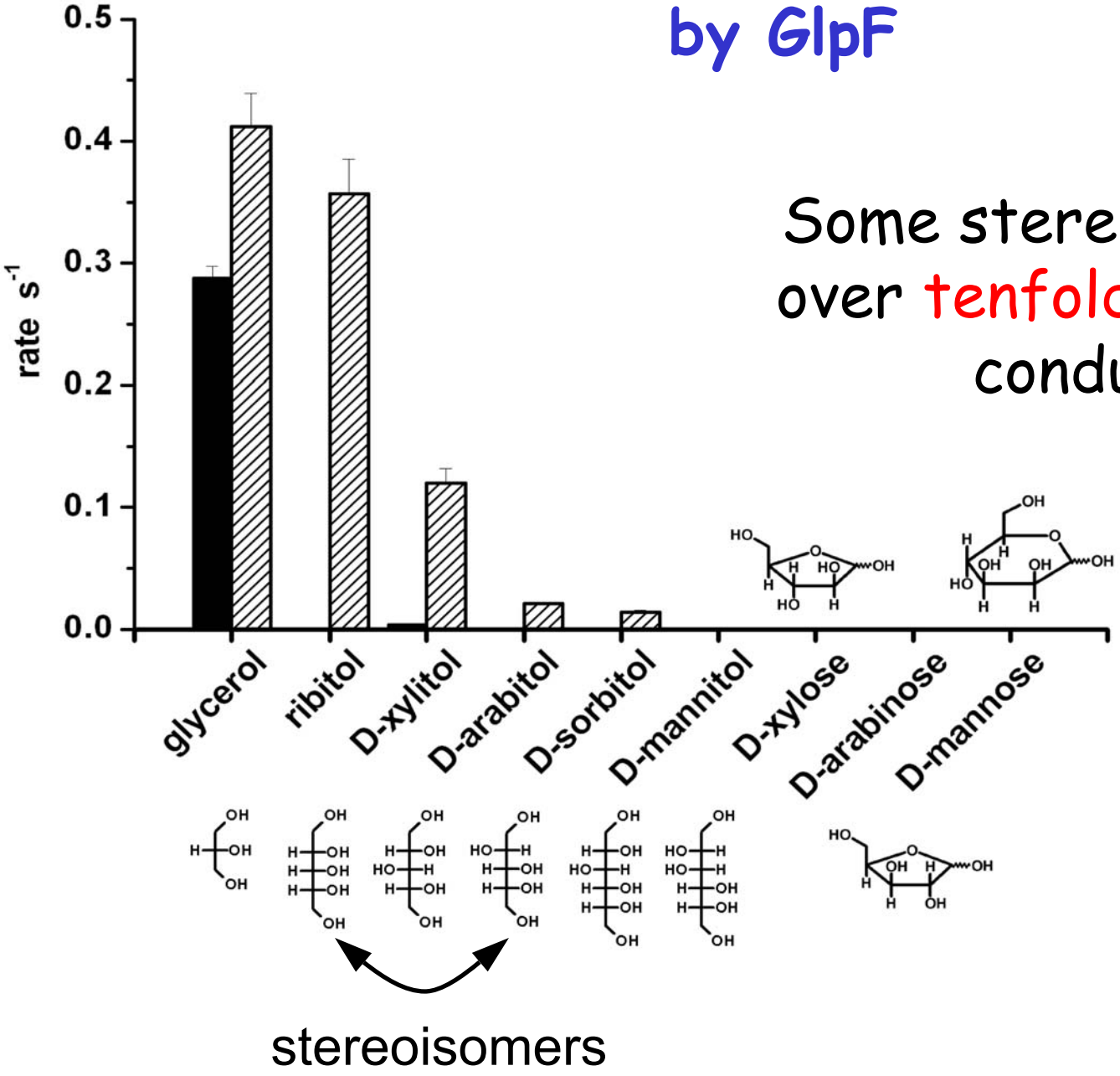


p_f: 1.4×10^{-13} cm^3/s



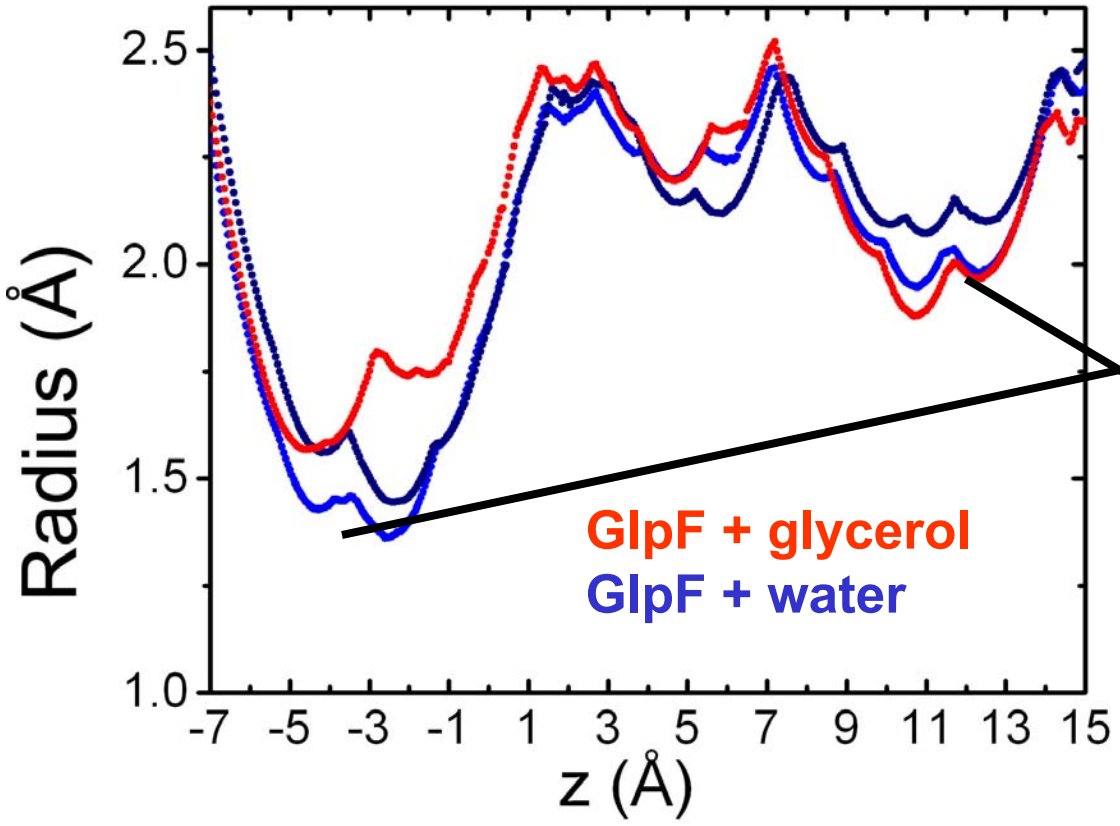
p_f: 7.0 ± 0.9 × 10^{-14} cm^3/s
Exp: 5.4 – 11.7 × 10^{-14} cm^3/s

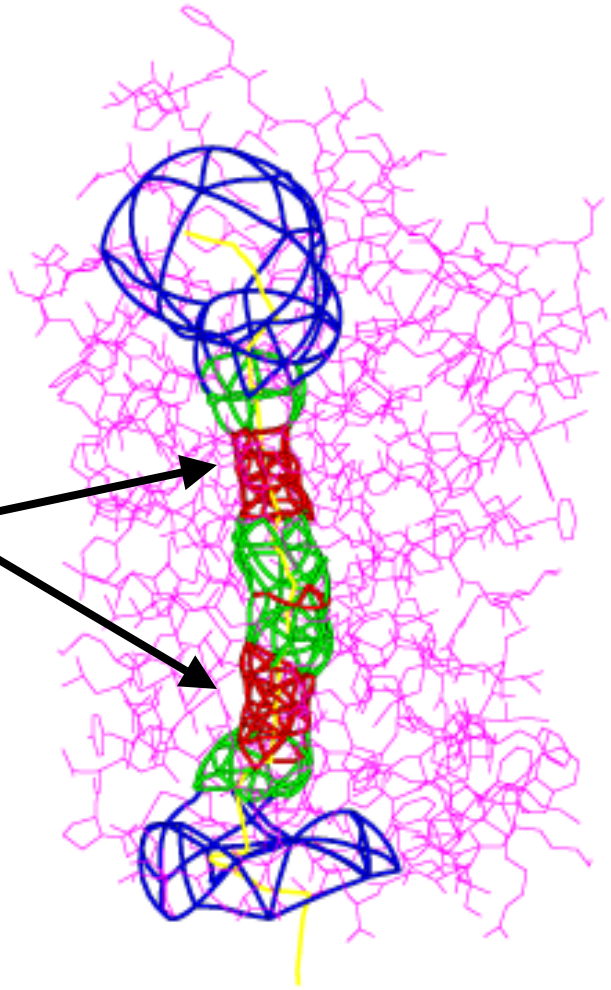
Stereoselective Transport of Carbohydrates by GlpF



Some stereoisomers show over tenfold difference in conductivity.

Channel Constriction

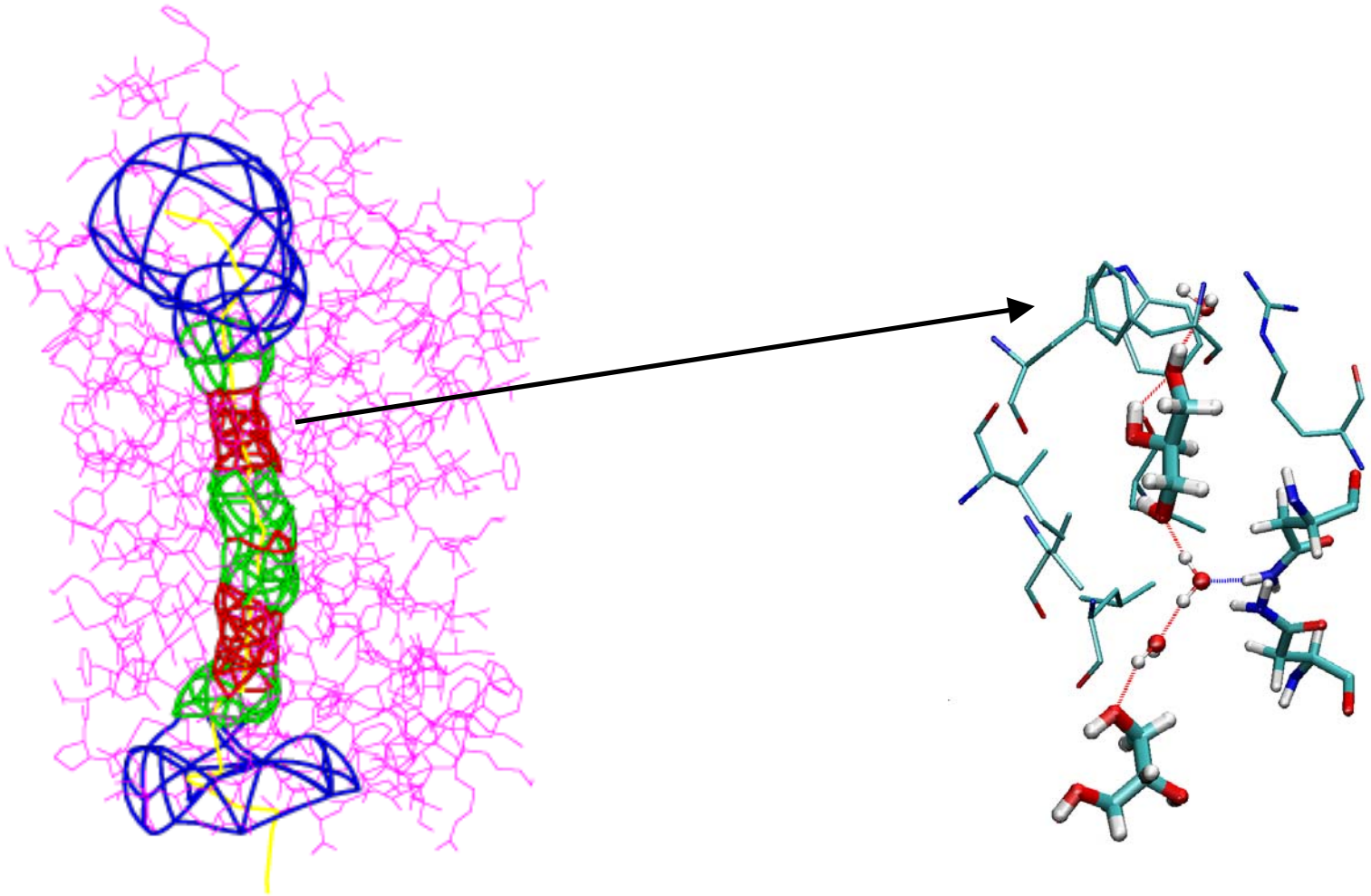




red < 2.3 Å
2.3 Å > green > 3.5 Å
blue > 3.5 Å

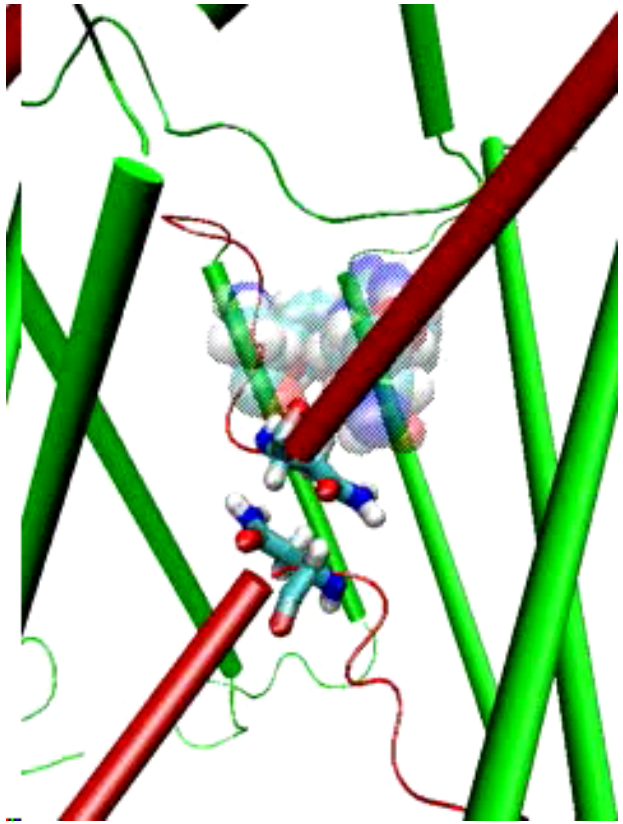
HOLE2: O. Smart et al., 1995

Selectivity filter

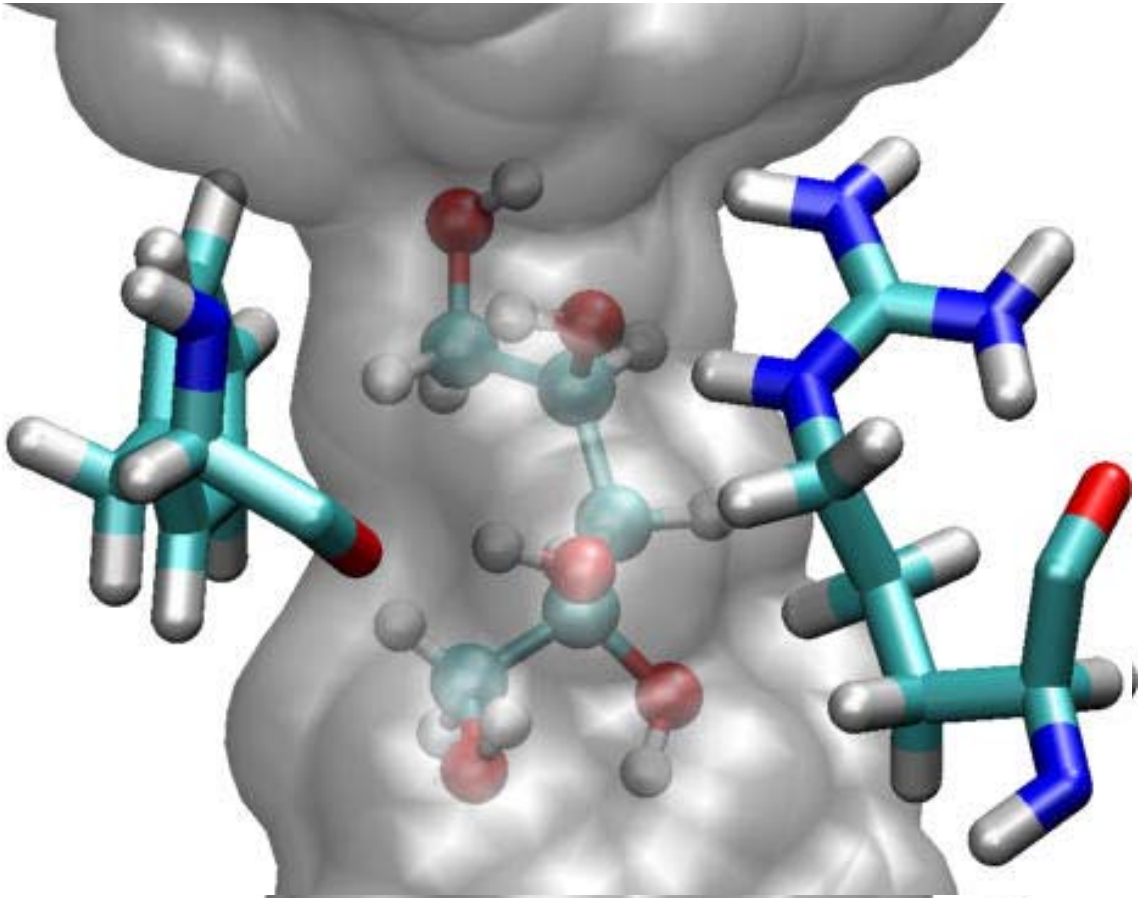


Interactive Molecular Dynamics

VMD ◄·····► NAMD

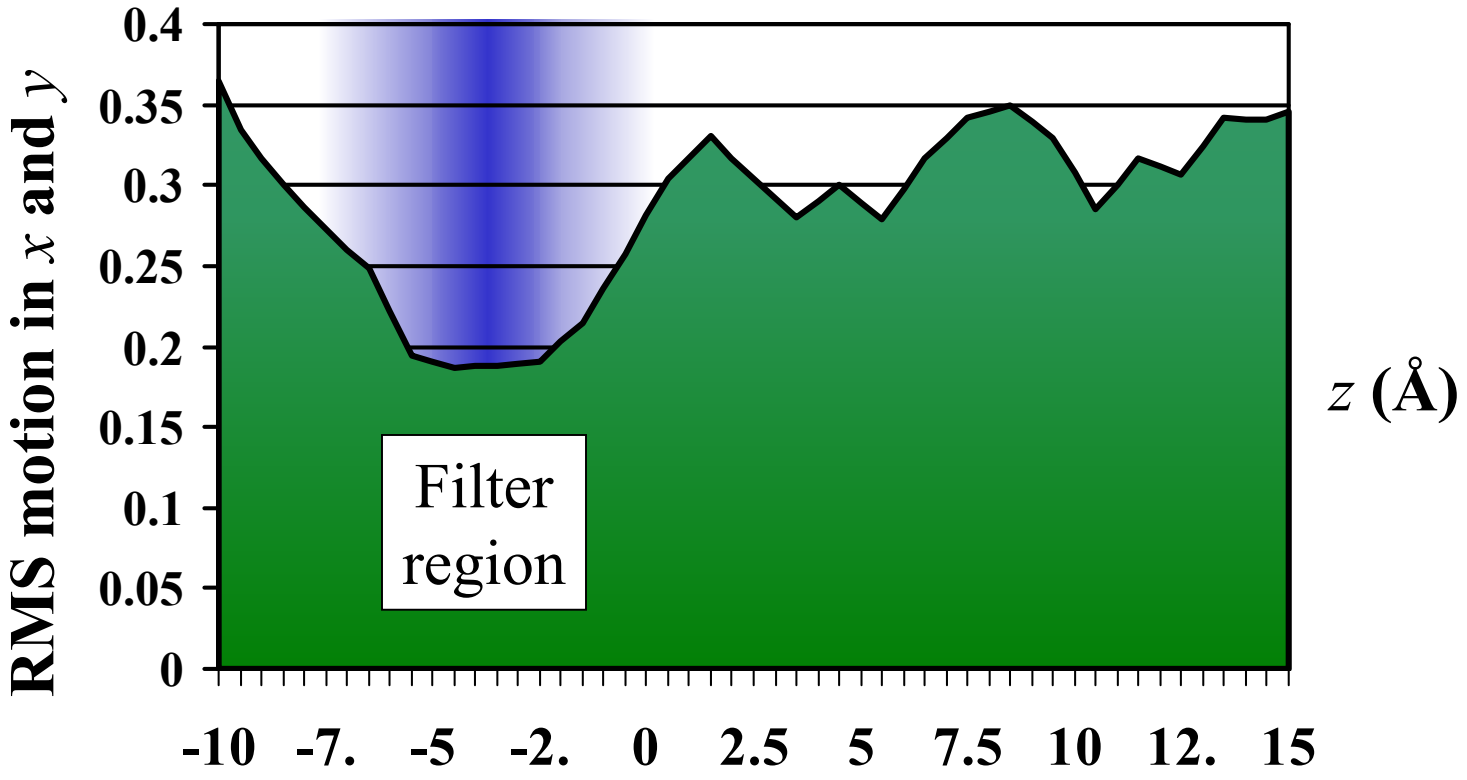


Observed Induced Fit in Filter



Confinement in Filter

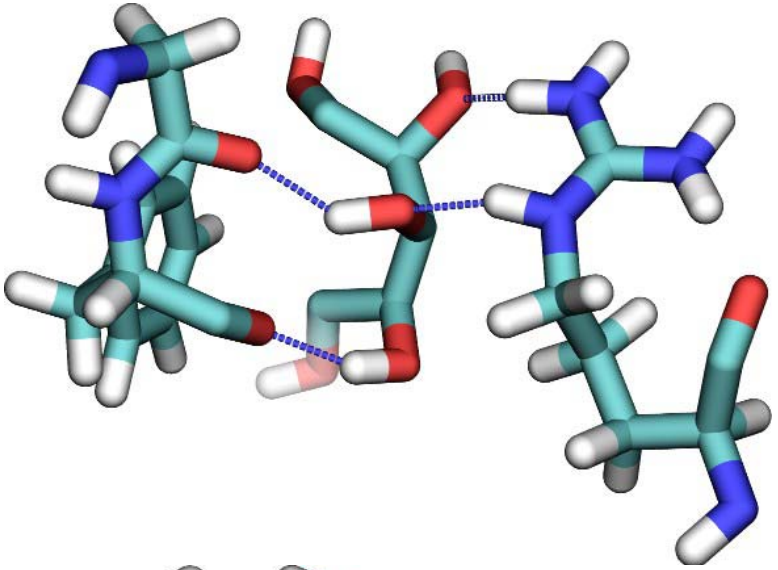
- Selection occurs in most constrained region.
- Caused by the locking mechanism.



Evidence for Stereoselectivity

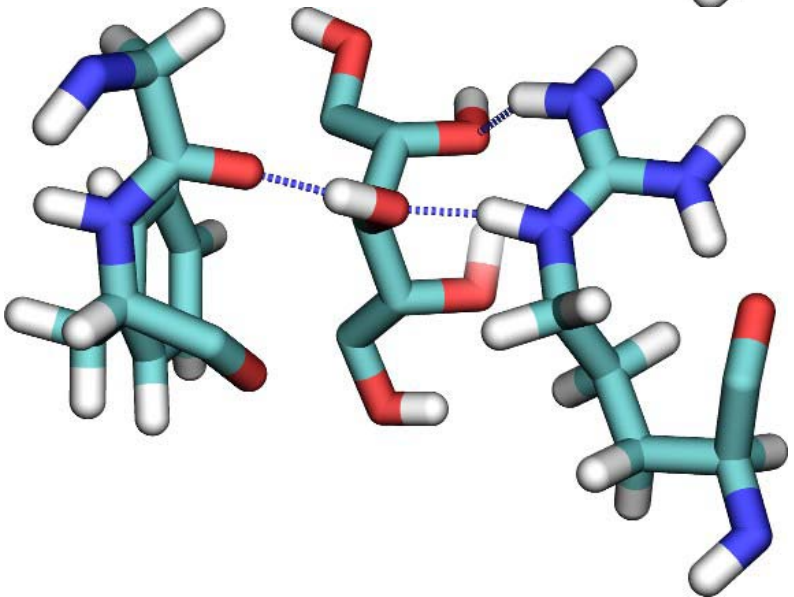
Ribitol

Optimal hydrogen bonding and hydrophobic matching



Arabitol

10 times slower



Dipole Reversal in Channel

- Dipole reversal pattern matches water.
- Selects large molecules with flexible dipole.