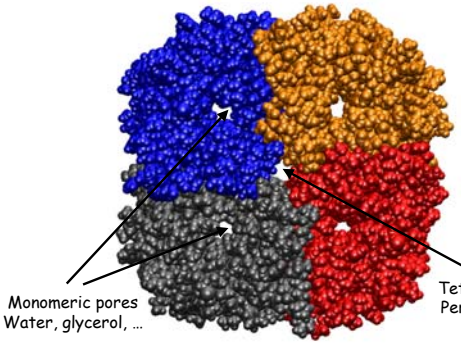
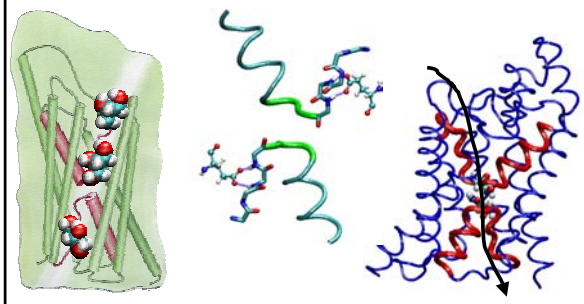
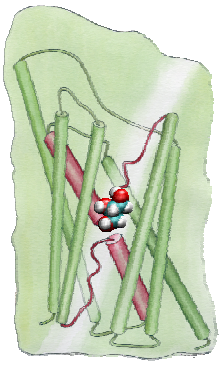


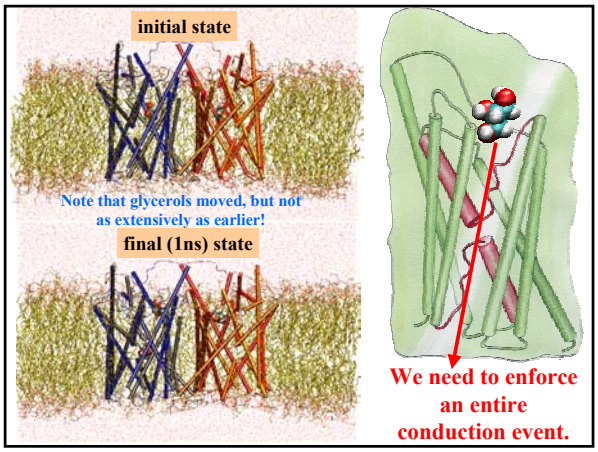
Aquaporins of known structure:
GlpF – E. coli glycerol channel (aquaglycerolporin)
AQP1 – Mammalian aquaporin-1 (pure water channel)

Revealing the Functional Role of Reentrant Loops



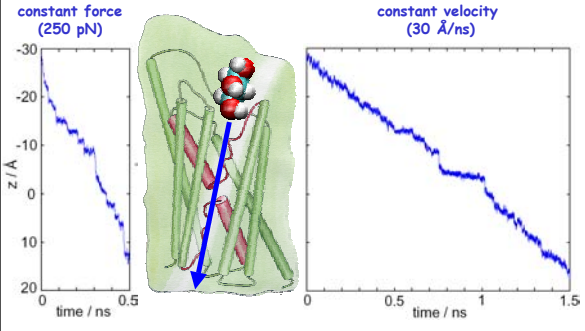
Single Glycerol per channel



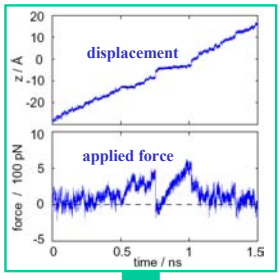


We need to enforce an entire conduction event.

Steered Molecular Dynamics



Free Energy Calculation in SMD



Free energy

SMD simulation
a non-equilibrium process

$$\Delta G \le \langle W \rangle$$

One needs to discount irreversible work

$$e^{-\Delta G / k_B T} = \left\langle e^{-W / k_B T} \right\rangle$$

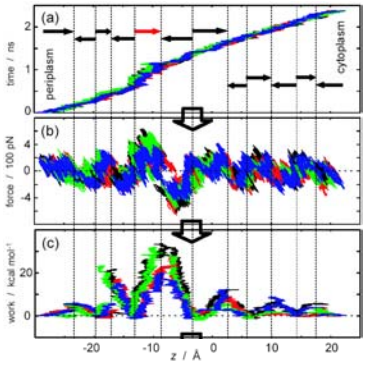
Jarzynski, *PRL* 1997
Hummer, *PNAS*, *JCP* 2001
Liphardt, et al., *Science* 2002

Constructing the Potential of Mean Force

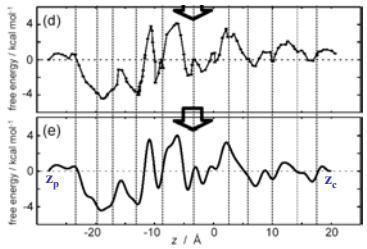
4 trajectories
v = 0.03, 0.015 Å/ps
k = 150 pN/Å

$$f(t) = -k[z(t) - z_0 - vt]$$

$$W(t) = \int_0^t dt' vf(t')$$



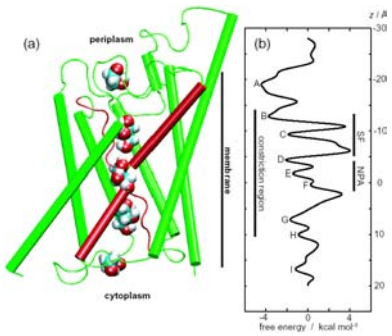
Constructing the Potential of Mean Force – cont.



$$G(z) = \sum_{m=1}^{M} a_m \sin[m\pi(z - z_p)/(z_c - z_p)]$$

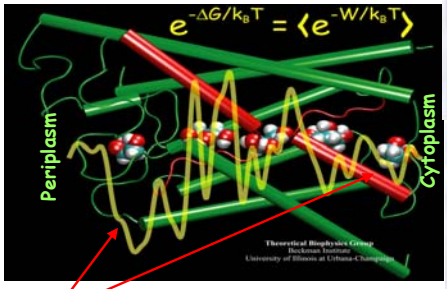
determined by minimizing the difference between (d) and (e)

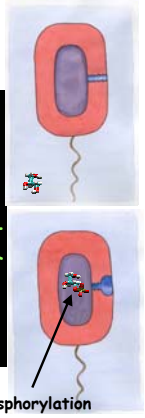
Features of the Potential of Mean Force



- Captures major features of the channel
- The largest barrier ≈ 7.3 kcal/mol; exp.: 9.6±1.5 kcal/mol

Asymmetry of the Potential of Mean Force

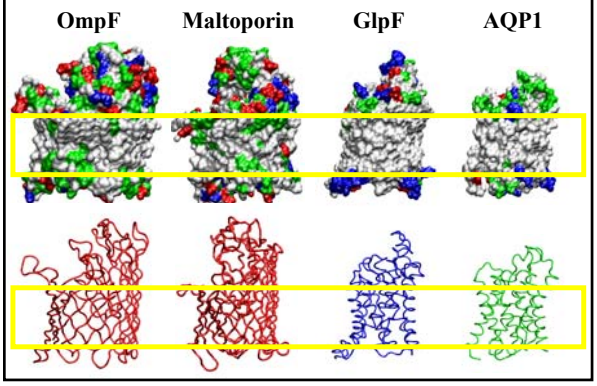




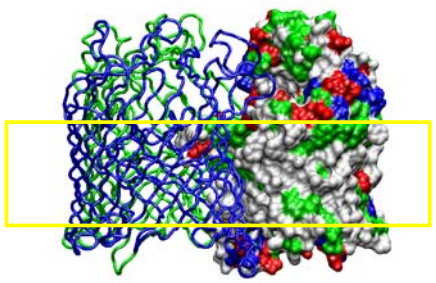
Asymmetric Profile in the Vestibules

phosphorylation

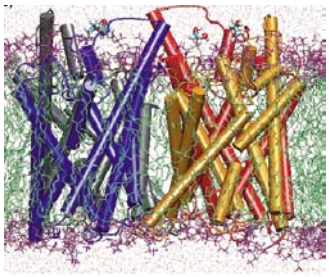
Assymetric structure; biological implication?

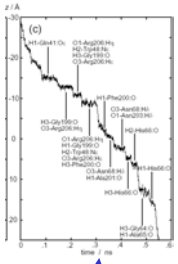


Asymmetric structure of maltoporin



SMD Simulation of Glycerol Passage





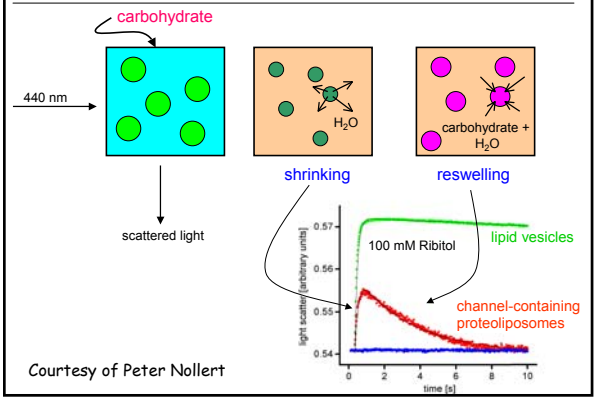
Trajectory of glycerol pulled by **constant force**

Aquaporins' Mechanisms of Selectivity

Protons, ions, and charged molecules cannot be transported.

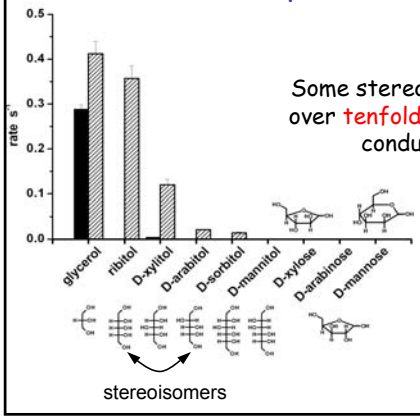
Aquaglyceroporins (GlpF) transport linear sugars in a highly stereo-selective manner

Liposome Swelling Assay



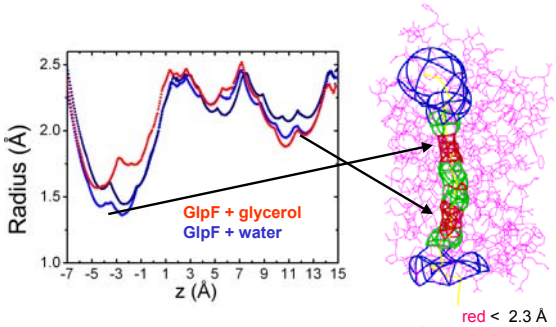
Courtesy of Peter Nollert

Stereoselective Transport of Carbohydrates



Some stereoisomers show over tenfold difference in conductivity.

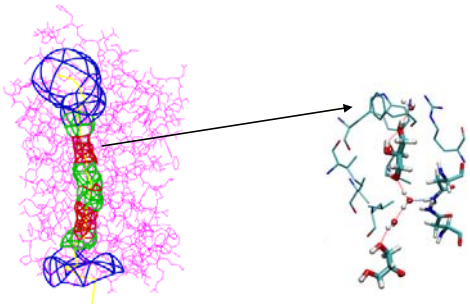
Channel Constriction



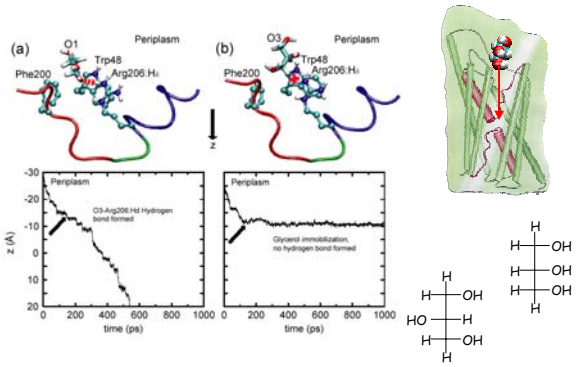
red < 2.3 Å
2.3 Å > green > 3.5 Å
blue > 3.5 Å

HOLE2: O. Smart et al., 1995

Selectivity filter

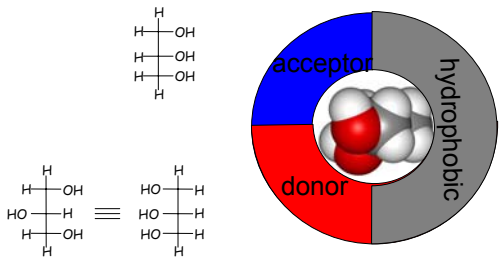


Evidence for Stereoselectivity of Glycerol



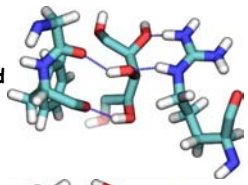
Cannot be verified by experimental measurements.

Complementarity
glycerol molecule ↔ channel

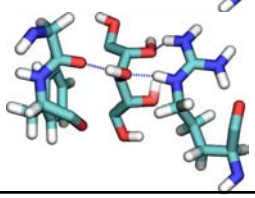


Evidence for Stereoselectivity by Interactive Molecular Dynamics

Ribitol
Optimal hydrogen bonding and hydrophobic matching



Arabitol
10 times slower

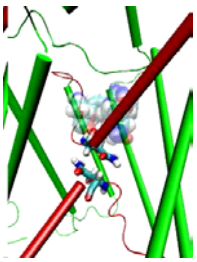


Interactive Molecular Dynamics

VMD ↔ NAMD

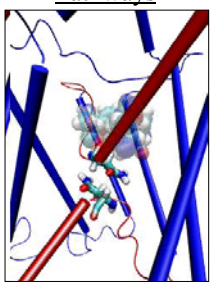
- Any PC/Workstation
- Supports 3D force-feedback devices for interaction

J. Stone, J. Gullingsrud, K. Schulten, and P. Grayson. ***A System for Interactive Molecular Dynamics Simulation.*** 2001 ACM Symposium on Interactive 3D Graphics, pp.191-194, ACM SIGGRAPH

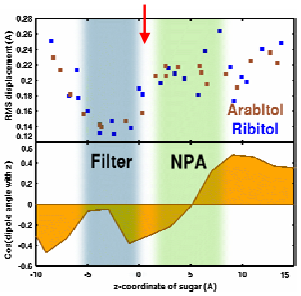


Results of Interactive Simulations

Pathways

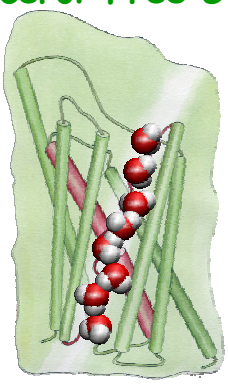


Restricted motion filter for both sugars

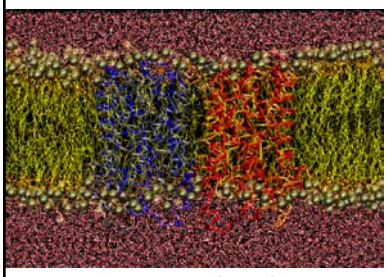


Dipole reversal for ribitol at NPA

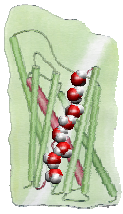
Glycerol-Free GlpF



Water permeation through GlpF



5 nanosecond Simulation



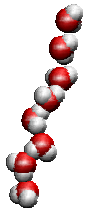
18 water conducted
In 4 monomers in 4 ns
1.125 water/monomer/ns

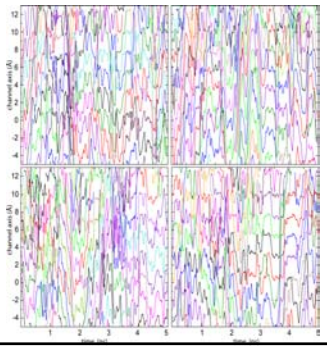
Exp. = ~ 1-2 /ns

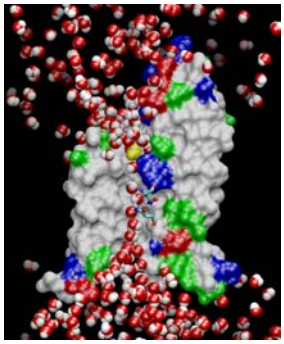
7-8 water molecules in each channel

Correlated Movement of Water in the Channel

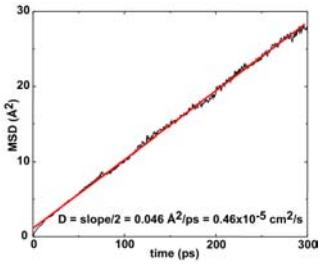
The single file of water molecules is maintained.

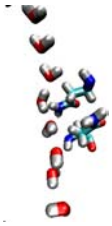






Diffusion of Water in the channel

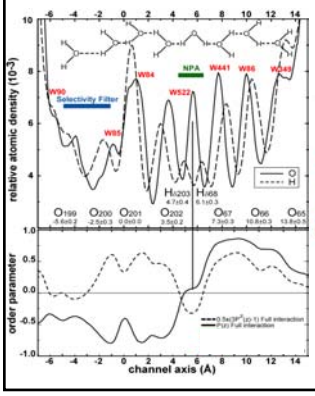


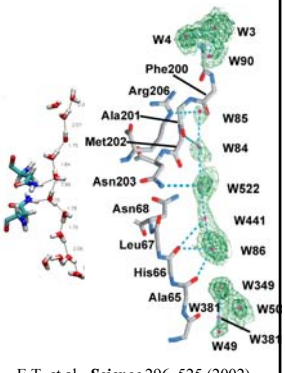


One dimensional diffusion: $2Dt = \langle S^2 \rangle$

Experimental value for AQP1: 0.4-0.8 e-5

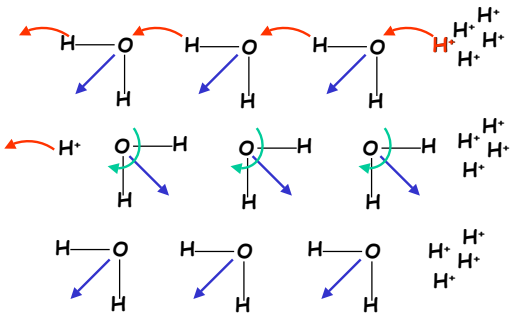
Water Bipolar Configuration in Aquaporins



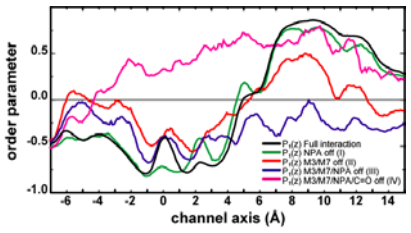


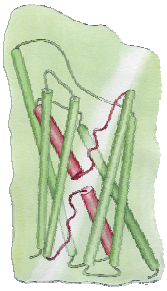
E.T. et al., ***Science*** 296, 525 (2002)

Proton transfer through water



Electrostatic Stabilization of Water Bipolar Arrangement





E.T. et al., ***Science*** 296, 525 (2002)

Proton Blocking by a Global Orientation Mechanism