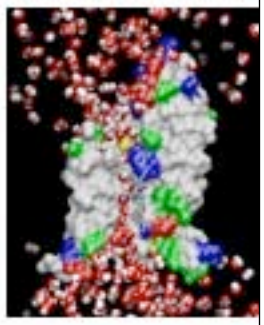
Sequence and Structure Alignment - Illustrated for the Water Channel Aquaporin

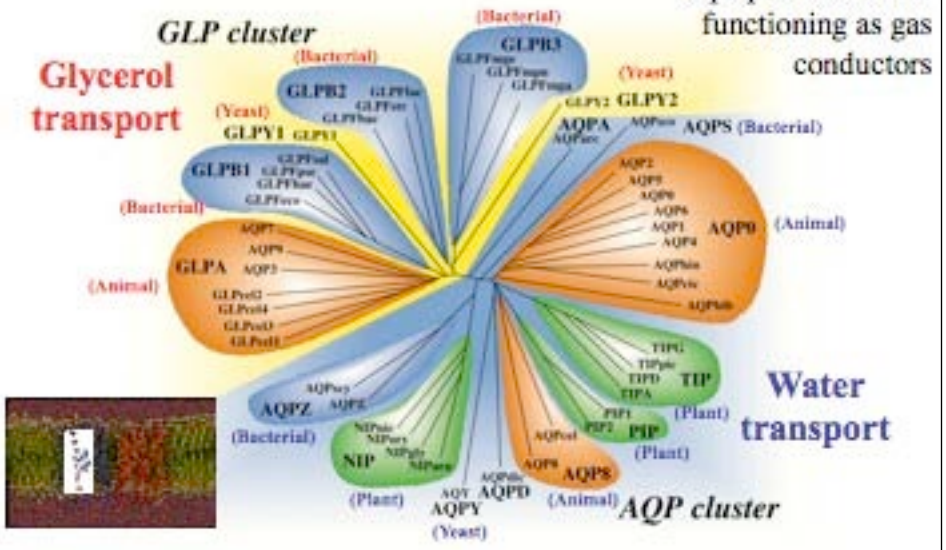


Physical Bioinformatics - A Case Study

Sequence and structure information are the bedrock on which an understanding of cellular functions and the underlying physical mechanisms can be built. This lecture illustrates how the two sources of information are combined to investigate by means of the program VMD function and mechanism of the aquaporin family of membrane channels that transport water and certain small solutes across cell walls. Introducing first the key architectural features of a single aquaporin, structures and sequences of four aquaporins are aligned and common features recognized. The shared and distinct features are examined closely and used as guideposts leading quickly to key questions regarding the mechanism underlying aquaporin's efficient conduction and selection.

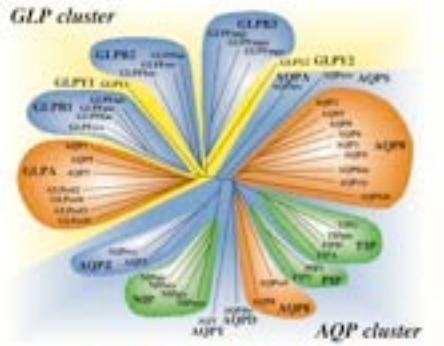
The Aquaporin Superfamily

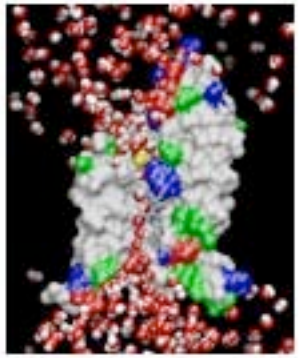
aquaporins are also functioning as gas conductors



Heymann and Engel *News Physiol. Sci.* **14**, 187 (1999)

Aquaporin Function and Human Aquaporins





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AQP1_HUMAN ---RNCLADVNGQGLGIEIIGTLQLVLCVLATTDR-RRRDLGGSAPLAIGLSVALGHLLAIDYTGCGI   191
AQP2_HUMAN ---VNALSNSTTAQGAVTVELFLTLQLVLCIFASTDE-RRGNNFGTPALSIGFSVALGHLLGIHYTGCSM   183
AQP3_HUMAN GIFATFPSGHLDMLNGFFDQFIGTAALIVCVLAIVDPYNNFVPRGLEAFTVGLVVLVIGTSMGFNSGYAV   214
AQP4_HUMAN ---VTKVIGMLTAGHGLLVELIITFQLVFTIFASCDS-KRTDVTGSIALAIGFSVAIGHLFAINYTGASM   212
AQP5_HUMAN ---VNALNNSTTQQSAMVVELILTFQLALCIFASTDS-RRTSPVGSPALSIGLSVTLGHLVGIYFTGCSM   184
AQP6_HUMAN ---INVVRNSVTTGQAVAVELLLTLQLVLCVFASTDS-KQTS--GSPADMIGIGMALGHLIGILFTGCSM   195
AQP7_HUMAN GIFATFLFDSMLLMRGFLMEANLTGNLQLCLFAITDQENNPALPGTEALVIGILVVIIGVSLGMNTGYAI   225
AQP8_HUMAN -AAFVTVQSQGQGVAGALVAEIILTTLLALAVCMGAIN--EKTKGPLAPFSIGFAVTVDILAGGPVSGGCM   209
AQP9_HUMAN NIFATFPAPYLGLAMSFAIQVVATMILLIIVFAIFDSRNLGAPRGLSPIAIGLLIIVIASSLGLNSGCAM   215
GLPF_ECOLI GIFSTFPNPHIHFVGAFAVEMVIIAILMGLILALTDDGNGVPRGPLAPLLIGLLIAVIGASMGPLTGFAM   202
      ruler ...180.......190.......200.......210.......220.......230.......240....
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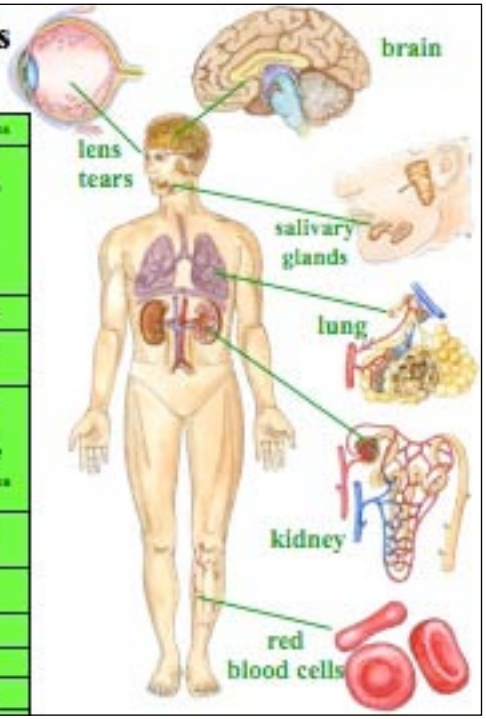
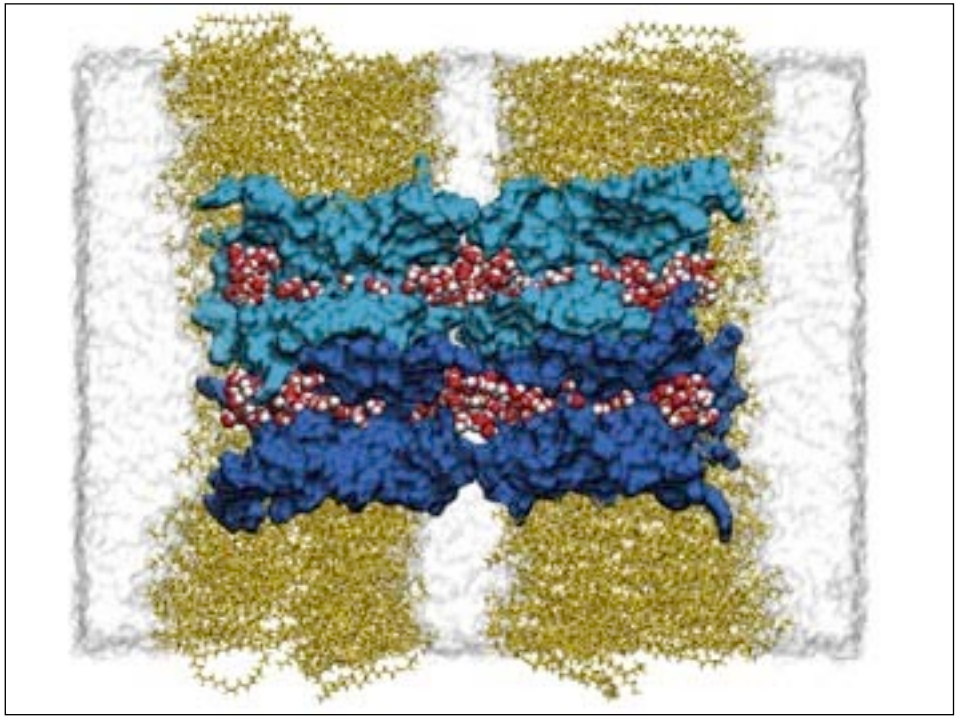
Water and Glycerol Channels in the Human Body

Aquaporin-0	Eye: lens fiber cells	Fluid balance of the lens
Aquaporin-1	Red blood cells	Osmotic protection
	Kidney: proximal tubules	Concentration of urine
	Eye: ciliary epithelium	Aqueous humor
	Brain: choriod plexus	Production of CSF
	Lung: alveolar epithelial cells	Alveolar hydration
Aquaporin-2	Kidney: collecting ducts	ADH hormone activity
Aquaporin-3	Kidney: collecting ducts	Reabsorption of water
	Trachea: epithelial cells	Secretion of water
Aquaporin-4	Kidney: collecting ducts	Reabsorption of water
	Brain: ependymal cells	CSF fluid balance
	Brain: hypothalamus	Osmosensing function?
	Lung: bronchial epithelium	Bronchial fluid secretion
Aquaporin-5	Salivary glands	Production of saliva
	Lacrimal glands	Production of tears
Aquaporin-6	Kidney	Very low water permeability!
Aquaporin-7	Testis and sperm	
Aquaporin-8	Testis, pancreas, liver	
Aquaporin-9	Leukocytes	

Additional members are suspected to exist

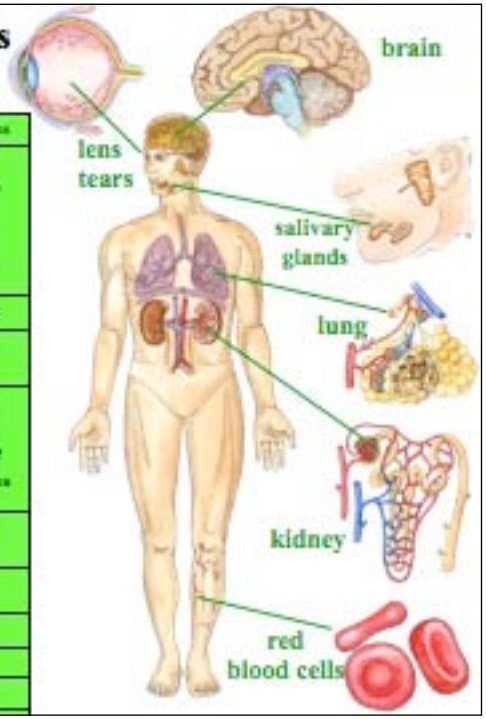




Water and Glycerol Channels in the Human Body

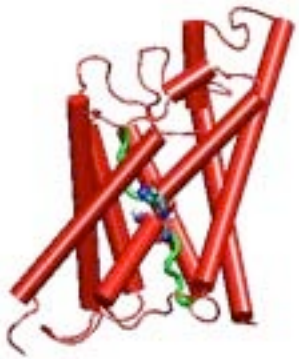
Aquaporin-0	Eye: lens fiber cells	Fluid balance of the lens
Aquaporin-1	Red blood cells Kidney: proximal tubules Eye: ciliary epithelium Brain: choriod plexus Lung: alveolar epithelial cells	Osmotic protection Concentration of urine Aqueous humor Production of CSF Alveolar hydration
Aquaporin-2	Kidney: collecting ducts	ADH hormone activity
Aquaporin-3	Kidney: collecting ducts Trachea: epithelial cells	Reabsorption of water Secretion of water
Aquaporin-4	Kidney: collecting ducts Brain: ependymal cells Brain: hypothalamus Lung: bronchial epithelium	Reabsorption of water CSF fluid balance Osmosensing function? Bronchial fluid secretion
Aquaporin-5	Salivary glands Lacrimal glands	Production of saliva Production of tears
Aquaporin-6	Kidney	Very low water permeability!
Aquaporin-7	Testis and sperm	
Aquaporin-8	Testis, pancreas, liver	
Aquaporin-9	Leukocytes	

Additional members are suspected to exist

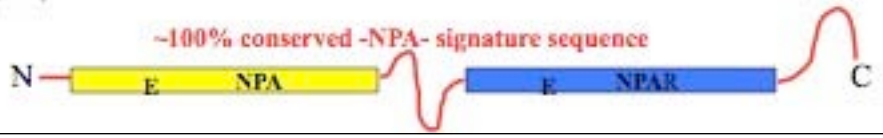


Functionally Important Features of Aquaporins

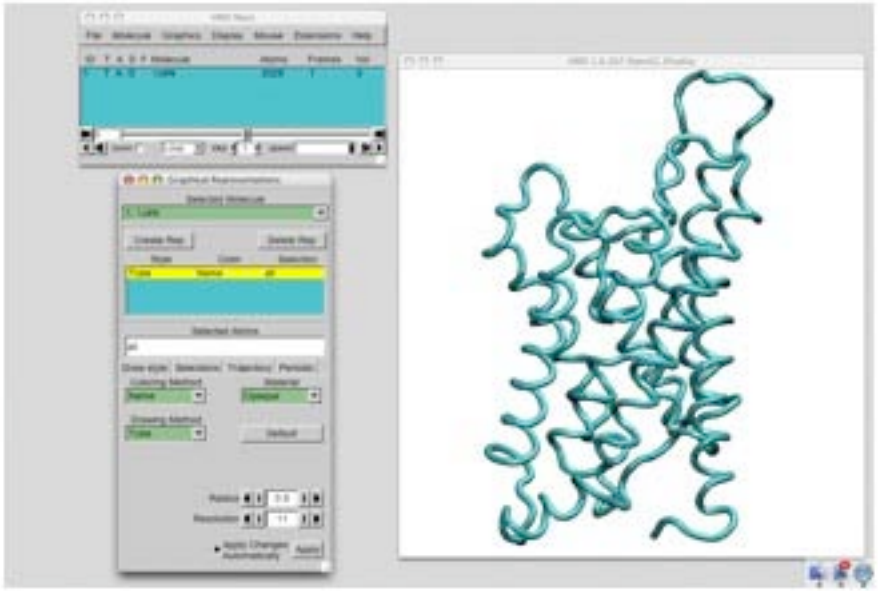
- Water, gas, and glycerol transport
- Exclusion of ions and protons
- Tetrameric arrangement in membrane



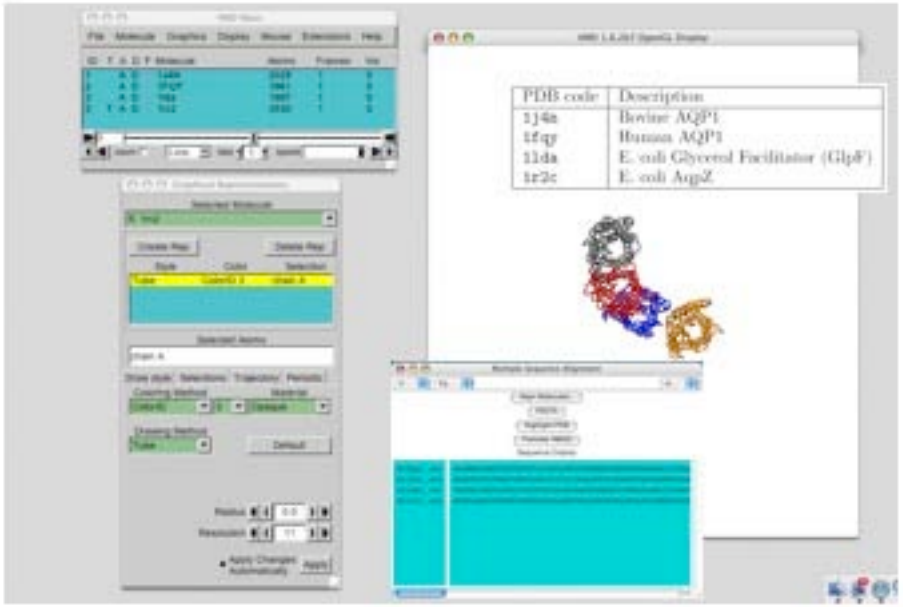
Aquaporins of known structure:
GlpF – E. coli glycerol channel (aquaglyceroporin) – Fu, et al., Science (2000)
AQP1 – Mammalian aquaporin-1 (pure water channel) -Sui et al, Nature (2001)
AQP1 - Bovine - Murata et al, Nature (2000)
AQPZ - E. coli water channel - Savage et al, PLOS Biol (2003)



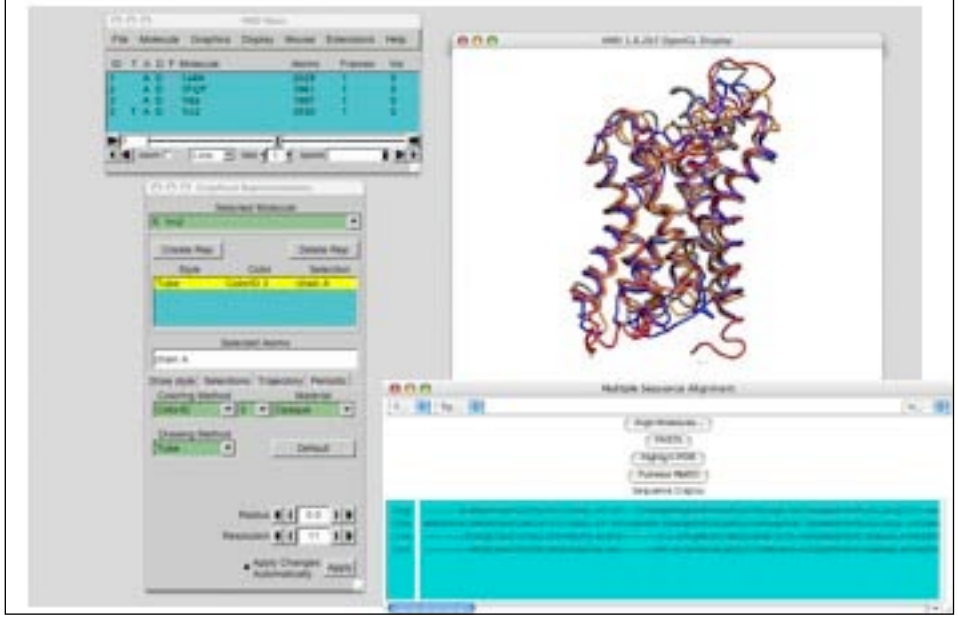
Load Aquaporin 1J4N into VMD



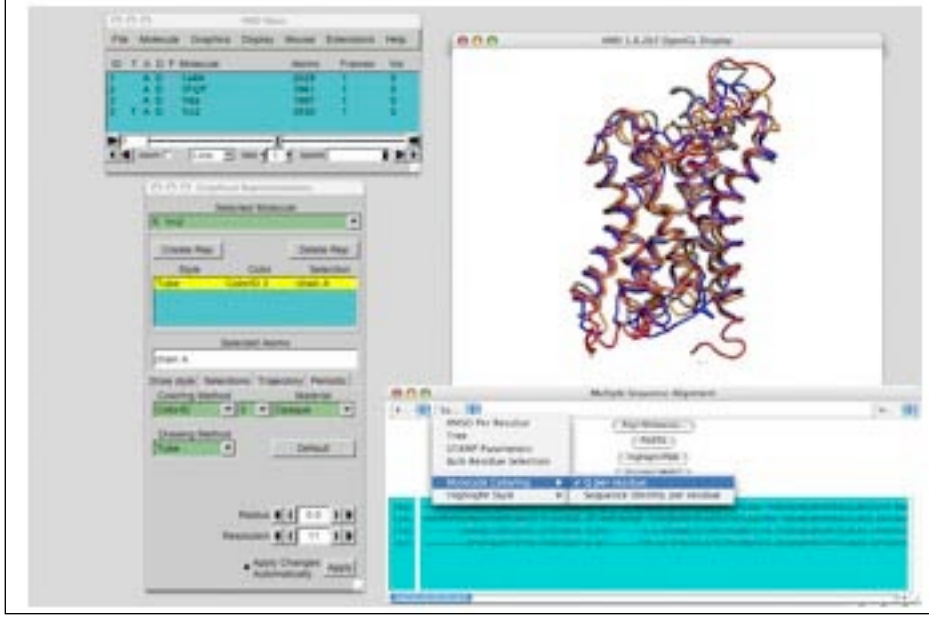
Load Aquaporins 1j4n, 1fqy, 1lda, 1rc2 into VMD



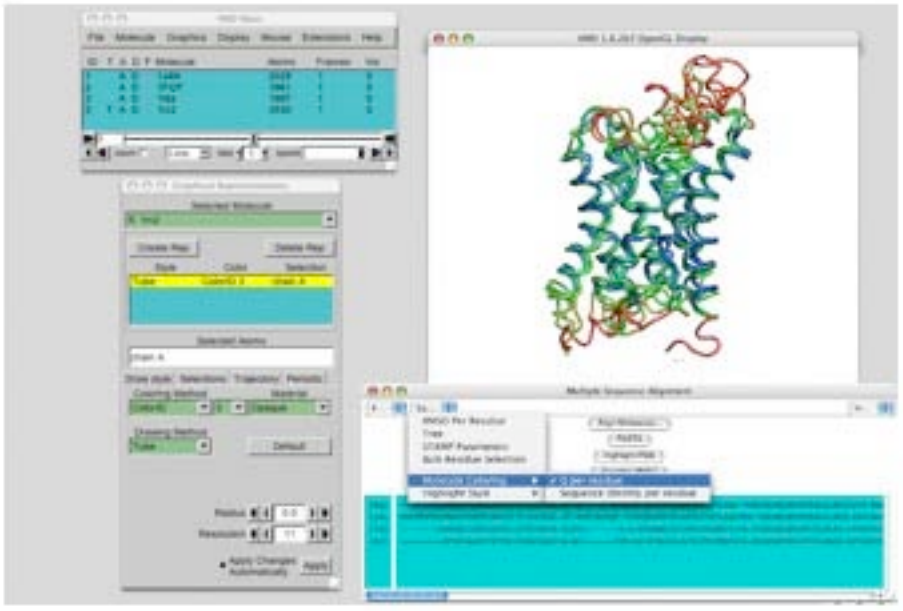
Aligning Structures and Sequences



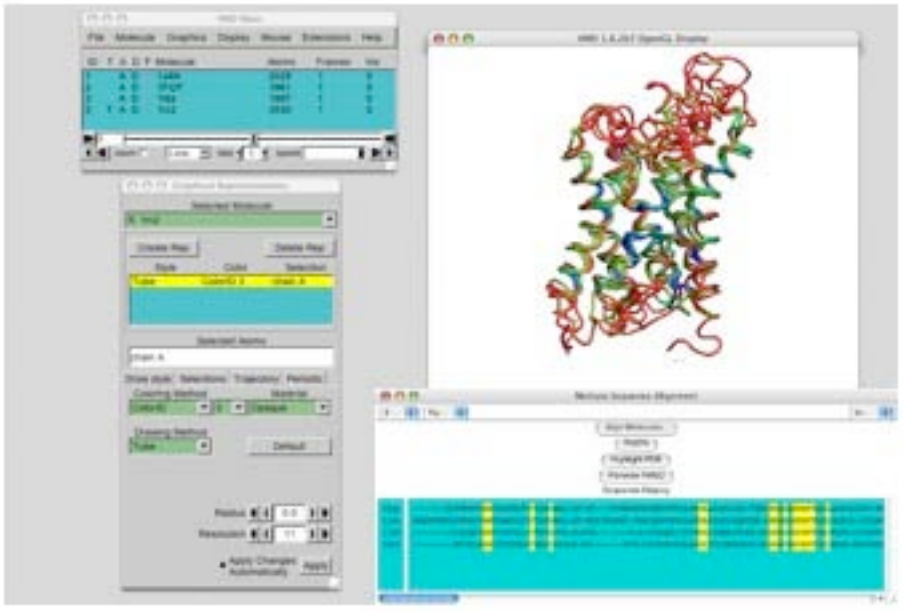
Comparing Structures by Similarity - Q Value



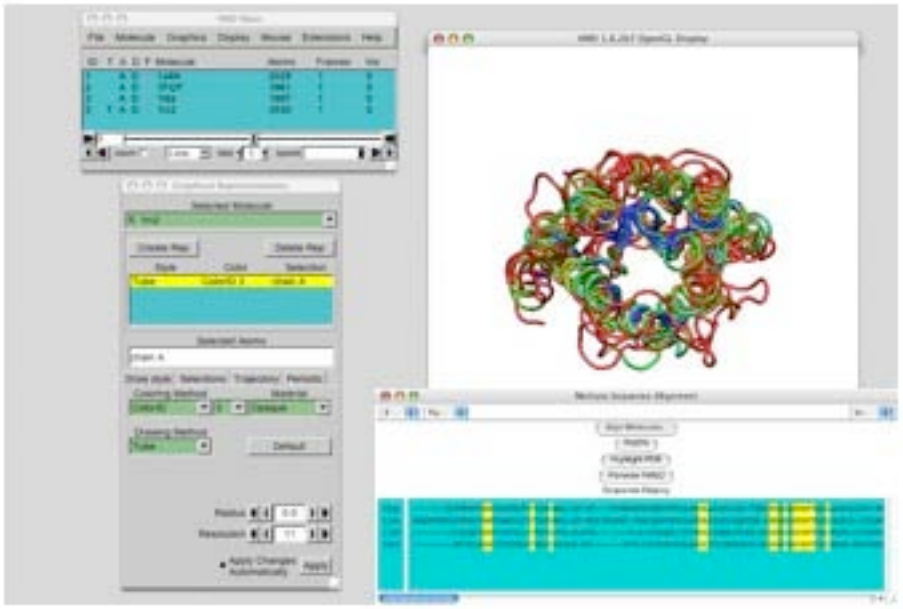
Comparing Structures by Similarity - Q Value



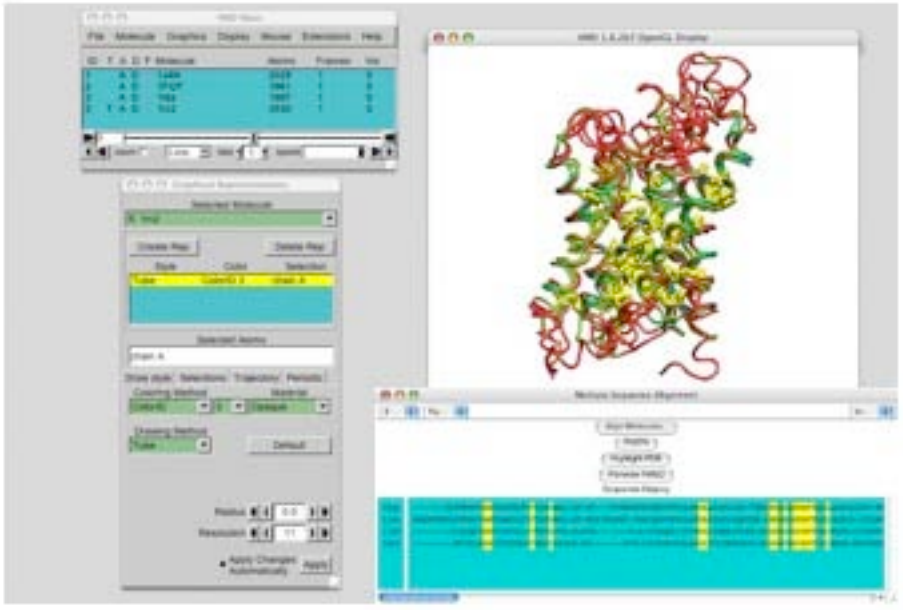
Exhibiting Sequence Identity - Side View



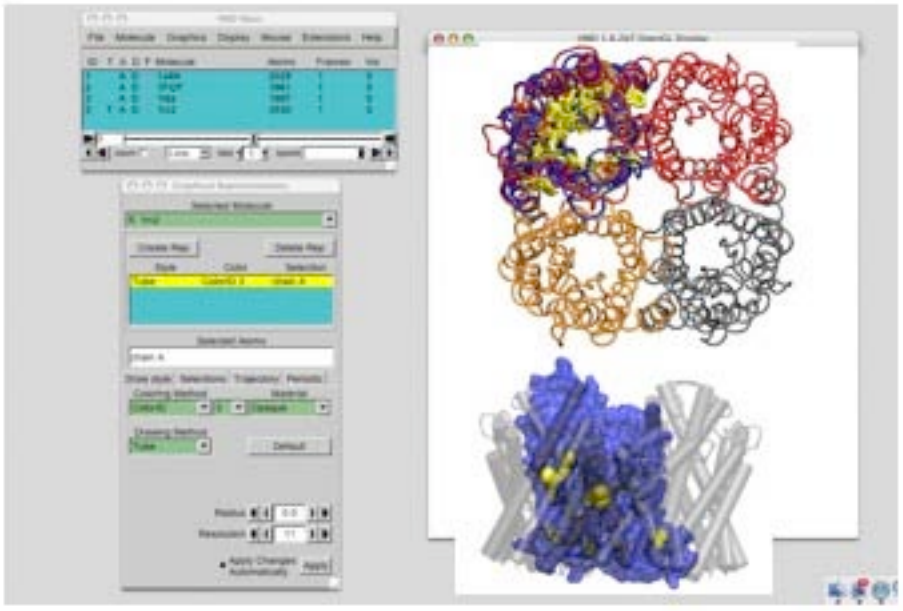
Exhibiting Sequence Identity - Top View



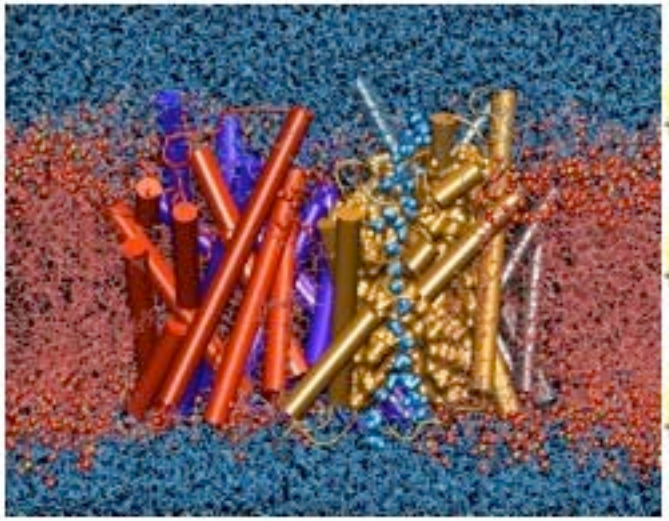
Showing Conserved Residues - Monomer



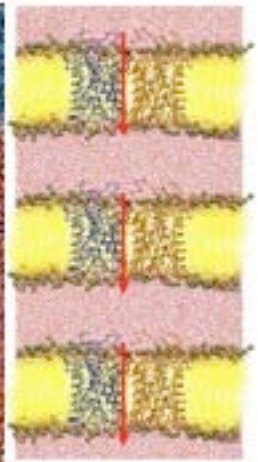
Showing Conserved Residues - Tetramer



Water Transport in Aquaporins



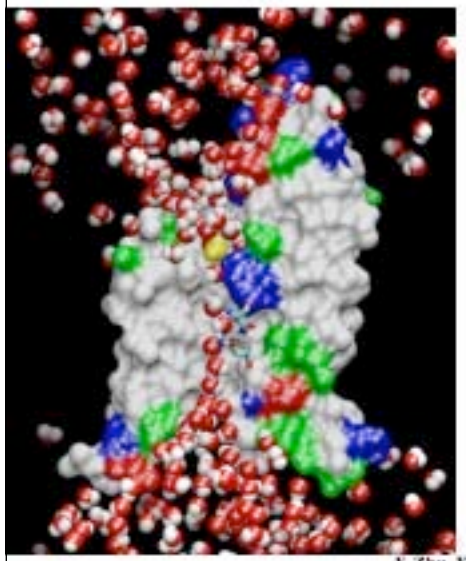
100,000 atoms

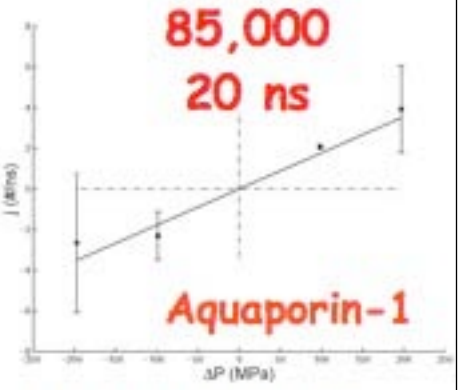


Simulation:

Apply constant force on bulk water molecules

Osmotic permeability of water channels

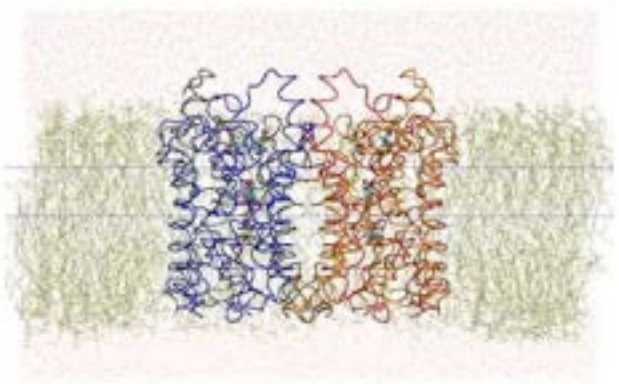


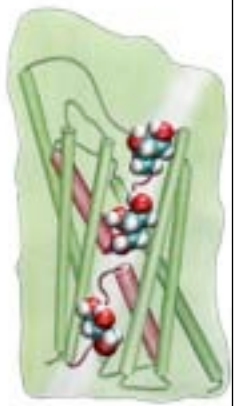


p_f: 7.0 ± 0.9 × 10^{-14} cm^3/s
Exp: 5.4 – 11.7 × 10^{-14} cm^3/s

F. Zhu, E.Tajkhorshid, K. Schulten, *Biophys. J.* **86:** 50-57 (2004)
F. Zhu, E.Tajkhorshid, K. Schulten, *Phys. Rev. Lett.* **93:** 224501 (2004)

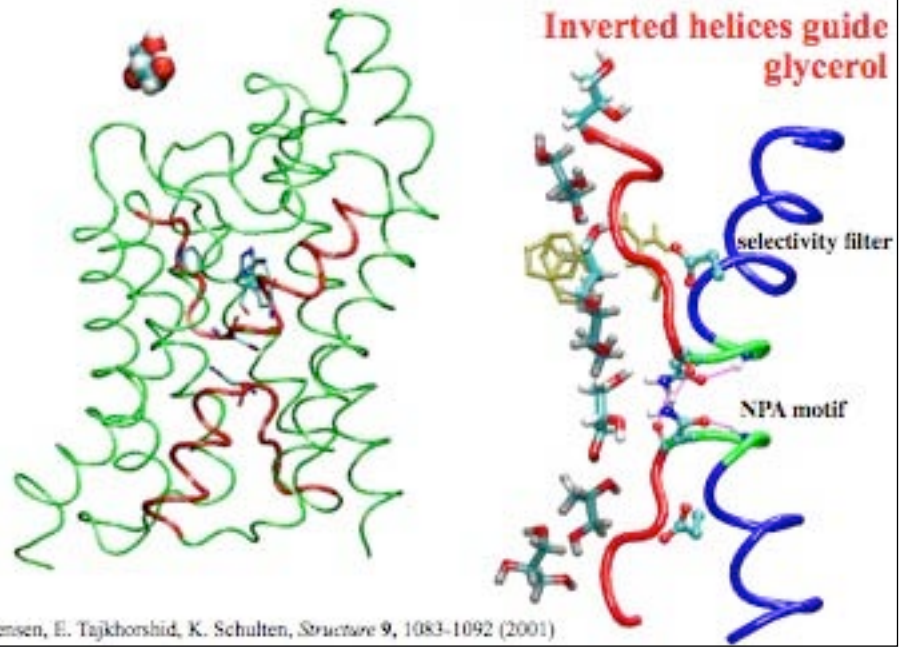
Dynamics of Protein, Lipid, Water System





M. Jensen, E. Tajkhorshid, K. Schulten, *Structure* **9**, 1083-1092 (2001)

Glycerol Conduction



M. Jensen, E. Tajkhorshid, K. Schulten, *Structure* **9**, 1083-1092 (2001)

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Aquaporins

Case study, see at
http://www.ks.uiuc.edu/
Training/CaseStudies/

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Brijeet Dhaliwal
Zan Luthey-Schulten